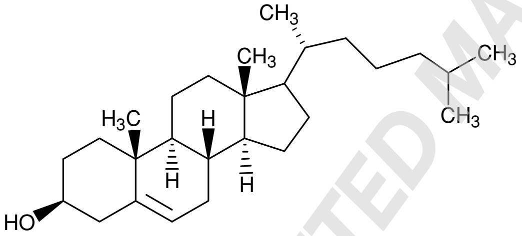
Chapter 1

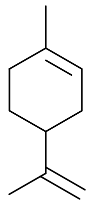
Synthetic Strategies

1.1 An introduction to organic synthesis

Organic synthesis is the construction of complex organic compounds from simple starting compounds by a series of chemical reactions. The compounds synthesized in nature are called **natural products**. Nature provides a plethora of organic compounds and many of these possess interesting chemical and pharmaceutical properties. Examples of natural products include cholesterol (**1.1**), a steroid found in most body tissues; limonene (**1.2**), a terpene found in lemon and orange oils; caffeine (**1.3**), a purine found in tea leaves and coffee beans; and morphine (**1.4**), an alkaloid found in opium.



1.1



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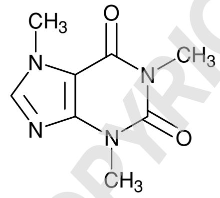

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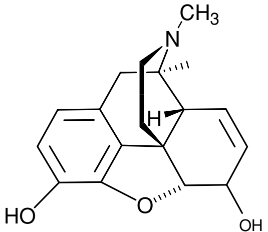
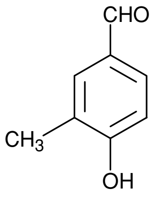


1.4

The synthesis of organic molecules is the most important aspect of organic chemistry. There are two main areas of research in the field of organic synthesis, namely **total synthesis** and **methodology**. A total synthesis is the complete chemical synthesis of complex organic molecules from simple, commercially available or natural precursors. Methodology research usually involves three main stages, namely discovery, optimization and the study of scope and limitations. Some research groups may perform a total synthesis to showcase the new methodology and thereby demonstrate its application for the synthesis of other complex compounds.

The compound to be synthesized may have a small carbon framework such as vanillin (**1.5**) (vanilla flavouring) or have more complex carbon framework such as penicillin G (**1.6**) (an antibiotic) and taxol (**1.7**) (used for the treatment of certain types of cancer). However, three challenges must be met in devising a synthesis for a specific compound: (1) the carbon atom framework or skeleton that is found in the desired compound must be assembled;

(2) the functional groups that characterize the desired compound must be introduced or transformed from other groups at appropriate locations; and (3) if stereogenic centres are present, they must be fixed in a proper manner.



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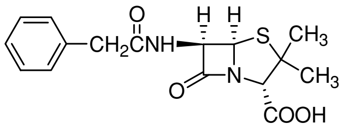

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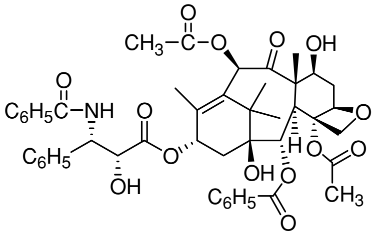


1.7

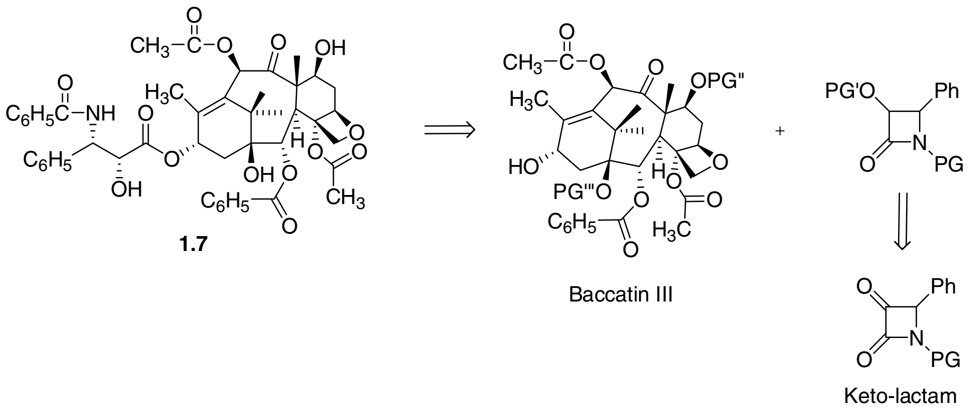
Thus, in order to understand the synthesis of a complex molecule, we need to understand the carbon–carbon bond forming reactions, **functional groups interconversions** and **stereochemistry** aspects.

Carbon–carbon bond forming reactions are the most important tool for the construction of organic molecules. The reaction in which one functional group is converted into another is known as functional group interconversion. The spatial arrangements of the substituents can have a significant impact on the reactivity and interaction towards other molecules. Many chiral drugs must be made with high enantiomeric purity because the other enantiomer may be inactive or has side effects. Thus, there is a need to develop methods to synthesize organic compounds as one pure enantiomer and the use of these techniques is referred to as **asymmetric synthesis** (section 1.5).

Therefore, carbon–carbon bond forming reactions, asymmetric synthesis, the design of new chiral ligands, environmental-friendly reactions and atom economical syntheses are the major aims of present-day research.

1.2 Retrosynthetic analysis (disconnection approach)

E. J. Corey[1,2] brought a more formal approach to synthesis design, known as retrosynthetic analysis. The analysis of synthesis in reverse manner is called **retrosynthetic analysis** or alternatively a **disconnection approach.** Retrosynthetic analysis or retrosynthesis is a technique for solving problems in synthesis planning, especially those presented by complex structures. In this approach, the synthesis is planned backwards starting from a relatively complex product to available simpler starting materials (Scheme 1.1). This approach requires construction of a carbon skeleton of the target molecule, placing the functional groups and appropriate control of stereochemistry.



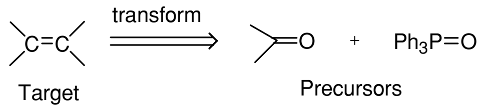
Scheme 1.1 Retrosynthetic analysis of taxol

Table 1.1 Synthetic versus retrosynthetic analysis

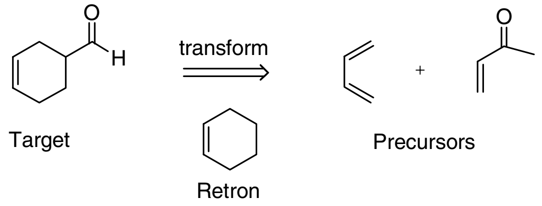
Direction	Synthetic	Retrosynthetic
Step	Reaction	Transform or retro-reaction
Arrow used in graphical depiction	⟶	⟹
Starting structure	Reactant	Target
Resulting structure	Product	Precursor
Substructure required for operation	Reacting functionality	Retron

The terminology used in synthetic and retrosynthetic analysis is shown in Table 1.1.

A transform in the case of the retrosynthetic counterpart of the Wittig reaction is shown below:



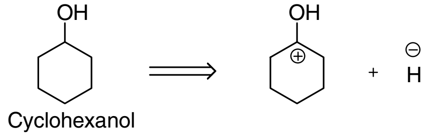
In a similar manner, the retrosynthetic analysis of the Diels–Alder reaction is represented below:



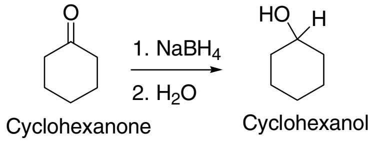
The retrosynthetic step involving the breaking of bond(s) to form two (or more) **synthons** is referred to as a **disconnection**. A synthon is an idealized fragment, usually a cation, anion or radical, resulting from a disconnection. One must select disconnections which correspond to the high yielding reactions.

Functional group interconversion is the process of the transformation of one functional group to another to help synthetic planning and to allow disconnections corresponding to appropriate reactions. In planning a synthetic strategy, apart from devising means of constructing the carbon skeleton with the required functionality, there are other factors which must be addressed including the control of regiochemistry and stereochemistry.

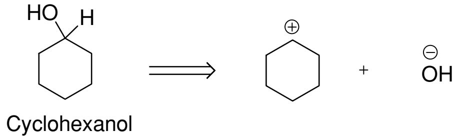
The above points are explained by discussing retrosynthetic analysis of cyclohexanol:



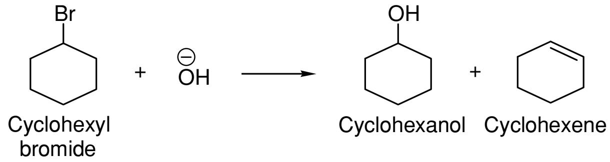
The hydroxycarbocation and the hydride ion formed after disconnection of cyclohexanol are synthons. The synthetic equivalents of hydroxycarbocation and the hydride ion are cyclohexanone and sodium borohydride, respectively. Thus, the target molecule cyclohexanol can be prepared by treating cyclohexanone with sodium borohydride.



The C–C bond of cyclohexanol can also be disconnected as shown below:



The synthetic equivalent for the cyclohexyl carbocation is cyclohexyl bromide. Thus, cyclohexanol can be prepared by the reaction of cyclohexyl bromide with hydroxide ion.



However, in this case cyclohexene is also formed; thus, this method may not be considered as effective as the previous one.

A **retrosynthetic tree** is a directed acyclic graph of several (or all) possible retrosyntheses of a single target. Retrosynthetic analysis, then, consists of applying transforms to a given target, thereby generating all precursors from which that target can be made in a single step. The analysis can be repeated for each precursor, generating a second level of precursors. Each precursor molecule so generated is in some way simpler than the target from which it was derived and then considered to be a target and analyzed similarly. The analysis terminates when precursors are elaborated, which are considered to be relatively simple or readily available, generating a tree of synthetic intermediates.

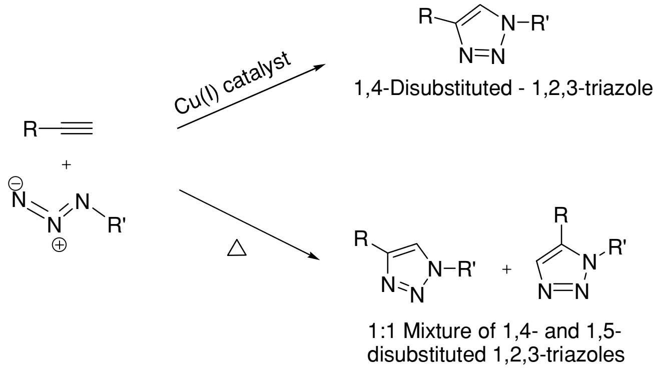
The final result is a complete retrosynthetic tree that will contain all possible syntheses of the given target – reasonable and unreasonable, efficient and cumbersome. Of course, such a tree would be unmanageably large both for humans and computers, even when the number of precursor levels is limited. To keep the size of the retrosynthetic tree under control, examine all possible disconnections – check which are chemically sound (corresponding to known reactions, reagents, directing effects). The guiding principles for this selection are called **strategies**.

Some **guidelines for retrosynthesis** are given below:

1. It is better to use convergent approach rather than divergent for many complex molecules.
2. Use only disconnections corresponding to disconnect C–C bonds and C–X bonds wherever possible.
3. Disconnect to readily recognizable synthons by using only known reactions (transform).
4. The synthesis must be short.
5. It is better to use those reactions which do not form mixtures.
6. The focus is on the removal of stereocentres under stereocontrol. Stereocontrol can be achieved through either mechanistic control or substrate control.

The computer-assisted synthetic analysis designated **OCSS** (*o*rganic *c*hemical *s*imulation of *s*ynthesis) and **LHASA** (*l*ogic and *h*euristics *a*pplied to *s*ynthetic *a*nalysis) were designed to assist chemists in synthetic analysis by Corey *et al.*^{3,4}. LHASA generates trees of synthetic intermediates from a target molecule by analysis in the retrosynthetic direction.

Click chemistry is a modular synthetic approach towards the assembly of new molecular entities. The nature has overall preference for carbon–heteroatom bonds over carbon–carbon bonds; e.g. all the proteins are created from 20 building blocks that are joined via reversible heteroatom links. Thus following nature's lead, the term 'click chemistry'^{5} was coined by Kolb, Finn and Sharpless in 2001 for synthesis restricted to molecules that are easy to make. The click chemistry as defined by Sharpless is reactions that are modular, wide in scope, high yielding, create only inoffensive products, are stereospecific, simple to perform and require the use of only benign solvent. Of all the reactions which fall under the umbrella of click chemistry, the Huisgen 1,3-dipolar cycloaddition of alkynes and azides to yield 1,2,3-triazoles is undoubtedly the premier example of a click reaction. The reaction is accelerated under copper(I) catalysis, requires no protecting groups, and almost complete conversion takes place. The reaction is selective, as only 1,4-disubstituted 1,2,3-triazole is the only product formed and there is no formation of 1,5-disubstituted triazole, which is also formed in the thermally induced Huisgen cycloaddition (Scheme 1.2).

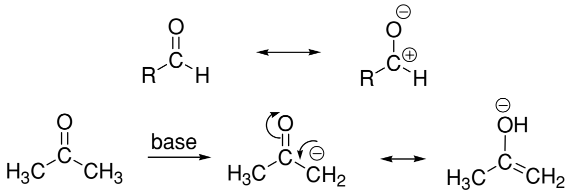


Scheme 1.2

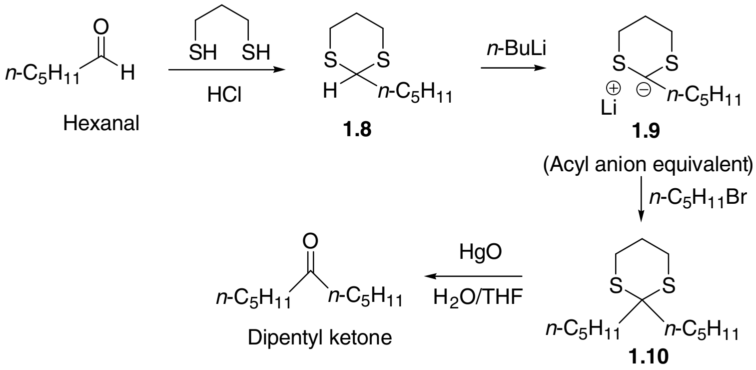
Due to the reliability, specificity and biocompatibility of **click chemistry**, its application is found in nearly all areas of modern chemistry from drug discovery to material science.

1.3 Umpolung strategy

Umpolung is a general class of reactions in which the characteristic reactivity of a group or an atom is temporarily reversed. The concept of umpolung is helpful especially with carbonyl groups. But to understand this concept, it is important to understand the normal reactivity of the carbonyl group. For example, under normal conditions carbonyl carbon is electrophilic and the α-carbon is nucleophilic because of the resonance, as shown below:



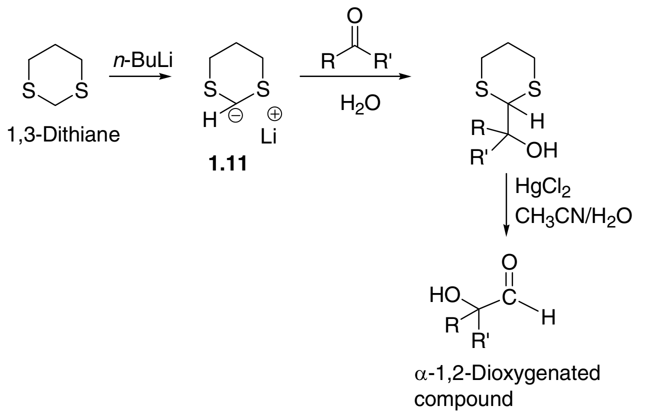
But if the polarity of a carbonyl compound is reversed, the acyl carbon becomes nucleophilic. This is achieved by first converting the carbonyl group into dithianes **1.8**, and then the carbon becomes nucleophilic. The strong base can remove the hydrogen adjacent to the sulfur in the dithiane to give 2-lithio-1,3-dithiane **1.9**. The acyl anion equivalent **1.9** generated in this manner reacts with an alkyl halide to give the alkylated product **1.10**. Finally, the carbonyl group is regenerated by unmasking the dithiane (Scheme 1.3). Thus, this type of inversion of the normal polarization of a functional group atom is known as umpolung.



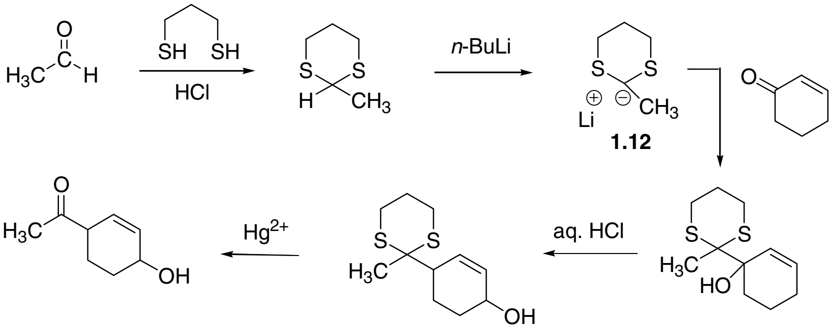
Scheme 1.3 Conversion of hexanal into dipentyl ketone (corey-seebach reaction)

In Scheme 1.3, hexanal on reaction with 1,3-propanedithiol gives the 1,3-dithiane derivative **1.8**. A strong base such as *n*-butyllithium abstracts the proton to give the corresponding 2-lithio-1,3-dithiane **1.9**, which reacts with 1-bromopentane to give alkylated product **1.10**. Treatment of **1.10** with HgO and BF_3 (boron trifluoride) in aqueous THF (tetrahydrofuran) yields the dipentyl ketone (the corey-seebach reaction[6]). Thus, dithianyllithium (2-lithio-1,3-dithiane) **1.9** is an 'acyl anion' synthetic equivalent.

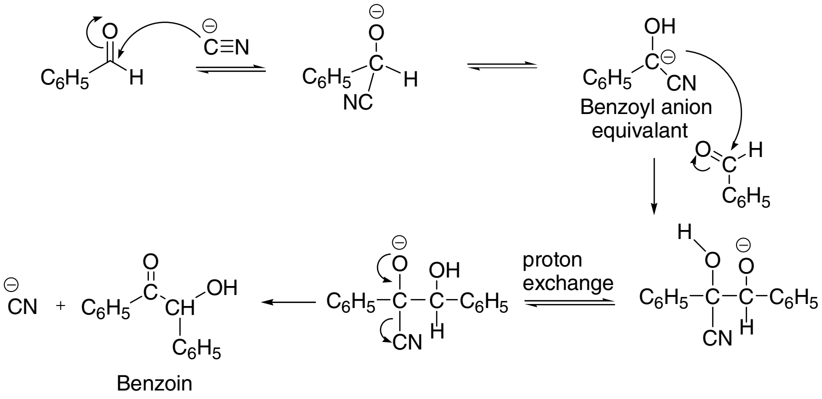
The dithiane anion **1.9** also reacts with acyl halides, ketones and aldehydes to give the corresponding dioxygenated compounds. Schemes 1.4 and 1.5 show the reaction of dithiane anions **1.11** and **1.12** with ketones. The most common example of umpolung reactivity of a carbonyl group is the benzoin condensation (Scheme 1.6).



Scheme 1.4

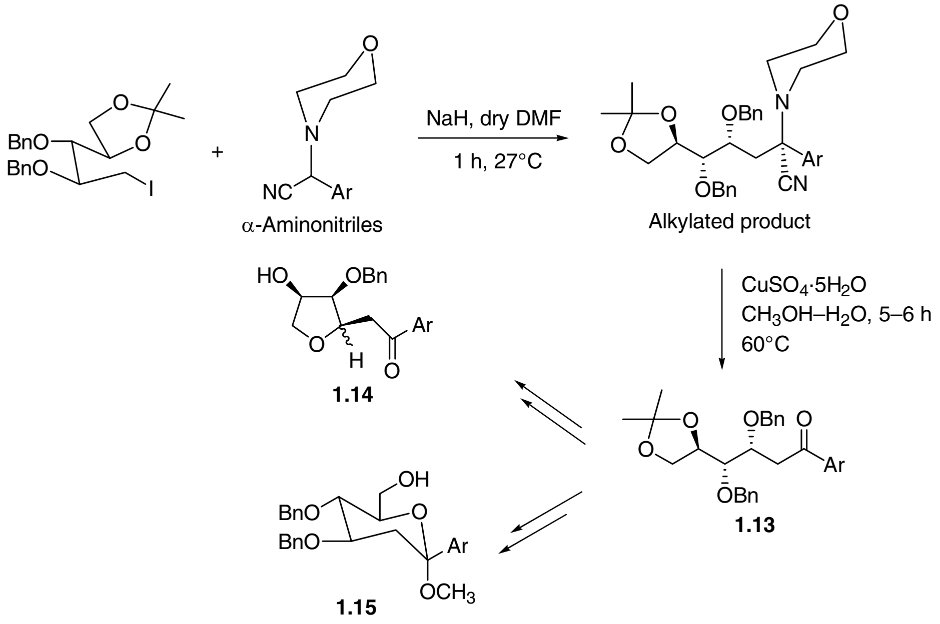


Scheme 1.5



Scheme 1.6 Mechanism of benzoin condensation

A synthetic route for the synthesis of 2-deoxy-*C*-aryl glycosides using an umpolung strategy has been reported by Aidhen and co-worker[7] (Scheme 1.7). The synthetic endeavour led to a versatile intermediate aryl ketone **1.13**, which has paved the way for two important classes of *C*-glycosides, i.e. *C*-alkyl furanosides **1.14** and methyl 2-deoxy-*C*-aryl pyranosides **1.15**.



Scheme 1.7 Synthesis of *C*-aryl glycosides

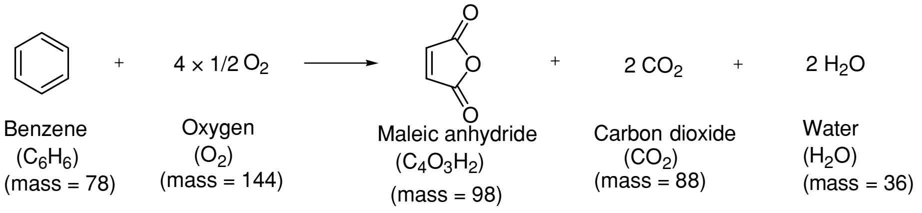
1.4 Atom economy

The concept of atom economy was developed by B. M. Trost[8,9] which deals with chemical reactions that do not waste atoms. Atom economy describes the conversion efficiency of a chemical process in terms of all atoms involved. It is widely used to focus on the need to improve the efficiency of chemical reactions.

A logical extension[10] of B. M. Trost's concept of atom economy is to calculate the **percentage atom economy**. This can be done by taking the ratio of the mass of the utilized atoms to the total mass of the atoms of all the reactants and multiplying by 100.

$$\text{Percentage atom economy} = \frac{\text{Mass of atoms in the final product}}{\text{Mass of atoms in reactants}} \times 100$$

R. A. Sheldon[11] has developed a similar concept called **percentage atom utilization**. For instance, the percentage atom economy and percentage atom utilization calculation for the oxidation reaction of benzene to maleic anhydride is given below:



$$\text{Percentage atom utilization} = \frac{\text{MFW of maleic anhydride}}{\text{MFW (maleic anhydride + 2 carbon dioxide + 2 water)}} \times 100$$

Even if the reaction were to proceed with 100% yield, only 44.14% (by weight) of the atoms of the reactants are incorporated into the desired product, with 55.86% of the reactant atoms ending up as unwanted by-products.

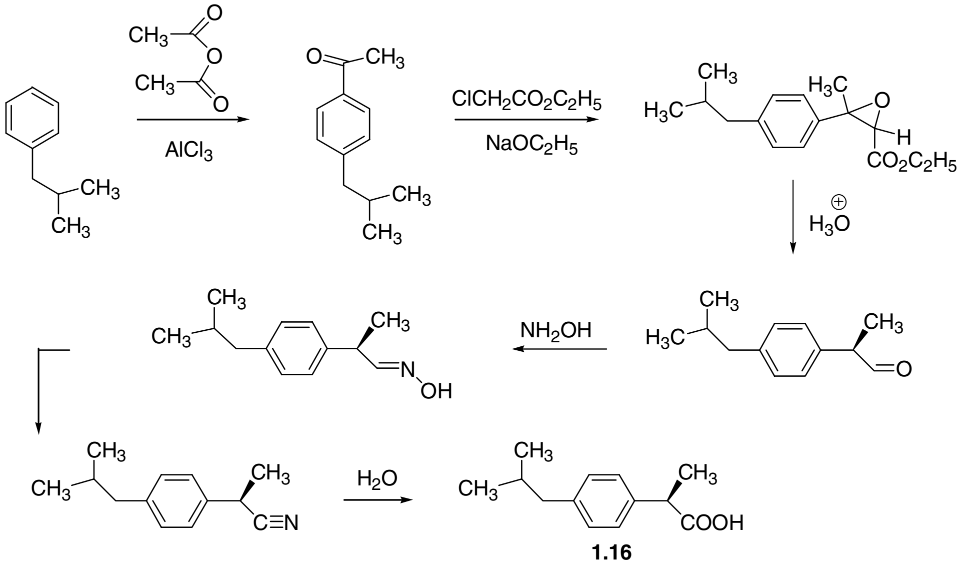
It is often difficult to know the structures of all the by-products; therefore, the percentage atom economy may be determined by dividing the molecular formula weight (MFW) of the desired product by the sum of the MFWs of all the reactants and multiplying by 100.

$$\text{Percentage atom economy} = \frac{98}{78 + 144} \times 100 = 44.14$$

The percentage atom economy of this reaction is 44.14. This means that 44.14% of the mass of the reactants ends up in the desired product.

Recent developments including the advent of green chemistry and high raw material (oil) prices increasingly demand high atom economy. In a chemical process involving simple additions, with anything else needed only catalytically, the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. The Diels–Alder reaction is an example of a potentially atom efficient reaction. Since so few of the existing used reactions are additions, synthesis of complex molecules requires the development of new atom economic methodology. Atom economy can be improved on by careful selection of starting materials and catalyst system.

A classic example of improving the route to a commercial product is **ibuprofen** (**1.16**), which is an analgesic (a pain reliever) and is also effective as a **non-steroidal anti-inflammatory drug**. Ibuprofen was produced using six steps (Scheme 1.8) by the Boots Company, with an overall atom economy of just 40%.

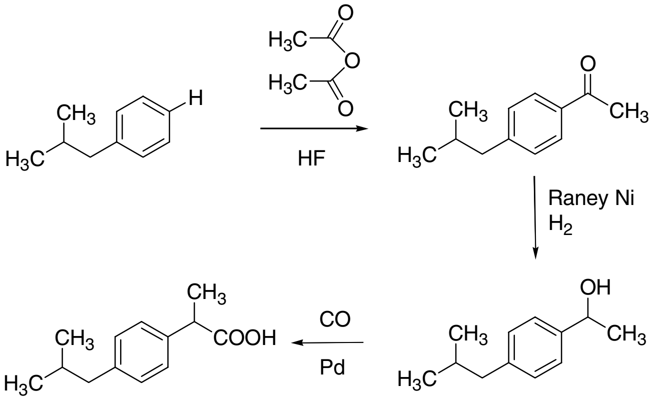


Scheme 1.8 Synthesis of ibuprofen by the Boots Company

The total MFW of all the reactants used is 514.5 ($C_{20}H_{42}NO_{10}ClN_9$) and the total MFW of atoms utilized is 206 (ibuprofen; $C_{13}H_{18}O_2$).

$$\text{Percentage atom economy} = \frac{\text{MFW of atoms utilized}}{\text{MFW of all reactants}} \times 100 = \frac{206}{514.5} \times 100 = 40$$

In the 1990s the Hoechst Celanese Corporation (together with the Boots company they formed the BHC process to prepare and market ibuprofen, **1.16**) developed a new three-stage process (Scheme 1.9), with an atom economy of 77.4%.



1.16

Scheme 1.9 Synthesis of ibuprofen by the BHC process

The total MFW of all the reactants used is 266 (all the reagents; $C_{15}H_{22}O_4$) and the total MFW of atoms utilized is 206 (ibuprofen; $C_{13}H_{18}O_2$).

$$\text{Percentage atom economy} = \frac{\text{MFW of atoms utilized}}{\text{MFW of all reactants}} \times 100 = \frac{206}{266} \times 100 = 77.4$$

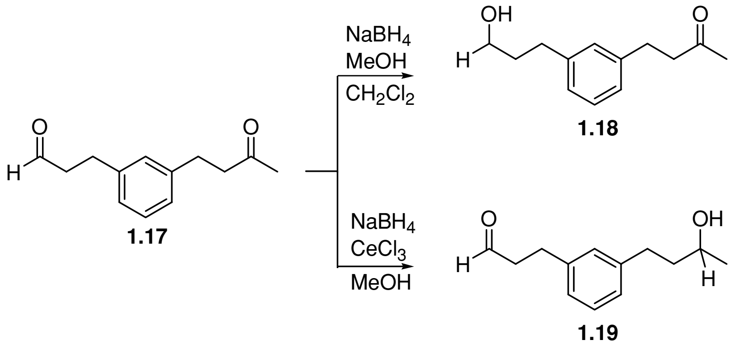
In addition to higher atom economy, in the BHC process, HF is used in catalytic amounts and is recovered and reused. However, in the first step in the Boots process, the $AlCl_3$ (aluminium chloride) hydrate is produced in large amounts as a by-product because $AlCl_3$ is used in stoichiometric amounts. Thus, there is a significant improvement in the BHC process over the Boots process.

1.5 Selectivity

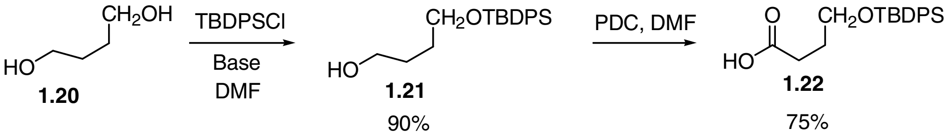
B. M. Trost has enunciated a set of criteria by which chemical processes can be evaluated. They fall under two categories: selectivity and atom economy. The atom economy has already been discussed in section 1.4. The issues of selectivity can be categorized under the following headings: chemoselectivity, regioselectivity, diastereoselectivity and enantioselectivity.

1.5.1 Chemoselectivity

Chemoselectivity is the differentiation among various functional groups in a polyfunctional molecule by preferential reactivity of one functional group over another. For example, chemoselective reduction of the aldehyde group in **1.17** occurs with $NaBH_4$ (sodium borohydride) in methanol at low temperature to give **1.18**. However, in the presence of $CeCl_3$ (ceric chloride), the keto group is reduced with $NaBH_4$ to give **1.19**.



Selective monoprotection[12] of 1,4-butanediol (**1.20**) with TBDPSCl (*tert*-butyldiphenylsilyl chloride) (see Table 1.2) is another example of chemoselectivity. Monoprotected alcohol **1.21** on oxidation with PDC (pyridinium dichromate) in DMF (dimethylformamide) afforded the corresponding carboxylic acid derivative **1.22** in 75% yield.



The chemoselective 1,2-reduction of αβ-unsaturated carbonyl compounds has been carried out with metal hydride or by hydrogenation. However, chemoselective 1,4-reduction of αβ-unsaturated carbonyl compounds is challenging. Recently, αβ-unsaturated carbonyl compounds **1.23**, **1.25** and **1.27** were selectively reduced to the corresponding saturated carbonyl compounds **1.24**, **1.26** and **1.28**, respectively, by cobalt octacarbonyl and water [$Co_2(CO)_8$–H_2O system][13].

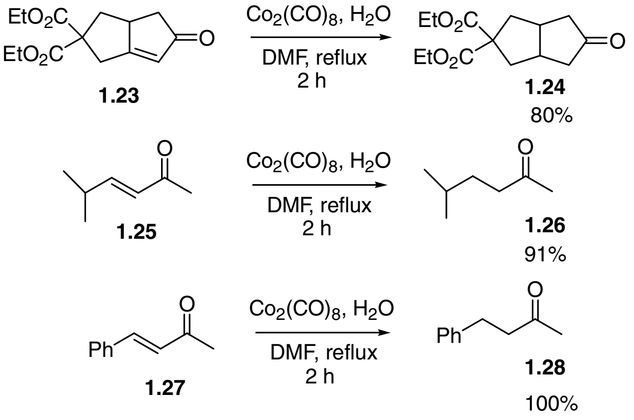
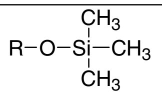
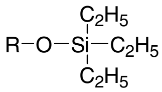
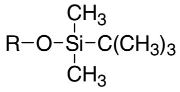
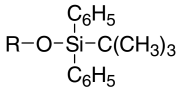
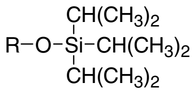
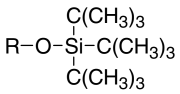
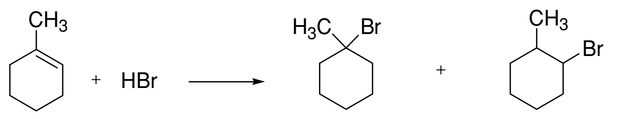


Table 1.2 Various trialkylsilyl chlorides (R'_3SiCl) used for the protection of R–OH as $ROSiR'_3$

R'_3SiCl Trialkylsilylchloride	$ROSiR'_3$ Trialkylsilylether
$(CH_3)_3SiCl$ Trimethysilyl chloride (TMSCl)	 $R{-}O{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}CH_3$ (TMSOR)
$(C_2H_5)_3SiCl$ Triethylsilyl chloride (TESCl)	 $R{-}O{-}\overset{C_2H_5}{\underset{C_2H_5}{Si}}{-}C_2H_5$ (TESOR)
$(CH_3)_3CSi(CH_3)_2Cl$ *t*-Butyldimethylsilyl chloride (TBSCl)	 $R{-}O{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}C(CH_3)_3$ (TBSOR)
$(CH_3)_3CSi(C_6H_5)_2Cl$ *t*-Butyldiphenylsilyl chloride (TBDPSCl)	 $R{-}O{-}\overset{C_6H_5}{\underset{C_6H_5}{Si}}{-}C(CH_3)_3$ (TBDPSOR)
$[(CH_3)_2CH]_3SiCl$ Triisopropylsilyl chloride (TIPSCl)	 $R{-}O{-}\overset{CH(CH_3)_2}{\underset{CH(CH_3)_2}{Si}}{-}CH(CH_3)_2$ (TIPSOR)
$[(CH_3)_3C]_3$ SiCl Tri-*t*-butylsilylchloride (TTBSCl)	 $R{-}O{-}\overset{C(CH_3)_3}{\underset{C(CH_3)_3}{Si}}{-}C(CH_3)_3$ (TTBSOR)

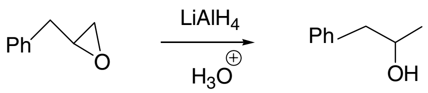
1.5.2 Regioselectivity

Regioselectivity (orientational control) is the formation of one constitutional isomer as the major product in which two or more constitutional isomers could be obtained. For example, addition of HBr (hydrogen bromide) to 1-methylcyclohexene (**1.29**) gives 1-bromo-1-methylcyclohexane (**1.30**) as the main product and 1-bromo-2-methylcyclohexane (**1.31**) is formed as the minor product.

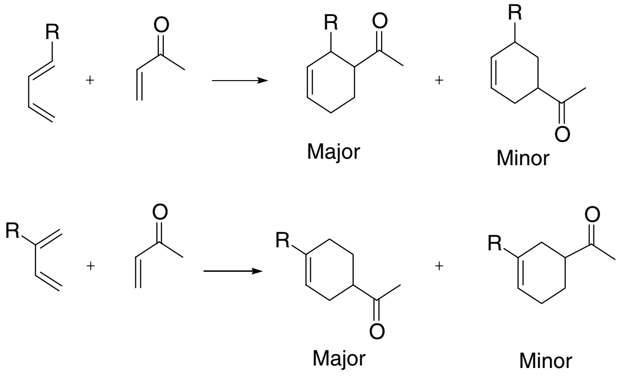


1.29 **1.30** (Major product) **1.31** (Minor product)

The $LiAlH_4$ (lithium aluminium hydride) attacks the epoxides on the sterically less hindered C–O bond to give the corresponding alcohol.



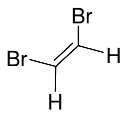
Regioselectivity is also observed in Diels–Alder reactions (also see Chapter 8, section 8.3.1).



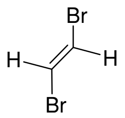
1.5.3 Stereoselectivity

Stereoisomerism is the arrangement of atoms in molecules whose connectivity remains the same but their arrangement in space is different in each isomer (atoms are connected in the same sequence). The two main types of stereoisomerism are ***cis–trans*** or ***Z–E*** **isomerism** and **optical isomerism**.

cis–trans **or** ***Z–E*** **isomerism:** The *cis*- and *trans*-1,2-dibromoethenes isomers cannot be easily interconverted because of restriction of carbon–carbon double bond. Both have the same molecular formula $C_2H_2Br_2$, but the arrangement of their atoms in space is different. The *cis*- and *trans*-1,2-dibromoethenes are not mirror images of each other; thus, they are not enantiomers and are therefore diastereomers.

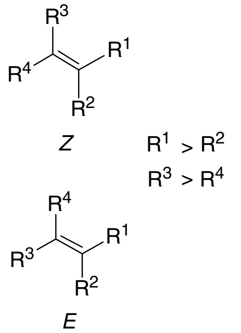


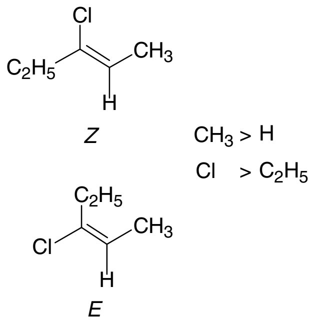
cis-1,2-Dibromoethene



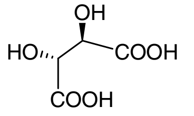
trans-1,2-Dibromoethene

If the alkene is trisubstituted or tetrasubstituted, the terms *cis* and *trans* are normally not applied but the *E–Z* system of nomenclature is applied to alkene diastereomers. Generally, **Cahn-Ingold-Prelog (CIP) rules** are used to assign priorities to each end of the double bond. If $R^1 > R^2$ and $R^3 > R^4$ then alkene with R^1 and R^3 on the same side is designated *Z* from the German word *Zusammen*, meaning together. If R^1 and R^3 are on the opposite side then alkene is designated *E* from the German word *Entgegen*, meaning opposite. For an example, (*Z*)- and (*E*)-3-chloro-2-pentenes are shown below:

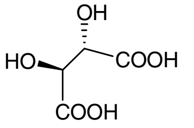




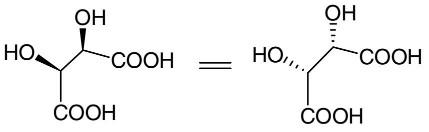
Optical isomers: Optical isomers are stereoisomers that can be formed around asymmetrical carbon(s) also known as **chiral** carbons. A **stereocentre** or chiral centre in organic chemistry generally refers to a carbon atom in a chemical compound that is an **asymmetric carbon atom** or a **chiral** carbon. A compound is chiral if it is non-superimposable on its mirror image. **Enantiomers** are two optical isomers that are reflections of each other. They have the same physical properties, except for their ability to rotate plane-polarized light, which they do in equal magnitudes but in opposite direction. A mixture of equal amounts of both enantiomers is said to be a **racemic mixture**. A racemic mixture does not rotate plane-polarized light. The assignment of each stereocentre as either *R* or *S* follows from the **CIP sequence rules**. Details of CIP sequence rules can be found in any undergraduate textbook on organic chemistry. **Diastereoisomers** are two optical isomers that are neither reflections of each other nor superimposable. Diastereomers can have different physical properties and different reactivities. A compound can have 2^n stereoisomers, where n is the number of stereocentres. Tartaric acid contains two asymmetric centres, but two of the configurations are equivalent and together are called ***meso* compounds**. A *meso* compound is optically inactive (or achiral) because it contains an internal plane of symmetry. The remaining two configurations are (+)- and (−)- mirror images, thus enantiomers. The *meso* form is a diastereomer of the other forms.



L(+)-Tartaric acid
(laevo-tartaric acid)



D-(−)-Tartaric acid
(dextro-tartaric acid)



meso-Tartaric acid

In a **stereoselective reaction**, one stereoisomer is formed in a major amount than another. When the stereoisomers are enantiomers the selectivity is known as **enantioselectivity**. The degree of enantiomeric purity of a solution is measured by its **enantiomeric excess, or ee.** The percentage enantiomeric excess is found by dividing the observed optical rotation by the optical rotation of pure enantiomer in excess and multiplying by 100.

$$\text{Optical purity} = \text{Percentage enantiomeric excess} = \frac{[\alpha]_{\text{mixture}}}{[\alpha]_{\text{pure sample}}} \times 100$$

For example, the observed specific rotation of the racemic mixture is +8.52 degrees of rotation. The specific rotation of the pure *S*-enantiomer is −15.00 degrees of rotation. Since the pure *S*-enantiomer has −15.00° and the specific rotation of mixture is +8.52°, then the *R*-configured isomer with specific rotation +15.00° is in excess. The percentage enantiomeric excess for the *R*-isomer is given as:

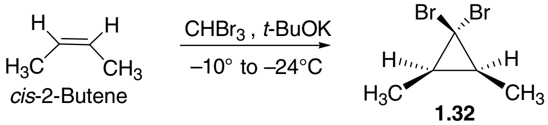
$$\text{Percenatge enantiomeric excess for } R\text{-isomer} = \frac{+8.52}{+15.00} \times 100 = 56.8$$

The 0% ee means 50:50 racemic mixture, while 50% ee means 75:25 mixture. Thus, **enantiomeric excess** or **ee** is a measure for how much of one enantiomer is present compared to the other. For example, in a sample with 40% ee in *R*, the remaining 60% is racemic with 30% of *R* and 30% of *S*, and so the total amount of *R* is 70%. Thus, the percentage enantiomeric excess is also written as:

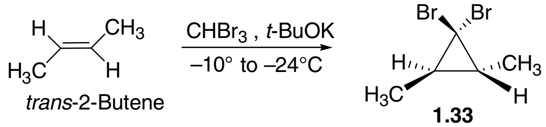
$$\text{Percentage enantiomeric excess} = \frac{\text{Major enantiomer} - \text{Minor enantiomer}}{\text{Major enantiomer} + \text{Minor enantiomer}} \times 100$$

Recently, the enantiomeric excess of α-amino acid ester hydrochlorides has been determined directly by using FAB (fast atom bombardment) mass spectrometry without chromatographic separation of the enantiomers[14].

When each stereoisomeric reactant forms a different stereoisomeric product the reaction is known as **stereospecific reaction**. For example, the addition of $:CBr_2$ (dibromocarbene, prepared from bromoform and base) to *cis*-2-butene gives *cis*-2,3-dimethyl-1,1-dibromocyclopropane (**1.32**), whereas addition of $:CBr_2$ to the *trans*-isomer exclusively yields the *trans*-cyclopropane **1.33**.



1.32

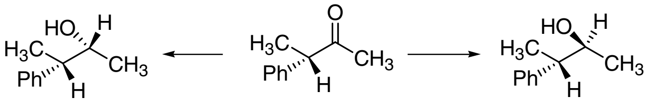


1.33

Bromination of alkenes is also a stereospecific reaction.

Therefore, all the stereospecific reactions are also stereoselective reactions. However, all the stereoselective reactions are not necessarily stereospecific.

When a molecule which already contains at least one stereocentre undergoes reaction in which a new stereocentre is created, there is a possibility of formation of two (or more) stereoisomeric products. For example, reduction of **1.34** leads to **diastereoisomeric** products **1.35** and **1.36** with diastereoselectivity (de) 83% (*si* face addition) (**1.35**). For more details about *re* or *si* face additions, see Chapter 6, section 6.4.2.

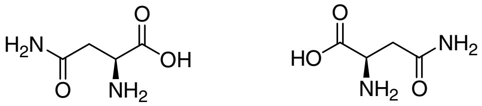


1.35 *si*-face addition **1.34** *re*-face addition **1.36**

de 83% *si*-face addition)
91.5: 8.5% (**1.35**:**1.36**)

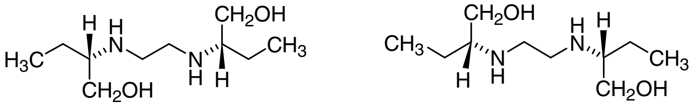
1.5.4 Asymmetric synthesis or chiral synthesis

A chiral substance is **enantiopure** or **homochiral** when only one of two possible enantiomers is present. A chiral substance is **enantioenriched** or **heterochiral** when an excess of one enantiomer is present but not to the exclusion of the other. If the desired product is an enantiomer, the reaction needs to be sufficiently stereoselective even when atom economy is 100%. For the biological usage we almost need one enantiomer and in high purity. This is because when biologically active chiral compounds interact with its receptor site which is chiral, the two enantiomers of the chiral molecule interact differently and can lead to different chemistry. For example, one enantiomer of asparagines (**1.37**) is bitter while the other is sweet. As far as medicinal applications are concerned, a given enantiomer of a drug may be effective while the other is inactive or potentially harmful. For example, one enantiomer of ethanbutol (**1.38**) is used as antibiotic and the other causes blindness.



Bitter Sweet

Asparagine (**1.37**)



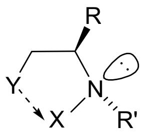
Antibiotic Causes blindness

Ethanbutol (**1.38**)

Despite its importance, the ability to obtain chiral molecules in enantiopure form is a difficult challenge. One strategy to make a pure enantiomer is to produce the racemic mixture and then separate both enantiomers and effectively throw away the undesired enantiomer. Separation of enantiomers is a very difficult endeavour, and destroying half the reaction product at every stereogenic step is not viable as yields in multi-step synthesis decrease exponentially.

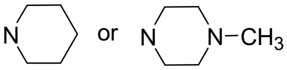
Chiral synthesis, also called **asymmetric synthesis**, is synthesis which preserves or introduces a desired chirality. Principally, there are three different methods to induce asymmetry in reactions. There can be either one or several stereogenic centres embedded in the substrate inducing chirality in the reaction (i.e. **substrate control**) or an external source providing the chiral induction (i.e. **reagent control**). In both cases the obtained stereoselectivity reflects the energy difference between the diastereomeric transition states.

The obvious approach for chiral synthesis would be to find a chiral starting material, such as a natural amino acid, carbohydrates, carboxylic acids or terpene. The major source of these chiral starting materials sometimes called **chirons** is nature itself. The synthesis of a complex enantiopure chemical compound from a readily available enantiopure substance such as natural amino acids is known as **chiral pool synthesis**. For example, chiral lithium amides[15a] **1.39** that are used for several types of enantioselective asymmetric syntheses can be prepared in both enantiomeric forms starting from the corresponding optically active amino acids, and these are often available commercially.



1.39

X = Li or H

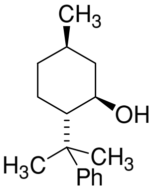
Y =  or

R' = CH_2Bu^t, CH_2CF_3

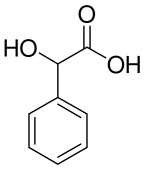
R = Ph, *t*-Bu

However, **chiral pool synthesis** is restricted by the number of possible starting enantiomeric pure compounds and requires a stoichiometric amount of the starting material, which may be scarce and expensive.

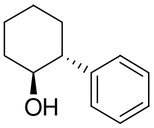
Chiral auxiliaries are optically active compounds which are used to direct asymmetric synthesis. The chiral auxiliary is temporarily incorporated into an organic synthesis which introduces chirality in otherwise racemic compounds. This temporary stereocentre then forces the asymmetric formation of a second stereocentre. The synthesis is thus **diastereoselective**, rather than enantioselective. After the creation of the second stereocentre the original auxiliary can be removed in a third step and recycled. E. J. Corey in 1975, B. M. Trost in 1980 and J. K. Whitesell in 1985 introduced the chiral auxiliaries 8-phenylmenthol[15b] (**1.40**), chiral mandelic acid[15c] (**1.41**) and *trans*-2-phenyl-1-cyclohexanol[15c] (**1.42**), respectively.



1.40



1.41

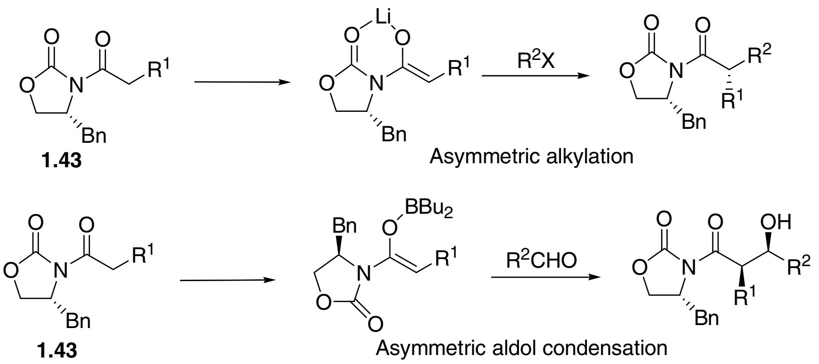


1.42

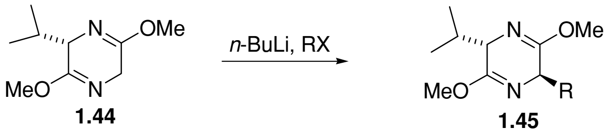
In order to maximize the diastereoselectivity observed for an auxiliary, it would appear reasonable that the stereocontrolling functional group is in a position in space as close as possible to the newly forming stereogenic centre. Chiral imide auxiliaries such as Evans' *N*-acyloxazolidinones (**1.43**) are used for asymmetric alkylation and asymmetric aldol condensation (Scheme 1.10).

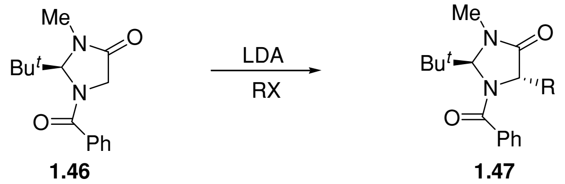
Many structural variants of *N*-acyloxazolidinones have been reported and exhibit different cleavage reactivity or complimentary diastereoselectivity compared to *N*-acyloxazolidinone (**1.43**).

Several examples of chiral auxiliaries[16] that rely on relatively remote stereogenic centres to control diastereoselectivity are known. For example, alkylation of the enolates of **1.44** and **1.46** to **1.45** and **1.47** is controlled via 1,4- and 1,3-asymmetric induction, respectively.

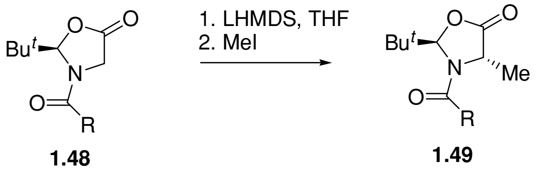


Scheme 1.10





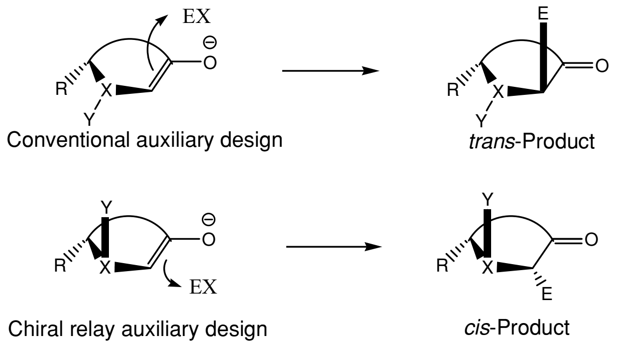
The steric and electronic factors combine to transfer or relay stereochemical information from the stereogenic centre to the site of reaction. Small changes in bond angles or heteroatom hybridization can result in large changes in diastereoselectivities. For example, changing the nitrogen protecting group in imidazolidinone-derived auxiliaries **1.48** results in significant improvements in the observed diastereoselectivities of **1.49** during enolate alkylation.



R	de
t-Bu	50%
Ph	88%
OPh	96%

The conformationally flexible group serves to both relay and amplify the stereochemical information of the existing stereogenic centre, thus enabling efficient control of diastereoselectivity (Scheme 1.11).

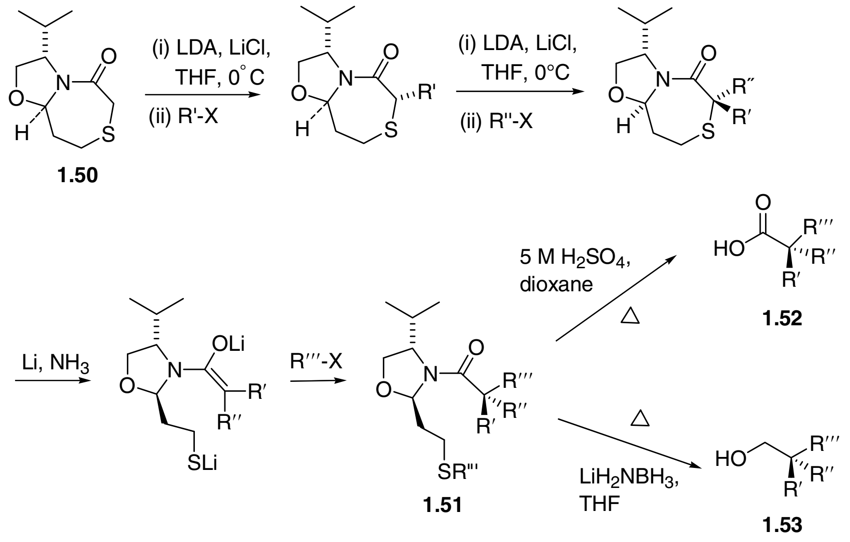
The chiral auxiliary method may be used for the synthesis of all-carbon quaternary stereocentres[17]. Thus, chiral bicyclic thioglycolate lactam **1.50** is alkylated three times and



X = heteroatom; R = stereocontrolling group; Y = relay group

Scheme 1.11

the alkylated products **1.51** may be cleaved under either acidic or reductive conditions to furnish either carboxylic acids **1.52** or primary alcohols **1.53**, respectively (Scheme 1.12).

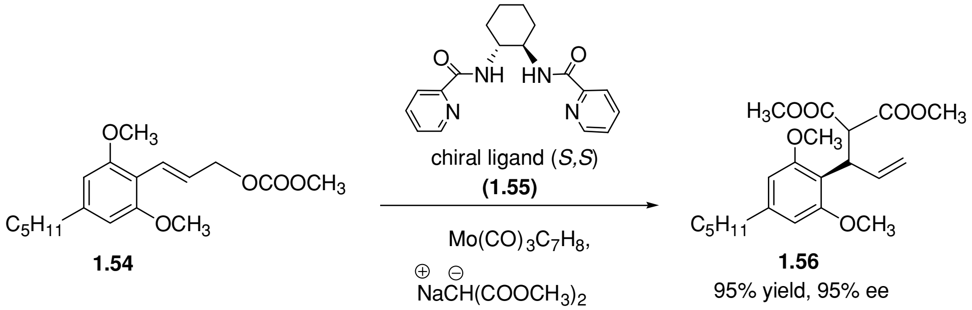


LiH_2NBH_3 = Lithium amidotrihydro borate

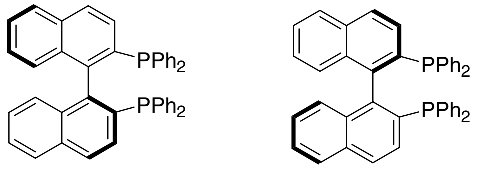
Scheme 1.12

The problem in the use of **chiral reagents** in chiral synthesis is that the chiral reagents are used up in the reaction. Thus, the most economic and convenient chiral synthesis is by the use of chiral catalysts where a small amount of chiral catalyst can produce large amounts of enantiomerically enriched product.

Asymmetric catalysis, the introduction of chirality into non-chiral reactants through usage of a chiral catalysts, is an important aspect of asymmetric synthesis. The most extensively studied asymmetric catalysis reaction is that of hydrogenation of alkenes. In addition to hydrogenation reactions, platinum group metal complexes can effectively be used for the asymmetric hydrosilations, allylic alkylations, isomerizations, hydroformylations and carbonylations. All members of the platinum group metals have been successfully used. The reaction of carbonate **1.54** with sodium dimethyl malonate with catalyst [$Mo(CO)_3C_7H_8$] and chiral ligand **1.55** gave branched product **1.56** in 95% yield and 95% ee[18].



Chiral ligands once attached to the starting materials physically dictate trajectory for attack, leaving only the desired trajectory open. One chiral ligand that is widely used for introducing chirality in combination with ruthenium or rhodium is **BINAP** (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (**1.57**). Both (*S*)-BINAP and (*R*)-BINAP are commercially available. It consists of two naphthyl groups linked by a single bond with diphenylphosphino groups at the end of each naphthyl group. Rotation about the single bond binding the two naphthyl groups is restricted because of the rigidity of their p system. Therefore, the angle made by the two p planes is fixed to approximately 90° and two separate enantiomers exist. BINAP is prepared from BINOL (1,1′-bis-2-naphthol) (see Chapter 6, section 6.1.1, Scheme 6.3).

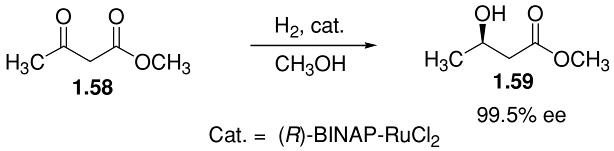


(*S*)-(−)-BINAP (*R*)-(+)-BINAP

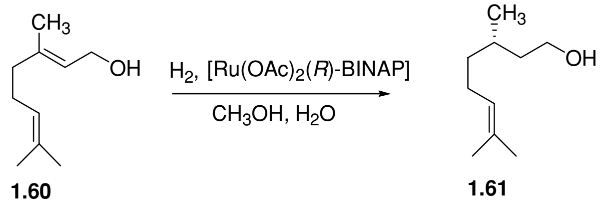
(*S*)-(−)-2,2′-Bis(diphenyl phosphino)-1,1′-binaphthyl (*R*)-(+)-2,2′-Bis(diphenyl phosphino)-1,1′-binaphthyl

1.57

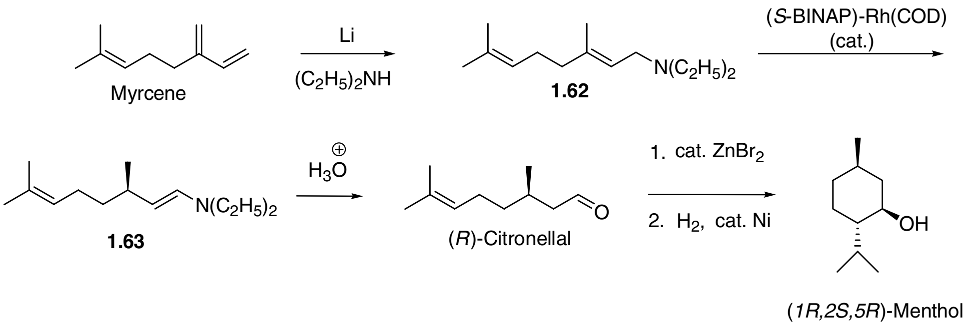
The chiral structure of BINAP enables highly enantioselective reactions in **organic synthesis.** The Ru– and Rh–BINAP complexes catalyze the hydrogenation of functionalized alkenes and carbonyls on only one face of the molecule. For example, asymmetric hydrogenation of methyl 3-oxobutanoate (**1.58**) using (*R*)-BINAP–ruthenium complex yields (*R*)-(−)-methyl 3-hydroxybutanoate (**1.59**) in 99.5% ee[19,20].



Similarly, catalytic hydrogenation of geraniol (**1.60**) in the presence of Ru–(*R*)-BINAP complex yields (*S*)-(−)-citronellol (**1.61**) in high yield[21,22].

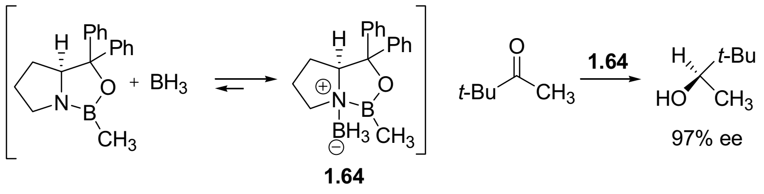


The use of chiral rhodium–BINAP complexes for the asymmetric isomerization of alkenes has been utilized in the industrial synthesis of menthol by Ryoji Noyori (winner of the 2001 Nobel Prize in Chemistry). This synthetic method was industrialized by Takasago International Corporation and provides (−)-menthol to pharmaceutical and food companies worldwide. In this case the catalyst [(*S*-BINAP)-Rh(COD)] or [(*S*-BINAP)$_2$-RuClO$_4$$^-$] is used for the asymmetric isomerization of diethylgeranylamine (**1.62**) to 3-(*R*)-citronellalenamine (**1.63**) (Scheme 1.13).



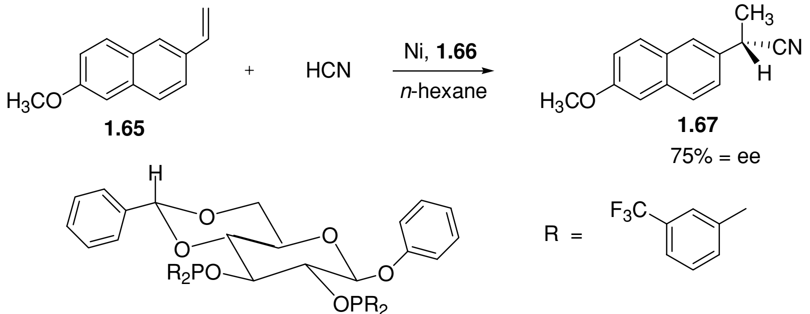
Scheme 1.13 Asymmetric synthesis of menthol by Takasago International Corporation

Several novel catalysts in which borohydride is complexed with a difunctional chiral ligand have been developed and used for the enantioselective reduction of prochiral ketones to chiral alcohols. **Corey–Bakshi–Shibata reduction**[23,24] (**CBS reduction**) is an organic reaction which reduces ketones enantioselectively into alcohols by using chiral oxazaborolidines and BH$_3$·THF or catecholborane as stoichiometric reductants (**CBS reagent**, **1.64**) (also see Chapter 6, section 6.4.2).



For example, (*S*)-2-methyl-CBS-oxazaborolidine binds reversibly with diborane to form the reactive reducing species **1.64**. Coordination of the ketone oxygen with the Lewis acidic boron orients and activates the carbonyl group for hydride transfer to its *si* face. The intramolecular hydride transfer mechanism serves as a model for achieving enantioselective reduction (see Scheme 6.20).

Naproxen, an anti-inflammatory drug, is synthesized by utilizing an asymmetric enantioselective hydrocyanation of vinylnaphthalene **1.65** utilizing a chiral ligand **1.66**. Since the S-enantiomer is medicinally desirable whereas the *R*-enantiomer produces harmful health effects, the enantioselectivity of this reaction is important. The synthesis of naproxen nitrile (**1.67**) shown below produces the *S*-(−)-enantiomer with 75% ee.



1.65

1.67

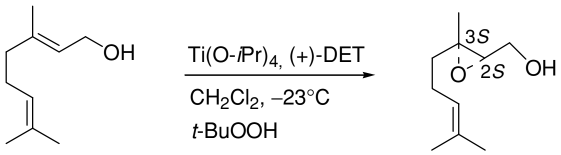
75% = ee

1.66

In 2001, K. B. Sharpless won the Nobel Prize in Chemistry for his work on **asymmetric aminohydroxylation**[25–27] and **asymmetric epoxidation**[28–30]. These stereoselective oxidation reactions are powerful catalytic asymmetric methods that have revolutionized synthetic organic chemistry.

Sharpless asymmetric epoxidation[28–30] is an enantioselective epoxidation of an allylic alcohol with *tert*-butyl hydroperoxide (*t*-BuOOH), titanium tetraisopropoxide [Ti(O-*i*Pr)$_4$] and (+)- or (−)-diethyl tartrate [(+)- or (−)-DET] to produce optically active epoxide from achiral allylic alcohol. The reaction is diastereoselective for α-substituted allylic alcohols. Formation of chiral epoxides is an important step in the synthesis of natural products because epoxides can be easily converted into diols and ethers.

For example, asymmetric epoxidation of geraniol (**1.60**) gives (2*S*,3*S*)-epoxygeranial (**1.68**) in 77% yield and 95% ee.

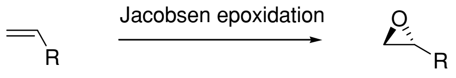


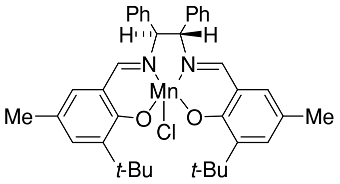
1.60

1.68

77% yield, 95% ee

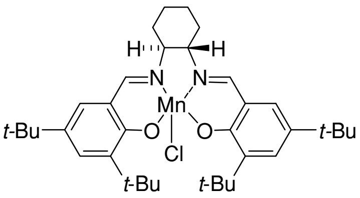
Epoxidation of alkenes with complex of a chiral **salen ligand** and manganese(III), **1.69** or **1.70**, is known as **Jacobsen epoxidation**[31,32].





1.69

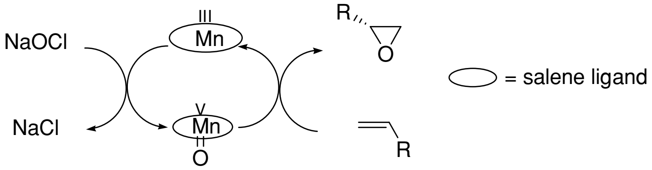
(Jacobsen catalysts)



1.70

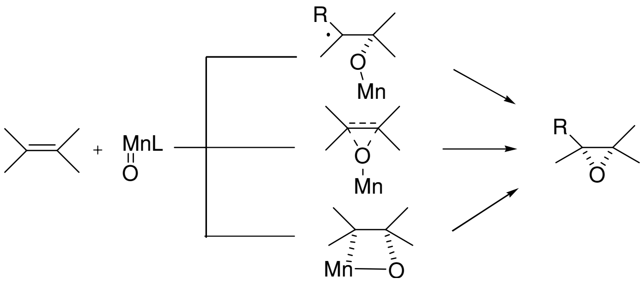
(More selective Jacobsen catalyst)

Mechanism of epoxidation:[33a] The oxygen transfer occurs by a two-step catalytic cycle (Scheme 1.14). In the first step oxygen is transferred to the Mn(III) by an oxidant. The oxygen coordinates to the metal. In the second step the activated oxygen is delivered to the alkene.



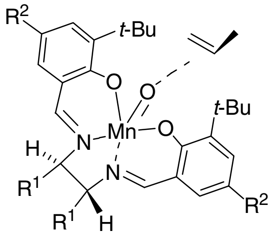
Scheme 1.14 The epoxidation of alkenes

The transfer of oxygen to alkene may occur by several different mechanisms (Scheme 1.15). Oxygen radicals may be formed as intermediates when radical stabilizing groups are attached. This mechanism is supported by the fact that *cis*-alkene gives both *cis*- and *trans*-epoxide. The formation of the metallaoxetane as an intermediate is also proposed by Norrby *et al.*[33b] However, concerted oxygen delivery has also been proposed.



Scheme 1.15 Possible modes of oxygen transfer from Mn to double bond

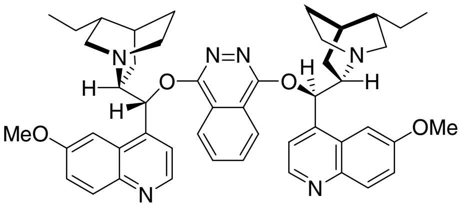
The selectivity of oxygen transfer from oxo–manganese complex to the alkene depends on the relative orientation of the activated catalyst and the alkene. The alkene approaches the salen ligand in such a manner so that it avoids the raised butyl groups and keeps its substituents as far from the **salen ligand** as possible.



$R^1 = –(CH_2)_4–$; $R^2 = t$-Bu
$R^1 = Ph$; $R^2 = CH_3$

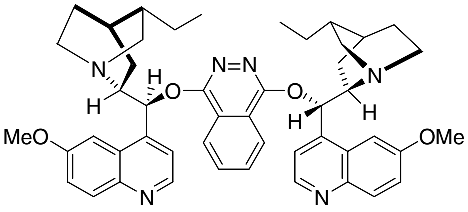
The **dihydroxylation of alkenes** with catalytic amount of osmium tetroxide in the presence of stoichiometric oxidizing reagent, like barium chlorate, *tert*-butyl hydroperoxide (*t*-BuOOH), *N*-methyl-*N*-oxo-morpholine (NMO), sodium peroxodisulphate ($Na_2S_2O_8$), iodine (I_2) or potassium ferricyanide [$K_3Fe(CN)_6$], is an important method for the production of diols. The reaction is stereospecific as *syn*-diols are obtained. However, the stereoselectivity varies depending on the structure of the alkene. **Sharpless** provided a method of asymmetric dihydroxylation[34] of alkene. When osmium tetroxide and an oxidizing agent like NMO or $K_3Fe(CN)_6$ are used in the presence of a chiral *cinchona alkaloid*, high enantiomeric excess (%ee) of the diol product is formed. It is the chiral cinchona alkaloid that provides the optically active component to the catalyst. The reaction is carried out in a buffered solution to ensure a stable pH. NMO or $K_3Fe(CN)_6$ is used for the regeneration of osmium(VIII).

These reagents are commercially available premixed: asymmetric dihydroxylation mix (AD-mix). **AD-mix** is available in two variations: **AD-mix *α*** is $(DHQ)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$ and **AD-mix** β is $(DHQD)_2PHAL + K_2OsO_2(OH)_4 + K_3Fe(CN)_6$. Ligand $(DHQ)_2PHAL$ is 1,4-bis(9-*O*-dihydroquinine)phthalazine (**1.71**) and ligand $(DHQD)_2PHAL$ is 1,4-bis(9-*O*-dihydroquinidine)phthalazine (**1.72**).



1.71

AD-mix α = $K_2OsO_2(OH)_4$ (cat.), K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$ (cat.)

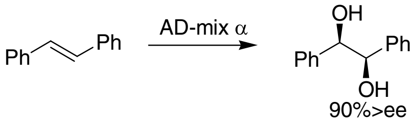


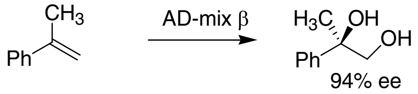
1.72

AD-mix β = $K_2OsO_2(OH)_4$ (cat.), K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2PHAL$ (cat.)

$K_2OsO_2(OH)_4$ = potassium osmate dihydrate

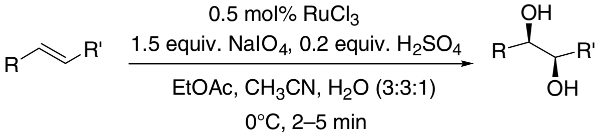
Sharpless AD reaction is extremely useful and efficient for the asymmetric dihydroxylation of alkenes.



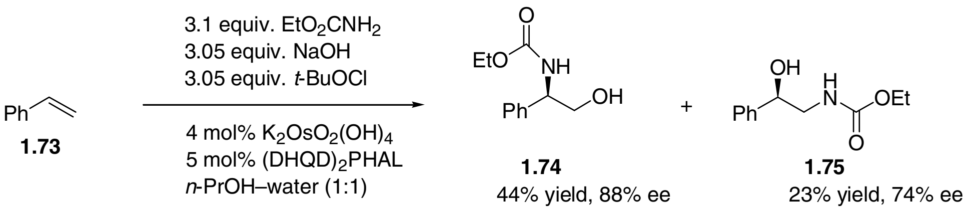


The reaction mechanism of the Sharpless dihydyroxylation is given in Chapter 7, section 7.5.

Ruthenium catalysis allows dihydroxylation providing an easy access to *syn*-diols, but over-oxidation is a common side reaction. The improved protocol for the Ru-catalyzed *syn*-dihydroxylation uses only 0.5 mol% catalyst under acidic conditions that gave products in high yields with only minor formation of side products[35].

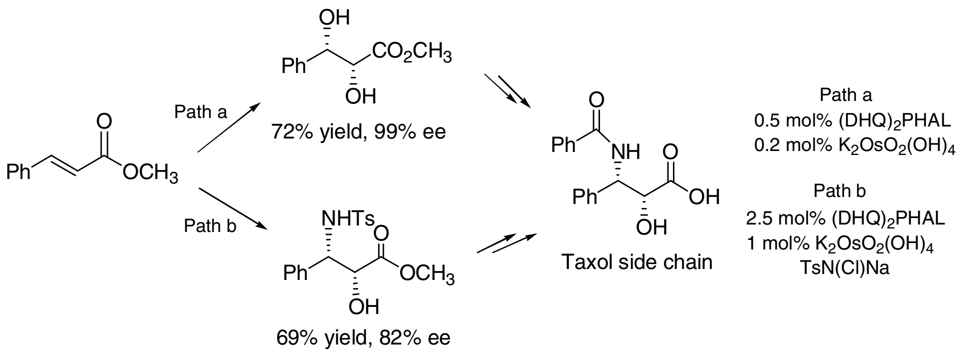


Sharpless and co-workers first reported the aminohydroxylation[25–27] of alkenes in 1975 and have subsequently extended the reaction into an efficient one-step catalytic **asymmetric aminohydroxylation**. This reaction uses an osmium catalyst [$K_2OsO_2(OH)_4$], chloramine salt (such as chloramine T; see Chapter 7, section 7.6) as the oxidant and cinchona alkaloid **1.71** or **1.72** as the chiral ligand. For example, asymmetric aminohydroxylation of styrene (**1.73**) could produce two regioisomeric amino alcohols **1.74** and **1.75**. Using Sharpless asymmetric aminohydroxylation, (1*R*)-*N*-ethoxycarbonyl-1-phenyl-2-hydroxyethylamine (**1.74**) was obtained by O'Brien *et al.*[36] as the major product and with high enantiomeric excess than its regioisomeric counterpart (*R*)-*N*-ethoxycarbonyl-2-phenyl-2-hydroxyethylamine (**1.75**). The corresponding free amino alcohols were obtained by deprotection of ethyl carbamate (urethane) derivatives.



Synthesis of the taxol side chain[37] involves the asymmetric aminohydroxylation reaction (Scheme 1.16).

The ability to select reaction conditions to provide an enantiomerically pure compound is important in industry. Methods to increase yields of specific enantiomers at low cost are in high demand, and this has resulted in research to develop new chiral building blocks, chiral ligands and catalysts. An additional problem encountered in industry is that catalysts are often expensive and difficult to recover, and research on catalyst recovery is important.

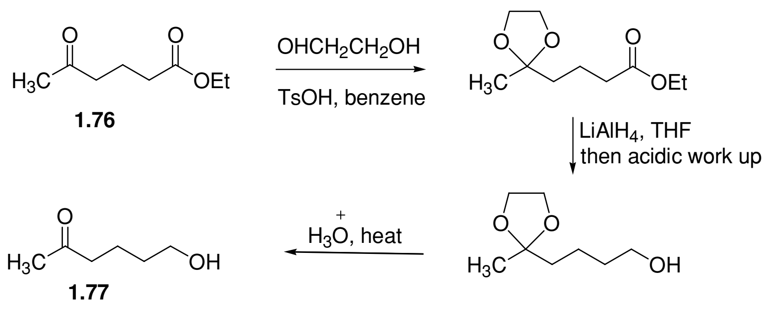


Scheme 1.16

1.6 Protecting groups

When a chemical reaction is to be carried out selectively at one reaction site in a multifunctional organic compound (organic molecule contains two or more than two reactive groups) and we want reaction at one reactive site, then other reactive sites must be temporarily blocked or protected. Many protecting groups have been, and are being, developed for this purpose. Whenever a protecting group is used to facilitate a synthetic operation, it normally must be removed once the operation is complete. This step is called **deprotection**. Protection and deprotection of functional groups have received attention in recent years not only because of their fundamental importance, but also for their role in multi-step synthesis.

The preparation of complex organic molecules demands the availability of different protecting groups to allow the survival of reactive functional groups during the various synthetic operations, finally resulting in the selective production of the target molecule. For example, in the conversion of ethyl 5-oxo-hexanoate (**1.76**) into 6-hydroxy-2-hexanone (**1.77**), it is required to block the ketone group first and then the ester group is reduced with $LiAlH_4$. The ketone group is protected as an acetal because an acetal group does not react with the reducing agent $LiAlH_4$. In the final step the acetal group is removed by treatment with acid. The overall scheme for this transformation is given in Scheme 1.17.



Scheme 1.17

A protecting group must fulfil a number of requirements. A good protecting group should be easy to put on, without the generation of new stereogenic centres, and easy to remove. The protecting group should have a minimum of additional functionality to avoid further sites of reaction. The protecting group should form a crystalline derivative with high reaction yields that can easily be separated from side products. The protecting group should not interfere with the reactions performed before it is removed.

Protecting groups can be cleaved under various conditions including basic solvolysis, acids, heavy metals, fluoride ions, reductive elimination, β-elimination, hydrogenolysis, oxidation, dissolving metal reduction, nucleophilic substitution, transition metal catalysis, light and enzymes. The assisted electrolytic and photolytic methods are the important methods for the removal of protecting groups. Photolabile groups are called **caged compounds** or phototriggers, deprotected on irradiation at wavelengths 254–350 nm with high quantum yield.

The protecting group must remain attached throughout the synthesis and may be removed after completion of synthesis. However, these protecting groups are not incorporated into the final product; thus, their use makes a reaction less atom economical. In other words, the use of protecting group should be avoided whenever possible.

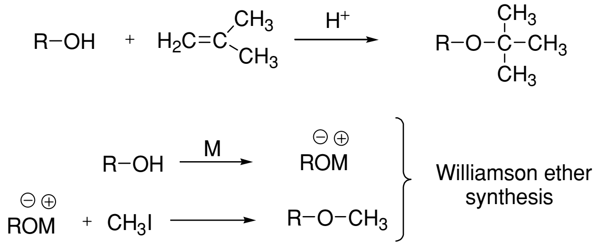
A wide range of protecting groups is currently available for the different functional groups. A very short overview of the most commonly used protecting groups is given in this chapter. They are classified according to the functional group they protect. Conditions for their lability are also discussed.

1.6.1 Common hydroxy protecting groups

Hydroxyl group must be protected during **oxidation**, **acylation**, **halogenation**, **dehydration** and other reactions to which it is susceptible. Hydroxyl groups are protected by forming their alkyl ethers, alkoxyalkyl ethers, silyl ethers and esters. However, ethers are preferred over esters because of their stability in acetic acid and basic conditions.

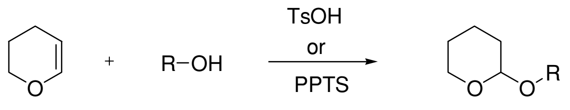
Alkyl and alkoxyalkyl ethers

Alkyl ethers are generally prepared by acid-catalyzed addition of alcohols to an alkene or by **Williamson ether synthesis** (Scheme 1.18).



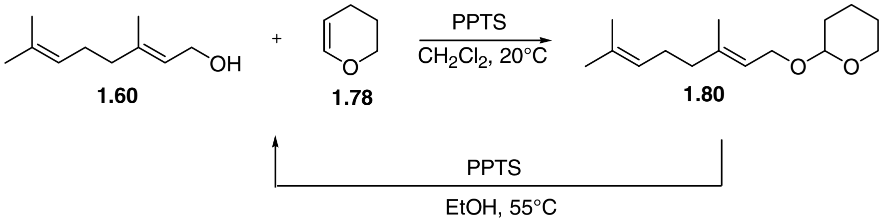
Scheme 1.18

Tetrahydropyranyl (THP) ethers **1.79** can be prepared from 3,4-dihydro-2*H*-pyran (DHP) **1.78** by an acid-catalyzed reaction[38].



1.78 **1.79**

Tetrahydropyranyl ethers are stable to bases and the protection is removed by acid-catalyzed hydrolysis. For example, geraniol (**1.60**) is protected as geraniol tetrahydropyranyl ether (**1.80**) in the presence of pyridinium *p*-toluenesulfonate (PPTS) reagent. These ethers are cleaved with PPTS in warm ethanol[39] (Scheme 1.19).

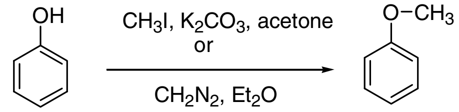


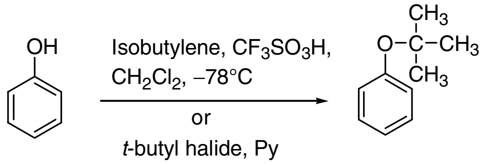
1.60 **1.78** **1.80**

Scheme 1.19

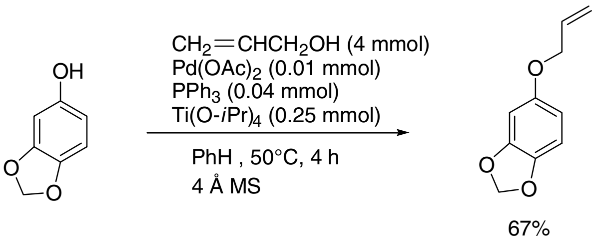
However, formation of THP ether introduces a new stereogenic centre. The introduction of the THP ether onto a chiral molecule therefore results in the formation of diastereoisomers.

Phenols are protected as their methyl ethers[40,41], *tert*-butyl ethers, allyl ethers and benzyl ethers.

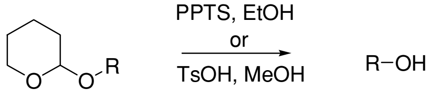




Miura and co-workers[42] reported the protection of phenols by allyl alcohols in the presence of catalytic amounts of palladium(II) acetate and titanium(IV) isopropoxide. The reaction is remarkably general; however, it fails in the case of 3,5-dimethoxyphenol because of the exclusive formation of a C-allylated product.

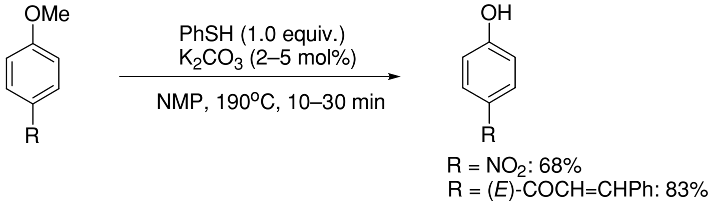


Ethers may be removed commonly by acid, with the THP derivative **1.79** reacting more rapidly than the *tert*-butyl ether. Benzyl ethers may be removed under a variety of conditions such as hydrogenolysis, dissolving metal reduction (Na in NH_3) and HBr (mild). Methyl ethers are cleaved[43] by refluxing with EtSNa and DMF. *tert*-Butyl ethers can be cleaved with trifluroacetic acid (CF_3COOH) at 25°C.



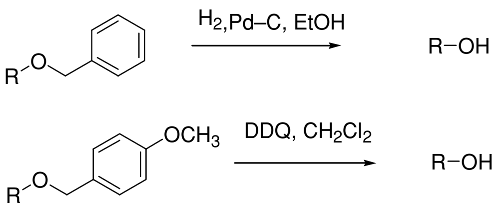
1.79

The nucleophilic cleavage of aryl alkyl ethers gives the corresponding phenol with only 1 equiv. of thiophenol in the presence of N-methyl-2-pyrrolidinone (NMP) in a catalytic amount of potassium carbonate[44]. The aromatic nitro and chloro substituents which are displaced with stoichiometric thiolates are preserved by this method. Moreover, αβ-unsaturated carbonyl compounds do not undergo Michael addition of thiolate under these conditions.



The tetrahydropyranylation of alcohols under solvent-free conditions is efficiently catalyzed by bismuth triflate (0.1 mol%). The experimental procedure is simple and works well with a variety of alcohols and phenols. The catalyst is insensitive to air and small amounts of moisture, easy to handle and relatively non-toxic. The deprotection of THP ethers is also catalyzed by bismuth triflate[45] (1.0 mol%).

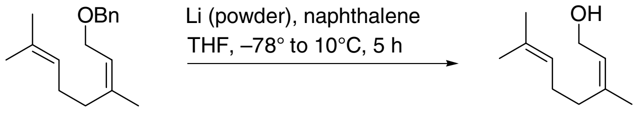
The benzyl (Bn) or *p*-methoxybenzyl groups (PMB) can be removed under reducing cleavage conditions (Scheme 1.20).



DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

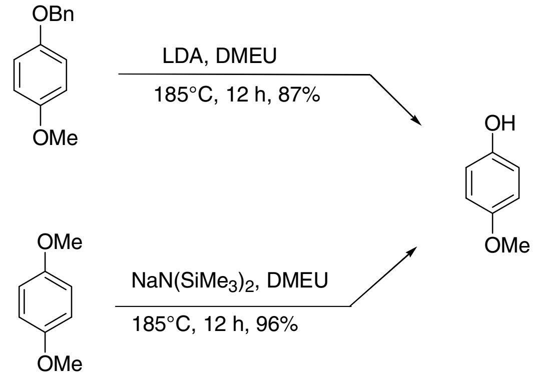
Scheme 1.20

Alkali metals (such as Li) in liquid ammonia are commonly applied for the deprotection of benzyl (Bn) ethers[46]. Lithium naphthalenide prepared from lithium and naphthalene in stoichiometric amount[47] or catalytic amount[48] is often used to deprotect benzyl ethers.



1.60

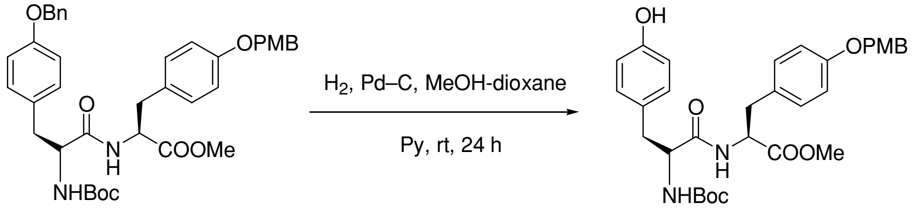
Hwu and co-workers[49] reported selective cleavage of a benzyl (Bn) ether with lithium diisopropylamide (LDA) in the presence of a methoxy group; however, by using sodium bis(trimethylsilyl)amide [$NaN(SiMe_3)_2$], the dimethoxybenzene undergoes selectively mono-O-demethylation (Scheme 1.21).



DMEU = 1,3-Dimethylimidazolidin-2-one

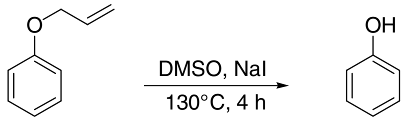
Scheme 1.21

Hirota and co-workers[50] reported the selective removal of the benzyl (Bn) group with Pd–C-catalyzed hydrogenolysis of PMB protected phenols. The removal of the PMB group is inhibited by the presence of pyridine.

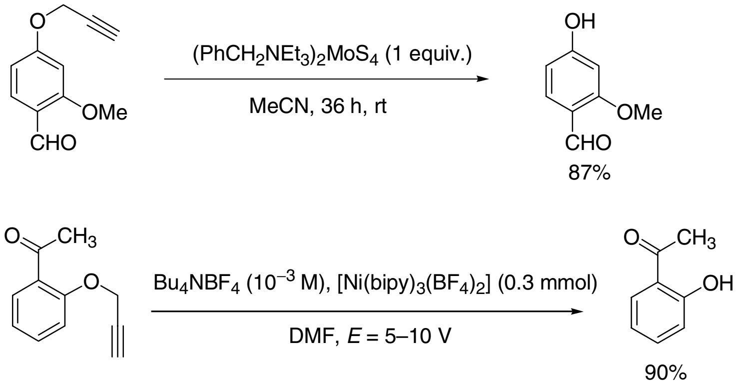


96%

The classical procedure for the removal of the allyl group involves a two-step sequence, where the allyl group is first isomerized to the corresponding propenyl function with a strong base such as potassium *tert*-butoxide (*t*-BuOK) or a metal catalyst such as Pd–C, followed by conversion of the propenyl group into free alcohol. However, recently several other methods were reported in the literature for the removal of the allyl group using various reagents such as DDQ, $CeCl_3{\cdot}7H_2O$/NaI, Ti(O-*i*Pr)$_4$ or *p*-TsOH. Another efficient method for allyl deprotection is by using DMSO (dimethylsulfoxide)/NaI reagent. The benzyl, ethyl and *tert*-butyl protecting groups were quite stable under these reaction conditions[51].

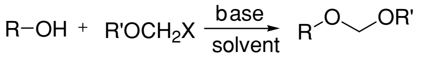


Propargylic aryl ethers (also esters) are cleaved by benzyltriethylammonium tetrathiomolybdate in acetonitrile at room temperature[52]. Allyl esters are not cleaved under these conditions. Electroreduction in the presence of Ni–bipyridine complex as catalyst is another method to affect the deprotection of propargyl ethers[53] (Scheme 1.22).

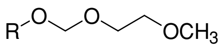


Scheme 1.22

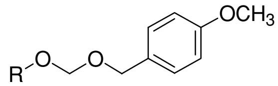
A general method for forming acyclic mixed acetals (alkoxyalkyl ethers) is given below:



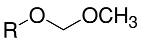
The following alkoxyalkyl ethers are commonly formed from hydroxy compounds:



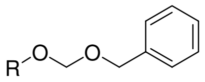
2-Methoxyethoxymethyl ether
(MEMOR)



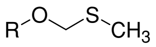
p-Methoxybenzyloxymethyl ether
(PMBMOR)



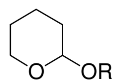
Methoxymethyl ether
(MOMOR)



Benzyloxymethyl ether
(BOMOR)

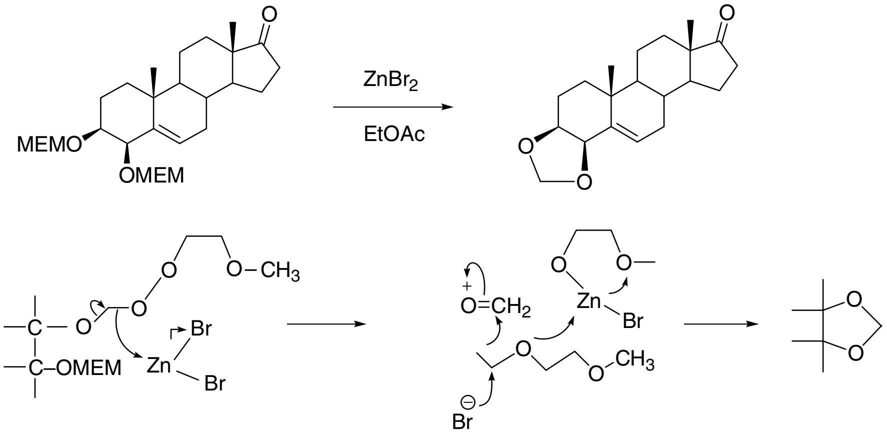


Methylthiomethyl ether
(MTMOR)



Tetrahydropyranyl ether
(THPOR)

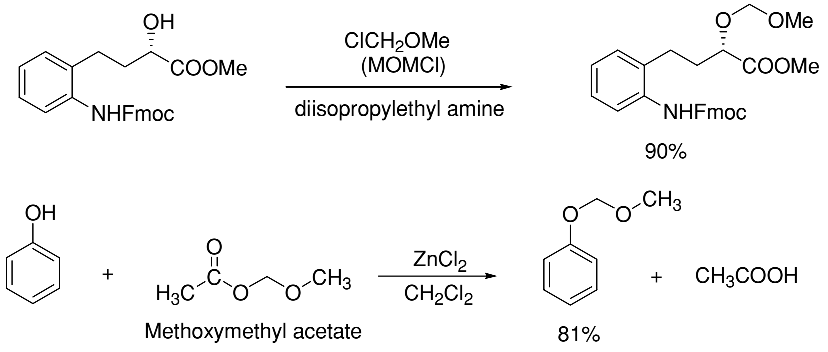
A **2-methoxyethoxymethyl ether (MEMOR)** is normally prepared under non-acidic conditions in methylene chloride solution or under basic conditions. The MEM ether group can be removed in excellent yield with trifluoroacetic acid (TFA) in dichloromethane (1:1). The MEM group can also be removed by treatment with zinc bromide (ZnBr$_2$), titanium chloride (TiCl$_4$) or bromocatechol borane. When MEM-protected diols are treated with zinc bromide (ZnBr$_2$) in ethyl acetate, 1,3-dioxane is formed and a mechanism of this reaction is given in Scheme 1.23.



Scheme 1.23

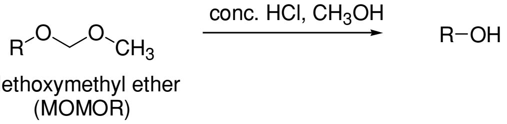
The **MEM group** can be selectively removed with trimethylsilyl iodide in acetonitrile without affecting a methyl ether or an ester group.

The **methoxymethyl (MOM) group** is one of the best protecting groups for alcohols and phenols[54]. The MOM ethers can be prepared by treating either alcohols or phenols with MOMCl (methoxymethyl chloride) or MOMOAc (methoxymethyl acetate) (Scheme 1.24). It is stable to a variety of commonly used reagents, such as strong bases, Grignard reagents, alkyllithiums and lithium aluminium hydride.



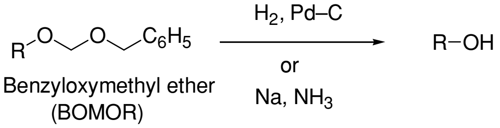
Scheme 1.24

Acid-catalyzed hydrolysis removes the MOM group.

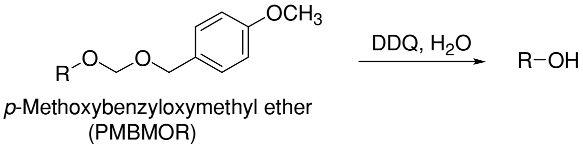


Bromocatechol borane or $LiBF_4$ (lithium fluoroborate) in acetonitrile (CH_3CN) and water has also been used for the deprotection of the MOM group.

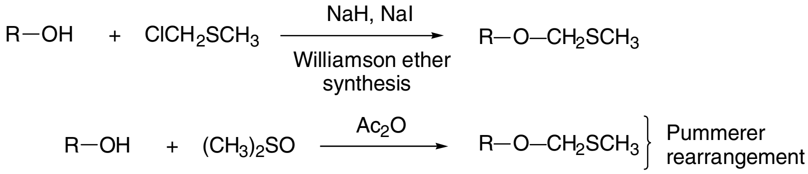
Benzyloxymethyl ethers (BOMOR) are usually prepared by reacting BOMCl (benzyloxymethyl chloride) with alcohols under basic conditions and can be selectively removed with H_2, Pd–C or Na/NH_3.



A ***p*-methoxybenzyloxymethyl (PMBM) group** is removed by acid hydrolysis or by reduction[55].



The methylthiomethyl ether (MTMOR): Tertiary hydroxyl groups, which are susceptible to acid-catalyzed dehydration, can be easily protected as MTM **ethers** and recovered in good yield. The MTM ether of a hydroxyl group can be formed either by a typical **Williamson ether synthesis** or on reaction with dimethylsulfoxide (DMSO) and acetic anhydride (Ac_2O). In the latter case, the reaction proceeds with the **Pummerer rearrangement**[56–58] (Scheme 1.25).



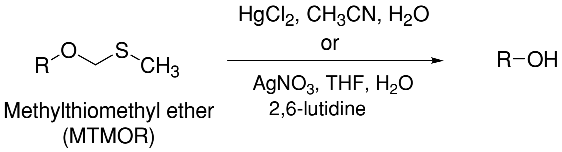
$$R{-}OH + ClCH_2SCH_3 \xrightarrow[\text{Williamson ether synthesis}]{NaH,\ NaI} R{-}O{-}CH_2SCH_3$$

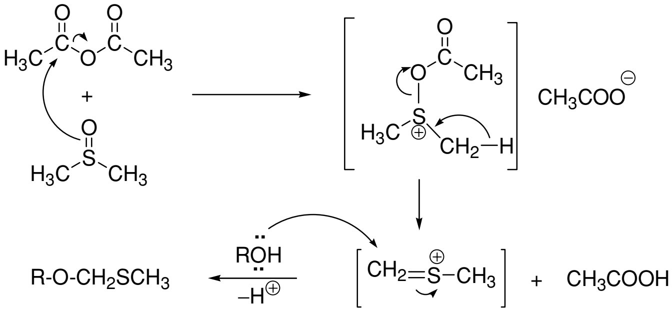
$$R{-}OH + (CH_3)_2SO \xrightarrow{Ac_2O} R{-}O{-}CH_2SCH_3 \quad \text{Pummerer rearrangement}$$

Scheme 1.25

The mechanism of the Pummerer rearrangement is given in Scheme 1.26.

A **methylthiomethyl (MTM) group** is removed by acid or can be cleaved by mild treatment with aqueous silver or mercury salts (neutral mercuric chloride) to which most other ethers are stable; as a result, the selective deprotection of polyfunctional molecules becomes possible using MTM ethers for the hydroxy groups.





Scheme 1.26 Mechanism of the Pummerer rearrangement

Silyl ethers

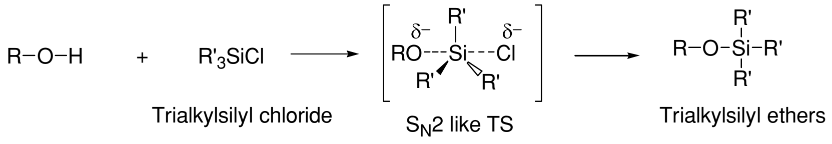
Protection of hydroxyl groups through the formation of silyl ethers has been extensively utilized in organic synthesis. Silyl ethers are resistant to oxidation, have good thermal stability, low viscosity and are easily recoverable from their starting compounds.

Numerous methods can be used for the synthesis of trialkylsilyl ethers (Scheme 1.27). Alcohols react rapidly with trialkylsilyl chloride (R'_3SiCl) to give trialkylsilyl ethers[59] ($ROSiR'_3$) in the presence of an amine base like triethylamine, pyridine, imidazole or 2,6-lutidine (Table 1.2).

$$\text{R−O−H} + \text{R}'_3\text{SiCl} \xrightarrow[\text{DMF}]{\text{amine base}} \text{R−O−SiR}'_3 + \text{HCl}$$

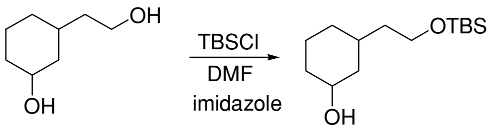
Scheme 1.27

Unlike 3°-alkyl halides, **trialkylsilyl chlorides** (R'_3SiCl) undergo nucleophilic substitution by a mechanism similar to the S_N2. Enolate anions obtained from alcohols react with trialkylsilyl chlorides (R'_3SiCl), generating trialkylsilyl ethers (R'_3SiOR) by substitution at oxygen. The exceptional strength of the Si–O bond combined with longer C–Si bond lengths (less steric crowding) serve to stabilize such transition states as shown in Scheme 1.28.



Scheme 1.28

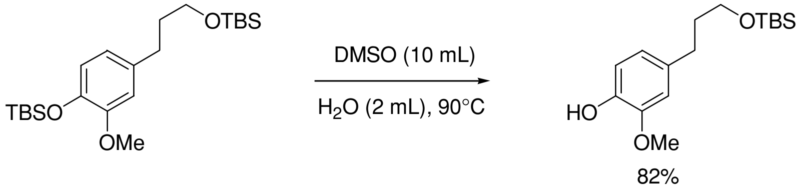
With bulkier groups, such as TBS, it is possible to distinguish between primary and secondary alcohols. This is an example of regiocontrol (see section 1.5).



Selective monoprotection of 1,4-butanediol (**1.20**) with TBDPSCl gave a 90% yield of the corresponding alcohol **1.21**[12].

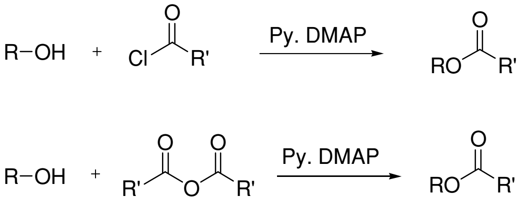
The removal of the TMS group is commonly carried out in the presence of a catalyst including iron(III) and tin(II) chlorides, copper(II) nitrate, cerium(III) nitrate, citric acid and sodium hydroxide or various fluoro derivatives. TMS derivatives are rather easily hydrolyzed to their alcohol precursors, but the bulkier silyl ethers are more resistant and are stable over a wide pH range. These protective groups are readily cleaved by fluoride anion, often introduced as a tetraalkylammonium salt such as tetrabutylammonium fluoride (TBAF).

Maiti and Roy[60] reported a selective method for deprotection of primary allylic, benzylic, homoallylic and aryl TBS ethers using aqueous DMSO at 90°C. All other TBS-protected groups, benzyl ethers, THP ethers as well as methyl ethers remain unaffected.



Esters

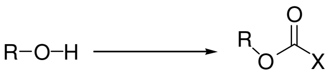
The acylation of alcohols represents an important reaction for the synthetic organic chemist; it was historically used for derivatization and characterization of alcohols. The acylation is usually performed by using acyl chlorides or the corresponding anhydrides in the presence of a base such as triethylamine or pyridine (Scheme 1.29). Faster reaction rates can be achieved by adding 4-(dimethylamino)pyridine (DMAP) as a co-catalyst.



Scheme 1.29

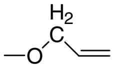
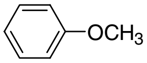
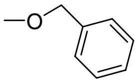
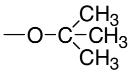
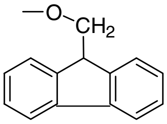
Under these conditions, base-sensitive substrates may undergo decomposition. To avoid this drawback, protic and Lewis acid can be utilized, such as *p*-toluenesulfonic acid, zinc chloride, cobalt chloride or scandium triflate.

Acetate, chloroacetate, benzoate, *p*-methoxy benzoate, benzyl carbonate (Cbz), *tert*-butyl carbonate (Boc) and 9-(fluorenylmethyl) carbonate (Fmoc) are commonly prepared to protect the hydroxyl group (Table 1.3).



Methyl carbonates are cleaved under basic conditions (K_2CO_3/MeOH). Fmoc can be cleaved with base like Et_3N, Py, morpholine or diisopropylethylamine. Allyl carbonates can be

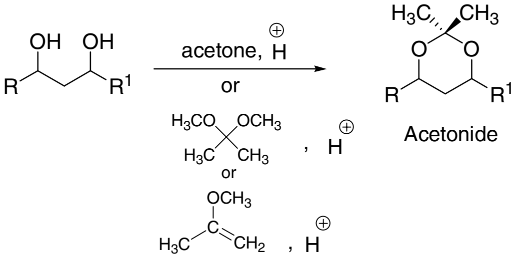
Table 1.3

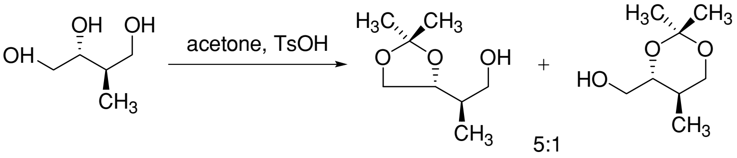
X	Ester	X	Carbonate
CH_3	Acetate	$—OCH_3$	Methyl carbonate
CH_2-Cl	Chloroacetate		
	Benzoate		Allyl carbonate (Alloc)
	*p*-Methoxy benzoate		Benzyl carbonate (Cbz)
		 $—O—C(CH_3)_3$	*t*-Butyl carbonate (Boc)
			9-(Fluorenylmethyl) carbonate (Fmoc)

cleaved by $Pd_2(dba)_3$/dppe/Et_2NH/THF. Benzyl carbonates can be cleaved with H_2, Pd–C, EtOH. The regeneration of alcohols from their esters can also be carried out under heterogeneous conditions by using some solid catalysts, such as zeolites, silica, alumina or acidic resins.

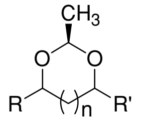
1.6.2 Common diols protecting groups

Diols (1,2 and 1,3) are commonly protected as their O,O-acetals and ketals. Acetals are compounds with general structure RR^1 C (OR^2) (OR^3), where R and R^1 may be H (but not necessary), but R^2 and $R^3 \neq$ H. Ketals are subclass of acetals where neither R nor R^1 is H.

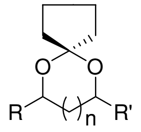




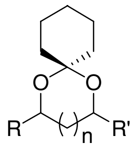
In a similar manner, ethylidene acetals, cyclopentylidene acetals, cyclohexylidene acetals, arylidene acetals and cyclic carbonates can be prepared.



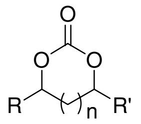
Ethylidene acetal



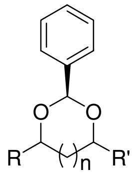
Cyclopentylidene acetal



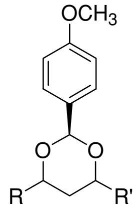
Cyclohexylidene acetal



Cyclic carbonate

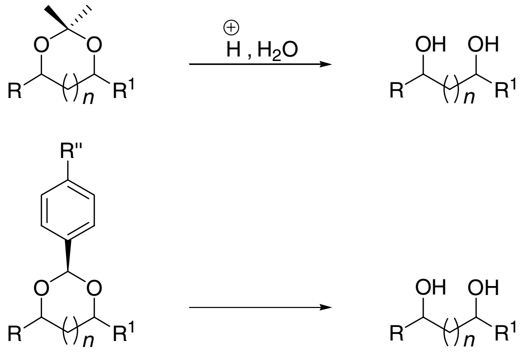


Benzylidene acetal



p-Methoxybenzylidene acetal

These acetals and ketals can be cleaved either under acidic conditions or by reduction (Scheme 1.30).

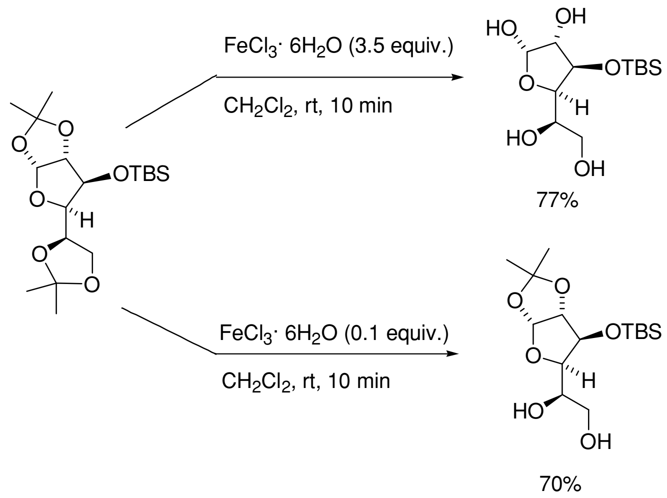


R^1 = H: H_2, Pd–C, AcOH or Birch reduction

$R^1 = OCH_3$: $Pd(OH)_2$, H_2, 25°C

Scheme 1.30 Deprotection of acetals and ketals

Acetals are also cleaved by ferric chloride either absorbed or not absorbed on silica gel. The TBS group (see Table 1.2) is not deprotected under these conditions. Depending on the number of equivalents of ferric chloride used, the selective deprotection of either one or both acetal groups can be achieved[61–63] (Scheme 1.31).

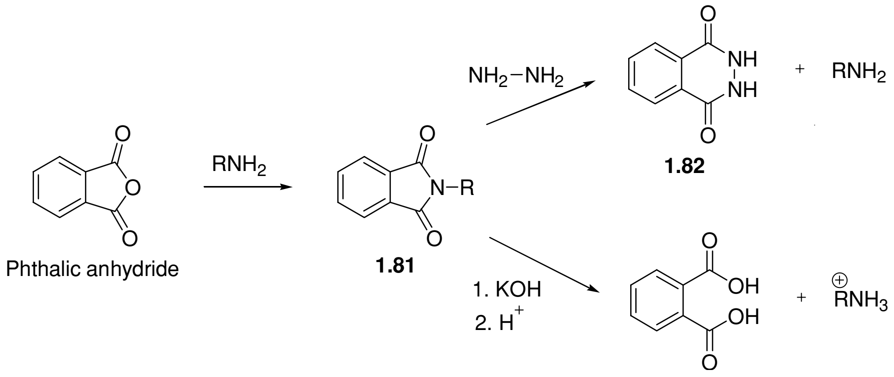


Scheme 1.31

1.6.3 Common amine protecting groups

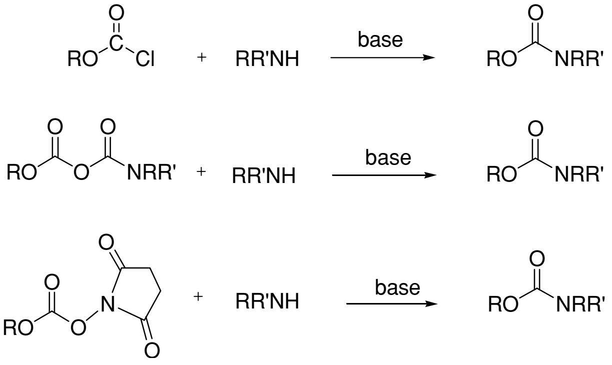
Nitrogen protection continues to attract a great deal of attention in a wide range of chemical fields, such as peptide, nucleoside, polymer and ligand synthesis. Moreover, in recent years, a number of nitrogen protecting groups have been used as chiral auxiliaries. Thus, the design of new, milder and more effective methods for nitrogen protection is still an active topic in synthetic chemistry.

Imide and amide protecting groups: The phthalimide group has been successfully used to protect the amino group. Cleavage of *N*-alkylphthalimide (**1.81**) is easily carried out with hydrazine, in a hot solution or in the cold for a prolonged period to give **1.82** and the amine. Base-catalyzed hydrolysis of *N*-alkylphthalimide **1.81** also gives the corresponding amine (Scheme 1.32).



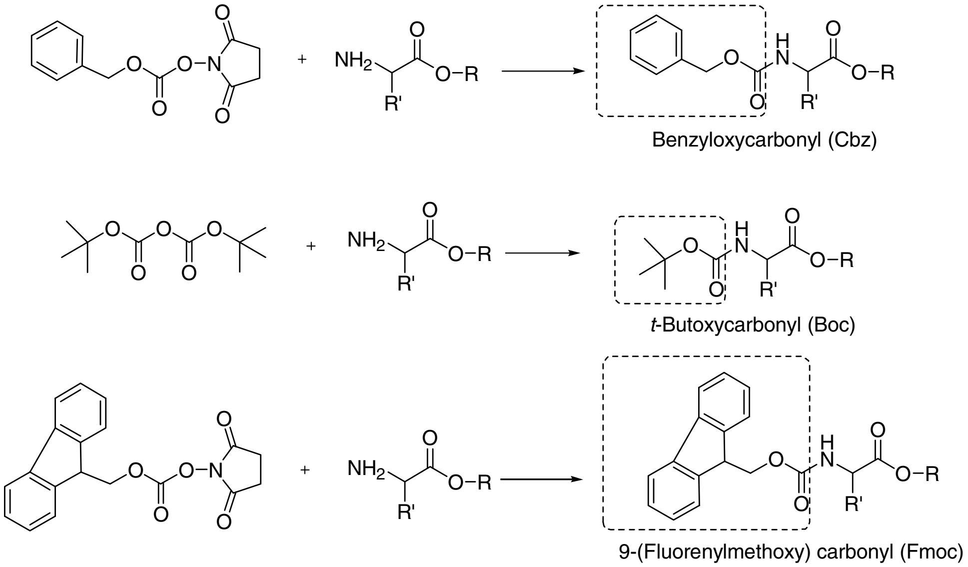
Scheme 1.32

Carbamate (urethane) protecting groups: The best amino group protection is carried out by the formation of the urethane (or carbamate) protecting groups. Carbamates are prepared from amines by the following methods (Scheme 1.33):



Scheme 1.33

For example, urethane protecting groups such as benzyloxycarbonyl (Cbz), *tert*-butoxycarbonyl (Boc) and (fluorenylmethoxy) carbonyl (Fmoc) are easily introduced as shown in Scheme 1.34:

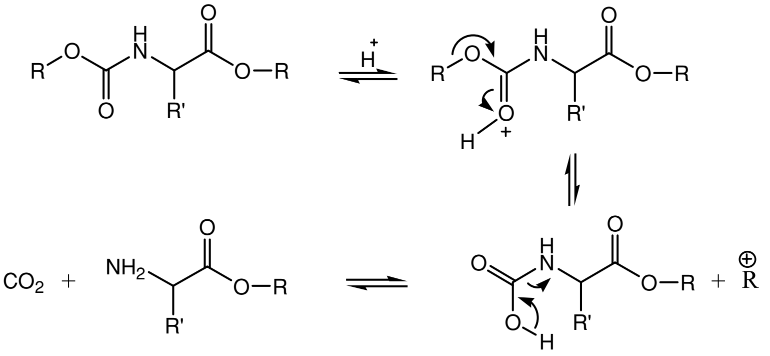


Scheme 1.34

These protecting groups withstand a variety of harsh reaction conditions.

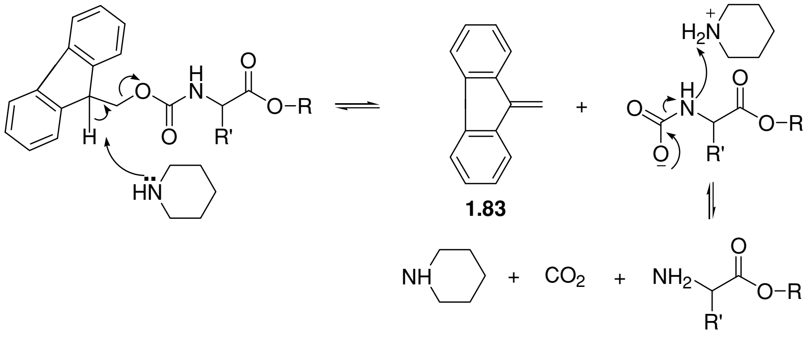
Boc is a good labile group because it is stable at room temperature and easily removed with dilute solution of TFA either neat or in dichloromethane. Other mineral acids or Lewis acids have also been used, although less frequently.

Fmoc is a base labile protecting group which is easily removed by reaction with concentrated solutions of amines. Both Cbz and the acid labile *t*Boc are commonly used. These owe their lability to the stability of the carbocation produced on deprotection (Scheme 1.35). The Boc group, which generates a stable tertiary cation on deprotection, is more prone to deprotection by weaker acids than is Cbz.



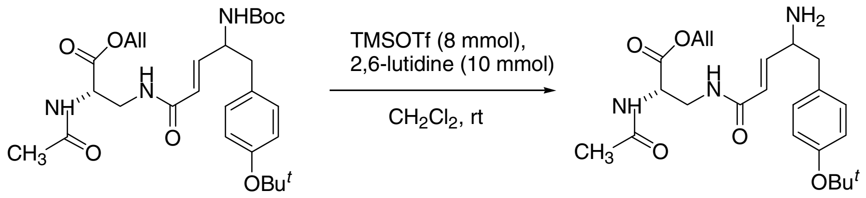
Scheme 1.35

The Fmoc group protection is common in solid-phase peptide synthesis. Fmoc is resistant to acidic conditions and easily deprotected by weak bases, particularly secondary amines. Deprotection occurs through base-catalyzed abstraction of the β-proton of the protecting group with elimination leading to formation of dibenzofulvene (**1.83**) (Scheme 1.36).

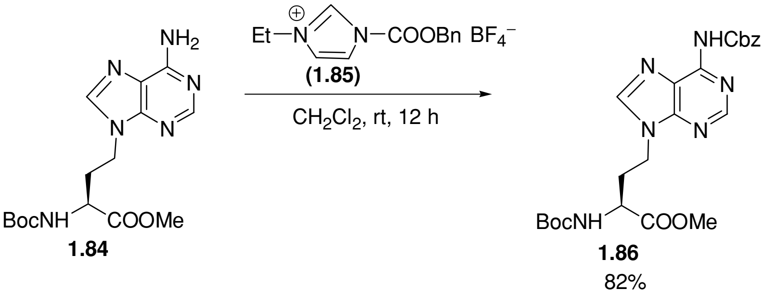


Scheme 1.36 Mechanism of deprotection of the Fmoc group

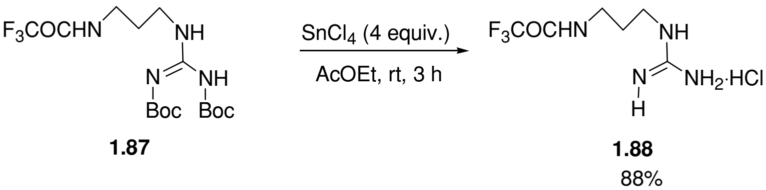
The different cleavage conditions for the above urethane protecting groups have enabled so-called *orthogonal* protection strategies to be developed, which in turn enable selective deprotection to be performed on different amines present in the same molecule. For example in peptide synthesis[64], the N-Boc group could be cleaved selectively using TMSOTf, followed by aqueous work up.



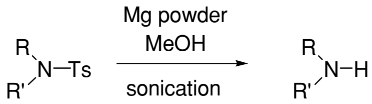
Treatment of the adenine derivative **1.84** with 1-(benzyloxycarbonyl)-3-ethylimidazolium tetrafluoroborate (Rapoport's reagent; **1.85**) forms **1.86** in 82% yield in which the NH_2 group is protected with Cbz.



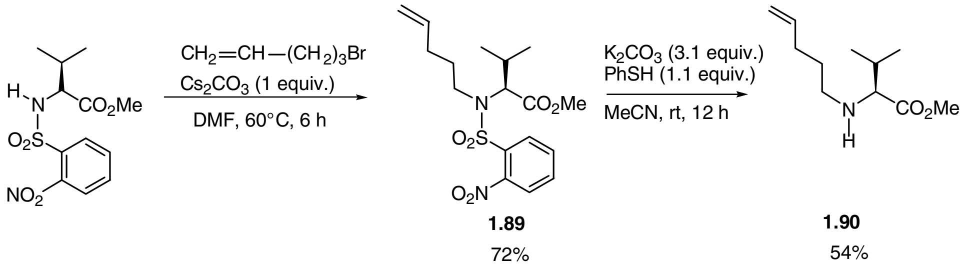
Both the Boc groups in substituted guanidine **1.87** can be removed with stannic chloride in ethyl acetate. The reagent is milder than the TFA and gives a high yield of deprotected product **1.88** in 88% yield.



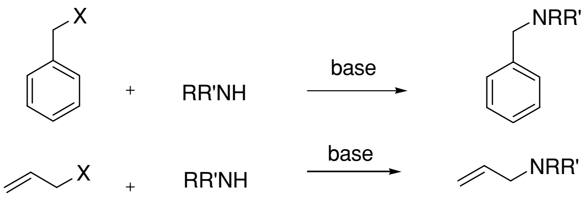
The *p*-toluenesulfonyl (Ts) group from *N*-arylsulfonylcarbamates and *N*-acylsulfonamides can be removed by the use of magnesium in anhydrous methanol under ultrasonic conditions.



The amino group can be protected by forming its sulfonyl [such as arylsulfonyl or 2-(trimethylsilyl) ethyl sulfonyl], sulfenyl and silyl derivatives. The 2- or 4-nitrophenylsulfonamide derivatives of amino acids are useful substrates for mono-N-alkylation using only cesium carbonate (Cs_2CO_3) as the base. The sulfonamide group can be removed in **1.89** by potassium phenyl thiolate (PhSH and K_2CO_3) in acetonitrile to give the N-alkylated α-amino esters **1.90** and the reaction occurs without racemization.

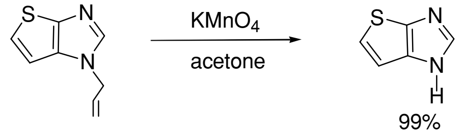


Benzyl and allyl amines: The amines can also be protected as benzylamines and allyl amines (Scheme 1.37).



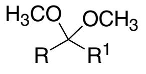
Scheme 1.37

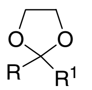
These amines can be deprotected under reduction conditions (Pd–C/ROH/HCO_2NH_4 or Na/NH_3). The allyl amines can be deprotected by oxidative cleavage with ozone (dimethylsulfide work up) or with $KMnO_4$ in acetone.

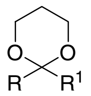


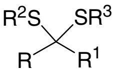
1.6.4 Common carbonyl protecting groups

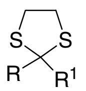
Carbonyls can be protected as acyclic or cyclic acetals, *S*,*S*′-dialkyl acetals, oxathiolanes, 1,1-diacetates and nitrogenous derivatives.


Dimethyl acetal

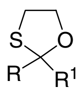

1,3-Dioxolane


1,3-Dioxane


S,*S*′-Dialkylthioacetal

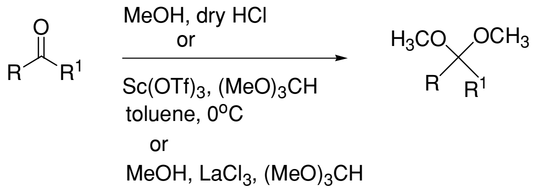

1,3-Dithiolane


1,3-Dithiane


1,3-Oxathiolane

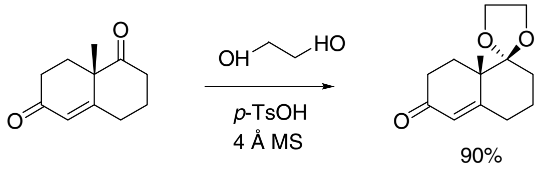
Acyclic and cyclic acetals are stable to base but removed with acid. Aliphatic aldehydes are more reactive than aromatic aldehydes, which in turn are more reactive than ketones.

Dimethyl acetals can be prepared under different conditions from aldehydes and ketones[65,66] as shown below:

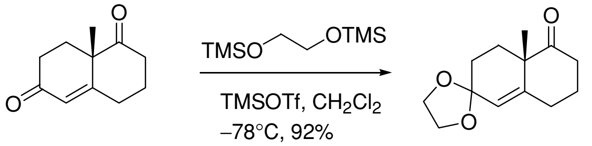


These acetals can be cleaved with HCl–water or dioxane–water. Cyclic acetals are cleaved more slowly than their open-chain analogues; for example, dimethyl acetals can be cleaved in the presence of a 1,3-dithiane and a dioxolane acetal by using TFA/$CHCl_3/H_2O$. *p*-Toluenesulfonic acid (TsOH)/acetone or 70% $H_2O_2/Cl_3CCOOH/CH_2Cl_2/t\text{-}BuOH/Me_2S$ can also be used for the cleavage of dimethyl acetals.

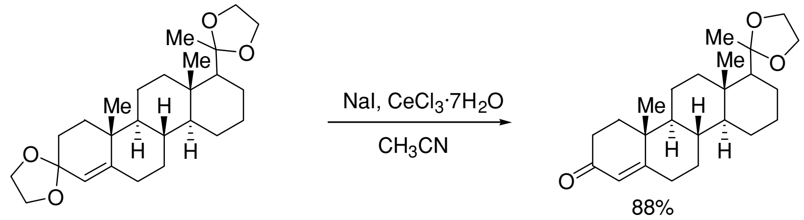
Formation of cyclic acetals of αβ-unsaturated carbonyls is usually slower than for the saturated carbonyls. Thus, saturated ketones can be selectively protected in the presence of αβ-unsaturated ketones with ethylene glycol and a stoichiometric amount of *p*-TsOH and water[67].



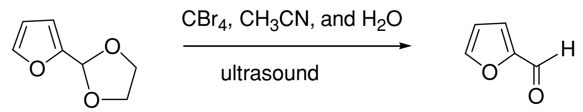
However, αβ-unsaturated ketones are also selectively protected as shown below[68]:



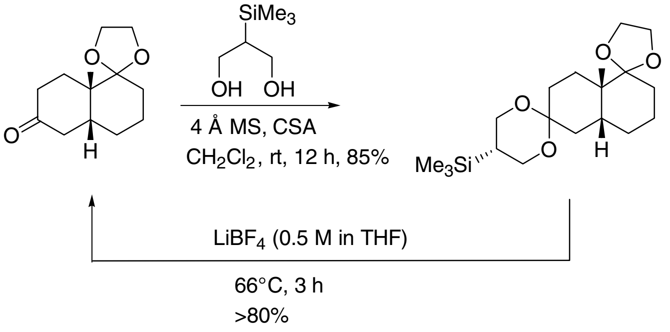
The selective cleavage[69] of cyclic acetal of αβ-unsaturated ketone over cyclic acetal of saturated ketone can be achieved by using NaI and $CeCl_3{\cdot}7H_2O$ in acetonitrile.



Acetals can be deprotected[70] to the corresponding carbonyl compounds using a catalytic amount of carbon tetrabromide (CBr_4) in the acetonitrile–water mixture under thermal or ultrasound conditions.



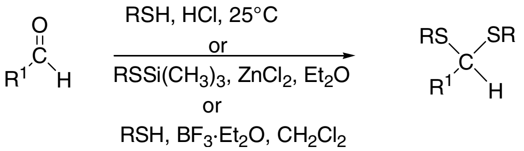
The selective deprotection[71] of acetal to a carbonyl group can be achieved with lithium tetrafluoroborate $LiBF_4$ in THF.



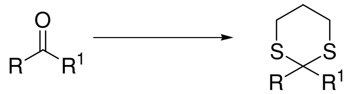
CSA = Camphorsulfonic acid

Open chain and cyclic thioacetals: 1,3-Dithiolane and 1,3-dithiane derivatives are versatile intermediates in the synthesis and interconversion of monocarbonyl and 1,2-dicarbonyl compounds. Protection of carbonyl groups as their open-chain and cyclic thioacetals is an important method in the synthesis of organic molecules[72]. Thioacetals are stable towards ordinary acidic and basic conditions and can act as acyl synthetic equivalent groups (see section 1.3). Although many procedures are available for preparing thioacetals, their deprotection is not a very easy process.

S,S′-Dialkyl thioacetals can be formed by reacting aldehydes with RSH or RSSi(CH_3)$_3$.

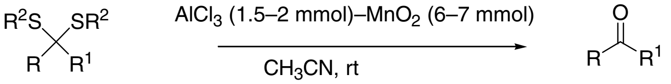


1,3-Dithiane works well for aromatic aldehydes and aromatic and aliphatic ketones, while 2-phenyl-1,3-dithiane should be used for aliphatic aldehydes[73].



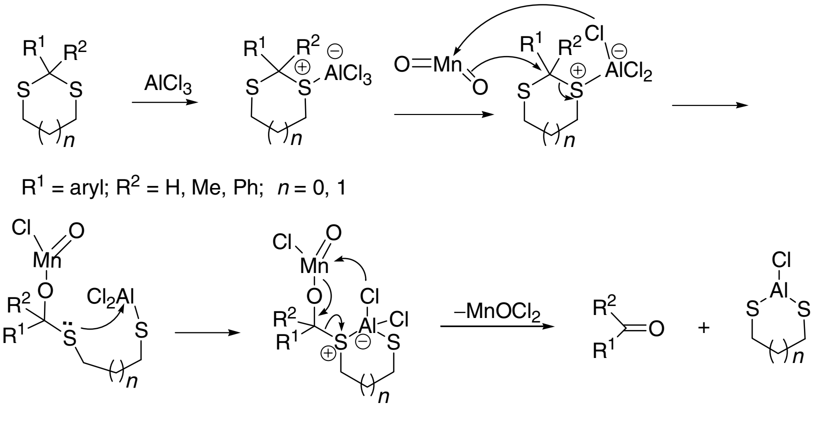
Many procedures[74] are available in the literature for the deprotection of *S,S′*-dialkyl thioacetals to their carbonyl compounds such as clay supported ammonium ion, ferric or cupric nitrates, zirconium sulfonyl phosphonate, oxides of nitrogen, DDQ, SeO_2/AcOH, DMSO/HCl/H_2O, TMSI(Br), LiN(*i*-C_3H_7)$_2$/THF, ceric ammonium nitrate in aqueous CH_3CN, $CuCl_2$/CuO/acetone and reflux, Hg(ClO_4)$_2$/chloroform and *m*-CPBA/Et_3N/Ac_2O/H_2O.

Recently new methods have been introduced using mercury(II) nitrate trihydrate[75], MnO_2, $KMnO_4$ and $BaMnO_4$ catalyzed with $AlCl_3$ in CH_3CN at room temperature for the deprotection of benzylic dithioacetals of aldehydes and non-enolizable ketones[76].



R^1 = H; R = aryl
R^2 = —(CH_2)$_3$,—(CH_2)$_2$—, *n*-Bu

A mechanism of deprotection of *S,S′*-thioacetals under non-aqueous reaction conditions has been suggested in which oxygen of MnO_2 acts as a nucleophilic species (Scheme 1.38).



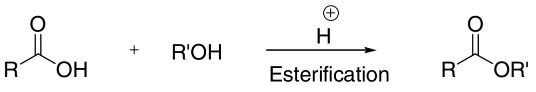
R^1 = aryl; R^2 = H, Me, Ph; *n* = 0, 1

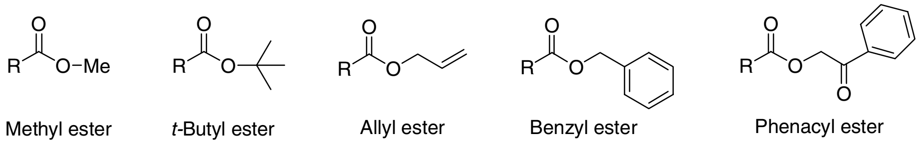
Scheme 1.38

A similar mechanism has also been proposed for deprotection of *S*,*S*′-thioacetals using seleninic anhydride.[77]

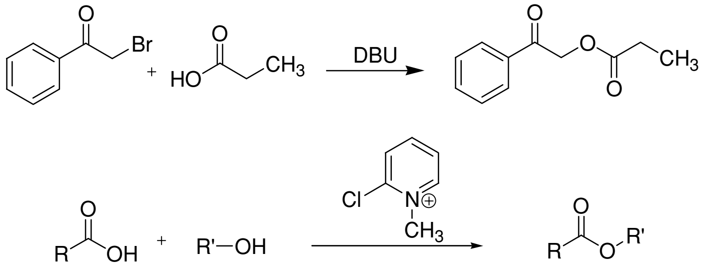
1.6.5 Common carboxylic acid protecting groups

Carboxylic acids are protected as their esters such as methyl esters, *tert*-butyl esters, allyl esters, benzyl esters, phenacyl esters and alkoxyalkyl esters. The esters are formed by the reaction of carboxylic acid with alcohol, and the reaction is known as esterification.





Although many useful and reliable methods for esterification of carboxylic acids are usually employed, there is need to find versatile processes to replace the classical methodologies with more benign alternatives, characterized by general applicability. Two new methods for the formation of esters from carboxylic acids are shown in Scheme 1.39.

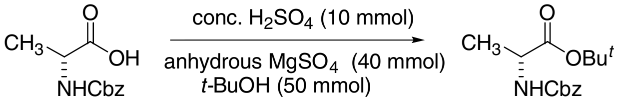


DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene

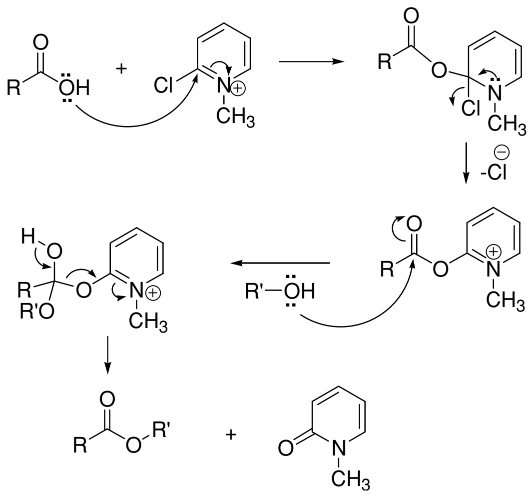
Scheme 1.39

The mechanism of Mukaiyama esterification is given in Scheme 1.40.

The *tert*-butyl esters are usually prepared by the reaction of an acid with isobutylene in the presence of an acidic catalyst. In the modified procedure instead of isobutylene, *tert*-butyl alcohol (*t*-BuOH) is used in the presence of heterogeneous acid catalyst[78].

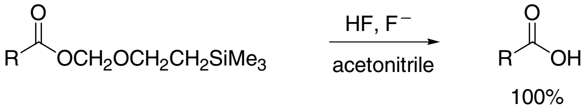


Allyl esters can be prepared by the reaction of carboxylic acid with allyl bromide in the presence of Cs_2CO_3 in DMF or allyl alcohol in the presence of TsOH in benzene.

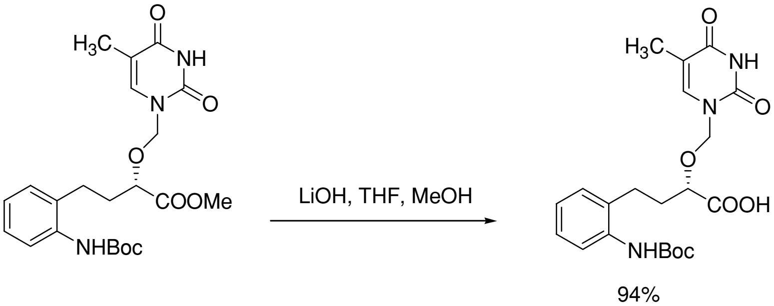


Scheme 1.40 Mechanism of Mukaiyama esterification

Alkoxyalkyl esters and silyl esters are also easily prepared and cleaved. For example, 2-(trimethylsilyl)ethoxymethyl esters are usually cleaved with HF in acetonitrile by fluoride ion.

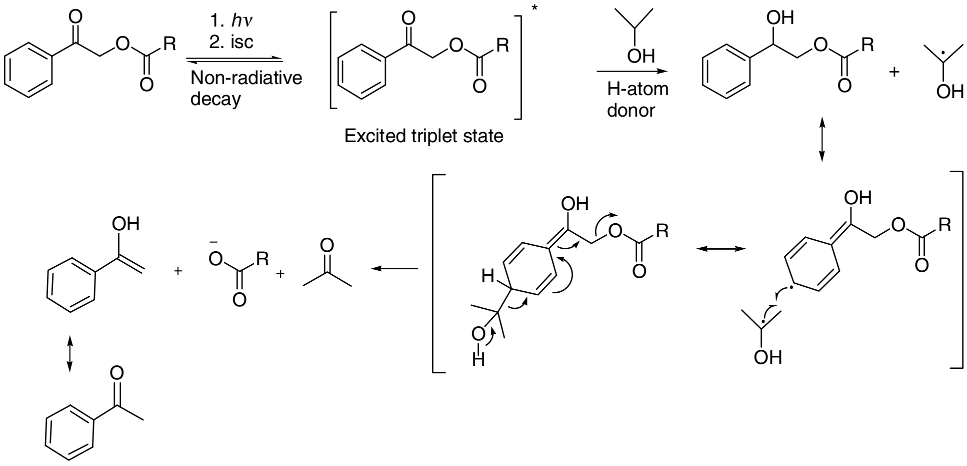


Methyl esters are removed by an acid or a base. The lithium hydroxide also cleaved the methyl ester group while the Boc group remained intact.



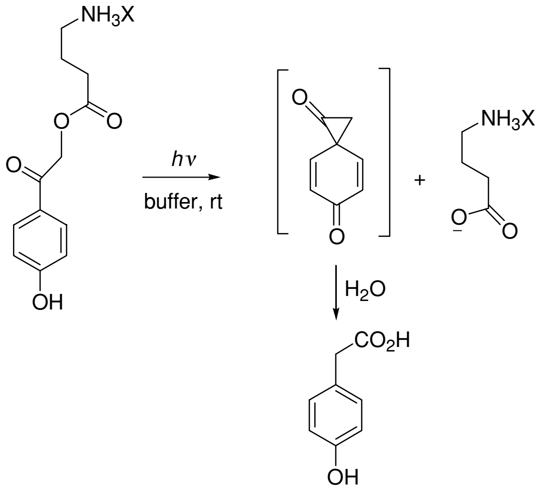
Benzyl esters can be removed by hydrogenolysis. *tert*-Butyl esters can be cleaved by CF_3COOH in CH_2Cl_2. Selective deprotection of *tert*-butyl esters in the presence of *N*-Boc protecting groups for several amino acids can be carried out with $CeCl_3{\cdot}7H_2O$–NaI. The main advantage of this method is the low cost of the reagents and mild nature of the ceric chloride interaction in comparison to other Lewis acids.

Phenacyl esters can be removed by light at wavelengths 308–313 nm with >70% yield. The mechanism of the photodeprotection of the phenacyl group is shown in Scheme 1.41:



Scheme 1.41 Mechanism of photodeprotection of the phenacyl group

However, irradiation of buffered solutions of esters of the *p*-hydroxy phenacyl at room temperature leads to the rapid release of carboxylate anion with the formation of *p*-hydroxyphenyl acetic acid[79,80] (**1.91**) (Scheme 1.42).



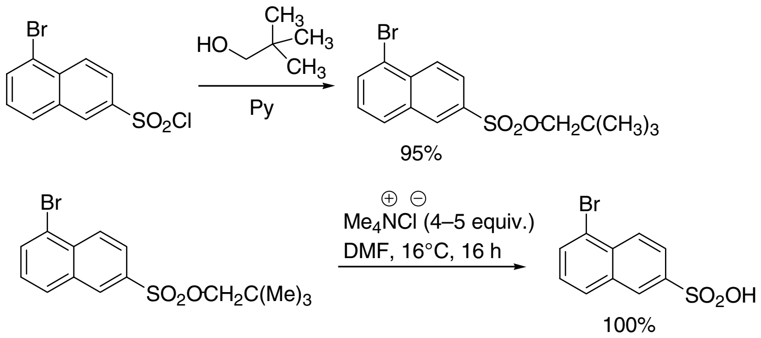
1.91

Scheme 1.42 Mechanism of photodeprotection of the *p*-hydroxyphenacyl esters

1.6.6 Common arenesulfonic acid protecting groups

Roberts and co-workers[81] prepared neopentyl (2,2-dimethylpropyl) esters of arenesulfonic acids which are compatible with a wide range of standard organic synthesis methodologies. These esters withstand several reagents such as *tert*-butyllithium, vinylmagnesium bromide, CrO_3, NBS (*N*-bromosuccinimide)–benzoyl peroxide, H_2–Raney Ni, DIBAL-H, NaI,

$HONH_2$, NaH, aqueous HBr and NaOH. Deprotection of these esters can be accomplished by heating the ester with excess of tetramethylammonium chloride in DMF (Scheme 1.43).



Scheme 1.43

1.6.7 Common alkyne protecting groups

Alkynes can be protected as their silyl derivatives and the most common silyl groups TMS, TES, TIPS and TBS are introduced by reacting alkyne with the corresponding trialkylsilyl chlorides (see Table 1.2 for the structures of R'_3SiCl).

$$R{-}{\equiv}{-}M \xrightarrow{R'_3SiX} R{-}{\equiv}{-}SiR'_3$$

M = Li, Mg; X = Cl, OTf

Cleavage of trialkylsilylalkynes can be achieved by using TBAF in the presence of THF.

$$R{-}{\equiv}{-}SiR'_3 \xrightarrow[\text{THF}]{\text{TBAF}} R{-}{\equiv}{-}H$$

Cleavage[82] of trimethylsilylalkynes can also be carried out by using KF/MeOH, $AgNO_3$/2,6-lutidine or K_2CO_3/MeOH.

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