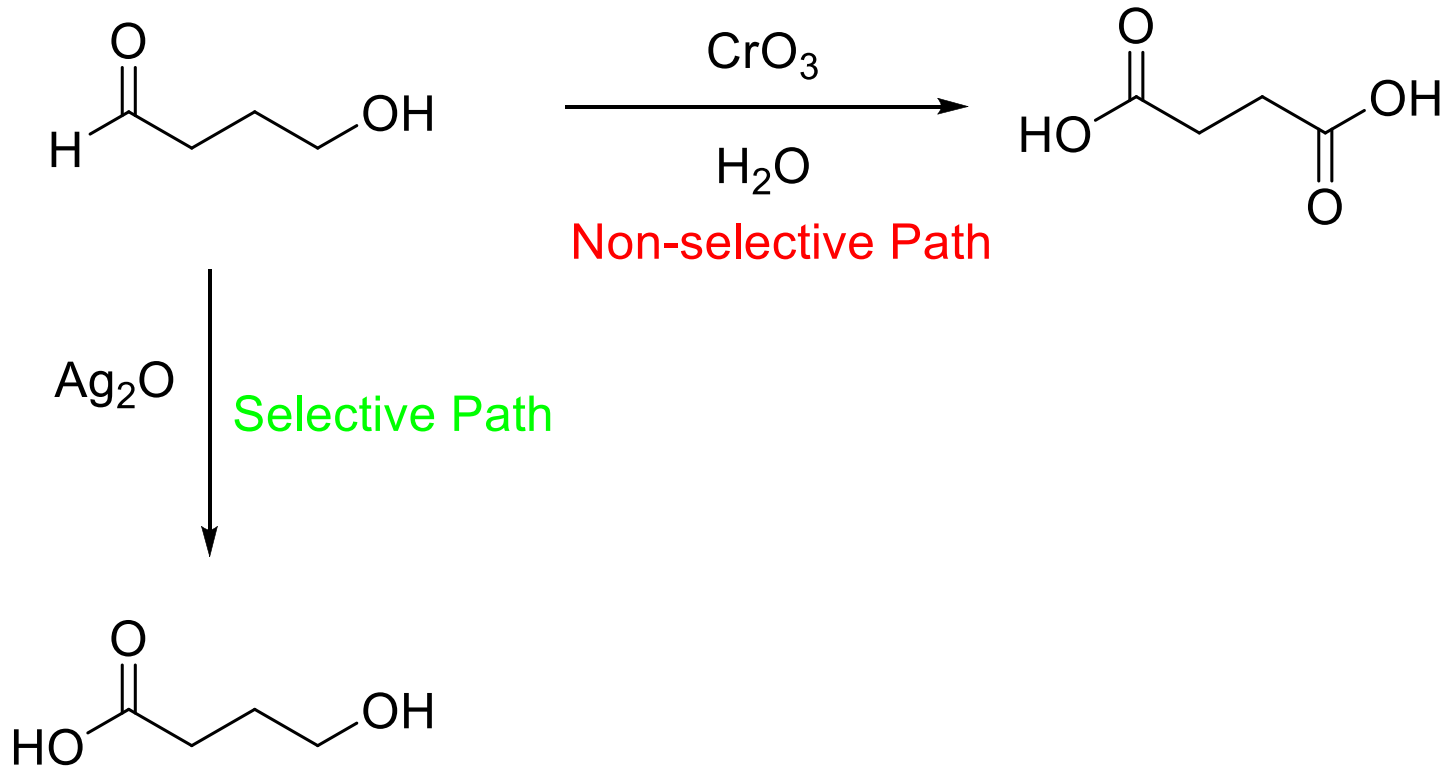
PROTECTING GROUPS IN ORGANIC SYNTHESIS

Challenges in Organic Synthesis

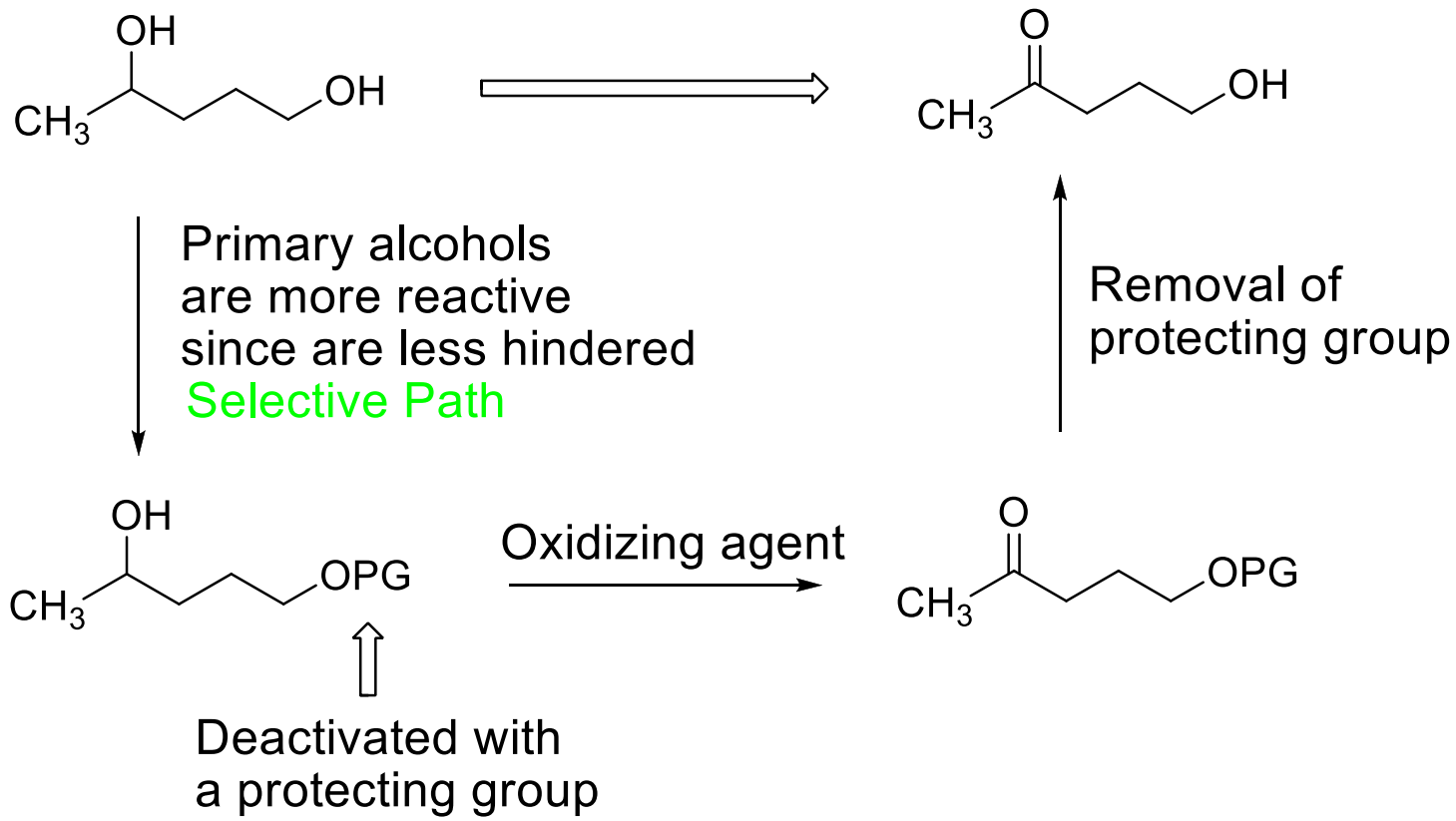
Chemoselective Oxidation



Selective functionalization of poly-functional molecules is an important and desirable attribute in multi-step organic synthesis.

Protecting Groups: A Necessary Evil

Building the Case for Protecting Groups

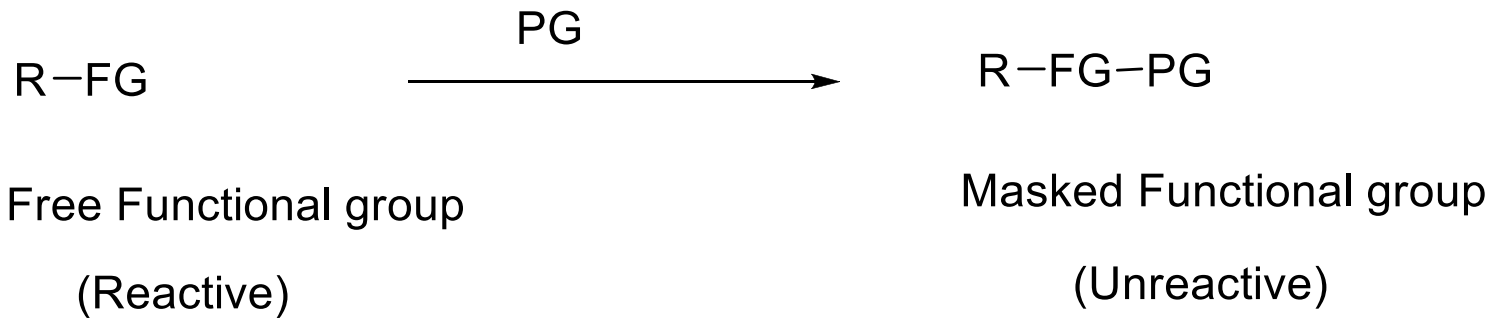


Note, however, that each protecting group incorporated in a multi-step synthesis increases the synthesis **by two non-productive steps reducing the overall yield and efficiency of the synthesis.**

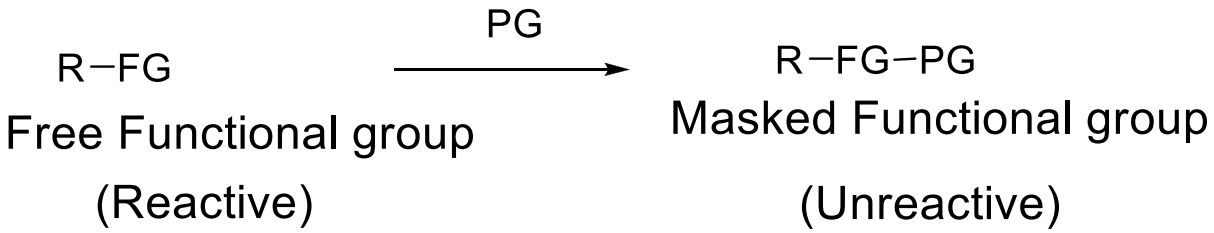
Protecting Groups in Organic Synthesis

What is a protecting group?

A protecting group (PG) is a molecular framework that is introduced onto a specific functional group (FG) in a poly-functional molecule to block its reactivity under reaction conditions needed to make modifications elsewhere in the molecule.



Qualities of a Good Protecting Group in Organic Synthesis



A good protecting group should be such that:

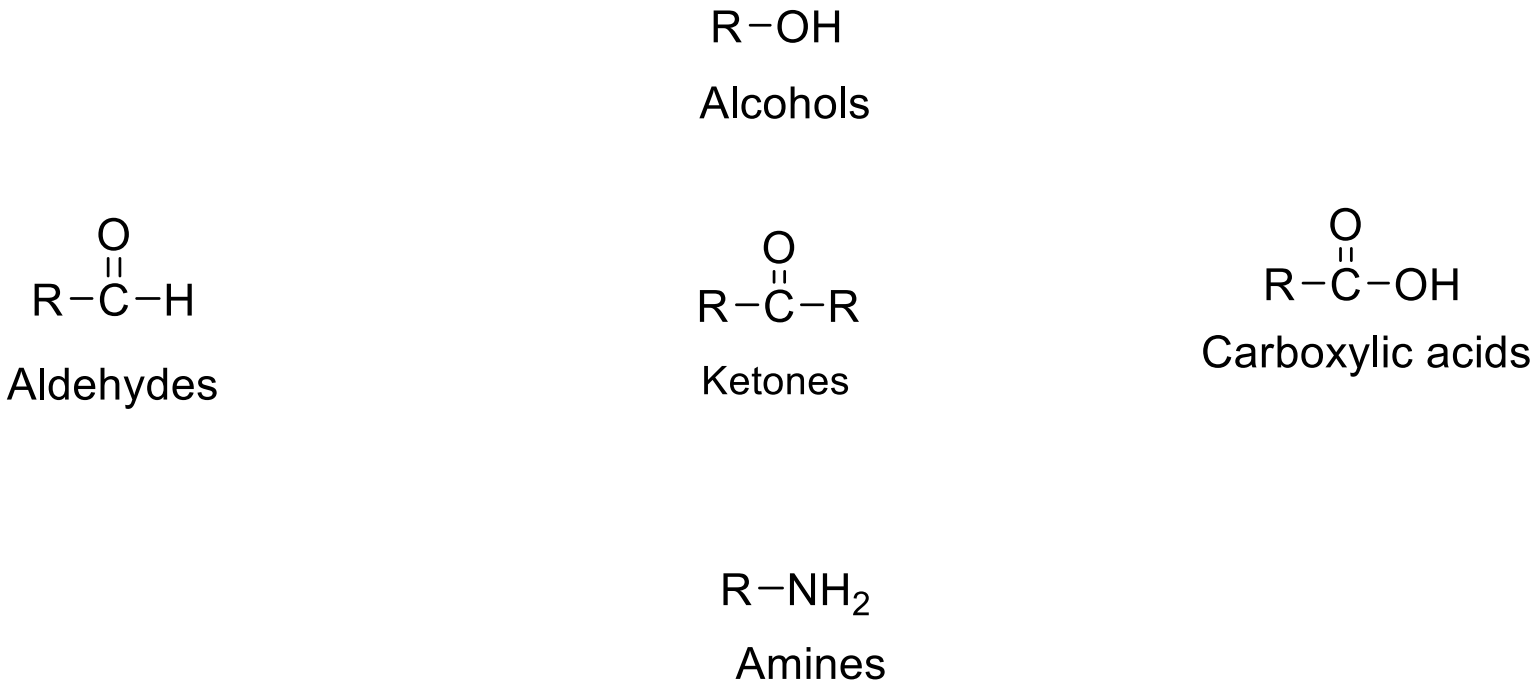
(a) It should be readily, but selectively introduced to the desired functional group in a poly-functional molecule.

(b) It should be stable / resistant to the reagents employed in subsequent reaction steps in which the group being masked (protected) is desired to remain deactivated (protected).

(c) It should be capable of being selectively removed under mild conditions when its protection is nolonger required.

Protecting Groups in Organic Synthesis

The Most Reactive Functional Groups Commonly Requiring Protection



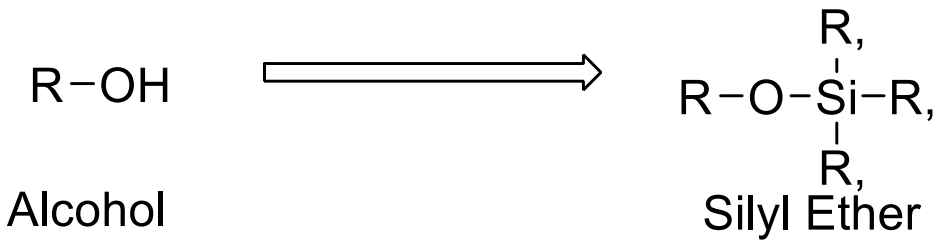
The commonly encountered functional groups in organic synthesis that are reactive to nucleophilic or electrophilic reagents whose selective transformation may present challenges do regularly require deactivation by masking with a protecting group.

Protecting Groups for Alcohols

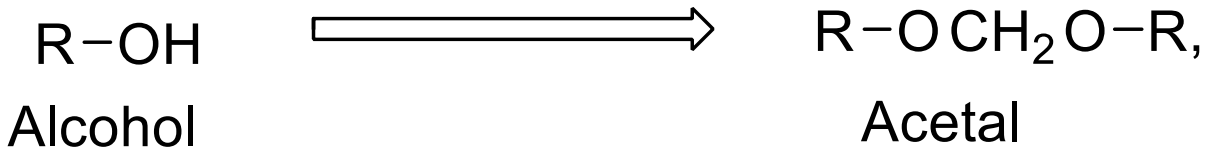
The common protecting groups for alcohols are ether-protecting groups. Ethers are among the least reactive of the organic functional groups

The ether protecting groups of alcohols can be grouped in the following categories:

(a) Silyl ether protecting groups



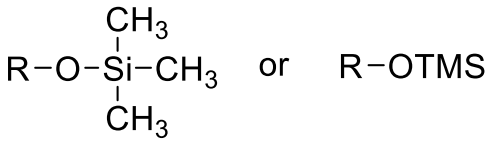
(b) Acetal protecting groups



These protections replace the acidic proton on an alcohol with an unreactive ether moiety.

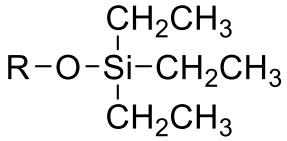
Protecting Groups for Alcohols

Common Silicon-Based Protecting Groups for Alcohols



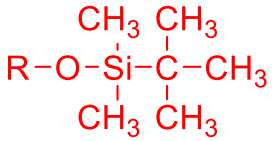
or R–OTMS

Trimethylsilyl

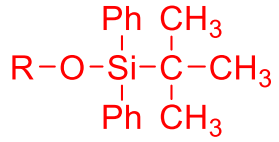


or R–OTES

Triethylsilyl



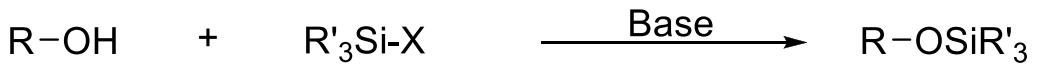
Tert-Butyldimethylsilyl (TBDMS)



Tert-Butyldiphenylsilyl (TBDPS)

Formation

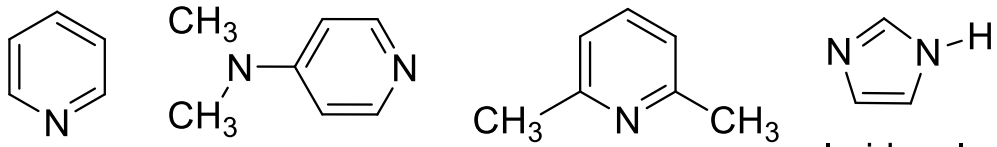
Silicon-Based Protecting Groups for Alcohols



X= Cl or OTf

Bases

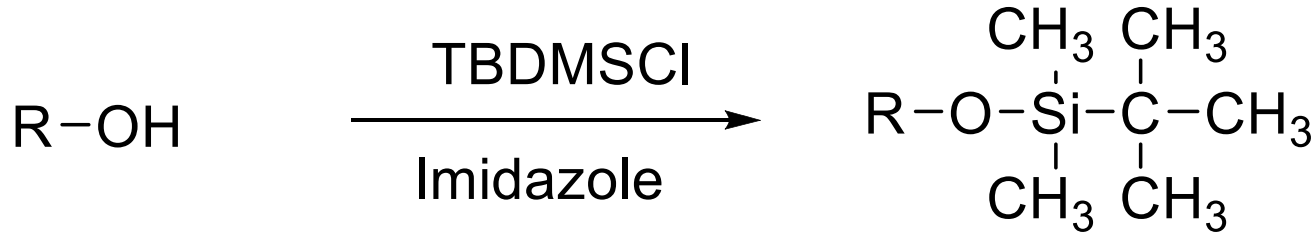
Et_3N / DMAP

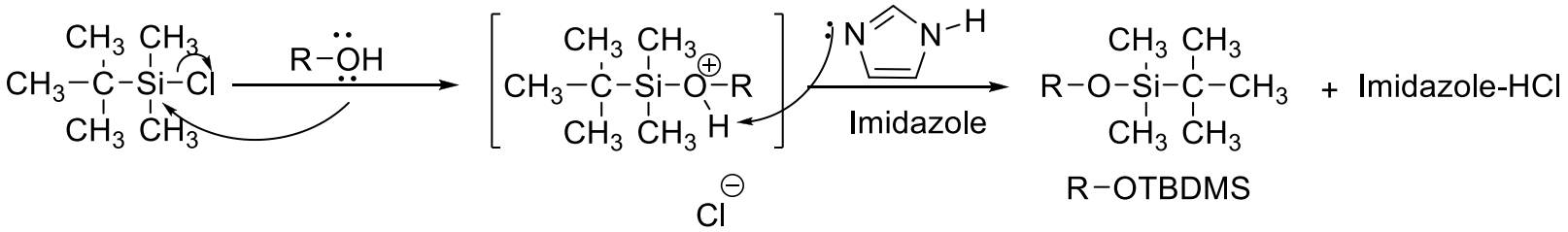


Pyridine DMAP 2,6-Lutidine Imidazole

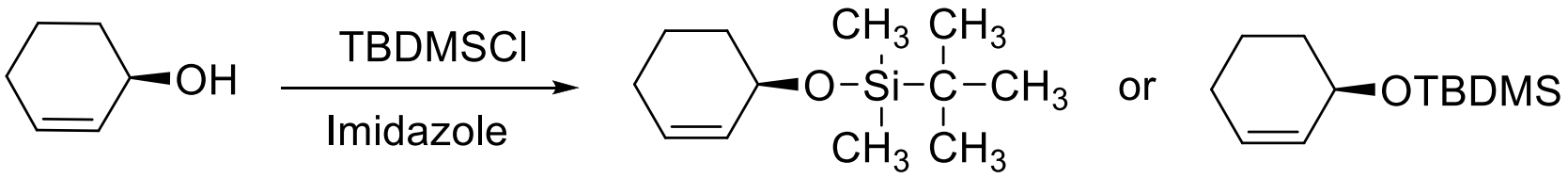
Protecting Groups for Alcohols

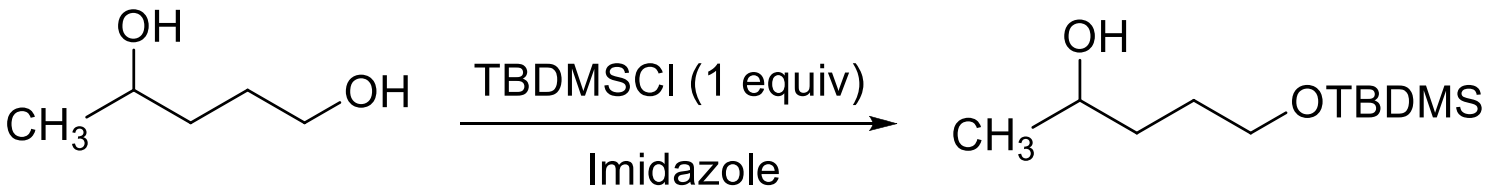
Tert-Butyldimethylsilyl ethers (TBDMS)





Example

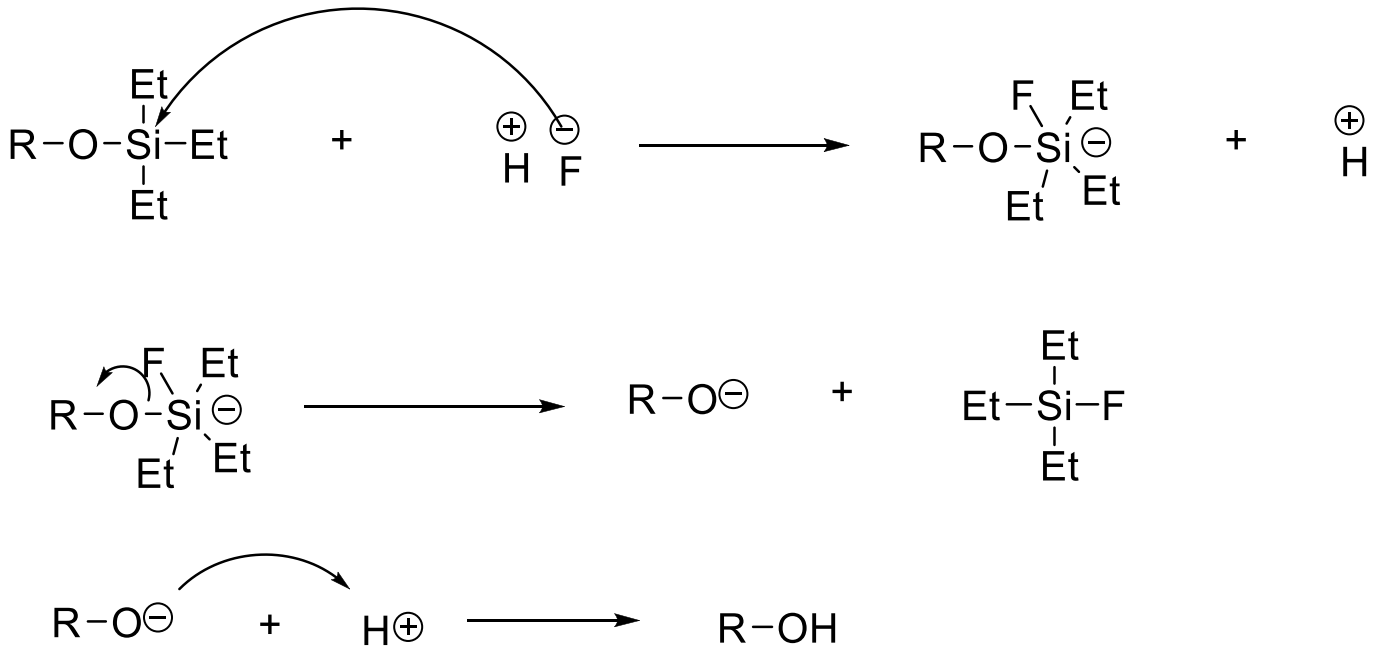




Protecting Groups for Alcohols
(Silyl Protecting Groups)

Cleavage

Deprotection of Silicon-Based Protecting Groups



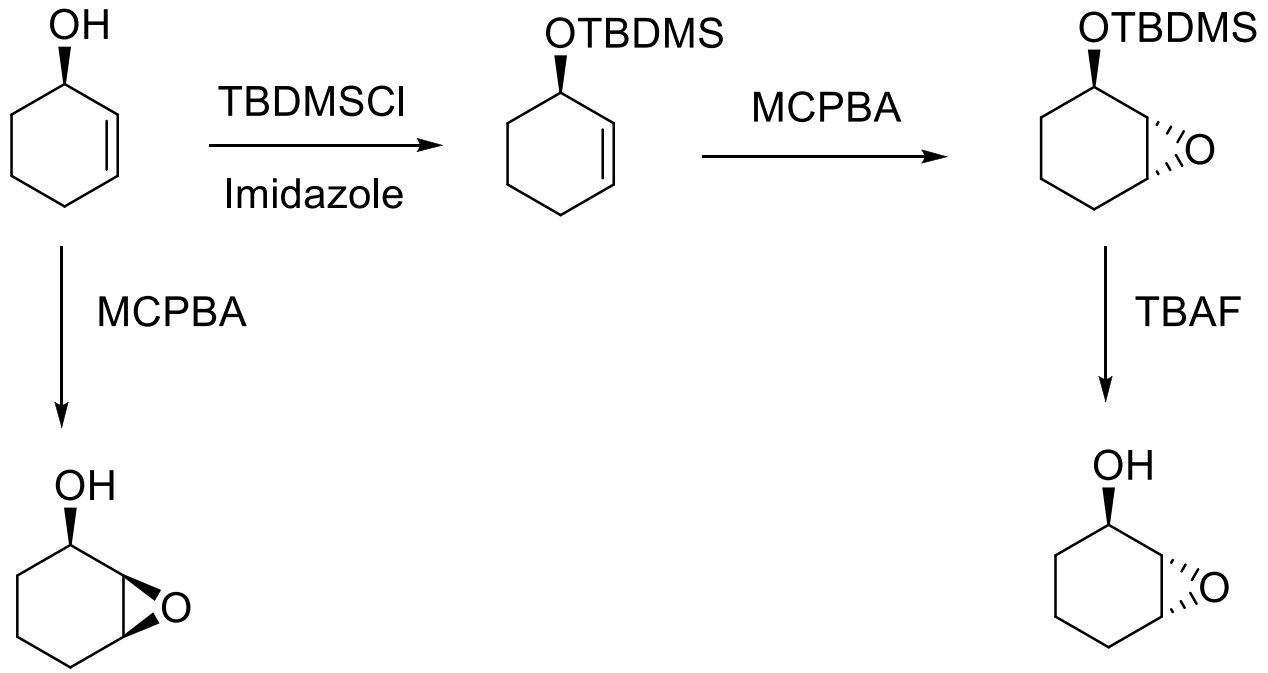
Fluoride sources:

Tetrabutylammonium fluoride, $Bu_4N^+F^-$ (TBAF)
Pyridine-HF
Hydrofluoric acid (HF)
Ammonium fluoride $NH_4^+F^-$

Protecting Groups for Alcohols
(Silyl Protecting Groups)

Synthetic Applications of Silyl Protecting Groups

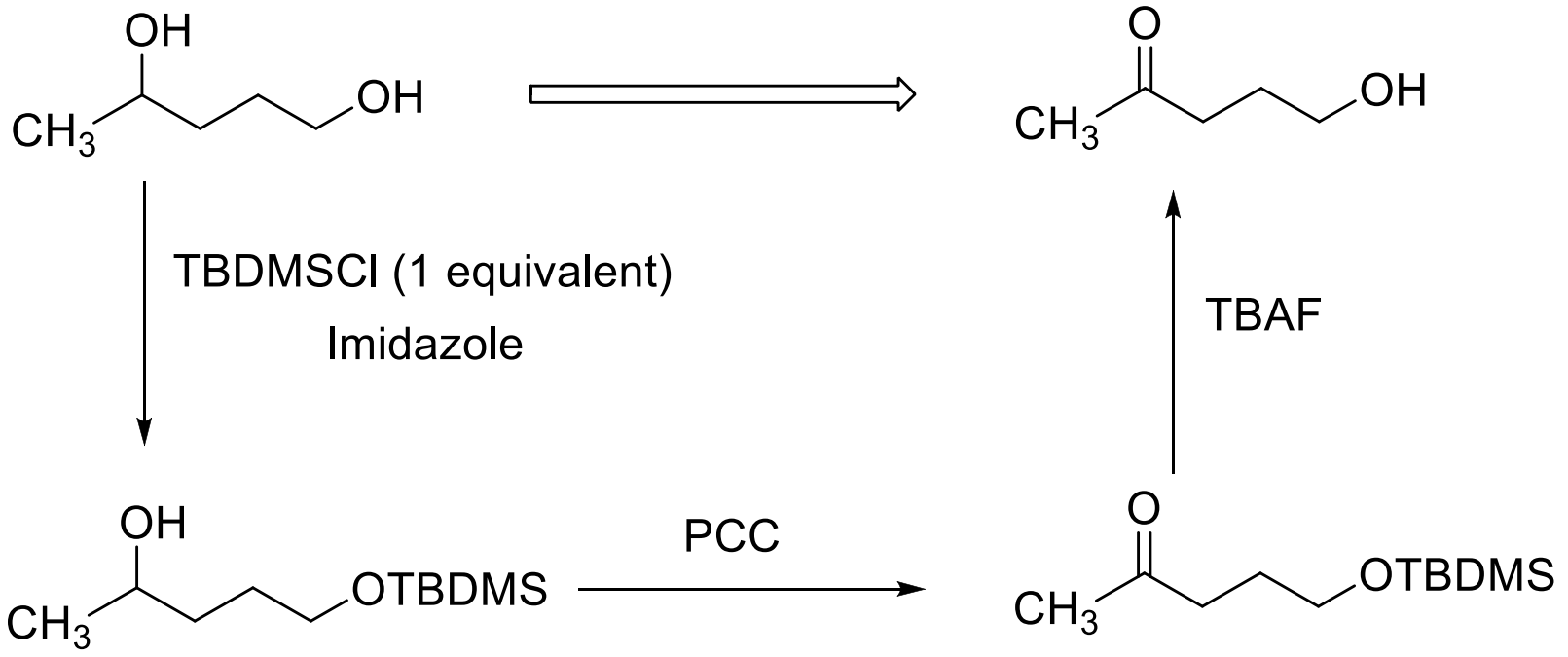
The bulkiness of TBDMS and TBDPS ether protecting groups can be used to advantage to suppress hydrogen-bonding to the oxygen restricting any incoming reagents to approach from the least hindered side of the molecule.



Protecting Groups for Alcohols
(Silyl Protecting Groups)

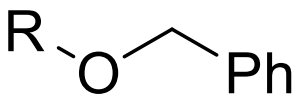
Synthetic Applications of Silyl Protecting Groups

The bulkiness of TBDMS and TBDPS ether protecting groups can also be exploited in incorporating the protecting group on less sterically encumbered primary hydroxyl groups selectively using sub-molar amounts of the silyl chloride.



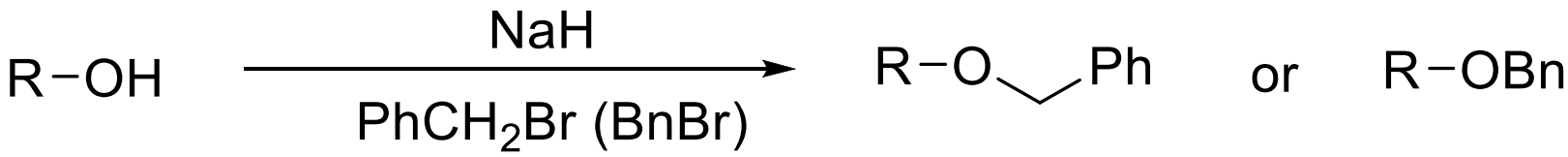
Protecting Groups for Alcohols
(Benzyl ether Protecting Groups)

Rarely are alkyl ethers used as protecting groups for alcohols, but benzyl ethers are special.



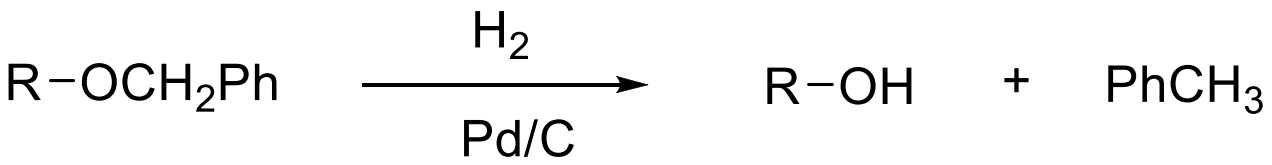
Benzyl ether
(Bn)

Formation



Cleavage

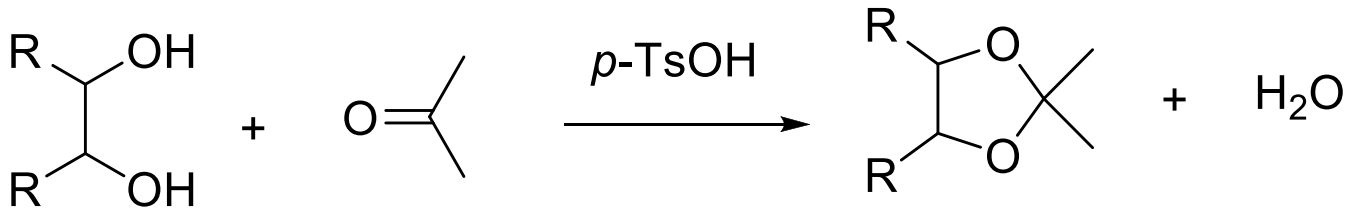
Hydrogenolysis is selectively used to cleave benzyl ether protecting groups



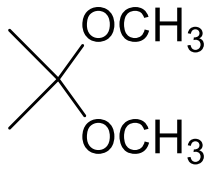
Protecting Groups for Alcohols
(Cyclic Acetal Protecting Groups)

Acetonide Protecting Groups for 1,2-Diols

Formation

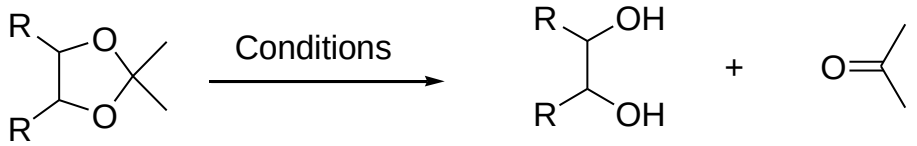


Other sources of the protecting group:



2,2-Dimethoxypropane

Cleavage

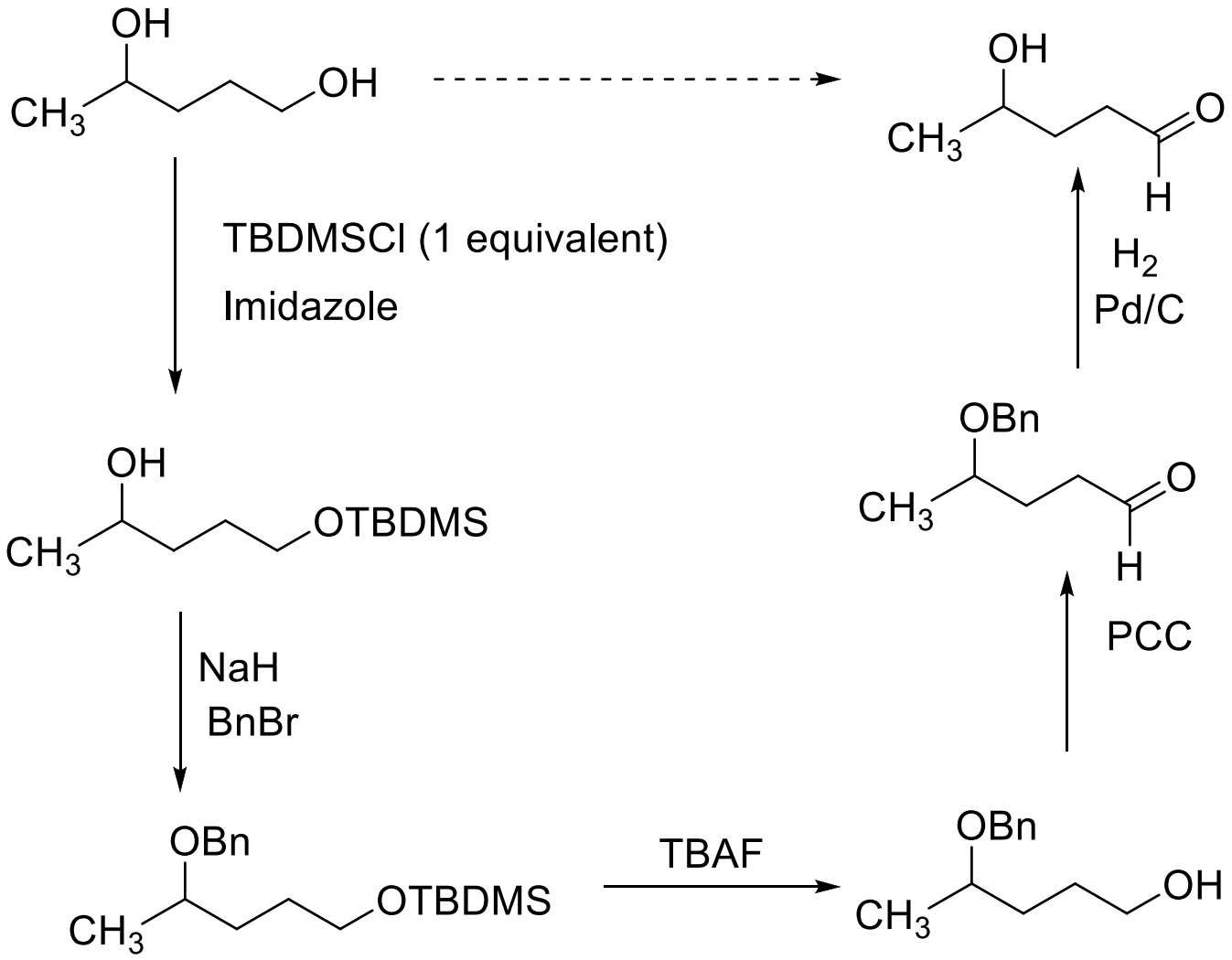


(a) Acid catalysed hydrolysis
H^+, H_2O

(b) AcOH / H_2O

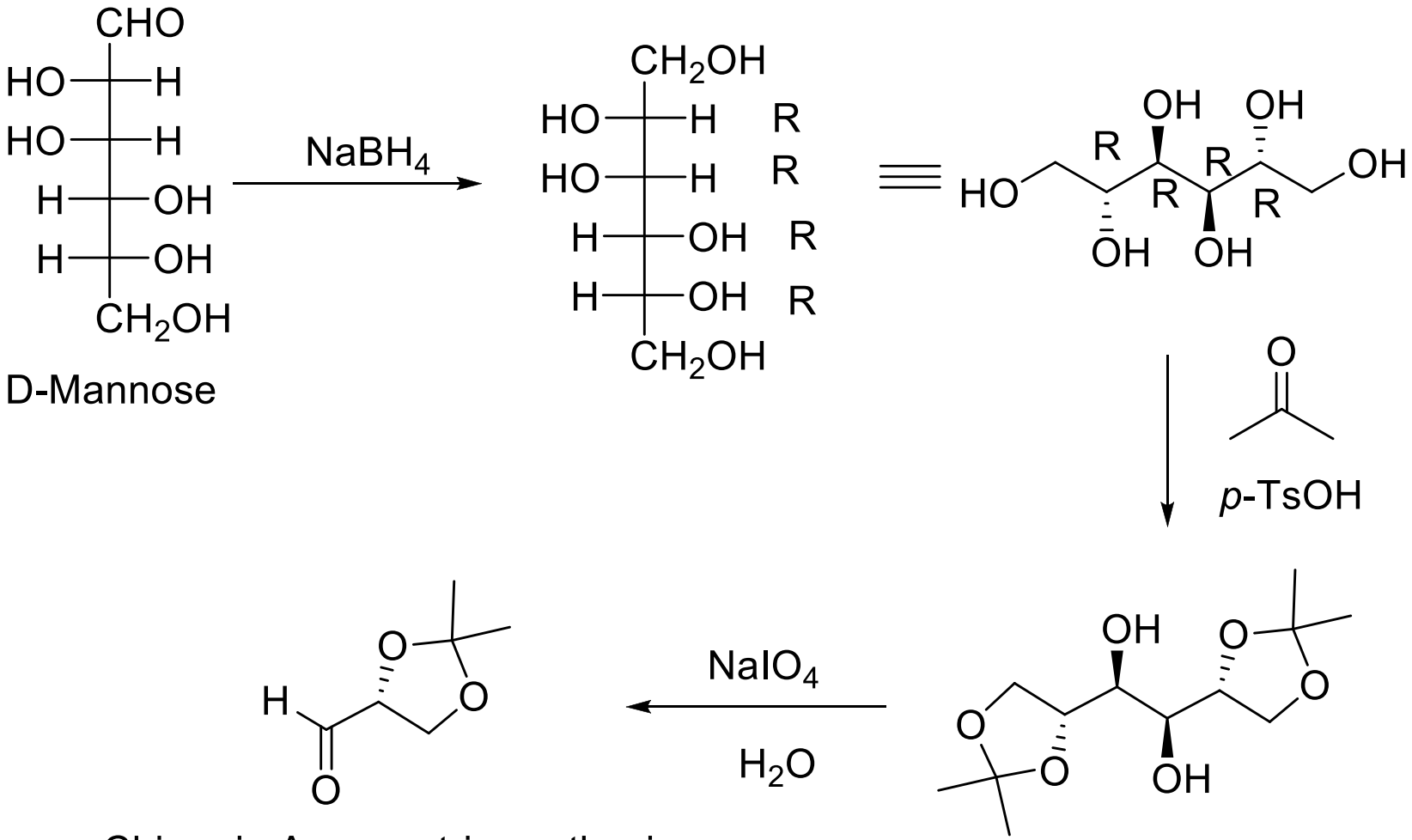
Protecting Groups for Alcohols
(Perspectives on their Synthetic Applications)

Synthetic Applications of Ether Protecting Groups



Protecting Groups for Alcohols
(Perspectives on their Synthetic Applications)

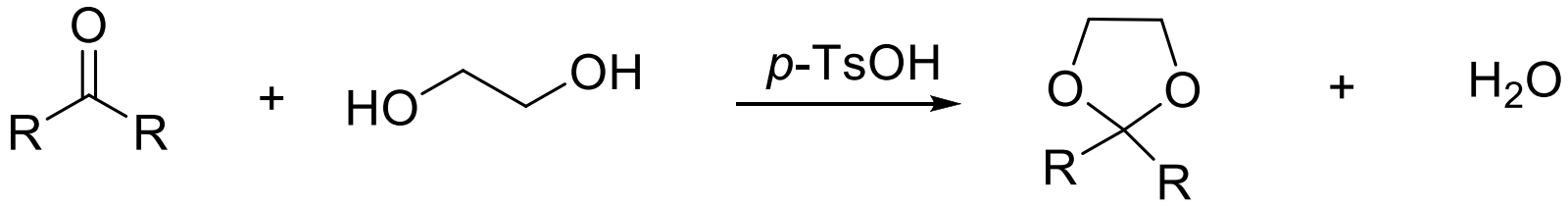
Synthetic Applications of Cyclic Acetal Protecting Groups



Protecting Groups for Aldehydes and Ketones
(Acetal and Ketal Protecting Groups)

Acetal Protecting Group

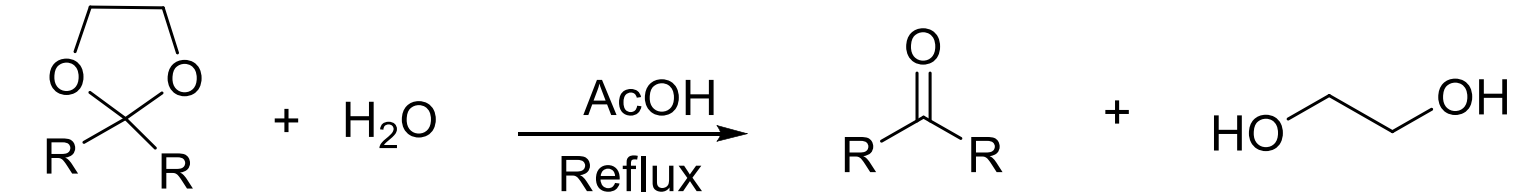
Formation



1,3-Dioxolane

Cleavage

Acid catalysed hydrolysis (dilute HCl or AcOH / H_2O or TFA/ H_2O or *p*-TsOH in acetone) can be used.

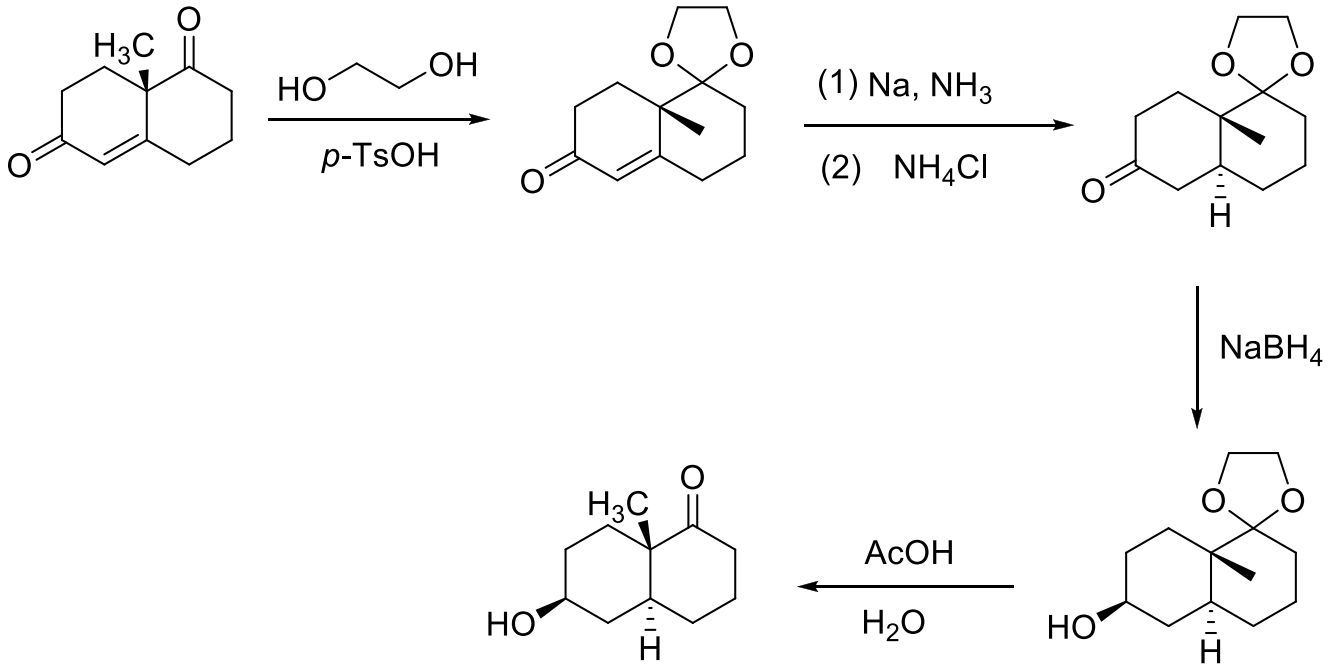


1,3-Dioxolane

Protecting Groups for Aldehydes & Ketones
(Acetal and Ketal Protecting Groups)

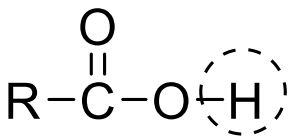
Synthetic Applications of the Acetal Protecting Group

The Wieland-Miescher ketone is a common intermediate in the synthesis of both natural and synthetic steroids.



Because of resonance stabilization, the carbonyl of the α,β-unsaturated ketone is less electrophilic and therefore less reactive to nucleophiles compared to an isolated ketone.

Protecting Groups for Carboxylic Acids
(Esters)

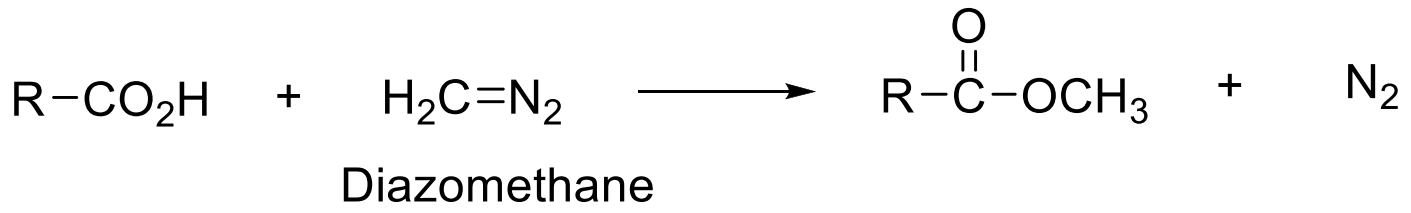


$\Longrightarrow$ Acidic proton can be abstracted by bases including organometallic reagents

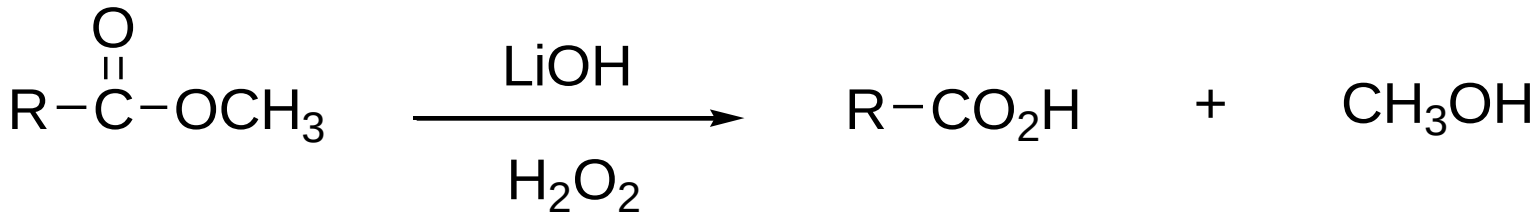
The common ester protecting groups for carboxylic acids are methyl, ethyl and benzyl esters.

Methyl Esters

Formation

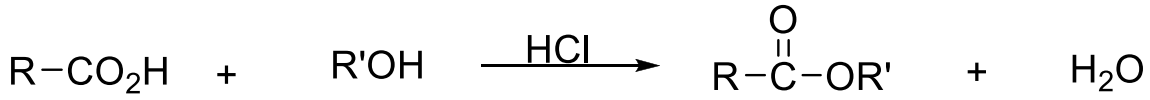


Cleavage



Protecting Groups for Carboxylic Acids
(Esters)

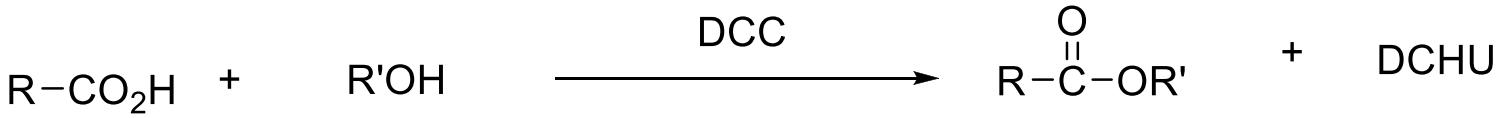
Ethyl and benzyl esters are prepared based on the following rationale:



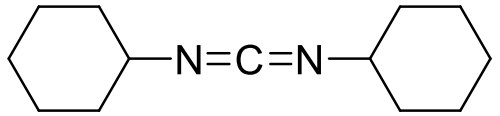
Fischer Esterification: Incompatible with α-enolizable carboxylic acids and other acid-labile protecting groups that may be already present in the polyfunctional molecule.

Best approach:

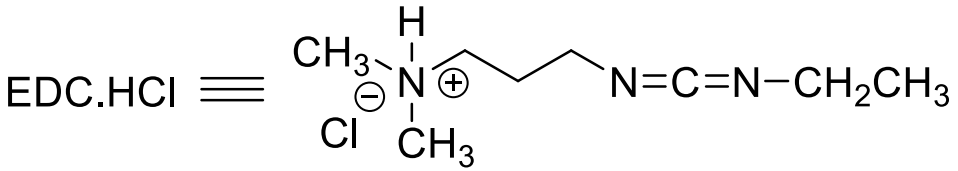
Milder conditions for esterification



DCC = 1,3-Dicyclohexyl carbodiimide



Other Coupling Reagents other than DCC



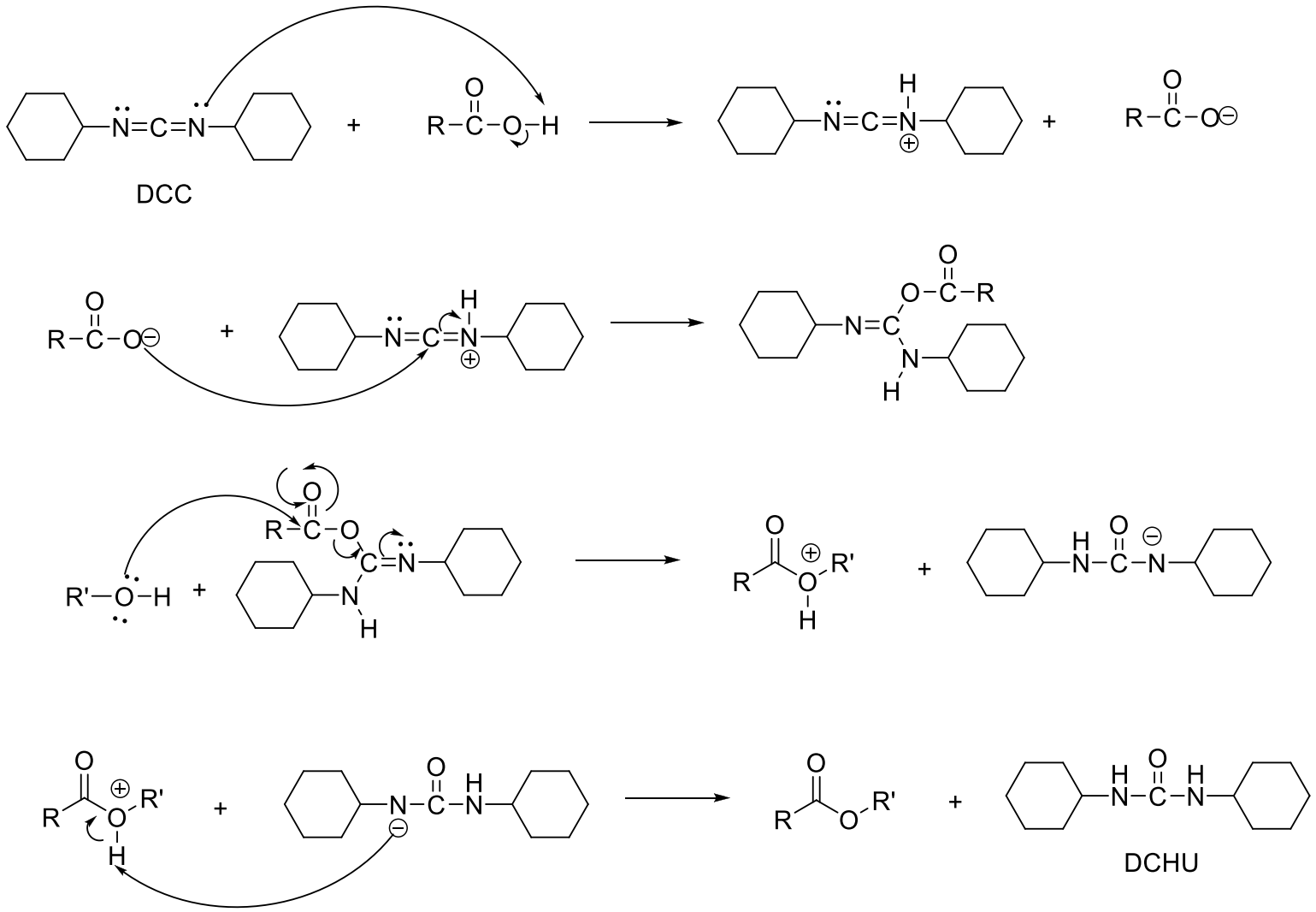
Water-soluble carbodiimide

EDC = 1-[3-(Dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride

EDC.HCl is more expensive, but the urea by-product derived from it is water soluble and simplifies the purification process

Protecting Groups for Carboxylic Acids
(Esters)

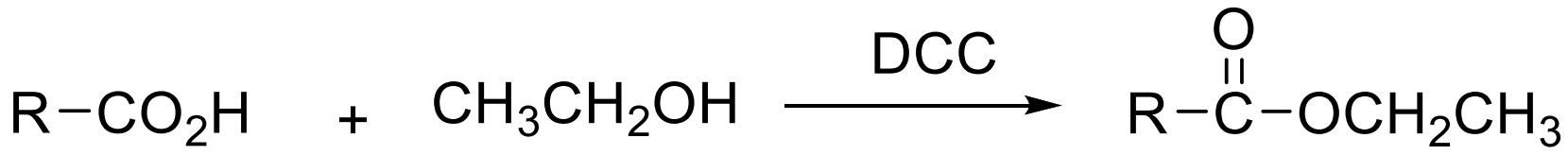
Mechanism of DCC coupling



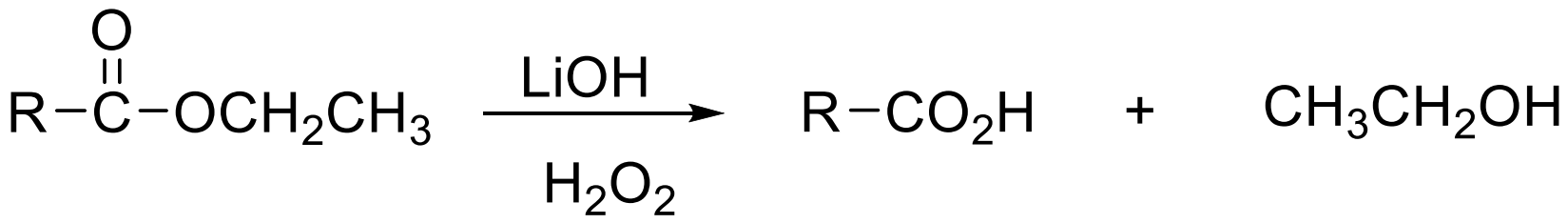
Protecting Groups for Carboxylic Acids
(Esters)

Ethyl Esters

Formation



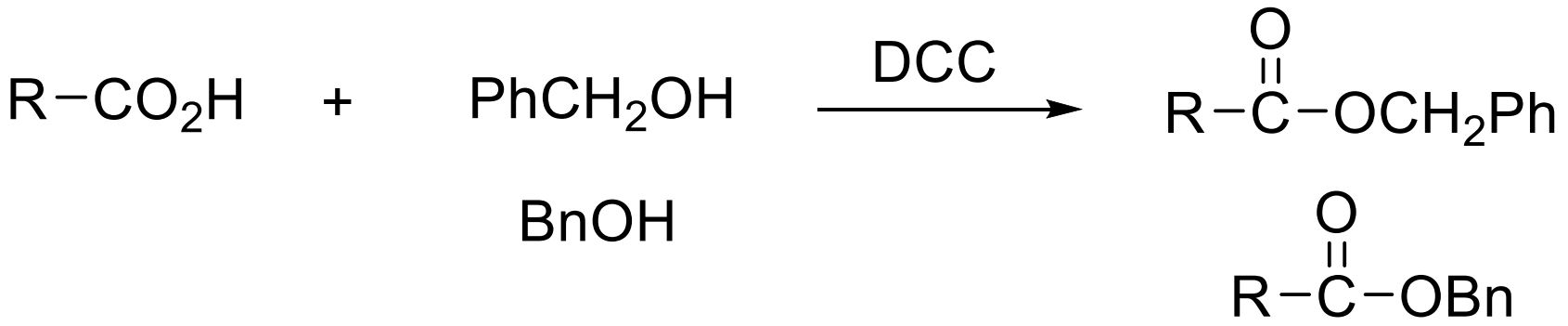
Cleavage



Protecting Groups for Carboxylic Acids
(Esters)

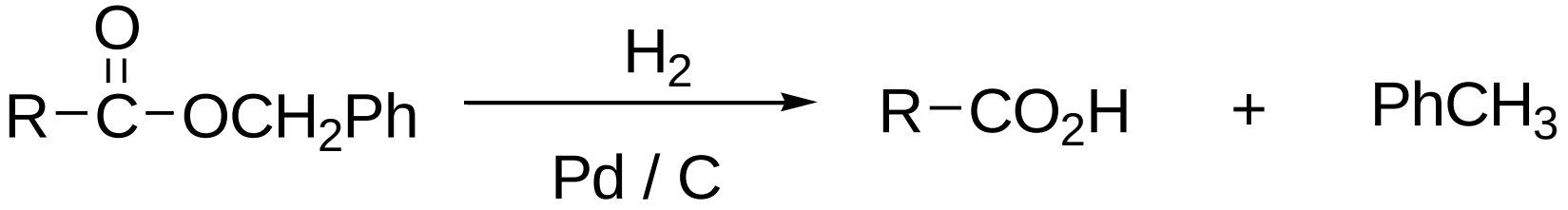
Benzyl Esters

Formation



Cleavage

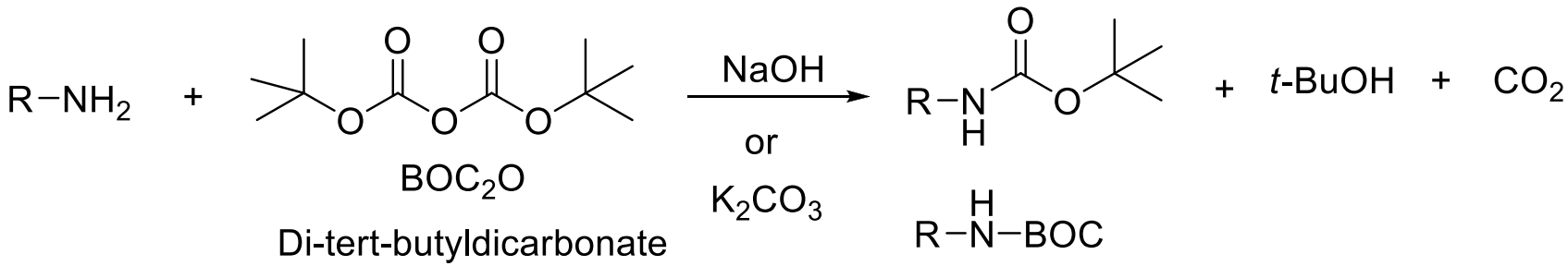
By hydrogenolysis: A very mild method for most functional groups except with alkenes, alkynes and nitriles.



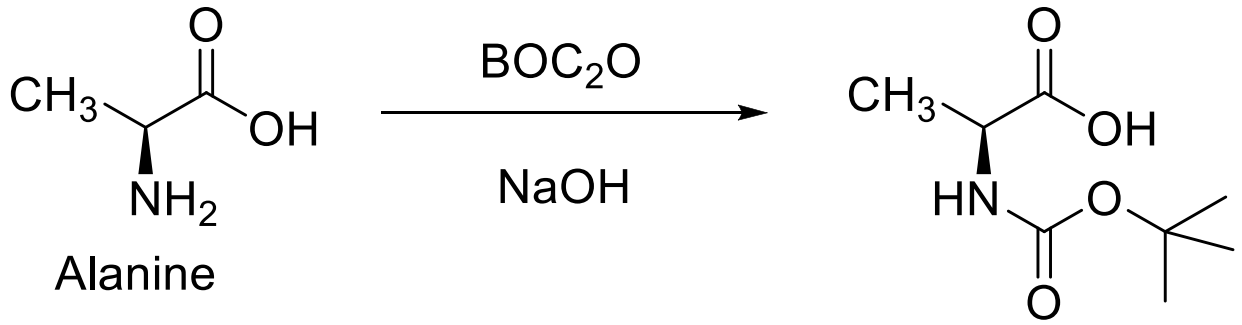
Protecting Groups for Amino Groups
(Carbamate Protecting Groups)

Tert-Butyloxycarbonyl Protecting Group (BOC)

Formation



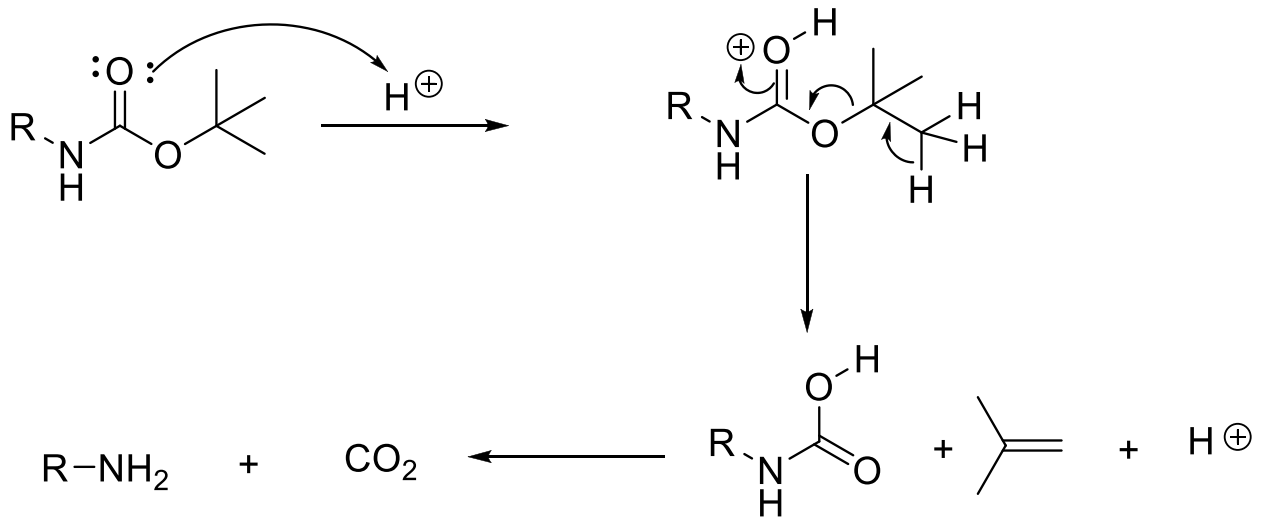
Example



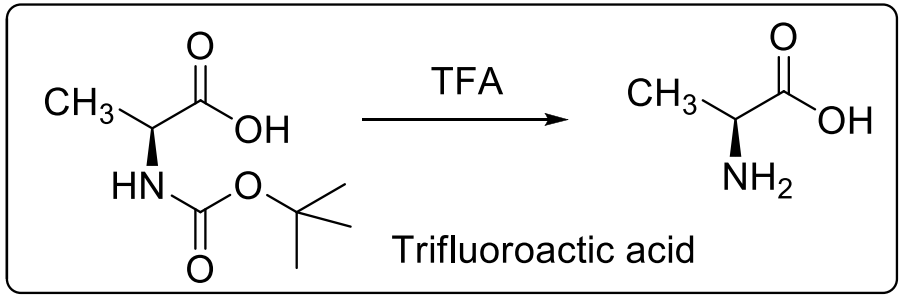
Protecting Groups for Amino Groups
(Carbamate Protecting Groups)

Tert-Butyloxycarbonyl Protecting Group (BOC)

Cleavage



Isobutene gas

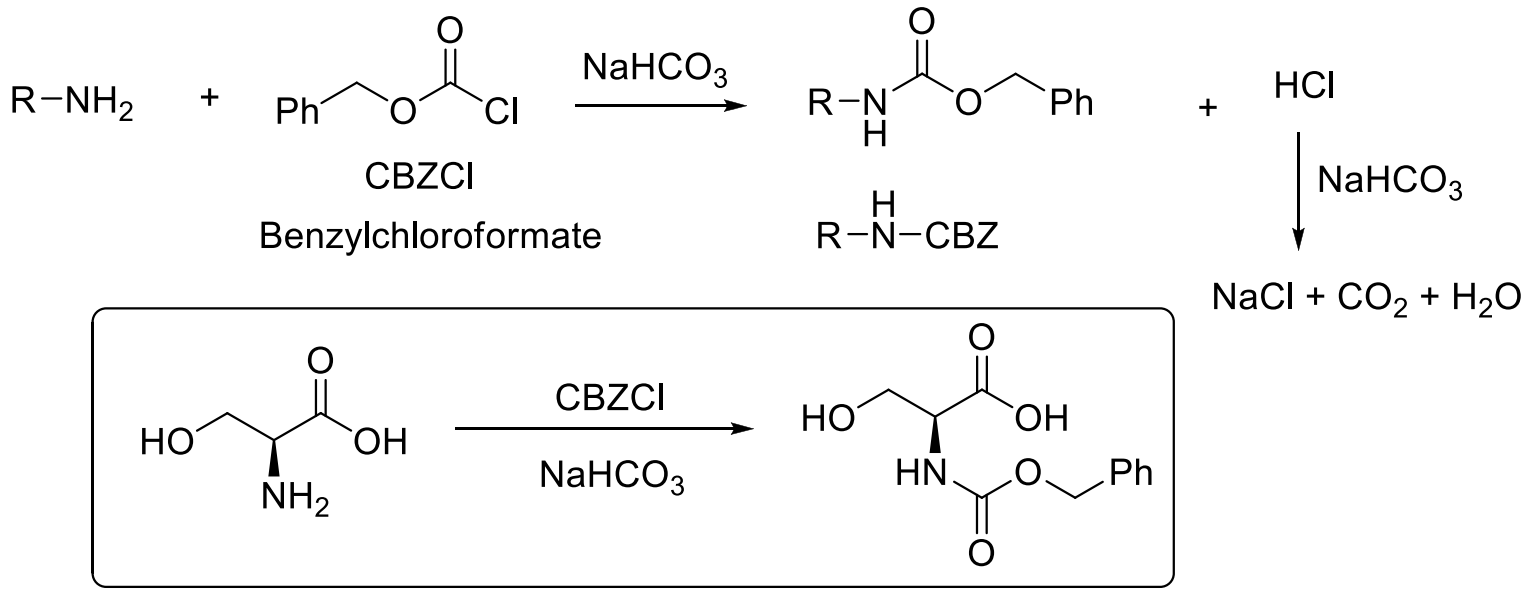


Protecting Groups for Amino Groups

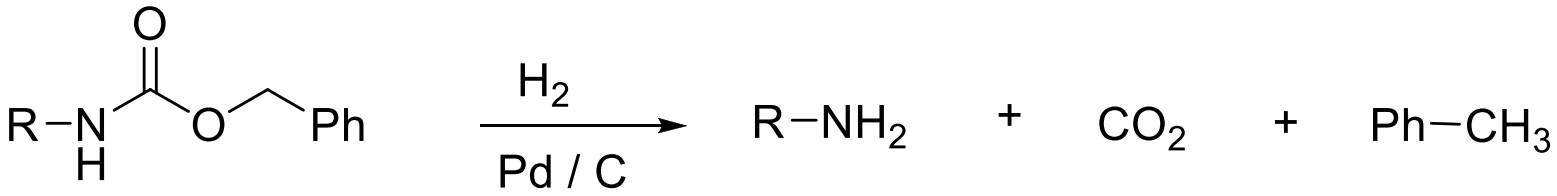
(Carbamate Protecting Groups)

Benzyloxycarbonyl Protecting Group (CBZ)

Formation

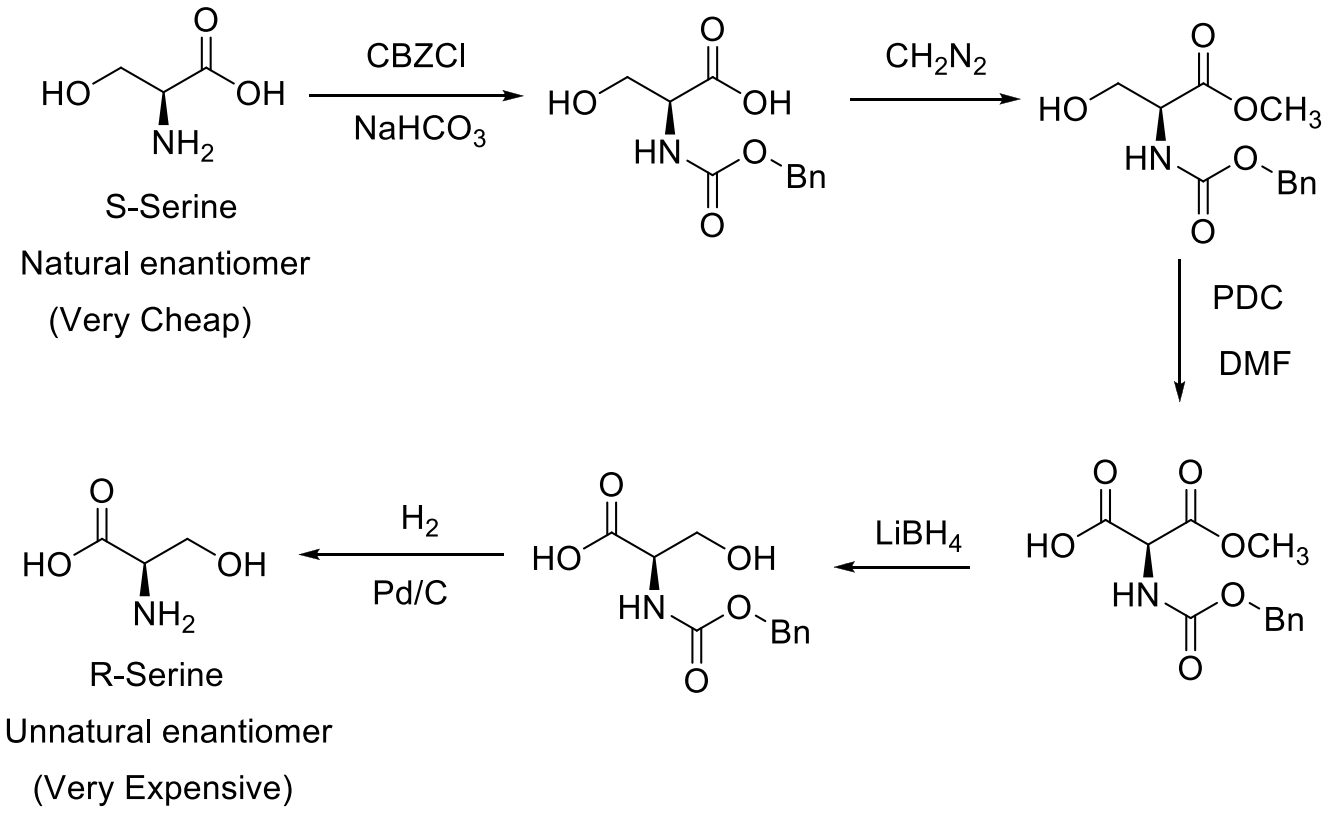


Cleavage



Protecting Groups for Carboxylic Acids
(Ester Protecting Groups)

Perspectives in the Synthetic Applications of the Ester Protecting Groups



Note that $LiBH_4$ can reduce the more reactive ester functional group leaving the less reactive carboxylic acid and carbamate groups unaffected.