

PART B

ORGANIC SYNTHESIS

What is Synthesis?

Synthesis involves combining two or more chemical entities through covalent bonds to generate a more complex molecule.

The covalent bonds formed between these chemical entities could be based on:

- a substitution reaction,
- an addition reaction

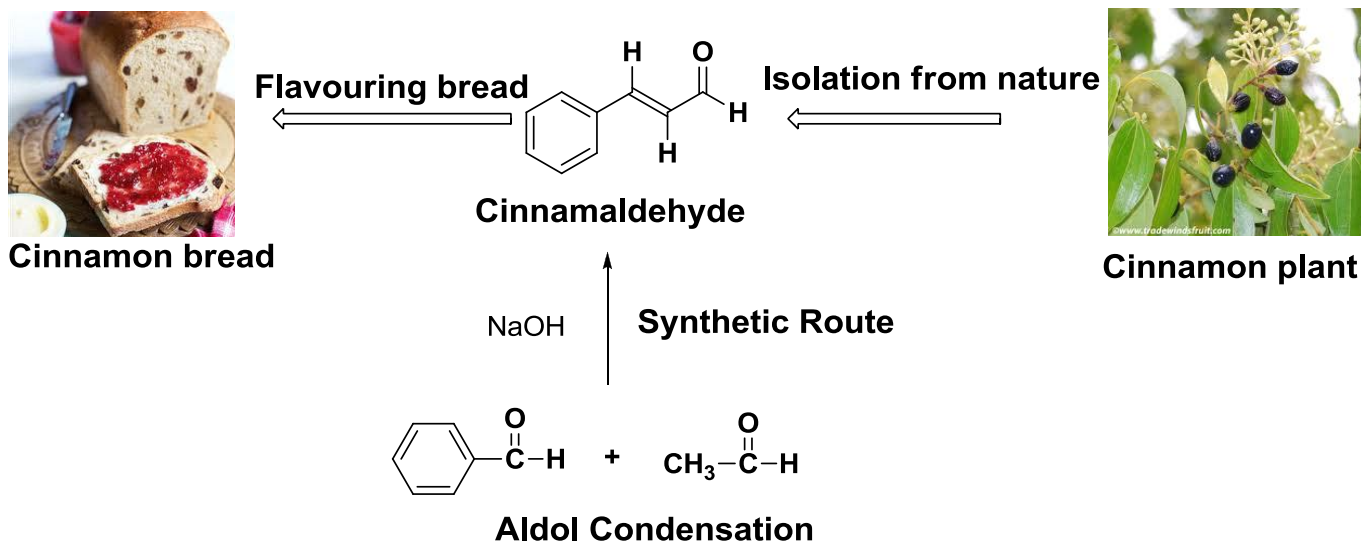
Since the new bonds formed during synthesis occur at functional groups inherent in polyfunctional molecules, it is usually necessary to use **protecting groups** to minimize the formation of side-products.

Is Synthesis of Any Value?

Synthesis is important to the food and cosmetics industry, but also finds wide application in medicine.

Although nature can provide the source of cinnamaldehyde (occurs in the cinnamon plant), its wide application as a flavouring agent requires that it be readily available in large quantities.

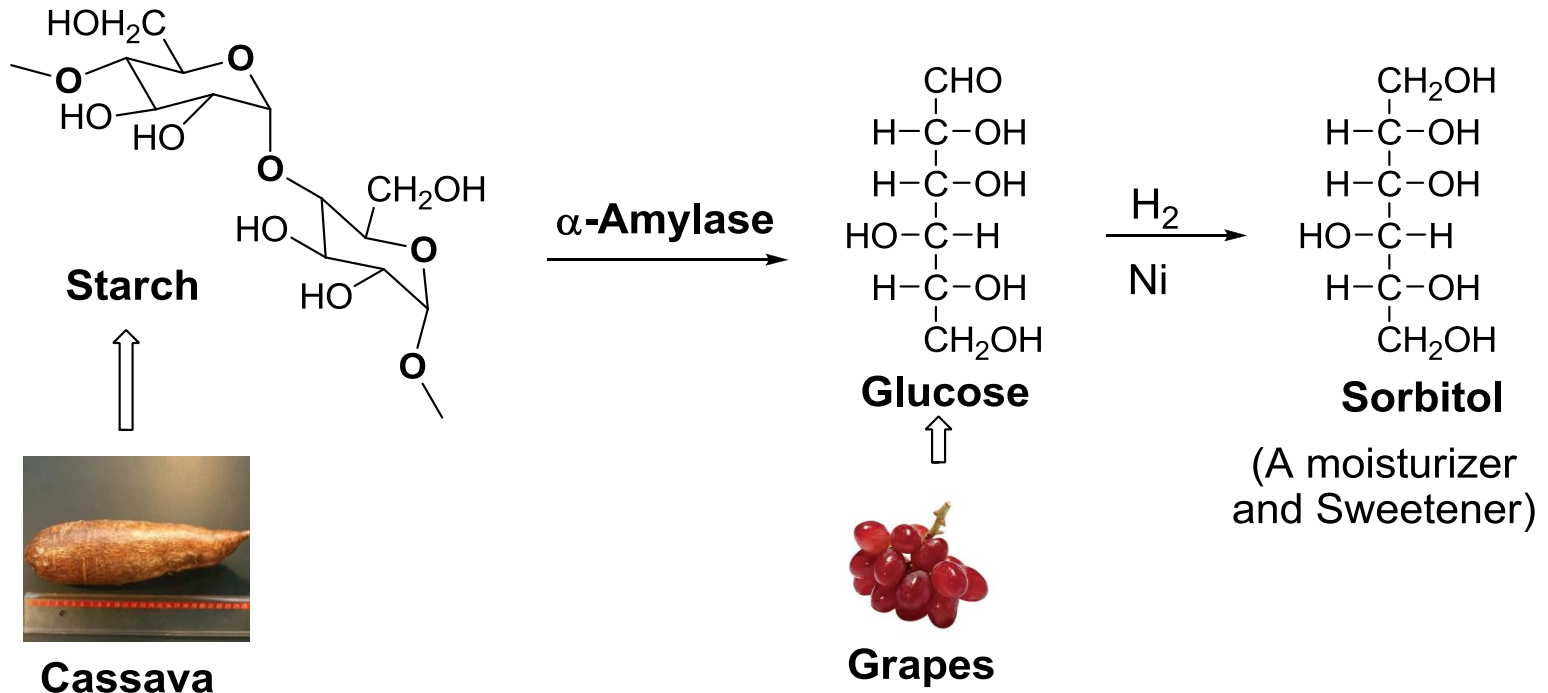
Synthesis has served to supplement the natural source.



Of What Value is Synthesis?

Synthesis of Moisturizers and Sweeteners

Enzymatic hydrolysis of starch provides glucose, which when reduced provides sorbitol, a moisturizer and sweetener.



Organic Synthesis

What are the Essentials in Synthesis?

Since organic synthesis is applied organic chemistry, to stand a realistic chance of succeeding in any synthesis, the student ought to have a good knowledge-base of organic chemistry in the following areas:

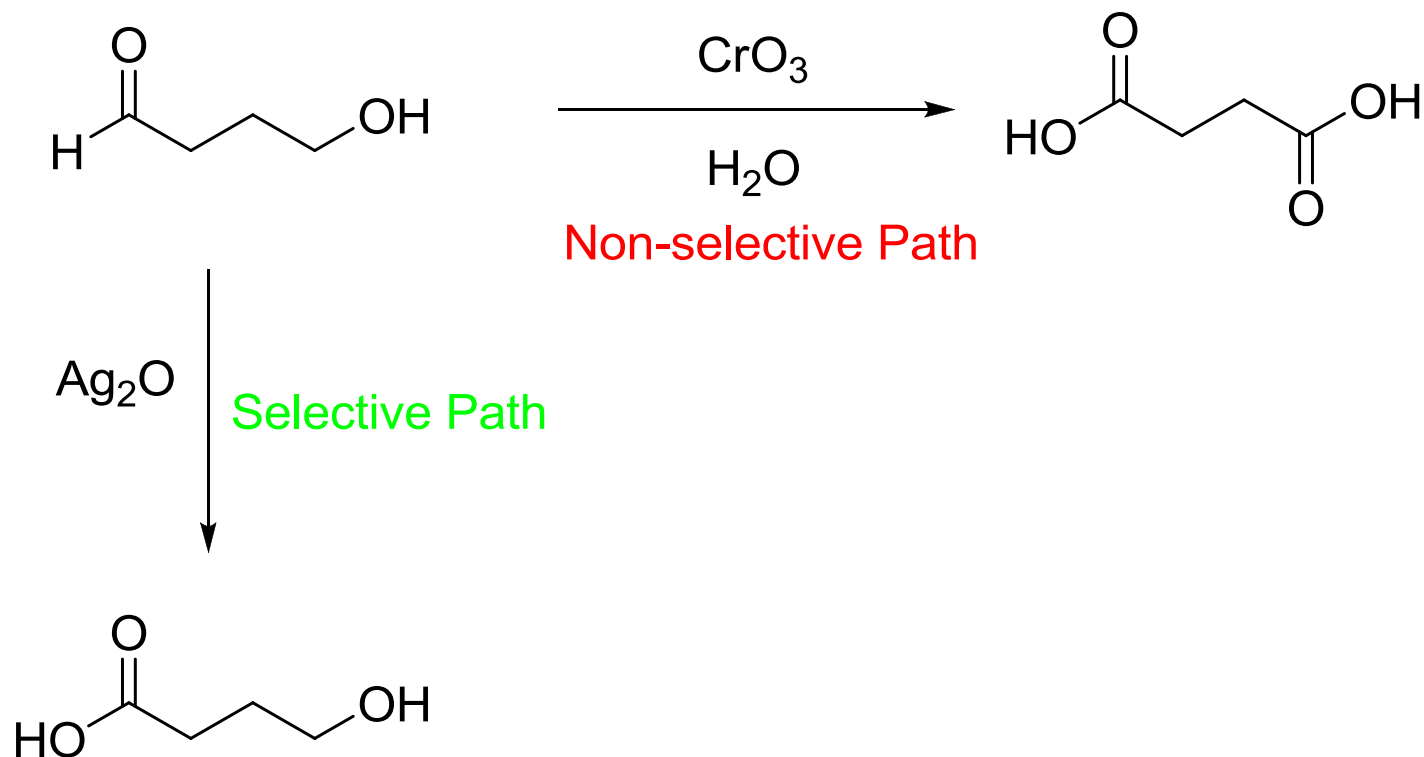
- Protecting group chemistry
- Asymmetric synthesis
- Functional group transformations (SCH 202 & SCH 206)
- Substitution reactions (SCH 102)
- Addition reactions (SCH 202 and SCH 206)
- Strategies for synthetic planning (Retrosynthetic analysis)

Protecting Groups in Organic Synthesis

Challenges in Organic Synthesis

Chemoselectivity can be Elusive

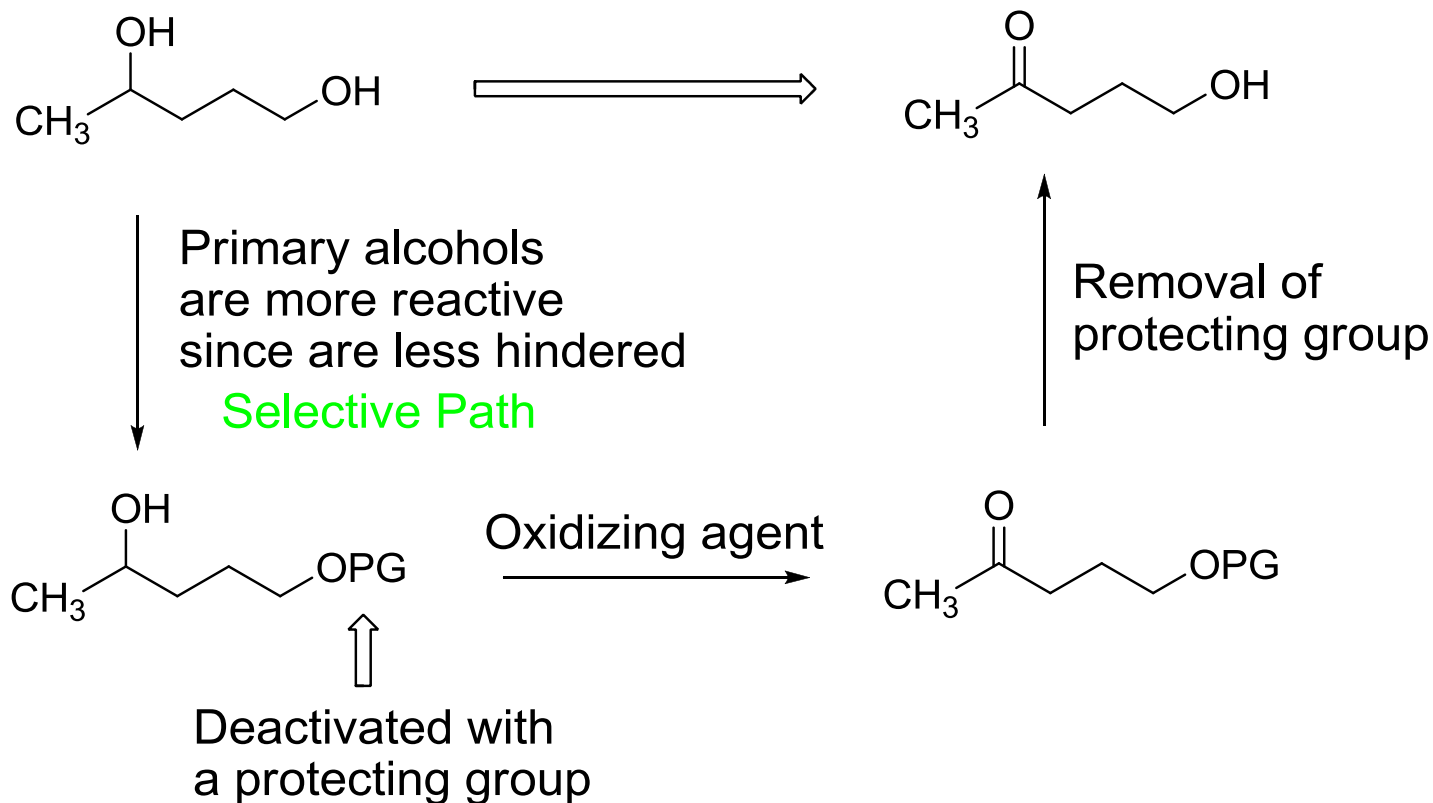
Chemoselective Oxidation



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

Protecting Groups: A Necessary Evil

Building the Case for Protecting Groups

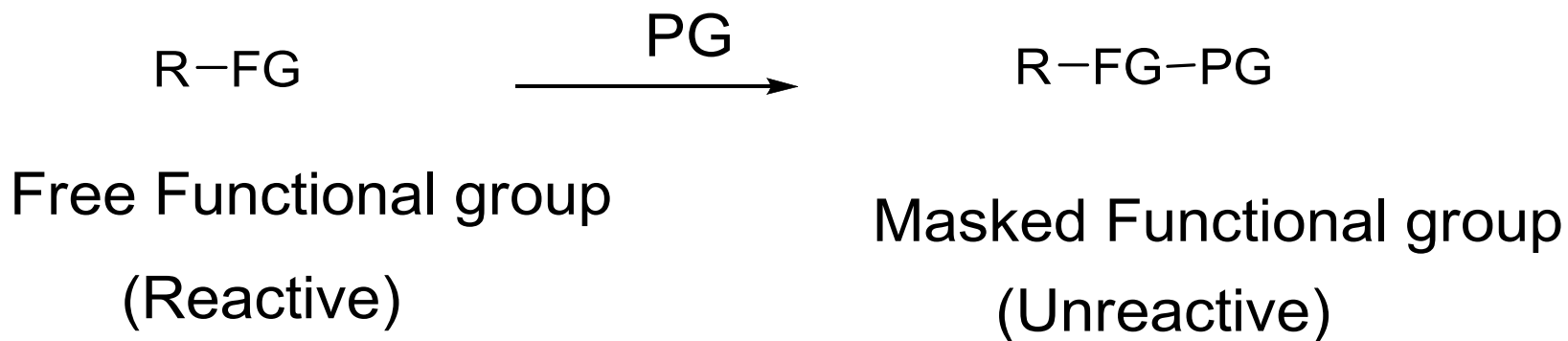


Note that the introduction of each protecting group in a multi-step synthesis increases the synthesis by two non-productive steps reducing the overall yield and efficiency of the synthesis.

Protecting Groups in Organic Synthesis

What is a protecting group?

A protecting group (PG) is a molecular unit 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.



Protecting Groups in Organic Synthesis

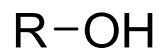
The Qualities of a Good Protecting Group

A good protecting group should be such that:

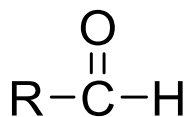
- (a) It should be readily and selectively introduced to the desired functional group in a poly-functional molecule.
- (b) It should be resistant (inert) to the reagents employed in the subsequent reaction steps in which the group being masked (protected) is desired to remain deactivated (protected).
- (c) It should be capable of being selectively removed under mild conditions when its protection is no longer required.

Protecting Groups in Organic Synthesis

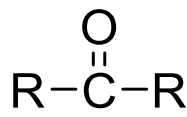
Groups that Commonly Require Protection



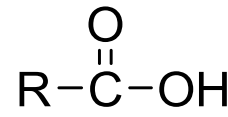
Alcohols



Aldehydes



Ketones



Carboxylic acids



Amines

The common functional groups 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

Why Ethers?

As derivatives of alcohols, ethers are among the least reactive of all classes of organic compounds.

No wonder, the common protecting groups for alcohols are ether-protecting groups.



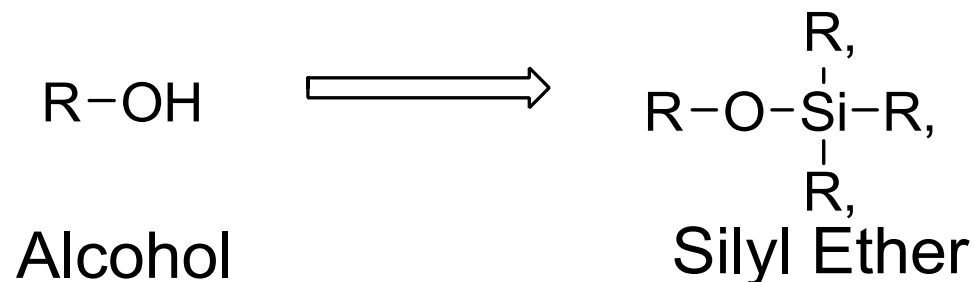
To achieve the desired protection, the conversion of alcohols to ethers replace the acidic proton on an alcohol with an unreactive alkyl moiety.

Protecting Groups for Alcohols

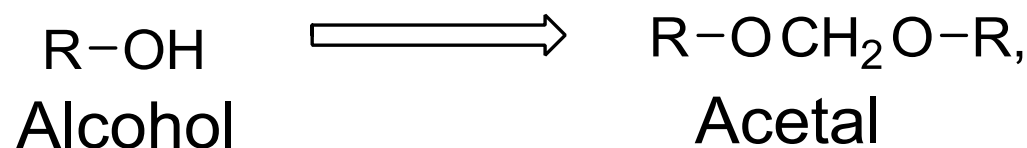
What Kind of Ethers?

Except for benzyl ethers, hardly are alcohols protected as alkyl ethers. The ether protecting groups of alcohols can be grouped into the following categories:

(a) Silyl ether protecting groups



(b) Acetal protecting groups

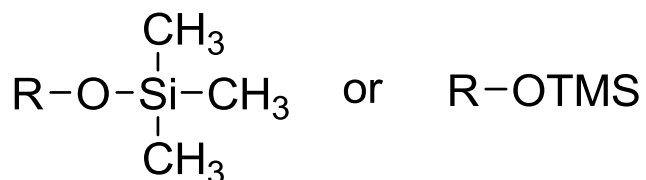


Protecting Groups for Alcohols

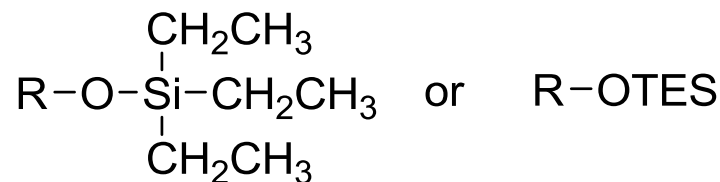
Silyl Ether Protecting Groups

Silicon ethers are the most commonly used alcohol protecting groups. The O-Si bond formed is strong and less reactive to strong bases compared to the O-H bond in the parent alcohol. Moreover, the bulkier silicon prevents easy access by electrophiles to the lone pairs of electrons on the oxygen atom.

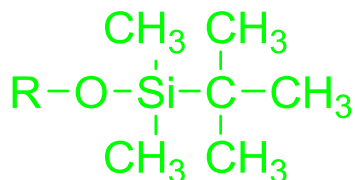
Common Silicon-Based Protecting Groups for Alcohols



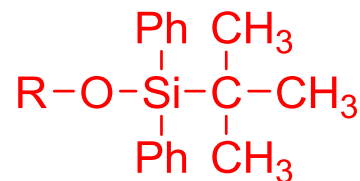
Trimethylsilyl



Triethylsilyl



Tert-Butyldimethylsilyl (TBDMS)

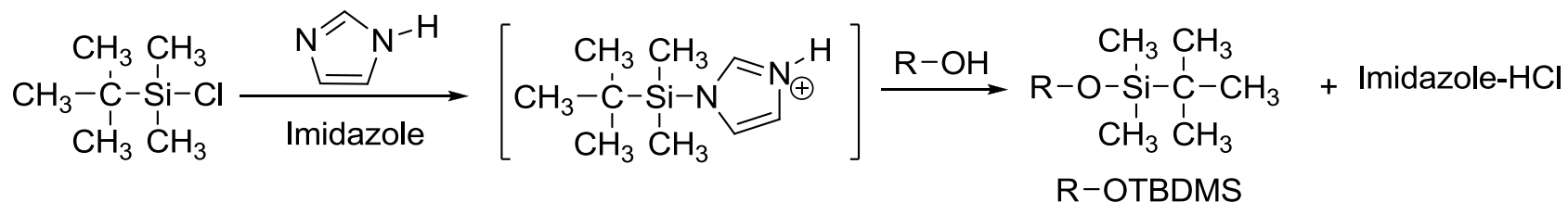
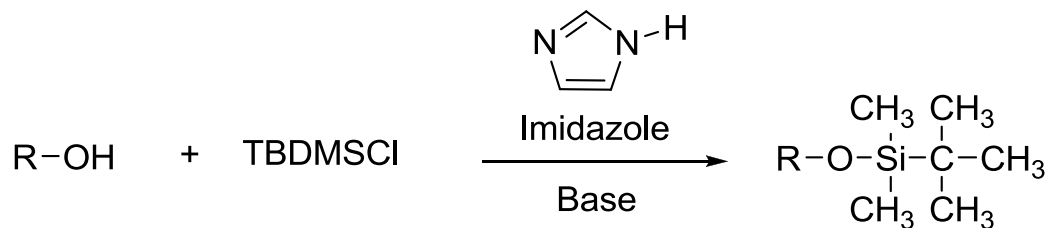


Tert-Butyldiphenylsilyl (TBDPS)

Protecting Groups for Alcohols

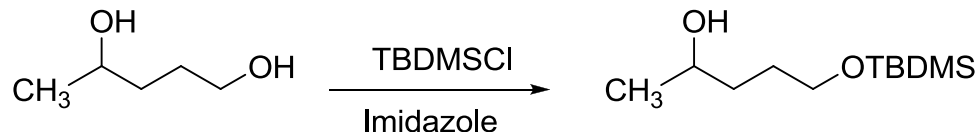
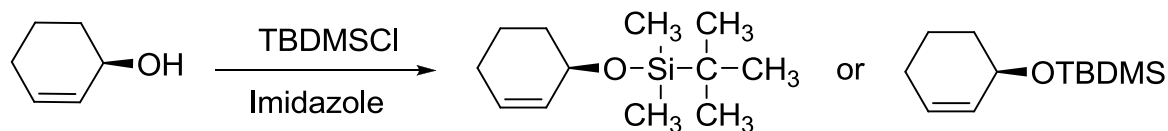
Tert-Butyldimethylsilyl Ether Protecting Group

Formation



Imidazole neutralizes the HCl produced in the reaction to suppress side-reactions that could arise from it.

Example

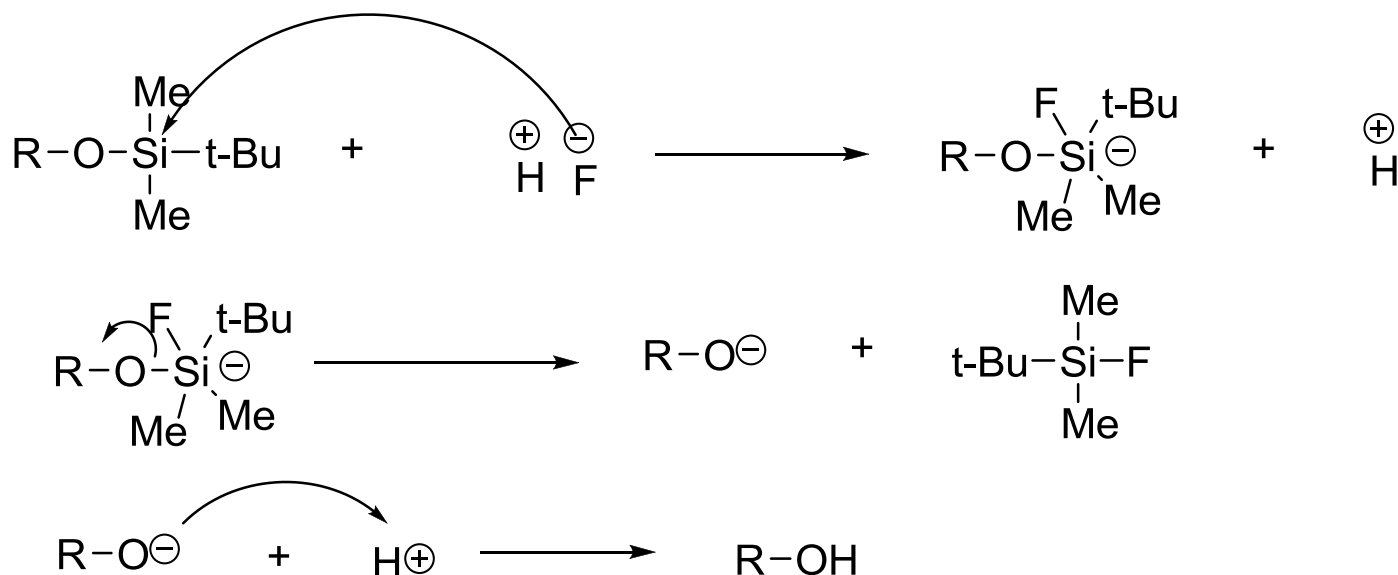


Protecting Groups for Alcohols

(Deprotection of Silyl Protecting Groups)

Cleavage

This takes advantage of the selective siliphilic property of fluoride ions.



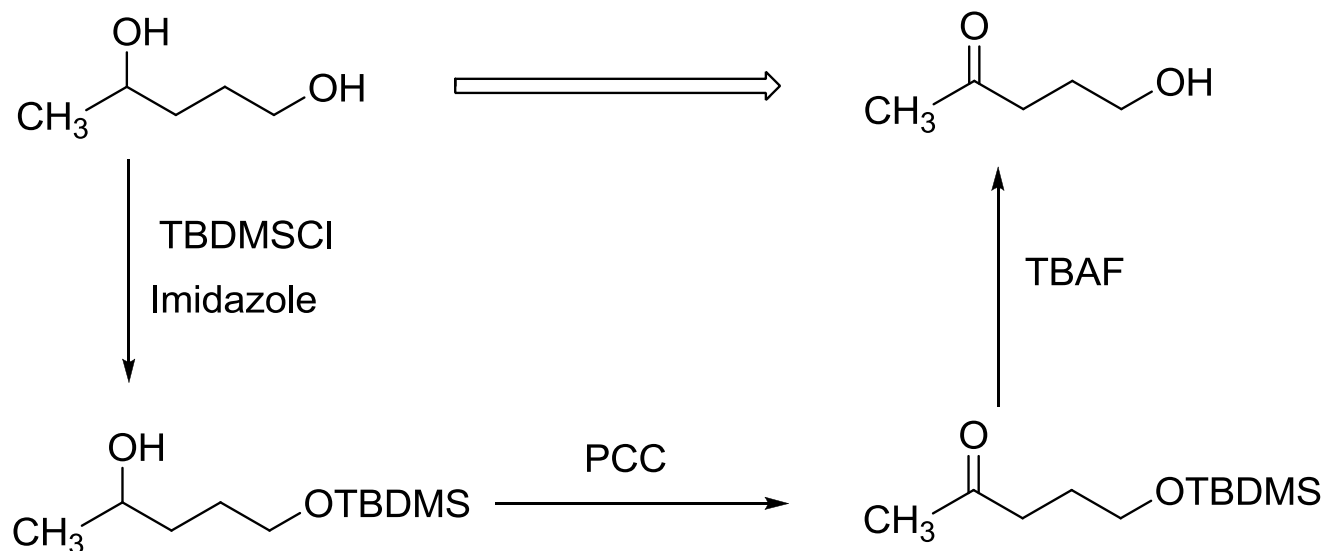
Fluoride sources:

- Hydrofluoric acid (HF)
- Tetrabutylammonium fluoride, $\text{Bu}_4\text{N}^+\text{F}^-$ (TBAF)

Protecting Groups for Alcohols

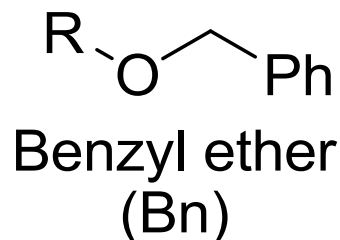
(Synthetic Applications using Silyl Protecting Groups)

The bulkiness of TBDMS and TBDPS ether protecting groups can be used to advantage to direct it to the least hindered primary hydroxyl group leading to selective protection of a primary hydroxyl group in the presence of a secondary hydroxyl group.

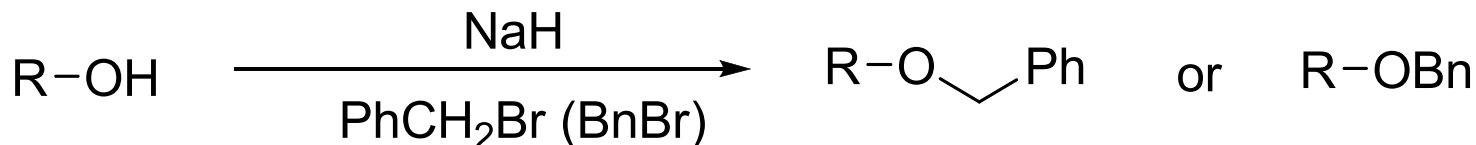


Protecting Groups for Alcohols

(Benzyl ether Protecting Groups)

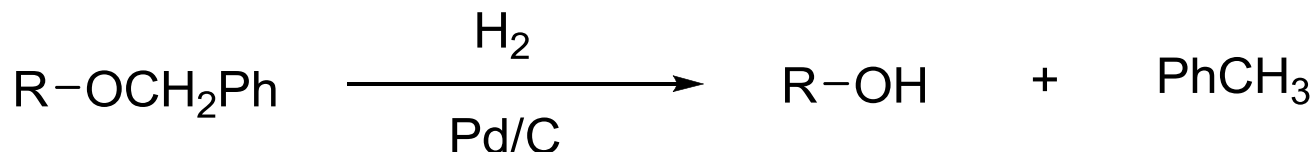


Formation



Cleavage

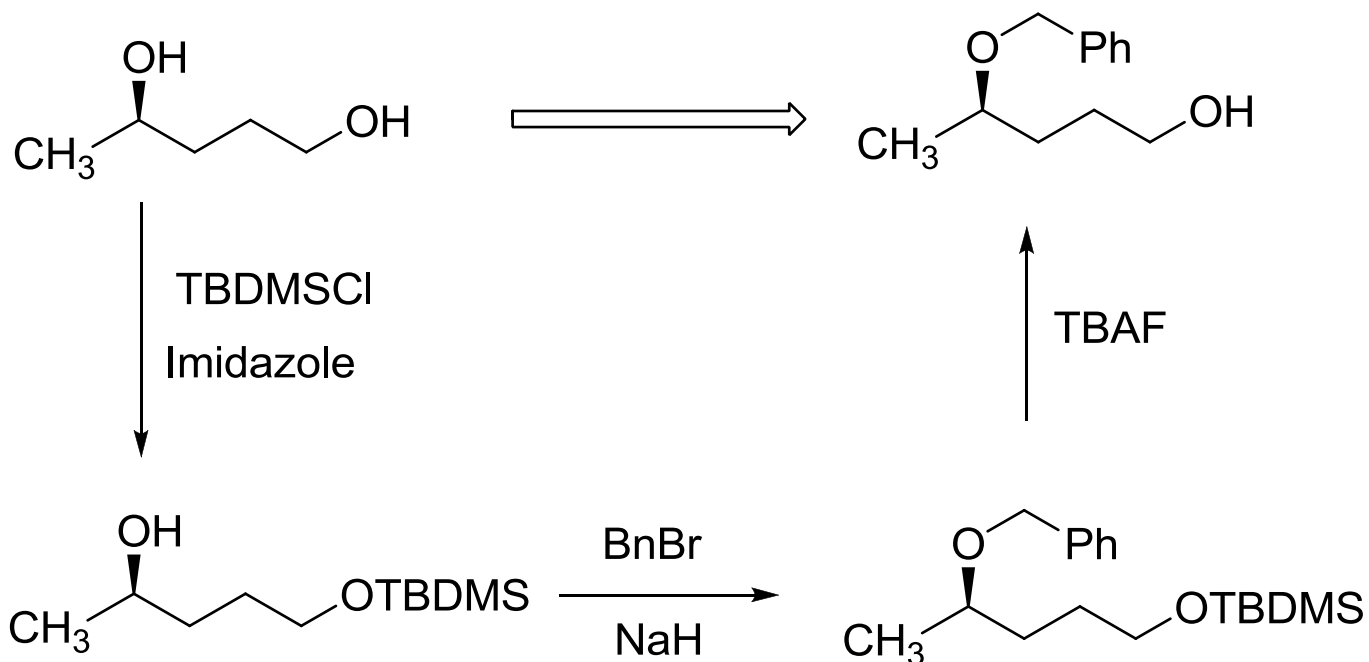
Although alkyl ethers are not commonly used as protecting groups for alcohols due to the harsh conditions required for their deprotection, benzyl ethers are unique since they can be easily be cleaved through hydrogenolysis.



Protecting Groups for Alcohols

(Perspectives in Synthesis)

Benzyl ether protecting groups can be used along with silyl ether protecting groups to protect poly alcohols during synthesis.



Note that whereas one can selectively protect a primary alcohol as a silylether in the presence of a secondary alcohol, such selectivity is not possible with benzyl ethers.

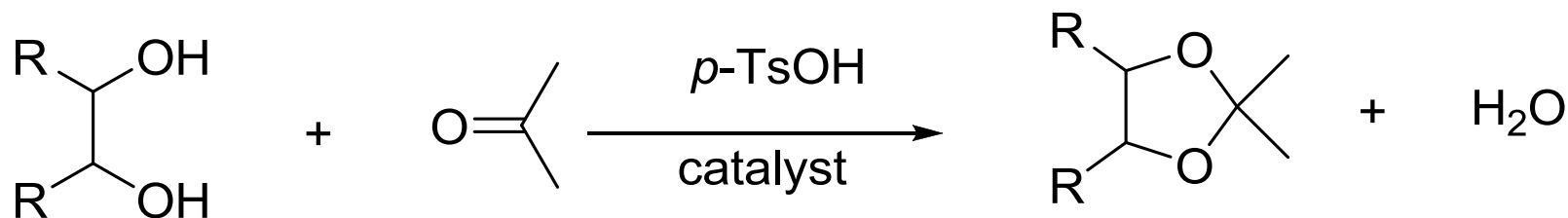
Protecting Groups for Diols

(Cyclic Acetal Protecting Groups)

Acetonide Protecting Groups for 1,2-Diols

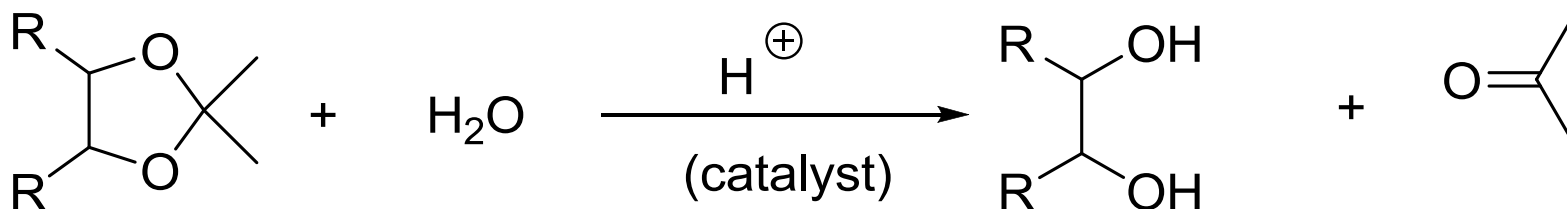
The formation of thermodynamically stable five membered ring systems is feasible.

Formation



Cleavage

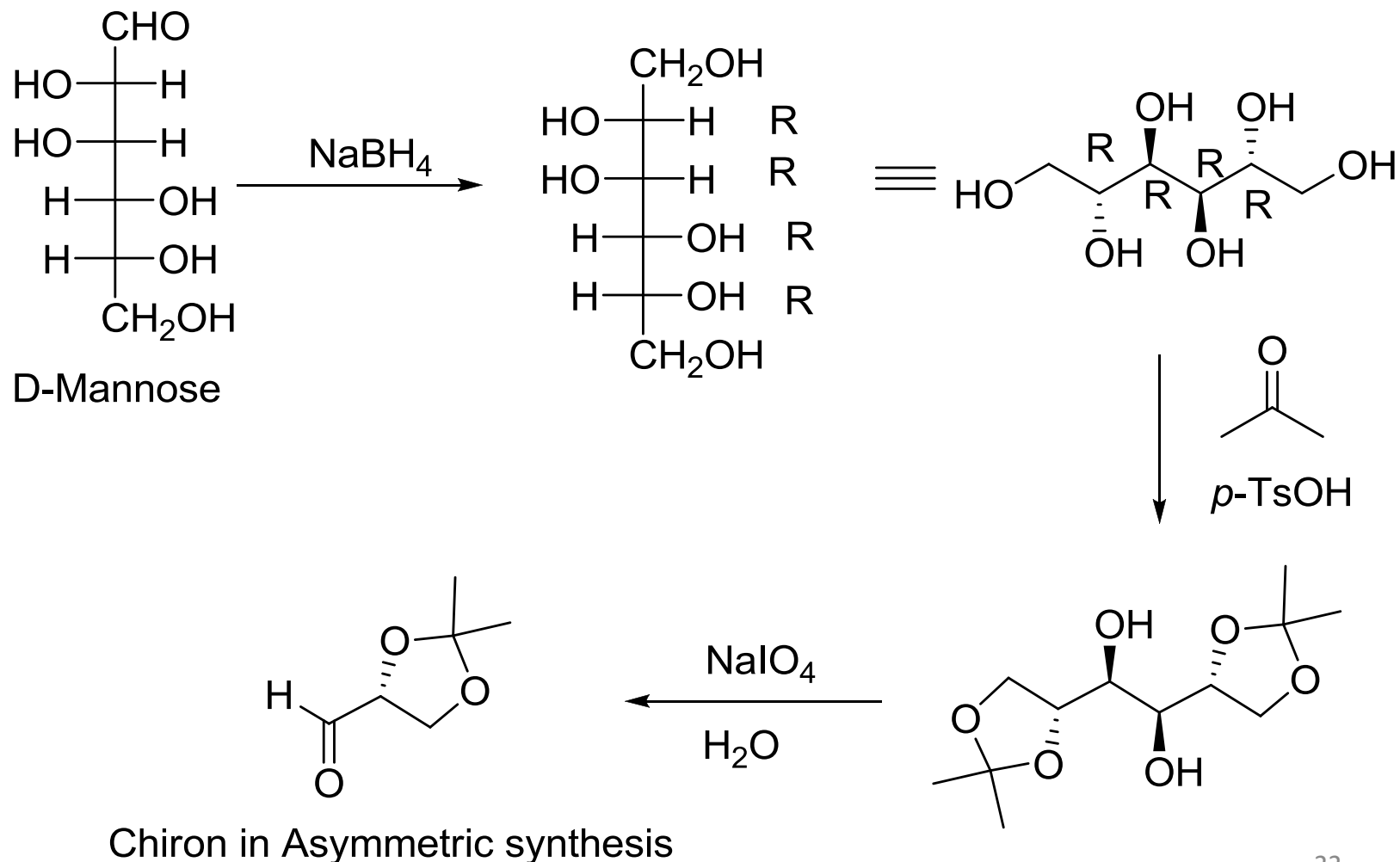
Exploits the reversibility of the acid-catalysed equilibrium.



Protecting Groups for Alcohols

(Perspectives in Synthesis)

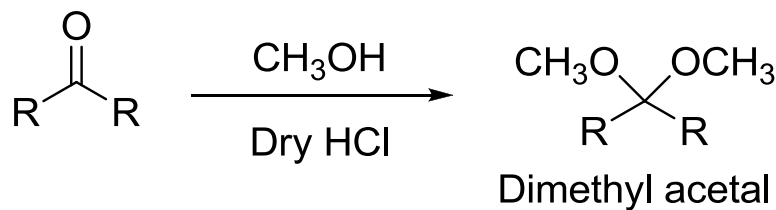
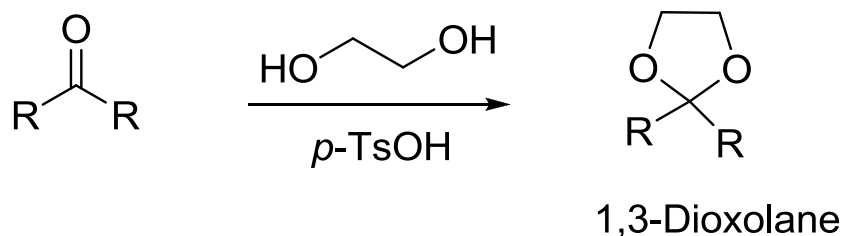
Synthetic Applications of Cyclic Acetal Protecting Groups



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

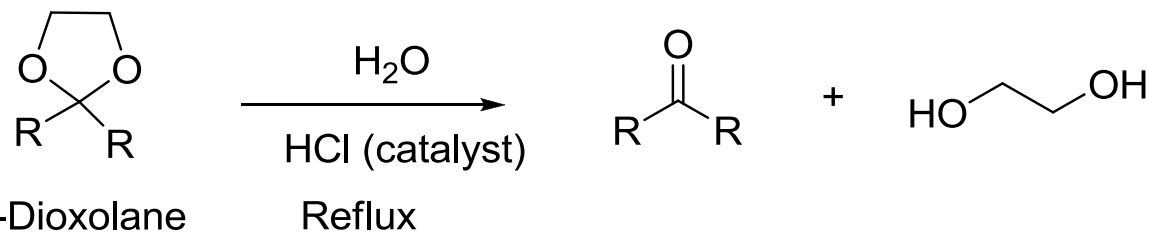
Acetal Protecting Group

Formation

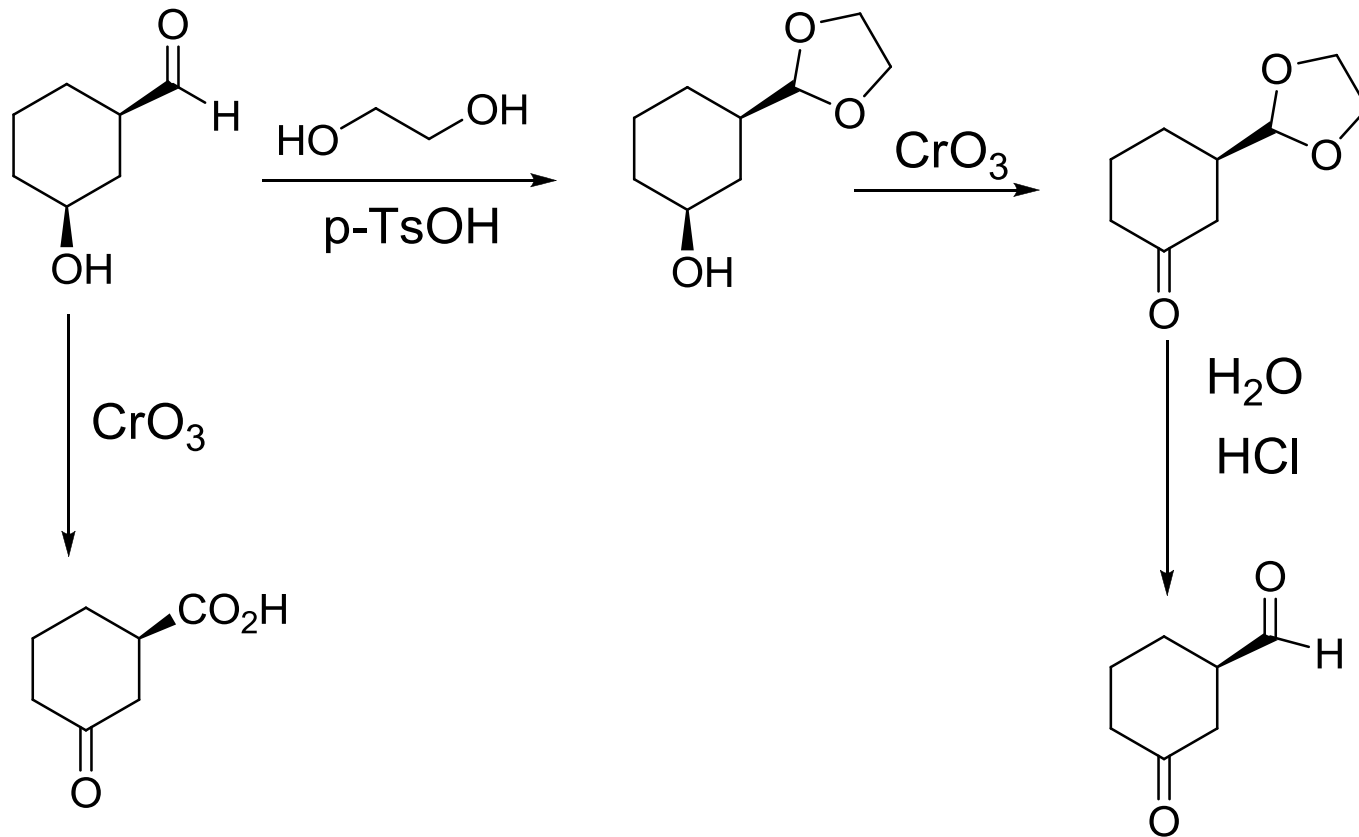


Cleavage

Acid catalysed hydrolysis (dilute HCl/ H₂O or TFA/ H₂O)



Protecting Groups for Aldehydes (Synthetic Perspectives)



Apart from the use of PCC, selective oxidation of an alcohol may be challenging to achieve in the presence of an aldehyde.

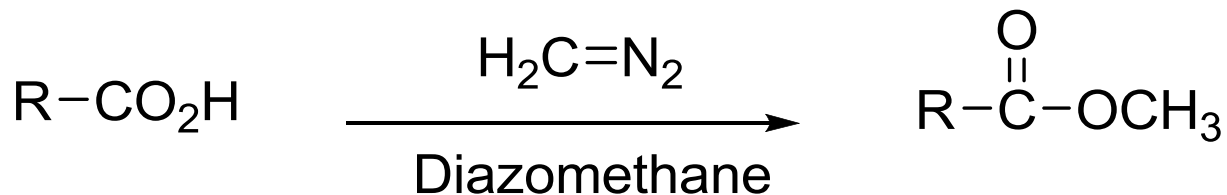
Protecting Groups for Carboxylic Acids (Esters)



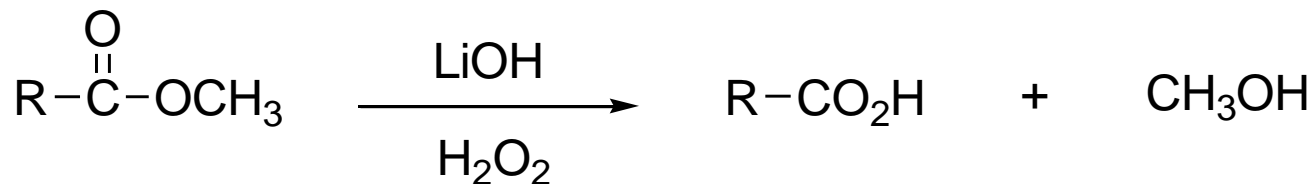
The common ester protecting groups for carboxylic acids are methyl, ethyl and benzyl esters.

Methyl Esters

Formation



Cleavage



Protecting Groups for Carboxylic Acids (Esters)

Methyl, ethyl and benzyl esters can be prepared based on the following rationale:



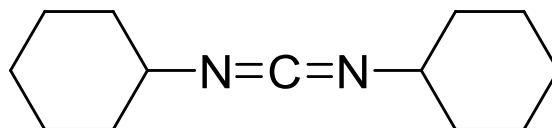
Fischer Esterification: Incompatible with α -enolizable carboxylic acids and other acid-labile protecting groups that may be already present in the polyfunctional molecule.

Best approach:

Milder conditions for esterification

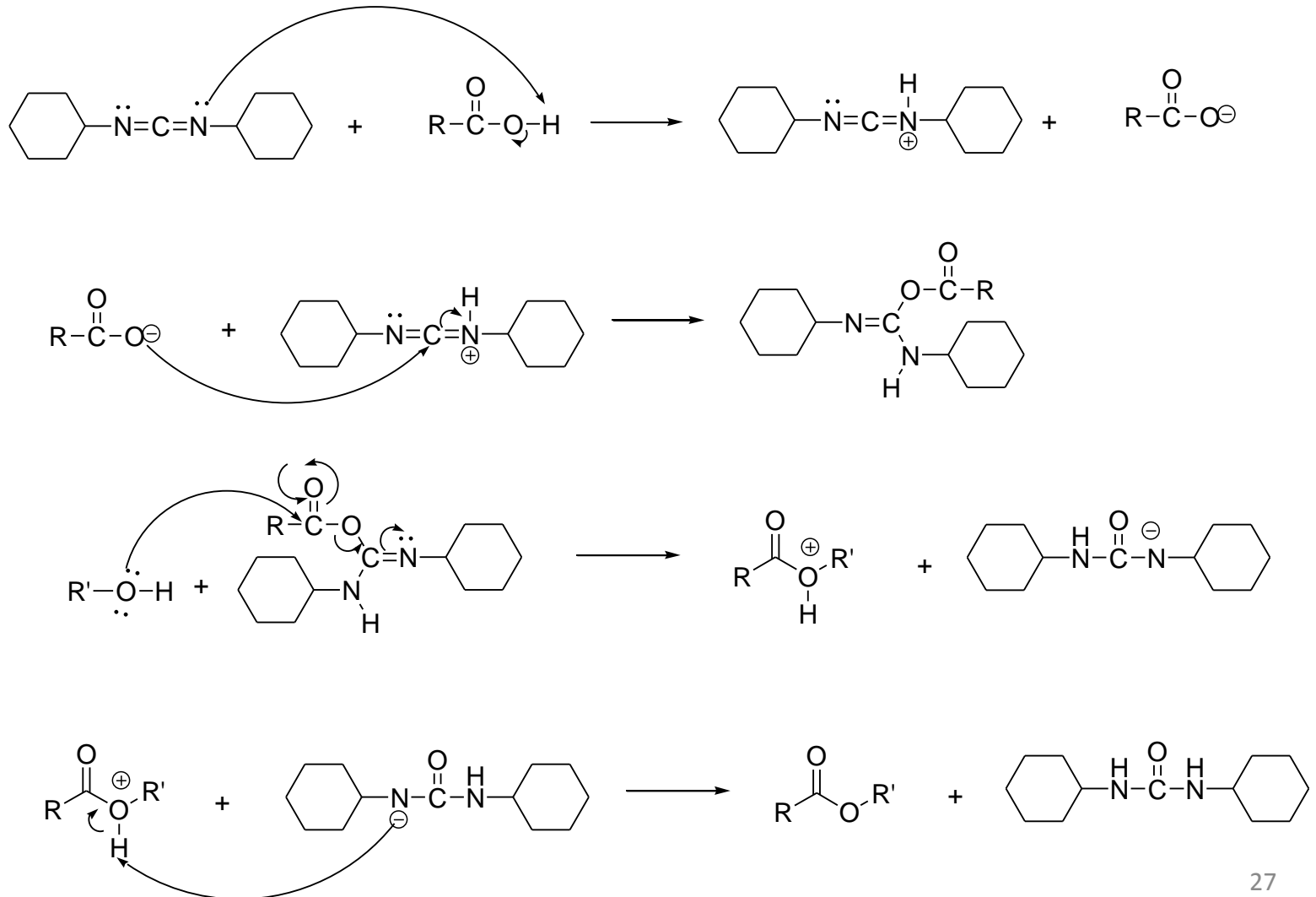


DCC = 1,3-Dicyclohexyl carbodiimide



Protecting Groups for Carboxylic Acids (Esters)

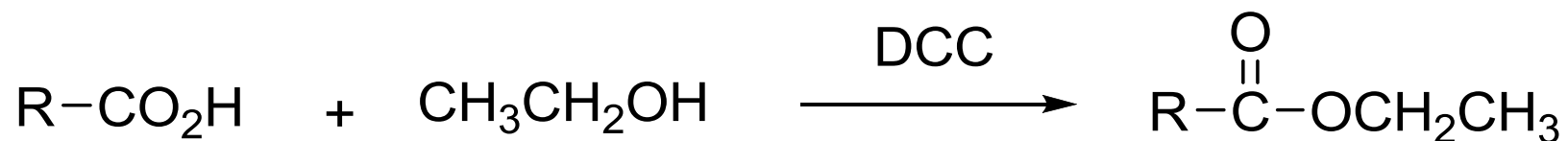
Mechanism of DCC coupling



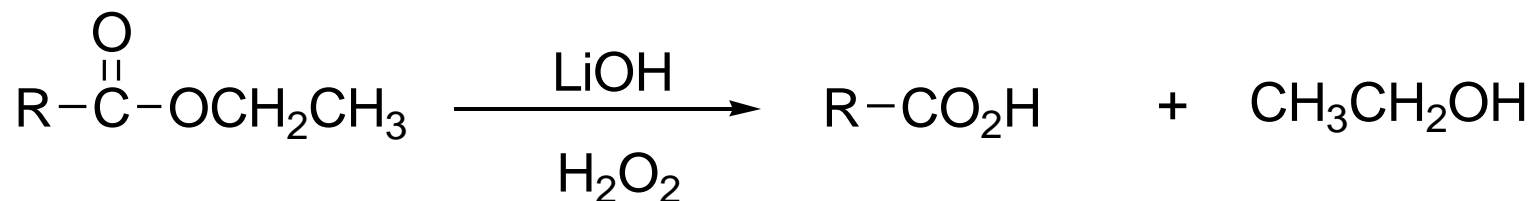
Protecting Groups for Carboxylic Acids (Esters)

Ethyl Esters

Formation



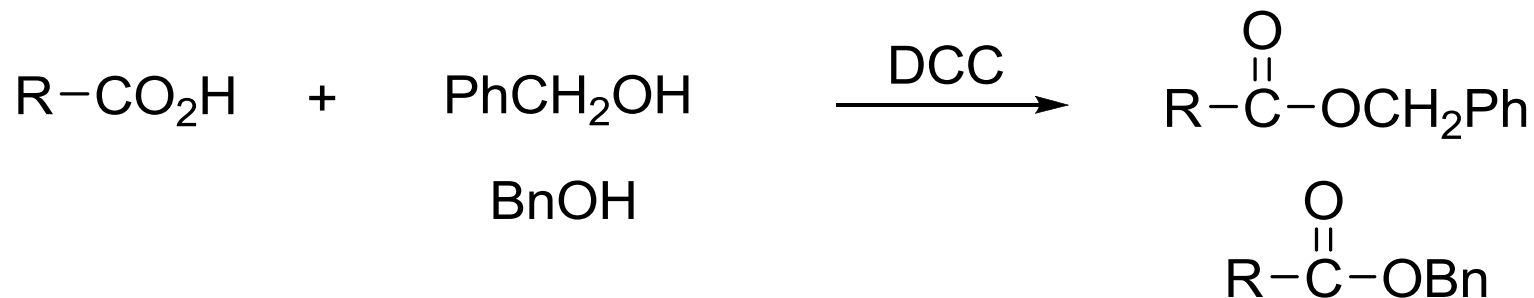
Cleavage



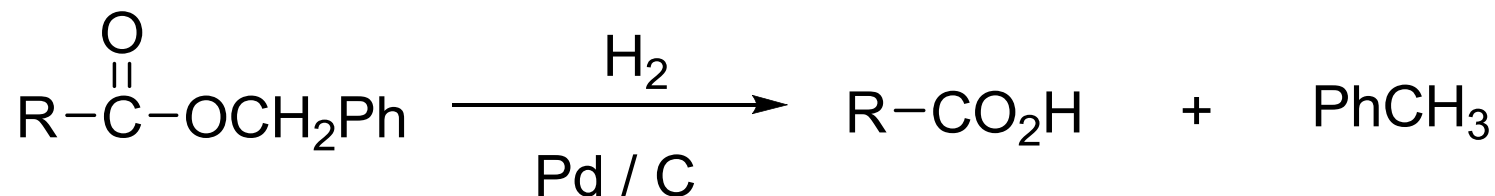
Protecting Groups for Carboxylic Acids (Esters)

Benzyl Esters

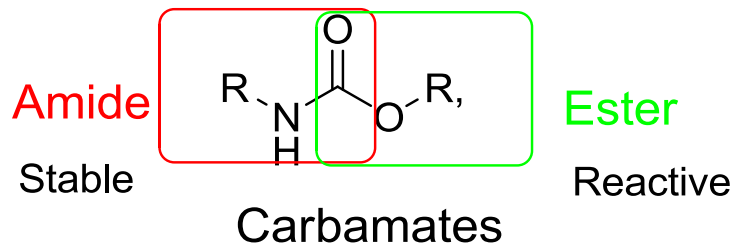
Formation



Cleavage: By hydrogenolysis



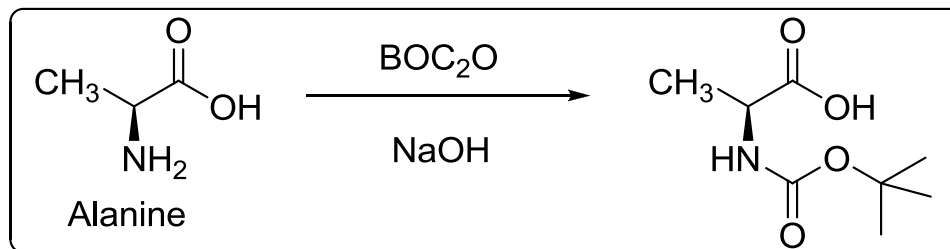
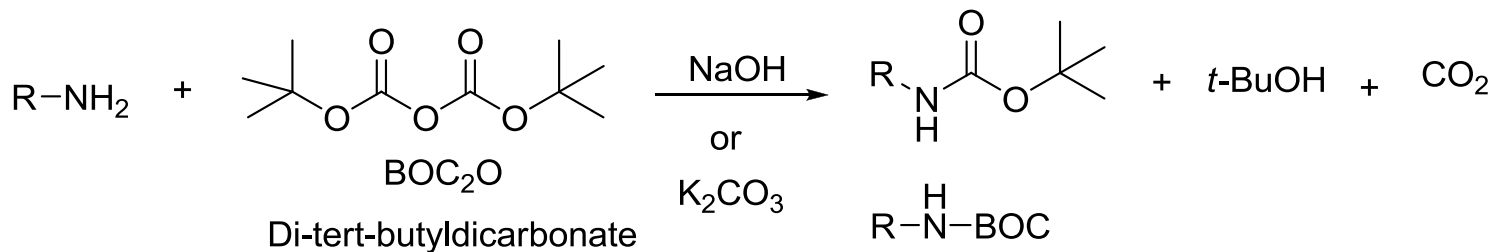
Protecting Groups for Amino Groups (Carbamate Protecting Groups)



Carbamates combine half of the stability of amides and half of the reactivity of esters.

Tert-Butyloxycarbonyl Protecting Group (BOC)

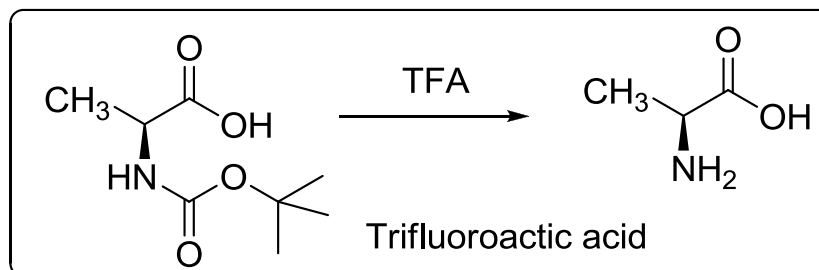
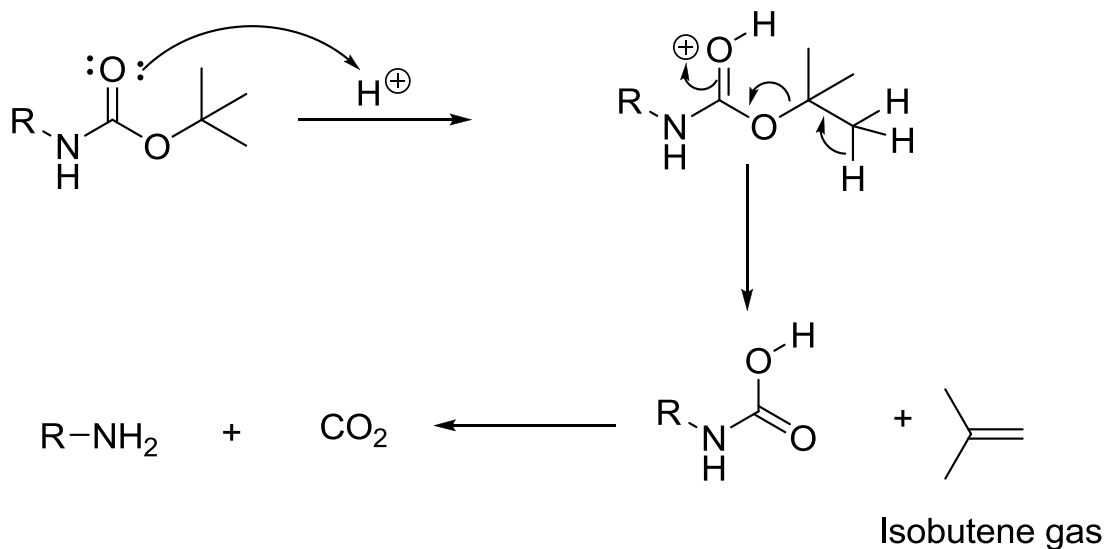
Formation



Protecting Groups for Amino Groups (Carbamate Protecting Groups)

Tert-Butyloxycarbonyl Protecting Group (BOC)

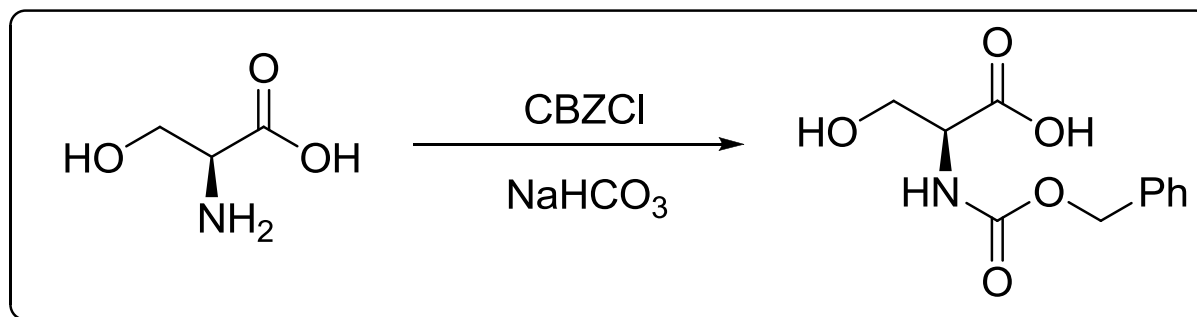
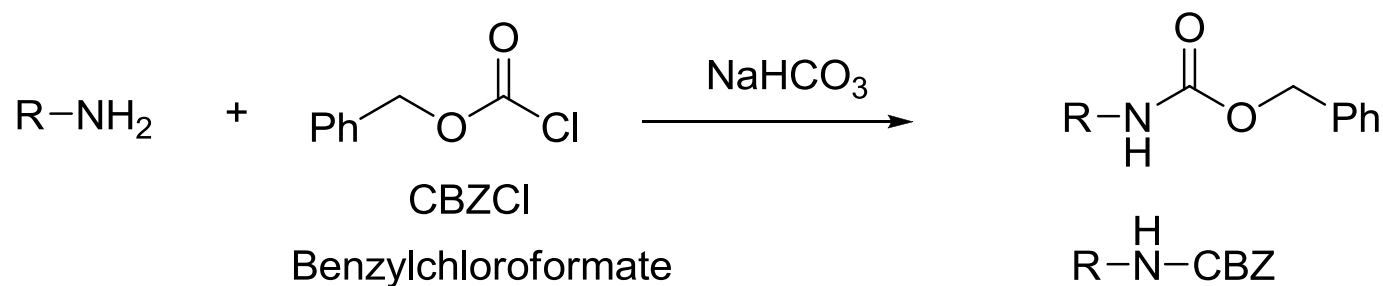
Cleavage: Accomplished under acidic conditions



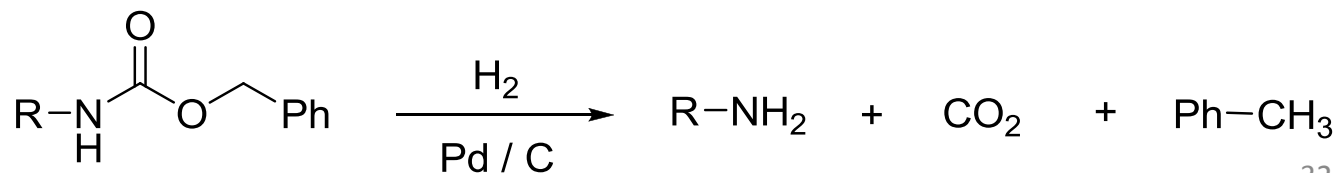
Protecting Groups for Amino Groups (Carbamate Protecting Groups)

Benzyloxycarbonyl Protecting Group (CBZ)

Formation



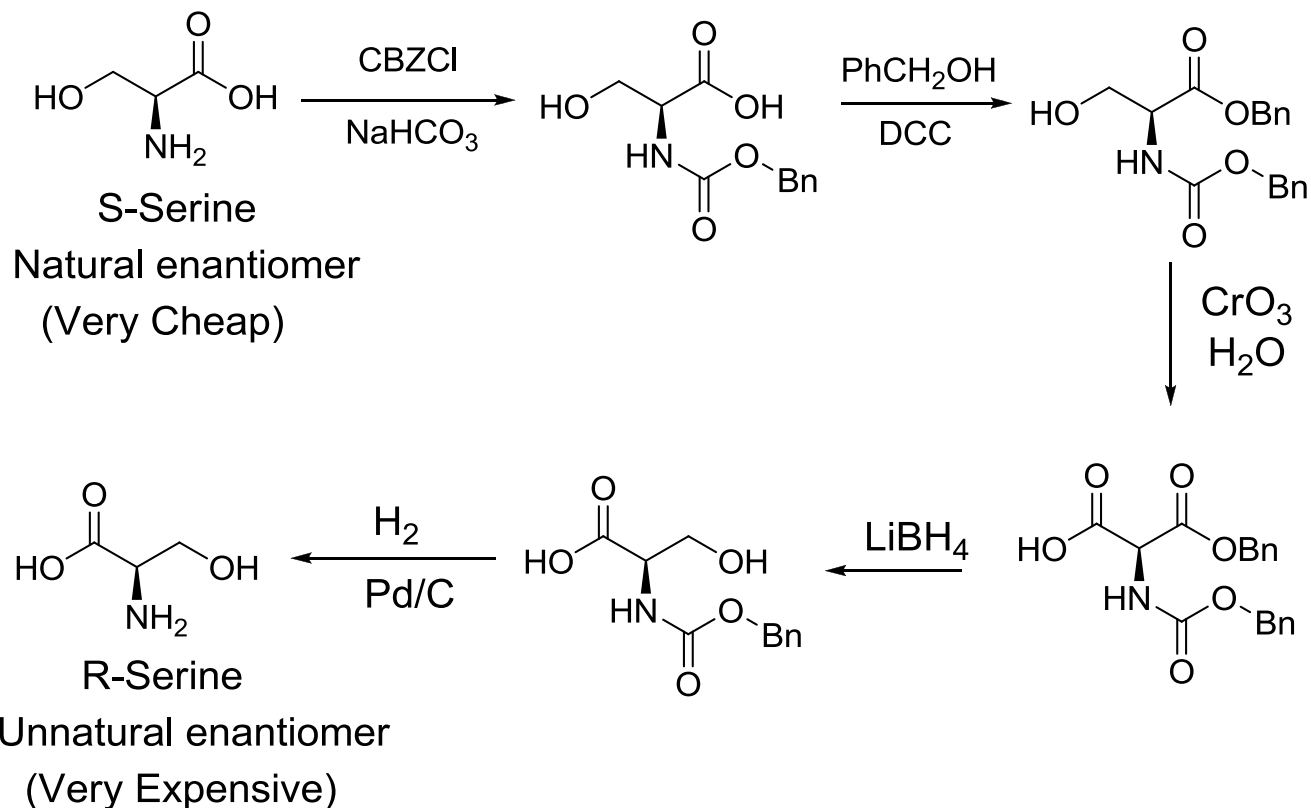
Cleavage



Protecting Groups for Carboxylic Acids

(Ester and Carbamate Protecting Groups)

Perspectives in the Synthetic Applications of the Ester and Carbamate Protecting Groups



LiBH₄ reduces the more reactive ester functional group leaving the less reactive carboxylic acid and carbamate groups unaffected.