Protecting Groups

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Protecting Groups

What are protecting groups?

Groups, which are temporarily attached to a functional group

Make these functional groups not to react under certain reaction conditions in subsequent steps.

Cleaved after its job is done

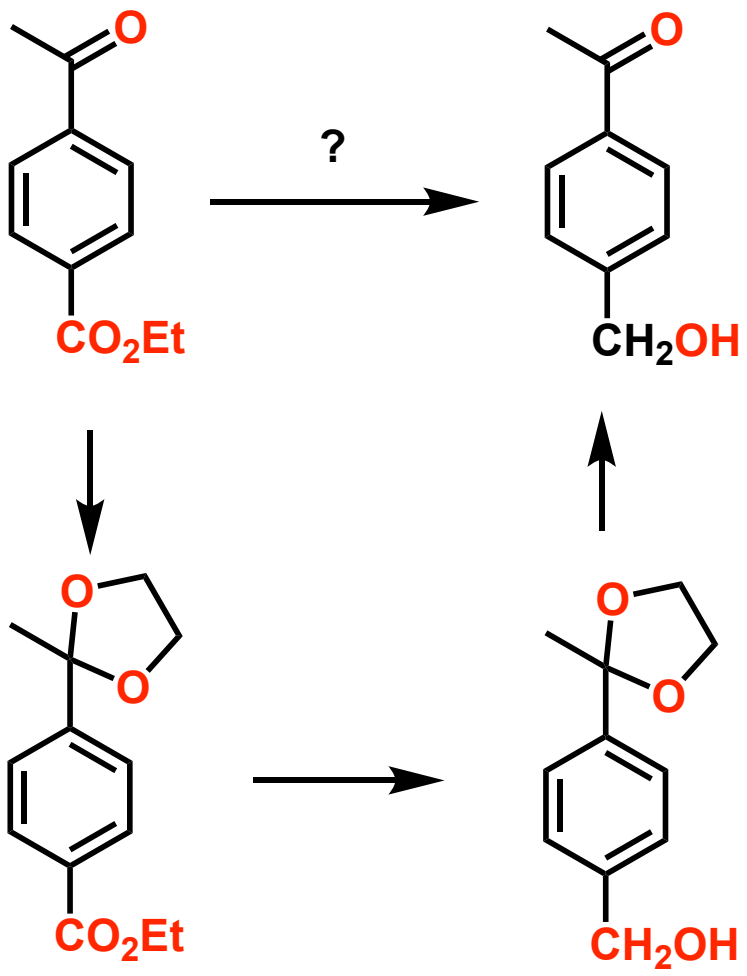
Why do you need protecting groups?

When a molecule has more than one functional group, then there is a likely possibility that functional groups interfering with each other while carrying out a reaction.

When principles of selectivity can't be applied, then protection of one functional group is really necessary to carry out a reaction on the other functional group.

Protecting Groups

Why do you need protecting groups?



Protecting Groups

Drawbacks

1. Two additional steps are required.

2. One for the introduction of the protecting group and the other for removing it.

3. So, more the number or protecting groups in your synthetic scheme, more the number of steps.

The best protecting group is "NO PROTECTING GROUP"

Protecting Groups

What is orthogonal protecting group strategy?

When more than one functional group of similar type, with very little difference in terms of reactivity, present in the molecule, selective protection of one can be achieved in the presence of other by taking advantage of steric effects, stereoelectronic effects etc.,

The development of such orthogonal protecting group strategies makes it possible to remove one set of protecting groups, in any order, using reagents and conditions that do not affect the protecting groups in other sets.

This orthogonal protecting group strategy is regularly utilized in the synthesis oligosaccharides where more number of hydroxyl groups with subtle difference in reactivity are present.

Protecting Groups

Types of Protecting Groups

Permanent: These are stable protecting groups, survives many steps in a long synthetic route (**early introduction & late removal**). These protecting groups are used for functional groups which require no manipulation for most of the steps

Temporary: These protecting groups (as the name suggests) should be selectively installed and removed as and when required without affecting the **permanent protecting groups**.

Protecting Groups

Criteria for selecting protecting groups

Should be cheap & commercially available

Should be easily introduced under milder conditions

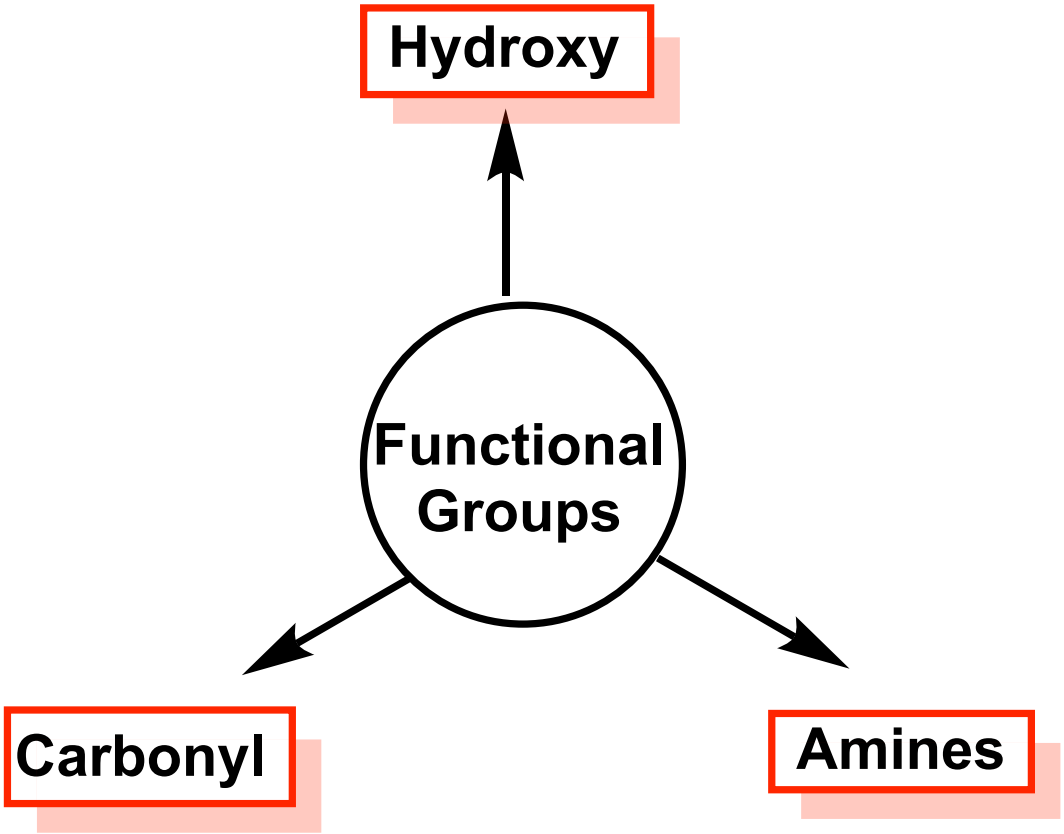
Should not create any additional stereocenters

Should be stable throughout the reaction, work up and purification

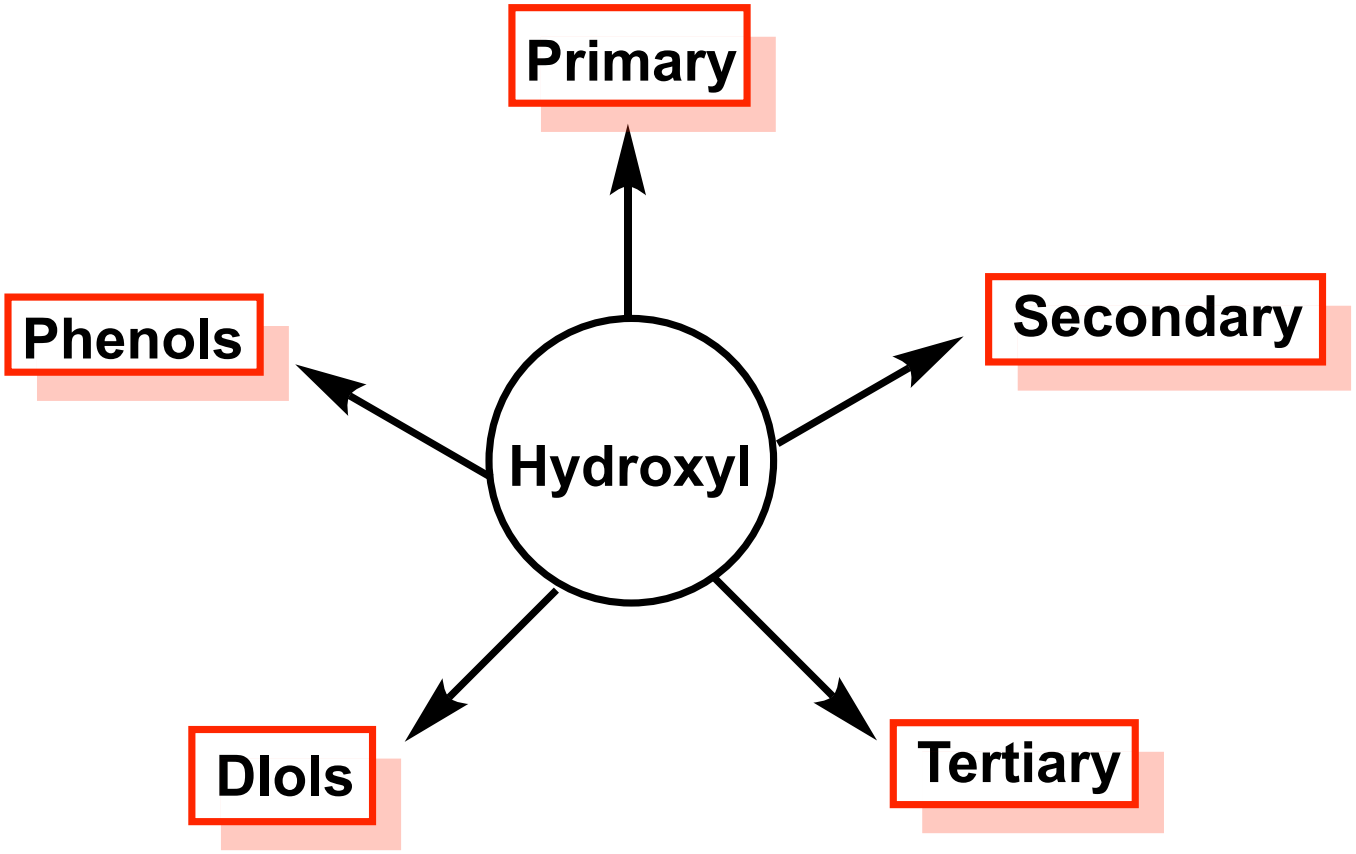
Should be easily removed under milder conditions

Byproducts should be easily separated from the required product

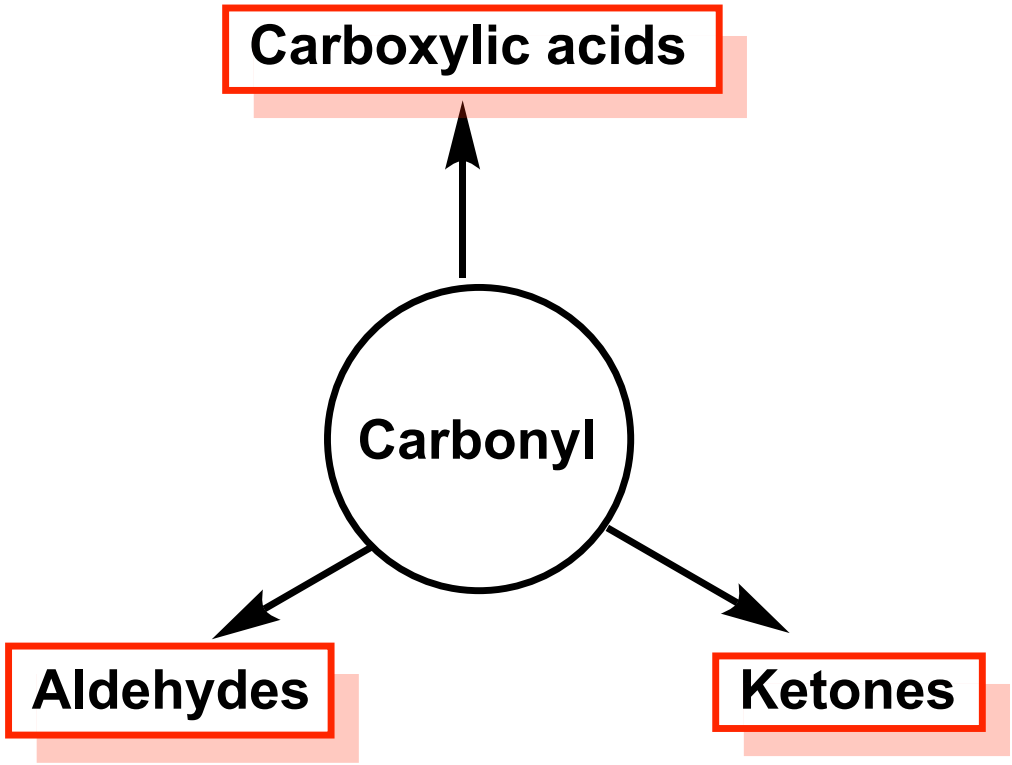
Functional Groups



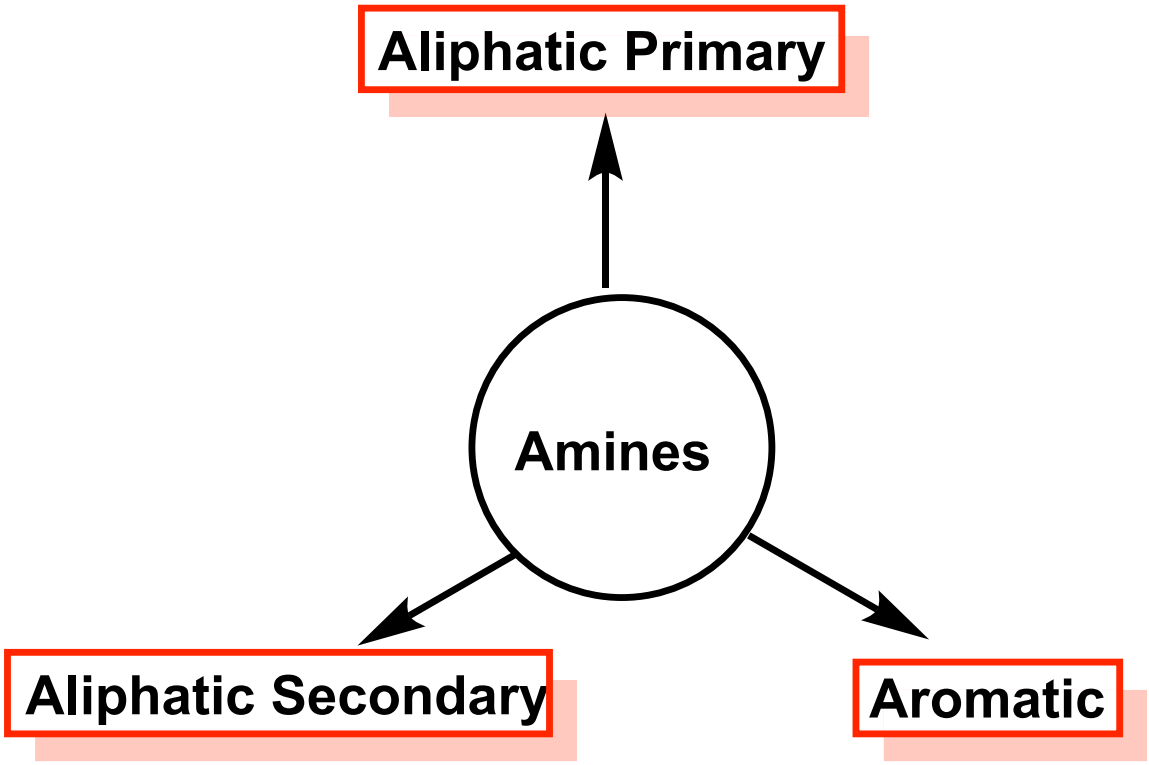
Hydroxyl Group



Carbonyl Group



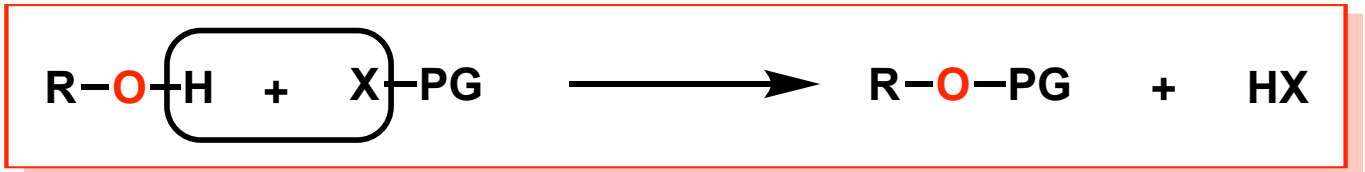
Amines



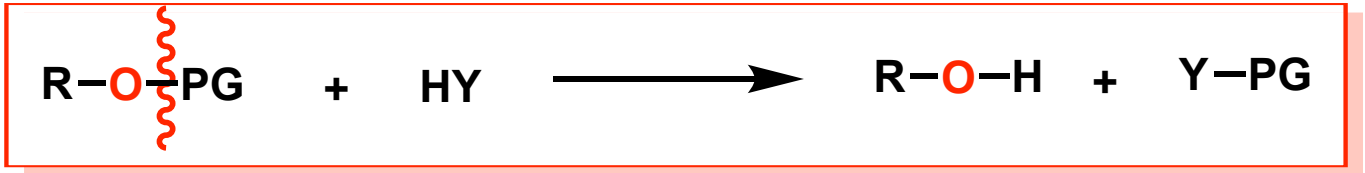
Protecting Groups for Alcohols

PG for Alcohols

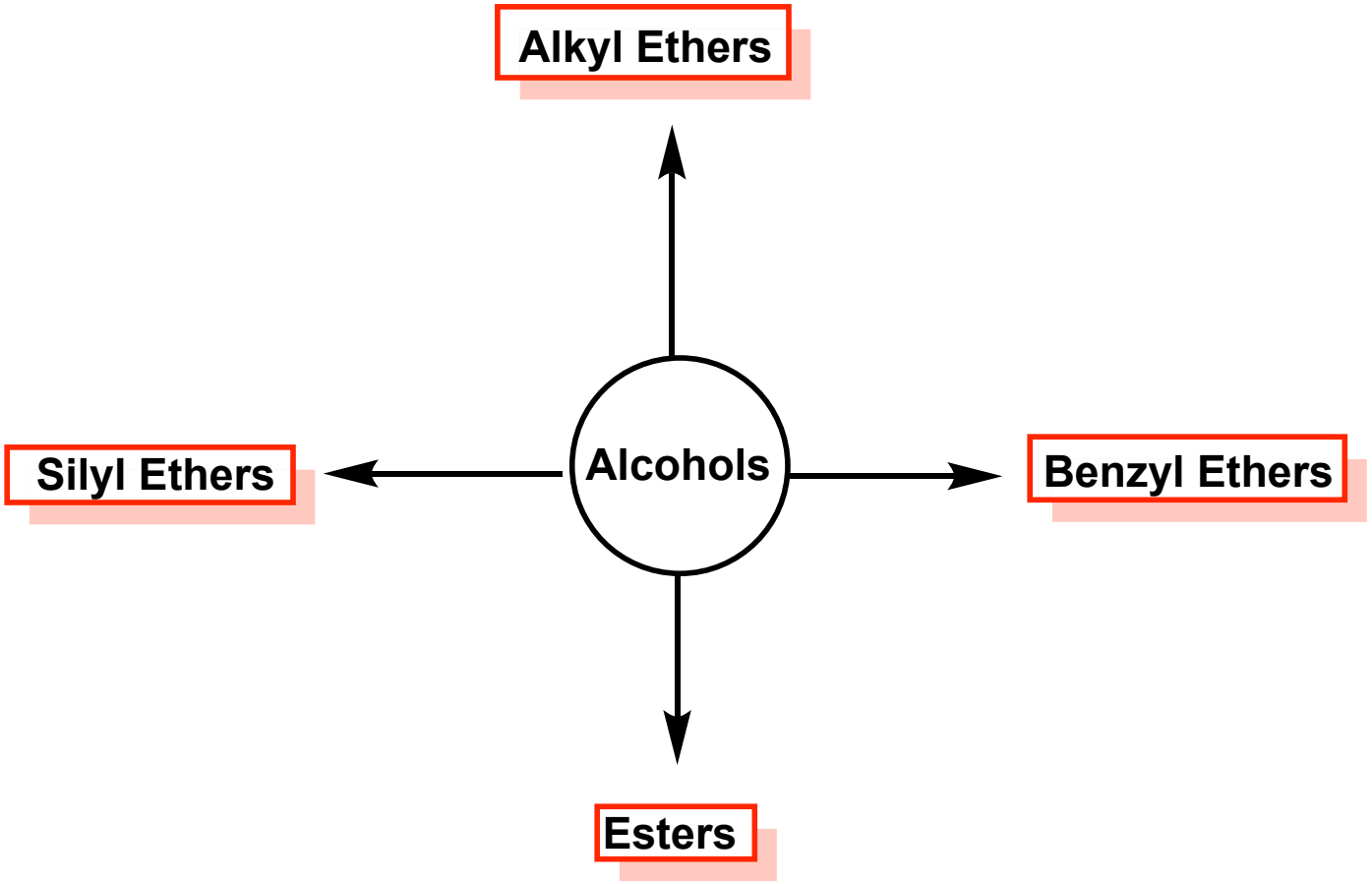
Introduction of protecting groups



Removal of protecting groups

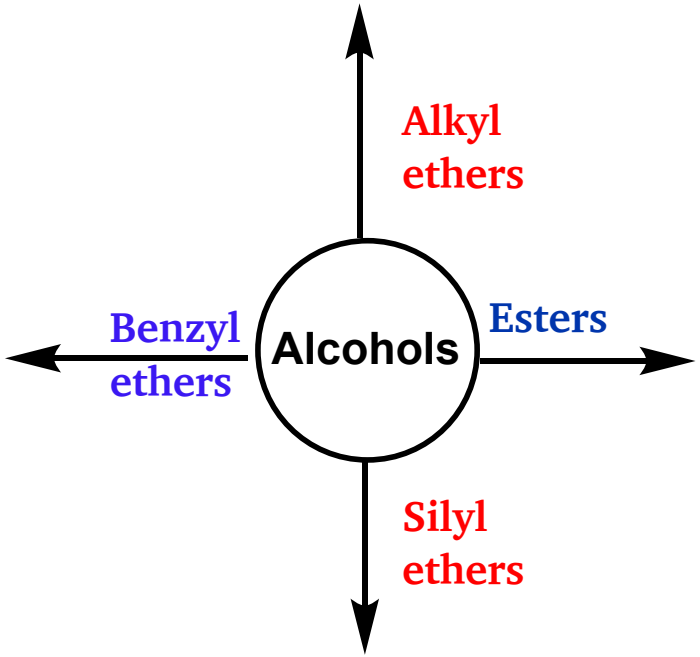


PG for Alcohols



PG for Alcohols

ROMe, ROMOM, ROMEM, ROBOM, ROTHP, ROEE

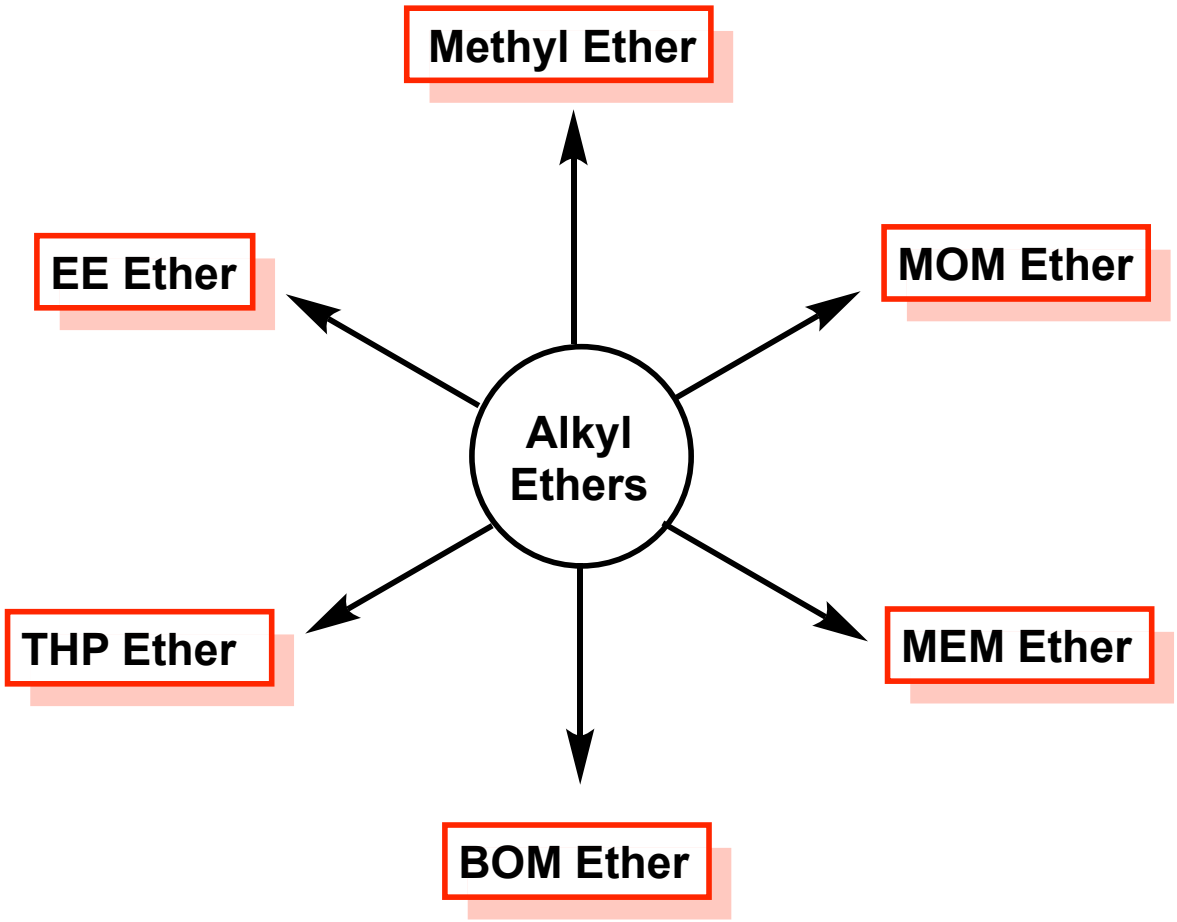


ROBn, ROPMB ROTr
RONAP, ROMeTr,
RO-*o*-NO_2Bn,
RO-*p*-NO_2Bn,

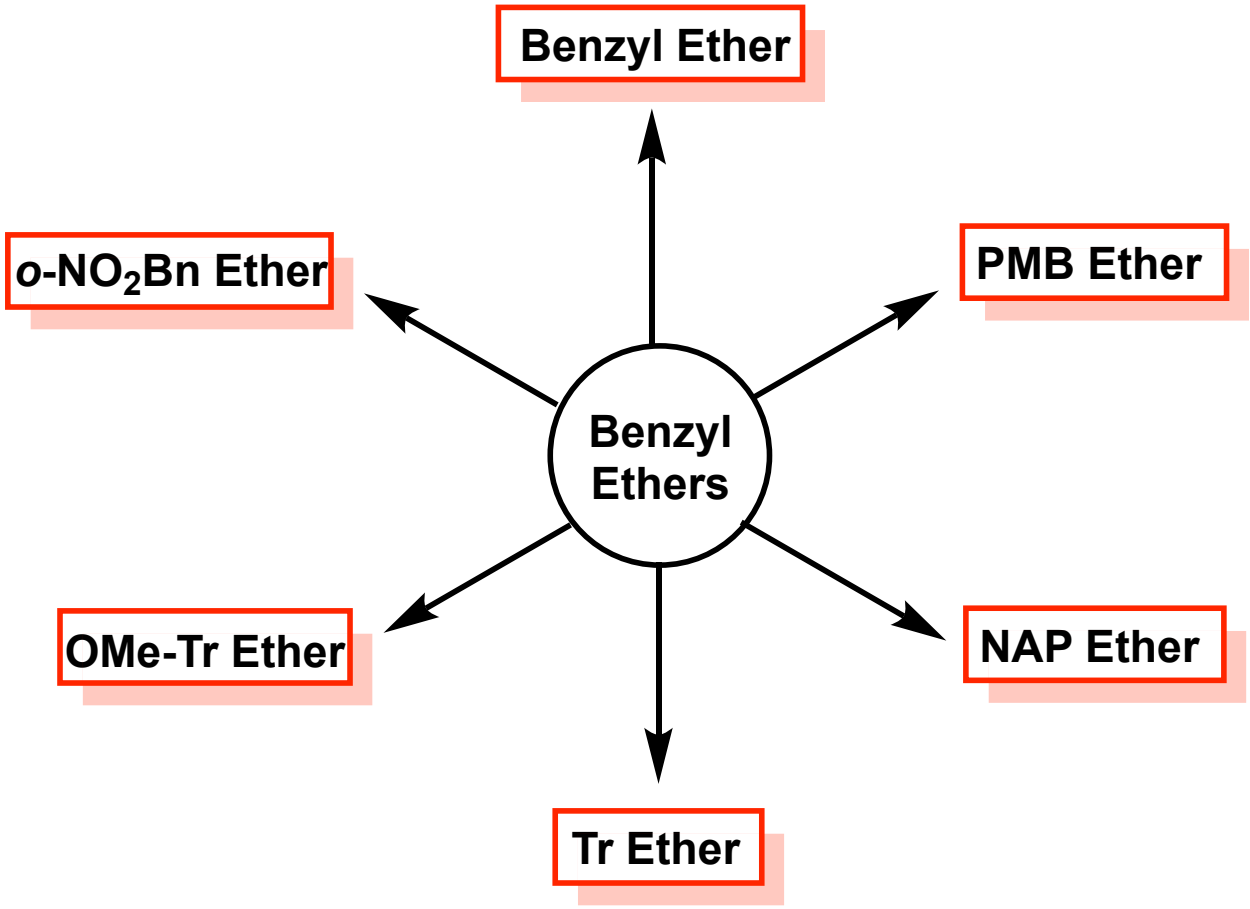
ROAc, ROAcCl, ROBz,
ROPiv, $ROCOCF_3$

ROTMS, ROTES ROTIPS, ROTBS, ROTBDPS

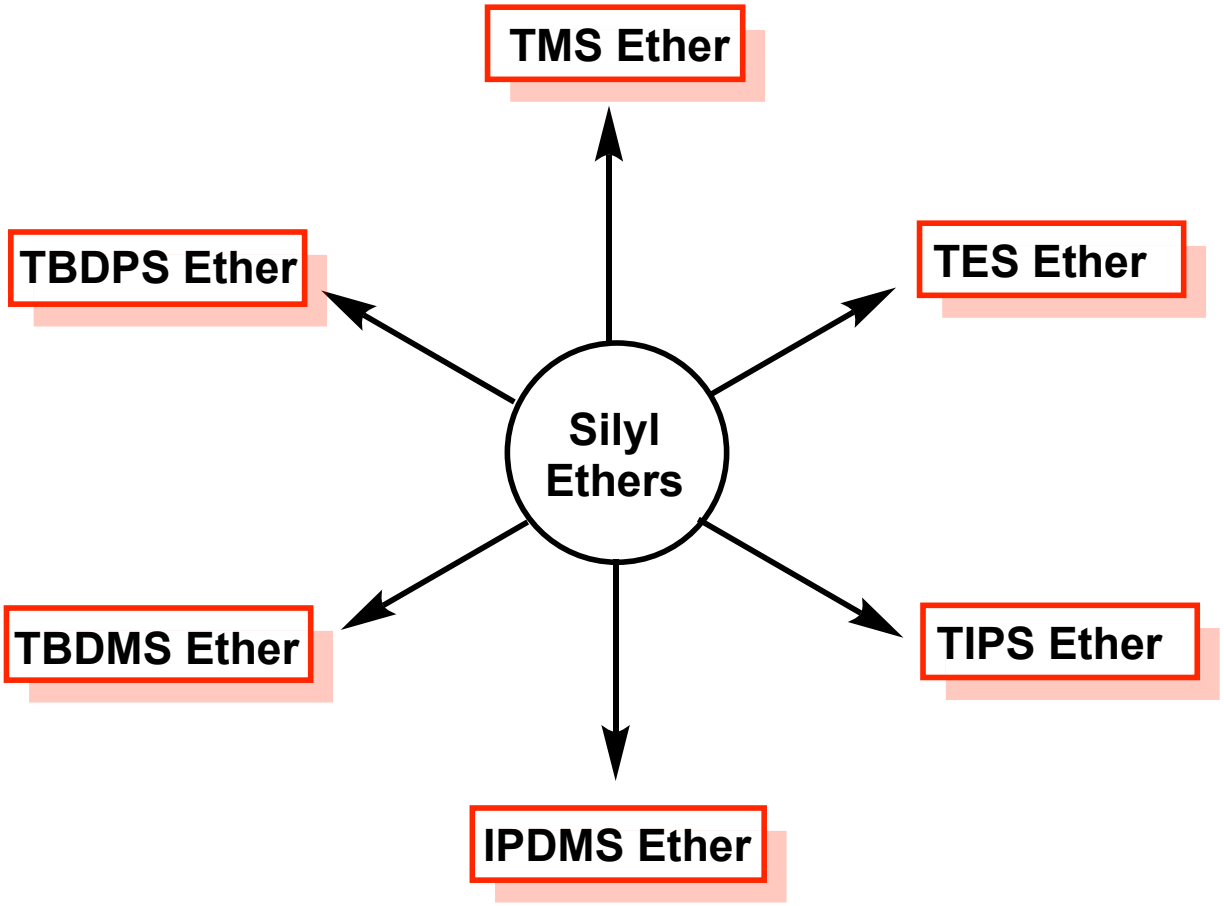
Alkyl Ethers



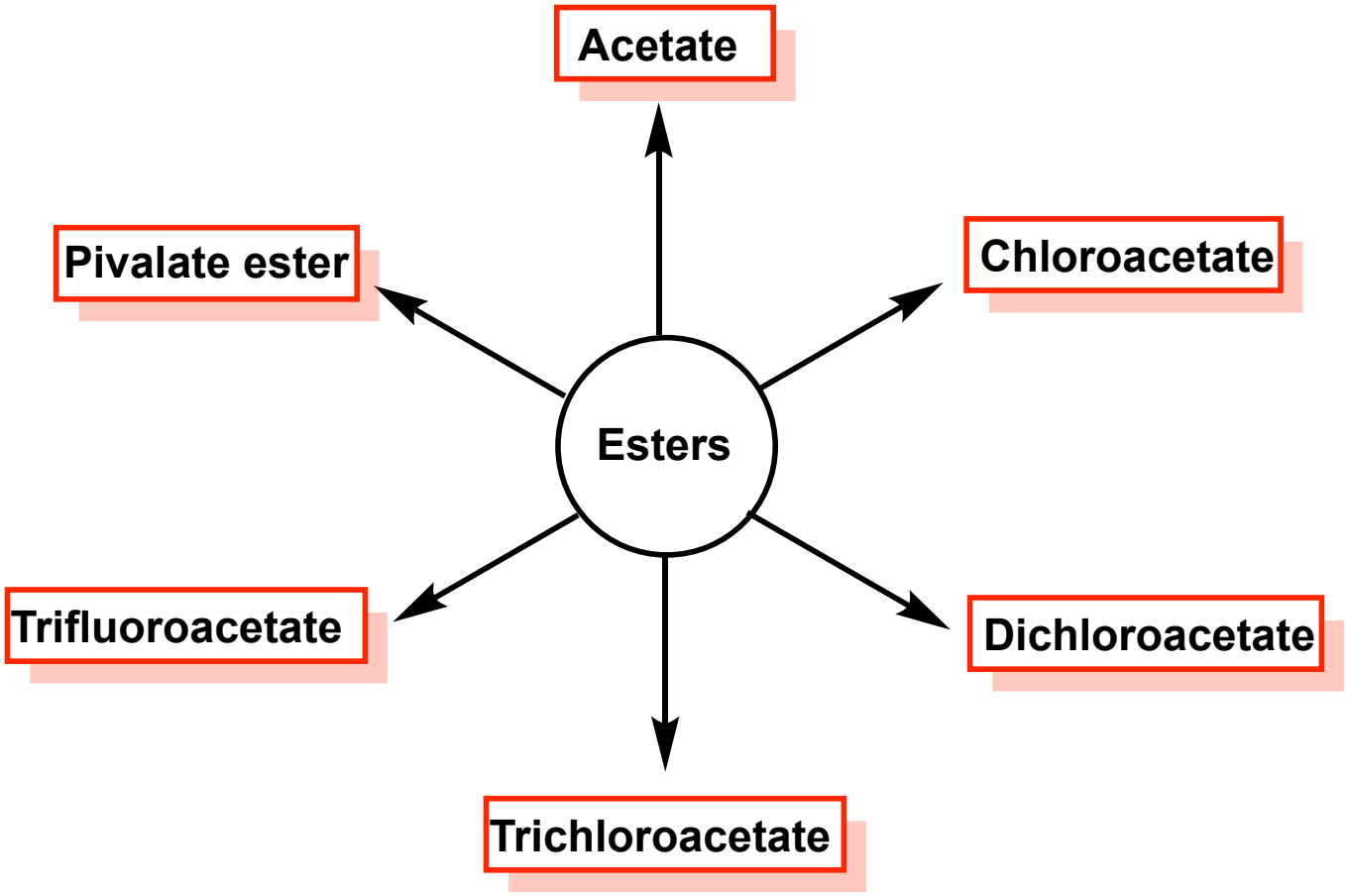
Benzyl Ethers



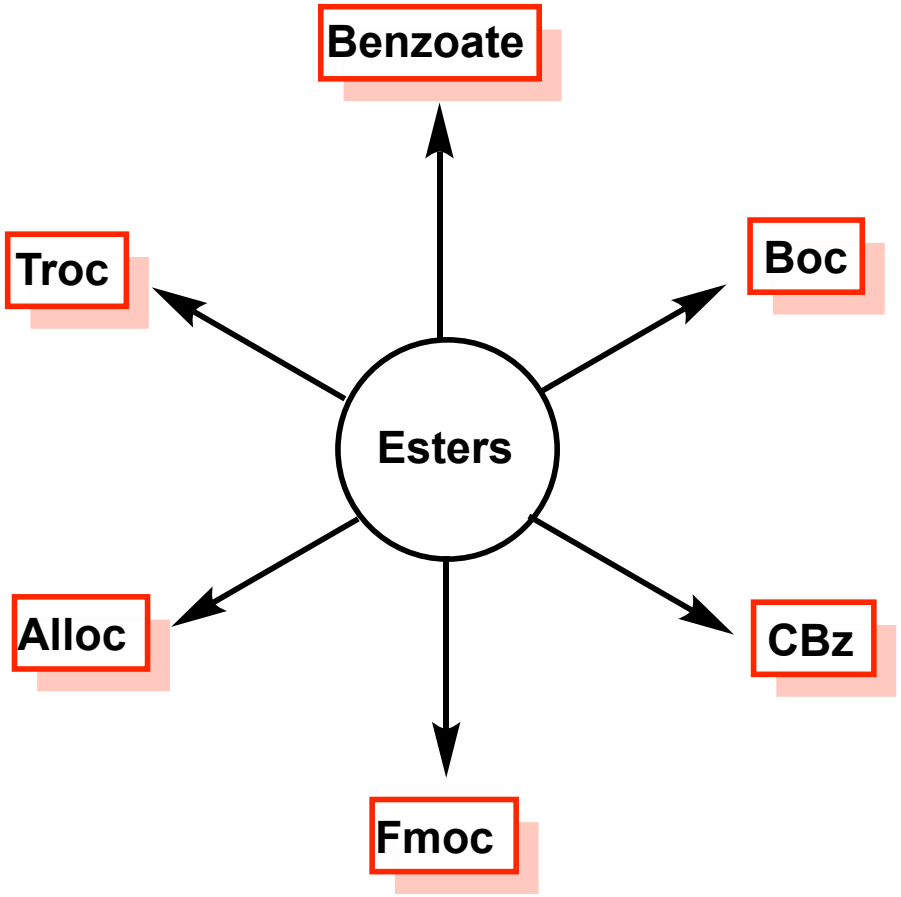
Silyl Ethers



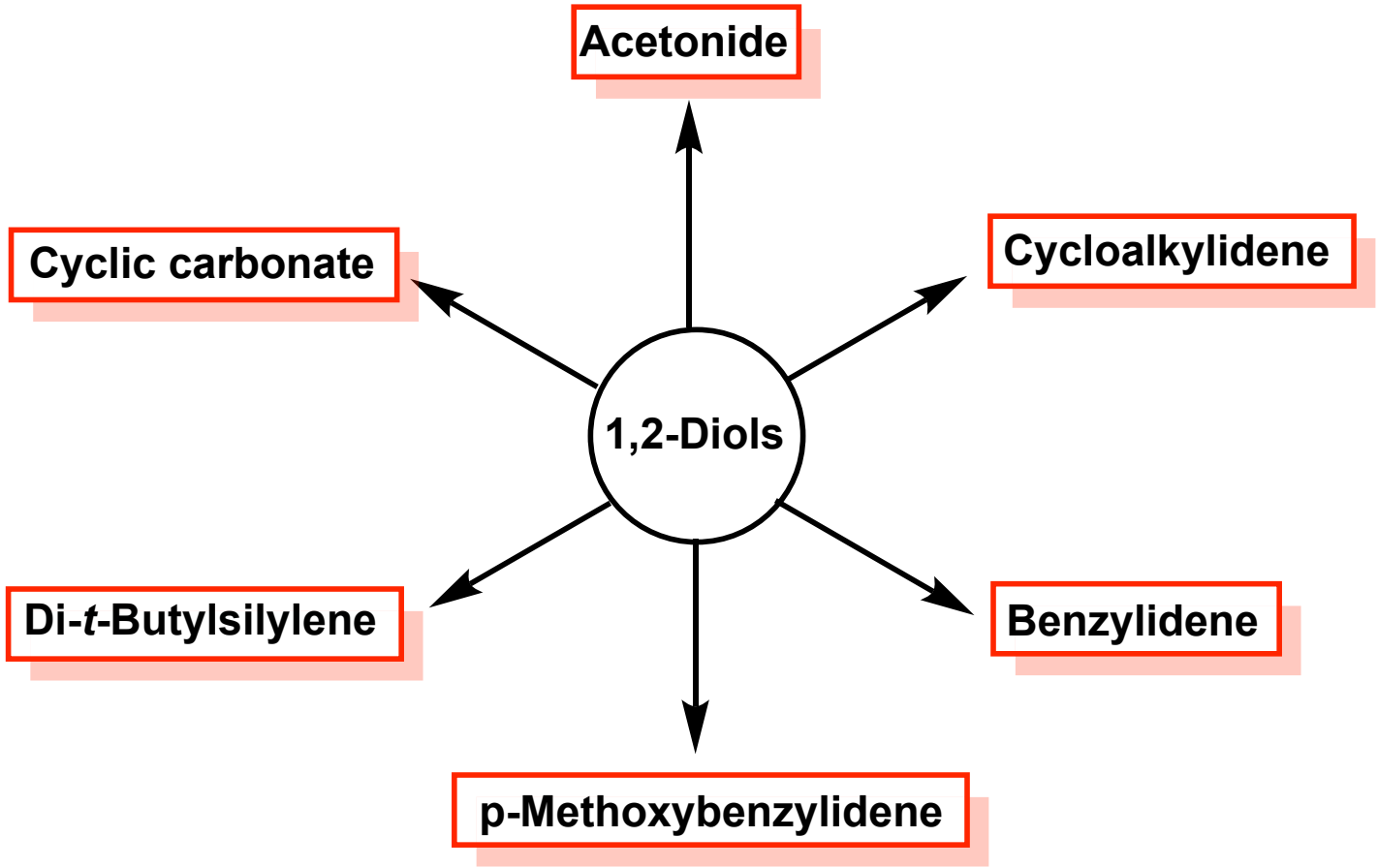
Esters


Acetate
Pivalate ester
Chloroacetate
Esters
Trifluoroacetate
Dichloroacetate
Trichloroacetate

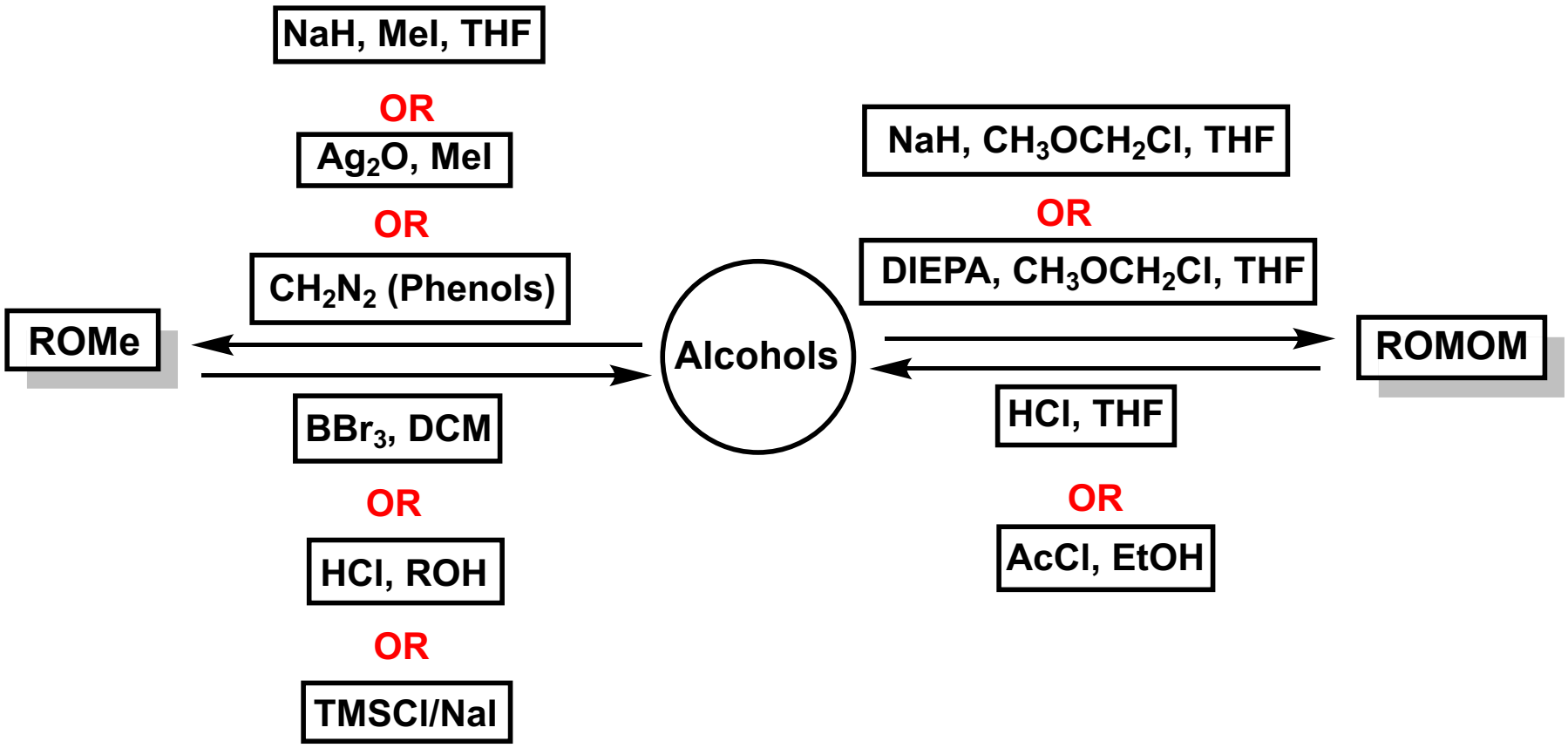
Esters



1,2-Diols


Acetonide
Cyclic carbonate
Cycloalkylidene
1,2-Diols
Di-t-Butylsilylene
Benzylidene
p-Methoxybenzylidene

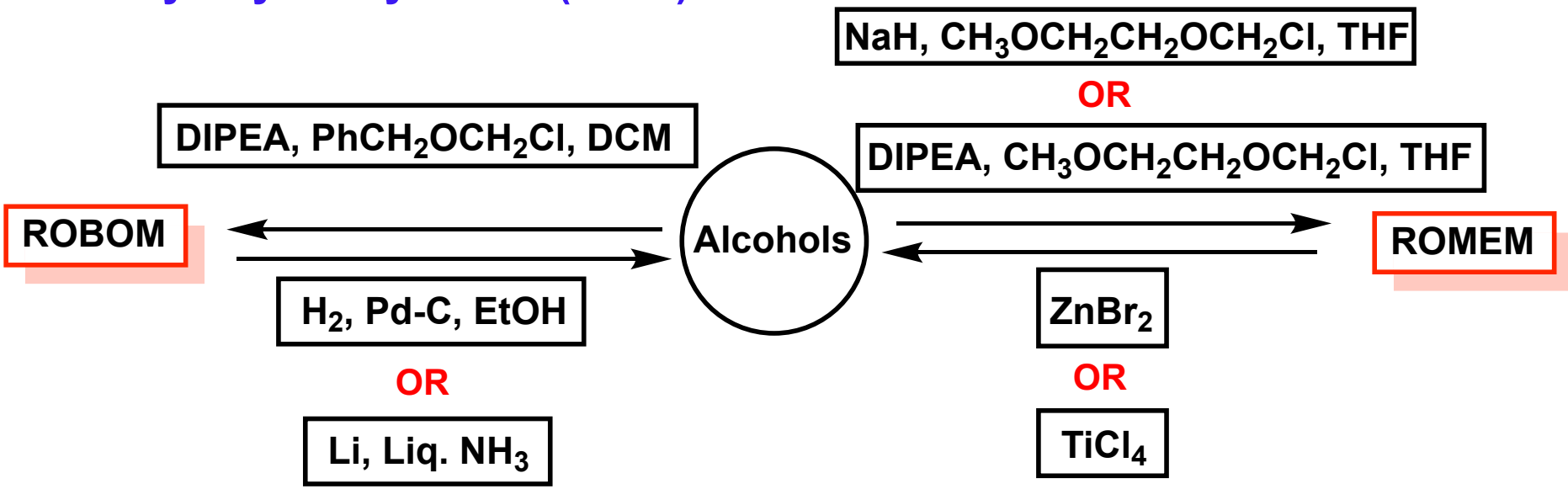
Alkylethers



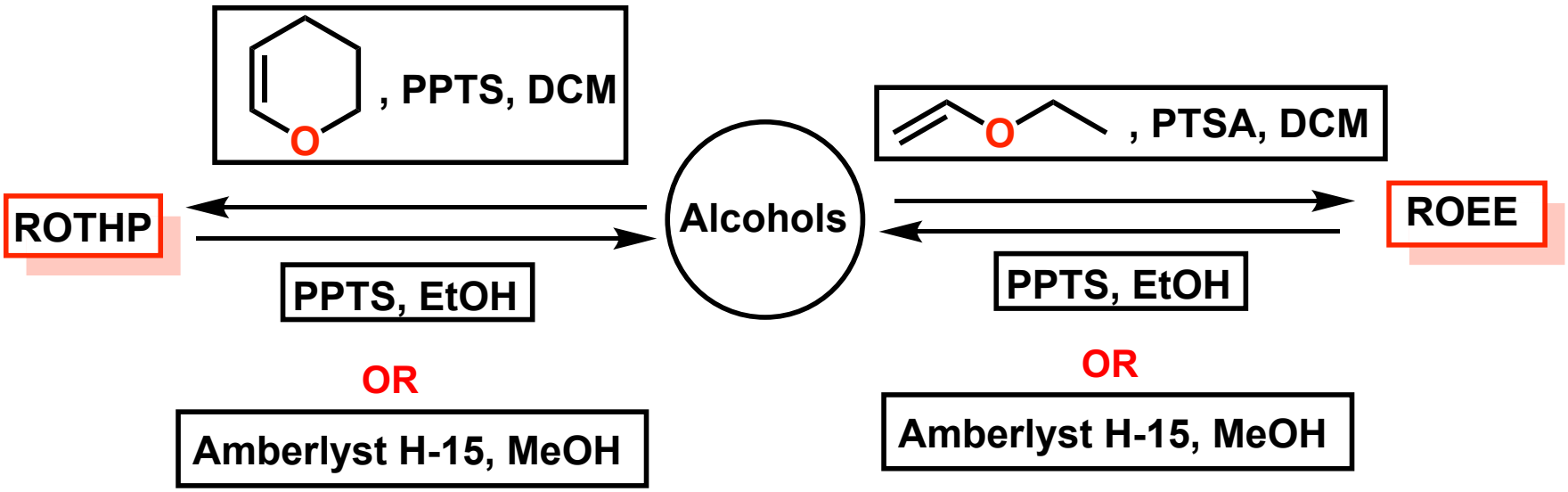
Difficult to cleave except for phenols

Alkylethers

Benzyloxymethyl ether (BOM)

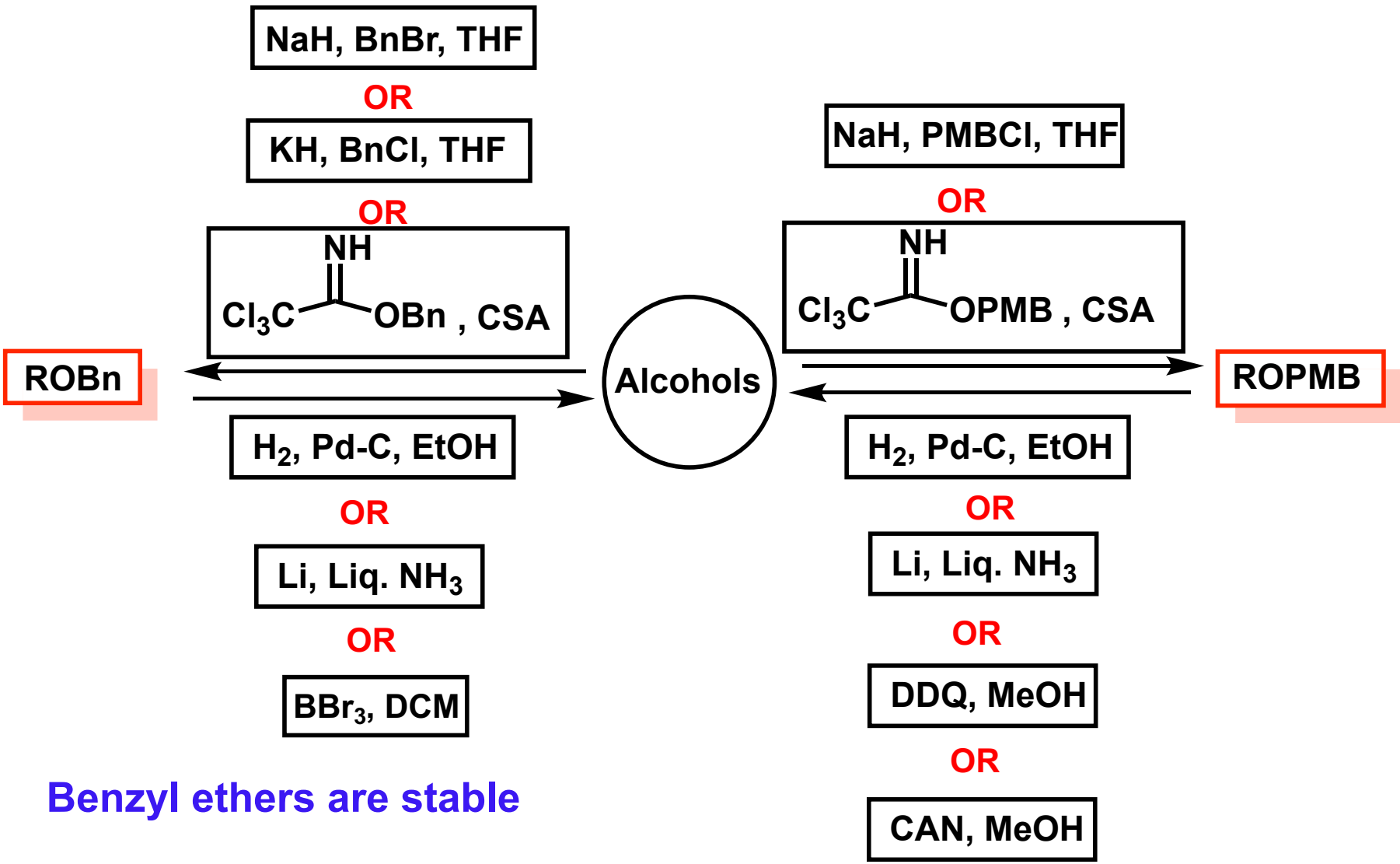


Alkylethers



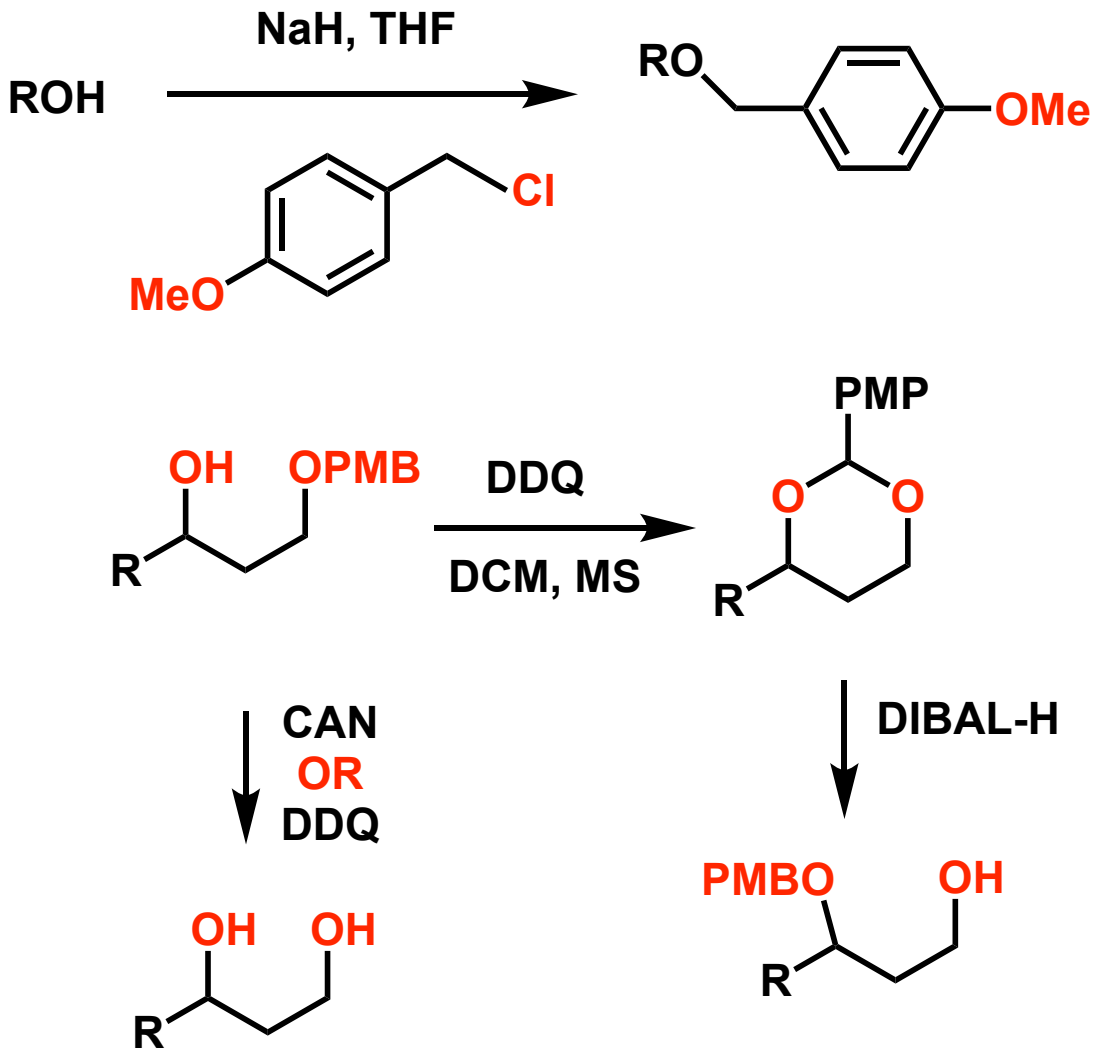
Creates one more chiral center

Benzylethers



Benzyl ethers are stable

PMB ethers

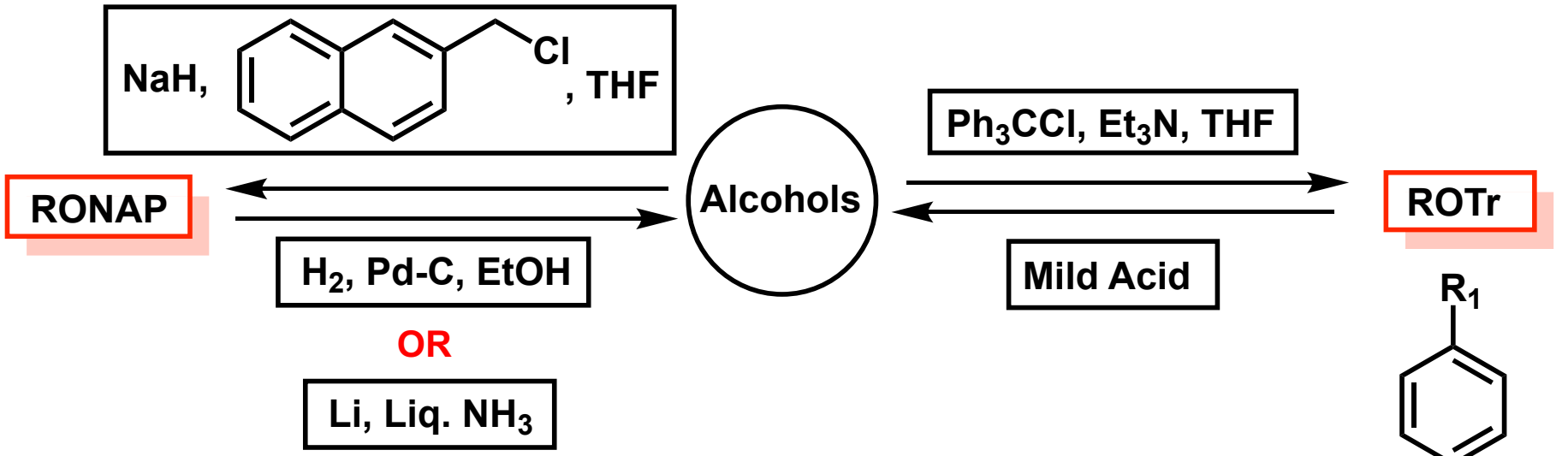

NaH, THF
ROH
RO
OMe
Cl
MeO
OH
OPMB
R
DDQ
DCM, MS
PMP
O
O
R
CAN
OR
DDQ
OH
OH
R
DIBAL-H
PMBO
OH
R

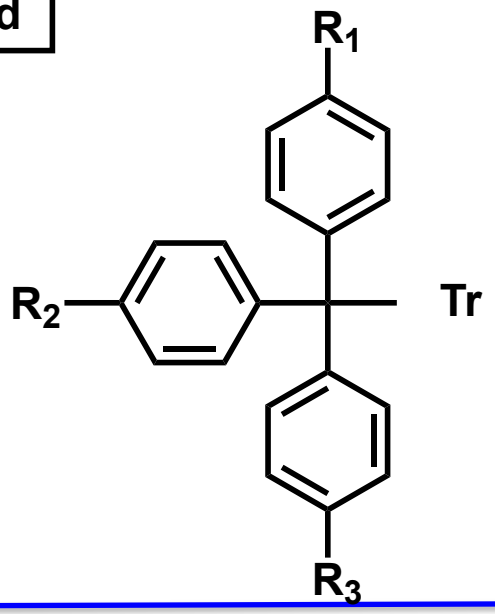
Benzyl Ethers

Selective for primary alcohols

Highly sensitive to acid

2-Naphthylmethyl ether (NAP)



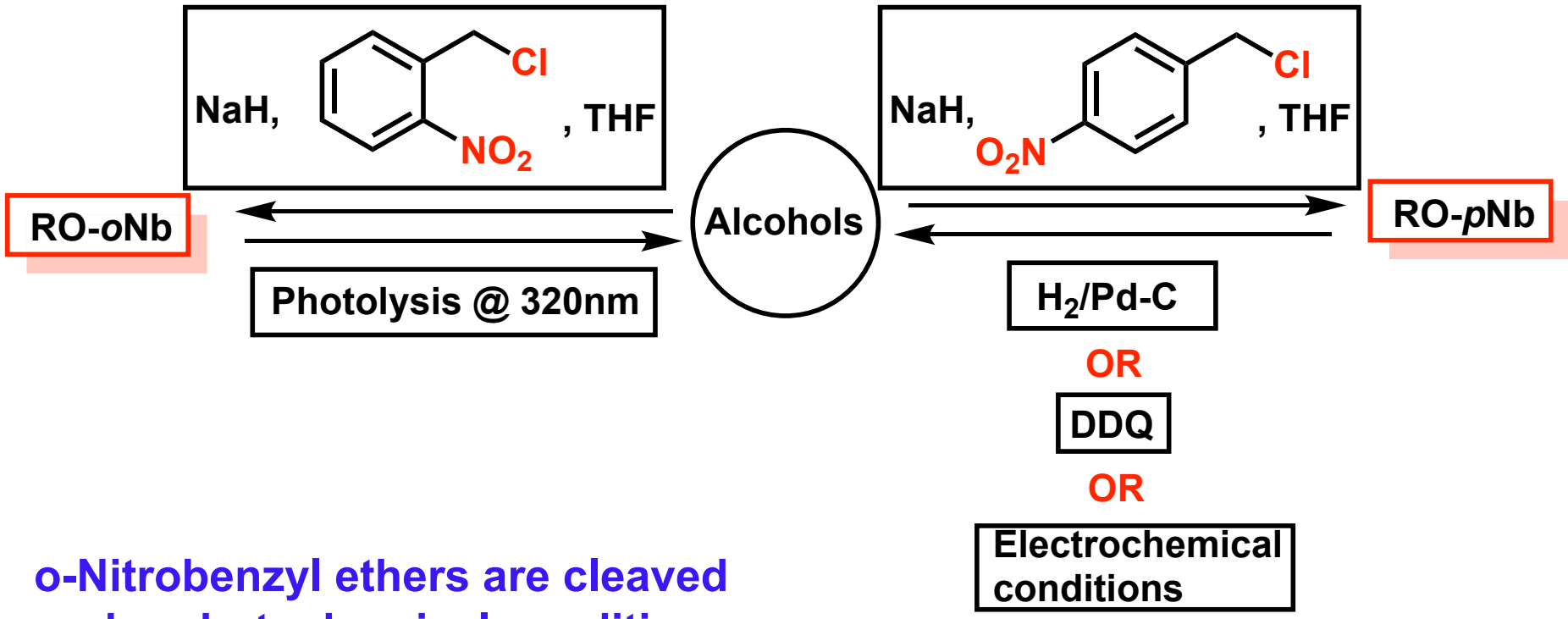


NAP ethers could be cleaved selectively in the presence of Bn ethers

Nitrobenzyl ethers

o-Nitrobenzyl ethers

p-Nitrobenzyl ethers

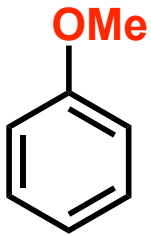


o-Nitrobenzyl ethers are cleaved under photochemical conditions

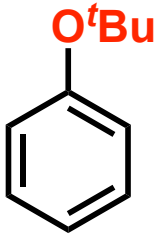
Protection of Phenols

Most of the protecting groups used for alcohols are applicable for phenols.

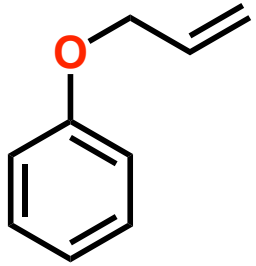
Common phenolic protecting groups are:



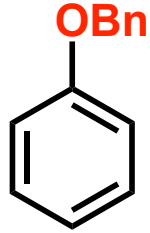
Methylether



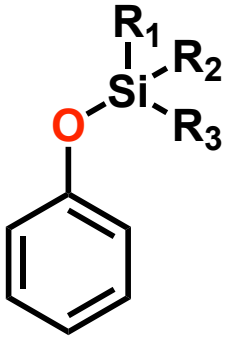
t-Butylether



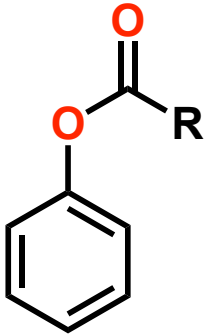
Allylether



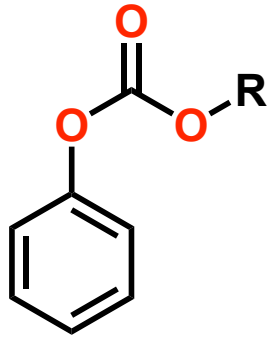
Benzylether



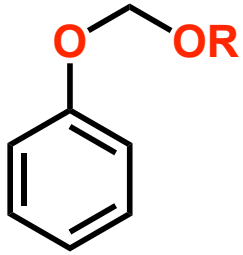
Silylethers



Phenyl esters



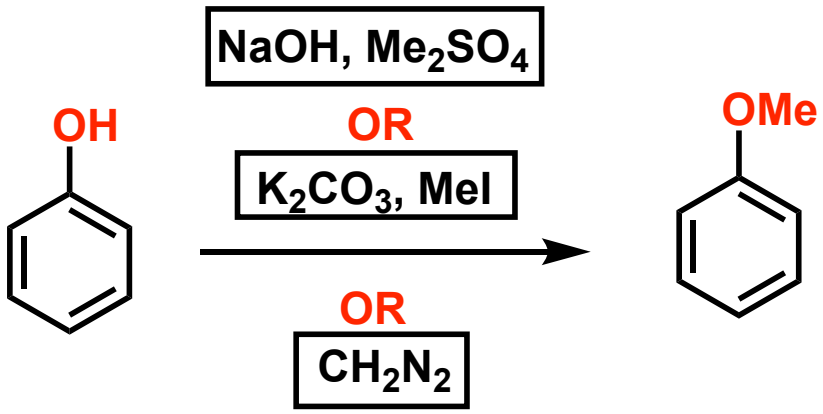
Phenyl carbonates



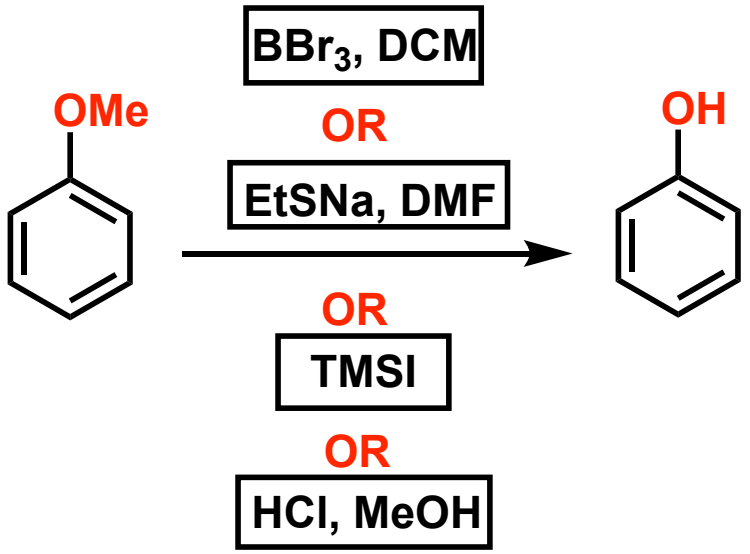
Acetals

Methyl Ethers

Protection



Deprotection



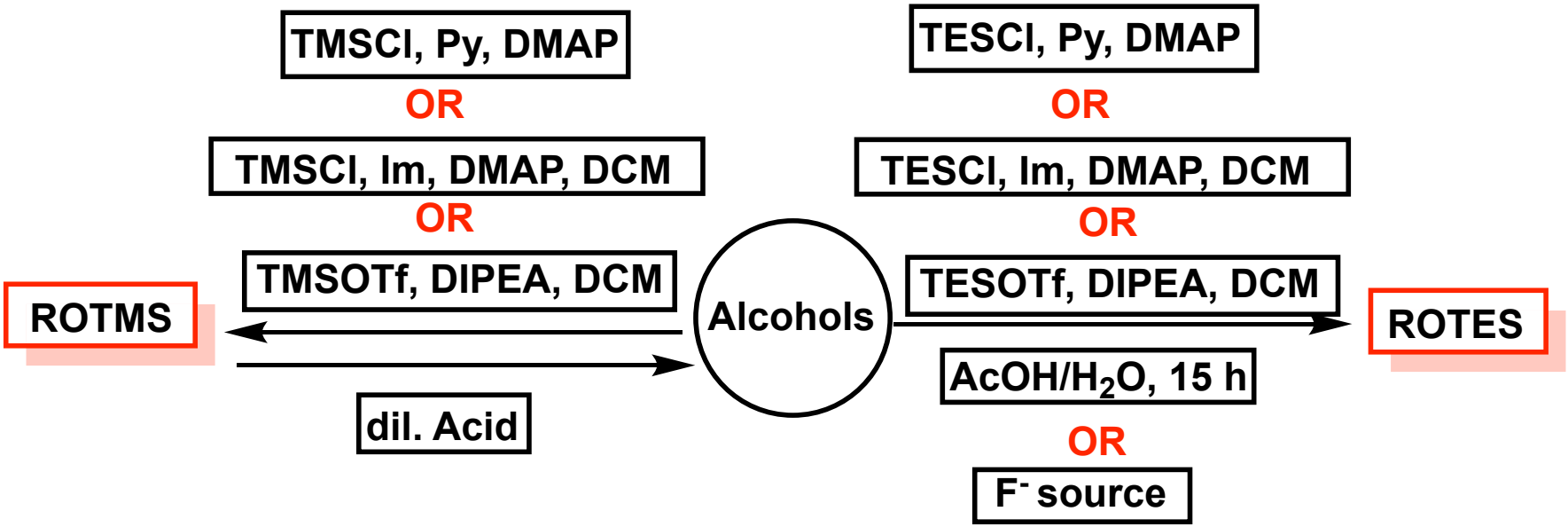
TMS and TES Ethers

TMS Ether

- Easy to introduce
- Used for transient protection
- Very labile to acid and water

TES Ether

- Easy to introduce
- More stable than TMS
- Selectively cleavable



TIPS and TBS Ethers

TIPS Ether

Easy to introduce

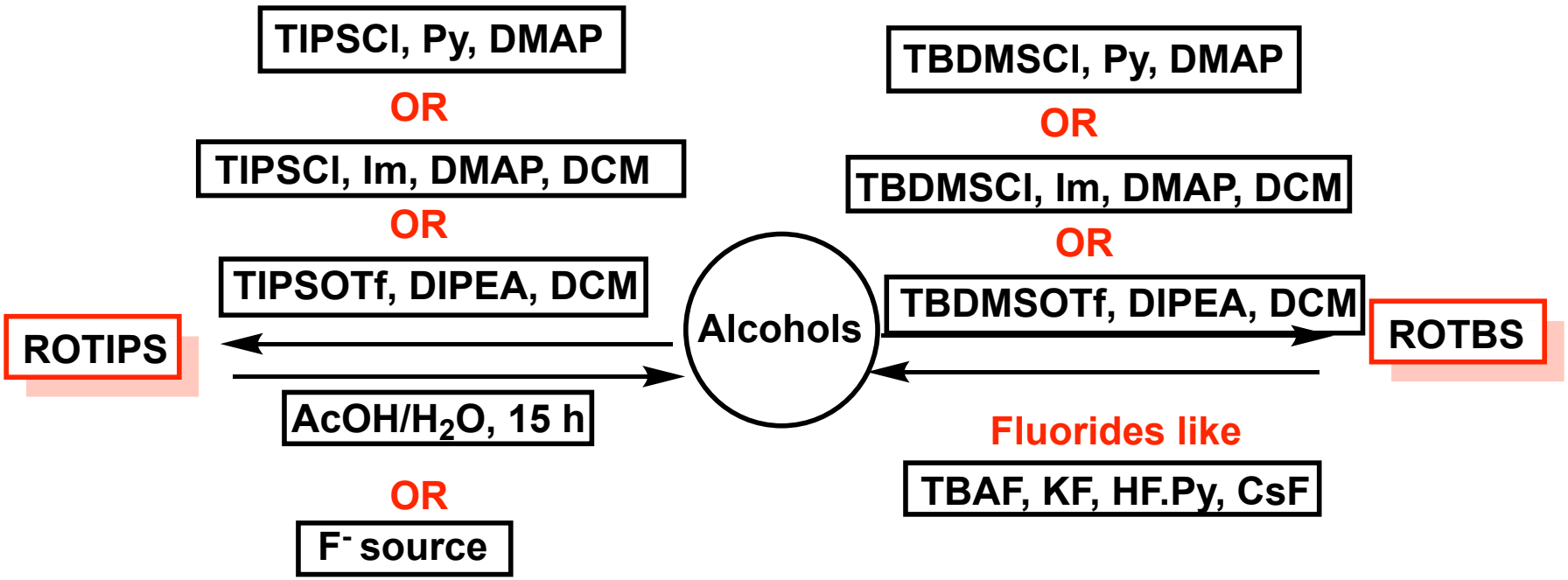
More stable than TMS/TES

TBS Ether

Selective protection of 1° alcohols

Stable to base and mild acid

TBSOTf is a good reagent for 2° alcohols



TBDPS ethers

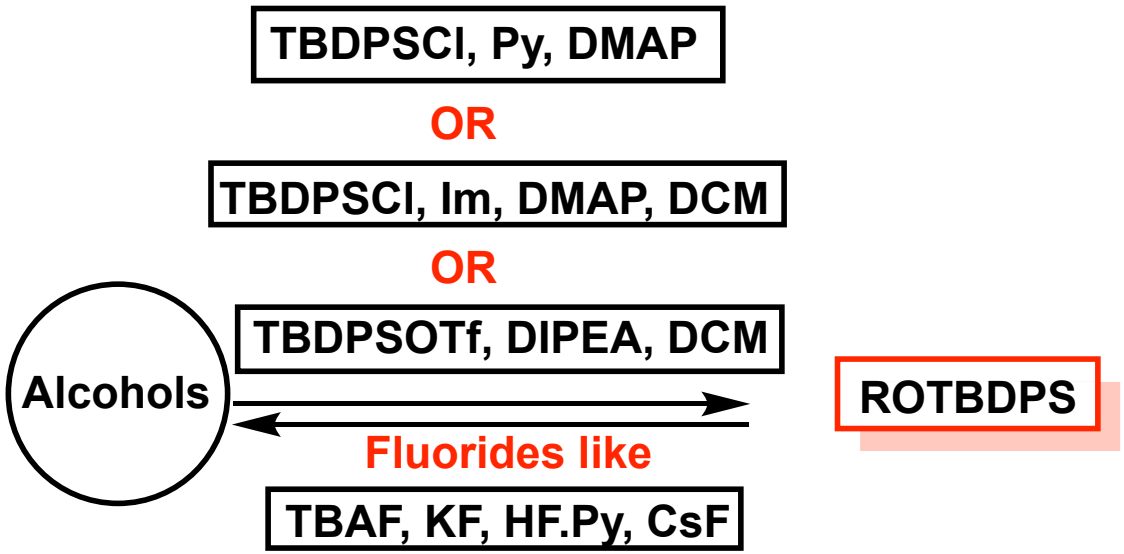
TBDPS Ether

Stable to base and acid

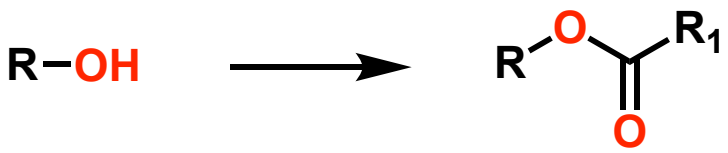
Selective for primary alcohols

TMS/TES/TIPS can be selectively removed in the presence of TBS/TBDPS

TBS can be selectively removed in the presence of TBDPS by acid



Esters



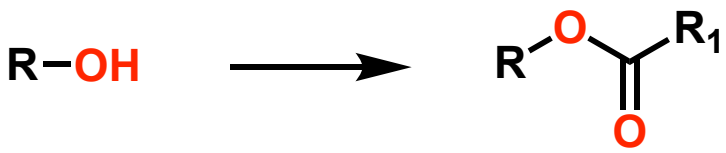
Formation: Activated acid, base, DMAP, solvent

Activated acid: Acid Chlorides, Anhydrides, Activating agents

Acid chloride: $SOCl_2$, Oxalylchloride, PCl_5

Activating agents: CDI, DCC, HOBT, NHS, PySSPy, Mukaiyama's reagent

Acetates



Properties: Stable to acid and mild base

Not compatible with strong nucleophiles such as organometallic reagents

Formation: Ac_2O, pyridine

Acetyl chloride, pyridine

Cleavage: K_2CO_3, MeOH, reflux

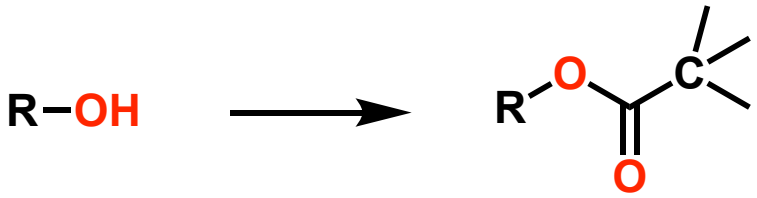
KCN, EtOH, reflux

NH_3, MeOH

LiOH, THF, H_2

Enzyme hydrolysis (Lipase)

Pivaloates



Properties: Selective for primary alcohols

Removed with mild bases

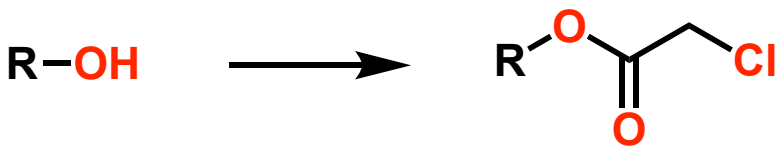
Formation: t-Butylacetyl chloride, Py

t-Butylacetic anhydride, Base

Cleavage: K_2CO_3, MeOH

LAH, Et_2O

Chloroacetates



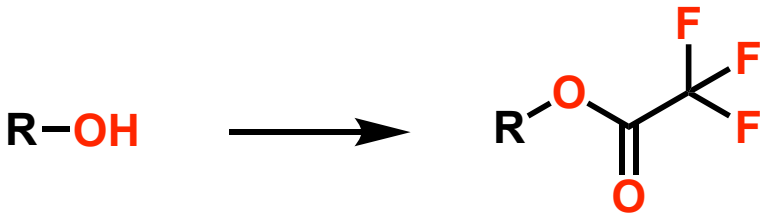
Properties: Removed with Zn dust or thiourea

Formation: Chloroacetyl chloride, Base

Cleavage: Zn dust

Thiourea

Trifluoroacetates



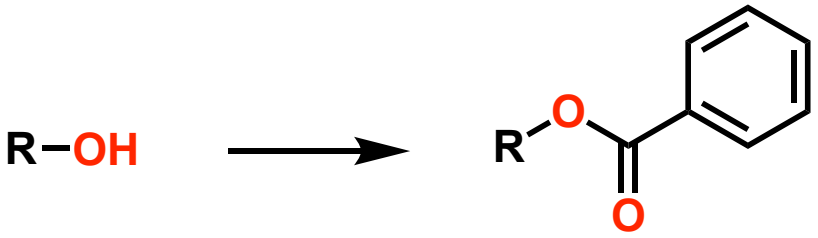
Properties: Removed with base

Formation: Trifluoroacetyl chloride, Base

Trifluoroacetic anhydride, Base

Cleavage: K_2CO_3, MeOH

Benzoates



Properties: More stable than acetates *wrt* hydrolysis

Formation: Benzoyl chloride, Base

Benzoyl cyanide, Base

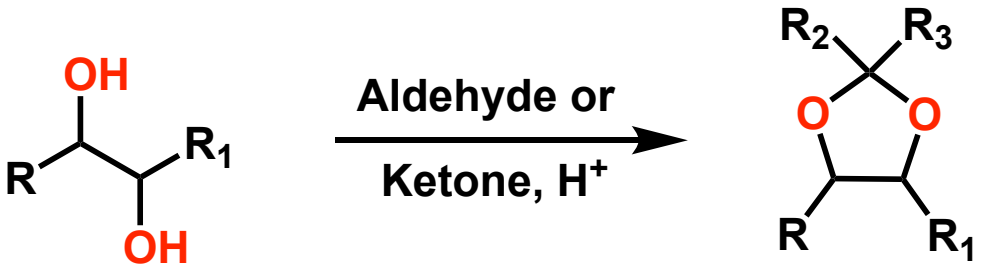
Benzoic anhydride, Base

Cleavage: K_2CO_3, MeOH

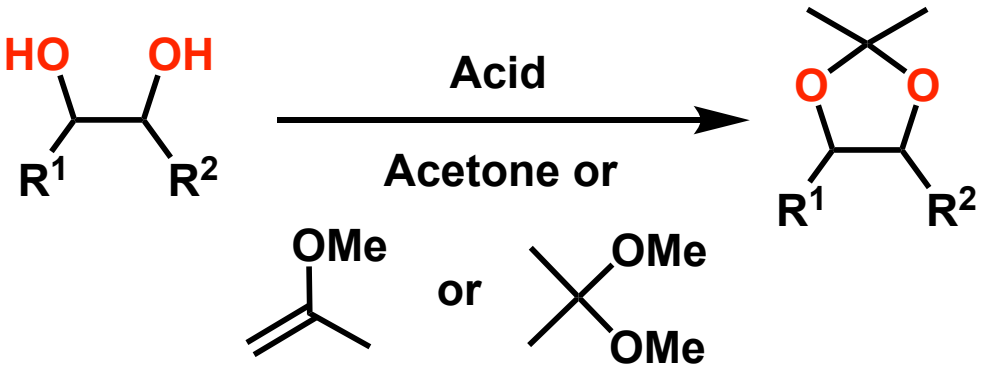
KCN, MeOH

Protecting Groups for Diols

1,2-Diols



Isopropylidenes (acetonides)

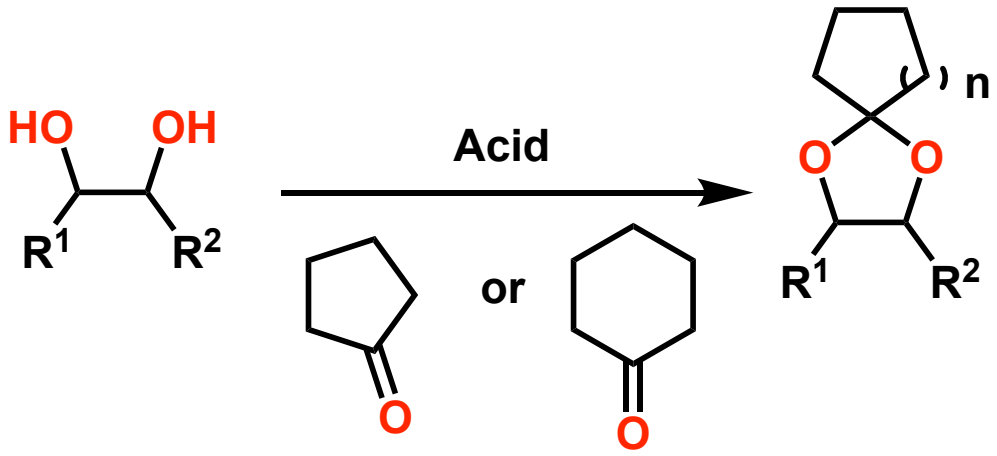


Cleavage Mild aqueous acid

1,2-acetonide formation is usually favored over 1,3-acetonides

1,2-Diols

Cycloalkylidene ketals

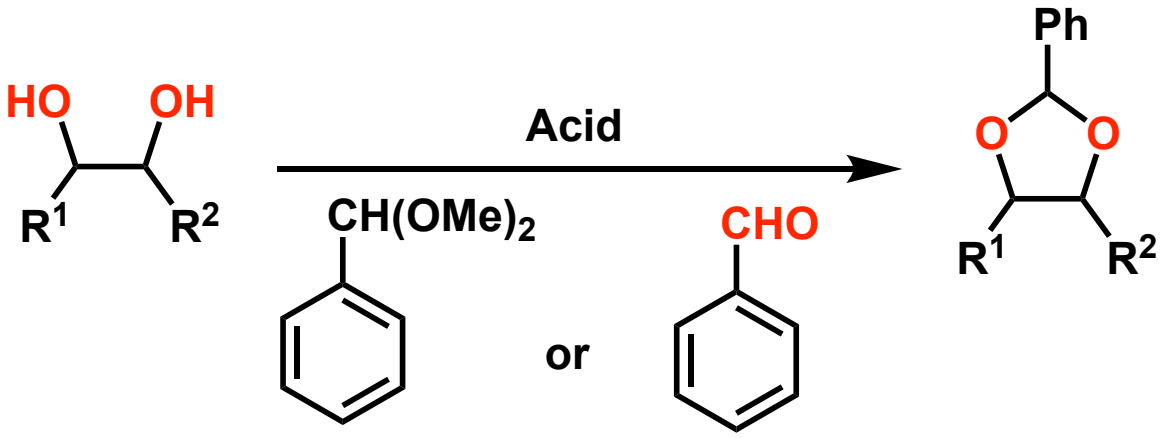


Cyclopentylidenes are slightly easier to cleave than acetonides

Cyclohexylidenes are slightly harder to cleave than acetonides

1,2-Diols

Benzylidene acetals



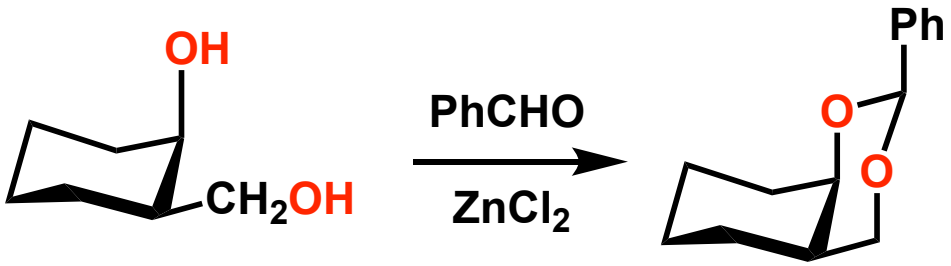
Cleavage: Acid hydrolysis or hydrogenolysis

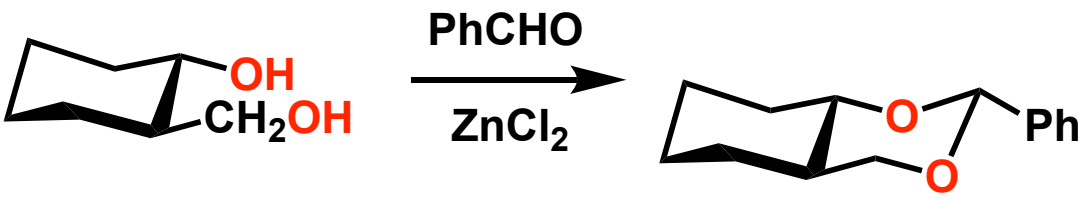
1,3-Benzylidene formation is usually favored over 1,2-Benzylidene

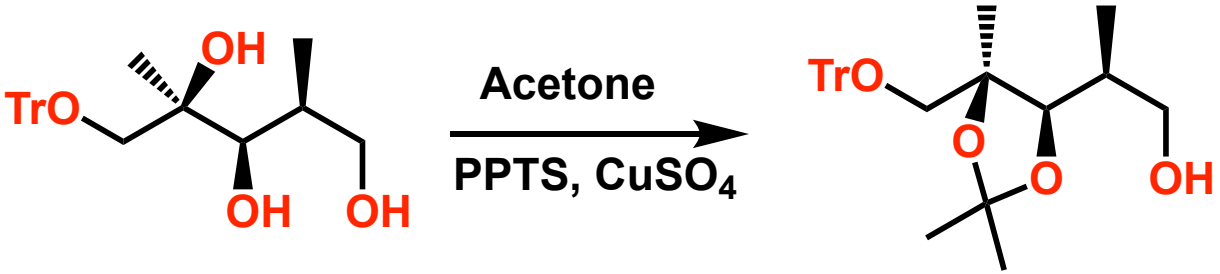
Benzylidenes are usually hydrogenolyed slower than benzyl ethers or olefins

1,2 & 1,3-Diols

Benzylidene acetals & Acetonides

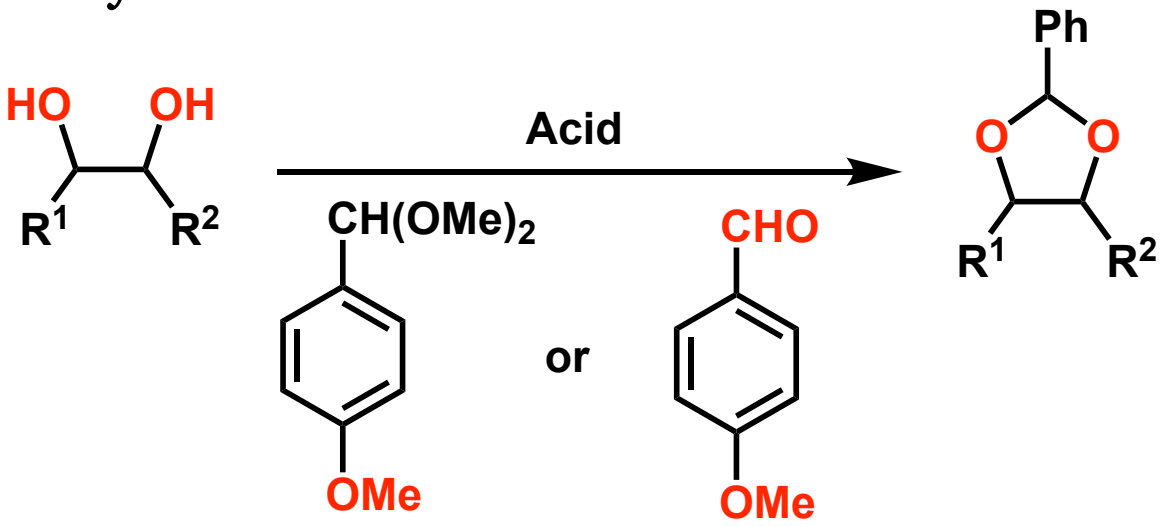






1,2-Diols

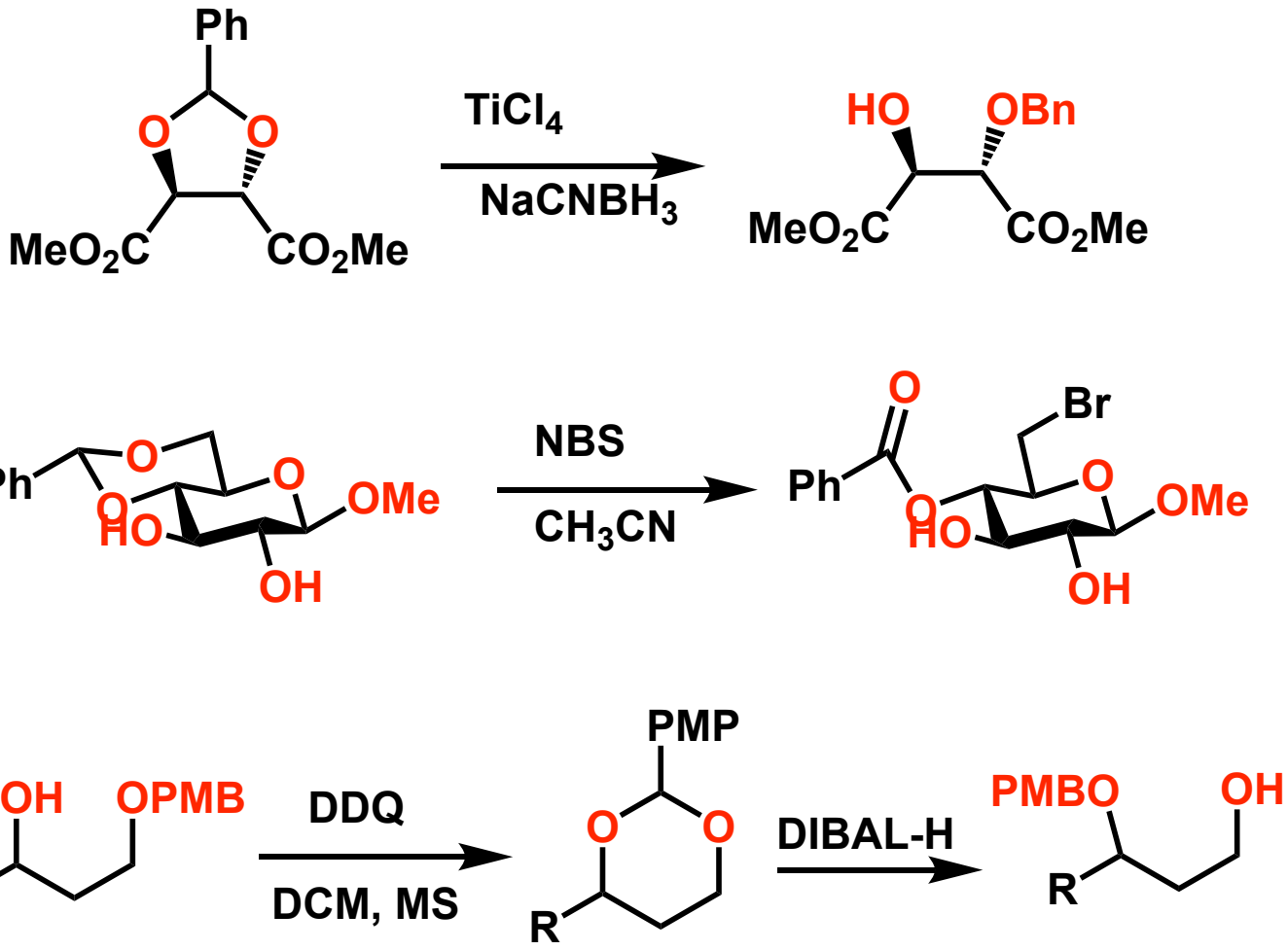
p-Methoxybenzylidene acetals



Cleavage: Acid hydrolysis or hydrogenolysis or DDQ or CAN

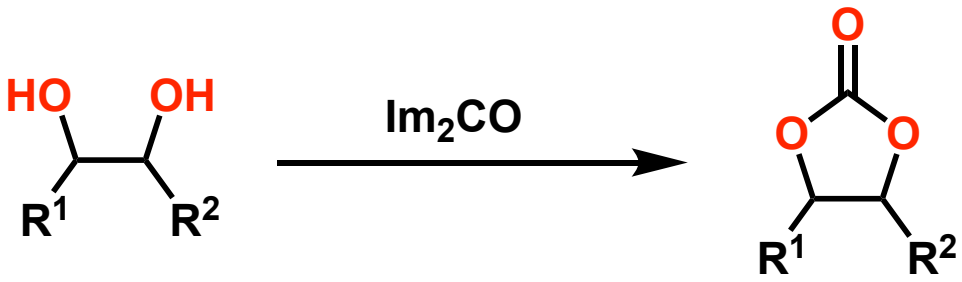
Hydrolyzed about 10 times faster than regular benzylidenes

Other Reactions



1,2-Diols

Cyclic Carbonates

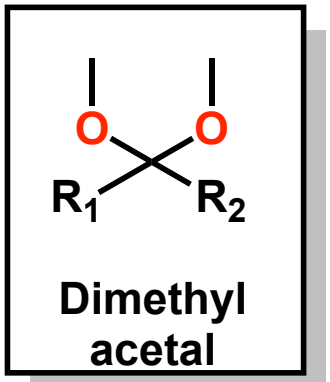


Formation: Im_2CO or phosgene or triphosgene

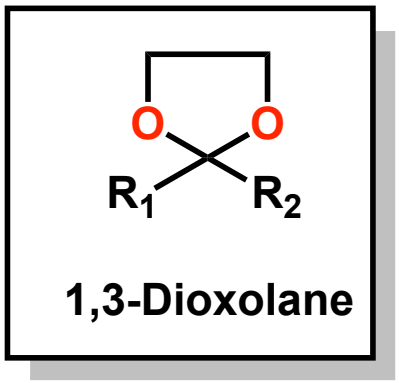
Cleavage: Removed with bases

Protecting Groups for Carbonyls

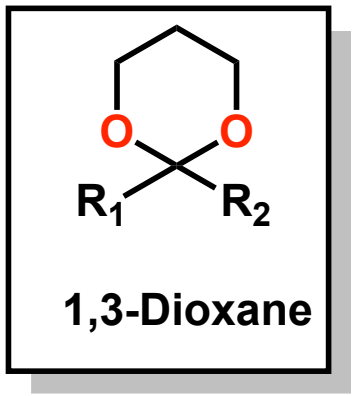
PG's for Aldehydes/Ketones



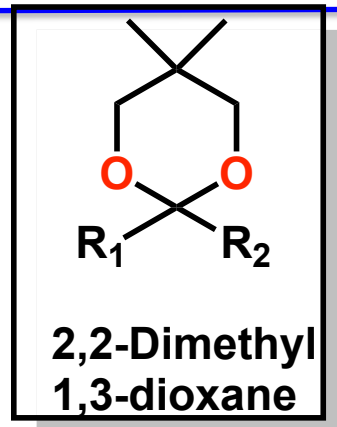
Dimethyl acetal



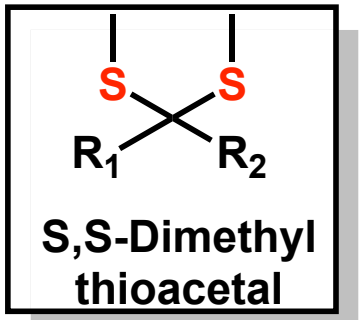
1,3-Dioxolane



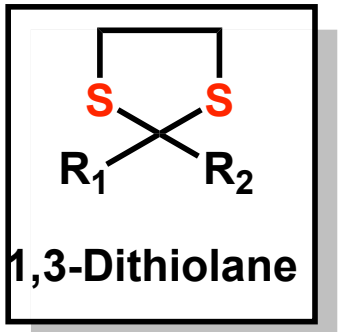
1,3-Dioxane



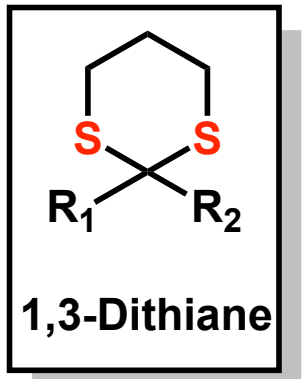
2,2-Dimethyl 1,3-dioxane



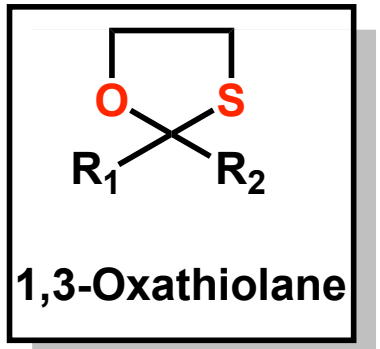
S,S-Dimethyl thioacetal



1,3-Dithiolane



1,3-Dithiane



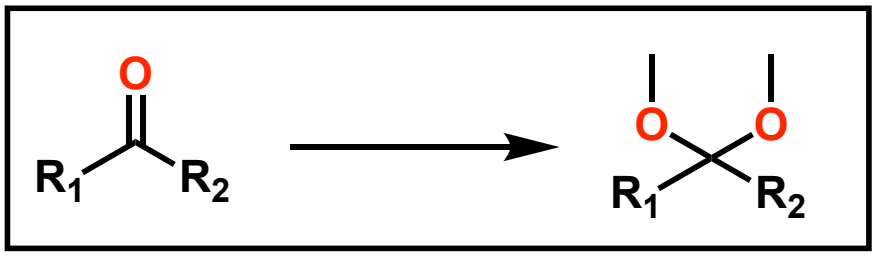
1,3-Oxathiolane

Order of Reactivity

Aldehydes > acyclic ketones = cyclohexanones > cyclopentanones >

α,β-unsaturated ketones = α,α-substituted ketones > aromatic ketones

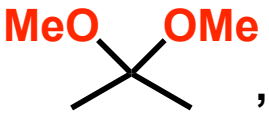
Dimethyl acetals/ketals



Formation

1. MeOH, Dry HCl

2. $Sc(OTf)_3$, $CH(OMe)_3$

3. 

, PTSA

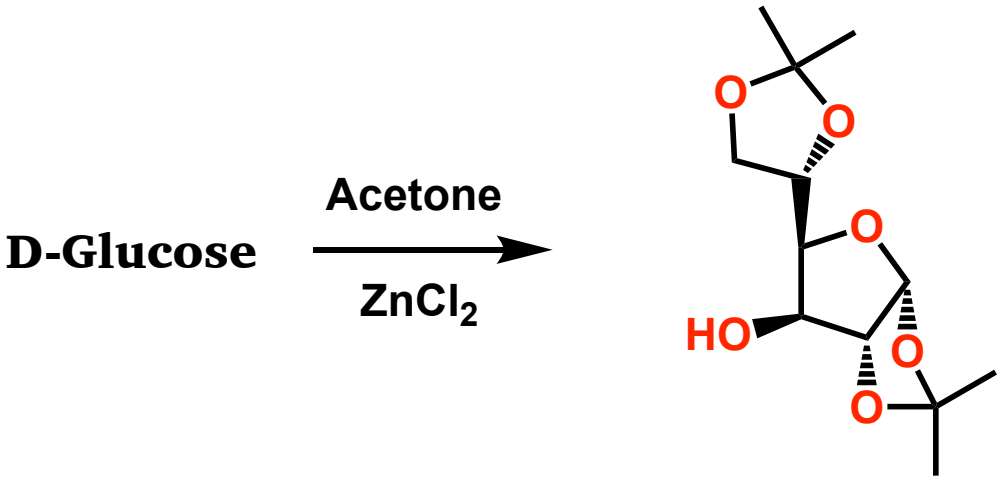
4. TMSOMe, TMSOTf, DCM

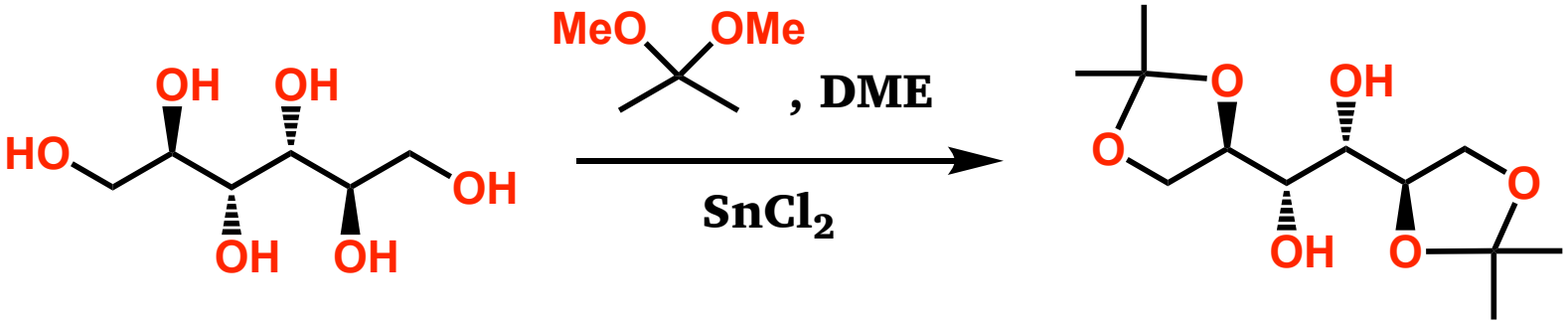
Cleavage

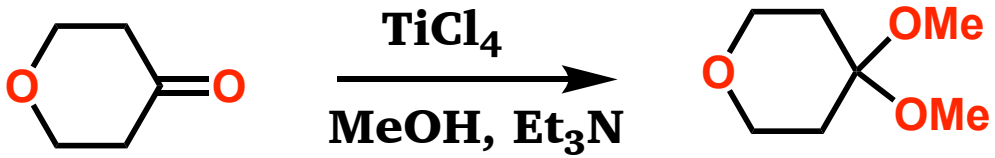
1. Acetone, PTSA

2. TFA, $CHCl_3$, H_2O

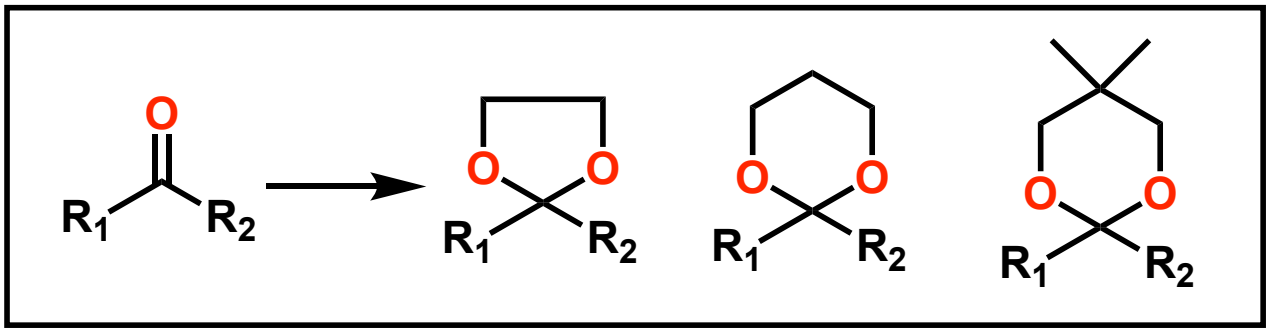
Dimethyl acetals/ketals



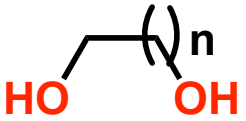




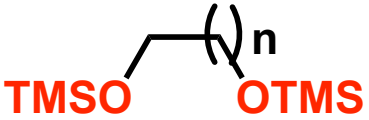
1,3-Dioxolones/1,3-Dioxanes



Formation



, Toluene, PTSA



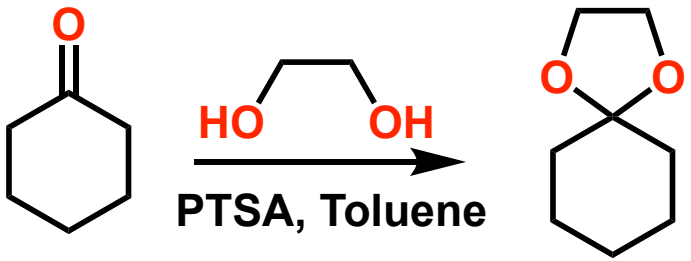
, TMSOTf, DCM

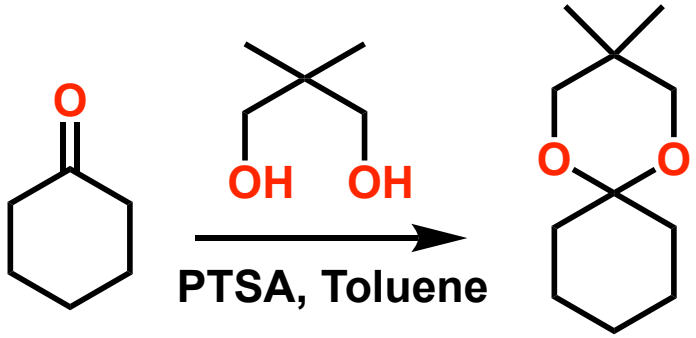
-78 °C

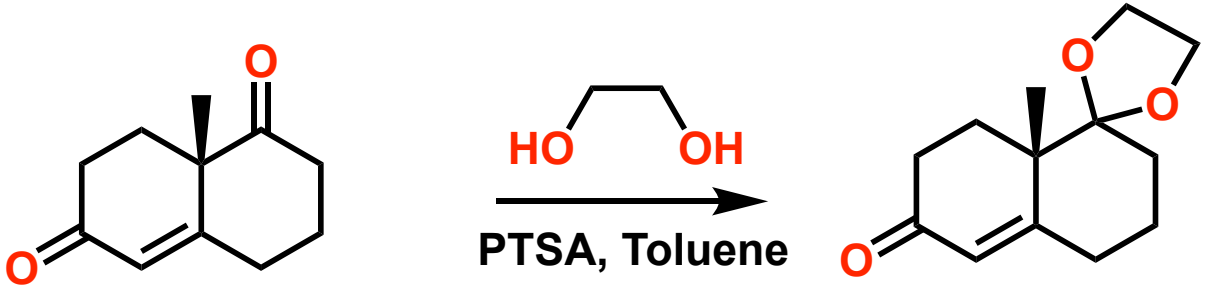
Cleavage

1. Acetone, PPTS, H_2O, Heat
2. 1M HCl, THF
3. Me_2BBr, DCM, -78 °C

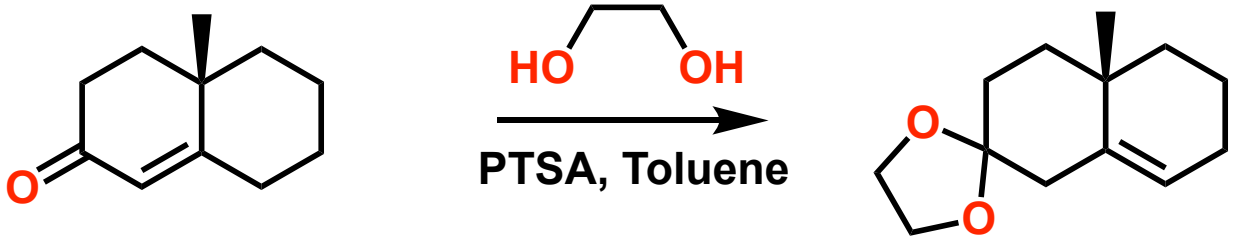
1,3-Dioxolones/1,3-Dioxanes



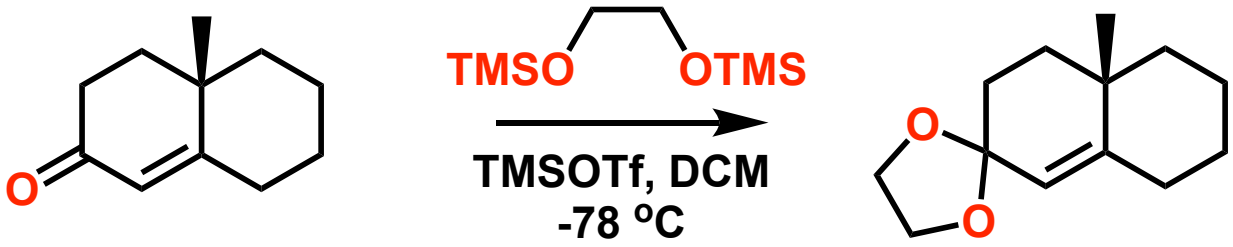




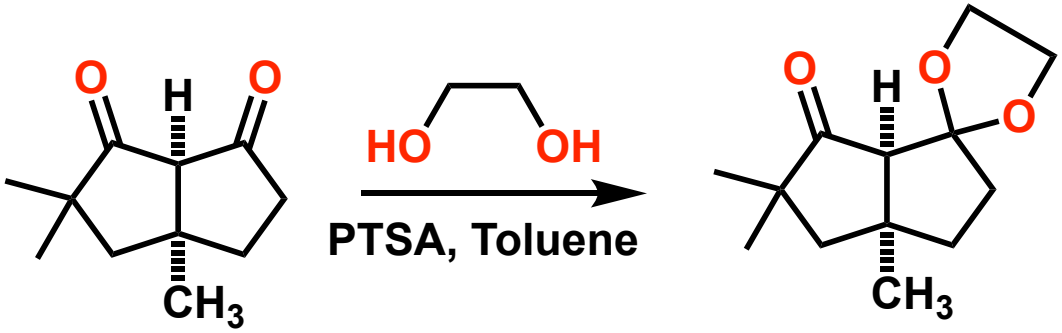
Double bond increases the electron density at the carbonyl carbon of the α,β-unsaturated ketones



1,3-Dioxolones/1,3-Dioxanes

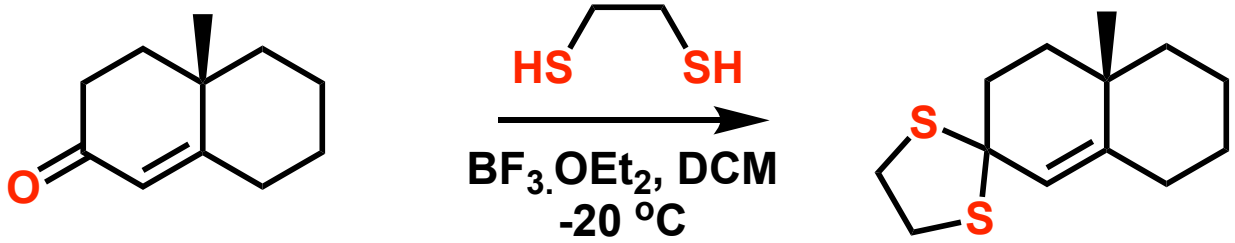


This procedure developed by Noyori, at lower temperature, the double bond doesn't migrate.



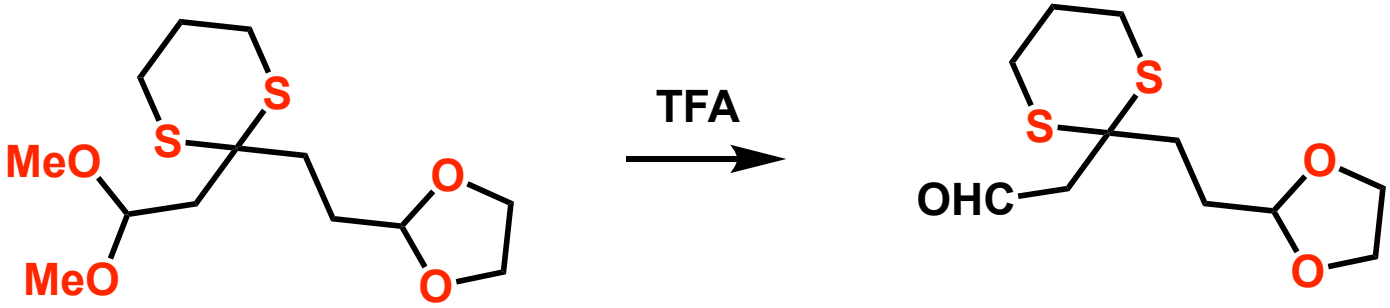
Steric hindrance could be used to selectively protect one of the carbonyl groups

1,3-Dithiolones/1,3-Dithianes



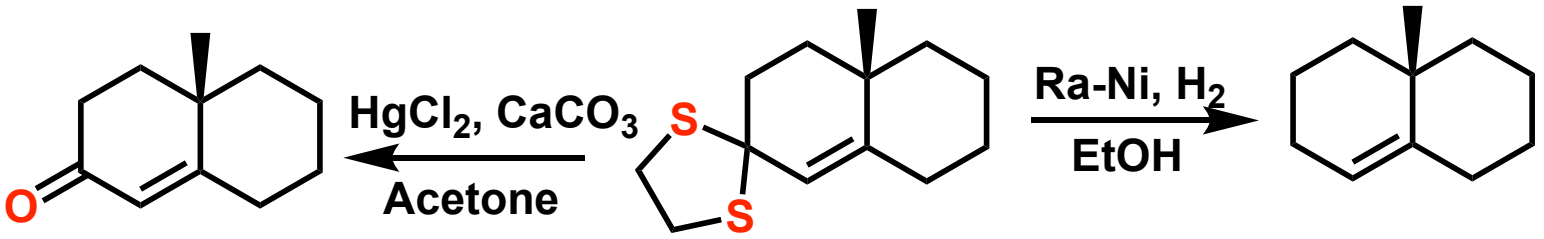
Since thioacetals are quite stable towards hydrolysis, no need to remove water from the reaction mixture.

Double bond migration is also not observed as this reaction is done at a lower temperature



Selective removal of acetal is possible in the presence of thioacetal

1,3-Dithiolones/1,3-Dithianes



Cleavage of dithianes and dithiolanes:

$Hg(ClO)_4$, MeOH, $CHCl_3$, 25 °C

NBS, acetone, 0 °C

I_2, DMSO

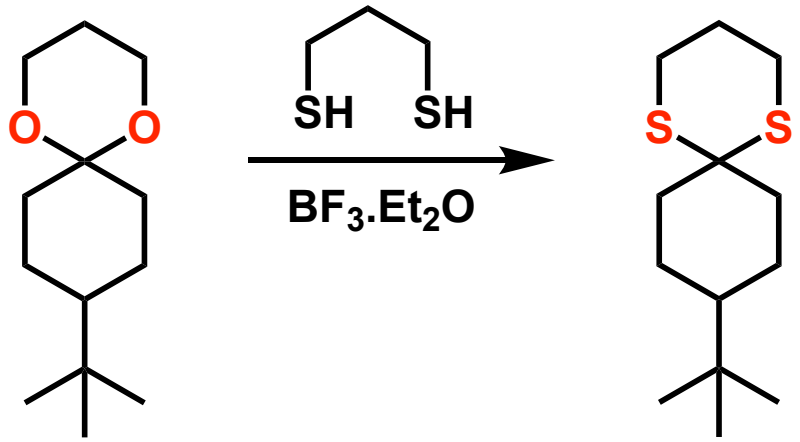
CAN, aq. CH_3CN

m-CPBA, Ac_2O

DDQ, aq. CH_3CN

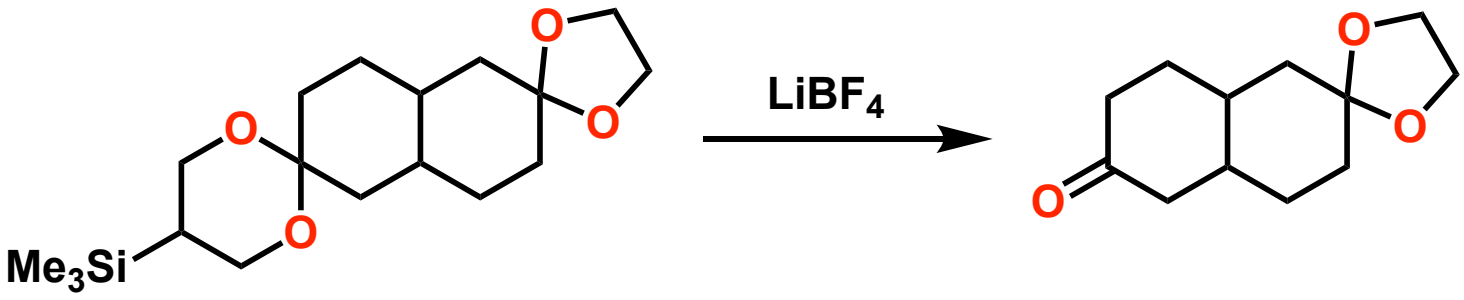
1,3-Dithioxolones/1,3-Dithianes

1,3-dioxolanes and 1,3-dioxanes can be readily converted into 1,3-dithiolanes and 1,3-dithianes

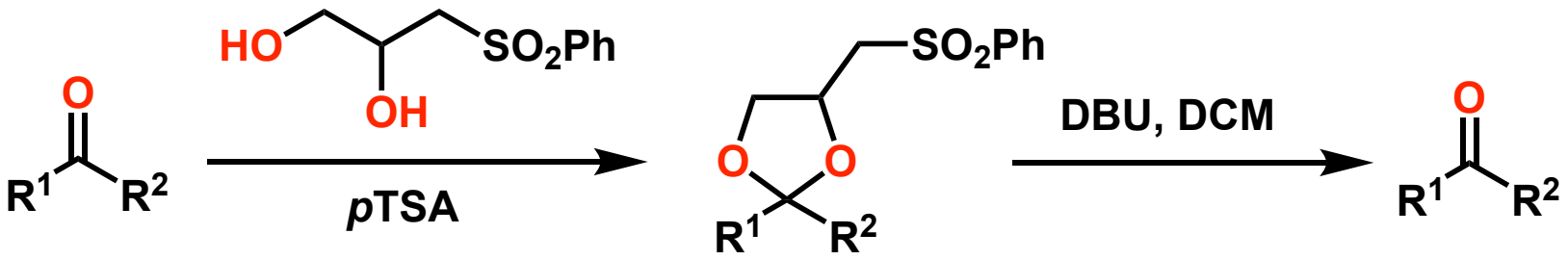


1,3-Dithioxolones/1,3-Dithianes

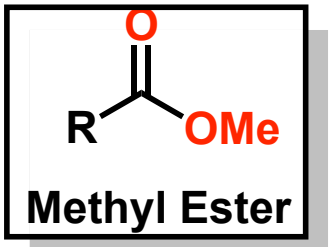
Fluoride cleavable ketal



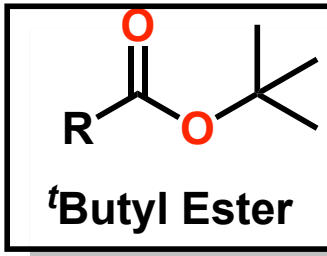
Base cleavable ketal



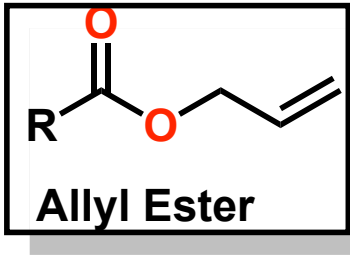
PGs for Carboxylic Acids



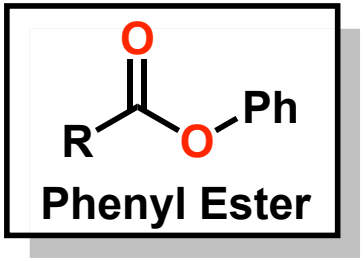
Methyl Ester



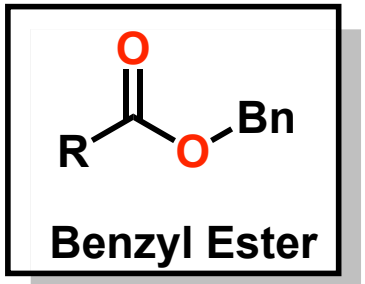
^{t}Butyl Ester



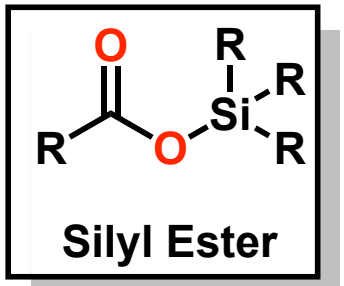
Allyl Ester



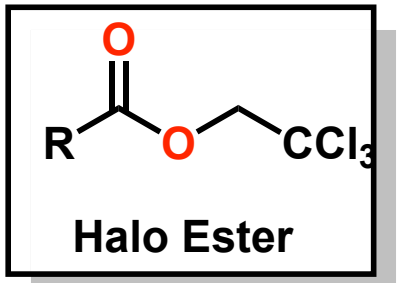
Phenyl Ester



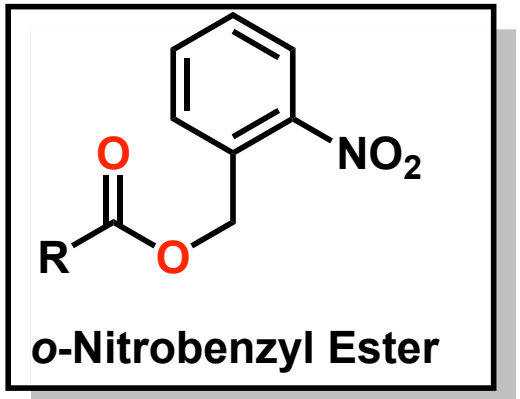
Benzyl Ester



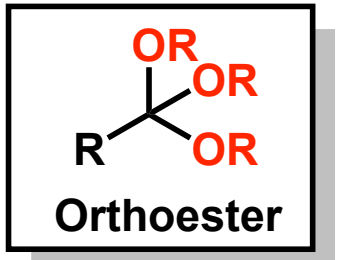
Silyl Ester



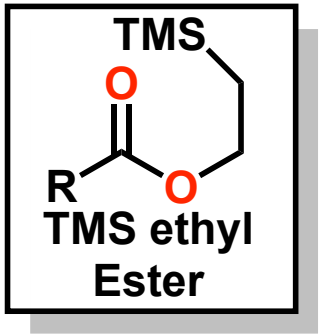
Halo Ester



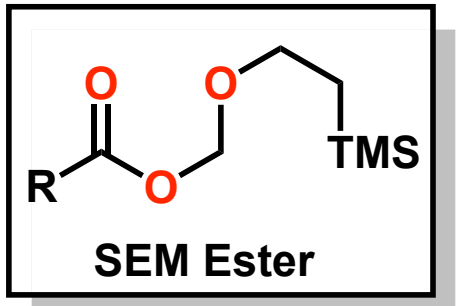
o-Nitrobenzyl Ester



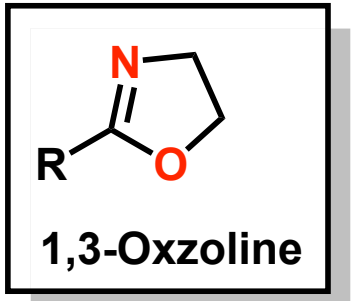
Orthoester



TMS ethyl Ester



SEM Ester



1,3-Oxzoline

PGs for Carboxylic Acids

1. Alkyl esters:

Formation:

Fischer esterification (RCOOH + R'OH + H^+)

Acid chloride + ROH, pyridine

t-Butyl esters: Isobutylene & acid

Methyl esters: Diazomethane

Cleavage:

LiOH, THF, H_2O

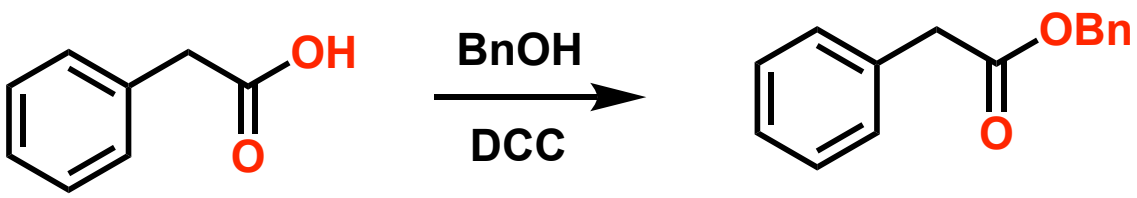
Enzyme hydrolysis

t-Butyl esters are cleaved with aq. acid

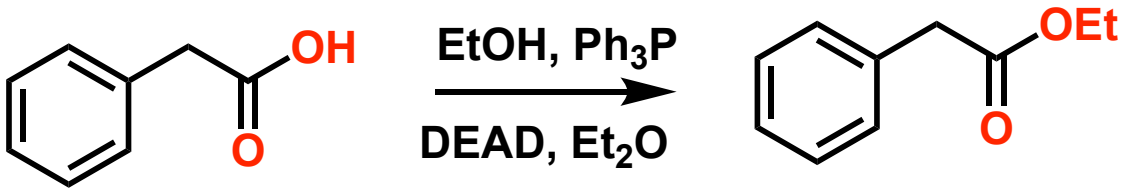
Bu_2SnO, PhH, reflux

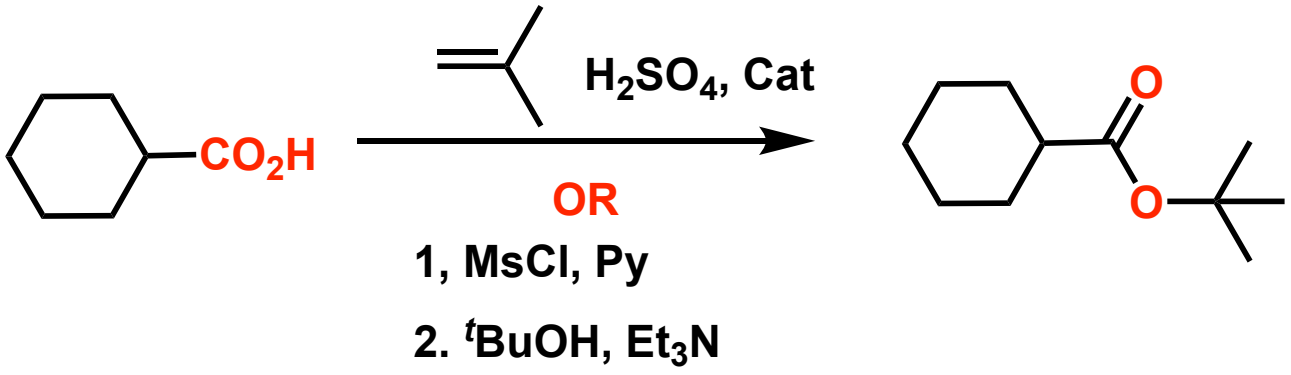
Alkyl Esters

DCC



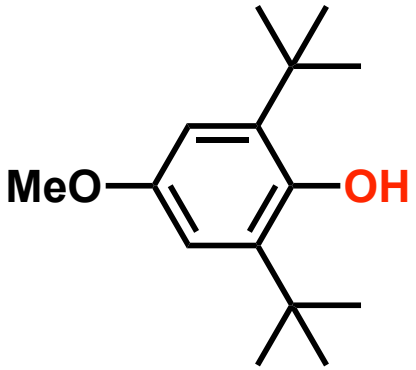
Mitsunobu Reaction



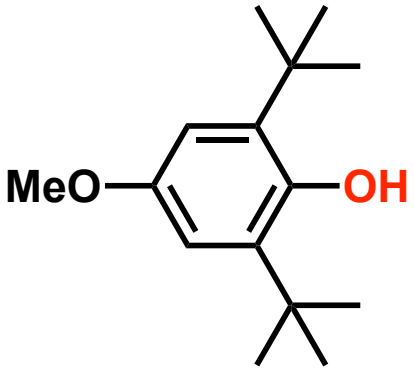


Aryl Esters

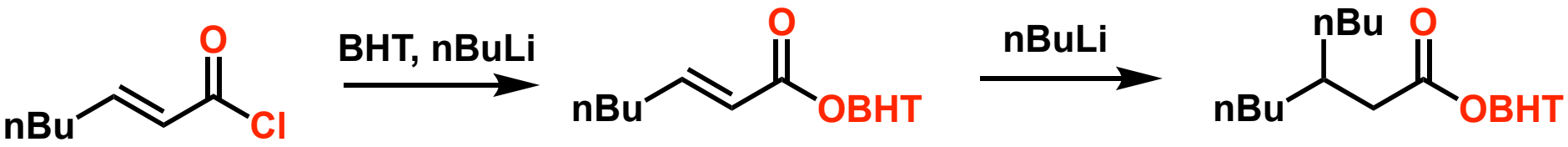
Due to steric hindrance, BHT and BHA do not react with organometallic reagents



BHT

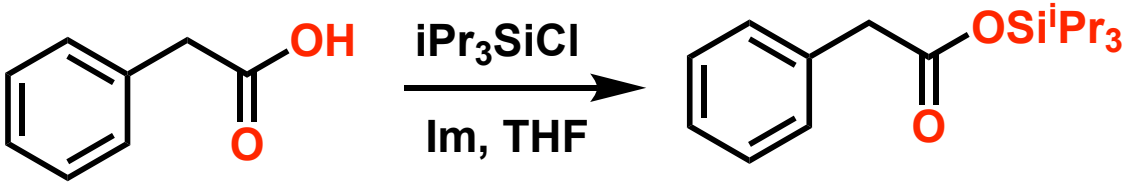


BHA

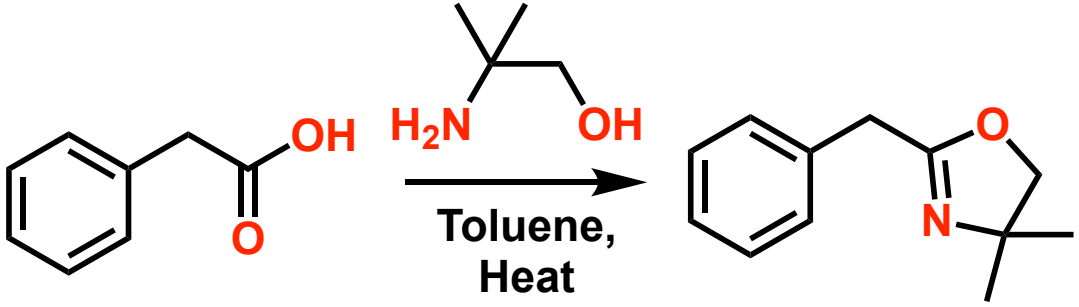


Silyl Esters & Oxazolines

Bulky silyl esters do not react with organometallic reagents; fluorides are required to hydrolyse



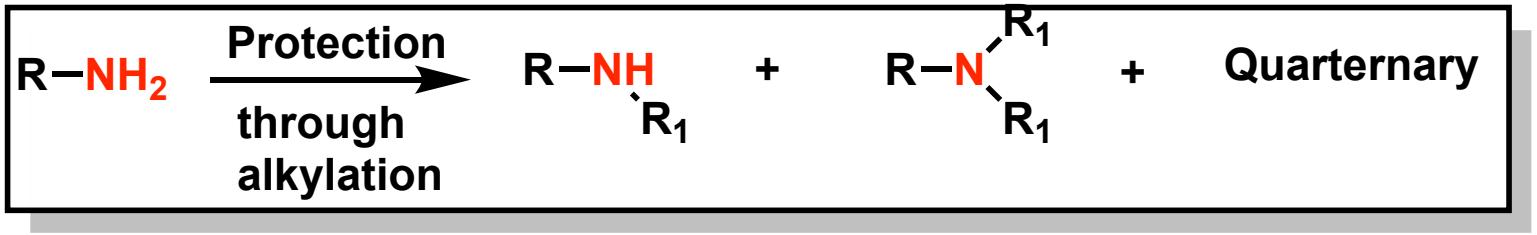
Oxazolines are stable to organometallic reagents, reducing agents like LAH etc.,



PGs for Amines

Introduction of protecting groups

Unlike alcohols, it is difficult to protect amines through alkylation



Primary and secondary amines are prone to oxidation

NH bonds undergo metallation on treatment with organometallic reagents

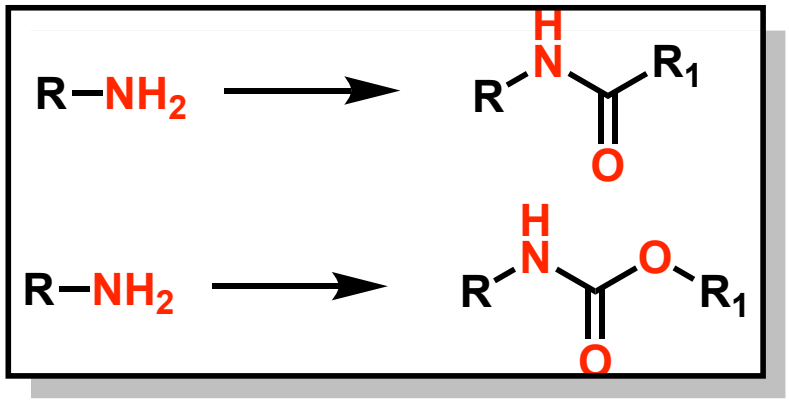
Because of the presence of the lone pair of electrons, Nitrogen could be protonated/alkylated.

PGs for Amines

Best ways to protect amines

It should be protected in such a way that further alkylation doesn't take place

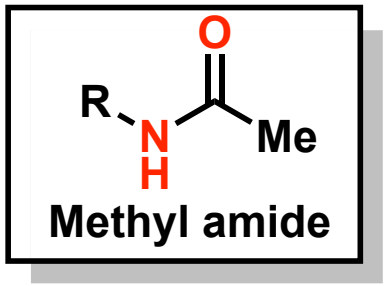
To make the lone pairs less reactive, it is better to attach a carbonyl group



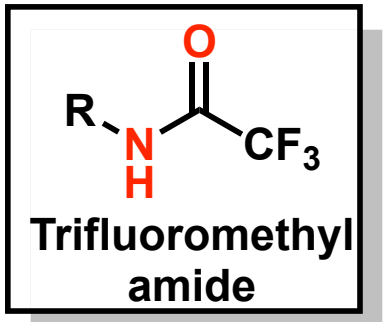
Amides could be cleaved by acids

Carbamates could be cleaved by a variety of reagents, depending on the nature of the carbamates

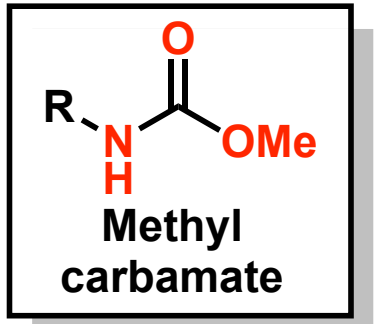
PGs for Amines



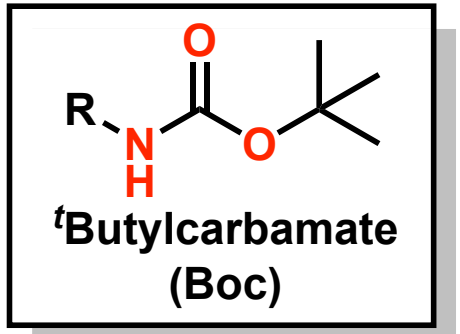
Methyl amide



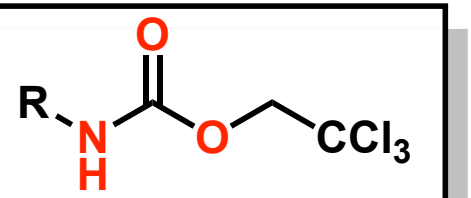
Trifluoromethyl amide



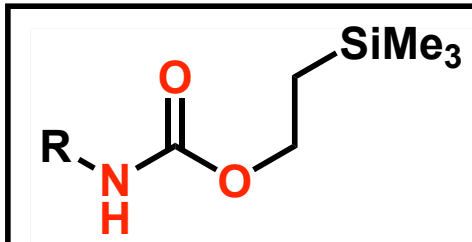
Methyl carbamate



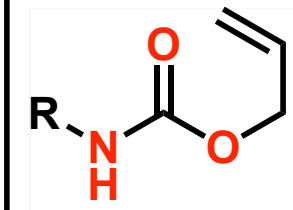
^{t}Butylcarbamate (Boc)



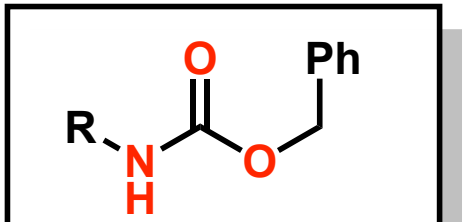
Trichloroethyl carbamate (Troc)



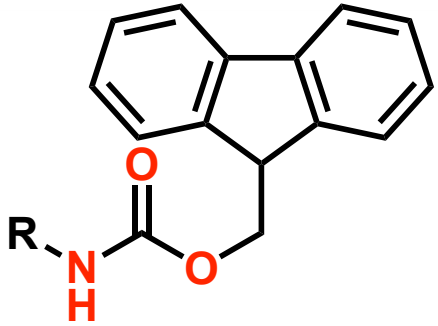
Trimethylsilylethyl carbamate (Teoc)



Allyl carbamate (Alloc)

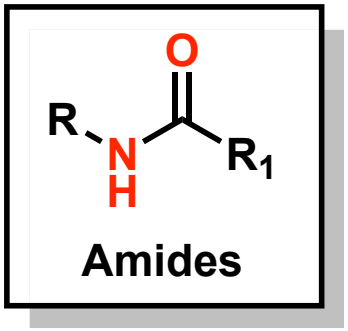


Benzylcarbamate (CBz)



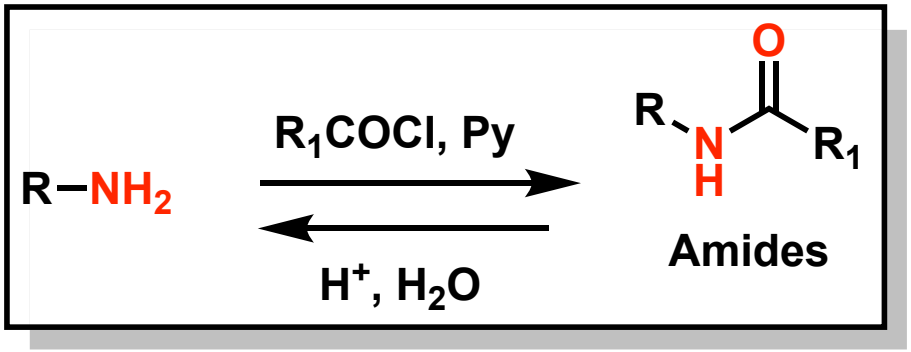
9-Fluroenylmethyl carbamate (Fmoc)

Amides

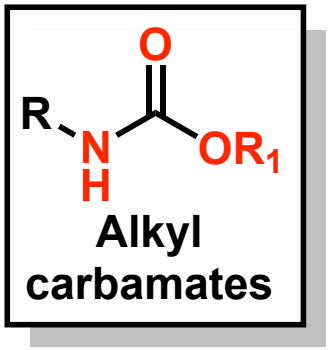


Basicity of nitrogen is reduced; so electrophilic attack on the nitrogen is reduced

Amides are stable to hydrogenation, oxidation, nucleophiles & organometallic (except organolithium) reagents

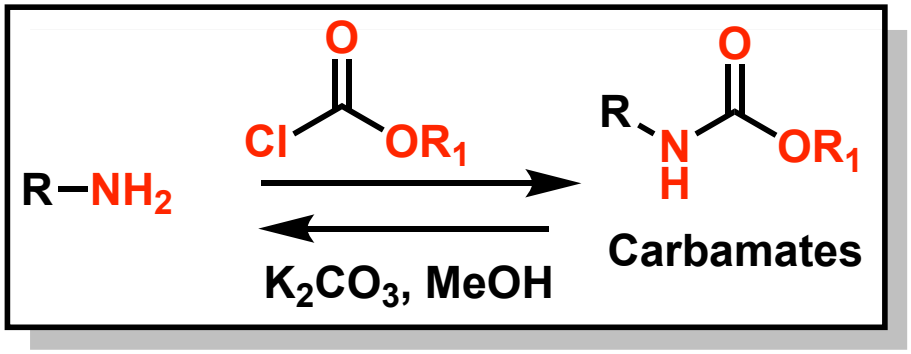


Carbamates

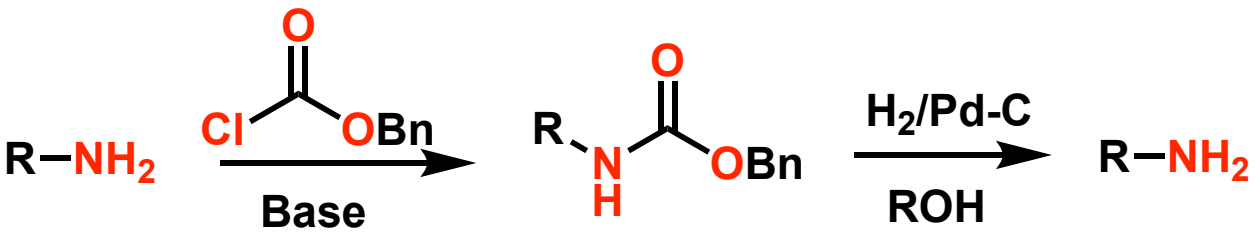


Carbamates are like amides and so can't act as a nucleophile

Carbmates are stable to oxidation and aqueous bases though it may react with reducing agents



Benzyl carbamates (Cbz or Z)



Formation: BnOCOCl, Na_2CO_3, H_2O

$(BnOCO)_2O$, dioxane, H_2O

Cleavage: H_2/ Pd-C

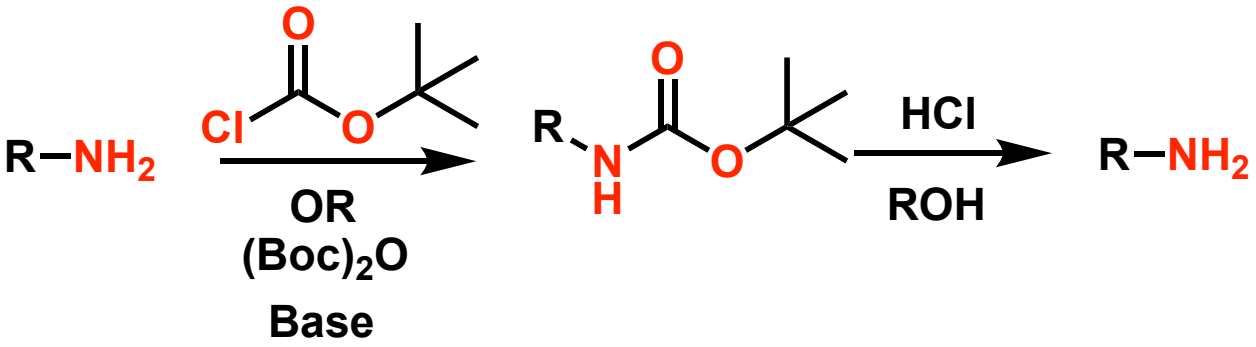
H_2/ Pd-C, NH_3

Pd-C, $HCOONH_4$

BBr_3, DCM

KOH, MeOH

^{t}Butyloxycarbonyl (Boc)



Formation:

$(Boc)_2O$, NaOH, H_2O, 25 ^{o}C

$(Boc)_2O$, TEA, MeOH/ DMF

$BocN_3$, DMSO

Cleavage:

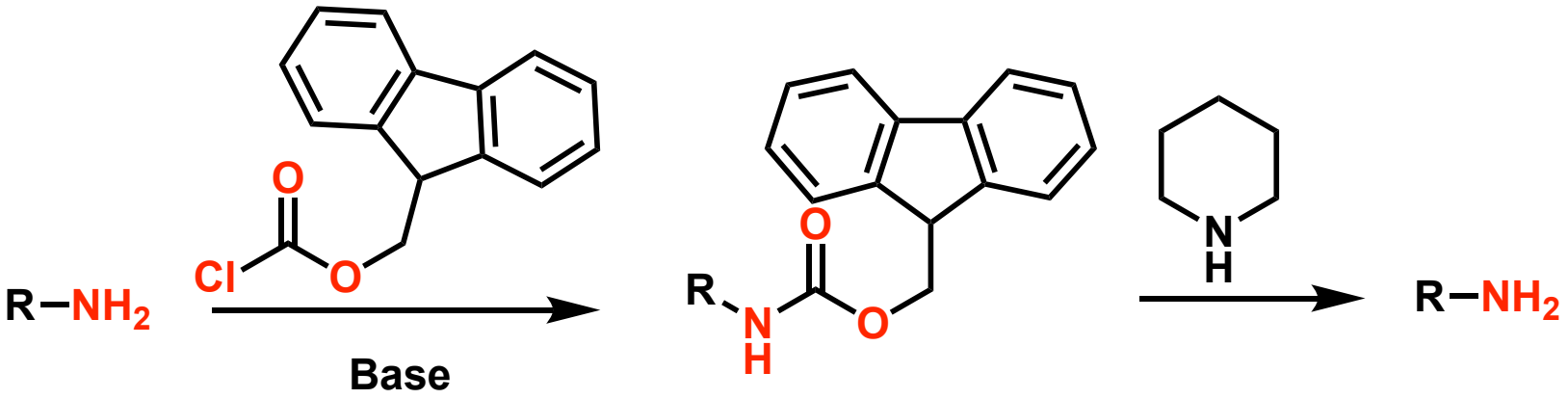
3M HCl, EtOAc

TFA, PhSH, DCM

AcCl, MeOH

CAN, CH_3CN

9-Fluroenylmethyloxy carbonyl (Fmoc)



Formation: Fmoc-Cl, $NaHCO_3$, aq. Dioxane

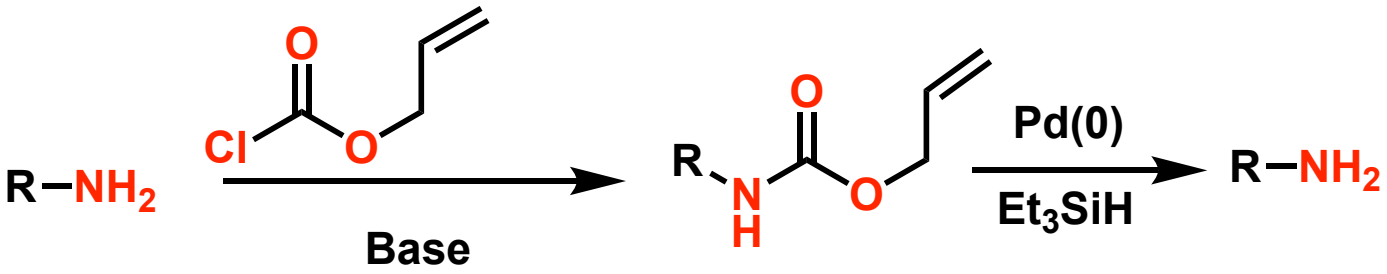
Fmoc-OC_6F_5, $NaHCO_3$, acetone

Cleavage: Amine bases

Piperidine, morpholine, diisopropylethyl amine

TBAF, DMF

Allyloxycarbonyl (Alloc)



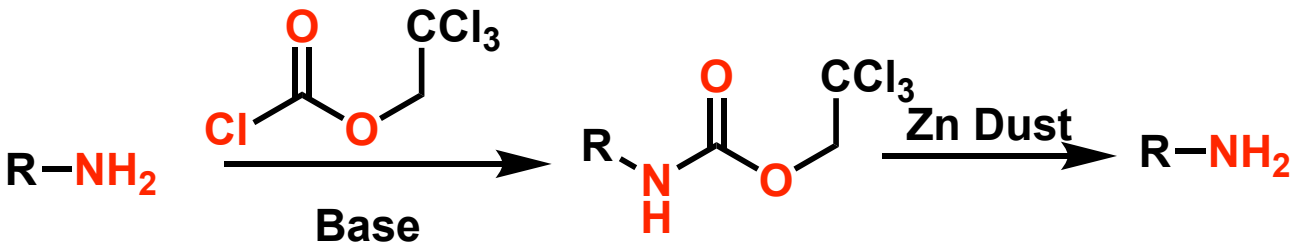
Formation: $CH_2=CHCH_2OCOCl$, py

$(CH_2=CHCH_2OCO)_2O$, DCM

Cleavage: $Pd(Ph_3P)_4$, TBTH, AcOH

$Pd(Ph_3P)_4$, Dimedone, THF

Trichloroethyloxycarbonyl (Troc)

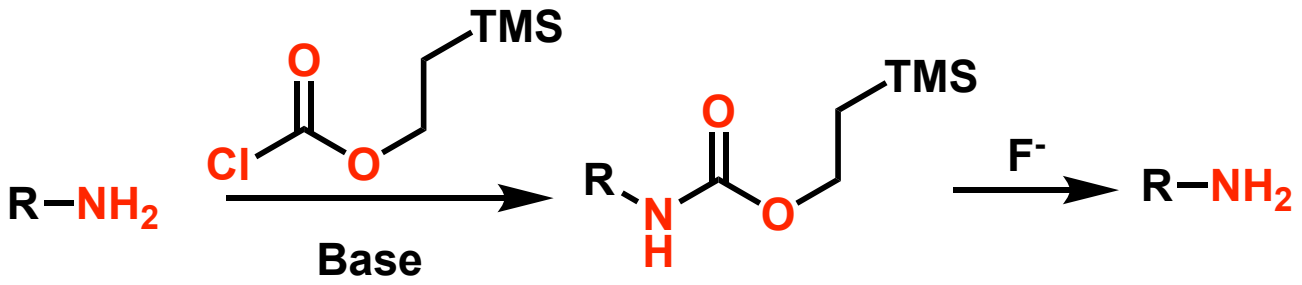


Formation: Cl_3CCH_2OCOCl, Py or aq. NaOH

Cleavage: Zn, THF, H_2O, pH= 4.2

Zn-Pb couple, 4:1 THF/ 1M NH_4OAc

Trimethylsilylethyloxycarbonyl (Teoc)



Formation: $TMSCH_2CH_2OCOCl$ (Teo-Cl) or Teoc-N3

Teoc-OC_6H_4-4-NO_2, NaOH

Teoc-OSu, TEA

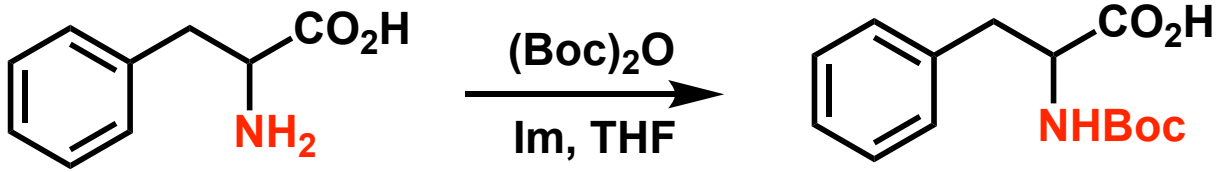
Cleavage: TBAF, CH_3CN

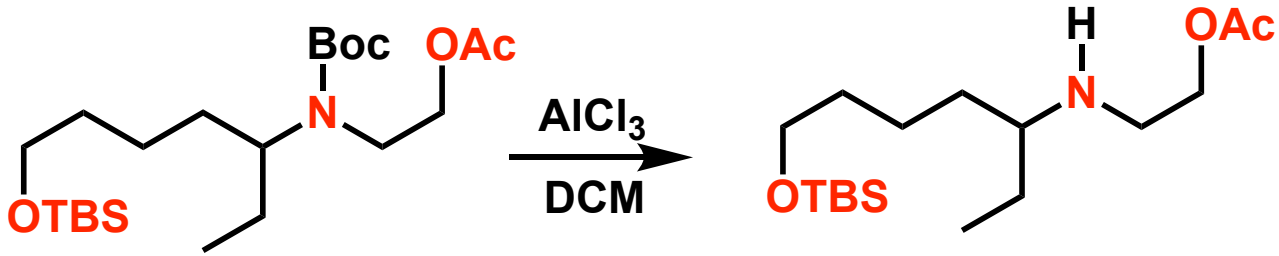
HF, Py, THF

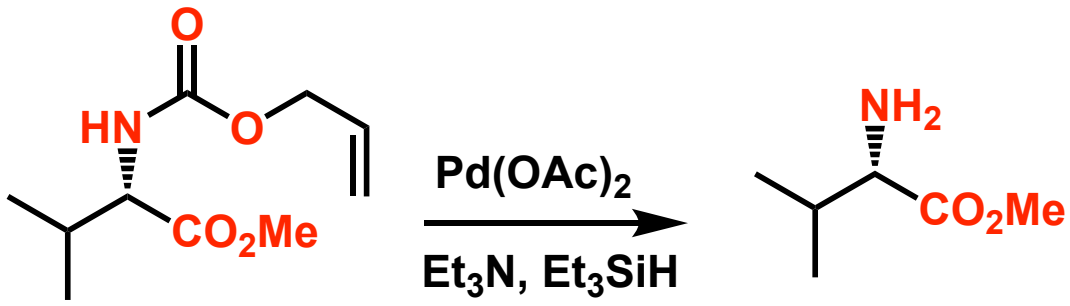
KF, CH_3CN

TAST, CH_3CN

Examples


CO2H
NH2
(Boc)2O
Im, THF
CO2H
NHBoc


Boc
OAc
N
OTBS
AlCl3
DCM
H
N
OAc
OTBS


O
HN
O
CO2Me
Pd(OAc)2
Et3N, Et3SiH
NH2
CO2Me