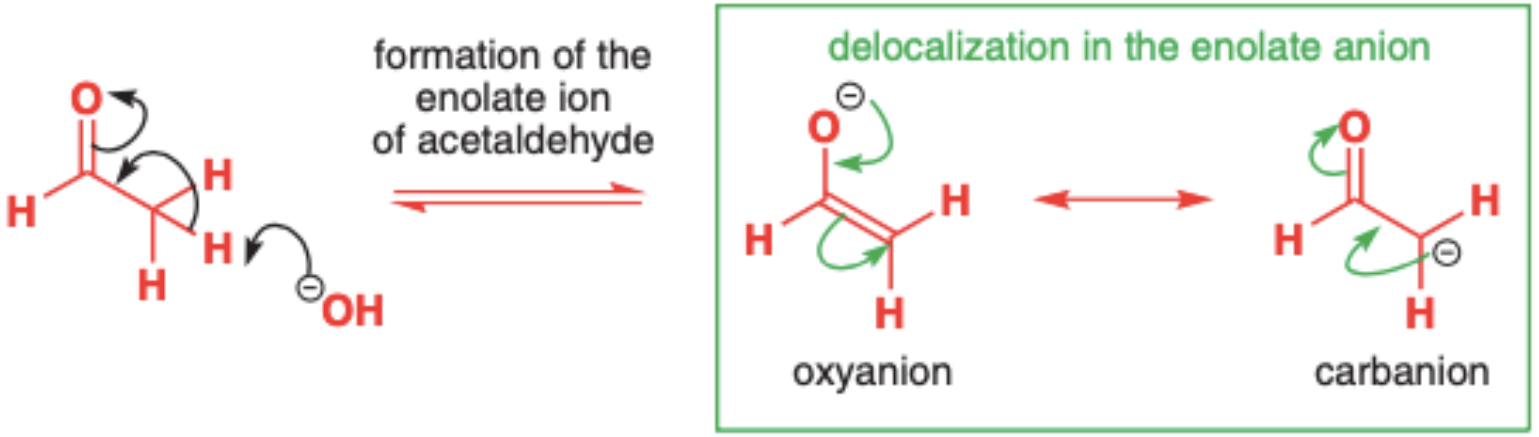
LS 2022

Lecture 2: 2022-12-13

Enol and enolates



The negative charge is mainly on oxygen,
the most electronegative atom.

Enol and enolates

typical reaction of an enolate at carbon:

reaction of an enolate with hard electrophiles (Me_3SiCl, Me_3O^+, AcCl) at oxygen

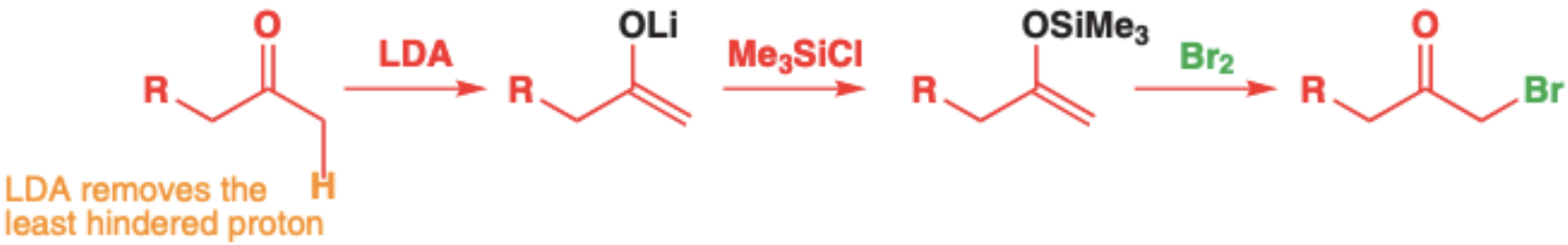
soft electrophiles react at C

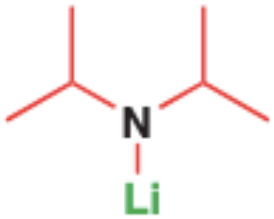
X = I, Br, Cl

hard electrophiles react at O

X = OMs, OSO_2OMe, $^+OMe_2$

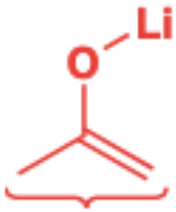
Enol and enolates



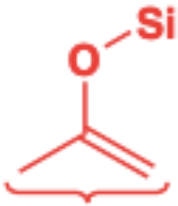


LDA =
lithium
disopropyl
amide

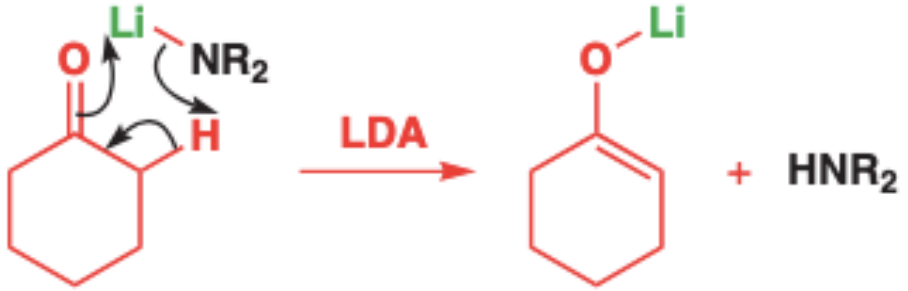
Stable equivalents of enolate ions



lithium enolate



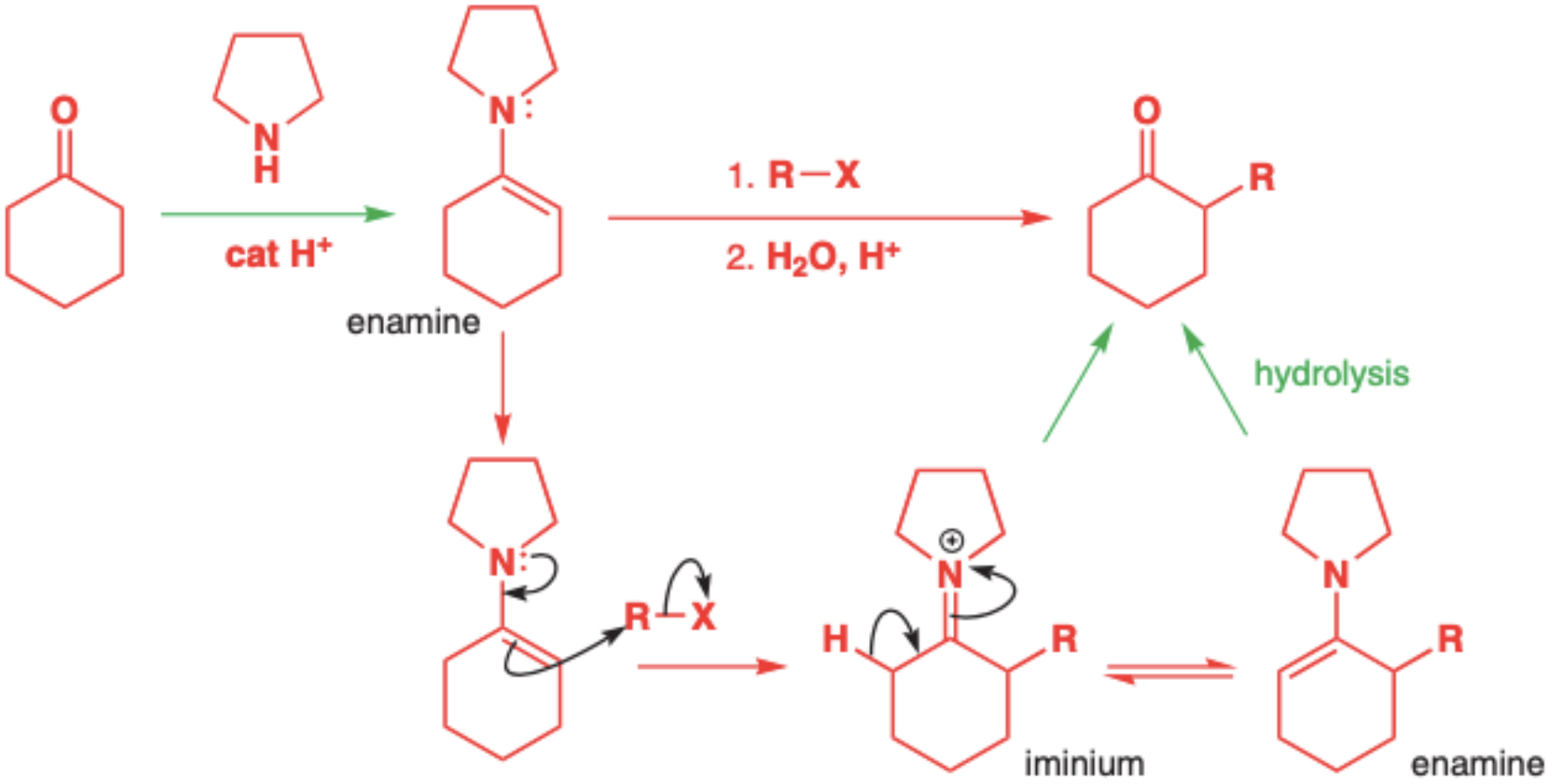
silyl enol ether



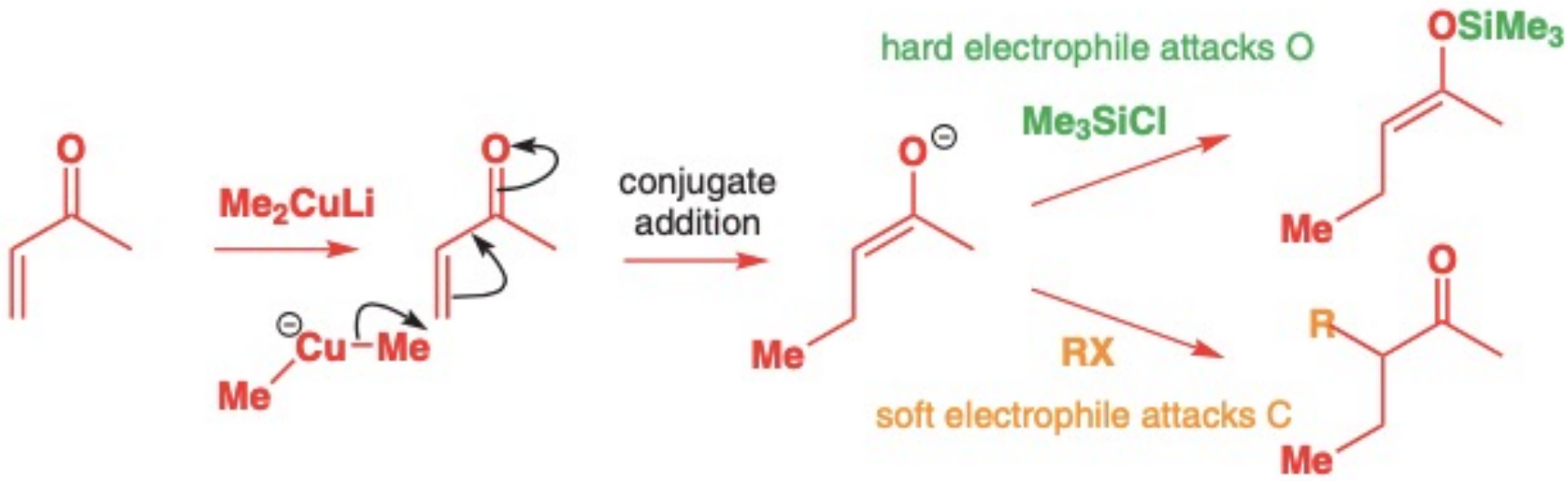
lithium enolate

silyl enol ether

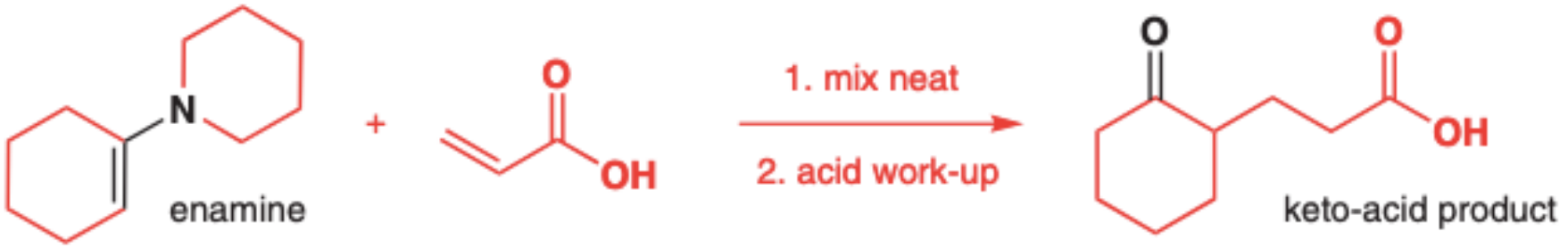
Enamines

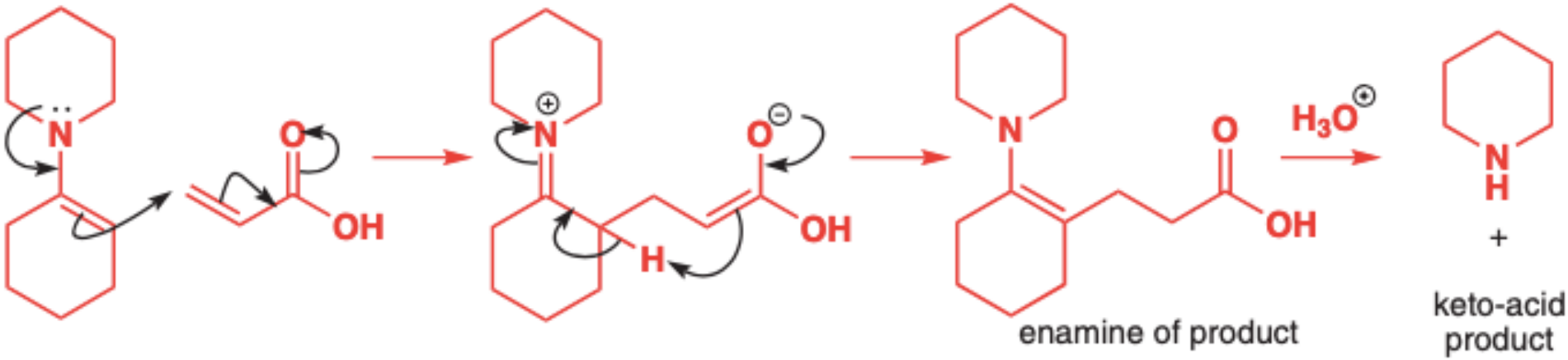

O
N
H
cat H+
N:
enamine
1. R—X
2. H2O, H+
O
R
hydrolysis
N:
R—X
N
H
R
iminium
N
R
enamine

Conjugated additions to enones



Conjugated additions

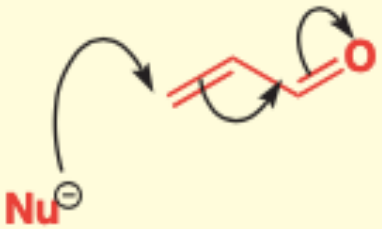




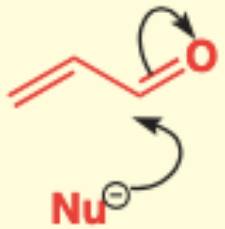
1,2-addition and 1,4-addition

Conjugate addition or direct addition?

- **Conjugate addition to C=C (also called 1,4-addition)**



- **Direct addition to C=O (also called 1,2-addition)**

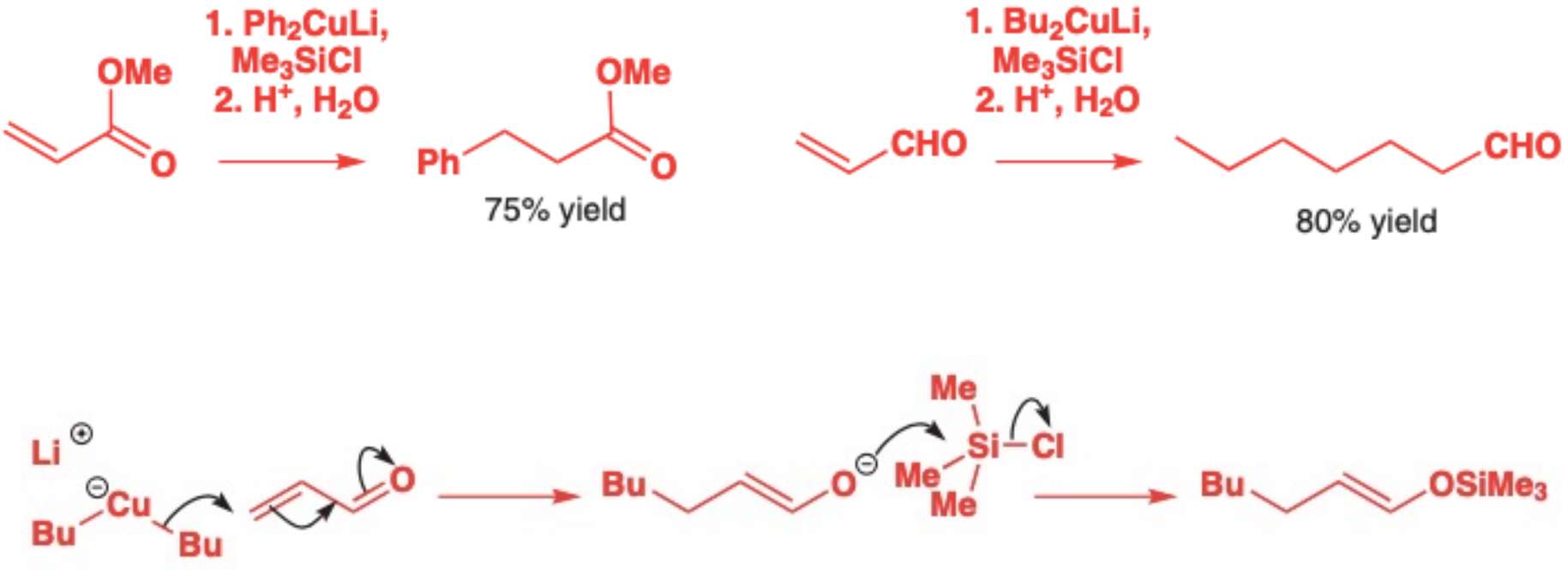


Hard and soft nucleophiles

Hard nucleophiles	Borderline	Soft nucleophiles
F^-, OH^-, RO^-, SO_4^{2-}, Cl^-	N_3^-, **CN^-**	**I^-, RS^-,** RSe^-, S^{2-}
H_2O, ROH, ROR′, RCOR′	**RNH_2, R^1R^2NH**	**RSH,** RSR′, R_3P
NH_3, RMgBr, RLi	**Br^-**	alkenes, aromatic rings

- **Hard/soft—direct/conjugate addition**
  - Hard nucleophiles tend to react at the carbonyl carbon (hard) of an enone.
  - Soft nucleophiles tend to react at the β carbon (soft) of an enone and lead to conjugate addition.

Conjugate addition or direct addition?



Selectivity

Conjugate (1,4 or Michael) vs direct (1,2) addition

	Conjugate addition favoured by	Direct addition to C=O favoured by
Reaction conditions (for reversible additions):	thermodynamic control: high temperatures, long reaction times	kinetic control: low temperatures, short reaction times
Structure of α,β-unsaturated compound:	unreactive C=O group (amide, ester)	reactive C=O group (aldehyde, acyl chloride)
	unhindered β carbon	hindered β carbon
Type of nucleophile:	soft nucleophiles	hard nucleophiles
Organometallic:	organocoppers or catalytic Cu(I)	organolithiums, Grignard reagents

Chemoselectivity and protecting groups

Selectivity

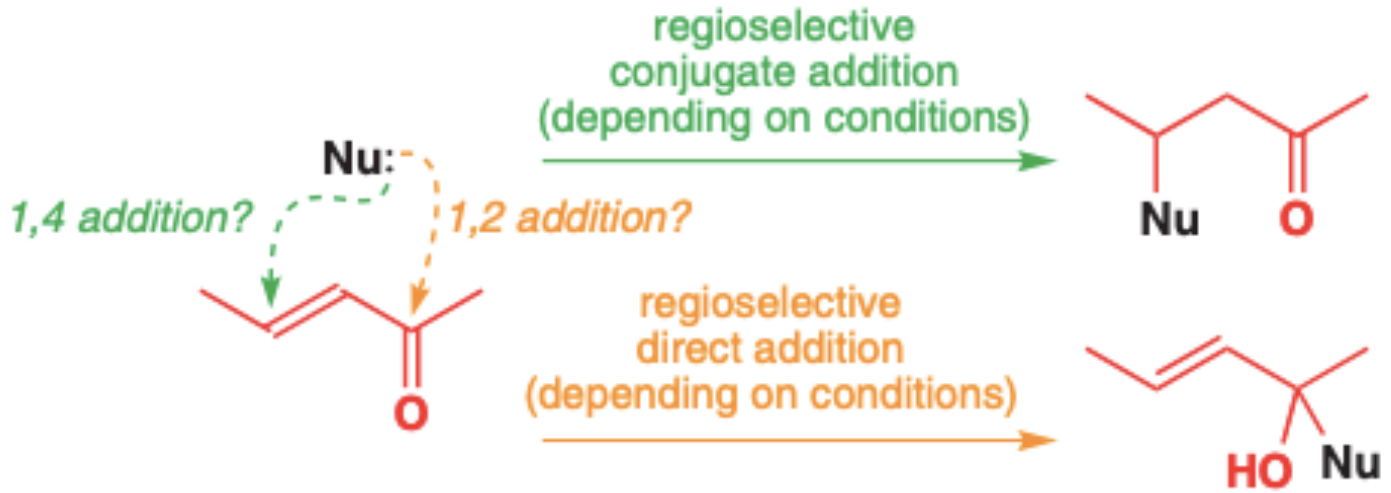
Most organic molecules contain more than one functional group, and most functional groups can react in more than one way.

Chemoselectivity: which functional group will react?

Regioselectivity: where it will react?

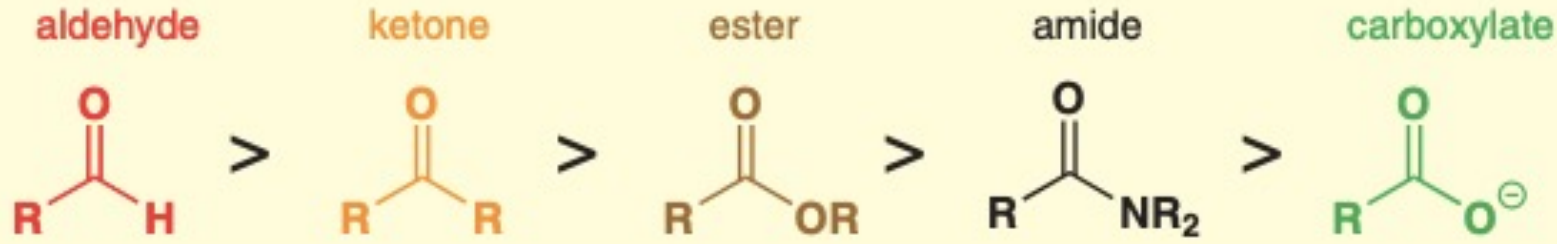
Stereoselectivity: how it will react (stereochemistry)

Selectivity

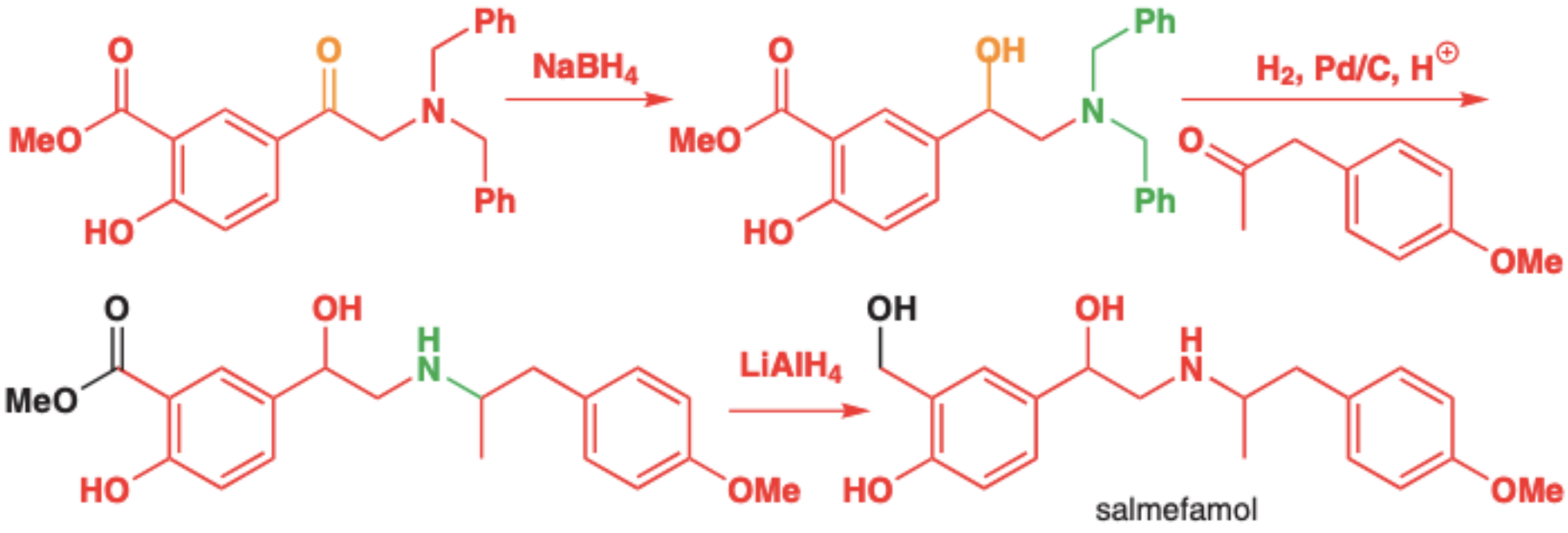


Carboxylic acid derivatives

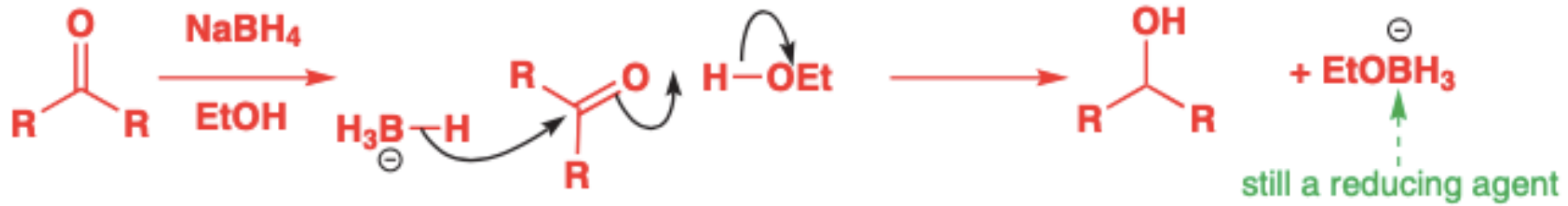
- **Reactivity towards nucleophiles**



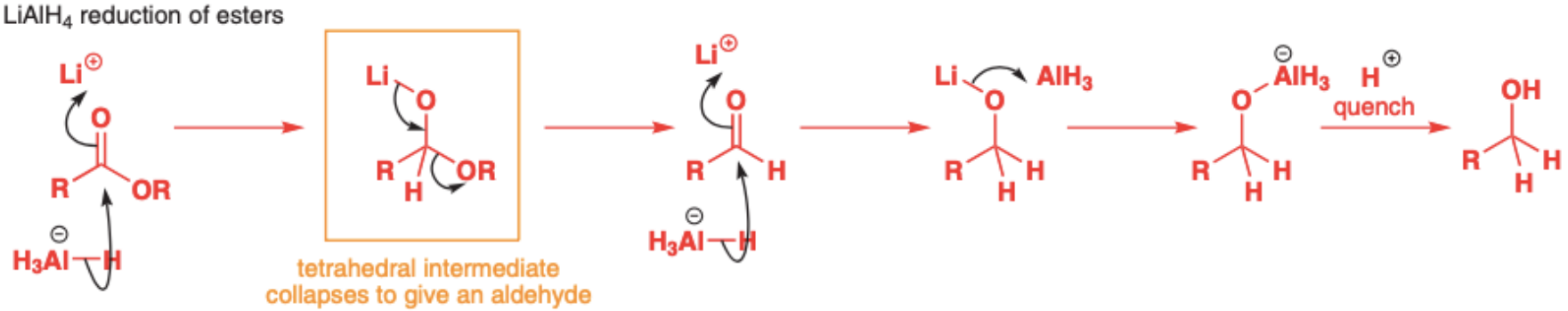
Reductions

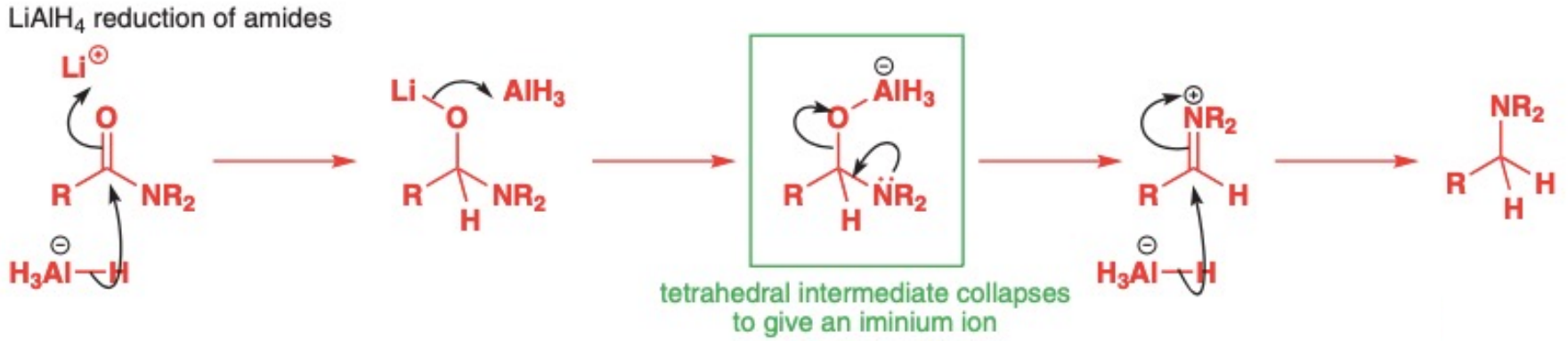


How to reduce aldehydes and ketones to alcohols

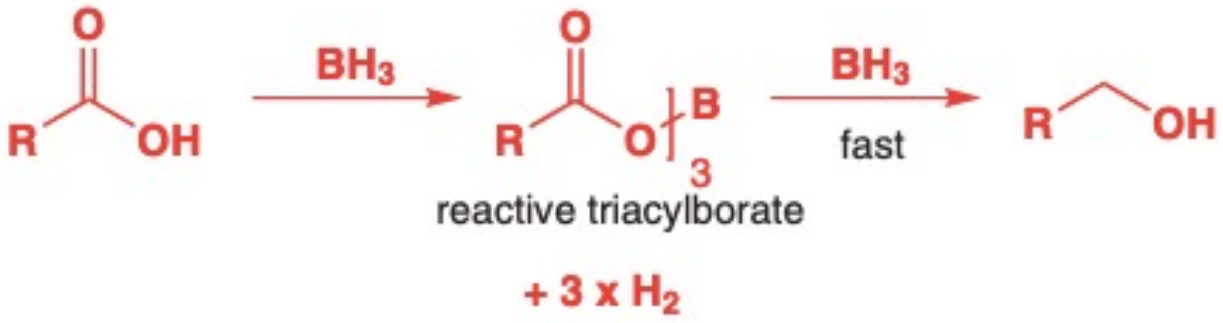


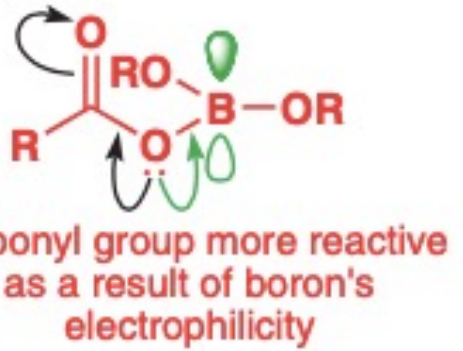
How to reduce esters and amides to alcohols



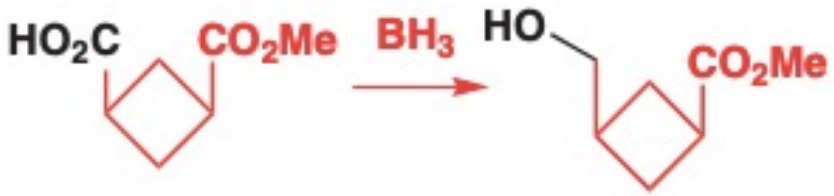


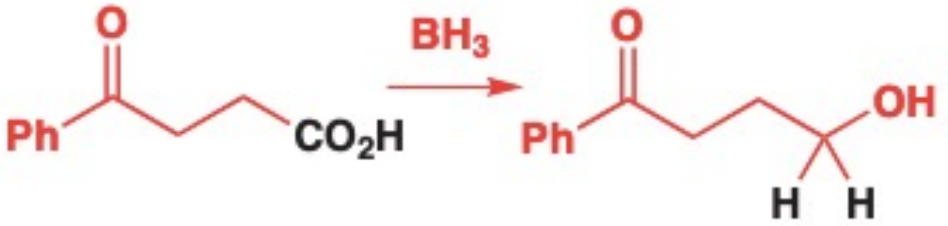
How to reduce carboxylic acids to alcohols



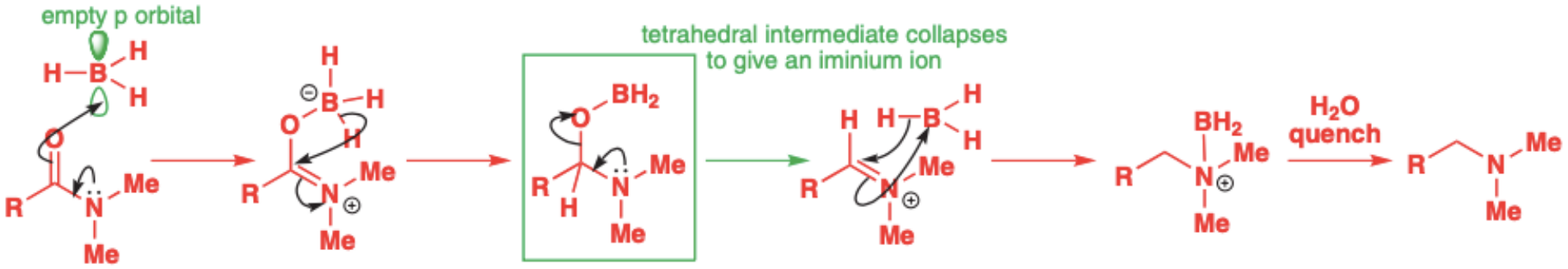


Chemoselectivity

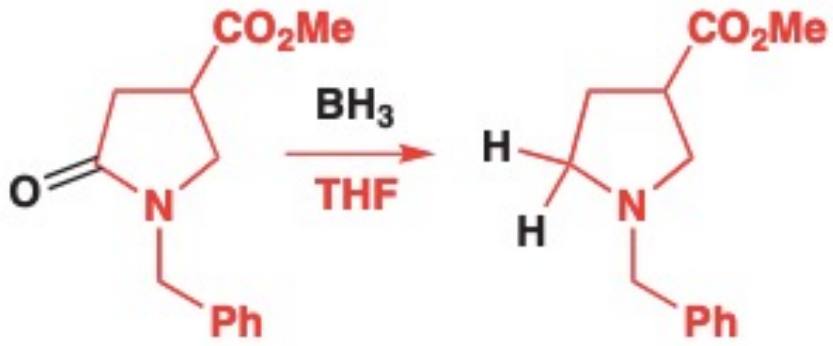




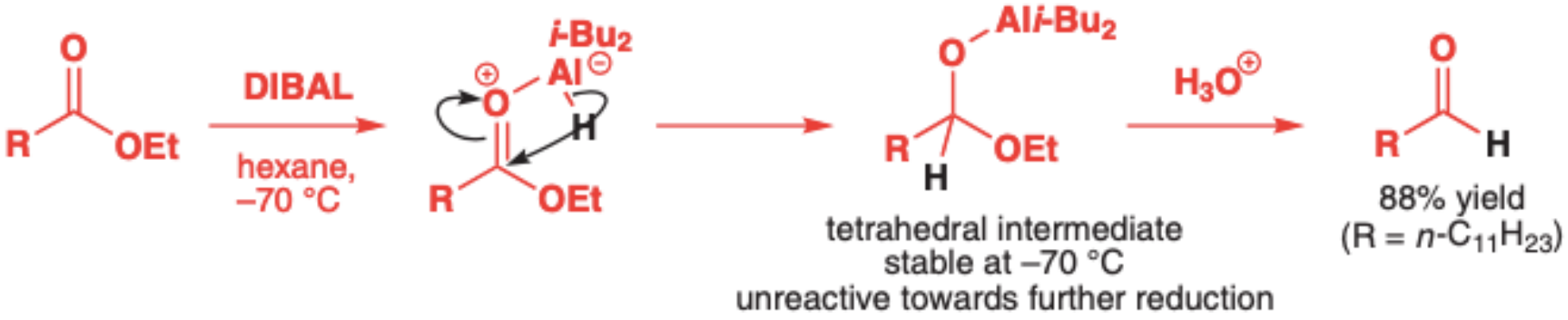
How to reduce amides to amines



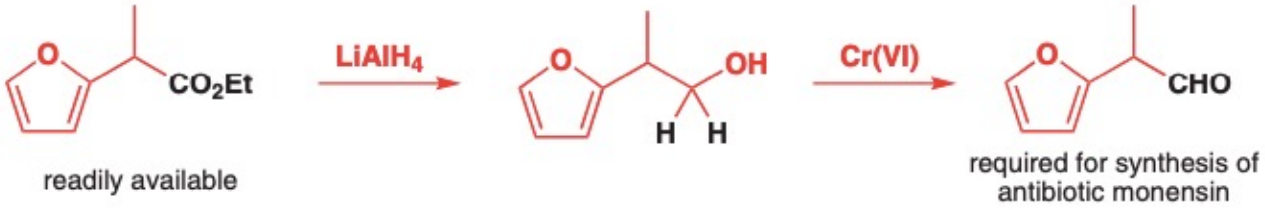
Chemoselectivity

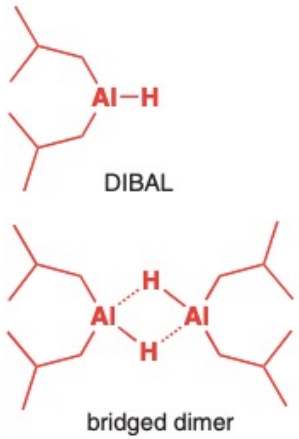


How to reduce esters or amides to aldehydes

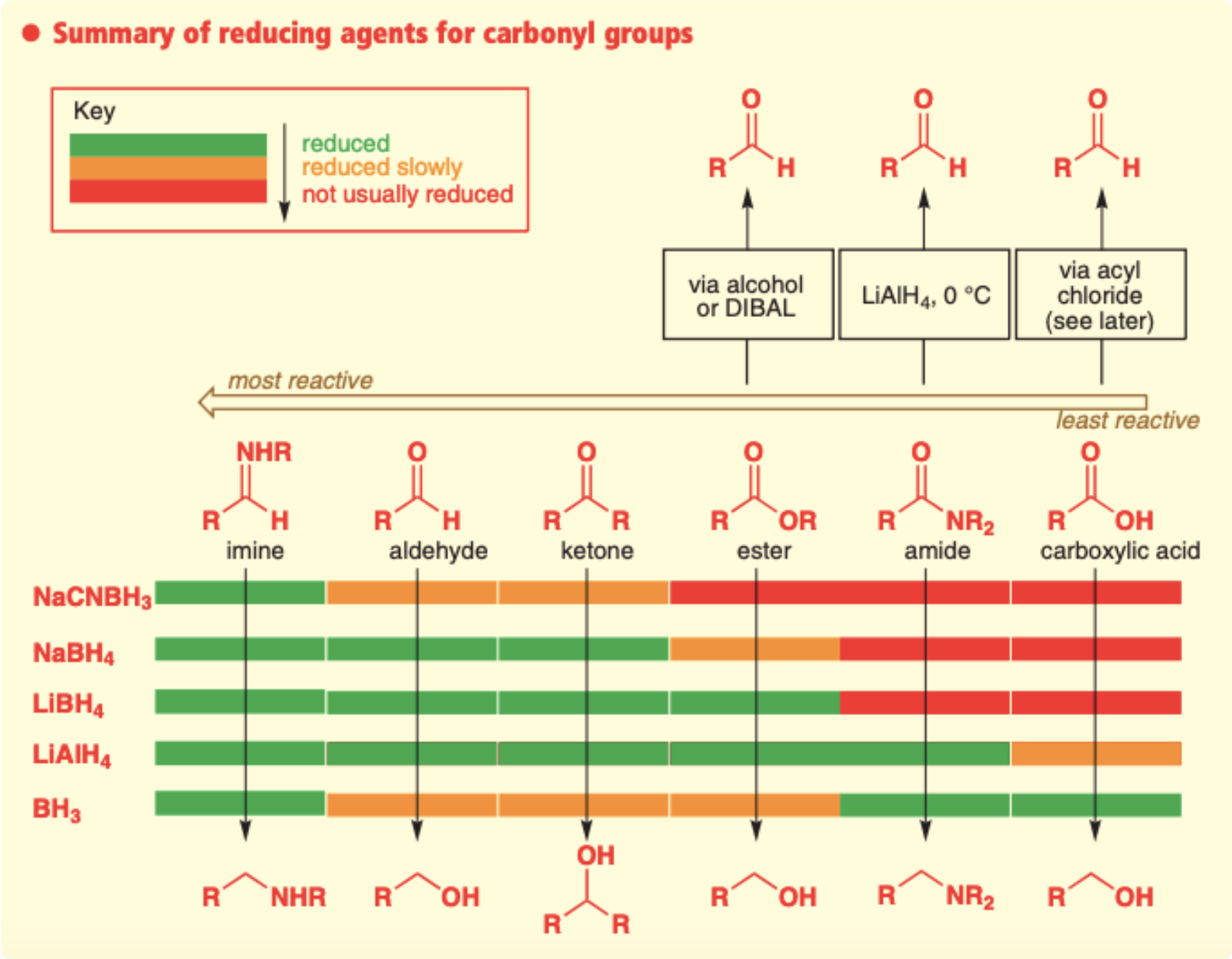


This is not a general reaction, and it will depends on substrate's "reactivity"

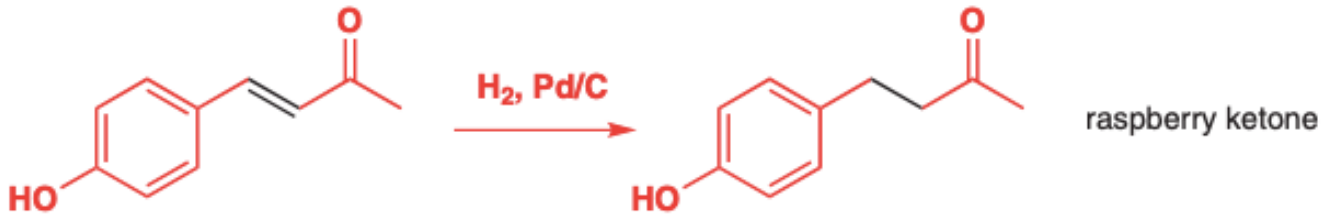




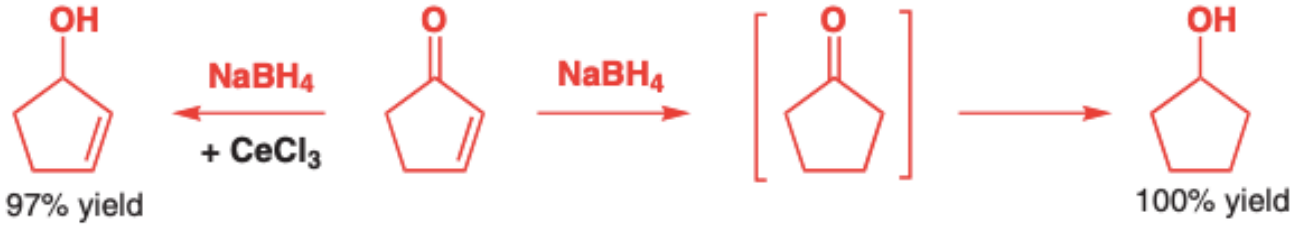
Summary 1


Summary of reducing agents for carbonyl groups
Key
reduced
reduced slowly
not usually reduced
via alcohol or DIBAL
LiAlH4, 0 °C
via acyl chloride (see later)
most reactive
least reactive
imine
aldehyde
ketone
ester
amide
carboxylic acid
NaCNBH3
NaBH4
LiBH4
LiAlH4
BH3

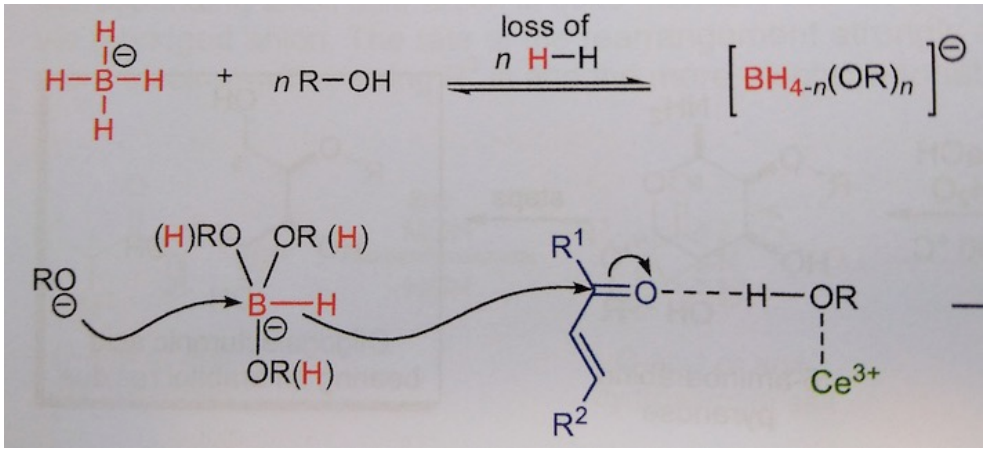
How to reduce α,β-unsaturated carbonyl compounds



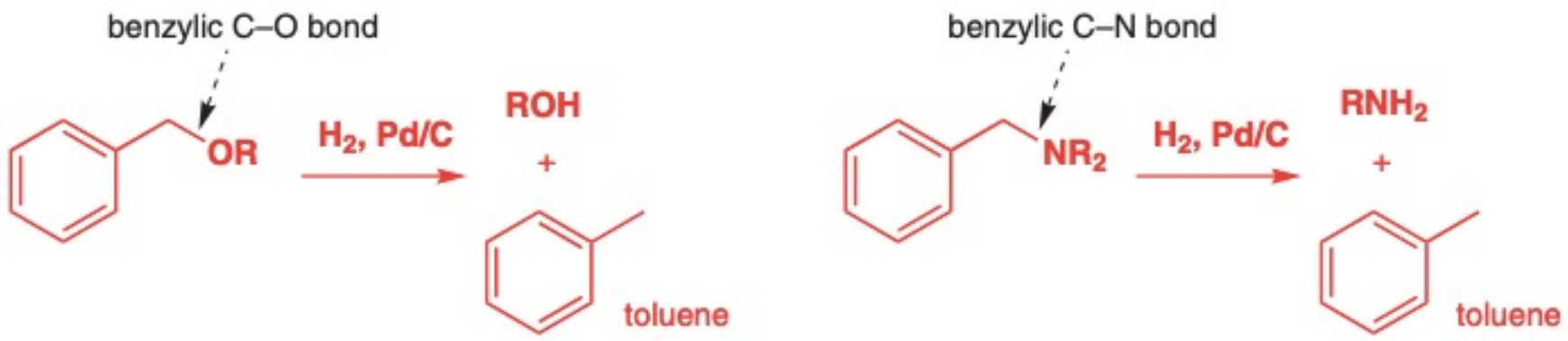
Chemoselectivity



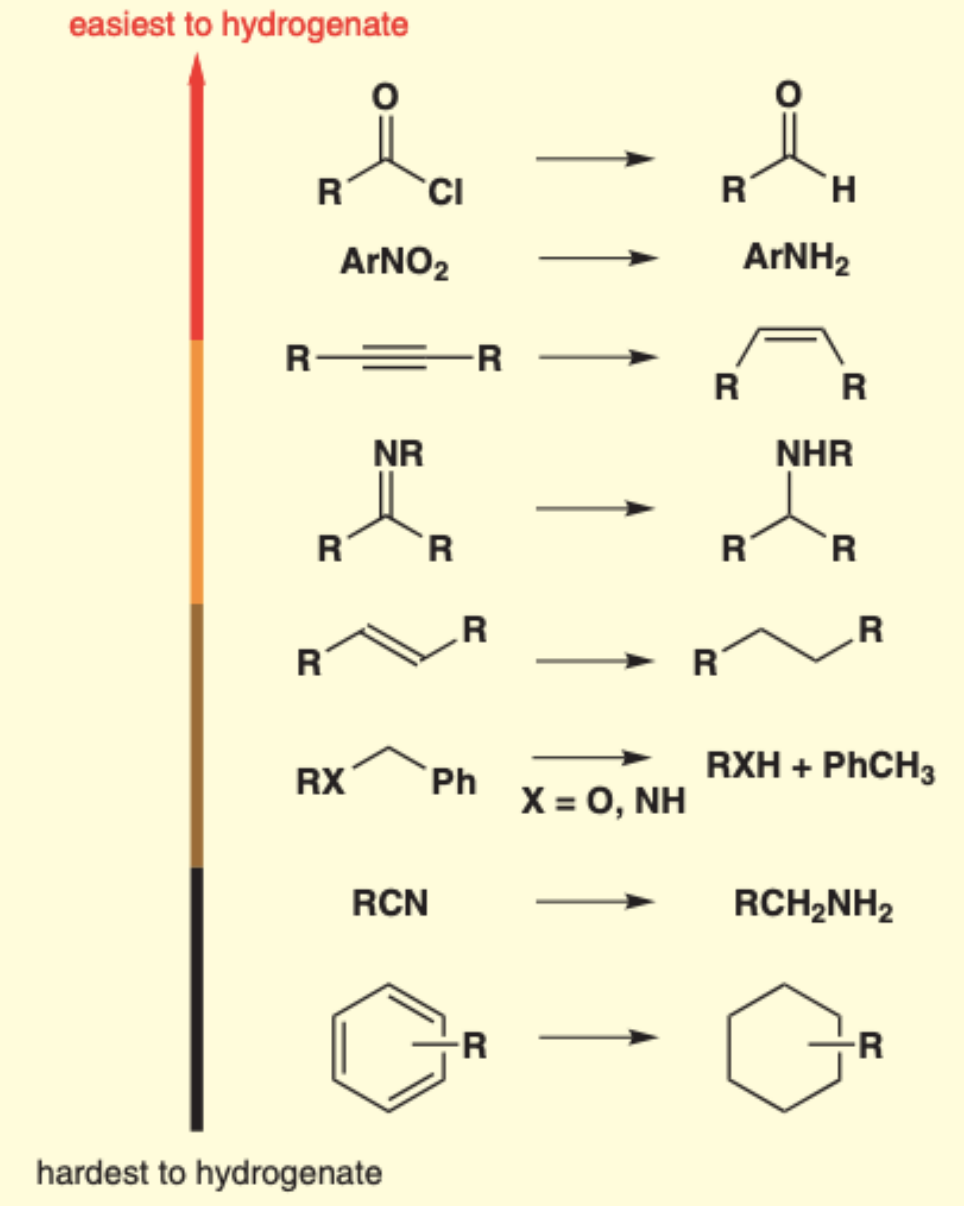
Luche reduction: Hard, Lewis-acidic metal salt ($CeCl_3$) in combination with $NaBH_4$ regioselectively reduces the carbonyl group.



Hydrogenolysis: breaking C-O and C-N bonds



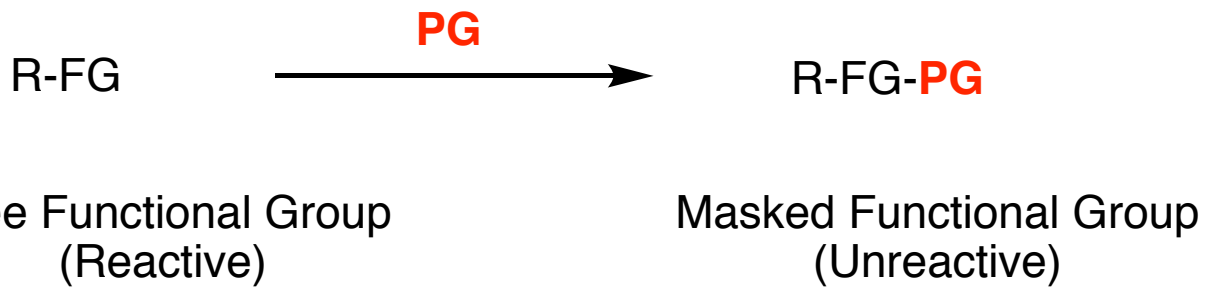
Summary 2


easiest to hydrogenate
O
R
Cl
O
R
H
ArNO2
ArNH2
R
R
R
R
NR
R
R
NHR
R
R
R
R
R
R
RX
Ph
X = O, NH
RXH + PhCH3
RCN
RCH2NH2
R
R
hardest to hydrogenate

Protecting Groups

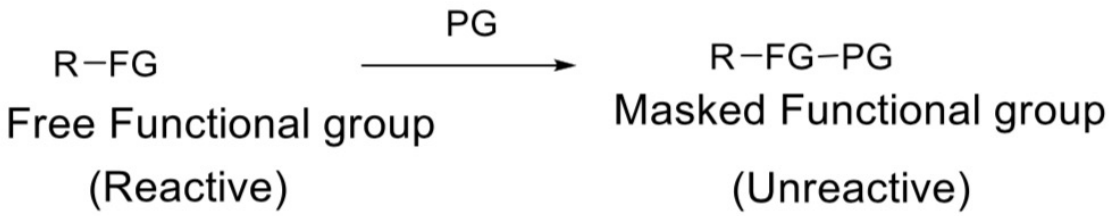
What is a protecting group?

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.



Protecting Groups

Qualities of a Good Protecting Group



A good protecting group should be such that:

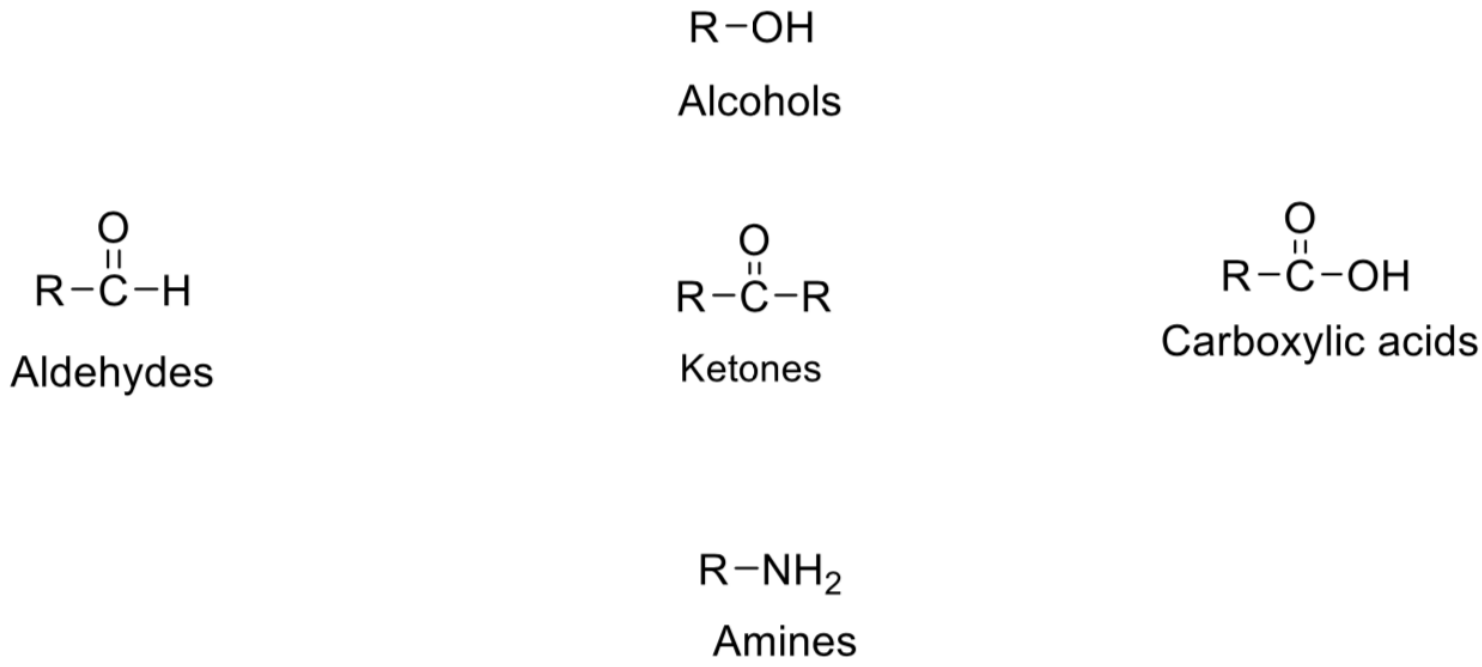
(a) It should be readily, but selectively introduced to the desired functional group in a poly-functional molecule.

(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.

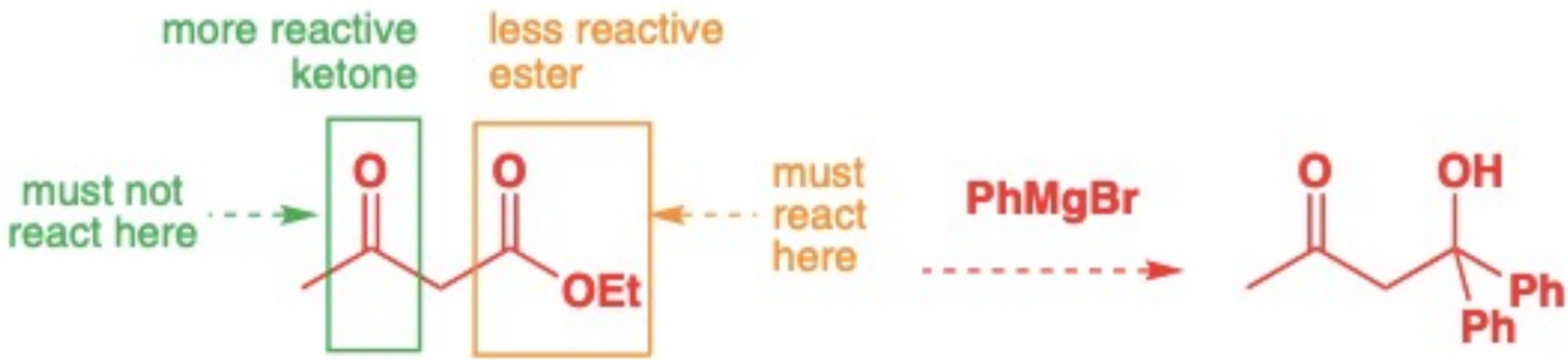
Protecting Groups

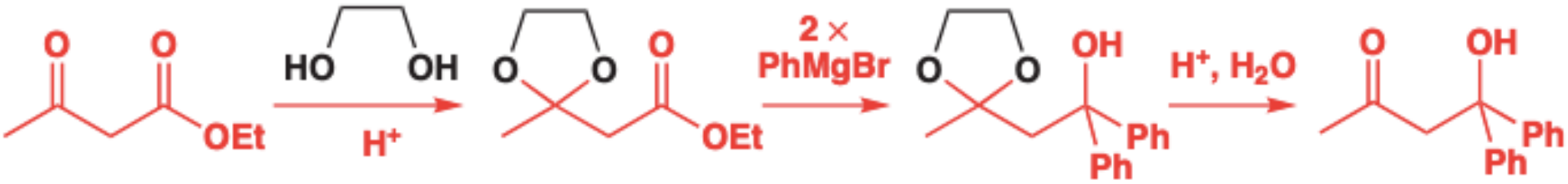
The Most Reactive Functional Groups Commonly Requiring Protection



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.

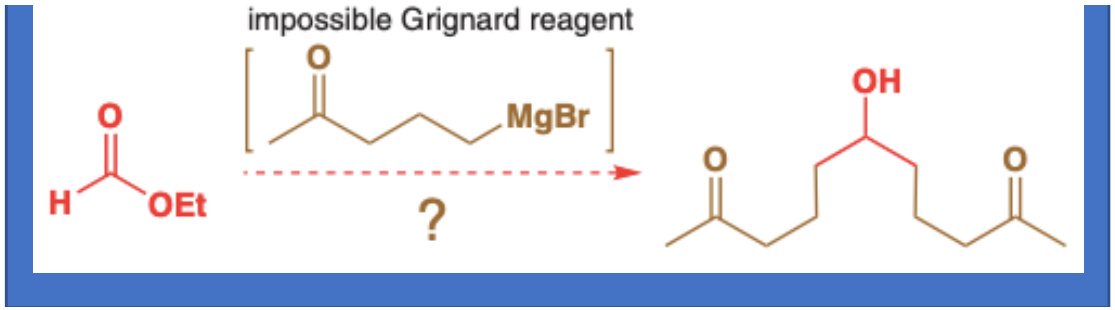
A survey of protecting groups

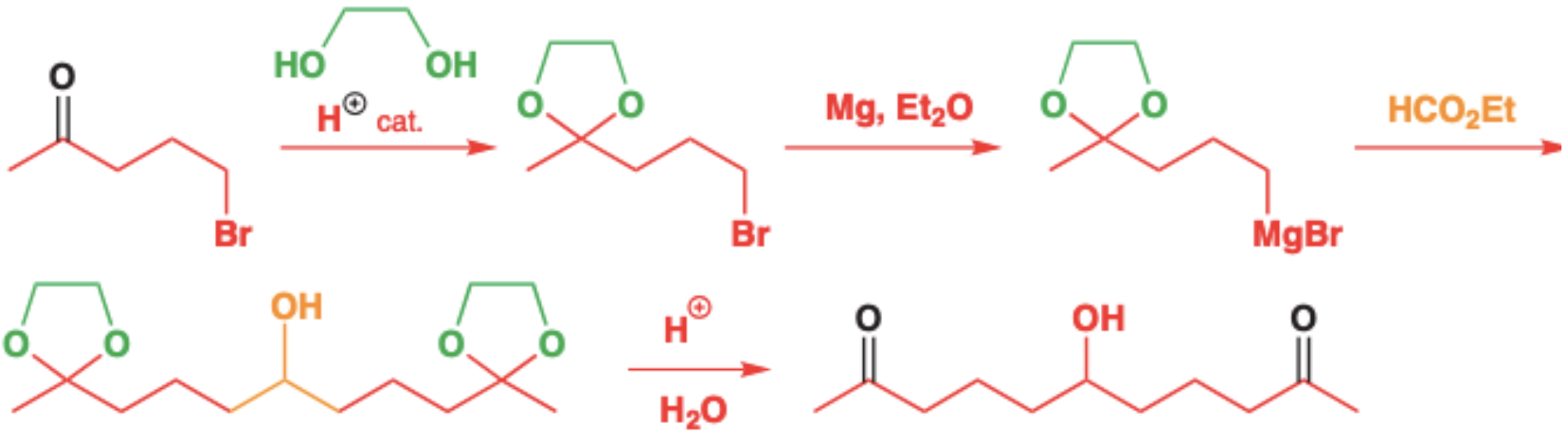




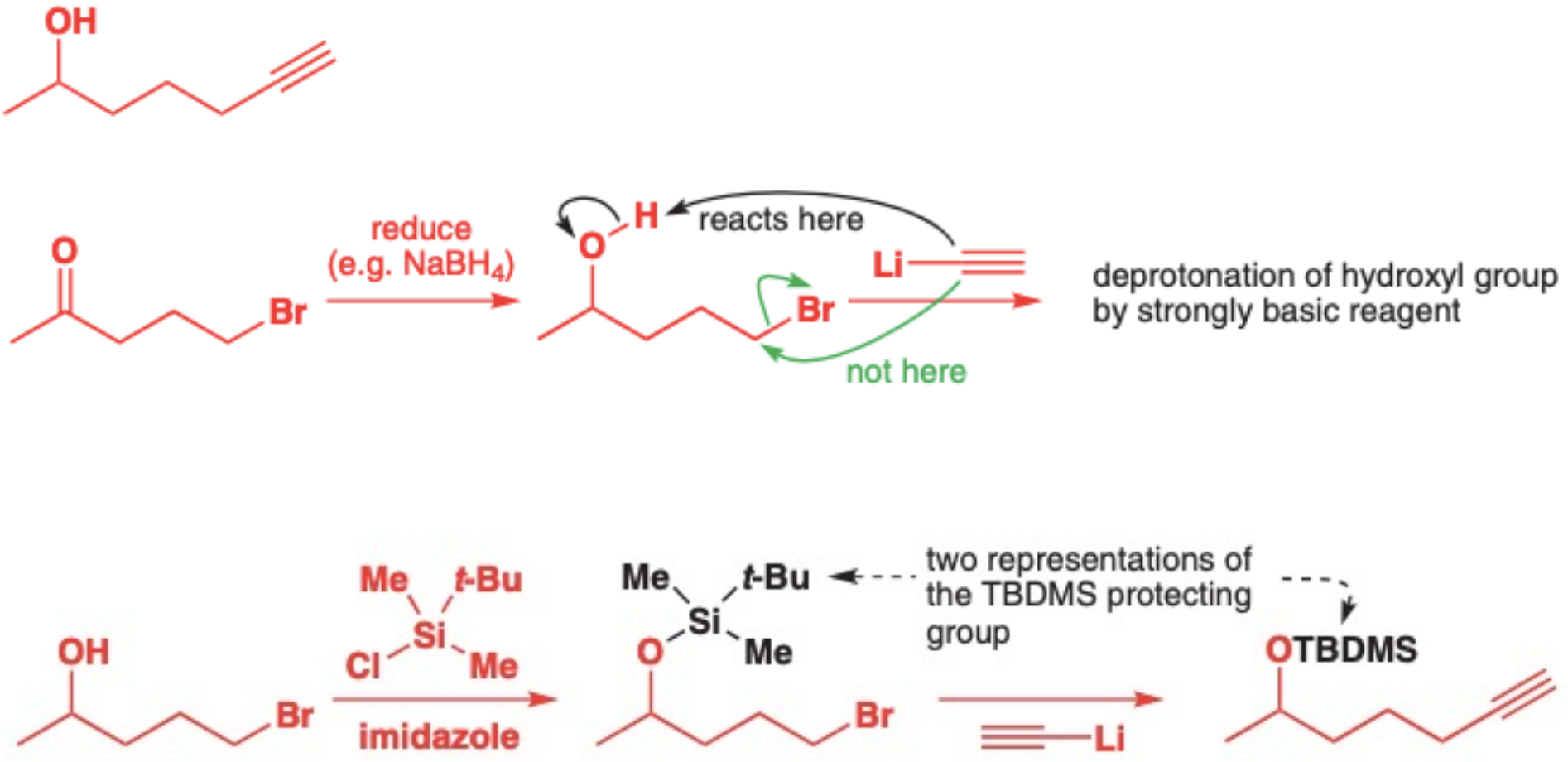
Protecting groups 1

Protecting group	Structure	Protects	From	To protect	To deprotect
acetal (dioxolane)		ketones, aldehydes	nucleophiles, bases		H^+, H_2O



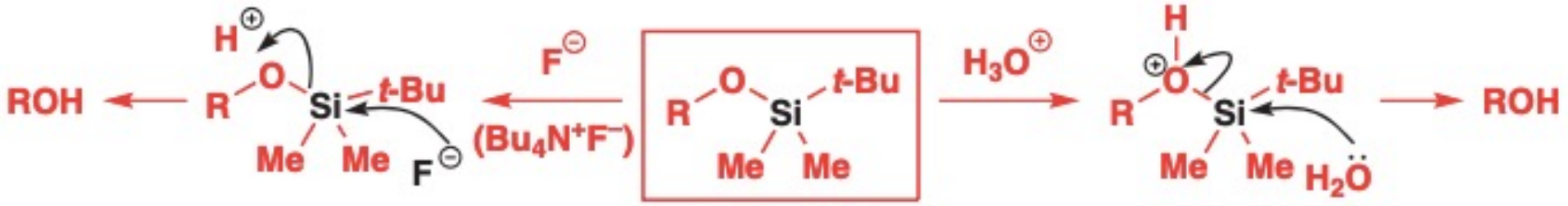


A survey of protecting groups

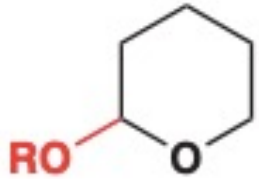


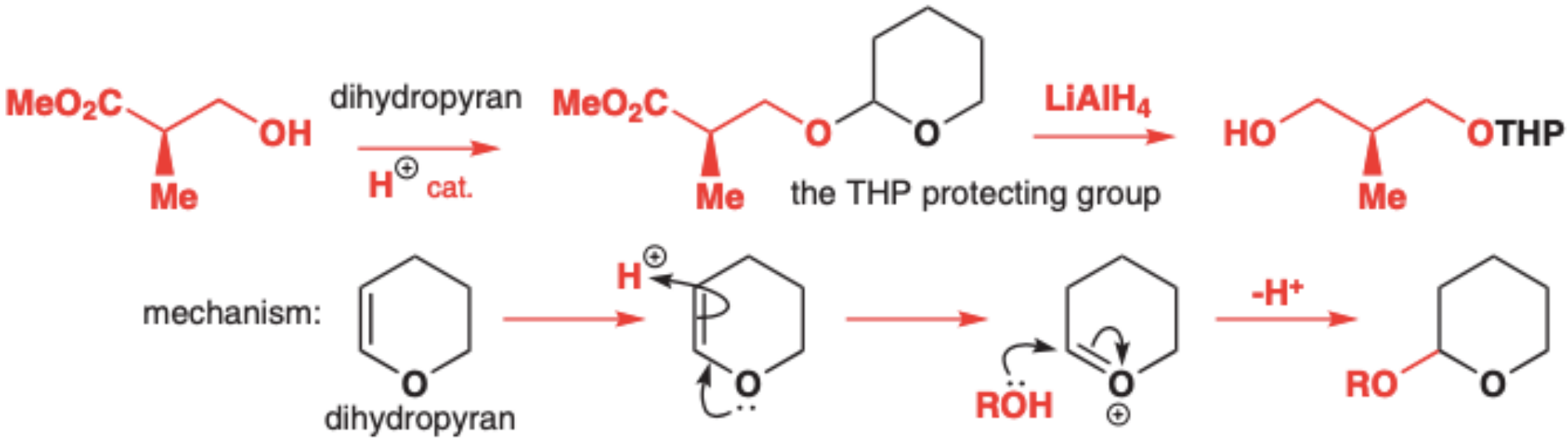
Protecting groups 2

Protecting group	Structure	Protects	From	Protection	Deprotection
trialkylsilyl R_3Si-, e.g. TBDMS	RO—$SiMe_3$ RO—$SiMe_2$*t*-Bu	alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-

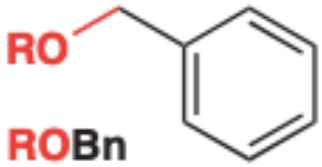
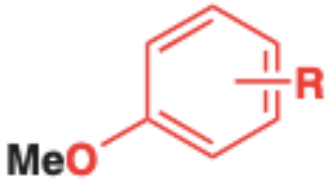


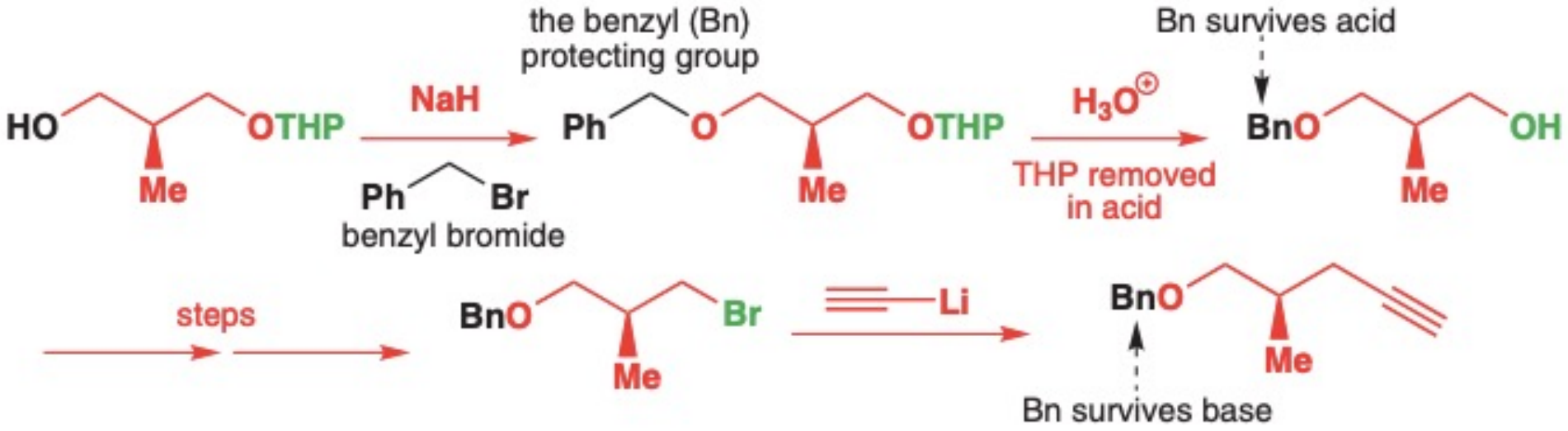
Protecting groups 3

Protecting group	Structure	Protects	From	To protect	To deprotect
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydro-pyran and acid	H^+, H_2O

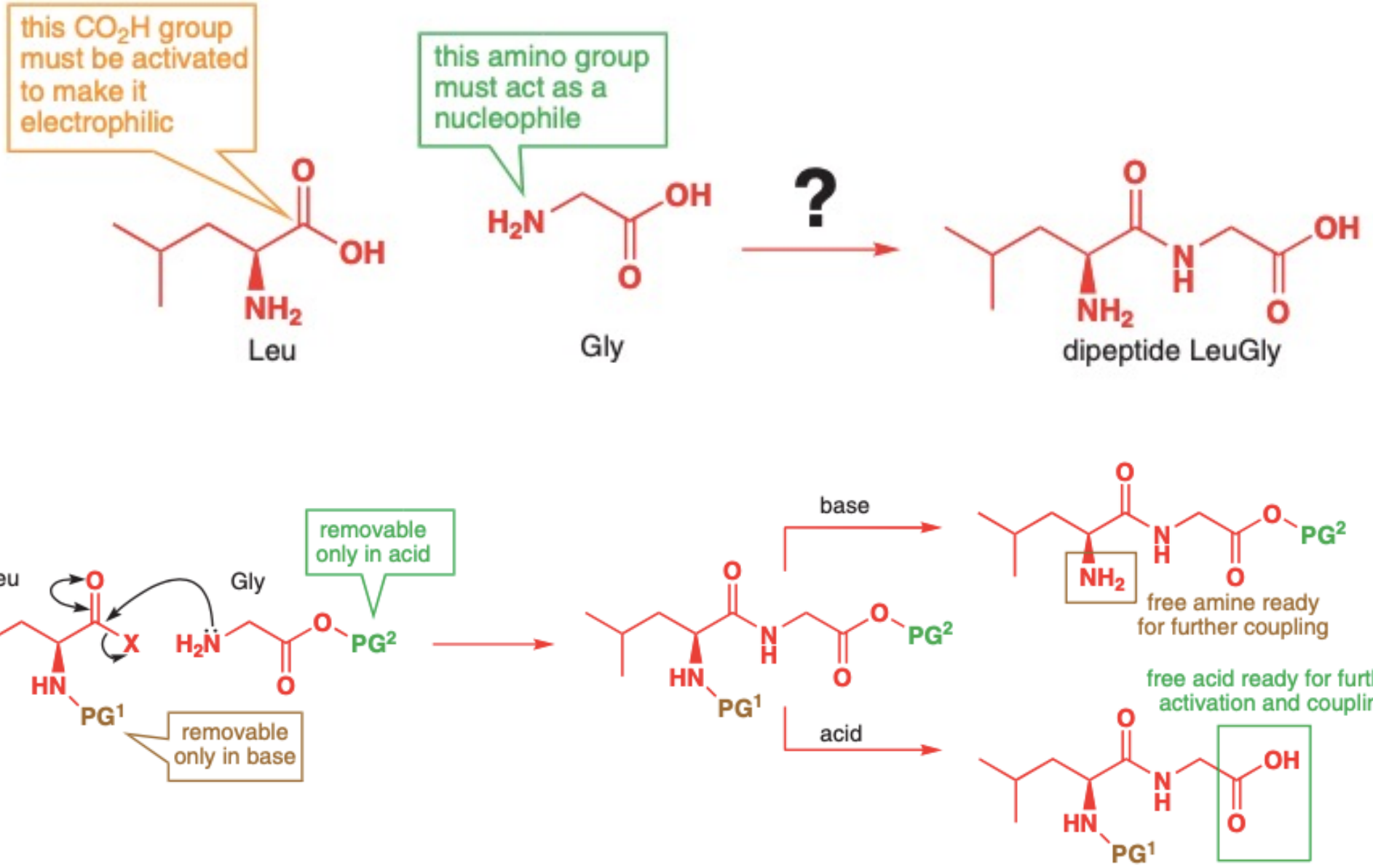


Protecting groups 4

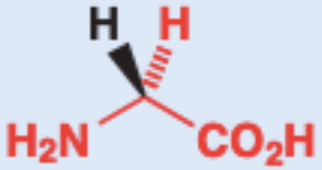
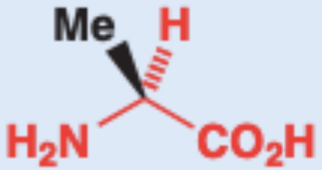
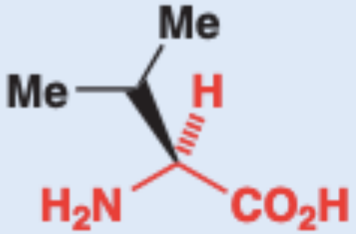
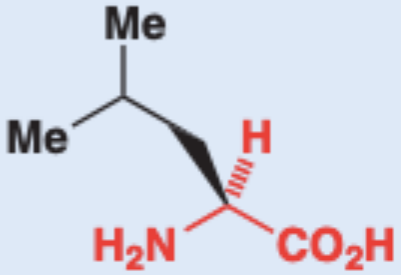
Protecting group	Structure	Protects	From	To protect	To deprotect
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI



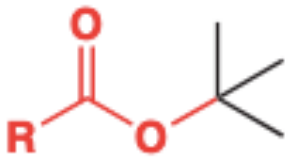
Peptide synthesis



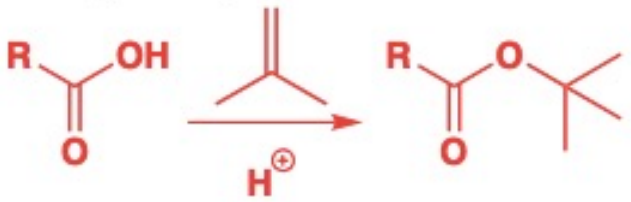
Some amino acids

Name	Three-letter code	One-letter code	Structure
glycine	Gly	G	
alanine	Ala	A	
valine	Val	V	
leucine	Leu	L	

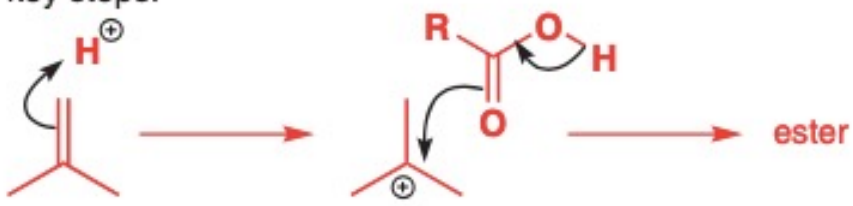
The (OtBu) protecting group

Protecting group	Structure	Protects	From	To protect	To deprotect
t-butyl ester (CO_2t-Bu)		carboxylic acids	nucleophiles	isobutene, H^+	strong acid

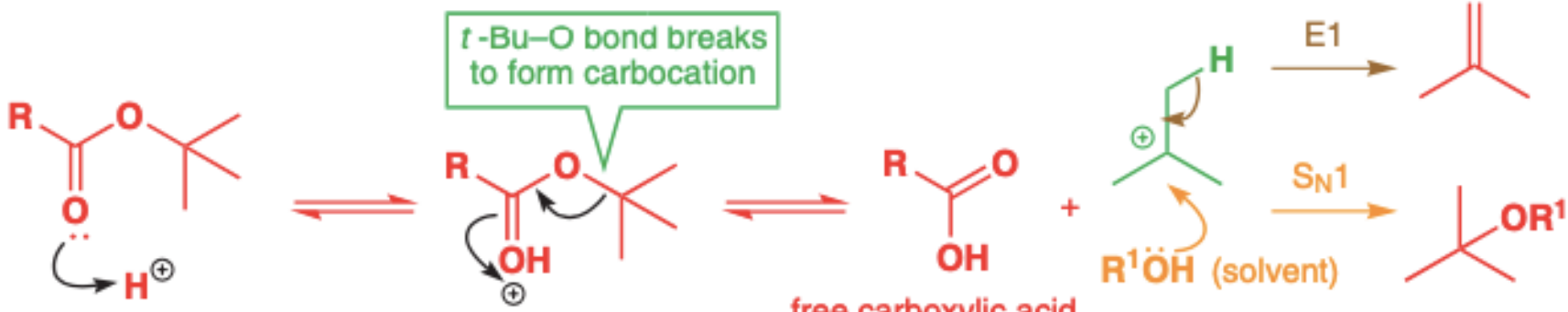
making a *t*-butyl ester



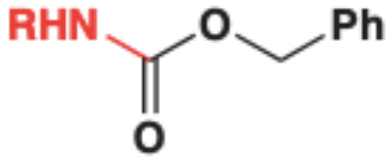
key steps:

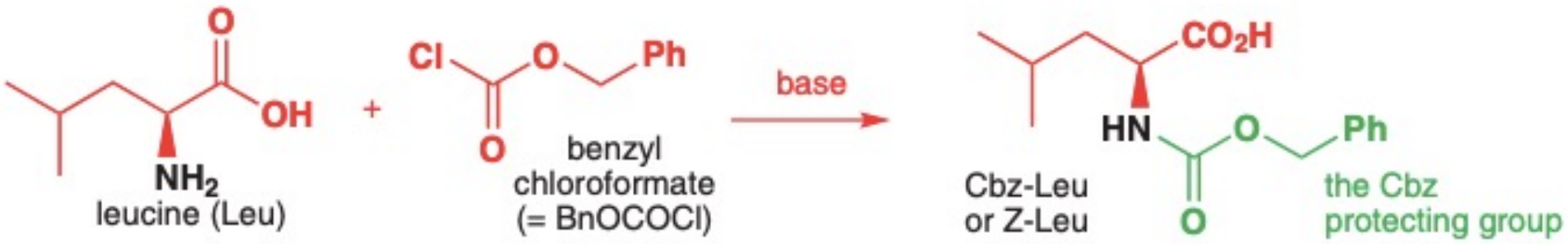


hydrolysis of *t*-butyl esters in acid:

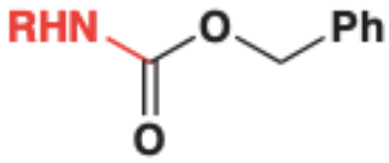


The Cbz protecting group

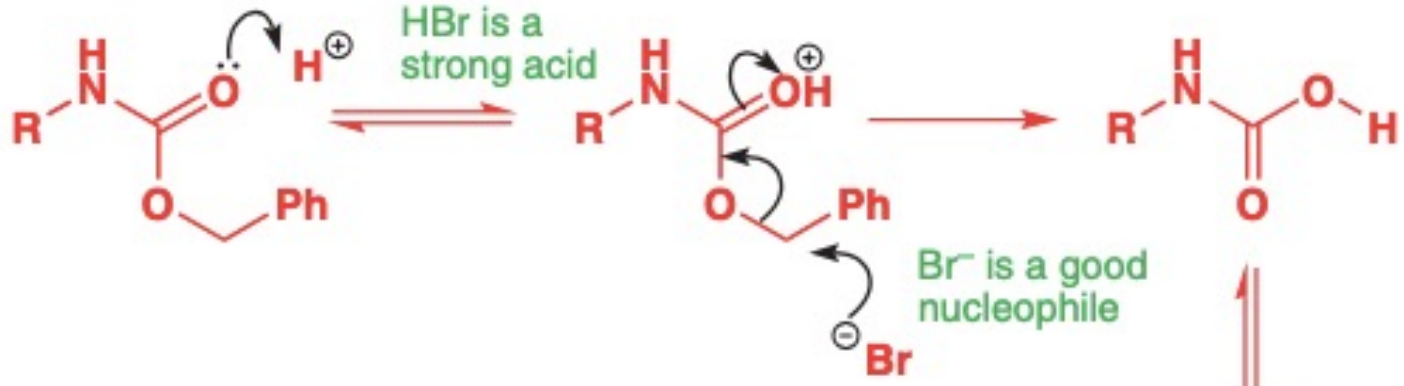
Protecting group	Structure	Protects	From	Protection	Deprotection
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH; or H_2, Pd



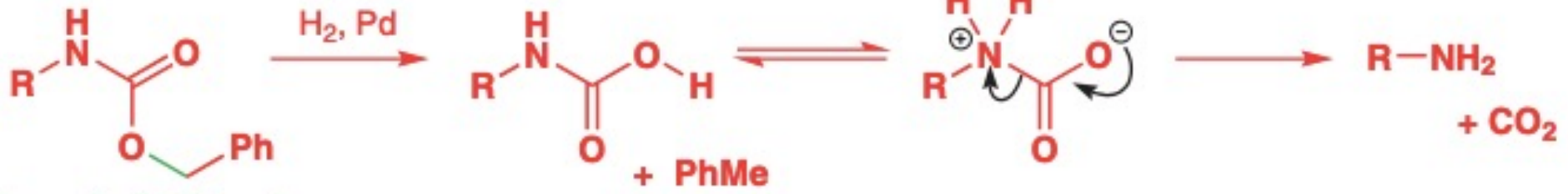
The Cbz protecting group

Protecting group	Structure	Protects	From	Protection	Deprotection
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH; or H_2, Pd

cleavage of Cbz (Z) in HBr/AcOH

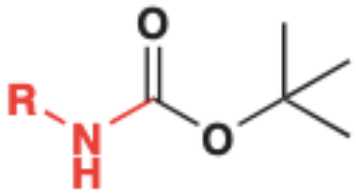


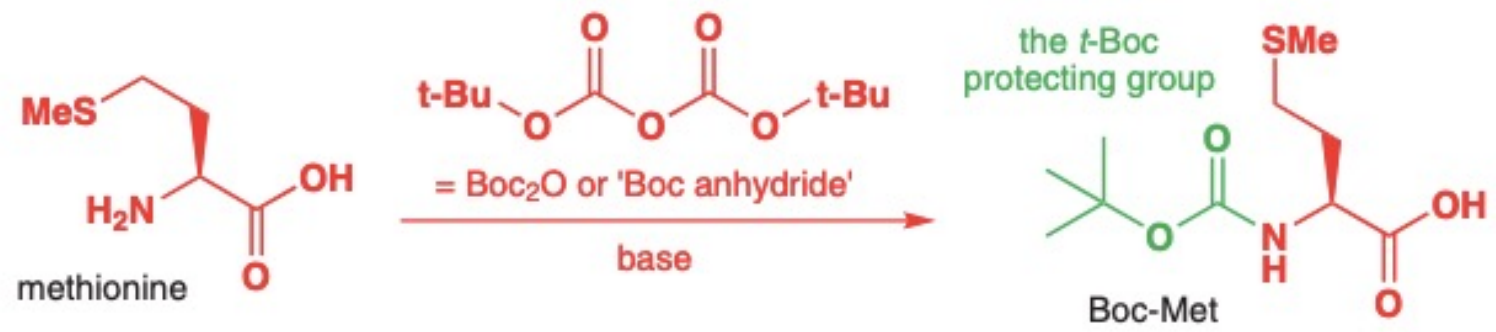
cleavage of Cbz (Z) by hydrogenolysis



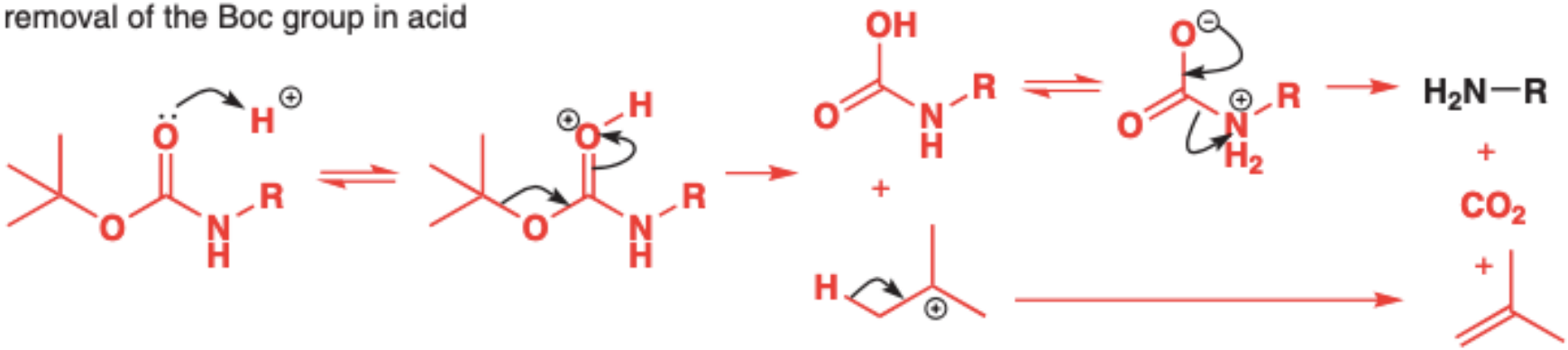
benzylic C–O bond

The Boc protecting group

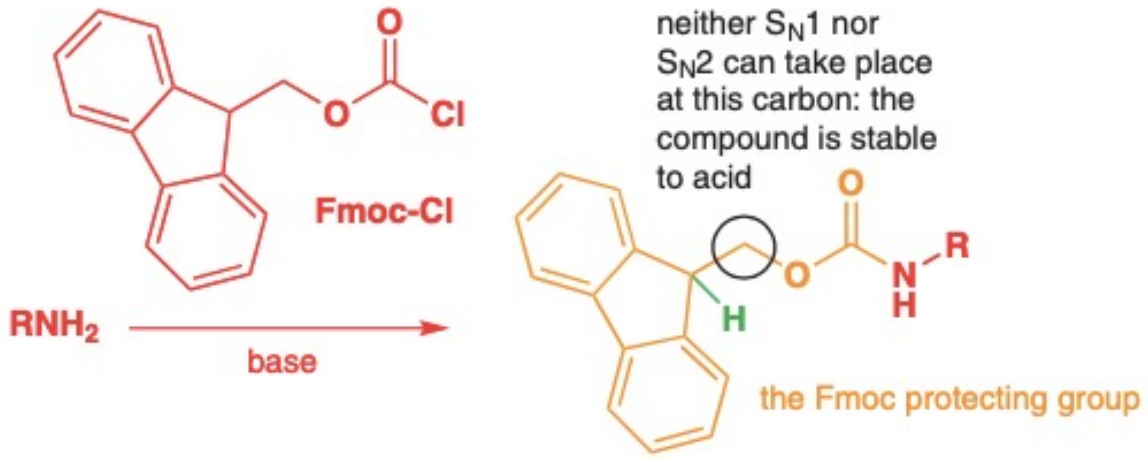
Protecting group	Structure	Protects	From	To protect	To deprotect
Boc (*t*-BuOCO)		amines	electrophiles	$(t\text{-BuOCO})_2O$, base	H^+, H_2O

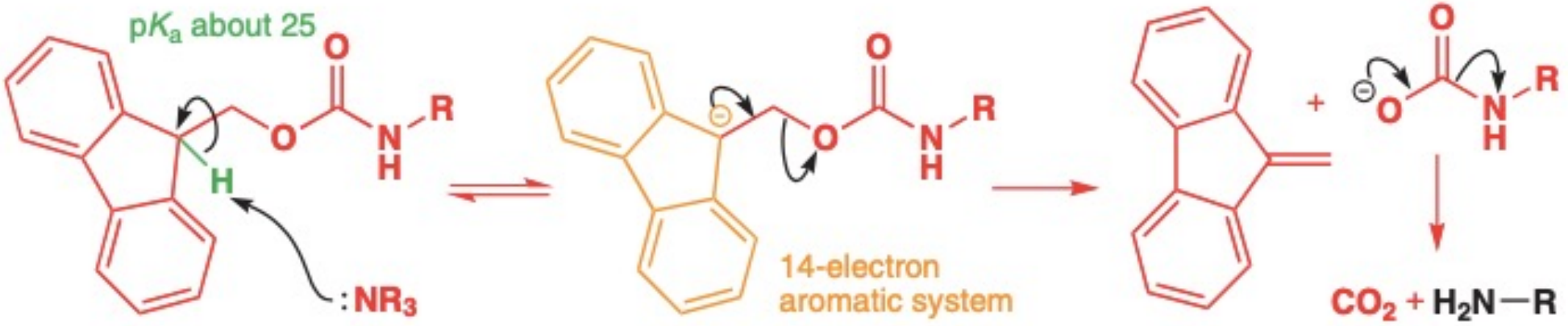


removal of the Boc group in acid

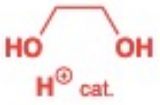
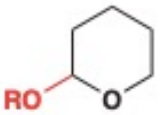
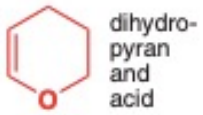
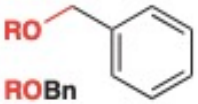
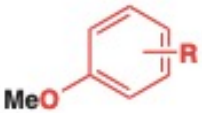
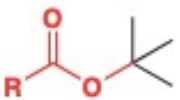
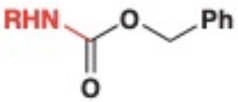
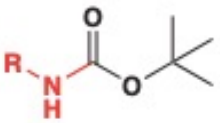


The Fmoc protecting group





Summary

Protecting group	Structure	Protects	From	To protect	To deprotect
acetal (dioxolane))		ketones, aldehydes	nucleophiles, bases		H^+, H_2O
trialkylsilyl R_3Si (e.g.TBDMS)	$RO–SiMe_3$ $RO–SiMe_2t\text{-}Bu$	alcohols (OH in general)	nucleophiles, C or N bases	R_3SiCl, base	H^+, H_2O, or F^-
tetrahydropyranyl (THP)		alcohols (OH in general)	strong bases	 dihydro-pyran and acid	H^+, H_2O
benzyl ether (OBn)		alcohols (OH in general)	almost everything	NaH, BnBr	H_2, Pd/C, or HBr
methyl ether (ArOMe)		phenols (ArOH)	bases	NaH, MeI, or $(MeO)_2SO_2$	BBr_3, HBr, HI, Me_3SiI
t-butyl ester (CO_2t-Bu)		carboxylic acids	nucleophiles	isobutene, H^+	strong acid
Cbz (Z) (OCOBn)		amines	electrophiles	BnOCOCl, base	HBr, AcOH; or H_2, Pd
t-Boc (OCO*t*-Bu)		amines	electrophiles	$(t\text{-}BuOCO)_2O$, base	H^+, H_2O
Fmoc	see text	amines	electrophiles	Fmoc-Cl	base, e.g. amine

Retrosynthesis:
a brief introduction

Most of the things we have discussed so far can be summarized on how to make molecules, that‘s what a Chemist do!!

The question now is
how to choose a good method to make them?

Vocabulary

Some definitions of terms used in synthesis

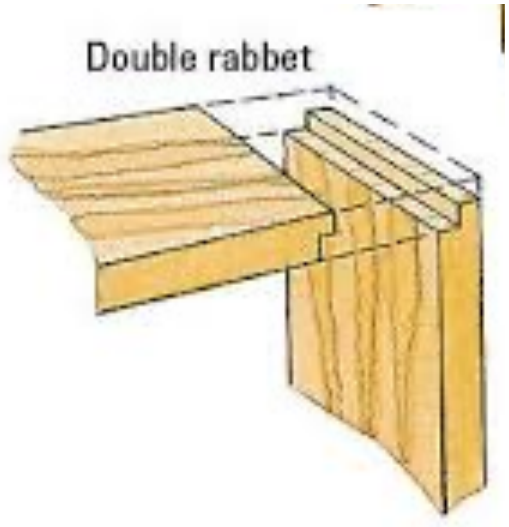
target molecule (or TM)	the molecule to be synthesized
retrosynthetic analysis or retrosynthesis	the process of mentally breaking down a molecule into starting materials
retrosynthetic arrow	an open-ended arrow, $\Longrightarrow$, used to indicate the reverse of a synthetic reaction
disconnection	an imaginary bond cleavage, corresponding to the reverse of a real reaction
synthon	idealized fragments resulting from a disconnection (*synthons* need to be replaced by *reagents* in a suggested synthesis)
reagent	a real chemical compound used in the synthesis, perhaps as the equivalent of a synthon

Retrosynthetic analysis: synthesis backwards

Synthetic planning starts with the product, which is fixed and unchangeable, and works backwards towards the starting materials.

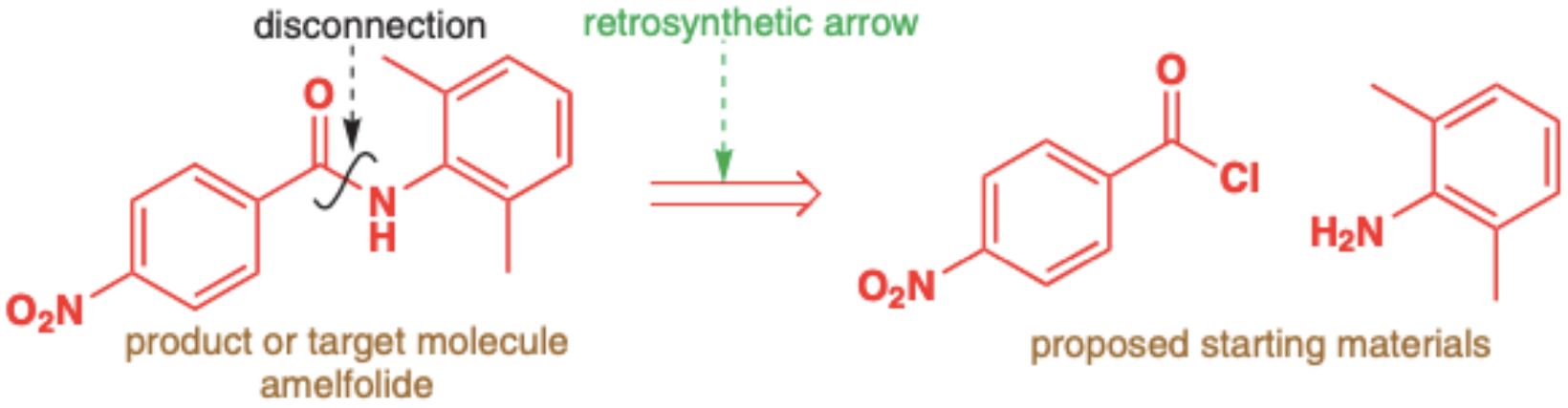
An insect repellent

The disconnection approach



The disconnection approach "fraction" the molecule into smaller starting materials (pieces), and then combine these by chemical reactions.

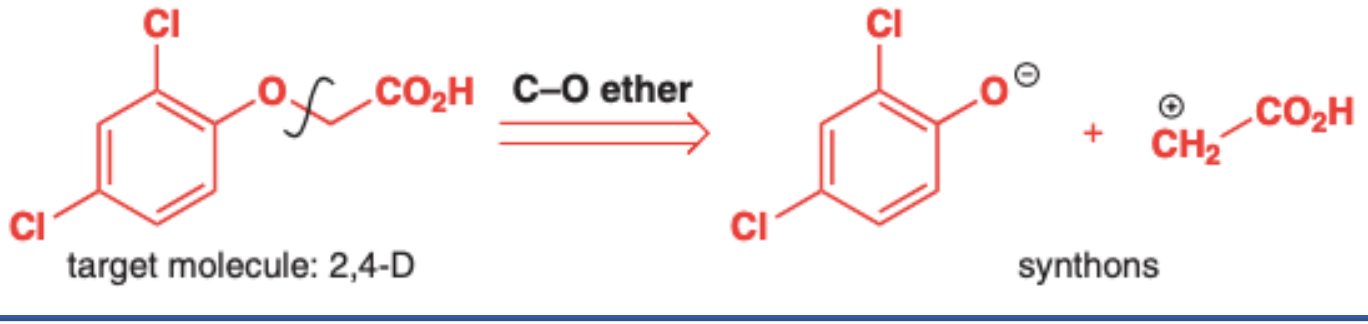
It requires a logic based on our chemical knowledge to choose the suitable starting materials. More than one approach is usually possible.



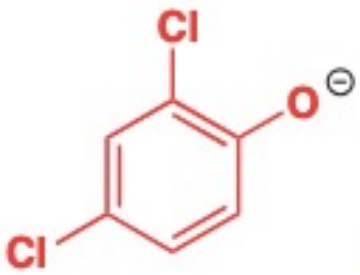
Synthons

Idealized reagents Synthons are fragments of molecules with an associated polarity (represented by a '+' or '–') which stand for the reagents we are going to use in the forward synthesis.

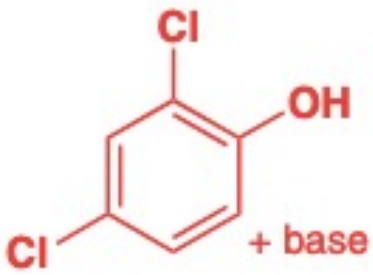
Herbicide compound



synthon



equivalent reagents



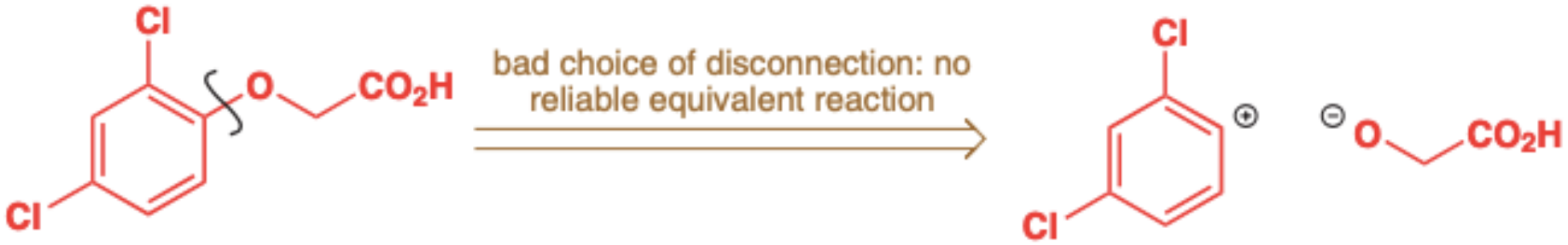
synthon 

equivalent reagents

Choosing disconnections

● Guideline 1

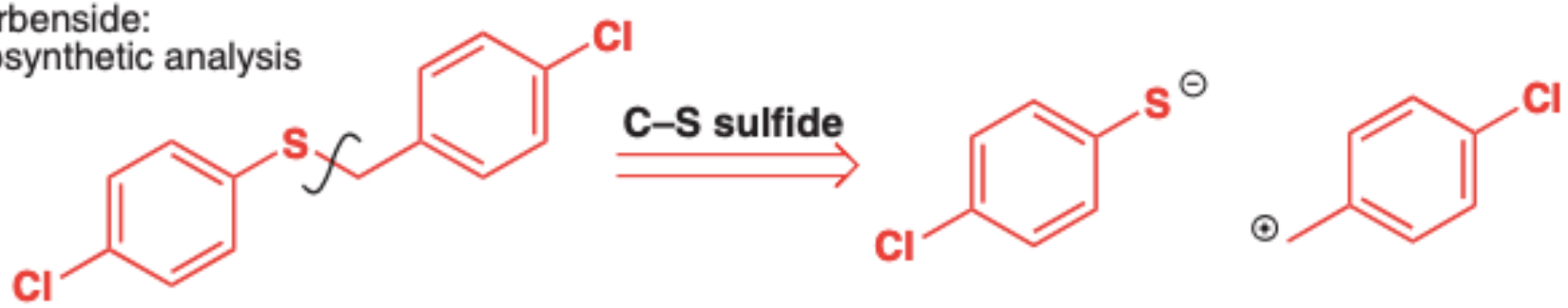
Disconnections must correspond to known, reliable reactions.



● Guideline 2

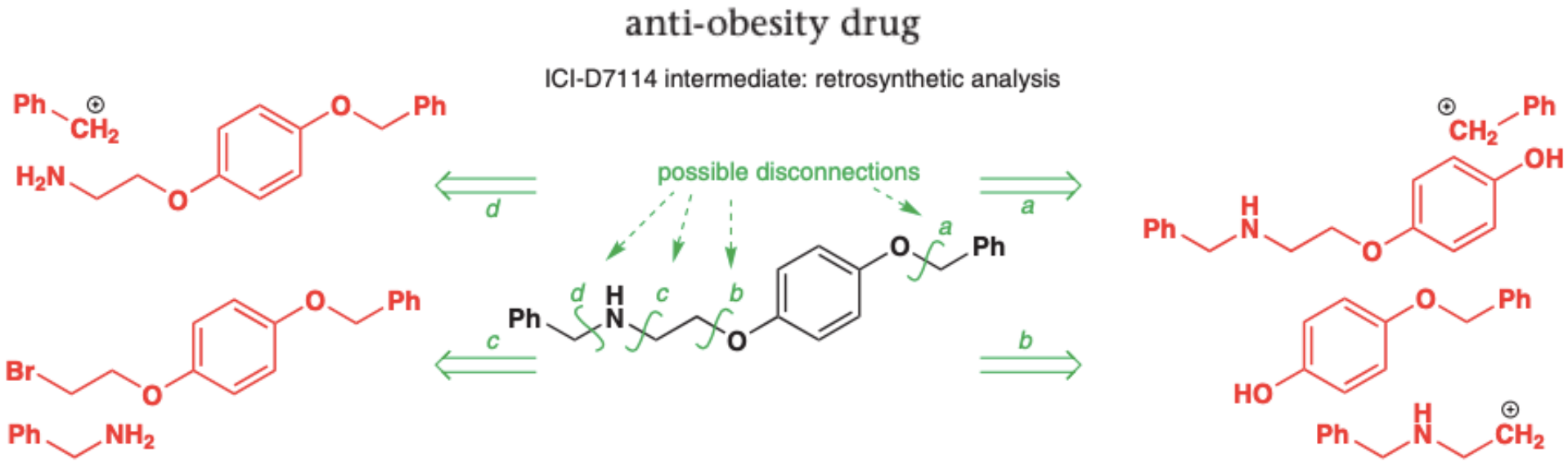
For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom.

chlorbenside:
retrosynthetic analysis



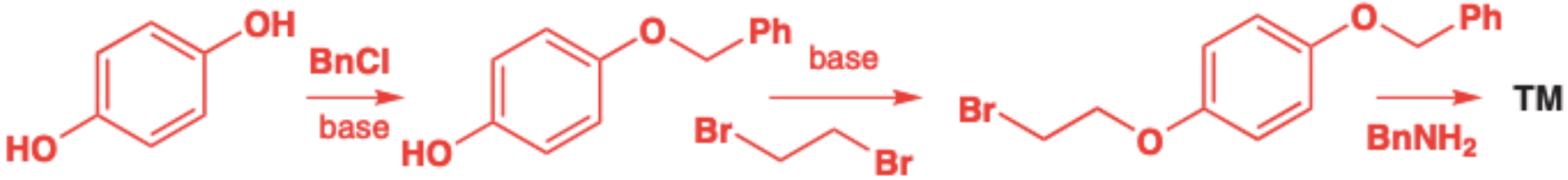
It kills ticks and mites

Multiple step syntheses: avoid chemoselectivity problems



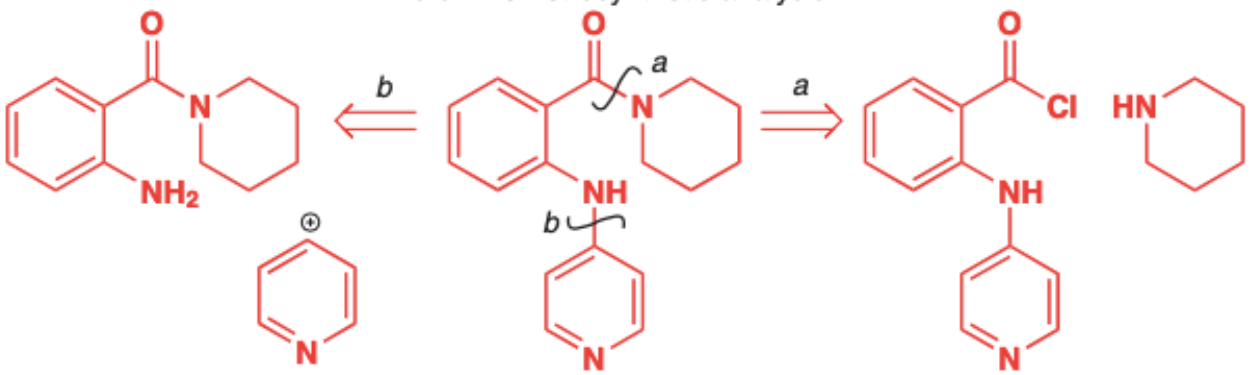
● Guideline 3

Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups first.

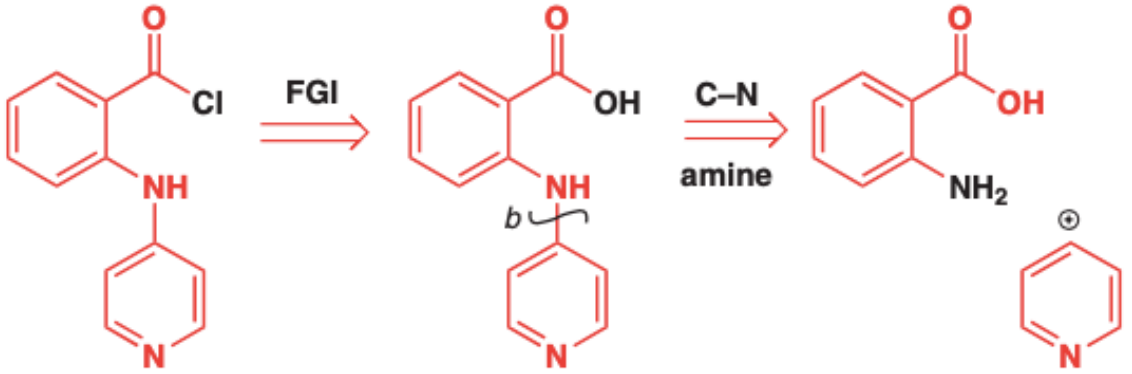


Functional group interconversion

ofornine: retrosynthetic analysis

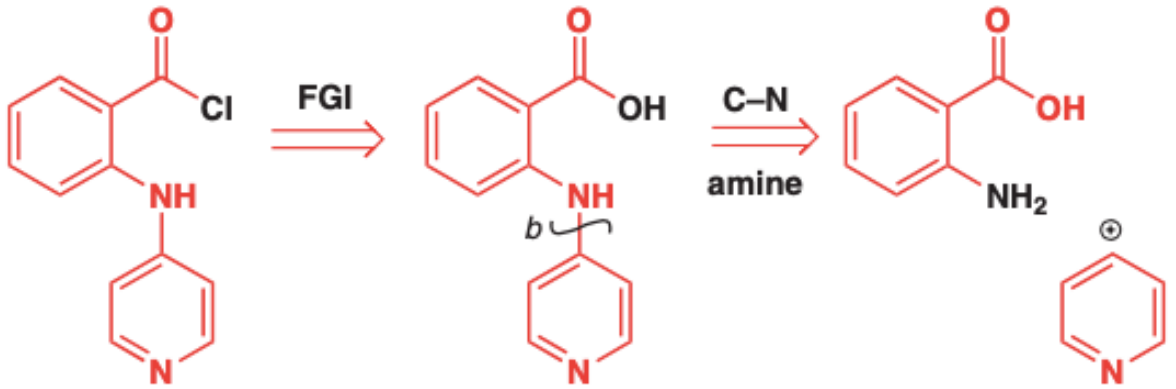


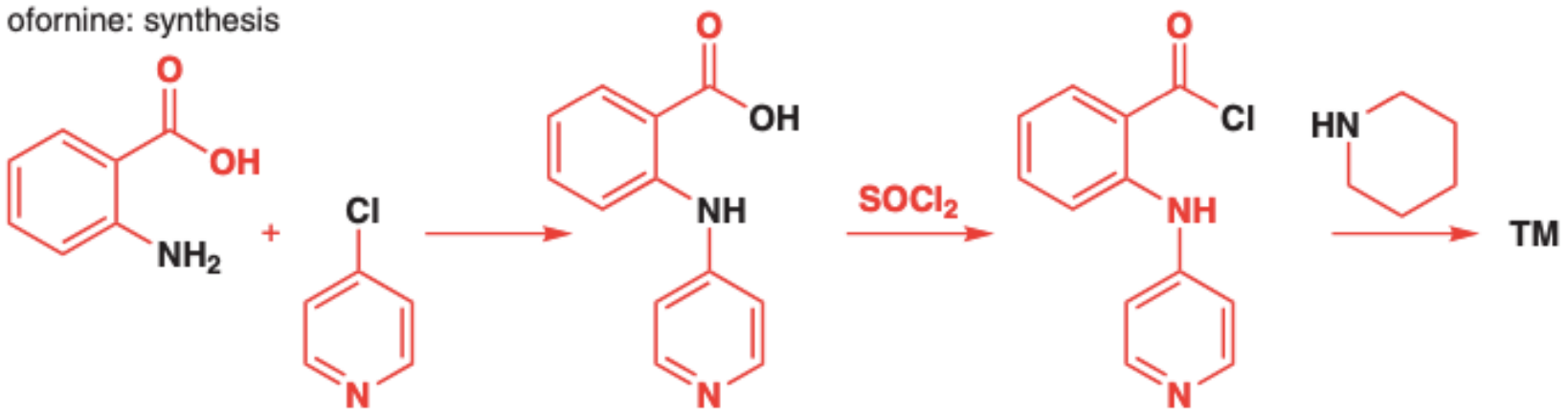
The antihypertensive drug ofornine contains an amide and an amine functional group, and we need to decide which to disconnect first. If we disconnect the secondary amine first (*b*), we will have chemoselectivity problems constructing the amide in the presence of the resulting NH_2 group.



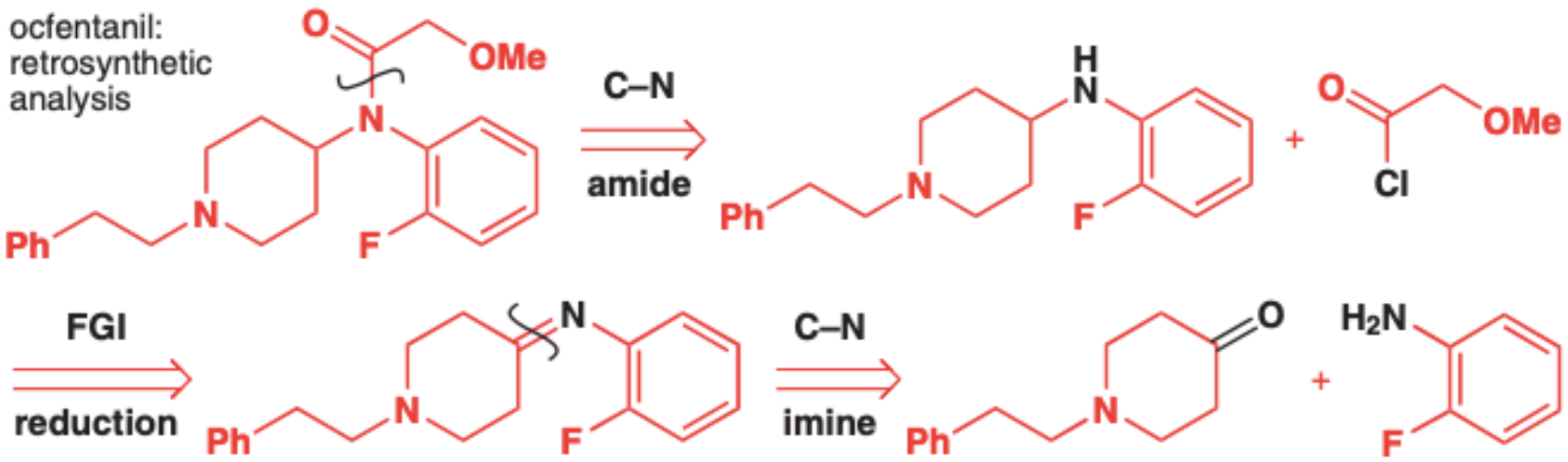
The retrosynthetic transformation of an acyl chloride to a carboxylic acid is not really a disconnection because nothing is being disconnected. We call it instead a functional group interconversion, or FGI, as written above the retrosynthetic arrow.

Functional group interconversion



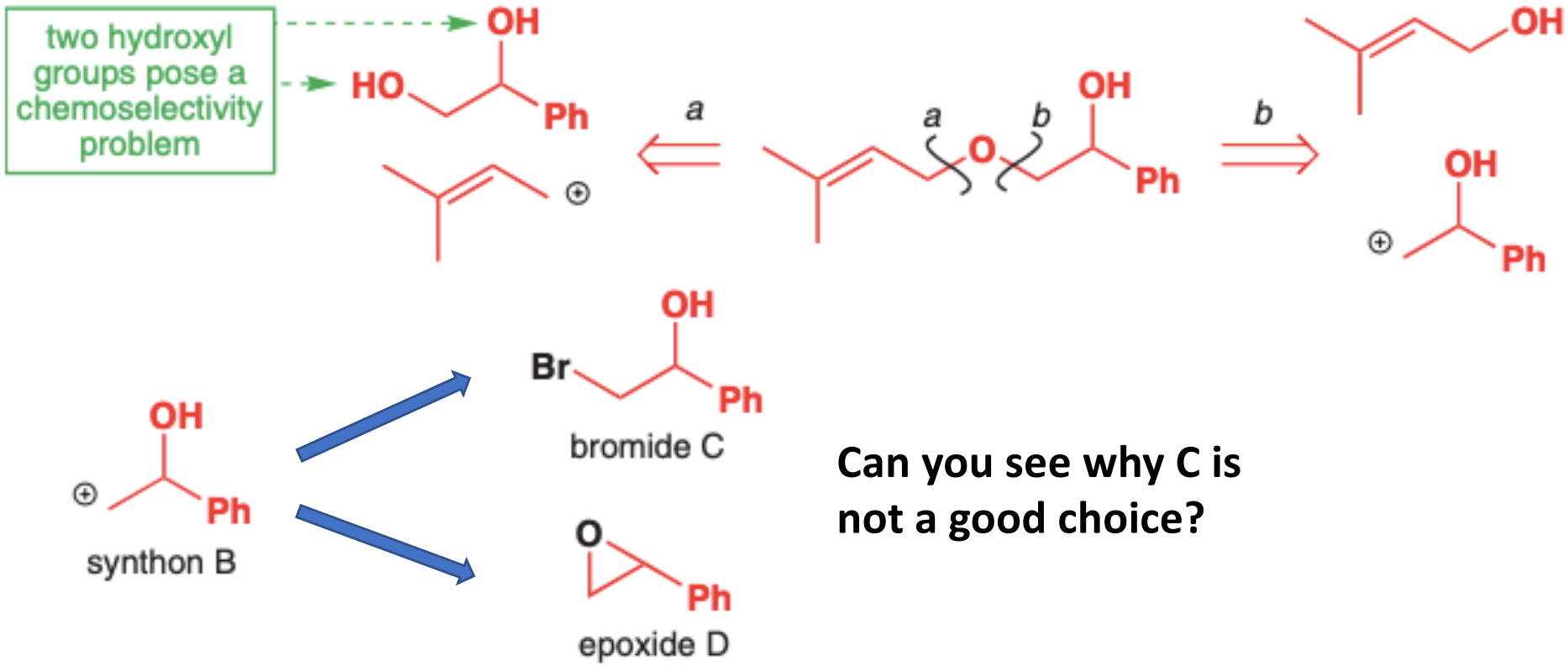


Amine synthesis by functional group interconversion



Ocfentanil is an opioid painkiller that lacks the addictive properties of morphine. Disconnection of the amide gives a secondary amine that we can convert to an imine for disconnection to a ketone plus 2-fluoroaniline.

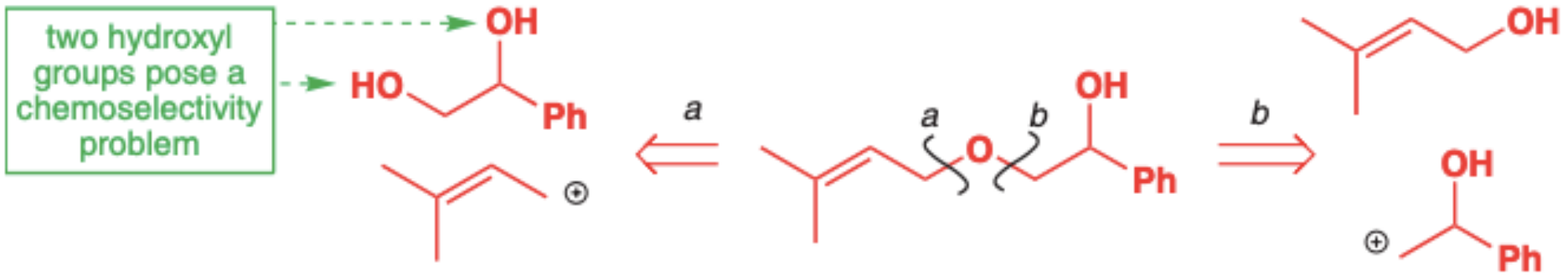
Two groups disconnection are better than one

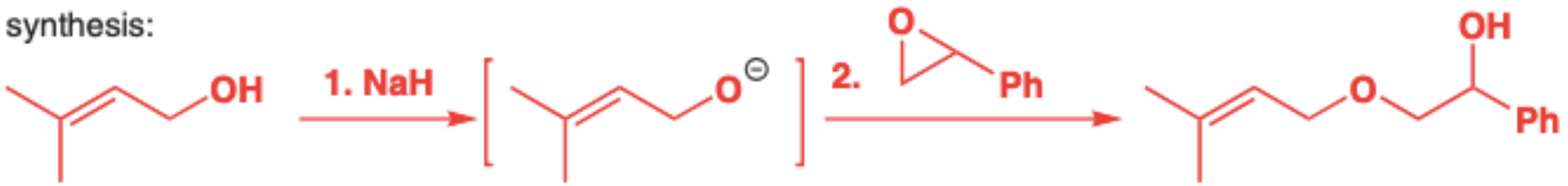


Can you see why C is not a good choice?

In using the epoxide we have gone one step beyond all the disconnections we have talked about so far because we have *used one functional group to help disconnect another*—in other words, we noticed the alcohol adjacent to the ether we wanted to disconnect and managed to involve them both in the disconnection. Such disconnections are known as two-group disconnections

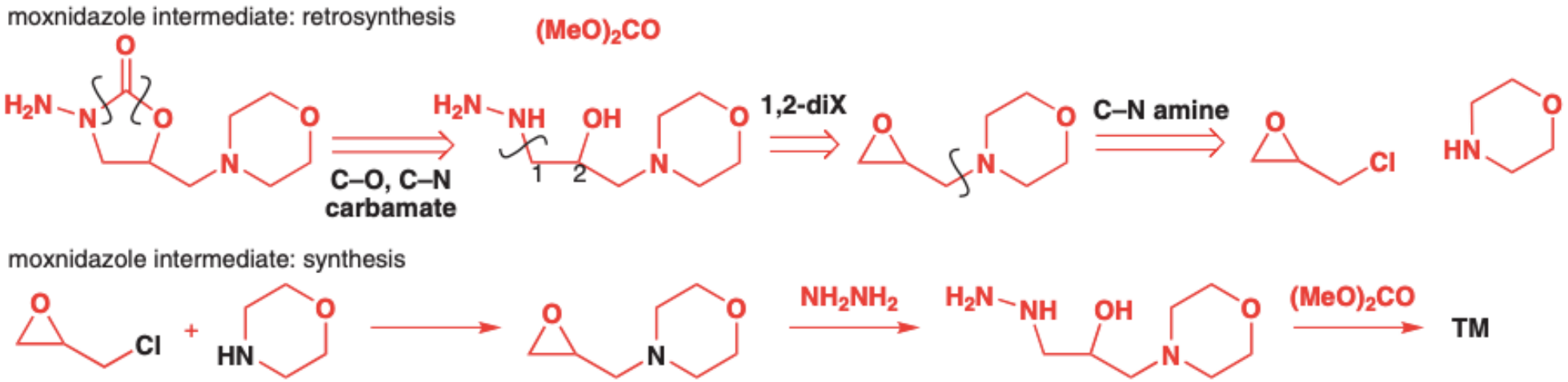
Two groups disconnection are better than one





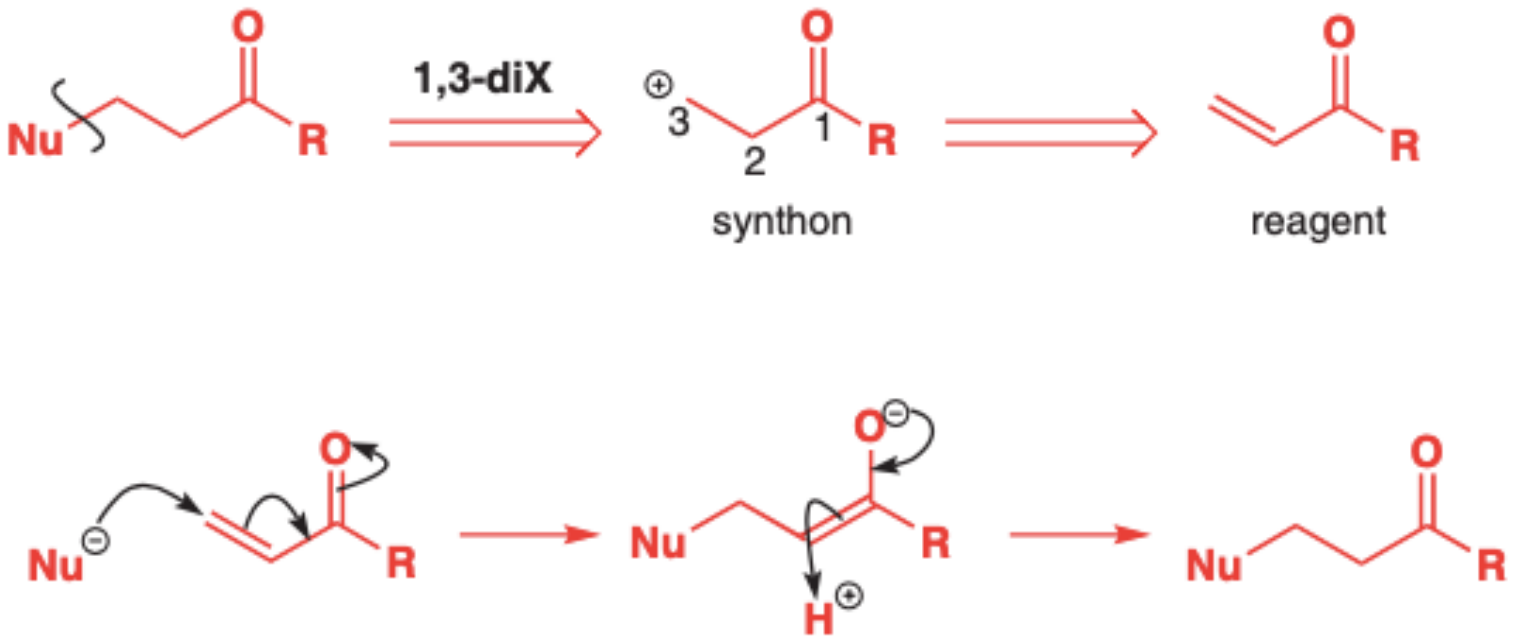
Two groups disconnection are better than one

Notice that we have written '1,2-diX' above the arrow to show that it's a two-group ('diX')



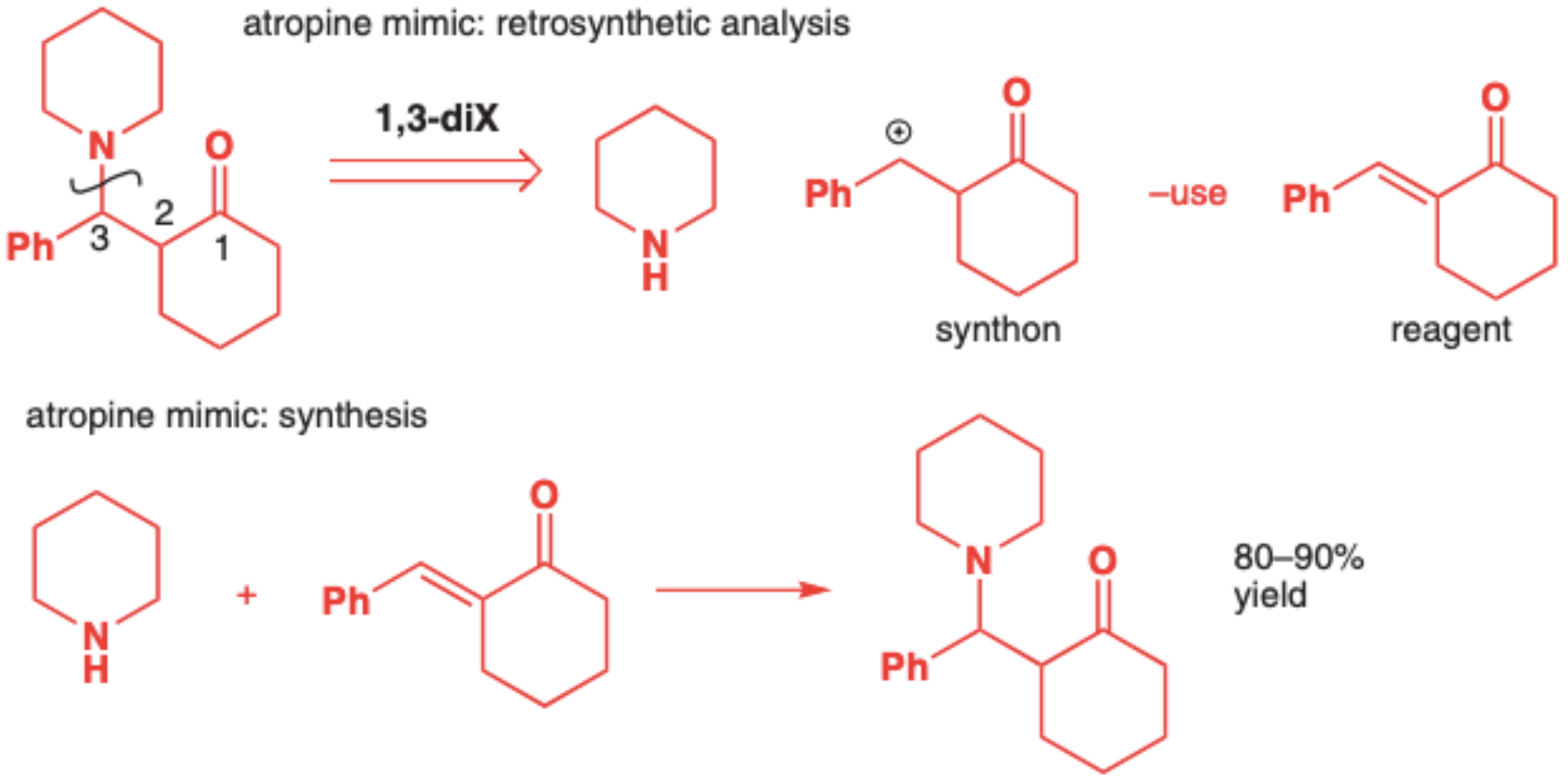
Moxnidazole is an antiparasitic drug, and our next target molecule is an important intermediate in its synthesis. The obvious first disconnection is of the carbamate group, revealing two 1,2-relationships. A 1,2-diX disconnection gives an epoxide that can be made by alkylation of morpholine with epichlorohydrin.

1,3-disconnections

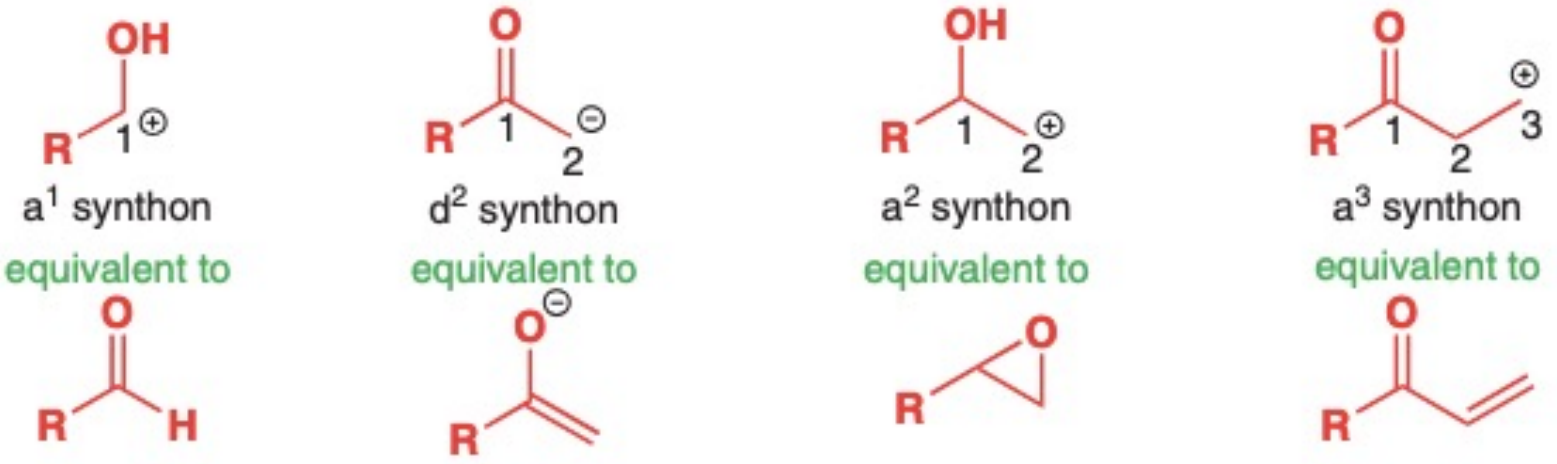


Remember that not all nucleophiles will successfully undergo Michael additions—you must bear this in mind when making a 1,3-disconnection of this type. Most reliable are those based on nitrogen, sulfur, and oxygen (enolates).

1,3-disconnections



Donors and acceptors synthons

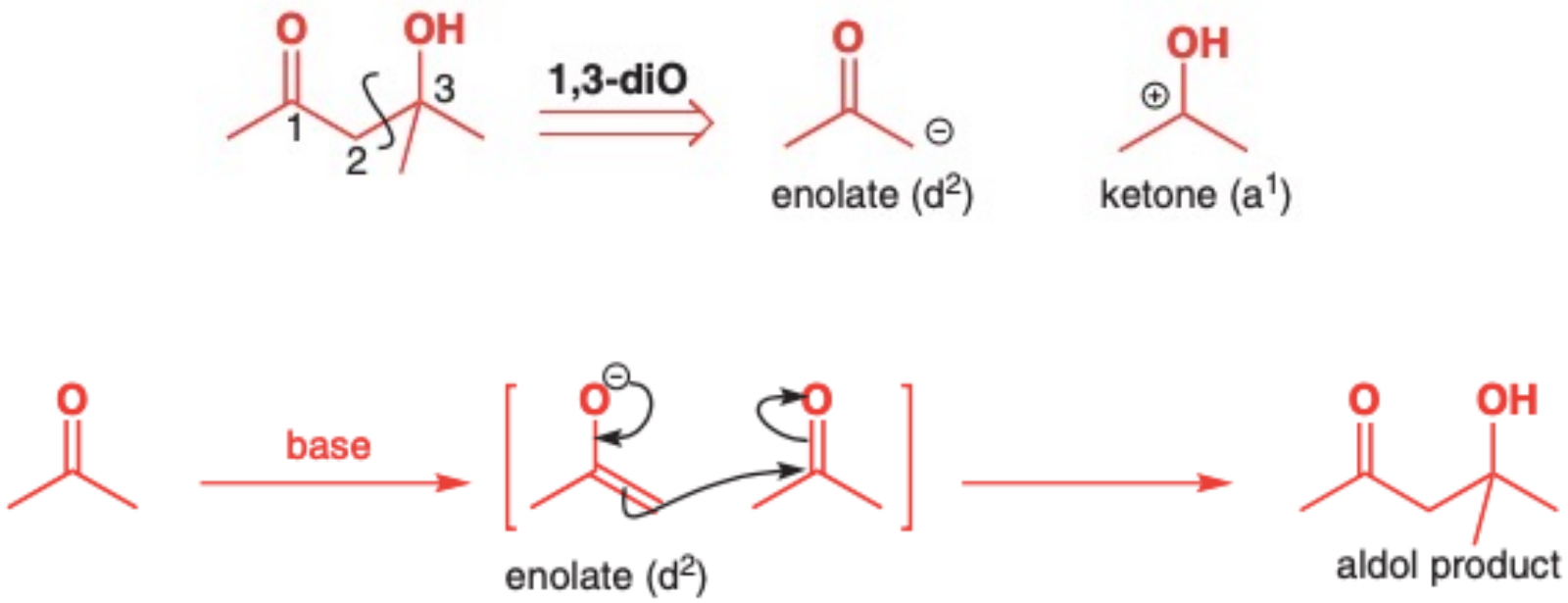


- **Synthons are classified as a (acceptor) or d (donor)**

  A number shows the position of the acceptor or donor site relative to a functional group.

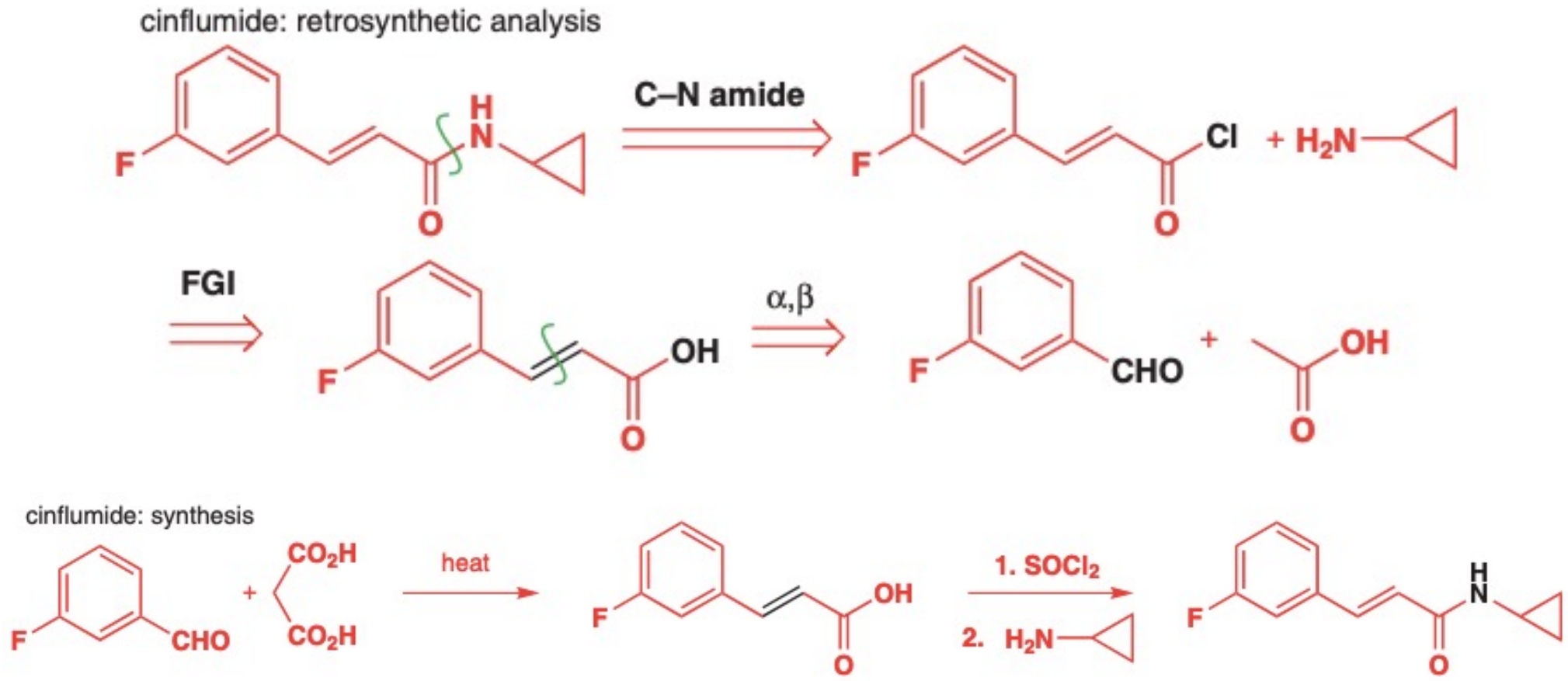
  An example of an a^1 synthon is a carbonyl compound and an example of a d^2 synthon is an enolate or an enolate equivalent.

Donors and acceptors synthons

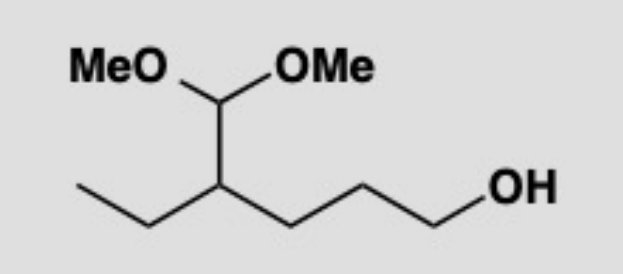


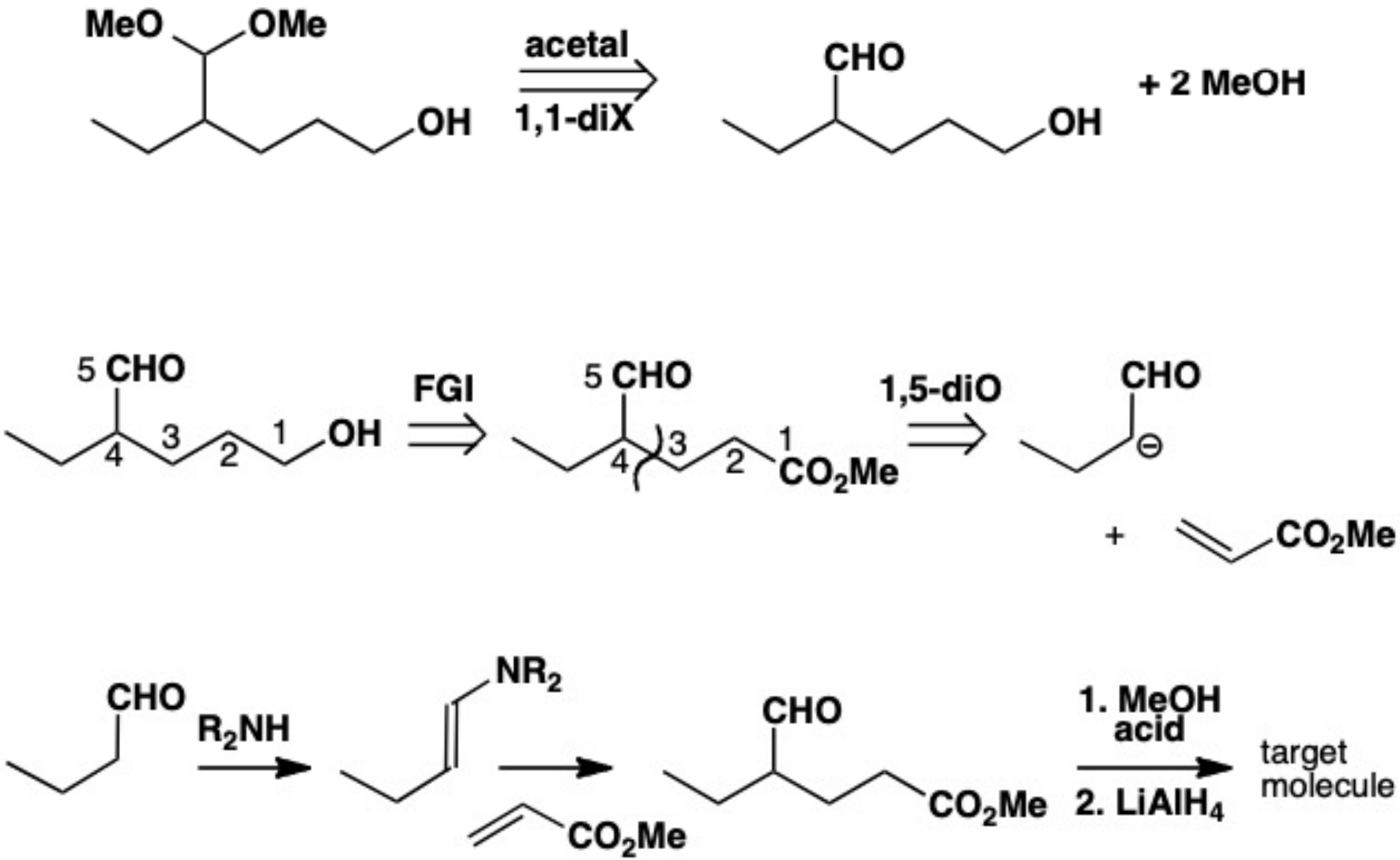
The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule—think aldol! In disconnection terms we can represent it like this.

Donors and acceptors synthons

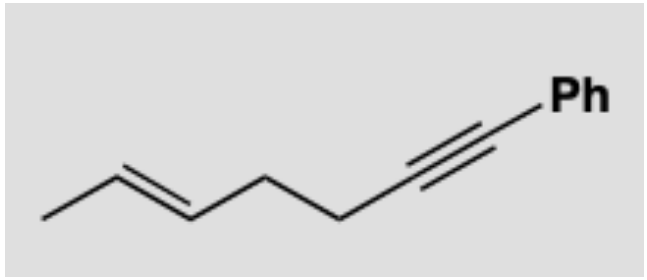


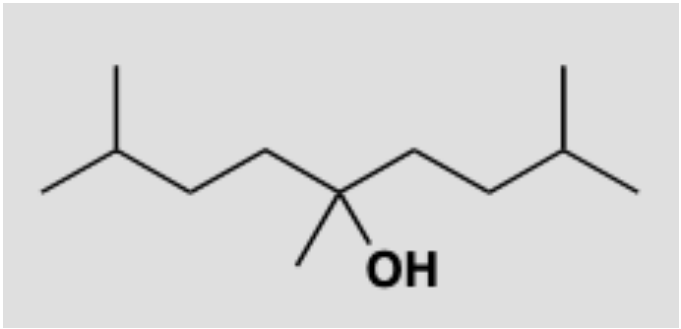
How would you synthesize this compound?



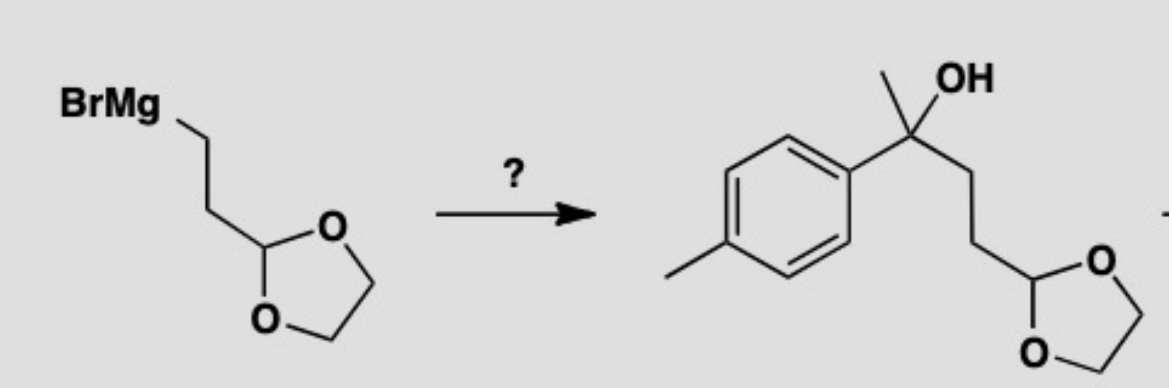

MeO
OMe
OH
acetal
1,1-diX
CHO
OH
+ 2 MeOH
5 CHO
4
3
2
1
OH
FGI
5 CHO
4
3
2
1
CO2Me
1,5-diO
CHO
+
CO2Me
CHO
R2NH
NR2
CO2Me
CHO
CO2Me
1. MeOH
acid
2. LiAlH4
target
molecule

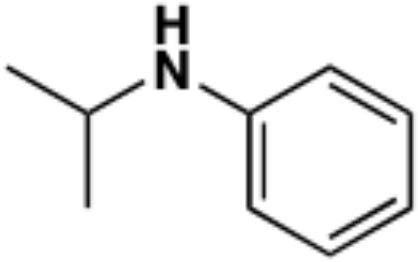
Suggest a method for the synthesis of the following molecules


Ph


OH

Show how to prepare the following molecules (several steps, two fragments




H
N