Master Course
in Organic Chemistry

2018-19

methods **and design** in organic synthesis

Pere Romea

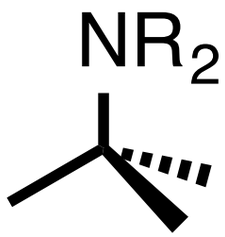
Rubik's cube

4.3. Functional groups

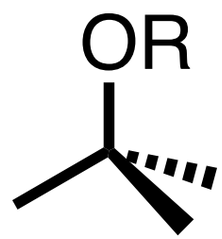
Just ONE functional group

R-⁞-*X* disconnection

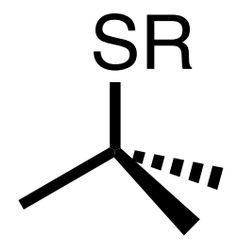
A single heteroatom bound to the backbone



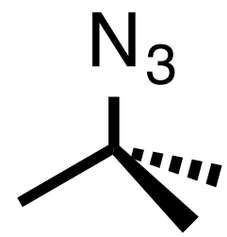
Amine



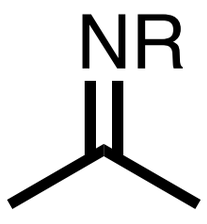
Alcohol
Ether



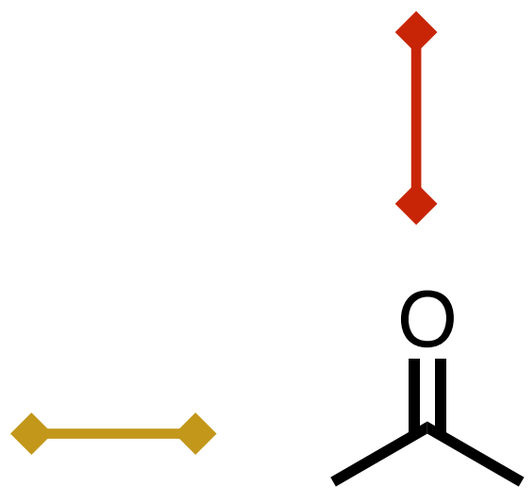
Thiol
Thioether



Azide

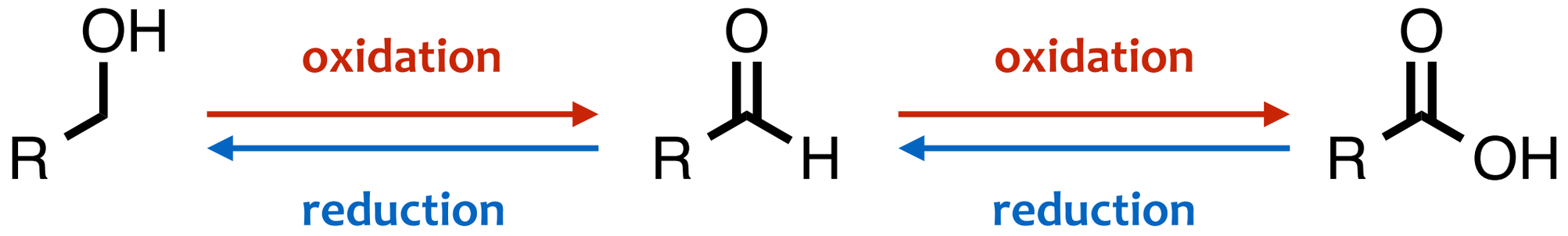


Imine

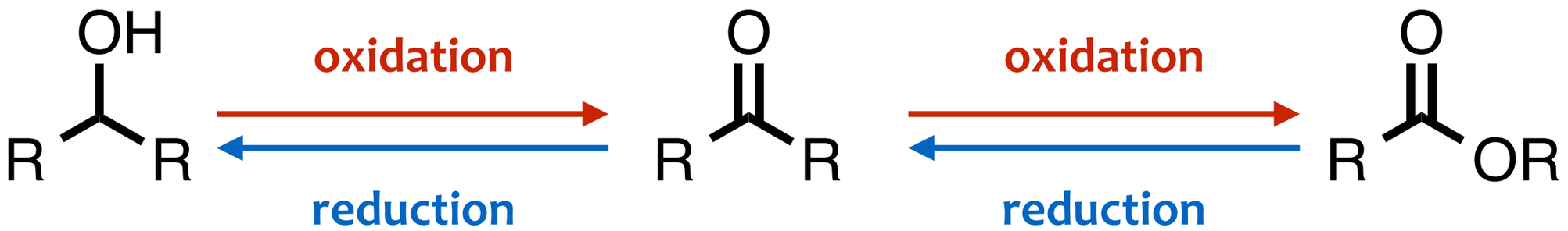


Aldehyde
Ketone

Nitrile



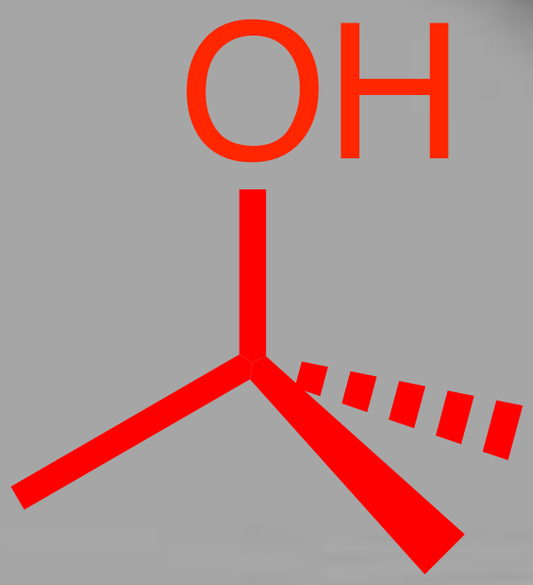
primary alcohol aldehyde carboxylic acid

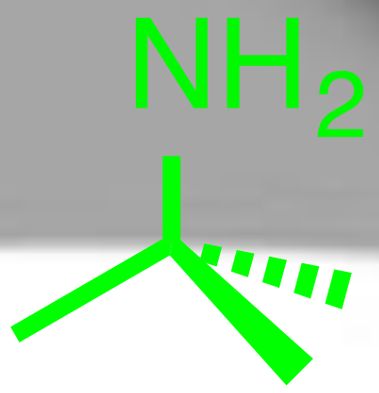


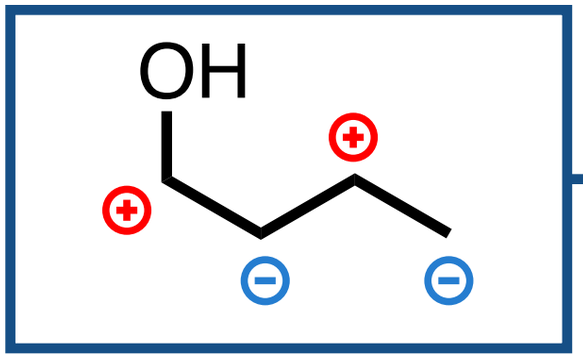
secondary alcohol ketone ester

alcohols?

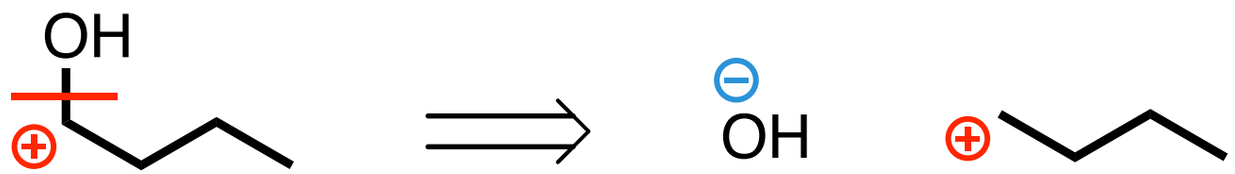
amines?



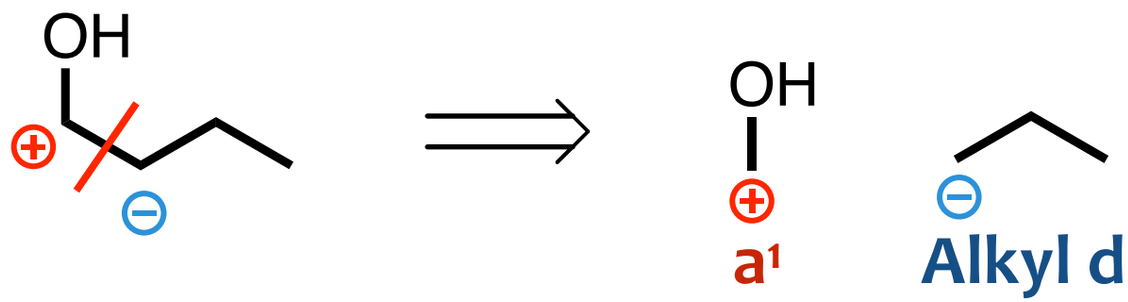




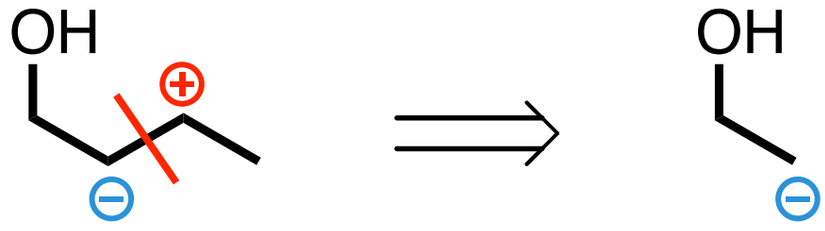
Natural charge distribution



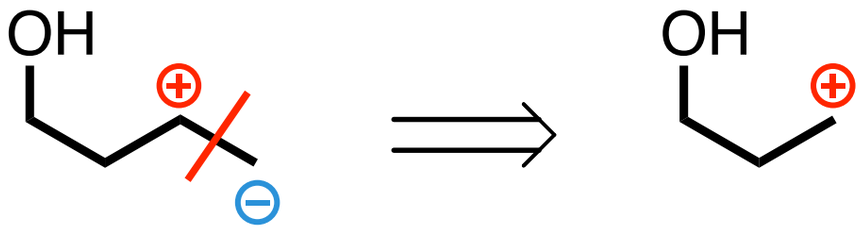
d^0 **Alkyl a**



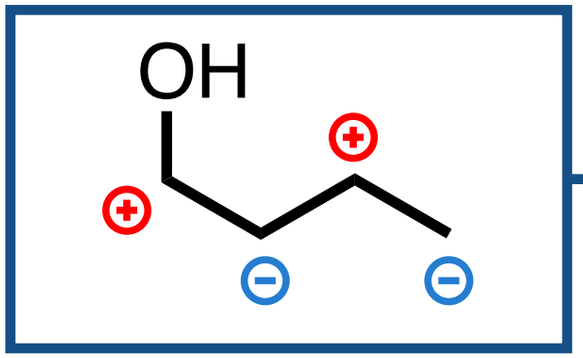
a^1 **Alkyl d**



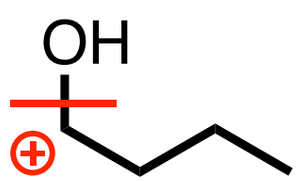
d^2 **Alkyl a**

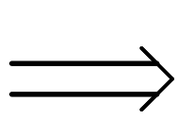


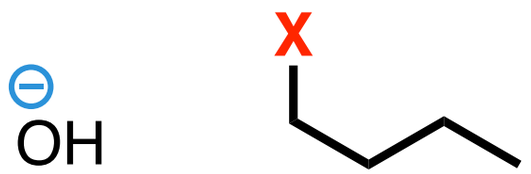
a^3 **Alkyl d**



Natural charge distribution

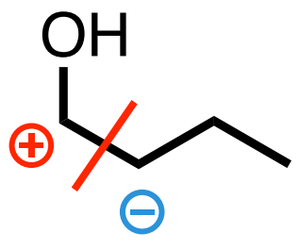


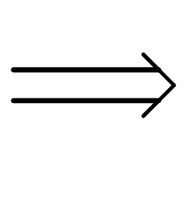


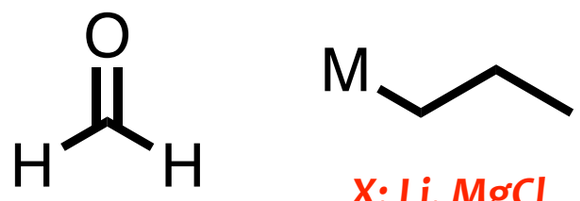


X: halide, sulfonate

S_N2

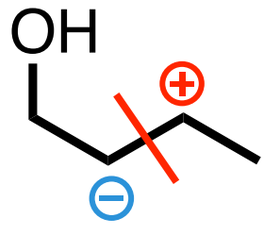


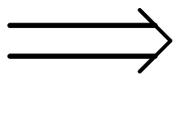


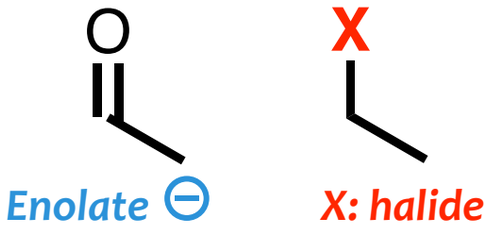


X: Li, MgCl

Ionic Additions to Carbonyls

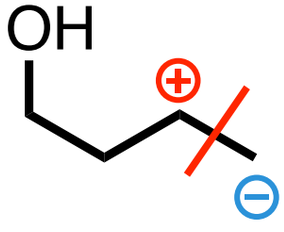


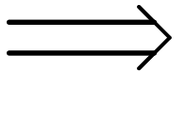


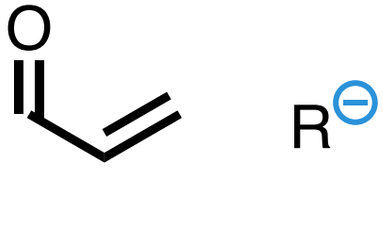


X: halide

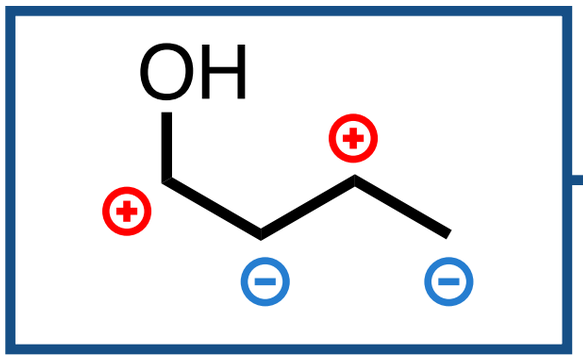
Alkylation of Enolates (or Enamines)



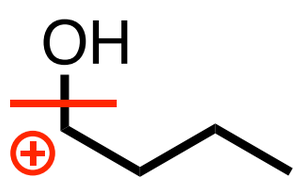


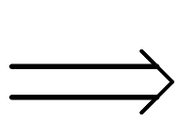


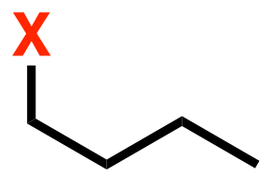
Michael



Natural charge distribution

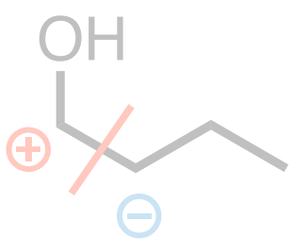


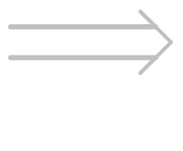


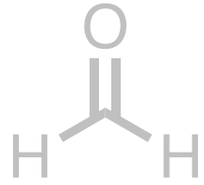


X: halide, sulfonate

S_N2

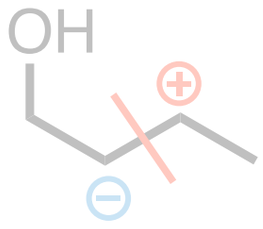


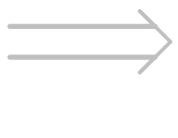




X: Li, MgCl

Ionic Additions to Carbonyls

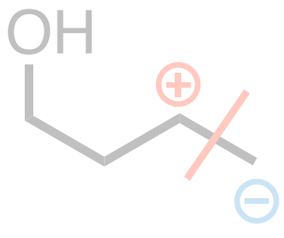


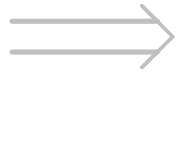


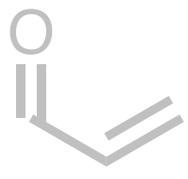
Enolate

X: halide

Alkylation of Enolates (or Enamines)



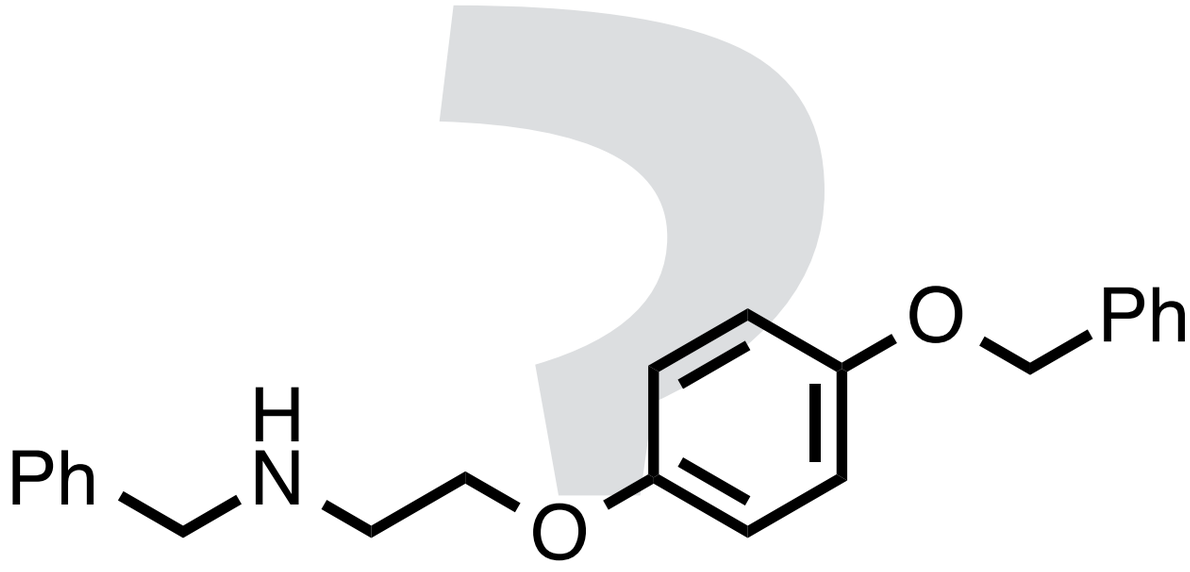




Michael

Jabba the Hutt
Star Wars

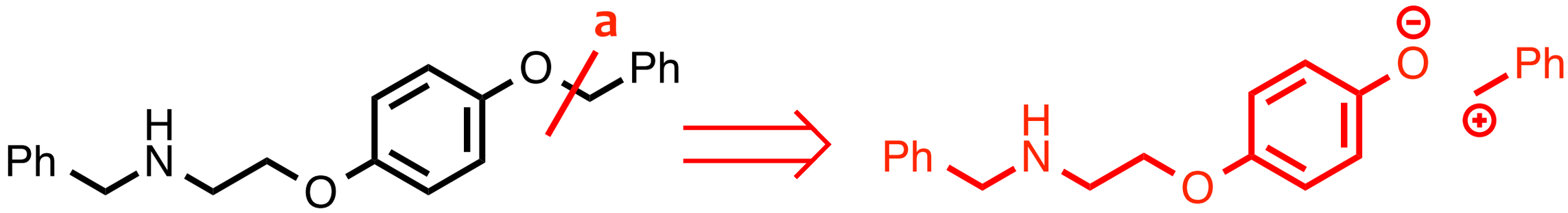
See Chapter 2. Concepts (II)



ICI-D7114 intermediate

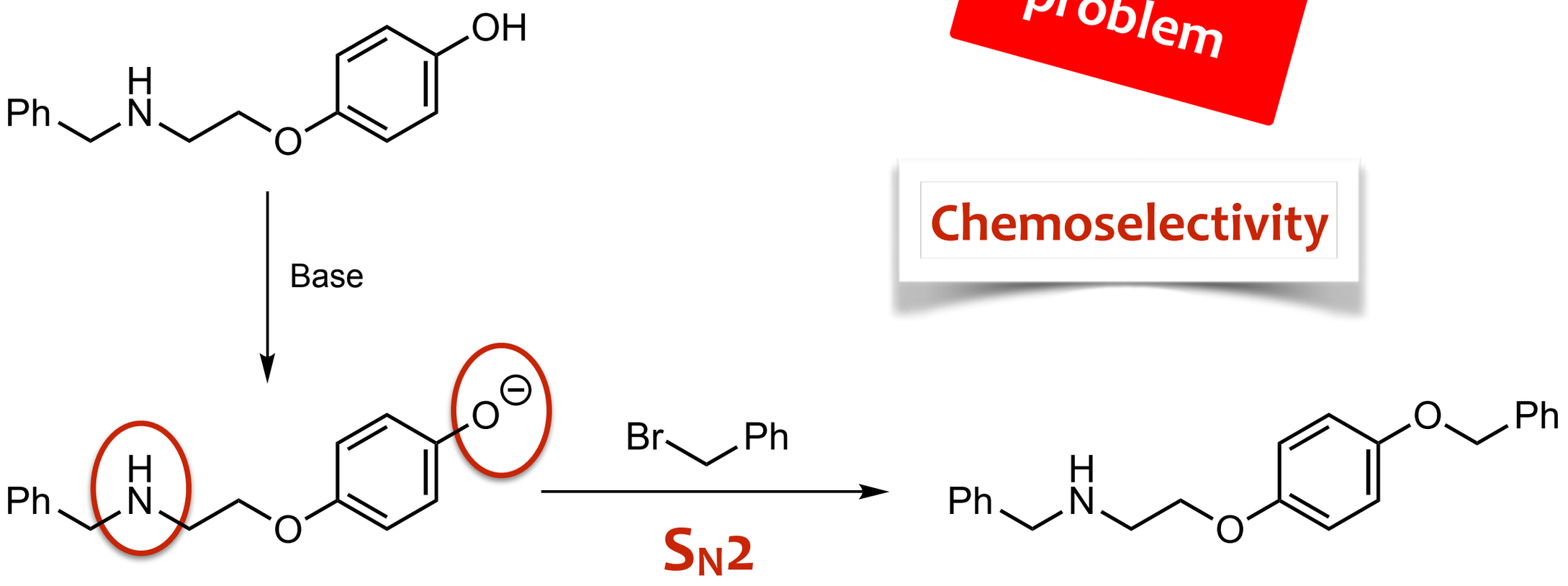
anti-obesity treatment

route A

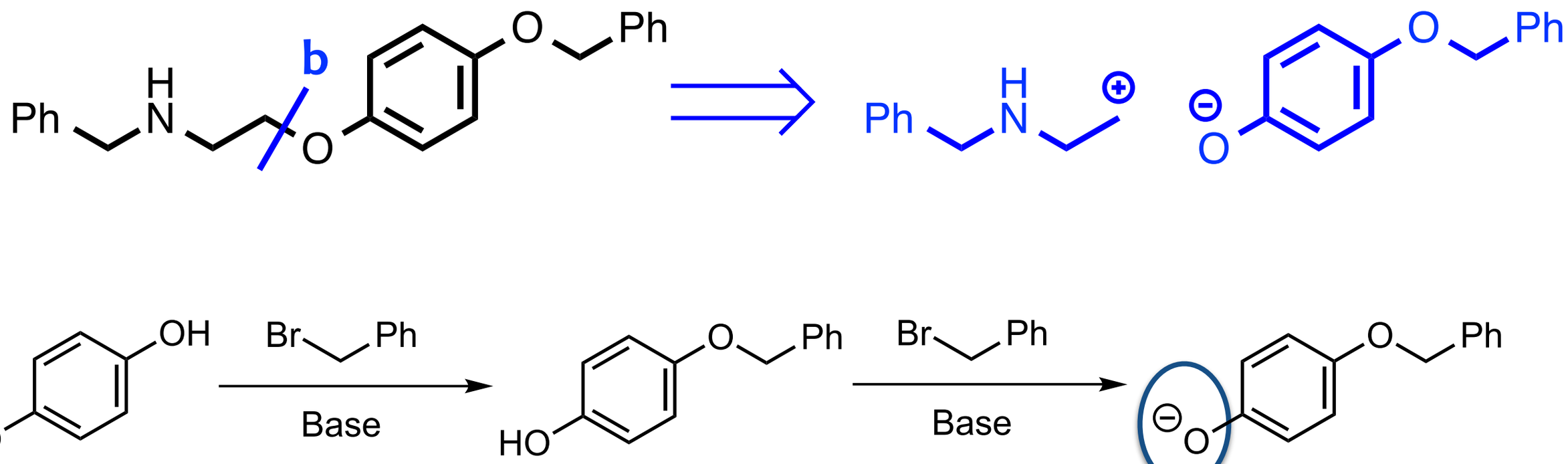


problem

Chemoselectivity



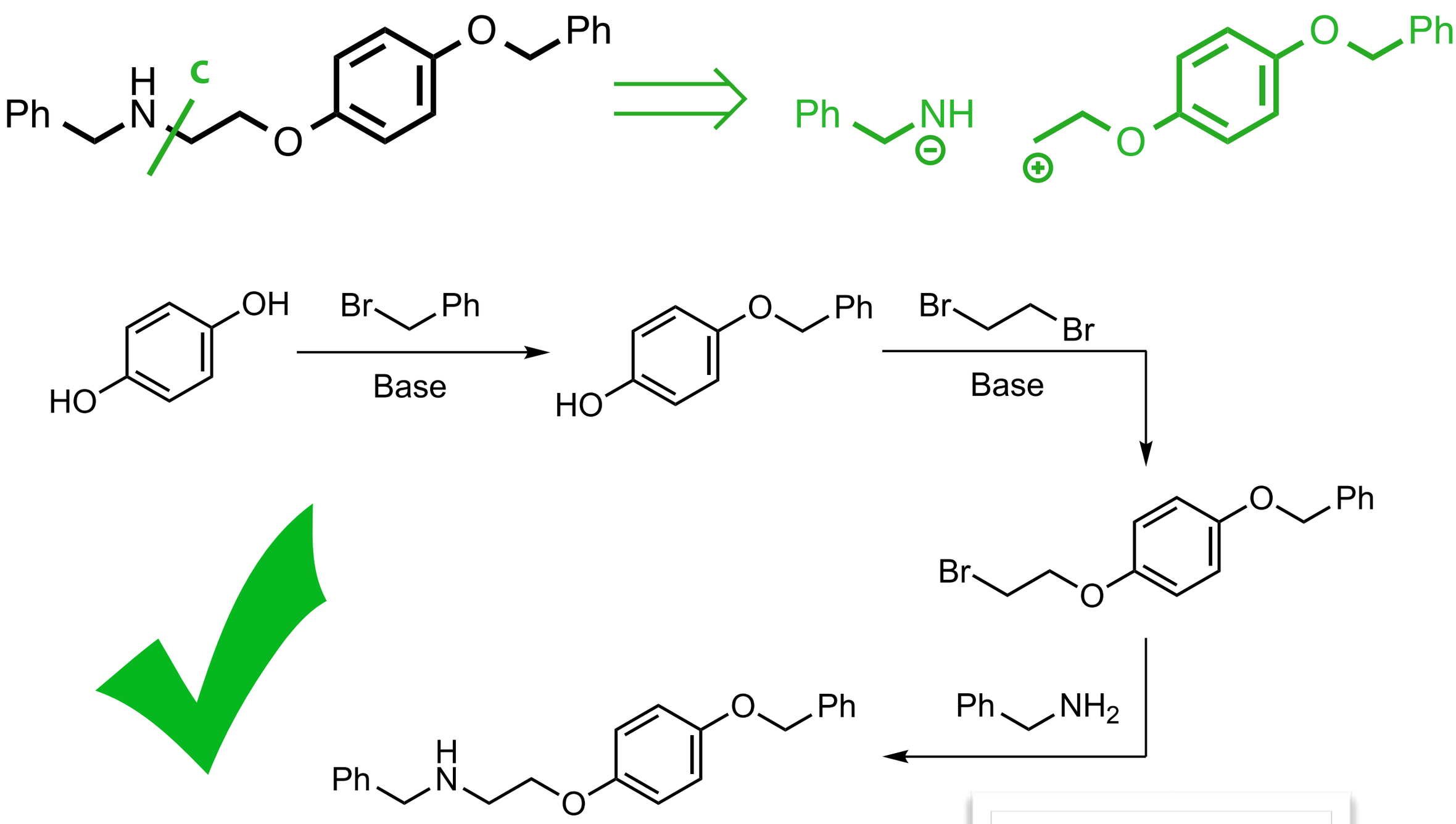
route B



problem(s)

Stability
Chemoselectivity

route C


Ph
H
N
C
O
O
Ph
Ph
NH
O
Ph
HO
OH
Br
Ph
Base
HO
O
Ph
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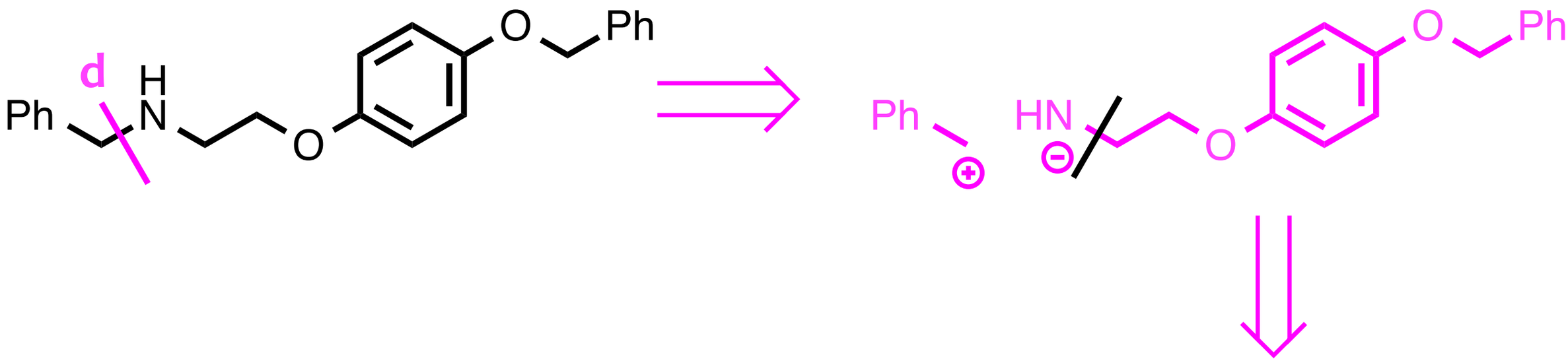
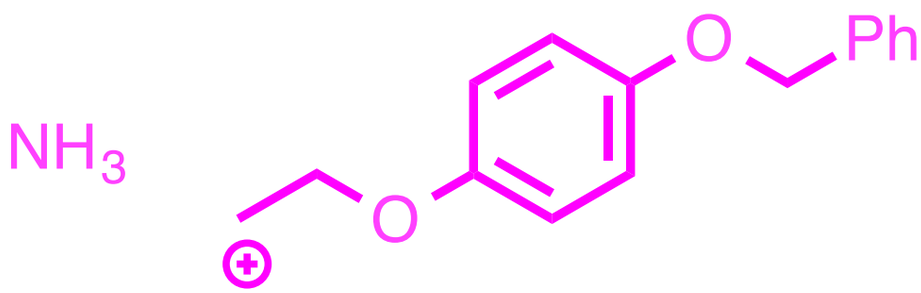
Br
Base
Br
O
O
Ph
Ph
NH2
Ph
H
N
O
O
Ph
Polyalkylation ?

route D



Be Careful! Long Way

Amines are always sensitive fellows

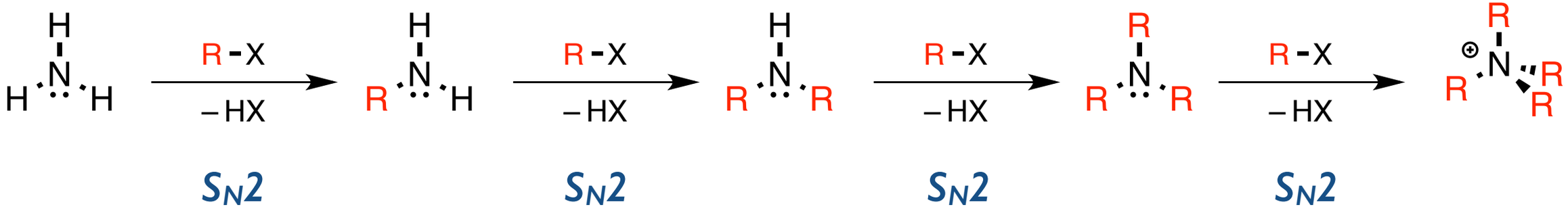


Apparently, ***SN2 MEDIATED ALKYLATION***

of ammonia, primary, secondary, or tertiary amines

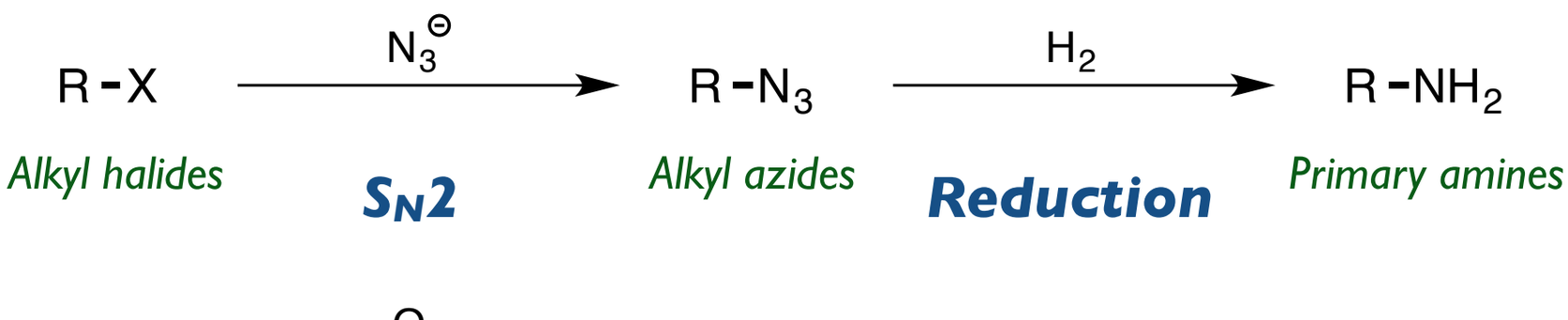
is the most appropriate way to prepare amines.

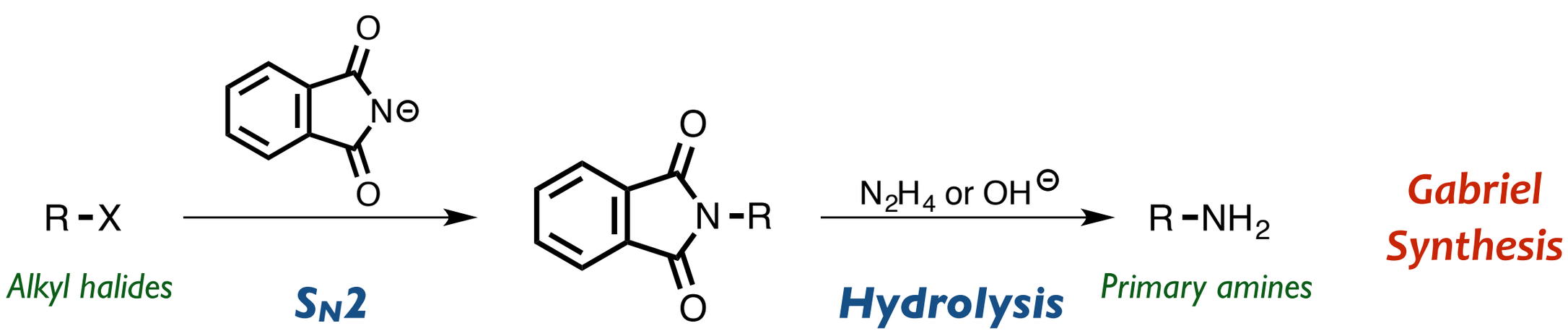
HOWEVER, POLYALKYLATION HAMPERS SUCH AN APPROACH

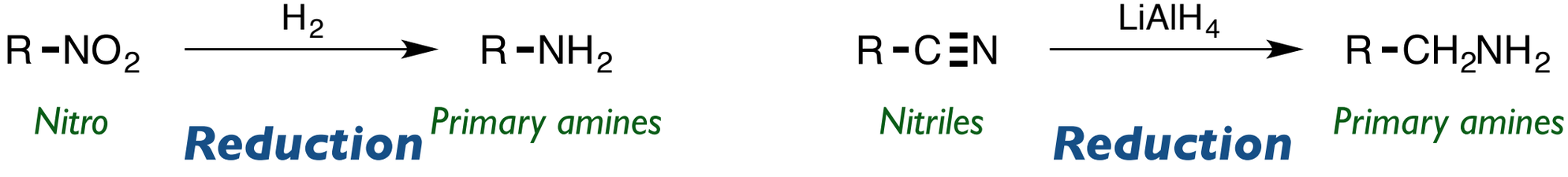


So, keep in mind different options …

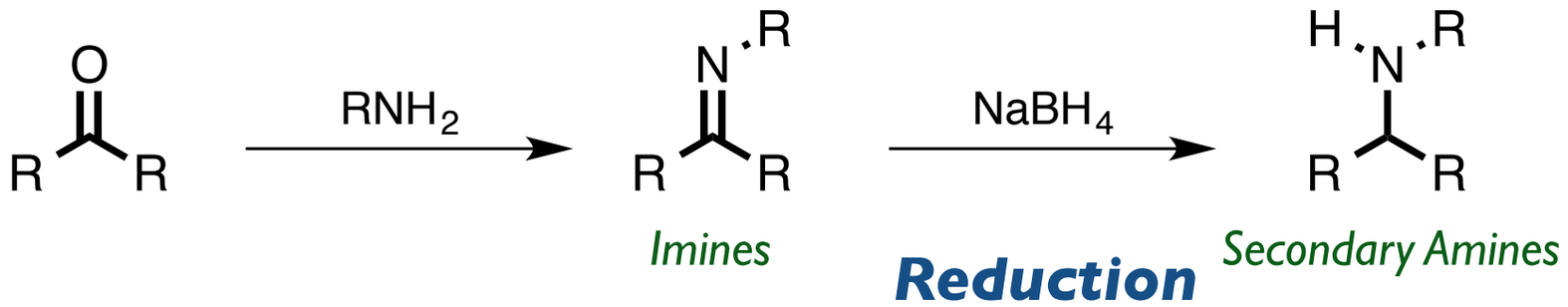
PRIMARY AMINES

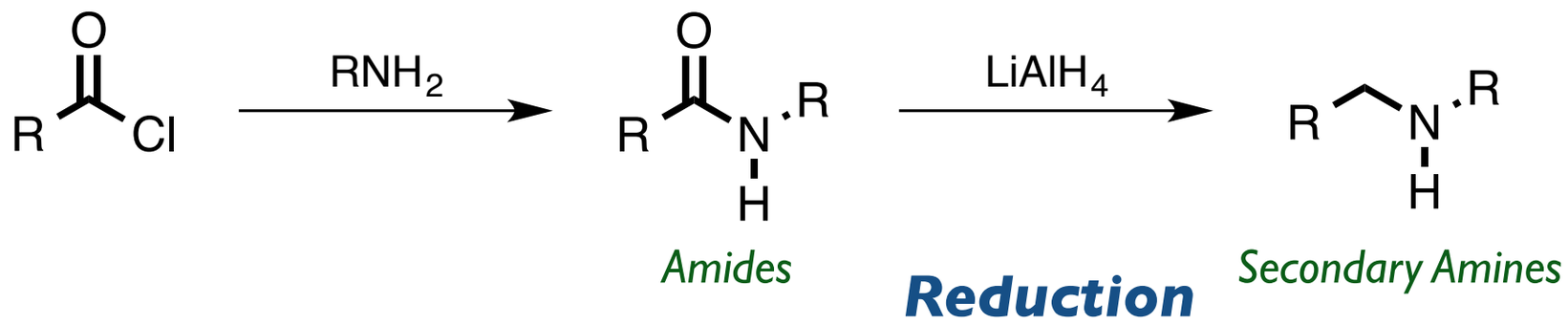




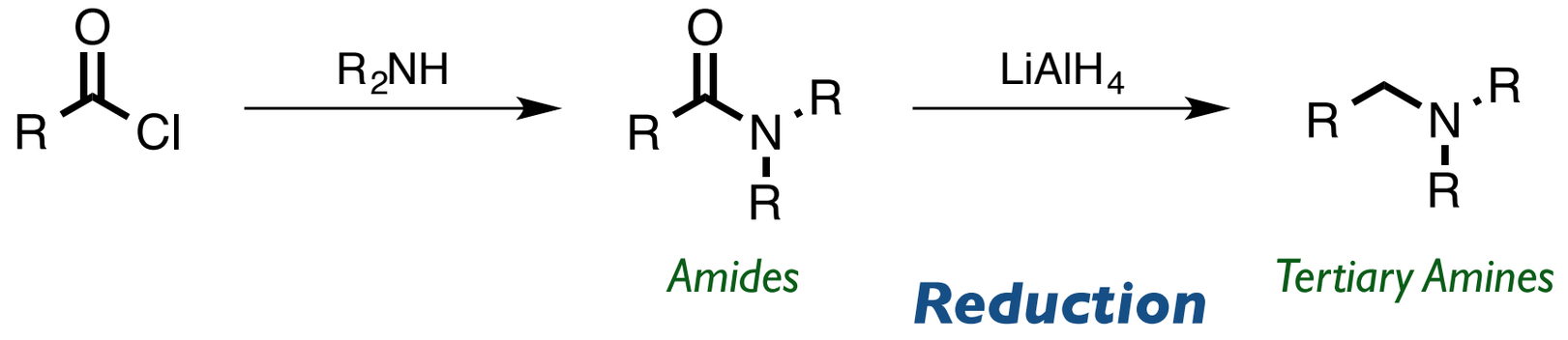


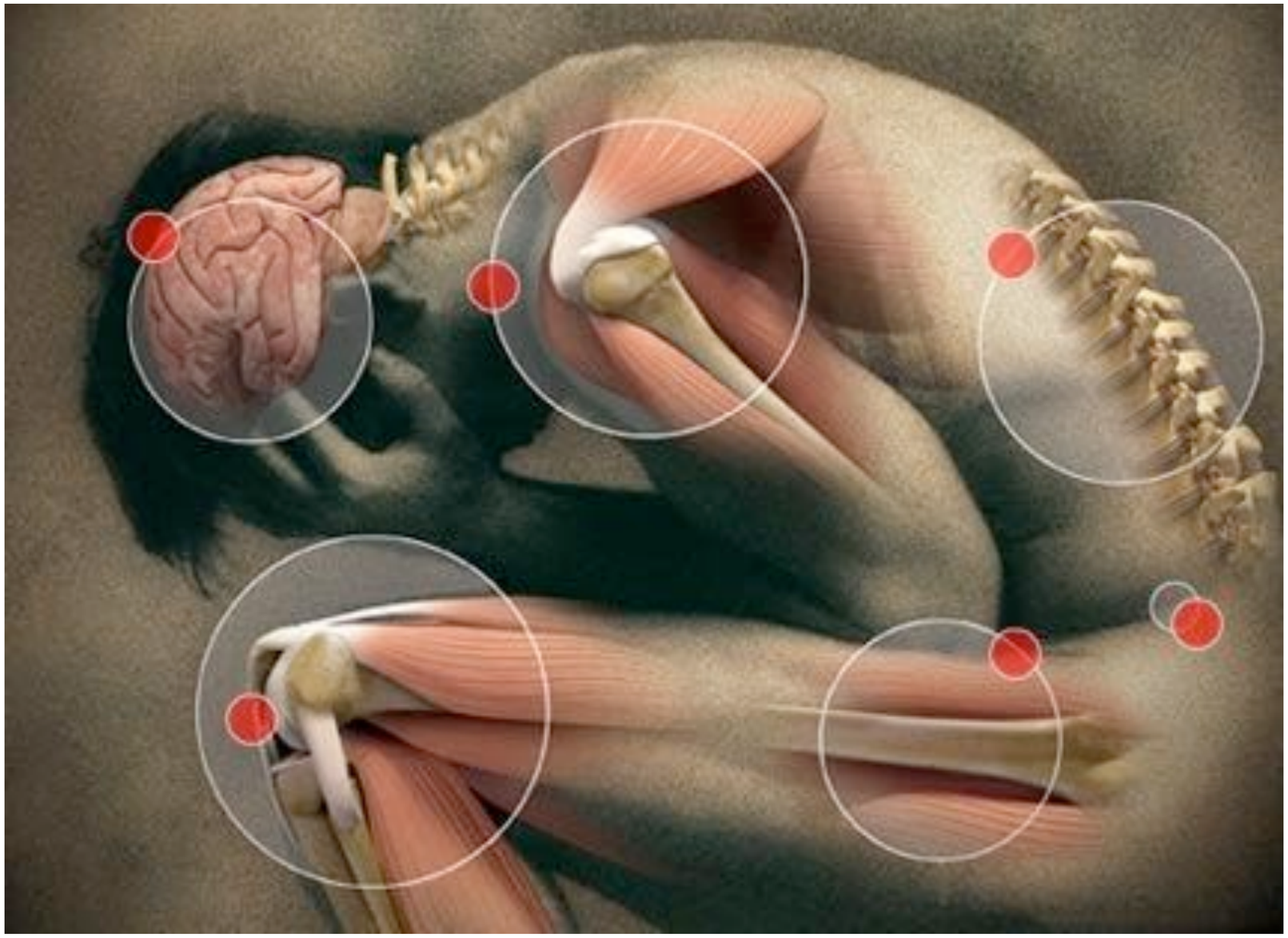
SECONDARY AMINES

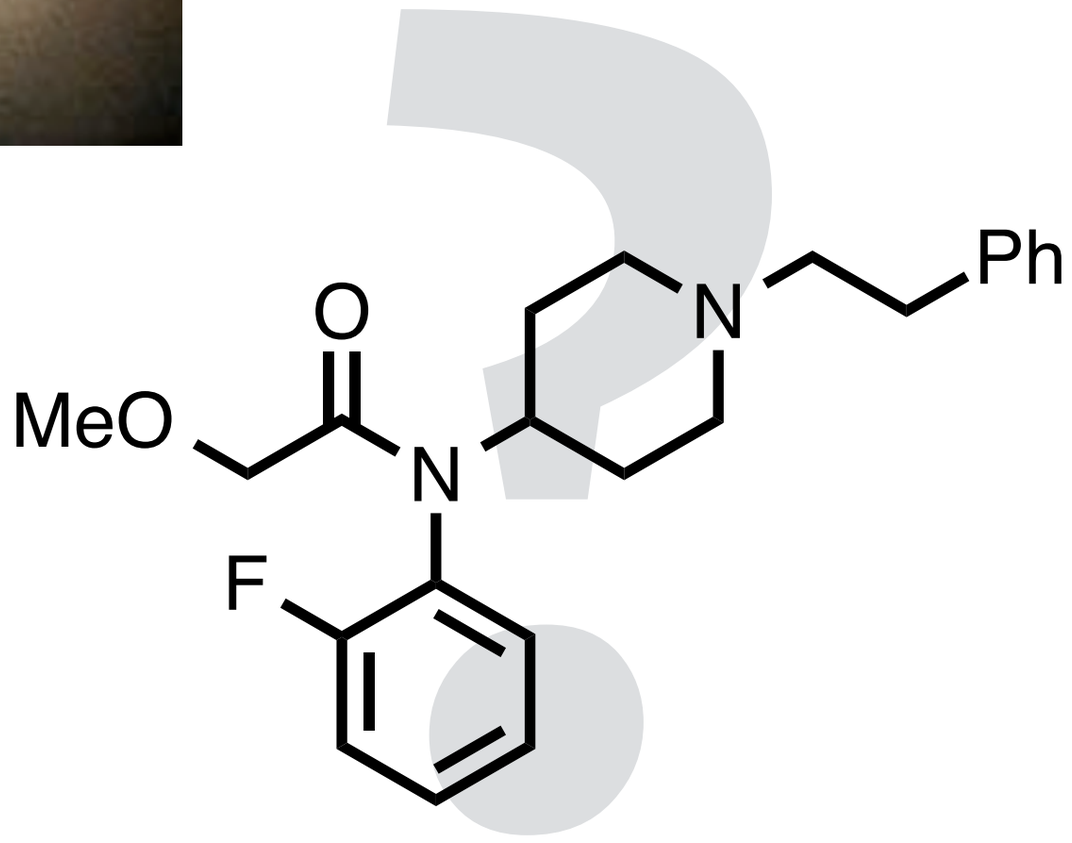




TERTIARY AMINES





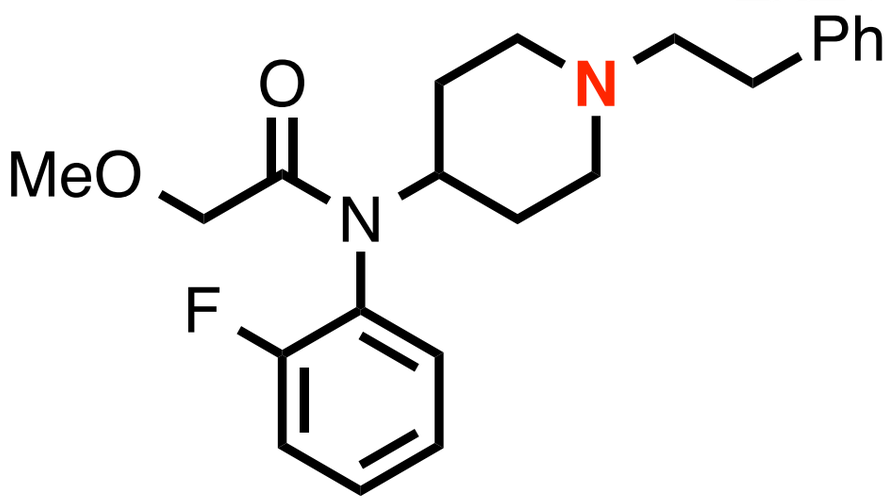


Ocfentanil (or A-3217)

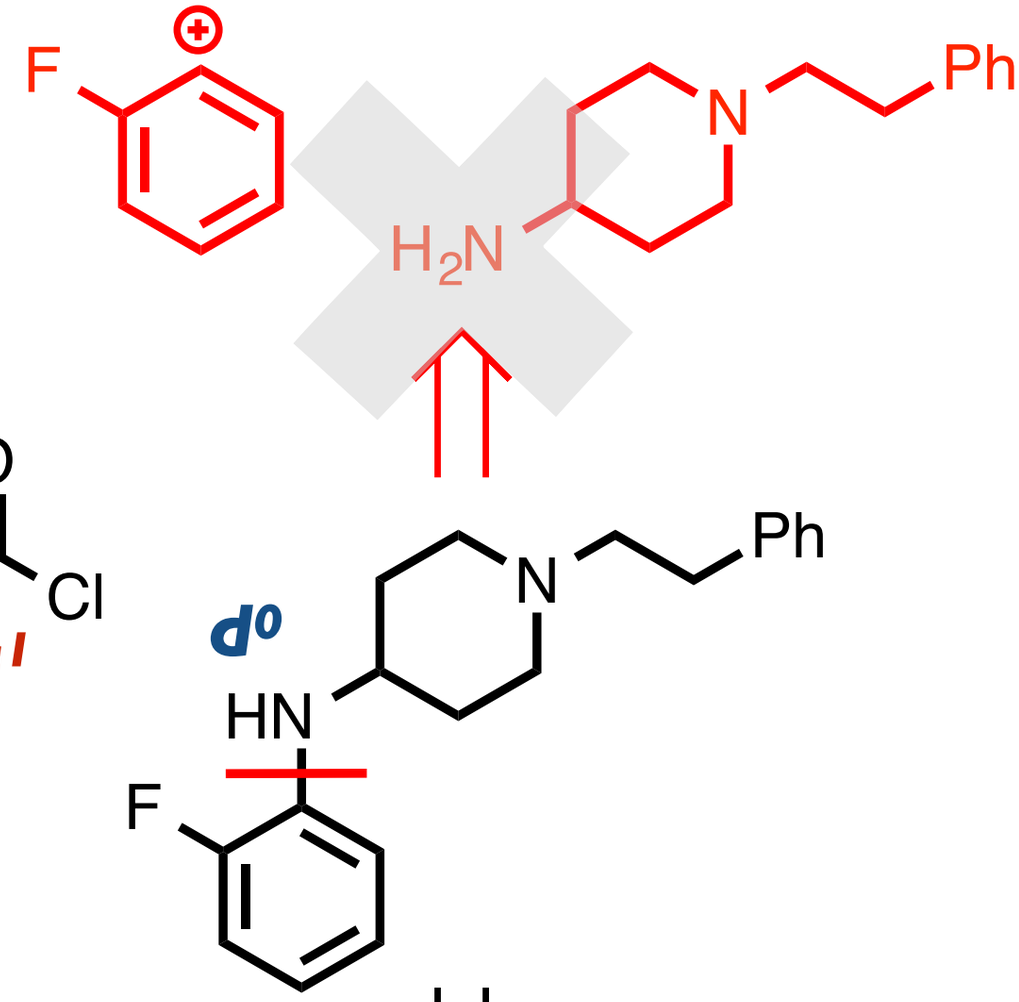
painkiller

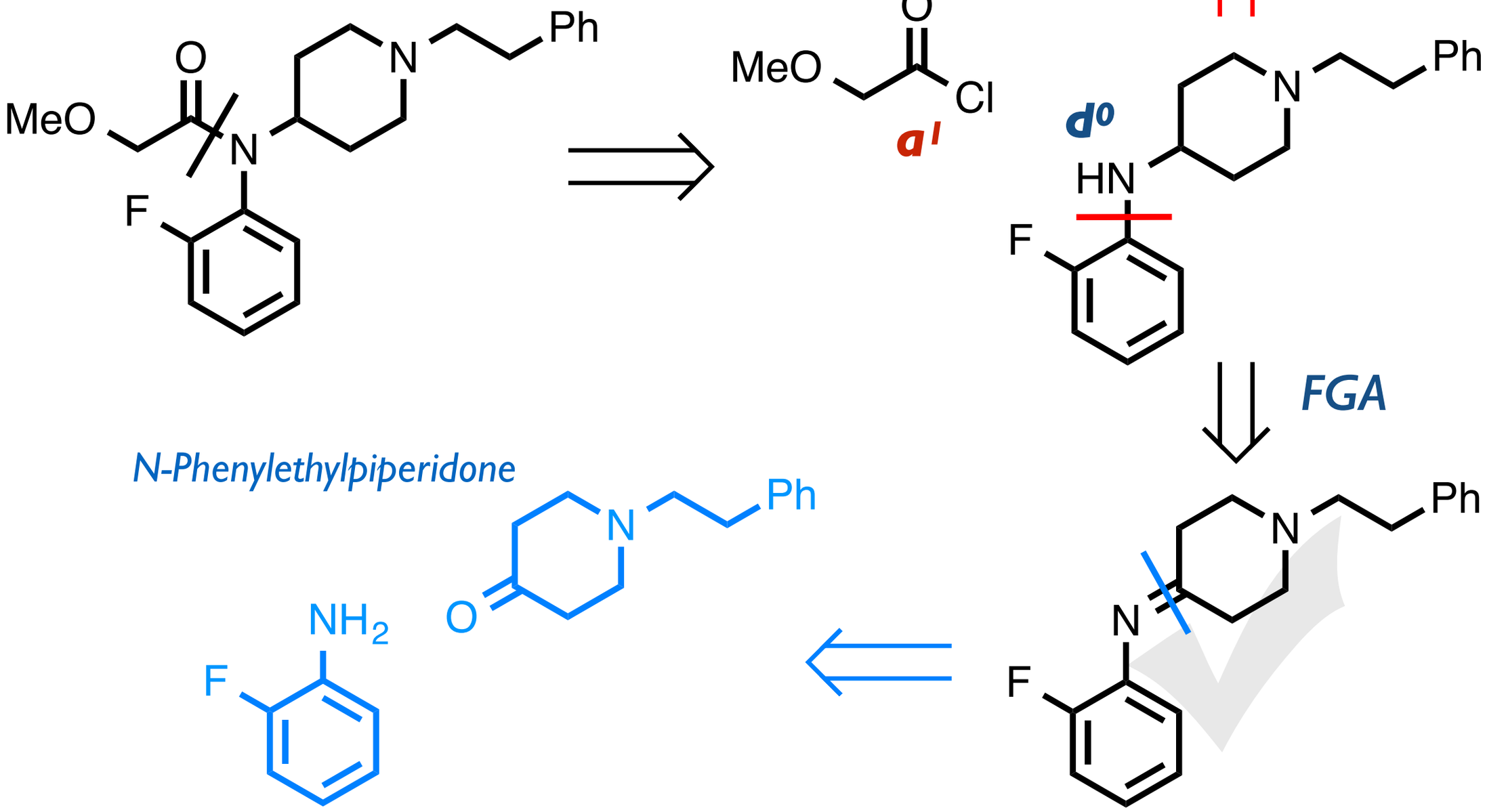
Don’t disconnect this nitrogen: heterocycle

BUILDING BLOCK

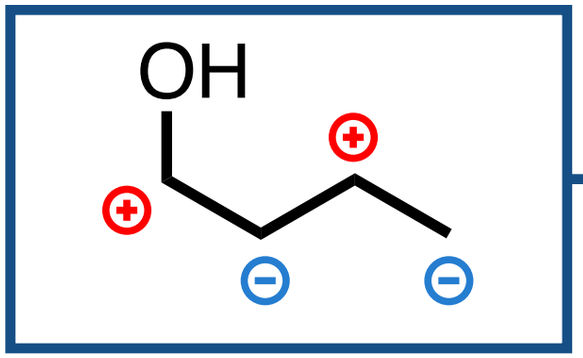


*However, pay attention to the **Buchwald-Hartwig** reaction*



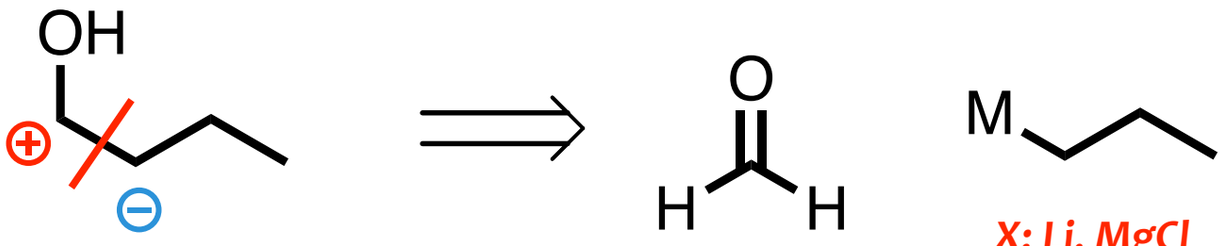


N-Phenylethylpiperidone

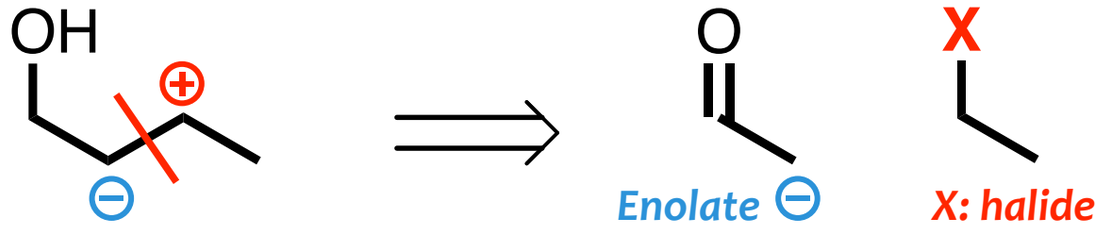


Natural charge distribution

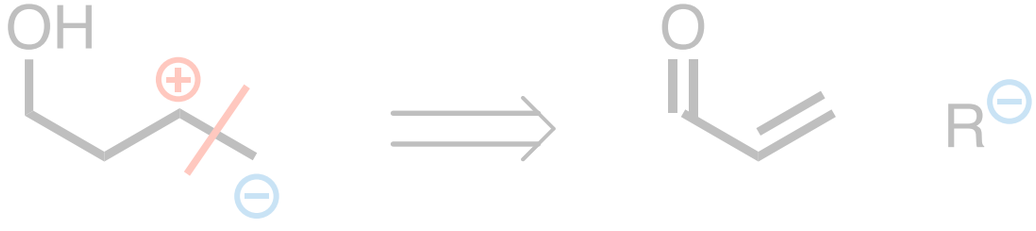
S_N2



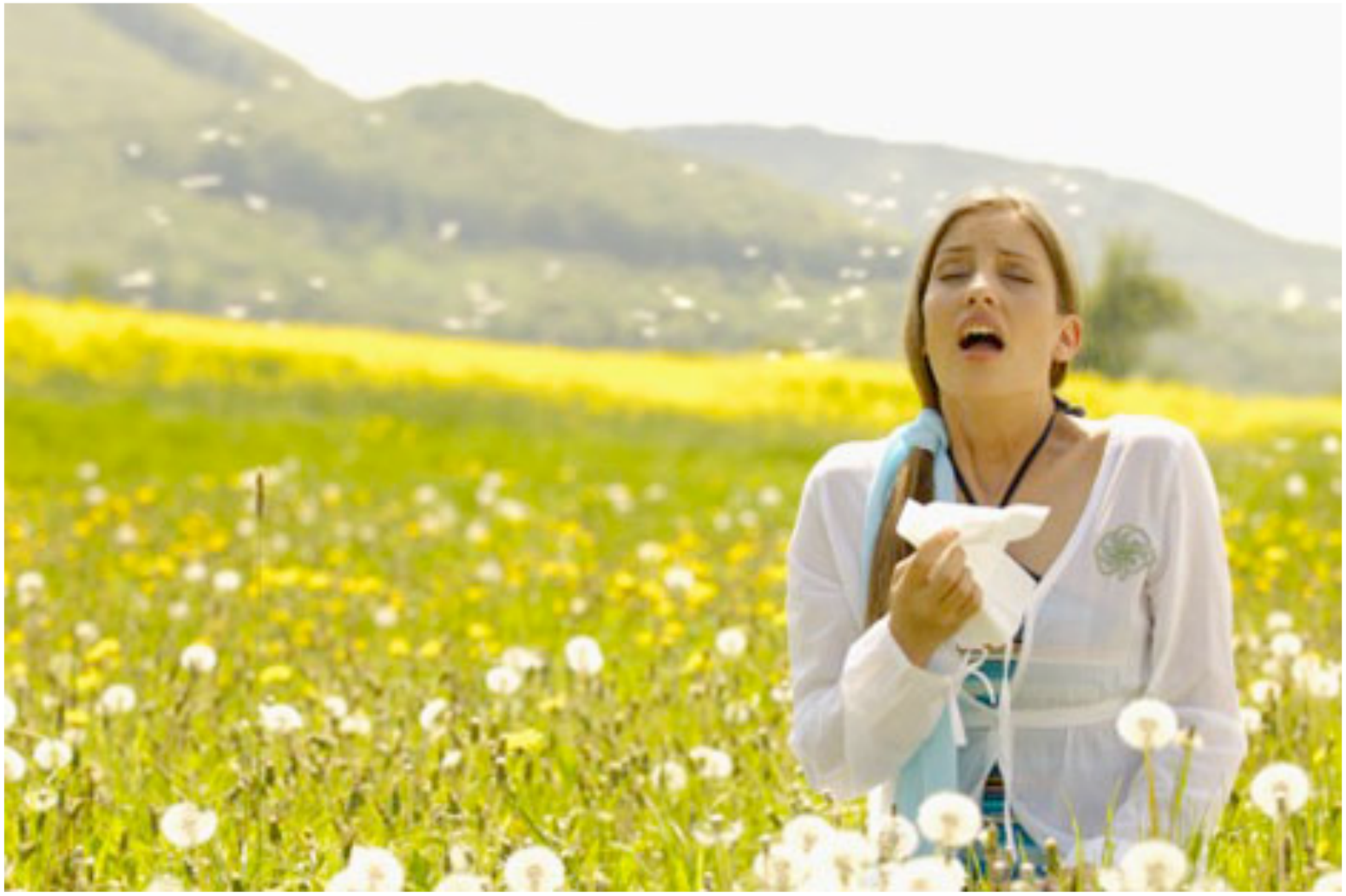
Ionic Additions to Carbonyls

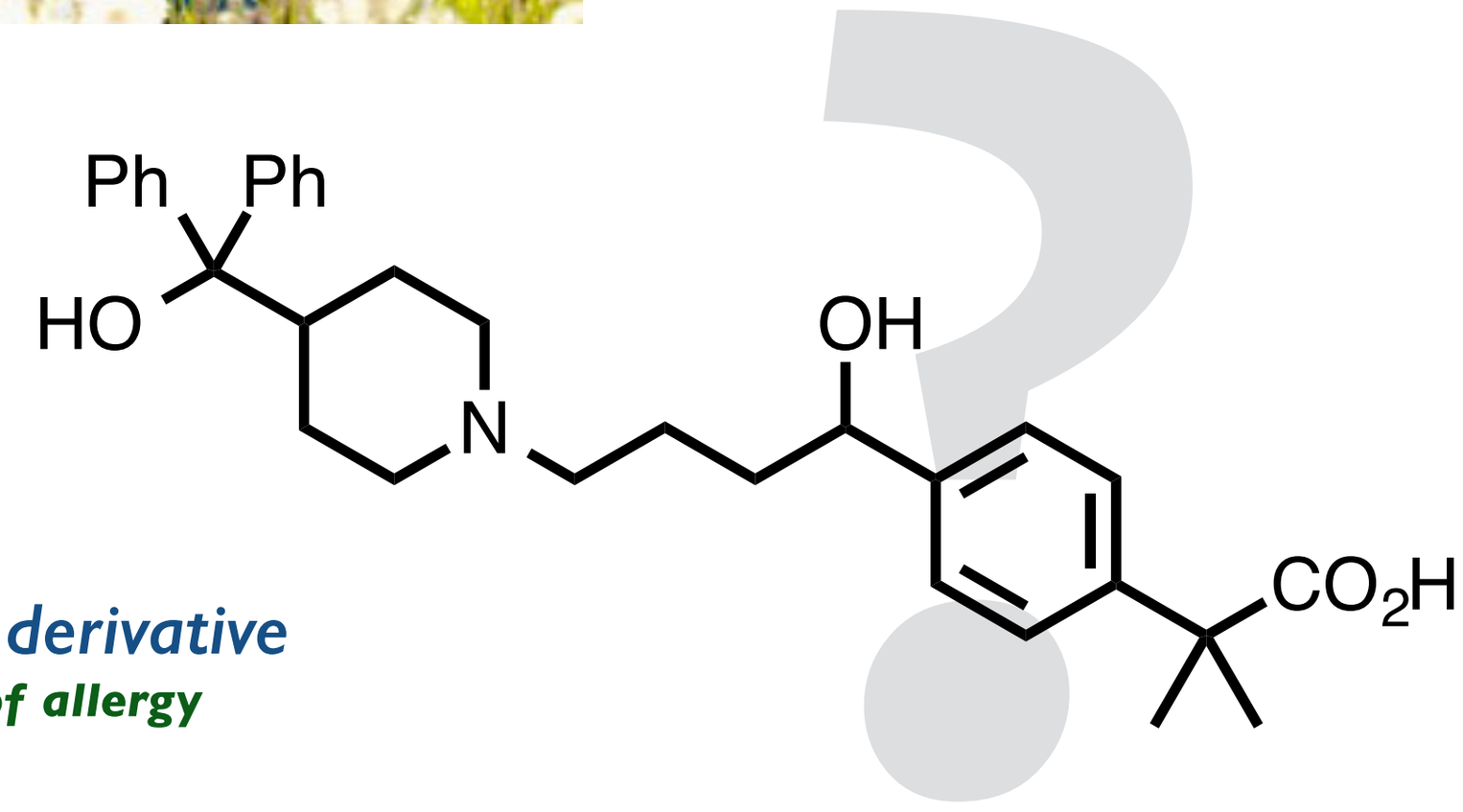


Alkylation of Enolates (or Enamines)



Michael



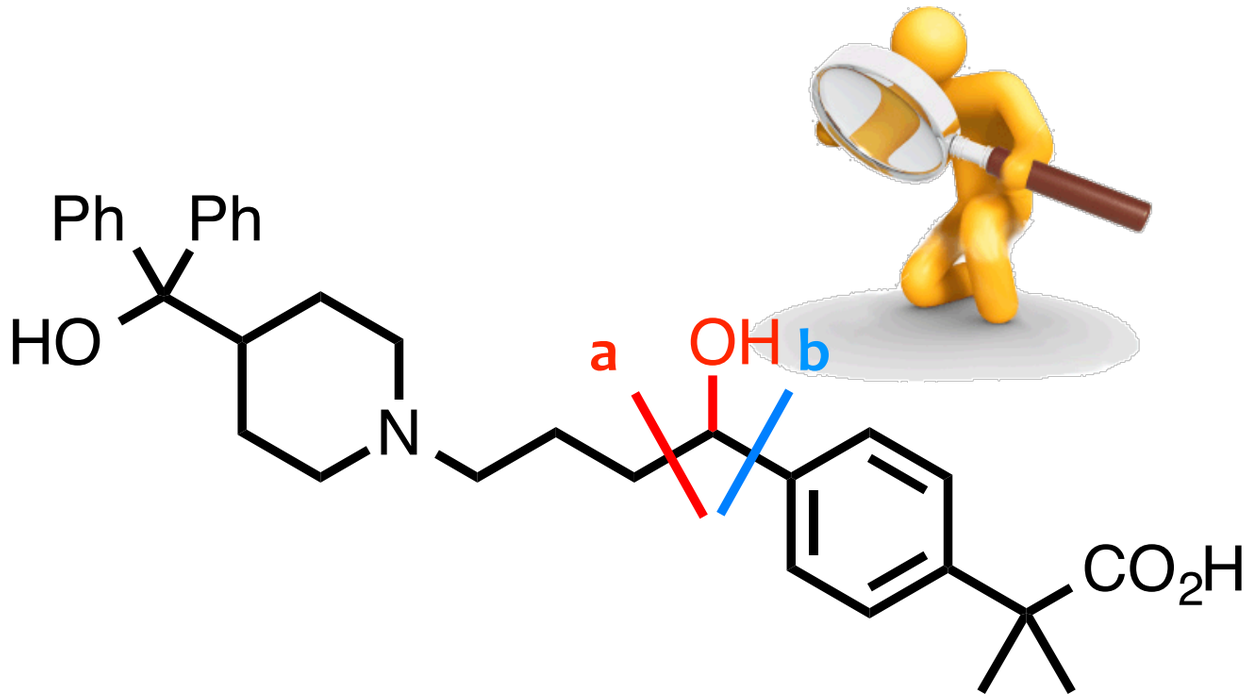


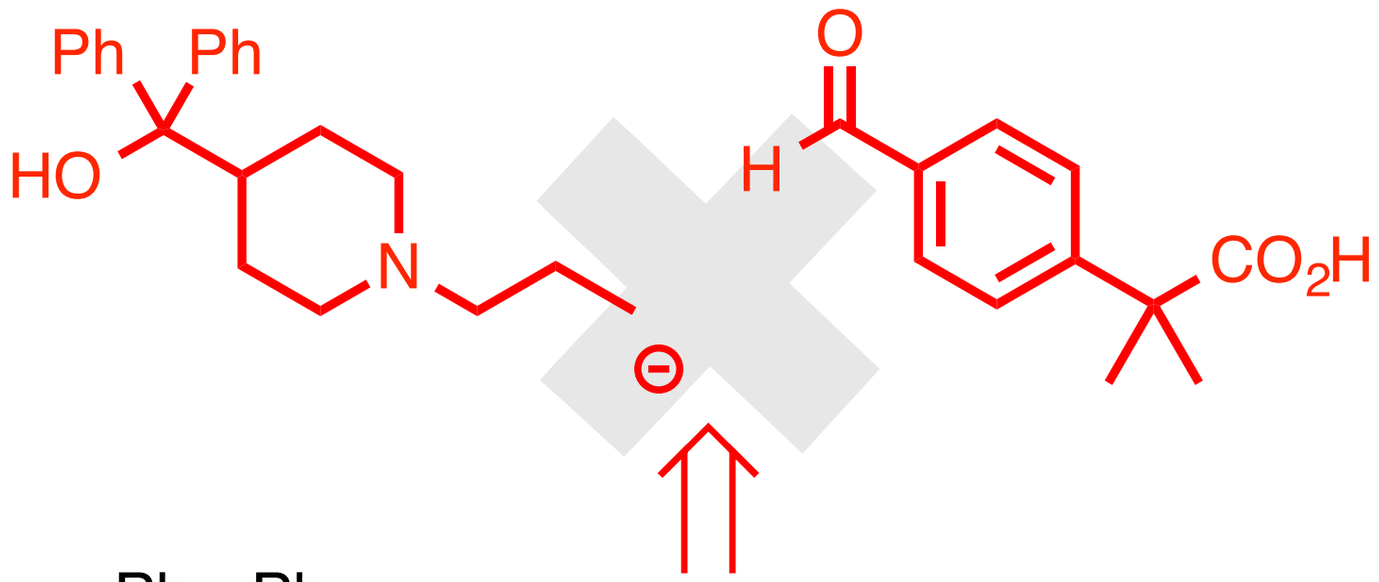
Terfenadine derivative

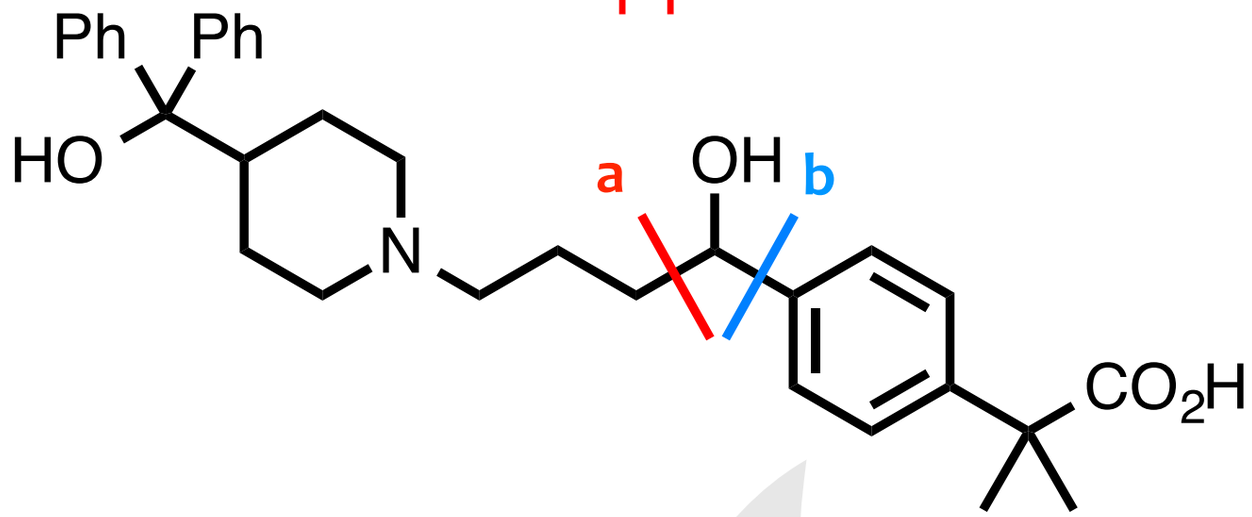
treatment of allergy

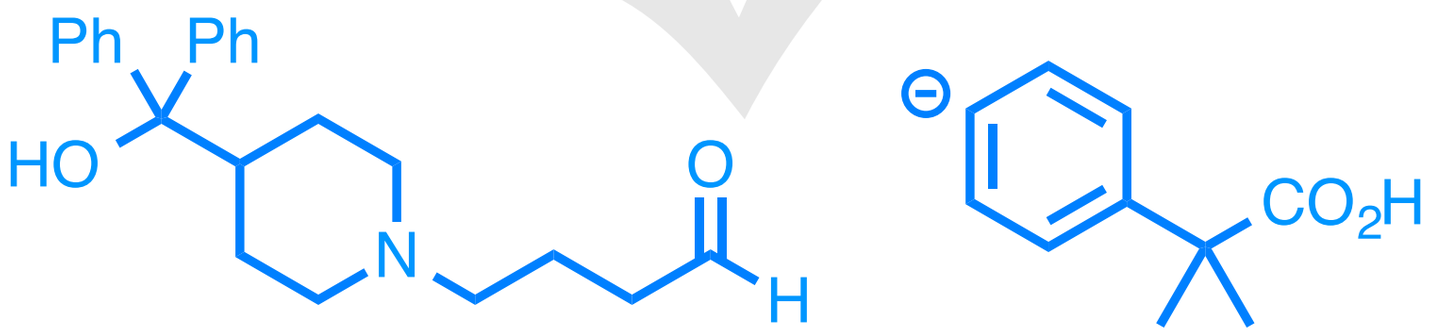
The disconnection of this alcohol produces two fragments of similar complexity:

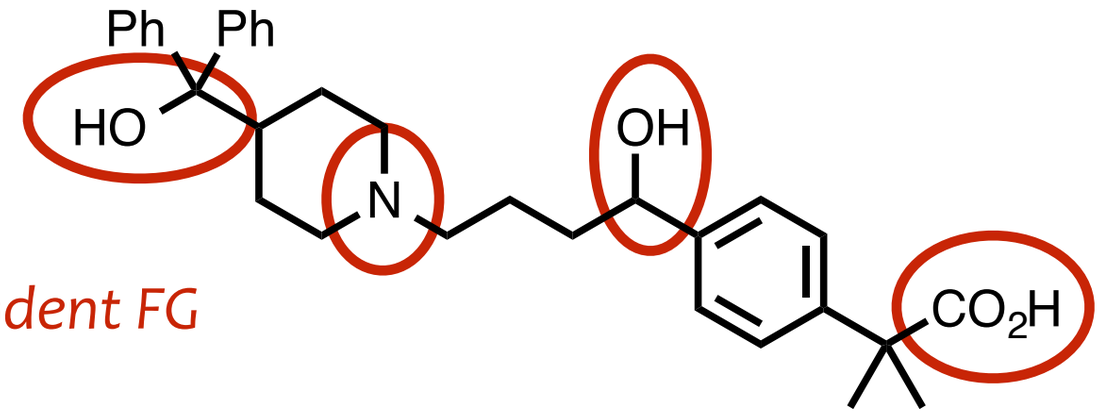
Two Options



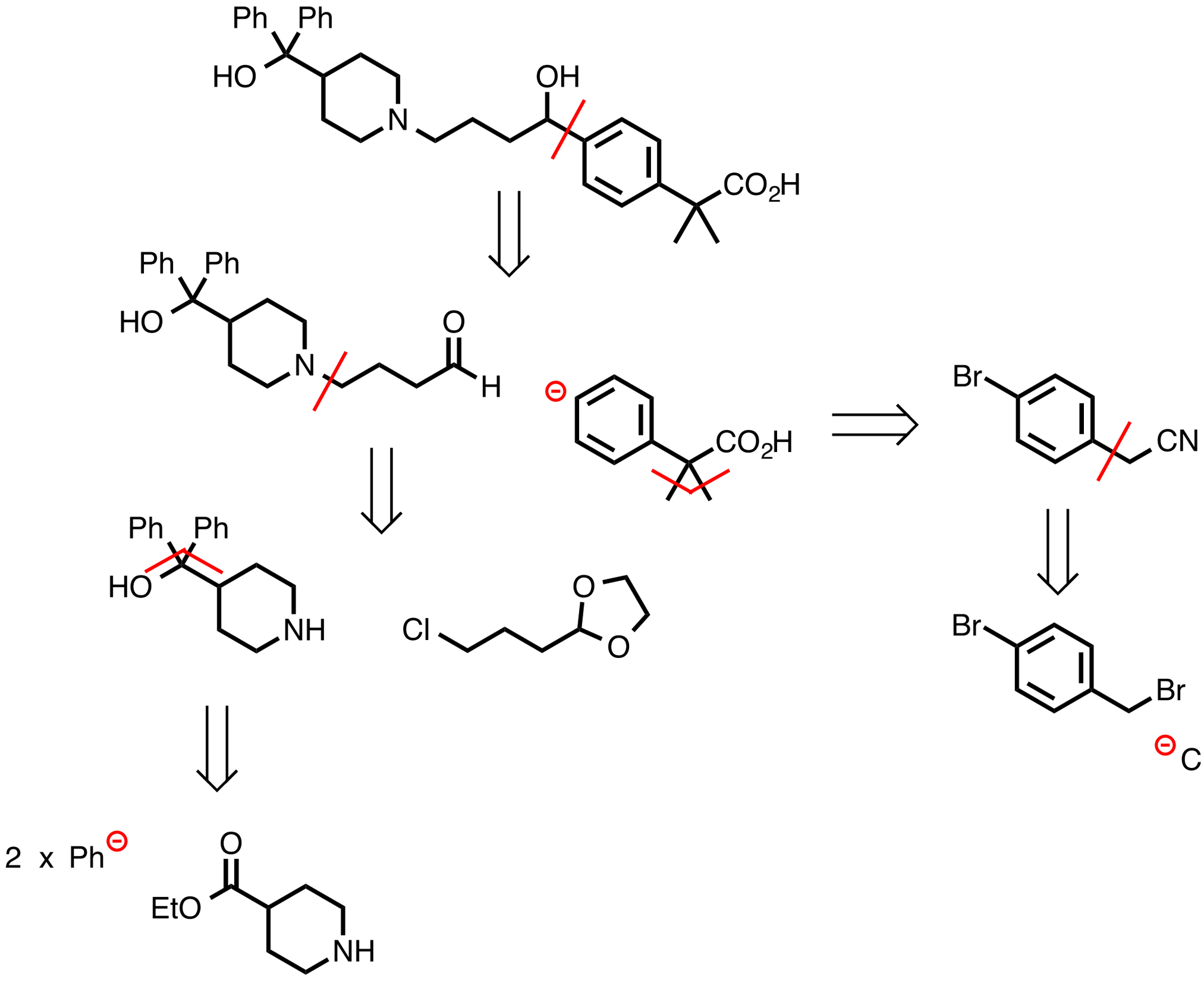

Ph
Ph
HO
N
O
H
CO2H

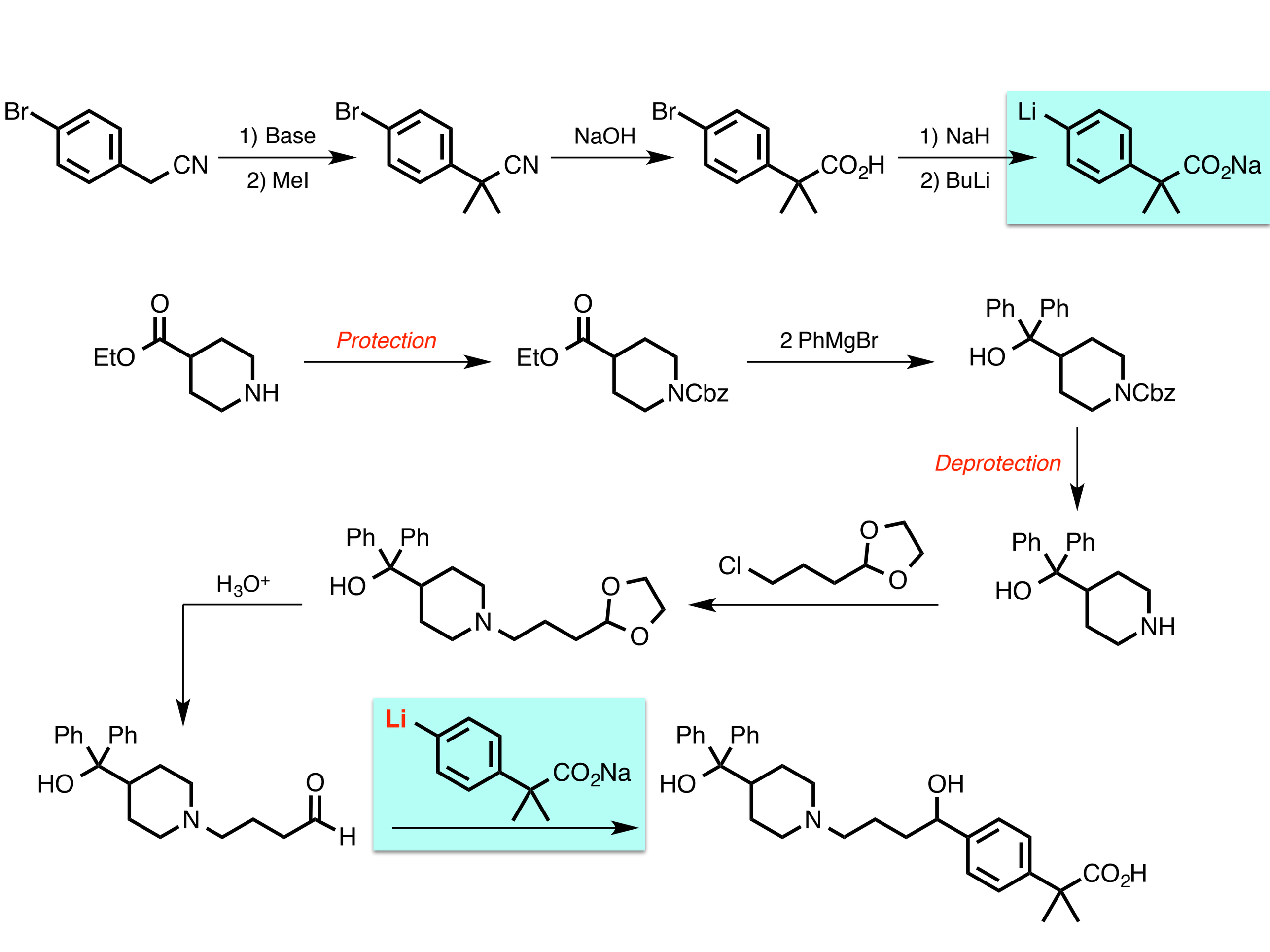

Ph
Ph
HO
N
a
OH
b
CO2H

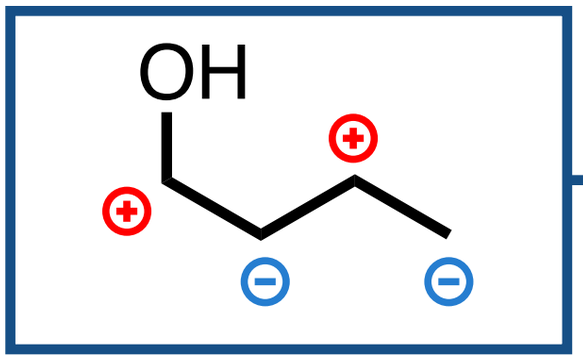

Ph
Ph
HO
N
O
H
CO2H



Four independent FG


Ph
Ph
HO
N
OH
CO2H
Ph
Ph
HO
N
O
H
CO2H
Br
CN
Ph
Ph
HO
NH
O
Cl
O
O
Br
Br
2 x Ph
O
EtO
NH
CN

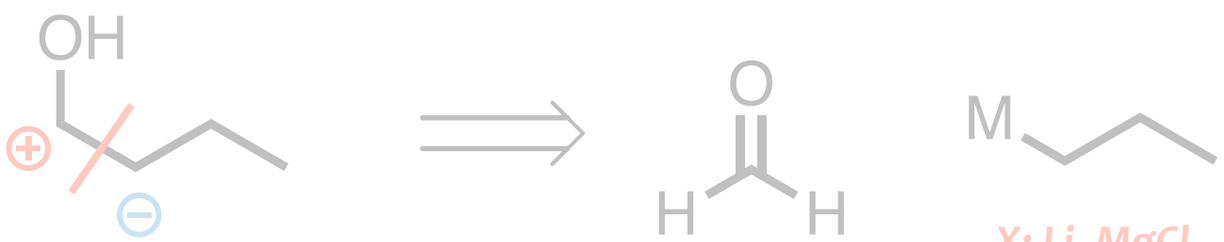

Br
CN
1) Base
2) MeI
Br
CN
NaOH
Br
CO2H
1) NaH
2) BuLi
Li
CO2Na
O
EtO
NH
Protection
O
EtO
NCbz
2 PhMgBr
Ph
Ph
HO
NCbz
Deprotection
H3O+
Ph
Ph
HO
N
O
O
Cl
O
O
Ph
Ph
HO
NH
Ph
Ph
HO
N
O
H
Li
CO2Na
Ph
Ph
HO
N
OH
CO2H



Natural charge distribution

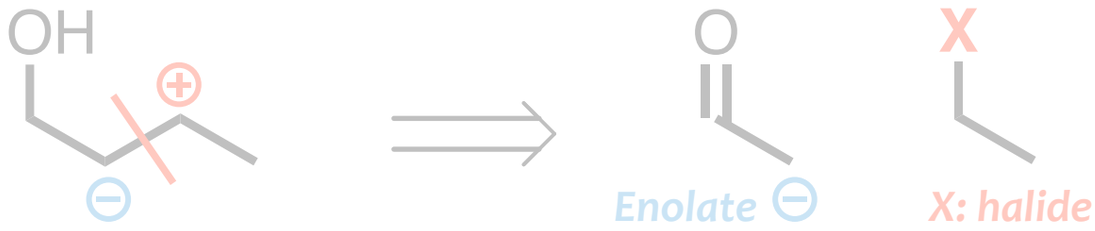
X: halide, sulfonate

S_N2



X: Li, MgCl

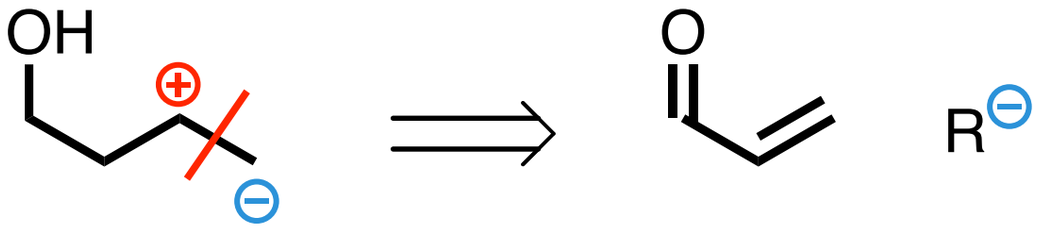
Ionic Additions to Carbonyls



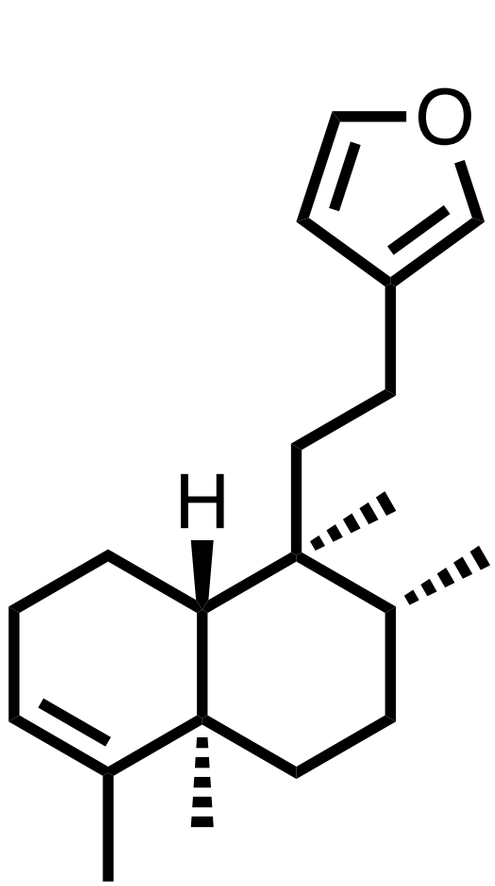
Enolate

X: halide

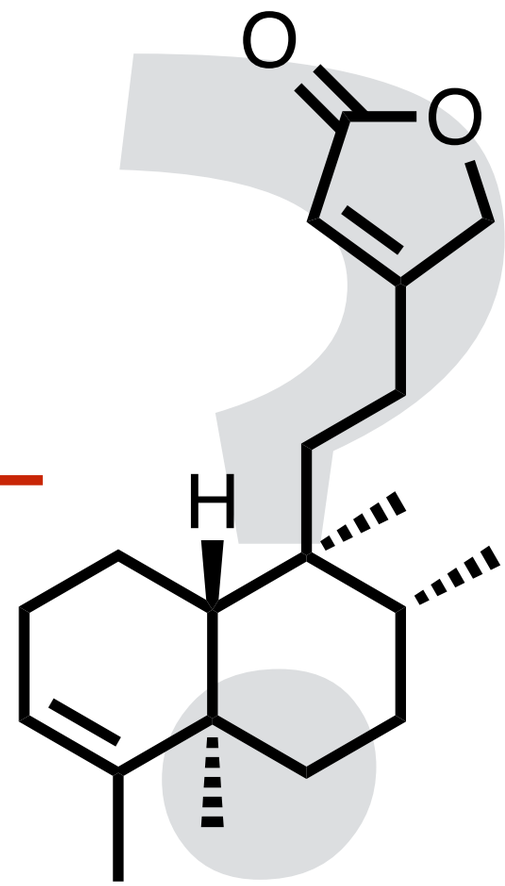
Alkylation of Enolates (or Enamines)



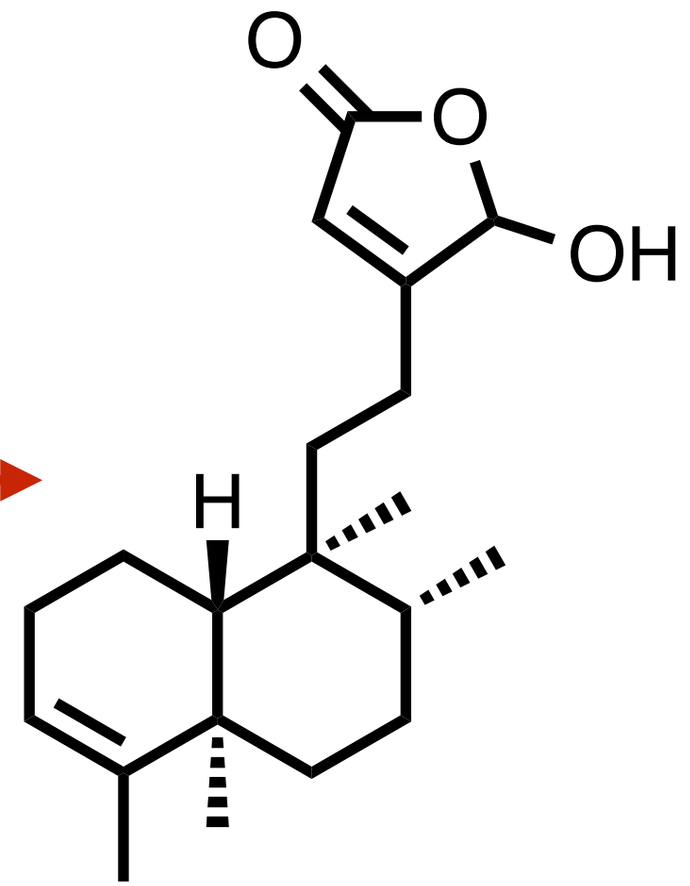
Michael



Annonene



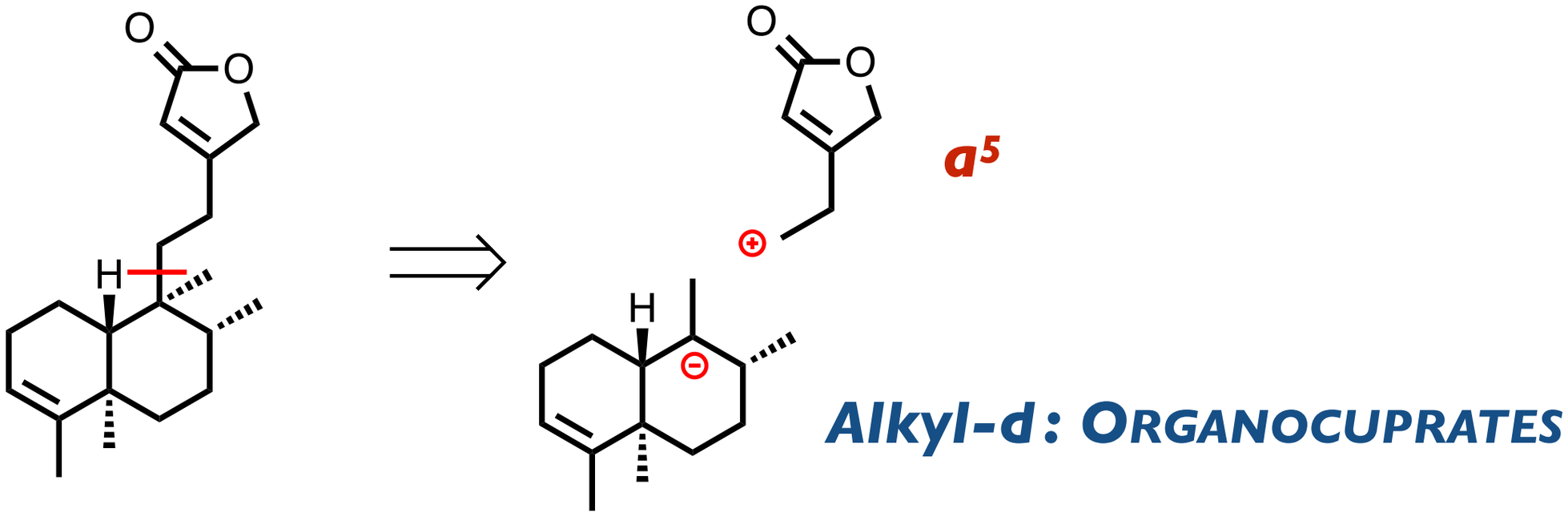
Solidagolactone

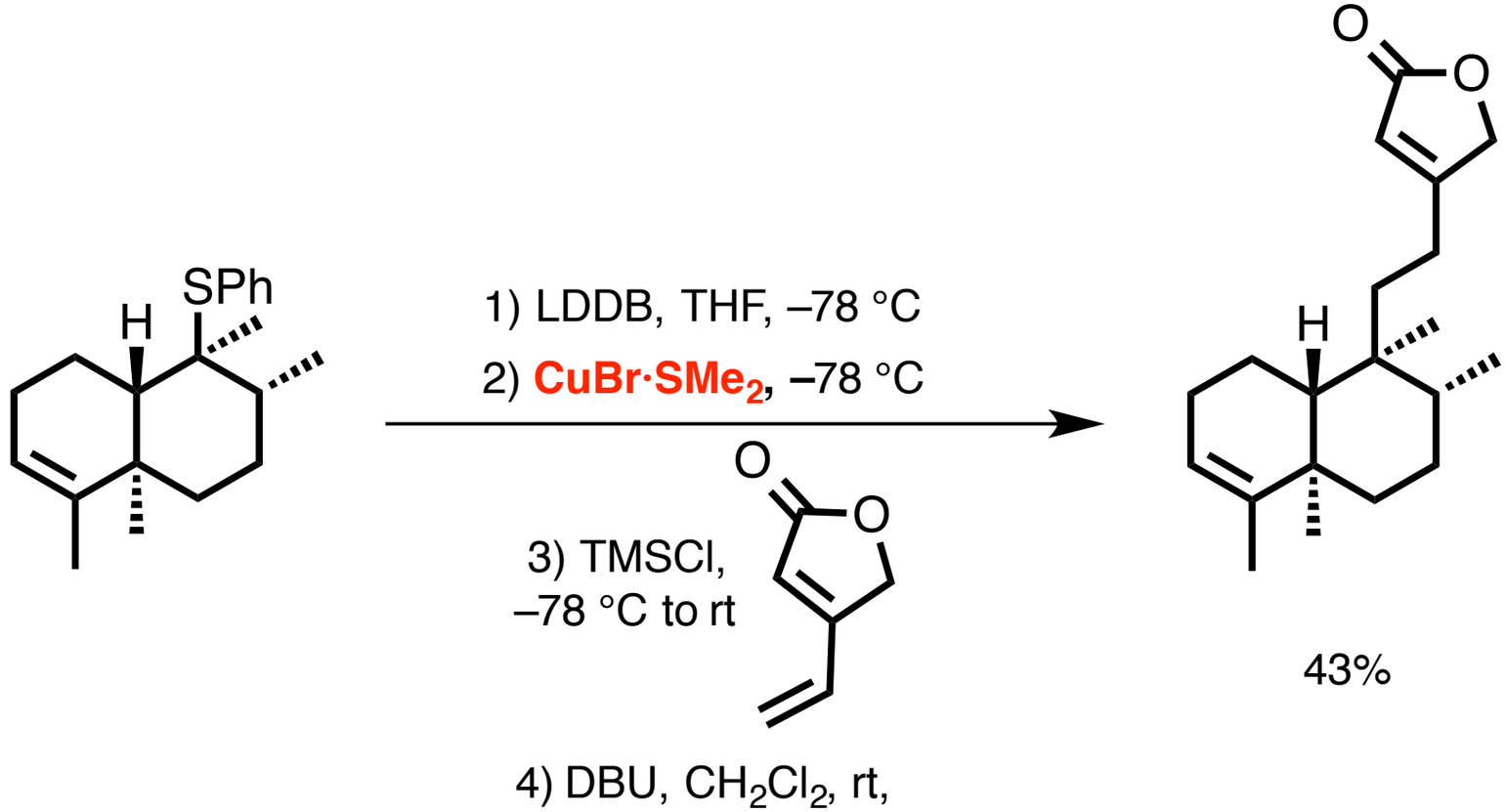


PL3

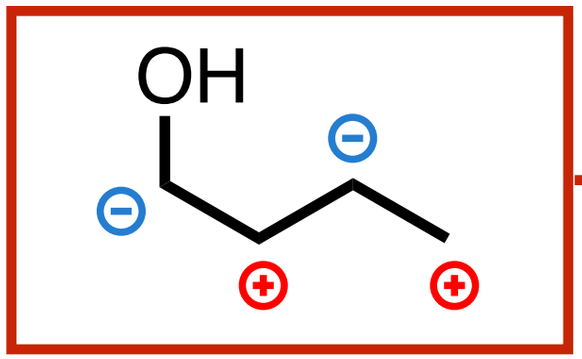
trans-Clerodane diterpenoids

antibacterial, antitumor, antifeedant activity



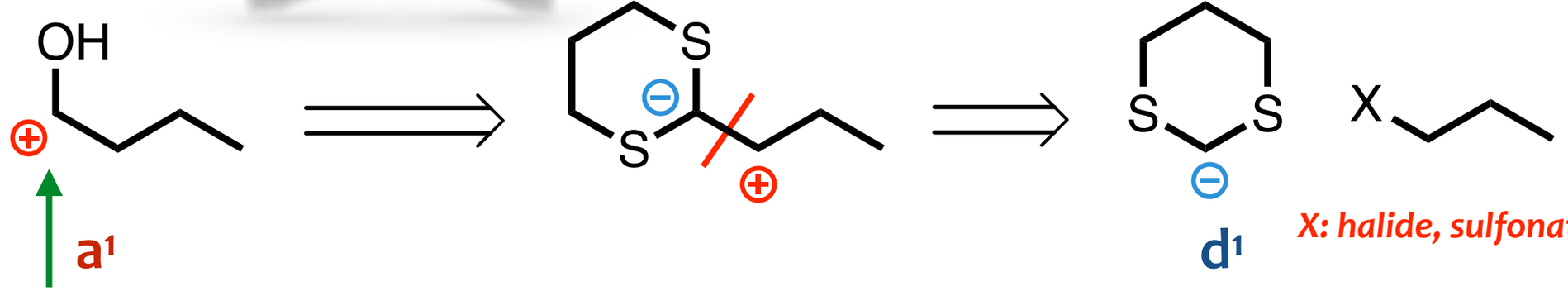


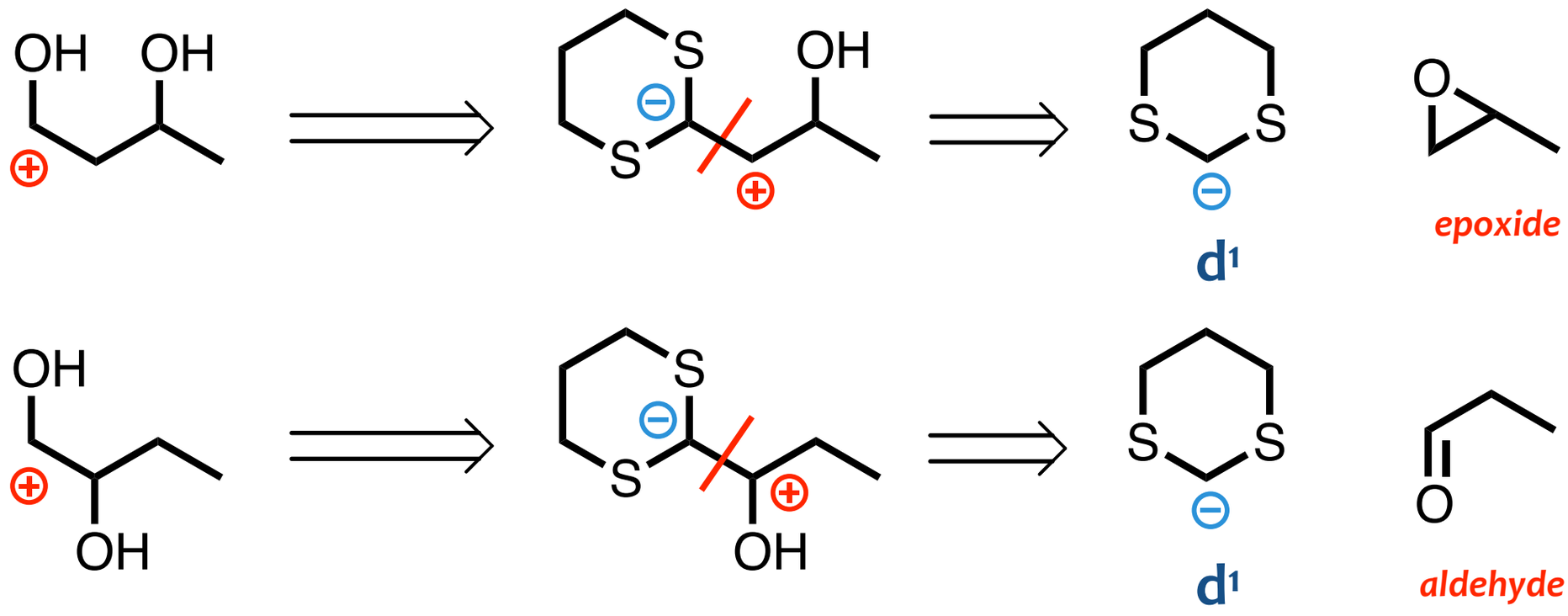
Overman, L. E. *JACS* **2015**, *137*, 660



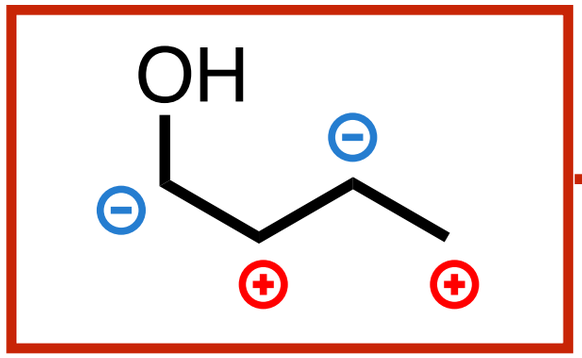
Non-Natural charge distribution

UMPOLUNG



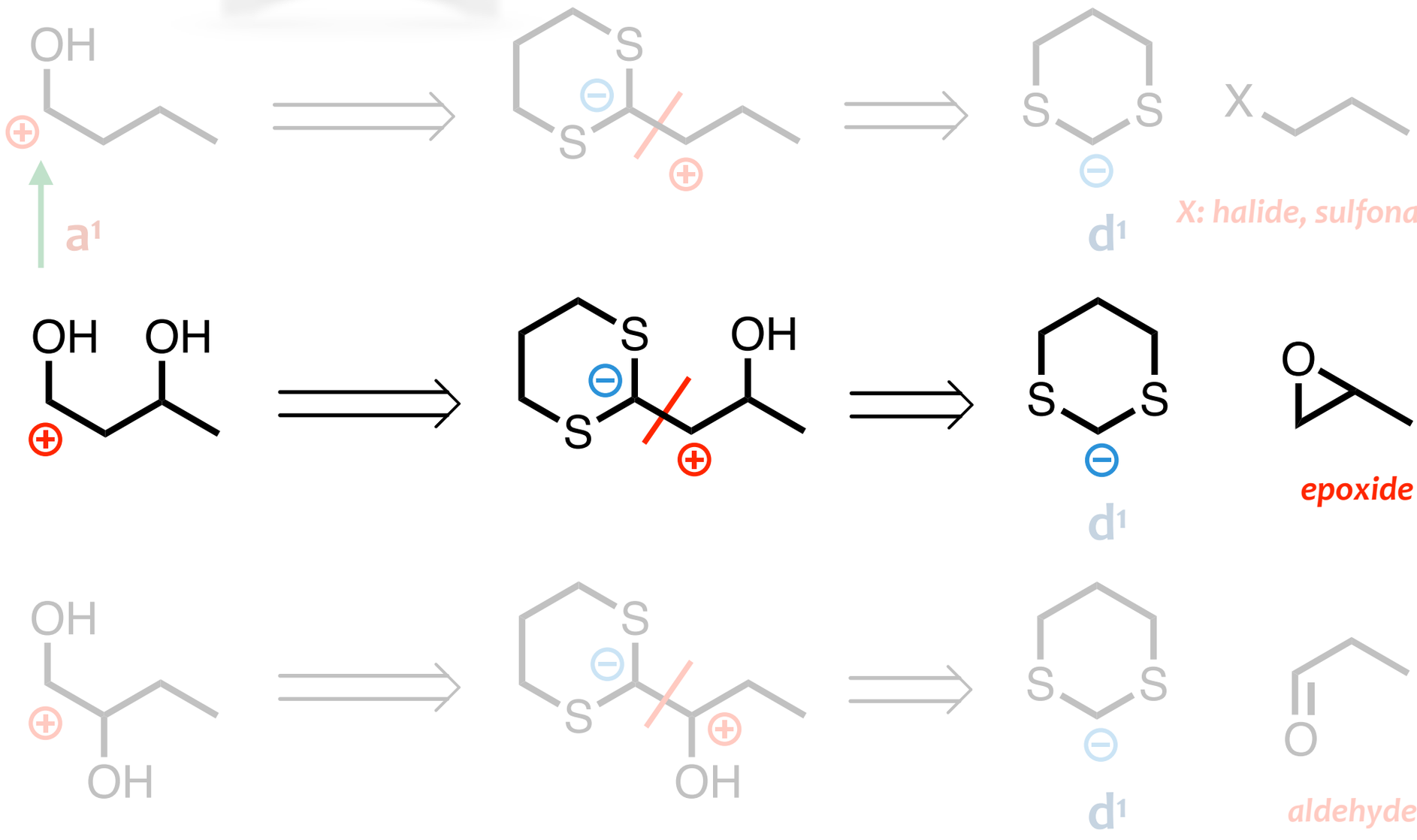


Smith, A. B. III, *ACR* **1998**, *31*, 35; **2004**, *37*, 365

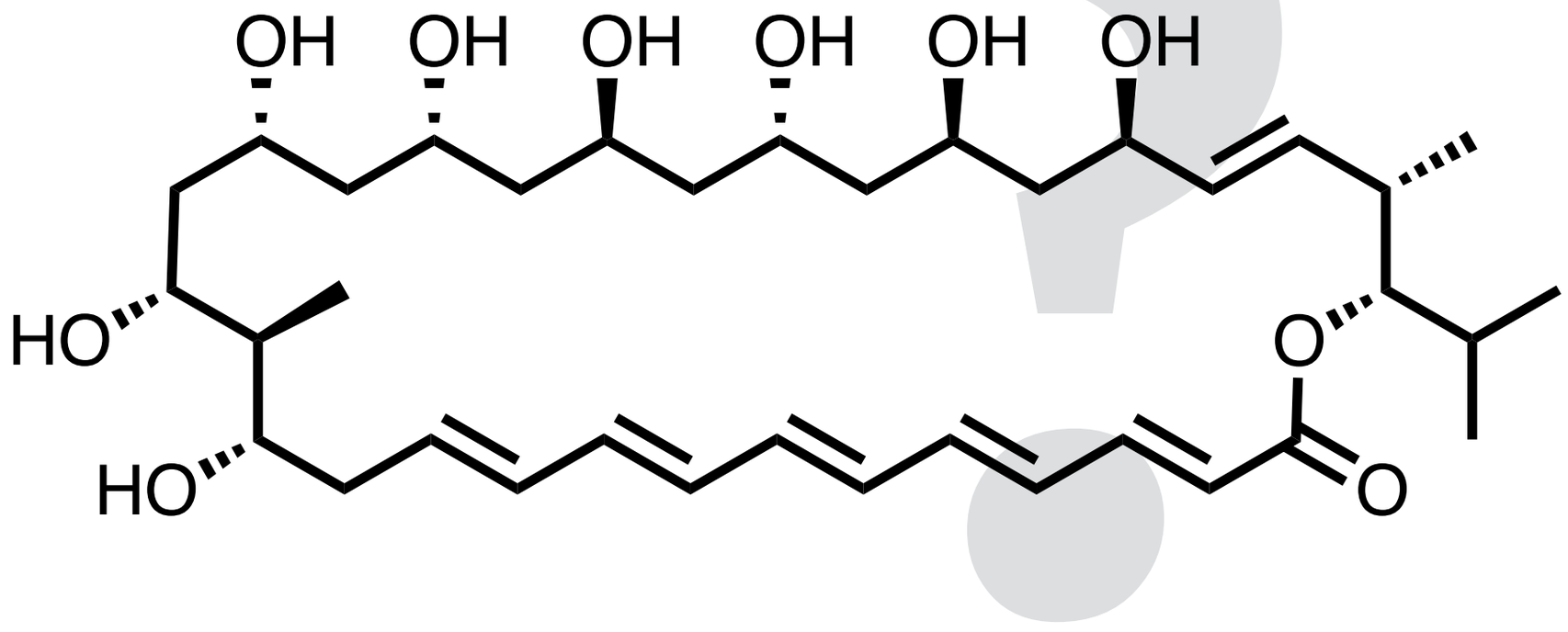


Non-Natural charge distribution

UMPOLUNG



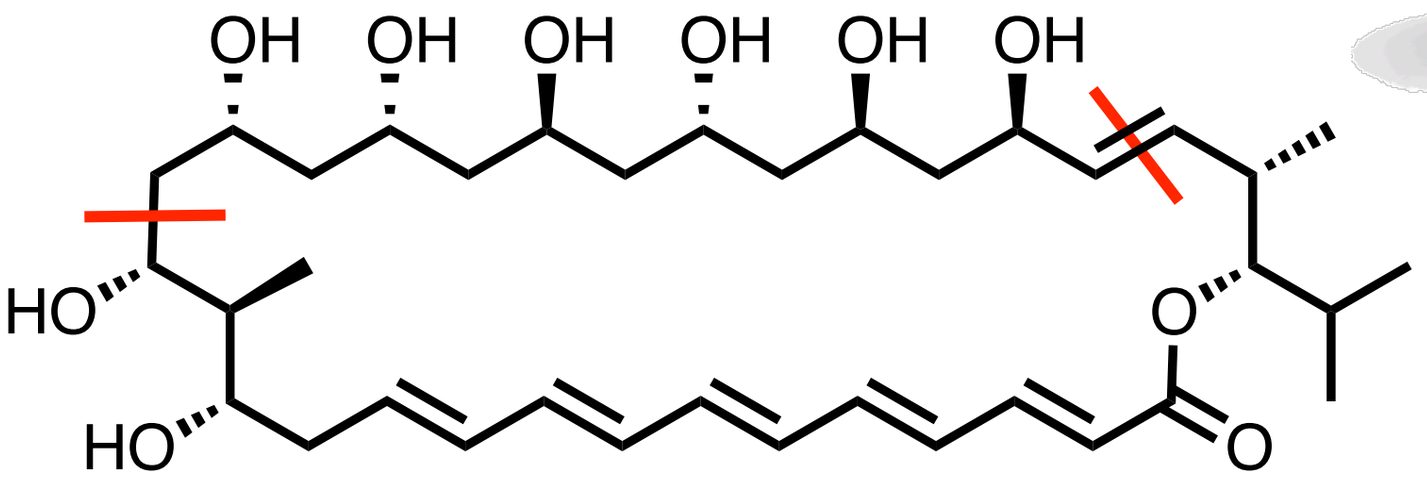
Smith, A. B. III, *ACR* **1998**, *31*, 35; **2004**, *37*, 365

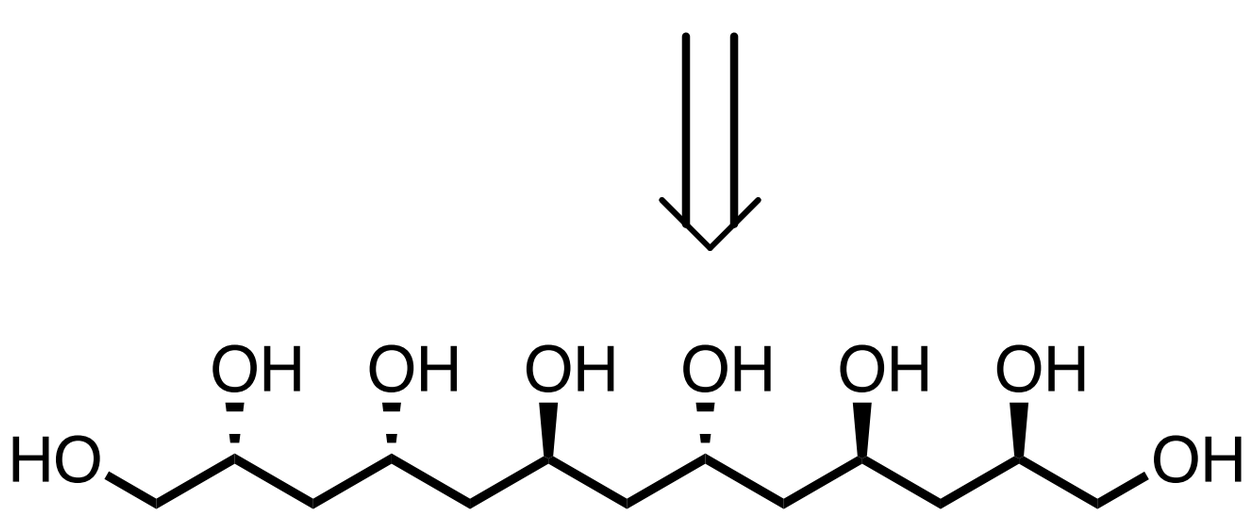


Mycoticin A

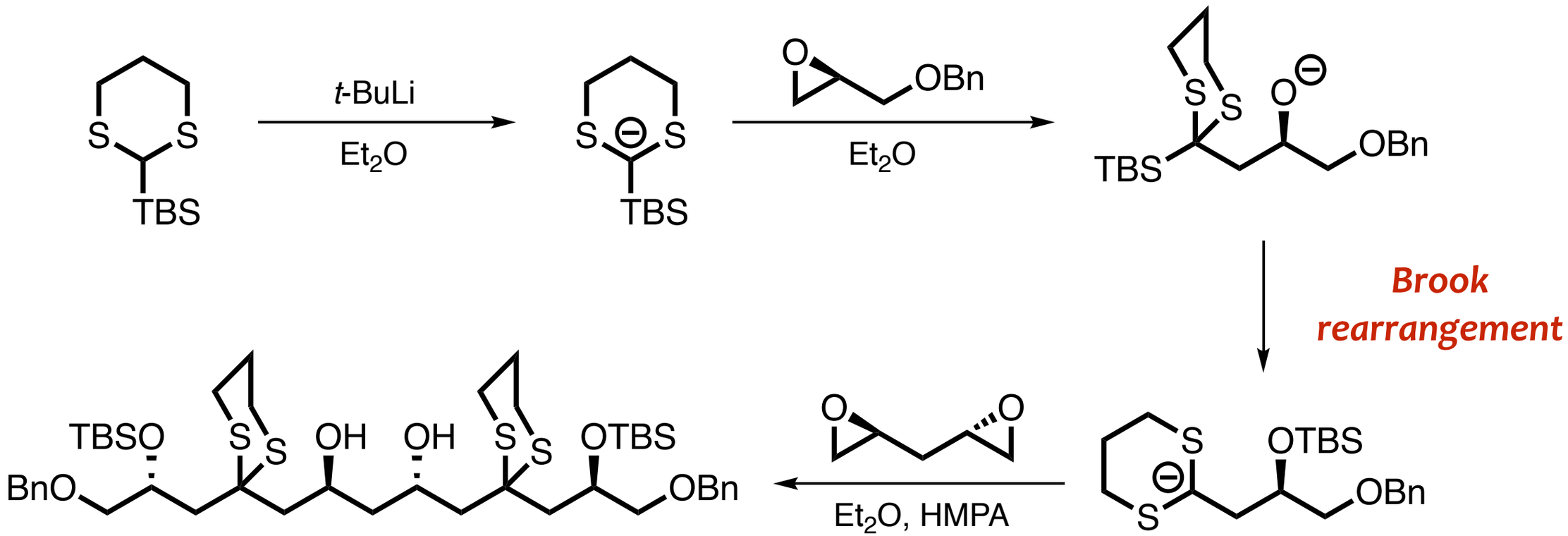
antifungi agent

The construction of the polyol fragment takes advantage of the symmetry

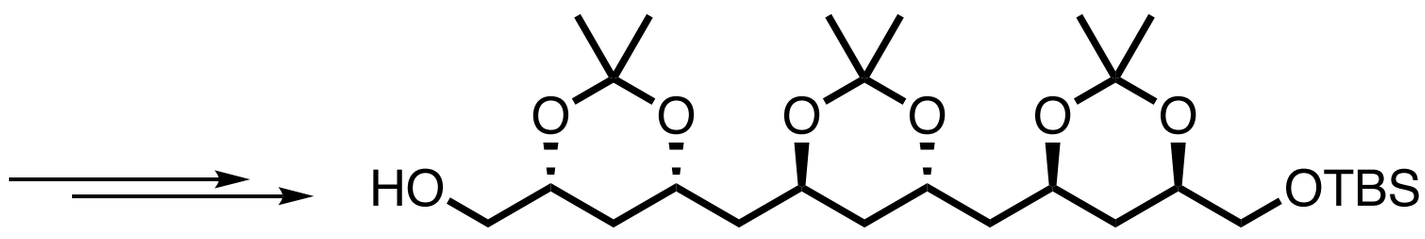




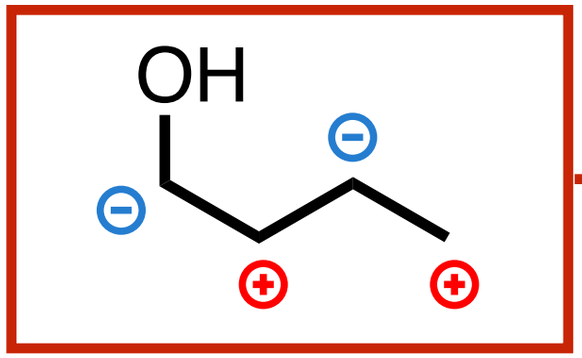
… and TACTICS may be based on the UMPOLUNG concept



Four new C–C bonds in one flask

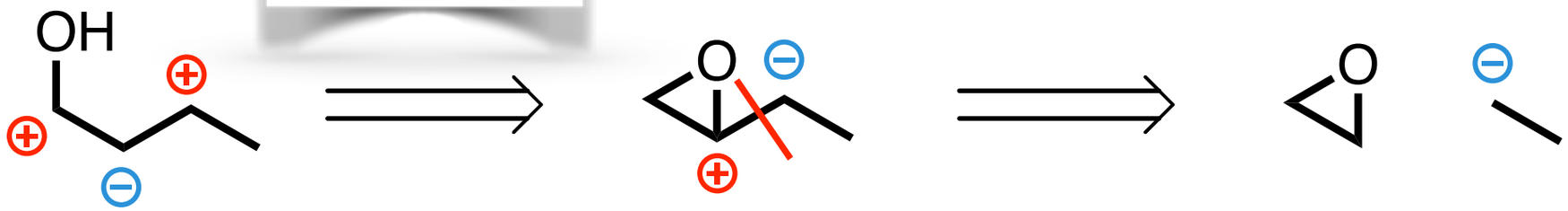


Smith, A. B., III. *OL* **1999,** *1,* 2001; *JACS* **2003,** *125,* 14445



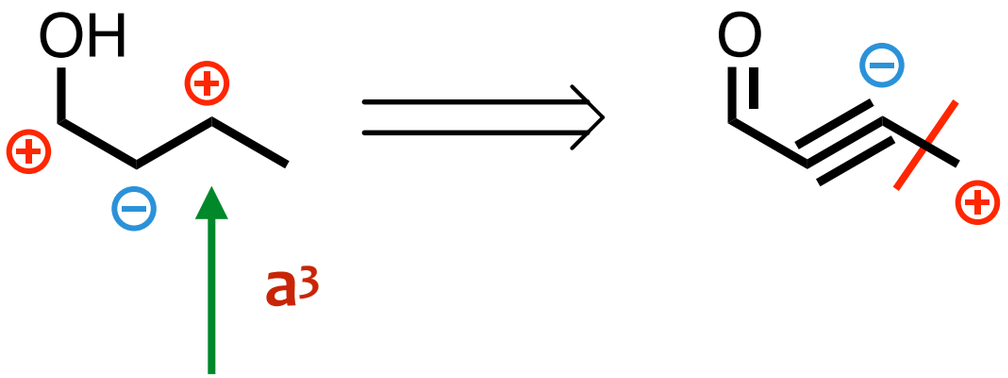
Non-Natural charge distribution

UMPOLUNG

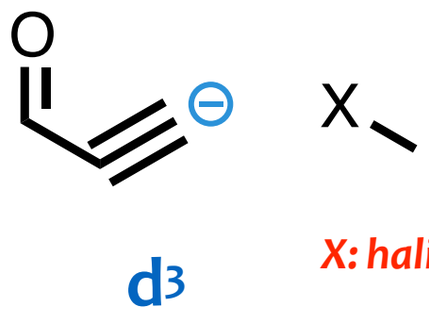


d²

a² *organocuprate*



a³



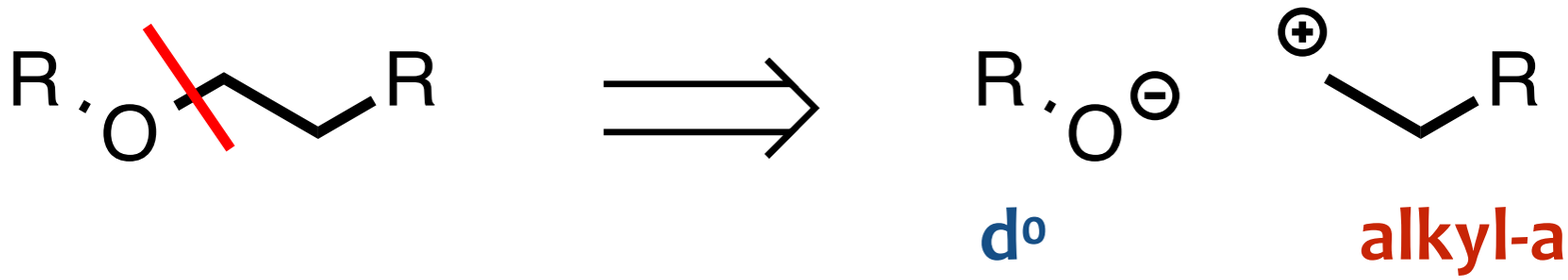
d³

X: halide, sulfonate

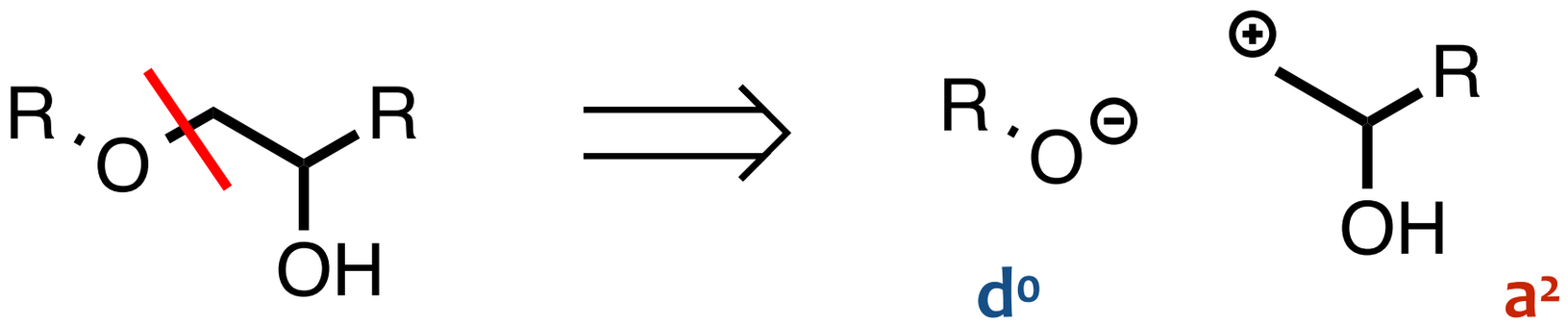
TWO functional groups

$Y\text{-}C_n\text{-}X$ which disconnection?

one-group disconnection

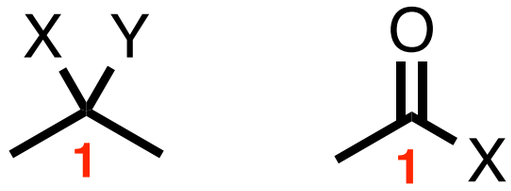


two-group disconnection

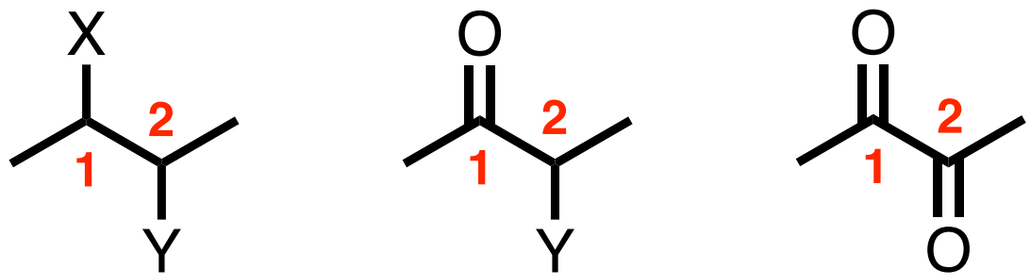


Relationships between two heteroatoms

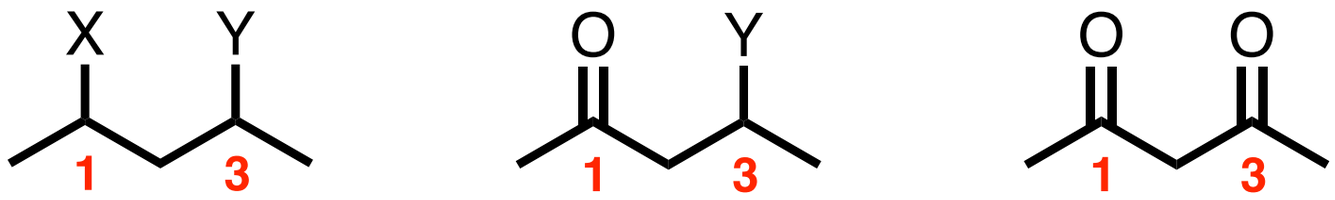
1,1-Relationship



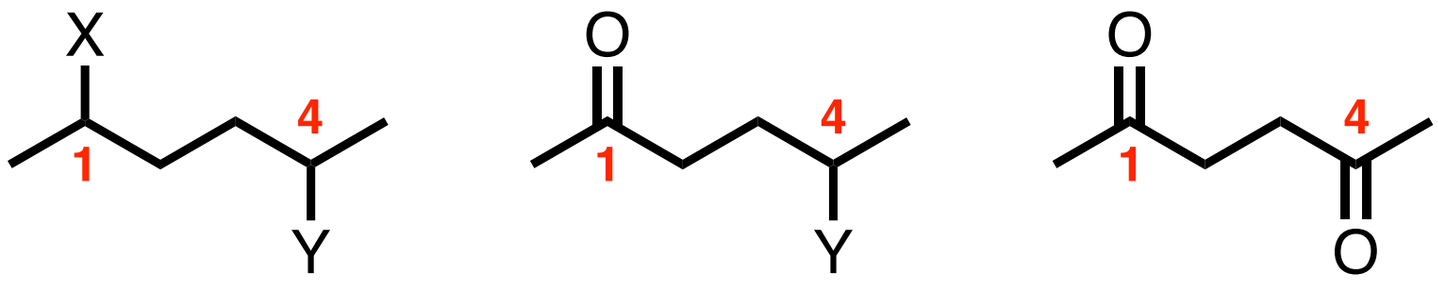
1,2-Relationship



1,3-Relationship



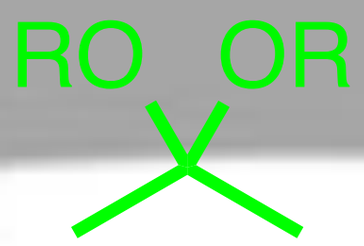
1,4-Relationship

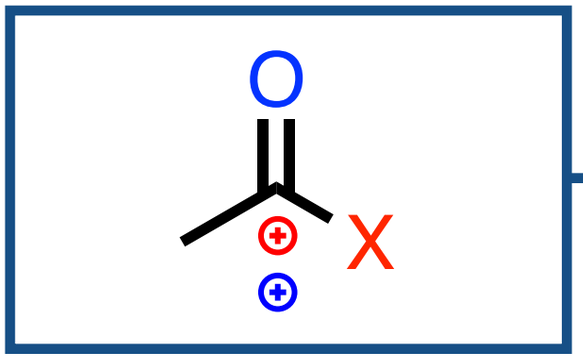


1,1-relationship?

esters?

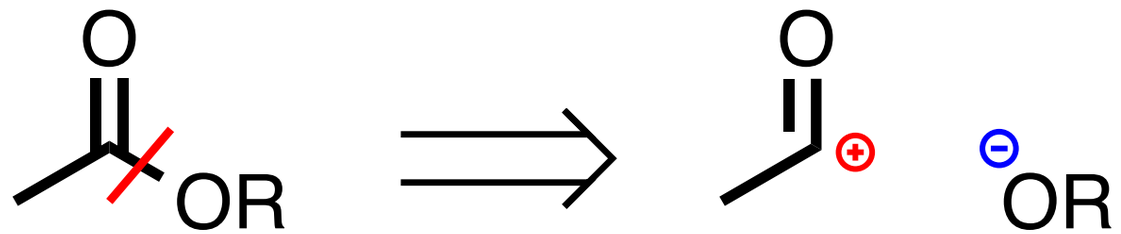
acetals?

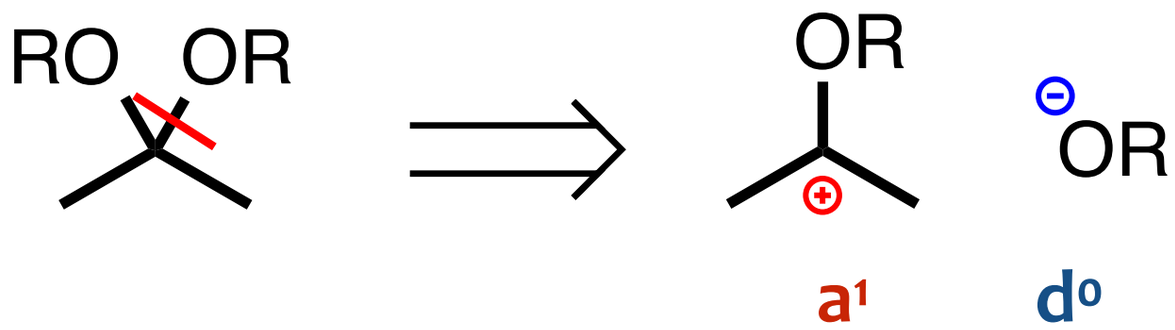


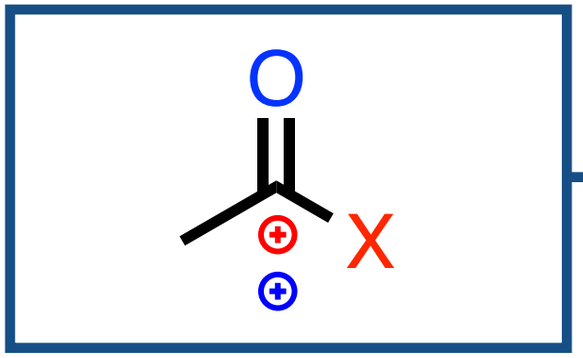


Consonant relationship

X: halide, OR, NR_2, SR

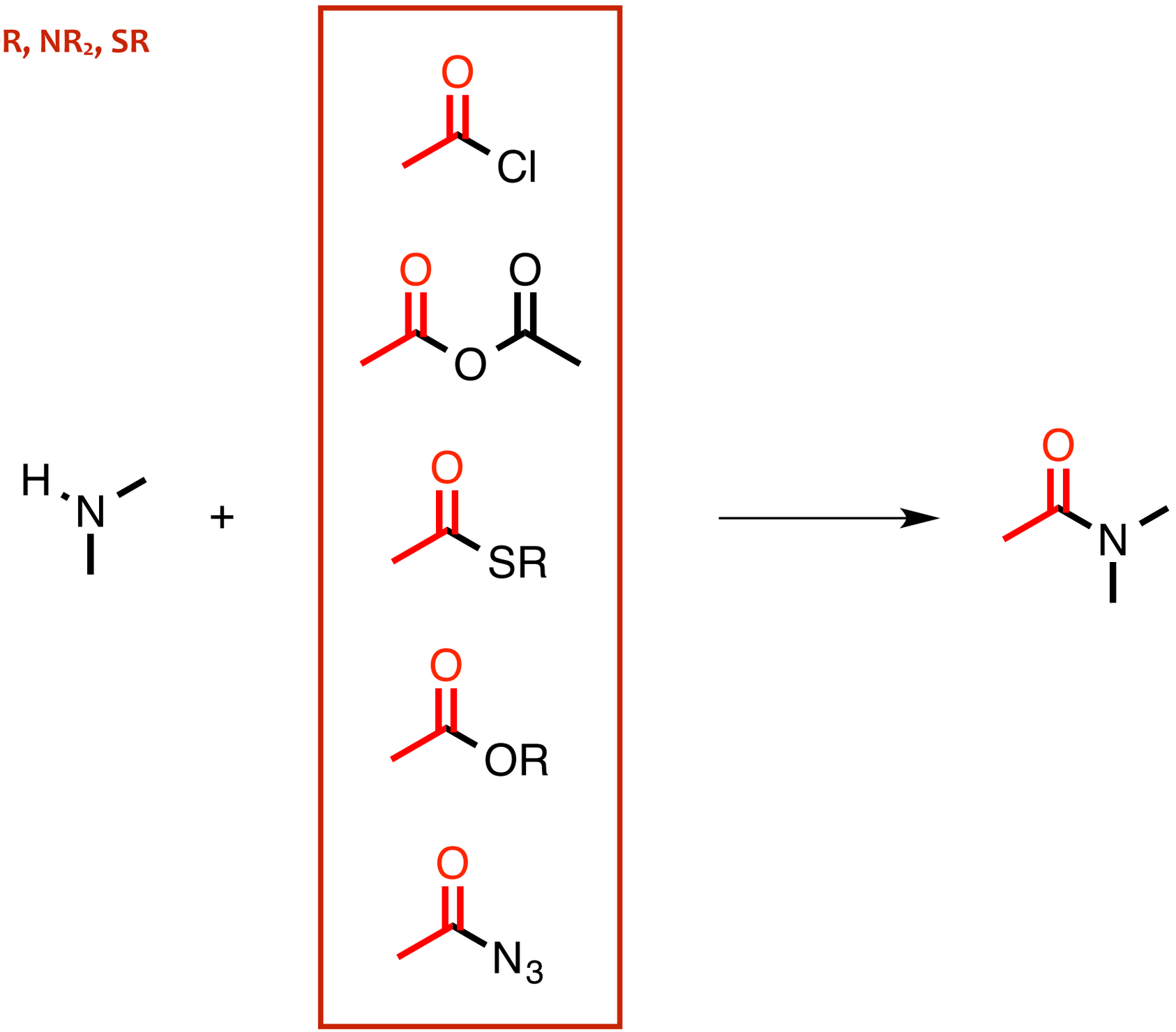






X: halide, OR, NR_2, SR

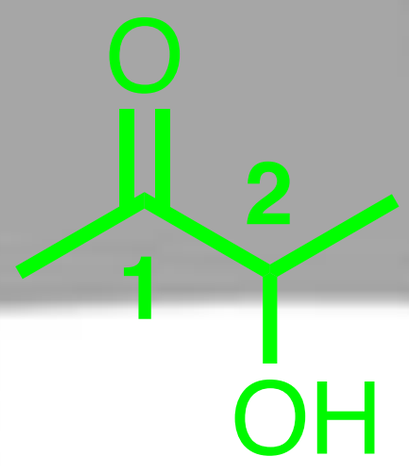
Consonant relationship

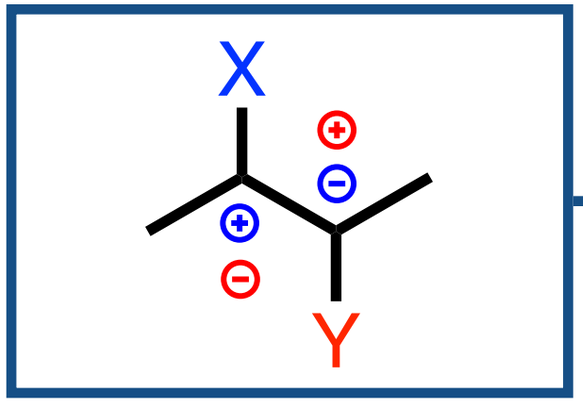


1,2-relationship?

1,2-diols?

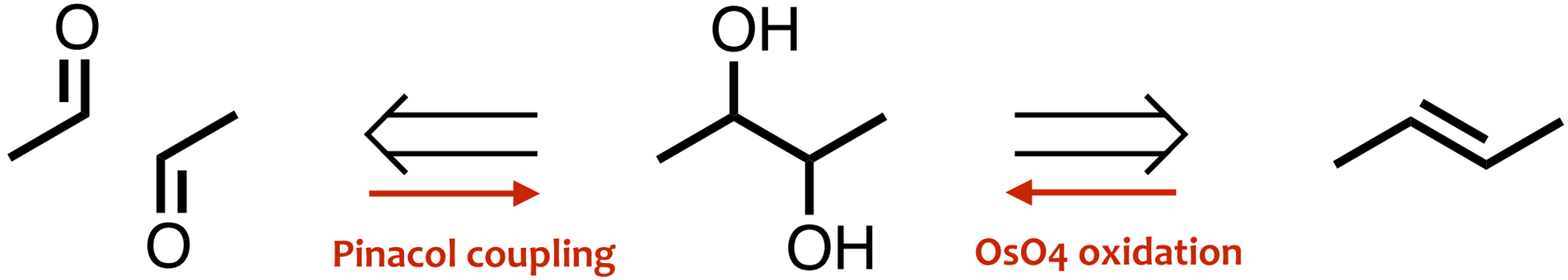
α-hydroxy ketones?

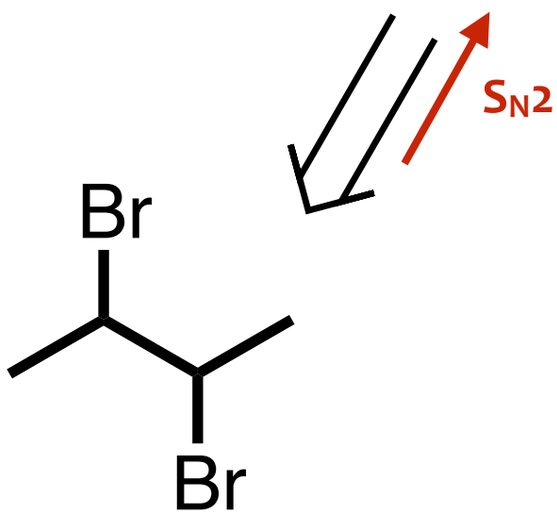




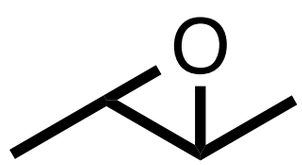
Dissonant relationship

X,Y: halide, OR, NR_2

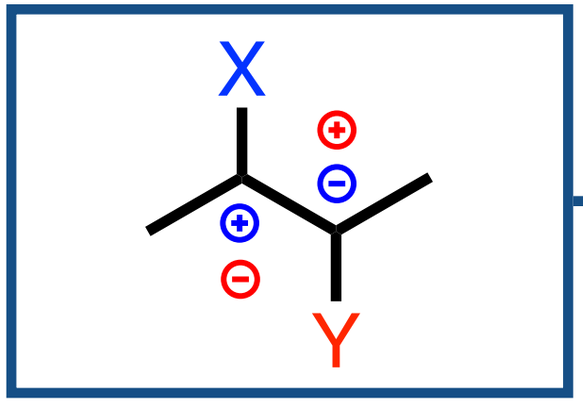




Epoxide opening

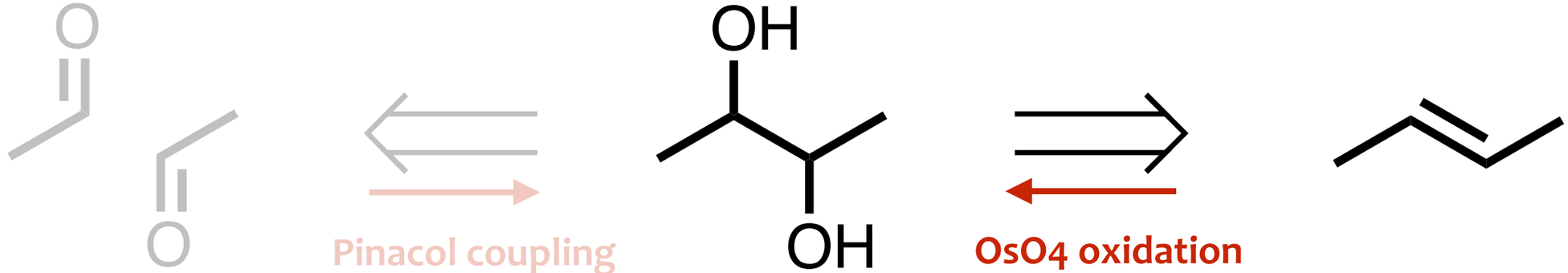


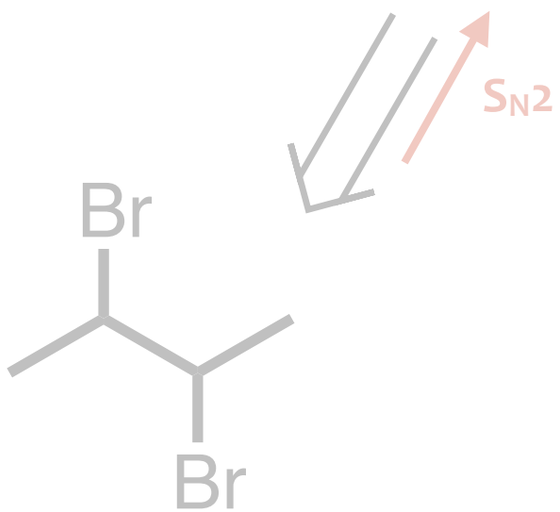
Epoxides play a crucial role in the synthesis of 1,2-diols

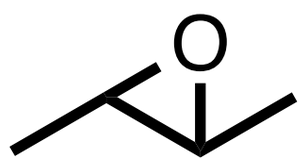


X,Y: halide, OR, NR_2

Dissonant relationship



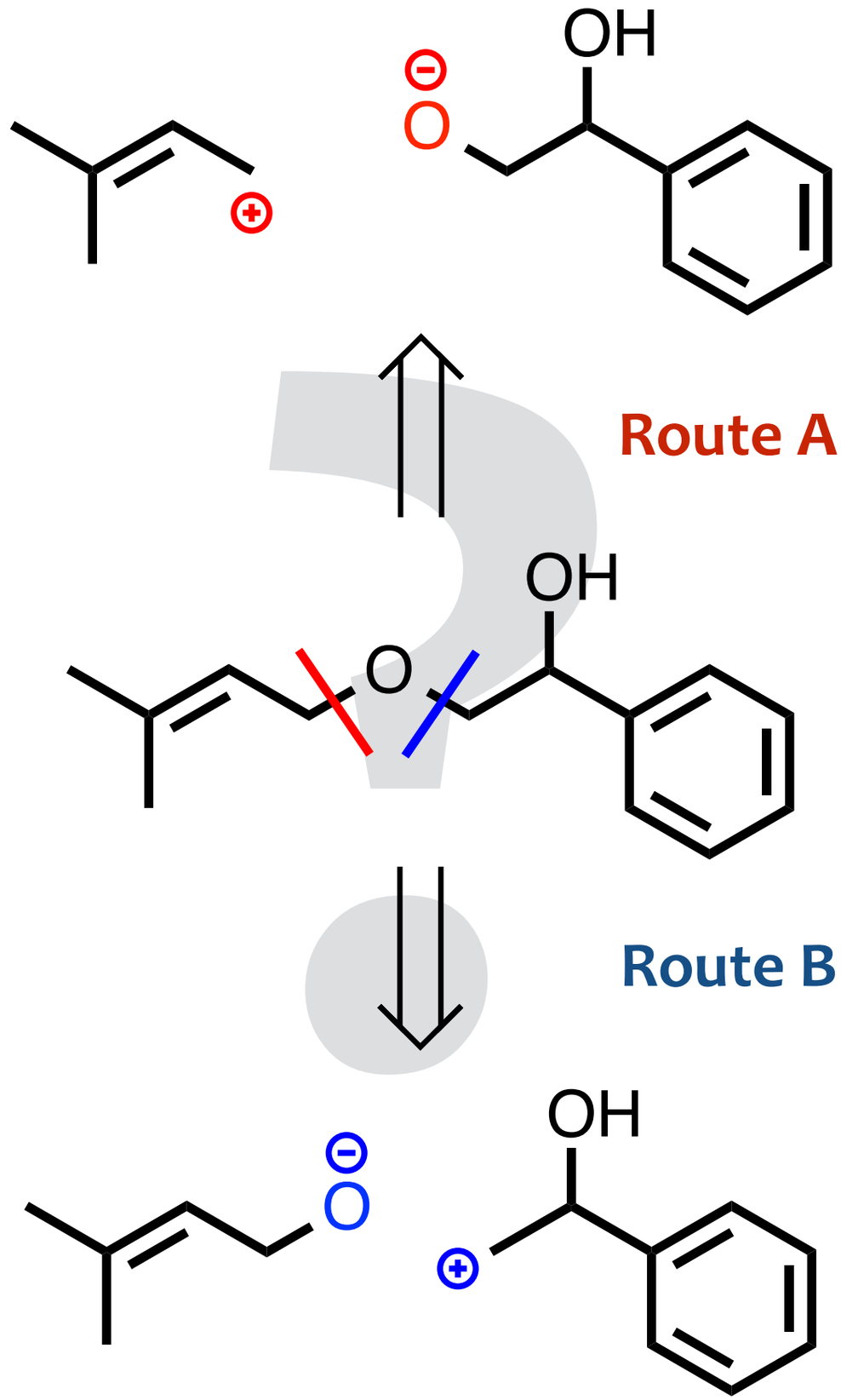




Epoxides play a crucial role in the synthesis of 1,2-diols

one-group disconnection

two-group disconnection

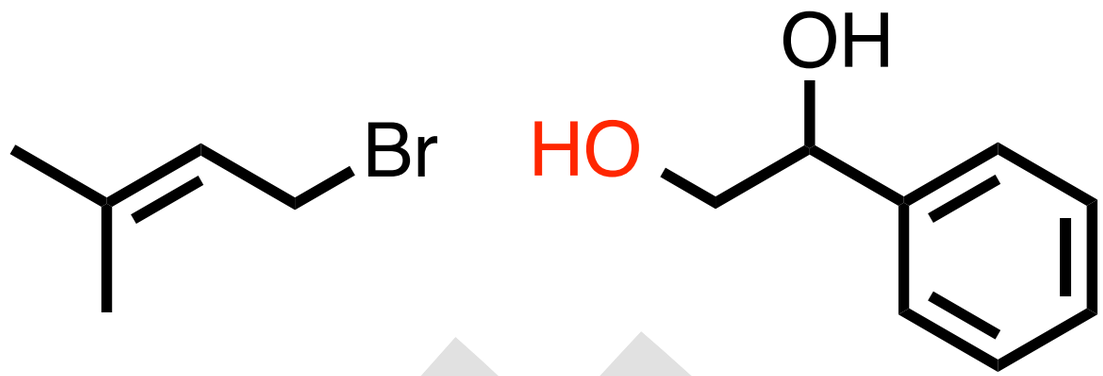


problem

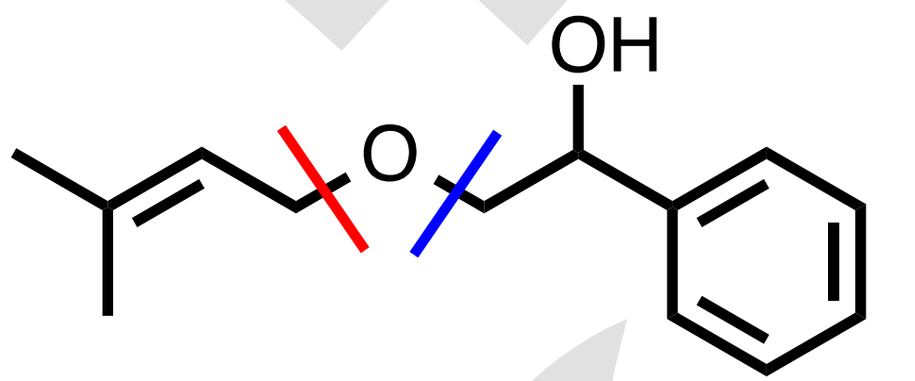
Siteselectivity

TACTIC

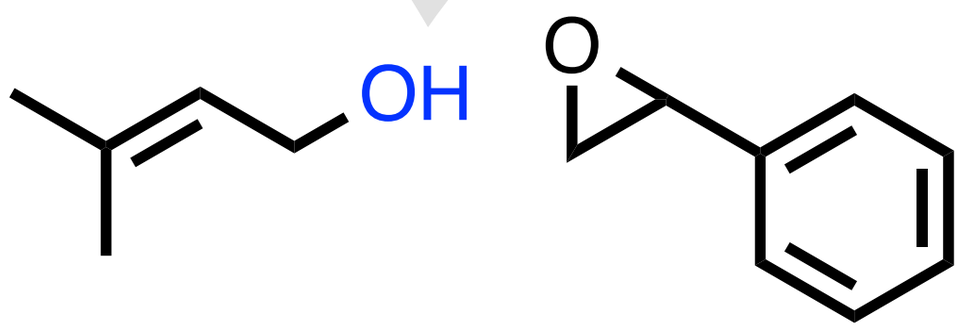
Reactivity of epoxides

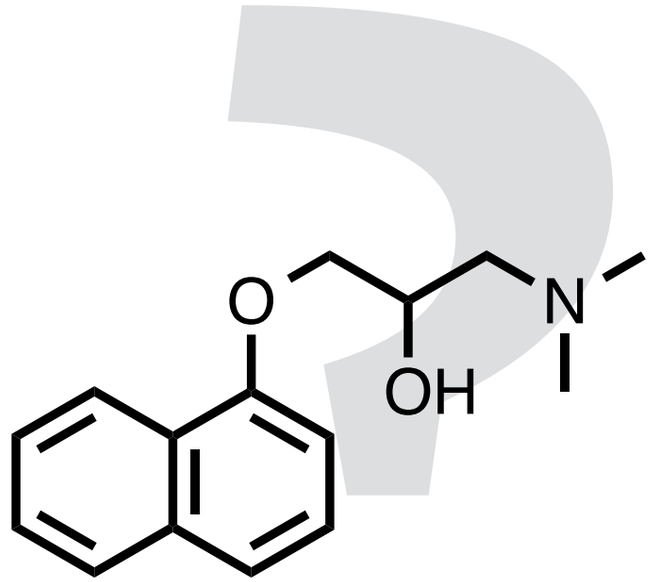


Route A



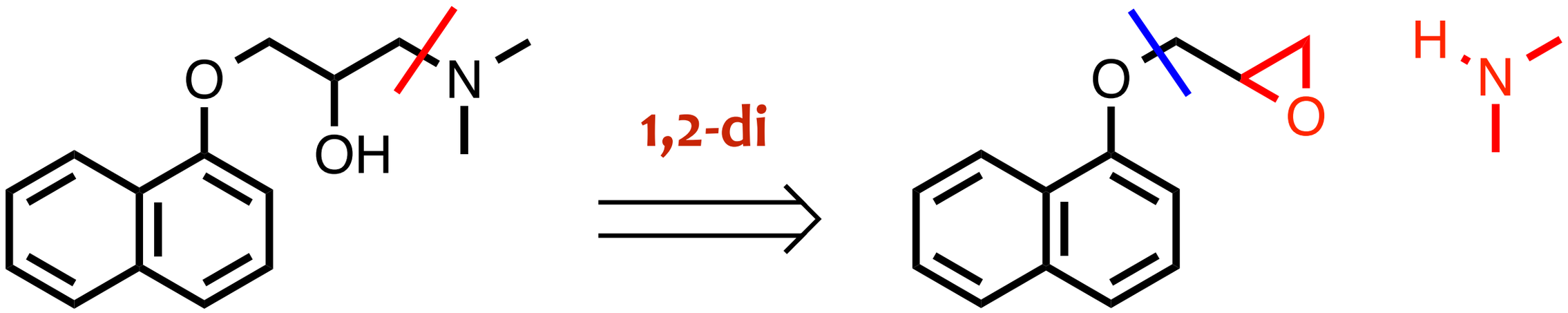
Route B



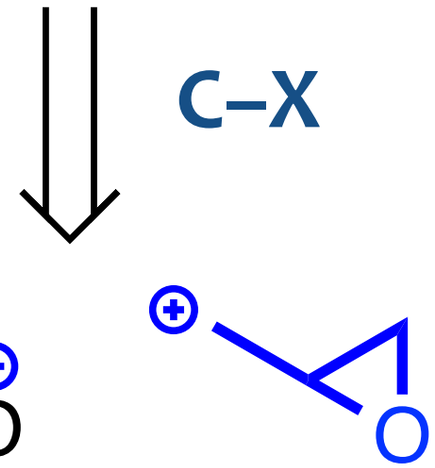


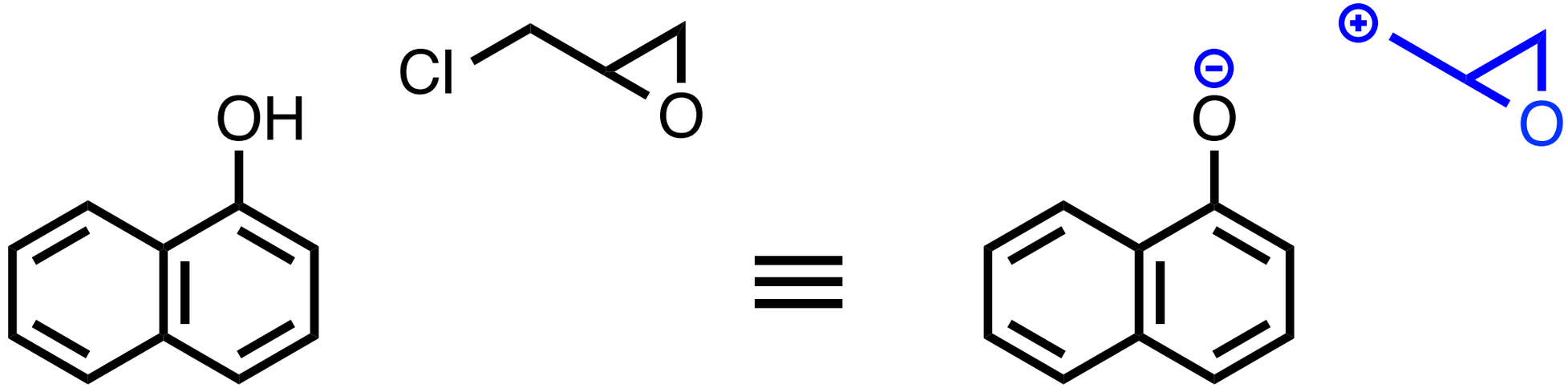
Propranolol

high blood pressure

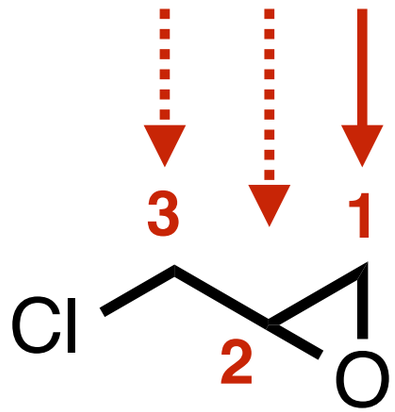


Pay attention to this system

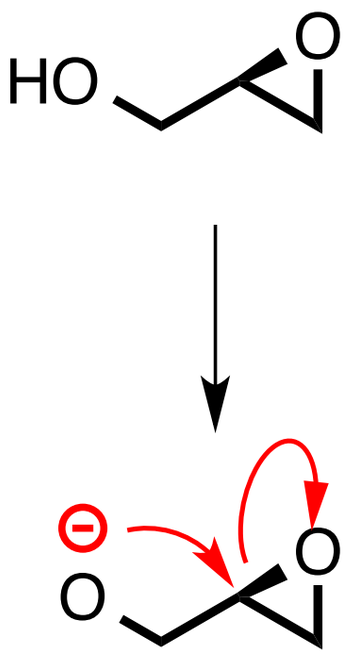


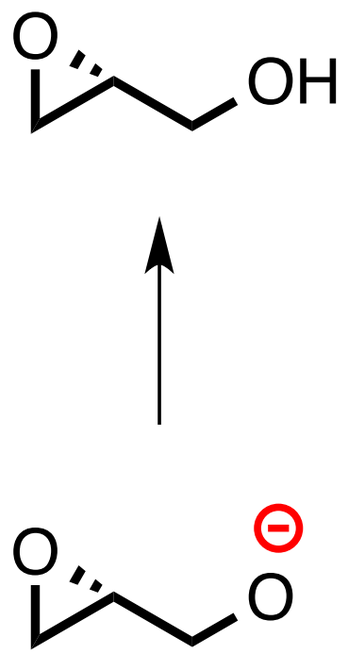


Three electrophilic sites



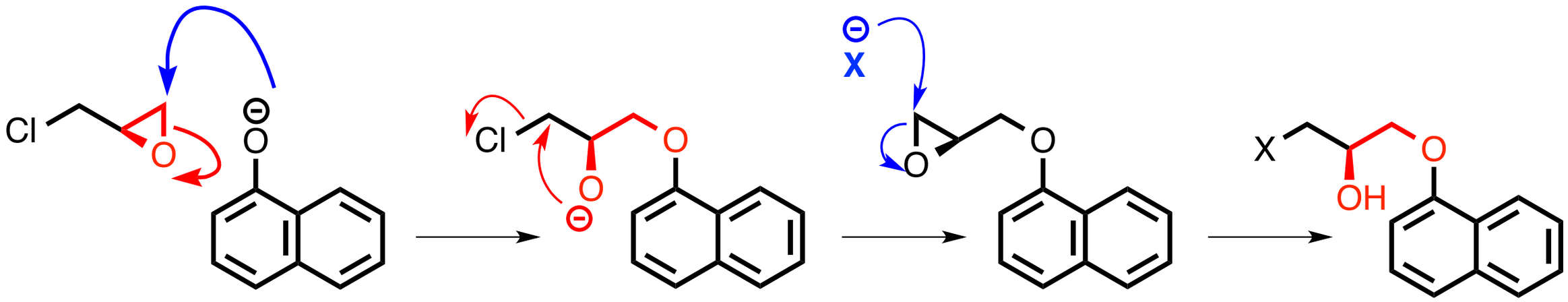
C1 is the most reactive one

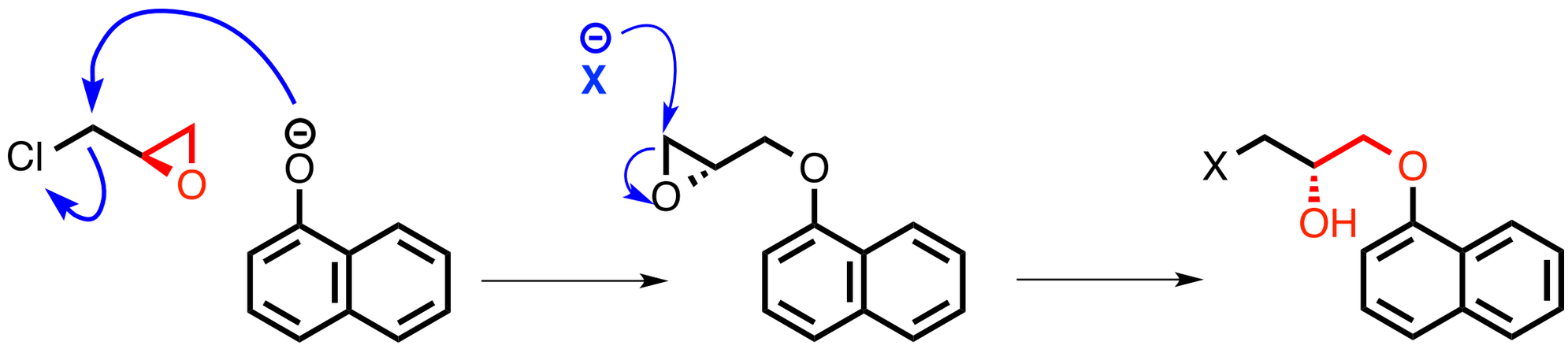


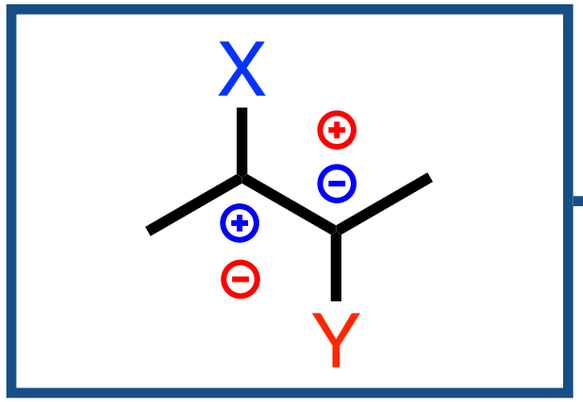


PAYNE REARRANGEMENT

The configuration of the chiral center can be dramatically affected

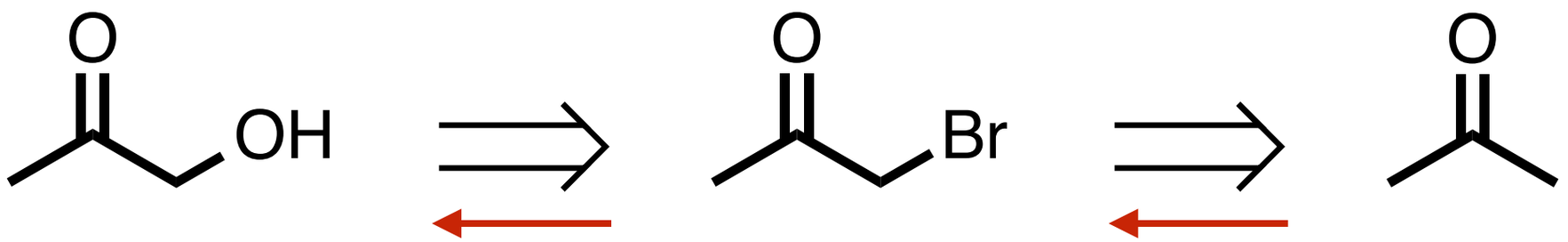






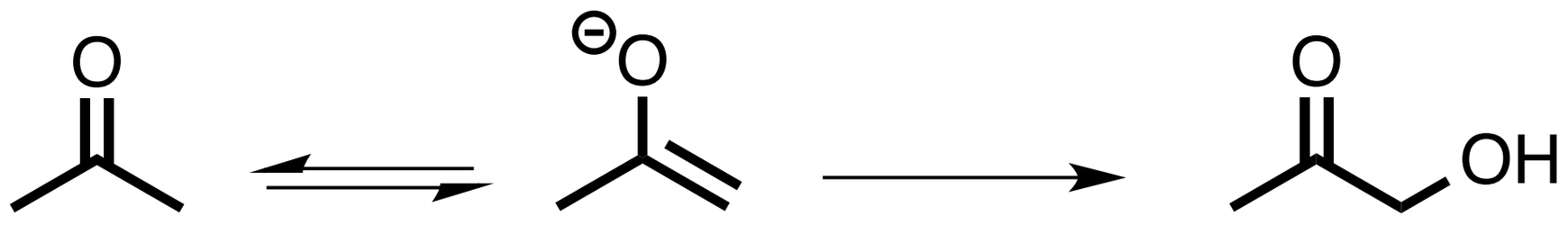
Dissonant relationship

X,Y: halide, OR, NR_2



S_N2 **Bromination**

In a general way,

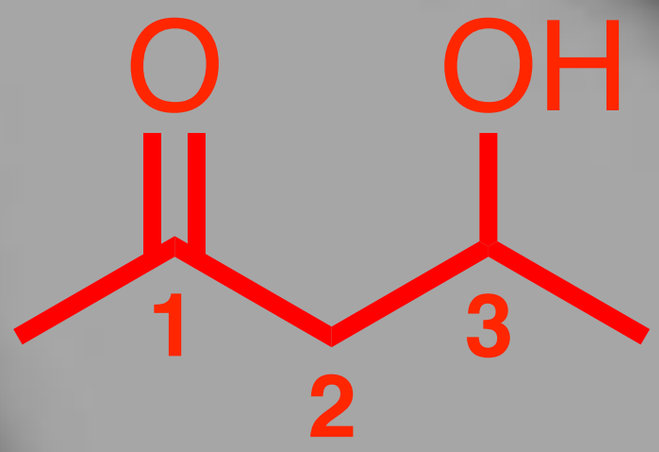


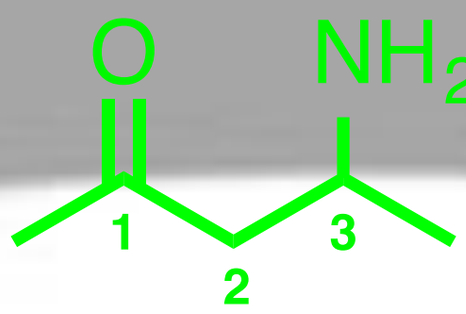
Oxidation of enolates, enols, or enamines

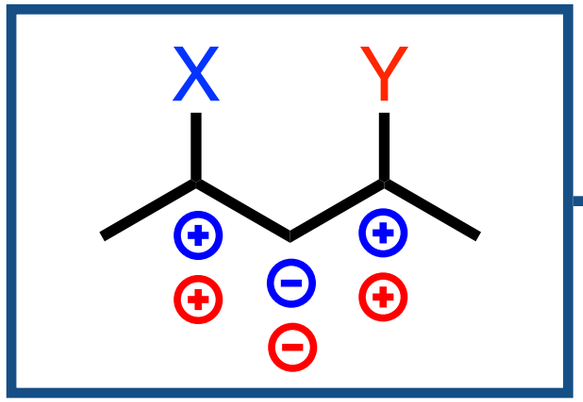
1,3-relationship?

ß-hydroxy carbonyl?

ß-amino carbonyl?

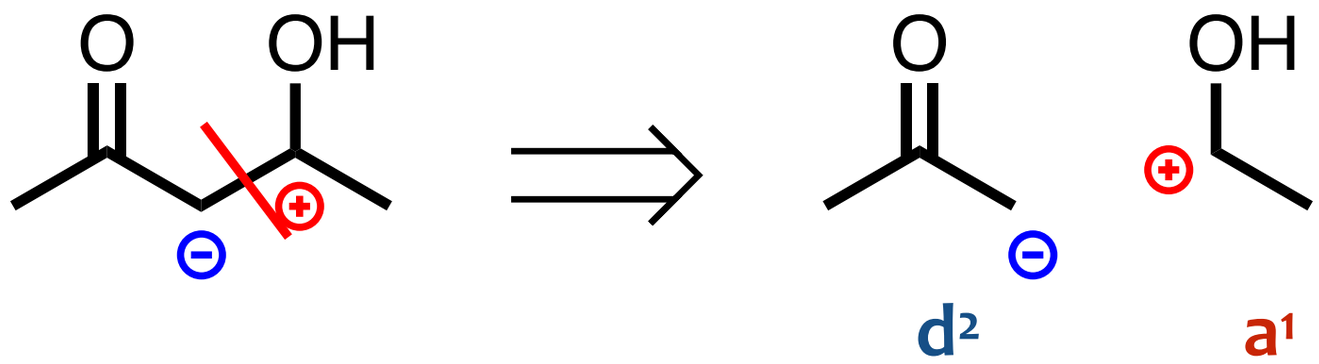




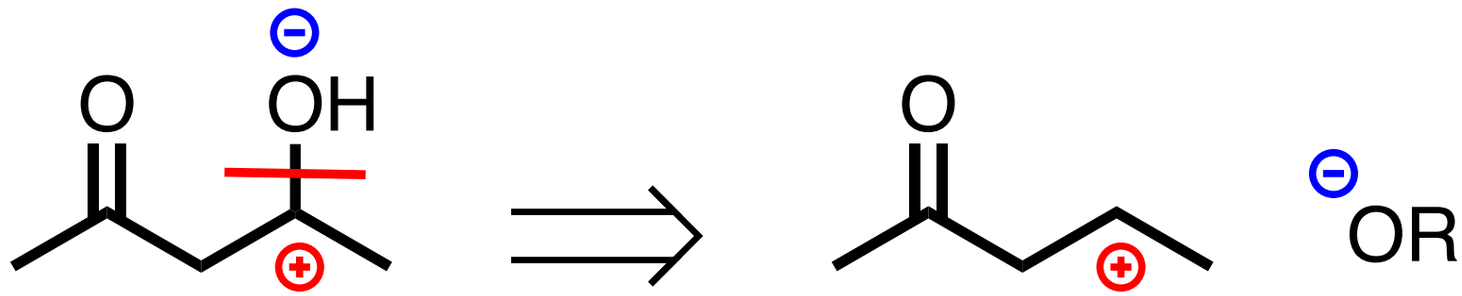


Consonant relationship

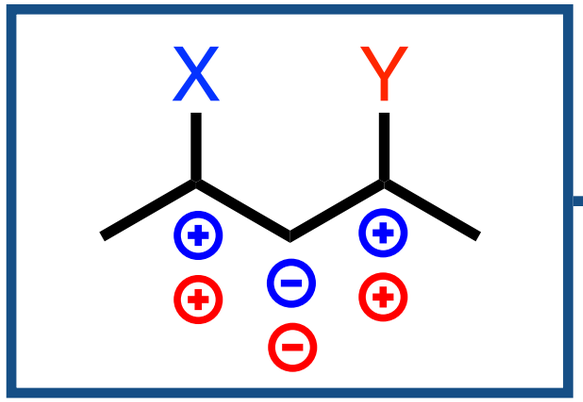
X,Y: O, N



d^2 a^1

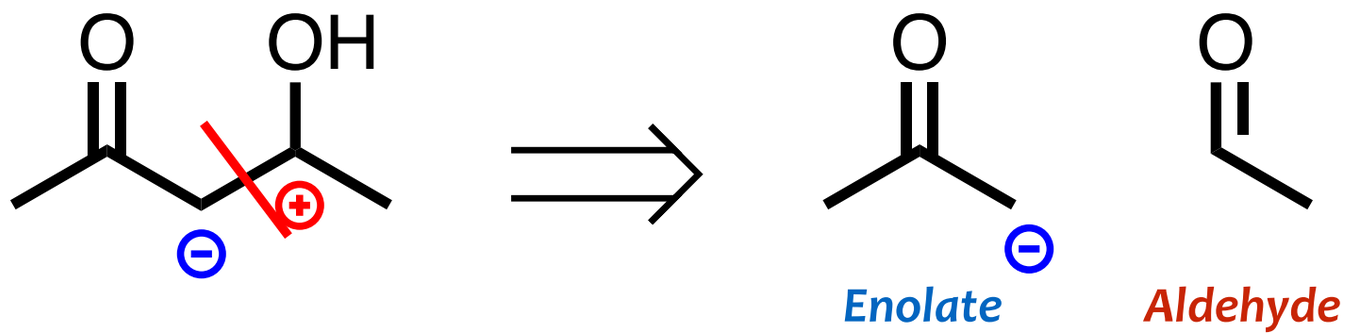


a^3 d^0



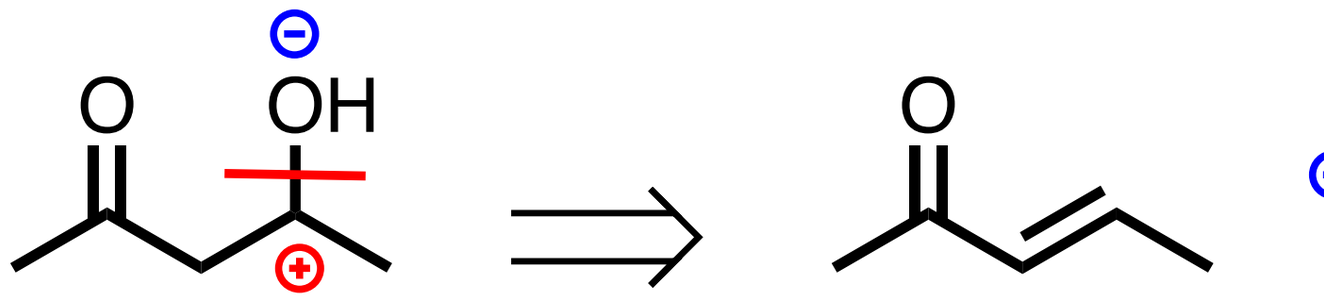
Consonant relationship

X,Y: O, N

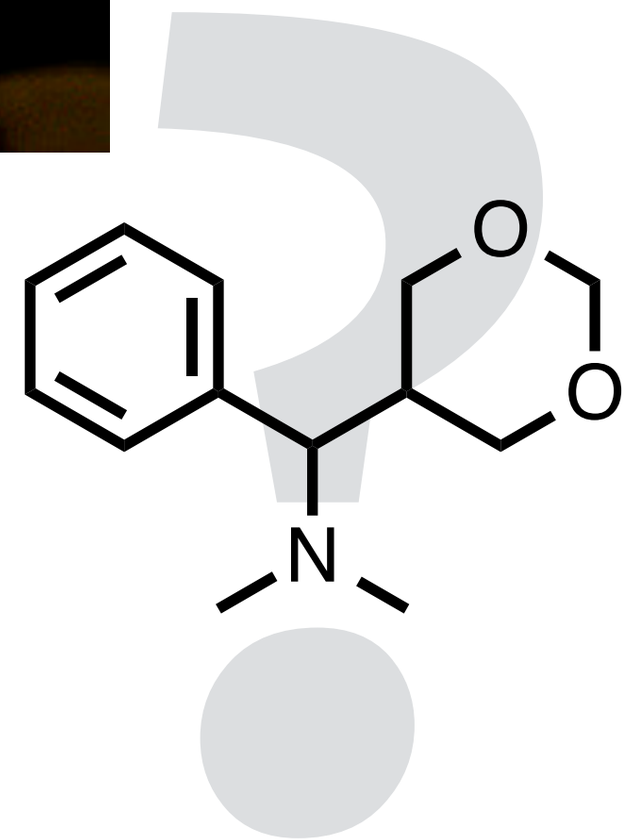


Enolate *Aldehyde*

Aldol



Oxa-Michael

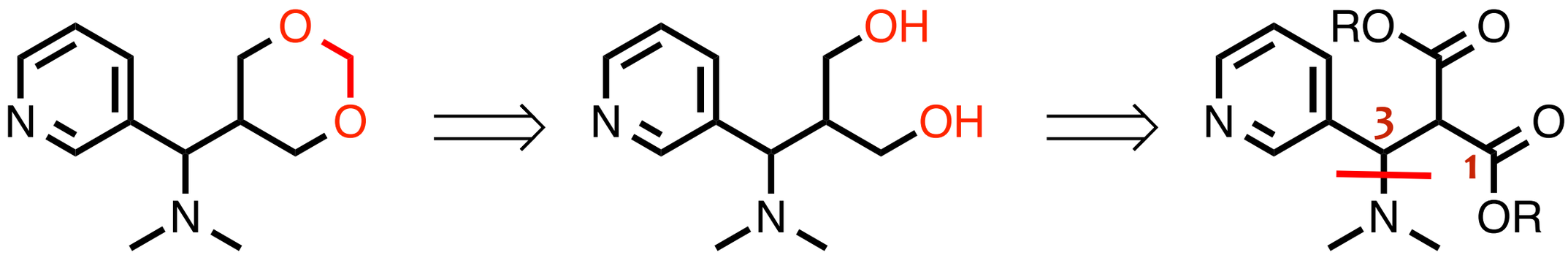


Doxpicomine

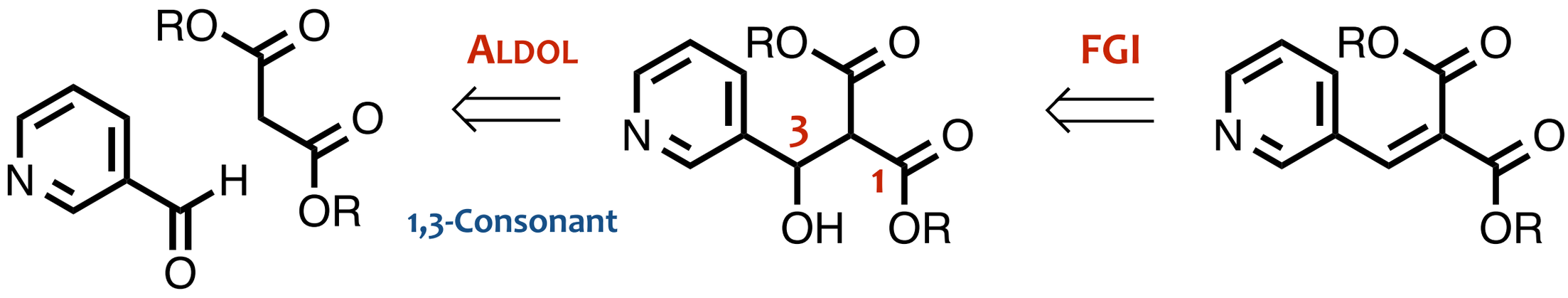
analgesic

ACETAL
a source of instability

SYMMETRY
take advantage

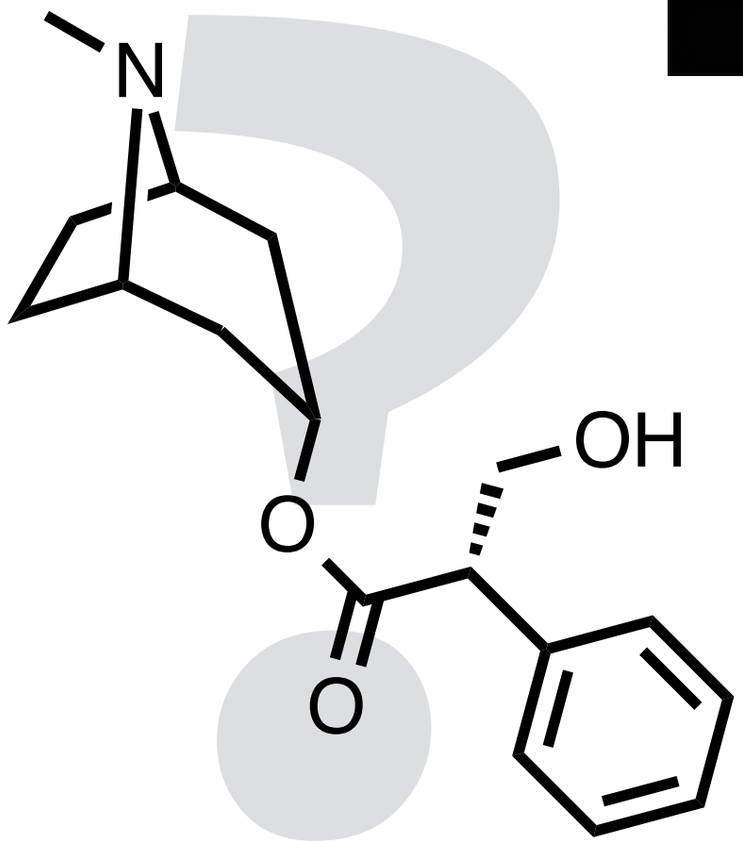


1,3-Consonant **AZA MICHAEL**



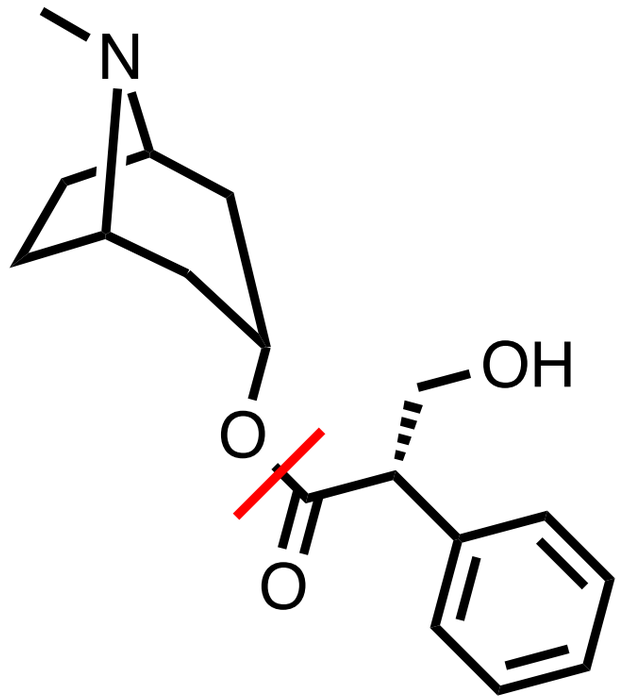
FGI

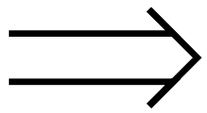
Conversion of an alkene into an alcohol is very useful

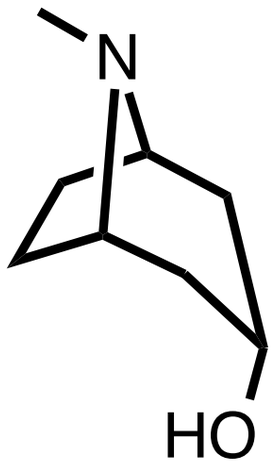


Atropine

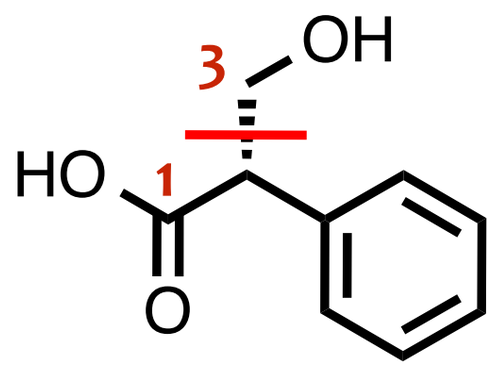
treatment of certain nerve agents and pesticide poisoning





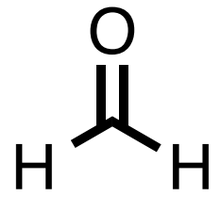


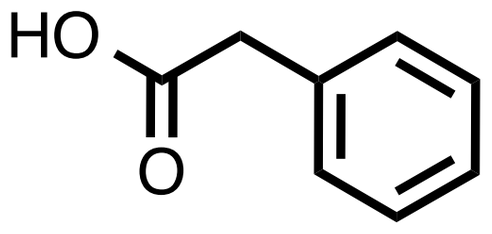
A Chiral ß-Hydroxy Acid

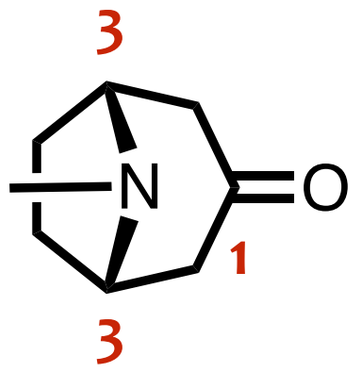


FGI

1,3-Consonant







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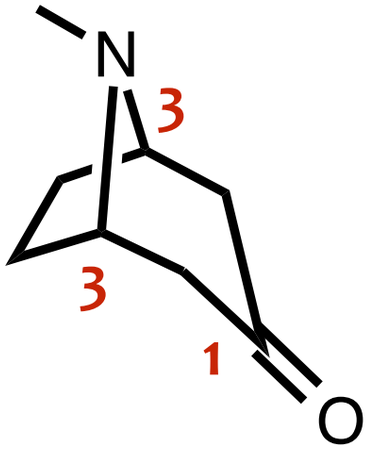
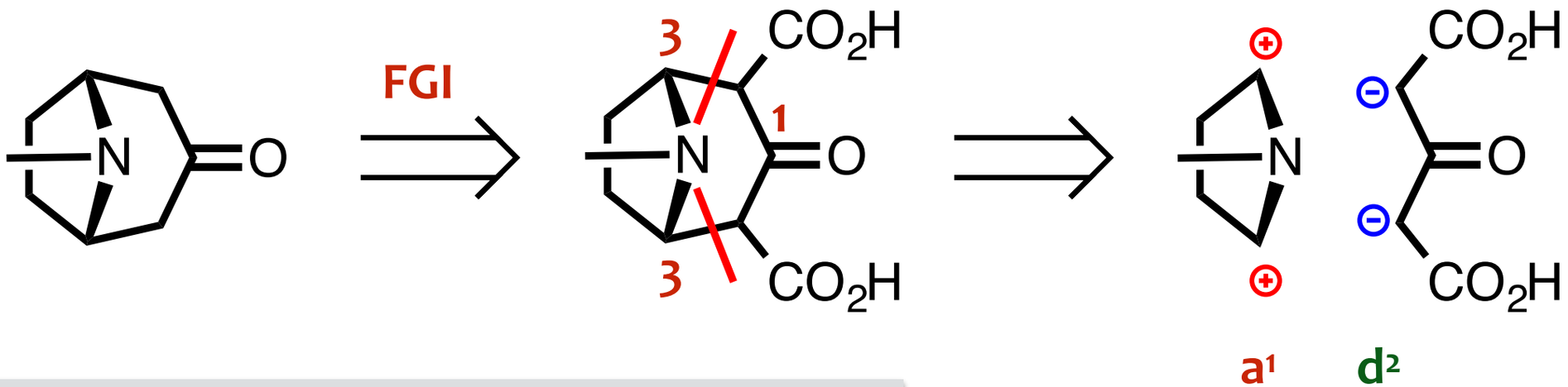


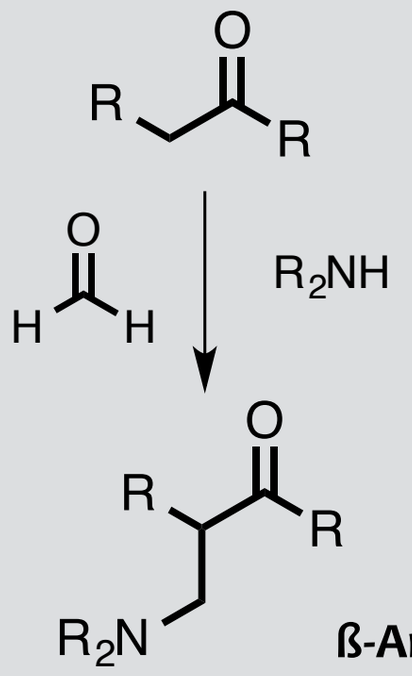
A Highly Symmetrical
ß-amino ketone

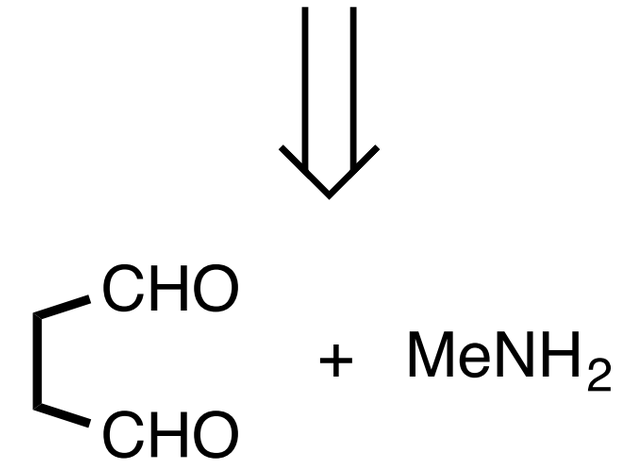
Keep in mind bidirectional syntheses



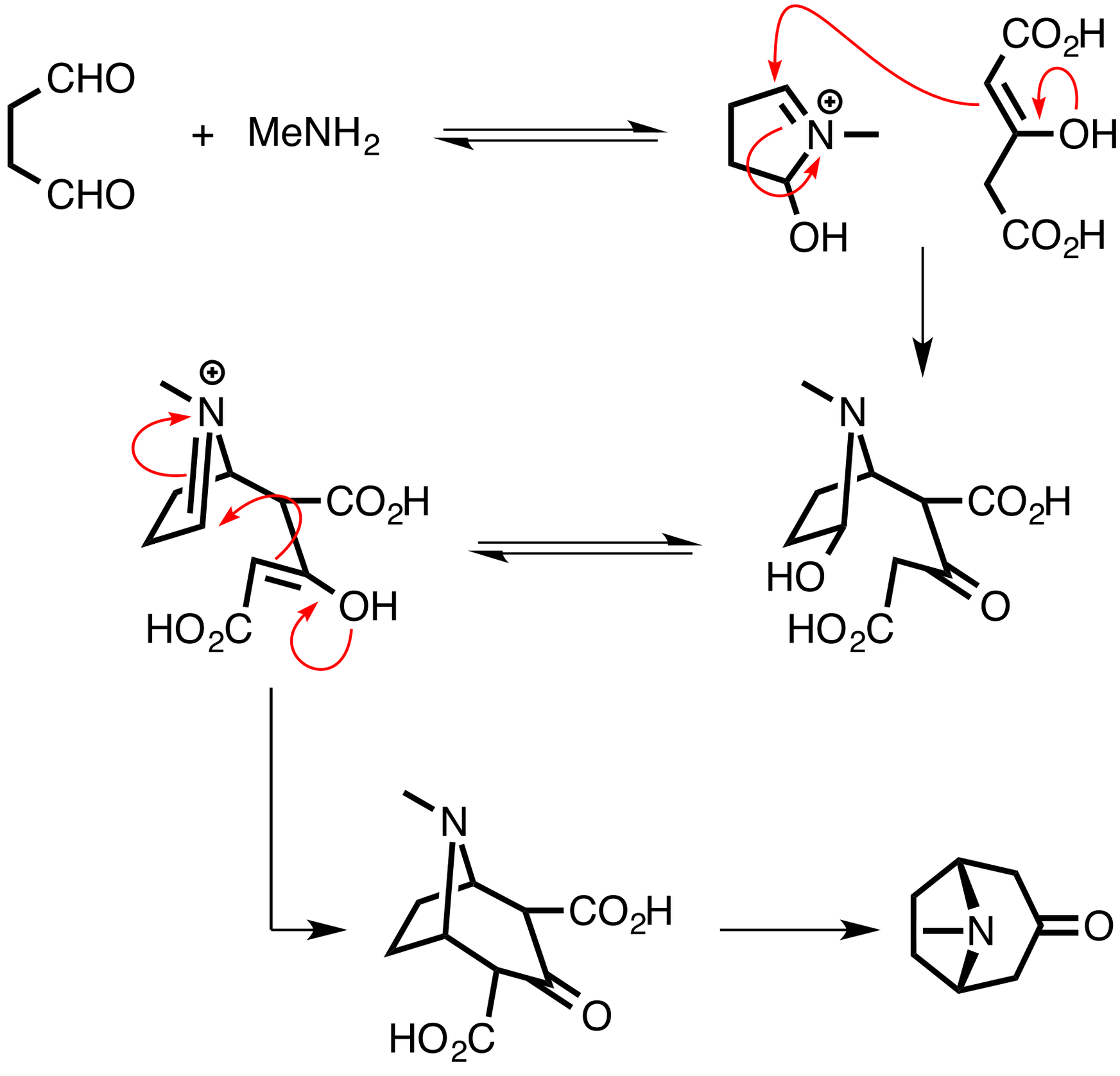
Mannich reaction

coupling of an enolizable carbonyl with formaldehyde and a 1ary or 2ary amine



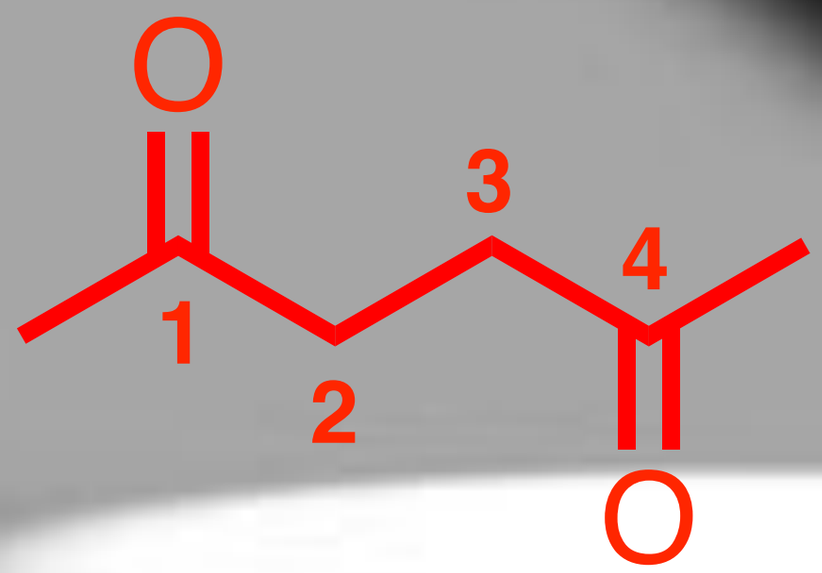


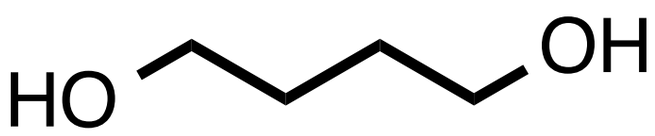
See Chapter 7

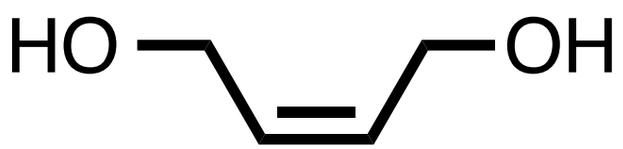

CHO
CHO
+ MeNH2
N
OH
CO2H
OH
CO2H
N
CO2H
HO2C
OH
N
HO
HO2C
O
N
CO2H
O
HO2C
N
O

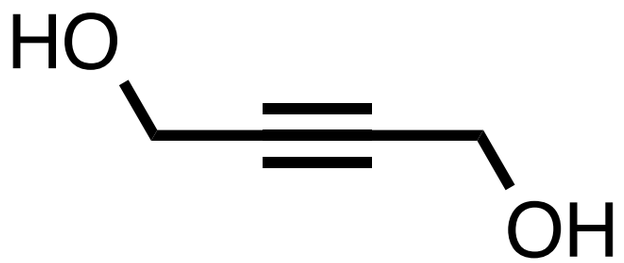
1,4-relationship?

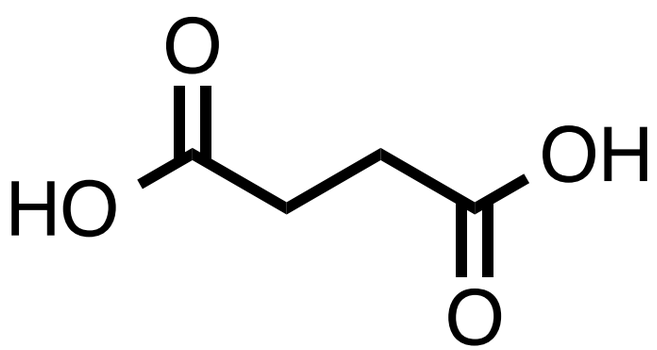
1,4-dicarbonyl compounds?



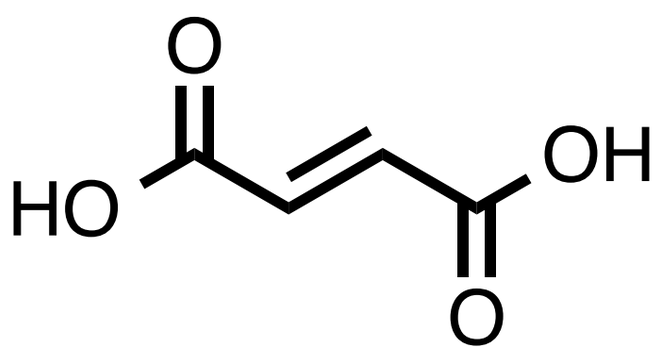




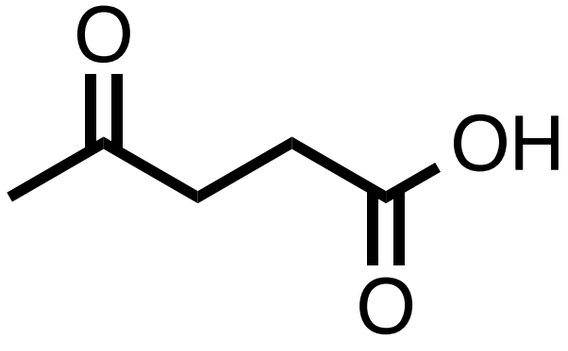




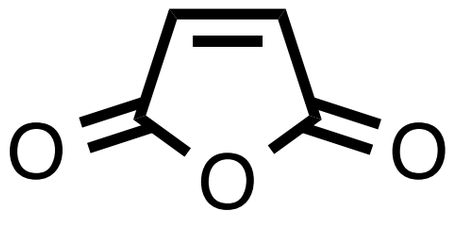
succinic acid



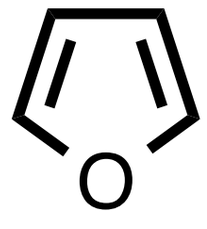
fumaric acid



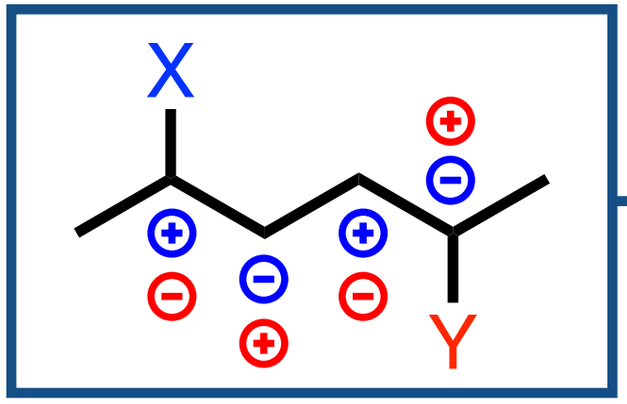
levulinic acid



maleic anhydride

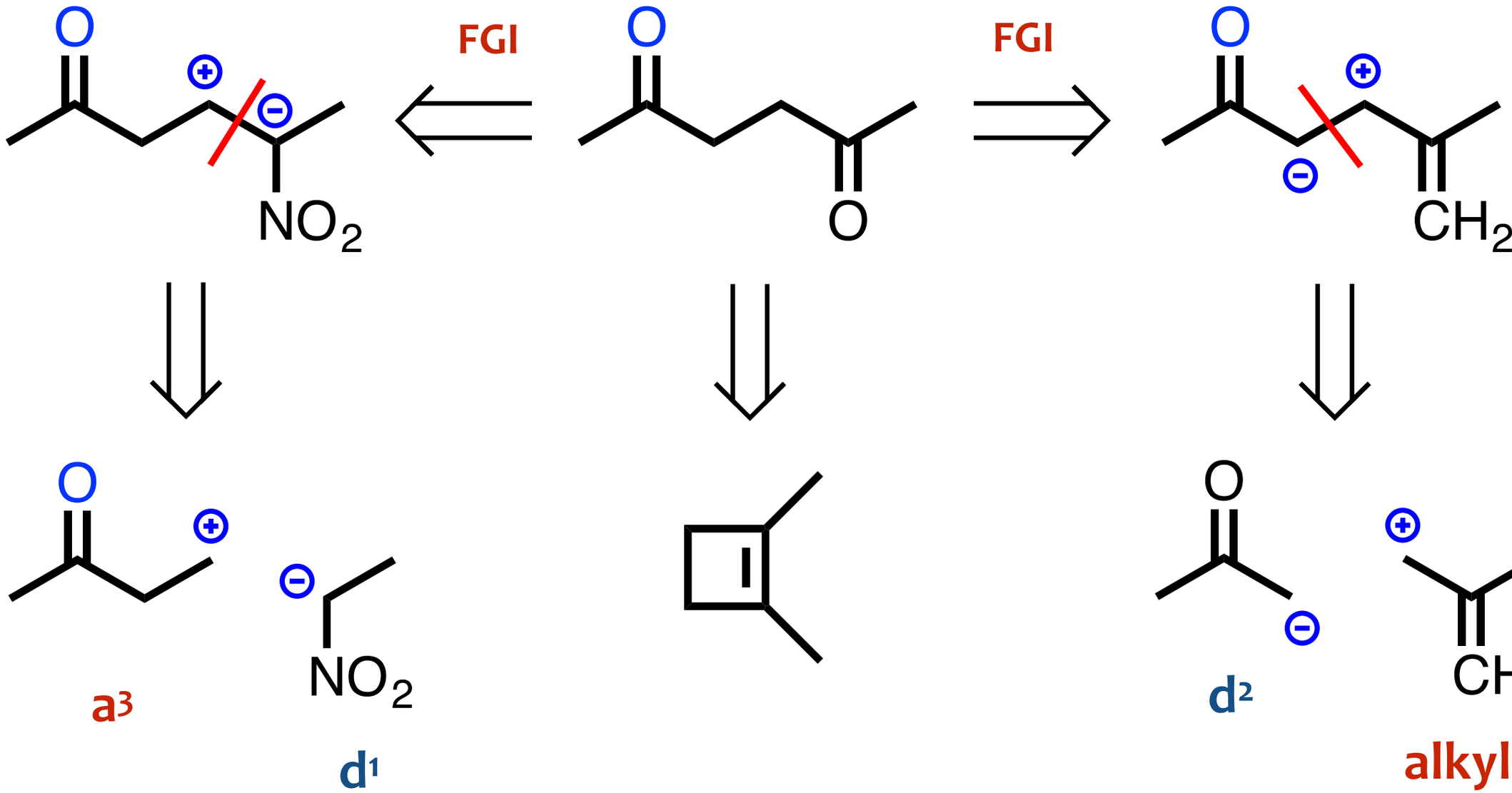


furan

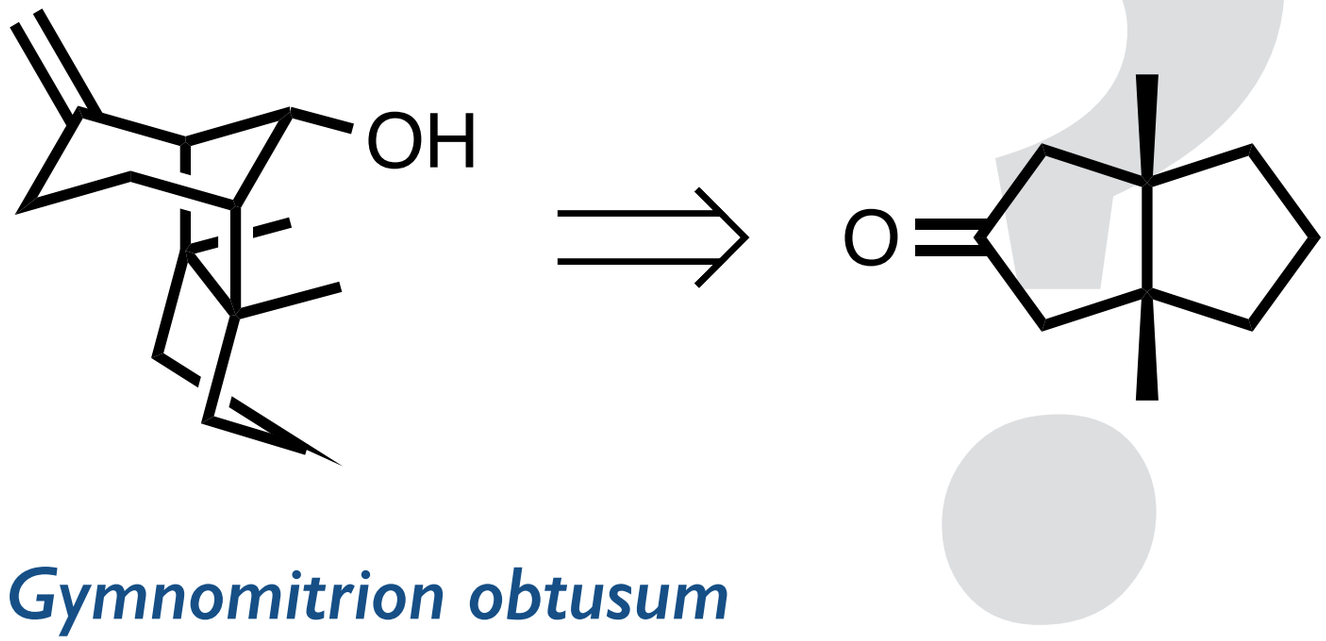


X,Y: O, N

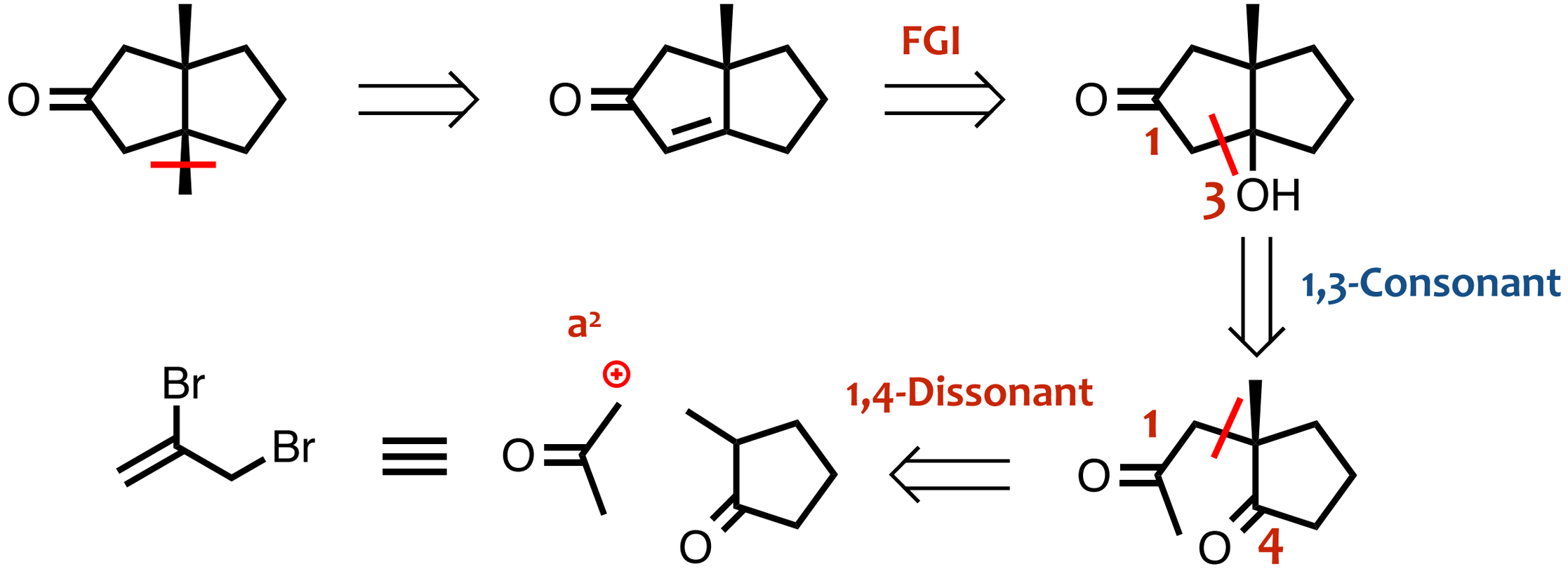
Dissonant relationship

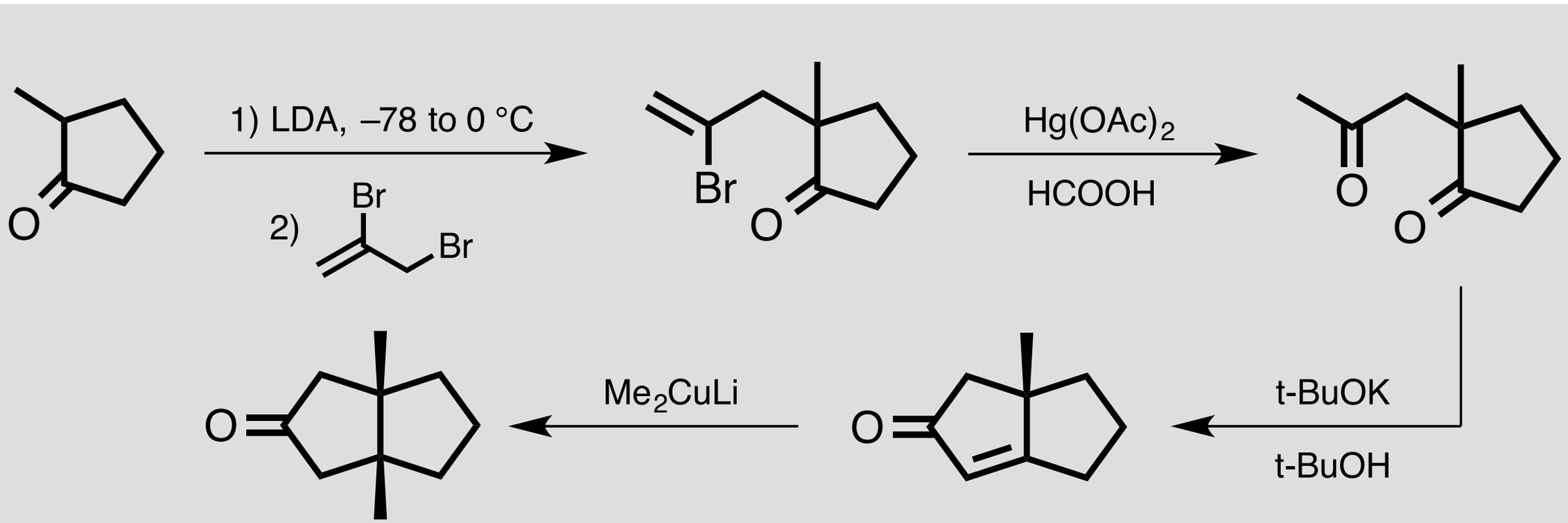


a³ d¹ d² alkyl a



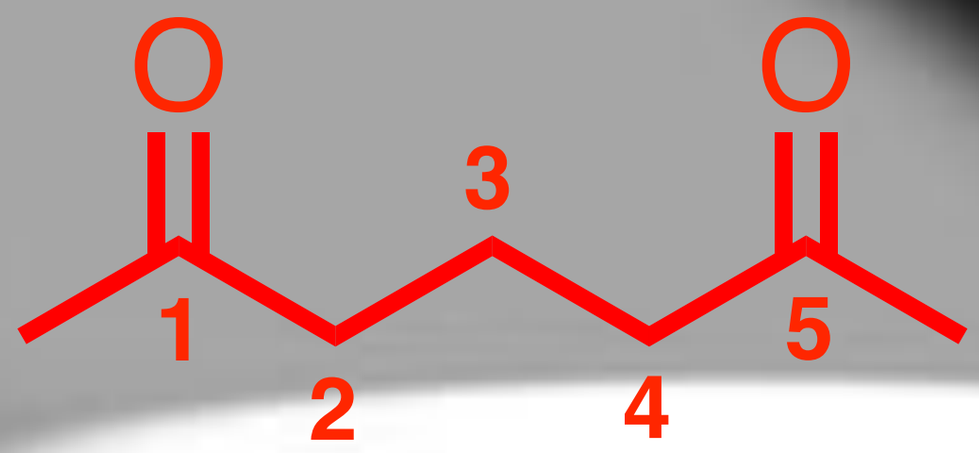
from Gymnomitrion obtusum

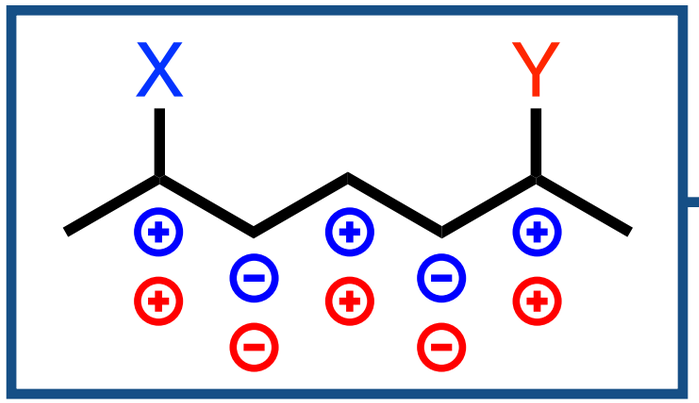

FGI
1
3 OH
1,3-Consonant
a²
1,4-Dissonant
Br
Br
1
4


1) LDA, –78 to 0 °C
2)
Br
Br
Hg(OAc)2
HCOOH
t-BuOK
t-BuOH
Me2CuLi

1,5-relationship?

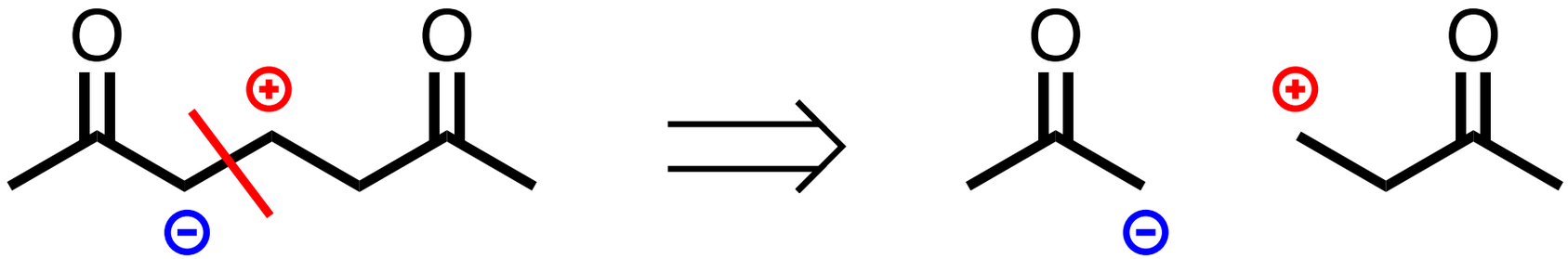
1,5-dicarbonyl compounds?





Consonant relationship

X,Y: O, N

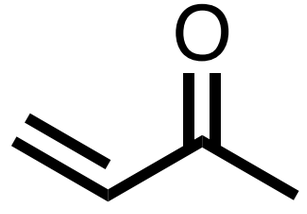


d^2

a^3

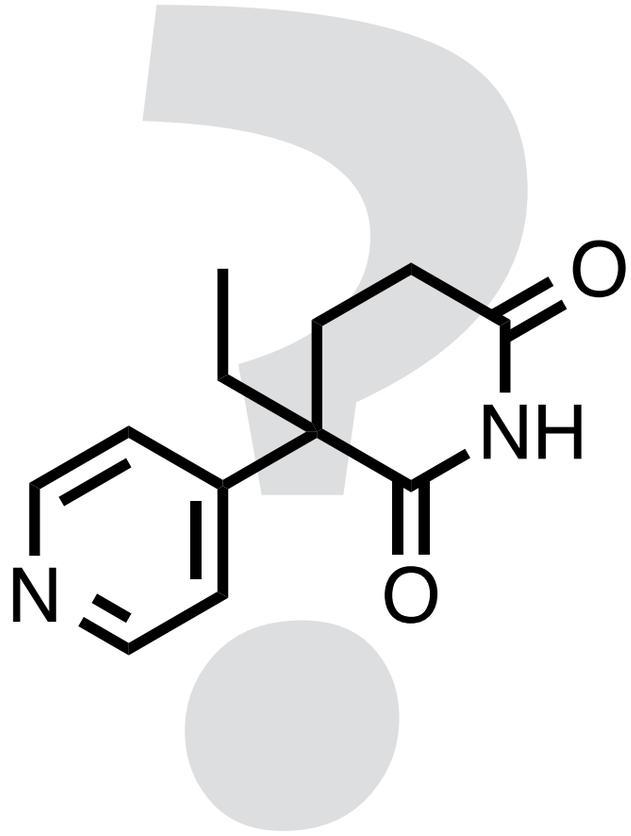
Enolate

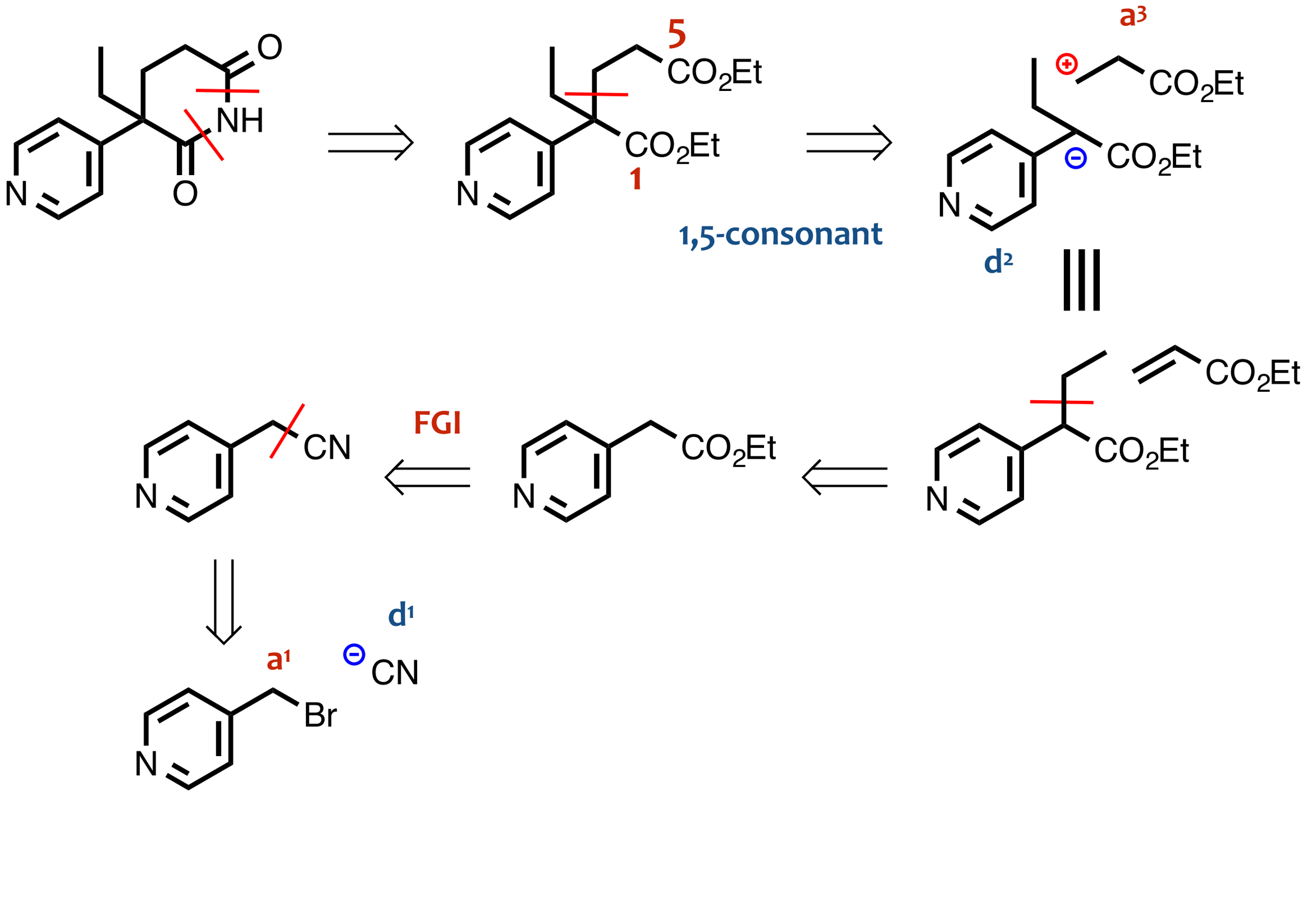
Michael

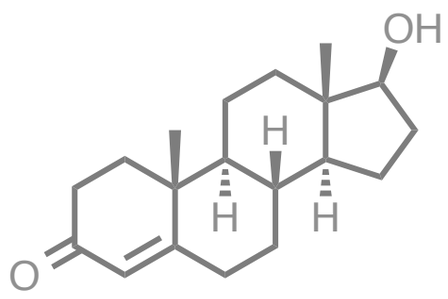


Rogletimide

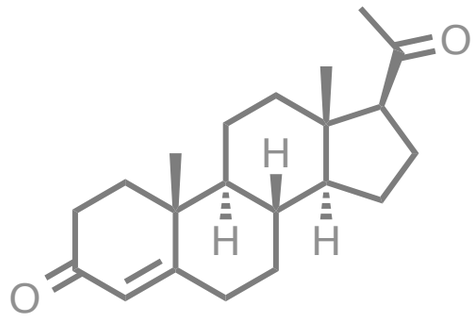
sedative




O
NH
O
N
5
CO2Et
CO2Et
1
N
1,5-consonant
a3
CO2Et
CO2Et
N
d2
CO2Et
CO2Et
N
FGI
CN
N
CO2Et
N
d1
a1
CN
Br
N

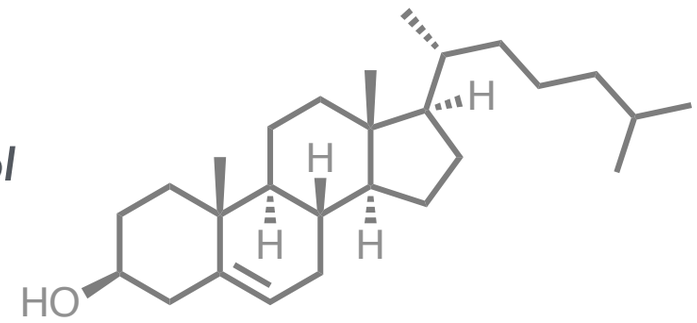


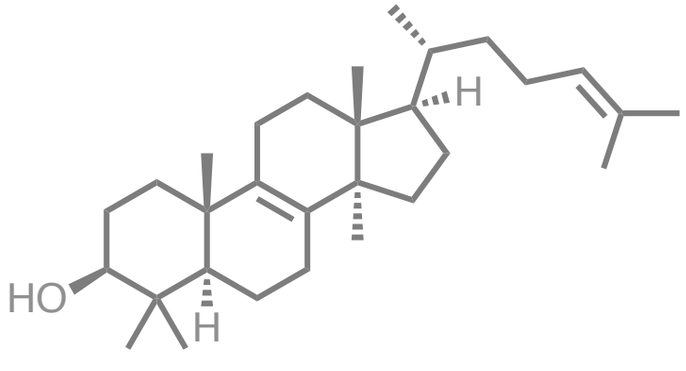
testosterone



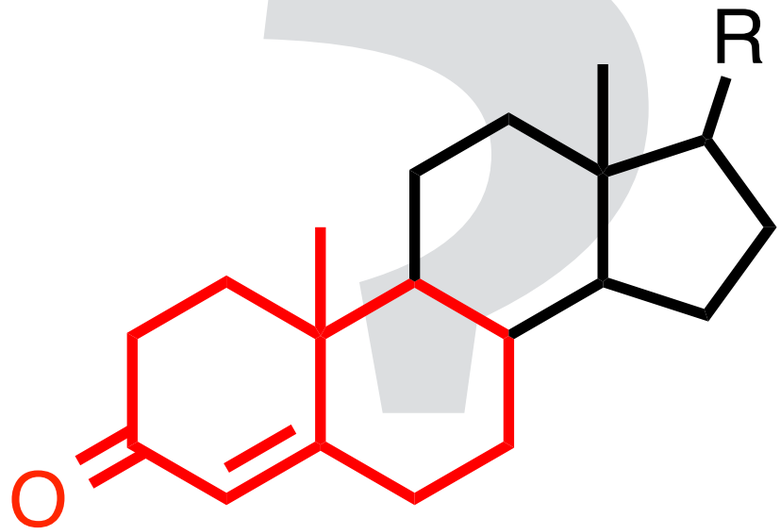
progesterone

cholesterol

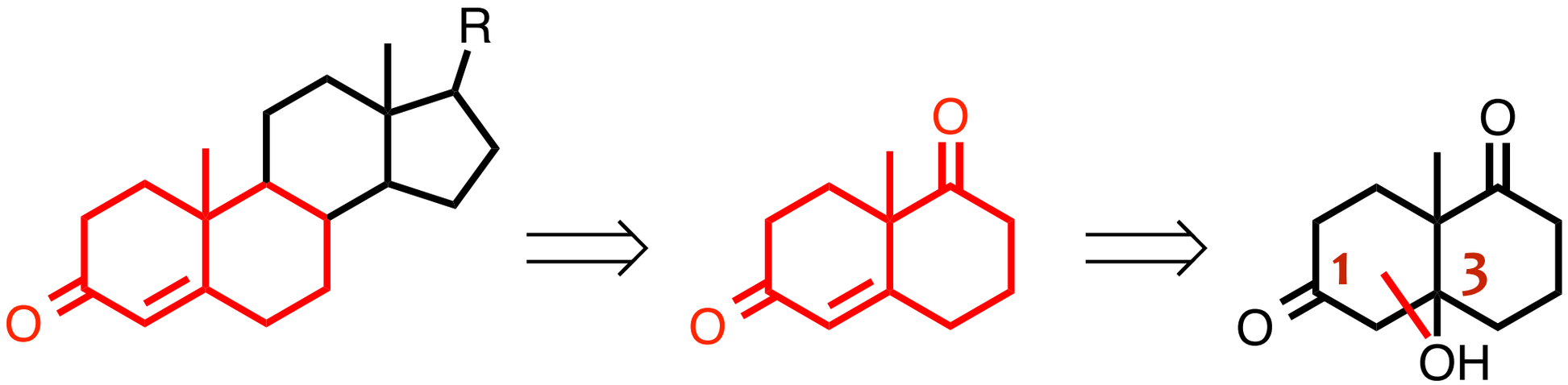




lanosterol

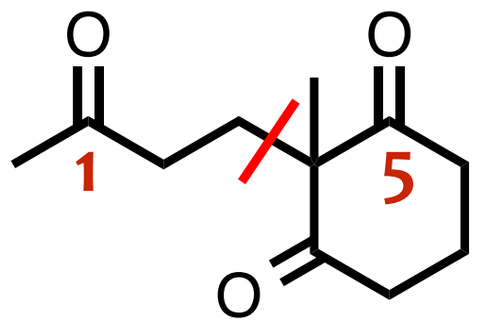


Steroid skeleton



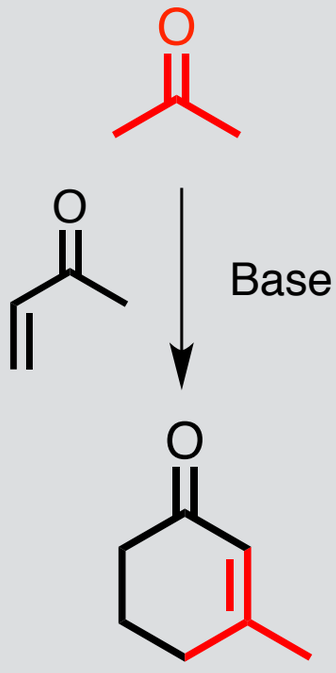
Wieland-Miescher Ketone

1,3-consonant



Robinson annulation

Michael addition of a carbonyl to an enone followed by an intramolecular aldol condensation



1,5-consonant