

Nucleophilic Addition Of Hard Anions To Aldehydes And Ketones

from chapter(s) _____ in the recommended text

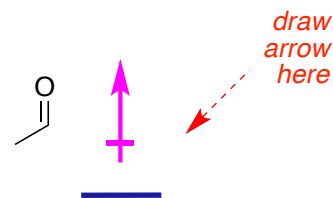
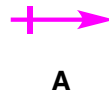
A. Introduction

B. Types Of Additions To Carbonyls

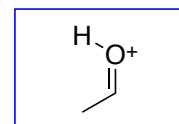
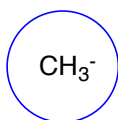
Polarity Of Carbonyls

positively polarized.

to carbonyl *carbons*
oxygen.



Reactivity Of Nucleophiles And Carbonyls At Different pH Values



more reactive
more reactive than ones that are not.

hard because
are likely to
cannot be used

completely wrong to show
neutral or basic conditions.

In the second edition of the book a somewhat ambiguous question has been changed from:

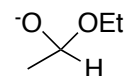
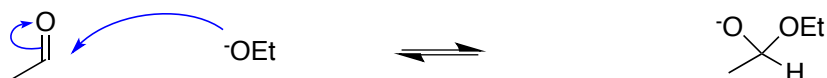
Additions of reactive basic anions to carbonyl compounds can/cannot be reversible if the anion involved is very stable.

to:

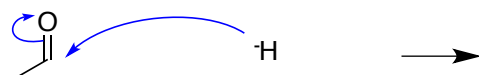
Additions of unstable, reactive, basic anions to carbonyl compounds tend to be reversible / irreversible.

the answer is *irreversible*.

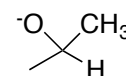
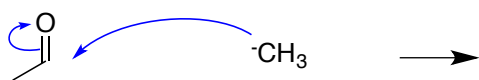
Formation Of Tetrahedral Intermediates



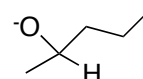
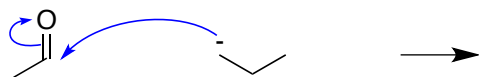
tetrahedral intermediate



tetrahedral intermediate



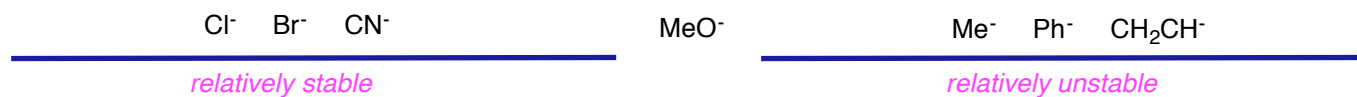
tetrahedral intermediate



tetrahedral intermediate

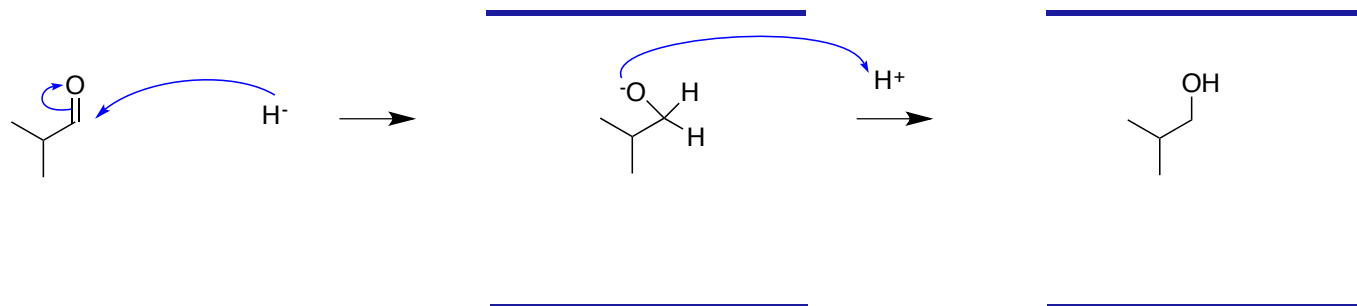
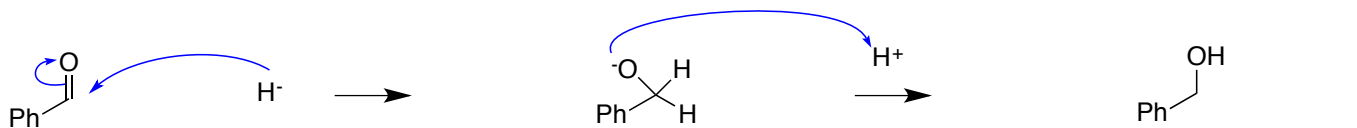
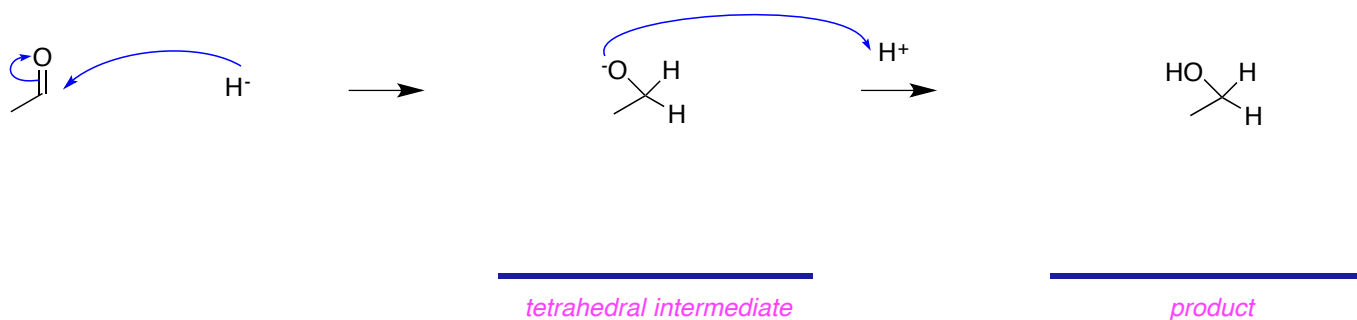
sp^3 hybridized.
 give *alcohols*.
 (this is *kinetics*),
 (*thermodynamics*).

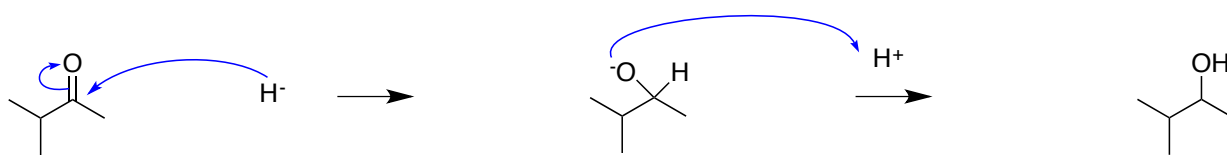
one C–O bond(s)
 one bond(s)
 the *starting materials*.
 it *will* be
 ie *irreversible* addition.

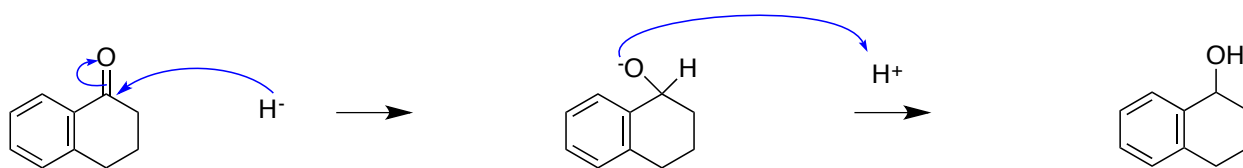


reversibly to ketones

C. Reactions of Aldehydes And Ketones With Hydridic Reducing Agents







NaBH_4

NaH

LiAlH_4

name: Sodium Borohydride

Sodium Hydride

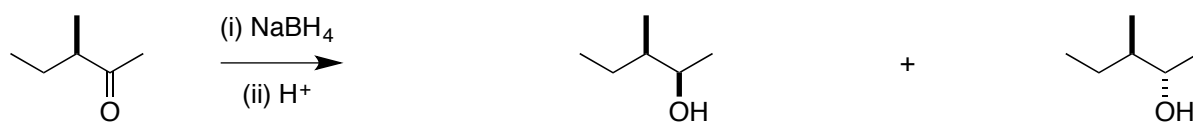
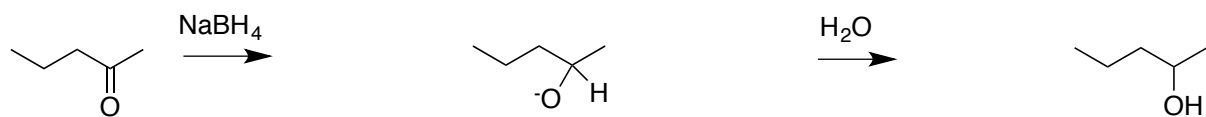
Lithium Aluminium Hydride

nucleophilic

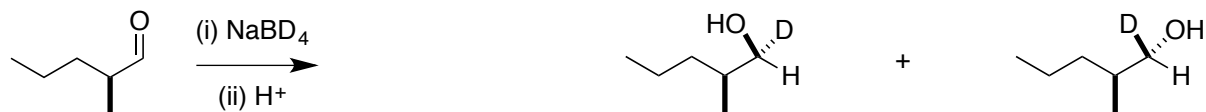
basic

nucleophilic

does not do

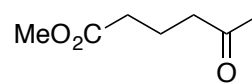
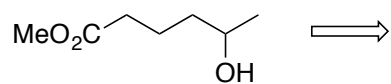
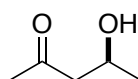
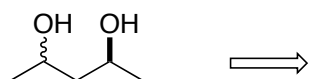
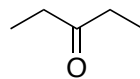
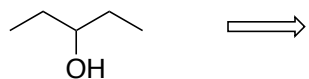
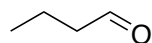
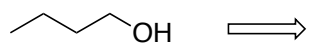


two diastereomers



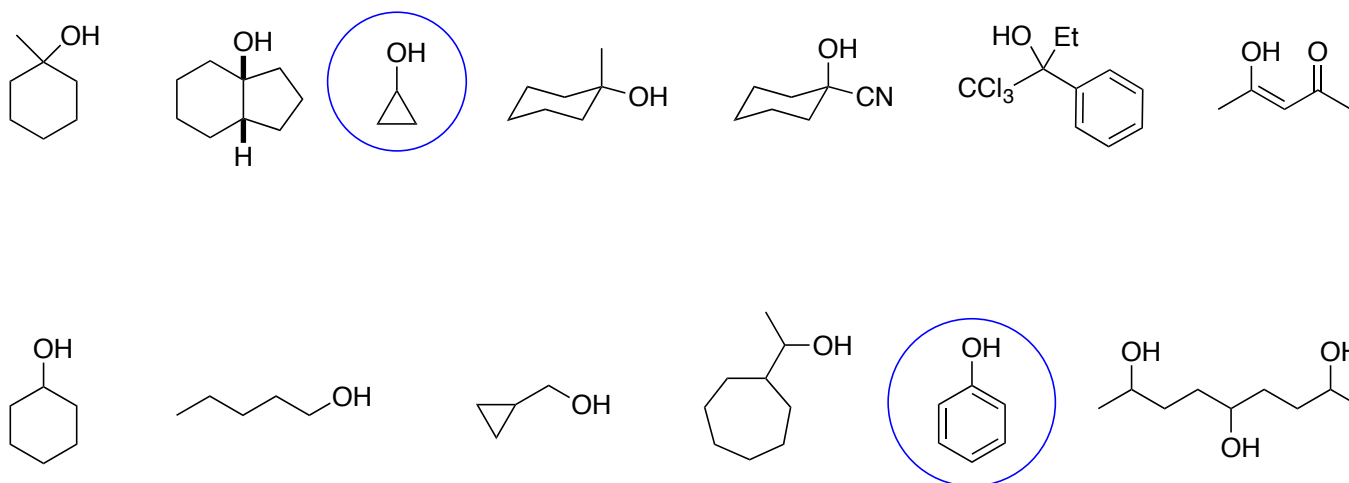
two diastereomers

reduction processes.



because:

Lithium aluminium hydride can reduce ester to alcohol, but sodium borohydride cannot.



D. Addition Of Carbanions

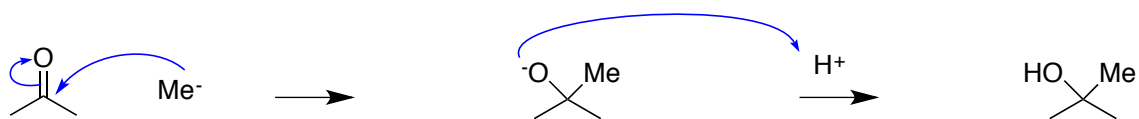
reactive

carbonyls *irreversibly*.

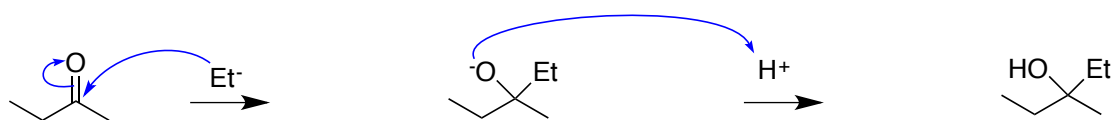
is *stronger* than

under *anhydrous* conditions.

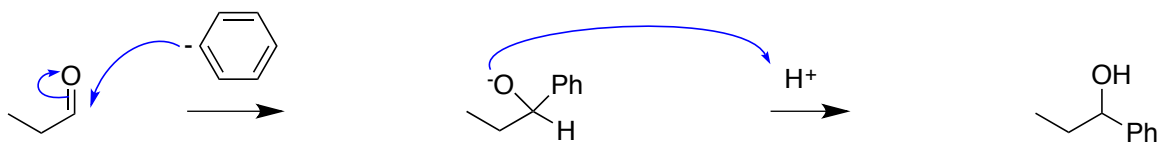
alkoxide *does not*



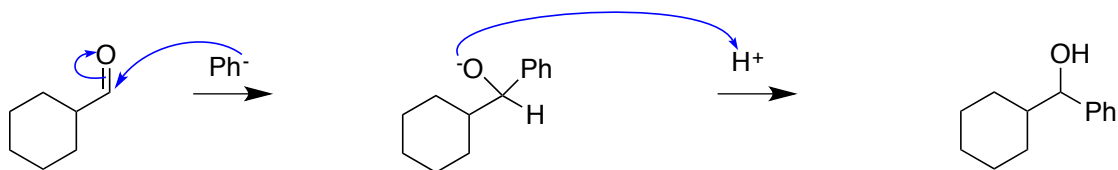
tetrahedral intermediate



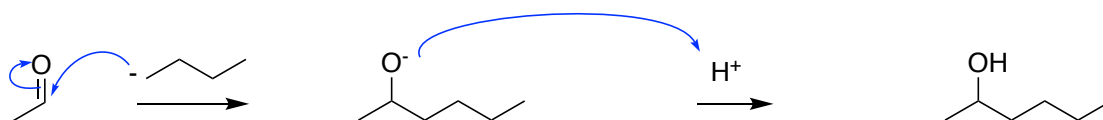
tetrahedral intermediate



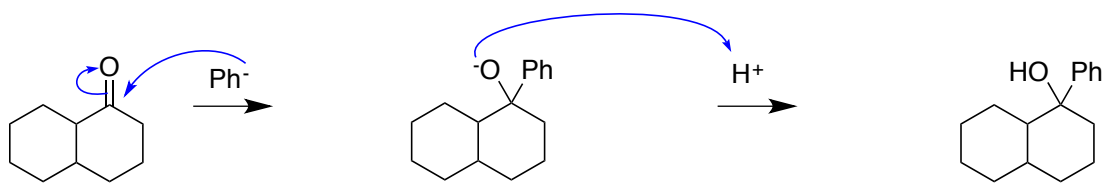
tetrahedral intermediate



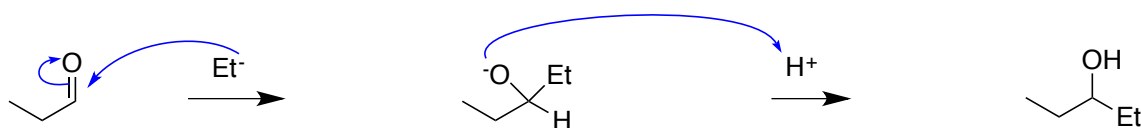
tetrahedral intermediate



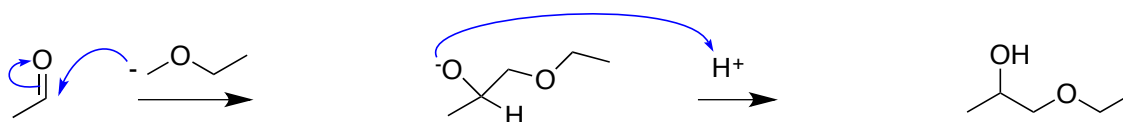
tetrahedral intermediate



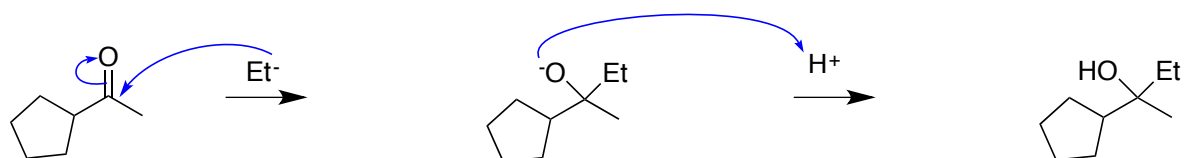
tetrahedral intermediate



tetrahedral intermediate

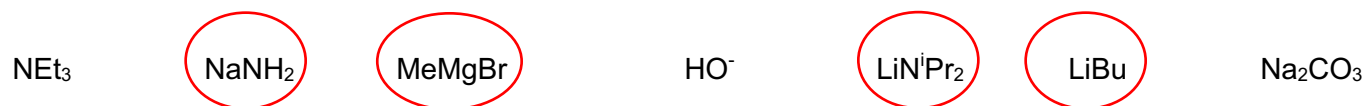


tetrahedral intermediate

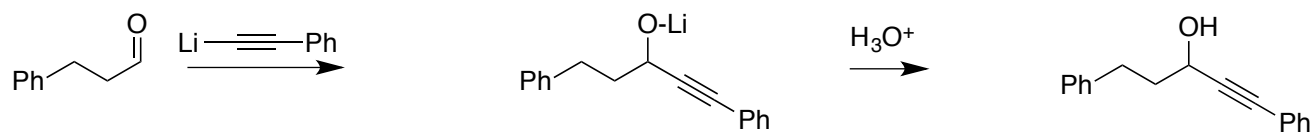


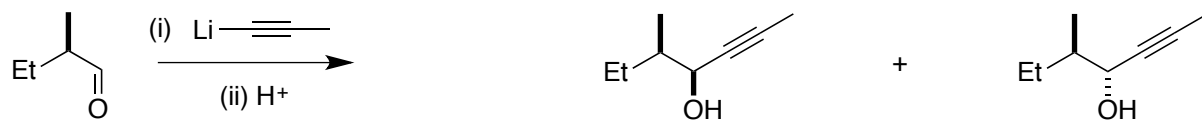
tetrahedral intermediate

E. Reactions Of Carbonyl Compounds With Acetylide Anions

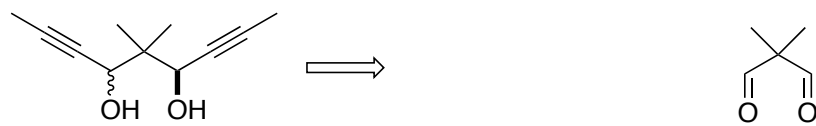


secondary or tertiary





two diastereomers



two diastereomers

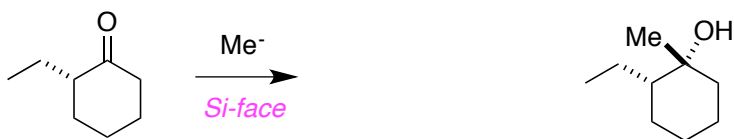
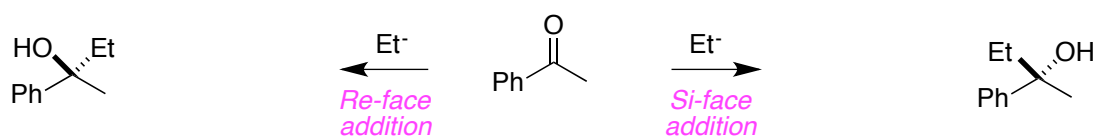


F. *Si* And *Re* Faces Revisited

enantiomers.

Re-face attack

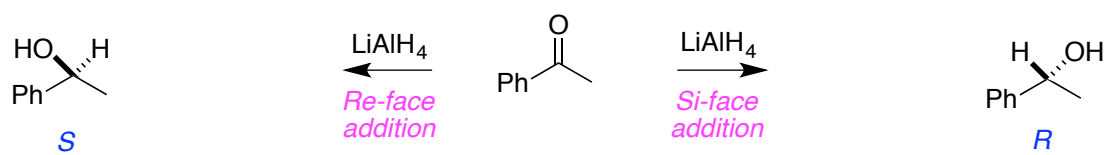
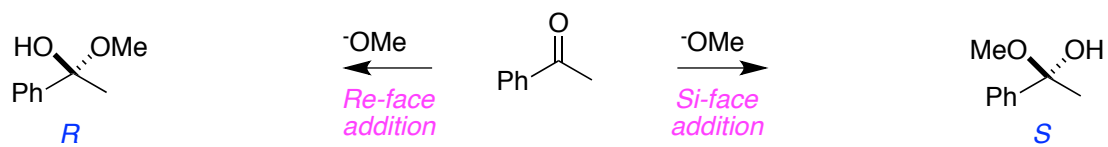
Si-face attack.





(R)-Alcohols *are not*

(S)-alcohols *are not*



Addition Of Grignard Reagents To Aldehydes And Ketones

from chapter(s) _____ in the recommended text

A. Introduction

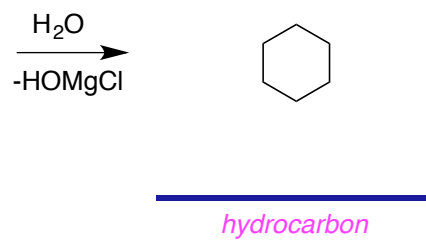
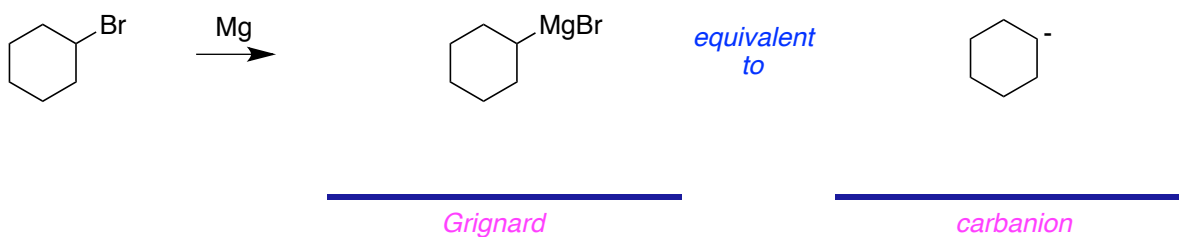
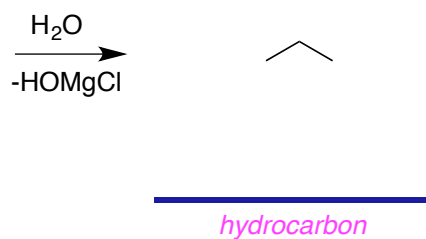
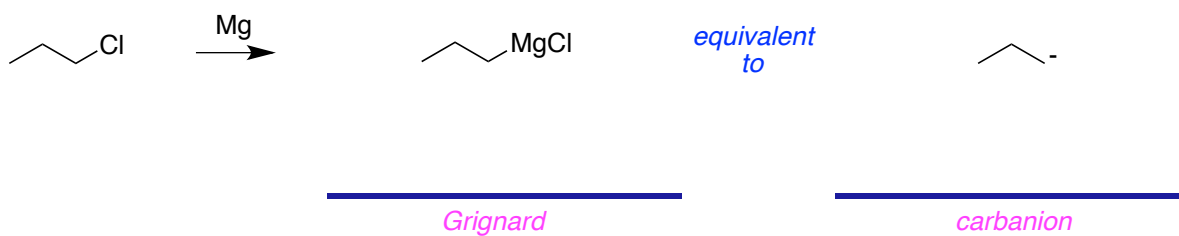
.

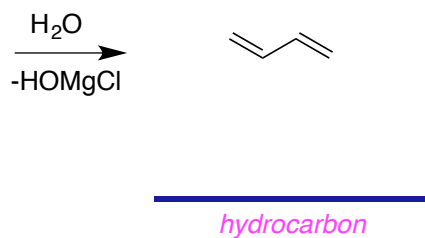
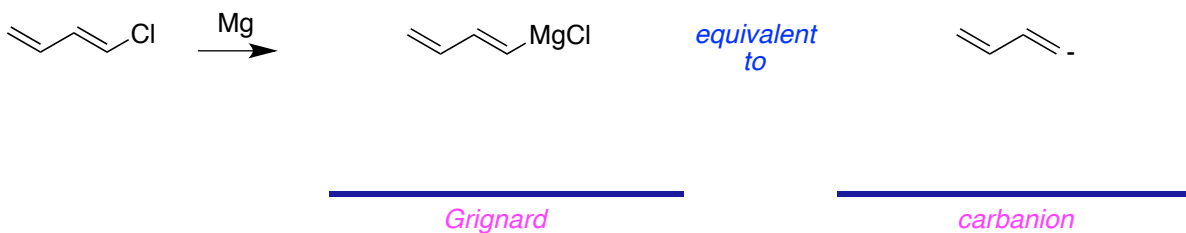
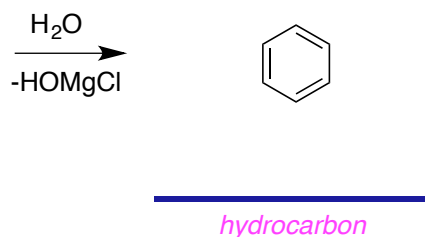
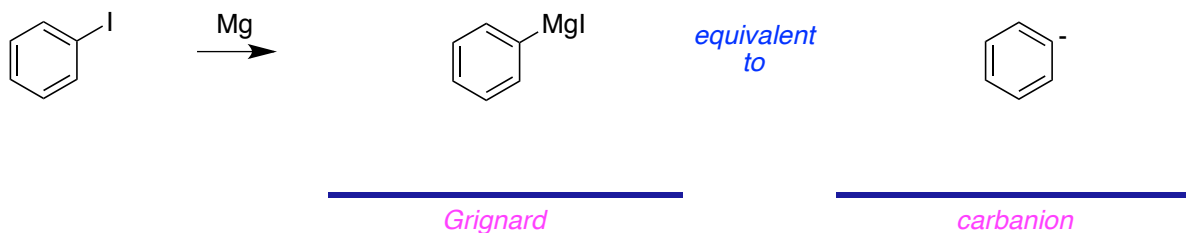
B. Grignard Reagents: A Type Of Carbanion Equivalents

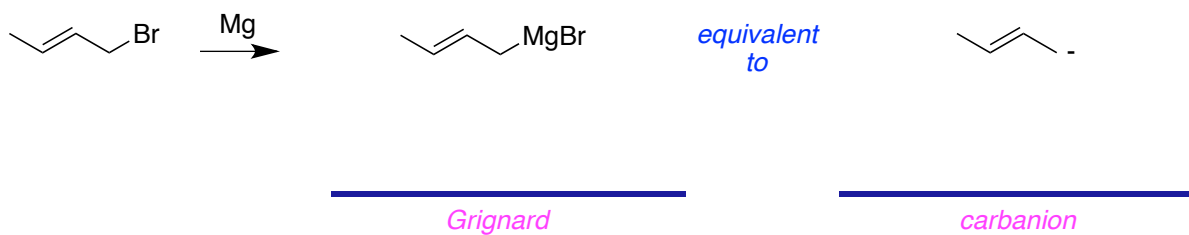
magnesium;

strong base

cannot be formed from compounds liberating *ethene*.



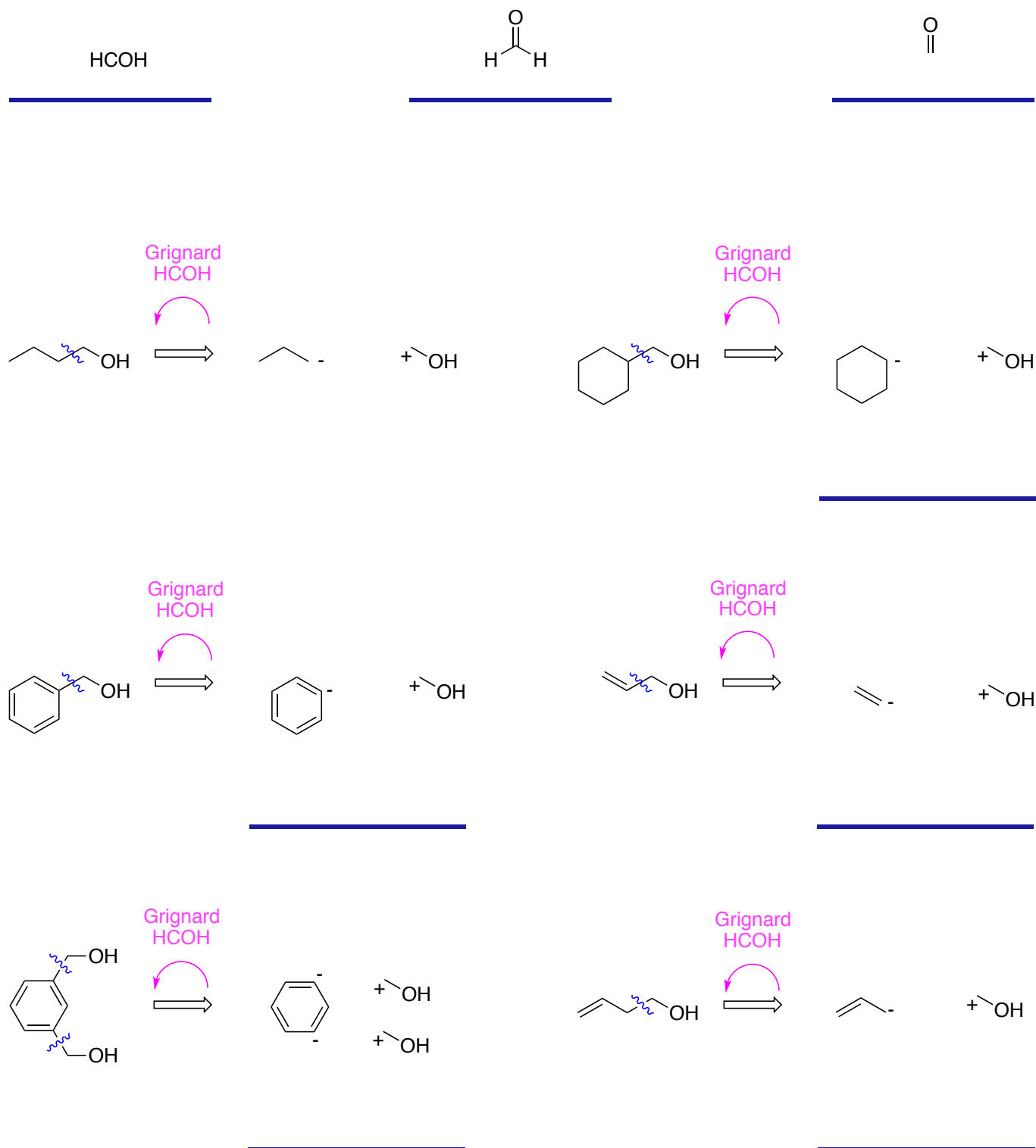


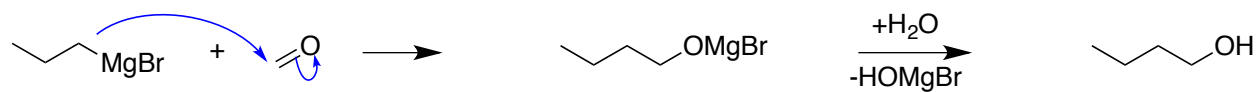


hydrocarbon

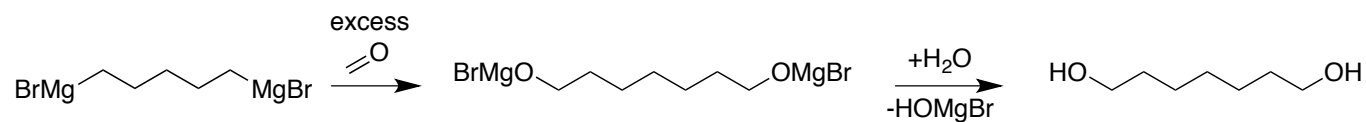
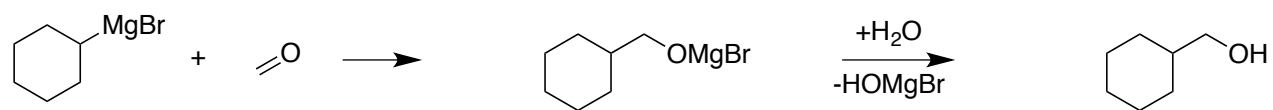
1,2-dichloroethane	bromobenzene	benzyl bromide	butane
allyl chloride	2-chloropropane	1,2-diiodopropane	2-chloroethanol
diethyl ether	fluoroethane	bromoethanal	3-iodopropanol
chloro(methoxy)methane	1-bromo-3-methoxy-ethanal		bromoethane

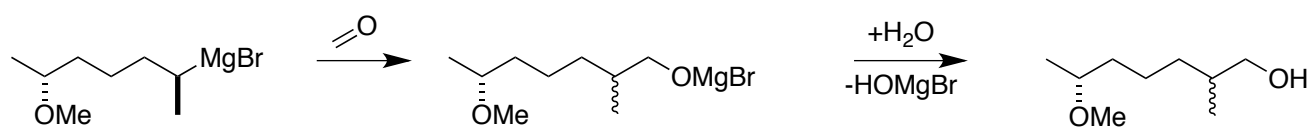
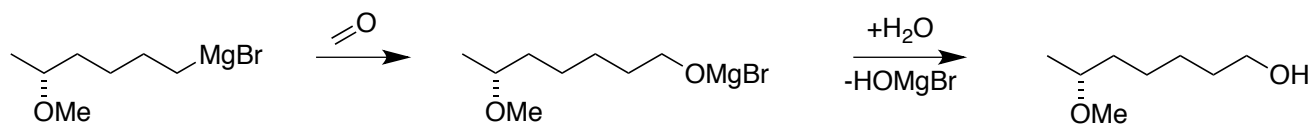
C. Reactions Of Methanal With Grignard Reagents



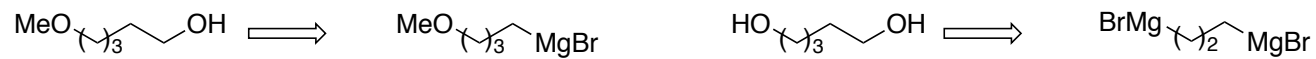
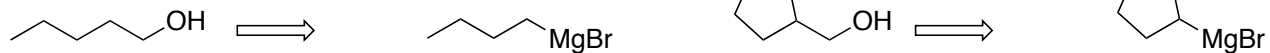


primary alcohols
one more

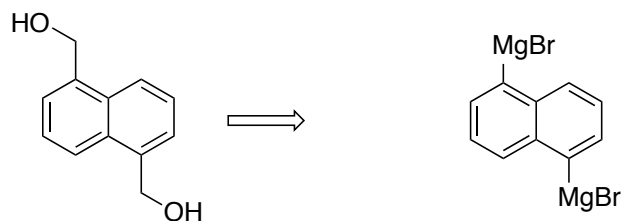
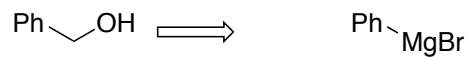




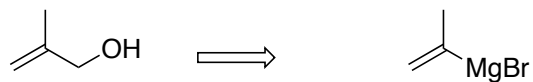
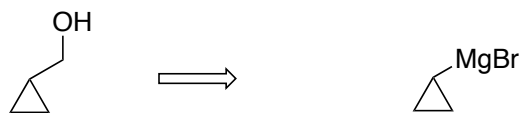
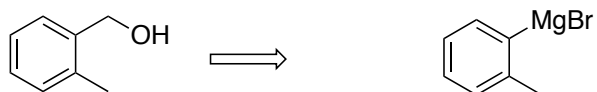
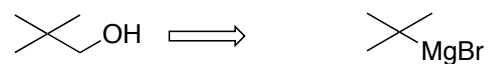
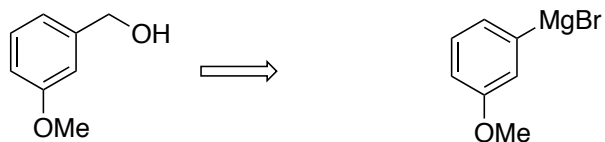
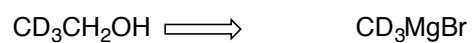
primary



a di-Grignard

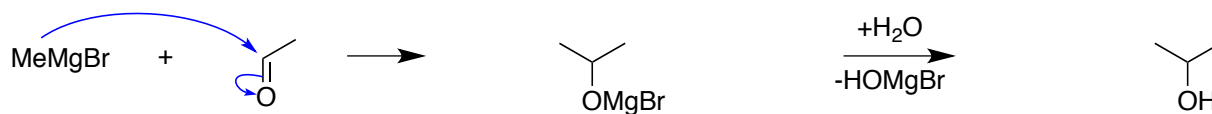


a di-Grignard

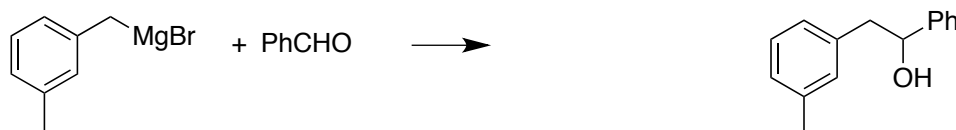
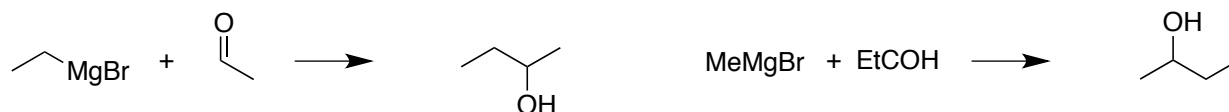


more basic than
 compounds *irreversibly*.
primary because methanal has *two*
secondary alcohols.
is unique

D. Reactions Of Other Aldehydes With Grignards



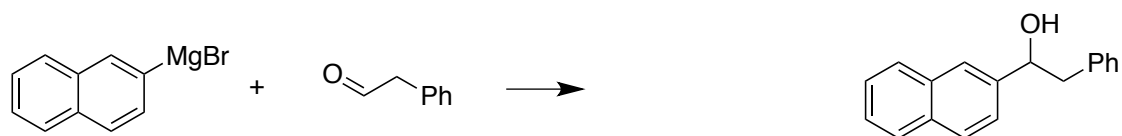
give *secondary* alcohols with *the same*



Grignard reagents are *more* basic than nucleophiles like methoxide, and add to carbonyl compounds *irreversibly*.

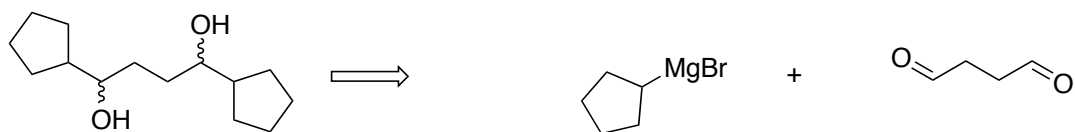
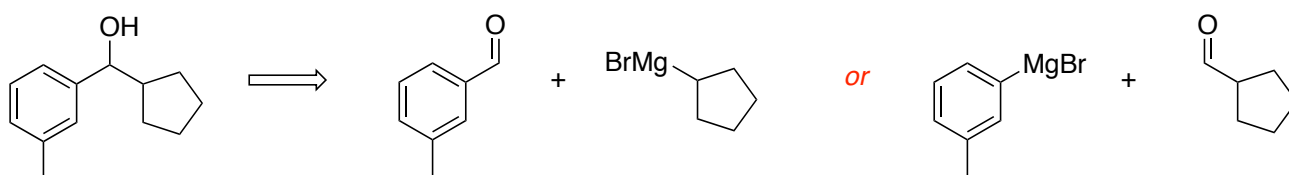
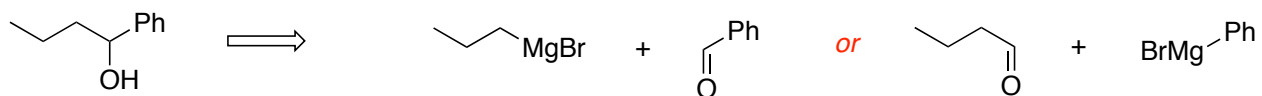
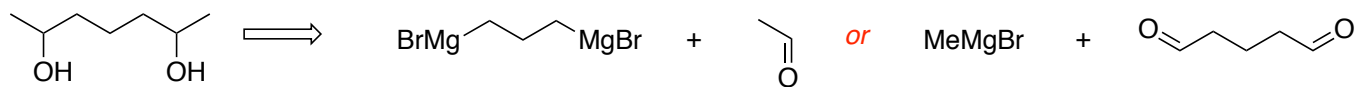
The alcohols from reactions of Grignards with methanal are *primary* because methanal has *two* hydrogens attached to the carbonyl group.

Reactions of Grignards with other aldehydes must give *secondary* alcohols; methanal *is* unique.

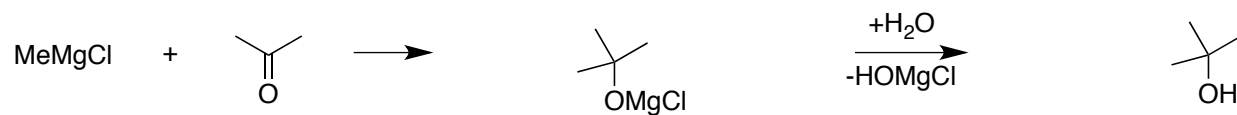


secondary alcohols

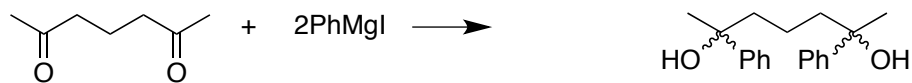
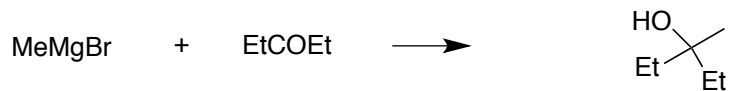
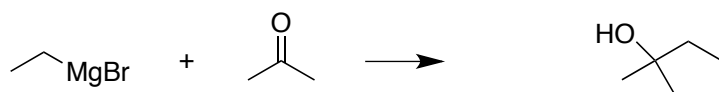


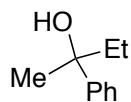
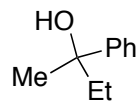
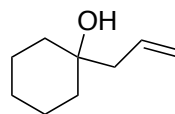
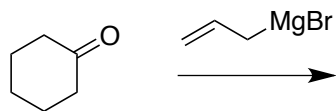
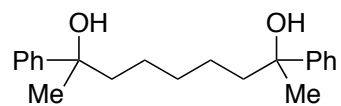
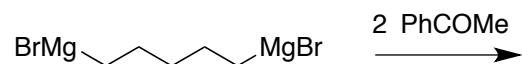


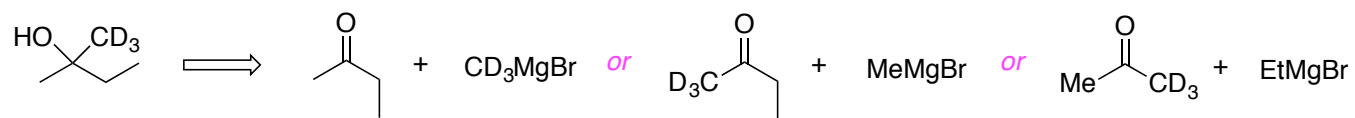
E. Reactions Of Ketones With Grignards



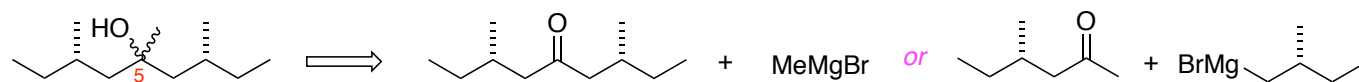
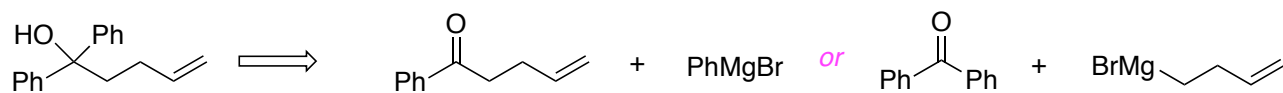
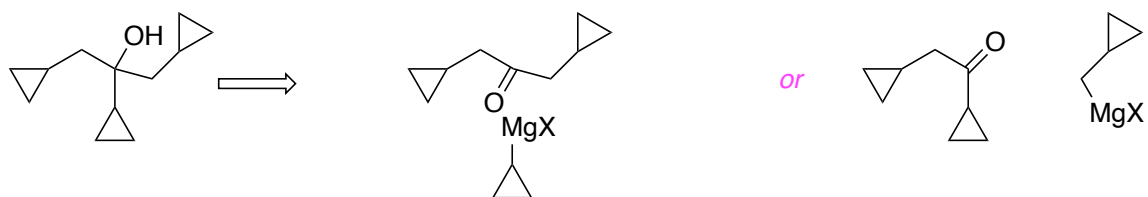
tertiary alcohols.
the same
must be the



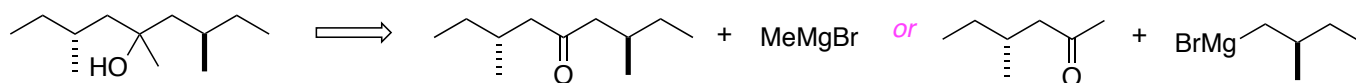




THIS PROBLEM HAS BEEN CHANGED FOR THE SECOND EDITION OF THE BOOK

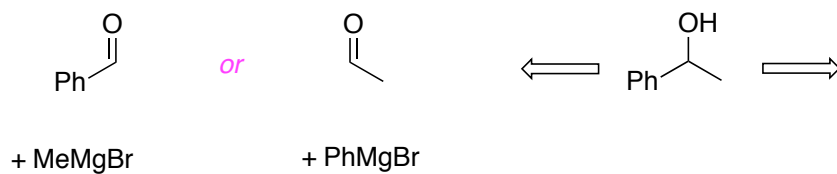


is
is not possible

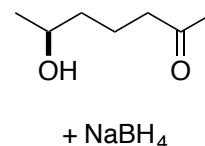
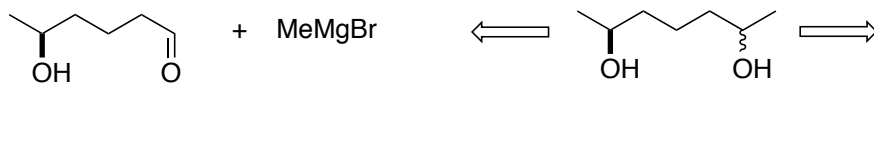
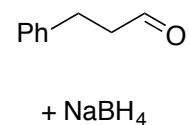
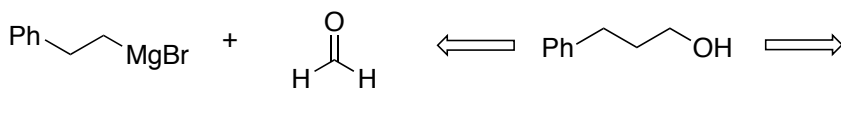
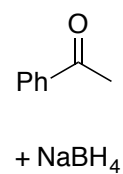


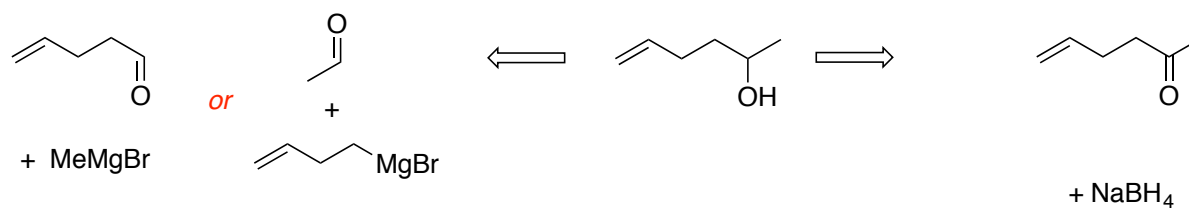
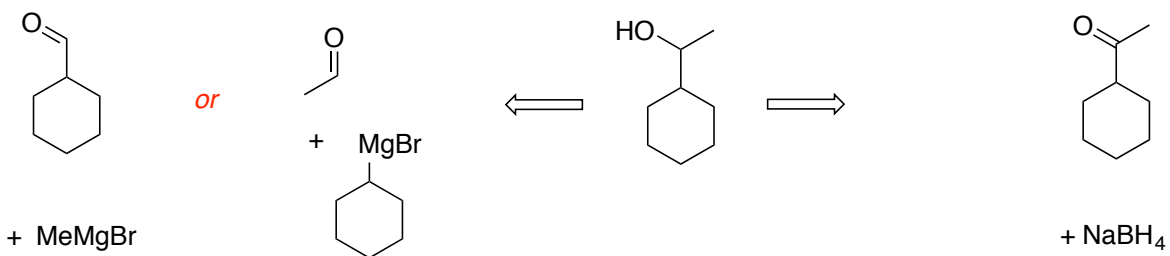
F. Complimentary Grignard and Hydride Reductions

a Grignard route

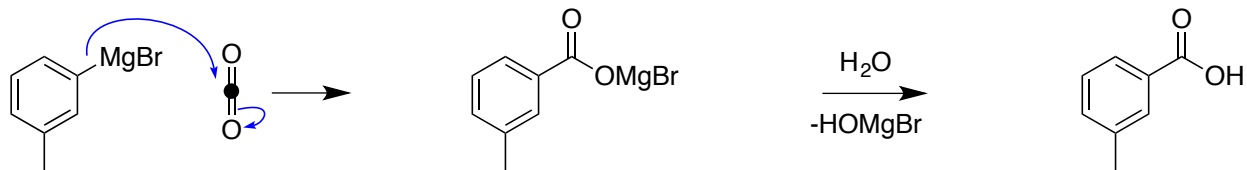


hydride route



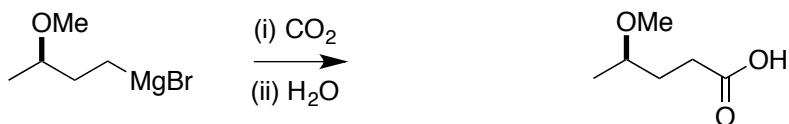


G. Reactions Of Carbon Dioxide With Grignards

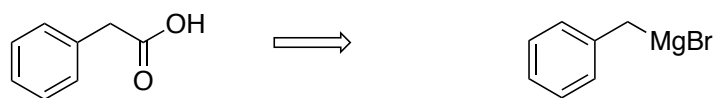


carboxylic acid.

one more carbon than the Grignard.







almost always

Addition Of Water And Alcohols To Aldehydes And Ketones

from chapter(s) _____ in the recommended text

A. Introduction

B. Relative Reactivities Of Aldehydes And Ketones

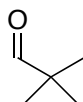
more



1



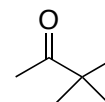
2



3



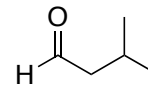
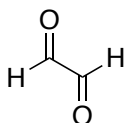
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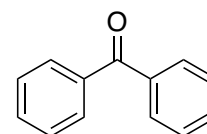
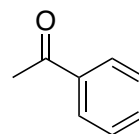
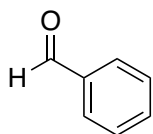
5

ie 120° to 109° .

closer thus accentuating



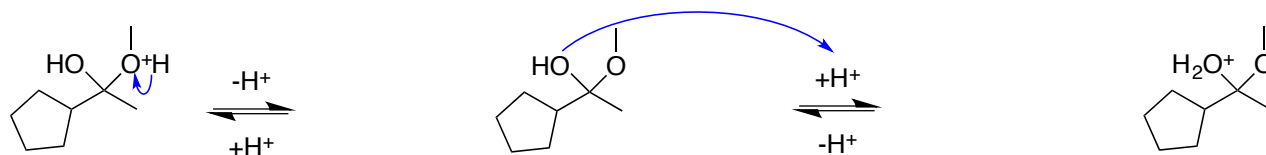
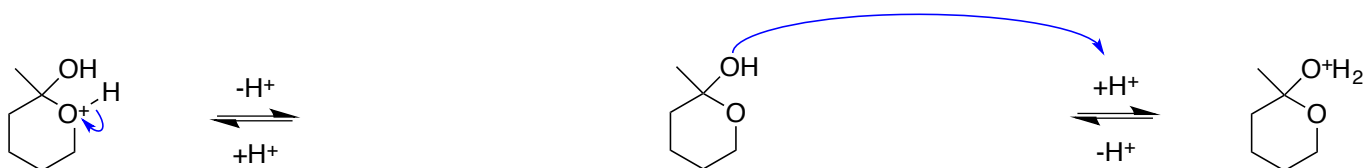
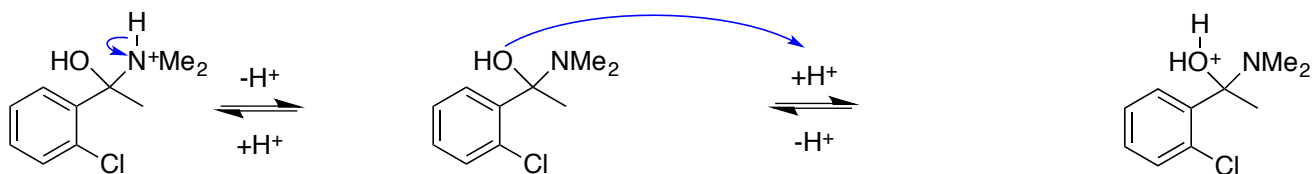
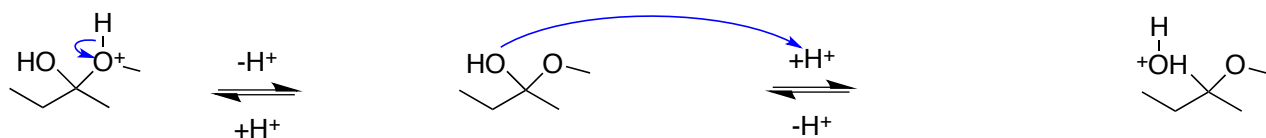
most reactive

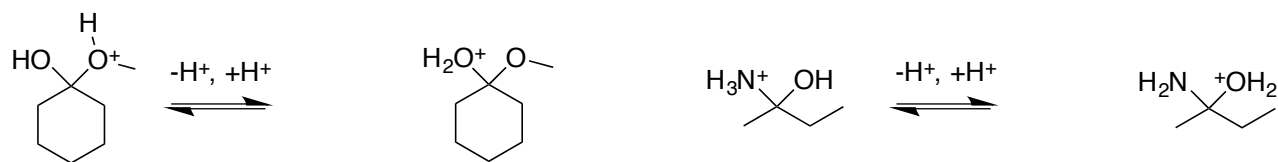
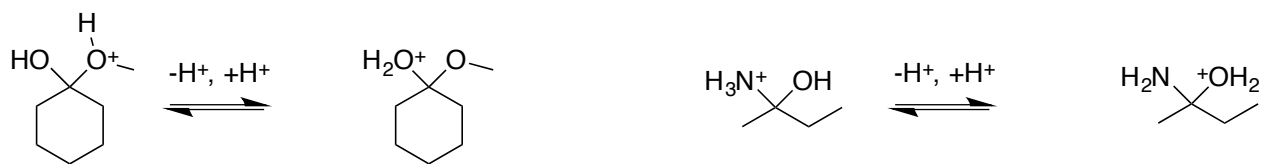
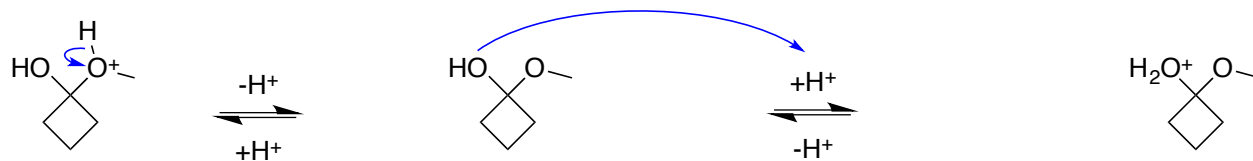


least reactive

C. Proton Transfer Steps

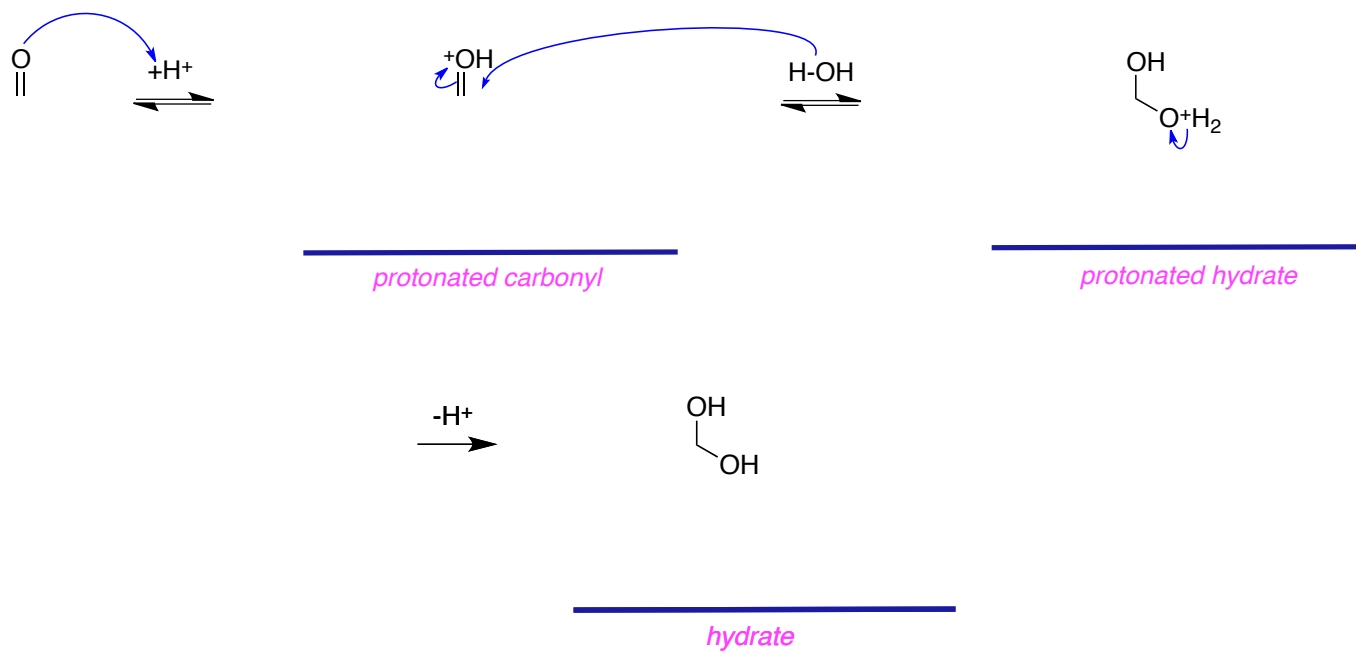
common



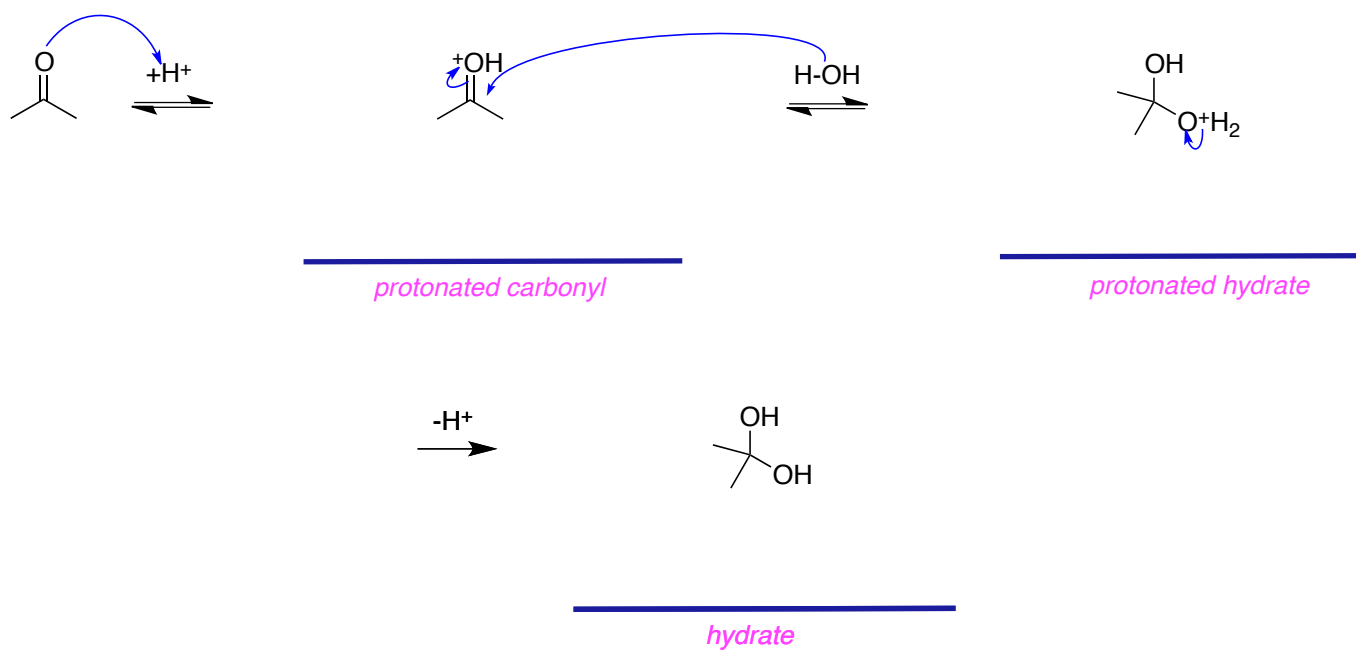


D. Addition Of Water

equilibrium
strongly

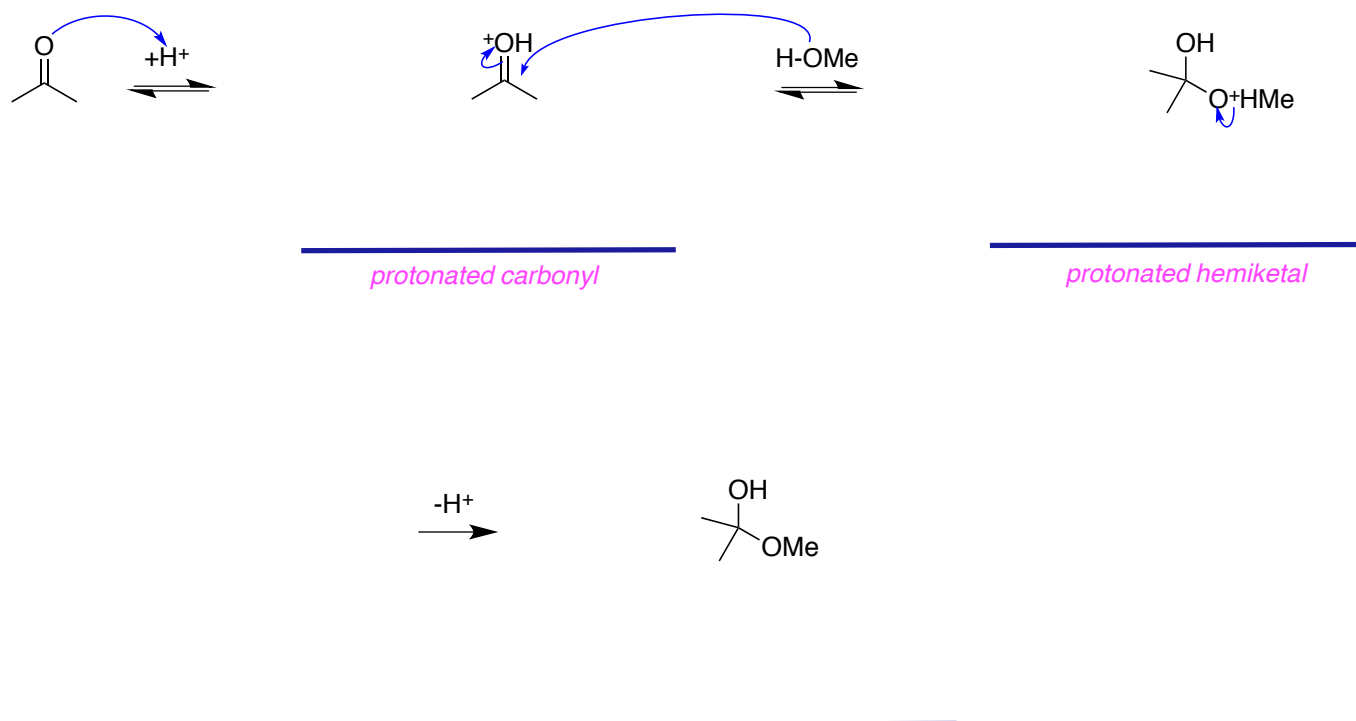


Draw the key intermediates for hydration of acetone using curly arrows to show electron flow.



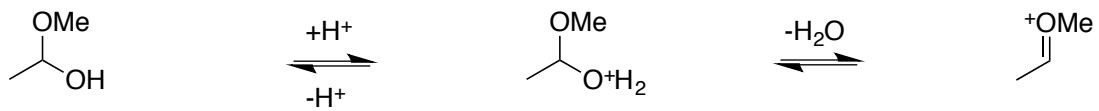
exactly 2 %.
 120° to 109°
 disfavored
 does

E. Additions Of Alcohols



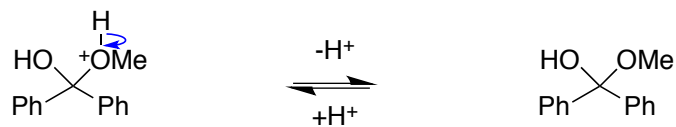
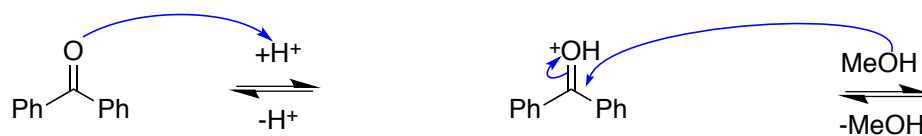
hemiketal
 called a *hemiacetal*.

hemiacetal
acetal.

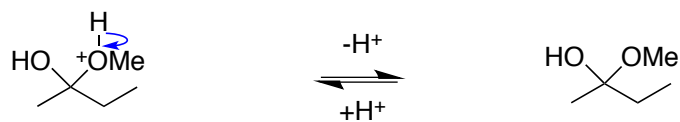
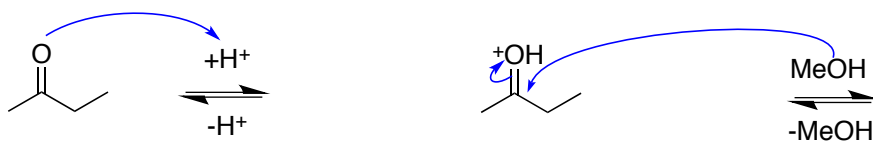


protonated acetal

do react



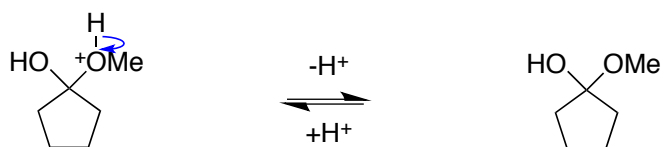
hemiketal

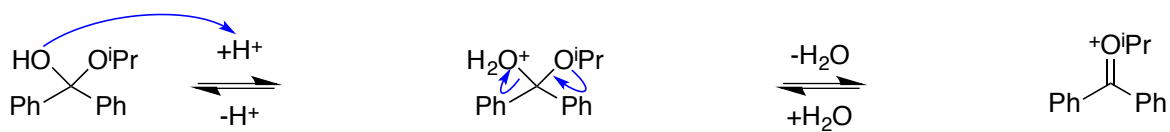


hemiketal



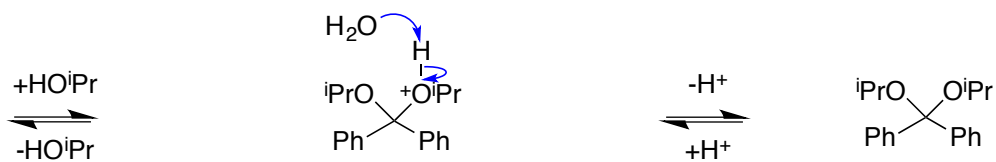
starting material?





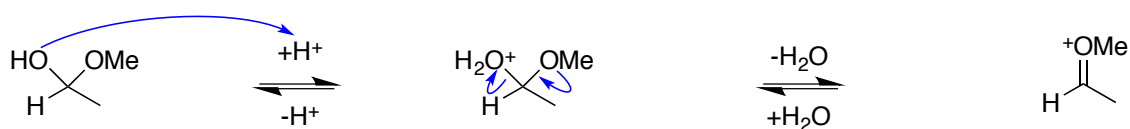
protonated on OH

oxonium ion



protonated ketal

an alcohol



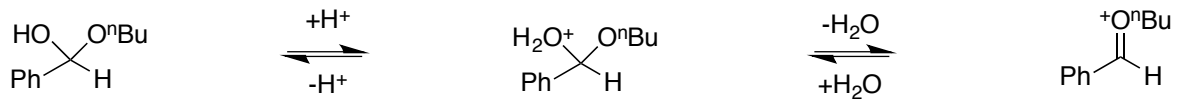
protonated on OH

oxonium ion



protonated acetal

acetal



protonated on OH

oxonium ion



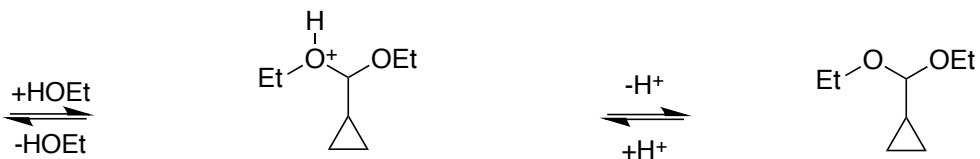
protonated acetal

acetal



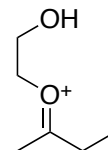
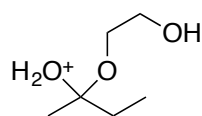
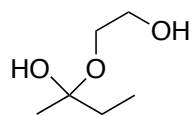
protonated on OH

oxonium ion



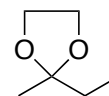
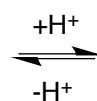
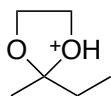
protonated acetal

acetal



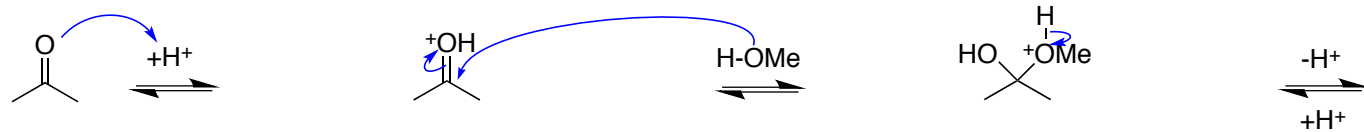
protonated on OH

oxonium ion



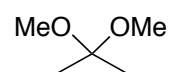
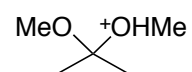
protonated ketal

ketal



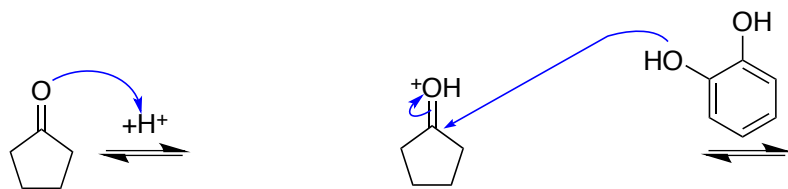
protonated carbonyl

protonated hemiacetal

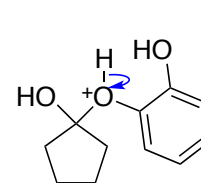


protonated ketal

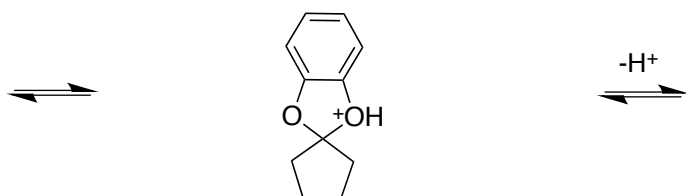
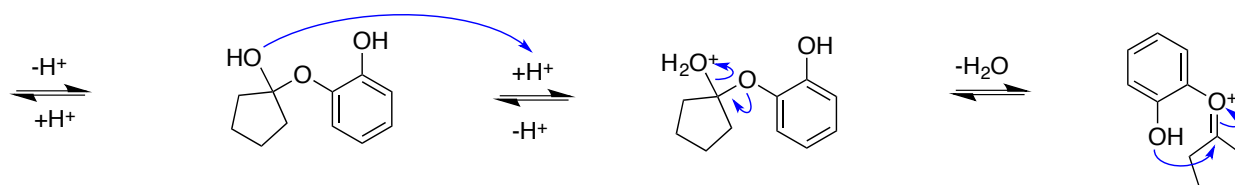
ketal



protonated carbonyl

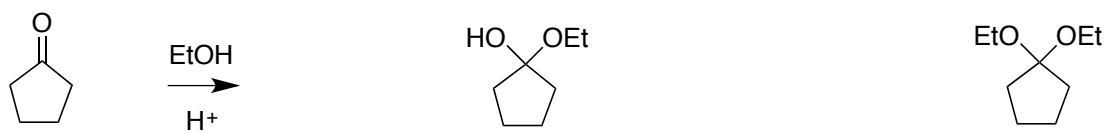


protonated hemiketal



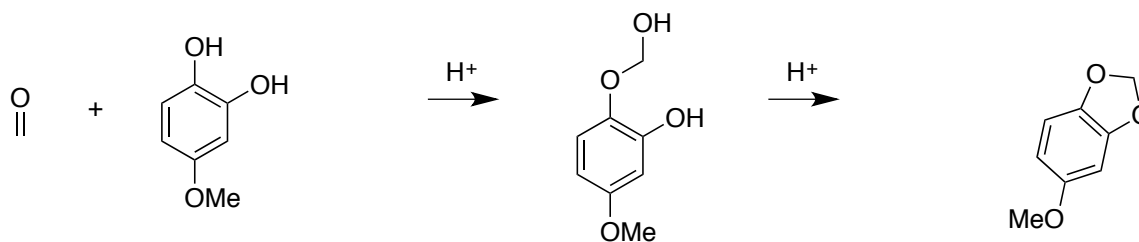
protonated ketal

ketal



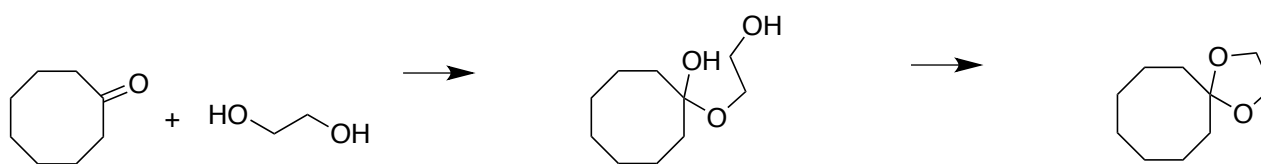
hemiketal

ketal



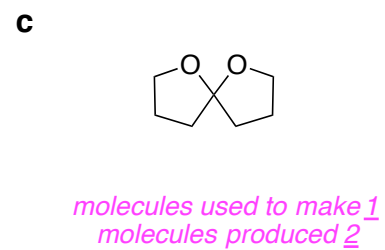
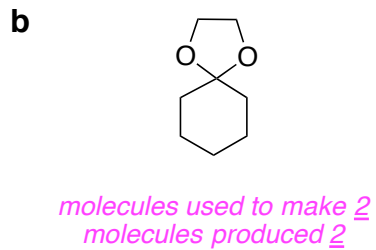
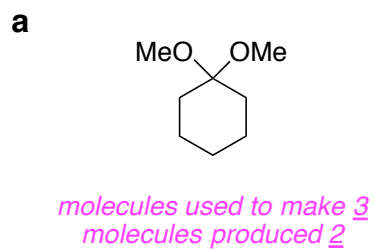
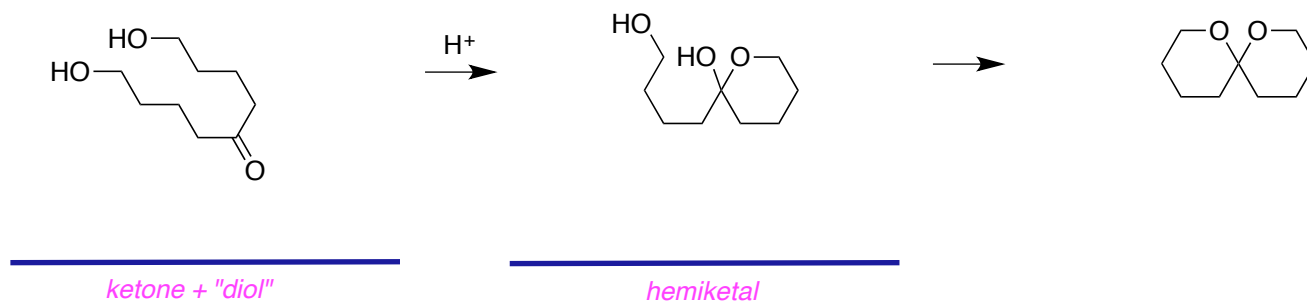
aldehyde + "diol"

acetal



ketone + "diol"

hemiketal



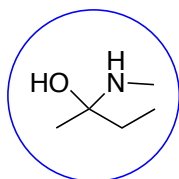
to acid is **c**.

Formation of Cyanohydrins, Imines, Enamines

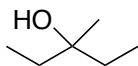
from chapter(s) _____ in the recommended text

A. Introduction

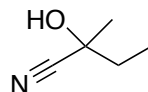
B. Tetrahedral Intermediates And Beyond



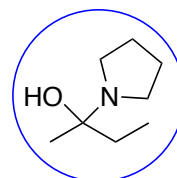
methylamine



EtMgX



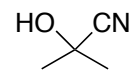
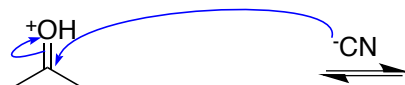
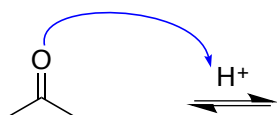
HCN



pyrrolidine

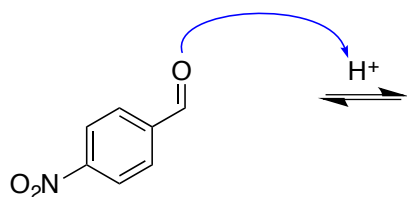
C. With HCN

weak

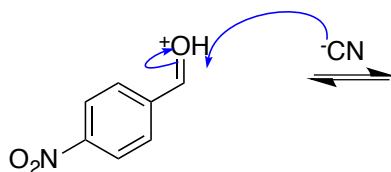


protonated carbonyl

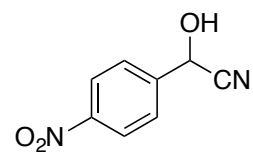
cyanohydrin adduct



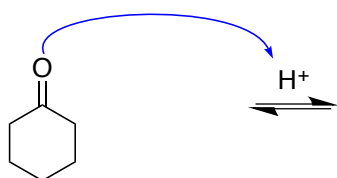
4-nitrobenzaldehyde



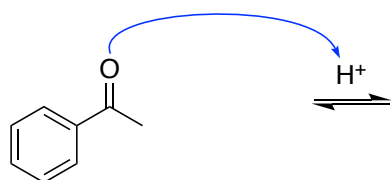
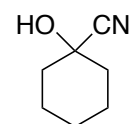
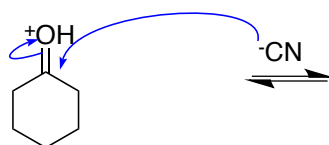
protonated carbonyl



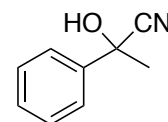
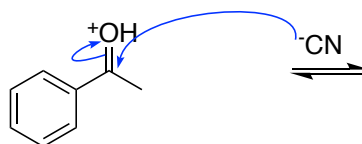
cyanohydrin adduct



cyclohexanone



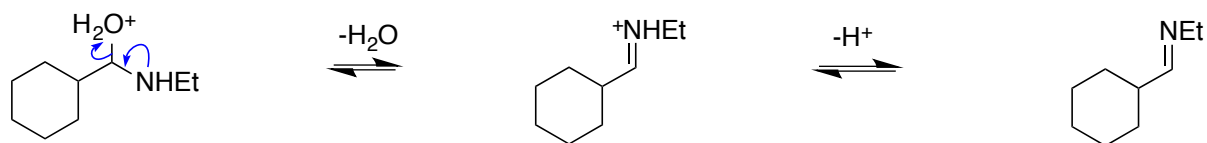
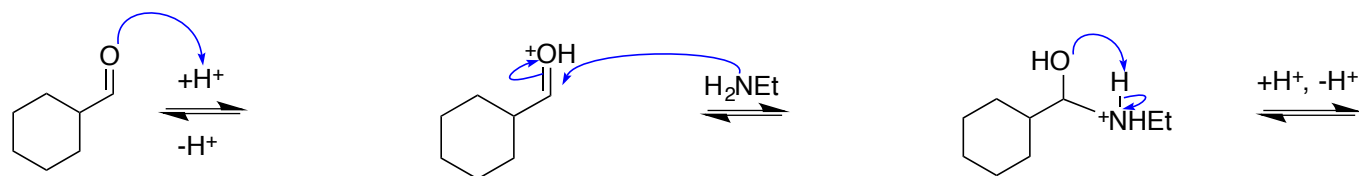
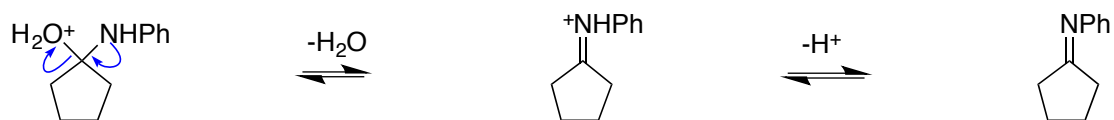
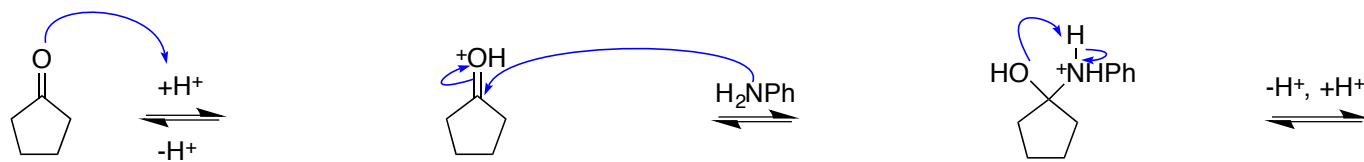
phenylethanone



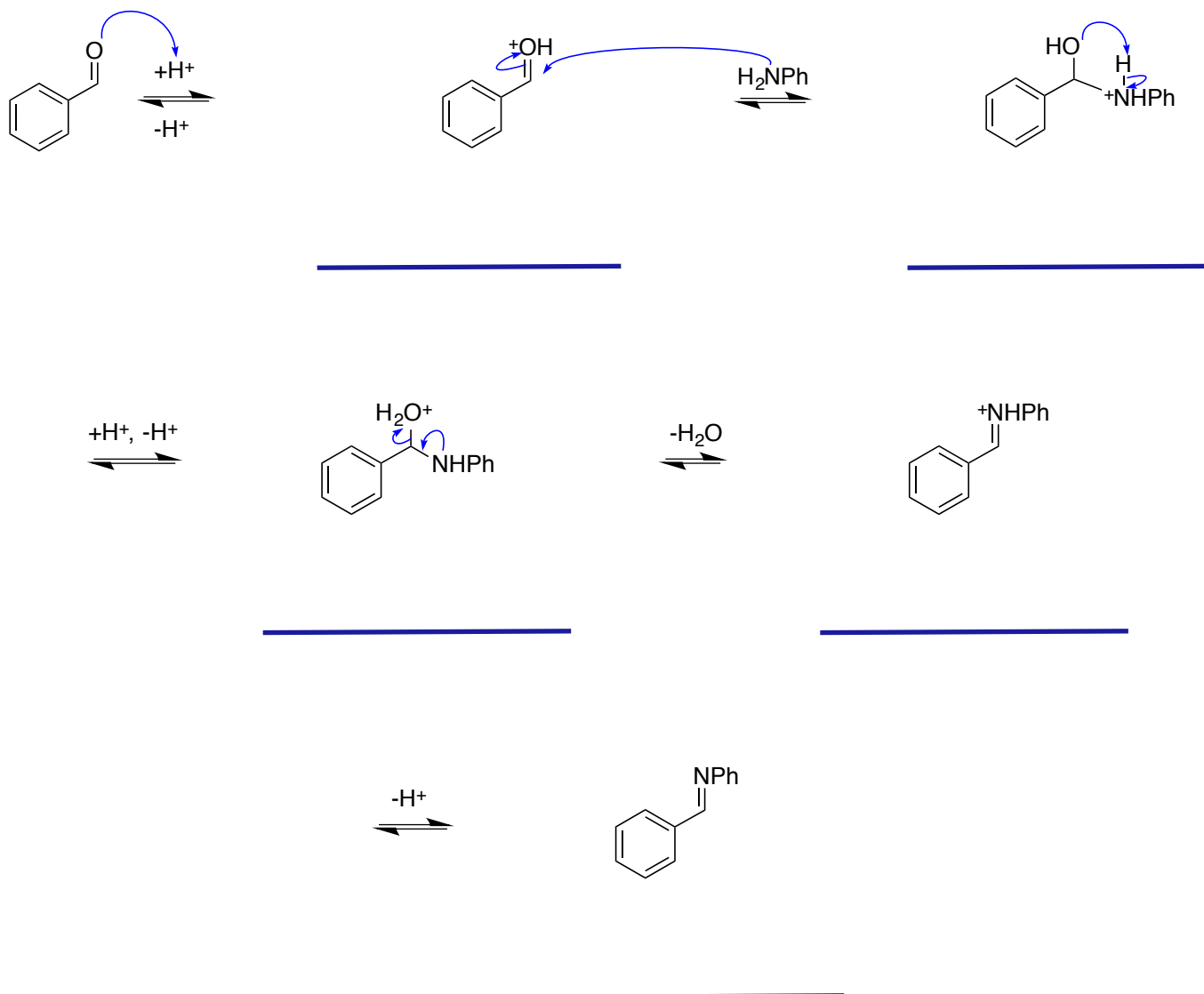
D. Condensations Of Aldehydes Or Ketones With $\text{H}_2\text{N-R}$ Or $\text{H}_2\text{N-X}$

Primary Amines Form Imines

(*loose* water)



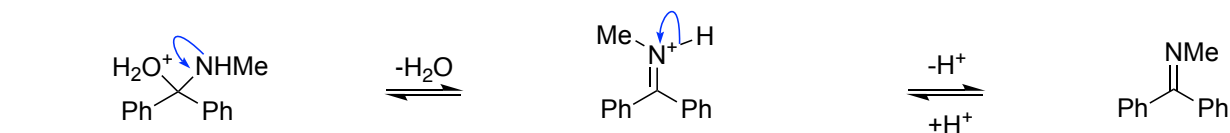
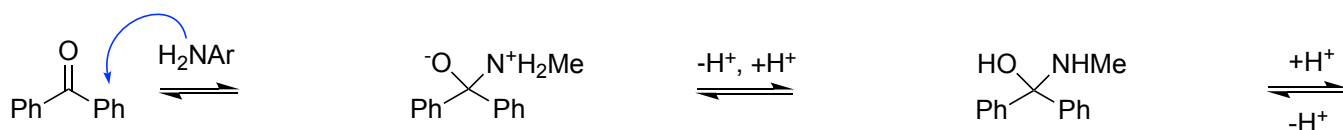
because: at this pH, the carbonyl will be protonated leading to activation of carbonyl group, facilitating the nucleophilic addition of amines. If the pH is lower than 4.5, most of the amine will be protonated making it non-nucleophilic, slowing the rate of reaction.



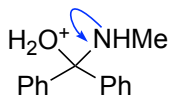
THE FOLLOWING IS A NEW SECTION, ADDED FOR THE SECOND EDITION OF THE BOOK

An Alternative Mechanism For Imine Formation

Draw a mechanism for imine formation that involves nucleophilic attack of an amine *without* protonation of the carbonyl first.



Identify the first intermediate that is common to both mechanisms, *ie* the one involving protonation of the carbonyl first, and the one above (it is the one that precedes loss of water).

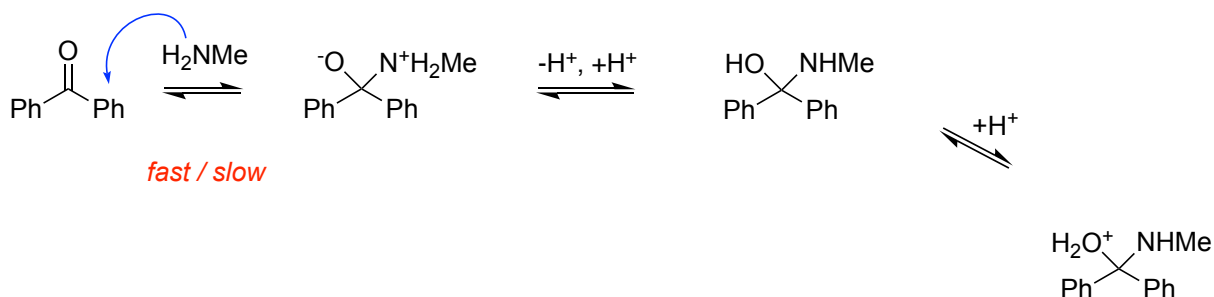


amino-oxonium intermediate

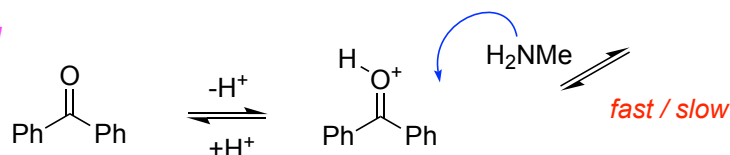
Condensation of amines with aldehydes and ketones proceeds most quickly at around pH 4. Under those conditions amines are *more / less* protonated than the carbonyl compounds they are mixed with. The mechanism used mostly in this chapter shows protonation of the carbonyl before attack of the amine, and under these conditions, pH 4, the amine is *mostly protonated / mostly present in the unprotonated form*.

An alternative mechanism that invokes shows nucleophilic attack on the carbonyl *without* protonation also involves attack of the free amine at pH 4, but on a neutral carbonyl, and this is likely to be *slower / faster* than attack of an amine on the same carbonyl, but when it is protonated. Indicate the relative rates of the two steps on the diagram below.

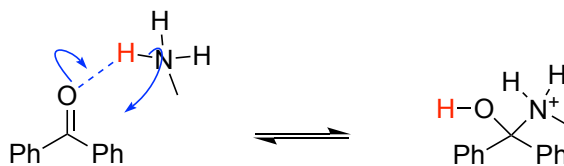
without protonation of the carbonyl



with protonation of the carbonyl



Draw yet another mechanism that involves formation of the amine-oxonium intermediate above in a single step which involves hydrogen bonding of the carbonyl with an ammonium salt formed from protonation of the amine at pH 4.



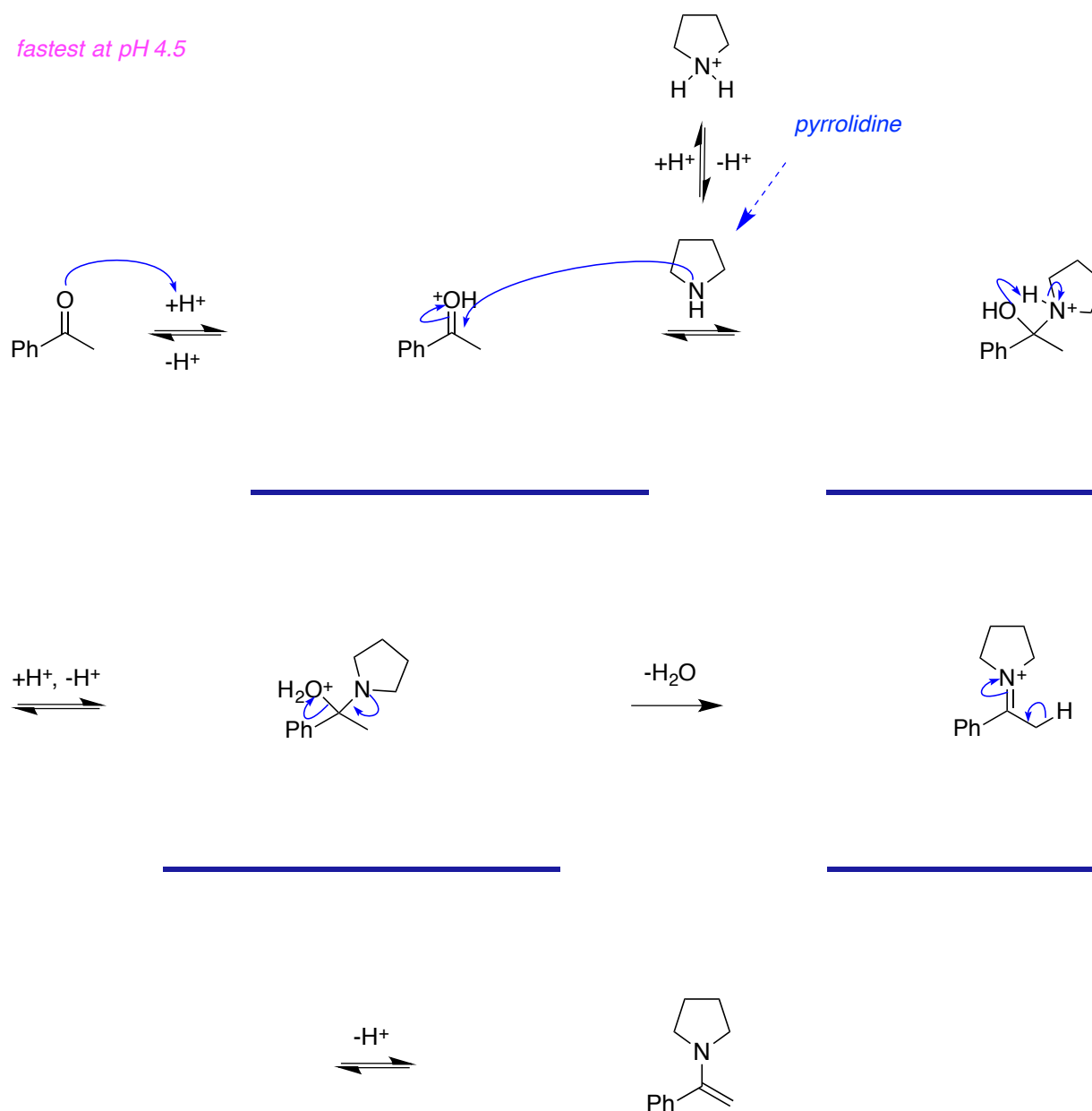
show H-bond and curly arrows

Secondary Amines Form Iminium Ions Then Enamines

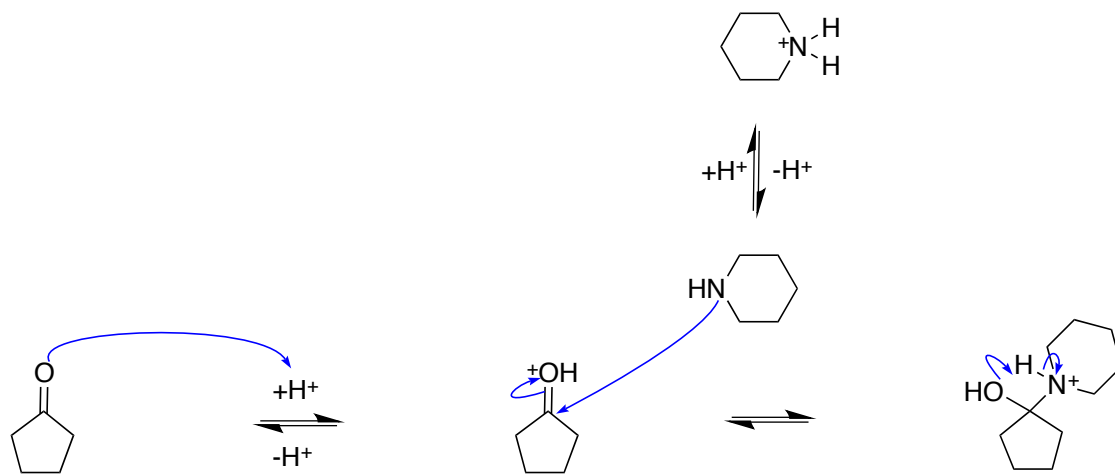
α carbon.

are reversible.

fastest at pH 4.5



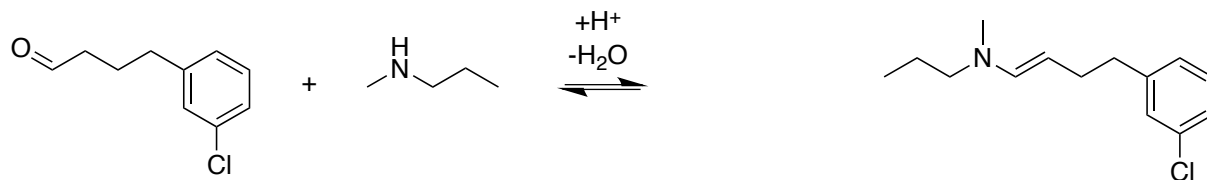
piperidine



cyclopentanone



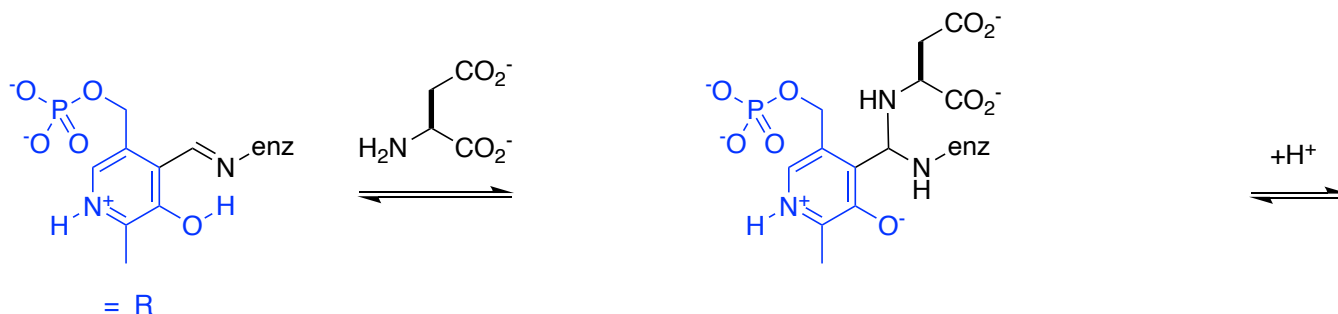
do hydrolyze



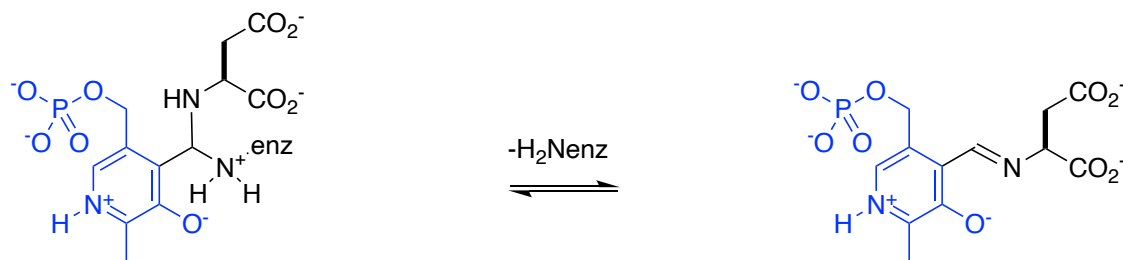
is:

Primary amines have two protons; one can be transferred to OH group then loss of water and another is removed to neutralize iminium to form imines. On the other hand, secondary amines have only one proton involved in dehydration step but no proton left to neutralize iminium ion. So the mechanism must involve losing a proton from the α -carbon to neutralize iminium ion thus forming enamines.

E. Transamination

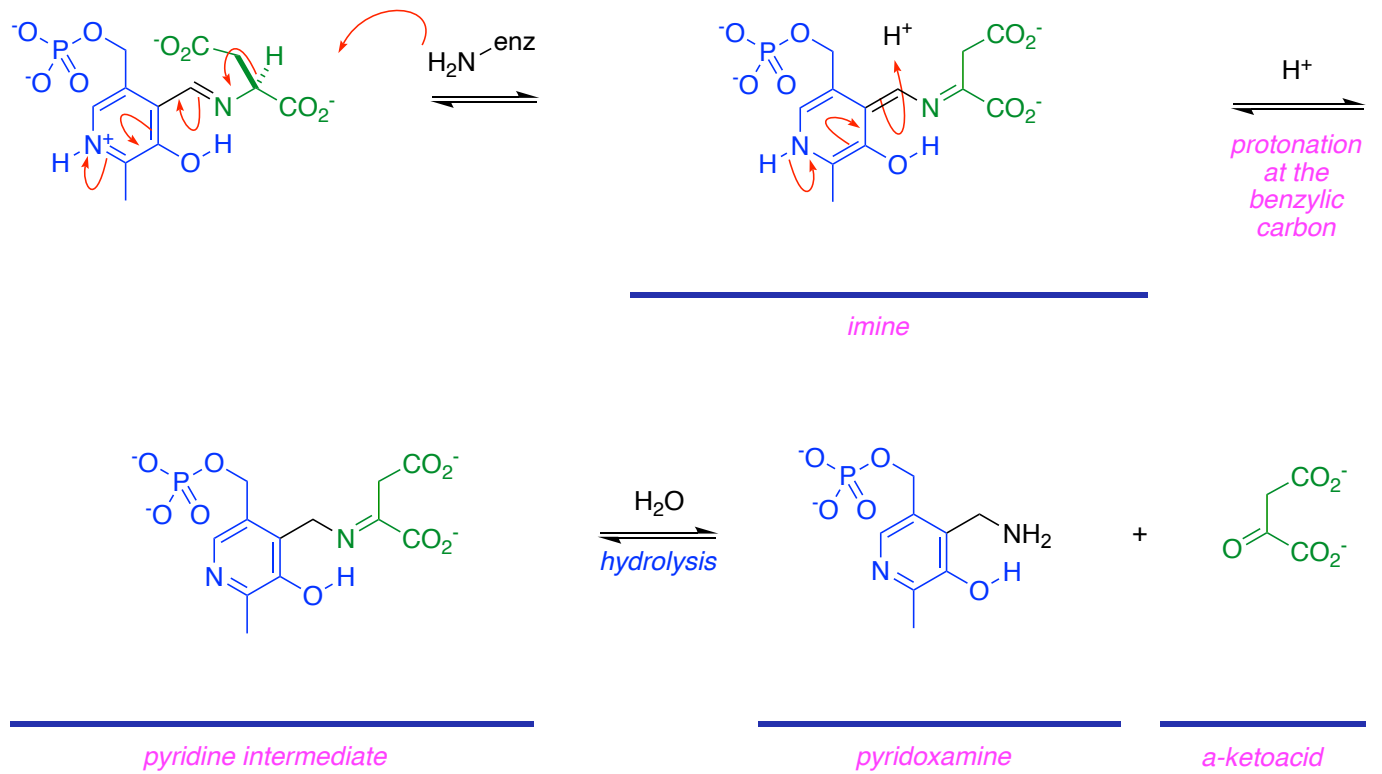


tetrahedral intermediate



tetrahedral intermediate

imine



oxidation of

amine

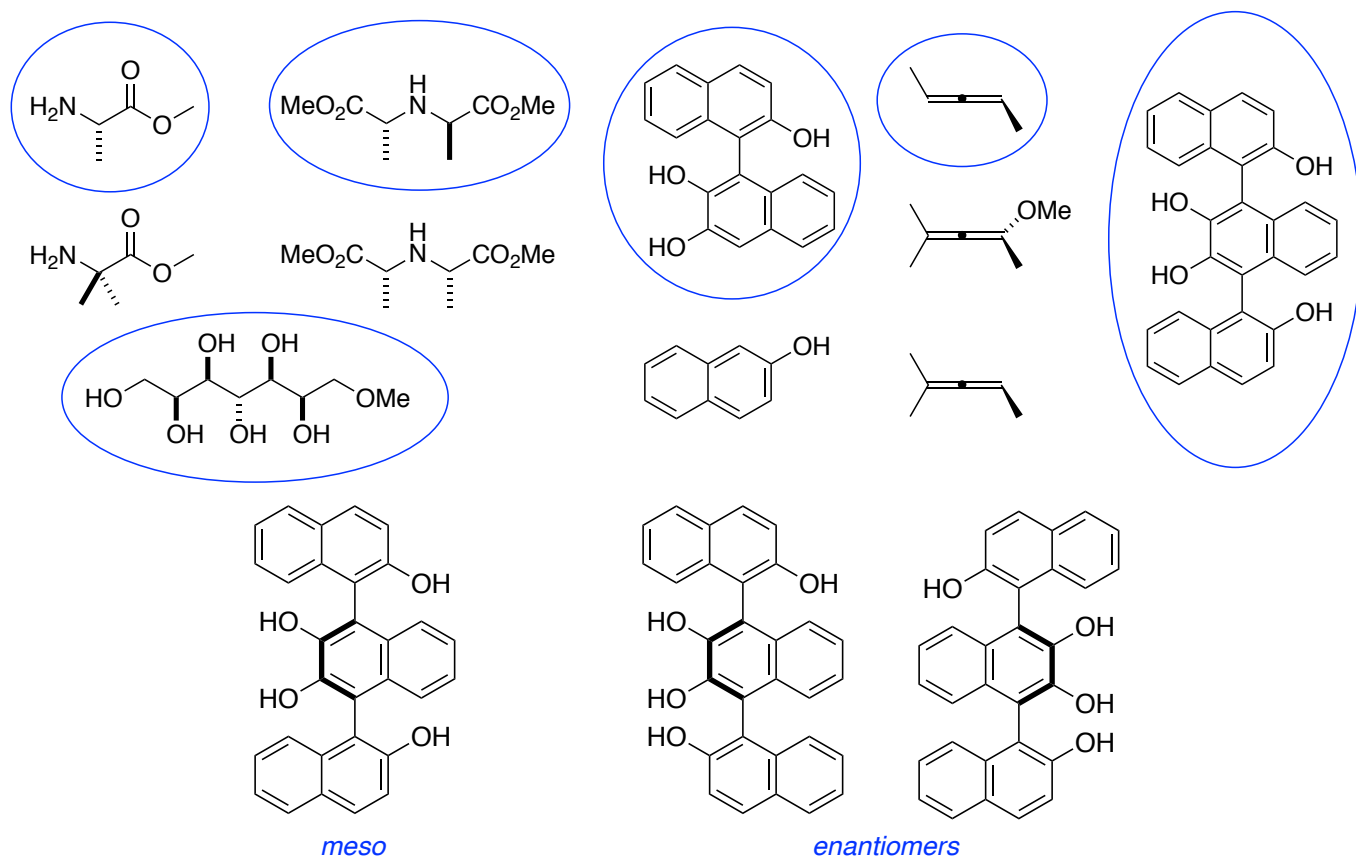
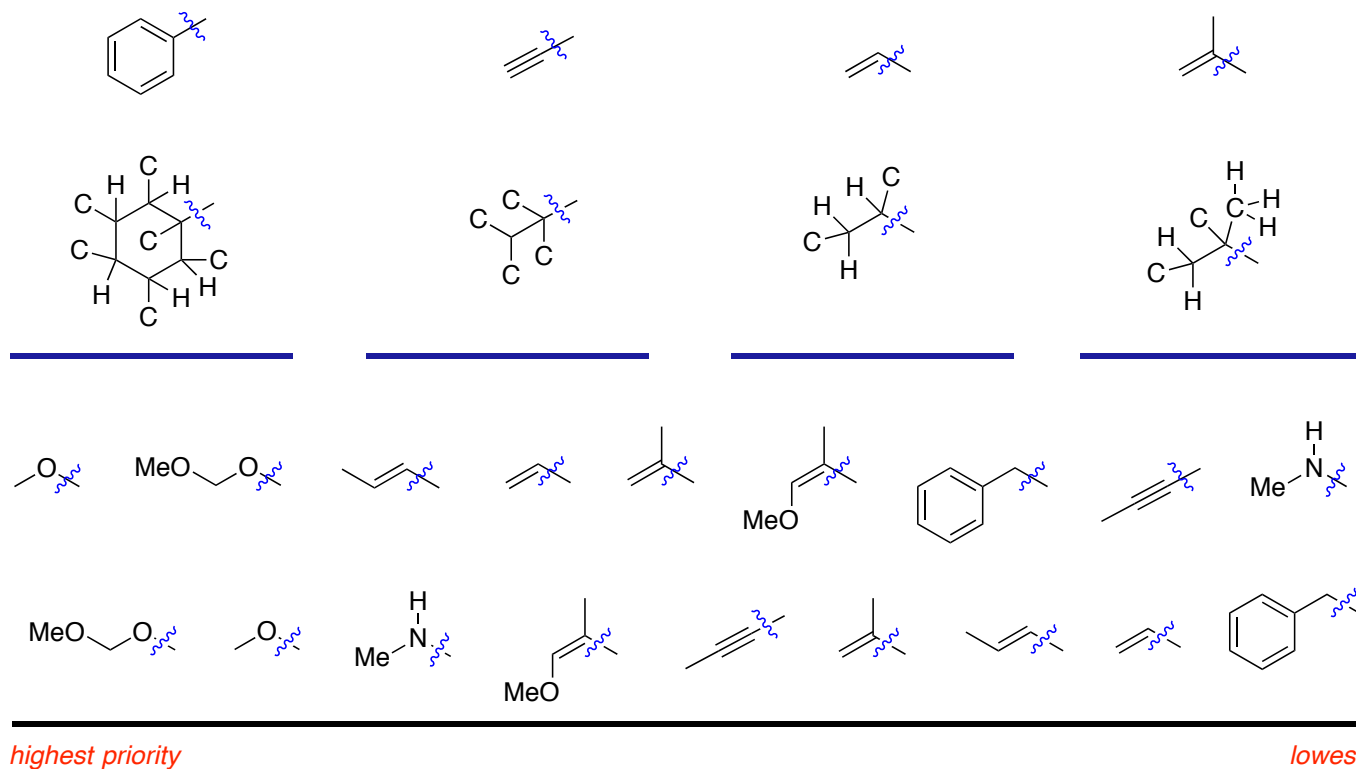
degrade one and form another.

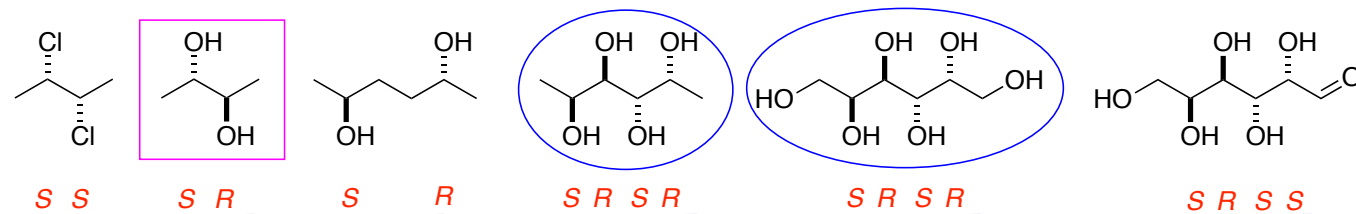
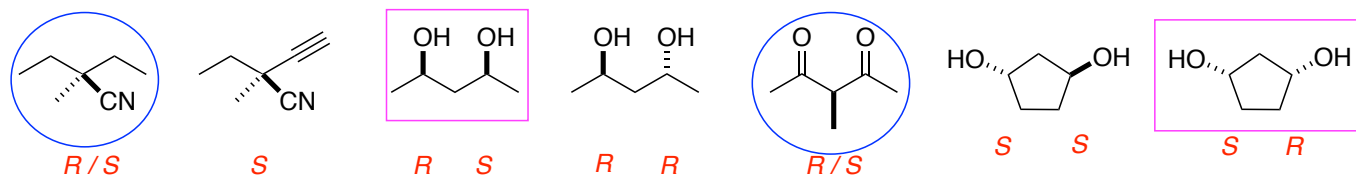
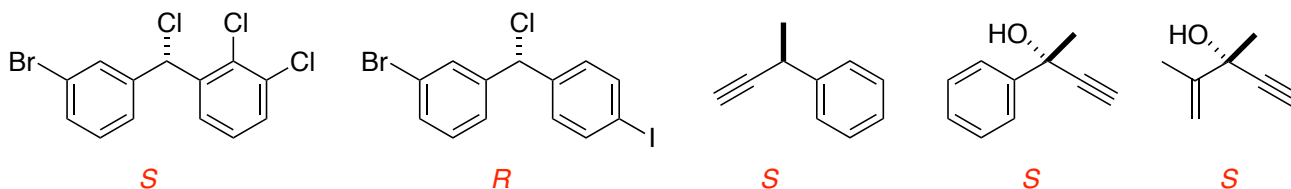
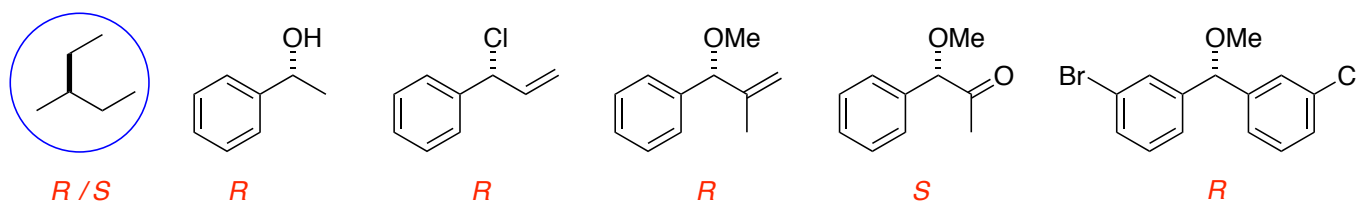
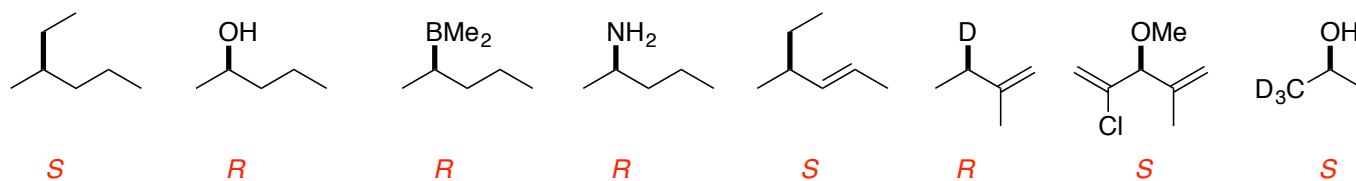
Stereochemistry Illustrated By Carbohydrates

from chapter(s) _____ in the recommended text

A. Introduction

B. Assigning *R*- and *S*-Configurations



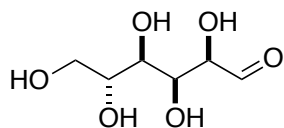


write assignments

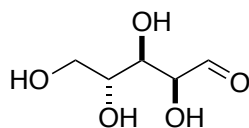
C. Stereochemical Representations Of Carbohydrates

are all used to describe compounds in this series.

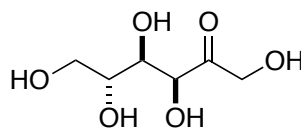
(eg **glucose**): if they contain an aldehyde they are called **aldoses**
ketoses.



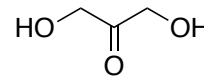
D-glucose
aldose



D-ribose
aldose

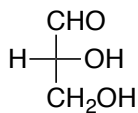


D-fructose
ketose

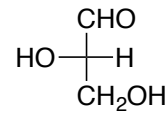


dihydroxyacetone
ketose

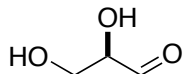
top



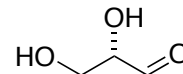
D-glyceraldehyde Fischer projection



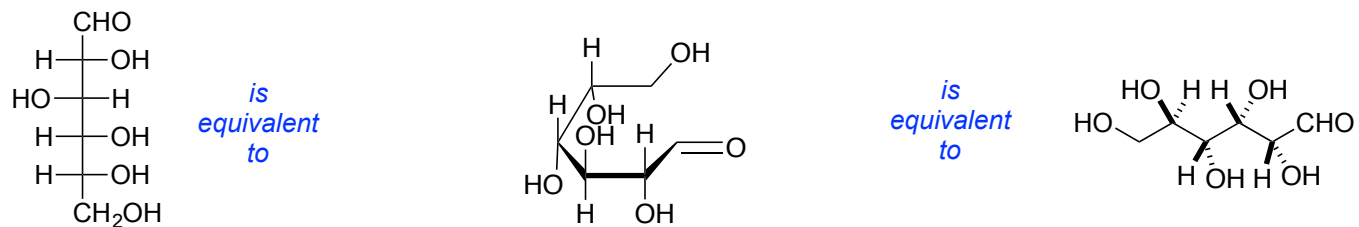
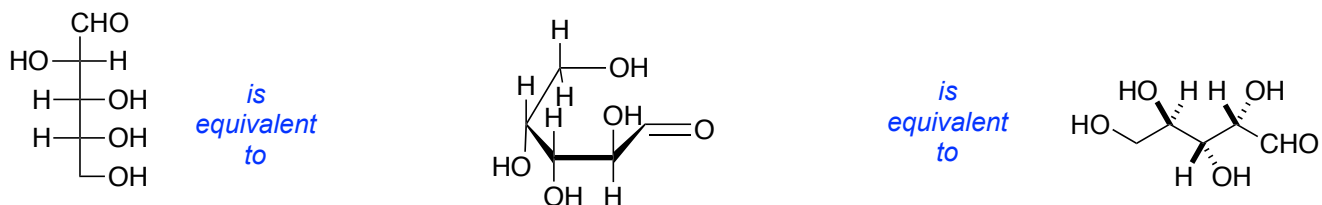
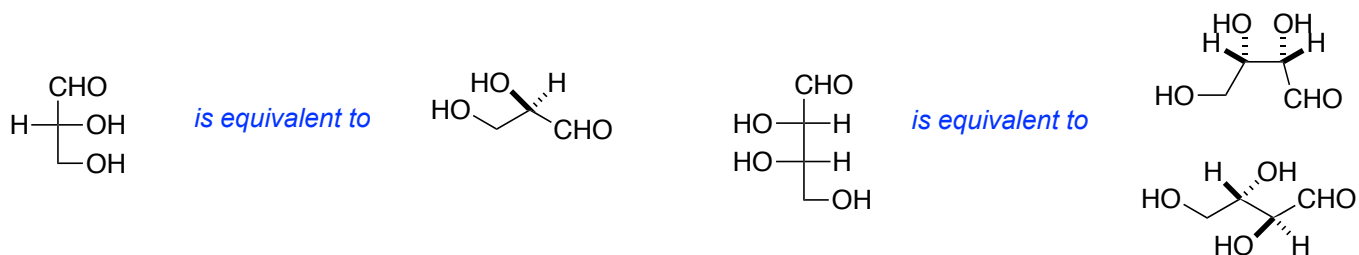
L-glyceraldehyde Fischer projection



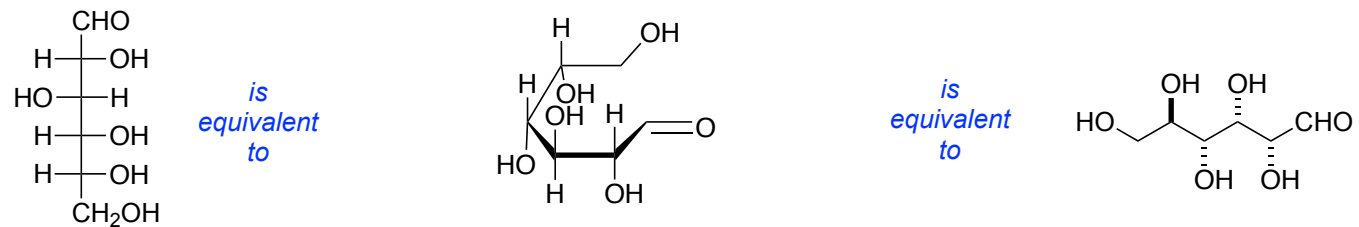
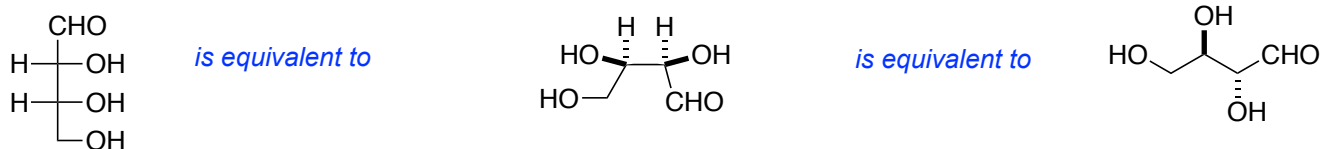
D-glyceraldehyde zig-zag



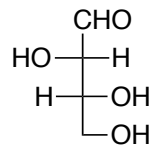
L-glyceraldehyde zig-zag

be *D*-.are *D*-.

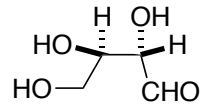
THESE ANSWERS ARE FOR THE UPDATED SECOND EDITION.



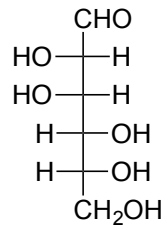
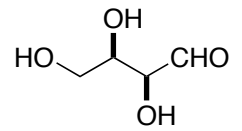
Extra examples:



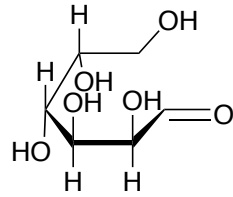
is equivalent to



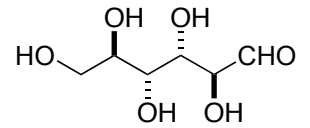
is equivalent to



*is
equivalent
to*



*is
equivalent
to*



D. Carbohydrates Can Cyclize To Hemiacetals Or Hemiketals



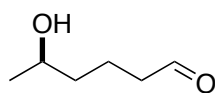
THF



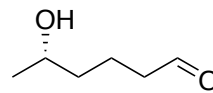
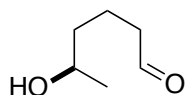
4H-pyran



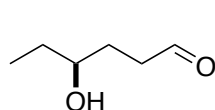
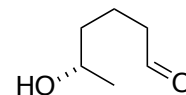
tetrahydropyran



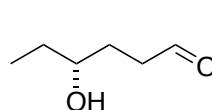
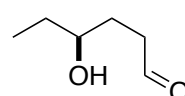
is the same as



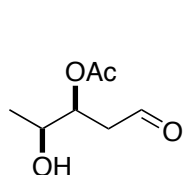
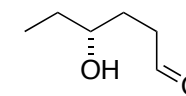
is the same as



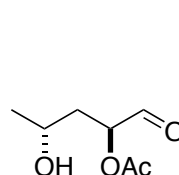
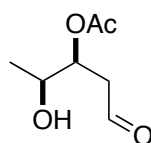
is the same as



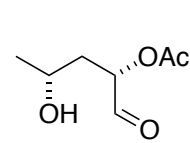
is the same as



is the same as

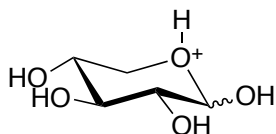
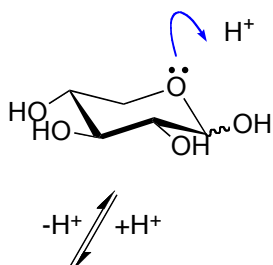


is the same as

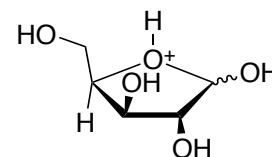
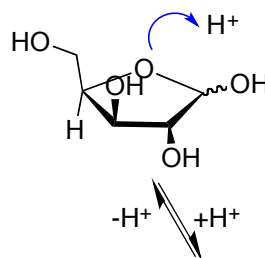


(*six*-membered ring)

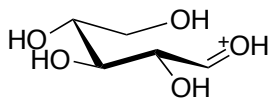
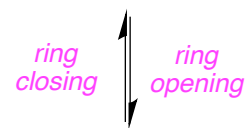
(*five*-membered ring)



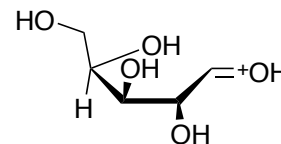
protonated pyranose form



protonated furanose form

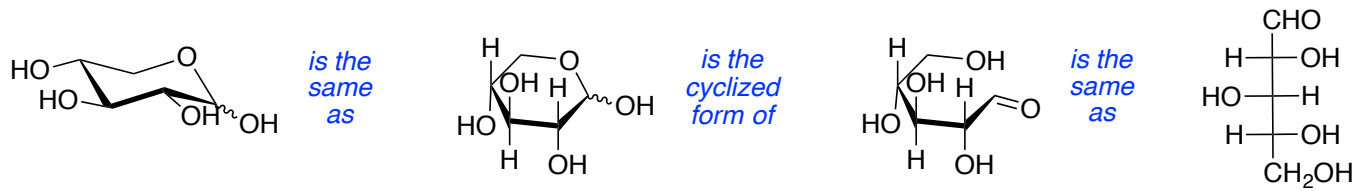
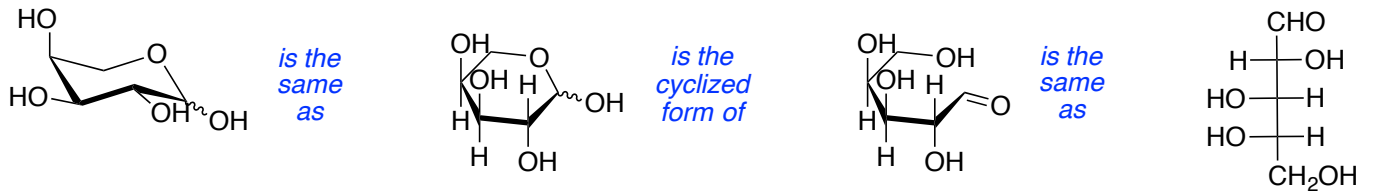


protonated aldehyde

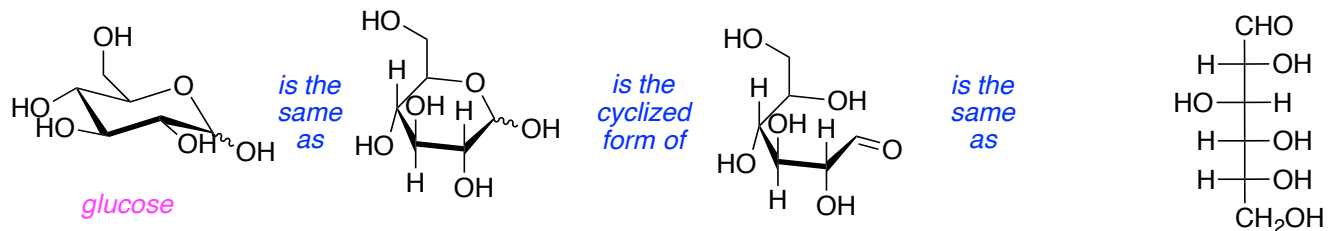


*protonated aldehyde redrawn
poised for 5-membered ring formation*

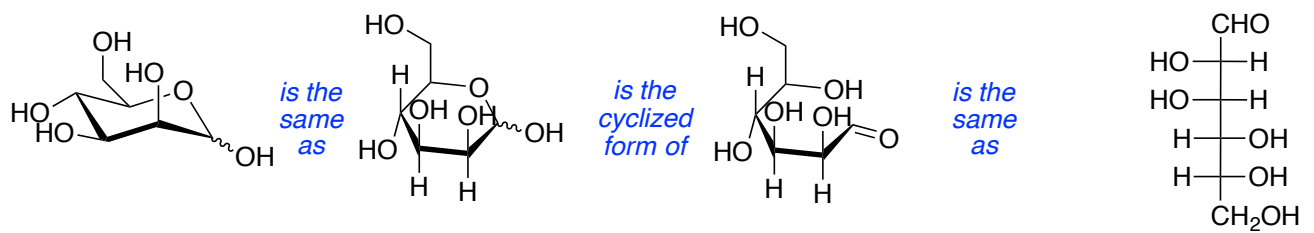
Glucose *and*

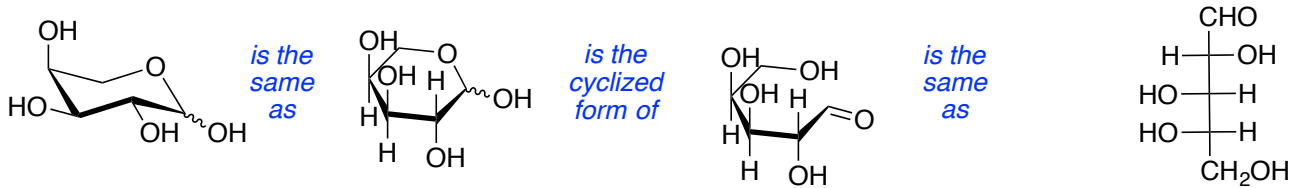
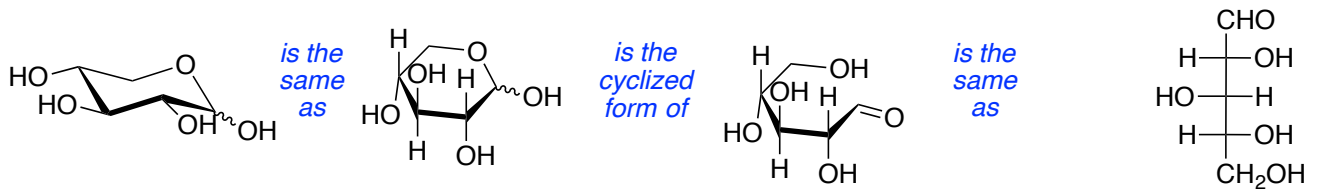
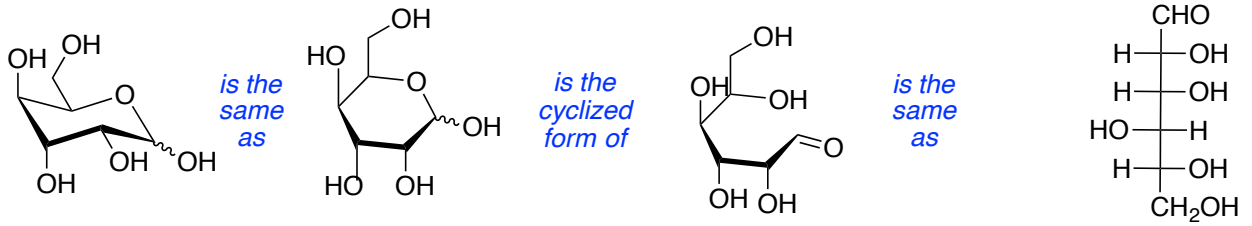


pyranose
 hexoses to Fischer projections.

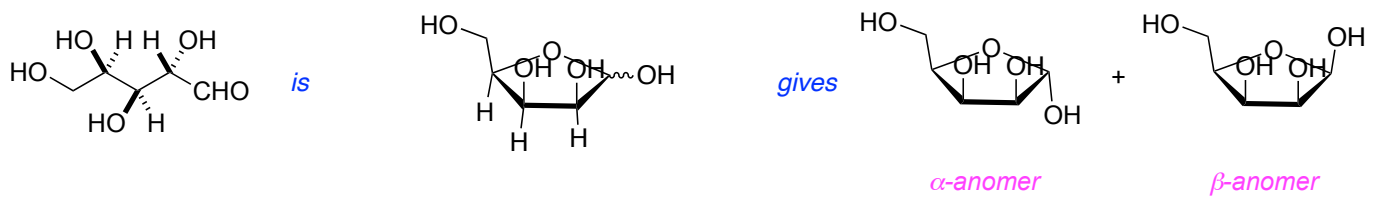


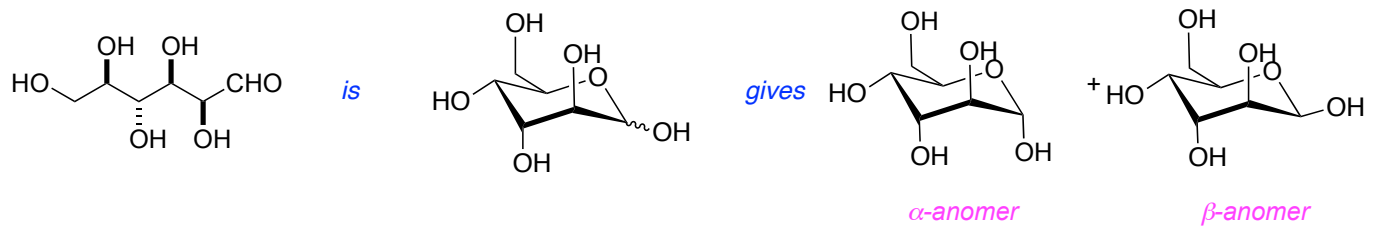
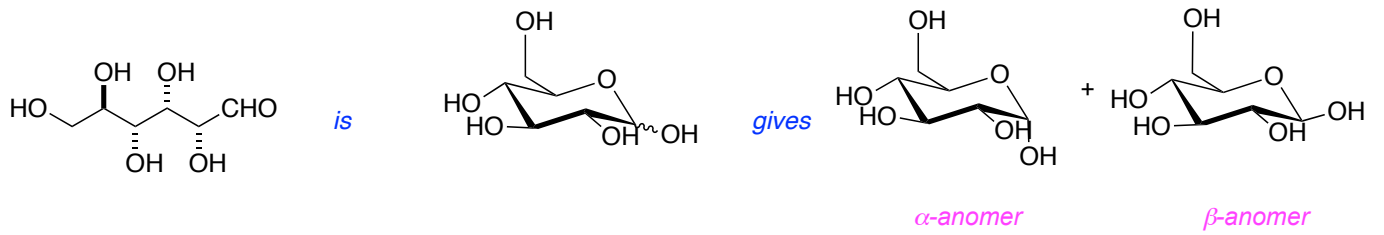
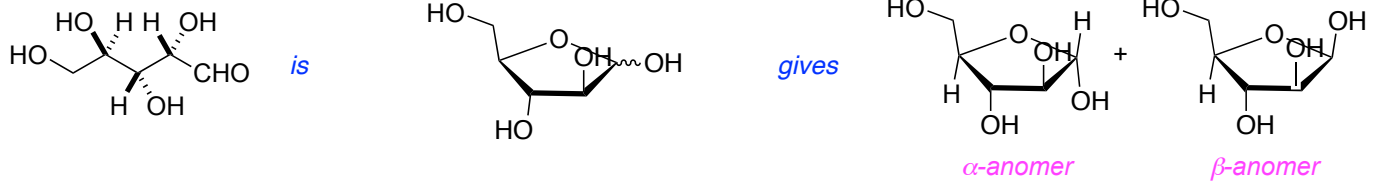
is β -.

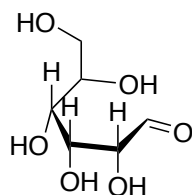
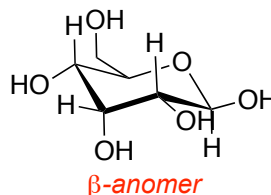
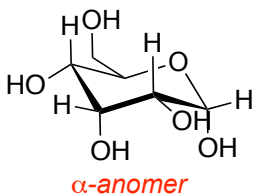
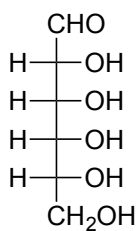




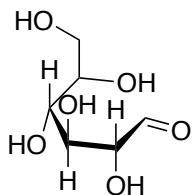
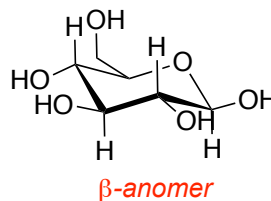
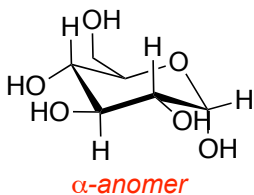
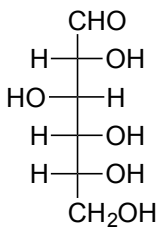
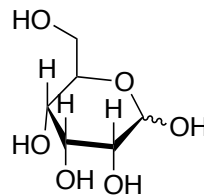
trans to the -CH₂OH



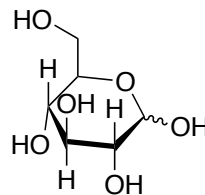


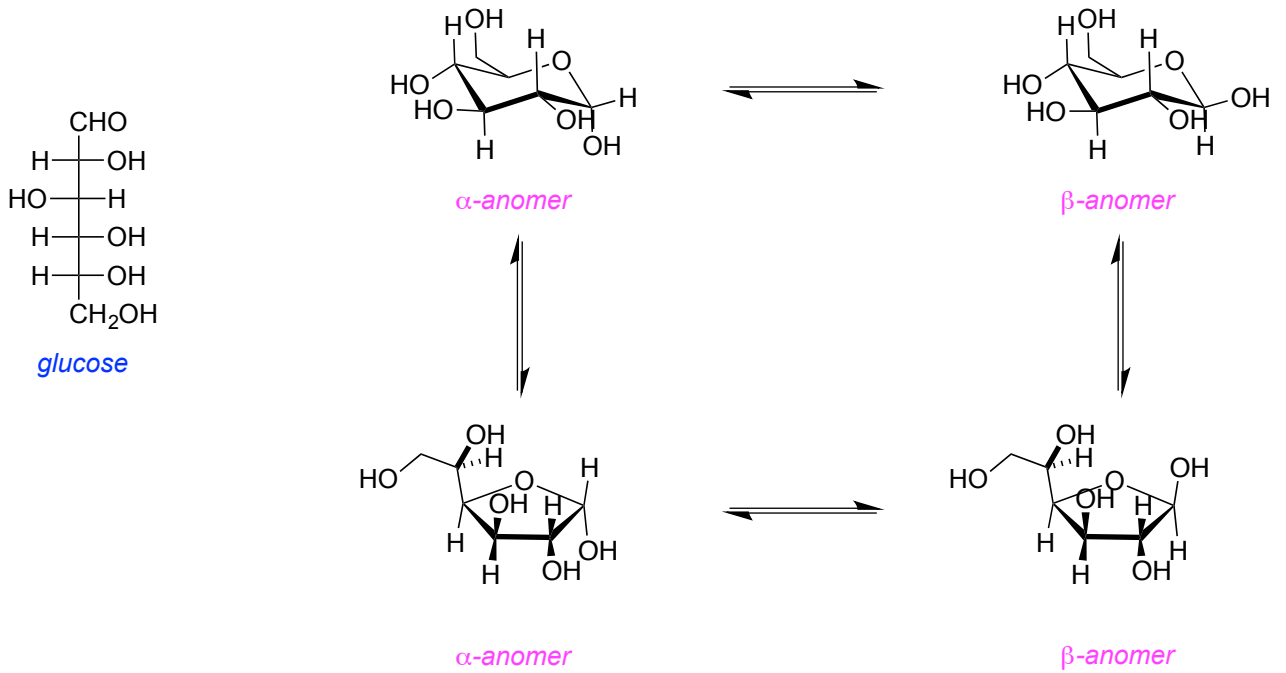


convert to the cyclized form

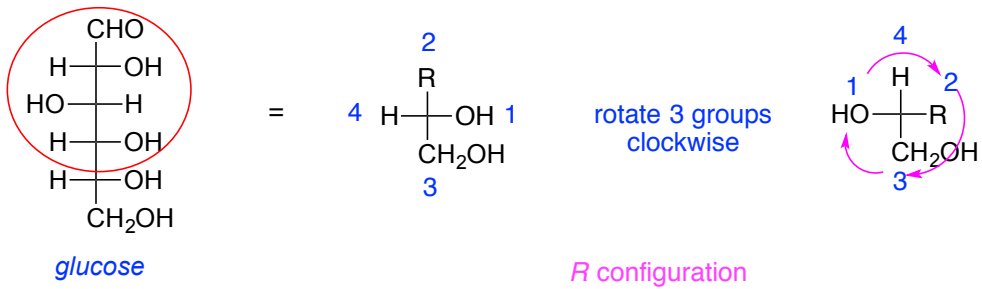


convert to the cyclized form





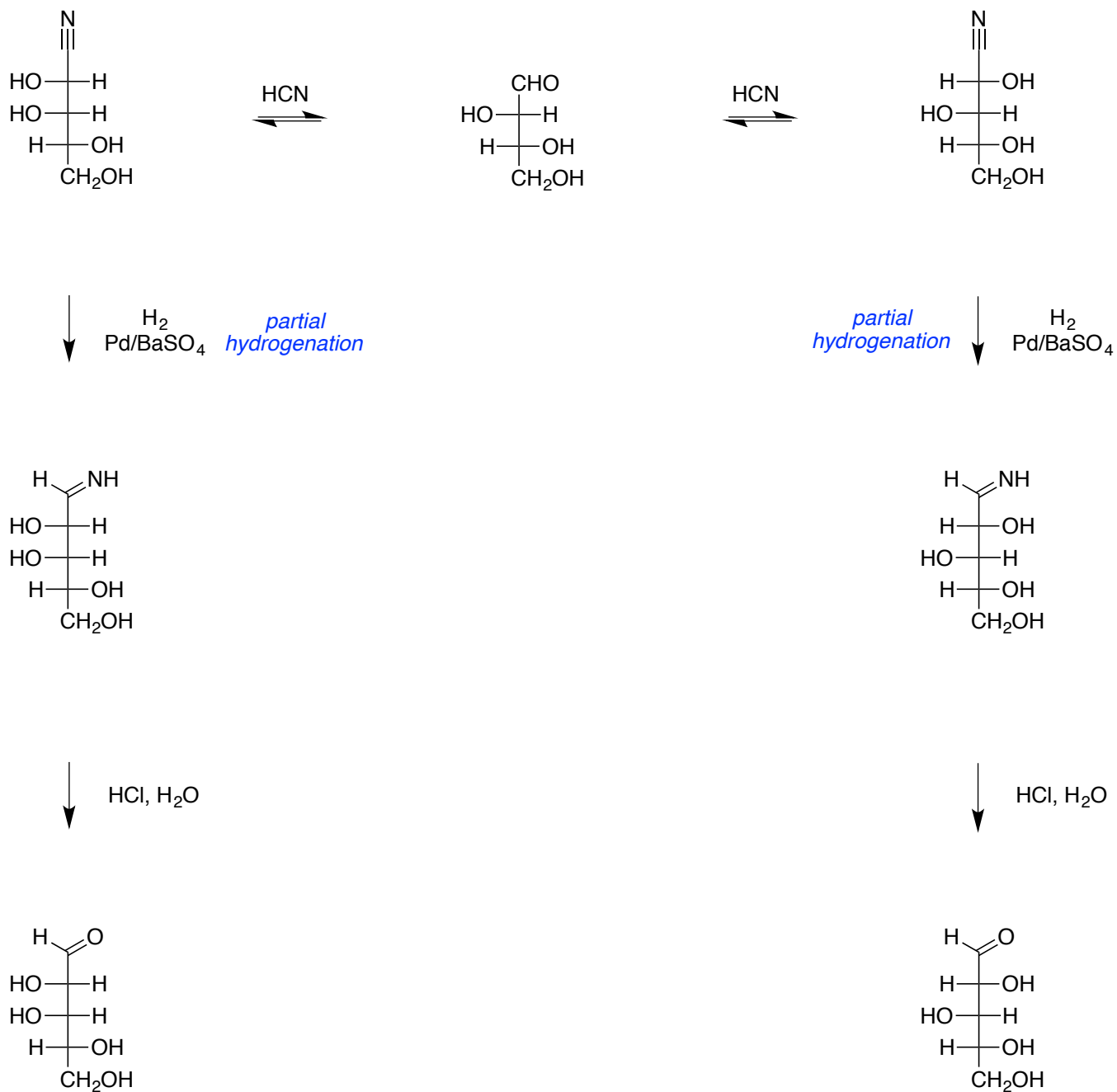
box for reasoning, write answers above



E. Homologation Of Sugars By Reaction With HCN

imines

aldoses

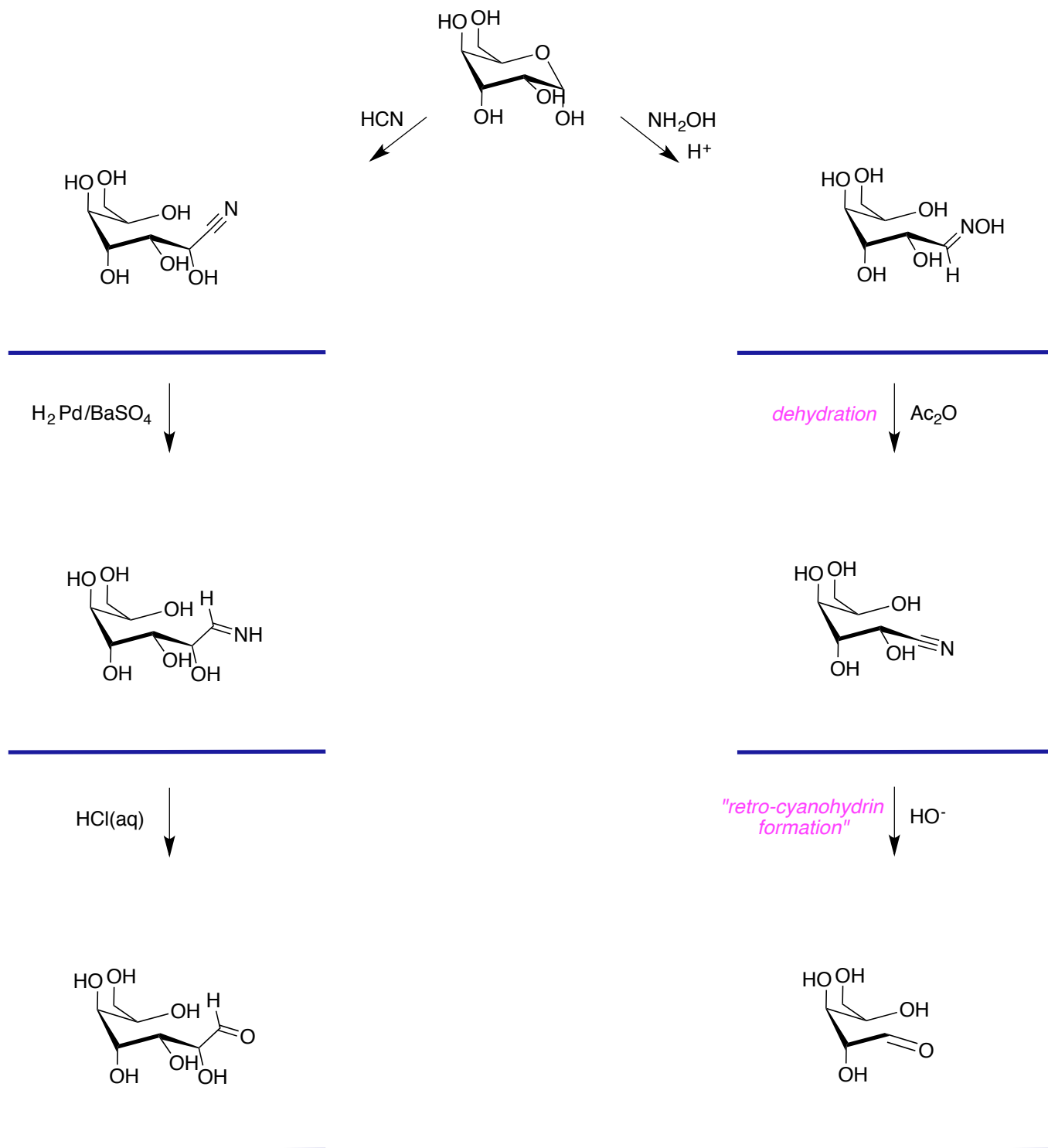


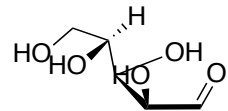
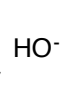
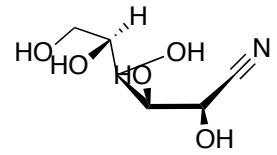
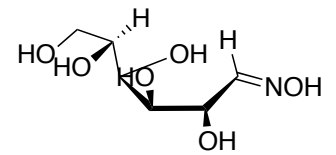
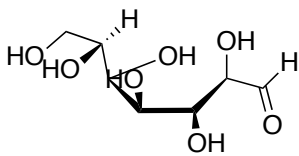
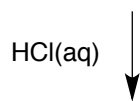
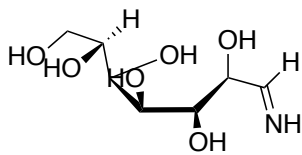
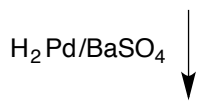
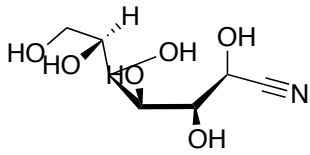
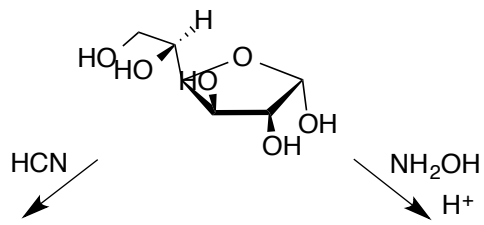
epimers

would be

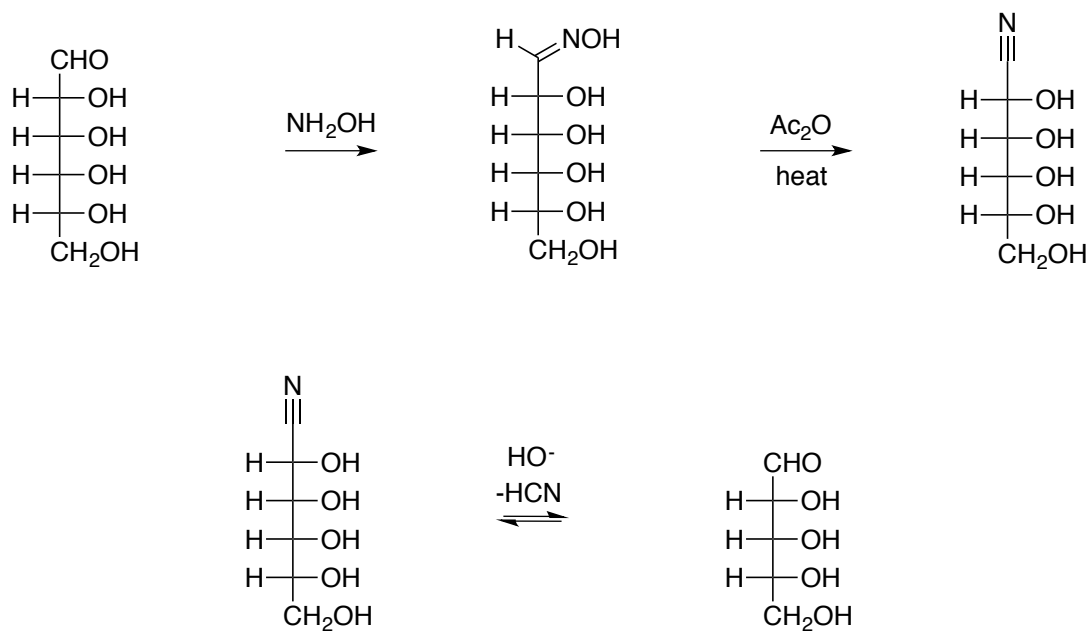
F. Conversion Of Aldoses To Lower Homologs

left
right.





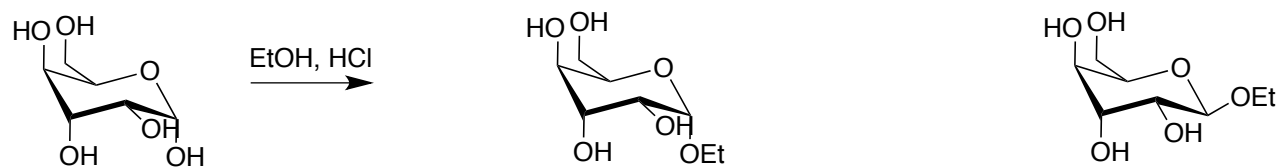
Fill in the gaps in the following sequence.



G. Other Reactions Of Sugars

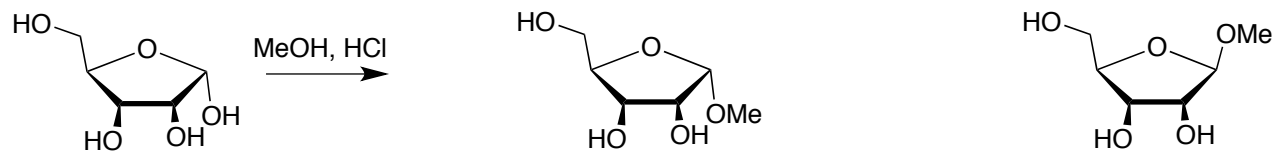
oxidized

reducing



α-anomer

β-anomer

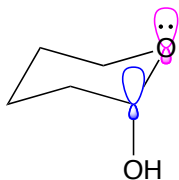


α-anomer

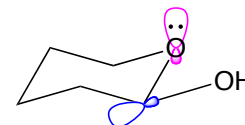
β-anomer

H. Relative Stabilities Of Anomers

axial non-bonded



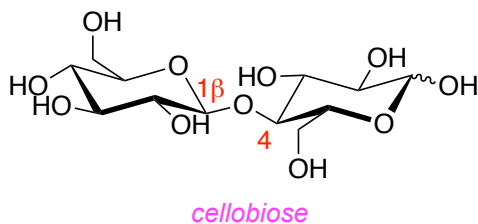
α -anomer
 σ -to- σ^* interactions possible

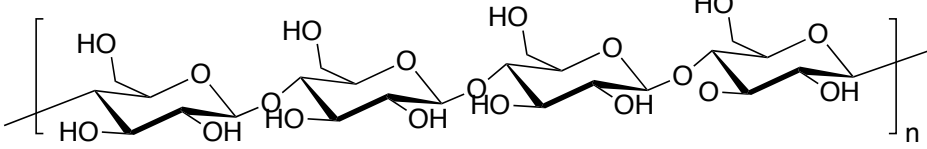
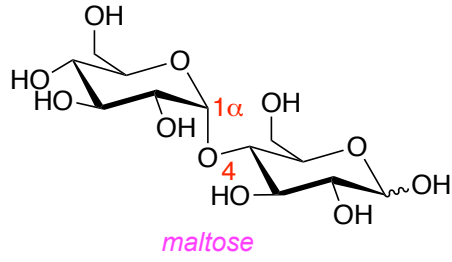


β -anomer
 σ -to- σ^* interactions impossible

I. Di- And Oligosaccharides

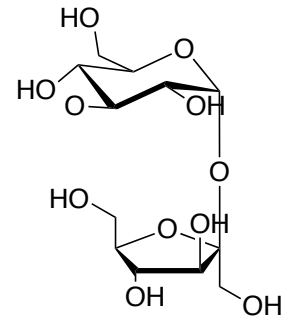
acetal or ketal





cellulose

linkages are: β -1,4

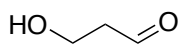


sucrose

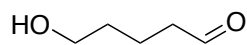
linkage is: α 1, β 2

poly-saccharide,
di-saccharide.
photosynthesis.

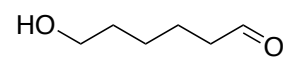
J. Carbohydrates In Summary



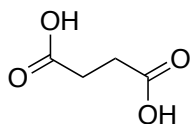
D-(+)-glyceraldehyde



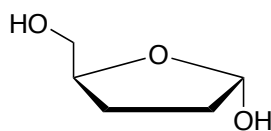
D-ribose



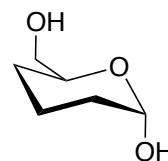
D-glucose



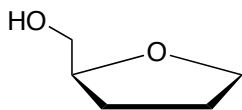
D-(-)-tartaric acid



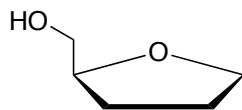
α-D-ribofuranose



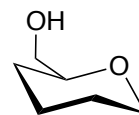
α-D-glucopyranose



β-D-2-deoxyribofuranose



β-D-ribofuranose



β-D-glucopyranose

β-D-ribofuranose.

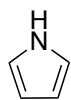
β-D-2-deoxyribofuranose.

Heterocycles In Biological Chemistry

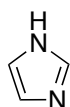
from chapter(s) _____ in the recommended text

A. Introduction

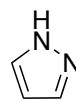
B. Names



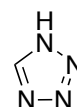
pyrrole



imidazole



pyrazole



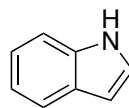
tetrazole



pyridine



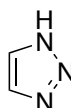
1,3-pyrimidine



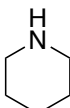
indole



thiophene



1,2,3-triazole



piperidine



pyrrolidine



aziridine



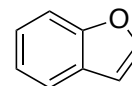
oxirane



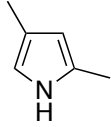
oxetane



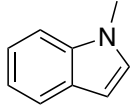
furan



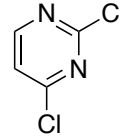
benzofuran



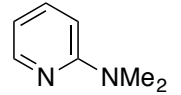
2,4-dimethylpyrrole



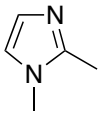
1-methylindole



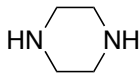
2,4-dichloropyrimidine



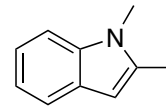
2-dimethylaminopyridine



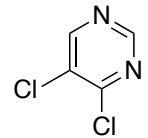
1,2-dimethylimidazole



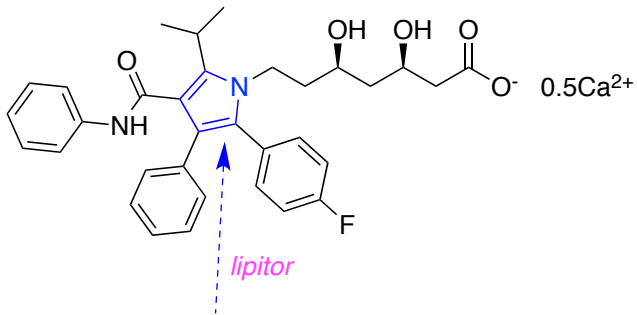
piperazine



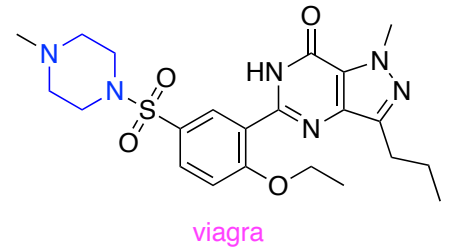
1,2-dimethylindole



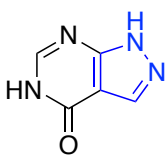
4,5-dichloropyrimidine



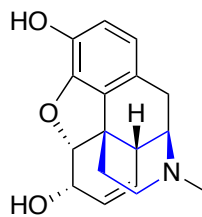
pyrrole



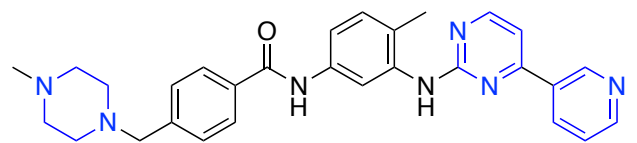
piperazine



allopurinol



morphine



piperazine and pyrimidine and pyridine

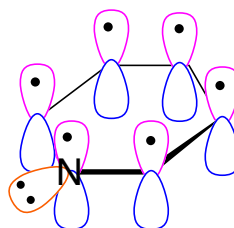
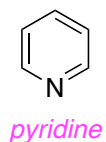
C. Aromaticity And Basicity Of Heterocycles

Pyridines And Pyrimidines

sp^2 hybridized with *a lone pair*

1 electron

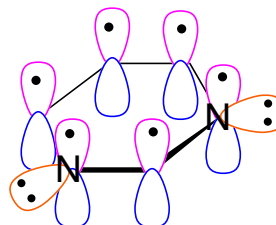
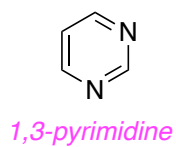
aromatic.



sp^2 hybridized with *a lone pair*

1 electron

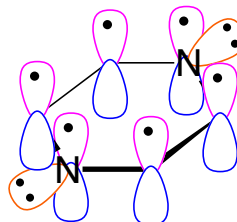
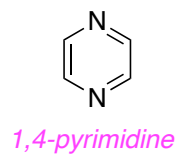
aromatic.



sp^2 hybridized with *a lone pair*

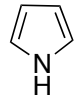
1 electron

aromatic.

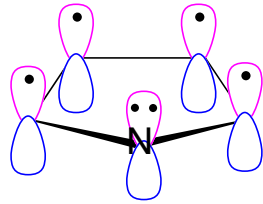


Pyrrole

sp^2 hybridized with 0
can
aromatic.

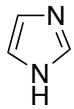


pyrrole

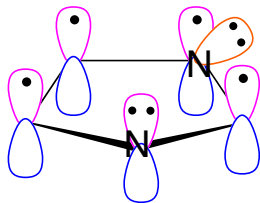


Imidazole

can
are both sp^2 hybridized, and one
is



imidazole

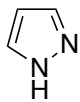


does influence

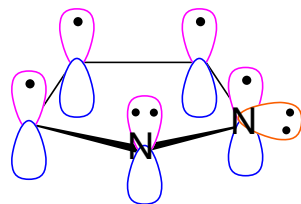
Pyrazole

cannot
are
one

Pyrazole is



pyrazole



aromatic stabilization.

1,3,4-Oxadiazole

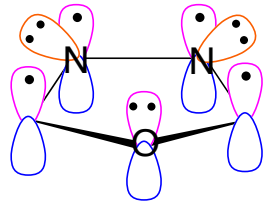
sp^2 hybridized and each contributes 1

sp^2 hybridized and contributes 2

aromatic.

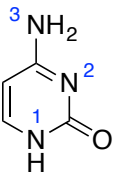


1,3,4-oxadiazole



does not
good base
is not lost.

Heterocycles In Nature

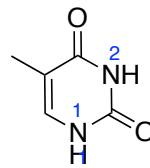


cytosine

$N^3: 0$

$N^2: 1$

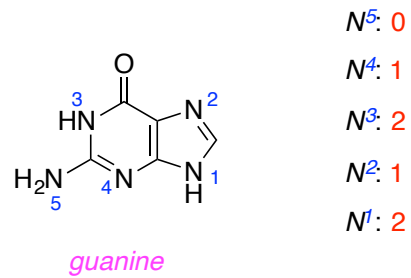
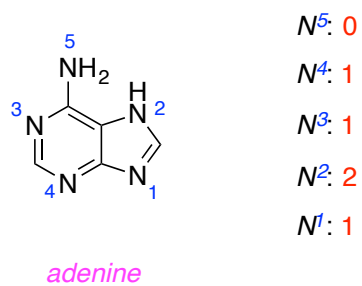
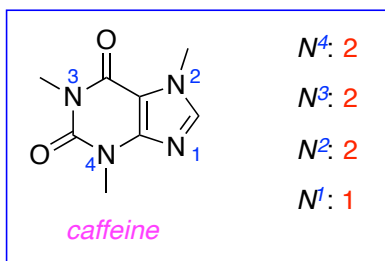
$N^1: 2$



thymine

$N^2: 2$

$N^1: 2$

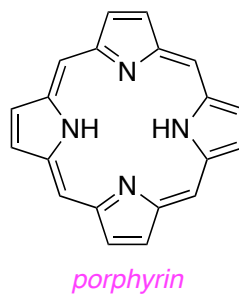


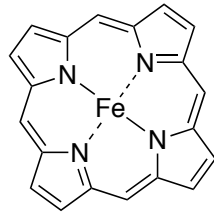
2 pyridine-like nitrogen atoms, 2

26 π -electrons

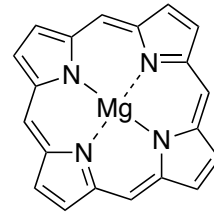
are aromatic.

2





Fe²⁺ complex overall charge 0



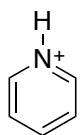
Mg²⁺ complex overall charge 0

Hemoglobin

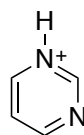
chlorophyll

): strongly UV absorbing / fluorescent / capable of redox chemistry.

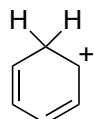
Aromatic Characteristics Of Protonated Heterocycles



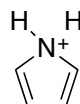
aromatic because it has
6 πe^- .



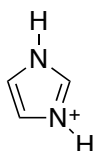
aromatic because it has
6 πe^- .



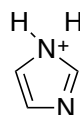
not aromatic because it has
4 πe^- .



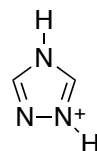
not aromatic because it has
4 πe^- .



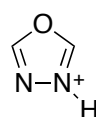
aromatic because it has
6 πe^- .



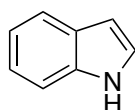
not aromatic because it has
4 πe^- .



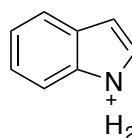
aromatic because it has
6 πe^- .



aromatic because it has
6 πe^- .



aromatic because it has
10 πe^- .

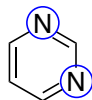


not aromatic because it has
8 πe^- .

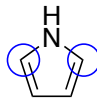
C³



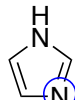
pyridine



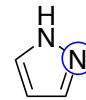
pyrimidine



pyrrole



imidazole



pyrrazole



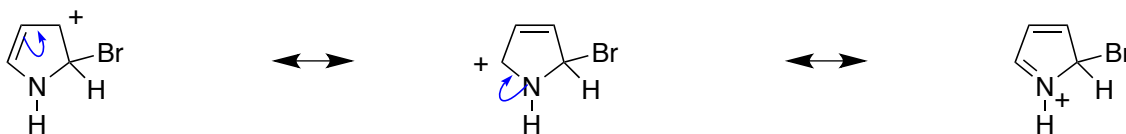
oxazole

D. Electrophilic Attack On Pyrrole And Indole Compared

Pyrrole

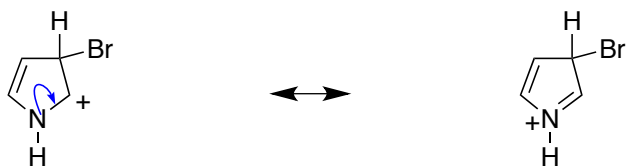
low

in the 2-position



complete diagrams and show arrows

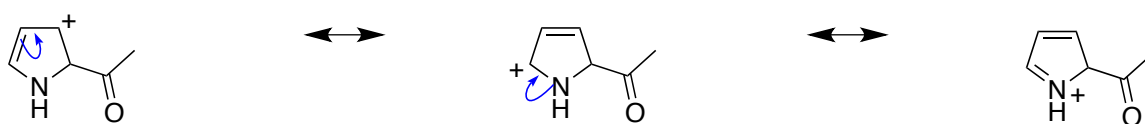
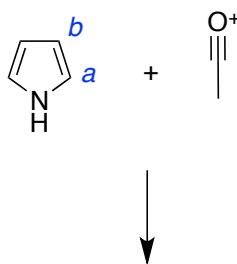
in the 3 position



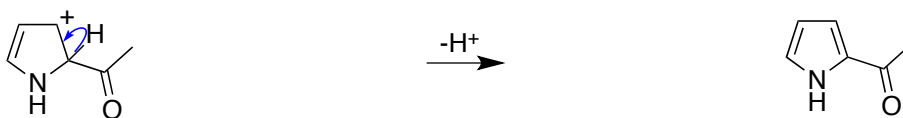
complete diagrams and show arrows

*2-position
thermodynamic*

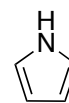
Hammond's postulate.



choose correct regiochemistry, show resonance structures, and electron flow that relates them using curly arrows



more electron rich than benzene, hence it reacts faster

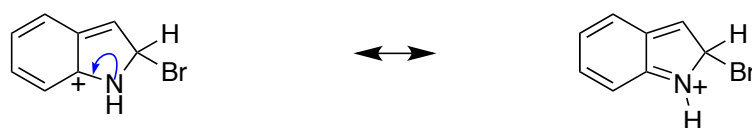
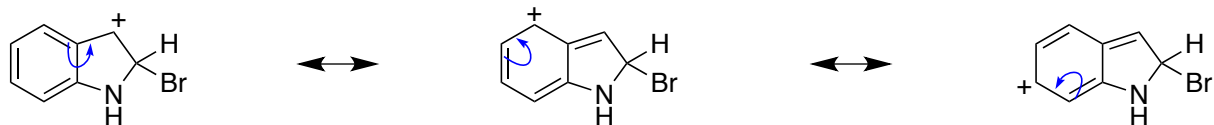


least reactive

most reactive

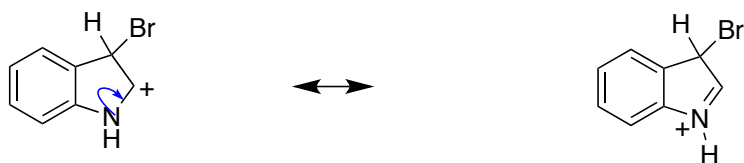
Indole

in the 2-position



*donation of the N-lone pair
does
disrupt aromaticity of the
benzene ring*

in the 3 position



*donation of the N-lone pair
need not
disrupt aromaticity of the
benzene ring*

3-position

because the positive charge can be delocalized onto the nitrogen without disrupting the aromaticity of the benzene, whereas for attack at the 2-position the aromaticity of the benzene must always be disrupted.

Nucleosides And Nucleotides

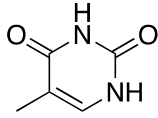
from chapter(s) _____ in the recommended text

A. Introduction

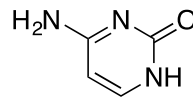
B. Nucleosides



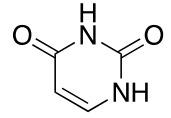
pyrimidine



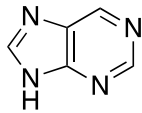
thymine
DNA



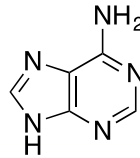
cytosine
both



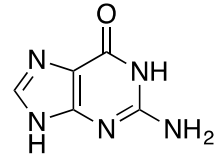
uracil
RNA



purine

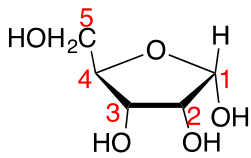


adenine
both

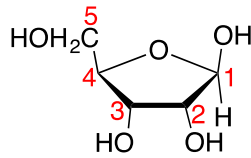


guanine
both

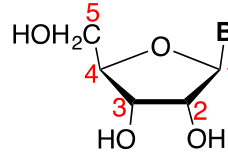
ribose in a *furanose*
β-anomer.
β-anomers.



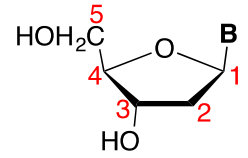
α-D-ribofuranose



β-D-ribofuranose



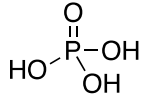
generic RNA



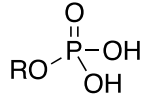
generic DNA

C. Nucleotides

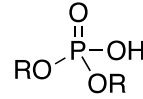
without a phosphate
phosphate esters.



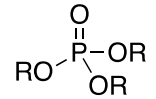
phosphoric
acid



phosphomonoester



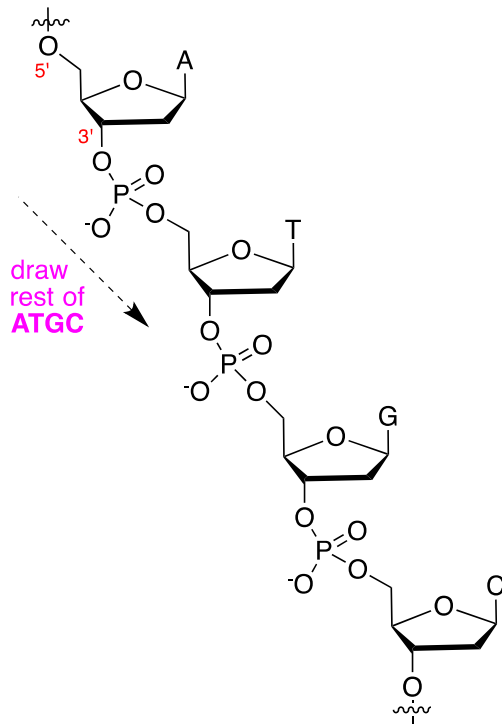
phosphodiester



phosphotriester

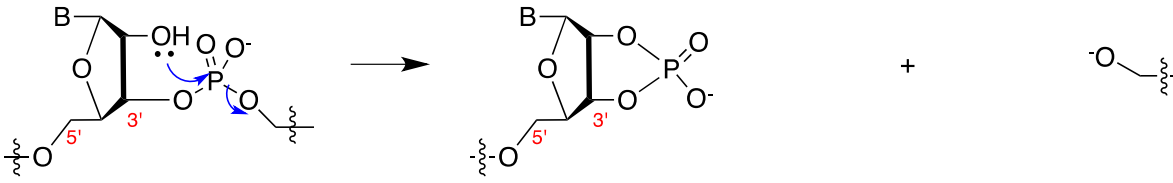
di-esters.

di-esters.



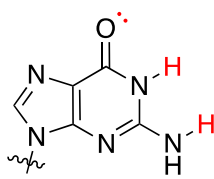
a different
3'- end.
the sugar part.
are not

RNA is *less*



2'-OH.

transcribed
translated



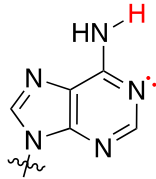
G

H-bond donors:

2

H-bond acc's:

1



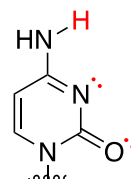
A

H-bond donors:

1

H-bond acc's:

1



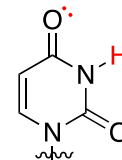
C

H-bond donors:

1

H-bond acc's:

2



U

H-bond donors:

1

H-bond acc's:

1

refers to H-bond acceptors and donors, as indicated in structure

C in DNA

C in RNA

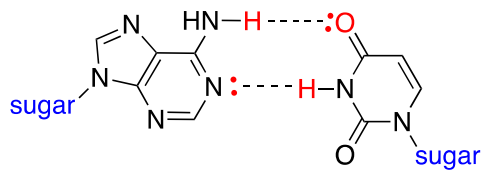
T in DNA

U in RNA

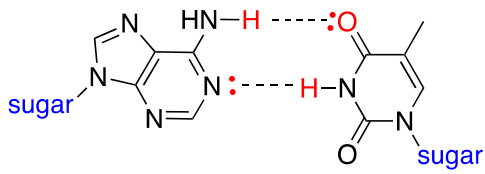
G in DNA

G in RNA

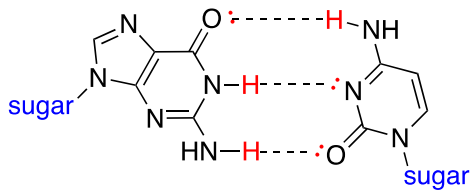
A in DNA



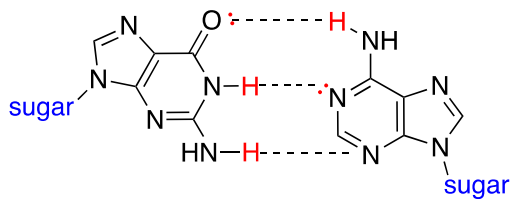
A H-bonded to U



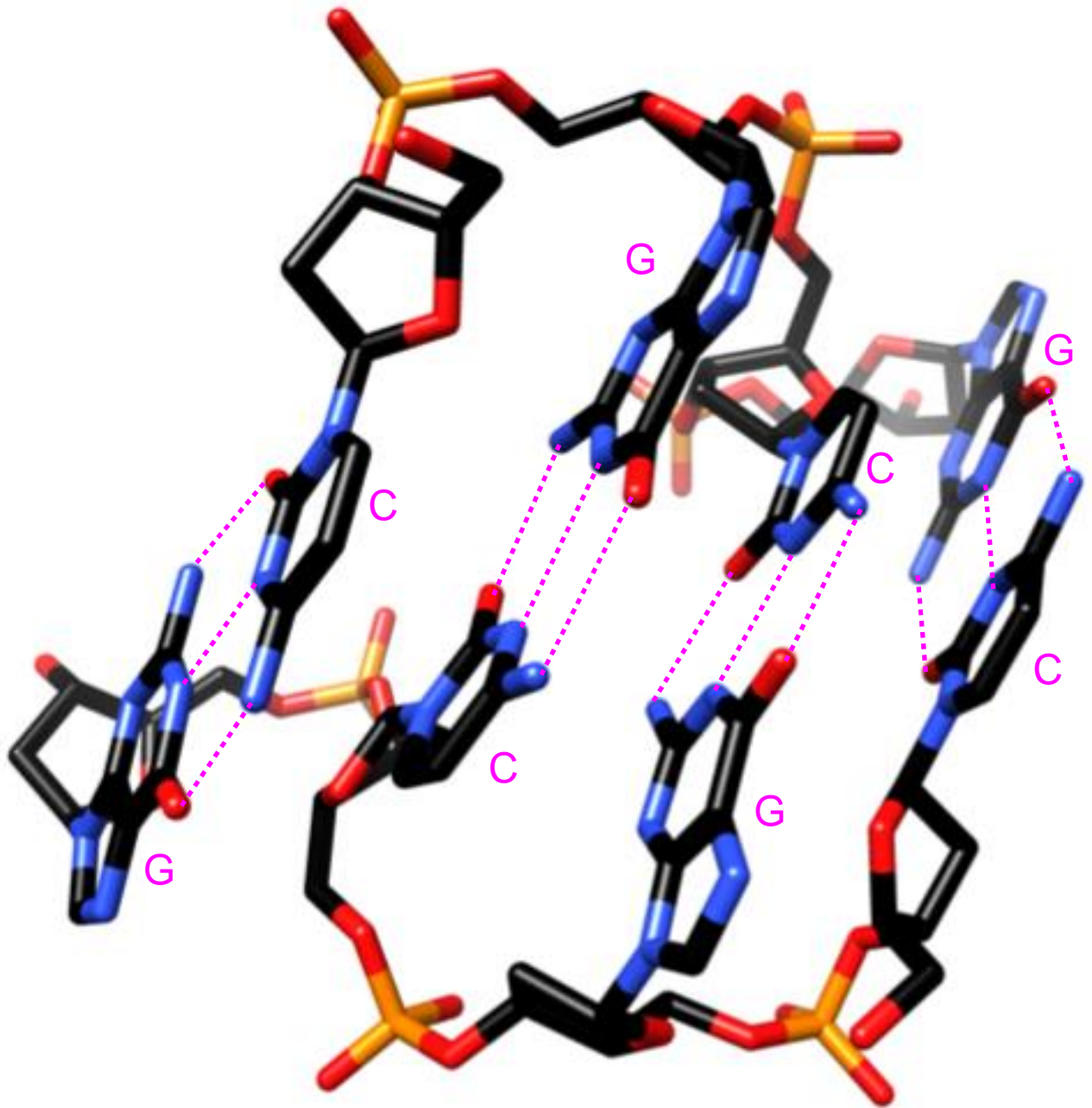
A H-bonded to T



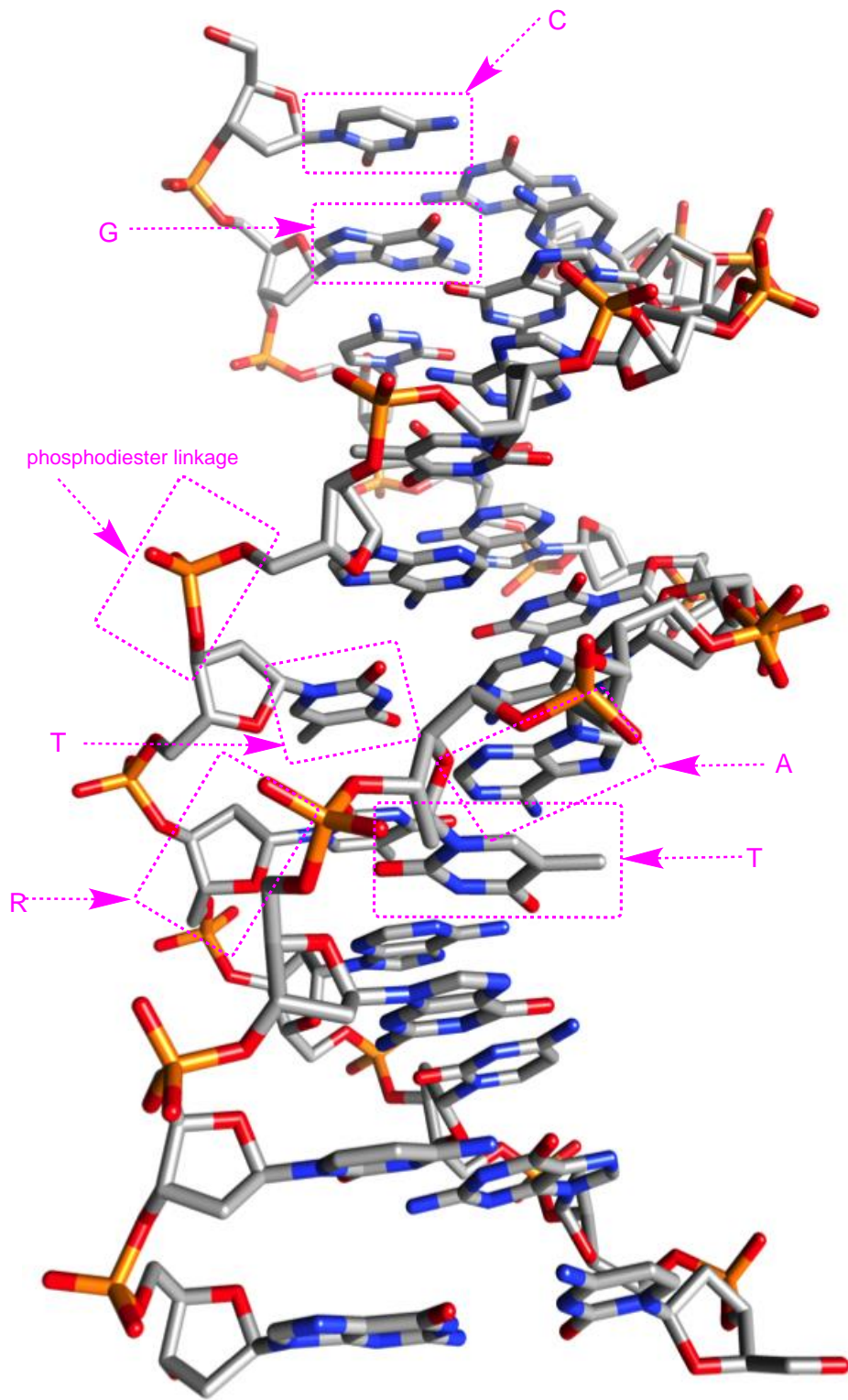
G H-bonded to C



*G H-bonded to A
does not match well*



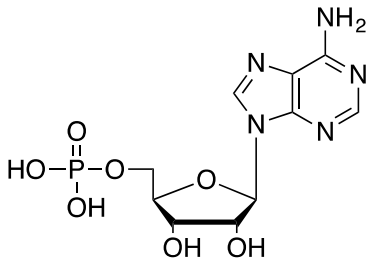
weaker
less



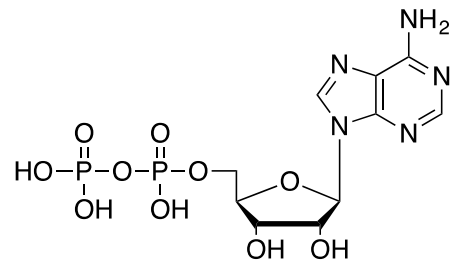
phosphodiester
nucleobases

C into **U**
right
the same as
less

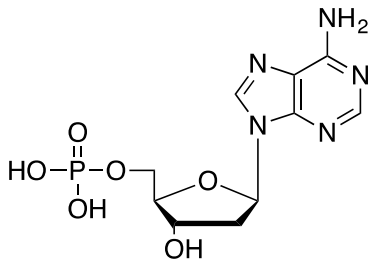
DNA
RNA.



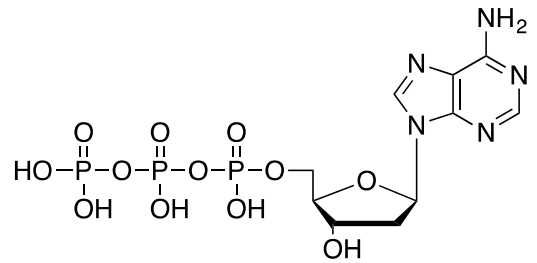
AMP



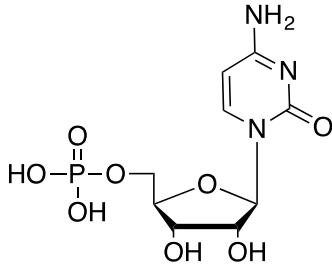
ADP



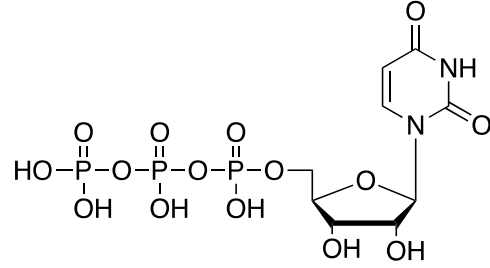
dAMP



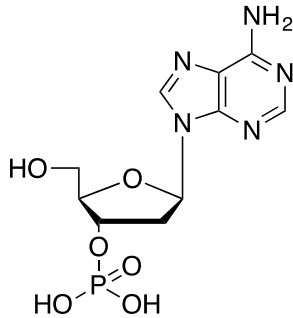
dATP



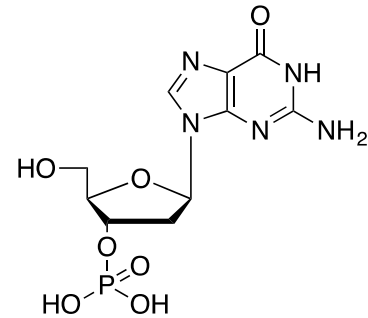
CMP



UTP



*2-deoxyadenosine
3'-monophosphate*



*2-deoxyguanosine
3'-monophosphate*

polymerases.

antiparallel

3'-end of the growing strand.

A *di*-phosphate

promoter

promoting

messenger RNA.

Ha! Caught you looking unnecessarily! codons.

Exon

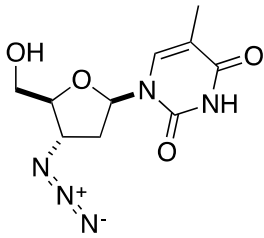
introns.

splicing.

transfer messenger

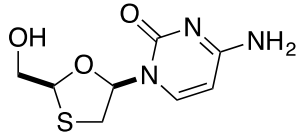
D. Nucleoside Drugs

*DNA
arresting*



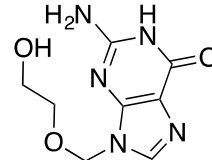
Zidovudine

treatment of HIV



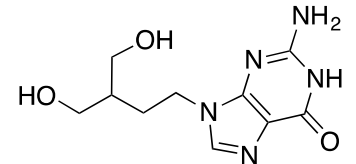
Lamivudine

treatment of HIV



Acyclovir

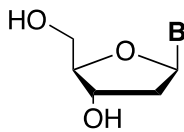
treatment of herpes



Penciclovir

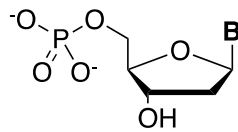
treatment of herpes

*nucleotide triphosphates.
kinase*



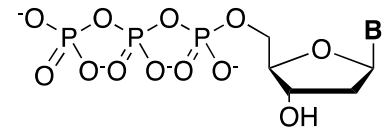
*cell permeability
likely*

kinase →



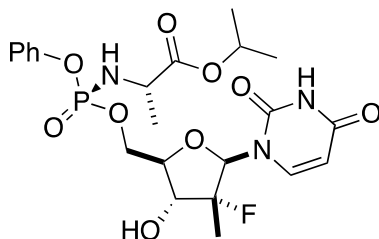
*cell permeability
unlikely*

kinase →



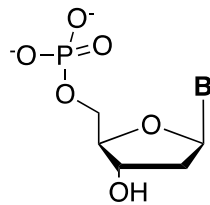
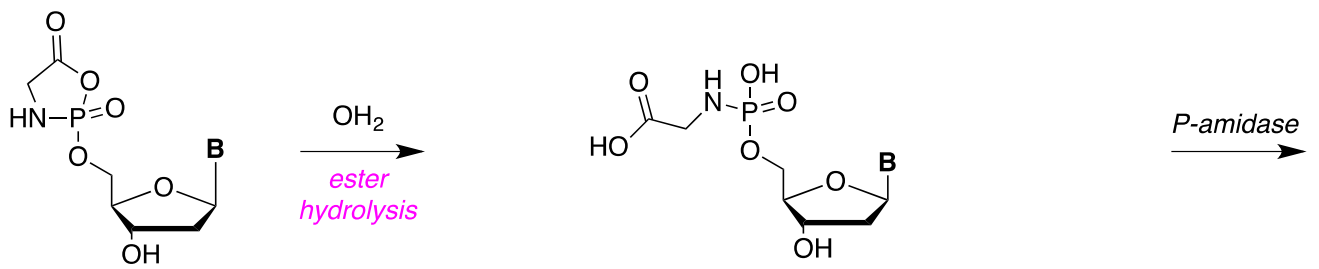
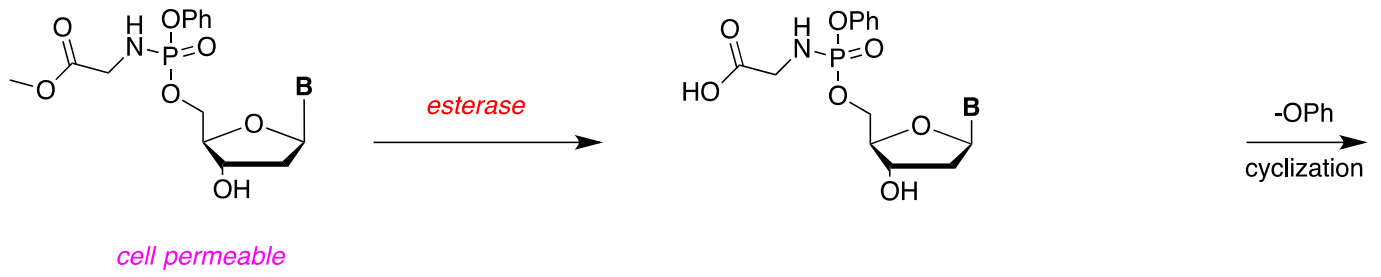
*cell permeability
unlikely*

*mono-
negatively
do not
do not*



*Sofosbuvir
treatment of hepatitis C*

Nucleotide Prodrugs
*neutral charged, cell
prodrug
ProTides.*

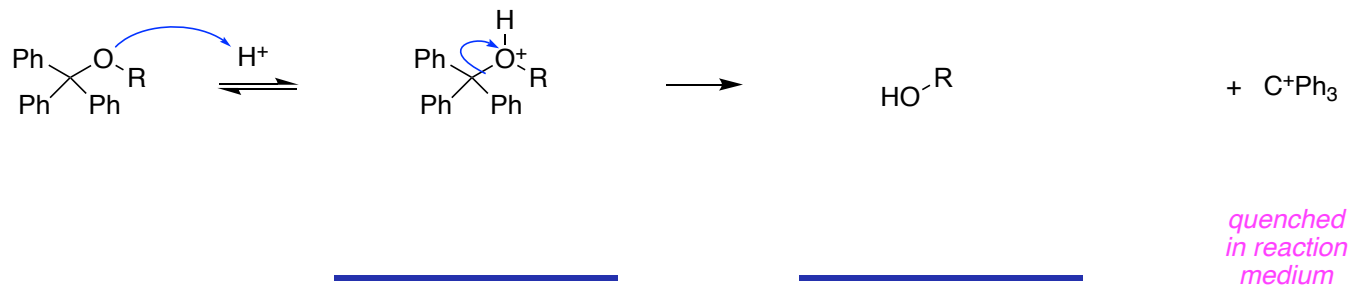


DNA Synthesis And Sequencing

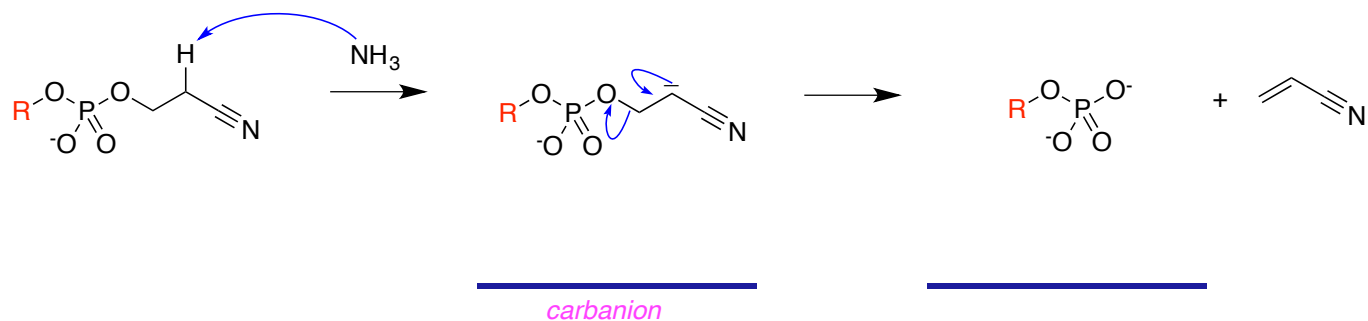
from chapter(s) _____ in the recommended text

A. Introduction

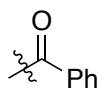
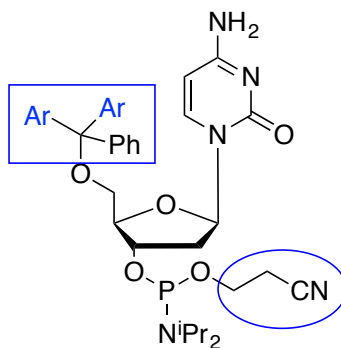
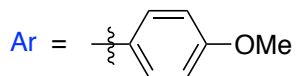
B. Chemical Synthesis Of DNA



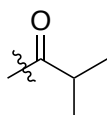
*S_N1
easier
more*



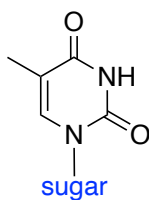
This is an *E1cb*



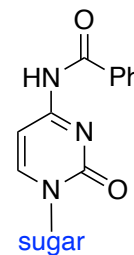
benzoyl
Bz



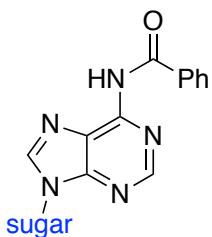
iso-butryl
COⁱBu



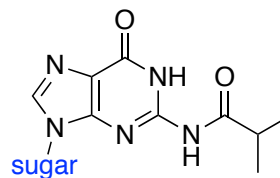
no protection
required



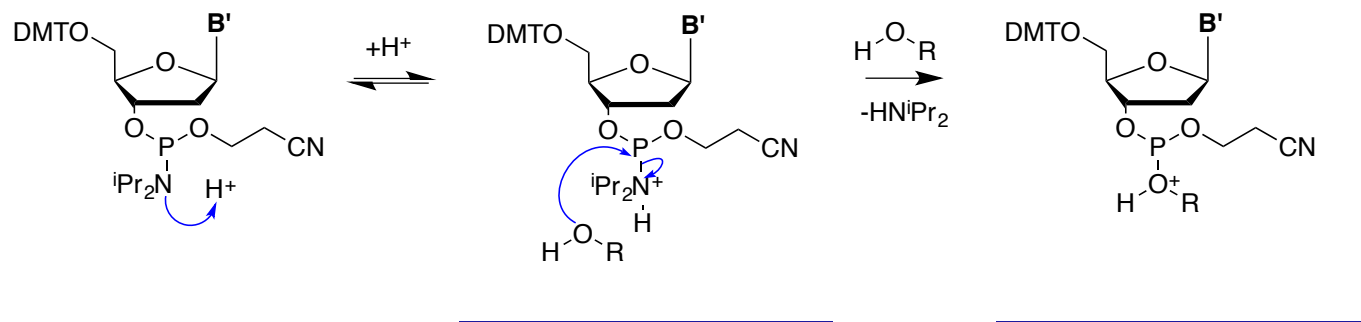
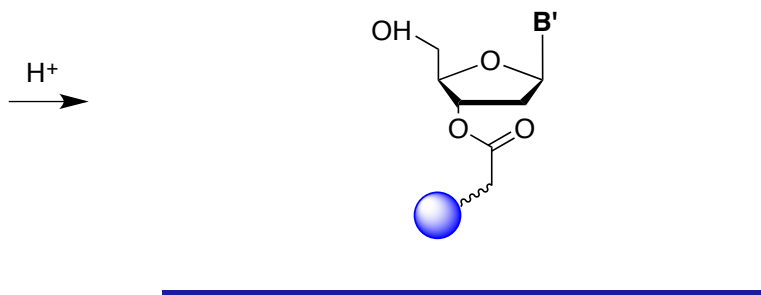
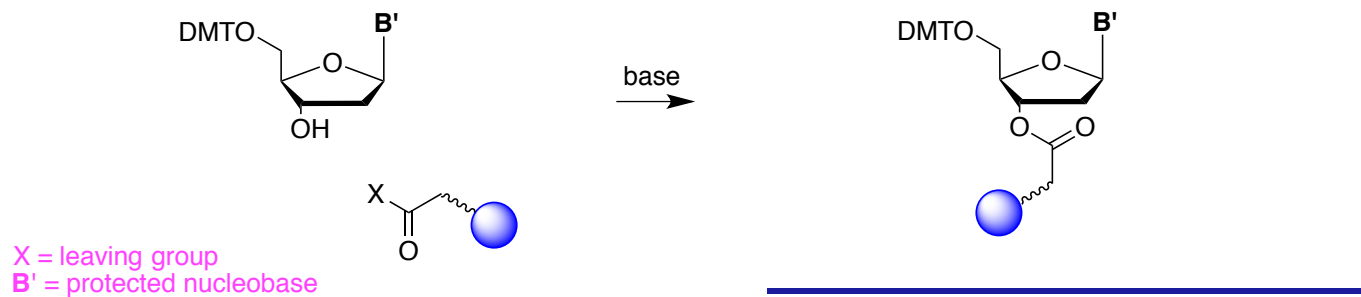
N-Bz C



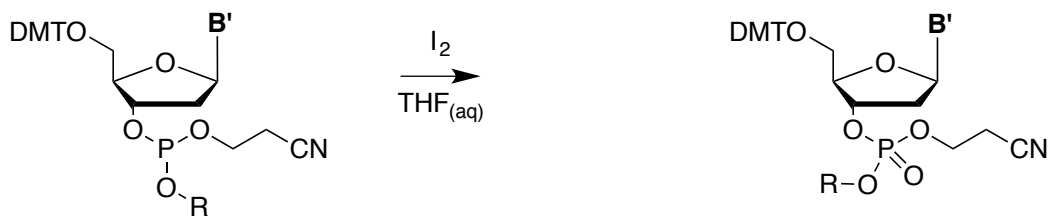
N-Bz A



N-iso-butryl G



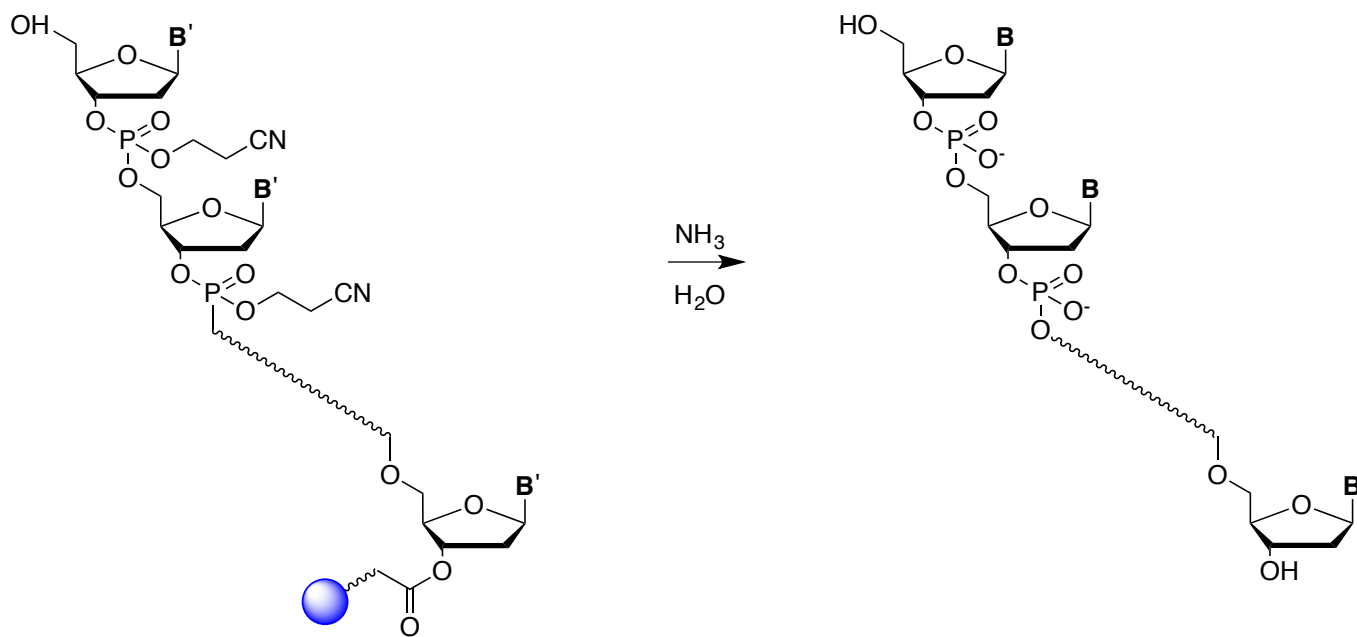
Tetrazole
oxidation

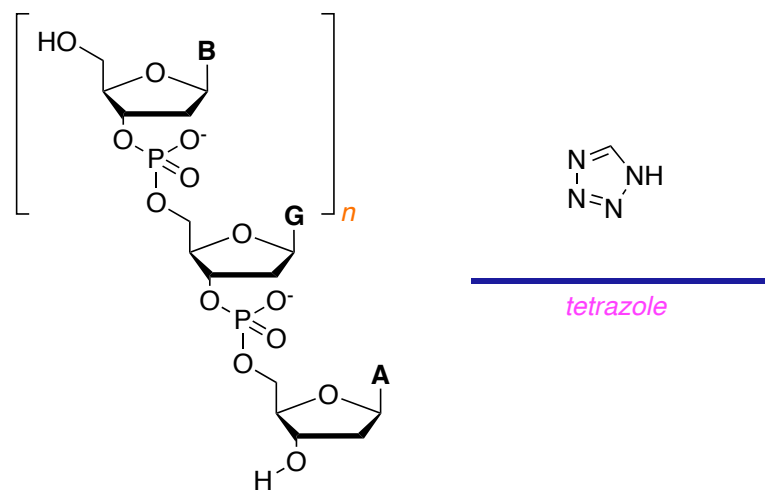
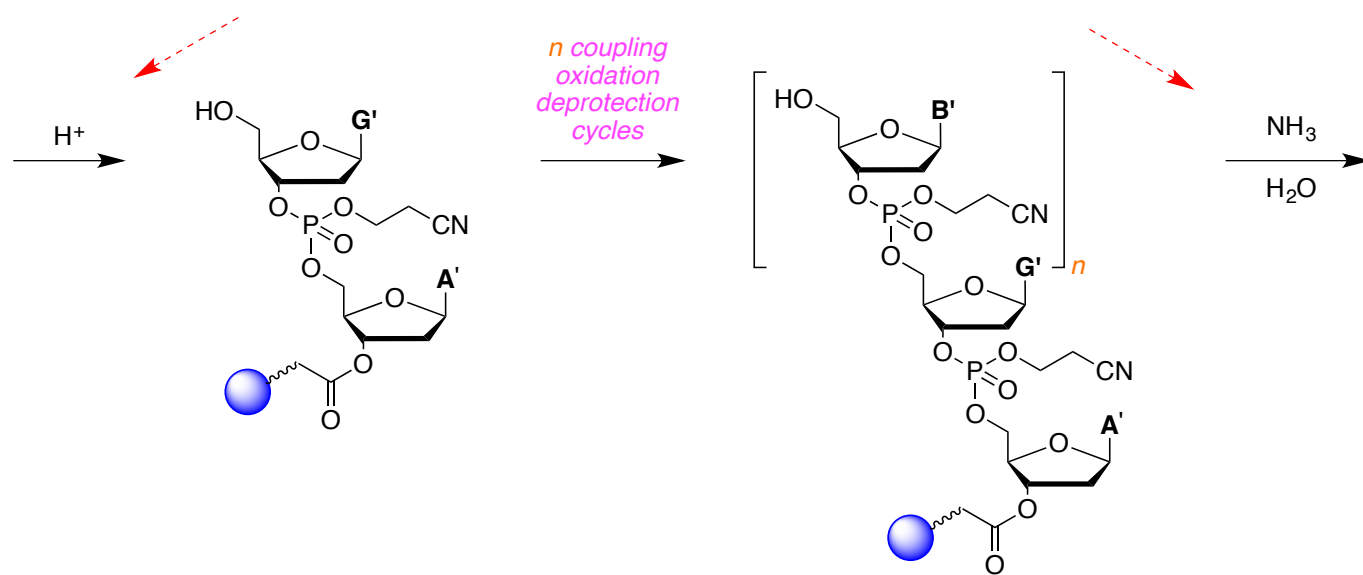
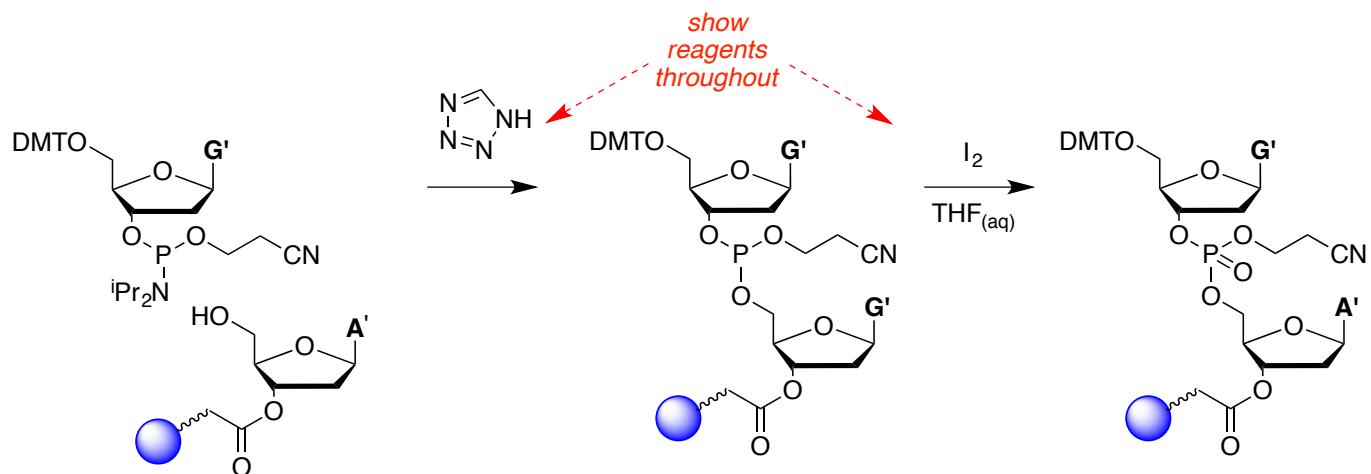


phosphotriester

3,
5.

also removes

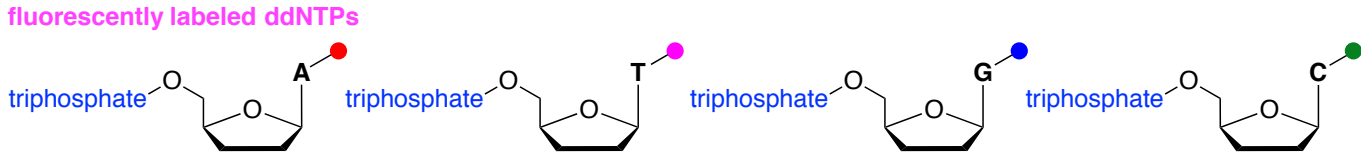
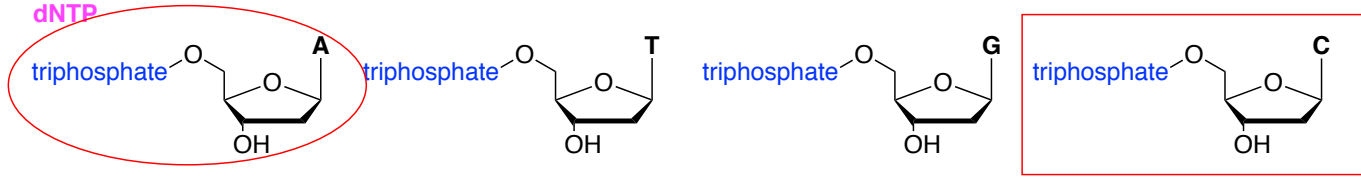




C. DNA Sequencing

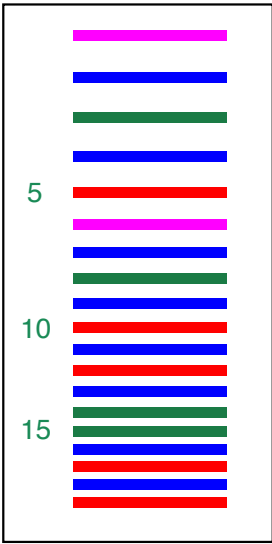
Sanger's Method

primer
template.



G
cannot

increasing size
↓



only one.

can
can

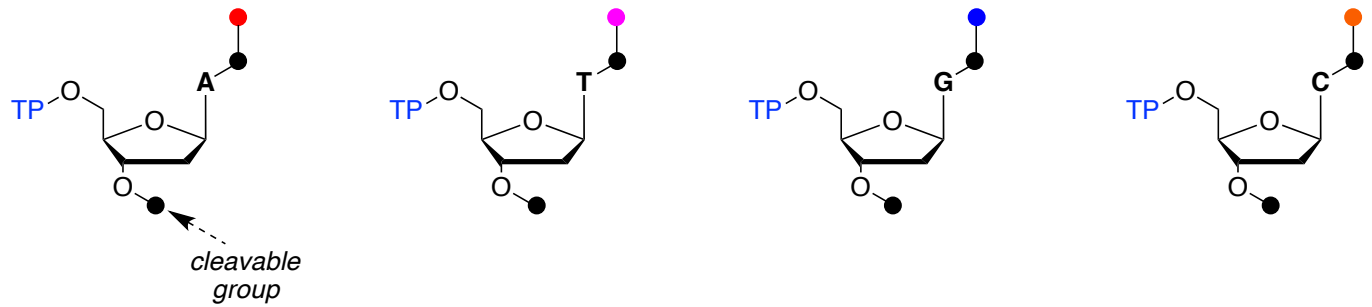
5'-TGCGATGCGAGAGCCGAGA-3'

5'-TCTCGGCTCTCGCATCGCA-3'

Sequencing By Synthesis

higher

fluorescently labeled, blocked, dNTPs



*would not
could*

would

Sanger.

*different
different*

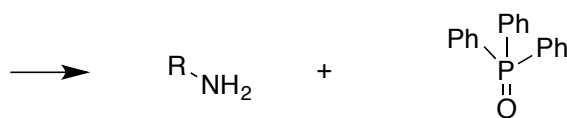
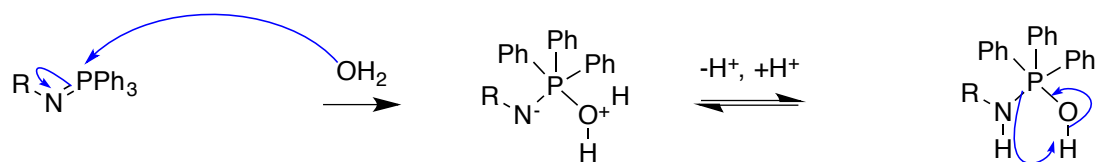
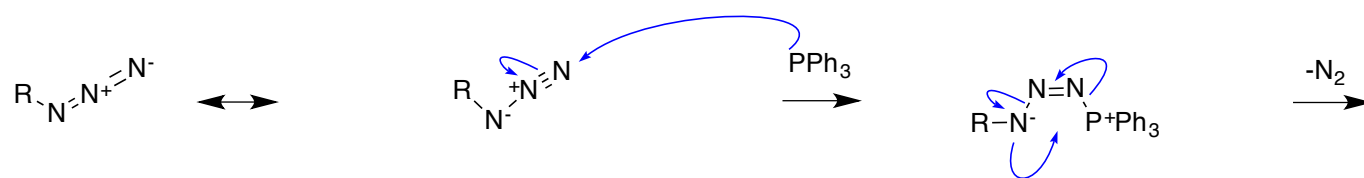
*y x n
more*

Reduction Of Azides By Phosphines And Azidomethyl Protection

remains annealed

gentle.

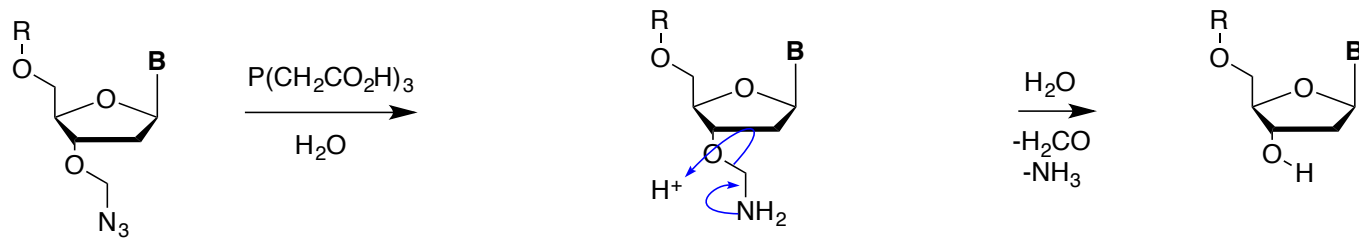
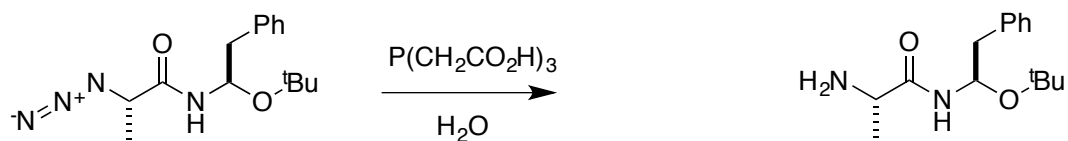
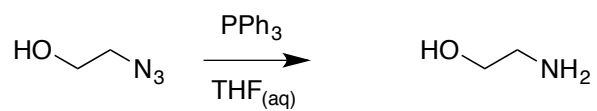
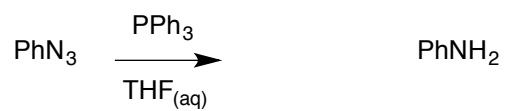
Staudinger



+3

+5

*oxidized.**reduced.*



aminal

azidomethyl

Ester Hydrolysis And Transesterification

from chapter(s) _____ in the recommended text

A. Introduction

B. Reactivity

less

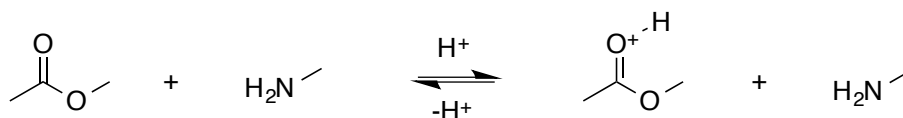
less

do not

more

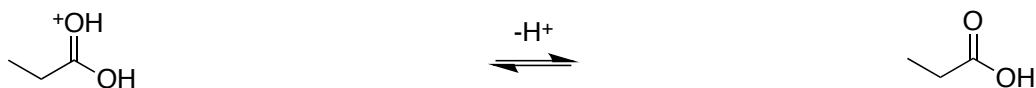
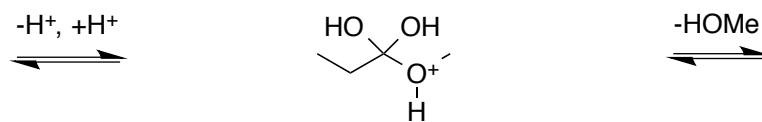
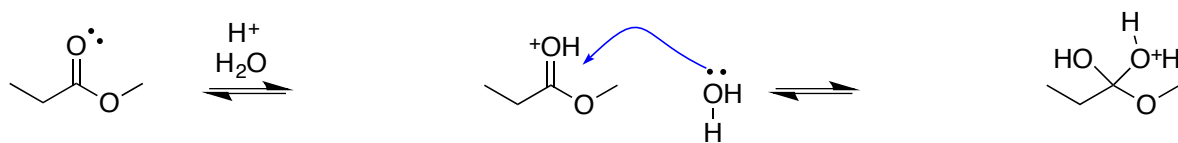
more

unlikely.

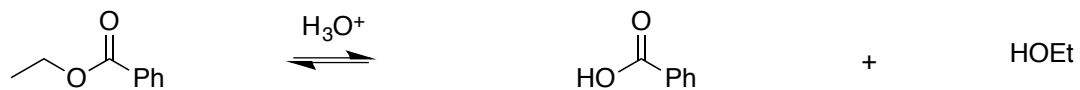
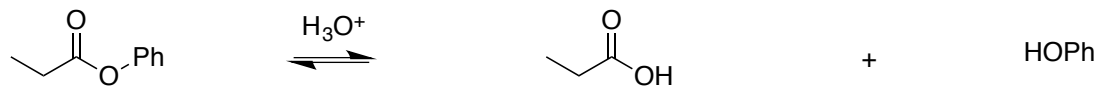
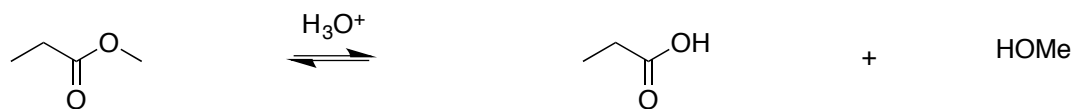


are not

C. Acid-mediated Hydrolysis

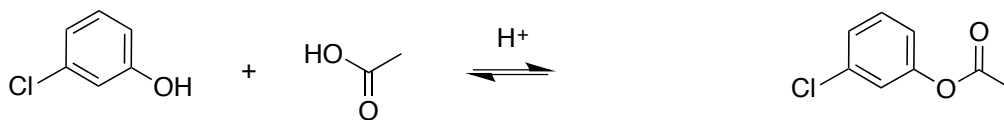
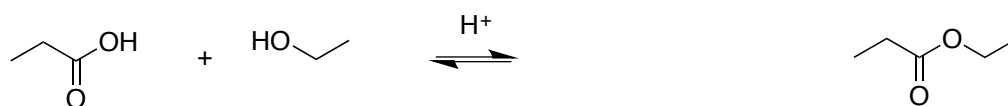


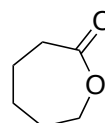
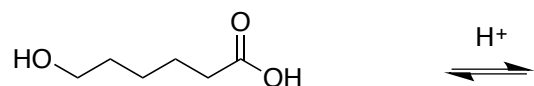
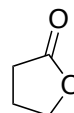
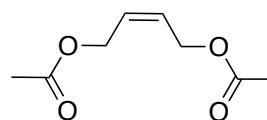
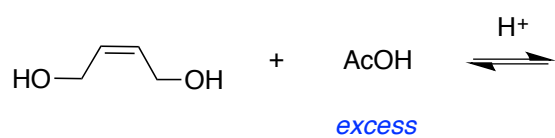
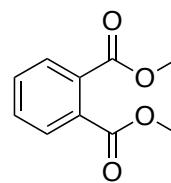
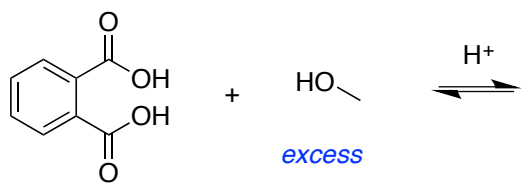
carboxylic acids
water.

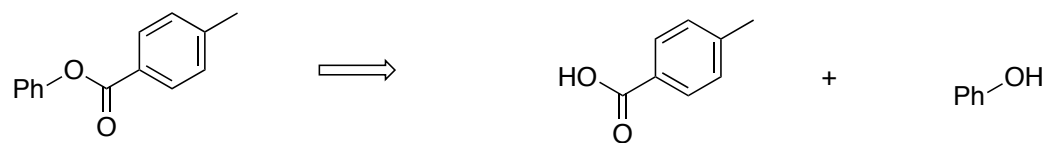
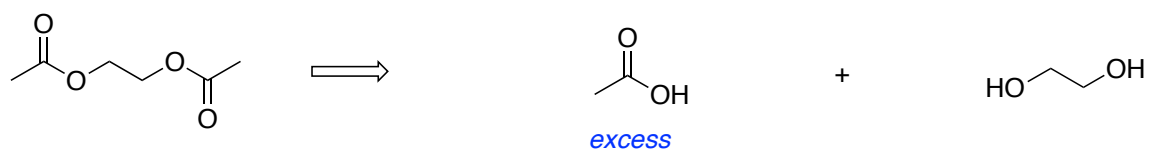
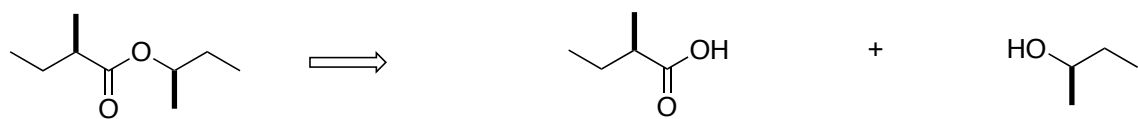


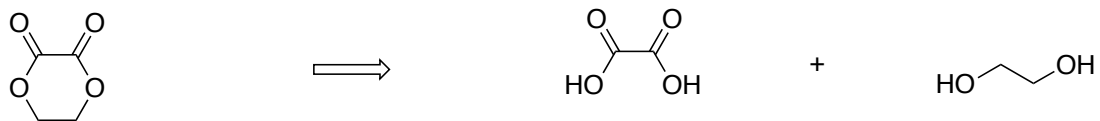


reversible,







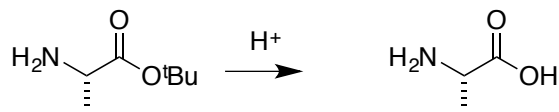
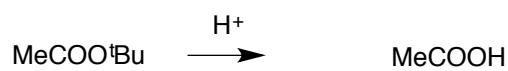
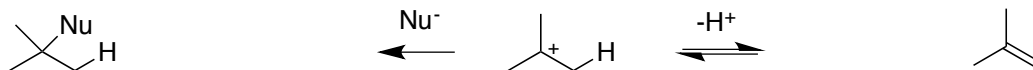


possibilities: forming a five-membered ring is more favorable than three- or four-membered ring due to ring strain of sp^3 carbons.

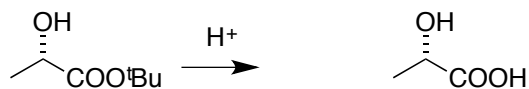
Hydrolysis Of *tert*-Butyl Esters Occurs Via A Different Mechanism

stable
without



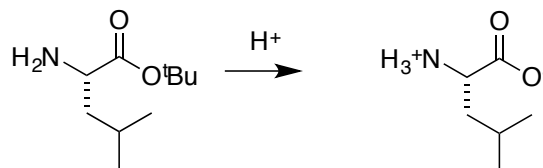
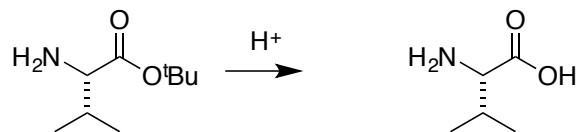


alanine



lactic acid

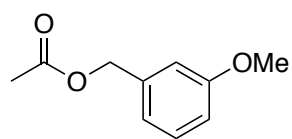
glycine



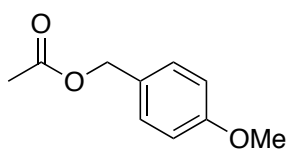
valine

leucine

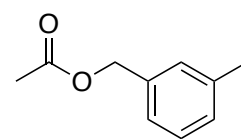
carbocation.



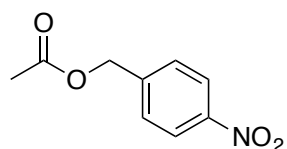
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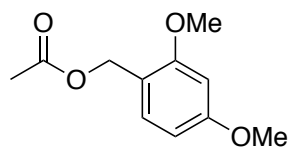
2



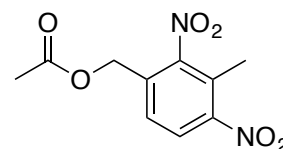
4



5



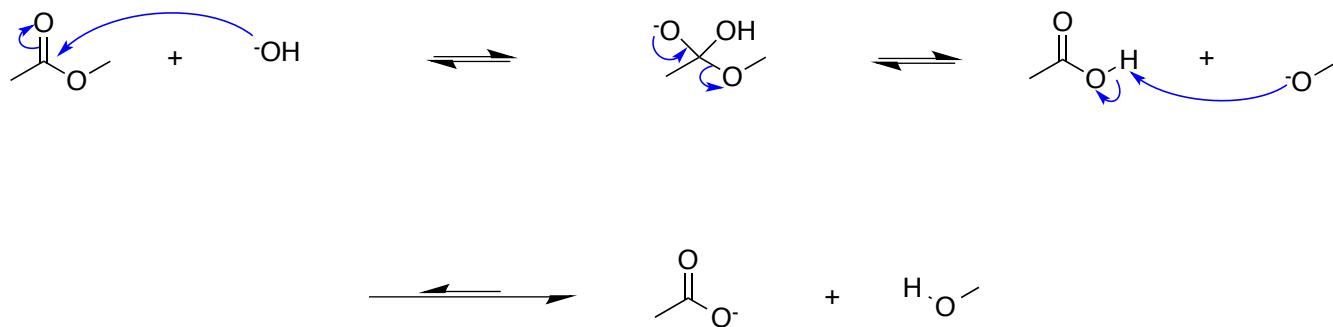
1



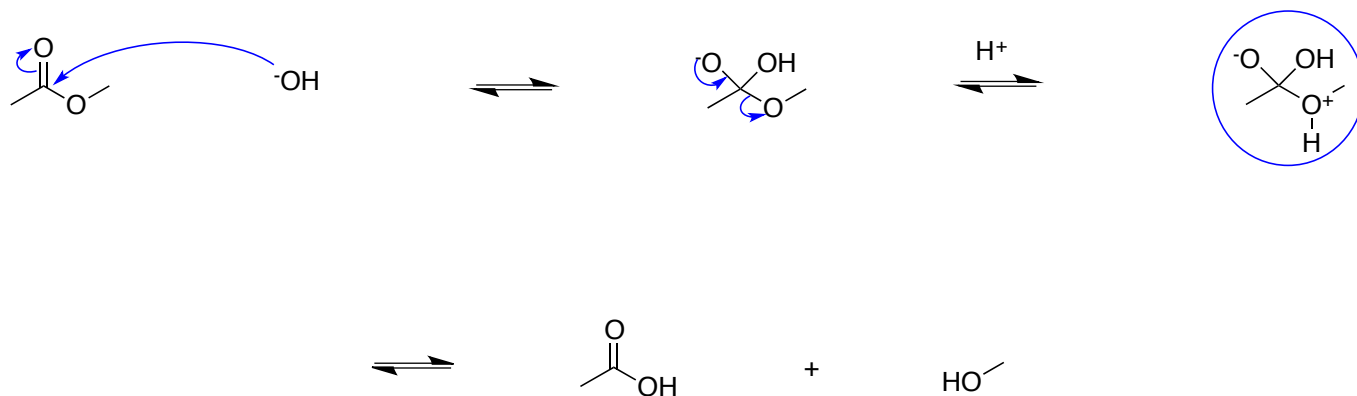
6

D. Base-mediated Hydrolysis

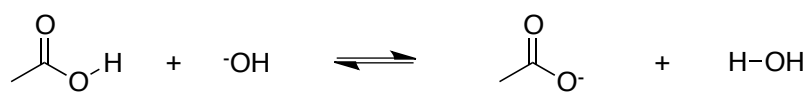
Mechanism



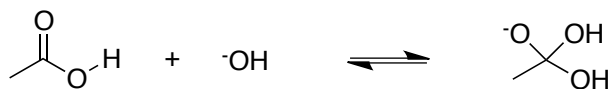
irreversible
reversible.



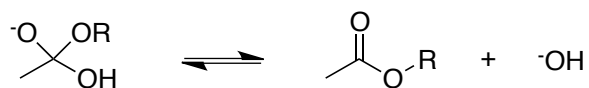
likely.

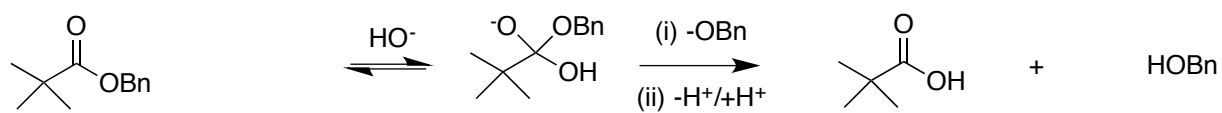
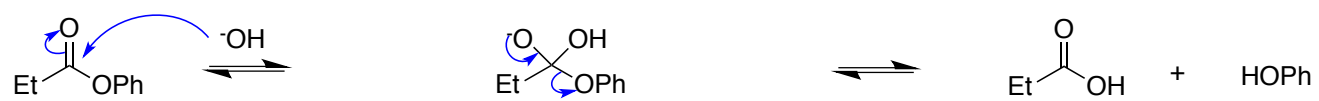


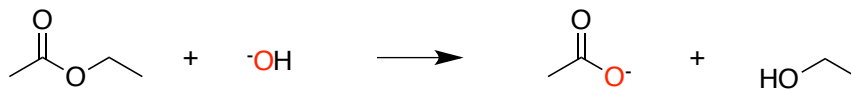
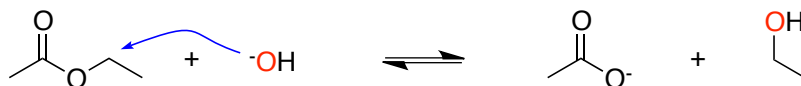
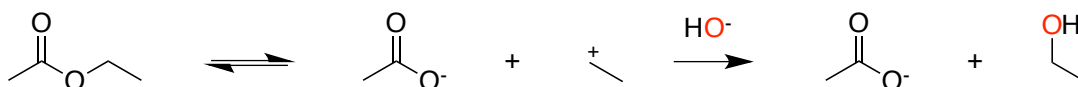
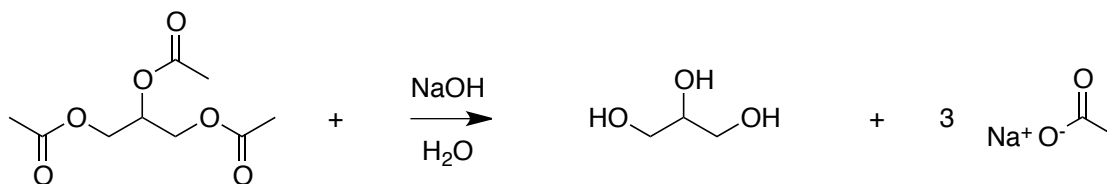
unlikely.



likely.



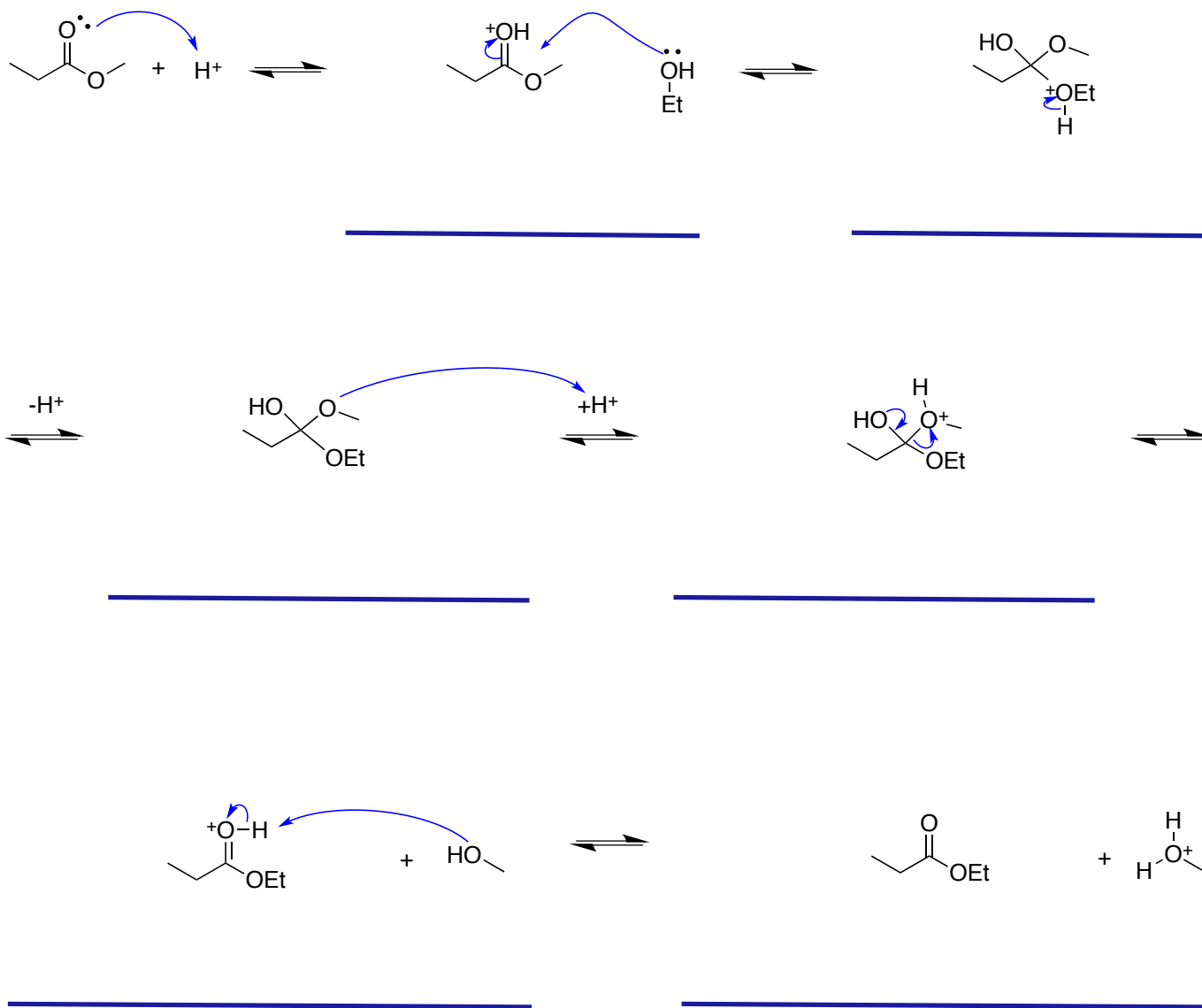


¹⁸O*would not**would not**can**soaps*

E. Transesterification Reactions

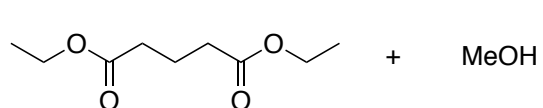
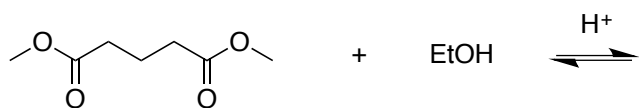
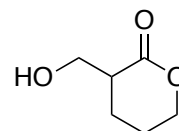
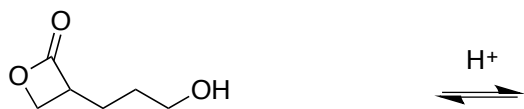
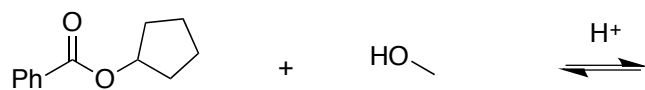
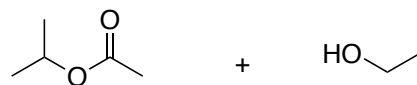
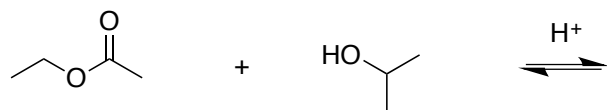
Mechanism Under Acidic Conditions

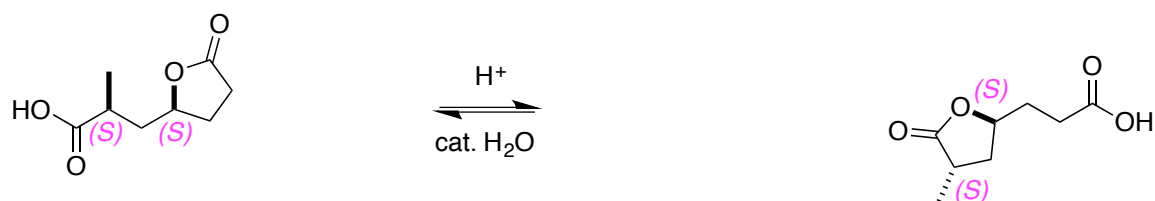
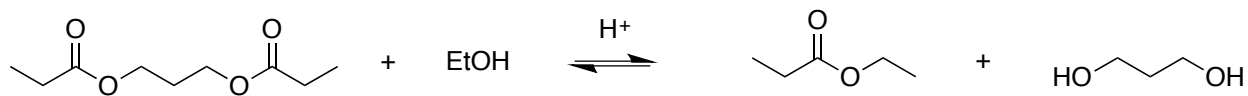
another ester.



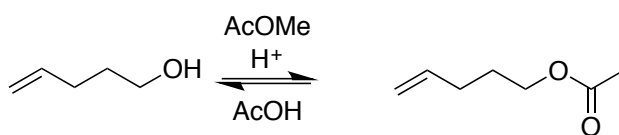
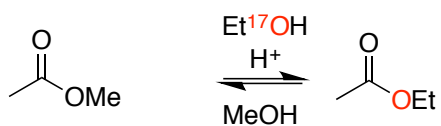
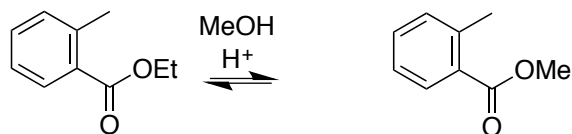
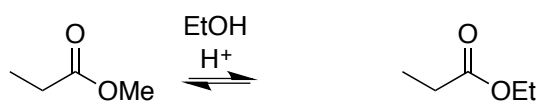
Examples Of Transesterifications

alkoxide



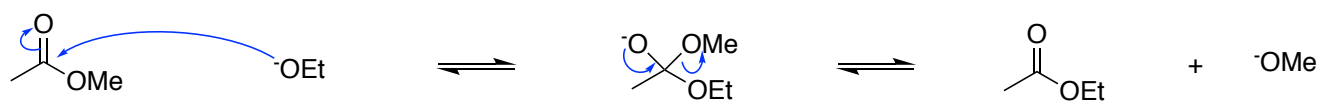


check by assigning (R)- or (S)-configurations



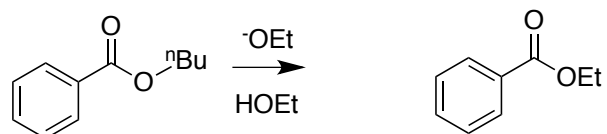
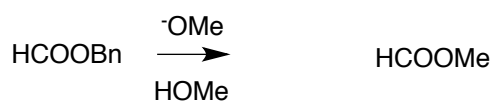
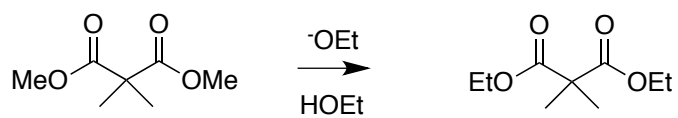
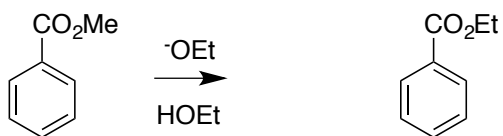
Mechanism Under Basic Conditions

alkoxides.



show arrows

Examples Of Base-Mediated Transesterifications



*more
sp³-
would not*

F. Ester Hydrolyses In Biochemistry In The Central Nervous System

esterases.

acetylcholinesterase.

*acetylcholine receptors
choline.*

*ACHE
paralysis.*

nerve gases.

In The Digestive System

long chain alkyl groups

triglyceride

catalysts.

neutral

nucleophiles

electrophiles.

can

metabolism of triglycerides

transesterifications.

lipases.

Hydrolysis And Dehydration Of Amides

from chapter(s) _____ in the recommended text

A. Introduction

B. Reactivity Of Amides

less

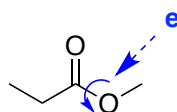
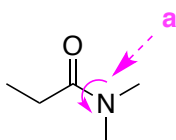
less

sp^2

pyramidal and sp^3

more

a than **e**.

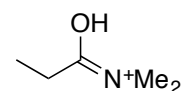
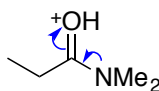
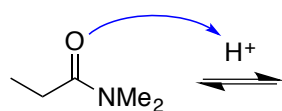
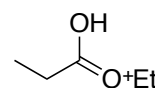
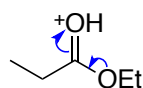
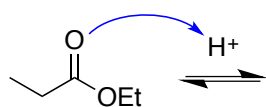


2

1 at elevated temperatures.

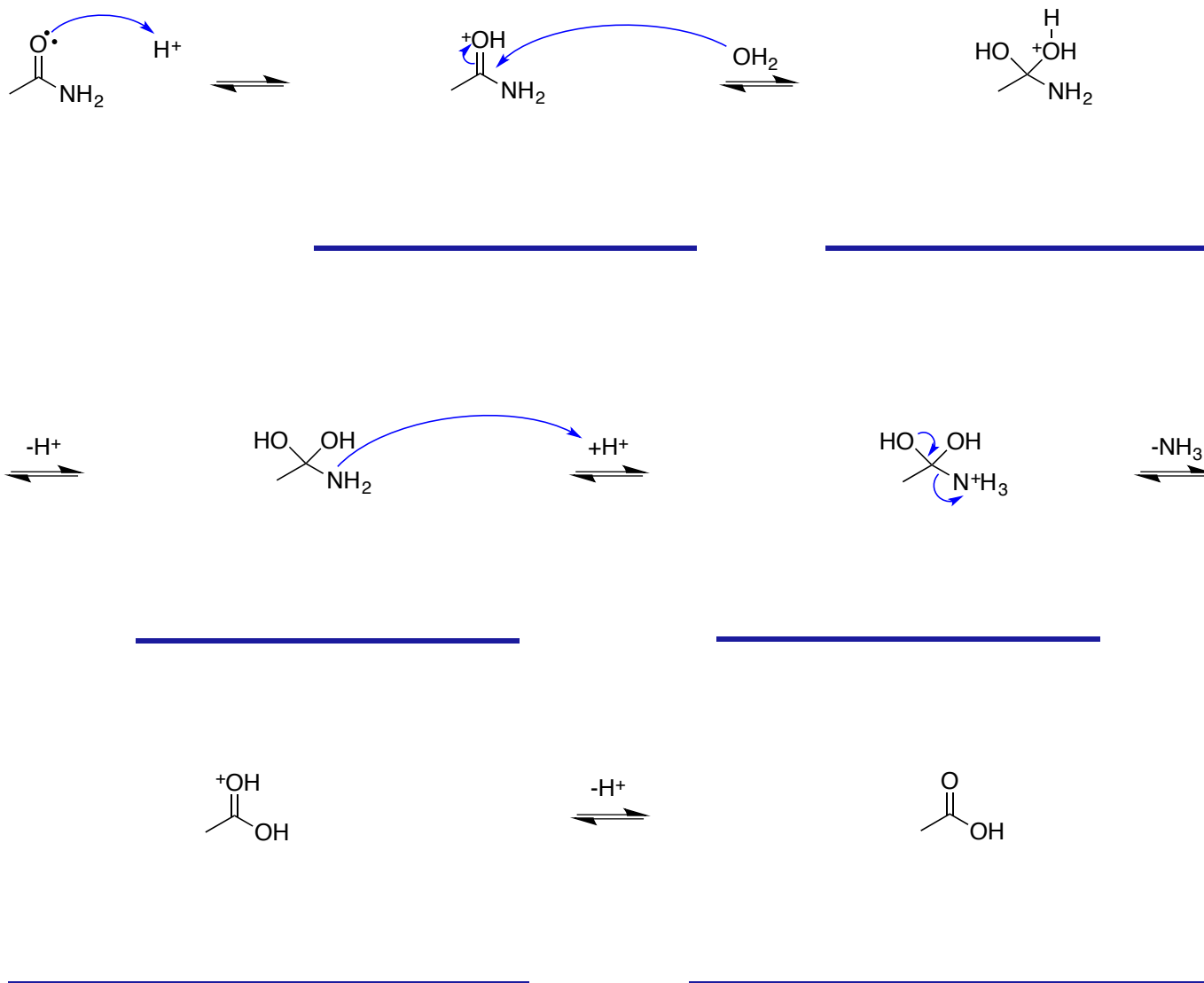
more

more



C. Hydrolysis Of Amides

tetrahedral

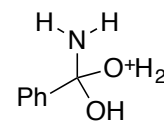
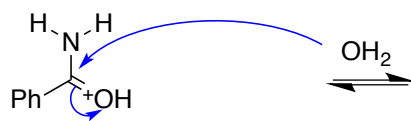
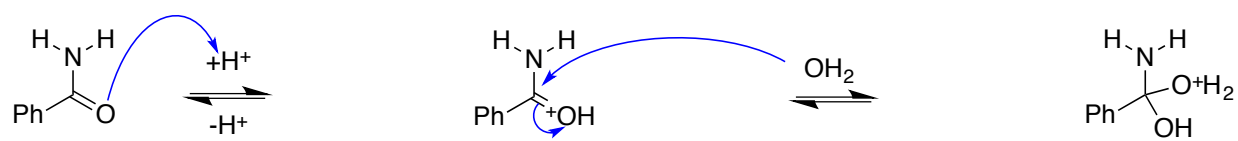


NH_4^+

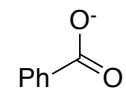
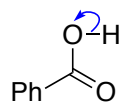
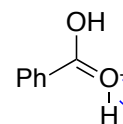
irreversible

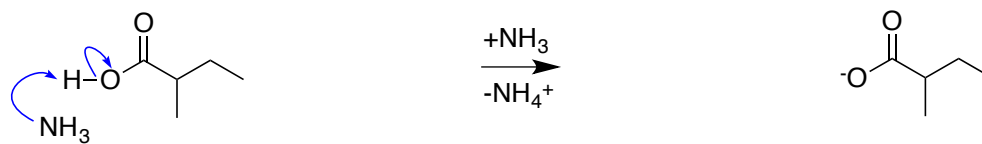
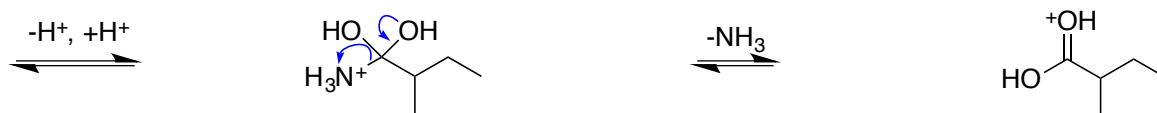
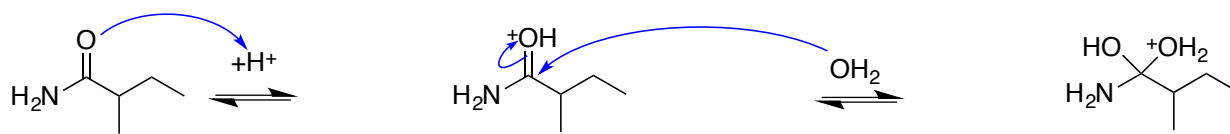
NH_4^+ is not nucleophilic and cannot attack carbonyl to form amide.

because carbonyl group on amide cannot be protonated under neutral condition, leading to inactivated carbonyl, then water cannot attach to carbonyl carbon.

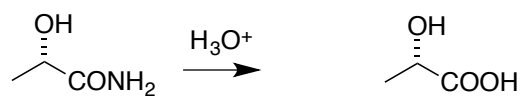


tetrahedral intermediate

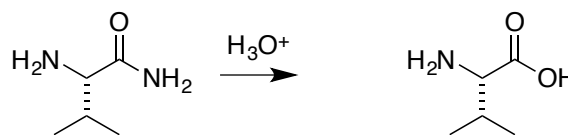




carboxylate



lactic acid



valine

D. Proteases

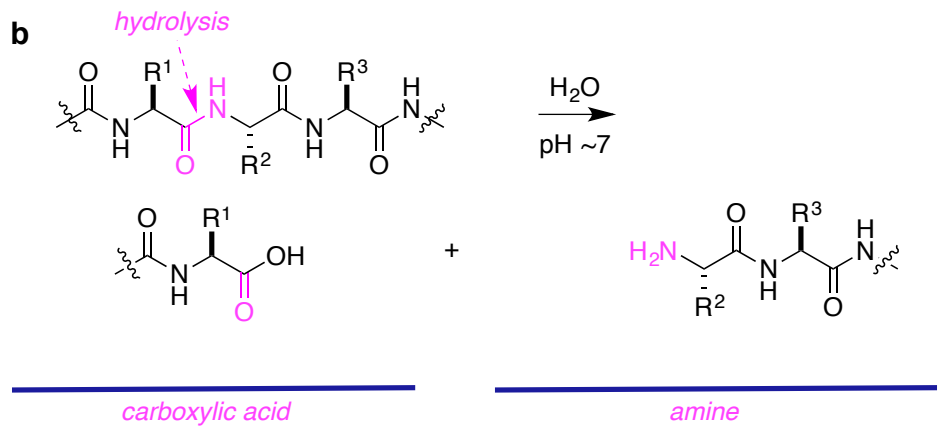
Function

esterases
proteases.

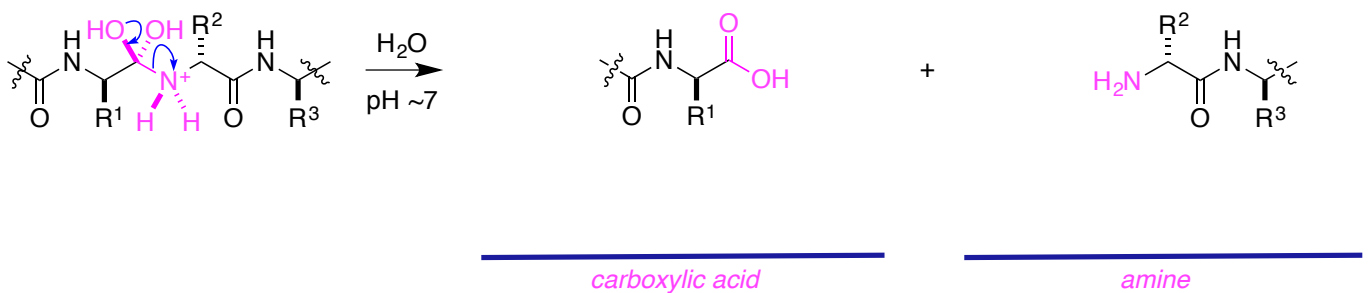
~7

Catalytic
enzymes
hydrogen bonding

do not
active-

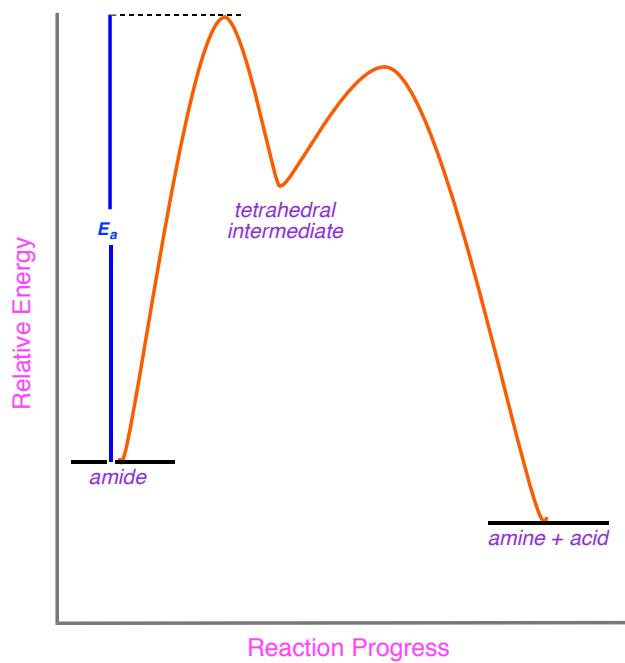


degrades

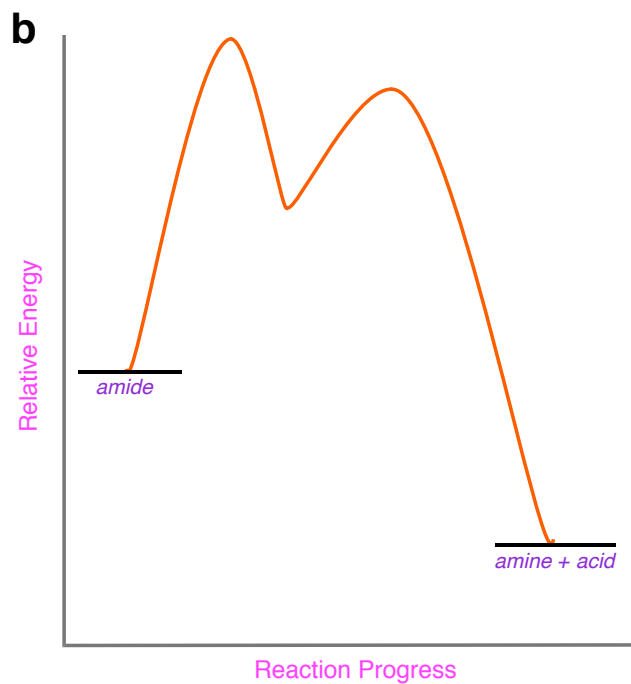
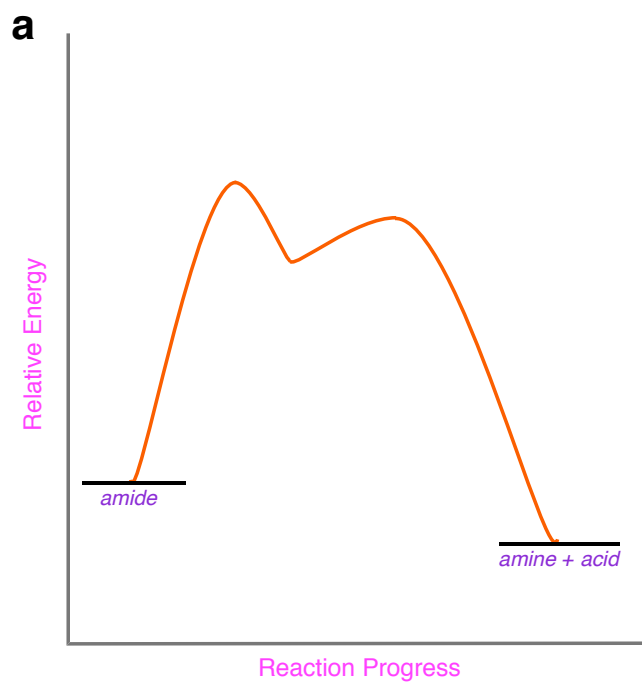


Catalysis

kinetic



destabilizing the substrate and/or stabilizing the intermediate.



situation **a**.
is the way

Protease Inhibitors

9 proteins

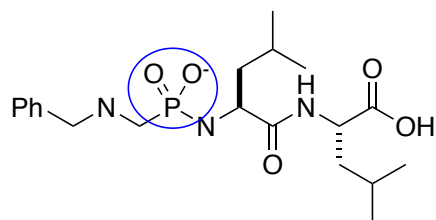
enzymes are *proteins* but not all *proteins* are *enzymes*.

active- site

a *high* affinity

the *alcohol* functionality

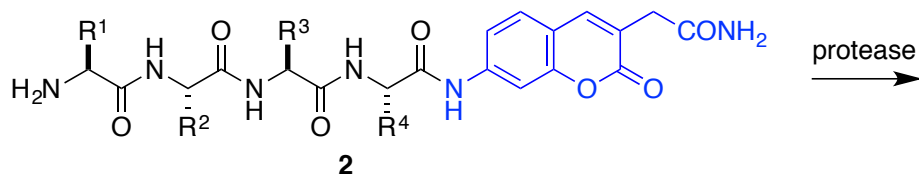
mimic the tetrahedral intermediate in amide hydrolysis.



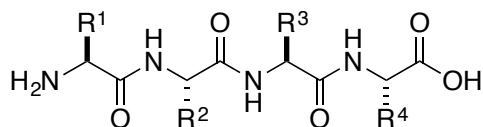
1

thermolysin inhibitor

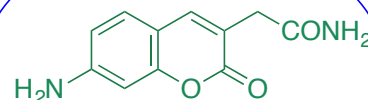
Detection Of Protease Substrate Selectivity



2



+

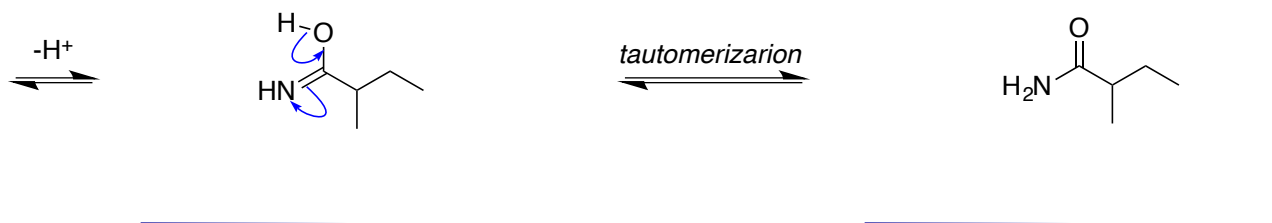
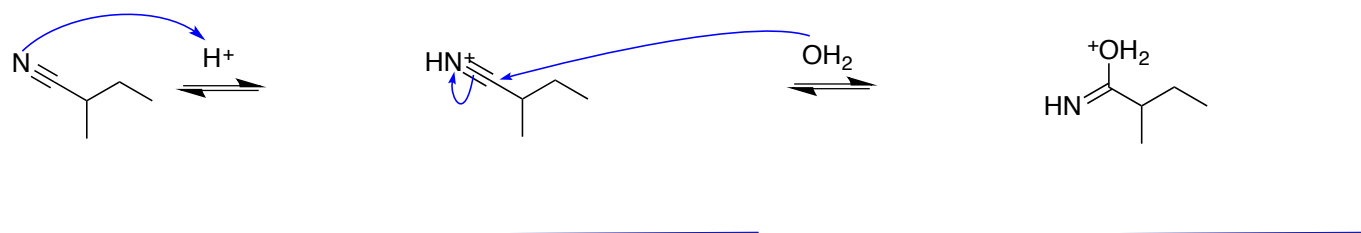
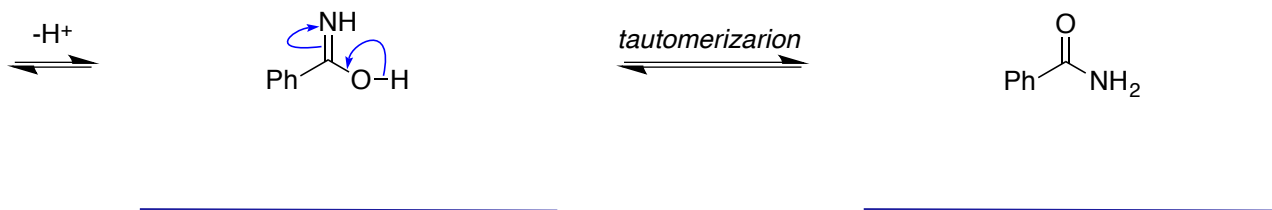
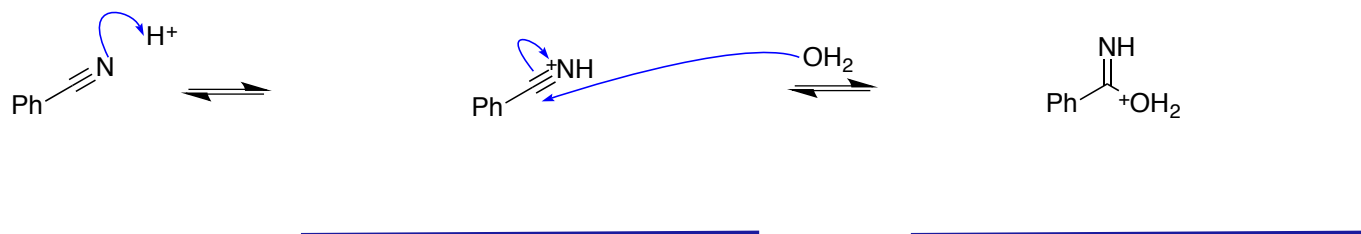


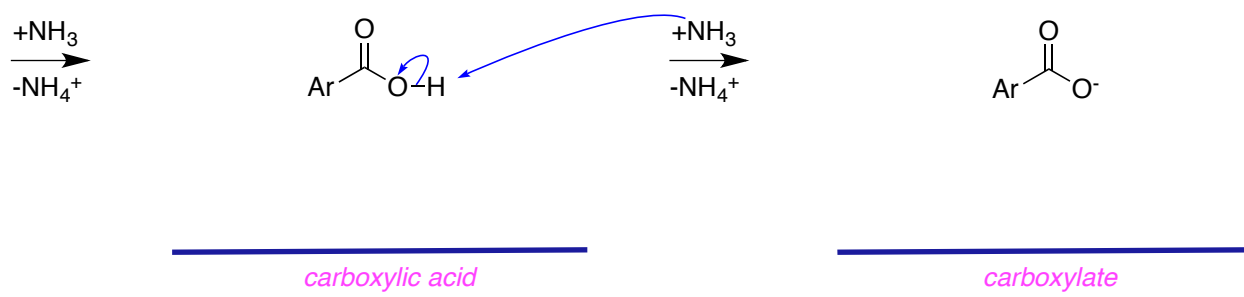
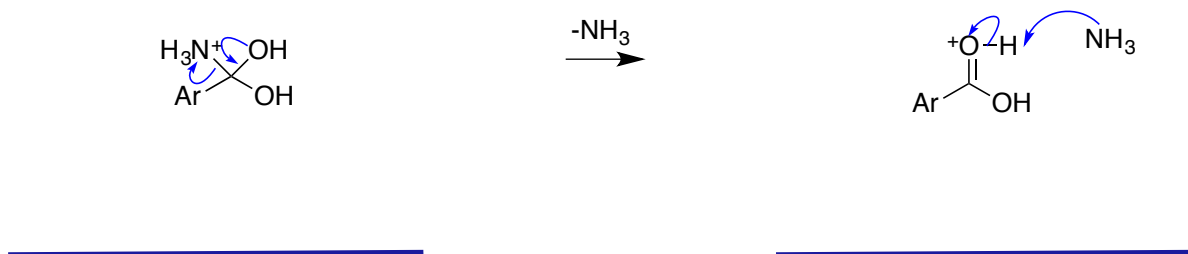
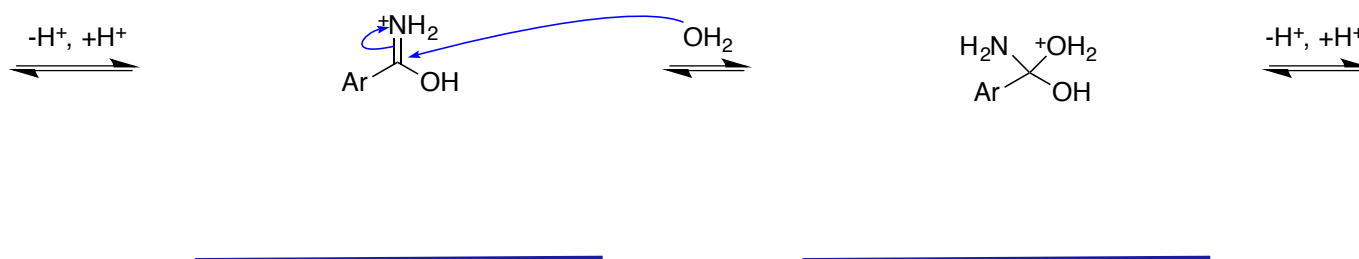
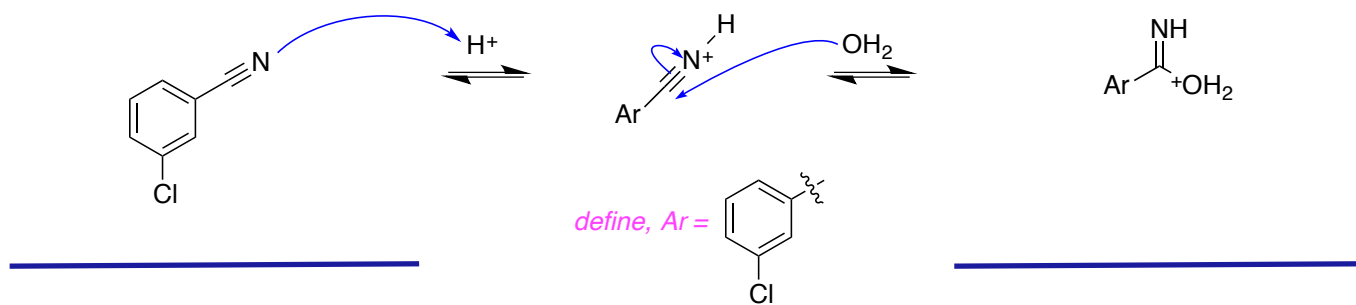
fluorescence.

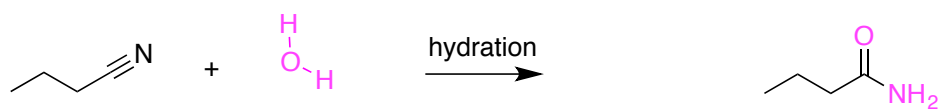
E. Hydrolysis Of Nitriles Involves Amide Intermediates

*carboxylic acids,
partial.*

Tautomerization







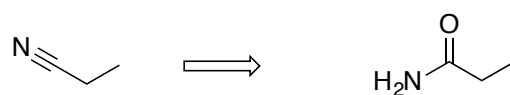
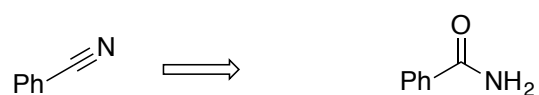
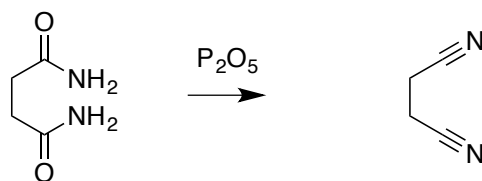
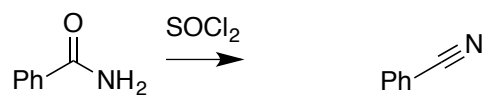
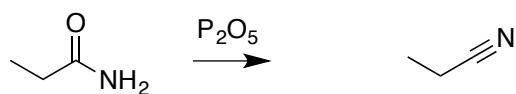
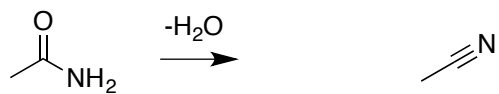
amide

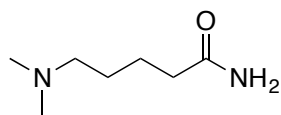
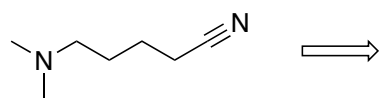
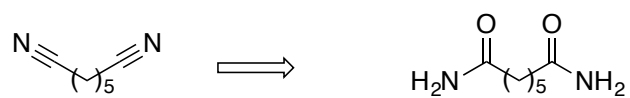
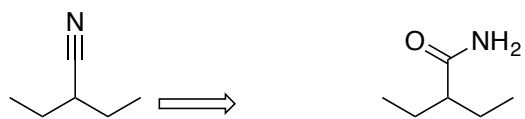


carboxylic acid

F. Dehydration Of Amides







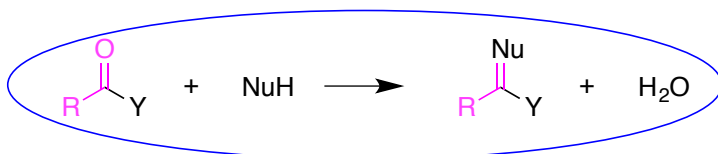
Reactivities Of Acylation Agents

from chapter(s) _____ in the recommended text

A. Introduction

B. Acylation Reactions

RCO

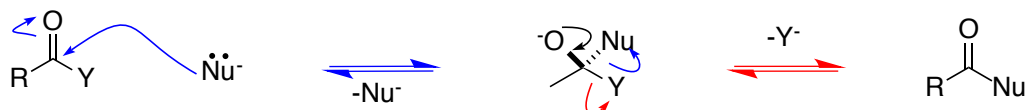


C. pH Dependence

Acylations Under Basic Conditions

readily receive

displaced



does

good

(eg *OMe*⁻)

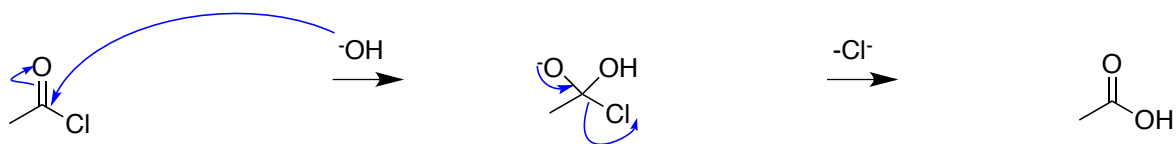
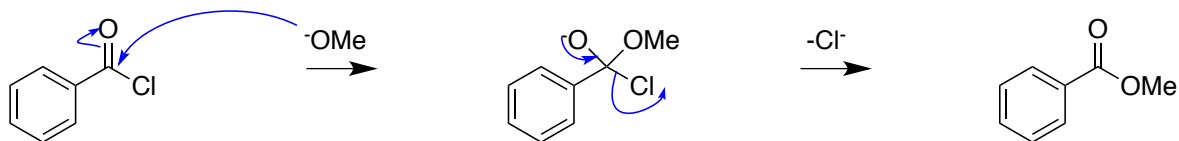
bad

(eg *Cl*⁻).

Cl⁻, *NO*₃⁻, *HSO*₄⁻, *H*₂*O*, *Br*⁻ (add some more)

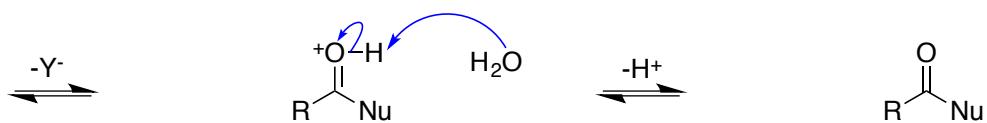
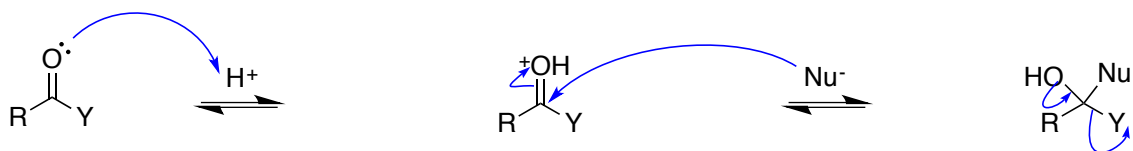
*Me*₂*N*⁻, *HO*⁻, *HS*⁻, *OMe*⁻, *CN*⁻ (add some)

most

tetrahedral*moderately
more**ethanoyl chloride**tetrahedral intermediate**ethanoic acid**benzoyl chloride**tetrahedral intermediate**methyl benzoate*

Acylation Under Acidic Conditions

increases



D. Reactivities Of Acylation Agents

Chemical Intuition

unreactive.

reactive

activate

reactive

cannot

less

more

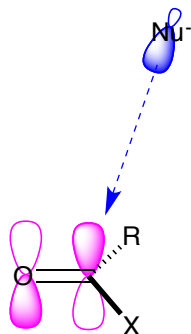
retard

unfavorable

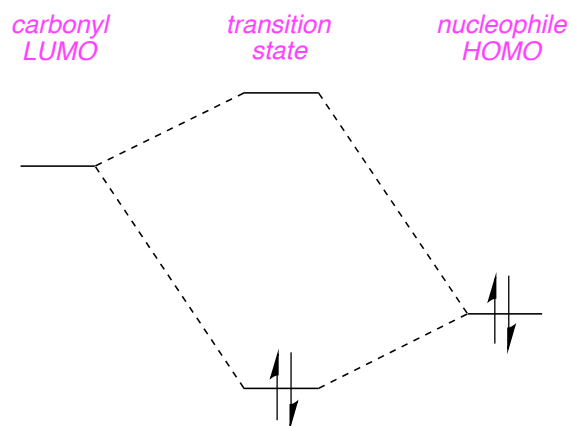
faster

Molecular Orbital Description Of Acylation

a



b



increase

lower its LUMO energy.

reactive

low energy LUMOs.

more stable

less reactive

high

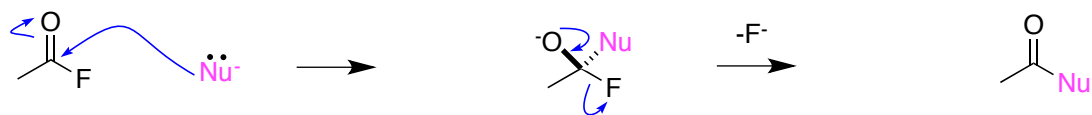
good

lower

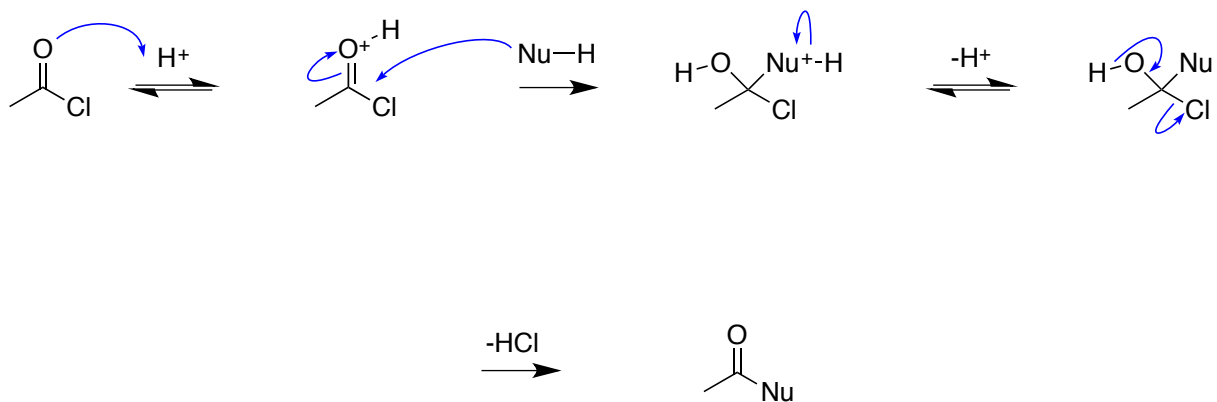
excellent

Relative Reactivities Of Functional Groups In Acylation Reactions

Carbonyl Halides (Acid Halides) Are Hot

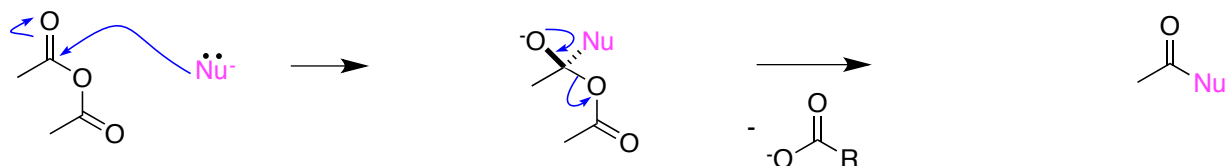
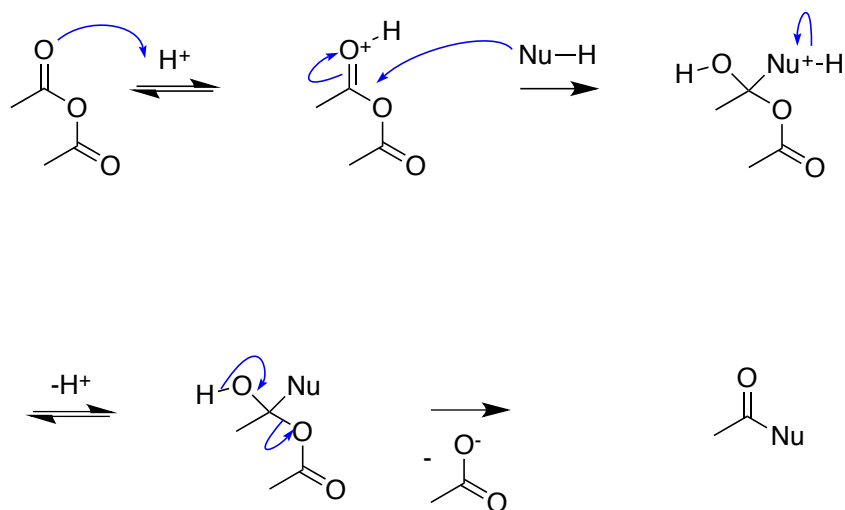


basic



acid conditions.

Carboxylic Acid Anhydrides Are Very Reactive

*lower**excellent* leaving groups.*under basic conditions**under acidic conditions*

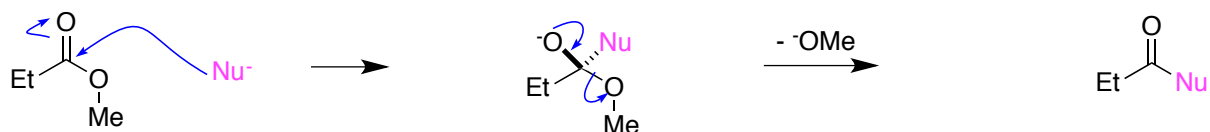
2 carboxylic

*an electrophile**carboxylate leaving group.*

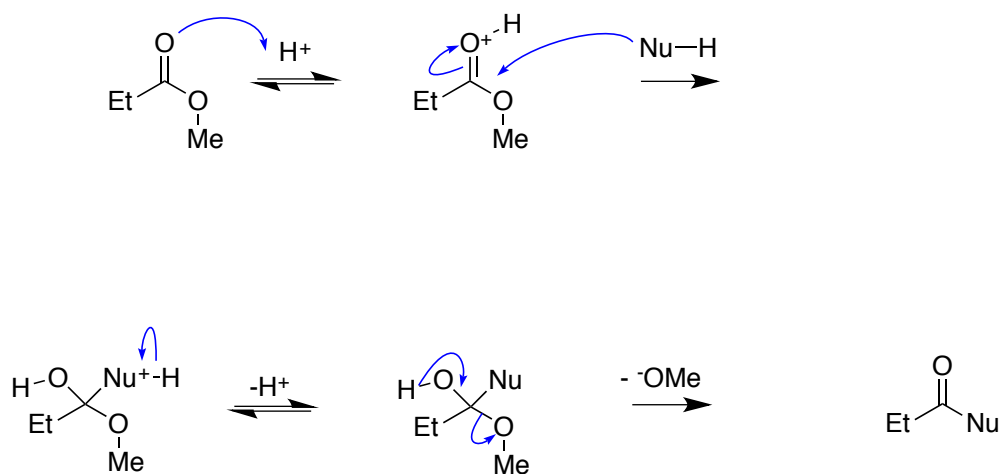
Esters Are Not Very Reactive

raises
inferior

under basic conditions



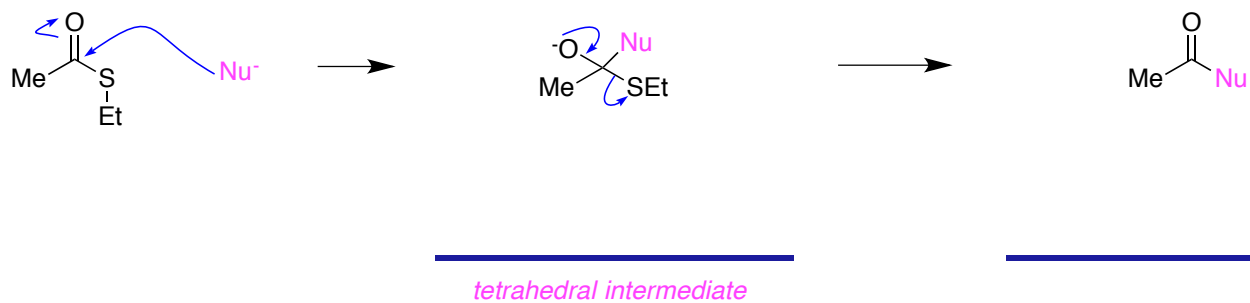
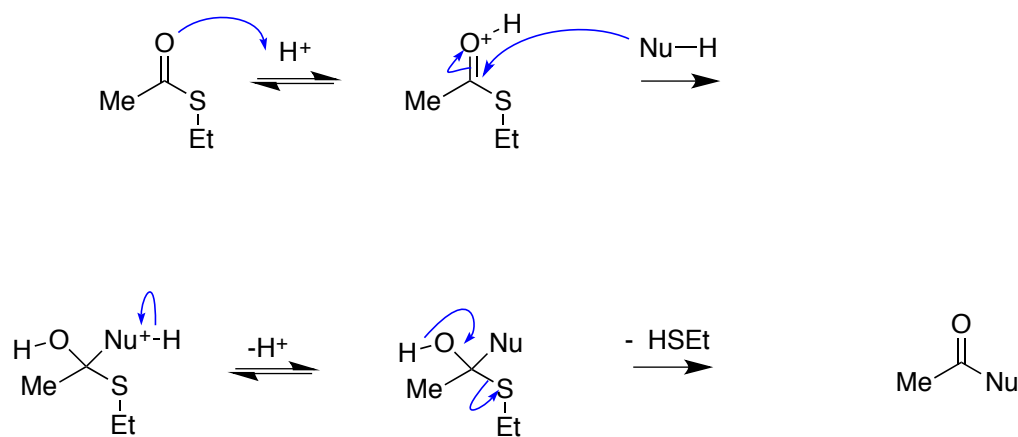
under acidic conditions



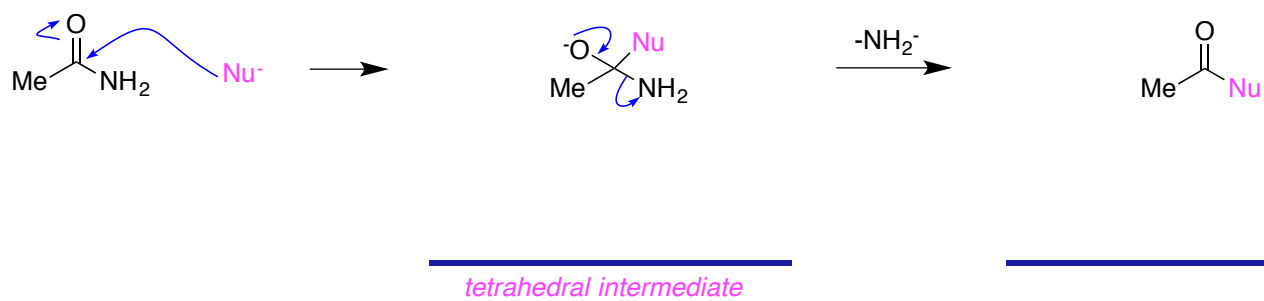
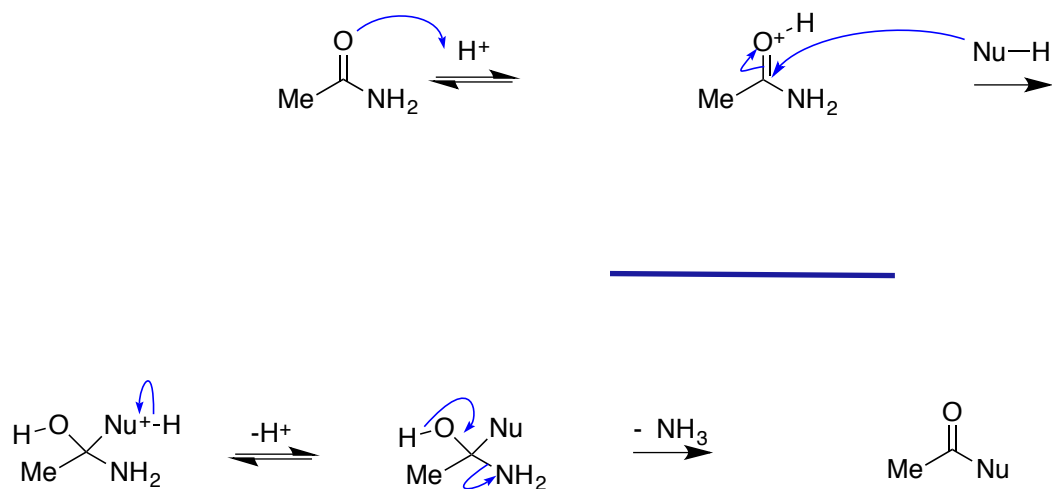
ester hydrolysis
transesterification

do not tend

Thioesters, Gentle Chemoselective Acylating Agents

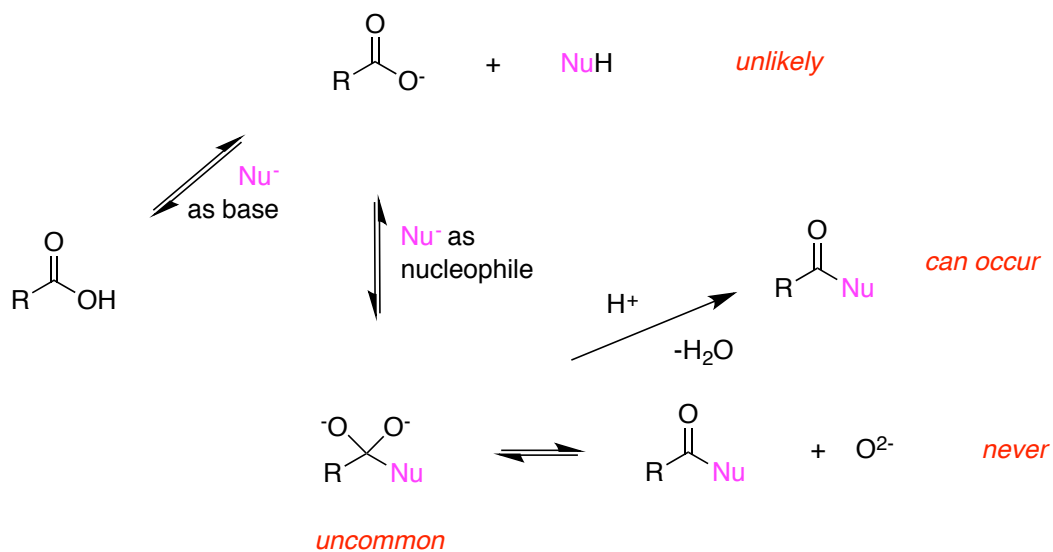
*better**less**under basic conditions**under acidic conditions**do* tend to

Amides, Poor Acylating Agents

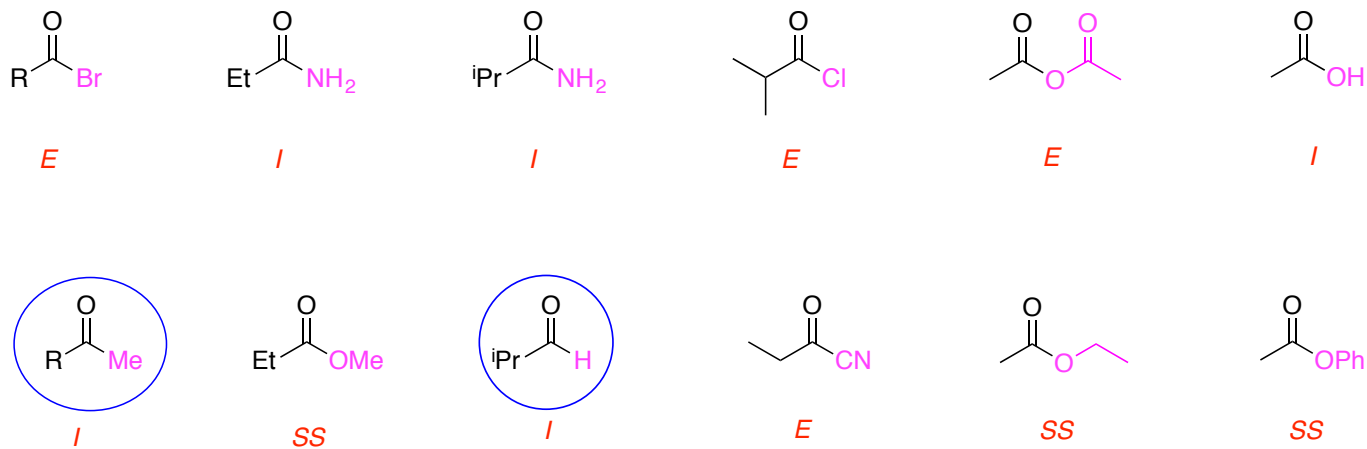
*worse**poor**more**under basic conditions**under acidic conditions*

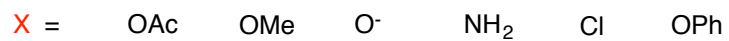
Carboxylic Acids Are Not Acylating Agents

(pKa = 3 – 5)

*extremely* basic and a very *poor*

Synopsis

*cannot*

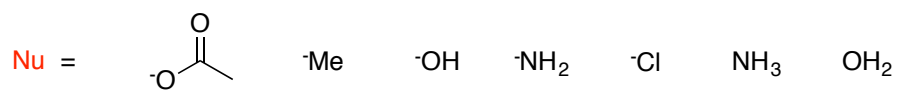
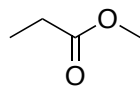


Cl

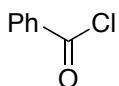
OAc

OPh

OMe

NH₂O⁻*most reactive**least reactive*Me⁻NH₂⁻OH⁻Cl⁻NH₃OH₂*most reactive**least reactive*

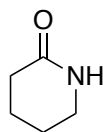
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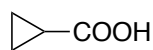
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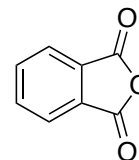
3



5



6



2

Acylation With Acid Chlorides And Anhydrides

from chapter(s) _____ in the recommended text

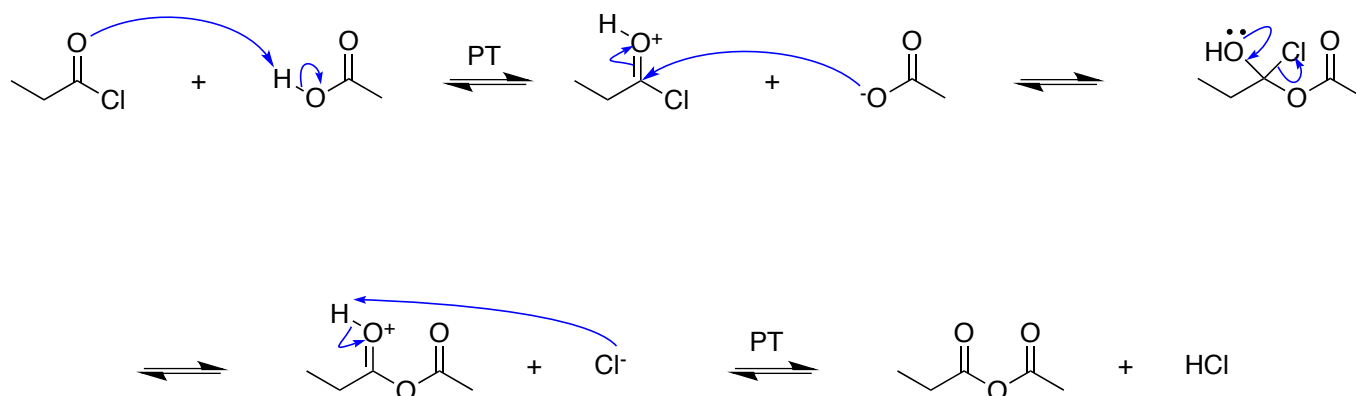
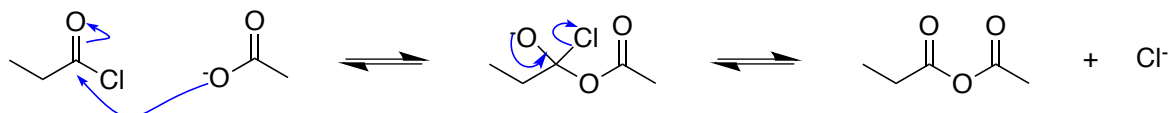
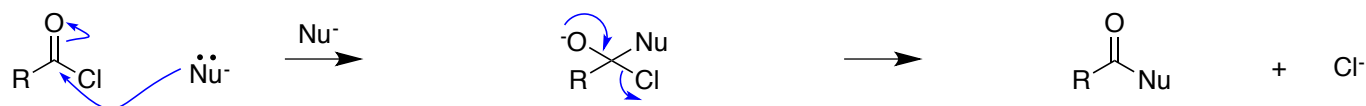
A. Introduction

B. Reactions Of Acyl Halides

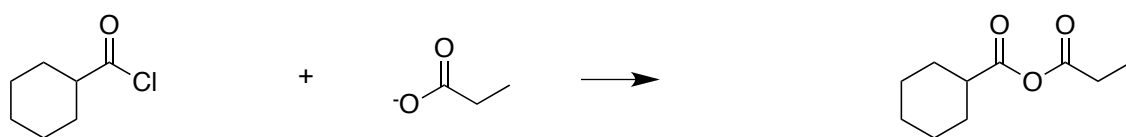
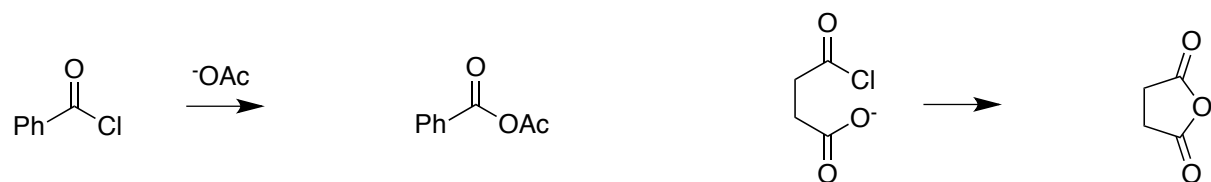
Under Basic Conditions

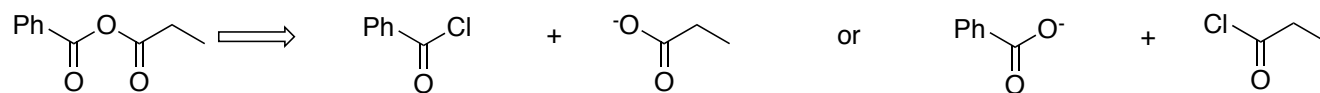
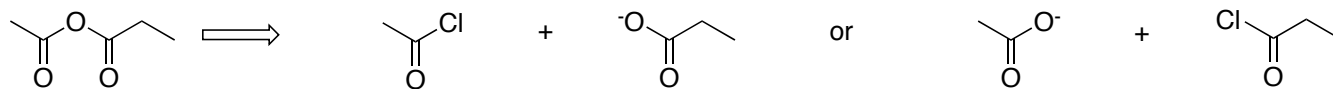
stable *many*

Chloride is a relatively *irreversible*.



Syntheses Of Anhydrides Via Acylation Of Carboxylates

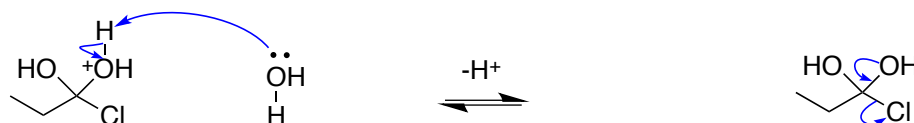




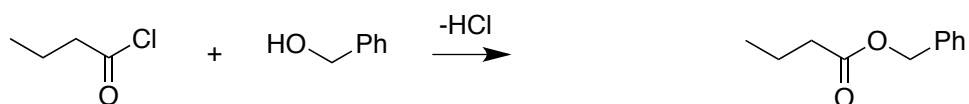
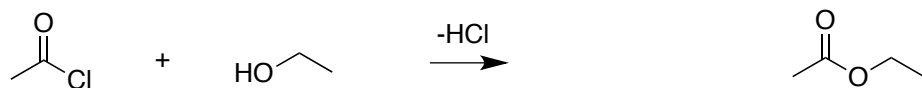
Hydrolysis Of Acid Chlorides To Form Carboxylic Acids

the nucleophile is *hydroxide*,
it is *water*,
acylation of water.

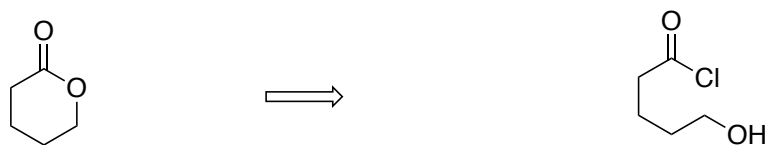
under *acidic* conditions.



Acylation Of Alcohols To Form Esters

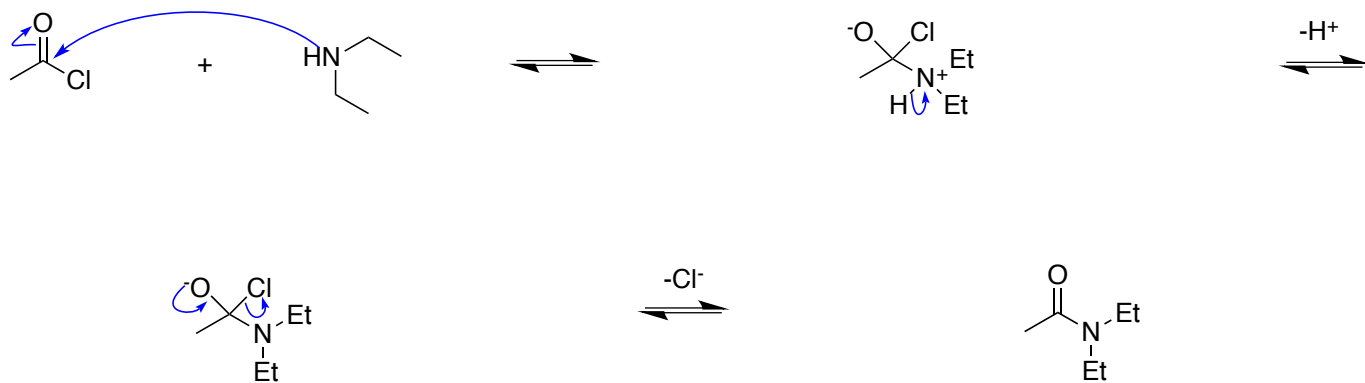


Indicate acid chloride and alcohol starting materials that could be used to make the following esters.

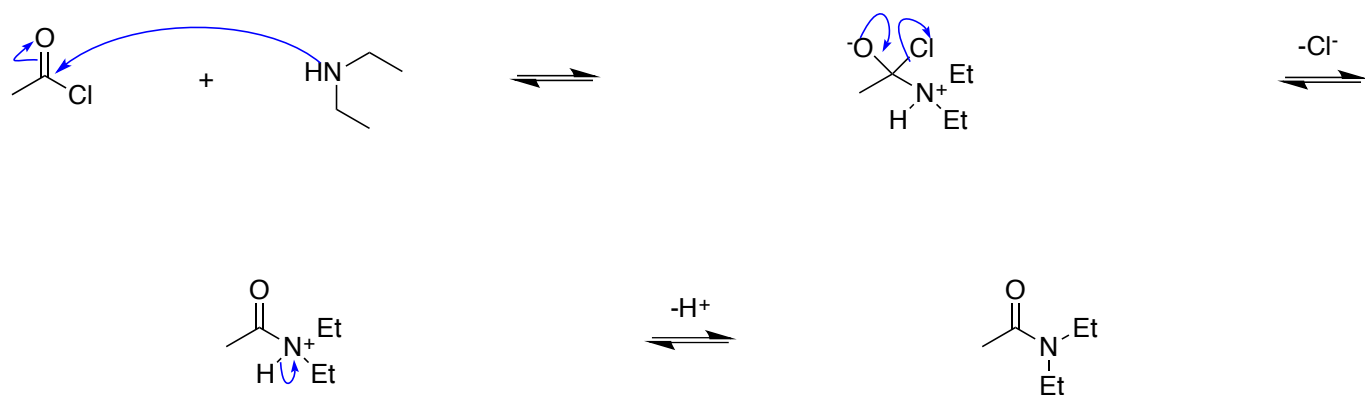




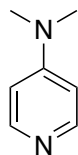
Acylation Of Amines To Give Amides



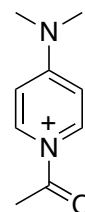
proton *before* chloride loss,
shows it *after*.



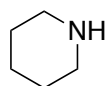
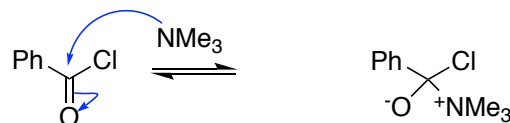
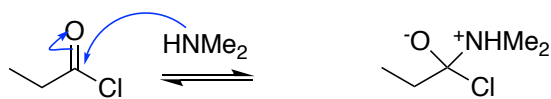
gives *unstable* products



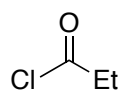
DMAP



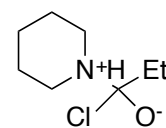
N-acetyl DMAP
good acylating agent for other nucleophiles



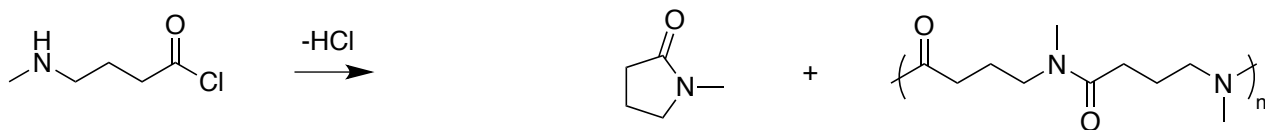
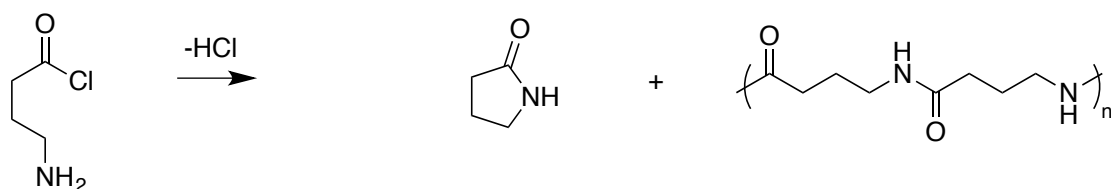
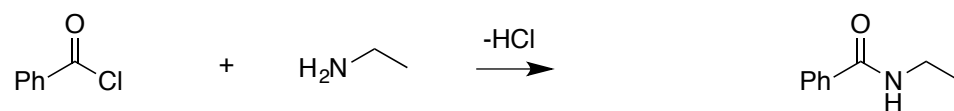
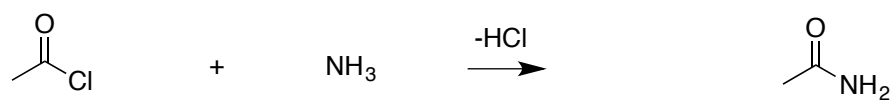
+

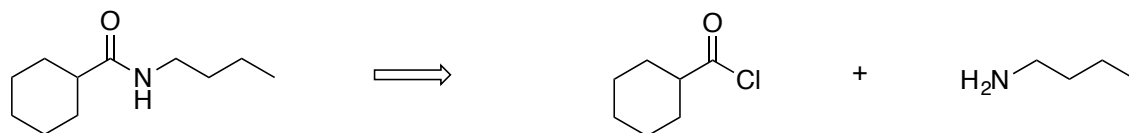
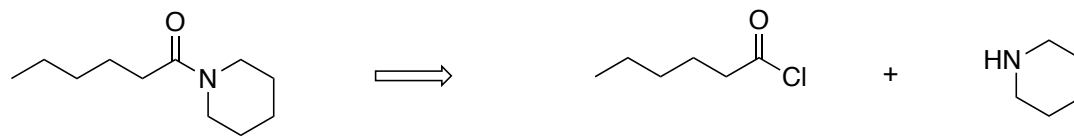
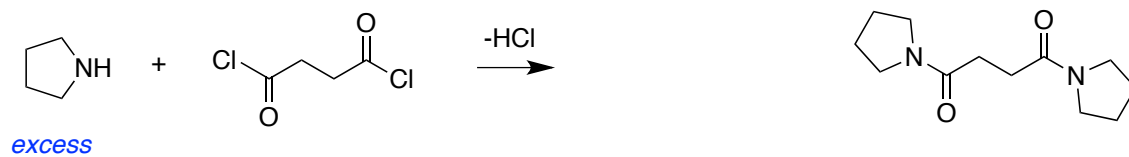


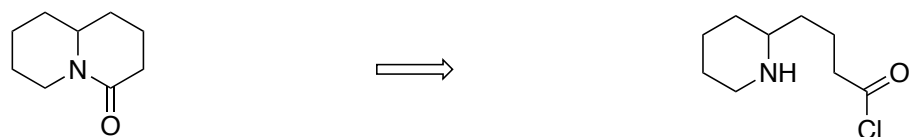
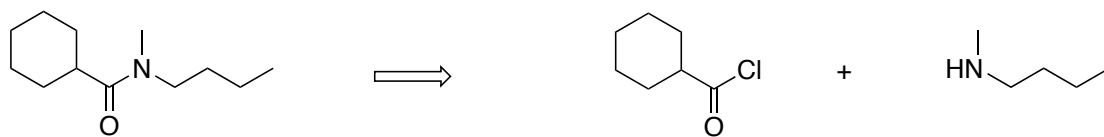
\rightleftharpoons



which amine?







give *esters*,
acids,
ammonia to give *amides*.

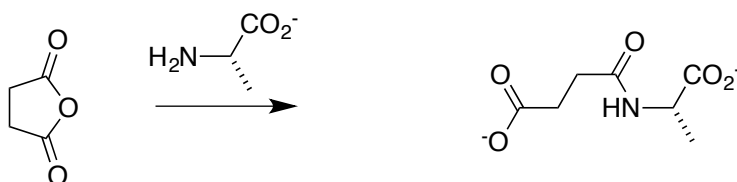
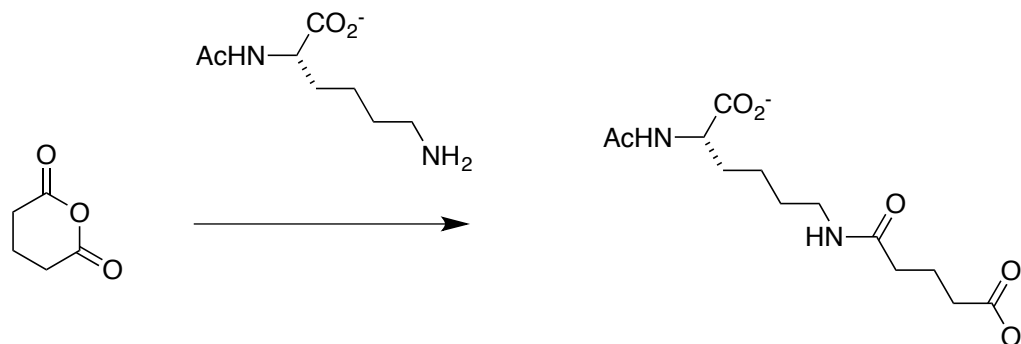
C. Acylation Reactions Of Carboxylic Acid Anhydrides

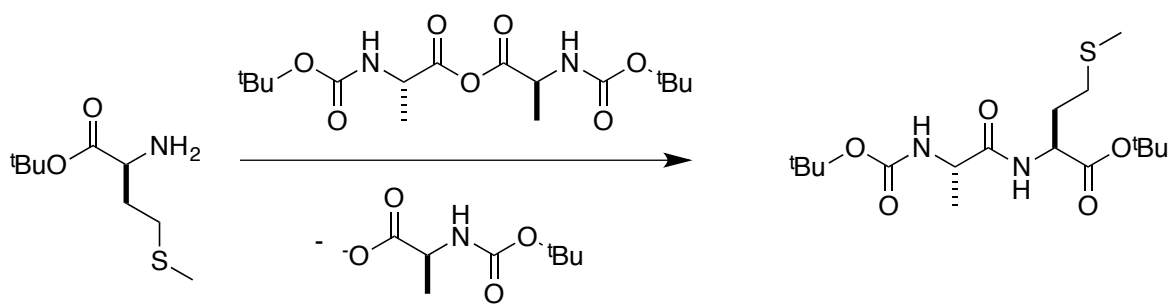
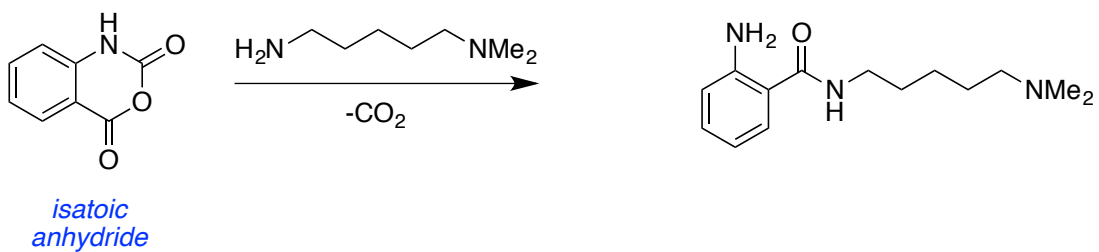
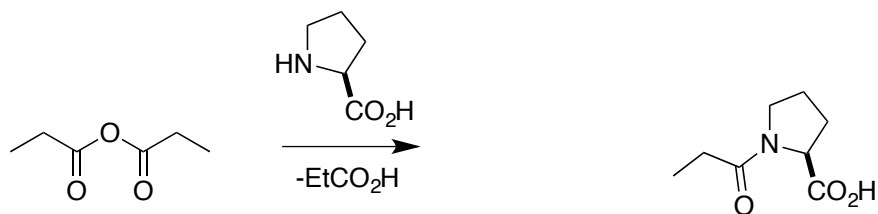
slightly less reactive

would be *the same*.

an electrophile and the

would be *a good strategy*.





Activation Of Carboxylic Acids

from chapter(s) _____ in the recommended text

A. Introduction

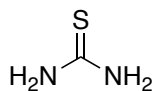
B. Reactivity

poor acylating agents because:

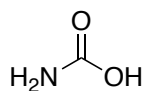
- (i) hydroxide is a *mediocre*
- (ii) exists *as a carboxylate*.

are reactive to nucleophiles.

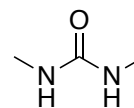
C. Common Carboxylic Acids Derivatives



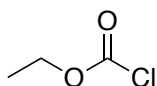
thiourea
C



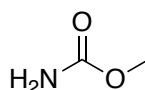
carbamic acid
B



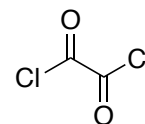
N,N'-dimethylurea
C



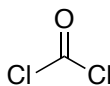
ethyl chlorocarbonate
D



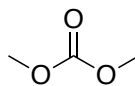
methyl carbamate
A or C



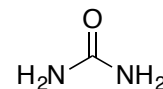
oxalyl chloride
D



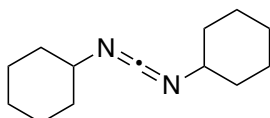
phosgene
D



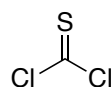
dimethyl carbonate
A



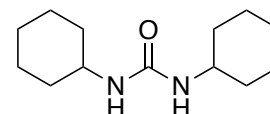
urea
C



dicyclohexylcarbodiimide (DCC)
E



thiophosgene
D

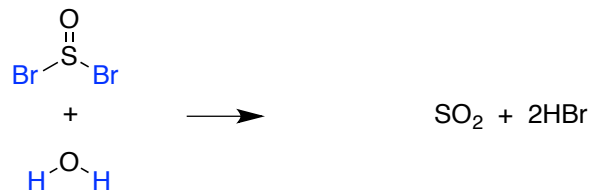
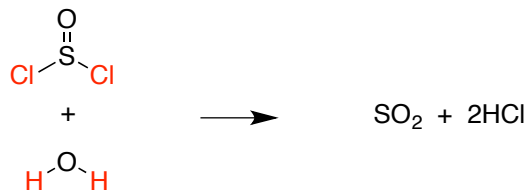


N,N'-dicyclohexylurea
C

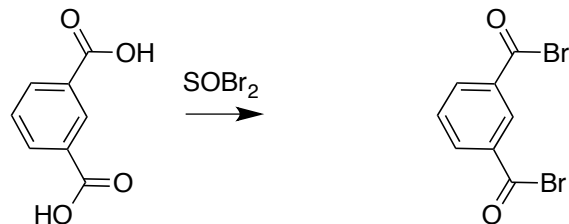
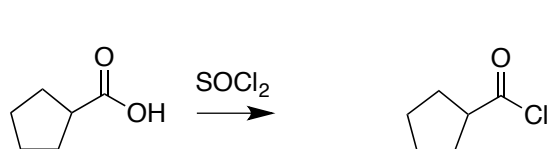
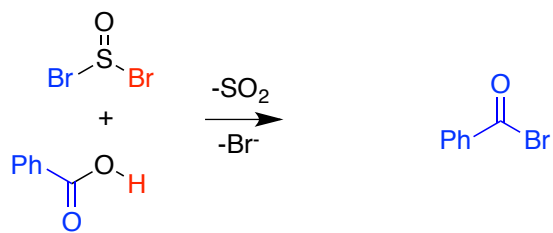
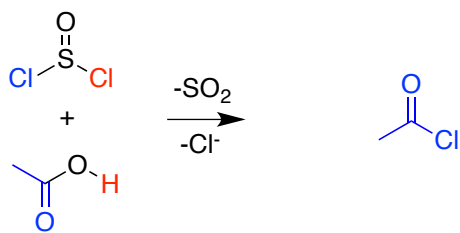
D. Activation Of Carboxylic Acids By Conversion To Acid Chlorides

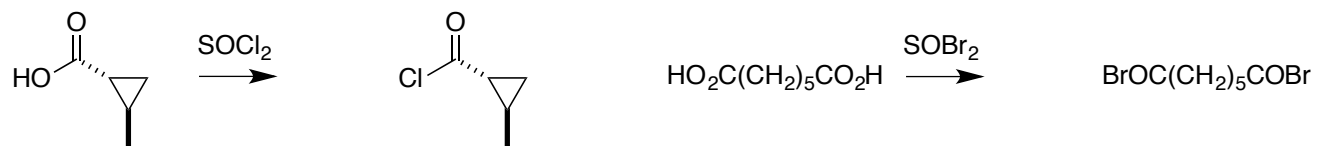
Thionyl Halides: Excellent Dehydrating Agents

formula: SOBr_2



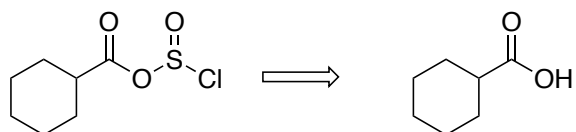
Thionyl Halide Plus Carboxylic Acid Gives Acid Halide, SO_2 , And HX
acid halides.

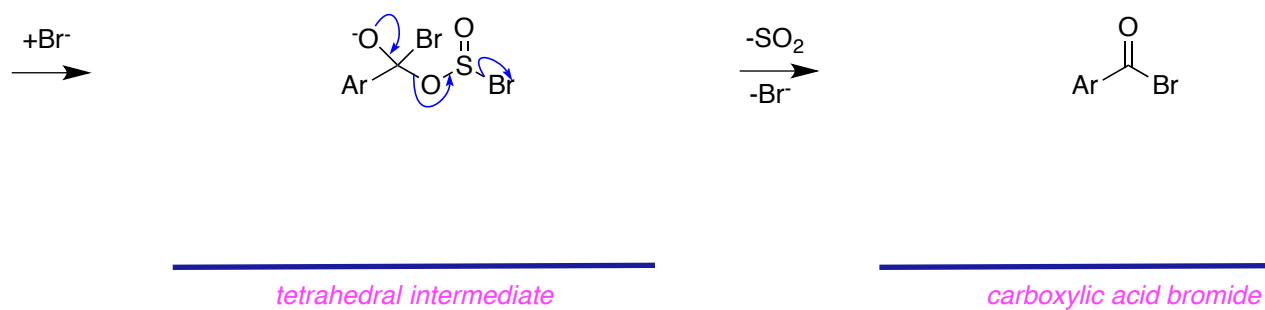
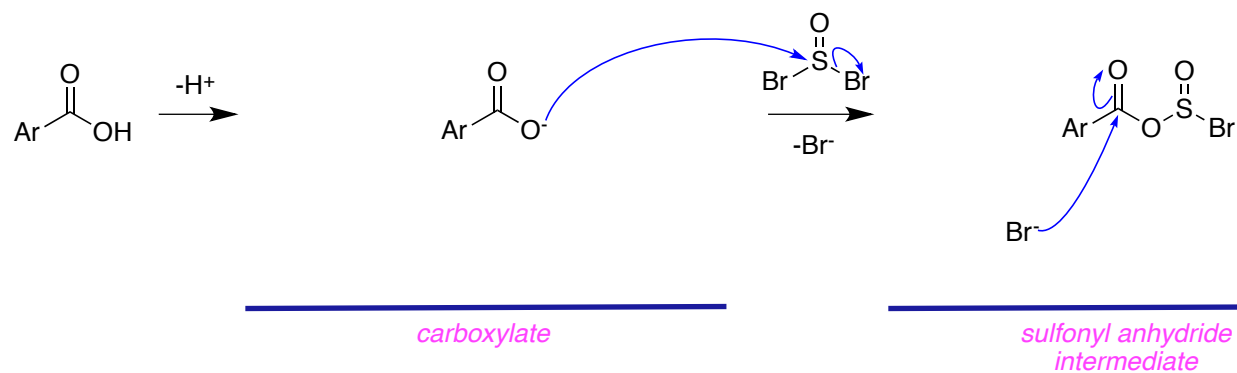




*sulfonyl anhydride
intermediate*

*sulfonyl anhydride
intermediate*



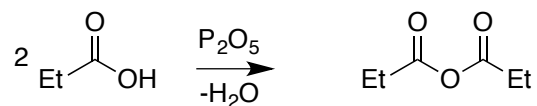


E. Activation By Forming Anhydrides

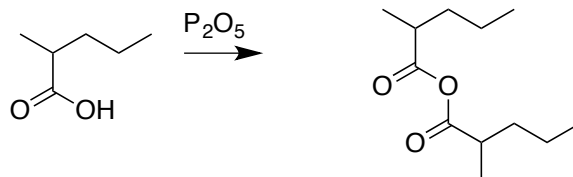
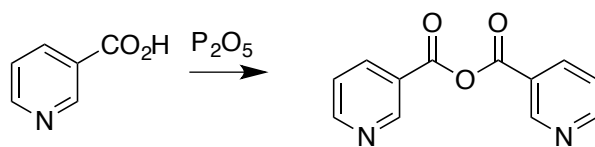
Symmetrical Anhydrides

2 molecules

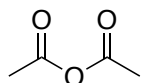
1 molecule



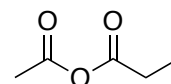
Symmetrical anhydrides
, but *unsymmetrical* ones



is *symmetrical*) and the *unsymmetrical* anhydride



acetic anhydride



anhydride from ethanoic and propionic acids

Unsymmetrical And Mixed Anhydrides

2

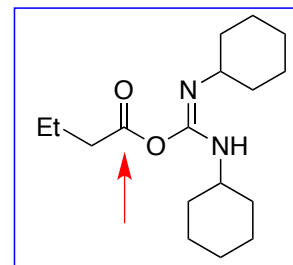
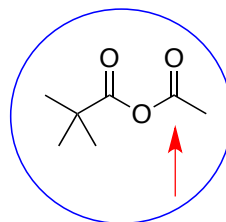
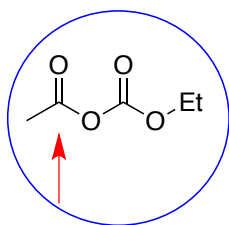
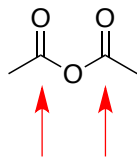
unsymmetrical.

another type of acid.

are not

that *can* be used

eg

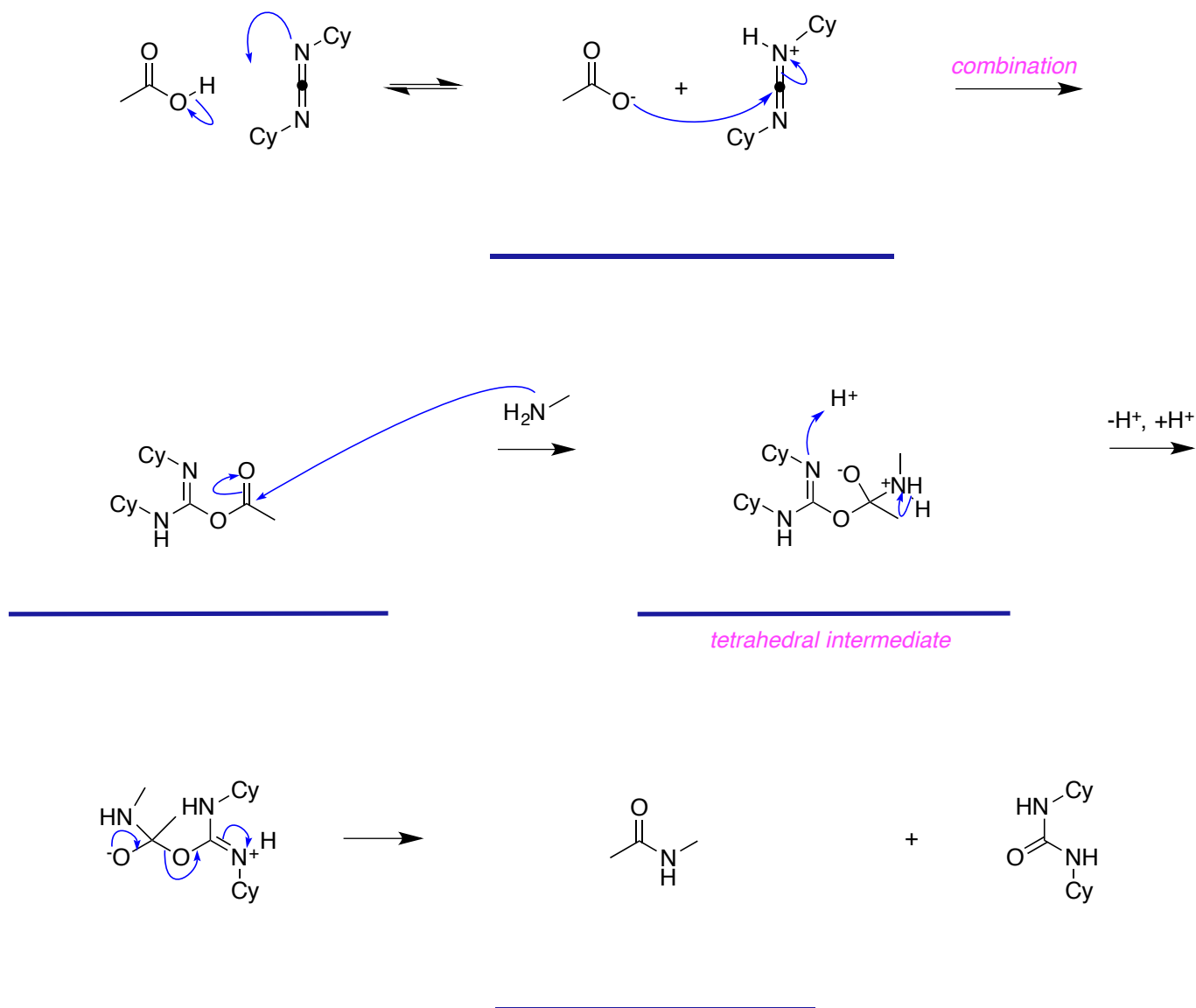


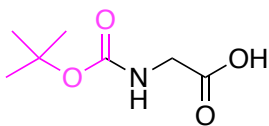
draw arrows to most reactive carbonyl carbon(s), circle unsymmetrical anhydrides, and box those that are mixed

different,

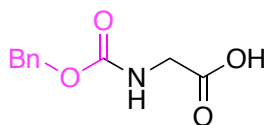
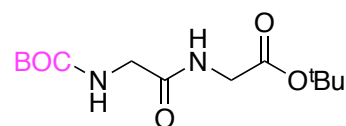
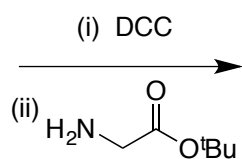
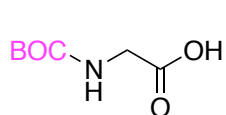
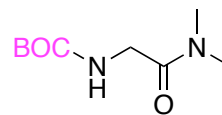
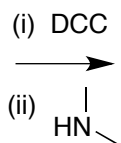
Formation Of Unsymmetrical Anhydride Derivatives Using Carbodiimides

urea.

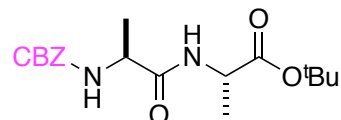
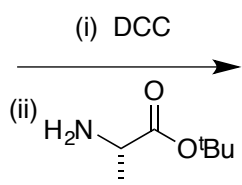
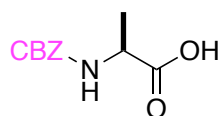
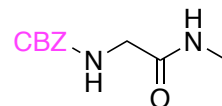
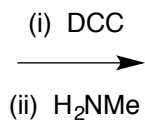




BOC
tert-ButylOxyCarbonyl



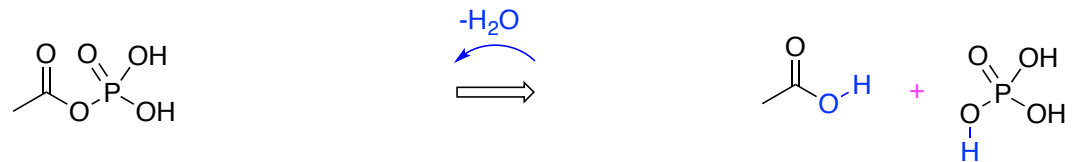
CBZ
CarboxyBenZyl



F. Activation Of Phosphate Acids In Cells Via Phosphate Anhydrides

Formation Of Mixed Anhydrides Of Phosphorus Acids

mixed anhydrides



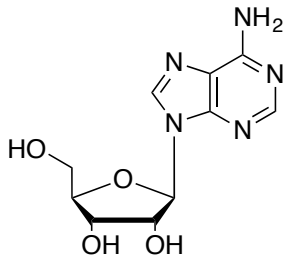
acyl phosphate

the *carbonyl* of
is a *better* leaving

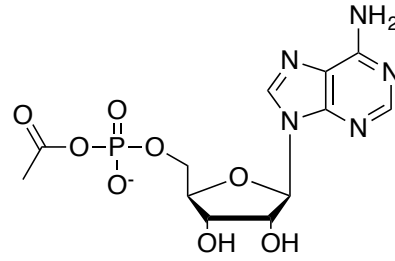


carboxylic and phosphoric acids

deprotonated

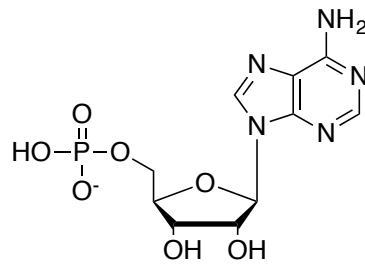


adenosine

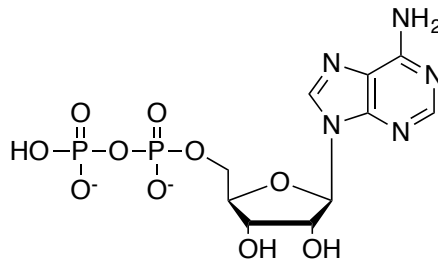


acyl adenylate

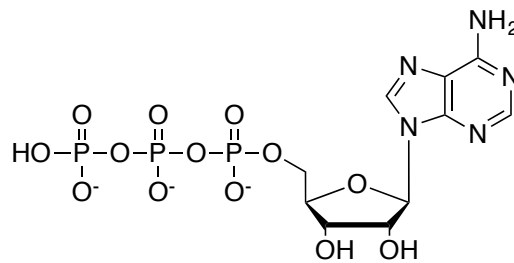
, *ADP / ATP*,



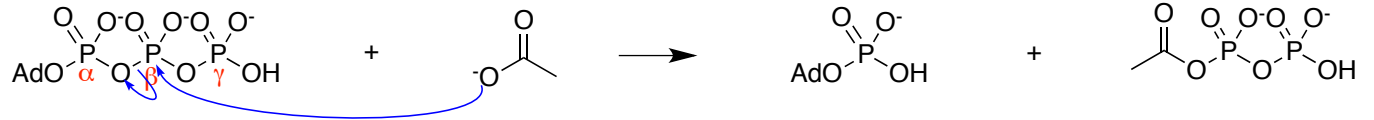
AMP



ADP



ATP



AMP and acyl pyrophosphate

β phosphorus.
on the γ phosphorus.

repel anionic
faster if encapsulated

Introducing, The Amino Acids!

from chapter(s) _____ in the recommended text

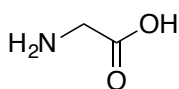
A. Introduction

B. Nomenclature And Conventions

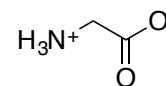
left,
right.

ammonium and a C-terminal *carboxylate*.

zwitterionic form.

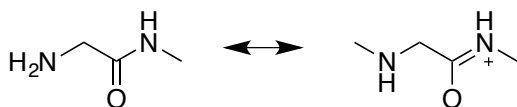


glycine, neutral form

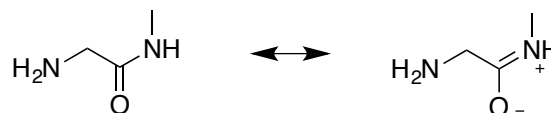


glycine, charged form

slow compared
resonance.



trans



cis

flat
sp²
alkenes.

trans
is not

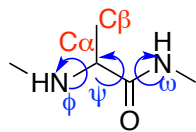
20 genetically

aliphatic

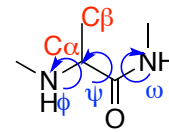
C α and the
 labeled *C β* .

C β .

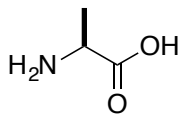
C. Amino Acids With Lypophilic Side Chains



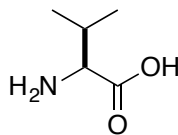
trans



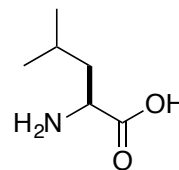
cis



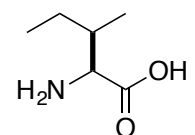
alanine, Ala, A



valine, Val, V



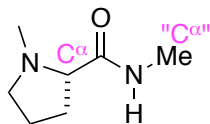
leucine, Leu, L



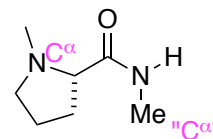
iso-leucine, Ile, I

L-configurations
the configuration of glyceraldehyde.

secondary amine.



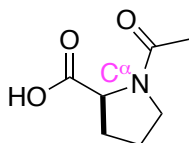
trans



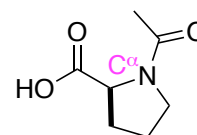
cis

Really the question and answer were intended to be (and will be in the second print):

Proline is an “odd-ball”: it is the only amino acid that is a *tertiary / secondary / primary* amine. Draw the *cis* and *trans* isomers of MeCO-Pro-OH.



trans



cis

more

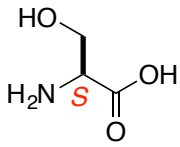
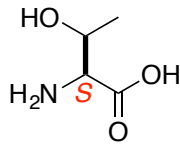
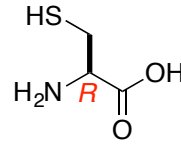
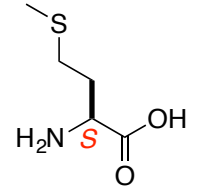
D. Alcohol And Thiol Amino Acids

Ser

Thr

Cys (CH₂SH)

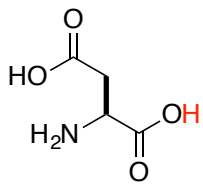
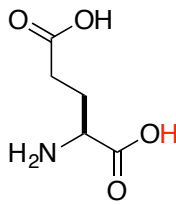
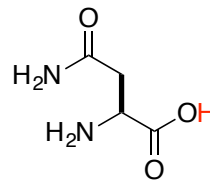
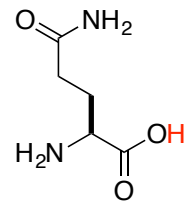
Met (CH₂CH₂SMe).

*serine**threonine**cysteine**methionine*

Cys,

sulfur atom connected to C β has higher priority than carbonyl group.

E. Acidic Amino Acids And Their Derivatives

*D**E**N**Q*

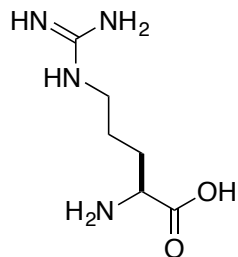
more acidic

F. Basic Amino Acids

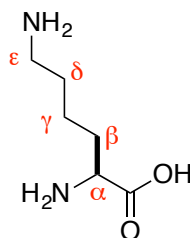
H

Lys

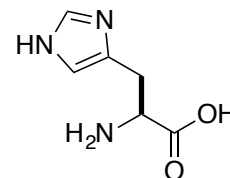
Arg ($\text{CH}_2\text{CH}_2\text{CH}_2\text{NHCNHNH}_2$)



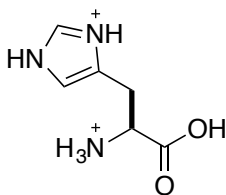
most basic



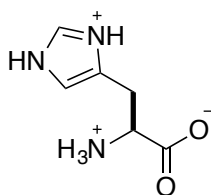
intermediate



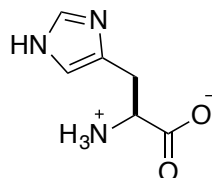
least basic



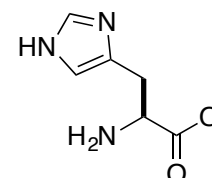
pH = 0
di-cation



4

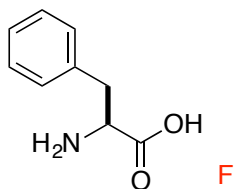


8

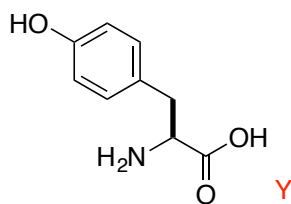


12
monoanion

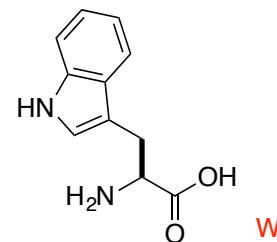
G. Aromatic Amino Acids



phenylalanine



tyrosine



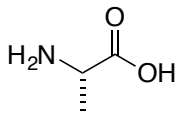
tryptophan

weaker

indole

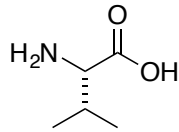
is not

H. Summary



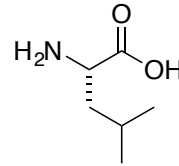
hydrophobic 1

name: alanine, Ala, A



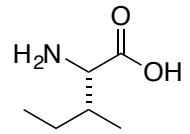
hydrophobic 2

valine, Val, V



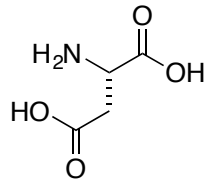
hydrophobic 3

leucine, Leu, L



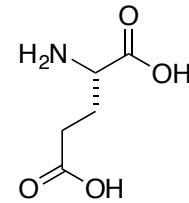
hydrophobic 4

iso-leucine, Ile, I



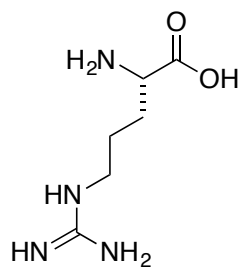
acidic 1

aspartic acid, Asp, D



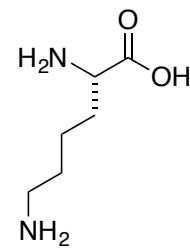
acidic 2

glutamic acid, Glu, E



basic 1

arginine, Arg, R



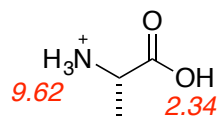
basic 2

lysine, Lys, K

I. Isoelectric Points

isoelectric point

midway between



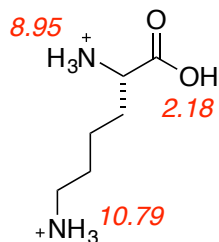
structure of alanine indicating pKa's

$$pI = \frac{pKa(\alpha\text{-COOH}) + pKa(\alpha\text{-NH}_3^+)}{2}$$

$$pI = (2.34 + 9.62)/2 = 5.98$$

calculation

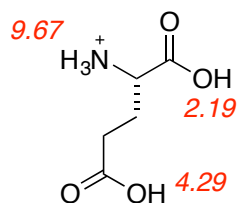
average



structure of Lys indicating pKa's

$$pI = (8.95 + 10.79)/2 = 9.87$$

calculation



structure of glutamic acid indicating pKa's

$$pI = (2.19 + 4.29)/2 = 3.24$$

calculation

Asp, *acid* Asn, *neutral* Arg, *basic*
 Glu, *acid* Gln, *neutral*
 Ser, *neutral* Thr, *neutral*

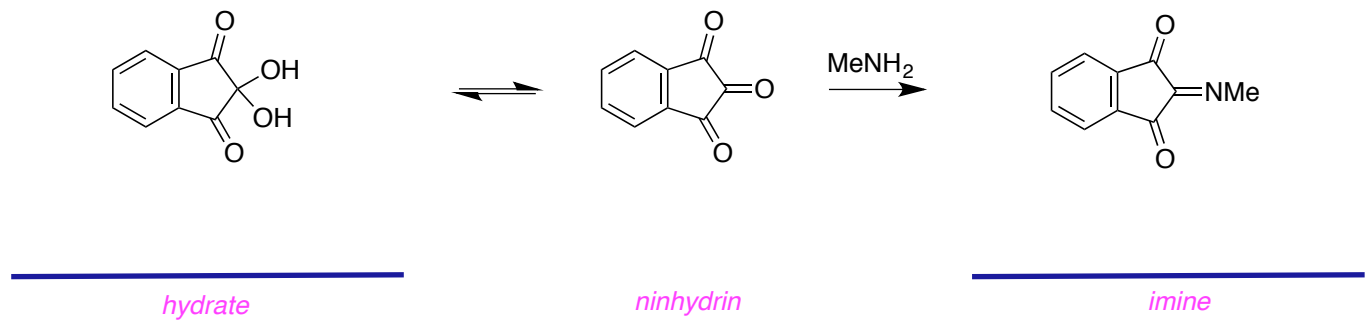
the *highest* pI value *Arg* the *lowest* pI value *Glu*
 most *negative* charge at pH 6 *Glu* most *positive* charge at pH 2 *Lys*

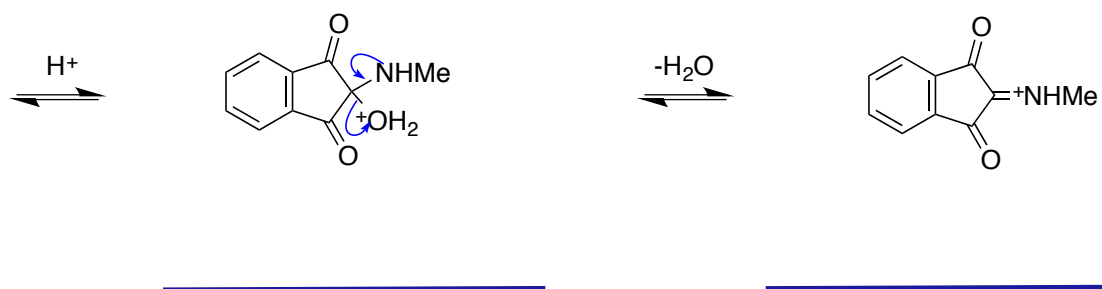
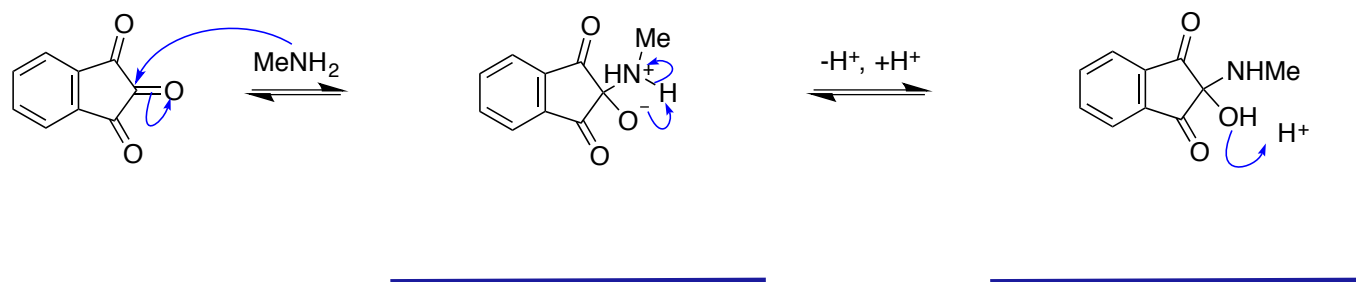
mass divided by charge.

Lys
not at all
migrate to the positive electrode.

J. The Ninhydrin Test

central

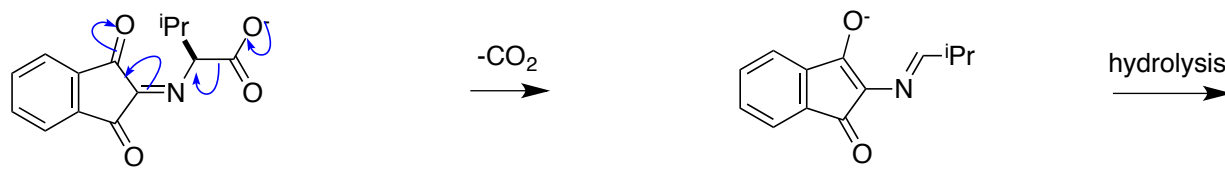
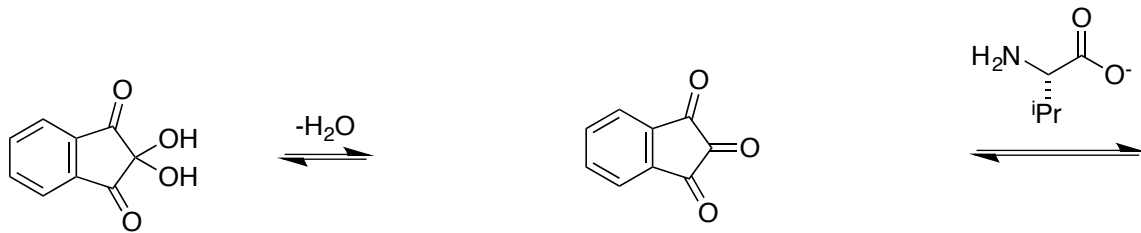




proline).

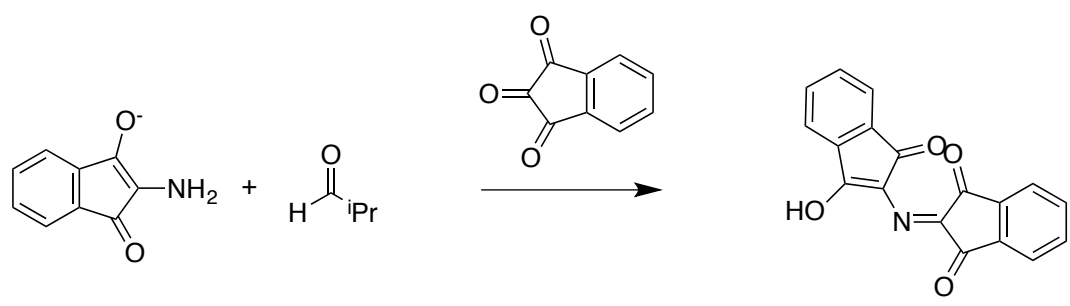
amine

Proline *does not*



imine

imine enolate



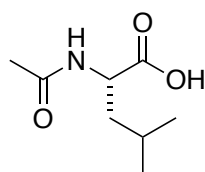
amine

purple

purple
can be quantified by UV.

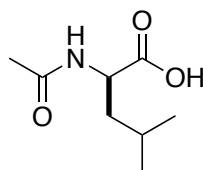
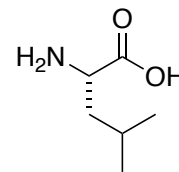
and to quantitate

perfect

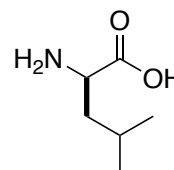


(S)-Ac-Leu

*pig kidney
aminoacylase*
→
fast



*pig kidney
aminoacylase*
→
slow



is *just under 50 %*.

is *just under 50 %*.

decreases with conversion, while that of the starting material *increases*.

Peptide Syntheses

from chapter(s) _____ in the recommended text

A. Introduction

do not
acid

H-Met-Phe-OH

H-Met-Met-OH

H-Phe-Phe-OH

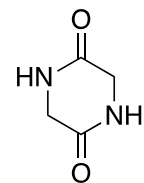
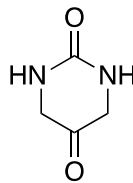
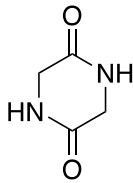
H-Phe-Met-OH

dipeptide

dipeptide

dipeptide

dipeptide



diketopiperazine

symmetrical diketopiperazine

unsymmetrical diketopiperazine

would also

impractical synthesis

N- protect one of the fragments and *C-* protect the other.

Reactions Of Unprotected Amino Acids

Carboxylic acids *do not* combine with amines
carboxylic acids to *acid* chlorides,

H-Met-Phe-OH

H-Met-Met-OH

H-Phe-Phe-OH

H-Phe-Met-OH

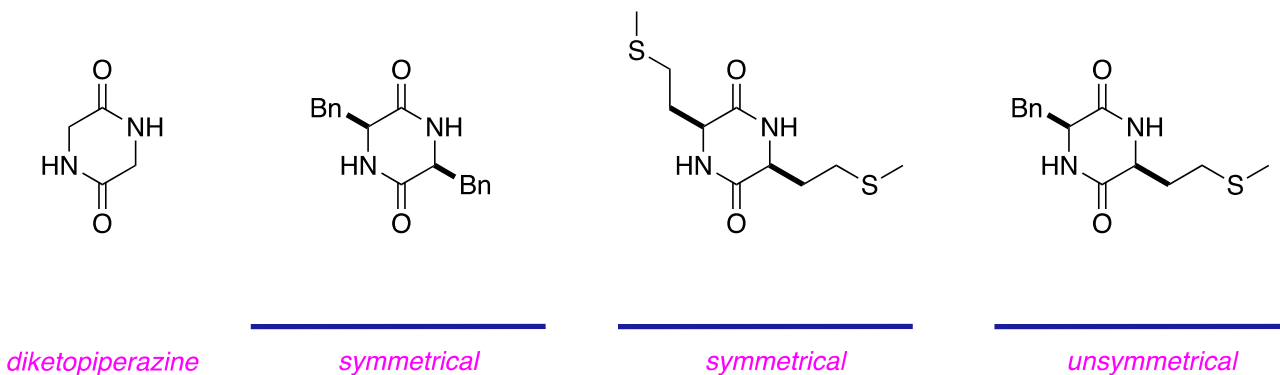
dipeptide

dipeptide

dipeptide

dipeptide

There are also three possible cyclic by-products, *diketopiperazines*, in the reaction above; show these:

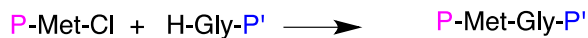


Polymeric materials *would* also be produced in this reaction.

Overall, this route would be a(n) *impractical*

To solve this problem it is necessary to *N*-protect one of the fragments and *C*-protect the other.

Reactions Of Protected Amino Acids

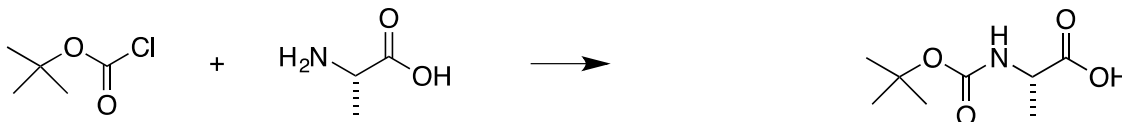


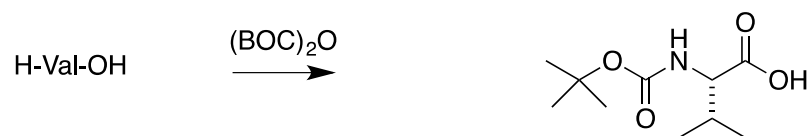
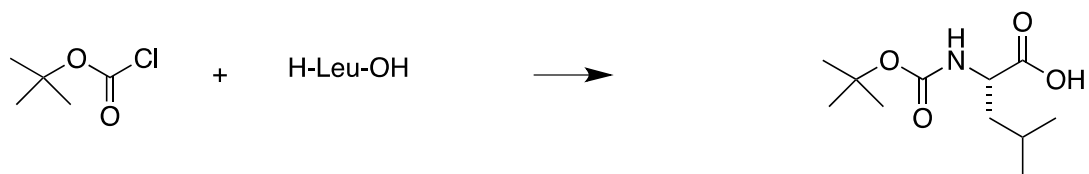
Illustrative Protection: BOC/^tBu

N-BOC Protected Amino Acids

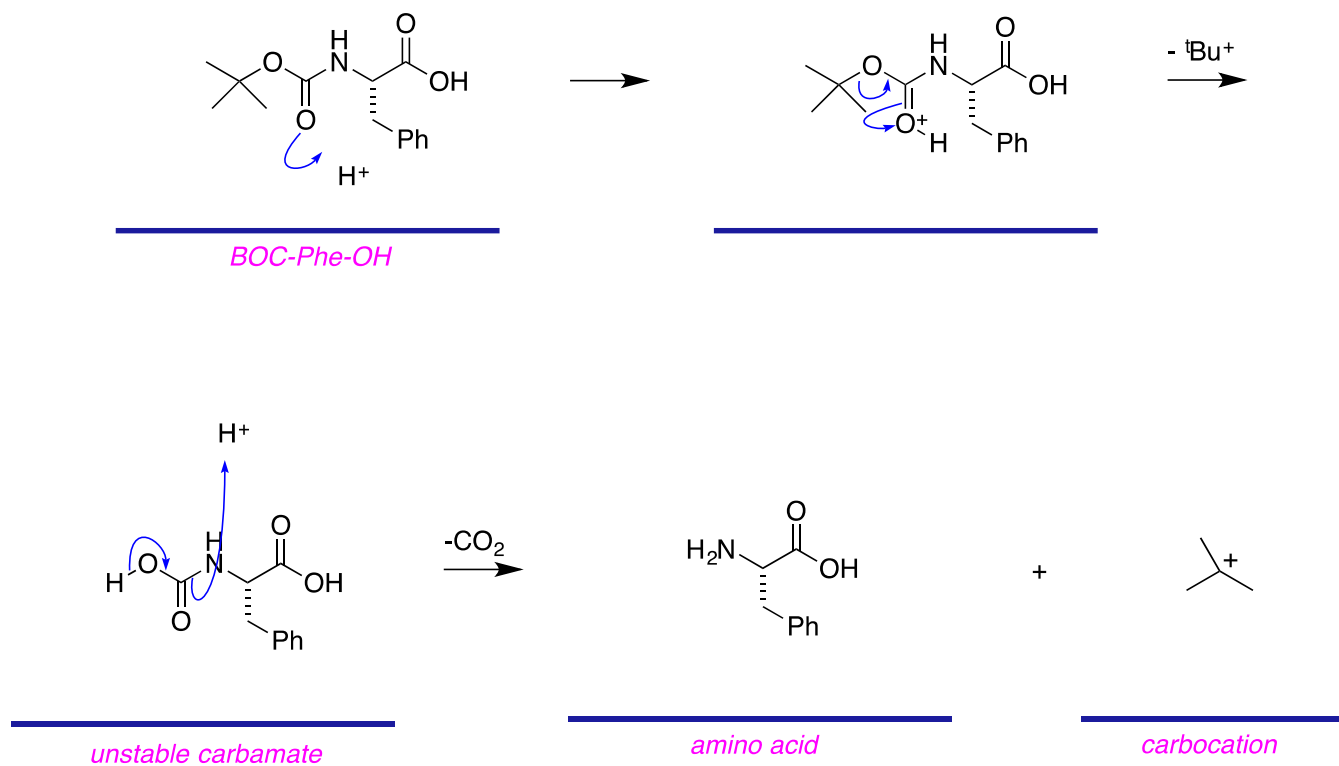
amines

amines.

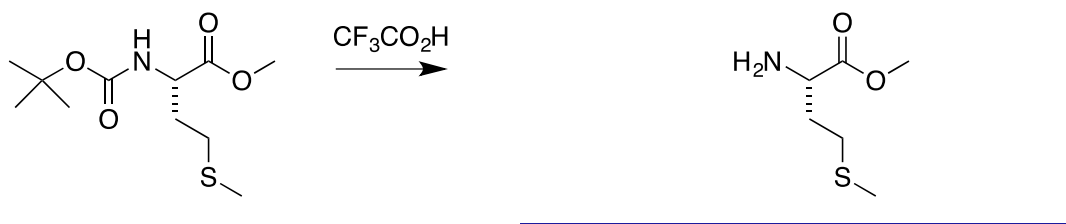




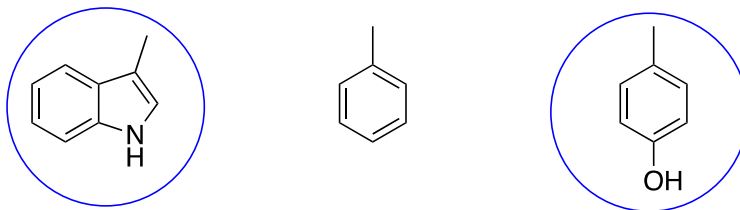
with *trifluoroacetic (TFA)* acid.

carbon *dioxide*.

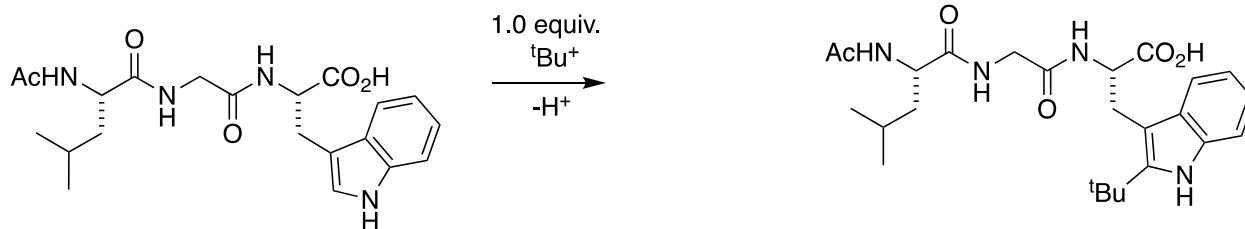
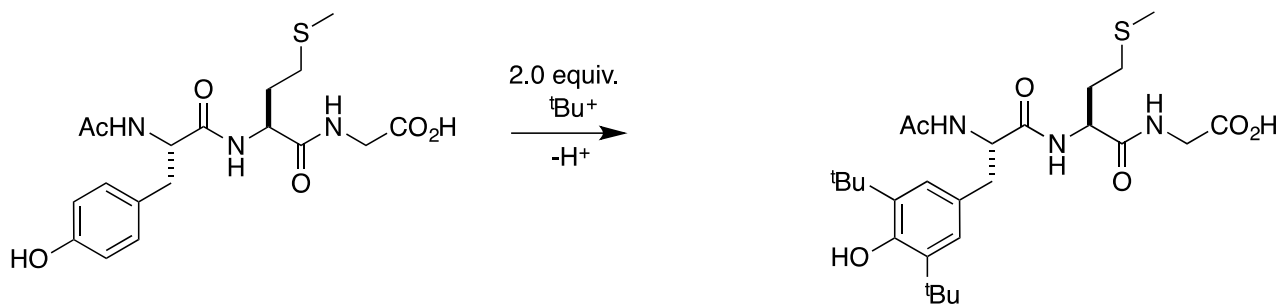
Give the products of the following reactions



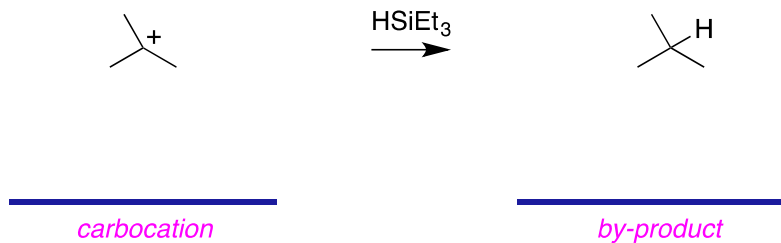
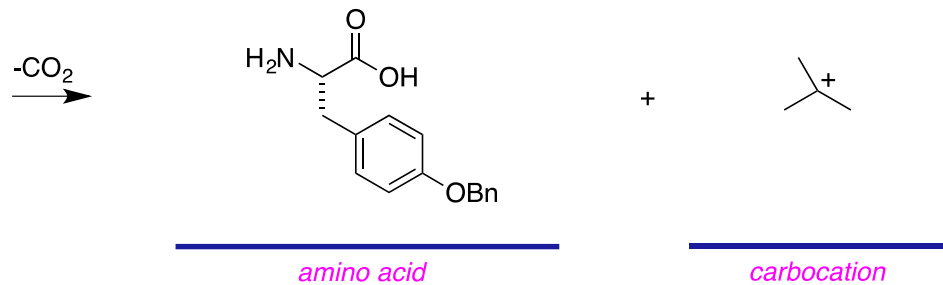
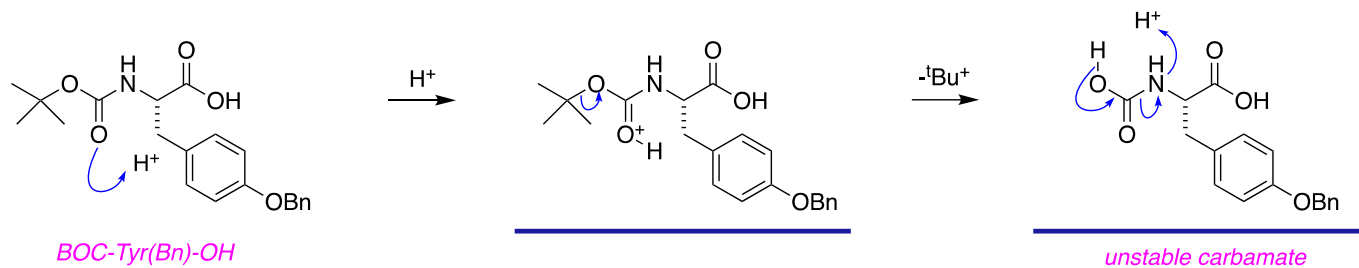
undesirable
HSiEt₃



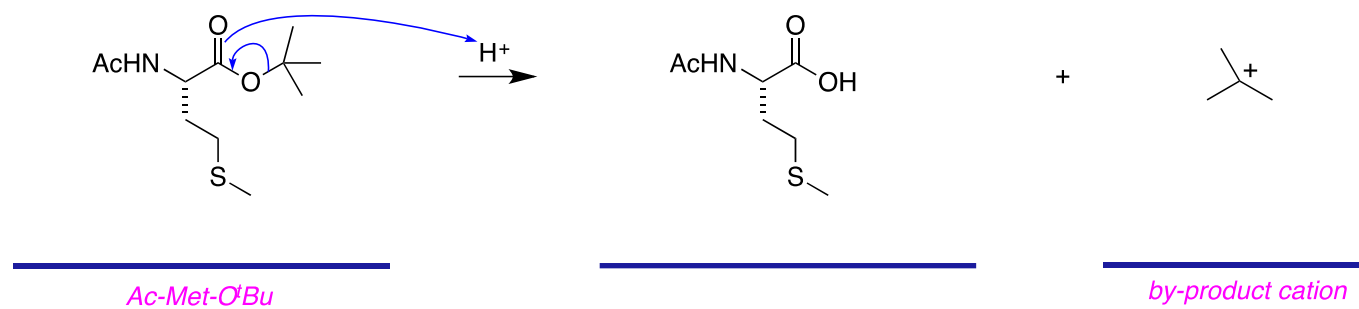
Tyr / Trp



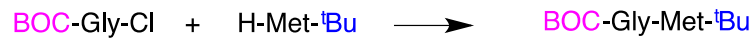
usually



C-Protection Of Amino Acids With ^tBu-Groups



1-Adamantyl esters *cannot*
are



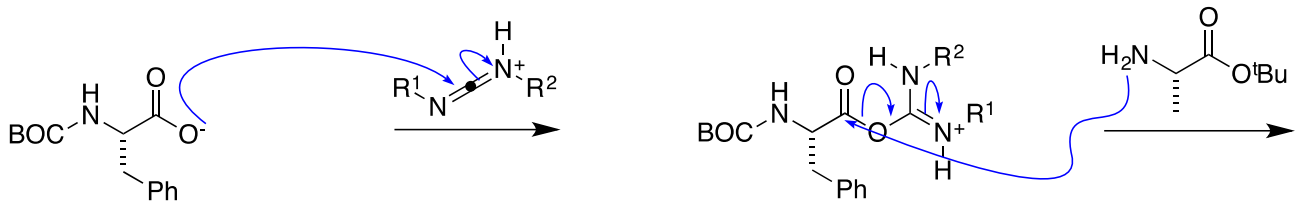
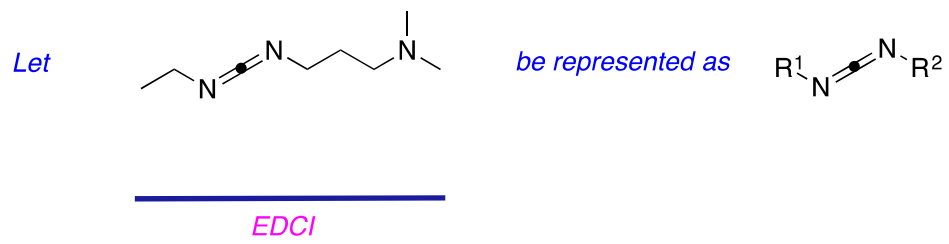
Activation Of *N*-Protected Amino Acids

too *reactive* for

using *carbodiimide* reagents

ie dicyclohexylurea,

because *the by-products can be protonated and are water-soluble.*



BOC-Phe-O⁻



BOC-Phe-Ala-O^tBu

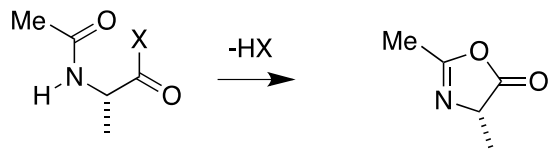
by-product

The Epimerization Problem

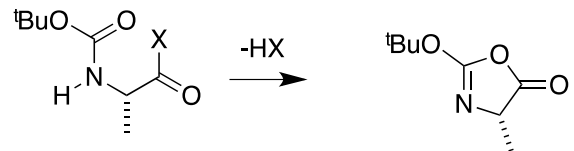
epimerize)
epimeric products.

difficult to separate

azlactone.



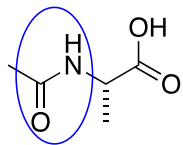
*azlactone
forms rapidly*



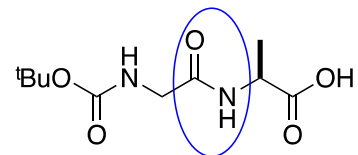
*azlactone
forms slowly*

is driven by aromatic stabilization in the product and simultaneous *loss carbamate*.

more



Ac-Ala-OH



BOC-Gly-Ala-OH

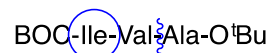
Strategies In Solution Phase Syntheses That Avoid Epimerization

will

will tend to



less prone to racemization



more prone to racemization

circle the one amino acid in one of these structures that is most vulnerable to epimerization

are

C- to N- direction

B. Solid Phase Peptide Syntheses

are mixed with

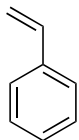
is usually required

easier to purify

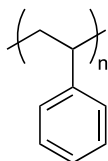
advantages of

are not optimally

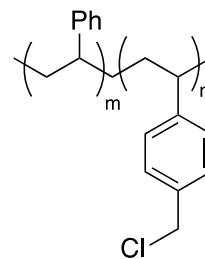
*C-*terminus.



styrene

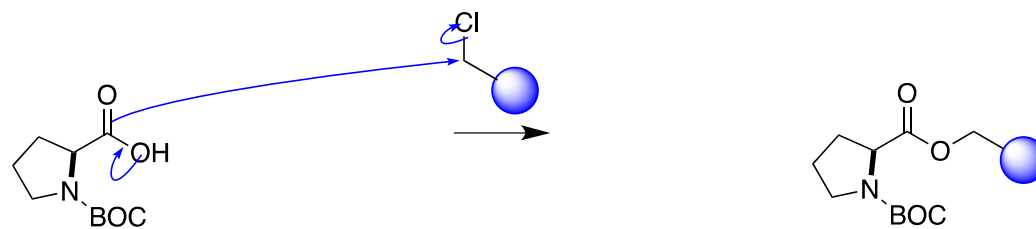


polystyrene



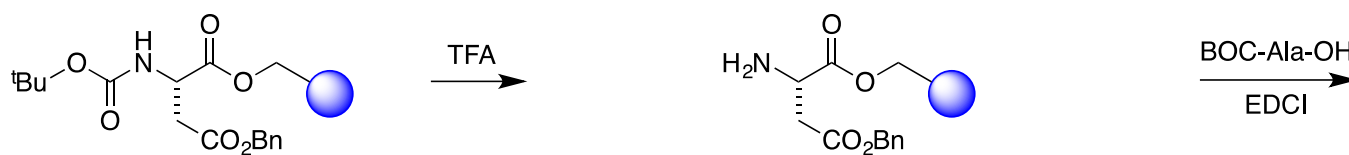
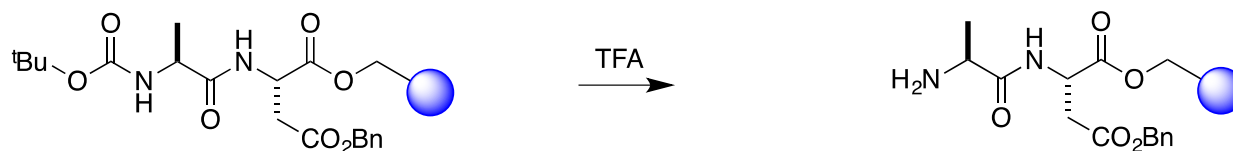
"4-chloromethylpolystyrene"

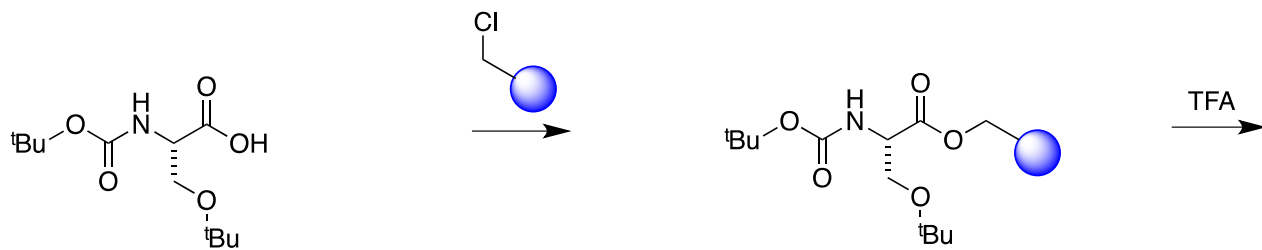
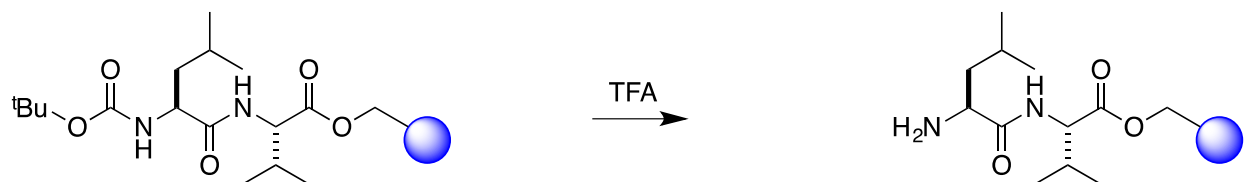
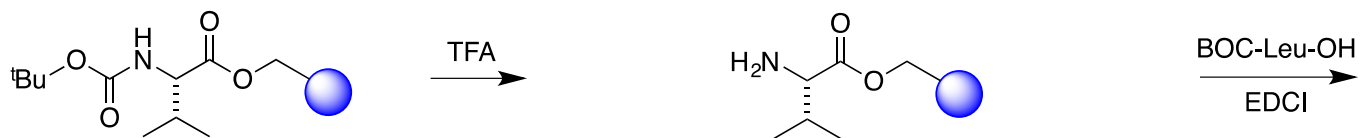
S_N2 reaction

*BOC-Pro-OH*

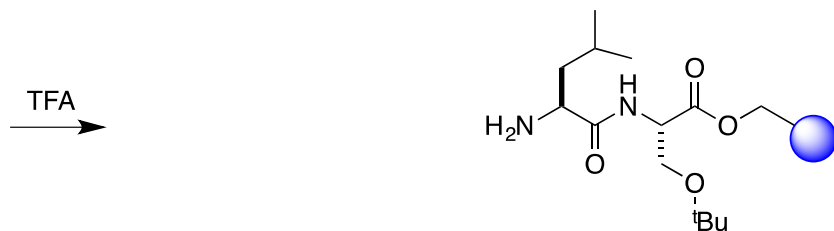
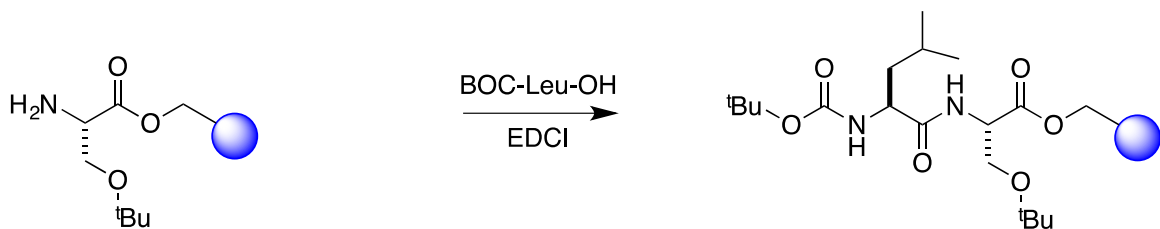
TFA often in the *presence* of a scavenger; this *does not*

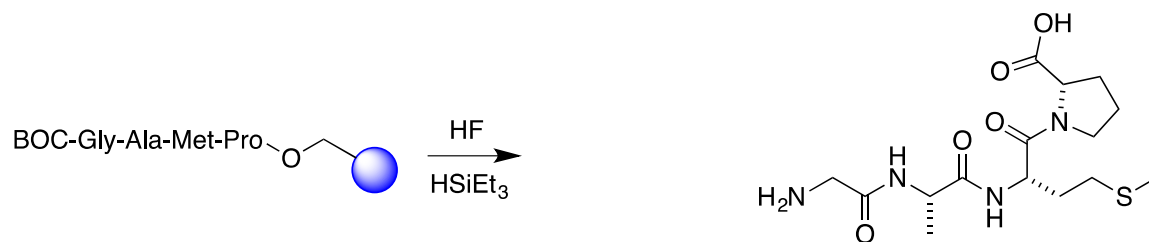
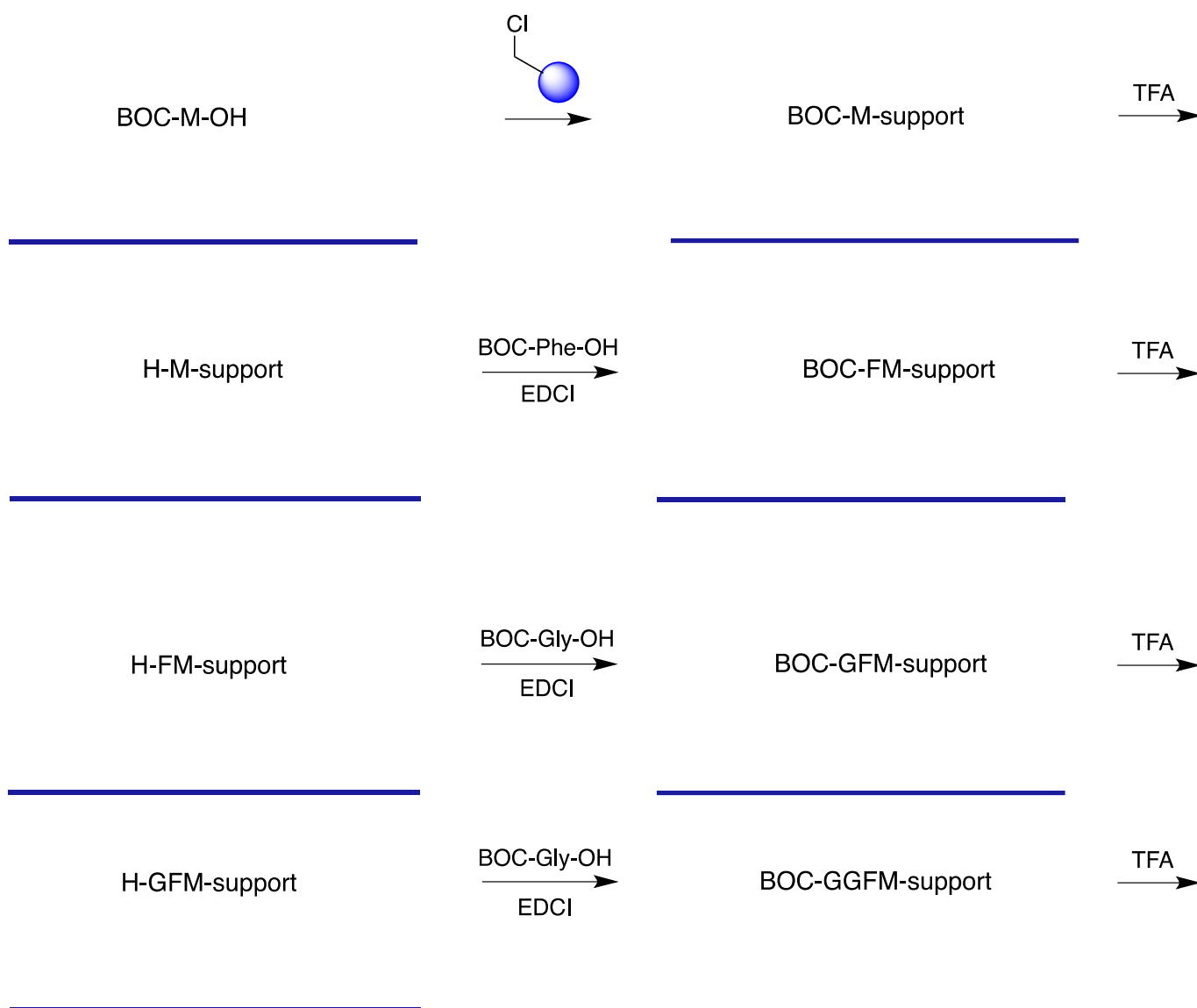
N-terminus

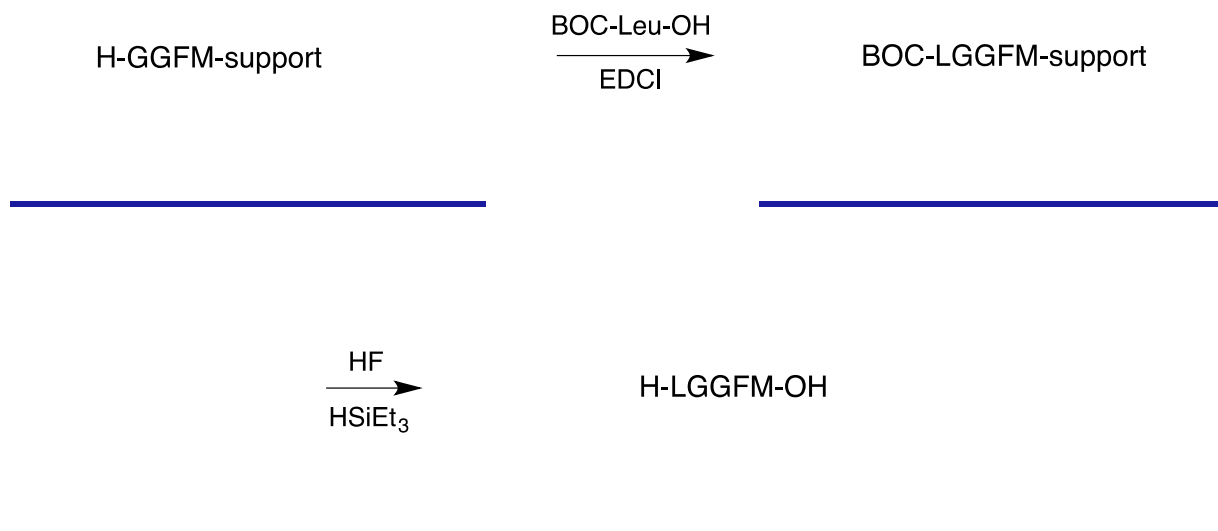
*BOC-Asp(Bn)-support*



BOC-Ser(O^tBu)-OH



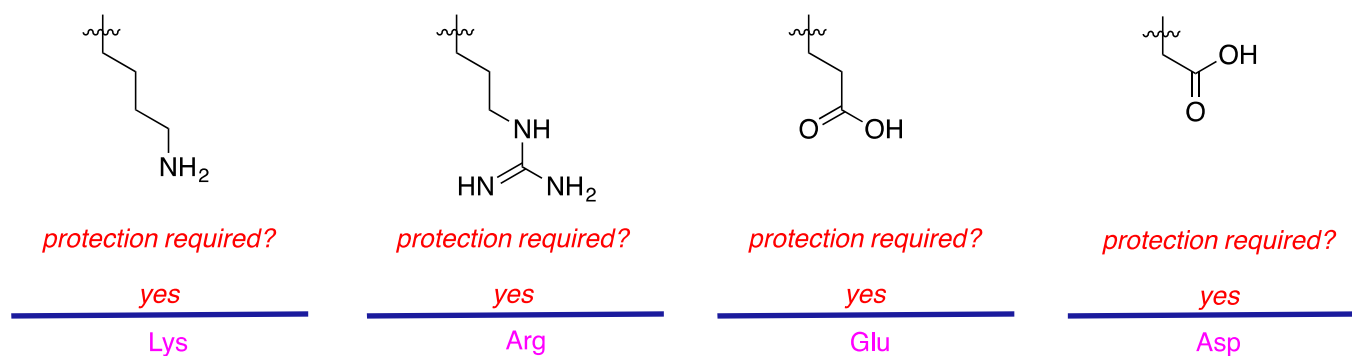
HF and scavengers*draw peptide*

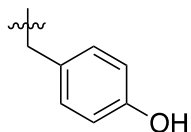


C. Side-chain Protection Of Amino Acids

may
is required.

undesirable
desirable

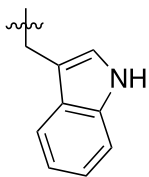




protection required?

yes

Tyr



protection required?

yes

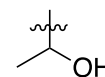
Trp



protection required?

yes

Ser



protection required?

yes

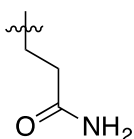
Thr



protection required?

yes

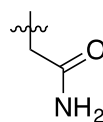
Cys



protection required?

yes

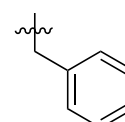
Gln



protection required?

yes

Asn



protection required?

no

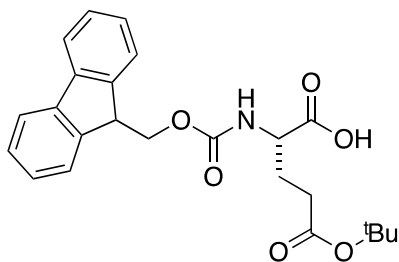
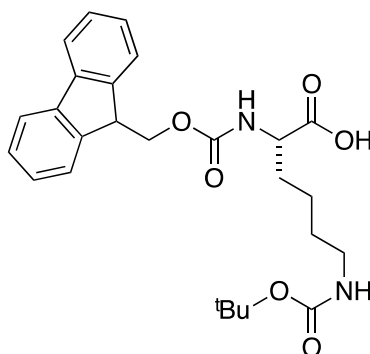
Phe

D. The Fmoc Approach

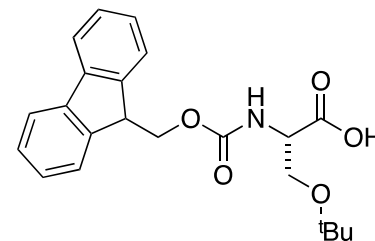
HF

base labile

via TFA.

Fmoc-Glu(^tBu)-OH

Fmoc-Lys(BOC)-OH

Fmoc-Ser(^tBu)-OH

Peptides And Proteins

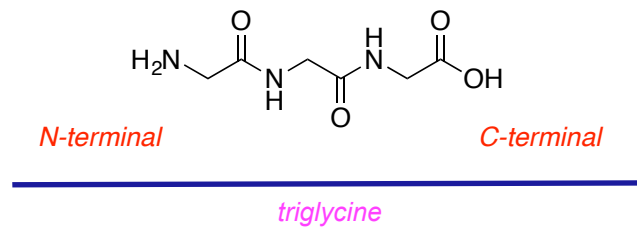
from chapter(s) _____ in the recommended text

A. Introduction

B. Nomenclature And Conventions

by *amide* bonds.

on the *left*,
right.



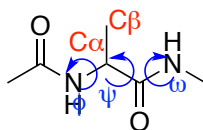
amine,
acid.

ammonium and a C-terminal *carboxylate*.

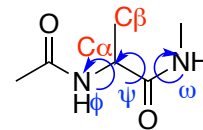
trans (based on the *peptide polyamide backbone alkenes*).

local conformations

like ϕ (the *N-C α* dihedral) | ψ (*C α -CO*), and ω (*CO-NH*)
 ω because of amide



trans



cis

C. Primary Structures

sequence of amino

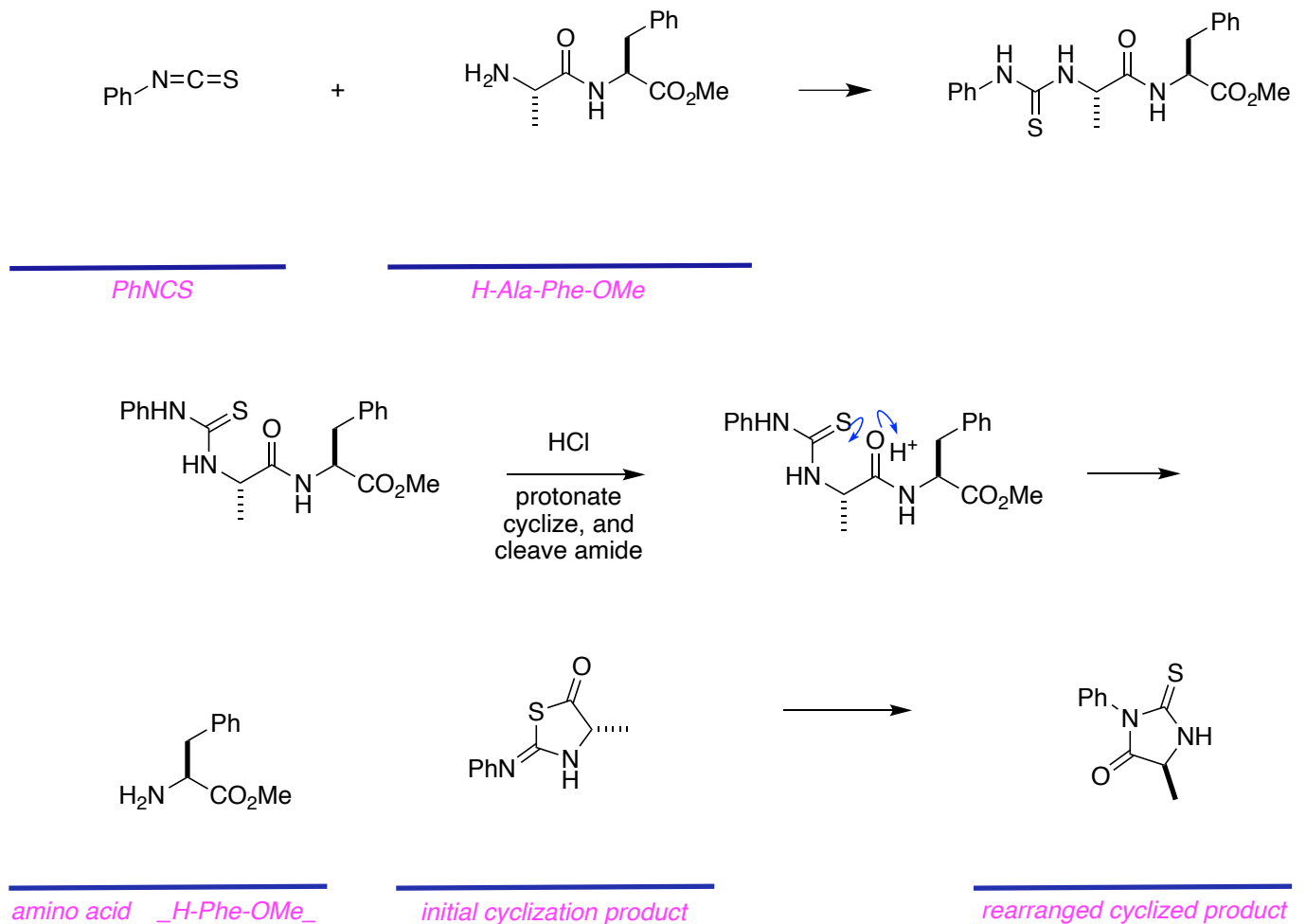
sequence of

similarity

fold into similar shapes.

Elucidation Of Primary Peptide Structure Via The Edman Degradation

primary structure

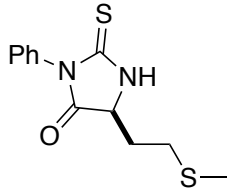


Chromatographic analysis

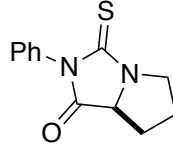
does require

It *is* possible.

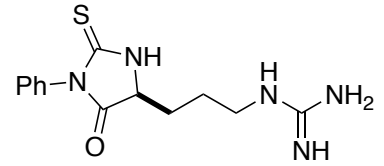
It *is not*



first thiohydantoin



second thiohydantoin



third thiohydantoin

Elucidation Of Primary Structure Via *Enzymatic* Cleavage And Mass Spectroscopy

mass spectrometry

so *proteases*

at predictable sites

within of a chain.

Positions of cleavage *vary*

fragment 1: H-Pro-Ala-Pro-Gly-Arg-Trp-OH

fragment 2: H-Ala-His-Gln-Met-Val-Lys-His-Lys-Ala-Trp-OH

fragment 3: H-Pro-Ser-Tyr-OH

fragment 4: H-Thr-Ala-OH

Chymotrypsin

fragment 1: H-Pro-Ala-Pro-Gly-Arg-Trp-OH

fragment 2: H-Ala-His-Gln-Met-Val-Lys-His-Lys-Pro-Trp-OH

fragment 3: H-Pro-Ser-Tyr-OH

fragment 4: H-Thr-Ala-OH

Elastase

fragment 1: H-Pro-Ala-OH

fragment 2: H-Pro-Gly-OH

fragment 3: H-Arg-Trp-Ala-OH

fragment 4: H-His-Gln-Met-Val-Lys-His-Lys-Pro-Trp-Pro-Ser-Tyr-Thr-Ala-OH

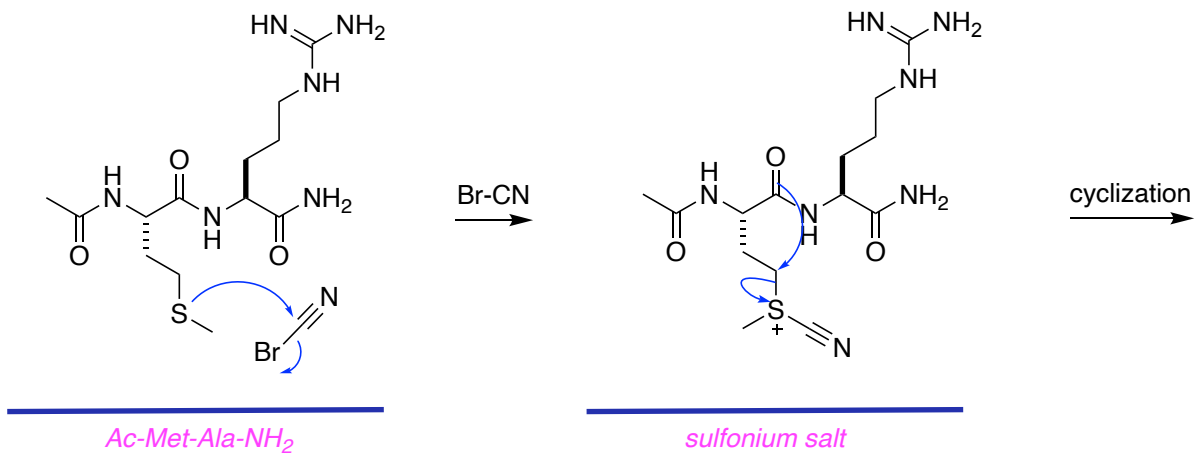
Elucidation Of Primary Structure Via Cyanogen Bromide Cleavage And Mass Spectroscopy

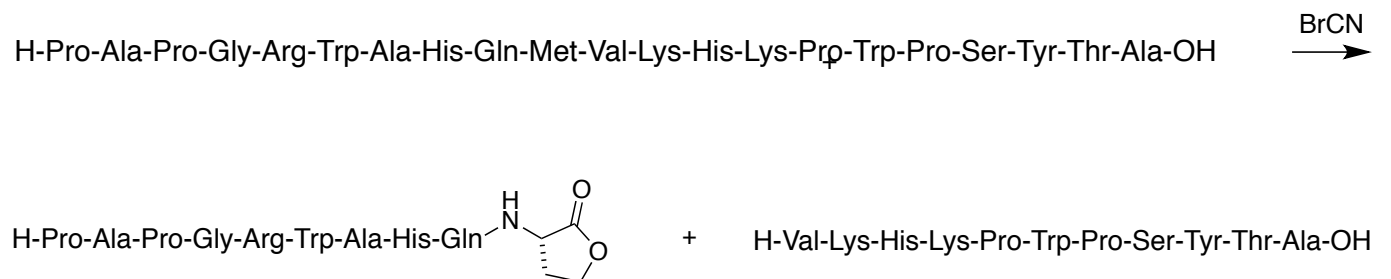
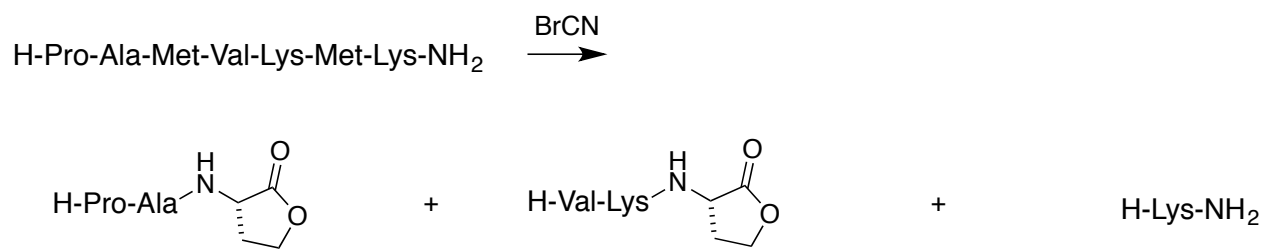
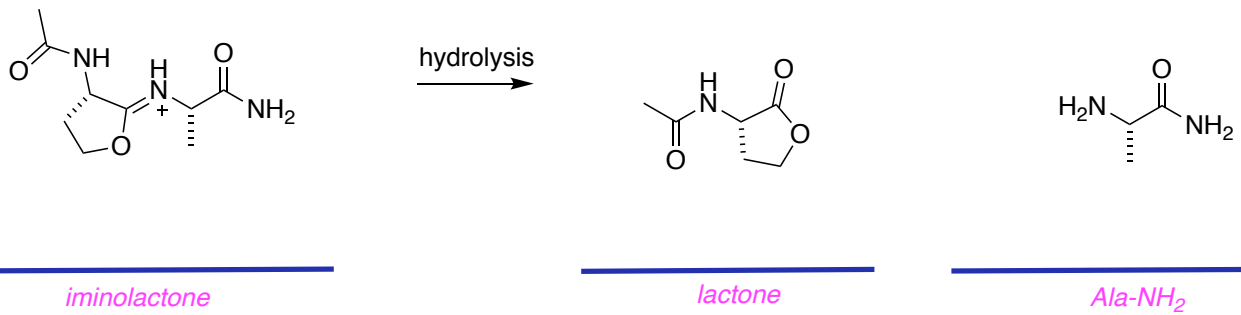
methionine

methionine

C_γ atom

iminolactone produced





D. Secondary Structures

hydrogen bonding between residues shielding of hydrophobic residues from aqueous surroundings
 entropy gains placing hydrophilic residues at the core placing hydrophilic residues at the periphery
 ionic interactions between charged side-chains stacking of aromatic rings
 packing of one chain against another overlap of orbitals containing C=O lone pairs with other C=O π^* orbitals
 increased temperature addition of high concentrations of guanidine hydrochloride

secondary structure.

primary structures.

are called *helices*.

right handed

does not matter (right helical in both directions)

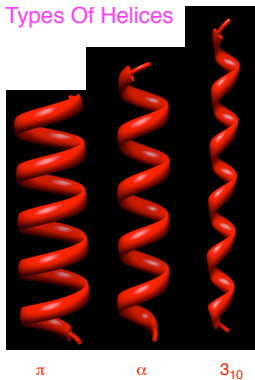
most common

3.6 amino acid

Pro is rarely

in *collagen*.

Types Of Helices



Amino acid blocks that coil into spring-like arrangements are called *helices*.

right handed corkscrew when viewed from *does not matter*.

most common, α -helices, have *3.6* amino acid residues per coil of the helix.

Pro is rarely found in α , π , or 3_{10} helices beca..... found in *collagen* /.

in *the same* directions.

in *opposite* directions.

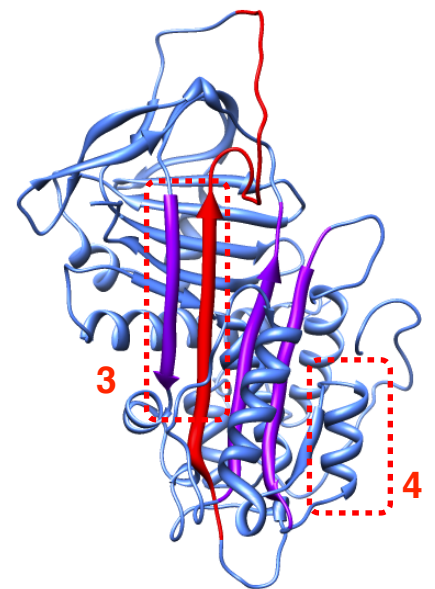
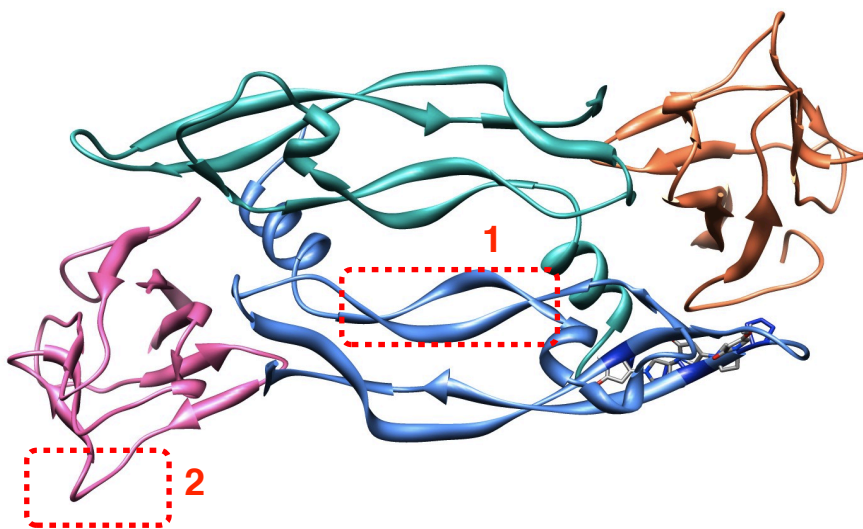
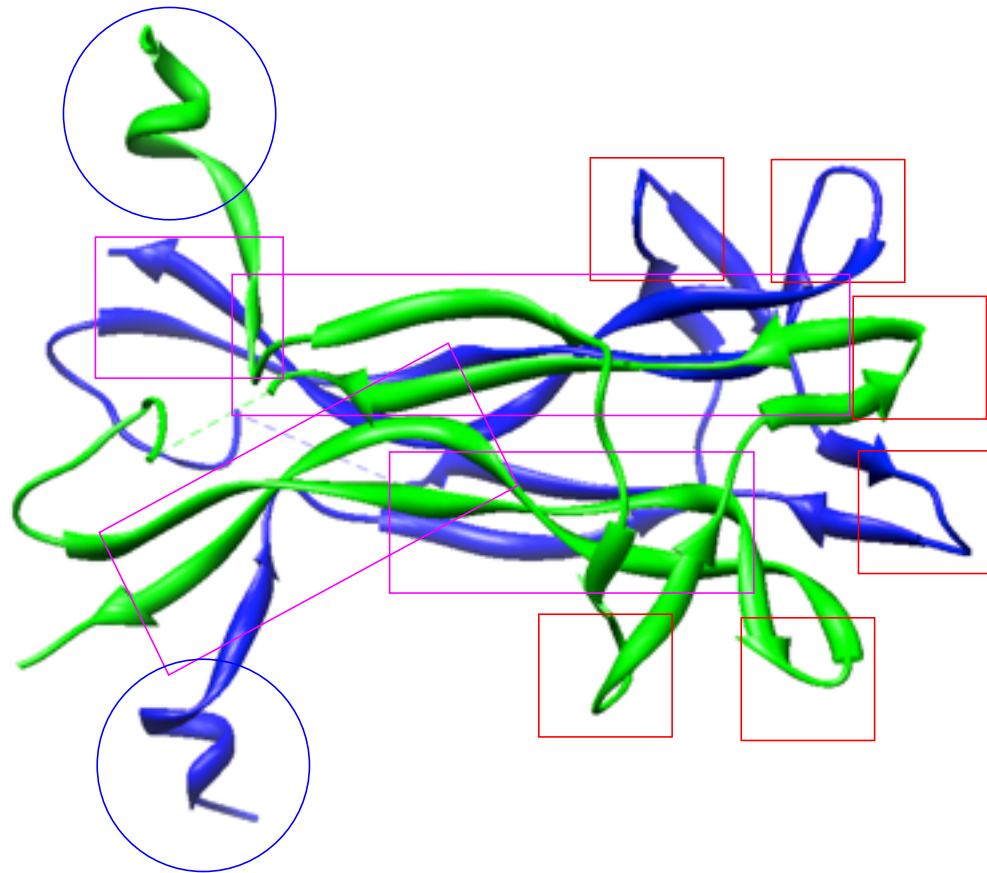
the strand loops back on itself.

β -turns, while *γ -turns*

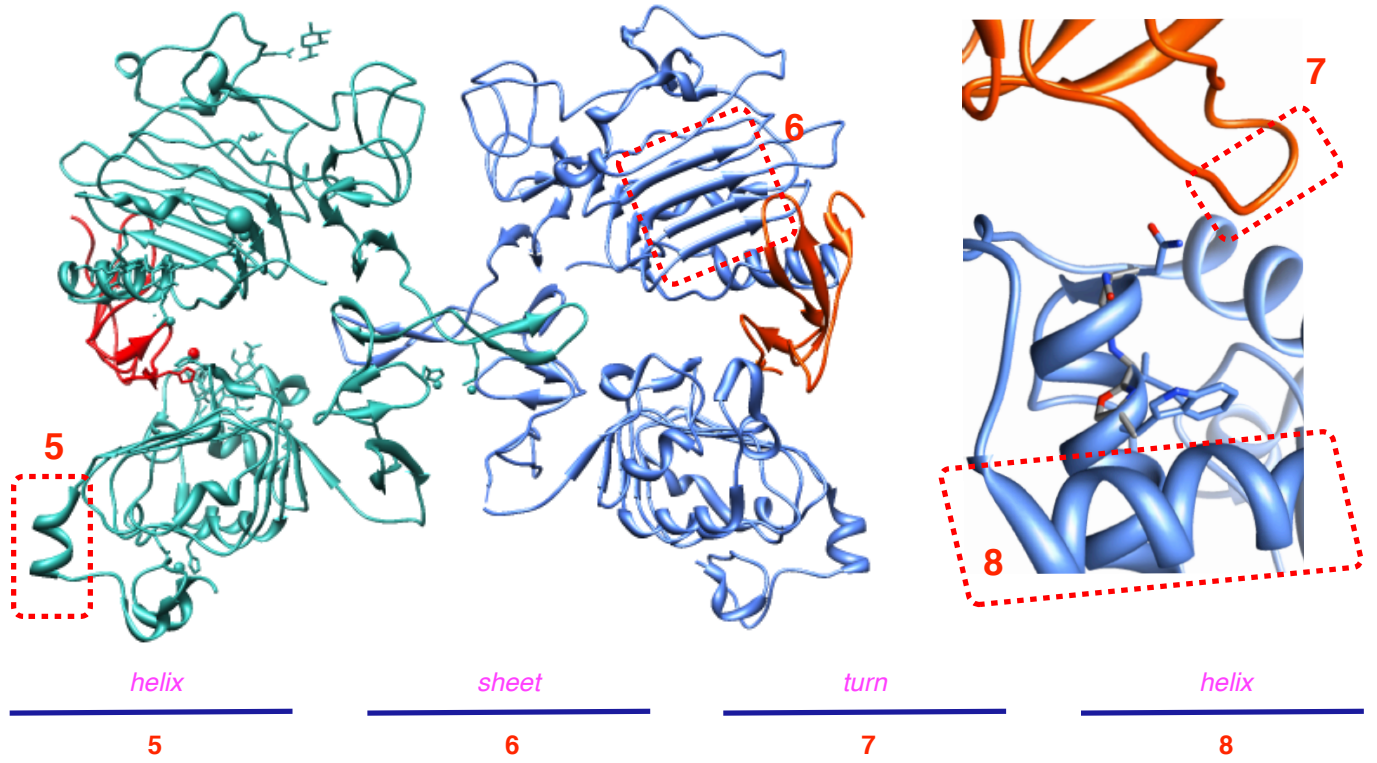
antiparallel β -sheets.

Different protein, Ha!

a *β -strand* b *sheet-turn-sheet* c *parallel β -sheet* d *antiparallel β -sheet*



sheet 1 turn 2 sheet 3 helix 4



E. Tertiary And Quaternary Structures

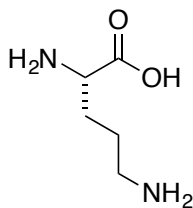
these protein units usually *are not* covalently

F. Constraints On Peptide And Protein Structures

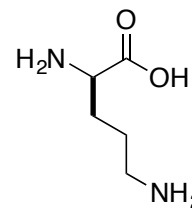
do not fold

cyclo(-Val-Orn-Leu-D-Phe-Pro-)₂

gramicidin S



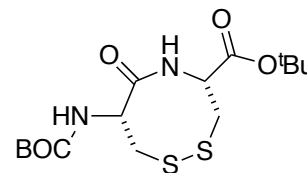
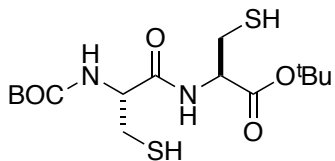
L-Orn



D-Orn

Cys residues.

oxidizing agents.



BOC-Cys-Cys-OtBu

BOC-Cys-Cys-OtBu

S—S

actually following should be shown with one letter codes where:

Cys = C

Tyr = Y

Ile = I

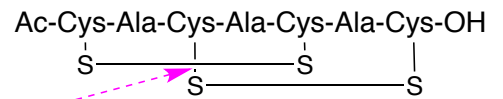
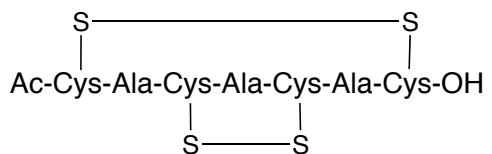
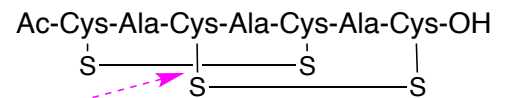
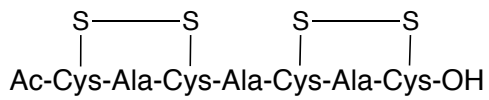
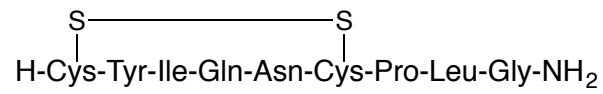
Gln = Q

Asn = N

Pro = P

Leu = L:

Gly = G



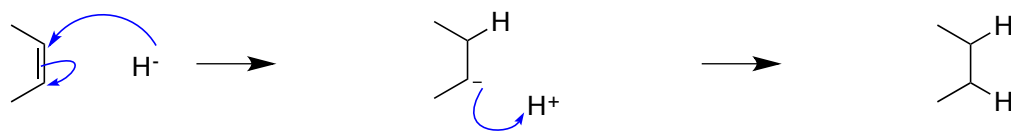
It *is* necessary
could be done

Hydridic Reductions

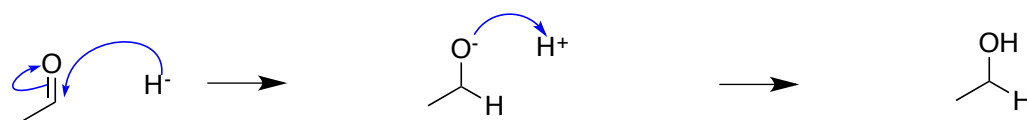
from chapter(s) _____ in the recommended text

A. Introduction

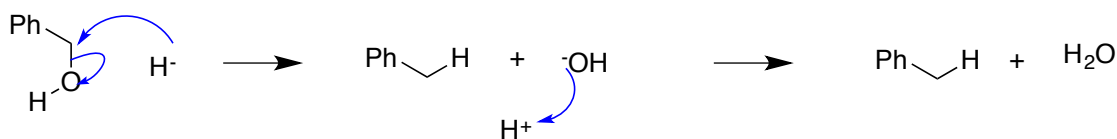
B. Mechanism



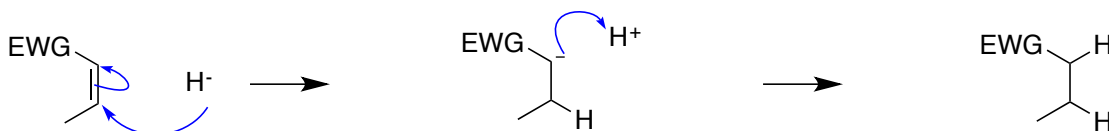
hard



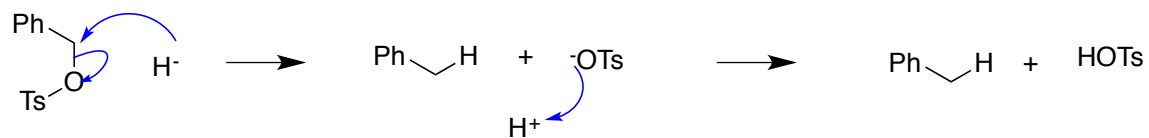
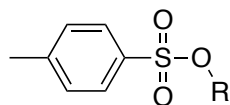
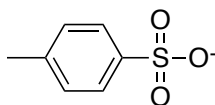
easy



hard



easy

*easy**Ts**TsO⁻*

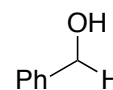
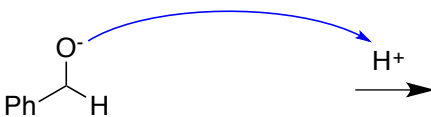
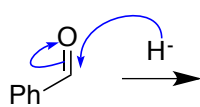
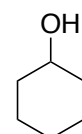
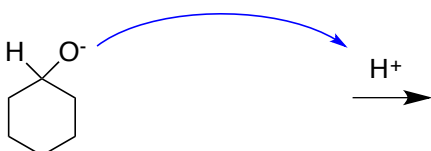
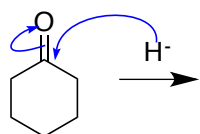
easy to reduce
hard to reduce them

tosylates are
tosyl groups are
ionic
chemoselective reductions

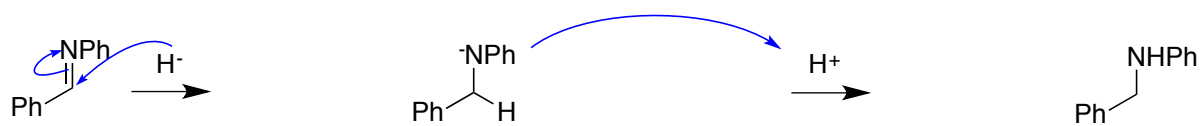
do not tend

C. Substrate Scope

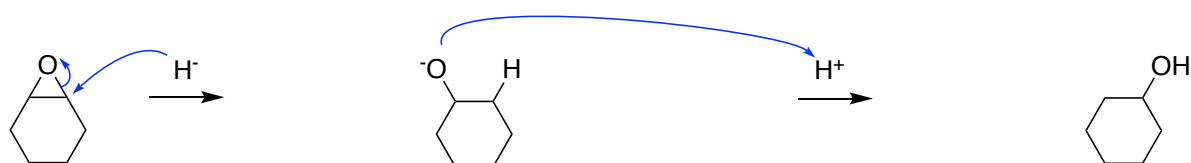
One Reduction

*alkoxide**alkoxide*

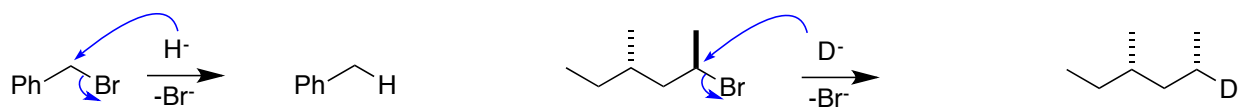
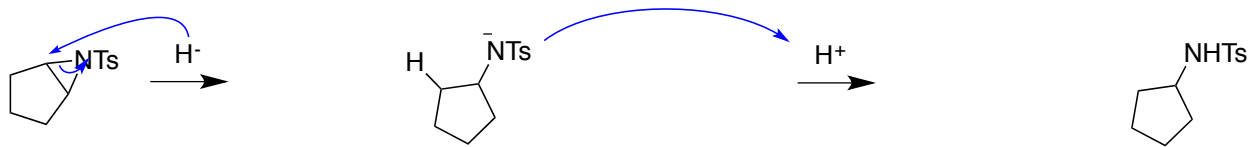
NaBH_4 because



amide anion



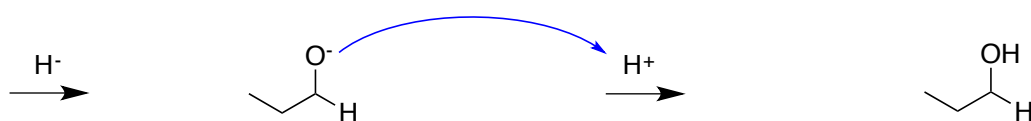
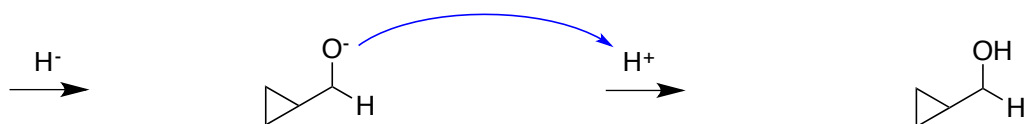
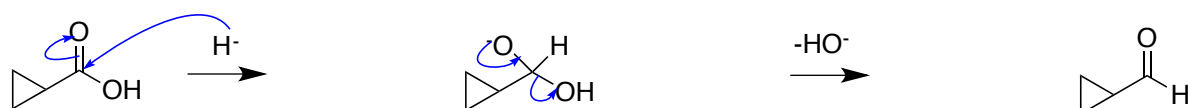
alkoxide

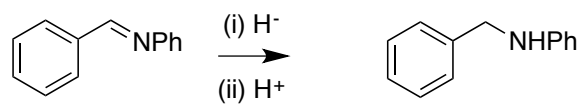
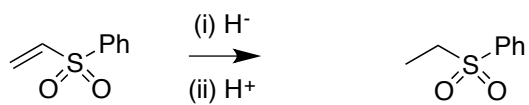
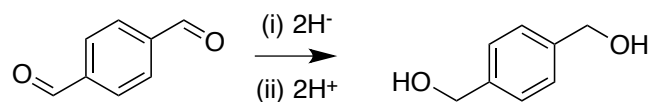
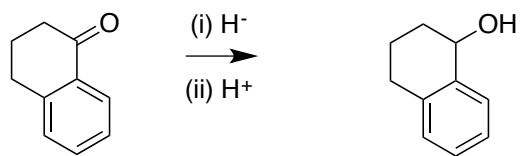
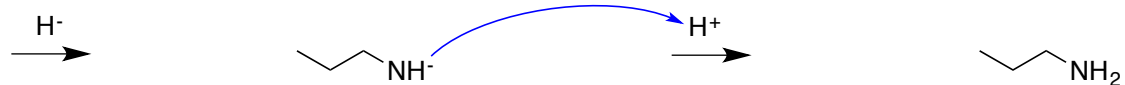


this reaction proceeds with inversion

It takes 2

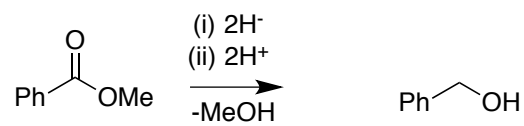
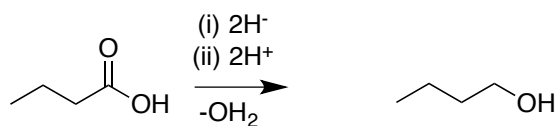
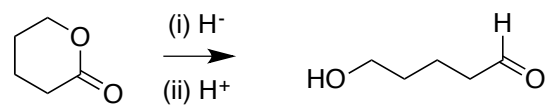
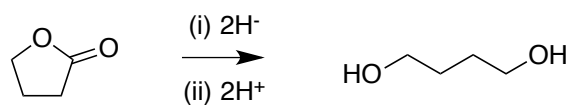
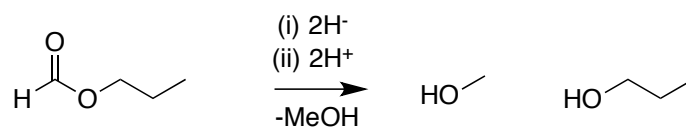
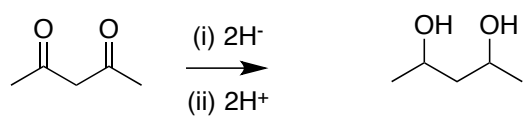
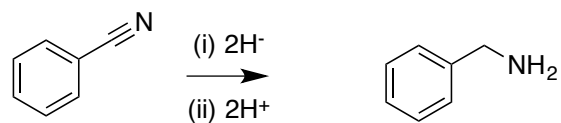
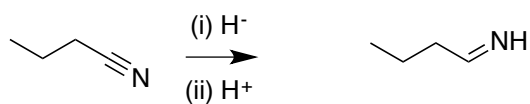
Two Step Reductions

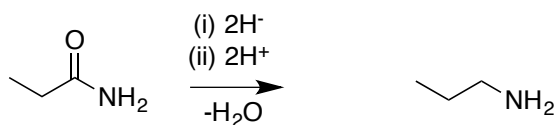
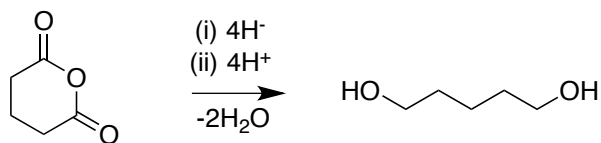
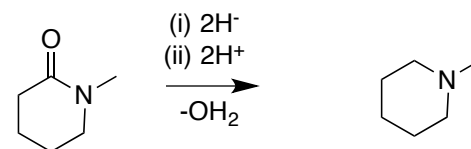
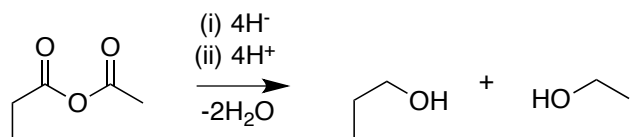
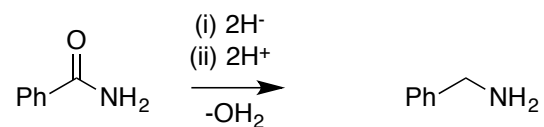
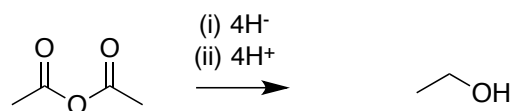
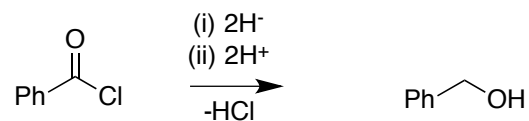
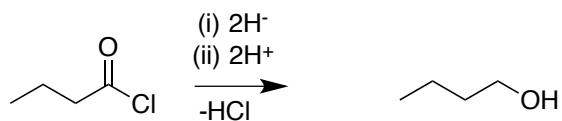
*alkoxide**alkoxide*



sulfone

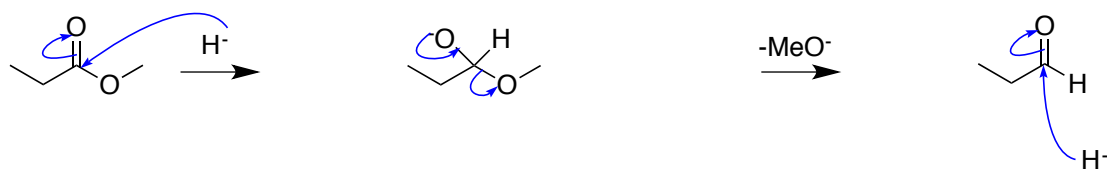
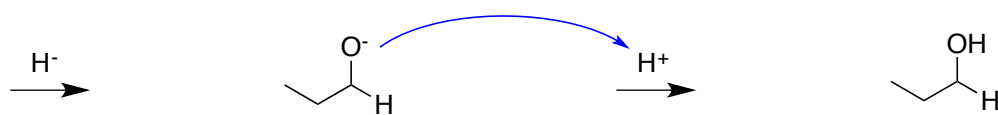
imine



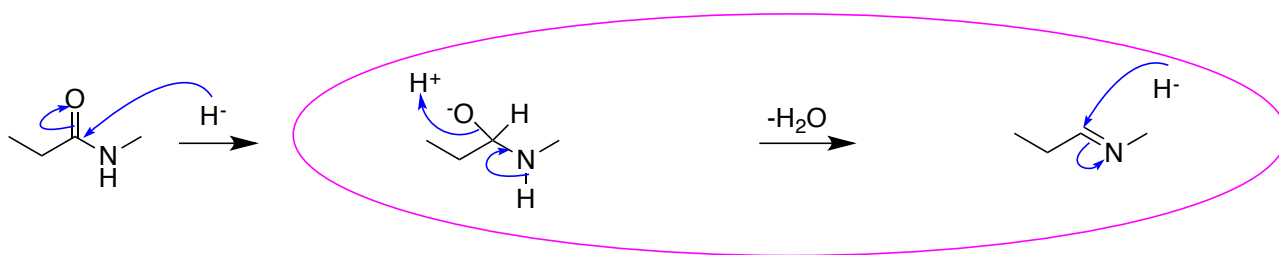
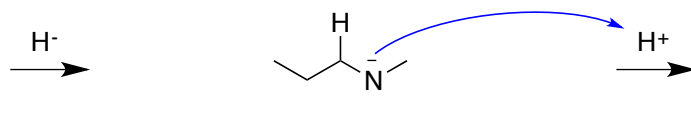


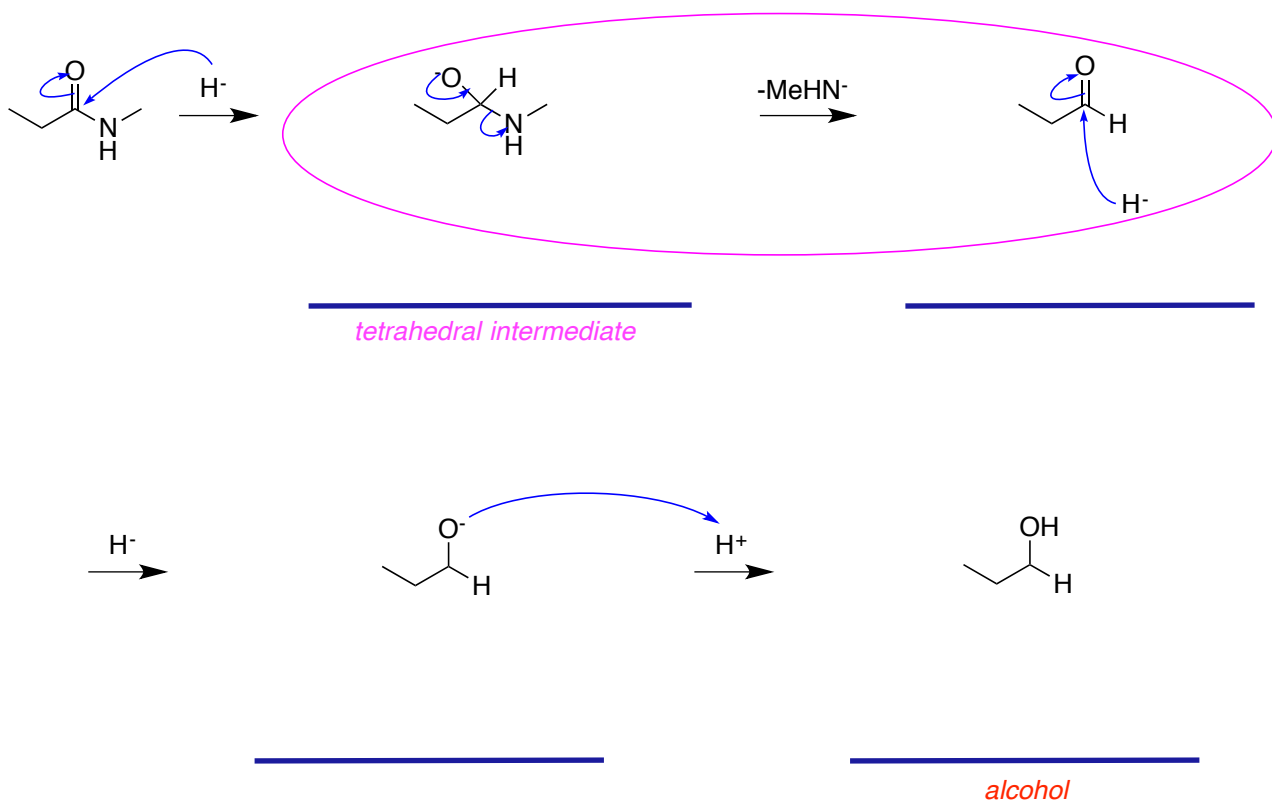
Difference Between Hydridic Reductions Of Amides And Esters

a

*tetrahedral intermediate**aldehyde**alkoxide*

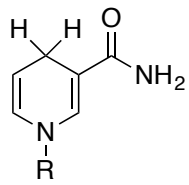
b

*tetrahedral intermediate**imine**amine*

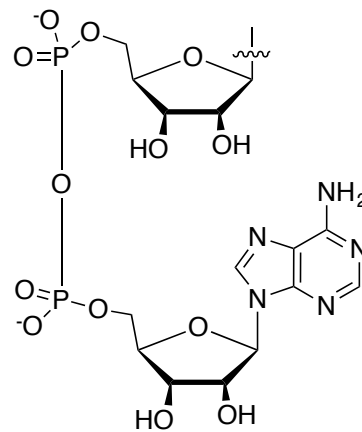
cmechanism **b**.

Because the amine anion is not a good leaving group.

D. NADH: A Hydride Source *In Vivo*



R =

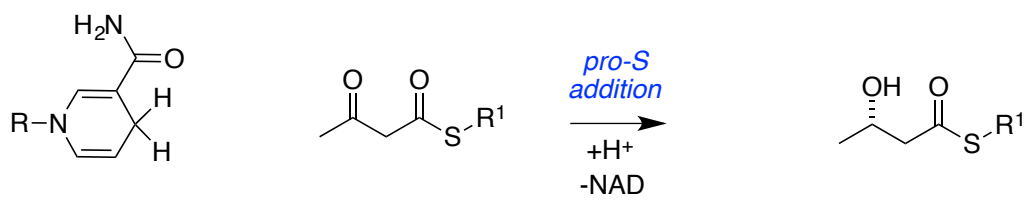


NADH full name: Reduced nicotinamide adenine dinucleotide



*by-product full name:
Nicotinamide adenine
dinucleotide (NAD)*

is *NAD*.



Reductions Via Electrons And Radicals

from chapter(s) _____ in the recommended text

A. Introduction

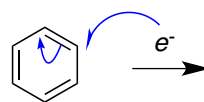
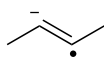
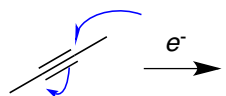
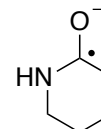
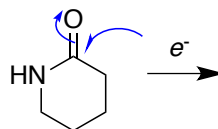
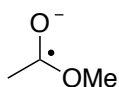
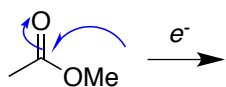
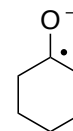
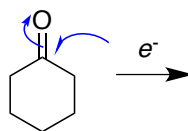
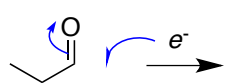
B. Reductions Via Free Electrons

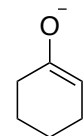
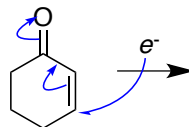
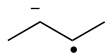
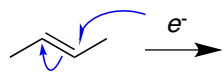
Addition Of One Electrons

a *radical anion*

proton orbited

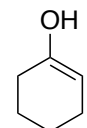
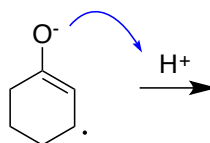
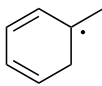
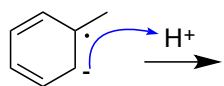
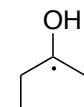
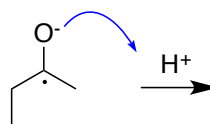
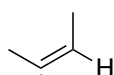
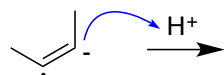
radical anion



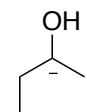
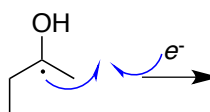
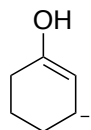
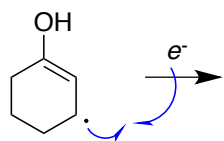


Addition Of One Electron Then Protonation

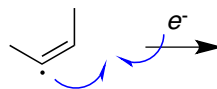
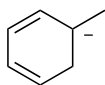
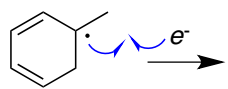
a radical



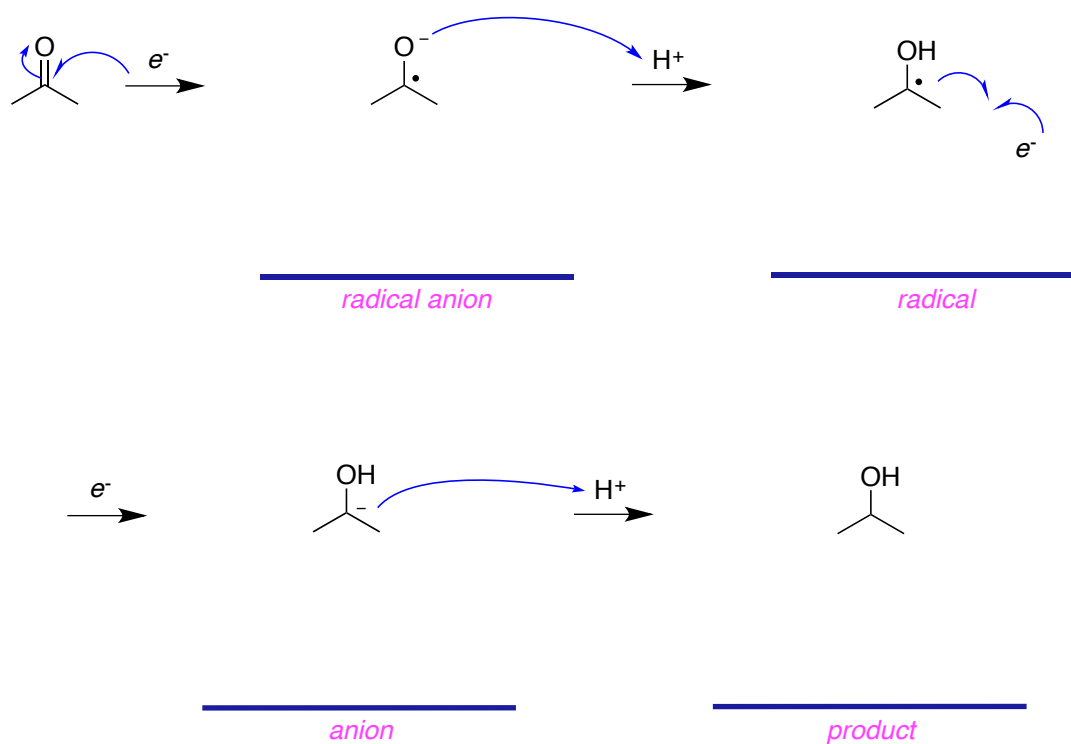
dianion
an anion



ANIONS LIKE THAT SHOWN ABOVE UNDERGO RAPID PROTON TRANSFER TO GIVE ALKOXIDES BEFORE PROTONATION

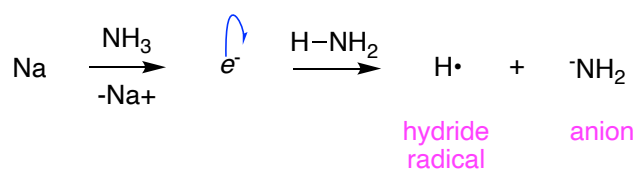


addition of two hydrogens.



ANIONS LIKE THAT SHOWN ABOVE WILL UNDERGO RAPID PROTON TRANSFER TO GIVE ALKOXIDES BEFORE PROTONATION

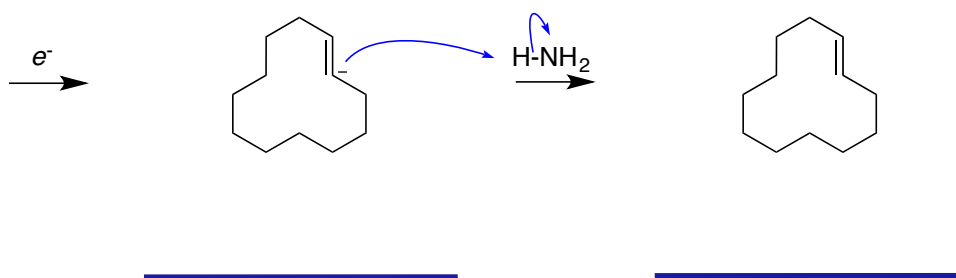
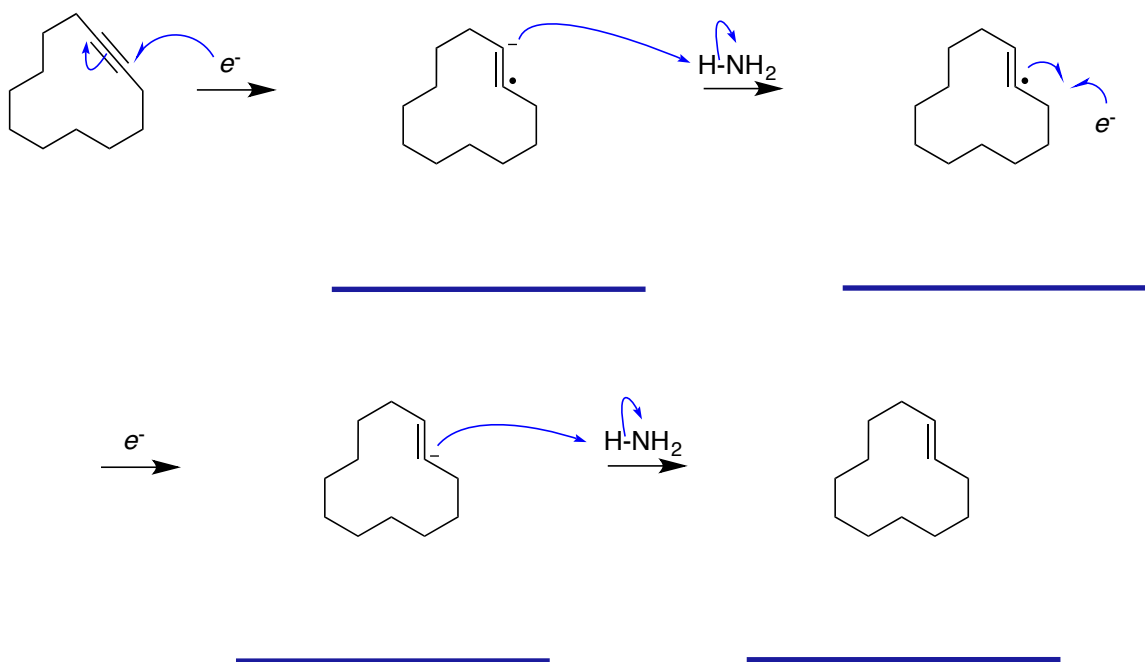
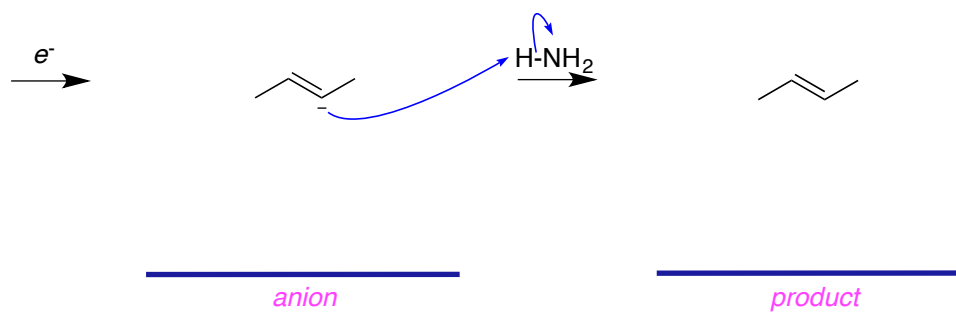
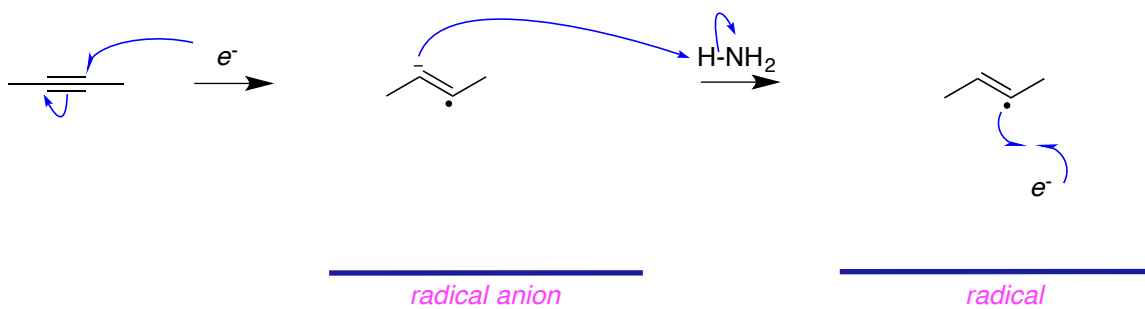
oxidize to Sm(3+)
sodium amalgam
inky-blue solution.



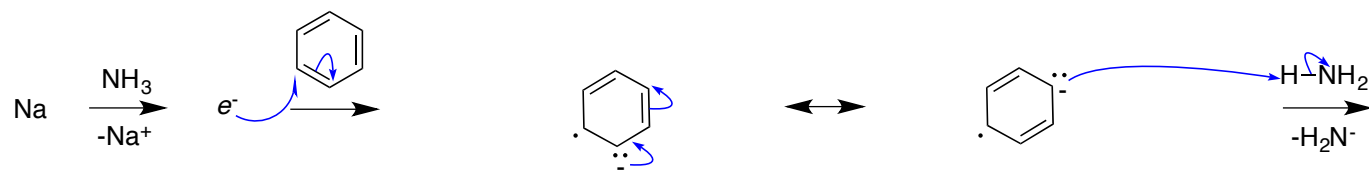
anion

Cycles Of Electron Addition Then Protonation

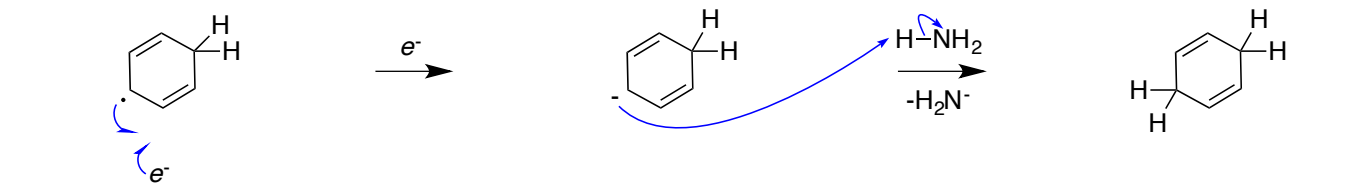
trans-geometry
equivalent to



a radical, then another electron to form *an anion*
2



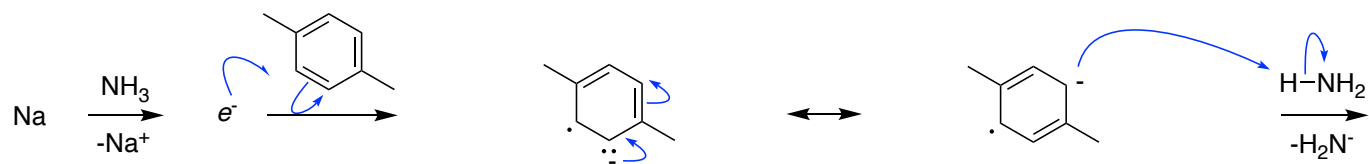
radical anion



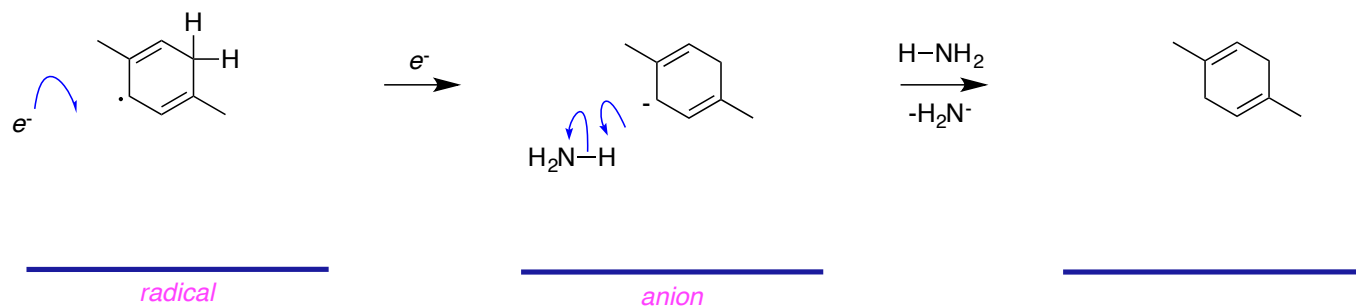
radical

anion

HOMO
non-conjugated

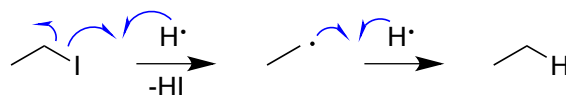


radical anion



C. Reductions Via Radicals

reduction

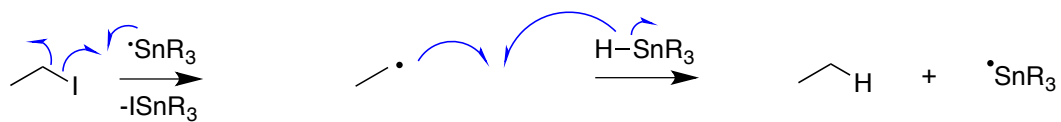


kinetic effects

more than stoichiometric amounts



chain initiation



chain propagation

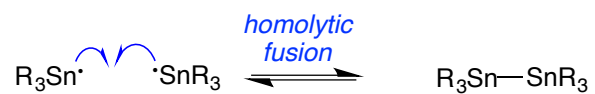
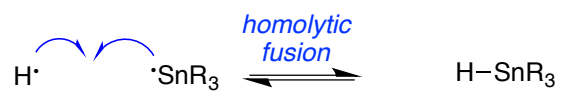
radical

products

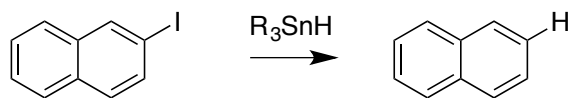
another tin radical.

regenerated many times.

concentration is *low*.



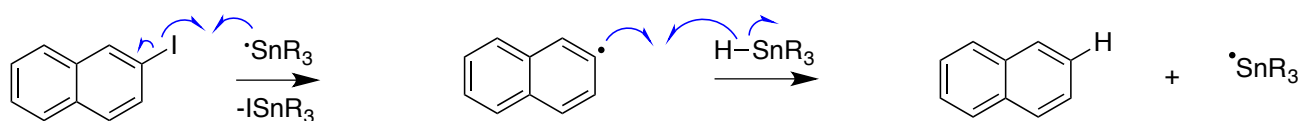
would not



chain initiation



chain propagation



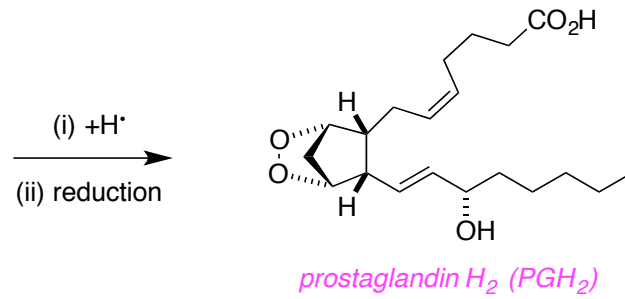
radical

products

chain termination

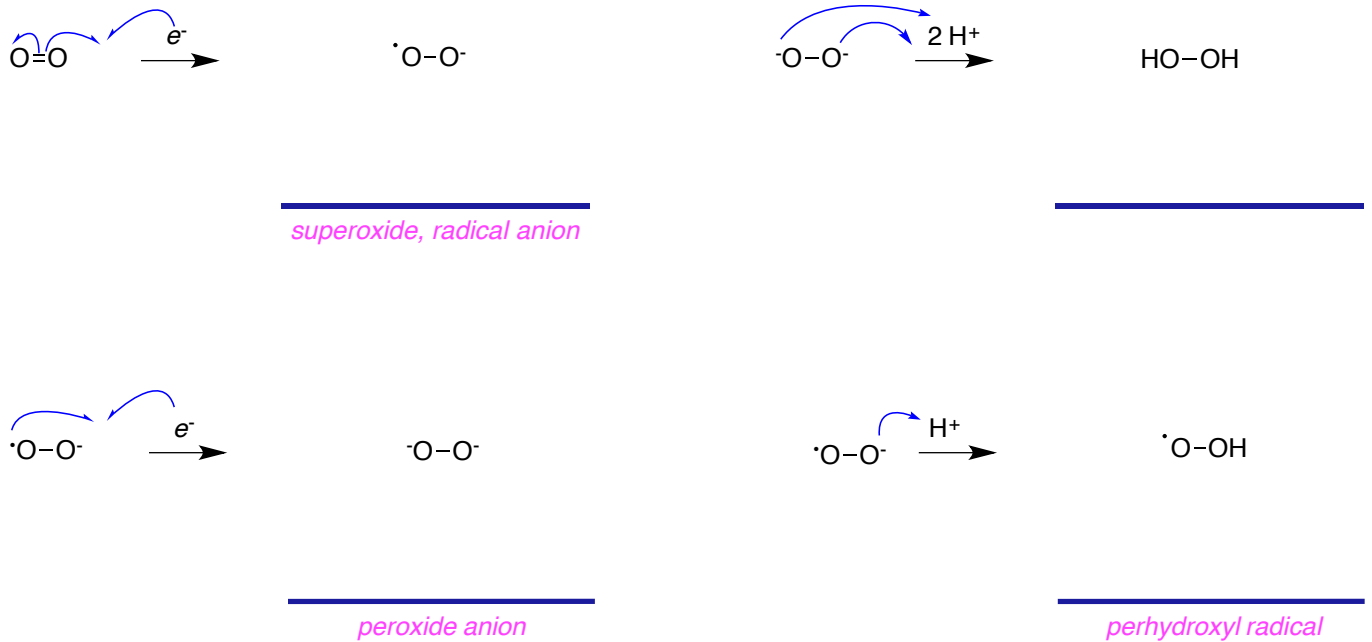


would not change



dilate blood vessels and are secreted in seminal fluid from the prostate gland

E. Reactive Oxygen Species



endoplasmic reticulum and mitochondria and peroxisomes

Oxidations

from chapter(s) _____ in the recommended text

A. Introduction

B. Amine Oxidations

increasing the

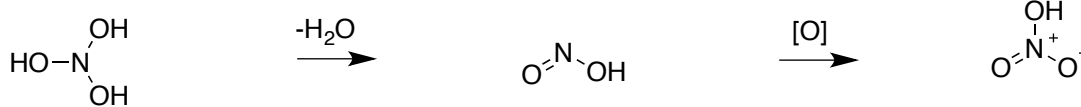
Ammonia

dehydrates
water.



hydroxylamine

dihydroxylamine or azinic acid



trihydroxylamine

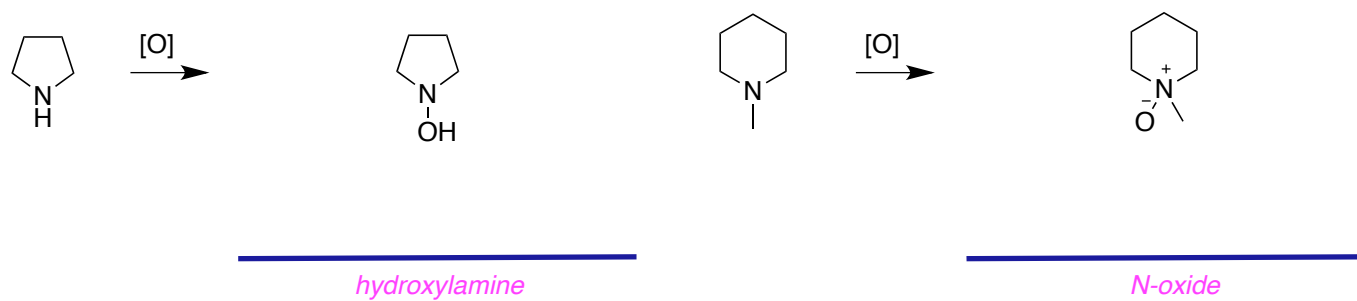
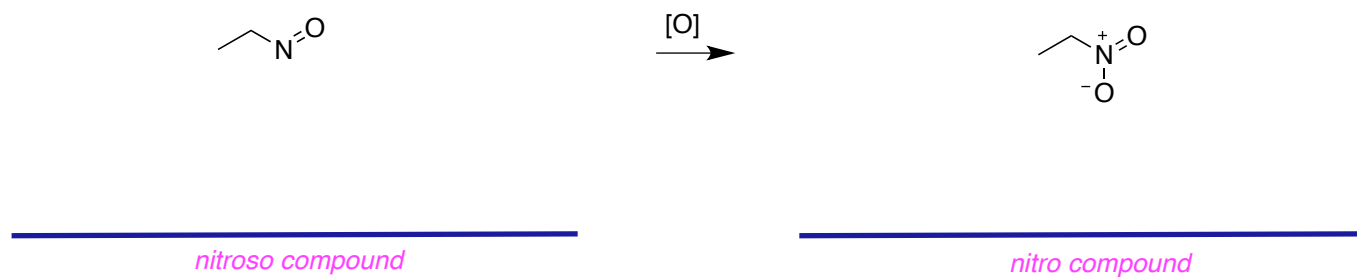
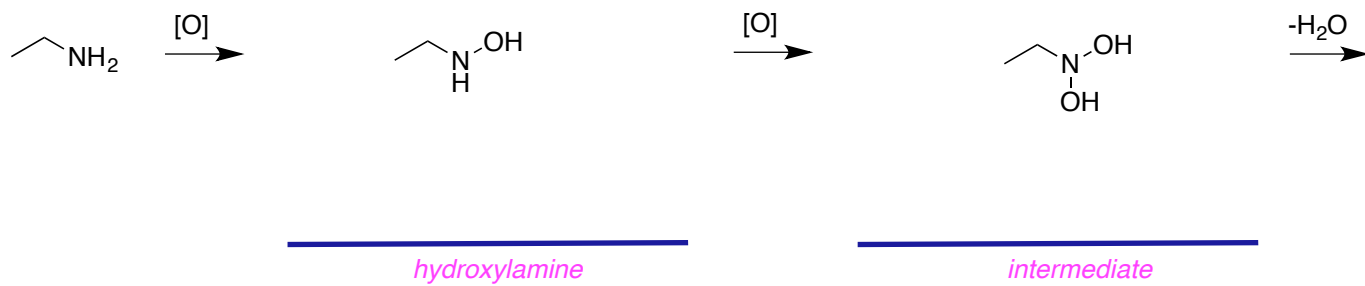
nitrous acid

nitric acid

tautomers.

do tend

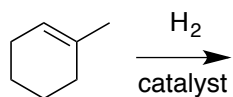
Organic Amines



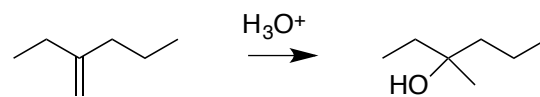
easier to

C. Oxidations Of Alkenes And Alkynes Via Additions Of Heteroatoms

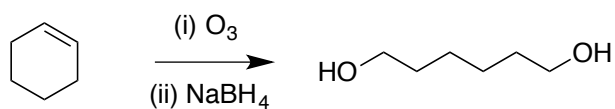
oxidation.



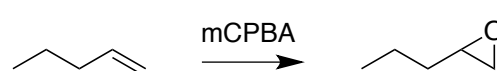
-1



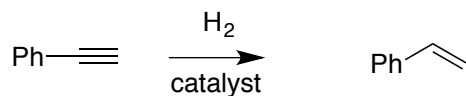
+1



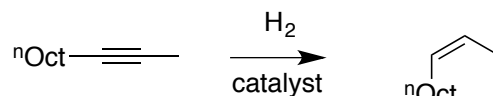
+1



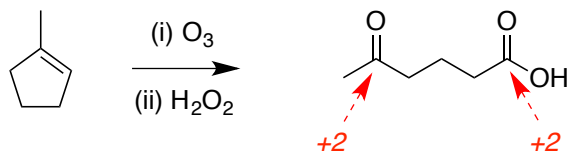
+1



-1

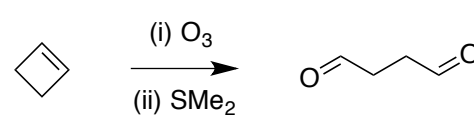


-1

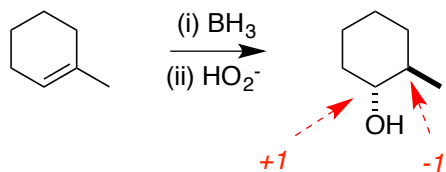


+2

+2

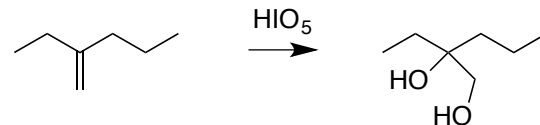


+2



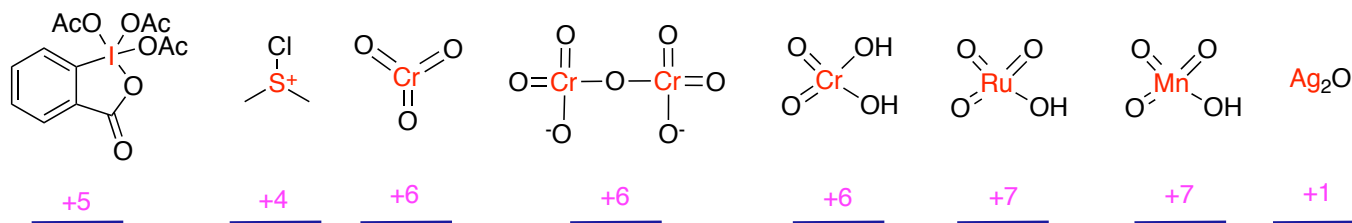
+1

-1



+1

D. Oxidation States Of Common Oxidants



high oxidation states

E. Dehydrogenation Reactions

oxidation reaction.

do not influence

does lower it

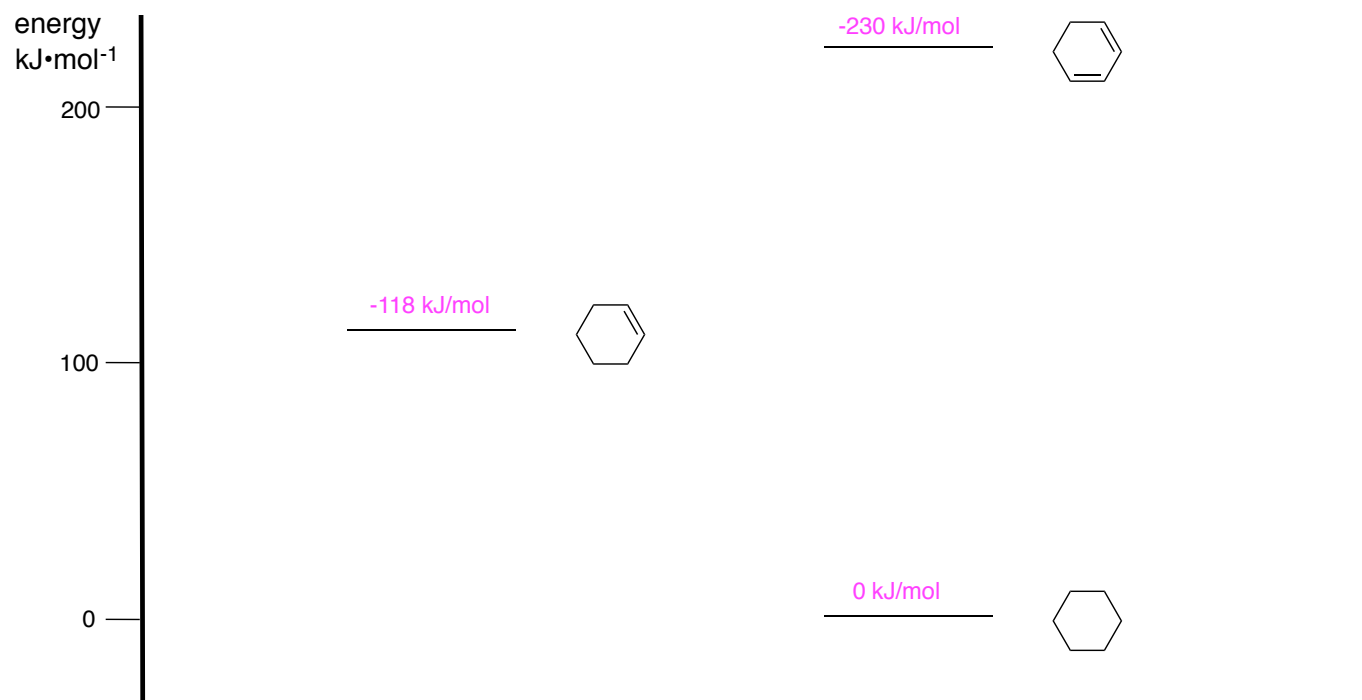
The Principle of Microscopic Reversibility.

kinetic barrier

enclosed from

easier to find

greater.

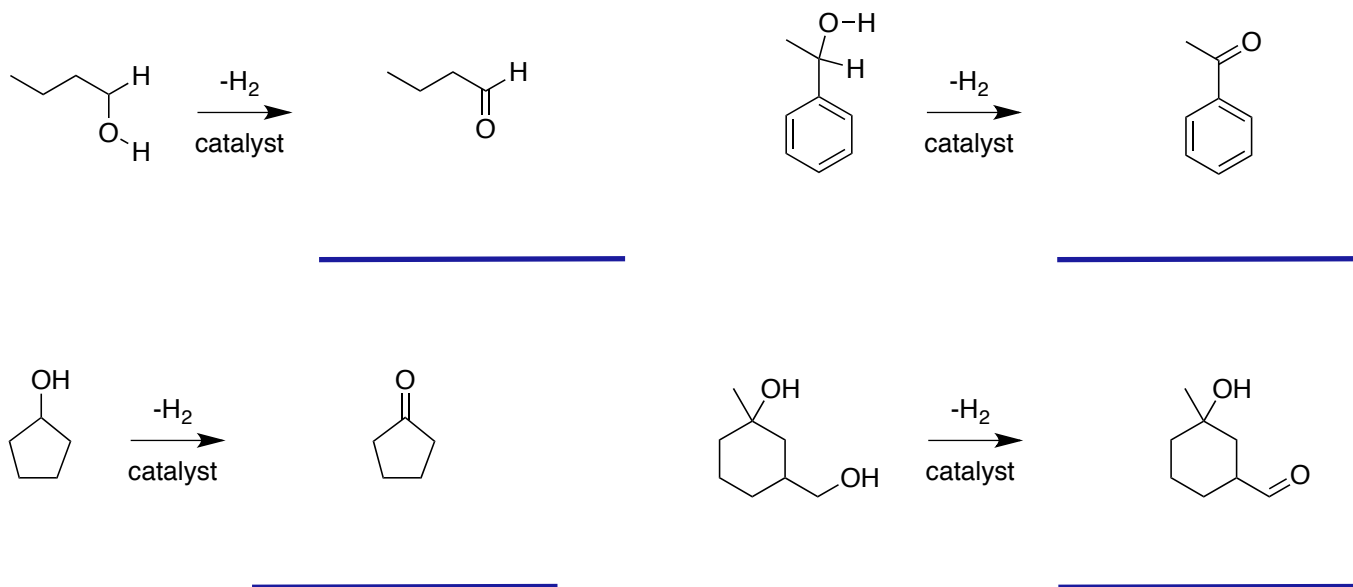


*downhill
oxidation*

F. Oxidation Of Alcohols

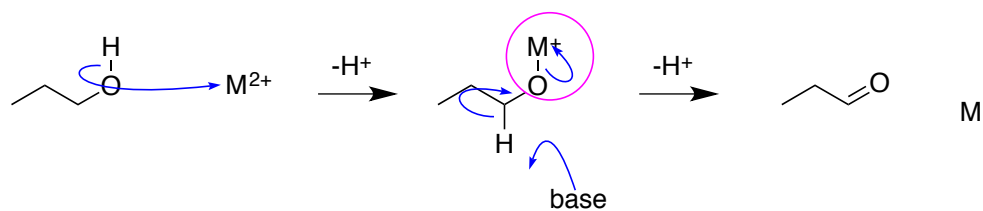
Catalytic Dehydrogenation

oxidize



primary / secondary and not *tertiary*
tertiary alcohols than *primary / secondary*

Elimination From Alkoxides: A Mechanistic Commonality Between Many Alcohol Oxidations



E_2 mechanism.

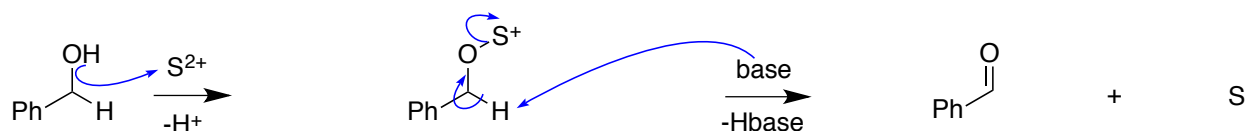
reduced;

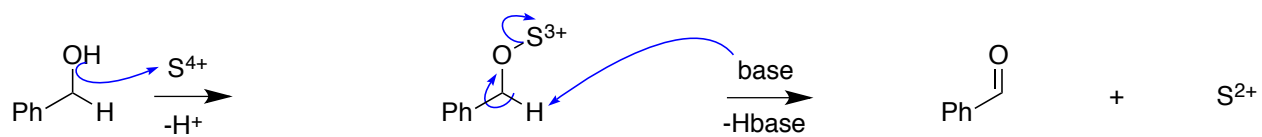
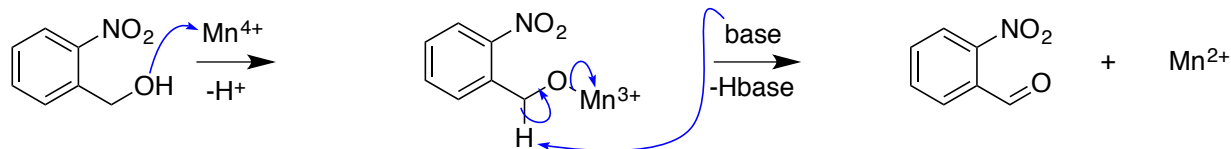
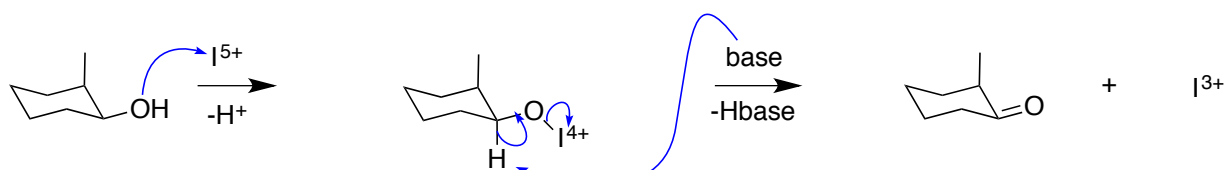
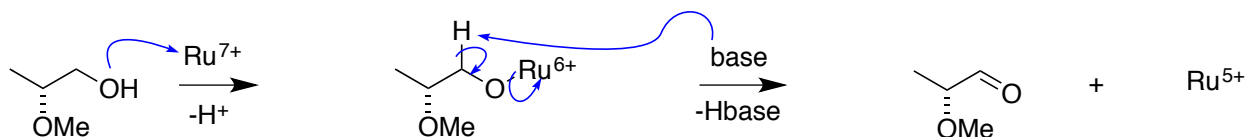
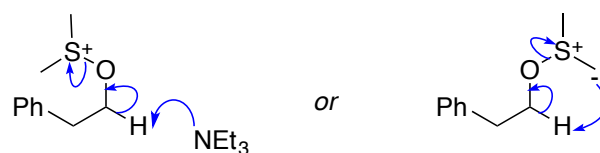
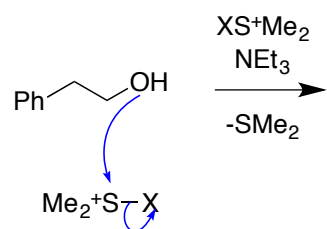
high oxidation

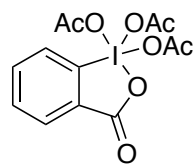
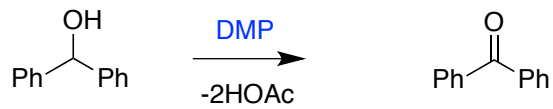
reduced.

It is *harder*

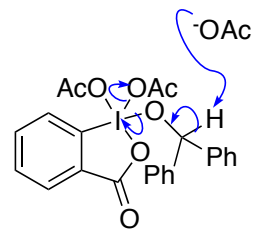
high oxidation state.



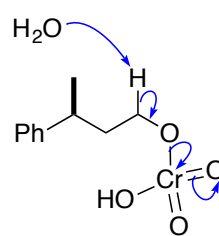
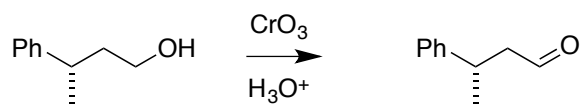
*alkoxide**alkoxide**alkoxide**alkoxide**intermolecular**intramolecular*



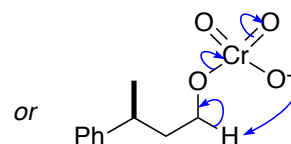
DMP



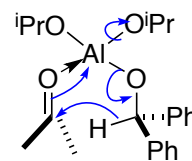
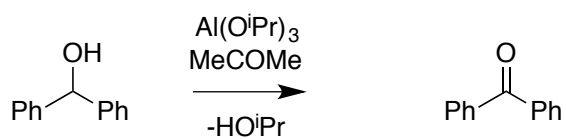
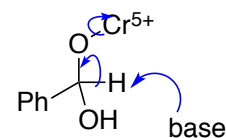
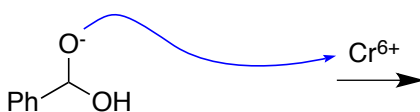
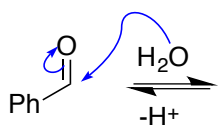
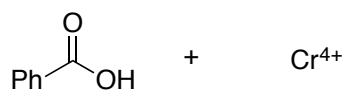
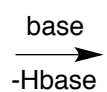
intermolecular



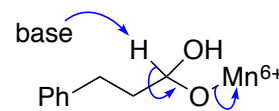
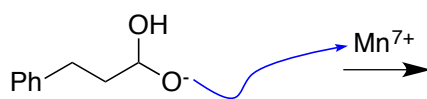
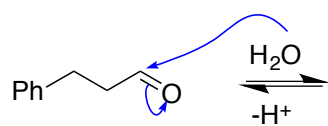
intermolecular

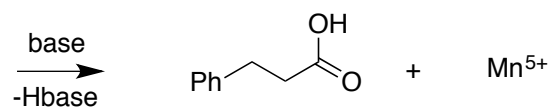


intramolecular

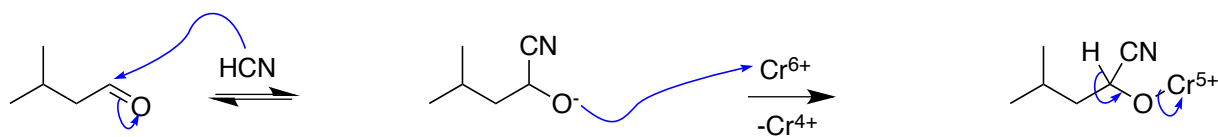
*intramolecular***G. Oxidation Of Aldehydes***hydrate**alkoxide*

indicate what happens to the metal here

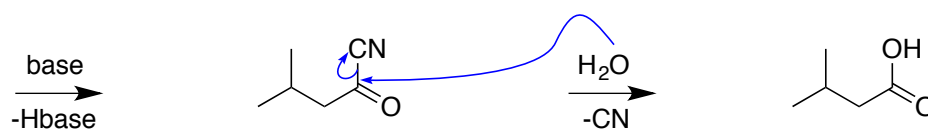
*hydrate**alkoxide*



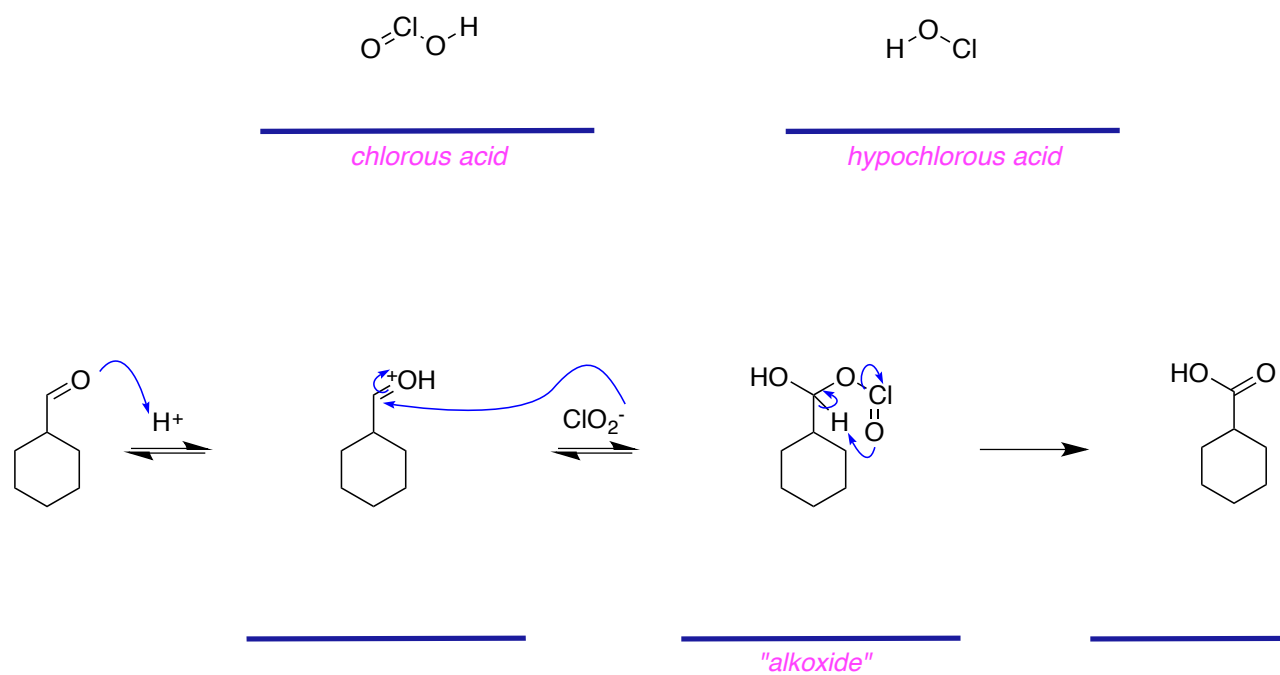
Ketones *cannot*
do not have



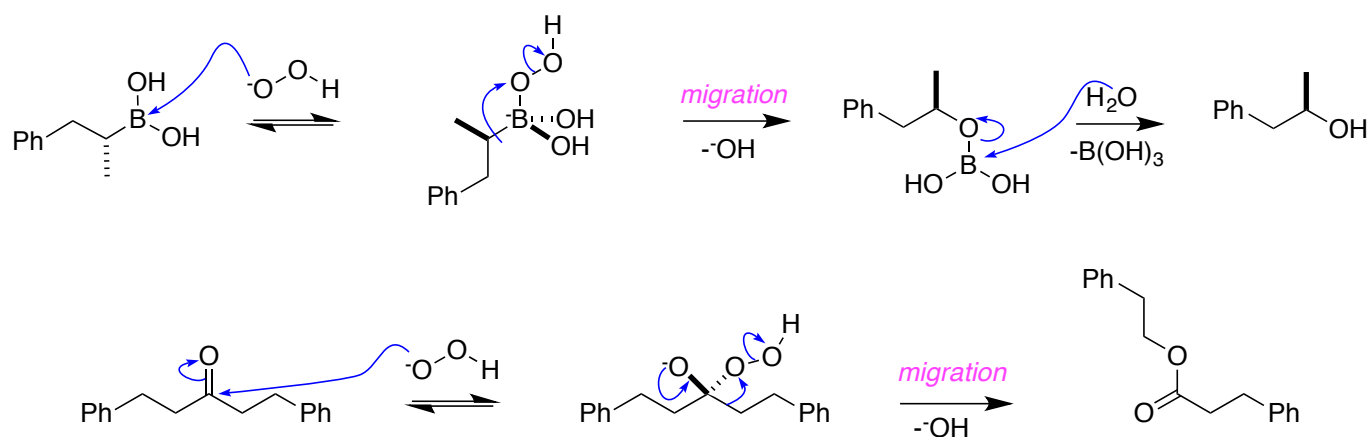
alkoxide



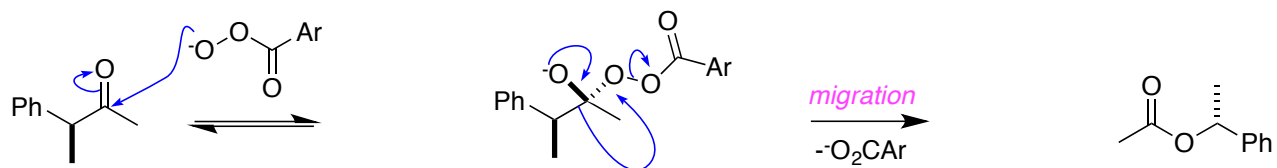
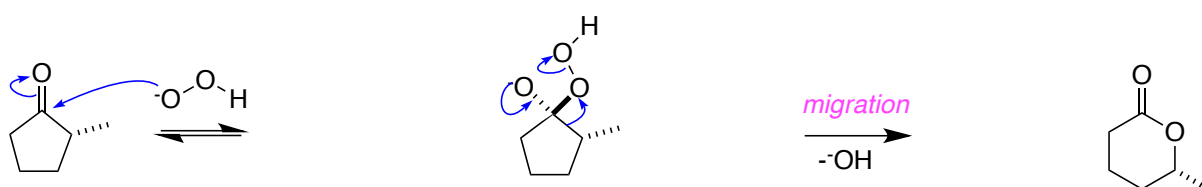
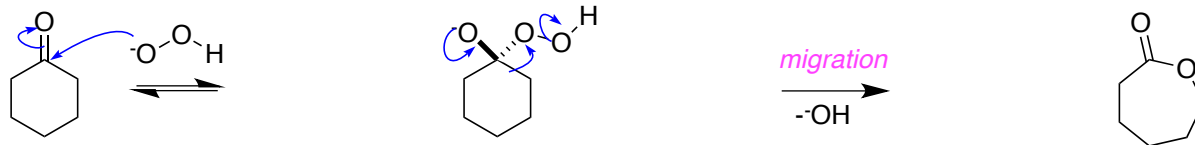
acyl nitrile



H. Oxidation Of Ketones



anti-periplanar in



Characteristics Of Enols and Enolates

from chapter(s) _____ in the recommended text

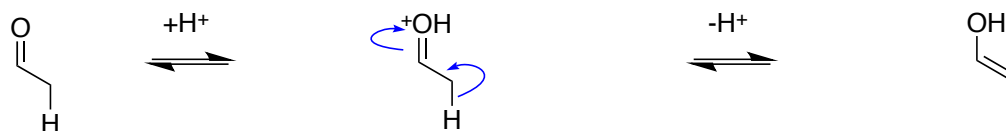
A. Introduction

B. Enols Form Under Acidic Conditions

Mechanism of Formation

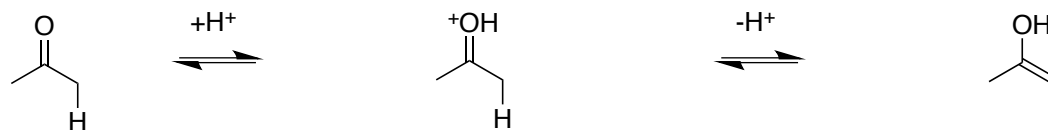
protonation

enol.



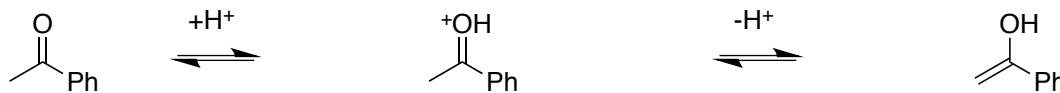
protonated carbonyl

enol form

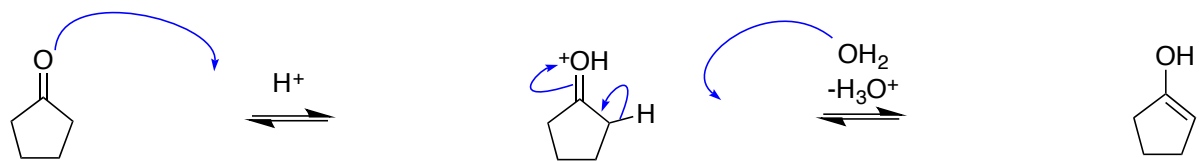


protonated carbonyl

enol form

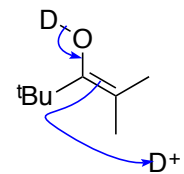
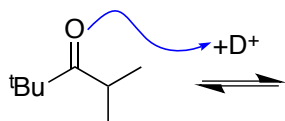


enol



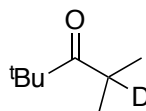
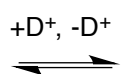
Deuterium Exchange

deuterons.

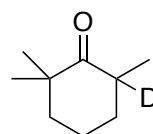
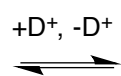
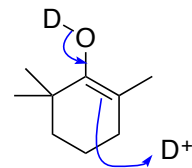
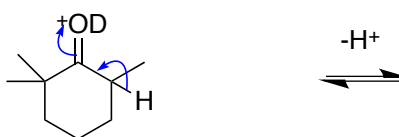
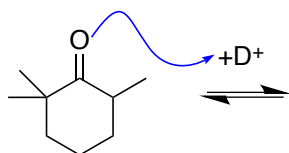


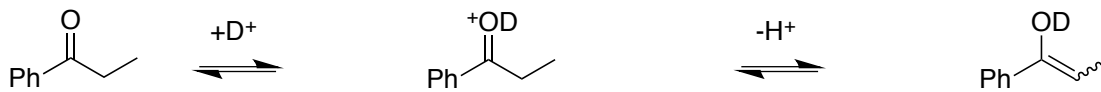
deuterated carbonyl

enol form



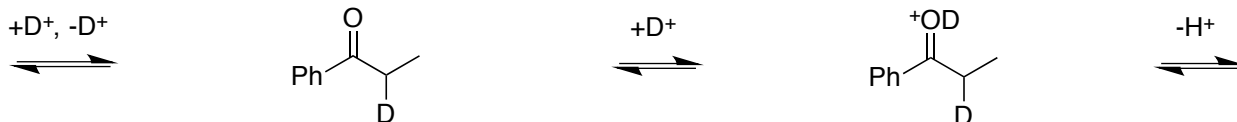
deuterated product





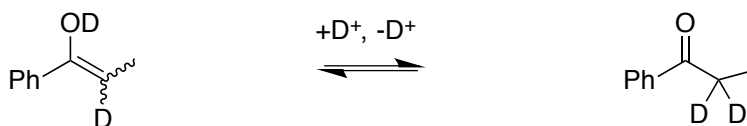
O-deuterated carbonyl

O-deuterated enol



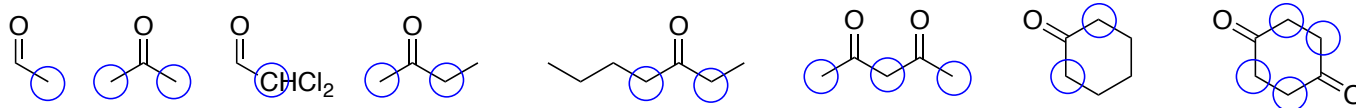
C-deuterated ketone

O-deuterated carbonyl



enol form

dideuterated ketone



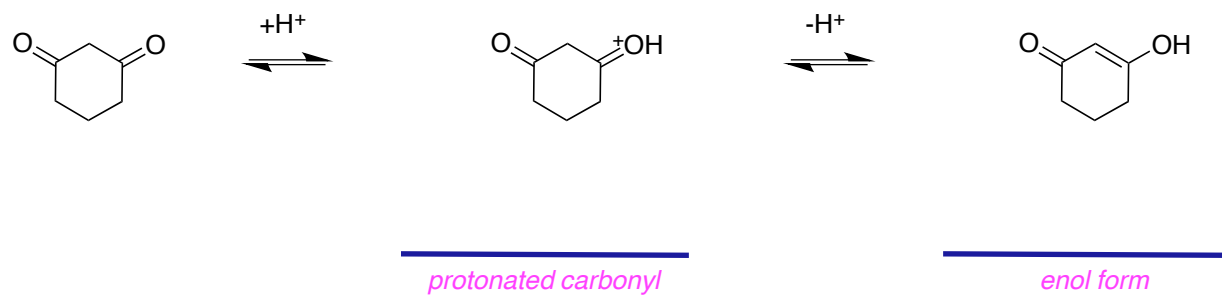
tautomerism;

Enols Of 1,2- And 1,3-Dicarbonyl Compounds

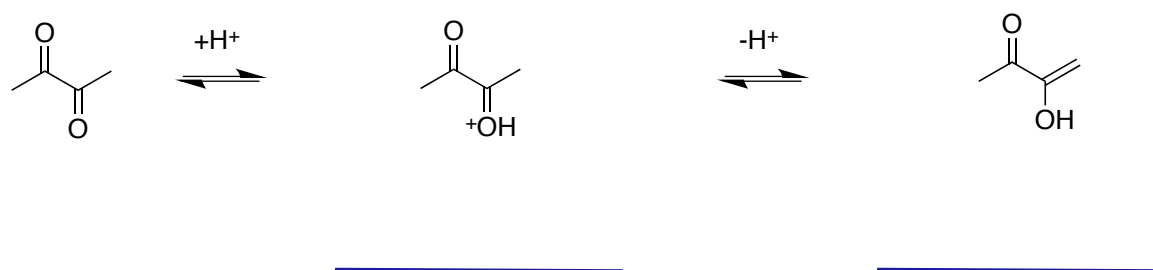
keto form

$10^6 : 1$.

enol

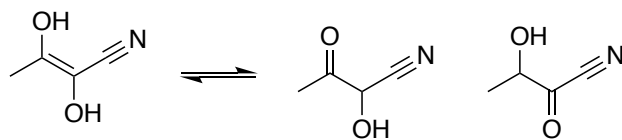
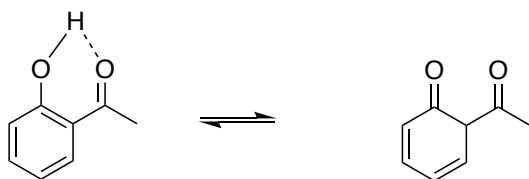
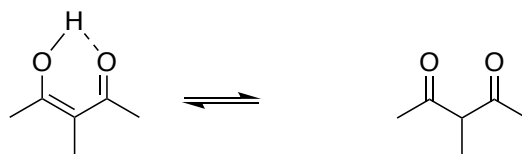
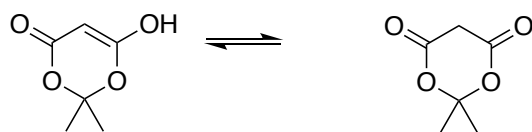
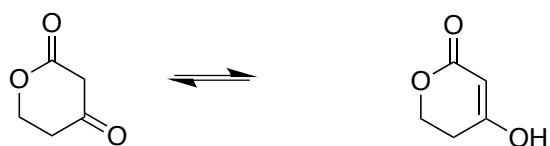
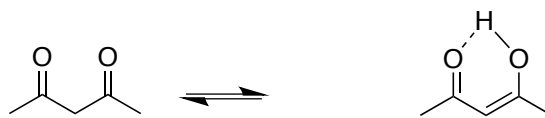
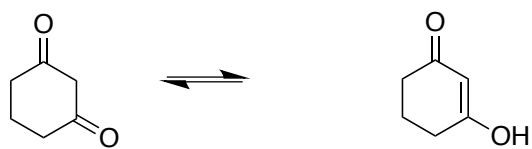


reason: Enolization of 1,3-cyclohexanedione forms conjugation between carbonyl and C=C which is stabilized by resonance, while the acetone does not have resonance effect.



reason: Compared to acetone, one carbonyl group in the 2,3-butanedione acts as electron withdrawing group that enhances acidity of α -H.

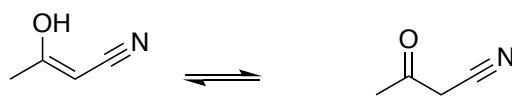
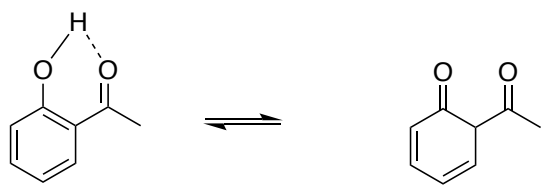
conjugates



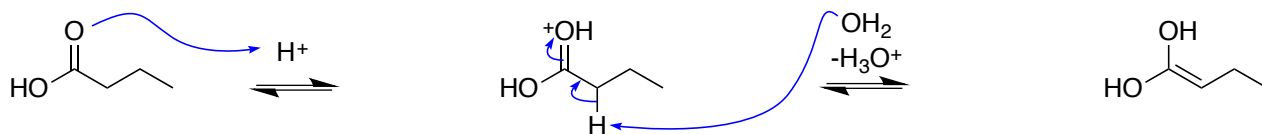
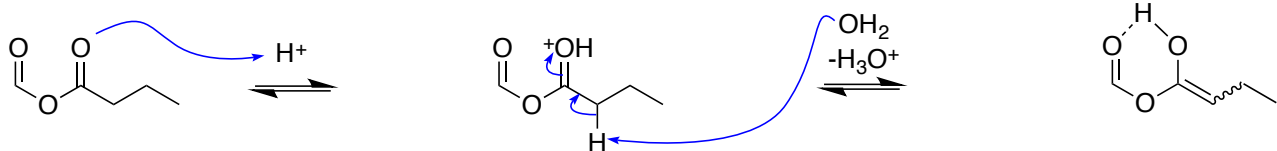
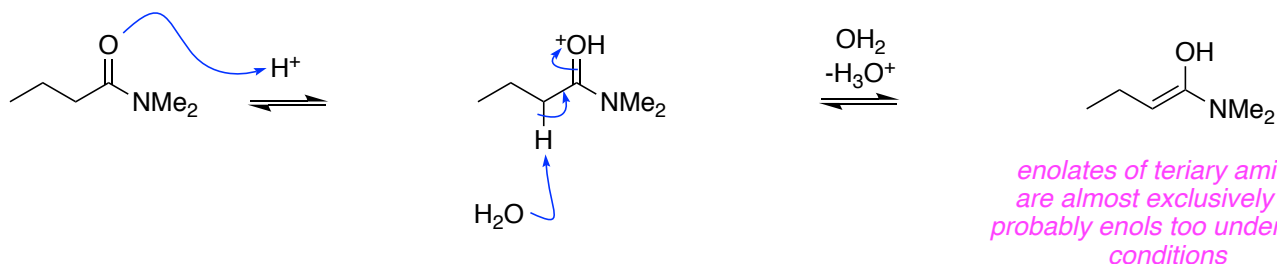
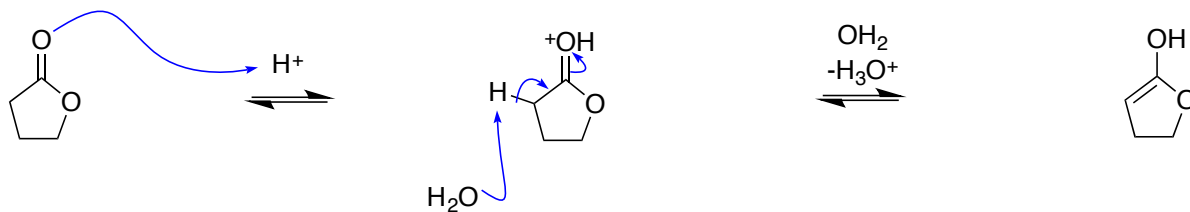
best

second best

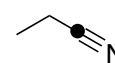
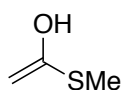
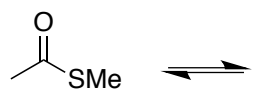
In the print the question above right will be changed to the following:



Enols Of Other Carbonyl Compounds

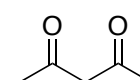
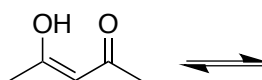
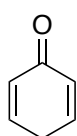
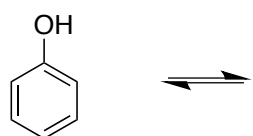


Keto-Enol Tautomers Of Other Compound Types



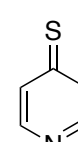
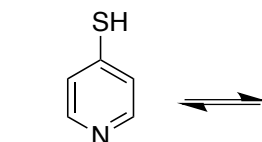
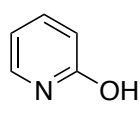
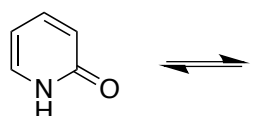
enol

keto



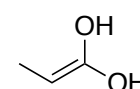
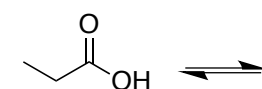
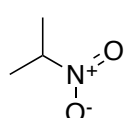
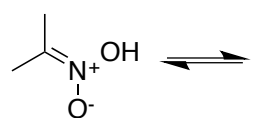
keto

keto



enol

keto



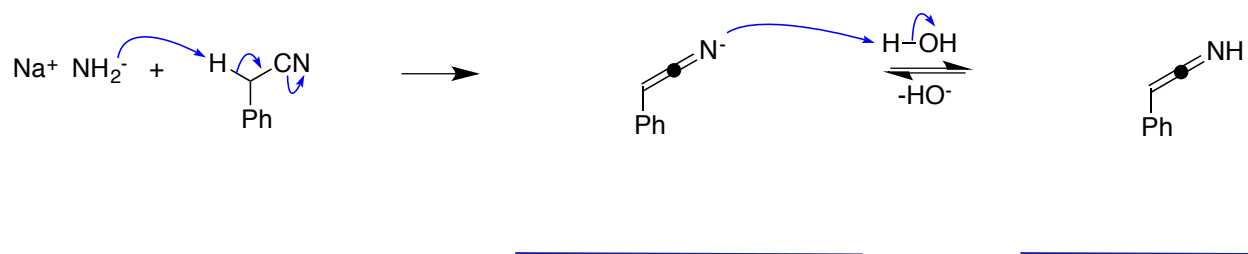
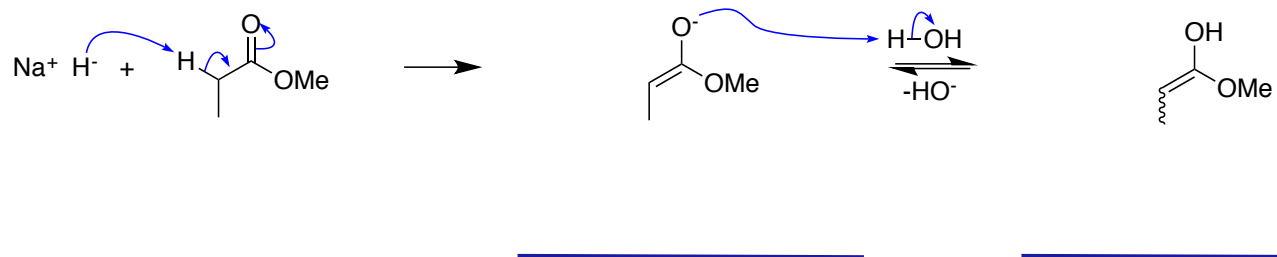
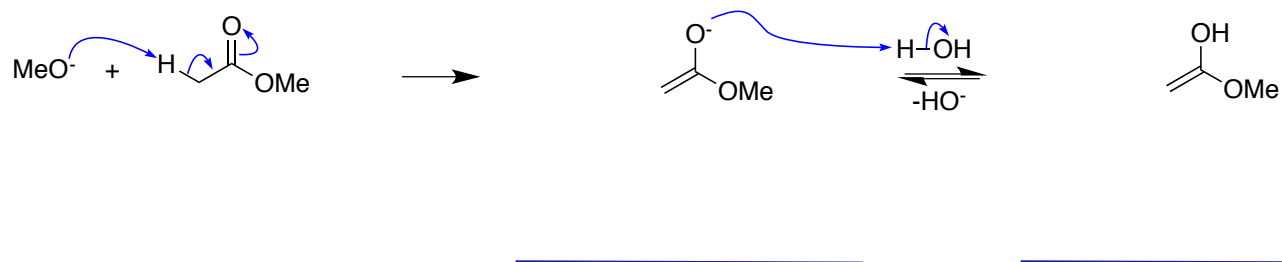
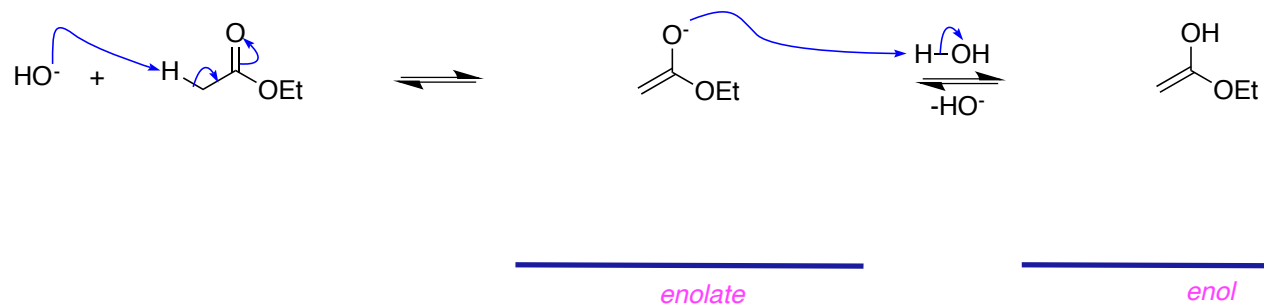
keto

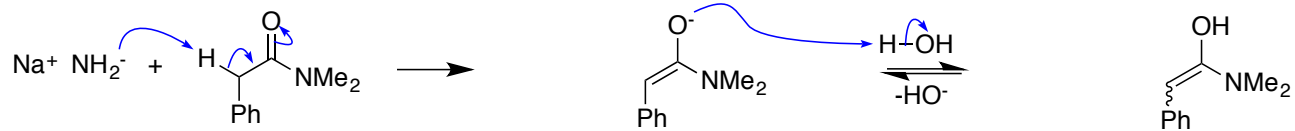
enol

incorrect
they are not resonance structures.

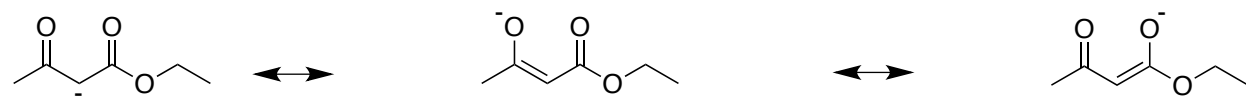
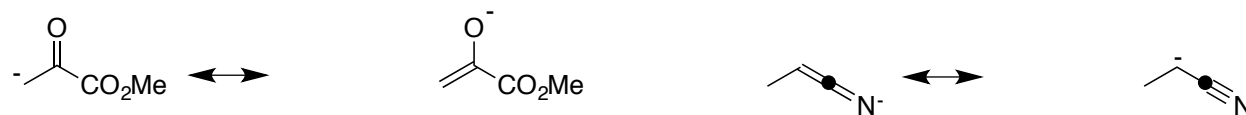
C. Enolates Form Under Basic Conditions

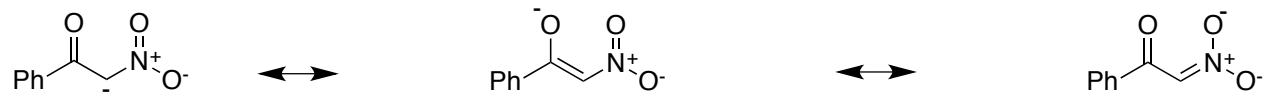
Mechanism Of Formation



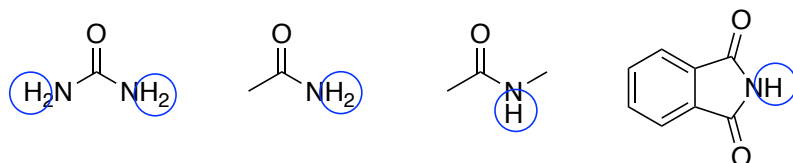


Resonance Structures Of Enolates





more
more



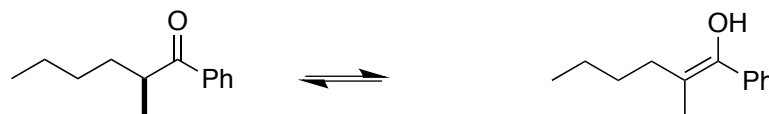
It *is not* easy
N-anions instead.

D. Effects Of Enolization

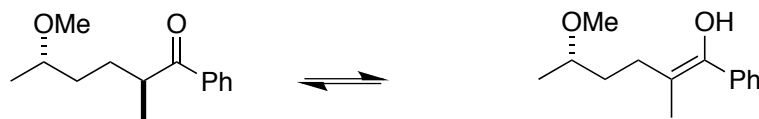
Racemization



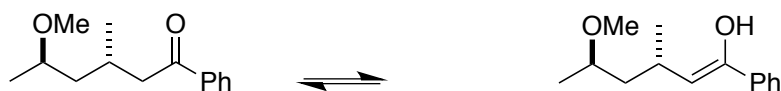
optically active



achiral

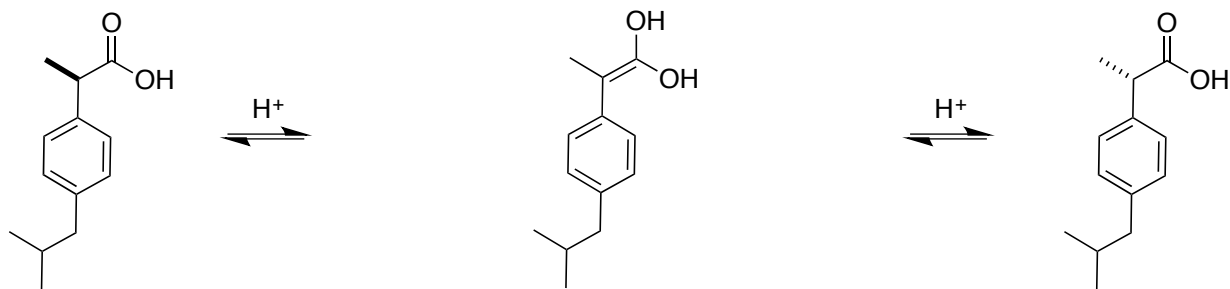


optically active



optically active

can racemize

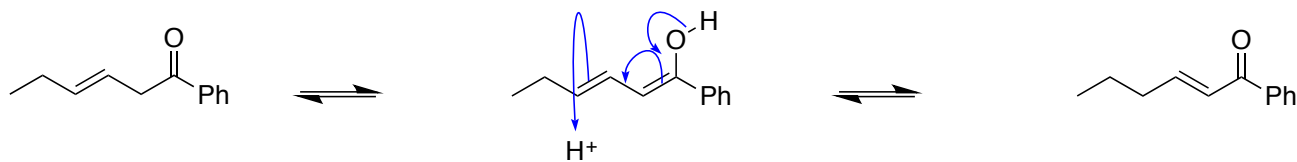


ibuprofen

enol

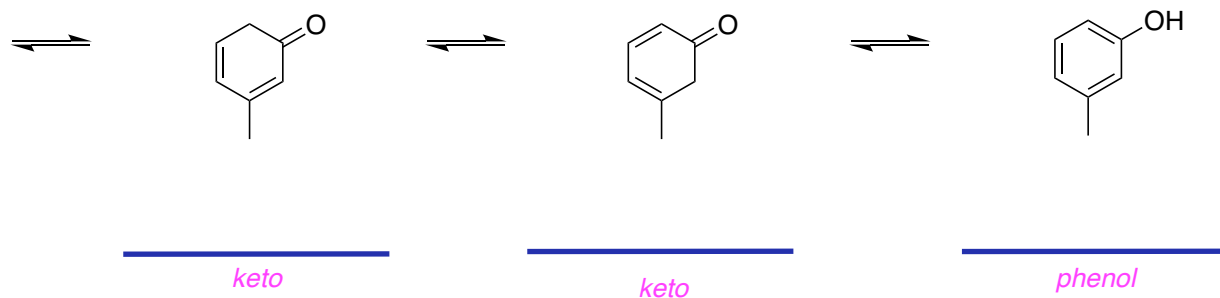
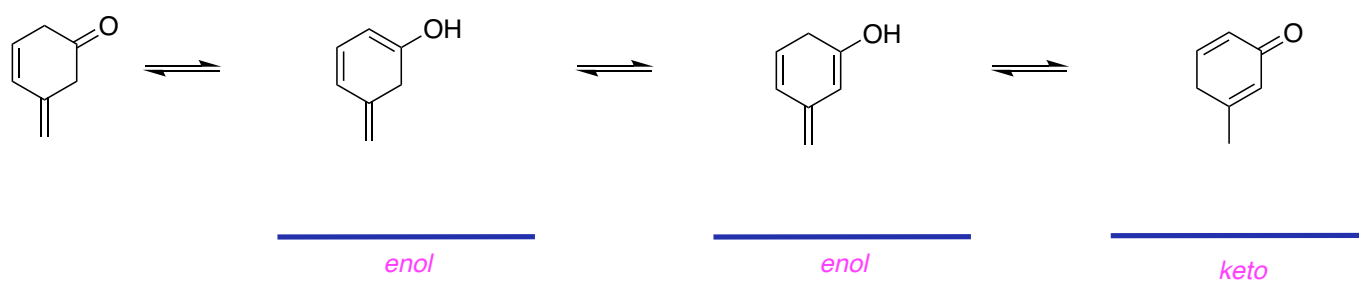
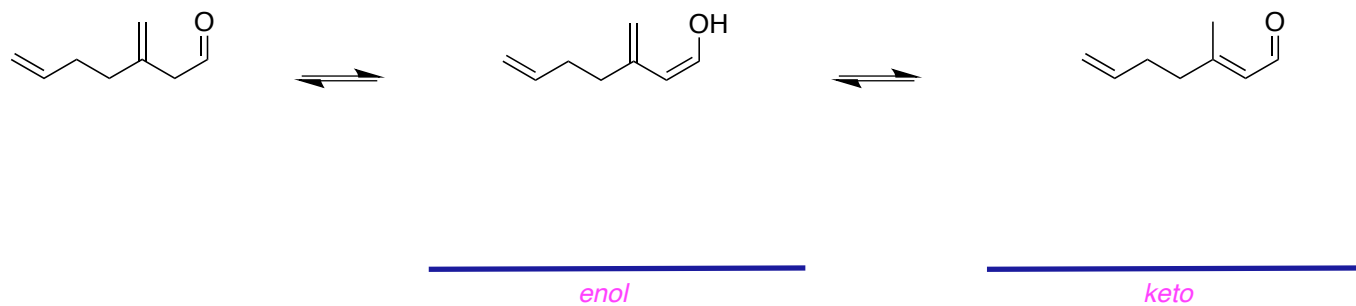
Double Bond Migration

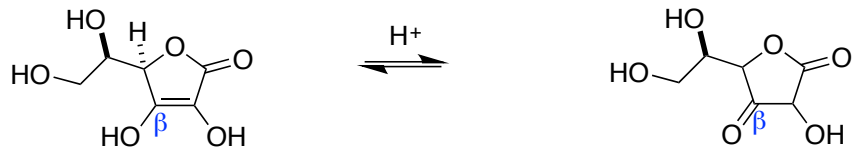
Migration



enol

keto



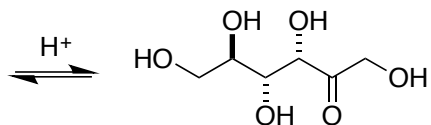


keto



glucose

enol



fructose

Halogenation Of Enolizable Carbonyl Compounds

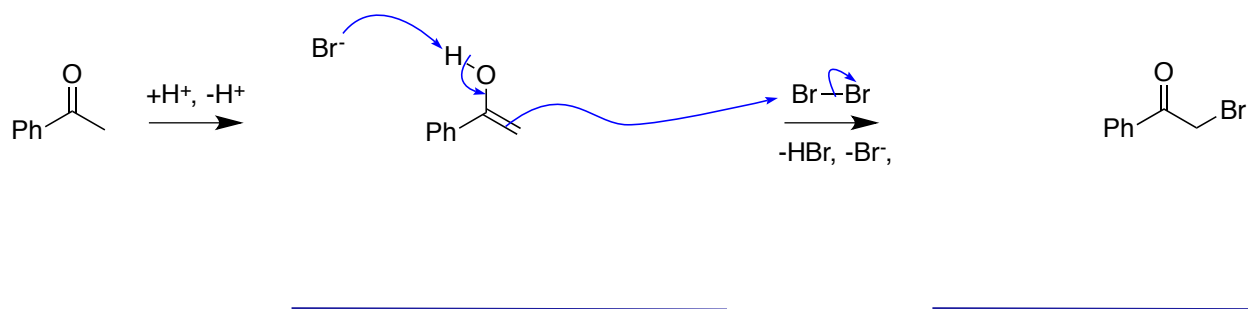
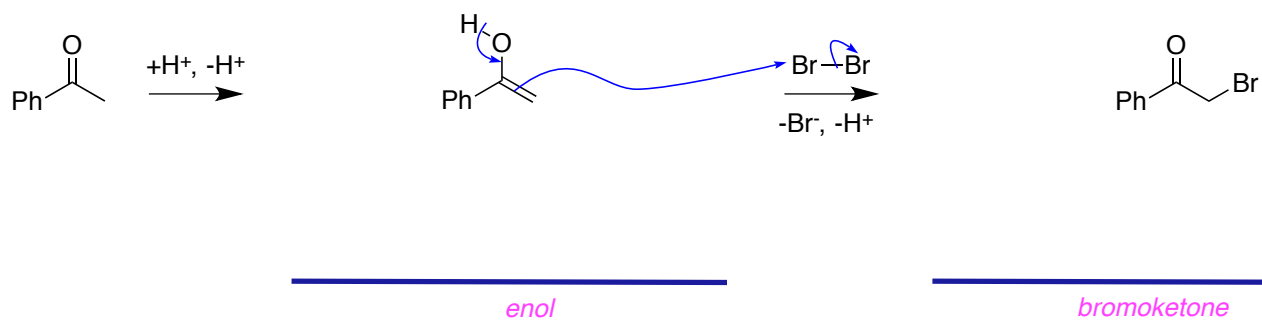
from chapter(s) _____ in the recommended text

A. Introduction

B. Halogenation Via Enols (Acidic Conditions)

Acidic Conditions Give Monohalogenation

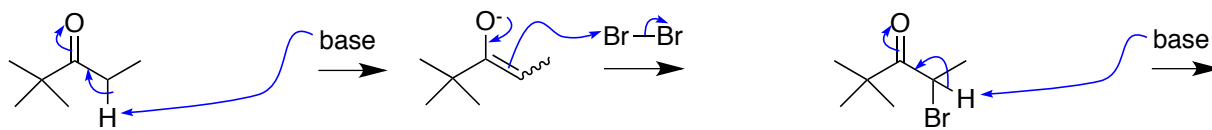
acidic conditions, whereas enolates form under *basic* *less*



less likely

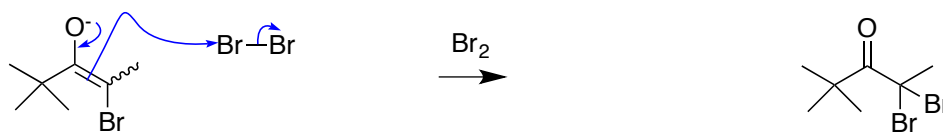
less

more
more



2,2-dimethylpentan-3-one

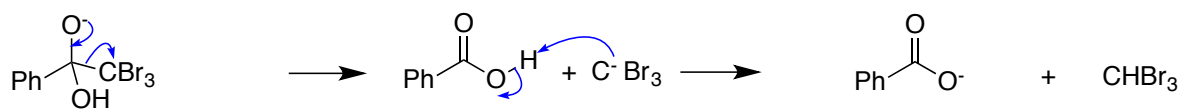
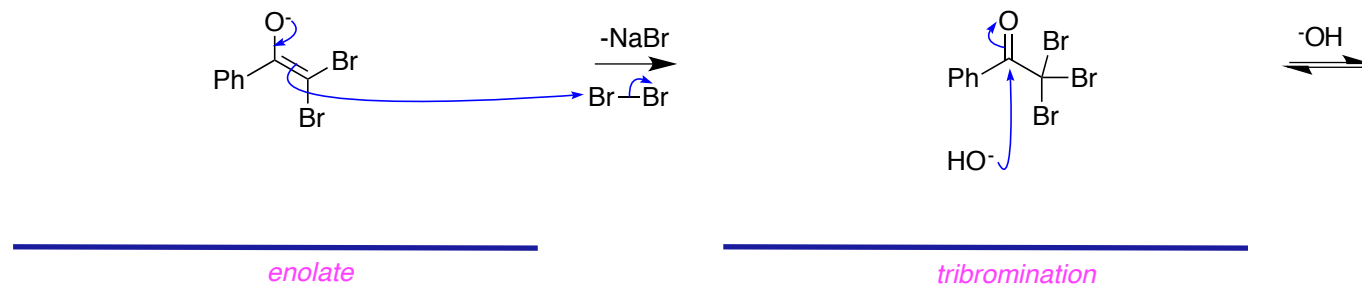
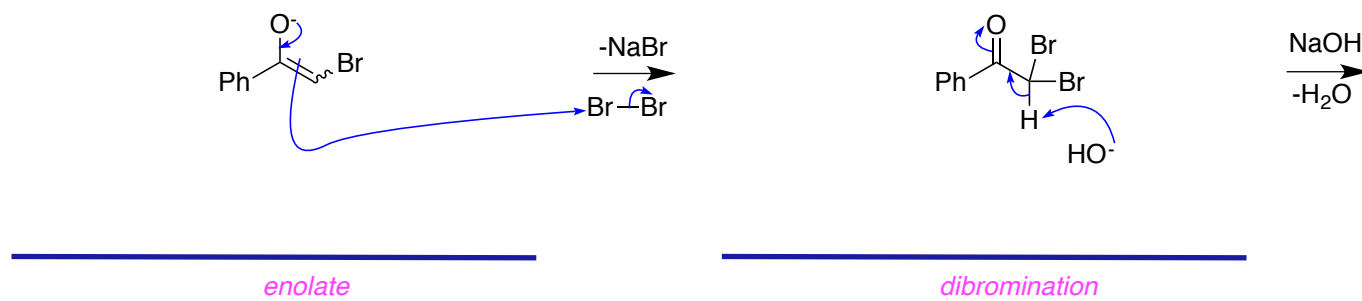
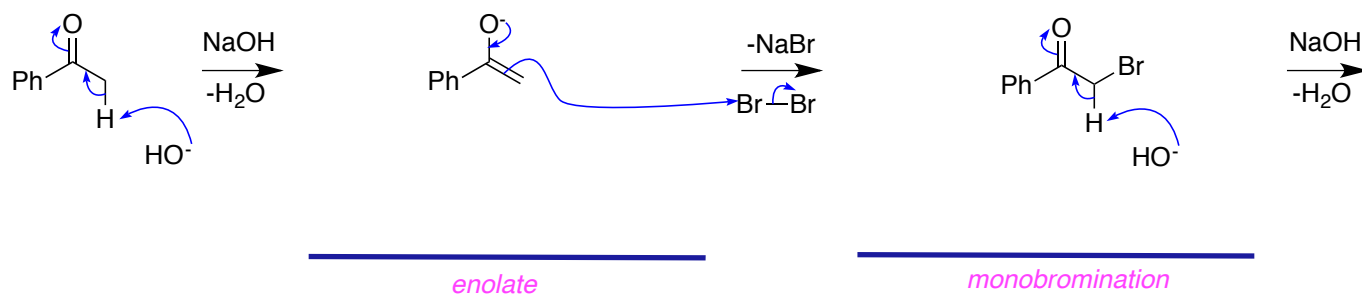
more likely to form enolate
than starting ketone



enolate

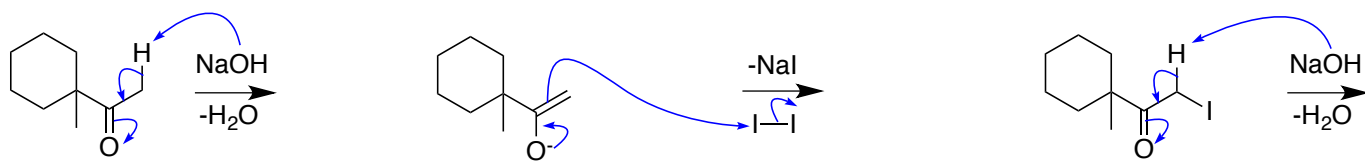
2,2-dibromo-4,4-dimethylpentan-3-one

would
more
haloform reaction.



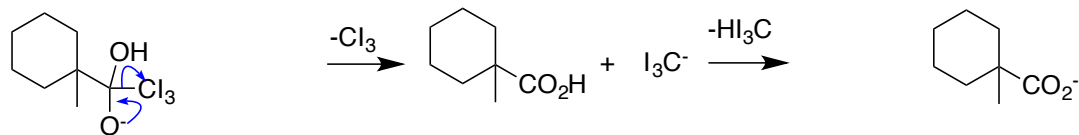
tetrahedral intermediate

could be



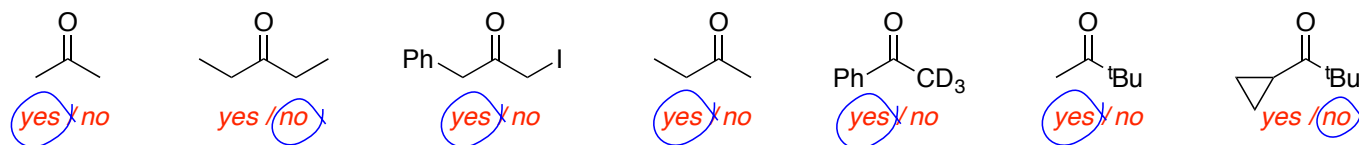
enolate

triiodination

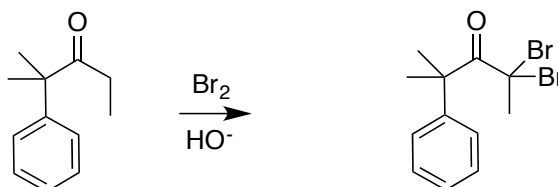
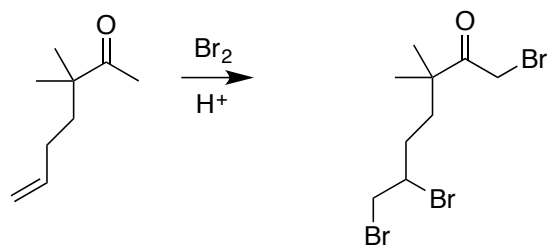
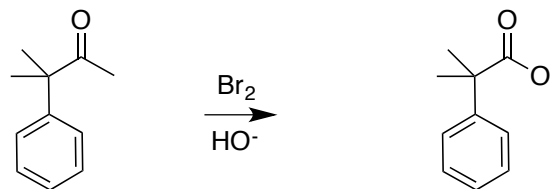
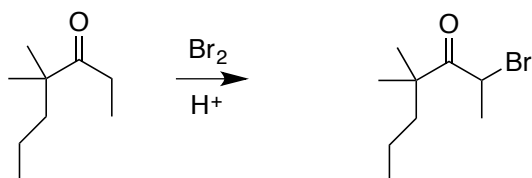
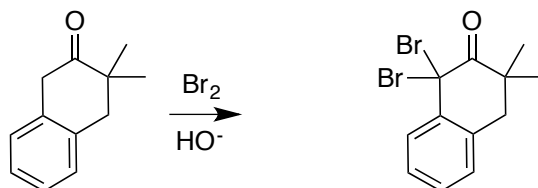
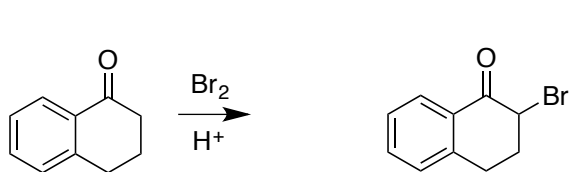


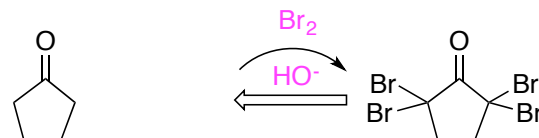
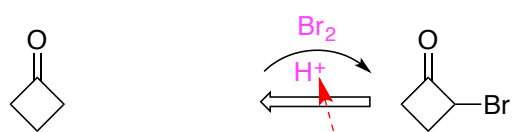
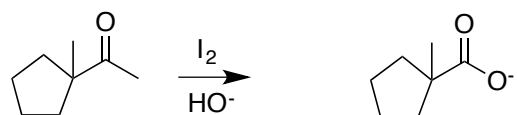
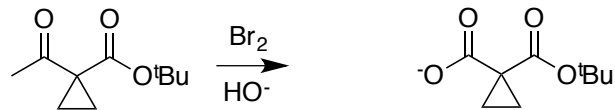
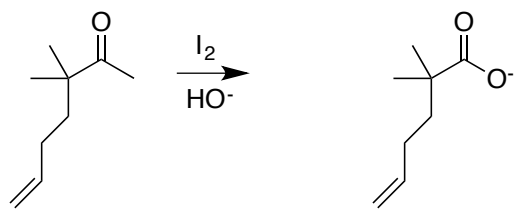
tetrahedral intermediate

slower

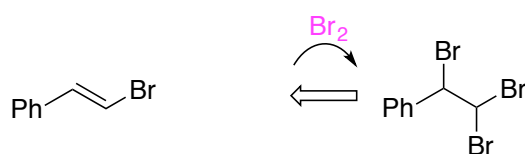
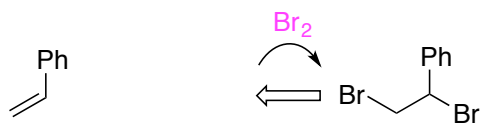


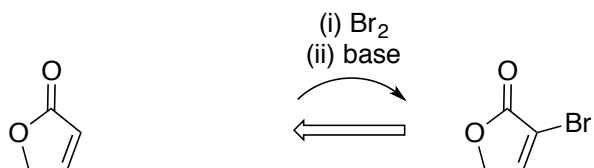
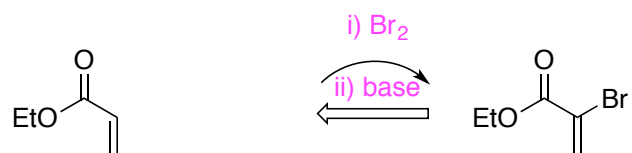
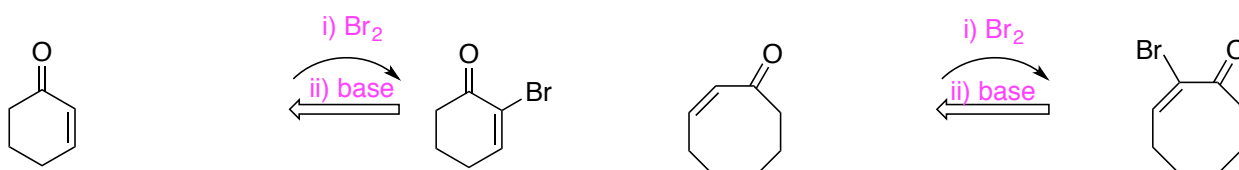
D. Choosing Acidic Or Basic Conditions For Halogenations





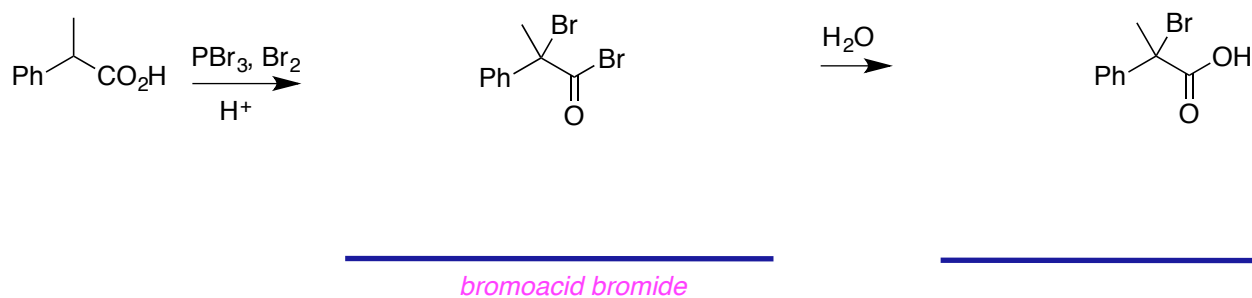
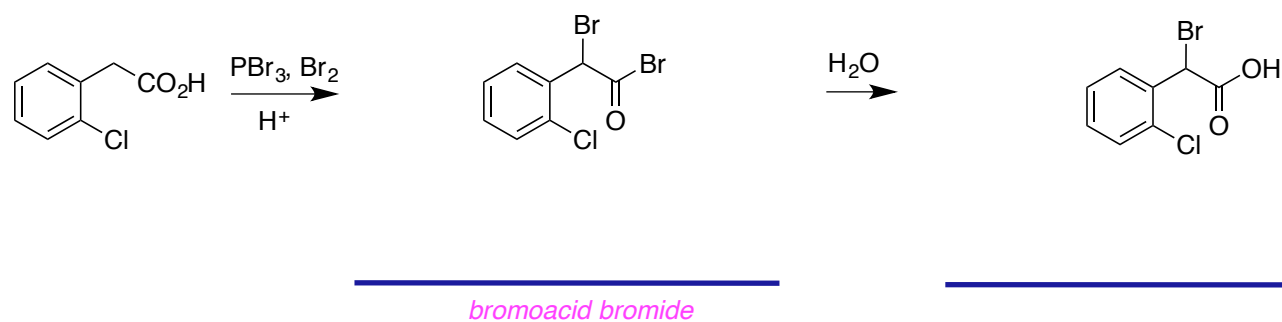
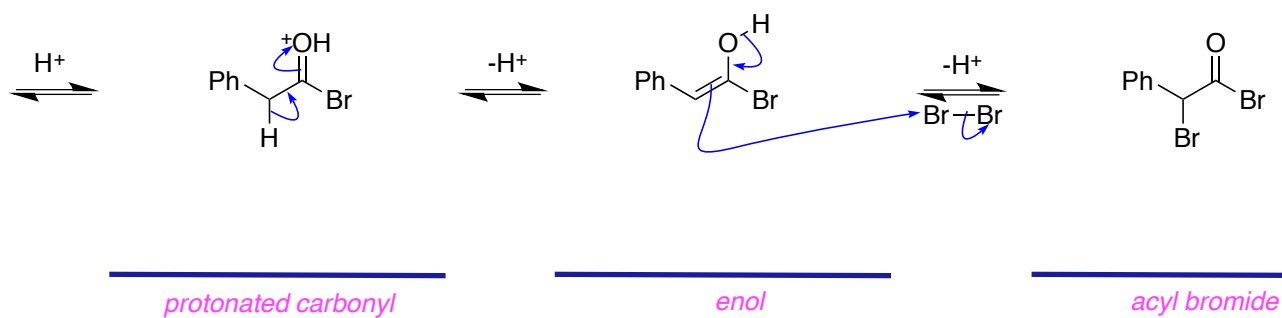
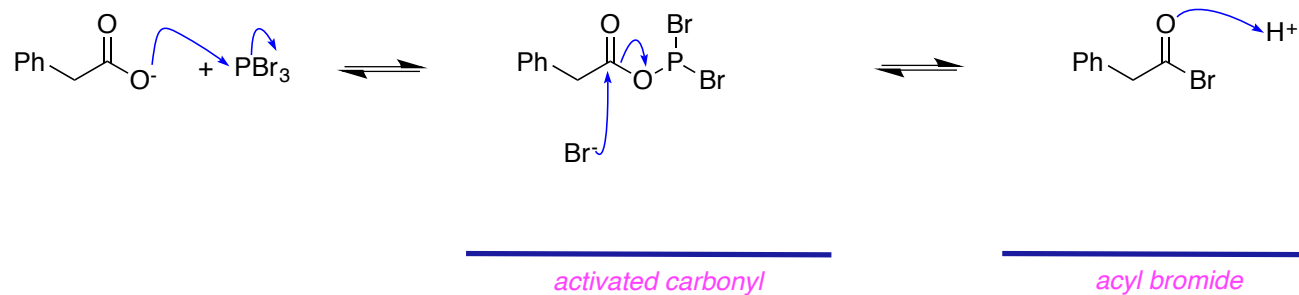
indicate conditions

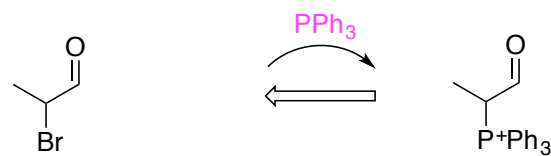
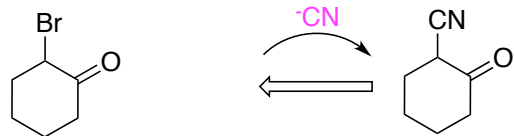
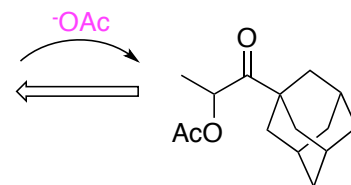
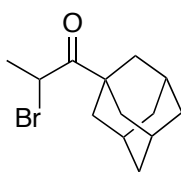
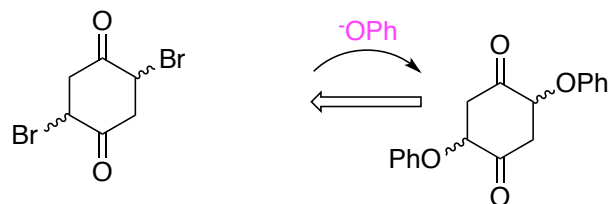
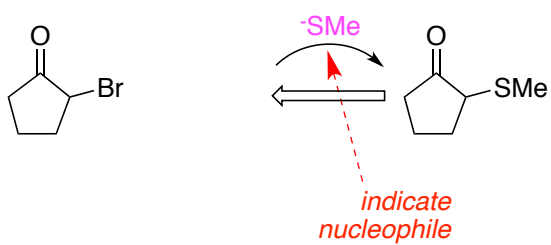
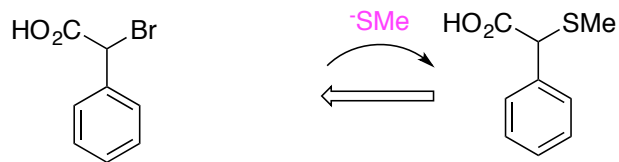
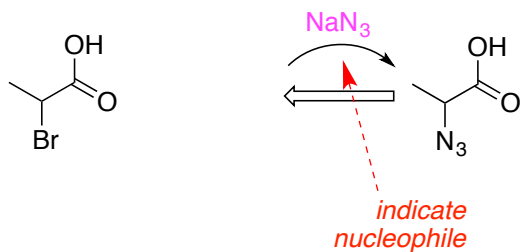


*E1cb*

E. α -Halogenation Of Carboxylic Acids

Mechanism



Syntheses Featuring α -Bromo Acids S_N2 

Reactions Of Enolizable Compounds With C-Electrophiles

from chapter(s) _____ in the recommended text

A. Introduction

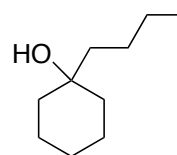
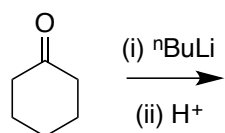
B. α -Alkylation Of Carbonyl Compounds Under Strongly Basic Conditions

C-Alkylation Of Ketones

nucleophilic

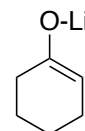
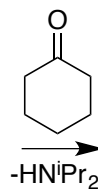
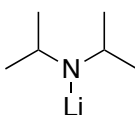
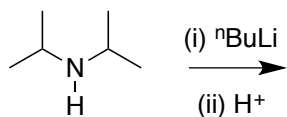
strong and *non-nucleophilic*.

hindered alkali



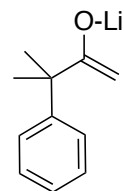
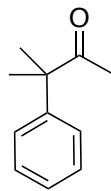
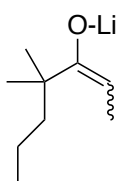
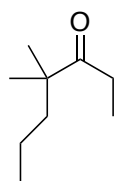
mostly

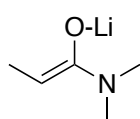
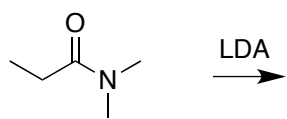
tertiary alcohol



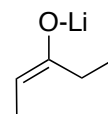
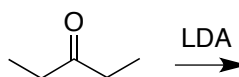
lithium diisopropylamide LDA
pKa 35

enolate

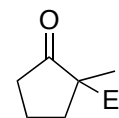
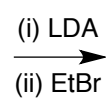
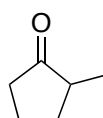
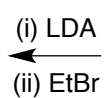
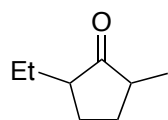




Z-enolate



draw E-enolate

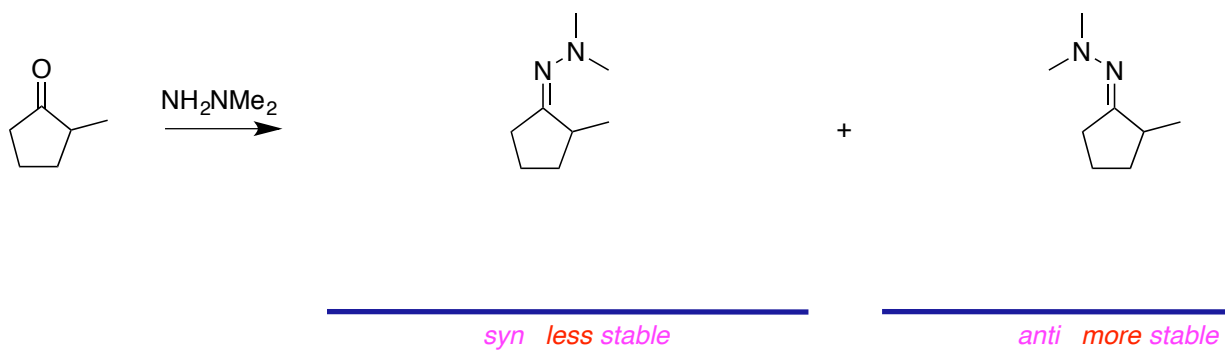
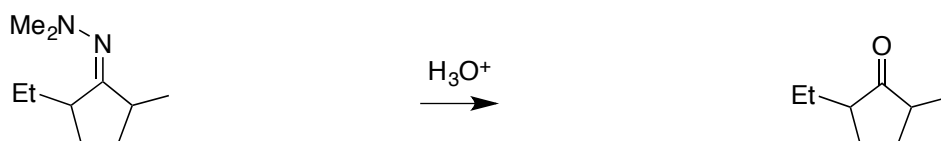
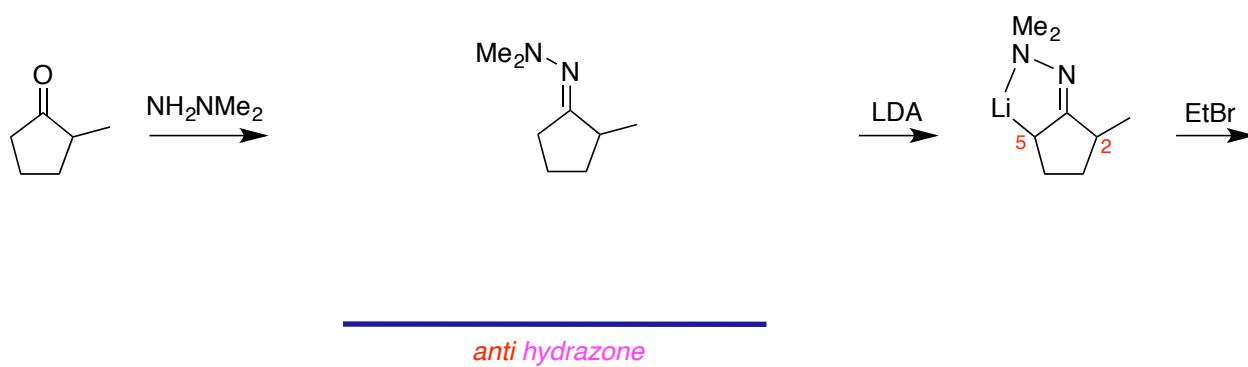


2,5-dialkyl product

2,2-dialkyl product

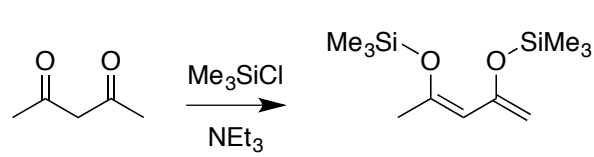
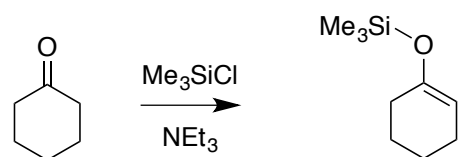
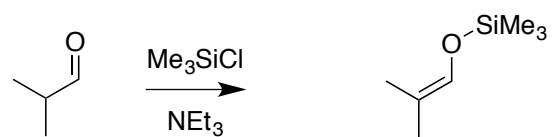
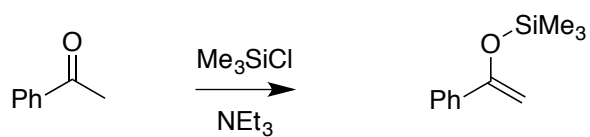
It is *difficult* to

Alkylation Of Hydrazones

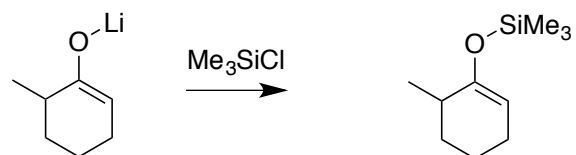
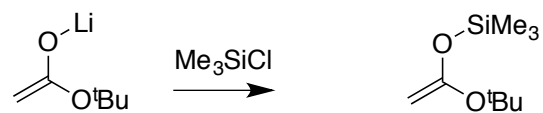
*thermodynamic**alkylation at least hindered carbon**2,5-dialkylation product*

Silylation and O-Methylation Of Aldehydes And Ketones

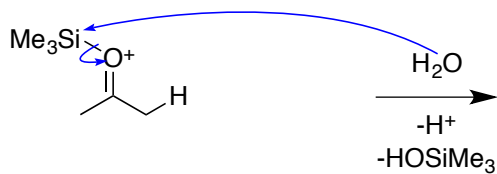
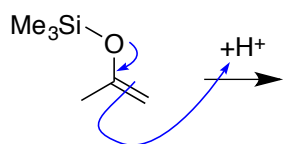
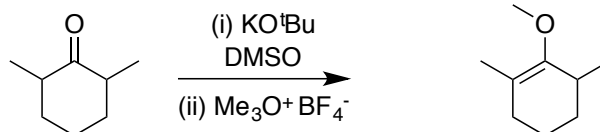
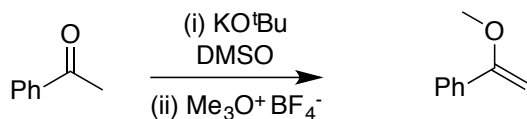
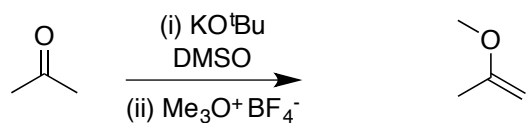
strong
O-atoms



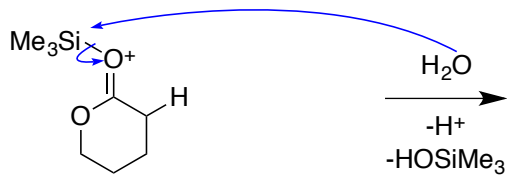
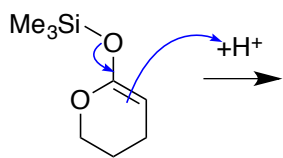
disilyl enol ether



carbon.
polar aprotic
O-alkylation
hard electrophiles
concentrated positive

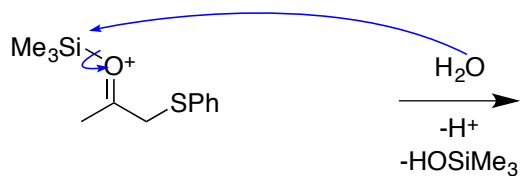
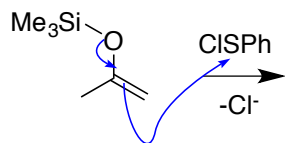


C-protonated form



C-protonated form

addition of a PhS⁺ electrophile

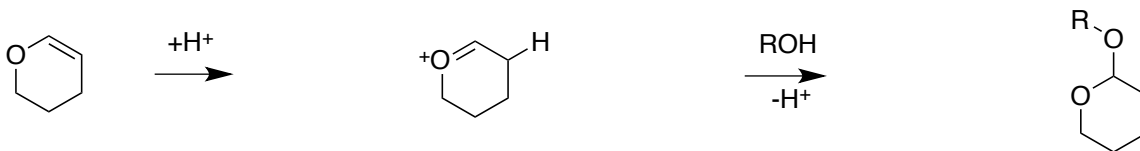


thioether silyloxonium ion

thioether

acetal; it is

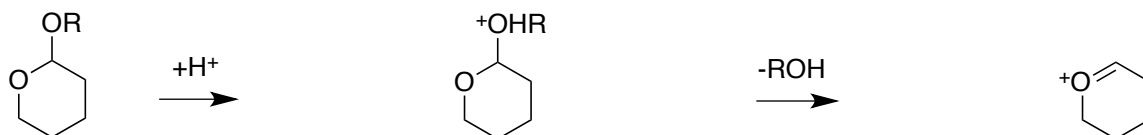
protonation then quench of the oxonium ion with an alcohol



dihydropyran

C-protonated form

THP-protected alcohol

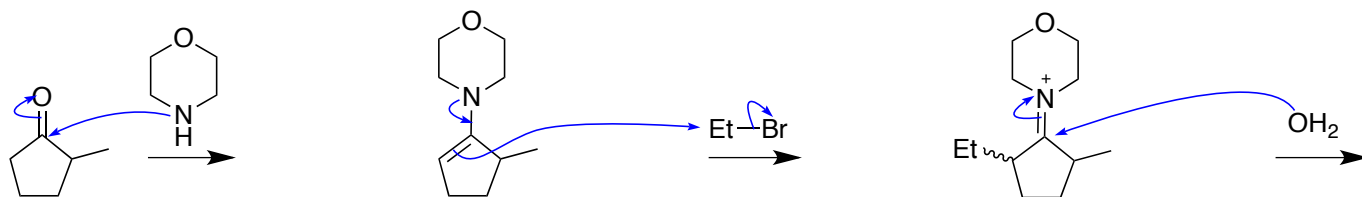


THP ether

C. α -Alkylation Of Carbonyl Compounds Under Near-neutral Conditions

Enamines From Ketones and Aldehydes

iminium ions



least hindered enamine

iminium



tetrahedral intermediate

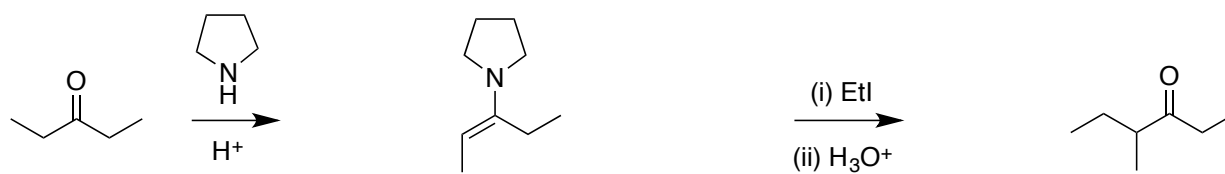
ammonium intermediate



protonated carbonyl

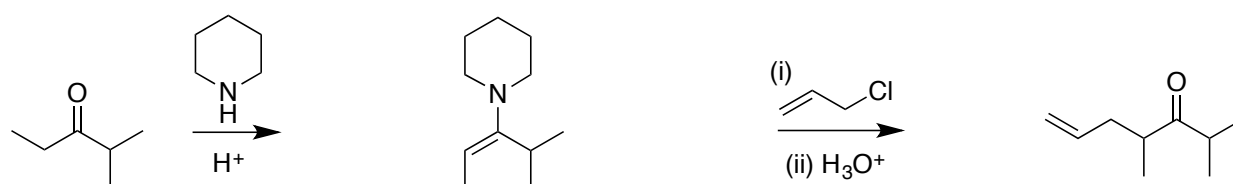
2

least substituted

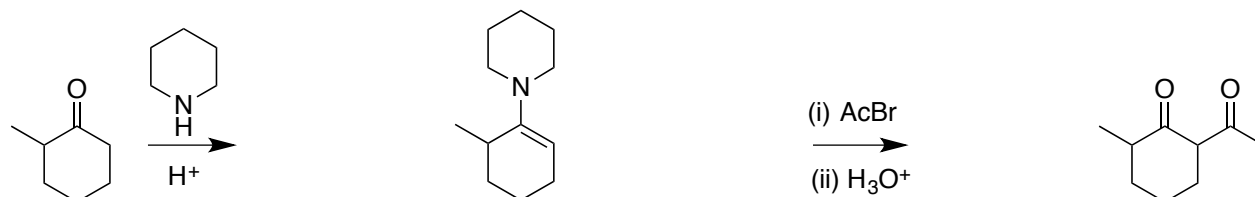
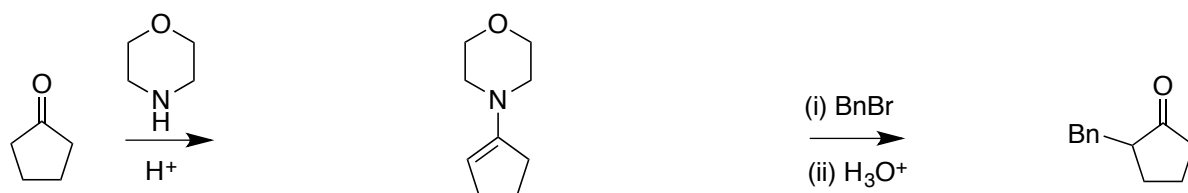


enamine

4-methyl-3-hexanone



enamine



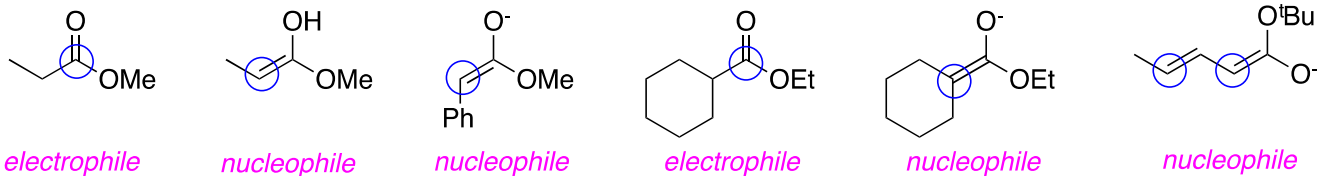
Reactions Of Ester Enolates With Esters

from chapter(s) _____ in the recommended text

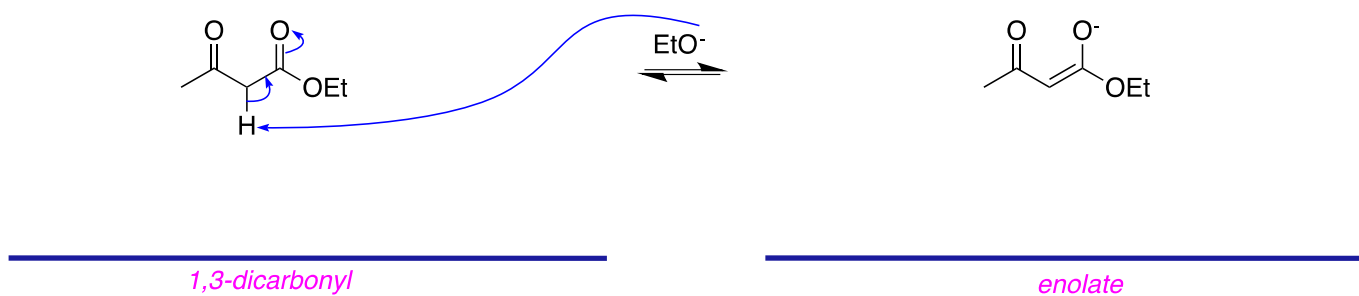
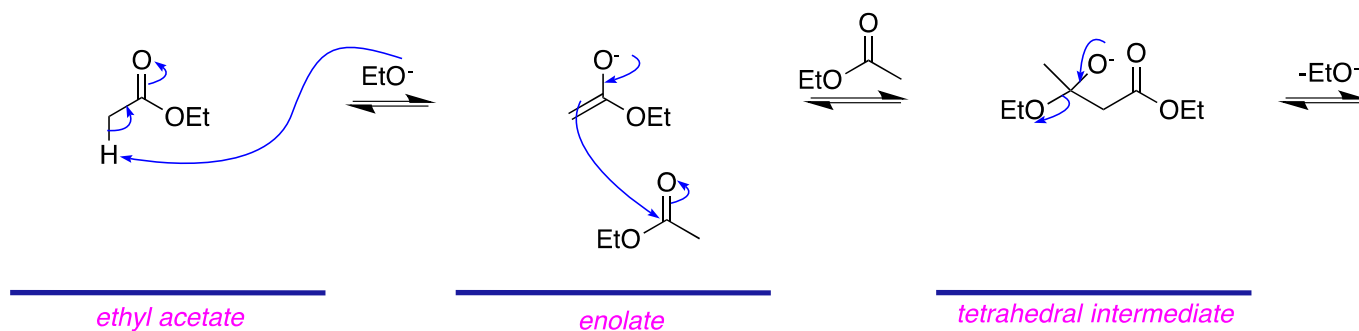
A. Introduction

B. Enolates With Ester Electrophiles (Claisen Condensations)

Homocoupling Of Esters



enolates with esters.

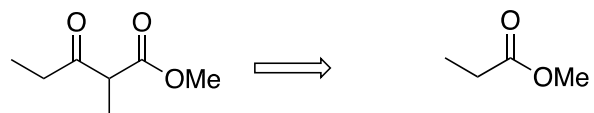


*more
stoichiometric.*

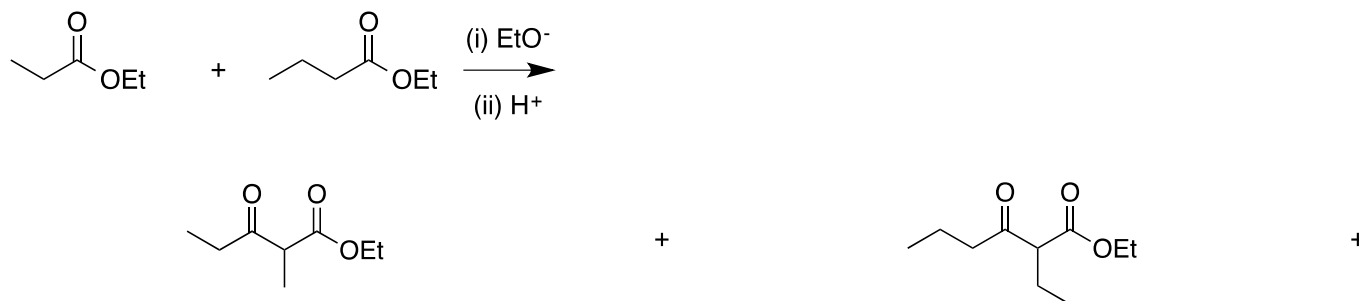
transesterification.



1,3-dicarbonyl

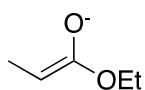
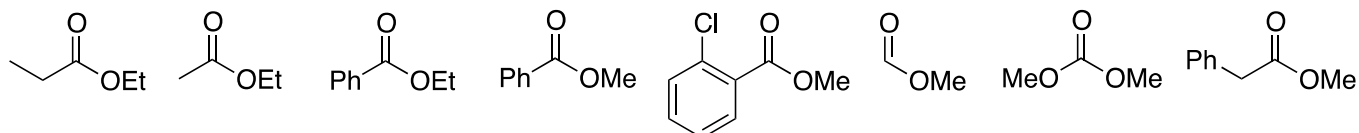


Uncontrolled Cross-Claisen Condensations

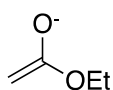


constitutional isomers

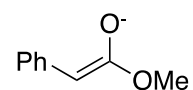
Controlled Cross-Claisen Condensations



enolate 1

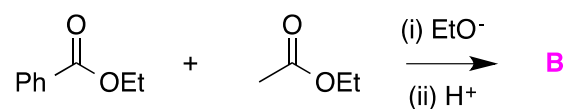
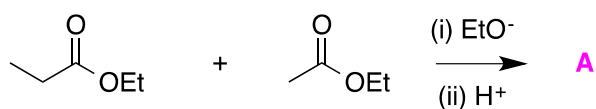


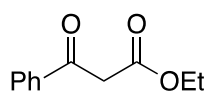
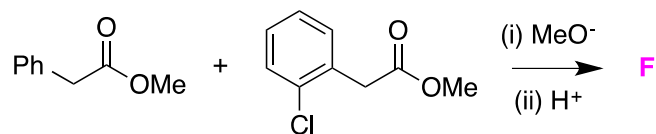
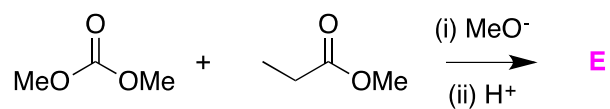
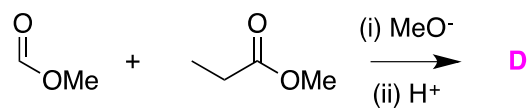
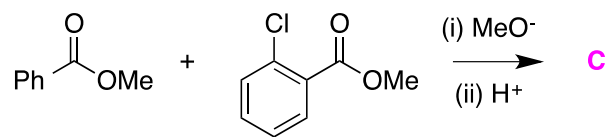
enolate 2



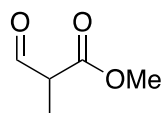
enolate 3

only one

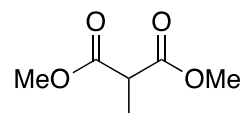




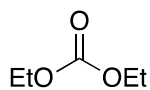
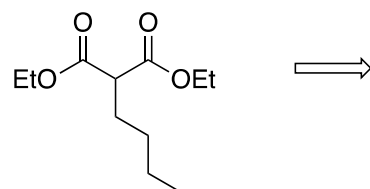
letter B



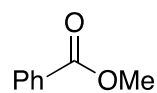
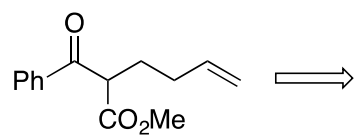
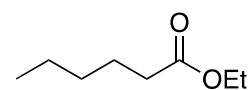
letter D



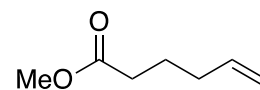
letter E



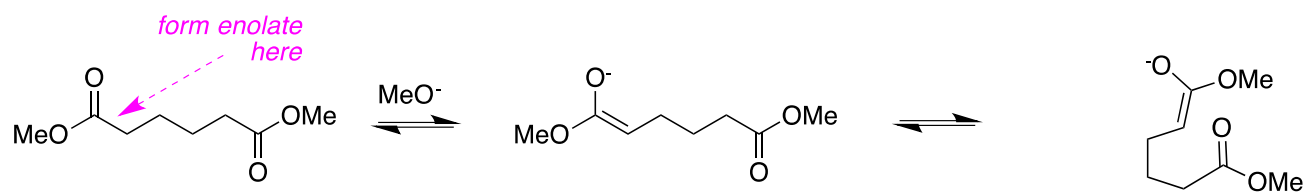
+



+



Intramolecular Reactions Of Ester Enolates With Esters (Dieckmann Reactions)

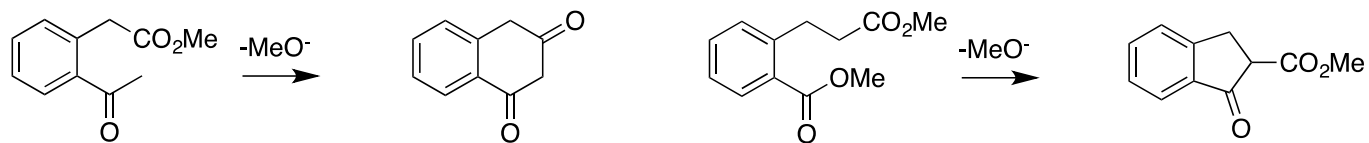


enolate

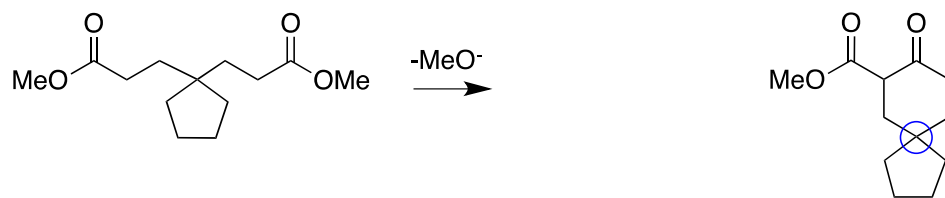
*enolate in conformation
for cyclization*



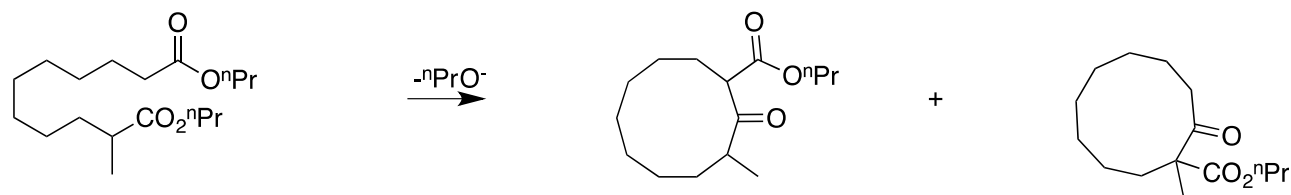
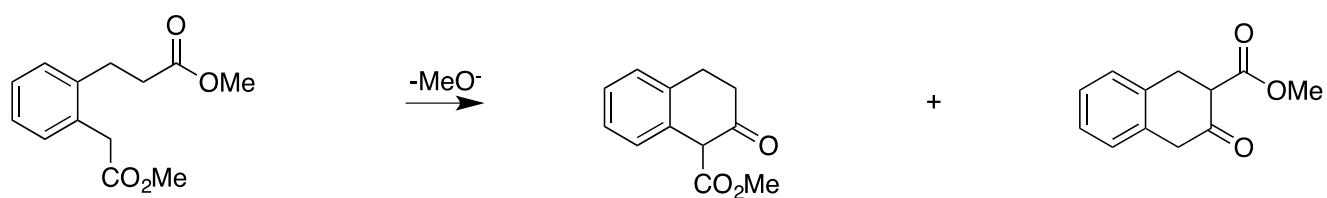
a cyclopentanone

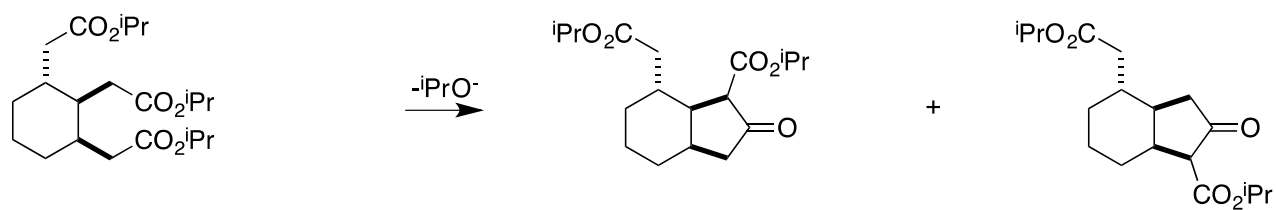


form a single point of contact between two rings.

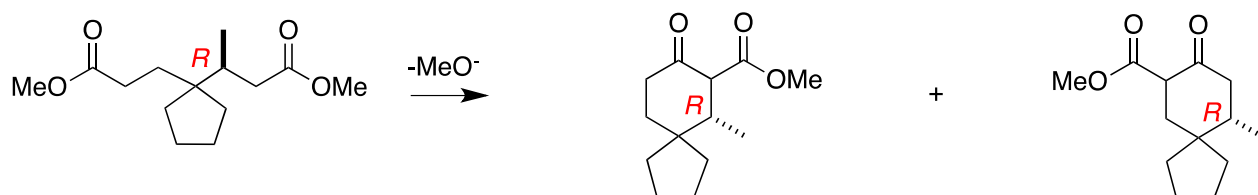


more than one
less
diminished in



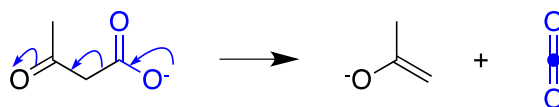


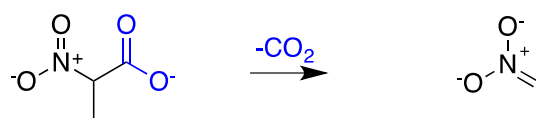
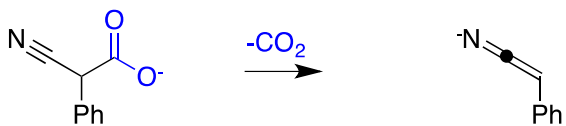
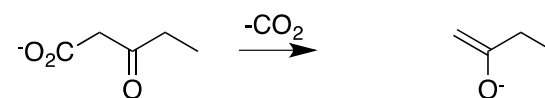
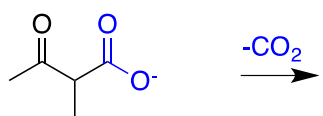
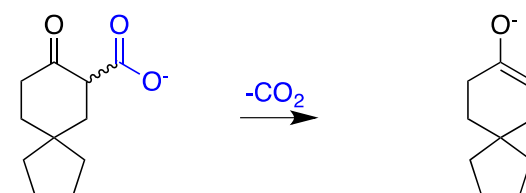
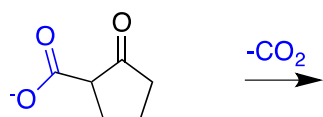
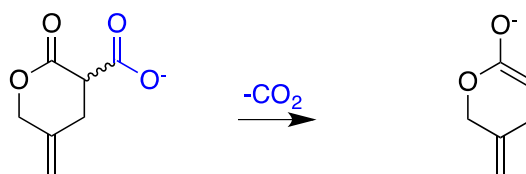
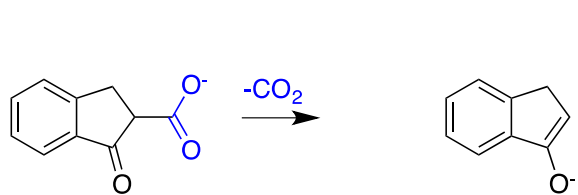
assume trans-fused 6,5-rings are not formed since they are less stable



the same configurations.

C. Decarboxylation Of 3-Oxocarboxylic Acids From Carboxylates

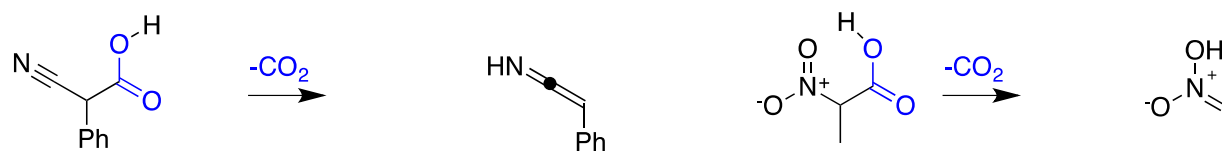
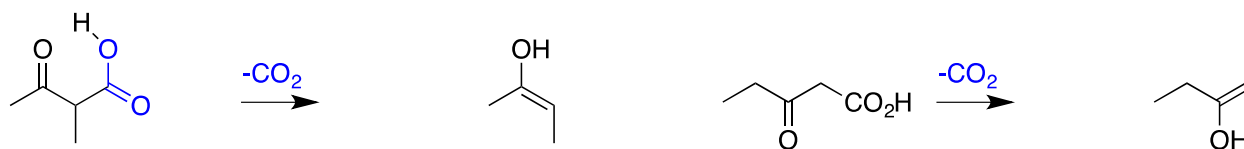
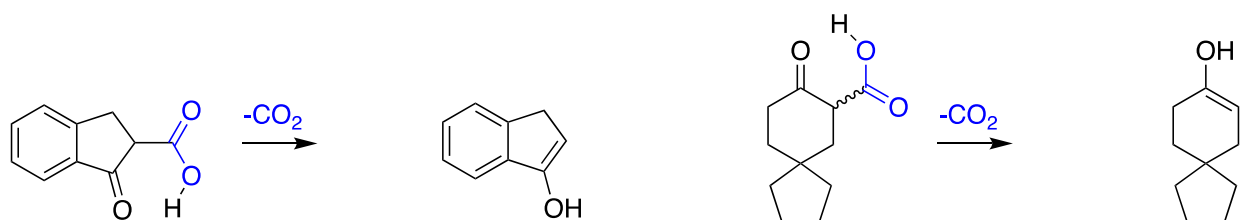
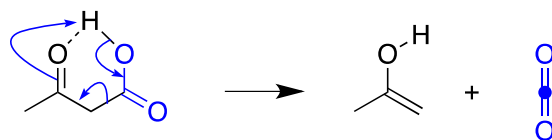




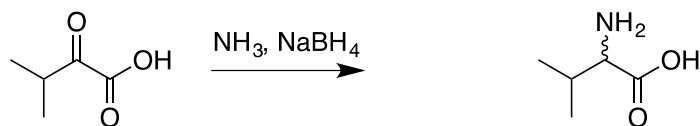
From Carboxylic Acids

carboxylates and *carboxylic acids*

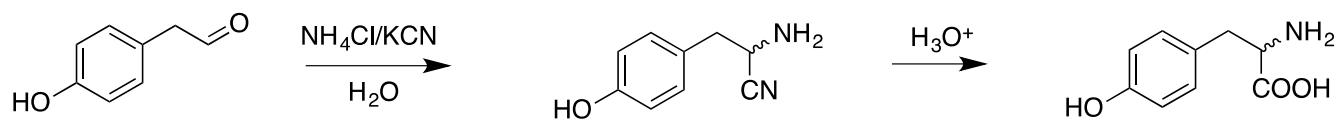
enols (whereas *carboxylates* produced *enolates*).



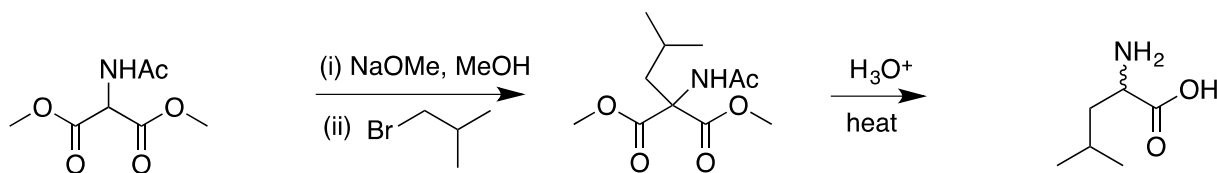
D. Classical Syntheses Of Amino Acids



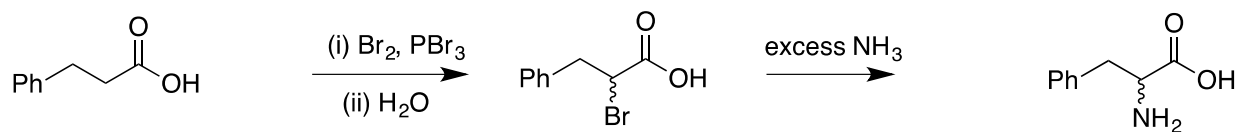
amino acid valine



amino acid tyrosine

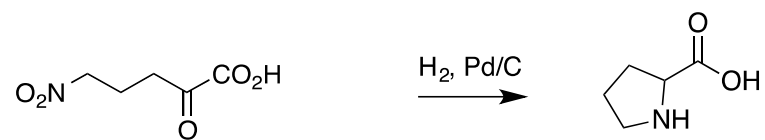
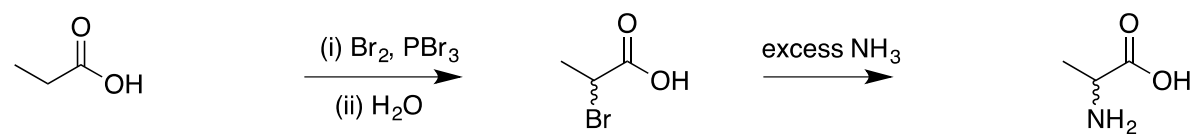
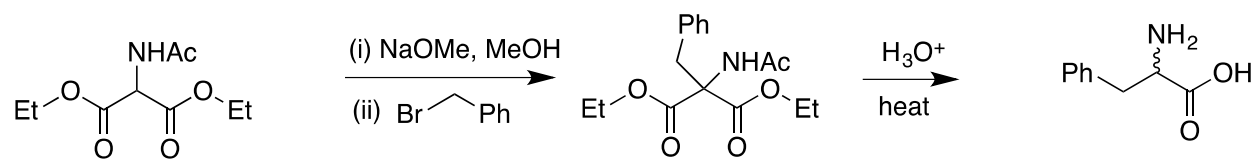


amino acid leucine



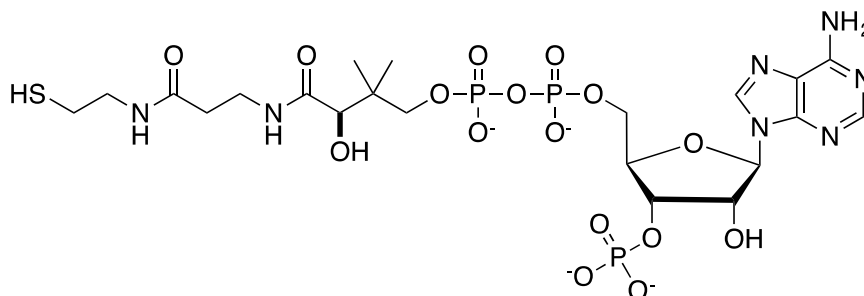
amino acid phenylalanine

racemates.

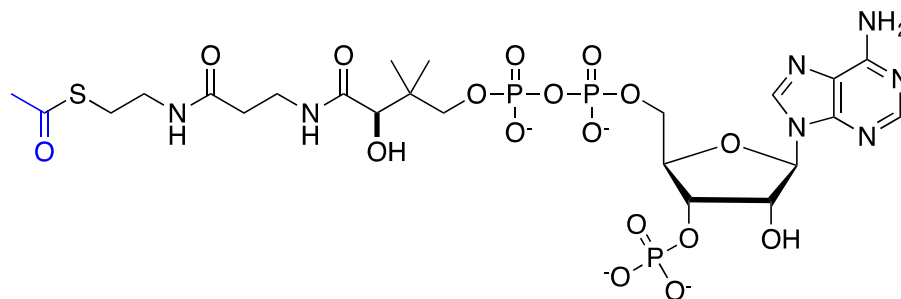


E. Thioesters Are More Reactive Than Esters

stronger
better
milder



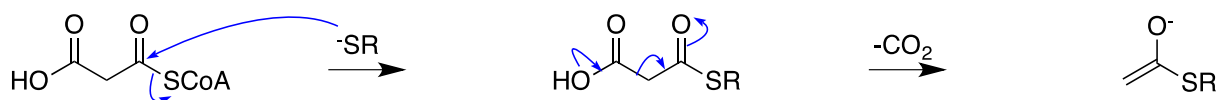
coenzyme A or CoASH



acyl coenzyme A or acyl-CoA

huge
better

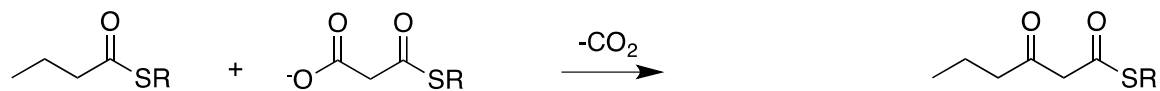
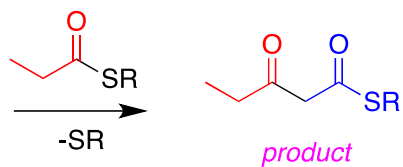
Nature's Equivalent To Claisen Condensations



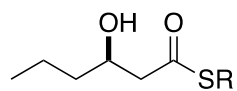
malonyl-CoA

transthioesterification product

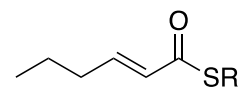
enolate of thioester



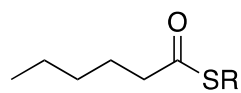
*ketone
reduction*
→
*show
Si-face addition
of hydride*



dehydration
→
-H₂O



hydrogenation
→
+H₂

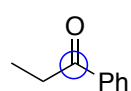


Aldol and Aldol Condensation Reactions

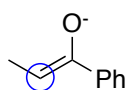
from chapter(s) _____ in the recommended text

A. Introduction

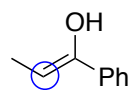
B. Acidities Of Carbonyl Compounds



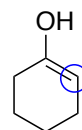
electrophile



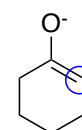
nucleophile



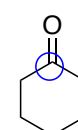
nucleophile



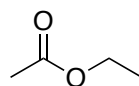
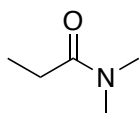
nucleophile



nucleophile

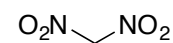
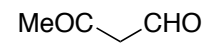
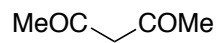
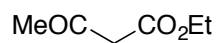
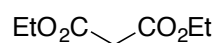


electrophile



increasingly acidic α CH

less



increasingly acidic α CH

*more
deprotonated* forms.

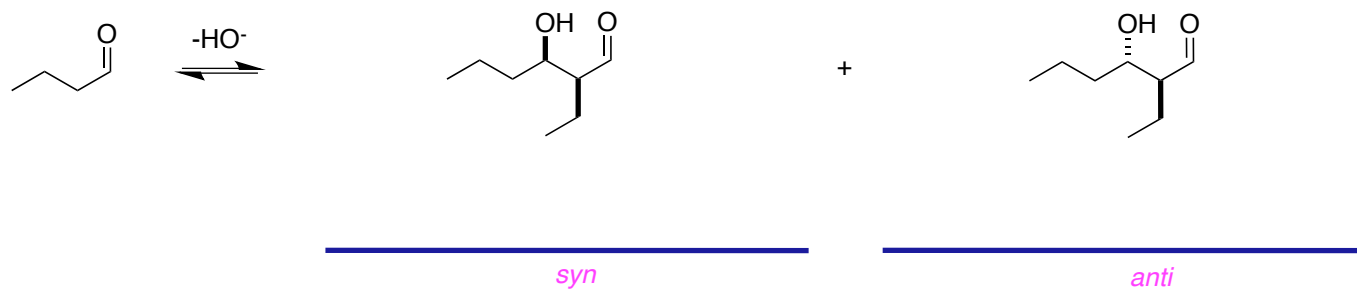
C. Aldol Reactions

nucleophile
electrophile.

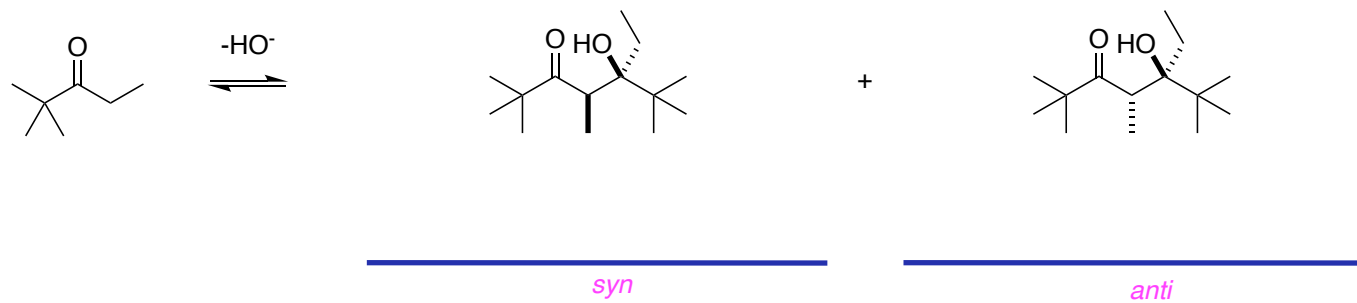
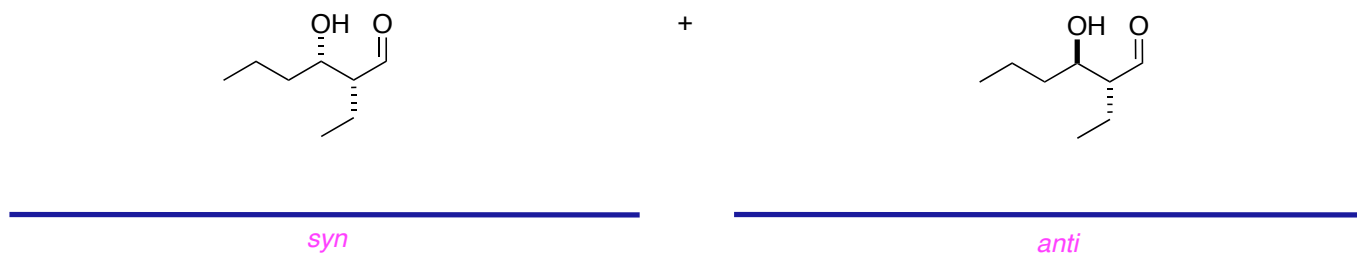


homo-coupling

equal
same

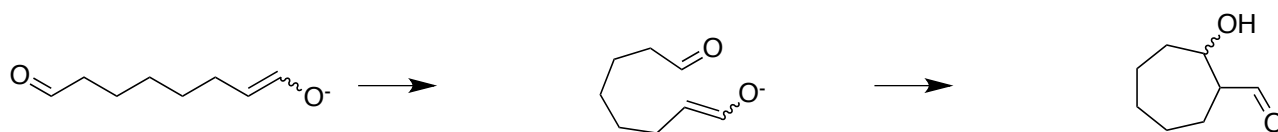
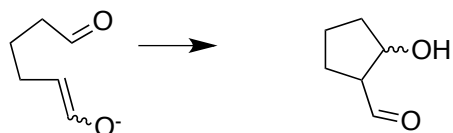


exactly
the same as



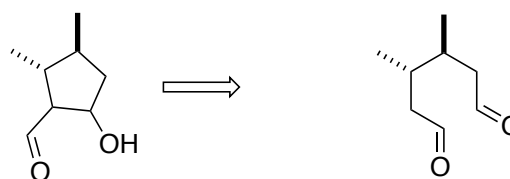
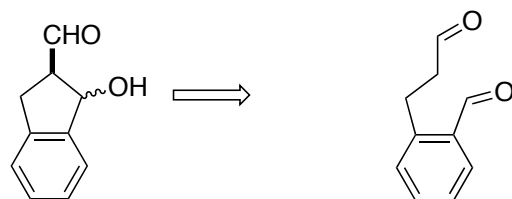
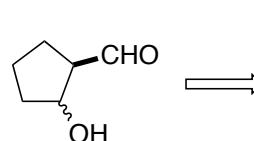
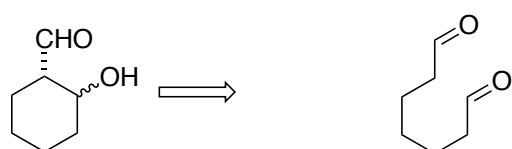
Intramolecular Aldol Reactions

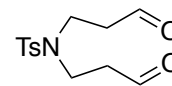
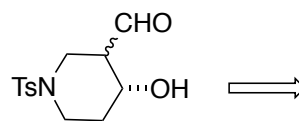
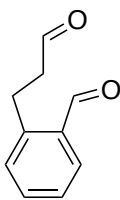
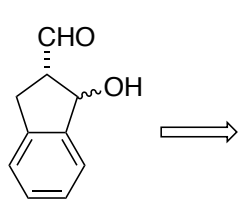
the same molecule.



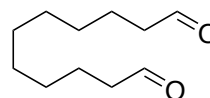
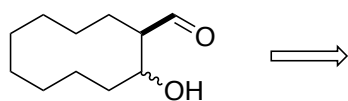
starting material re-drawn

product

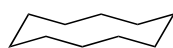




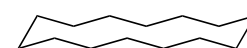
(question changed
from 1 st to 2 nd edition)



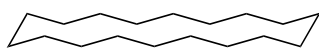
trans-decalin



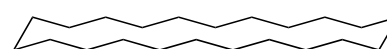
cyclo-C₁₀H₂₀



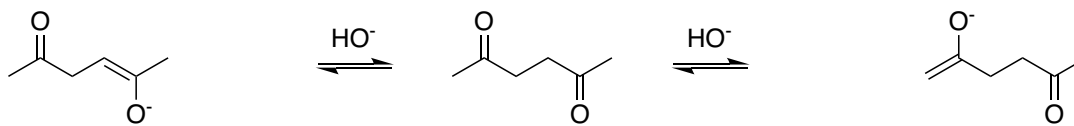
cyclo-C₁₄H₂₈



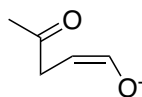
cyclo-C₁₈H₃₆



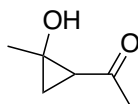
cyclo-C₂₂H₄₄



internal enolate
(extended conformation)

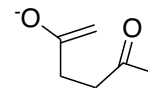


internal enolate
(conformation to give cyclopropane)

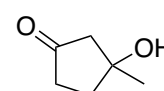


kinetic alkoxide

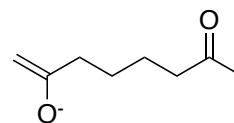
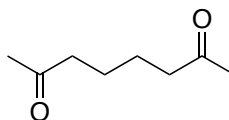
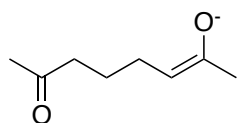
terminal enolate
(extended conformation)



terminal enolate
(conformation to give cyclopentane)



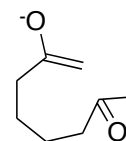
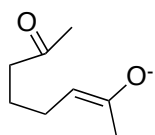
thermodynamic alkoxide



*internal enolate
(extended conformation)*

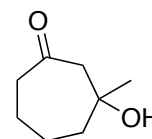
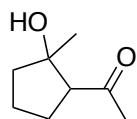
2,7-octanedione

*terminal enolate
(extended conformation)*



*internal enolate
(conformation to give
5-membered ring)*

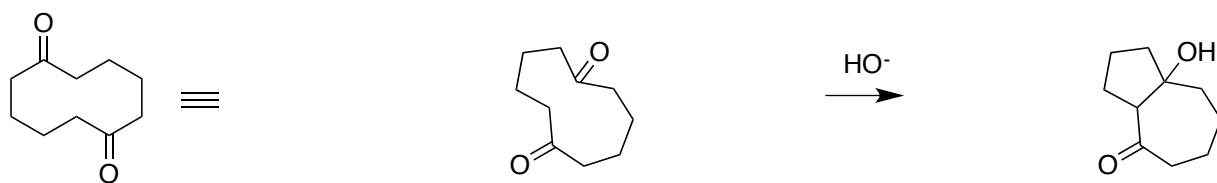
*terminal enolate
(conformation to give
7-membered ring)*



alkoxide from a cyclopentanol

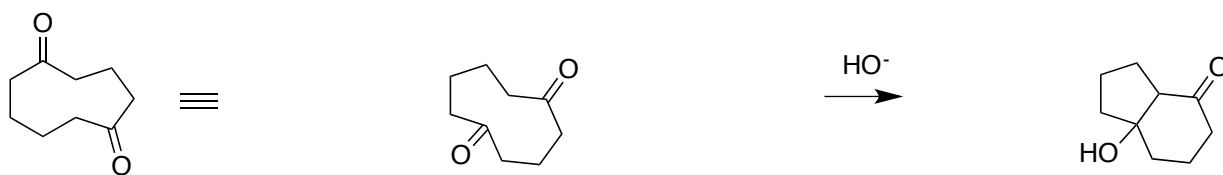
alkoxide from a cycloheptanol

neither the thermodynamic or the kinetic product.



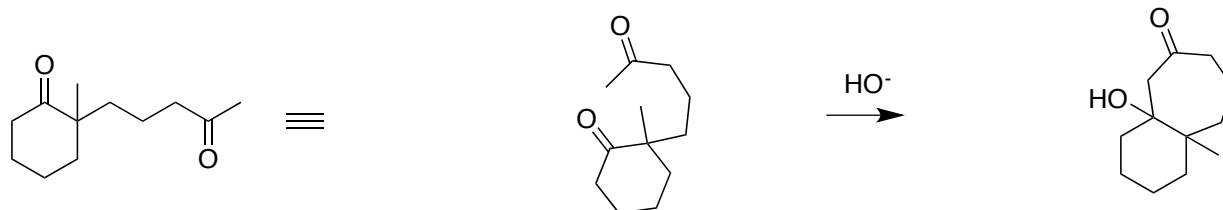
starting material re-drawn

product
(edge shared
7 and 5-membered rings)



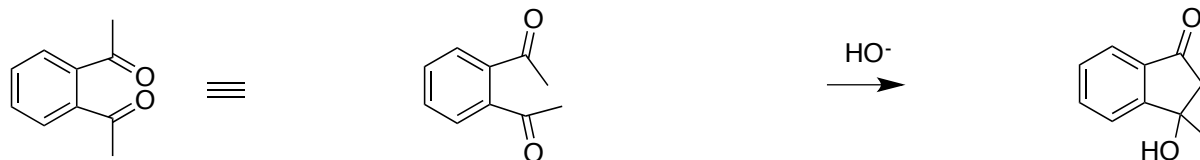
starting material re-drawn

product



starting material re-drawn

favored product

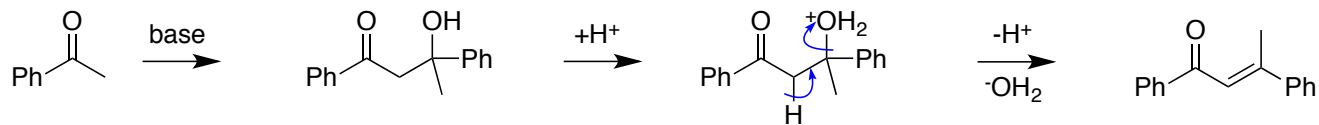


starting material re-drawn

favored product

D. Dehydration Of Aldol Products: Aldol Condensations

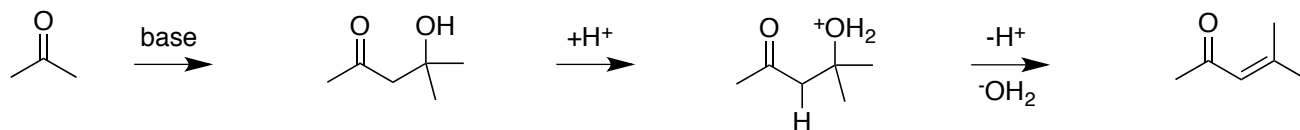
Homocouplings



*aldol product after
protonation with water*

oxonium

enone



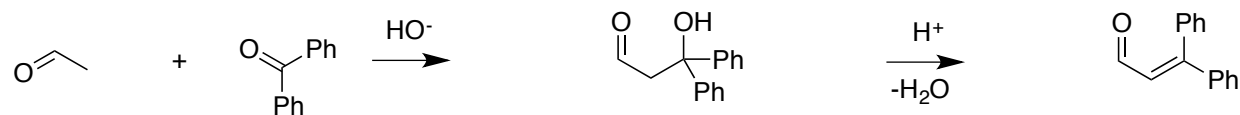
*aldol product after
protonation with water*

oxonium

enone

Cross Condensations

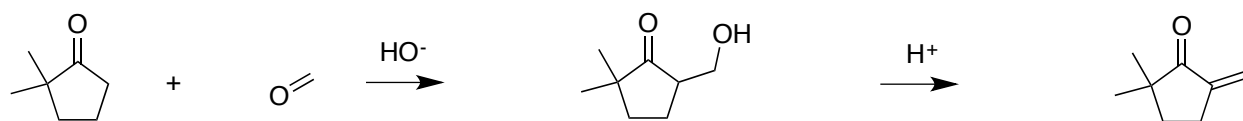
Featuring One Enolizable Component



intermolecular cross aldol

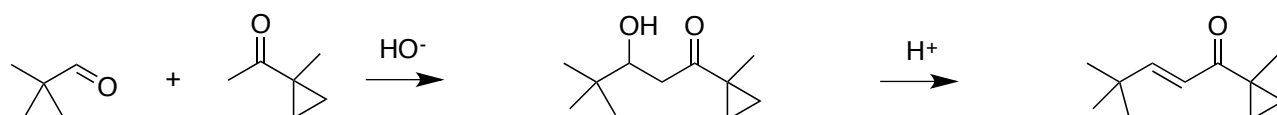
enone

more reactive



intermolecular aldol

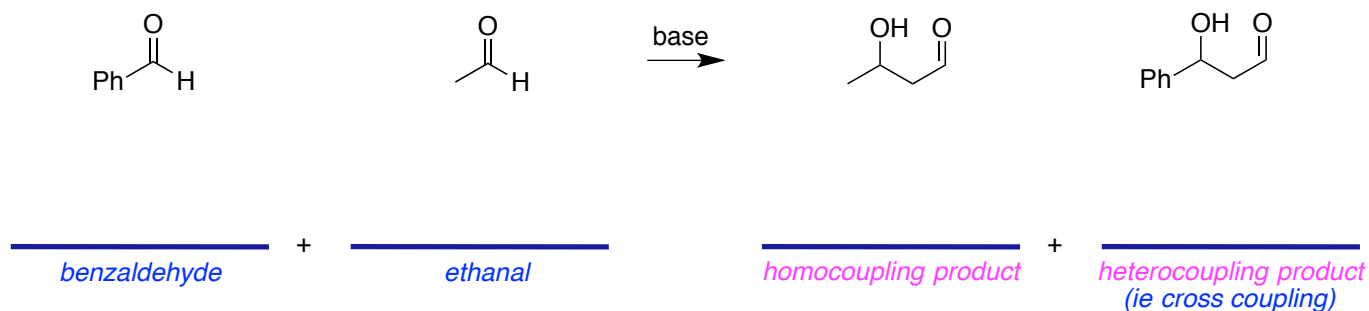
dehydration to enone



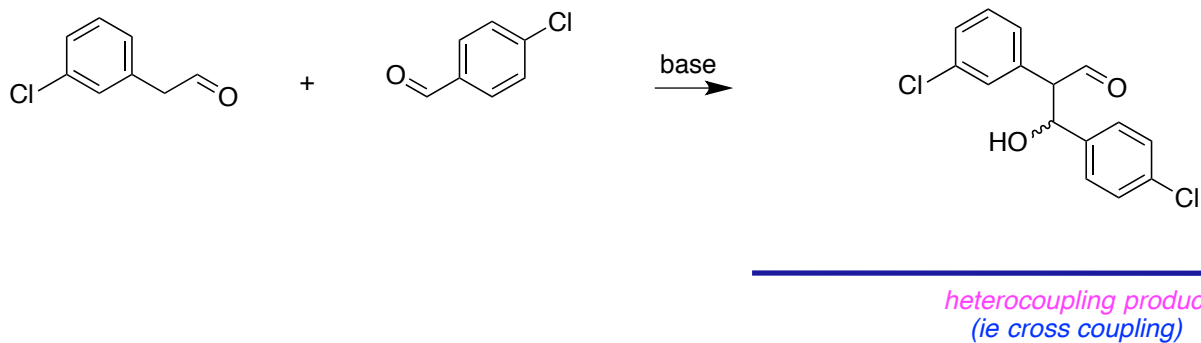
intermolecular aldol

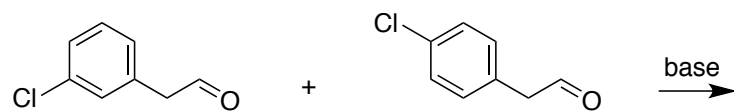
dehydration to enone

One
one of the components



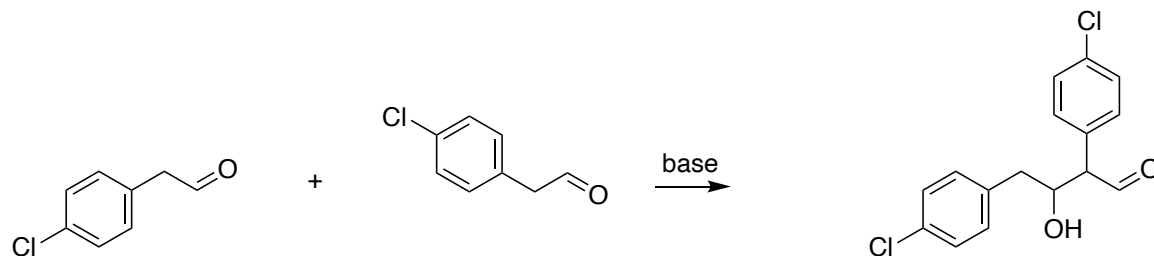
benzaldehyde and the one added slowly to this would be **ethanal**.



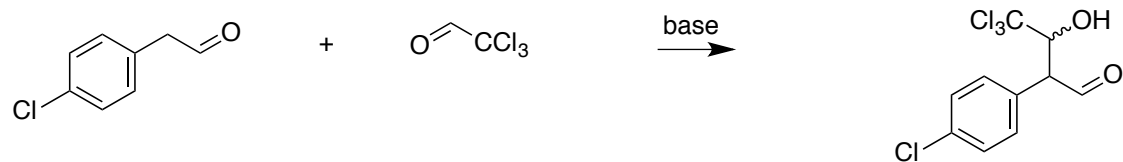


mixture

*heterocoupling product
(ie cross coupling)*

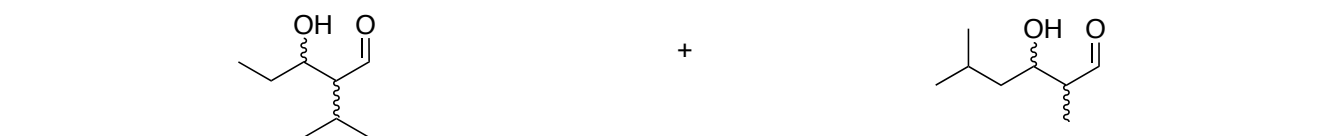


homocoupling product

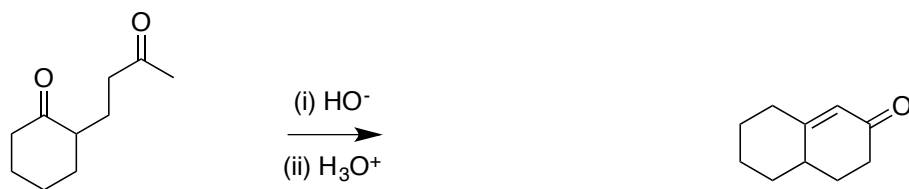
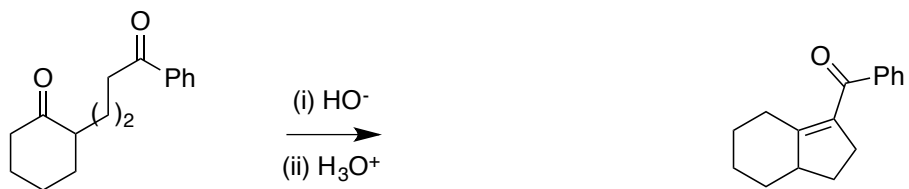


*heterocoupling product
(ie cross coupling)*

Aldol Condensations Are Hard To Control When Two Enolizable Fragments Are Used

*homocoupling product 1**homocoupling product 2
(two diastereomers)**heterocoupling product 1**heterocoupling product 2
(two diastereomers)**homocoupling product 1**homocoupling product 2
(two diastereomers)**heterocoupling product 1**heterocoupling product 2
(two diastereomers)*

Intramolecular Condensations

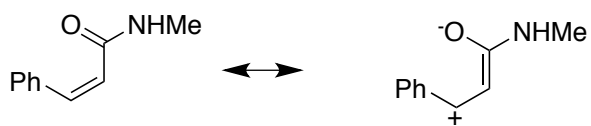
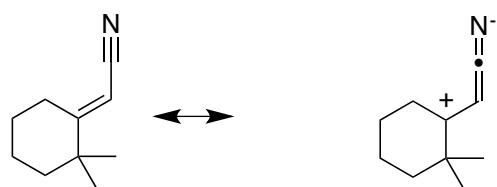
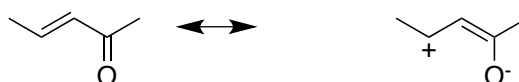


25 Conjugate Additions

from chapter(s) _____ in the recommended text

A Introduction

B Polarization Of α,β -Unsaturated Carbonyl Compounds

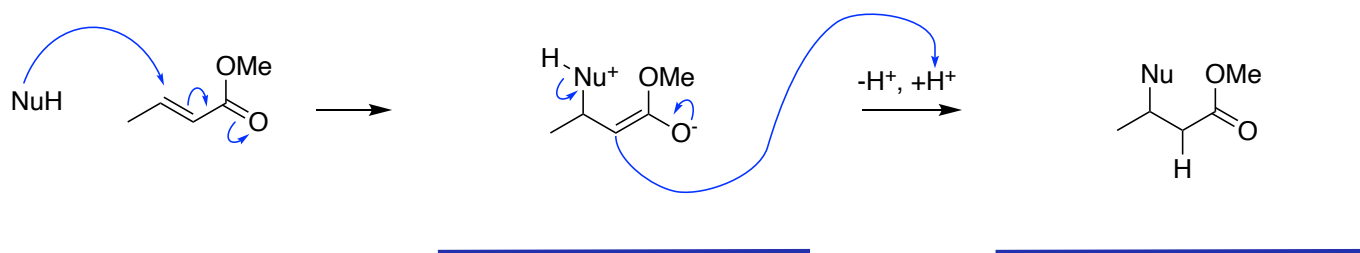
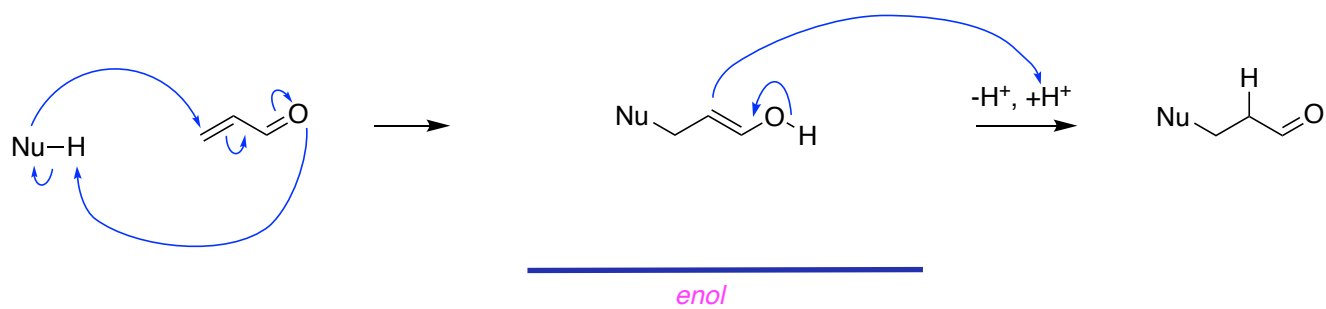
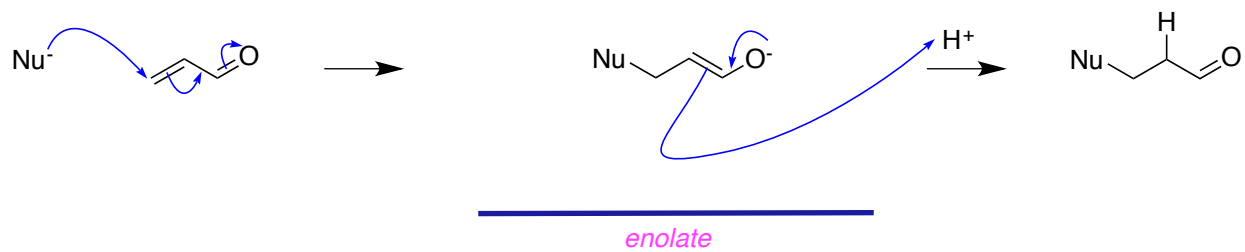


is always on the β -carbon

LUMO

more / less stable

C Mechanism Of Conjugate Addition

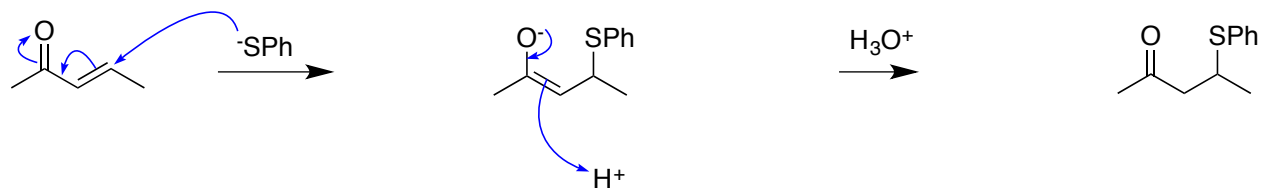


D Examples Of Conjugate Additions

Amines And Thiols

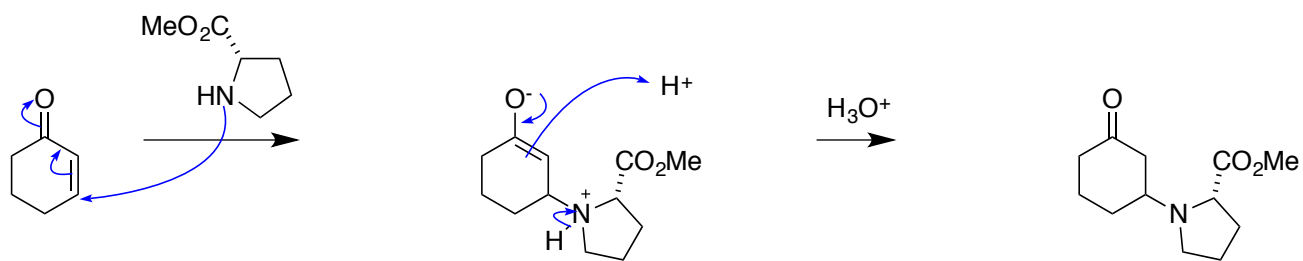
the *nucleophile* adds to the 4-position

the *proton* adds to the oxygen



enolate intermediate

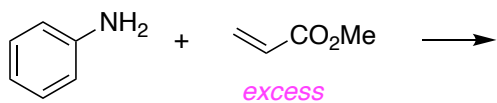
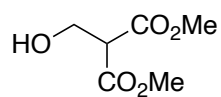
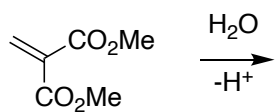
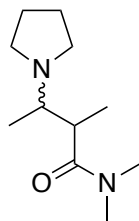
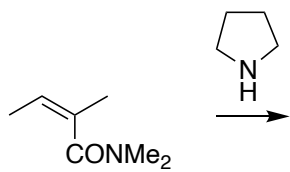
1,4-addition product



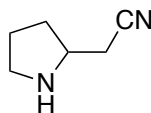
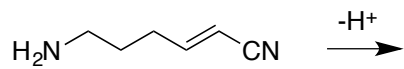
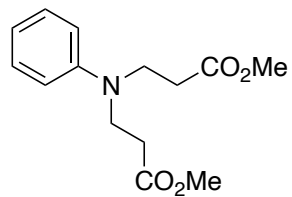
enolate intermediate

1,4-addition product

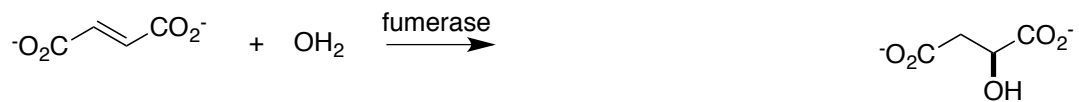
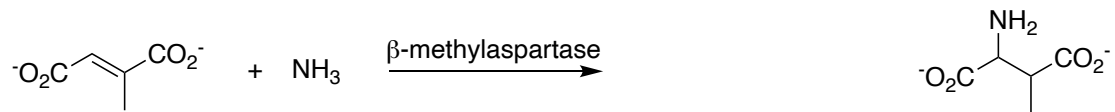




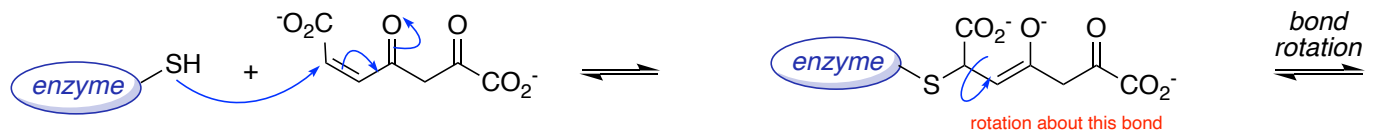
excess



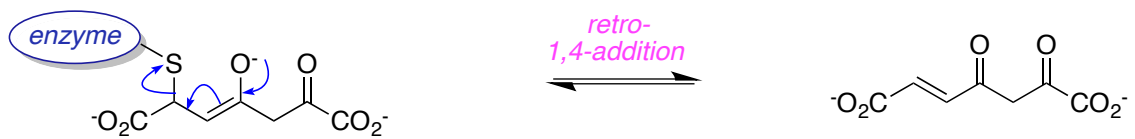
Enzyme-mediated Conjugate Additions



S-product



adduct

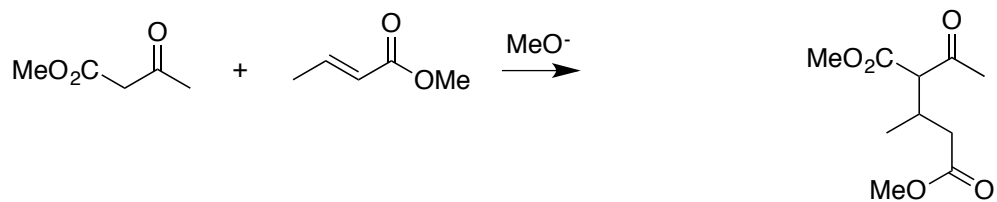
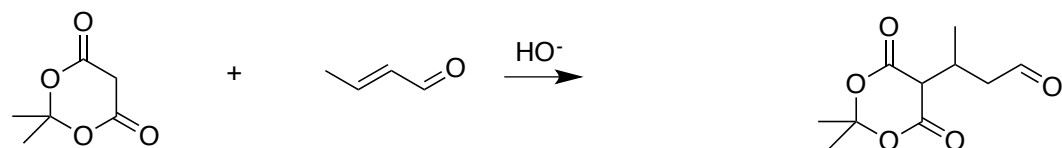
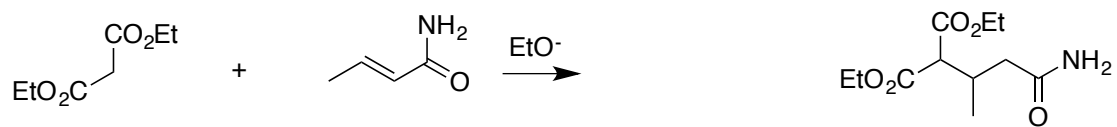


rotamer of initial adduct

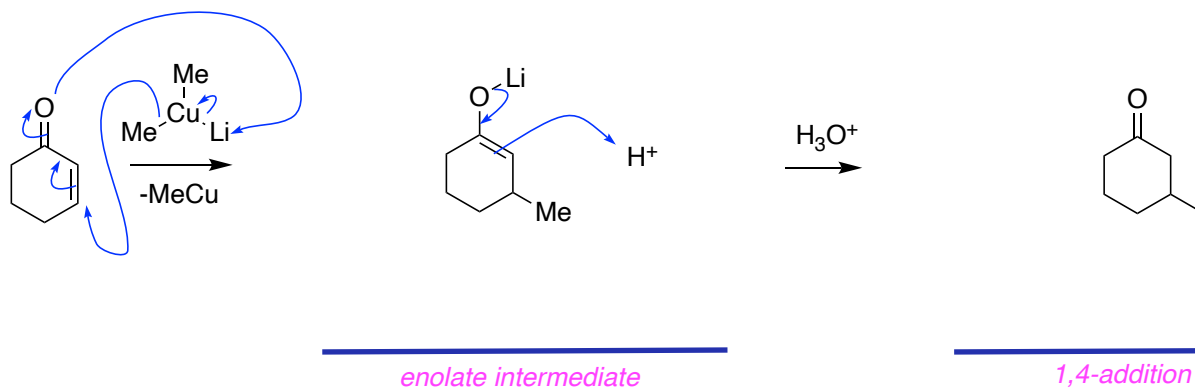
isomerized product

Stabilized C-Anion Nucleophiles

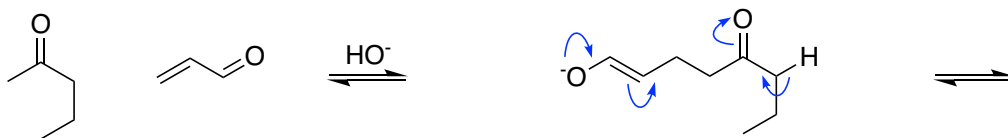
the base is required in *stoichiometric* quantities.



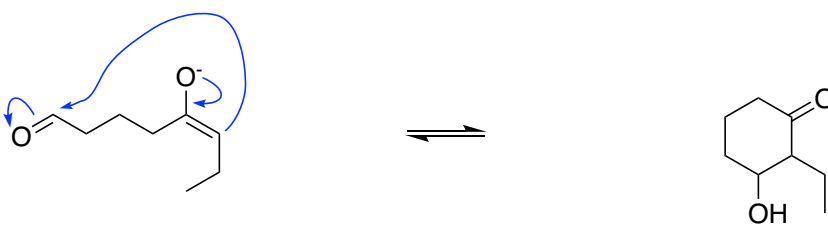
Organometallic Agents In Laboratory Chemistry



E Conjugate Addition Then Aldol Condensation



conjugate addition product



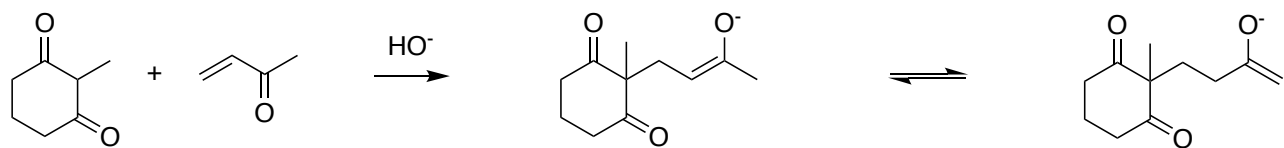
an enolate that can cyclize easily

cyclization product



cyclic aldol/dehydration product

Predict the products of the following reactions.



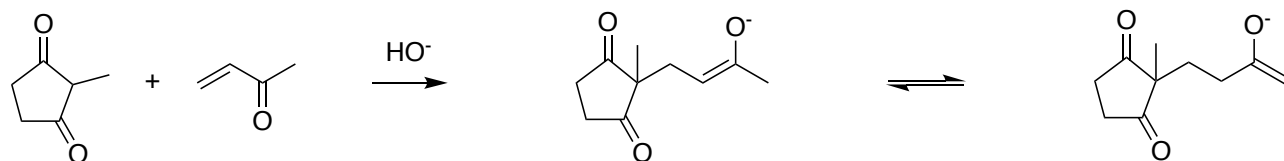
enolate from conjugate addition

terminal enolate



intramolecular cyclization product

enone



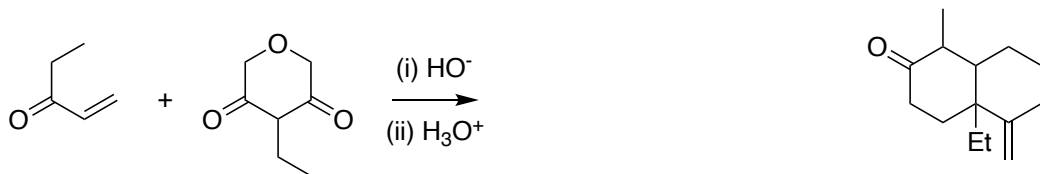
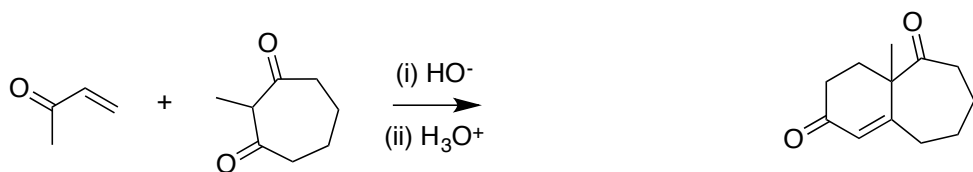
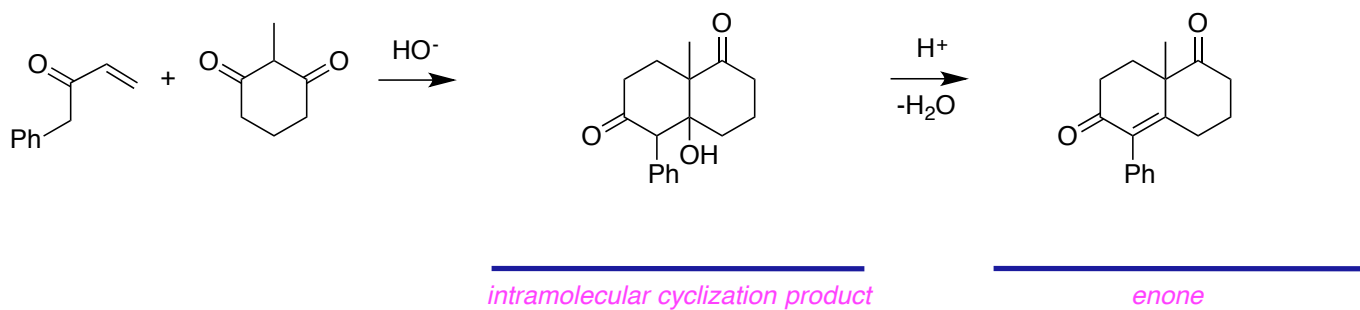
enolate from conjugate addition

terminal enolate



intramolecular cyclization product

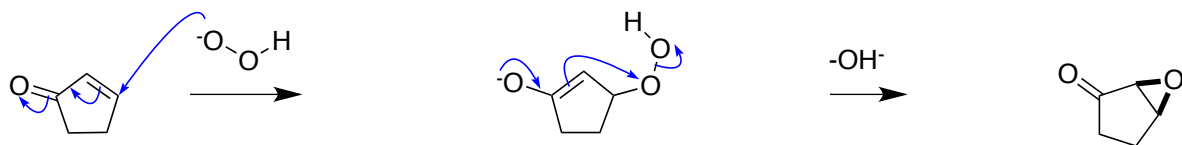
enone



F Nucleophilic Epoxidation

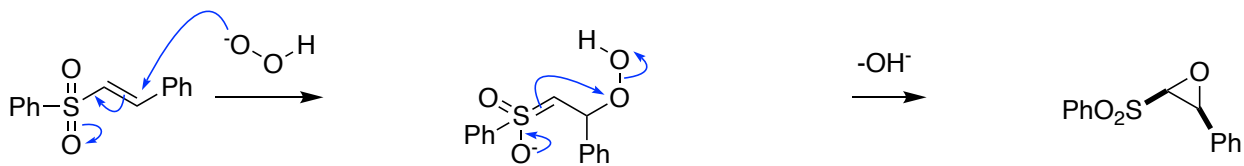
α -effect

more acidic than water



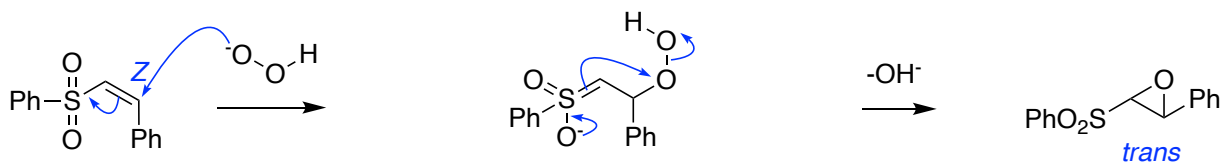
enolate intermediate

epoxide



enolate

epoxide

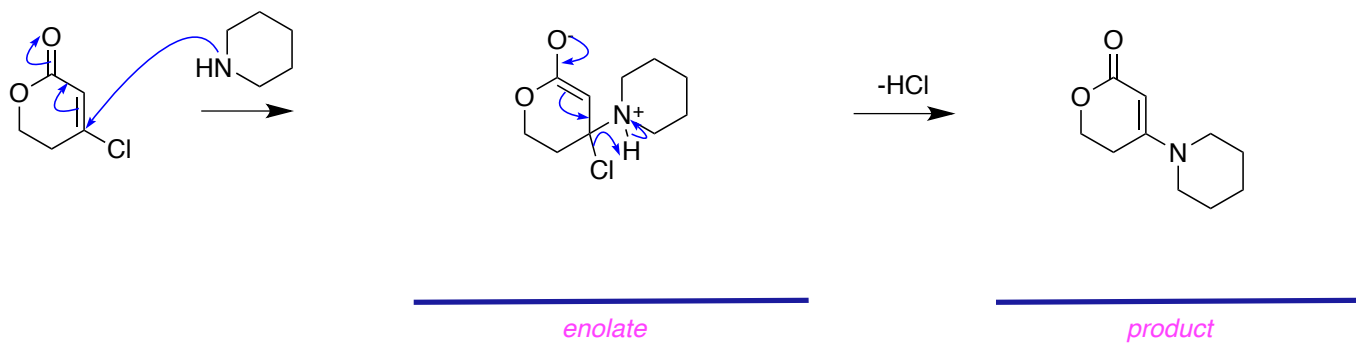
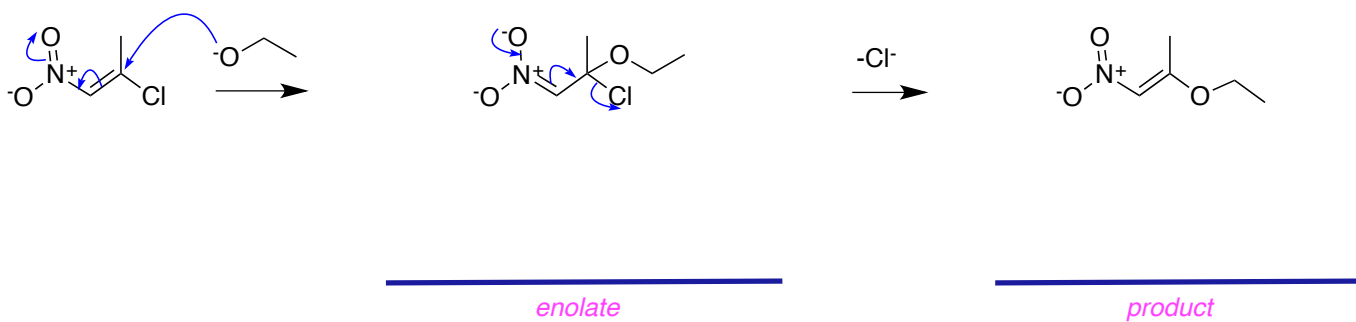
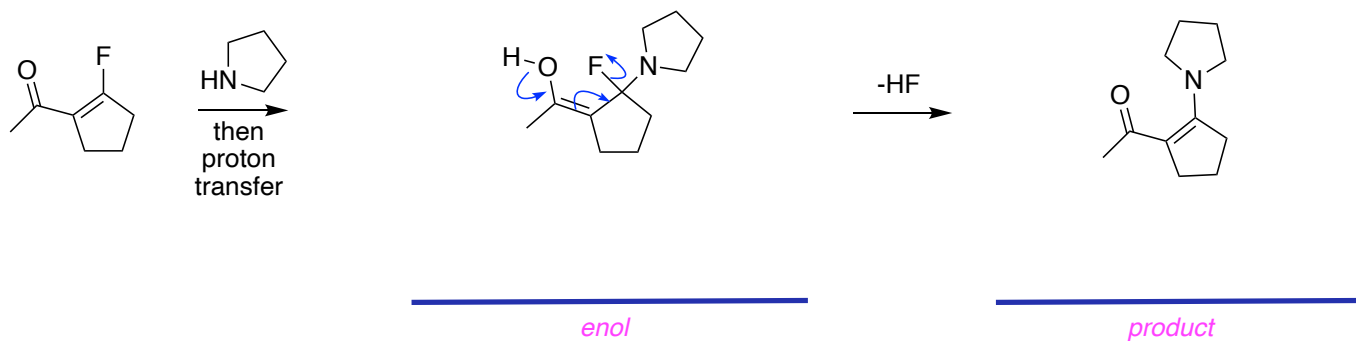


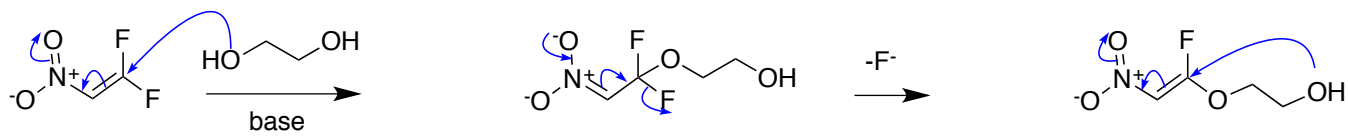
enolate intermediate

trans

It *is not* possible

G Addition Elimination Reactions





enolate

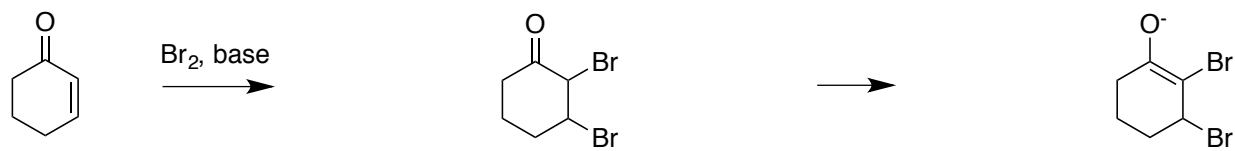
intermediate



enolate

product

Formation Of α -Bromo Enones



dibromide intermediate

enolate



monobrominated product

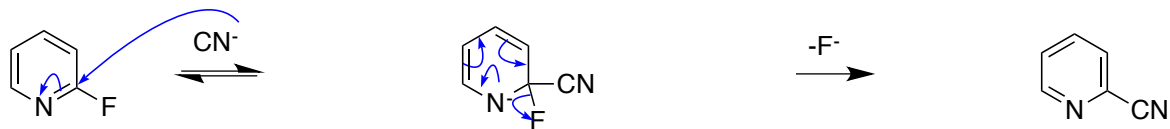
H Nucleophilic Aromatic Substitution

S_NAr processes.

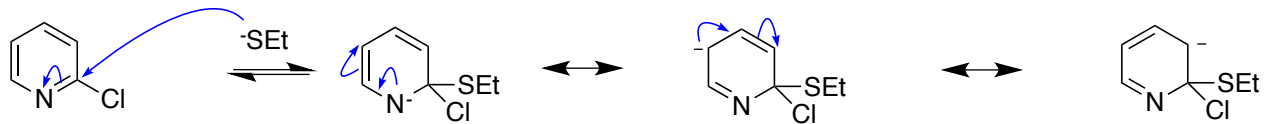
They involve *rate-limiting* addition

anionic intermediates

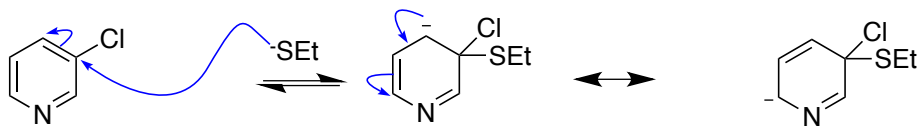
sp^3 hybridized C-atom.



2-chloropyridine



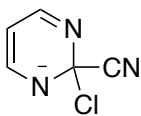
3-chloropyridine



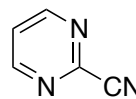
2- isomer.

Addition occurs fastest for the 2- and 4-isomers

2-chloro-1,3-pyrimidine reacted with cyanide



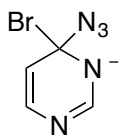
intermediate



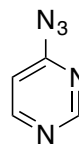
product

fast

4-bromo-1,3-pyrimidine reacted with azide



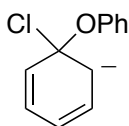
intermediate



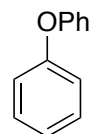
product

slow

chlorobenzene reacted with phenoxide



intermediate



product

slow