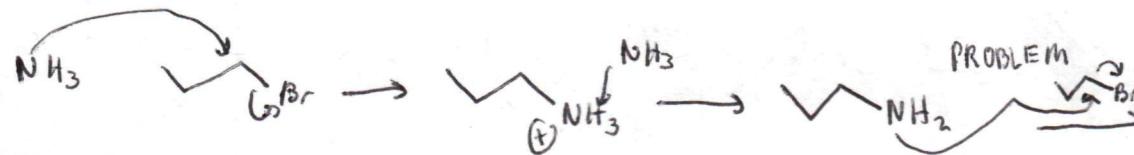
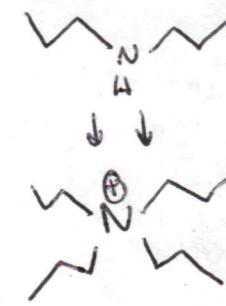
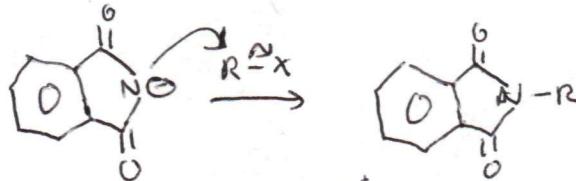
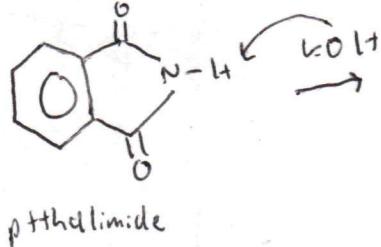


Preparation of Amines

Goal:  $\text{CH}_3\text{CH}_2\text{NH}_2$

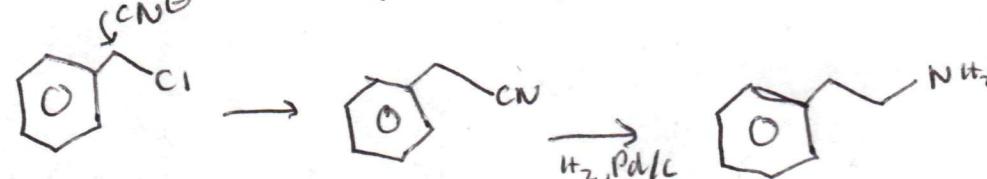
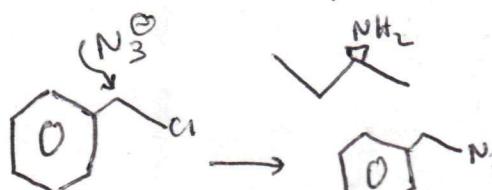
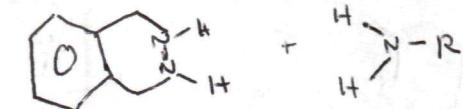
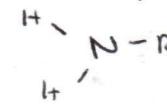
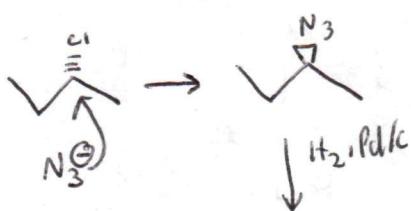


Use protecting groups



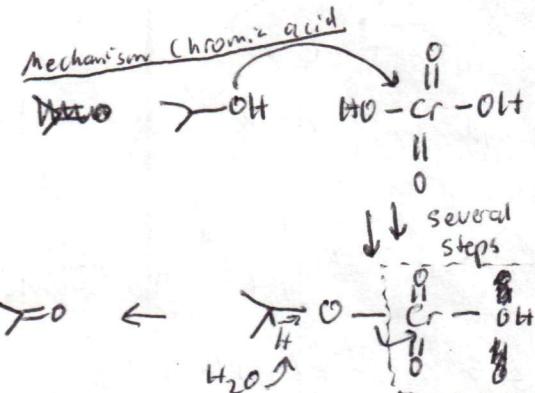
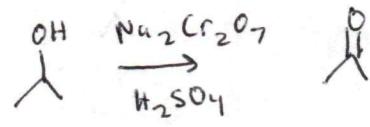
Cryptic amines w/o basic issues

$\text{N}_3^-$

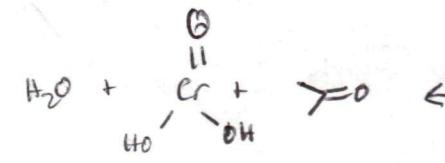
Alcohol Oxidation

Alcohol  $\rightarrow$  Ketone / Aldehyde /  $\alpha$  Oil = Oxidation is losing carboxylic acid

CANNOT OXIDIZE  $3^\circ$ !

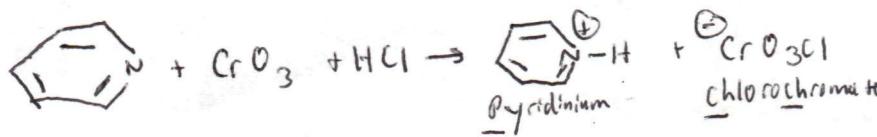
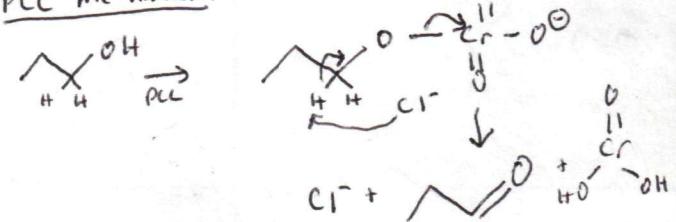


PCC: stop @ aldehyde for  $1^\circ$  alcohols



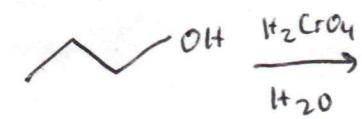
Chromic acid: oxidize to carboxylic acid

PCC formation:

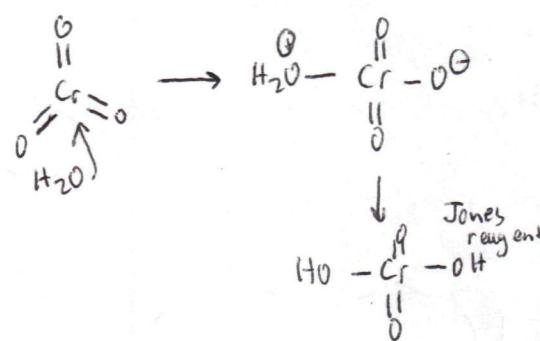
PCC Mechanism

Alcohol Oxidation cont.

Overoxidation to Carboxylic Acid:



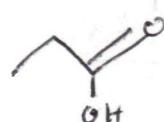
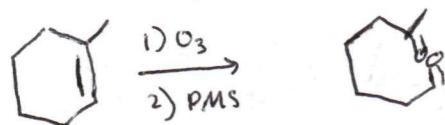
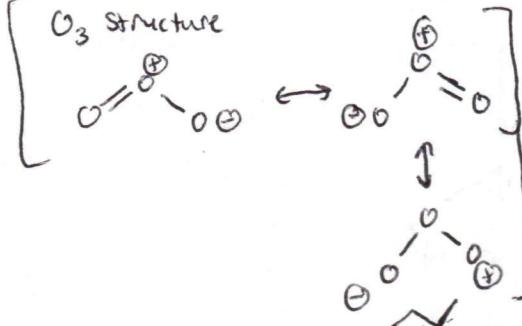
water attacks  $\text{C}=\text{O}$   
to create hydrate  
Hydrate

Jones reagent:  $\text{H}_2\text{CrO}_4, \text{H}_2\text{SO}_4$ 

PCC in water - optional  
chromic acid has to be in water

Alcohols w/ higher sterics react 1st

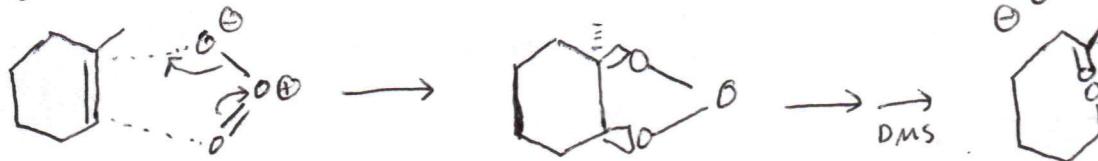
$$\text{2}^\circ > \text{1}^\circ$$

Ozonolysiscleave alkene, esp w/ oxygen  $\text{C}=\text{O}$  $\text{O}_3$  structure

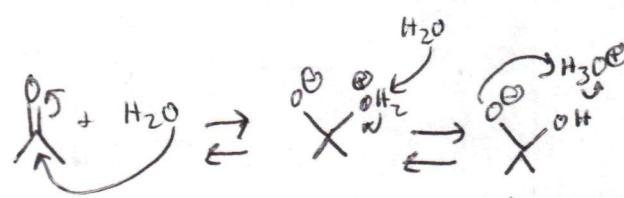
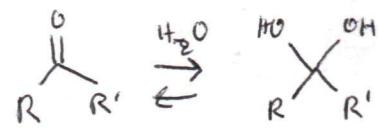
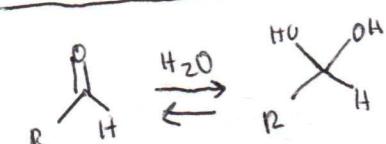
DMS structure



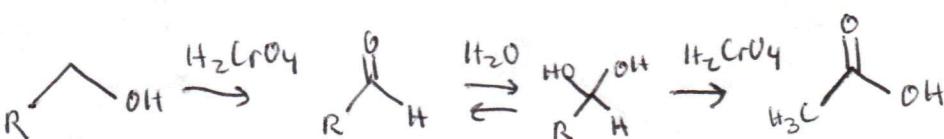
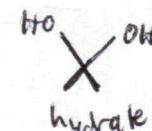
Methanation



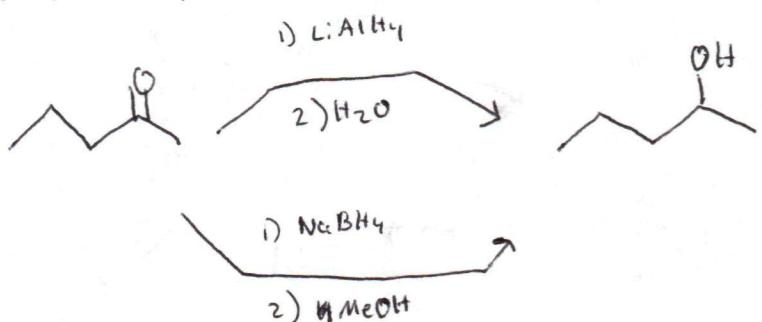
DMS breaks ozonide

Hydrate Equilibrium

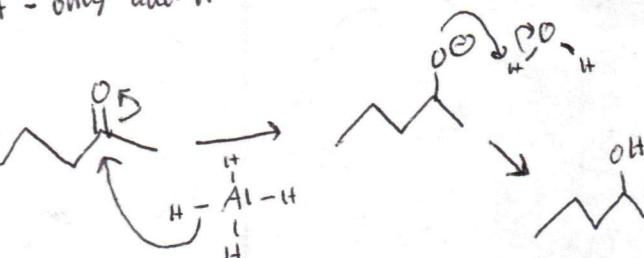
aldehyde favor hydrate, otherwise favor carbonyl

hydrate reacting w/  
 $\text{H}_2\text{CrO}_4$  driving rxn forward

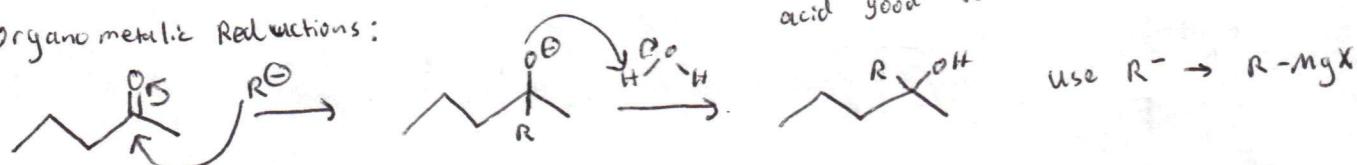
$$\Delta G^\circ \approx 3-5 \text{ kcal/mol}$$

Alcohol ReductionKetone / Aldehyde  $\rightarrow$  alcohol

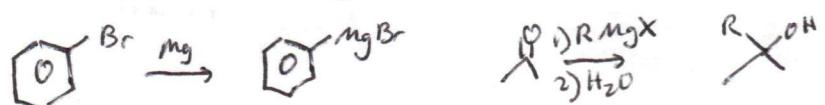
$\text{LiAlH}_4$  - too strong base to use in acidic conditions  
 $\text{NaBH}_4$  - weak enough to use w/ water  
 $\text{LAH}$  - only add it



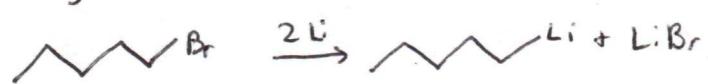
Multiple  $\text{C=O}$  and xs. oxidizing agent, aldehydes first, then ketones  
acid good to have or left w/  $\text{OH}$

Organometallic Reductions:

Making Grignard - Better over cold

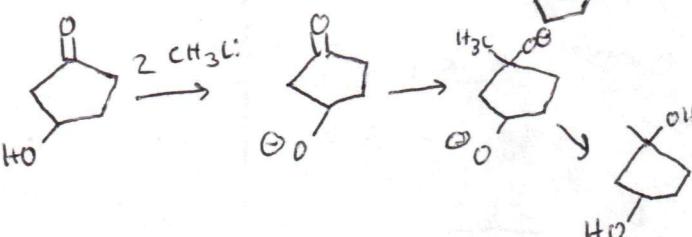
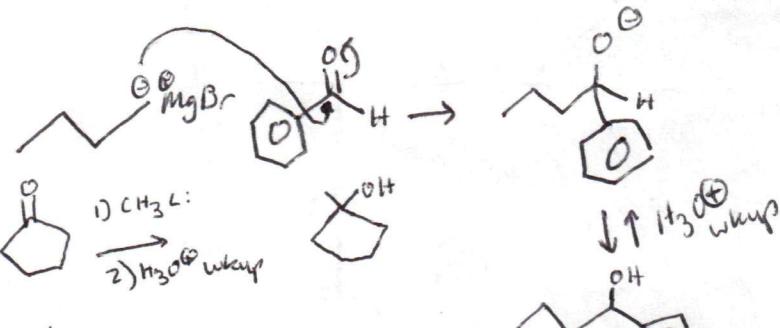
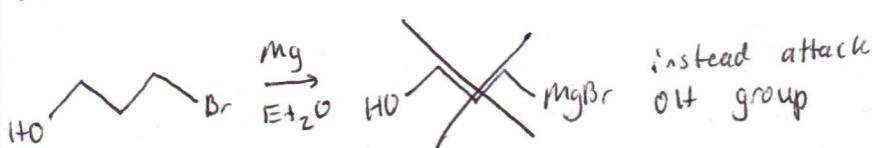
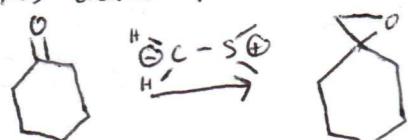


Grignard fails in proton source - too basic  
Grignard agents can't have acidic protons

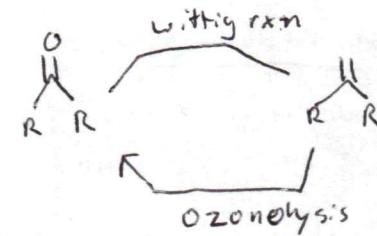
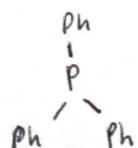
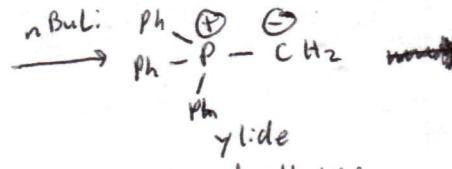
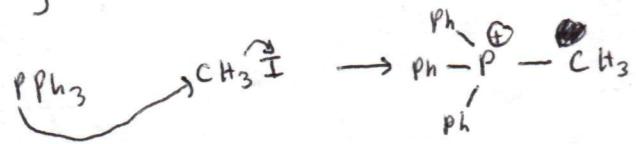
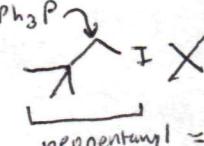
Making organolithium reagents

Adding R group w/ organometallic = create enantiomers

If lots of steric hindrance, 1 enantiomer will be favored

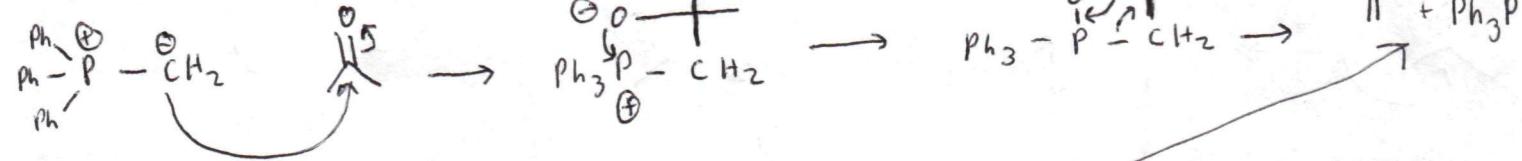
Epoxyde SynthesisDMS creates epoxide from  $\text{C=O}$ 

For alkene, use mCPBA

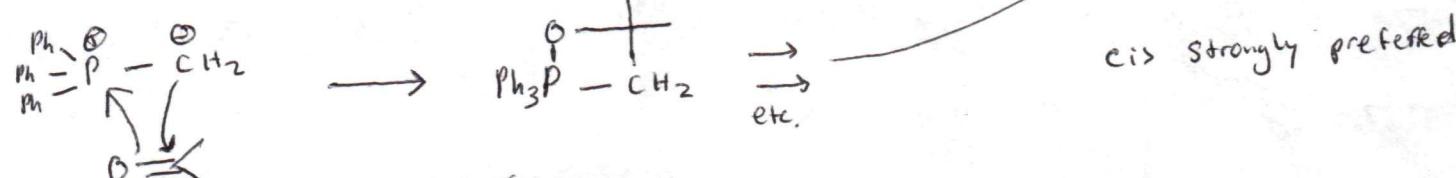
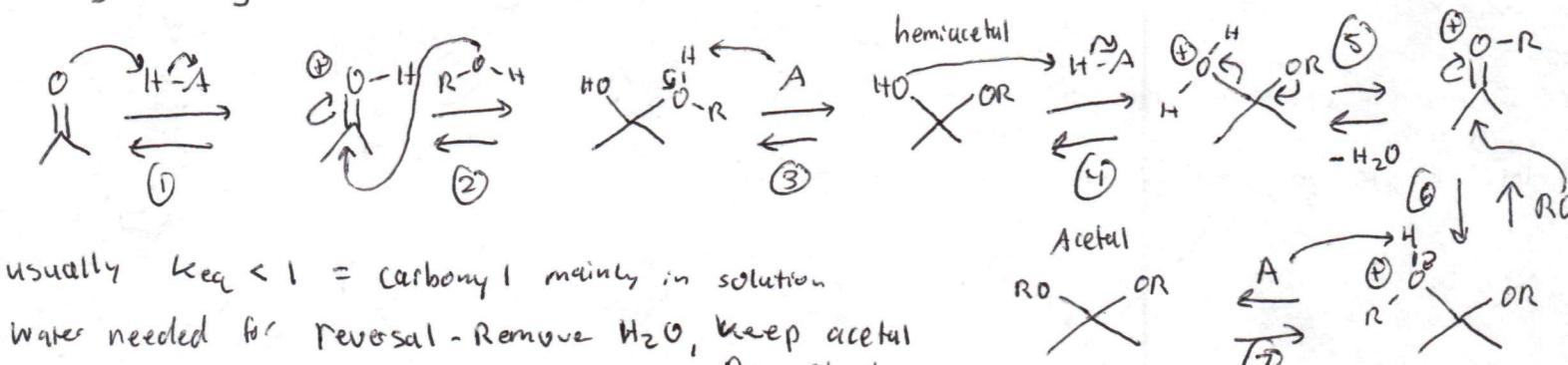
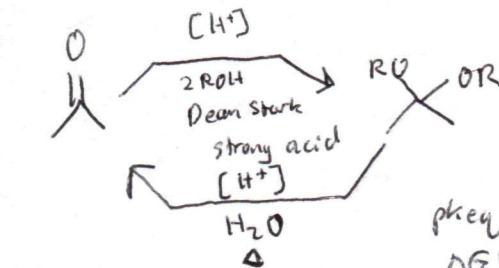
Alkene Synthesis $\text{Ph}_3\text{P} = \text{triphenylphosphine}$  =Wittig Formation:Ylide  
basic - don't use  
in acidic environmentOnly works if  $S_N^2$   
favored

neopentyl = steric issue

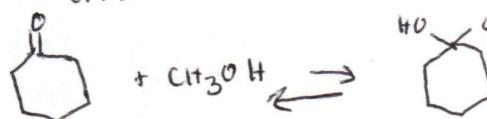
## 1) Stepwise



## 2) Concerted

Acid Catalysis of Carbonyls (PADPEAD)~~Marking w/ thing~~usually  $K_{eq} < 1$  = carbonyl mainly in solutionWater needed for reversal - Remove  $\text{H}_2\text{O}$ , keep acetal  
Dean Stark

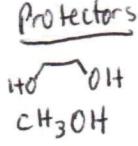
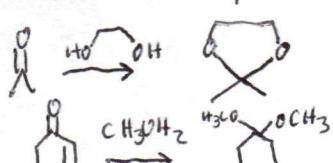
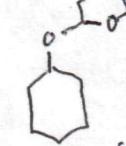
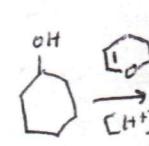
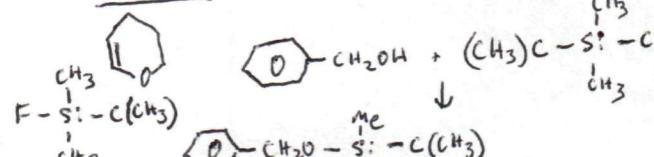
Hemiacetals not stable in acid



! Cannot form acetals in base!

Protecting Groups

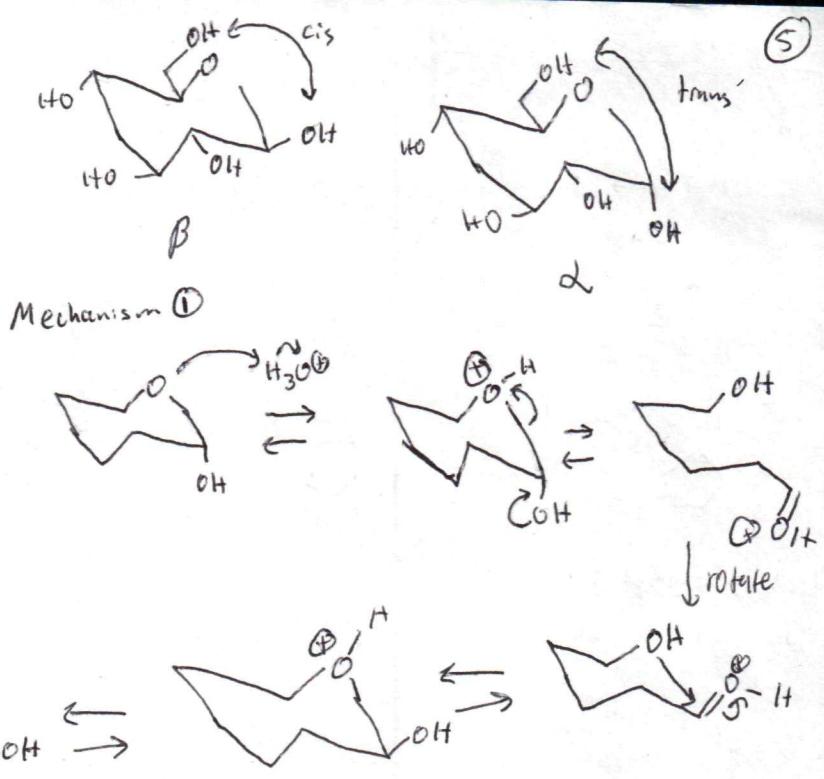
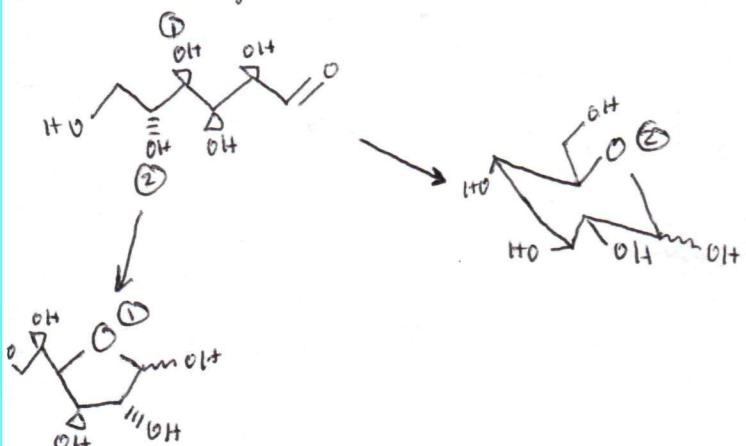
## Ketones / Aldehydes

Alcohols  
Protectors

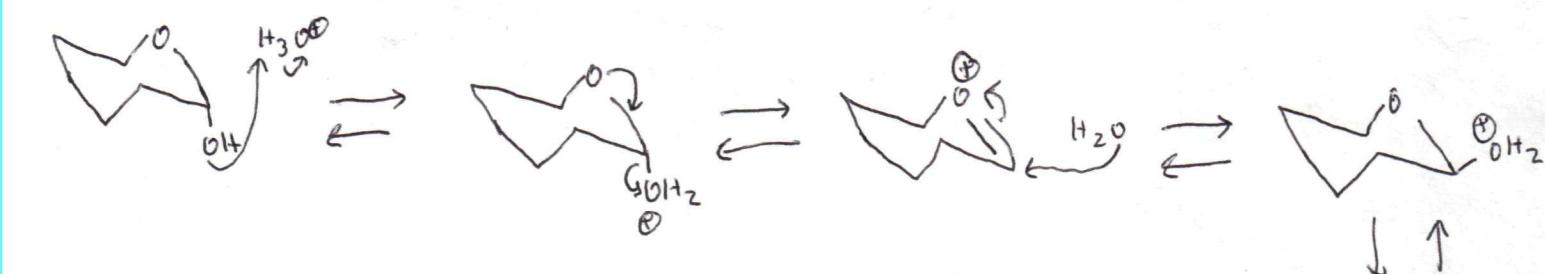
# Reactions Chem 35

## Sugars Reactions

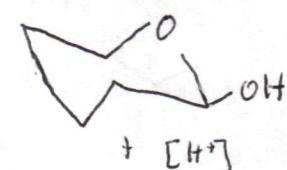
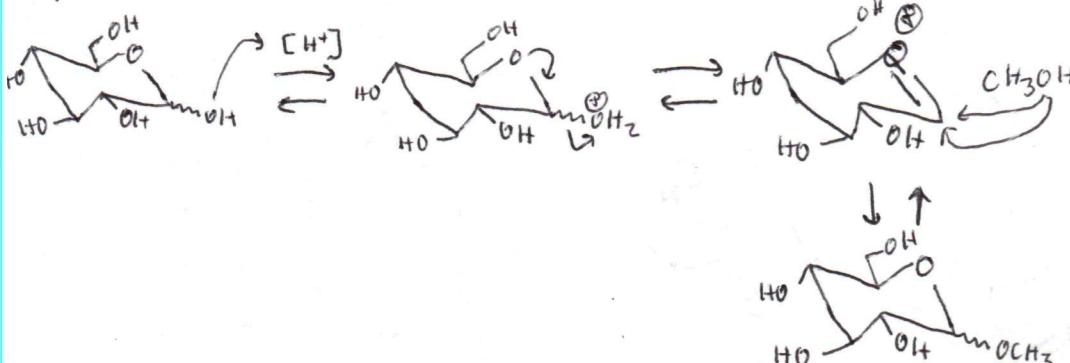
Mutarotation:



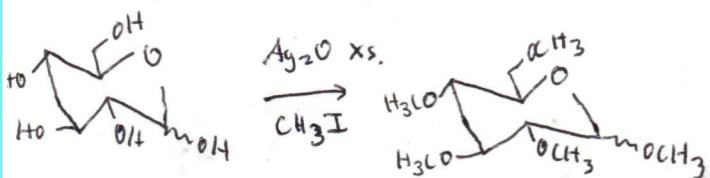
Mechanism ②:



Glycoside Formation:

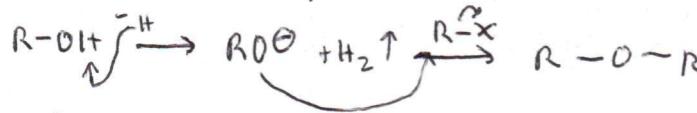


Methylation:

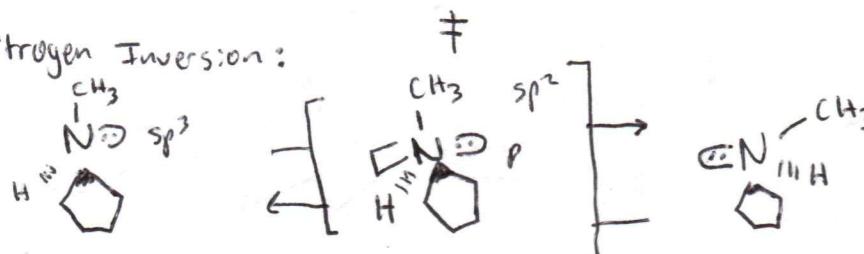


Review Session Additions

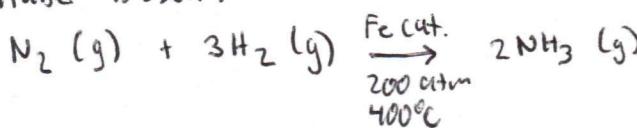
Williamson Ether Synthesis:



Nitrogen Inversion:



Haber-Bosch:



1) Memorize Bases ✓

2) PKa's ✓

3)  $\Delta G^\circ$ 

4) A, B DNA ✓

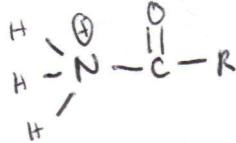
5) IR

6) C3' vs C2' endo ✓

 $\Delta G^\circ$  ValuesAcidic pKa

4.63

Aniline



-5

Amide

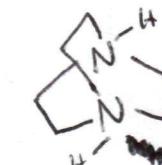


5.21

Pyridine



9

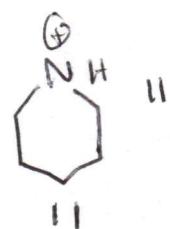
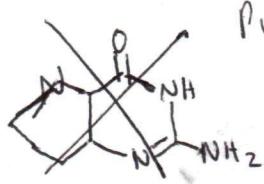


3

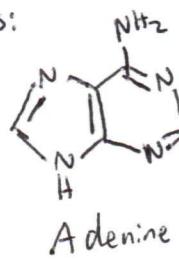
H-N3    H-CN

5

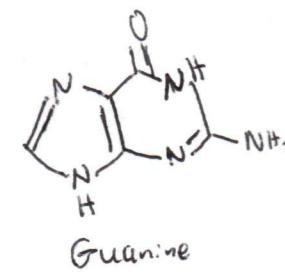
9

Bases

Purines:



Adenine



Guanine

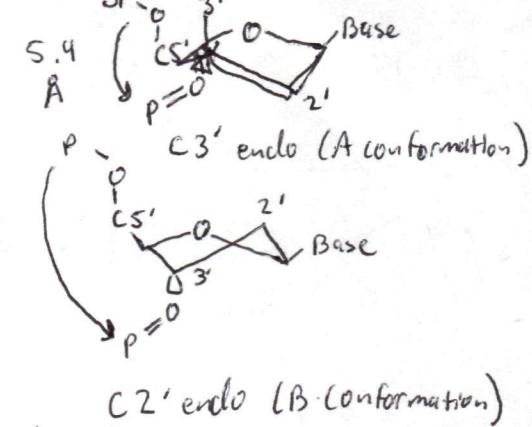
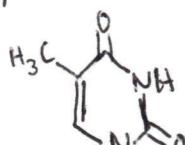
DNA, RNA

A-DNA RNA preferred

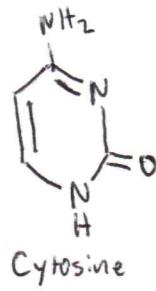
B-DNA DNA preferred

Major Groove larger in B-DNA

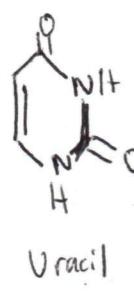
Sugar Conformations:

Pyrimidines

Thymine



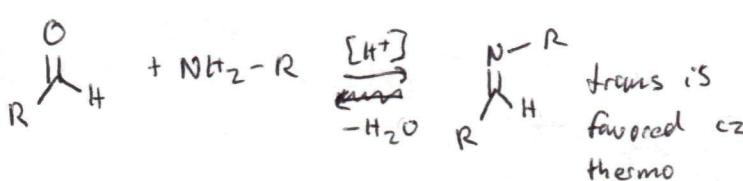
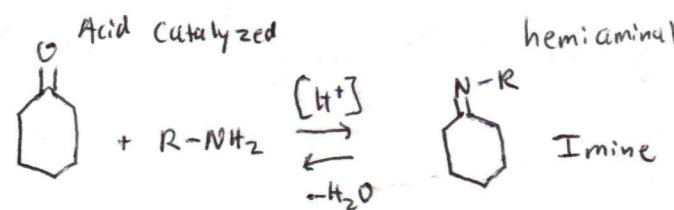
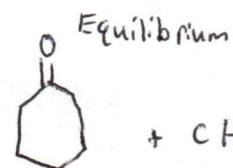
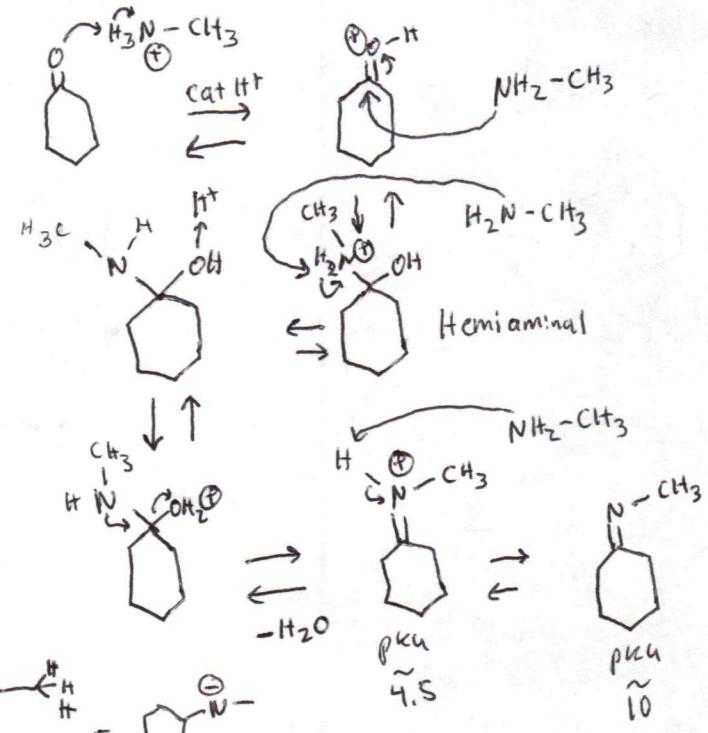
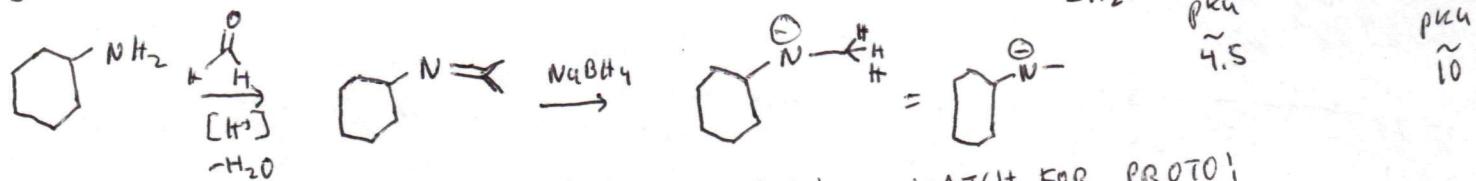
Cytosine



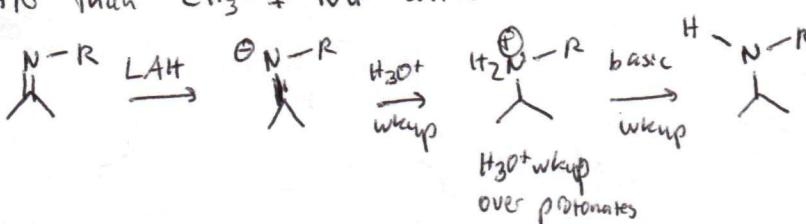
Uracil

C2' endo - 3' down

C3' endo - 3' up

IminesMechanism + PreparationOrganometallic Addition

better than  $\text{CH}_3-\ddot{\text{I}}$  Nu- attack - risks overalkylation      WATCH FOR PROTO!

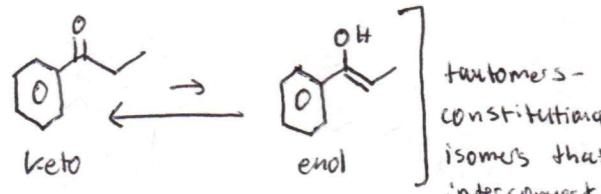
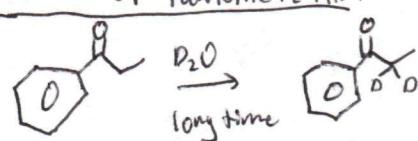
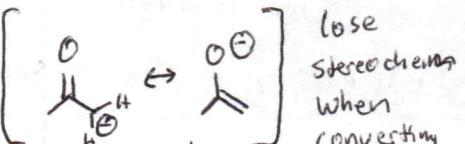
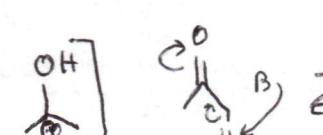
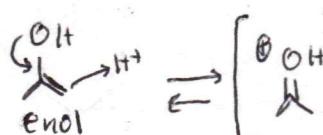


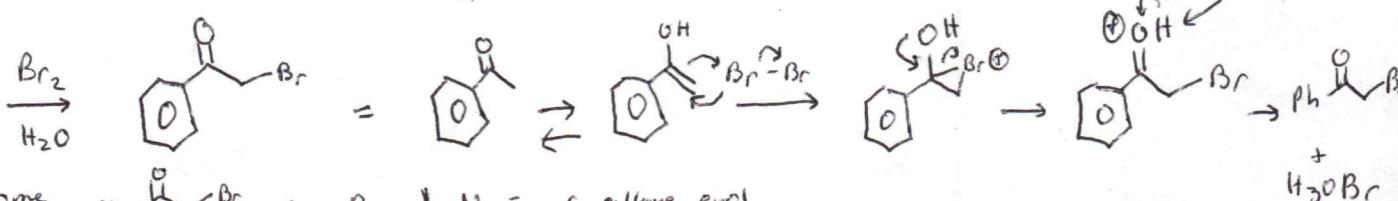
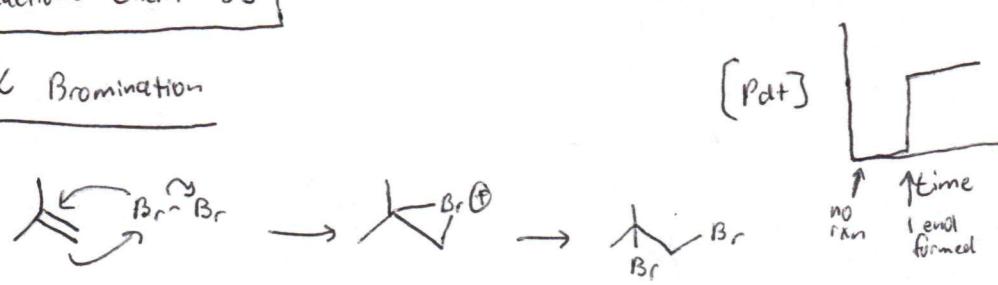
1 equiv of Grignard not selective enough - use protection first

Basic Conditions

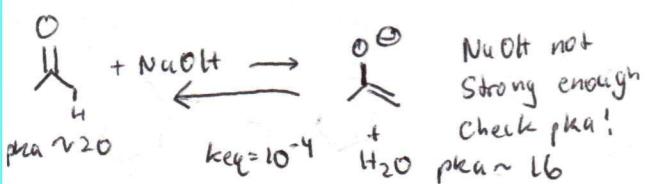
$K_{eq}$

$\Delta G^\circ = 10 - 13 \text{ kJ/mol}$

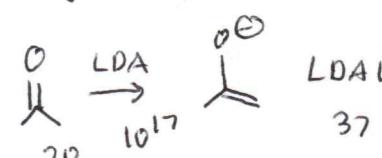
Keto-enol TautomerizationMechanism

$\alpha$  Bromination

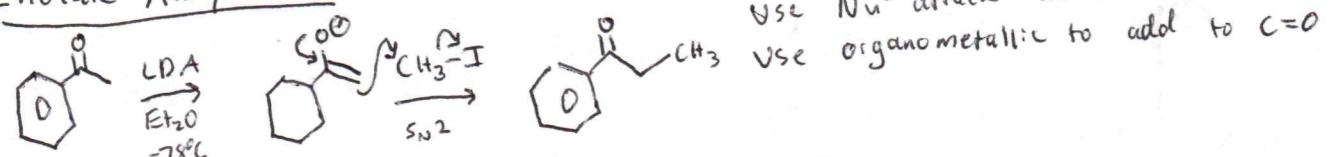
Doesn't become  $\text{Ph}-\overset{\text{O}}{\underset{\text{Br}}{\text{C}}}-\text{Br}$  cz  $\text{Br}^- \downarrow \text{Nu}^-$  of alkene enol

Enolization

Stronger base!

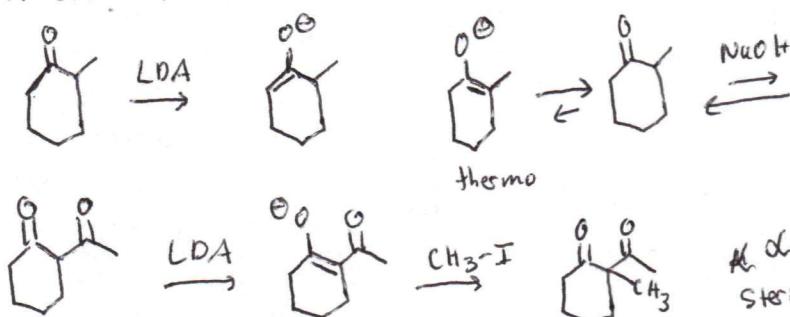


Can't use  $n\text{BuLi}$  cz it will act as  $\text{Nu}^- - \text{LDA}$  is sterically hindered

Enolate Alkylation

Use  $\text{Nu}^-$  attack to extend C-C bond  
use organometallic to add to  $\text{C=O}$

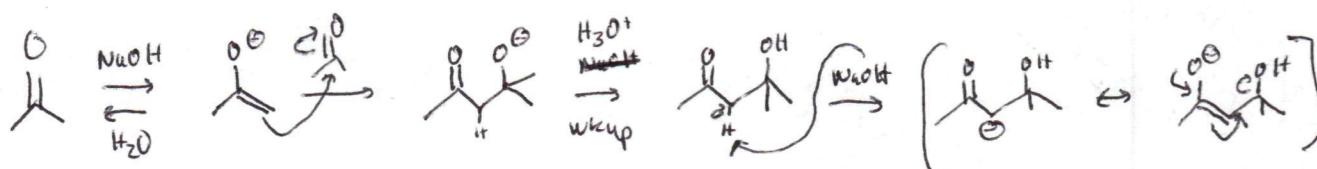
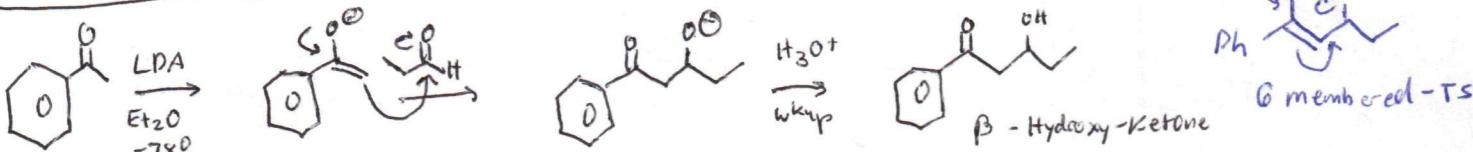
LDA sterically selective - favor less sterically hindered & H



still w/ H's = but decision = more alkylatior

same  $\text{pK}_{\text{a}}$  - go for sterics

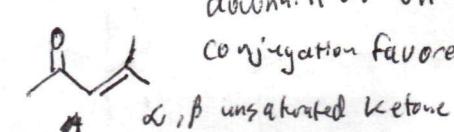
Abt ch. btwn  $\text{C=O}$ 's  $\text{pK}_{\text{a}} \sim 9$  vs  $\sim 20$   
sterics don't matter w/ such a large  $\text{pK}_{\text{a}}$  diff

Aldol Reaction

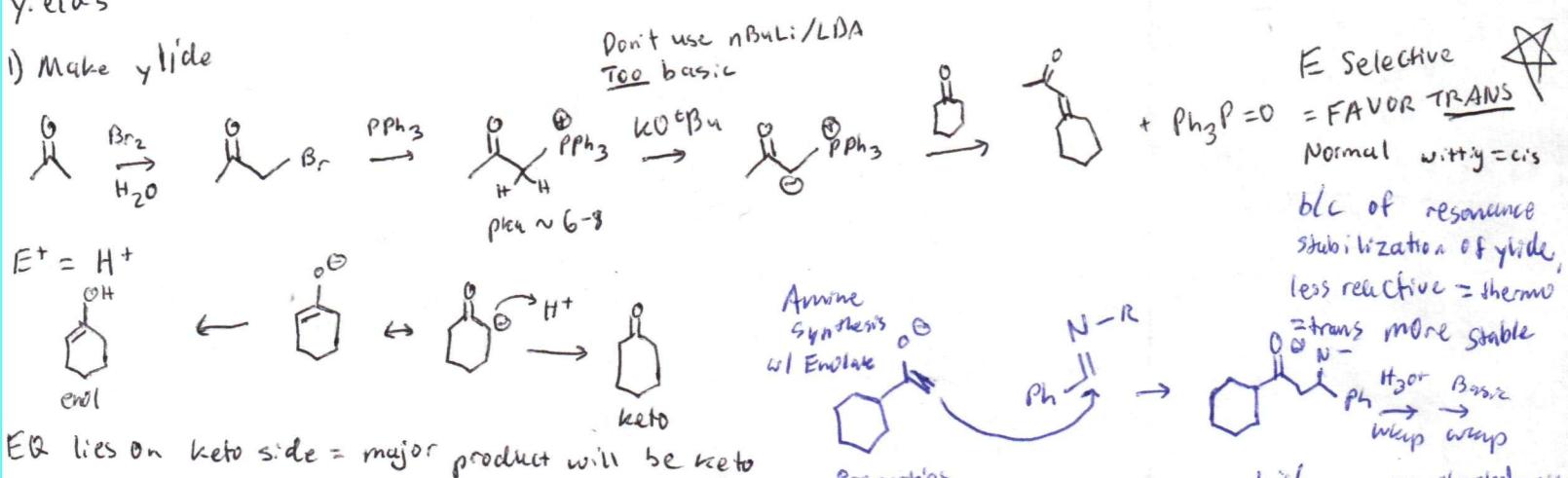
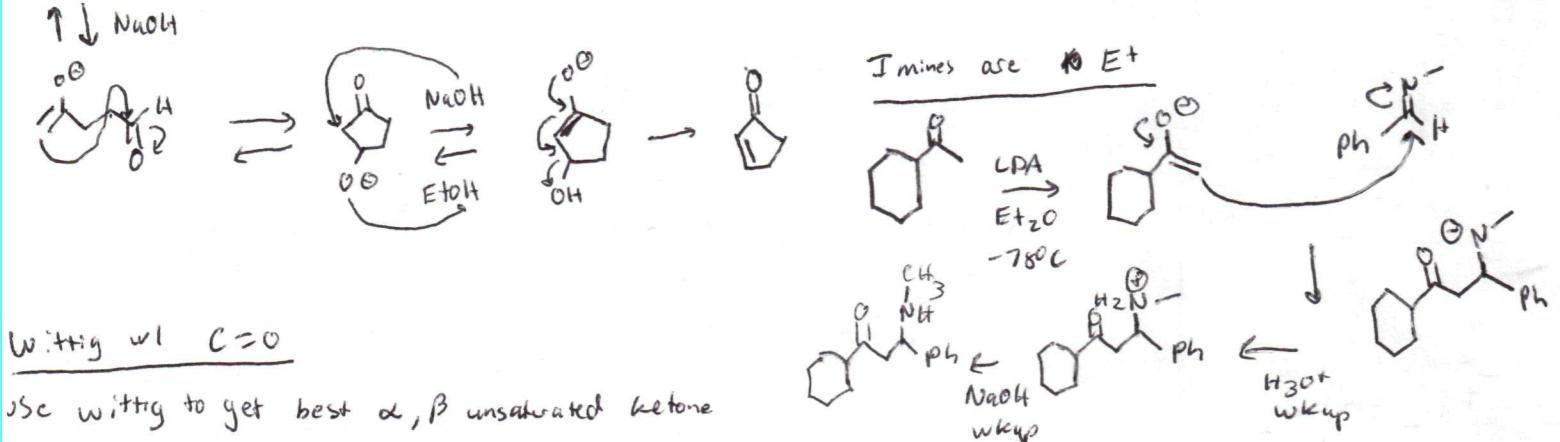
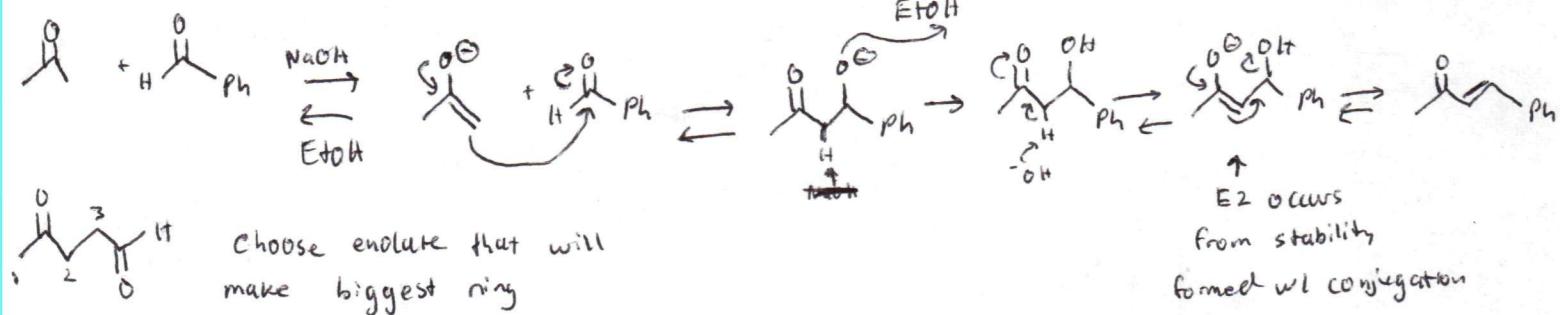
using  $\text{NaOEt}$  = lots of products cz no selectivity - get both cis and trans



downhill w/  $\text{OH}^-$  leaving conjugation favored

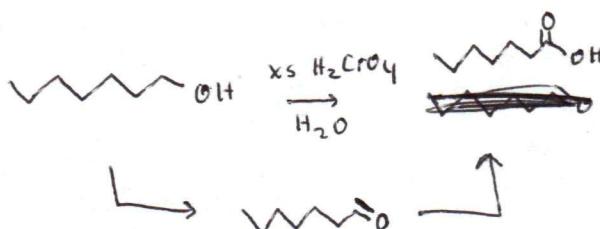


Symmetrical - USE either LDA or NaOH

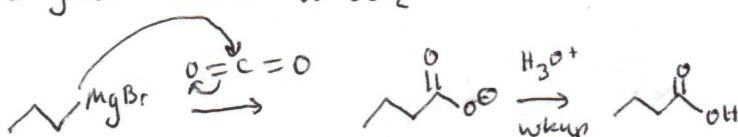


### Preparation Carboxylic Acids

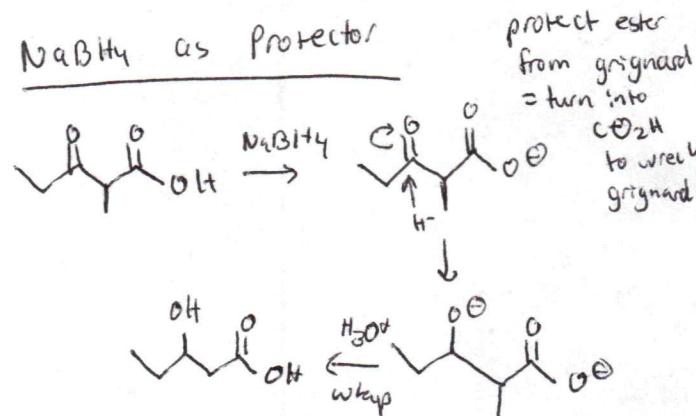
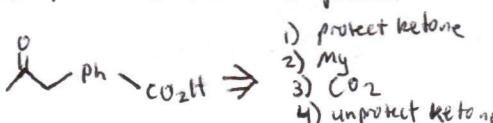
#### D) Oxidation

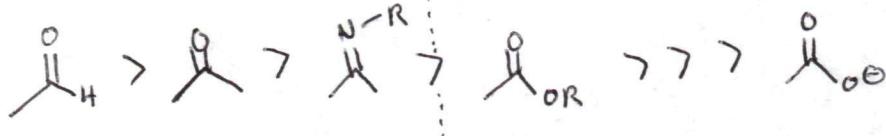


#### 2) Grignard Addition w/ $\text{CO}_2$

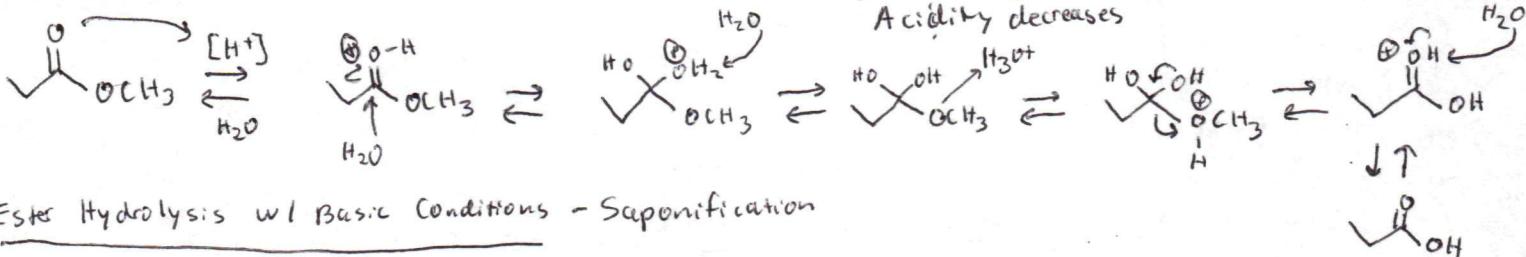
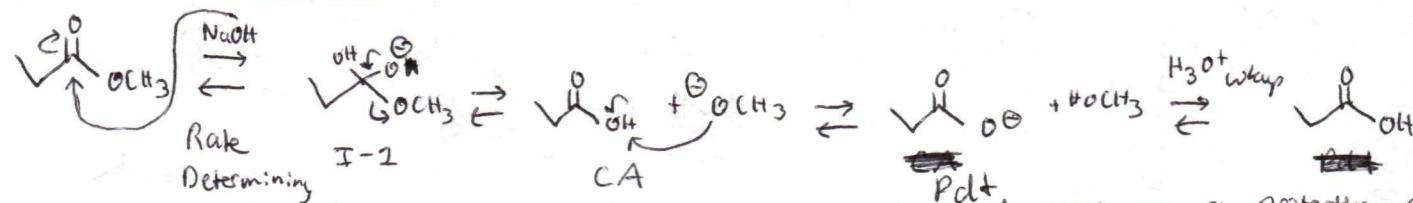


Adding another carbon to chain! Make sure to protect needed groups first

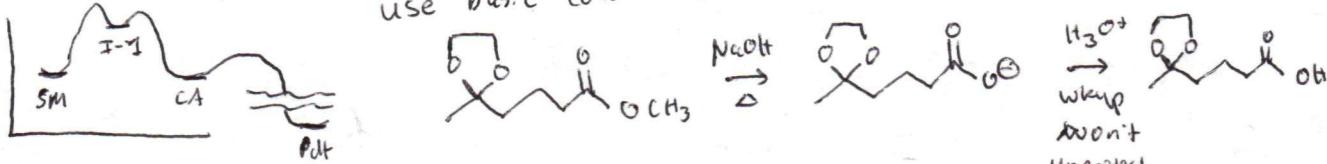
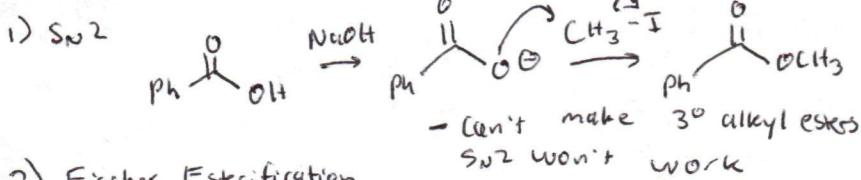


Reactions Chem 35]ReactivityNaBH<sub>4</sub> won't workEster Reactions

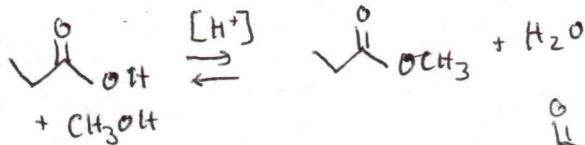
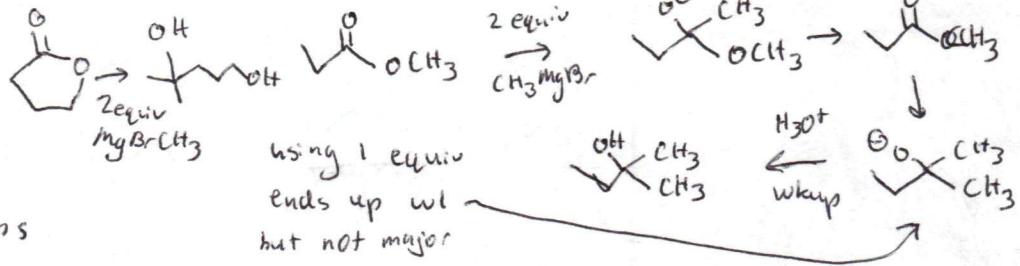
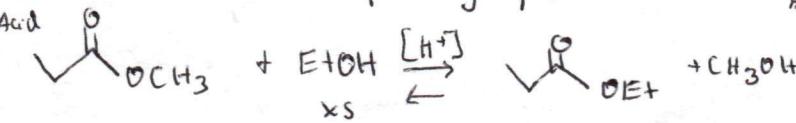
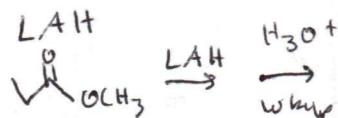
$\delta^+$  decreasing  
Acidity decreases

Ester Hydrolysis w/ AcidEster Hydrolysis w/ Basic Conditions - Saponification

use basic conditions when acid would mess up a protecting group

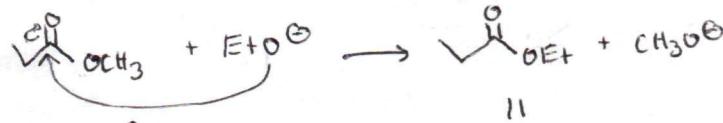
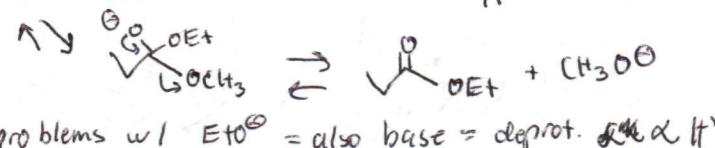
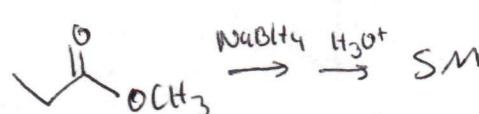
Protecting Group CleavageEster Preparation

Lactones = cyclic esters

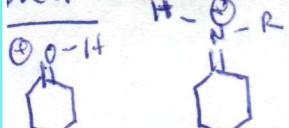
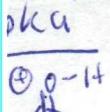
2) Fischer Esterification2) Grignard AdditionEster Reactions1) Transesterification - swap OR groups3) H- Additions

LAH = give 4 H's

Basic

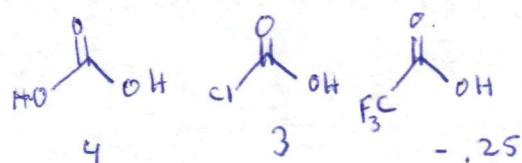
Mild  
= selectivityproblems w/  $\text{EtO}^-$  = also base = deprot. of Alt'

Midterm 2 extra stuff



-5

4.5



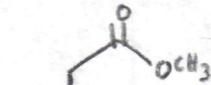
$\alpha \text{ H } \text{pK}_a$

ketone



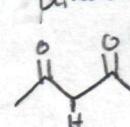
~20

ester



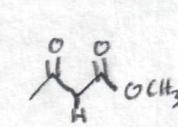
~24

diketone



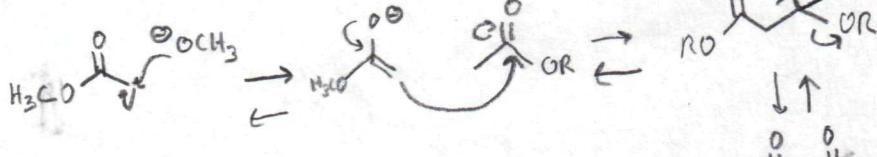
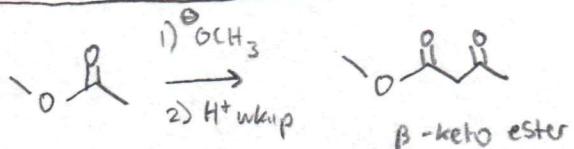
~9

B-keto ester

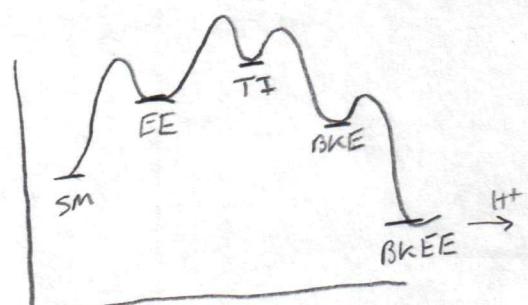
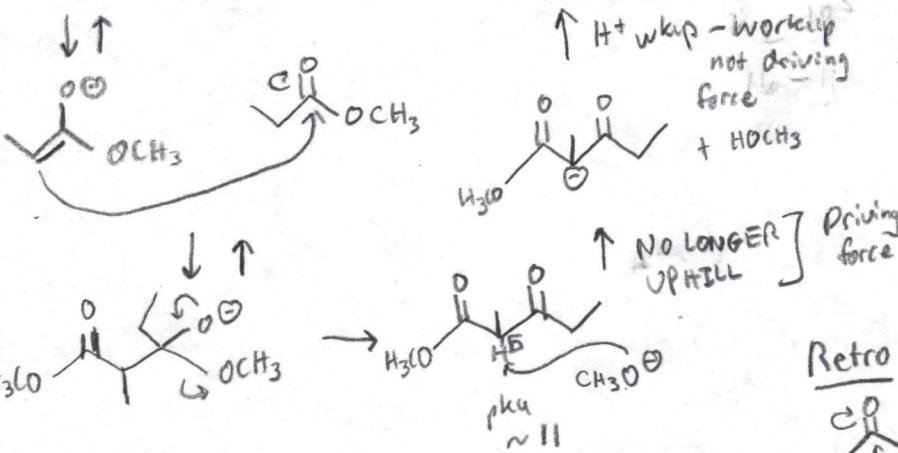
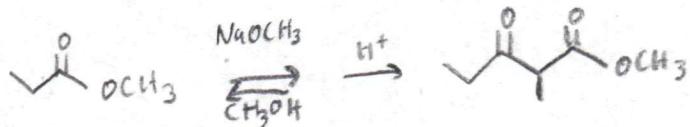
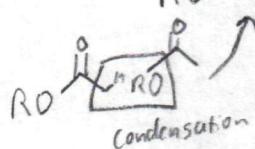
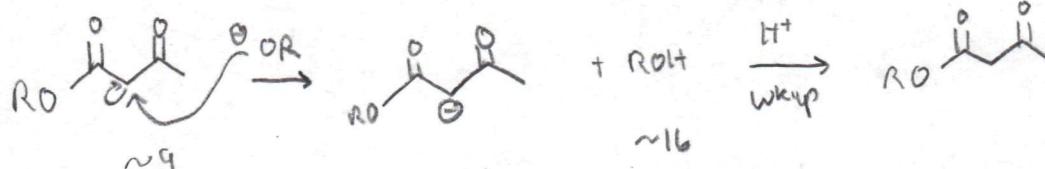


~11

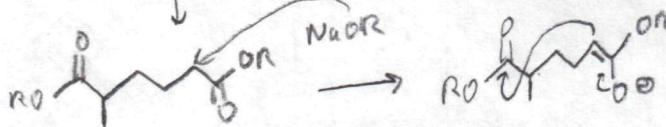
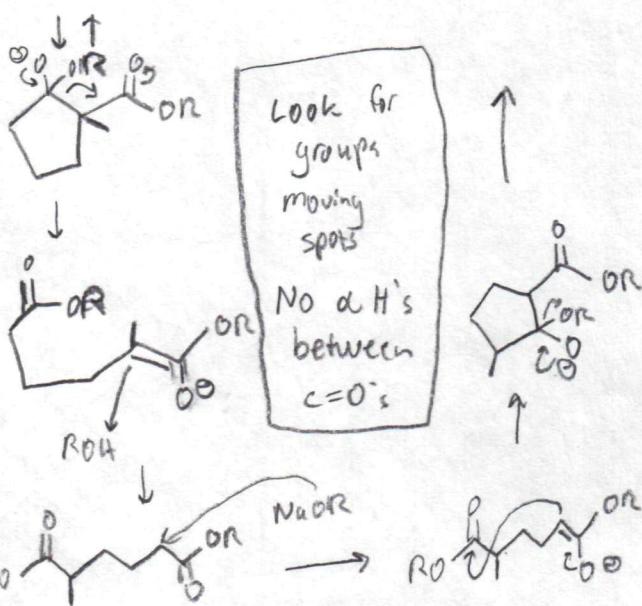
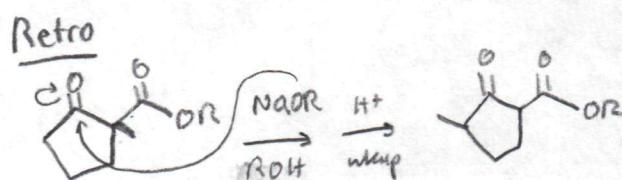
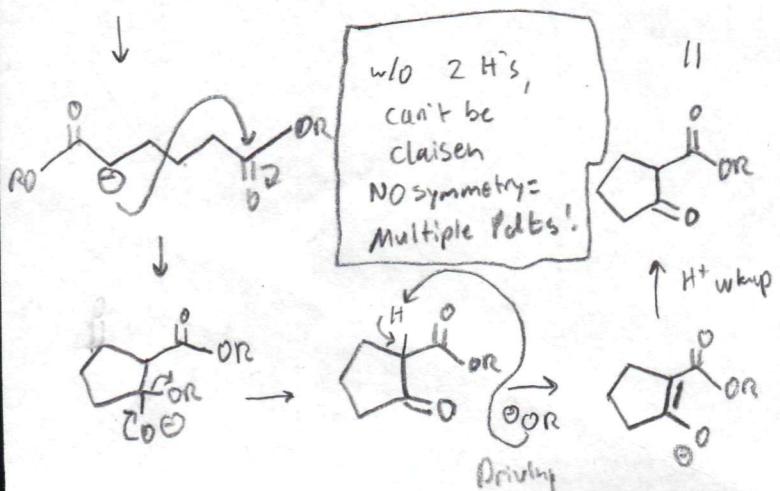
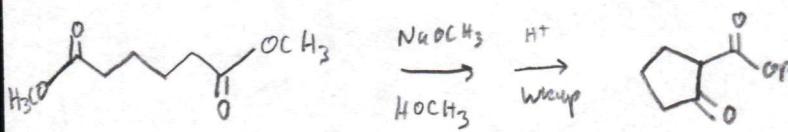
Claisen Condensation



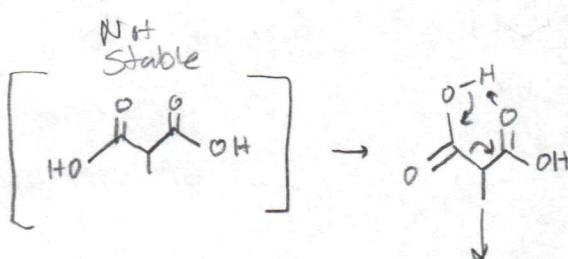
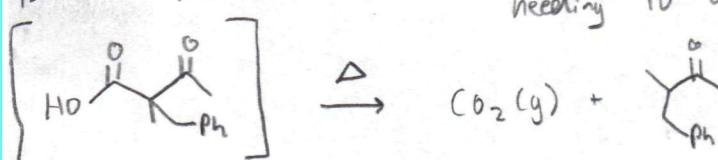
Use same  $\text{^{\ominus}}\text{OR}'$  base as ester component! Must have 2 H's at  $\alpha$  carbon  
 - Else just revert back



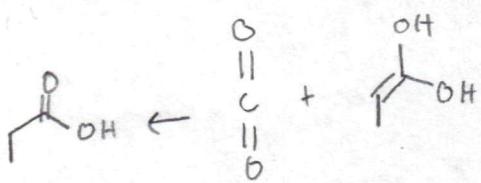
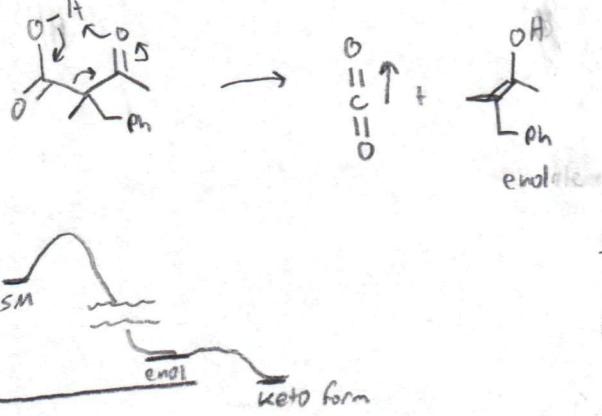
Intramolecular - Need 1,6 or 1,7 dicarbonyl!



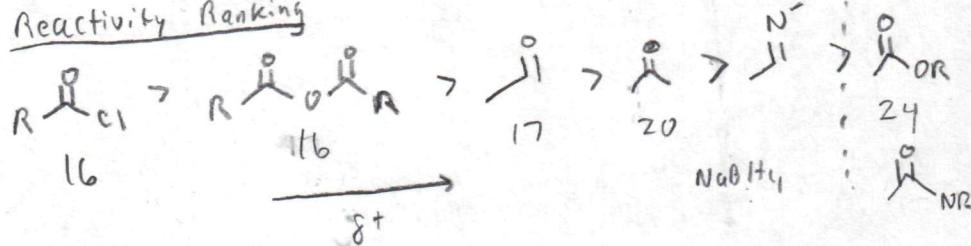
Decarboxylation - Any  $\beta$  carbonyl acid  
 $\beta$ -keto Acid Unstable!  $\hookrightarrow$  convert to acid if  
 needing to lose  $\text{CO}_2$



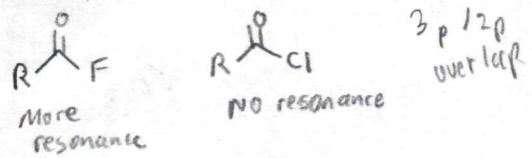
↓ bond rotation



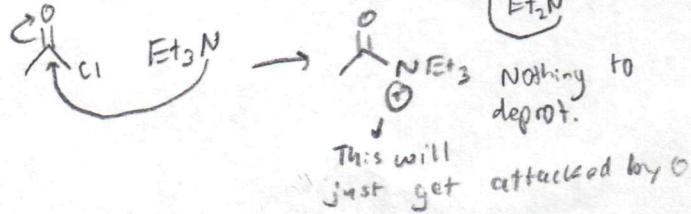
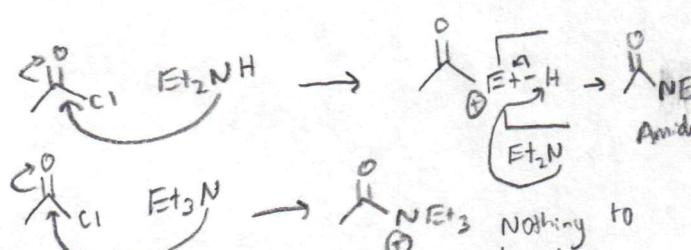
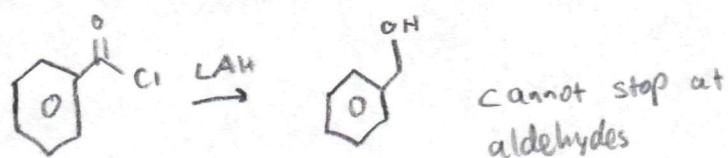
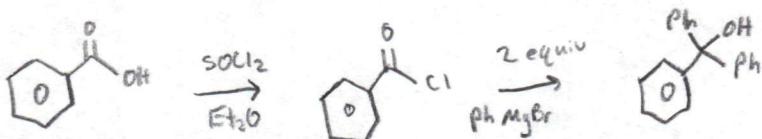
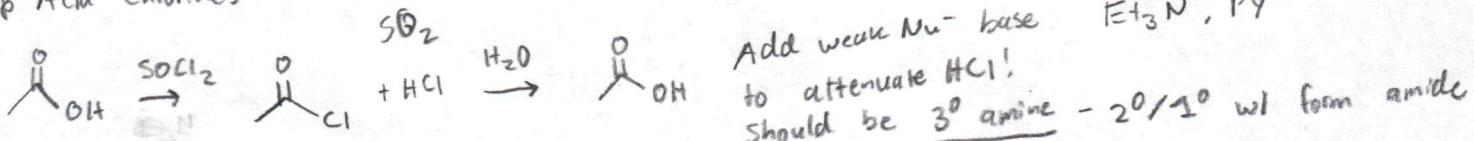
### Reactivity Ranking



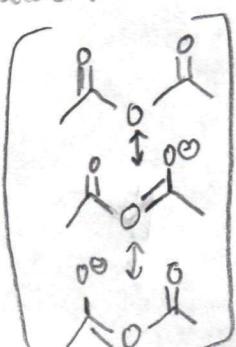
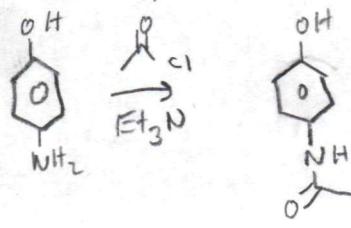
### Carboxylic Acid Derivatives



### Prep Acid Chlorides



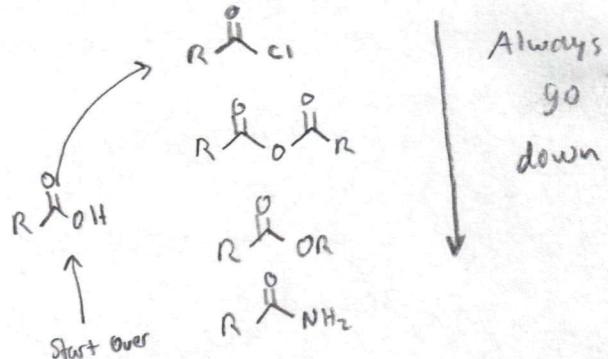
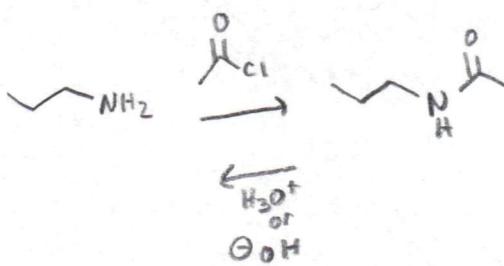
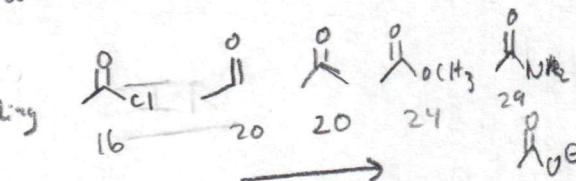
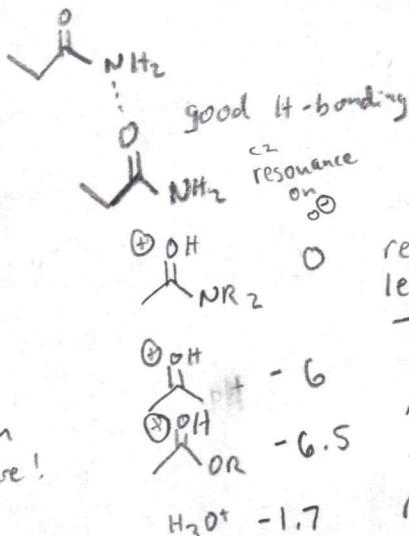
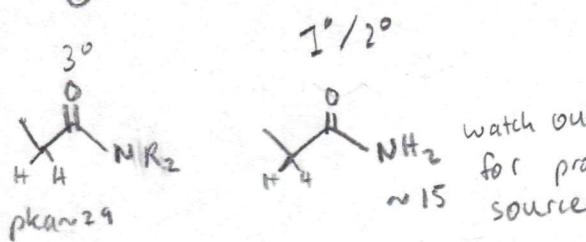
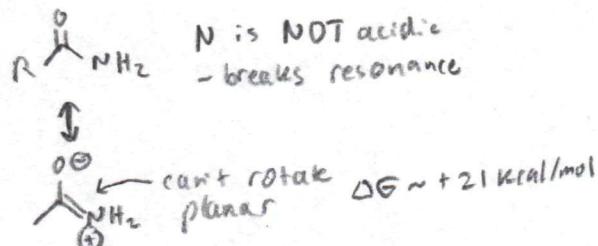
### Chemoslectivity



This will just get attacked by O

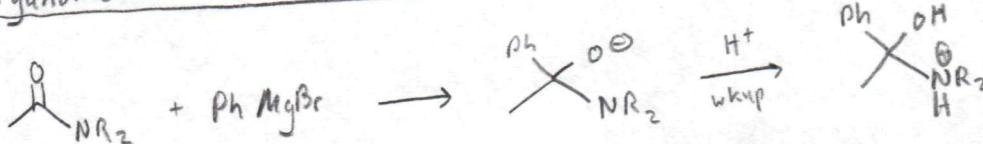
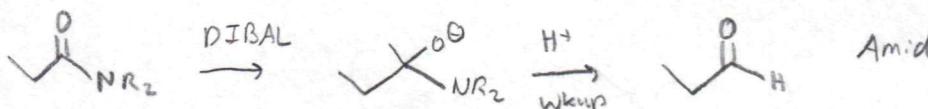
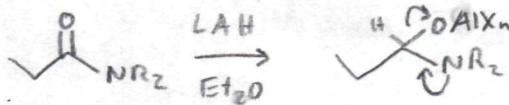
Synthesis Ladder

Acyl group

Amides Good SM to make ketone High mp!

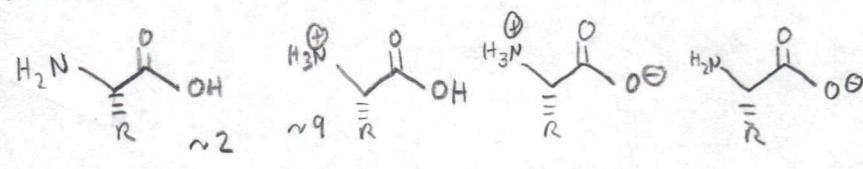
resonance structures make less acidic

3° amines not good  $\text{Nu}^-$  - good bases  
Making ketone - 1 grignard  
- wait collapse until  $\text{H}^+$  w/kmp, preventing over alkylation as everything in TI - only works w/ 3°

Organometallics w/ AmidesNaBH<sub>4</sub> - no rxn

DIBAL w/ Amide - Aldehyde - kick out Amine

LAH w/ Amide - Amine - kick out O → N=C, then attack N=C

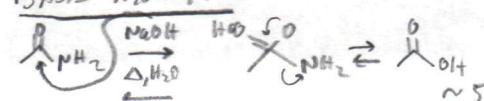
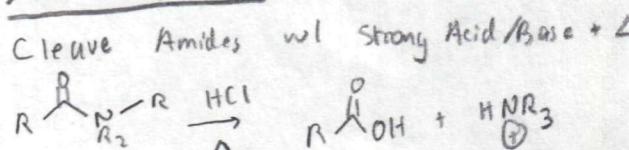
Amino Acids / Proteins

N terminus C terminus

pH = pKa = 5.0; 5.0

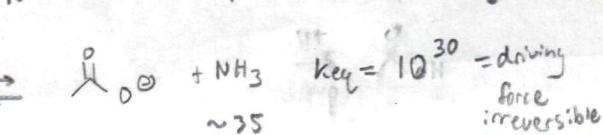
pH : pKa = 10:1

O 2 100:1

Base HydrolysisAmide Hydrolysis

Safe to unprotect acetal w/ amide

NOTE - Final proton transfer driving force



Protein SynthesisExtra

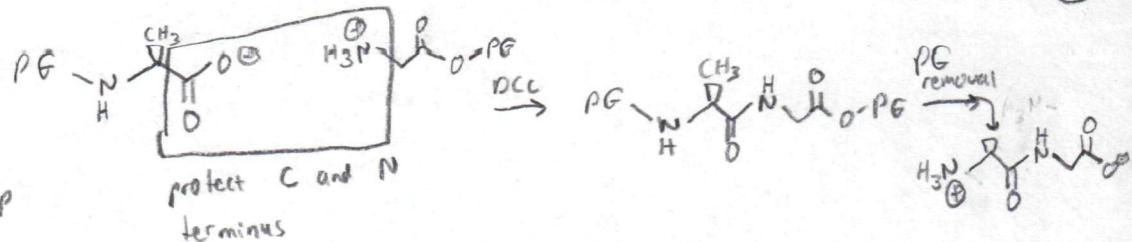
IR = higher wavenumber = stronger bond

Conjugation = closer HOMO-LUMO gap  
= less Energy

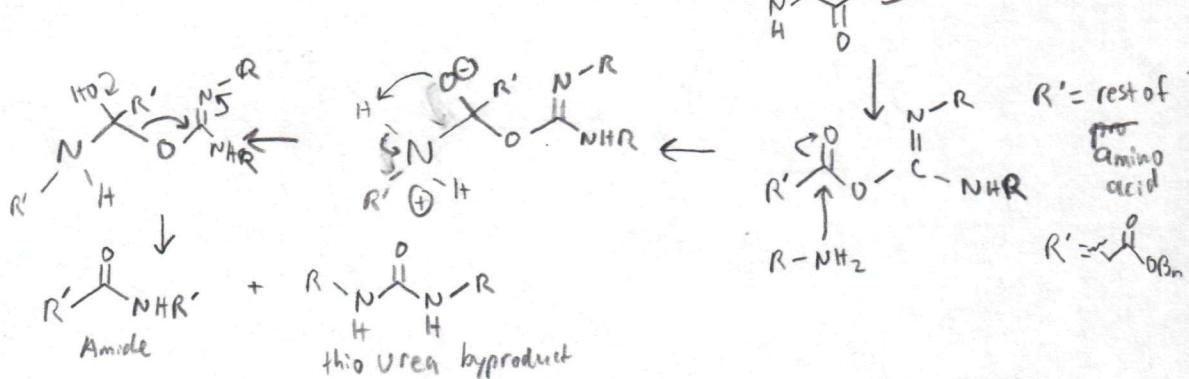
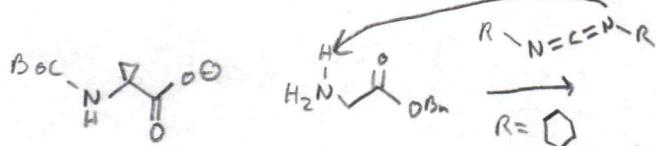
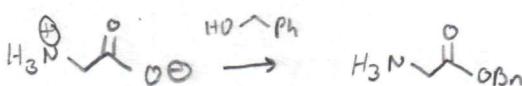
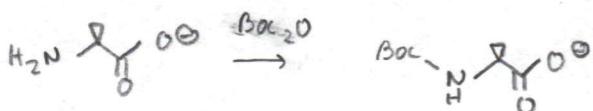
E inversely prop. to wavelength  $\lambda$

$$\downarrow E = \propto \lambda$$

$$\tau_{\text{conj.}} = \propto \lambda_{\text{max}}$$



Boc<sub>2</sub>O for Amine

Amino Acids

glycine - No steric interactions

Proline - Clashes w/ other structures so can force turns in helices

Cysteine : Form disulfide bonds w/ each other