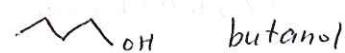
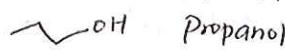
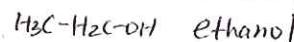


# CHEM 307 - Organic Chemistry II

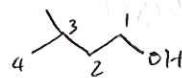
## Chapter 10 - Alcohols and thiols

Functional group -OH (hydroxyl) bound to  $sp^3$  carbon

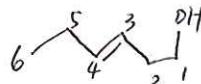
Nomenclature



find the longest chain containing -OH and give it the lowest possible #!



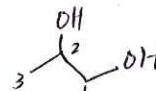
3-methylbutanol (isomeric alcohol)



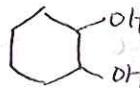
(3E)-3-hexen-1-ol



1,2-ethanediol or ethane-1,2-diol

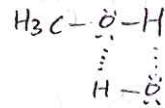


1,2-propanediol or propane-1,2-diol



1,2-cyclohexanediol or cyclohexane-1,2-diol

Physical Properties



covalent bond  $\text{O}-\text{H} \approx 500 \text{ kJ/mol}$   
H-bond  $\text{O} \cdots \text{H} \approx 21 \text{ kJ/mol}$

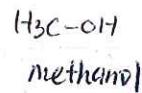
Weak intermolecular forces w/ important cumulative effect  
→ alcohols have a rel. high bp

Solubility in water decreases w/ increasing MW

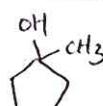
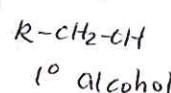
EN 2.4 3.5 2.1  
 $\text{R}-\ddot{\text{O}}-\text{H}$   
8+ 8- 8+

can function as weak acids and weak bases.  
= amphoteric

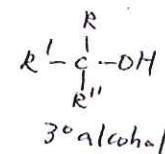
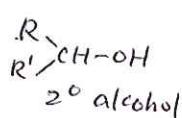
Acidity/Basicity



2° cyclic  
cyclopentanol



3° cyclic



Reactivity of alcohols depends upon their substitution

## Reactions of Alcohols

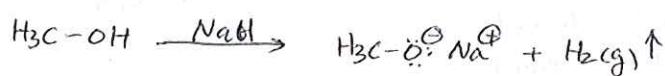
used in non-aq. conditions  
Strong base ( $\text{E}_2$ ). Strong nuc ( $\text{SIV}_2$ )  $\text{H}_3\text{C}-\text{CH}_2-\ddot{\text{O}}\text{K}^\ominus$

A. Alkoxide formation  $\text{R}-\ddot{\text{O}}^\ominus \text{M}^\oplus \quad \text{M}^\oplus = \text{Na}^+, \text{Li}^+, \text{k}^+$  potassium ethoxide

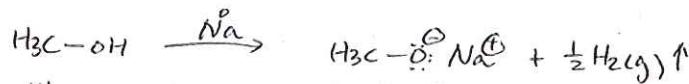
1. w/ metal hydrides  $\text{NaH} \rightleftharpoons \text{Na}^\oplus + \text{H}^\ominus$



Lithium butoxide



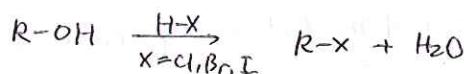
2. w/ active metals  $\text{Na}$



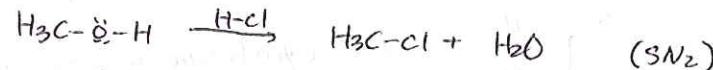
## B. Substitution Reactions



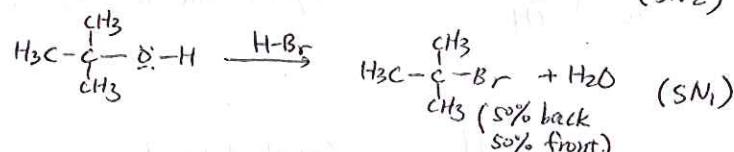
1. w/ H-X to form R-X



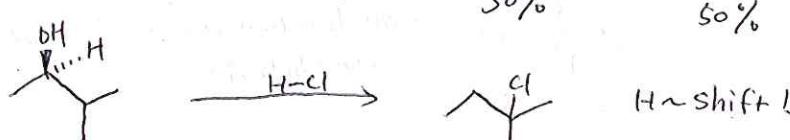
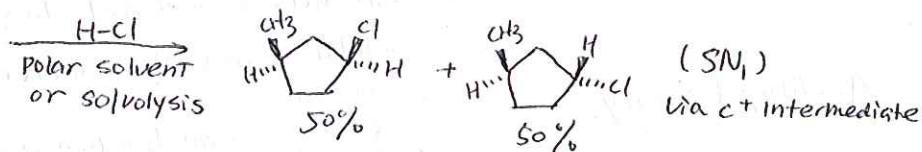
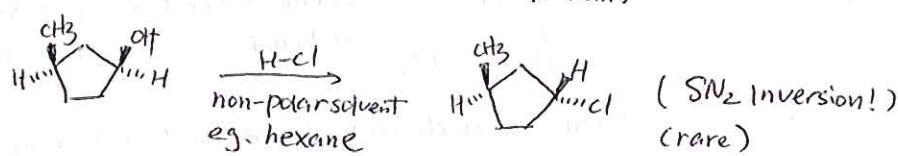
1° alcohol



3° alcohol

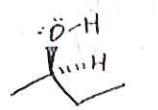


2° alcohol



2. w/  $PBr_3$  and  $SOCl_2$  (w/ 1° and 2° alcohols)

thionyl chloride

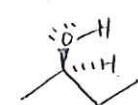
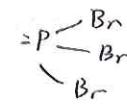


$PBr_3$   
Pyridine



(+  $Br_2$ ,  $Br^- +$  other p-n salts)

$PBr_3$

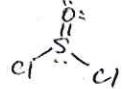


$SOCl_2$   
Pyridine

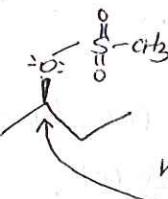
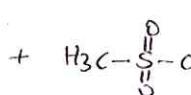
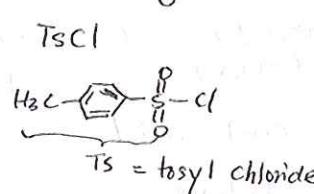
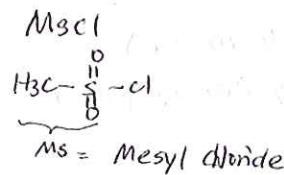


( $SN_2$ )

$SOCl_2$

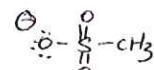


### C. Conversion to Sulfonates ( $R-\overset{\text{O}}{\underset{\text{S}}{\text{O}}}^{\text{2-}}-\text{OR}'$ )



$SN_2$

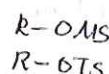
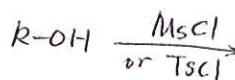
Inversion!



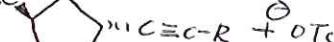
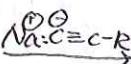
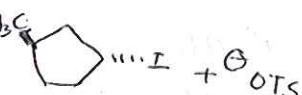
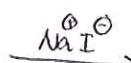
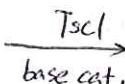
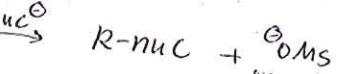
great LG

Resonance stab.

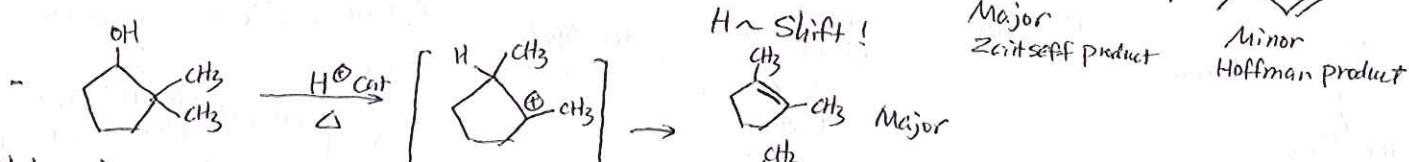
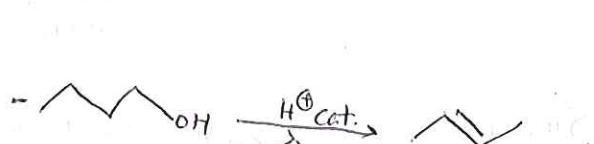
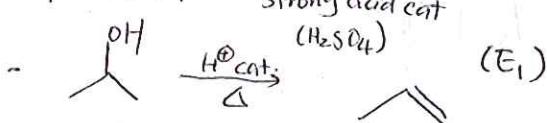
general:



no nuc added,  
 $\text{Cl}^-$  will act as nuc



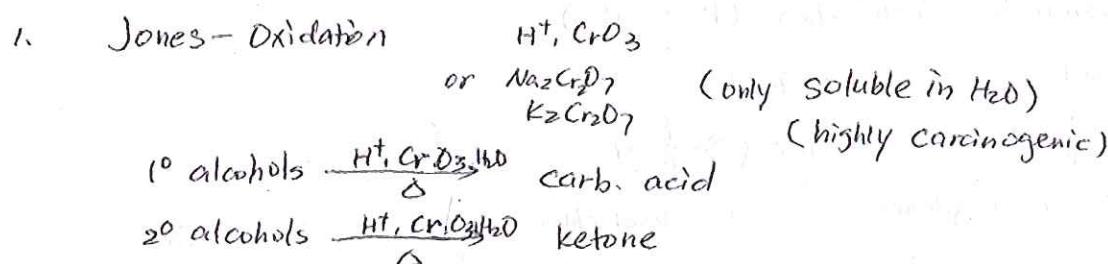
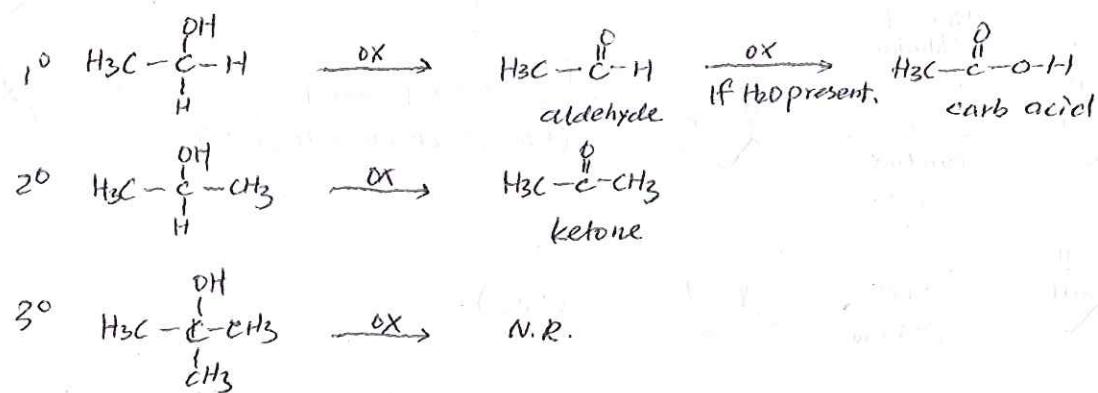
### D. Dehydration



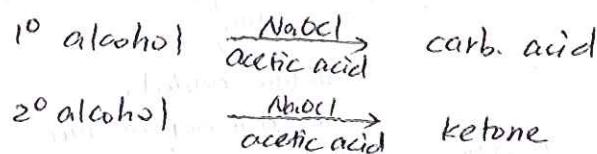
(High temp)  
heat required  
for alkene formation

very minor

## E. Oxidation

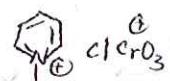
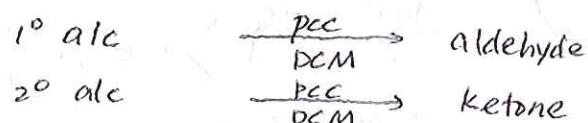


### 2. Sodium hypochlorite (aka Bleach)



(green chemistry)

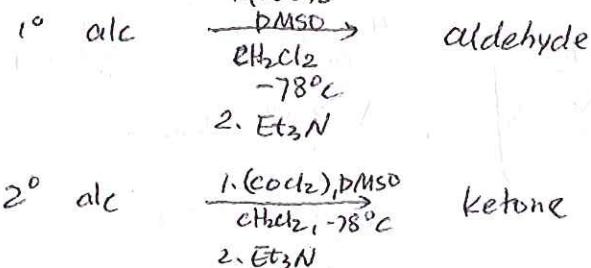
### 3. Pyridinium Chloro Chromate (PCC)



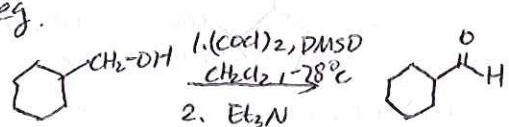
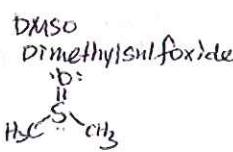
(soluble in organic solvents)  
 usually  $\text{CH}_2\text{Cl}_2$  (DCM)



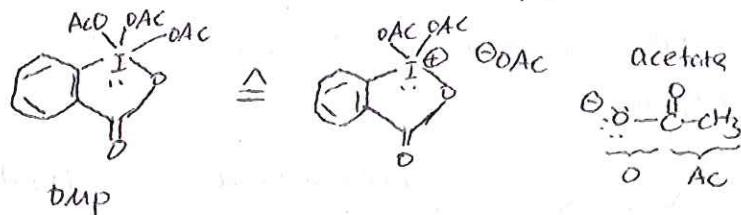
### 4. Swern



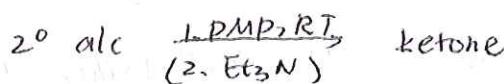
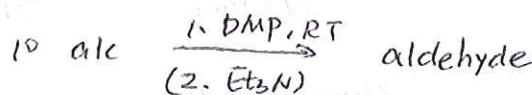
(stinks,  $-78^\circ\text{C}$  otherwise explosive!)



### 5. Dess-Martin-Periodinane (DMP)



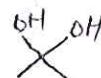
green, no chromium salts  
mild temp, easier work-up  
high yields, more expensive



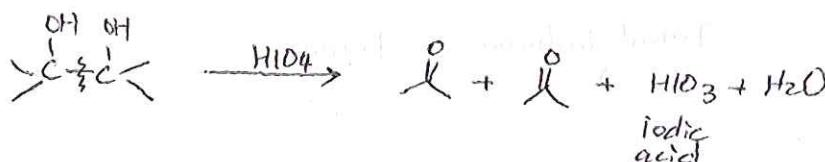
## 6. Periodic Acid Oxidation of Glycols



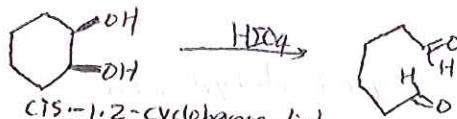
$1,2\text{-diol}$  = glycol = vicinal diol



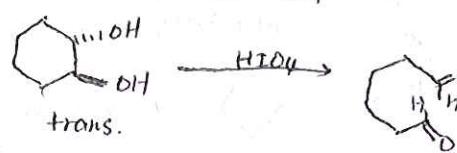
1,1-diol = geminal diol



example.



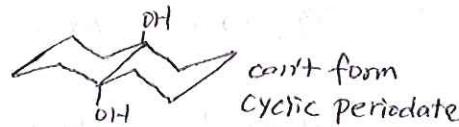
### CIS-1,2-CYCLOHEXANE DIOL



trans



Same outcome



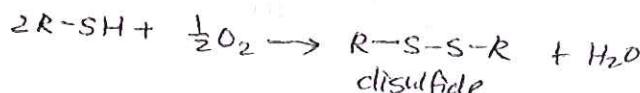
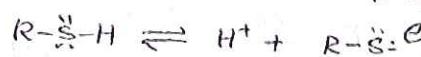
## Thiols (aka Mercaptans)

## Sulfur analogs of alcohols

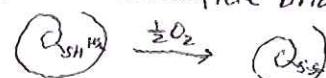
- S - H      Sulphydryl

bond almost non-polar

Stronger acid than alcohols



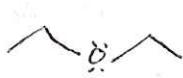
A protein w/ cysteine (protein) residues may form disulfide bridges



## Chapter 11 - Ethers, Epoxides

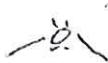
Ethers  $R-O-R'$  polar, unreactive, good solvents  
 $R$  = alkyl groups

### Nomenclature



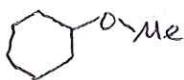
common name  
diethyl ether

(IUPAC name  
ethoxy ethane



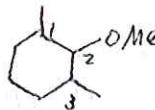
dimethyl ether

methoxy methane



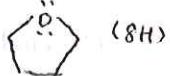
cyclohexylmethyl ether

methoxy cyclohexane

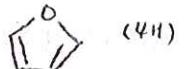


N/A

2-methoxy-1,3-dimethyl  
cyclohexane



Tetrahydrofuran  
(THF)



Furan

### Ether Synthesis

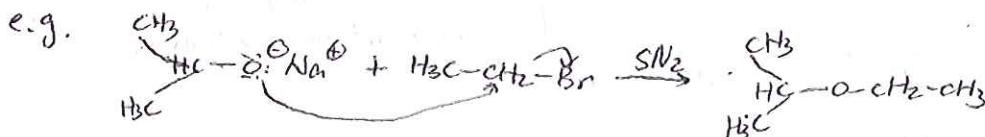
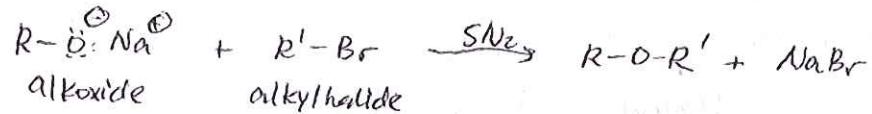
#### 1. Symmetric ethers: acid catalyzed dehydration



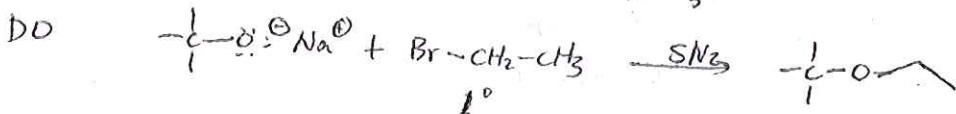
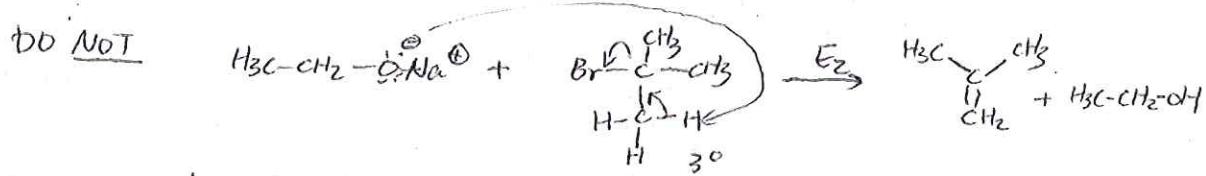
Compared to acid cat. dehydration of alcohols, ether formation requires only low temp.

#### 2. Unsymmetric Ethers.

##### (1) Williamson ether synthesis

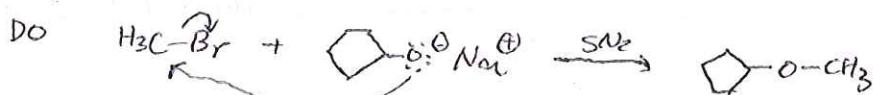
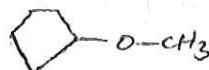


Note = Prepare  $\text{H}_3\text{C}-\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}-\text{O}-\text{CH}_2-\text{CH}_3$

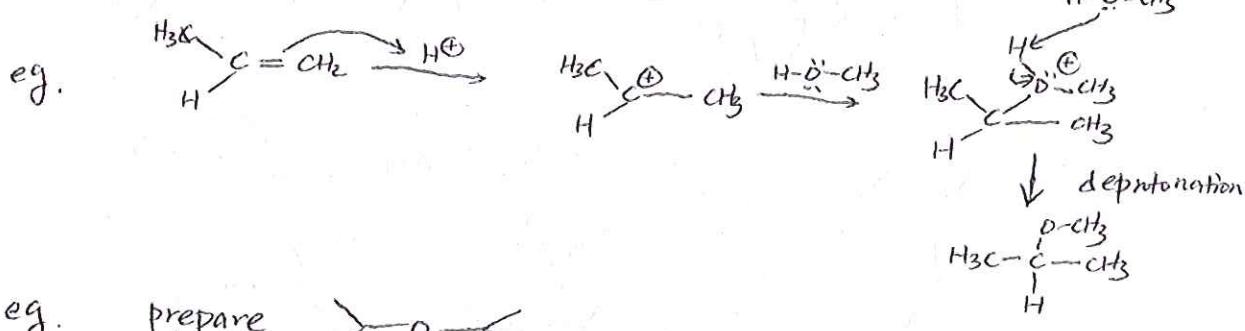
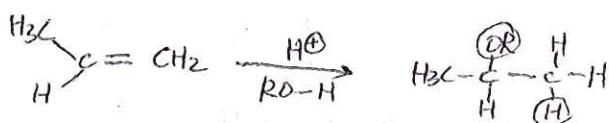


- place halide on  $1^\circ$  substrate or a methyl
- halide on  $2^\circ$  substrate, mix of  $\text{SN}_2$  (ether) and  $\text{E}_2$  product.
- halide on  $3^\circ$  substrate, only  $\text{E}_2$  product

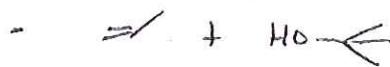
e.g. prepare



## (2) Acid cat. addition of alcohols to alkenes



e.g. prepare  $\text{CH}_3-\text{O}-\text{CH}_3$

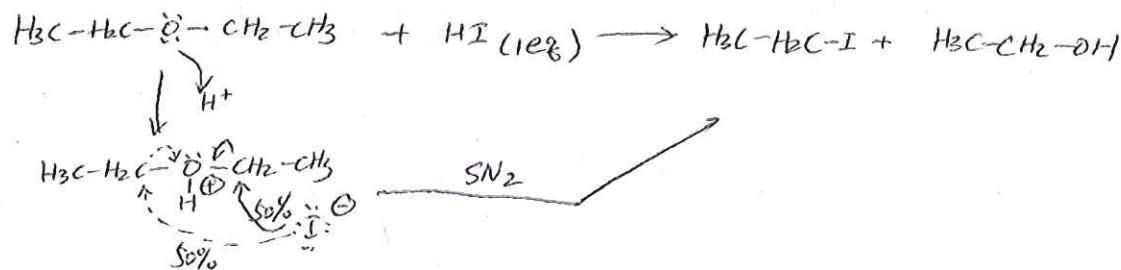


DO NOT USE Williamson

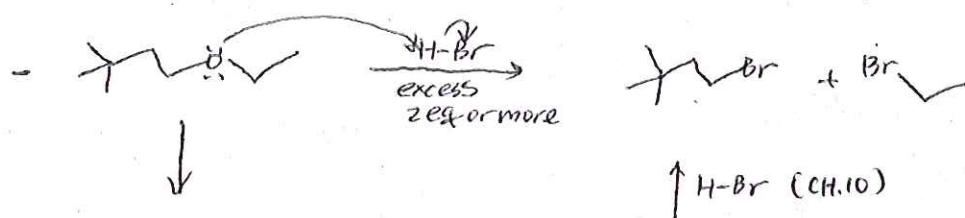
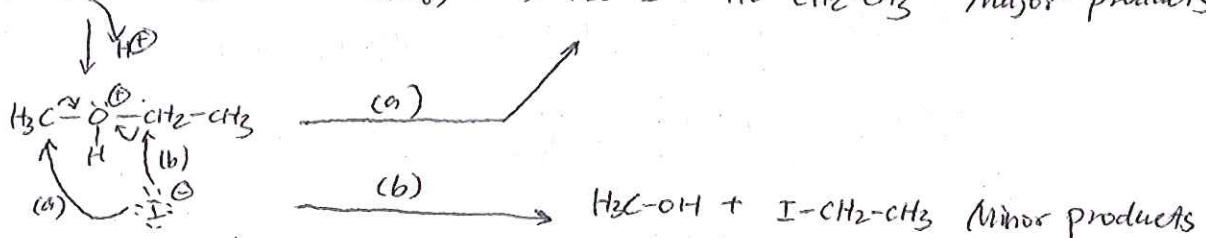
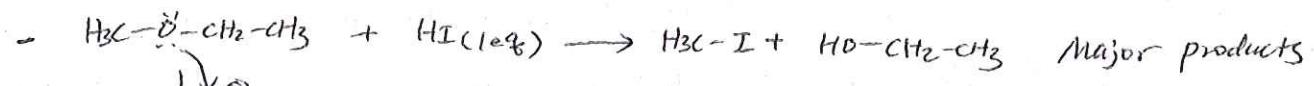


## Cleavage of Ether using H<sub>2</sub> or HBr.

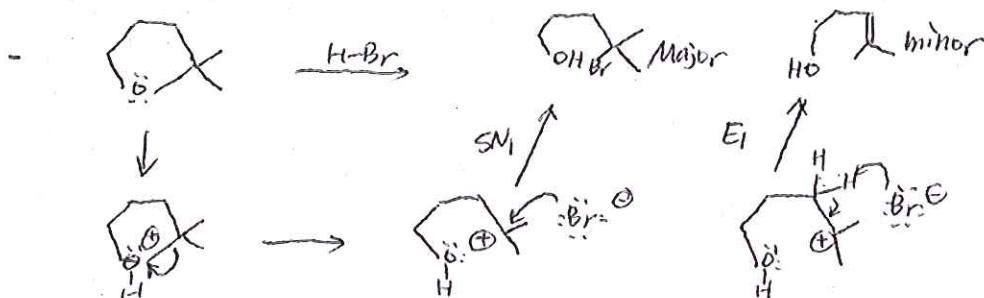
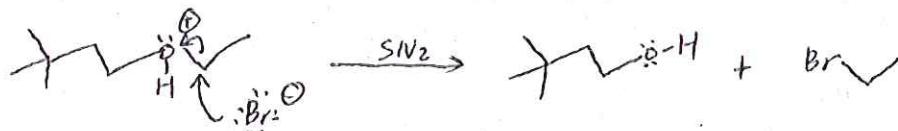
### Symmetrical ethers



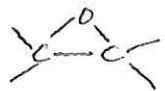
### unsymmetrical ethers



If both C's are either  
are  $1^\circ$ , rxn is  $\text{SN}_2$ .  
Otherwise,  $\text{SN}_1$ .



## Époxide

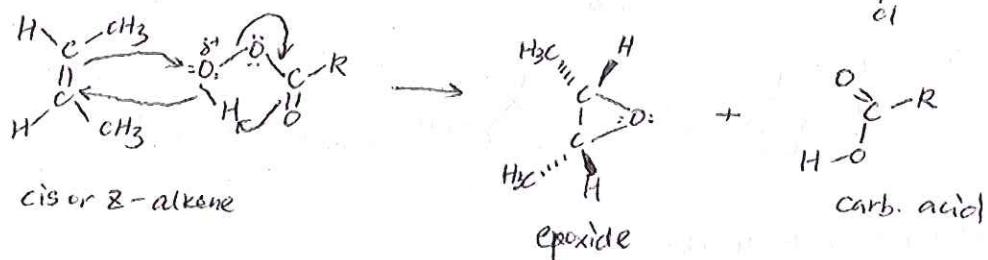


cyclic ethers w/ 3 membered ring.  
polar, very reactive  
(ring-opening rxns)

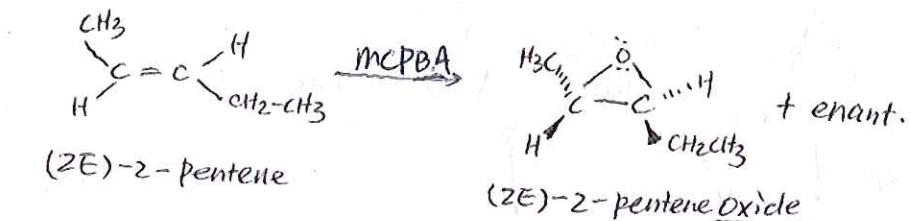
## Synthesis of Epoxide

- (1) peracids w/ alkenes       $\text{R}-\overset{\overset{\text{O}}{\parallel}}{\underset{\text{C}}{\text{C}}}-\text{O}-\text{O}-\text{H} \xrightarrow{\text{H}_2\text{C}=\text{CH}_2} \text{RCOOH}$       Commonly used: mCPBA  
 $\text{H}_2\text{C}=\text{CH}_2 + \text{H}_2\text{C}-\overset{\overset{\text{O}}{\parallel}}{\underset{\text{C}}{\text{C}}}-\text{H}_2 \longrightarrow$       meta-Chloroperbenzoic acid

Mechanism = Concerted



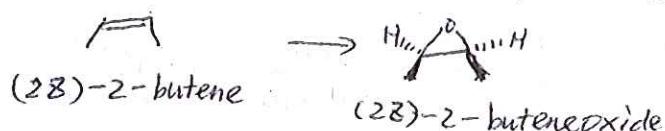
e.g.



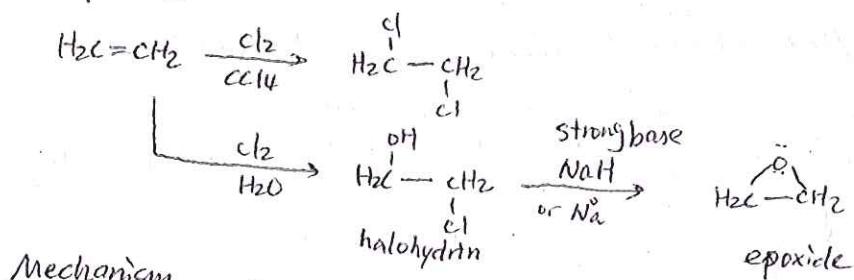
Stereochem of the product depends on the stereochem of alkene, epoxidation rxn is stereospecific

Nomenclature: add -oxide to the end. alkene name is preserved!

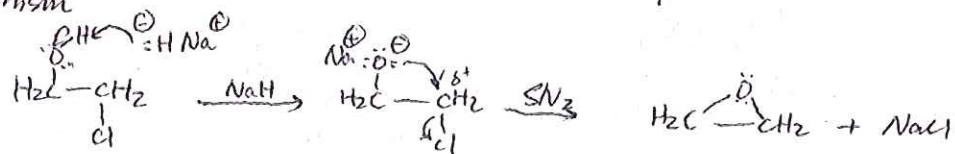
e.g.



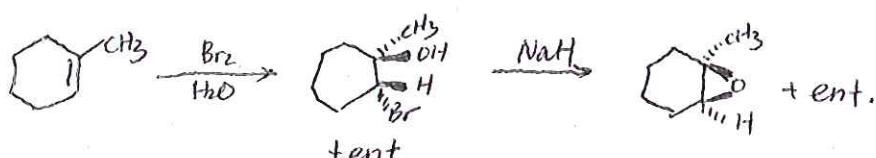
## (2) Halohydrins



## Mechanism

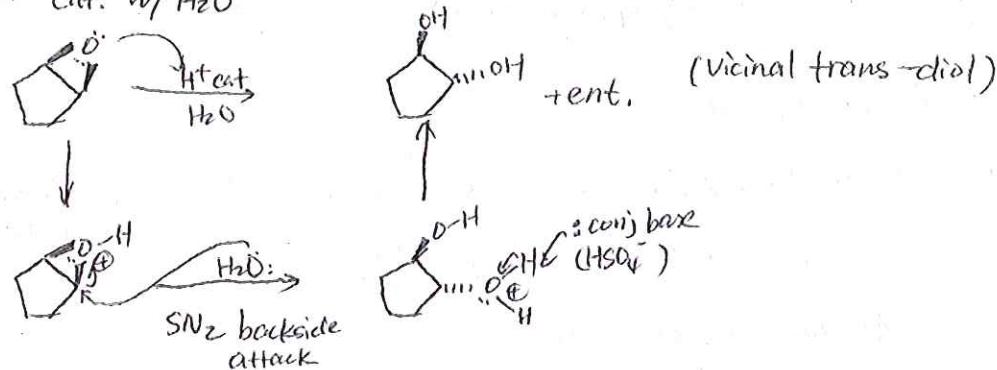


eg

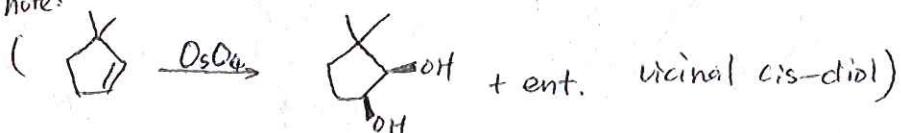


## Ring opening rxns.

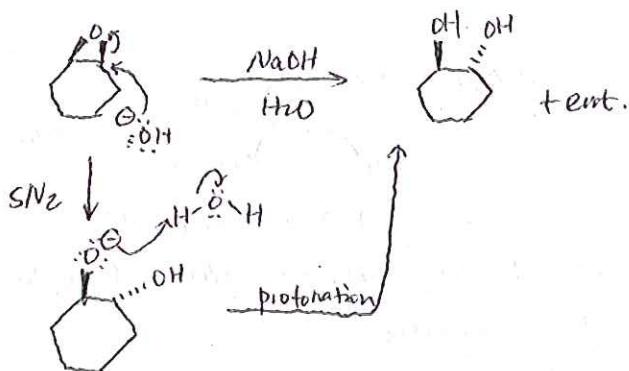
(a)  $\text{H}^+$  cat. w/  $\text{H}_2\text{O}$



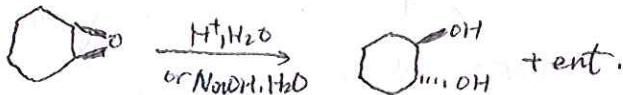
note:



(b)  $\text{OH}^-$  cat. w/  $\text{H}_2\text{O}$

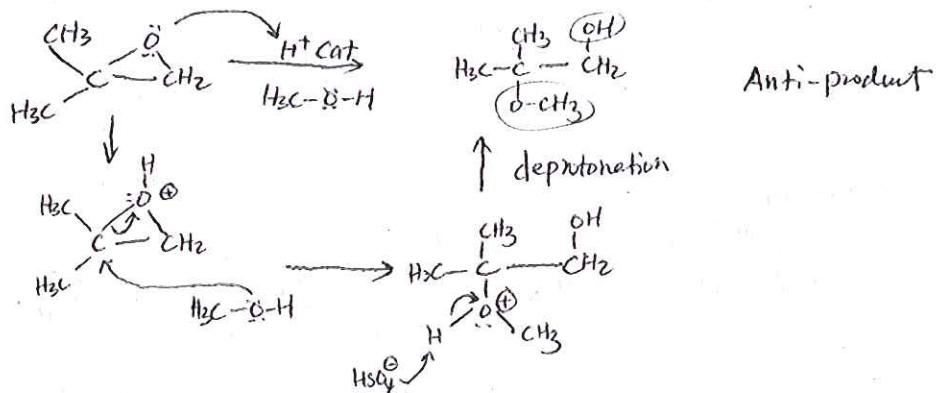


In general,



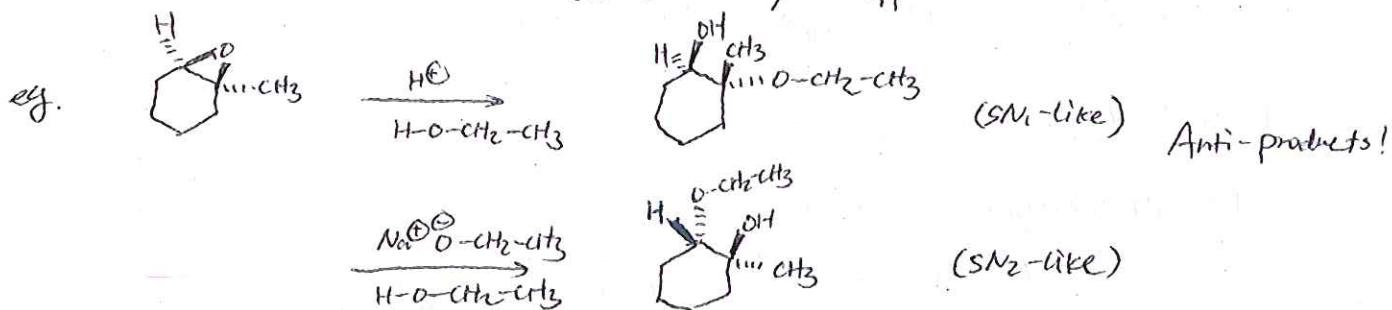
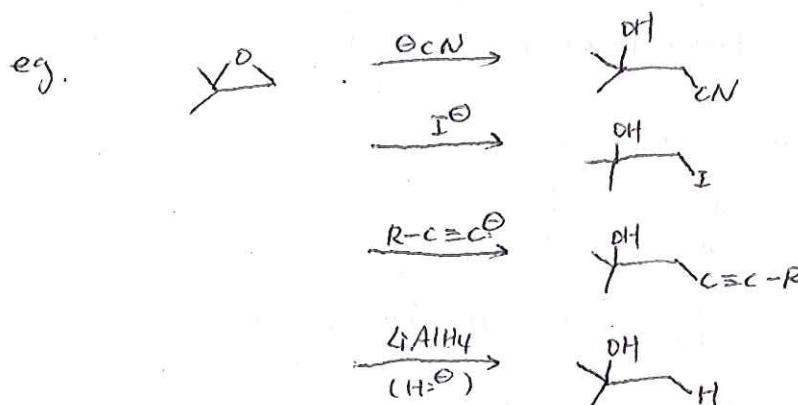
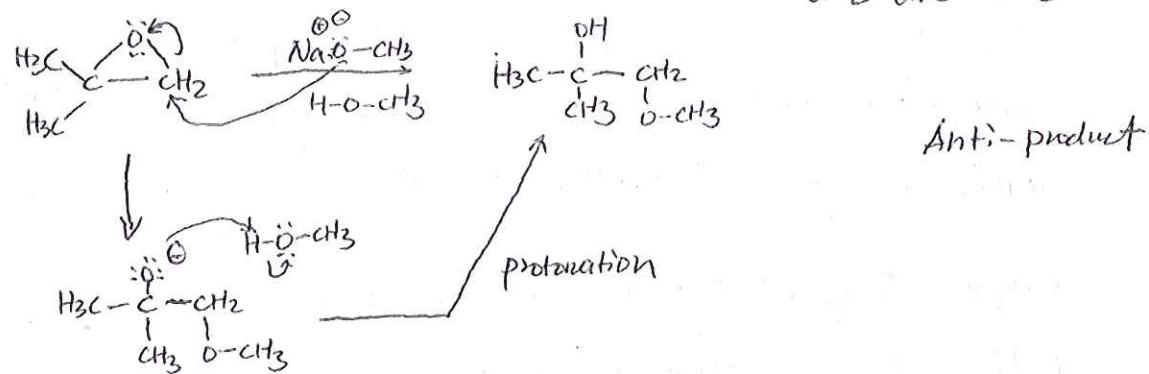
(c) Other nucs.

(i) weak/neutral nuc + acid.  $\text{SN}_1$ -like  $\text{SN}_2$  rxn

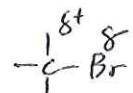


(2) Strong nuc in absence of acid (anionic or organometallic)

$SN_2$ -like  $SN_2$  rxn

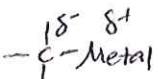


## Chapter 15 - Organometallics



carbon is electrophile

vs



carbon is nuc.

→ allows formation of new C-C bonds

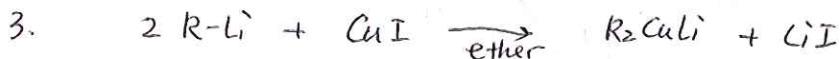
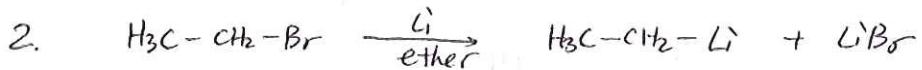
other C-nucs:  $\ddot{\text{O}}:\text{C}\equiv\text{N}$ ,  $\ddot{\text{O}}:\text{C}\equiv\text{C}-\text{R}$

1 -  $\text{RMgX}$  Grignard Reagent  $X = \text{Br}, \text{I}, (\text{Cl})$

2 -  $\text{R-Li}$  Organo Lithium Reagent

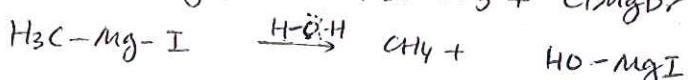
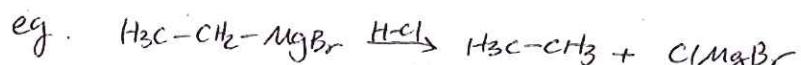
3 -  $\text{R}_2\text{CuLi}$  Gilman Reagent (organo Copper)

### Preparation of Organometallic Compounds



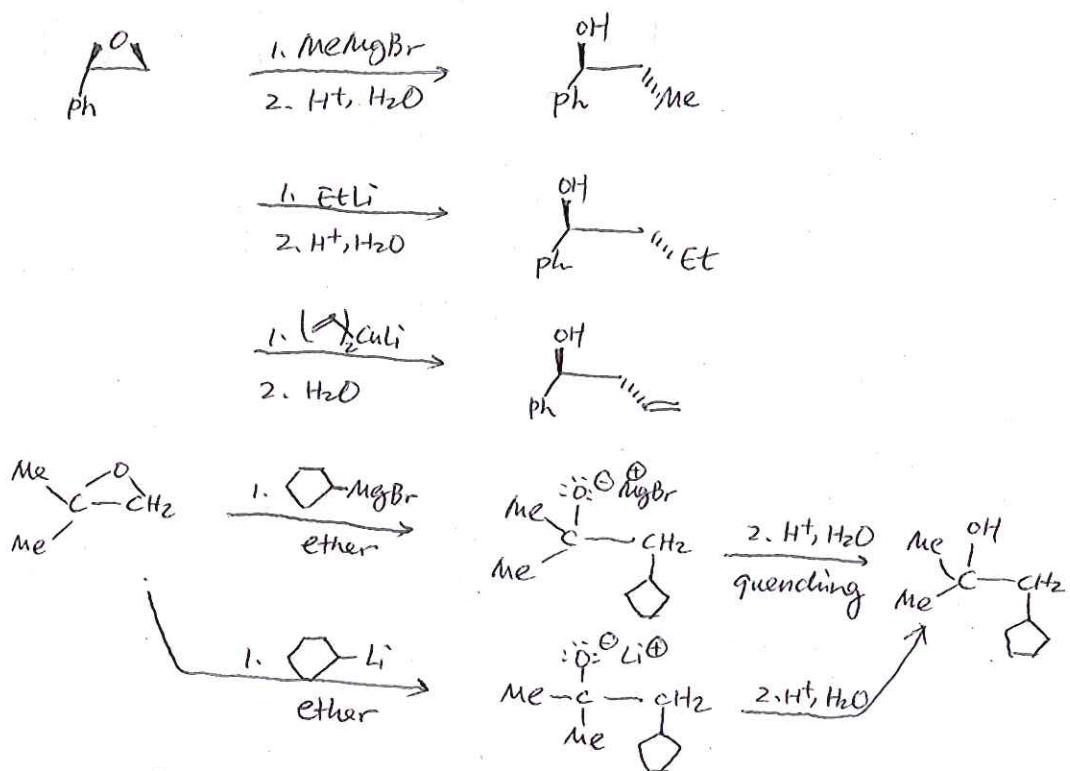
### Selected Reaction

(1) protonation w/ proton acids



Grignard & Organolithium act as strong base w/ acid or  $\text{H}_2\text{O}$   
 Gilman does NOT act as strong base.

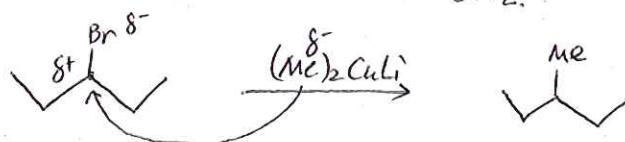
## (2) Epoxide - Opening



## (3) Coupling w/ Alkyhalides

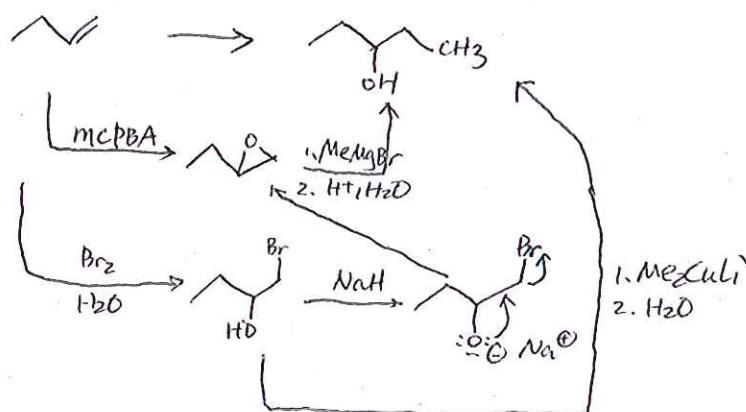
Gringard +  $\text{R-Li}$  are too basic  $\Rightarrow$  do  $E_2$ .

only Gilman will do  $SN_2$ .

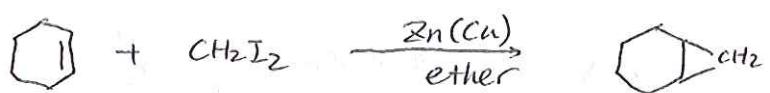


only one R-group act as nucleophile

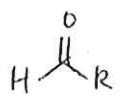
### Multistep rxn



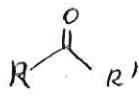
(4) Simmons-Smith



## Chapter 16 - Aldehydes and ketones



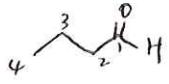
Aldehyde



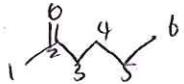
Ketone



carbonyl carbon = great electrophile!



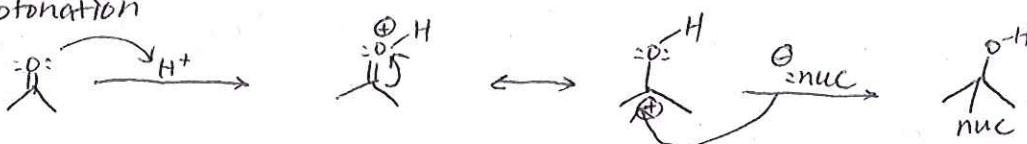
butanal



2-hexanone

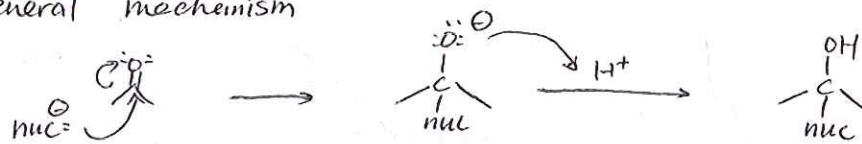
### Reactions

#### 1. Protonation

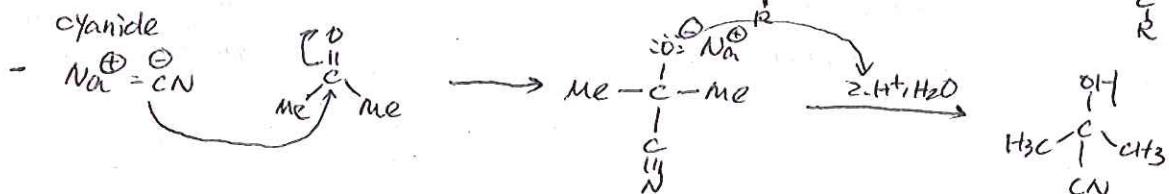
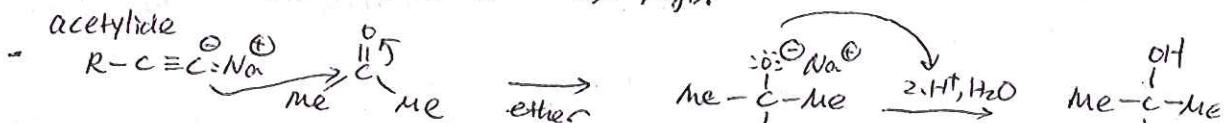
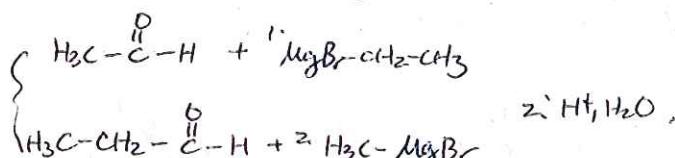
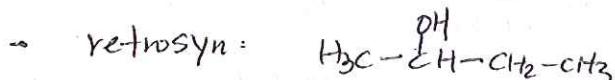
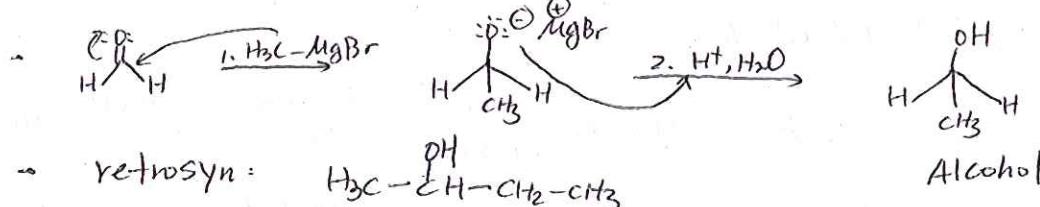


#### 2. Nucleophilic Acyl Addition

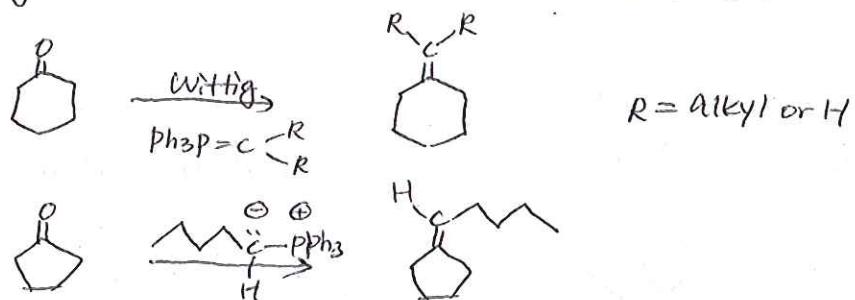
##### general mechanism



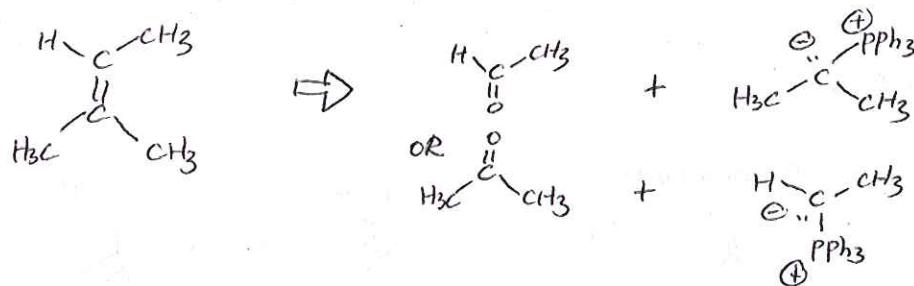
(A) Carbon nuc:  $\text{RMgX}$ ,  $\text{RLi}$ ,  $\text{R}_2\text{CuLi}$ ,  $\text{R}-\text{C}\equiv\text{C}^-\text{Na}^+$ ,  $\text{NC}^-\text{Na}^+$ , Wittig



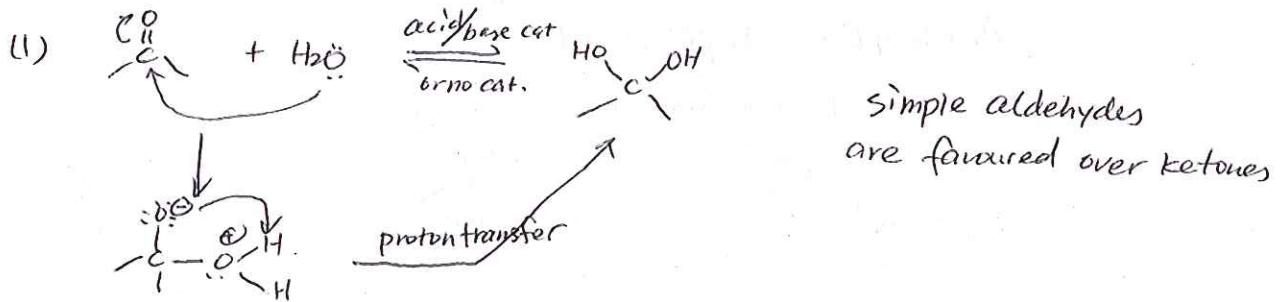
- Wittig Reaction (Mechanism Omitted in final)



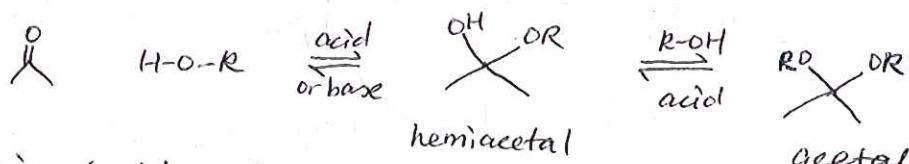
Retrosyn:



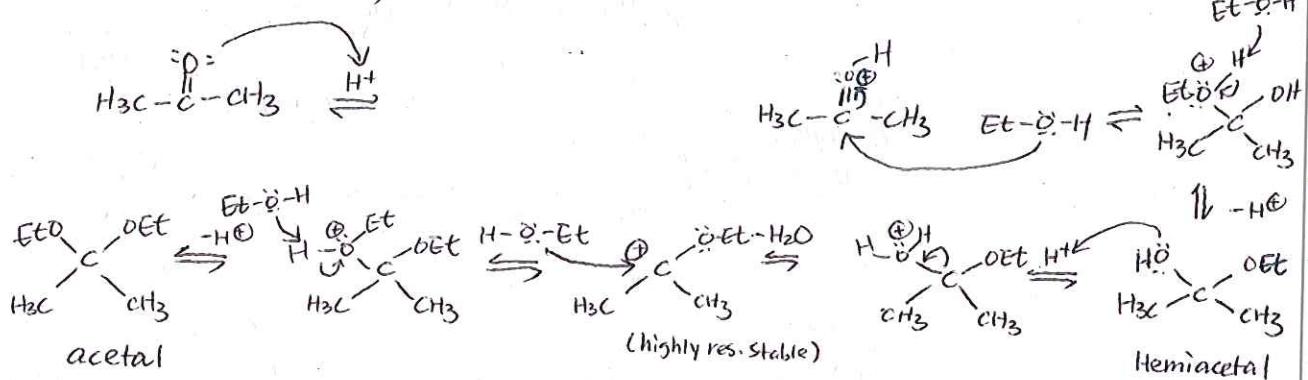
(B) Oxygen Nuc



(2) w/ alcohols

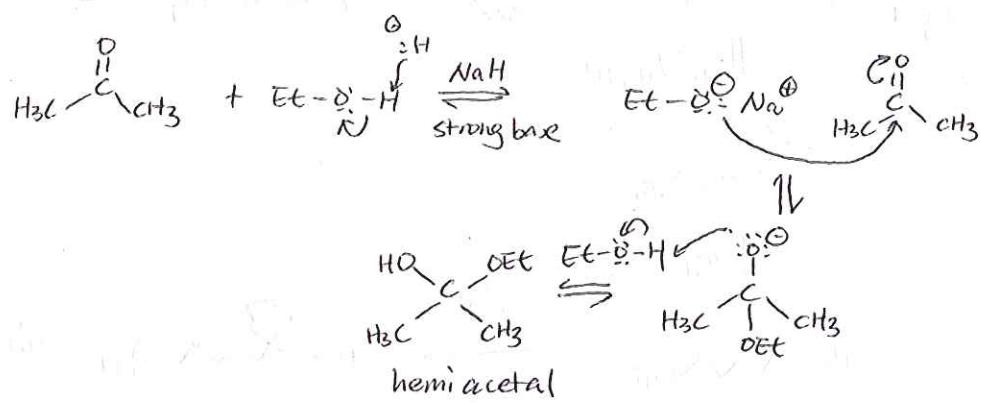


Mechanism (acid-cat.)

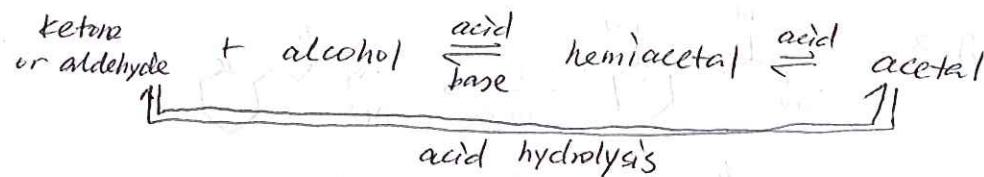


Hemiacetal can be both acid or base cat-  
but acetal can only be acid catalyzed! (must form  $\text{H}-\ddot{\text{O}}-\text{H}$  LG!)

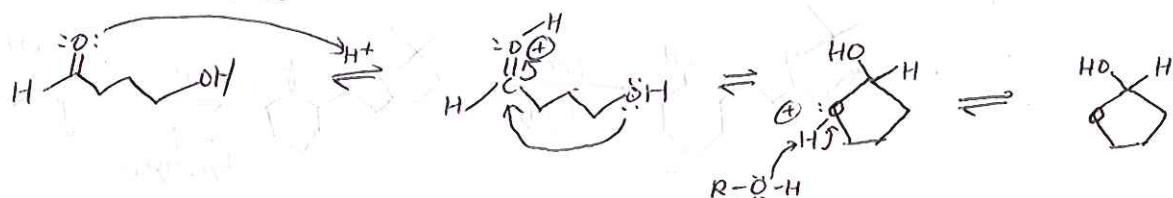
base-cat mechanism



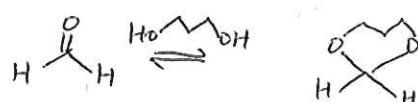
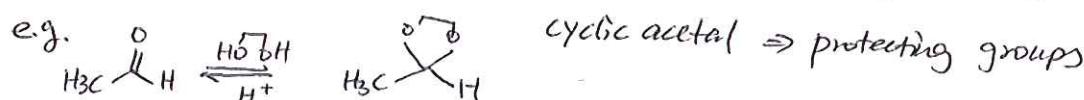
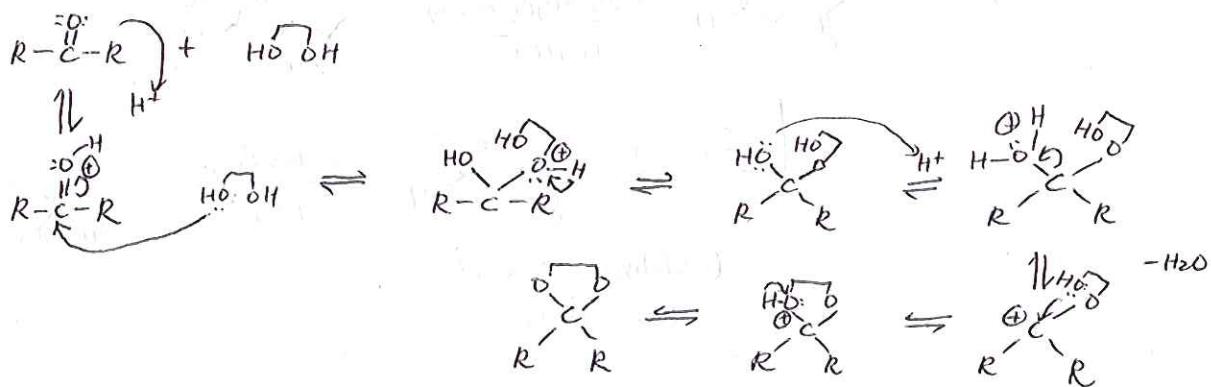
Acetal formation is reversible



Cyclic hemiacetals

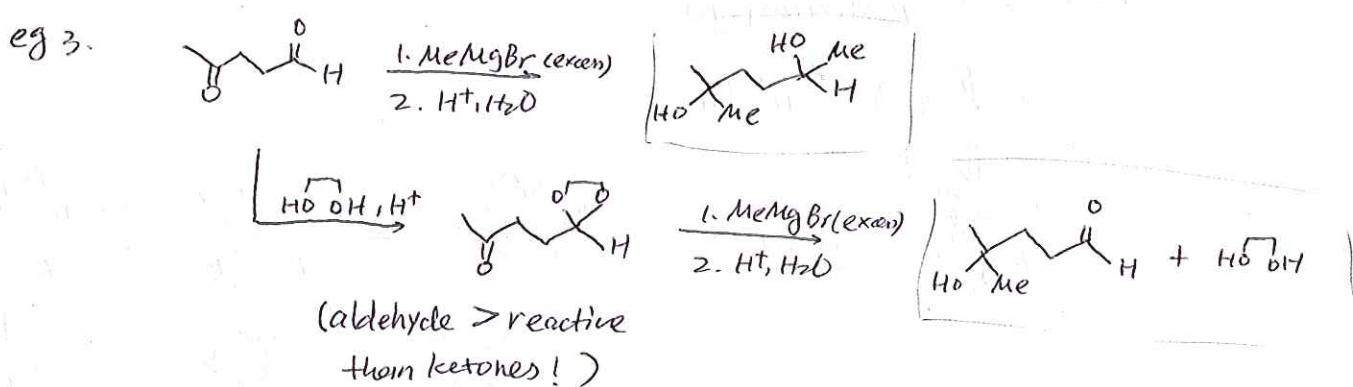
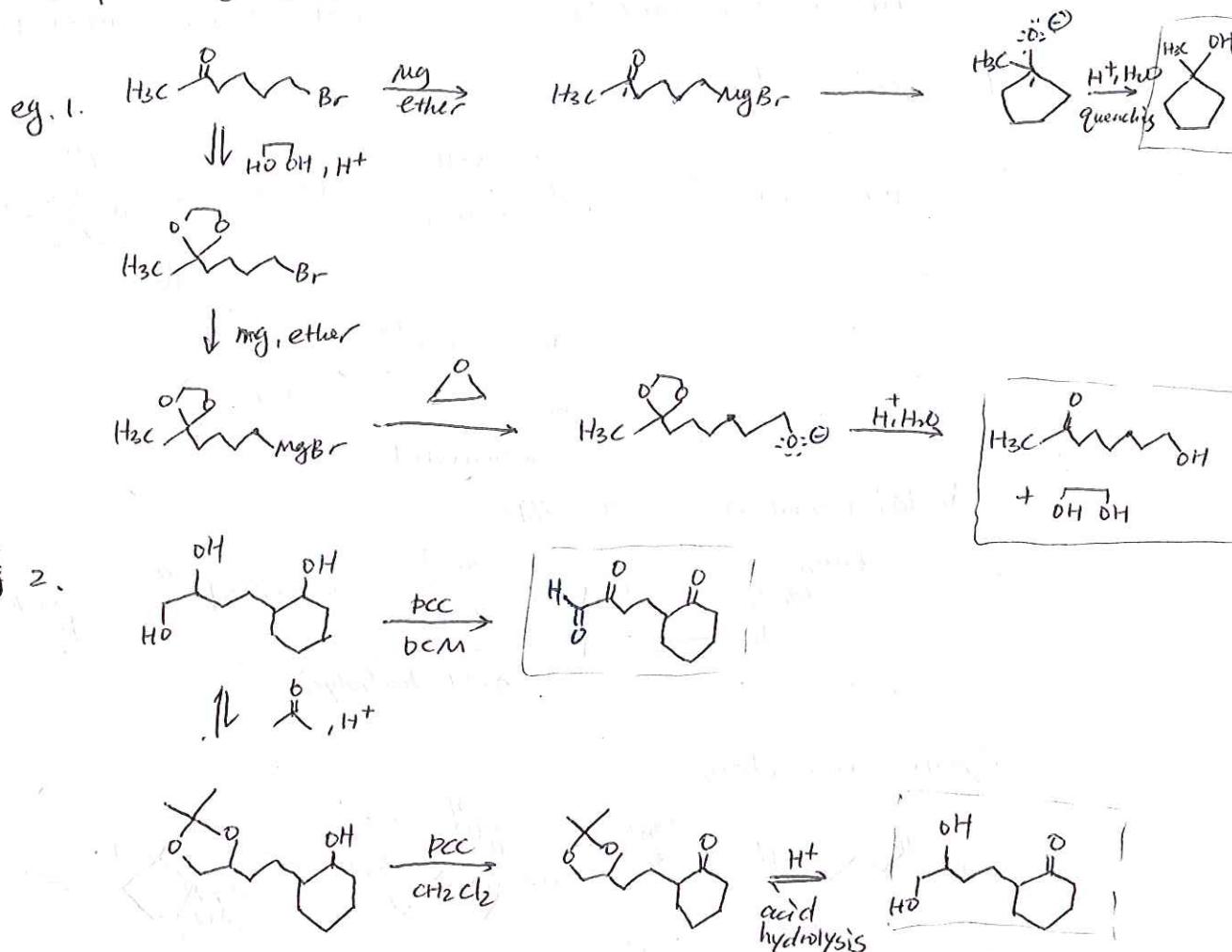


acetals as protecting groups



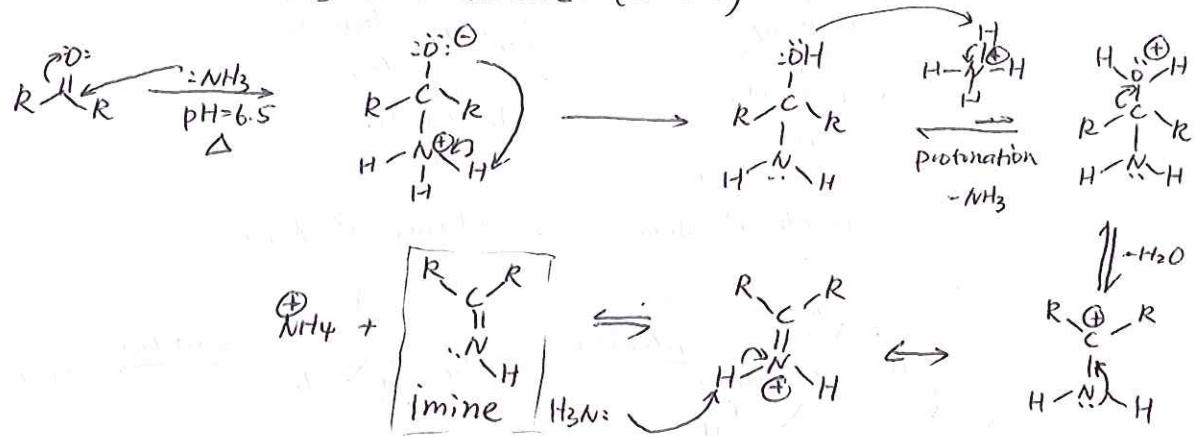
cyclic acetal  $\Rightarrow$  protecting groups

as protecting group. (cont.)

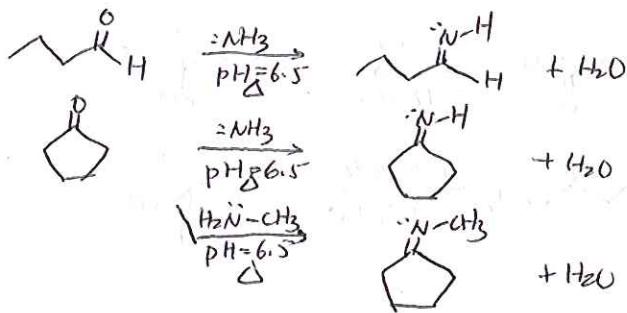


## (C) Nitrogen Nuc.

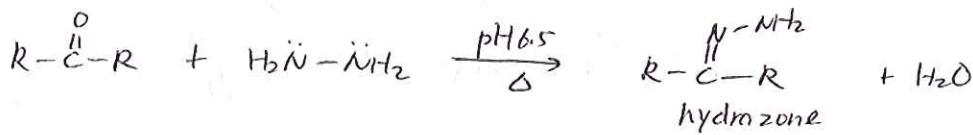
(1) with ammonia =  $\text{NH}_3$  and  ${}^1\text{O}$  amine. ( $\text{R}-\ddot{\text{N}}\text{H}_2$ )



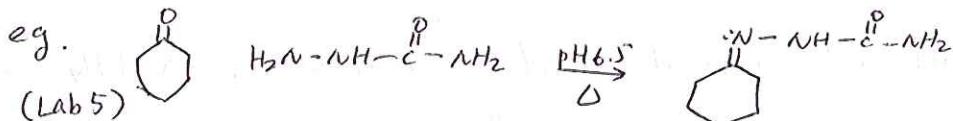
e.g.



(2) with hydrazine ( $\text{H}_2\ddot{\text{N}}-\ddot{\text{N}}\text{H}_2$ )

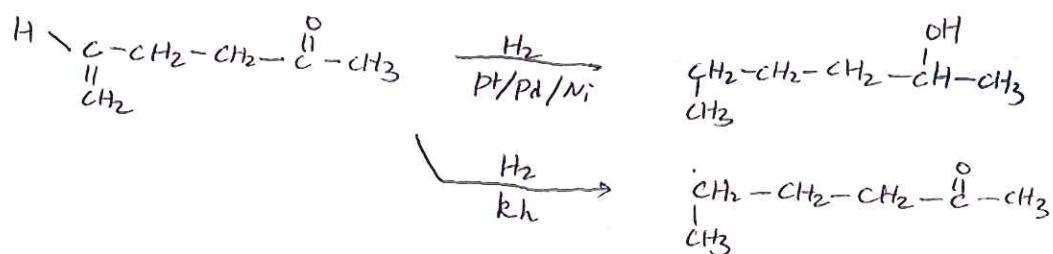


e.g.

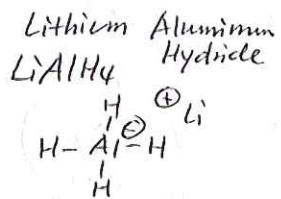
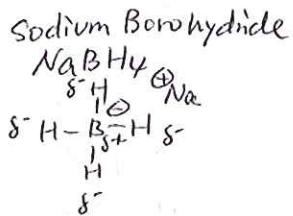


## (D) Hydrogen Nuc (Reduction)

(1) with  $\text{H}_2$  gas

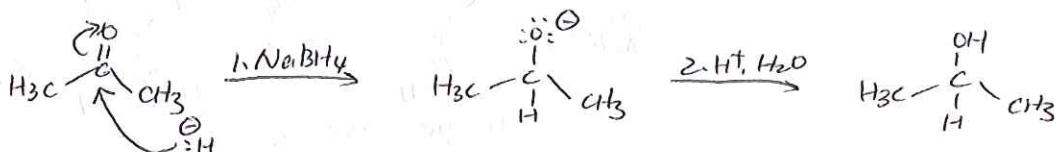


(2) w/ Metalhydrides

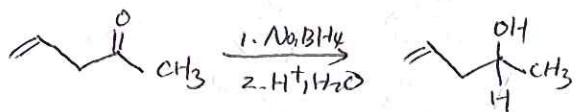
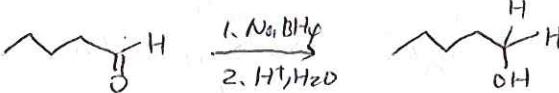


Weak  $\text{H}^\ominus$  donor

Strong  $\text{H}^\ominus$  donor



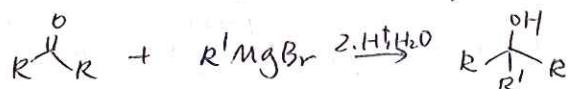
e.g.



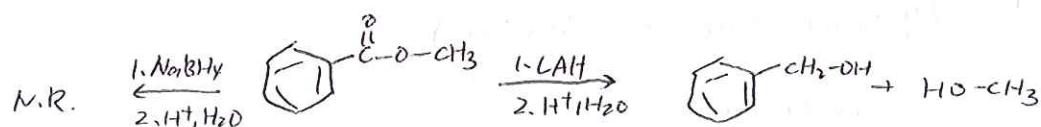
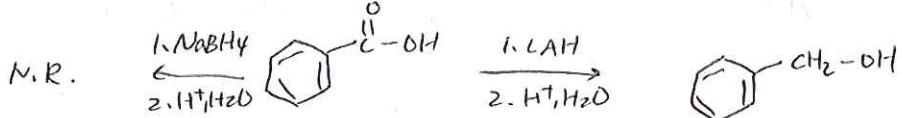
$\text{NaBH}_4 + \text{LAH}$  are nucleophilic

but alkenes are not electrophilic

- $\text{NaBH}_4 + \text{LAH} \rightarrow$  no difference in reducing aldehydes + ketones  
 $3^\circ$  alcohols cannot be synthesized by reduction!

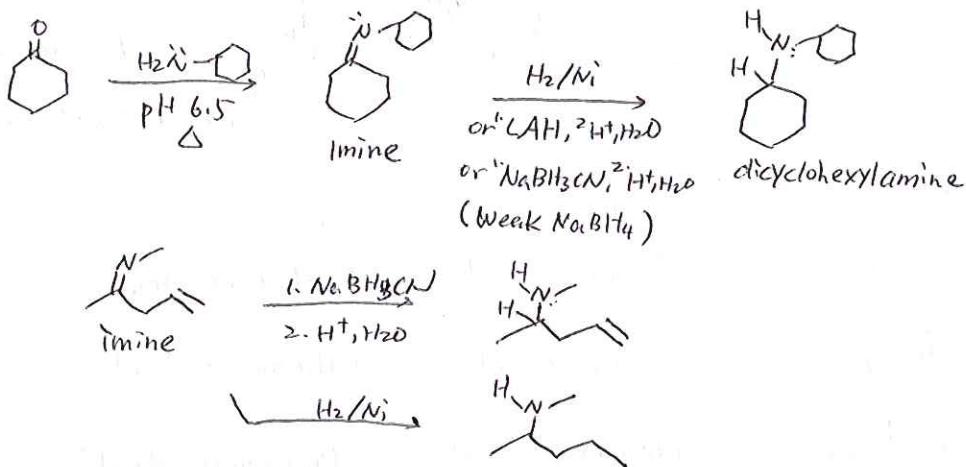


- LAH reduces carb. acids + esters but  $\text{NaBH}_4$  does NOT.

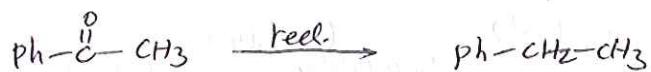


(E) Reductive Amination

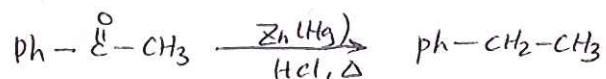
Synthesizing  $2^{\circ}$  amine  $R-\overset{R'}{\underset{|}{\overset{\text{O}}{\underset{\text{C}}{\text{||}}}}-\text{H}$  from  $1^{\circ}$  amine  $R-\overset{\text{H}}{\underset{|}{\overset{\text{O}}{\underset{\text{C}}{\text{||}}}}-\text{H}$



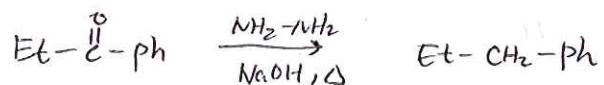
(F) Reduction to Alkanes,



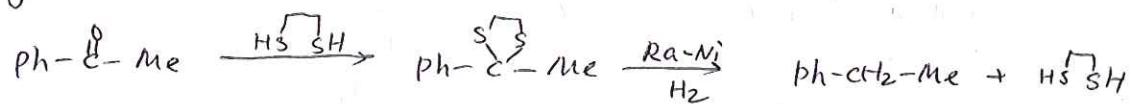
(1) Clemmensen.



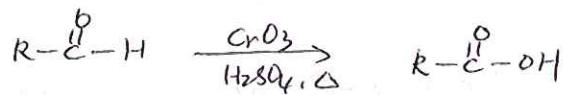
(2) Wolff-Kishner



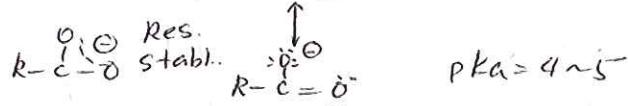
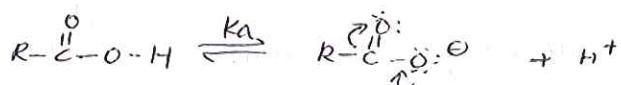
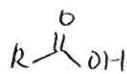
(3) Mozingo



(G) Oxidation of Aldehydes



## Chapter 17 - Carboxylic Acids

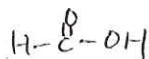


$$pK_a = 4 \sim 5$$

$$pK_a \text{ of } R\text{COH} \text{ (alcohol)} = 16 \sim 18$$

### Nomenclature

common name      IUPAC



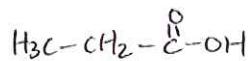
formic acid

Methanoic Acid



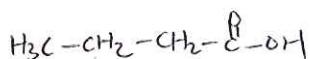
Acetic Acid

Ethanoic Acid



Propionic Acid

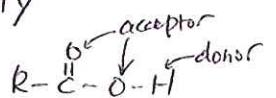
Propanoic Acid



Butyric Acid

Butanoic Acid

### Acidity



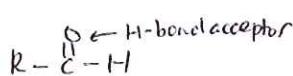
BP (H-bond)

1

Solubility (polarity)

1

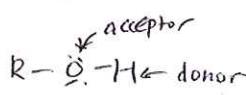
(1-3 High-Low)



3

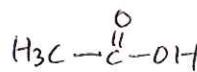
3

as carb. acid gets longer,  
solubility in  $\text{H}_2\text{O}$  decreases.



2

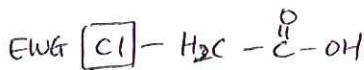
2



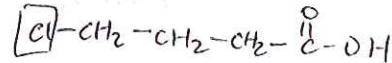
pKa

4.76

pKa

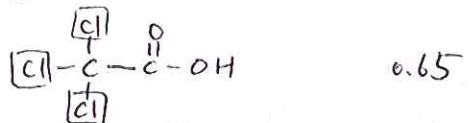


2.86

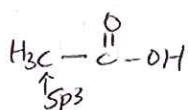


4.52

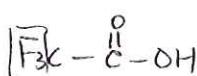
- Inductive effect falls off w/ distance



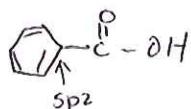
0.65



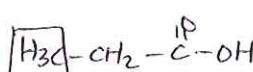
4.76



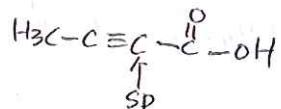
-0.5



4.19



4.82



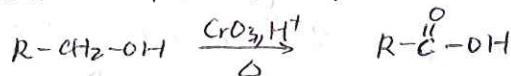
1.8

EDG

\* Higher s-character, more acidic

# Synthesis of Carb Acids

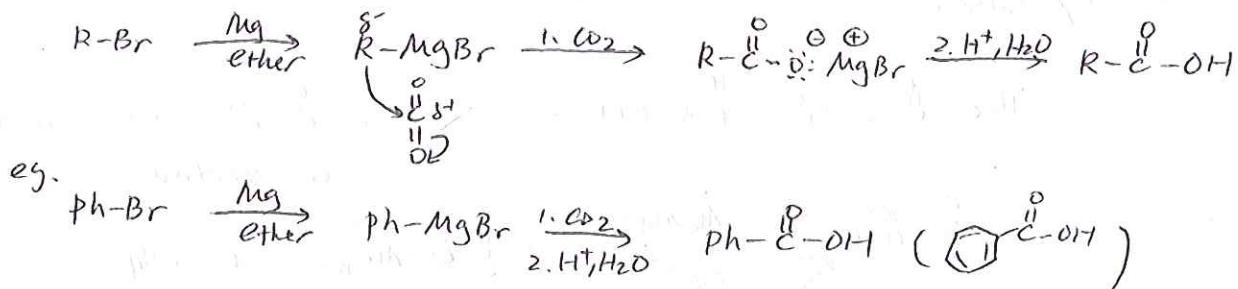
(A) Oxidation of 1° alcohol



Jones Oxidation

(c) hydrolysis of carb acid derivatives  
(CH 18)

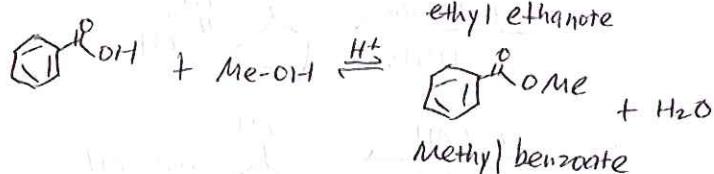
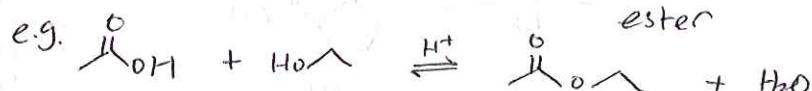
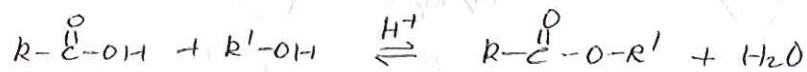
(B) Grignard reaction



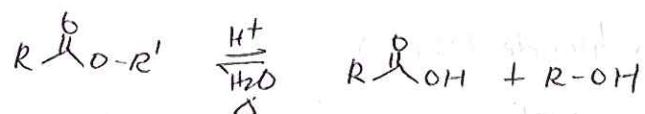
# Reactions of Carb Acids

## 1. Esterification

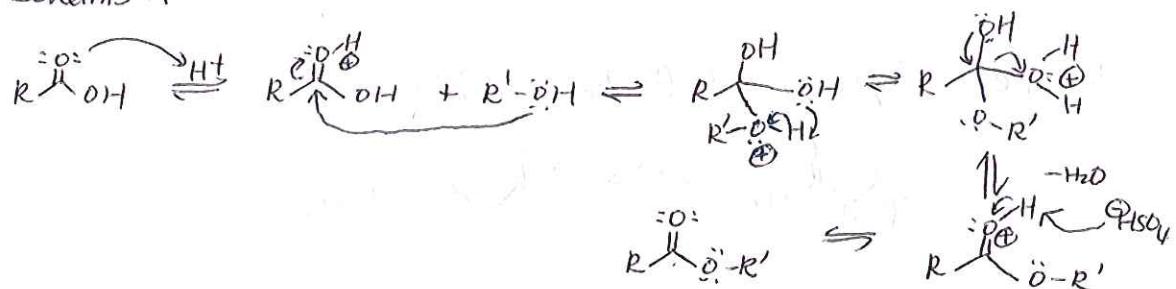
(A) Fisher Esterification (N.A.S.)



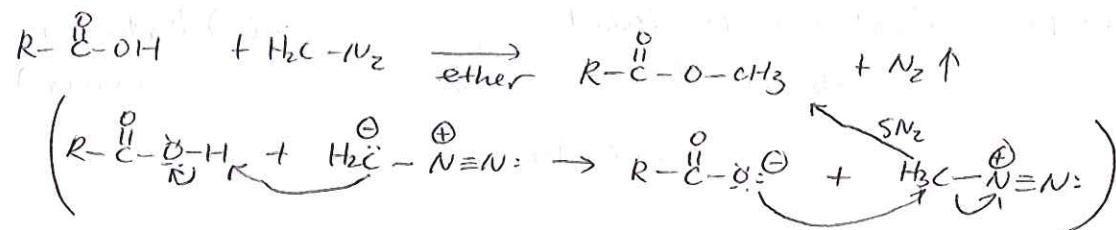
Esterification is reversible via acid cat. hydrolysis.



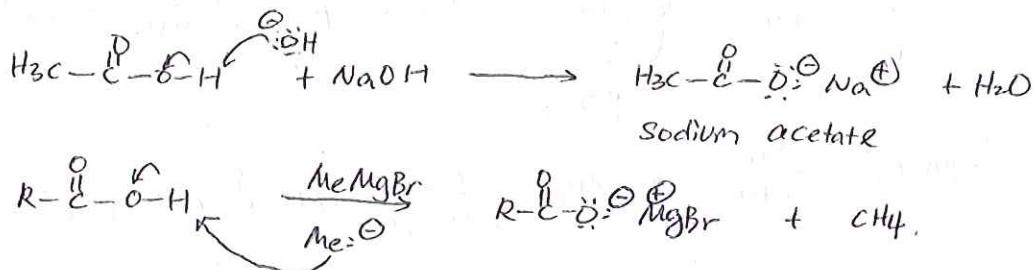
Mechanism



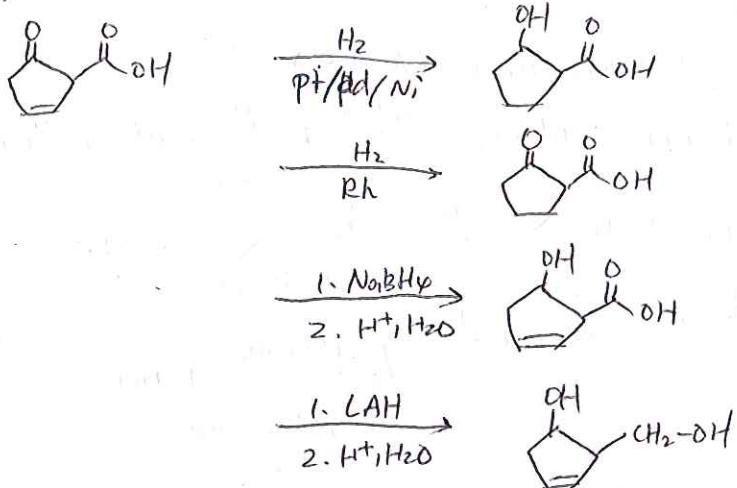
### (B) Methyl-Esters formation via Diazomethane



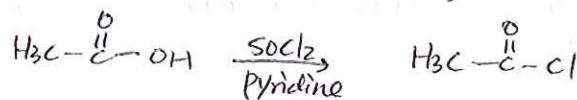
### 2. w/ Bases



### 3. Reduction



### 4. React w/ Thionyl Chloride ( $\text{SOCl}_2$ )

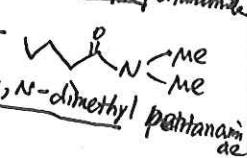
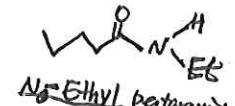
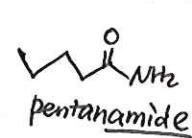
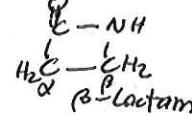
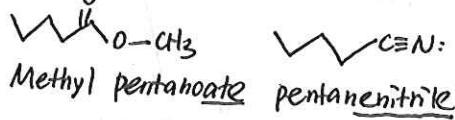
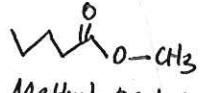
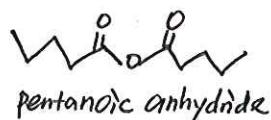
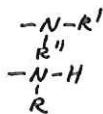
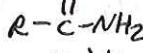
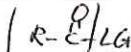
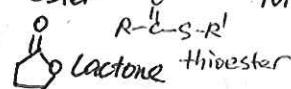
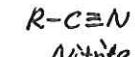
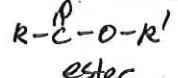
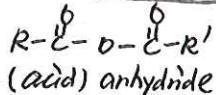


### 5. Decarboxylation of $\beta$ -keto acids.



# CHAPTER 18 - Carboxylic Acid Derivatives

$R-C-X$   
acid halide  
(acyl)  
 $X = Cl, Br$

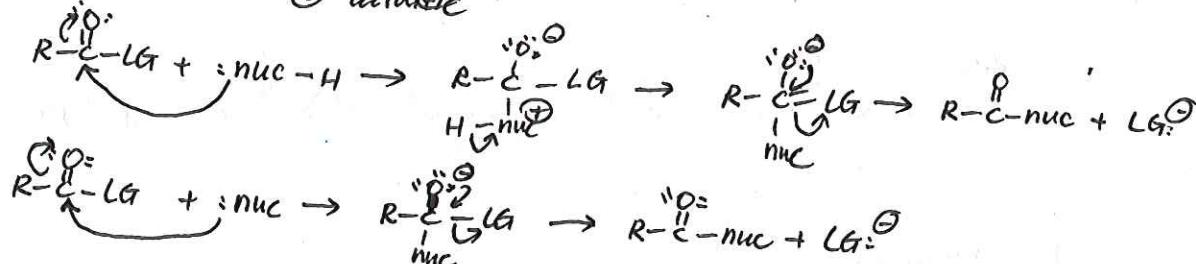


## Nucleophilic Acyl Subst.

- ① Neutral
- ② basic
- ③ acidic

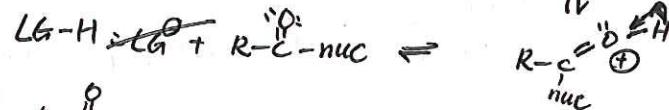
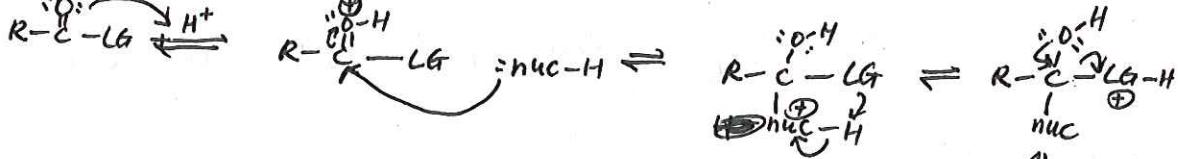
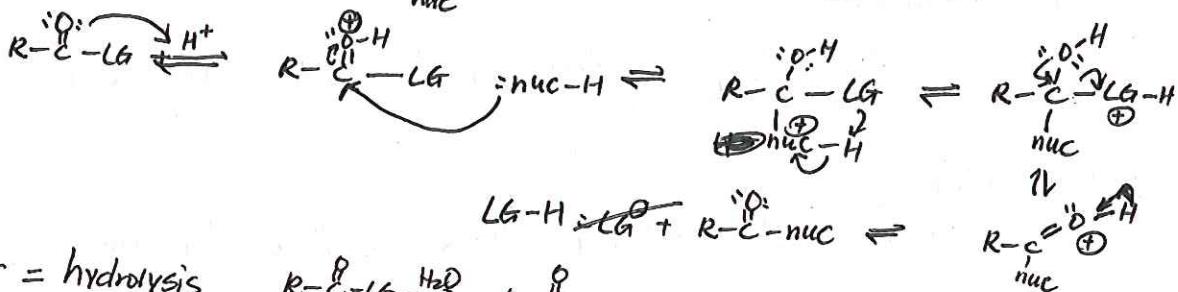
Acid Chlorides + anhydrides ONLY

② Basic

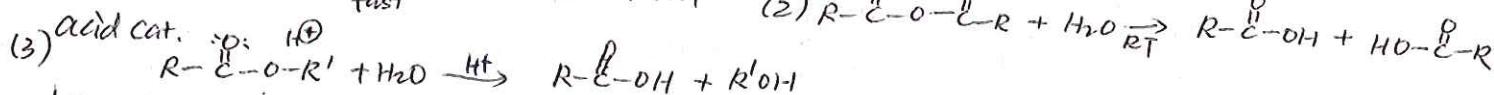
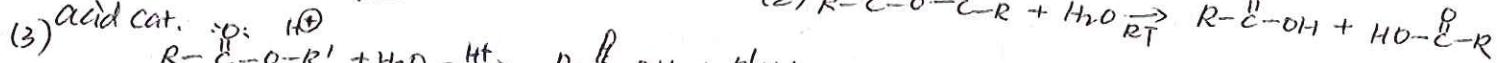
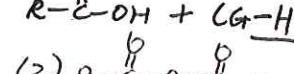
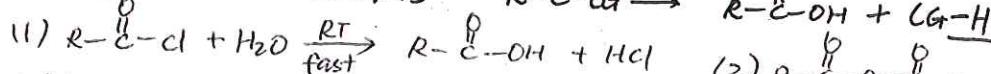


③ acidic

= Fischer



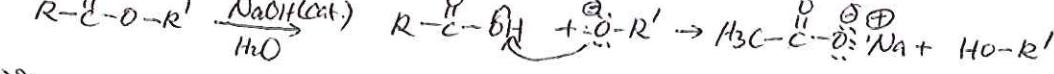
1. Rxns w/ Water = hydrolysis



base cat.



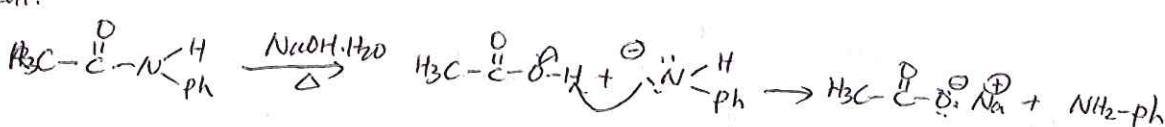
spontaneous!



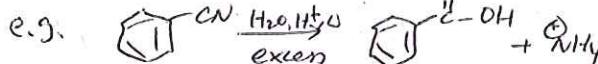
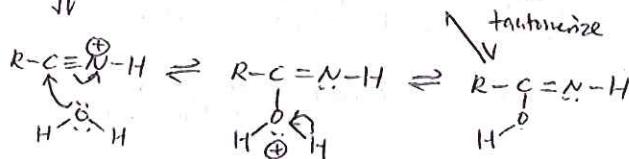
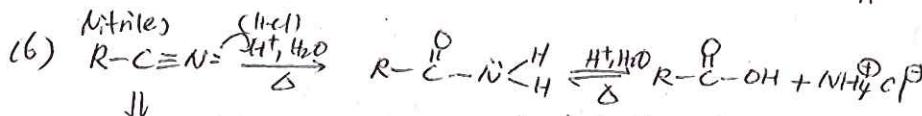
acid c.



base cat.

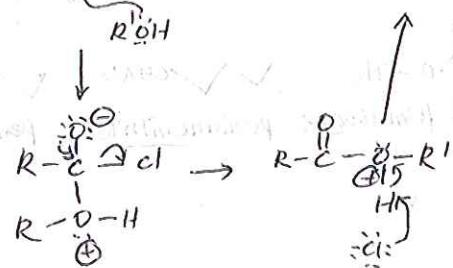


5) Cyclic.

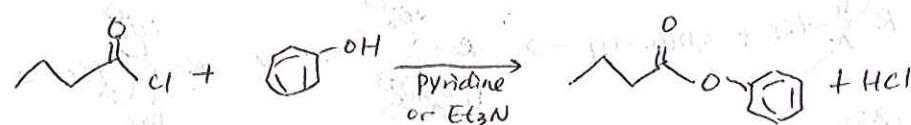


## 2. Alcoholsysis / Esterification

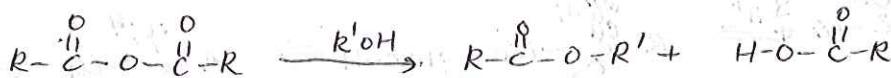
### (1) acid chlorides



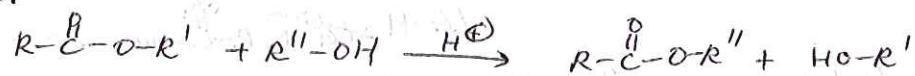
e.g.



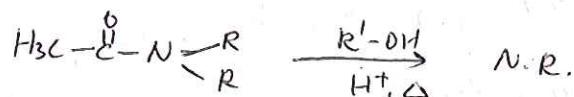
### (2) Anhydrides



### (3) ester

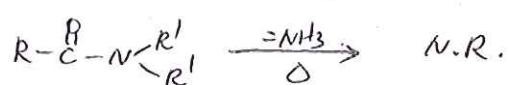
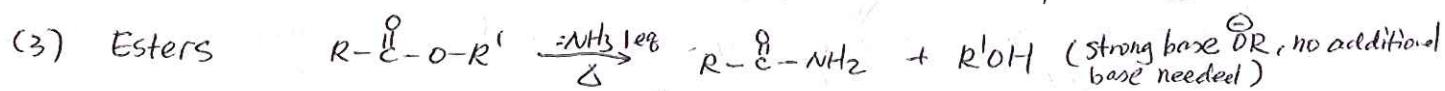
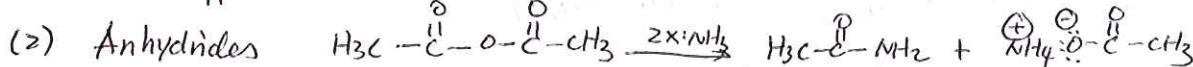
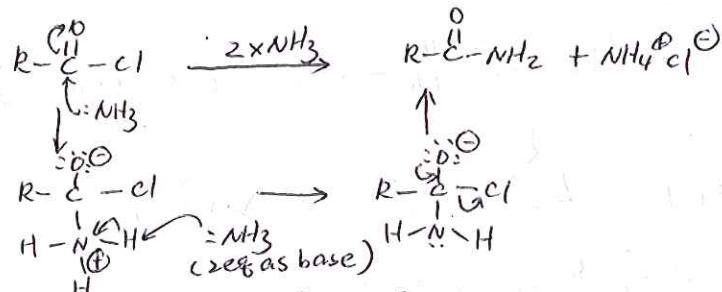


### (4) Amides

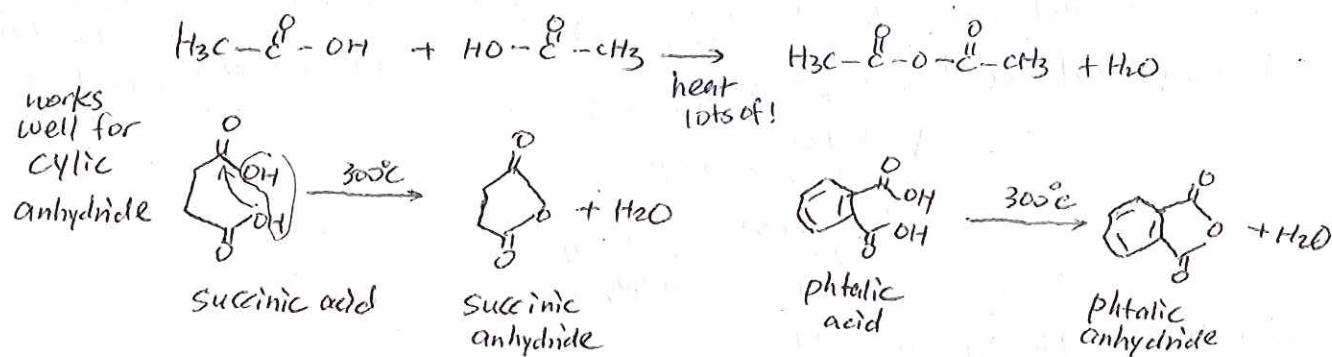


## 3. Aminolysis

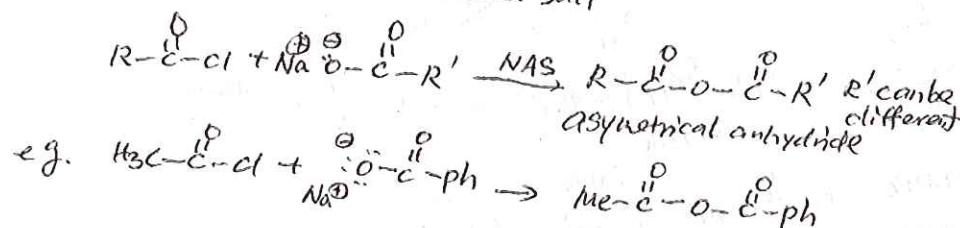
### (1) acid chlorides



## 4. Formation of Acid anhydrides

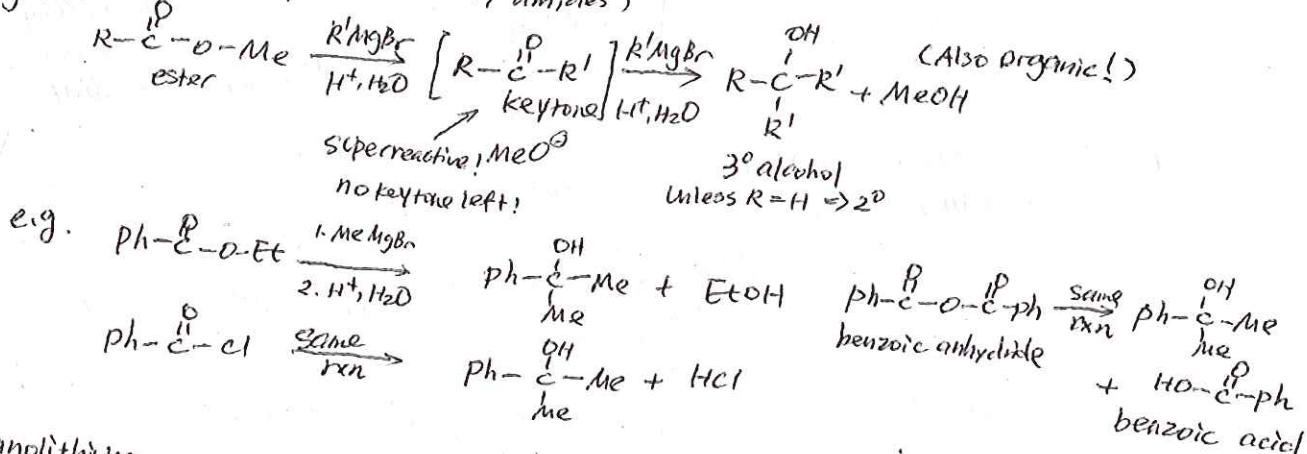


Best way: acid chloride + cab. salt

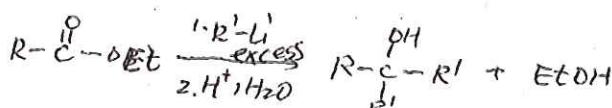


## 5. With Organometallic Compounds

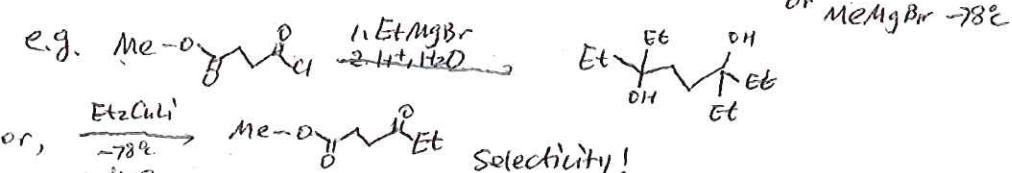
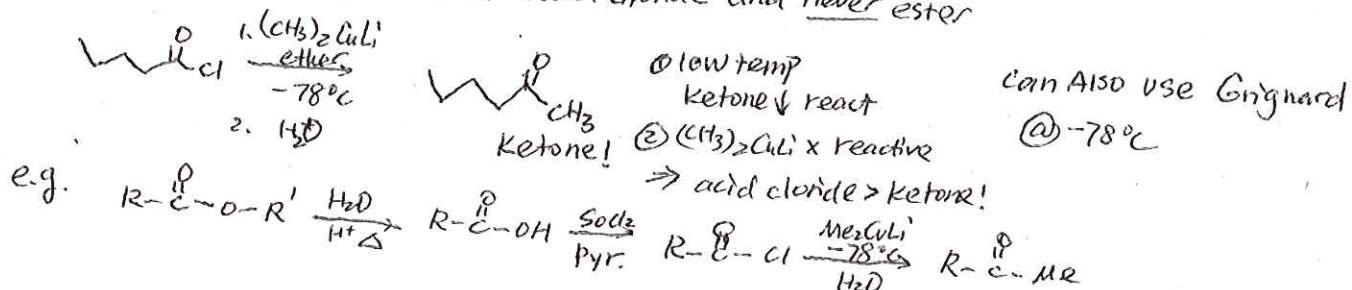
A. Grignard (Don't worry abt nitriles/amides)



B. organolithium



C. Gilman  $\text{R}_2\text{CuLi}$  only react w/ acid chloride and never ester

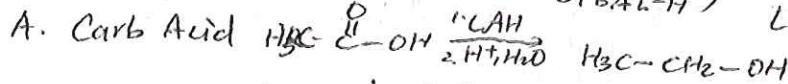


## 6. w/ Reducing Agents

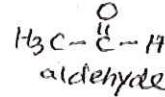
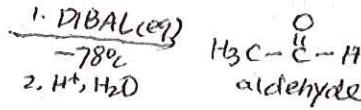
Diisobutyl Aluminum hydride (DIBAL)  
 DIBAL-H

$\text{Al}-\text{H}$  modified  
reducing agent

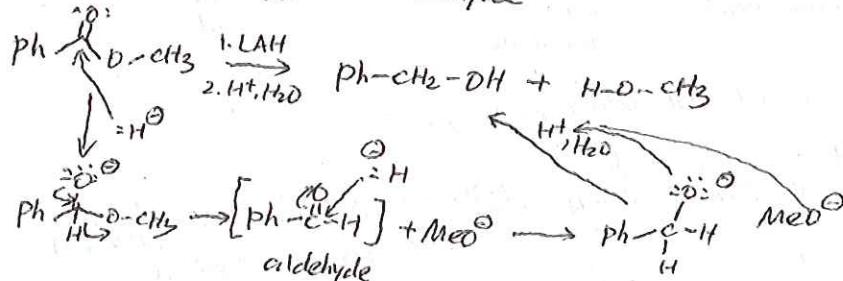
ketone & aldehyde  
no difference



$\text{LiAlH}_4 > \text{DIBAL} > \text{NaBH}_4$  Carb. acid  
different!

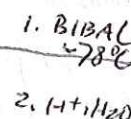
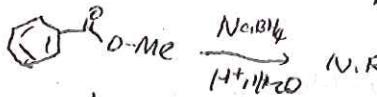
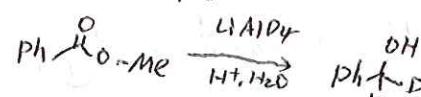


### B. Esters



If use  $\text{LiAlH}_4$

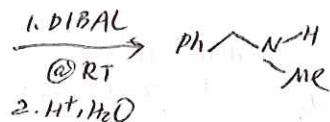
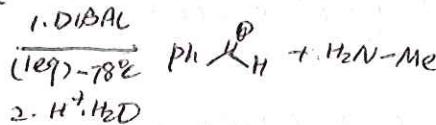
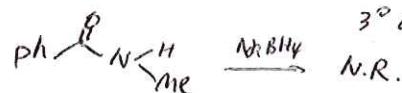
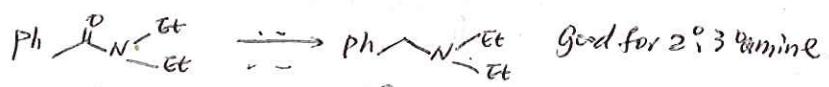
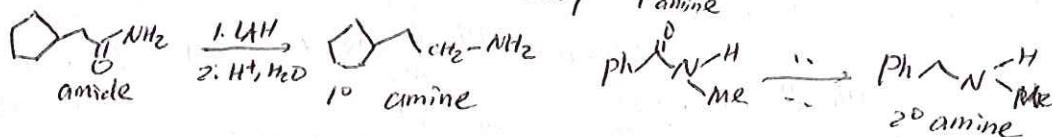
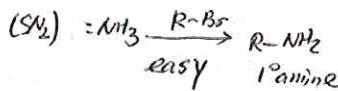
ester  ~~$\text{NaBH}_4$~~



room temp  
same outcome  
w/ LAH

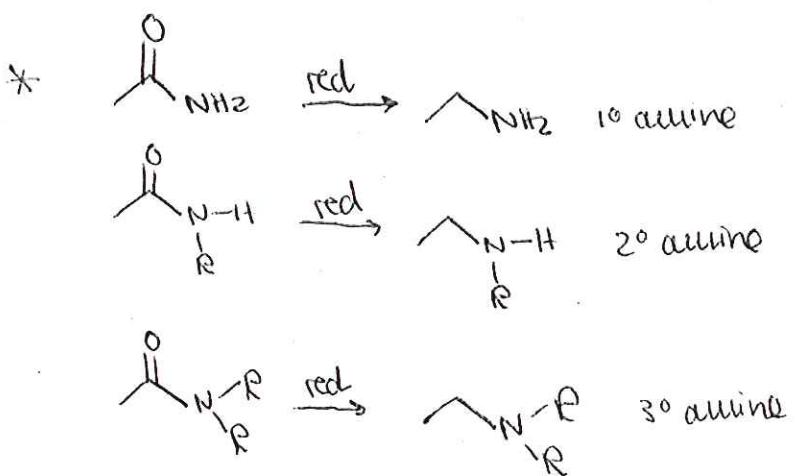
### C. Amides (no mechanism needed)

With LAH reduced to 1-3° amine.

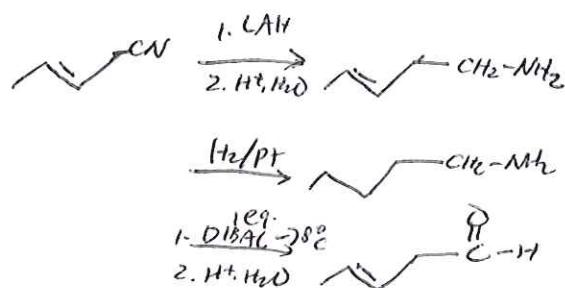
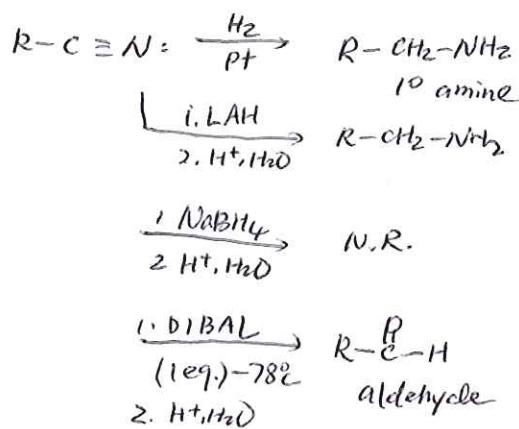


## Reduction Reactions

reducing agent Substrate	H <sub>2</sub> /Pt or Pd or Ni	H <sub>2</sub> /Rh	1. NaBH <sub>4</sub> 2. H <sup>+</sup> , H <sub>2</sub> O	1. LiAlH <sub>4</sub> 2. H <sup>+</sup> , H <sub>2</sub> O	1. DIBAL, 180° -78°C 2. H <sup>+</sup> , H <sub>2</sub> O	1. DIBAL, excess room temp. 2. H <sup>+</sup> , H <sub>2</sub> O
Alkene $\text{C}=\text{C}\text{C}$	✓	✓	X	X	X	X
Aldehyde $\text{R}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\text{H}$	✓	X	✓	✓	✓	✓
Ketone $\text{R}-\overset{\text{O}}{\underset{\text{H}}{\text{C}}}-\text{R}$	✓	X	✓	✓	✓	✓
Carb. acid / Ester	X	X	X	✓	✓	✓
R-C(=O)-NR <sub>2</sub>	X	X	X	✓ X 1° amine 2° amine 3° amine	✓ aldehyde	✓ X 1° amine 2° amine 3° amine
nitrile R-C≡N	✓	X	X	✓ 1° amine	✓ aldehyde	✓ 1° amine

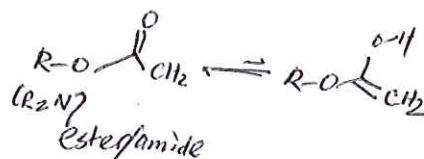
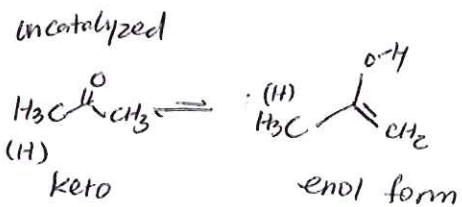
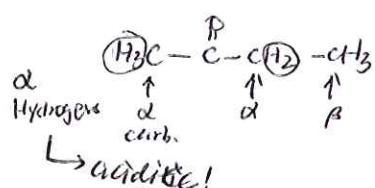


## D. Nitriles

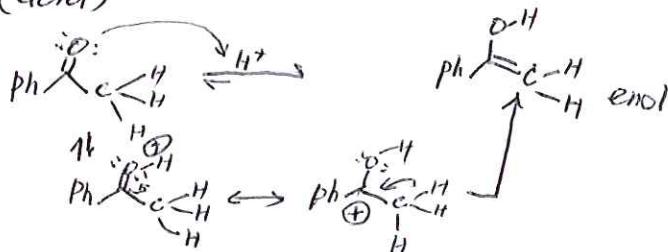


## CH 19 Intro (Ch. 16 stuff)

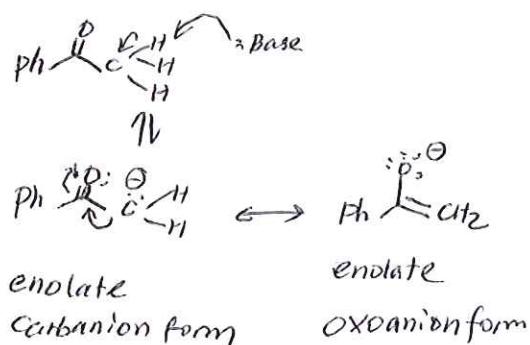
### Acidity of $\alpha$ -carbon hydrogens



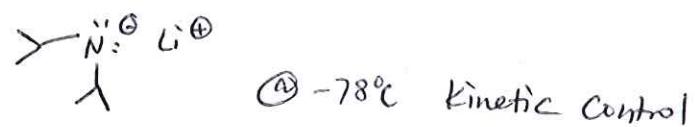
### Cat. (acid)



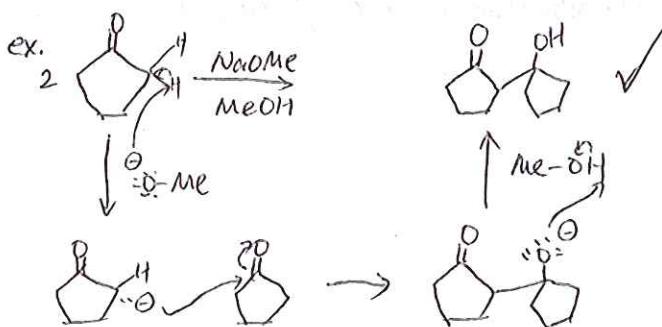
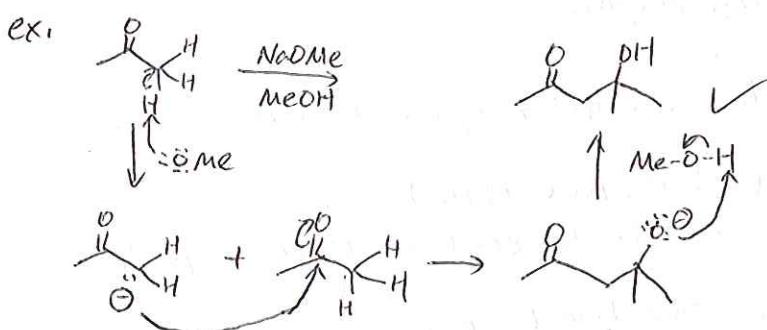
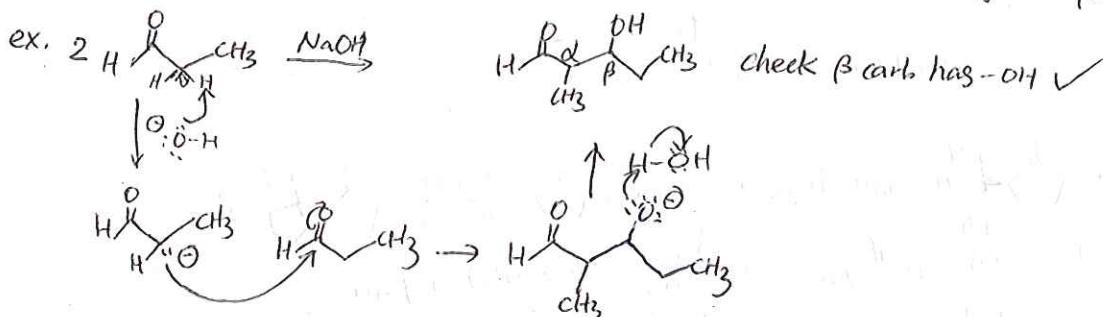
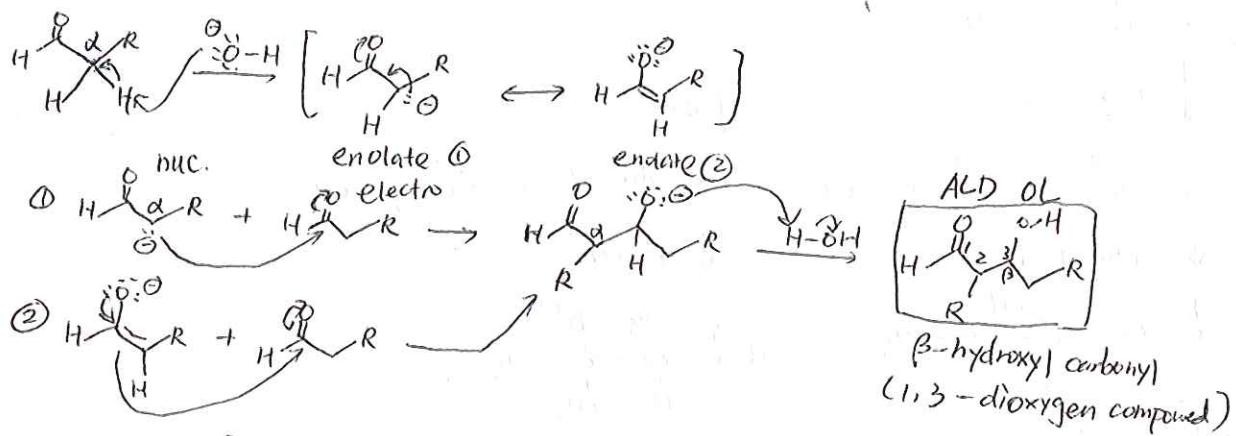
Basic cat more common!



LDA = Lithium Diisopropyl Amide

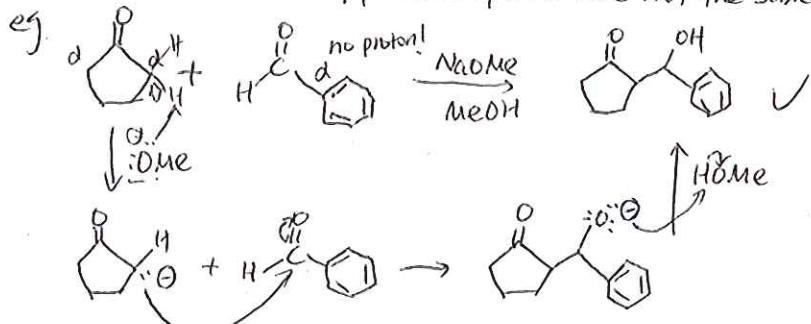


## Aldol Reaction



### Crossed/Mixed Aldol Reactions

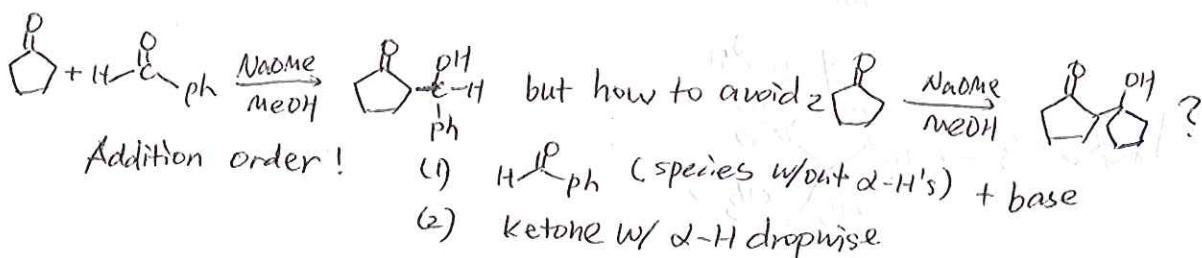
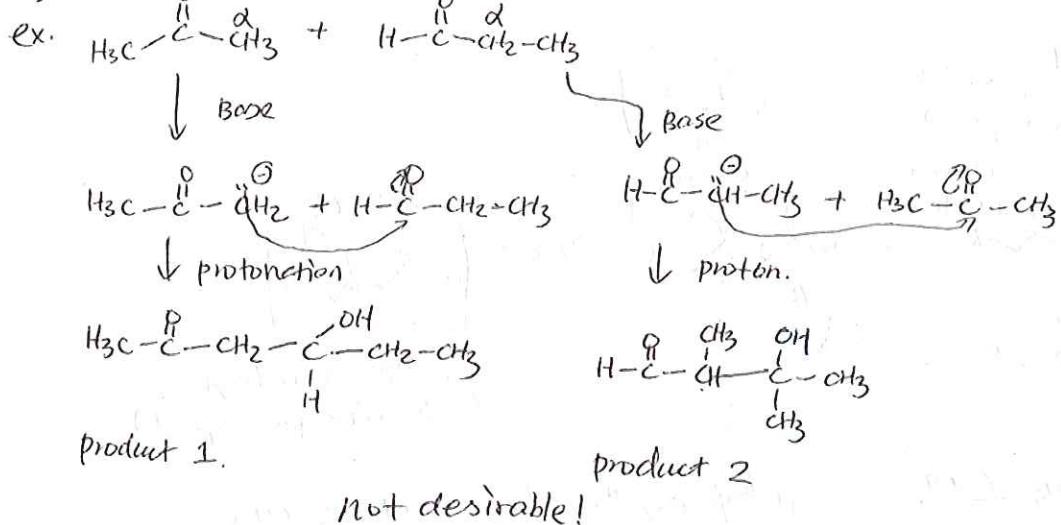
enolate & carbonyl electrophile are not the same molecule.



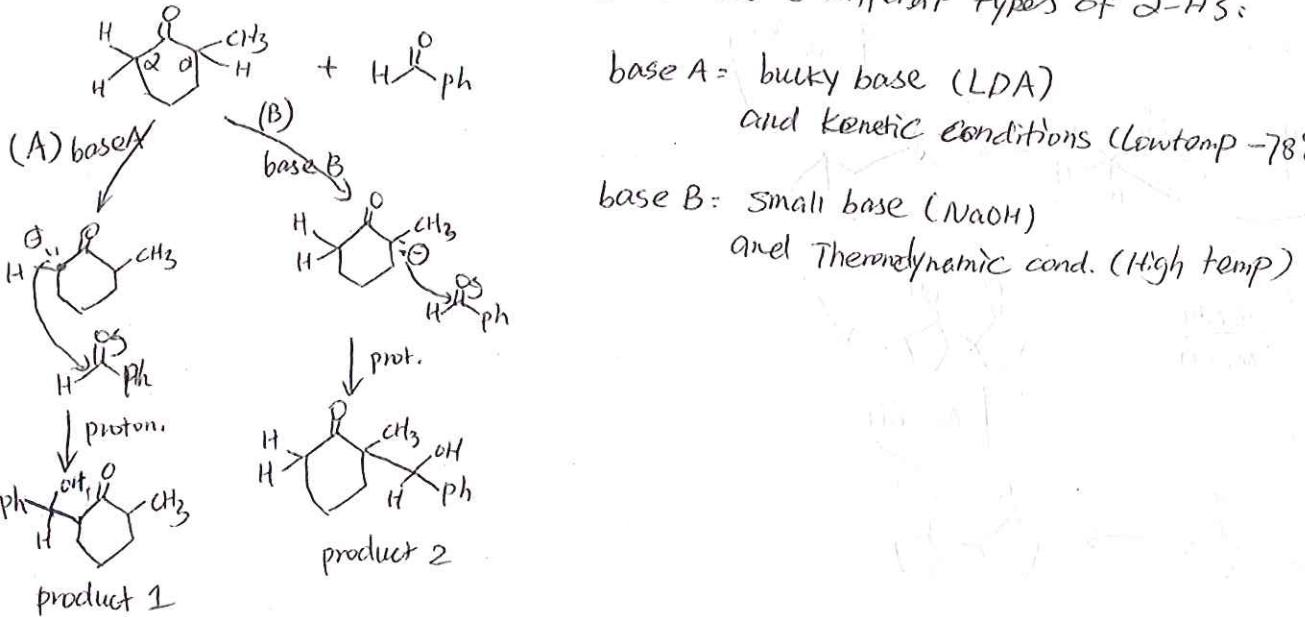
one of these reagents should NOT have  $\alpha$ -hydrogens to avoid mixture forming.

Mix

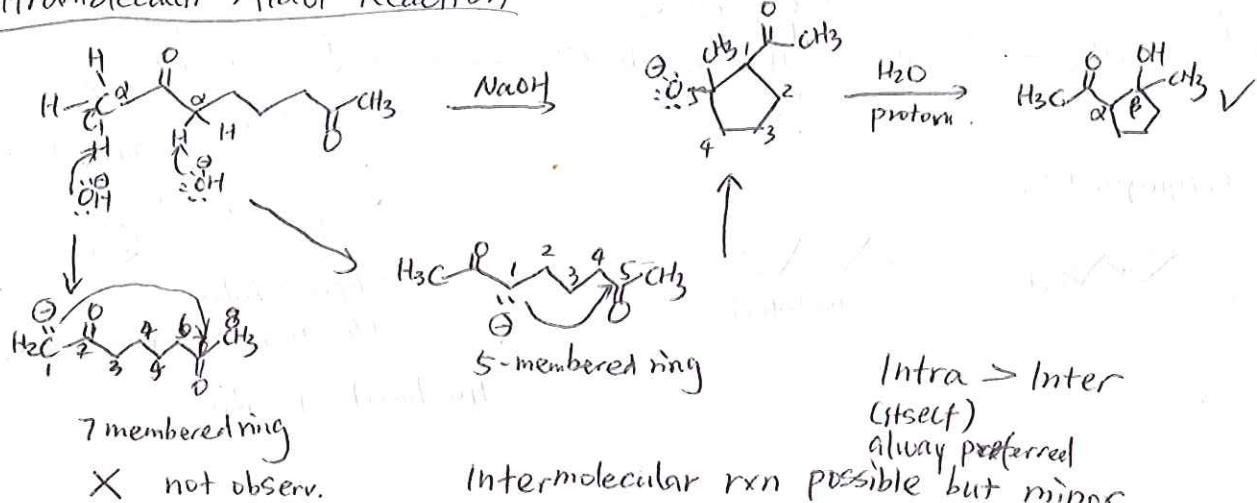
If not,



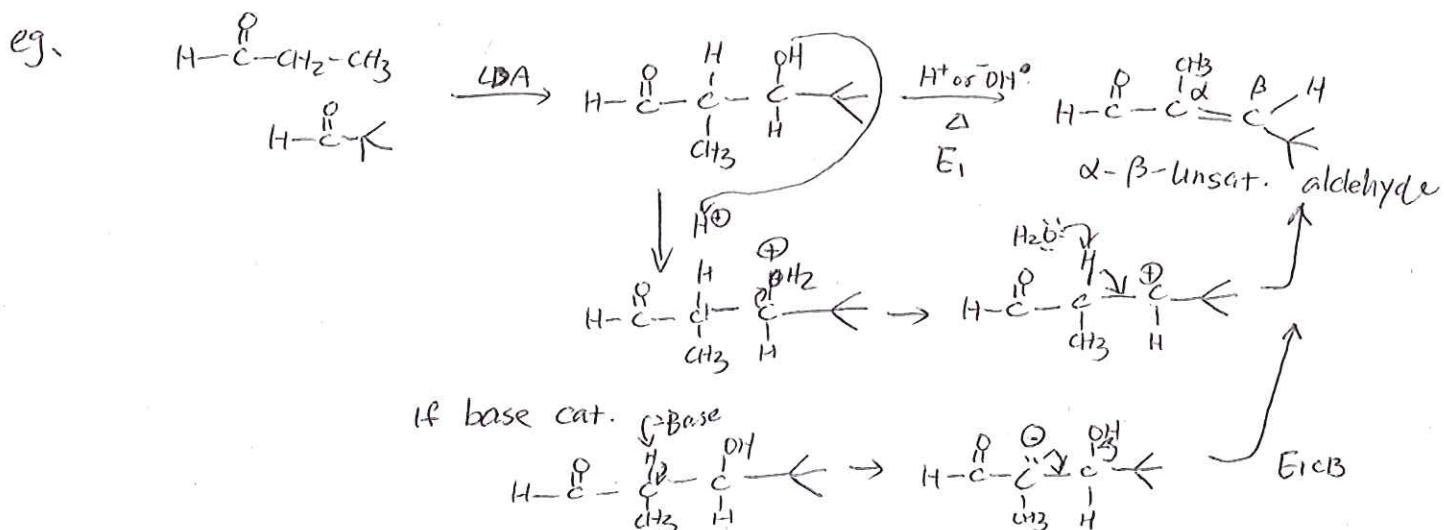
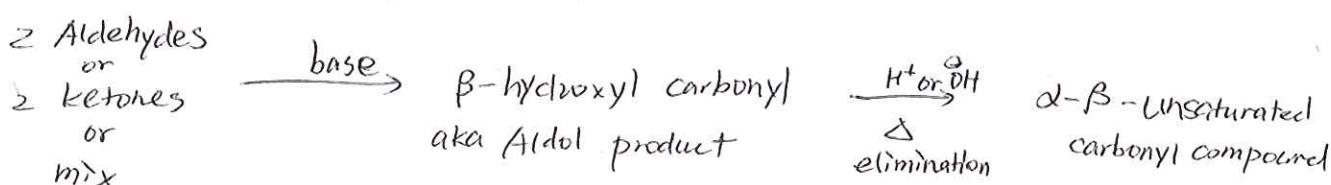
- Mix also occurs if one of reagents has 2 different types of  $\alpha$ -H's:



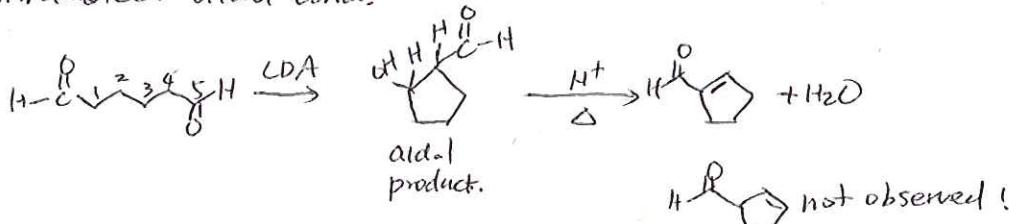
## Intramolecular Aldol Reaction



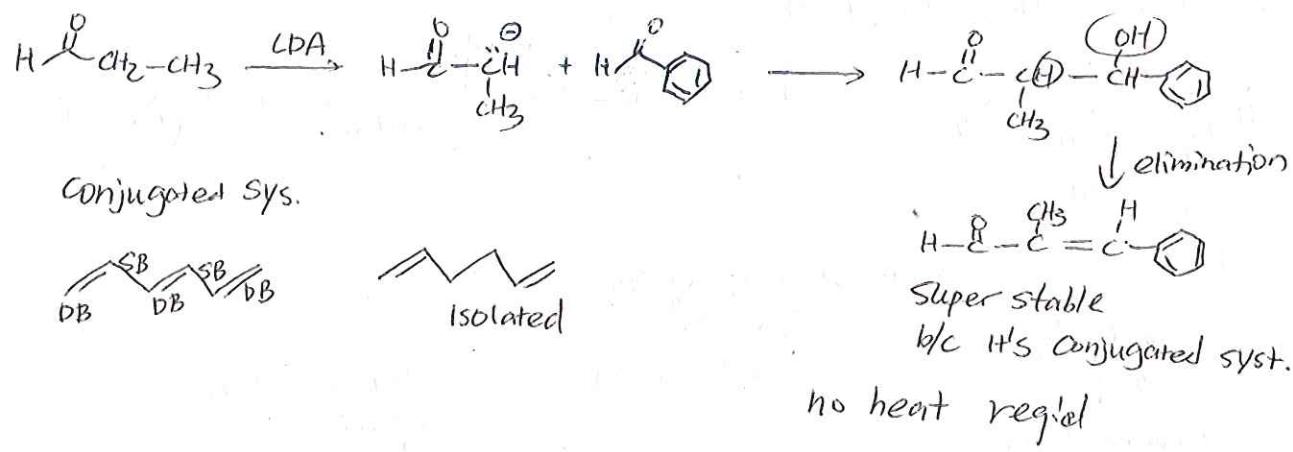
## Aldol Condensation

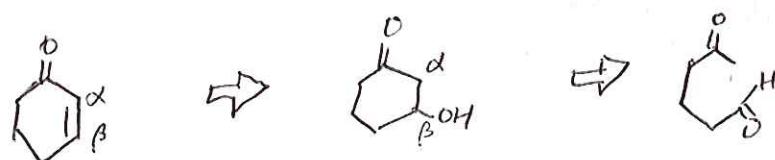
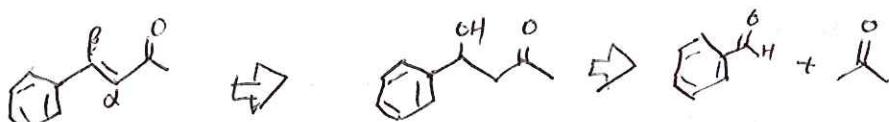


- Intramolec. aldol cond.

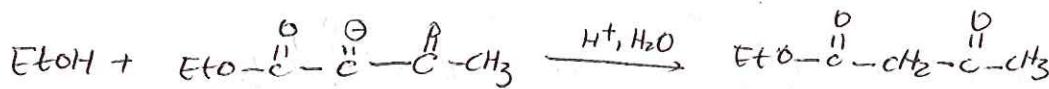
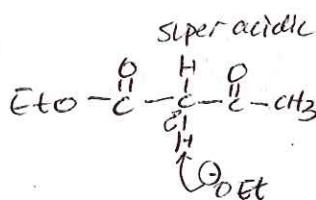
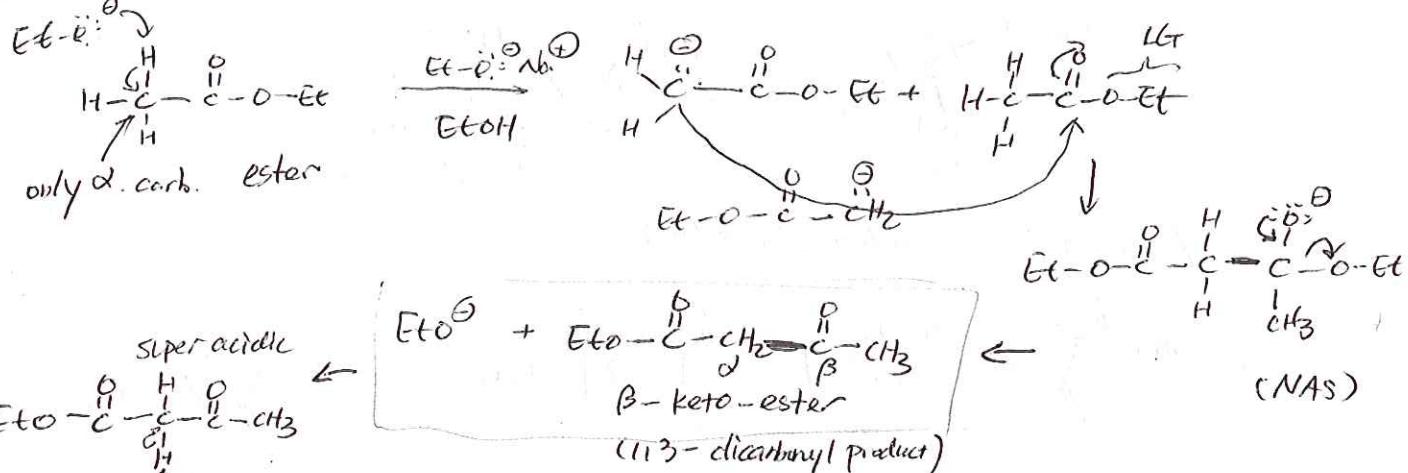


no heat is required if the cond product has a Double Bond Conjugated to a benzene ring

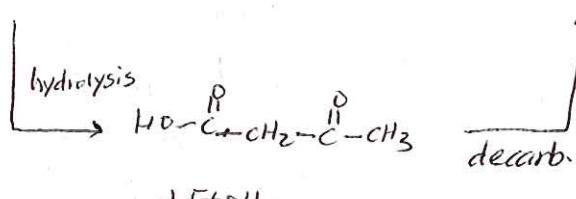




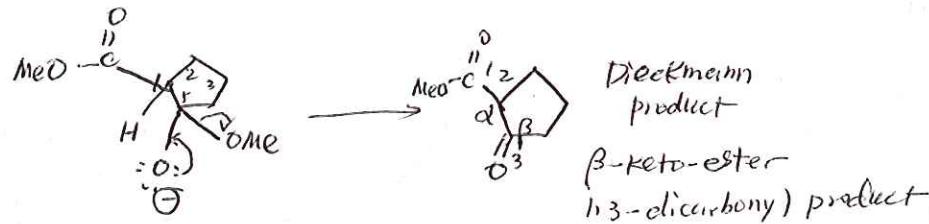
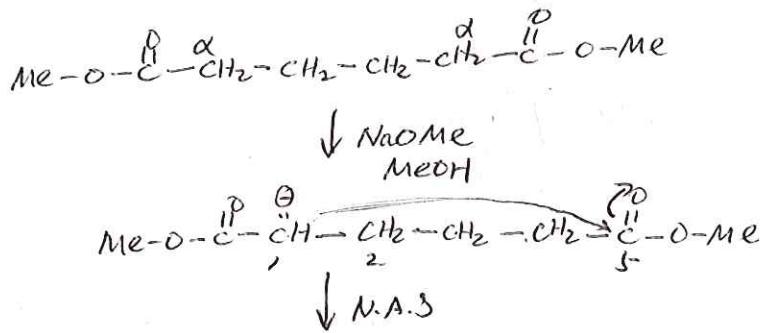
(3a) Claisen Condensation



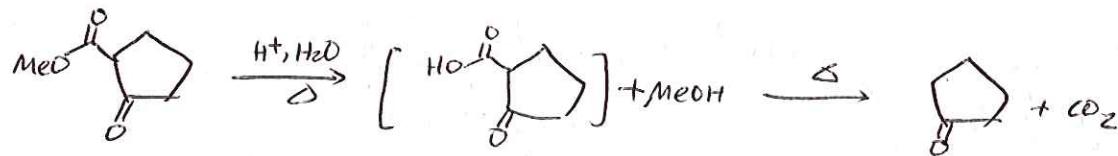
w/ claisen product...



(3b) Dieckmann = Intramol. Claisen

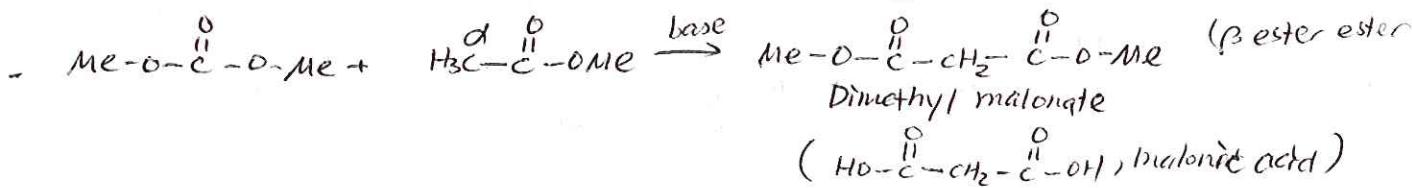
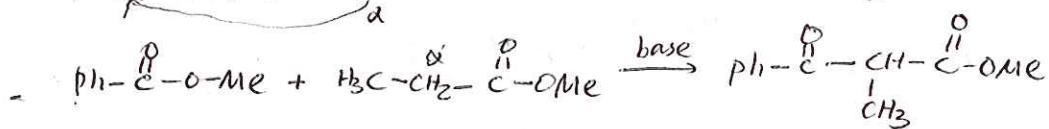
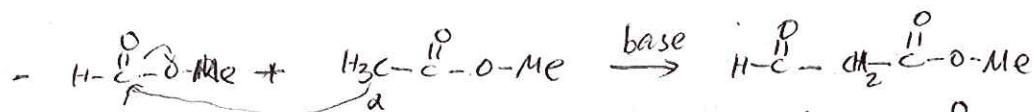
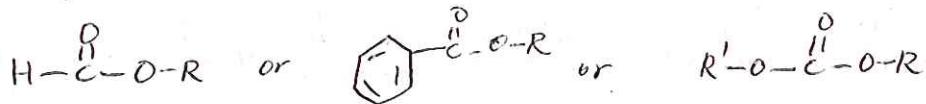


w/ dieckmann condens. product. -

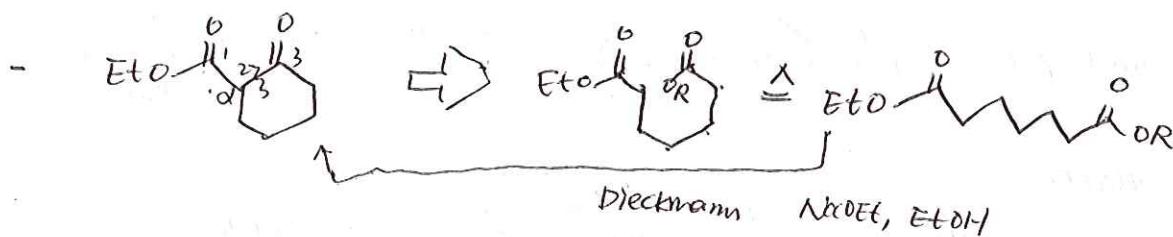
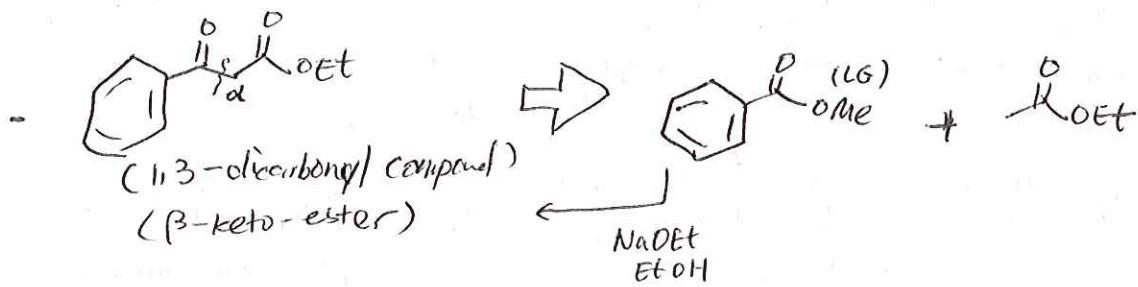


(2c) Crossed Claisen Condens.

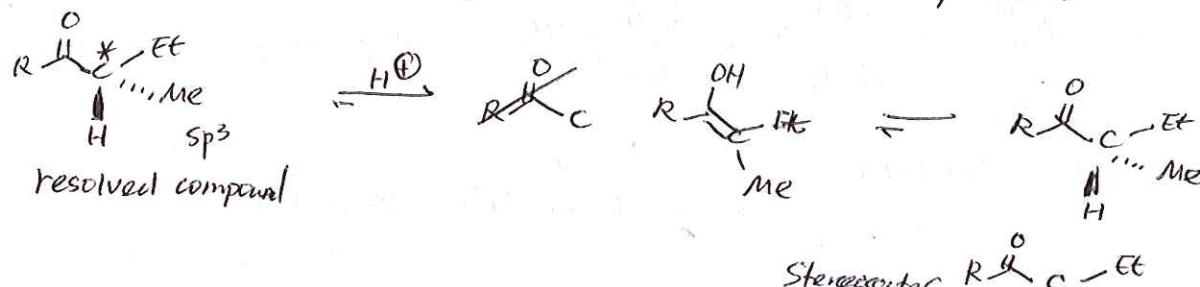
only synthetically useful when one of the ester does not have  $\alpha$ -H's.



Retrosyn.

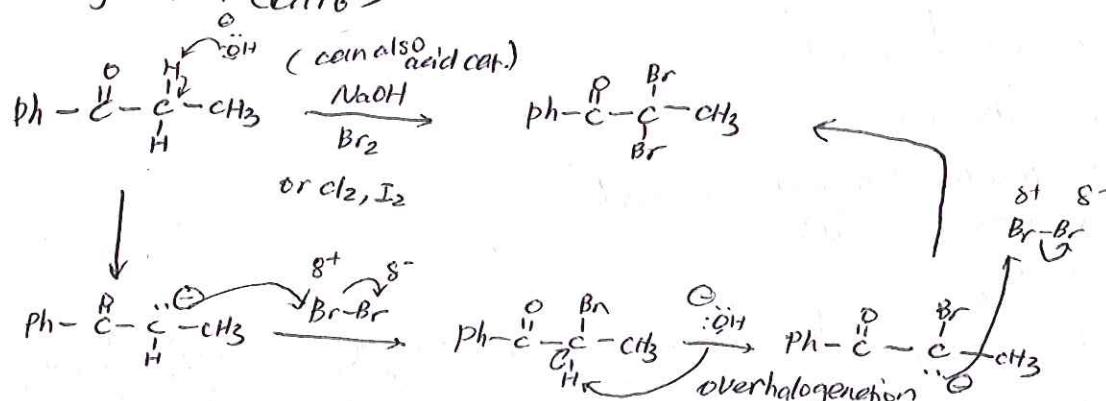


(4) Racemization (ch 16) only when  $\alpha$ -C is a chirality center



Stereocenter gene.  
 $\xrightarrow{\text{S}^+$  }  $\xleftarrow{\text{Br}^-}$  50/50 mix

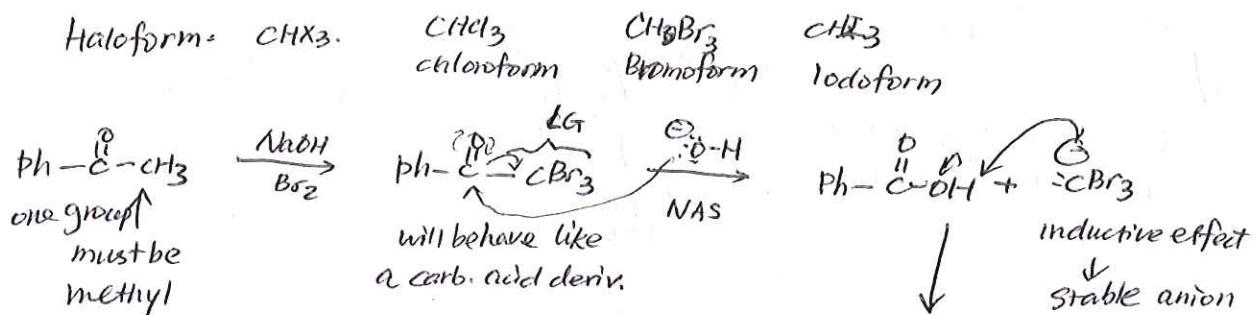
(5)  $\alpha$ -halogenation (ch 16)



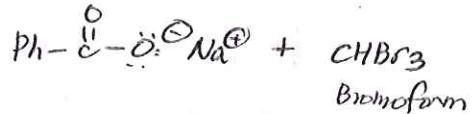
acid cat.  $\rightarrow$  only adds 1 eq halogen. may occur  
 base  $\rightarrow$  overhalog. overhalog. does not occur

### (6) Haloform rxn (Ketone)

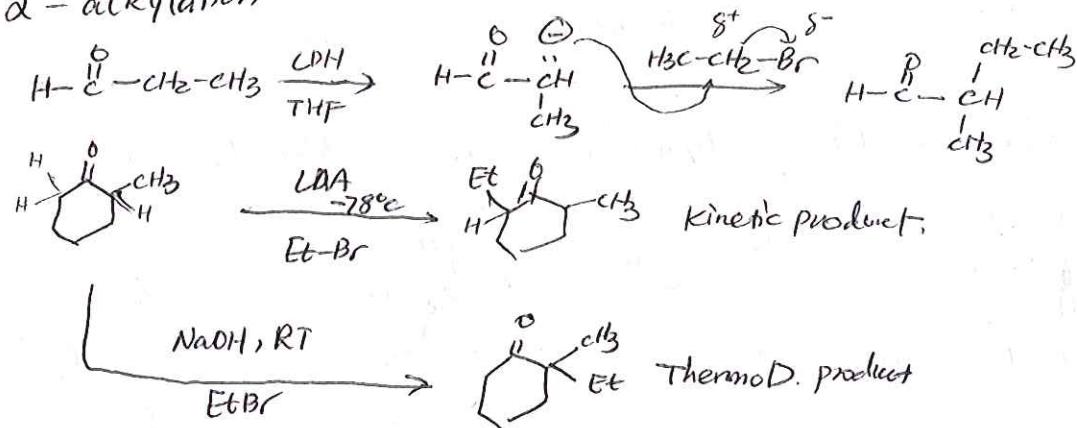
only works for methyl ketone



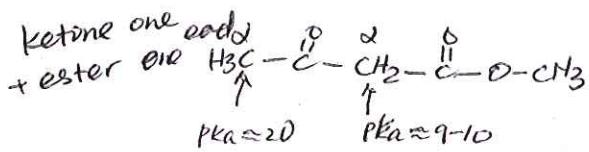
(Industrial synthesis of bromochloroform)



### (7) $\alpha$ -alkylation

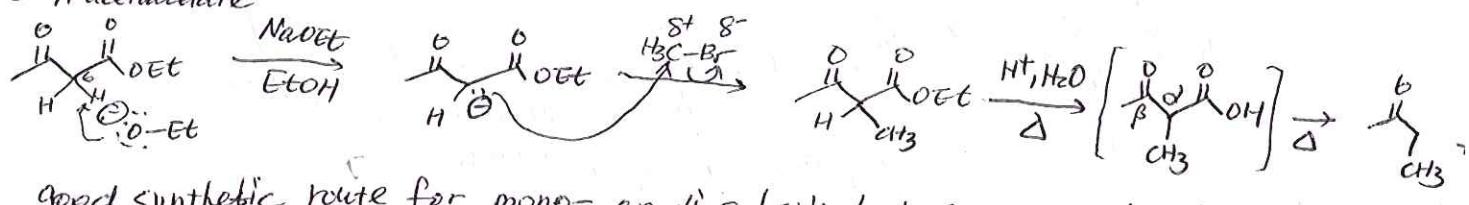


### (8) Acetoacetic ester synthesis (AAES)

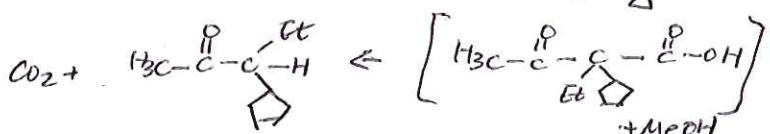
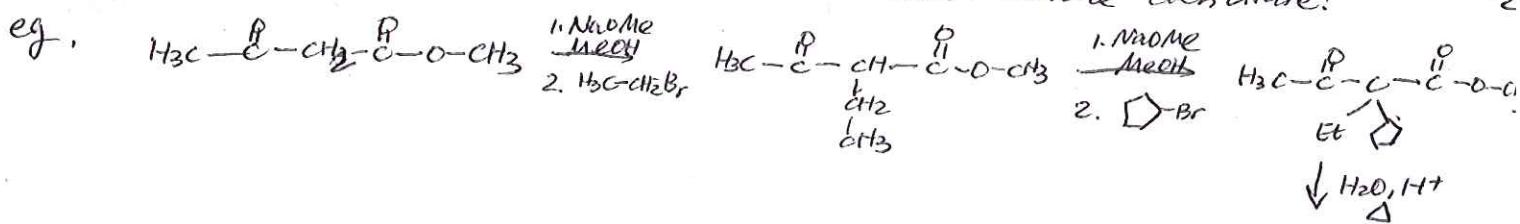


$\alpha'$ -H's located between two carbonyl are exceptionally acidic!

ethyl acetoacetate



good synthetic route for mono- or di-substituted acetone dianion!



product of AAES

for  
(retrosyn.)

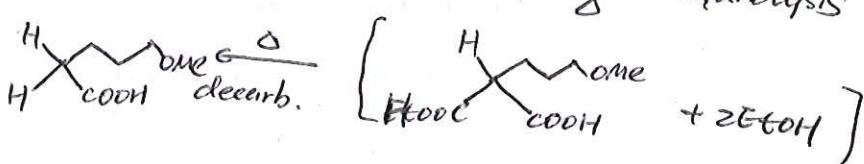
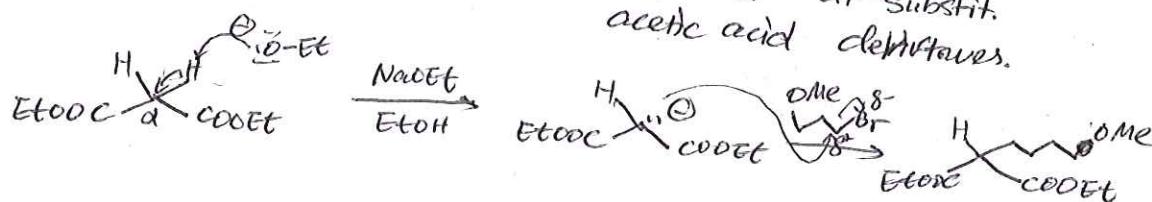


(9) Malonic ester Syn.

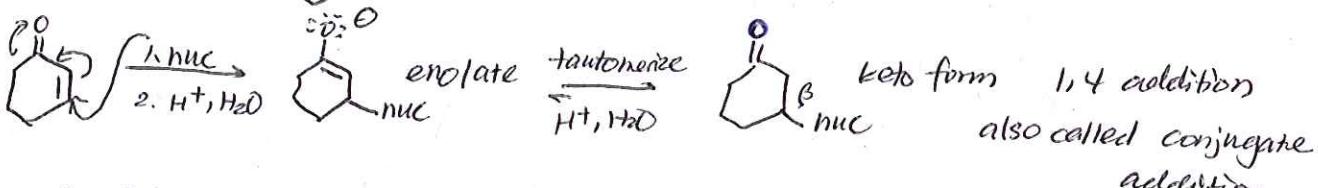
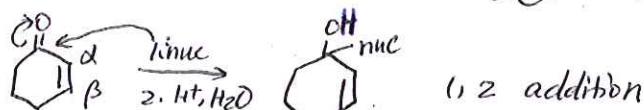
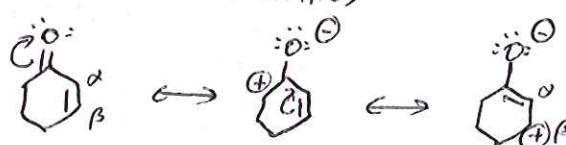
ester  
two ends



mono- or di-substit.  
acetic acid derivatives.



(10) Michaeli Addition (Intro)



Some reagents prefer 1,4 addition

nuc/reagents

mode

hard nuc {  $\text{R}-\text{Li}^\ominus$   
(strong)  $\text{R}-\text{Mg}-\text{X}$

1,2 (unless steric hindrance)



soft nuc  $\text{R}_2\text{CuLi}$

1,4

$\text{R}-\text{C}\equiv\text{C}^\ominus \text{Na}^\oplus$

1,4

$\text{Na}^\oplus=\text{C}\equiv\text{N}$

1,4

enolate anion

1,4

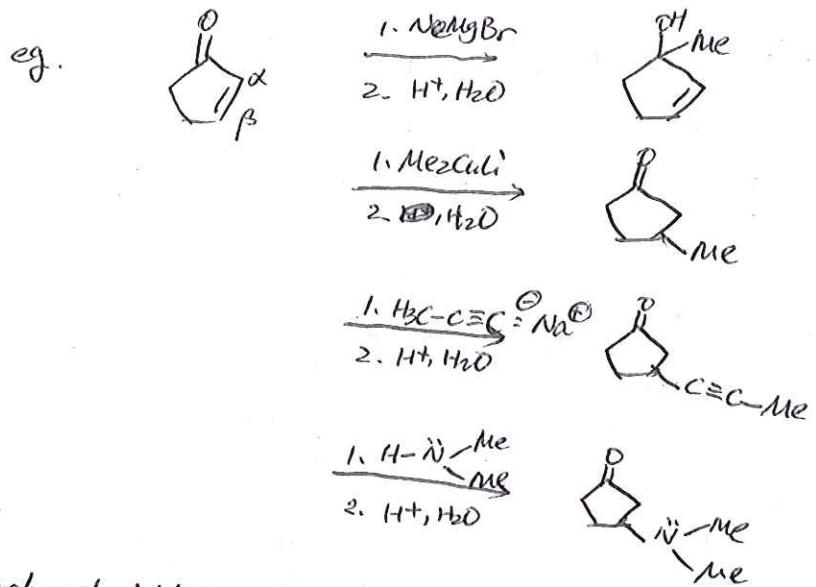
Nitrogen nuc  
(e.g.  $\text{Me}_2\text{NH}$ )

1,4

everything else

1,4

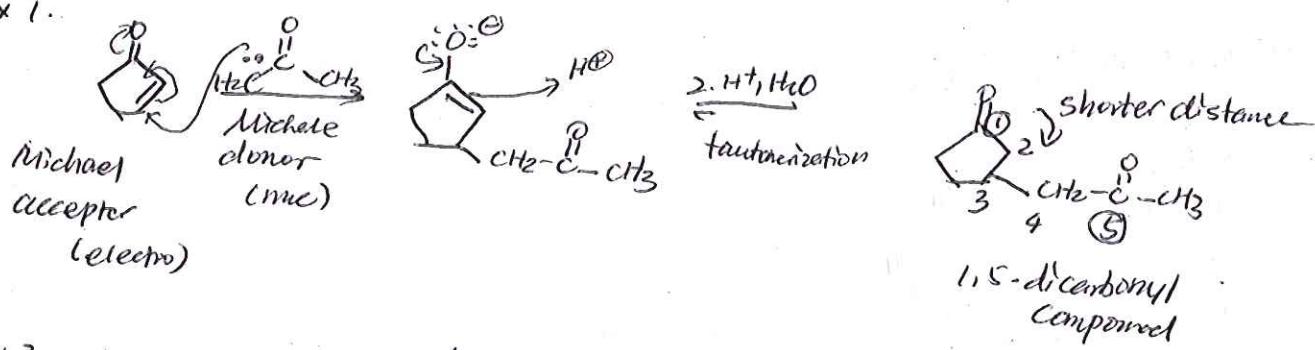
co



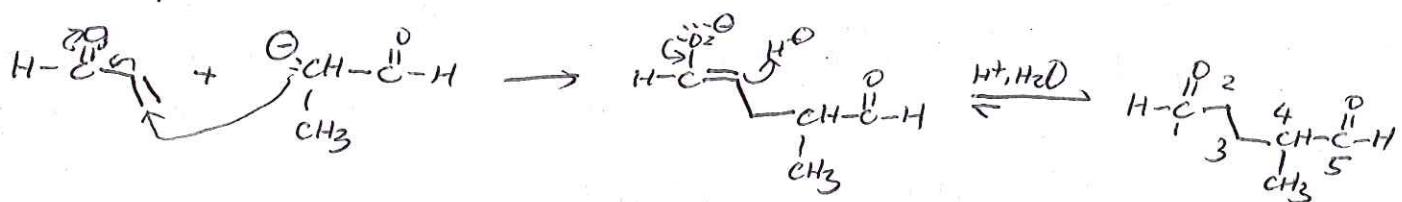
### Michael Addition (rxn)

When the nucleophile that attacks the  $\beta$  carbon of a  $\alpha,\beta$ -unsaturated ketone or aldehyde or ester, is an enolate anion  $\Rightarrow$  Michael rxn (addition)

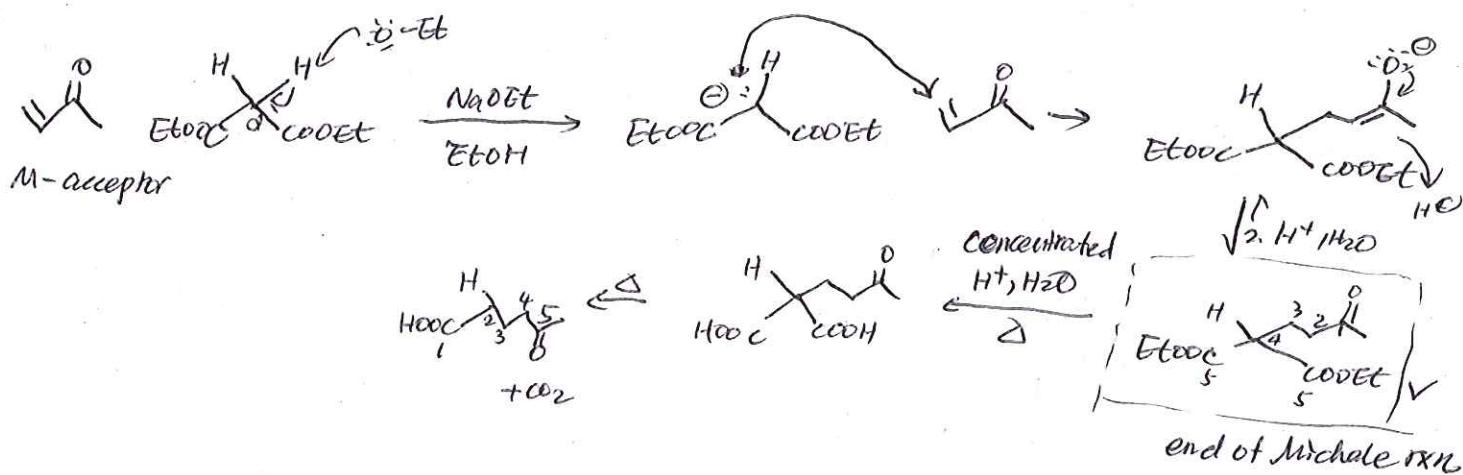
Ex 1.



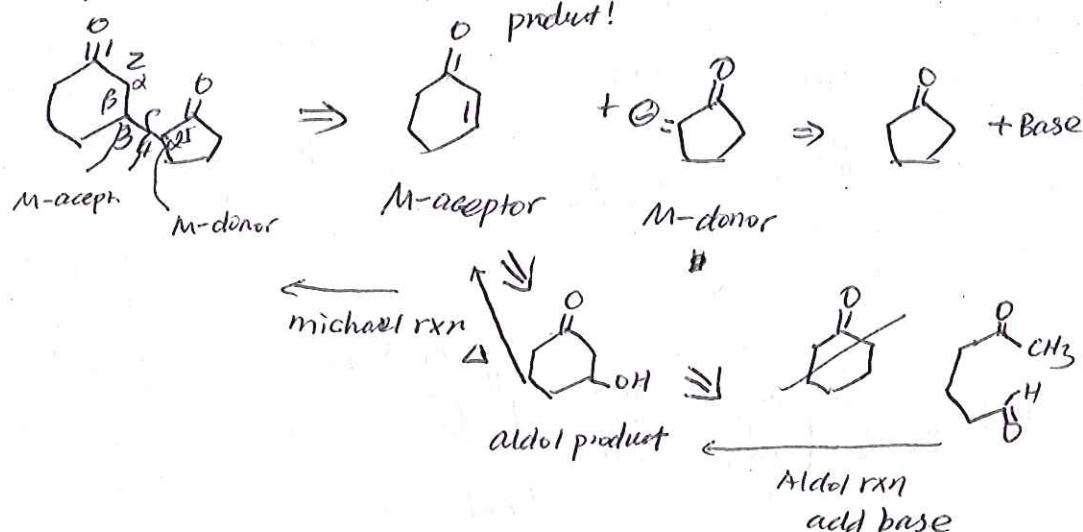
Ex 2 M-acceptor      M-donor



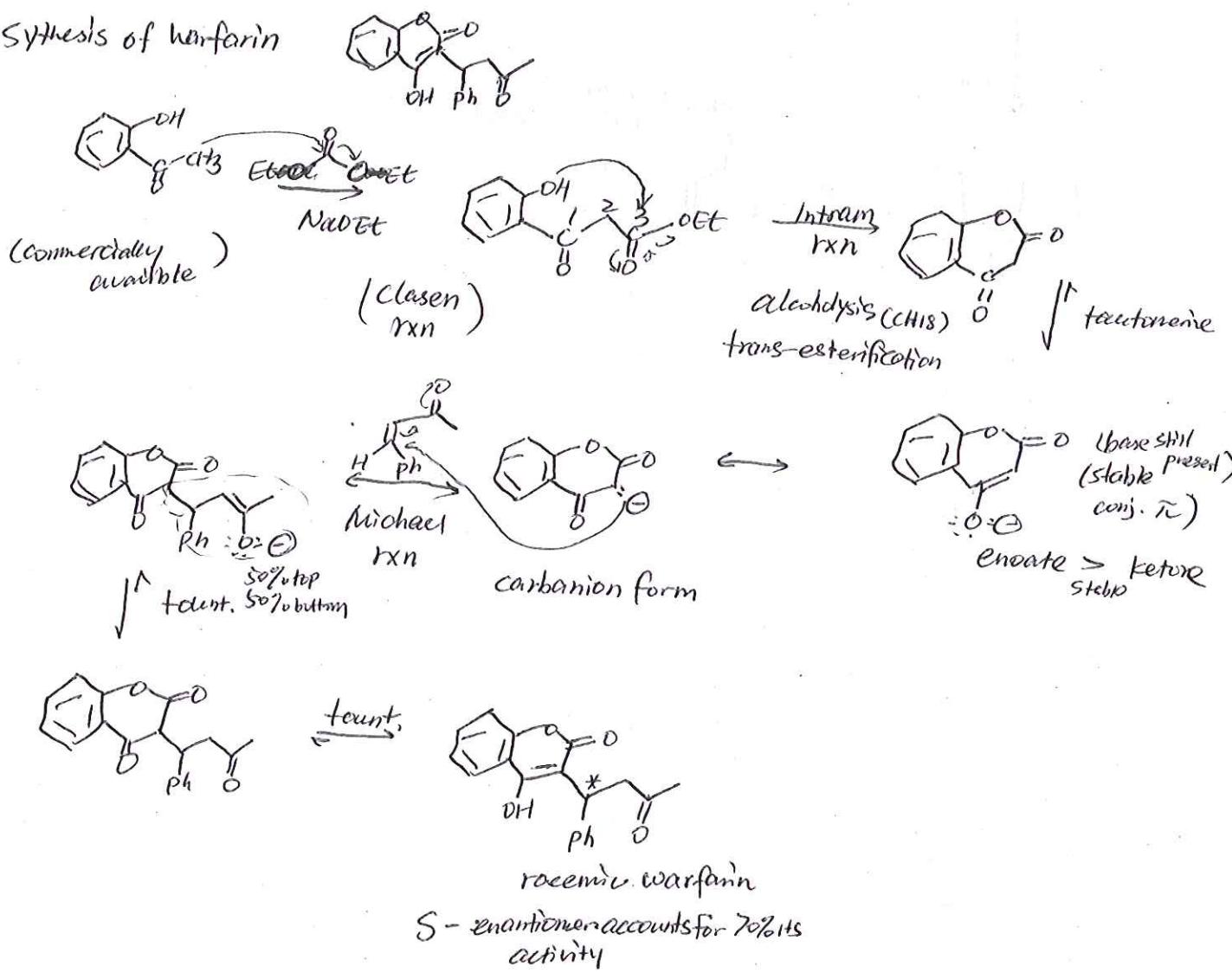
Ex 3



## Retrosynthetic

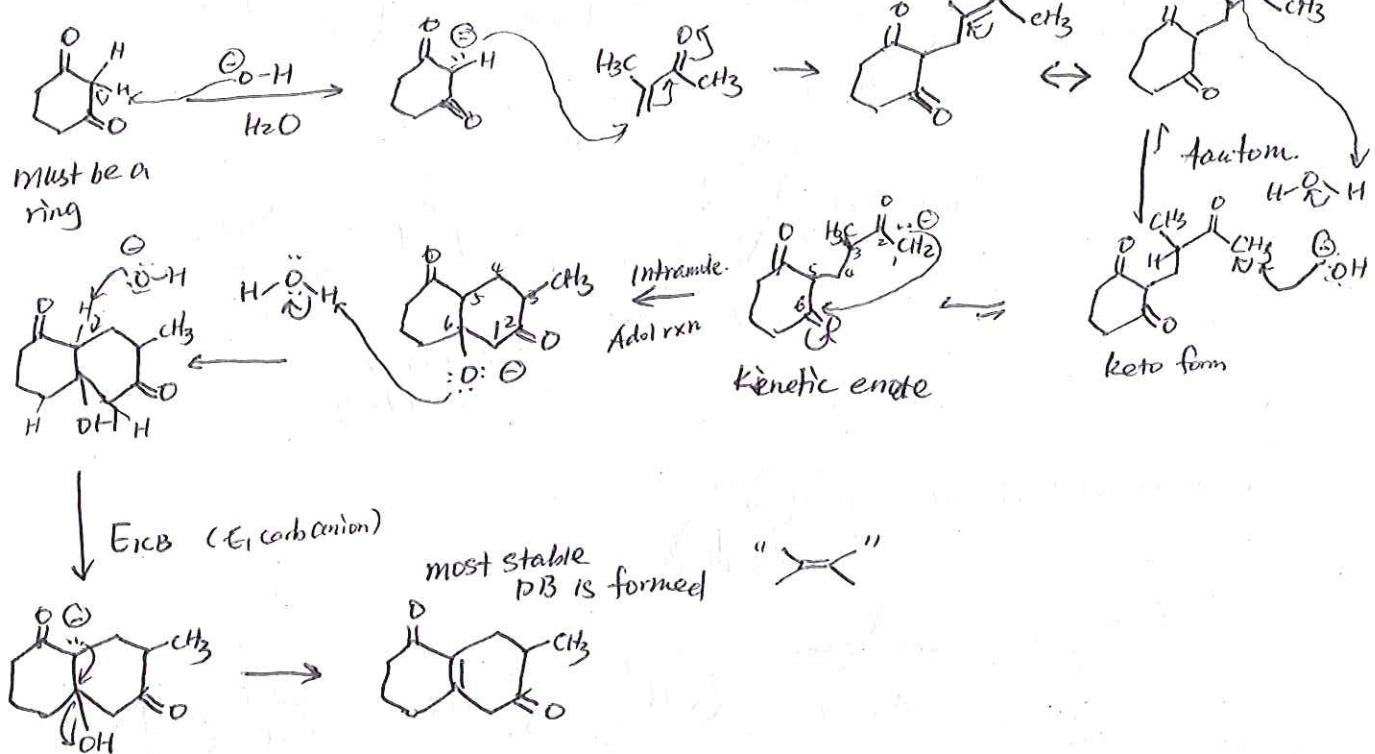


## Synthesis of warfarin



II) Robinson Annulation  $\xrightarrow{\text{2 rings fixed each other}}$

Tandem rxn: Michael rxn  $\rightarrow$  Aldol rxn  $\rightarrow$  Aldon cond. rxn



## Chapter 20 – Dienes, conj syst., pericyclic reactions

Dienes - two carbon-carbon double bonds  $c=c$

3 classes ①  $\text{H}_2\text{C} = \overset{\text{sp}^2}{\underset{\text{very unstable}}{\text{C}}} = \overset{\text{sp}^2}{\underset{\text{reactive}}{\text{C}}} < \overset{\text{H}}{\text{C}_2\sim\text{CH}_3}$  Cumulated Diene  
 (allene)

(2)  $\text{H}_2\text{C}=\text{CH}-\text{CH}_3-\text{CH}=\text{CH}_2$   
 $\text{sp}^2 \quad \text{sp}^2 \quad \text{sp}^3 \quad \text{sp}^2 \quad \text{sp}^2$

= 

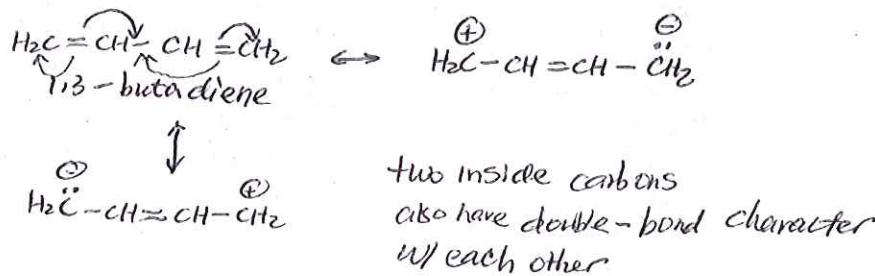


*Isolated Diene  
at least 1 sp<sup>3</sup> carbon  
between sp<sup>2</sup> carbons.*

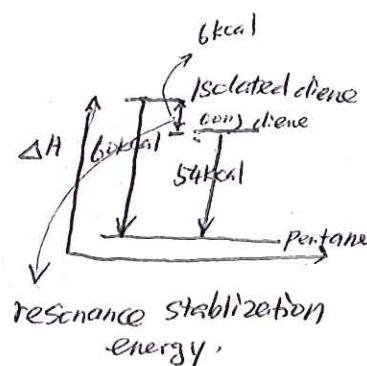
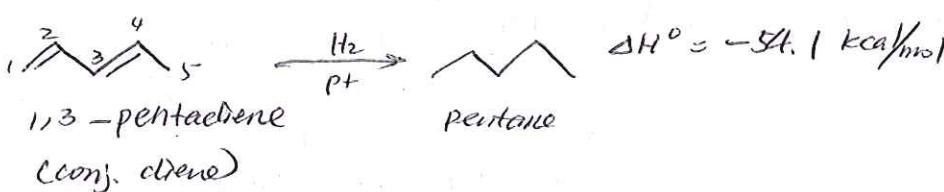
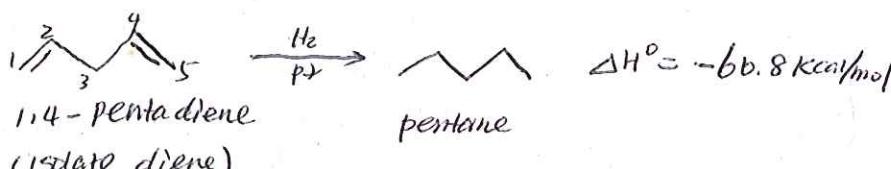
③  $\text{H}_2\text{C}=\text{CH}-\text{CH}=\text{CH}-\text{CH}_3$       Conjugated Diene  
                 ↑↑  
                 DBs are separated by exactly one single bond

*conjugated* 

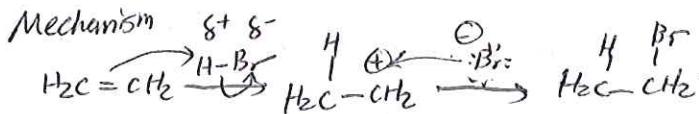
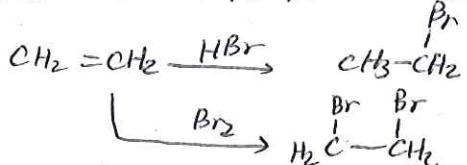
## Resonance



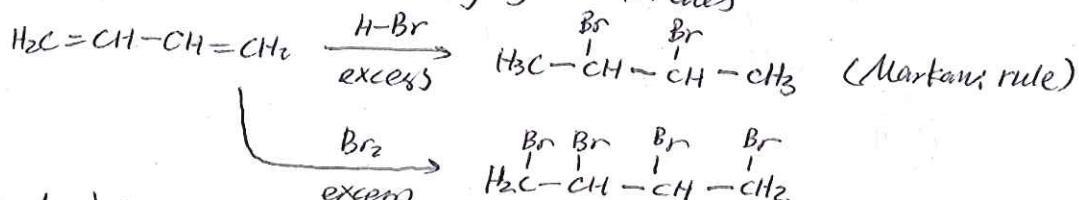
## Conjugated vs isolated Dienes



## Review: addition to Alkene (Orgo 1)

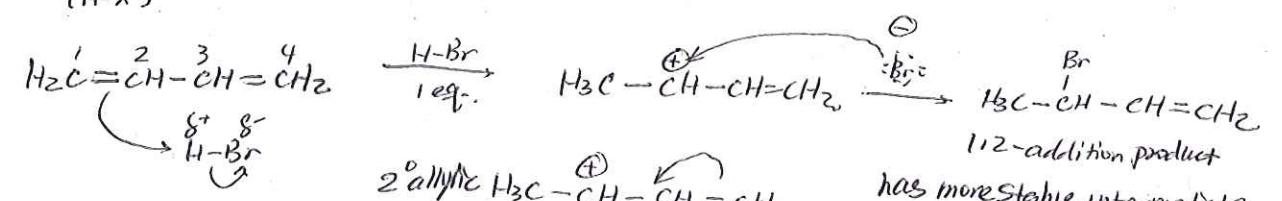


## Electrophilic Addition to Conjugated Dienes



## Mechanism

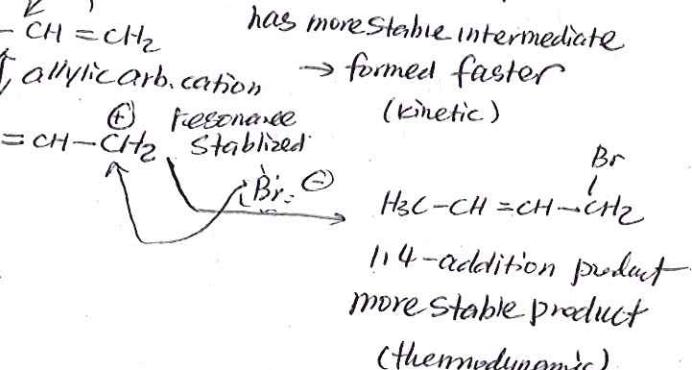
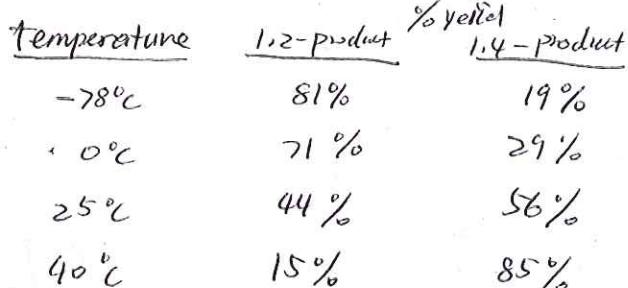
When only leg. present  
(H-X)



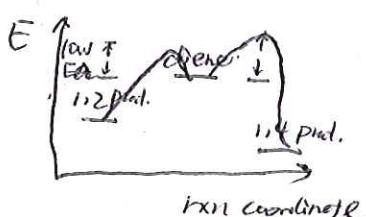
$\text{④} \begin{array}{c} \diagup \\ \diagdown \end{array} \approx \begin{array}{c} \diagdown \\ \diagup \end{array} \text{⑤}$

1° allylic      3° car

Superstable



1,4-product, more stable, formed @ High Temp  
⇒ TD product

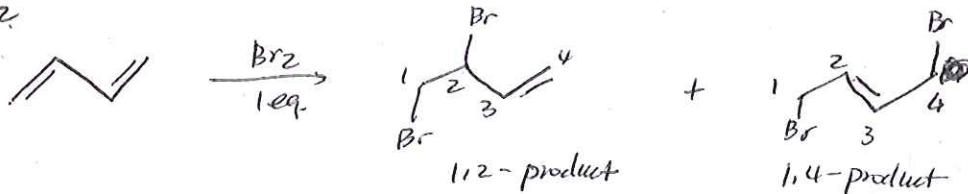


1) 2-Product, formed faster, stable intermediate,  
     formed low Temp  $\Rightarrow$  kinetic product  
 In this case (depends on diene)  
     ONLY

Note = 1.4 Product is not always more stable!

more stable means more highly substituted  $C=C$   
 a terminal alkene will be less stable than internal  
 formation of conjugated diene  $\rightarrow \uparrow$  stable alkene

Eg 2.

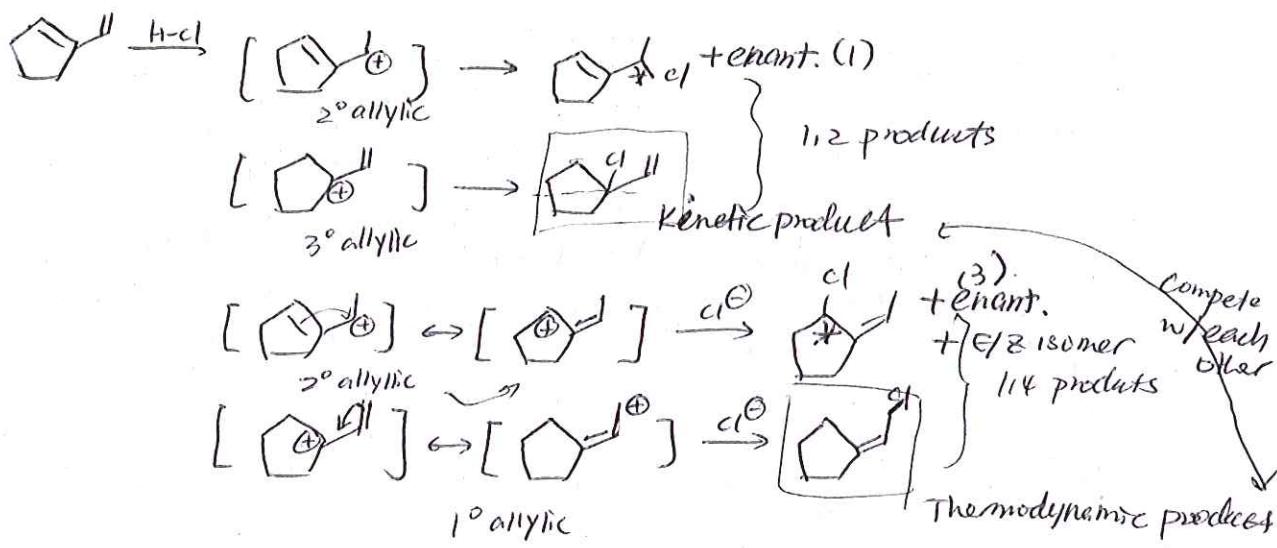


Question:



What it include stereochem?

Which is TD? Which is kinetic product?



total product    4 product + 4 enant. = 8 products    Stable?    # of substituents  
 size of subst.

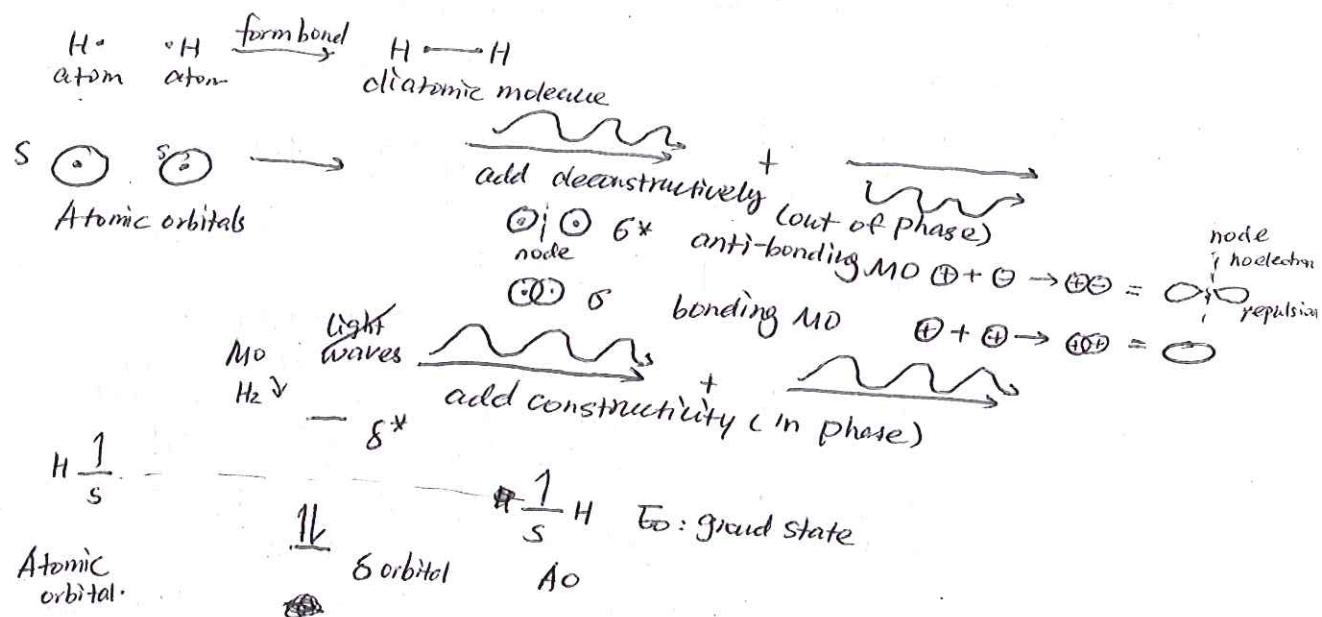
# orbitals review

see pdf.

## Molecular Orbitals (MOs)

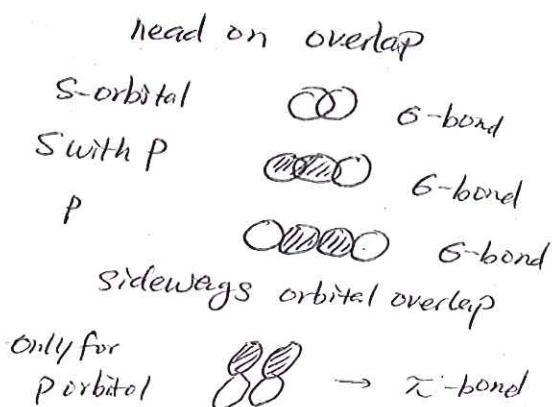
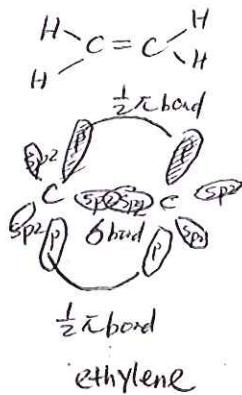
orbitals are mathematical functions describing the wave-like properties of an  $e^-$  in an atom or a molecule.

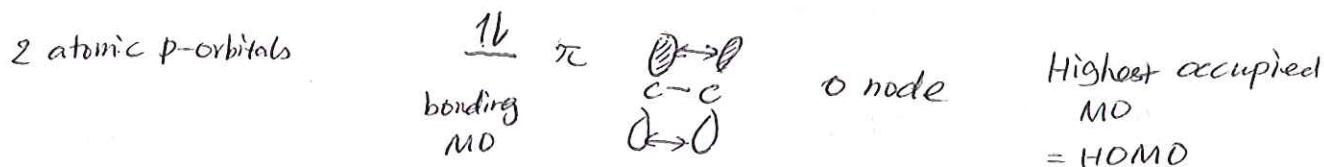
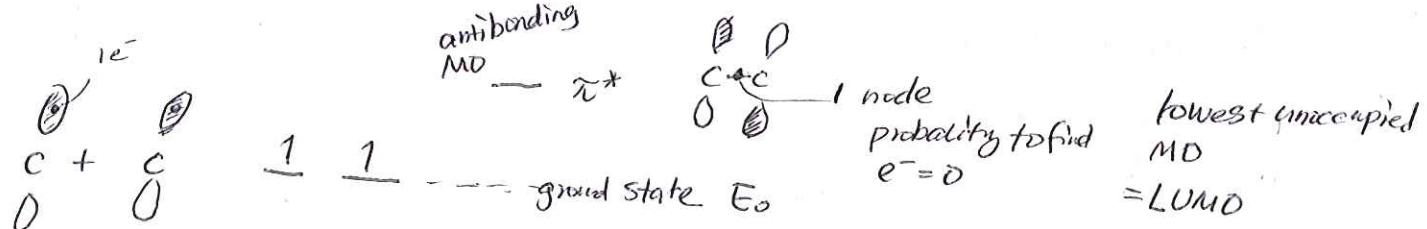
MOs:



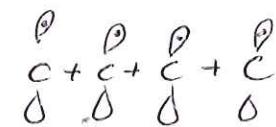
When filling orbitals: Pauli Aufbau principle + Hund's rule

## MOs of organic molecules w/ double bonds ( $\pi$ -bonds)

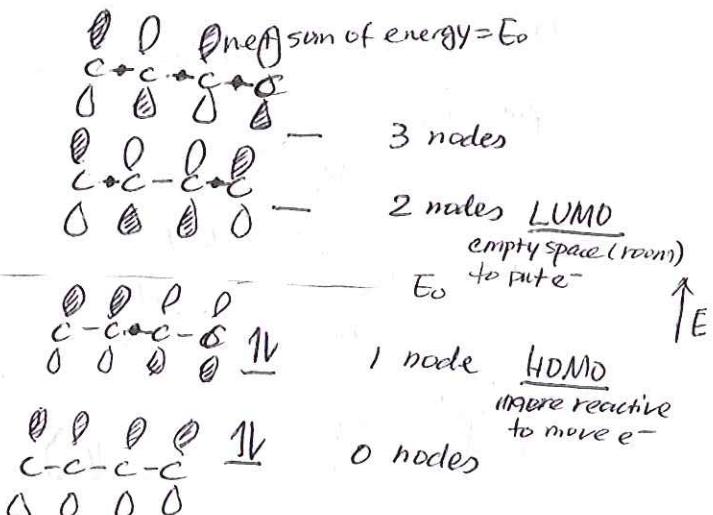




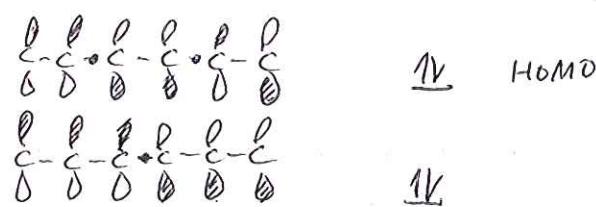
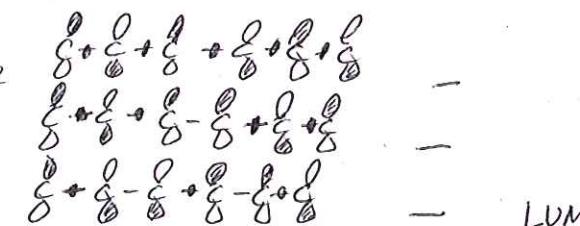
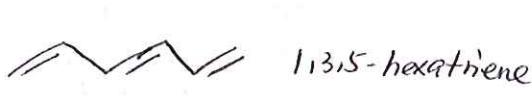
$\text{C-C}$   
 e<sup>-</sup> are able to move freely between the two carbons  
 i.e. delocalized



4 atomic p-orbitals



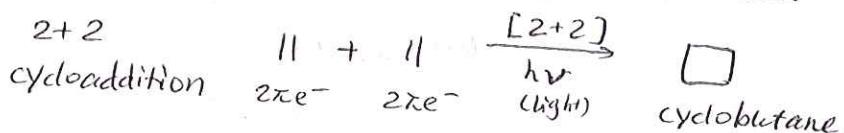
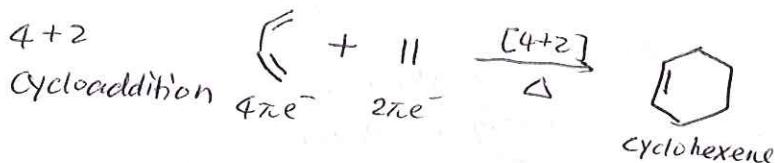
HW



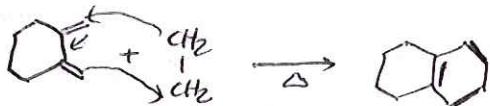
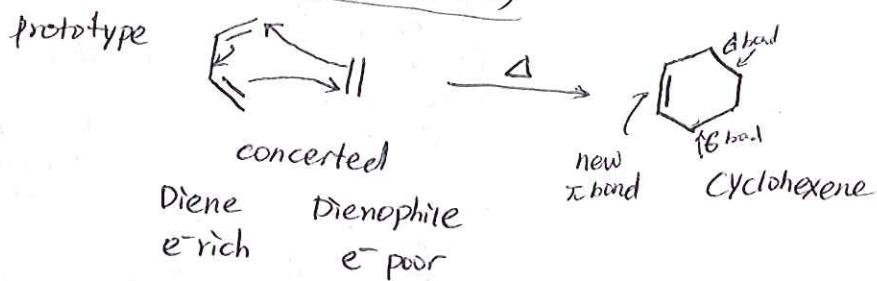
# Pericyclic Reactions

- Cycloadditions
- Sigmatropic rearrangement  
(in advanced orgo)

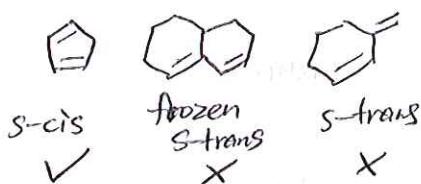
Cycloadditions: 2 types



## Diels-Alder reaction ( $4+2$ )



DA:



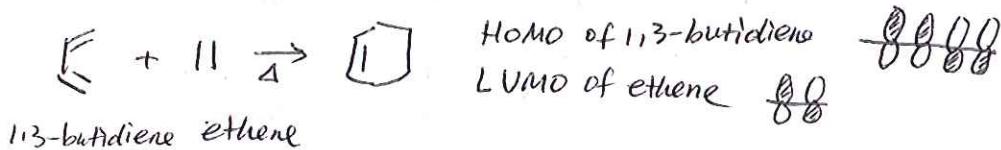
diene must be  $s\text{-cis}$  conformation  
single bond

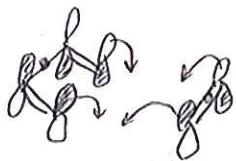


$s\text{-cis}$        $s\text{-trans}$   
different conformation  
for same compound

Single bond can rotate if  
not frozen!

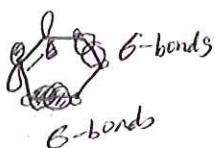
During DA, the HOMO of diene interacts w/ LUMO of dienophile





Con rotatory motion

both moving in the same direction



Substituent Effect that enhances rxn

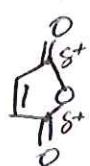
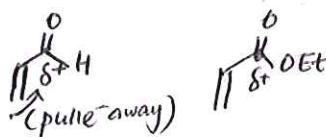
- e<sup>-</sup> donating group (EDG) on diene (e<sup>-</sup> rich)

- alkyl groups (weakly)
- $\text{H}_2\text{O}$
- $\text{NR}_2$  amino
- $\text{O}-\text{R}$  ether

- e<sup>-</sup> withdrawing group (EWG) on dienophile (e<sup>-</sup> poor)

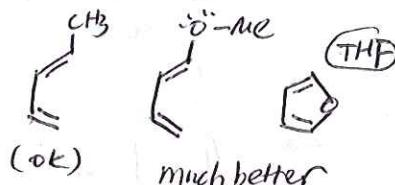
- halogens
- carbonyl group
- nitriles
- nitro group ( $-\text{NO}_2$ )

Nice dienophiles



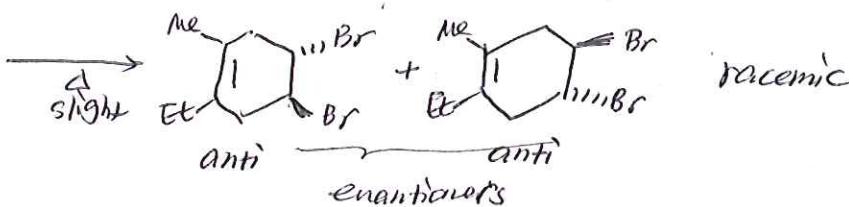
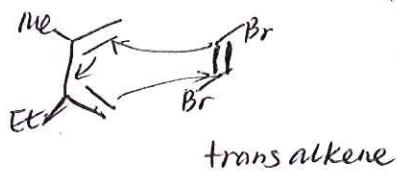
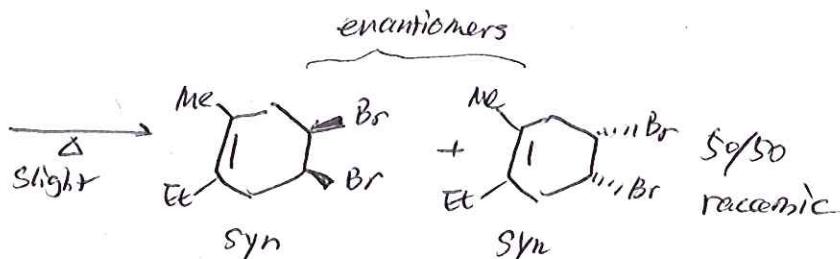
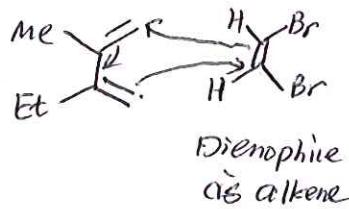
Maleic anhydride

Nice dienes



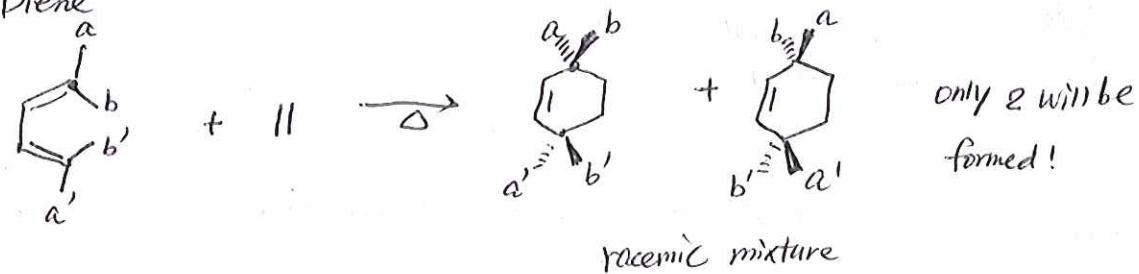
Stereochem

### 1. Dienophile

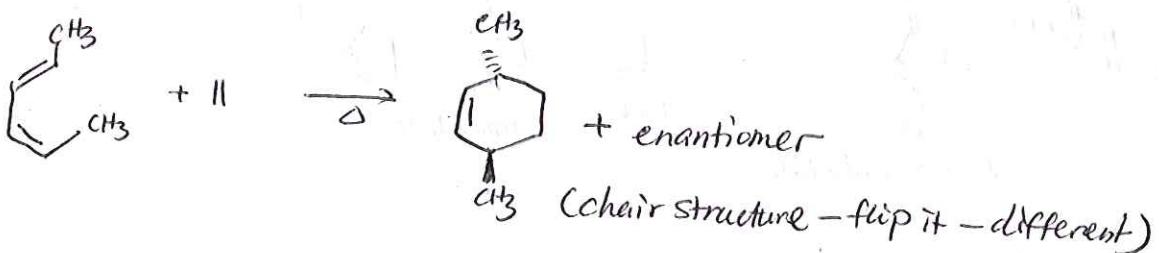
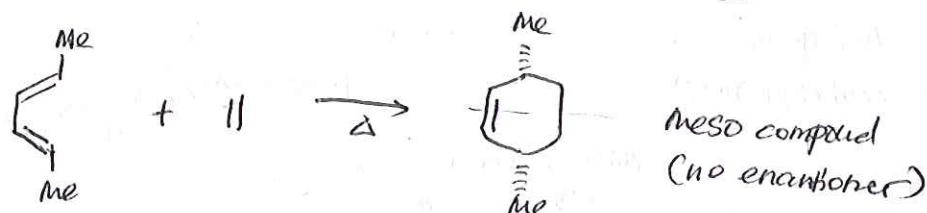
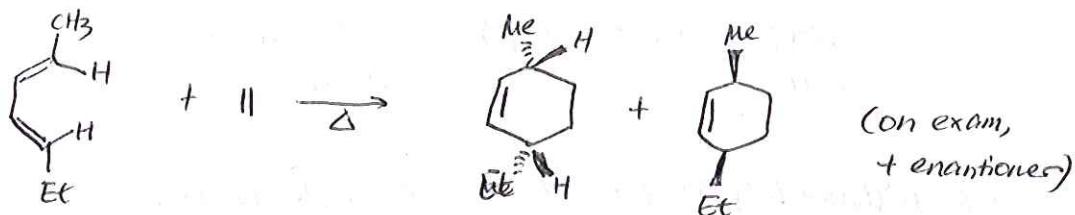


⇒ Stereochemistry of dienophile is preserved

2. Diene

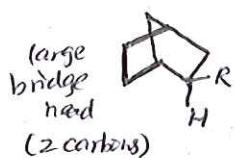


actual example

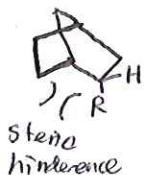


## ENDO- Preference of the D-A reaction

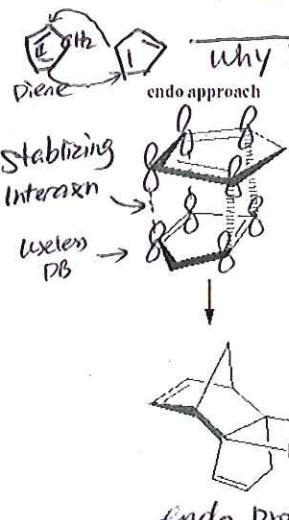
Terminology for fused ring systems w/ bridges



exo: if substituents pointing away from large bridgehead  
(always preferred)  
not in D-A



endo: substituent is pointing toward the large bridge head  
(is always preferred)



useless DB  
(no interaction)

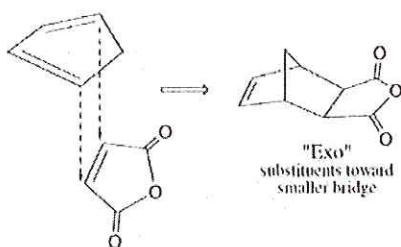
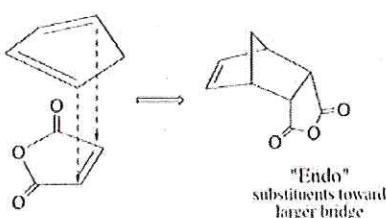
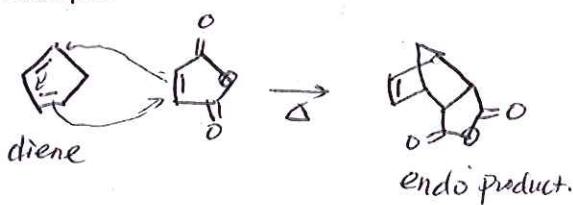


endo preference

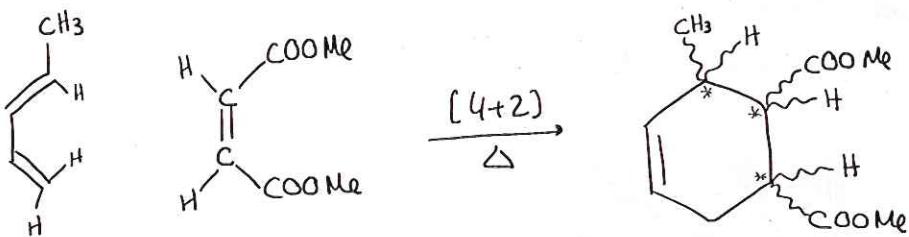
Secondary orbital interaction of the  $\pi$  orbitals of the dienophile subst. Stabilize the endo transition state.

As a result,  $e^-$  W/G on the dienophile point inward in TS despite the steric hindrance.

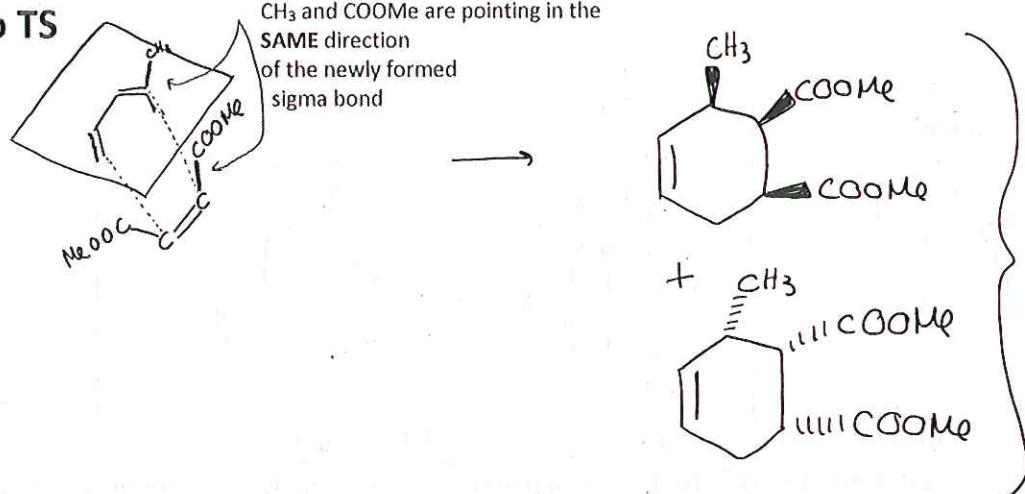
Another example:



**Stereochemistry of D-A-reaction:** Relative stereochemistry between diene and dienophile substituents.

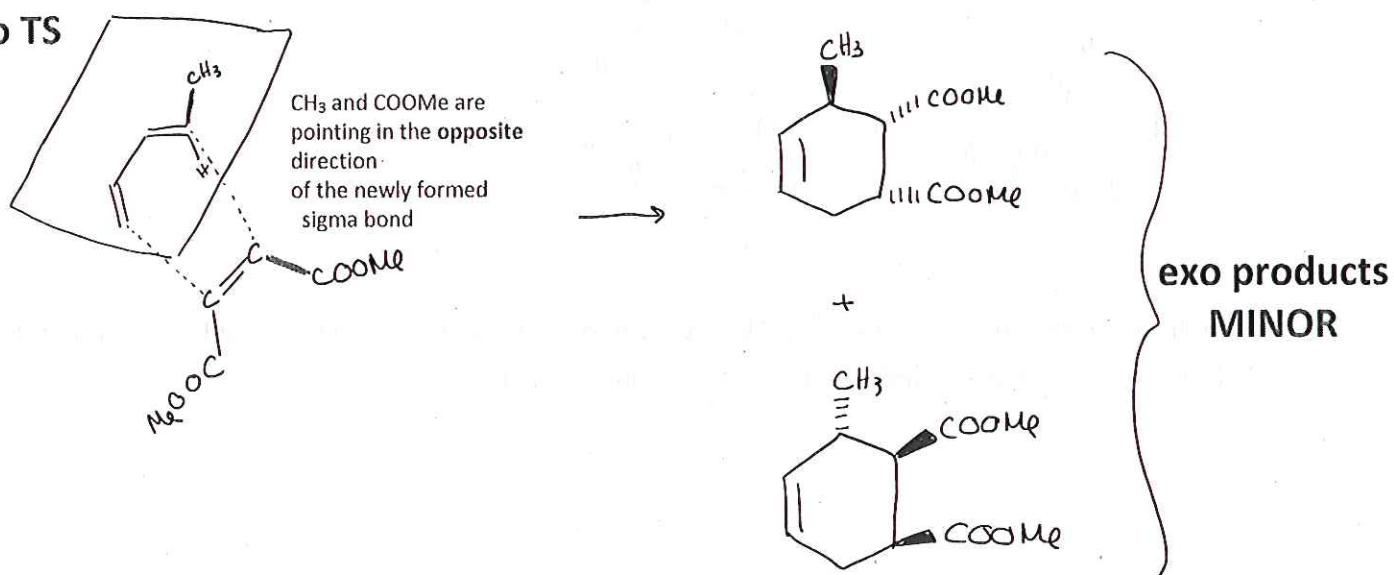


**Endo TS**



**endo products  
MAJOR**

**Exo TS**



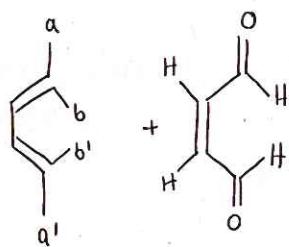
**exo products  
MINOR**



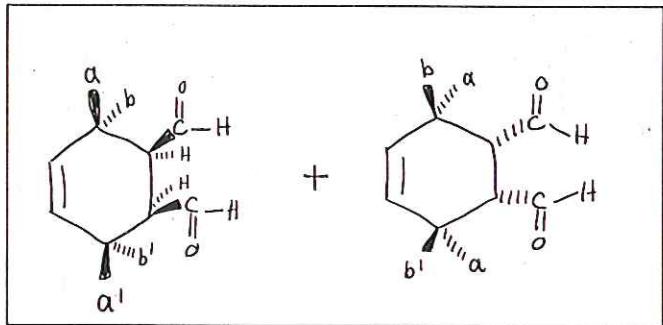
## How to solve Diels-Alder Stereochemistry

**LIKE A  
BOSS**

Diene      Dienophile



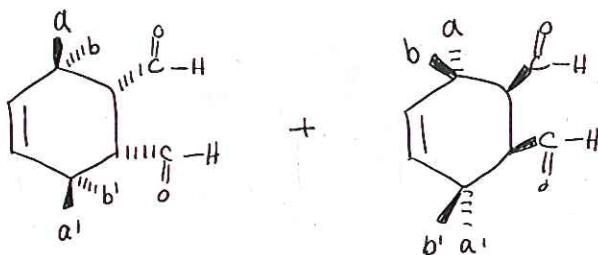
MAJOR PRODUCTS



Follow this rule to get the correct stereochemistry for the major ENDO products:

In the endo product **a** and **a'** will be **SYN** to the dienophile substituents that have  $\pi$ -orbitals (or are EWGs)  
(in other words **b** and **b'** will be **ANTI** to those substituents)

The minor EXO products formed from this same reaction are:



In the minor exo products **a** and **a'** will be **ANTI** to the dienophile substituents that have  $\pi$ -orbitals (or are EWGs)  
(in other words **b** and **b'** will be **SYN** to those substituents)

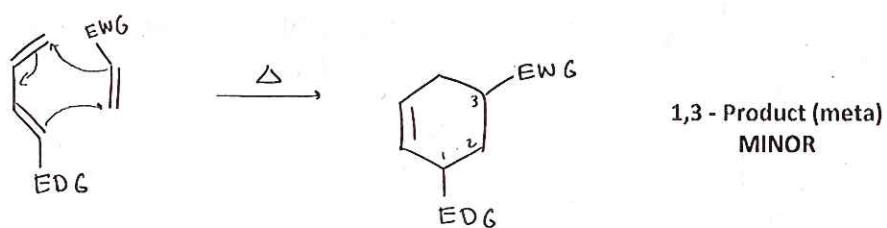
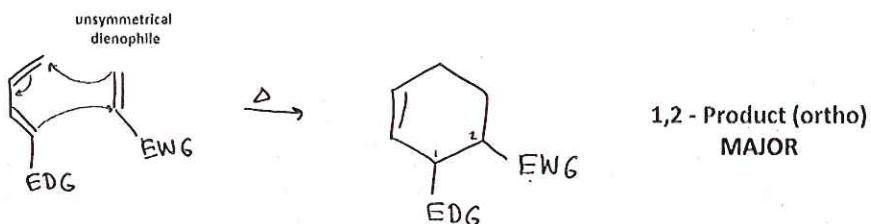
## Regiochemistry in the Diels-Alder reaction:

Regiochemistry must be considered when you have an unsymmetrical dienophile.

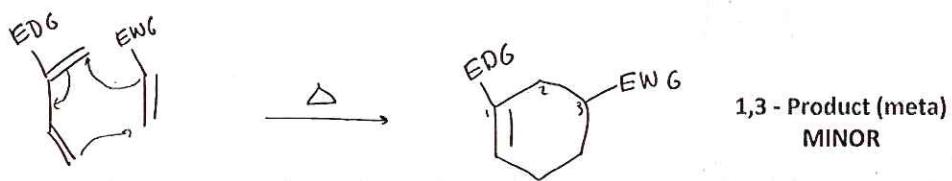
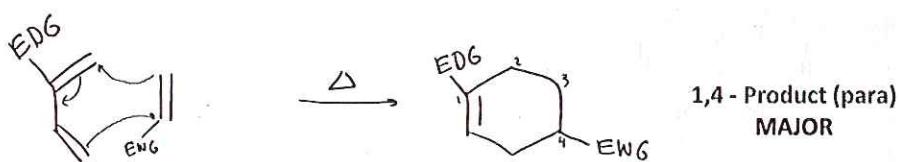
There will be two scenarios:

Due to electronic effect

Scneario #1:



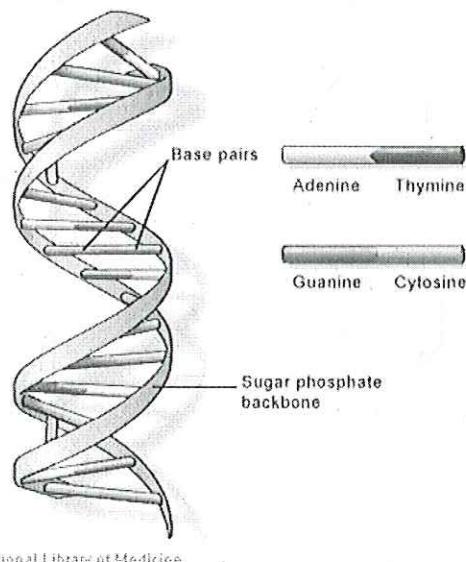
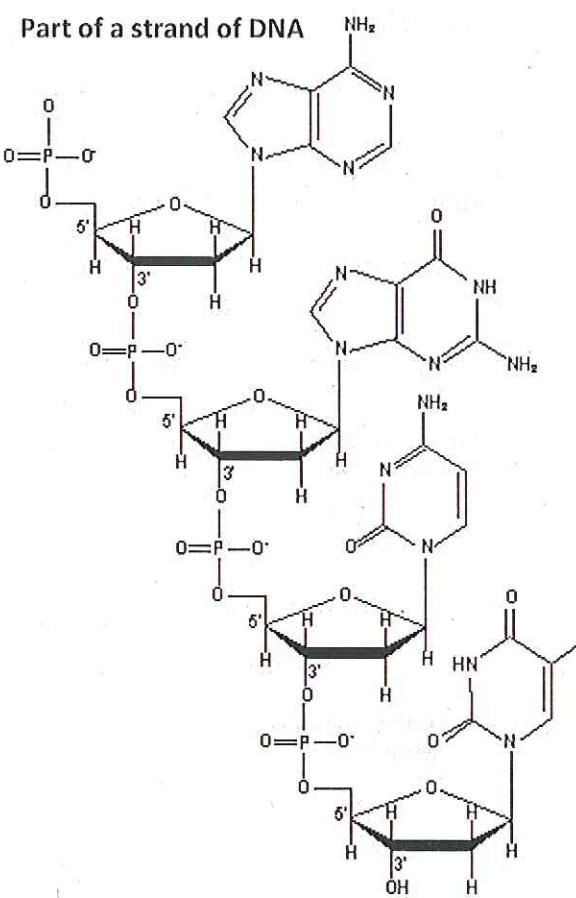
Scneario #2:



**Conclusion: When possible, ortho and para products are preferred !**

**Pro-Tip:** Sometimes there will be several different substituents on the diene and/or the dienophile. When determining regiochemistry only consider EDG on the Diene and EWG on the Dienophile. All other substituents should be ignored.

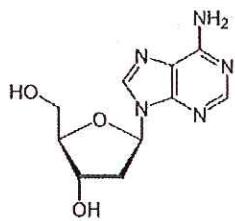
## Building blocks of DNA / RNA :



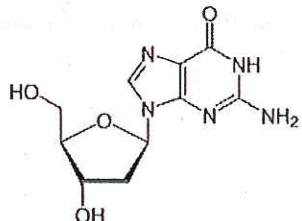
U.S. National Library of Medicine

**DNA (also RNA) Building blocks (without the phosphate) are called nucleosides.**

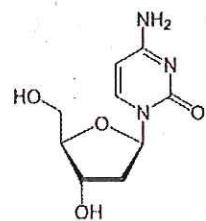
There are 5 of them:



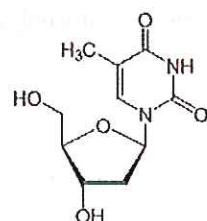
Deoxy Adenosine



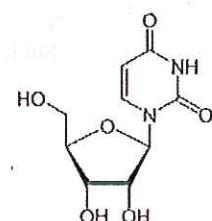
Deoxy Guanosine



Deoxy Cytidine



Thymidine



Uridine

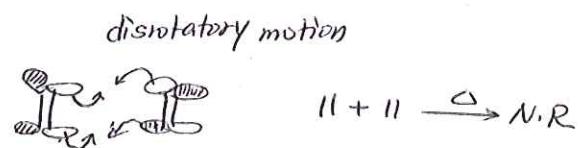
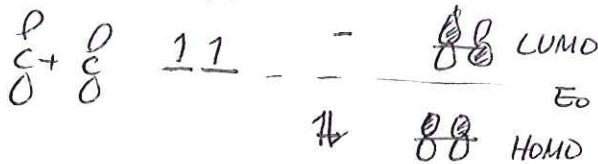
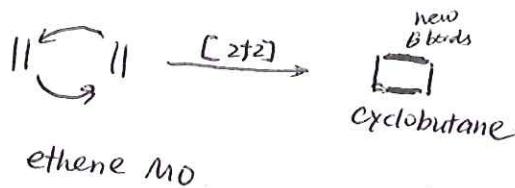
## Alkynes as dienophiles



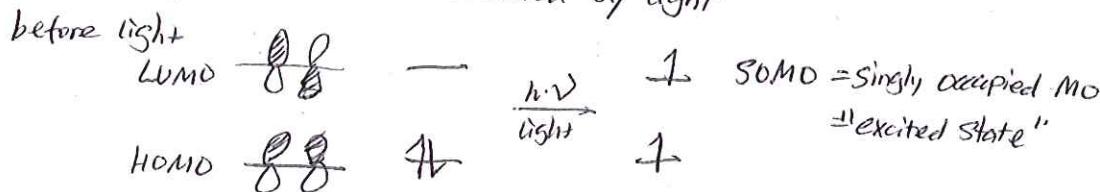
Another ex.



## 2+2 Cycloadditions



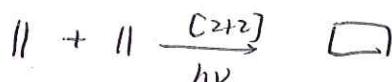
but, [2+2] cycloaddition is activated by light



orbital  
sym  
now  
matches



$2 \text{ SOMOs}$   
 $\rightarrow$  bonding  
possible



Woodward  
- Hoffmann

Rules

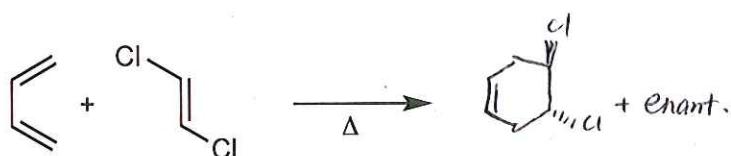
[2+2] cycloaddition requires light: photochemically allowed  
thermally forbidden

[4+2] requires heat: thermally allowed  
photochemically forbidden

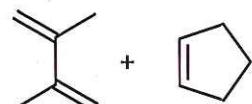
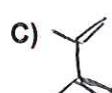
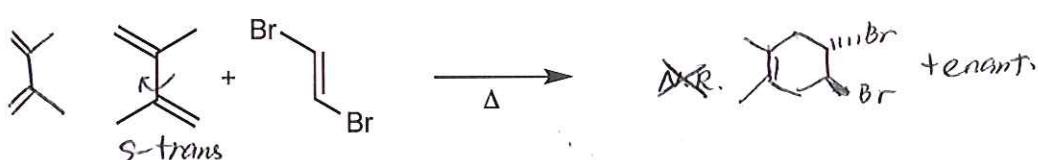
## Set 1: Simple

## Diels-Alder-Reaction Practice CHEM 307

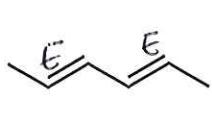
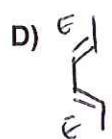
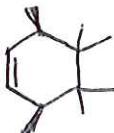
A)

chiral  $\rightarrow$  no meso

B)

 $\Delta$ 

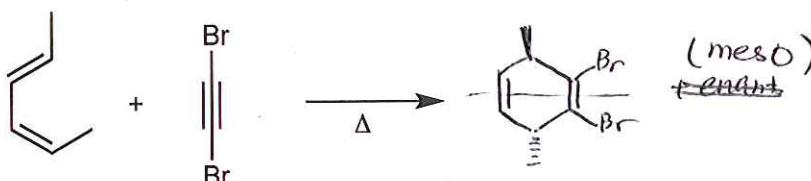
(meso)

 $\Delta$ 

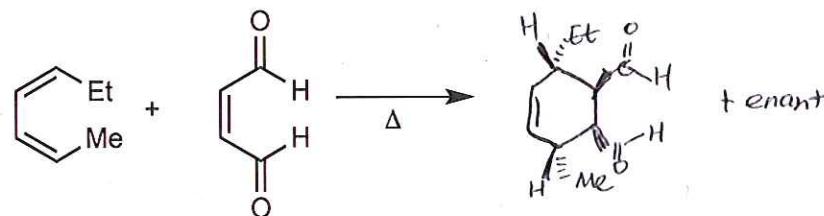
(meso)

Set 2: More advanced (consider relative stereochemistry / regiochemistry)

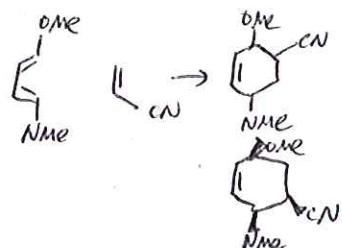
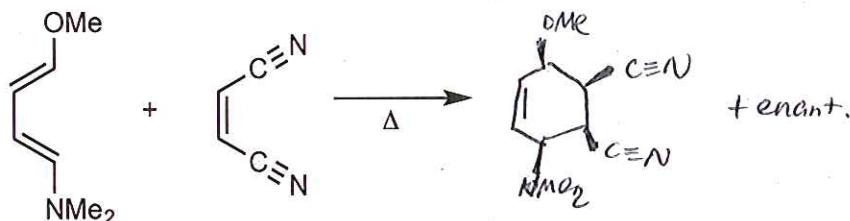
E)

double bond  $\Rightarrow$  like a chiral plane

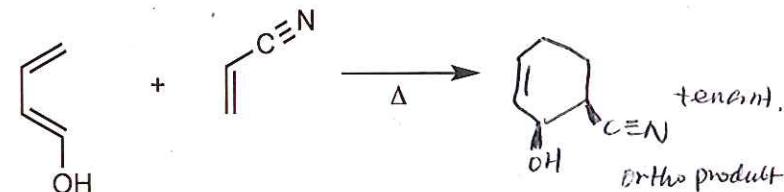
F)



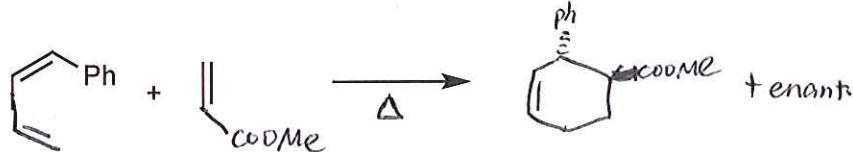
G)



H)

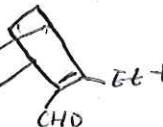
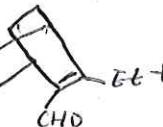
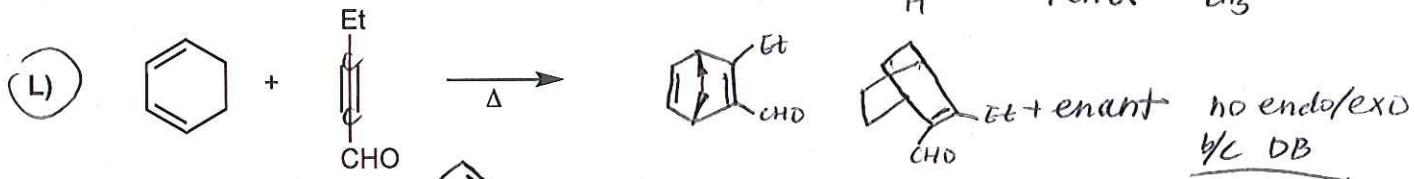
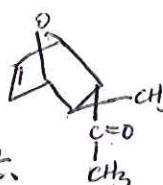
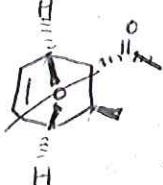
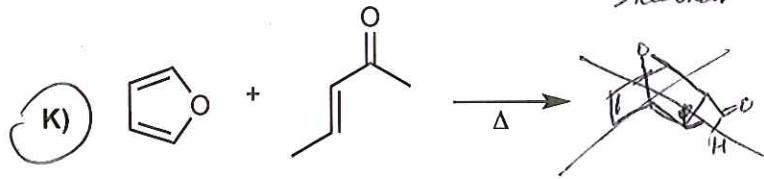
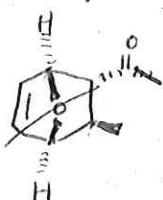
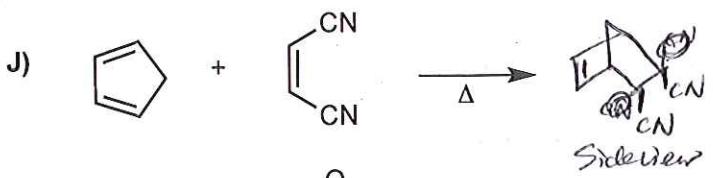


I)

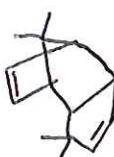
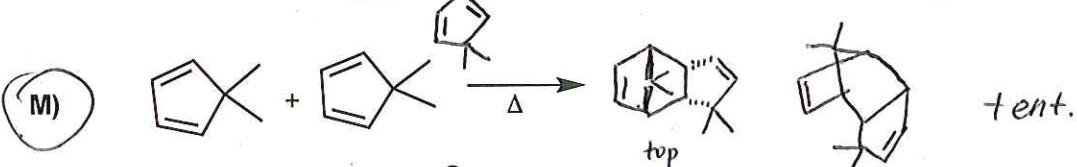


Side / top ? please draw both!

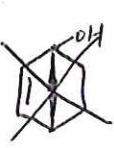
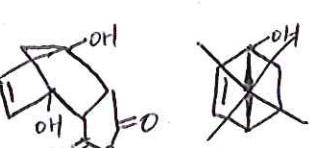
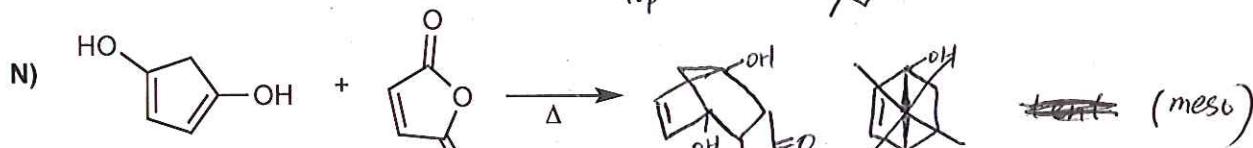
Set 3: harder ones (may require side-view of product to show endo-preference and bridged ring-systems)



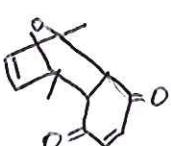
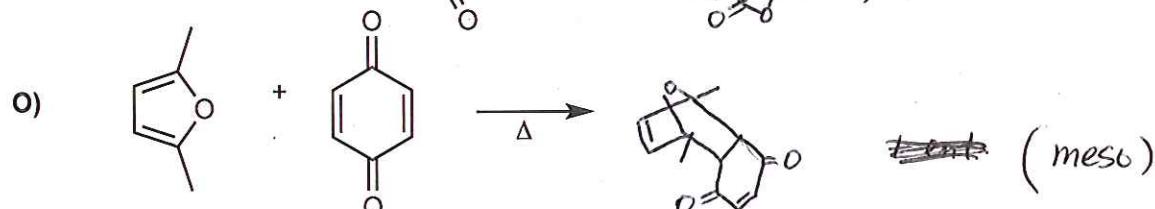
no endo/exo  
by C DB



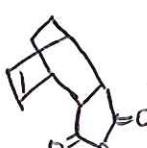
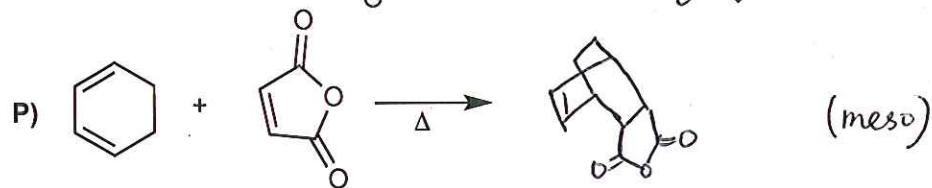
tent.



~~(meso)~~

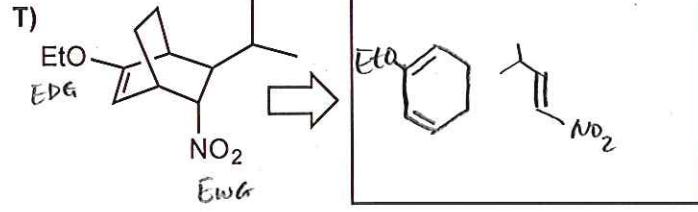
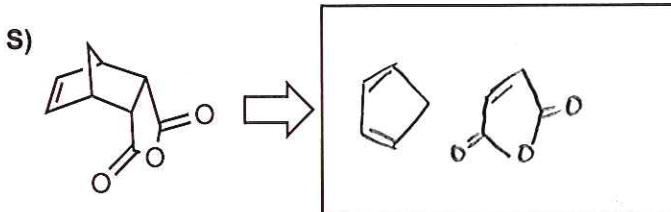
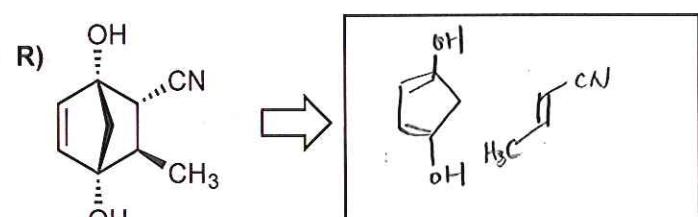
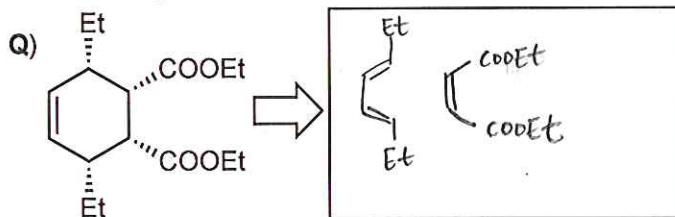


~~(meso)~~



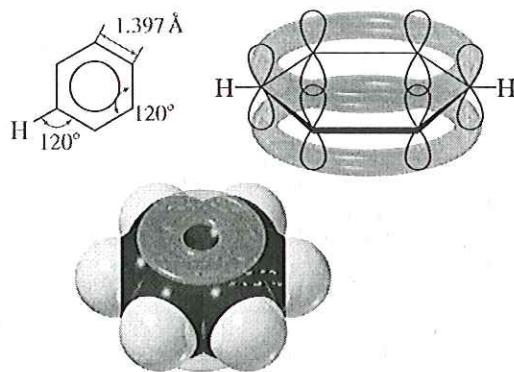
~~(meso)~~

Set 4: Retrosynthesis: what were the starting materials for the shown Diels-Alder products?



## Chapter 21

### Benzene and Aromaticity



**What does it mean when a molecule is aromatic?**

In Orgo: **aromatic  $\neq$  fragrant**

Instead: **aromatic = unusually stable system due to electron resonance**

In order to be considered aromatic by organic definition a compound has to fulfill a set of rules.  
More about this later...

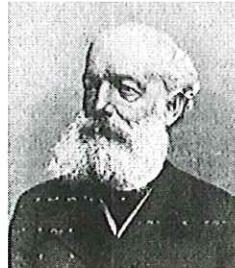
### The discovery of the structure of Benzene

In the 1800s Benzene was a very important compound for industrial use. But no one understood what its structure was.

But Benzene's empirical formula  $C_6H_6$  was long known.

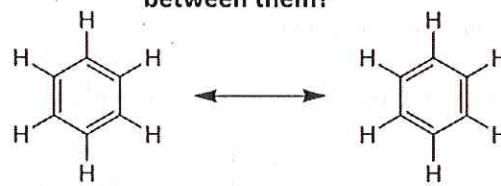
August Kekulé was one of the most prominent chemists in Europe (from the 1850s until his death 1896).

He solved the mystery of the structure of Benzene...in his dream!



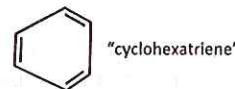
OK, so benzene is cyclic, but we still have some problems:

**Problem 1: Which of the carbons have double bonds between them?**



**Problem 2: If there are fixed positions, then the shape should not be perfectly hexagonal:**

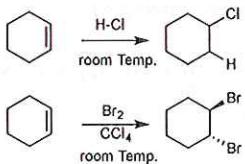
Single bond C-C : 154 pm  
Double bond C=C : 134 pm



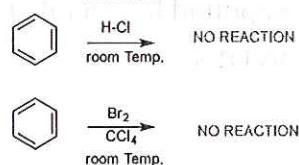
"cyclohexatriene"

Problem 3: Benzene does not undergo addition reactions or hydrogenation reactions in the way that we know from other alkenes:

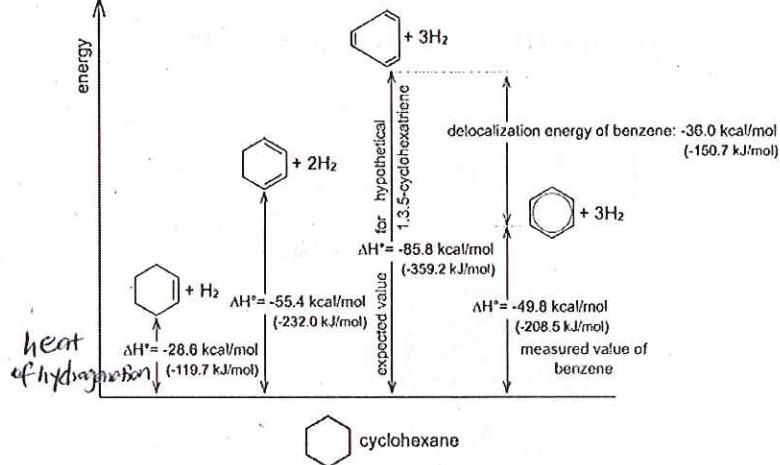
normal alkenes:



BENZENE:



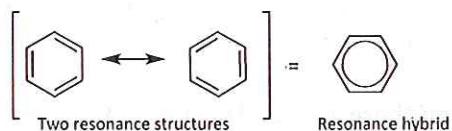
### Hydrogenation of Benzene vs different cycloalkenes



More facts about the structure of benzene discovered later:

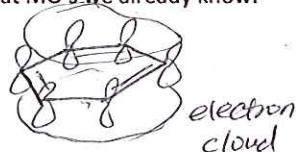
- All bonds in benzene are 139 pm (medium value between DB and SB)
- C-C bond angles are all 120°

→ The structure must be hexagonal and planar:

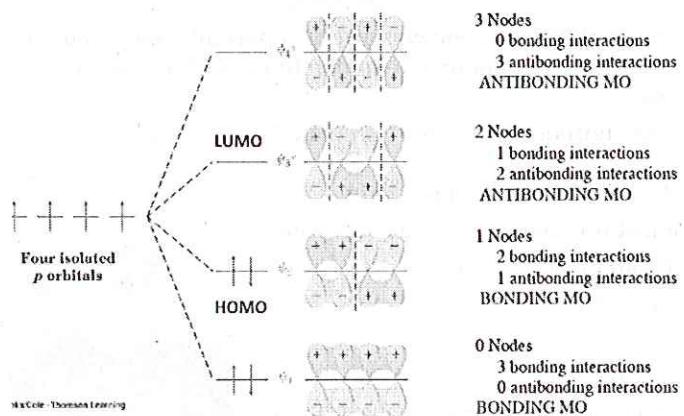


### What does the MO of Benzene look like?

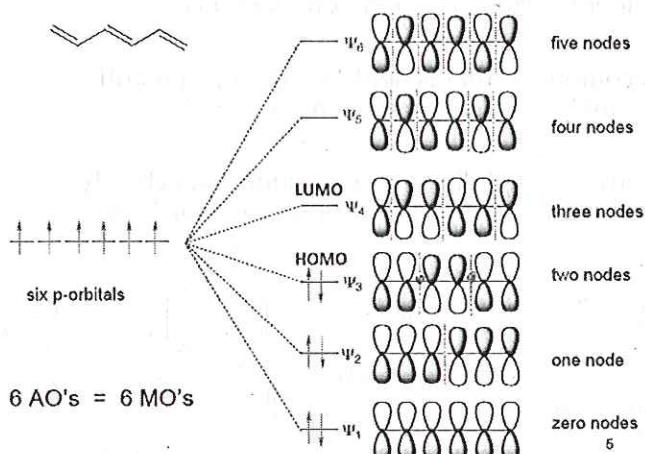
Let's first take a look at MO's we already know:



### MO of 1,3-butadiene

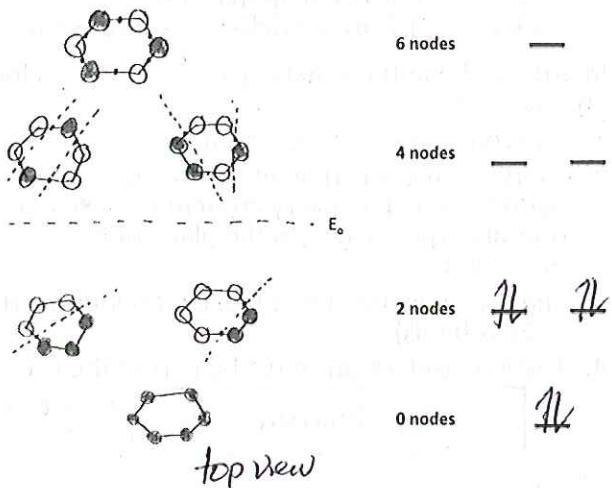


## MO of 1,3,5-hexatriene

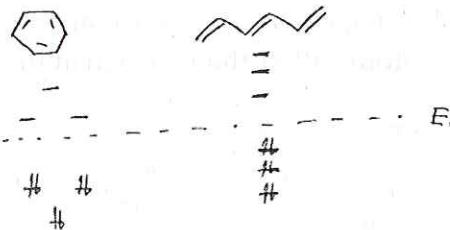


## MO of Benzene

(top view = p-orbitals shown from top)



## Comparing MO of Hexatriene to Benzene:



HOMO of hexatriene:  
3 binding interactions – 2 non-binding interactions = 1 binding interaction net

Either HOMO of Benzene:  
4 binding interactions – 2 non-binding interactions = 2 binding interaction net

More stable HOMO = less reactive = more stable !

## Predicting Aromaticity: Hückel's Rules

In order to be aromatic:

1. The compound must be **cyclic**
2. Every atom in the ring must be capable of  **$sp^2$ -hybridization** (i.e. every atom must have a p-orbital perpendicular to the plane of the molecule)
3. The ring must be **planar** (i.e. continuous overlap of 2P orbitals) *up to 7C's in the ring*
4. The # of  $\pi$ -electrons must be part of the set:

$$\# \text{ of } \pi\text{-electrons} = 4n + 2$$

where  $n = 0, 1, 2, 3, 4, \dots$

Compounds can also be in an unusual state of **INSTABILITY** called anti-aromaticity.

### Predicting anti-aromaticity - Hueckel's Rules:

In order to be anti-aromatic: (rule 1-3 same as for aromaticity)

1. The compound must be **cyclic**
2. Every atom in the ring must be capable of  **$sp^2$ -hybridization** (i.e. every atom must have a p-orbital perpendicular to the plane of the molecule)
3. The ring must be **planar** (i.e. continuous overlap of 2P orbitals)
4. The # of  $\pi$ -electrons must be part of the set:

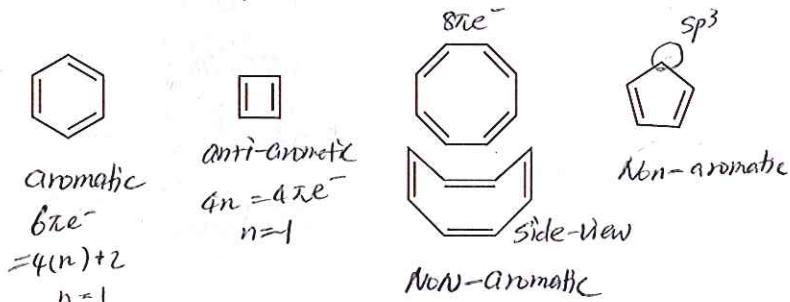
$$\# \text{ of } \pi\text{-electrons} = 4n$$

where  $n = 1, 2, 3, 4, \dots$

Anti-aromatic compounds are very reactive undergo alkene like addition reactions.

A compound that is neither aromatic nor anti-aromatic is called **non-aromatic**.

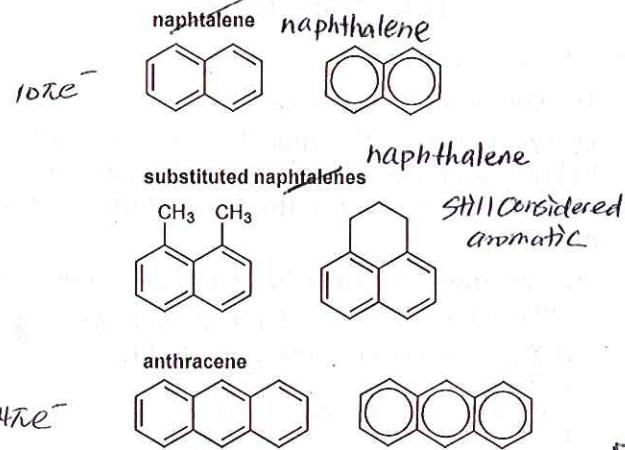
Consider the following compounds and classify them as aromatic, anti-aromatic or non-aromatic:



Anti-aromatic  
→ unstable

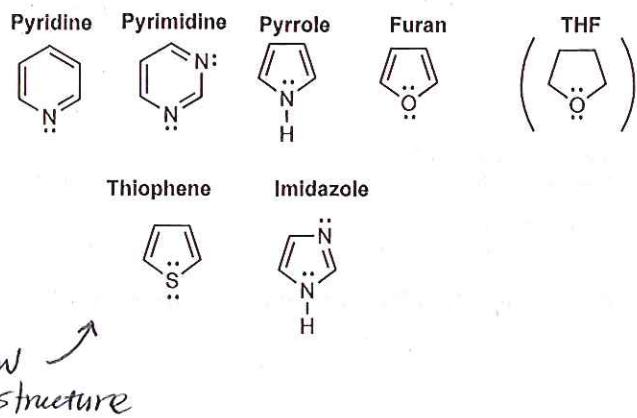
Up to 7 C's in the ring  
consider planar  
otherwise, non-planar

### Fused aromatic rings



### Aromatic Heterocycles:

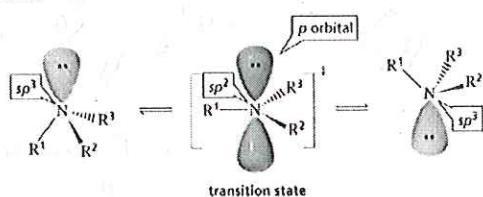
Let's look at important aromatic compounds that have atoms other than Carbon in the ring.



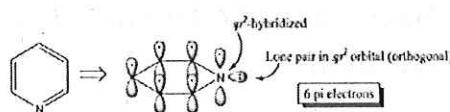
## Hybridization of heteratoms in aromatic heterocycles:

Heteroatoms with lone-pairs are able to be  $sp^2$  hybridized or  $sp^3$  hybridized!!!

amine inversion

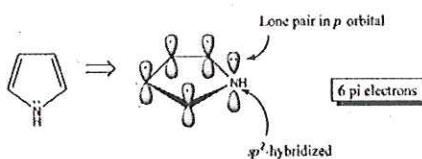


Scenario #1: Heteroatom involved in a double bond



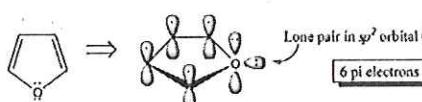
LP of heteroatoms, which are involved in a DB will not be contributed to the  $\pi$ -system.  
The LP e<sup>-</sup> are located on the heteroatom and can be used in reactions.

Scenario #2: Heteroatom has two single bonds and one lone-pair



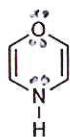
Heteroatoms single-bonded to other atoms with one LP will contribute this ONE LP to the  $\pi$ -system.  
The LP e<sup>-</sup> are delocalized across the ring and not available to react in reactions.

Scenario #3: Heteroatom has two single bonds and two lone-pairs



If the single-bonded heteroatom has a second LP then only ONE LP will contribute to the delocalized  $\pi$ -system (inside a p-orbital).  
The other LP will be orthogonal inside an  $sp^2$  hybrid orbital and can be used for reactions.

Exercise problems:  
Aromatic or not?



$$\# \text{of } \pi e^- = 8 \pi e^-$$

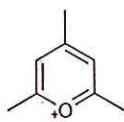
$$4n+2 = 8 ? \quad \text{No}$$

$$4n = 8 \quad \checkmark \quad n=2$$

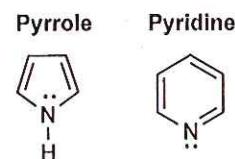
Anti-aromatic

$$6 \pi e^- = 4n+2 \quad \checkmark$$

aromatic



Which is more basic Pyrrole or Pyridine?

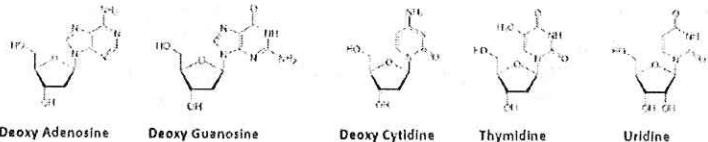


base  $\rightarrow$  available to  
 $lp \rightarrow$  grab proton  
 $pK_a = 16.5$        $pK_a = 25$

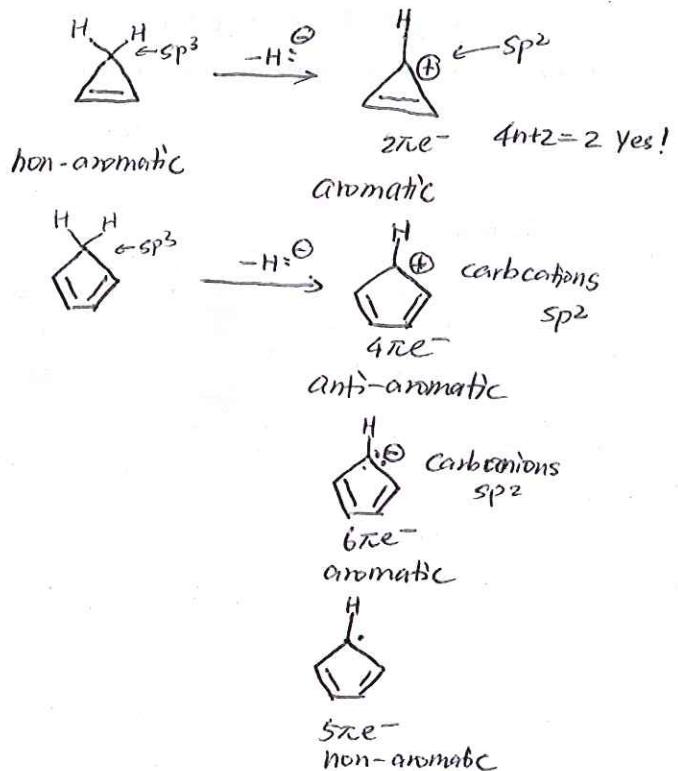
b/c  $lp$  is available in Pyridine  
it's not part of aromatic syst.  
 $lp$  is unavailable in Pyrrole

## The Heterocyclic bases in DNA/ RNA are also aromatic:

DNA (also RNA) Building blocks (without the phosphate) are called nucleosides.  
There are 5 of them:



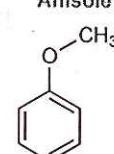
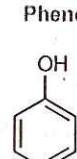
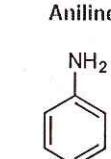
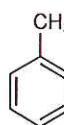
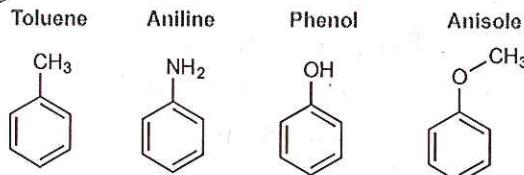
## Aromatic Ions



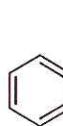
## Aromatic Ions

## Common names of important Benzene Derivatives

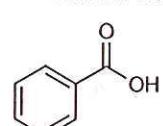
*know the name*



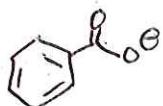
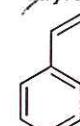
Benzaldehyde



Benzoic Acid



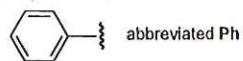
Styrene



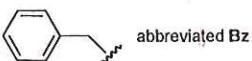
benzoate

## Benzene and aromatics as substituents:

If a benzene ring is a substituent it is called phenyl (not benzyl!).  
If there is an additional carbon outside the benzene ring then it is called benzyl.

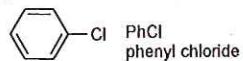


abbreviated Ph

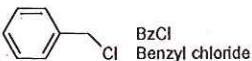


abbreviated Bz

e.g.:



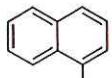
PhCl  
phenyl chloride



BzCl  
Benzyl chloride

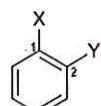
Aromatic compounds in general are called **arenes** and abbreviated Ar.

e.g. Ar-Cl =

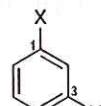


## Disubstituted Benzene Derivatives:

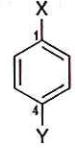
When a Benzene ring has 2 substituents there are 3 different arrangements:



1,2- compound  
aka  
ortho- or o-

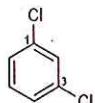


1,3- compound  
aka  
meta or m-

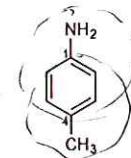


1,4- compound  
aka  
para or p-

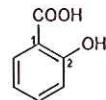
Examples:



1,2-dichlorobenzene  
or  
meta-dichlorobenzene  
or  
m-dichlorobenzene



para-methylaniline  
or  
p-aminotoluene



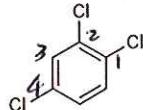
ortho-hydroxy  
benzoic acid

Only 2 subst.

## Multisubstituted Benzene Derivatives:

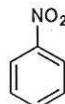
o/p/m does not apply here. Try to find the lowest possible combination of numbers for the substituents!

Examples:

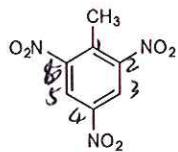


1,2,4 < 1,2,5

1,2,4-trichlorobenzene



nitrobenzene



2,4,6-trinitrotoluene

(TNT)

## Acidity of Benzene Derivatives

## Reactions of Benzene Derivatives

### 1. Oxidation at the Benzylic Position

(a) (na) (aa)  
Exercise : Classify these compounds as aromatic, non-aromatic or anti-aromatic.



A



B



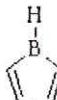
C



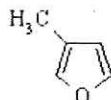
D



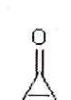
E



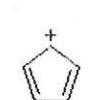
AB



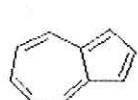
AC



AD

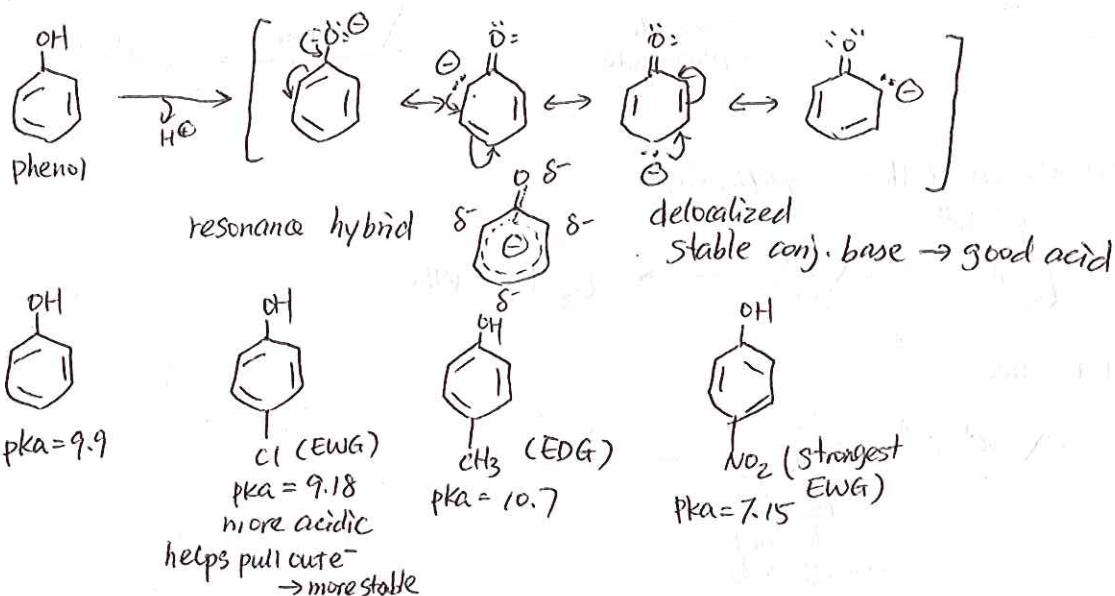
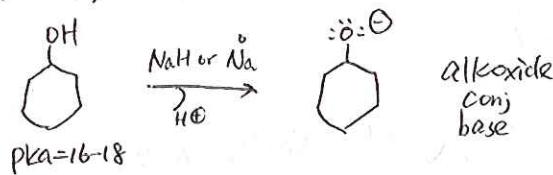


AE



BC

## Acidity of Benzene Derivatives

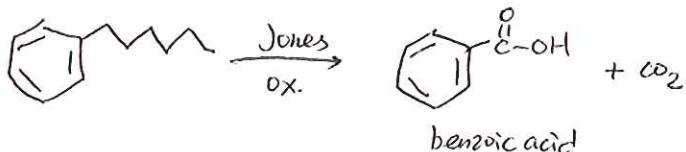
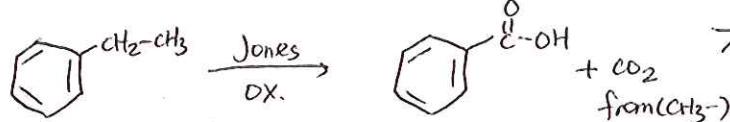
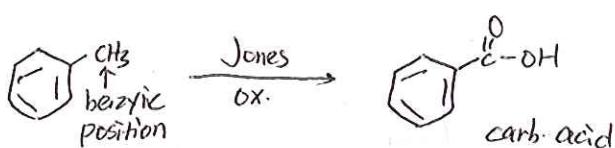
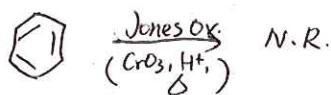


Effect is highest on para position

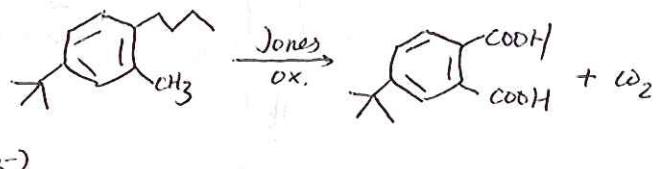
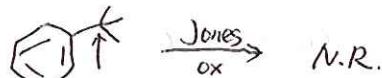
EWG enhances acidity  
EDG lowers acidity

## Reactions Benzene Derivatives

### 1. Oxidation at benzylic position

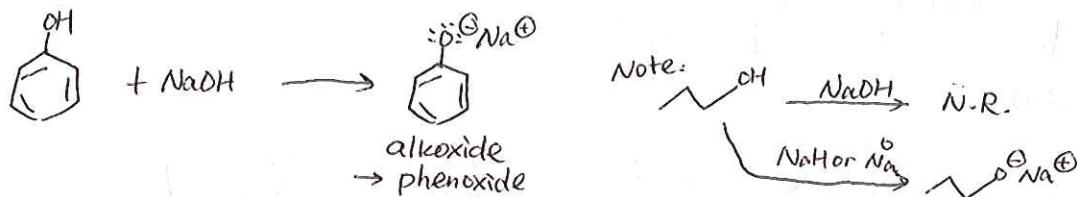


benzoic position  
needs at least 1 hydrogen

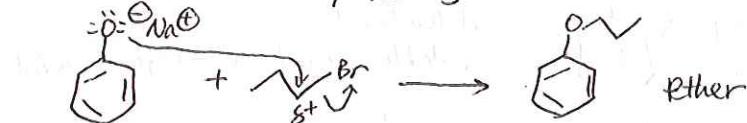


## 2. Reactions of Phenols

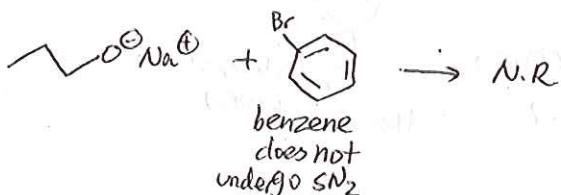
### (A) Reaction w/ bases (salt formation)



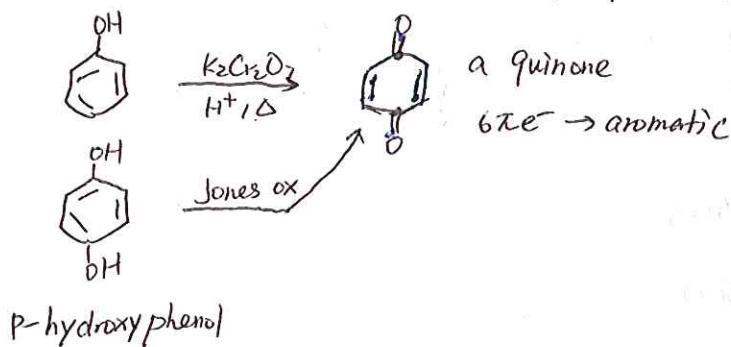
### (B) Williamson Ether Synthesis



Not Do this

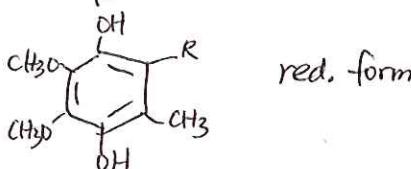
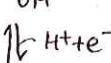
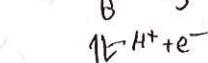
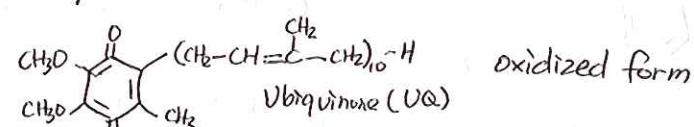


### (c) Oxidation reaction of phenols to quinones



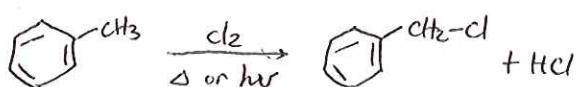
Biochem (respiration)

Coenzyme Q

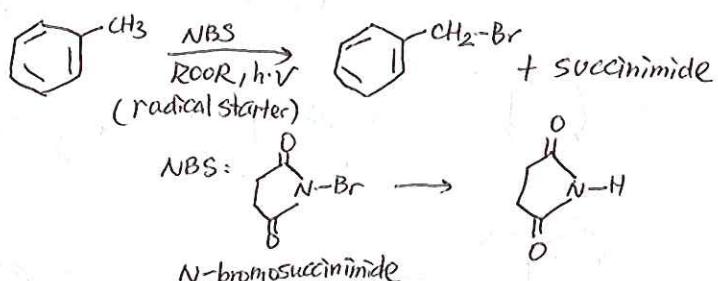


### 3. Substitution Reaction at Benzylic Position

Chlorination:



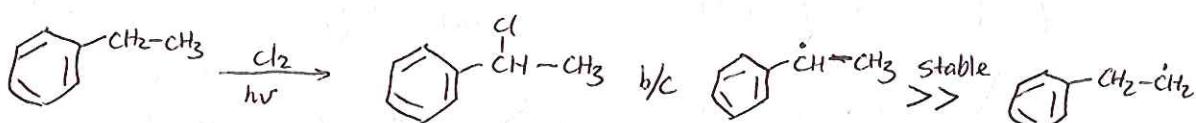
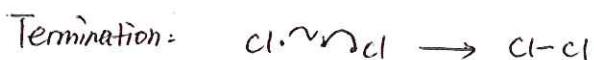
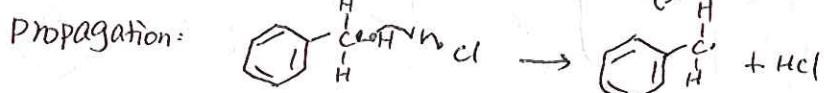
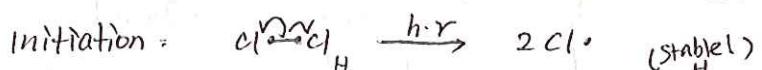
Bromination



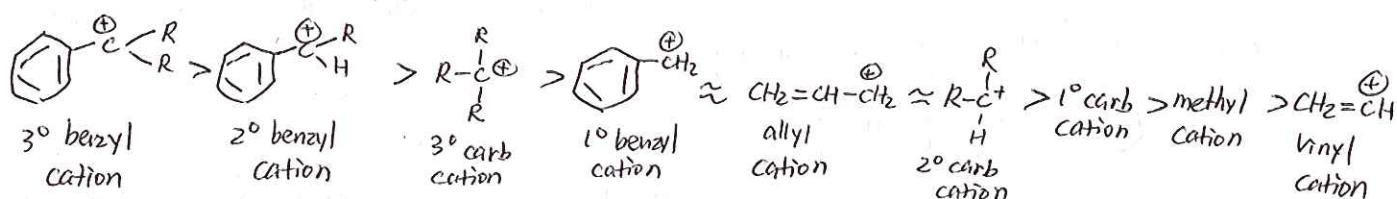
Why is the substitution occurring at benzylic pos.?

1. benzene ring itself is inert  $\rightarrow$  sidechain only reactive position
2. benzylic radicals are extremely stable

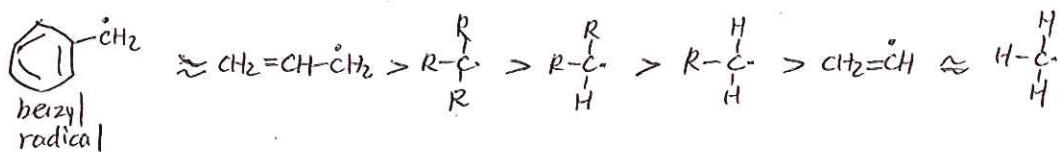
Mechanism for chlorination (Not covered in Exam 3)



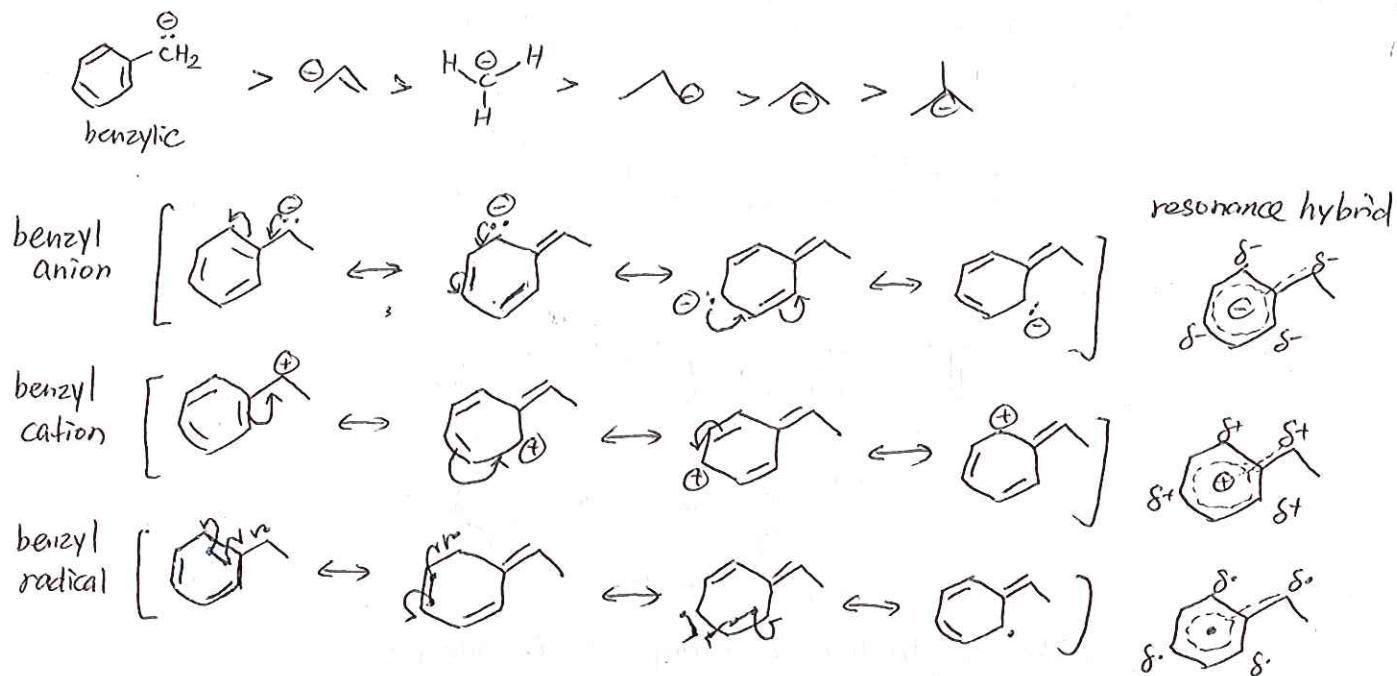
Relative Stabilities of Carbocations



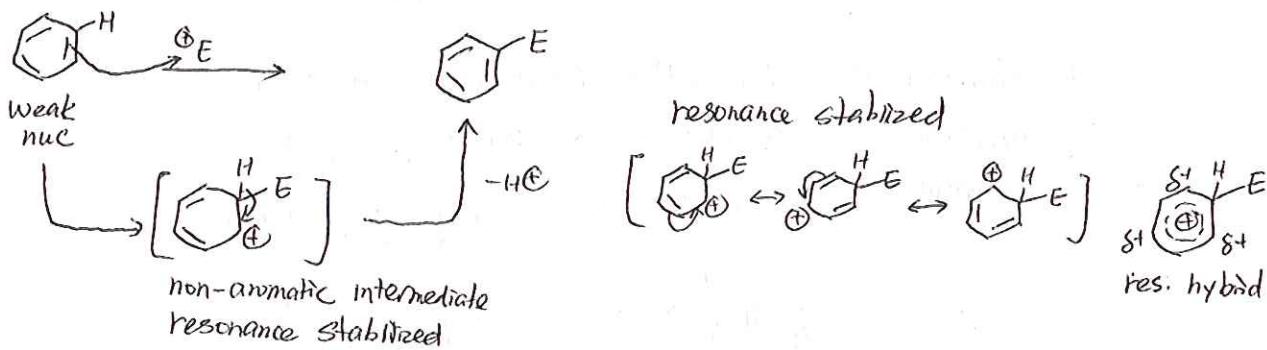
Relative Stabilities of Radicals



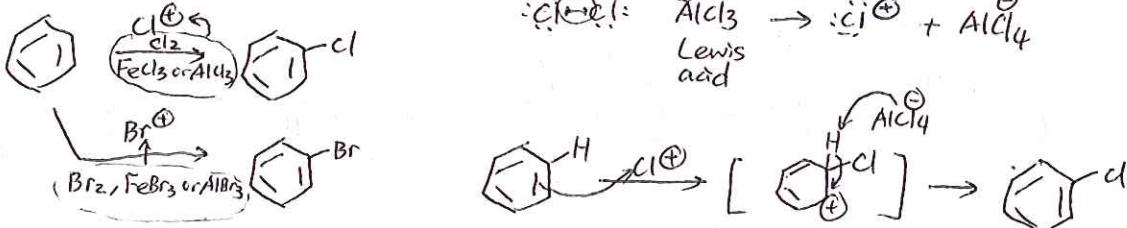
## Stab. of carbanions



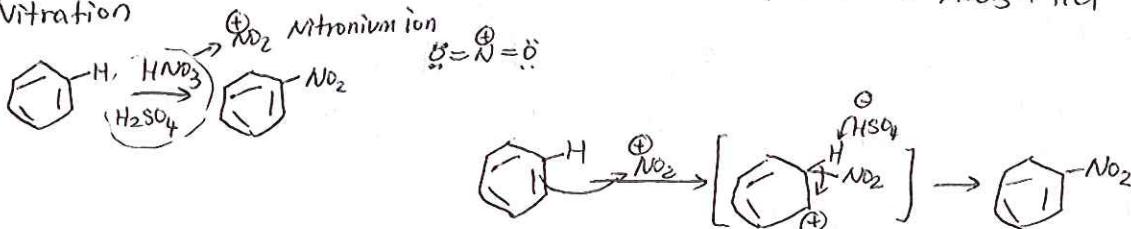
## 4. Electrophilic Aromatic Substitution (EAS)



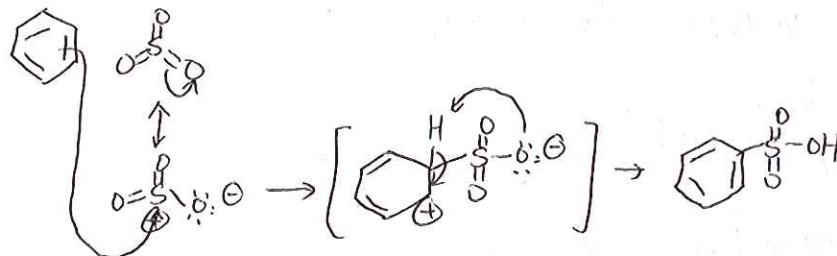
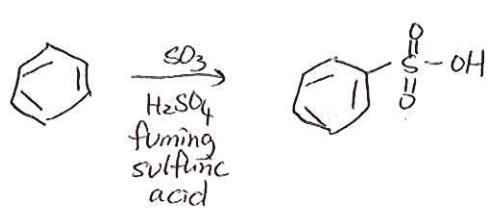
### (1) Halogenation



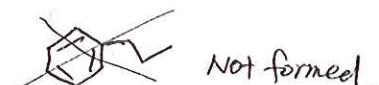
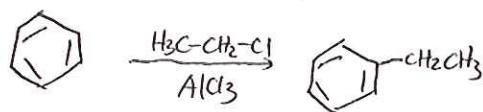
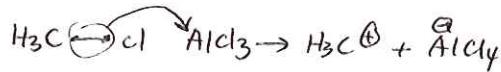
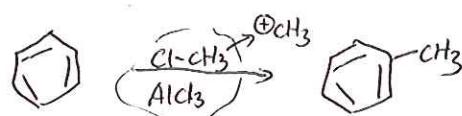
### (2) Nitration



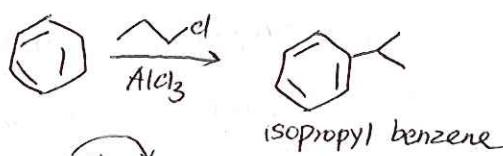
### (3) Sulfonation



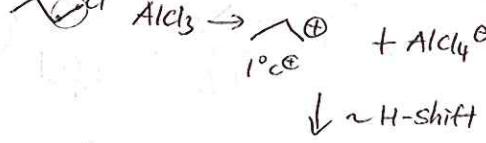
### (4) Friedel-Crafts Alkylation



Not formed.



isopropyl benzene



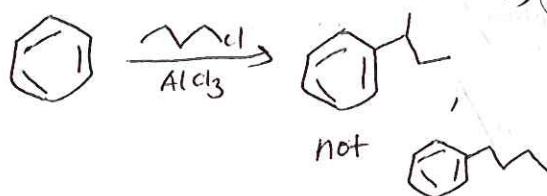
$\downarrow \sim \text{H-shift}$

For the F-C-alkylation

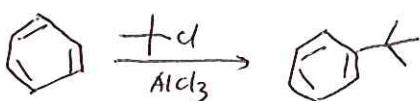
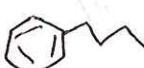
beyond 2 carbons on the alkyl chain  $\Rightarrow$

Watch out for C $^\oplus$  rearrangements!

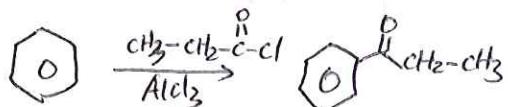
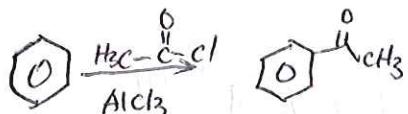
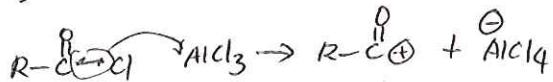
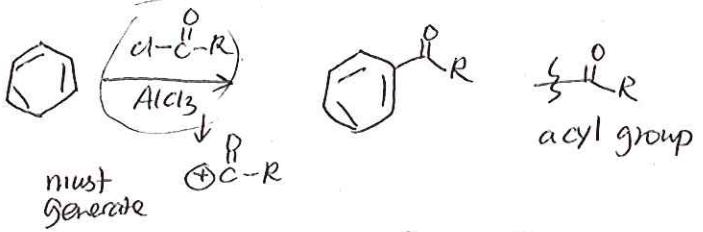
(H $\sim$ shift or Alkyl $\sim$ shift)



not



## (5) Friedel-Crafts Acylation



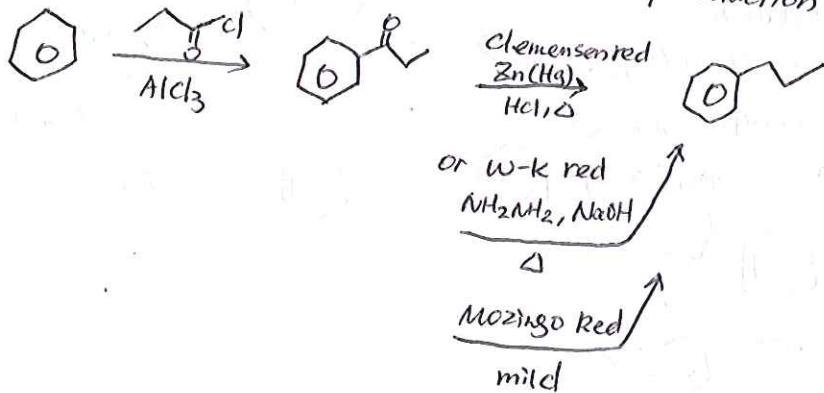
(no worry about  $\text{C}^+$  rearrangement)

Tricky scenarios



F-C alkylation does not work

Instead, do the F-C acylation, followed by reduction



## Substituent effect on EAS



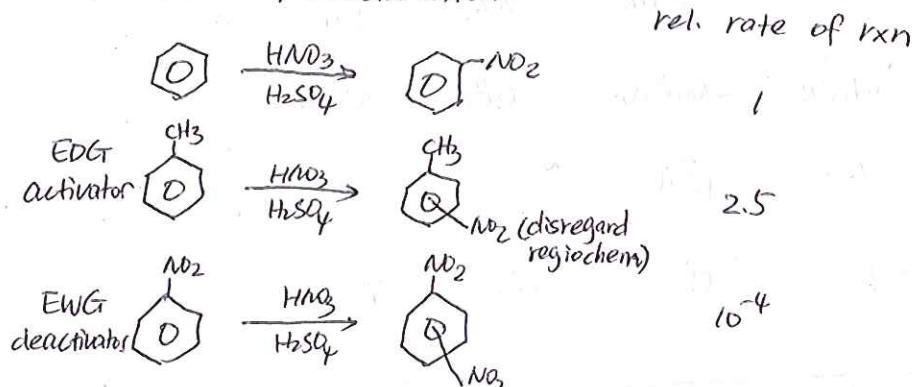
Two main effect (1) Activation / Deactivation

of the benzene ring due to substituent

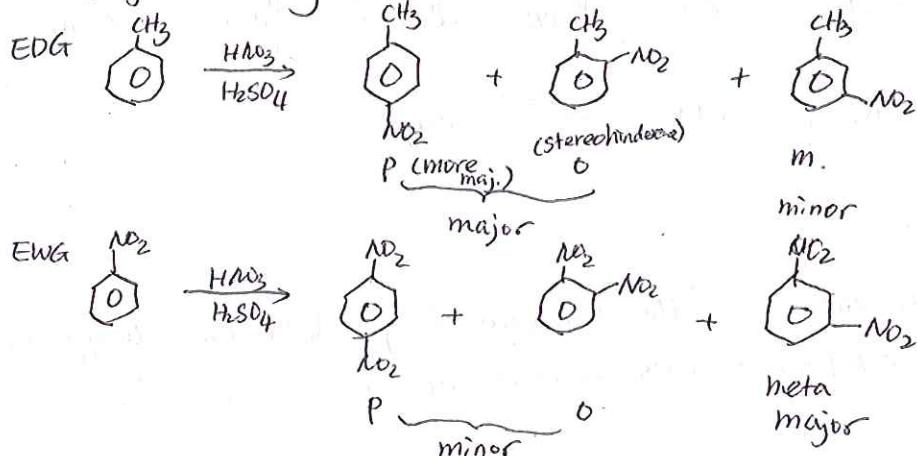
## (2) Regiochemistry

Will the new group go o, m, or p relative to existing substituent?

## (1) Activation / Deactivation

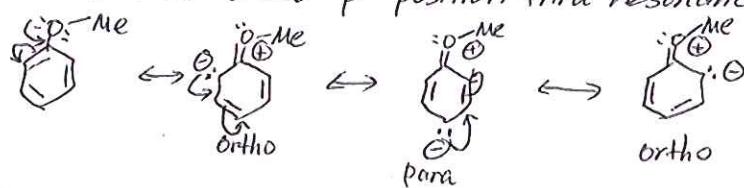


## (2) Regiochemistry



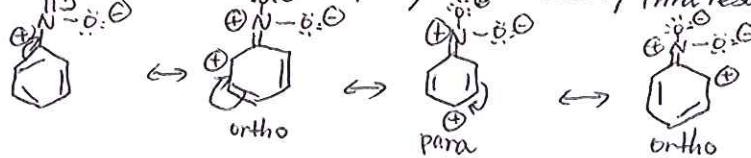
Why?

EDGs: activate  $\sigma$  and  $p$  position thru resonance. Benzene ring  $\rightarrow e^-$  rich



para > ortho b/c steric hindrance

EWG: deactivate O and P by  $\downarrow$  density thru resonance.  $\text{ring} \rightarrow e^- \downarrow \rightarrow \downarrow$  reactive in O, P.



$\uparrow$  reactive in meta.

## Directing effects of substituents on Further Substitution

Activator: all alkyl groups, groups having a  $\text{LP}$  on the atom adjacent to the benzene ring.  $\Rightarrow \text{o/p directing}$

Exception: Halogens are deactivators but still o/p directors

b/c they're EDG by resonance via LP

they're EWG by inductive effect due to electronegativity

Table 22.2

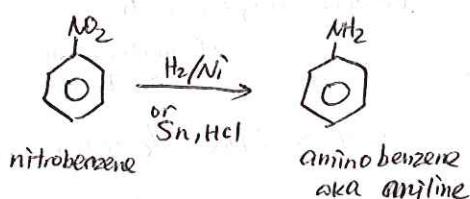
- ortho para	Strong activating	$-\text{NH}_2$	$-\text{NHR}$	$-\text{NR}_2$	$-\text{OR}$	$-\text{OH}$
Directing	Moder. activ.	$-\text{NHCOR}$	$-\text{NHC}^{\text{O}}\text{Ar}$	$-\text{OC}^{\text{O}}\text{R}$	$-\text{OC}^{\text{O}}\text{Ar}$	
	Weak activ.	$-\text{R}$				
	Weak deactv.	$-\text{F}:$	$-\text{Cl}:$	$-\text{Br}:$	$-\text{I}:$	

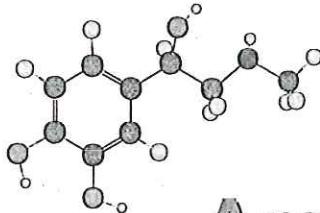
Meta	Mode. deactv.	$-\text{C}^{\text{O}}\text{R}$	$-\text{OH}$	$-\text{OR}$	$-\text{NH}_2$	$-\text{SO}_3\text{H}$	$-\text{C}\equiv\text{N}$
Directing	Strong deactv.	$-\text{NO}_2$	$-\text{NH}_3^+$	$-\text{CF}_3$	$-\text{CD}_3$		

- If there're multiple subst. on the benzene ring, Activator always beats the deactivators (look for activator's preference aka ortho & para)

Additional rxn

Reduction of nitrobenzene





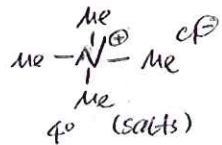
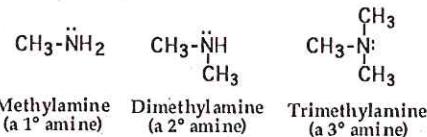
# Amines

Chapter 23

## Structure & Classification

◆ Amines are classified as:

- 1°, 2°, or, 3° amines: Amines in which there are 1, 2, or 3 alkyl or aryl groups.

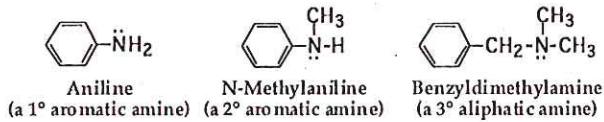


23-1

23-2

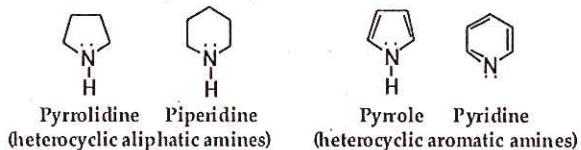
## Structure & Classification

- ◆ Amines are further divided into aliphatic, aromatic, and heterocyclic amines:
- **Aliphatic amine:** An amine in which nitrogen is bonded only to alkyl groups.
  - **Aromatic amine:** An amine in which nitrogen is bonded to one or more aryl groups.



## Structure & Classification

- **Heterocyclic amine:** An amine in which nitrogen is one of the atoms of a ring.

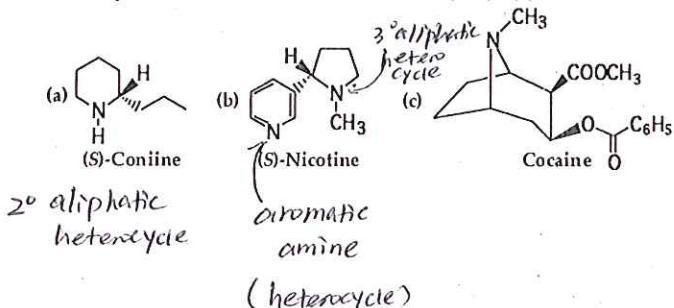


23-3

23-4

## Structure & Classification

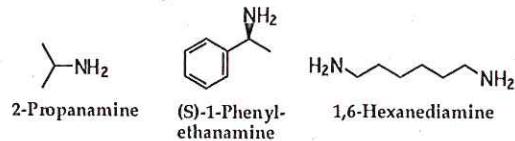
Example: Classify each amino group by type.



23-5

## Nomenclature

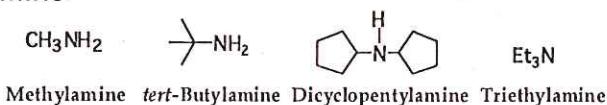
♦ Aliphatic amines: replace the suffix -e of the parent alkane by -amine.



23-6

## Nomenclature

♦ Common names for most aliphatic amines are derived by listing the alkyl groups bonded to nitrogen in one word ending with the suffix -amine.

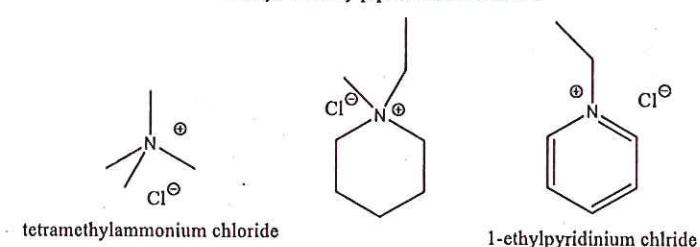


23-7

## Nomenclature

♦ When four groups are bonded to nitrogen, the compound is named as a salt of the corresponding amine.

1-ethyl-1-methylpiperidinium chloride



23-8

## Basicity-Aliphatic Amines

### ♦ Aliphatic Amines

- note that  $pK_a + pK_b = 14$

Amine	Structure	$pK_a$	$pK_b$
Ammonia	$\text{NH}_3$	9.26	4.74
Primary Amines			
methylamine	$\text{CH}_3\text{NH}_2$	10.64	3.36
ethylamine	$\text{CH}_3\text{CH}_2\text{NH}_2$	10.81	3.19
cyclohexylamine	$\text{C}_6\text{H}_{11}\text{NH}_2$	10.66	3.34
Secondary Amines			
dimethylamine	$(\text{CH}_3)_2\text{NH}$	10.73	3.27
diethylamine	$(\text{CH}_3\text{CH}_2)_2\text{NH}$	10.98	3.02
Tertiary Amines			
trimethylamine	$(\text{CH}_3)_3\text{N}$	9.81	4.19
triethylamine	$(\text{CH}_3\text{CH}_2)_3\text{N}$	10.75	3.25

Stronger bases

$2^o > 1^o > 3^o$

$\text{CH}_3 \text{ EPG}$   
unlike get bulky

23-9

## Basicity-Aromatic Amines

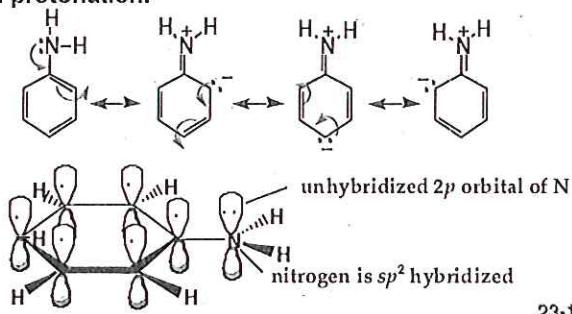
Amine	Structure	$pK_a$ of Conjugate Acid	
Aromatic Amines			resonance possible
Aniline		4.63	$\rightarrow$ Stable not reactive
4-Methylaniline		5.08	Weaker bases
4-Chloroaniline		4.15	
4-Nitroaniline		1.0	
Heterocyclic Aromatic Amines			
Pyridine		5.25	Intermediate
Imidazole		6.95	

23-10

## Basicity-Aromatic Amines

- Aromatic amines are weaker bases than aliphatic amines :

- Resonance stabilization of the free base, which is lost on protonation.



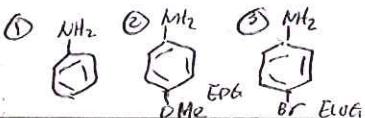
23-11

## Basicity-Aromatic Amines

And note the effect of substituents

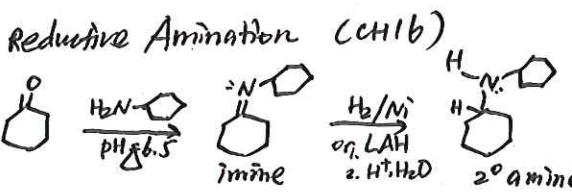
- Electron-Donating groups, such as alkyl groups, increase the basicity of aromatic amines.

- Electron-withdrawing groups, such as halogens, the nitro group, and a carbonyl group decrease the basicity of aromatic amines by a combination of resonance and inductive effects.



Intermediate Strongest base Weakest

23-12

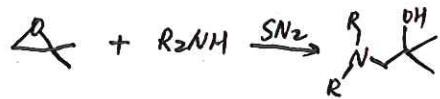


## Preparation

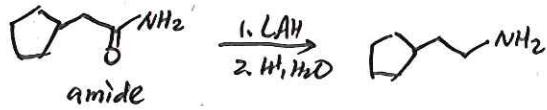
- ◆ We have already covered these methods
  - nucleophilic ring opening of epoxides by ammonia and amines.
  - addition of nitrogen nucleophiles to aldehydes and ketones to form imines, followed by reduction of imines to amines REDUCTIVE AMINATION
  - reduction of amides to amines by  $\text{LiAlH}_4$
  - reduction of nitriles to a 1° amine by  $\text{LiAlH}_4$
  - nitration of arenes followed by reduction of the  $\text{NO}_2$  group to a 1° amine  
(using  $\text{Sn}\cdot\text{HCl}$  or  $\text{H}_2/\text{Ni}^+$ )

23-13

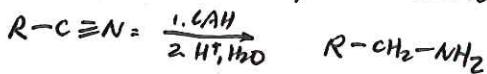
(CH11)



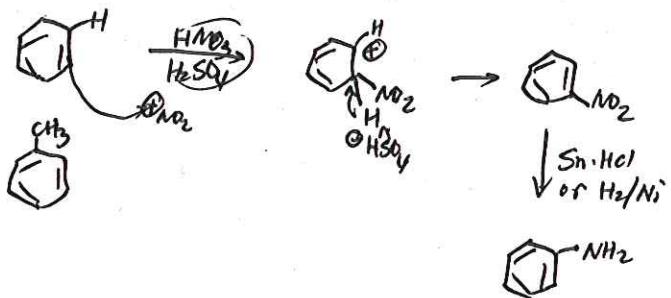
### Reduction of amides by LAH (CH18)



### Reduction of Nitriles by LAH (CH18)



### Nitration of benzene + red.



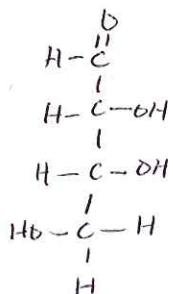
## Chapter 25 - Carbohydrates aka Sugars, Saccharides

- provide energy through oxidation
- Supply carbon for synthesis of cell components
- serve as storage form of chemical energy
- Structural elements of some cells and tissues

Bio molecules: Compounds that are essential to life

Biochemistry: Study of compounds and processes associated w/ living organisms

Carbohydrates are polyhydroxy aldehydes or ketones



classified as:

- Monosaccharides: one subunit
- Disaccharides: two subunits
- Polysaccharides: typically thousands of units

(Monosaccharides)

General formula:  $C_nH_{2n}O_n$  or  $C_n(H_2O)_n$

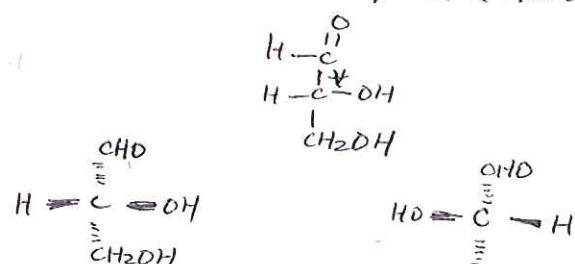
$$3 \leq n \leq 8$$

Aldose: sugar monosaccharides w/ aldehyde group  
Ketose: ketone group

classified by # of carbons.

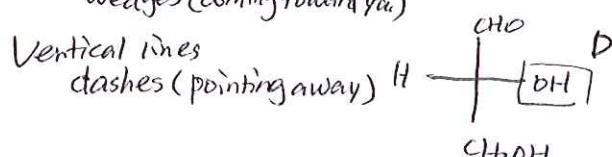
Triose, Tetrose, Pentose, Hexose, Heptose, Octose

Smallest carbohydrate = Glyceraldehyde (triose)

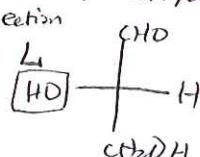


place the most highly oxidized functional group on top  
 (in last \* group)

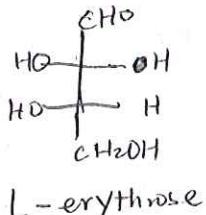
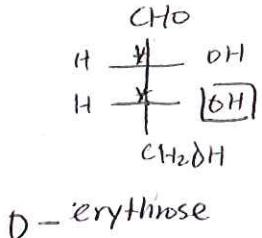
horizontal lines: (R) - Glyceraldehyde  
 wedges (coming toward you)



Fischer (S) projection



on right  $\rightarrow$  D sugar  
 on left  $\rightarrow$  L sugar  
 D,L HO relation to direction of polarization angle



The hydroxyl group on the chiral carbon farthest from the carbonyl group determines whether carbohydrate is D (right) or L (left)

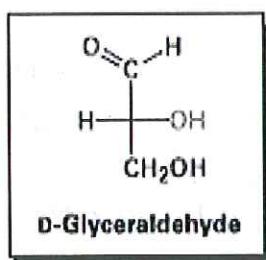
D-L doesn't correlate w/ R-S.

D,L designations have No relevance to the direction in which polarized light is rotated by these carbohydrates

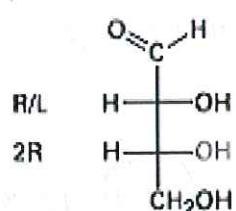
All naturally occurring carbohydrates are in the D-form

Amino Acids

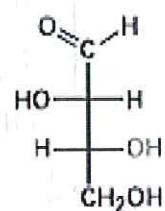
L-form



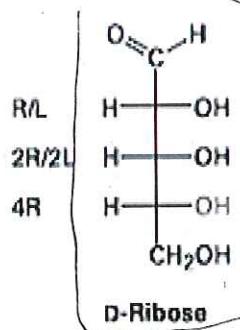
memorize  
structure/name  
of circled.



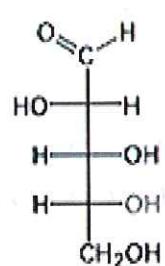
**D-Erythrose**



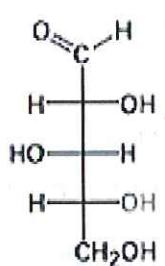
**D-Threose**



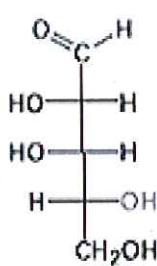
**D-Ribose**



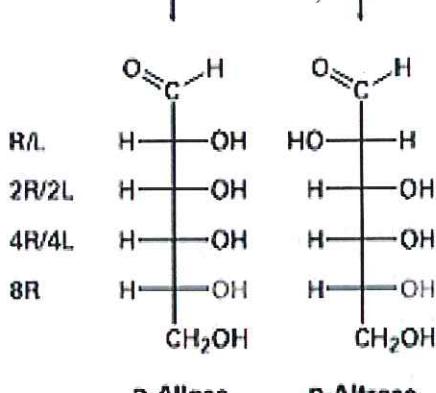
**D-Arabinose**



**D-Xylose**

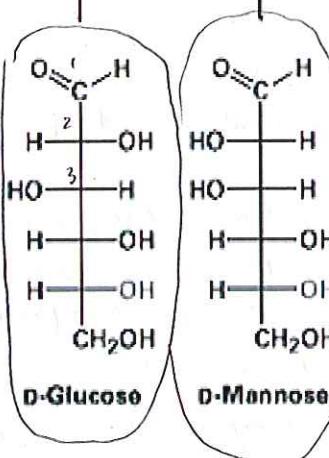


**D-Lyxose**

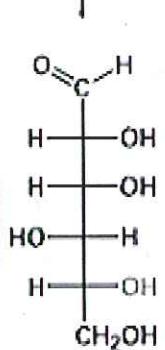


**D-Allose**

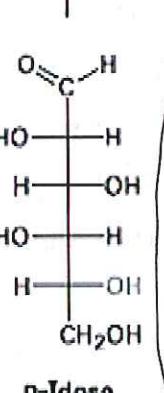
**D-Altrose**



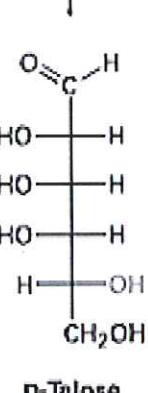
**D-Mannose**



**D-Gulose**



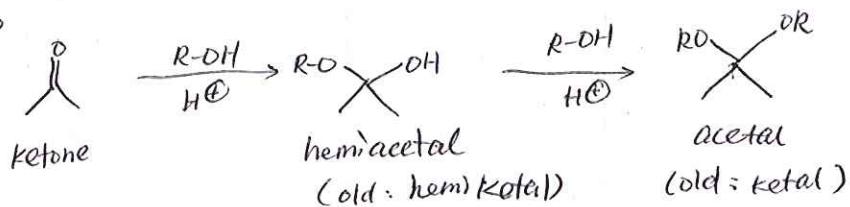
**D-Galactose**



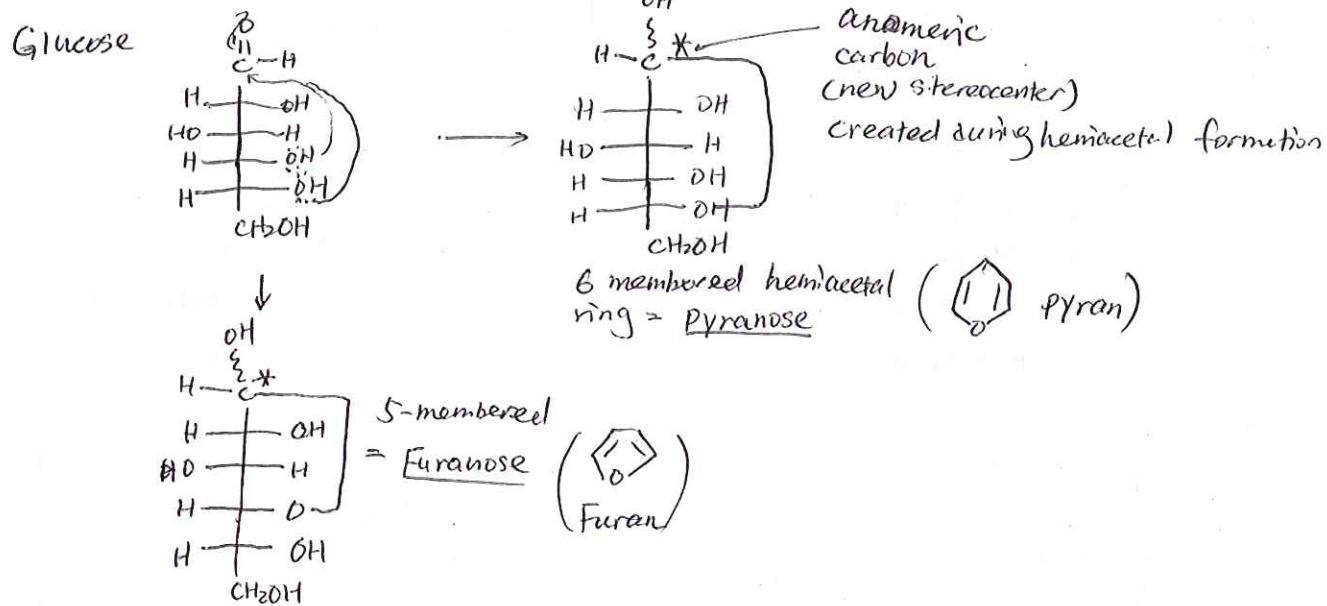
**D-Talose**

## Review hemiacetal formation

CH16

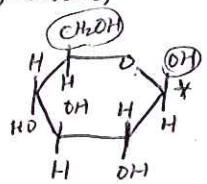


Glucose



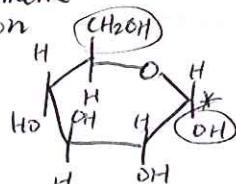
Haworth Projections

planar hexagon



Same direction

\*: anomeric carbon

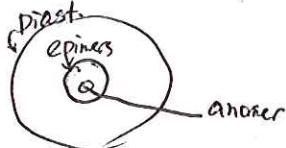


opposite direction

Anomers: Carbohydrates / Molecules that differ in configuration at anomeric carbon (special case of diastereomer) or epimers

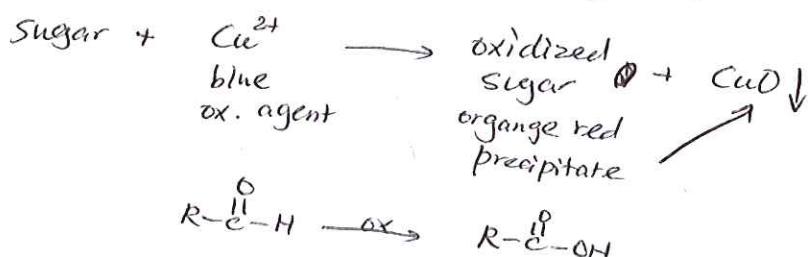
Memorize the Haworth Proj of Glucose then generate others

Epimers: diastereomers that differ only in the config. of a single stereocenter



A reducing sugar is easily oxidized  
all monosaccharides are reducing sugar

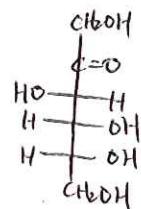
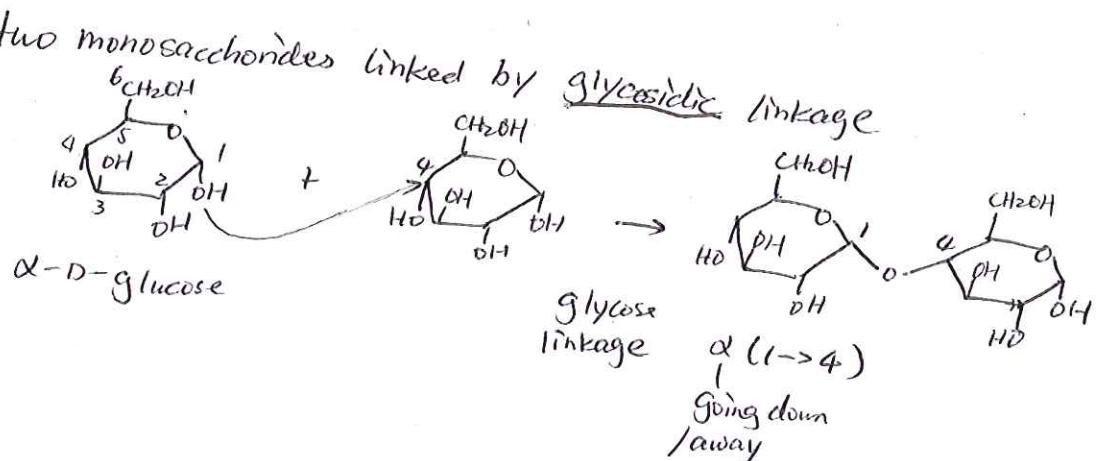
## Benedict's reagent tests for reducing Sugars



## Important monosaccharides

- Glucose: most nutritionally important aka dextrose or blood sugar
  - Galactose: a component of a disaccharide, lactose.
  - Fructose: a ketohexose, the sweetest monosaccharide

## Disaccharides



## Poly saccharide

polymers of carbohydrates. typically 1000s subunits

(1) Structural polysaccharides  
eg. cellulose

(2) Nutritional polysaccharides  
e.g. starch

## MONOSACCHARIDE CLASSIFICATION (continued)

- Most monosaccharides are aldoses.
- Almost all natural monosaccharides belong to the D series.
- The maximum number of possible stereoisomers is  $2^n$ , where n = number of chiral carbon atoms.
- Half of stereoisomers are D and the other half are L.

# of Carbon Atoms	Name of Sugar Class	# of Chiral Carbon Atoms (n)	# of Stereoisomers ( $2^n$ )	# of D Stereoisomers	# of L Stereoisomers
3	triose	1	2	1	1
4	tetrose	2	4	2	2
5	pentose	3	8	4	4
6	hexose	4	16	8	8

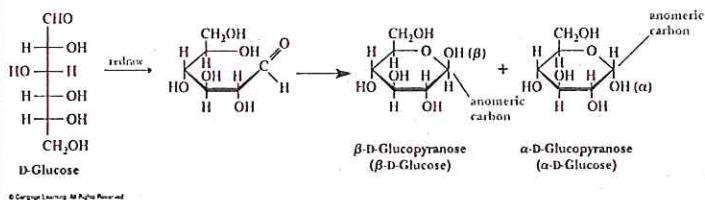
## PHYSICAL PROPERTIES OF MONOSACCHARIDES

- Most are called sugars because they taste sweet.
- All carbohydrates are solids at room temperature.
- Because of the many -OH groups, they form hydrogen bonds with water molecules and are extremely water soluble.

The Relative Sweetness of Sugars (Sucrose = 1.00)

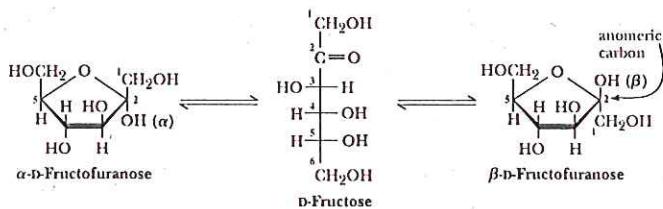
Sugar	Relative Sweetness	Type
Lactose	0.16	Disaccharide
Galactose	0.22	Monosaccharide
Maltose	0.32	Disaccharide
Xylose	0.40	Monosaccharide
Glucose	0.74	Monosaccharide
Sucrose	1.00	Disaccharide
Invert sugar	1.30	Mixture of glucose and fructose
Fructose	1.73	Monosaccharide

## Haworth Projections



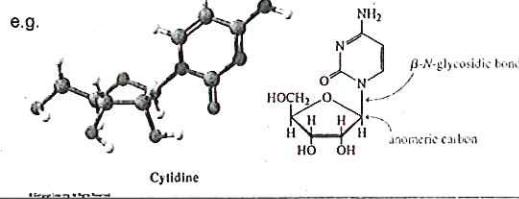
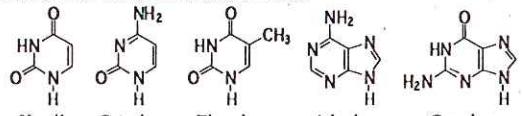
## Conformational Representations

- Other monosaccharides also form cyclic hemiacetals.  
e.g. D-fructose.



## N-Glycosides: DNA/RNA Nucleosides

- The anomeric carbon of a cyclic hemiacetal also undergoes reaction with the N-H group of an amine to form an N-glycoside.
  - N-glycosides of the following purine and pyrimidine bases are structural units of nucleic acids.



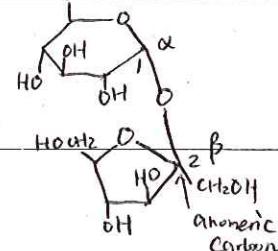
## IMPORTANT DISACCHARIDES (continued)

### Some Important Disaccharides

Name	Monosaccharide Constituents	Glycoside Linkage	Source
Maltose	Two glucose units	$\alpha(1 \rightarrow 4)$	Hydrolysis of starch
Lactose	Galactose and glucose	$\beta(1 \rightarrow 4)$	Mammalian milk
<b>Sucrose</b>	Glucose and fructose	$\alpha-1 \rightarrow \beta-2$	Sugar cane and sugar beet juices

*not reducing*

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## POLYSACCHARIDES

**Table 25.2** Relative Sweetness of Some Carbohydrates and Artificial Sweetening Agents\*

Carbohydrate	Sweetness Relative to Sucrose	Artificial Sweetener	Sweetness Relative to Sucrose
Fructose	1.74	Saccharin	450
Invert sugar	1.25	Acesulfame-K	200
Sucrose (table sugar)	1.00	Aspartame	160
Honey	0.97		
Glucose	0.74		
Maltose	0.33		
Galactose	0.32		
Lactose (milk sugar)	0.16		

\*We have no mechanical way to measure sweetness. Such testing is done by having a group of people taste solutions of varying sweetness and ranking them in order by taste.

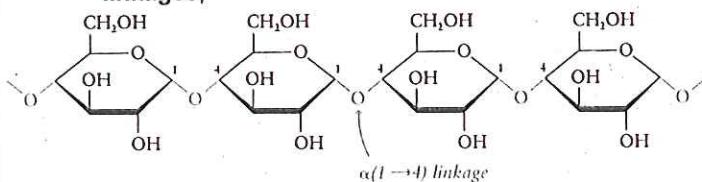
Properties of Polysaccharides Compared with Those of Monosaccharides and Disaccharides

Property	Monosaccharides and Disaccharides	Polysaccharides
Molecular weight	Low	Very high
Taste	Sweet	Tasteless
Solubility in water	Soluble	Insoluble or form colloidal dispersions
Size of particles	Pass through a membrane	Do not pass through a membrane
Test with $\text{Cu}^{2+}$ for reducing sugars	Positive (except for sucrose)	Negative

## IMPORTANT POLYSACCHARIDES

### Starch

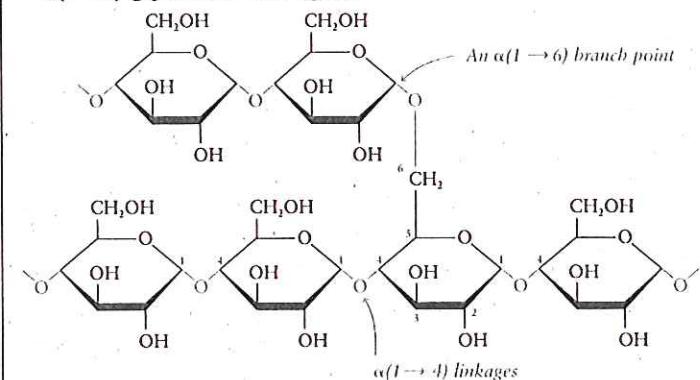
- a polymer consisting of glucose units.
- a major storage form of D-glucose in plants.
- one of two forms, which are:
  - unbranched amylose (10-20%), which is composed of 1000-2000 glucose units with  $\alpha(1 \rightarrow 4)$  glycosidic linkages;



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## IMPORTANT POLYSACCHARIDES

- and branched amylopectin (80-90%) with  $\alpha(1 \rightarrow 4)$  and  $\alpha(1 \rightarrow 6)$  glycosidic linkages.



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## IMPORTANT POLYSACCHARIDES

### Glycogen (animal starch)

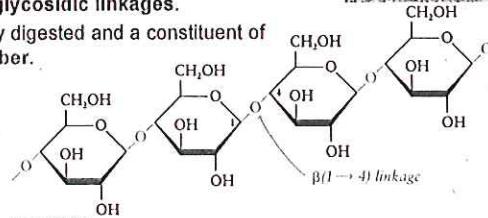
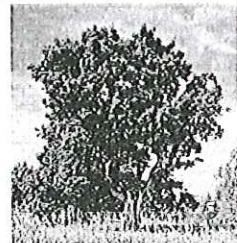
- a polymer of glucose units.
- used by animals to store glucose, especially in the liver and muscles.
- structurally similar to amylopectin with  $\alpha(1 \rightarrow 4)$  and  $\alpha(1 \rightarrow 6)$  linkages, but more highly branched.



## IMPORTANT POLYSACCHARIDES

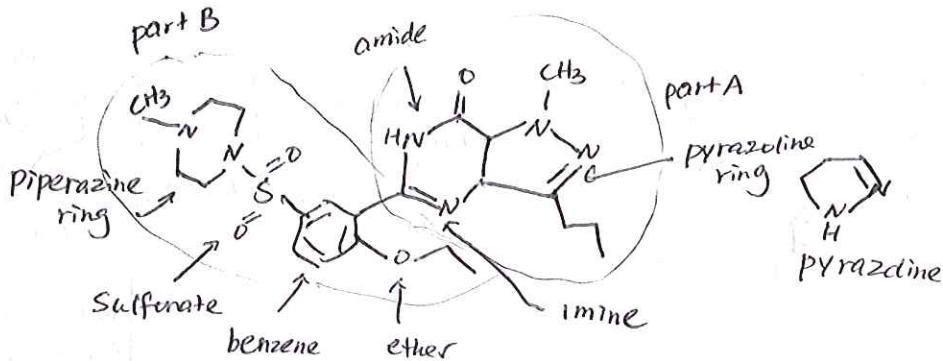
### Cellulose:

- a polymer of glucose units.
- the most important structural polysaccharide.
- the most abundant organic compound on earth.
- found in plant cell walls.
- a linear polymer like amylose, but has  $\beta(1 \rightarrow 4)$  glycosidic linkages.
- not easily digested and a constituent of dietary fiber.

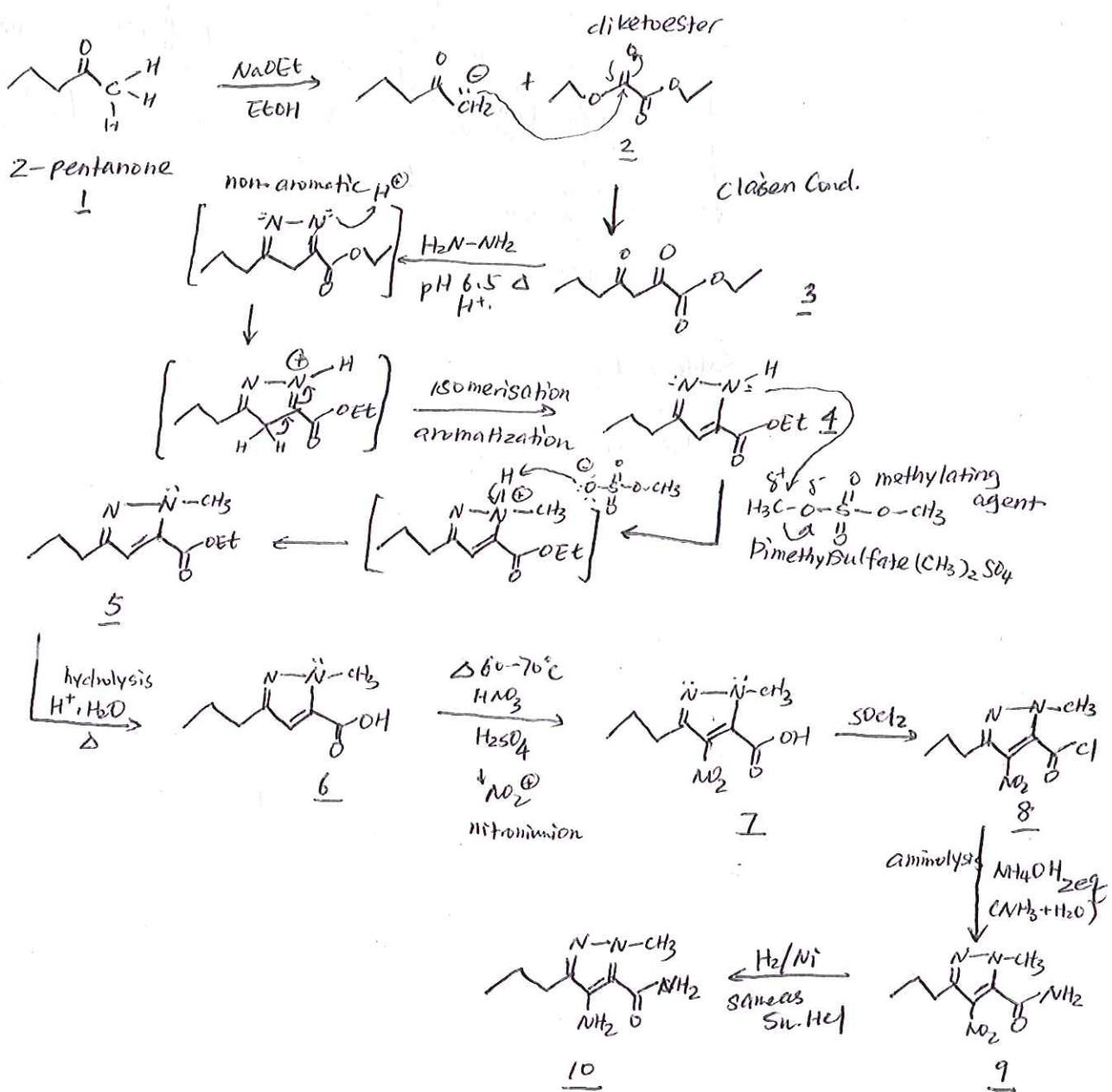


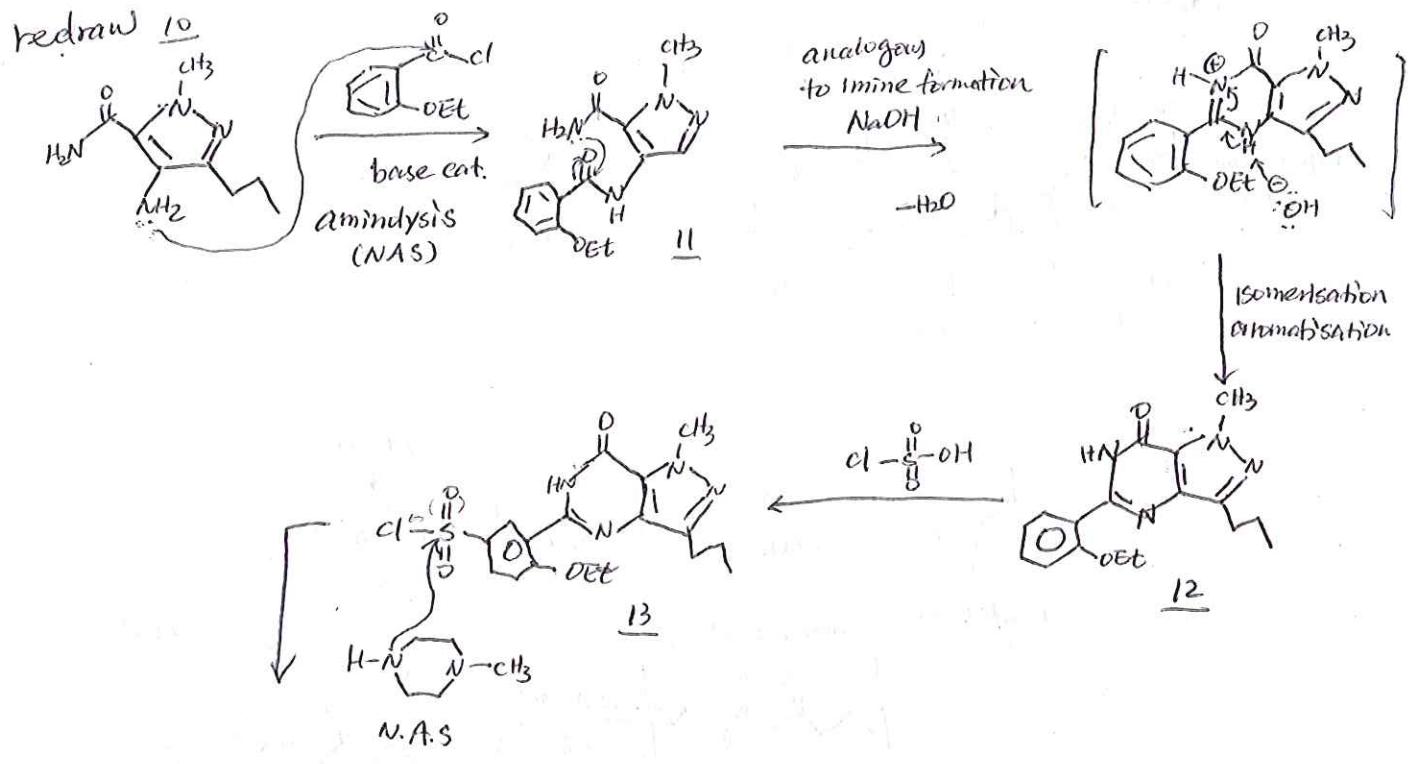
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# Total Synthesis of Viagra (Sildenafil)



Start.





Sildenafil  
 aka  
 Viagra

## Total Synthesis of Diazepam (Valium)

