# Chapter 21: Synthesis

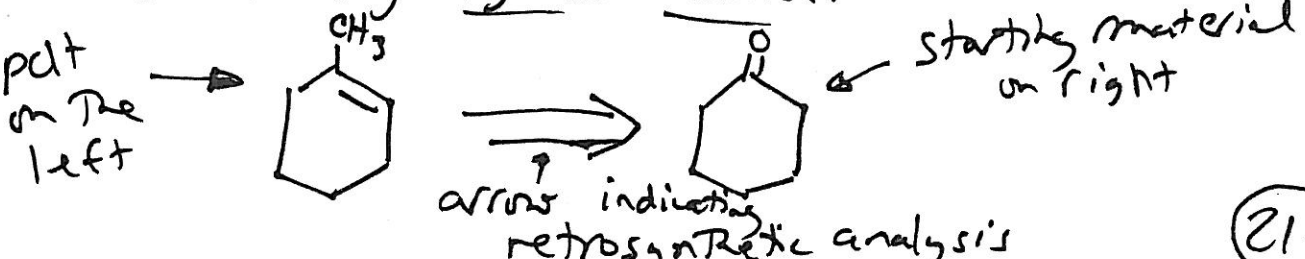
## Retrosynthetic Analysis

– a method chemists use where they work backward from the product to determine the starting material from which the pdt can be made.

- A specific type of arrow is used to show a retrosynthetic analysis:

| Type of arrow | Depicts |
|---|---|
| → | SM to pdt |
| ⇌ | equilibrium |
| ↔ | resonance |
| ⟹ | retrosynthetic analysis |

Example: Synthesize 1-methyl cyclohexene from cyclohexanone and any organic alcohol.



- In a retrosynthetic analysis one needs to Think backwards:

← How can we form an alkene?

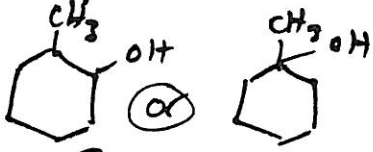
- dehydration of an alcohol
- dehydrohalogenation
- reduction of an alkyne w/ poisoned catalyst

etc...

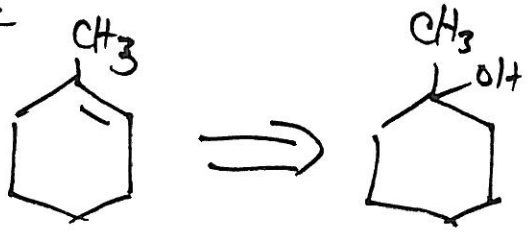
- Which one seems best, considering the starting material (right now) structure?

→ dehydration of an alcohol (why? (have oxygen in SM)) → 

What alcohol? Two are possible:



Choose:

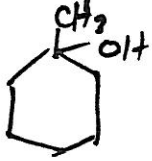


But could also have chosen (then would have different synthesis)

(sometimes there is more than one way to make a cmpd)

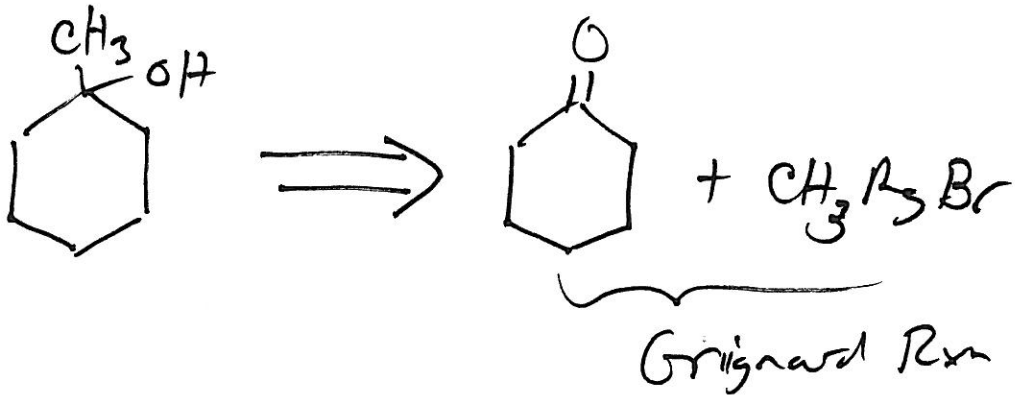
Next, Think backwards again... (look at SM)

- Is it possible to make



from  ??

How?




- But question says use cyclohexanone and any organic alcohol. This synthesis shows cyclohexanone + $CH_3MgBr$

$CH_3MgBr \Longrightarrow CH_3OH$ ?? Prepare Grignard reagent from alcohol

→ can this be done in 1 step?

No. $CH_3MgBr \Longrightarrow CH_3Br \Longrightarrow CH_3OH$

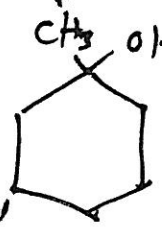
another possibility $CH_3MgBr \Rightarrow CH_3Br \Downarrow CH_3OTs \Downarrow CH_3OH$

- Now outline the synthesis (with reagents) using the retrosynthetic analysis information.

$CH_3OH \xrightarrow[\text{or } HBr]{PBr_3} CH_3Br \xrightarrow{Mg} CH_3MgBr$

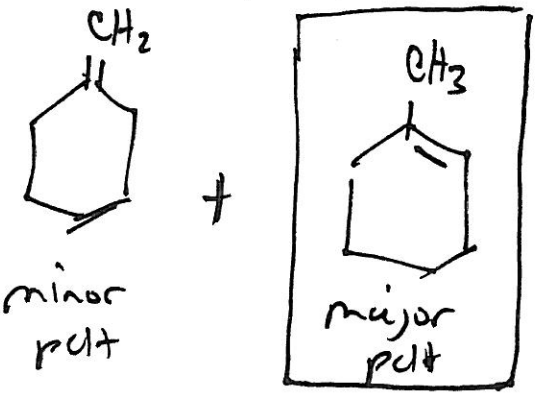
1) 

2) $H_3O^+$



$\xrightarrow[\Delta]{\text{conc. } H_2SO_4}$ (acid catalyzed dehydration)

Saytzeff's rule



- Sometimes it's useful in a retrosynthetic analysis to use a structure called a SYNTHON

Synthon = a unit that may be found in a number of different actual reagents

Example:

In the previous retrosynthetic analysis the grignard reagent could've been an organolithium reagent as well. A synthon for this step would be:


→ Either $CH_3MgX$ or $CH_3Li$ would work for that step (both reagents act like $CH_3^\ominus$).

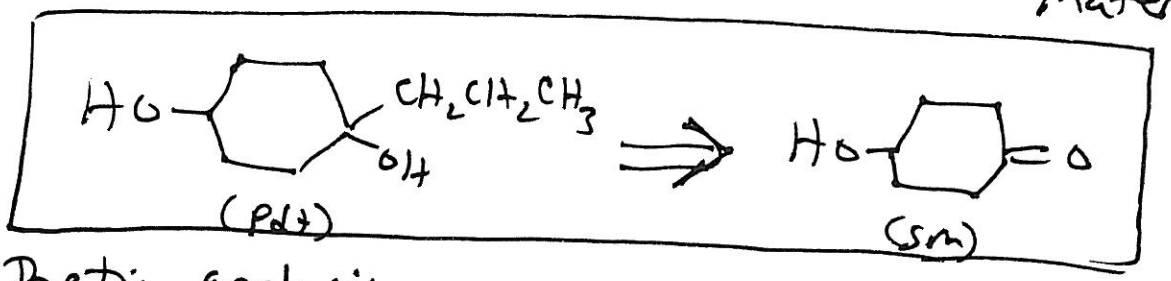
## Synthesis of Compounds with More than One Functional Group

Compounds with more than one functional group sometimes need protecting groups to be used in their synthesis. (we talked about protecting groups already in the synthesis of peptides Ch. 15) (Boc + Cbz)

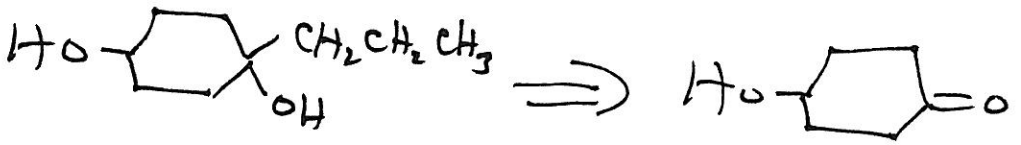
→ we will look at specific protecting group in the next section, but for now.....

.... Let's do an example with a generic Protecting Group (PG).

- Using a generic protecting group(s), synthesize the following compound from the given starting material.



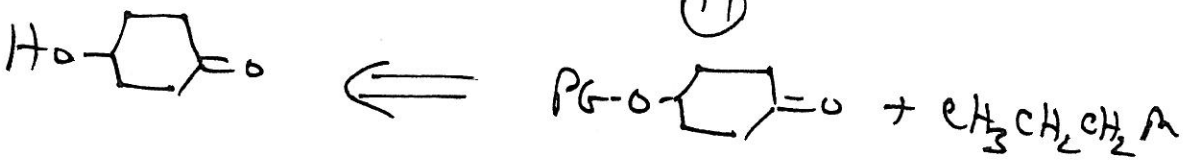

- Retrosynthetic analysis



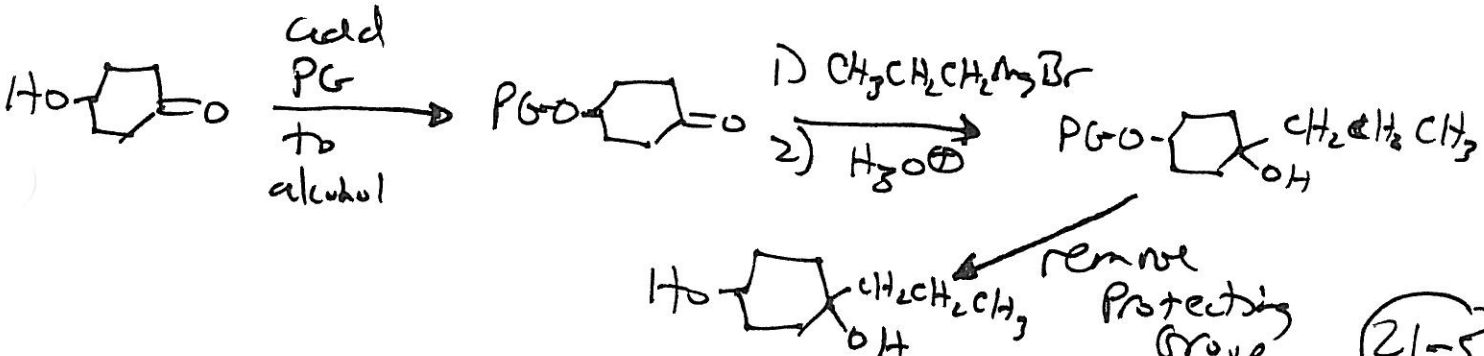

+ $CH_3CH_2CH_2M$ (Grignard or organolithium)

PROBLEM - organolithium or grignard reagent will react with O-H group & form propane → need to protect the OH group so...

Retrosynthetic Analysis


Synthesis

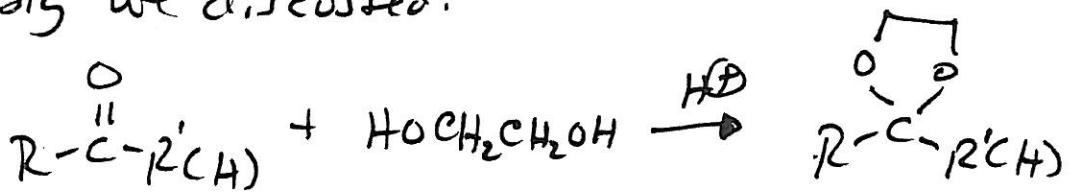


# Protecting Groups in Synthesis

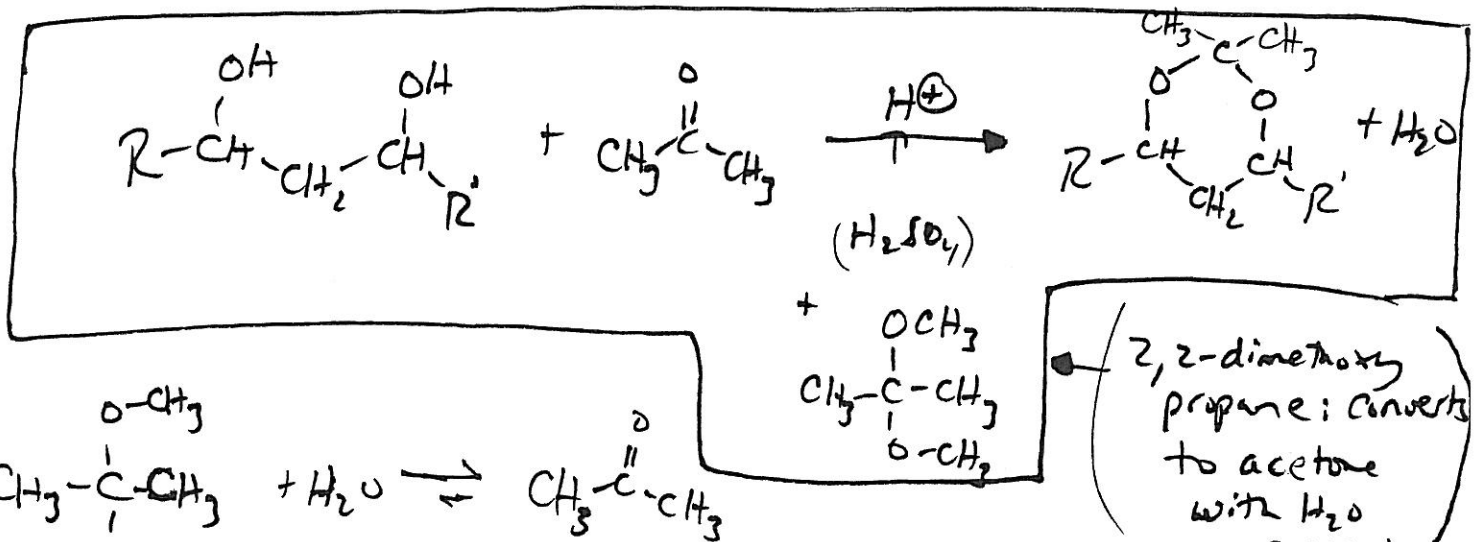
- Protecting groups convert a functional group that is "sensitive" to a specific reagent(s) to one that is not.
- The protecting group can be easily removed to give back the original functional group.

## Acetals + ketals

Previously we discussed:

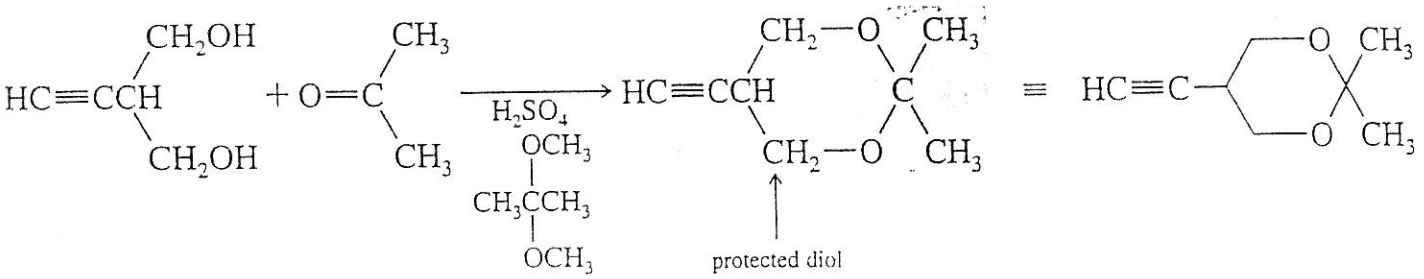


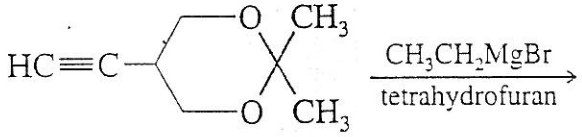
Can also protect 1,2-diols + 1,3-diols as ketals, acetals

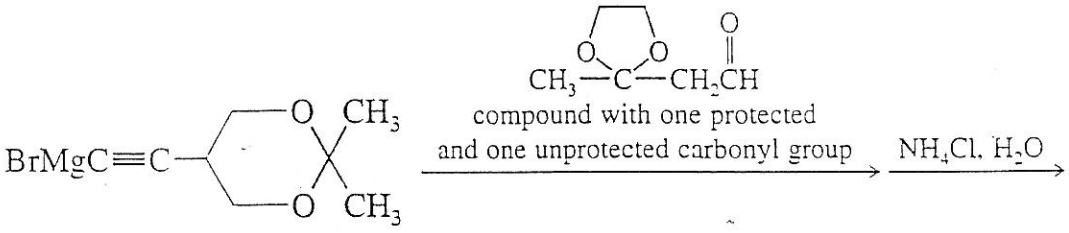


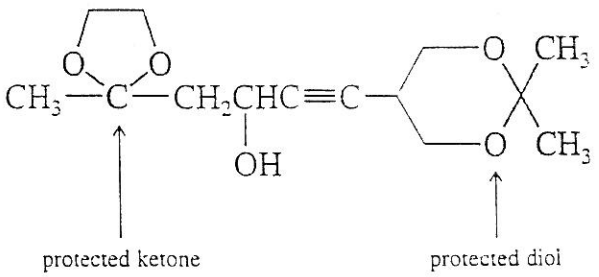

(hydrolysis of a ketal)

# Example of Protecting Group Use (from text) p844

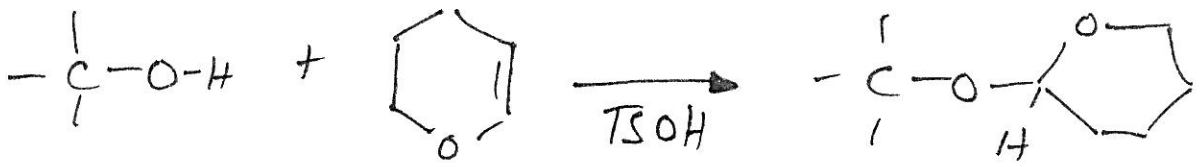



- Can protect -O-H groups as **Acetals**

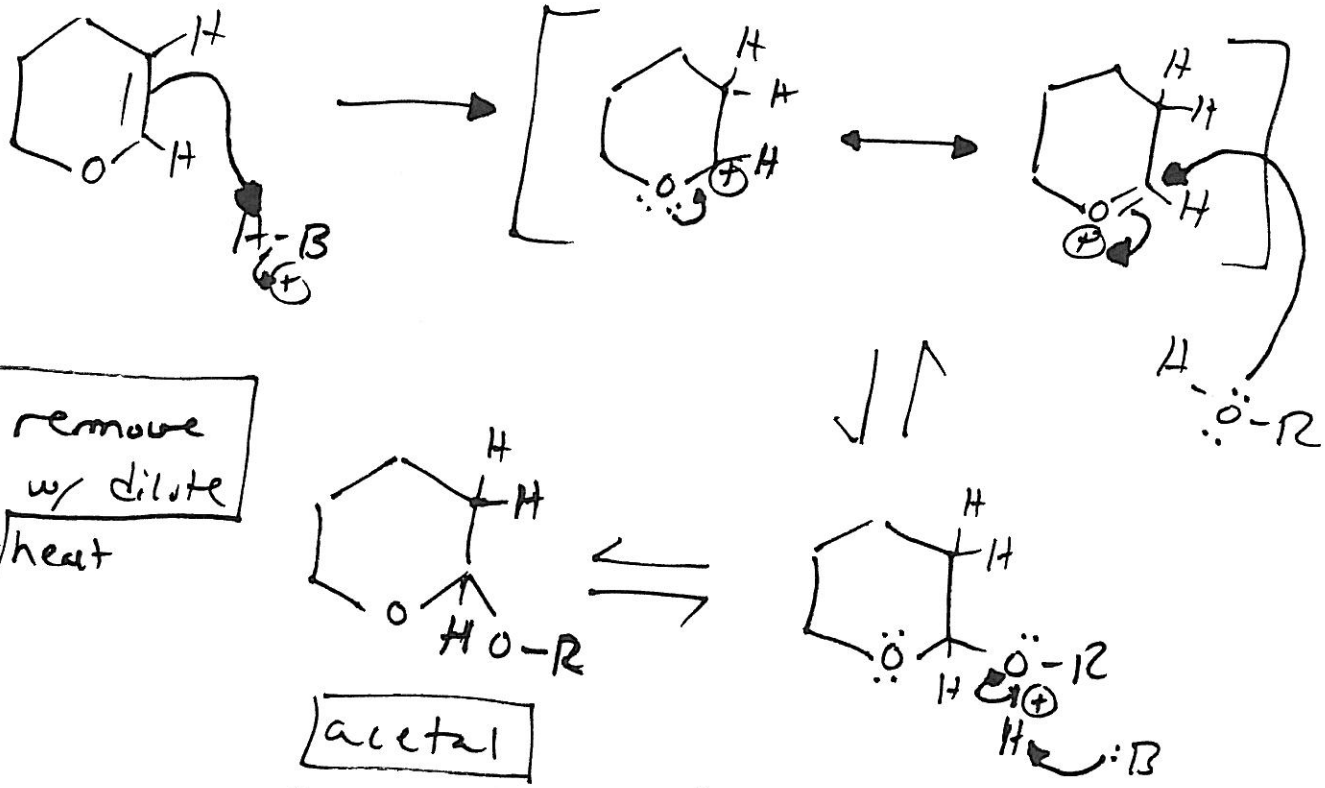



dihydropyran (DHP)

tetrahydro pyranyl group (THP)

—C—O—THP

# Mechanism

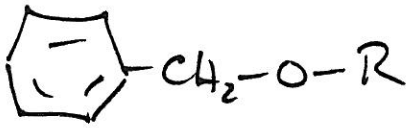


- Can remove THP w/ dilute $H^+$ / heat / $H_2O$

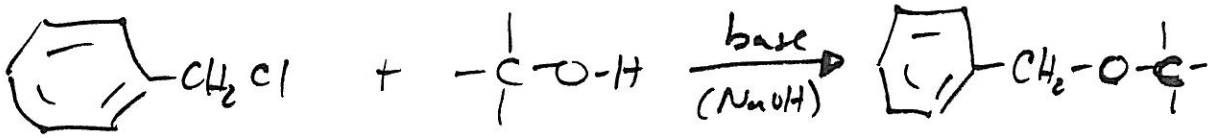


acetal (protected alcohol)

# Ethers as Protecting Groups (protect alcohols)

- Benzyl ethers 

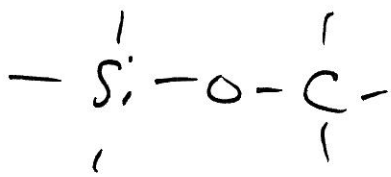
To make:



benzyl chloride

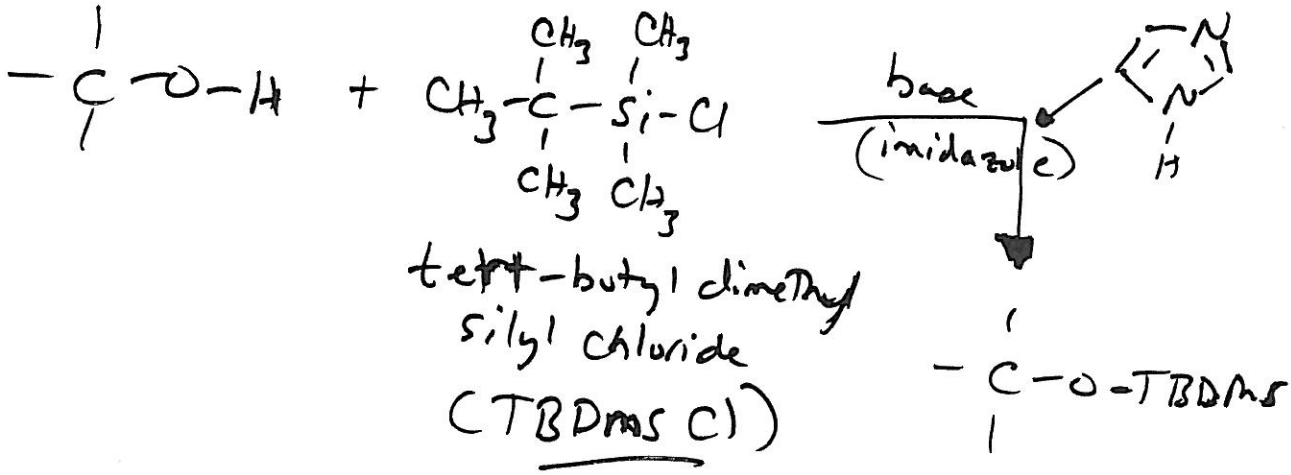
- benzyl ethers are NOT cleaved by acidic conditions. They are removed by a Hydrogenation Rxn ($H_2$, Pt) or Pd/C

# Silyl Ethers

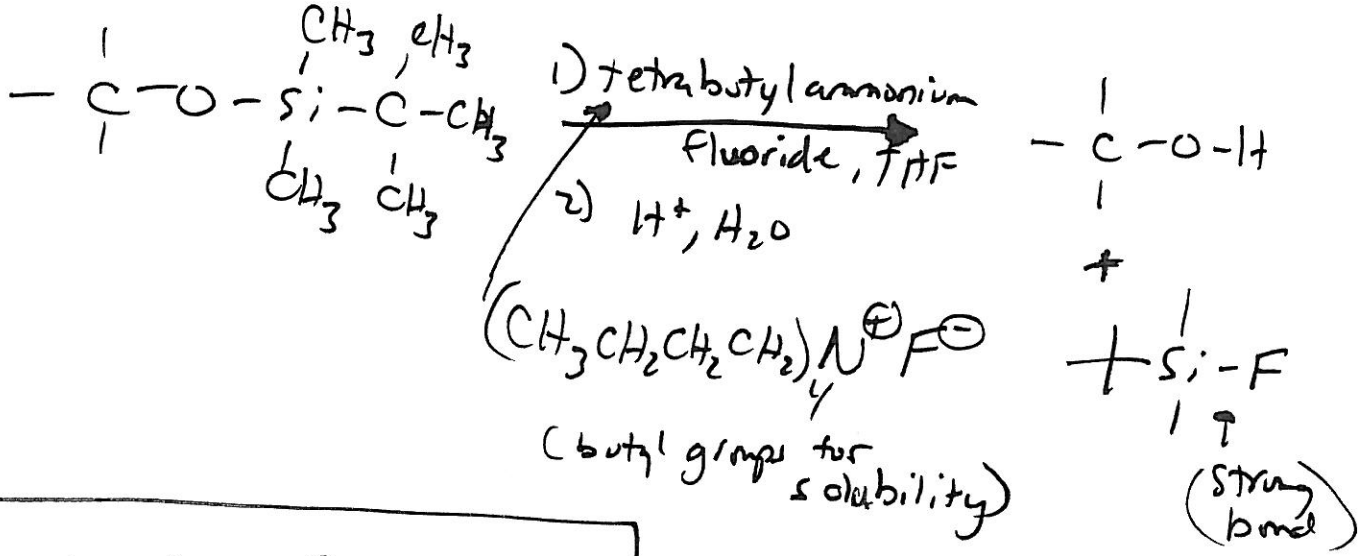


(protecting group for alcohols)

## Protection

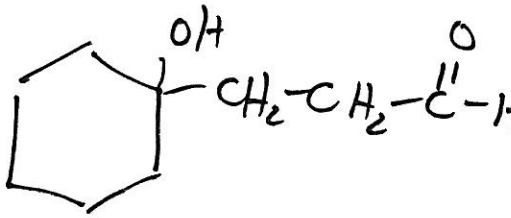


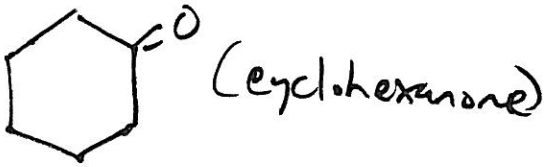

## Deprotection

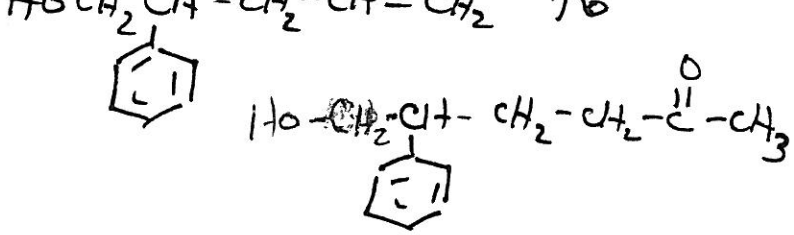



# Designing Syntheses

## Example #1

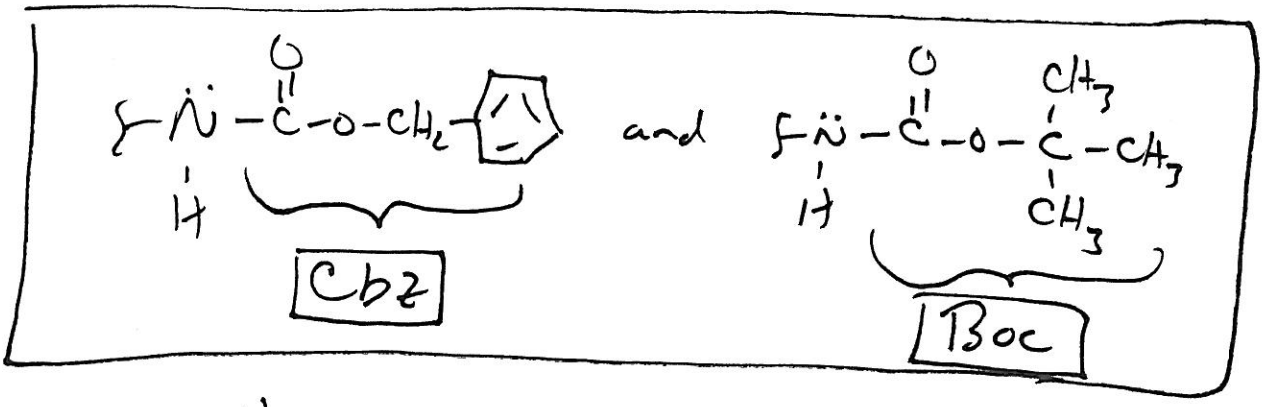
Synthesize  from

 (cyclohexanone) and any other needed reagents.

**Problem #2** Convert  to

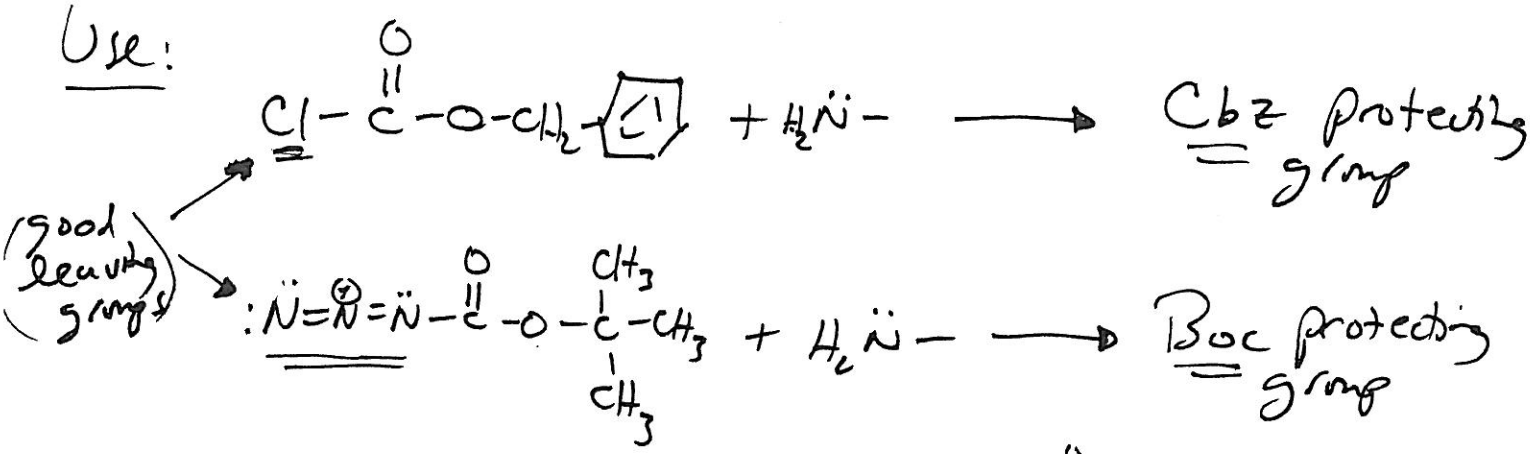
# Protecting Groups for Amines

- In Chapter 15 we discussed two amine protecting groups used in the synthesis of peptides:




- These protecting groups can also be used in the synthesis of other amine containing cmpds that are not peptides

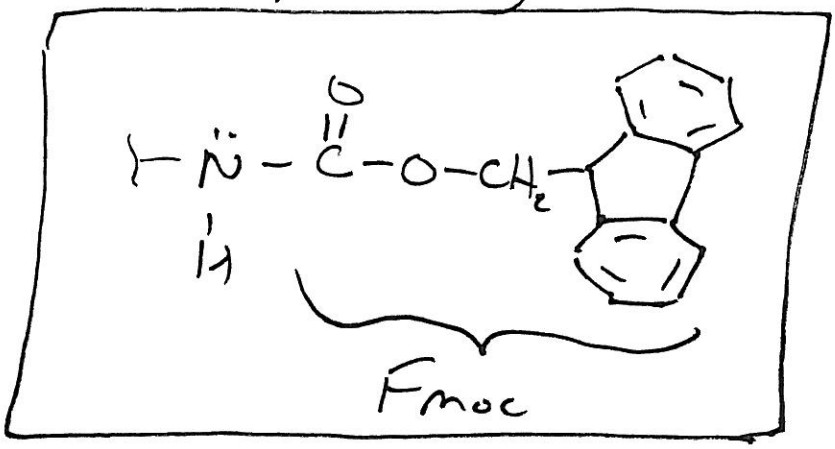
Use:




- to remove Boc → use: dry $CF_3CO_2H$ in $CH_2Cl_2$ (or) dry HBr in ether
- to remove Cbz → use: dry HBr in $CH_3CO_2H$ (or) $H_2$, Pd/C

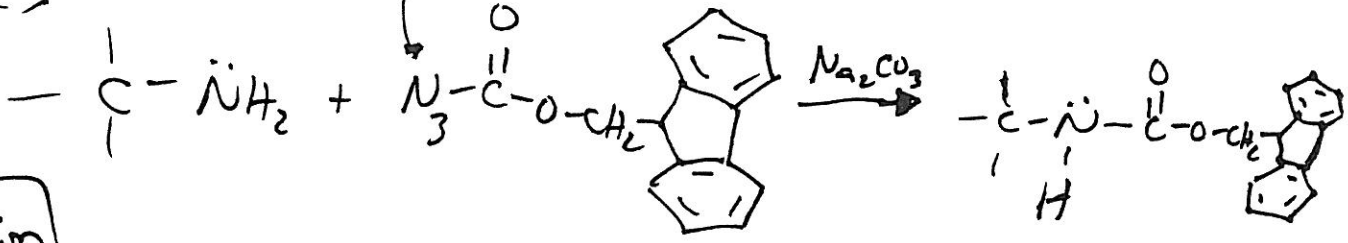
(*) Note: both removed by dry Acids

- Another amine protecting group is Fmoc

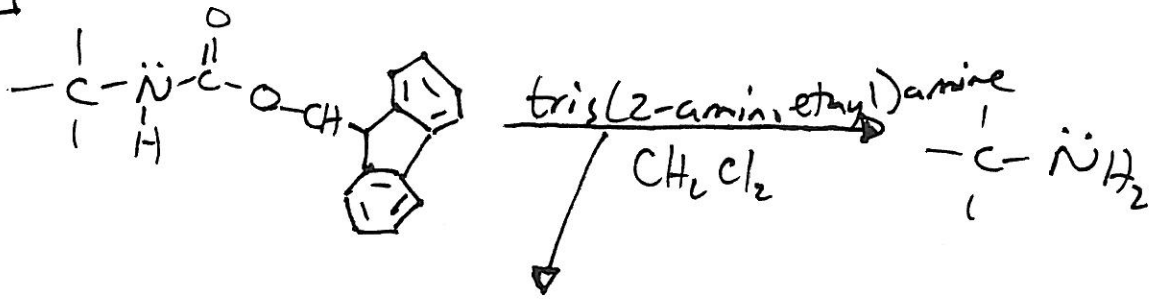



Fmoc is an amine protecting group that is resistant to acidic conditions (removed by base instead).

**Protection**




**Deprotection**



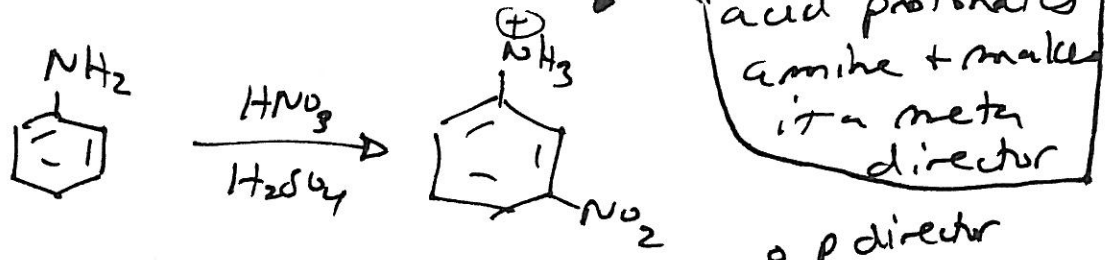

- Note similarity of Cbz, Boc + Fmoc structures (all are carbamates)

- Can choose the appropriate amine protecting group (Cbz/Boc or Fmoc) depending on if the multistep synthesis uses acidic or basic conditions

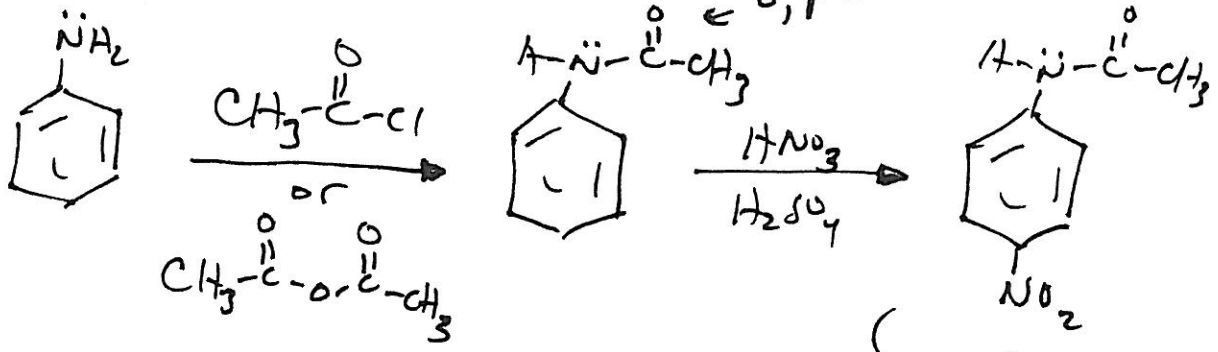
- Amides can also be protecting groups for amines, however, they are only used if the cmpd can stand up to harsh amide removal conditions.

→ Simple amides often used as protecting groups with aromatic amines

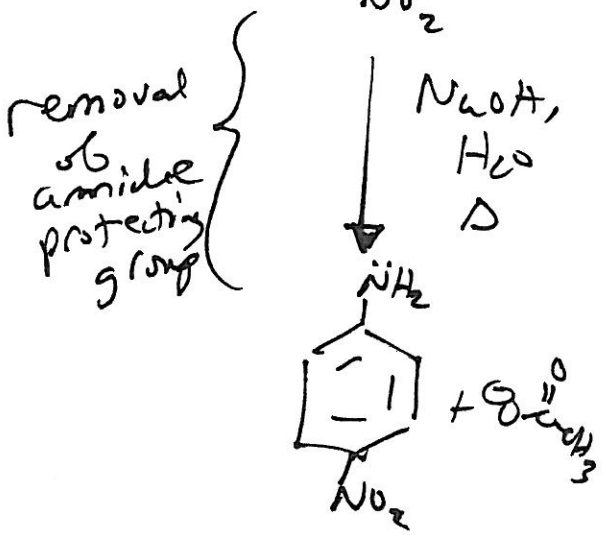
If:




Instead:




- If one uses $CF_3\overset{O}{\overset{\|}{C}}-Cl$ as the acylating agent (to protect an amine) the amide that is formed can be hydrolyzed (to remove the protecting group) under much less harsh conditions

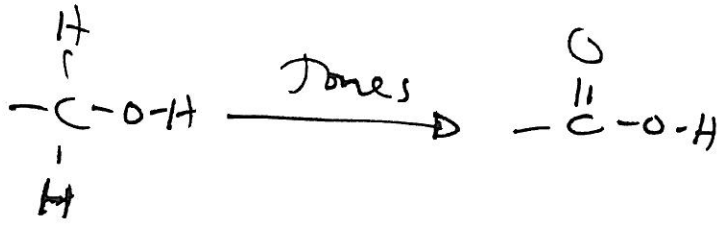



uses: $\boxed{TsCl/H_2O}$ weak base / less time / less heat

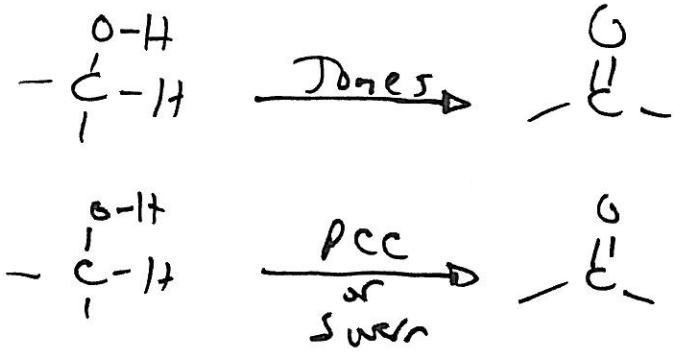
# Oxidation-Reduction Reactions in Functional Group Transformations

## Review

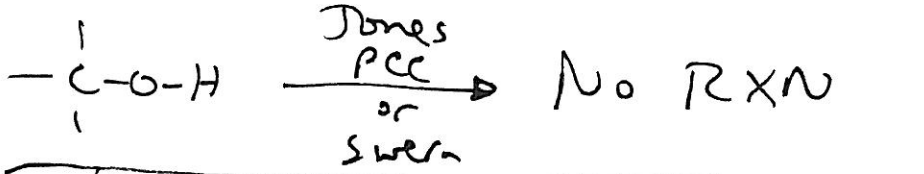
**1° alcohols**

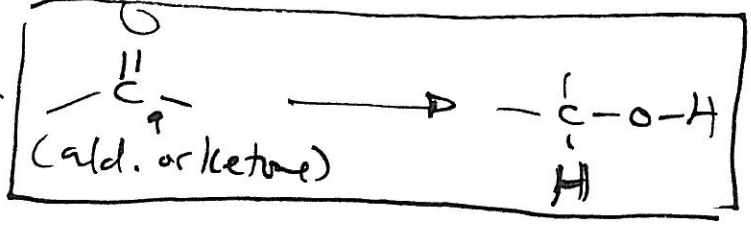



**2° alcohols**




**3° alcohols** – not reactive to oxidation




- To go from 


Use: 1) $NaBH_4$ (or) 2) $LiAlH_4$

↑ weaker reducing agent; only reduces aldehyde + ketones

↖ stronger reducing agent; reduces ald. + ketone and other carboxylic acid derivatives

# Reduction of Carboxylic Acids + Their Derivatives

- Lithium Aluminum hydride ($LiAlH_4$) or (LAH) reduces acids + acid derivatives

**Carboxylic acid** $R-\overset{O}{\overset{\|}{C}}-O-H \xrightarrow{1)\ LAH} \xrightarrow{2)\ H_3O^{\oplus}} R-CH_2-OH$ (1° alcohol) ← (difficult to do, though)

**Ester** $R-\overset{O}{\overset{\|}{C}}-O-R' \xrightarrow{1)\ LAH} \xrightarrow{2)\ H_3O^{\oplus}} R-CH_2-OH + HO-R'$ (1° alcohol) + (alcohol)

**N,N-disubst. amides** $R-\overset{O}{\overset{\|}{C}}-N(R'')-R' \xrightarrow{1)\ LAH} \xrightarrow{2)\ H_3O^{\oplus}} R-CH_2-N(R'')-R'$ ← N,N-disubst. amine

**nitrile** $R-C\equiv N \xrightarrow{1)\ LAH} \xrightarrow{2)\ H_3O^{\oplus}} R-CH_2-NH_2$ ← 1° amine

(already saw this in Ch. 20) $R-\overset{O}{\overset{\|}{C}}-O-H$ and $R-\overset{O}{\overset{\|}{C}}-NH_2$ reductions

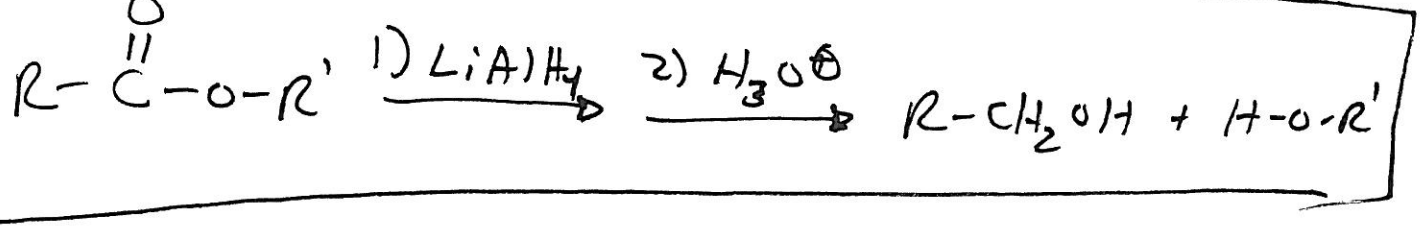
$R-\overset{O}{\overset{\|}{C}}-O-H$: Carboxylic acid

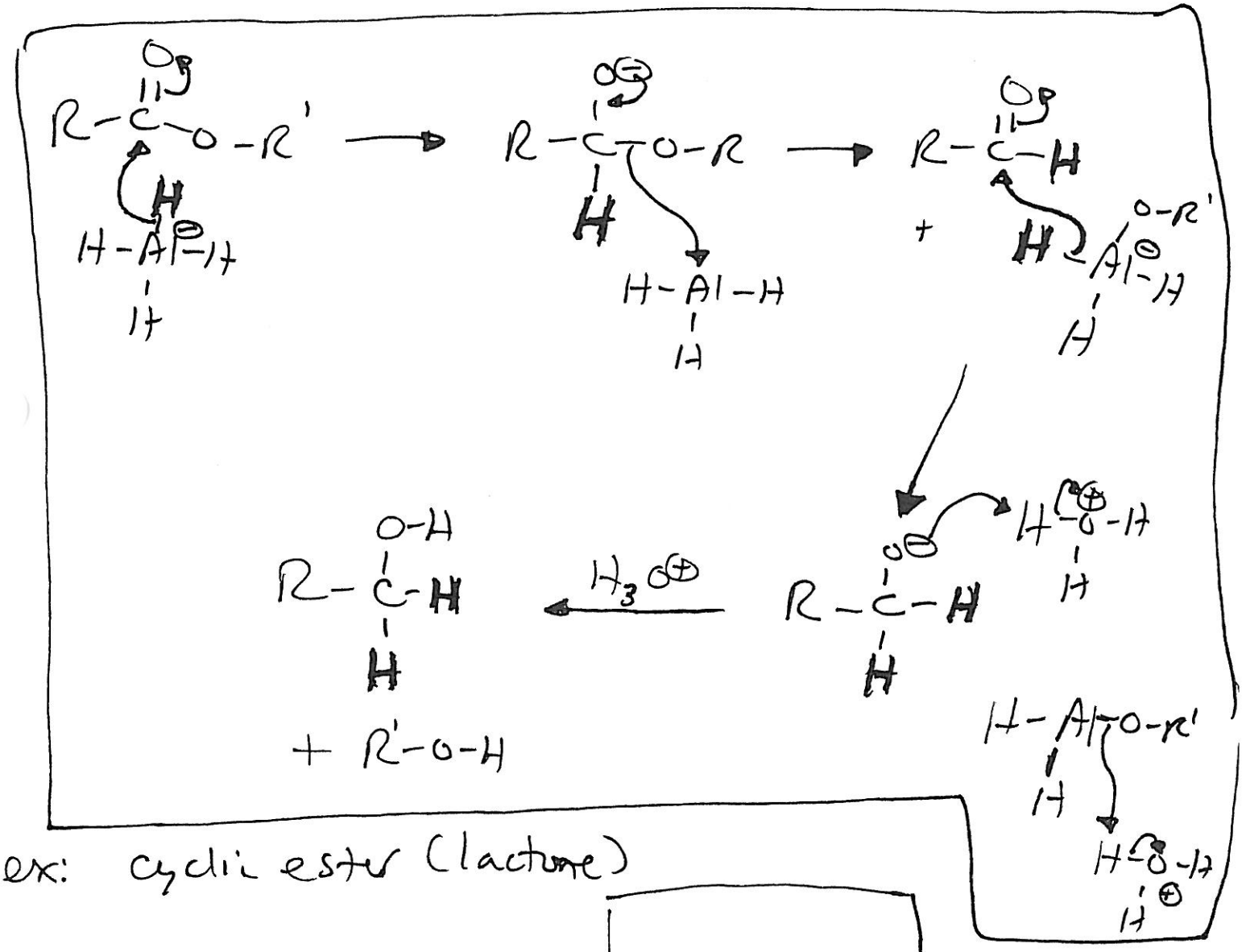
$R-\overset{O}{\overset{\|}{C}}-NH_2$: Unsubstituted amides (Can mono substituted amides)

with $LiAlH_4$ are more difficult to do (but can be done - usually lower yield though) than reduction of esters + N,N-disubstituted amides. WHY?

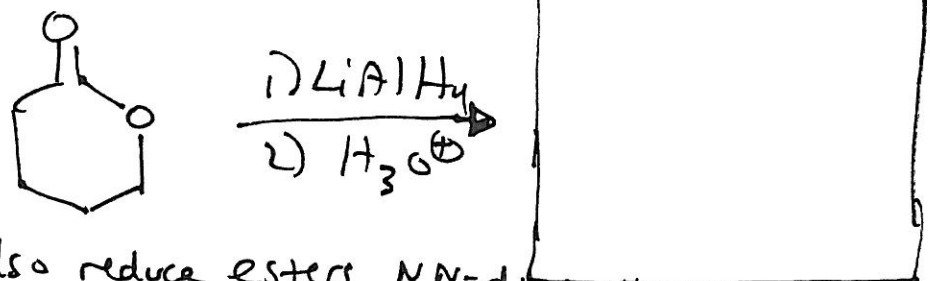
→ Because LAH deprotonates $R-\overset{O}{\overset{\|}{C}}-O-\underline{H}$ and $R-\overset{O}{\overset{\|}{C}}-\underset{H}{N}-\underline{H}$ + make insoluble salts + anions that are more resistant to nucleophilic attack by $H:^{\ominus}$

# Mechanism of Ester Reduction by $LiAlH_4$



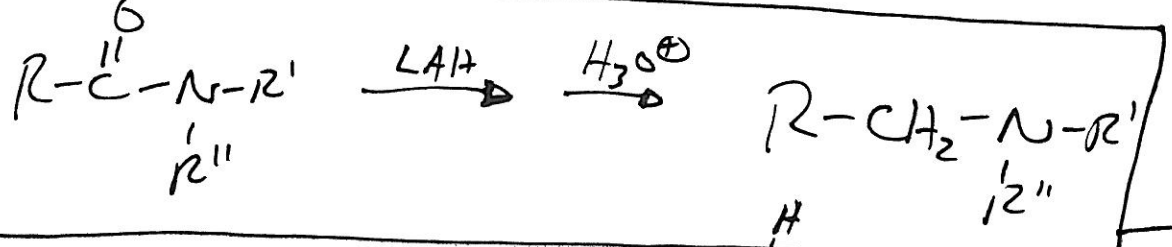



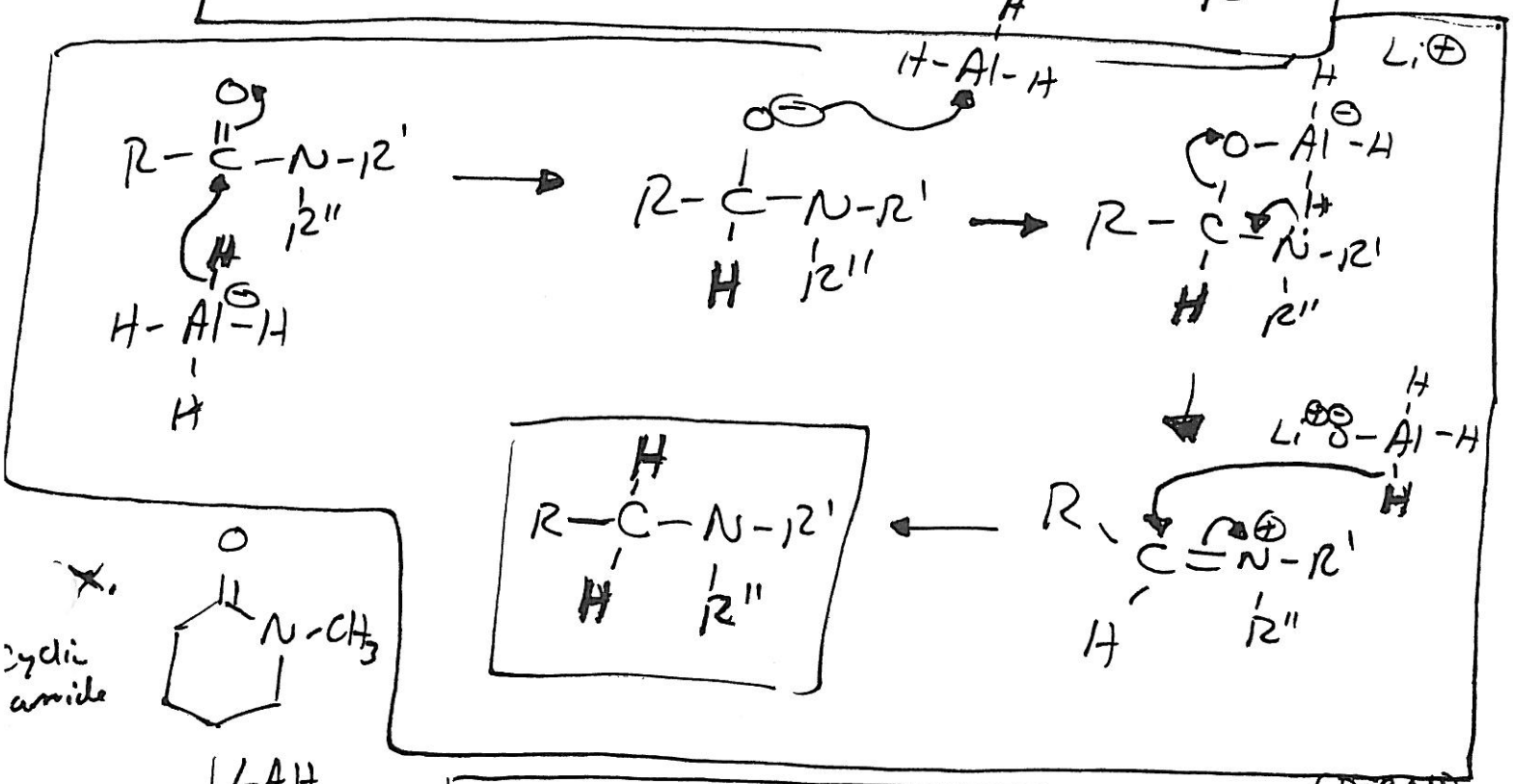

ex: cyclic ester (lactone)




⊛Can also reduce esters, N,N-disubstituted amides & nitriles to amines with $BH_3 \cdot S(CH_3)_2$ in THF

# N, N-disubstituted Amides w/ LAH (Mechanism)

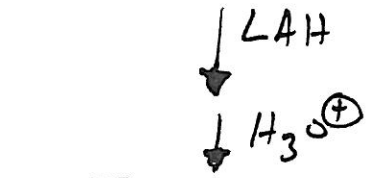


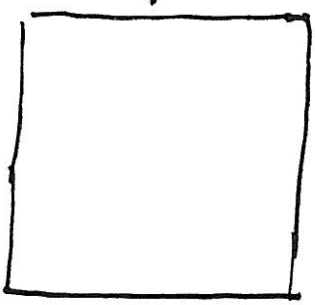






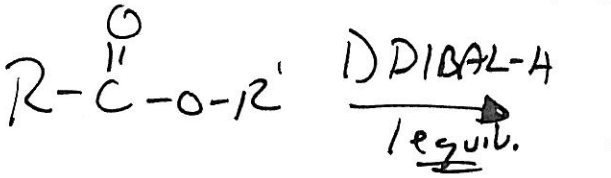
cyclic amide

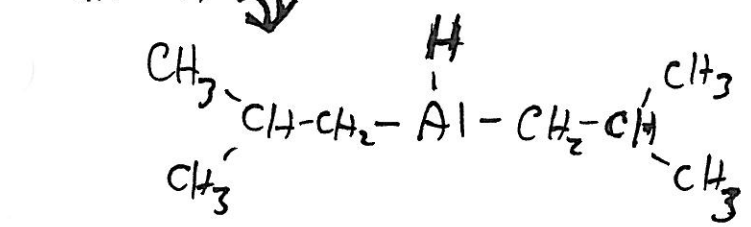




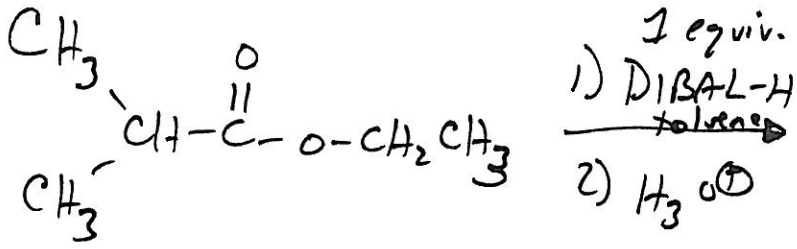
## Diisobutyl aluminum hydride (DIBAL-H)

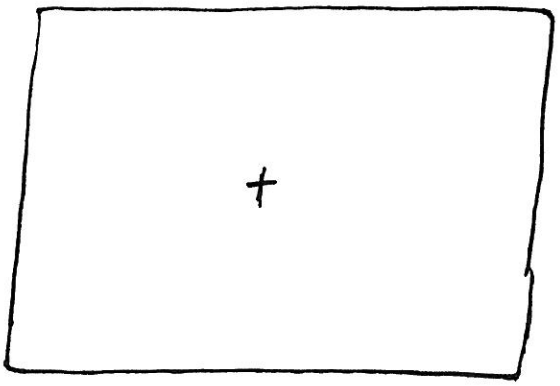
- milder reducing agent
- used to reduce esters + nitriles ⇒ aldehydes



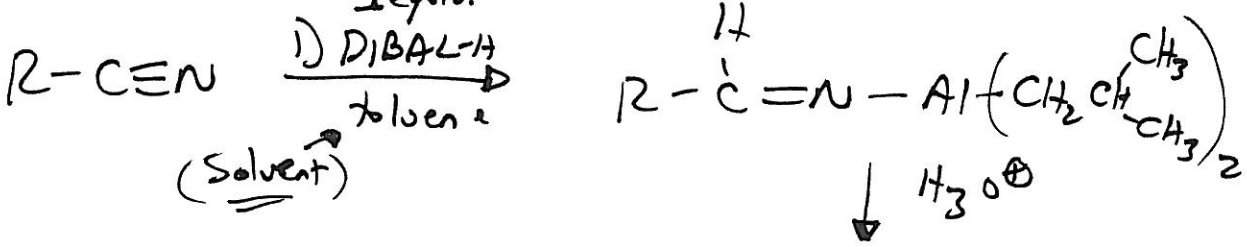


ex:

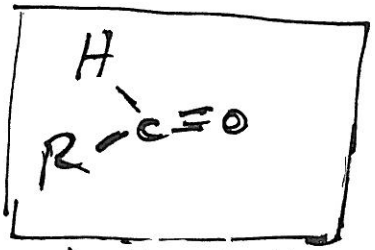


- Nitriles to aldehydes




(*) if one uses 4 equiv. DIBAL-H will reduce ester → 1° alcohol
nitrile → amide



- skip N-methoxy-N-methylamide reagent that stops at aldehyde stage (P861+862)

**Problem Solving** How would you carry out the following transformation?

# Carbon Nucleophiles Revisited

- Remember Grignard and organolithium reagents? (Of course you do!)

  → both react with carbonyl groups of aldehydes and ketones ($-\overset{\delta-}{\underset{\delta+}{C}}=O$)

  but don't react with electrophilic carbons of alkyl halides ($-\overset{\delta+}{C}-X$)

- Organocuprates do react with react with the electrophilic carbons of alkyl halides but don't react with $\overset{\delta-}{O}$ of aldehydes & ketones.

## Organocuprate Reagents

**Preparation:** (to make R-Li: (organolithium) $R-X + 2Li \longrightarrow R-Li + LiX$)

lithium organocuprate

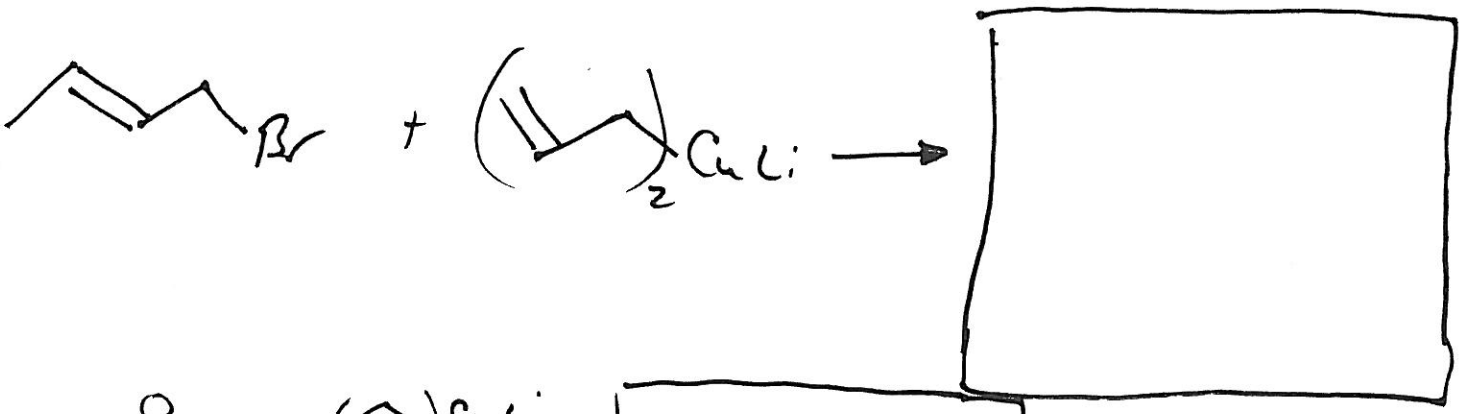
$$2\ R-Li + CuI \xrightarrow[\text{diethyl ether}\ 0^\circ C]{} R_2CuLi + LiI$$

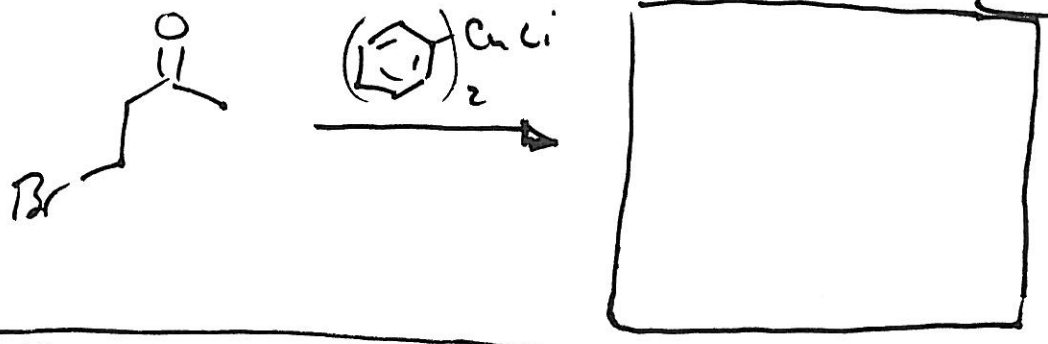
**Example:**

$$CH_3-\overset{\delta-}{Br} + \left(\begin{matrix} CH_3 \\ \diagdown \\ CH \\ \diagup \\ CH_3 \end{matrix}\right)_2 CuLi \longrightarrow \begin{matrix} CH_3 \\ \diagdown \\ CH-CH_3 \\ \diagup \\ CH_3 \end{matrix}$$

new C-C bond!

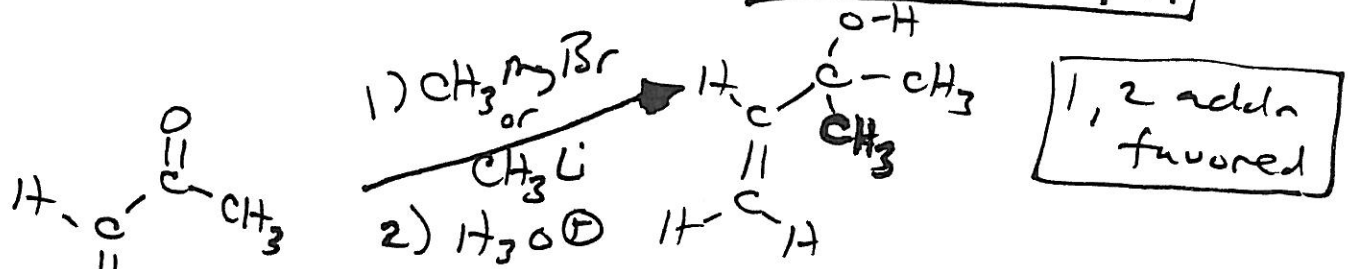
like $R^\ominus$



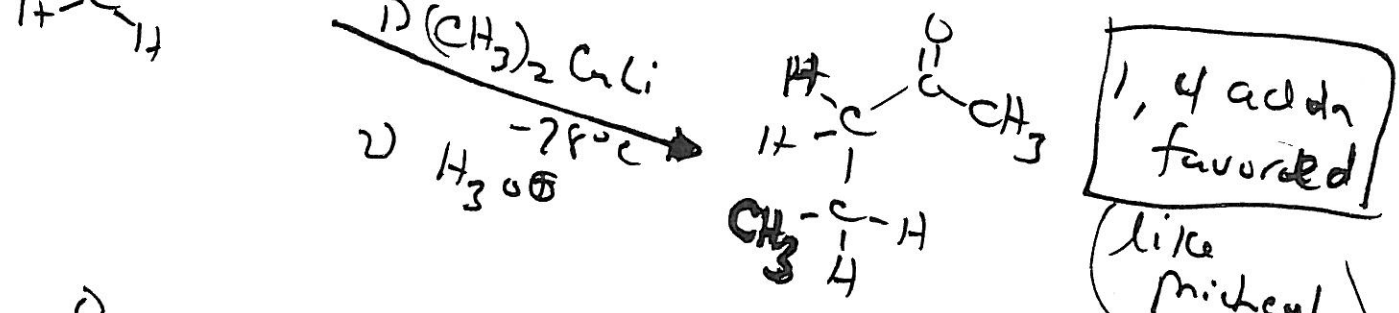


- an organolithium ($R_2Li$) or grignard reagent would attack C=O group, not an $S_N2$ displacement of Br

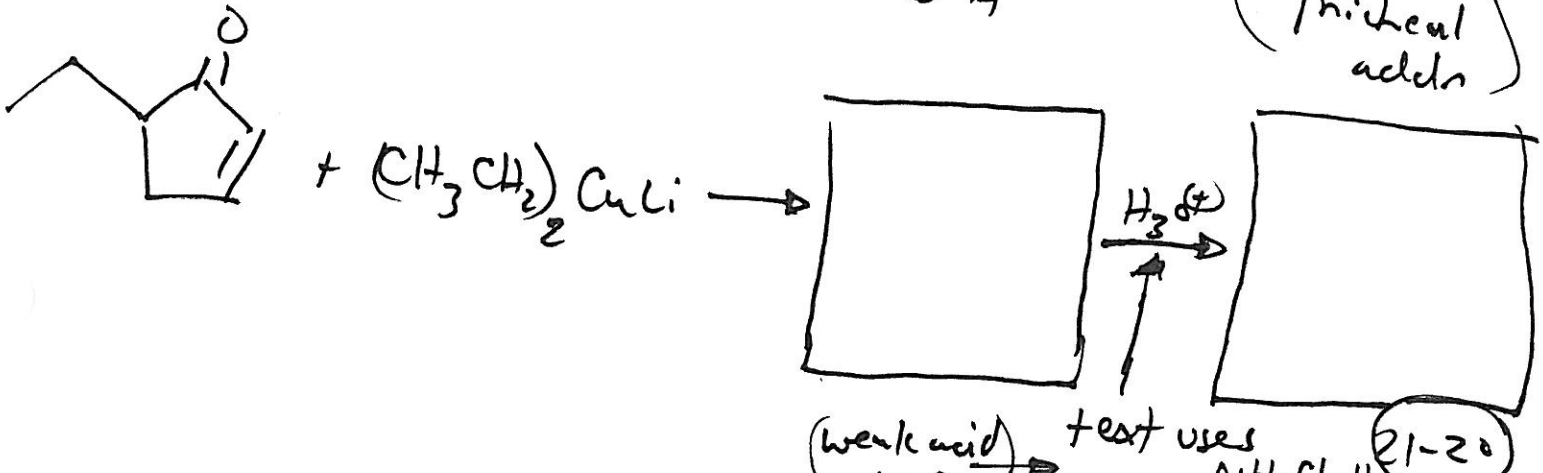
- What if you have an α, β unsat. carbonyl cmpd?



1, 2 addn favored



1, 4 addn favored (like Michael addn)



test uses $NH_4Cl, H_2O$ 21-20

# Regioselectivity of The Enolization Rxn

- Thermodynamic versus Kinetic Enolates

* triethyl amine - relatively weak base

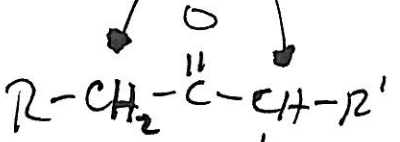
2 possible α-hydrogens to pull off. Which enolate forms?

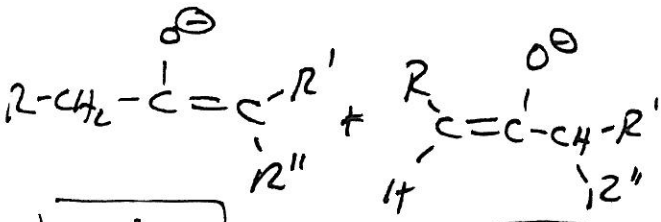
Rxn (A)

1) $(CH_3CH_2)_3N$:

DMF

Δ (high temp)

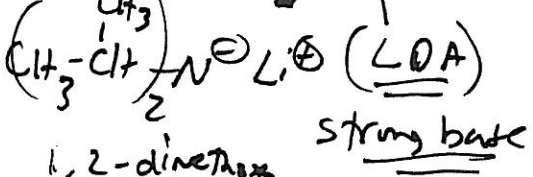




major enolate

minor enolate

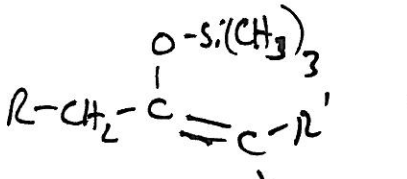
Rxn (B)



1,2-dimethoxy ethane

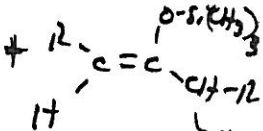
0°C (cold)

strong base

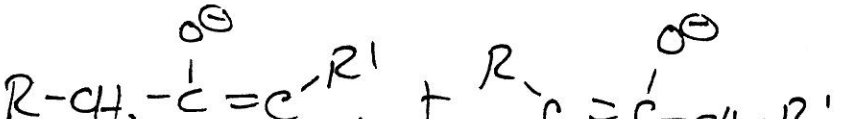


Thermodynamic Pdt

major pdt



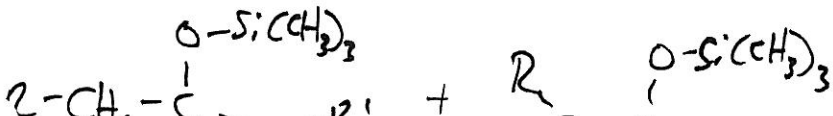
minor pdt



minor enolate

major enolate

$(CH_3)_3SiCl$



minor pdt

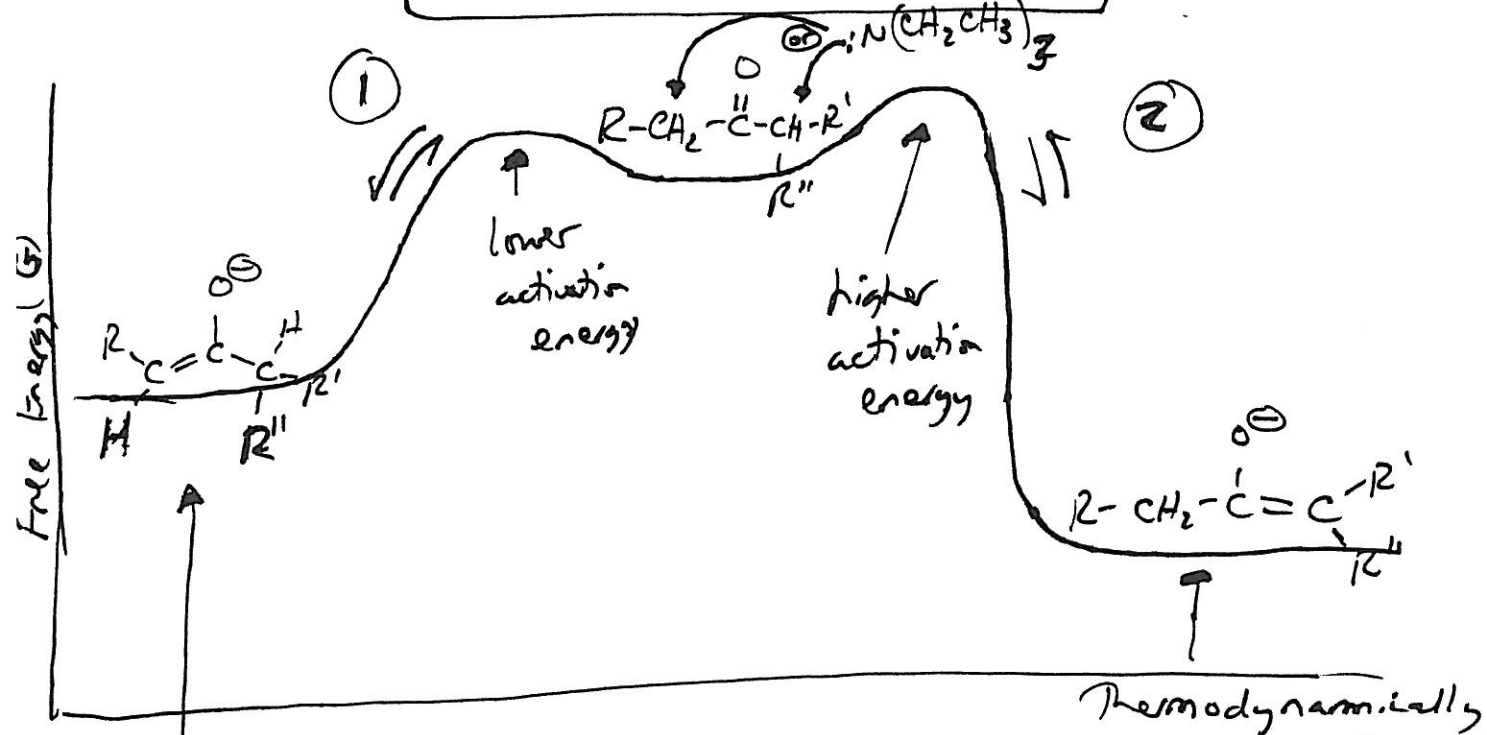


Kinetic pdt

major pdt

- Rxn (A) run under conditions where the Thermodynamic enolate is favored (most Thermodynamically stable enolate)
- Rxn (B) run under conditions where kinetic enolate favored - least hindered α-H abstracted by very strong base

# Free Energy Diagram of Thermodynamic + Kinetic Enolates

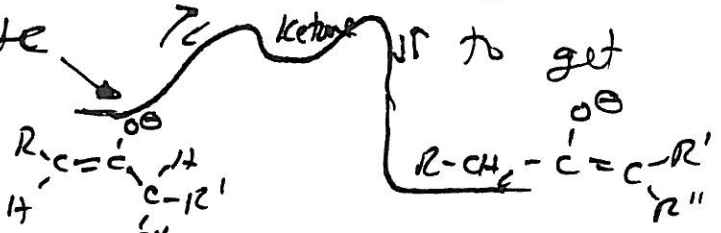



- Conditions → weak base $(CH_3CH_2)_3N:$ & high temps

- equilibrium exists between the two enolate forms (thru ketone intermediate)
- Although Rxn (1) enolate (kinetic enolate) forms faster - (because of 2 α-hydrogens vs. 1 α-hydrogen that can be abstracted by the base) - when the reaction is allowed to reach equilibrium then more of the more highly substituted enolate will be present. The thermodynamic pdt is favored

- Conditions that favor the thermodynamic enolate are a weak base and higher temps. Why?
  ( $(CH_3CH_2)_3N:$ )  ( $\Delta$ )

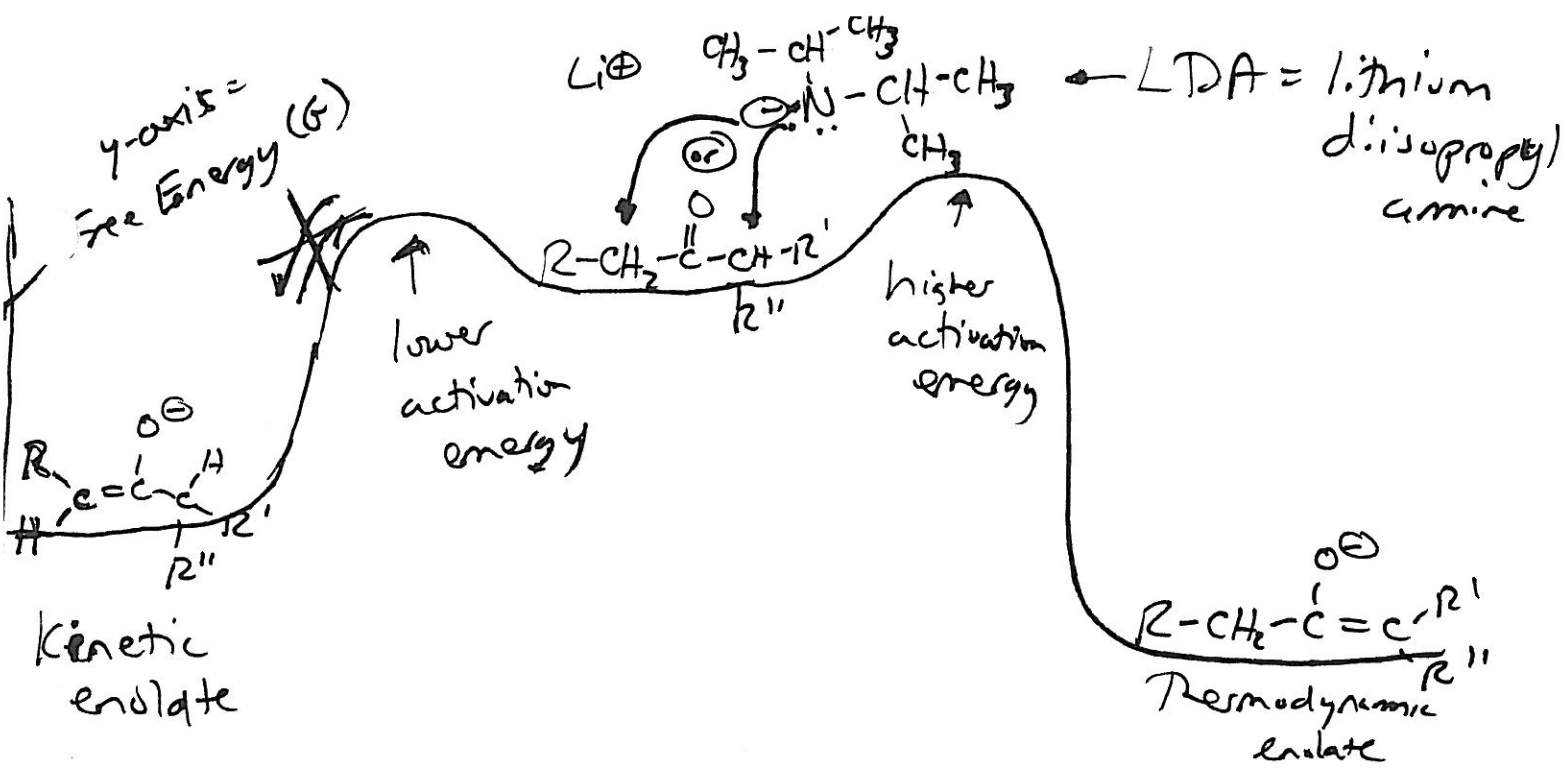
→ The higher temps. allow enough energy for the kinetic enolate




back up over the energy barrier to reform the ketone so it can go on to form the more stable thermodynamic enolate.

→ The triethylamine $(CH_3CH_2)_3N:$ – a weak base – is protonated after it abstracts an α-hydrogen. This conjugate acid $(CH_3CH_2)_3\overset{+}{N}-H$ is a strong enough acid to allow its proton to be abstracted to reform the ketone – it allows equilibrium to be established.

→ When the rxn goes on long enough eventually you will have more of the more stable pdt – the thermodynamic enolate.



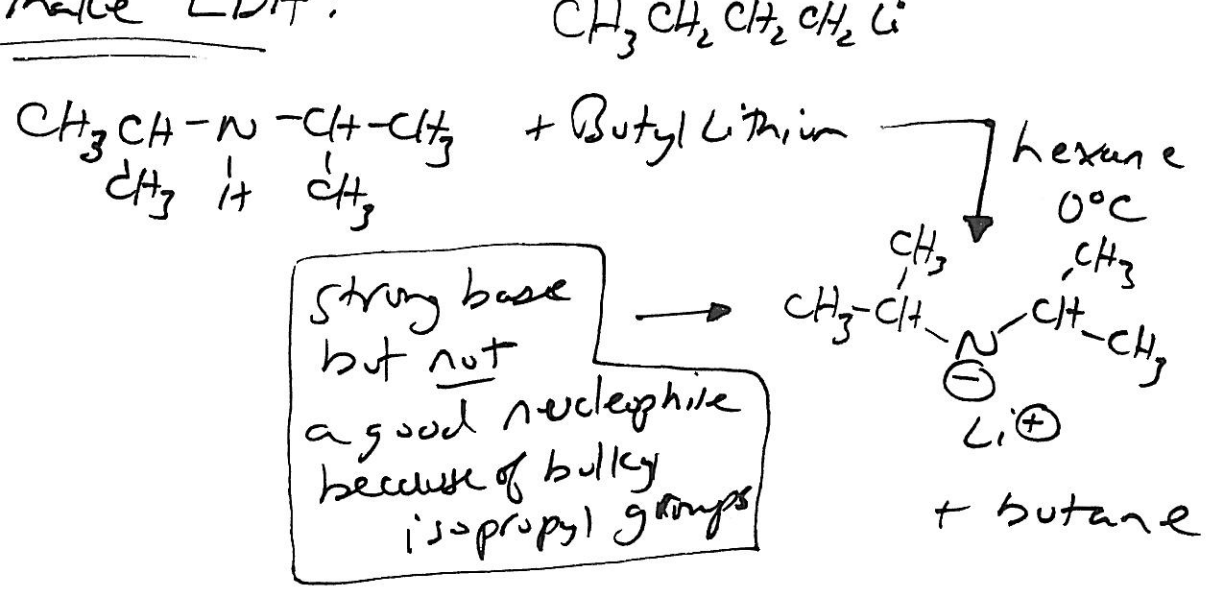

---

| • conditions → strong base (LDA) + low temps | Kinetic Enolate Conditions |
|---|---|

- To form the kinetic enolate there are 2 possible protons to abstract (plus they are less hindered). Consequently, the kinetic enolate forms much faster than the thermodynamic enolate. ← (only 1 proton to abstract & more hindered) (also, activation energy lower)
- With a strong base such as LDA + cold temps equilibrium is not established – the lower temps don't allow enough energy for the kinetic enolate to get back up over the energy barrier + the protonated LDA is NOT a strong enough acid for reprotonation to occur to reform the ketone. Consequently, once the kinetic enolate forms it can't easily go back.

- To favor the kinetic enolate use LDA and cold temps and always have LDA in excess over the ketone (add the ketone to the LDA soln)

- To make LDA:

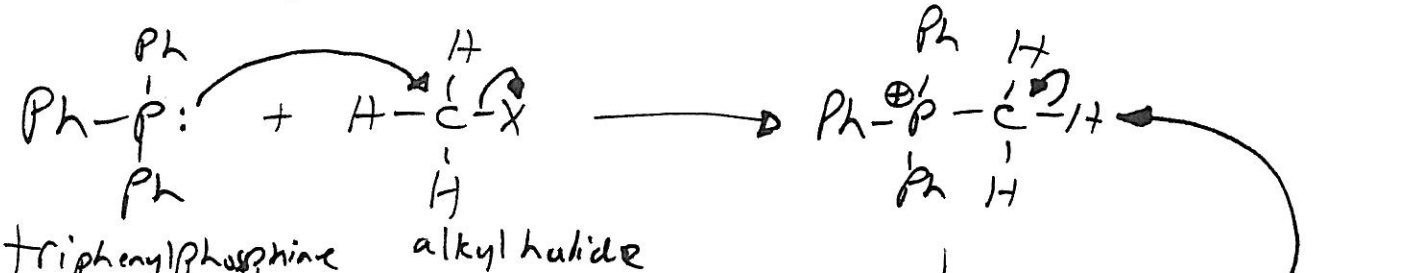



## Carbanions Stabilized by Phosphorus

Phosphonium Ylides → stabilized carbanions next to ⊕ charged phosphorus

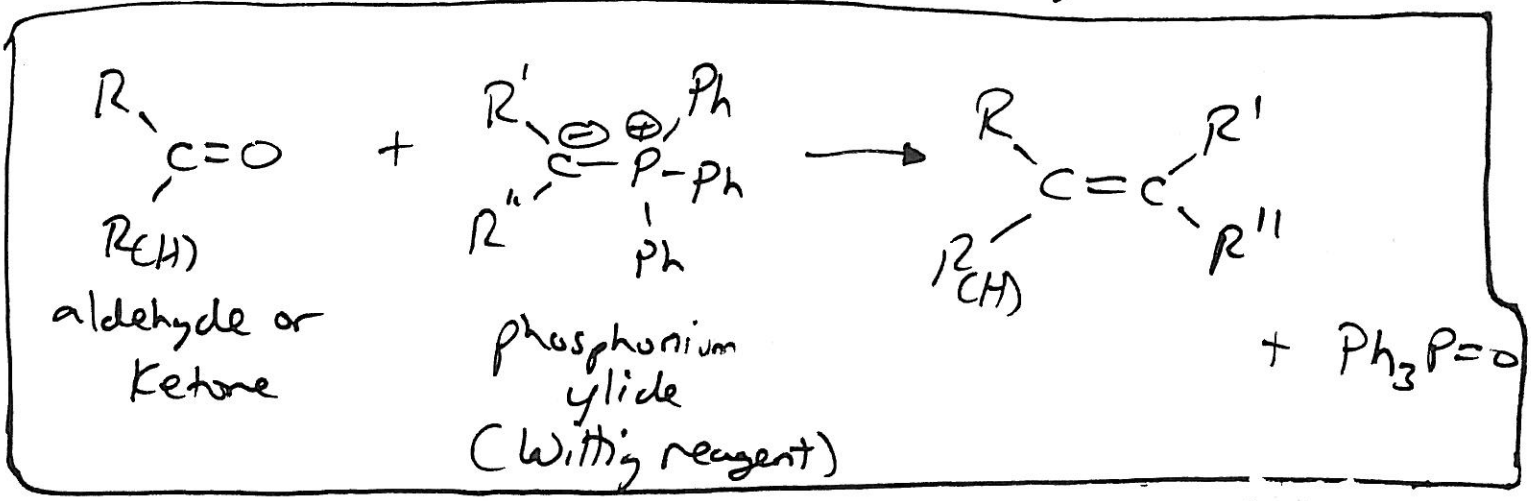
preparation of ylides:

ex:

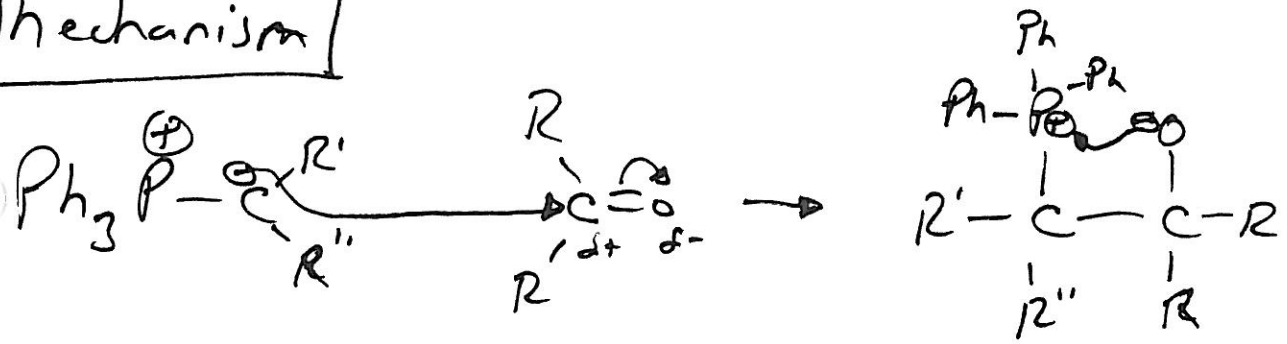


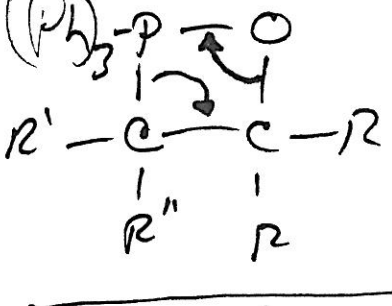

Ph = 

# The Wittig Reaction → uses ylides and aldehyde or ketone

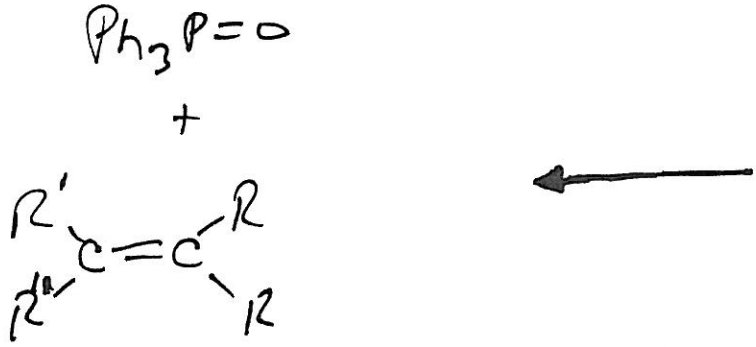



## Mechanism



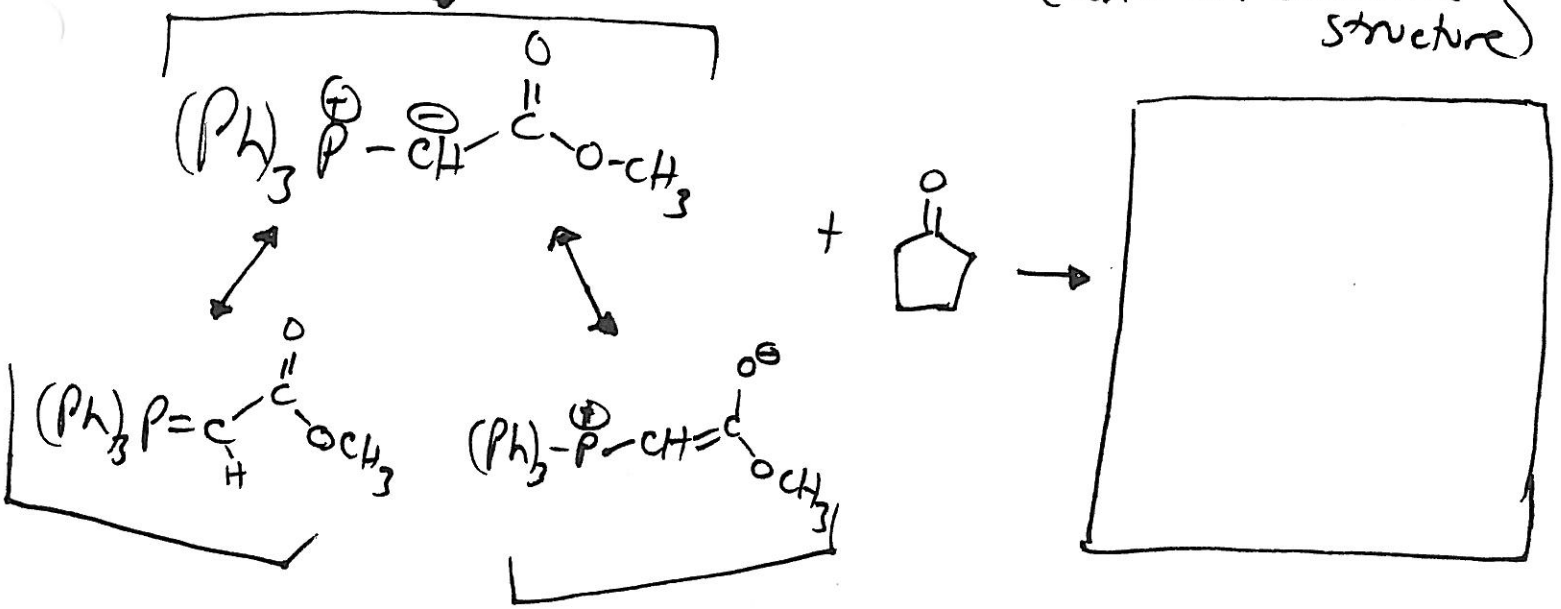


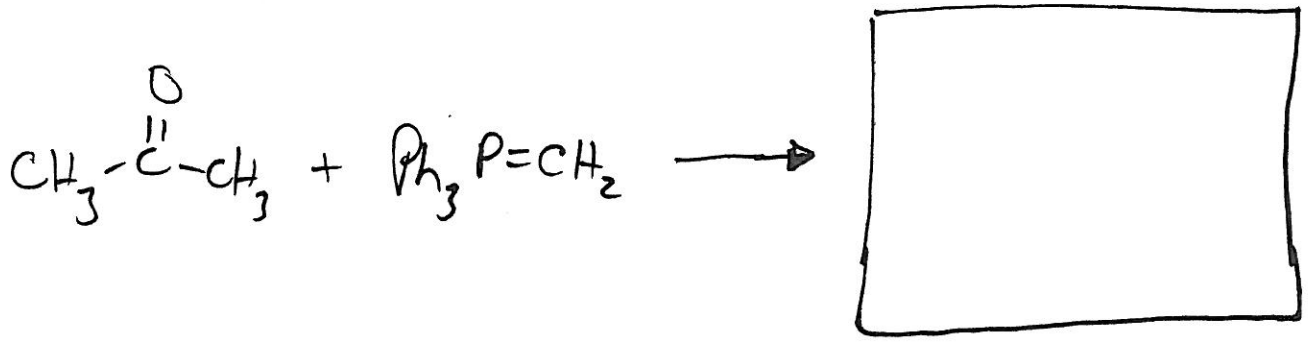
oxaphosphatane



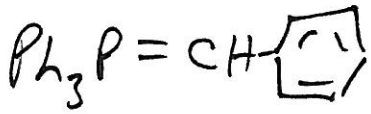
- part of driving force for the rxn → formation of very stable P=O bond in $Ph_3P=O$

Another Wittig reagent → more stabilized ylide (extra resonance structure)

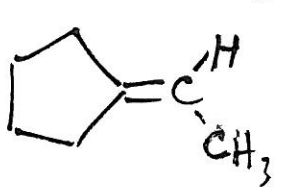




- Outline a synthesis of the following Wittig reagent from $Ph_3P$ and an alkyl halide

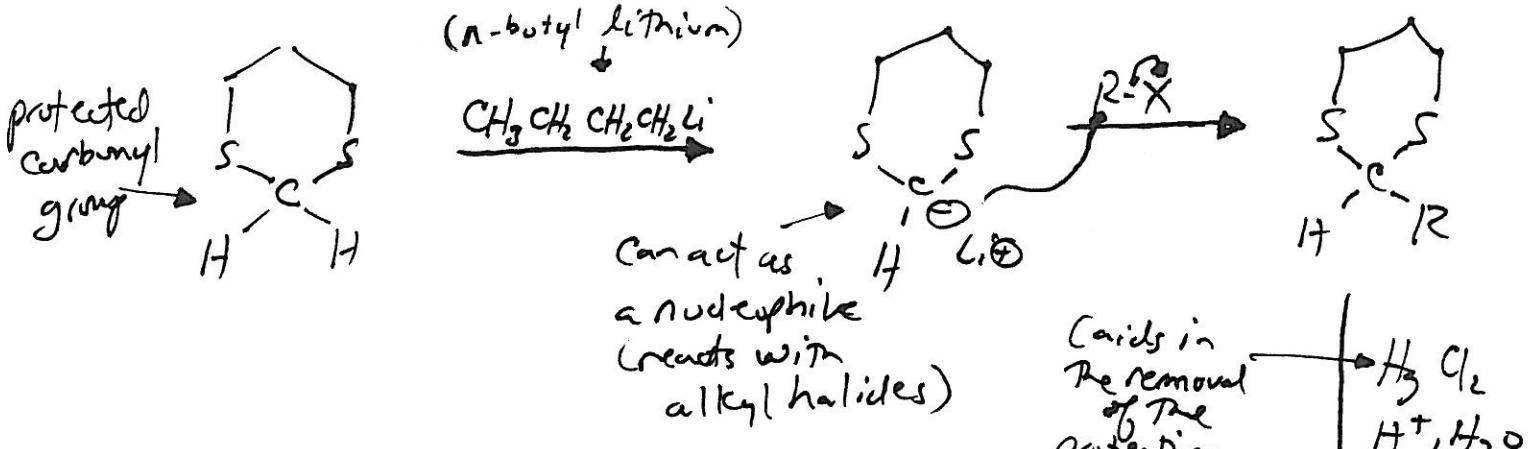


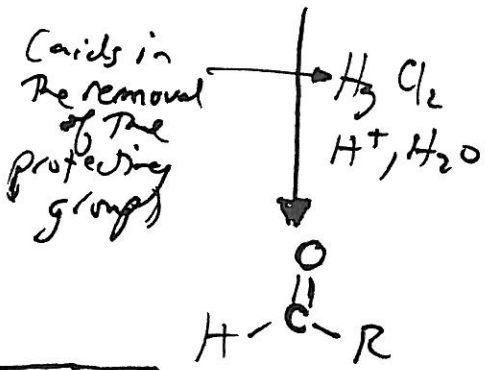
- What starting materials are needed to synthesize the alkene below by a Wittig rxn? (Pick starting materials that give best yield)



# Dithiane Anions

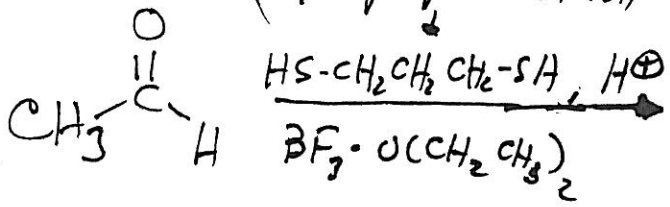
1,3-dithiane – a weak acid that can be deprotonated by a strong base

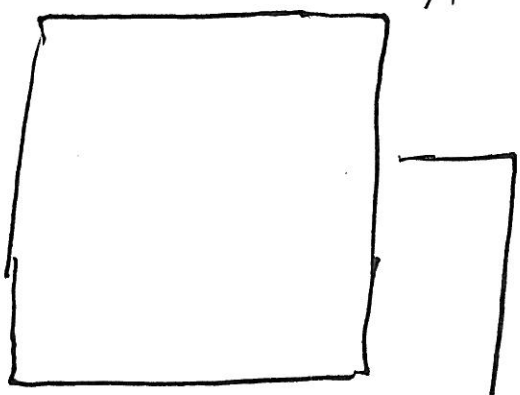


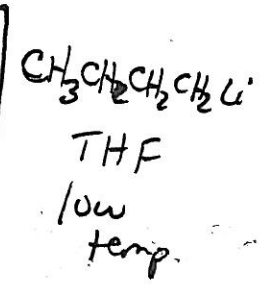



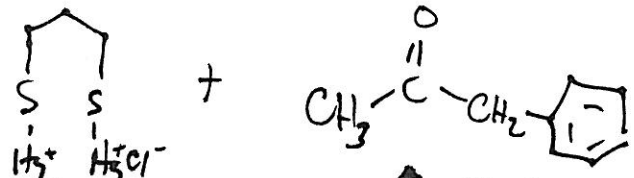

- To prepare dithiane derivative use an aldehyde starting material

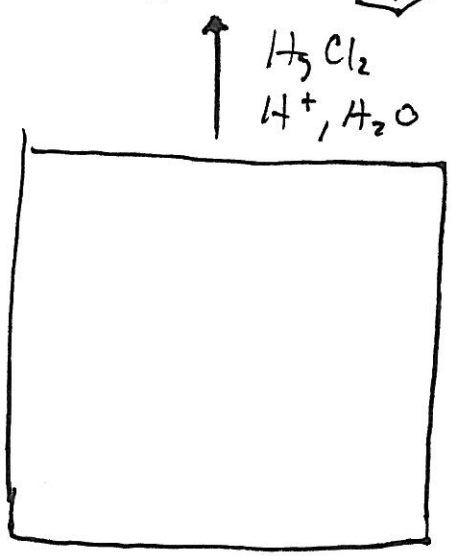
ex.

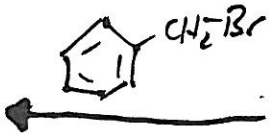


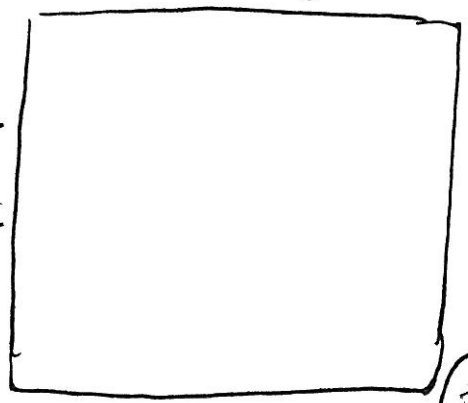





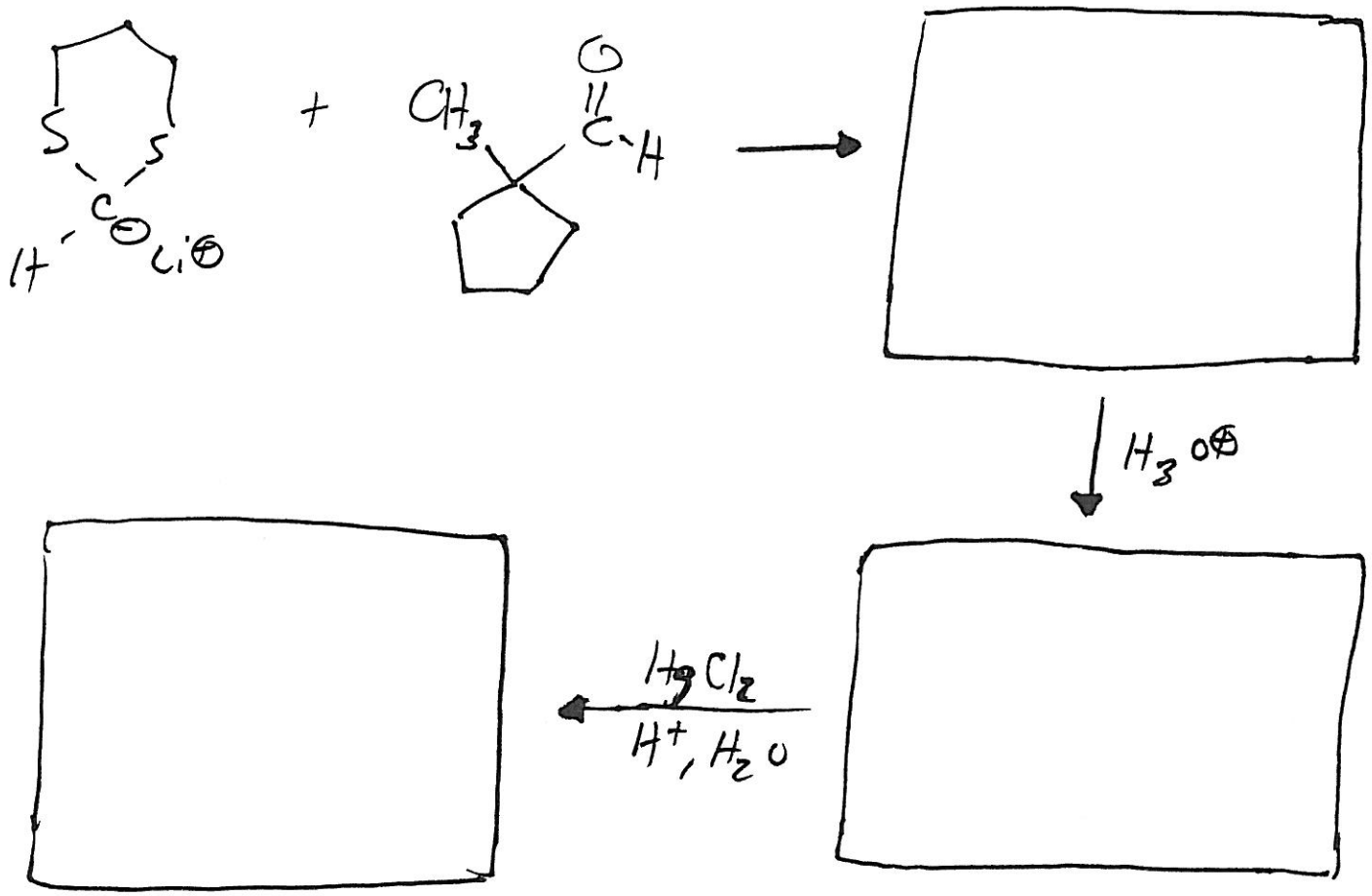



- Dithiane nucleophiles can also add to aldehydes + ketones




## Carbon Nucleophiles in Synthesis

- Organometallic reagents can react with carboxylic acid derivatives (not just aldehydes & ketones)

Two types: Grignard & organolithium reagents

Cue will focus on Grignard reagents)

# Grignard Reagents with Esters

$$R\text{-}X + Mg \xrightarrow[\text{(dry)}]{\text{ether}} RMgX$$

$$2\ RMgX + R'\text{-}C(=O)\text{-}O\text{-}R'' \longrightarrow R'\text{-}C(O^{\ominus}MgX^{\oplus})(R)_2$$

R'' = leaving group

$$R'\text{-}C(O^{\ominus}MgX^{\oplus})(R)_2 \xrightarrow{H_3O^{\oplus}} R'\text{-}C(OH)(R)_2 + H\text{-}O\text{-}R''$$

3° alcohol

## Mechanism for Grignard reagent Rxn with an Ester

$$R\text{-}MgX + R'\text{-}C(=O)\text{-}O\text{-}R''$$

1st equivalent

$$R'\text{-}C(O^{\ominus}MgX^{\oplus})(O\text{-}R'')(R) \longrightarrow R'\text{-}C(=O)\text{-}R + R\text{-}MgX$$

2nd equiv.

$$R'\text{-}C(=O)\text{-}R \xrightarrow{R\text{-}MgX} R'\text{-}C(O^{\ominus}MgX^{\oplus})(R)_2 \xrightarrow[\text{2nd step}]{H_3O^{\oplus}} R'\text{-}C(OH)(R)_2$$

ex:

$$Ph\text{-}C(=O)\text{-}O\text{-}CH_3 + 2\ CH_3CH_2MgBr \longrightarrow \xrightarrow{H_3O^{\oplus}}$$

- p876-877 N-methoxy-N-methylamides + grignards in text

Don't need to know

# Reactions of Enolates Revisited

- In Ch. 17 we discussed numerous rxns with enols and enolate anions:

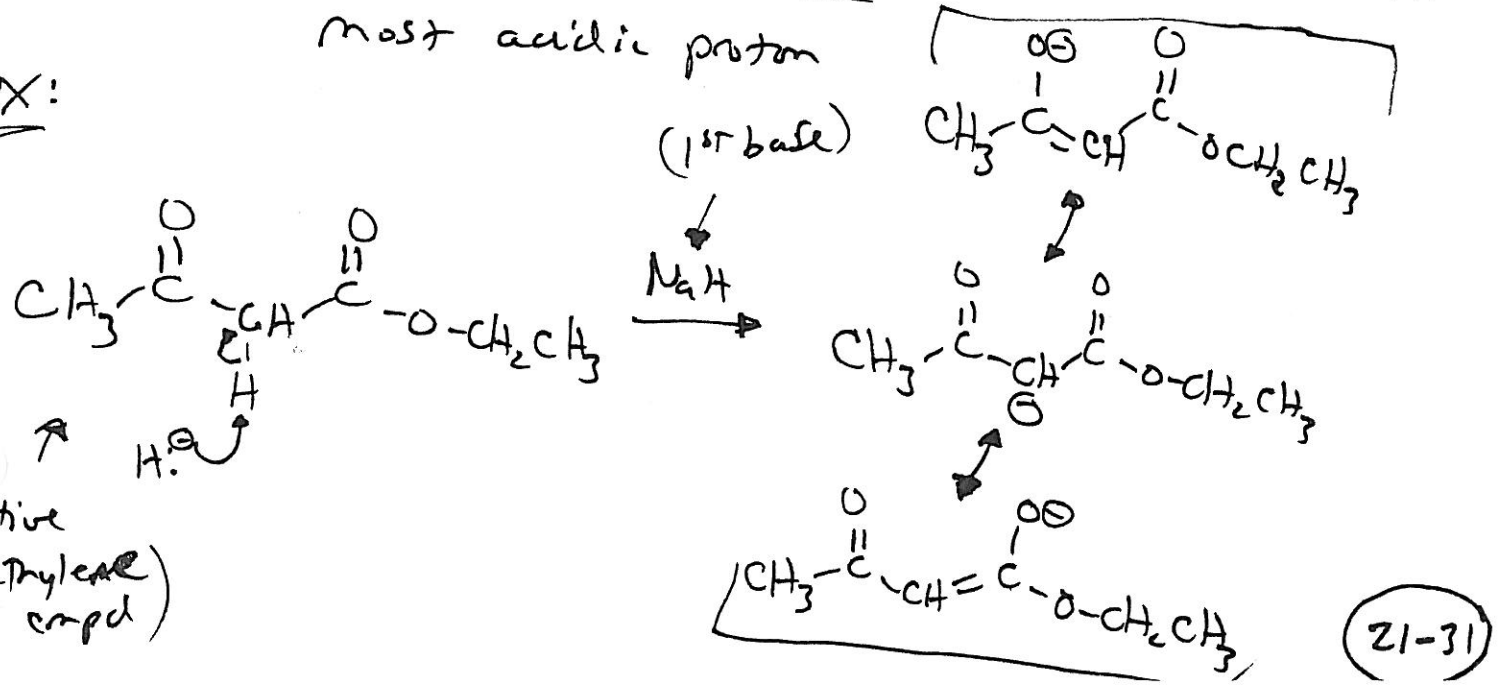
You need to remember these for multistep synthesis:

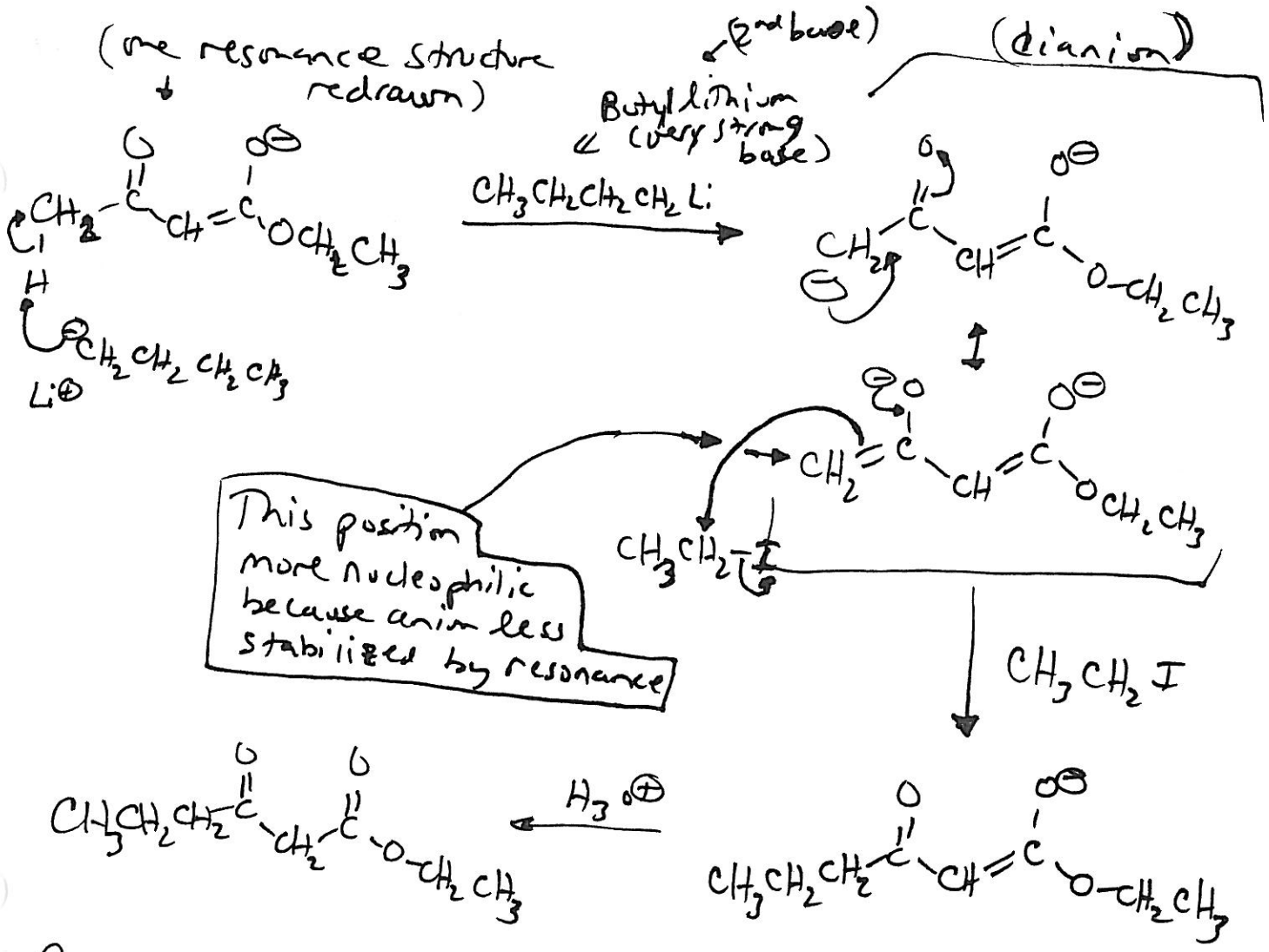
a) halogenation of enols
b) alkylation of enolates
c) Aldol condensations
d) Claisen-type condensations
e) Alkylation of Active-methylene cmpds (+ decarboxylation)

Dianions can also be formed from some active methylene cmpds. How?

→ use 1-base to pick off the most acidic proton (the active methylene hydrogen) and then use a more powerful base to abstract the next most acidic proton

ex:






- Can also do INTRAmolecular rxns of enolates to form cyclic cmpds:

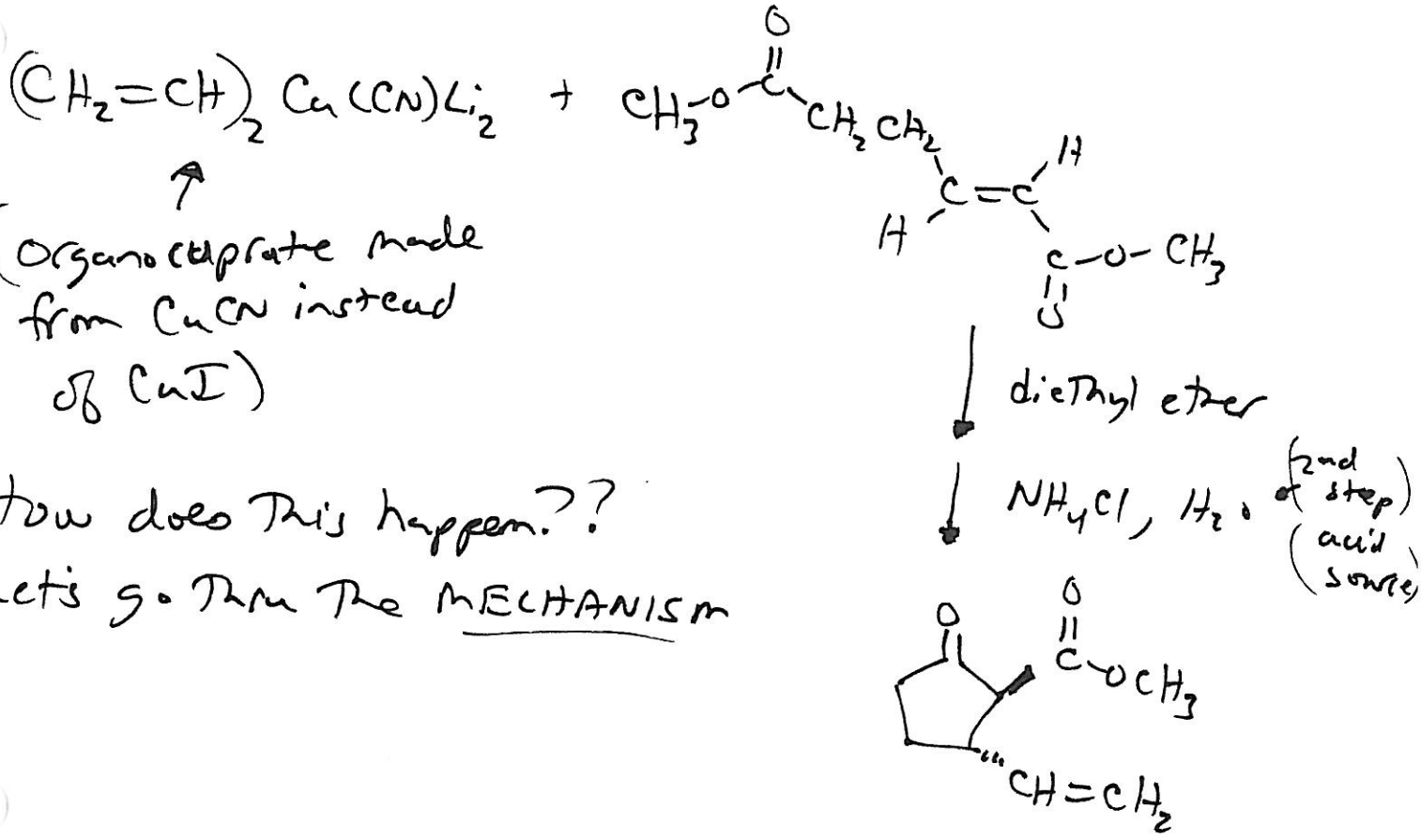
We've already seen examples in Ch. 17 lecture notes

a) **Intramolecular Alkylation** (see pg 879 in text; p 17-4 in notes)
→ from either kinetic or thermodynamic enolate
(kinetic: use LDA)
(thermodynamic: use NaOH, $H_2O$ or $RO^{\ominus}M^{\oplus}$ / ROH)

b) **Intramolecular Aldol Condensations** (see p 880 in text; p 17-12 in notes problem #1)
or $CH_3-\underset{CH_3}{\overset{CH_3}{C}}-O^{\ominus}M^{\oplus}$

c) **Intramolecular Claisen Condensations** (see pp 881-882 in text; p 17-11 in notes)
(also called Dieckmann condensation)

Example in text (p882)




How does this happen??
Let's go thru the MECHANISM

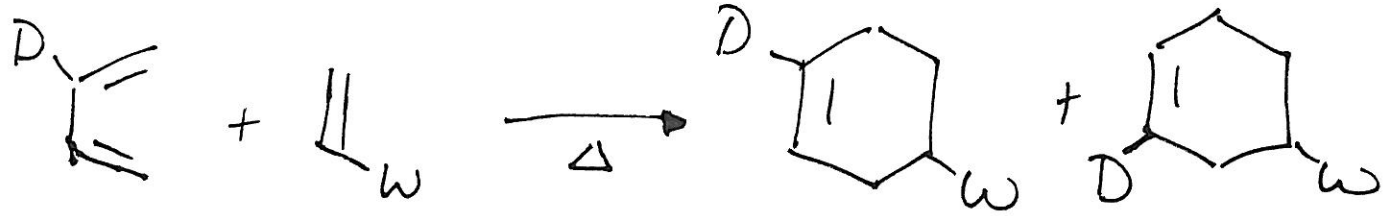
21.5© SOME CASE STUDIES

We won't go thru these examples in class but READ and UNDERSTAND THIS SECTION

→ Good examples of multistep synthesis and explanation of the thinking necessary to do these types of problems (21-33)

# Diels-Alder Reactions of Unsymmetrical Dienes & Dienophiles

## 1,4 product formation

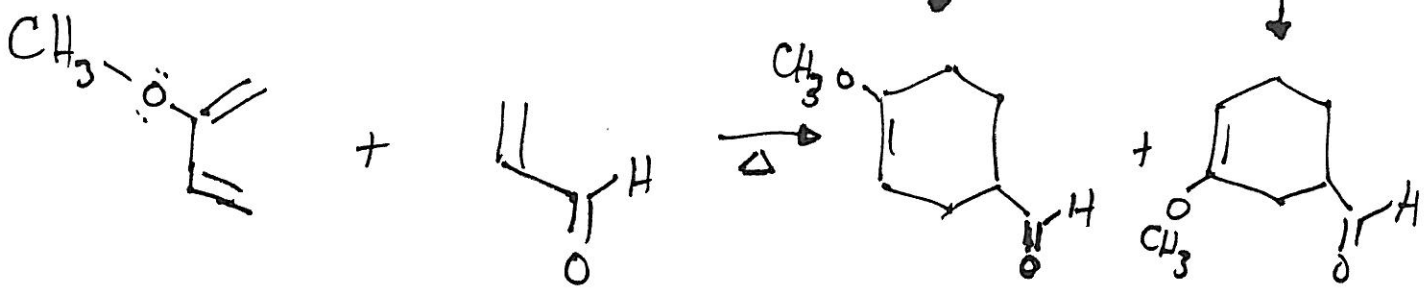



D = electron donating group
W = electron withdrawing group

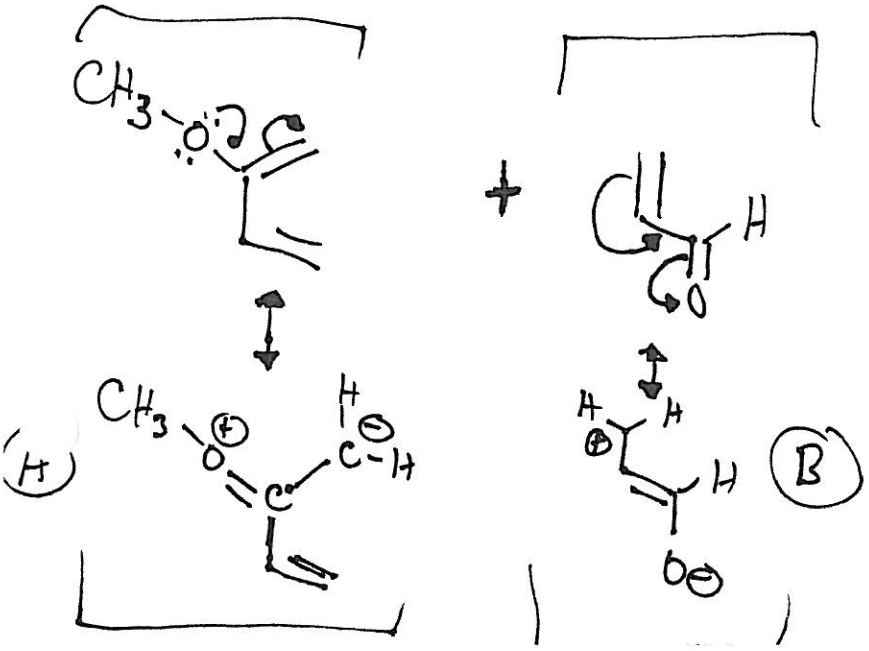
1,4 pdt → major pdt

1,3 pdt → minor pdt

ex:

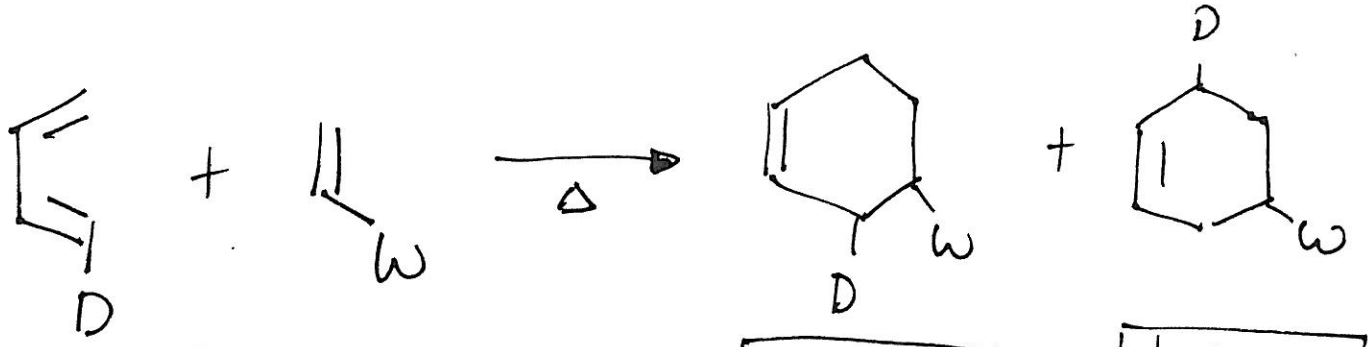



Why is the 1,4 product the major pdt?




- In resonance structure (A) the (-) end of the diene prefers to line up with the (+) end of resonance structure (B) (the dienophile). This orientation gives the 1,4 product.

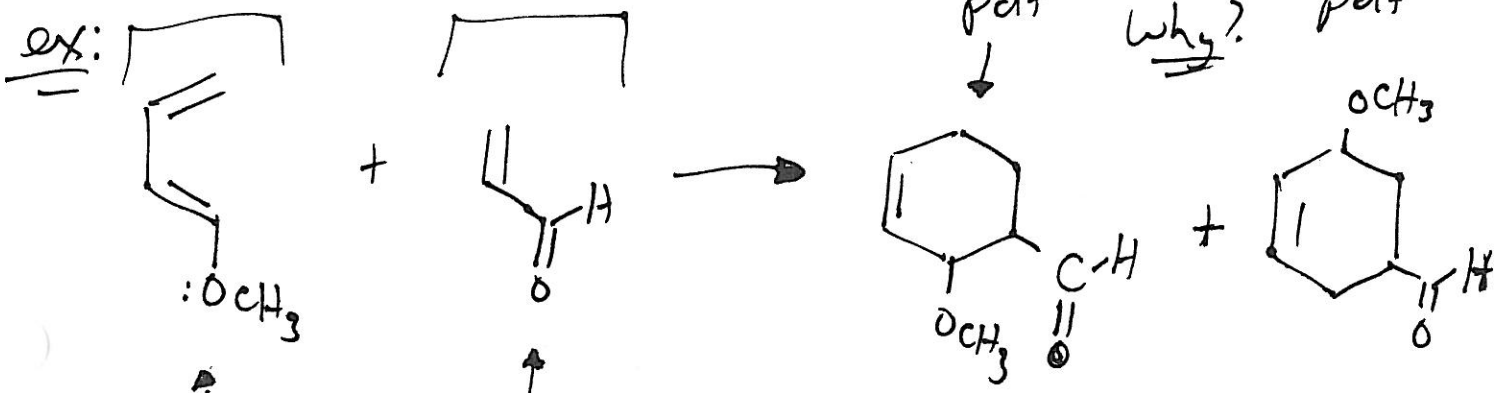
# 1,2 product formation



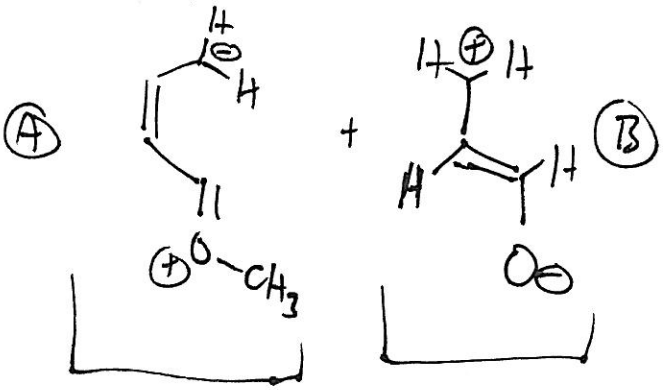

1,2 pdt — major pdt

1,3 pdt — minor pdt

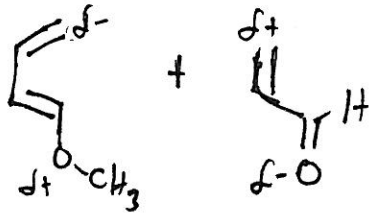
ex:




Why? 1,2 pdt is the major pdt

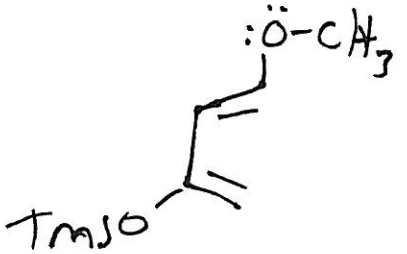



- Once again, the positive + negative formal charges in resonance structures (A) + (B) prefer to be lined up as shown to give the 1,2 pdt as the major pdt. (Energy is lower for this orientation than in orientation to give the 1,3 pdt).

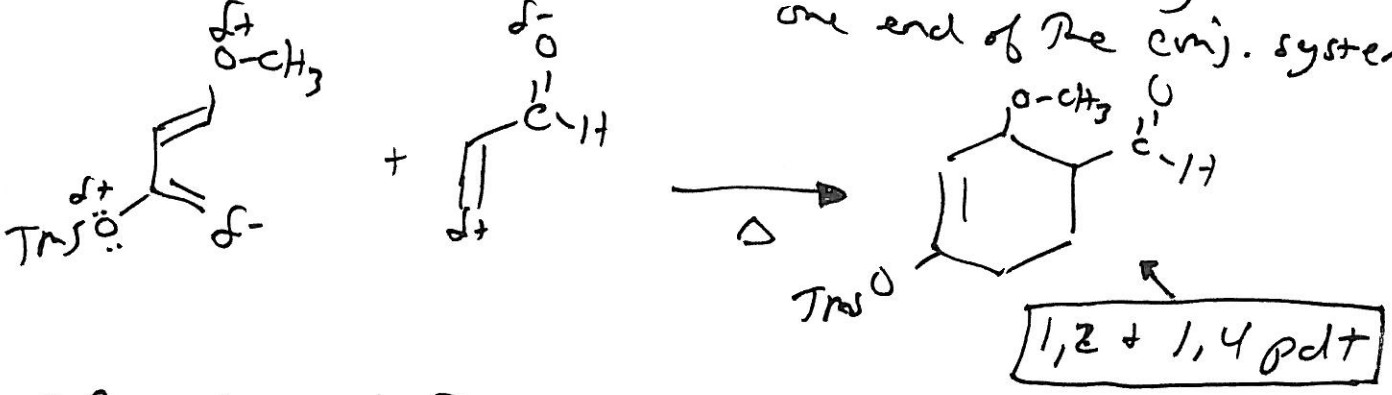



* The 1,3 product is the minor product for ALL unsymmetrical Diels-Alder rxns.

## Danishefsky Diene – gives good regioselectivity in a Diels-Alder Rxn

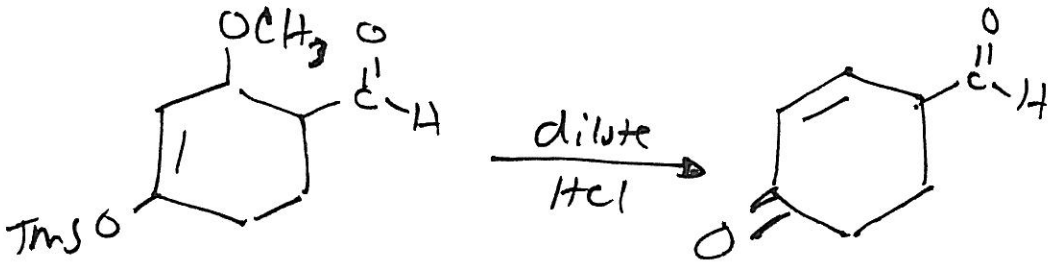


- TMS = trimethylsilyl $(CH_3)_3Si-$
- both oxygen substituents donate $e^-$ density towards one end of the conj. system



1,2 + 1,4 pdt

- Can convert Diels-Alder product of Danishefsky Diene to an α,β unsaturated ketone

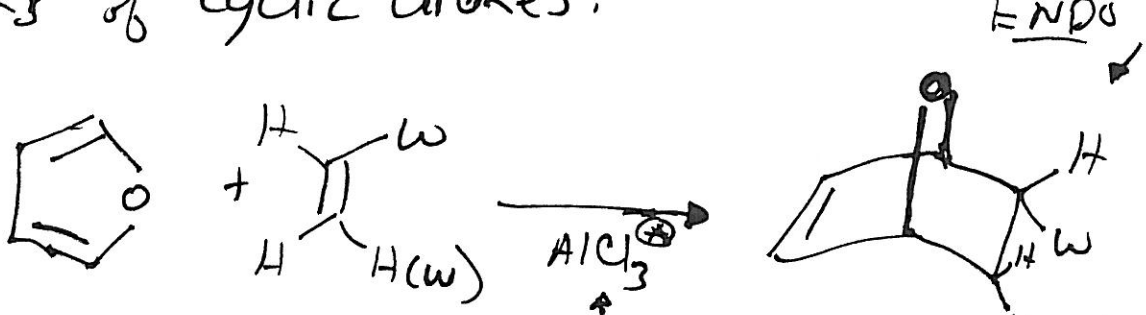



- see text p5 856 for mechanism

# Diels-Alder Reaction Stereochemistry

(review)

- In chapter 18 we discussed the preference for ENDO stereochemistry in Diels-Alder Rxns of cyclic dienes:



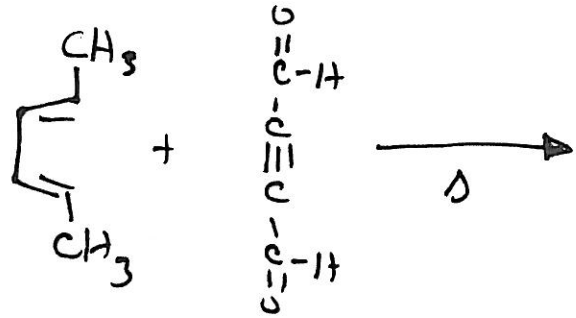

(new info)

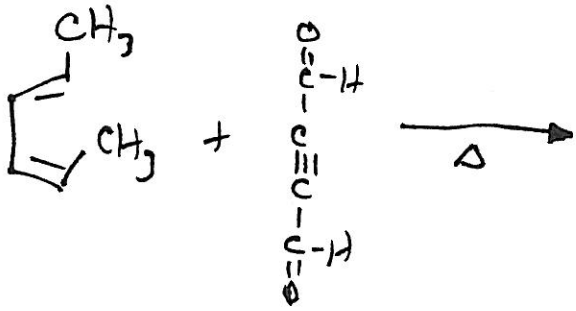
⊕ presence of a Lewis acid catalyst (like $AlCl_3$) increases the yield of ENDO pdt (catalyst complexes with the electron withdrawing group (W))

- We also discussed the stereochemistry of Diels-Alder pdts derived from 1,4-disubstituted dienes:

Remember? (p 18-10 in notes)

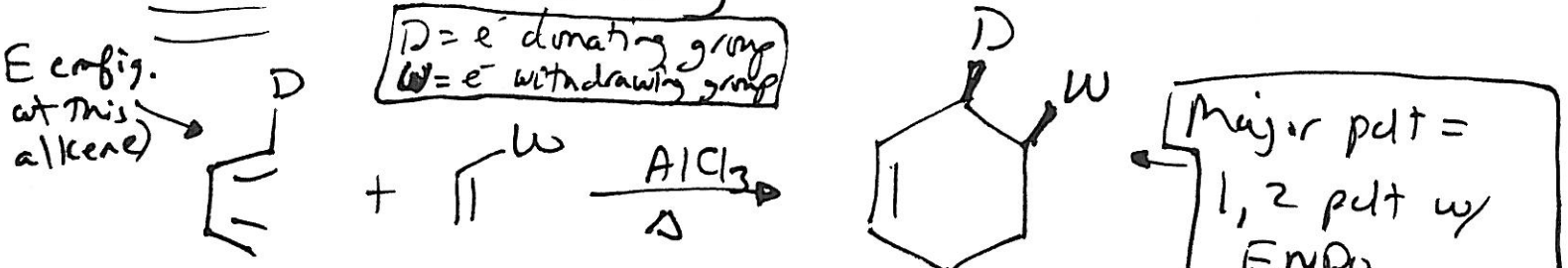
(Review)



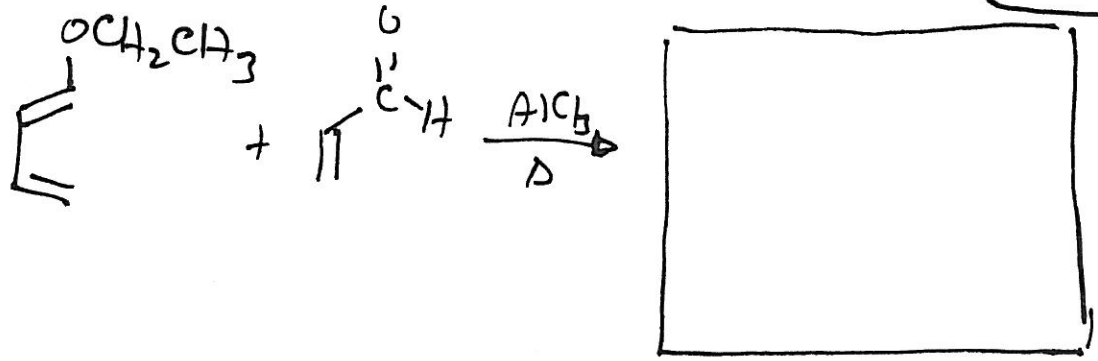



(New info)

- If one has a diene with a C-1 substituent (w/ the E configuration at that double bond) and we use a Lewis Acid catalyst in the Diels-Alder Rxn (like $AlCl_3$) there is a large preference for the 1,2 pdt with ENDO stereochemistry

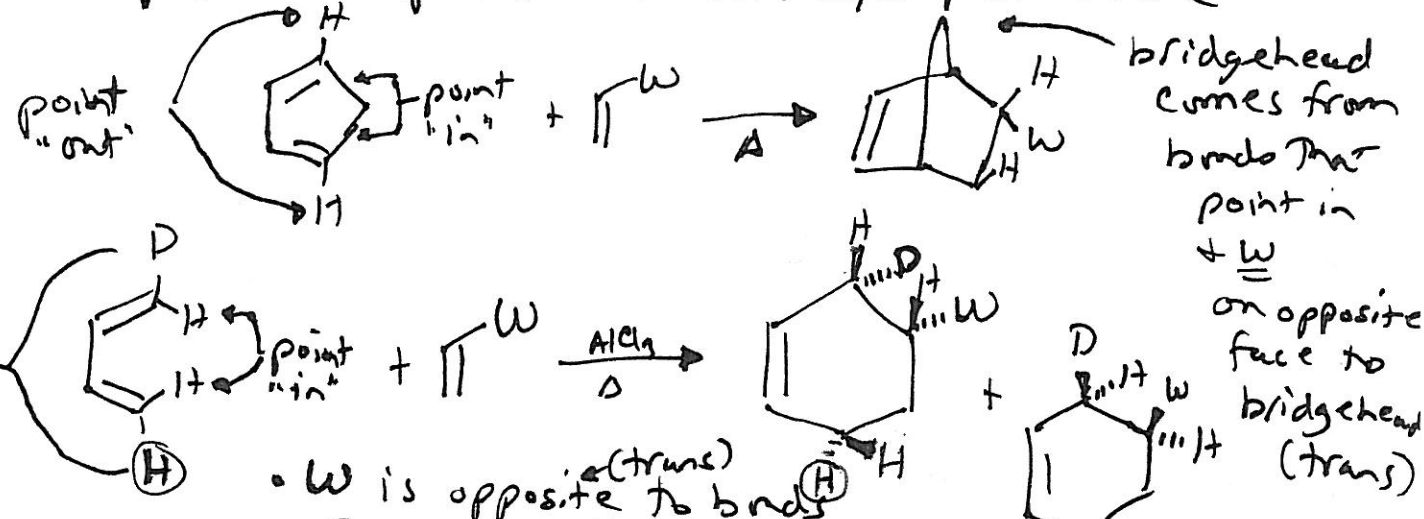



ex:




Why is cis-configuration ENDO?

→ Compare example above with cyclopentadiene

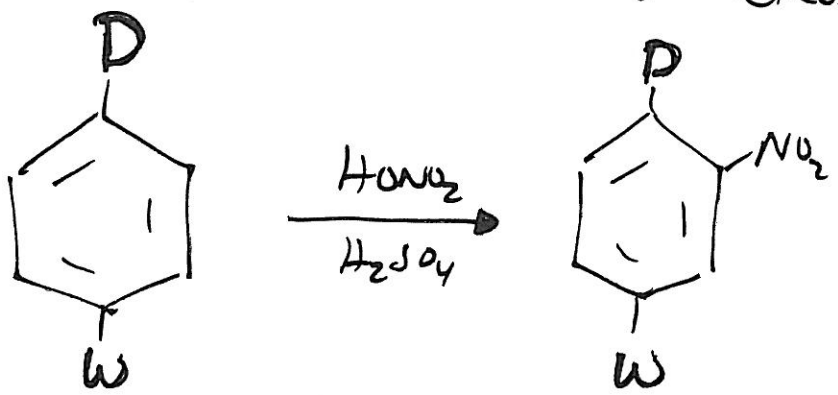



- W is opposite to bonds that point "in" so is on same side (cis) to groups that point "out"

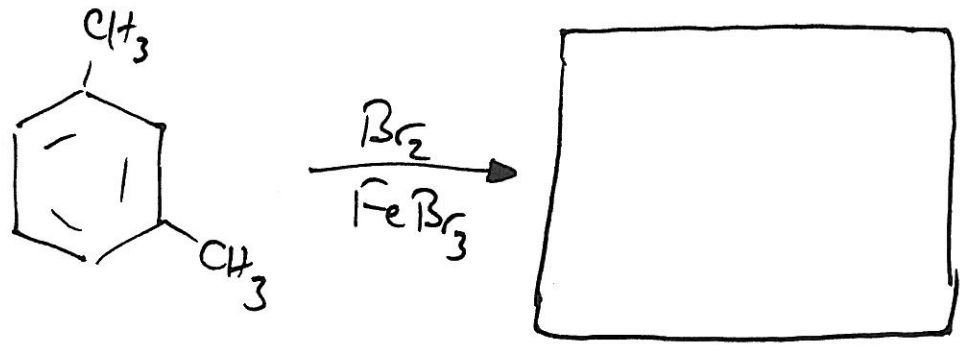
# Substitution on Multiply Substituted Aromatic Compounds

D = electron donating substituent (o,p director)

W = electron withdrawing substituent (meta director)



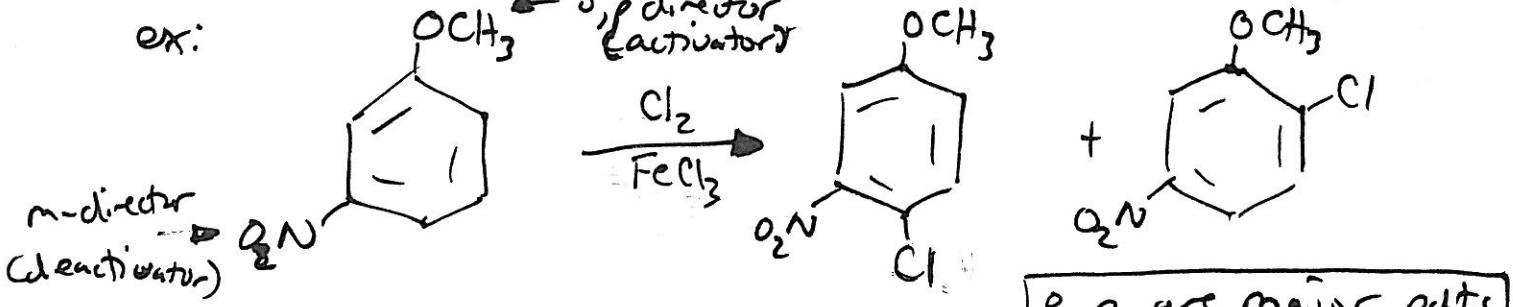

← Each substituent directs incoming nitronium ion electrophile to same position on ring.




← pick ONE major pdt

- But, what if we have an activator (o,p director) with a deactivator (meta director) on the ring that are in conflict with each other for the substitution product?

ex:




o,p are major pdts

Generally - activating groups are usually stronger directors than deactivating groups

p 895 - top of page → relative effectiveness of substituent in directing an incoming electrophile

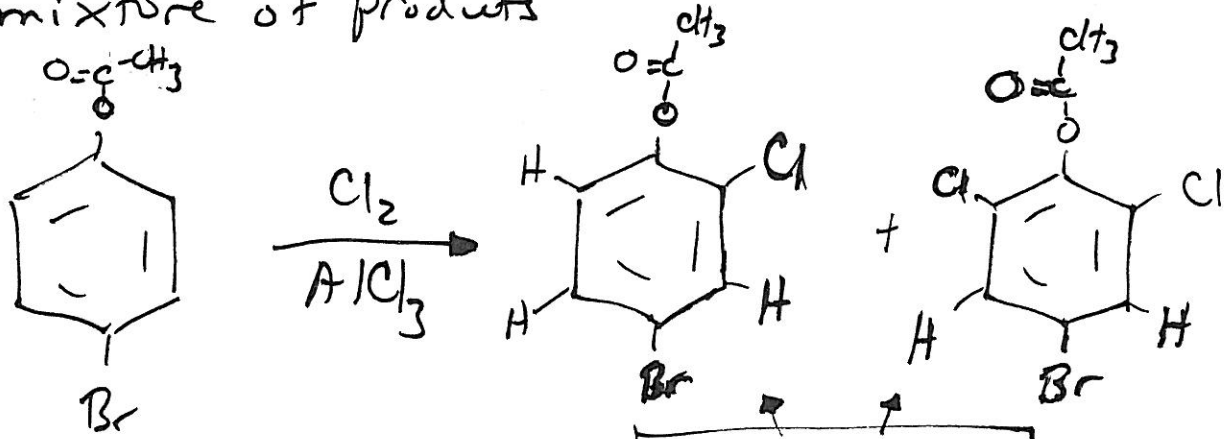
$-NH_2$, $-O-H$, $-O^{\ominus}$ > $-O-CH_3$ ≥ $-O-\overset{O}{\overset{\|}{C}}-R$, $-\underset{H}{N}-\overset{O}{\overset{\|}{C}}-R$ > X > $-CH_3$

Strongest o, p directors

Need to know

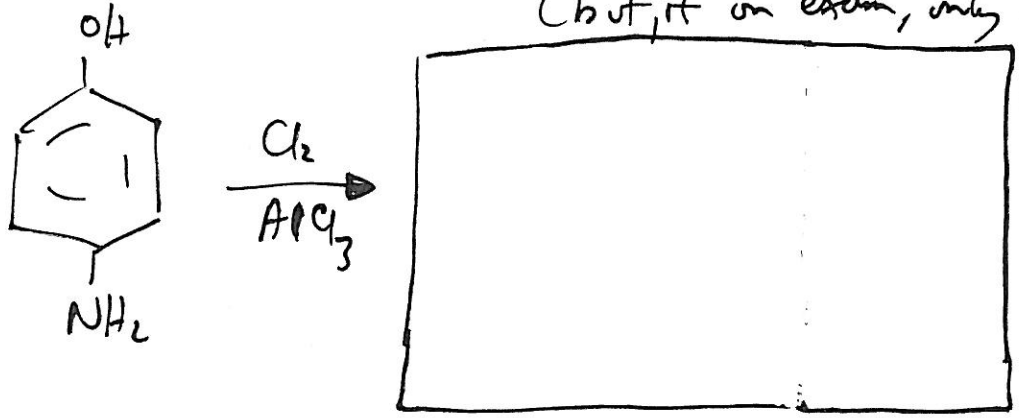
Weakest o, p directors

- If two substituents direct an incoming electrophile to different sites, the stronger subst. predominates.
- If the strength of the substituents for directing an electrophile is more or less equal, you will get a mixture of products

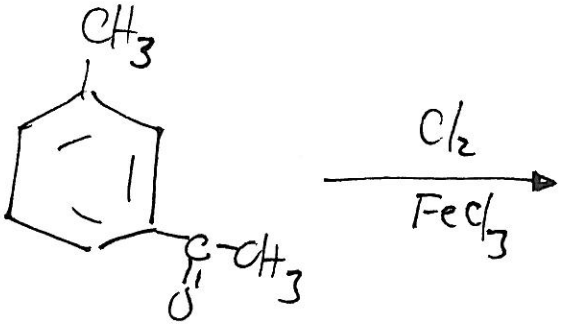


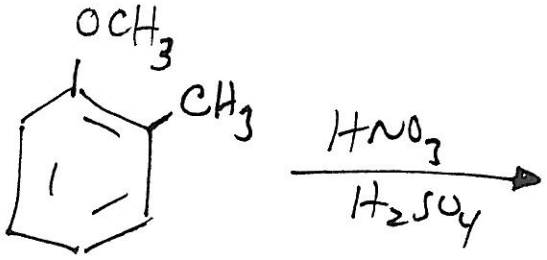

major products

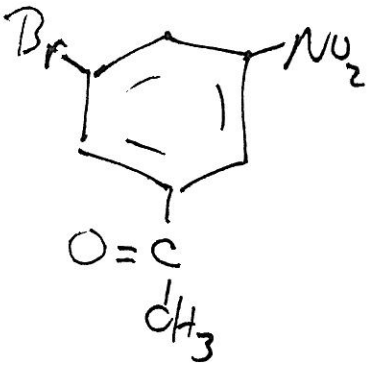
Chat: if on exam, only need to write monochlorination pdt

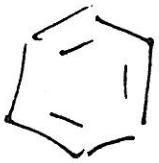


- Predict the major pdt(s) of the following rxns:

a) 

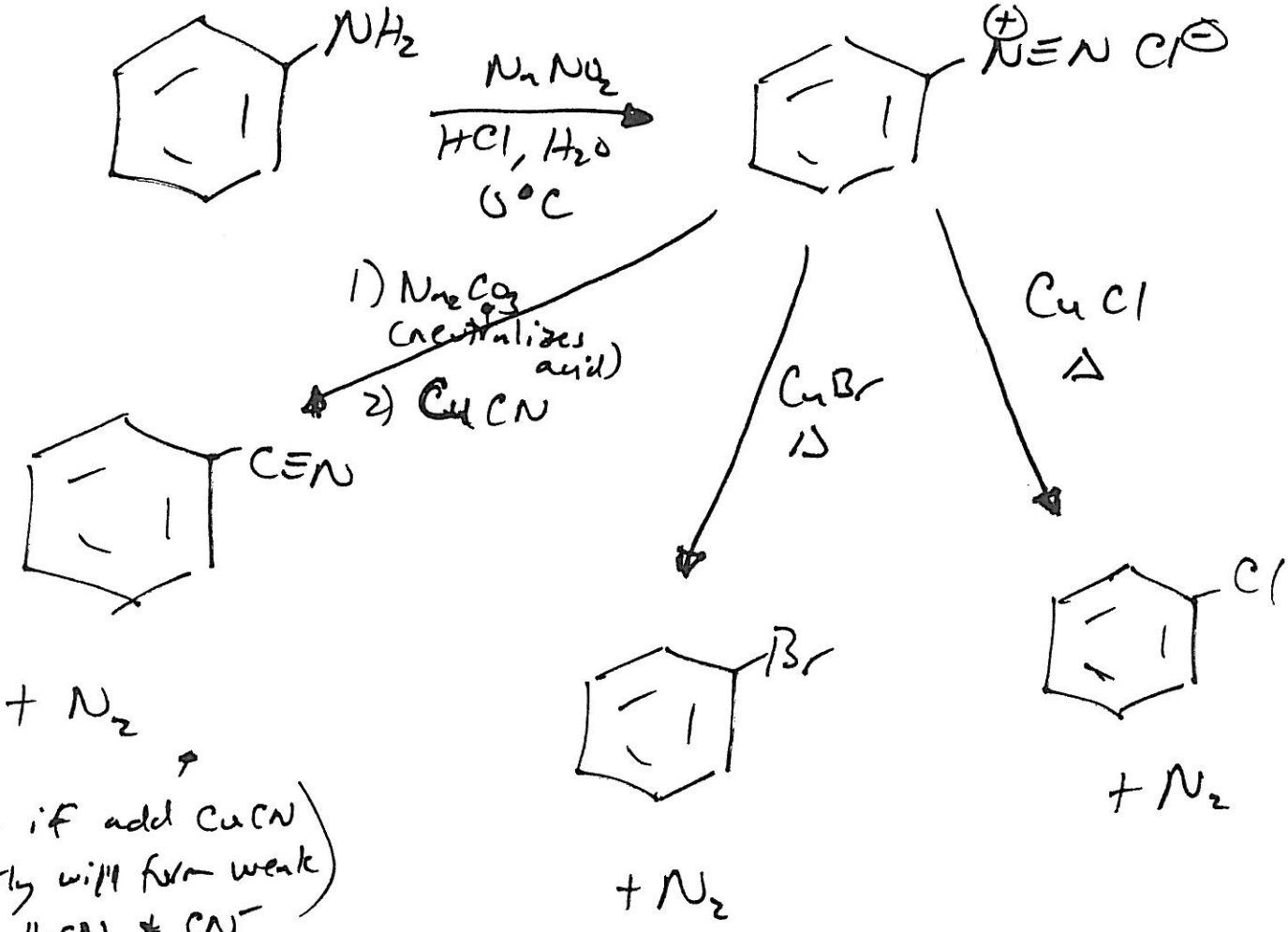

b) 


- Prepare 

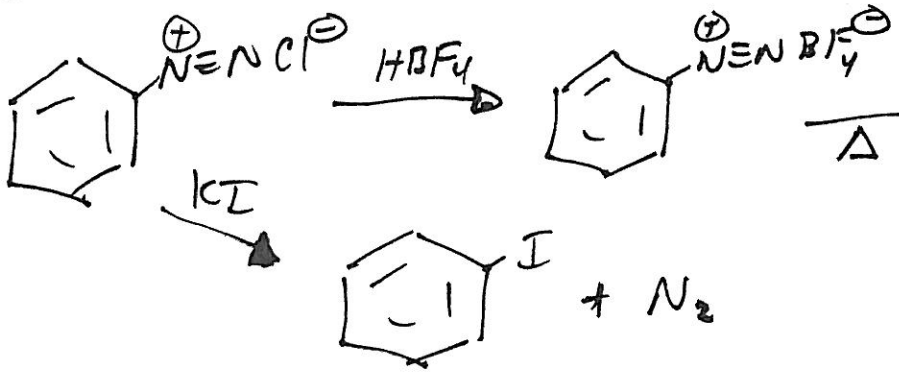
from 

# Replacement of Nitrogen In Diazonium Ions

**Sandmeyer Rxns** – require catalysis by copper metal or copper salts

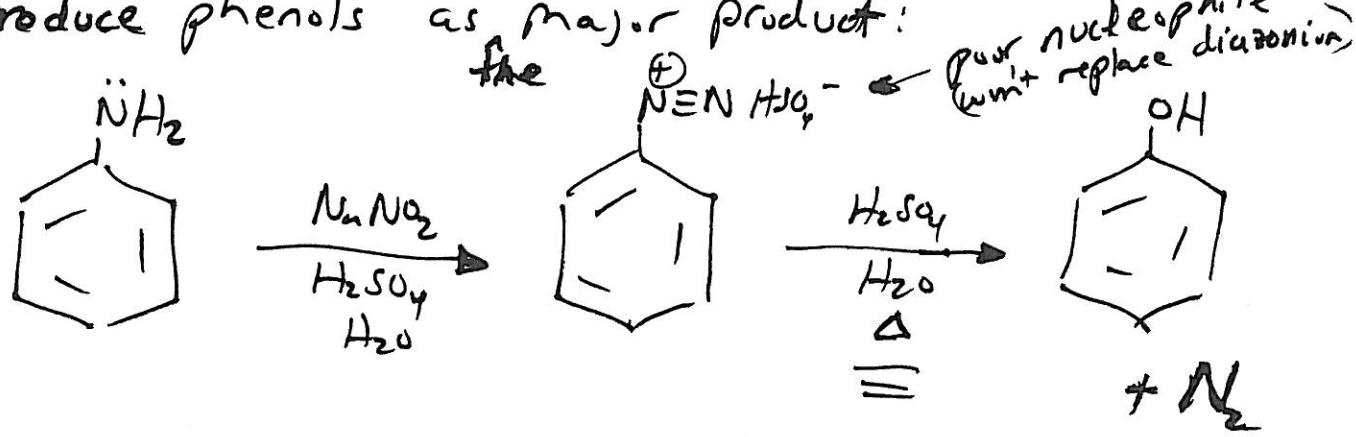



## Replacement of Diazonium group by Fluoride or Iodide



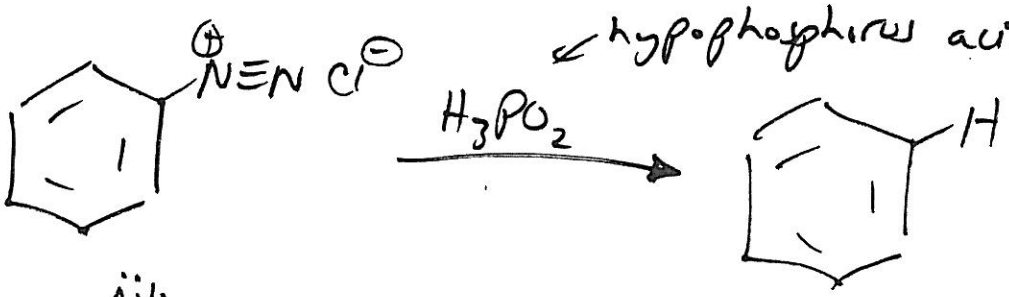
- Phenols are produced as side products in <u>all</u> the diazonium replacement reactions
  (diazonium ions react with $H_2O$)

- To produce phenols as major product:

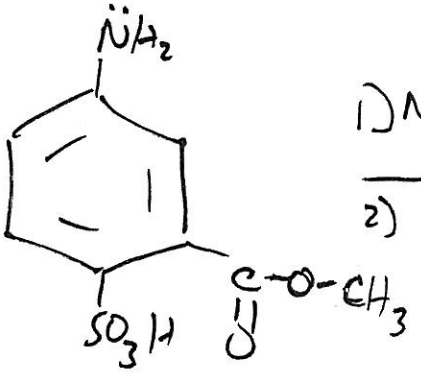



## Deamination of Aniline

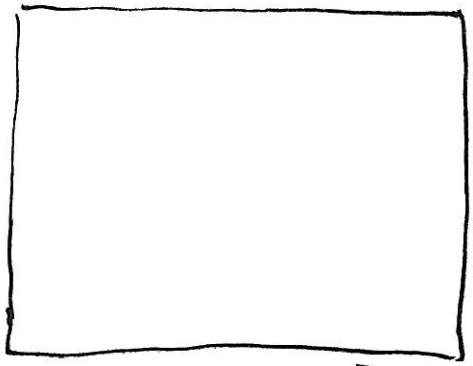
→ Reduction of diazonium group to hydrogen




or



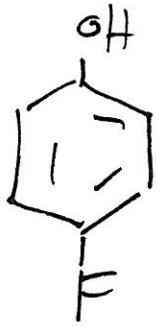
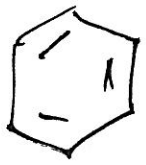

1) $NaNO_2$, HCl, $H_2O$
2) $H_3PO_2$



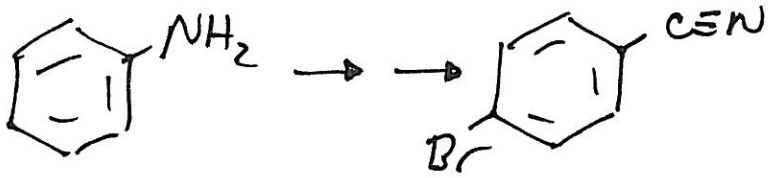
Note: remember ester hydrolysis

Why would we want to remove an amino group?

→ Amine can be used for directing an incoming electrophile + Then $-NH_2$ group removed

- Prepare  from 

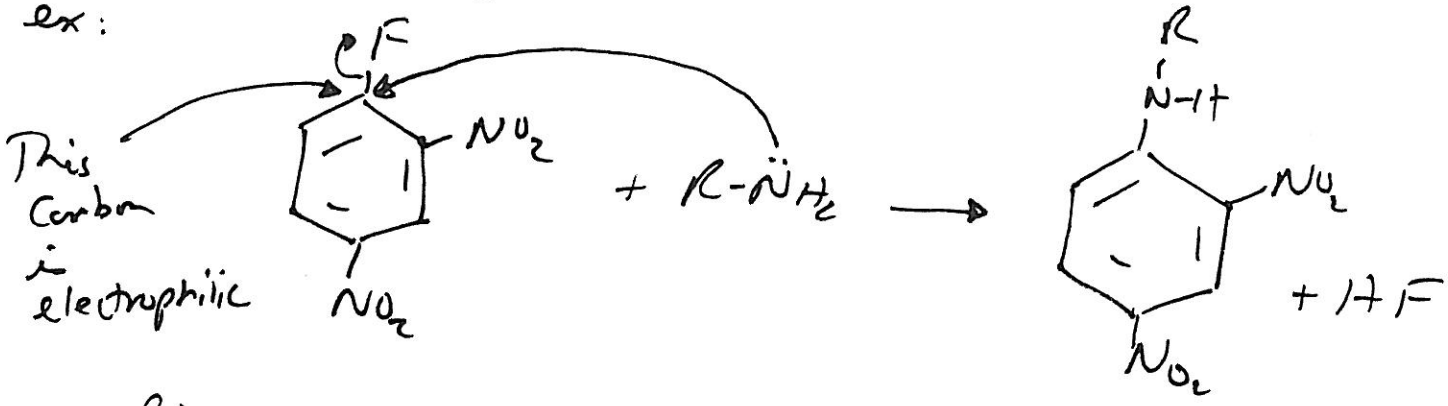
- How would you carry out this transformation?



# Nucleophilic Aromatic Substitution

→ Can not be done on "normal" benzene; needs to have powerful <u>electron withdrawing</u> groups on ring (not the mechanism)

ex:




- fluoride is the best halogen to displace in these <u>nucleophilic</u> aromatic substitutions. <u>WHY?</u>
  (normally not so in SN2 substitution)

- Fluorine is a good leaving group in nucleophilic aromatic substitution because:
  1) it is a very electronegative element & pulls away alot of e⁻ density from the electrophilic carbon that will be attacked by the nucleophile.
  2) it is a smaller halide, so it is not as sterically hindered as the other halides.

??? What is the <u>MECHANISM</u> for Nucleophilic Aromatic Subst.?? (21-45)

# Mechanism for Nucleophilic Aromatic Substitution