

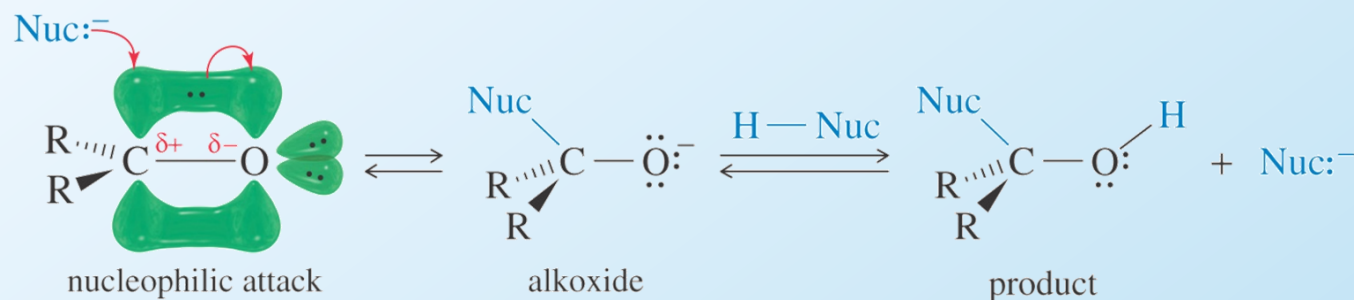
# **Aldehydes and Ketones Reactions**

Dr. Sapna Gupta

# Reactions of Aldehydes and Ketones

## Nucleophilic Addition

- A strong nucleophile attacks the carbonyl carbon, forming an alkoxide ion that is then protonated.
- A weak nucleophile will attack a carbonyl if it has been protonated, thus increasing its reactivity.
- Aldehydes are more reactive than ketones. (WHY?)



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# Reactions of Aldehydes and Ketones

## 1) Nucleophilic addition

### a) Carbon nucleophile

- i. Grignard reaction
- ii. Addition of HCN
- iii. Wittig reaction

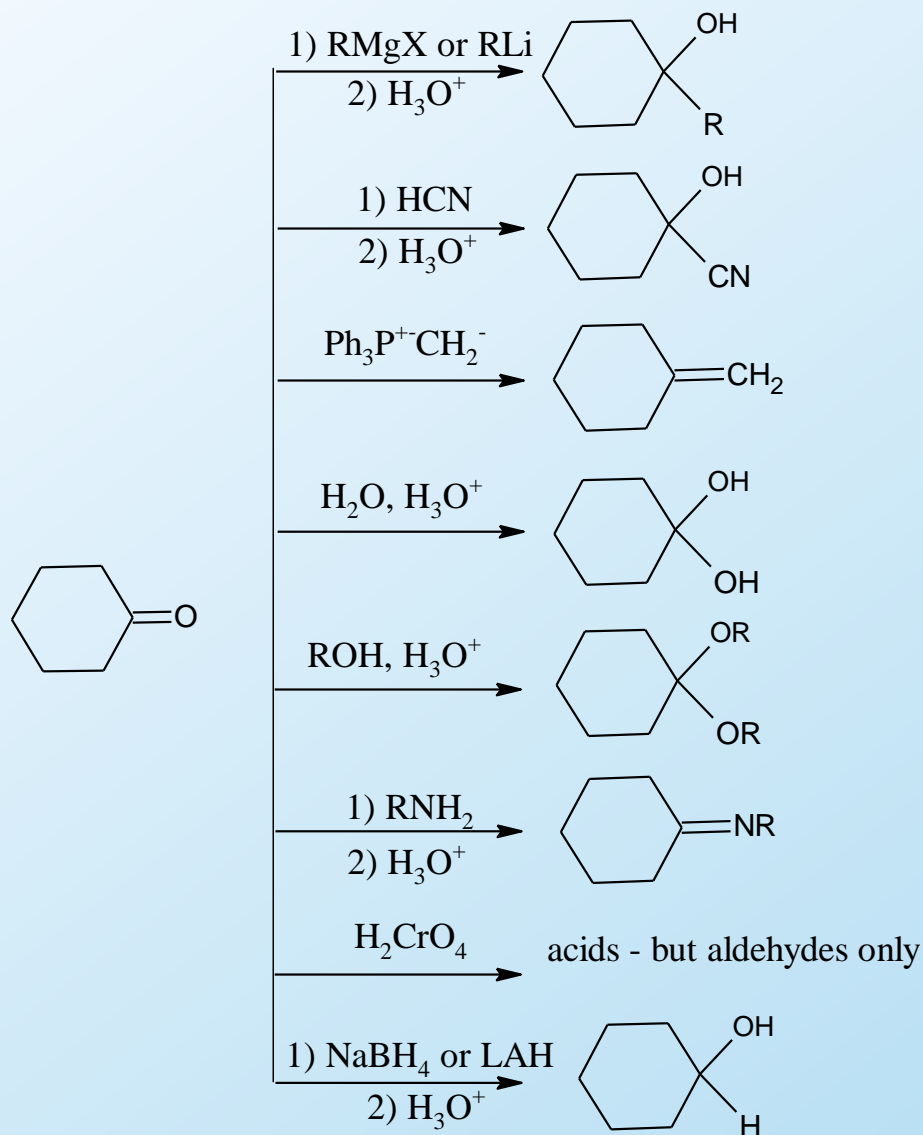
### b) Oxygen nucleophile

- i. Addition of water
- ii. Addition of alcohol

### c) Nitrogen nucleophile

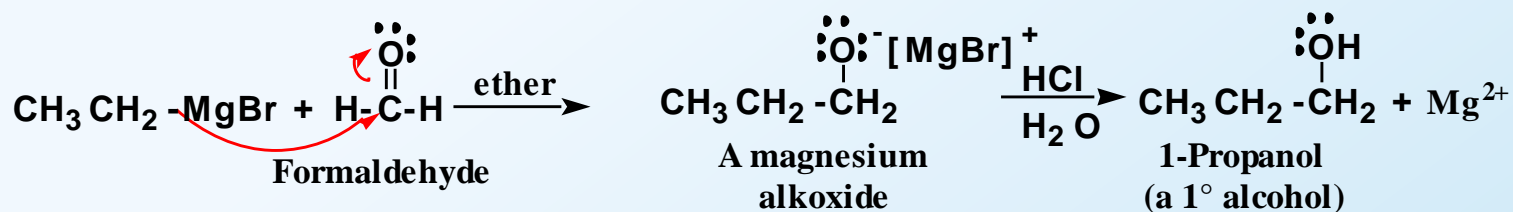
## 2) Oxidation

## 3) Reduction

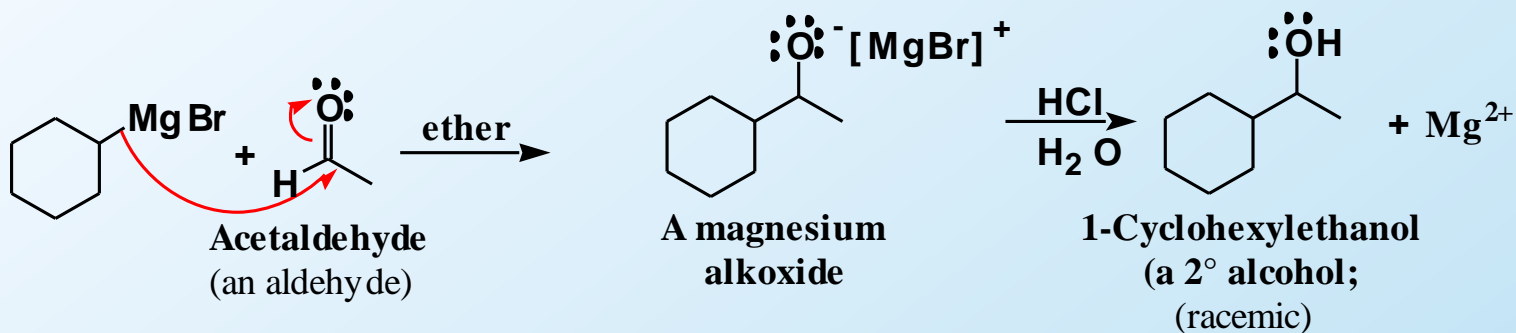


# (C-Nu) Grignard Reactions

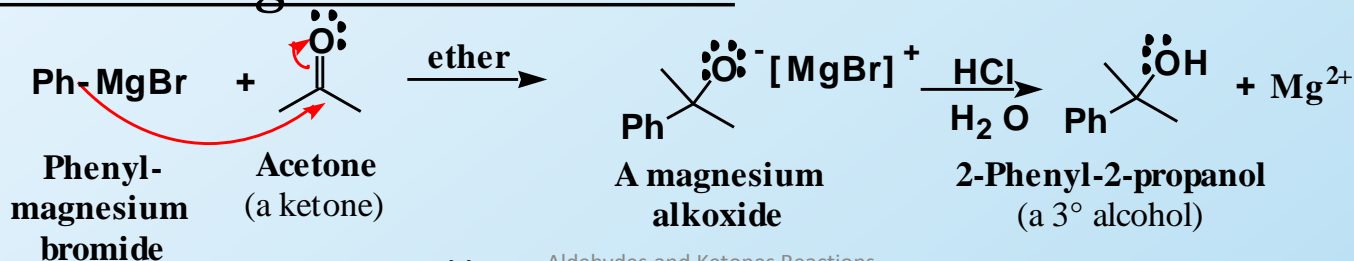
- GR + Formaldehyde gives a 1° alcohol.



- GR + any other RCHO gives a 2° alcohol.

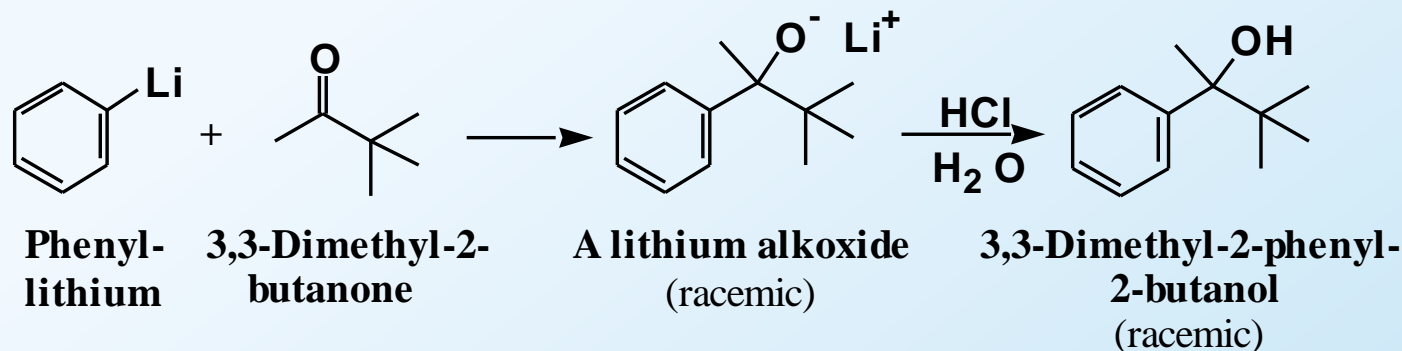


- GR + ketone gives a 3° alcohol.

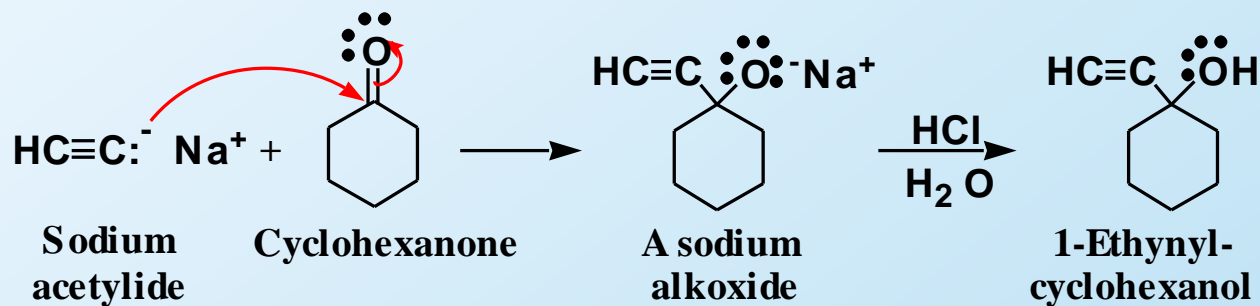


# (C-Nu) Other Organometallics

- Organolithium compounds are generally more reactive in C=O addition reactions than RMgX, and typically give higher yields.

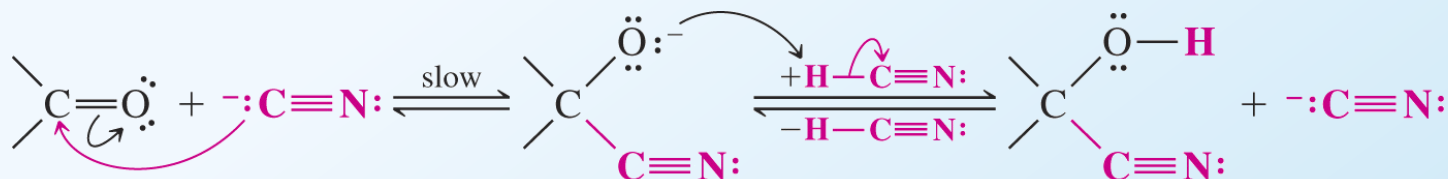


- Addition of an alkyne anion followed by treatment with  $\text{H}_3\text{O}^+$  gives an  $\alpha$ -acetylenic alcohol.

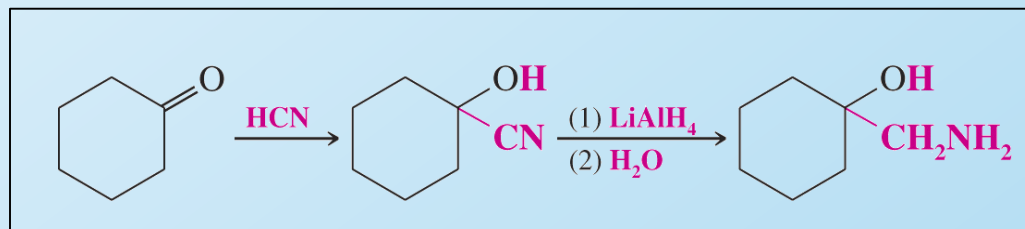
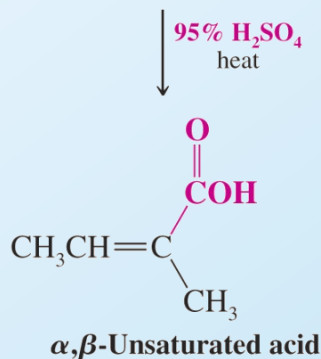
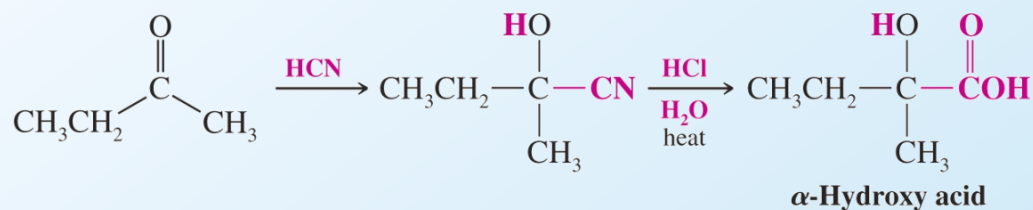


# (C-Nu) Addition of HCN

- HCN is highly toxic.
- Use NaCN or KCN in base to add cyanide, then protonate to add H.
- Reactivity formaldehyde > aldehydes > ketones >> bulky ketones.

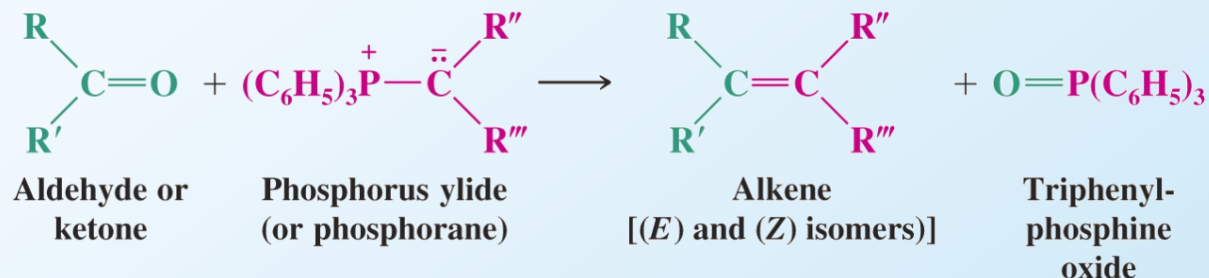


- The cyano group can be hydrolyzed or reduced
  - Hydrolysis of a cyanohydrin produces an  $\alpha$ -hydroxycarboxylic acid (Sec. 18.8H)
  - Reduction of a cyanohydrin produces a  $\beta$ -aminoalcohol

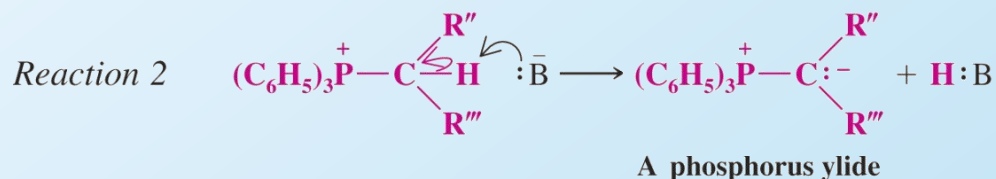
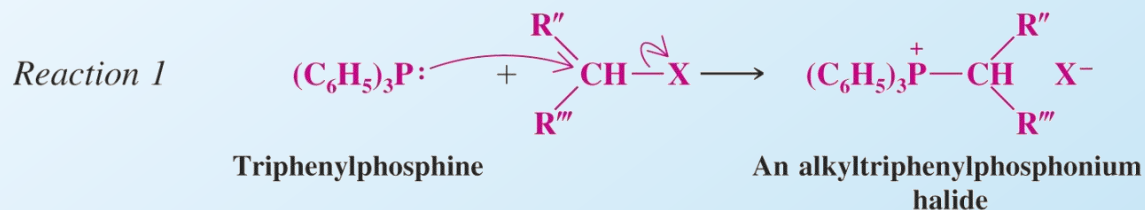


# (C-Nu) Wittig Reaction

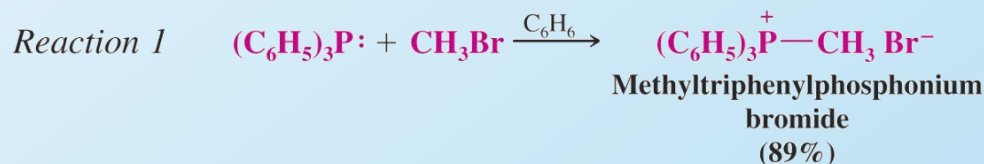
- Nucleophilic addition of phosphorus ylides.
- Product is alkene.
- C=O becomes C=C.



## General Reaction

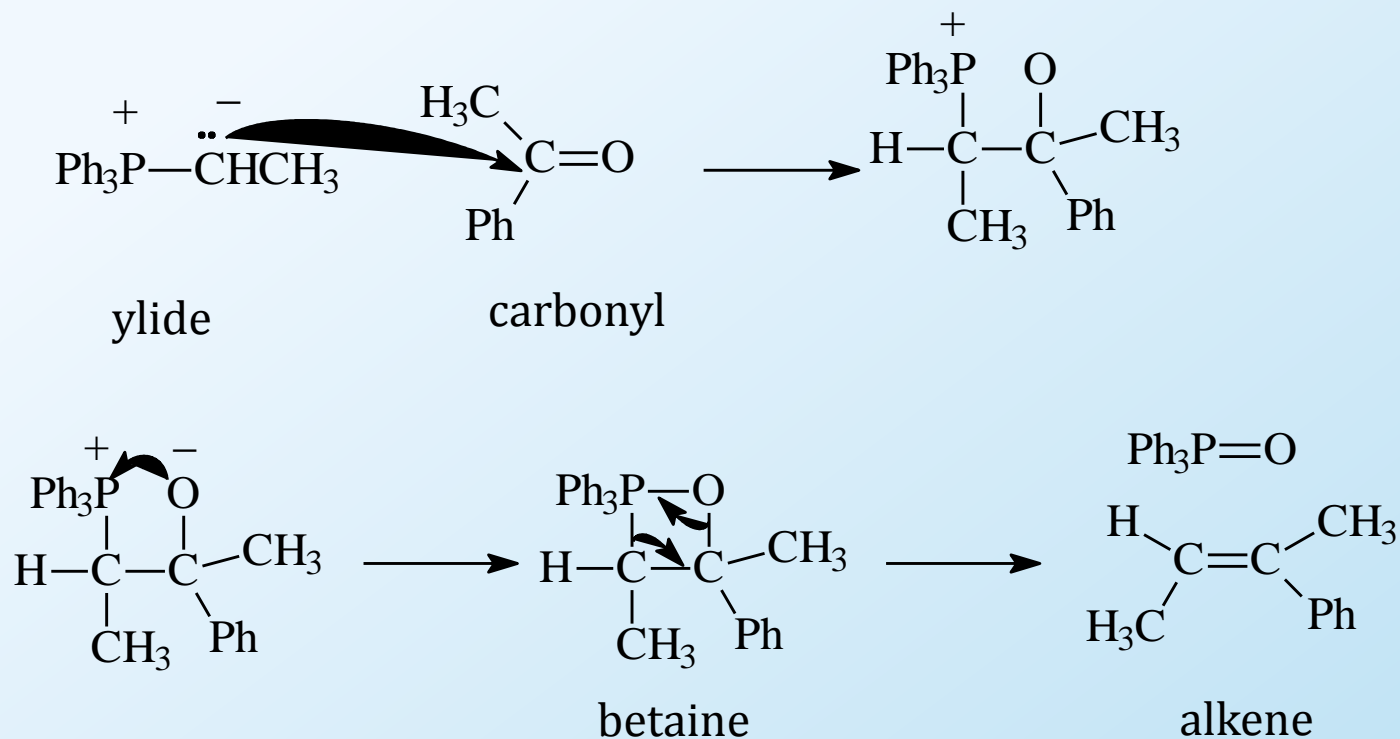


## Specific Example



# (C-Nu) Mechanism of Wittig Reaction

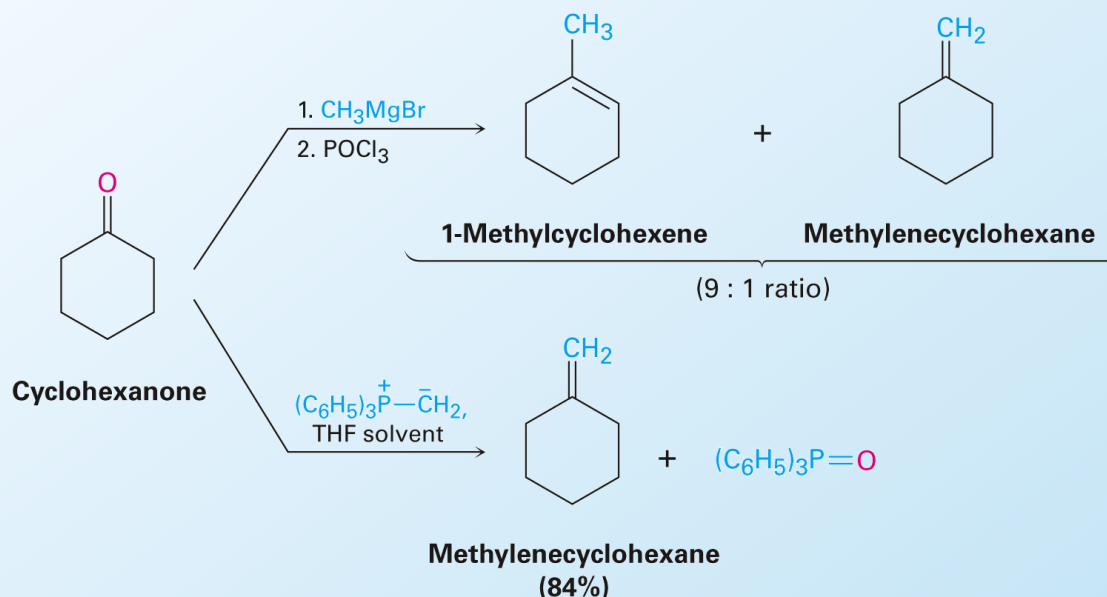
- The negative C on ylide attacks the positive C of carbonyl to form a betaine.
- Oxygen combines with phosphine to form the phosphine oxide.





# (C-Nu) Wittig Reaction – contd...

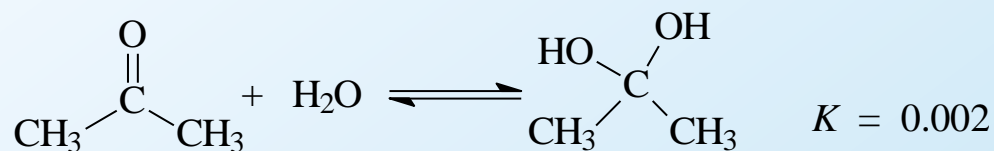
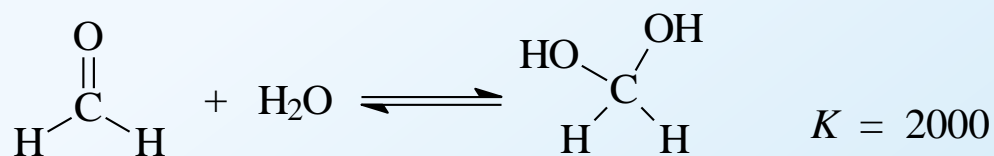
- Can be used for monosubstituted, disubstituted, and trisubstituted alkenes but not tetrasubstituted alkenes The reaction yields a pure alkene of known structure
- For comparison, addition of  $\text{CH}_3\text{MgBr}$  to cyclohexanone and dehydration with, yields a mixture of two alkenes



# (O-Nu) Addition of Water

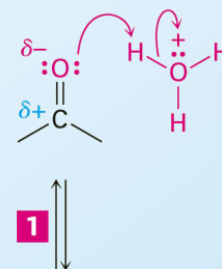
## Formation of Hydrate (gem diol)

- In acid, water is the nucleophile.
- In base, hydroxide is the nucleophile.

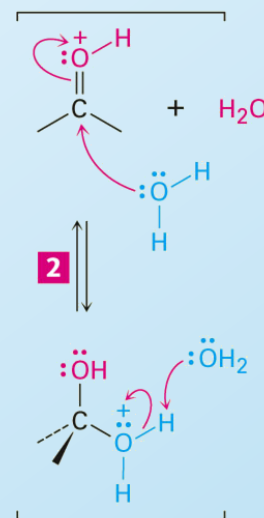


## Mechanism

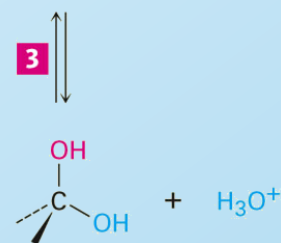
**1** The carbonyl oxygen is protonated by acid  $\text{H}_3\text{O}^+$ , making the carbon more strongly electrophilic



**2** The neutral nucleophile  $:\ddot{\text{O}}\text{H}_2$  adds to the electrophilic carbon, pushing the  $\pi$  electrons from the  $\text{C}=\text{O}$  onto oxygen. The oxygen becomes neutral, and the nucleophile gains the + charge.



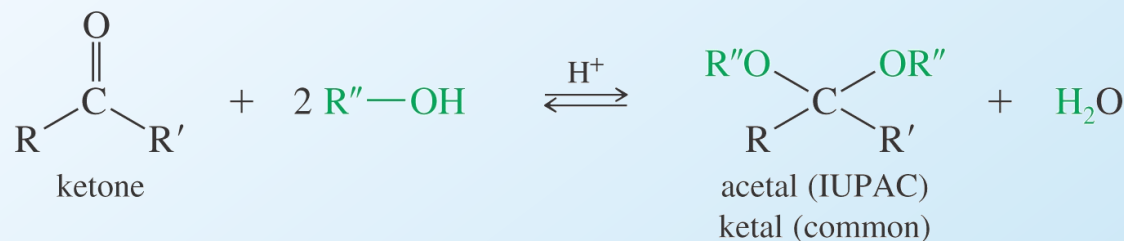
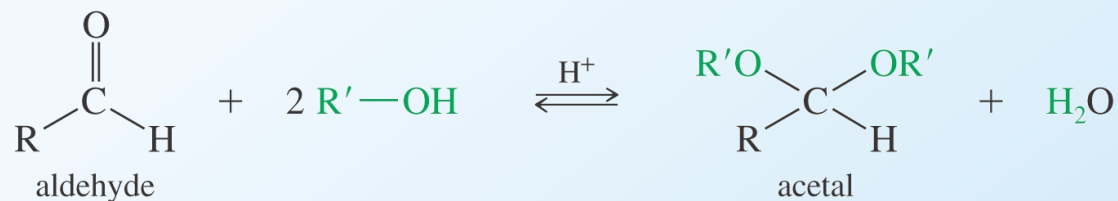
**3** Water deprotonates the intermediate, giving the neutral hydrate addition product and regenerating the acid catalyst  $\text{H}_3\text{O}^+$ .



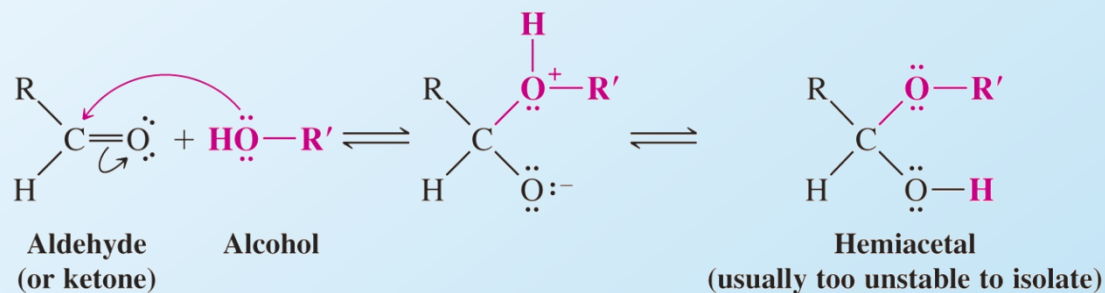
Hydrate  
(gem diol)

# (O-Nu) Addition of Alcohol - Acetals

- Reaction of alcohol with aldehyde gives acetals
- Reaction of alcohol with ketone gives ketals



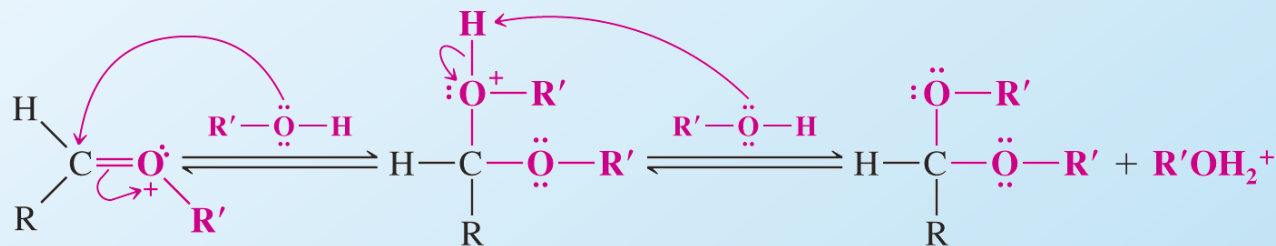
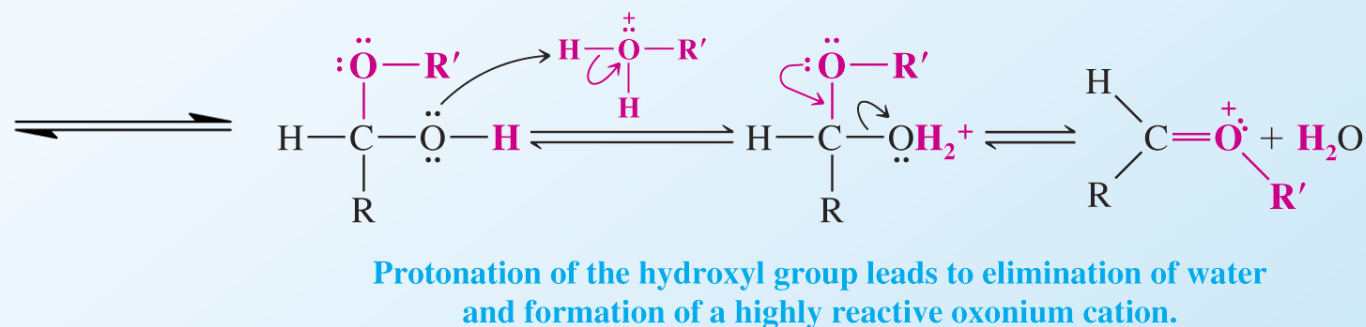
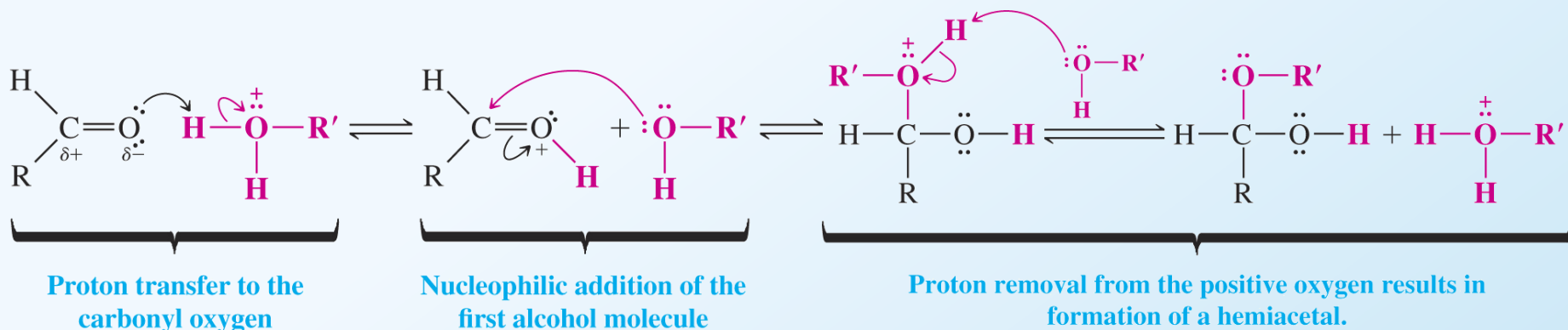
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# (O-Nu) Mechanism of Acetal Formation

- Is acid-catalyzed.
- Adding  $\text{H}^+$  to carbonyl makes it more reactive with weak nucleophile, ROH.
- Hemiacetal forms first, then acid-catalyzed loss of water, then addition of second molecule of ROH forms acetal.
- All steps are reversible.
- Mechanism – next slide.....

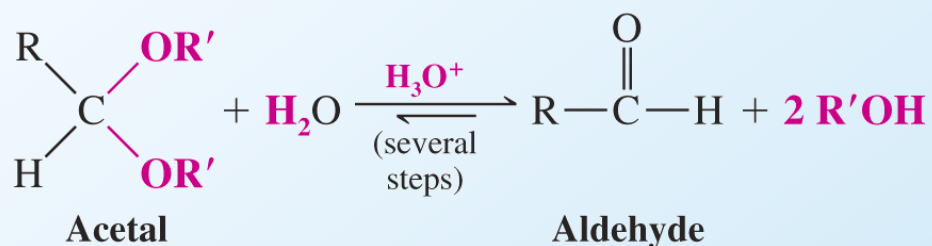
# (O-Nu) Mechanism of Acetal Formation



**Attack on the carbon of the oxonium ion by a second molecule of the alcohol, followed by removal of a proton, leads to the acetal.**

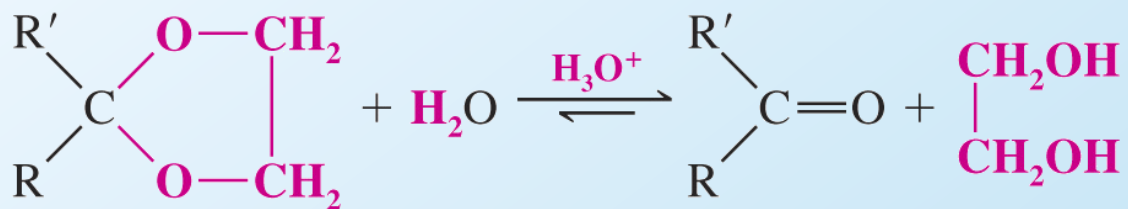
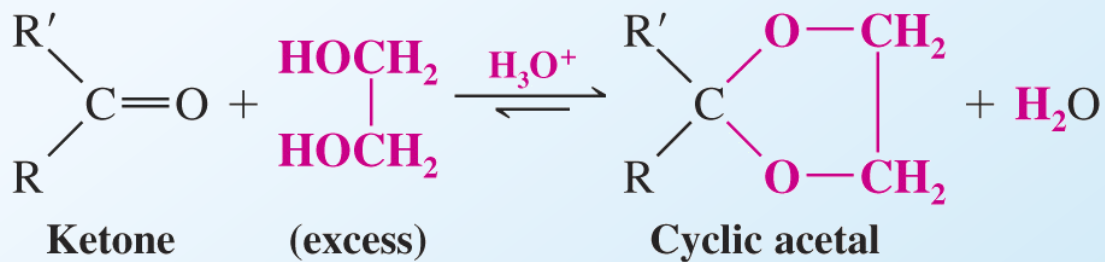
# (O-Nu) Hydrolysis of the Acetal

- Since all acetal formations are reversible; they can be converted back to aldehyde or ketone using water.



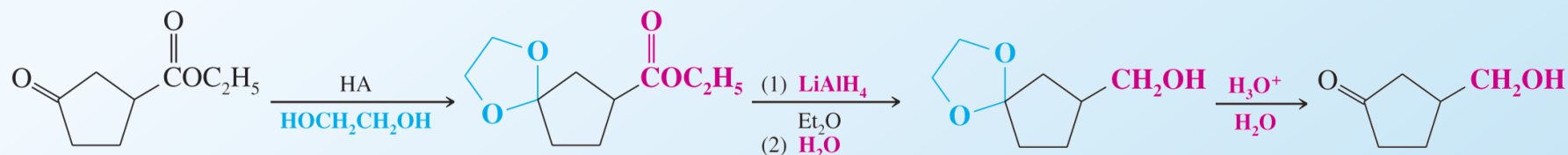
# (O-Nu) Cyclic Acetals

- Addition of a diol produces a cyclic acetal.
- Sugars commonly exist as acetals or hemiacetals.



# (O-Nu) Acetals as Protecting Groups

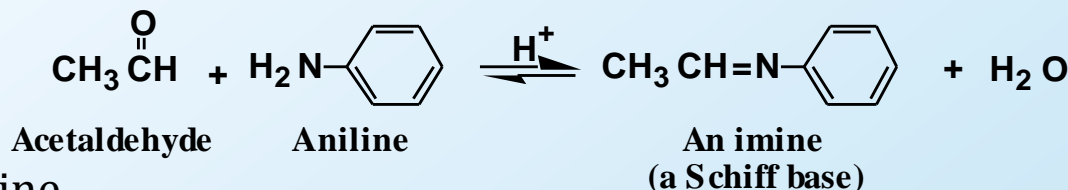
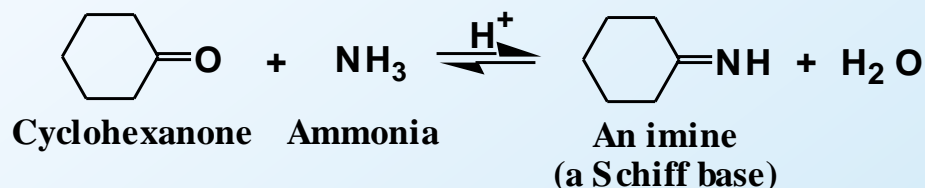
- Acetal protecting groups are stable to most reagents except aqueous acid
- Aldehydes more reactive than ketones so if there is an aldehyde and ketone to protect then aldehyde will be protected first.
- Example: An ester can be reduced in the presence of a ketone protected as an acetal



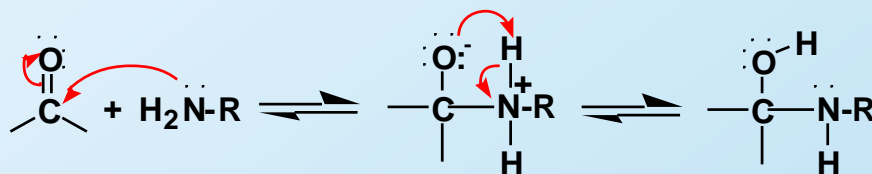


# (N-Nu) Addition of Ammonia and Amines

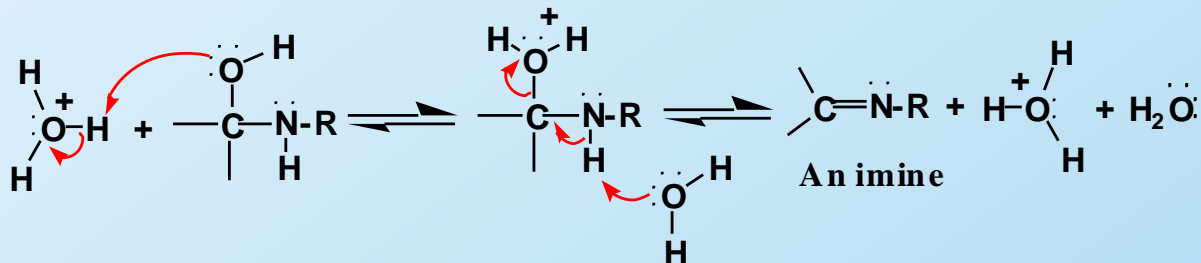
- Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give imines (Schiff bases).



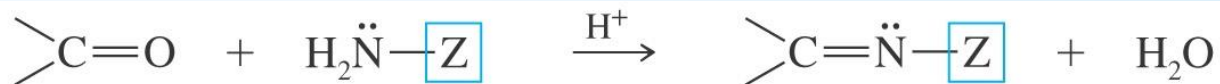
- Formation of an imine occurs in two steps:
- Step 1: Carbonyl addition followed by proton transfer.



- Step 2: Loss of H<sub>2</sub>O and proton transfer to solvent.



# (N-Nu) Other Ammonia Derivatives



*Z in Z—NH<sub>2</sub>*

*Reagent*

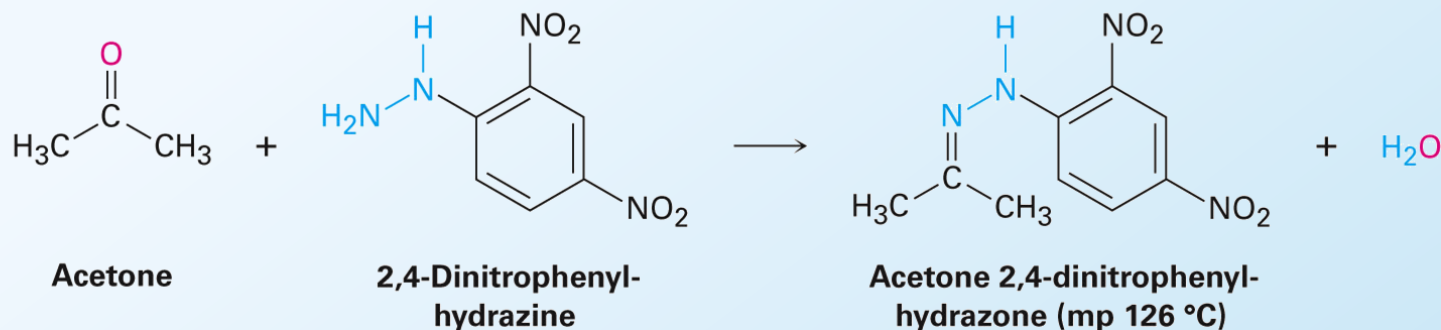
*Product*

—H	$\text{H}_2\ddot{\text{N}}-\boxed{\text{H}}$ ammonia	$>\text{C}=\ddot{\text{N}}-\boxed{\text{H}}$ an imine
—R	$\text{H}_2\ddot{\text{N}}-\boxed{\text{R}}$ primary amine	$>\text{C}=\ddot{\text{N}}-\boxed{\text{R}}$ an imine (Schiff base)
—OH	$\text{H}_2\ddot{\text{N}}-\boxed{\text{OH}}$ hydroxylamine	$>\text{C}=\ddot{\text{N}}-\boxed{\text{OH}}$ an oxime
—NH <sub>2</sub>	$\text{H}_2\ddot{\text{N}}-\boxed{\text{NH}_2}$ hydrazine	$>\text{C}=\ddot{\text{N}}-\boxed{\text{NH}_2}$ a hydrazone
—NHPh	$\text{H}_2\ddot{\text{N}}-\boxed{\text{NHPh}}$ phenylhydrazine	$>\text{C}=\ddot{\text{N}}-\boxed{\text{NHPh}}$ a phenylhydrazone
$\text{—NHC(=O)NH}_2$	$\text{H}_2\ddot{\text{N}}-\boxed{\text{NH—C(=O)—NH}_2}$ semicarbazide	$>\text{C}=\ddot{\text{N}}-\boxed{\text{NH—C(=O)—NH}_2}$ a semicarbazone

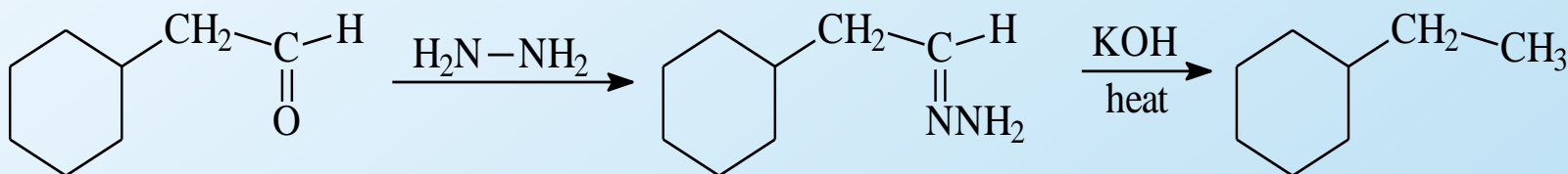
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# (N-Nu) Specific Reactions of Amines

- The reaction of carbonyl with 2,4-dinitrophenyl hydrazine is used as a qualitative test. The product is usually a solid and a stable compound (and orange!)

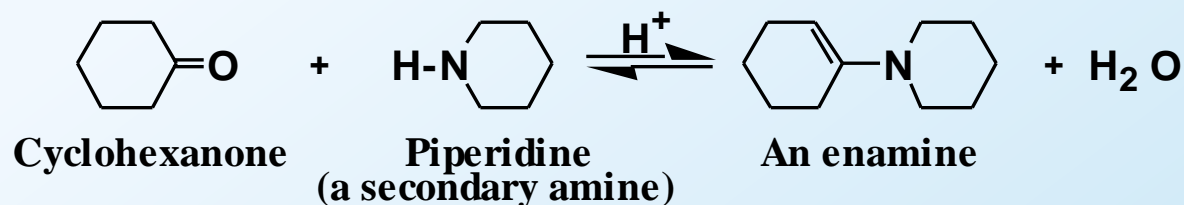


- Wolf Kishner Reduction: Reaction with hydrazine followed by reaction with KOH reduces the ketone to methylene.



# (N-Nu) Reactions with Secondary Amines

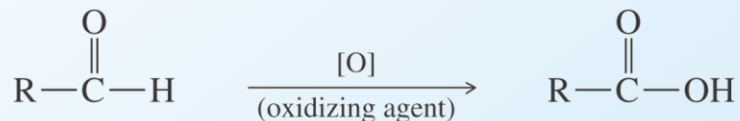
- Secondary amines react with the C=O group of aldehydes and ketones to form enamines.



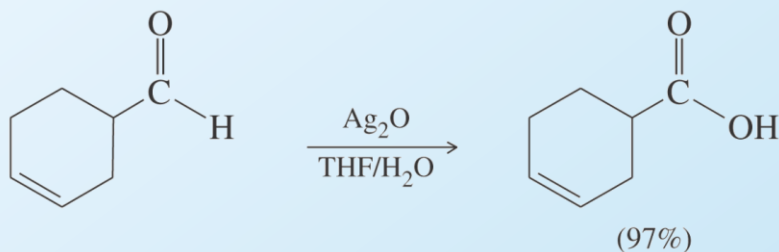
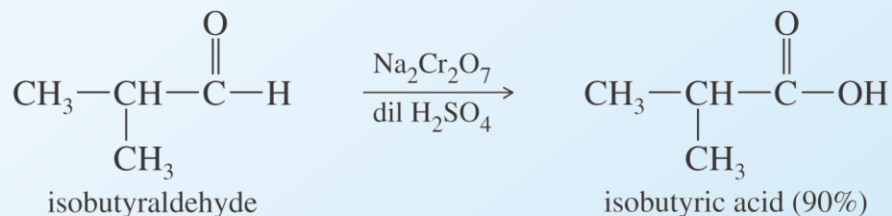
- The mechanism of enamine formation involves formation of a tetrahedral carbonyl addition compound followed by its acid-catalyzed dehydration.
- We discuss the chemistry of enamines in more detail in amines.

# Oxidation: Of Aldehydes

- Easily oxidized to carboxylic acids.

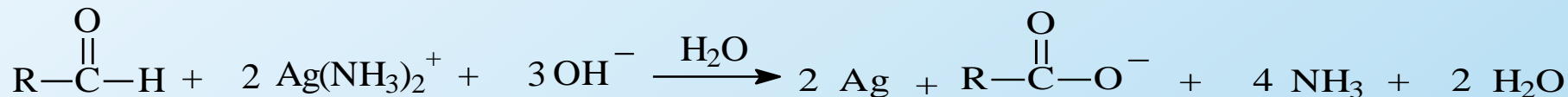


*Examples*



Tollens Test:

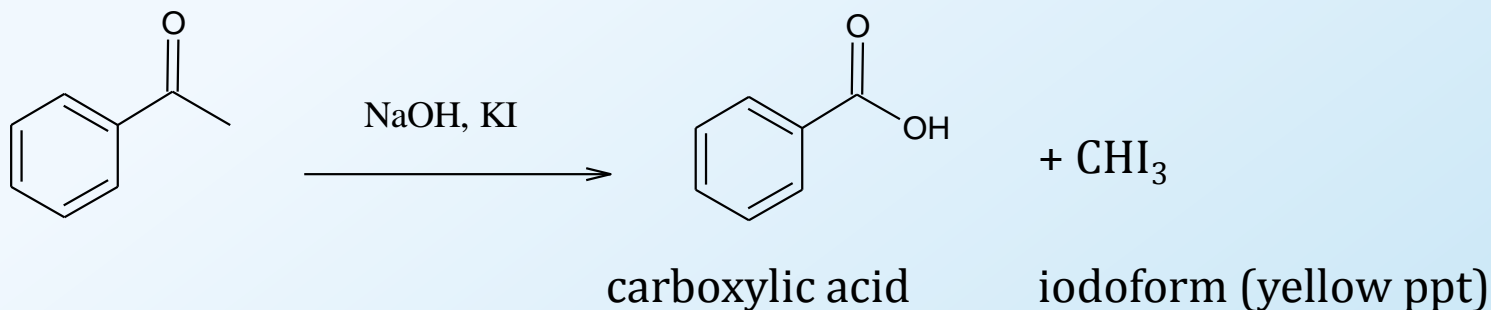
- Add ammonia solution to  $\text{AgNO}_3$  until precipitate dissolves. Aldehyde reaction forms a silver mirror.



# Oxidation: Of Ketones

## Iodoform Test

Methyl ketones oxidize to carboxylic acids with NaOH and KI.

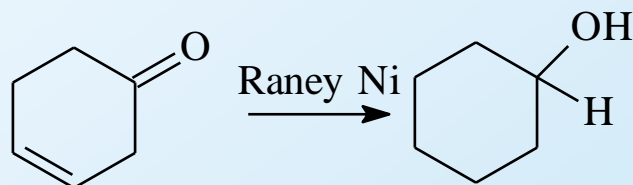


# Reduction: Of Aldehydes and Ketones

- Sodium borohydride,  $\text{NaBH}_4$ , reduces  $\text{C}=\text{O}$ , but not  $\text{C}=\text{C}$ .
- Lithium aluminum hydride,  $\text{LiAlH}_4$ , much stronger, difficult to handle.

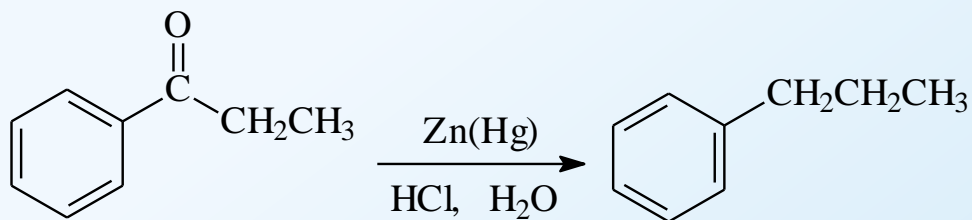
## Catalytic Hydrogenation

- Hydrogen gas with catalyst also reduces the  $\text{C}=\text{C}$  bond.
- Raney nickel, fine Ni (or Pt or Rh) powder saturated with hydrogen gas.

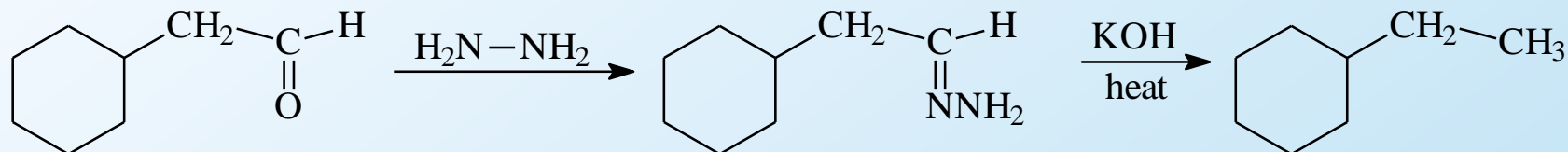


# Reduction: Of Carbonyl to Methylene

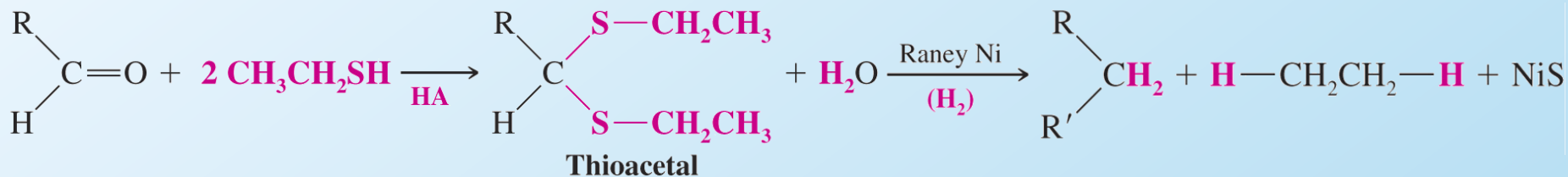
- Clemmensen reduction if molecule is stable in hot acid.



- Wolff-Kishner reduction if molecule is stable in very strong base.



- Using thioacetal (like acetals but using thiols instead of alcohols)





# Key Concepts

- 1) Nucleophilic addition
  - a) Carbon nucleophile
    - i. Grignard reaction
    - ii. Addition of HCN
    - iii. Wittig reaction
  - b) Oxygen nucleophile
    - i. Addition of water
    - ii. Addition of alcohol
  - c) Nitrogen nucleophile
- 2) Oxidation
- 3) Reduction