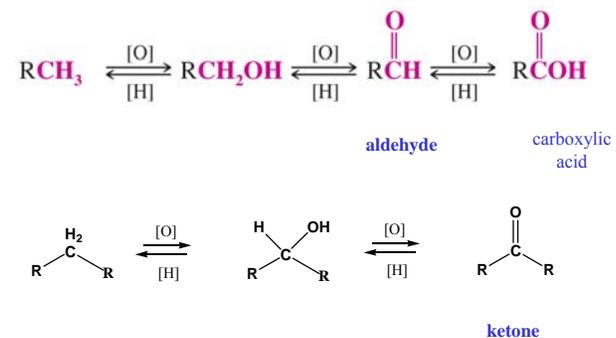


## Chapter 12

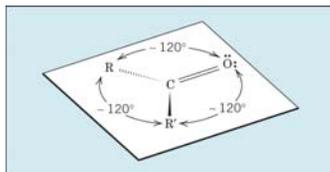
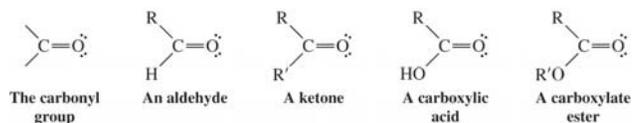
### Alcohols from Carbonyl Compounds: Oxidation-Reduction

### Central linking role of alcohols and carbonyls



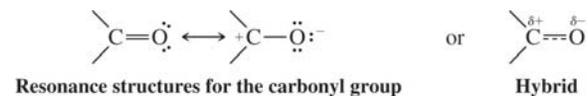
[O] and [H] are generic symbols for oxidation and reduction

### Structure of Carbonyl Group



**Carbonyl carbon =  $sp^2$  hybridized and trigonal planar**  
**All three atoms attached to the carbonyl group lie in one plane**

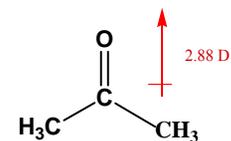
### Carbonyl bond is highly polar

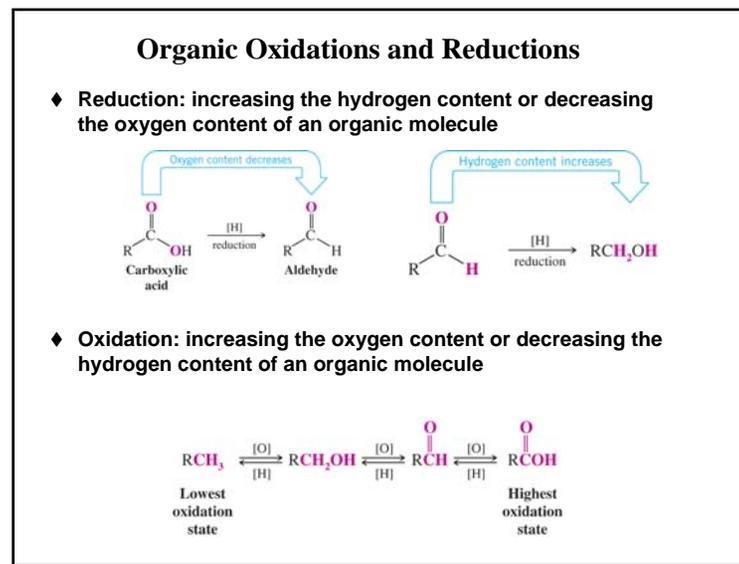
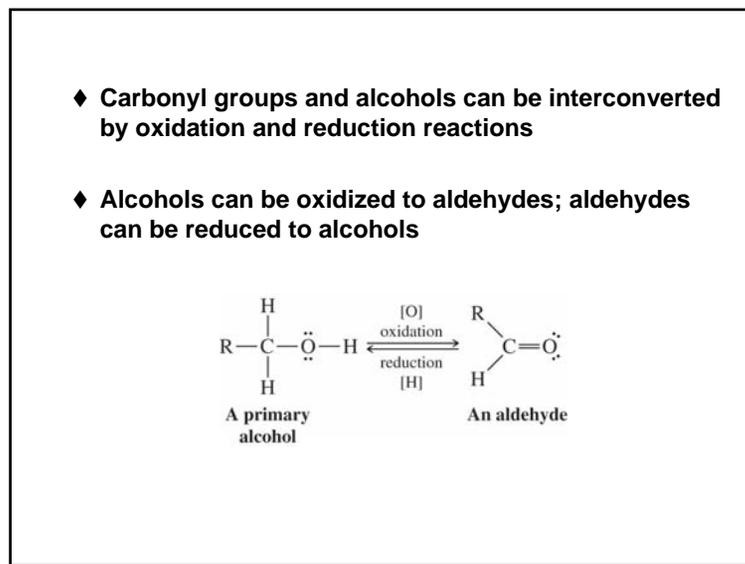
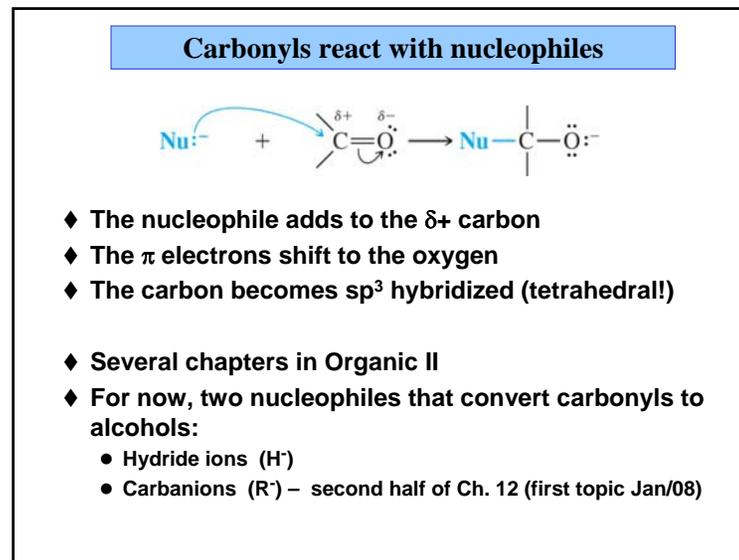
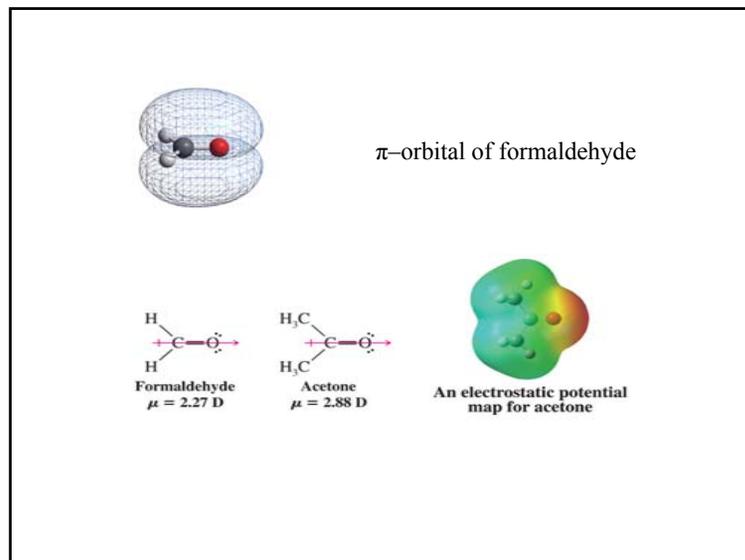


**Substantial  $\delta^+$  charge on the carbon !**

Dipole Moments (Debyes)

Water	1.85
Methanol	1.70
Acetone	2.88





## Reduction by addition of two hydrogens

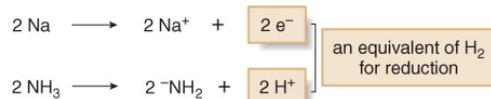
Three types of reductions: differing in how H<sub>2</sub> is added.

1. Simplest reducing agent is **molecular H<sub>2</sub>**. Reductions using H<sub>2</sub> require a metal catalyst.

- Used for alkenes or alkynes, less for carbonyl groups

2. Add two protons and two electrons to a substrate—that is, H<sub>2</sub> = **2H<sup>+</sup> + 2e<sup>-</sup>**.

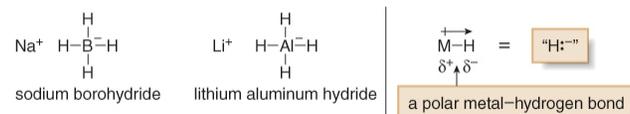
- Dissolving metal reductions use alkali metals as source of electrons, and liquid ammonia as source of protons.



- Used to convert alkynes to trans alkenes

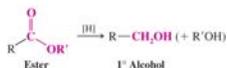
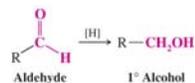
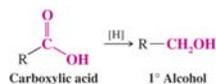
## The Third Way

- 3. Add hydride (H<sup>-</sup>) and then a proton (H<sup>+</sup>). (=H<sub>2</sub>)
- The most common hydride reducing agents contain a hydrogen atom bonded to boron or aluminum.
- NaBH<sub>4</sub> and LiAlH<sub>4</sub> deliver H<sup>-</sup> to the substrate, and then a proton is added from H<sub>2</sub>O or an alcohol.

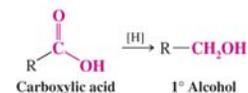


## Reductions of carbonyls to alcohols

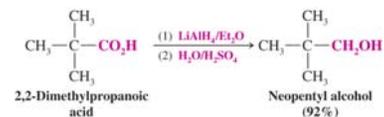
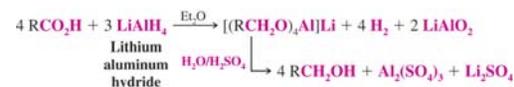
Several carbonyl compounds can be reduced to alcohols



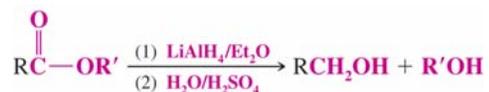
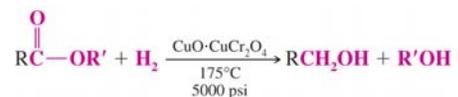
## Carboxylic acids can be reduced to primary alcohols



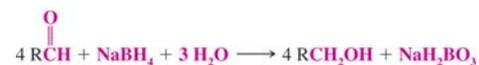
A difficult reduction, requires the powerful reducing agent such as lithium aluminum hydride (LiAlH<sub>4</sub> also abbreviated LAH)



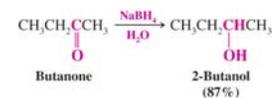
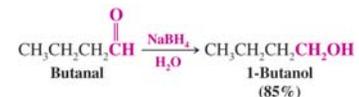
- ◆ Esters are also reduced to primary alcohols
  - LAH or high pressure hydrogenation can accomplish this transformation



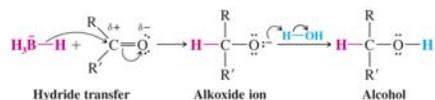
### Aldehydes and ketones are reduced to 1° and 2° alcohols respectively



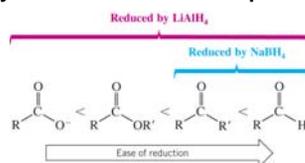
- ◆ Aldehydes and ketones are reduced relatively easily; the mild reducing agent sodium borohydride (NaBH<sub>4</sub>) is typically used
- ◆ LAH or hydrogenation with a metal catalyst can also be used



### Key step is reaction of hydride with carbonyl carbon



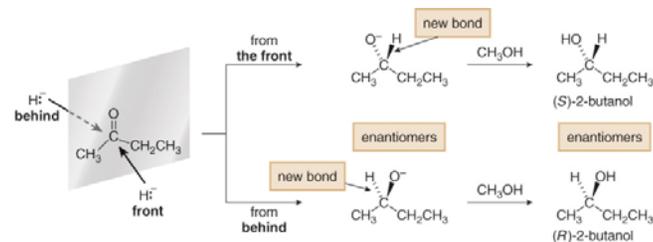
- ◆ Carboxylic acids and esters are less reactive to reduction than aldehydes and ketones and require the use of LAH



- ◆ Lithium aluminium hydride is very reactive with water and must be used in an anhydrous solvent such as ether
- ◆ Sodium borohydride is considerably less reactive and can be used in solvents such as water or an alcohol

### Stereochemistry of Carbonyl Reductions

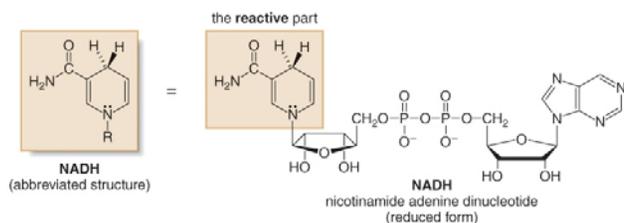
- Hydride converts a planar *sp*<sup>2</sup> hybridized carbonyl carbon to a tetrahedral *sp*<sup>3</sup> hybridized carbon.



Conclusion: with achiral reducing agents, racemic mixture is produced

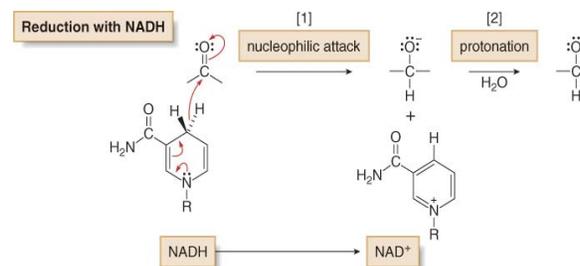
## Enantioselective Carbonyl Reductions

- Biological reductions that occur in cells always proceed with complete selectivity, forming a single enantiomer.
- In cells, a common reducing agent is NADH.
- NADH is a coenzyme—an organic molecule that can function only in the presence of the enzyme.

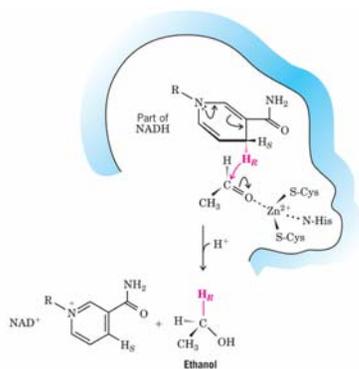


## Enantioselective Carbonyl Reductions

- The active site of the enzyme binds both the carbonyl substrate and NADH, keeping them in close proximity.
- NADH then donates  $\text{H}^-$  in much the same way as a hydride reducing agent.

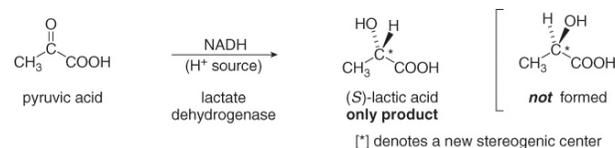


## Partial active site of alcohol dehydrogenase with NADH



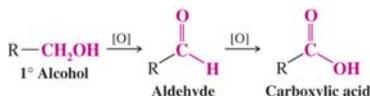
## Enantioselective Carbonyl Reductions

- The reaction is completely enantioselective. Reduction of pyruvic acid with NADH catalyzed by lactate dehydrogenase affords solely the *S* enantiomer.
- NADH reduces a variety of different carbonyl compounds in biological systems. The configuration of the product (*R* or *S*) depends on the enzyme used to catalyze the process.



### Oxidation of Alcohols

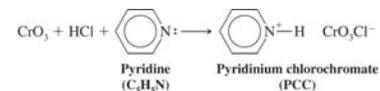
- ◆ Primary alcohols can be oxidized to aldehydes or to carboxylic acids
- ◆ The oxidation is difficult to stop at the aldehyde stage and usually proceeds on to the carboxylic acid



### Oxidation of Alcohols

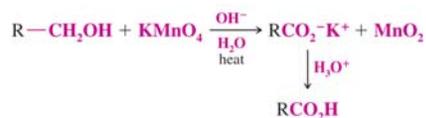
To stop at the **aldehyde** stage, use pyridinium chlorochromate (PCC)

- PCC is made from chromium trioxide under acidic conditions
- It is used in organic solvents such as methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>)



### Oxidation of Primary Alcohols to Carboxylic Acids

Potassium permanganate (KMnO<sub>4</sub>) is a typical reagent used for oxidation of a primary alcohol to a carboxylic acid

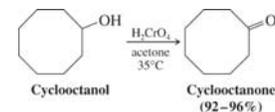
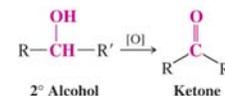


- ◆ The reaction is generally carried out in aqueous solution; purple of MnO<sub>4</sub><sup>-</sup> becomes the brown precipitate of MnO<sub>2</sub>

### Oxidation of Secondary Alcohols to Ketones

Oxidation of a secondary alcohol produces a ketone

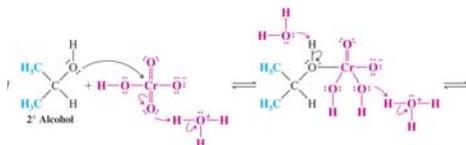
- Many oxidizing agents can be used, including chromic acid (H<sub>2</sub>CrO<sub>4</sub>), KMnO<sub>4</sub>, or Jones reagent (CrO<sub>3</sub> in acetone)



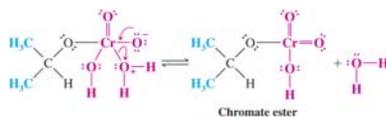
## Example of oxidation mechanism

### Mechanism of Chromate Oxidation

- Step 1: A chromate ester is formed from the alcohol hydroxyl

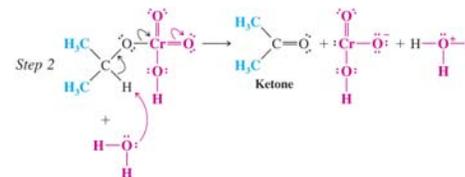


Alcohol adds to chromate



and a water molecule departs

- Step 2: An elimination reaction occurs by removal of a hydrogen atom from the alcohol carbon and departure of the chromium group with a pair of electrons.



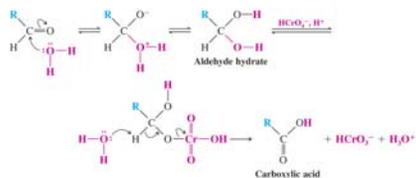
Cr atom departs with pair of electrons originally on the alcohol oxygen  
Hence organic compound is oxidized

Oxidation state of chromium is reduced from +6 to +4

## Why stopping oxidation of 1° ROH at aldehyde is difficult

Aldehydes form hydrates in water (an equilibrium)

- An aldehyde hydrate is a diol and can react by the same mechanism to produce a carboxylic acid



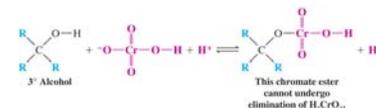
Pyridinium chlorochromate (PCC) reactions are run in anhydrous methylene chloride and the aldehyde cannot form a hydrate

- The oxidation of a primary alcohol therefore stops at the aldehyde stage

## Tertiary alcohols are not oxidized

- Tertiary alcohols can form the chromate ester but cannot eliminate because they have no hydrogen on the alcohol carbon

- Tertiary alcohols are therefore not oxidized



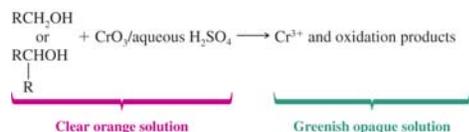
## Identification of the hydroxy group

- Spectroscopic Evidence for Alcohols

→ Alcohol O-H infrared stretching absorptions appear as strong, broad peaks around 3200-3600  $\text{cm}^{-1}$

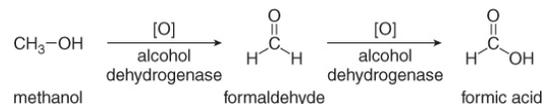
- A Chemical Test for Primary and Secondary Alcohols

→ Chromium oxide in acid has a clear orange color which changes to greenish opaque if an oxidizable alcohol is present



## The Oxidation of Ethanol in the body

- Ingested ethanol is oxidized in the liver first to  $\text{CH}_3\text{CHO}$  (acetaldehyde), and then to  $\text{CH}_3\text{COO}^-$  (the acetate anion).
- This oxidation is catalyzed by alcohol dehydrogenase.
- If more ethanol is ingested than can be metabolized, the concentration of acetaldehyde increases. Acetaldehyde, which is toxic, is responsible for the feelings associated with a hangover.



## Oxidation of 1<sup>o</sup> Alcohols - breathalyzers

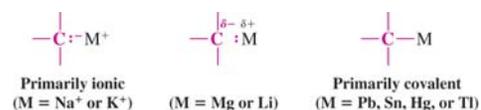
- Early breathalyzers were based on  $\text{Cr}^{6+}$  oxidations, as the red-orange  $\text{Cr}^{6+}$  reagent is reduced to green  $\text{Cr}^{3+}$ .



- Individual blows into a tube containing  $\text{K}_2\text{Cr}_2\text{O}_7$ ,  $\text{H}_2\text{SO}_4$ .
- The higher the concentration of  $\text{CH}_3\text{CH}_2\text{OH}$  in the breath, the farther the green  $\text{Cr}^{3+}$  color extends down the sample tube.
- This extent of the green color is then correlated with blood alcohol levels.

## ♦ Organometallic Compounds

→ Carbon-metal bonds vary widely in character from mostly covalent to mostly ionic depending on the metal



→ The greater the ionic character of the bond, the more reactive the compound

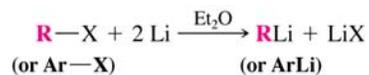
† Organopotassium compounds react explosively with water and burst into flame when exposed to air

## ◆ Preparation of Organolithium and Organo-magnesium Compounds

### ● Organolithium Compounds

→ Organolithium compounds can be prepared by reaction of an alkyl halide with lithium metal in an ether solvent

⚡ The order of reactivity of halides is R-I > R-Br > R-Cl (R-F is seldom used)



Diethyl ether  
(Et<sub>2</sub>O)

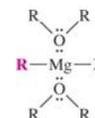
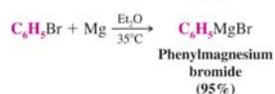
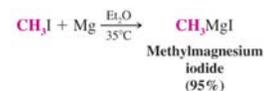


Tetrahydrofuran  
(THF)

### ● Grignard Reagents

→ Grignard reagents are prepared by the reaction of organic halides with magnesium turnings

⚡ An ether solvent is used because it forms a complex with the Grignard reagent which stabilizes it

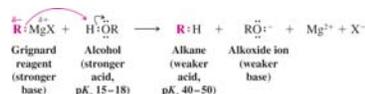
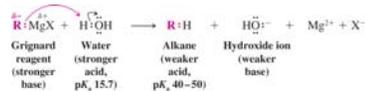


## ◆ Reactions of Organolithium and Organo-magnesium Compounds

### ● Reactions with Compounds Containing Acidic Hydrogen Atoms

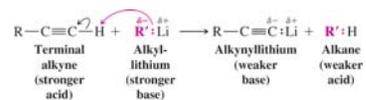
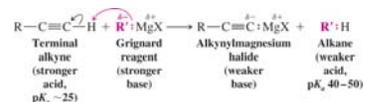
→ Organolithium and Grignard reagents behave as if they were carbanions and they are therefore very strong bases

⚡ They react readily with hydrogen atoms attached to oxygen, nitrogen or sulfur, in addition to other acidic hydrogens (water and alcohol solvents cannot be used)



→ Organolithium and Grignard reagents can be used to form alkynides by acid-base reactions

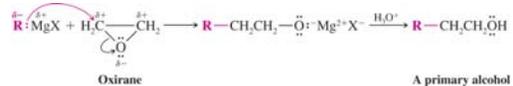
⚡ Alkynylmagnesium halides and alkynyllithium reagents are useful nucleophiles for C-C bond synthesis



● **Reactions of Grignard Reagents with Oxiranes (Epoxides)**

→ Grignard reagents are very powerful nucleophiles and can react with the  $\delta^+$  carbons of oxiranes

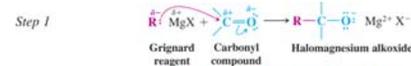
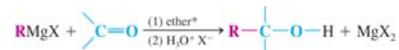
- The reaction results in ring opening and formation of an alcohol product
- Reaction occurs at the least-substituted ring carbon of the oxirane
- The net result is carbon-carbon bond formation two carbons away from the alcohol



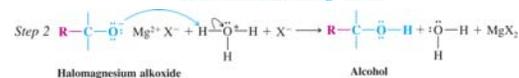
● **Reaction of Grignard Reagents with Carbonyl Compounds**

→ Nucleophilic attack of Grignard reagents at carbonyl carbons is the most important reaction of Grignard reagents

- Reaction of Grignard reagents with aldehydes and ketones yields a new carbon-carbon bond and an alcohol



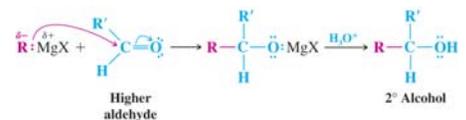
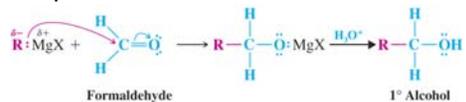
The strongly nucleophilic Grignard reagent uses its electron pair to form a bond to the carbon atom. One electron pair of the carbonyl group shifts out to the oxygen. This reaction is a nucleophilic addition to the carbonyl group, and it results in the formation of an alkoxide ion associated with  $\text{Mg}^{2+}$  and  $\text{X}^-$ .



In the second step, the addition of aqueous HX causes protonation of the alkoxide ion; this leads to the formation of the alcohol and  $\text{MgX}_2$ .

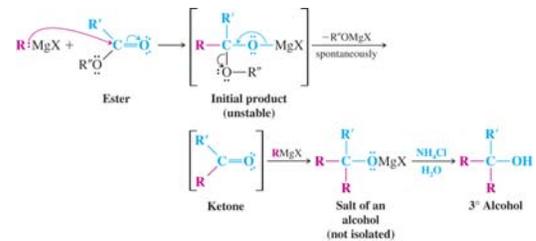
◆ **Alcohols from Grignard Reagents**

→ Aldehydes and ketones react with Grignard reagents to yield different classes of alcohols depending on the starting carbonyl compound



→ Esters react with two molar equivalents of a Grignard reagent to yield a tertiary alcohol

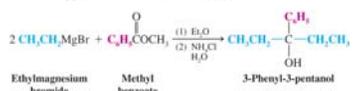
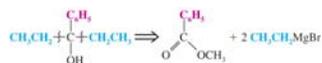
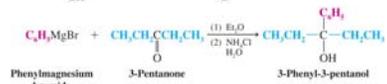
- A ketone is formed by the first molar equivalent of Grignard reagent and this immediately reacts with a second equivalent to produce the alcohol
- The final product contains two identical groups at the alcohol carbon that are both derived from the Grignard reagent



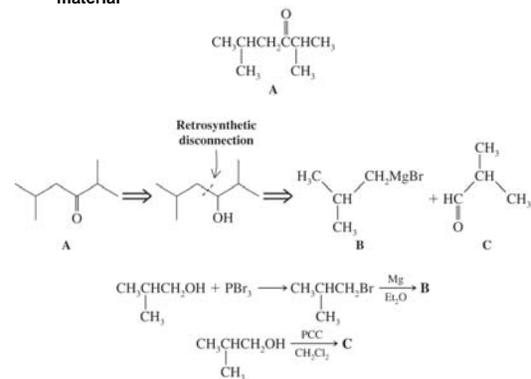
## ● Planning a Grignard Synthesis

### → Example : Synthesis of 3-phenyl-3-pentanol

- ⚡ The starting material may be a ketone or an ester
- ⚡ There are two routes that start with ketones (one is shown)



### → Solved Problem: Synthesize the following compound using an alcohol of not more than 4 carbons as the only organic starting material

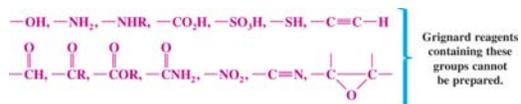


## ● Restrictions on the Use of Grignard Reagents

### → Grignard reagents are very powerful nucleophiles and bases

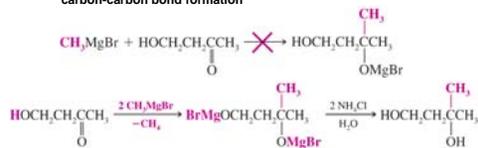
- ⚡ They react as if they were carbanions

### → Grignard reagents cannot be made from halides which contain acidic groups or electrophilic sites elsewhere in the molecule



### → The substrate for reaction with the Grignard reagent cannot contain any acidic hydrogen atoms

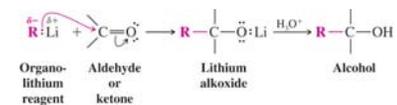
- ⚡ The acidic hydrogens will react first and will quench the Grignard reagent
- ⚡ Two equivalents of Grignard reagent could be used, so that the first equivalent is consumed by the acid-base reaction while the second equivalent accomplishes carbon-carbon bond formation



## ● The Use of Lithium Reagents

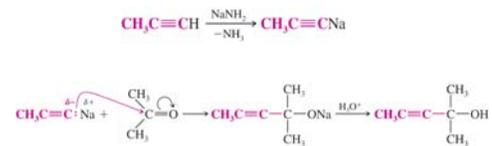
### → Organolithium reagents react similarly to Grignard reagents

- ⚡ Organolithium reagents tend to be more reactive



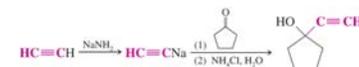
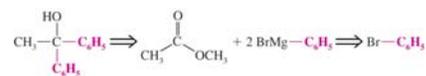
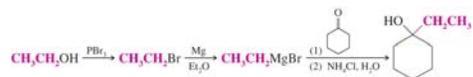
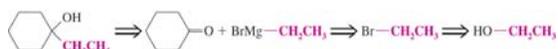
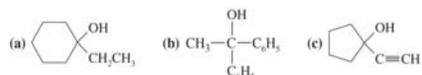
## ● The Use of Sodium Alkynides

### → Sodium alkynides react with carbonyl compounds such as aldehydes and ketones to form new carbon-carbon bonds



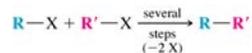
● Solved Problem

→ Synthesize the following compounds using reagents of 6 carbons or less



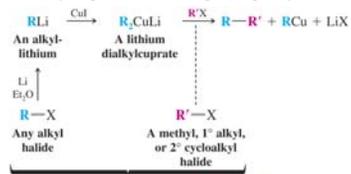
◆ Lithium Dialkylcuprates: The Corey-Posner, Whitesides-House Synthesis

→ This is an alternative formation of carbon-carbon bonds which, in effect, couples two alkyl halides



→ One of the halides is converted to a lithium dialkylcuprate by a two step sequence

→ Treatment of the lithium dialkylcuprate with the other halide results in coupling of the two organic groups



These are the organic starting materials. The R- and R'- groups need not be different.

