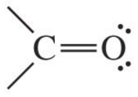
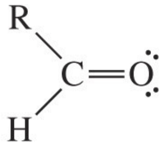
Chapter 12
Alcohols from Carbonyl Compounds: Oxidation-Reduction and Organometallic Compounds

♦ Introduction

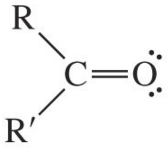
- ➔ **Several functional groups contain the carbonyl group**
  - **Carbonyl groups can be converted into alcohols by various reactions**



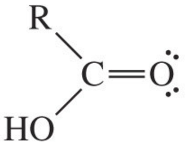
The carbonyl group



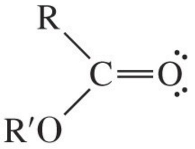
An aldehyde



A ketone



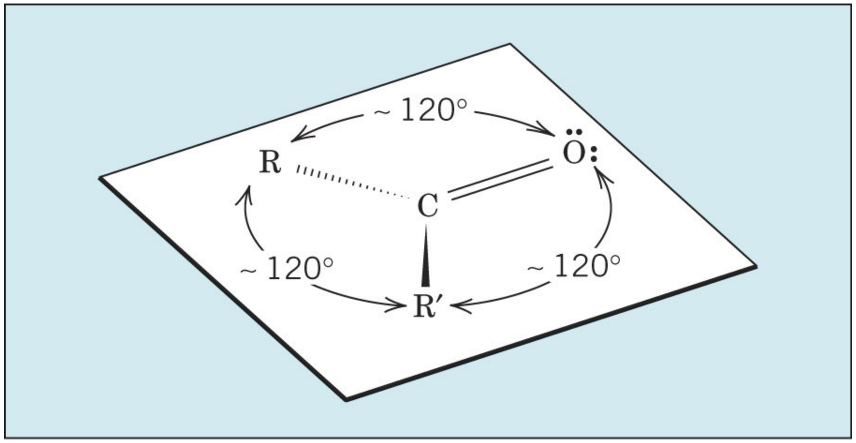
A carboxylic acid



A carboxylate ester

● Structure of the Carbonyl Group

- ➔ **The carbonyl carbon is sp^2 hybridized and is trigonal planar**
  - **All three atoms attached to the carbonyl group lie in one plane**



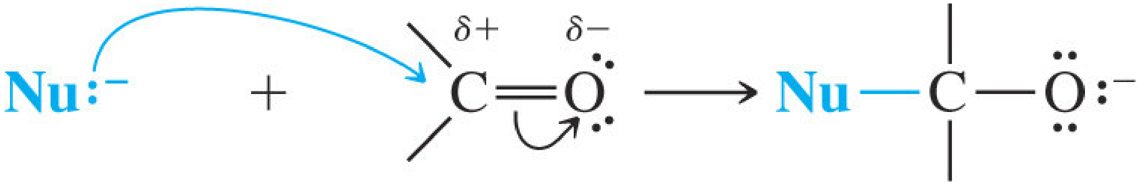
➔ **The carbonyl group is polarized; there is substantial δ+ charge on the carbon**

Resonance structures for the carbonyl group **Hybrid**

Reactions of Carbonyl Compounds with Nucleophiles

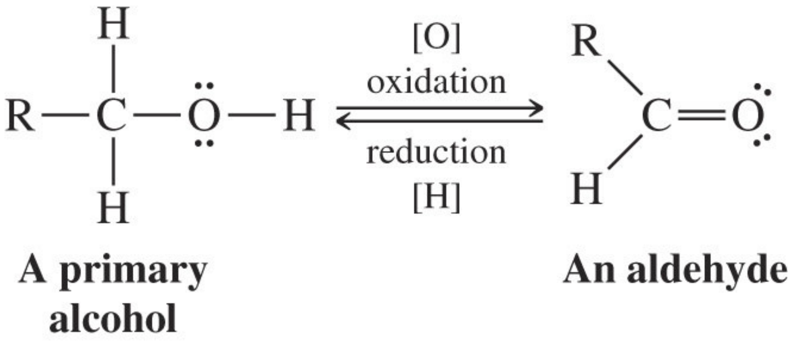
➔Carbonyl groups can undergo nucleophilic addition

- The nucleophile adds to the δ+ carbon
- The π electrons shift to the oxygen
- The carbon becomes sp^3 hybridized and therefore tetrahedral
- Hydride ions and carbanions are two examples of nucleophiles that react with the carbonyl carbon



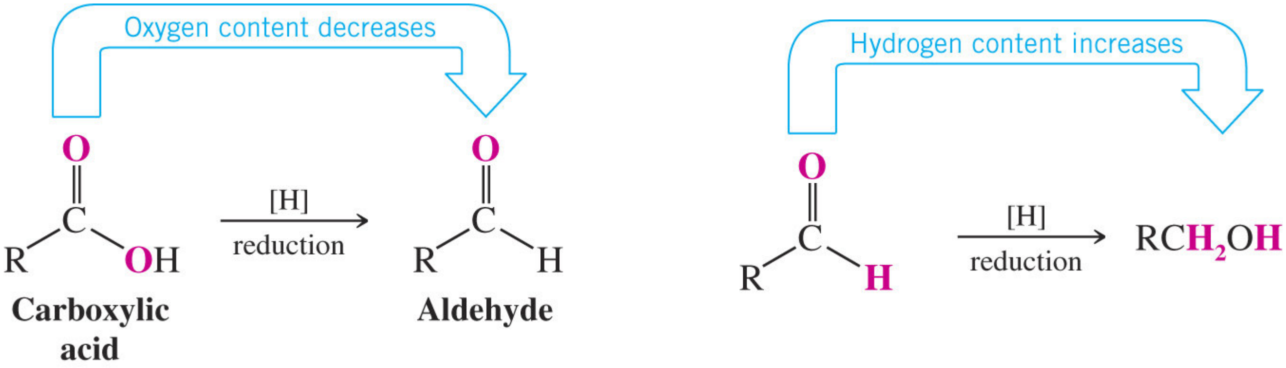
➔Carbonyl groups and alcohols can be interconverted by oxidation and reduction reactions

- Alcohols can be oxidized to aldehydes; aldehydes can be reduced to alcohols

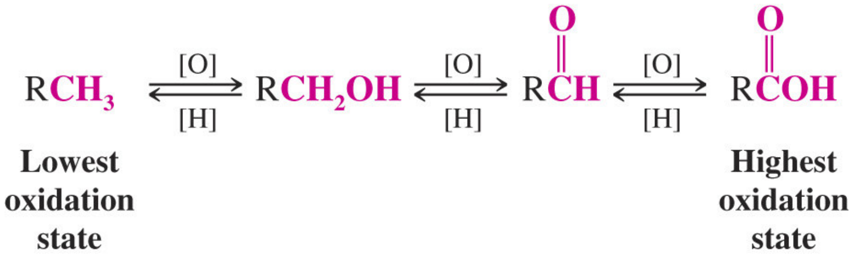


♦ Oxidation-Reduction Reactions in Organic Chemistry

- ➔ Reduction: increasing the hydrogen content or decreasing the oxygen content of an organic molecule
  - A general symbol for reduction is [H]



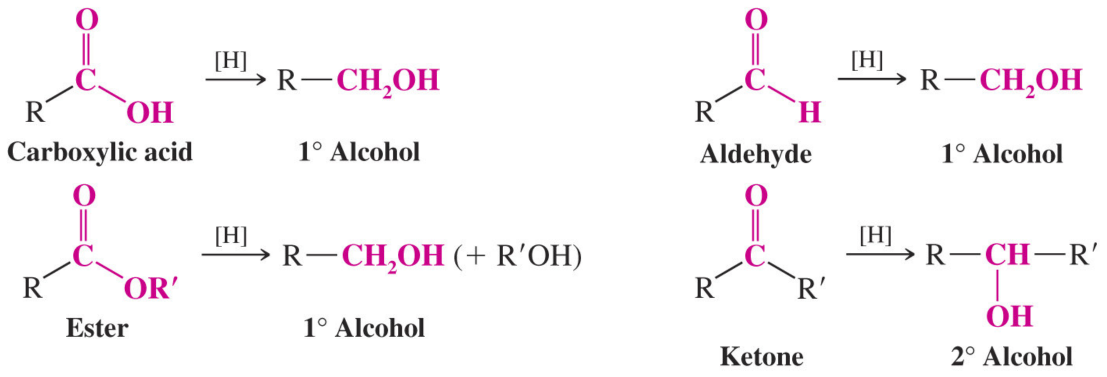
- ➔ Oxidation: increasing the oxygen content or decreasing the hydrogen content of an organic molecule
  - A general symbol for oxidation is [O]
  - Oxidation can also be defined as a reaction that increases the content of any element more electronegative than carbon



$$RCH_3 \underset{[H]}{\overset{[O]}{\rightleftharpoons}} RCH_2OH \underset{[H]}{\overset{[O]}{\rightleftharpoons}} R\overset{\overset{\displaystyle O}{\|}}{C}H \underset{[H]}{\overset{[O]}{\rightleftharpoons}} R\overset{\overset{\displaystyle O}{\|}}{C}OH$$

♦ Alcohols by Reduction of Carbonyl Compounds

➔ A variety of carbonyl compounds can be reduced to alcohols



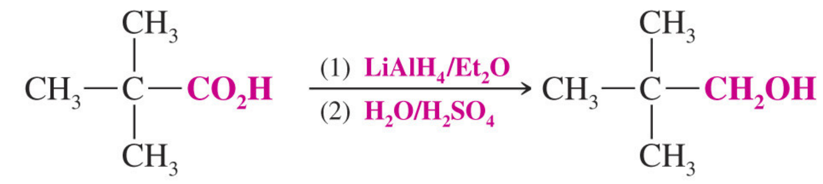
➔ Carboxylic acids can be reduced to primary alcohols

- These are difficult reductions and require the use of powerful reducing agents such as lithium aluminum hydride ($LiAlH_4$ also abbreviated LAH)

$$4\,RCO_2H + 3\,LiAlH_4 \xrightarrow{Et_2O} [(RCH_2O)_4Al]Li + 4\,H_2 + 2\,LiAlO_2$$

$$\xrightarrow{H_2O/H_2SO_4} 4\,RCH_2OH + Al_2(SO_4)_3 + Li_2SO_4$$

Lithium aluminum hydride

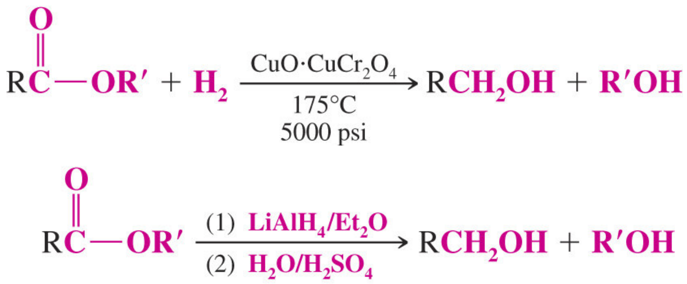


$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CO_2H \xrightarrow[(2)\ H_2O/H_2SO_4]{(1)\ LiAlH_4/Et_2O} CH_3-\underset{CH_3}{\overset{CH_3}{C}}-CH_2OH$$

2,2-Dimethylpropanoic acid **Neopentyl alcohol (92%)**

➔ Esters are also reduced to primary alcohols

- LAH or high pressure hydrogenation can accomplish this transformation

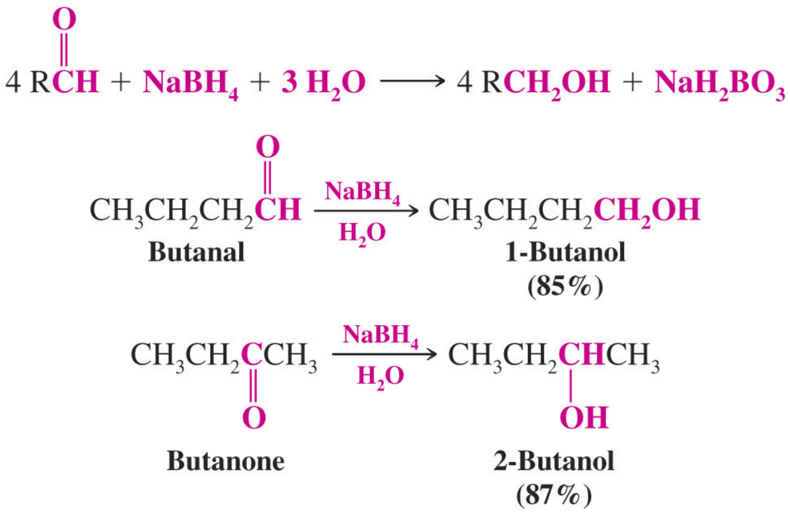


$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}OR' + H_2 \xrightarrow[\text{175°C, 5000 psi}]{CuO\cdot CuCr_2O_4} RCH_2OH + R'OH}$$

$$\mathrm{R\overset{O}{\overset{\|}{C}}{-}OR' \xrightarrow[(2)\ H_2O/H_2SO_4]{(1)\ LiAlH_4/Et_2O} RCH_2OH + R'OH}$$

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

- Aldehydes and ketones are reduced relatively easily; the mild reducing agent sodium borohydride ($NaBH_4$) is typically used
- LAH and hydrogenation with a metal catalyst can also be used

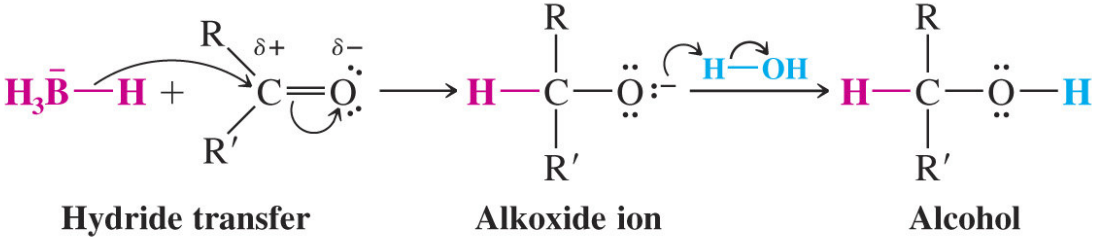


$$\mathrm{4\,R\overset{O}{\overset{\|}{C}}H + NaBH_4 + 3\,H_2O \longrightarrow 4\,RCH_2OH + NaH_2BO_3}$$

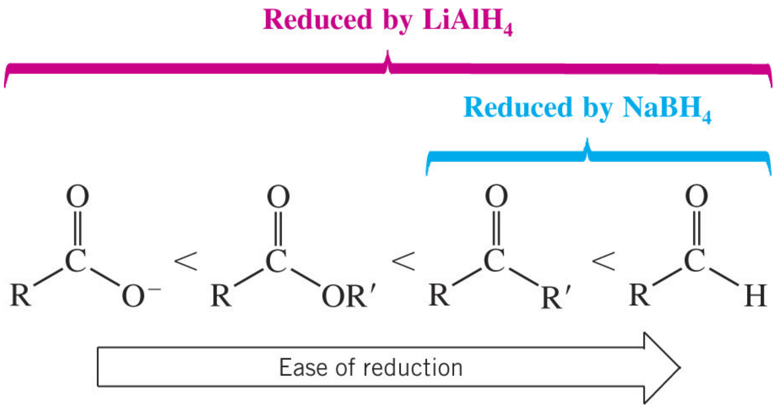
$$\underset{\textbf{Butanal}}{\mathrm{CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}H}} \xrightarrow[H_2O]{NaBH_4} \underset{\textbf{1-Butanol (85\%)}}{\mathrm{CH_3CH_2CH_2CH_2OH}}$$

$$\underset{\textbf{Butanone}}{\mathrm{CH_3CH_2\underset{\underset{O}{\|}}{C}CH_3}} \xrightarrow[H_2O]{NaBH_4} \underset{\textbf{2-Butanol (87\%)}}{\mathrm{CH_3CH_2\underset{\underset{OH}{|}}{C}HCH_3}}$$

- ➔ **The key step in the reduction is reaction of hydride with the carbonyl carbon**



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



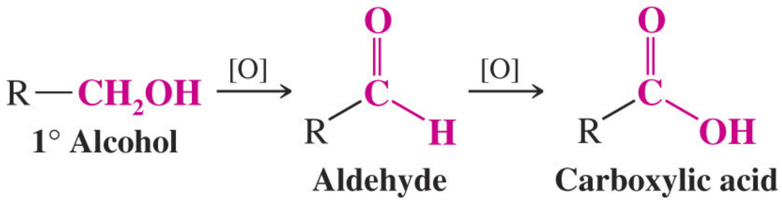
- ➔ **Lithium aluminium hydride is very reactive with water and must be used in an anhydrous solvent such as ether**
  - **Sodium borohydride is considerably less reactive and can be used in solvents such as water or an alcohol**

♦ Oxidation of Alcohols

● Oxidation of Primary Alcohols to Aldehydes

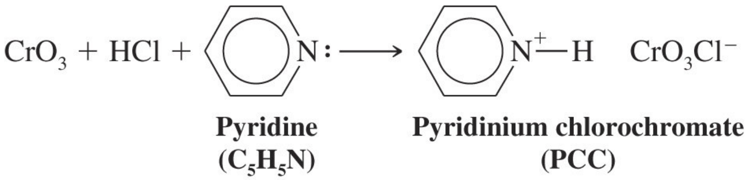
➔ **A primary alcohol can be oxidized to an aldehyde or a carboxylic acid**

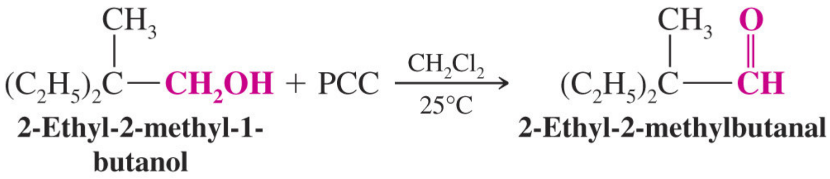
- **The oxidation is difficult to stop at the aldehyde stage and usually proceeds to the carboxylic acid**



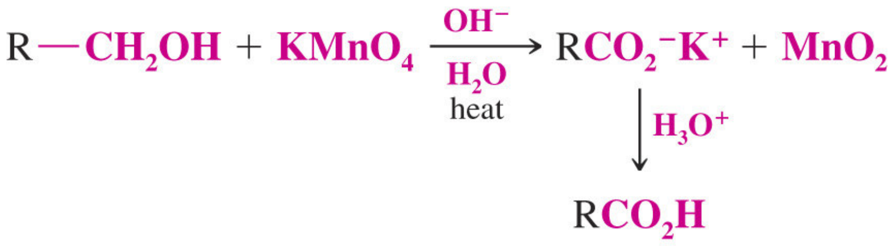
➔ **A reagent which stops the oxidation at the aldehyde stage is pyridinium chlorochromate (PCC)**

- **PCC is made from chromium trioxide under acidic conditions**
- **It is used in organic solvents such as methylene chloride (CH_2Cl_2)**





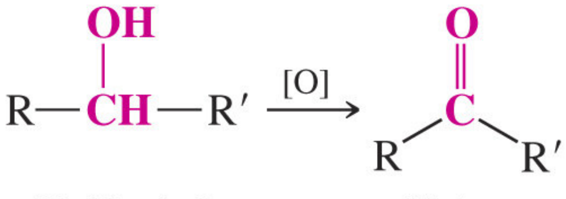
- **Oxidation of Primary Alcohols to Carboxylic Acids**
  - ➔ Potassium permanganate ($KMnO_4$) is a typical reagent used for oxidation of a primary alcohol to a carboxylic acid
    - The reaction is generally carried out in aqueous solution; a brown precipitate of MnO_2 indicates that oxidation has taken place



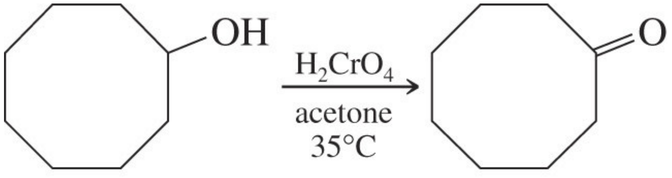
$$R{-}CH_2OH + KMnO_4 \xrightarrow[\substack{H_2O\\ \text{heat}}]{OH^-} RCO_2^-K^+ + MnO_2$$

$$RCO_2^-K^+ \xrightarrow{H_3O^+} RCO_2H$$

- **Oxidation of Secondary Alcohols to Ketones**
  - ➔ Oxidation of a secondary alcohol stops at the ketone
    - Many oxidizing agents can be used, including chromic acid (H_2CrO_4) and Jones reagent (CrO_3 in acetone)



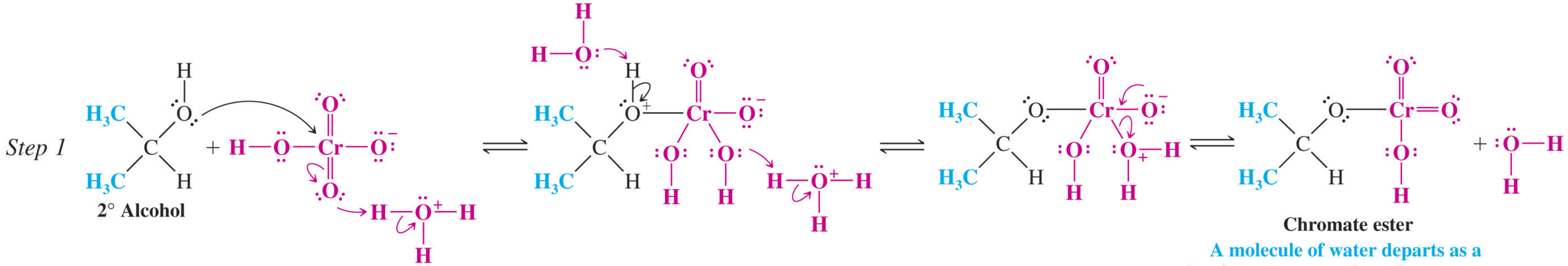
2° Alcohol Ketone



Cyclooctanol

Cyclooctanone (92–96%)

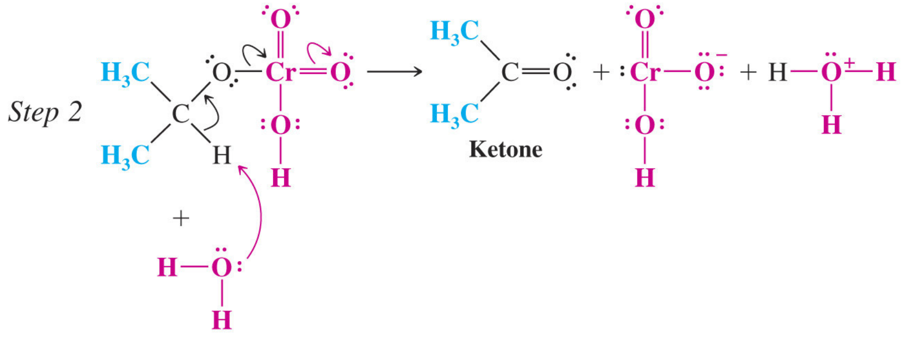
- **Mechanism of Chromate Oxidation**
  - ➔Step 1: A chromate ester is formed from the alcohol hydroxyl
  - ➔Step 2: An elimination reaction occurs by removal of a hydrogen atom from the alcohol carbon and departure of the chromium group with a pair of electrons.



The alcohol donates an electron pair to the chromium atom, as an oxygen accepts a proton.

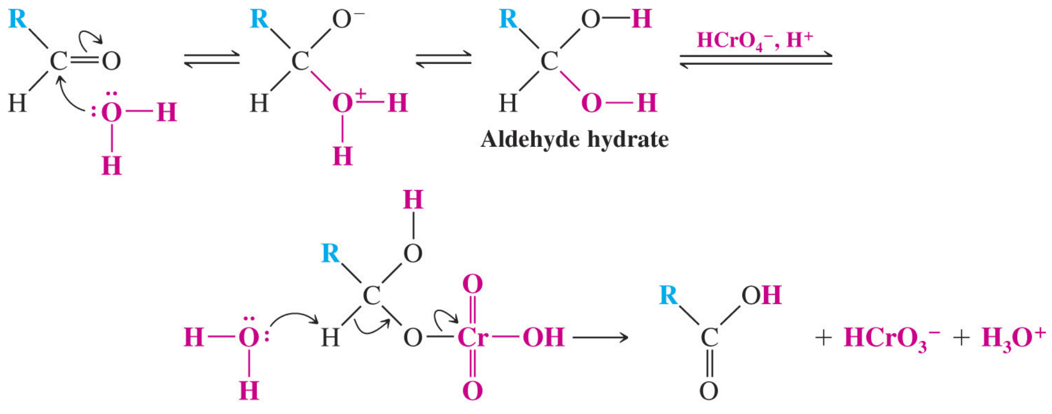
One oxygen loses a proton; another oxygen accepts a proton.

A molecule of water departs as a leaving group as a chromium–oxygen double bond forms.



The chromium atom departs with a pair of electrons that formerly belonged to the alcohol; the alcohol is thereby oxidized and the chromium reduced.

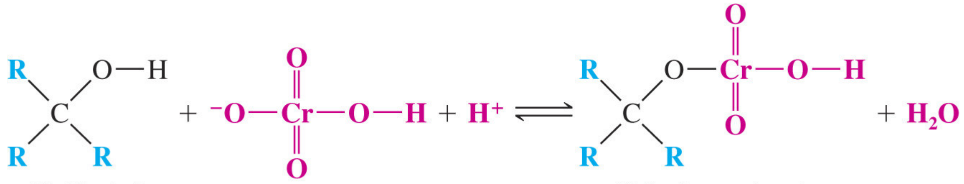
- ➔ **Aldehydes form hydrates in water**
  - An aldehyde hydrate can react to form a chromate ester which can subsequently undergo elimination to produce a carboxylic acid



Aldehyde hydrate

Carboxylic acid

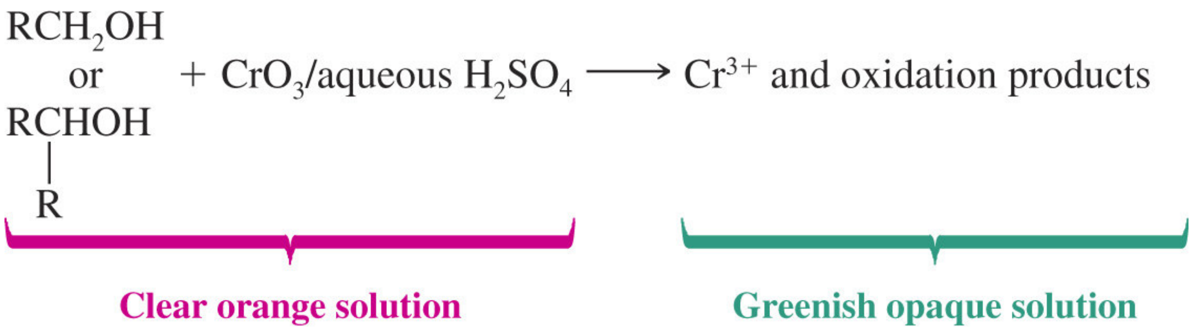
- ➔ **Pyridinium chlorochromate reactions are run in anhydrous methylene chloride and the aldehyde cannot form a hydrate**
  - The oxidation of a primary alcohol therefore stops at the aldehyde stage
- ➔ **Tertiary alcohols can form the chromate ester but cannot eliminate because they have no hydrogen on the alcohol carbon**
  - Tertiary alcohols are therefore not oxidized by chromium based reagents



3° Alcohol

This chromate ester cannot undergo elimination of H_2CrO_3.

- **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**

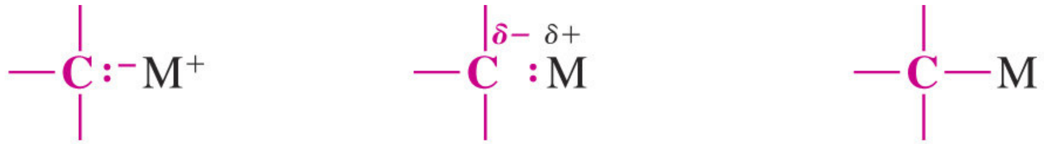


$$\underbrace{\begin{array}{c} RCH_2OH \\ \text{or} \\ R\underset{\substack{|\\R}}{C}HOH \end{array} + CrO_3/\text{aqueous } H_2SO_4}_{\text{Clear orange solution}} \longrightarrow \underbrace{Cr^{3+} \text{ and oxidation products}}_{\text{Greenish opaque solution}}$$

- **Spectroscopic Evidence for Alcohols**
  - ➔ **Alcohol O-H infrared stretching absorptions appear as strong, broad peaks around 3200-3600 cm^{-1}**
  - ➔ **Alcohol ^{1}H NMR signals for hydroxyl protons are often broad; the signal disappears on treatment with D_2O**
    - **The protons on the hydroxyl carbon appear at δ 3.3 to 4.0**
  - ➔ **Alcohol ^{13}C NMR signals for the hydroxyl carbon appear between δ 50 and δ 90**

♦ Organometallic Compounds

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



Primarily ionic
(M = Na^+ or K^+)

(M = Mg or Li)

Primarily covalent
(M = Pb, Sn, Hg, or Tl)

- ➔ 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 Organomagnesium Compounds

● Organolithium Compounds

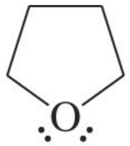
➔ Organolithium compounds can be prepared by reaction of an alkyl halide with lithium metal in an ether solvent

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

$$\underset{\text{(or Ar—X)}}{R\text{—}X} + 2\,Li \xrightarrow{Et_2O} \underset{\text{(or ArLi)}}{RLi} + LiX$$

$$CH_3CH_2\ddot{\underset{..}{O}}CH_2CH_3$$

Diethyl ether
(Et_2O)

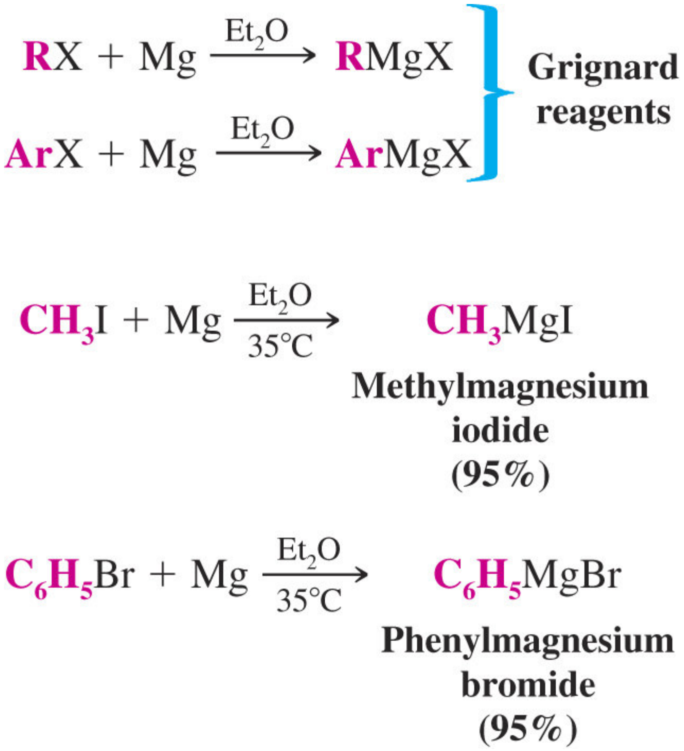


Tetrahydrofuran
(THF)

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**



$$RX + Mg \xrightarrow{Et_2O} RMgX$$

$$ArX + Mg \xrightarrow{Et_2O} ArMgX$$

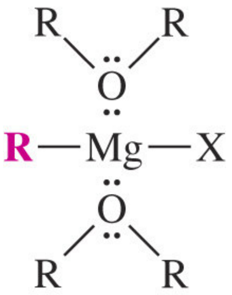
Grignard reagents

$$CH_3I + Mg \xrightarrow[35°C]{Et_2O} CH_3MgI$$

Methylmagnesium iodide (95%)

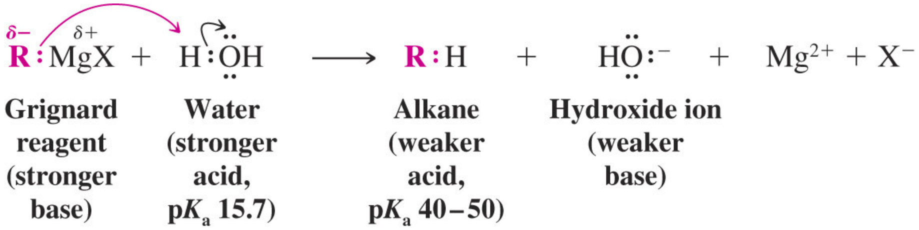
$$C_6H_5Br + Mg \xrightarrow[35°C]{Et_2O} C_6H_5MgBr$$

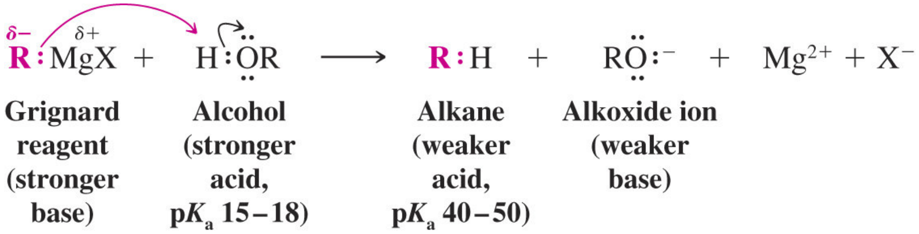
Phenylmagnesium bromide (95%)



♦ Reactions of Organolithium and Organomagnesium Compounds

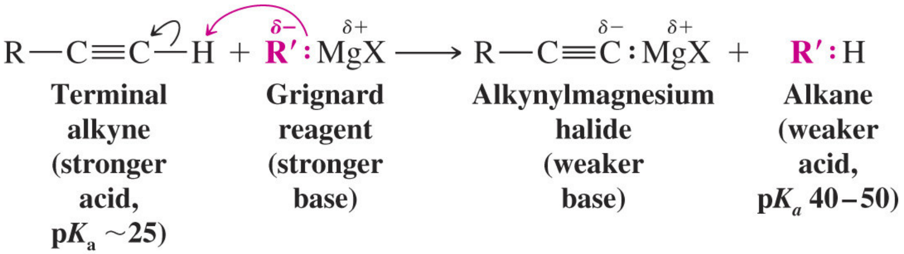
- **Reactions with Compounds Containing Acidic Hydrogen Atoms**
  - ➔ **Organolithium and Grignard reagents behave as if they were carbanions and they are therefore very strong bases**
    - **They react readily with hydrogen atoms attached to oxygen, nitrogen or sulfur, in addition to other acidic hydrogens (water and alcohol solvents cannot be used)**

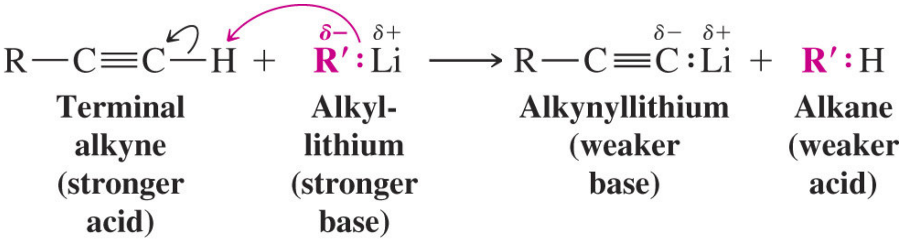




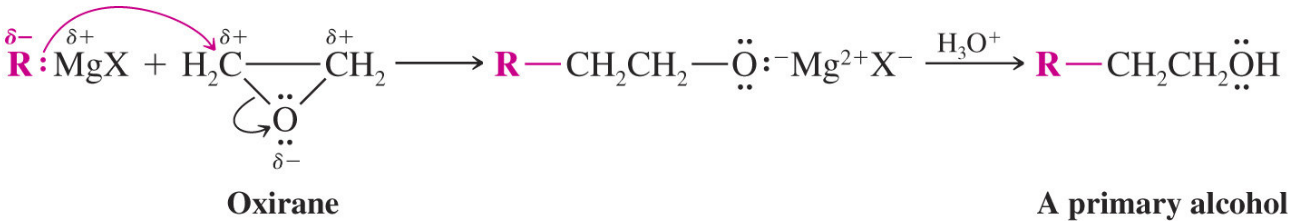
➔ Organolithium and Grignard reagents can be used to form alkynides by acid-base reactions

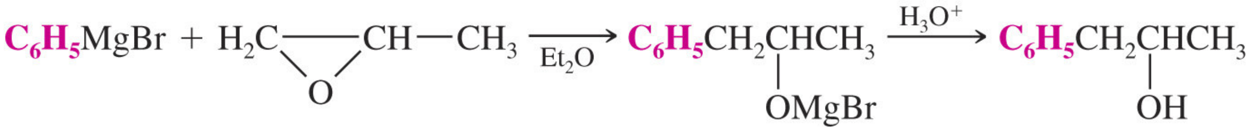
- **Alkynylmagnesium halides and alkynyllithium reagents are useful nucleophiles for C-C bond synthesis**



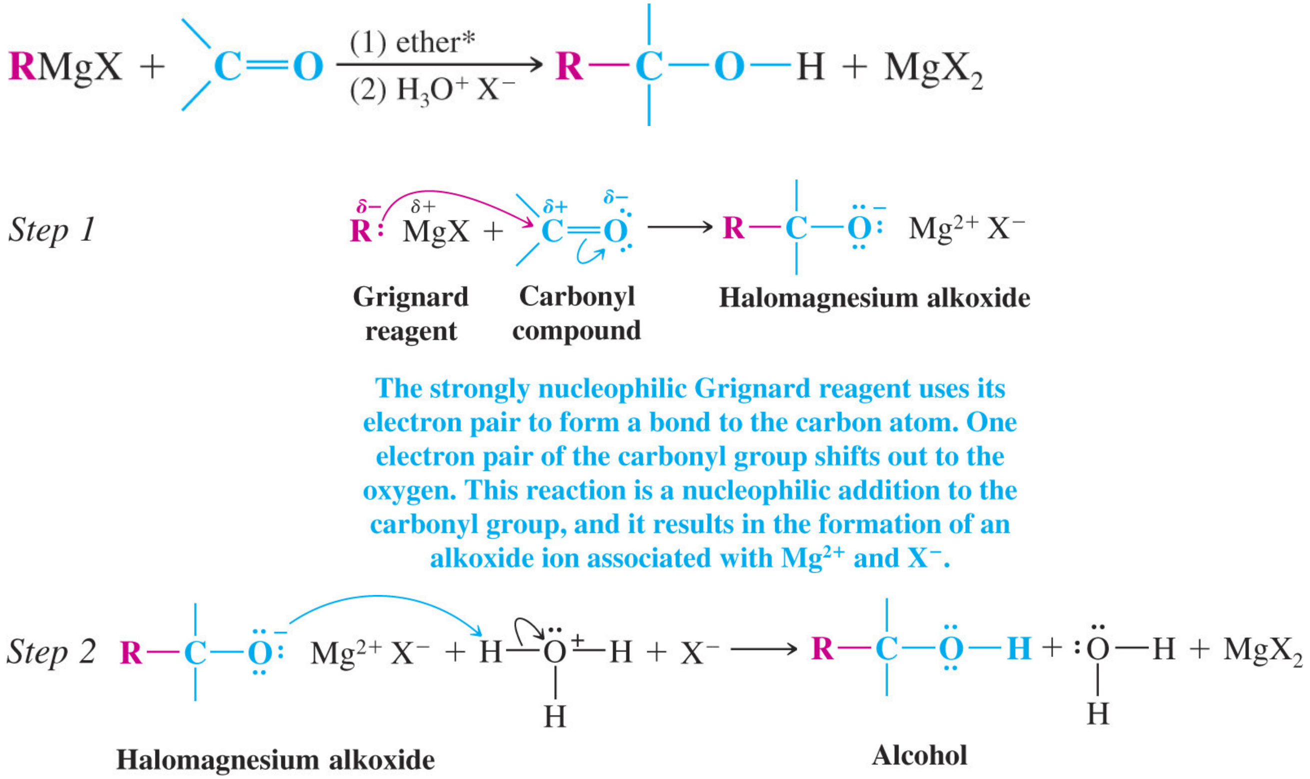


- **Reactions of Grignard Reagents with Oxiranes (Epoxides)**
  - ➔ **Grignard reagents are very powerful nucleophiles and can react with the δ+ carbons of oxiranes**
    - **The reaction results in ring opening and formation of an alcohol product**
    - **Reaction occurs at the least-substituted ring 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**

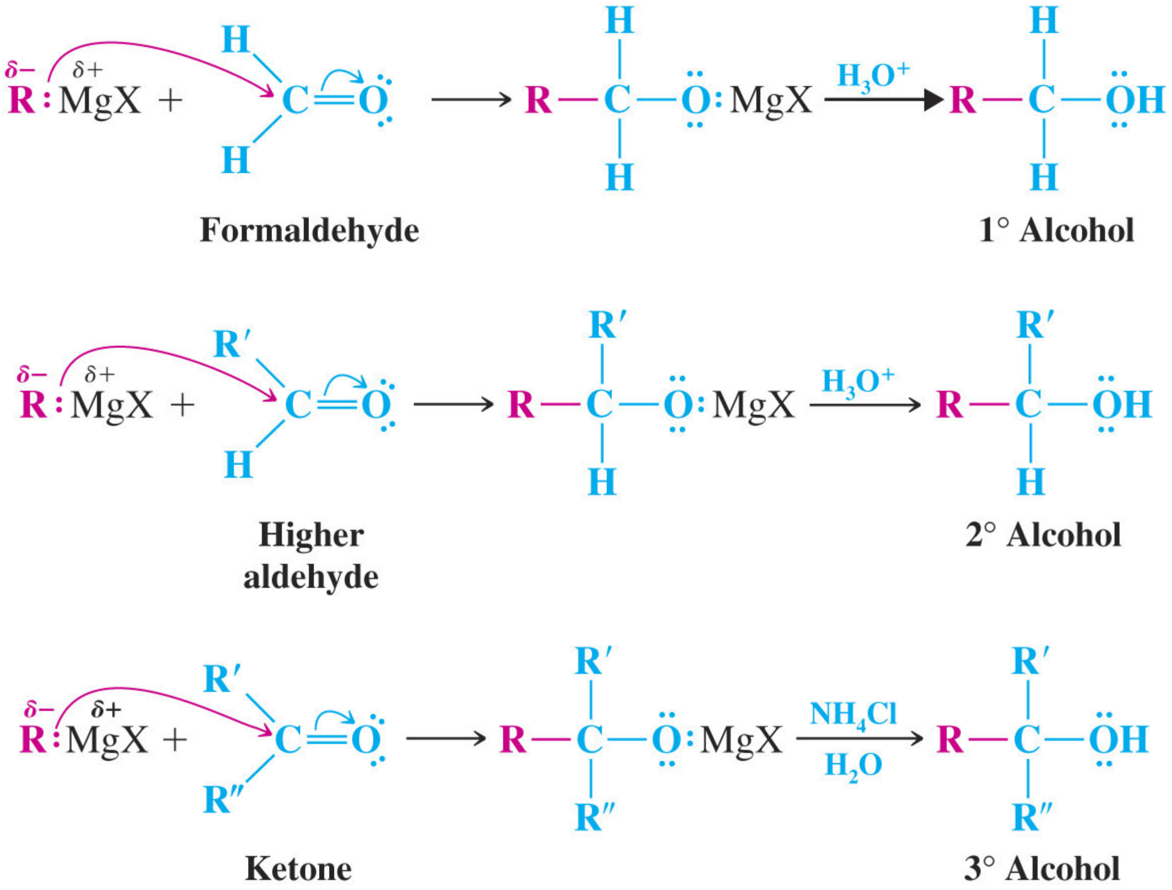


The strongly nucleophilic Grignard reagent uses its electron pair to form a bond to the carbon atom. One electron pair of the carbonyl group shifts out to the oxygen. This reaction is a nucleophilic addition to the carbonyl group, and it results in the formation of an alkoxide ion associated with Mg^{2+} and 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 MgX_2.

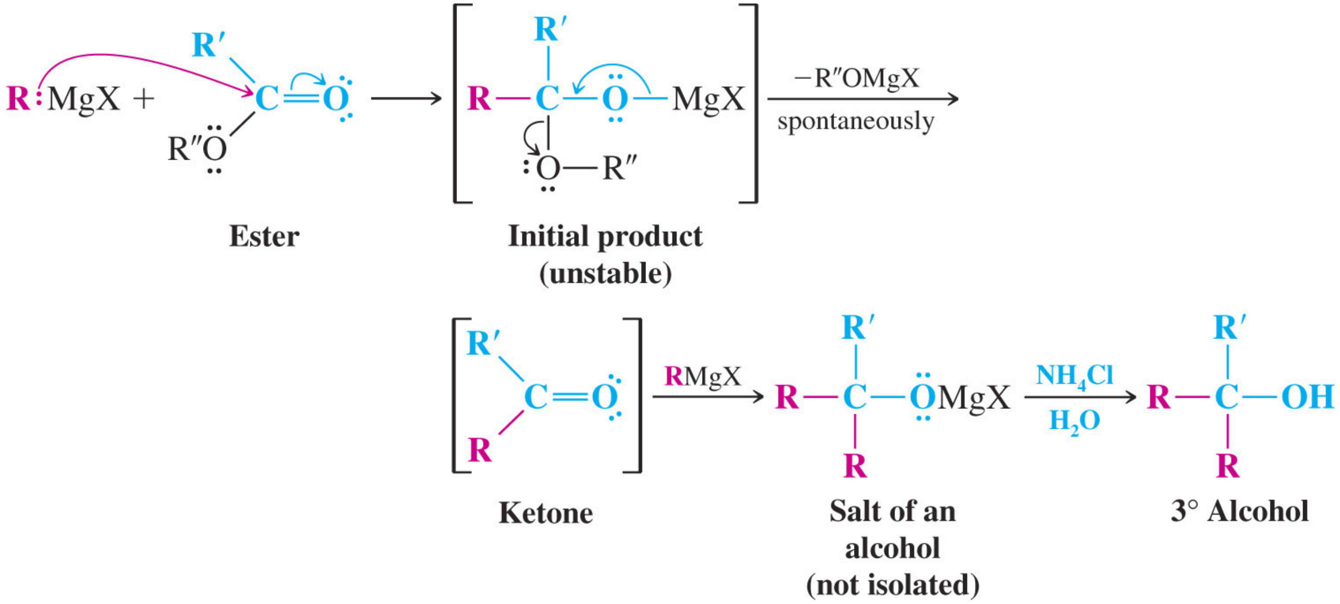
♦ Alcohols from Grignard Reagents

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



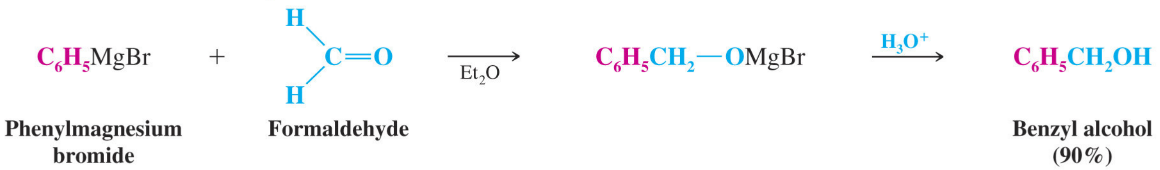
➔ **Esters react with two molar equivalents of a Grignard reagent to yield a tertiary alcohol**

- **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**



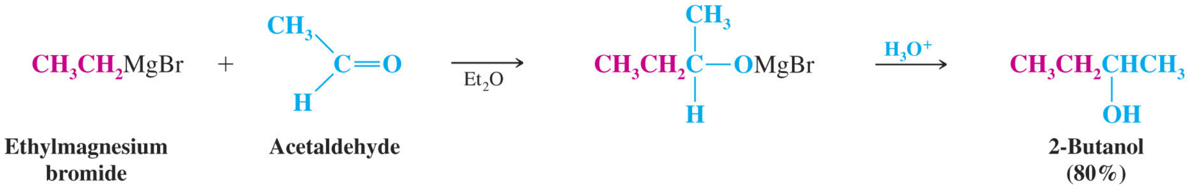
Grignard Reagent | Carbonyl Reactant | Final Product

Reaction with Formaldehyde



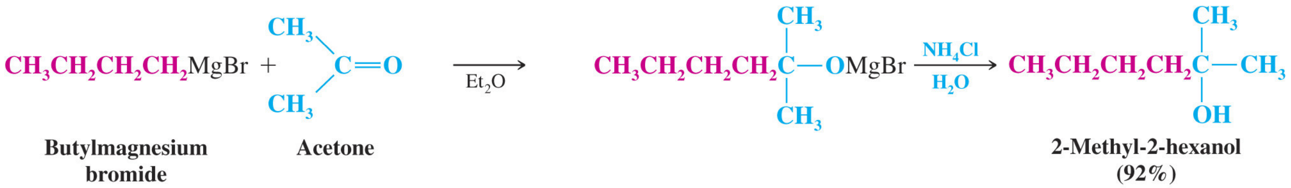
$$C_6H_5MgBr + H_2C{=}O \xrightarrow{Et_2O} C_6H_5CH_2{-}OMgBr \xrightarrow{H_3O^+} C_6H_5CH_2OH$$

Reaction with a Higher Aldehyde



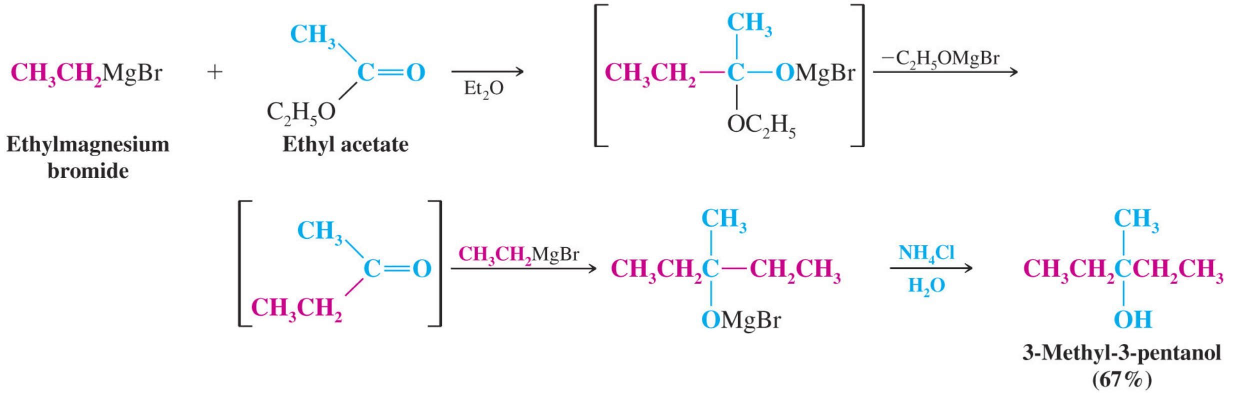
$$CH_3CH_2MgBr + CH_3CH{=}O \xrightarrow{Et_2O} CH_3CH_2C(CH_3)(H){-}OMgBr \xrightarrow{H_3O^+} CH_3CH_2CH(OH)CH_3$$

Reaction with a Ketone



$$CH_3CH_2CH_2CH_2MgBr + (CH_3)_2C{=}O \xrightarrow{Et_2O} CH_3CH_2CH_2CH_2C(CH_3)_2{-}OMgBr \xrightarrow[H_2O]{NH_4Cl} CH_3CH_2CH_2CH_2C(CH_3)_2{-}OH$$

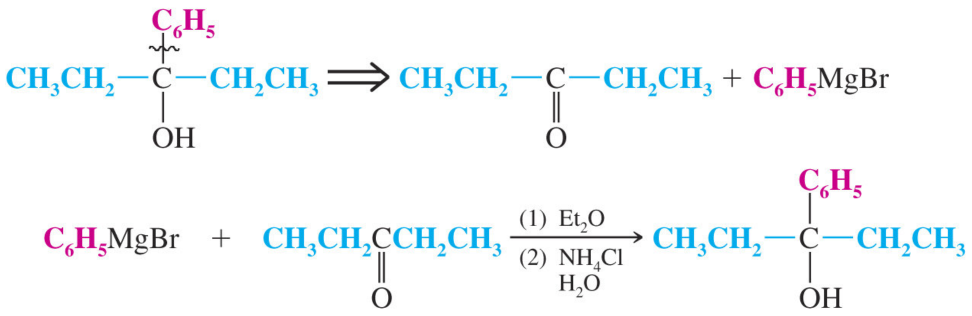
Reaction with an Ester



$$CH_3CH_2MgBr + CH_3C(=O)OC_2H_5 \xrightarrow{Et_2O} \left[CH_3CH_2{-}C(CH_3)(OC_2H_5){-}OMgBr\right] \xrightarrow{-C_2H_5OMgBr}$$

$$\left[(CH_3)(CH_3CH_2)C{=}O\right] \xrightarrow{CH_3CH_2MgBr} CH_3CH_2C(CH_3)(OMgBr){-}CH_2CH_3 \xrightarrow[H_2O]{NH_4Cl} CH_3CH_2C(CH_3)(OH)CH_2CH_3$$

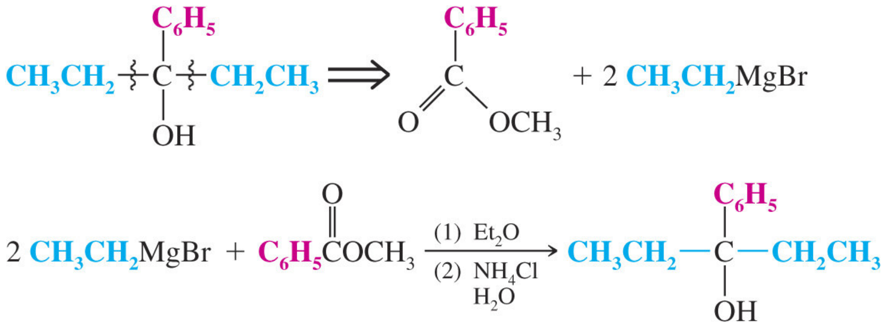
- **Planning a Grignard Synthesis**
  - ➔ **Example : Synthesis of 3-phenyl-3-pentanol**
    - **The starting material may be a ketone or an ester**
    - **There are two routes that start with ketones (one is shown)**



$$CH_3CH_2C(C_6H_5)(OH)CH_2CH_3 \Longrightarrow CH_3CH_2C(=O)CH_2CH_3 + C_6H_5MgBr$$

$$C_6H_5MgBr + CH_3CH_2C(=O)CH_2CH_3 \xrightarrow[\text{(2) } NH_4Cl,\ H_2O]{\text{(1) } Et_2O} CH_3CH_2C(C_6H_5)(OH)CH_2CH_3$$

Phenylmagnesium bromide **3-Pentanone** **3-Phenyl-3-pentanol**

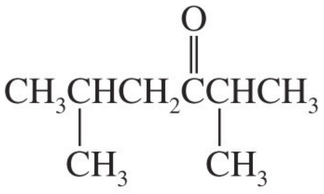


$$CH_3CH_2C(C_6H_5)(OH)CH_2CH_3 \Longrightarrow C_6H_5C(=O)OCH_3 + 2\ CH_3CH_2MgBr$$

$$2\ CH_3CH_2MgBr + C_6H_5COCH_3 \xrightarrow[\text{(2) } NH_4Cl,\ H_2O]{\text{(1) } Et_2O} CH_3CH_2C(C_6H_5)(OH)CH_2CH_3$$

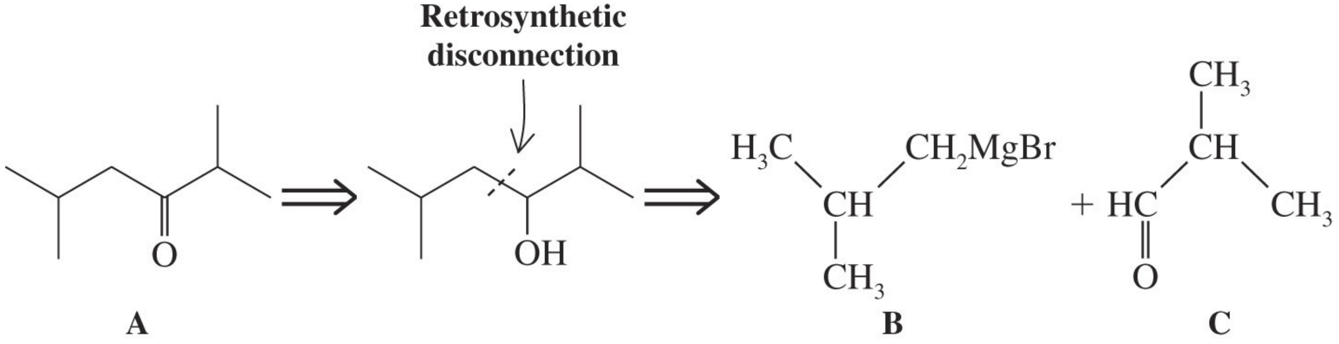
Ethylmagnesium bromide **Methyl benzoate** **3-Phenyl-3-pentanol**

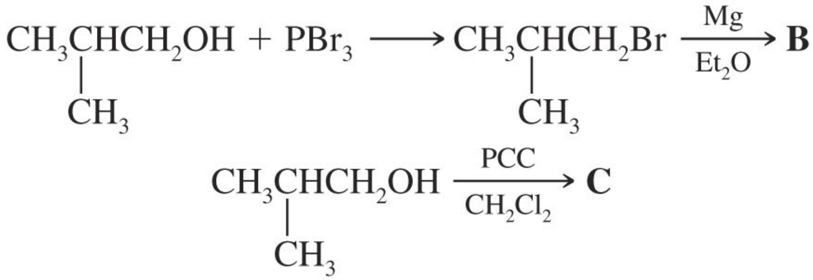
➔**Solved Problem: Synthesize the following compound using an alcohol of not more than 4 carbons as the only organic starting material**



$$\mathrm{CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2\overset{\displaystyle O}{\overset{\|}{C}}\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3}$$

A



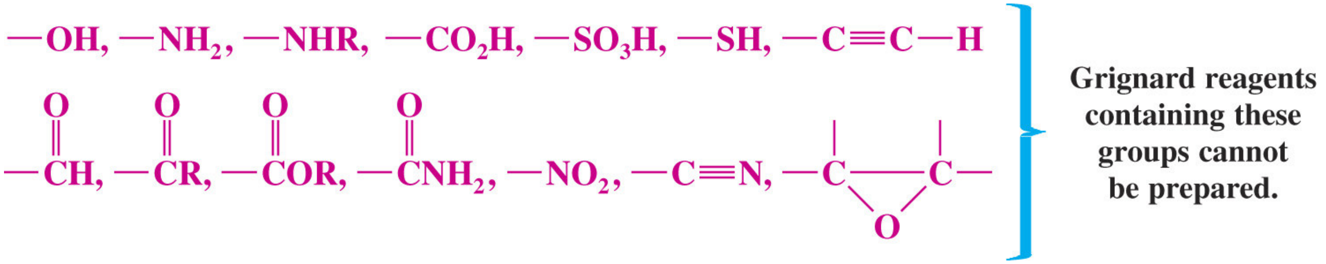


$$\mathrm{CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH + PBr_3 \longrightarrow CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2Br \xrightarrow[Et_2O]{Mg} \mathbf{B}}$$

$$\mathrm{CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2OH \xrightarrow[CH_2Cl_2]{PCC} \mathbf{C}}$$

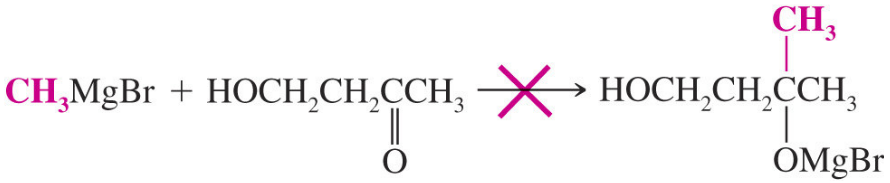
Restrictions on the Use of Grignard Reagents

- ➔ 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



Grignard reagents containing these groups cannot be prepared.

- ➔ 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

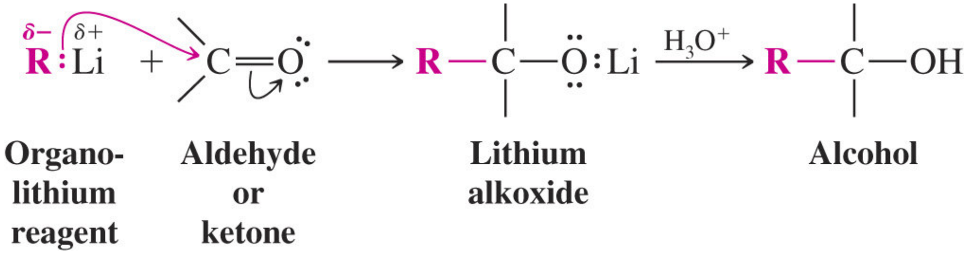


$$\mathrm{CH_3MgBr + HOCH_2CH_2\underset{\overset{\|}{O}}{C}CH_3 \xrightarrow{\times} HOCH_2CH_2\overset{CH_3}{\underset{OMgBr}{C}}CH_3}$$

$$\mathrm{HOCH_2CH_2\underset{\overset{\|}{O}}{C}CH_3 \xrightarrow[-CH_4]{2\ CH_3MgBr} BrMgOCH_2CH_2\overset{CH_3}{\underset{OMgBr}{C}}CH_3 \xrightarrow[H_2O]{2\ NH_4Cl} HOCH_2CH_2\overset{CH_3}{\underset{OH}{C}}CH_3}$$

The Use of Lithium Reagents

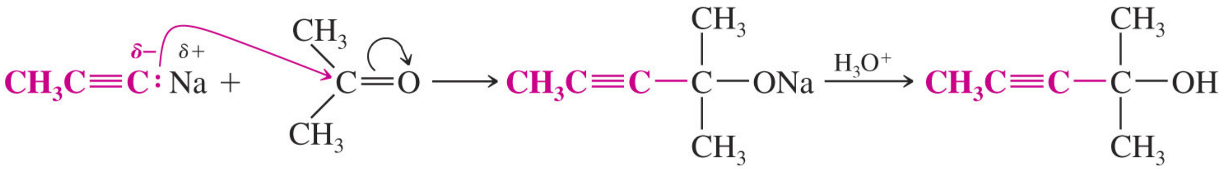
- ➔ **Organolithium reagents react similarly to Grignard reagents**
  - **Organolithium reagents tend to be more reactive**



The Use of Sodium Alkynides

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

$$CH_3C\equiv CH \xrightarrow[-NH_3]{NaNH_2} CH_3C\equiv CNa$$

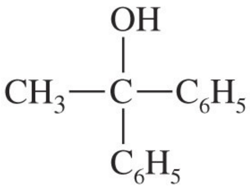


$$CH_3C\equiv C{:}Na + (CH_3)_2C{=}O \longrightarrow CH_3C\equiv C{-}C(CH_3)_2{-}ONa \xrightarrow{H_3O^+} CH_3C\equiv C{-}C(CH_3)_2{-}OH$$

- **Solved Problem**
  - ➔ **Synthesize the following compounds using reagents of 6 carbons or less**

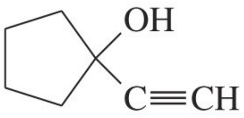
(a)

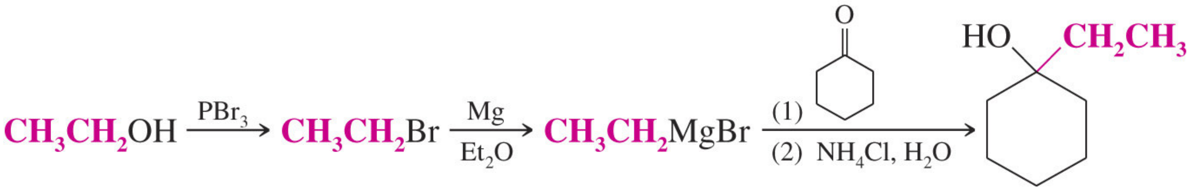
(b)

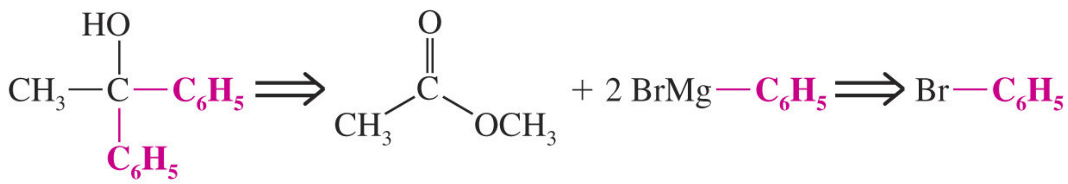


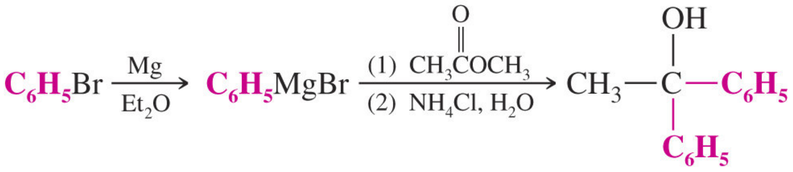
$$CH_3-\overset{\displaystyle OH}{\underset{\displaystyle C_6H_5}{C}}-C_6H_5$$

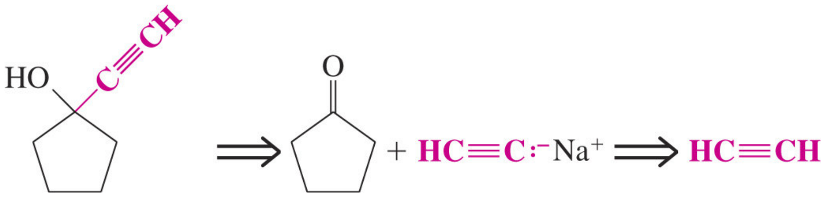
(c)

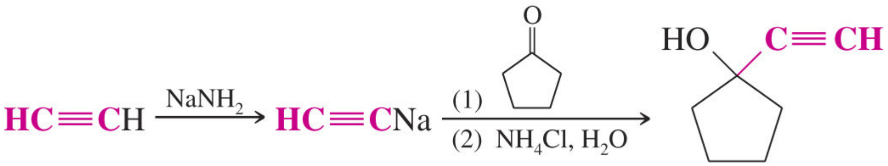










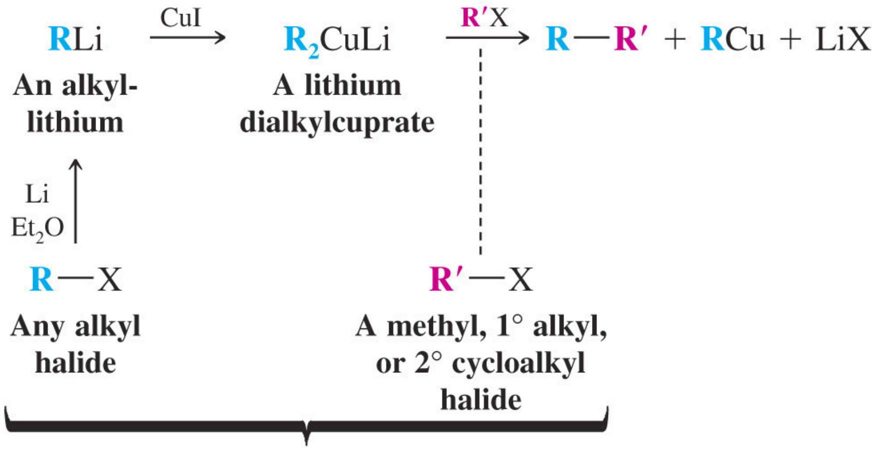


♦ Lithium Dialkylcuprates: The Corey-Posner, Whitesides-House Synthesis

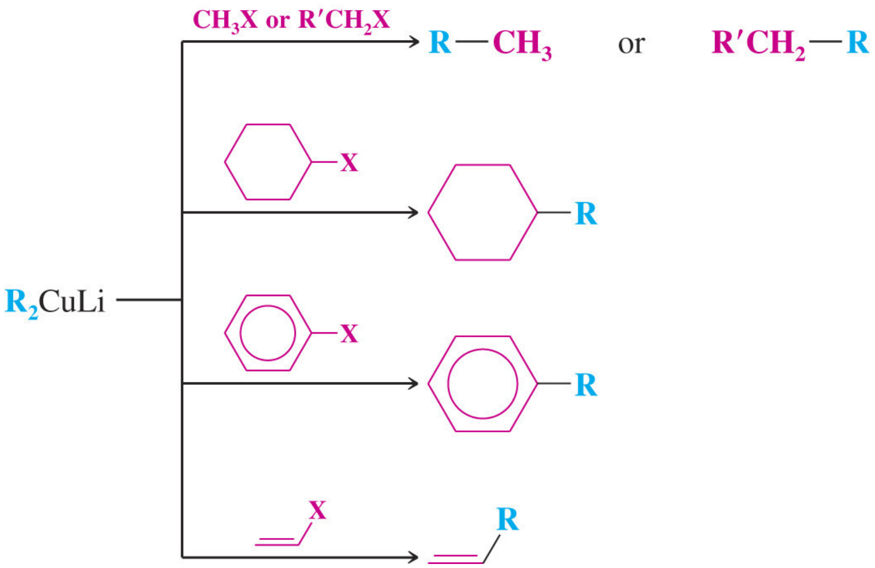
- ➔ This is an alternative formation of carbon-carbon bonds which, in effect, couples two alkyl halides

$$R{-}X + R'{-}X \xrightarrow[\text{steps}\ (-2\,X)]{\text{several}} R{-}R'$$

- ➔ 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

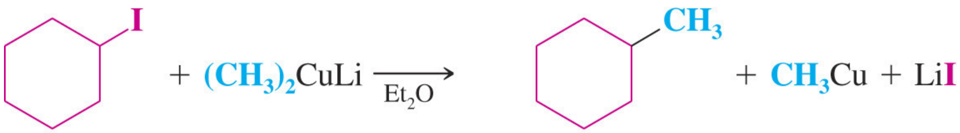


These are the organic starting materials. The R— and R′— groups need not be different.



$$\mathrm{CH_3I \xrightarrow[Et_2O]{Li} CH_3Li \xrightarrow{CuI} (CH_3)_2CuLi \xrightarrow{CH_3CH_2CH_2CH_2CH_2I} CH_3{-}CH_2CH_2CH_2CH_2CH_3}$$

Hexane
(98%)



Methylcyclohexane
(75%)