Organic Chemistry, *Fourth Edition*

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Chapter 20
Lecture Outline

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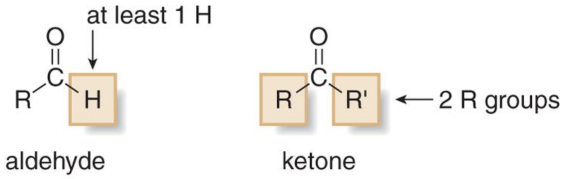
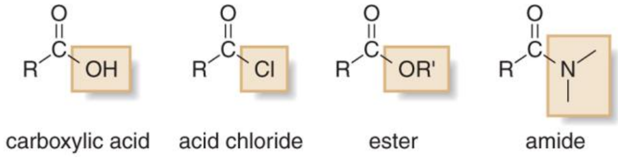
Compounds Containing Carbonyl Groups

Two broad classes of compounds contain the carbonyl group:

[1] Compounds that have only carbon and hydrogen atoms bonded to the carbonyl.

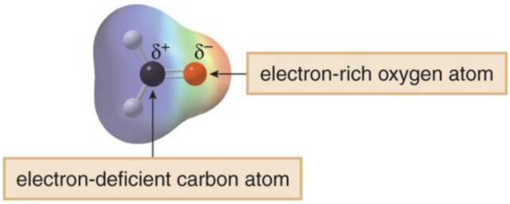


[2] Compounds that contain an electronegative atom bonded to the carbonyl.



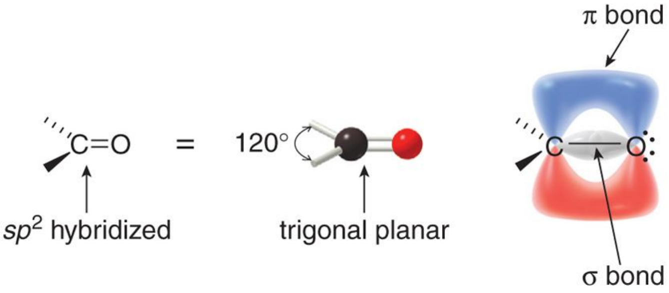
Electrostatic Potential Map of a Carbonyl Group

- An electrostatic potential map shows the electron-deficient carbon and the electron rich oxygen atom of the carbonyl group.



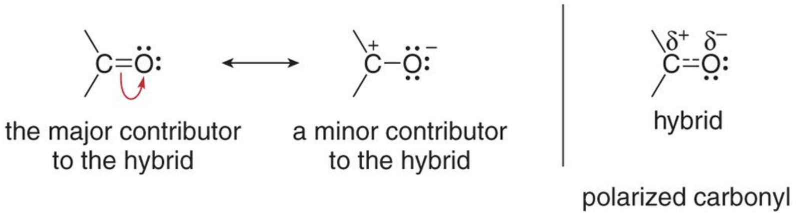
Carbonyl Group Structure

- The presence or absence of a leaving group on the carbonyl determines the type of reactions the carbonyl compound will undergo.
- Carbonyl carbons are sp^2 hybridized, trigonal planar, and have bond angles that are ~120º.
- In these ways, the carbonyl group resembles the trigonal planar sp^2 hybridized carbons of a C=C.

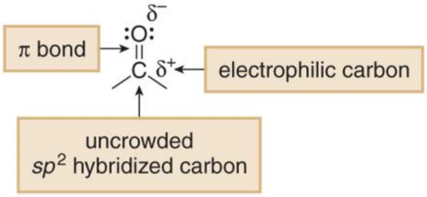


Polarity of Carbonyl Groups

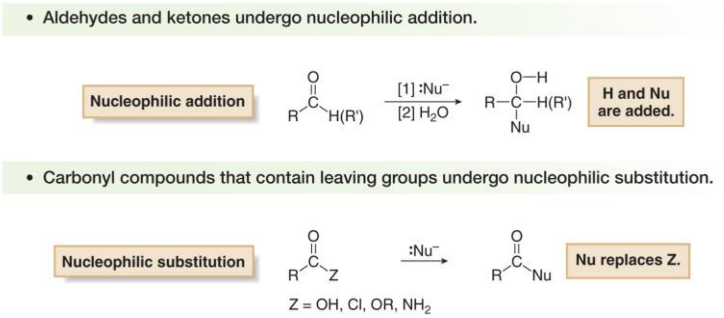
- **In one important way, the C=O and C=C are very different.**
- **The electronegative oxygen atom in the carbonyl group means that the bond is polarized, making the carbonyl carbon electron deficient.**
- **Using a resonance description, the carbonyl group is represented by two resonance structures.**



General Reactions of Carbonyl Compounds



- **Carbonyl carbons are electrophilic and react with nucleophiles.**



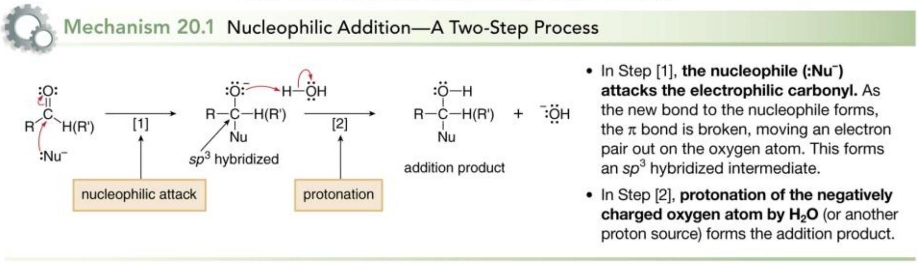
- Aldehydes and ketones undergo nucleophilic addition.

- Carbonyl compounds that contain leaving groups undergo nucleophilic substitution.

$Z = OH, Cl, OR, NH_2$

Nucleophilic Addition

- **Aldehydes and ketones react with nucleophiles to form addition products by a two-step process: nucleophilic attack followed by protonation.**
- **This mechanism is called nucleophilic addition.**

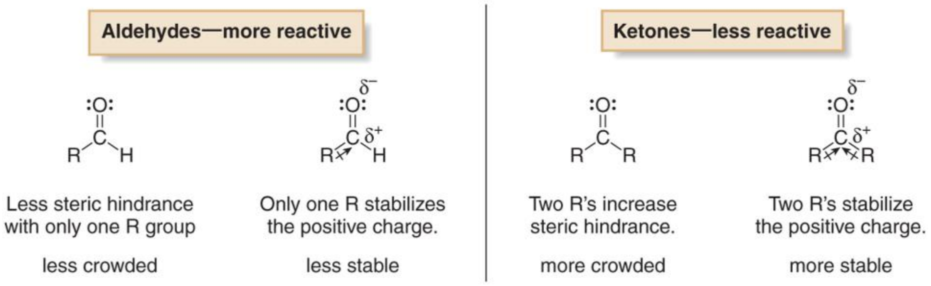


Mechanism 20.1 Nucleophilic Addition—A Two-Step Process

- In Step [1], **the nucleophile (:Nu⁻) attacks the electrophilic carbonyl.** As the new bond to the nucleophile forms, the π bond is broken, moving an electron pair out on the oxygen atom. This forms an sp^3 hybridized intermediate.
- In Step [2], **protonation of the negatively charged oxygen atom by H_2O** (or another proton source) forms the addition product.

Reactivity to Nucleophilic Addition

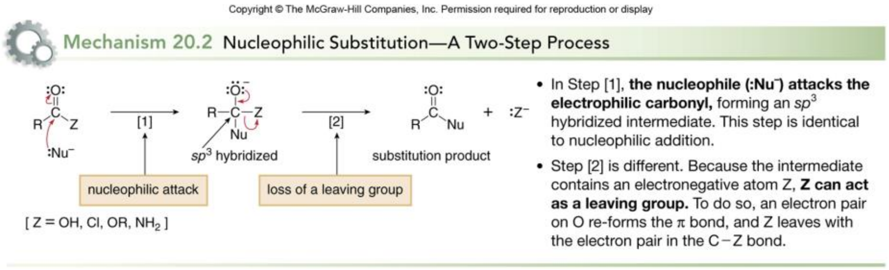
- **The net result is that the π bond is broken, two new σ bonds are formed, and the elements of H and Nu are added across the π bond.**
- **Aldehydes are more reactive than ketones towards nucleophilic attack for both steric and electronic reasons.**



Aldehydes—more reactive		Ketones—less reactive	
Less steric hindrance with only one R group	Only one R stabilizes the positive charge.	Two R's increase steric hindrance.	Two R's stabilize the positive charge.
less crowded	less stable	more crowded	more stable

Nucleophilic Substitution

- **Carbonyl compounds with leaving groups react with nucleophiles to form substitution products by a two-step process: nucleophilic attack, followed by loss of the leaving group.**



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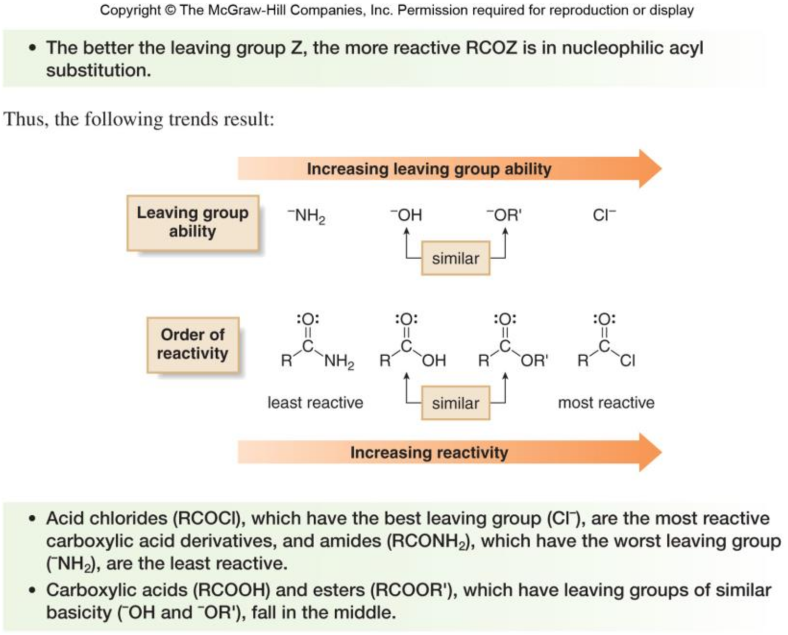
Mechanism 20.2 Nucleophilic Substitution—A Two-Step Process

- In Step [1], **the nucleophile (:Nu⁻) attacks the electrophilic carbonyl,** forming an sp^3 hybridized intermediate. This step is identical to nucleophilic addition.
- Step [2] is different. Because the intermediate contains an electronegative atom Z, **Z can act as a leaving group.** To do so, an electron pair on O re-forms the π bond, and Z leaves with the electron pair in the C−Z bond.

- **The net result is that Nu replaces Z, a nucleophilic substitution reaction.**
- **This reaction is often called nucleophilic acyl substitution.**

Reactivity to Nucleophilic Substitution



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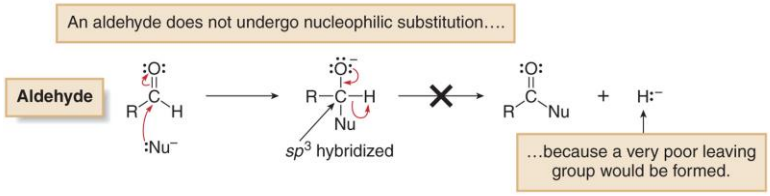
- The better the leaving group Z, the more reactive RCOZ is in nucleophilic acyl substitution.

Thus, the following trends result:

- Acid chlorides (RCOCl), which have the best leaving group (Cl⁻), are the most reactive carboxylic acid derivatives, and amides (RCONH$_2$), which have the worst leaving group (⁻NH$_2$), are the least reactive.
- Carboxylic acids (RCOOH) and esters (RCOOR'), which have leaving groups of similar basicity (⁻OH and ⁻OR'), fall in the middle.

Comparison of Carbonyl Reaction Types

- **Nucleophilic addition and nucleophilic acyl substitution involve the same first step—nucleophilic attack on the electrophilic carbonyl carbon to form a tetrahedral intermediate.**
- **The difference between the two reactions is what then happens to the intermediate.**
- **Aldehydes and ketones cannot undergo substitution because they do not have a good leaving group bonded to the newly formed *sp*^{3} hybridized carbon.**

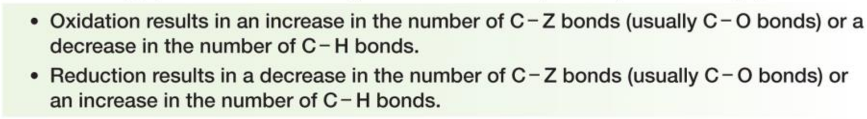

An aldehyde does not undergo nucleophilic substitution….

Aldehyde

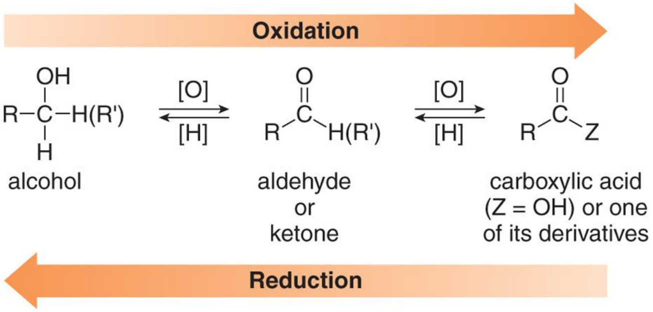
sp^3 hybridized

…because a very poor leaving group would be formed.

Preview of Oxidation and Reduction

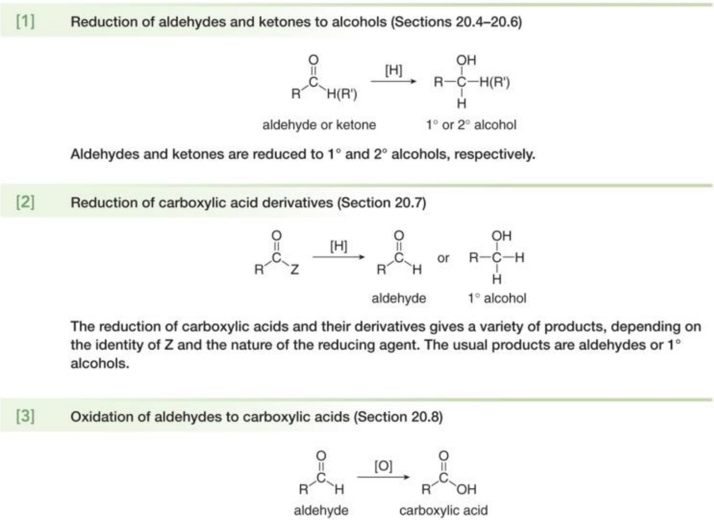

- Oxidation results in an increase in the number of C – Z bonds (usually C – O bonds) or a decrease in the number of C – H bonds.
- Reduction results in a decrease in the number of C – Z bonds (usually C – O bonds) or an increase in the number of C – H bonds.

- **Carbonyl compounds can be either reactants or products in oxidation–reduction reactions.**



Oxidation and Reduction of Carbonyl Compounds

- The three most useful oxidation and reduction reactions of carbonyl starting materials can be summarized as follows:



[1] Reduction of aldehydes and ketones to alcohols (Sections 20.4–20.6)

Aldehydes and ketones are reduced to 1° and 2° alcohols, respectively.

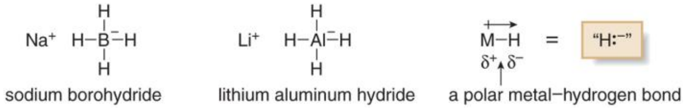
[2] Reduction of carboxylic acid derivatives (Section 20.7)

The reduction of carboxylic acids and their derivatives gives a variety of products, depending on the identity of Z and the nature of the reducing agent. The usual products are aldehydes or 1° alcohols.

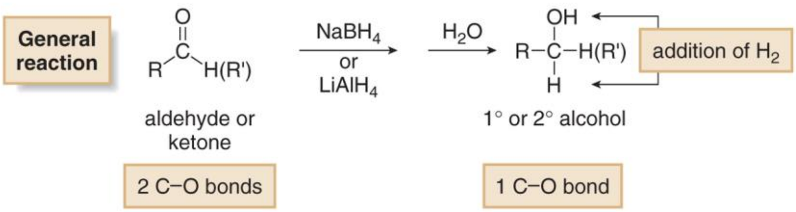
[3] Oxidation of aldehydes to carboxylic acids (Section 20.8)

Reduction of Aldehydes and Ketones

- The most useful reagents for reducing aldehydes and ketones are the **metal hydride reagents**.



- Treating an aldehyde or ketone with $NaBH_4$ or $LiAlH_4$, followed by H_2O or some other proton source affords an alcohol.



Metal Hydride Reduction of Carbonyls

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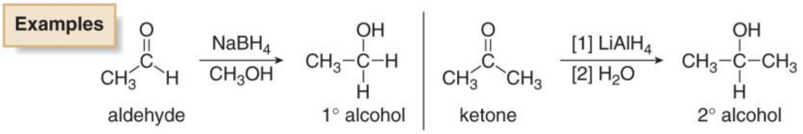

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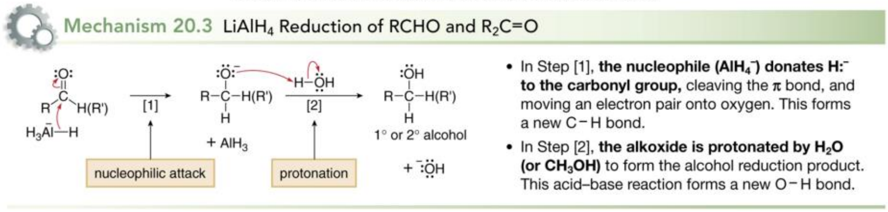

- In Step [1], **the nucleophile (AlH_4^-) donates H:⁻ to the carbonyl group,** cleaving the π bond, and moving an electron pair onto oxygen. This forms a new C–H bond.
- In Step [2], **the alkoxide is protonated by H_2O (or CH_3OH)** to form the alcohol reduction product. This acid–base reaction forms a new O–H bond.

- **The net result of adding H:⁻ (from $NaBH_4$ or $LiAlH_4$) and H^+ (from H_2O) is the addition of the elements of H_2 to the carbonyl π bond.**

Catalytic Hydrogenation of Carbonyls

- **Catalytic hydrogenation also reduces aldehydes and ketones to 1° and 2° alcohols, respectively, using H_2 and a catalyst.**

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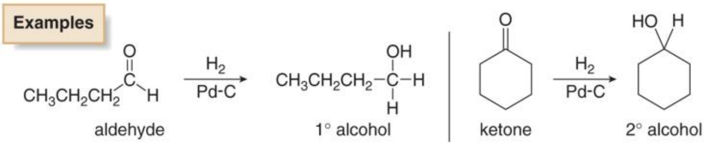
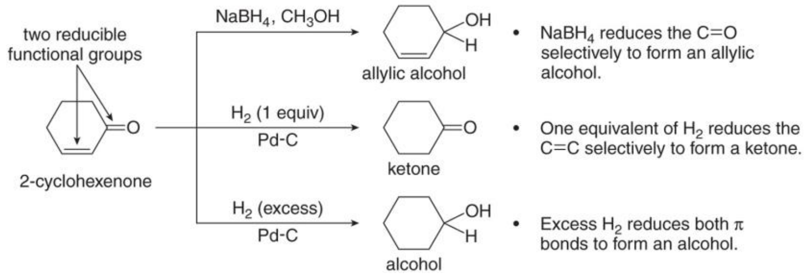


- **When a compound contains both a carbonyl group and a carbon–carbon double bond, selective reduction of one functional group can be achieved by proper choice of the reagent.**
  - **A C=C is reduced faster than a C=O with H_2 (Pd–C).**
  - **A C=O is readily reduced with $NaBH_4$ and $LiAlH_4$, but a C=C is inert.**

Comparison of Carbonyl Reductions

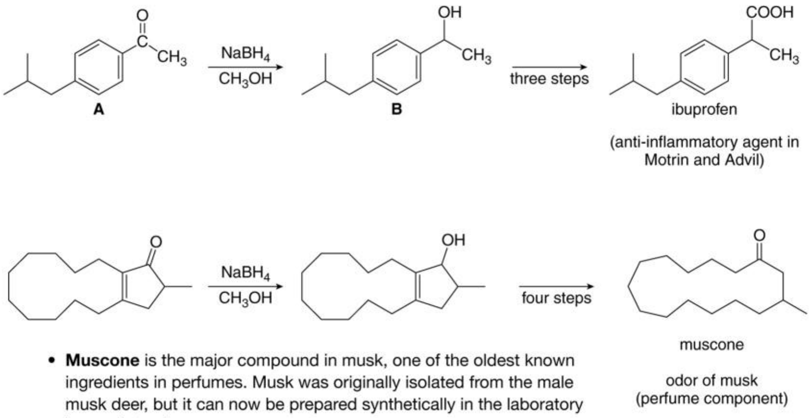
- **Thus, 2-cyclohexenone, which contains both a C=C and a C=O, can be reduced to three different compounds depending upon the reagent used.**



- NaBH$_4$ reduces the C=O selectively to form an allylic alcohol.
- One equivalent of H$_2$ reduces the C=C selectively to form a ketone.
- Excess H$_2$ reduces both π bonds to form an alcohol.

Sodium Borohydride Reductions in Synthesis

Figure 20.2



- **Muscone** is the major compound in musk, one of the oldest known ingredients in perfumes. Musk was originally isolated from the male musk deer, but it can now be prepared synthetically in the laboratory in a variety of ways.

Stereochemistry of Carbonyl Reduction

- Hydride converts a planar *sp*^{2} hybridized carbonyl carbon to a tetrahedral *sp*^{3} hybridized carbon.
- When an achiral reagent is used, a racemic product is obtained.
- Both enantiomers are formed in equal amounts.

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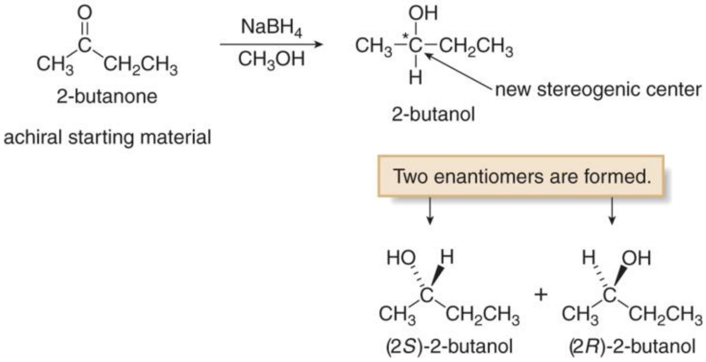

Racemic Products of Carbonyl Reduction

- Why is the product racemic?
  - Since the carbonyl is planar, the hydride can approach the double bond with equal probability from both sides.

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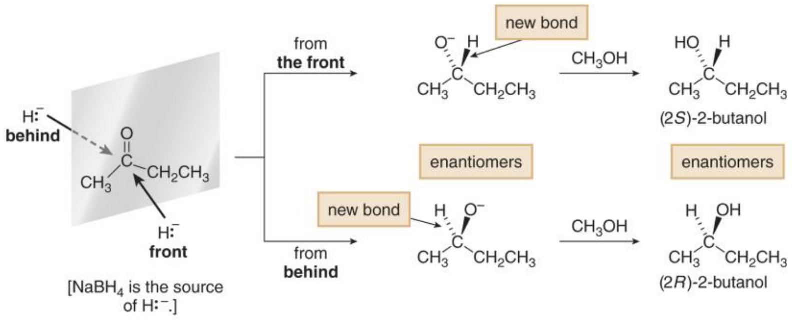


- Conclusion: Hydride reduction of an achiral ketone with $LiAlH_4$ or $NaBH_4$ gives a racemic mixture of two alcohols when a new stereogenic center is formed.

Enantioselective Carbonyl Reductions

- **Selective formation of one enantiomer over another can occur if a chiral reducing agent is used.**
- **A reduction that forms one enantiomer predominantly or exclusively is an enantioselective or asymmetric reduction.**
- **An example of chiral reducing agents are the enantiomeric CBS reagents.**

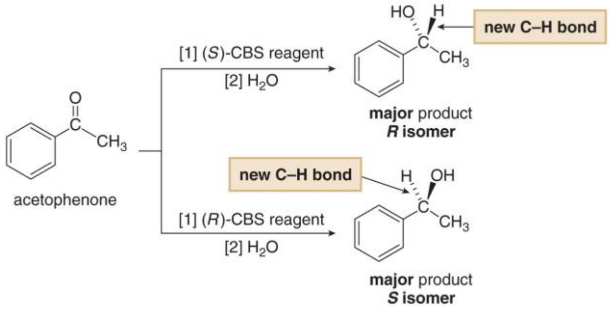
Two enantiomers of the chiral CBS reducing agent

(*S*)-2-methyl-**CBS**-oxazaborolidine | (*R*)-2-methyl-**CBS**-oxazaborolidine

(*S*)-CBS reagent | **(*R*)-CBS reagent**

CBS Reducing Agents

- **CBS refers to <u>C</u>orey, <u>B</u>akshi, and <u>S</u>hibata, the chemists who developed these versatile reagents.**
- **One B–H bond serves as the source of hydride in this reduction.**
- **The (*S*)-CBS reagent delivers (H:⁻) from the front side of the C=O. This generally affords the *R* alcohol as the major product.**
- **The (*R*)-CBS reagent delivers (H:⁻) from the back side of the C=O. This generally affords the *S* alcohol as the major product.**



Enantioselectivity of CBS Reagents

- **These reagents are highly enantioselective.**
- **For example, treatment of propiophenone with the (*S*)-CBS reagent forms the *R* alcohol in 97% enantiomeric excess (*ee*).**

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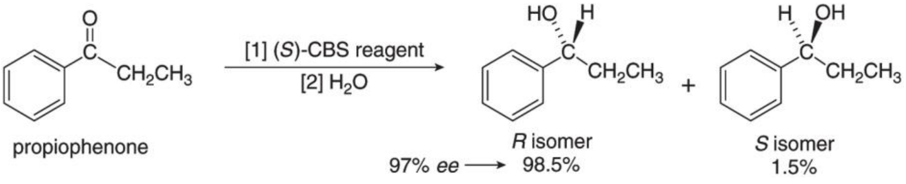

Enantioselective Reductions in Synthesis

- **Enantioselective reductions are key steps in the synthesis of several widely used drugs, including salmeterol, a long-acting bronchodilator.**

Figure 20.3

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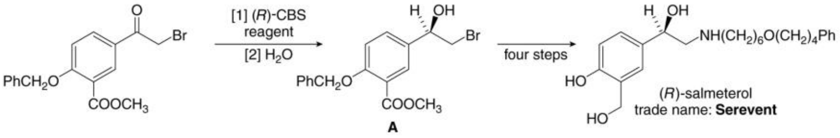
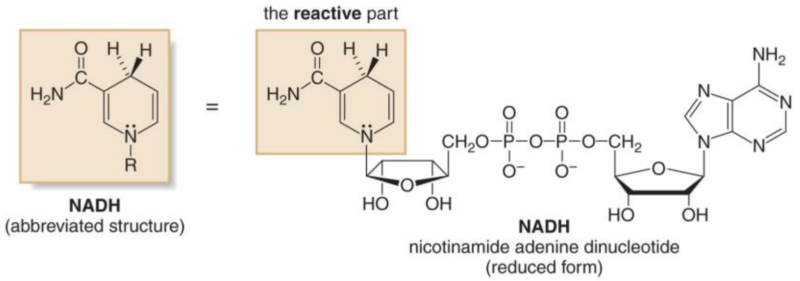


- (*R*)-Salmeterol is a long-acting bronchodilator used for the treatment of asthma.
- In this example, the (*R*)-CBS reagent adds the new H atom from behind, the same result observed with acetophenone and propiophenone. In this case, however, alcohol **A** has the *R* configuration using the rules for assigning priority in Chapter 5.

Biological Reductions

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



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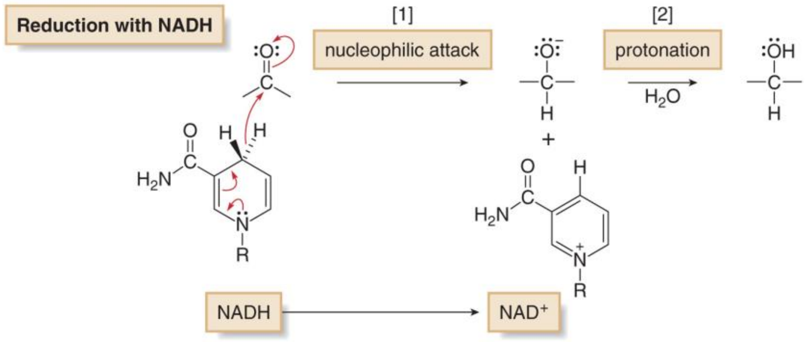
Mechanism of NADH Reductions

- **The active site of the enzyme binds both the carbonyl substrate and NADH, keeping them in close proximity.**
- **NADH then donates H:⁻ in much the same way as a hydride reducing agent.**



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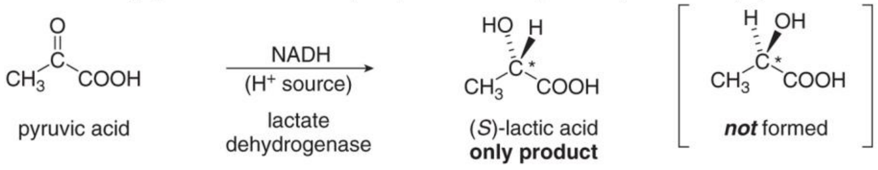
Enantioselectivity of NADH Reduction

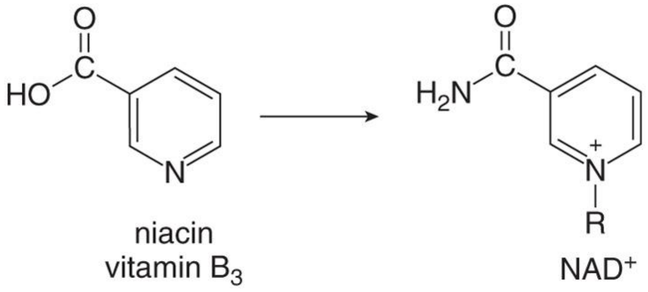
- **The reaction is completely enantioselective.**
- **For example, reduction of pyruvic acid with NADH catalyzed by lactate dehydrogenase affords a single enantiomer with the *S* configuration.**
- **NADH reduces a variety of different carbonyl compounds in biological systems.**
- **The configuration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



[* denotes a new stereogenic center]

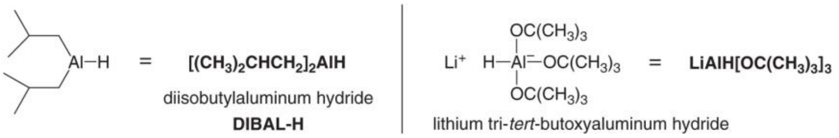
NAD⁺ —Biological Oxidizing Agent

- **NAD⁺, the oxidized form of NADH, is a biological oxidizing agent capable of oxidizing alcohols to carbonyl compounds (it forms NADH in the process).**
- **NAD⁺ is synthesized from the vitamin niacin.**



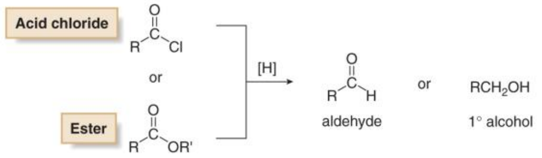
Other Metal Hydride Reducing Agents

- **$LiAlH_4$ is a strong reducing agent that reacts with all carboxylic acid derivatives.**
- **Diisobutylaluminum hydride $[(CH_3)_2CHCH_2]_2AlH$, abbreviated DIBAL-H, has two bulky isobutyl groups which makes this reagent less reactive than $LiAlH_4$.**
- **Lithium tri-*tert*-butoxyaluminum hydride, $LiAlH[OC(CH_3)_3]_3$, has three electronegative O atoms bonded to aluminum, which makes this reagent less nucleophilic than $LiAlH_4$.**

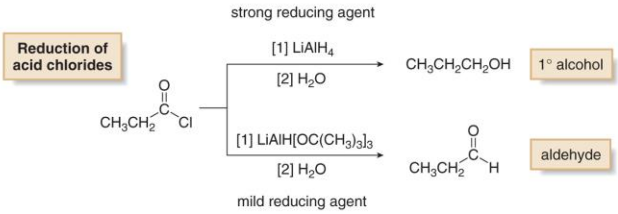


Reduction of Acid Halides and Esters

- **Acid chlorides and esters can be reduced to either aldehydes or 1° alcohols depending on the reagent.**

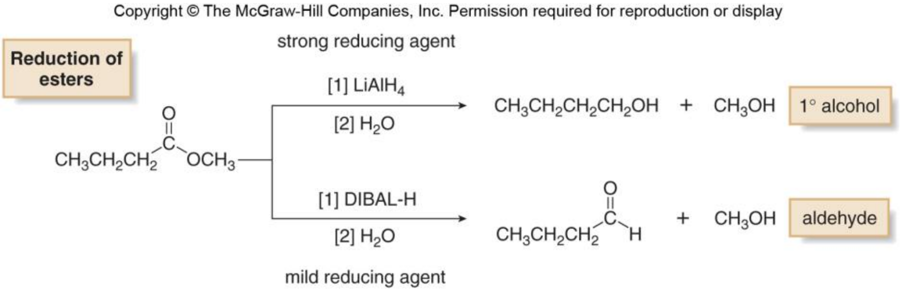


- $LiAlH_4$ converts RCOCl and RCOOR' to 1° alcohols.
- A milder reducing agent (DIBAL-H or $LiAlH[OC(CH_3)_3]_3$) converts RCOCl or RCOOR' to RCHO at low temperatures.



Reduction of Esters

- **In the reduction of an acid chloride, Cl^- comes off as the leaving group.**
- **In the reduction of the ester, CH_3O^- comes off as the leaving group, which is then protonated by H_2O to form CH_3OH.**



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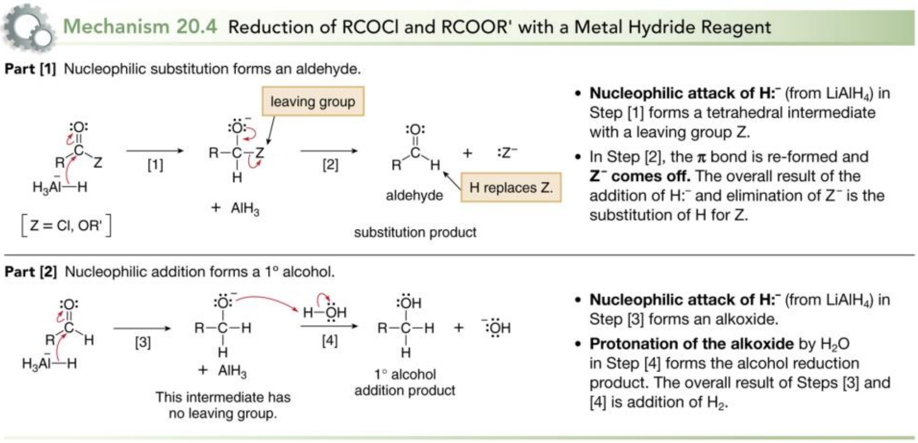
Mechanism 20.4 Reduction of RCOCl and RCOOR' with a Metal Hydride Reagent

Part [1] Nucleophilic substitution forms an aldehyde.



- **Nucleophilic attack of $H:^-$** (from $LiAlH_4$) in Step [1] forms a tetrahedral intermediate with a leaving group Z.
- In Step [2], the π bond is re-formed and **Z^- comes off.** The overall result of the addition of $H:^-$ and elimination of Z^- is the substitution of H for Z.

Part [2] Nucleophilic addition forms a 1° alcohol.

- **Nucleophilic attack of $H:^-$** (from $LiAlH_4$) in Step [3] forms an alkoxide.
- **Protonation of the alkoxide** by H_2O in Step [4] forms the alcohol reduction product. The overall result of Steps [3] and [4] is addition of H_2.

DIBAL-H Reduction of an Ester

Figure 20.4
The DIBAL-H reduction of an ester to an aldehyde in the synthesis of the marine neurotoxin ciguatoxin CTX3C

Thousands of people contract ciguatera seafood poisoning each year from ingesting tropical reef fish containing ciguatoxin. Even very low concentrations of ciguatoxin CTX3C cause gastrointestinal and neurological problems, leading to paralysis and sometimes death.

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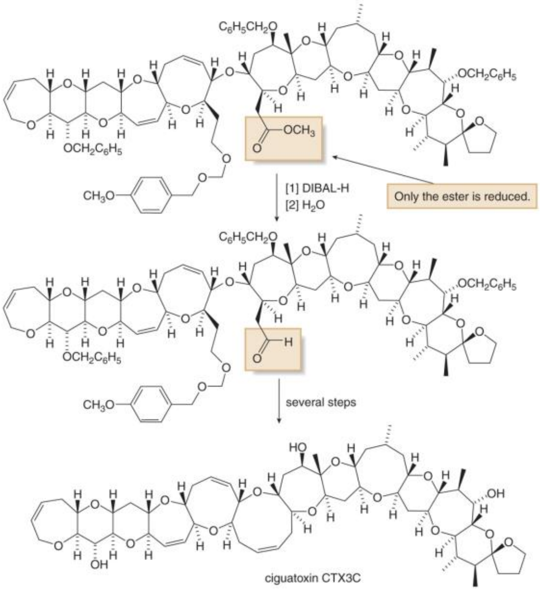
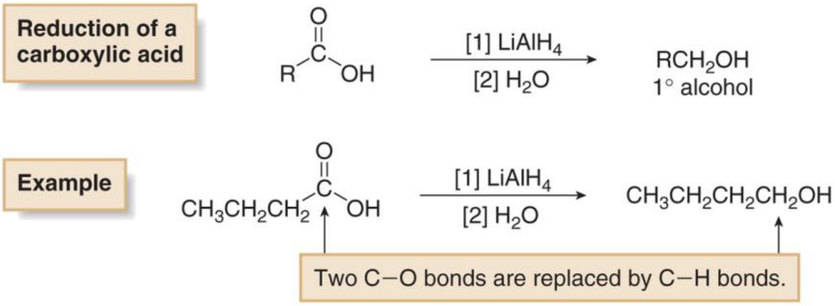


Only the ester is reduced.

ciguatoxin CTX3C

$LiAlH_4$ Reductions

- Carboxylic acids are reduced to 1° alcohols with $LiAlH_4$.
- $LiAlH_4$ is too strong of a reducing agent to stop the reaction at the aldehyde stage, but milder reagents are not strong enough to initiate the reaction in the first place.



Reduction of a carboxylic acid

$$RCOOH \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} RCH_2OH$$

1° alcohol

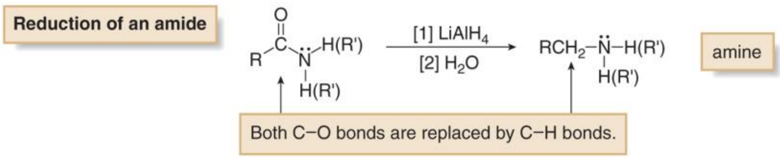
Example

$$CH_3CH_2CH_2COOH \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} CH_3CH_2CH_2CH_2OH$$

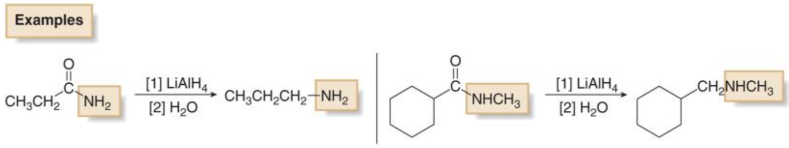
Two C−O bonds are replaced by C−H bonds.

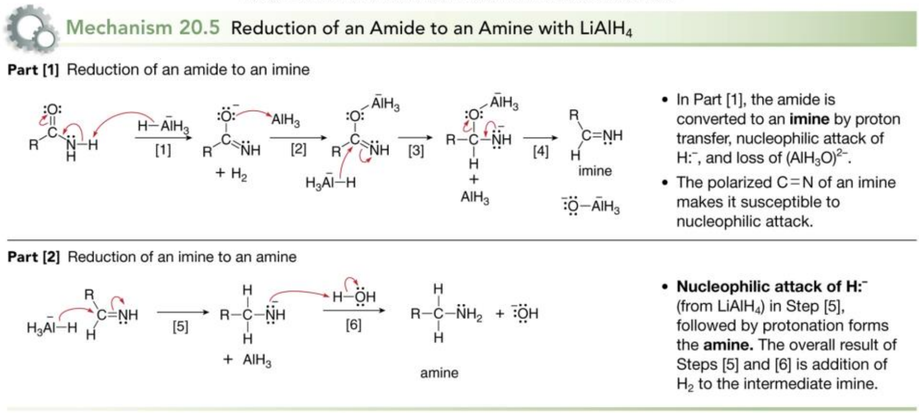
$LiAlH_4$ Reduction of Amides

- **Unlike the $LiAlH_4$ reduction of all other carboxylic acid derivatives, which affords 1° alcohols, the $LiAlH_4$ reduction of amides forms amines.**



- **Since $^{-}NH_2$ is a very poor leaving group, it is never lost during the reduction, and therefore an amine is formed.**





- In Part [1], the amide is converted to an **imine** by proton transfer, nucleophilic attack of $H:^-$, and loss of $(AlH_3O)^{2-}$.
- The polarized C=N of an imine makes it susceptible to nucleophilic attack.

- **Nucleophilic attack of $H:^-$** (from $LiAlH_4$) in Step [5], followed by protonation forms the **amine.** The overall result of Steps [5] and [6] is addition of H_2 to the intermediate imine.

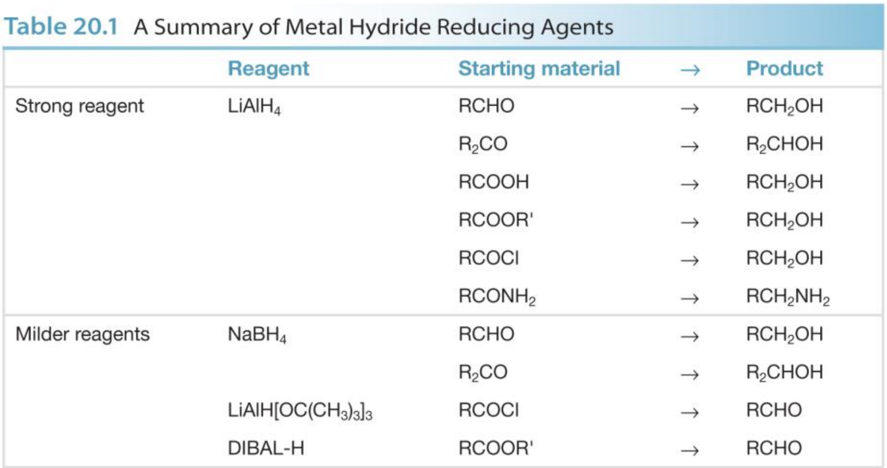
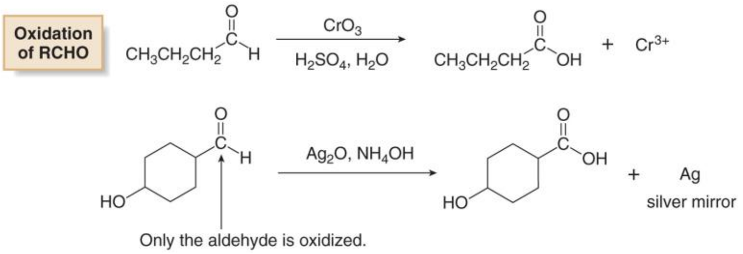


Table 20.1 A Summary of Metal Hydride Reducing Agents

	Reagent	Starting material	→	Product
Strong reagent	$LiAlH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
		RCOOH	→	RCH_2OH
		RCOOR'	→	RCH_2OH
		RCOCl	→	RCH_2OH
		$RCONH_2$	→	RCH_2NH_2
Milder reagents	$NaBH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
	$LiAlH[OC(CH_3)_3]_3$	RCOCl	→	RCHO
	DIBAL-H	RCOOR'	→	RCHO

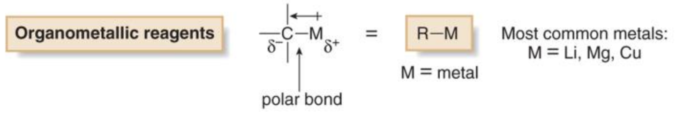
Oxidation of Aldehydes

- **A variety of oxidizing agents can be used, including CrO_3, $Na_2Cr_2O_7$, $K_2Cr_2O_7$, and $KMnO_4$.**
- **Aldehydes can also be oxidized selectively in the presence of other functional groups using silver(I) oxide in aqueous ammonium hydroxide (Tollen's reagent).**
- **Since ketones have no H on the carbonyl carbon, they do not undergo this oxidation reaction.**

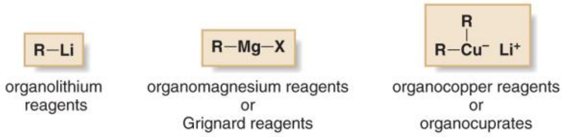


Organometallic Reagents

- *Organometallic reagents* contain a carbon atom bonded to a metal.



- Li, Mg, and Cu are the most common organometallic metals.
- Other metals found in organometallic reagents are Sn, Si, Tl, Al, Ti, and Hg.
- General structures of common organometallic reagents are shown:



organolithium reagents

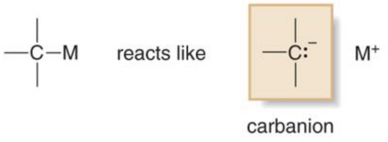
organomagnesium reagents or Grignard reagents

organocopper reagents or organocuprates

- The more polar the carbon–metal bond, the more reactive the organometallic reagent.

Reactivity of Common Organometallic Compounds

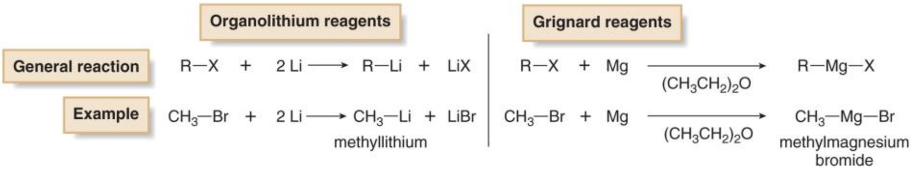
- Since both Li and Mg are very electropositive metals, organolithium (RLi) and organomagnesium (RMgX) reagents contain very polar carbon-metal bonds and are therefore very reactive reagents.
- Organomagnesium reagents are called Grignard reagents.
- Organocopper reagents (R_2CuLi), also called organocuprates, have a less polar carbon–metal bond and are therefore less reactive.
- Although they contain two R groups bonded to Cu, only one R group is utilized in the reaction.
- In organometallic reagents, carbon bears a δ− charge.



a base and a nucleophile

Preparation of Organolithium Compounds

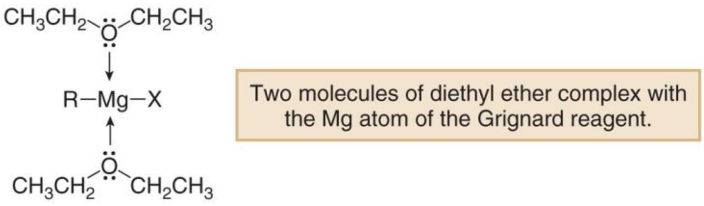
- **Organolithium and Grignard reagents are typically prepared by reaction of an alkyl halide with the corresponding metal.**



- **With lithium, the halogen and metal exchange to form the organolithium reagent.**
- **With Mg, the metal inserts in the carbon–halogen bond, forming the Grignard reagent.**

Solvent Stabilization of Grignard Reagents

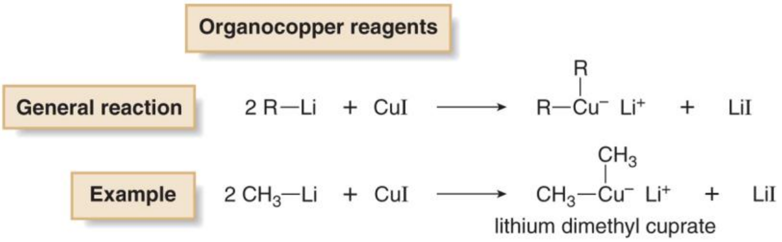
- **Grignard reagents are usually prepared in diethyl ether ($CH_3CH_2OCH_2CH_3$) as solvent.**
- **It is thought that two ether O atoms complex with the Mg atom, stabilizing the reagent by Lewis Base–Lewis Acid interactions.**



Two molecules of diethyl ether complex with the Mg atom of the Grignard reagent.

Preparation of Organocuprate Compounds

- **Organocuprates are prepared from organolithium reagents by reaction with a Cu^+ salt, often CuI.**



Organocopper reagents

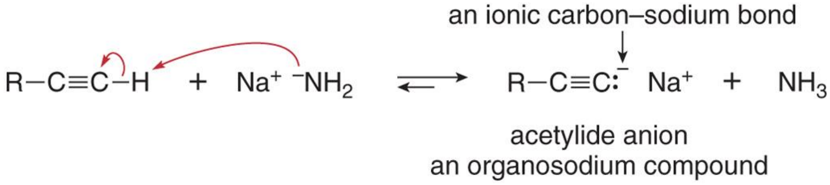
General reaction $2\ R{-}Li + CuI \longrightarrow R{-}\overset{R}{\overset{|}{Cu^-}}\ Li^+ + LiI$

Example $2\ CH_3{-}Li + CuI \longrightarrow CH_3{-}\overset{CH_3}{\overset{|}{Cu^-}}\ Li^+ + LiI$

lithium dimethyl cuprate

Preparation of Acetylide Ions

- **Acetylide ions are another example of “organometallic reagents”.**
- **Acetylide ions can be thought of as “organosodium reagents”.**
- **Since sodium is even more electropositive than lithium, the C–Na bond of these organosodium compounds is best described as ionic, rather than polar covalent.**



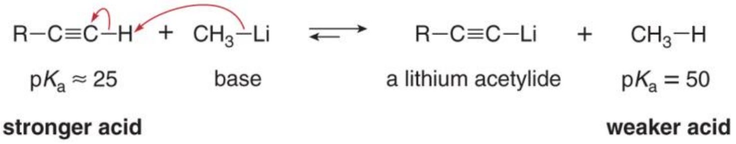
an ionic carbon–sodium bond

$$R{-}C{\equiv}C{-}H + Na^+\ {}^-NH_2 \rightleftharpoons R{-}C{\equiv}C{:}^-\ Na^+ + NH_3$$

acetylide anion
an organosodium compound

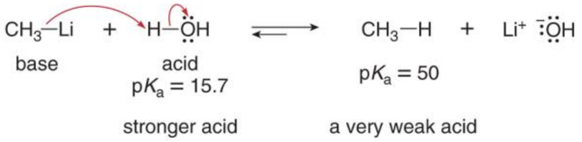
Preparation of Lithium Acetylides

- An acid–base reaction can also be used to prepare *sp* hybridized organolithium compounds.
- Treatment of a terminal alkyne with CH_3Li affords a lithium acetylide.
- The equilibrium favors the products because the *sp* hybridized C–H bond of the terminal alkyne is more acidic than the *sp*^{3} hybridized conjugate acid, CH_4, that is formed.

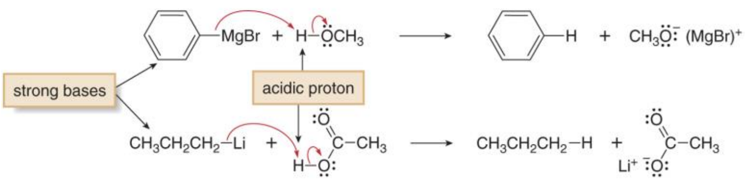


Acid–Base Reactions of Organometallics

- Organometallic reagents are strong bases that readily abstract a proton from water to form hydrocarbons.

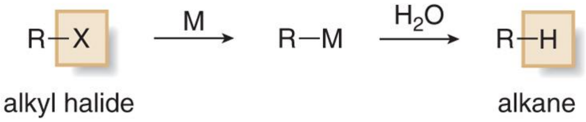


- Similar reactions occur with the O–H proton of alcohols and carboxylic acids, and the N–H protons of amines.



Uses of Organometallic Compounds

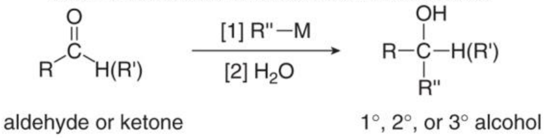
- **Since organolithium and Grignard reagents are themselves prepared from alkyl halides, a two-step method converts an alkyl halide into an alkane (or other hydrocarbon).**



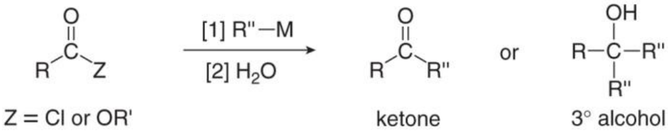
- **Organometallic reagents are also strong nucleophiles that react with electrophilic carbon atoms to form new carbon–carbon bonds.**
- **These reactions are very valuable in forming the carbon skeletons of complex organic molecules.**

Functional Group Transformations Involving Organometallic Compounds

[1] Reaction of R–M with aldehydes and ketones to afford alcohols

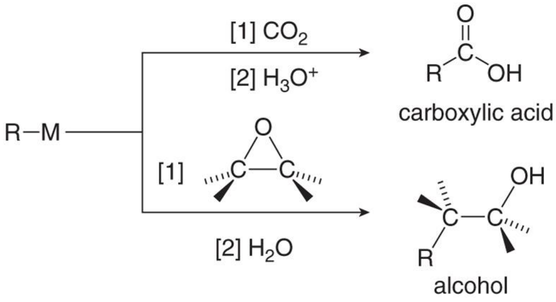


[2] Reaction of R–M with carboxylic acid derivatives



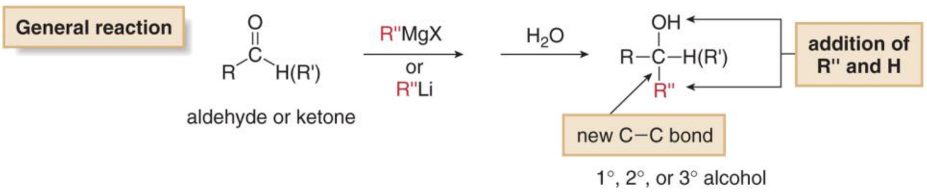
Functional Group Transformations Involving Organometallic Compounds

[3] Reaction of R–M with other electrophilic functional groups

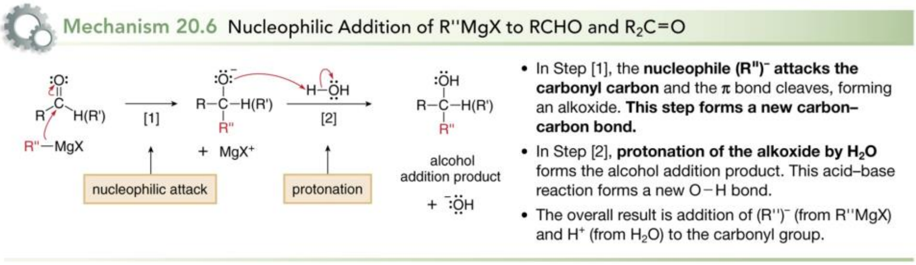


Addition of Organometallics to Aldehydes and Ketones

- Treatment of an aldehyde or ketone with either an organolithium or Grignard reagent followed by water forms an alcohol with a new carbon–carbon bond.
- This reaction is an addition because the elements of R’’ and H are added across the π bond.



Nucleophilic Addition of Grignard Reagents

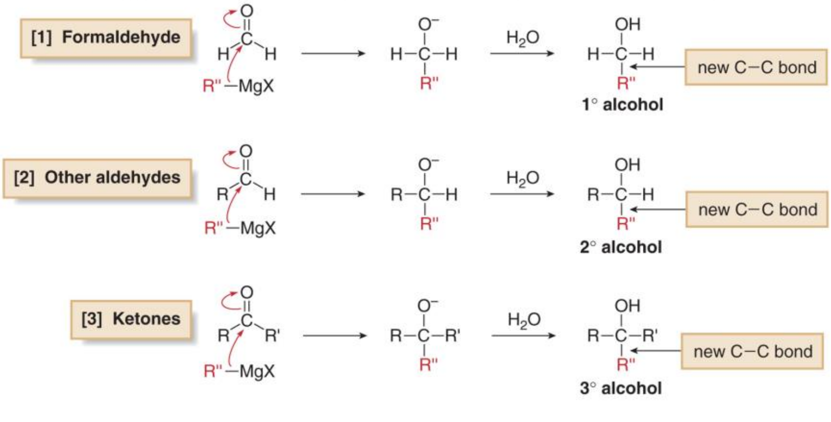


Mechanism 20.6 Nucleophilic Addition of R''MgX to RCHO and $R_2C{=}O$

- In Step [1], the **nucleophile (R")⁻ attacks the carbonyl carbon** and the π bond cleaves, forming an alkoxide. **This step forms a new carbon–carbon bond.**
- In Step [2], **protonation of the alkoxide by H_2O** forms the alcohol addition product. This acid–base reaction forms a new O–H bond.
- The overall result is addition of (R'')⁻ (from R''MgX) and H^+ (from H_2O) to the carbonyl group.

- **This reaction follows the general mechanism for nucleophilic addition—that is, nucleophilic attack by a carbanion followed by protonation.**
- **Mechanism 20.6 is shown using R''MgX, but the same steps occur with RLi reagents and acetylide anions.**

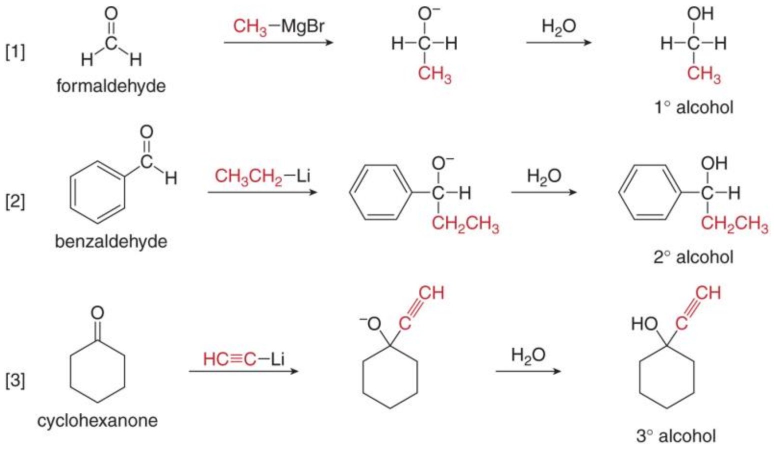
Mechanism of Organometallic Addition



[1] Addition of R"MgX to formaldehyde ($CH_2{=}O$) forms a 1° alcohol.
[2] Addition of R"MgX to all other aldehydes forms a 2° alcohol.
[3] Addition of R"MgX to ketones forms a 3° alcohol.

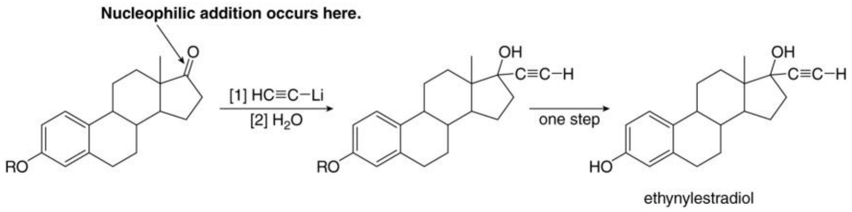
Alcohols Formed by Organometallic Addition

- **This reaction is used to prepare 1°, 2°, and 3° alcohols.**



Synthesis of Ethynylestradiol

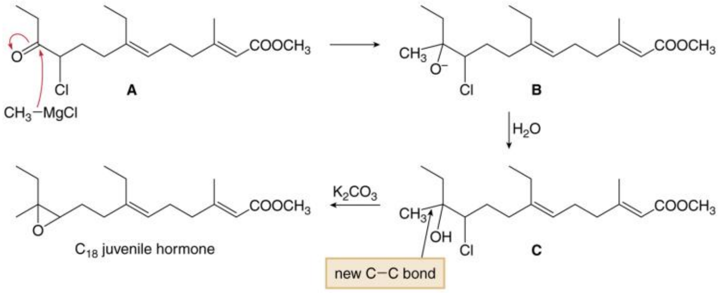
Figure 20.5



Synthesis of C_{18} Juvenile Hormone

- C_{18} juvenile hormone helps to regulate the complex life cycle of insects.

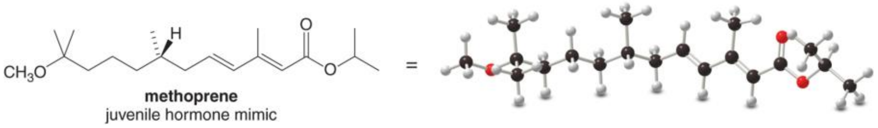
Figure 20.6



- Addition of CH_3MgCl to ketone **A** gives an alkoxide, **B,** which is protonated with H_2O to form 3° alcohol **C.** Although the ester group ($–COOCH_3$) can also react with the Grignard reagent (Section 20.13), it is less reactive than the ketone carbonyl. Thus, with control of reaction conditions, nucleophilic addition occurs selectively at the ketone.
- Treatment of halohydrin **C** with K_2CO_3 forms the C_{18} juvenile hormone in one step. Conversion of a halohydrin to an epoxide was discussed in Section 9.6.

Juvenile Hormone Mimics

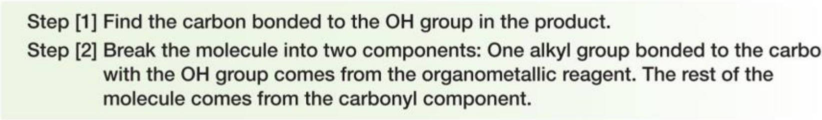
- Juvenile hormones maintain the juvenile stage of an insect until it is ready for adulthood.
- Juvenile hormone *mimics* have been used to effectively control insect populations.
- Application of these synthetic hormones to egg or larva prevents maturation.
- Methoprene is used in cattle salt blocks to control hornflies and on dogs and cats to control fleas.



methoprene
juvenile hormone mimic

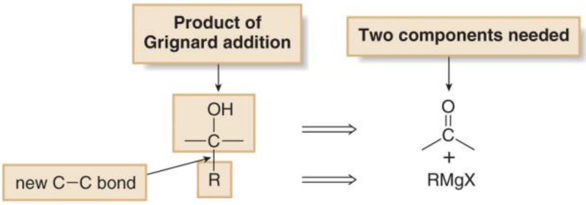
Retrosynthetic Analysis of Grignard Products

- To determine what carbonyl and Grignard components are needed to prepare a given compound, follow these two steps:



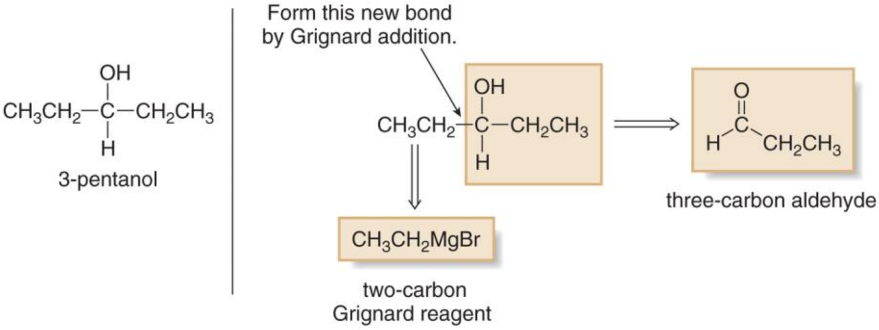
Step [1] Find the carbon bonded to the OH group in the product.

Step [2] Break the molecule into two components: One alkyl group bonded to the carbon with the OH group comes from the organometallic reagent. The rest of the molecule comes from the carbonyl component.



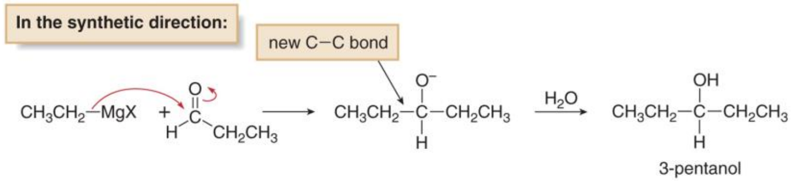
Retrosynthetic Analysis of 3-pentanol

Retrosynthetic analysis for preparing 3-pentanol



Synthesis of 3-pentanol

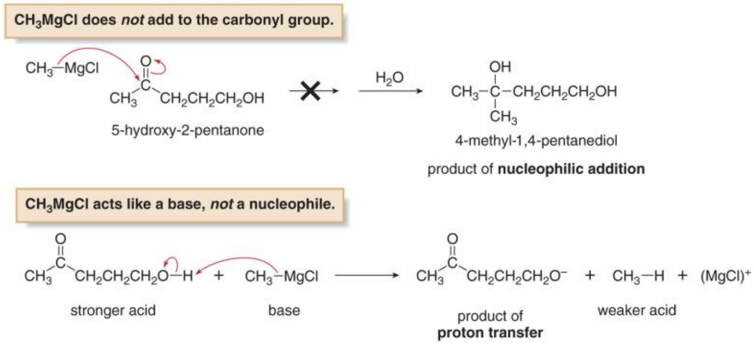
- Writing the reaction in the synthetic direction—that is, from starting material to product—shows whether the synthesis is feasible and the analysis is correct.



- Note that there is often more than one way to synthesize a 2° alcohol by Grignard addition.

Limitations of Organometallic Reagents

- Addition of organometallic reagents cannot be used with molecules that contain both a carbonyl group and N–H or O–H bonds.
- Carbonyl compounds that also contain N–H or O–H bonds undergo an acid–base reaction with organometallic reagents, not nucleophilic addition.



Use of Protecting Groups

Solving this problem requires a three-step strategy:

[1] Convert the OH group into another functional group that does not interfere with the desired reaction.

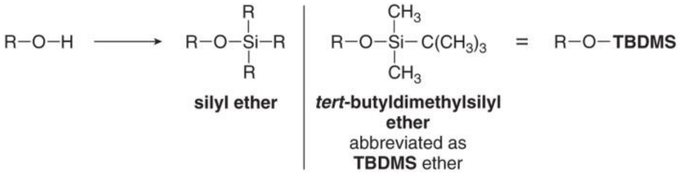
- **This new blocking group is called a protecting group, and the reaction that creates it is called "protection".**

[2] Carry out the desired reaction.

[3] Remove the protecting group.

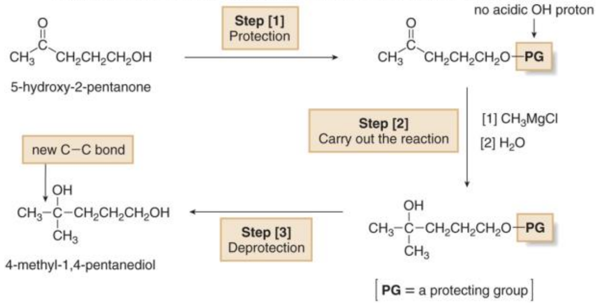
- **This reaction is called "deprotection".**

- **A common OH protecting group is a silyl ether.**



General Protecting Group Strategy

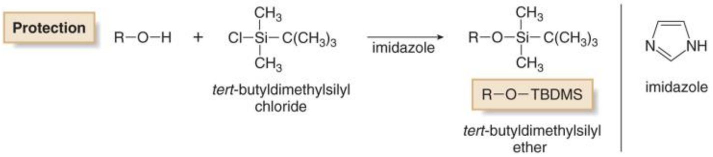
Figure 20.7



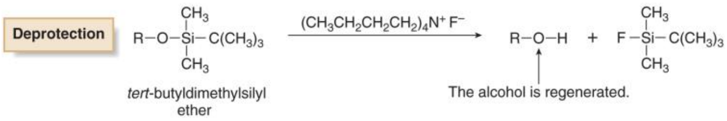
- **In Step [1], the OH proton in 5-hydroxypentanone is replaced with a protecting group, written as PG.**
- **Because the product no longer has an OH proton, it can now undergo nucleophilic addition.**
- **In Step [2], CH_3MgCl adds to the carbonyl group to yield a 3^o alcohol after protonation with water.**
- **Removal of the protecting group in Step [3] forms the desired product.**

Preparing Silyl Ethers

- ***tert*-butyldimethylsilyl ethers** **are prepared from alcohols by reaction with *tert*-butyldimethylsilyl chloride and an amine base, usually imidazole.**

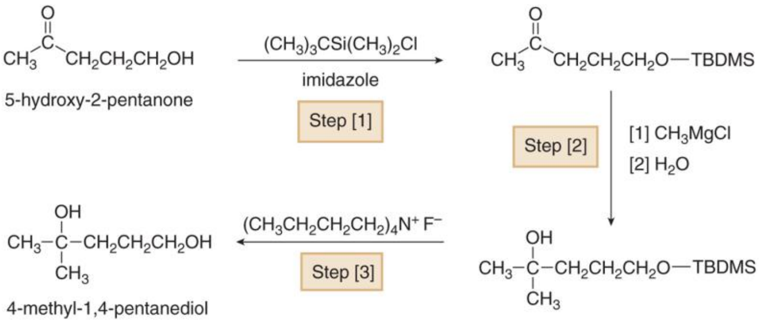


- **The silyl ether is typically removed with a fluoride salt such as tetrabutylammonium fluoride $(CH_3CH_2CH_2CH_2)_4N^+F^-$.**



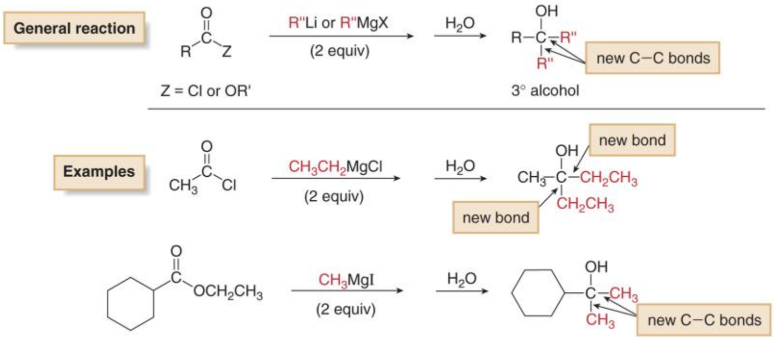
Preparing Silyl Ethers

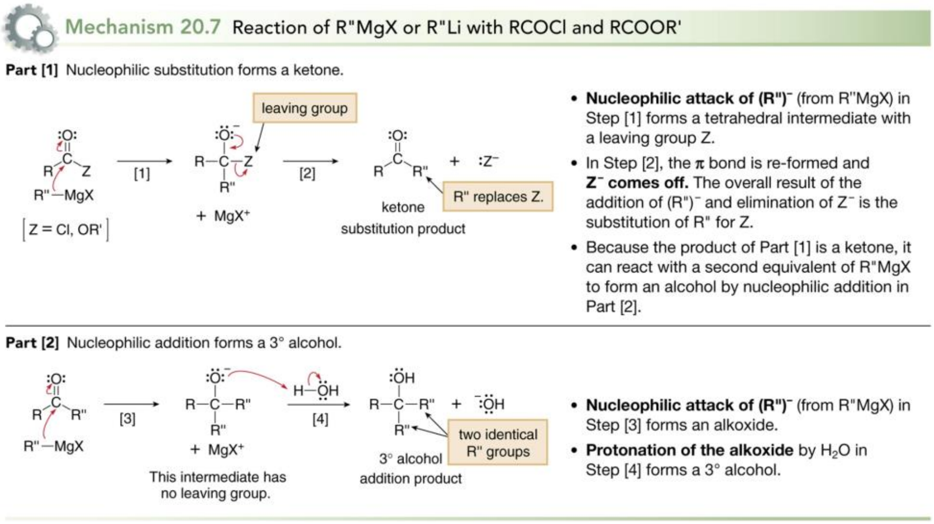
- **The use of *tert*-butyldimethylsilyl ether as a protecting group makes possible the synthesis of 4-methyl-1,4-pentanediol by a three-step sequence.**



Organometallic Reactions with Esters and Acid Chlorides

- **Both esters and acid chlorides form 3° alcohols when treated with two equivalents of either Grignard or organolithium reagents.**





Mechanism 20.7 Reaction of R"MgX or R"Li with RCOCl and RCOOR'

Part [1] Nucleophilic substitution forms a ketone.

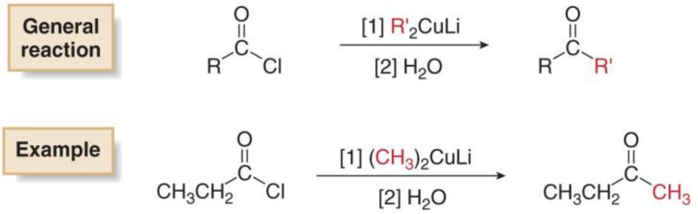
- **Nucleophilic attack of (R")⁻** (from R"MgX) in Step [1] forms a tetrahedral intermediate with a leaving group Z.
- In Step [2], the π bond is re-formed and **Z⁻ comes off.** The overall result of the addition of (R")⁻ and elimination of Z⁻ is the substitution of R" for Z.
- Because the product of Part [1] is a ketone, it can react with a second equivalent of R"MgX to form an alcohol by nucleophilic addition in Part [2].

Part [2] Nucleophilic addition forms a 3° alcohol.

- **Nucleophilic attack of (R")⁻** (from R"MgX) in Step [3] forms an alkoxide.
- **Protonation of the alkoxide** by H_2O in Step [4] forms a 3° alcohol.

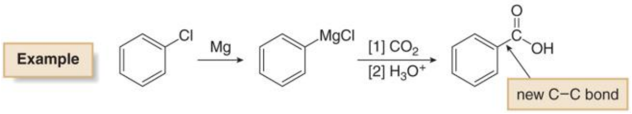
Organocuprates—a Less Reactive Organometallic

- To form a ketone from a carboxylic acid derivative, a less reactive organometallic reagent—namely an organocuprate—is needed.
- Acid chlorides, which have the best leaving group (Cl^-) of the carboxylic acid derivatives, react with R'_2CuLi to give a ketone as the product.
- Esters, which contain a poorer leaving group (^-OR), do not react with R'_2CuLi.

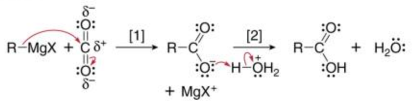


Grignard Reaction with CO_2

- Grignards react with CO_2 to give carboxylic acids after protonation with aqueous acid.
- This reaction is called carboxylation.
- The carboxylic acid formed has one more carbon atom than the Grignard reagent from which it was prepared.



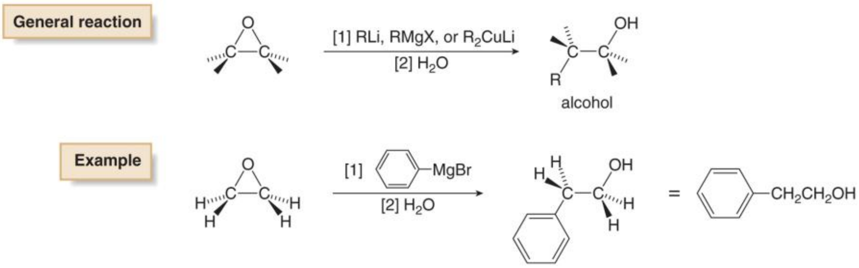
Mechanism 20.8 Carboxylation—Reaction of RMgX with CO_2



- In Step [1], the nucleophilic Grignard reagent attacks the electrophilic carbon atom of CO_2, cleaving a π bond and forming a new carbon–carbon bond.
- The carboxylate anion is protonated with aqueous acid in Step [2] to form the carboxylic acid.

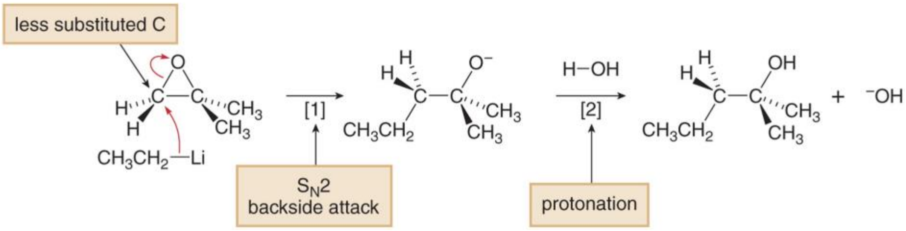
Organometallic Reactions with Epoxides

- **Like other strong nucleophiles, organometallic reagents—RLi, RMgX, and R_2CuLi—open epoxide rings to form alcohols.**



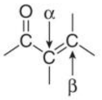
Organometallic Reactions with Epoxides

- **The reaction follows the same two-step process as opening of epoxide rings with other negatively charged nucleophiles—that is, nucleophilic attack from the back side of the epoxide, followed by protonation of the resulting alkoxide.**
- **In unsymmetrical epoxides, nucleophilic attack occurs at the less-substituted carbon atom.**



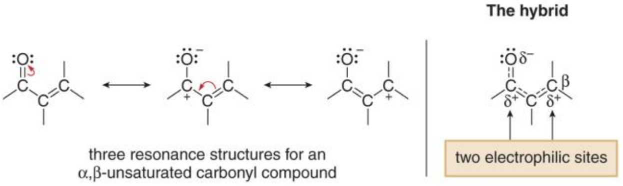
Organometallic Reactions with α,β-Unsaturated Carbonyl Compounds

- **α,β-Unsaturated carbonyl compounds are conjugated molecules containing a carbonyl group and a C=C separated by a single σ bond.**



α,β-unsaturated carbonyl compound

- **Resonance shows that the carbonyl carbon and the β carbon bear a partial positive charge.**

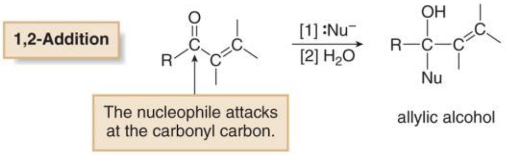


three resonance structures for an α,β-unsaturated carbonyl compound

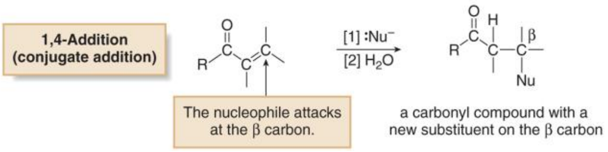
α,β-Unsaturated Carbonyl Compounds

- **This means that α,β-unsaturated carbonyl compounds can react with nucleophiles at two different sites.**

- Addition of a nucleophile to the carbonyl carbon, called 1,2-addition, adds the elements of H and Nu across the C=O, forming an allylic alcohol.

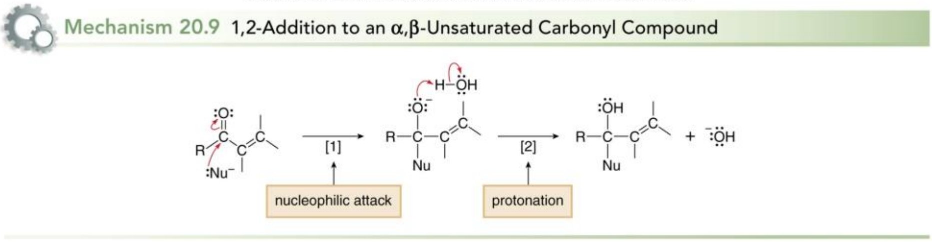


- Addition of a nucleophile to the β carbon, called 1,4-addition or conjugate addition, forms a carbonyl compound.

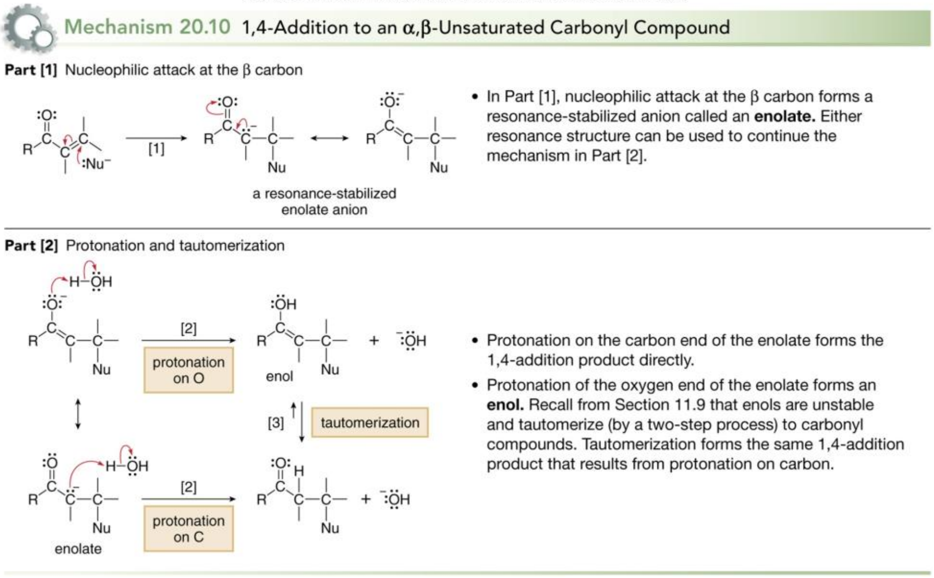


1,2-Addition Mechanism

- **The steps for the mechanism of 1,2-addition are exactly the same as those for the nucleophilic addition of an aldehyde or a ketone—that is, nucleophilic attack, followed by protonation.**



Mechanism 20.9 1,2-Addition to an α,β-Unsaturated Carbonyl Compound



Mechanism 20.10 1,4-Addition to an α,β-Unsaturated Carbonyl Compound

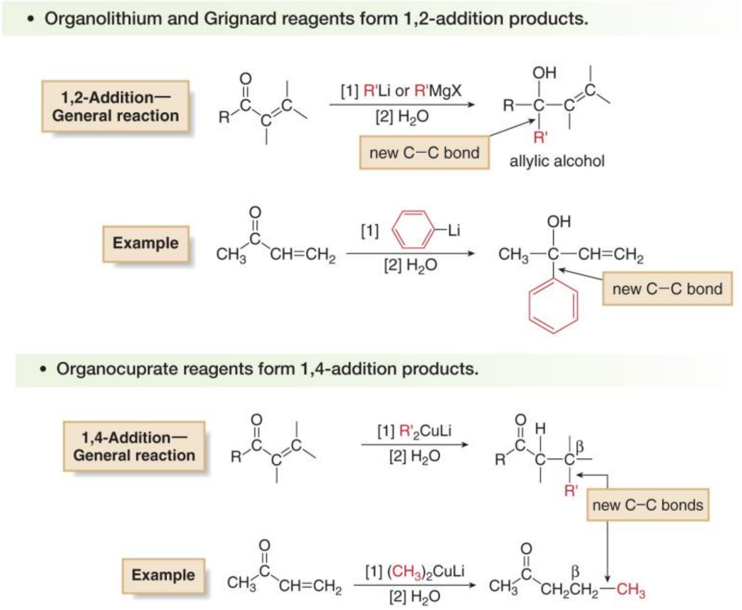
Part [1] Nucleophilic attack at the β carbon

- In Part [1], nucleophilic attack at the β carbon forms a resonance-stabilized anion called an **enolate.** Either resonance structure can be used to continue the mechanism in Part [2].

Part [2] Protonation and tautomerization

- Protonation on the carbon end of the enolate forms the 1,4-addition product directly.
- Protonation of the oxygen end of the enolate forms an **enol.** Recall from Section 11.9 that enols are unstable and tautomerize (by a two-step process) to carbonyl compounds. Tautomerization forms the same 1,4-addition product that results from protonation on carbon.

1,2 vs. 1,4-Addition Products

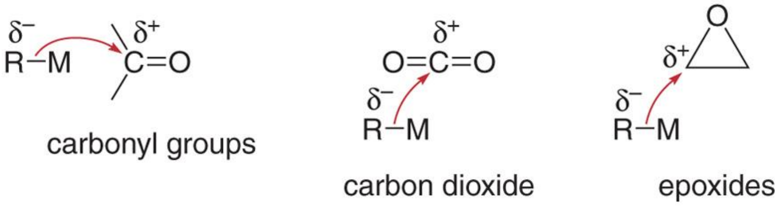


- Organolithium and Grignard reagents form 1,2-addition products.

- Organocuprate reagents form 1,4-addition products.

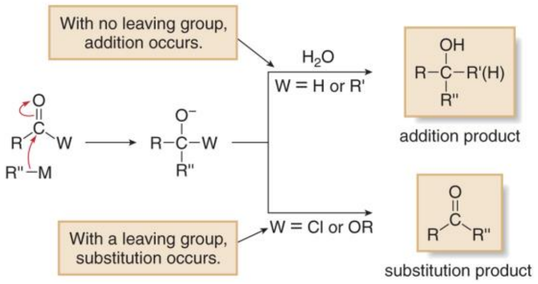
Summary of Organometallic Reactions

[1] Organometallic reagents (R–M) attack electrophilic atoms, especially the carbonyl carbon.



Summary of Organometallic Reactions

[2] After an organometallic reagent adds to the carbonyl group, the fate of the intermediate depends on the presence or absence of a leaving group.



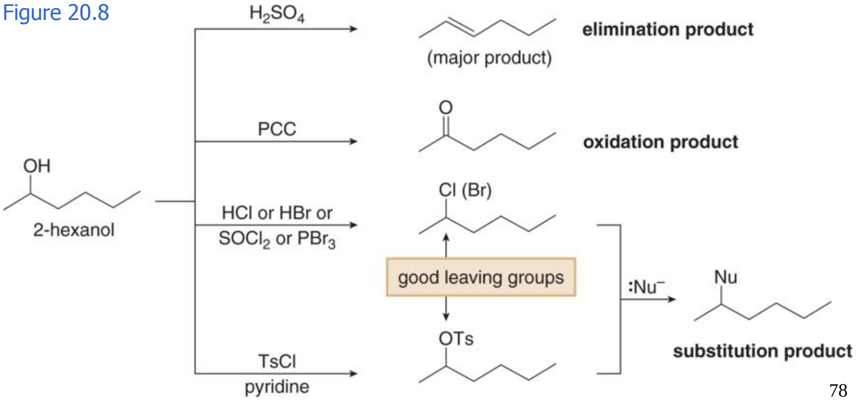
[3] The polarity of the R–M bond determines the reactivity of the reagents:

- RLi and RMgX are very reactive reagents.
- R_2CuLi is much less reactive.

Synthesis

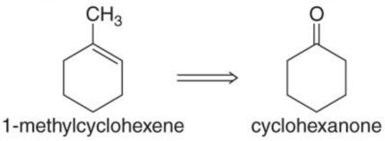
- Oxidation and reduction reactions are extremely useful in organic synthesis.
- Conversion of a functional group to a good leaving group also allows for other reactions.

Figure 20.8

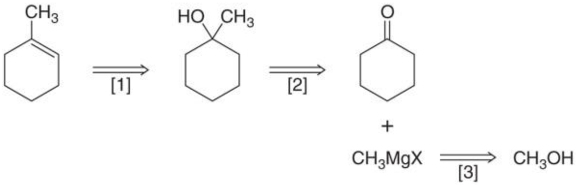


Synthesis Practice

- **Synthesize 1-methylcyclohexene from cyclohexanol and any organic alcohol.**

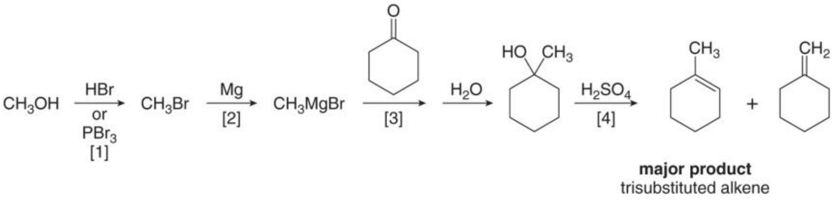


- **Begin with Retrosynthetic Analysis:**
  - **Form double bond from alcohol dehydration.**
  - **Make the 3º alcohol by Grignard addition.**
  - **Prepare the Grignard from methanol.**



Synthesis Practice

- **Four steps are required to accomplish the synthesis.**



- **Convert methanol to the Grignard reagent by forming the alkyl halide, followed by reaction with Mg.**
- **Add the Grignard reagent to cyclohexanone, followed by protonation, to form the alcohol.**
- **Acid-catalyzed elimination of water forms the desired product as the major product.**