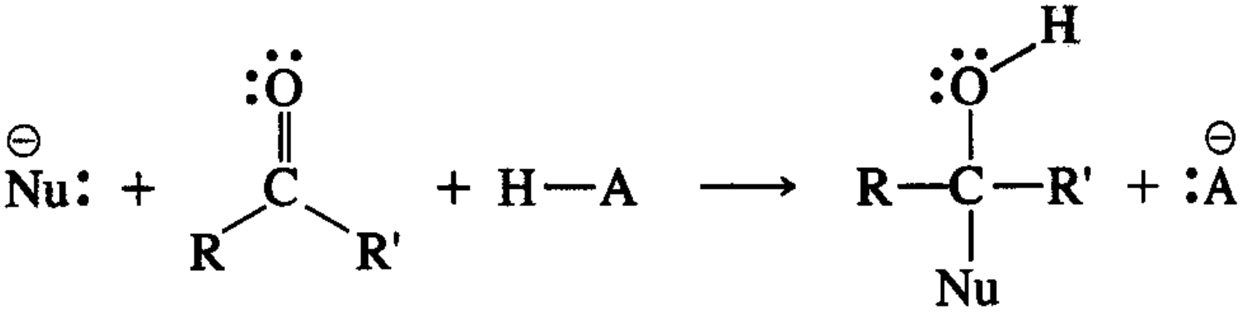
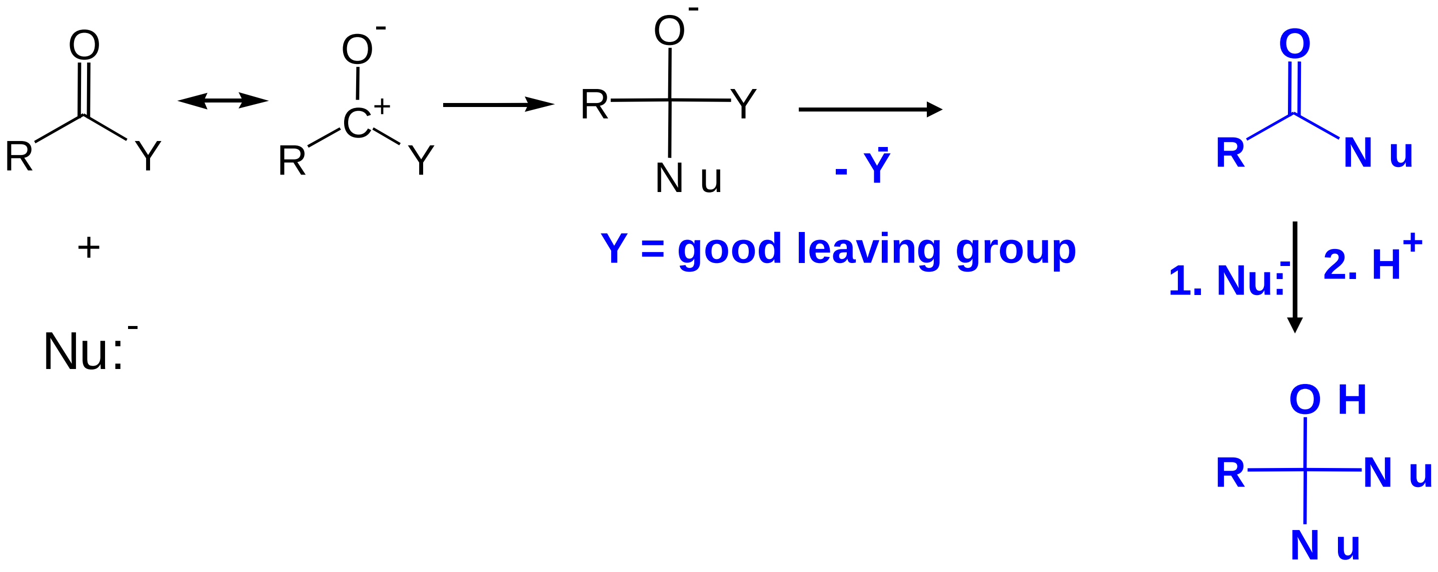
Chapter 19 Substitutions at the Carbonyl Group

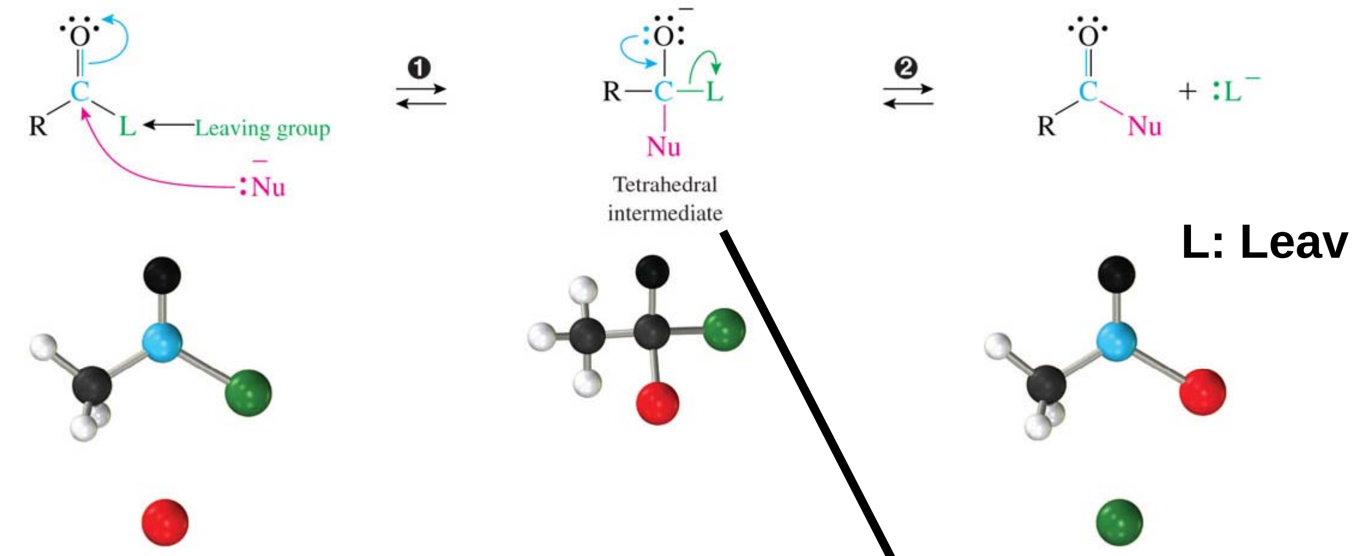
In Chapter 18 Additions to the Carbonyl Groups



In Chapter 19 Substitutions at the Carbonyl Group



19.1 General Mechanism



① The first step of this mechanism is exactly the same as the first step for nucleophilic addition to aldehydes and ketones under basic conditions (see Figure 18.1). The nucleophile may be uncharged in some cases.

This mechanism is sometimes called the **tetrahedral mechanism** because of this sp^3-hybridized intermediate with tetrahedral geometry. If L is H or R, it is too basic to leave as an anion, so aldehydes and ketones stop at this point. When L is Cl or an N or O group, it can better support a negative charge and is capable of acting as a leaving group.

② The overall result is a substitution of Nu for L. L^- must be a better leaving group (less basic) than H^- or R_3C^-.

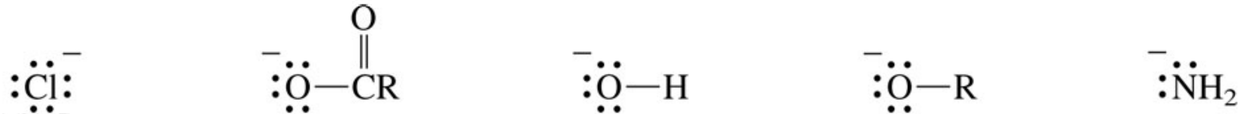
L: Leaving group

Tetrahedral intermediate (sp^3 hybrized carbon)

If L = -CH_3 or -H (ketone or aldehyde), it stops here. Because they are poor leaving group, or H^- and CH_3^- are both too basic (unstable).

⇒ L must be a better leaving group than -CH_3 or H^- .

⇒L =

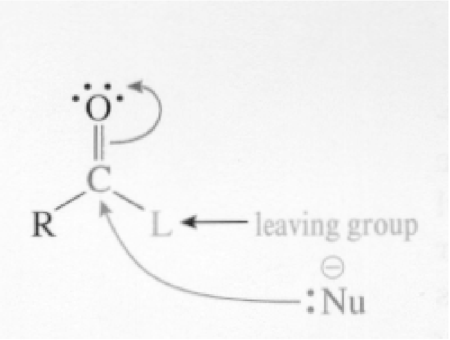


$:\ddot{Cl}:^-$ $\quad$ $^-:\ddot{O}-\overset{O}{\overset{\|}{C}}R$ $\quad$ $^-:\ddot{O}-H$ $\quad$ $^-:\ddot{O}-R$ $\quad$ $^-:\ddot{N}H_2$

⇒ less basic

Reactivity of carbonyls

1. **Steric effect:** **Steric hindrance decrease the reactivity**



Bulky

2. Inductive effect: e- w/drawing group → increase the reactivity

because the carbonyl carbon becomes more electrophilic

: e- donating group → decrease the reactvity

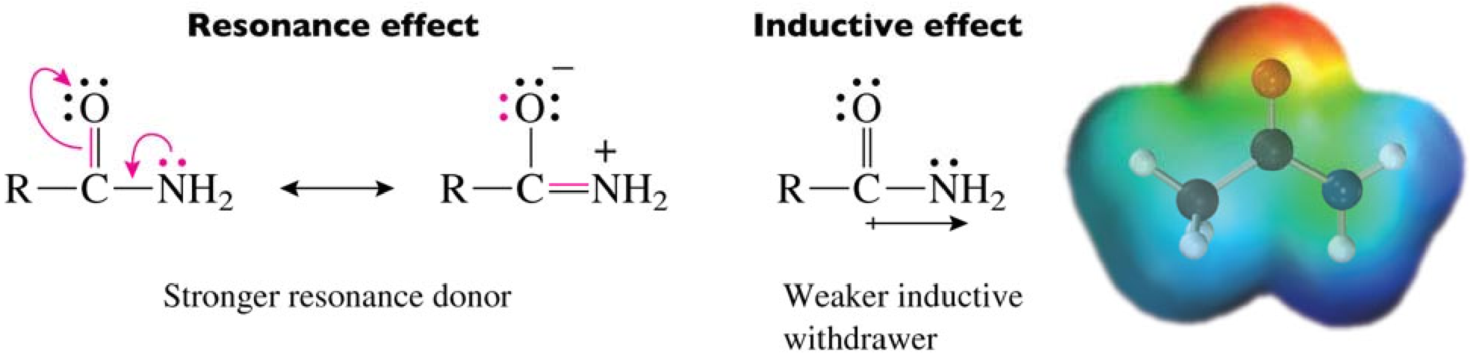
3. Resonance effect: resonance e- w/drawing group

→ increase the reactvity

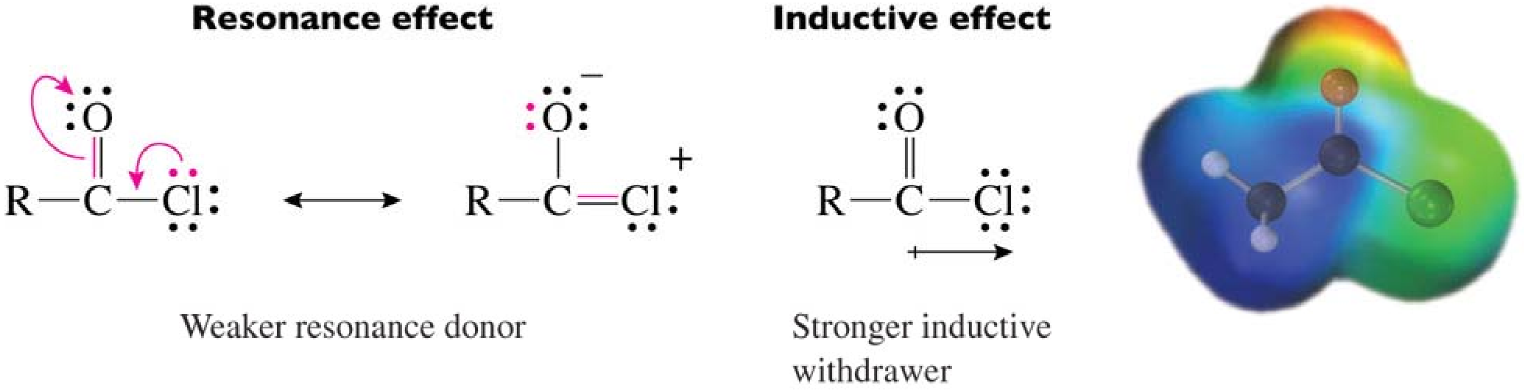
because the carbonyl carbon becomes more electrophilic

: resonance e- donating group → decrease the reactvity

Examples



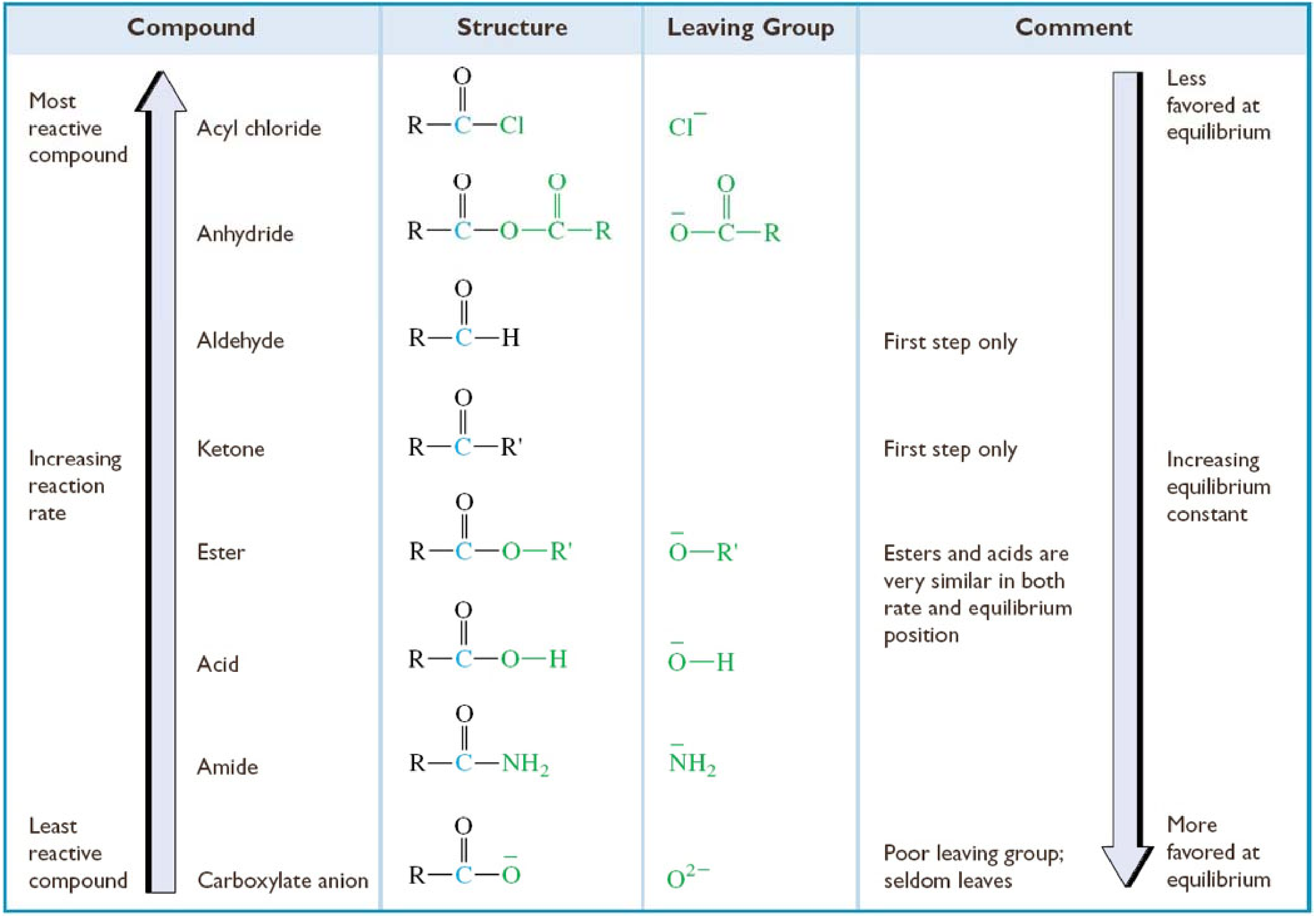
⇒ **decrease the reactivity very much** ⇒ **increase the reactivity slightly**



⇒ **decrease the reactivity slightly** ⇒ **increase the reactivity very much**

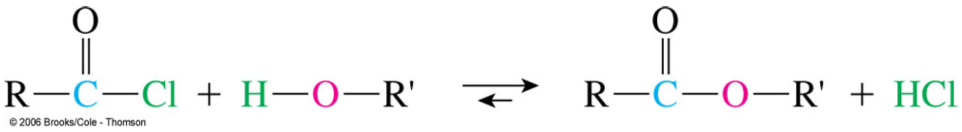
Therefore acyl chloride is much more reactive than amide !

Reactivity scale



Compound		Structure	Leaving Group	Comment	
Most reactive compound	Acyl chloride	$R-\overset{\overset{O}{\|}}{C}-Cl$	Cl^-		Less favored at equilibrium
	Anhydride	$R-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-R$	$\bar{O}-\overset{\overset{O}{\|}}{C}-R$		
	Aldehyde	$R-\overset{\overset{O}{\|}}{C}-H$		First step only	
Increasing reaction rate	Ketone	$R-\overset{\overset{O}{\|}}{C}-R'$		First step only	Increasing equilibrium constant
	Ester	$R-\overset{\overset{O}{\|}}{C}-O-R'$	$\bar{O}-R'$	Esters and acids are very similar in both rate and equilibrium position	
	Acid	$R-\overset{\overset{O}{\|}}{C}-O-H$	$\bar{O}-H$		
	Amide	$R-\overset{\overset{O}{\|}}{C}-NH_2$	$\bar{N}H_2$		
Least reactive compound	Carboxylate anion	$R-\overset{\overset{O}{\|}}{C}-\bar{O}$	O^{2-}	Poor leaving group; seldom leaves	More favored at equilibrium

⇒ **determines the equilibrium**



$$R-\overset{\overset{O}{\|}}{C}-Cl + H-O-R' \rightleftarrows R-\overset{\overset{O}{\|}}{C}-O-R' + HCl$$

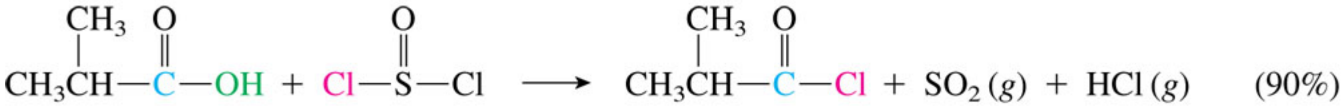
19.2 Preparation of Acyl Chloride

Why?

Because acyl chloride has the highest reactivity.
Conversion to other compounds is very easy.

How?

Use thionyl chloride($SOCl_2$) or phosphorus pentachloride (PCl_5).



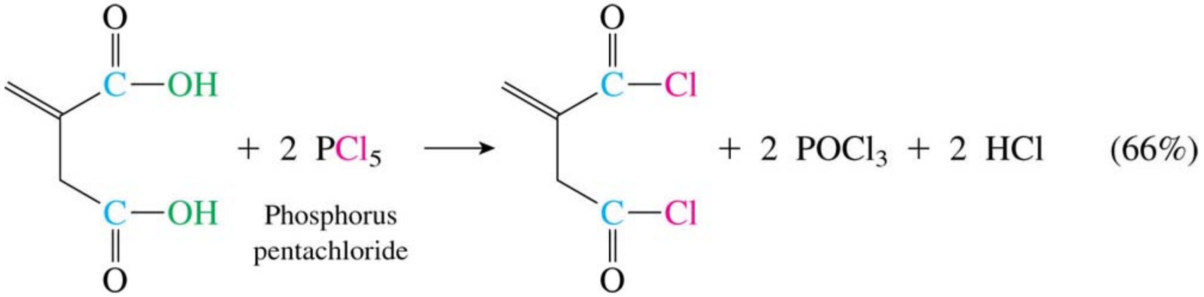
$$\mathrm{CH_3\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-OH} + \mathrm{Cl-\overset{\overset{O}{\|}}{S}-Cl} \longrightarrow \mathrm{CH_3\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-Cl} + SO_2\,(g) + HCl\,(g) \quad (90\%)$$

2-Methylpropanoic acid

Thionyl chloride

2-Methylpropanoyl chloride

Gas formation makes thionyl chloride very reactive.



$+ 2\ PCl_5 \longrightarrow + 2\ POCl_3 + 2\ HCl \quad (66\%)$

Phosphorus pentachloride

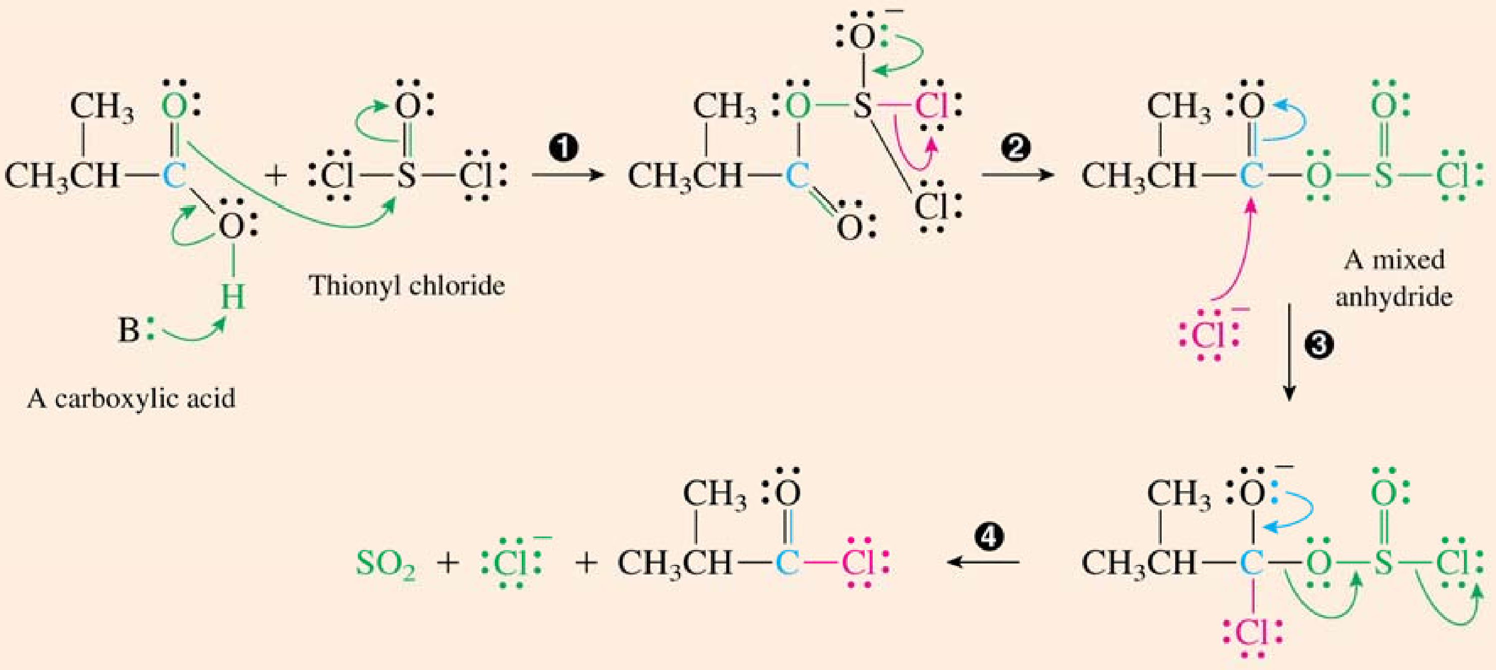
Mechanism

❶ Thionyl chloride reacts like an acyl chloride. In this step, its sulfur–oxygen double bond plays the role of the carbonyl group of an acyl chloride. The nucleophile, the oxygen of the carboxylic acid, attacks the sulfur and displaces the pi electrons onto the oxygen.

❷ The reaction continues like the mechanism in Figure 19.1, but at sulfur rather than carbon. The electrons on the oxygen help displace the chloride.

This compound is a mixed anhydride of the carboxylic acid and sulfurous acid and is more reactive than the acyl chloride.

❸ The nucleophilic chloride anion bonds to the carbon, displacing the pi electrons onto the oxygen.



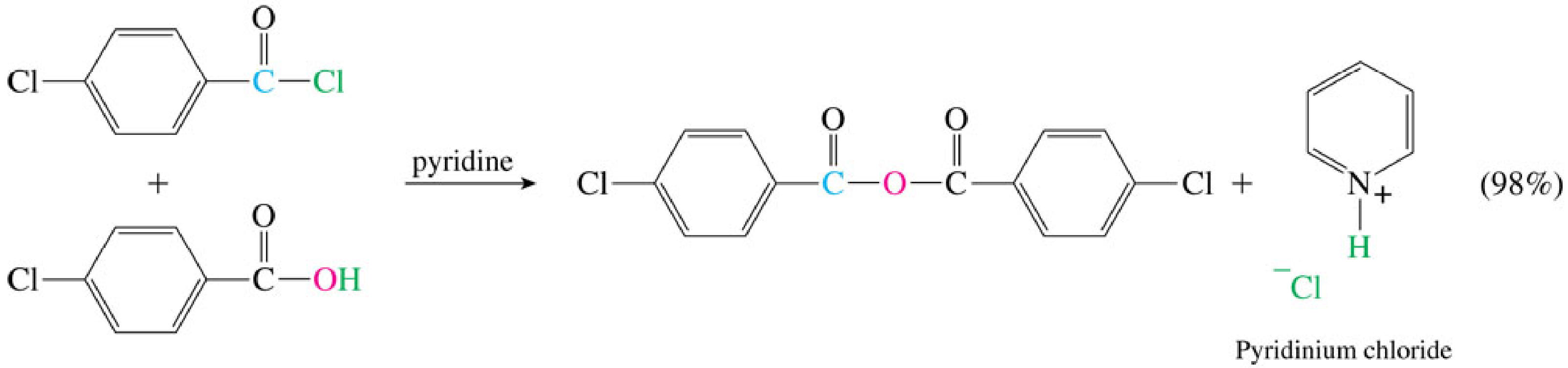
❹ The electrons on the oxygen help displace the leaving group, which fragments to SO_2 and Cl^-.

19.3 Preparation of Anhydride

How?

1. Using a carboxylic acid or its conjugated base with an acyl chloride

$R\text{-}CO_2^-\ M^+$ also can be used

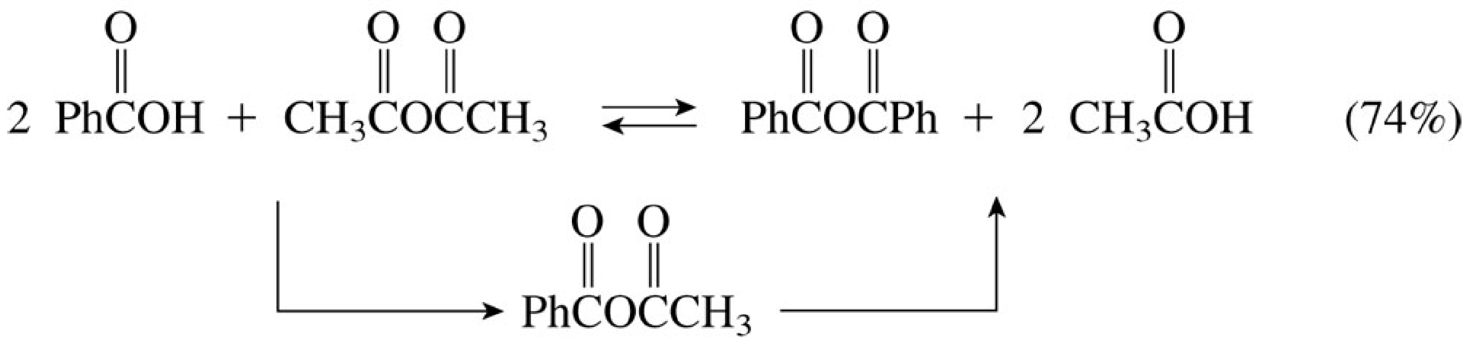


Pyridine is added or used as a solvent

- **a.** **Salt formation → precipitaion**
- **b.** **Prevent the reaction mixture from becoming strongly acidic**

How?

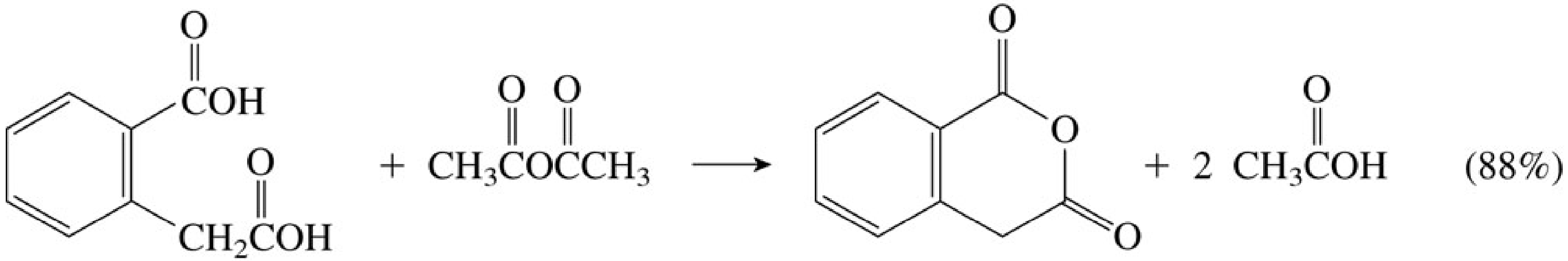
2. Using a carboxylic acid with an other anhydride



$$2\ \text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OH} + \text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_3 \rightleftharpoons \text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{Ph} + 2\ \text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OH} \quad (74\%)$$

$$\text{Ph}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{CH}_3$$

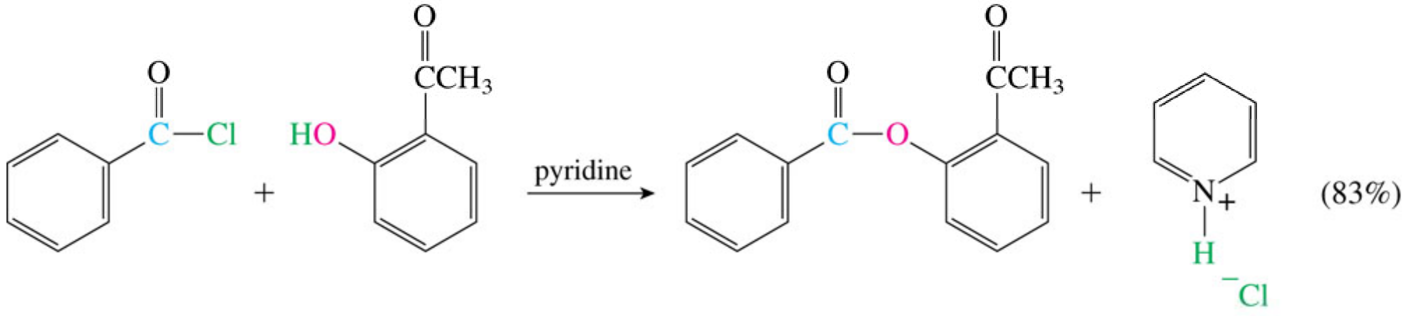
Removal of the acetic acid can drive the equilibrium to the product

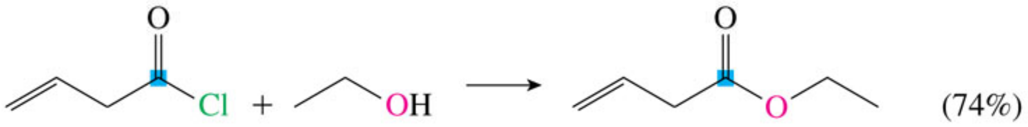


19.4 Preparation of Esters

How?

1. By reaction of an alcohol with ether an acyl chloride or an anhydride





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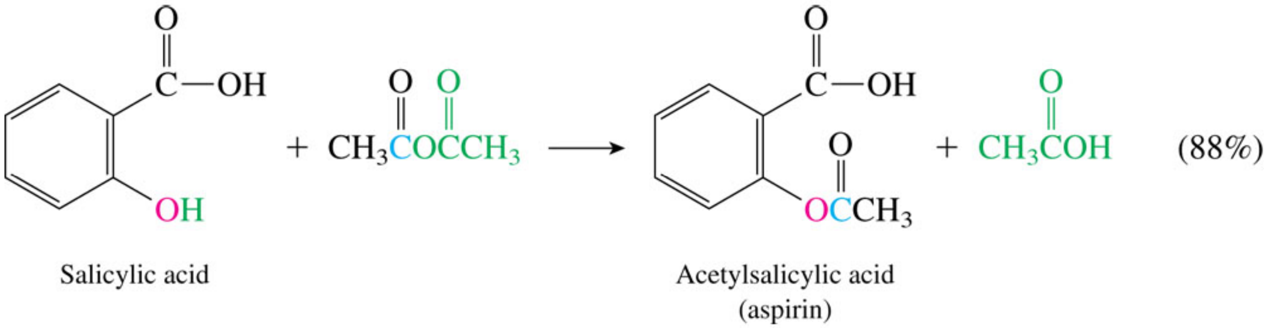

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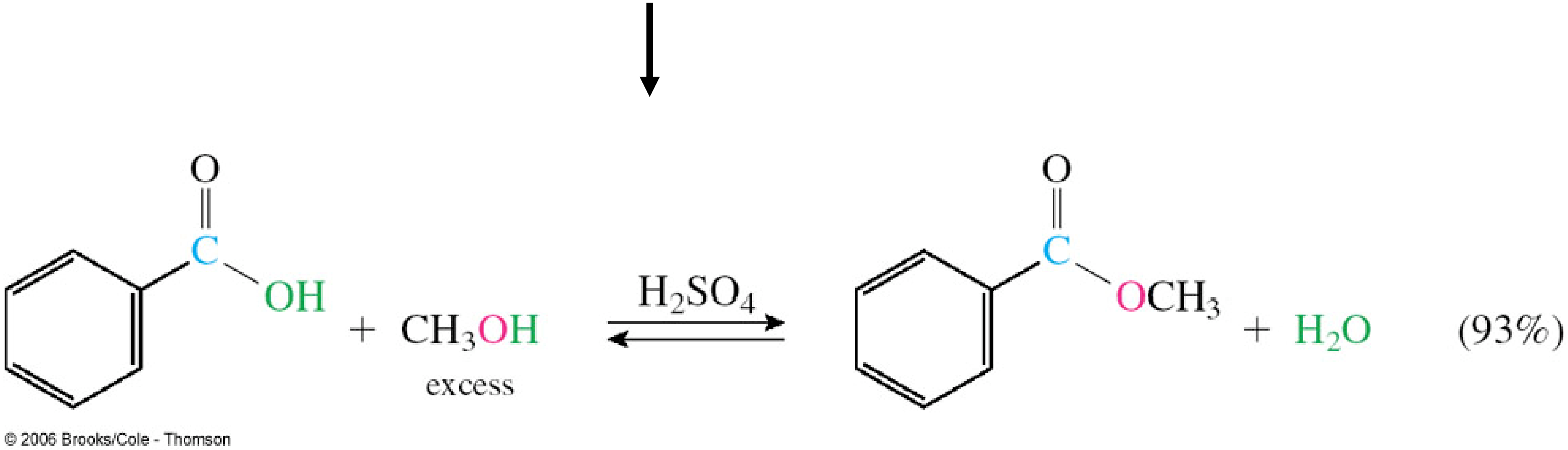
How?

2. By reaction of an alcohol with a carboxylic acid

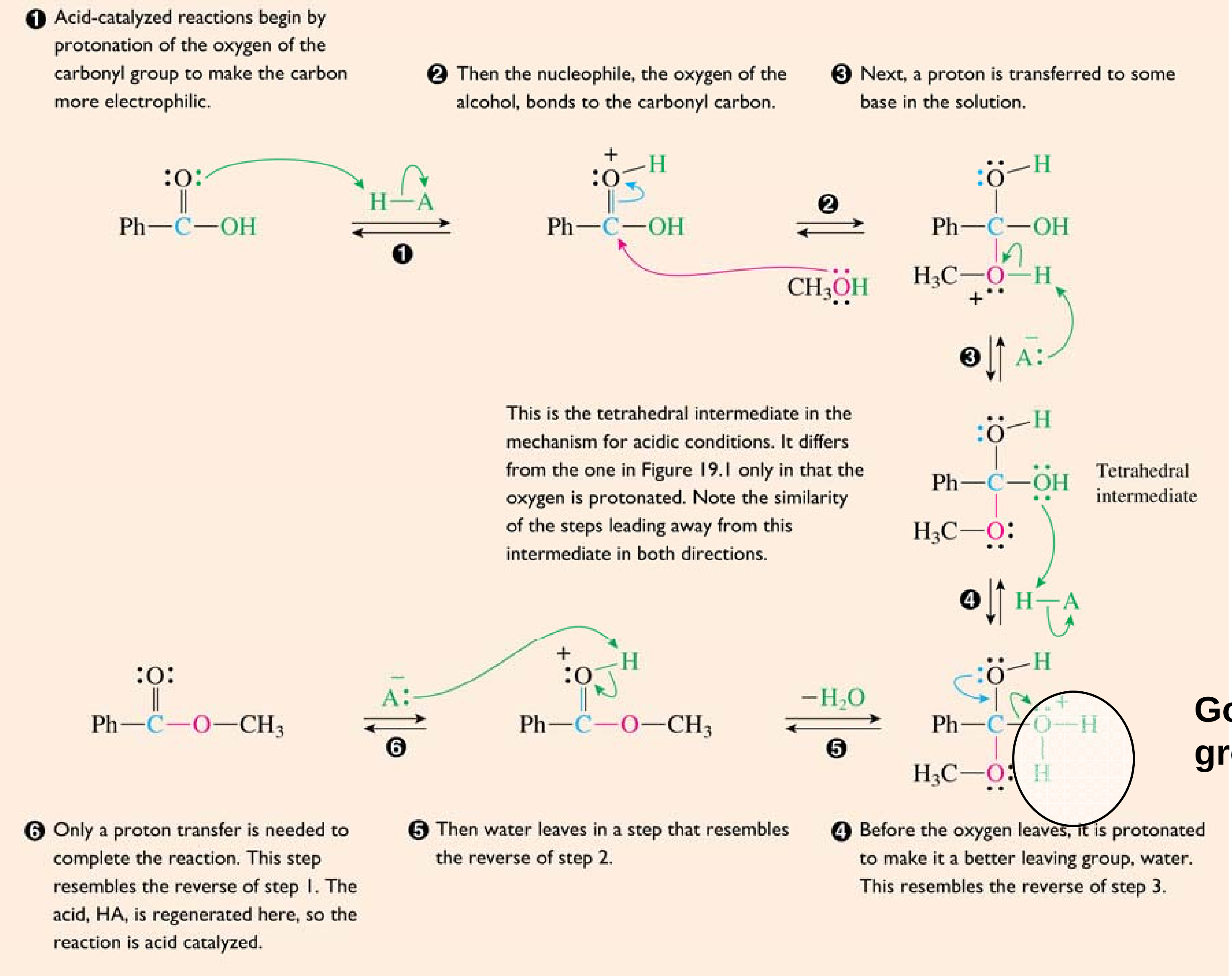
⇒ **Fisher esterification**



a. Using excess amount of alcohol: although K (0.1~1) is low, anyhow the product will be obtained

b. Removal of the water can derive the equilibrium to right

Fisher esterification



❶ Acid-catalyzed reactions begin by protonation of the oxygen of the carbonyl group to make the carbon more electrophilic.

❷ Then the nucleophile, the oxygen of the alcohol, bonds to the carbonyl carbon.

❸ Next, a proton is transferred to some base in the solution.

This is the tetrahedral intermediate in the mechanism for acidic conditions. It differs from the one in Figure 19.1 only in that the oxygen is protonated. Note the similarity of the steps leading away from this intermediate in both directions.

❻ Only a proton transfer is needed to complete the reaction. This step resembles the reverse of step 1. The acid, HA, is regenerated here, so the reaction is acid catalyzed.

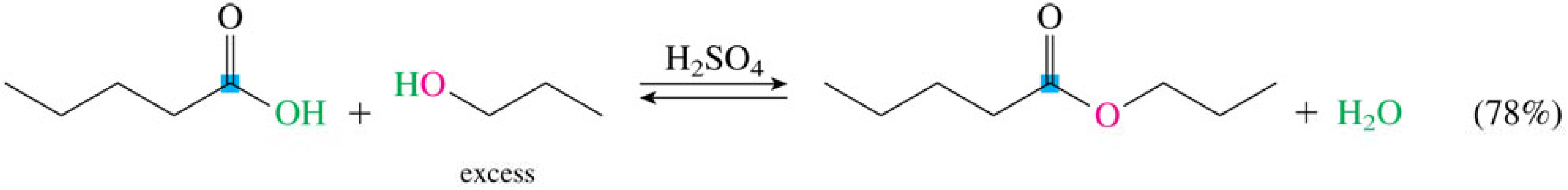
❺ Then water leaves in a step that resembles the reverse of step 2.

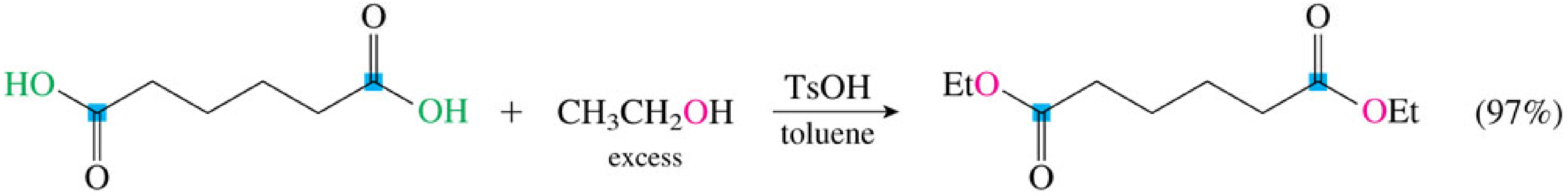
❹ Before the oxygen leaves, it is protonated to make it a better leaving group, water. This resembles the reverse of step 3.

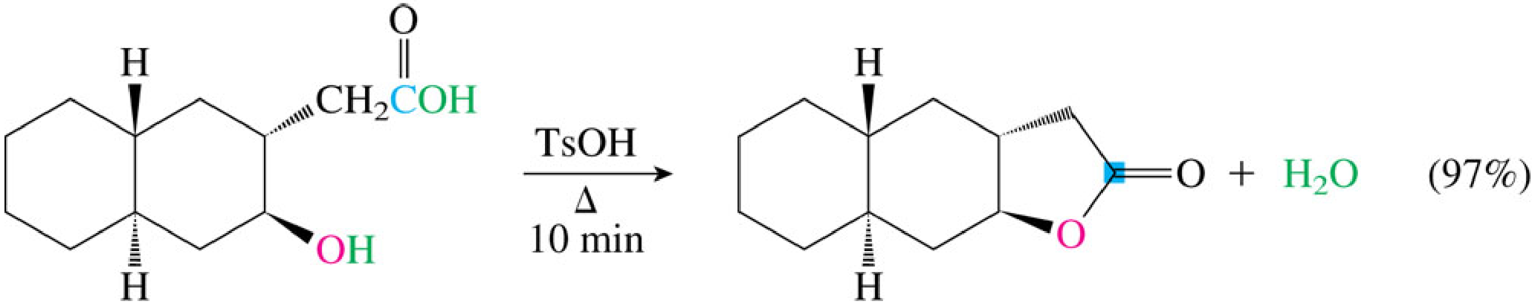
Good leaving group

Acid such as sulfuric acid, hydrochloric acid, or p-toluenesulfonic acid is used as a catalyst.

Examples







A lactone
(a cyclic ester)

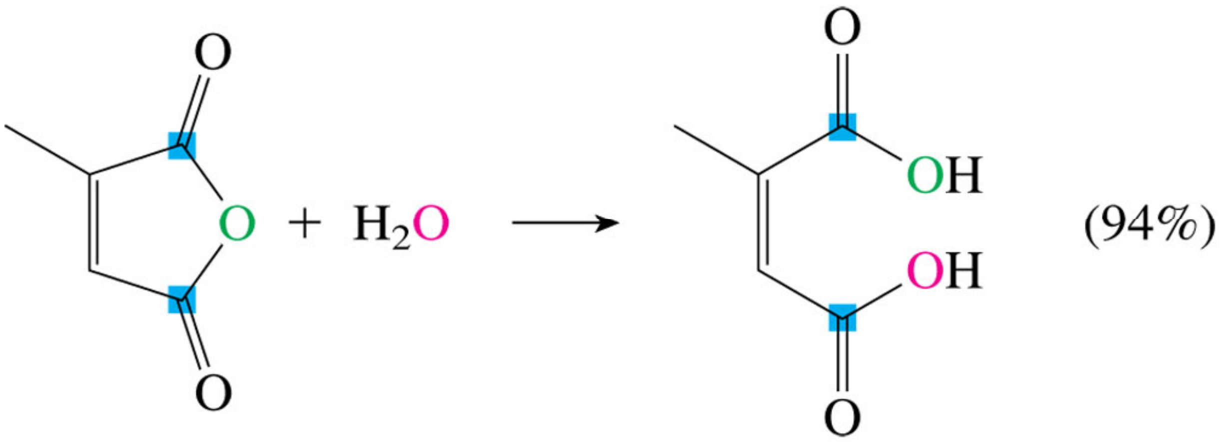
19.5 Preparation of Carboxylic Acids

How?

$$\text{Carboxylic acid derivatives} + H_2O \xrightarrow[\text{Acidic or basic condition}]{\text{Hydrolysis}} \text{Carboxylic acid}$$

1. From an acyl chloride or an anhydride

Just add some water → Vigorous reaction

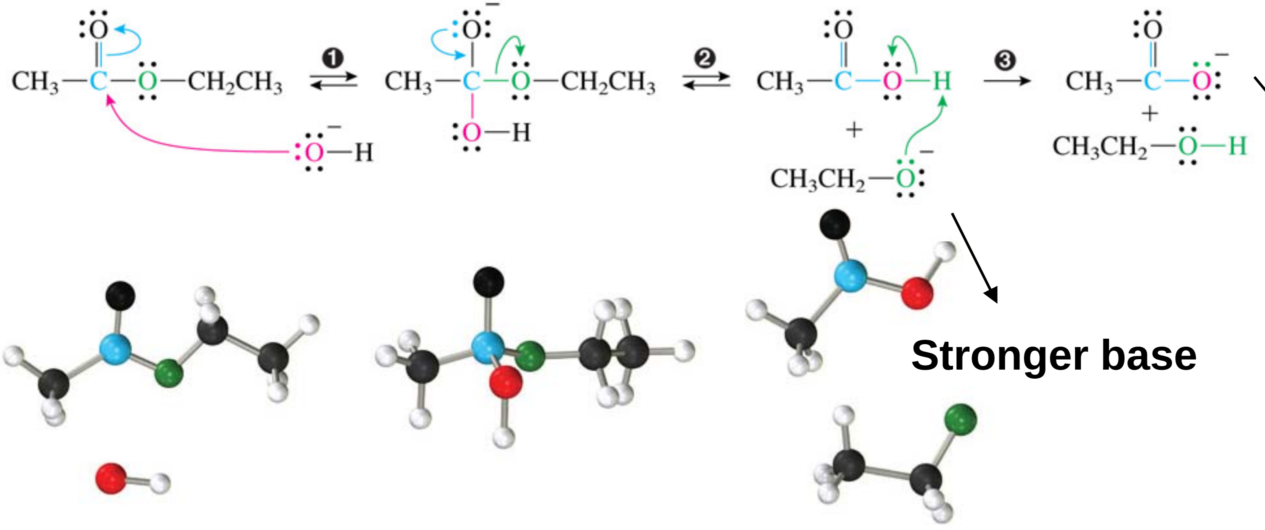


2. From Esters

Ester can be hydrolyzed under either acidic or basic conditions

a. Acidic condition: the reverse of the Fisher esterification

b. Basic condition: saponification



Stronger base

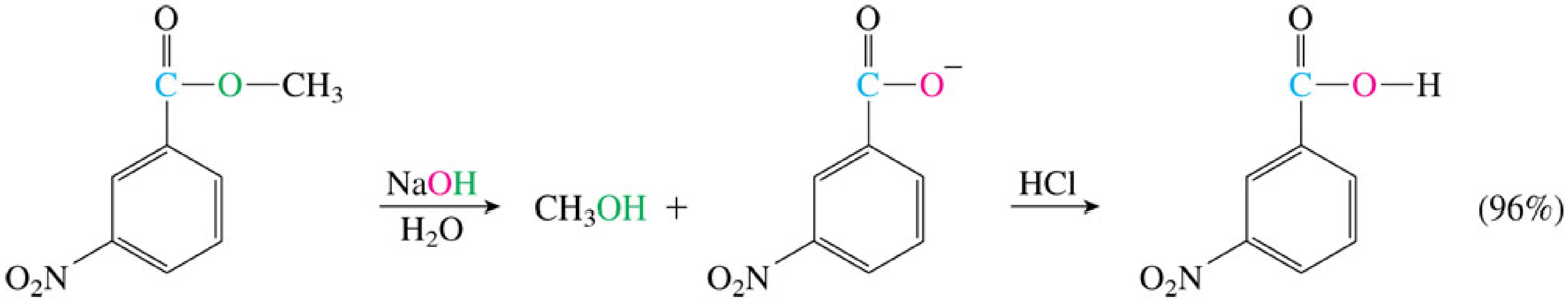
weaker base; more stable

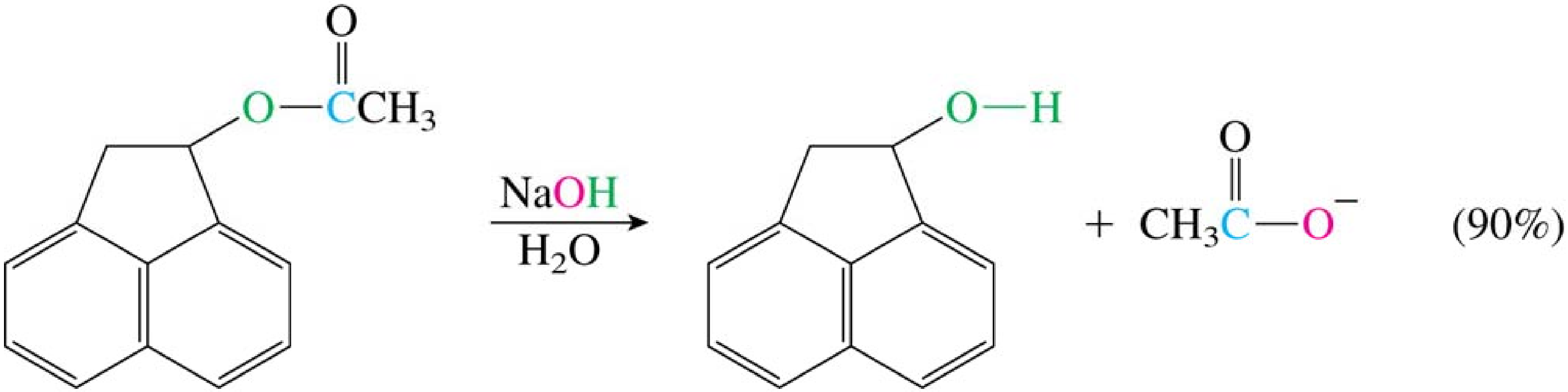
❶ This step is the same as the first step of Figure 19.1. The nucleophile, hydroxide ion in this case, bonds to the carbonyl carbon, displacing the pi electrons onto the oxygen.

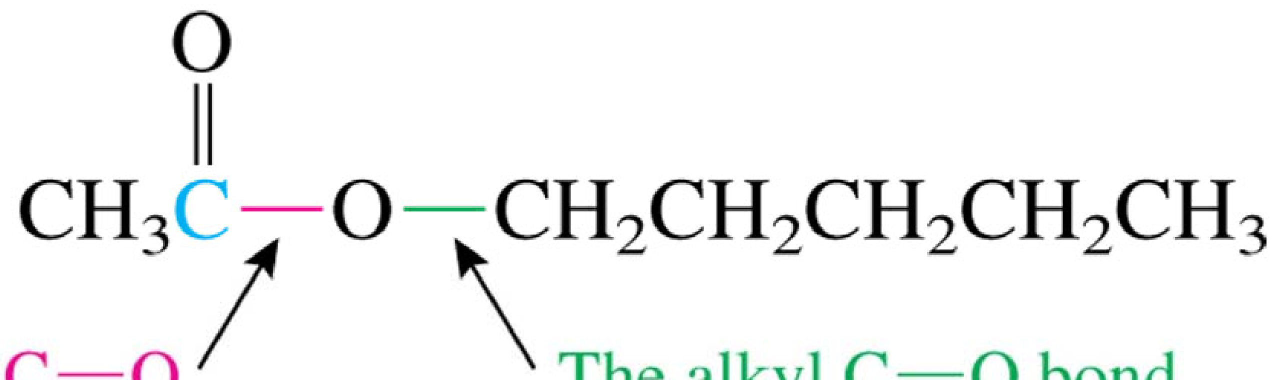
❷ Next, the leaving group, ethoxide ion, departs as an electron pair from the negative oxygen reforms the double bond of the carbonyl group.

❸ Ethoxide ion, a strong base, removes a proton from acetic acid. The formation of the weak base, acetate ion, in this step drives the equilibrium to the final products, the alcohol and the carboxylate anion.

Examples


O
C—O—CH3
O2N
NaOH
H2O
CH3OH +
O
C—O−
O2N
HCl
O
C—O—H
O2N
(96%)


O
O—CCH3
NaOH
H2O
O—H
O
+ CH3C—O−
(90%)

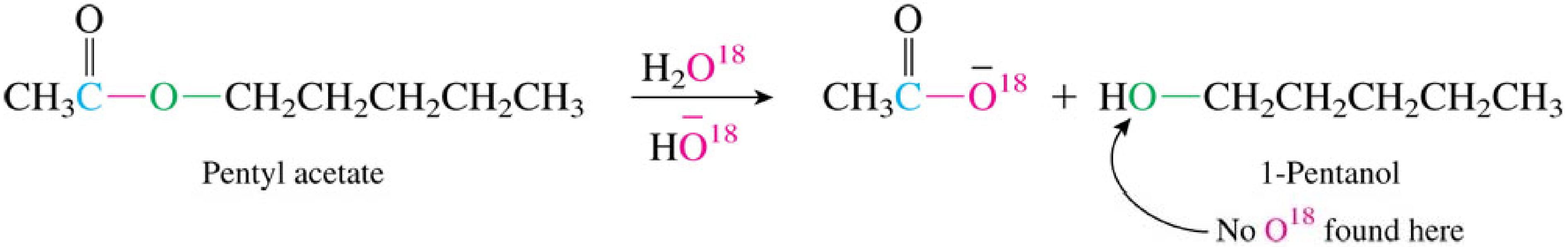


$$CH_3\overset{O}{\overset{\|}{C}}-O-CH_2CH_2CH_2CH_2CH_3$$

The acyl C—O bond is cleaved.

The alkyl C—O bond remains intact.

Clue



$$CH_3\overset{O}{\overset{\|}{C}}-O-CH_2CH_2CH_2CH_2CH_3 \xrightarrow[H\bar{O}^{18}]{H_2O^{18}} CH_3\overset{O}{\overset{\|}{C}}-\bar{O}^{18} + HO-CH_2CH_2CH_2CH_2CH_3$$

Pentyl acetate

1-Pentanol

No O^{18} found here

3. From Amide (Amide Hydrolysis)

Amide is less reactive than ester!

Therefore it requires vigorous heating in acidic or basic conditions

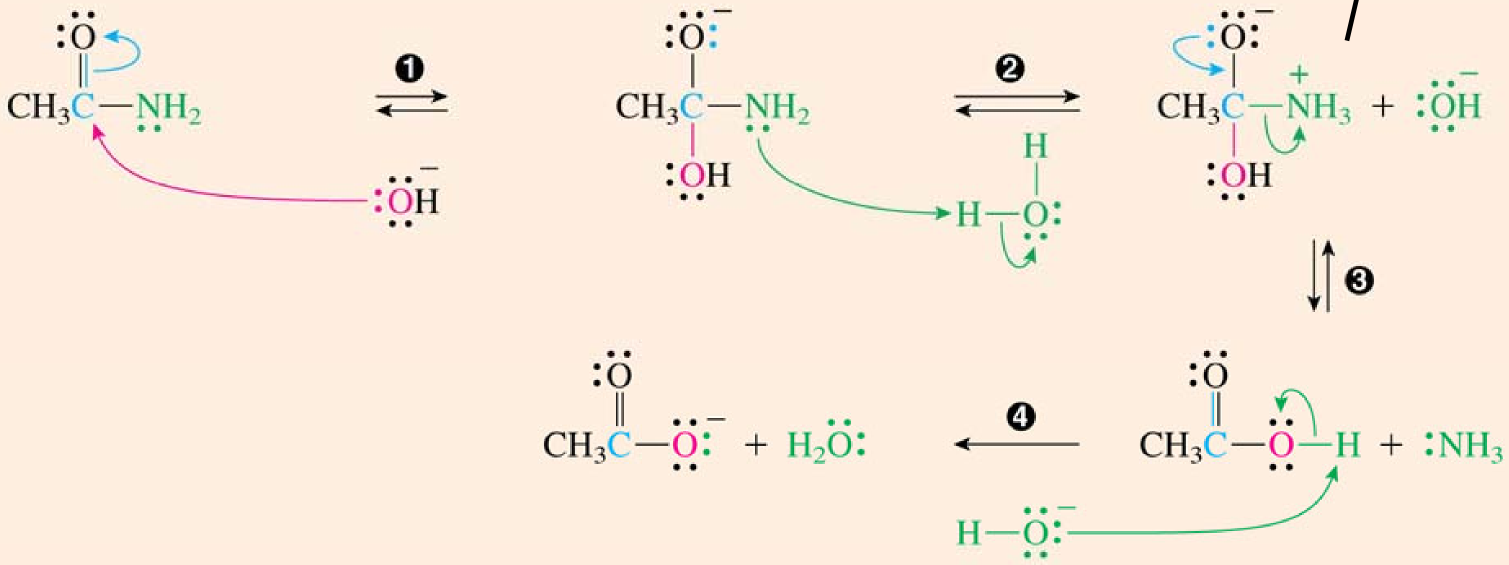
Mechanism in basic condition

❶ A hydroxide ion nucleophile bonds to the carbon of the carbonyl group, exactly as the mechanism for the saponification of an ester begins.

❷ At this point, this mechanism deviates slightly from the ester saponification mechanism. Because amide ion (NH_2^-) is a poor leaving group, the nitrogen is first protonated by the solvent to convert it to a better leaving group.

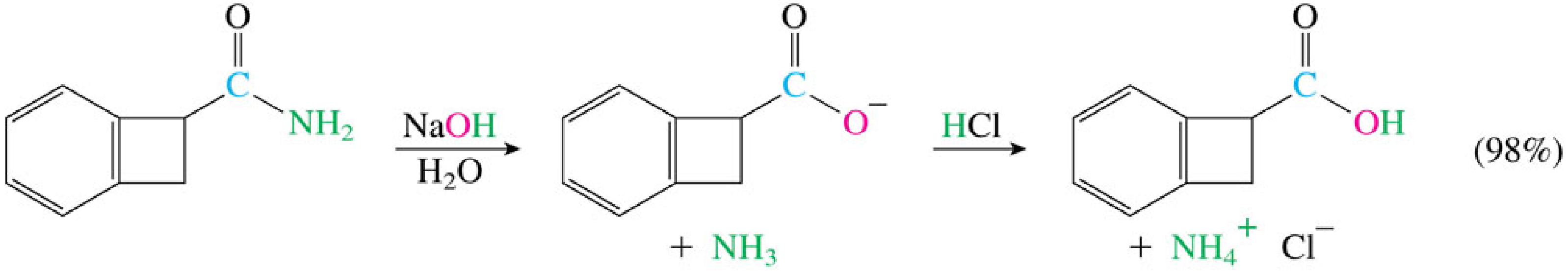
$-NH_3^+$ is bettern leving group than $-NH_2$

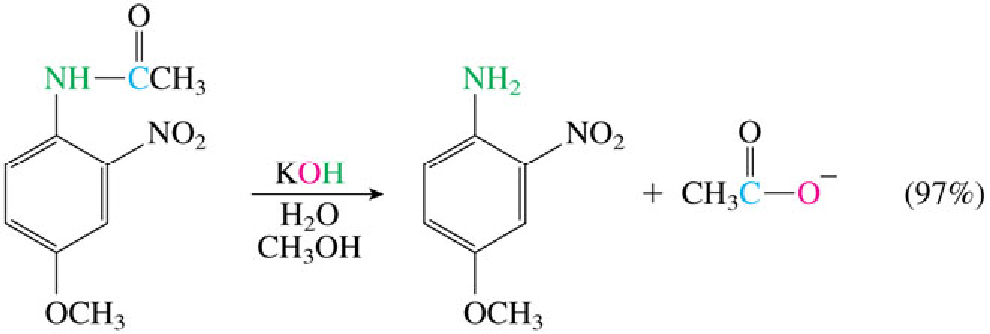
❸ Ammonia leaves while an electron pair from the negative oxygen reforms the double bond of the carbonyl group.

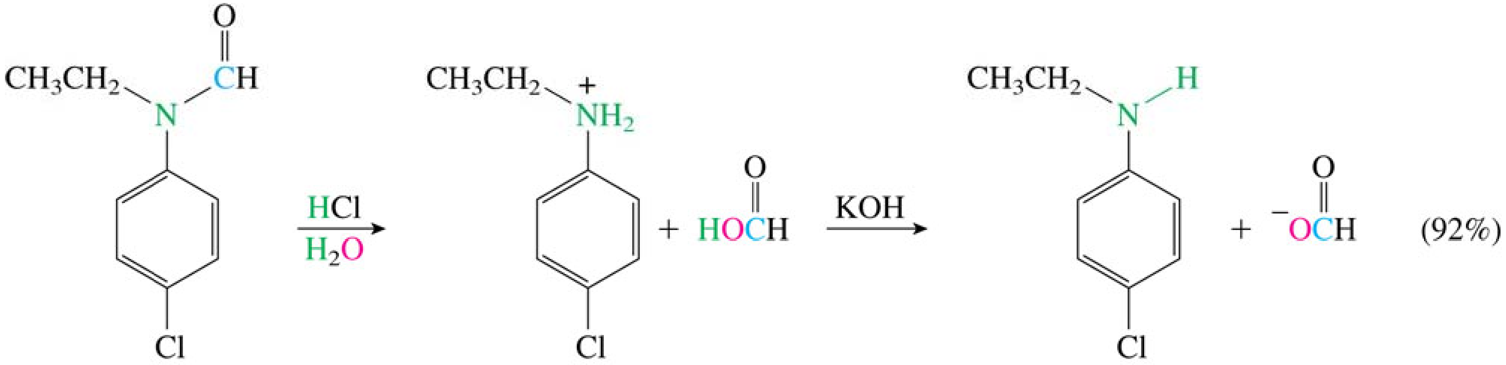


❹ A proton transfer from the carboxylic acid to a hydroxide ion completes the process.

Examples



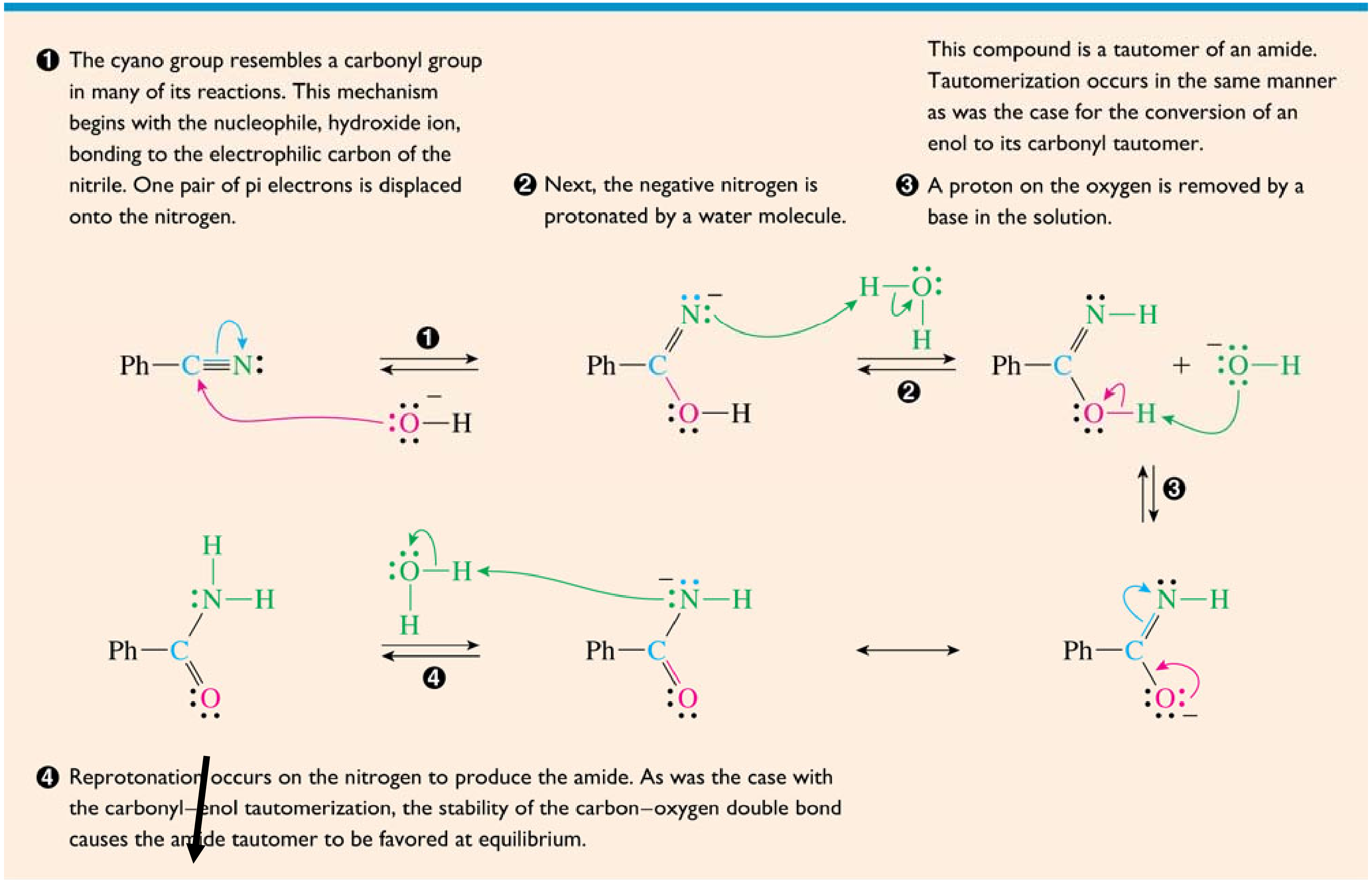




4. From Nitrile (Nitrile Hydrolysis)

Nitrile → Amide → Carboxylic acid

basic or acidic conditions



❶ The cyano group resembles a carbonyl group in many of its reactions. This mechanism begins with the nucleophile, hydroxide ion, bonding to the electrophilic carbon of the nitrile. One pair of pi electrons is displaced onto the nitrogen.

❷ Next, the negative nitrogen is protonated by a water molecule.

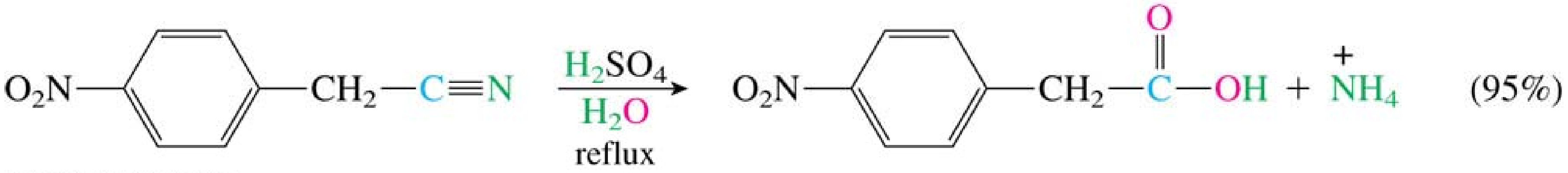
This compound is a tautomer of an amide. Tautomerization occurs in the same manner as was the case for the conversion of an enol to its carbonyl tautomer.

❸ A proton on the oxygen is removed by a base in the solution.

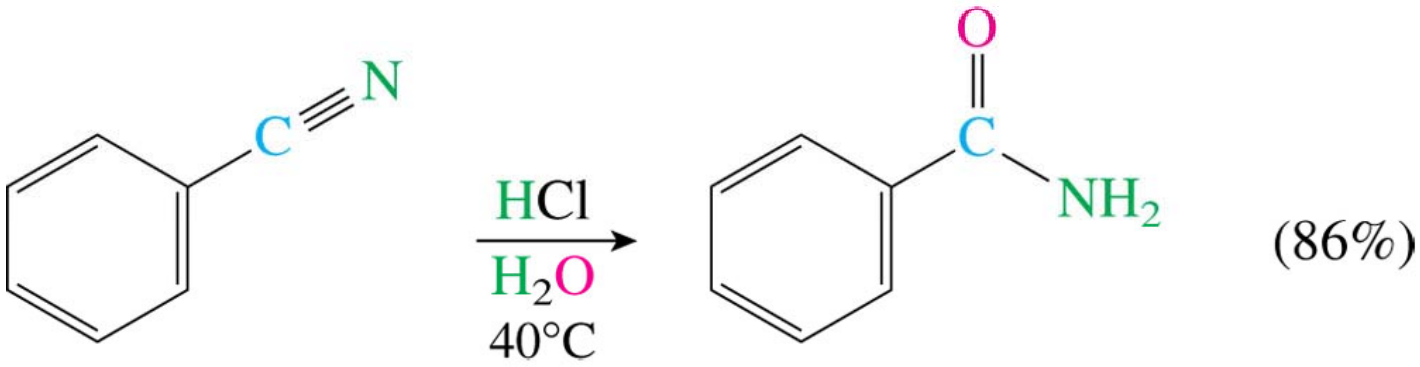
❹ Reprotonation occurs on the nitrogen to produce the amide. As was the case with the carbonyl–enol tautomerization, the stability of the carbon–oxygen double bond causes the amide tautomer to be favored at equilibrium.

Carboxylic acid

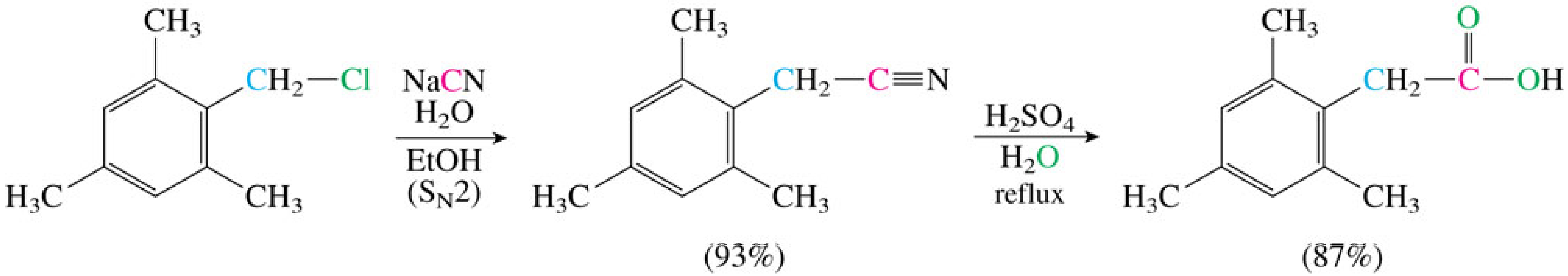
Examples



O_2N
CH_2
$C\equiv N$
H_2SO_4
H_2O
reflux
O
O_2N
CH_2
C
OH
+
$\overset{+}{N}H_4$
(95%)



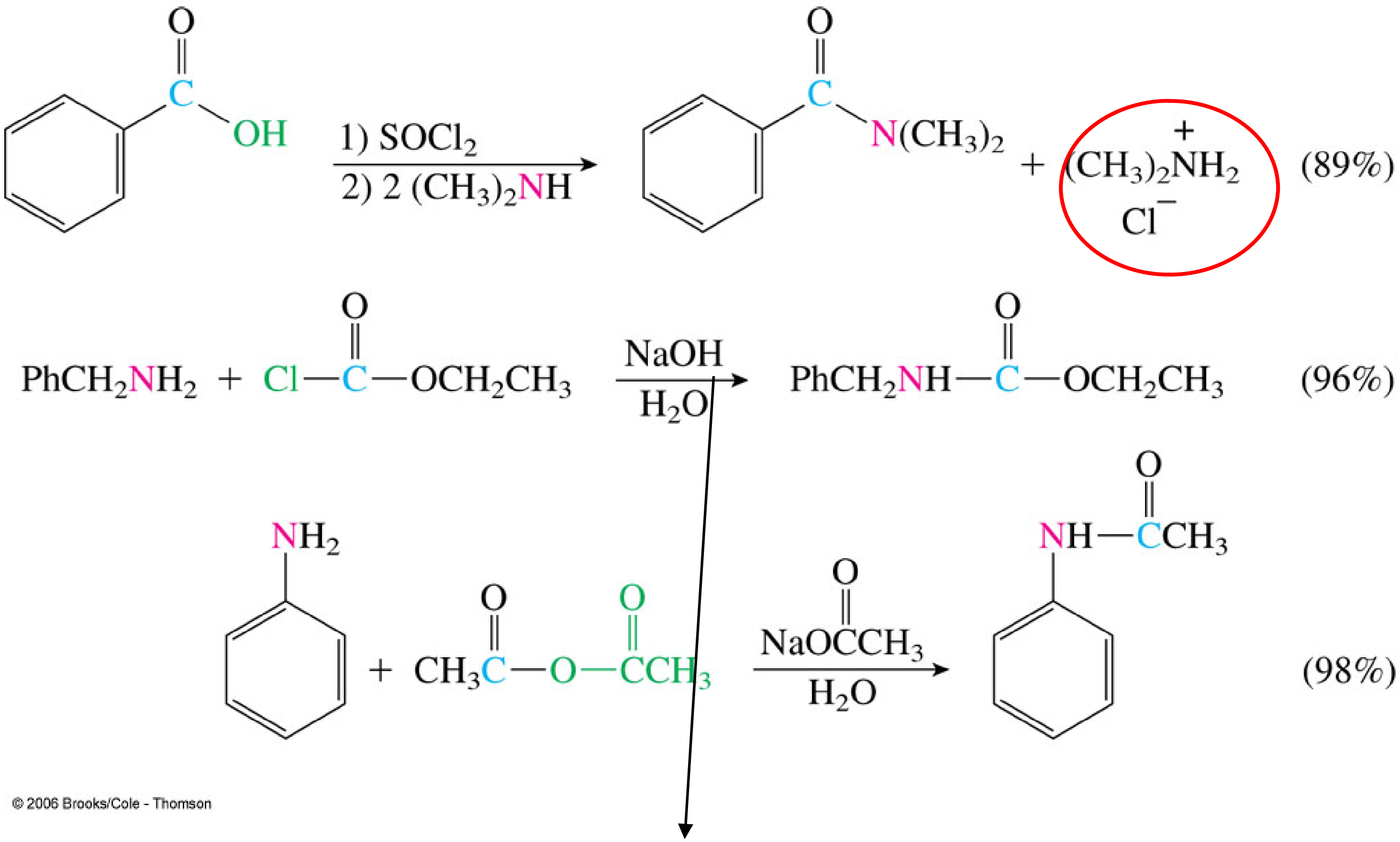
C
N
HCl
H_2O
40°C
O
C
NH_2
(86%)



CH_3
CH_2
Cl
H_3C
CH_3
NaCN
H_2O
EtOH
(S_N2)
CH_3
CH_2
$C\equiv N$
H_3C
CH_3
(93%)
H_2SO_4
H_2O
reflux
CH_3
O
CH_2
C
OH
H_3C
CH_3
(87%)

19.6 Preparation of Amides

By the reaction of an acyl chloride or an anhydride with ammonia or an amine



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To make the rxn condition not too acidic: HCl is the by product.

In acidic condition → hydrolysis

How about carboxylic acid + amine ?

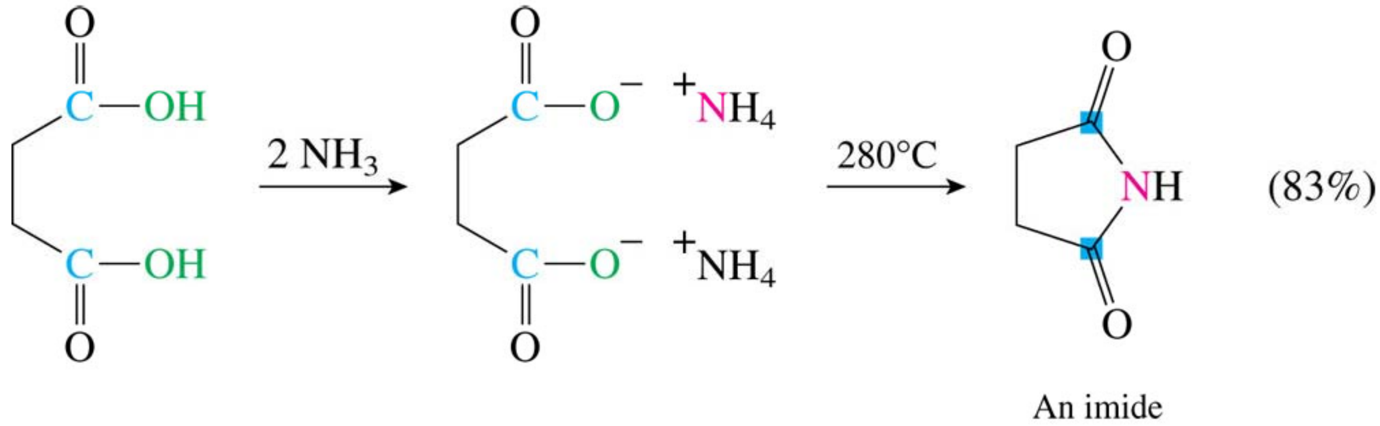
Then carboxylate anion and the ammonium cation are formed !

Because of the acid base reaction.

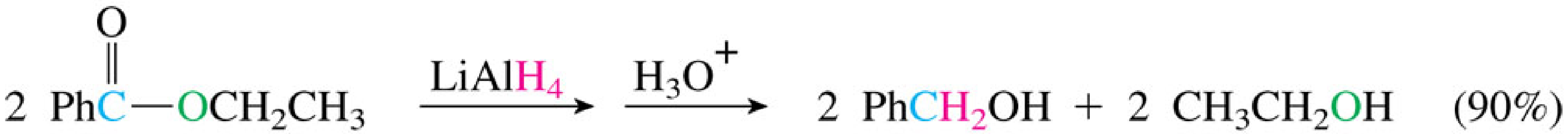
Vigorous heating: water is distilled off

Amide

Example



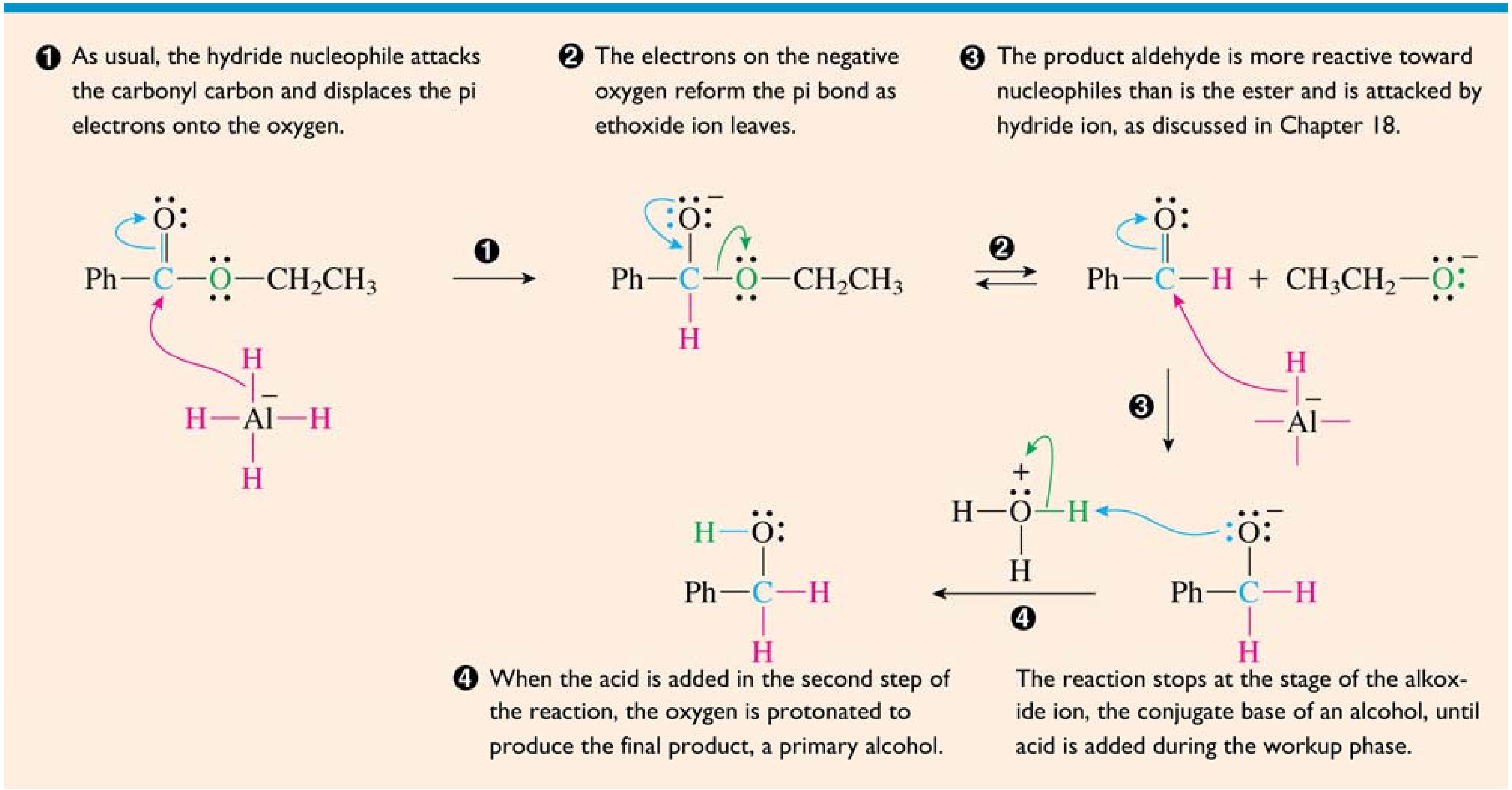
19.7 Reaction with Hydride Nucleophiles



$$2\ \mathrm{Ph}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{{-}OCH_2CH_3} \xrightarrow{\mathrm{LiAlH_4}} \xrightarrow{\mathrm{H_3O^+}} 2\ \mathrm{PhCH_2OH} + 2\ \mathrm{CH_3CH_2OH} \quad (90\%)$$

workup

Mechanism



❶ As usual, the hydride nucleophile attacks the carbonyl carbon and displaces the pi electrons onto the oxygen.

❷ The electrons on the negative oxygen reform the pi bond as ethoxide ion leaves.

❸ The product aldehyde is more reactive toward nucleophiles than is the ester and is attacked by hydride ion, as discussed in Chapter 18.

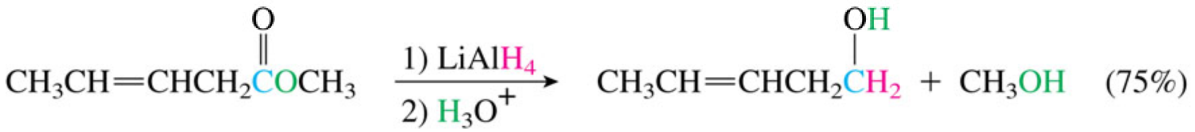
❹ When the acid is added in the second step of the reaction, the oxygen is protonated to produce the final product, a primary alcohol.

The reaction stops at the stage of the alkoxide ion, the conjugate base of an alcohol, until acid is added during the workup phase.

H^- is a very strong nucleophile

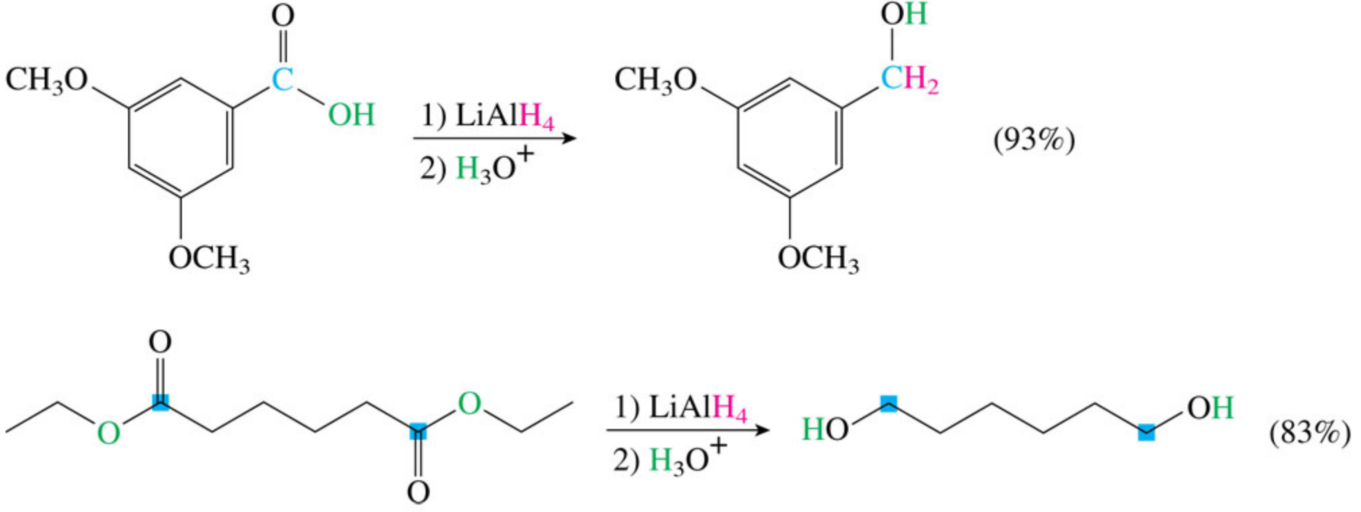
1. **One $LiAlH_4$ can reduce two ester**
2. **If less $LiAlH_4$ is used, still ester and alcohol is formed (no aldehyde), because the aldehyde reacts with the hydride as fast as it is formed. Aldehyde is more reactive than ester!**

Examples

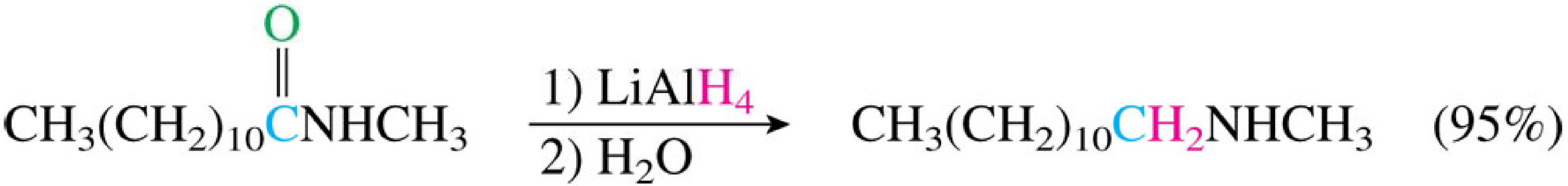


$$CH_3CH{=}CHCH_2\overset{O}{\overset{\|}{C}}OCH_3 \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4} CH_3CH{=}CHCH_2\overset{OH}{\overset{|}{C}}H_2 + CH_3OH \quad (75\%)$$

Not the double bond !

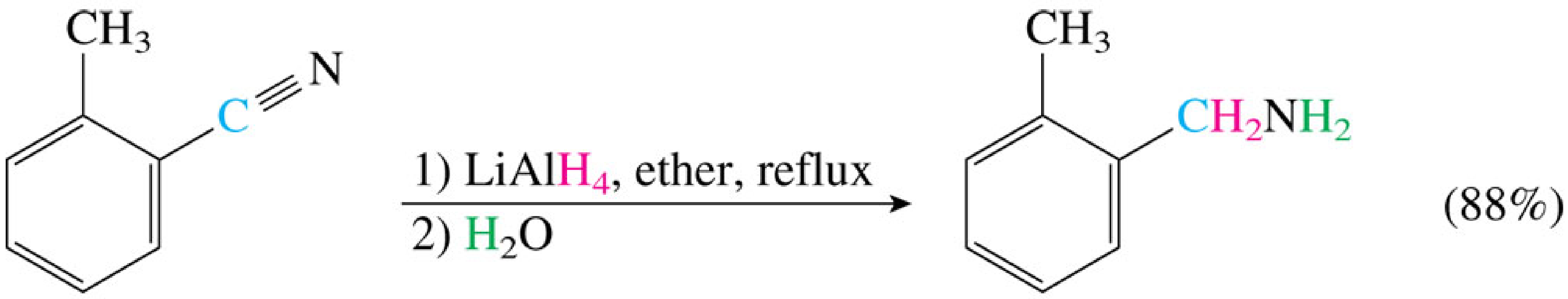


Reduction of amide with $LiAlH_4$



$$CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}NHCH_3 \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} CH_3(CH_2)_{10}CH_2NHCH_3 \quad (95\%)$$

Reduction of Nitrile with $LiAlH_4$

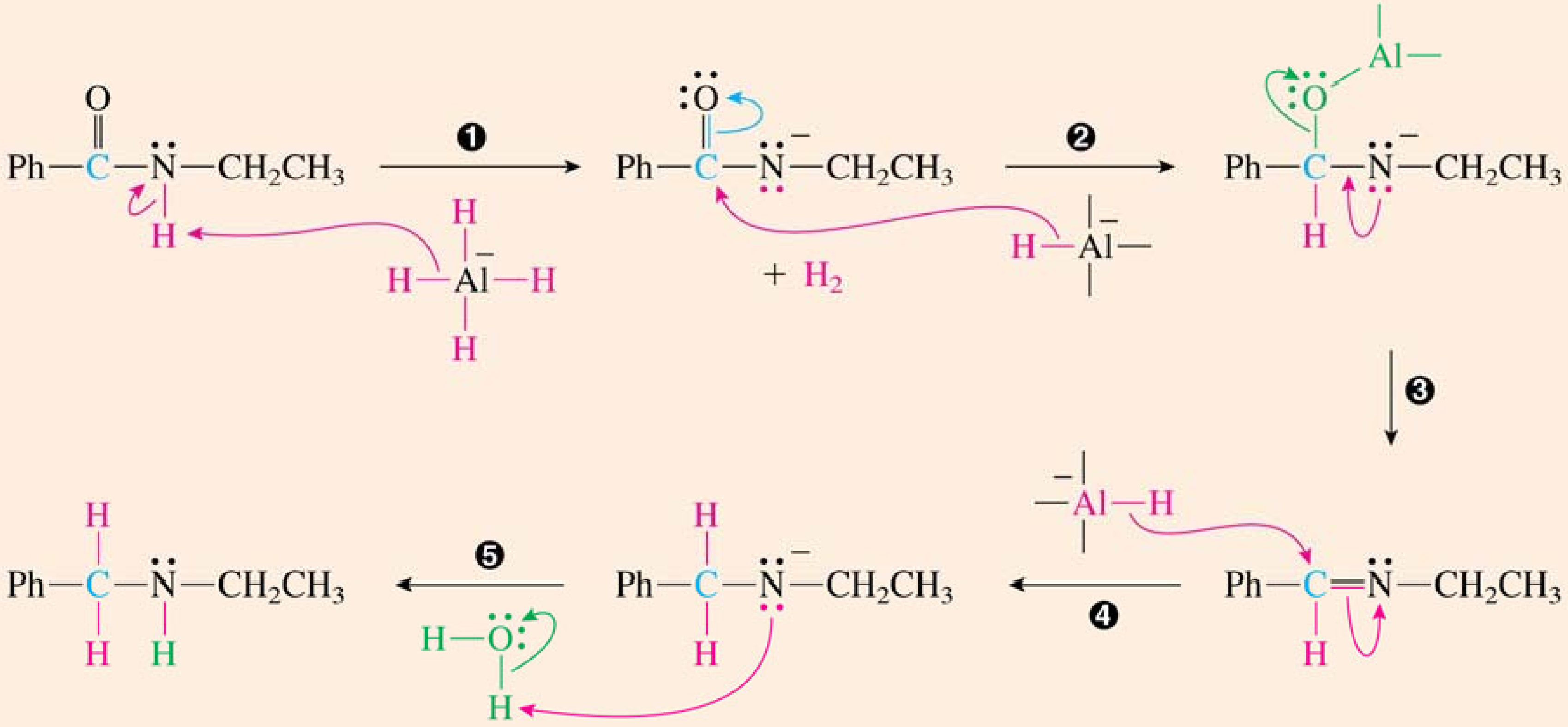


Mechanism for the reduction of an amide to an amine

❶ Like the reaction shown in Figure 19.8, the mechanism begins with the basic hydride ion removing an acidic proton. Here, it is the proton on the nitrogen.

❷ Next, another hydride ion acts as a nucleophile, attacking the carbon of the carbonyl group.

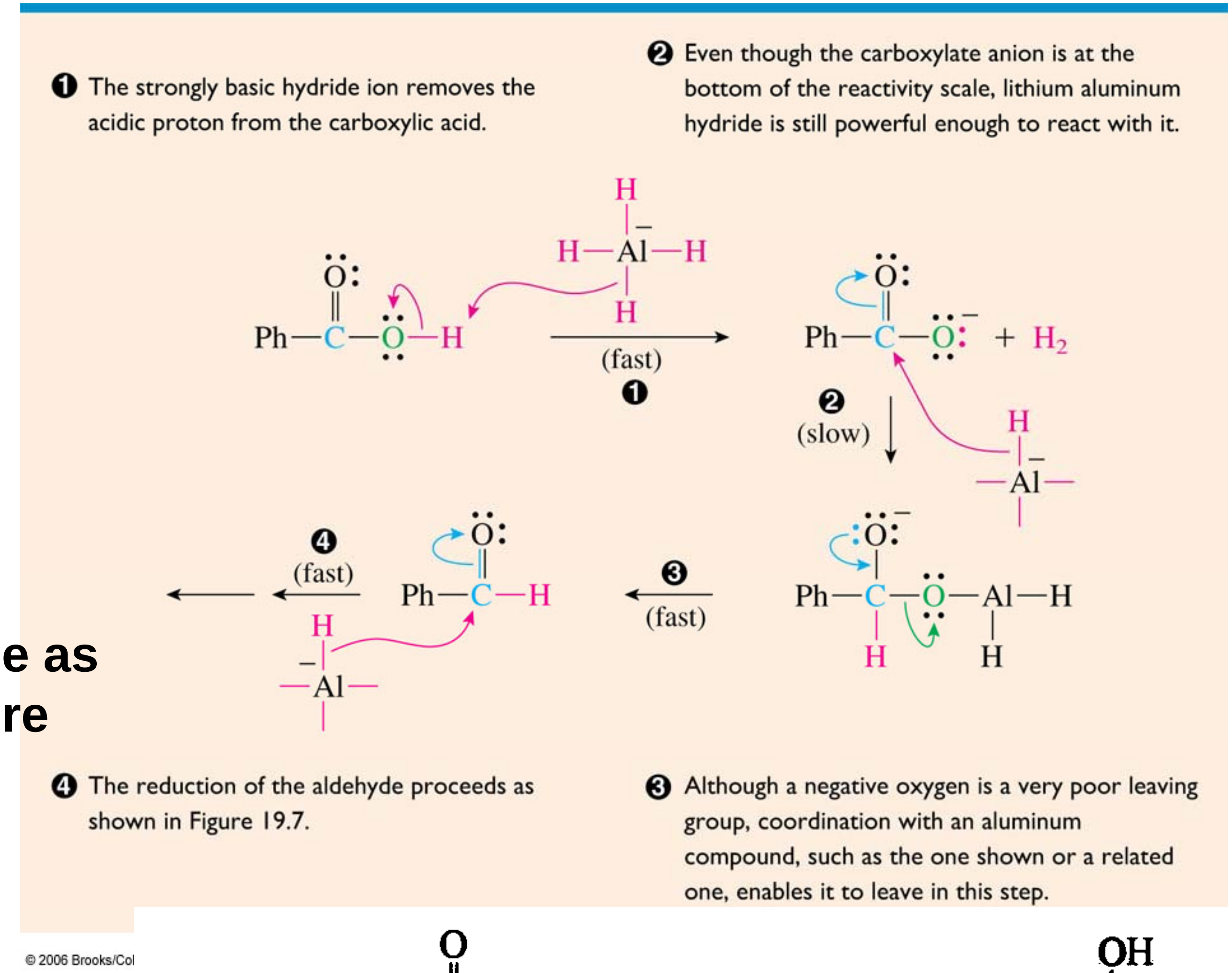
❸ The oxygen, coordinated with aluminum, leaves in this step rather than the nitrogen because the oxygen is a weaker base and therefore a better leaving group.



❺ The final step in the mechanism is protonation of the negative nitrogen by water that is added during the workup.

❹ The carbon–nitrogen double bond of the imine is attacked by the hydride nucleophile just like a carbon–oxygen double bond.

Reduction of carboxylic acids



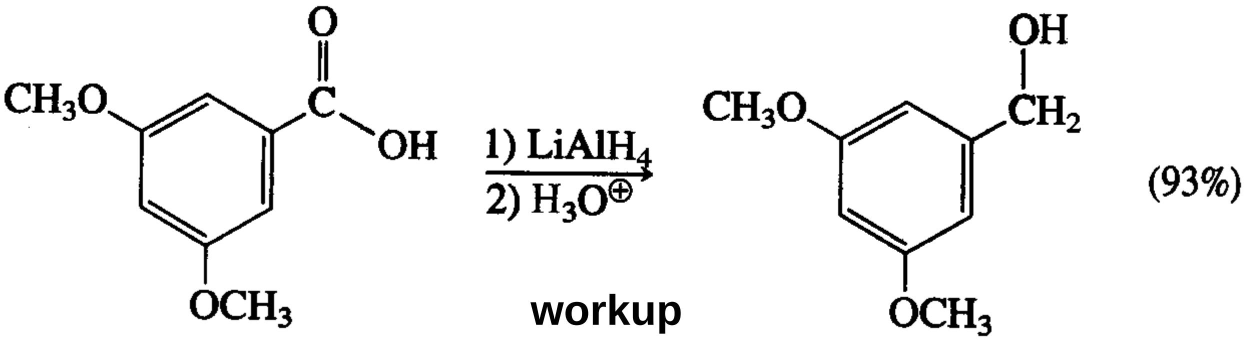
❶ The strongly basic hydride ion removes the acidic proton from the carboxylic acid.

❷ Even though the carboxylate anion is at the bottom of the reactivity scale, lithium aluminum hydride is still powerful enough to react with it.

❸ Although a negative oxygen is a very poor leaving group, coordination with an aluminum compound, such as the one shown or a related one, enables it to leave in this step.

❹ The reduction of the aldehyde proceeds as shown in Figure 19.7.

Same as before

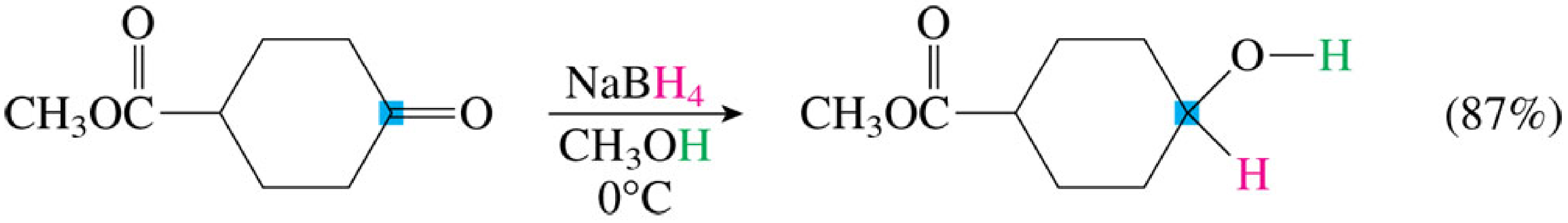


workup

Sodium borohydride ($NaBH_4$)

→ **much less reactive than $LiAlH_4$**

→ **can reduce aldehydes or ketones, while cannot reduce esters**



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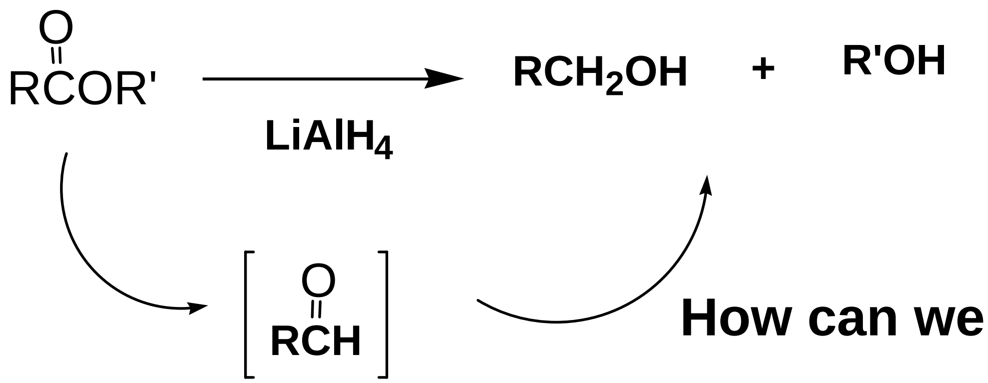
19.8 Reduction of Acid Derivatives to Aldehyde



How can we get aldehyde?

$RCOCl > RCO_2COR > \underline{RCOH} > RCO_2R > RCO_2H > RCONH_2 > RCO_2^-$

$\longleftarrow$

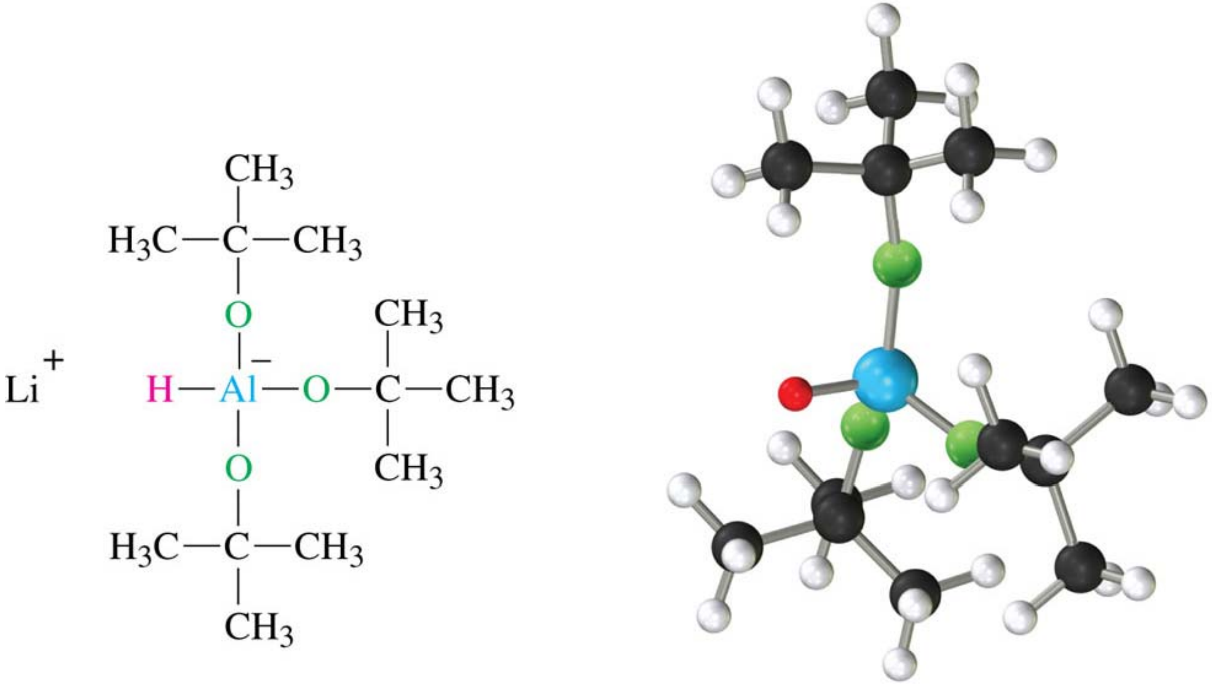
Unstable (high reactivity)

Stable (low reactivity)

To get aldehyde, use RCOCl or RCO_2COR + lithium tri-*t*-butoxyaluminum hydride

1. use RCOCl or RCO_2COR + lithium tri-*t*-butoxyaluminum hydride

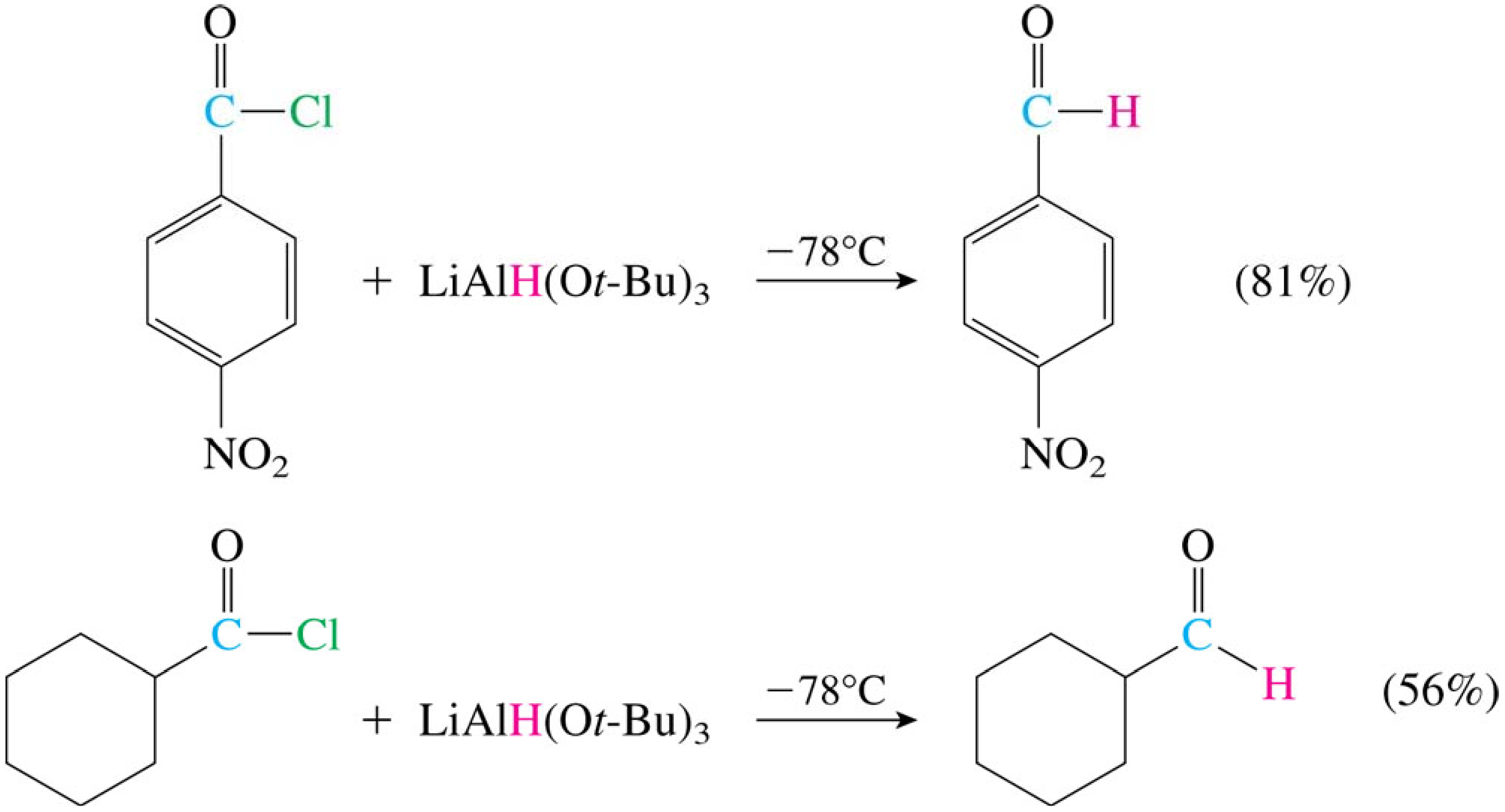
Lithium tri-*t*-butoxyaluminum hydride



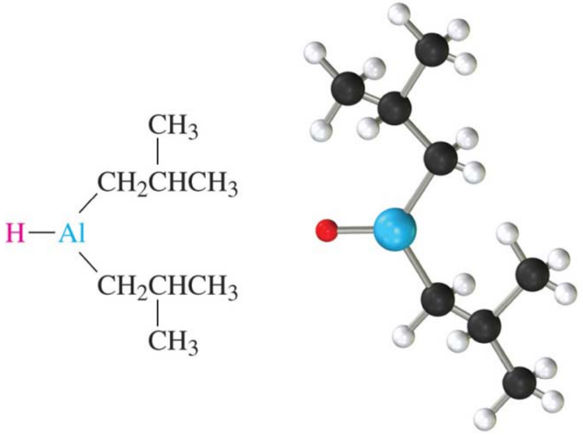
Lithium tri-*t*-butoxyaluminum hydride [$LiAlH(Ot\text{-}Bu)_3$]
(reduces an acyl chloride but not an aldehyde)

At low temperature (-78 ^oC), it does not react with aldehyde, probably due to the steric effect

Examples

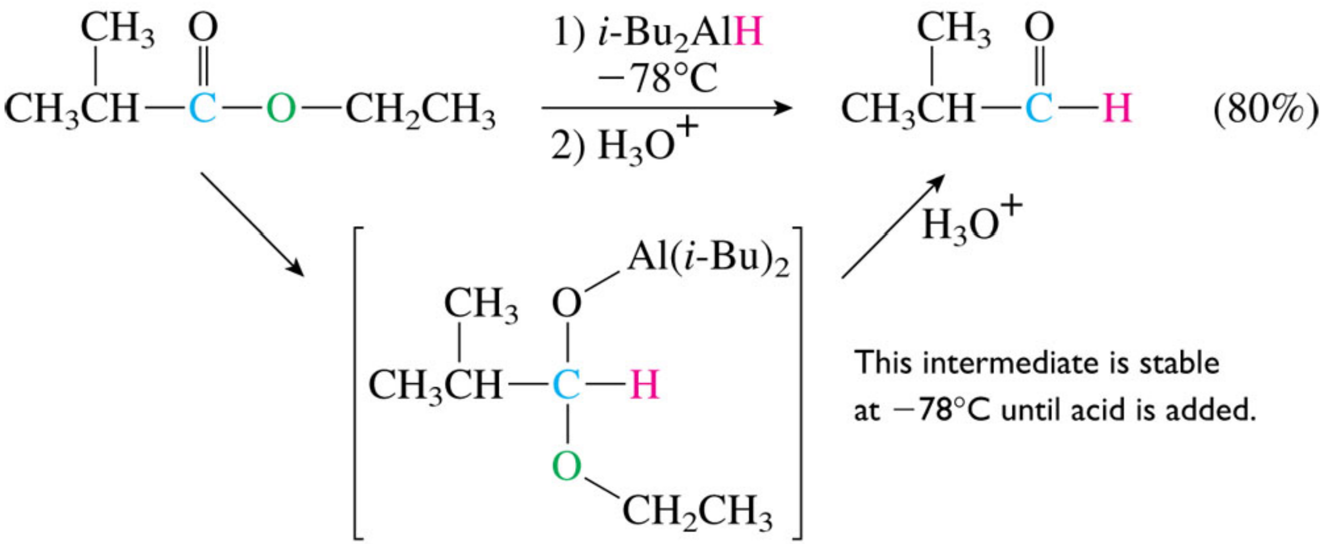

O
C
Cl
NO2
+ LiAlH(Ot-Bu)3
−78°C
O
C
H
NO2
(81%)
O
C
Cl
+ LiAlH(Ot-Bu)3
−78°C
O
C
H
(56%)

2.Use diisobutylaluminium hydride to reduce esters to aldehyde at low temperatures



Diisobutylaluminum hydride
(DIBALH or i-Bu_2AlH)

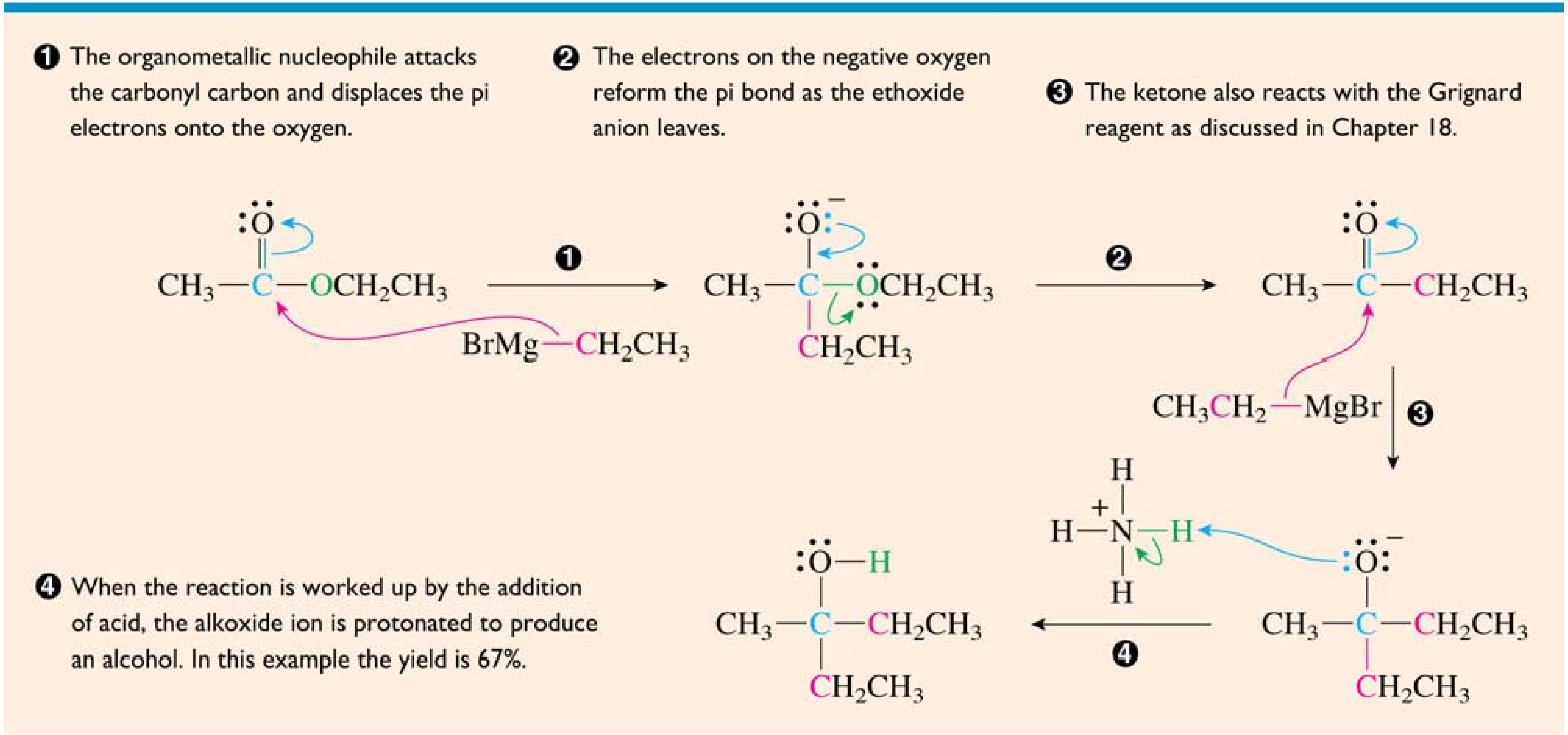
Example



This intermediate is stable at −78°C until acid is added.

19.9 Reactions with Organometallic Nucleophiles

The reaction of Grignard reagents with esters



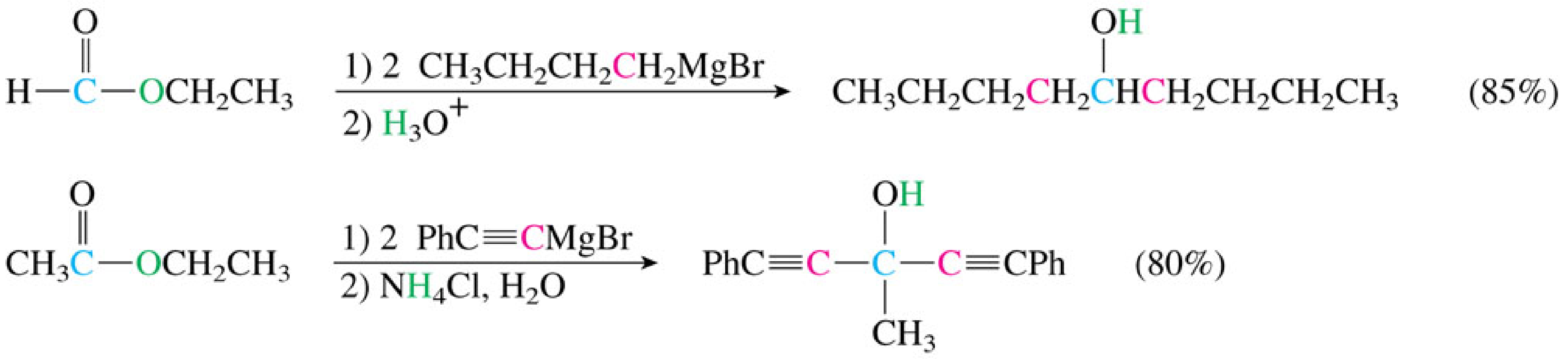
❶ The organometallic nucleophile attacks the carbonyl carbon and displaces the pi electrons onto the oxygen.

❷ The electrons on the negative oxygen reform the pi bond as the ethoxide anion leaves.

❸ The ketone also reacts with the Grignard reagent as discussed in Chapter 18.

❹ When the reaction is worked up by the addition of acid, the alkoxide ion is protonated to produce an alcohol. In this example the yield is 67%.

Examples

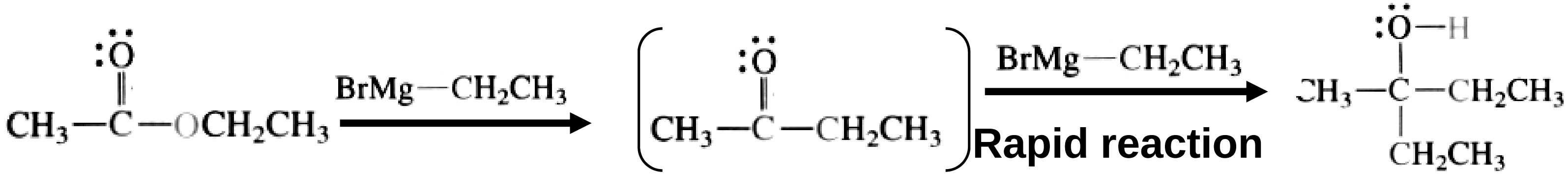


$$H-\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_3 \xrightarrow[\text{2) } H_3O^+]{\text{1) 2 } CH_3CH_2CH_2CH_2MgBr} CH_3CH_2CH_2CH_2\overset{\overset{\displaystyle OH}{|}}{C}HCH_2CH_2CH_2CH_3 \quad (85\%)$$

$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}-OCH_2CH_3 \xrightarrow[\text{2) } NH_4Cl,\ H_2O]{\text{1) 2 } PhC\equiv CMgBr} PhC\equiv C-\underset{\underset{\displaystyle CH_3}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}-C\equiv CPh \quad (80\%)$$

19.10 Preparation of Ketones

Cannot be prepared using Grignard reagent



Rapid reaction

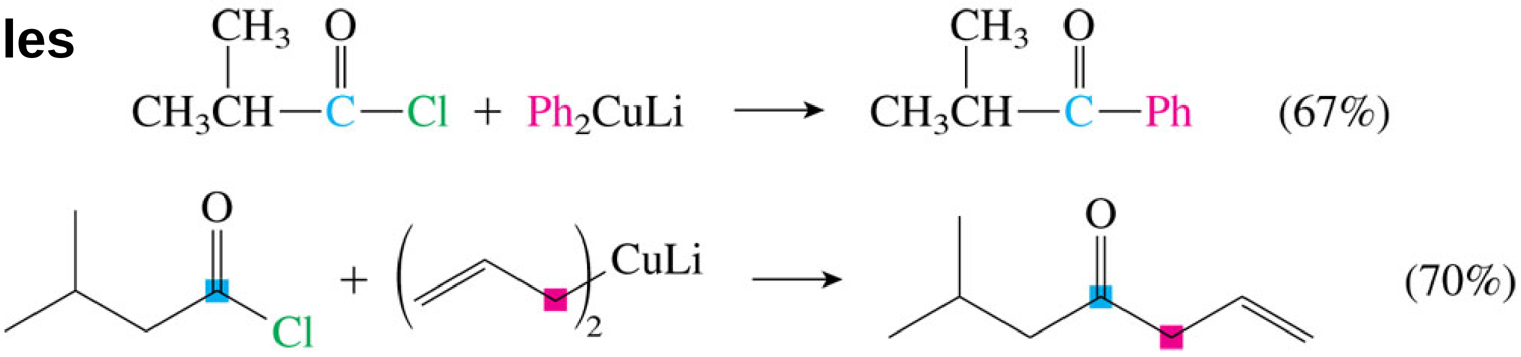
Then how?

1. Using lithium diorganocuprate with acyl chloride

$$\longrightarrow \quad 2\ CH_3Li + CuI \longrightarrow (CH_3)_2CuLi + LiI$$

Methyllithium — Lithium dimethylcuprate

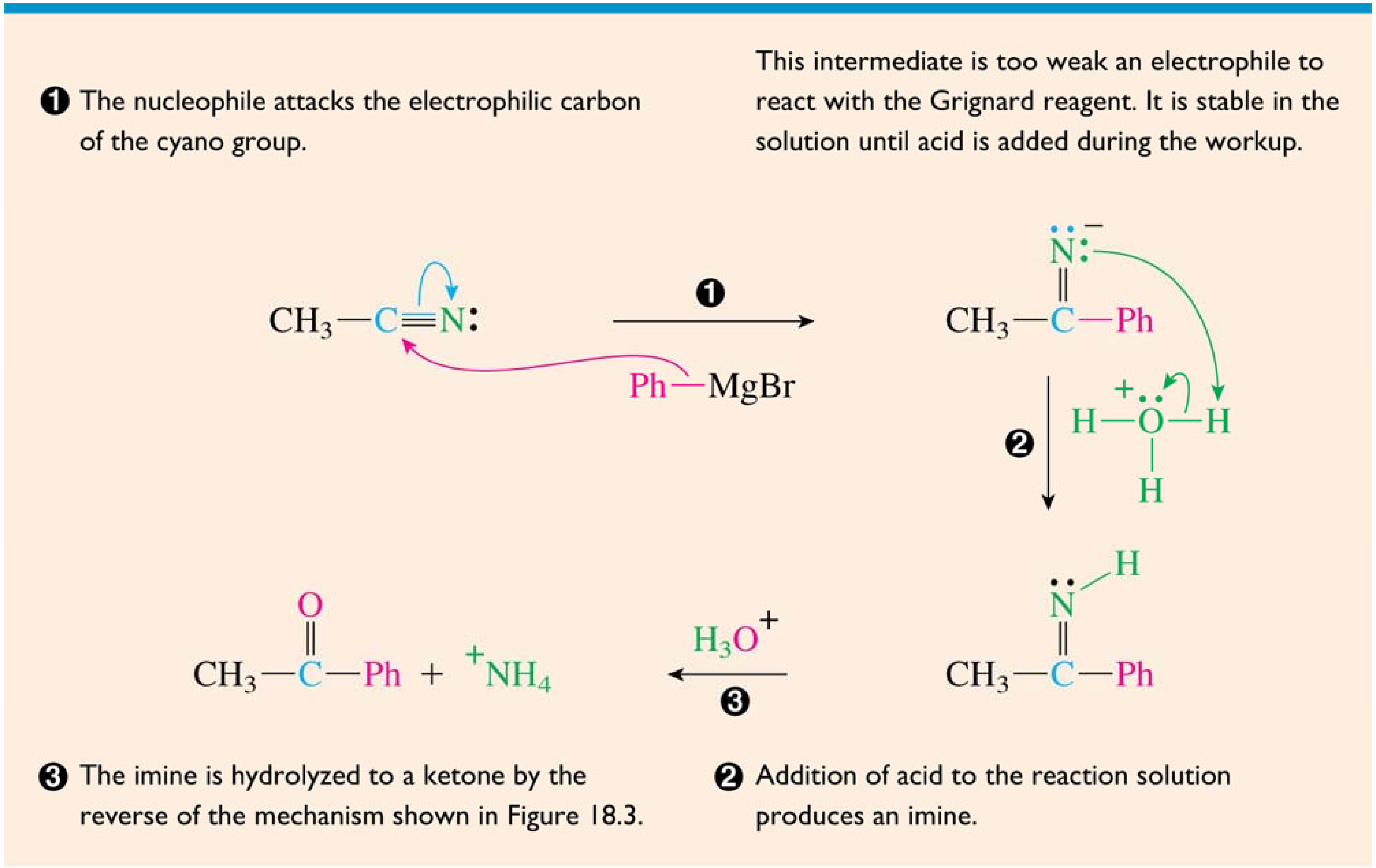
Examples



$$CH_3\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-Cl + Ph_2CuLi \longrightarrow CH_3\overset{\overset{CH_3}{|}}{C}H-\overset{\overset{O}{\|}}{C}-Ph \quad (67\%)$$

2. Using Grignard reagents with Nitriles

Mechanism



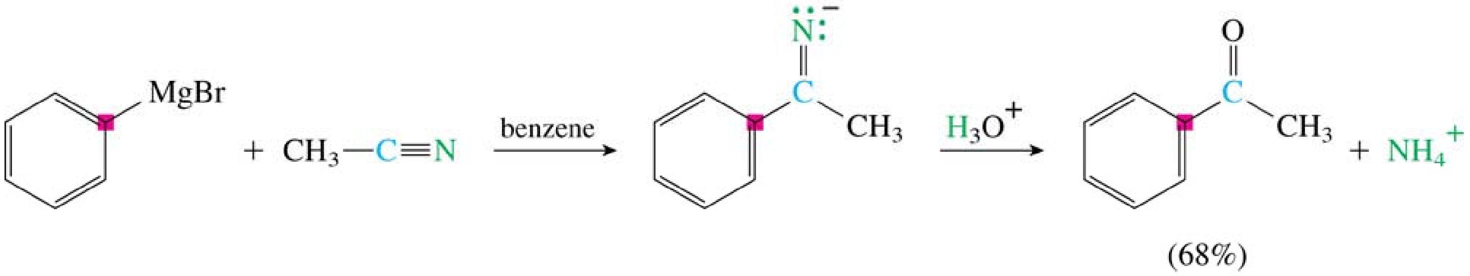
➊ The nucleophile attacks the electrophilic carbon of the cyano group.

This intermediate is too weak an electrophile to react with the Grignard reagent. It is stable in the solution until acid is added during the workup.

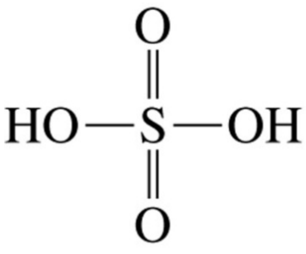
➋ Addition of acid to the reaction solution produces an imine.

➌ The imine is hydrolyzed to a ketone by the reverse of the mechanism shown in Figure 18.3.

Example

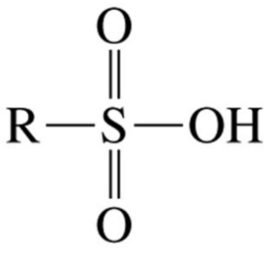


19.11 Derivatives of Sulfur and Phosphorus Acids



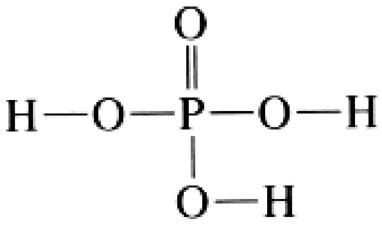
$\mathrm{HO{-}S(=O)_2{-}OH}$

Sulfuric acid



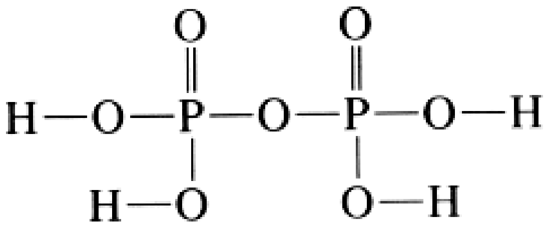
$\mathrm{R{-}S(=O)_2{-}OH}$

A sulfonic acid



$\mathrm{H{-}O{-}P(=O)(O{-}H){-}O{-}H}$

phosphoric acid



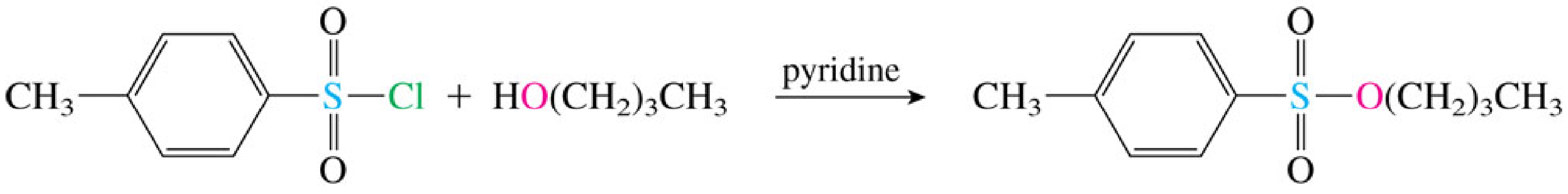
$\mathrm{H{-}O{-}P(=O)(O{-}H){-}O{-}P(=O)(O{-}H){-}O{-}H}$

pyrophosphoric acid

The Chemical behavior is similar to that of carboxylic acids,

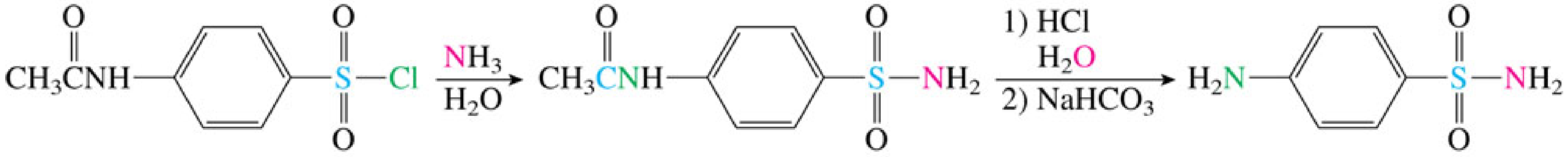
While they are stronger acid than the carboxylic acids!

Examples

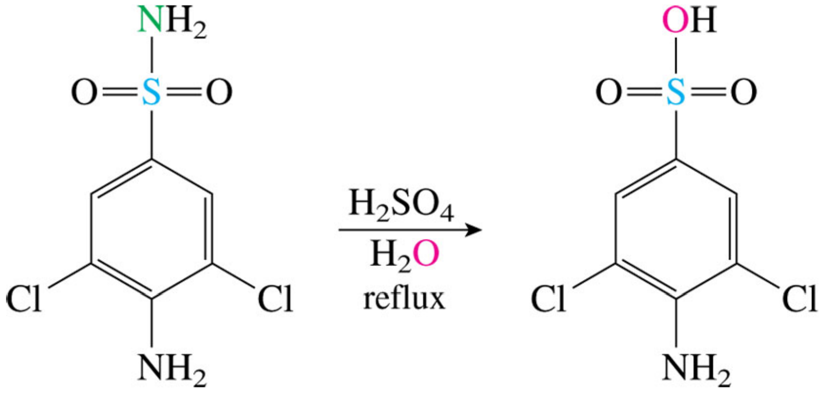


p-Toluenesulfonyl chloride

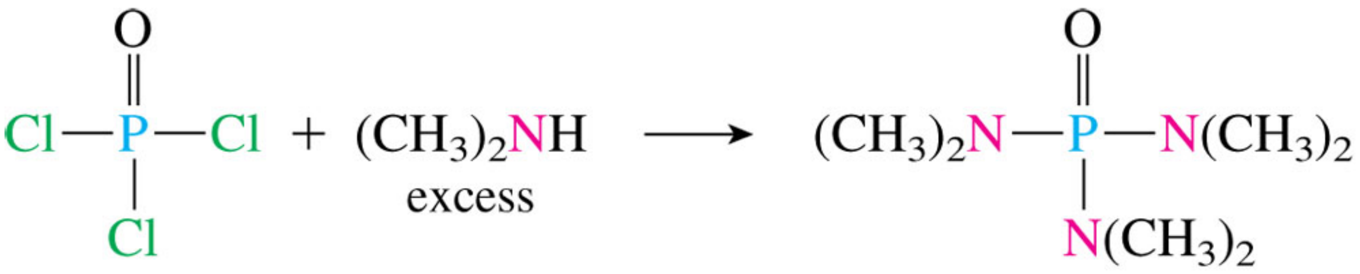
(90%)
A toluenesulfonate ester



p-Aminobenzenesulfonamide
(sulfanilamide)

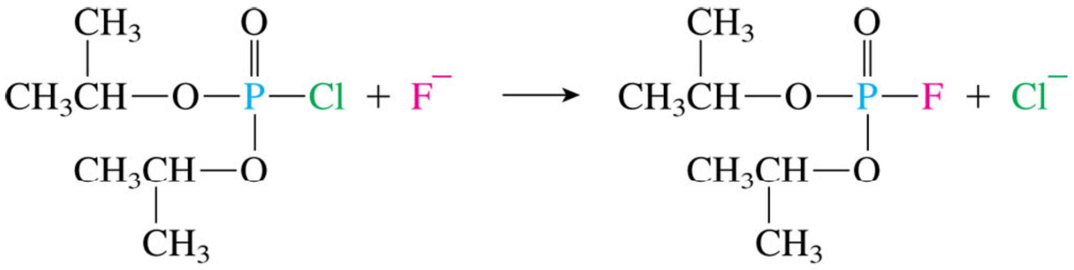


(80%)

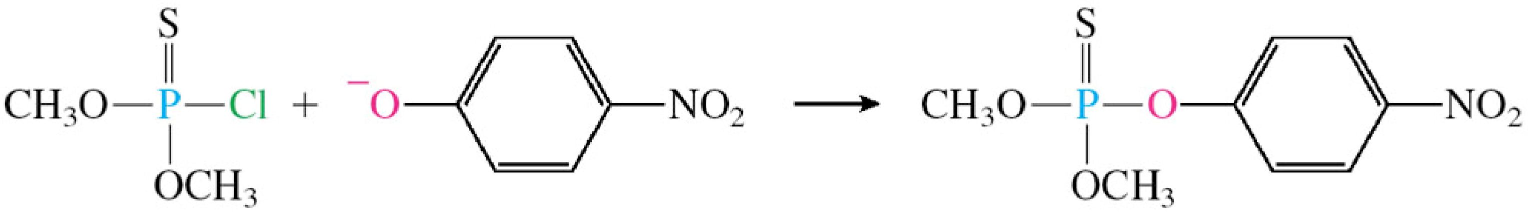


Phosphorus oxychloride

Hexamethylphosphoric triamide (HMPA)

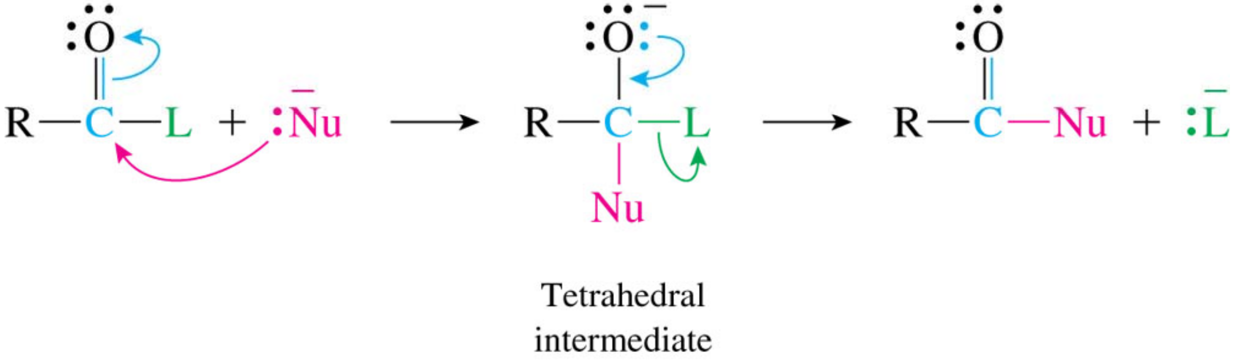


Diisopropylphosphorofluoridate (DFP)



Methyl parathion

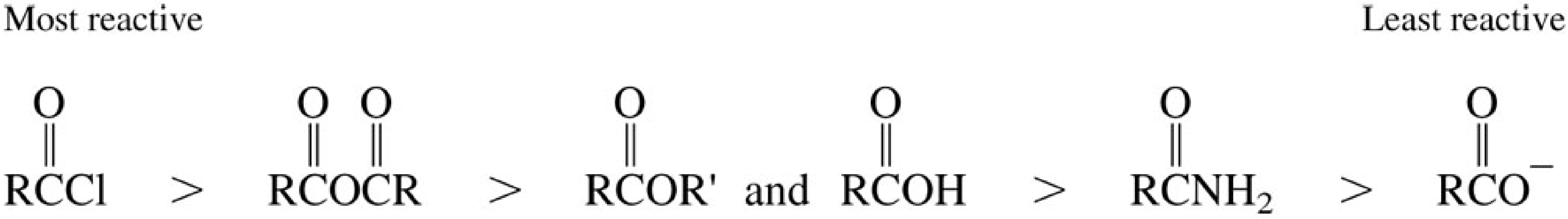
Summary



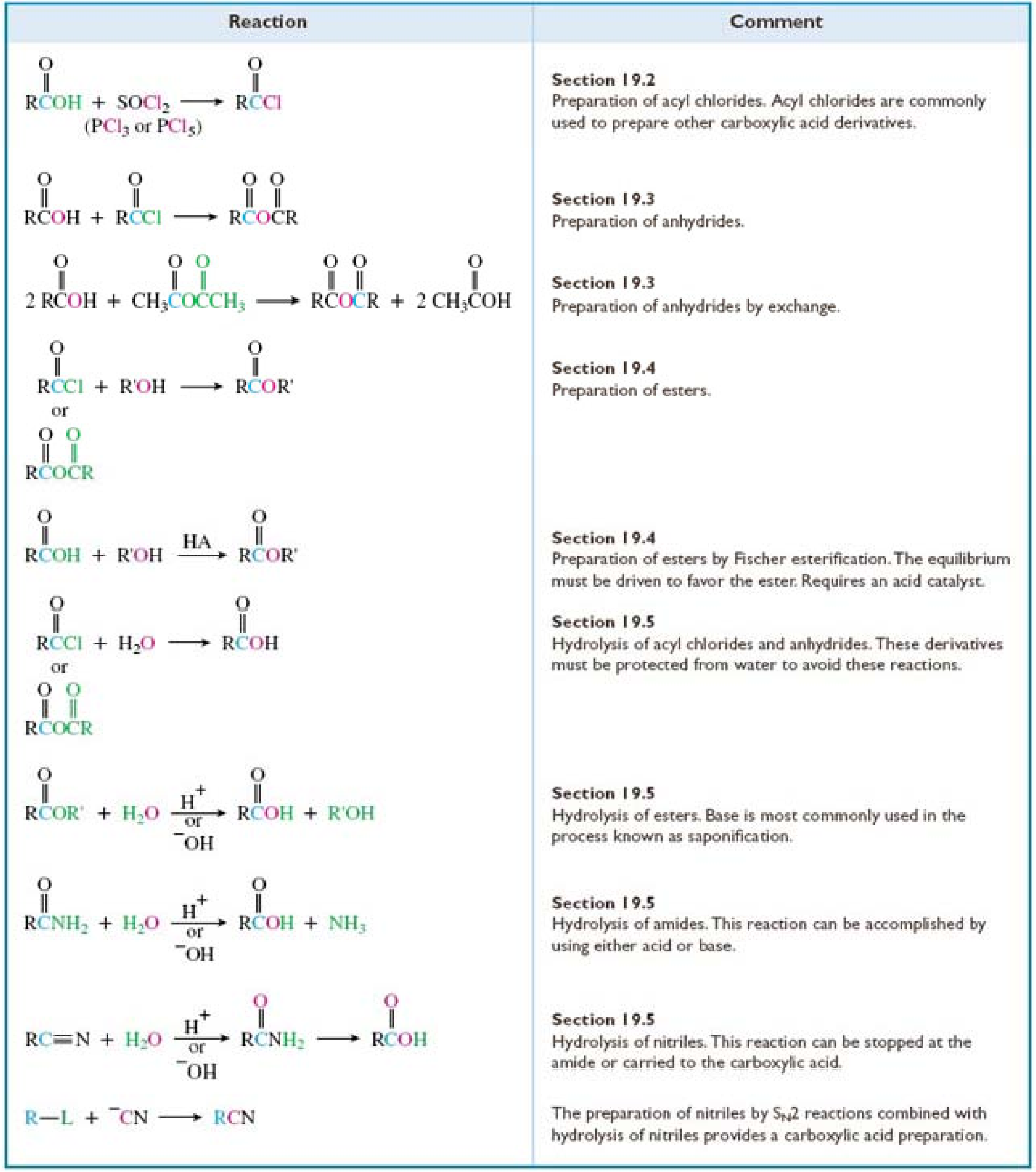
Resonance effects: Electron donors slow the reaction; withdrawers accelerate it

Inductive effects: Electron withdrawers accelerate the reaction

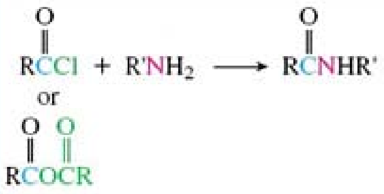
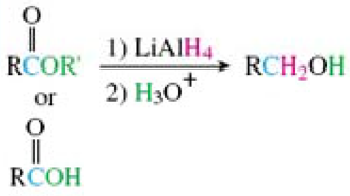
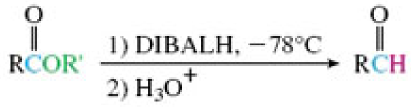
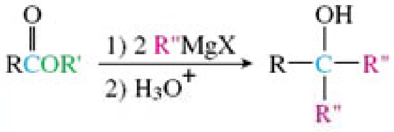
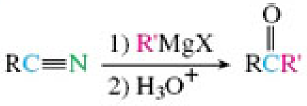
Streric effects: Steric hindrance slows the approach of the nucleophiles



$$\mathrm{R\overset{O}{\overset{\|}{C}}Cl} > \mathrm{R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R} > \mathrm{R\overset{O}{\overset{\|}{C}}OR'}\ \text{and}\ \mathrm{R\overset{O}{\overset{\|}{C}}OH} > \mathrm{R\overset{O}{\overset{\|}{C}}NH_2} > \mathrm{R\overset{O}{\overset{\|}{C}}O^-}$$



Reaction	Comment
$R\overset{O}{\overset{\|}{C}}OH + \underset{(PCl_3 \text{ or } PCl_5)}{SOCl_2} \longrightarrow R\overset{O}{\overset{\|}{C}}Cl$	**Section 19.2** Preparation of acyl chlorides. Acyl chlorides are commonly used to prepare other carboxylic acid derivatives.
$R\overset{O}{\overset{\|}{C}}OH + R\overset{O}{\overset{\|}{C}}Cl \longrightarrow R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R$	**Section 19.3** Preparation of anhydrides.
$2\ R\overset{O}{\overset{\|}{C}}OH + CH_3\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R + 2\ CH_3\overset{O}{\overset{\|}{C}}OH$	**Section 19.3** Preparation of anhydrides by exchange.
$R\overset{O}{\overset{\|}{C}}Cl + R'OH \longrightarrow R\overset{O}{\overset{\|}{C}}OR'$ or $R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R$	**Section 19.4** Preparation of esters.
$R\overset{O}{\overset{\|}{C}}OH + R'OH \xrightarrow{HA} R\overset{O}{\overset{\|}{C}}OR'$	**Section 19.4** Preparation of esters by Fischer esterification. The equilibrium must be driven to favor the ester. Requires an acid catalyst.
$R\overset{O}{\overset{\|}{C}}Cl + H_2O \longrightarrow R\overset{O}{\overset{\|}{C}}OH$ or $R\overset{O}{\overset{\|}{C}}O\overset{O}{\overset{\|}{C}}R$	**Section 19.5** Hydrolysis of acyl chlorides and anhydrides. These derivatives must be protected from water to avoid these reactions.
$R\overset{O}{\overset{\|}{C}}OR' + H_2O \xrightarrow[\text{or} \atop {}^-OH]{H^+} R\overset{O}{\overset{\|}{C}}OH + R'OH$	**Section 19.5** Hydrolysis of esters. Base is most commonly used in the process known as saponification.
$R\overset{O}{\overset{\|}{C}}NH_2 + H_2O \xrightarrow[\text{or} \atop {}^-OH]{H^+} R\overset{O}{\overset{\|}{C}}OH + NH_3$	**Section 19.5** Hydrolysis of amides. This reaction can be accomplished by using either acid or base.
$RC{\equiv}N + H_2O \xrightarrow[\text{or} \atop {}^-OH]{H^+} R\overset{O}{\overset{\|}{C}}NH_2 \longrightarrow R\overset{O}{\overset{\|}{C}}OH$	**Section 19.5** Hydrolysis of nitriles. This reaction can be stopped at the amide or carried to the carboxylic acid.
$R{-}L + {}^-CN \longrightarrow RCN$	The preparation of nitriles by S_N2 reactions combined with hydrolysis of nitriles provides a carboxylic acid preparation.

Reaction	Comment
 $R\overset{\overset{O}{\|}}{C}Cl + R'NH_2 \longrightarrow R\overset{\overset{O}{\|}}{C}NHR'$ or $R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R$	**Section 19.6** Preparation of amides.
 $R\overset{\overset{O}{\|}}{C}OR'$ or $R\overset{\overset{O}{\|}}{C}OH \xrightarrow[2)\ H_3O^+]{1)\ LiAlH_4} RCH_2OH$	**Section 19.7** Reduction of esters or acids to alcohols.
 $R\overset{\overset{O}{\|}}{C}NHR' \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} RCH_2NHR'$	**Section 19.7** Reduction of amides to amines.
$RC{\equiv}N \xrightarrow[2)\ H_2O]{1)\ LiAlH_4} RCH_2NH_2$	**Section 19.8** Reduction of nitriles to primary amines.
 $R\overset{\overset{O}{\|}}{C}Cl \xrightarrow[-78°C]{LiAlH(Ot\text{-}Bu)_3} R\overset{\overset{O}{\|}}{C}H$	**Section 19.8** Reduction of acyl chlorides to aldehydes.
 $R\overset{\overset{O}{\|}}{C}OR' \xrightarrow[2)\ H_3O^+]{1)\ DIBALH,\ -78°C} R\overset{\overset{O}{\|}}{C}H$	**Section 19.8** Reduction of esters to aldehydes.
 $R\overset{\overset{O}{\|}}{C}OR' \xrightarrow[2)\ H_3O^+]{1)\ 2\ R''MgX} R-\underset{\underset{R''}{\vert}}{\overset{\overset{OH}{\vert}}{C}}-R''$	**Section 19.9** Preparation of alcohols from esters.
 $R\overset{\overset{O}{\|}}{C}Cl \xrightarrow{R'_2CuLi} R\overset{\overset{O}{\|}}{C}R'$	**Section 19.10** Preparation of ketones from acyl chlorides.
 $RC{\equiv}N \xrightarrow[2)\ H_3O^+]{1)\ R'MgX} R\overset{\overset{O}{\|}}{C}R'$	**Section 19.10** Preparation of ketones from nitriles.