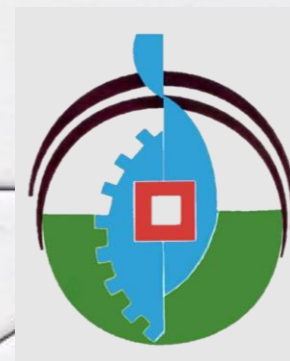


# Organic Chemistry



**Paula Yurkanis Bruice**



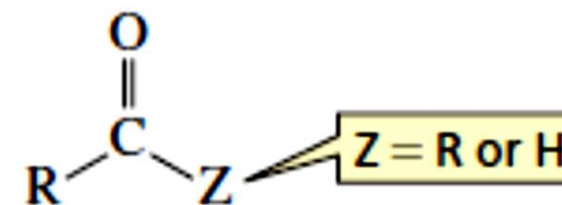
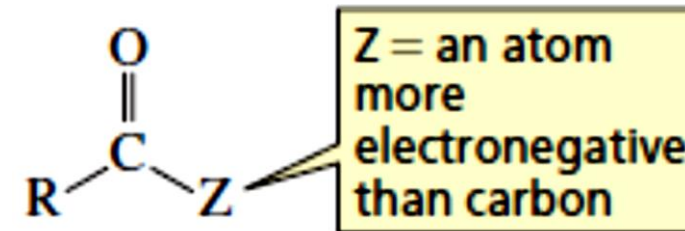
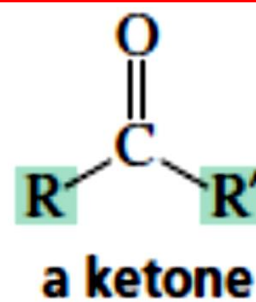
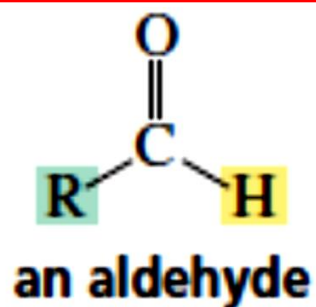
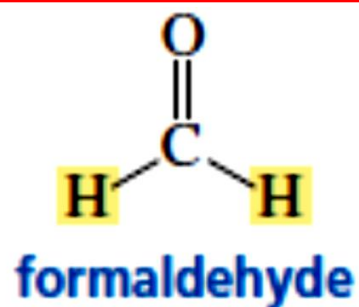
# Organic Chemistry

- Aldehyde & Ketones
  - *Structure and physical properties.*
  - *Synthesis and reactions*
- Carboxylic acids and their derivatives
  - *Structure and physical properties.*
  - *Synthesis and reactions*
- Amines
  - *Structure and physical properties.*
  - *Synthesis and reactions*

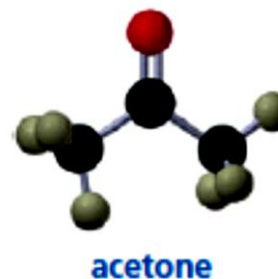
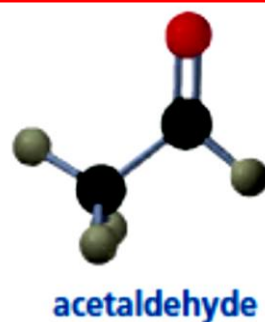
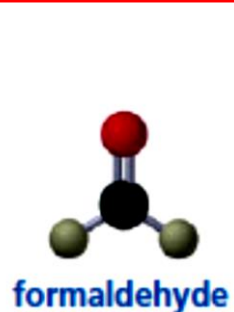


- Aldehyde & Ketones:
  - *Structure and physical properties:*
    - *The Nomenclature of Aldehydes and Ketones.*
    - *Functional Group Nomenclature.*
    - *The Relative Reactivities of Carbonyl Compounds.*
  - *Synthesis and reactions:*
    - *The Reaction with Grignard Reagents.*
    - *The Reaction with Acetylides Ions.*
    - *The Reaction with Cyanide Ions.*
    - *The Reaction with Hydride Ions.*
  - *The Reaction with amines.*
  - *The Reaction with water.*
  - *The Reaction with alcohol.*
  - *The Reaction with Hydride Ions.*

# Carbonyl Compounds



The carbonyl carbon of **formaldehyde**; the simplest aldehyde, is bonded to two hydrogens. The carbonyl carbon of all other **aldehydes** is bonded to a hydrogen and to an alkyl group (R). The carbonyl carbon of a **ketone** is bonded to two R groups.



# The Nomenclature of Aldehydes and Ketones

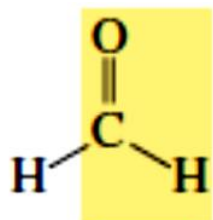


## Naming Aldehydes

The **systematic (IUPAC) name** of an aldehyde is obtained by replacing the final “e” on the name of the original hydrocarbon with “al.” The position of the carbonyl carbon is always at the end of the parent hydrocarbon (or else the compound would not be an aldehyde), so it always has the 1-position.

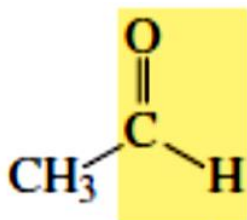
The **common name** of an aldehyde is the same as the common name of the corresponding carboxylic acid, except that “aldehyde” is substituted for “oic acid” (or “ic acid”).

Using a lowercase Greek letter to indicate the position of the substituent. The carbonyl carbon is not given a letter, so the carbon adjacent to the carbonyl carbon is the  $\alpha$ -carbon.

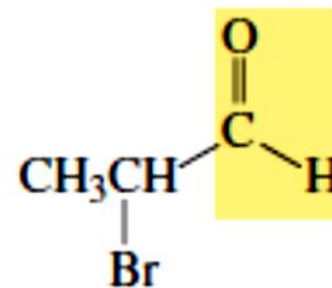


**systematic name:**  
**common name:**

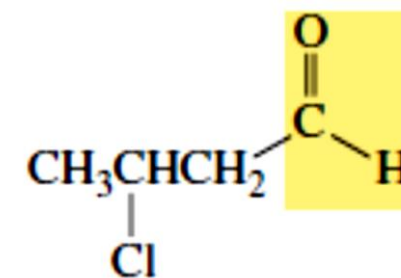
**methanal**  
**formaldehyde**



**ethanal**  
**acetaldehyde**



**2-bromopropanal**  
 **$\alpha$ -bromopropionaldehyde**



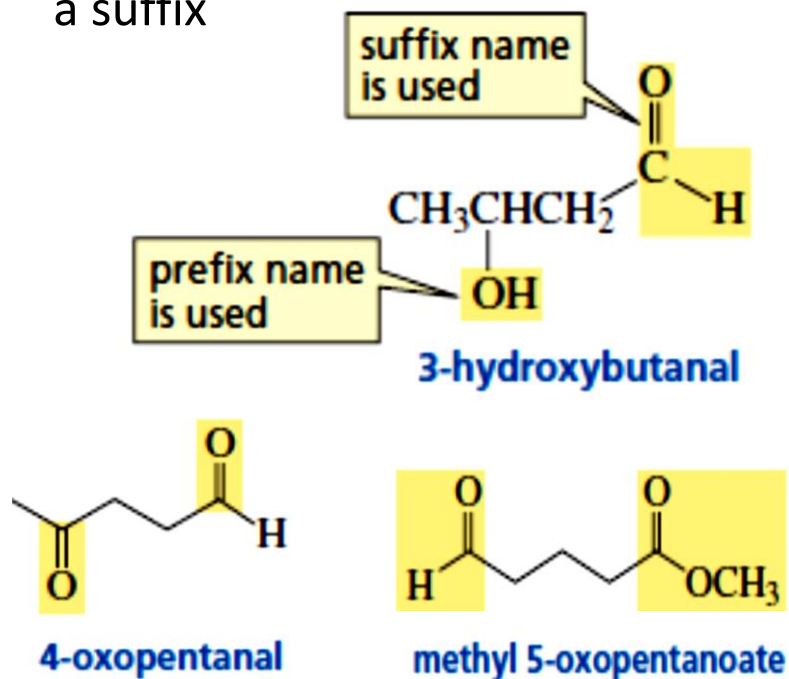
**3-chlorobutanal**  
 **$\beta$ -chlorobutyraldehyde**




# Functional Group Nomenclature



If a compound has two functional groups, the one with the lower priority is indicated by a prefix and the one with the higher priority by a suffix



	Class	Prefix name	Suffix name
 increasing priority	Carboxylic acid	Carboxy	-oic acid
	Ester	Alkoxycarbonyl	-oate
	Amide	Amido	-amide
	Nitrile	Cyano	-nitrile
	Aldehyde	Oxo ( $=\text{O}$ )	-al
	Aldehyde	Formyl ( $\text{CH}=\text{O}$ )	-al
	Ketone	Oxo ( $=\text{O}$ )	-one
	Alcohol	Hydroxy	-ol
	Amine	Amino	-amine
	Alkene	Alkenyl	-ene
	Alkyne	Alkynyl	-yne
	Alkane	Alkyl	-ane
	Ether	Alkoxy	—
	Alkyl halide	Halo	—

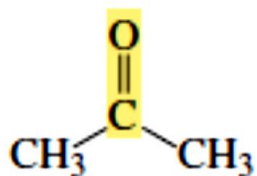
# The Nomenclature of Aldehydes and Ketones



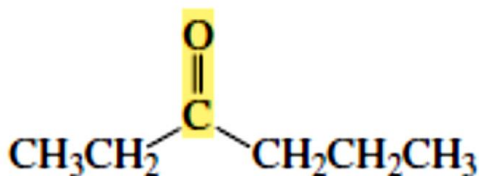
## Naming Ketones

The **systematic (IUPAC) name** of a ketone is obtained by replacing the final “e” on the name of the original hydrocarbon with “one.” The chain is numbered in the direction that gives the carbonyl carbon the smaller number. Cyclic ketones do not need a number because the carbonyl carbon is assumed to be at the 1-position.

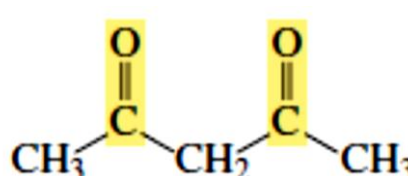
The **common name** Only a few ketones have common names. The smallest ketone, propanone, is usually referred to by its common name, acetone. Common names are also used for some phenyl-substituted ketones; the number of carbons is indicated by the common name of the corresponding carboxylic acid, substituting “ophenone” for “ic acid.”



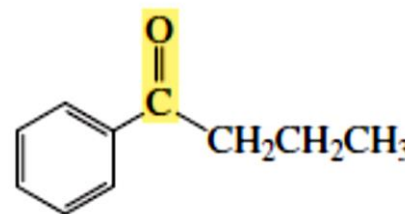
systematic name: **propanone**  
common name: **acetone**  
derived name: **dimethyl ketone**



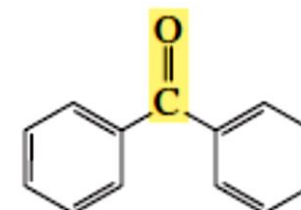
**3-hexanone**  
**ethyl propyl ketone**



**2,4-pentanedione**  
**acetylacetone**



**butyrophenone**  
**phenyl propyl ketone**

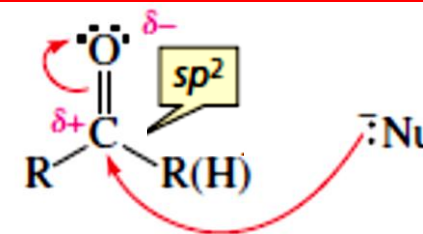


**benzophenone**  
**diphenyl ketone**

# The Relative Reactivities of Carbonyl Compounds

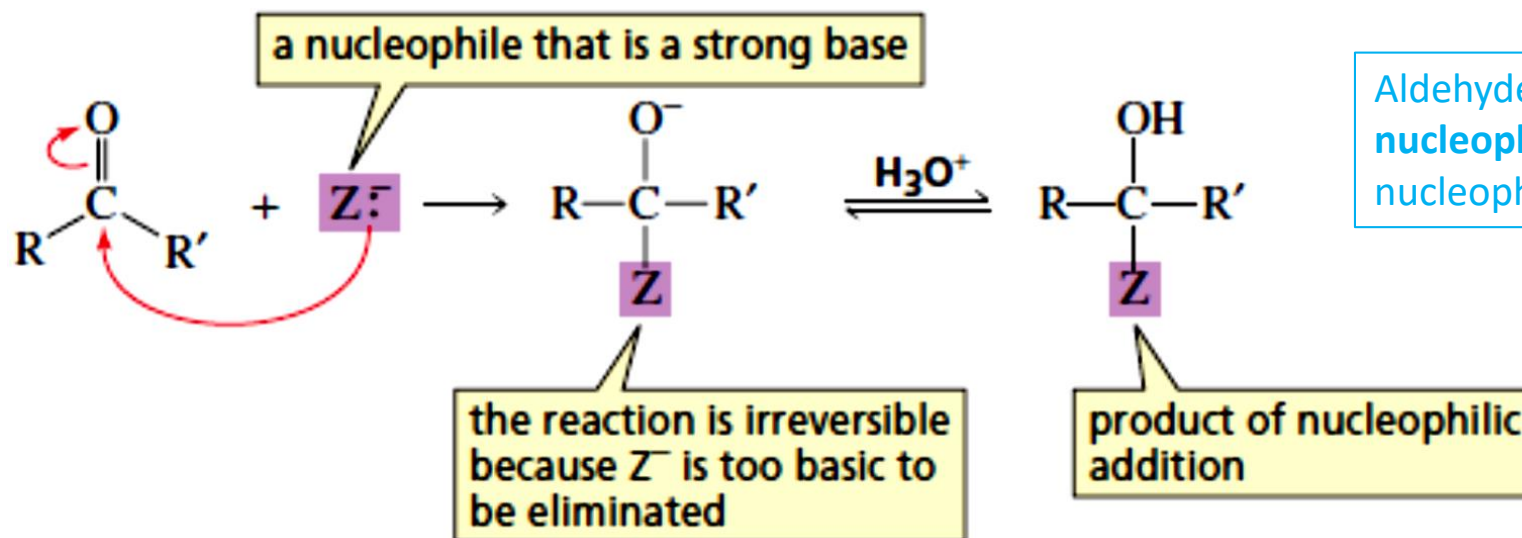


The reactivity of carbonyl compounds is due to the polarity of the carbonyl group, which results from oxygen being more electronegative than carbon. The carbonyl carbon is therefore electron deficient (an electrophile), so it reacts with nucleophiles.



**How Aldehydes and Ketones React?** The carbonyl group is attached to a group that is too **strong a base** (H- or R-)

The tetrahedral compound will be stable because it will not have a group that can be eliminated, so it cannot be replaced by another group.



Aldehydes and ketones undergo *irreversible nucleophilic addition reactions* with nucleophiles that are strong bases.

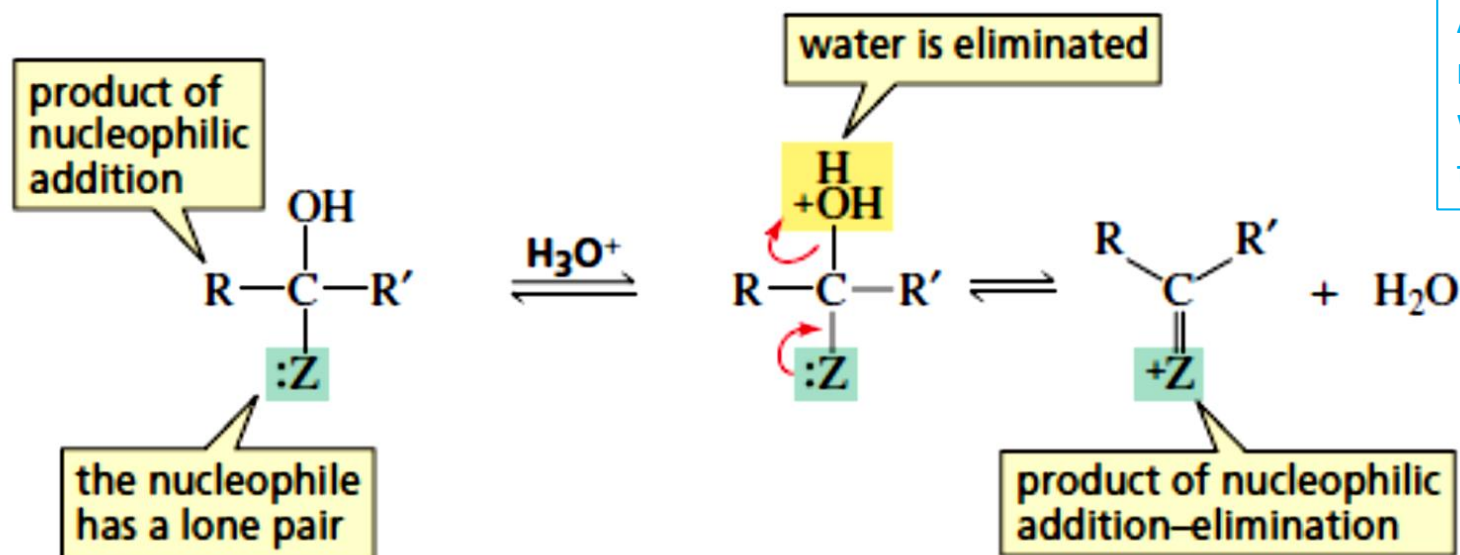


# The Relative Reactivities of Carbonyl Compounds



## How Aldehydes and Ketones React?

If the attacking atom of the nucleophile is **an oxygen or a nitrogen** and there is enough acid in the solution to protonate the OH group of the tetrahedral compound, then water can be eliminated from the addition product by a lone pair on the oxygen or nitrogen. The reaction is *reversible* because there are two electronegative groups attached to the tetrahedral intermediate, either one of which can be protonated and therefore eliminated.



Aldehydes and ketones undergo **nucleophilic addition-elimination reactions** with nucleophiles that have a lone pair on the attacking atom.

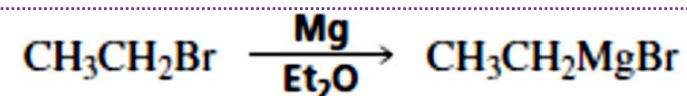
# The Reaction with Grignard Reagents

nucleophilic addition reactions



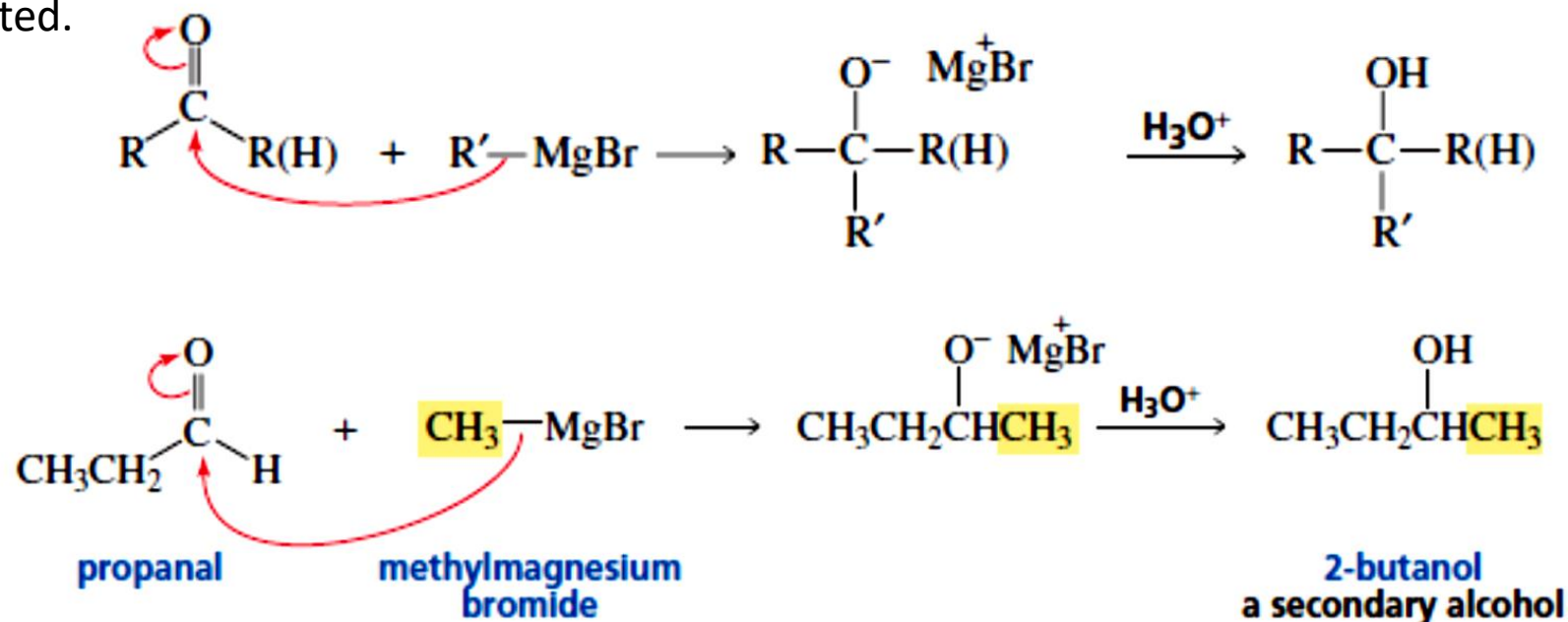
Grignard reagent is prepared by adding an alkyl halide to magnesium shavings in diethyl ether under anhydrous conditions.

Grignard reagent reacts as if it were a carbanion



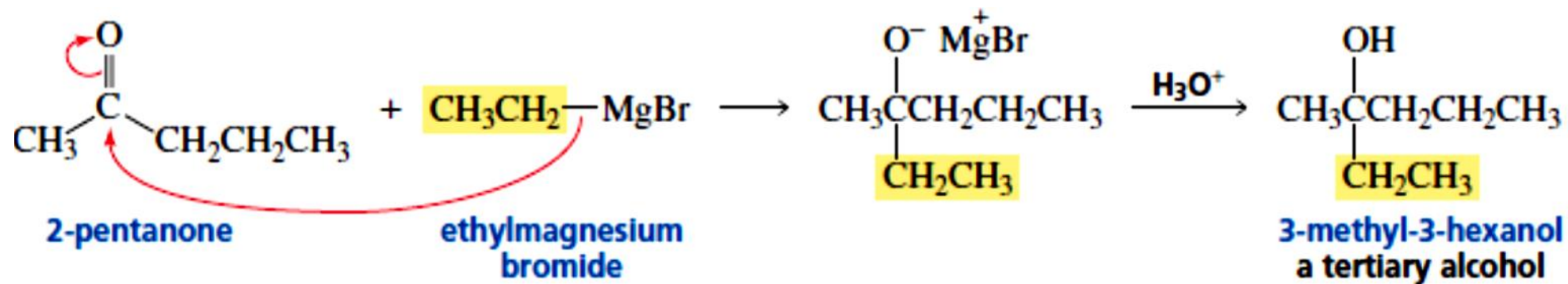
The reaction of an aldehyde or a ketone with a Grignard reagent is a **nucleophilic addition reaction**.

The nucleophile adds to the carbonyl carbon. The tetrahedral alkoxide ion is stable because it does not have a group that can be eliminated.

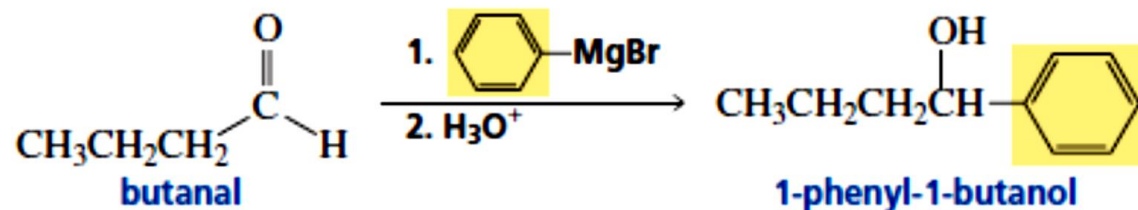
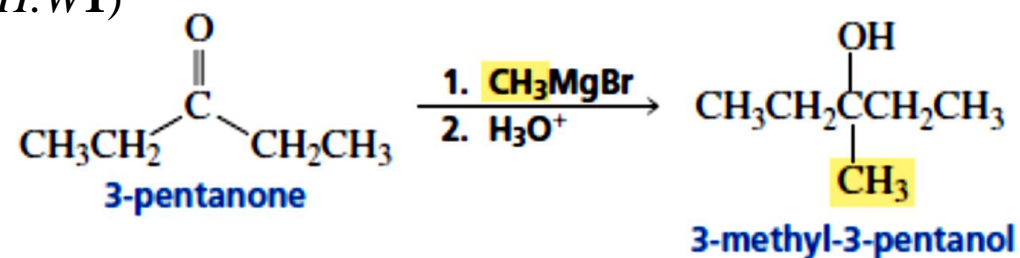


# The Reaction with Grignard Reagents

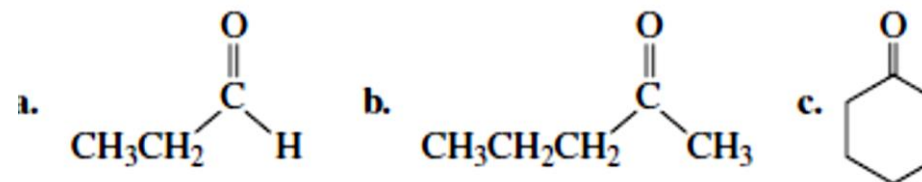
nucleophilic addition reactions



H.W1)



H.W2) What products are formed when the following compounds react with  $\text{CH}_3\text{MgBr}$ , followed by the addition of dilute acid?



# The Reaction with Acetylides Ions

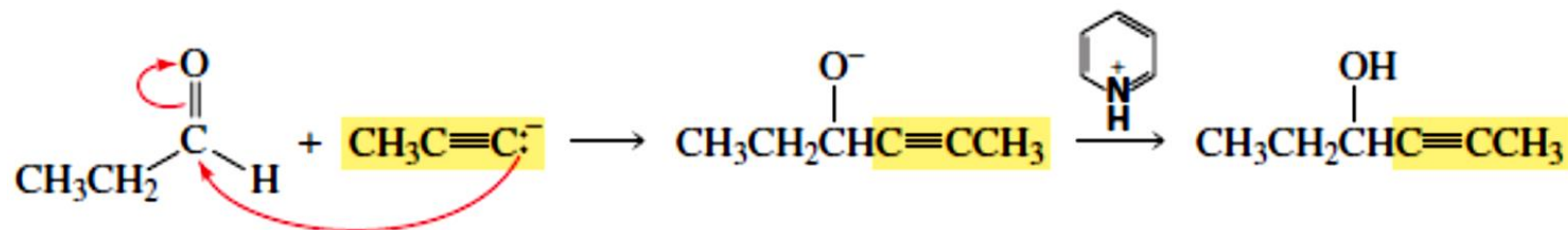
nucleophilic addition reactions



A terminal alkyne can be converted into an acetylide ion by a strong base. An acetylide ion is another example of a carbon nucleophile that reacts with an aldehyde or a ketone to form a **nucleophilic addition product**



When the reaction is over, a weak acid (one that will not react with the triple bond, such as the pyridinium ion shown here) is added to the reaction mixture to protonate the alkoxide ion.



*H.W1)* 3-methyl-3-hexanol can be synthesized from the reaction of 2-pentanone with ethylmagnesium bromide. What other combinations of ketone and Grignard reagent could be used to prepare the same tertiary alcohol?

*H.W2)* Show how the following compounds can be prepared, using ethyne as one of the starting materials. Explain why ethyne should be alkylated before, rather than after, nucleophilic addition.

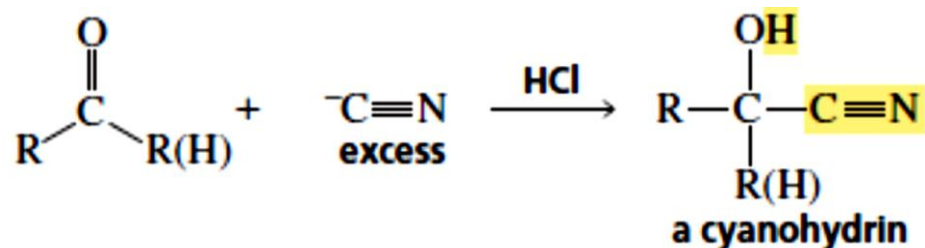
**a.** 1-pentyn-3-ol **b.** 1-phenyl-2-butyne-1-ol **c.** 2-methyl-3-hexyn-2-ol

# The Reaction with Cyanide Ions

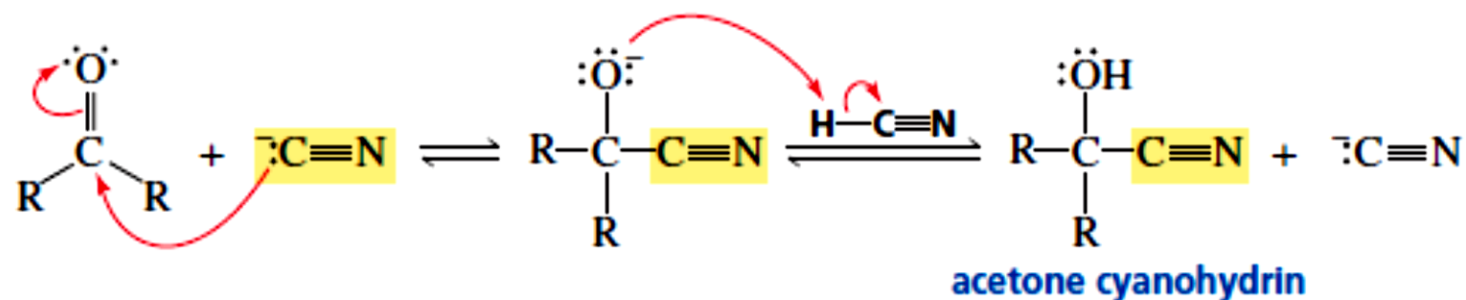
nucleophilic addition reactions



Cyanide ion is another carbon nucleophile that can add to an aldehyde or a ketone. The product of the reaction is a **cyanohydrin**. Unlike the addition reactions of other nucleophiles, the addition of cyanide ion has to be carried out under acidic conditions. Excess cyanide ion is used to ensure that some cyanide ion is not protonated by the acid and, therefore, is available to act as a nucleophile.



Explain why aldehydes and ketones react with a weak acid such as hydrogen cyanide but do not react with strong acids such as HCl or H<sub>2</sub>SO<sub>4</sub> (other than being protonated by them).



Compared with Grignard reagents and acetylide ions, cyanide ion is a relatively weak base.

The pK<sub>a</sub> of CH<sub>3</sub>CH<sub>2</sub> is > 60 and the pK<sub>a</sub> of RC≡CH is 25, but the pK<sub>a</sub> of HC≡N is 9.14.

The stronger the acid, the weaker the conjugate base.

Therefore, the cyano group, unlike the R- or RC≡C- groups, can be eliminated from the addition product.



# The Reaction with amines

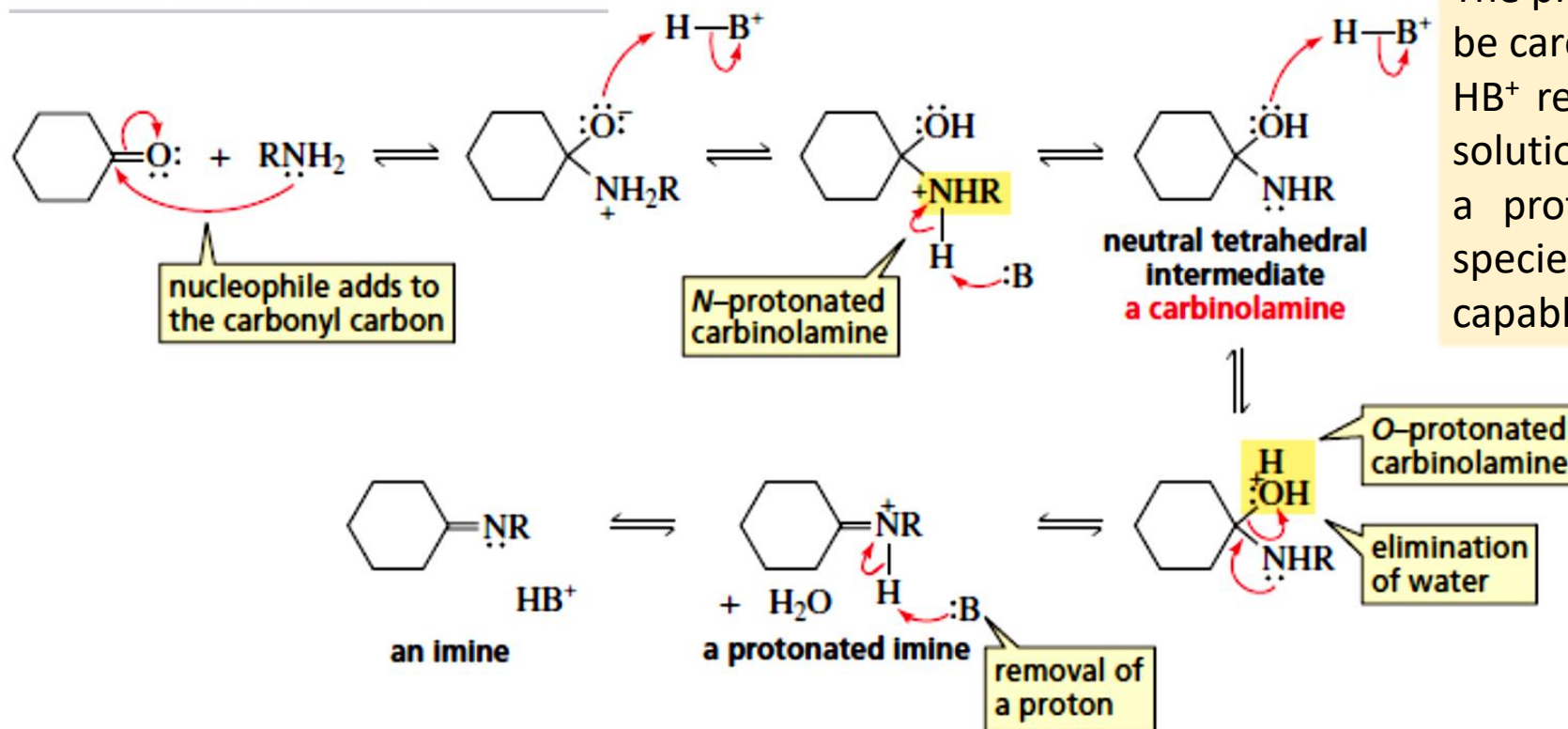


## nucleophilic addition-elimination reactions

### Formation of Imines Derivatives

An aldehyde or a ketone reacts with **a primary amine** to form an imine. An **imine**; sometimes called a **Schiff base**, is a compound with a carbon–nitrogen double bond. The reaction requires a trace amount of acid. Notice that imine formation replaces a C=O with a C=NR.

#### MECHANISM FOR IMINE FORMATION



The pH of the reaction mixture must be carefully controlled.

$\text{HB}^+$  represents any species in the solution that is capable of donating a proton, and  $\text{:B}$  represents any species in the solution that is capable of removing a proton.

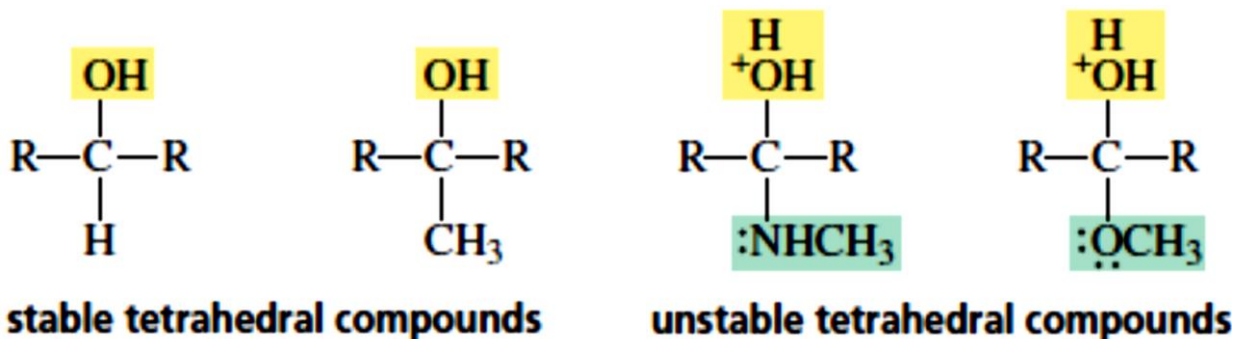
A proton is removed from the positively charged nitrogen in the last step of the mechanism, forming a neutral imine.

# The Reaction with amines

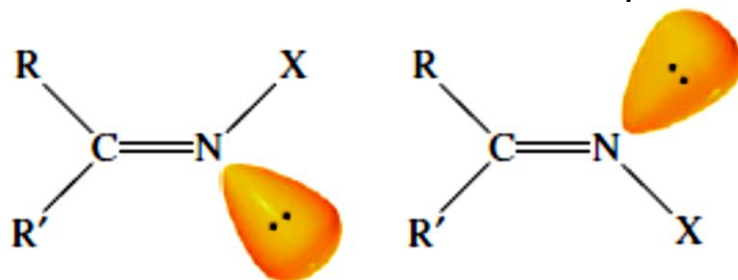
## nucleophilic addition-elimination reactions



Unlike the stable tetrahedral compounds that are formed when a Grignard reagent or a hydride ion adds to an aldehyde or a ketone, this tetrahedral is unstable because it contains a group that can be protonated and thereby become a weak enough base to be eliminated by the lone pair on the other electronegative atom.



Imines can exist as stereoisomers. The isomers are named by the E,Z system of nomenclature. The lone pair has the lowest priority



Imine formation is reversible because there are two protonated tetrahedral intermediates that can eliminate a group. The equilibrium favours the nitrogen-protonated tetrahedral intermediate because nitrogen is more basic than oxygen. However, the equilibrium can be forced toward the oxygen-protonated tetrahedral intermediate and therefore toward the imine by removing water as it is formed.

Draw the structure of each of the following compounds:

a- the (E)-hydrazone of benzaldehyde

b- the (Z)-oxime of propiophenone

**Q1)** Demonstrate the mechanism of preparing 2-methyl-3-hexyn-2-ol, using ethyne as one of the starting materials.

**Q2)** 3-methyl-3-hexanol can be synthesized from the reaction of 2-pentanone with ethylmagnesium bromide. What other combinations of ketone and Grignard reagent could be used to prepare the same tertiary alcohol?

# The Reaction with amines



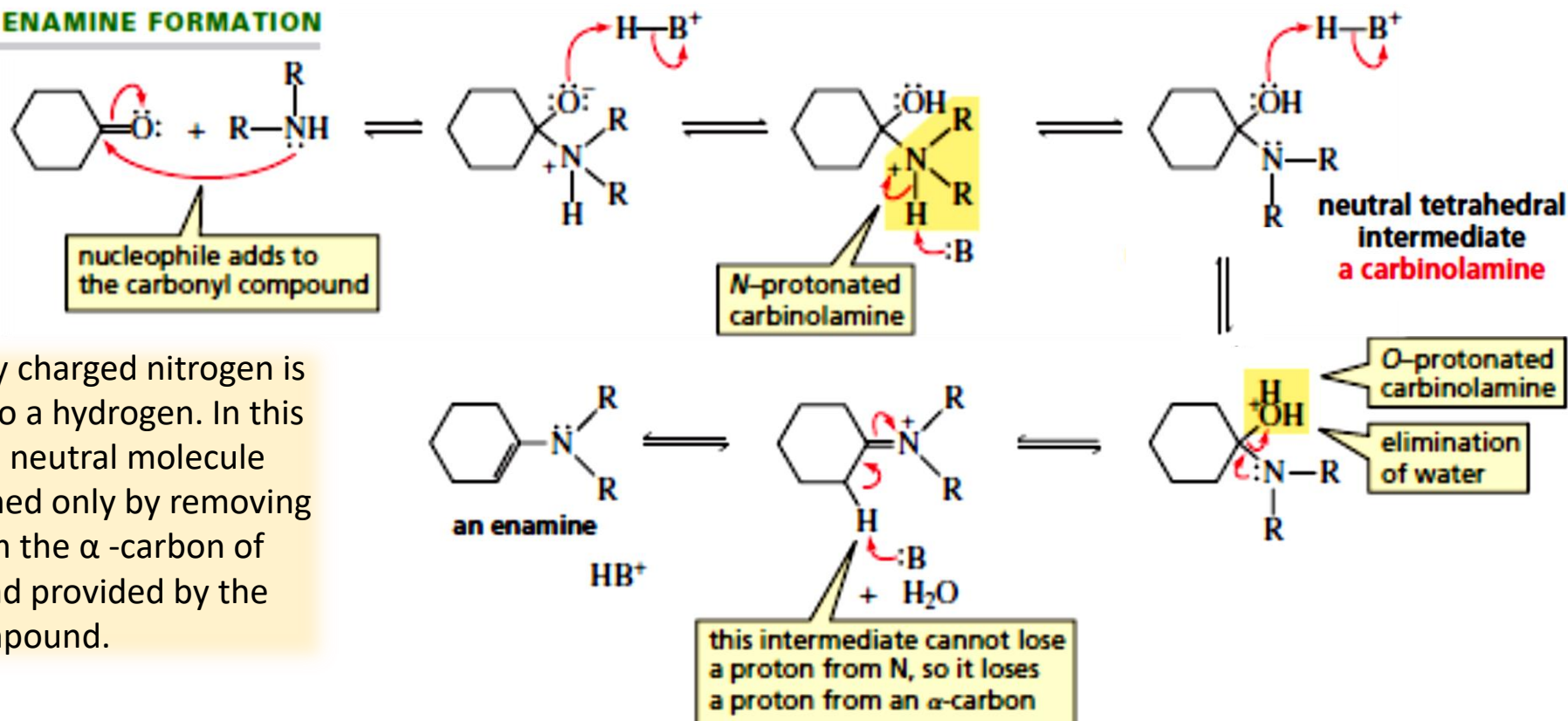
nucleophilic addition-elimination reactions

## Formation of Enamines Derivatives

An aldehyde or a ketone reacts with a **secondary amine** to form an enamine (pronounced “ENE-amine”).

An **enamine** is an  $\alpha, \beta$ -unsaturated tertiary amine. Like imine formation, the reaction requires a trace amount of an acid catalyst.

### MECHANISM FOR ENAMINE FORMATION



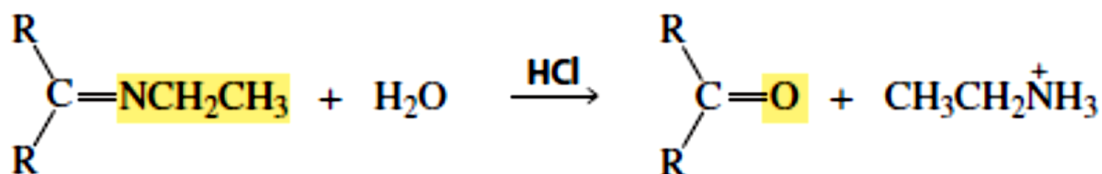
The positively charged nitrogen is not bonded to a hydrogen. In this case, a stable neutral molecule can be obtained only by removing a proton from the  $\alpha$ -carbon of the compound provided by the carbonyl compound.

# The Reaction with amines

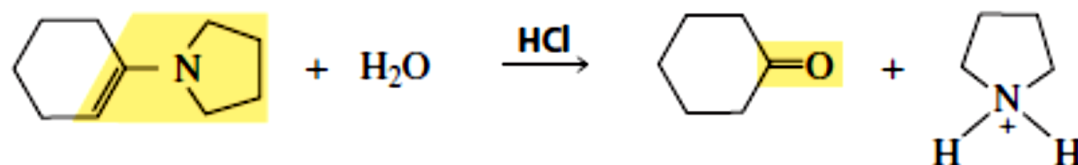
## nucleophilic addition-elimination reactions



In an aqueous acidic solution, an imine can be hydrolyzed back to the carbonyl compound and the amine. This reaction is irreversible because the amine is protonated in the acidic solution, so it is unable to react with the carbonyl compound to re-form the imine. An enamine is also hydrolyzed back to the carbonyl compound and secondary amine in acidic solution.



An imine undergoes acid-catalyzed hydrolysis to form a carbonyl compound and a primary amine.



An enamine undergoes acid-catalyzed hydrolysis to form a carbonyl compound and a secondary amine

What are the products of the following reactions? (A trace amount of acid is present in each case.)

a. cyclopentanone + ethylamine

c. acetophenone + hexylamine

b. cyclopentanone + diethylamine

d. acetophenone + cyclohexylamine



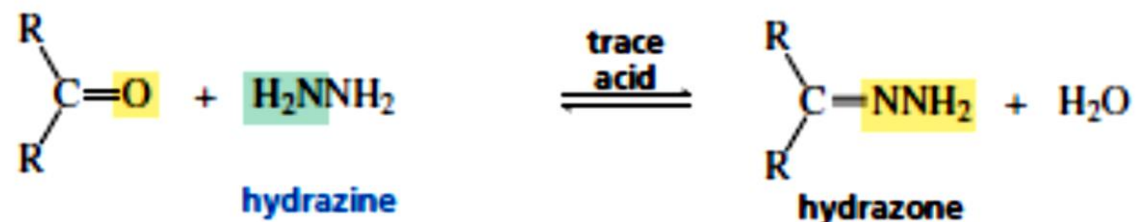
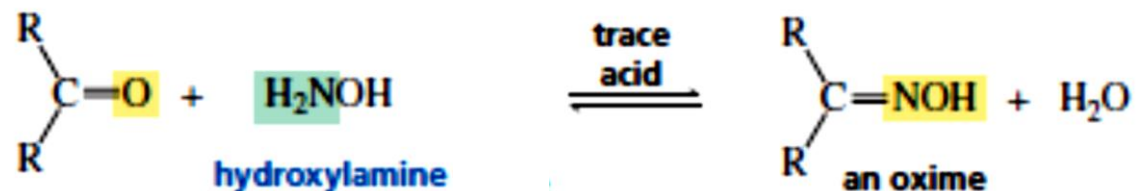
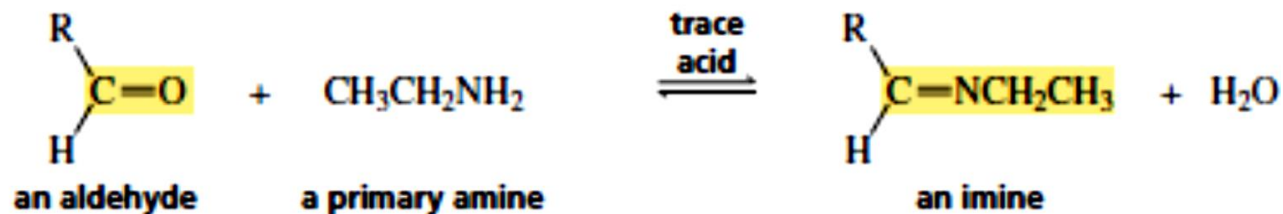
# The Reaction with amines

nucleophilic addition-elimination reactions



## Formation of Imine Derivatives

Compounds such as hydroxylamine and hydrazine are similar to primary amines in that they have an  $\text{NH}_2$  group. Thus they react with aldehydes and ketones to form imines—called *imine derivatives* because the substituent attached to the imine nitrogen is not an R group.



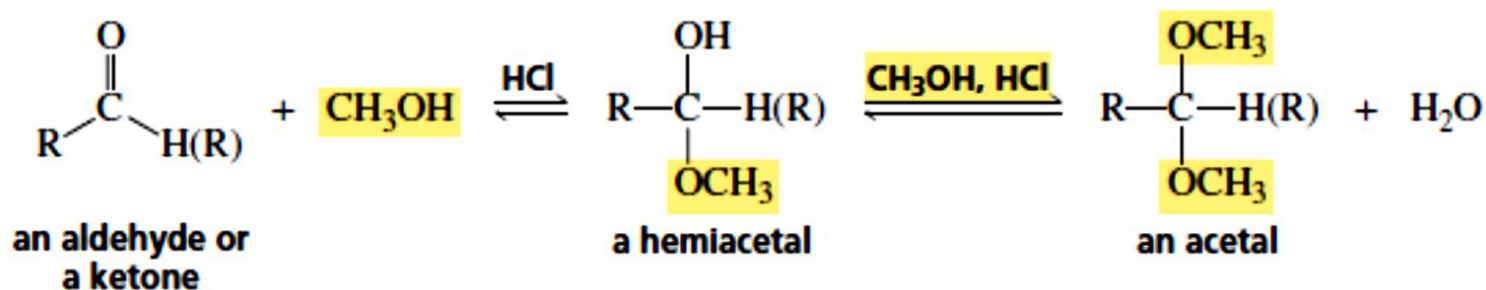
Imine formation and hydrolysis are important reactions in biological systems. For example, all the reactions that require vitamin B6 involve imine formation, and imine hydrolysis is the reason that DNA contains T nucleotides instead of U nucleotides.

# The Reaction with alcohols



## nucleophilic addition-elimination reactions

**Hemiacetal** form when one equivalent of an alcohol adds to an *aldehyde* or a *ketone*. While an **acetal** formed when a second equivalent of alcohol is added. Like water, an **alcohol is a poor nucleophile**, so **an acid catalyst is required** for the reaction to take place at a reasonable rate. Occasionally the terms **hemiketal** and **ketal** used instead of *hemiacetal* and *acetal* for the products of the reaction of an alcohol with a ketone.



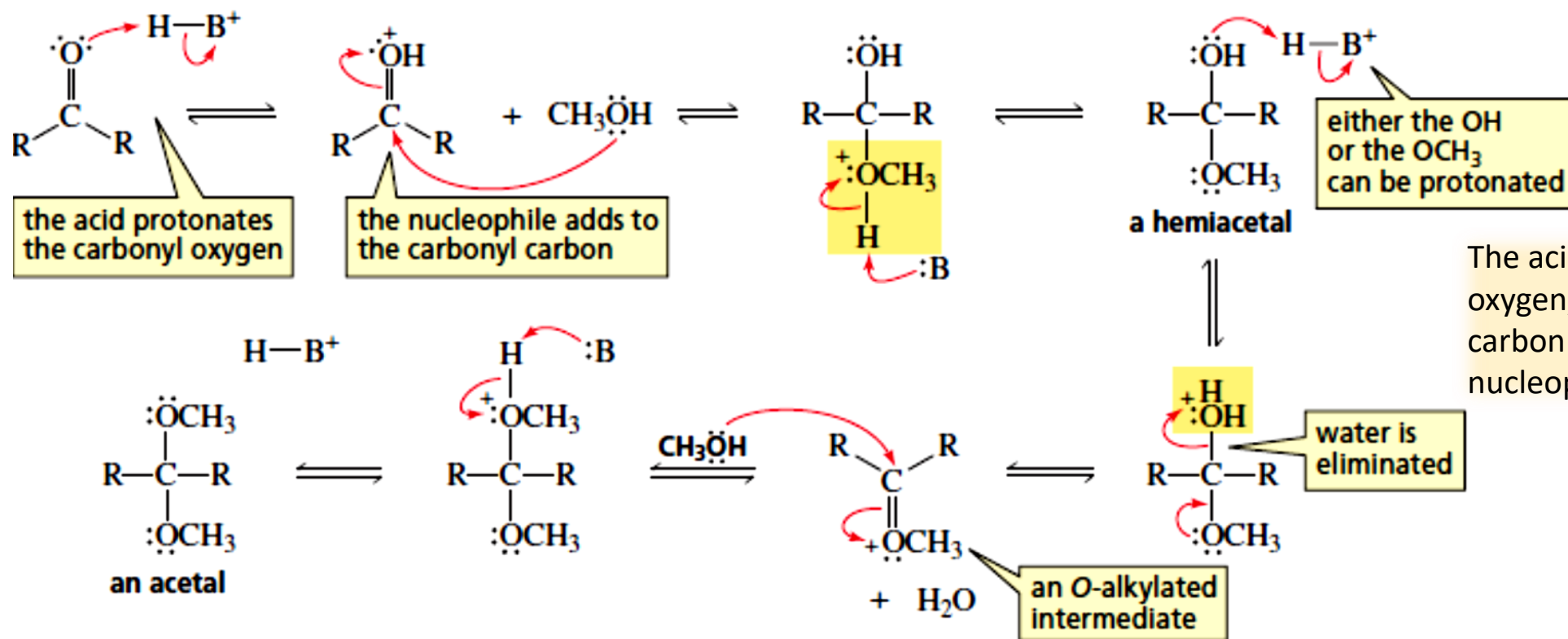
The acid protonates the carbonyl oxygen, which makes the carbonyl carbon more susceptible to nucleophilic attack.

**H.W1.** Would you expect hemiacetals to be stable in basic solutions? Explain your answer.

**H.W2.** Acetal formation must be catalyzed by an acid. Explain why it cannot be catalyzed by  $\text{CH}_3\text{O}^-$ .

# The Reaction with alcohols

nucleophilic addition-elimination reactions

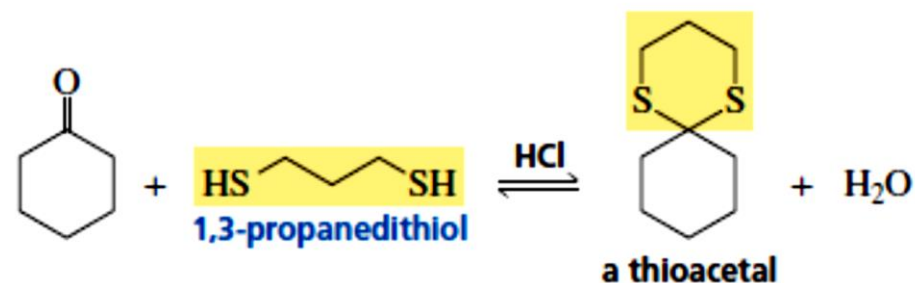
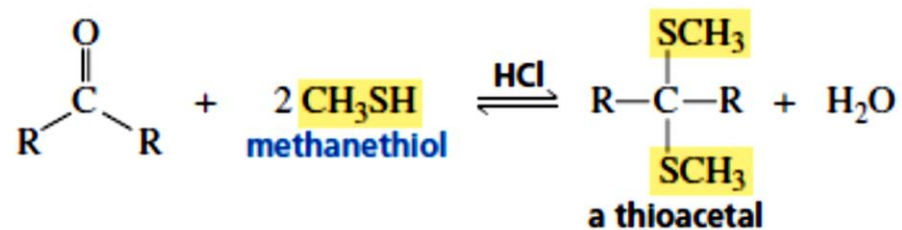


# The Addition Of Sulfur Nucleophiles

nucleophilic addition-elimination reactions

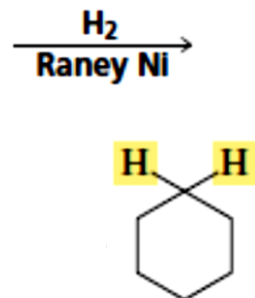


Aldehydes and ketones react with thiols (the sulfur analogues of alcohols) to form **thioacetals**. The mechanism for the addition of a thiol is the same as the mechanism for the addition of an alcohol.



Thioacetal formation is useful in organic synthesis because a thioacetal is desulfurized when it reacts with  $\text{H}_2$  and Raney nickel. **Desulfurization** replaces the  $\text{C}-\text{S}$  bonds with  $\text{C}-\text{H}$  bonds.

Thioacetal formation followed by desulfurization provides a way to convert a carbonyl group into a methylene group.



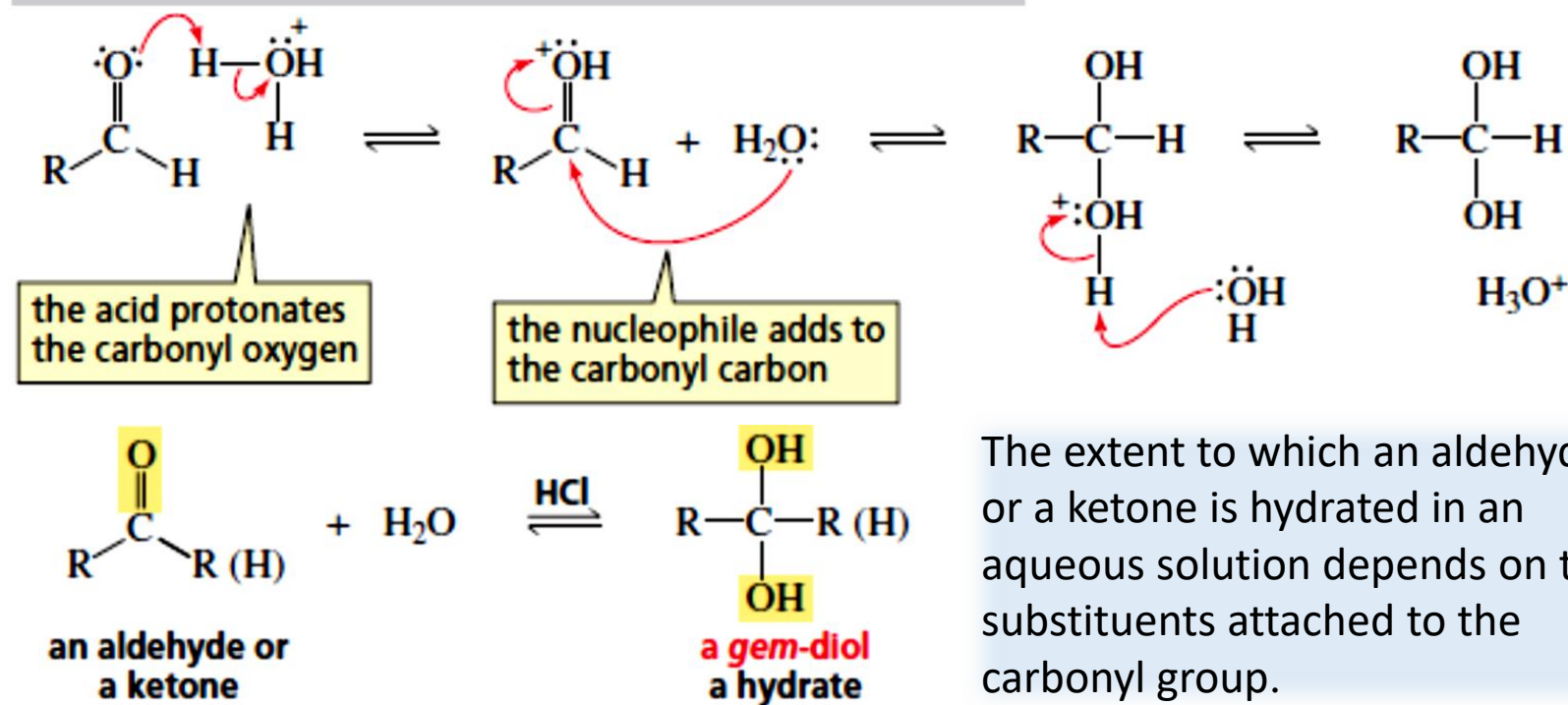
# The Reaction with water



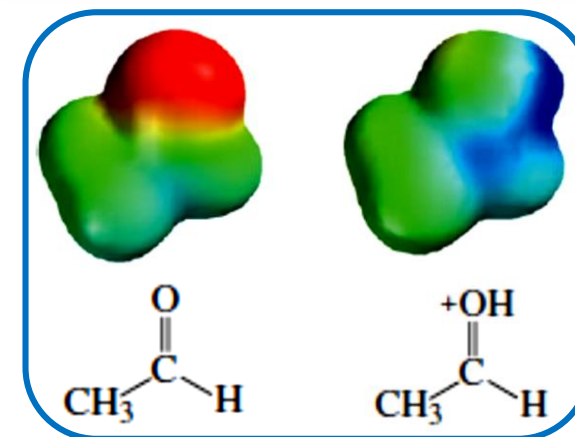
## nucleophilic addition reactions

The addition of water to an aldehyde or a ketone forms a *hydrate*. A **hydrate** is a molecule with two OH groups bonded to the same carbon. Hydrates are also called **gem-diols**. Water is a poor nucleophile and therefore adds relatively slowly to a carbonyl group. The rate of the reaction can be increased by an acid catalyst. A catalyst affects the *rate* at which an aldehyde or a ketone is converted to a hydrate.

### MECHANISM FOR ACID-CATALYZED HYDRATE FORMATION



The acid protonates the carbonyl oxygen, which makes the carbonyl carbon more susceptible to nucleophilic attack.



The extent to which an aldehyde or a ketone is hydrated in an aqueous solution depends on the substituents attached to the carbonyl group.

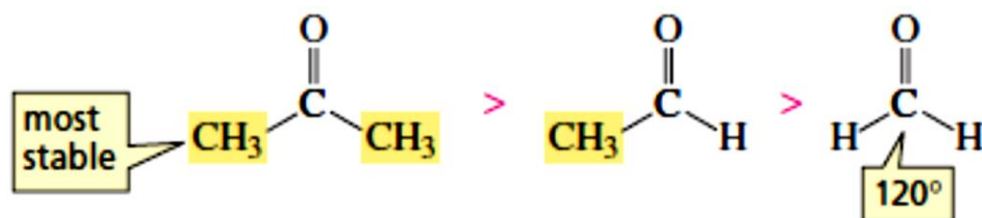


# The Reaction with water

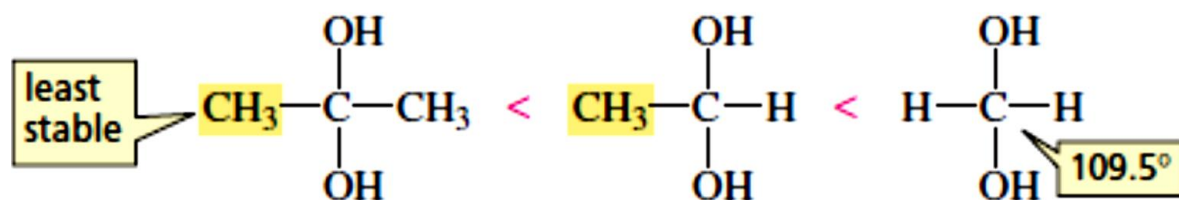


## nucleophilic addition reactions

The equilibrium constant for a reaction depends on the relative stabilities of the reactants and products. The equilibrium constant for hydrate formation, which is a measure of the extent of hydration, depends, therefore, on the relative stabilities of the carbonyl compound and the hydrate.



electron-donating alkyl groups make a carbonyl compound *more stable* (less reactive).

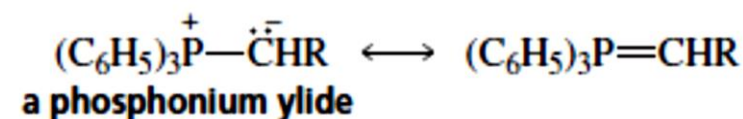
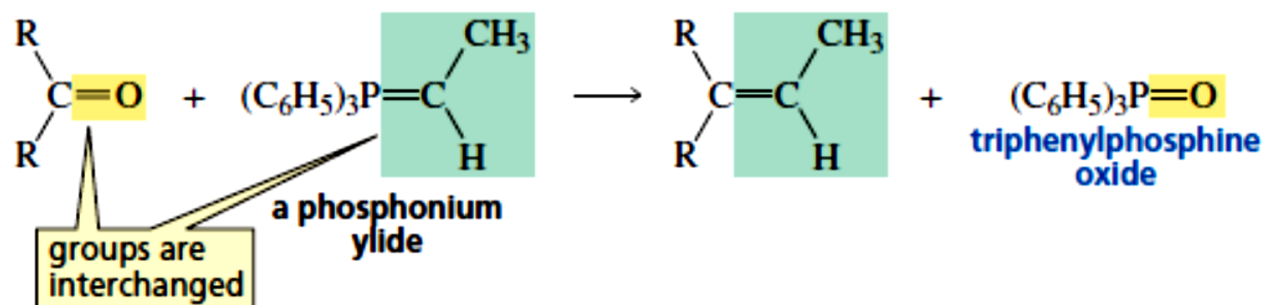


In contrast, alkyl groups make the hydrate *less stable* because of steric interactions between the alkyl groups when the bond angles change from 120° to 109.5°.

# The Wittig Reaction Forms An Alkene

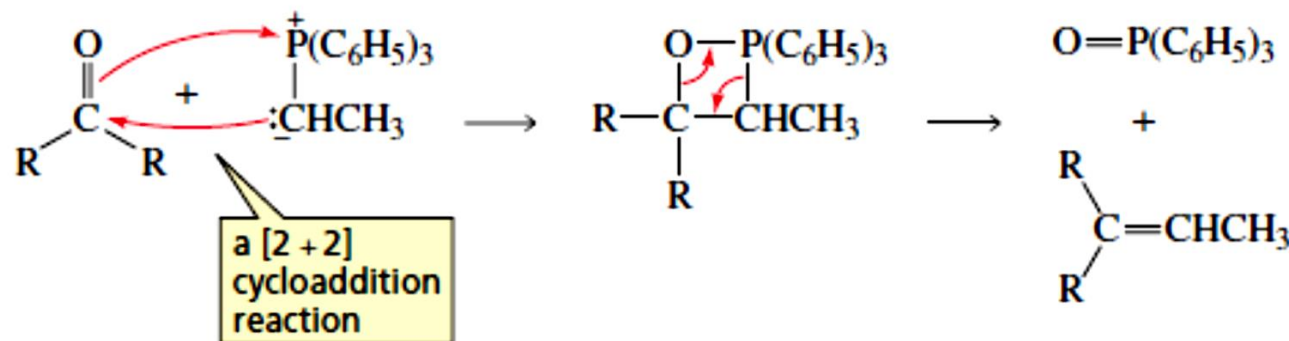


An aldehyde or a ketone reacts with a *phosphonium ylide* to form an alkene. This reaction, called a **Wittig reaction**, interchanges the double-bonded oxygen of the carbonyl compound with the double-bonded carbon group of the phosphonium ylide. An **ylide** is a compound with opposite charges on adjacent covalently bonded atoms that have complete octets.



The ylide can be written in the double-bonded form because phosphorus can have more than eight valence electrons

## MECHANISM FOR THE WITTIG REACTION

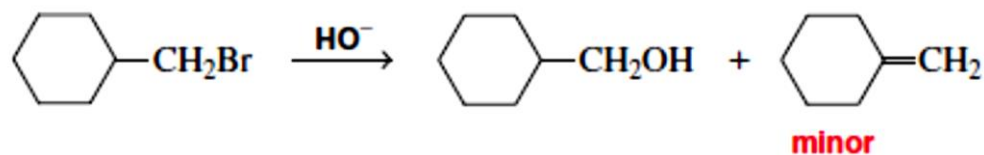
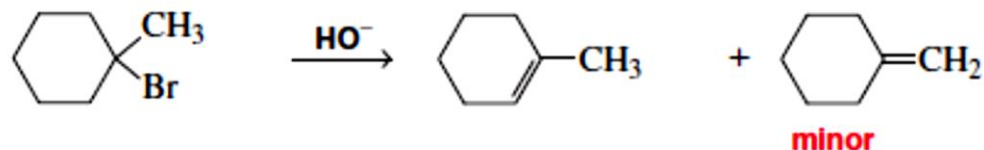
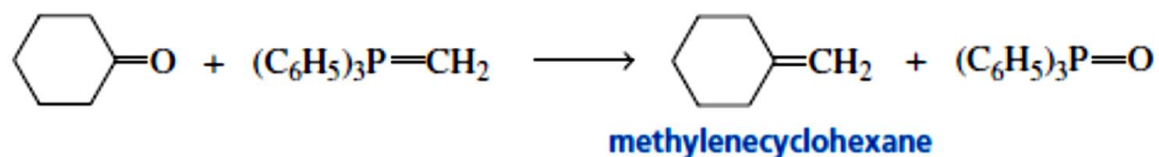
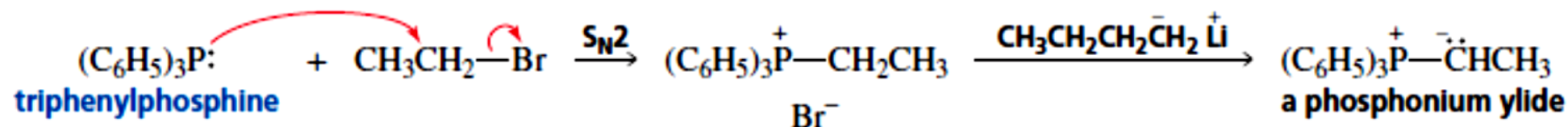


The phosphonium ylide needed for a particular synthesis is obtained by an  $S_N2$  reaction between triphenylphosphine and an alkyl halide with the appropriate number of carbons.

# The Wittig Reaction Forms An Alkene



A proton on the carbon adjacent to the positively charged phosphorus atom is sufficiently acidic ( $pK_a = 35$ ) to be removed by a strong base such as butyllithium. The Wittig reaction is a powerful way to make an alkene because the reaction is completely regioselective. The double bond will be in only one place.



The Wittig reaction is the best way to make a terminal alkene, such as the one just shown, because other methods would form a terminal alkene only as a minor product

# Relative reactivities of carboxylic acids and carboxylic acid derivatives



There are two steps in a nucleophilic addition–elimination reaction: *formation* of a tetrahedral intermediate and *collapse* of the tetrahedral intermediate.

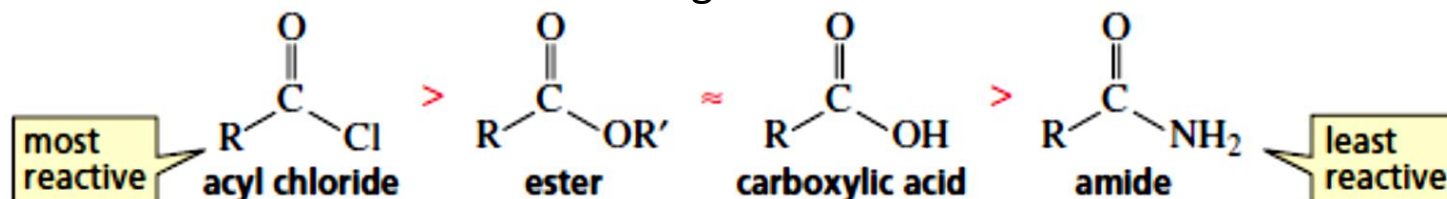
relative basicities of the leaving groups

weakest base



strongest base

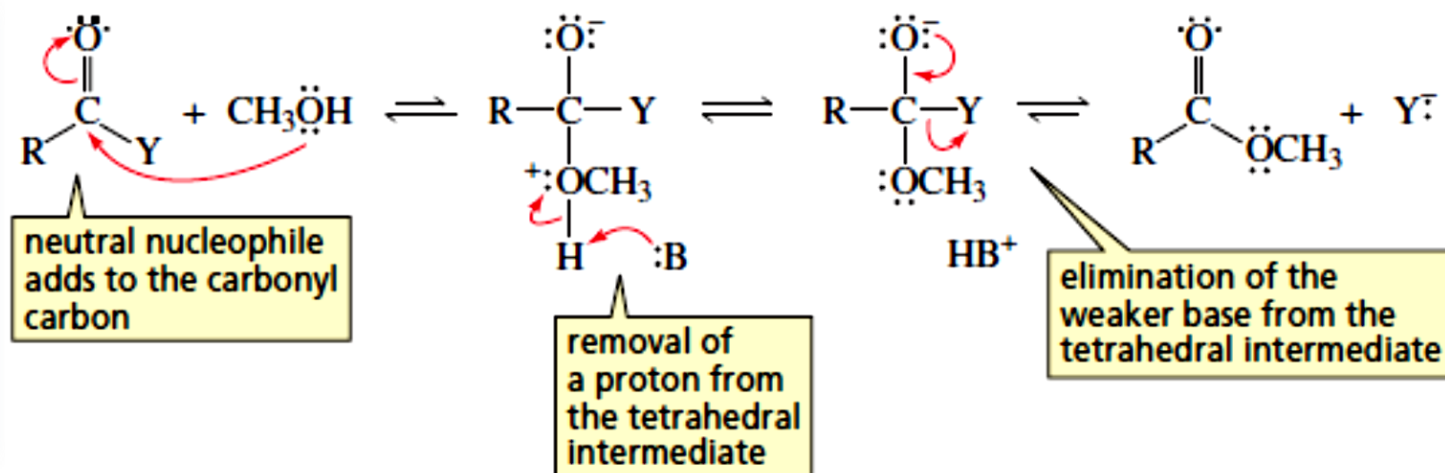
The weaker the base attached to the acyl group, the easier it is for *both steps* of the reaction to take place. Therefore, carboxylic acid derivatives have the following relative reactivities:



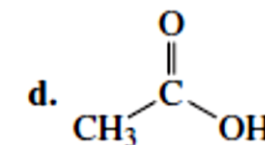
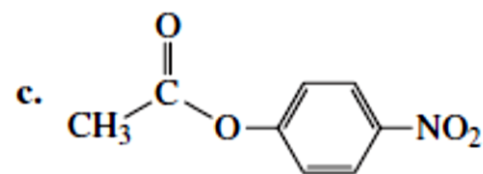
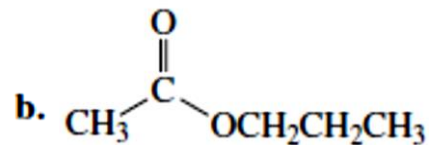
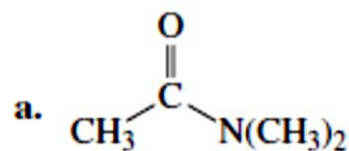
## The reactions of acyl halides:

Acyl chlorides react with water to form carboxylic acids, with amines to form amides and with alcohols to form esters because, in each case, the incoming nucleophile is a stronger base than the departing halide ion. All mentioned reactions followed the same mechanism.

### MECHANISM FOR A NUCLEOPHILIC ADDITION-ELIMINATION REACTION WITH A NEUTRAL NUCLEOPHILE



**Q1/** Starting with acetyl chloride, what neutral nucleophile would you use to make each of the following:



**Q2/** Why is only one amide obtained from the reaction of acetyl chloride with an equivalent of ethylamine and an equivalent of triethylamine?

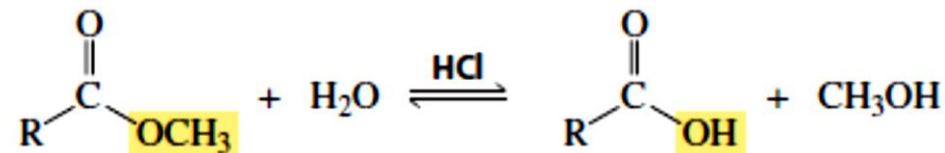
### The reactions of esters:

Esters do not react with chloride ion because it is a much weaker base than the  $\text{RO}^-$  group of the ester, so  $\text{Cl}^-$  (not  $\text{RO}^-$ ) would be the base eliminated from the tetrahedral intermediate.

Both the hydrolysis and the alcoholysis of an ester are very slow reactions because water and alcohols are poor nucleophiles and the  $\text{RO}^-$  group of an ester is a poor leaving group. Therefore, these reactions are always catalyzed when carried out in the laboratory.

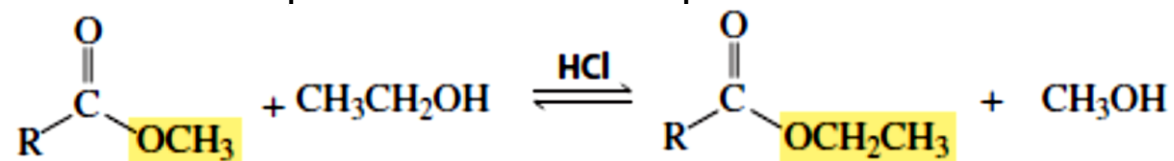
#### a hydrolysis reaction

An ester reacts with water to form a carboxylic acid and an alcohol. This is an example of a hydrolysis reaction. A hydrolysis reaction is a reaction with water that converts one compound into two compounds.



#### a transesterification reaction

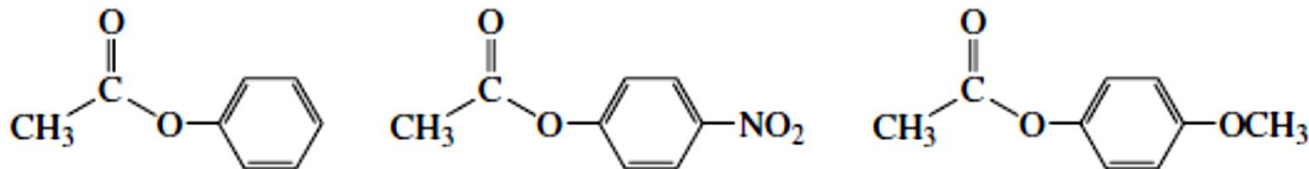
An ester reacts with an alcohol to form a new ester and a new alcohol. This is an example of an alcoholysis reaction —a reaction with an alcohol that converts one compound into two compounds.





**Q1/** What is a transesterification reaction? An alcoholysis reaction of esters is also called a **transesterification reaction** because one ester is converted to another ester.

**Q2/** List the following esters in order from most reactive to least reactive toward hydrolysis: *Why?*

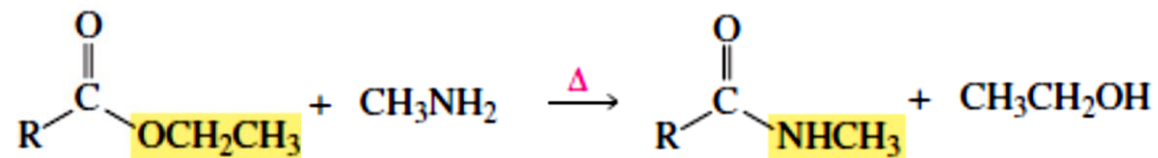


### The reactions of esters:

An amine is a better nucleophile. This is fortunate because the reaction cannot be catalyzed by an acid. The acid would protonate the amine, and a protonated amine is not a nucleophile. The rate of the reaction, however, can be increased by heat.

#### an aminolysis reaction

Esters react with amines to form an amides and an alcohol. The reaction of an ester with an amine is not as slow as the reaction of an ester with water or an alcohol.



**Q1/** Write the aminolysis mechanism of phenyl formate, using methylamine.

**Q2/** Which is faster, the hydrolysis of an ester or the aminolysis of the same ester? Explain your answer.

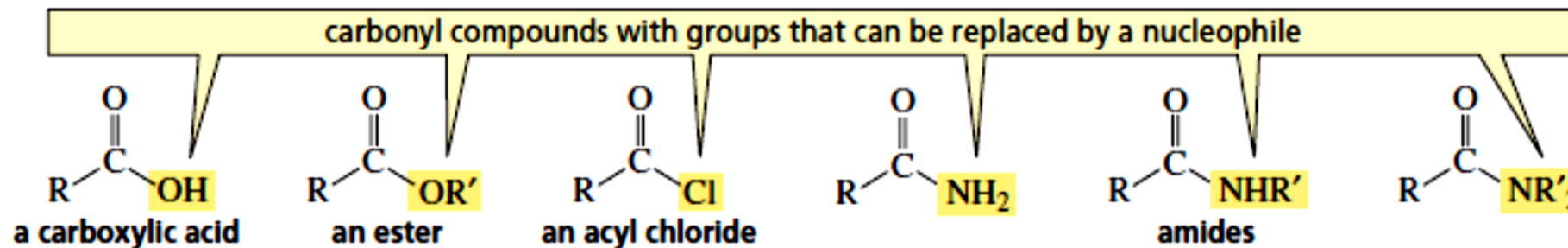
# The relative reactivities of carboxylic acids and carboxylic acid derivatives

The lower the  $pK_a$ , the stronger the acid and the weaker its conjugate base. The acyl groups of carboxylic acids and carboxylic acid derivatives are attached to weaker bases than are the acyl groups of aldehydes and ketones. The hydrogen of an aldehyde and the alkyl group of a ketone are too basic to be replaced by another group.

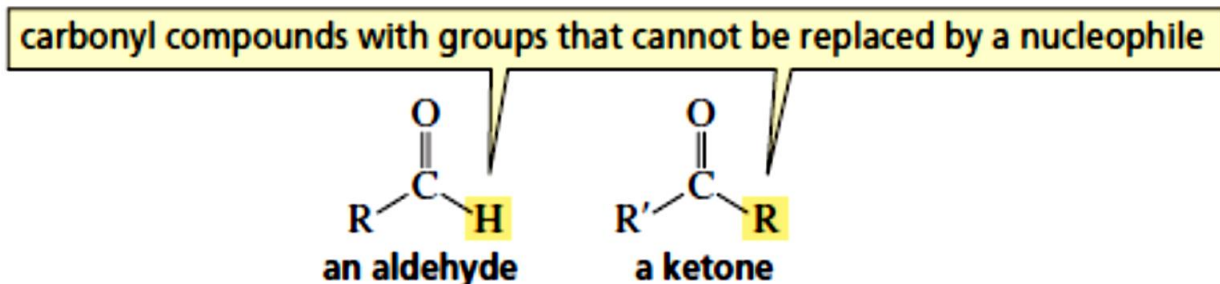
The  $pK_a$  Values of the Conjugate Acids of the Leaving Groups of Carbonyl Compounds

Carbonyl compound	Leaving group	Conjugate acid of the leaving group	$pK_a$
<b>Carboxylic Acids and Carboxylic Acid Derivatives</b>			
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{Cl} \end{array}$	$\text{Cl}^-$	HCl	-7
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{OR}' \end{array}$	$^-\text{OR}'$	$\text{R}'\text{OH}$	~15-16
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{OH} \end{array}$	$^-\text{OH}$	$\text{H}_2\text{O}$	15.7
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{NH}_2 \end{array}$	$^-\text{NH}_2$	$\text{NH}_3$	36*
<b>Aldehydes and Ketones</b>			
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{H} \end{array}$	$\text{H}^-$	$\text{H}_2$	35
$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}-\text{C}-\text{R} \end{array}$	$\text{R}^-$	$\text{RH}$	> 60

# Reactions of Carboxylic Acids and Carboxylic Acid Derivatives



Esters, acyl chlorides, and amides are called **carboxylic acid derivatives** because they differ from a carboxylic acid only in the nature of the group or atom that replaced the OH group of the carboxylic acid. These compounds undergo substitution reactions, because they have an acyl group attached to a group that can be replaced by a nucleophile.



The second class of carbonyl compounds; aldehydes and ketones, are those in which the acyl group is attached to a group that *cannot* be readily replaced by another group. These compounds *do not* undergo substitution reactions because their acyl group is attached to a group that *cannot* be replaced by a nucleophile.