The Chemistry of Carbonyl Compounds

6th Lec. Of medical chemistry

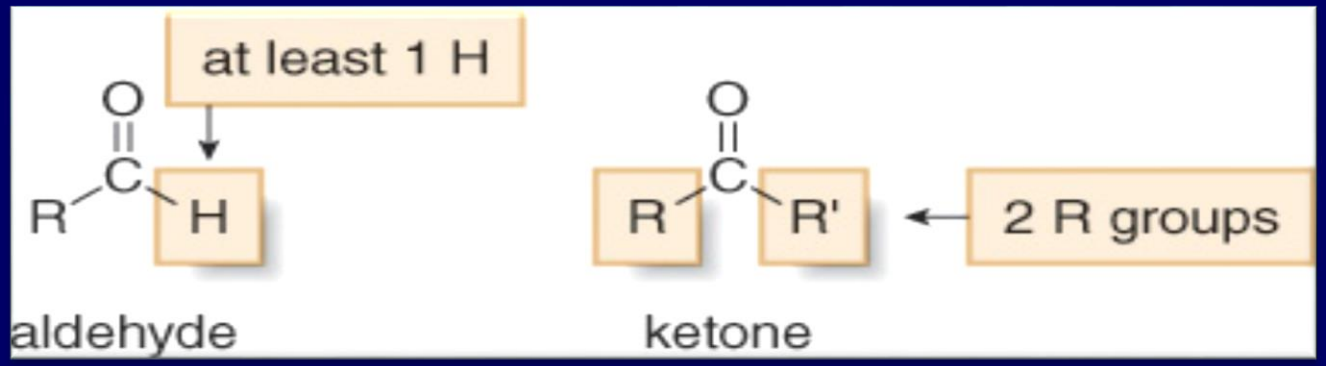
by

Dr. Salih Mahdi Salman

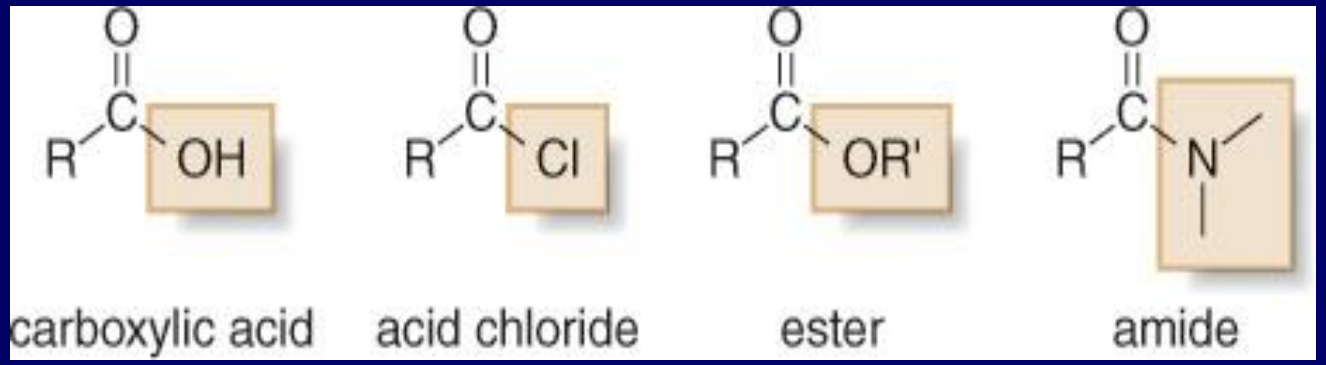
Introduction

Two broad classes of compounds contain the carbonyl group

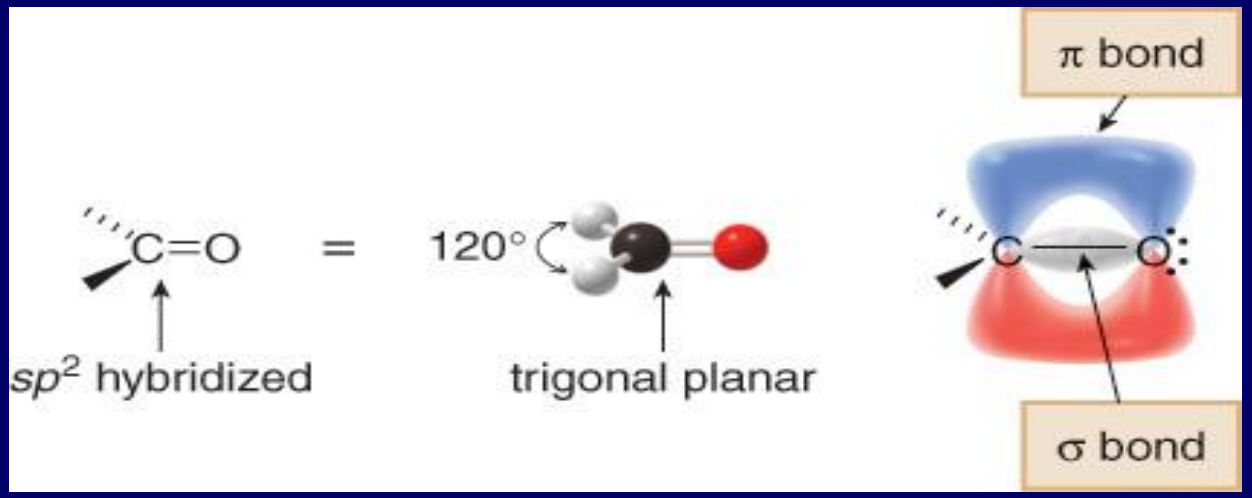
1. Compounds that have only carbon and hydrogen atoms bonded to the carbonyl



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

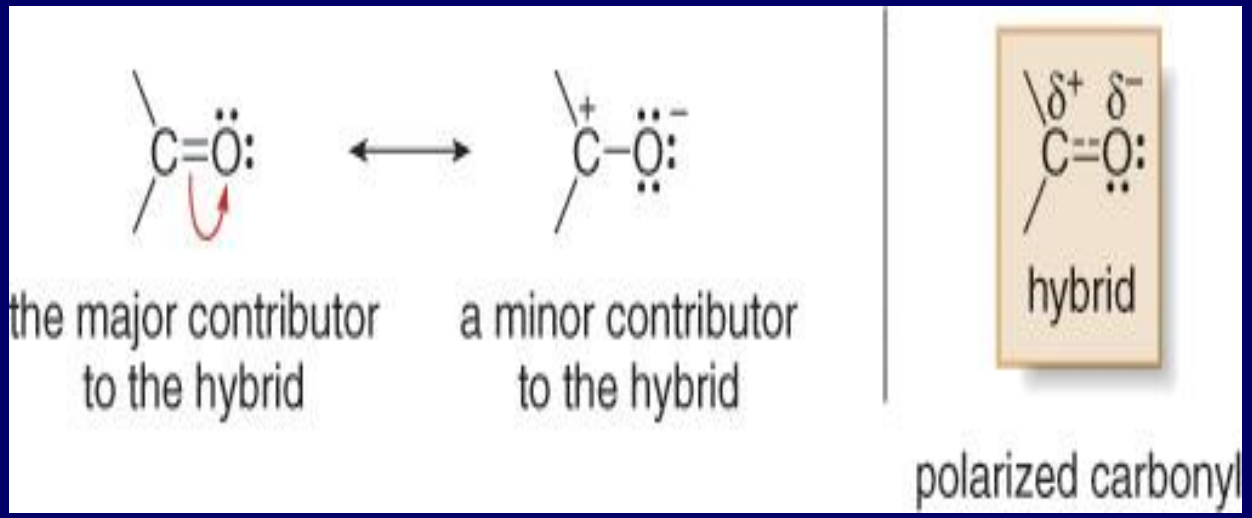


Carbonyl carbons are sp^2 hybridized, trigonal planar, and have bond angles that are ~120^0. In these ways, the carbonyl group resembles the trigonal planar sp^2 hybridized carbons of a C=C.

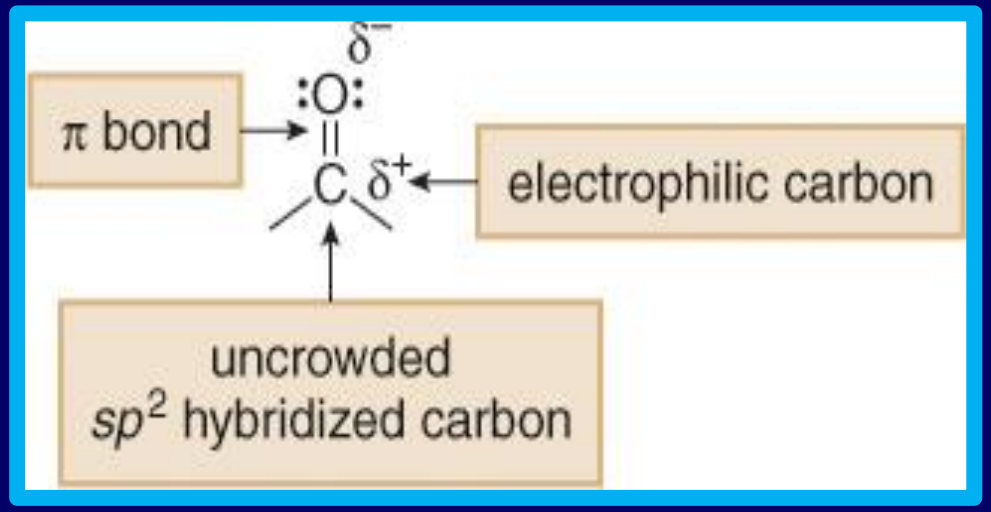


The electronegative oxygen atom in the carbonyl group means that the bond is polarized, making the carbonyl carbon electron deficient.

Using a resonance description, the carbonyl group is represented by two resonance structures.



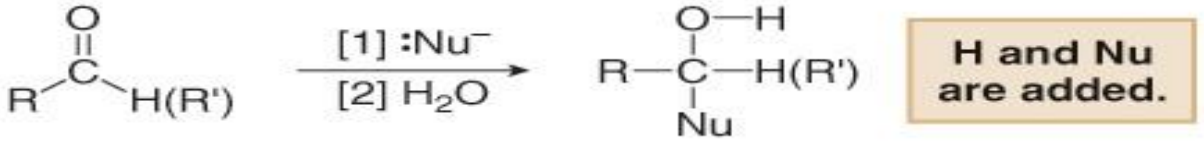
General Reactions of Carbonyl Compounds



1. Carbonyls react with nucleophiles.

- Aldehydes and ketones undergo nucleophilic addition.

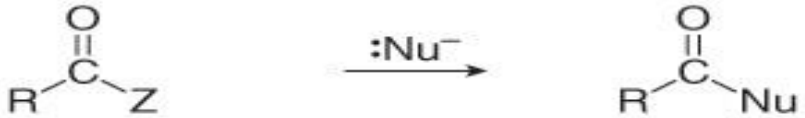
Nucleophilic addition—General reaction



H and Nu are added.

- Carbonyl compounds that contain leaving groups undergo nucleophilic substitution.

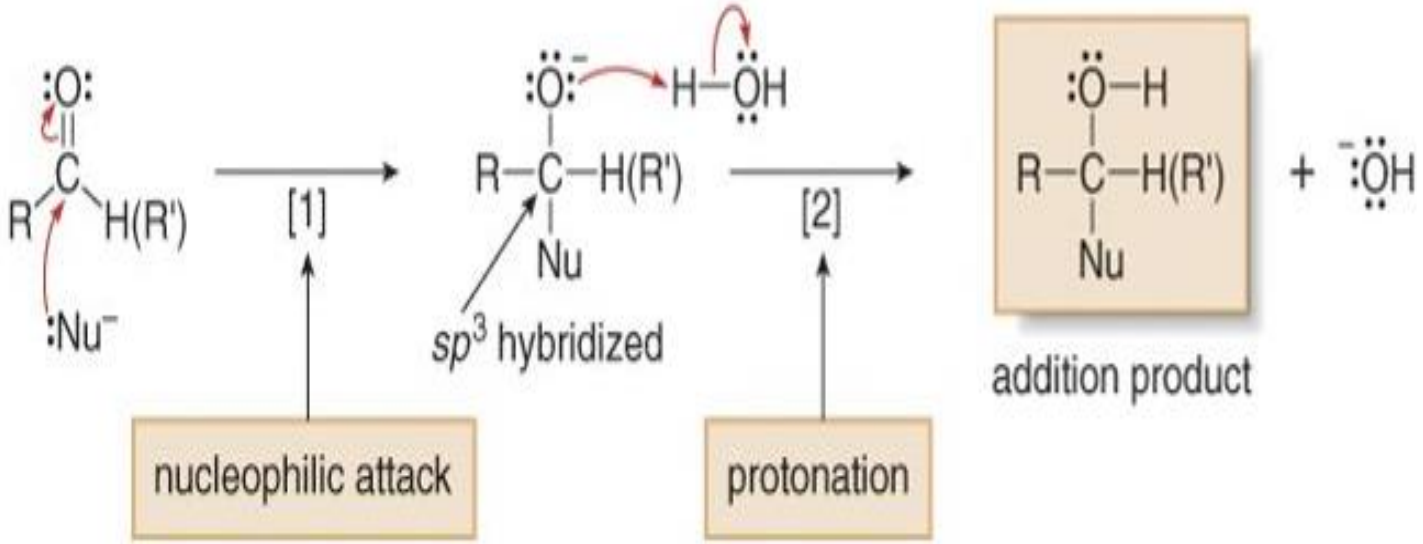
Nucleophilic substitution—General reaction



Z = OH, Cl, OR, NH_2

Nu replaces Z.

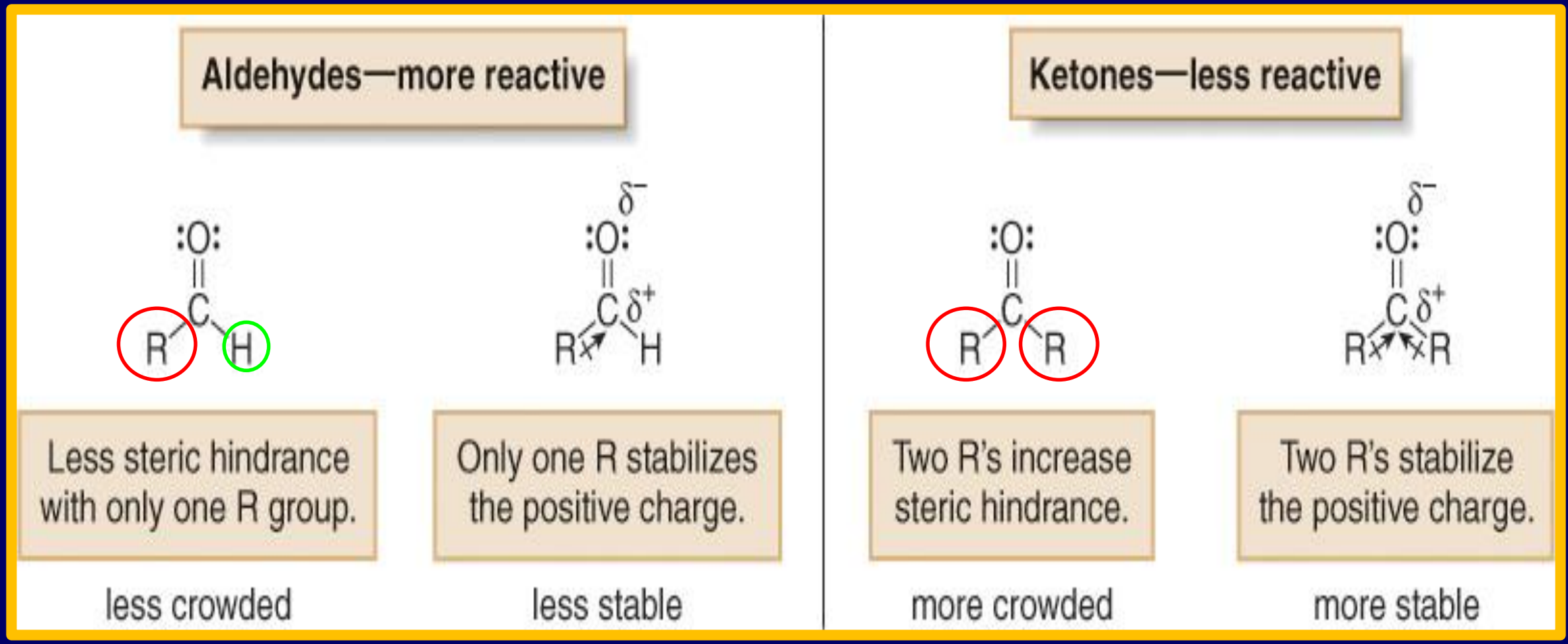
Aldehydes and ketones react with nucleophiles to form addition products by a two-step process: **nucleophilic attack** followed by **protonation**.



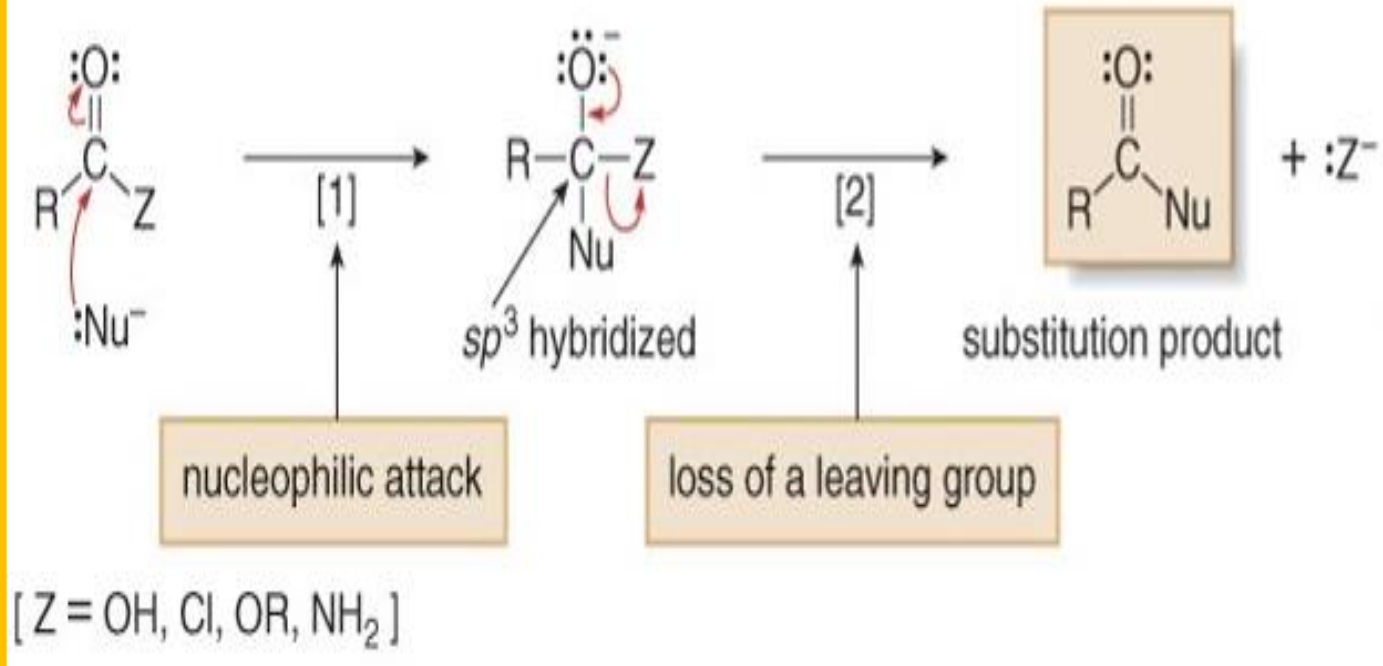
- In Step [1], **the nucleophile (:Nu⁻) attacks the electrophilic carbonyl.** As the new bond to the nucleophile forms, the π bond is broken, moving an electron pair out on the oxygen atom. This forms an sp^3 hybridized intermediate.
- In Step [2], **protonation of the negatively charged oxygen atom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

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**.



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.**

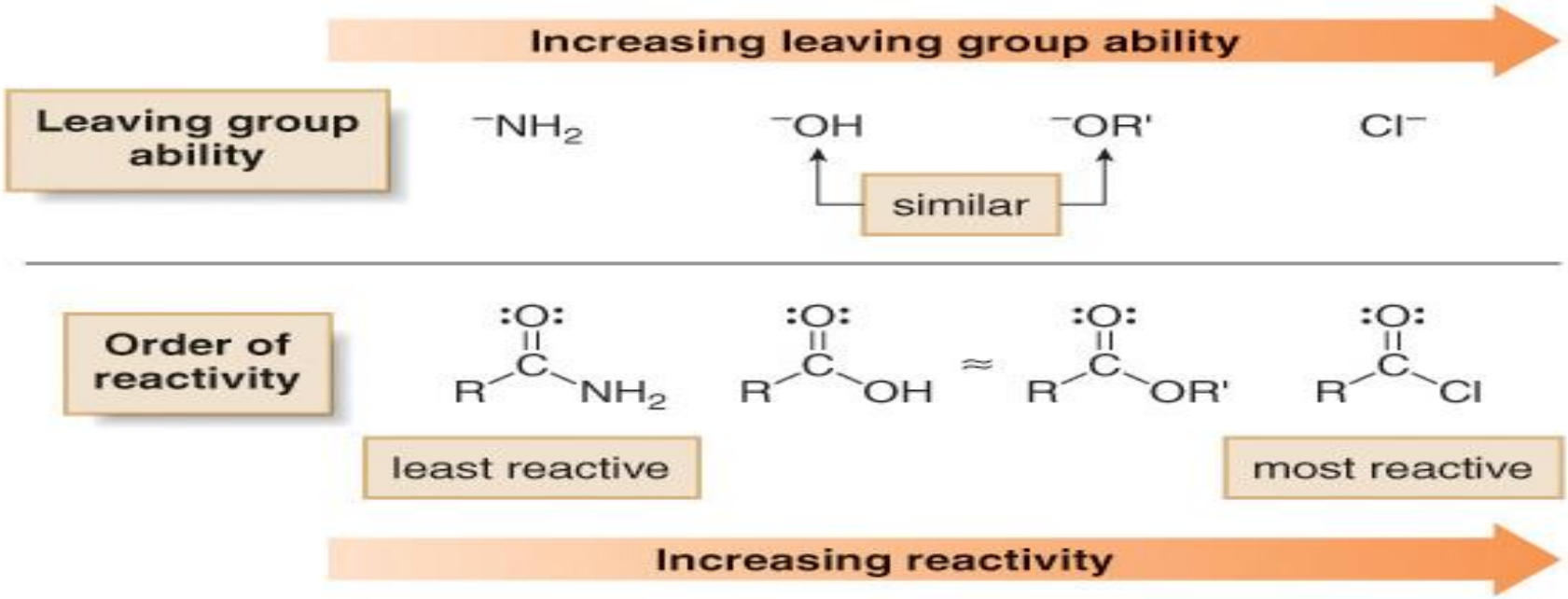


- In Step [1], **the nucleophile (:Nu⁻) attacks the electrophilic carbonyl,** forming an sp^3 hybridized intermediate. This step is identical to nucleophilic addition.
- Step [2] is different. Because the intermediate contains an electronegative atom Z, **Z can act as a leaving group.** To do so, an 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 in a nucleophilic substitution reaction. This reaction is often called **nucleophilic acyl substitution.**

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

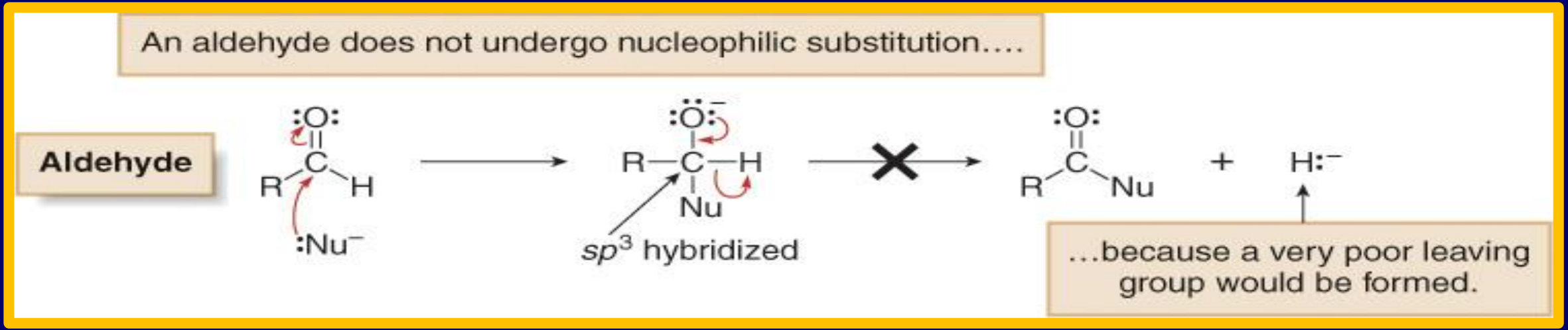
Thus, the following trends result:



- 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.

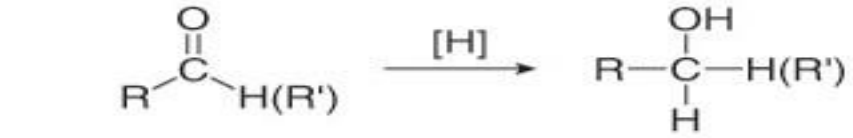
- **Nucleophilic addition** and **nucleophilic acyl substitution** involve the same first step nucleophilic attack on the electrophilic carbonyl carbon to form a tetrahedral intermediate.
- The difference between the two reactions is what then happens to the intermediate.
- **Aldehydes and ketones**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



2. Oxidation and Reduction

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

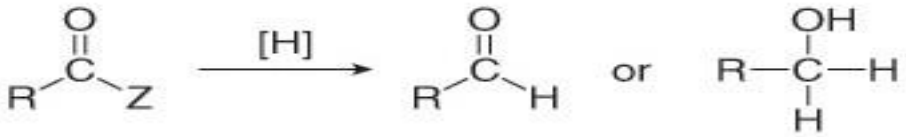
[1] Reduction of aldehydes and ketones to alcohols



aldehyde or ketone 1° or 2° alcohol

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

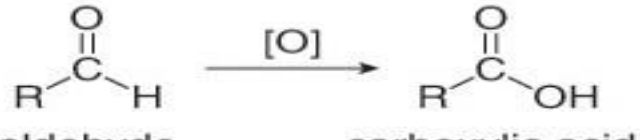
[2] Reduction of carboxylic acid derivatives



aldehyde 1° alcohol

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.

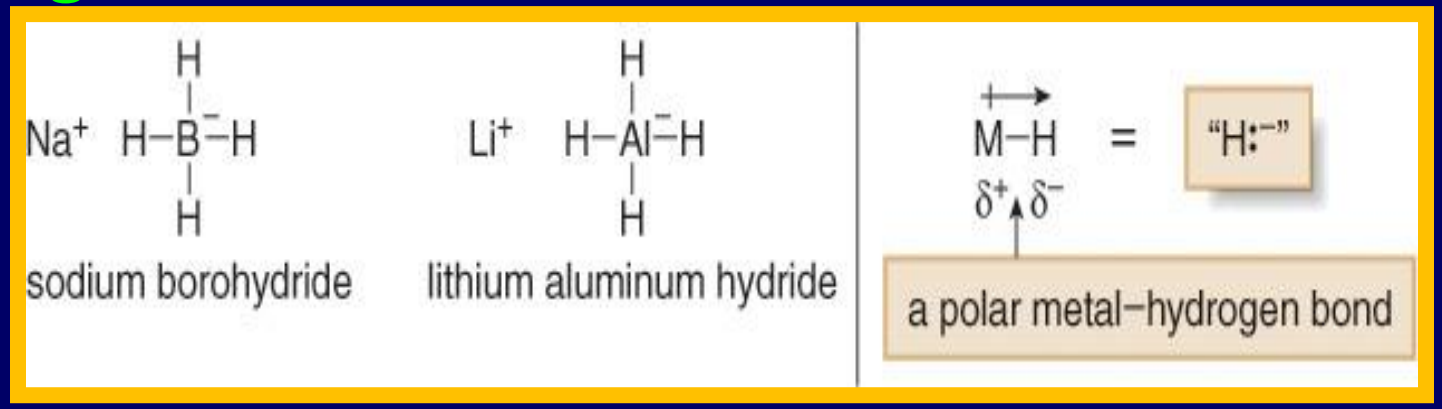
[3] Oxidation of aldehydes to carboxylic acids



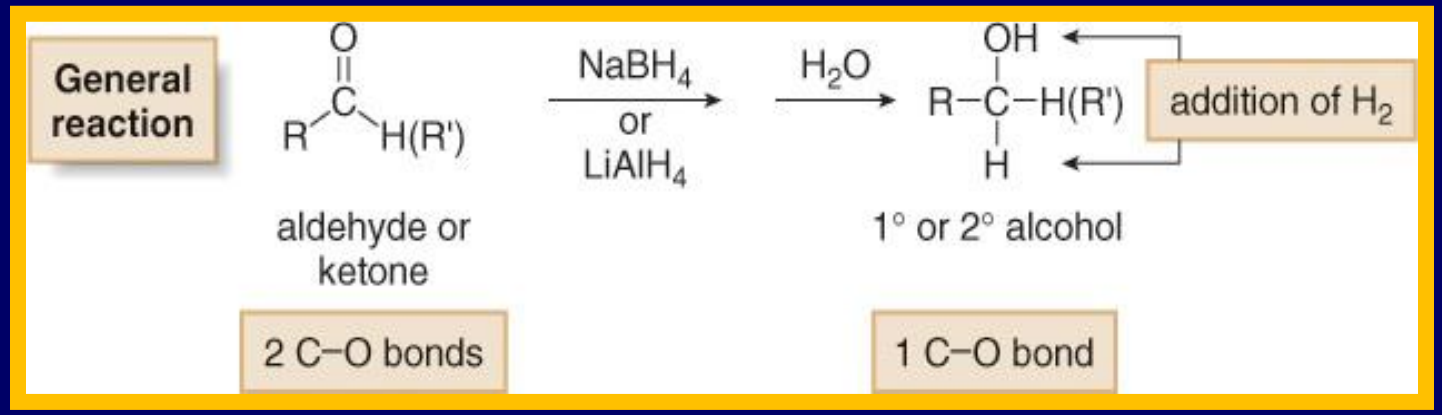
aldehyde carboxylic acid

Reduction of Aldehydes and Ketones

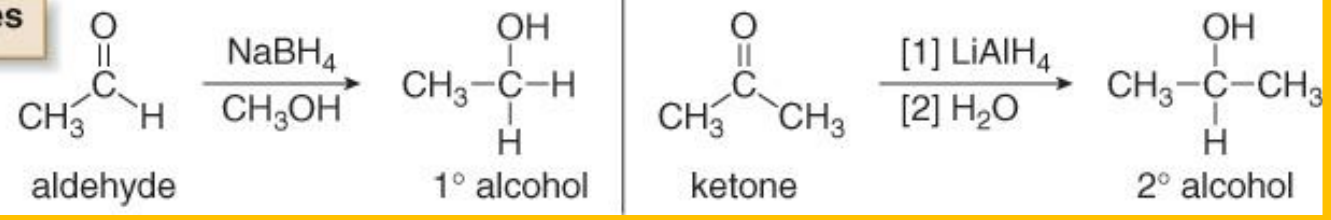
The most useful reagents for reducing aldehydes and ketones are the **metal hydride reagents.**



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

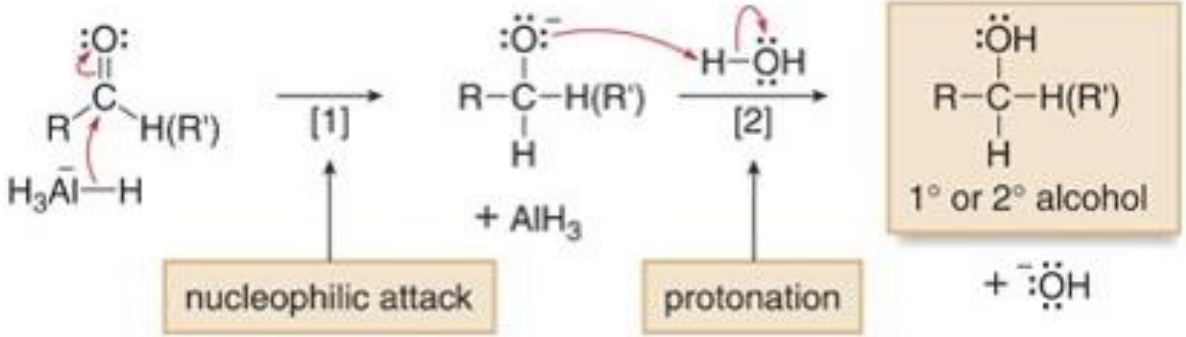


Examples



MECHANISM

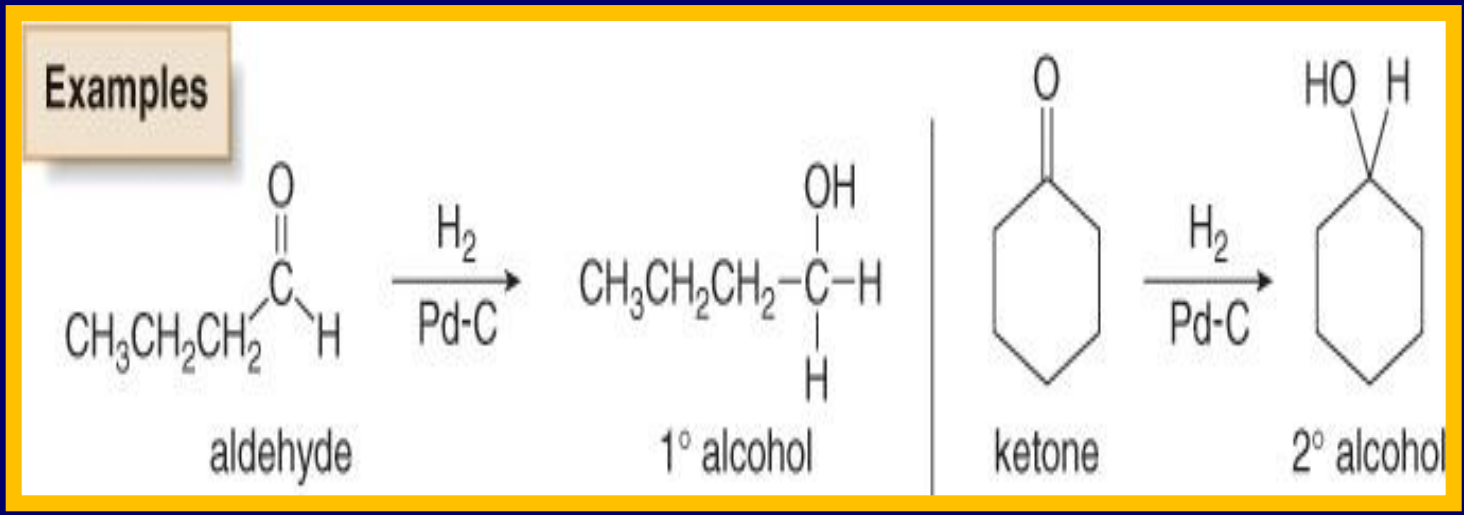
$LiAlH_4$ Reduction of RCHO and $R_2C{=}O$



- In Step [1] **the carbo**, **the nucleophile (AlH_4^-) donates $H:^-$ to** an electro**nyl group,** cleaving the π bond, and moving n 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 also reduces aldehydes and ketones to 1^0 and 2^0 alcohols respectively, using H_2 and a catalyst.

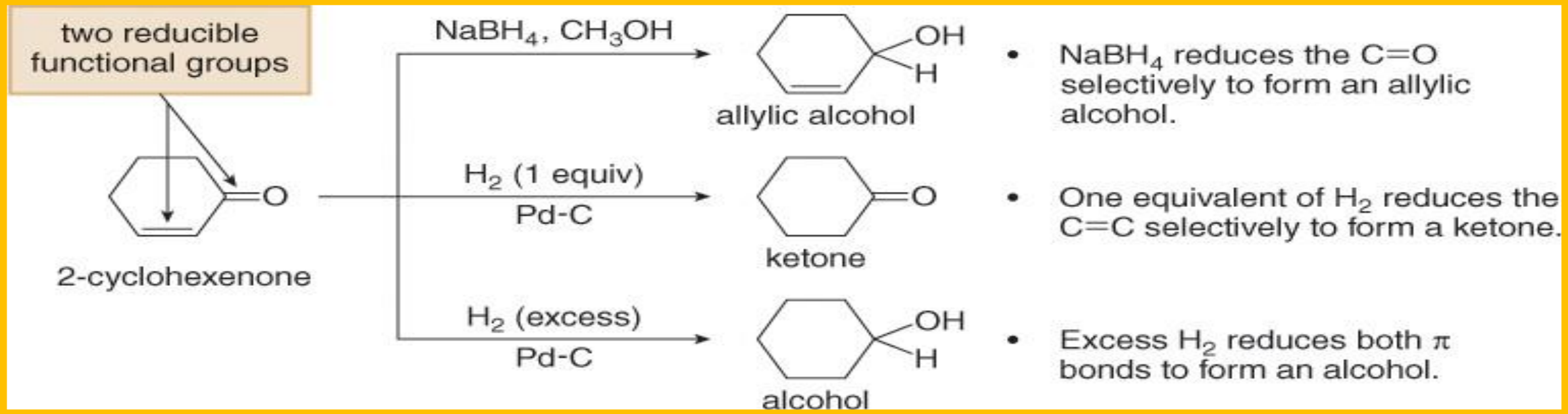


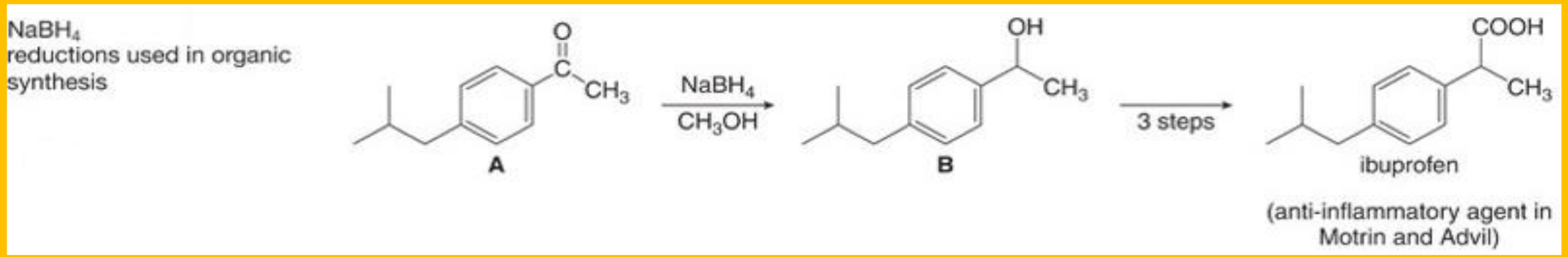
- When a compound contains both a carbonyl group and a carbon—carbon double bond, selective reduction of one functional group can be achieved by proper choice of the reagent.

  -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.

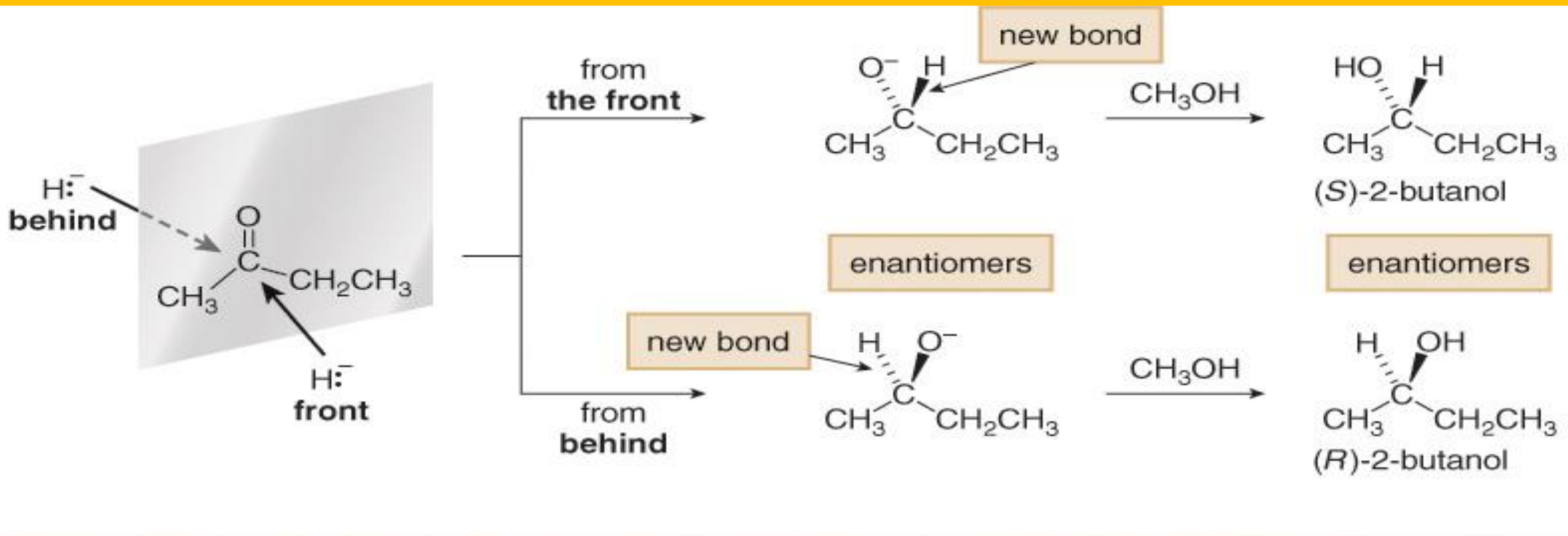
Thus, 2-cyclohexenone, which contains both a C=C and a C=O, can be reduced to three different compounds depending upon the reagent used.





The Stereochemistry of Carbonyl Reduction

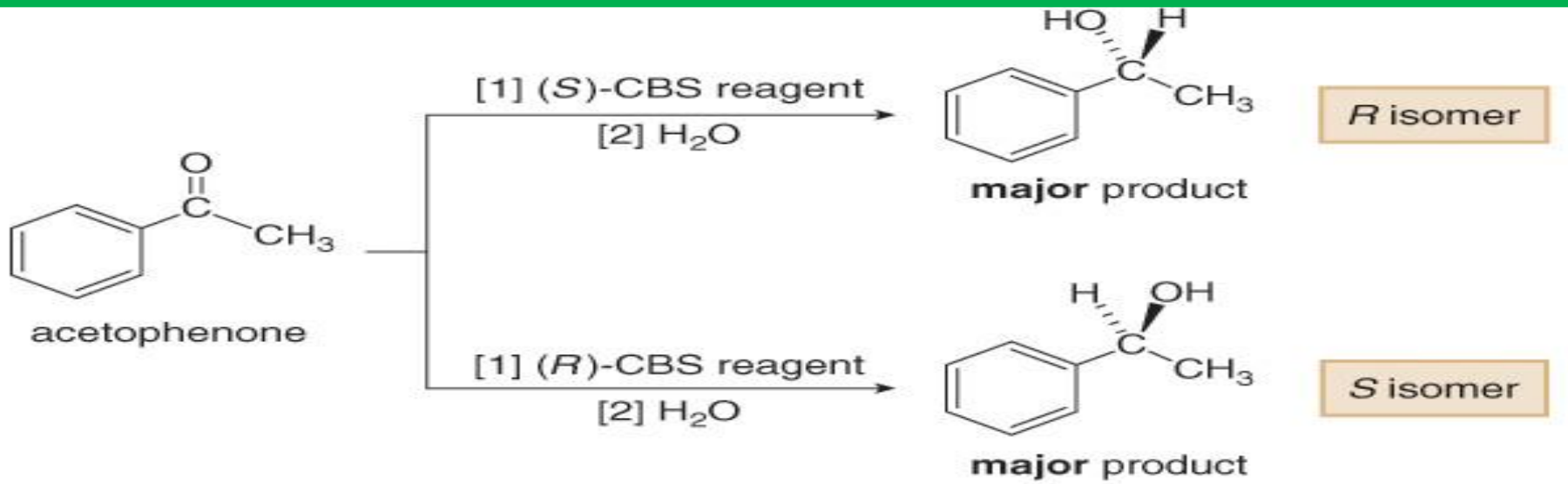
Hydride converts a planar sp^2 hybridized carbonyl carbon to a tetrahedral sp^3 hybridized carbon.



- 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.

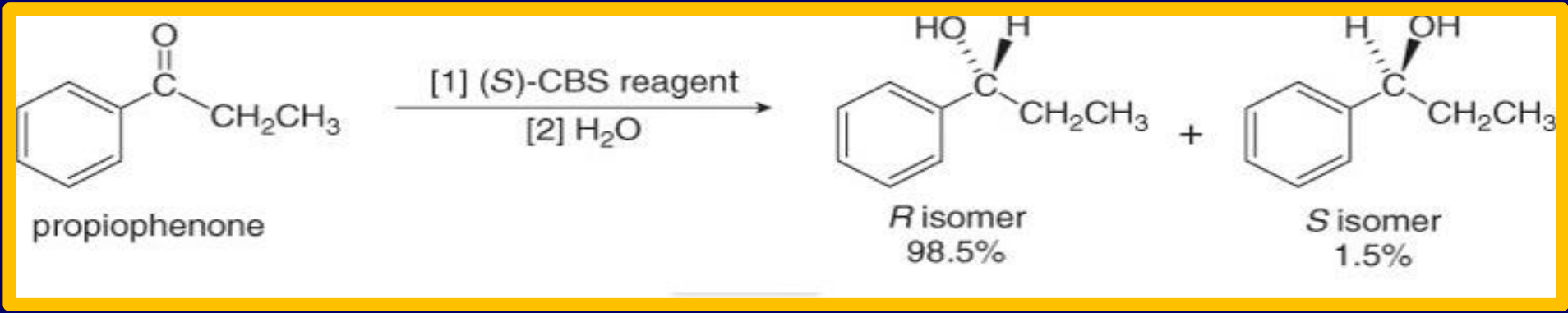
Enantioselective Carbonyl Reductions

- CBS refers to Corey, Bakshi and Shibata, the chemists who developed these versatile reagents.
- One B—H bond serves as the source of hydride in this reduction.
- CBS reagents predictably give one enantiomer as the major product of ketone reduction, as illustrated with acetophenone as the starting material.

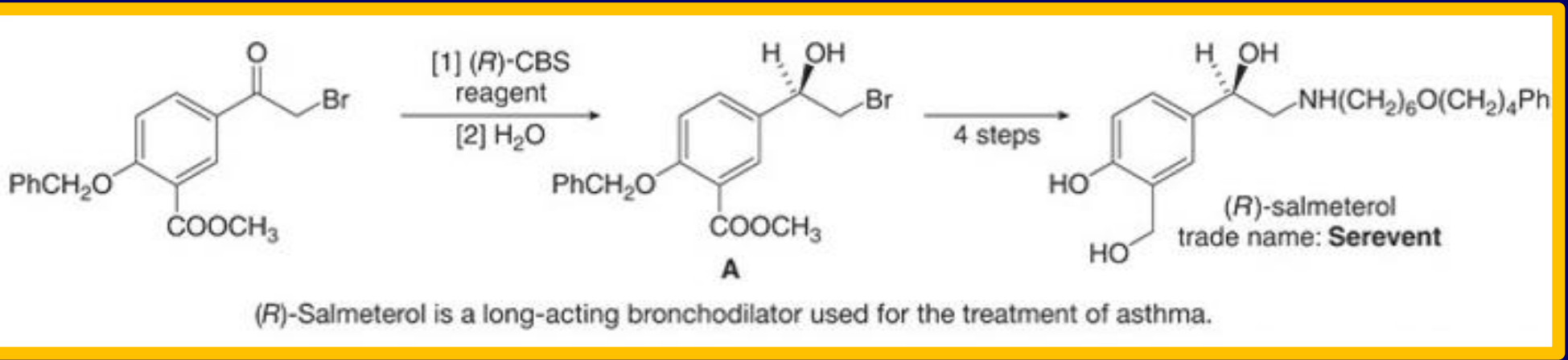


- The (S)-CBS reagent generally gives the R alcohol as major product.
- The (R)-CBS reagent generally gives the S alcohol as major product.

These reagents are highly enantioselective. For example, treatment of propiophenone with the (*S*)-CBS reagent forms the *R* alcohol in 98.5%

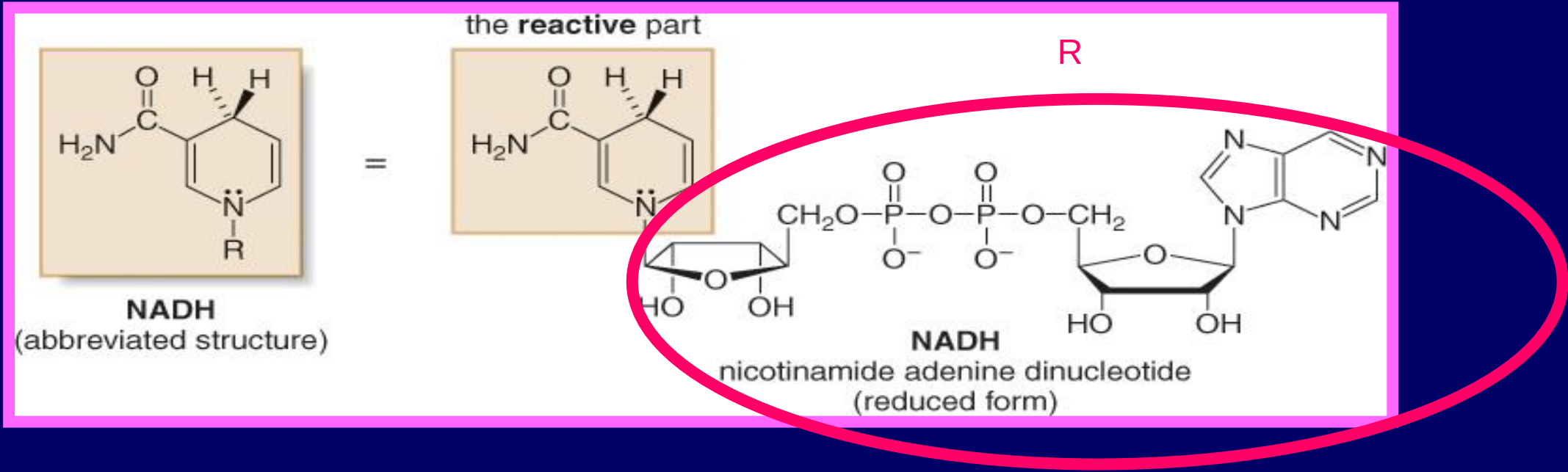


Enantioselective reduction using these reagents has provided the key step in the synthesis of several widely used drugs, including **salmeterol**, a long-acting bronchodilator.

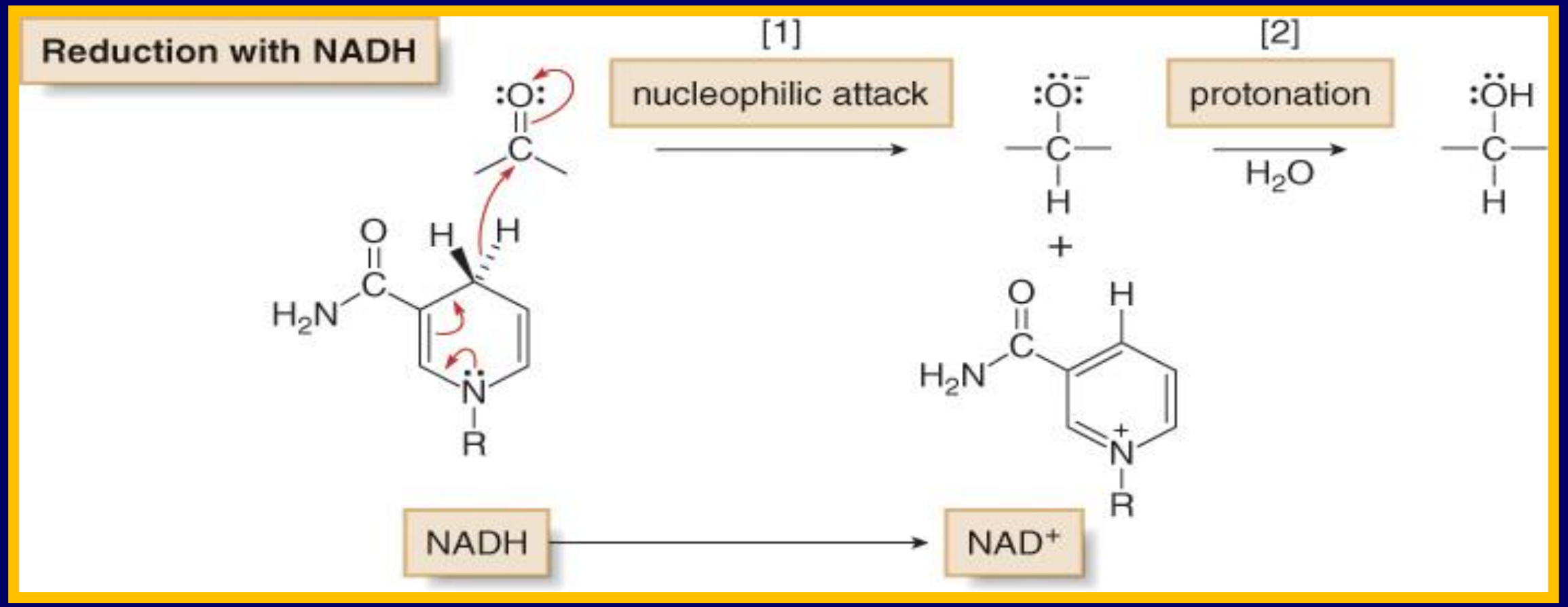


(*R*)-Salmeterol is a long-acting bronchodilator used for the treatment of asthma.

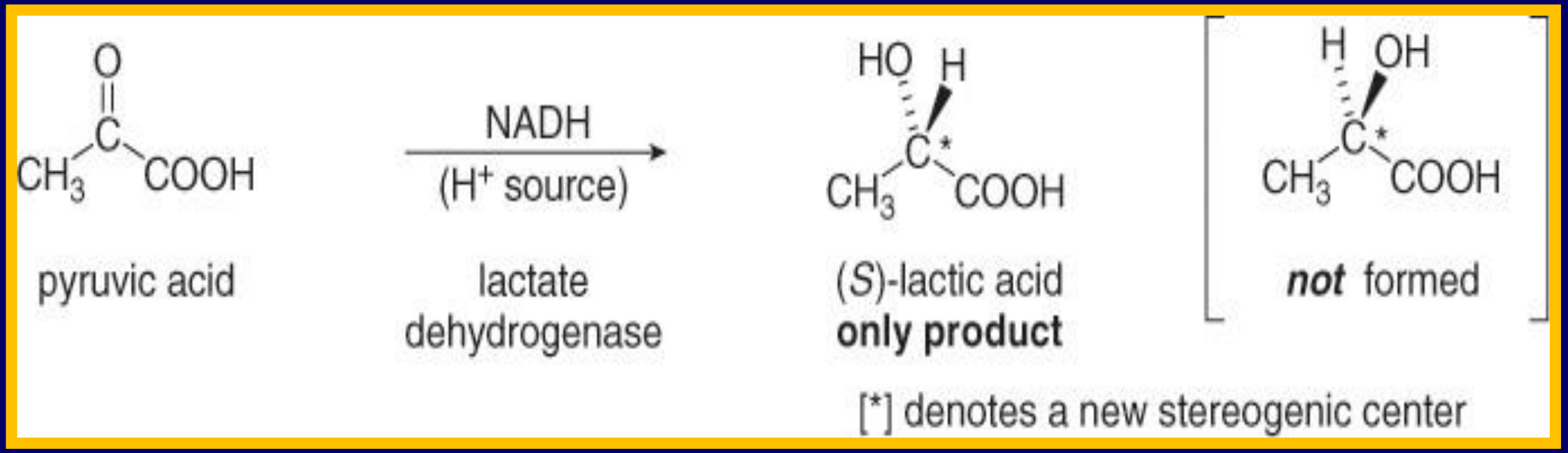
- Biological reductions that occur in cells always proceed with complete selectivity, forming a single enantiomer.
- In cells, the reducing agent is NADH.
- NADH is a coenzyme—an organic molecule that can function only in the presence of the enzyme.



- 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.

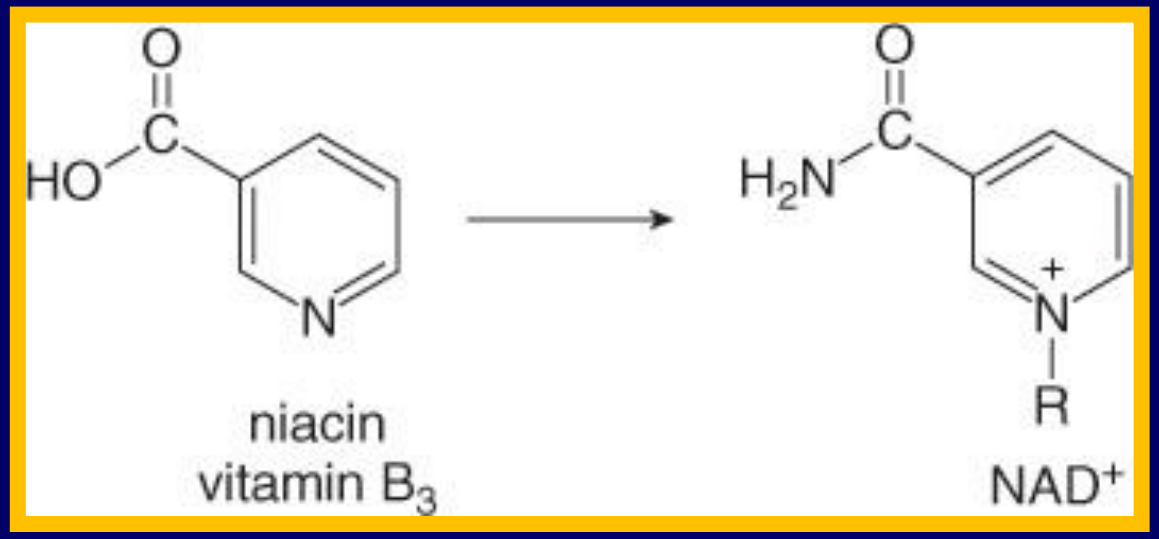


- The reaction is completely enantioselective. For example, reduction of pyruvic acid with NADH catalyzed by lactate dehydrogenase affords a single enantiomer with the *S* configuration.
- NADH reduces a variety of different carbonyl compounds in biological systems. The configuration of the product (*R*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



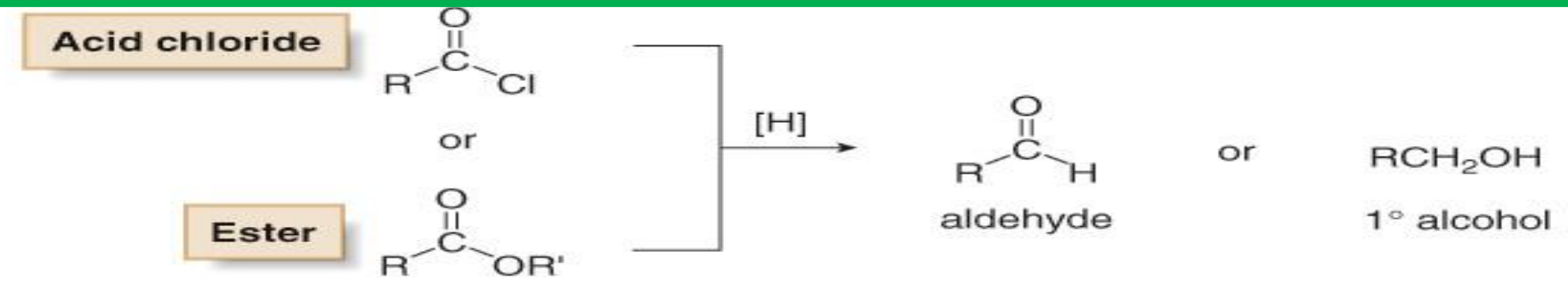
- NAD^+, the oxidized form of NADH, is a biological oxidizing agent capable of oxidizing alcohols to carbonyl compounds (it forms NADH in the process).

- NAD^+ is synthesized from the vitamin niacin.

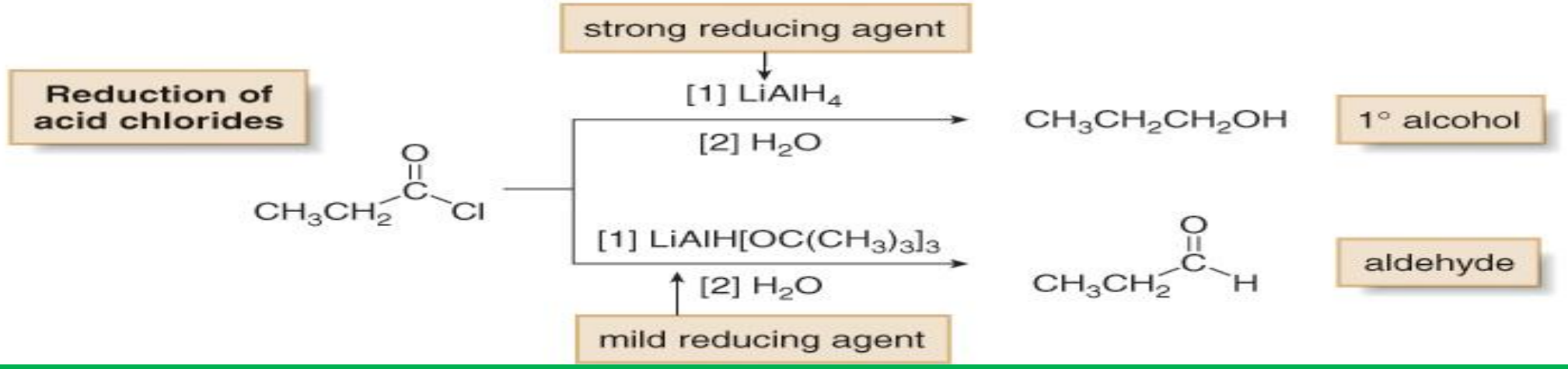


Reduction of Carboxylic Acids and Their Derivatives

Acid chlorides and esters can be reduced to either aldehydes or 1^0 alcohols depending on the reagent.



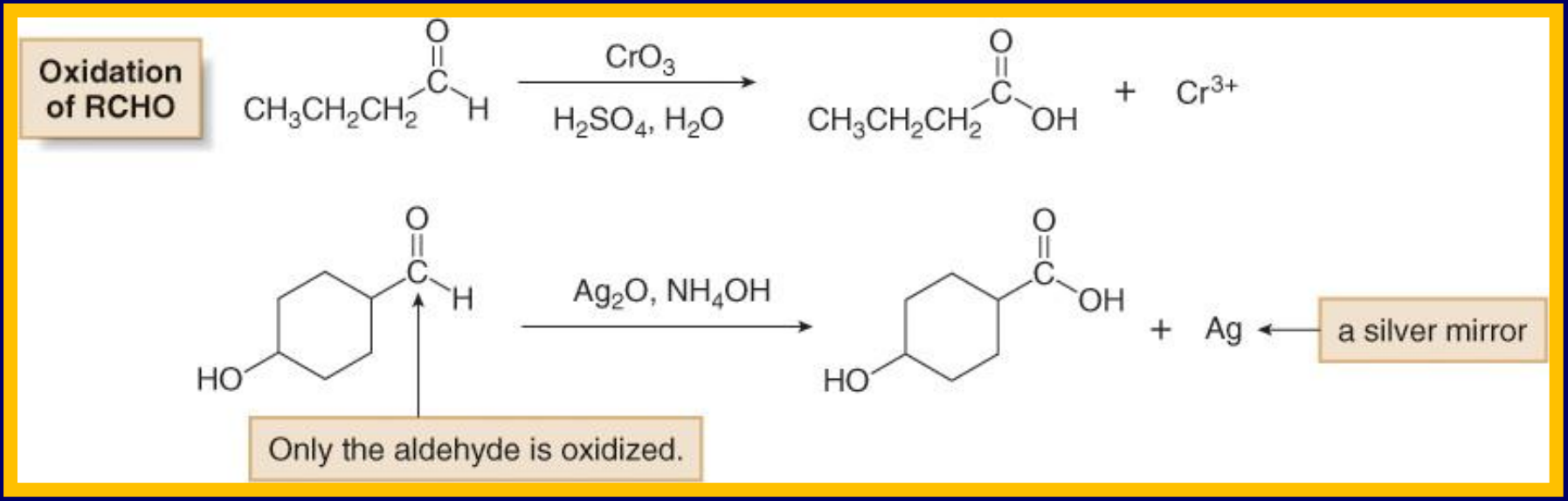
- $LiAlH_4$ converts RCOCl and RCOOR' to 1° alcohols.
- A milder reducing agent (DIBAL-H or $LiAlH[OC(CH_3)_3]_3$) converts RCOCl or RCOOR' to RCHO at low temperatures.



Oxidation of Aldehydes

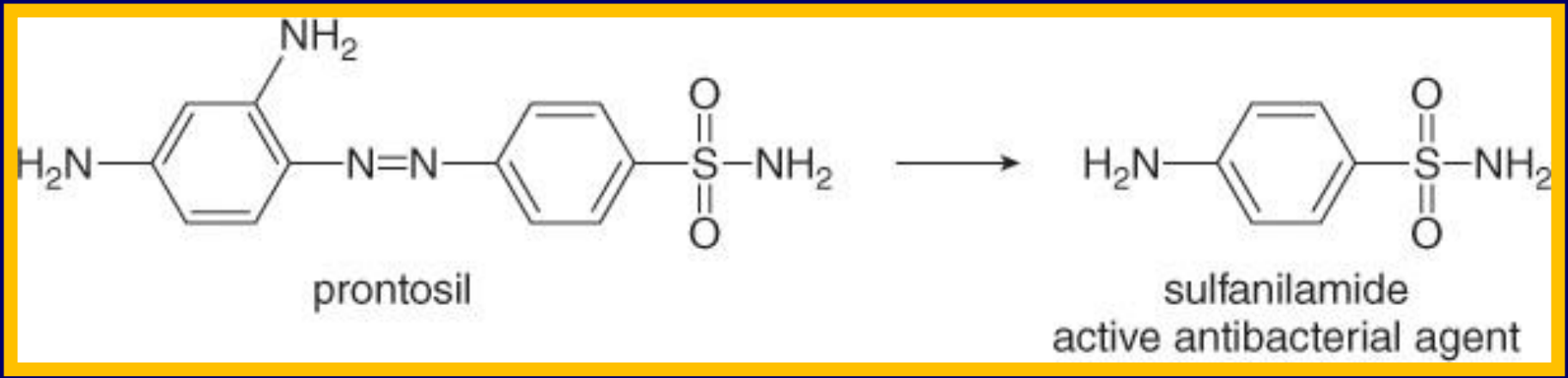
- A variety of oxidizing agents can be used, including CrO_3, $Na_2Cr_2O_7$, $K_2Cr_2O_7$, and $KMnO_4$.
- Aldehydes can also be oxidized selectively in the presence of other functional groups using silver(I) oxide in aqueous ammonium hydroxide (Tollen's reagent).

Since ketones have no H on the carbonyl carbon, they do not undergo this oxidation reaction.

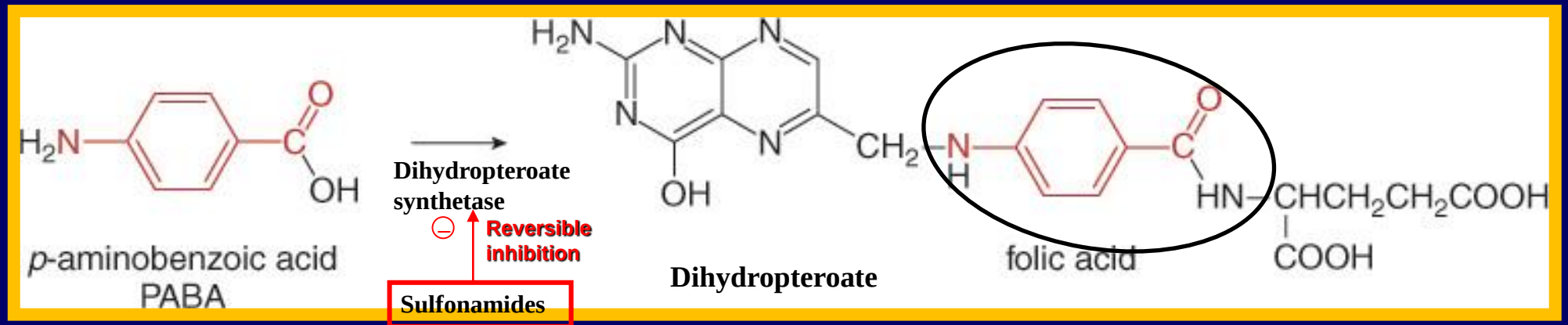


Sulfa Drugs

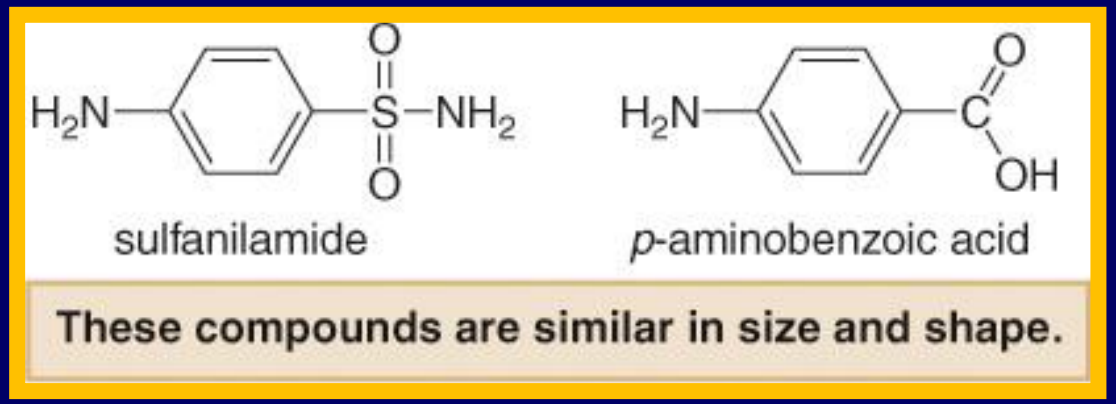
- In 1935, Gerhard Domagk first used a synthetic dye, prontosil, to kill bacteria.
- Prontosil and other sulfur containing antibiotics are collectively known as sulfa drugs.
- Prontosil is not the active ingredient itself.
- In cells, it is metabolized to sulfanilamide, the active drug.

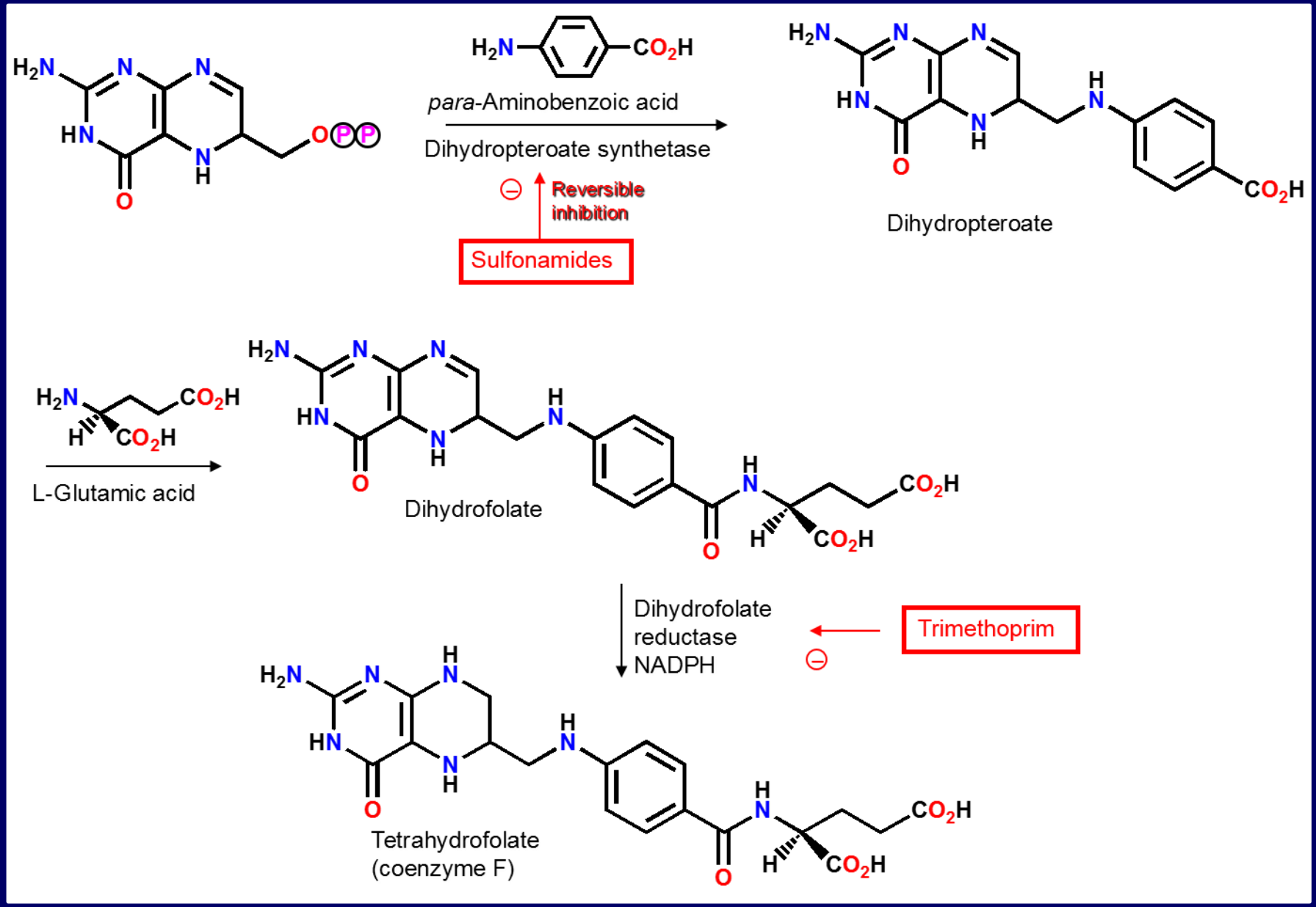


- To understand how sulfanilamide functions as an antibacterial agent, we must examine folic acid, which microorganisms synthesize from *p*-aminobenzoic acid.

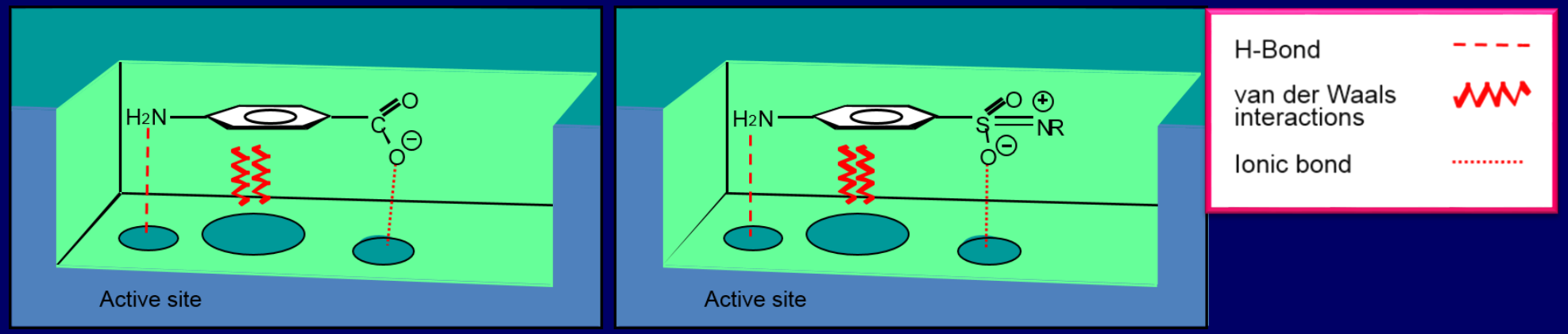


- Sulfanilamide and *p*-aminobenzoic acid are similar in size and shape and have related functional groups.

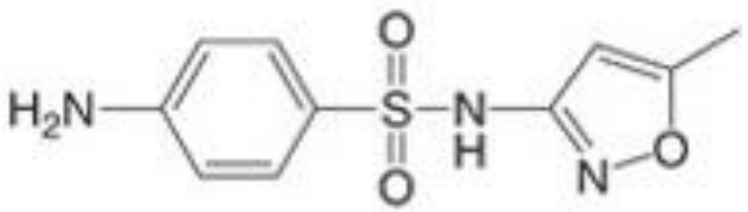



para-Aminobenzoic acid
Dihydropteroate synthetase
Reversible inhibition
Sulfonamides
Dihydropteroate
L-Glutamic acid
Dihydrofolate
Dihydrofolate reductase
NADPH
Trimethoprim
Tetrahydrofolate
(coenzyme F)

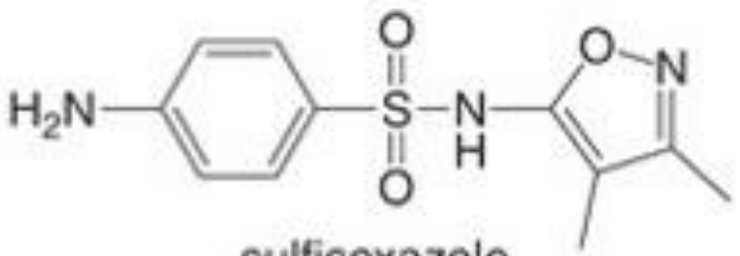
- When sulfanilamide is administered, bacteria attempt to use it in place of *p*-aminobenzoic acid to synthesize folic acid.
- Derailing folic acid synthesis means that the bacteria cannot grow and reproduce.
- Sulfanilamide only affects bacterial cells, because humans do not synthesize folic acid, and must obtain it from their diets.



Two common sulfa drugs



sulfamethoxazole



sulfisoxazole

- Sulfamethoxazole is the sulfa drug in Bactrim, and sulfisoxazole is sold as Gantrisin. Both drugs are commonly used in the treatment of ear and urinary tract infections.


Thank you for your attention