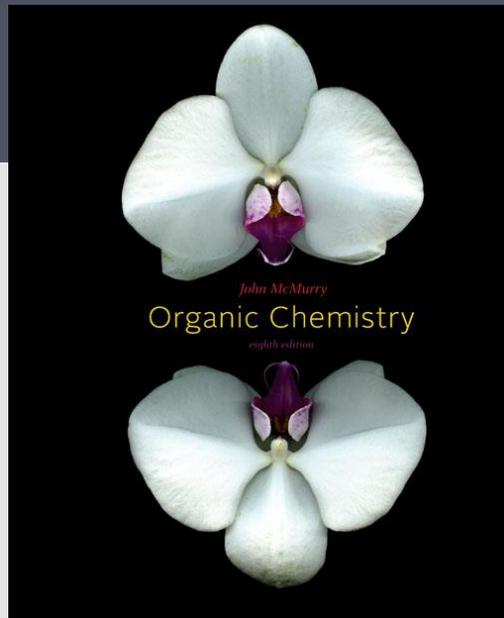


John E. McMurry

www.cengage.com/chemistry/mcmurry



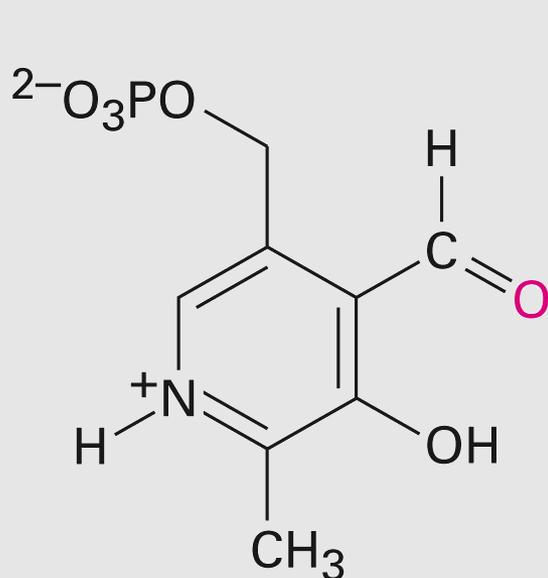
Chapter 19

Aldehydes and Ketones: Nucleophilic Addition Reactions

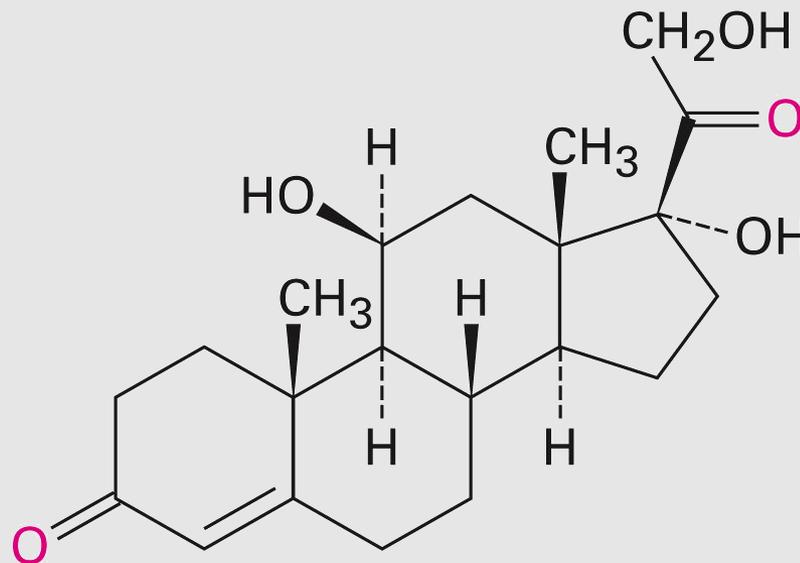
Aldehydes and Ketones



- Aldehydes (RCHO) and ketones (R_2CO) are characterized by the carbonyl functional group ($\text{C}=\text{O}$)
- The compounds occur widely in nature as intermediates in metabolism and biosynthesis



**Pyridoxal
phosphate (PLP)**



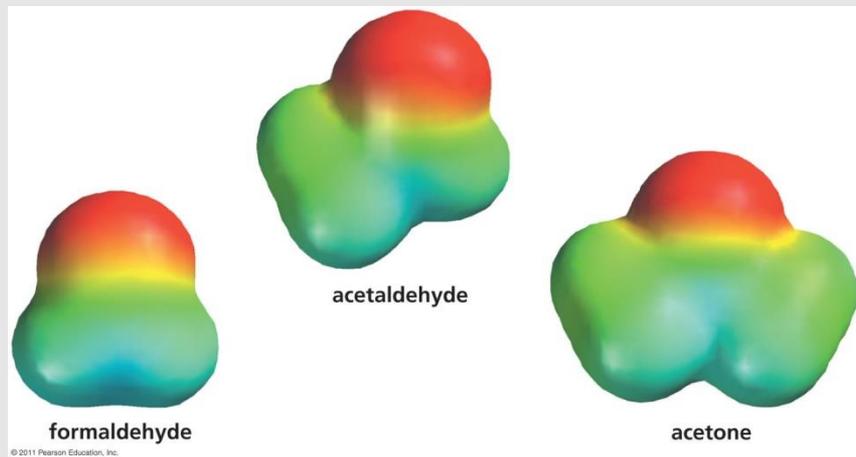
Hydrocortisone

Why this Chapter?

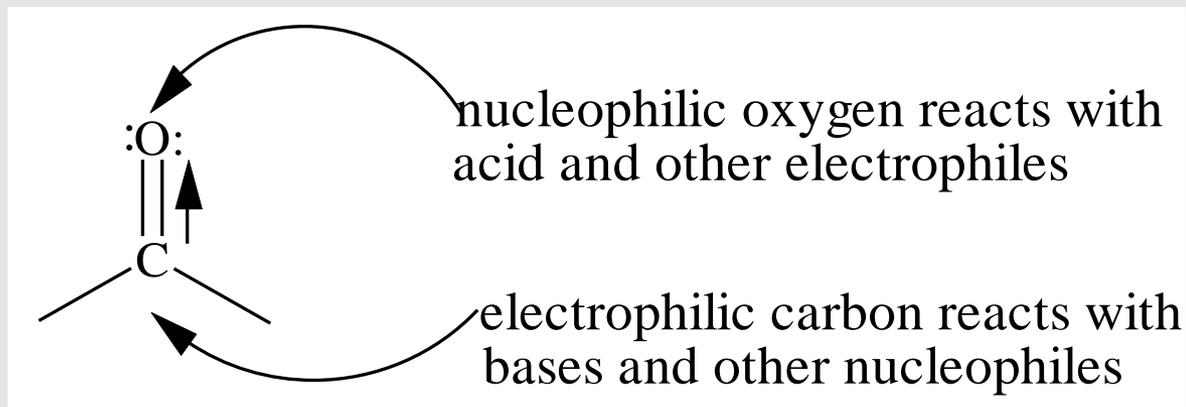


- Much of organic chemistry involves the chemistry of carbonyl compounds
- Aldehydes/ketones are intermediates in synthesis of pharmaceutical agents, biological pathways, numerous industrial processes
- An understanding of their properties is essential

Polarity of the Carbonyl Groups



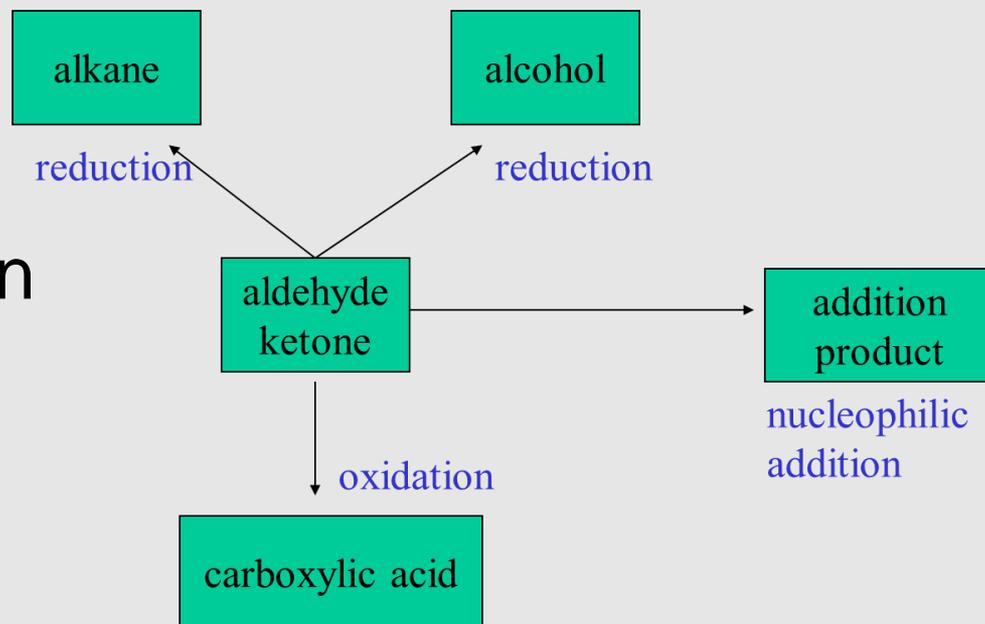
The carbon-oxygen double bond of the carbonyl group is extremely polarized in the direction of the highly electronegative oxygen. This polarization is responsible for the characteristic reactions of carbonyl compounds



Reactions of aldehydes and ketones



- oxidation
- reduction
- nucleophilic addition



- 1) Aldehydes are easily oxidized, ketones are not.
- 2) Aldehydes are more reactive in nucleophilic additions than ketones.

The reactivity of carbonyl compounds is also related to the basicity of Y⁻:

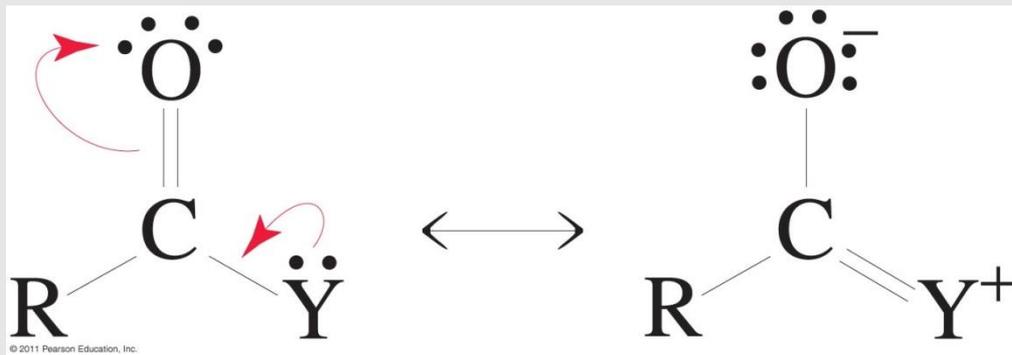


relative reactivities of carbonyl compounds

acyl halide > acid anhydride > aldehyde > ketone > ester ~ carboxylic acid > amide > carboxylate ion

most reactive

least reactive



Oxidation of Aldehydes and Ketones

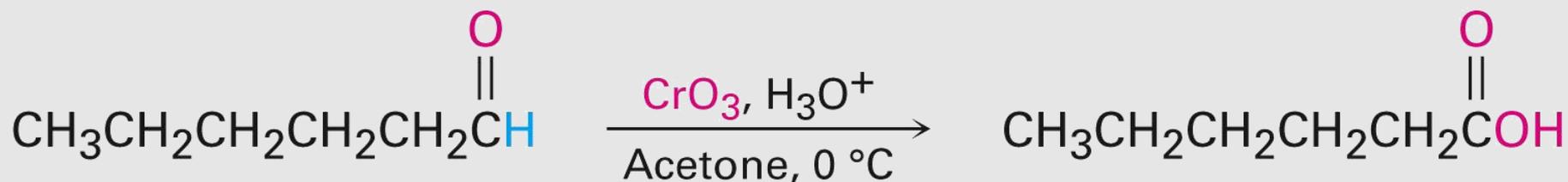


- Aldeídos: facilmente oxidados para produzir os ácidos carboxílicos
- Cetonas: normalmente inertes à oxidação
- Diferença: aldeídos têm um hidrogênio $-CHO$ que pode ser abstraído como um próton durante a oxidação, mas as cetonas não

Oxidation of Aldehydes and Ketones

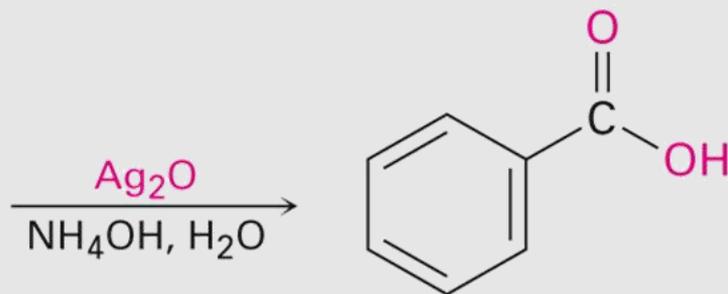
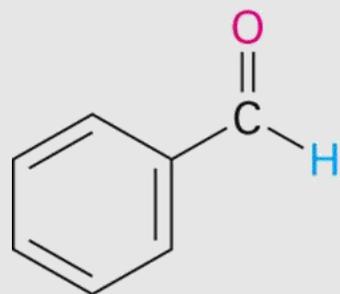


- CrO_3 in aqueous acid oxidizes aldehydes to carboxylic acids efficiently
- Silver oxide, Ag_2O , in aqueous ammonia (Tollens' reagent) oxidizes aldehydes



Hexanal

Hexanoic acid (85%)



Benzaldehyde

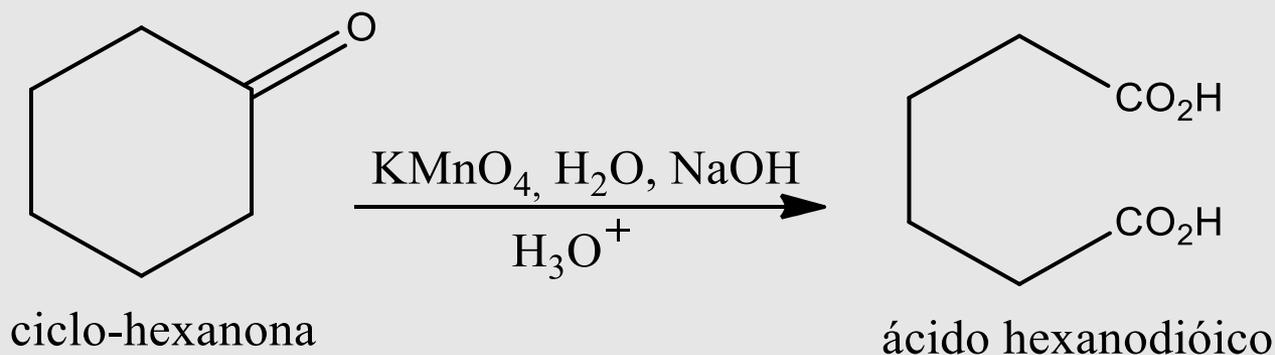
Benzoic acid



Oxidation of Aldehydes and Ketones



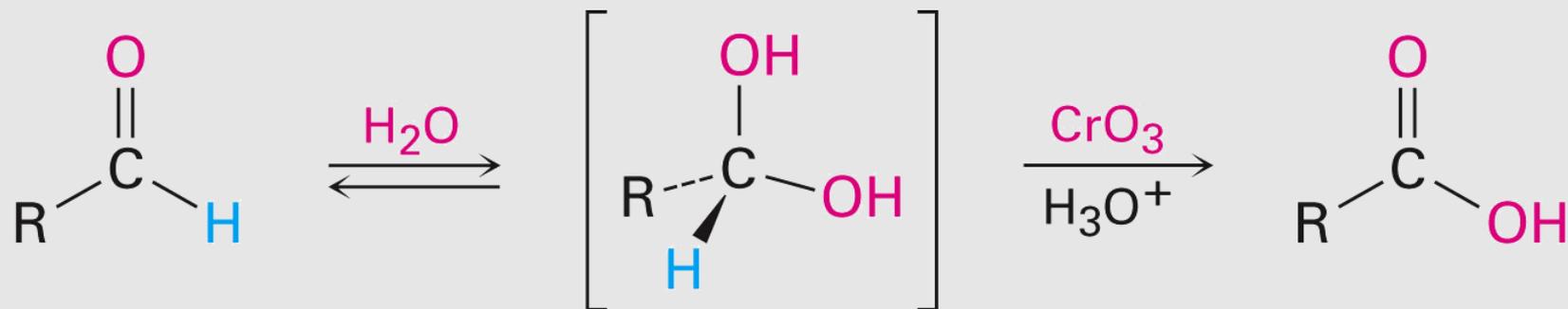
- CrO_3 em ácido aquoso: oxidação rápida, à temperatura ambiente e com bom rendimento.
- Outros agentes oxidantes: KMnO_4 , HNO_3 a quente



Hydration of Aldehydes



- Aldehyde oxidations occur through 1,1-diols (“hydrates”)
- Reversible addition of water to the carbonyl group
- Aldehyde hydrate is oxidized to a carboxylic acid by usual reagents for alcohols



An aldehyde

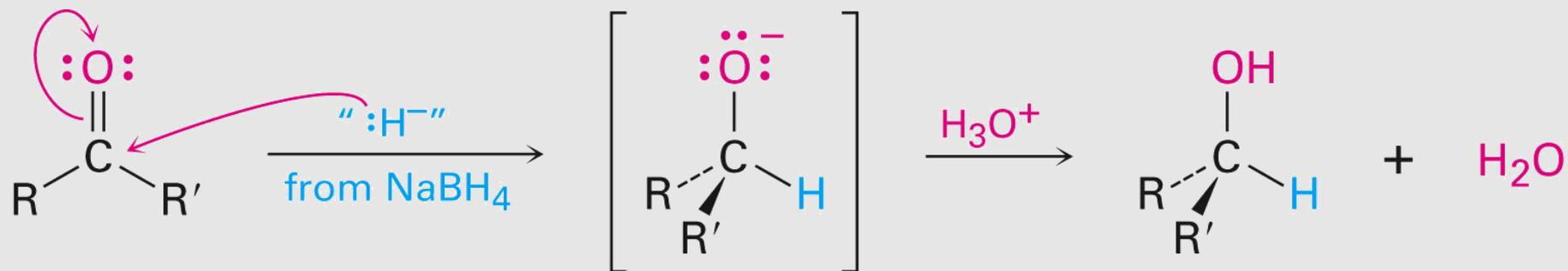
A hydrate

A carboxylic acid

Hydride Addition



- Convert C=O to CH-OH
- LiAlH_4 and NaBH_4 react as donors of hydride ion
- Protonation after addition yields the alcohol

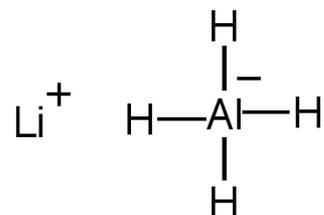


Hydride Reducing Agents

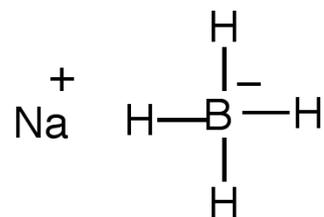


HYDRIDE REDUCTION

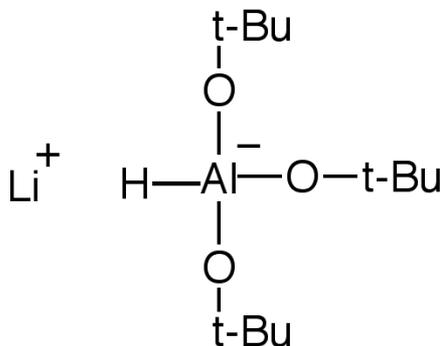
REDUCING STRENGTH ↑



ESTERS, KETONES, ALDEHYDES TO ALCOHOLS

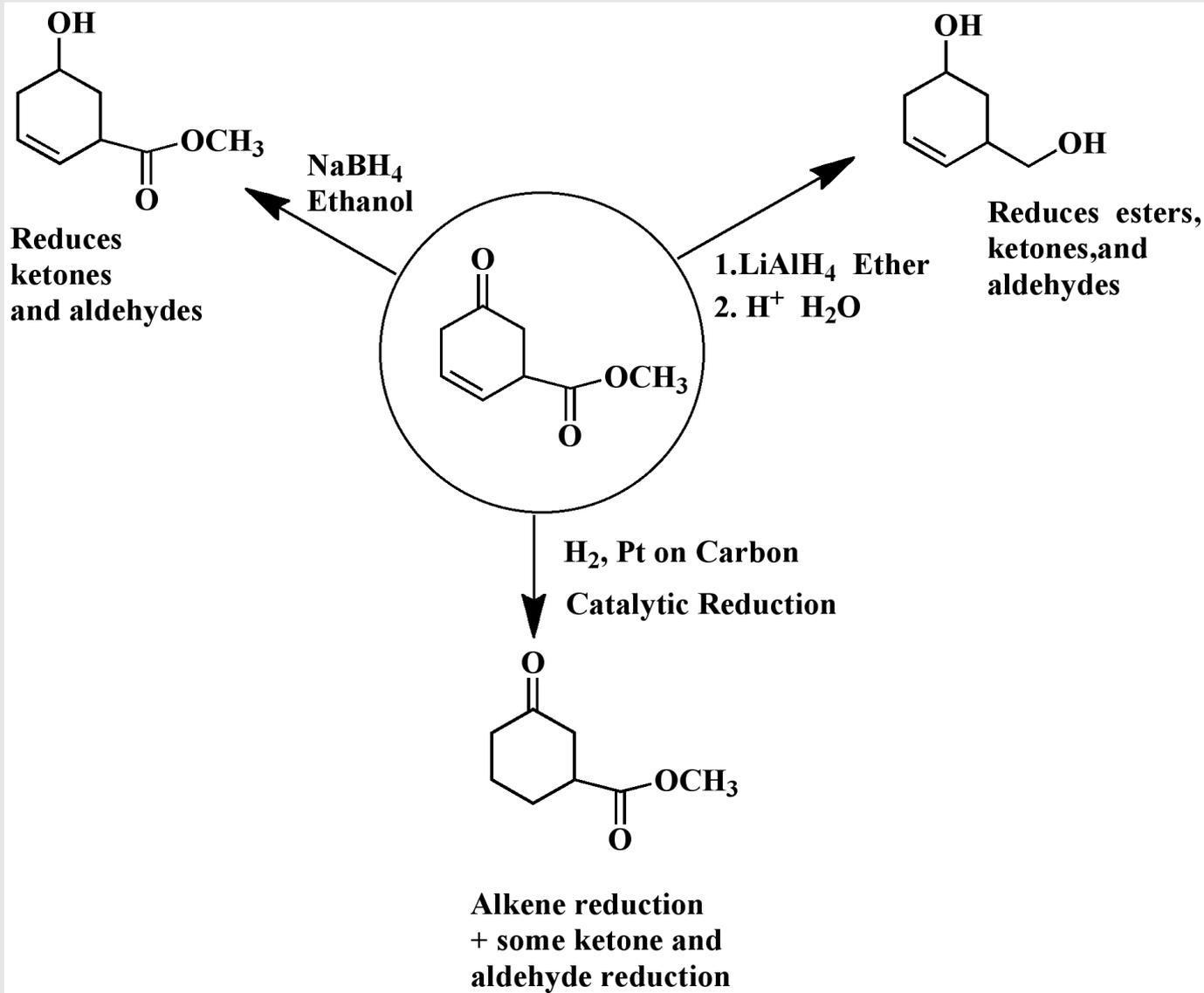


KETONES, ALDEHYDES TO ALCOHOLS

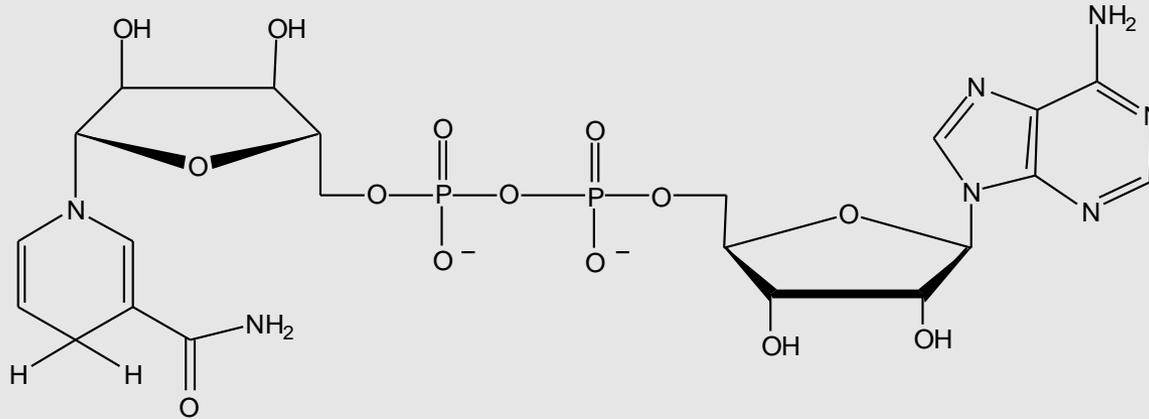


ACIDS AND ACID CHLORIDES TO ALDEHYDES

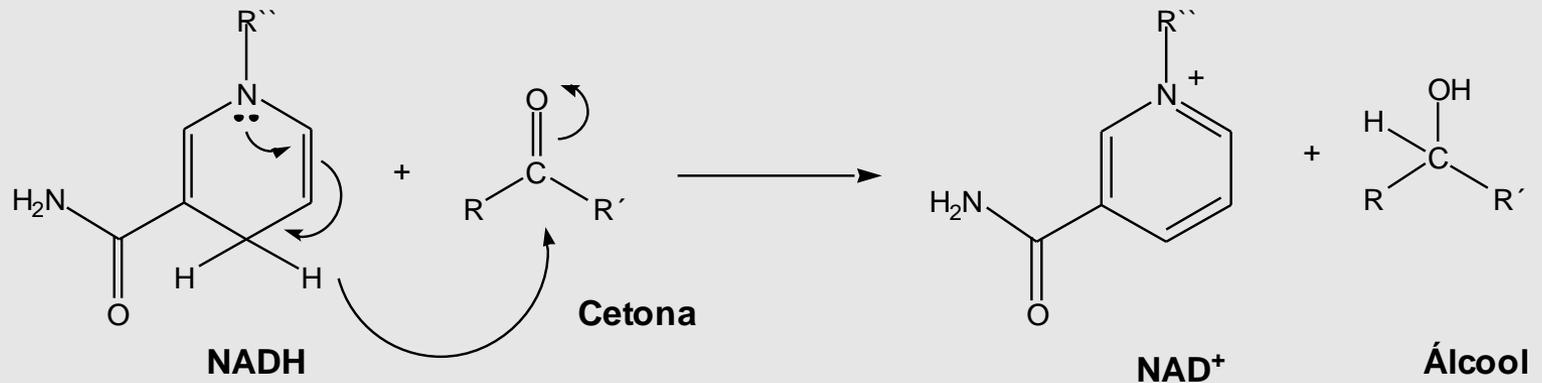
Selectivity of Reductions



Biological Reductions



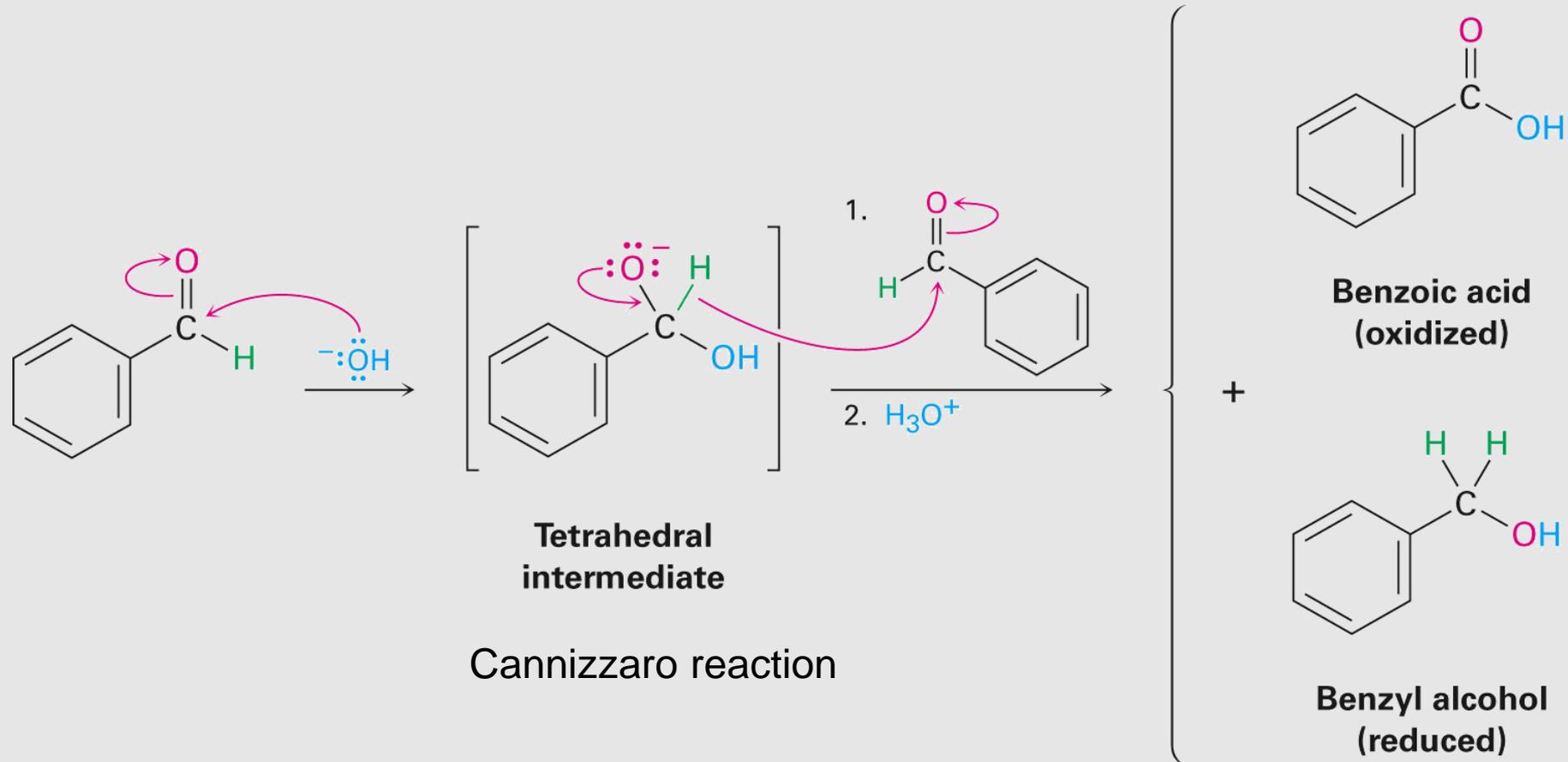
Nicotinamida Adenina Dinucleótídeo reduzida



Biological Reductions



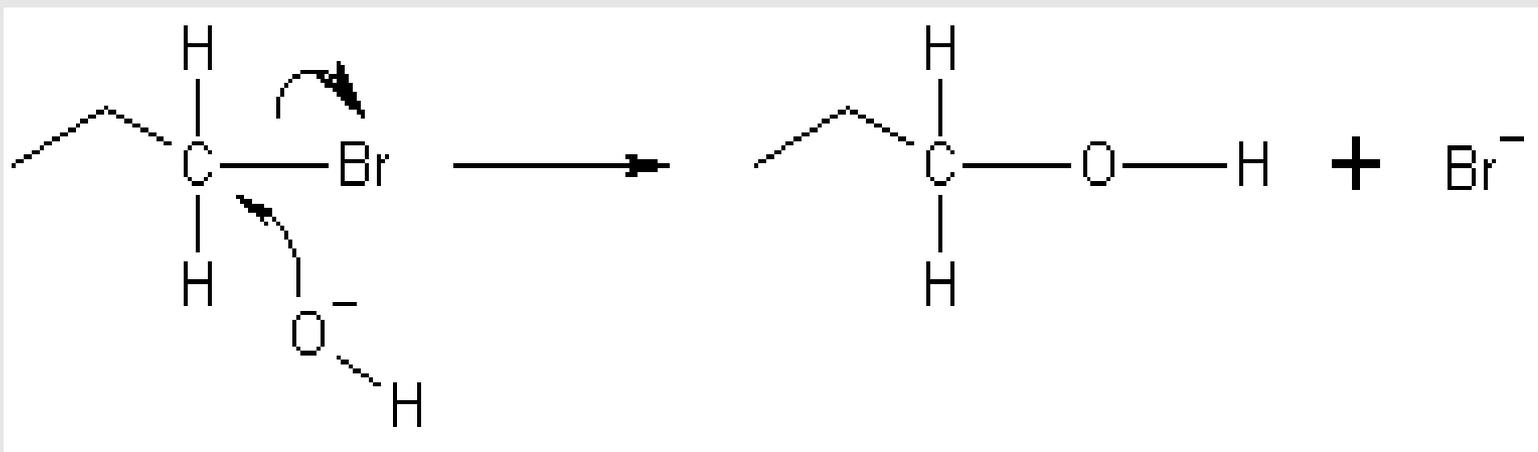
- The adduct of an aldehyde and OH^- can transfer hydride ion to another aldehyde $\text{C}=\text{O}$ resulting in a simultaneous oxidation and reduction (*disproportionation*)



Nucleophiles



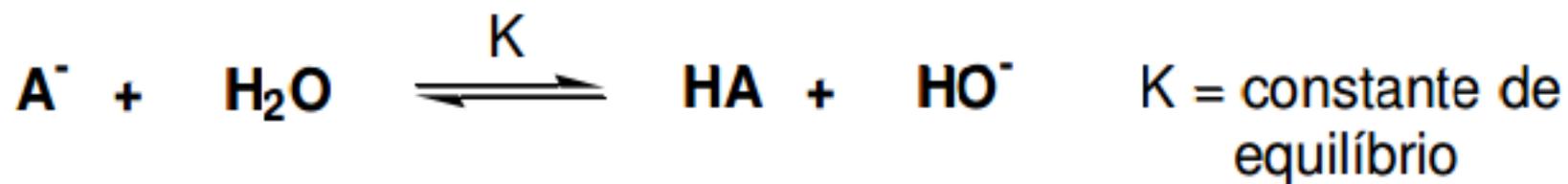
- doa par de elétrons para um eletrófilo para formar uma ligação
- moléculas ou íons com um par de elétrons livre ou com uma ligação π
- são bases de Lewis



Nucleophiles



- Basicidade vs nucleofilicidade
 - Basicidade é uma propriedade termodinâmica:



- Nucleofilicidade: conceito cinético:



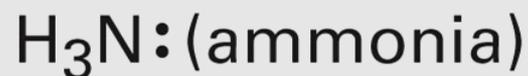
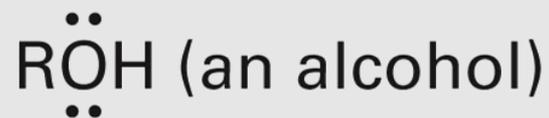
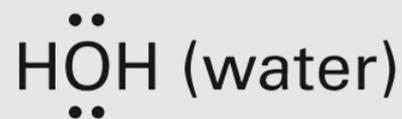
- Bases fortes são tipicamente bons nucleófilos

Nucleophiles



- Nucleophiles can be negatively charged ($:\text{Nu}^-$) or neutral ($:\text{Nu}$) at the reaction site
- The *overall charge* on the nucleophilic species is not considered

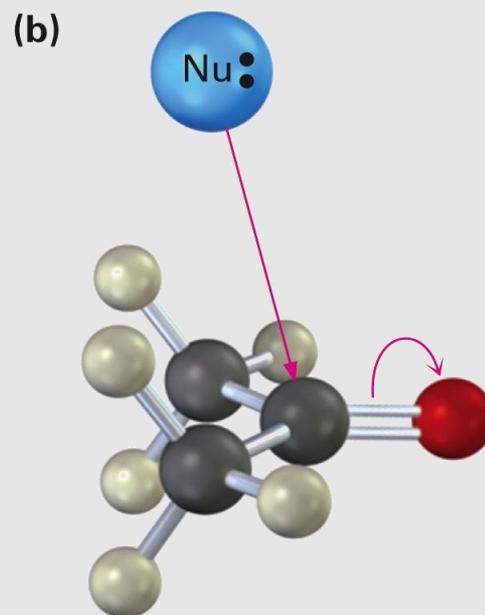
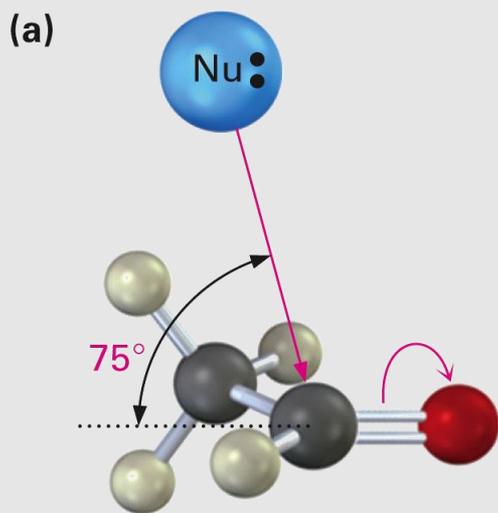
Some neutral nucleophiles



Relative Reactivity of Aldehydes and Ketones



- Aldehydes are generally more reactive than ketones in nucleophilic addition reactions
- The transition state for addition is less crowded and lower in energy for an aldehyde (a) than for a ketone (b)
- Aldehydes have one large substituent bonded to the C=O: ketones have two



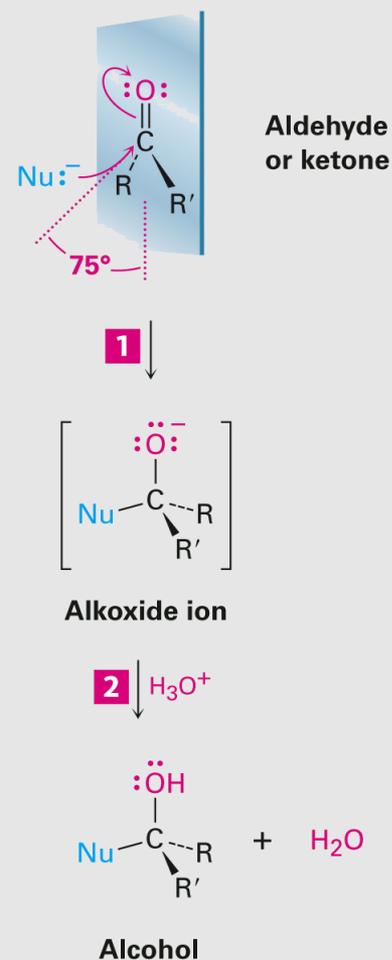
Nucleophilic Addition Reactions of Aldehydes and Ketones



- Nu⁻ approaches 75° to the plane of C=O and adds to C
- A tetrahedral alkoxide ion intermediate is produced

1 An electron pair from the nucleophile adds to the electrophilic carbon of the carbonyl group, pushing an electron pair from the C=O bond onto oxygen and giving an alkoxide ion intermediate. The carbonyl carbon rehybridizes from sp^2 to sp^3 .

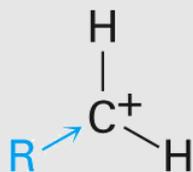
2 Protonation of the alkoxide anion intermediate gives the neutral alcohol addition product.



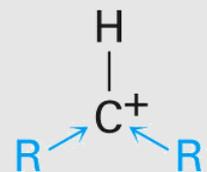
Electrophilicity of Aldehydes and Ketones



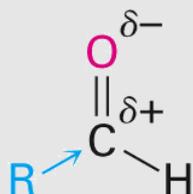
- Aldehyde C=O is more polarized than ketone C=O
- As in carbocations, more alkyl groups stabilize + character
- Ketone has more alkyl groups, stabilizing the C=O carbon inductively



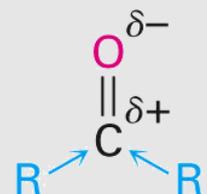
1° carbocation
(less stable, more reactive)



2° carbocation
(more stable, less reactive)



Aldehyde
(less stabilization of δ^+ , more reactive)

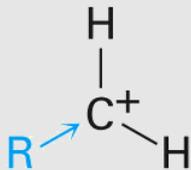


Ketone
(more stabilization of δ^+ , less reactive)

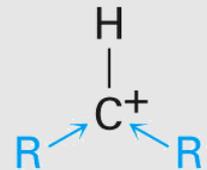
Reactivity of Aromatic Aldehydes



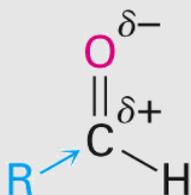
- Less reactive in nucleophilic addition reactions than aliphatic aldehydes
- Electron-donating resonance effect of aromatic ring makes C=O less reactive electrophile than the carbonyl group of an aliphatic aldehyde



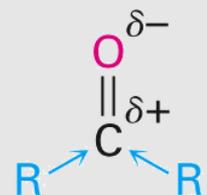
1° carbocation
(less stable, more reactive)



2° carbocation
(more stable, less reactive)



Aldehyde
(less stabilization of $\delta+$, more reactive)

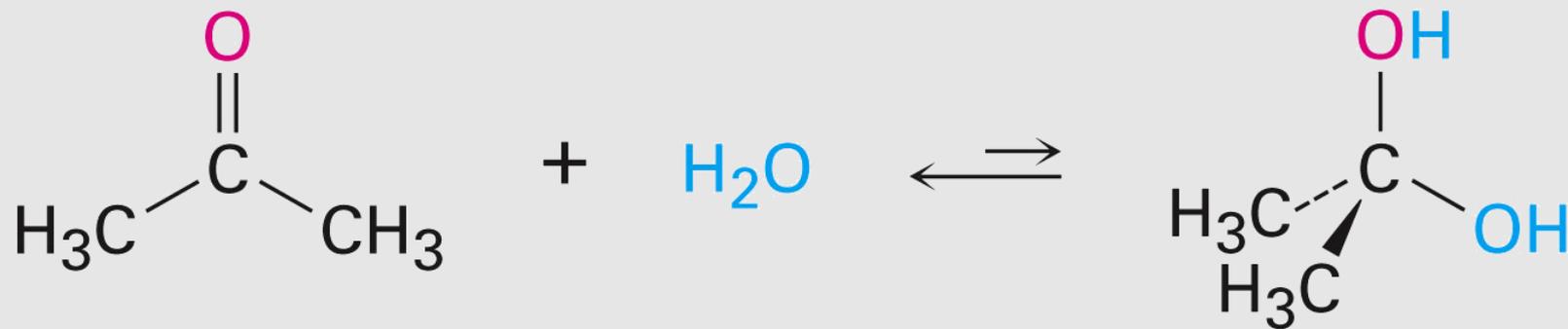


Ketone
(more stabilization of $\delta+$, less reactive)

Nucleophilic Addition of H₂O: Hydration



- Aldehydes and ketones react with water to yield 1,1-diols (**geminal (gem) diols**)
- Hydration is reversible: a gem diol can eliminate water



Acetone (99.9%)

Acetone hydrate (0.1%)

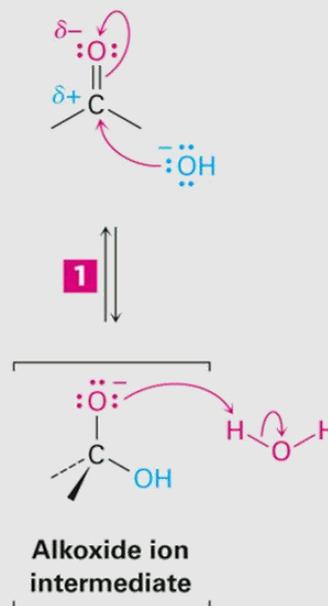
Base-Catalyzed Addition of Water



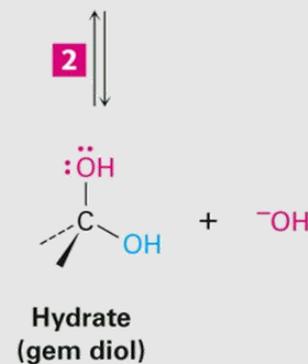
- Addition of water is catalyzed by both acid and base
- The base-catalyzed hydration nucleophile is the hydroxide ion, which is a much stronger nucleophile than water

(a) Basic conditions

1 The negatively charged nucleophile OH^- adds to the electrophilic carbon and pushes π electrons from the $\text{C}=\text{O}$ bond onto oxygen, giving an alkoxide ion.



2 The alkoxide ion is protonated by water to give the neutral hydrate as the addition product and regenerating OH^- .



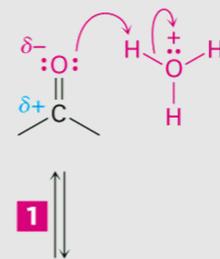
Acid-Catalyzed Addition of Water



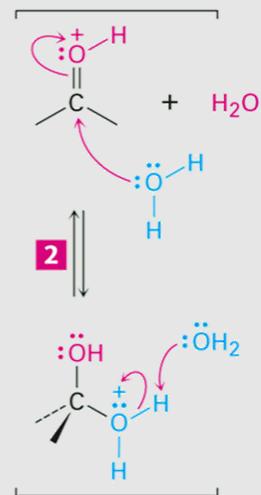
- Protonation of $C=O$ makes it more electrophilic

(b) Acidic conditions

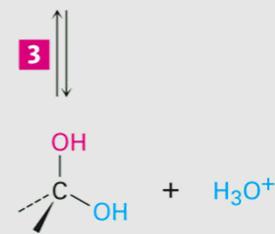
- The carbonyl oxygen is protonated by acid H_3O^+ , making the carbon more strongly electrophilic



- The neutral nucleophile $:OH_2$ adds to the electrophilic carbon, pushing the π electrons from the $C=O$ onto oxygen. The oxygen becomes neutral, and the nucleophile gains the + charge.



- Water deprotonates the intermediate, giving the neutral hydrate addition product and regenerating the acid catalyst H_3O^+ .

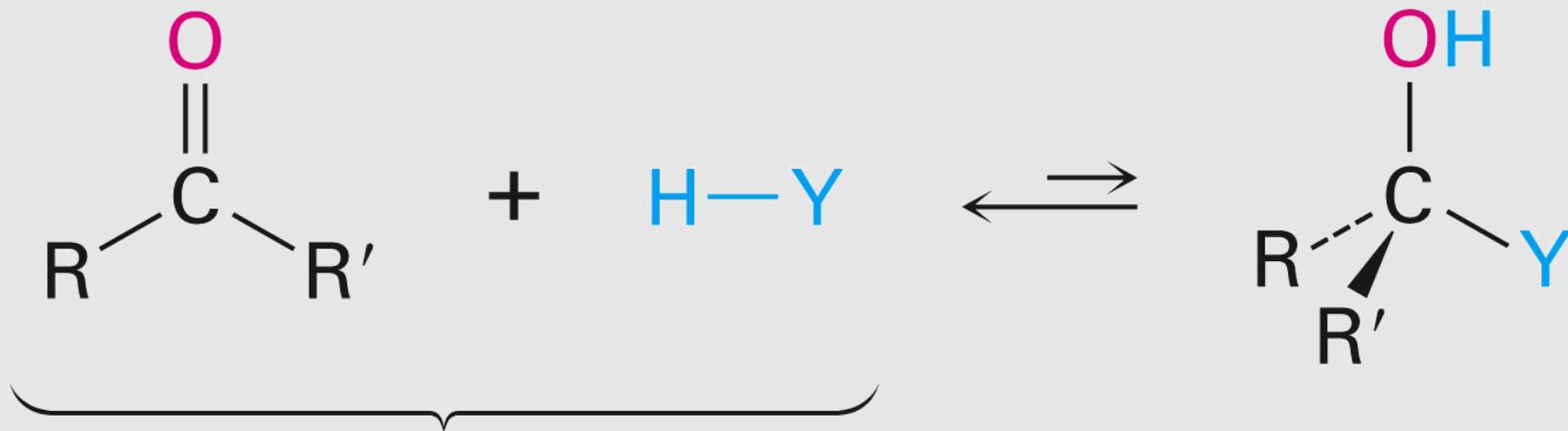


Hydrate
(gem diol)

Addition of H–Y to C=O



- Reaction of C=O with H-Y, where Y is electronegative, gives an addition product (“adduct”)
- Formation is readily reversible



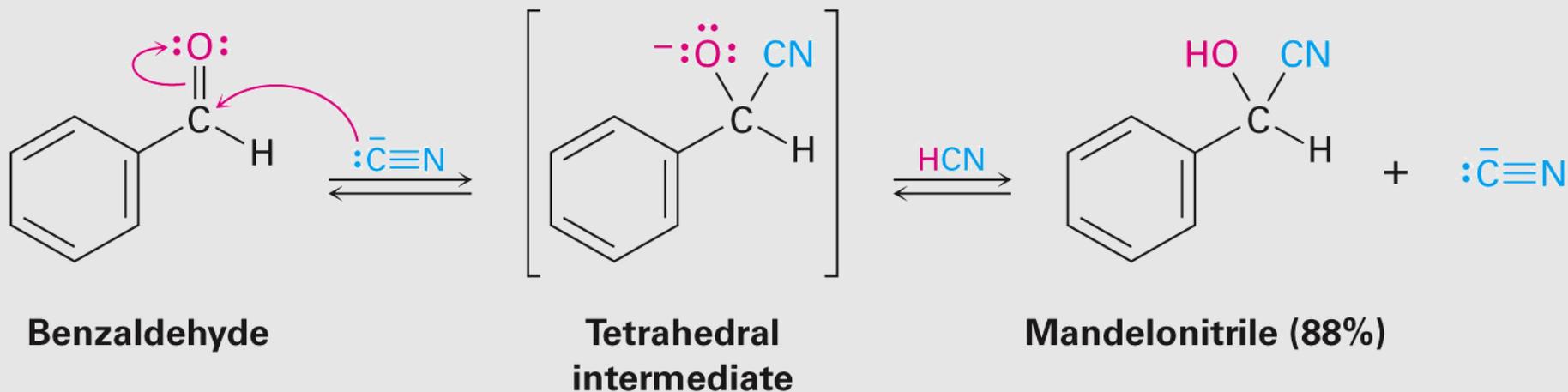
Favored when



Nucleophilic Addition of HCN: Cyanohydrin Formation



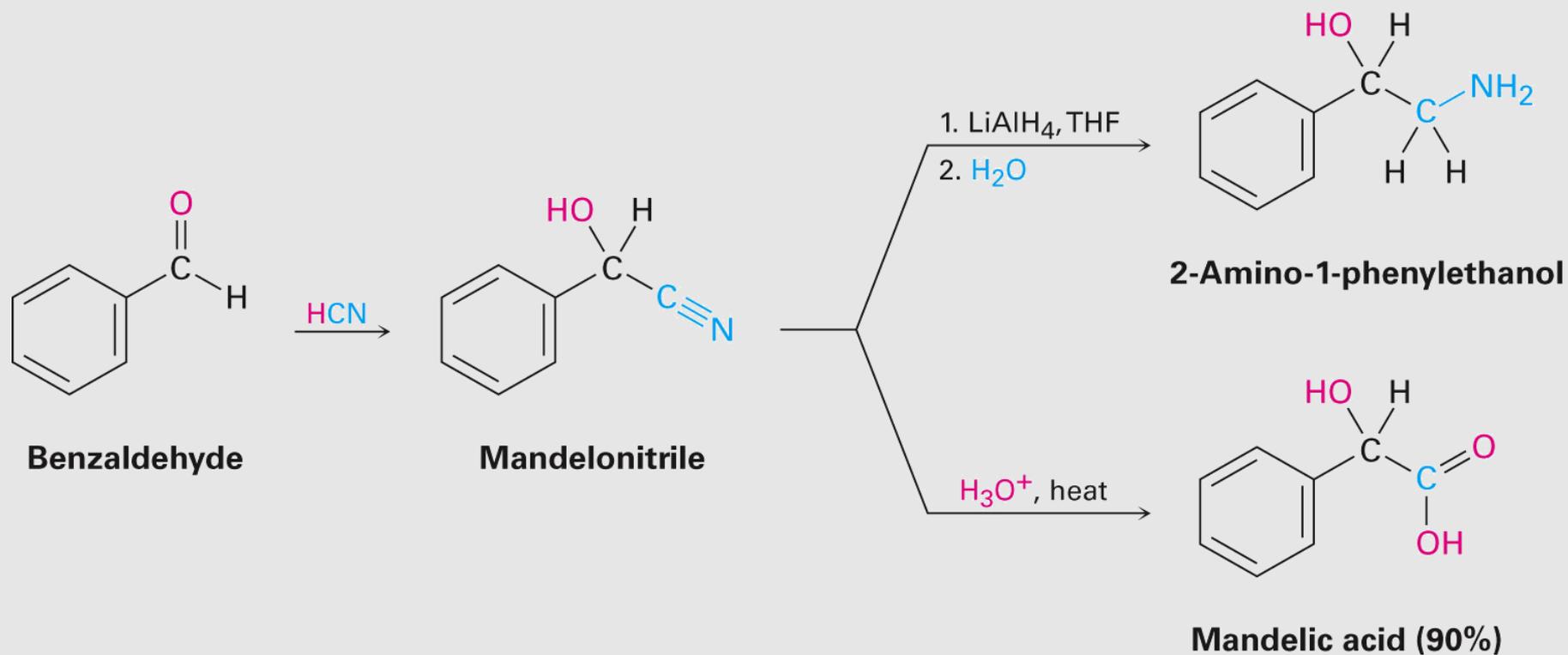
- Aldehydes and unhindered ketones react with HCN to yield cyanohydrins, $\text{RCH}(\text{OH})\text{C}\equiv\text{N}$
- Addition of HCN is reversible and base-catalyzed, generating nucleophilic cyanide ion, CN^-
- Addition of CN^- to $\text{C}=\text{O}$ yields a tetrahedral intermediate, which is then protonated
- Equilibrium favors adduct



Uses of Cyanohydrins



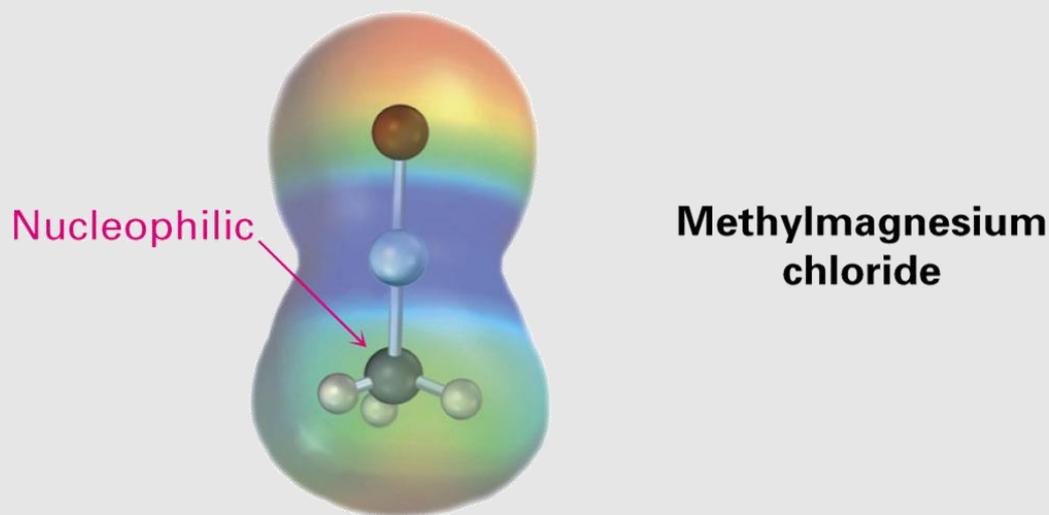
- The nitrile group ($\text{—C}\equiv\text{N}$) can be reduced with LiAlH_4 to yield a primary amine (RCH_2NH_2)
- Can be hydrolyzed by hot acid to yield a carboxylic acid



Nucleophilic Addition of Grignard Reagents and Hydride Reagents: Alcohol Formation



- Treatment of aldehydes or ketones with Grignard reagents yields an alcohol
 - Nucleophilic addition of the equivalent of a *carbon* anion, or **carbanion**. A carbon–magnesium bond is strongly polarized, so a Grignard reagent reacts for all practical purposes as $R: - MgX^+$.



Mechanism of Addition of Grignard Reagents

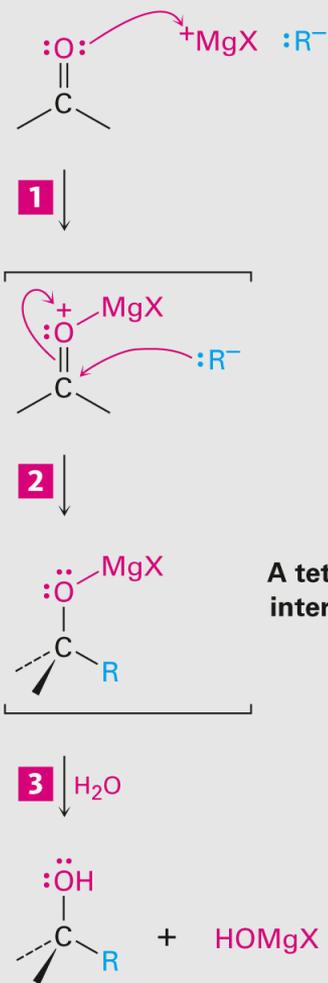


- Complexation of C=O by Mg^{2+} , Nucleophilic addition of $R:^-$, protonation by dilute acid yields the neutral alcohol
- Grignard additions are irreversible because a carbanion is not a leaving group

1 The Lewis acid Mg^{2+} first forms an acid-base complex with the basic oxygen atom of the aldehyde or ketone, thereby making the carbonyl group a better acceptor.

2 Nucleophilic addition of an alkyl group $:R^-$ to the aldehyde or ketone produces a tetrahedral magnesium alkoxide intermediate...

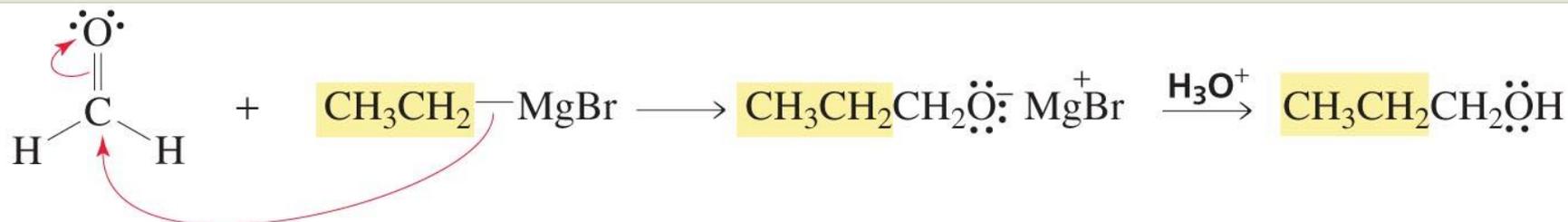
3 ... which undergoes hydrolysis when water is added in a separate step. The final product is a neutral alcohol.



A tetrahedral intermediate

An alcohol

Grignard reagents are used to prepare alcohols:



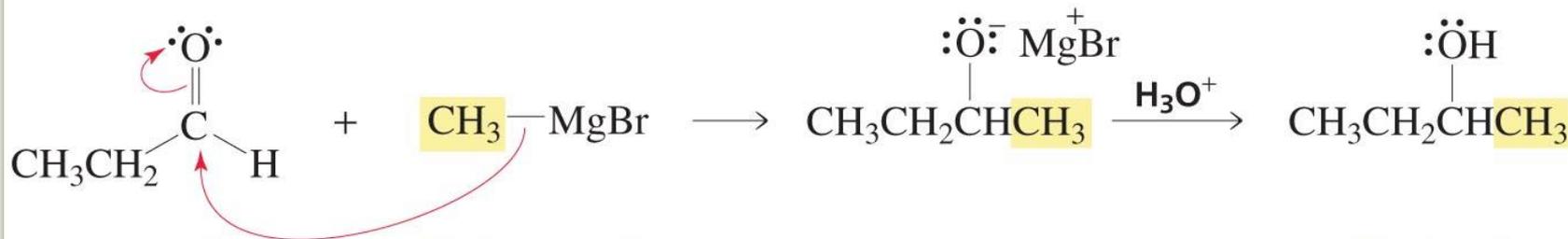
formaldehyde

ethylmagnesium
bromide

an alkoxide ion

1-propanol
a primary alcohol

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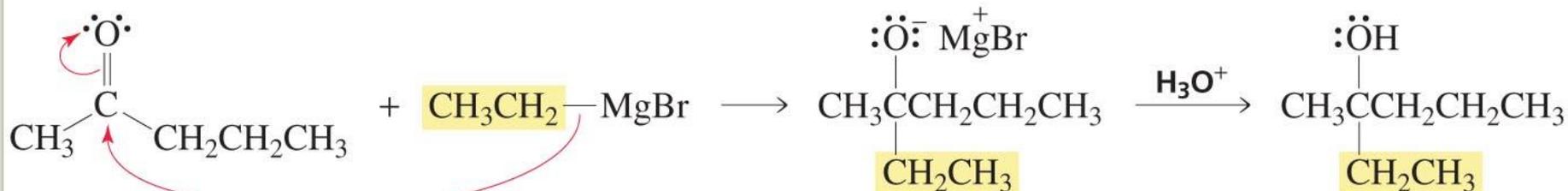


propanal

methylmagnesium
bromide

2-butanol
a secondary alcohol

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2-pentanone

ethylmagnesium
bromide

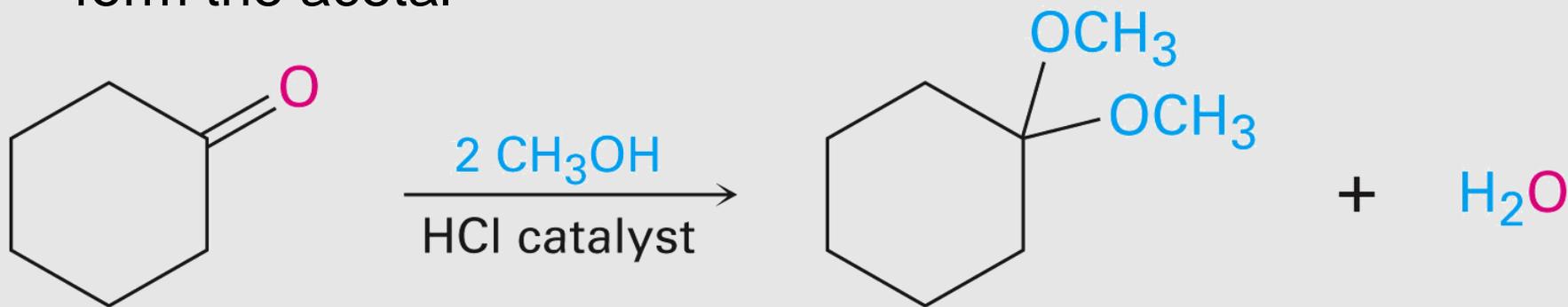
3-methyl-3-hexanol
a tertiary alcohol

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Nucleophilic Addition of Alcohols: Acetal Formation



- Alcohols are weak nucleophiles but acid promotes addition forming the conjugate acid of C=O
- Addition yields a hydroxy ether, called a hemiacetal (reversible); further reaction can occur
- Protonation of the -OH and loss of water leads to an oxonium ion, $R_2C=OR^+$ to which a second alcohol adds to form the acetal



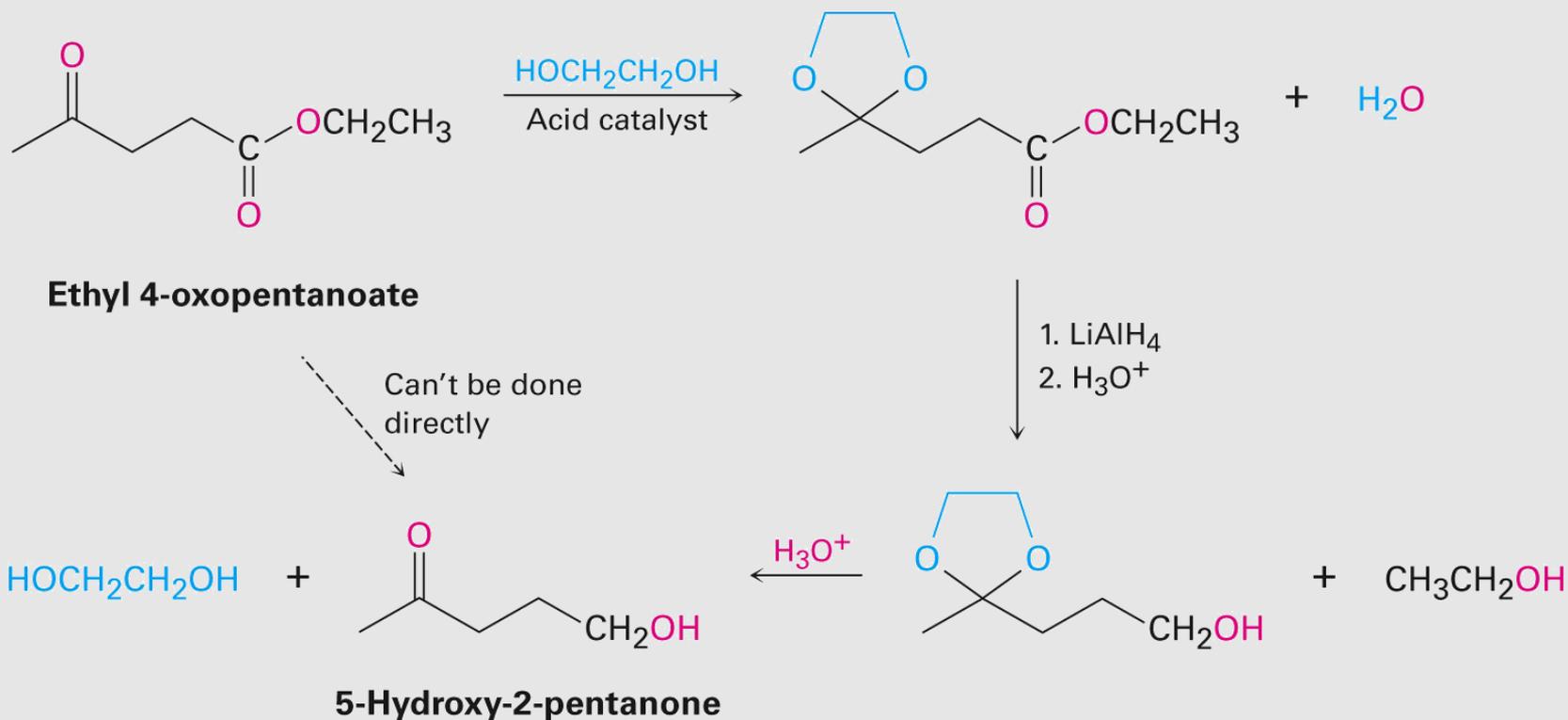
Cyclohexanone

**Cyclohexanone
dimethyl acetal**

Uses of Acetals



- Acetals can serve as protecting groups for aldehydes and ketones
- It is convenient to use a diol to form a *cyclic* acetal (the reaction goes even more readily)



Nucleophilic Addition of Hydrazine: The Wolff–Kishner Reaction



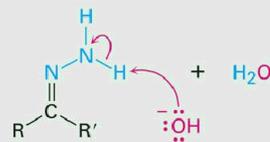
- Treatment of an aldehyde or ketone with hydrazine, H_2NNH_2 , and KOH converts the compound to an alkane
- Originally carried out at high temperatures but with dimethyl sulfoxide as solvent takes place near room temperature

1 Reaction of the aldehyde or ketone with hydrazine yields a hydrazone in the normal way.



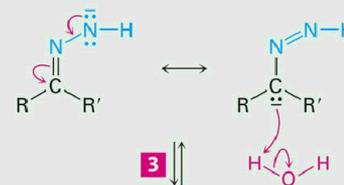
1 ↓

2 Base abstracts a weakly acidic N–H proton, yielding a hydrazone anion. This anion has a resonance form that places the negative charge on carbon and the double bond between nitrogens.



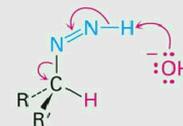
2 ↓

3 Protonation of the hydrazone anion takes place on carbon to yield a neutral intermediate.



3 ↓

4 Deprotonation of the remaining weakly acidic N–H occurs with simultaneous loss of nitrogen to give a carbanion ...

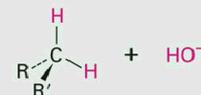


4 ↓



5 ... which is protonated to give the alkane product.

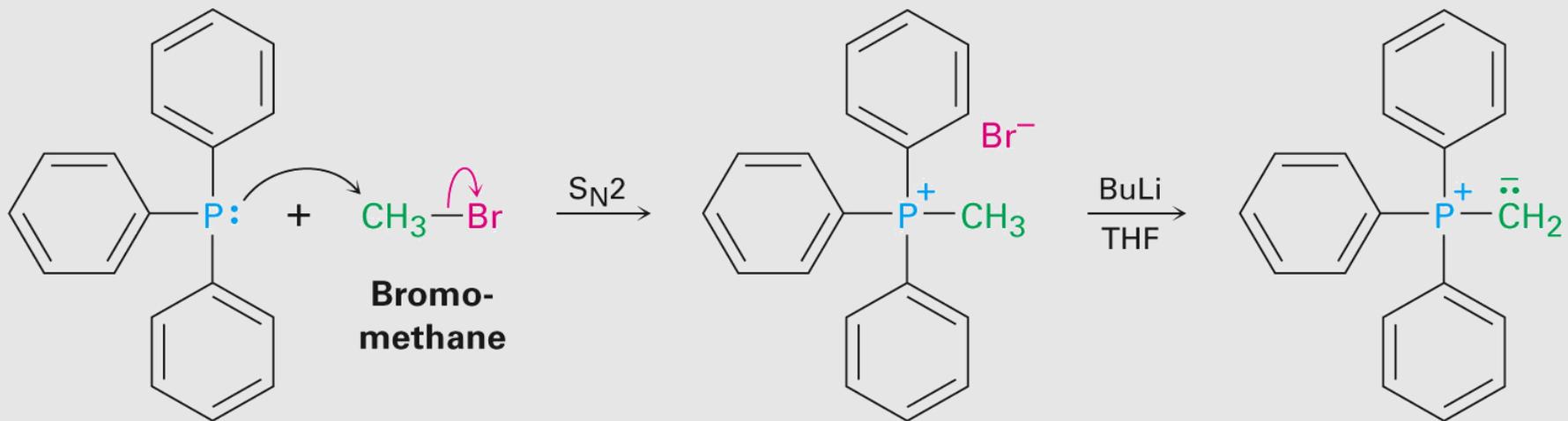
5 ↓ H_2O



Nucleophilic Addition of Phosphorus Ylides: The Wittig Reaction



- The sequence converts C=O to C=C
- A phosphorus *ylide* adds to an aldehyde or ketone to yield a dipolar intermediate called a *betaine*
- The intermediate spontaneously decomposes through a four-membered ring to yield alkene and triphenylphosphine oxide, (Ph)₃P=O
- Formation of the ylide is shown below



Triphenylphosphine

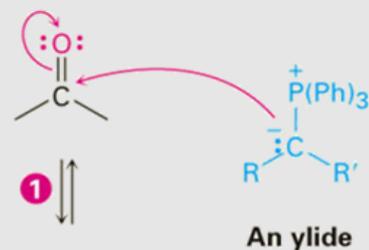
Methyltriphenylphosphonium bromide

Methylenetriphenylphosphorane

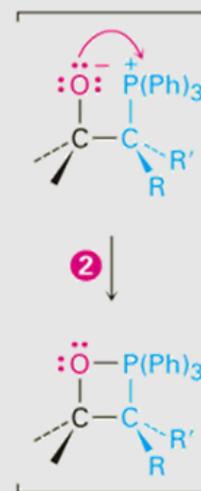
Mechanism of the Wittig Reaction



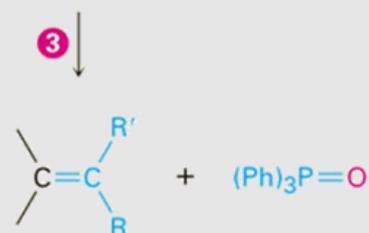
- 1 The nucleophilic carbon atom of the phosphorus ylide adds to the carbonyl group of a ketone or aldehyde to give an alkoxide ion intermediate.



- 2 The alkoxide ion then undergoes intramolecular O-P bond formation to produce a four-membered ring . . .



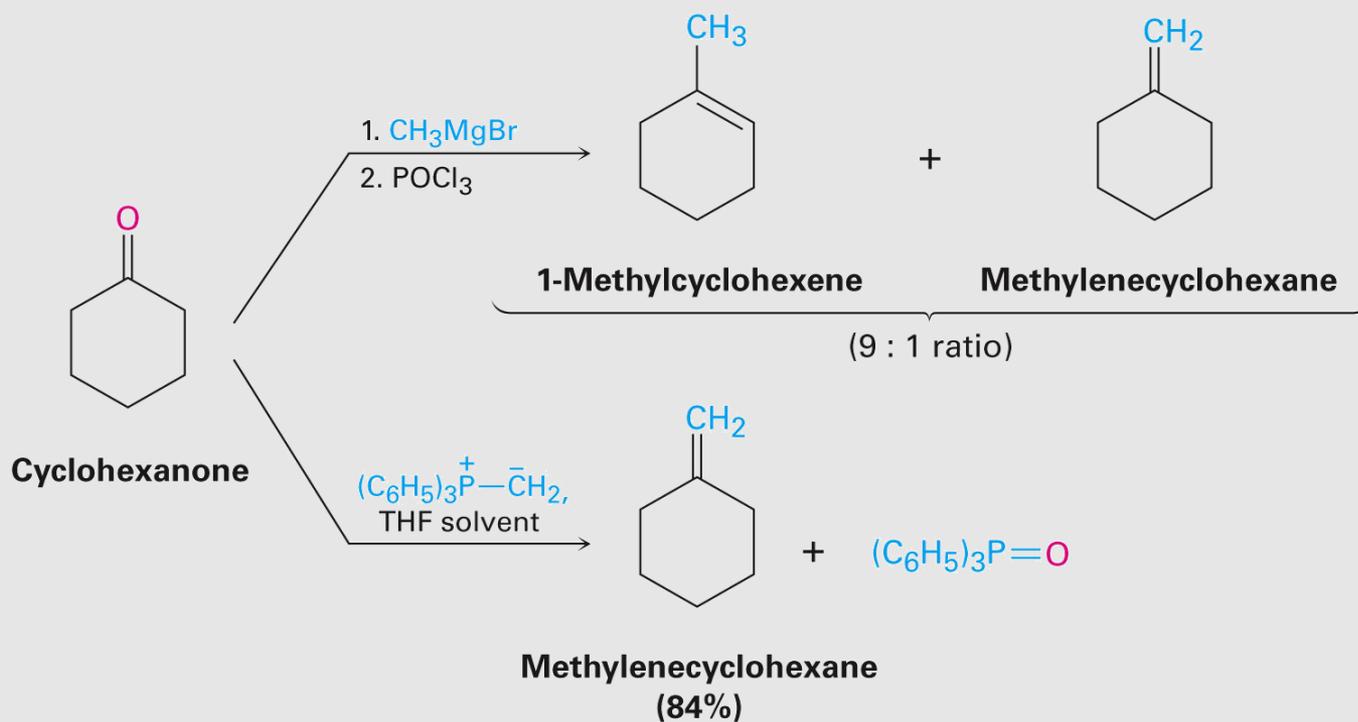
- 3 . . . which spontaneously decomposes to give an alkene and triphenylphosphine oxide.



Uses of the Wittig Reaction



- Can be used for monosubstituted, disubstituted, and trisubstituted alkenes but not tetrasubstituted alkenes. The reaction yields a pure alkene of known structure.
- For comparison, addition of CH_3MgBr to cyclohexanone and dehydration with POCl_3 yields a mixture of two alkenes.

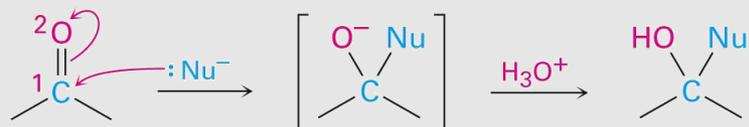


Conjugate Nucleophilic Addition to α,β -Unsaturated Aldehydes and Ketones

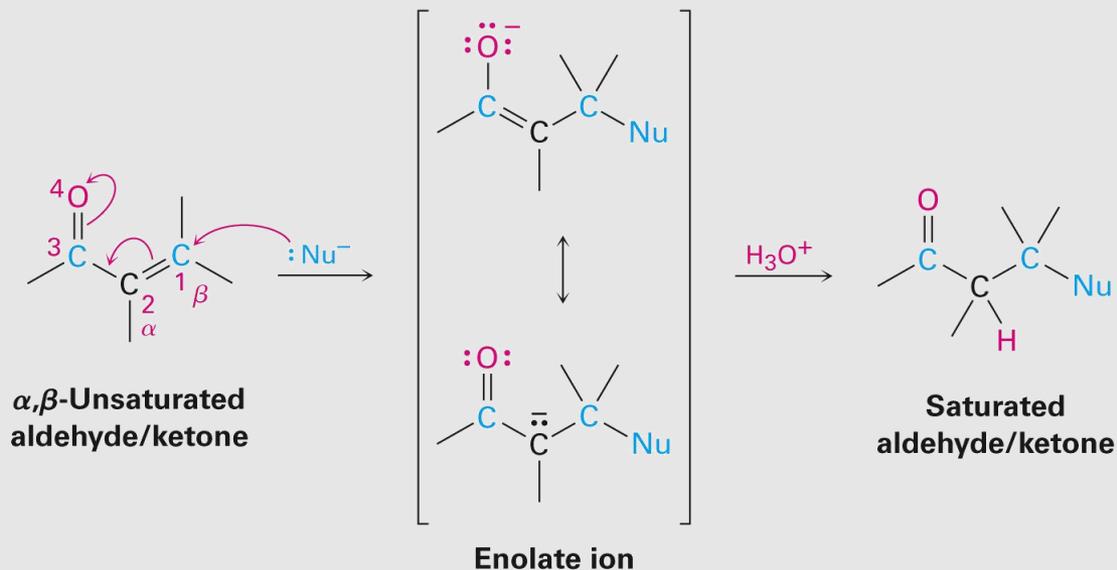


- A nucleophile can add to the C=C double bond of an α,β -unsaturated aldehyde or ketone (conjugate addition, or 1,4 addition)
- The initial product is a resonance-stabilized enolate ion, which is then protonated

Direct (1,2) addition



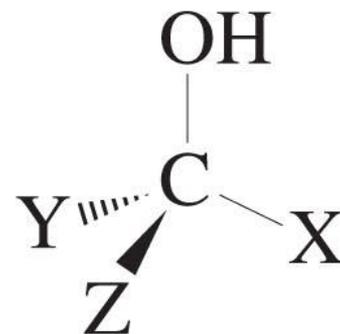
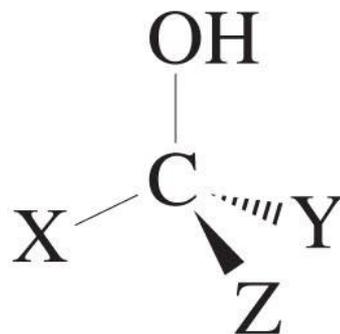
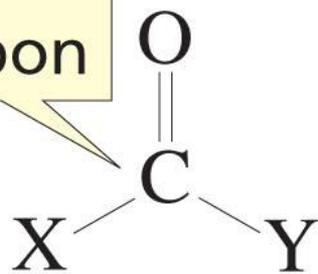
Conjugate (1,4) addition



Stereochemistry of Nucleophilic Addition Reaction



a prochiral
carbonyl carbon

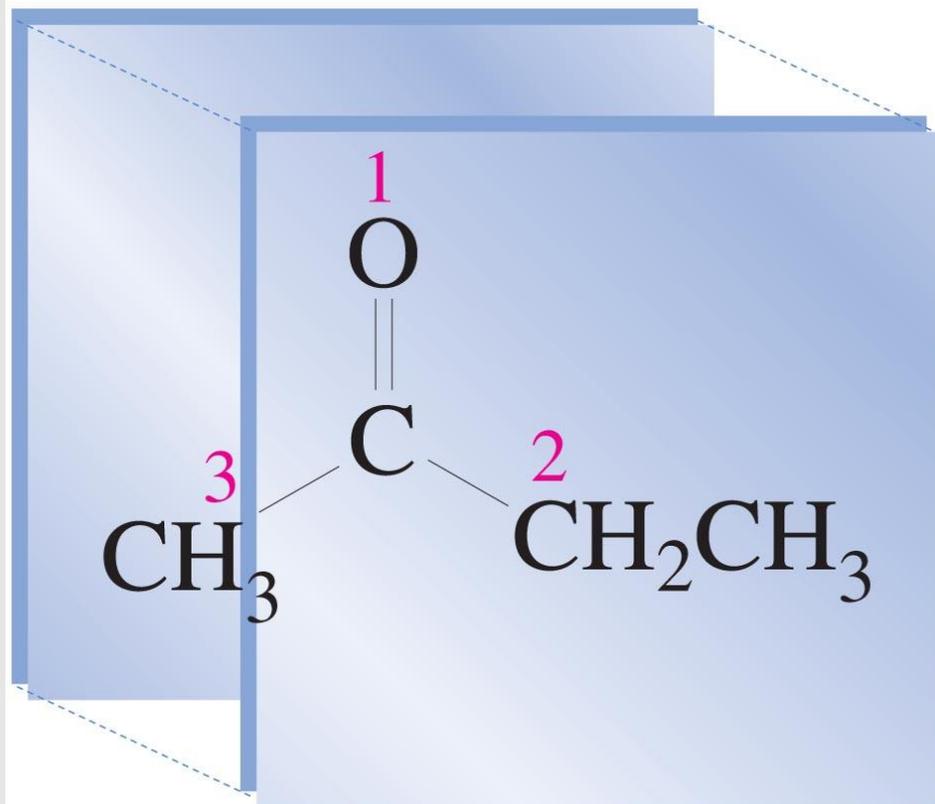


a pair of enantiomers

Stereochemistry of Nucleophilic Addition Reaction



the *Si* face



the *Re* face

Stereochemistry of Nucleophilic Addition Reaction

