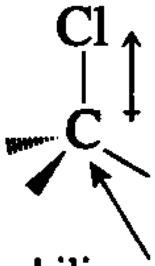
Chapter 18 Additions to the Carbonyl Groups

Nucleophilic substitution (S_N2 and S_N1) reaction occurs at *sp*3 hybridized carbons with electronegative leaving groups

Why?

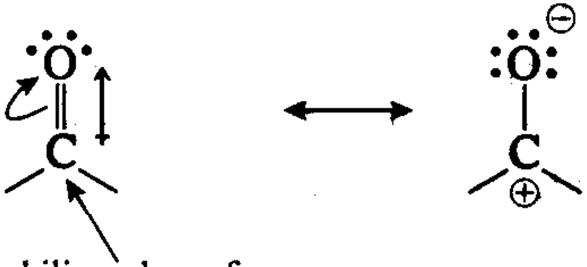
The carbon is electrophilic!



electrophilic carbon in S_N1 and S_N2 reactions

Addition to the carbonyl group also occurs at the carbon of a carbonyl groups which is also electrophilic.

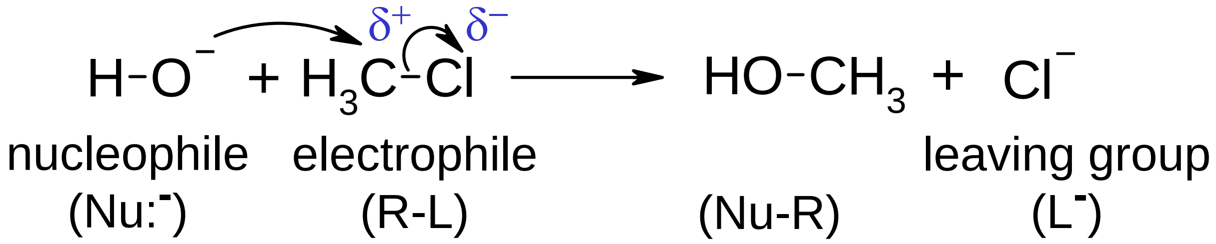
Why?

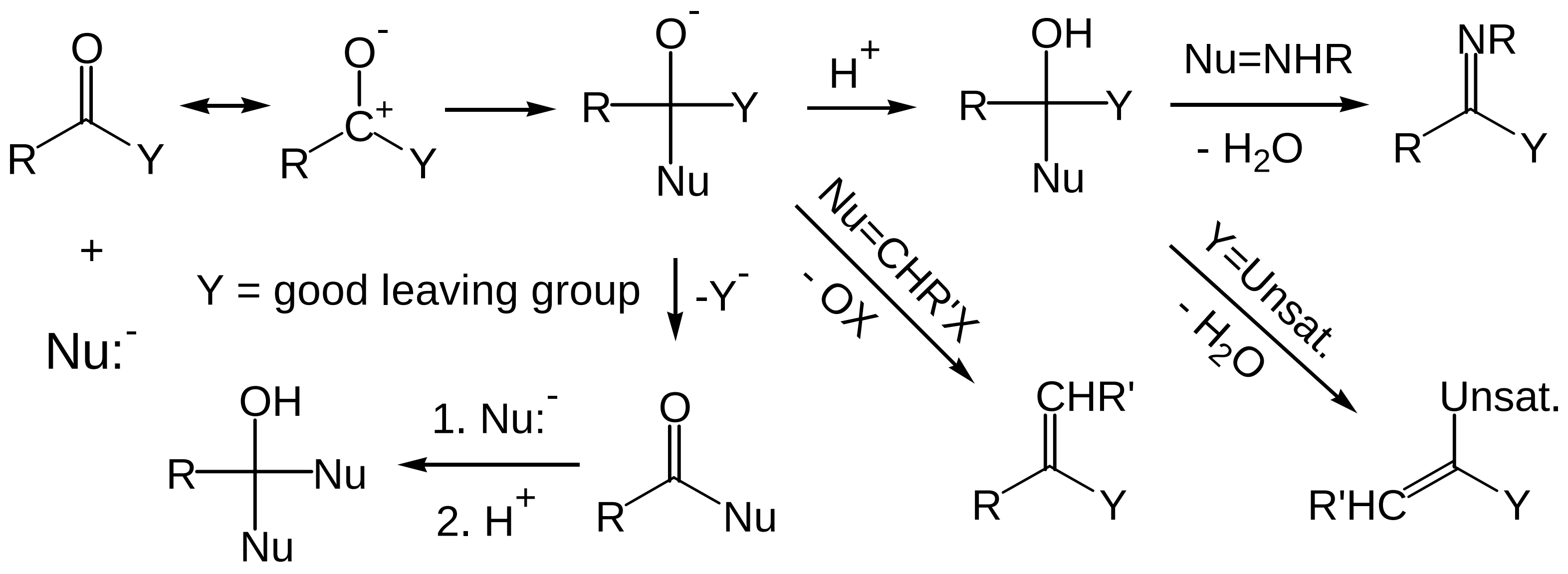


electrophilic carbon of the carbonyl group

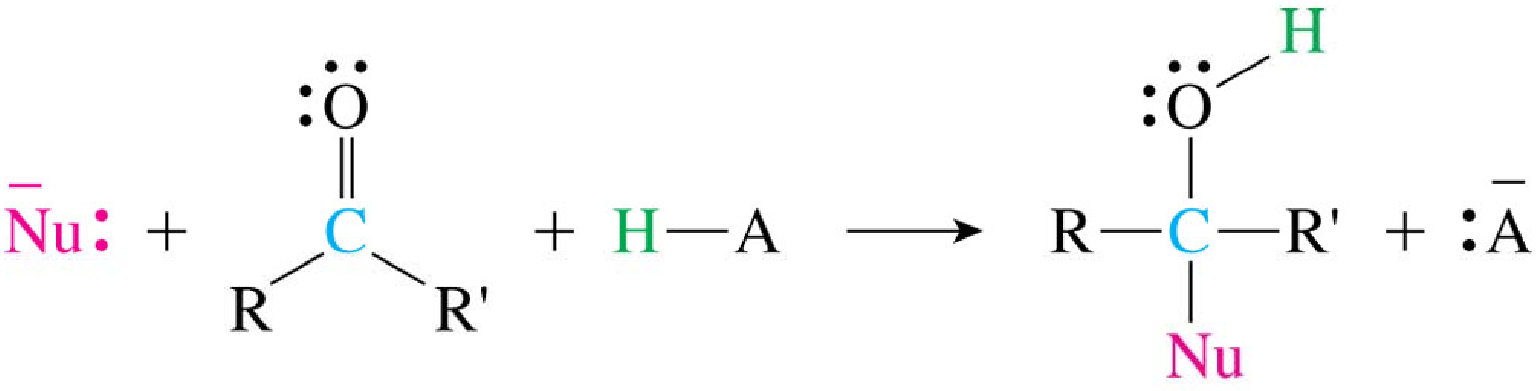
Substitution vs. Addition

substitution reaction





18.1 General Mechanisms



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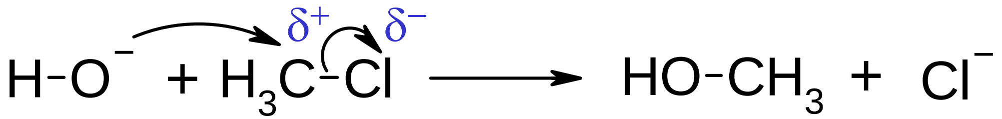
Possible both in basic and acidic conditions !

substitution reaction



$$H\text{-}O^{-} + H_3\overset{\delta+}{C}\text{-}\overset{\delta-}{Cl} \longrightarrow HO\text{-}CH_3 + Cl^{-}$$

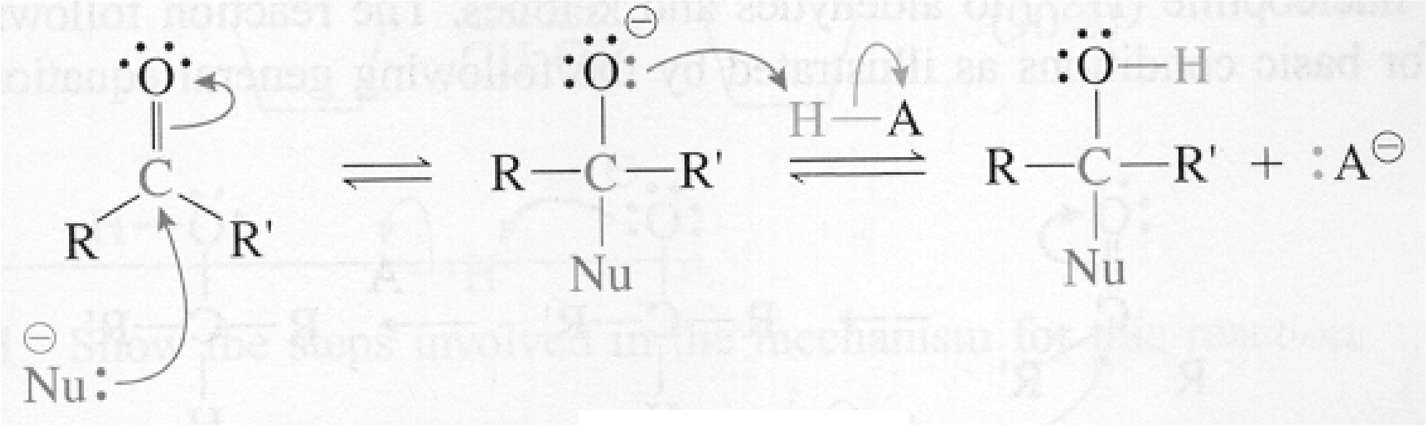
nucleophile (Nu:$^-$)

electrophile (R-L)

(Nu-R)

leaving group (L$^-$)

1. Mechanism under basic condition



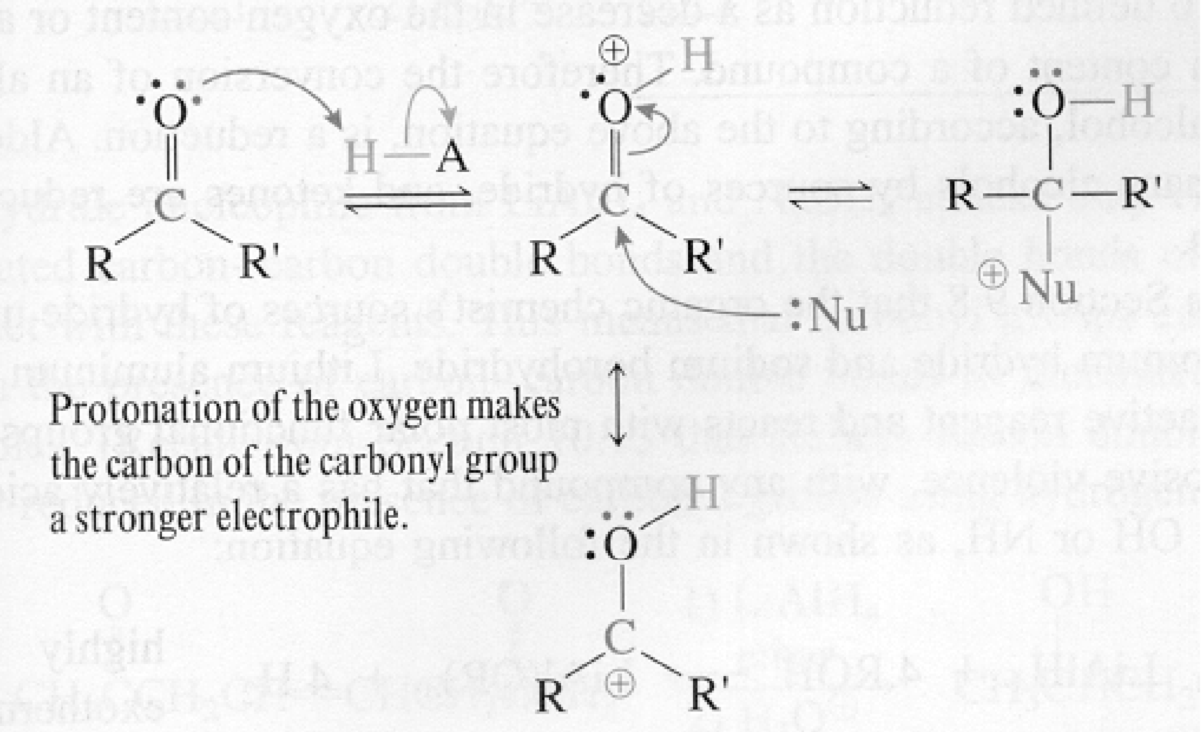
a. **Nu: can be neutral**

b. **If Nu: is a strong base, acidic solvents (H_2O, alcohol) must be avoided. Then solvent without acidic proton such as ether is used. Acid is added after the anionic compound is formed (during workup).**

c. **If Nu: is less basic, acidic solvents can be used.**

d. **If Nu: is less nucleophilic, use acidic condition!**

2. Mechanism for acidic condition



Protonation of the oxygen makes the carbon of the carbonyl group a stronger electrophile.

Typical Features

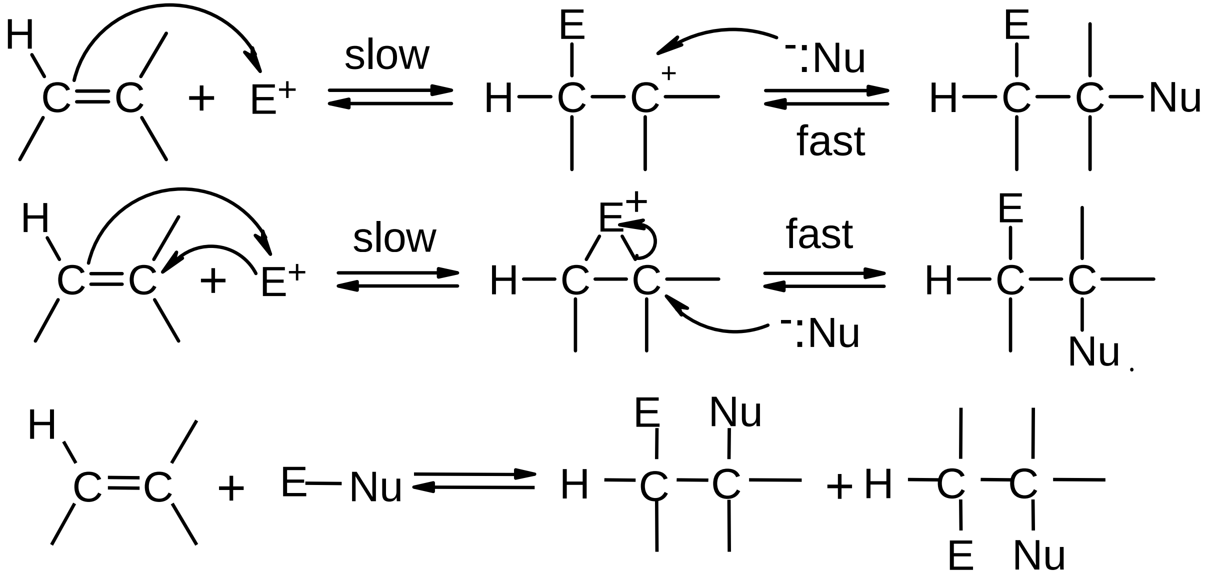
a. Stereochemistry is not a concern (no way to determine whether syn or anti addition)

b. Equilibrium favors the products or the reactants

⇒ strong Nu:, equilibrium is toward the product

⇒ Structural effect, which will be discussed

Electrophilic additions to C=C vs to C=O

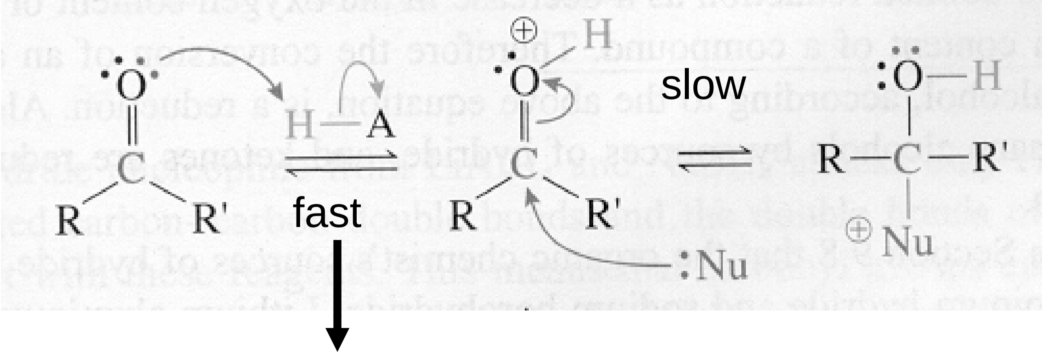


regioselective
non-stereoselective
(Anti + syn addition)

regioselective
Stereoselective
(Anti addition)

regioselective
Stereoselective
(syn addition)

See p454-456

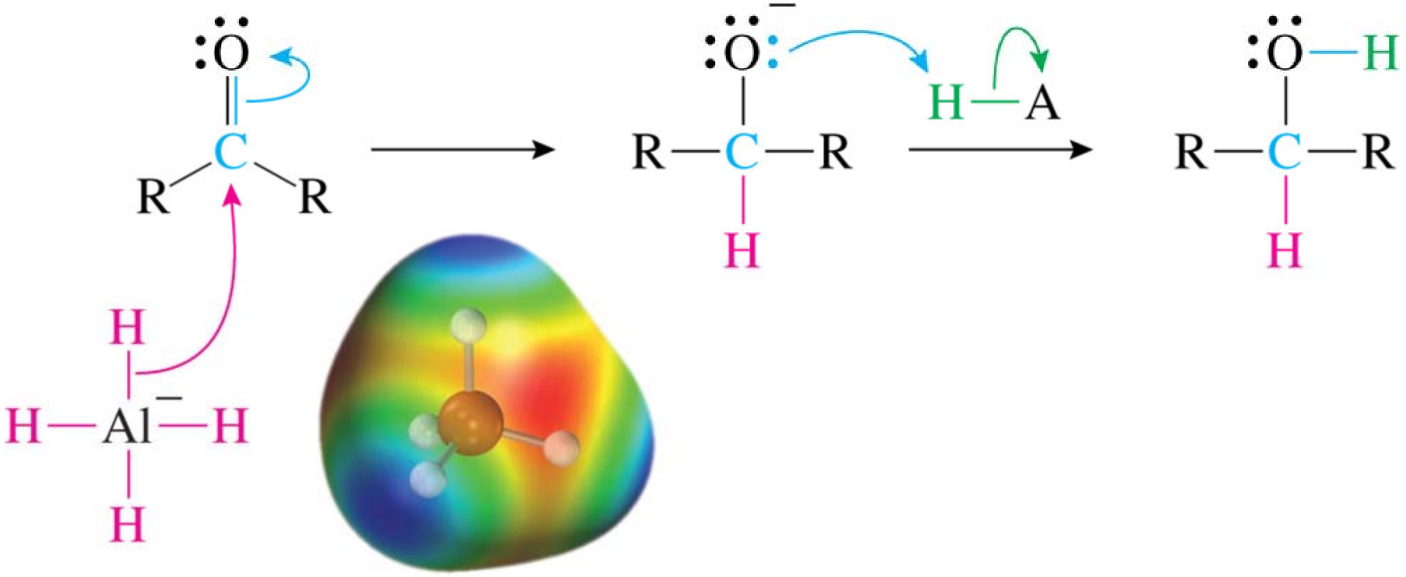


Nothing to do with regiochemistry and stereochemistry

Acid base reaction

18.2 Addition of Hydride; Reduction of Aldehydes and Ketones

Hydride ⇒ $H:^{\ominus}$ ⇒ very strong nucleophile (pKa of H_2 = 35)



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This is a reduction, because hydrogen content increase

Aldehyde ⇒ primary alcohol, Ketone ⇒ secondary alcohol

Sources of hydride nucleophile: Lithium aluminium hydride ($LiAlH_4$)

or Sodium borohydride ($NaBH_4$)

$LiAlH_4$ and $NaBH_4$ only react with carbonyls not C-C double bonds!

$LiAlH_4$ vs $NaBH_4$

$LiAlH_4$ is very reactive ⇒ cannot use a solvent with acidic proton

alcohol ⇒ explosove!

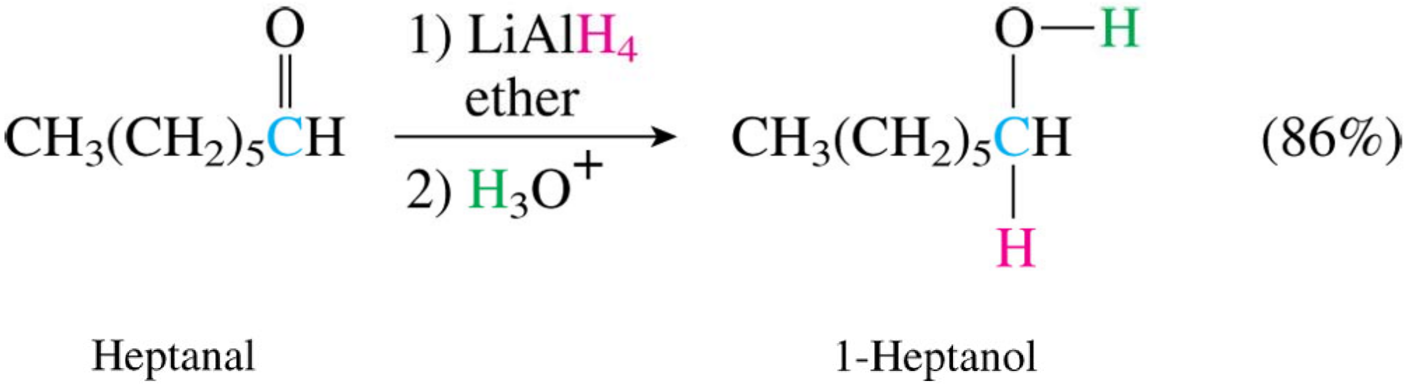
Ether can be used as a solvent!

$NaBH_4$ is less reactive, therefore alcohols can be used as solvents

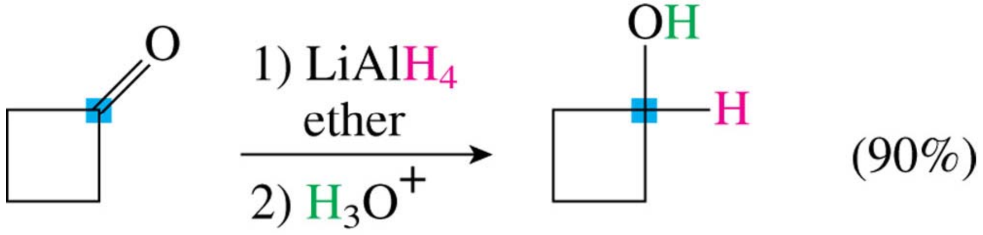
$$LiAlH_4 + 4\,ROH \longrightarrow LiAl(OR)_4 + 4\,H_2$$

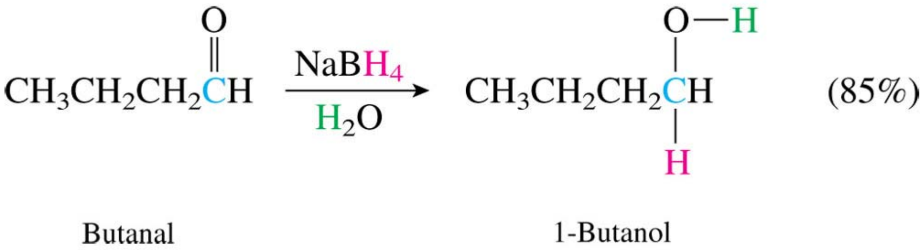
Highly exothermic

Examples

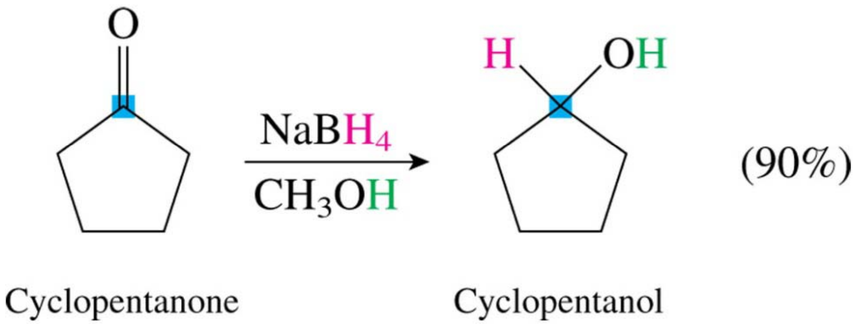


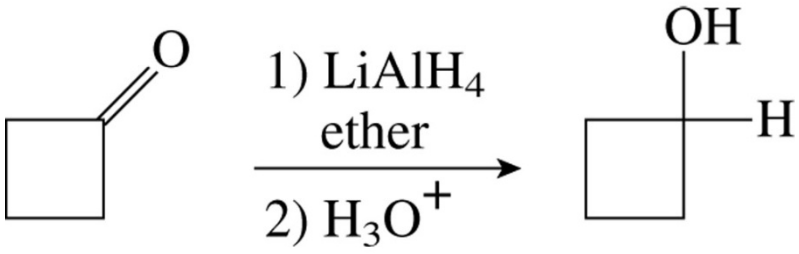
$$CH_3(CH_2)_5\overset{\overset{O}{\|}}{C}H \xrightarrow[\text{2) } H_3O^+]{\text{1) } LiAlH_4 \text{, ether}} CH_3(CH_2)_5\overset{\overset{O-H}{|}}{\underset{\underset{H}{|}}{C}}H \quad (86\%)$$



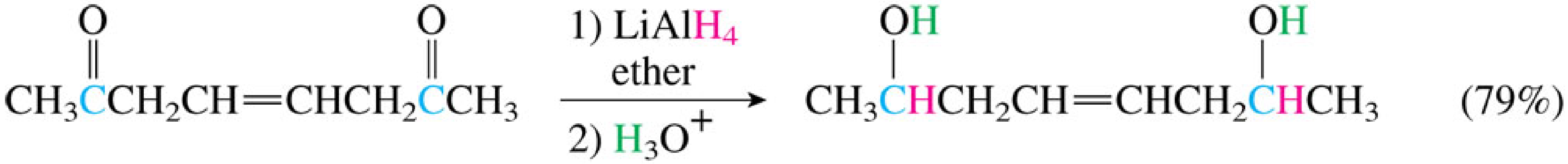


$$CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H \xrightarrow[H_2O]{NaBH_4} CH_3CH_2CH_2\overset{\overset{O-H}{|}}{\underset{\underset{H}{|}}{C}}H \quad (85\%)$$

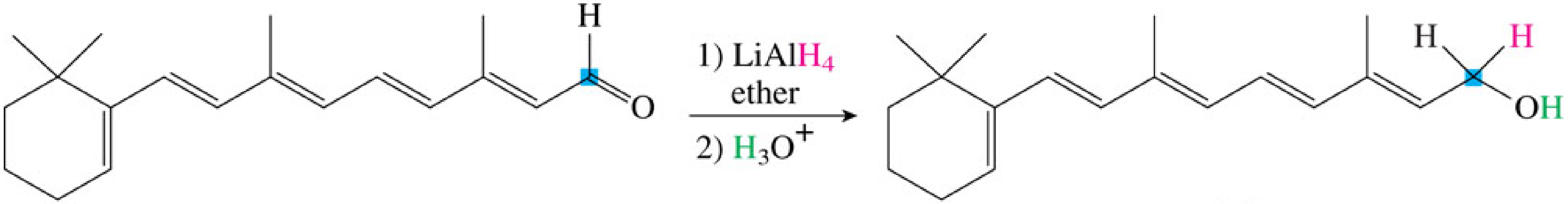




$LiAlH_4$ and $NaBH_4$ only react with carbonyls not C-C double bonds!

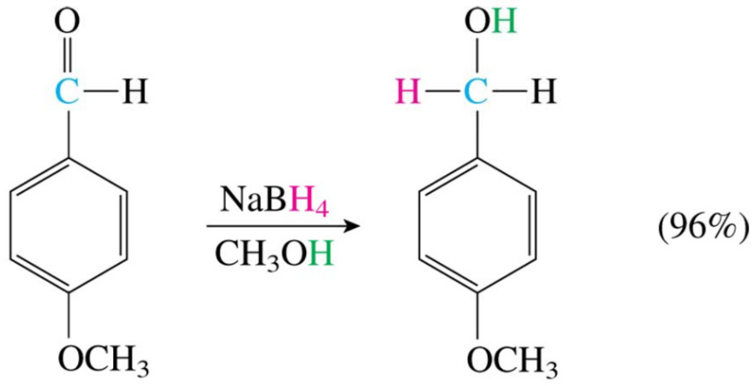


$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH{=}CHCH_2\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow[\text{2) } H_3O^+]{\substack{\text{1) } LiAlH_4 \\ \text{ether}}} CH_3\overset{OH}{\overset{|}{C}}HCH_2CH{=}CHCH_2\overset{OH}{\overset{|}{C}}HCH_3 \quad (79\%)$$



Vitamin A aldehyde
(retinal)

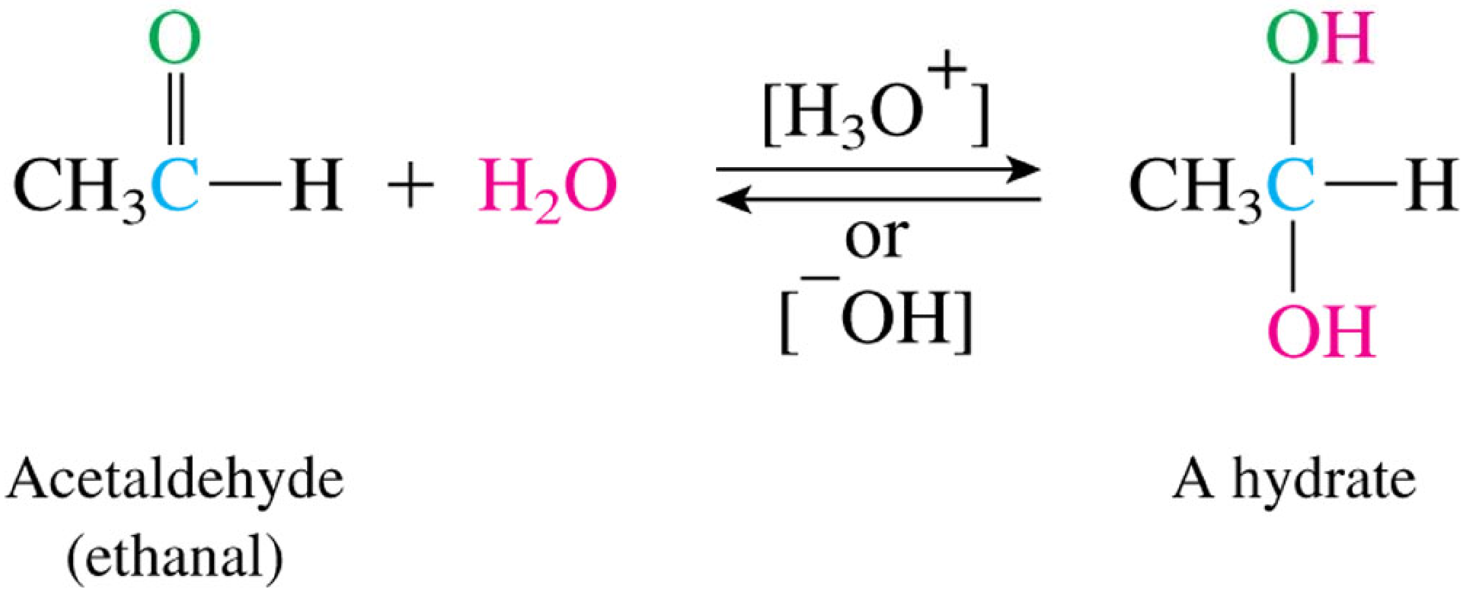
(75%)
Vitamin A
(retinol)



p-Methoxybenzaldehyde

p-Methoxybenzyl alchohol

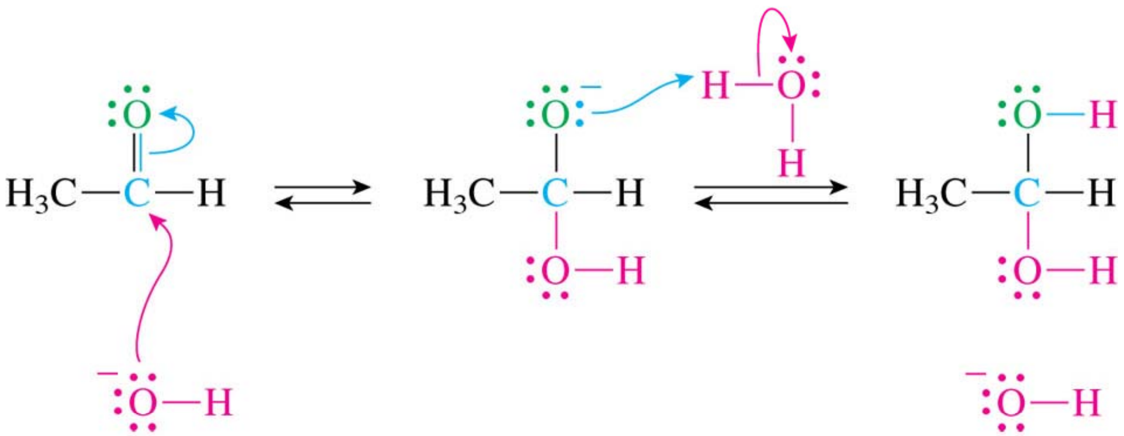
18.3 Addition of Water



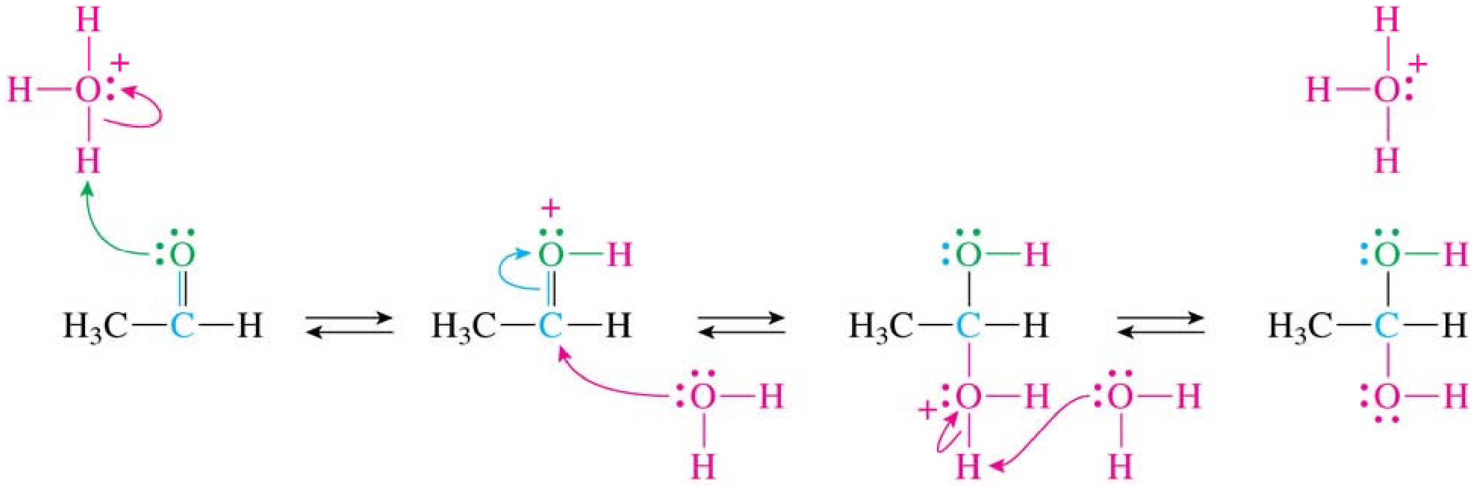
$$CH_3\overset{O}{\overset{\|}{C}}{-}H + H_2O \underset{\text{or } [^{-}OH]}{\overset{[H_3O^+]}{\rightleftharpoons}} CH_3\underset{OH}{\overset{OH}{C}}{-}H$$

Possible both in basic and acidic conditions !

Mechanism in Base



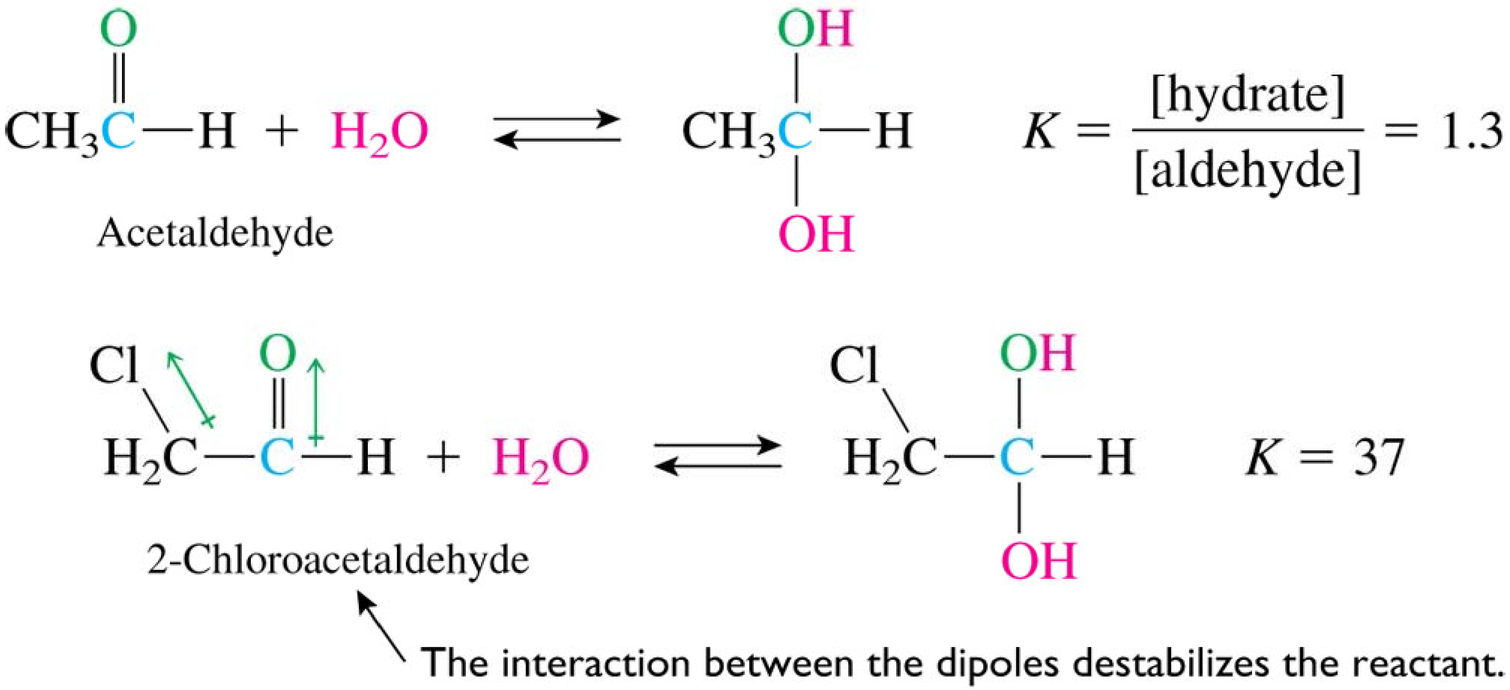
Mechanism in Acid



Acid and base is consumed in the first step and then regenerated in the last step, therefore it is a acid catalyzed or base catalyzed reaction

The structure of the carbonyl compound on the equilibrium constant

1. Inductive effect



The interaction between the dipoles destabilizes the reactant.

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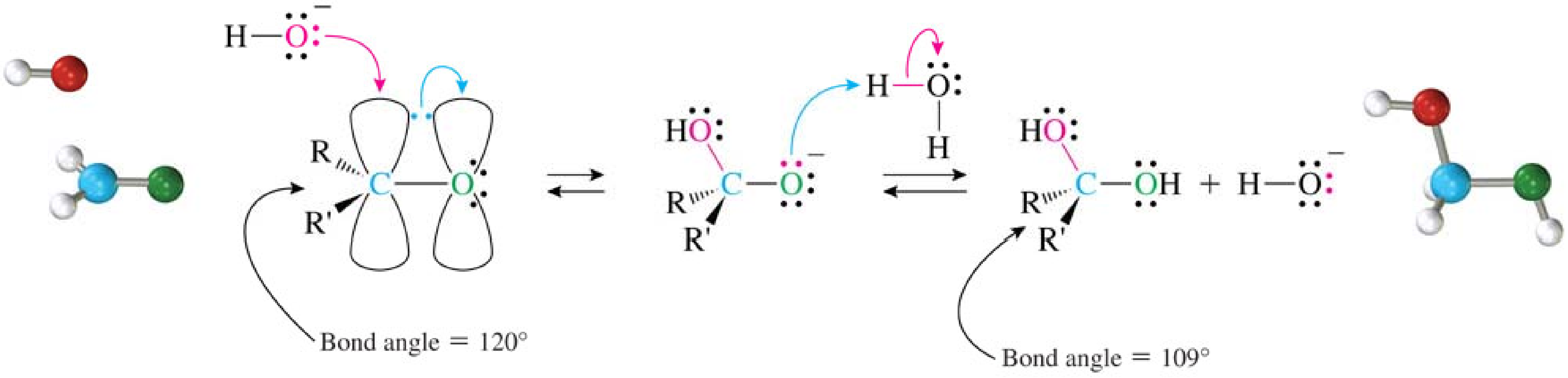
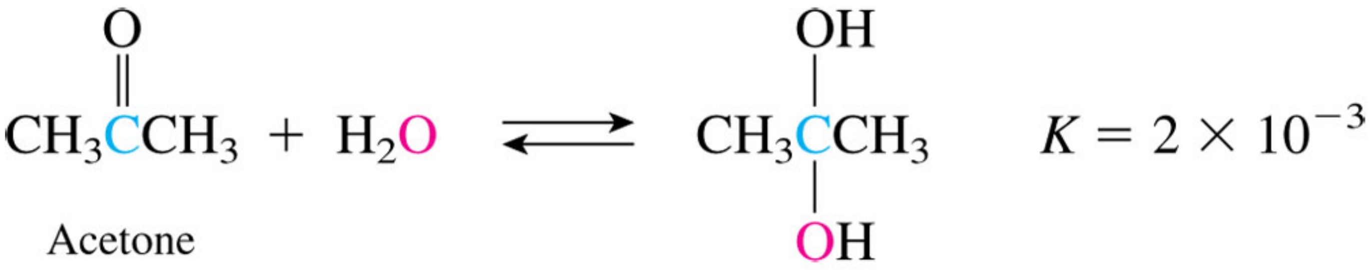
e^- w/drawing group: destabilize the aldehyde or ketone

e^- donating group: stabilize the aldehyde or ketone

2. Steric effect

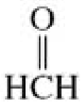
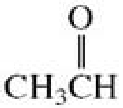
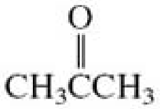
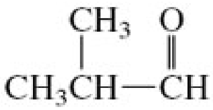
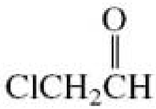
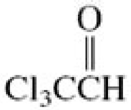


Larger substituent shift the equilibrium toward the reactant

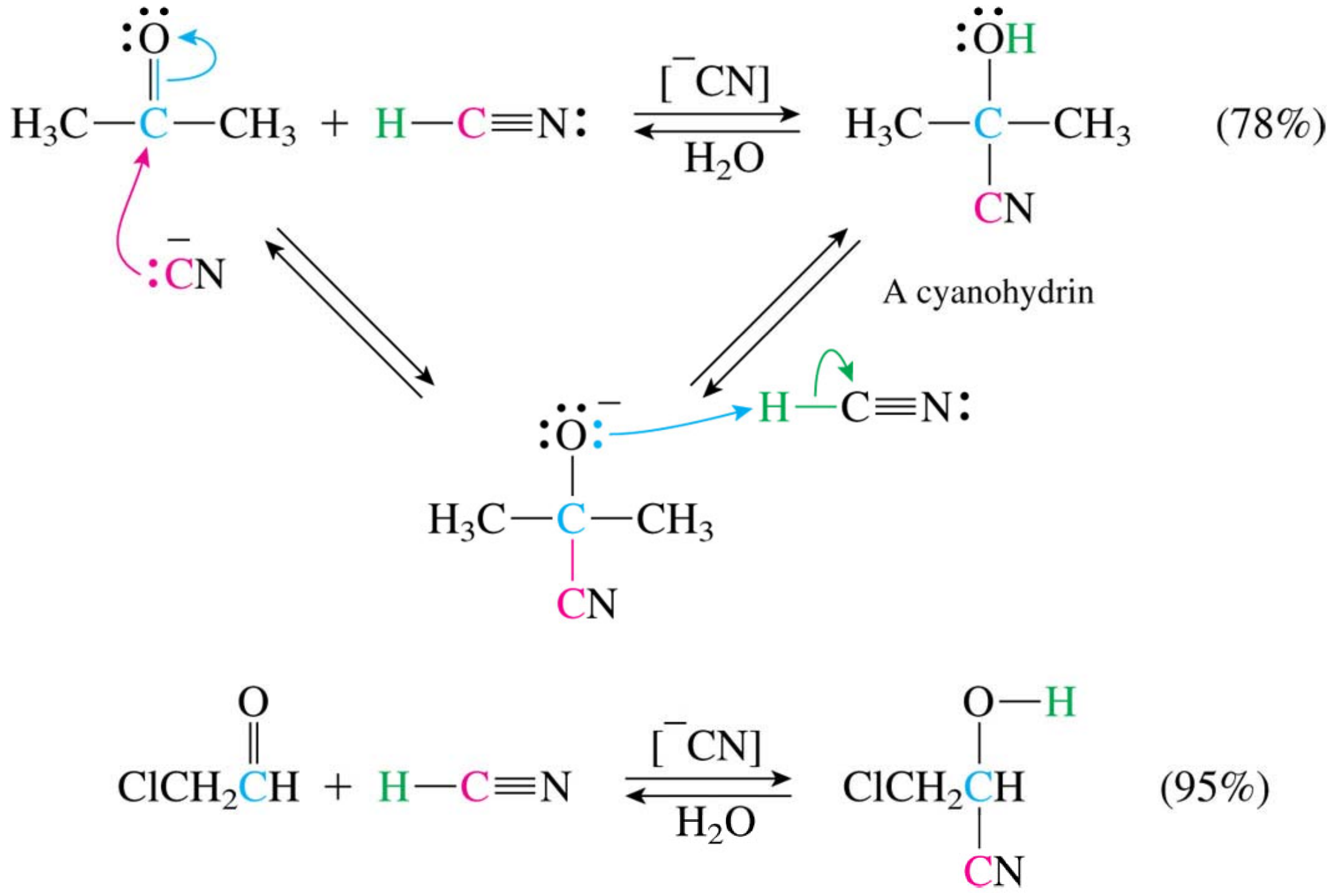


$$CH_3\overset{\overset{\displaystyle O}{\|}}{C}CH_3 + H_2O \rightleftharpoons CH_3\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle OH}{|}}{C}}CH_3 \qquad K = 2 \times 10^{-3}$$

Acetone

Compound	*K*	Comments
 $\mathrm{H\overset{\overset{O}{\|}}{C}H}$ Formaldehyde	2×10^3	Formaldehyde has a large equilibrium constant for hydrate formation because it has no bulky, electron-donating alkyl groups. It is more than 99.9% in the hydrated form in aqueous solution. The "formaldehyde" or formalin used to preserve biological samples is actually a concentrated solution of the hydrate in water. Formaldehyde itself is a gas.
 $\mathrm{CH_3\overset{\overset{O}{\|}}{C}H}$ Acetaldehyde	1.3	The more hindered carbonyl carbon of acetaldehyde is less reactive. Acetaldehyde is slightly more than 50% hydrated in aqueous solution.
 $\mathrm{CH_3\overset{\overset{O}{\|}}{C}CH_3}$ Acetone	2×10^{-3}	Acetone, with an even more hindered carbonyl carbon, forms only a negligible amount of hydrate.
 $\mathrm{CH_3CH_2\overset{\overset{O}{\|}}{C}H}$	0.71	As can be seen by comparing these two examples to acetaldehyde, an increase in steric hindrance further from the carbonyl carbon results in only a small decrease in the equilibrium constant.
 $\mathrm{CH_3\overset{\overset{CH_3}{|}}{C}H{-}\overset{\overset{O}{\|}}{C}H}$	0.44	
 $\mathrm{ClCH_2\overset{\overset{O}{\|}}{C}H}$	37	As can be seen by comparing these two examples to acetaldehyde, the inductive effect of chlorine shifts the equilibrium toward the hydrate. When three chlorines are present, the product, known as chloral hydrate, can be isolated (mp = 57°C). It is a powerful hypnotic and is the active ingredient of a "Mickey Finn," or knockout drops.
 $\mathrm{Cl_3C\overset{\overset{O}{\|}}{C}H}$	2.8×10^4	

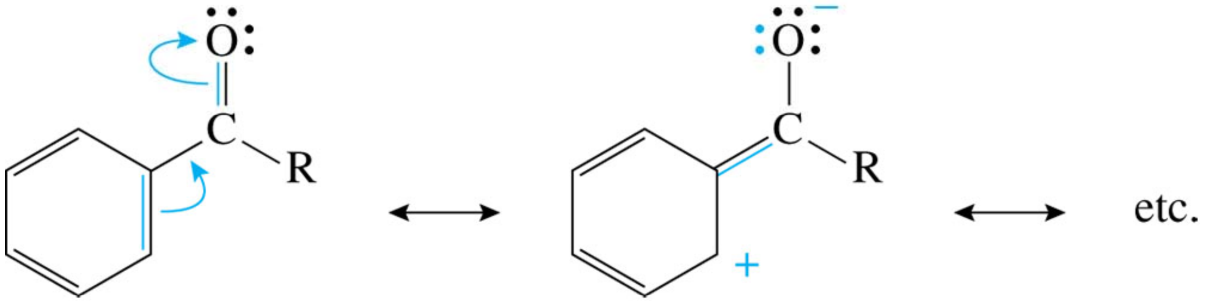
18.4 Addition of Hydrogen Cyanide



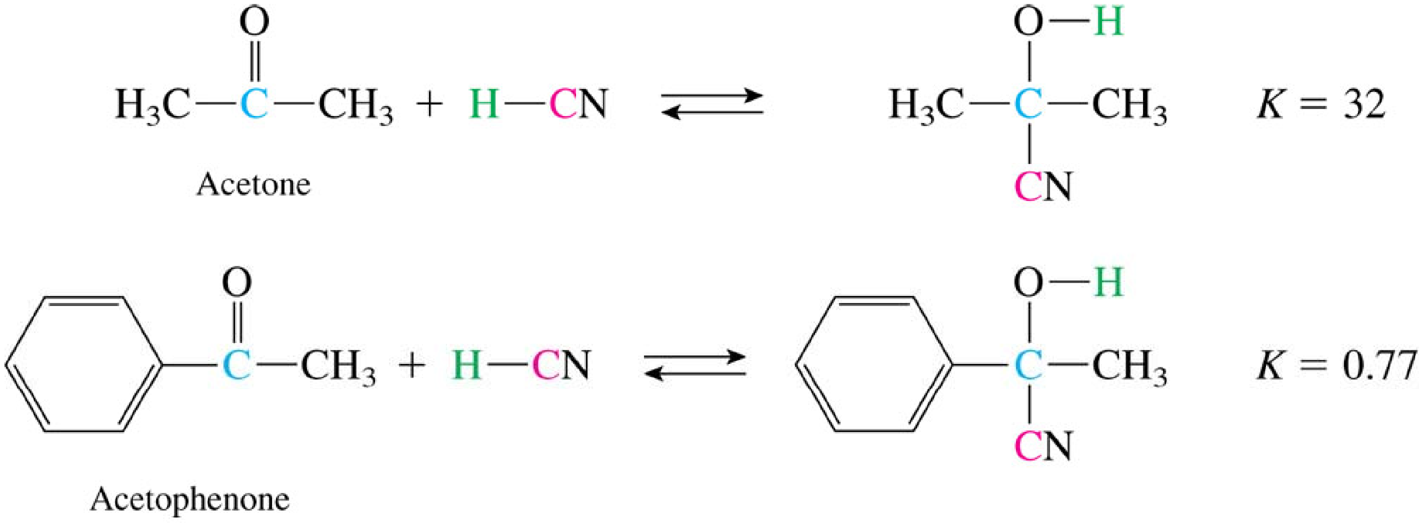
$K_{\text{cyanohydrin formation}} > K_{\text{hydrate formation}}$

⇒ CN^- is stronger nucleophile than H2O

Unfavorable equilibrium constant for ketones conjugated with benzene



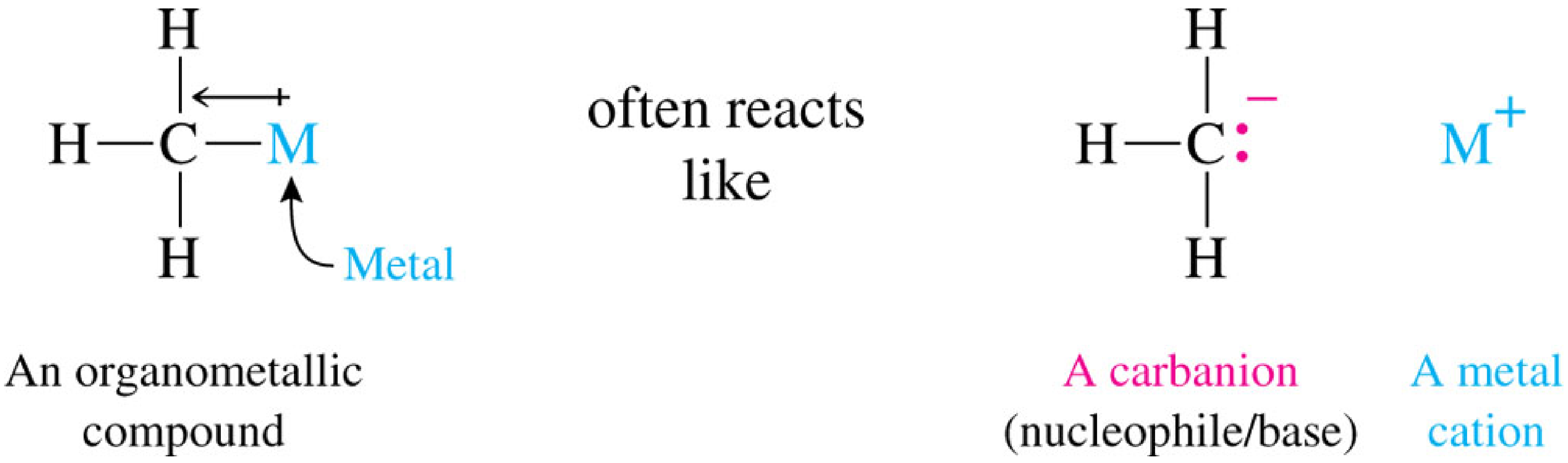
Reactant has resonance stabilization
⇒ reduced electrophilicity of the carbonyl carbon



18.5 Preparation and Properties of Organometallic Nucleophiles

Organometallic Nu: R-M(metal) ≡ $R^{\delta-}M^{\delta+}$

⇒ R is more electronegative



Examples

1. Acetylide anion (see Section 10.12): 1-alkyne + sodium amide

⇒ Hydrogens bonded to *sp*^{3} and *sp*^{2} C's cannot be removed because not acidic enough (*sp*: pKa ~25, *sp*^{2}: pKa ~45, *sp*^{3} pKa ~50)

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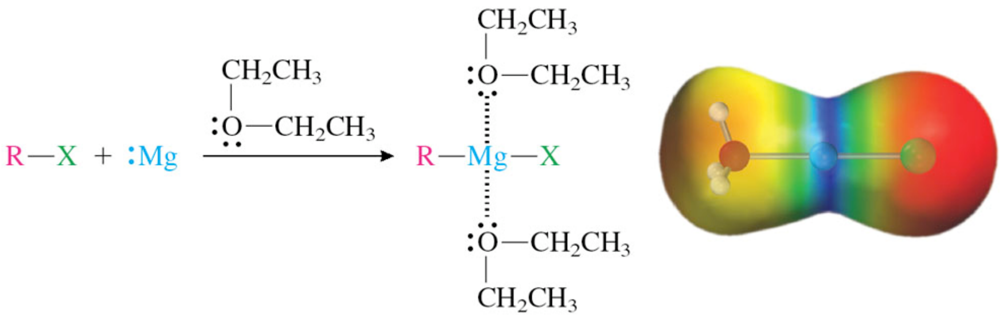
2. Grignard reagent (organometallic halides)



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Reactivity of R-X

R-I > R-Br > R-Cl, R-F is not used ⇒ see leaving group property

3. Organolithium reagent

R-X + 2Li → RLi + LiX

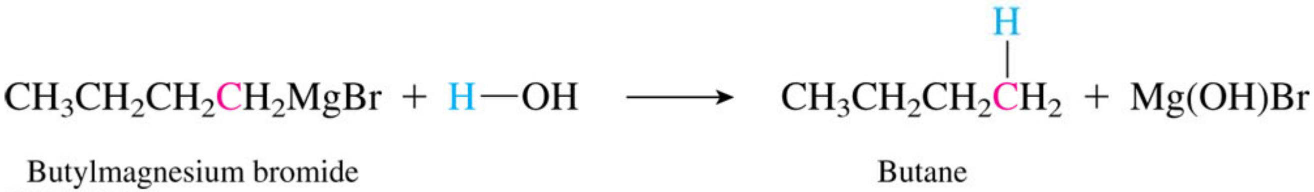
Chemical behavior of organometallic reagent

Very close to carbanion and strong base, although M-R is a covalent bond(?)

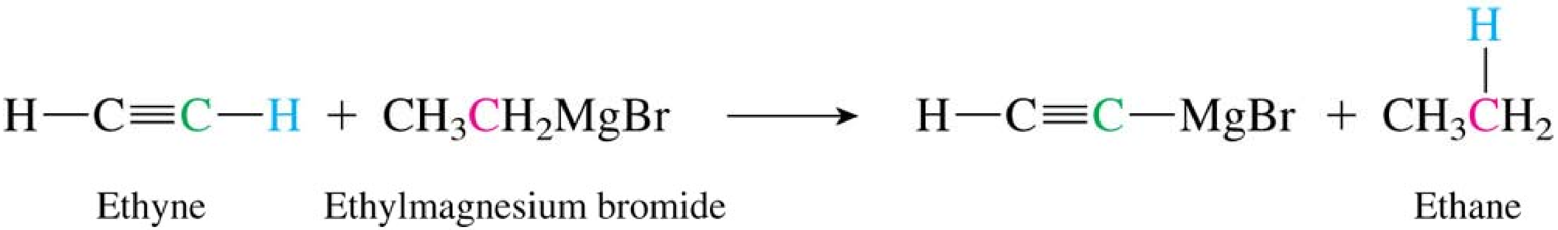
Therefore it react rapidly with even with weak acids

⇒ avoid compounds with acidic proton (-OH, -NH, ≡C-H…)

Examples



$$CH_3CH_2CH_2CH_2MgBr + H{-}OH \longrightarrow CH_3CH_2CH_2\overset{H}{\overset{|}{C}}H_2 + Mg(OH)Br$$



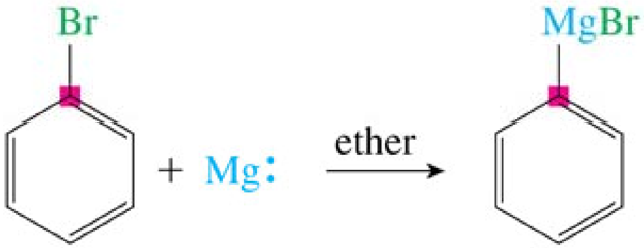
$$H{-}C{\equiv}C{-}H + CH_3CH_2MgBr \longrightarrow H{-}C{\equiv}C{-}MgBr + CH_3\overset{H}{\overset{|}{C}}H_2$$

Therefore solvents for the reactions should be very dry !

$$CH_3{-}I + Mg\colon \xrightarrow{\text{ether}} CH_3MgI$$

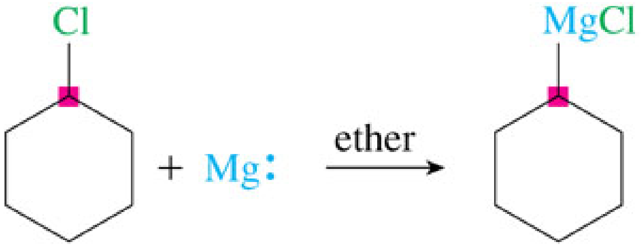
Iodomethane
(methyl iodide)

Methylmagnesium
iodide



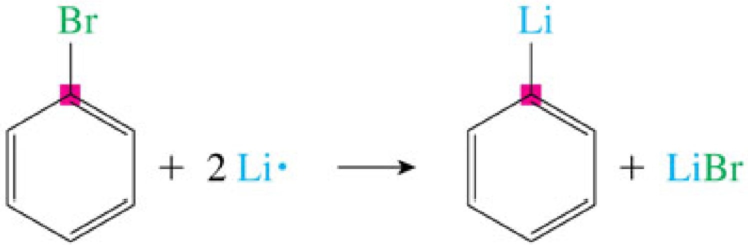
Bromobenzene

Phenylmagnesium
bromide



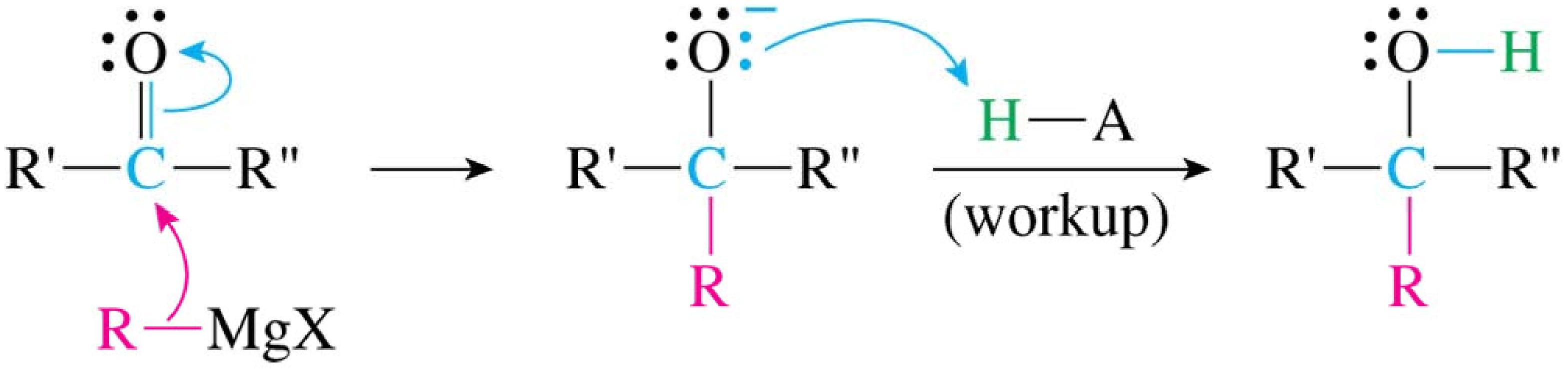
Chlorocyclohexane

Cyclohexylmagnesium
chloride



Phenyllithium

18.6 Addition of Organometallic Nucleophiles



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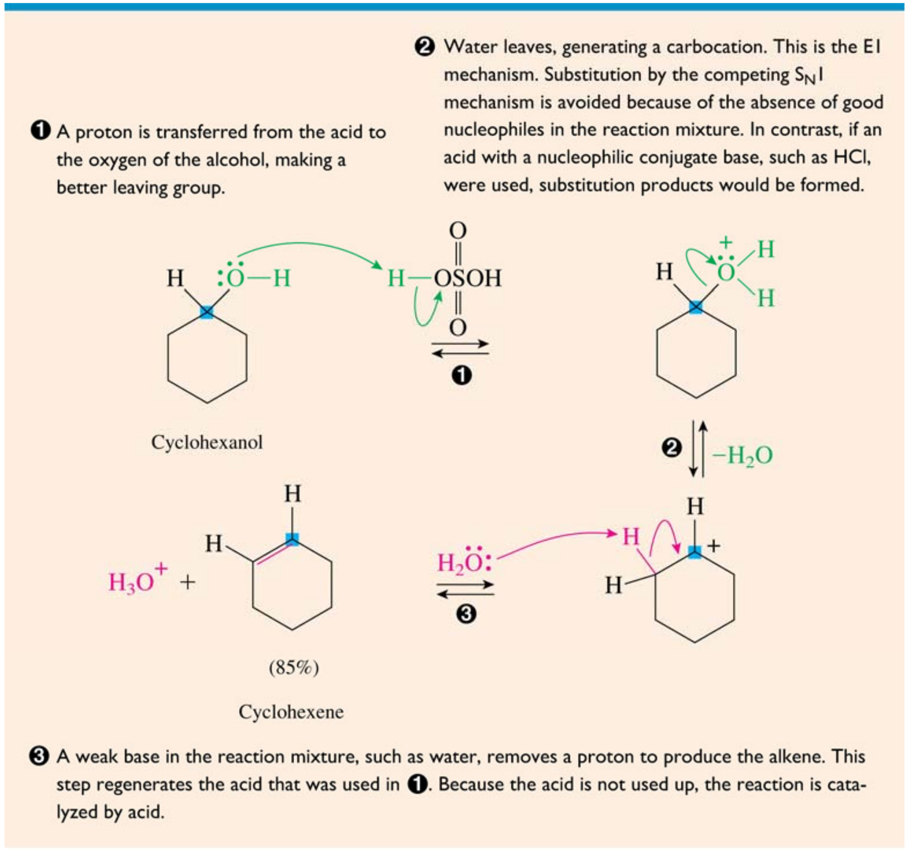
1. **This reaction is conducted in basic condition**
2. **As ⁻R: is very strong nucleophile the reaction is irreversible.**
3. **In the protonation step, use weaker acids such as NH_4Cl (pK_a~ 9)** ⇒
   strong acid:acid catalyzed elimination rxn

(see ch9. P378, next page)

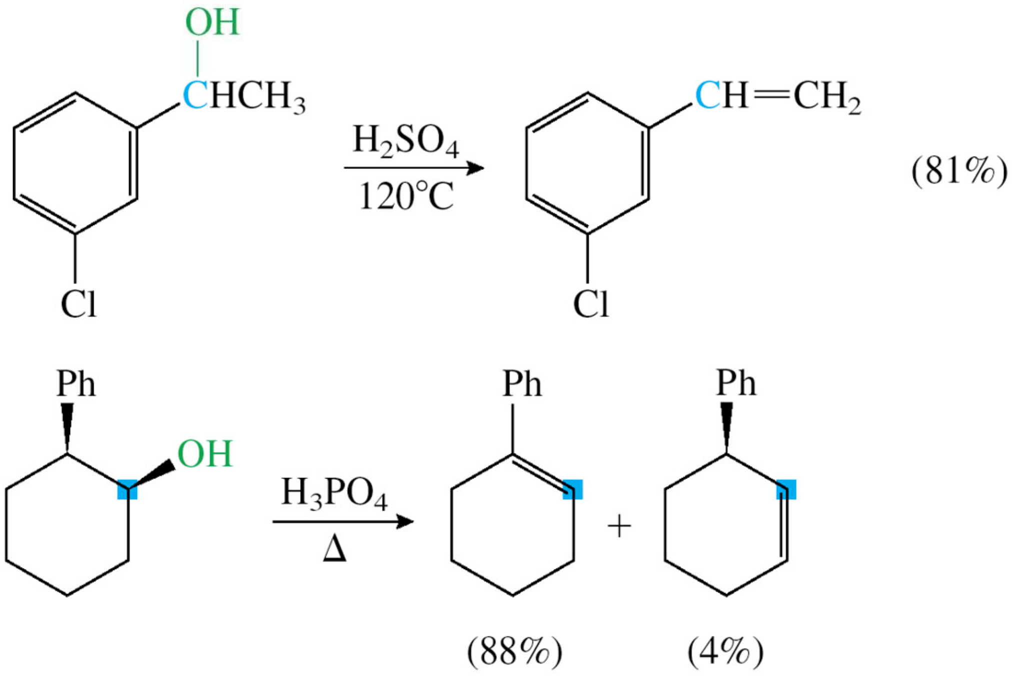
Examples See p 379



❶ A proton is transferred from the acid to the oxygen of the alcohol, making a better leaving group.

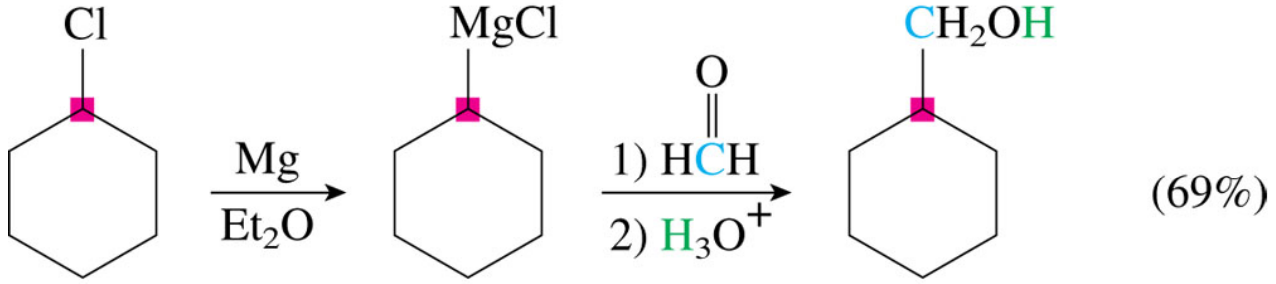
❷ Water leaves, generating a carbocation. This is the E1 mechanism. Substitution by the competing S_N1 mechanism is avoided because of the absence of good nucleophiles in the reaction mixture. In contrast, if an acid with a nucleophilic conjugate base, such as HCl, were used, substitution products would be formed.

❸ A weak base in the reaction mixture, such as water, removes a proton to produce the alkene. This step regenerates the acid that was used in ❶. Because the acid is not used up, the reaction is catalyzed by acid.

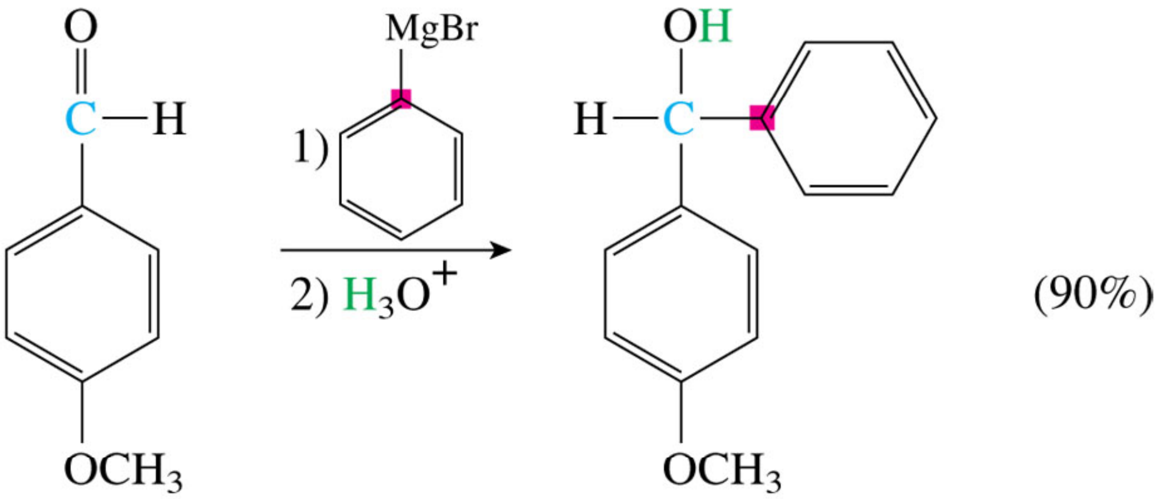


Reactions of Grignard reagent

Grignard reagent ⇒ formation of alcohols

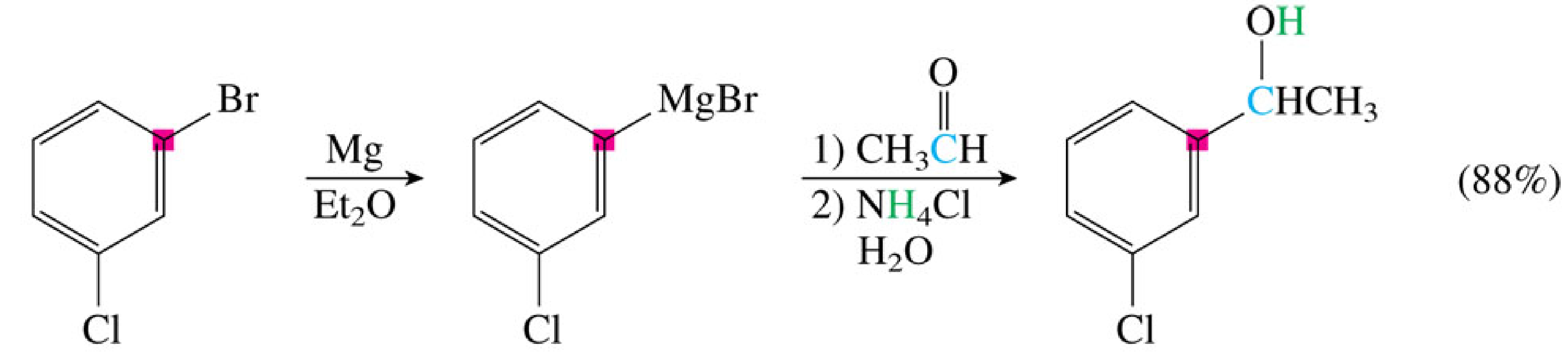


Primary alcohol formation



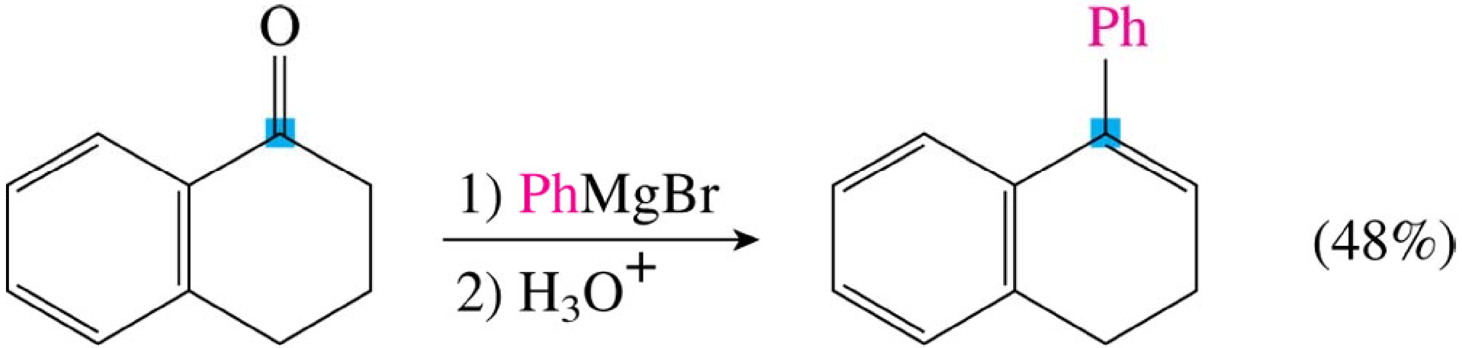
p-Methoxybenzaldehyde

Secondary alcohol formation



m-Bromochlorobenzene

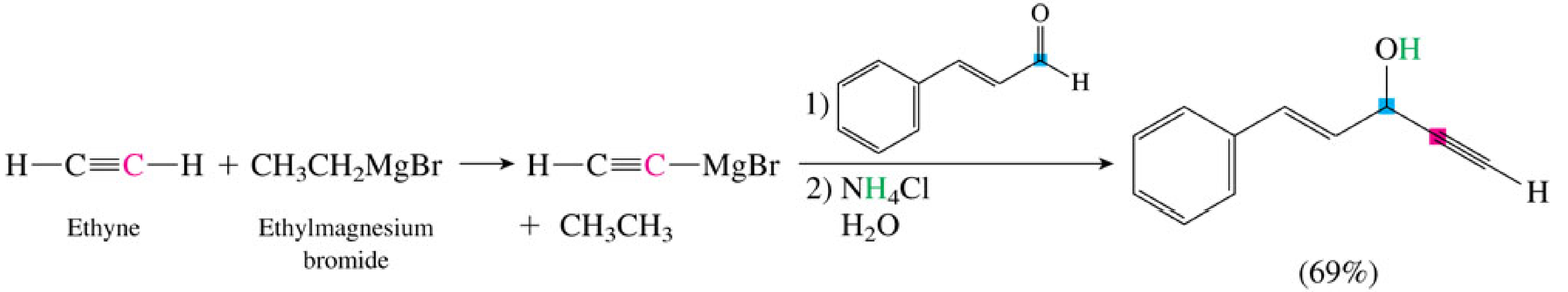
Br is more reactive



α-Tetralone

When strong acid is used

Reactions of Grignard reagent



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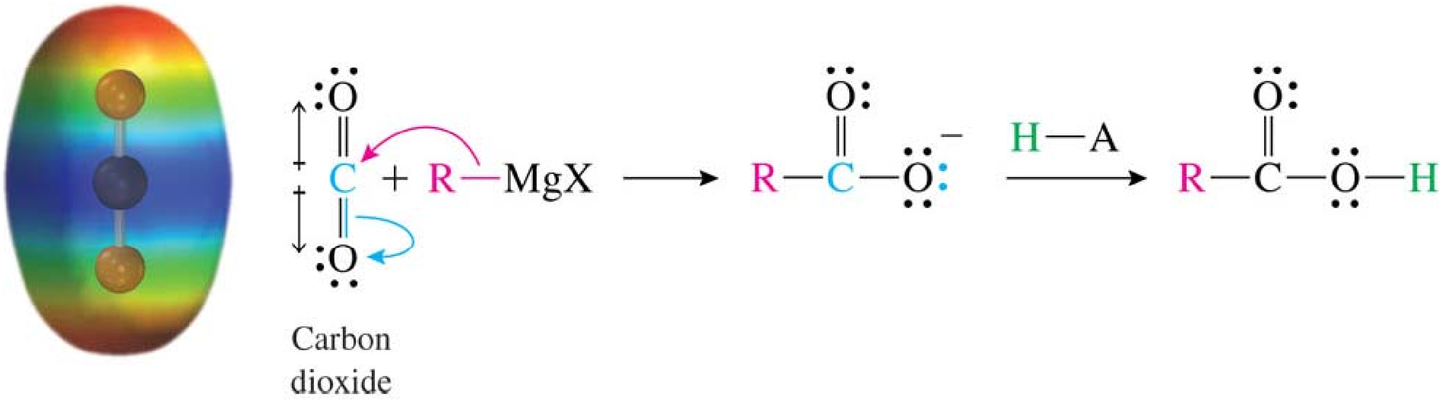

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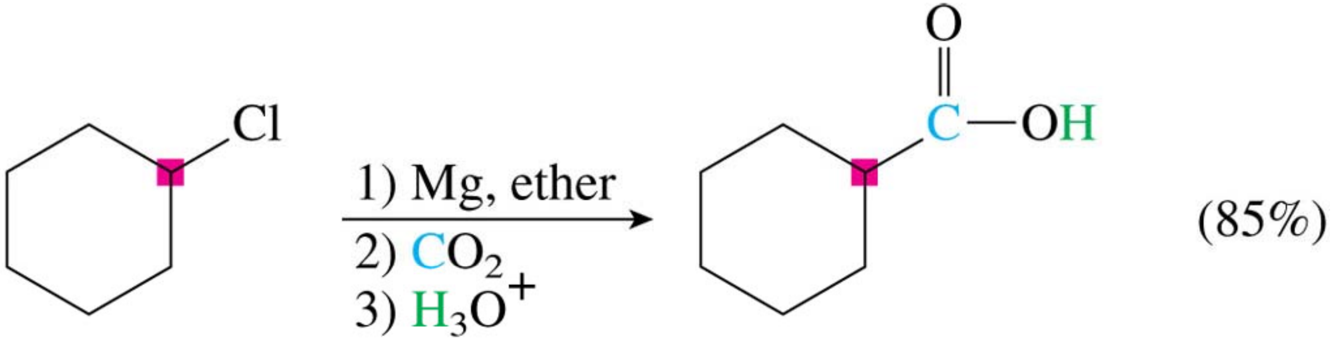
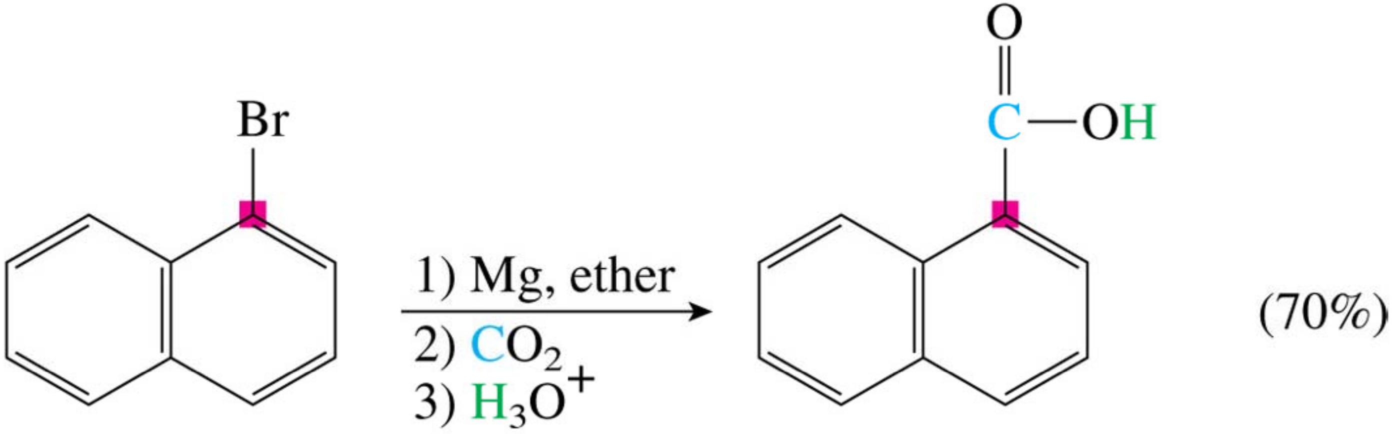
Reactions of Grignard reagent

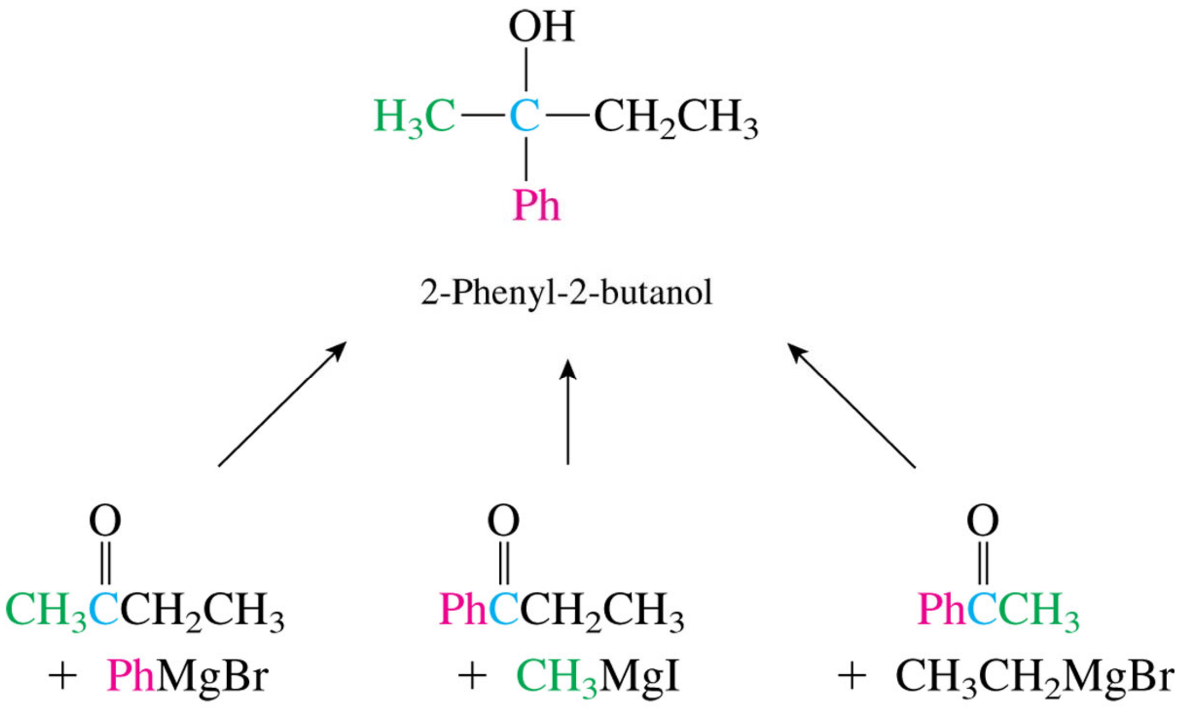


Chlorocyclohexane

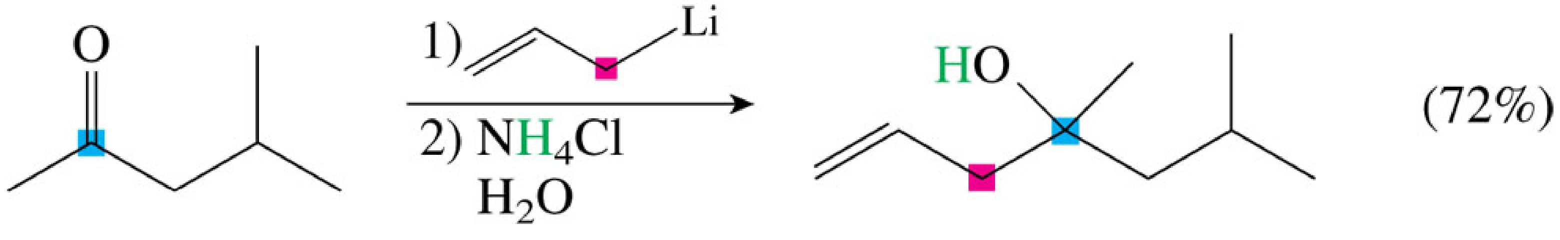


1-Bromonaphthalene

Reactions of Grignard reagent



Organolithium reagent ⇒ formation of alcohols

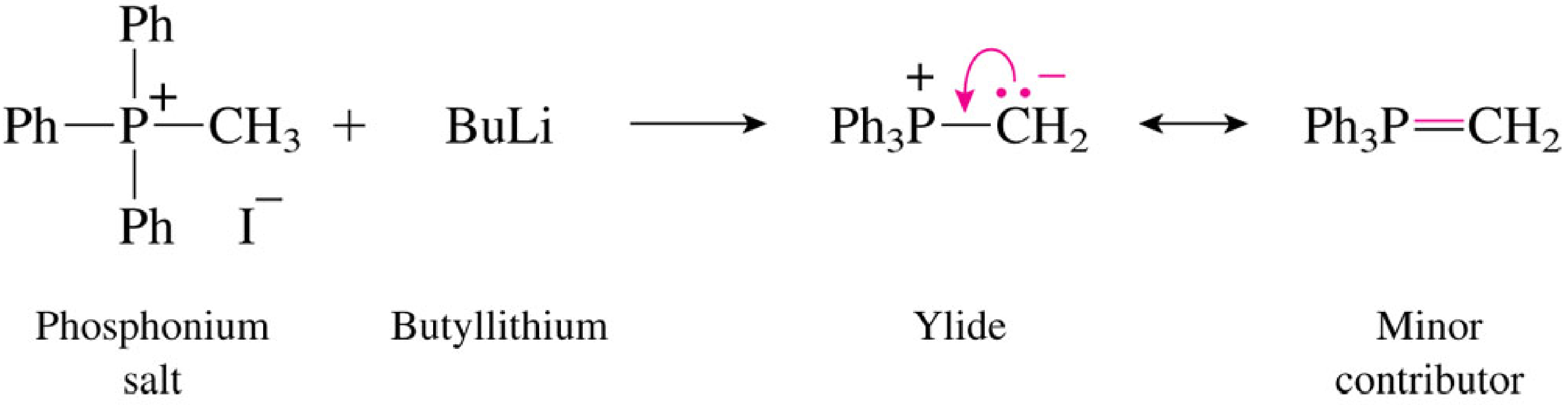


4-Methyl-2-pentanone

18.7 Addition of Phosphorus Ylides; The Wittig Reaction

⇒ **Method for the synthesis of alkene**

⇒ **1979 Nobel prize Georg Wittig**



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Acid + base rxn

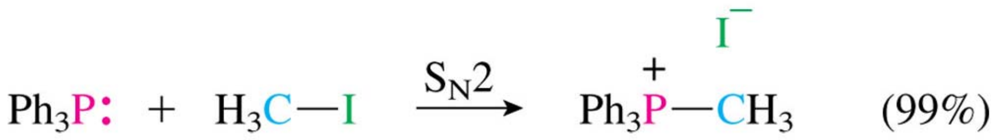
Or S_N2

+

LiCl + butane

$P(Ph)_3 + CH_3I$

(triphenyl phosphine)



$$Ph_3P: + H_3C-I \xrightarrow{S_N2} Ph_3\overset{+}{P}-CH_3 \; I^- \quad (99\%)$$

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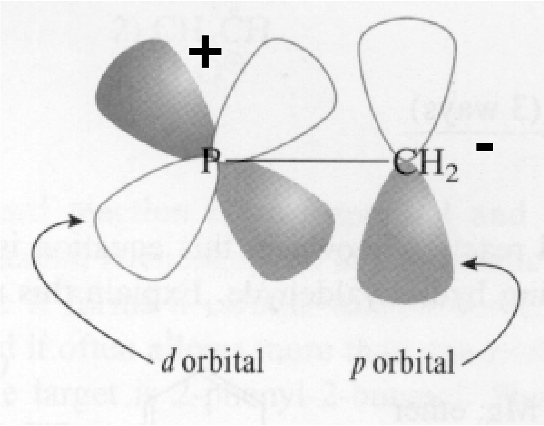
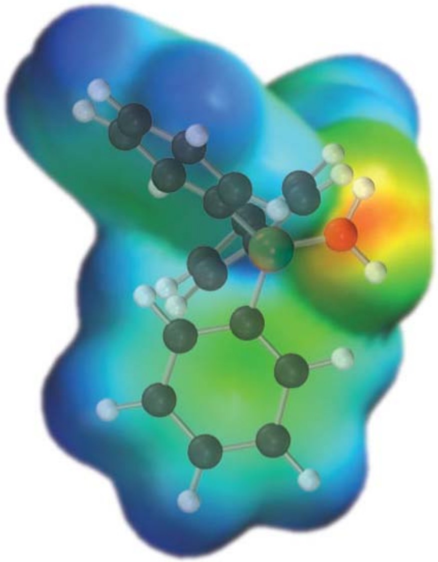
Ylide





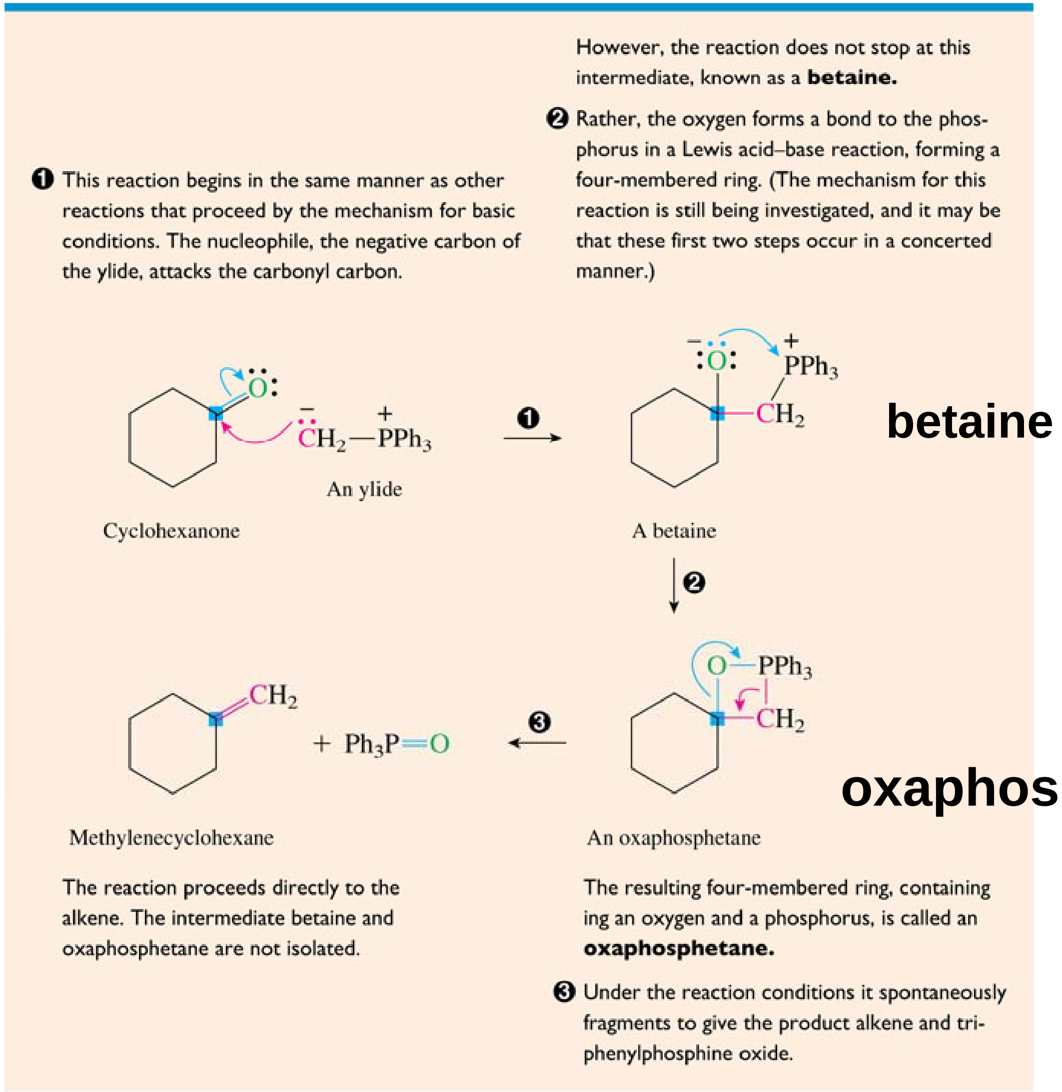
Electrostatic potential map of $Ph_3\overset{+}{P}-\overset{\cdot\cdot\,-}{C}H_2$

Ylide is stabilized by

1. **Inductive effect of the positive P atom**
2. **Delocalization of the e$^-$ pairs by the overlap**

Mechanism of the Wittig Reaction

⇒ **Addition-elimination reaction**



❶ This reaction begins in the same manner as other reactions that proceed by the mechanism for basic conditions. The nucleophile, the negative carbon of the ylide, attacks the carbonyl carbon.

However, the reaction does not stop at this intermediate, known as a **betaine.**

❷ Rather, the oxygen forms a bond to the phosphorus in a Lewis acid–base reaction, forming a four-membered ring. (The mechanism for this reaction is still being investigated, and it may be that these first two steps occur in a concerted manner.)

The resulting four-membered ring, containing ing an oxygen and a phosphorus, is called an **oxaphosphetane.**

❸ Under the reaction conditions it spontaneously fragments to give the product alkene and triphenylphosphine oxide.

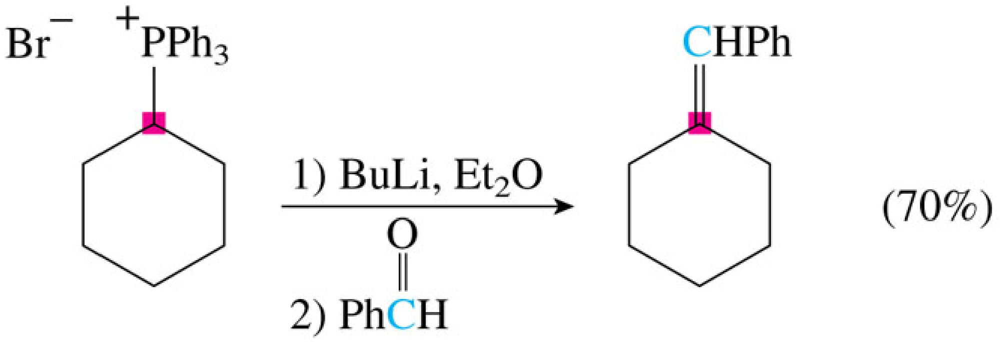
The reaction proceeds directly to the alkene. The intermediate betaine and oxaphosphetane are not isolated.

betaine

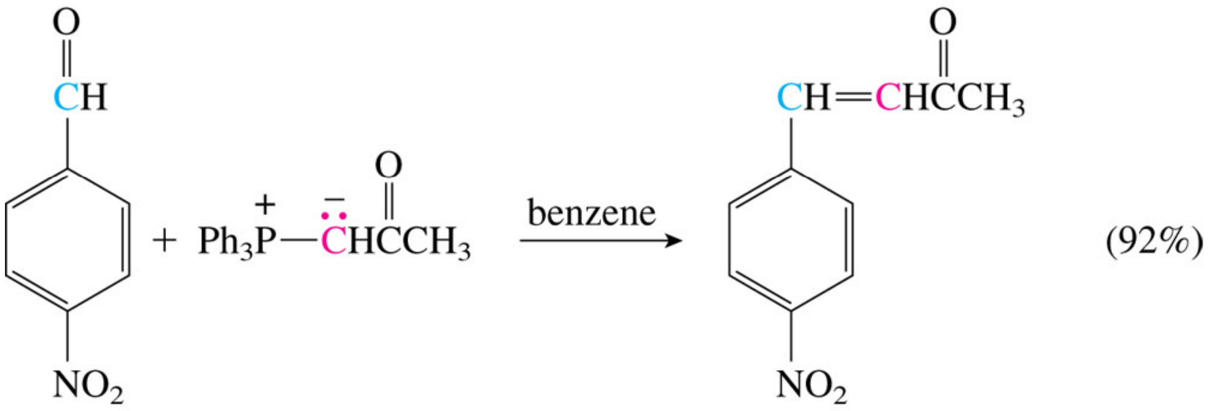
Never been isolated

oxaphosphetane

Examples of the Wittig Reaction

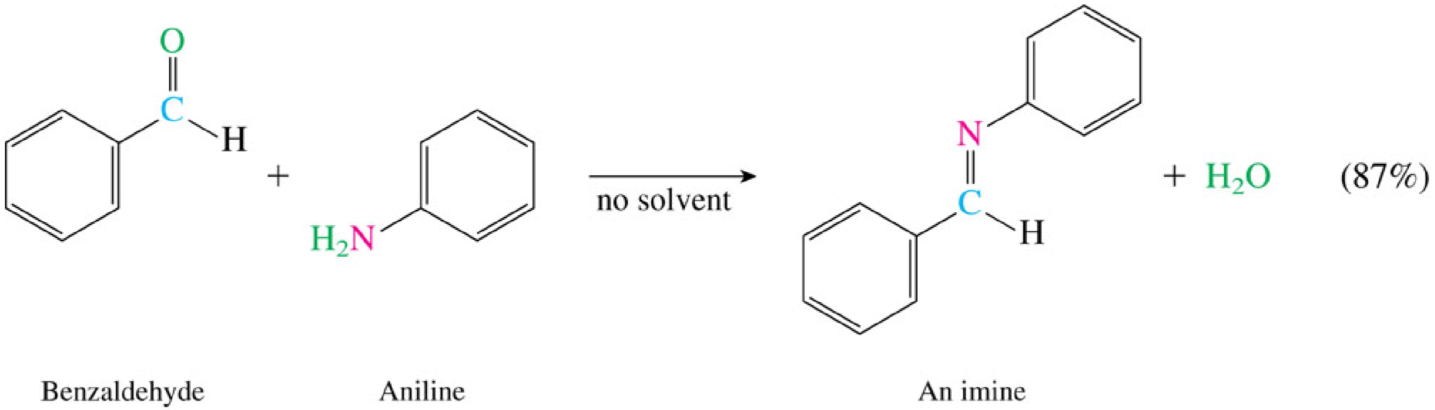


$$PhCH{=}CH\overset{O}{\overset{\|}{C}}H + Ph_3\overset{+}{P}-\overset{-}{\ddot{C}}HPh \xrightarrow{EtOH} PhCH{=}CHCH{=}CHPh \quad (84\%)$$



18.8 Addition of Nitrogen Nucleophiles

Aldehyde or ketone + Amine → imine + H_2O



It is Addition + Elimination.

Optimum pH = 4 ~ 6

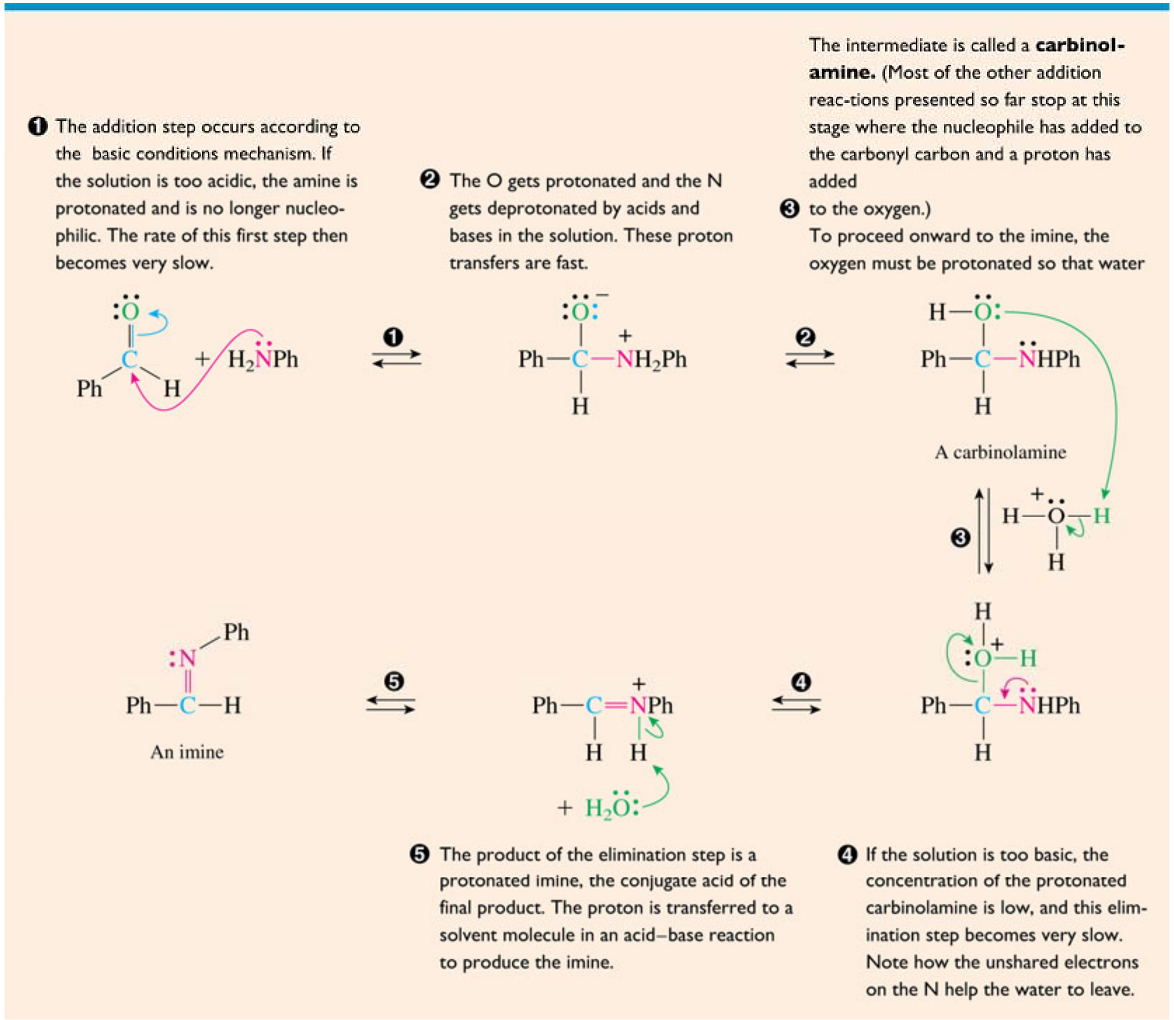
If too acidic, the amine nucleophile is protonated.

If too basic, the concentration of the protonated carbinolamine is low.

Mechanism for the addition of an amine to an aldehyde to form an imine

At low pH, this amine is protonated.

Then the conc. of Nu: is very low



❶ The addition step occurs according to the basic conditions mechanism. If the solution is too acidic, the amine is protonated and is no longer nucleophilic. The rate of this first step then becomes very slow.

❷ The O gets protonated and the N gets deprotonated by acids and bases in the solution. These proton transfers are fast.

The intermediate is called a **carbinolamine.** (Most of the other addition reac-tions presented so far stop at this stage where the nucleophile has added to the carbonyl carbon and a proton has added

❸ to the oxygen.)
To proceed onward to the imine, the oxygen must be protonated so that water

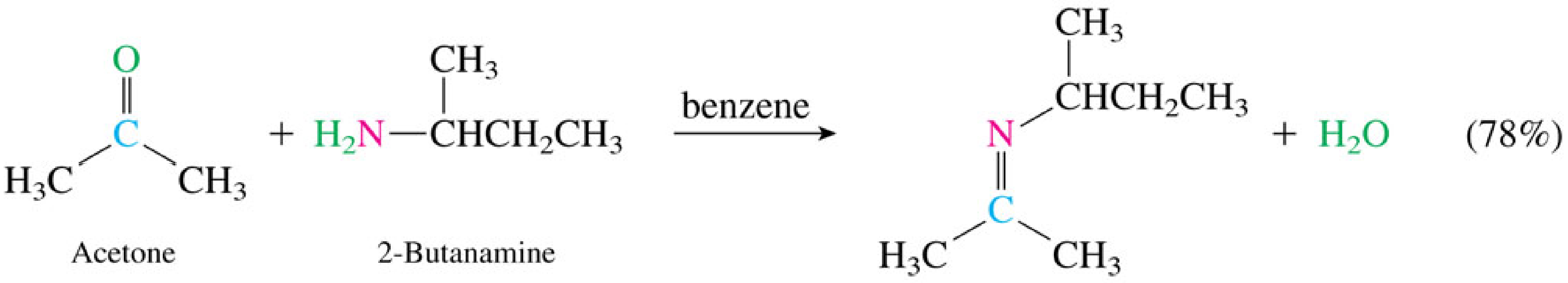
❹ If the solution is too basic, the concentration of the protonated carbinolamine is low, and this elimination step becomes very slow. Note how the unshared electrons on the N help the water to leave.

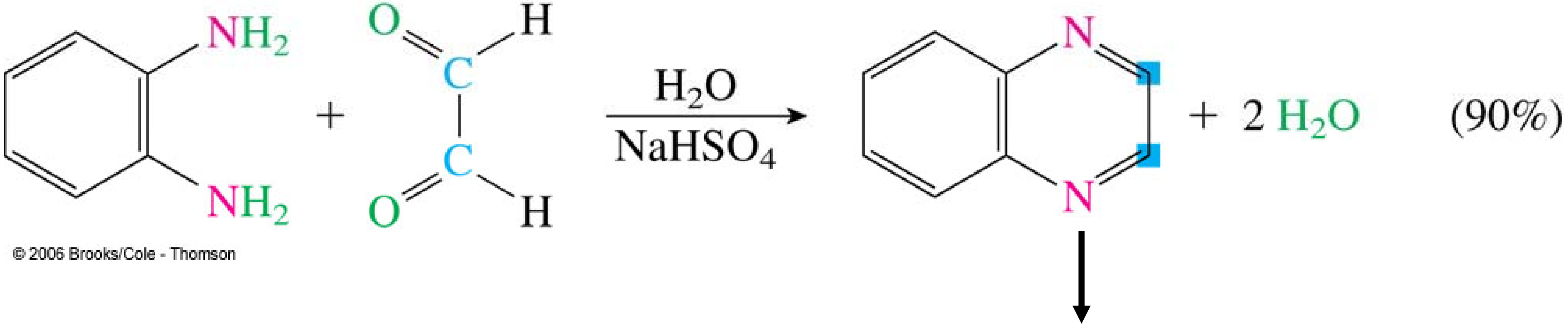
❺ The product of the elimination step is a protonated imine, the conjugate acid of the final product. The proton is transferred to a solvent molecule in an acid–base reaction to produce the imine.

Optimum pH = 4 ~ 6 !

At higher pH, the conc. of H_3O^+ is low. Then the conc. of the protonated carbinolamine is low

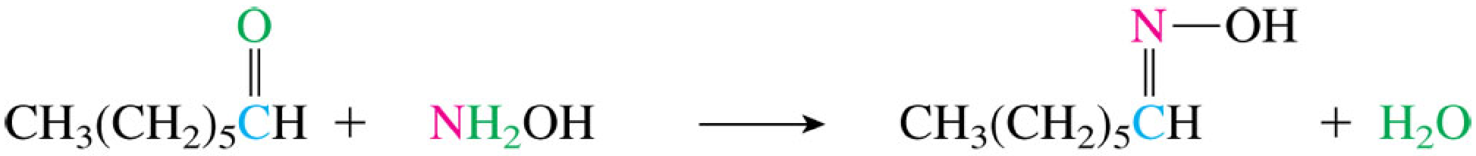
C=O bond is stronger than C=N bond.
To shift the equilibrium, remove the water!





Equilibrium favors the product, because the product is very stable (resonance stabilization → aromatic ring formation)

Examples

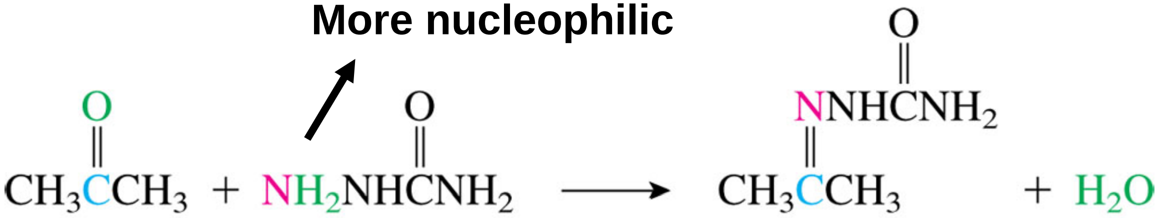


$$CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}H + NH_2OH \longrightarrow CH_3(CH_2)_5\overset{N-OH}{\overset{\|}{C}}H + H_2O$$

Hydroxylamine

mp: 57–58°C
An oxime

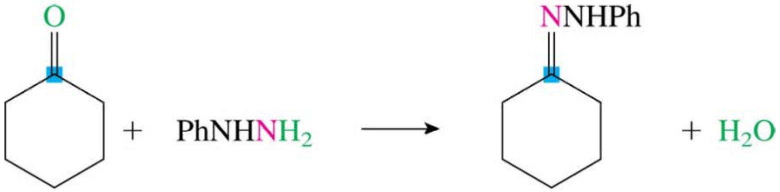
More nucleophilic



$$CH_3\overset{O}{\overset{\|}{C}}CH_3 + NH_2NH\overset{O}{\overset{\|}{C}}NH_2 \longrightarrow CH_3\overset{NNH\overset{O}{\overset{\|}{C}}NH_2}{\overset{\|}{C}}CH_3 + H_2O$$

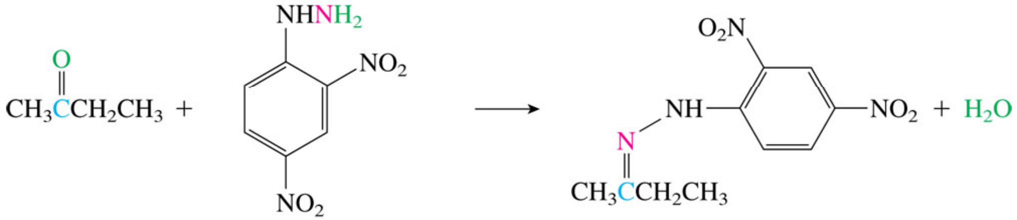
Semicarbazide

mp: 187°C
A semicarbazone



Phenylhydrazine

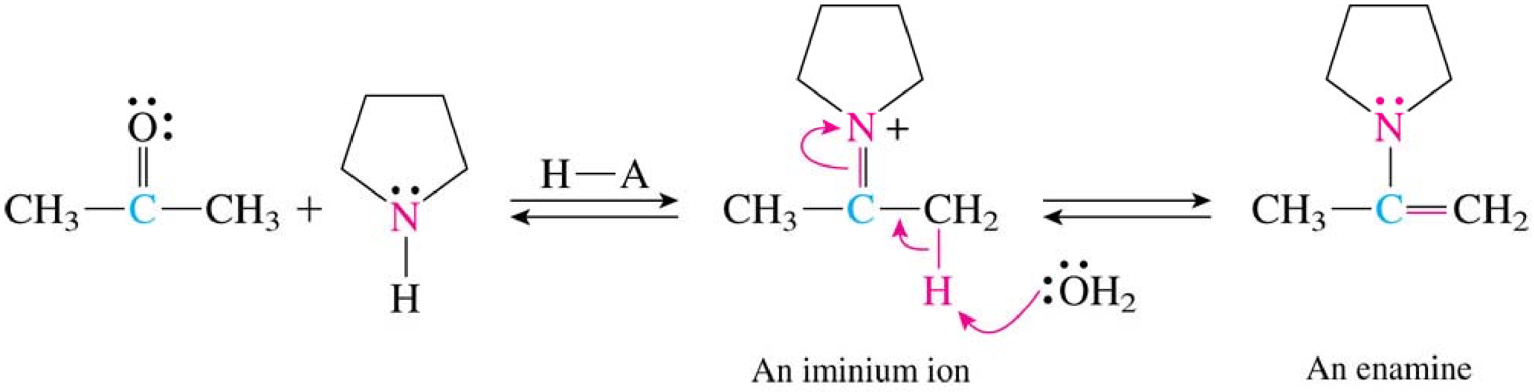
mp: 77°C
A phenylhydrazone

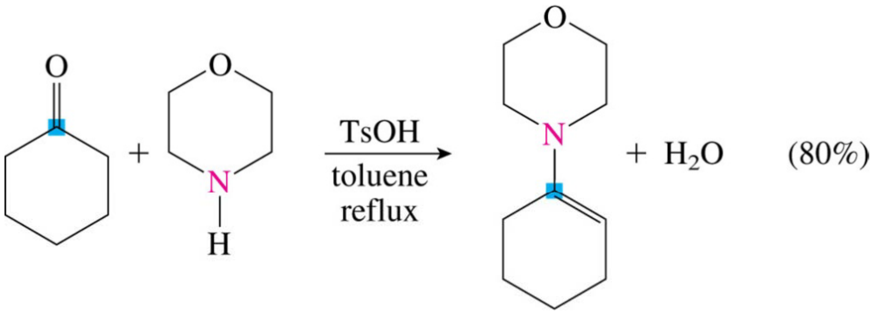


2,4-Dinitrophenylhydrazine

mp: 117°C
A 2,4-dinitrophenylhydrazone

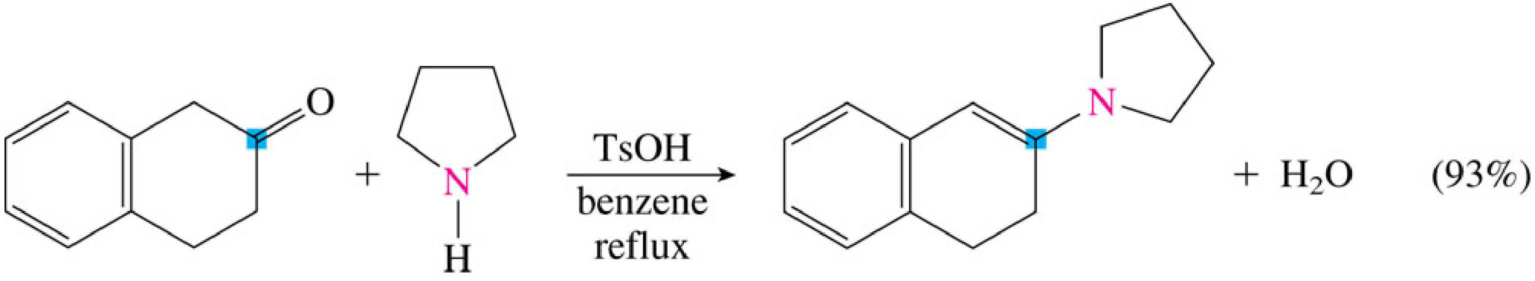
Until now, the rxn of primary amines, How about secondary amines? → Enamines are formed





TsOH + reflux →removal of water

Using Dean-Stark water separator

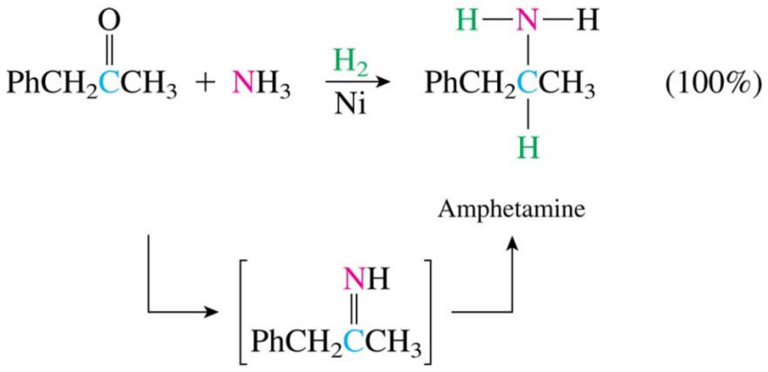


Imine ⟶ **Amine**

Reductive amination

Using reducing agent such as <u>hydrogen and catalyst</u>

It does not reduce the aldehydes and ketones



$$PhCH_2C(=O)CH_3 + NH_3 \xrightarrow[Ni]{H_2} \left[PhCH_2C(=NH)CH_3\right] \longrightarrow PhCH_2CH(NH_2)CH_3$$

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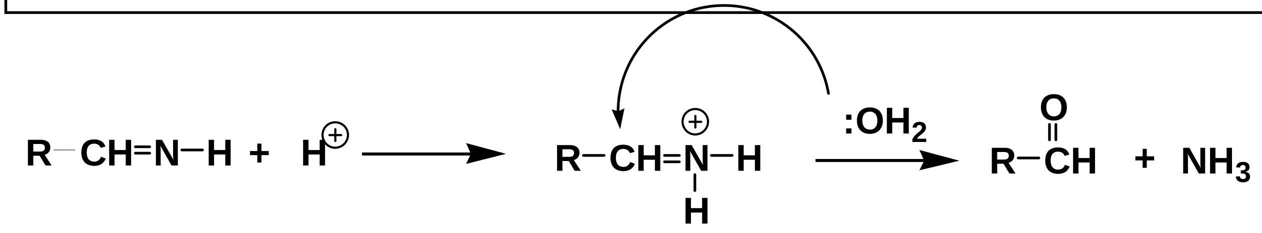
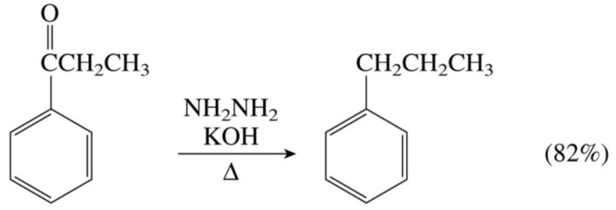
Unstable! Cannot be isolated! Because it can be easily hydrolyzed



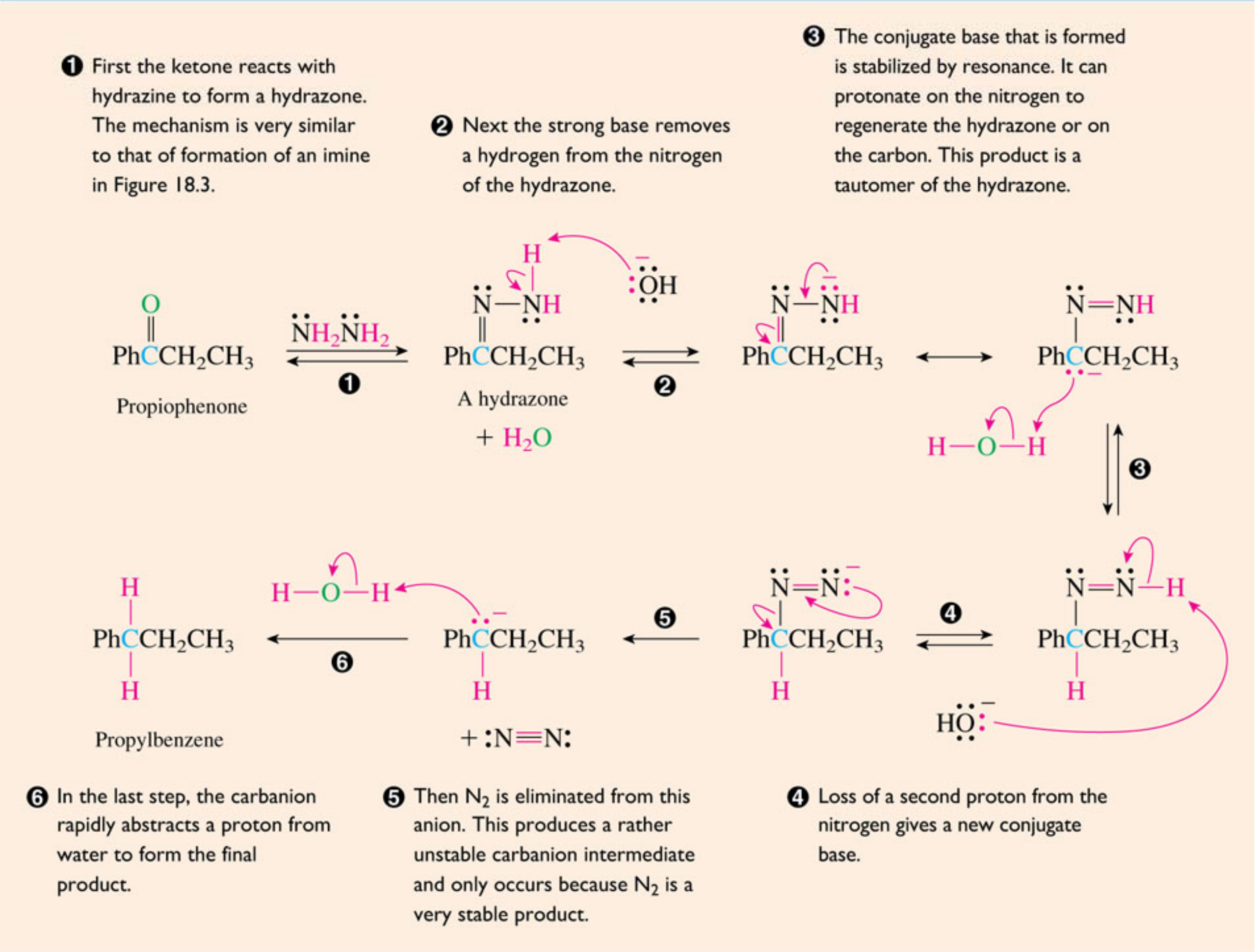
$$R{-}CH{=}N{-}H + H^{\oplus} \longrightarrow R{-}CH{=}\overset{\oplus}{N}H{-}H \xrightarrow{:OH_2} R{-}\overset{O}{\overset{\|}{C}}H + NH_3$$

Wolff-Kishner reduction (17.13); carbonyl groups can be converted to CH_2 groups



1-Phenyl-1-propanone (propiophenone)

Propylbenzene



❶ First the ketone reacts with hydrazine to form a hydrazone. The mechanism is very similar to that of formation of an imine in Figure 18.3.

❷ Next the strong base removes a hydrogen from the nitrogen of the hydrazone.

❸ The conjugate base that is formed is stabilized by resonance. It can protonate on the nitrogen to regenerate the hydrazone or on the carbon. This product is a tautomer of the hydrazone.

❹ Loss of a second proton from the nitrogen gives a new conjugate base.

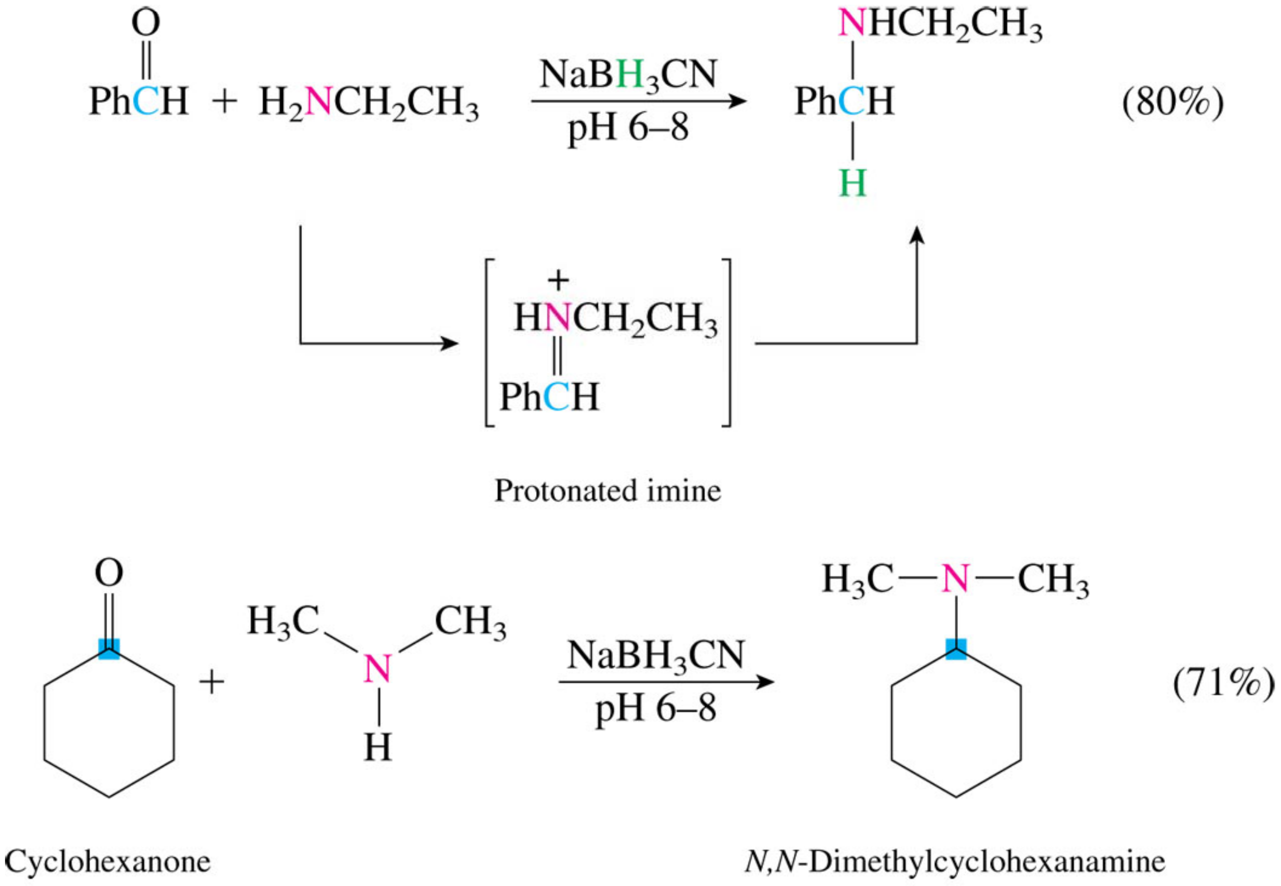
❺ Then N_2 is eliminated from this anion. This produces a rather unstable carbanion intermediate and only occurs because N_2 is a very stable product.

❻ In the last step, the carbanion rapidly abstracts a proton from water to form the final product.

Another reducing agent
→ sodium cyanoborohydride

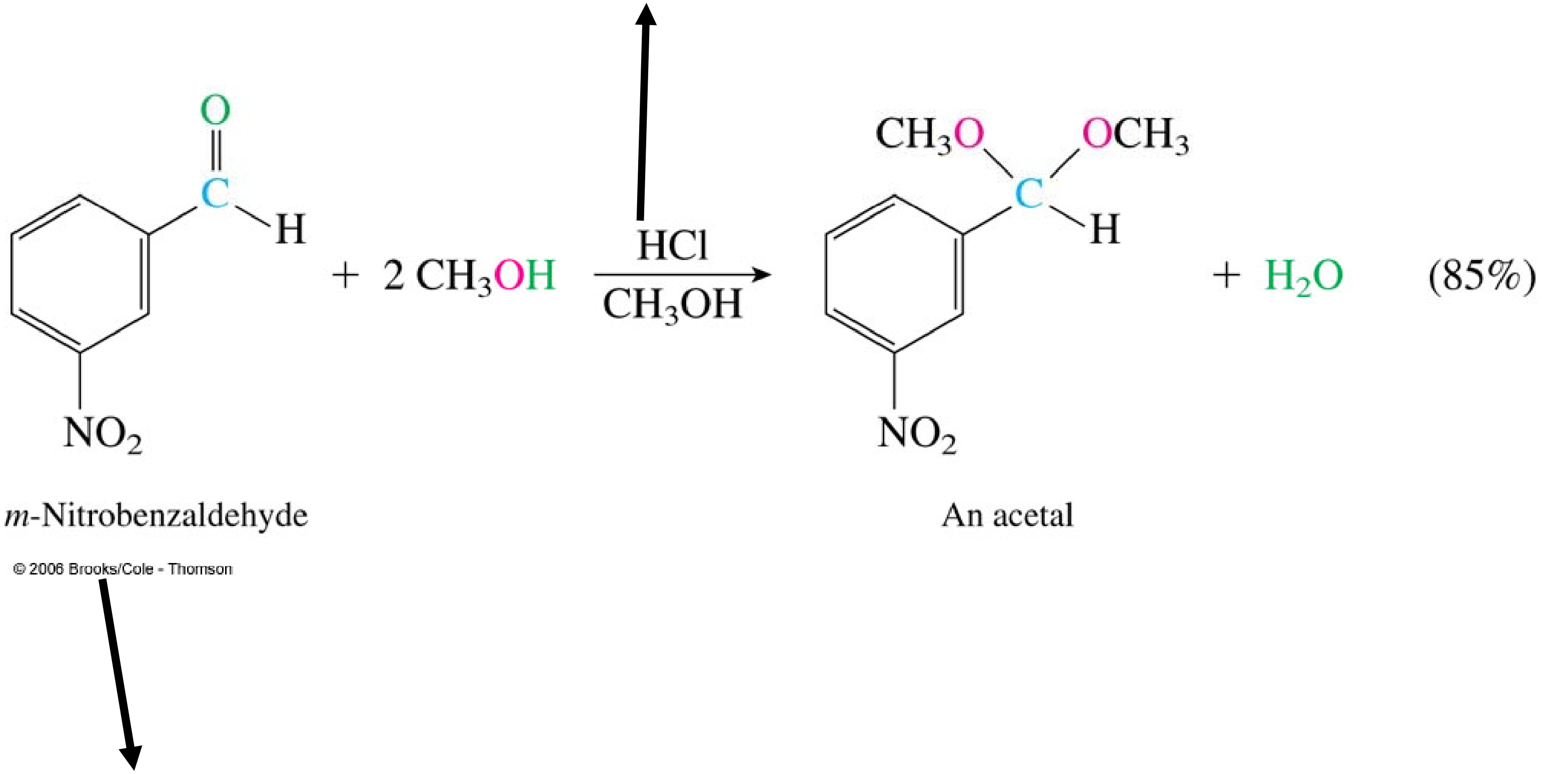
Sodium cyanoborohydride is less nucleophilic than sodium borohydride. → CN is electro withdrawing group

Therefore it do not react with aldehyde and ketone.



18.9 Addition of Alcohol

Acidic condition → to remove the water



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Electro withdrawing groups in the reactant → destabilize the reactant

Mechanism

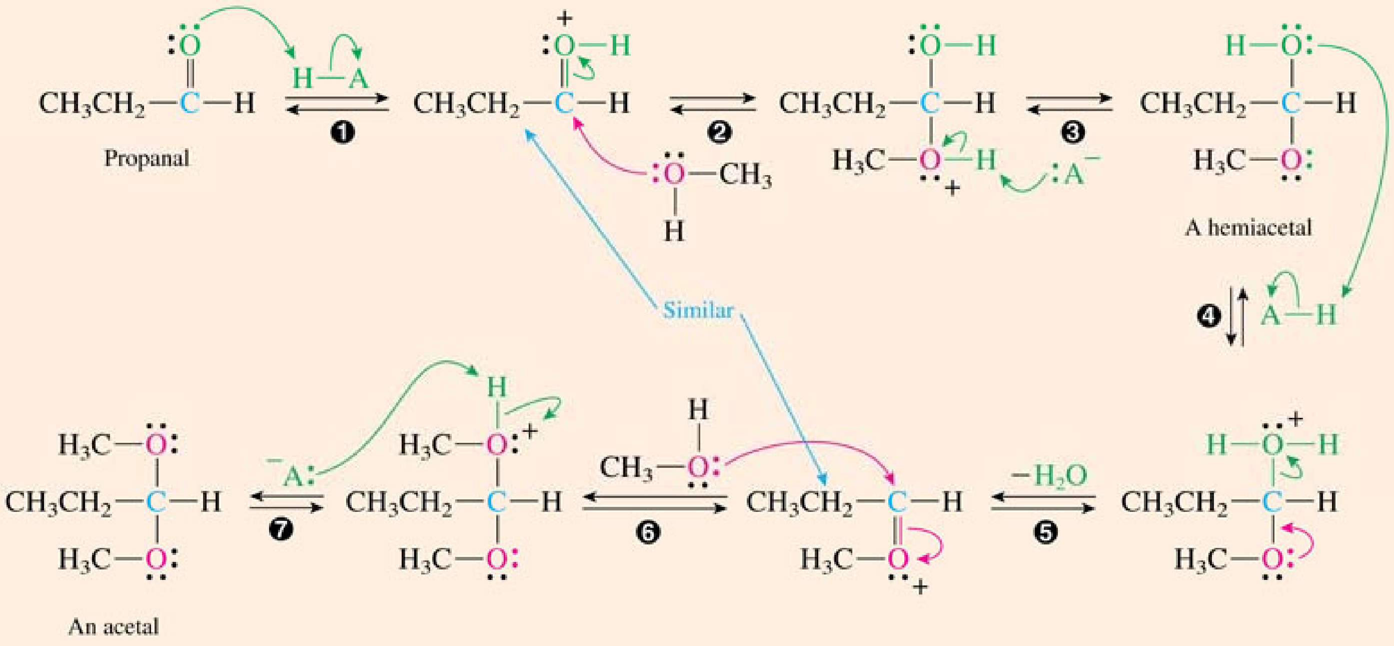
This addition product is called a hemiacetal. It resembles a carbinolamine, and the next two steps are similar to those in imine formation.

❶ The reaction follows the acidic conditions mechanism. First, the carbonyl oxygen is protonated, making the carbon more electrophilic. (HA represents an acid in the solution.)

❷ Then the oxygen of an alcohol molecule acts as a nucleophile.

❸ Next a proton is transferred to some base. This could be the conjugate base of the acid or even CH_3OH.

❹ The oxygen is protonated. Step 4 and the reverse of step 3 are nearly identical. They differ only in which oxygen is protonated.



This intermediate resembles the product of step 2 but with a methyl replacing one hydrogen.

This intermediate resembles the protonated aldehyde above.

❺ The electron pair on the ether oxygen helps water leave.

❼ Transfer of a proton to some base in the solution produces the final product, an acetal.

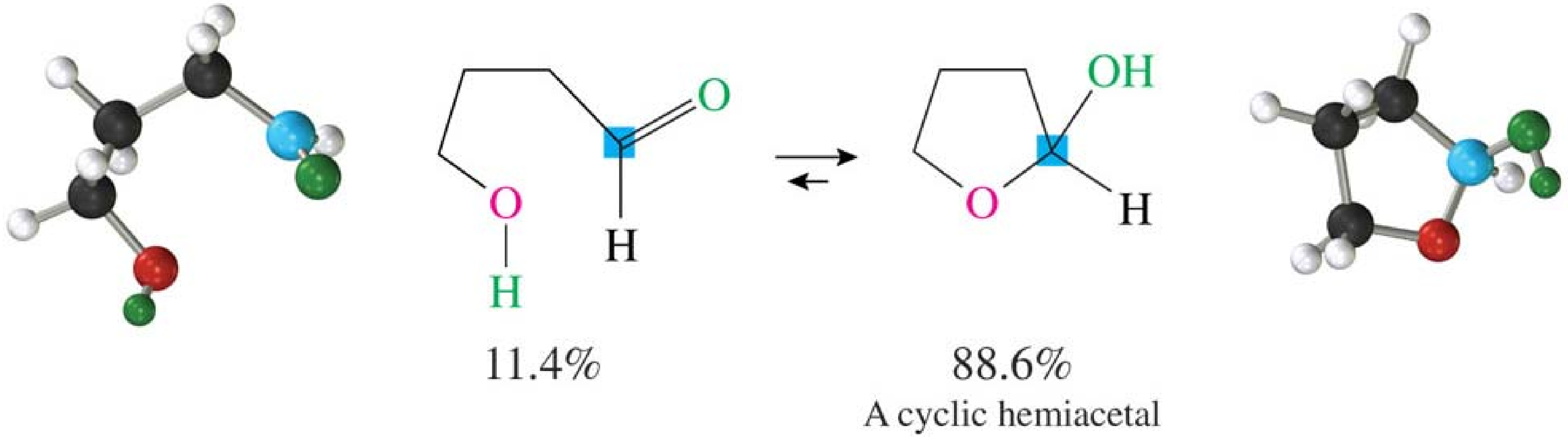
❻ It reacts in a similar fashion: steps 6 and 7 are quite similar to steps 2 and 3.

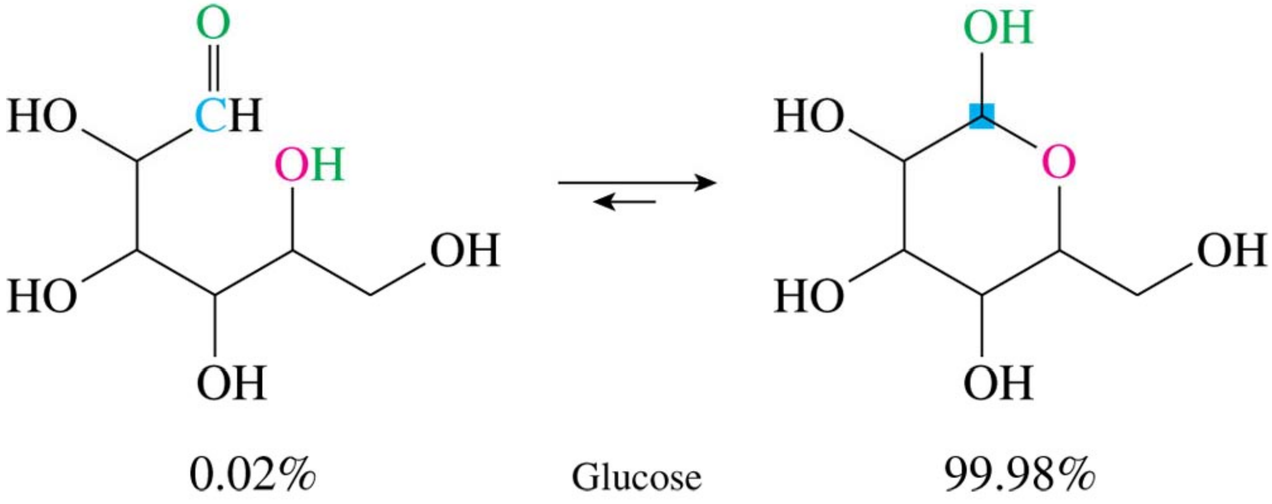
The equilibrium does not favor the product, because alcohols are weak nucleophile.

To shift the equilibrium

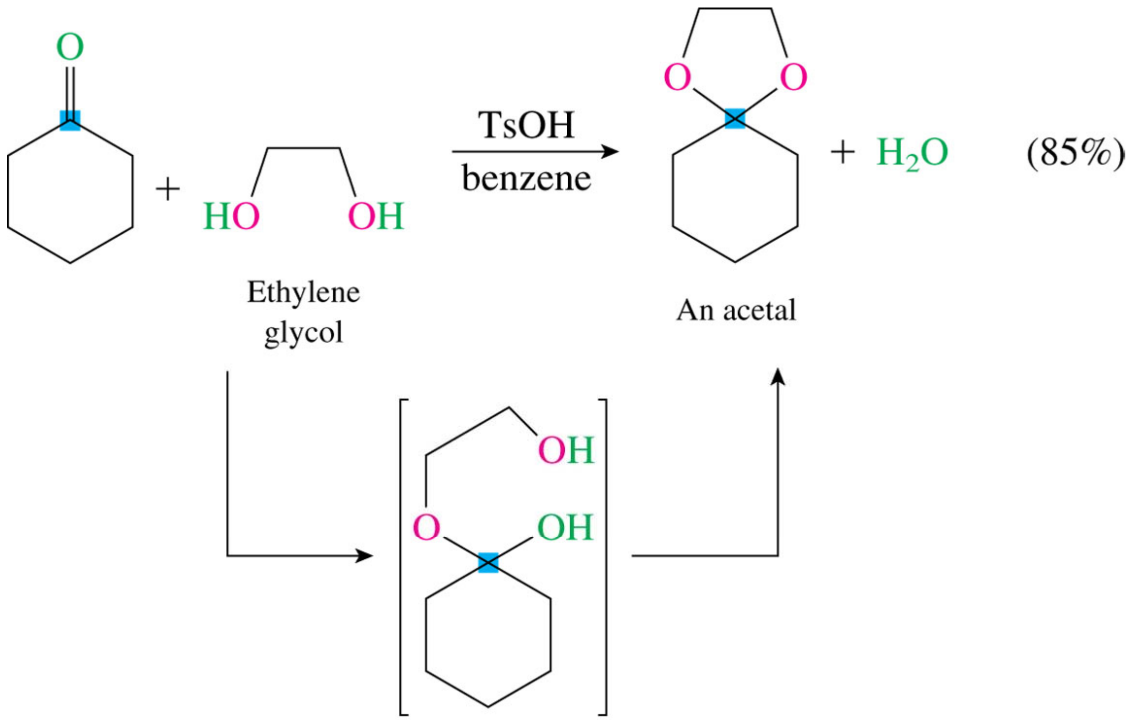
1. **Electro withdrawing groups in the reactant → destabilize the reactant**
2. **The alcohol nucleophile is part of the same molecule, then form 5- or 6-membered rings**
3. **Remove the water using acids such as TsOH**
4. **Use difunctional alcohol or dithiol → intramolecular reaction**

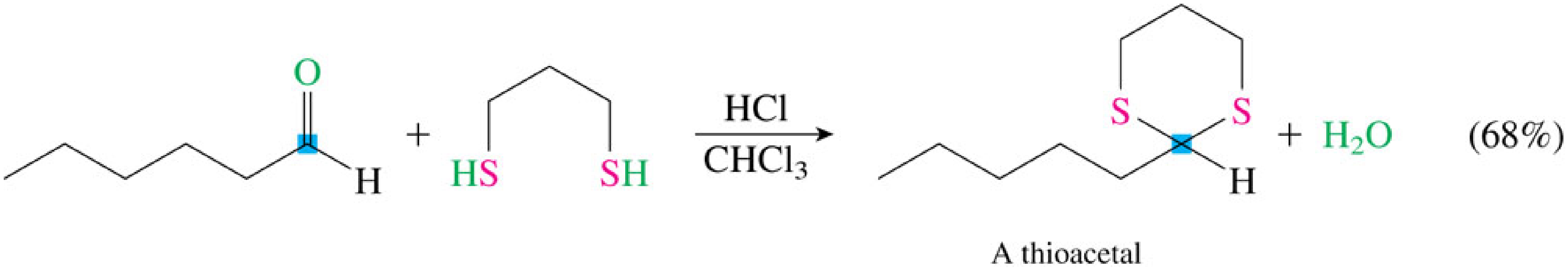
The alcohol nucleophile is part of the same molecule, then form 5- or 6-membered rings



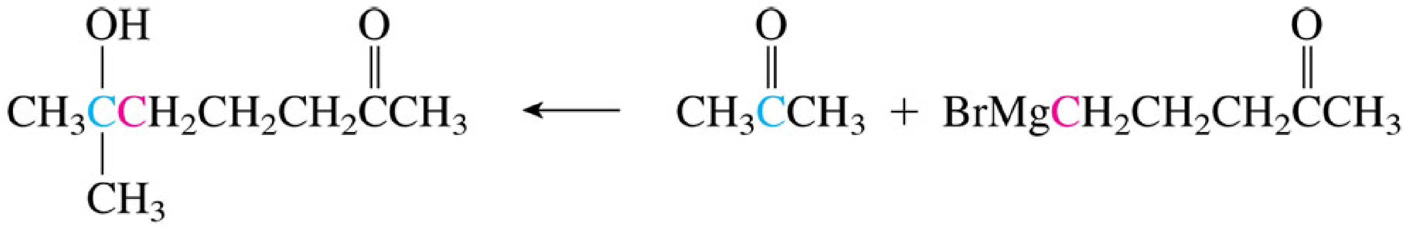


Use difunctional alcohol or dithiol → intramolecular reaction





A major use of acetals (cyclic) → protective groups for aldehyde and ketone



$$CH_3\underset{CH_3}{\overset{OH}{C}}CH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3 \longleftarrow CH_3\overset{O}{\overset{\|}{C}}CH_3 + BrMgCH_2CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$$

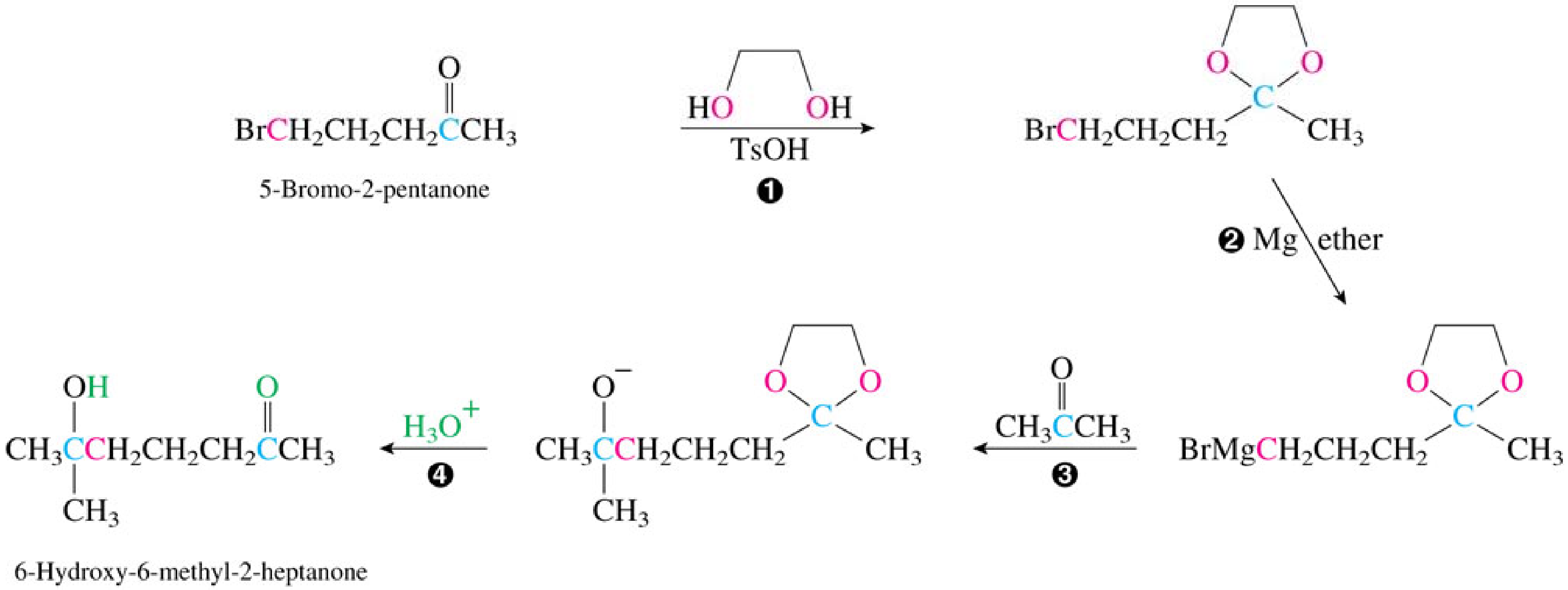
6-Hydroxy-6-methyl-2-heptanone
(synthetic target)

This reagent cannot be prepared because the carbonyl group and the Grignard reagent are incompatible.

An attempt to form a Grignard reagent from 5-bromo-2-pentanone is doomed to failure because the Grignard will react with the carbonyl group.

❶ Therefore, the carbonyl group is first protected as an ethylene glycol acetal.

❷ Because the acetal group does not react with Grignard reagents (or other basic or nucleophilic reagents), the Grignard reagent can be prepared from this compound. The acetal is being used as a protecting group for the carbonyl group.

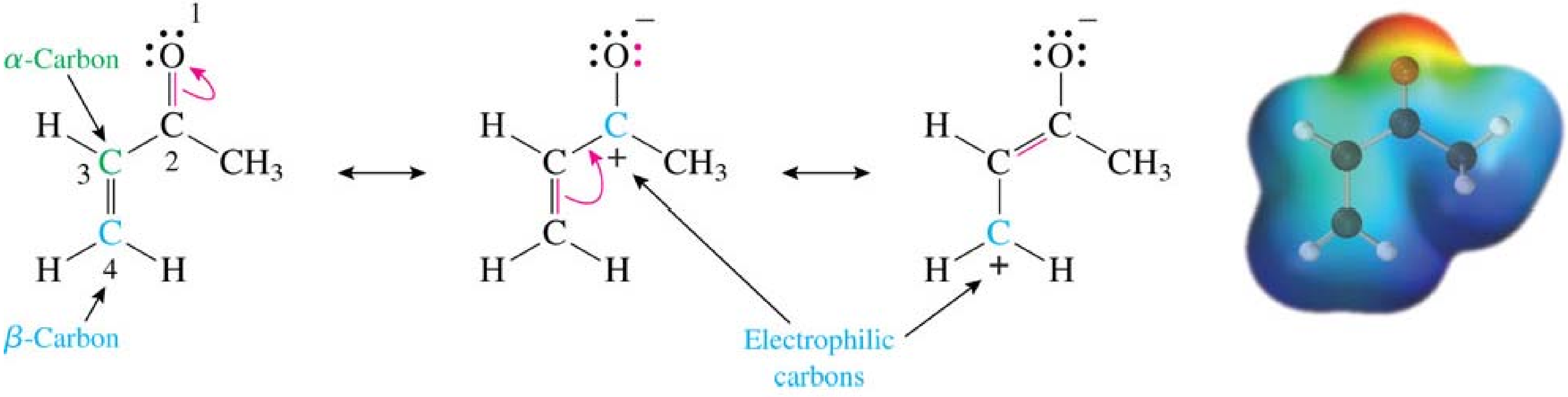


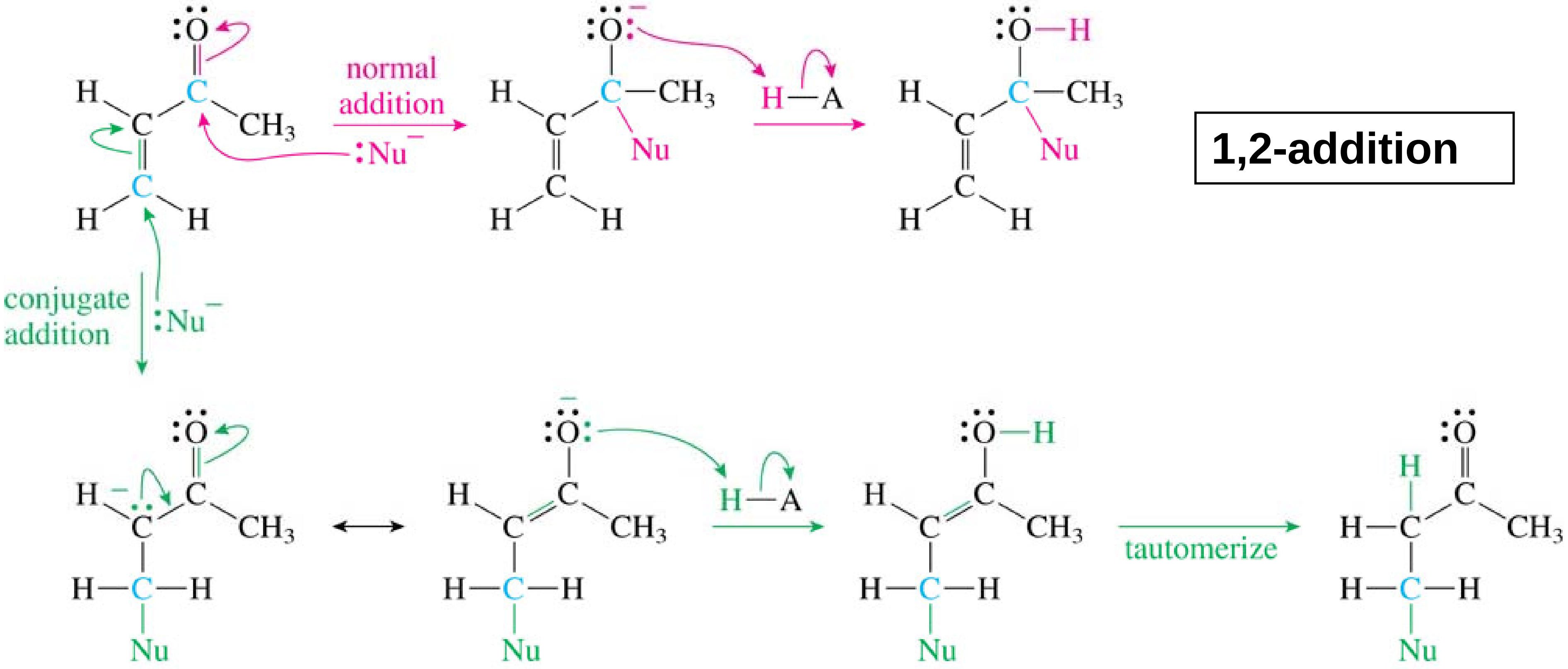
❹ When the reaction is worked up with aqueous acid, not only is the alkoxide group protonated but the acetal is also hydrolyzed back to the ketone and ethylene glycol. Easy removal is an important feature of protecting groups.

❸ This Grignard reagent reacts like any other Grignard reagent.

18.10 Conjugated Addition

→ α,β-unsaturated carbonyl compound



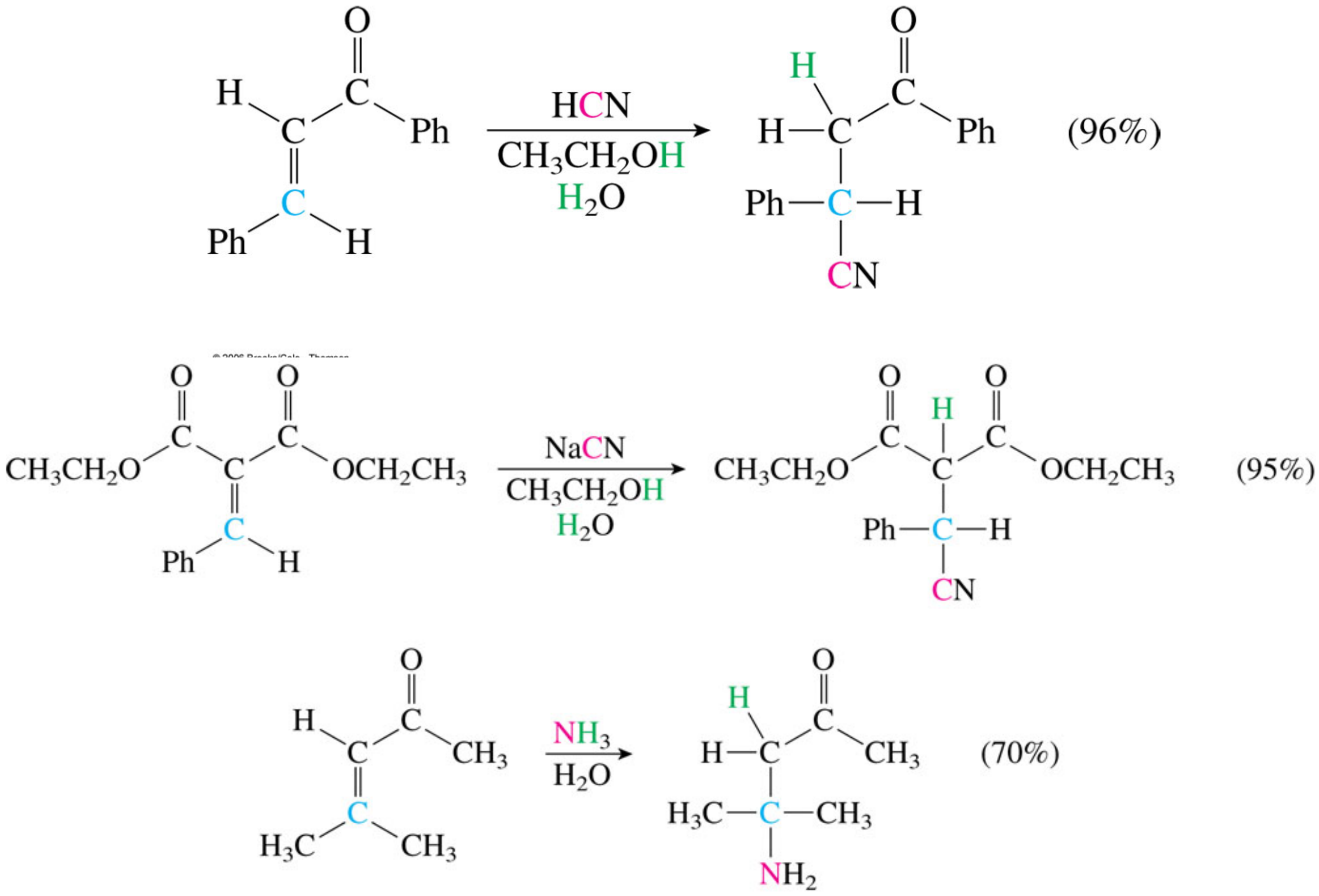


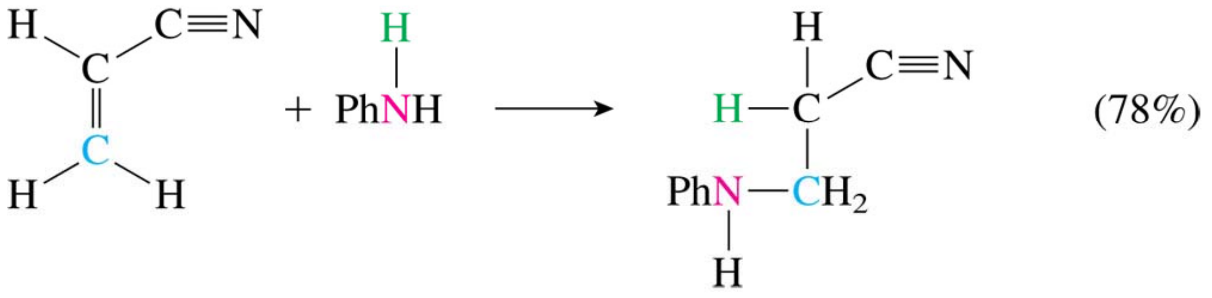
1,2-addition

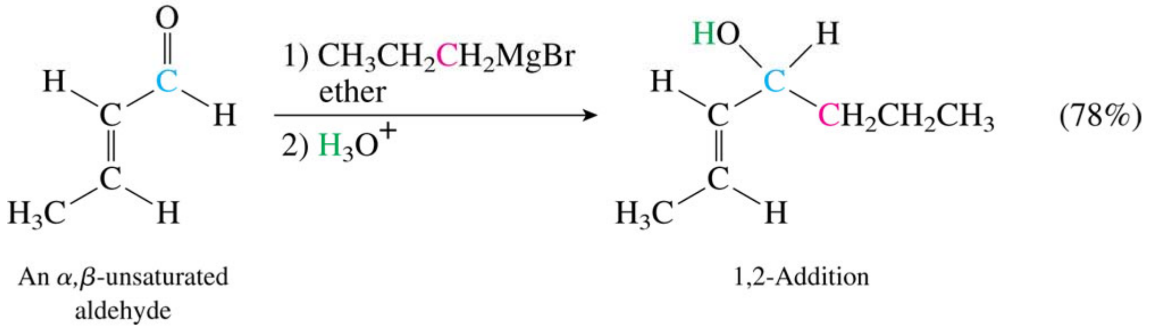
1,4-addition

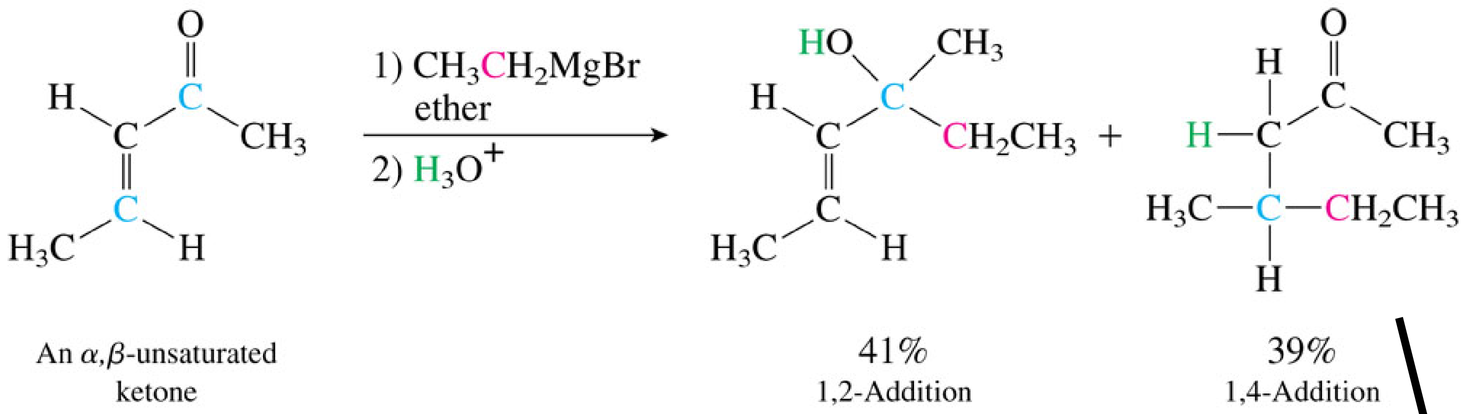
1,2-addition or 1,4-addition

1. **Highly reactivenucleophile: Grignard reagent → 1,2 additon**
2. **Less reactive nucleophile: cyanide, amine → 1,4 additon**





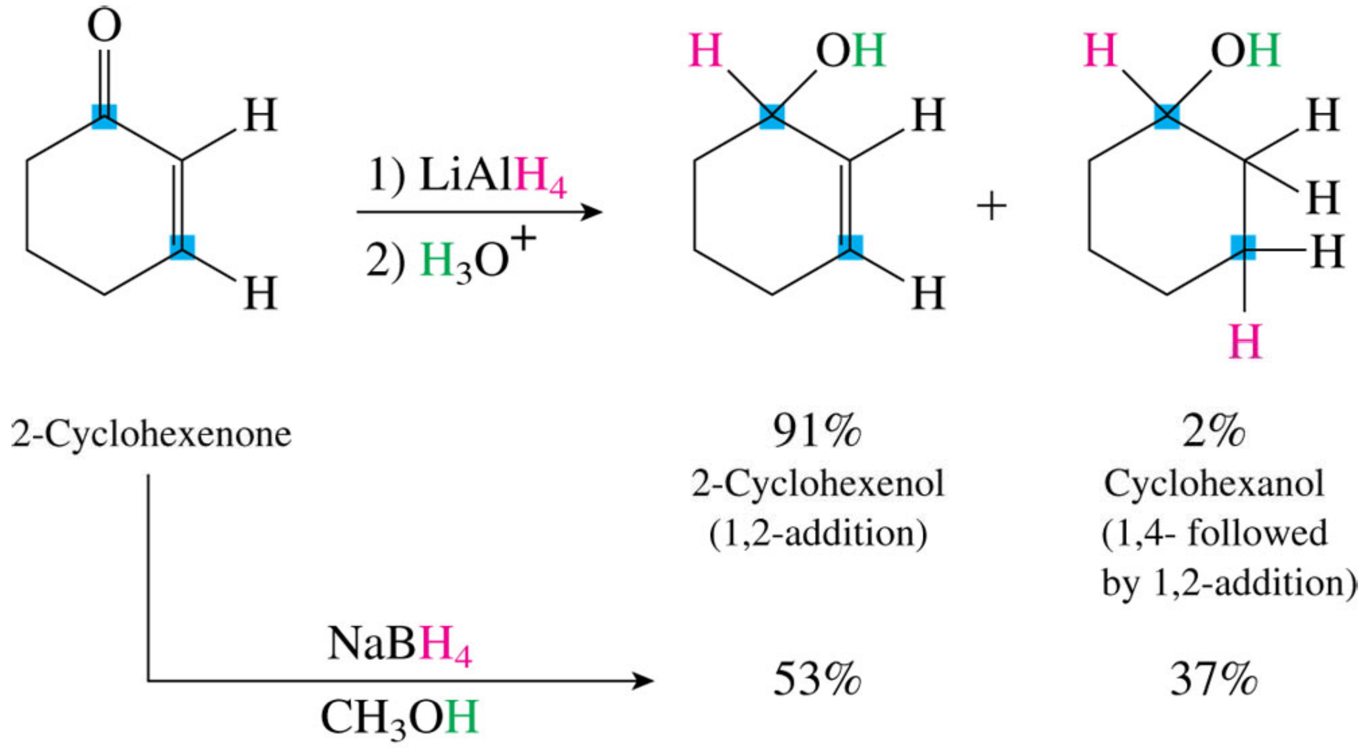




Steric hindrance

Hydride nucleophile

1. $LiAlH_4$: 1,2 additon > 1,4 additon
2. $NaBH_4$: 1,2 additon < 1,4 additon

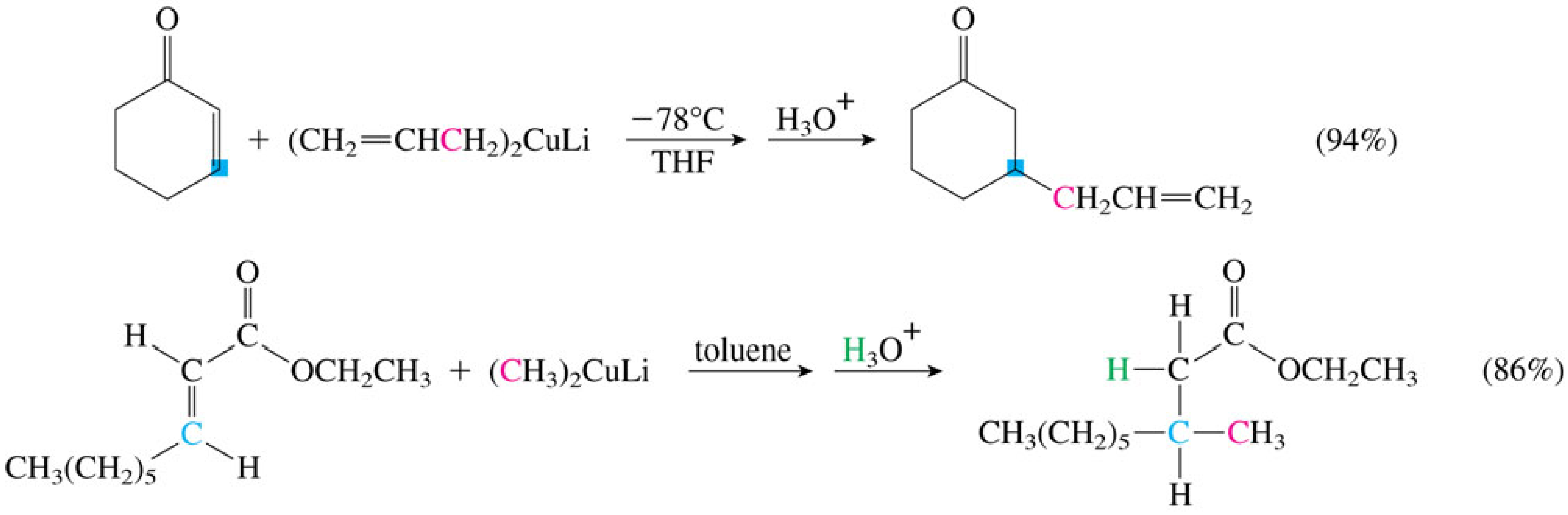


Lithium diorganocuprates

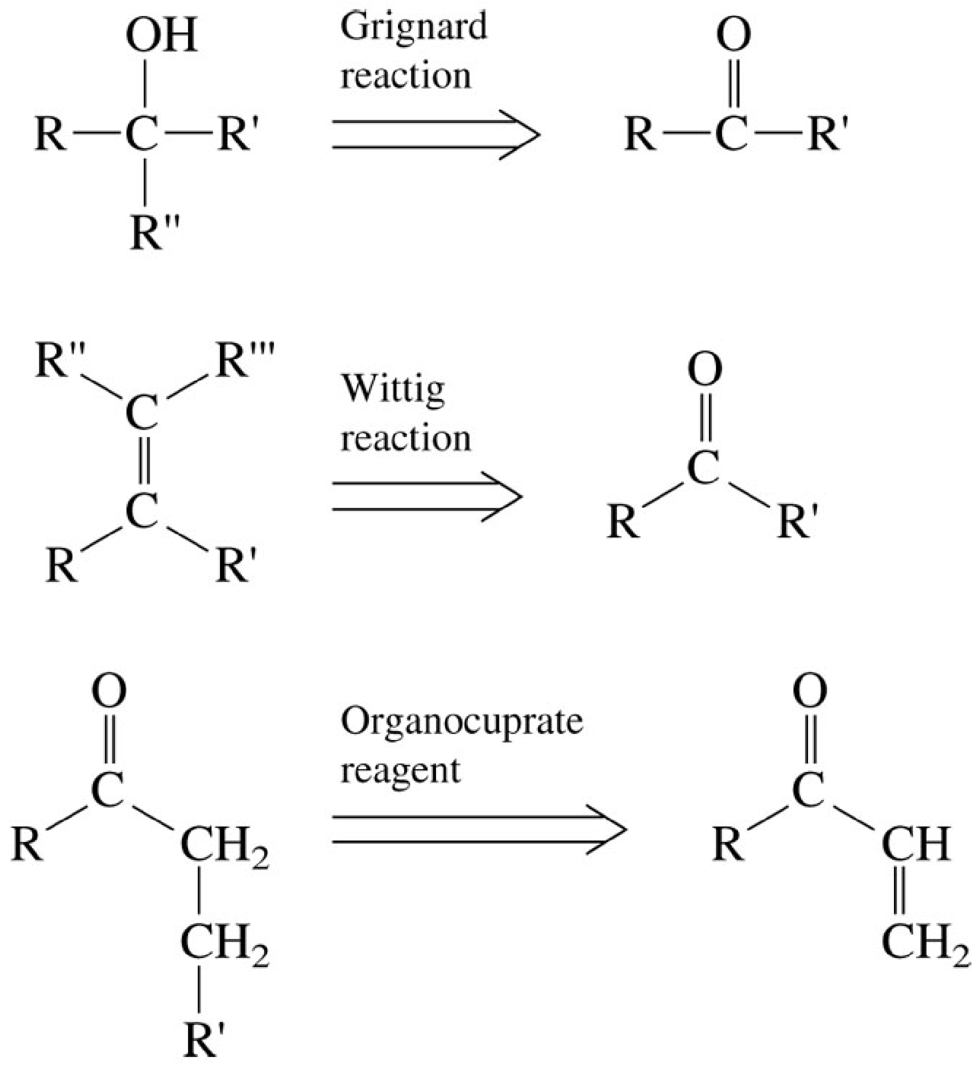
→ 1,4-addition

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

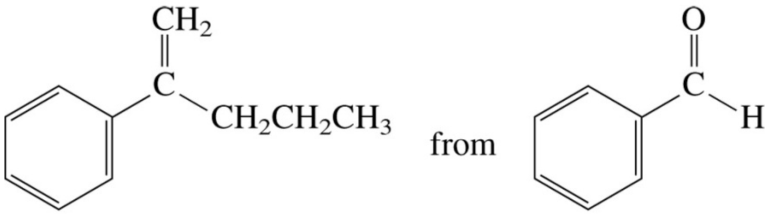
Methyllithium — Lithium dimethylcuprate



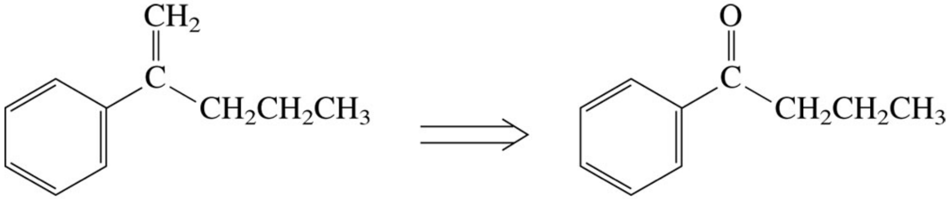
18.11 Synthesis

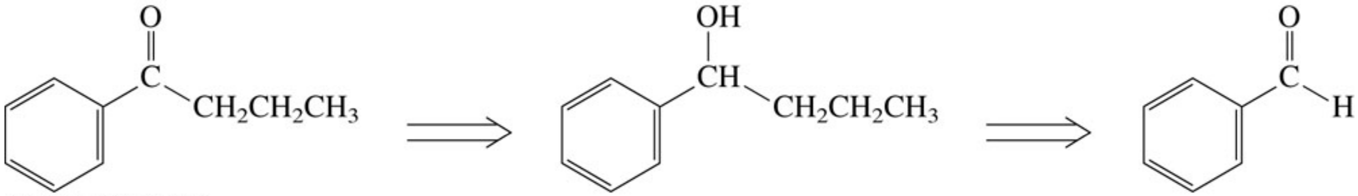


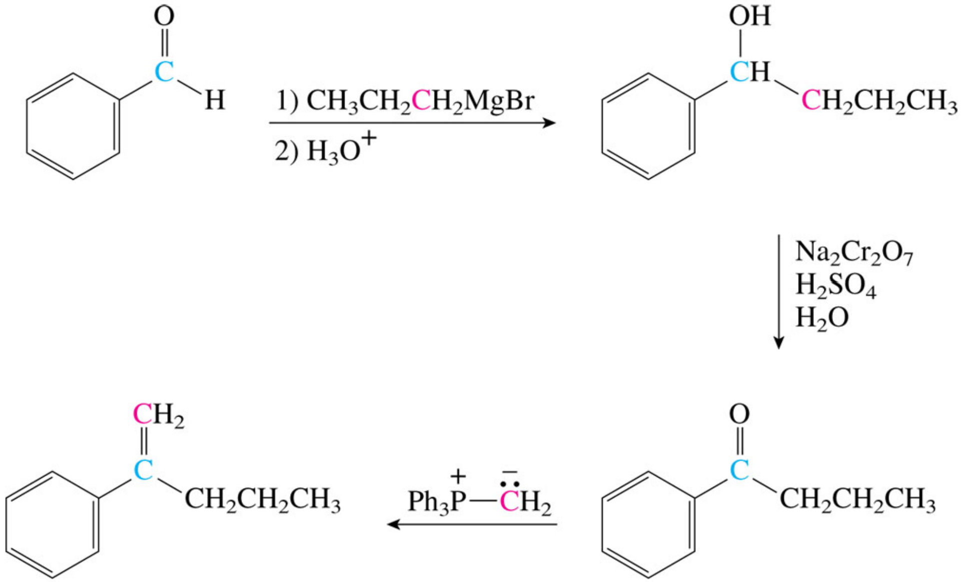
Example



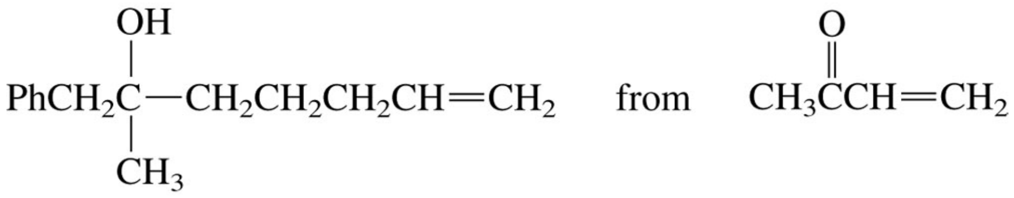
2-Phenyl-1-pentene Benzaldehyde







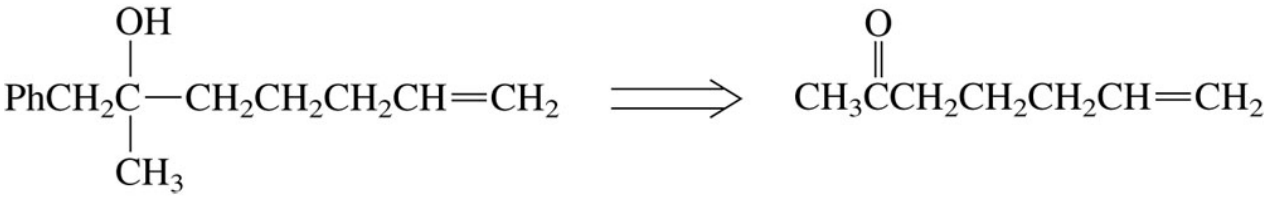
Example



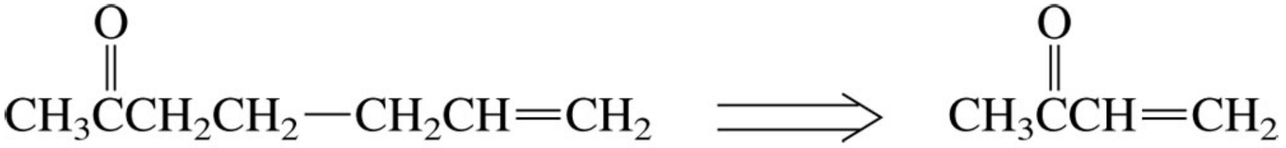
$$PhCH_2\underset{CH_3}{\overset{OH}{C}}-CH_2CH_2CH_2CH=CH_2 \quad \text{from} \quad CH_3\overset{O}{\overset{\|}{C}}CH=CH_2$$

2-Methyl-1-phenylhept-6-en-2-ol

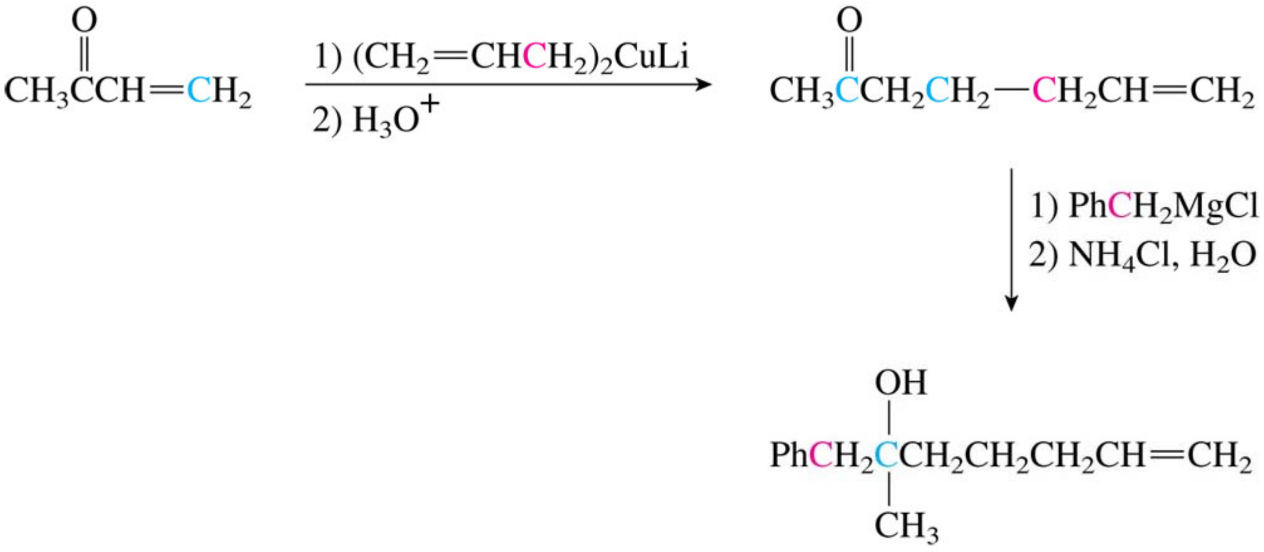
But-3-en-2-one



$$PhCH_2\underset{CH_3}{\overset{OH}{C}}-CH_2CH_2CH_2CH=CH_2 \Longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2CH_2CH=CH_2$$



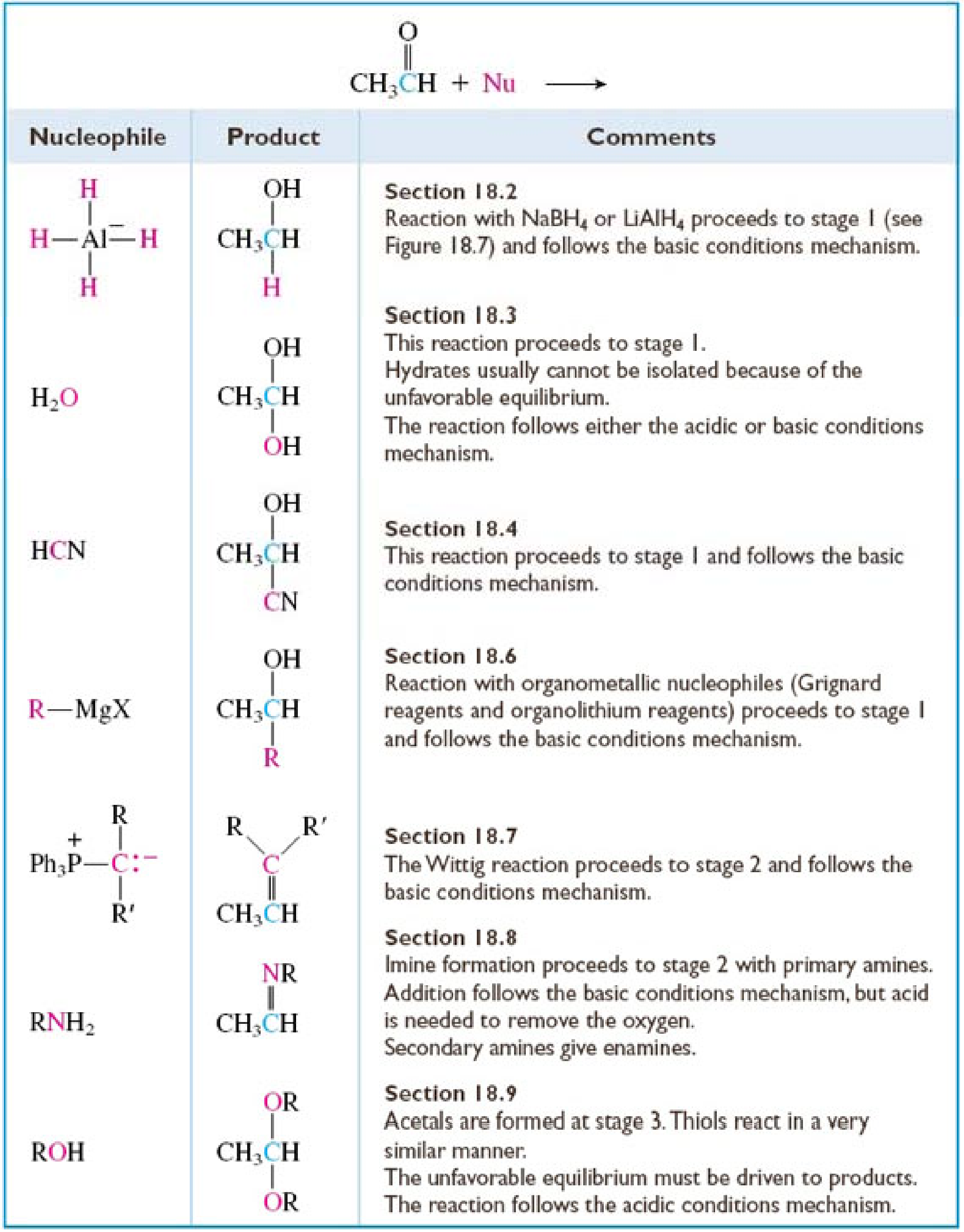
$$CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2-CH_2CH=CH_2 \Longrightarrow CH_3\overset{O}{\overset{\|}{C}}CH=CH_2$$



$$CH_3\overset{O}{\overset{\|}{C}}CH=CH_2 \xrightarrow[2)\ H_3O^+]{1)\ (CH_2=CHCH_2)_2CuLi} CH_3\overset{O}{\overset{\|}{C}}CH_2CH_2-CH_2CH=CH_2$$

$$\Big\downarrow \begin{array}{l} 1)\ PhCH_2MgCl \\ 2)\ NH_4Cl,\ H_2O \end{array}$$

$$PhCH_2\underset{CH_3}{\overset{OH}{C}}CH_2CH_2CH_2CH=CH_2$$



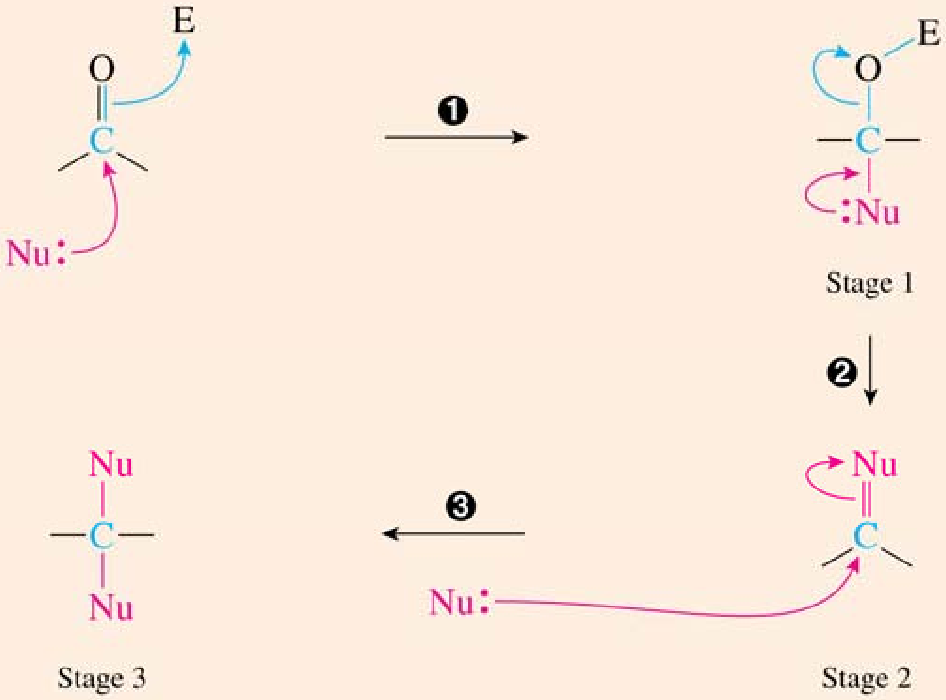
$$CH_3\overset{\overset{O}{\|}}{C}H + Nu \longrightarrow$$

Nucleophile	Product	Comments
$H-\underset{H}{\overset{H}{Al}}^{-}-H$	$CH_3\underset{H}{\overset{OH}{C}}H$	**Section 18.2** Reaction with $NaBH_4$ or $LiAlH_4$ proceeds to stage 1 (see Figure 18.7) and follows the basic conditions mechanism.
H_2O	$CH_3\underset{OH}{\overset{OH}{C}}H$	**Section 18.3** This reaction proceeds to stage 1. Hydrates usually cannot be isolated because of the unfavorable equilibrium. The reaction follows either the acidic or basic conditions mechanism.
HCN	$CH_3\underset{CN}{\overset{OH}{C}}H$	**Section 18.4** This reaction proceeds to stage 1 and follows the basic conditions mechanism.
$R-MgX$	$CH_3\underset{R}{\overset{OH}{C}}H$	**Section 18.6** Reaction with organometallic nucleophiles (Grignard reagents and organolithium reagents) proceeds to stage 1 and follows the basic conditions mechanism.
$Ph_3\overset{+}{P}-\underset{R'}{\overset{R}{C}}{:}^{-}$	$CH_3CH{=}C(R)R'$	**Section 18.7** The Wittig reaction proceeds to stage 2 and follows the basic conditions mechanism.
RNH_2	$CH_3\overset{\overset{NR}{\|}}{C}H$	**Section 18.8** Imine formation proceeds to stage 2 with primary amines. Addition follows the basic conditions mechanism, but acid is needed to remove the oxygen. Secondary amines give enamines.
ROH	$CH_3\underset{OR}{\overset{OR}{C}}H$	**Section 18.9** Acetals are formed at stage 3. Thiols react in a very similar manner. The unfavorable equilibrium must be driven to products. The reaction follows the acidic conditions mechanism.

❶ All of these reactions begin this way. The electrophile (E) is usually hydrogen, but in the case of the Wittig reaction, it is phosphorus. Under basic conditions, Nu adds first. Under acidic conditions, E (a proton) adds first.

The reaction stops at stage 1 if the original Nu has only one unshared pair of electrons (CN^-, hydrides, organometallic nucleophiles).

❷ If the nucleophile has a second pair of electrons (or can generate one), then the oxygen is eliminated. The O must be protonated first, unless E is phosphorus.



The reaction proceeds to stage 3 for alcohols and thiols as nucleophiles.

The reaction stops at stage 2 if this species is uncharged (Wittig reaction, imines).

❸ When the doubly bonded Nu has a positive charge, the reaction proceeds further. If Nu is a secondary amine, a proton is lost to form an enamine. If Nu is ROH or RSH, a second Nu attacks.