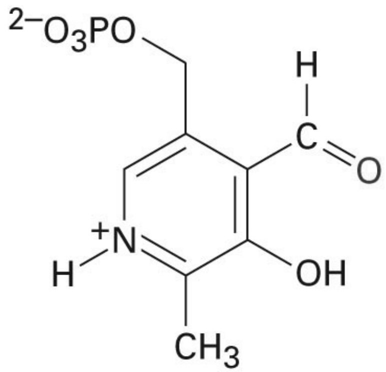
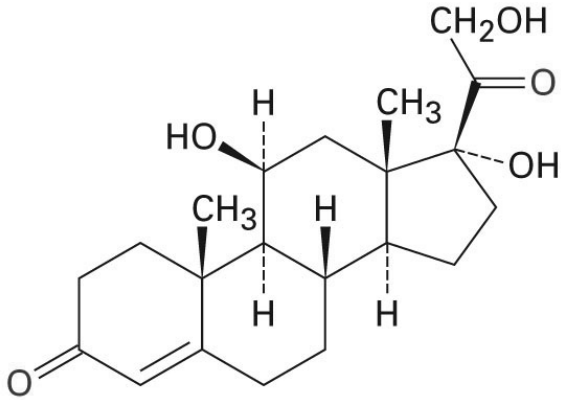
Aldehydes & Ketones

เอกสารประกอบการสอน รายวิชา 01403224

ดร.นงพงา จรัสโสภณ



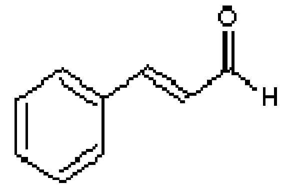
Pyridoxal phosphate (PLP)



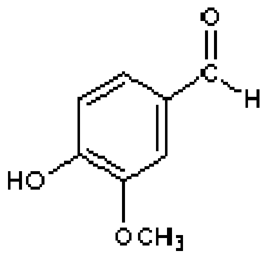
Hydrocortisone

Occurrence of Aldehydes and Ketones

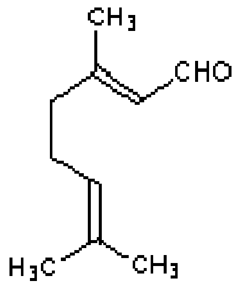
Natural Product



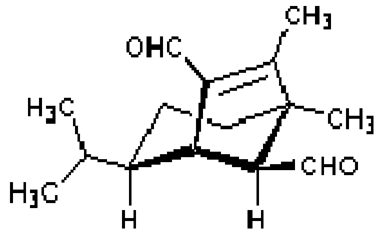
cinnamaldehyde
(cinnamon bark)



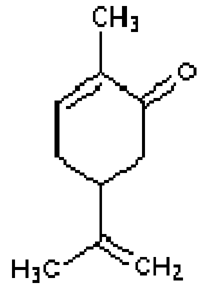
vanillin
(vanilla bean)



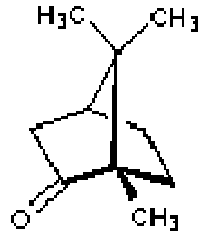
citral
(lemongrass)



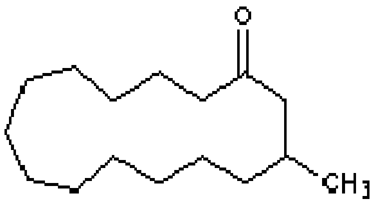
helminthosporal
(a fungal toxin)



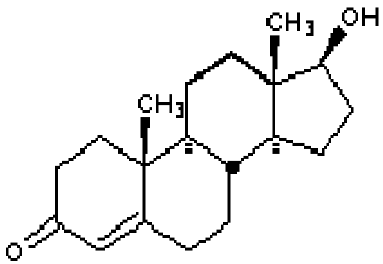
carvone
(spearmint & caraway)



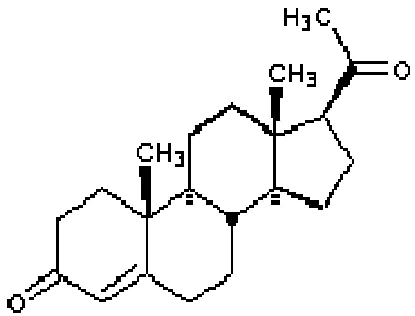
camphor
(camphor tree)



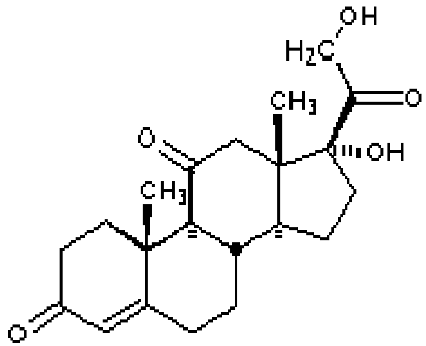
muscone
(musk deer)



testosterone
(male sex hormone)



progesterone
(female sex hormone)



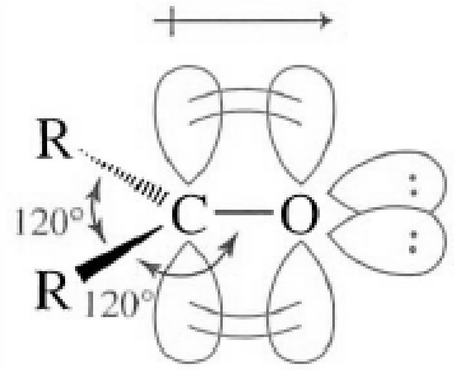
cortisone
(adrenal hormone)

Carbonyl Compounds

TABLE 18-1 Some Common Classes of Carbonyl Compounds

Class	General Formula	Class	General Formula
ketones	$R-C(=O)-R'$	aldehydes	$R-C(=O)-H$
carboxylic acids	$R-C(=O)-OH$	acid chlorides	$R-C(=O)-Cl$
esters	$R-C(=O)-O-R'$	amides	$R-C(=O)-NH_2$

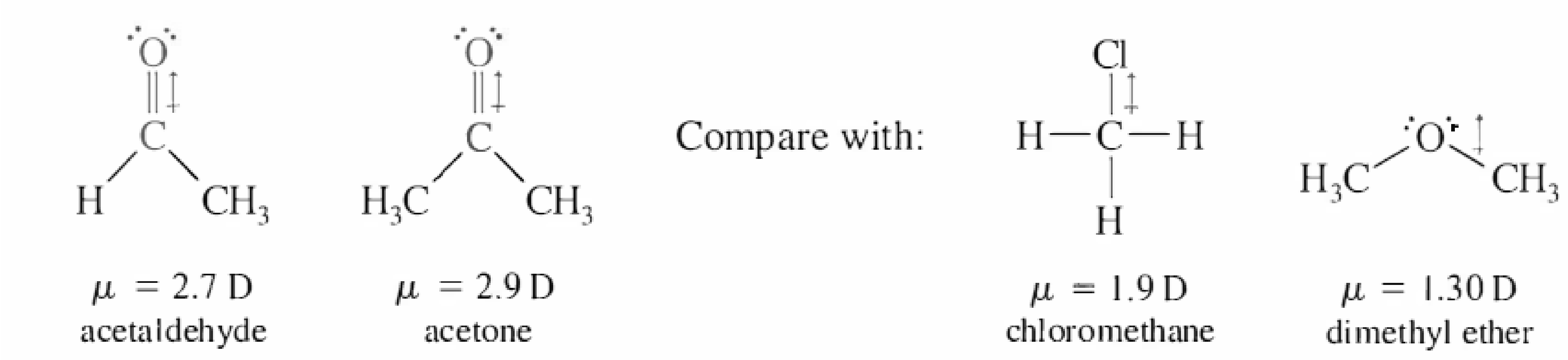
Structure of carbonyl group



	length	*energy*
ketone C═O bond	1.23 Å	745 kJ/mol (178 kcal/mol)
alkene C═C bond	1.34 Å	611 kJ/mol (146 kcal/mol)

- Carbon is sp^2 hybridized.
- C═O bond is shorter, stronger, and more polar than C═C bond in alkenes.

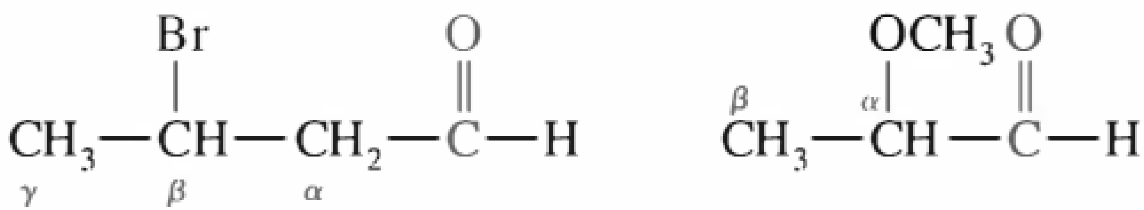
Dipole moment of carbonyl compound



Nomenclature: Common Name

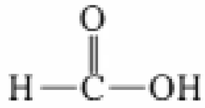
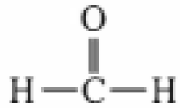
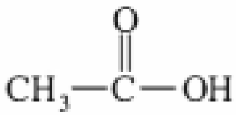
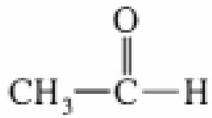
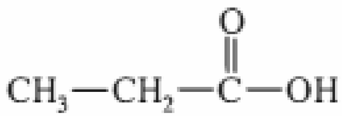
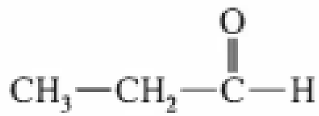
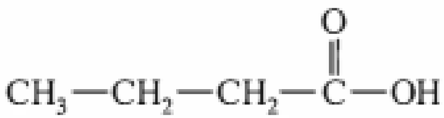
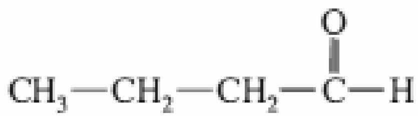
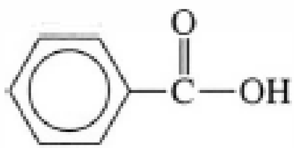
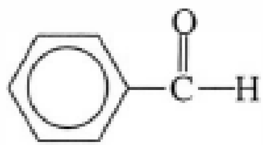
Aldehydes

- ❖ Aldehydes are derived from the common names of carboxylic acids .
- ❖ Give the locations of substituents. The first letter (α) is given to the carbon atom next to the carbonyl group.

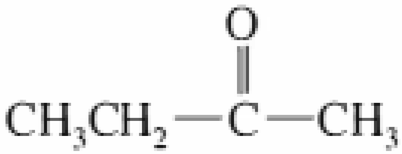


Common name:	β-bromobutyraldehyde	α-methoxypropionaldehyde
IUPAC name:	3-bromobutanal	2-methoxypropanal

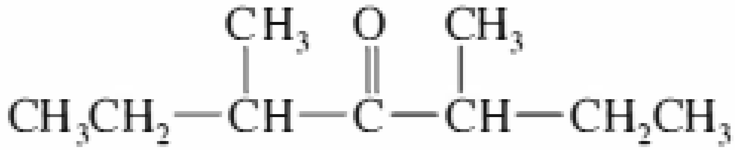
TABLE 18-2 Common Names of Aldehydes

Carboxylic Acid	Derivation	Aldehyde
 formic acid	*formica*, "ants"	 formaldehyde (methanal)
 acetic acid	*acetum*, "sour"	 acetaldehyde (ethanal)
 propionic acid	*protos pion*, "first fat"	 propionaldehyde (propanal)
 butyric acid	*butyrum*, "butter"	 butyraldehyde (butanal)
 benzoic acid	*gum benzoin*, "blending"	 benzaldehyde

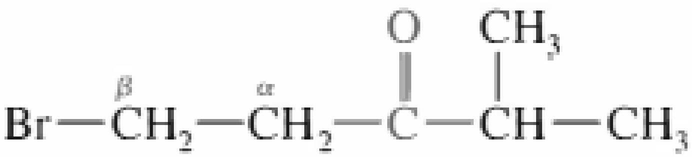
Ketones



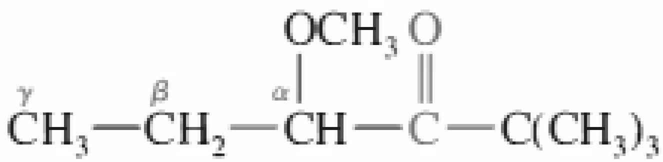
methyl ethyl ketone



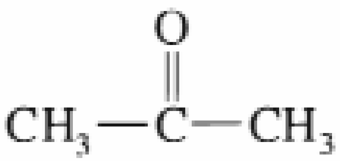
di-*sec*-butyl ketone



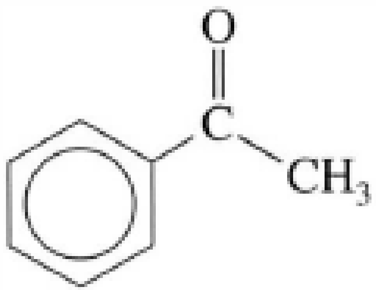
β-bromoethyl isopropyl ketone



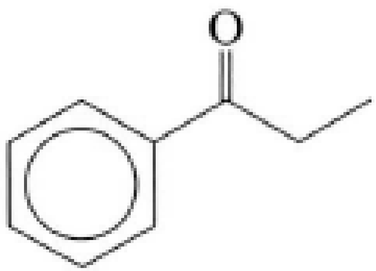
t-butyl α-methoxypropyl ketone



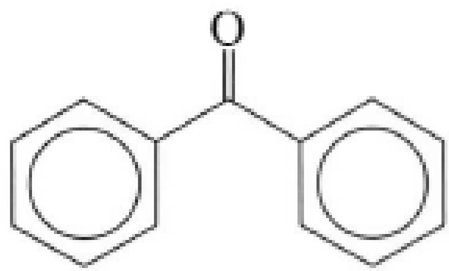
acetone



acetophenone



propiophenone

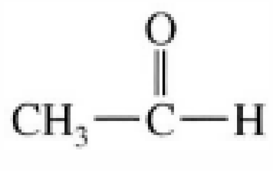


benzophenone

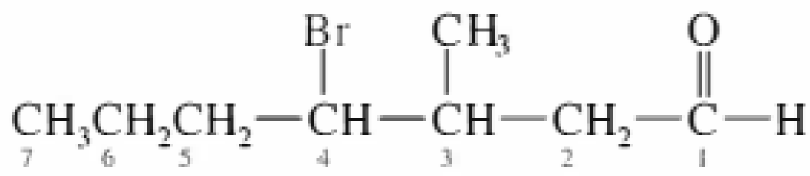
Nomenclature: IUPAC name

- **Aldehydes are named by replacing the terminal -e of the corresponding alkane name with –*al***
- **The parent chain must contain the —CHO group**

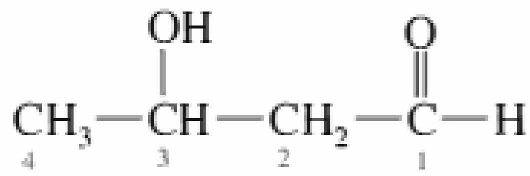
  The —CHO carbon is numbered as C1
- **If the —CHO group is attached to a ring, use the suffix carbaldehyde.**



ethanal

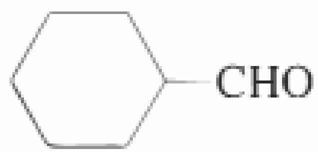


4-bromo-3-methylheptanal

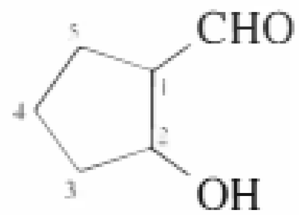


3-hydroxybutanal

2-pentenal
pent-2-enal



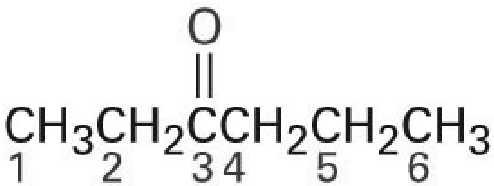
cyclohexanecarbaldehyde



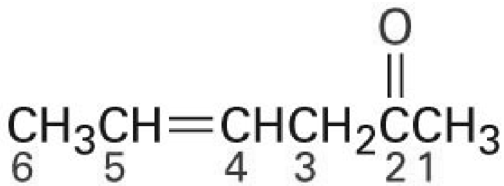
2-hydroxycyclopentane-1-carbaldehyde

Naming Ketones

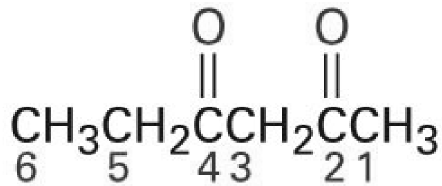
- Replace the terminal -*e* of the alkane name with *–one*
- Parent chain is the longest one that contains the ketone group
  - Numbering begins at the end nearer the carbonyl carbon



3-Hexanone
(New: Hexan-3-one)



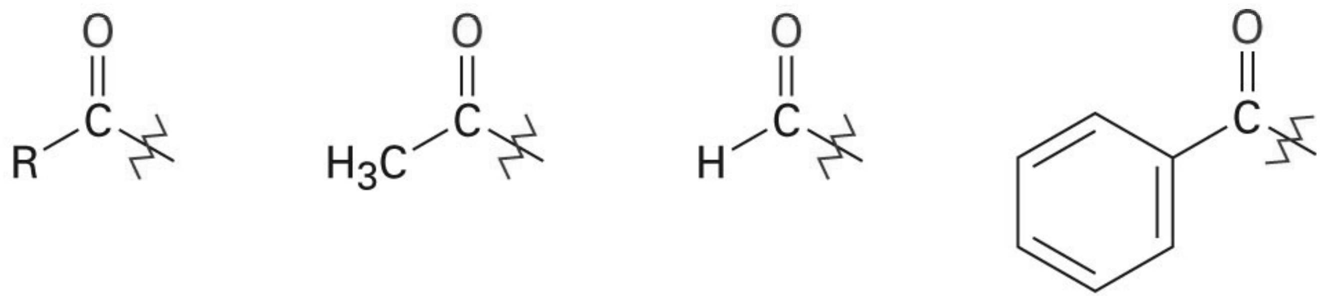
4-Hexen-2-one
(New: Hex-4-en-2-one)



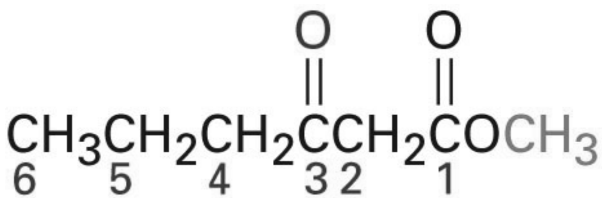
2,4-Hexanedione
(New: Hexane-2,4-dione)

Ketones and Aldehydes as Substituents

- The R–C=O as a substituent is an acyl group, used with the suffix -yl from the root of the carboxylic acid
  - CH_3CO: acetyl; CHO: formyl; C_6H_5CO: benzoyl
- The prefix *oxo*- is used if other functional groups are present and the doubly bonded oxygen is labeled as a substituent on a parent chain

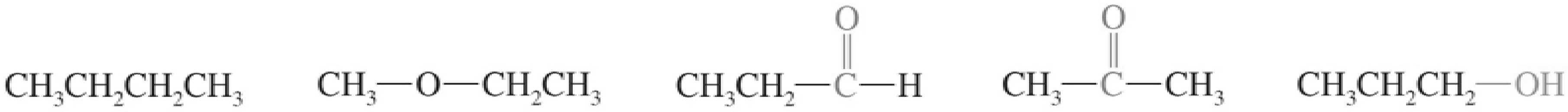


An acyl group **Acetyl** **Formyl** **Benzoyl**



Methyl 3-oxohexanoate

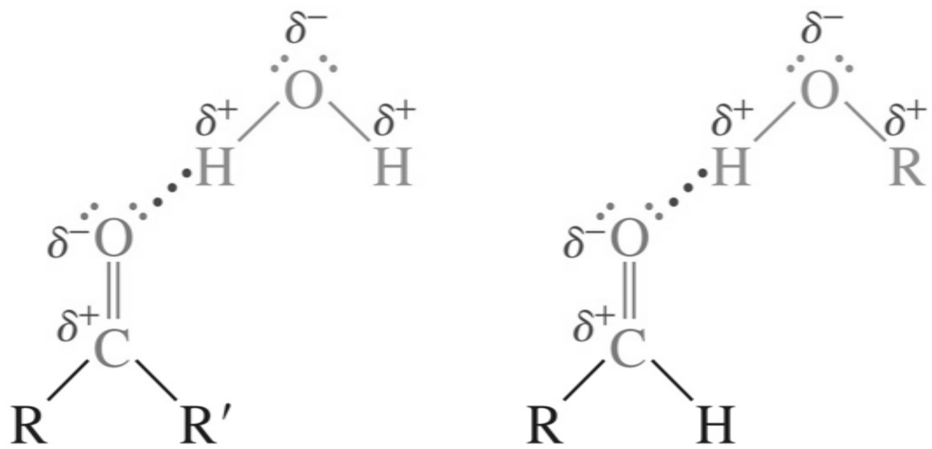
Boiling Points



butane, bp 0 °C — methoxyethane, bp 8 °C — propanal, bp 49 °C — acetone, bp 56 °C — 1-propanol, bp 97 °C

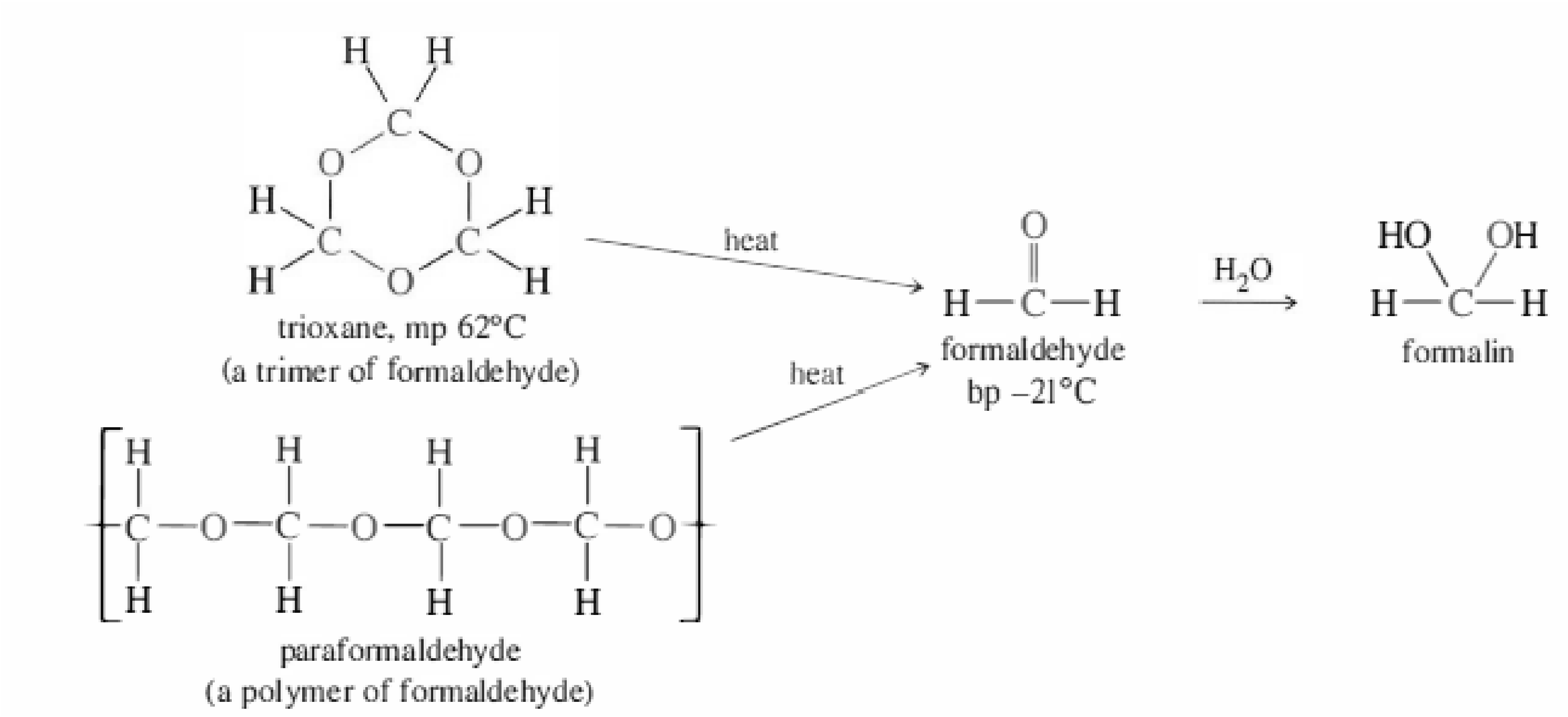
- Ketones and aldehydes are more polar, so they have a higher boiling point than comparable alkanes or ethers.
- They cannot hydrogen-bond to each other, so their boiling point is lower than comparable alcohol.

Solubility of Ketones and Aldehydes



- Good solvent for alcohols.
- Lone pair of electrons on oxygen of carbonyl can accept a hydrogen bond from O—H or N—H.
- Acetone and acetaldehyde are miscible in water.

Formaldehyde



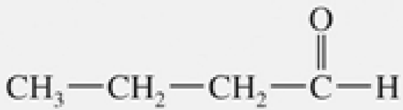
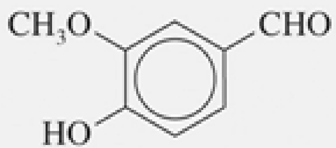
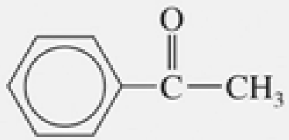
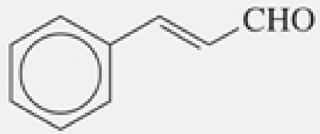
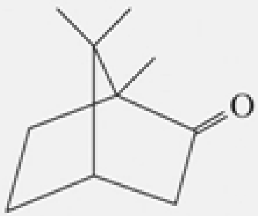
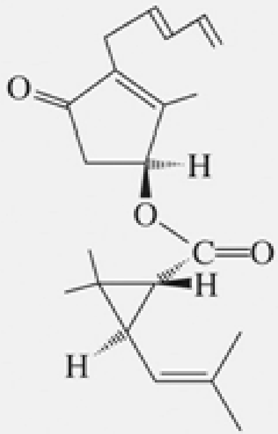
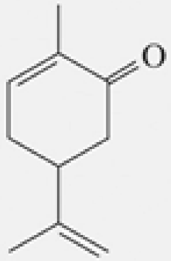
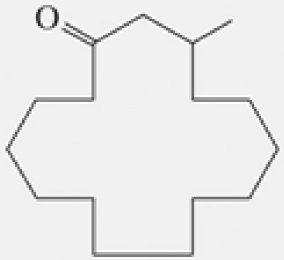
- Gas at room temperature.
- Formalin is a 40% aqueous solution.

Industrial Importance

- Acetone and methyl ethyl ketone are important solvents.
- Formaldehyde is used in polymers like Bakelite.
- Flavorings and additives like vanilla, cinnamon, and artificial butter.

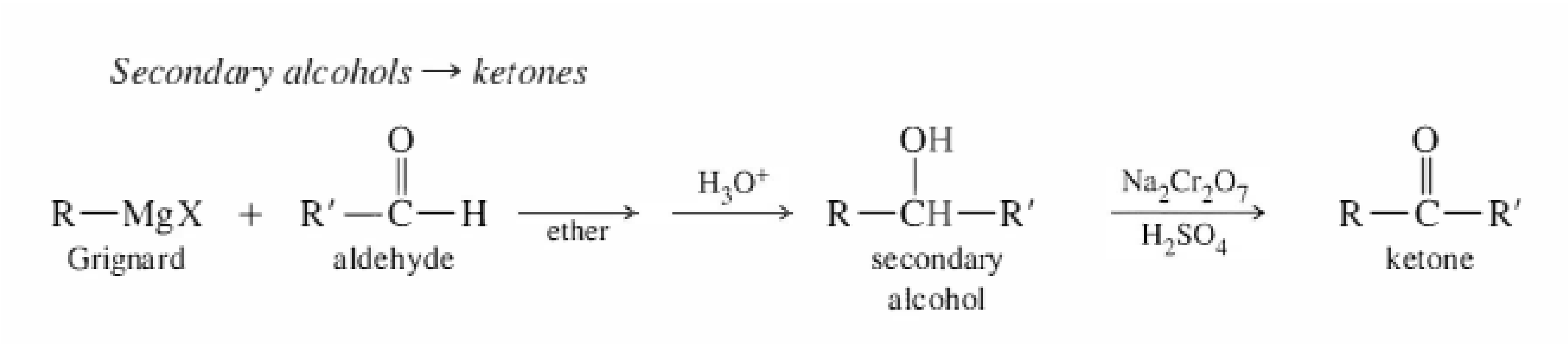
TABLE 18-4

Ketones and Aldehydes Used in Household Products

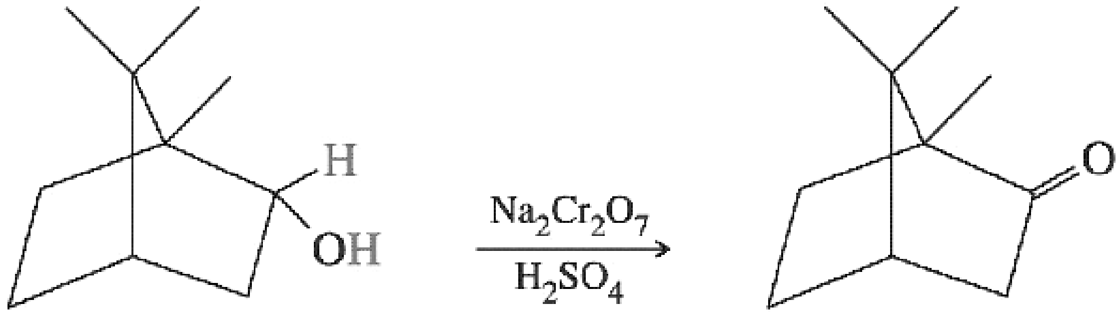
	 butyraldehyde	 vanillin	 acetophenone	 *trans*-cinnamaldehyde
Odor:	buttery	vanilla	pistachio	cinnamon
Uses:	margarine, foods	foods, perfumes	ice cream	candy, foods, drugs
	 camphor	 pyrethrin	 carvone	 muscone
Odor:	"camphoraceous"	floral	(−) enantiomer: spearmint (+) enantiomer: caraway seed	musky aroma
Uses:	liniments, inhalants	plant insecticide	candy, toothpaste, etc.	perfumes

Synthesis of aldehydes & ketones

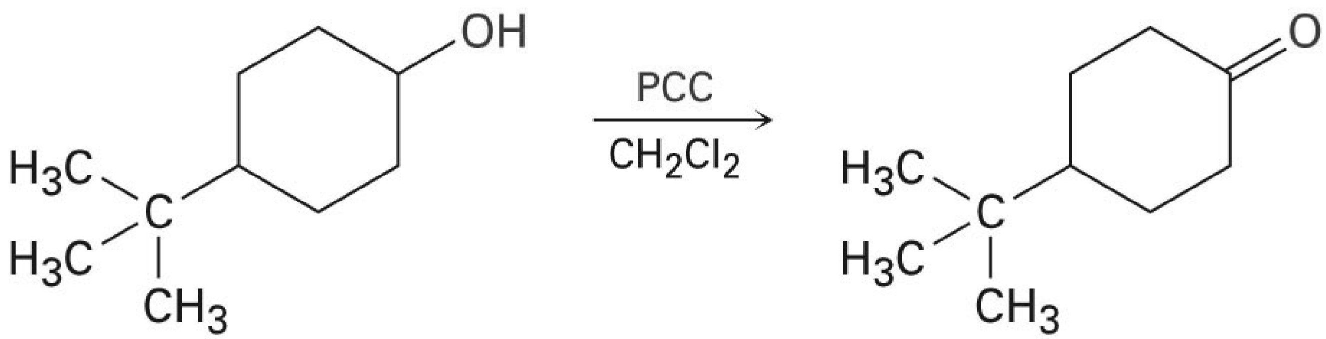
1. Oxidation of Alcohols to Aldehydes and Ketones



- Secondary alcohols are readily oxidized to ketones with sodium dichromate ($Na_2Cr_2O_7$) in sulfuric acid or by potassium permanganate ($KMnO_4$).

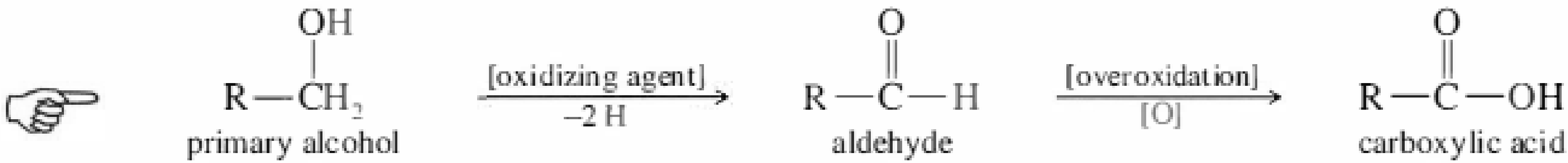


borneol camphor (88%)

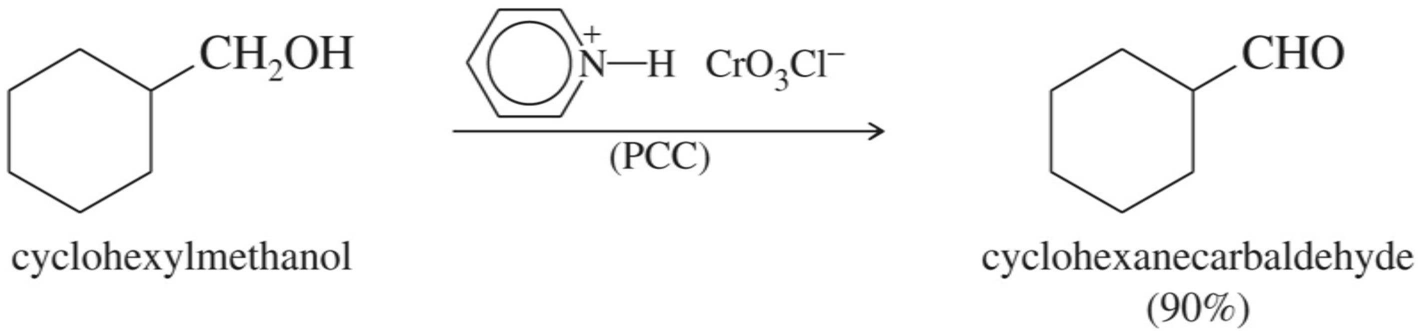


4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (90%)**

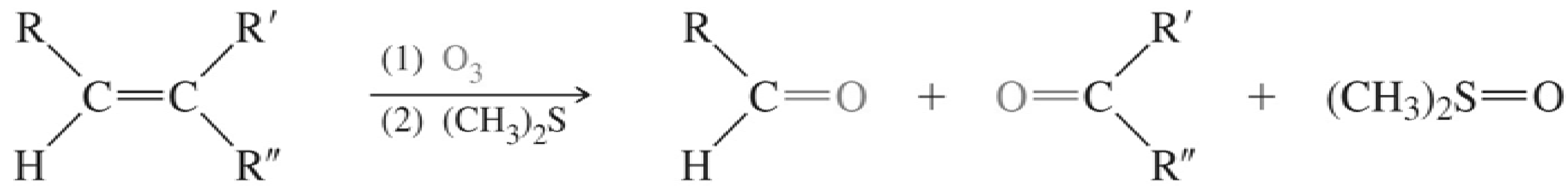
Primary alcohols → aldehydes



- Pyridinium chlorochromate (PCC) is selectively used to oxidize primary alcohols to aldehydes.

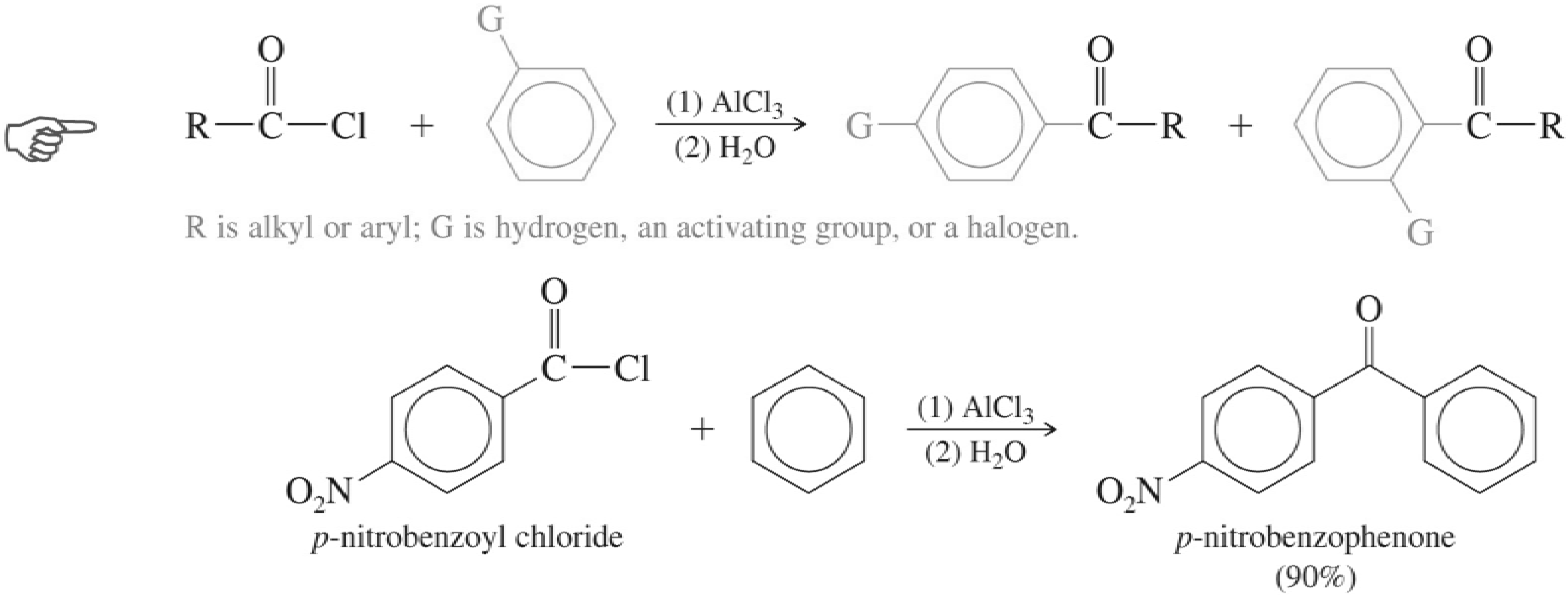


2. Ozonolysis of Alkenes



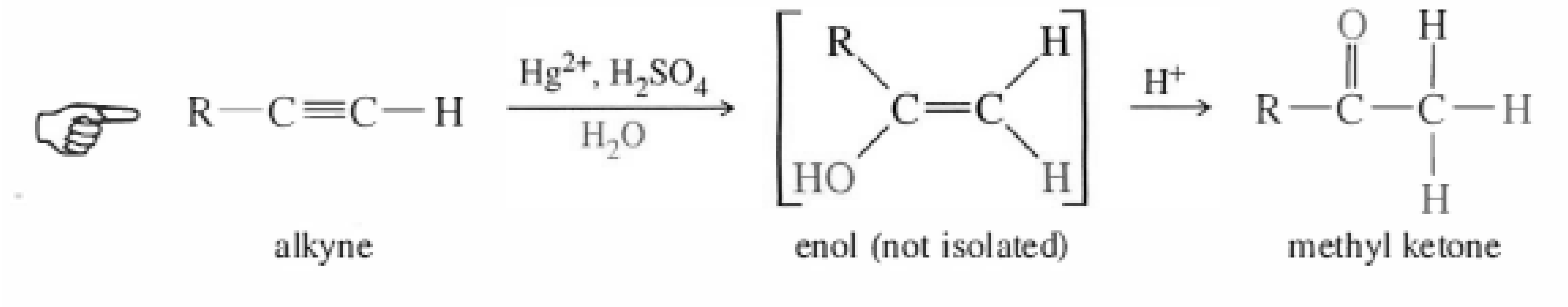
- The double bond is oxidatively cleaved by ozone followed by reduction.
- Ketones and aldehydes can be isolated as products.

3. Friedel–Crafts Reaction



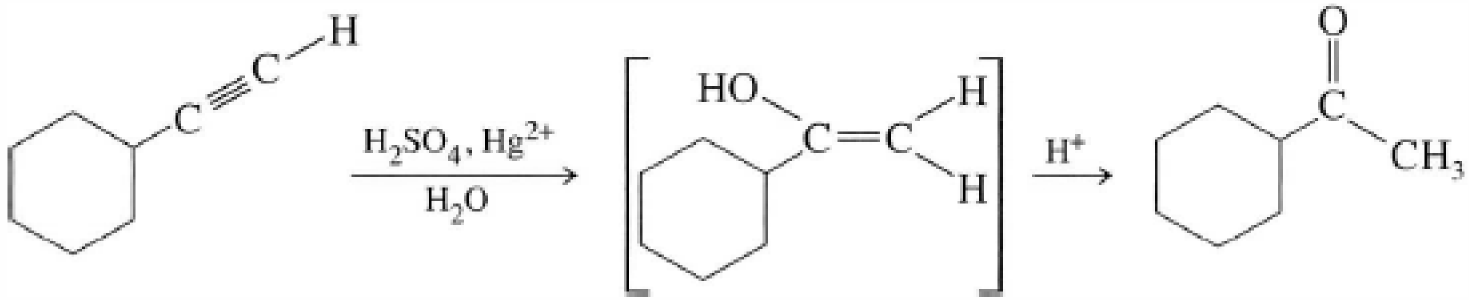
- Reaction between an acyl halide and an aromatic ring will produce a ketone.

4. Hydration of Alkynes

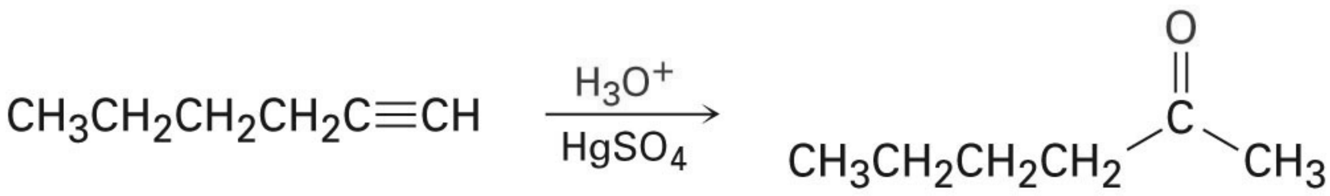


- The initial product of Markovnikov hydration is an enol, which quickly tautomerizes to its keto form.
- Internal alkynes can be hydrated, but mixtures of ketones often result.

Example

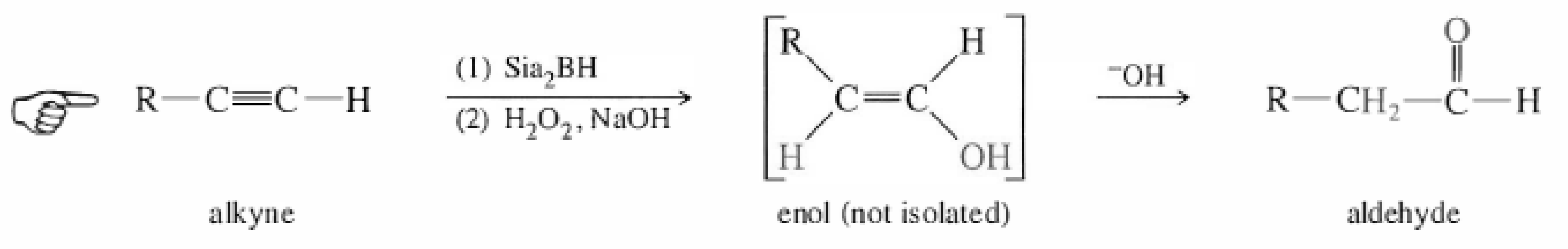


ethynylcyclohexane | enol | cyclohexyl methyl ketone (90%)

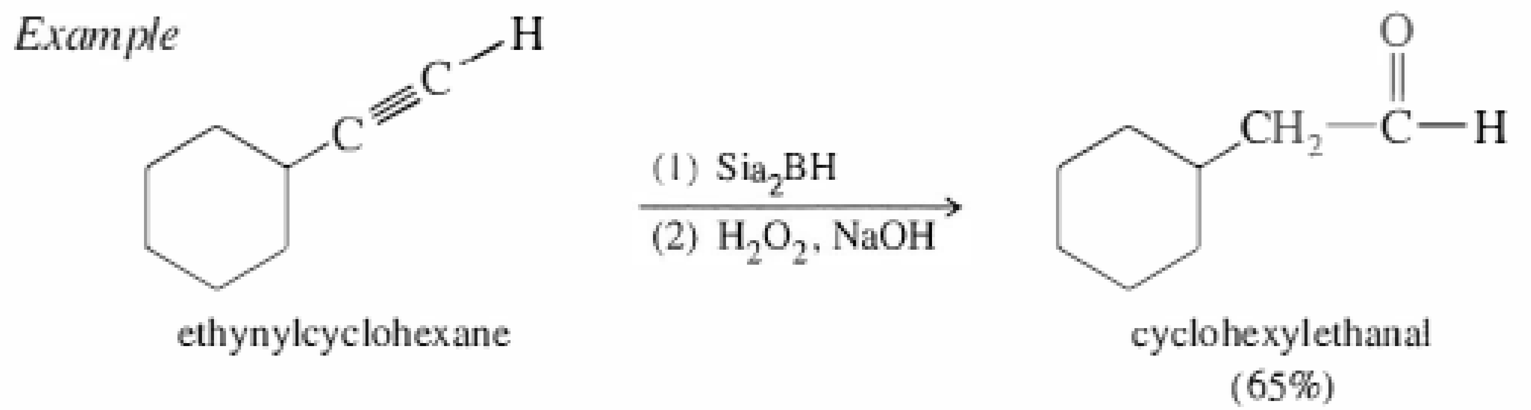


1-Hexyne | **2-Hexanone (78%)**

5. Hydroboration–Oxidation of Alkynes



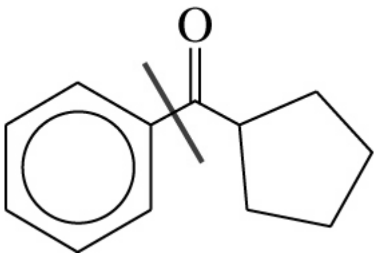
- Hydroboration–oxidation of an alkyne gives anti-Markovnikov addition of water across the triple bond.



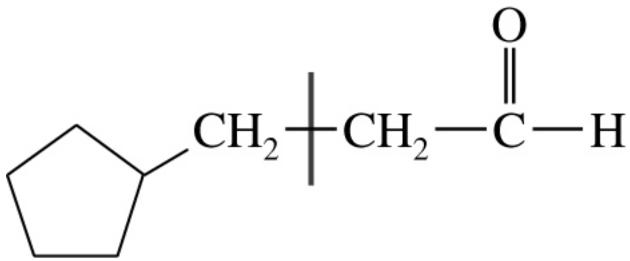
Solved Problem 1

Show how you would synthesize each compound from starting materials containing no more than six carbon atoms.

(a)

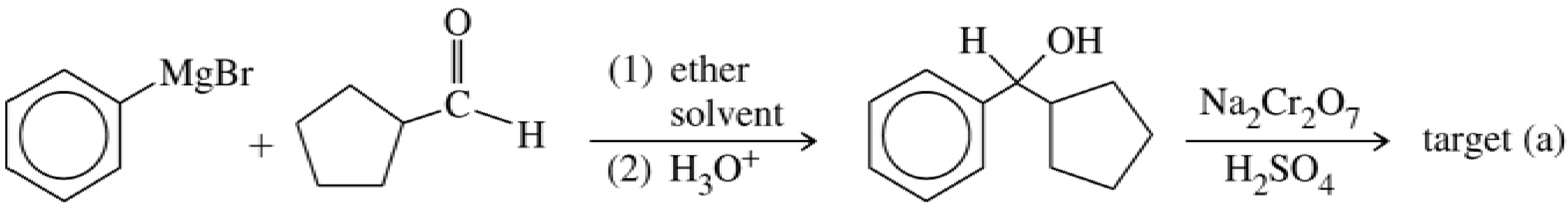


(b)



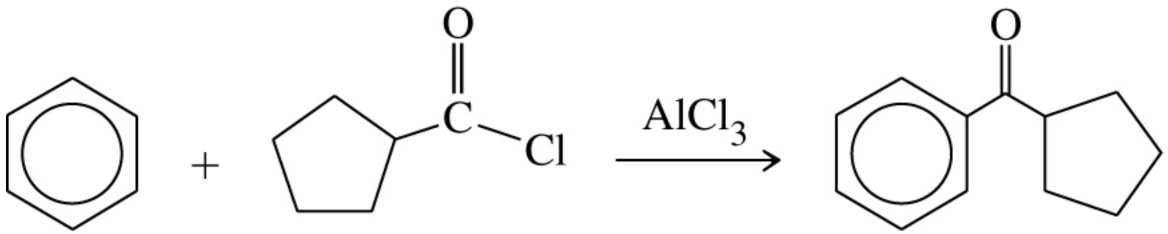
Solution

(a) This compound is a ketone with 12 carbon atoms. The carbon skeleton might be assembled from two six-carbon fragments using a Grignard reaction, which gives an alcohol that is easily oxidized to the target compound.

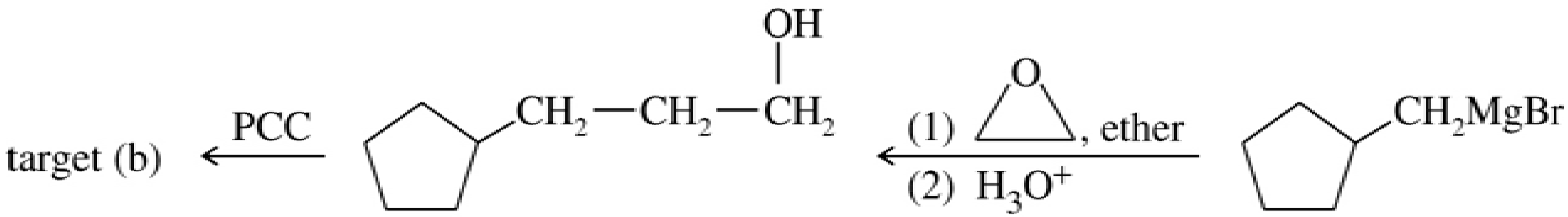


Solution (Continued)

An alternative route to the target compound involves Friedel–Crafts acylation.

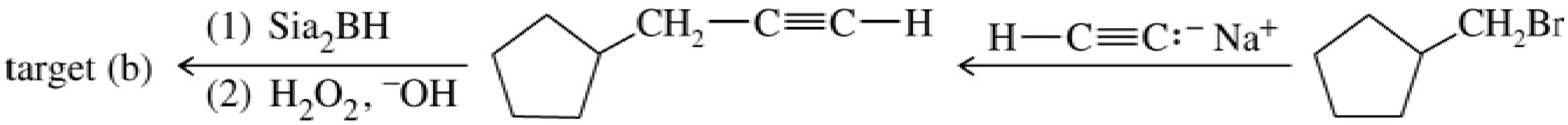


(b) This compound is an aldehyde with eight carbon atoms. An aldehyde might come from oxidation of an alcohol (possibly a Grignard product) or hydroboration of an alkyne. If we use a Grignard, the restriction to six-carbon starting materials means we need to add two carbons to a methylcyclopentyl fragment, ending in a primary alcohol. Grignard addition to an epoxide does this.

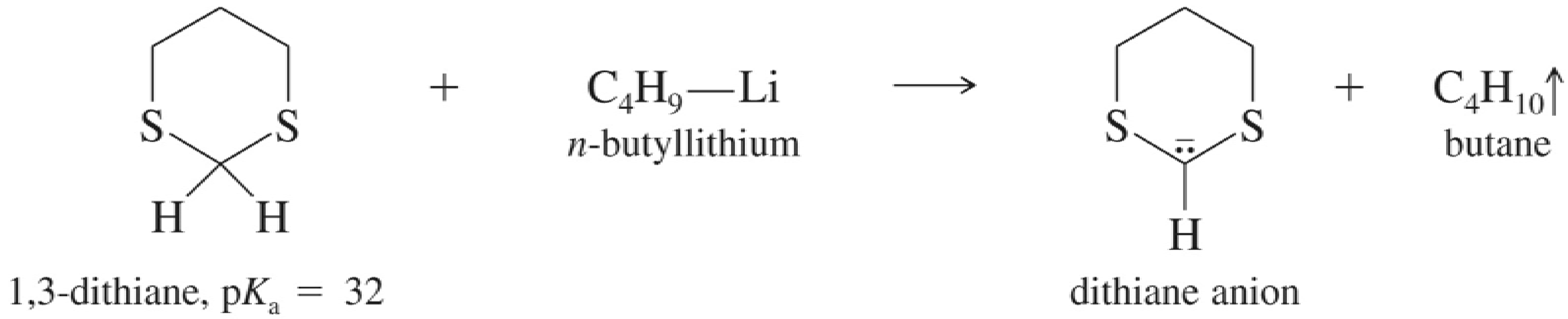


Solution (Continued)

Alternatively, we could construct the carbon skeleton using acetylene as the two-carbon fragment. The resulting terminal alkyne undergoes hydroboration to the correct aldehyde.

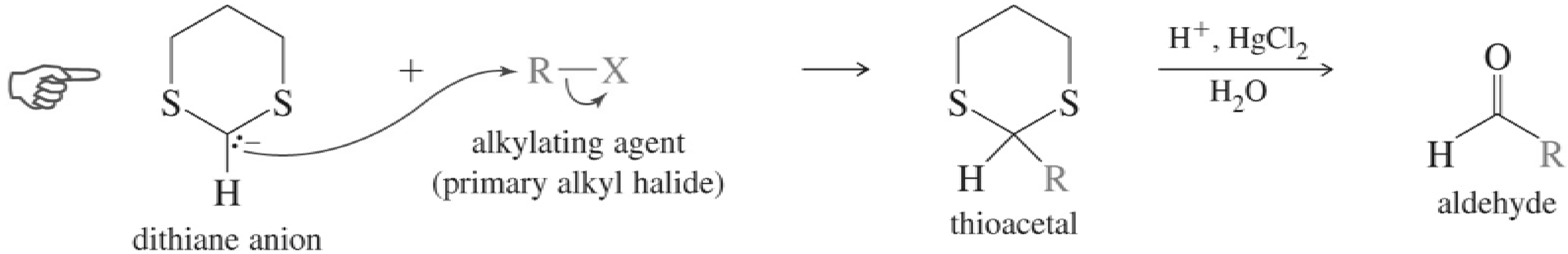


6. Synthesis of Ketones and Aldehydes Using 1,3-Dithianes



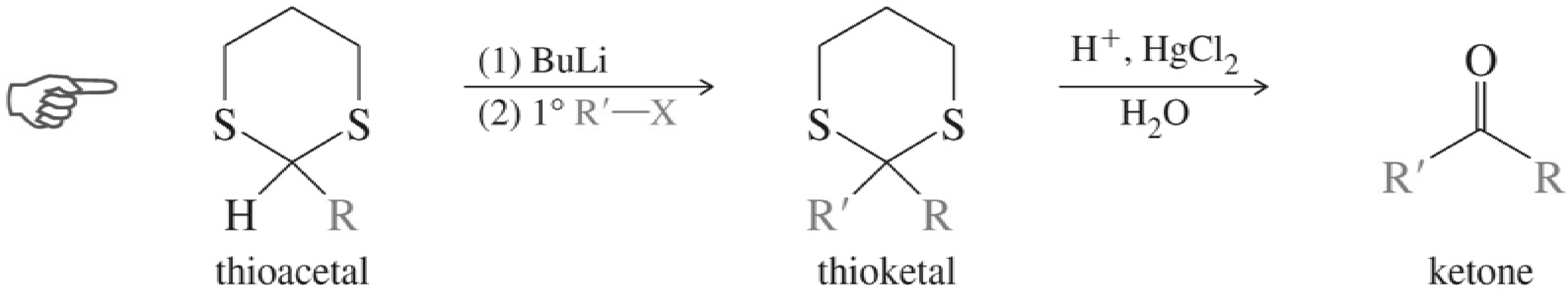
- 1,3-Dithiane can be deprotonated by strong bases such as *n*-butyllithium.
- The resulting carbanion is stabilized by the electron-withdrawing effects of two polarizable sulfur atoms.

Alkylation of 1,3-Dithiane



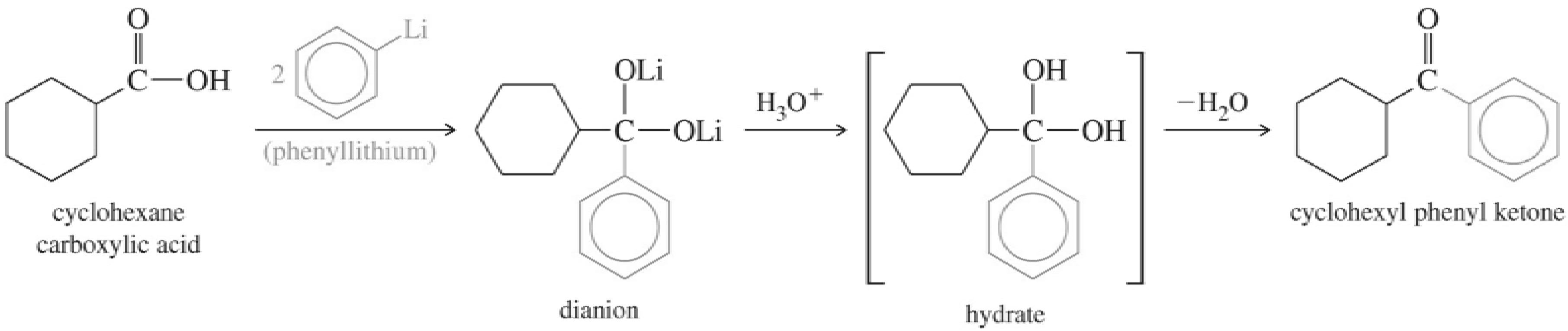
- Alkylation of the dithiane anion by a primary alkyl halide or a tosylate gives a thioacetal that can be hydrolyzed into the aldehyde by using an acidic solution of mercuric chloride.

Ketones from 1,3-Dithiane



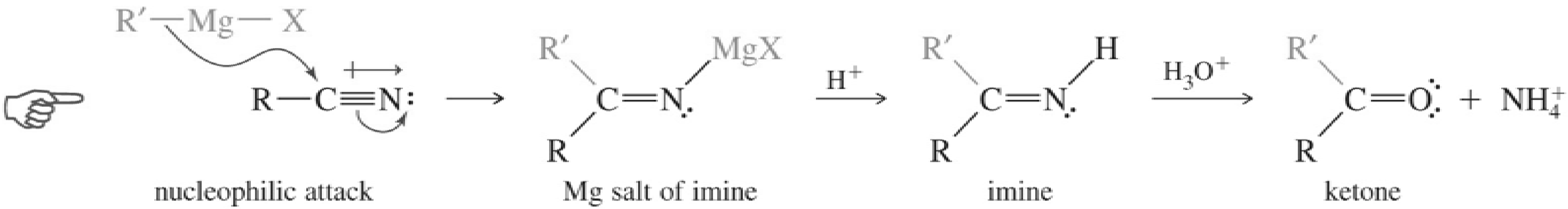
- The thioacetal can be isolated and deprotonated.
- Alkylation and hydrolysis will produce a ketone.

7. Synthesis of Ketones from Carboxylic Acids



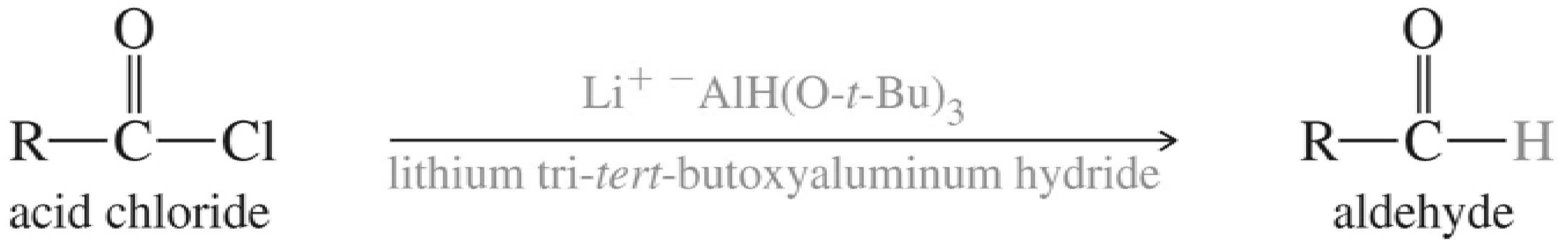
- Organolithiums will attack the lithium salts of carboxylate anions to give dianions.
- Protonation of the dianion forms the hydrate of a ketone, which quickly loses water to give the ketone.

8.Ketones from Nitriles



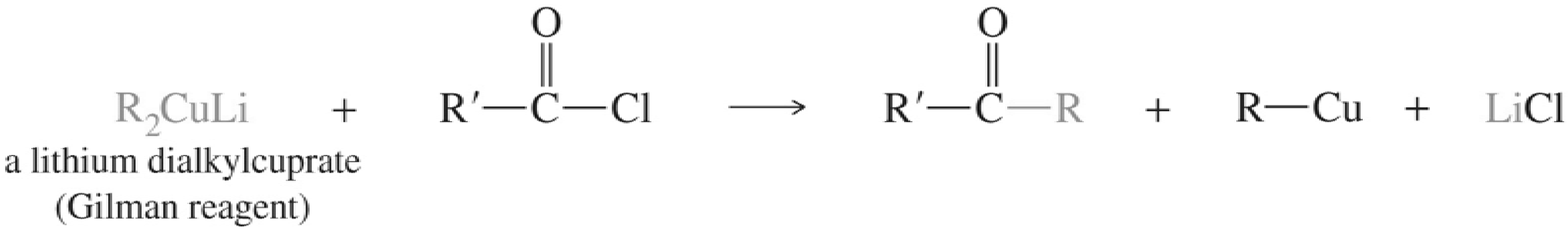
- A Grignard or organolithium reagent can attack the carbon of the nitrile.
- The imine is then hydrolyzed to form a ketone.

9. Aldehydes from Acid Chlorides



- Lithium aluminum tri(*t*-butoxy)hydride is a milder reducing agent that reacts faster with acid chlorides than with aldehydes.

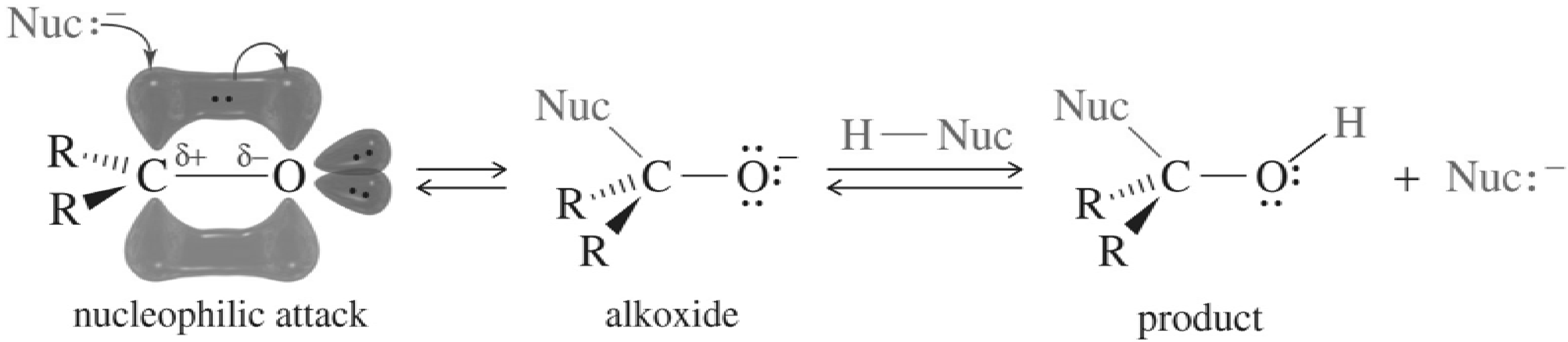
10. Lithium Dialkyl Cuprate Reagents



- A lithium dialkylcuprate (Gilman reagent) will transfer one of its alkyl groups to the acid chloride.

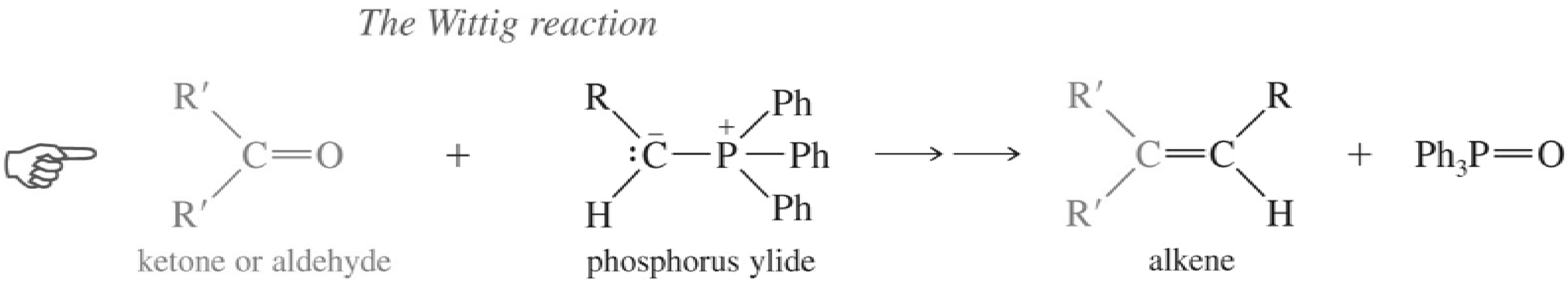
Reaction of Aldehydes & Ketones

1. Nucleophilic Addition



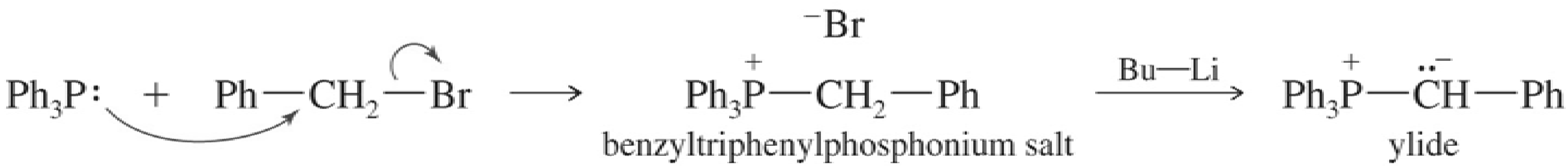
- A strong nucleophile attacks the carbonyl carbon, forming an alkoxide ion that is then protonated.
- Aldehydes are more reactive than ketones.

2. The Wittig Reaction



- The Wittig reaction converts the carbonyl group into a new C=C double bond where no bond existed before.
- A phosphorus ylide is used as the nucleophile in the reaction.

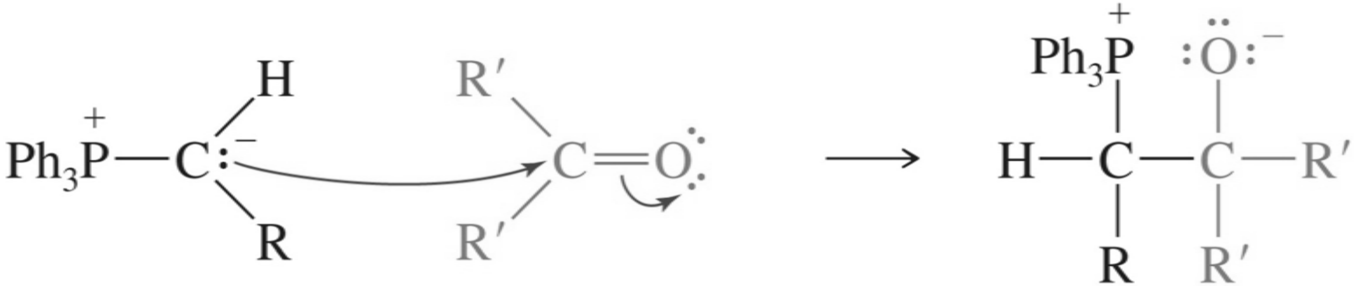
Preparation of Phosphorus Ylides



- Prepared from triphenylphosphine and an unhindered alkyl halide.
- Butyllithium then abstracts a hydrogen from the carbon attached to phosphorus.

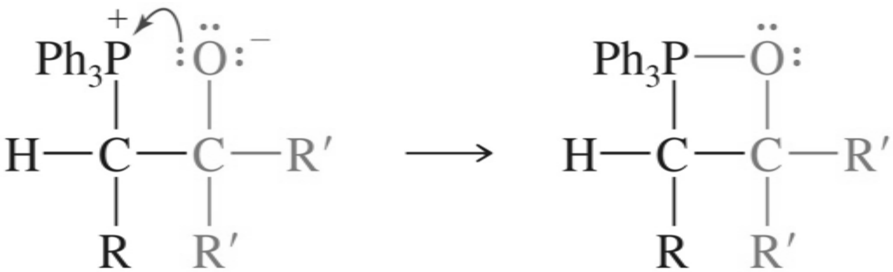
Mechanism of the Wittig Reaction

Betaine formation



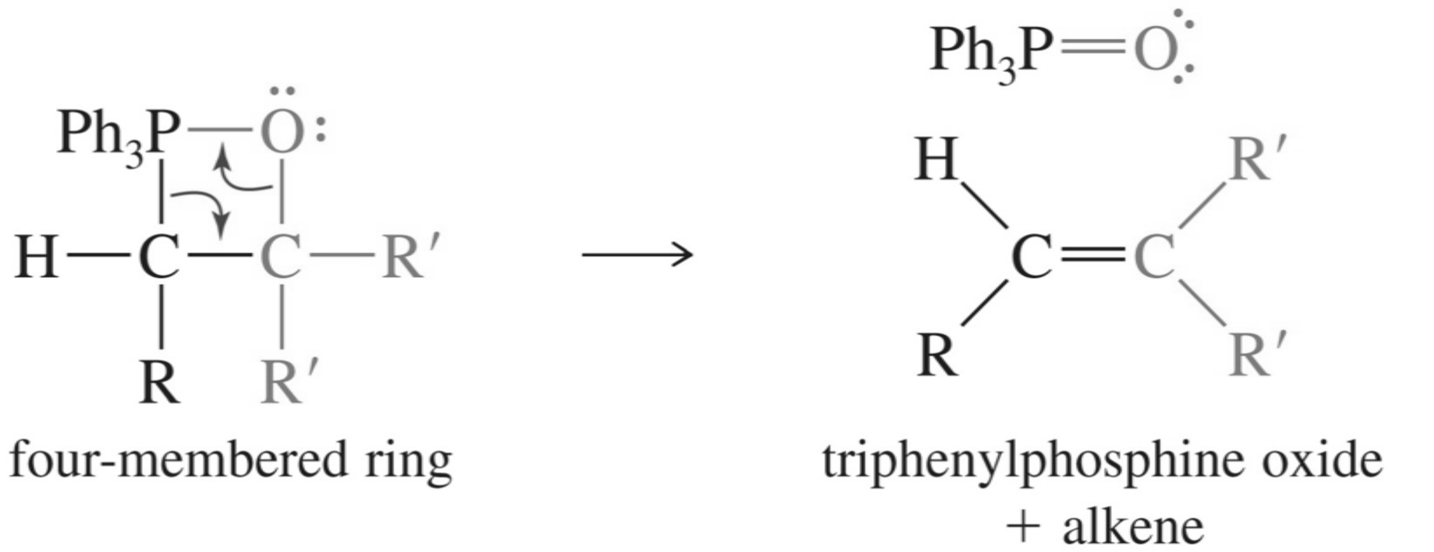
ylide ketone or aldehyde a betaine

Oxaphosphetane formation



a betaine oxaphosphetane

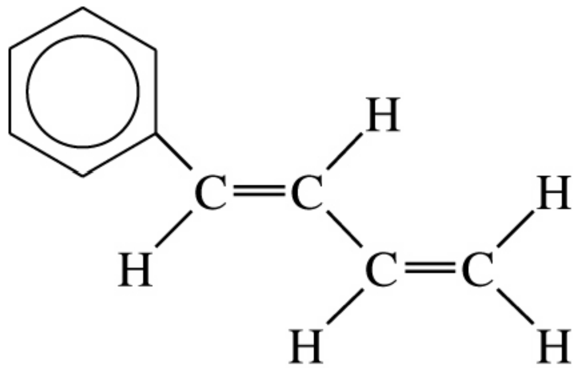
Mechanism for Wittig



- The oxaphosphetane will collapse, forming carbonyl (ketone or aldehyde) and a molecule of triphenyl phosphine oxide.

Solved Problem 2

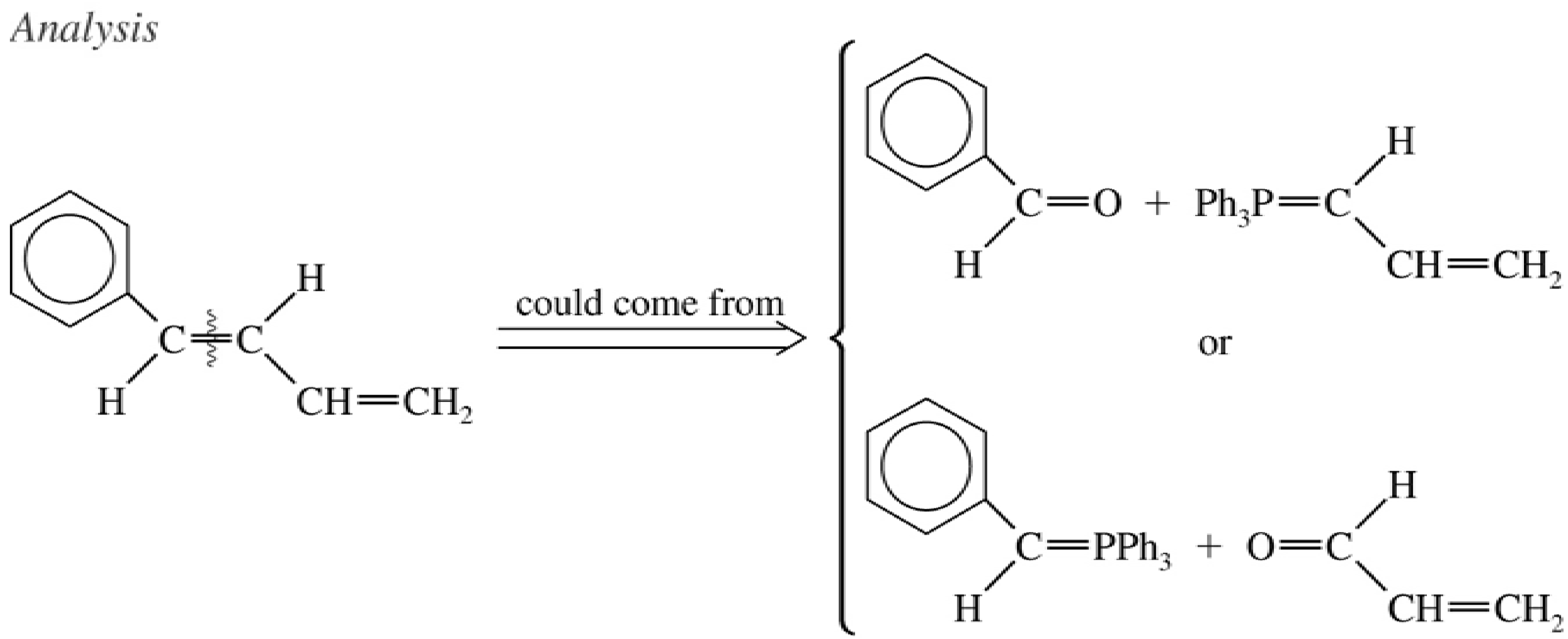
Show how you would use a Wittig reaction to synthesize 1-phenyl-1,3-butadiene.



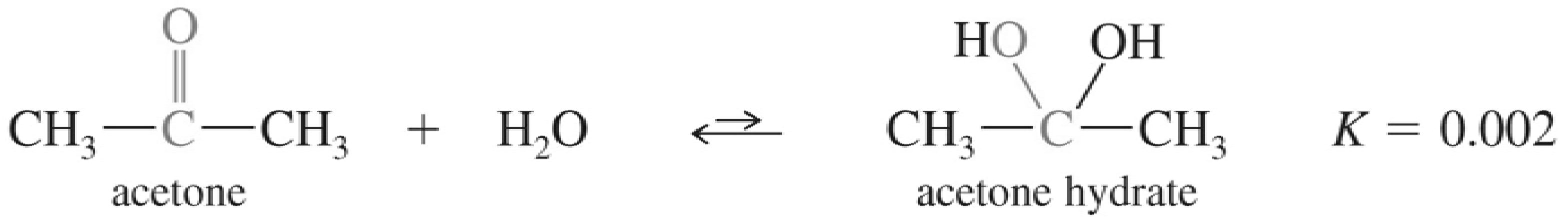
1-phenyl-1,3-butadiene

Solution (Continued)

This molecule has two double bonds that might be formed by Wittig reactions. The central double bond could be formed in either of two ways. Both of these syntheses will probably work, and both will produce a mixture of cis and trans isomers.

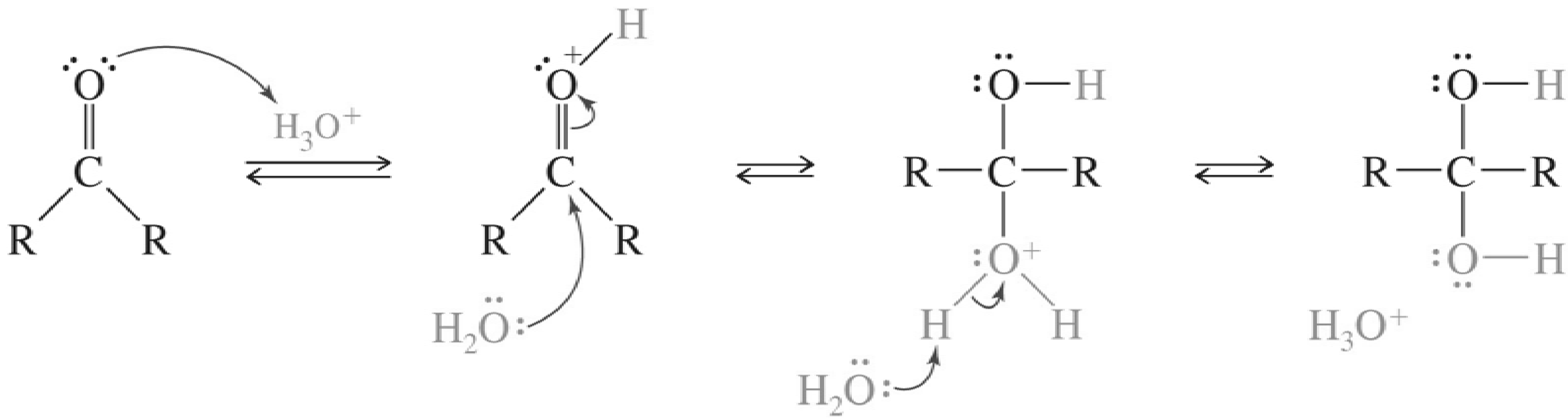


3. Hydration of Ketones and Aldehydes



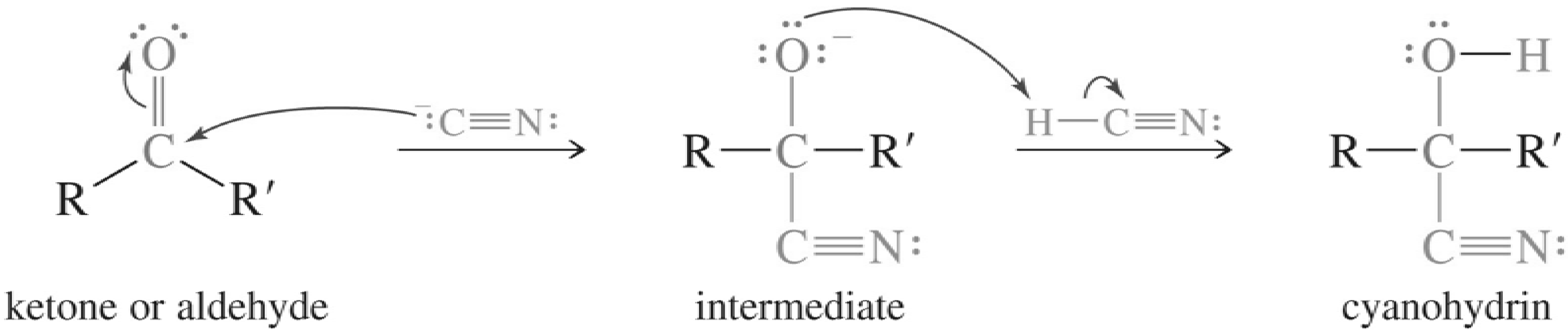
- In an aqueous solution, a ketone or an aldehyde is in equilibrium with its hydrate, a geminal diol.
- With ketones, the equilibrium favors the unhydrated keto form (carbonyl).

Mechanism of Hydration of Ketones and Aldehydes



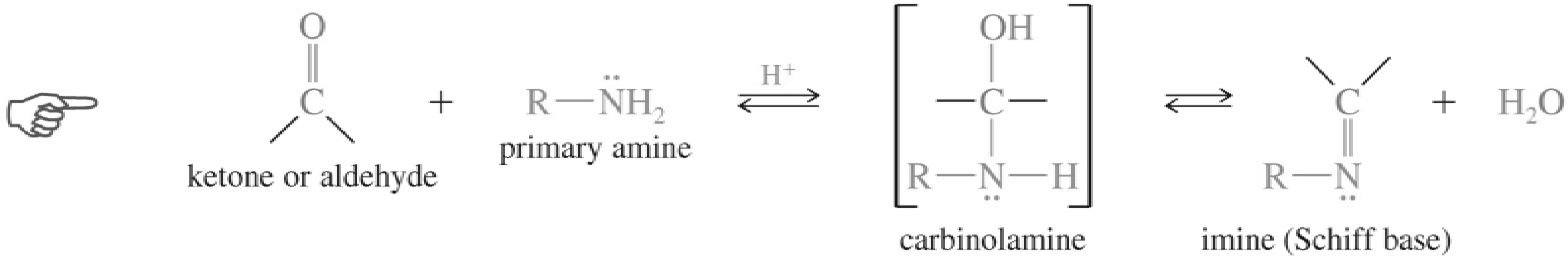
- Hydration occurs through the nucleophilic addition mechanism, with water (in acid) or hydroxide (in base) serving as the nucleophile.

4. Cyanohydrin Formation



- The mechanism is a base-catalyzed nucleophilic addition: Attack by cyanide ion on the carbonyl group, followed by protonation of the intermediate.
- HCN is highly toxic.

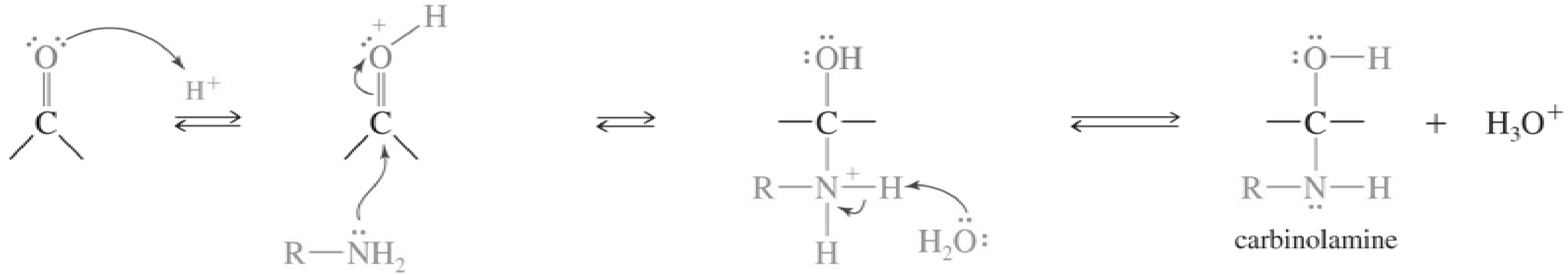
5. Formation of Imines



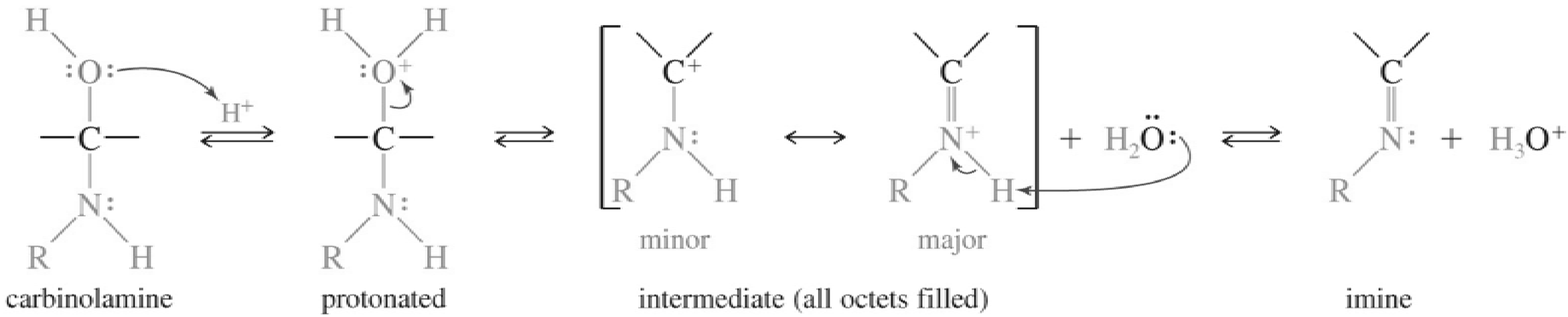
- Ammonia or a primary amine reacts with a ketone or an aldehyde to form an imine.
- Imines are nitrogen analogues of ketones and aldehydes with a C═N bond in place of the carbonyl group.
- Optimum pH is around 4.5

Mechanism of Imine Formation

Acid-catalyzed addition of the amine to the carbonyl compound group.



Acid-catalyzed dehydration.

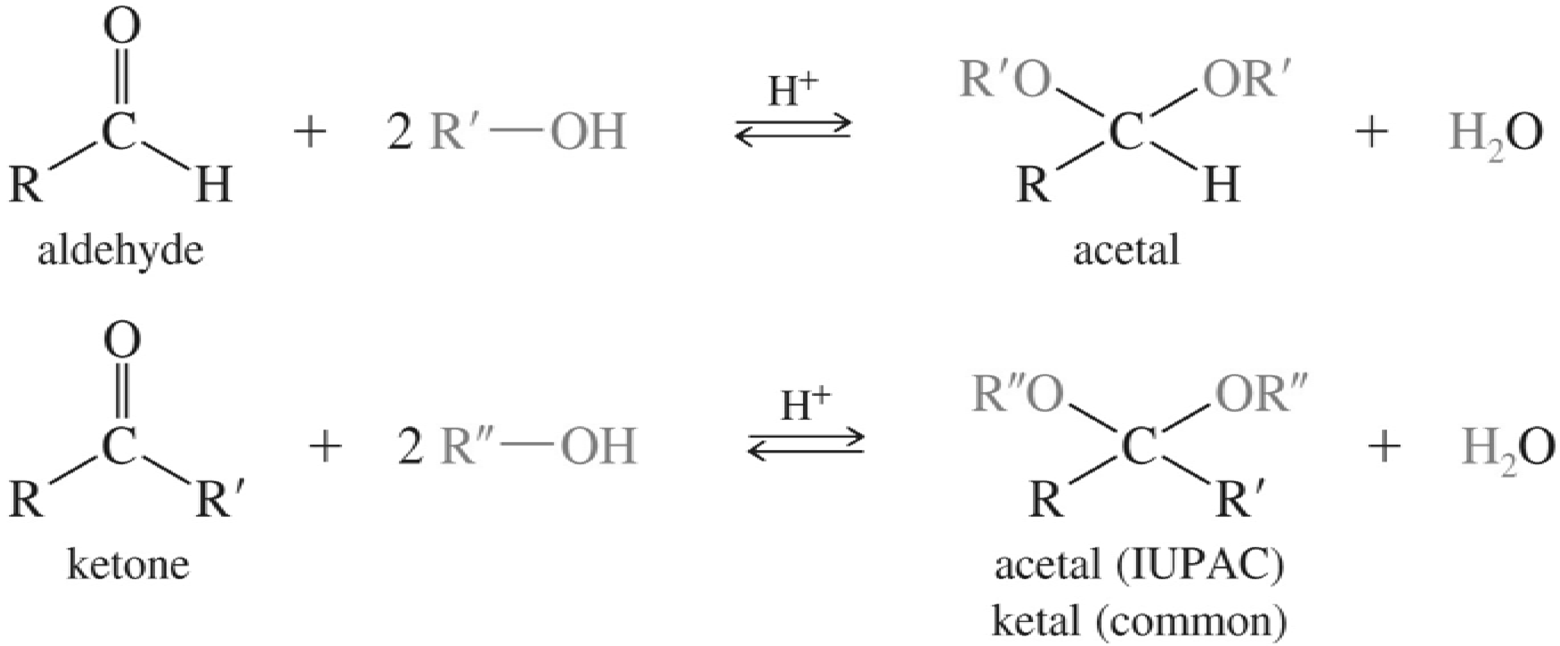


Other Condensations with Amines

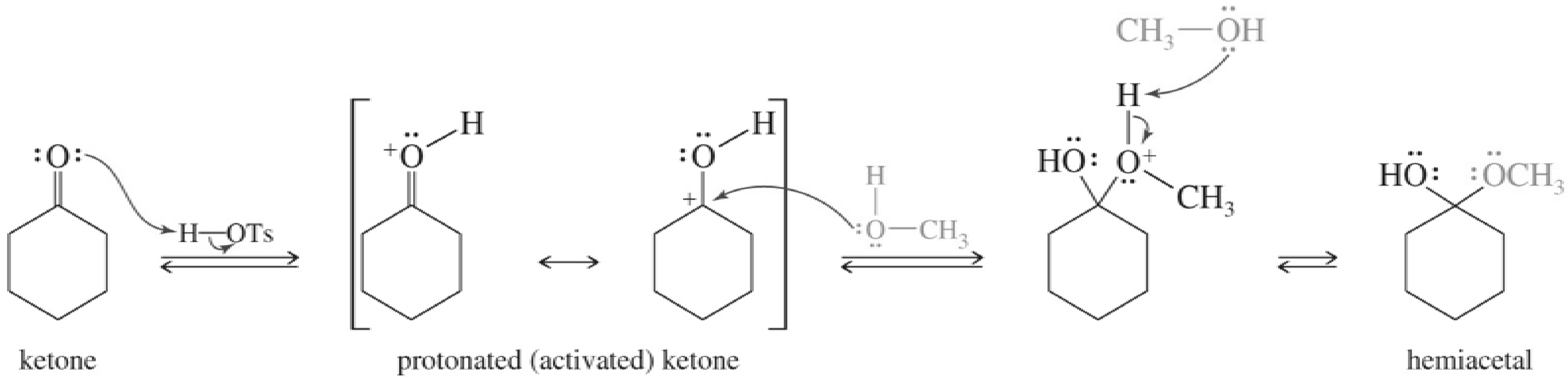
$$>C{=}O \; + \; H_2\ddot{N}{-}\boxed{Z} \;\xrightarrow{H^+}\; >C{=}\ddot{N}{-}\boxed{Z} \; + \; H_2O$$

Z in Z—NH$_2$	*Reagent*		*Product*	
—H	$H_2\ddot{N}{-}\boxed{H}$	ammonia	$>C{=}\ddot{N}{-}\boxed{H}$	an imine
—R	$H_2\ddot{N}{-}\boxed{R}$	primary amine	$>C{=}\ddot{N}{-}\boxed{R}$	an imine (Schiff base)
—OH	$H_2\ddot{N}{-}\boxed{OH}$	hydroxylamine	$>C{=}\ddot{N}{-}\boxed{OH}$	an oxime
—NH$_2$	$H_2\ddot{N}{-}\boxed{NH_2}$	hydrazine	$>C{=}\ddot{N}{-}\boxed{NH_2}$	a hydrazone
—NHPh	$H_2\ddot{N}{-}\boxed{NHPh}$	phenylhydrazine	$>C{=}\ddot{N}{-}\boxed{NHPh}$	a phenylhydrazone
—NHC(=O)NH$_2$	$H_2\ddot{N}{-}\boxed{NH{-}C(=O){-}NH_2}$	semicarbazide	$>C{=}\ddot{N}{-}\boxed{NH{-}C(=O){-}NH_2}$	a semicarbazone

6. Formation of Acetals

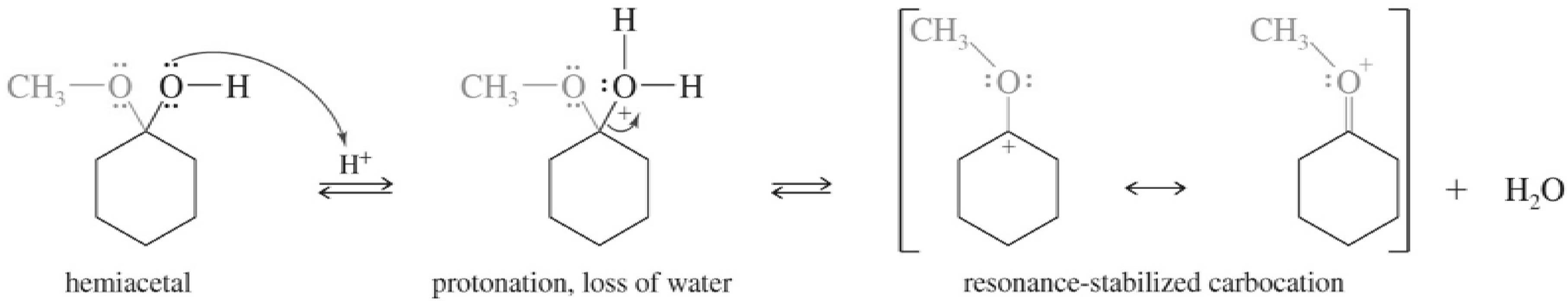


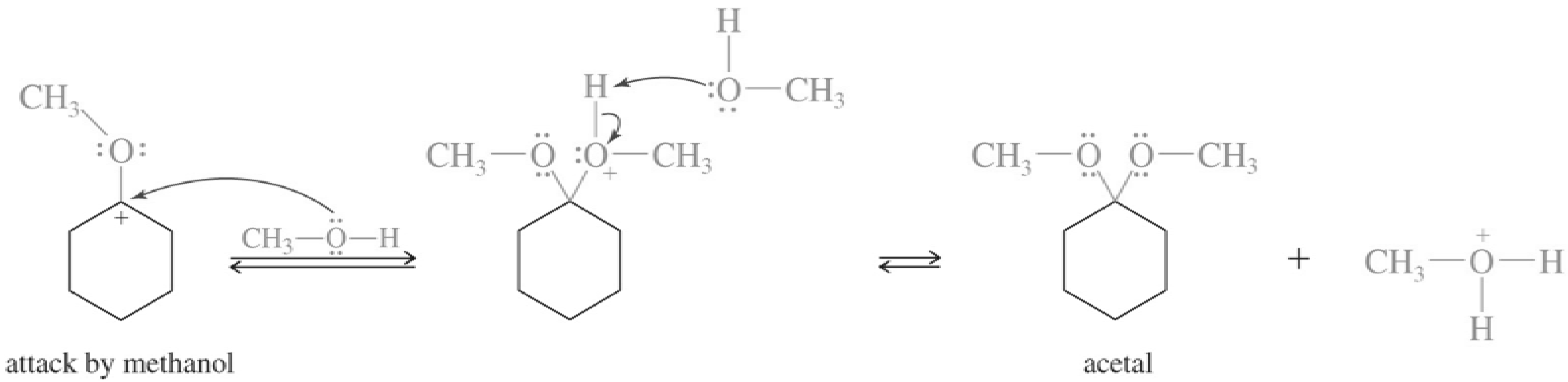
Mechanism for Hemiacetal Formation



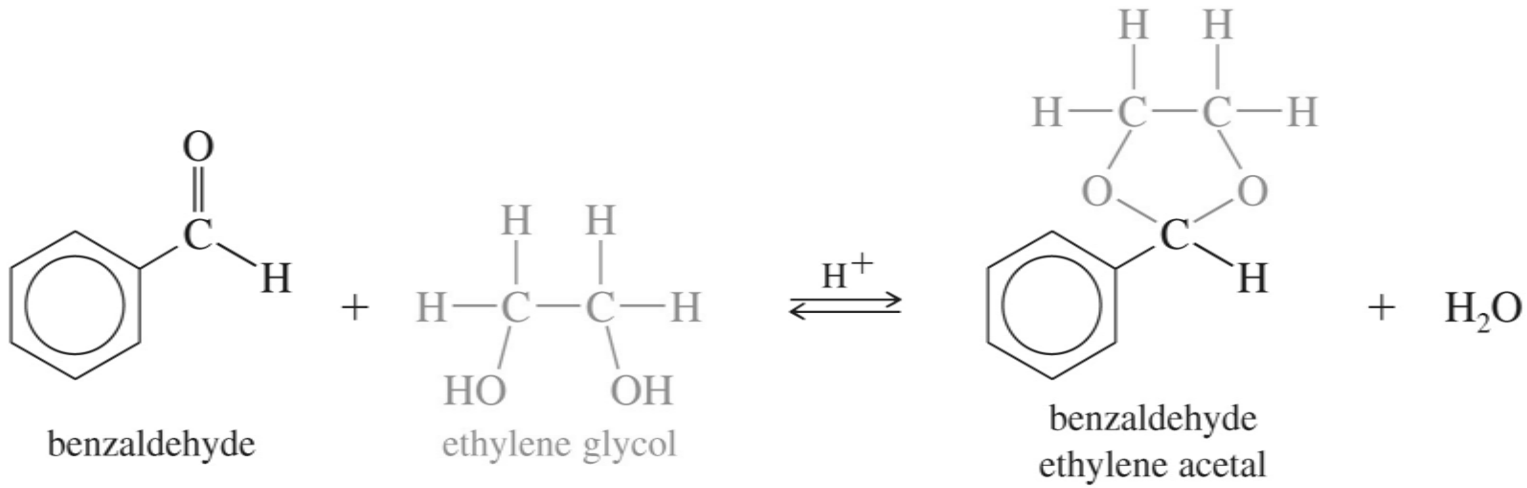
- Must be acid-catalyzed.
- Adding H^+ to carbonyl makes it more reactive with weak nucleophile, ROH.

Acetal Formation



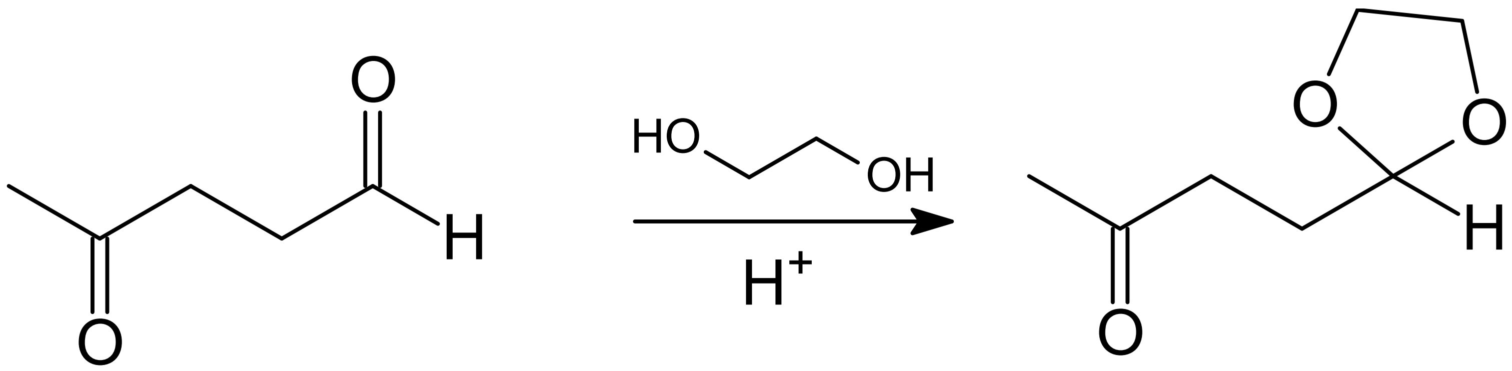


Cyclic Acetals



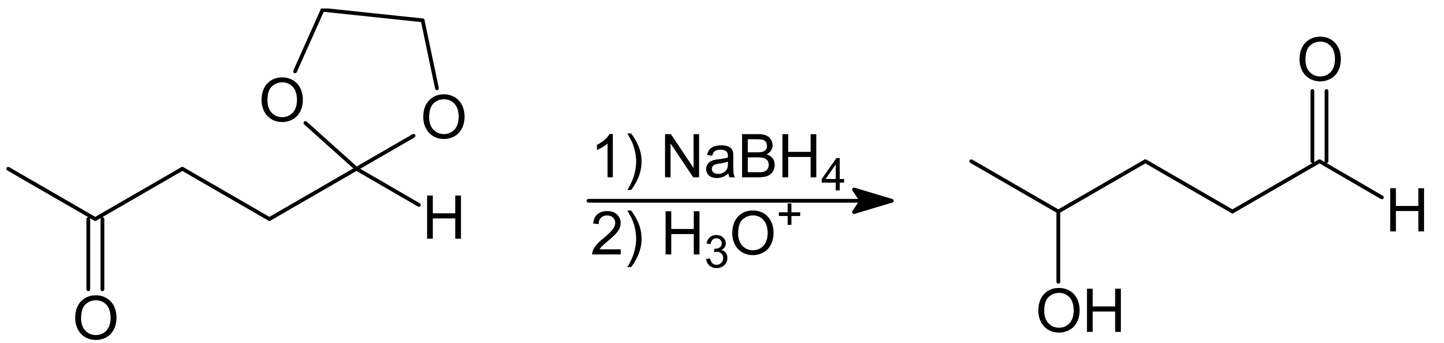
- Addition of a diol produces a cyclic acetal.
- The reaction is reversible.
- This reaction is used in synthesis to protect carbonyls from reaction

Acetals as Protecting Groups



- Hydrolyze easily in acid; stable in base.
- Aldehydes are more reactive than ketones.

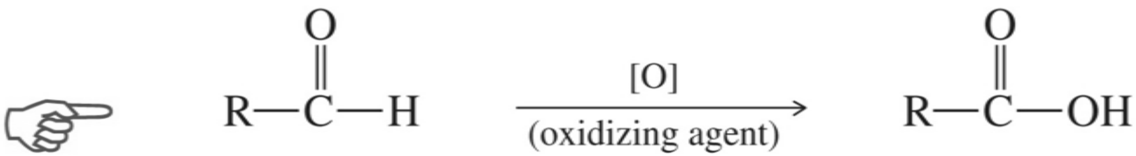
Reaction and Deprotection



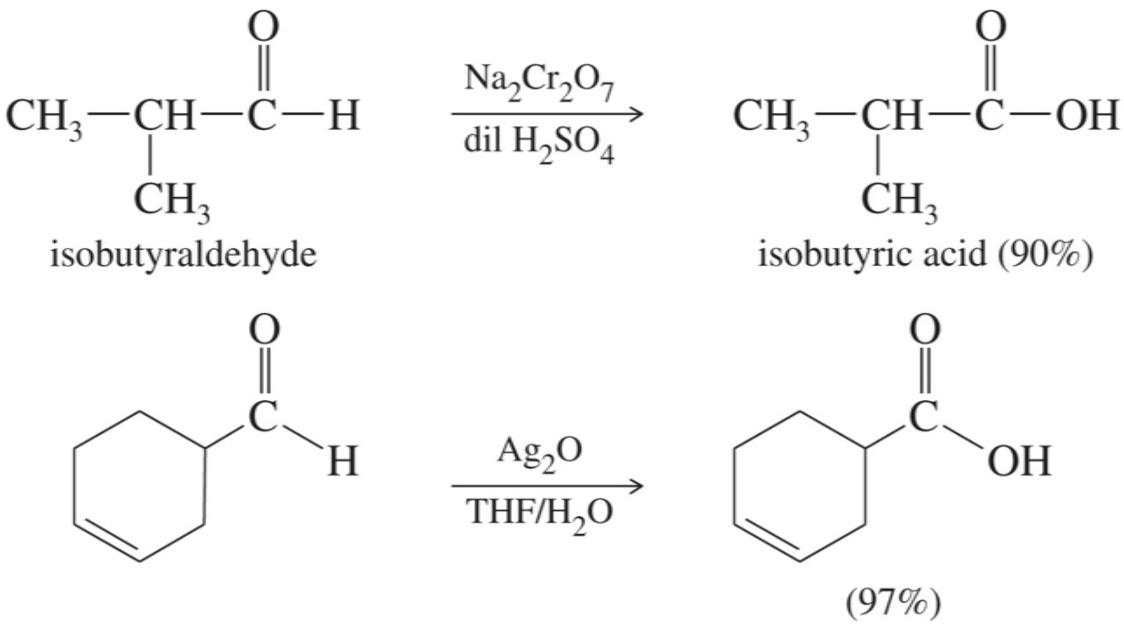
- The acetal will not react with $NaBH_4$, so only the ketone will get reduced.
- Hydrolysis conditions will protonate the alcohol and remove the acetal to restore the aldehyde.

7.Oxidation of Aldehydes

7.1 Simple Oxidation



Examples



Aldehydes are easily oxidized to carboxylic acids.

7.2 Tollen's reagent

aldehyde ถูกออกซิไดส์ด้วย diamminosilver (I) ion ($Ag(NH_3)_2^+$) ให้ carboxylate ion และ Ag จับข้างหลอดลักษณะเหมือนกระจกเงิน (silver mirror)

$$R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}H + 2Ag(NH_3)_2OH \longrightarrow 2Ag\downarrow + R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}\overset{-}{O}\overset{+}{N}H_4 + H_2O + 3NH_3$$

silver ammonium hydroxide

$$R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R' + 2Ag(NH_3)_2OH \;\not\longrightarrow$$

7.3 Fehling's reagent

$$R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}H + 2Cu^{2+} + 5OH^{-} \longrightarrow R\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}O^{-} + 3H_2O + Cu_2O\downarrow$$

copper tartrate complex

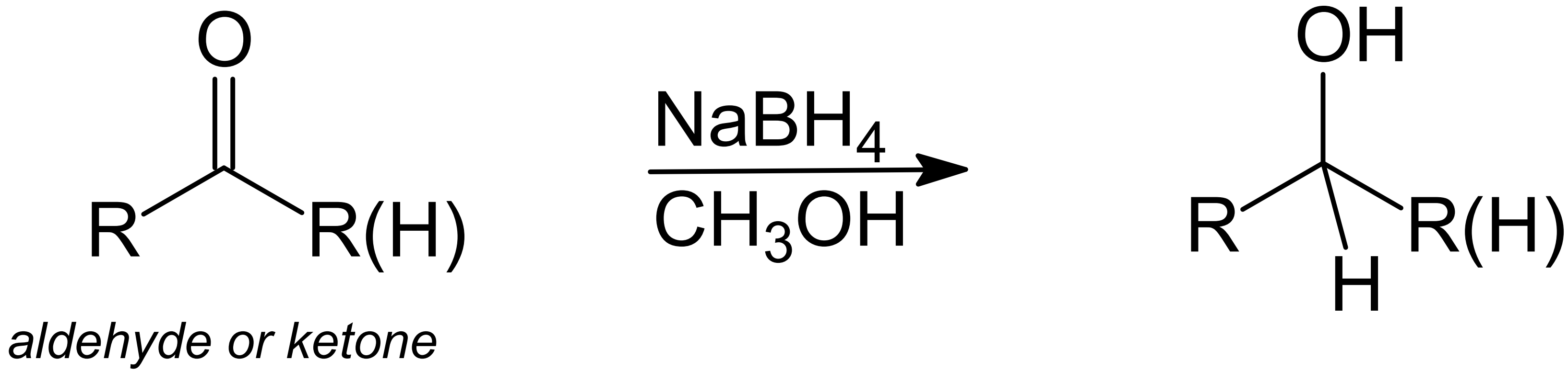
ตะกอนสีอิฐ

ทดสอบเฉพาะ aliphatic aldehyde

8. Reduction Reagents

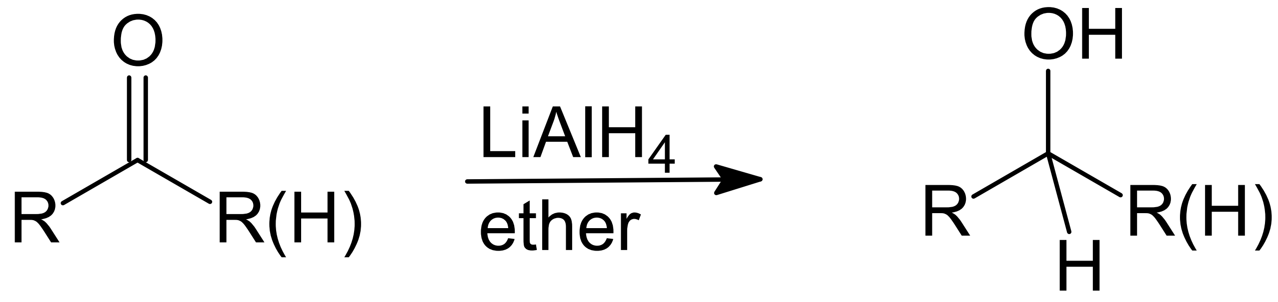
- Sodium borohydride, $NaBH_4$, can reduce ketones to secondary alcohols and aldehydes to primary alcohols.
- Lithium aluminum hydride, $LiAlH_4$, is a powerful reducing agent, so it can also reduce carboxylic acids and their derivatives.
- Hydrogenation with a catalyst can reduce the carbonyl, but it will also reduce any double or triple bonds present in the molecule.

Sodium Borohydride



- $NaBH_4$ can reduce ketones and aldehydes, but not esters, carboxylic acids, acyl chlorides, or amides.

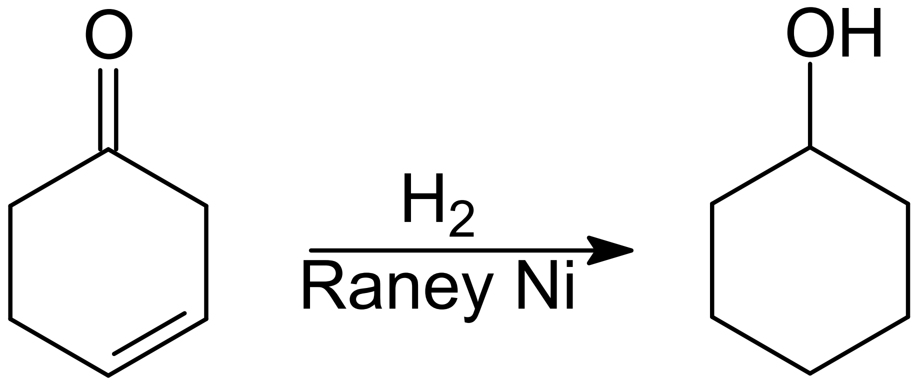
Lithium Aluminum Hydride



aldehyde or ketone

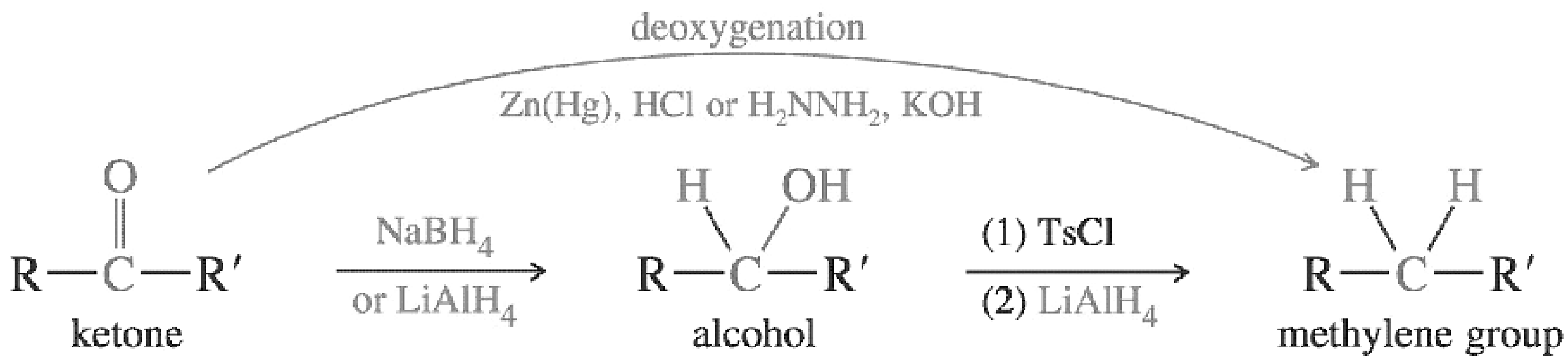
- $LiAlH_4$ can reduce any carbonyl because it is a very strong reducing agent.
- Difficult to handle.

8. Catalytic Hydrogenation



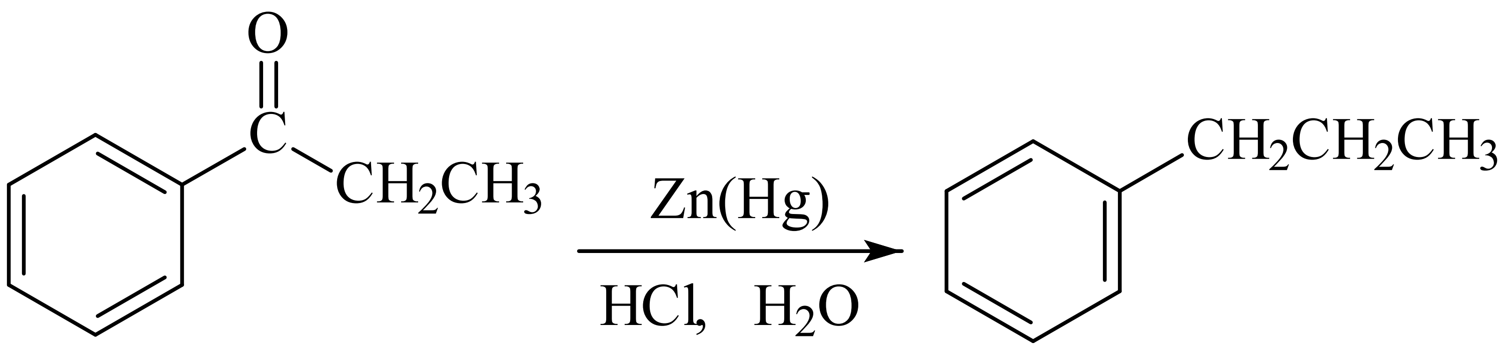
- Widely used in industry.
- Raney nickel is finely divided Ni powder saturated with hydrogen gas.
- It will attack the alkene first, then the carbonyl.

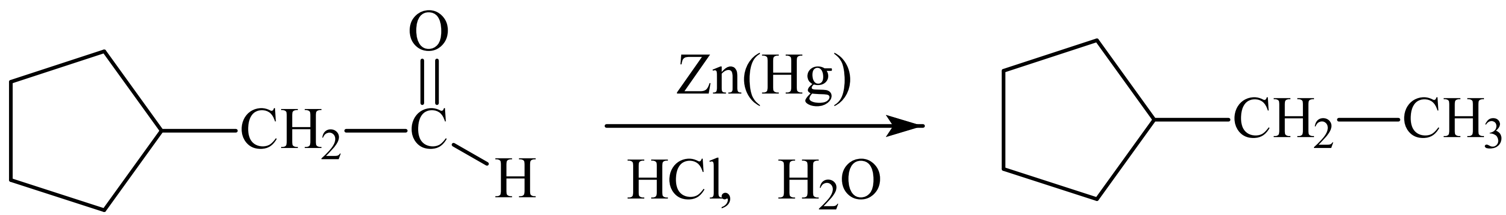
9. Deoxygenation of Ketones and Aldehydes



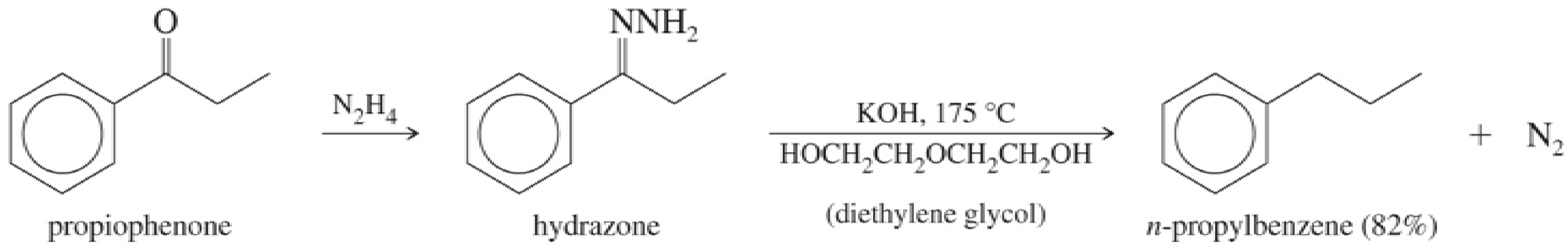
- The Clemmensen reduction or the Wolff–Kishner reduction can be used to deoxygenate ketones and aldehydes.

10. Clemmensen Reduction





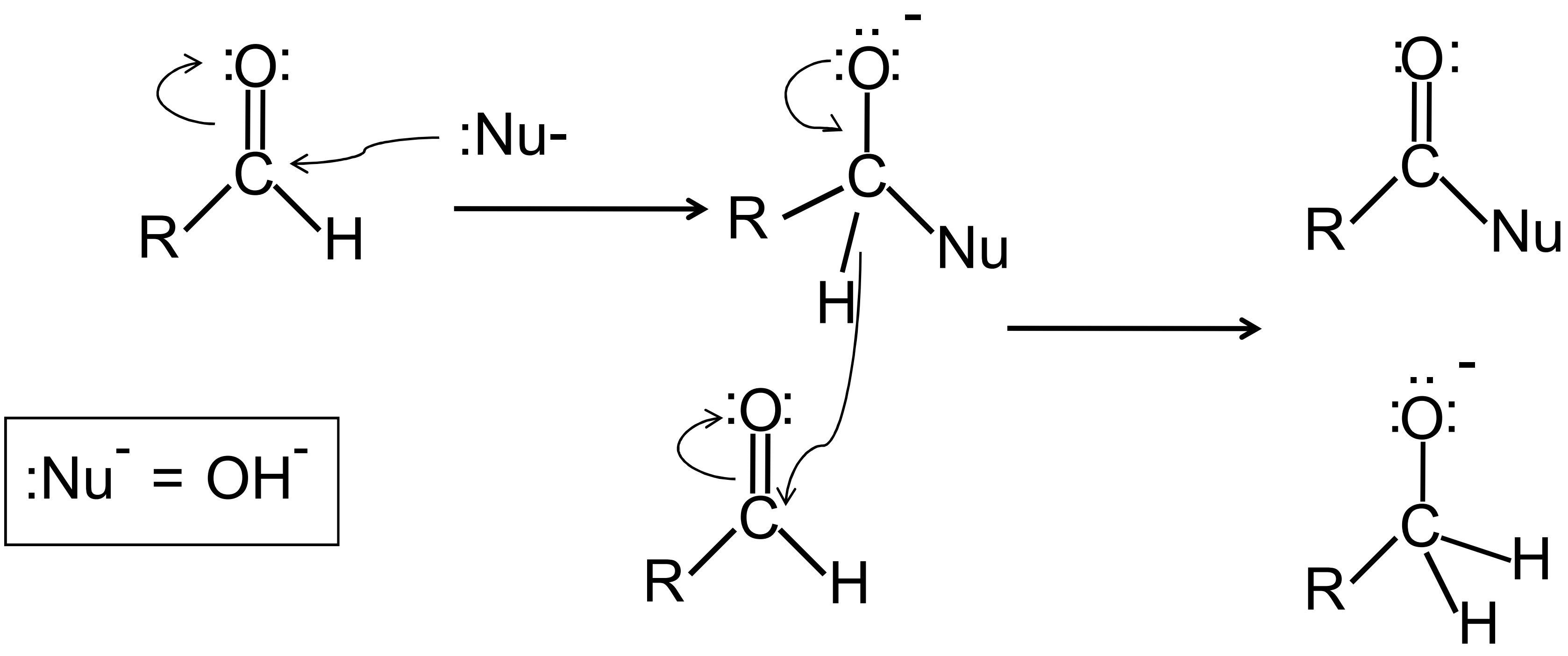
11. Wolff–Kishner Reduction



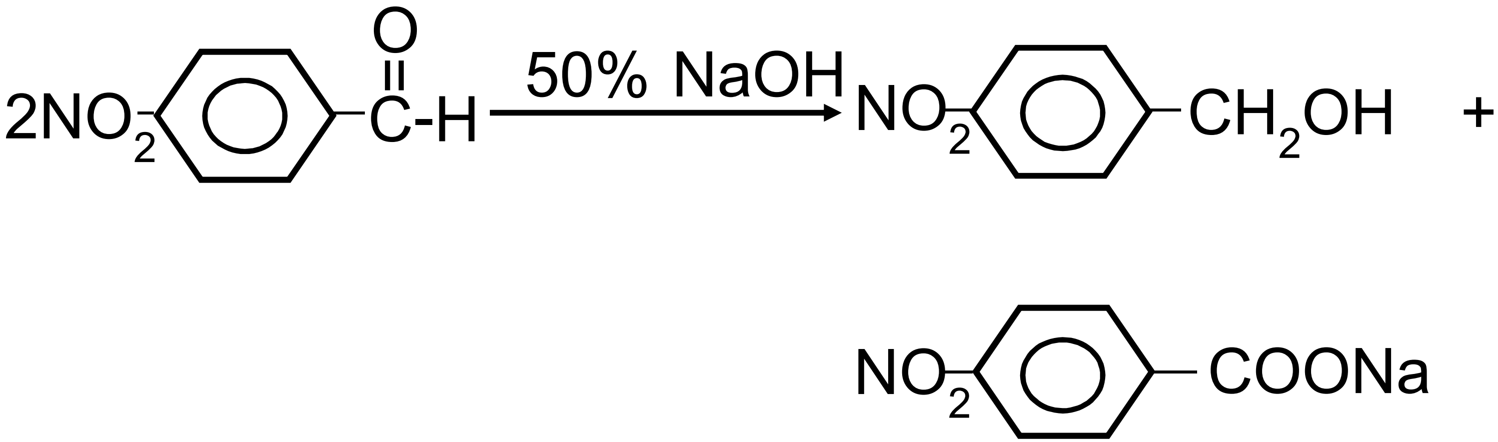
- Forms hydrazone, then heat with strong base like KOH or potassium *tert*-butoxide.
- Use a high-boiling solvent: ethylene glycol, diethylene glycol, or DMSO.
- A molecule of nitrogen is lost in the last steps of the reaction.

12. Cannizzaro reaction

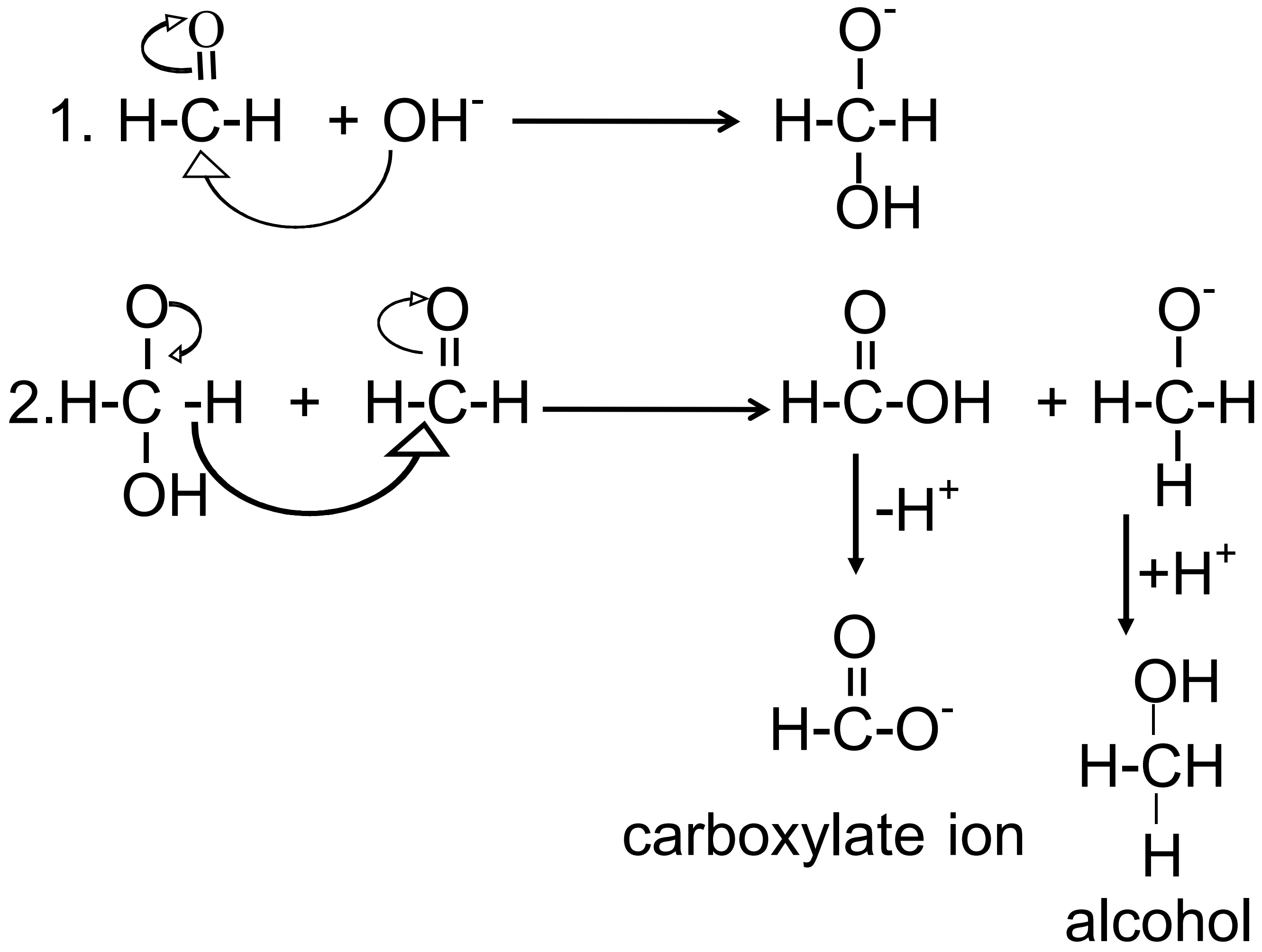
แอลดีไฮด์ที่ไม่มี α-hydrogen ทำปฏิกิริยากับเบสแก่เข้มข้น ให้ carboxylate ion และ alcohol ที่สมนัยกัน



$$2\,H\text{-}\overset{\displaystyle O}{\overset{\|}{C}}\text{-}H \xrightarrow{50\%\ NaOH} CH_3OH + HCOONa$$



การเกิดปฏิกิริยา

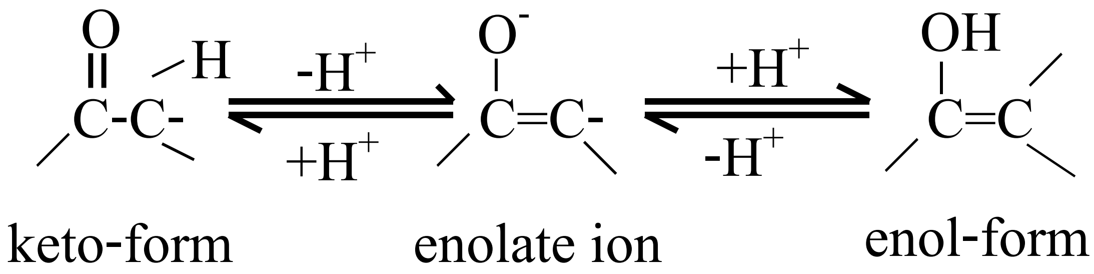


13. Enolate reaction

เป็นปฏิกิริยาที่ α-carbon กับ carbonyl group

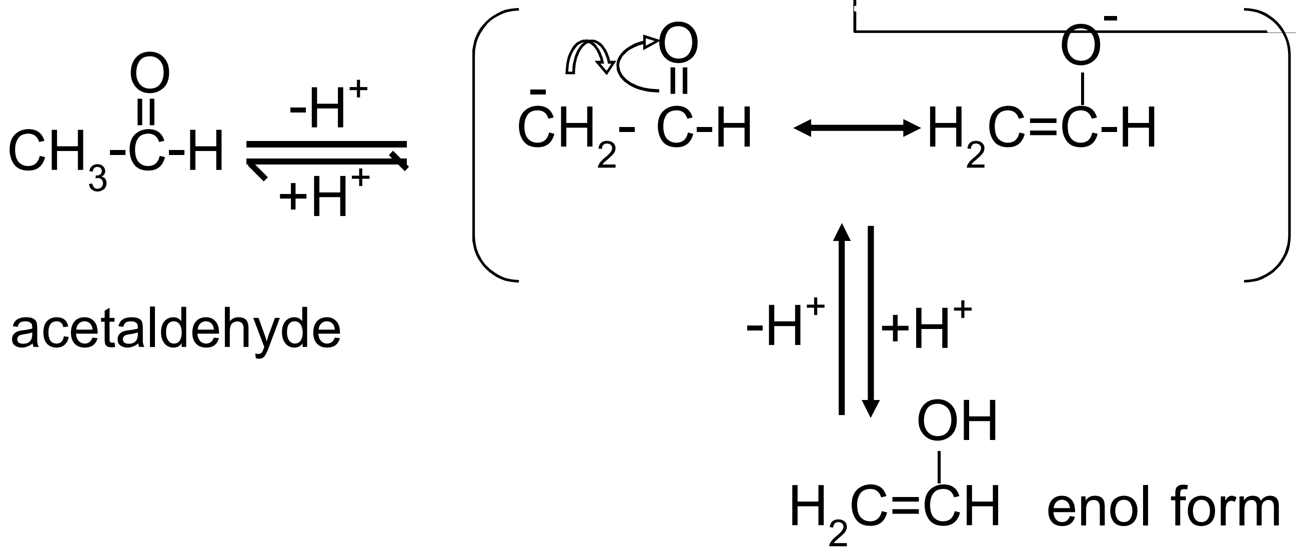
13.1 Keto-enol equilibrium

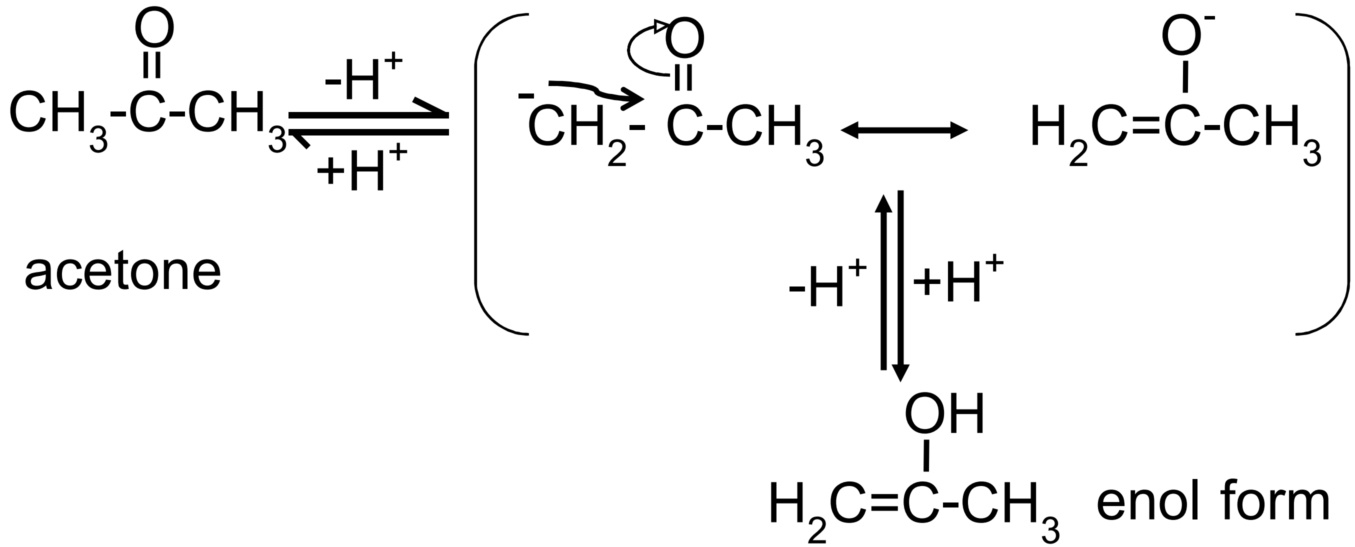
ในสารประกอบ carbonyl ที่มี α-H พบว่า α-H นี้มีสภาพกรดสูง pKa ≈19-20

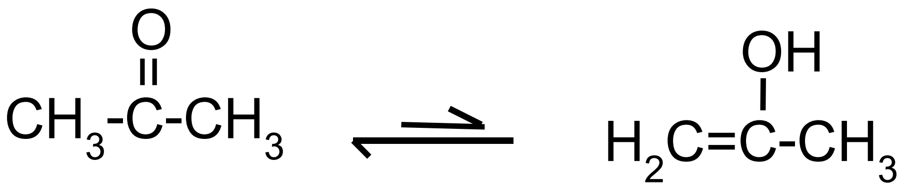


keto-enol tautomerism

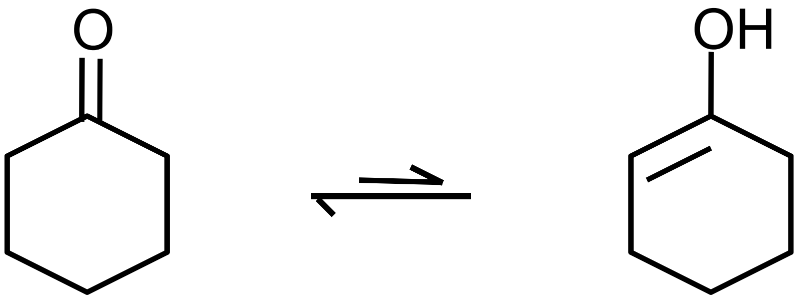
H-atom หลุดเป็น H^+ และประจุลบที่ α–carbon ซึ่งสามารถ delocalize ทำให้เกิด resonance structure ที่เรียกว่า <u>enolate anion</u>


CH3-C(=O)-H
-H+
+H+
acetaldehyde
CH2- C-H
H2C=C-H
O-
-H+
+H+
OH
H2C=CH enol form

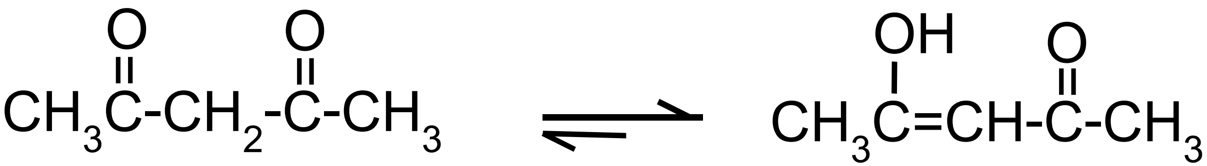

CH3-C(=O)-CH3
-H+
+H+
acetone
CH2- C-CH3
H2C=C-CH3
O-
-H+
+H+
OH
H2C=C-CH3 enol form



Acetone >99% enol form 0.00015%



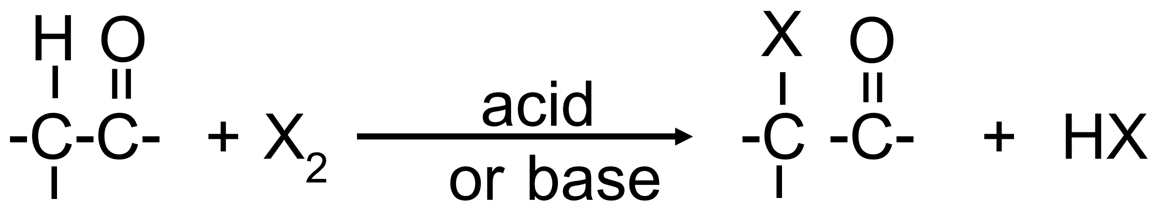
Cyclohexanone 98.8% enol form 1.2%



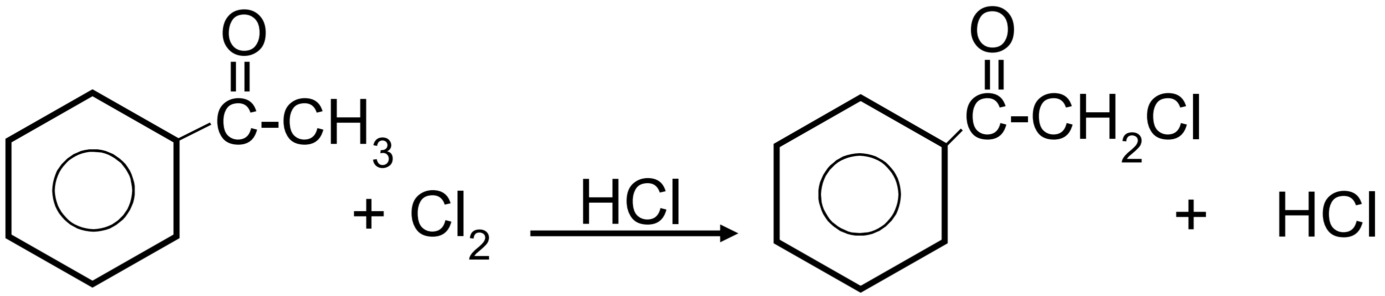
Pentane-2,4-dione 24% enol form 76%

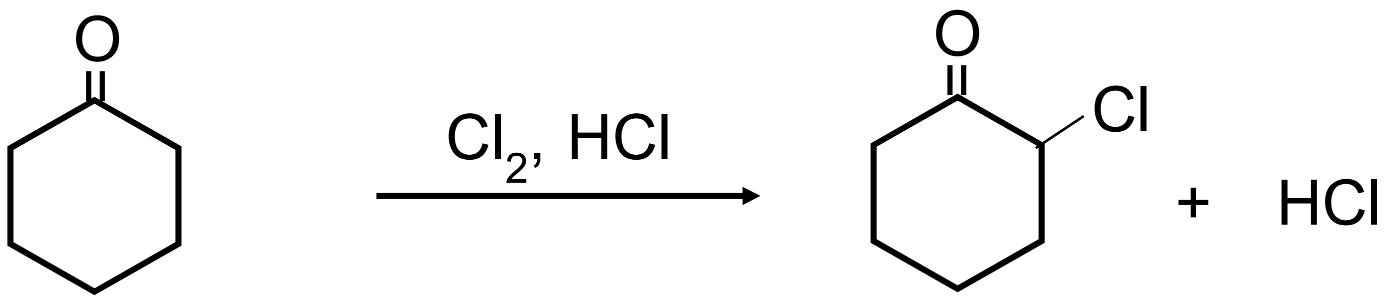
13.2 Halogenation

แอลดีไฮด์หรือคีโตนที่มี α-hydrogen ทำปฏิกิริยากับแฮโลเจนในสารละลายกรด/ด่าง โดยแฮโลเจนแทนที่ไฮโดรเจนได้ผลิตภัณฑ์เป็น α-haloaldehyde หรือ α-haloketone



$X_2 = Cl_2, Br_2, I_2$





cyclohexanone

2-chlorocyclohexanone

แอลดีไฮด์หรือคีโตน ที่มีหมู่ acetyl, $CH_3-\overset{\overset{O}{\|}}{C}-$ **ในโมเลกุลทำปฏิกิริยากับ** X_2 **ในสารละลายเบส ให้กรดคารุบอกซิลิก และ haloform เรียกว่า haloform test**

I_2 / KI และ NaOH ⟶ iodoform test

$$R-\overset{\overset{O}{\|}}{C}-CH_3 + I_2 / KI \xrightarrow{NaOH} CH_3I + R-\overset{\overset{O}{\|}}{C}-O^-$$

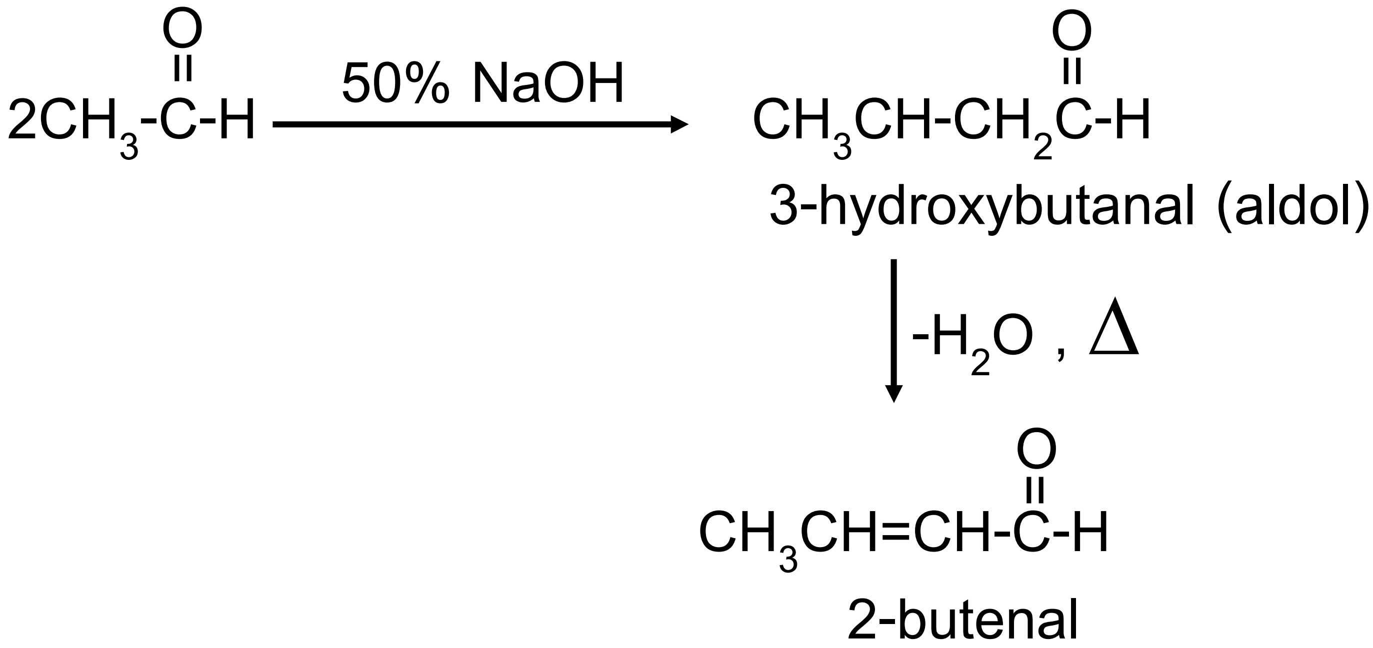
$$1.\ R-\overset{\overset{O}{\|}}{C}-CH_3 + 3I_2 + 3NaOH \longrightarrow R-\overset{\overset{O}{\|}}{C}-CI_3 + 3I^- + 3H_2O$$

$$2.\ R-\overset{\overset{O}{\|}}{C}-CI_3 + NaOH \longrightarrow R-\overset{\overset{O}{\|}}{C}-O^- + CHI_3\downarrow$$

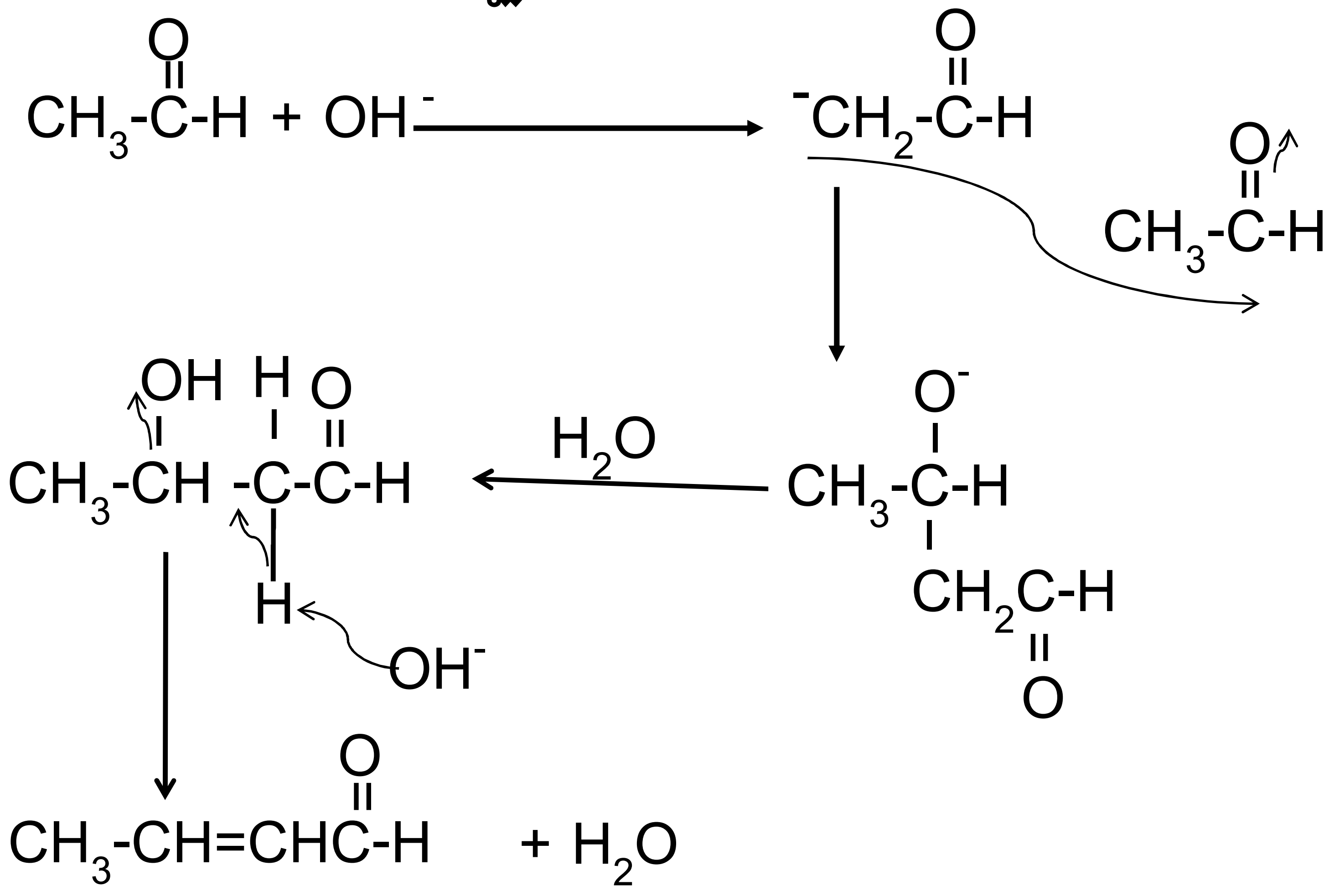
ตะกอนสีเหลือง

13.3 Aldol condensation

แอลดีไฮด์ที่มี α-hydrogen ทำปฏิกิริยากับเบสแก่เข้มข้น ให้ β-hydroxy aldehyde เรียกว่า aldol ซึ่งจะสูญเสียน้ำได้ง่ายให้ alkene ชนิด α,β-unsaturated aldehyde

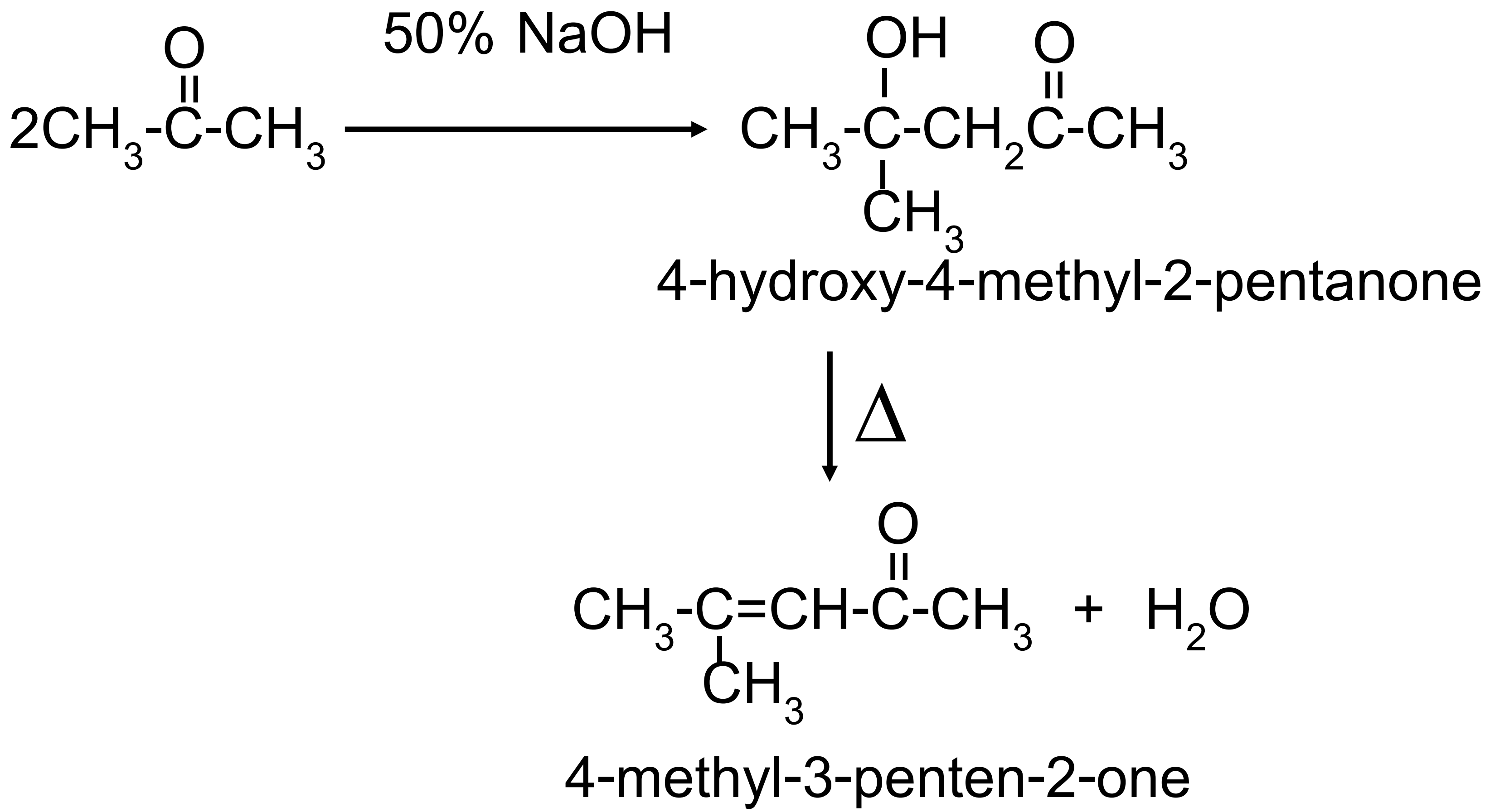


การเกิดปฏิกิริยา



-unsaturated aldehyde

ส่วน ketone ทำปฏิกิริยากับเบสแก่เข้มข้นให้ β-hydroxy ketone ซึ่งสูญเสียน้ำได้ง่ายให้ α,β-unsaturated ketone



การทดสอบแอลดีไฮด์และคีโตน

1. การละลาย

Aldehyde , Ketone เป็นโมเลกุลมีขั้วแต่ไม่มากเท่ากับ alcohol ดังนั้นโมเลกุลขนาดเล็กละลายน้ำได้ แต่ขนาดใหญ่การละลายลดลง

2. ทดสอบอนุพันธ์ของแอมโมเนีย

→ 2,4-dinitrophenylhydrazine → ตะกอนเหลือง, ส้ม, (แดง)

→ semicarbazide → ตะกอนขาว (semicarbazone)

3. ทดสอบ aldehyde ด้วย Oxidizing agent

→ Tollen's reagent ให้ silver mirror (Ag)

→ Fehling's reagent ให้ ตะกอนสีแดงอิฐ (Cu_2O)