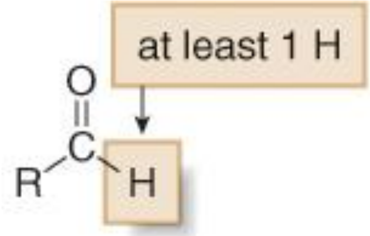
Carbonyl Compounds

Introduction

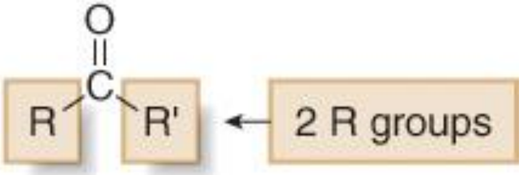
Introduction

Two broad classes of compounds contain the carbonyl group:

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

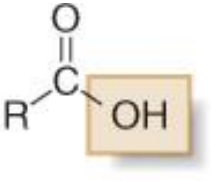


aldehyde

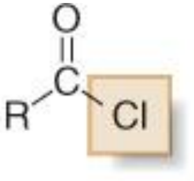


ketone

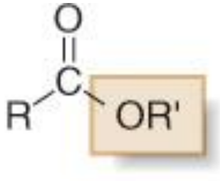
[2] Compounds that contain an eteroatom (N, O, S, Cl) bonded to the carbonyl



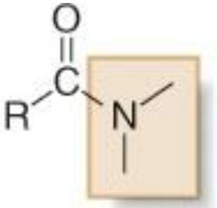
carboxylic acid



acid chloride



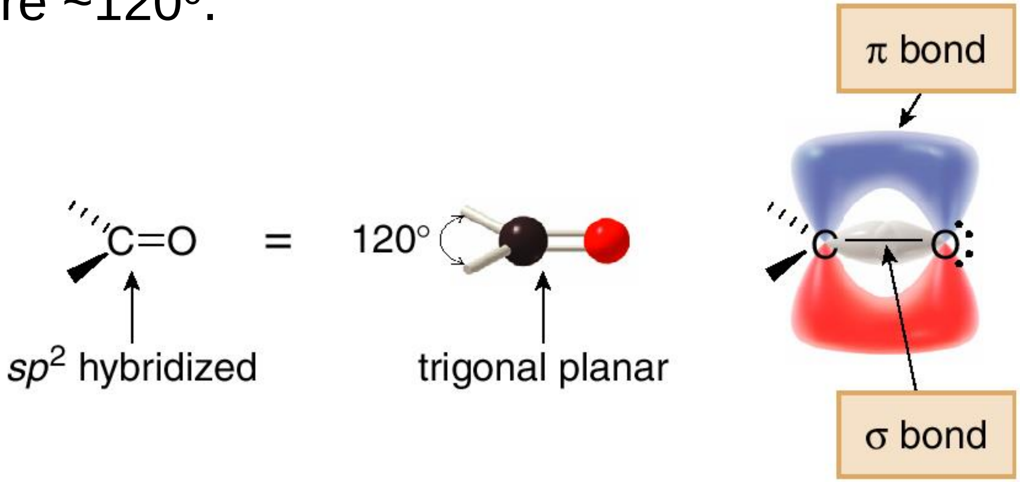
ester



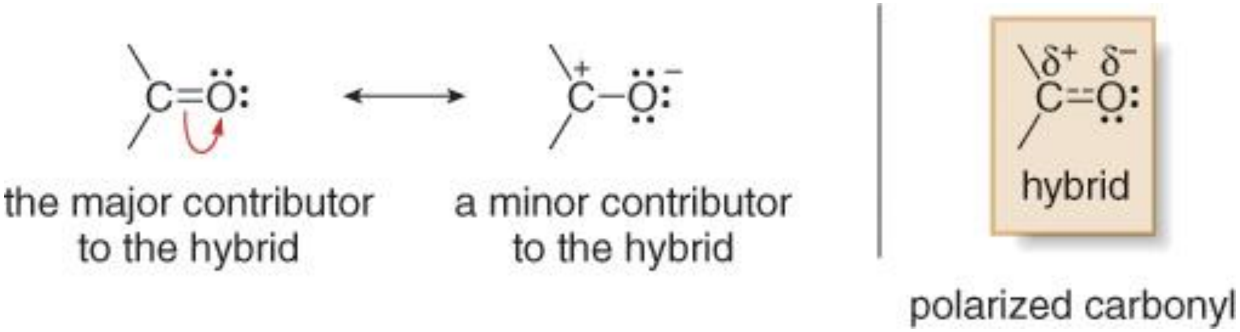
amide

Introduction

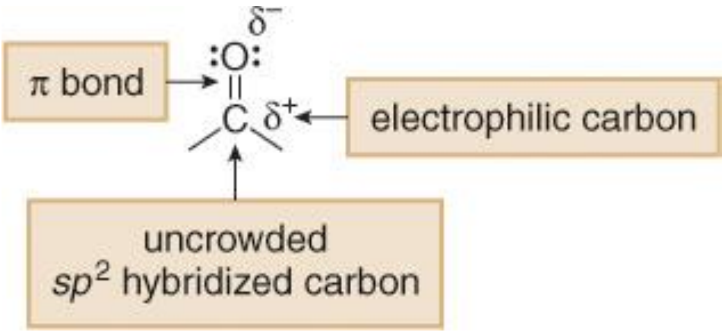
- Carbonyl carbons are *sp*^{2} hybridized, trigonal planar, and have bond angles that are ~120^0.



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



General Reactions of Carbonyl Compounds



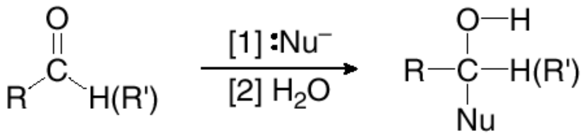
π bond

electrophilic carbon

uncrowded
*sp*² hybridized carbon

- Aldehydes and ketones undergo nucleophilic addition.

Nucleophilic addition—
General reaction

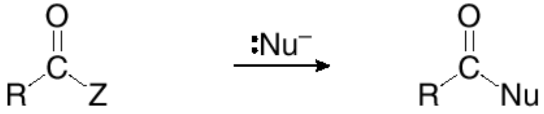


$$RC(=O)H(R') \xrightarrow[\text{[2] } H_2O]{\text{[1] :Nu}^-} R-C(OH)(Nu)-H(R')$$

H and Nu
are added.

- Carbonyl compounds that contain leaving groups undergo nucleophilic substitution.

Nucleophilic substitution—
General reaction

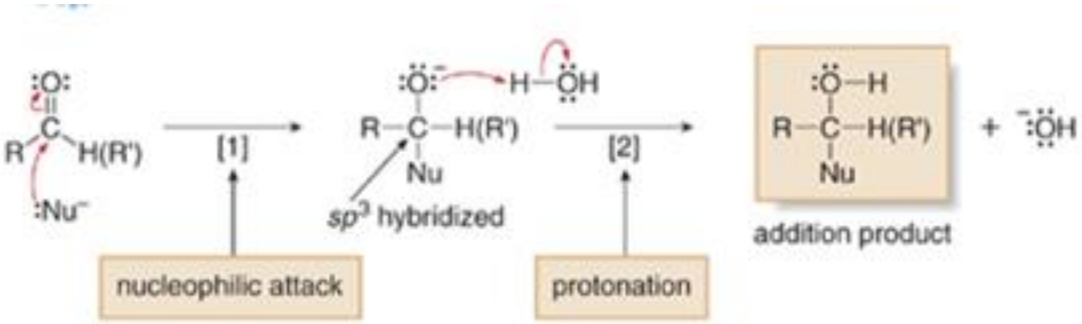


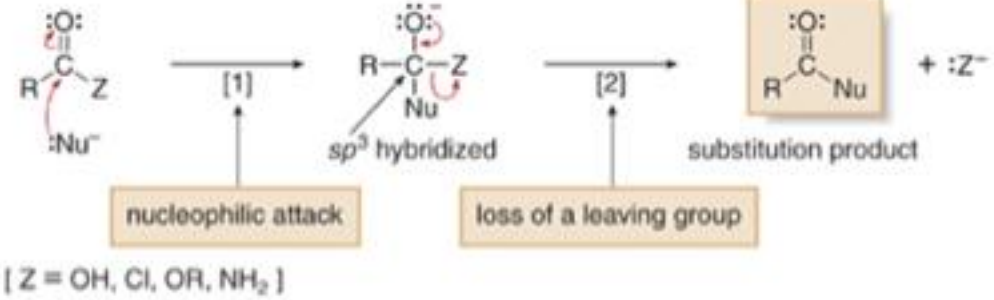
$$RC(=O)Z \xrightarrow{:Nu^-} RC(=O)Nu$$

$Z = OH, Cl, OR, NH_2$

Nu replaces Z.

General Reactions of Carbonyl Compounds





Aldehydes and Ketones

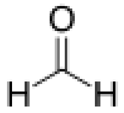
Chapter 19

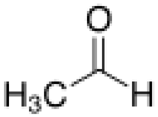
Organic Chemistry, *8th Edition*

John McMurry

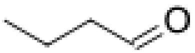
Nomenclature of Aldehydes

- Find the longest chain containing the CHO group, and change the –*e* ending of the parent alkane to the suffix *–al*. If the CHO group is bonded to a ring, name the ring and add the suffix *–carbaldehyde*.
- A common name for an aldehyde is formed by taking the common parent name and adding the suffix –*aldehyde*.


methanal
(formaldehyde)

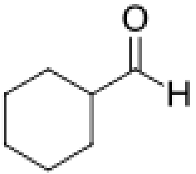

ethanal
(acetaldehyde)

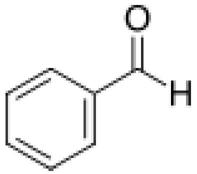

propanal
(propionald.)

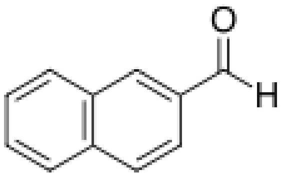

butanal
(butyraldehyde)

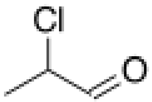

pentanal
(valeraldehyde)

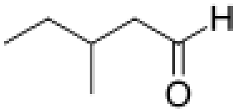

hexanal
(caproic aldehyde)

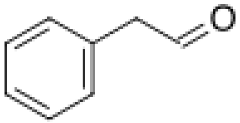

cyclohexanecarbaldehyde


benezenecarbaldehyde
(benzaldehyde)

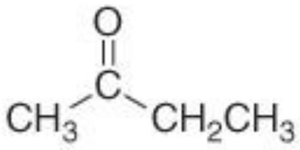

2-naphthalenecarbaldehyde


2-chloropropanal

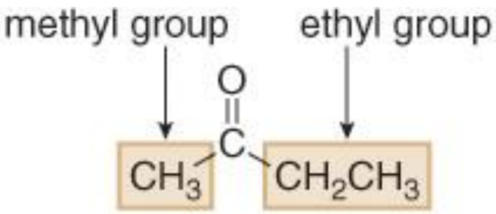

3-methylhexanal


phenylethanal

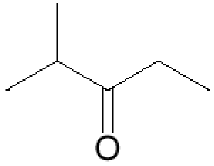
Nomenclature of Ketones



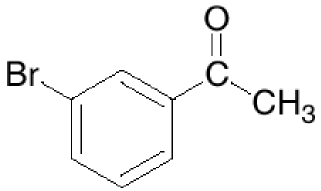
IUPAC name: **2-butanone**



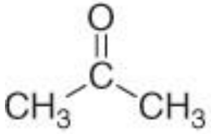
Common name: **ethyl methyl ketone**



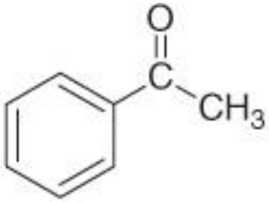
IUPAC name: 2-methyl-3-pentanone
Common name: ethyl isopropyl ketone



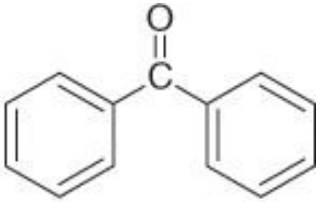
m-bromoacetophenone
or
3-bromoacetophenone



acetone

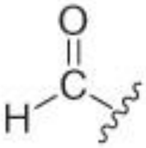


acetophenone

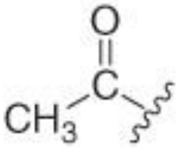


benzophenone

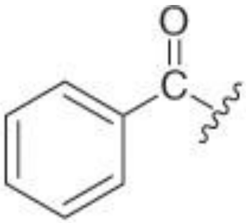
Nomenclature of Aldehydes and Ketones



formyl group

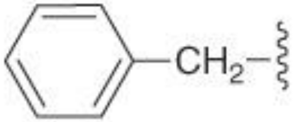


acetyl group



benzoyl group

Do not confuse a **benzyl** group with a **benzoyl** group.



benzy*l* group

Physical Properties

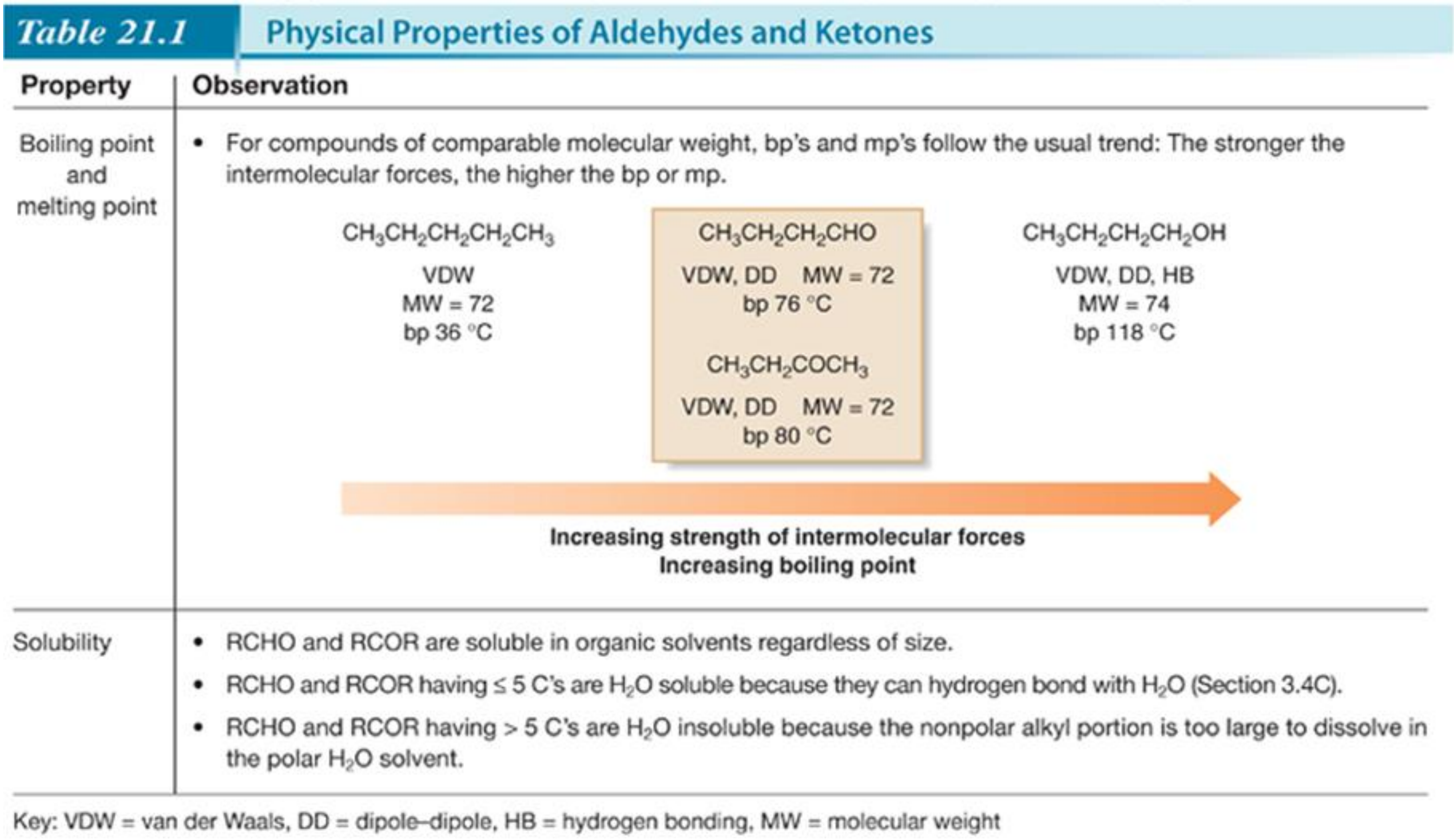
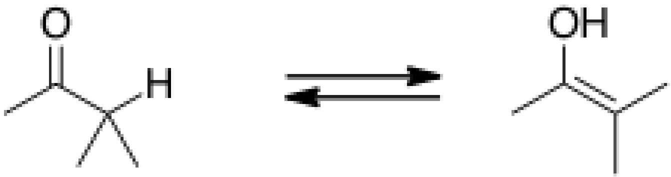


Table 21.1 Physical Properties of Aldehydes and Ketones

Property	Observation
Boiling point and melting point	• For compounds of comparable molecular weight, bp's and mp's follow the usual trend: The stronger the intermolecular forces, the higher the bp or mp. $CH_3CH_2CH_2CH_2CH_3$ VDW MW = 72 bp 36 °C $CH_3CH_2CH_2CHO$ VDW, DD MW = 72 bp 76 °C $CH_3CH_2COCH_3$ VDW, DD MW = 72 bp 80 °C $CH_3CH_2CH_2CH_2OH$ VDW, DD, HB MW = 74 bp 118 °C **Increasing strength of intermolecular forces** **Increasing boiling point**
Solubility	• RCHO and RCOR are soluble in organic solvents regardless of size. • RCHO and RCOR having ≤ 5 C's are H_2O soluble because they can hydrogen bond with H_2O (Section 3.4C). • RCHO and RCOR having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent.

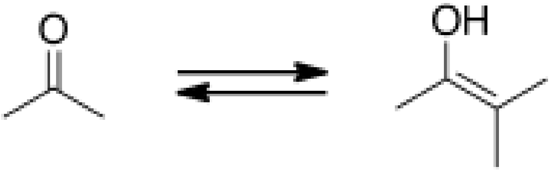
Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding, MW = molecular weight

Keto-Enol Tautomerism



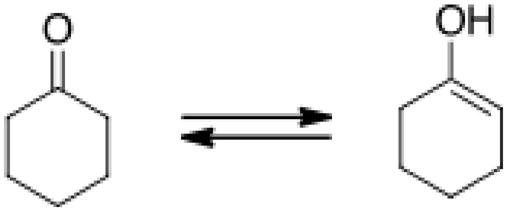
Keto tautomer

Enol tautomer



99,9999999%

0,0000001%



99,9999%

0,0001%

Interesting Aldehydes and Ketones

formaldehyde

$CH_2=O$

Billions of pounds of formaldehyde are produced annually from the oxidation of methanol. It is sold as a 37% solution called formalin which is used as a disinfectant, antiseptic, and preservative for biological specimens. It is a product of incomplete combustion of coal, and is partly responsible for the irritation caused by smoggy air.

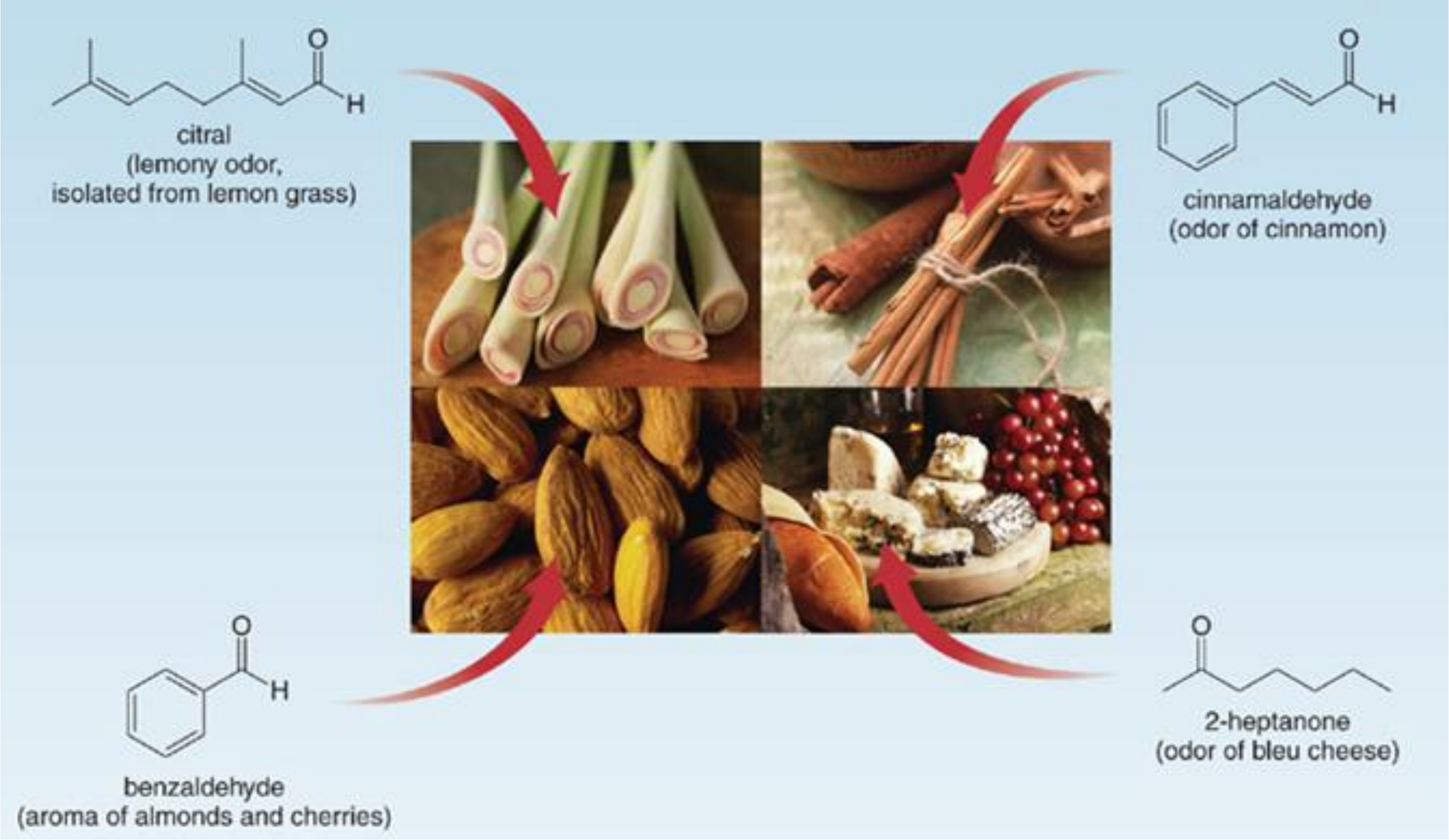
acetone

$(CH_3)_2C=O$

Acetone is an industrial solvent. It is also produced in vivo during breakdown of fatty acids. Diabetics often have unusually high levels of acetone in their blood streams.

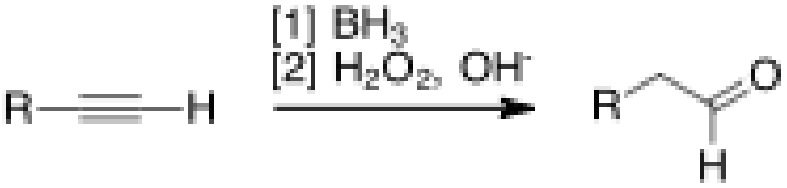
Interesting Aldehydes and Ketones

Many aldehydes and ketones with characteristic odors occur in nature.

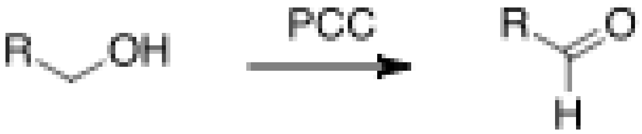


Preparation of Aldehydes

Hydration of an alkyne
(hydroboration-oxidation)



Oxidation of 1^{ry} alcohols

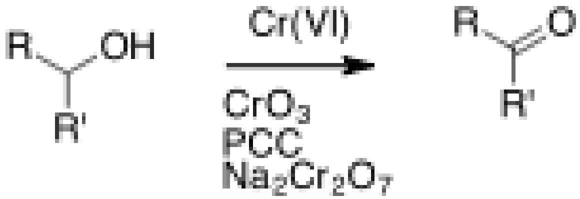


Reduction of esters and
acyl chlorides

Preparation of Ketones

Hydration of alkynes

Oxidation of 2^{ry} alcohols

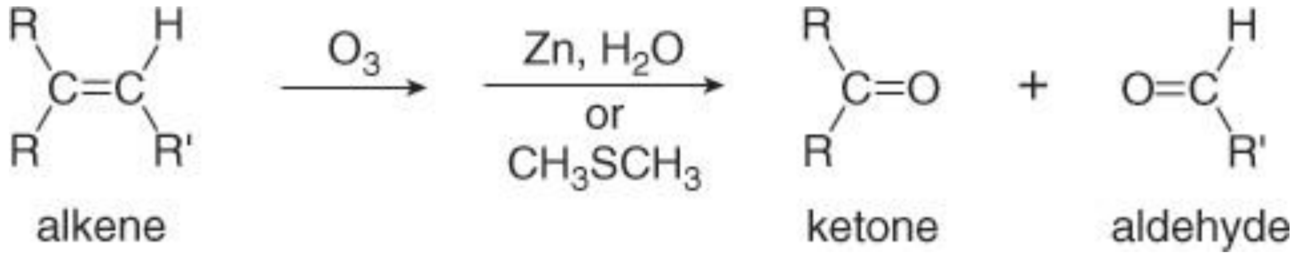


Friedel-Crafts acylation

Acylation of organocuprates

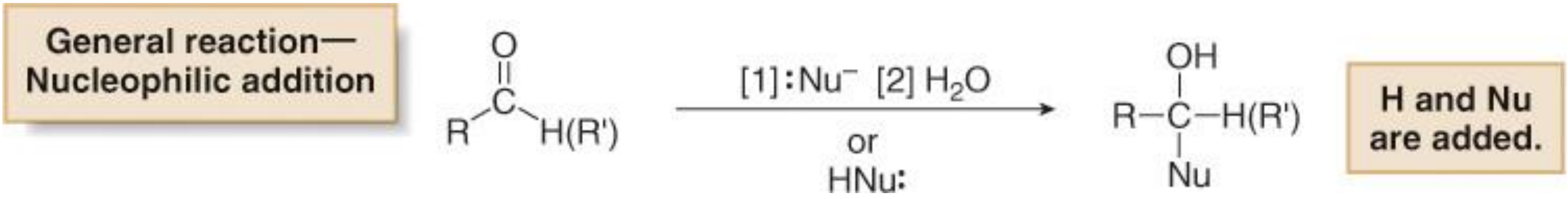
Preparation of Aldehydes and Ketones

Aldehydes and ketones are also both obtained as products of the oxidative cleavage of alkenes.



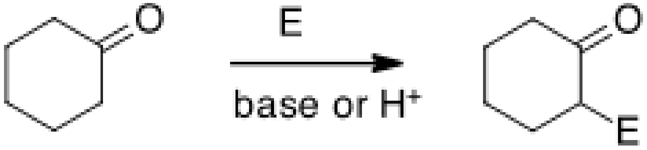
Reactions of Aldehydes and Ketones—General

[1] Nucleophilic addition

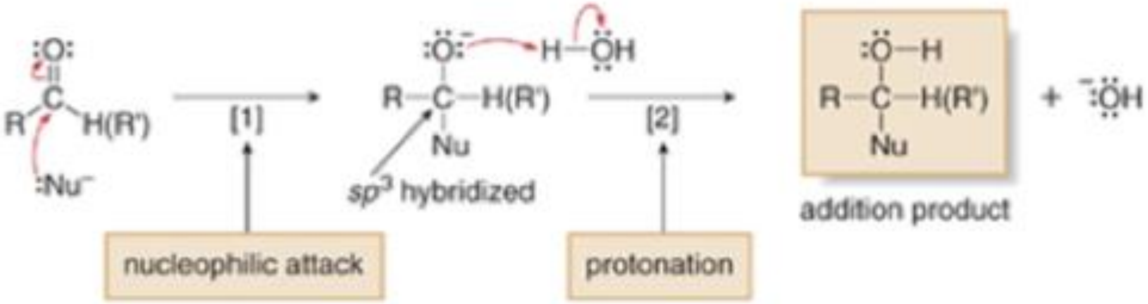


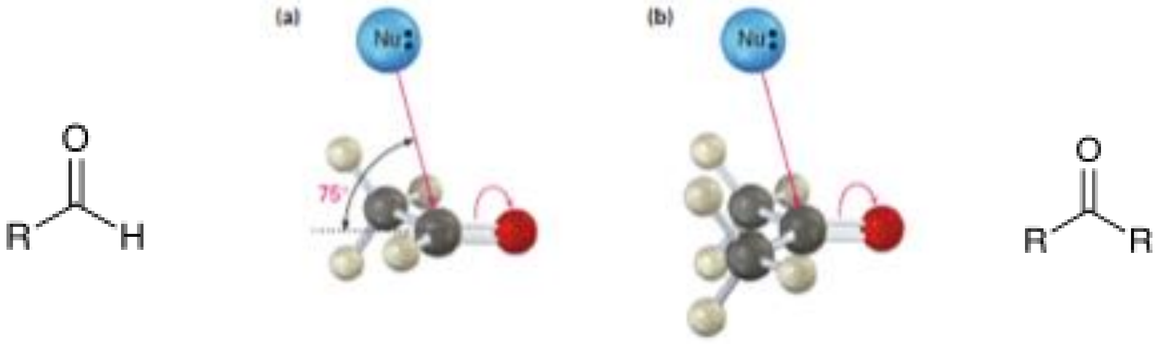
[2] Oxidation

[3] Reaction at the α carbon



Nucleophilic Addition



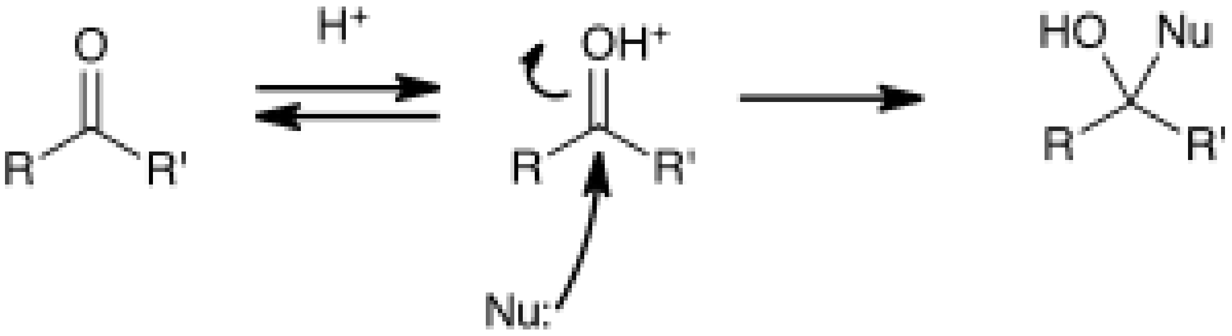


aldehyde
less crowded
more reactive

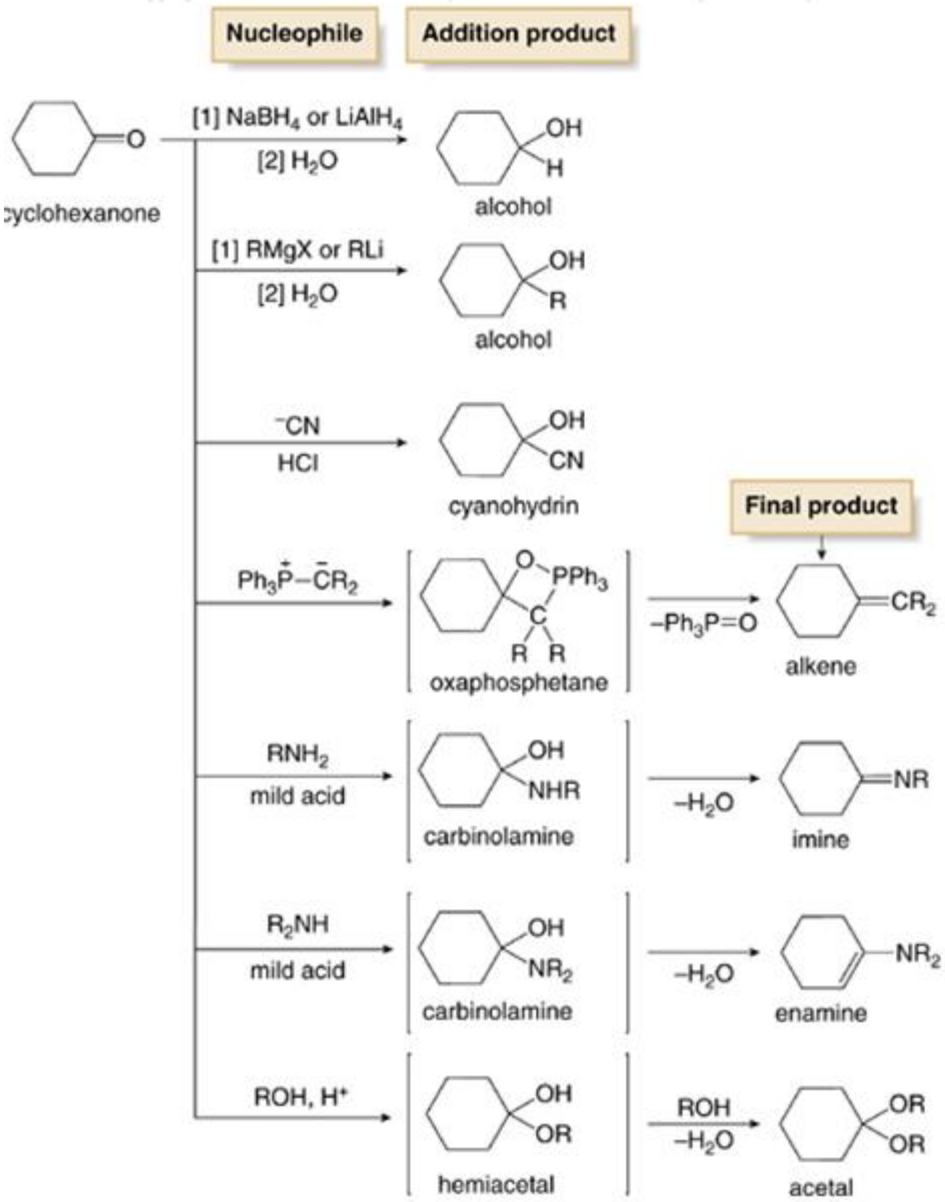
ketone
more crowded
less reactive

Acid Catalysis

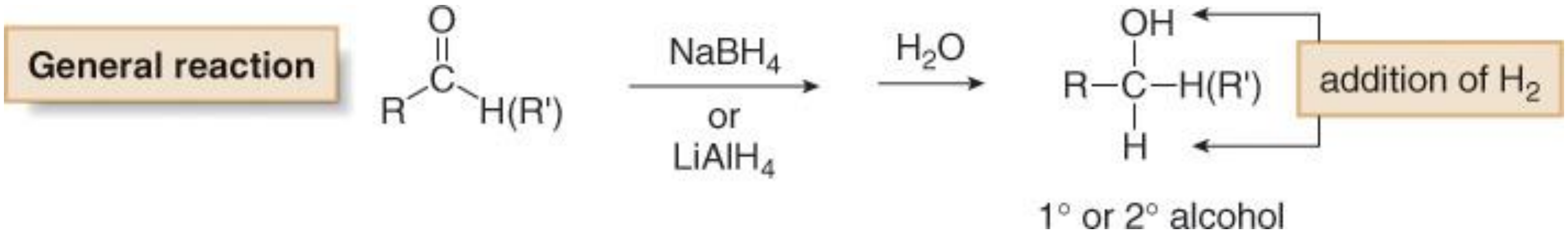
more
reactive



Nucleophilic Addition

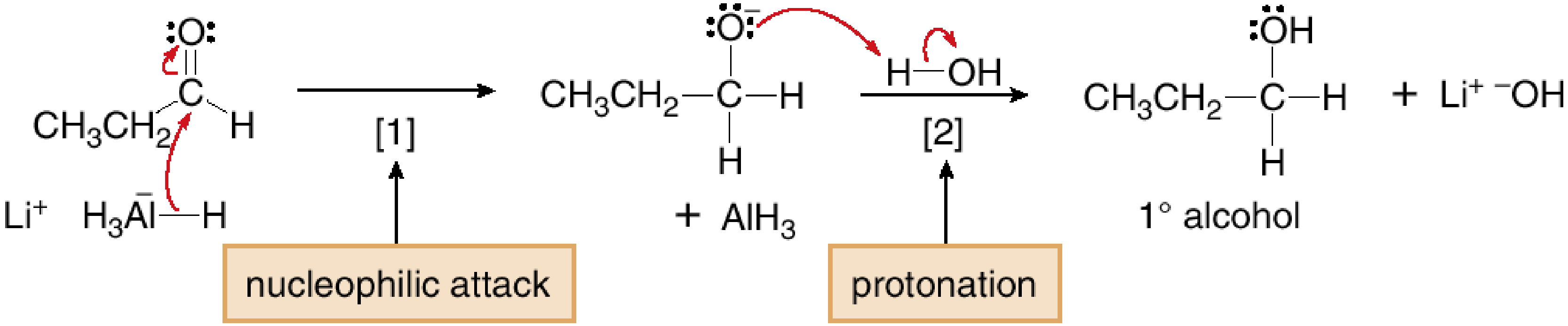


Nucleophilic Addition of H$^-$ and R$^-$ — A Review


General reaction

addition of H_2

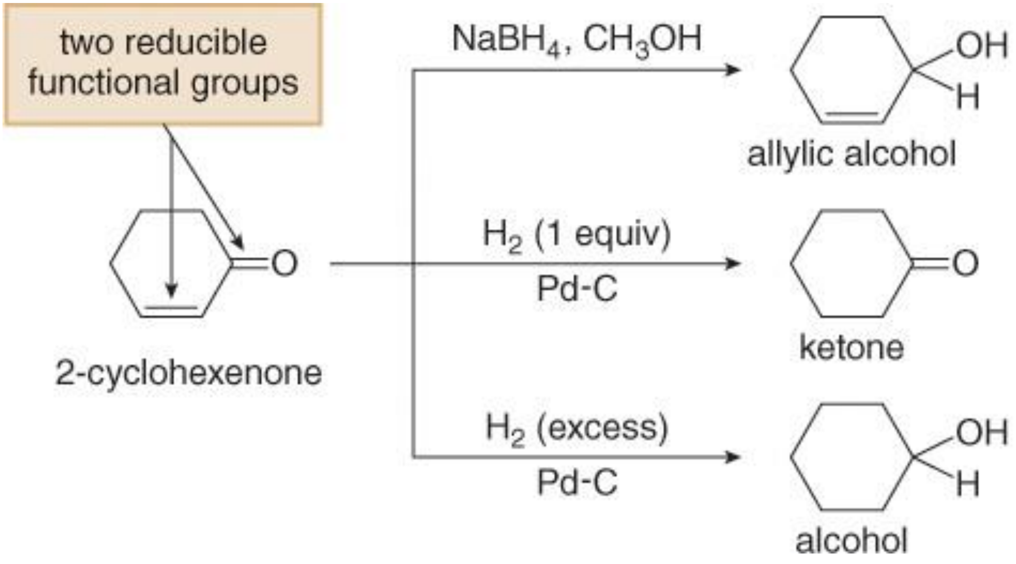
1° or 2° alcohol


nucleophilic attack

protonation

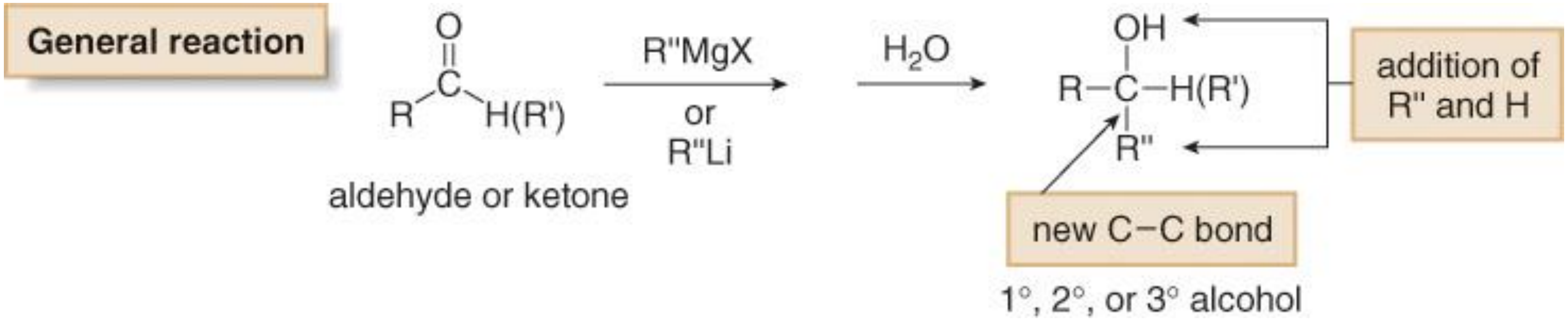
1° alcohol

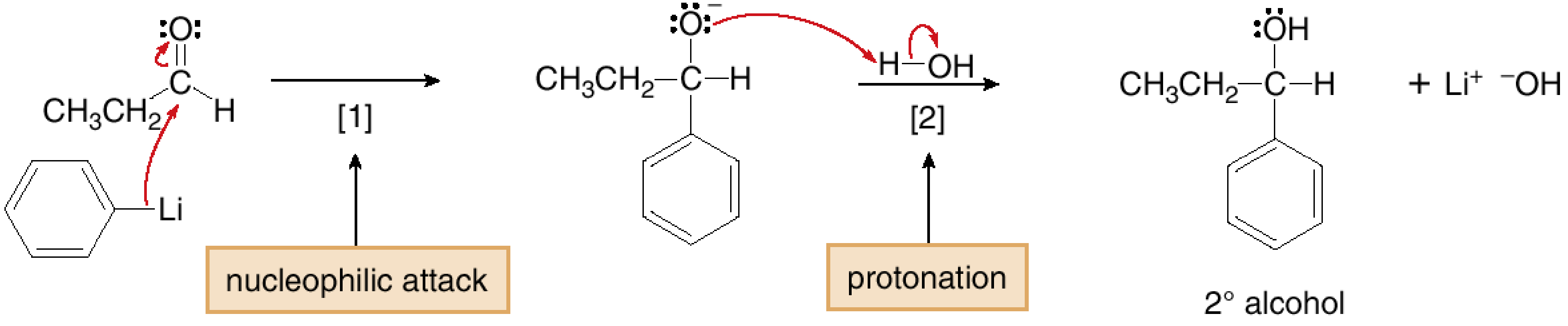
Nucleophilic Addition of H^- and R^- — A Review



- $NaBH_4$ reduces the C=O selectively to form an allylic alcohol.
- One equivalent of H_2 reduces the C=C selectively to form a ketone.
- Excess H_2 reduces both π bonds to form an alcohol.

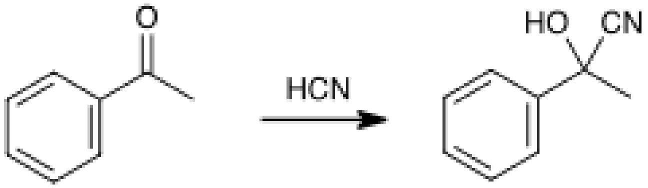
Nucleophilic Addition of H^- and R^- — A Review



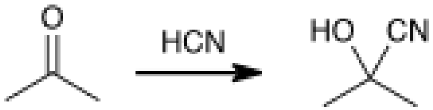


Nucleophilic Addition of CN^-

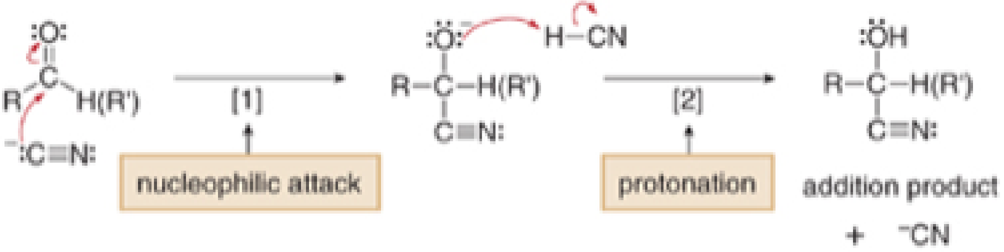
- Treatment of an aldehyde or ketone with HCN gives a cyanohydrin.



benzaldehyde cyanohydrin

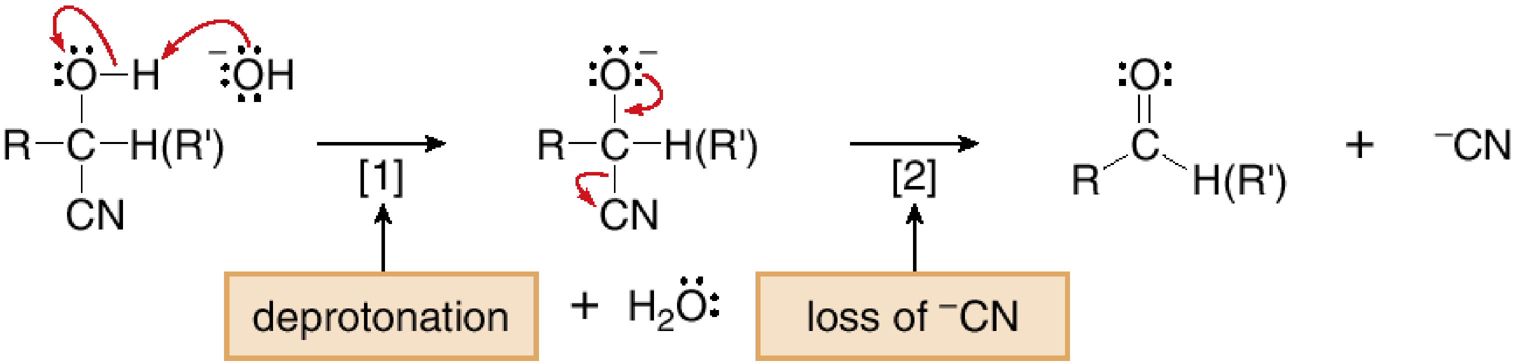


aceton cyanohydrin

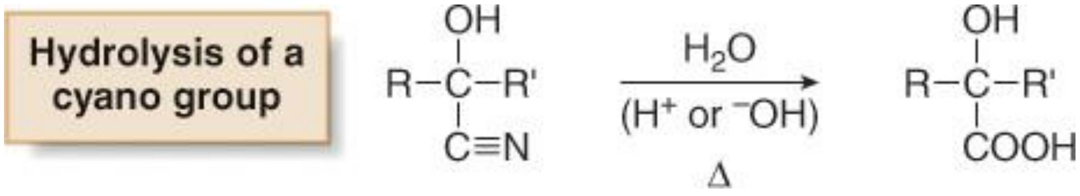


Nucleophilic Addition of CN^-

- Cyanohydrins can be reconverted to carbonyl compounds by treatment with base. This process is just the reverse of the addition of HCN: deprotonation followed by elimination of ^-CN.

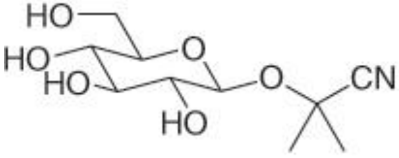


- The cyano group of a cyanohydrin is readily hydrolyzed to a carboxy group by heating with aqueous acid or base.

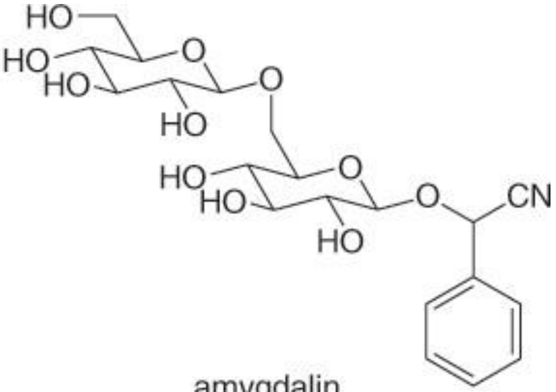


Nucleophilic Addition of CN^-

- Linamarin and Amygdalin are two naturally occurring cyanohydrin derivatives.



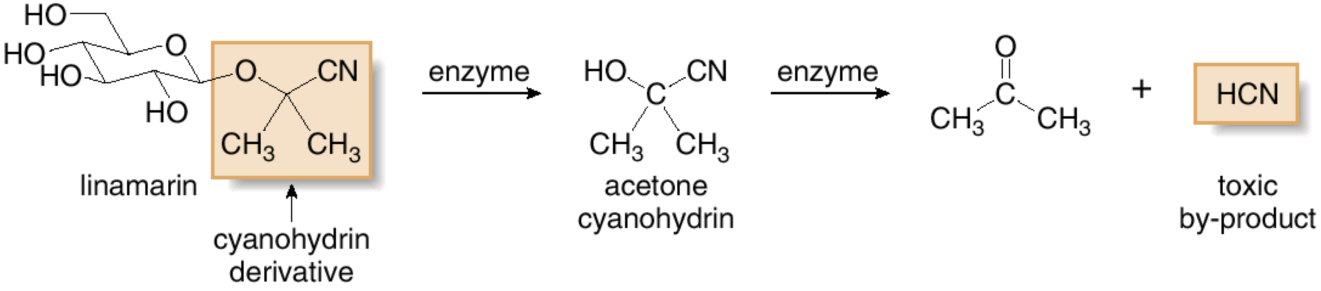
linamarin
(found in cassava root)



amygdalin
(commonly called laetrile)

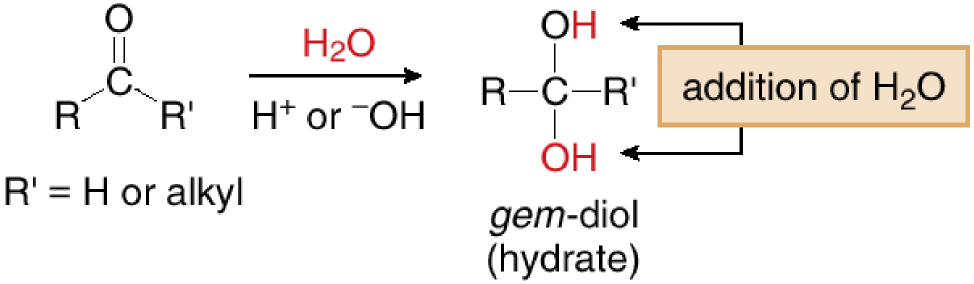
- Both compounds are toxic because they are metabolized to cyanohydrins, which are hydrolyzed to carbonyl compounds and HCN gas.

The breakdown of linamarin to HCN



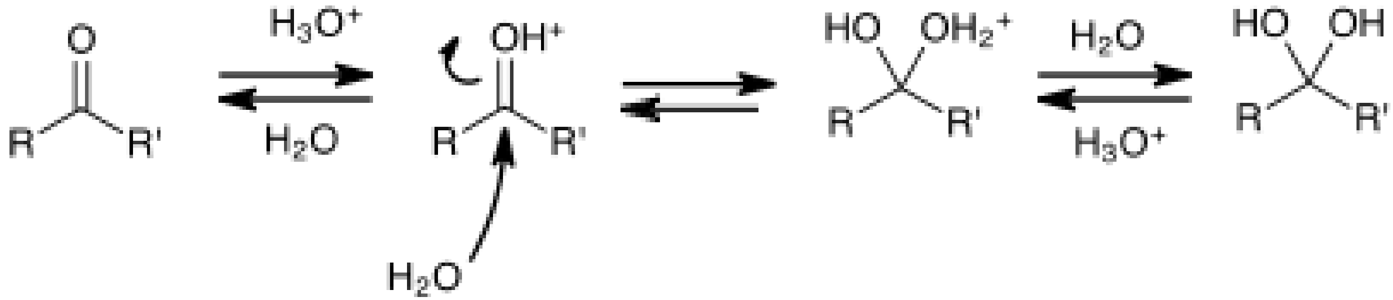
Addition of H_2O—Hydration

Nucleophilic addition of H_2O



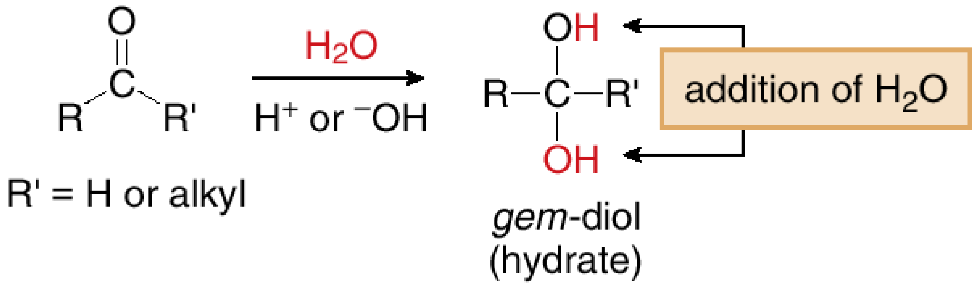
R' = H or alkyl

gem-diol
(hydrate)



Addition of H_2O—Hydration

Nucleophilic addition of H_2O



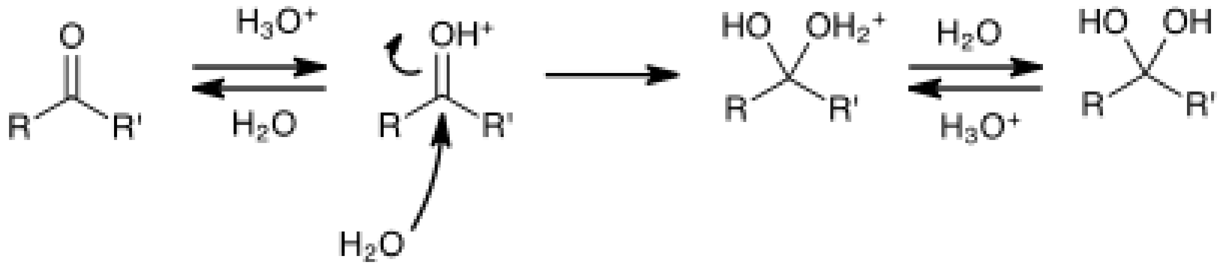
R' = H or alkyl

gem-diol
(hydrate)

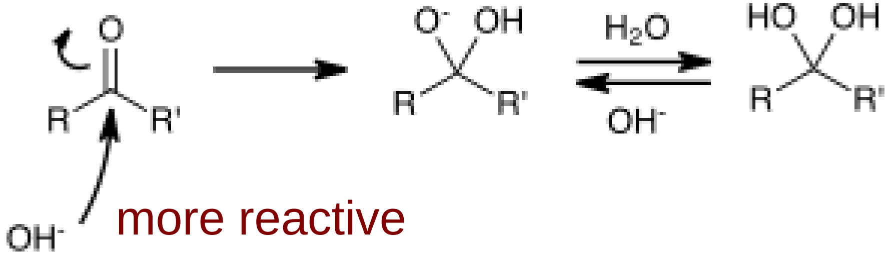
Both acid and base catalyze the addition of H_2O to the carbonyl group.

more reactive
electrophile

acid:

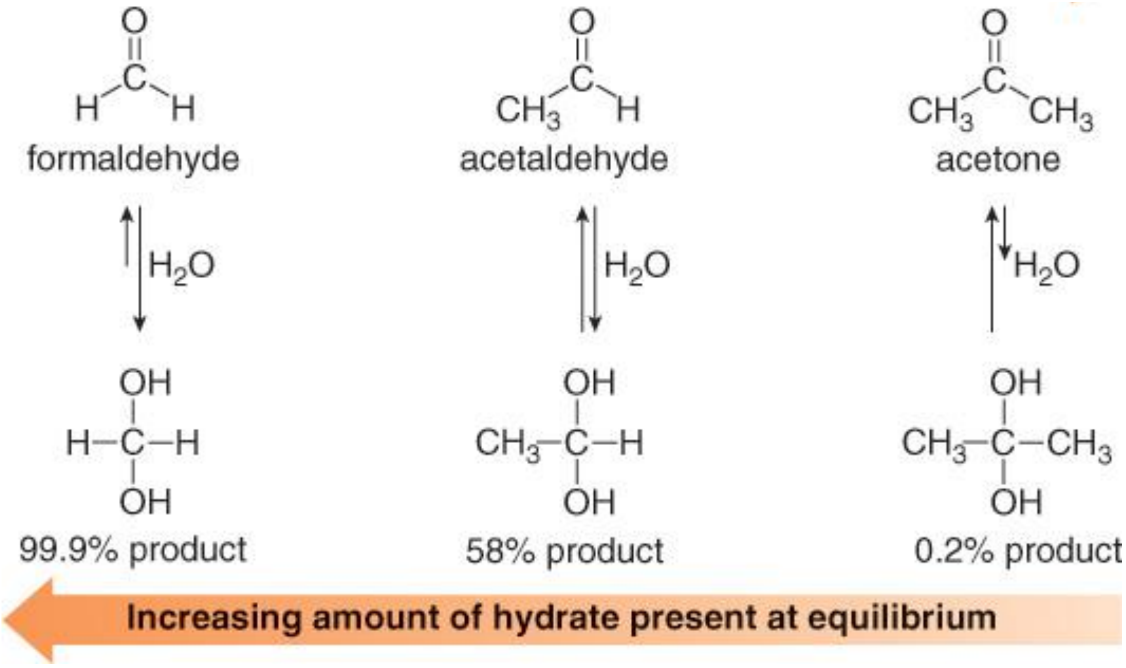


base:



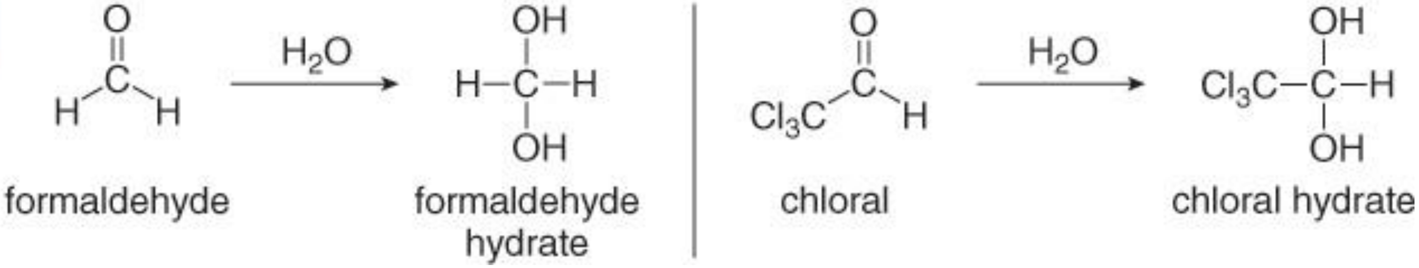
more reactive
nucleophile

Addition of H_2O—Hydration



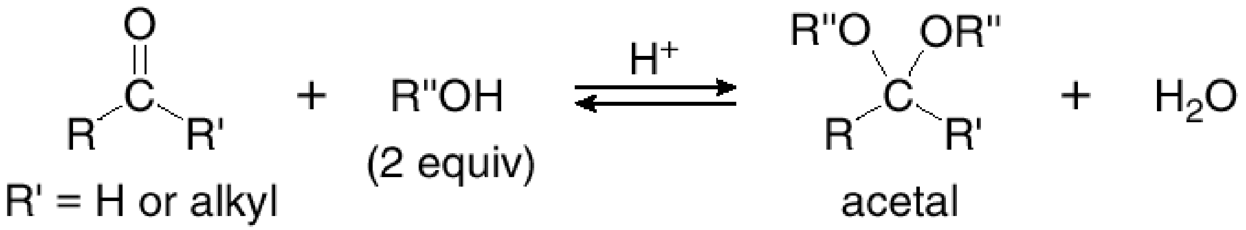
- *Gem*-diol product yields are good only when unhindered aldehydes or aldehydes with nearby electron withdrawing groups are used.

Examples

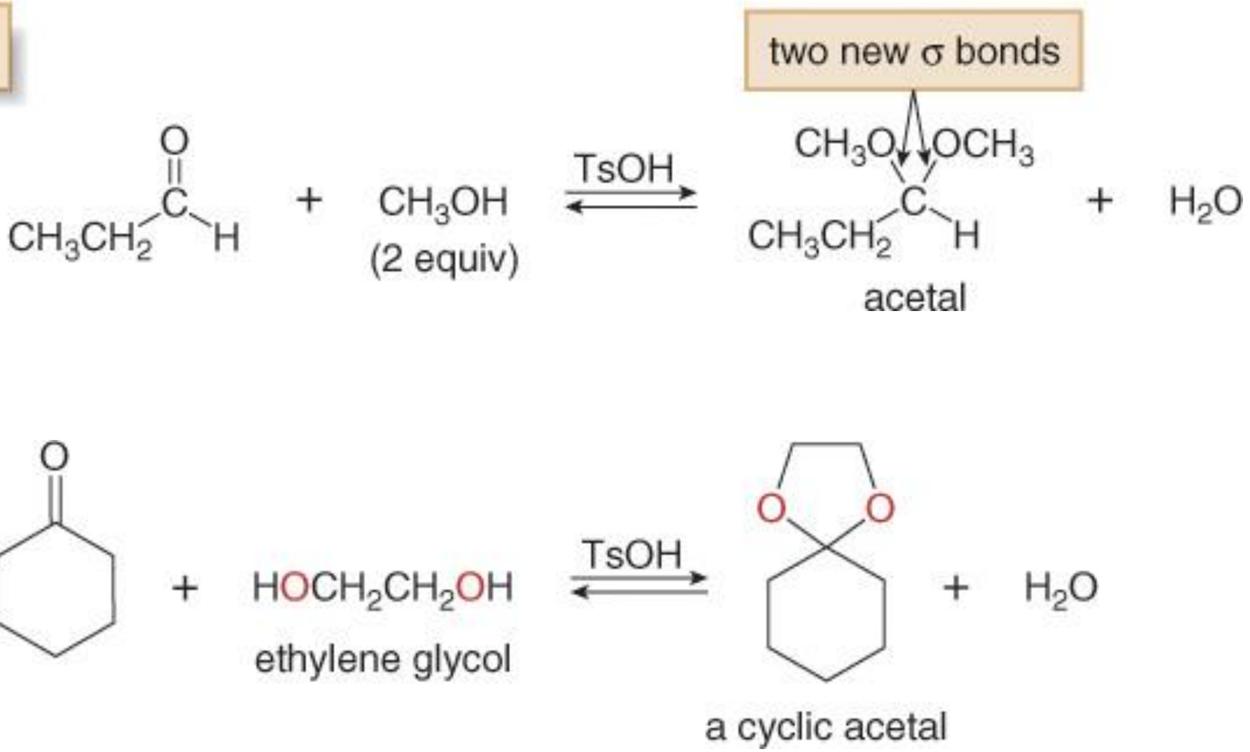


Addition of Alcohols—Acetal Formation

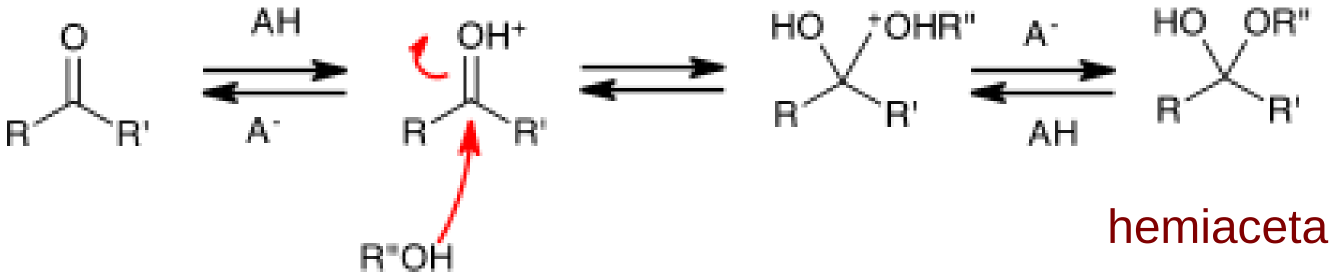
Acetal formation



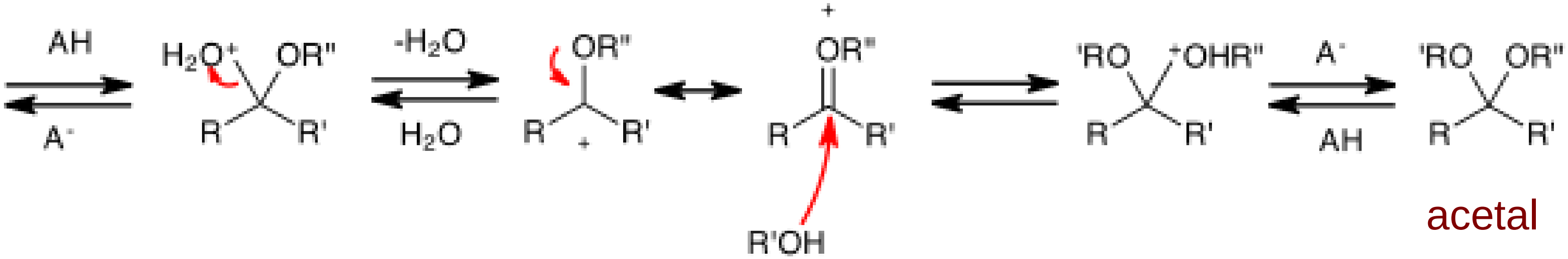
Example



Addition of Alcohols—Acetal Formation



hemiacetal

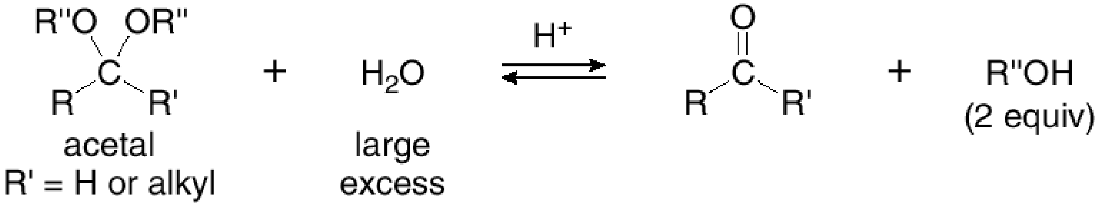


resonance stabilized carbocation

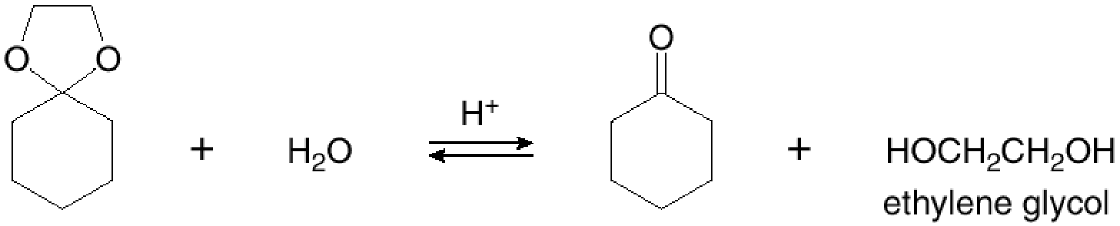
acetal

Acetal Hydrolysis

Acetal hydrolysis

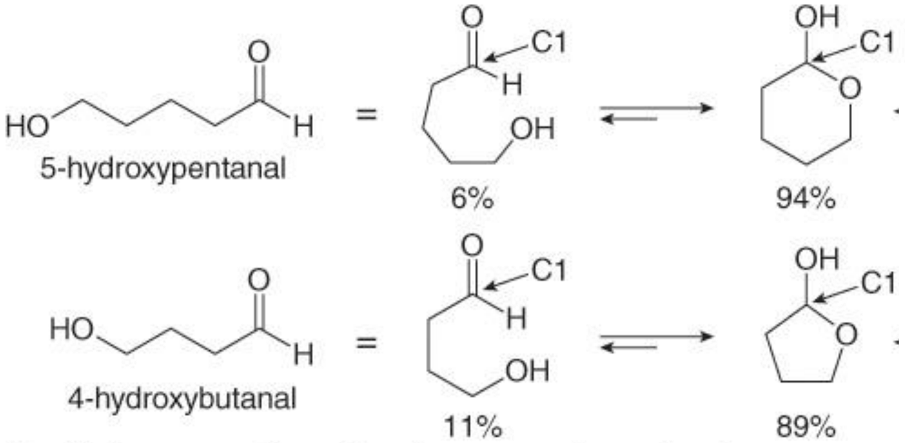


Example



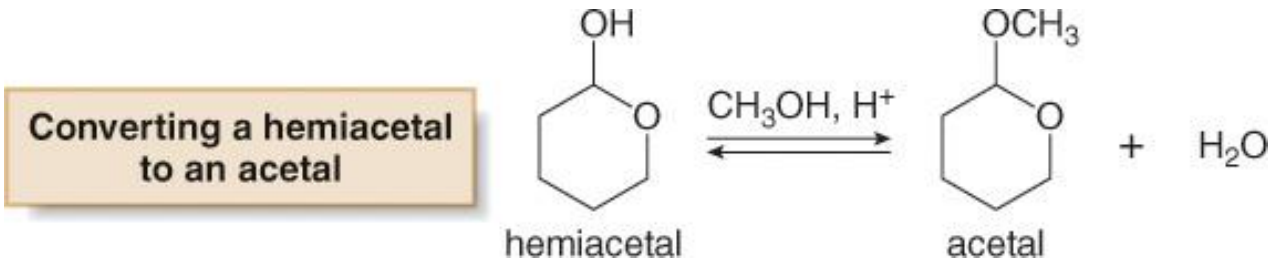
Cyclic Hemiacetals and Acetals

Cyclic hemiacetals are formed by intramolecular cyclization of hydroxy aldehydes.



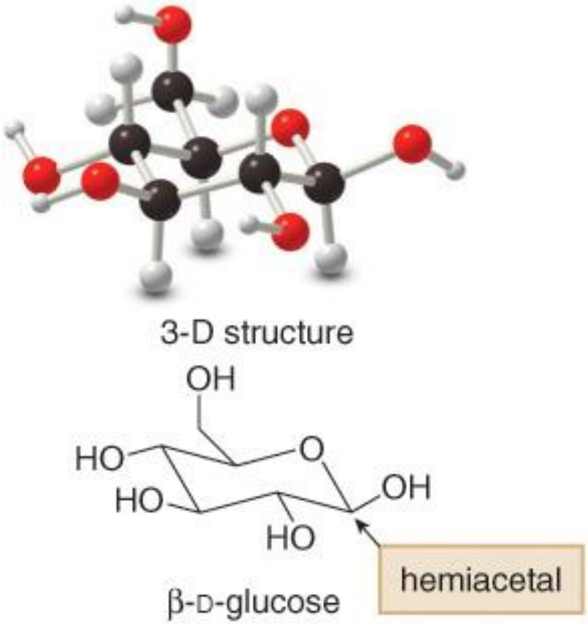
[Equilibrium proportions of each compound are given.]

Cyclic hemiacetals can be converted to acetals by treatment with an alcohol and acid.

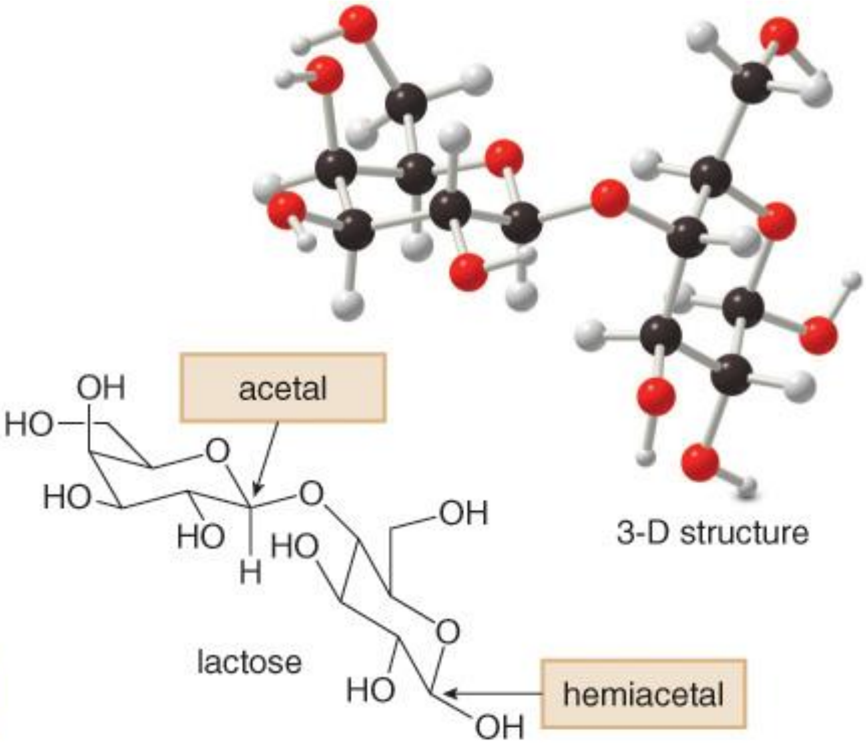


Introduction to Carbohydrates

- Carbohydrates, commonly referred to as sugars and starches, are polyhydroxy aldehydes and ketones, or compounds that can be hydrolyzed to them.
- Many carbohydrates contain cyclic acetals or hemiacetals. Examples include glucose and lactose.

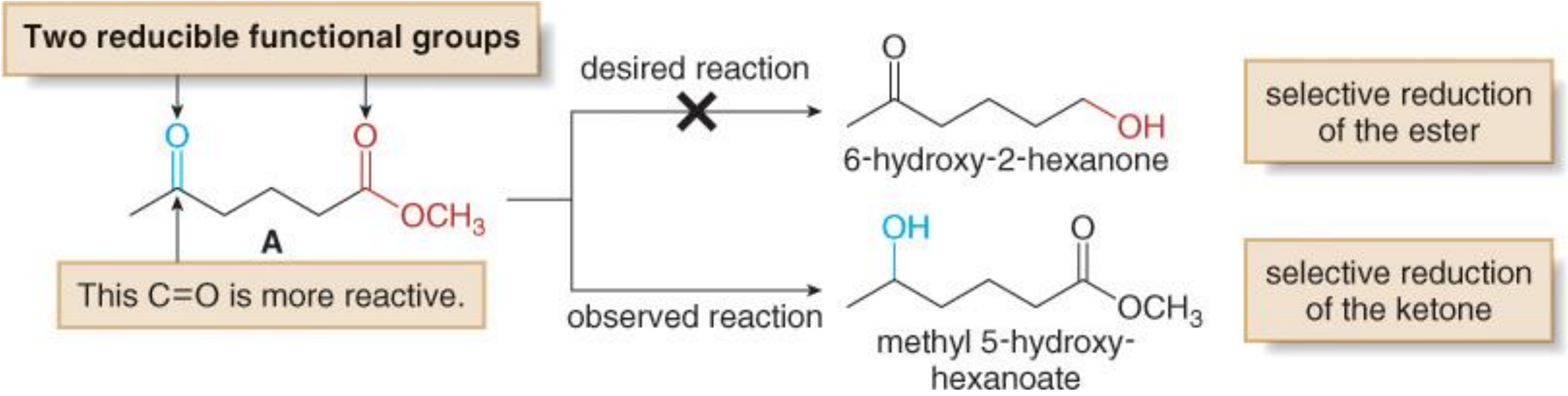


β-D-glucose
(one form of glucose)



lactose

Acetals as Protecting Groups



Two reducible functional groups

This C=O is more reactive.

A

OCH_3

desired reaction

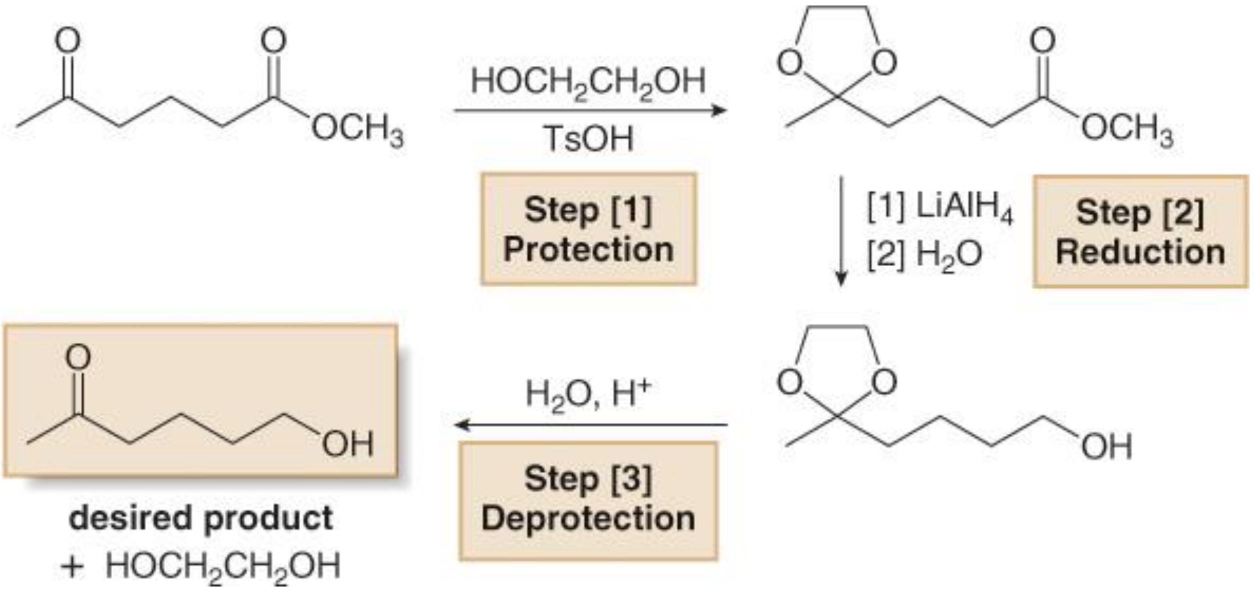
6-hydroxy-2-hexanone

selective reduction of the ester

observed reaction

methyl 5-hydroxy-hexanoate

selective reduction of the ketone



$HOCH_2CH_2OH$

TsOH

Step [1] Protection

[1] $LiAlH_4$
[2] H_2O

Step [2] Reduction

H_2O, H^+

Step [3] Deprotection

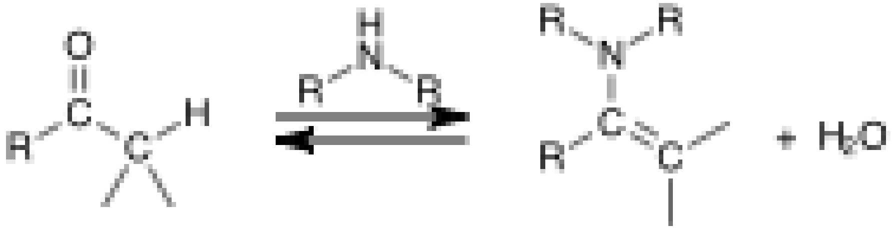
desired product
+ $HOCH_2CH_2OH$

Addition of Amines

- Treatment of an aldehyde or a ketone with a 1ry amine affords an imine (also called a Schiff base).

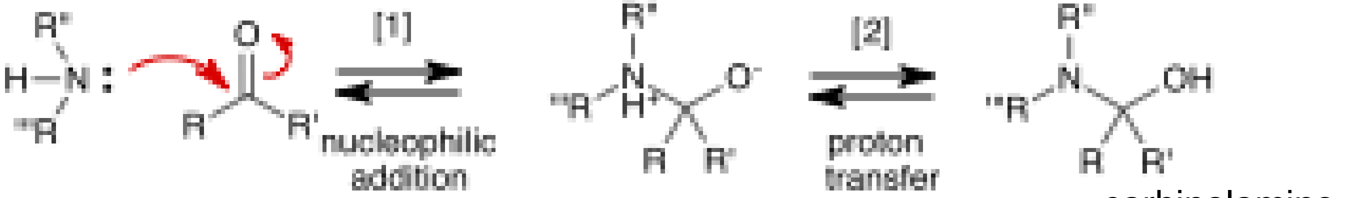
The N atom of an imine is *sp*^{2} hybridized, making the C—N—R bond angle 120°, (not 180°).

- Treatment of an aldehyde or a ketone with a 2ry amine affords an enamine.



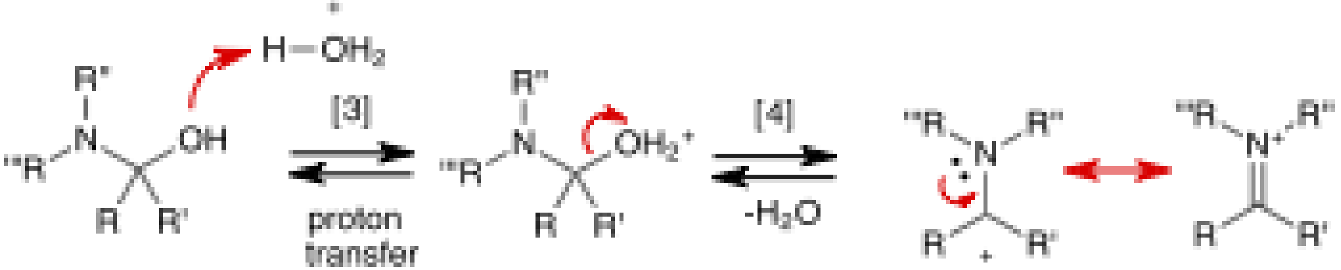
Imines and Enamines: Mechanism

1. Amine addition

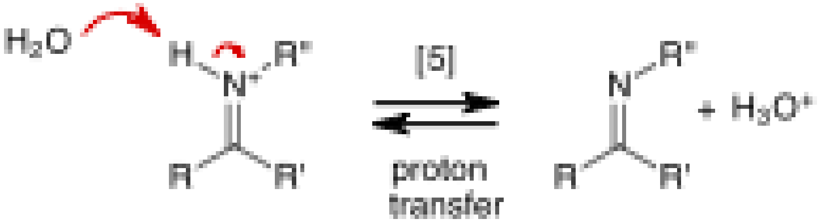


carbinolamine

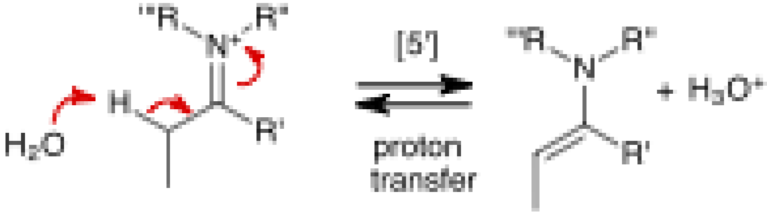
2. Elimination of water



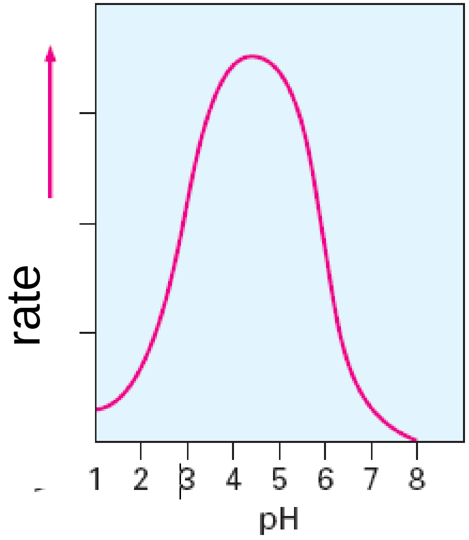
a: NH_3, $R''NH_2$



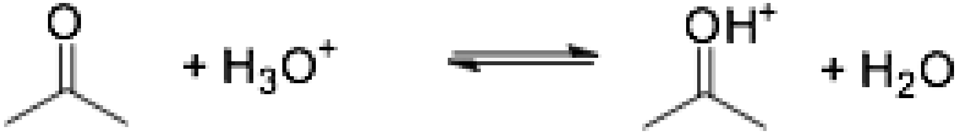
b: $R''R'''NH$



Addition of Amines – Effect of pH



General pH-rate profile for addition of amines to carbonyl compounds

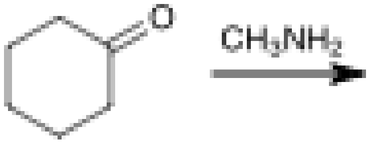


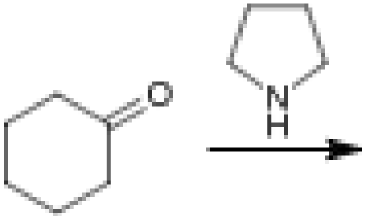
protonation activates the electrophile

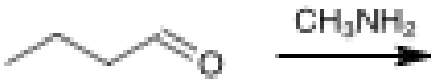
$R-NH_2 + H_3O^+ \rightleftharpoons R-NH_3^+ + H_2O$

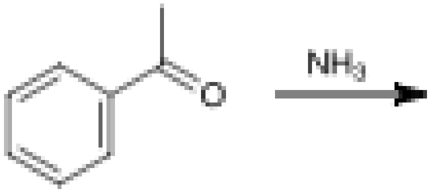
protonation deactivates the nucleophile

Addition of Amines







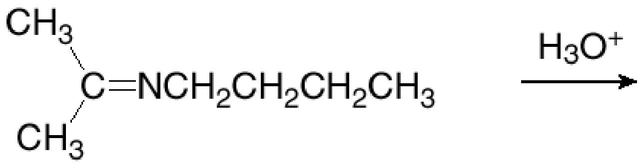


Imine and Enamine Hydrolysis

- Because imines and enamines are formed by a reversible set of reactions, both can be converted back to carbonyl compounds by hydrolysis with mild acid.
- The mechanism of hydrolysis is the exact reverse of the mechanism written for formation of imines and enamines.

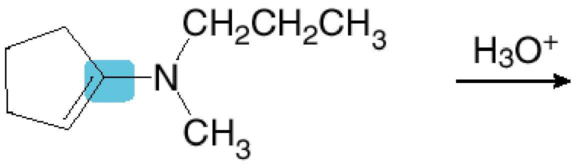
- **Hydrolysis of imines and enamines forms aldehydes and ketones.**

Imine hydrolysis

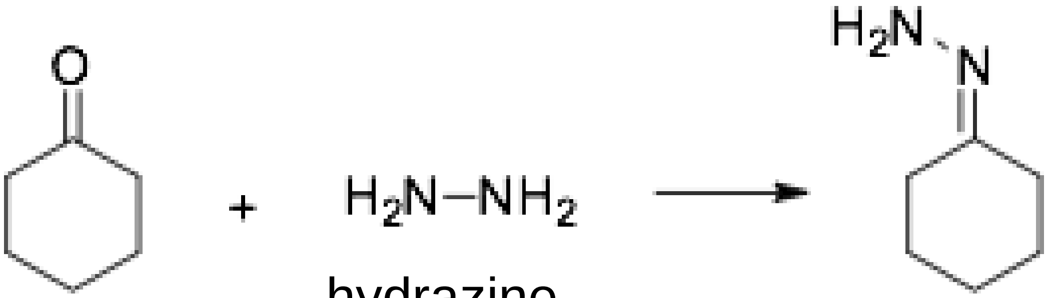


$$(CH_3)_2C{=}NCH_2CH_2CH_2CH_3 \xrightarrow{H_3O^+}$$

Enamine hydrolysis



Other Amines



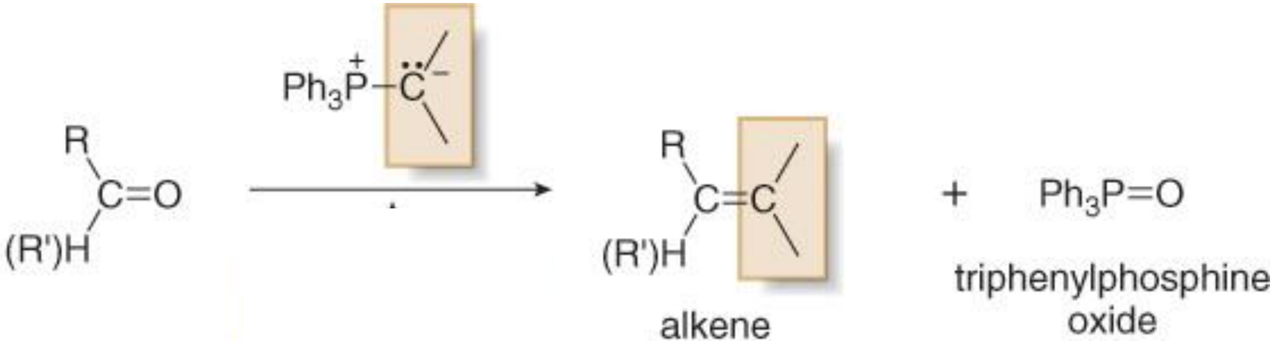
hydrazine

hydrazone

hydroxylamine

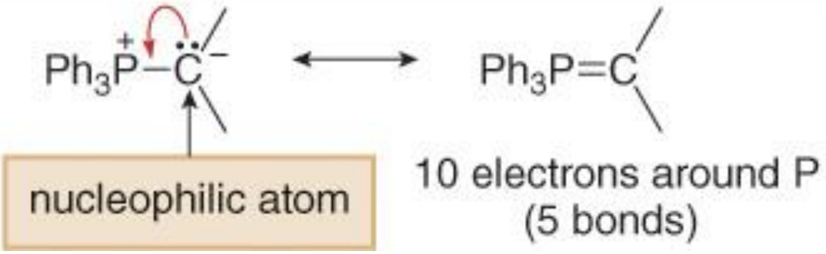
oxime

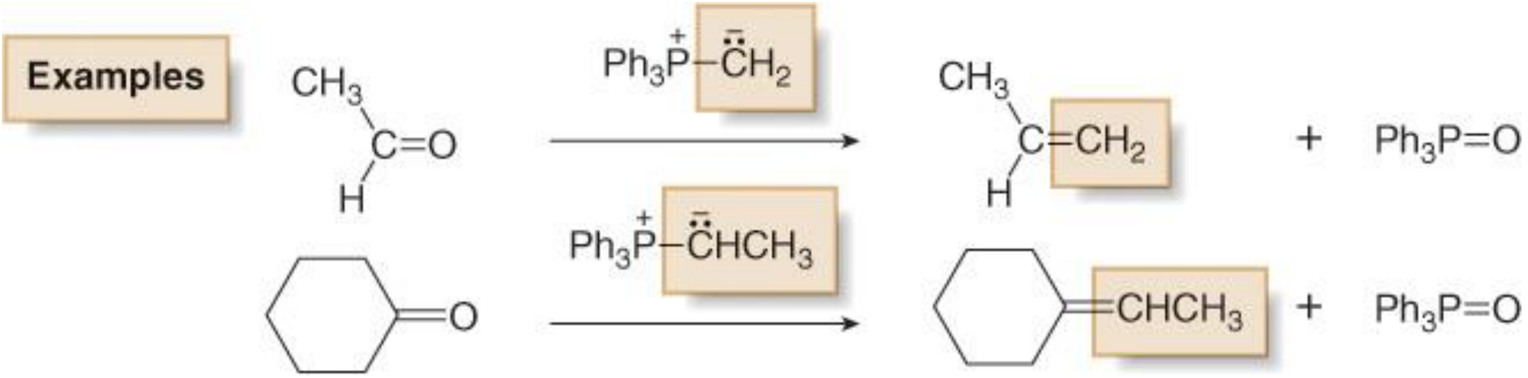
The Wittig Reaction



Two resonance structures for the Wittig reagent

phosphonium ylids
(Wittig reagents)

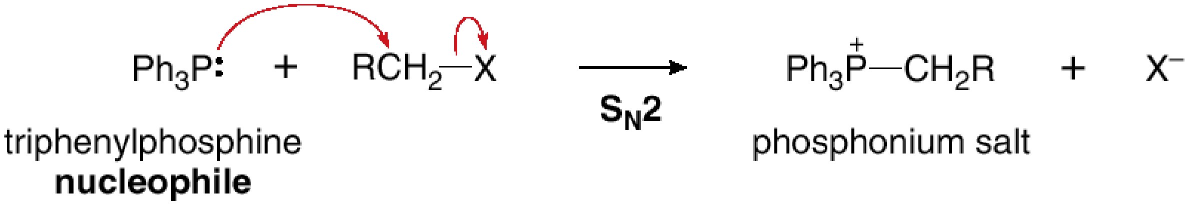




The Wittig Reaction

Preparation of phosphorus ylides (phosphoranes)

Step [1] S_N2 reaction of triphenylphosphine with an alkyl halide forms a phosphonium salt.

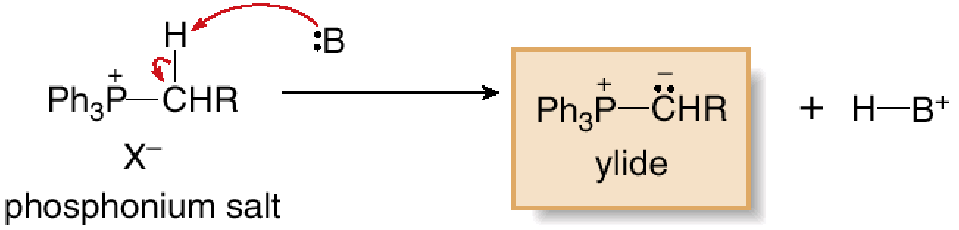


$$Ph_3P: + RCH_2-X \xrightarrow{S_N2} Ph_3\overset{+}{P}-CH_2R + X^-$$

triphenylphosphine
nucleophile

phosphonium salt

Step [2] Deprotonation of the phosphonium salt with a strong base (:B) forms the ylide.



$$Ph_3\overset{+}{P}-CH(H)R \; X^- + :B \longrightarrow Ph_3\overset{+}{P}-\overset{-}{\ddot{C}}HR + H-B^+$$

phosphonium salt

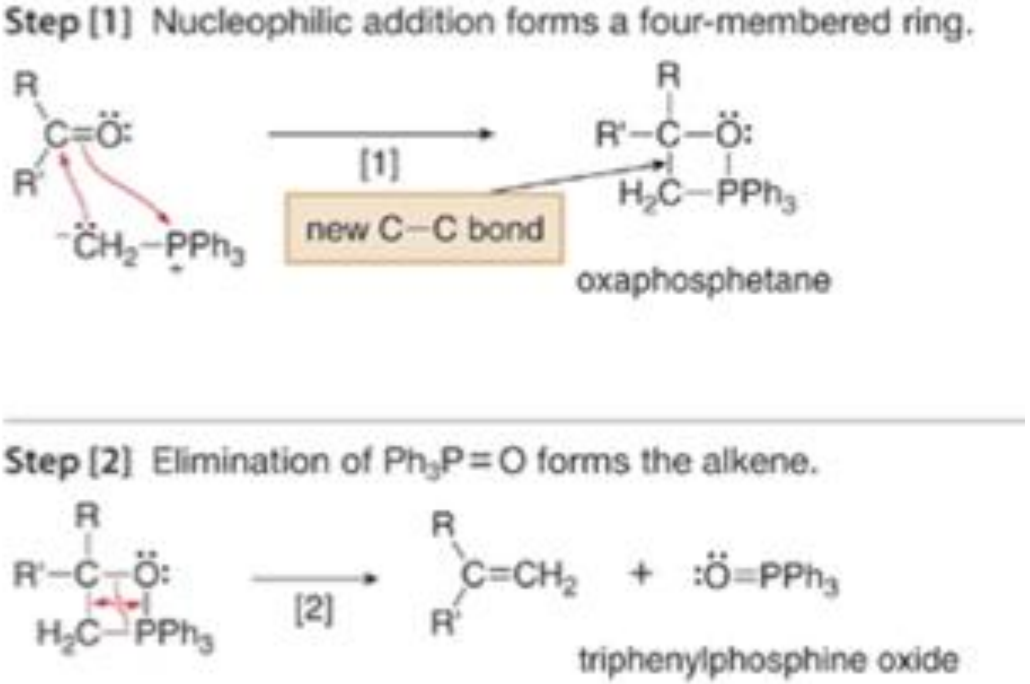
ylide

Typical strong base:

$CH_3CH_2CH_2CH_2-Li$

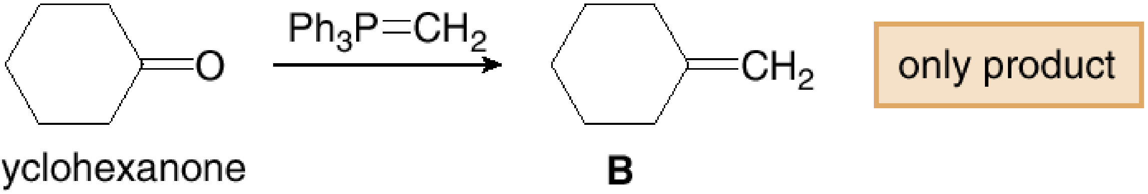
$Bu-Li$

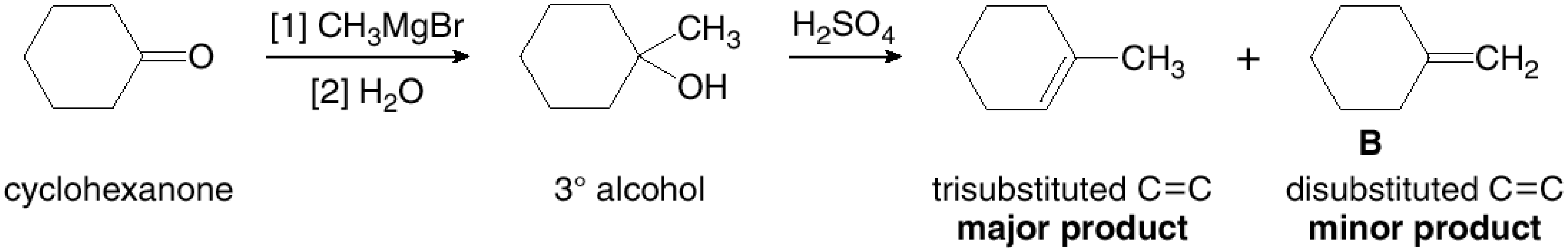
The Wittig Reaction



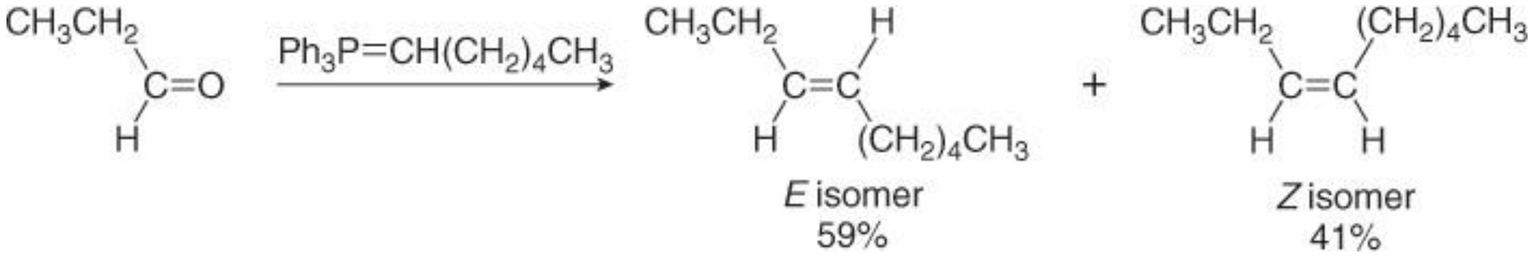
The Wittig Reaction

- Advantage: the Wittig reaction always gives a single constitutional isomer.

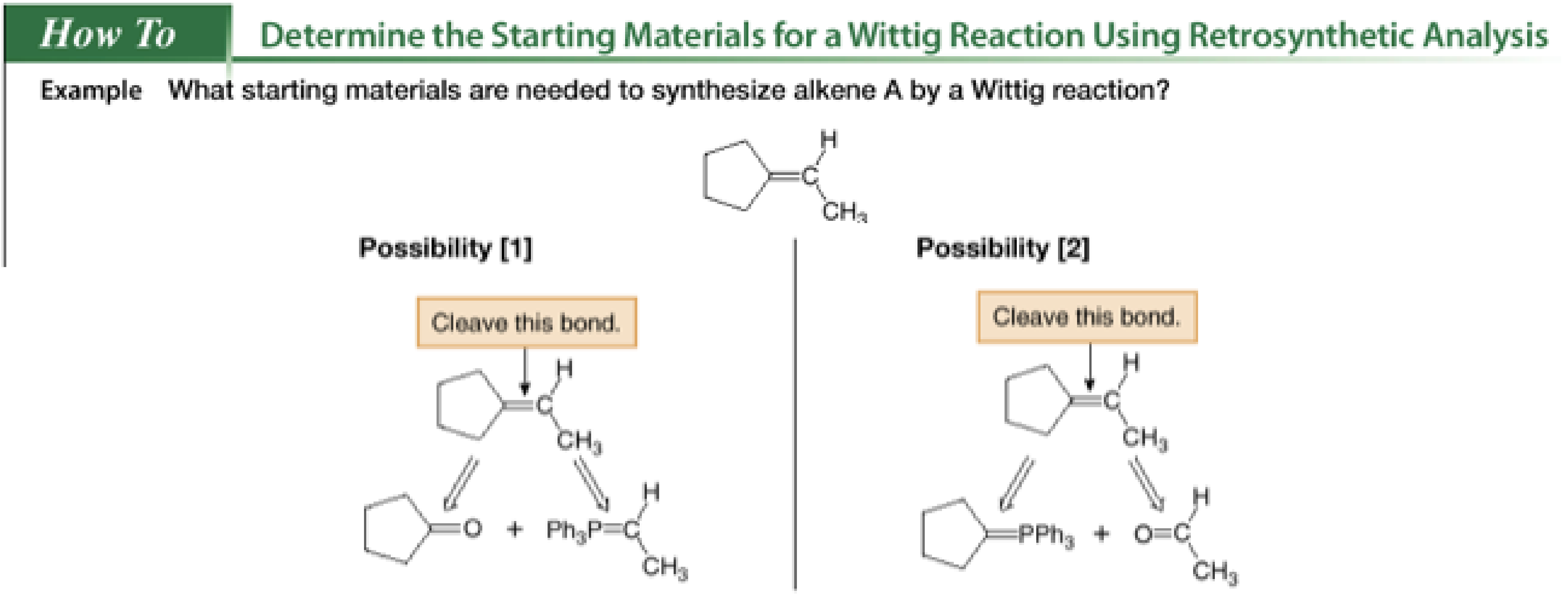




- Limitation: a mixture of stereoisomers is sometimes formed.



The Wittig Reaction



How To Determine the Starting Materials for a Wittig Reaction Using Retrosynthetic Analysis

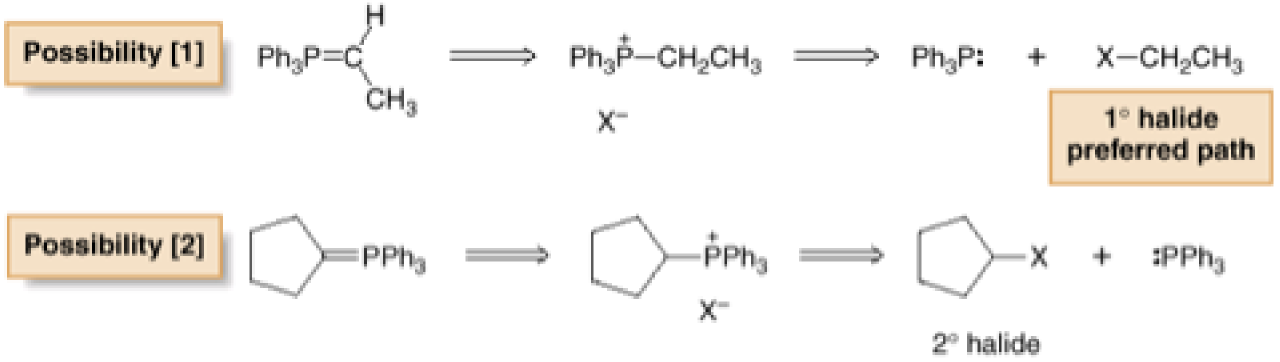
Example What starting materials are needed to synthesize alkene A by a Wittig reaction?

Possibility [1]

Cleave this bond.

Possibility [2]

Cleave this bond.



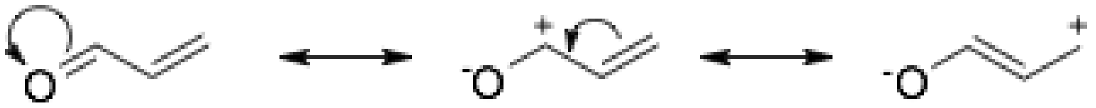
Possibility [1]

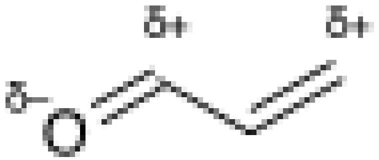
Possibility [2]

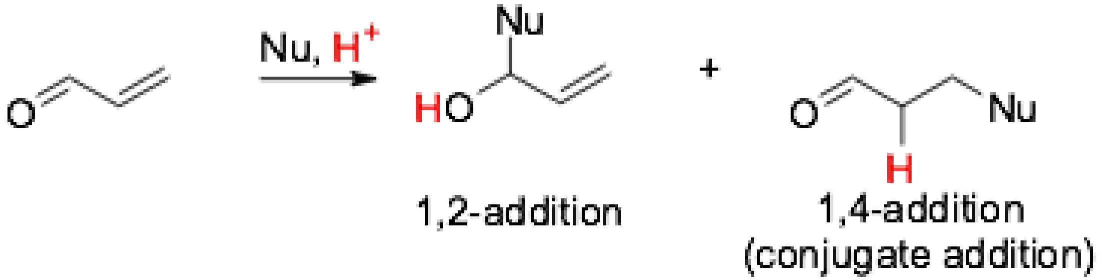
1° halide preferred path

2° halide

α,β-Unsaturated Carbonyl Compounds

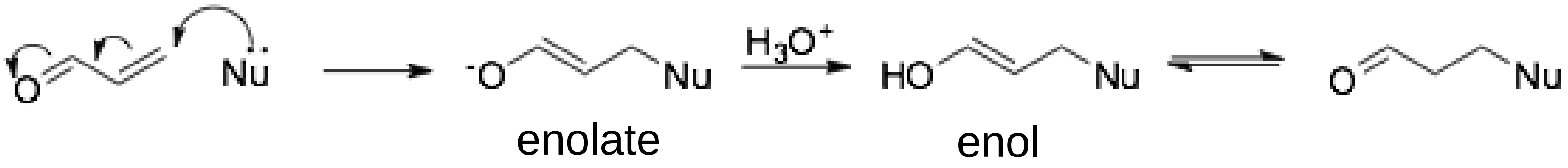




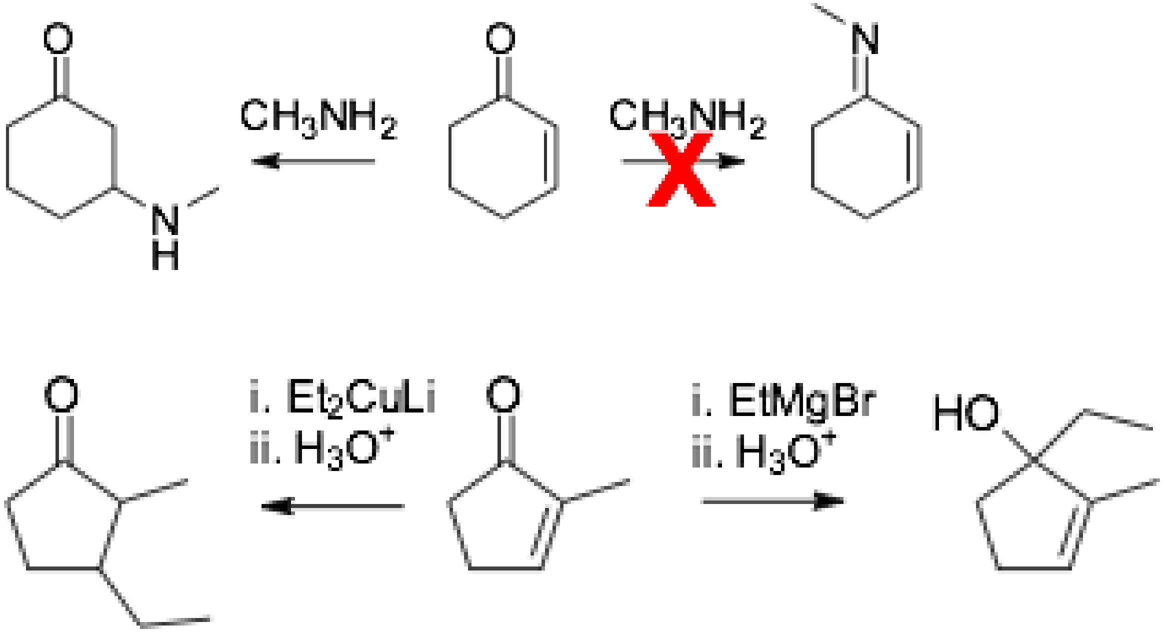


Conjugate Addition

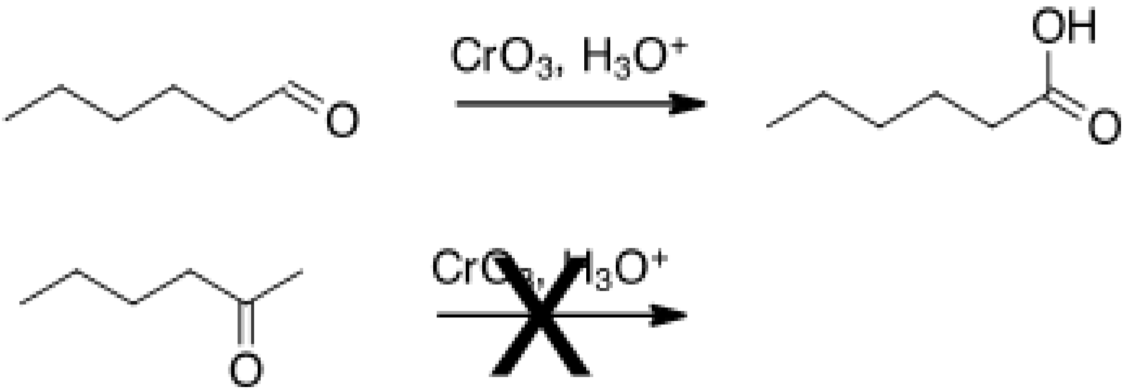
general mechanism:



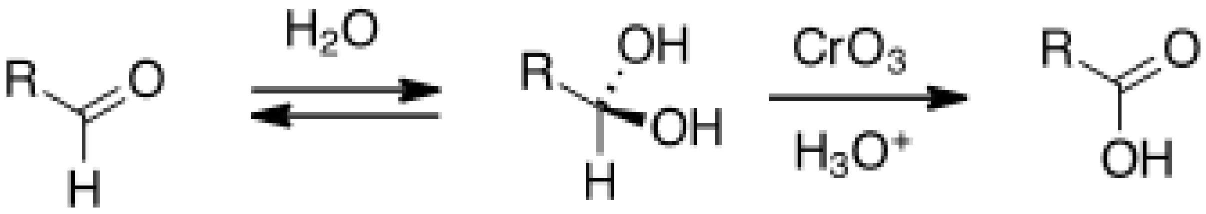
examples:



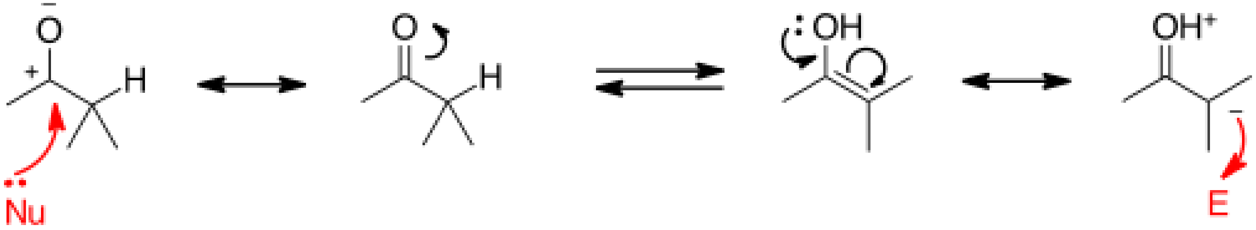
Oxidation



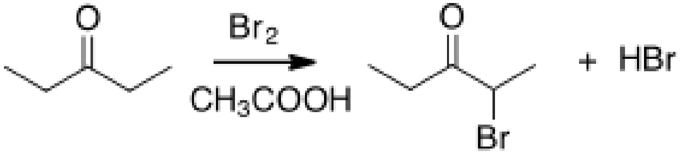
mechanism



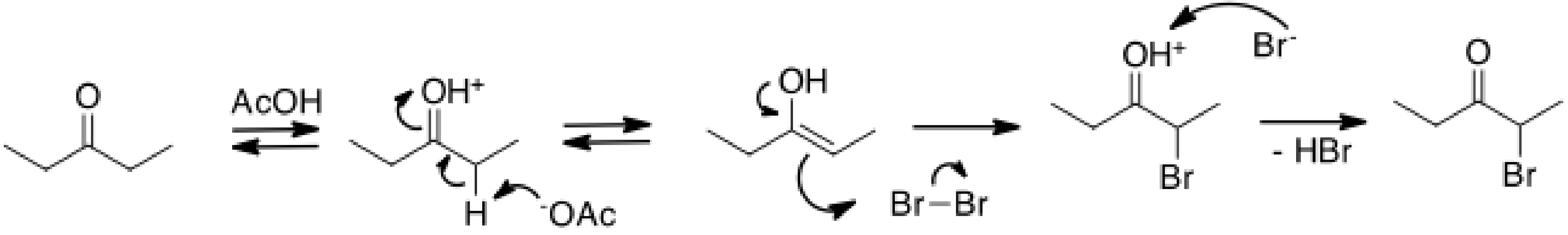
Keto-Enol Tautomerism. Reaction at the α-Carbon



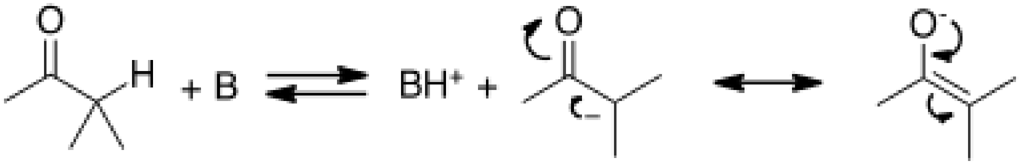
α-halogenation:



mechanism:



Enolates. Reaction at the α-Carbon



Carbanion

Enolate

pKa ≈ 20

Example: 2-methylcyclohexanone