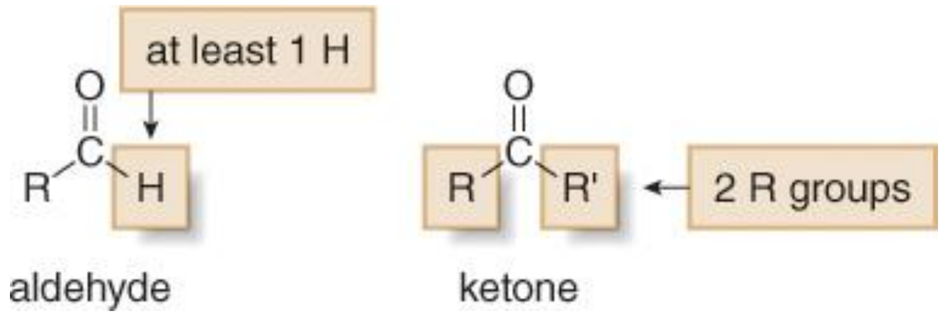
Carbonyl Compounds

Introduction

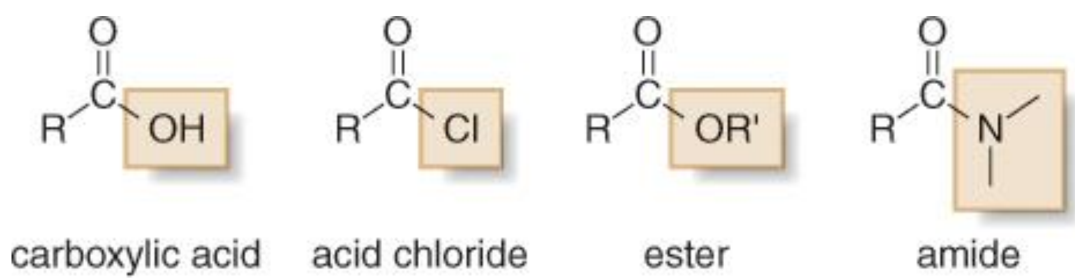
Introduction

Two broad classes of compounds contain the carbonyl group:

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

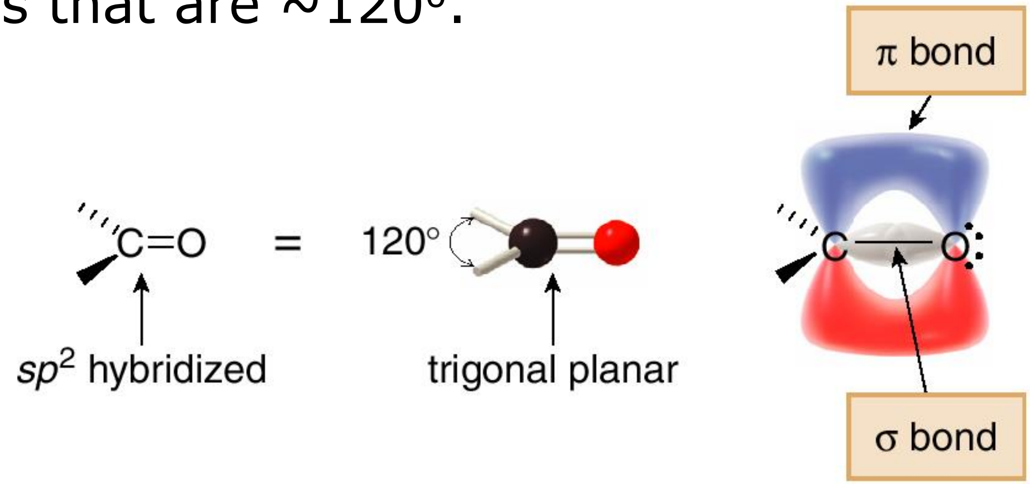


[2] Compounds that contain an eteroatom (N, O, S, Cl) bonded to the carbonyl

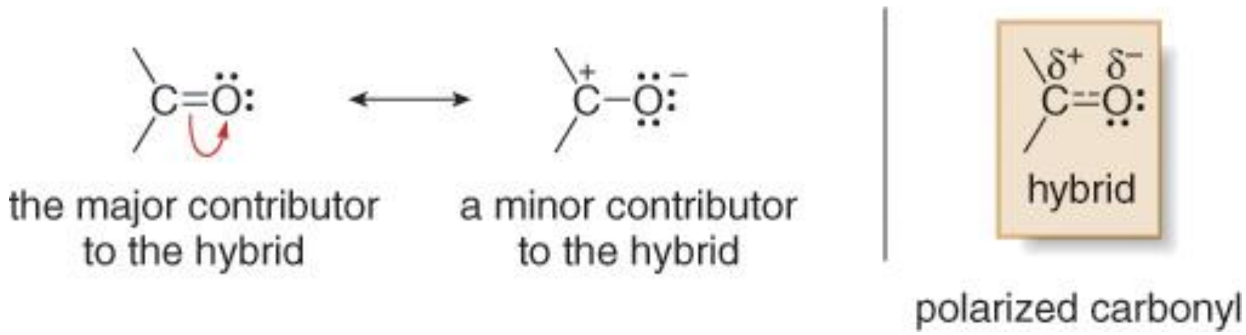


Introduction

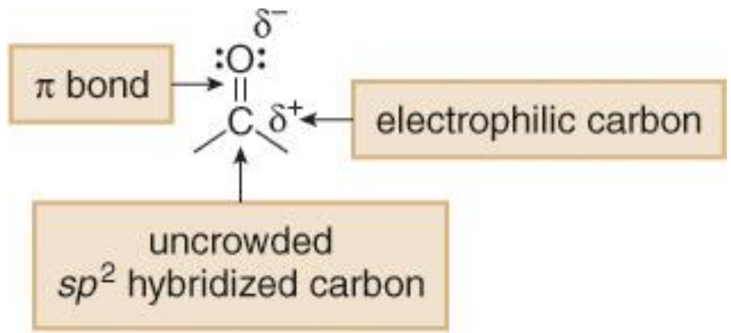
- Carbonyl carbons are *sp*^{2} hybridized, trigonal planar, and have bond angles that are ~120^0.



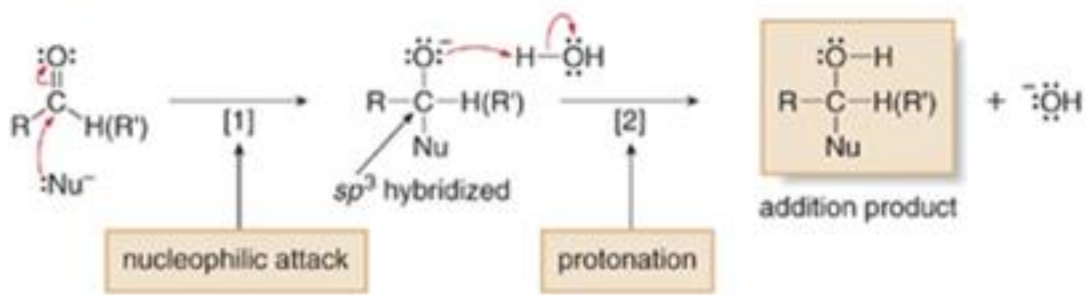
- The electronegative oxygen atom in the carbonyl group means that the bond is polarized, making the carbonyl carbon electron deficient.



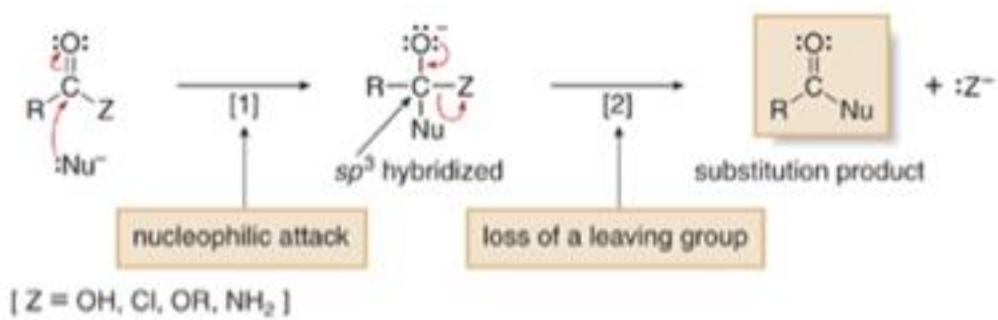
General Reactions of Carbonyl Compounds



Aldehydes and ketones



Acyl derivatives



Aldehydes and Ketones

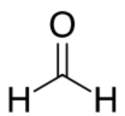
Chapter 19

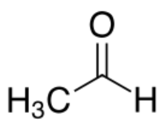
Organic Chemistry, *8th Edition*

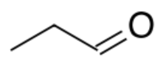
John McMurry

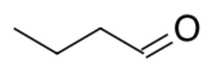
Nomenclature of Aldehydes

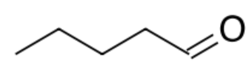
- Find the longest chain containing the CHO group, and change the –*e* ending of the parent alkane to the suffix *–al*. If the CHO group is bonded to a ring, name the ring and add the suffix *–carbaldehyde*.
- A common name for an aldehyde is formed by taking the common parent name and adding the suffix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

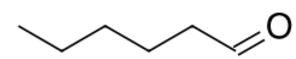

methanal (formaldehyde)

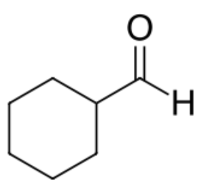

ethanal (acetaldehyde)

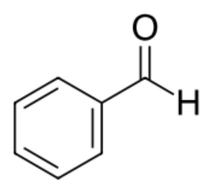

propanal (propionald.)

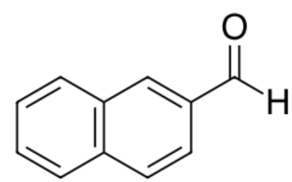

butanal (butyraldehyde)

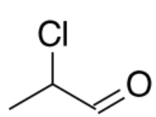

pentanal (valeraldehyde)

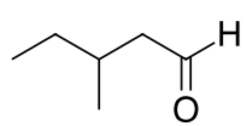

hexanal (caproic aldehyde)

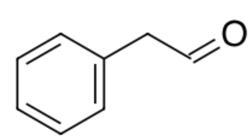

cyclohexanecarbaldehyde


benezenecarbaldehyde (benzaldehyde)

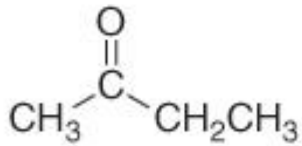

2-naphthalenecarbaldehyde


2-chloropropanal

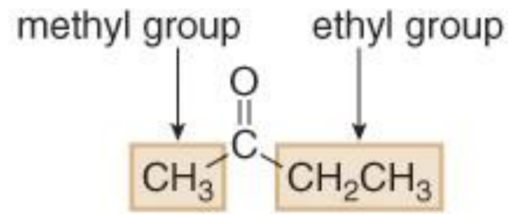

3-methylpentanal


phenylethanal

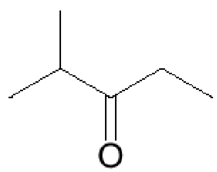
Nomenclature of Ketones



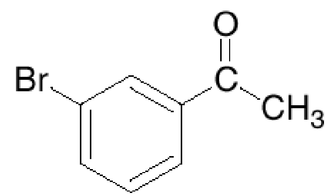
IUPAC name: **2-butanone**



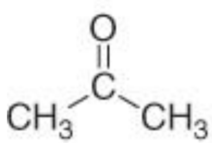
Common name: **ethyl methyl ketone**



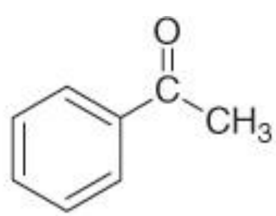
IUPAC name: 2-methyl-3-pentanone
Common name: ethyl isopropyl ketone



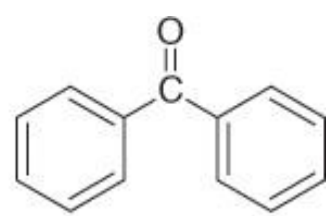
m-bromoacetophenone
or
3-bromoacetophenone



acetone

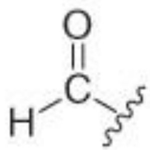


acetophenone

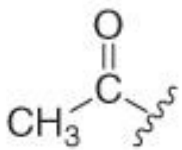


benzophenone

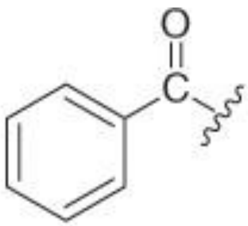
Nomenclature of Aldehydes and Ketones



formyl group

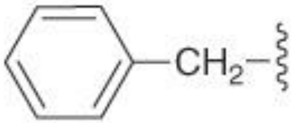


acetyl group



benzoyl group

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



benz*yl* group

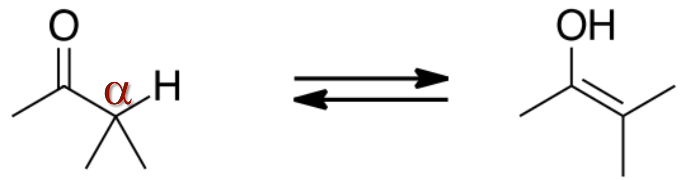
Physical Properties

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.

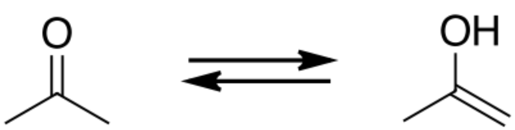
Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding, MW = molecular weight

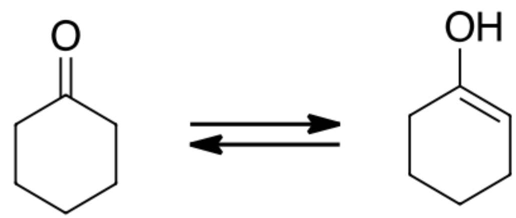
Keto-Enol Tautomerism



Keto tautomer

Enol tautomer



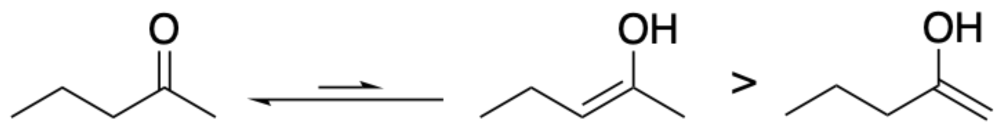


99,9999999%   0,0000001%   99,9999%   0,0001%

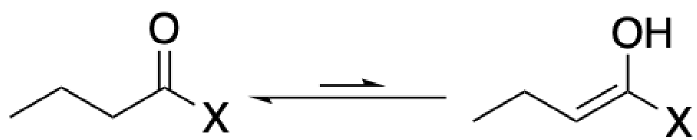
Keto-Enol Tautomerism

Aldehydes: 1 enol

Ketones: 2 enols

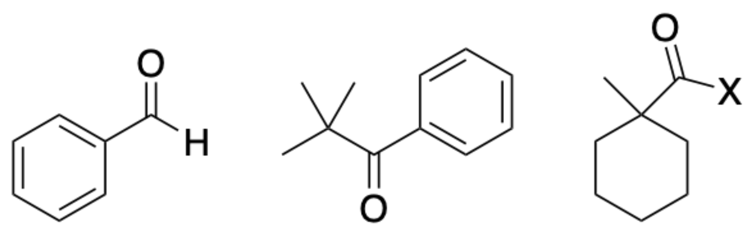


Acid derivatives:
1 enol



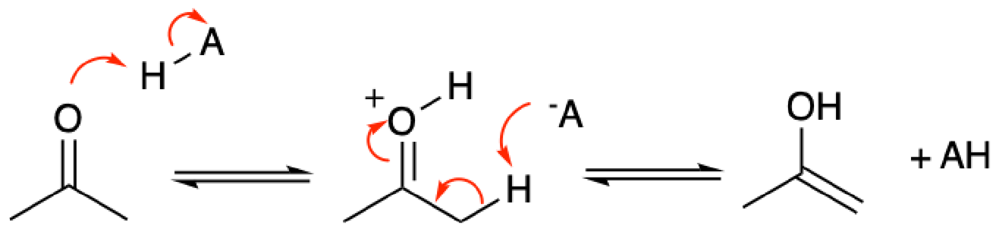
X = OH, OR, NR2,..

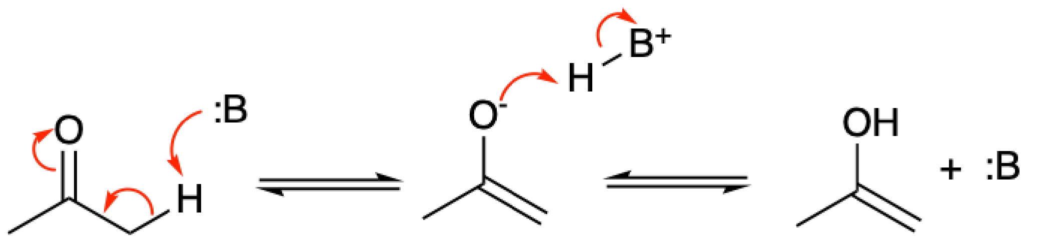
Non-enolizable



Keto-Enol Tautomerism

Enolization is catalyzed by both acids and bases





The catalyst accelerates the equilibrium; it does not influence its position

Interesting Aldehydes and Ketones

formaldehyde
$CH_2{=}O$

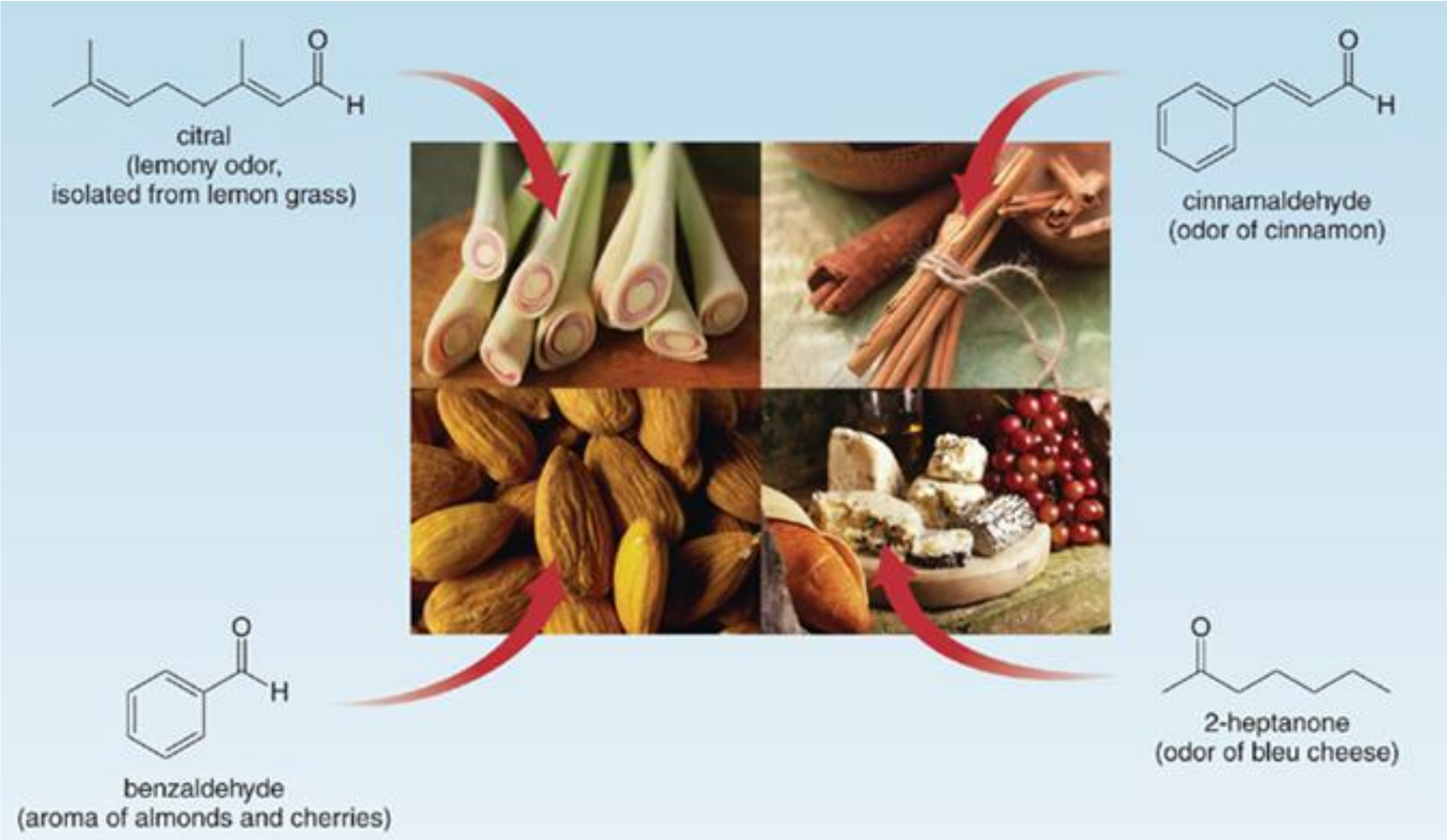
Billions of pounds of formaldehyde are produced annually from the oxidation of methanol. It is sold as a 37% solution called formalin which is used as a disinfectant, antiseptic, and preservative for biological specimens. It is a product of incomplete combustion of coal, and is partly responsible for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

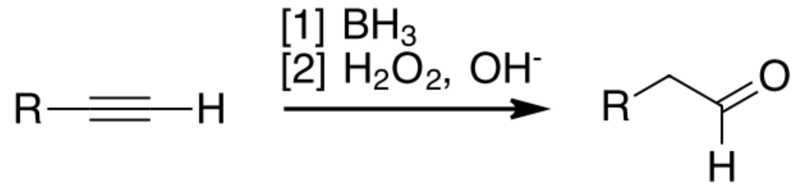
Interesting Aldehydes and Ketones

Many aldehydes and ketones with characteristic odors occur in nature.

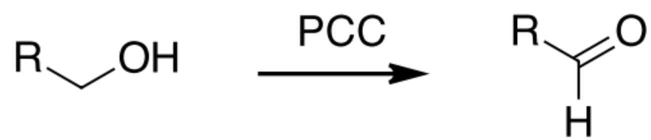


Preparation of Aldehydes

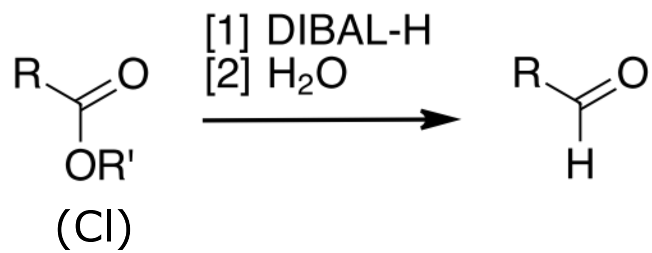
Hydration of an alkyne (hydroboration-oxidation)



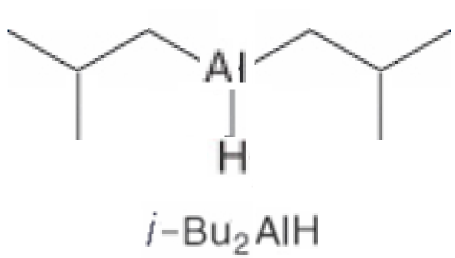
Oxidation of 1ry alcohols



Reduction of esters and acyl chlorides

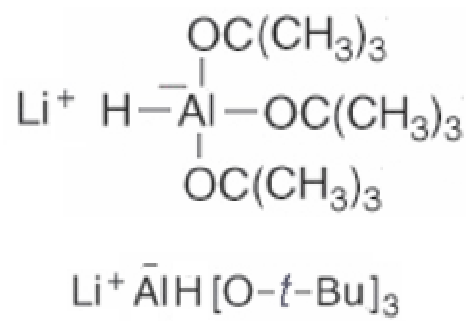


Preparation of Aldehydes and Ketones



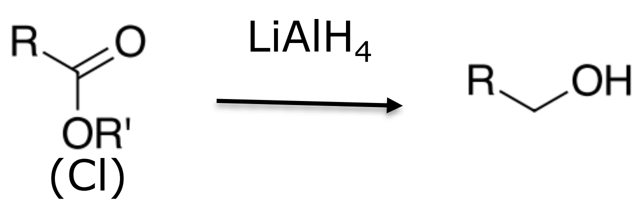
DIBAL-H

Diisobutilaluminium hydride



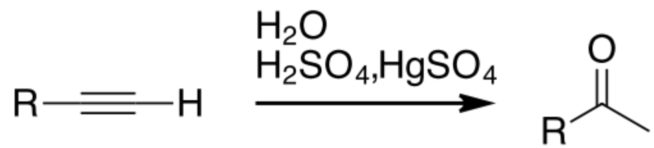
Lithium tri-*tert*-butoxyaluminium hydride

Sterically hindered - Less reactive than $LiAlH_4$

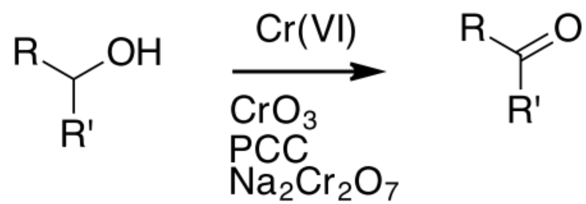


Preparation of Ketones

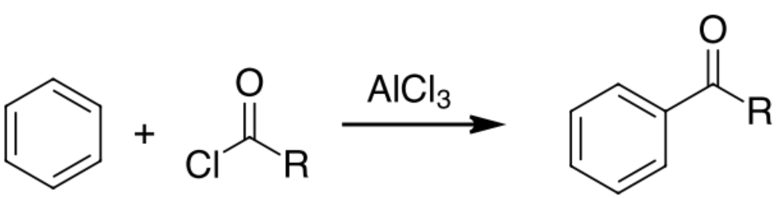
Hydration of alkynes



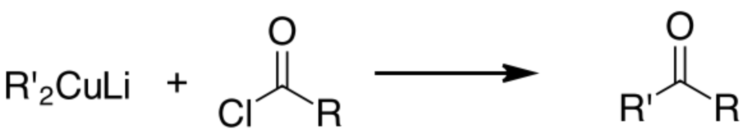
Oxidation of 2^{ry} alcohols



Friedel-Crafts acylation

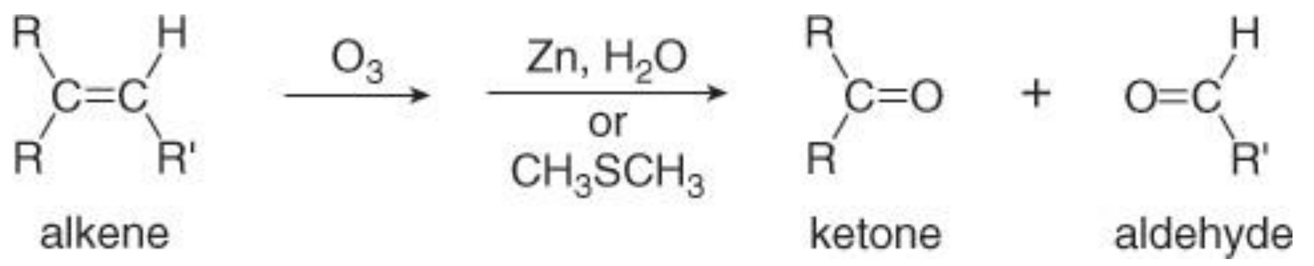


Acylation of organocuprates



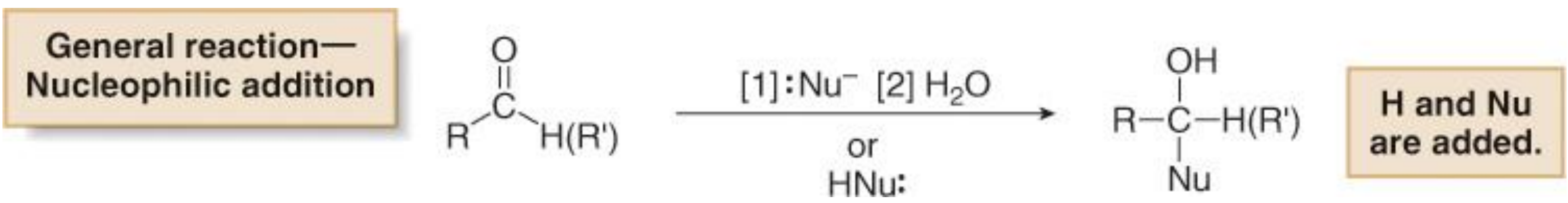
Preparation of Aldehydes and Ketones

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



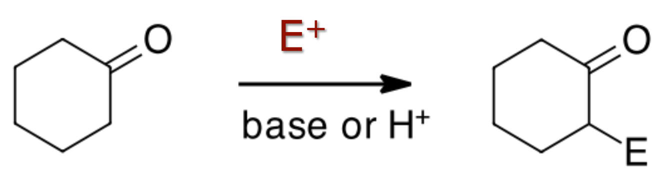
Reactions of Aldehydes and Ketones—General

[1] Nucleophilic addition



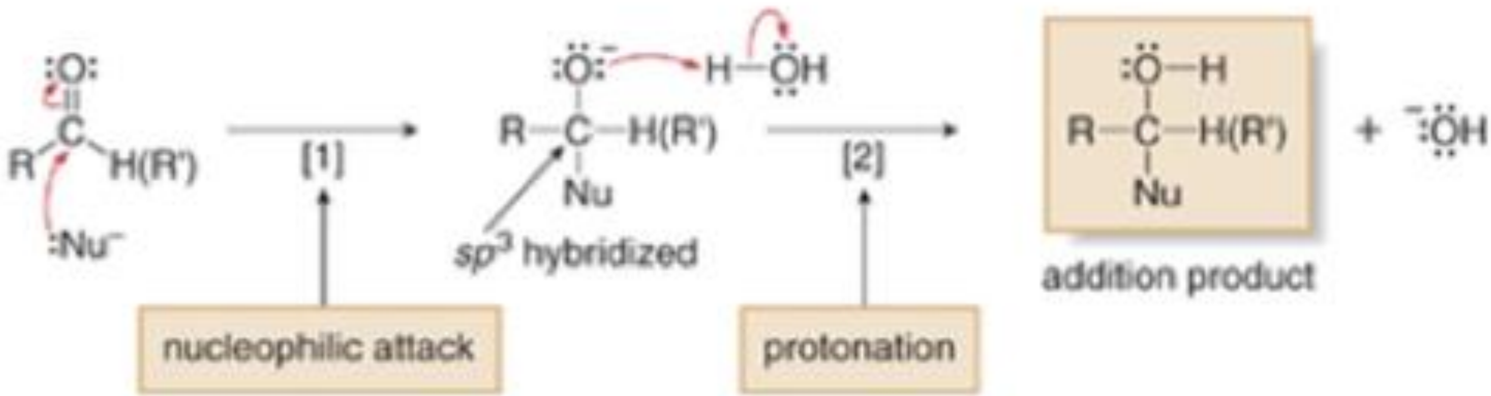
[2] Oxidation

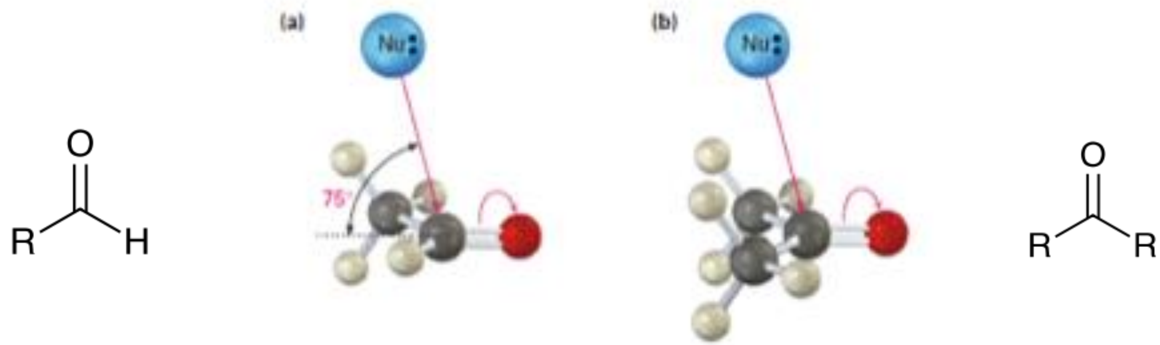
[3] Reaction at the α carbon



Nucleophilic Addition

Alcoholate intermediate

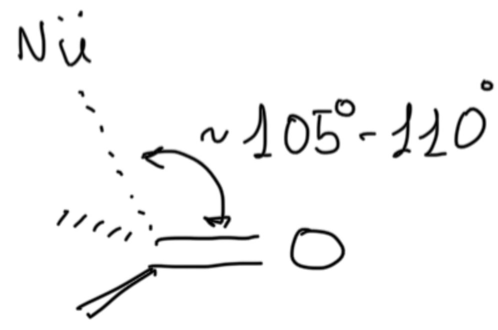




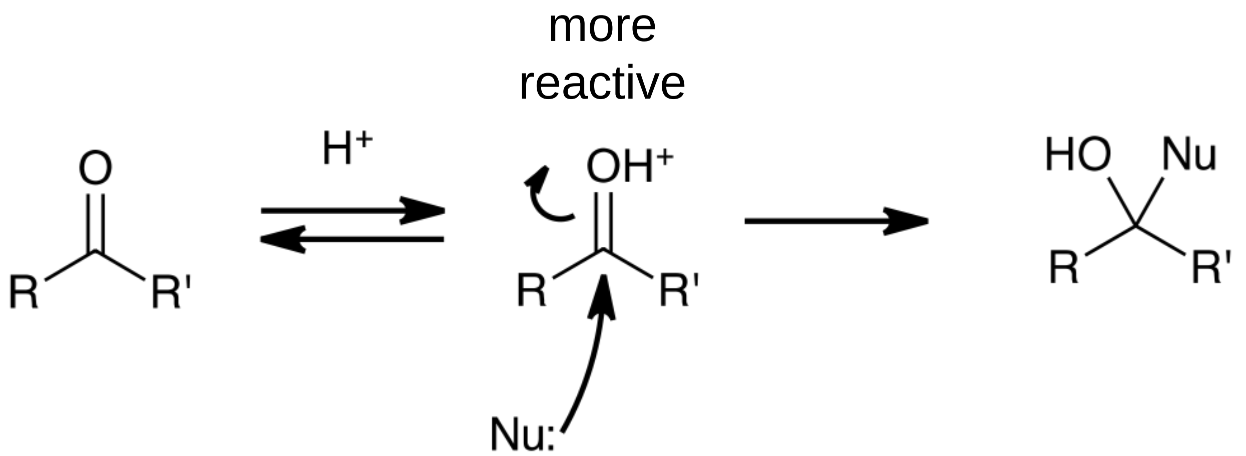
aldehyde
less crowded
more reactive

ketone
more crowded
less reactive

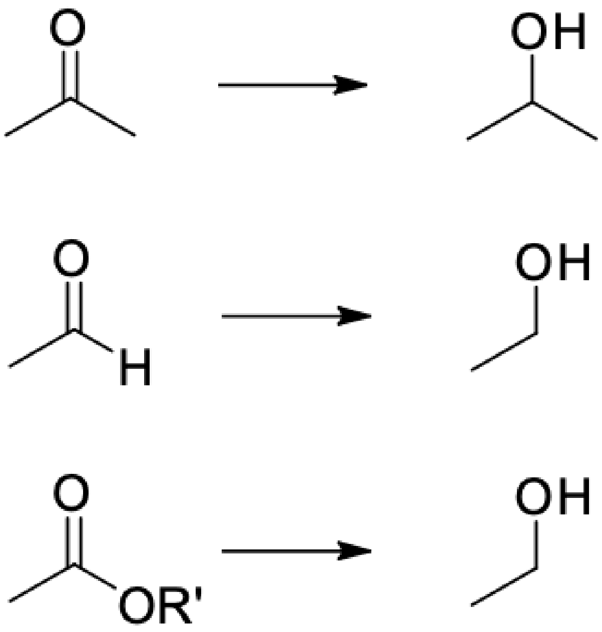
Nucleophilic Addition: Geometry



Acid Catalysis



Reduction



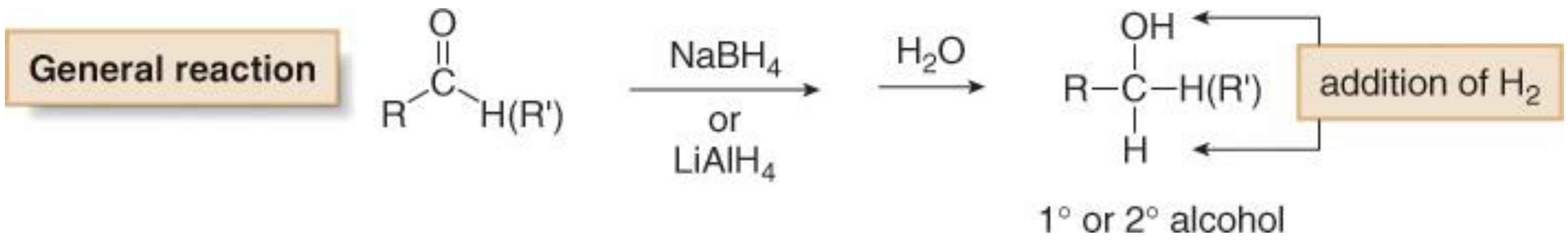
secondary alcohol

primary alcohol

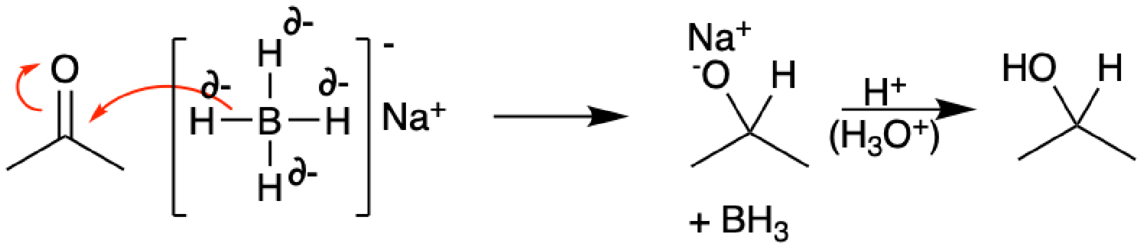
H_2/Pd reduces also C=C

$NaBH_4$, $LiAlH_4$ selective for C=O

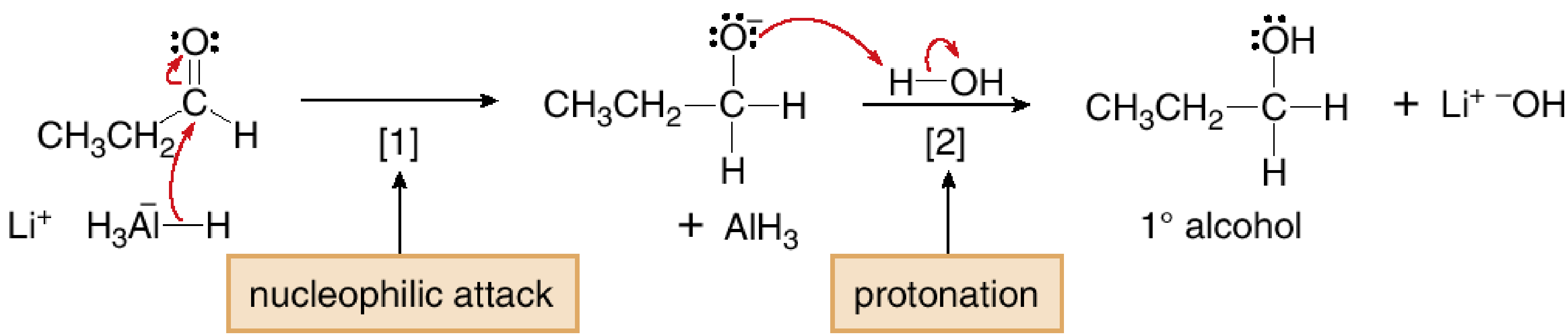
Reduction



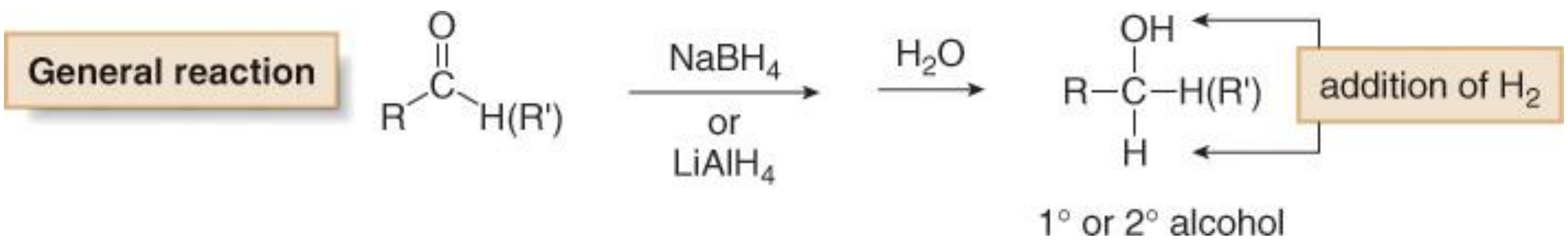
Mechanism: nucleophilic addition of H^- to the C=O bond



H is transferred as [H^-]



Reduction



Comparison $NaBH_4$ / $LiAlH_4$

$LiAlH_4$ (LAH) is more reactive and less selective than $NaBH_4$:

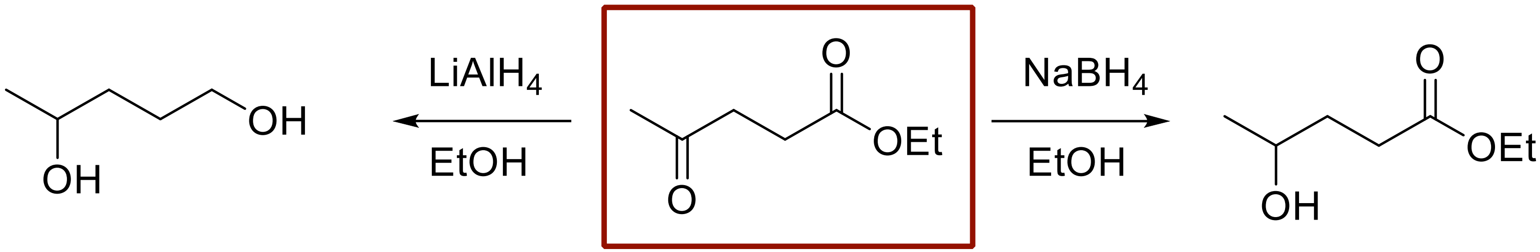
$NaBH_4$ reduces only aldehydes and ketones,
LAH reduces also esters, amides and nitriles.

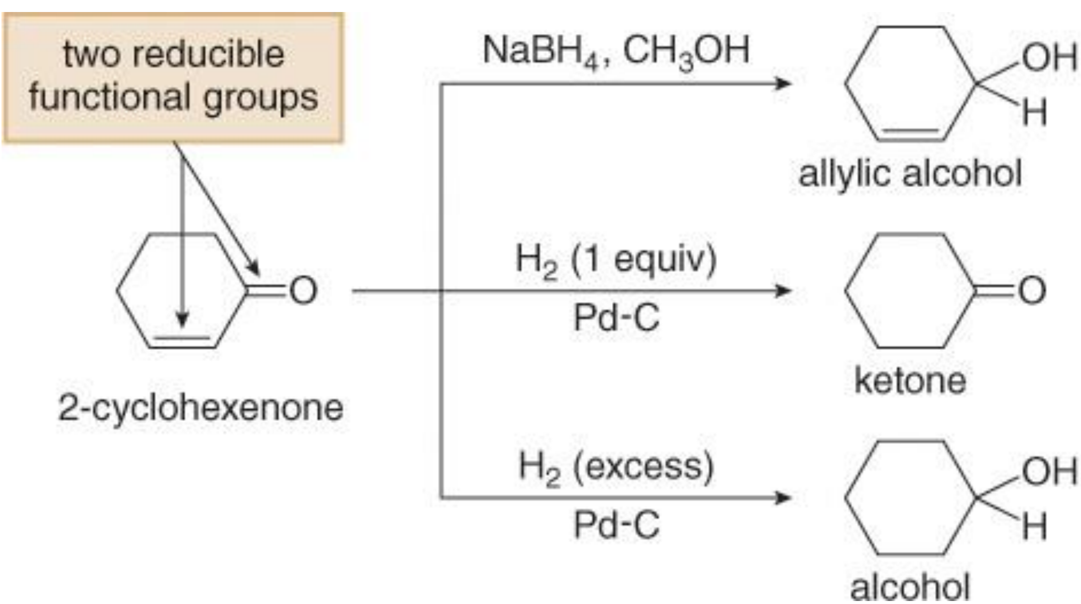
$NaBH_4$ can be used in protic solvents (alcohols and H_2O)
LAH must be used in non protic, anhydrous solvents (diethyl ether, THF), due to hydrolysis reaction:

$NaBH_4 + H_2O \longrightarrow NaOH + B(OH)_3 + H_2$ very slow

$LiAlH_4 + H_2O \longrightarrow LiOH + Al(OH)_3 + H_2$ very fast

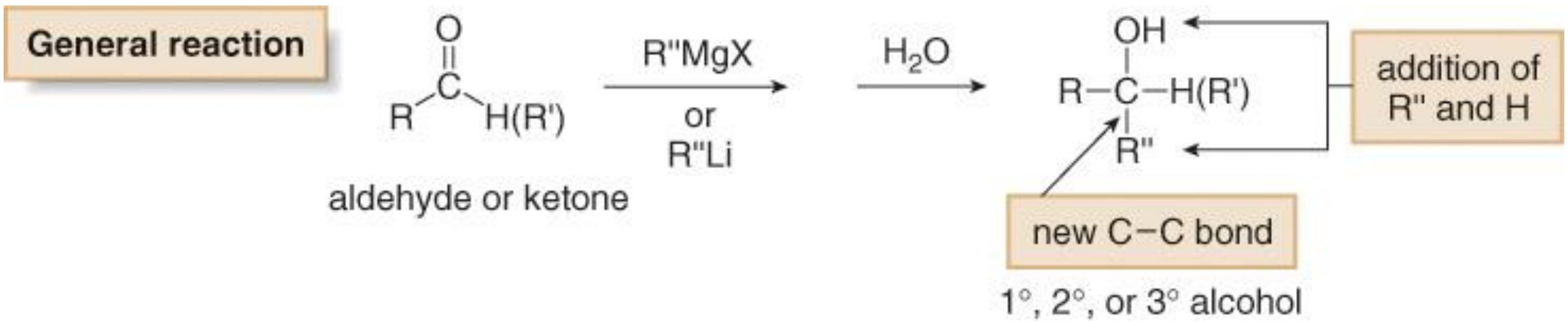
Selectivity in reduction



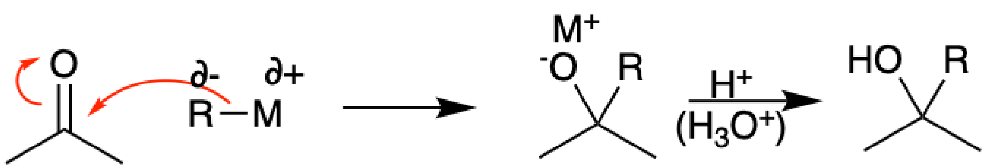


- $NaBH_4$ reduces the C=O selectively to form an allylic alcohol.
- One equivalent of H_2 reduces the C=C selectively to form a ketone.
- Excess H_2 reduces both π bonds to form an alcohol.

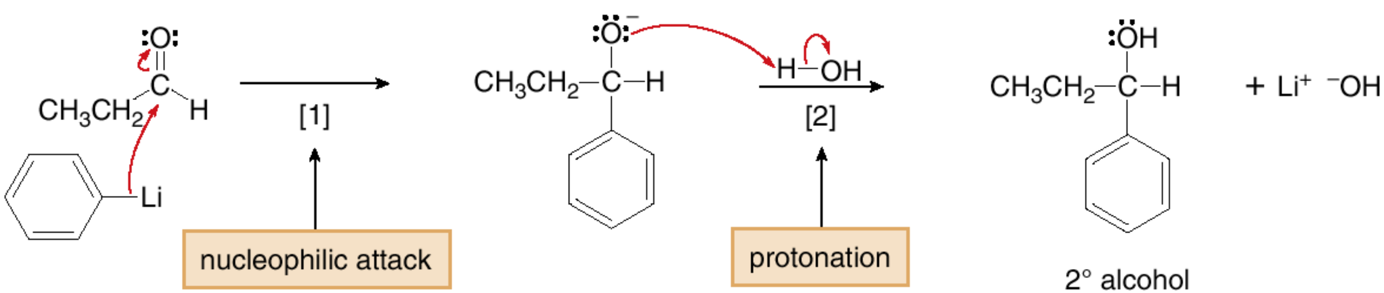
Nucleophilic Addition of Organometallic Reagents



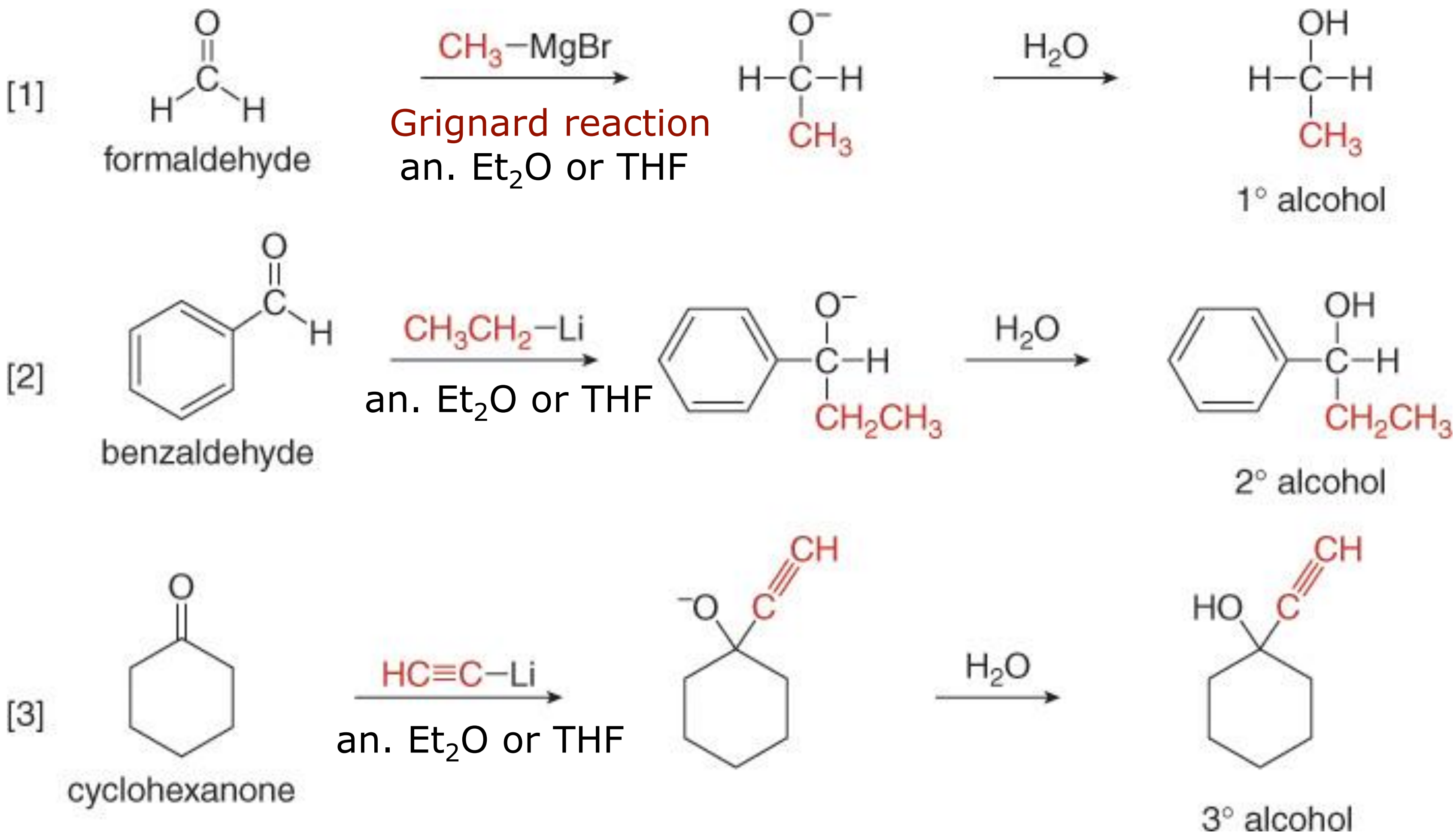
Mechanism: nucleophilic addition to the C=O bond



R is transferred as $[R^-]$



Reaction of carbonyl compounds with organometallic reagents



Organometallic reagents

Organometallic reagents must be prepared and used in anhydrous aprotic solvents (EtOEt, THF, toluene)

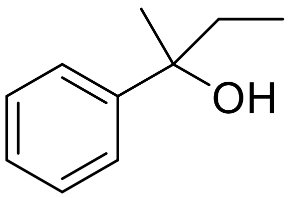
$$RX + Mg \xrightarrow{\text{an. THF}} RMgX$$

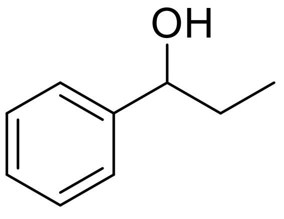
$$RMgX + H_2O \longrightarrow RH + \text{hydroxides}$$

pKa 15.75 pKa 50

H_2O (pKa 16) , alcohols (pKa 16 -18), amines (pKa 35) destroy Grignard and lithiumorganic reagents by protonation and conversion to the corresponding alkane

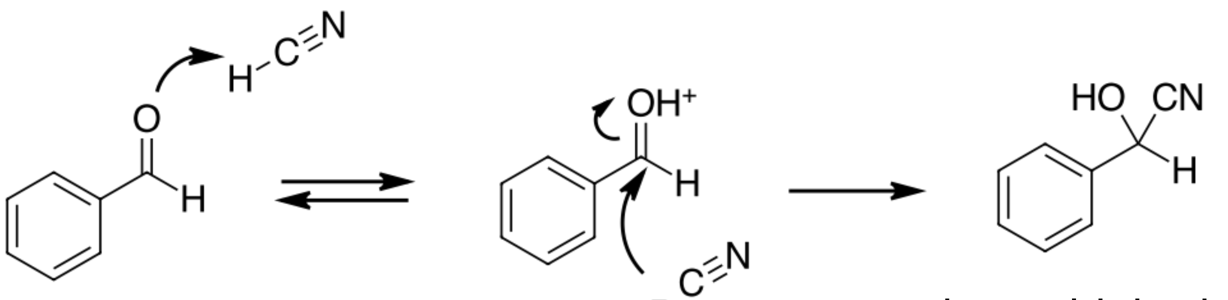
Synthesis of alcohols



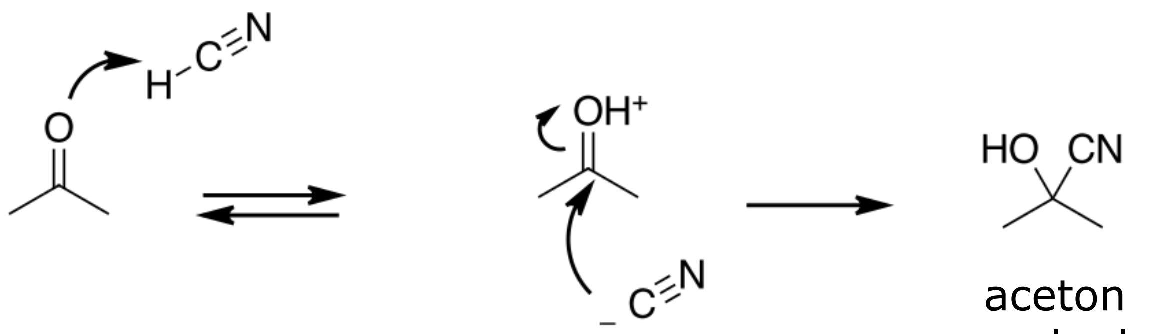


Nucleophilic Addition of CN^-

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



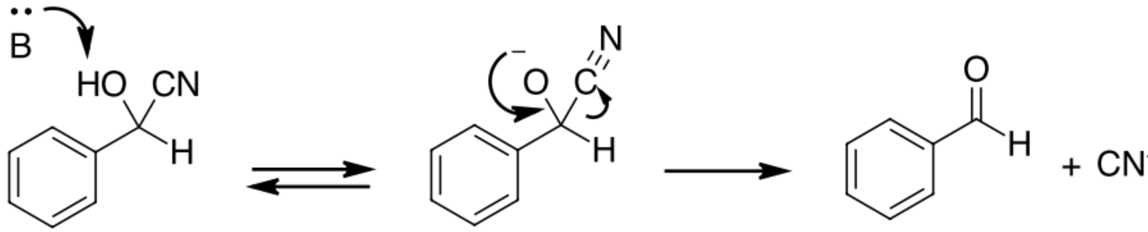
benzaldehyde
cyanohydrin



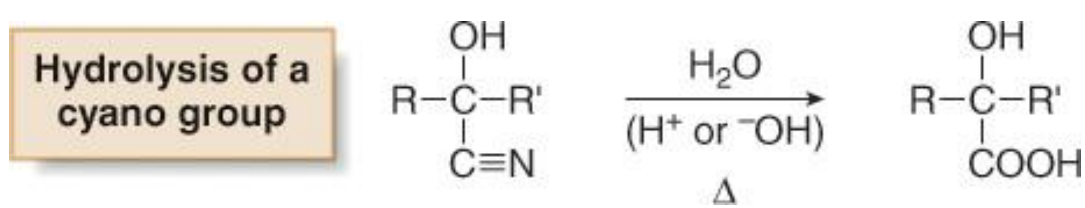
aceton
cyanohydrin

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.

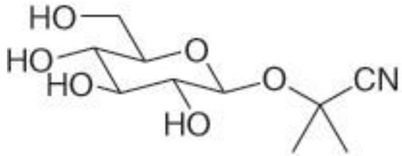


- The cyano group of a cyanohydrin is readily hydrolyzed to a carboxy group by heating with aqueous acid or base.

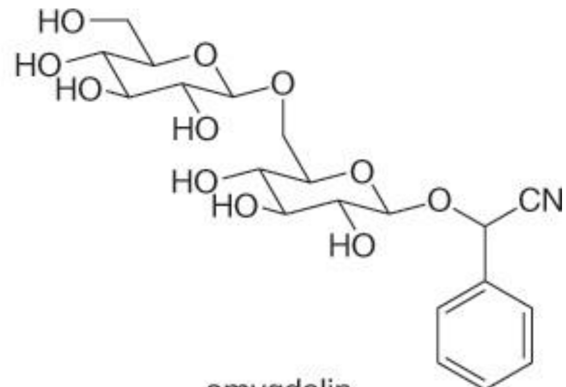


Nucleophilic Addition of CN^-

- Linamarin and Amygdalin are two naturally occurring cyanohydrin derivatives.

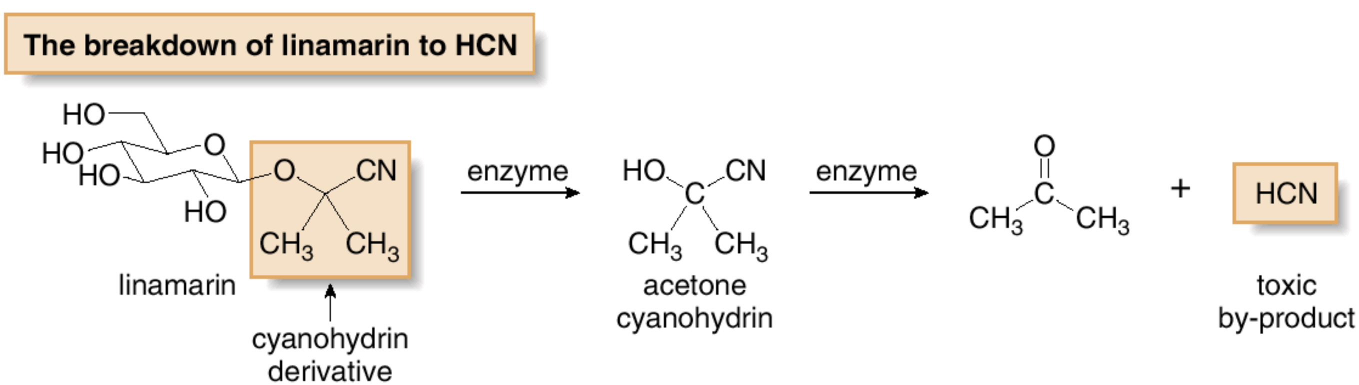


linamarin
(found in cassava root)



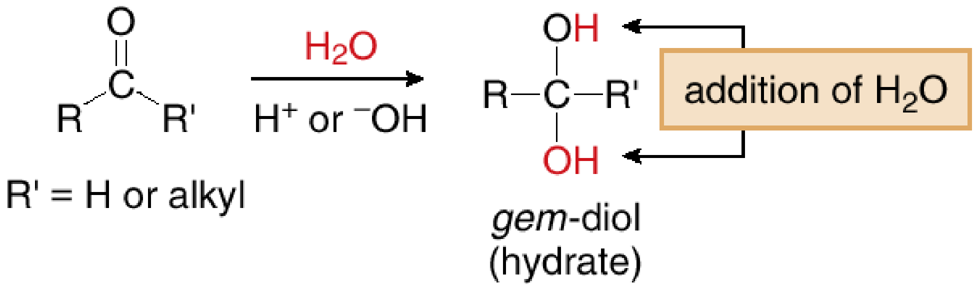
amygdalin
(commonly called laetrile)

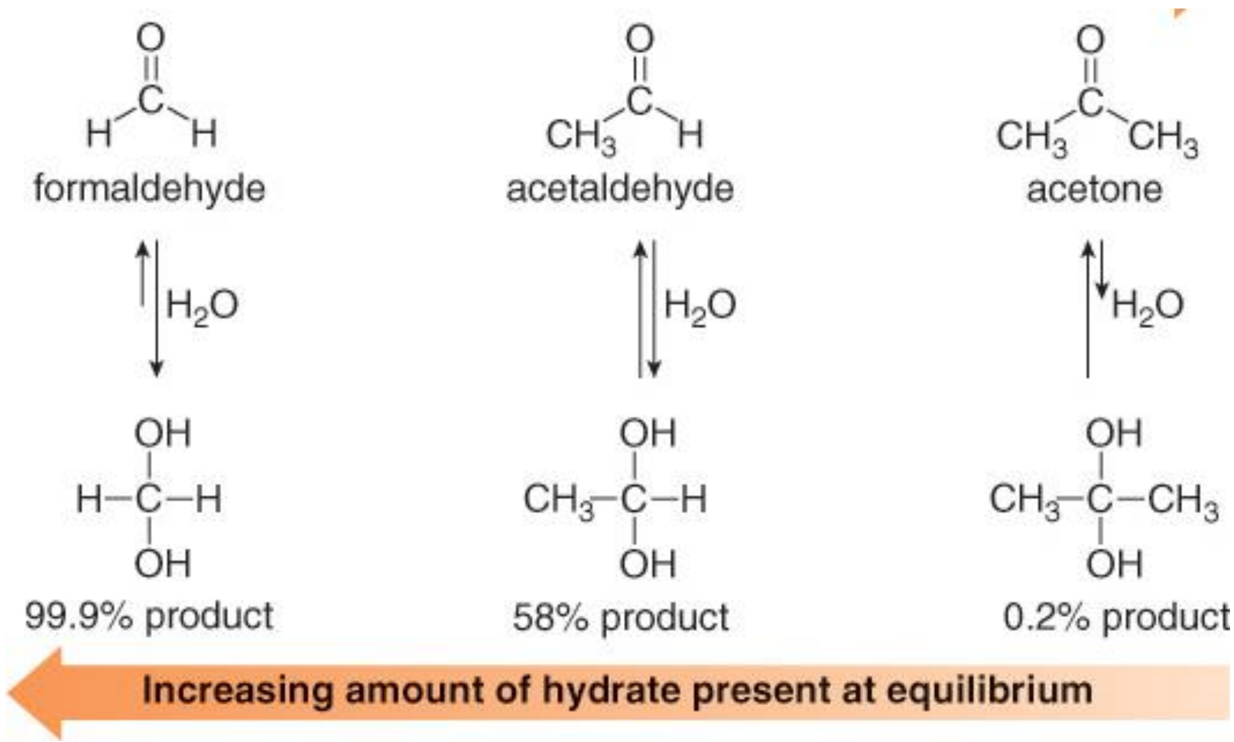
- Both compounds are toxic because they are metabolized to cyanohydrins, which are hydrolyzed to carbonyl compounds and HCN gas.



Addition of H_2O — Hydration

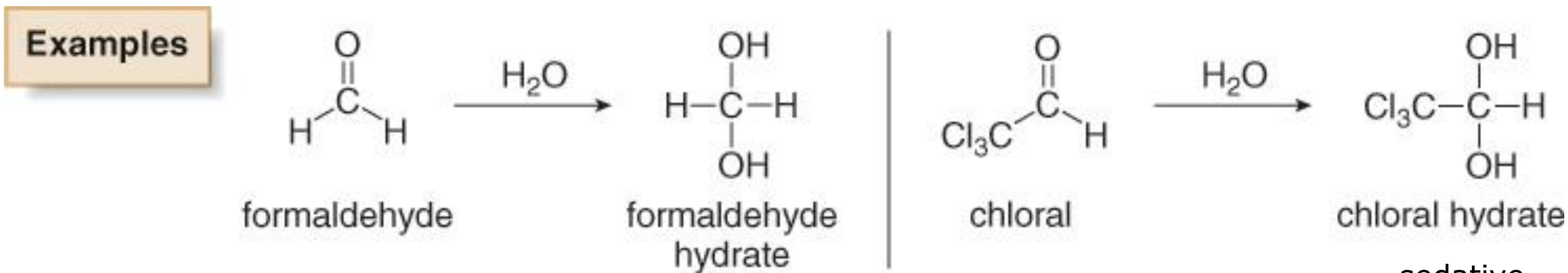
Nucleophilic addition of H_2O





Addition of H_2O — Hydration

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

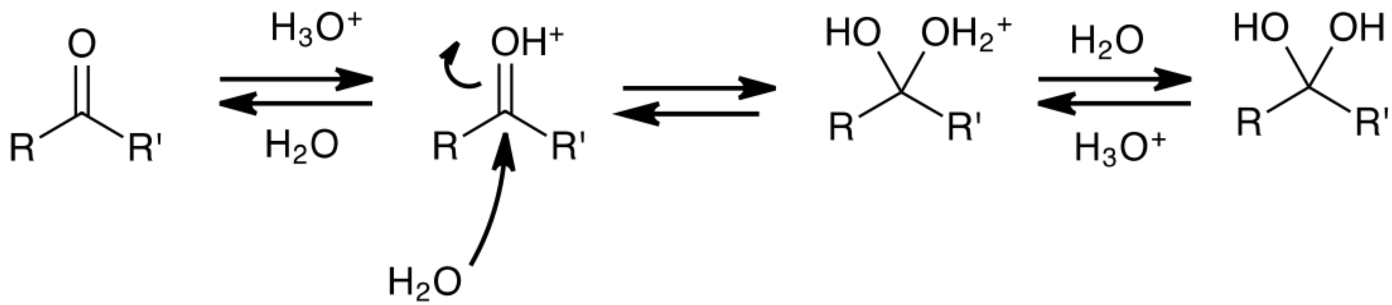


sedative

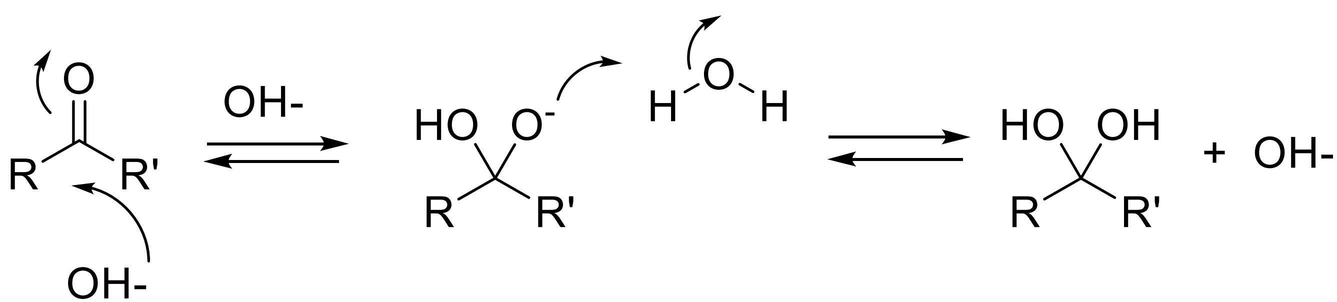
Addition of H_2O — Hydration

Addition of H_2O is generally slow but can be catalyzed by OH- or H^+

Acid catalysis:

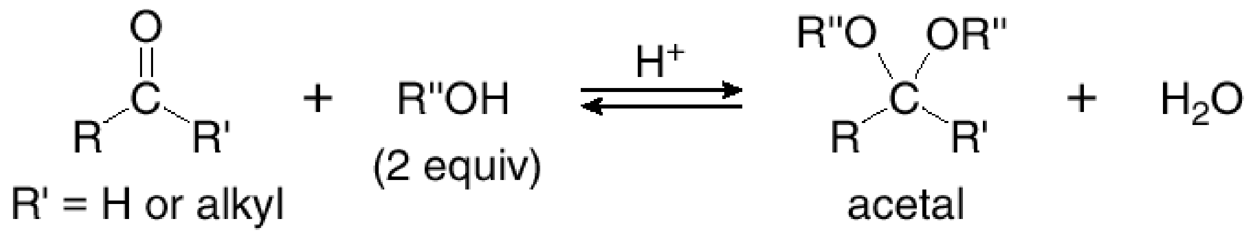


Basic catalysis:

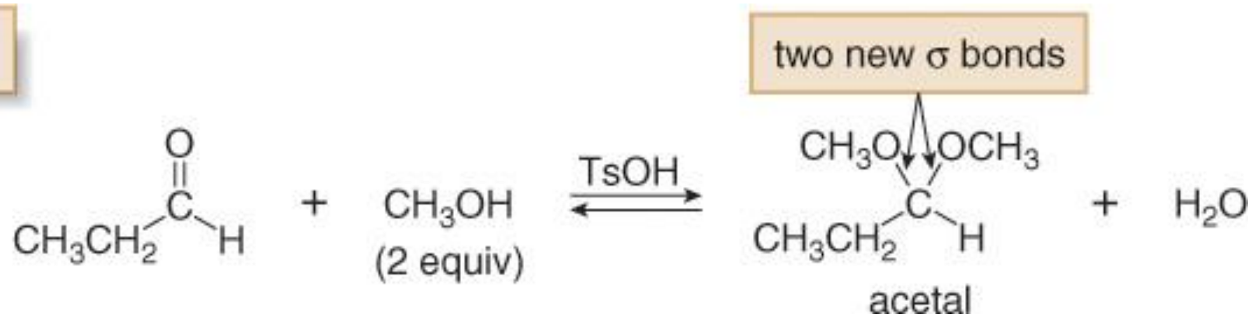


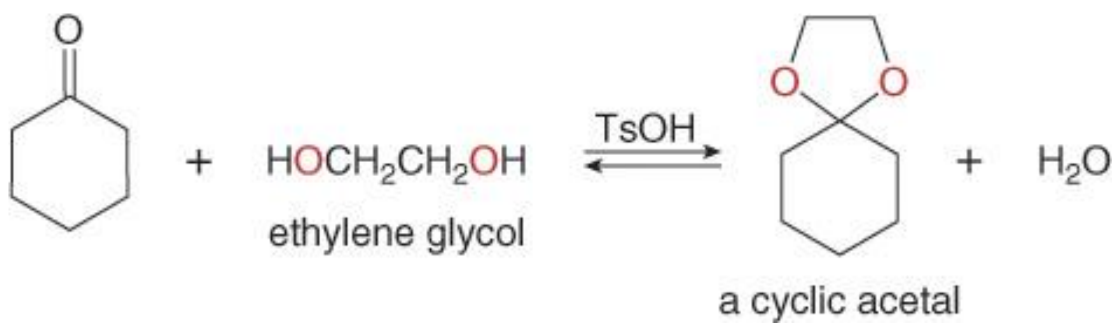
Addition of Alcohols — Acetal Formation

Acetal formation

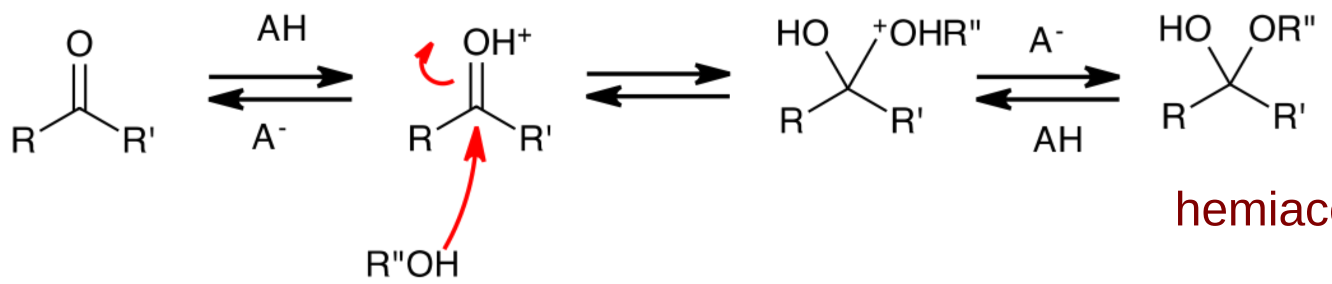


Example

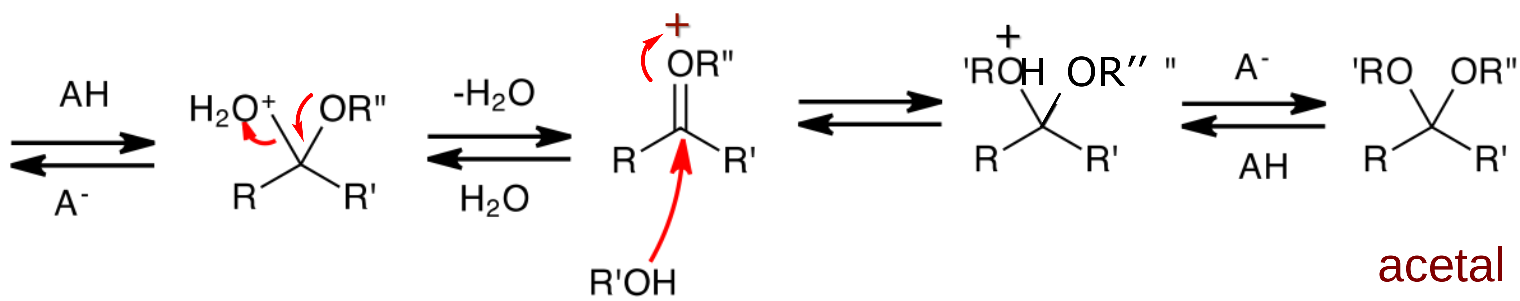




Addition of Alcohols — Acetal Formation



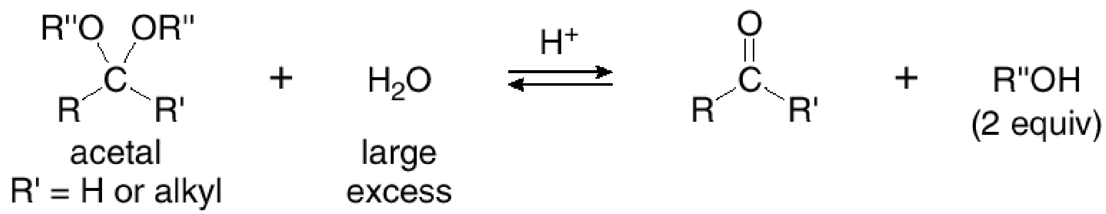
hemiacetal



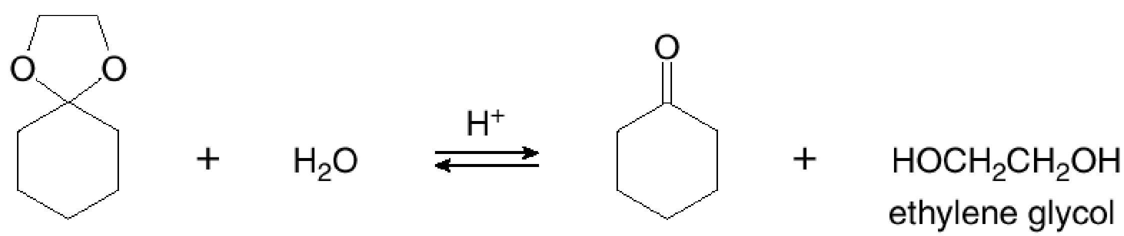
acetal

Acetal Hydrolysis

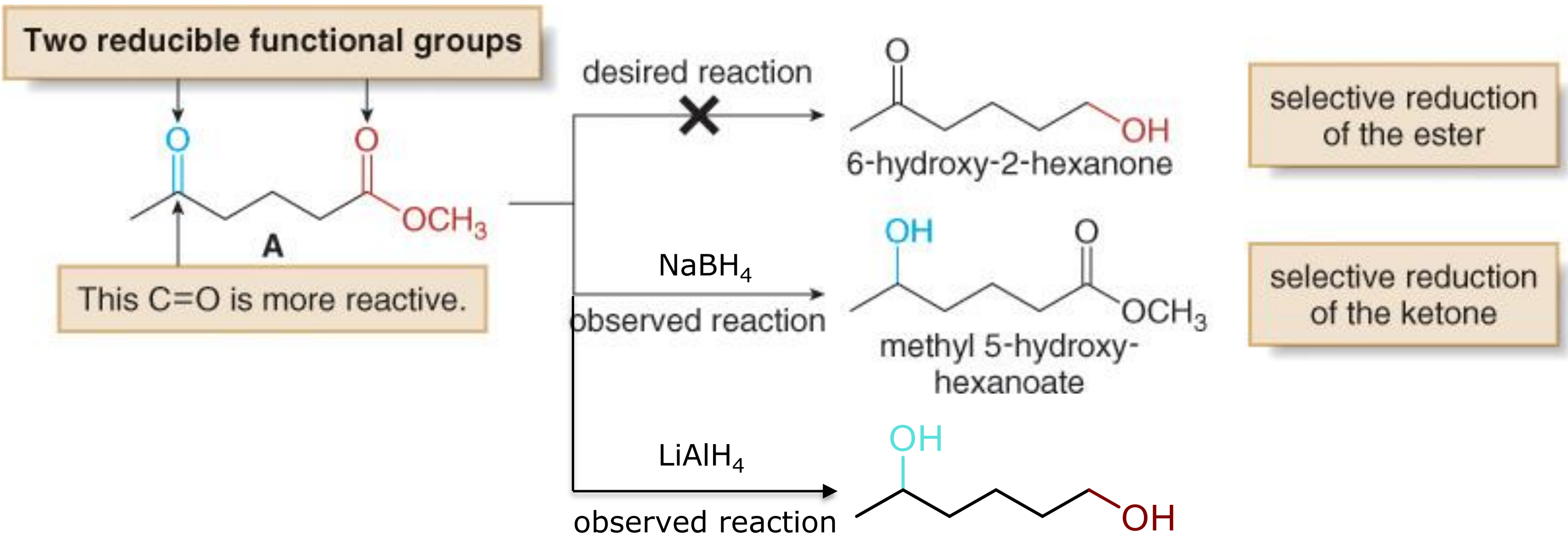
Acetal hydrolysis



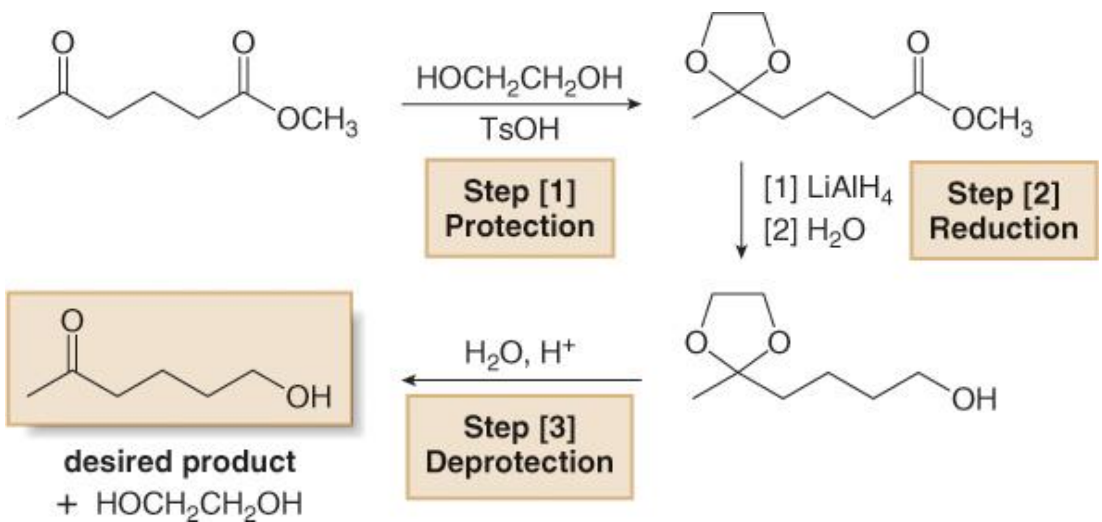
Example



Acetals as Protecting Groups

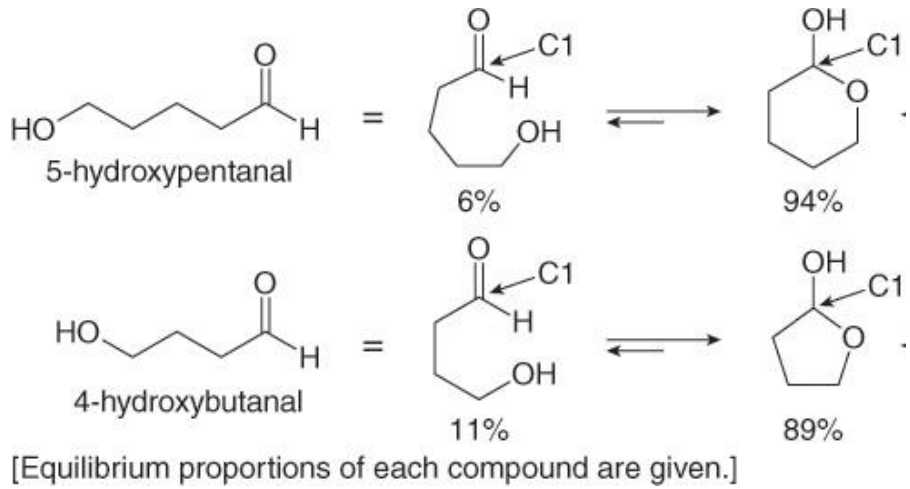


Solution:

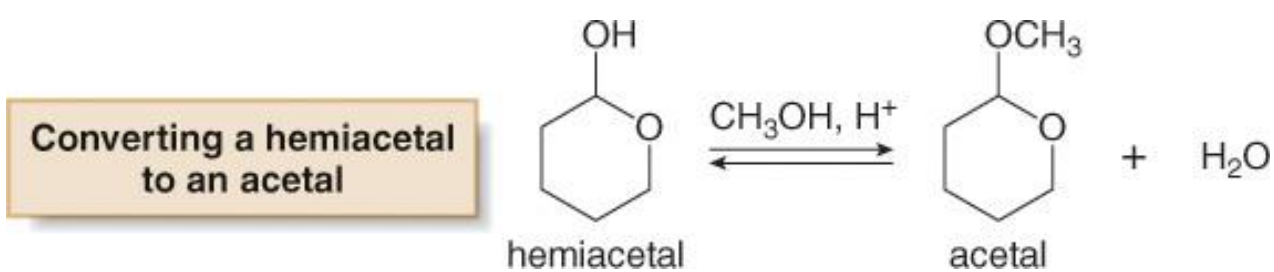


Cyclic Hemiacetals and Acetals

Cyclic hemiacetals are formed by intramolecular cyclization of hydroxy aldehydes.

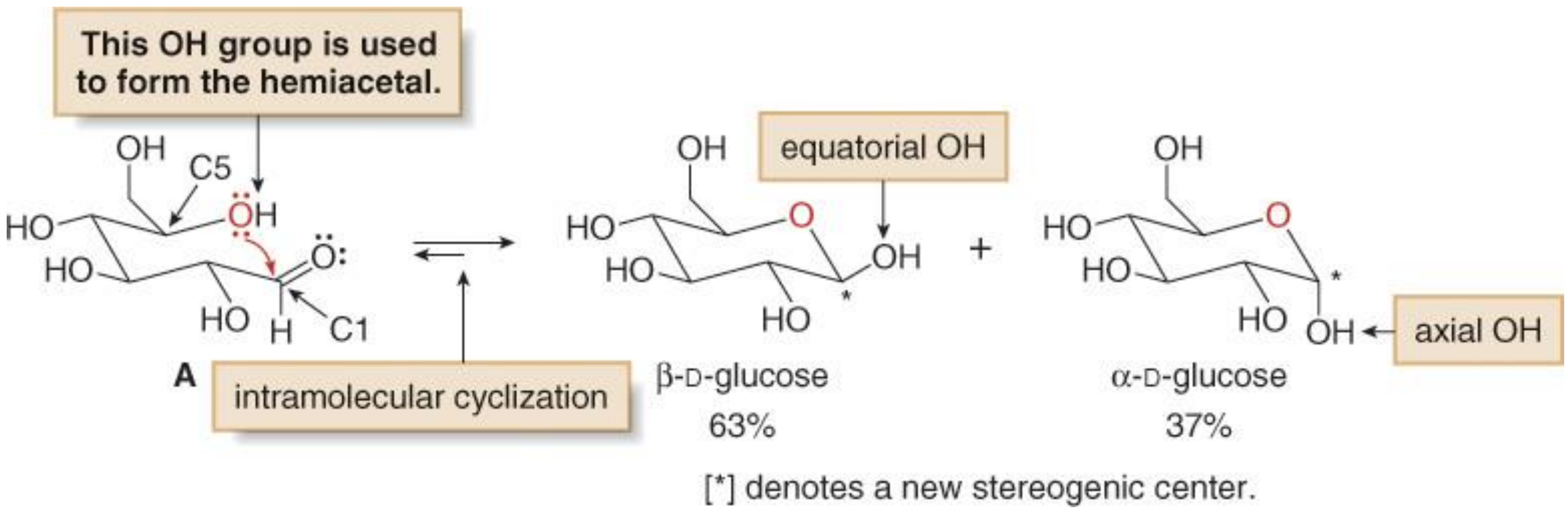


Cyclic hemiacetals can be converted to acetals by treatment with an alcohol and acid.

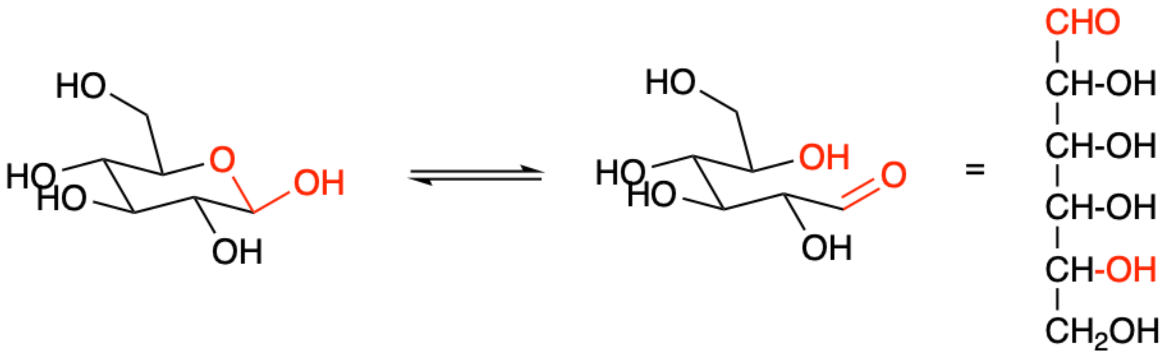


Introduction to Carbohydrates

- 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.



Equilibrium Between Hemiacetal and Open Chain Forms of Glucose



Introduction to Carbohydrates

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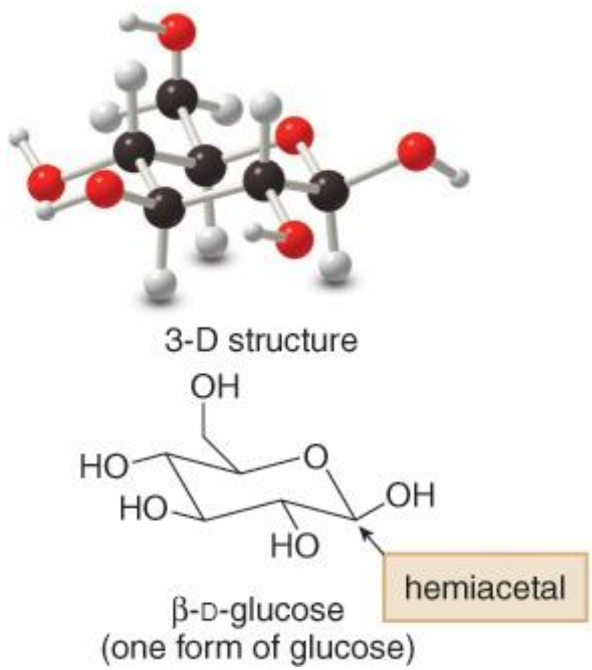
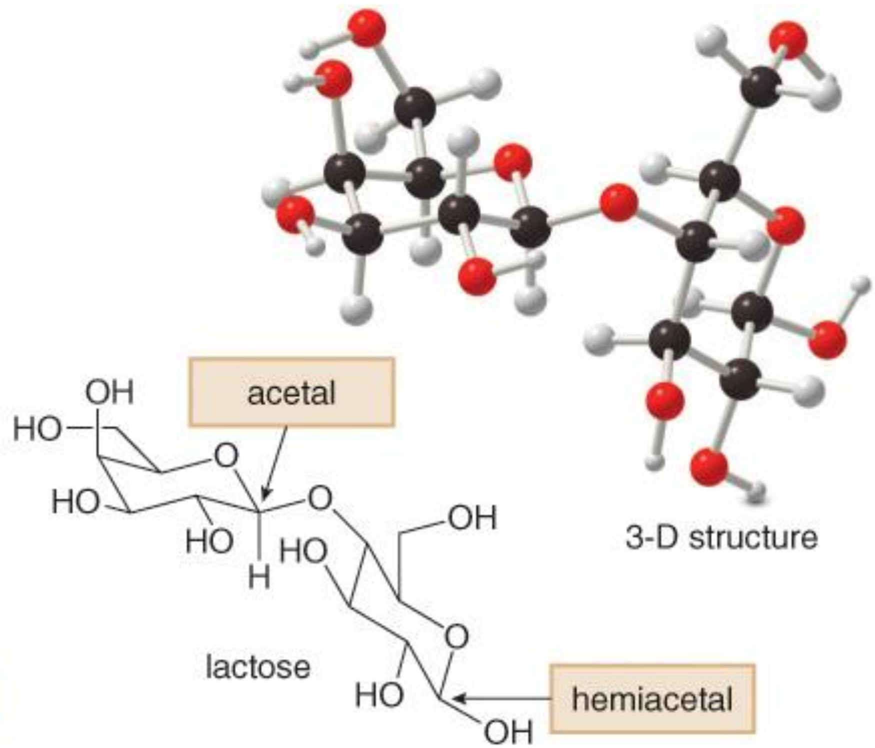
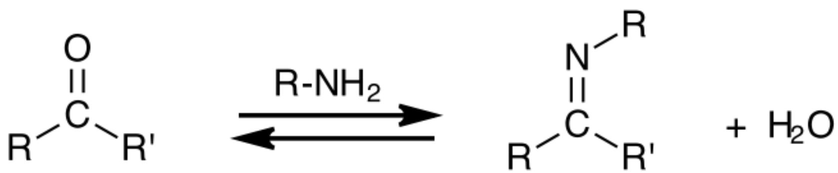




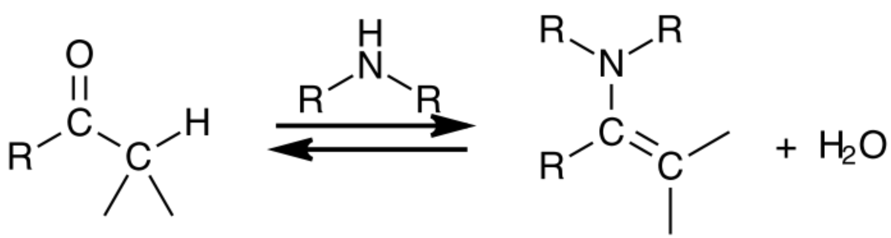
Addition of Amines

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



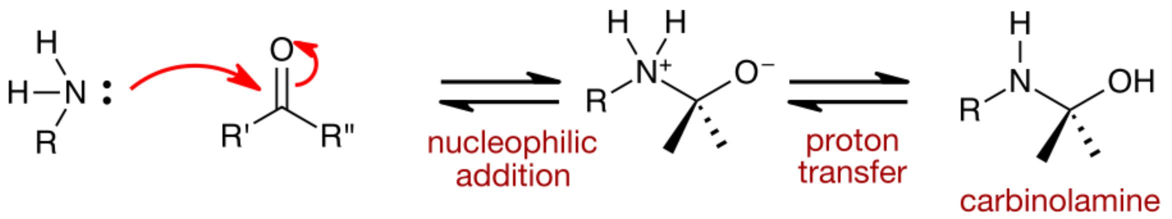
The N atom of an imine is sp^2 hybridized, making the C—N—R bond angle 120° (not 180°).

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

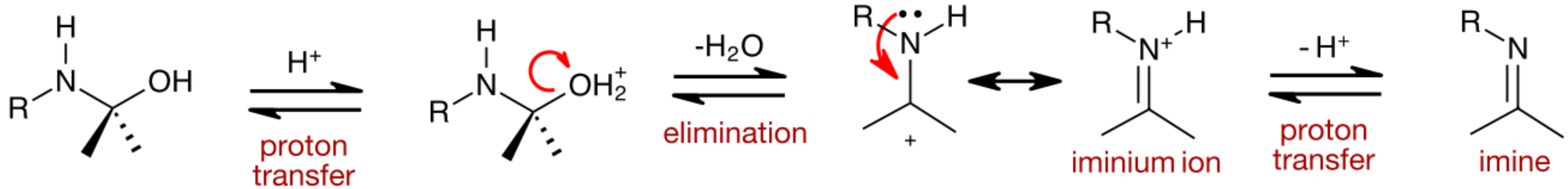


Primary Amines: Complete Mechanism

1. Amine addition

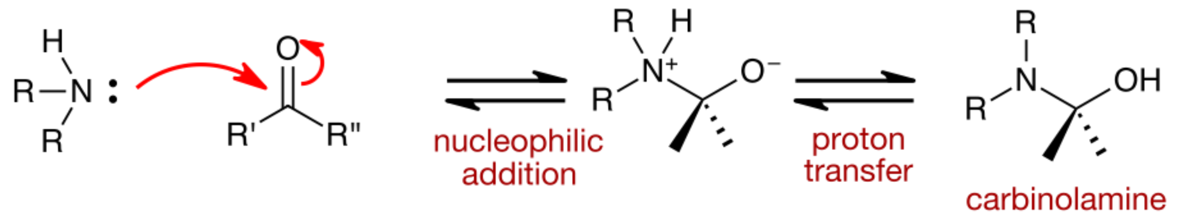


2. Elimination of water (E1)

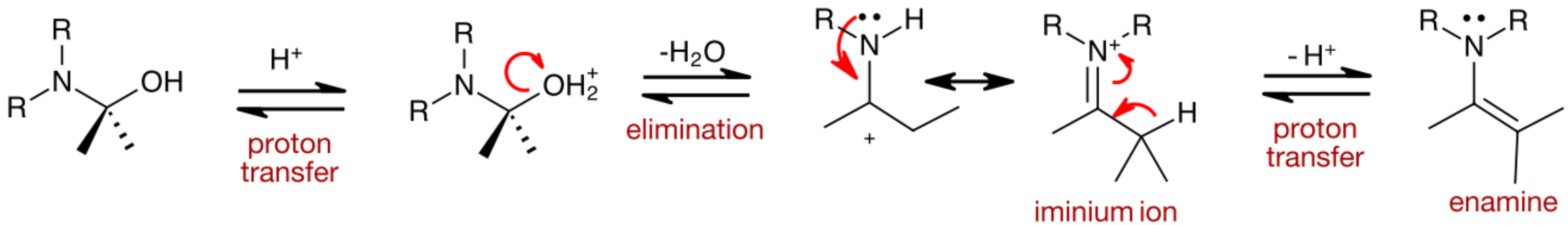


Secondary Amines: Complete Mechanism

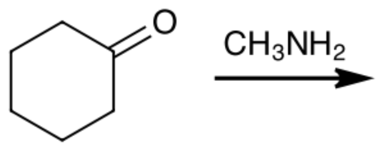
1. Amine addition

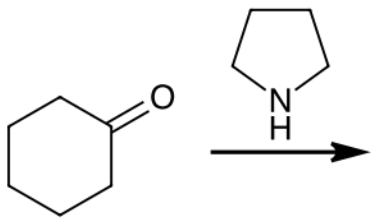


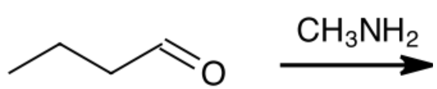
2. Elimination of water (E1)

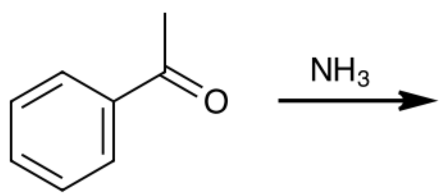


Addition of Amines







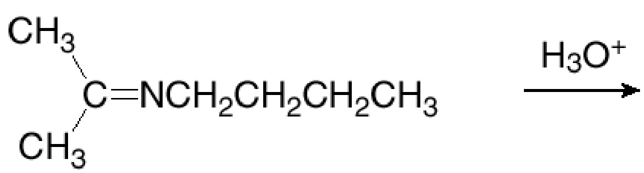


Imine and Enamine Hydrolysis

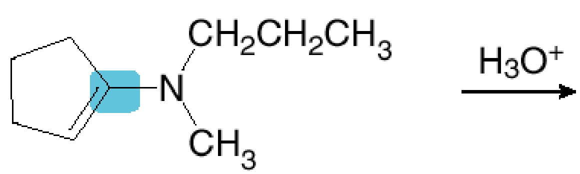
- Because imines and enamines are formed by a reversible set of reactions, both can be converted back to carbonyl compounds by hydrolysis with mild acid.
- The mechanism of hydrolysis is the exact reverse of the mechanism written for formation of imines and enamines.

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

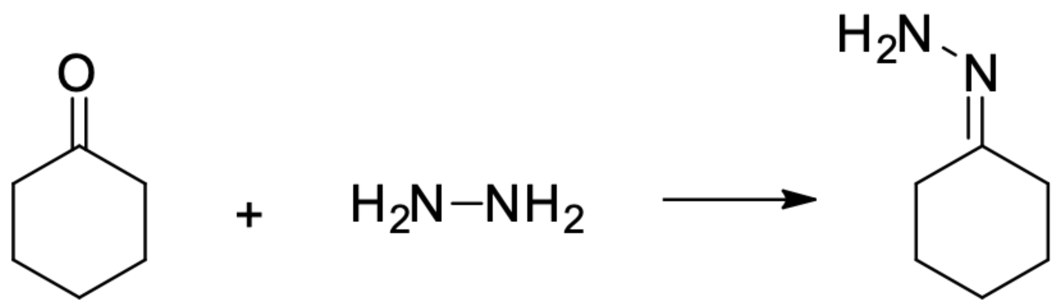
Imine hydrolysis



Enamine hydrolysis



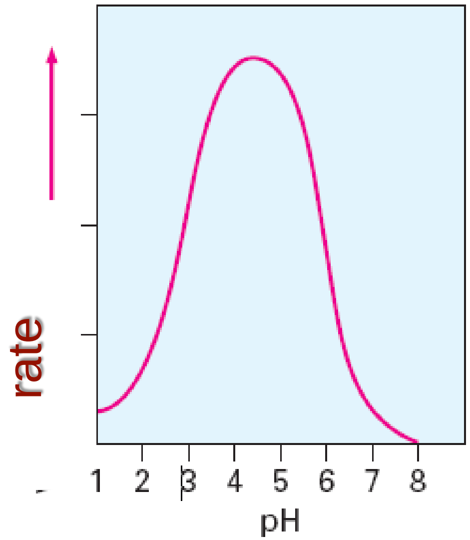
Other Amines



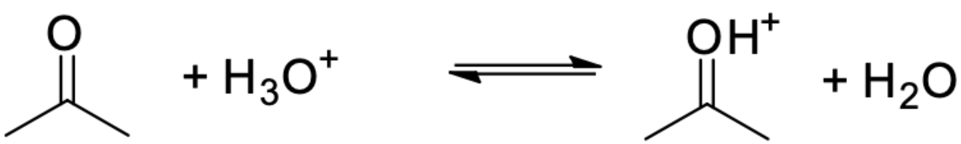
hydrazine hydrazone

hydroxylamine oxime

Addition of Amines – Effect of pH



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

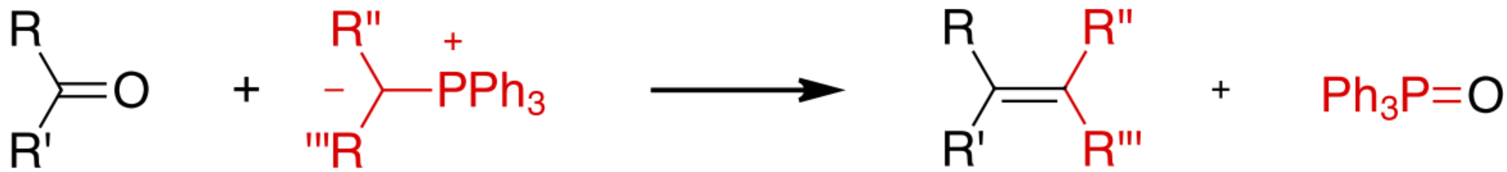


protonation activates the electrophile

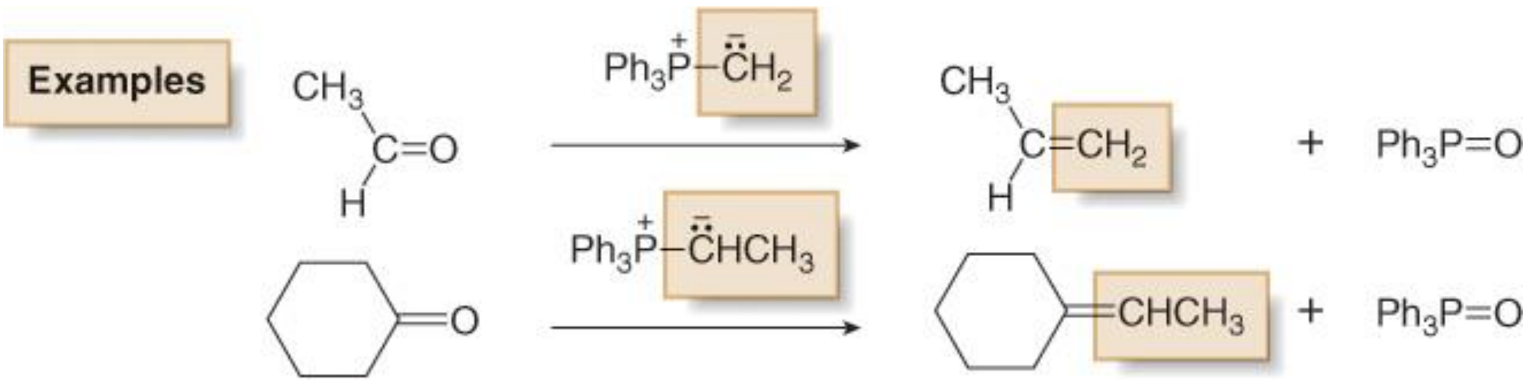
$$R{-}NH_2 + H_3O^+ \rightleftharpoons R{-}NH_3^+ + H_2O$$

protonation deactivates the nucleophile

The Wittig Reaction

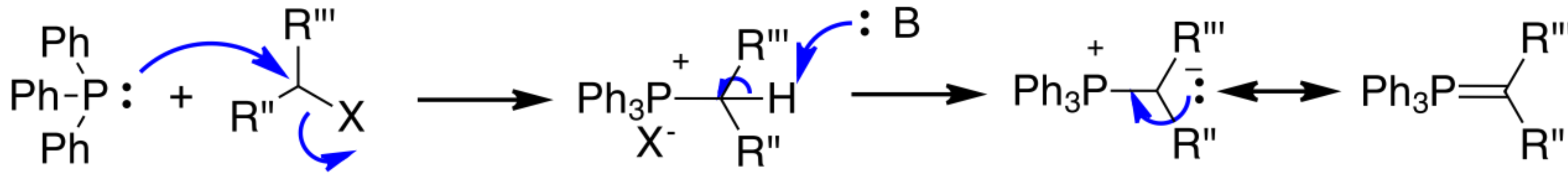


phosphonium ylids
(Wittig reagents)



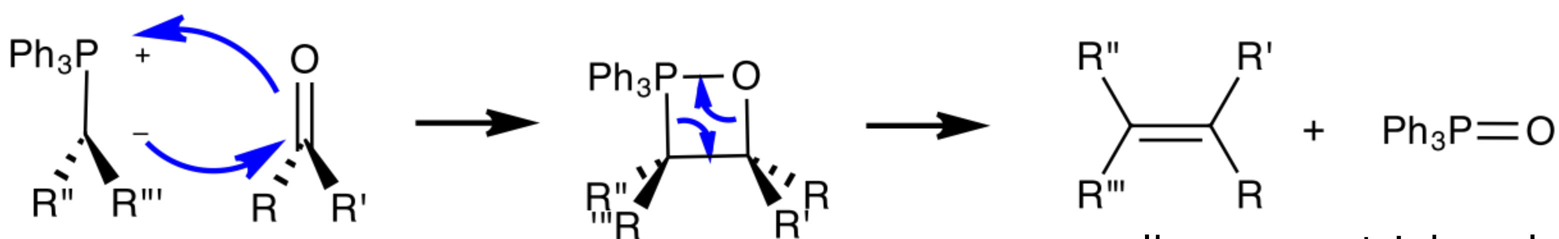
The Wittig Reaction

Preparation of phosphorus ylides (phosphoranes) B: nBuLi, $NaNH_2$, NaH



triphenylphosphine phosphonium salt phosphonium ylide

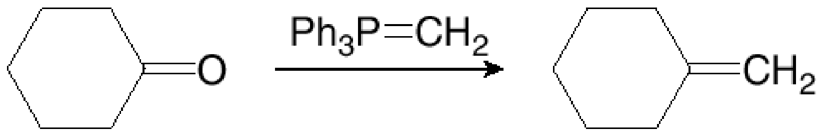
Reaction of phosphorus ylides with carbonyl compounds



alkene triphenylphosphine oxide

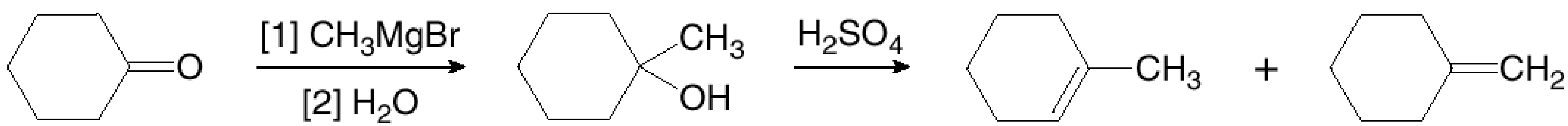
The Wittig Reaction

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



cyclohexanone B

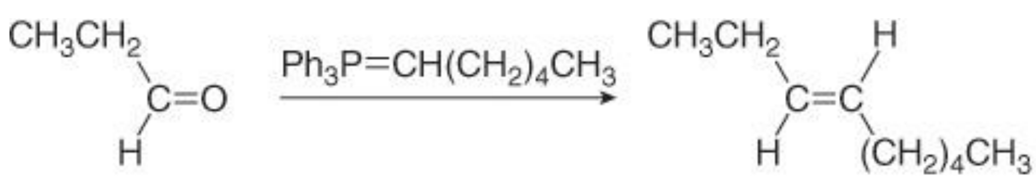
only product



B

cyclohexanone | 3° alcohol | trisubstituted C=C **major product** | disubstituted C=C **minor product**

Limitation: a mixture of stereoisomers is sometimes formed.



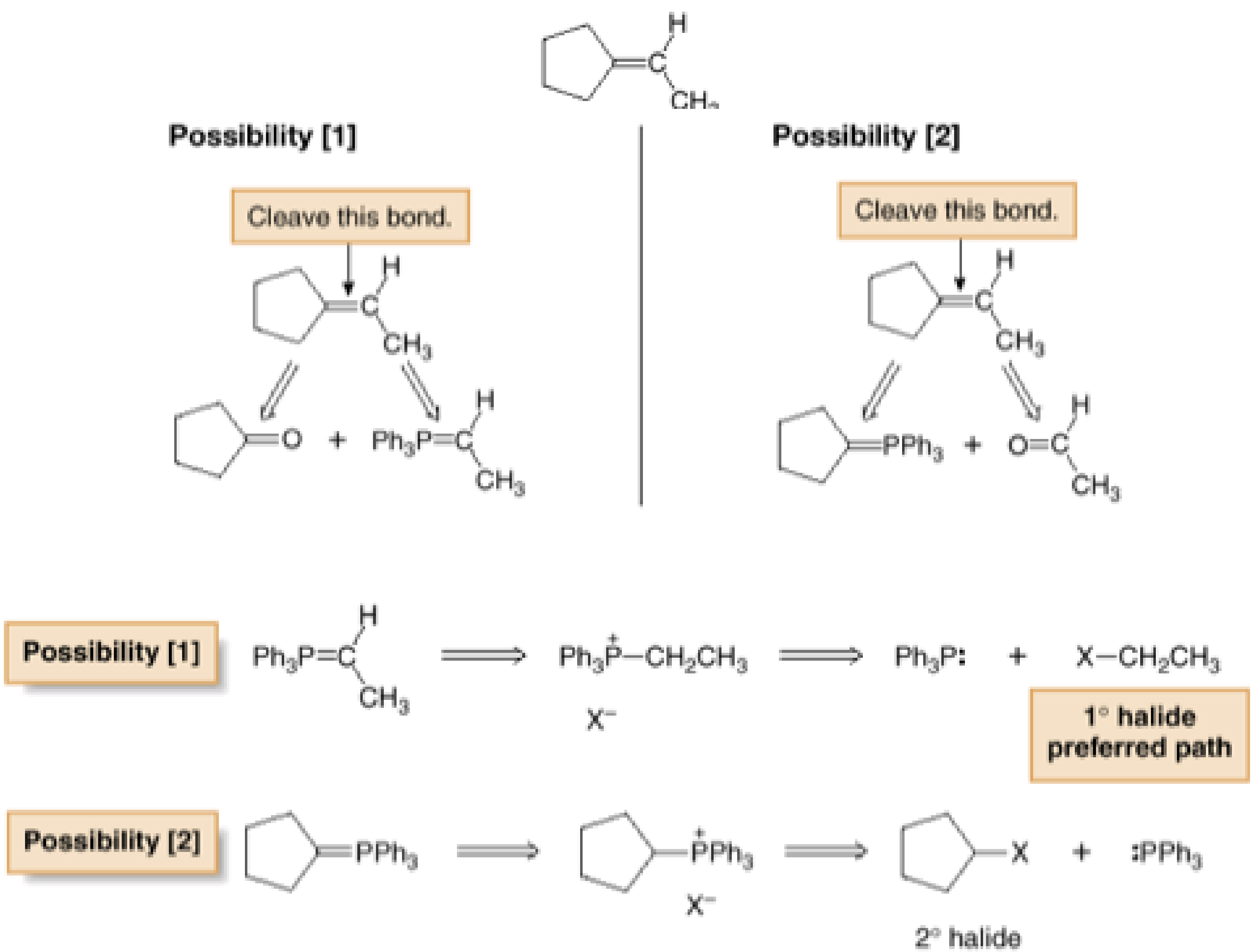
E isomer 59%

Z isomer 41%

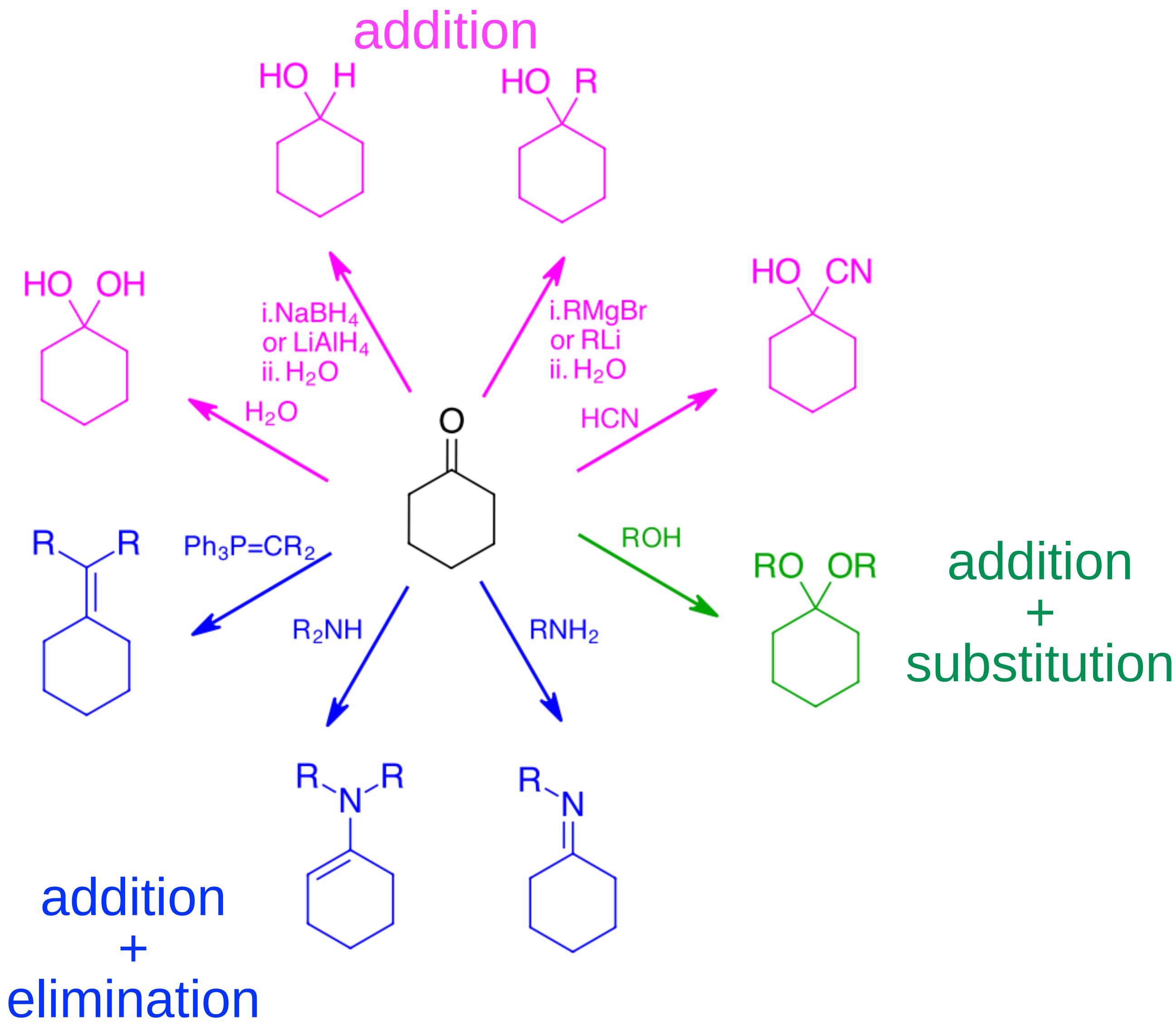
The Wittig Reaction

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

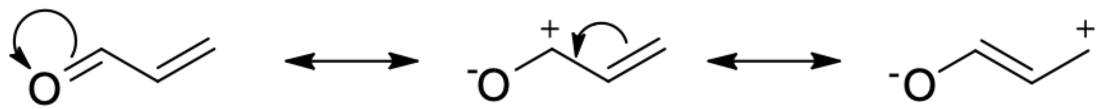
Example What starting materials are needed to synthesize alkene A by a Wittig reaction?

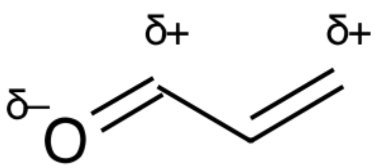


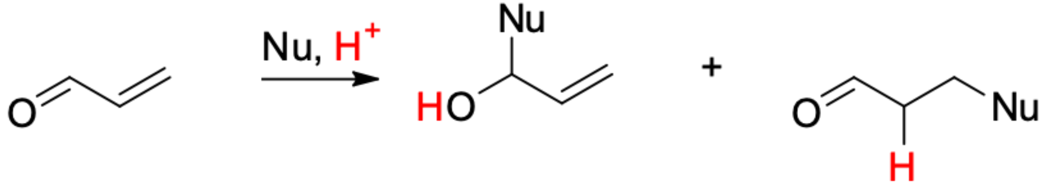
Nucleophilic Addition



α,β-Unsaturated Carbonyl Compounds





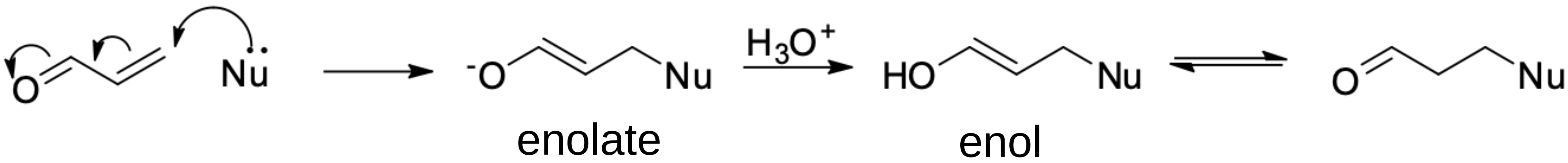


1,2-addition

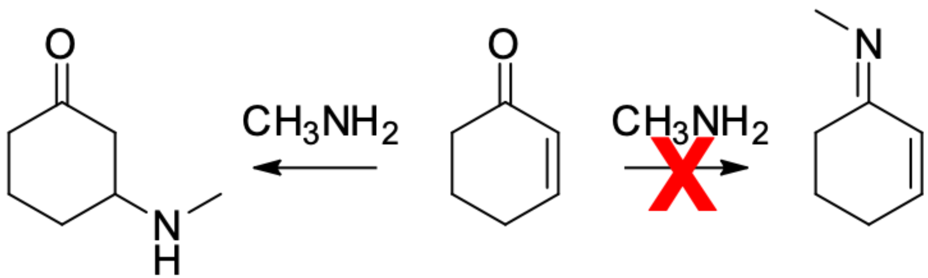
1,4-addition
(conjugate addition)

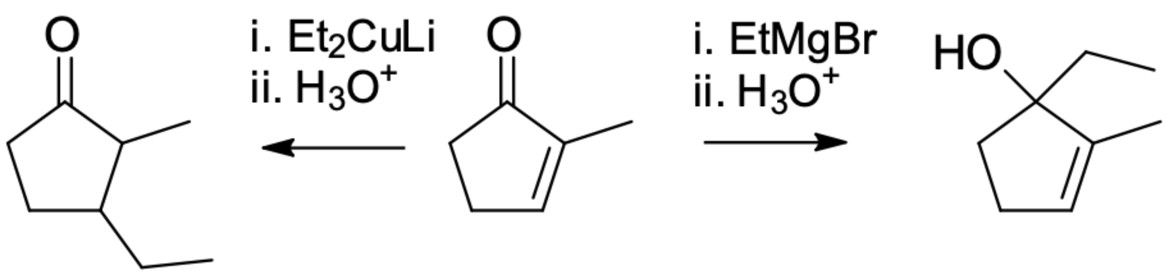
Conjugate Addition

general mechanism:

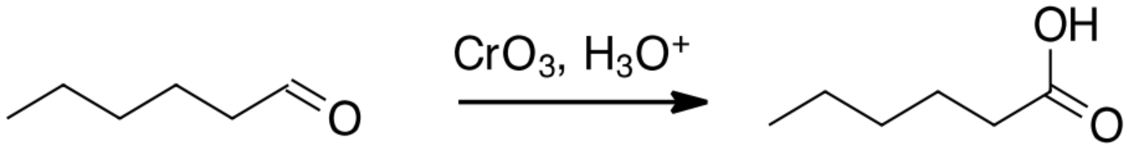


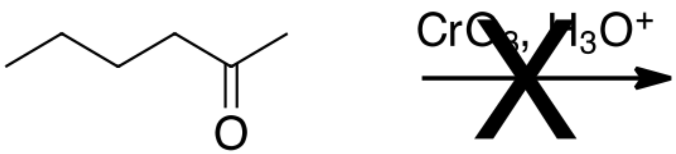
examples:



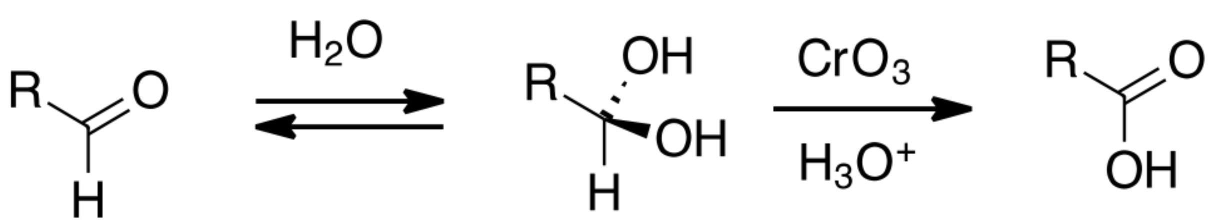


Oxidation

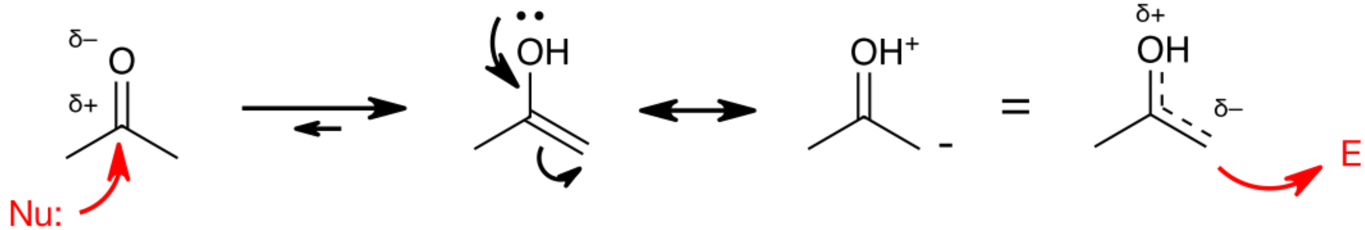




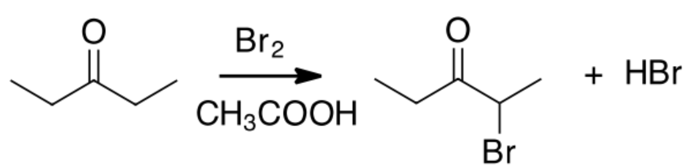
mechanism



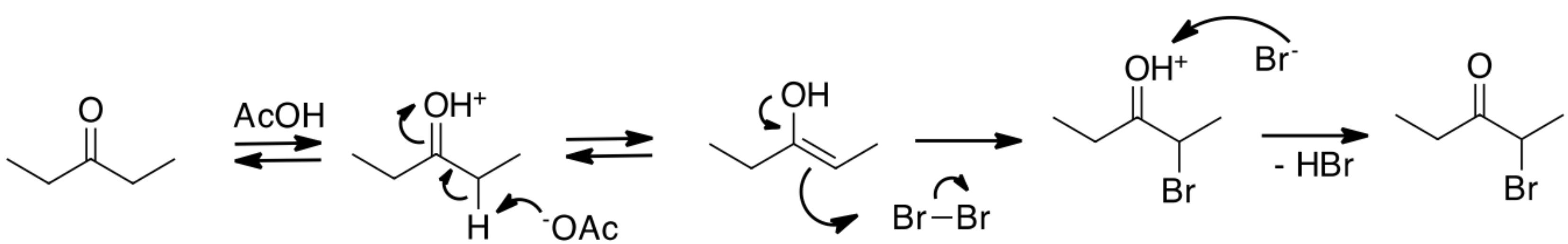
Keto-Enol Tautomerism.
Reaction at the α-Carbon



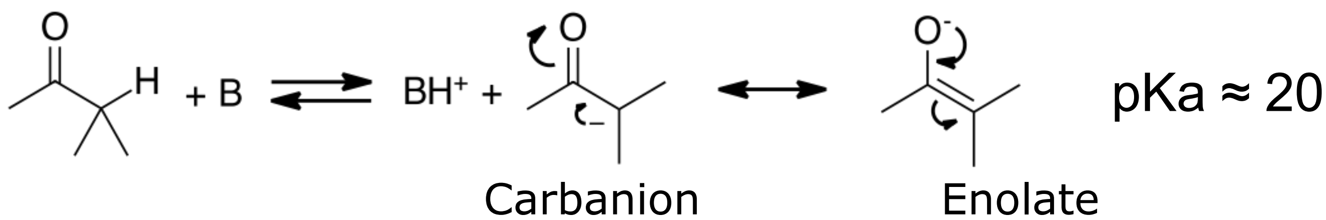
α-halogenation:



mechanism:



Enolates. Reaction at the α-Carbon



Example: 2-methylcyclohexanone