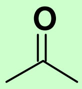
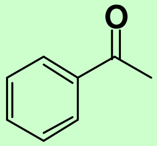
Aldehydes And Ketones

IUPAC names

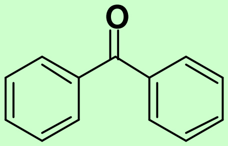
- the parent alkane is the longest chain that contains the carbonyl group
- for ketones, change the suffix -e to -one
- number the chain to give C=O the smaller number
- the IUPAC retains the common names acetone, acetophenone, and benzophenone



Propanone (Acetone)

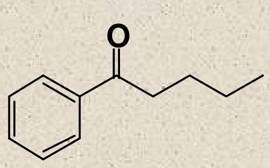


Acetophenone



Benzophenone

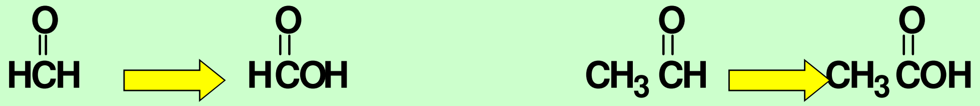
Commit to memory



1-Phenyl-1-pentanone

Common Names

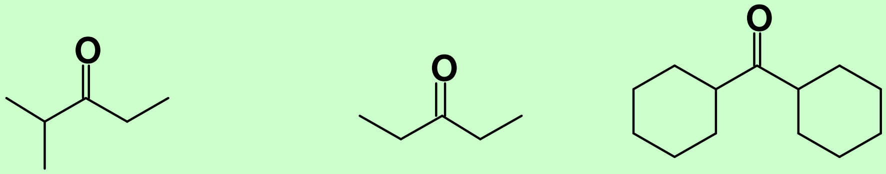
- for an **aldehyde**, the common name is derived from the common name of the corresponding carboxylic acid



$$H\overset{O}{\overset{\|}{C}}H \rightarrow H\overset{O}{\overset{\|}{C}}OH \qquad CH_3\overset{O}{\overset{\|}{C}}H \rightarrow CH_3\overset{O}{\overset{\|}{C}}OH$$

Formaldehyde Formic acid Acetaldehyde Acetic acid

- for a **ketone**, name the two alkyl or aryl groups bonded to the carbonyl carbon and add the word ketone



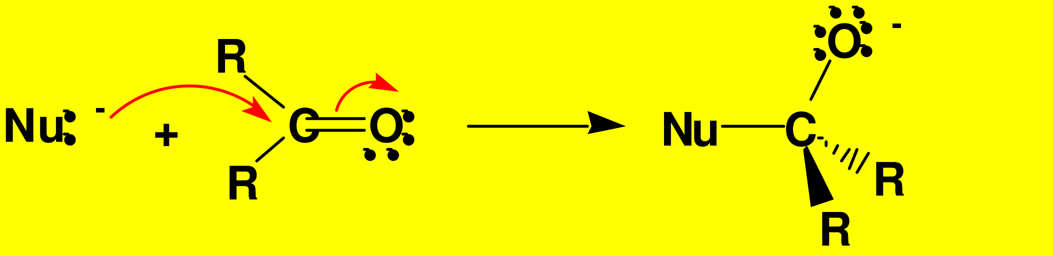
Ethyl isopropyl ketone Diethyl ketone Dicyclohexyl ketone

Drawing Mechanisms

- Use double-barbed arrows to indicate the flow of pairs of e^-
- Draw the arrow from higher e^- density to lower e^- density **i.e. from the nucleophile to the electrophile**
- Removing e^- density from an atom will create a formal ⊕ charge
- Adding e^- density to an atom will create a formal ⊖ charge
- Proton transfer is fast (kinetics) and usually reversible

Reaction Themes

One of the most common reaction themes of a carbonyl group is **addition** of a nucleophile to form a tetrahedral carbonyl addition compound (intermediate).

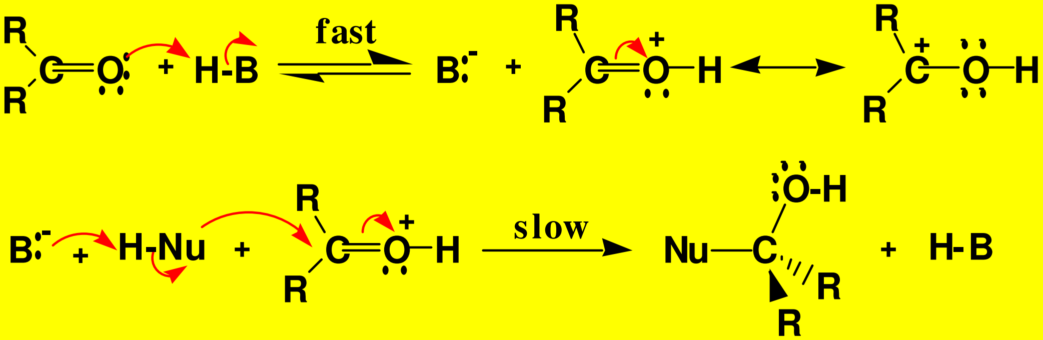


Tetrahedral carbonyl addition compound

Reaction Themes

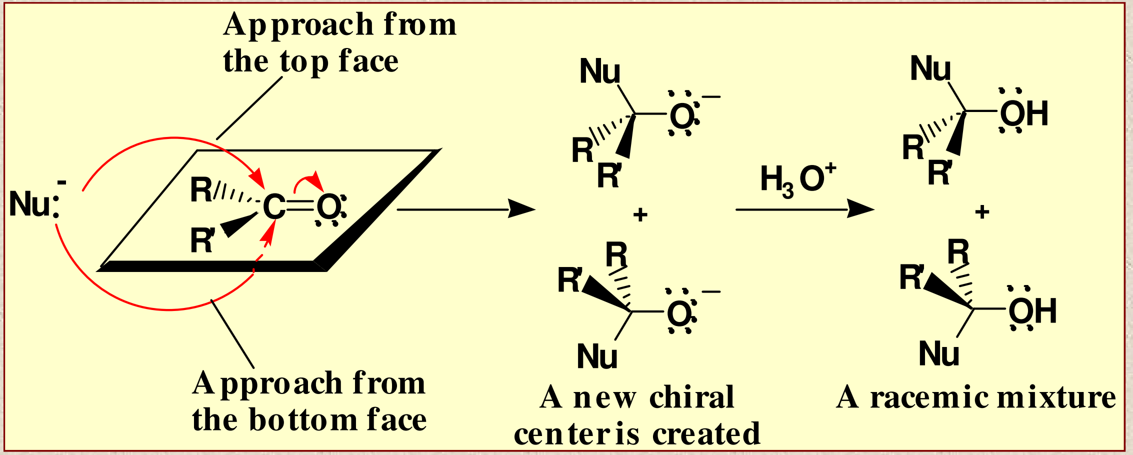
A second common theme is reaction with a proton or other Lewis acid to form a resonance-stabilized cation--

- protonation increases the electron deficiency of the carbonyl carbon and makes it more reactive toward nucleophiles



Tetrahedral carbonyl addition compound

- often the tetrahedral product of addition to a carbonyl is a new chiral center
- if none of the starting materials is chiral and the reaction takes place in an achiral environment, then enantiomers will be formed as a racemic mixture


Approach from the top face
Nu:⁻
R
R'
C=O
Approach from the bottom face
Nu
R
R'
O⁻
+
H_3O^+
OH
A new chiral center is created
A racemic mixture

Addition of C Nucleophiles

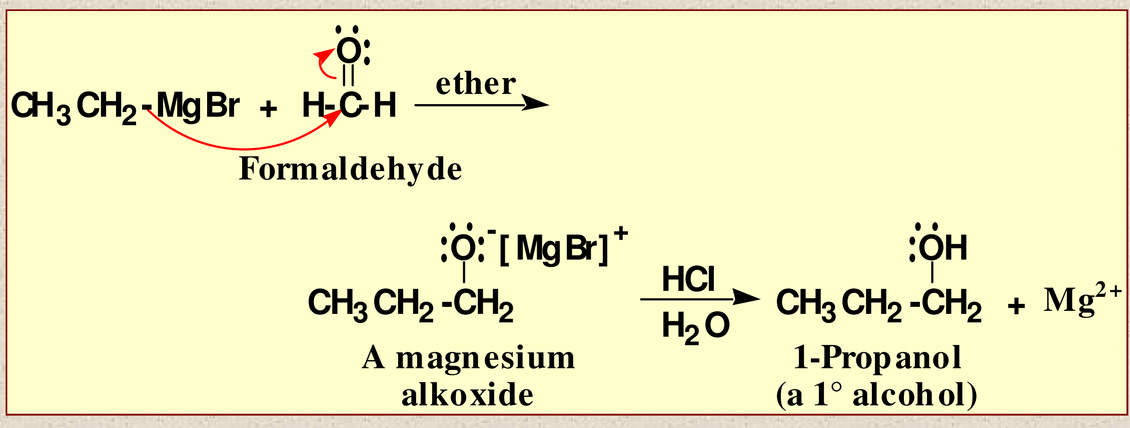
Addition of carbon nucleophiles is one of the most important types of nucleophilic additions to a **C=O** group

- a new **carbon-carbon bond** is formed in the process
- Focus on addition of these carbon nucleophiles:

RMgX	RLi	RC≡C:⁻	⁻:C≡N:
A Grignard reagent	An organolithium reagent	An alkyne anion	Cyanide ion

Grignard Reagents

- addition of a Grignard reagent to formaldehyde followed by H_3O^+ gives a 1° alcohol



CH_3CH_2-MgBr + $H-C(=O)-H$
ether
$CH_3CH_2-CH_2-O^-[MgBr]^+$
HCl
H_2O
$CH_3CH_2-CH_2-OH$ + Mg^{2+}

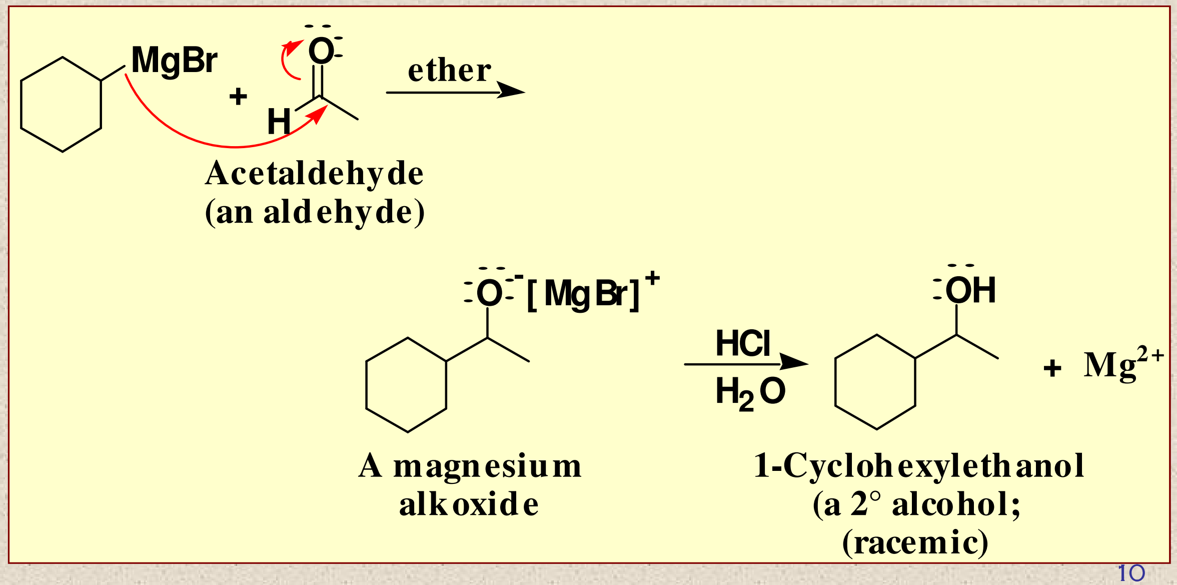
Formaldehyde

A magnesium alkoxide

1-Propanol (a 1° alcohol)

Grignard Reagents

- addition to any other RCHO gives a 2° alcohol



MgBr
+
H
ether
$O^-[MgBr]^+$
HCl
H_2O
OH
+ Mg^{2+}

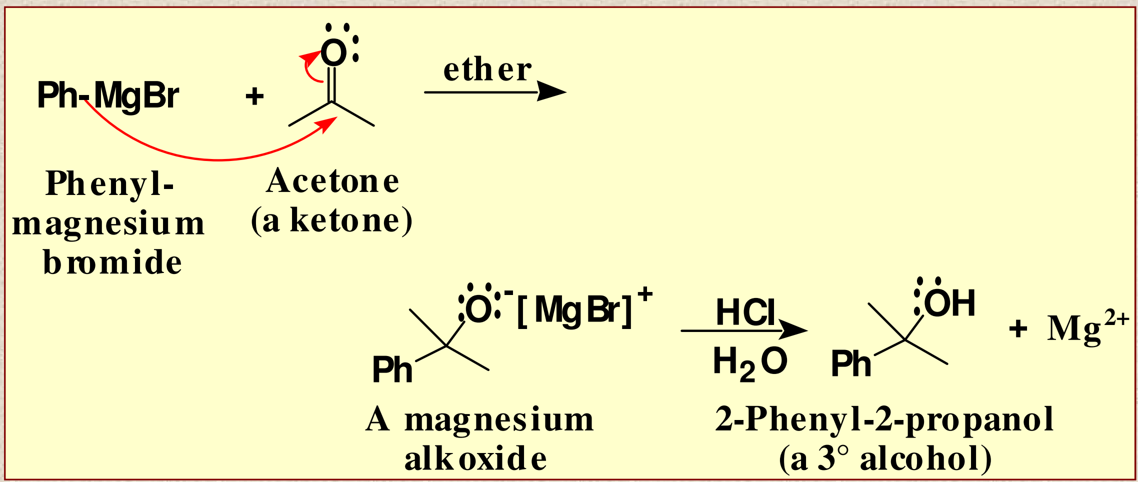
Acetaldehyde (an aldehyde)

A magnesium alkoxide

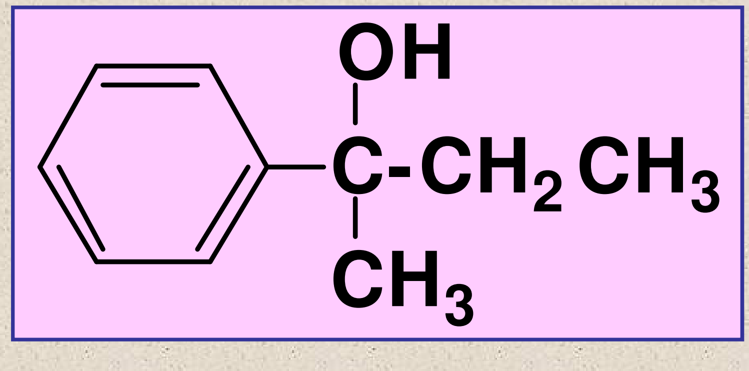
1-Cyclohexylethanol (a 2° alcohol; (racemic)

Grignard Reagents

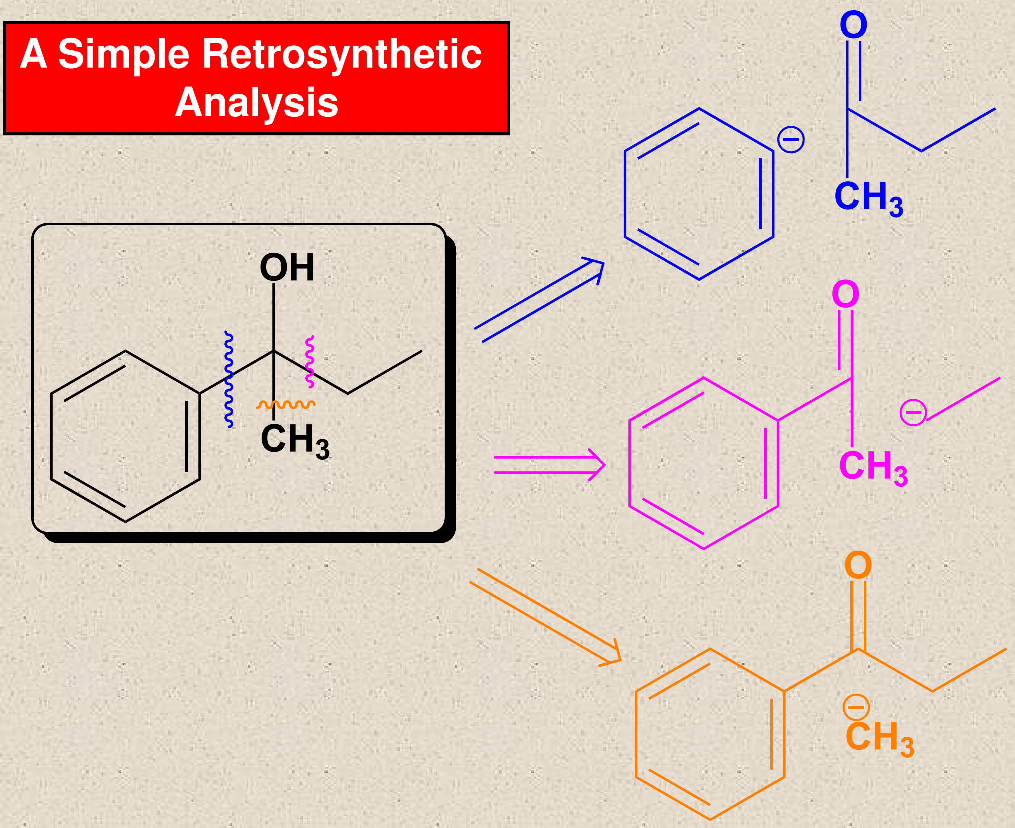
– addition to a ketone gives a 3° alcohol

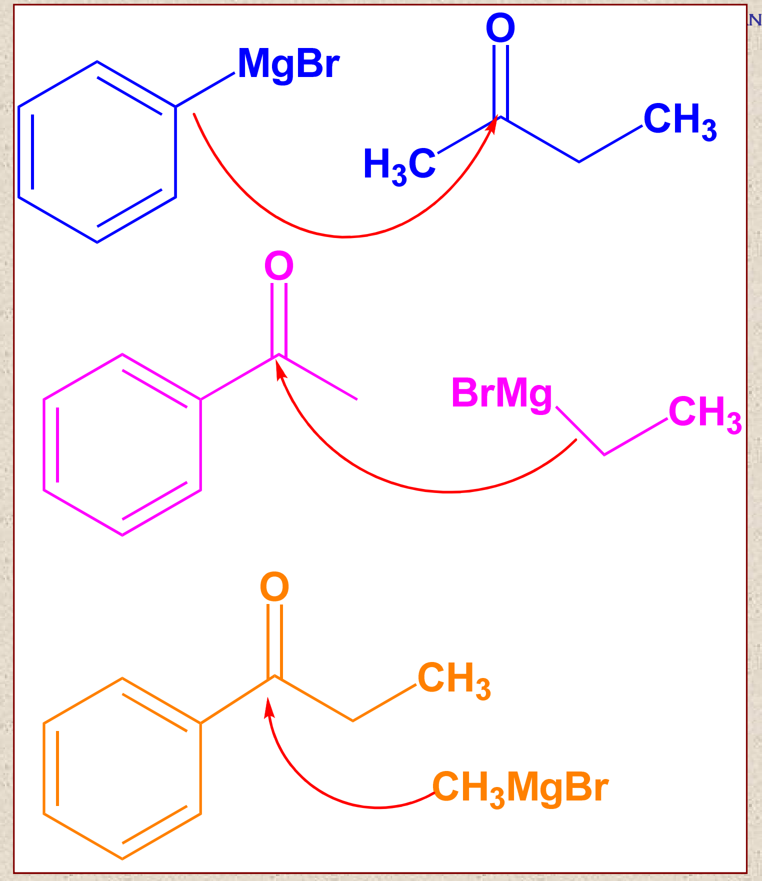

Ph-MgBr
+
ether
Phenyl-magnesium bromide
Acetone (a ketone)
[MgBr]+
HCl
H2O
Ph
OH
+ Mg2+
A magnesium alkoxide
2-Phenyl-2-propanol (a 3° alcohol)

Problem: 2-phenyl-2-butanol can be synthesized by three different combinations of a Grignard reagent and a ketone. Show each combination.

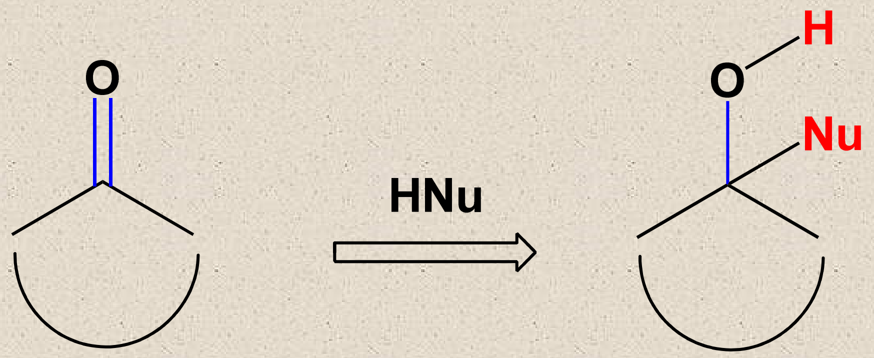

OH
C-CH2CH3
CH3

A Simple Retrosynthetic Analysis


OH
CH3
O
CH3
O
CH3
O
CH3


MgBr
O
H3C
CH3
O
BrMg
CH3
O
CH3
CH3MgBr

Addition Reactions to Carbonyl Compounds



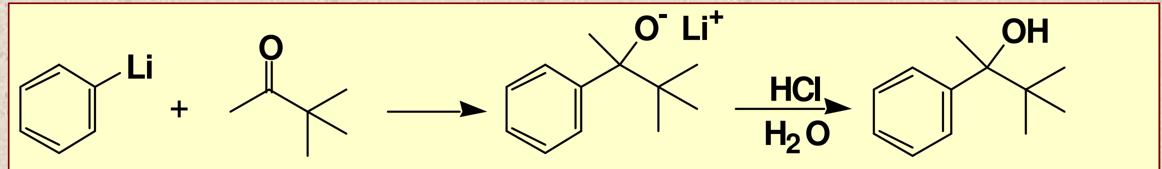
KETONE
CAN BE
CYCLIC

ALCOHOLS
OR THEIR
DERIVATIVES

Note: Water can also be added to ketones & aldehydes.

Organolithium Reagents

Organolithium compounds are generally more reactive in C=O addition reactions than RMgX, and typically give higher yields



Phenyllithium

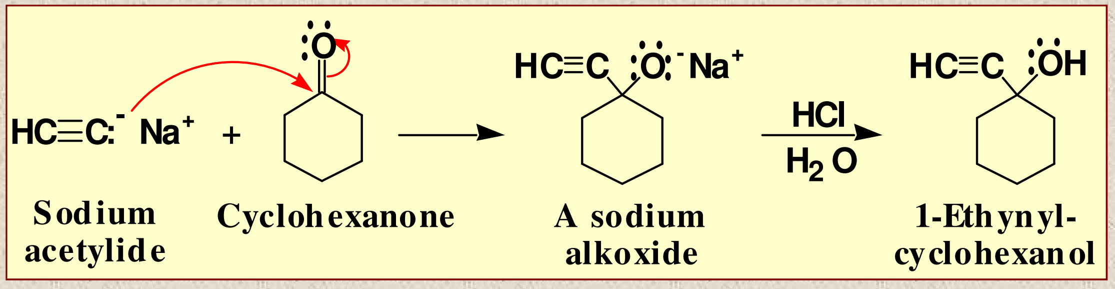
3,3-Dimethyl-2-butanone

A lithium alkoxide (racemic)

3,3-Dimethyl-2-phenyl-2-butanol (racemic)

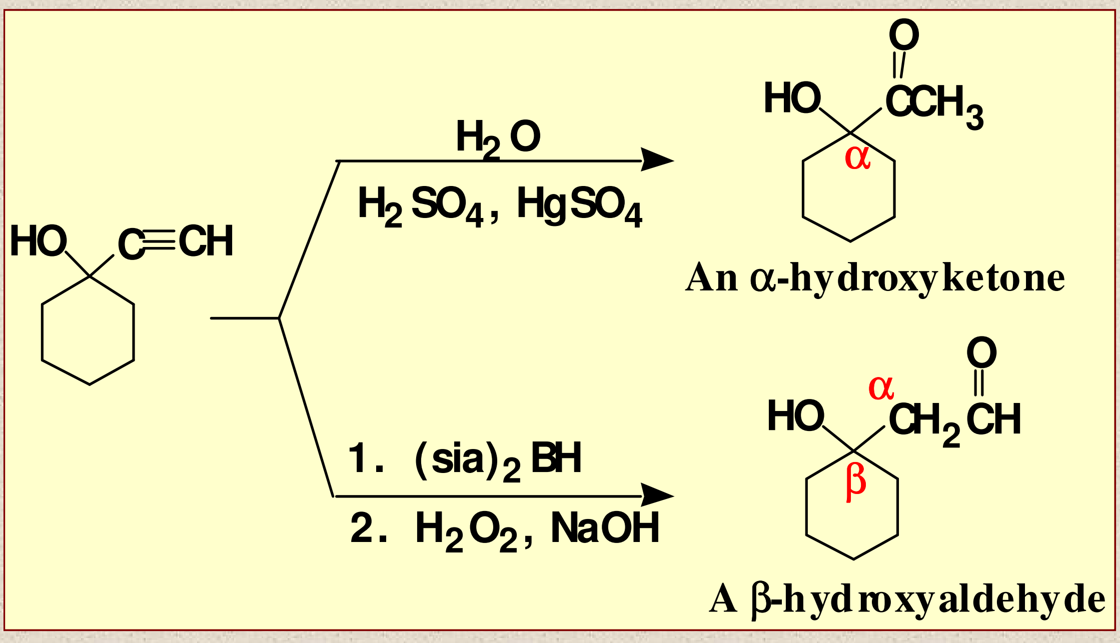
Salts of Terminal Alkynes

- Addition of an alkyne anion followed by H_3O^+ gives an α-acetylenic alcohol
- Note: this is a 2-C homologation


HC≡C:⁻ Na⁺
+
HC≡C
O⁻ Na⁺
HCl
H2O
HC≡C
OH
Sodium acetylide
Cyclohexanone
A sodium alkoxide
1-Ethynyl-cyclohexanol

Homologation is a term used for extending a carbon chain

Oxidation of Terminal Alkynes

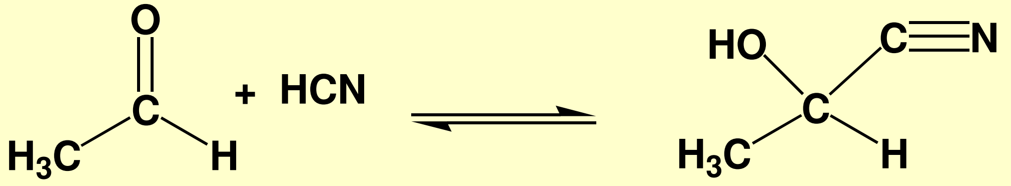

HO
C≡CH
H2O
H2SO4, HgSO4
HO
O
CCH3
α
An α-hydroxyketone
1. (sia)2BH
2. H2O2, NaOH
HO
O
α
CH2CH
β
A β-hydroxyaldehyde

(these reactions are from O-chem I)

Pg 285: use of $(sia)_2BH$

Addition of HCN

- HCN adds to the C=O group of an aldehyde or ketone to give a cyanohydrin
- Cyanohydrin: a molecule containing an -OH group and a -CN group bonded to the same carbon

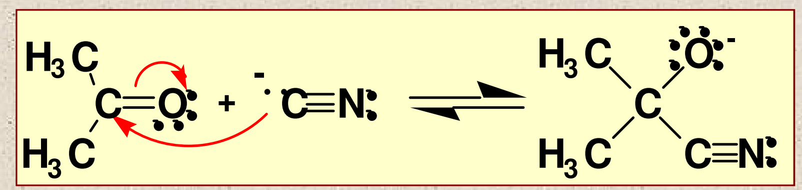


Acetaldehyde

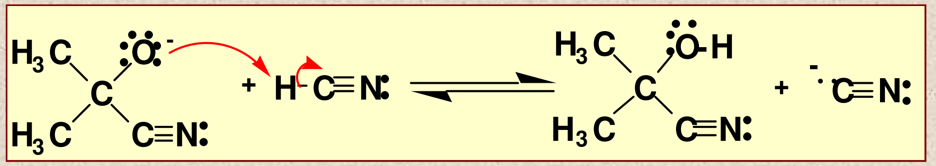
2-Hydroxypropanenitrile
(Acetaldehyde cyanohydrin)

Addition of HCN

- Mechanism of cyanohydrin formation
  - **Step 1:** nucleophilic addition of cyanide to the carbonyl carbon



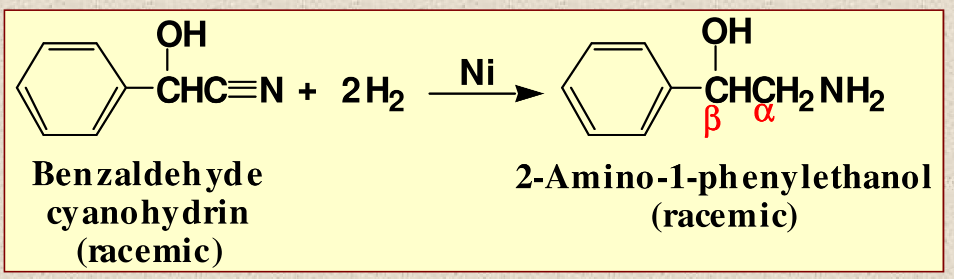
  - **Step 2:** proton transfer from HCN gives the cyanohydrin and regenerates cyanide ion



pKa=9.3

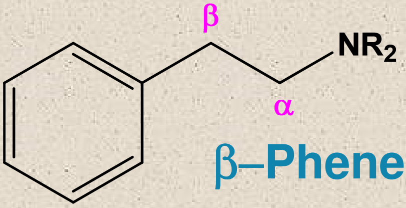
Cyanohydrins

- catalytic reduction of the cyano group gives a 1° amine


OH
CHC≡N + 2H₂
Ni
OH
CHCH₂NH₂
β
α

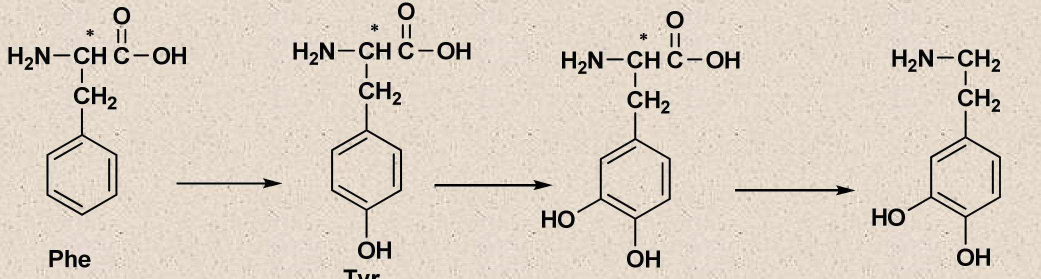
Benzaldehyde cyanohydrin (racemic)

2-Amino-1-phenylethanol (racemic)



β–Phenethylamines

Biosynthesis of Dopamine


H₂N–CH C–OH
O
*
CH₂
HO
OH

Phe

Tyr

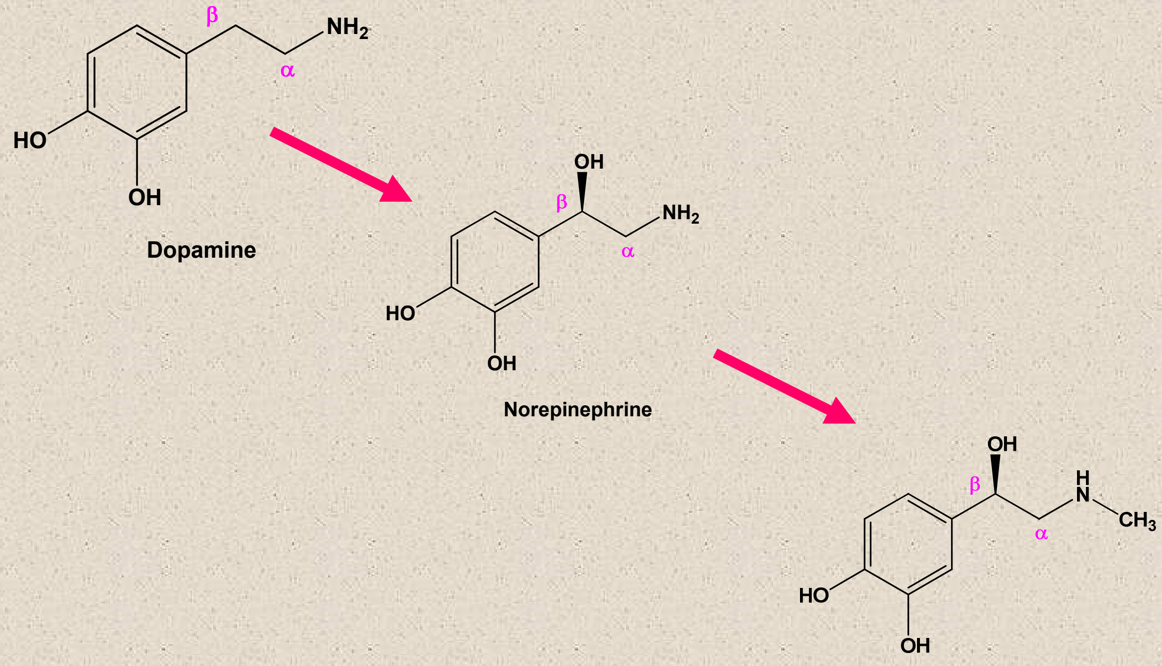
L-DOPA

(3,4-Dihydroxyphenylanaline)

Dopamine

L-Phenylalanine → L-Tyrosine → L-DOPA → Dopamine

β–Phenethylamines (Natural)

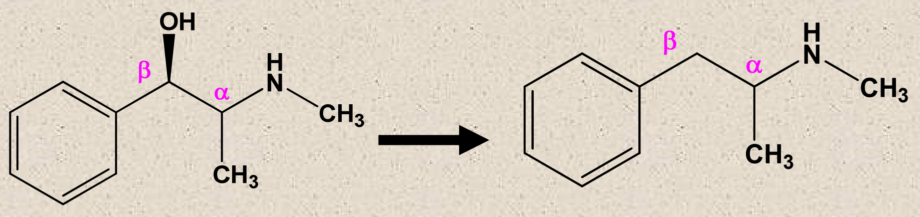

β
α
NH$_2$
HO
OH
OH
β
NH$_2$
α
HO
OH
OH
β
H
N
CH$_3$
α
HO
OH

Dopamine

Norepinephrine

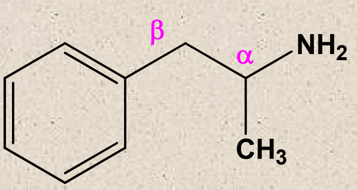
Epinephrine (adrenaline)

β–Phenethylamines (synthetic)

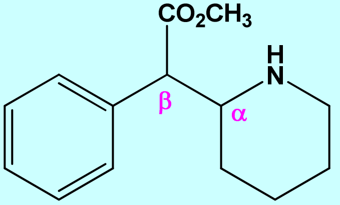

OH
β
α
H
N
CH$_3$
CH$_3$
β
α
H
N
CH$_3$
CH$_3$

Ephedrine

N-methylamphetamine

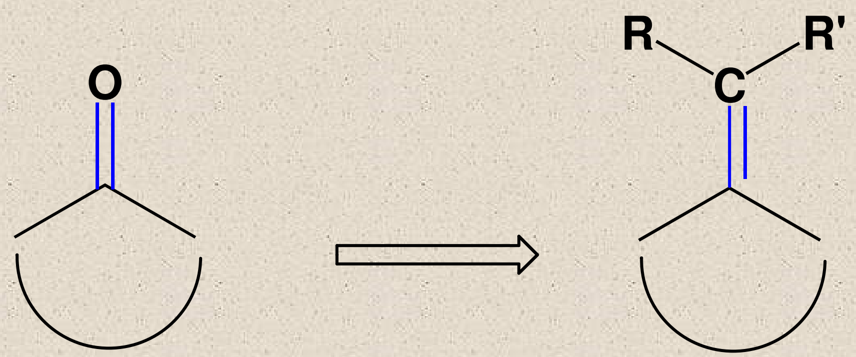


amphetamine


CO$_2$CH$_3$
H
N
β
α

Methylphenidate (Ritalin®)

Overall Synthetic Transformation of Wittig Reagents & Its Variations

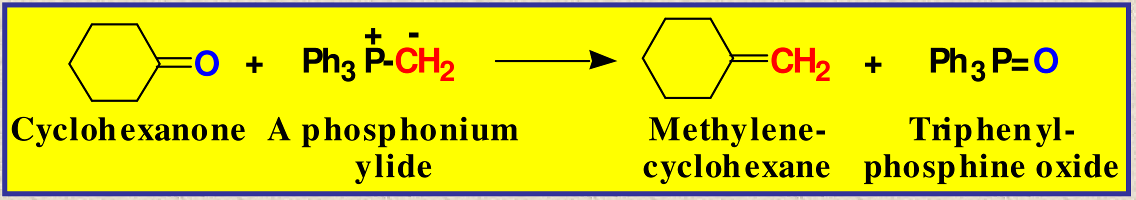


KETONE CAN BE CYCLIC

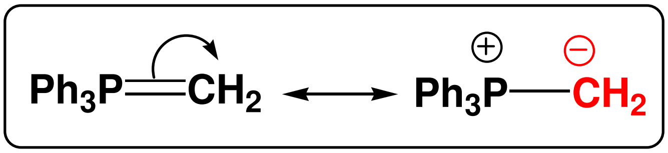
ALKENES OR OLEFINS

Wittig Reaction

The Wittig reaction is a very versatile synthetic method for the synthesis of alkenes (olefins) from aldehydes and ketones


O
+
$Ph_3\overset{+}{P}\text{-}\overset{-}{C}H_2$
CH_2
+
$Ph_3P{=}O$
Cyclohexanone
A phosphonium ylide
Methylene-cyclohexane
Triphenyl-phosphine oxide

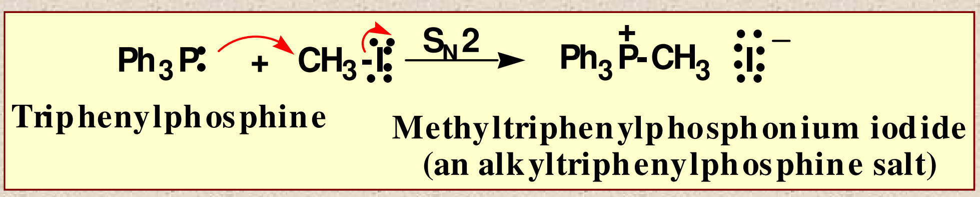
Ylides are reagents (or reactive intermediates) which have adjacent charges:


$Ph_3P{=}CH_2$
$Ph_3\overset{\oplus}{P}\text{—}\overset{\ominus}{C}H_2$

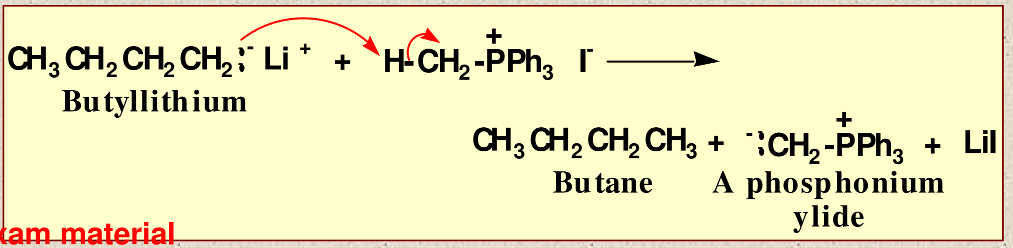
Phosphonium ylides

Phosphonium ylides are formed in two steps:

Step 1: nucleophilic displacement of iodine by triphenylphosphine


Ph3P:
+
CH3-I:
SN2
Ph3P-CH3
:I:−
Triphenylphosphine
Methyltriphenylphosphonium iodide
(an alkyltriphenylphosphine salt)

Step 2: treatment of the phosphonium salt with a very strong base, most commonly BuLi, NaH, or $NaNH_2$

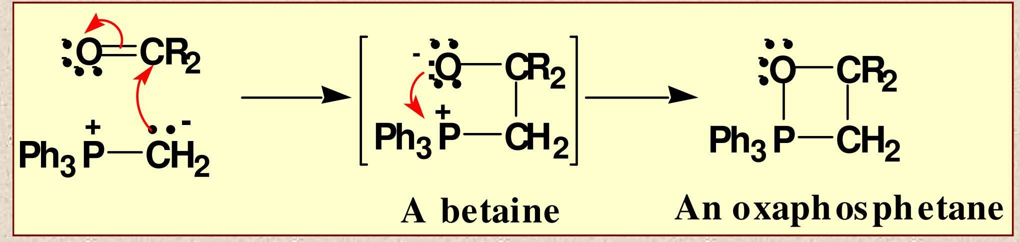

CH3CH2CH2CH2:− Li+
+
H-CH2-PPh3 I−
Butyllithium
CH3CH2CH2CH3
+
:CH2-PPh3
+
LiI
Butane
A phosphonium ylide

Not exam material

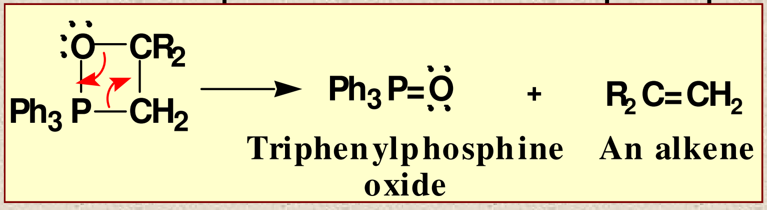
Wittig Reaction

Phosphonium ylides react with the C=O group of an aldehyde or ketone to give an alkene

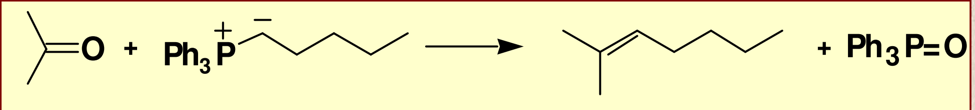
Step 1: nucleophilic addition of the ylide to the electrophilic carbonyl carbon


:O=CR2
Ph3P—CH2
:O—CR2
Ph3P—CH2
:O—CR2
Ph3P—CH2
A betaine
An oxaphosphetane

Step 2: decomposition of the oxaphosphatane

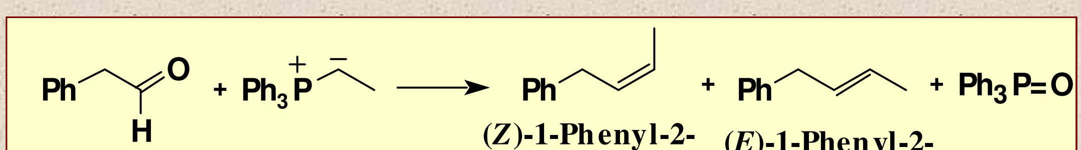

:O—CR2
Ph3P—CH2
Ph3P=O:
+
R2C=CH2
Triphenylphosphine oxide
An alkene

Wittig Reaction


O
+
$Ph_3\overset{+}{P}$
−
+ $Ph_3P{=}O$

Acetone

2-Methyl-2-heptene

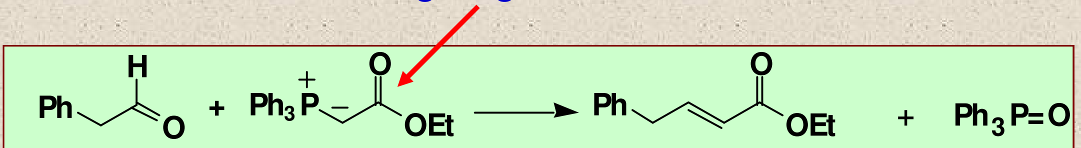

Ph
O
H
+ $Ph_3\overset{+}{P}$
−
Ph
+
Ph
+ $Ph_3P{=}O$

Phenyl-acetaldehyde

(*Z*)-1-Phenyl-2-butene (87%)

(*E*)-1-Phenyl-2-butene (13%)

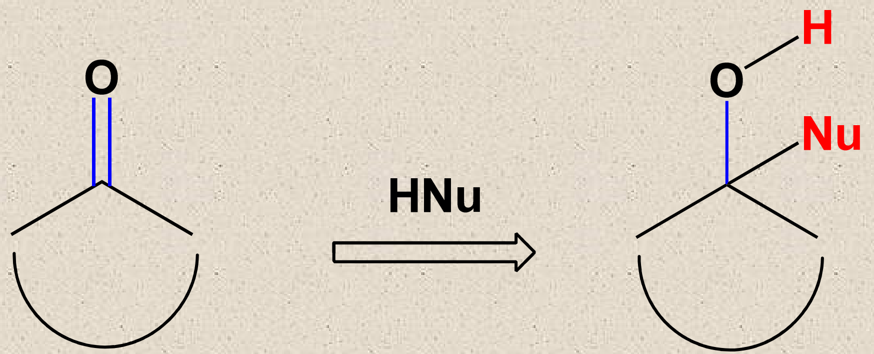
Resonance stabilized Wittig reagent:


H
Ph
O
+
$Ph_3\overset{+}{P}$
−
O
OEt
Ph
O
OEt
+
$Ph_3P{=}O$

Phenyl-acetaldehyde

Ethyl (*E*)-4-phenyl-2-butenoate (only the E isomer is formed)

Addition Reactions to Carbonyl Compounds



Ketone Can Be Cyclic

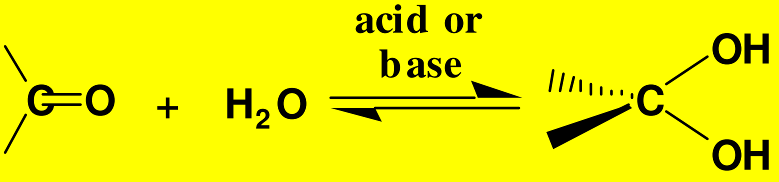
Alcohols or Their Derivatives

Note: Water can be added to ketones & aldehydes.

Addition of H_2O to Carbonyls

Addition of water (**hydration**) to the carbonyl group of an aldehyde or ketone gives a geminal diol, commonly referred to a gem-diol

- gem-diols are also referred to as **hydrates**

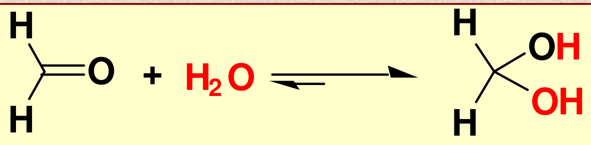


Carbonyl group of an aldehyde or ketone

A hydrate (a gem-diol)

Addition of H_2O to Carbonyls

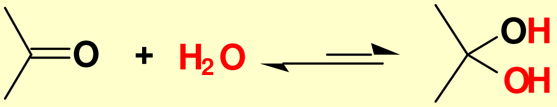
- when formaldehyde (*g*) is dissolved in water at 20℃, the carbonyl group is more than 99% hydrated



Formaldehyde

Formaldehyde hydrate (>99%)

- the equilibrium concentration of a hydrated ketone is considerably smaller

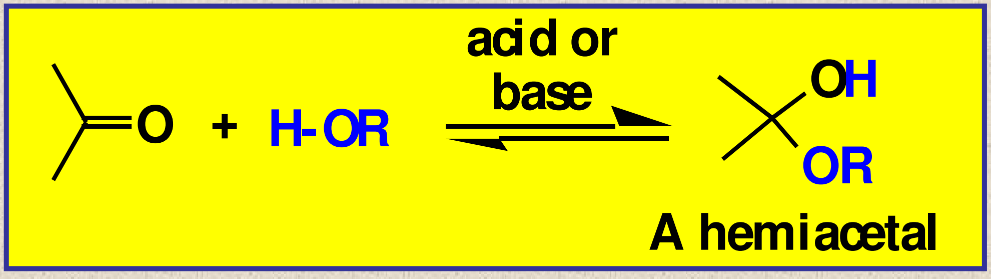


Acetone (99.9%)

2,2-Propanediol (0.1%)

Addition of Alcohols to Carbonyls

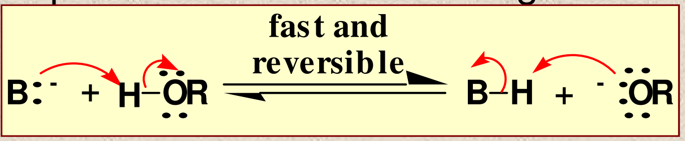
- Addition of one molecule of alcohol to the C=O group of an aldehyde or ketone gives a hemiacetal
- **Hemiacetal:** a molecule containing an -OH and an -OR or -OAr bonded to the same carbon


O
+
H-OR
acid or base
OH
OR

A hemiacetal

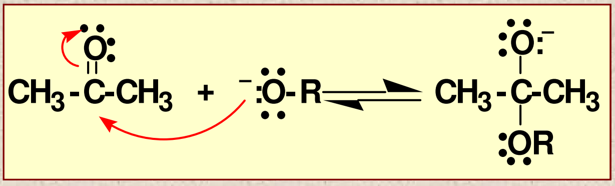
Formation of a hemiacetal-- base catalyzed

- Step 1: proton transfer from HOR gives an alkoxide

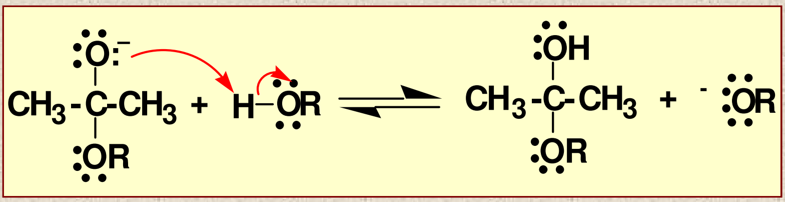

B:⁻
+
H–ÖR
fast and reversible
B–H
+
⁻:ÖR

Na$^+$ $^-$OCH$_3$

- Step 2: attack of RO$^-$ on the carbonyl carbon

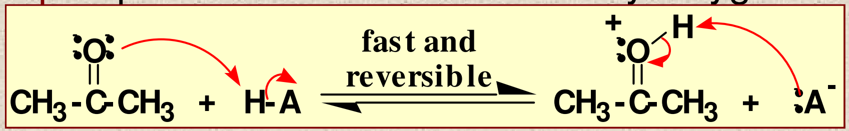

CH3-C-CH3
O
+
⁻:O-R
:O:⁻
CH3-C-CH3
:OR

- Step 3: proton transfer from the alcohol to O$^-$ gives the hemiacetal and generates a new base catalyst

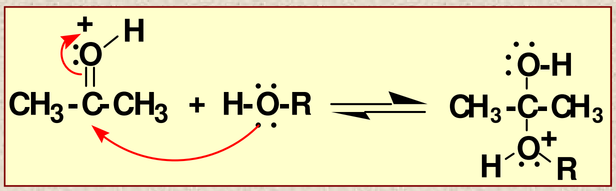

:O:⁻
CH3-C-CH3
:OR
+
H–ÖR
:OH
CH3-C-CH3
:OR
+
⁻:ÖR

Formation of a hemiacetal --acid catalyzed

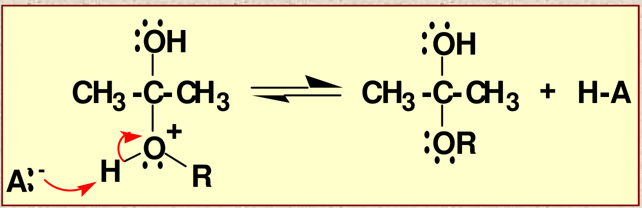
Step 1: proton transfer to the carbonyl oxygen


CH3-C-CH3 + H-A
fast and reversible
CH3-C-CH3 + :A-

Step 2: attack of ROH on the carbonyl carbon


CH3-C-CH3 + H-O-R
CH3-C-CH3
O-H
H O+ R

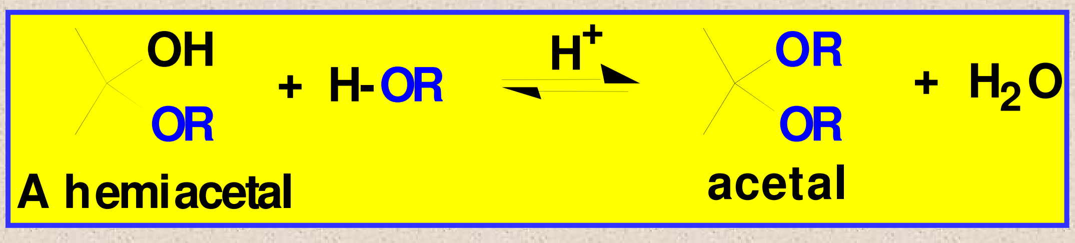
Step 3: proton transfer from the oxonium ion to A$^-$ gives the hemiacetal and generates a new acid catalyst


:OH
CH3-C-CH3
A:-
H O+ R
CH3-C-CH3 + H-A
:OR

Addition of Alcohols to Carbonyls

- Hemiacetals react with alcohols to form acetals

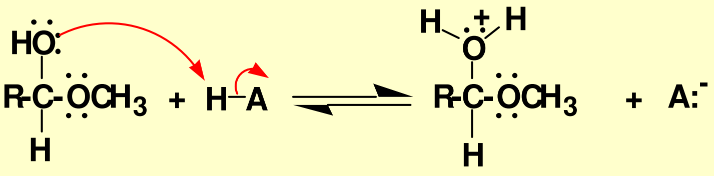
Acetal: a molecule containing two -OR or -OAr groups bonded to the same carbon


OH
OR
A hemiacetal
+ H-OR
H+
OR
OR
acetal
+ H2O

***Nota Bene*: acetals are STABLE in base**

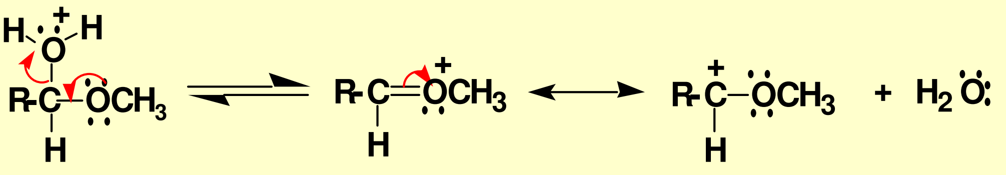
Begin Mechanism from the hemiacetal stage:

Step 1: proton transfer from HA gives an oxonium ion



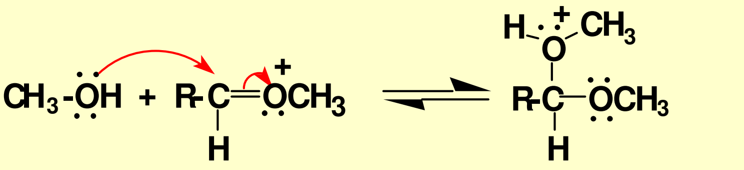
An oxonium ion

Step 2: loss of water gives a resonance-stabilized cation



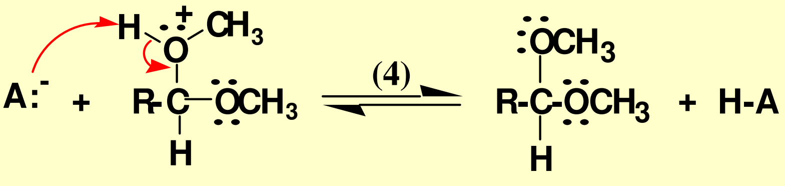
A resonance-stabilized cation

Step 3: reaction of the cation (an electrophile) with methanol (a nucleophile) gives the conjugate acid of the acetal



A protonated acetal

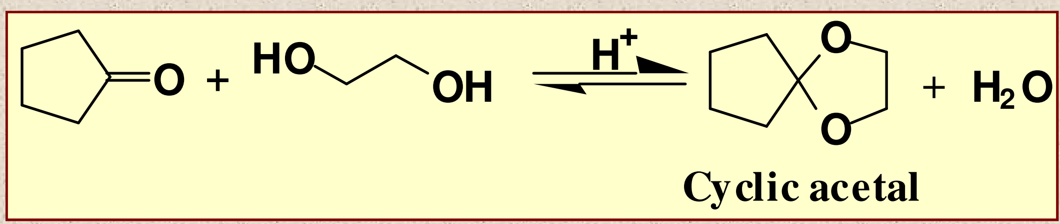
Step 4: proton transfer to A⁻ gives the acetal and generates a new acid catalyst

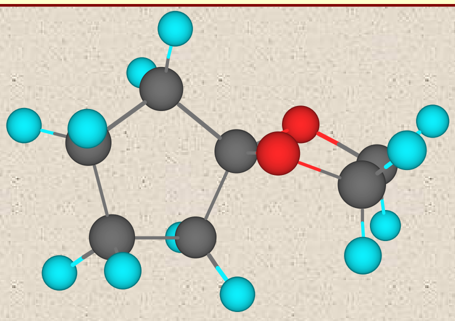


An acetal

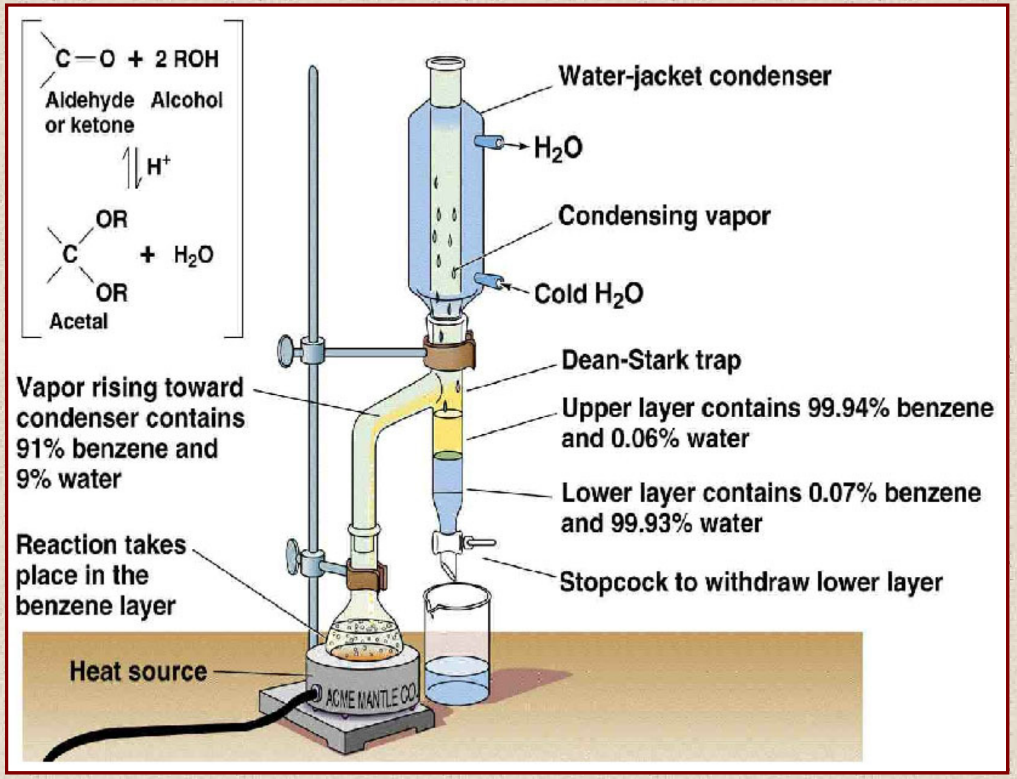
Addition of Alcohols to Carbonyls

- with ethylene glycol and other glycols, the product is a five-membered cyclic acetal
- this a method of “protecting” ketones


HO
OH
H+
O
O
+ H2O
Cyclic acetal

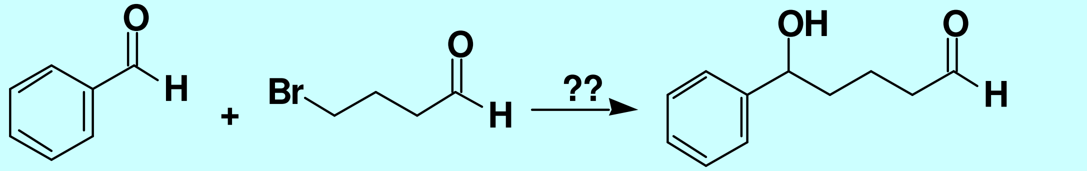


Dean-Stark Trap

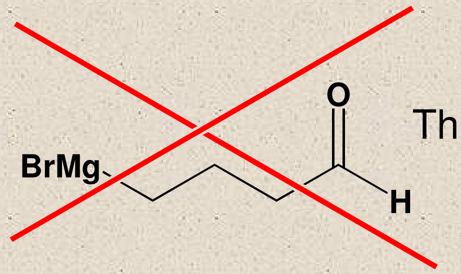

C—O + 2 ROH
Aldehyde or ketone
Alcohol
H+
OR
C
OR
+ H2O
Acetal
Water-jacket condenser
H2O
Condensing vapor
Cold H2O
Dean-Stark trap
Upper layer contains 99.94% benzene and 0.06% water
Lower layer contains 0.07% benzene and 99.93% water
Stopcock to withdraw lower layer
Vapor rising toward condenser contains 91% benzene and 9% water
Reaction takes place in the benzene layer
Heat source
ACME MANTLE CO.

Acetals as Protecting Groups

- How to bring about a Grignard reaction between these compounds:



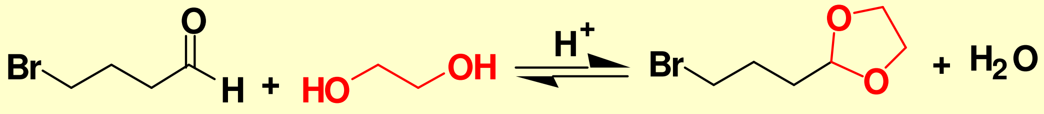
Benzaldehyde + 4-Bromobutanal → 5-Hydroxy-5-phenylpentanal (racemic)



This Grignard cannot be made!!

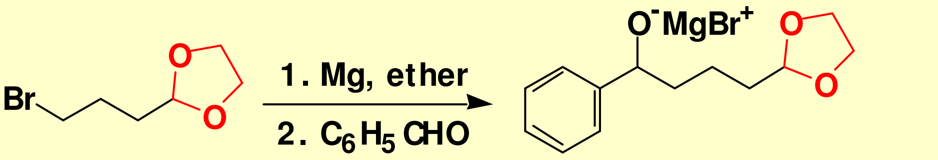
Acetals as Protecting Groups

- a Grignard reagent prepared from 4-bromobutanal will self-destruct (**decompose**).
  - first protect the -CHO group as an acetal:



A cyclic acetal

  - then prepare the Grignard reagent:

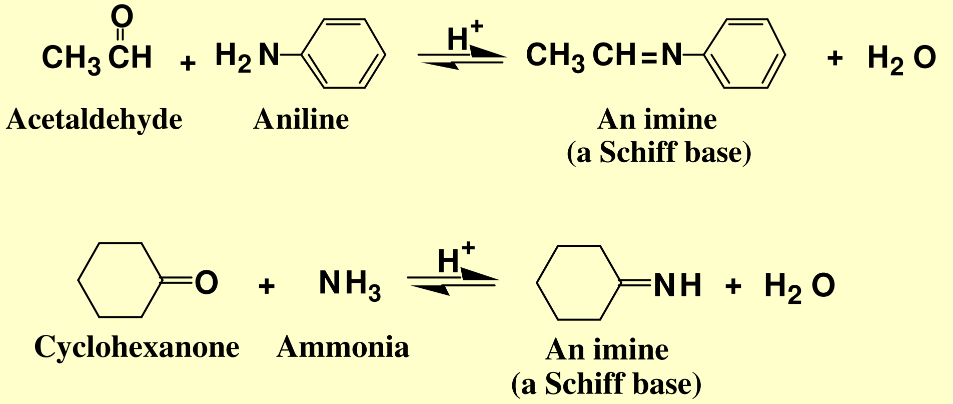


A chiral magnesium alkoxide (produced as a racemic mixture)

  - hydrolysis (not shown) gives the target molecule

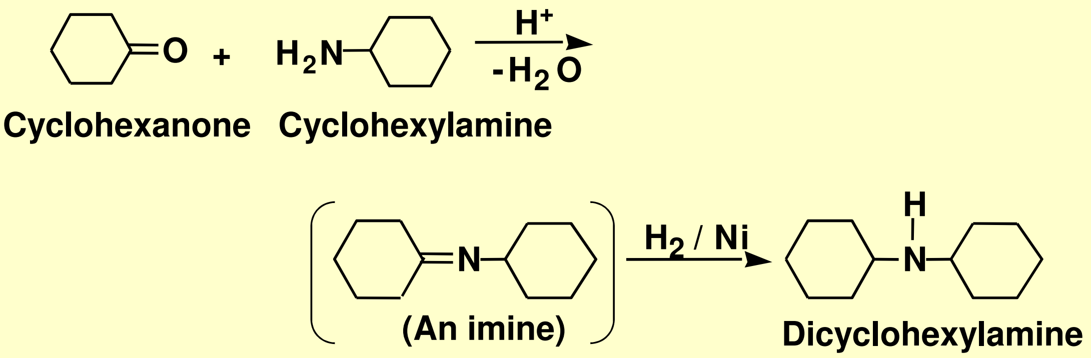
Addition of Nitrogen Nucleophiles

- Ammonia, 1° aliphatic amines, and 1° aromatic amines react with the C=O group of aldehydes and ketones to give **imines** (Schiff bases)
- Water is removed by Dean-Stark trap or chemical dehydration (e.g. molecular sieves)


$CH_3\overset{O}{\overset{\|}{C}}H$ + H_2N
H^+
$CH_3CH{=}N$ + H_2O
Acetaldehyde
Aniline
An imine
(a Schiff base)
O
+ NH_3
H^+
NH + H_2O
Cyclohexanone
Ammonia
An imine
(a Schiff base)

Addition of Nitrogen Nucleophiles

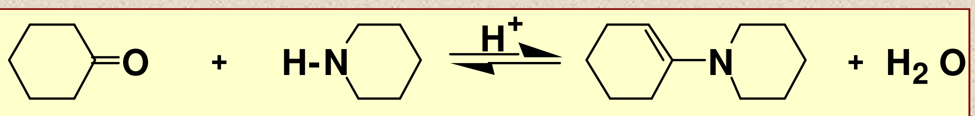
– a value of imines is that the carbon-nitrogen double bond can be reduced to a carbon-nitrogen single bond


O
+ H_2N
H^+
$-H_2O$
Cyclohexanone
Cyclohexylamine
N
(An imine)
H_2 / Ni
H
N
Dicyclohexylamine

Does not have to isolated

Addition of Nitrogen Nucleophiles

- Secondary amines react with the C=O group of aldehydes and ketones to form **enamines (alkene and amine)**



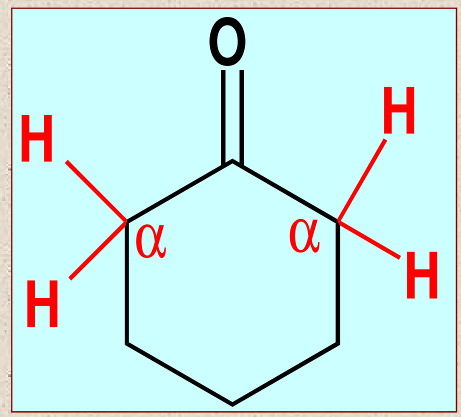
Cyclohexanone **Piperidine (a secondary amine)** **An enamine**

  - the mechanism of enamine formation involves formation of a tetrahedral carbonyl addition compound followed by its acid-catalyzed dehydration

---

Acidity of α-Hydrogens

Hydrogens alpha to a carbonyl group are more acidic than hydrogens of other hydrocarbons (e.g. alkanes, alkenes, aromatic).



$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

$$K_{eq} = \frac{[H_3O^+][A^-]}{[HA][H_2O]}$$

Note: ℓ and s are not used in K

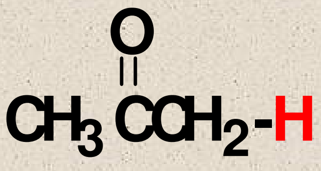
$$[H_2O]\,K_{eq} = \frac{[H_3O^+][A^-]}{[HA]}$$

Freshman Flashback!!

$$\boxed{K_a = \frac{[H_3O^+][A^-]}{[HA]}}$$

Acidity of α-Hydrogens

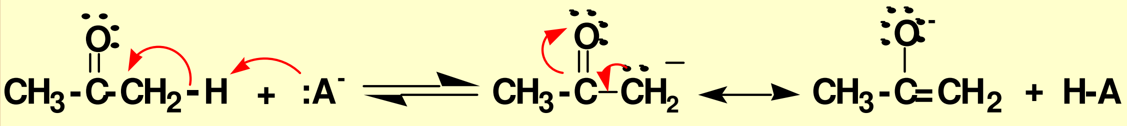
Hydrogens alpha to a carbonyl group are more acidic than hydrogens of alkanes, alkenes, and alkynes but less acidic than the hydroxyl hydrogen of alcohols

Type of Bond	pK_a
$CH_3CH_2O\text{-}H$	16
 $CH_3C(=O)CH_2\text{-}H$	20
$CH_3C{\equiv}C\text{-}H$	25
$CH_2{=}CH\text{-}H$	44
$CH_3CH_2\text{-}H$	51

pKa = -log Ka

α-Hydrogens are more acidic **because the enolate anion is stabilized by**:

1. delocalization of its negative charge (resonance effect)
2. the electron-withdrawing inductive effect of the adjacent electronegative oxygen

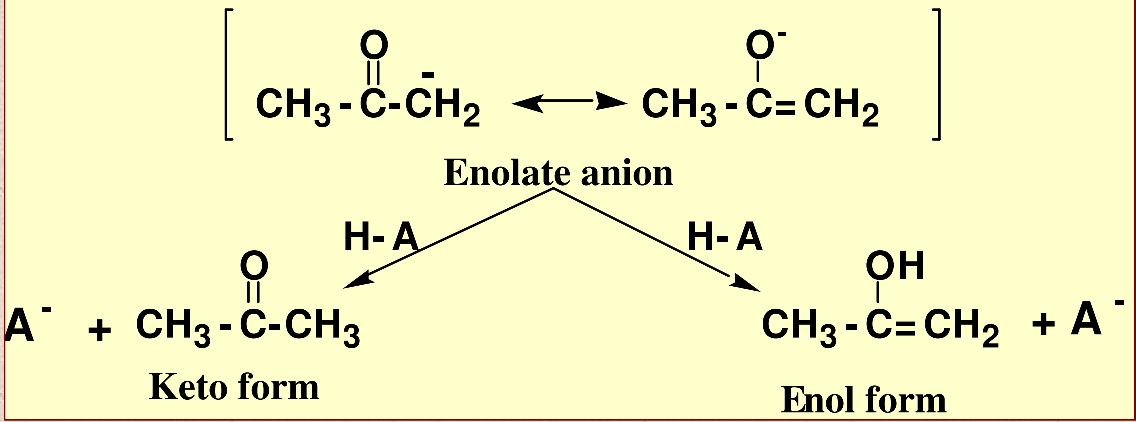


$$CH_3-\overset{\ddot{O}:}{\overset{\|}{C}}-CH_2-H + :A^- \rightleftharpoons CH_3-\overset{\ddot{O}:}{\overset{\|}{C}}-\overset{\cdot\cdot\;-}{CH_2} \longleftrightarrow CH_3-\overset{:\ddot{O}:^-}{\overset{|}{C}}=CH_2 + H-A$$

Resonance-stabilized enolate anion

Keto-Enol Tautomerism

- protonation of the enolate anion on oxygen gives the **enol form***; protonation on carbon gives the **keto form**



$$\left[CH_3-\overset{O}{\overset{\|}{C}}-\overset{-}{CH_2} \longleftrightarrow CH_3-\overset{O^-}{\overset{|}{C}}=CH_2 \right]$$

Enolate anion

$$A^- + CH_3-\overset{O}{\overset{\|}{C}}-CH_3 \xleftarrow{H-A} \text{Enolate anion} \xrightarrow{H-A} CH_3-\overset{OH}{\overset{|}{C}}=CH_2 + A^-$$

Keto form

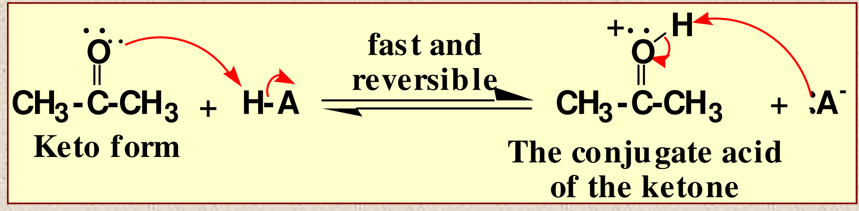
Enol form

*Enol: made from 2 functional groups-alkene and alcohol

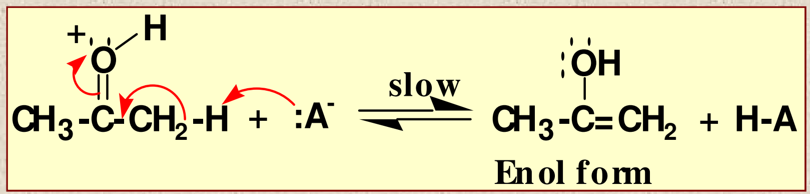
Keto-Enol Tautomerism

- acid-catalyzed equilibration of keto and enol tautomers occurs in two steps

Step 1: proton transfer to the carbonyl oxygen

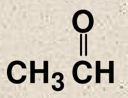
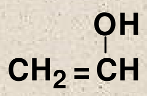
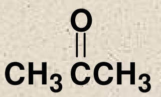
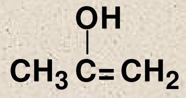
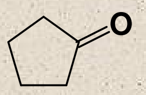
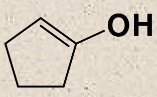
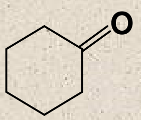
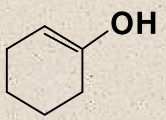

CH3-C-CH3
O
+
H-A
Keto form
fast and
reversible
+
O
H
CH3-C-CH3
+
:A-
The conjugate acid
of the ketone

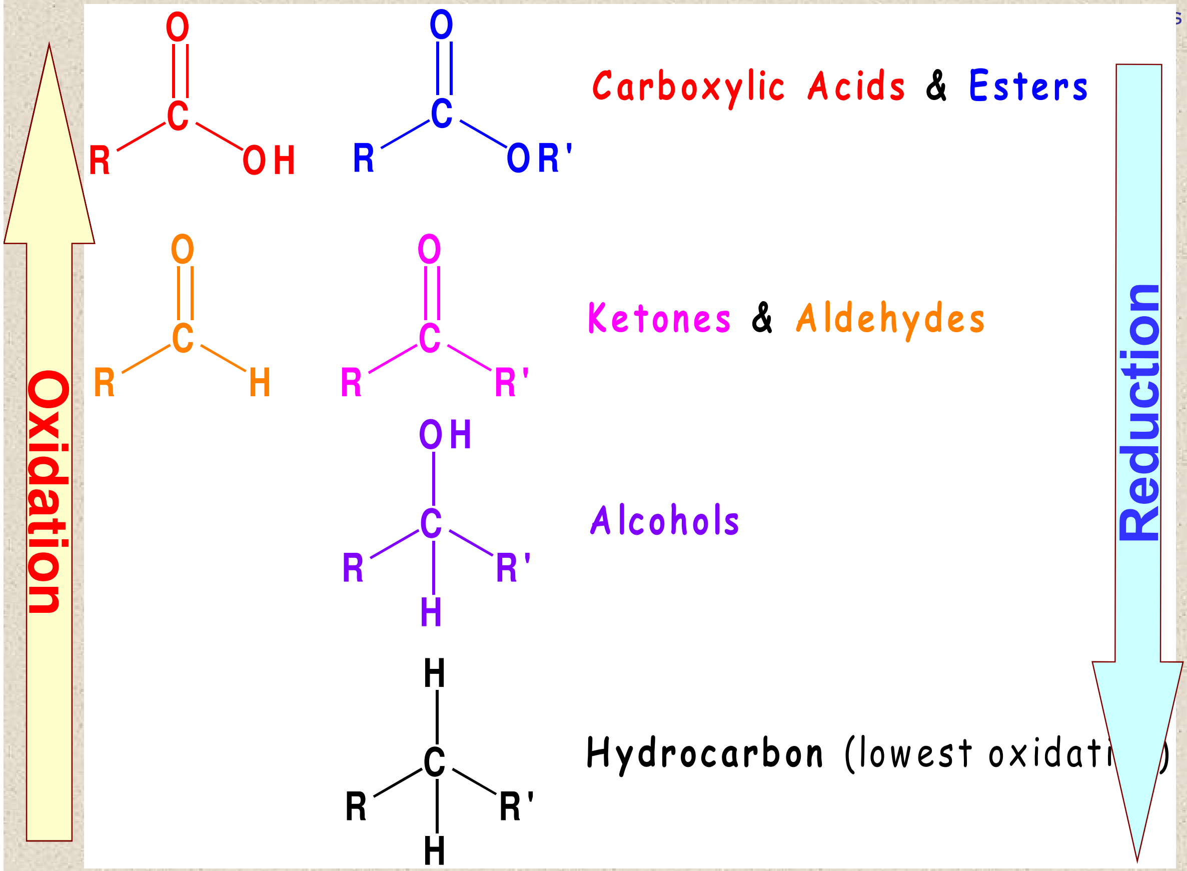
Step 2: proton transfer to the base A$^-$


+
O
H
CH3-C-CH2-H
+
:A-
slow
OH
CH3-C=CH2
+ H-A
Enol form

Keto-Enol Tautomerism

Keto-enol equilibria for simple aldehydes and ketones lie far toward the keto form

Keto form	Enol form	% Enol at Equilibrium
 $CH_3\overset{O}{\overset{\Vert}{C}}H$	 $CH_2=\overset{OH}{\overset{\vert}{C}}H$	6 x 10^{-5}
 $CH_3\overset{O}{\overset{\Vert}{C}}CH_3$	 $CH_3\overset{OH}{\overset{\vert}{C}}=CH_2$	6 x 10^{-7}
		1 x 10^{-6}
		4 x 10^{-5}


Oxidation
Reduction

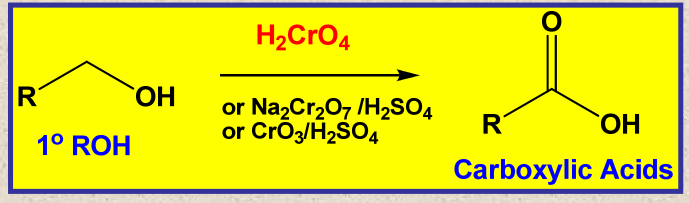
Carboxylic Acids & Esters

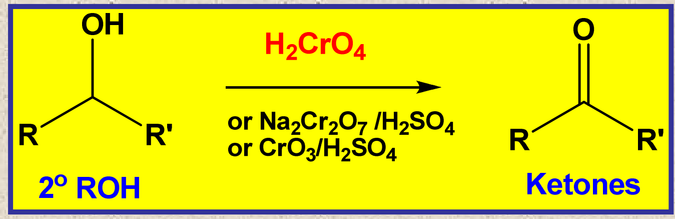
Ketones & Aldehydes

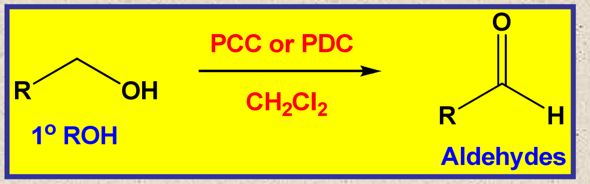
Alcohols

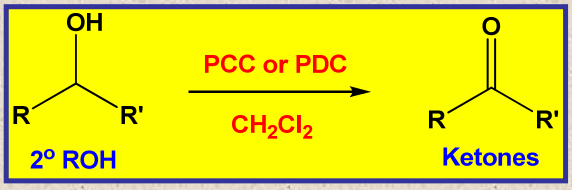
Hydrocarbon (lowest oxidati)

Oxidation from O-Chem I


R
OH
1° ROH
H2CrO4
or Na2Cr2O7 /H2SO4
or CrO3/H2SO4
O
R
OH
Carboxylic Acids

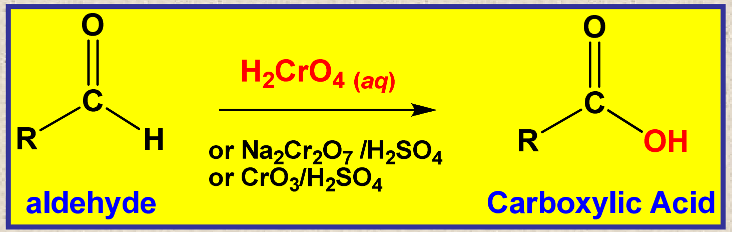

OH
R
R'
2° ROH
H2CrO4
or Na2Cr2O7 /H2SO4
or CrO3/H2SO4
O
R
R'
Ketones

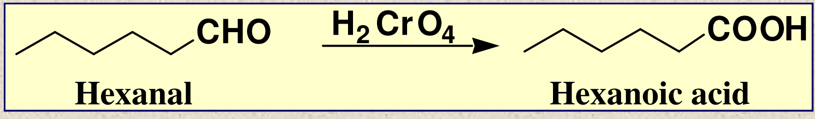

R
OH
1° ROH
PCC or PDC
CH2Cl2
O
R
H
Aldehydes


OH
R
R'
2° ROH
PCC or PDC
CH2Cl2
O
R
R'
Ketones

Oxidation of Aldehydes

Aldehydes are oxidized to carboxylic acids by a variety of oxidizing agents, including $^*H_2CrO_4$

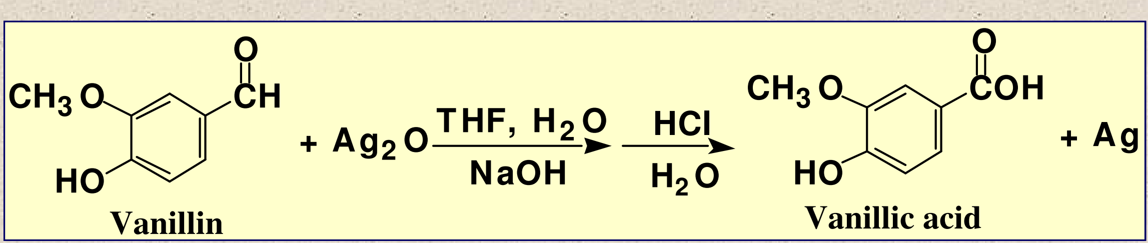

O
C
R
H
H_2CrO_4 (aq)
or $Na_2Cr_2O_7$ /H_2SO_4
or CrO_3/H_2SO_4
O
C
R
OH
aldehyde
Carboxylic Acid


CHO
H_2CrO_4
COOH
Hexanal
Hexanoic acid

* See 10.8 for Jones reagent & PCC: pyridine$^+$•$ClCrO_3^-$

Oxidation of Aldehydes

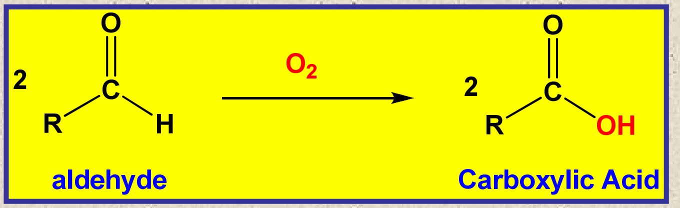
- They are also oxidized by Ag(I)
  - in one method, a solution of the aldehyde in aqueous ethanol or THF is shaken with a slurry of silver oxide

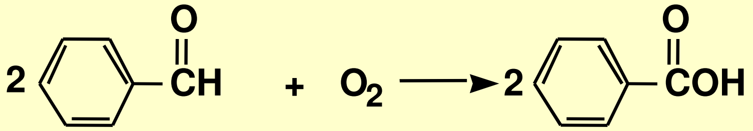

O
CH_3O
CH
HO
Vanillin
+ Ag_2O
THF, H_2O
NaOH
HCl
H_2O
O
CH_3O
COH
HO
Vanillic acid
+ Ag

Oxidation of Aldehydes

Aldehydes are oxidized by O_2 in a radical chain reaction

- liquid aldehydes are so sensitive to air that they must be stored under N_2

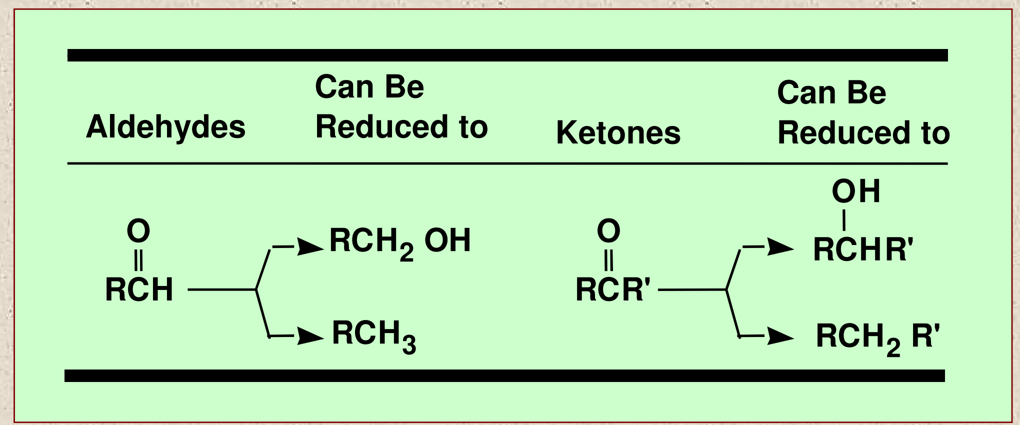




Benzaldehyde **Benzoic acid**

Reduction

- aldehydes can be reduced to 1° alcohols
- ketones can be reduced to 2° alcohols
- the C=O group of an aldehyde or ketone can be reduced to a $-CH_2-$ group

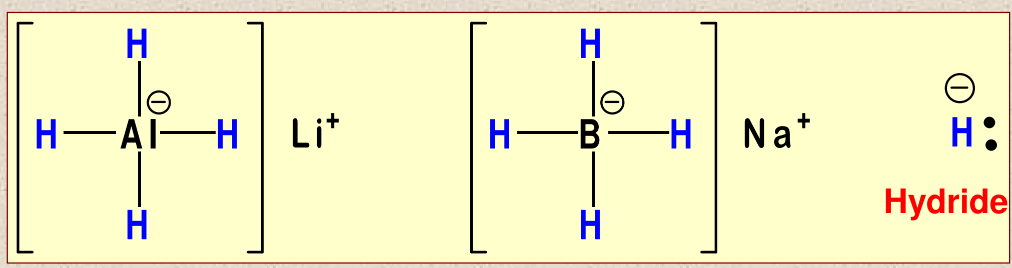


Aldehydes	Can Be Reduced to	Ketones	Can Be Reduced to
$R\overset{O}{\overset{\Vert}{C}}H$	RCH_2OH RCH_3	$R\overset{O}{\overset{\Vert}{C}}R'$	$R\overset{OH}{\overset{\vert}{C}}HR'$ RCH_2R'

Metal Hydride Reduction

The most common laboratory reagents for the reduction of aldehydes and ketones are $NaBH_4$ and $LiAlH_4$

- both reagents are sources of hydride ion, $H:^-$ a very powerful nucleophile

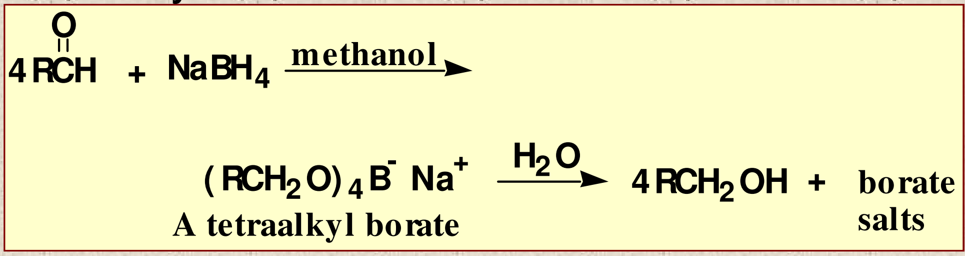


Lithium Aluminum Hydride
LAH

Sodium Borohydride
$NaBH_4$

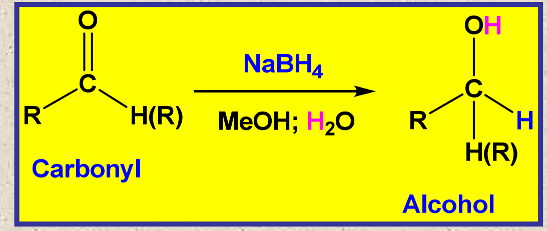
Sodium Borohydride Reduction

- reductions with $NaBH_4$ are most commonly carried out in aqueous methanol, in pure methanol, or in ethanol
- one mole of $NaBH_4$ reduces four moles of aldehyde or ketone



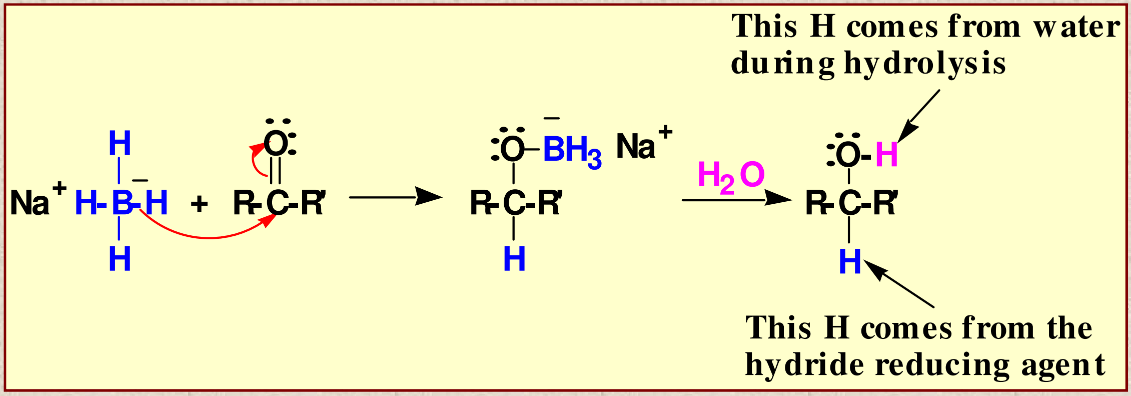
$$4\,R\overset{O}{\overset{\|}{C}}H + NaBH_4 \xrightarrow{\text{methanol}} (RCH_2O)_4B^- Na^+ \xrightarrow{H_2O} 4\,RCH_2OH + \text{borate salts}$$

A tetraalkyl borate



Sodium Borohydride Reduction

- The key step in metal hydride reduction is transfer of a hydride ion to the C=O group to form a tetrahedral carbonyl addition compound



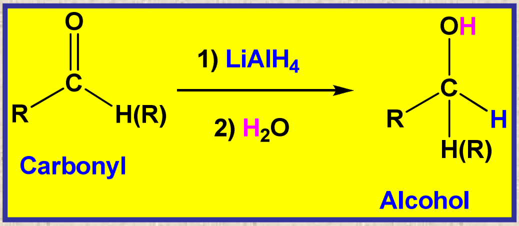
This H comes from water during hydrolysis

This H comes from the hydride reducing agent

Not exam material

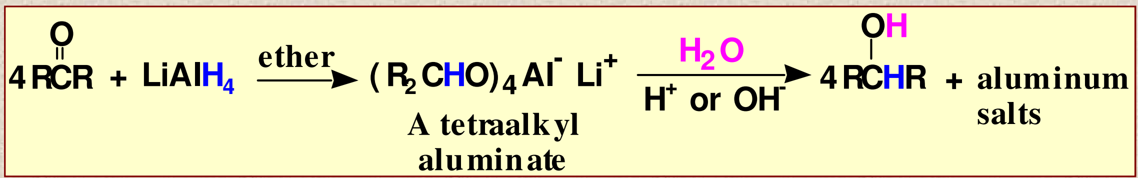
LAH Reduction

- unlike $NaBH_4$, $LiAlH_4$ reacts violently with water, methanol, and other protic solvents
- reductions using it are carried out in dry (anhydrous) diethyl ether or tetrahydrofuran (THF)



Carbonyl

Alcohol

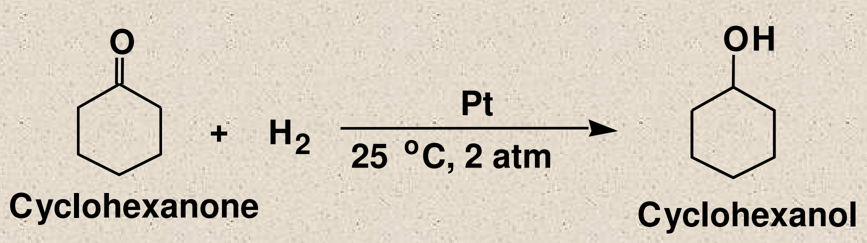


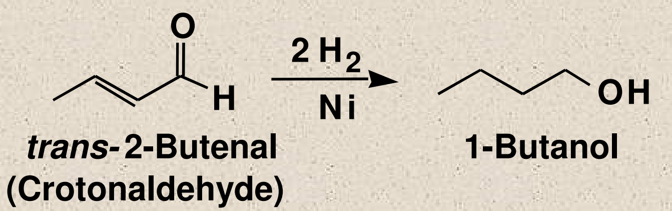
$$4\,R\overset{O}{\overset{\|}{C}}R + LiAlH_4 \xrightarrow{\text{ether}} (R_2CHO)_4Al^- \, Li^+ \xrightarrow[H^+ \text{ or } OH^-]{H_2O} 4\,R\overset{OH}{\overset{|}{C}}HR + \text{aluminum salts}$$

A tetraalkyl aluminate

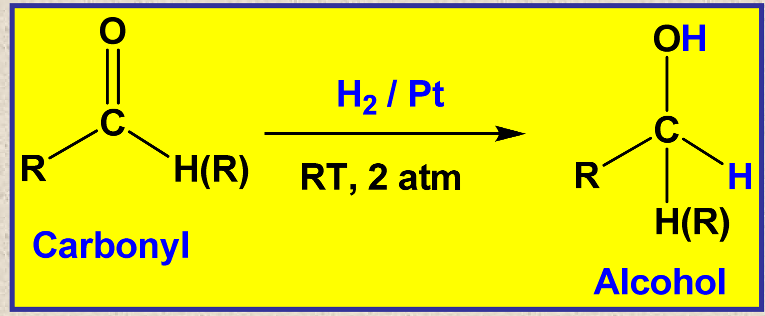
Catalytic Reduction

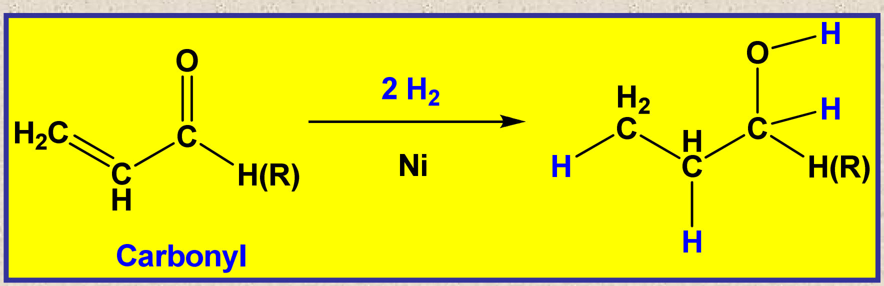
- Catalytic reductions are generally carried out at from 25° to 100°C and 1 to 5 atm H_2


O
+ H2
Pt
25 °C, 2 atm
OH
Cyclohexanone
Cyclohexanol


O
H
2 H2
Ni
OH
trans-2-Butenal
(Crotonaldehyde)
1-Butanol

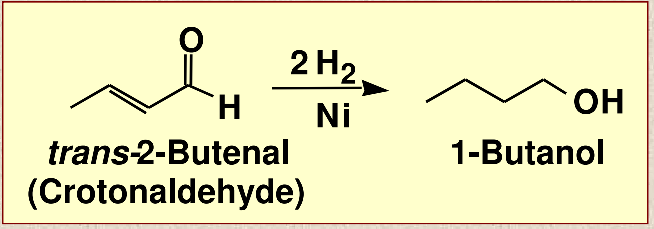
Note: Both the olefin and the carbonyl are reduced


O
C
R
H(R)
Carbonyl
H2 / Pt
RT, 2 atm
OH
C
R
H
H(R)
Alcohol


O
H2C
C
C
H
H(R)
Carbonyl
2 H2
Ni
O
H
H2
C
H
C
H
C
H
H
H(R)
H

Catalytic Reduction

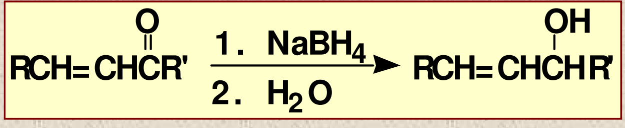
- A carbon-carbon double bond may also be reduced under these conditions:



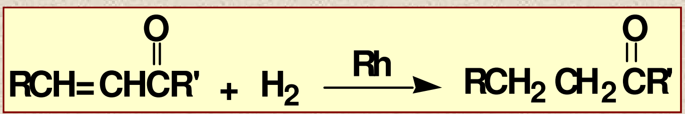
trans-2-Butenal (Crotonaldehyde)

1-Butanol

  - by careful choice of experimental conditions, it is often possible to selectively reduce a carbon-carbon double in the presence of an aldehyde or ketone



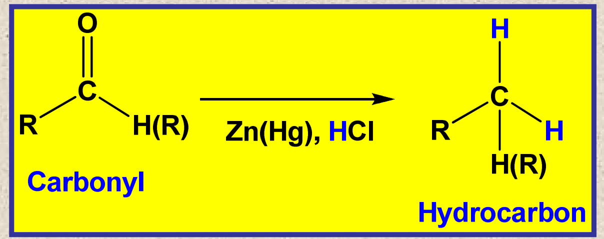
$$RCH{=}CH\overset{O}{\overset{\|}{C}}R' \xrightarrow[2.\ H_2O]{1.\ NaBH_4} RCH{=}CH\overset{OH}{\overset{|}{C}}HR'$$

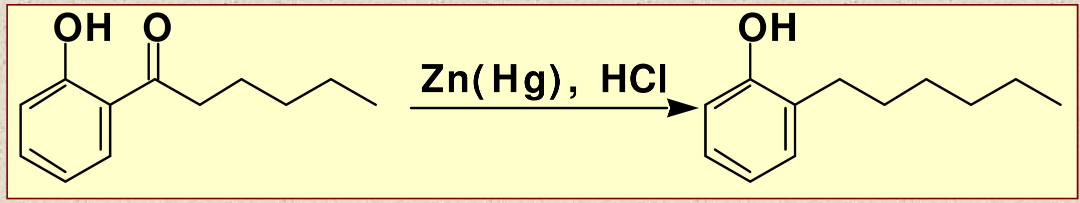


$$RCH{=}CH\overset{O}{\overset{\|}{C}}R' + H_2 \xrightarrow{Rh} RCH_2CH_2\overset{O}{\overset{\|}{C}}R'$$

Clemmensen Reduction

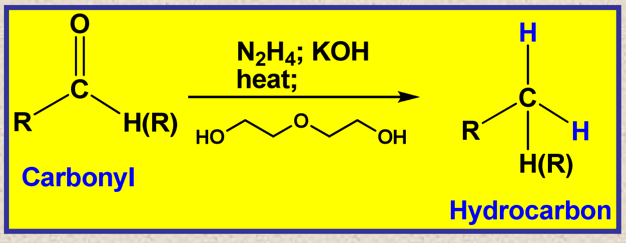
- refluxing an aldehyde or ketone with amalgamated zinc in concentrated HCl converts the carbonyl group to a methylene group
- Classic reaction but harsh conditions limit its use

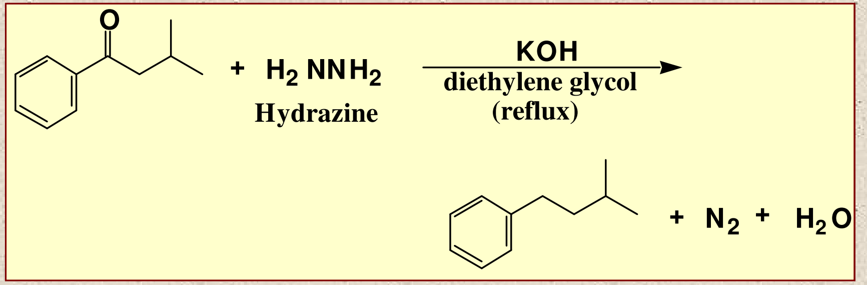




Wolff-Kishner Reduction

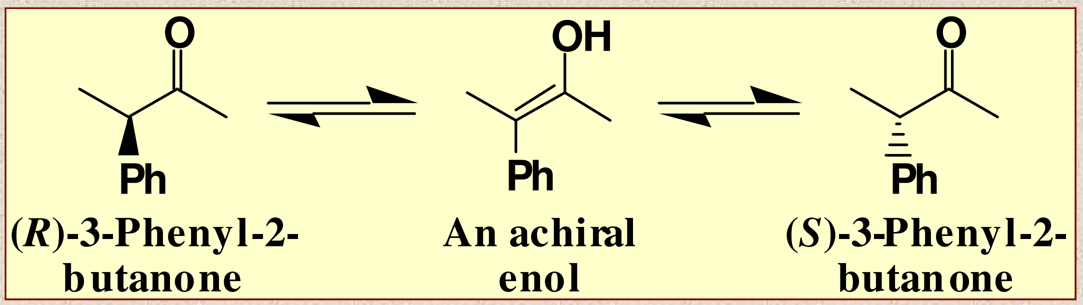
- in the original procedure, the aldehyde or ketone and hydrazine are refluxed with KOH in a high-boiling solvent
- the same reaction can be brought about using hydrazine and potassium *tert*-butoxide in DMSO (Di-methyl sulfoxide)


O
C
R
H(R)
Carbonyl
N2H4; KOH
heat;
HO
O
OH
H
C
R
H
H(R)
Hydrocarbon


O
+ H2 NNH2
Hydrazine
KOH
diethylene glycol
(reflux)
+ N2 + H2 O

Racemization

- Racemization at an α-carbon may be catalyzed by either acid or base
- Once stereochemistry is set, this is usually an undesirable side reaction.


O
Ph
OH
Ph
O
Ph

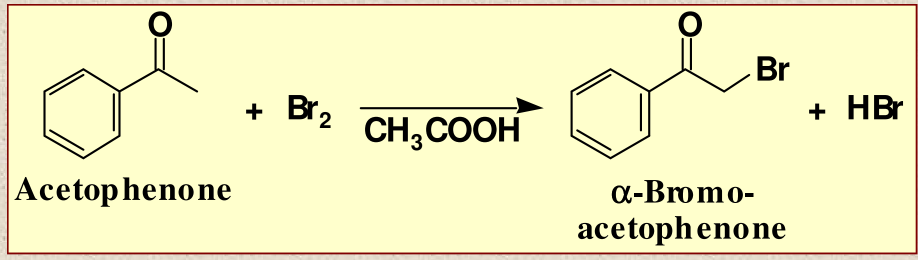
(*R*)-3-Phenyl-2-butanone

An achiral enol

(*S*)-3-Phenyl-2-butanone

α-Halogenation

- α-Halogenation: aldehydes and ketones with at least one α-hydrogen react at an α-carbon with Br_2 and Cl_2

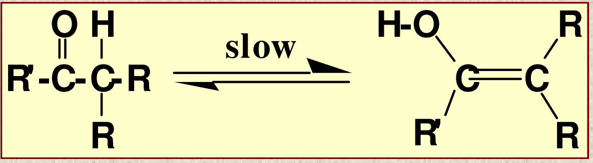

Acetophenone
+ Br2
CH3COOH
α-Bromo-acetophenone
+ HBr

  - reaction is catalyzed by both acid and base
  - **Caution!! These are lachrymators**

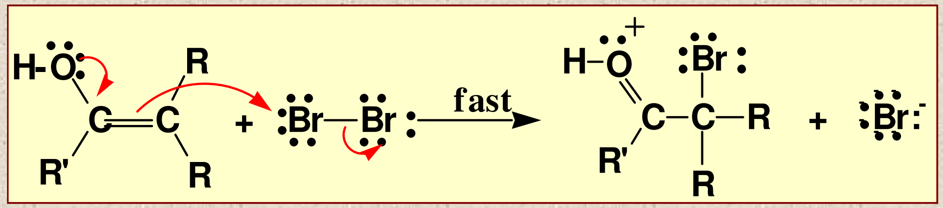
α-Halogenation

- Acid-catalyzed α-halogenation

Step 1: acid-catalyzed enolization- forms the **enol**



Step 2: nucleophilic attack of the enol on halogen

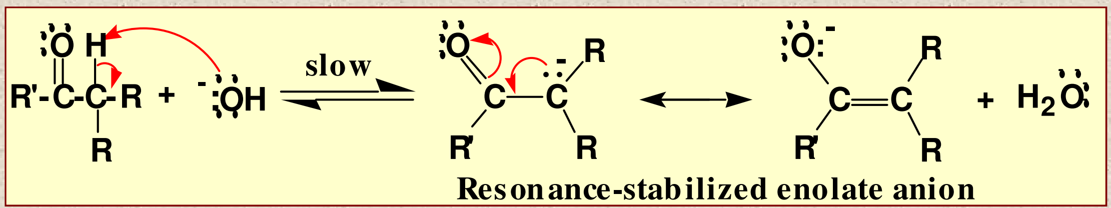


Step 3: (not shown) proton transfer to solvent completes the reaction

α-Halogenation

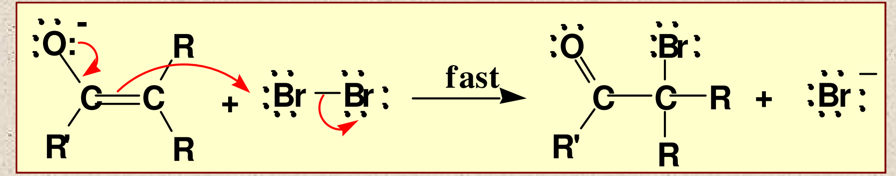
- Base-promoted α-halogenation

Step 1: formation of an **enolate anion**



Resonance-stabilized enolate anion

Step 2: nucleophilic attack of the enolate anion on halogen



α-Halogenation

- **Acid-catalyzed α-halogenation:**
  - introduction of a second halogen is slower than the first
  - introduction of the electronegative halogen on the α-carbon decreases the basicity of the carbonyl oxygen toward protonation
- **Base-promoted α-halogenation:**
  - each successive halogenation is more rapid than the previous one
  - the introduction of the electronegative halogen on the α-carbon increases the acidity of the remaining α-hydrogens and, thus, each successive α-hydrogen is removed more rapidly than the previous one