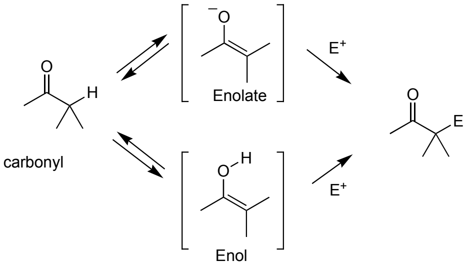
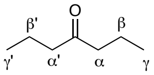
## Chapter 18: Enols and Enolates



### 18.1: The α-Carbon Atom and its p$K_a$



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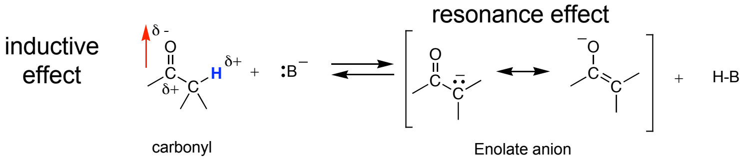
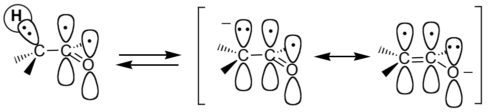
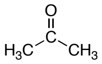
The inductive effect of the carbonyl causes the α-protons to be more acidic. The negative charge of the enolate ion (the conjugate base of the aldehyde or ketone) is stabilized by resonance delocalization. The p$K_a$ of the α-protons of aldehydes and ketones is in the range of 16-20 (Table 18.1, p. 754)





$H_3C-CH_3$

ethane
p$K_a$= 50-60

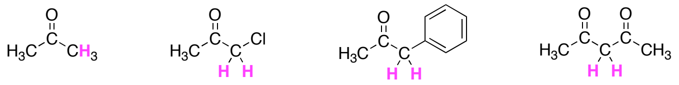


$H_3C-C(=O)-CH_3$

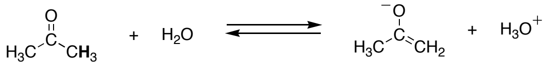
acetone
p$K_a$= 19

$H_3CH_2COH$

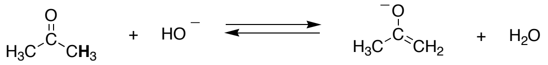
ethanol
p$K_a$= 16



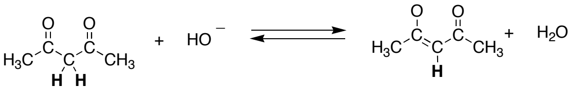
| | | | | |
|---|---|---|---|---|
| p$K_a$ | 19 | 14 | 16 | 9 |



| | acid | base | conjugate base | conjugate acid |
|---|---|---|---|---|
| p$K_a$ | 19 | | | -1.7 |
| | (weaker acid) | (weaker base) | (stronger base) | (stronger acid) |

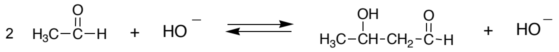


| | acid | base | conjugate base | conjugate acid |
|---|---|---|---|---|
| p$K_a$ | 19 | | | 15.7 |
| | (weaker acid) | (weaker base) | (stronger base) | (stronger acid) |



| | acid | base | conjugate base | conjugate acid |
|---|---|---|---|---|
| p$K_a$ | 9 | | | 15.7 |
| | (stronger acid) | (stronger base) | (weaker base) | (weaker acid) |

**18.2: The Aldol Condensation-** An enolate of one carbonyl (nucleophile) reacts with the carbonyl carbon (electrophile) of a second carbonyl compound resulting in the formation of a new C-C bond

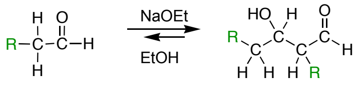


acetaldehyde

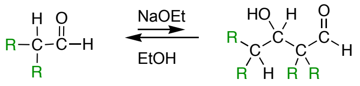
3-hydroxybutanal
(β-hydroxy aldehyde)

## Mechanism of the base-catalyzed aldol condensation (Fig. 18.1)

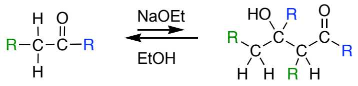
The position of the equilibrium for the aldol reaction is highly dependent on the reaction conditions, substrates, and steric considerations of the aldol product. Low temperature tends to favor the aldol product.



aldol reactions involving α-monosubstituted aldehydes are generally favorable



aldol reactions involving α,α-disubstituted aldehydes are generally unfavorable

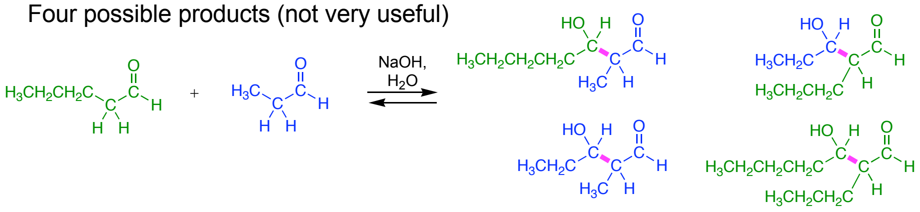


aldol reactions involving ketones are generally unfavorable

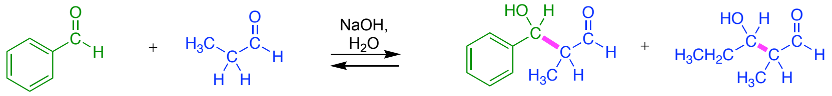
The aldol product can undergo base-catalyzed dehydration to an α,β-unsaturated carbonyl. The dehydration is essentially irreversible. The dehydration is favored at higher temperatures. (mechanism Fig. 18.2)

## **18.3: Mixed Aldol Reactions** - Aldol reaction between two different carbonyl compounds

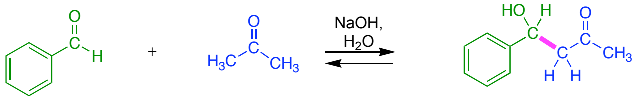
Four possible products (not very useful)



Aldehydes with no α-protons can only act as the electrophile



Preferred reactivity



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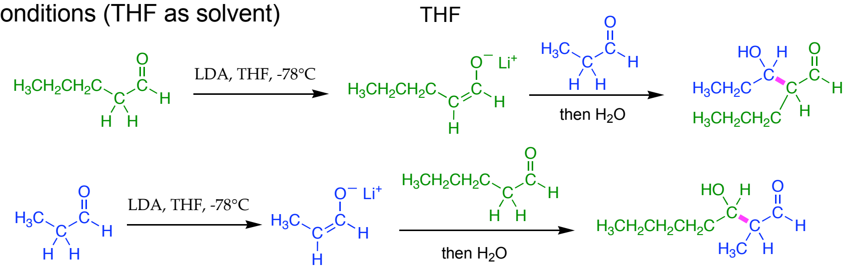
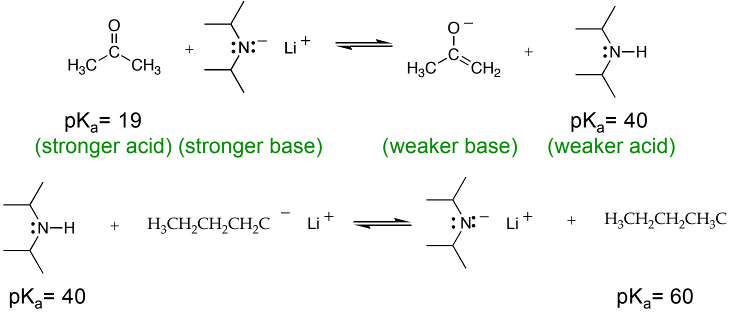
Discrete generation of an enolate with lithium diisopropyl amide (LDA) under aprotic conditions (THF as solvent)



### Lithium diisopropylamide (LDA): a very strong base



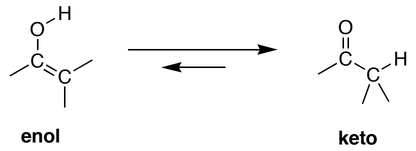
**18.4: Alkylation of Enolate Ions** - enolate anions can react with other electrophiles such as alkyl halides and tosylates to form a new C-C bonds. The alkylation reaction is an $S_N2$ reaction.

Reaction works best with the discrete generation of the enolate by LDA in THF, then the addition of the alkyl halide

**18.5: Enolization and Enol Content**

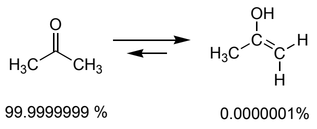
Tautomers: isomers, usually related by a proton transfer, that are in equilibrium

Keto-enol tautomeric equilibrium lies heavily in favor of the keto form.



| | | | |
|---|---|---|---|
| C=C | ΔH° = 611 KJ/mol | C=O | ΔH° = 735 KJ/mol |
| C-O | 380 | C-C | 370 |
| O-H | 426 | C-H | 400 |

**ΔH° = -88 KJ/mol**



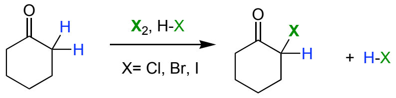
Enolization is acid- and base-catalyzed

Base-catalyzed mechanism (Figure 18.3, 9.764):

Acid-catalyzed mechanism (Figure 18.4, p. 765):

## 18.6: Stabilized enols (please read)

**18.7: α Halogenation of Aldehydes and Ketones**- α-proton of aldehydes and ketones can be replaced with a -Cl, -Br, or -I (-X) through the acid-catalyzed reaction with $Cl_2$ , $Br_2$ , or $I_2$ , ($X_2$) respectively. The reaction proceeds through an enol.



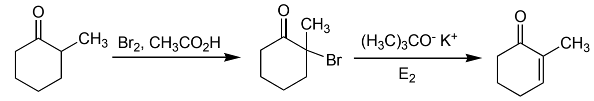
## 18.8: Mechanism of α Halogenation of Aldehydes and Ketones

Acid-catalyzed mechanism (Fig. 18.5, p. 769)

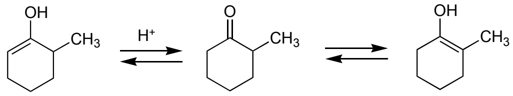
Rate= *k* [ketone/aldehyde] [$H^+$]
rate dependent on enol formation and not [$X_2$]

$\alpha,\beta$-unsaturated ketones and aldehydes:

$\alpha$ -bromination followed by elimination

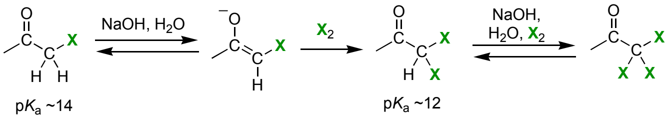


Why is one enol favored over the other?



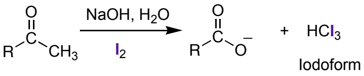
**18.9: The Haloform Reaction.** Mechanism of the base-promoted $\alpha$-halogenation of aldehydes and ketones (Fig. 18.6, p. 770)

In the base promoted reaction, the product is more reactive toward enolization and resulting in further $\alpha$-halogenation of the ketone or aldehyde. For methyl ketone, an $\alpha$, $\alpha$, $\alpha$ -trihalomethyl ketone is produced.



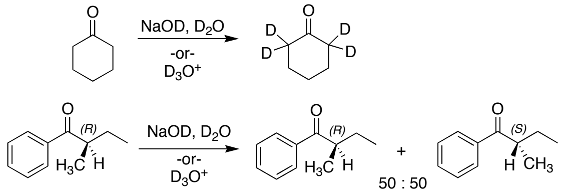
The $\alpha$, $\alpha$, $\alpha$ -trihalomethyl ketone reacts with aquous hydroxide to give the carboxylic acid and haloform ($HCX_3$)

*Iodoform reaction*: chemical tests for a methyl ketone



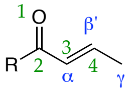
Iodoform: bright yellow precipitate

## 18.10: Some Chemical and Stereochemical Consequences of Enolization (please read)



## 18.11: Effects of Conjugation in α,β-Unsaturated Aldehydes and Ketones.

α,β -Unsaturated carbonyl have a conjugated C=C



R= H, α,β-unsaturated aldehyde= enal

R≠ H, α,β-unsaturated ketone= enone

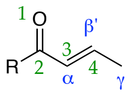
Conjugation of the π-electrons of the C=C and C=O is a stabilizing interaction

α,β -Unsaturated ketones and aldehydes are prepared by:

a. Aldol reactions with dehydration of the aldol
b. α-halogenation of a ketone or aldehyde followed by E2 elimination

## 18.12: Conjugate Addition to α,β-Unsaturated Carbonyl Compounds.

The resonance structures of an α,β-unsaturated ketone or aldehyde suggest two sites for nucleophilic addition; the carbonyl carbon and the β-carbon



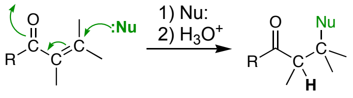
Organolithium reagents, Grignard reagents and $LiAlH_4$ reaction α,β-unsaturated ketone and aldehydes at the carbonyl carbon. This is referred to as *1,2-addition*.

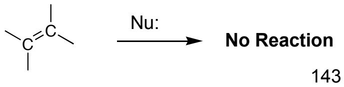
Organocopper reagents, enolates, amines, cyanide react at the β-carbon of α,β-unsaturated ketone and aldehydes. This is referred to a *1,4-addition* or *conjugate addition*.

When a reaction can take two possible path, it is said to be under *kinetic control* when the products are reflective of the path that reacts fastest. The reaction is said to be under *thermodynamic control* when the most stable product is obtained from the reaction. In the case of 1,2- versus 1,4 addition of an α,β-unsaturated carbonyl, 1,2-addition is kinetically favored and 1,4-addition is thermodynamically favored.

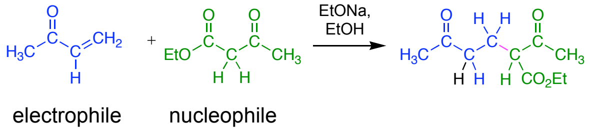
## 1,2 vs 1,4-addition α,β-unsaturated ketone and aldehydes

NOTE: conjugation to the carbonyl activates the β-carbon toward nucleophilic addition. An isolated C=C does not normally react with nucleophiles

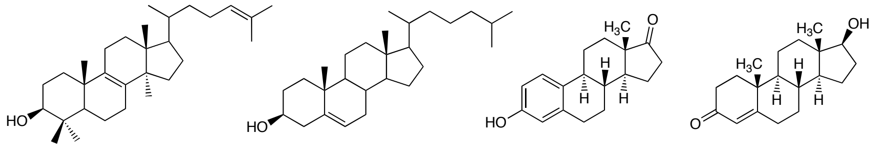




**18.13: Addition of Carbanions to α,β-Unsaturated Carbonyl Compounds: The Michael Reaction.** The conjugate addition of a enolate ion to an α,β-unsaturated carbonyl. The Michael reaction works best with enolates of β-dicarbonyls.



The product of a Michael reaction is a 1,5-dicarbonyl compound, which can undergo a subsequent intramolecular aldol reaction to give a cyclic α,β-unsaturated ketone or aldehyde. This is Known as a *Robinson annulation*.

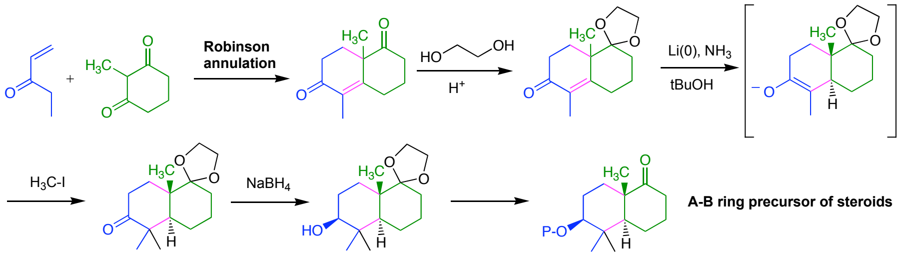


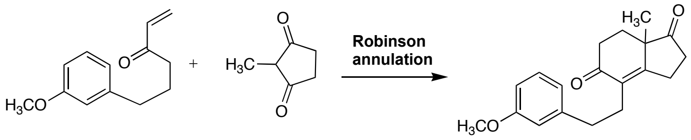
Lanosterol

Cholesterol

Estrone

Testosterone





## 18.14: Conjugate Addition of Organocopper Reagents to α,β-Unsaturated Carbonyl Compounds

Recall from Ch. 14.11 the preparation of organocopper reagents

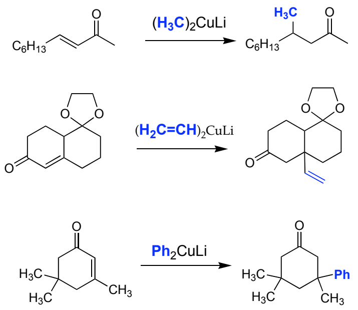
$$\text{R-X} \xrightarrow[\text{pentane}]{\text{2 Li}^{(0)}} \text{R-Li} + \text{LiX}$$

$$2\ \text{R}_2\text{Li} + \text{CuI} \xrightarrow{\text{ether}} \underset{\substack{\text{diorganocopper reagent}\\ \text{(cuprate, Gilman's reagent)}}}{\text{R}_2\text{CuLi}} + \text{LiI}$$

Dialkylcopper lithium: $(H_3C)_2CuLi$

Divinylcopper lithium: $(H_2C{=}CH)_2CuLi$

Diarylcopper lithium: $Ar_2CuLi$



α,β -unsaturated ketones and aldehydes react with diorganocopper reagents to give 1,4-addition products (C-C bond forming reaction)