

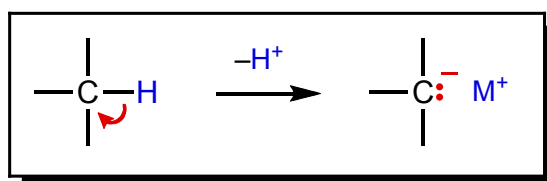
3.1 Enolates: Electron Rich Carbons 2

How do you prepare electron rich carbon?

- **metal–halogen exchange** ✓
- **metal–hydrogen exchange**

For **metal–hydrogen exchange**

- use a base to remove H^+
- the C–H bond must be easy to cleave
 - implies that the substrate must be **acidic**



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3.2 Acidity

For the reaction of any generalised acid HA, the acidity constant K_a is

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$
$$\begin{array}{lcl} \text{HA} + \text{H}_2\text{O} & \rightleftharpoons & \text{H}_3\text{O}^+ + \text{A}^- \quad (\text{in water}) \\ \text{HA} & \rightleftharpoons & \text{H}^+ + \text{A}^- \end{array}$$

Because K_a s span a wide range, acid strengths are normally given using $\text{p}K_a$ values

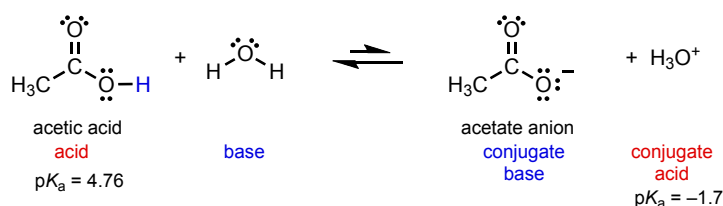
$$\text{p}K_a = -\log K_a = -\log \left[\frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \right]$$

acid strength	K_a	$\text{p}K_a$
very strong acid	> 10	< -1
moderately strong acids	$0.001 - 10$	$-1 - 3$
weak acids	$0.00001 - 0.001$	$3 - 5$
very weak acids	$10^{-15} - 10^{-5}$	$5 - 15$
extremely weak acids	$< 10^{-15}$	> 15

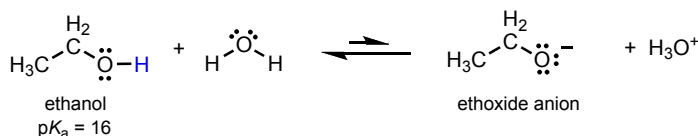
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3.2 Organic Acids

The most common organic acids are carboxylic acids (pK_a 3 – 5):



Alcohols:



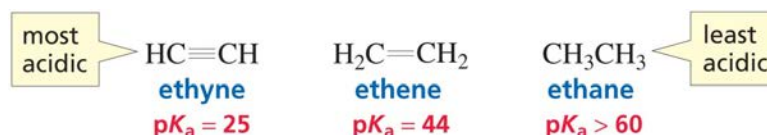
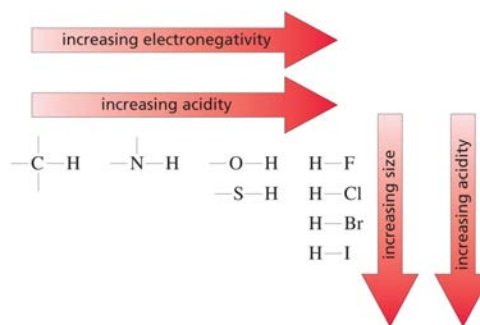
Acid	Name	K_a	pK_a
HCl	hydrochloric acid	10,000,000	
CF ₃ CO ₂ H	trifluoroacetic acid	1.6	
CH ₃ CO ₂ H	acetic (ethanoic) acid	0.00002	
H ₂ O	water	1.8×10^{-16}	
CH ₃ CH ₂ OH	ethanol	1×10^{-16}	

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3.2 Factors Affecting Acid Strength

Organic acid strength depends on five factors:

- **Size:** as the atom attached to the hydrogen *increases* in size (down a column of the periodic table), the strength of acid *increases*
- **Electronegativity:** as the atom attached to the hydrogen *increases* in electronegativity, (across row of periodic table), the strength of acid *increases*
- **Hybridisation:** the relative electronegativities of an atom are $sp > sp^2 > sp^3$



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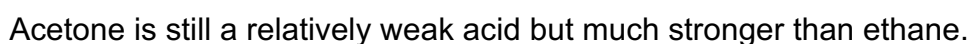
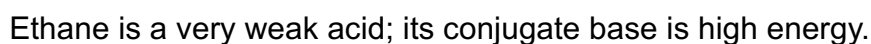
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- **Inductive effect:** an electron-withdrawing group (EWG) increases acid strength; the more *electronegative* the EWG and the *closer* it is to the acidic hydrogen, the *stronger* the acid



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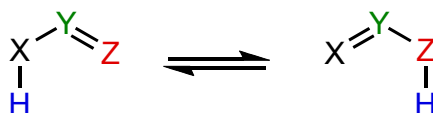
A compound that contains a *relatively* acidic hydrogen attached to carbon is called a **carbon acid**.



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3.3 Keto-Enol Tautomerism

Tautomers are constitutional isomers that differ from one another through the rearrangement of a double bond and a hydrogen that is positioned α to the double bond.

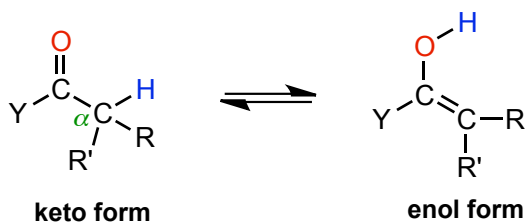


- interconversion of tautomers can be *catalysed* by acid or base
- the *position* of equilibrium is determined by the relative *stability* of the isomers

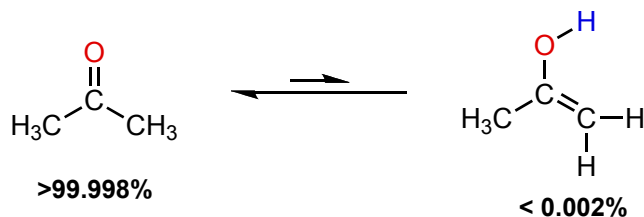
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3.3 Keto-Enol Tautomerism

Carbonyl compounds [aldehydes, ketones, carboxylic acids and acid derivatives] with at least *one* α -hydrogen can exist in either **keto** or **enol** tautomeric forms:



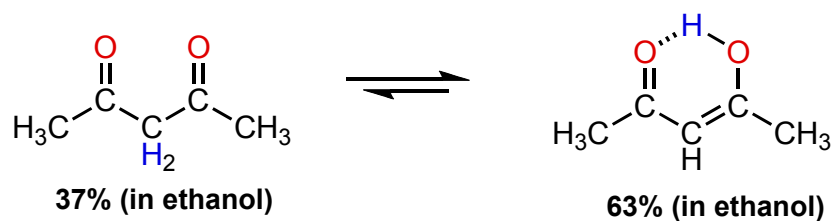
- for the vast majority of carbonyl compounds, the keto form is greatly preferred



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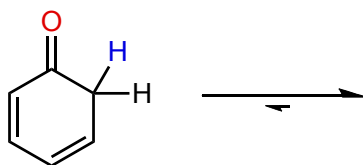
3.3 Keto-Enol Tautomerism

- In some cases the enol form is favoured:



- the enol is stabilised by conjugation and intramolecular H-bonding

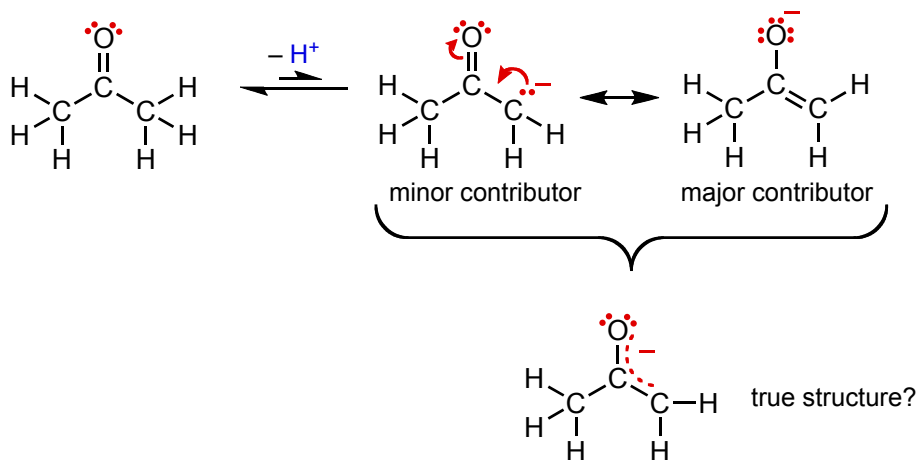
An extreme case:



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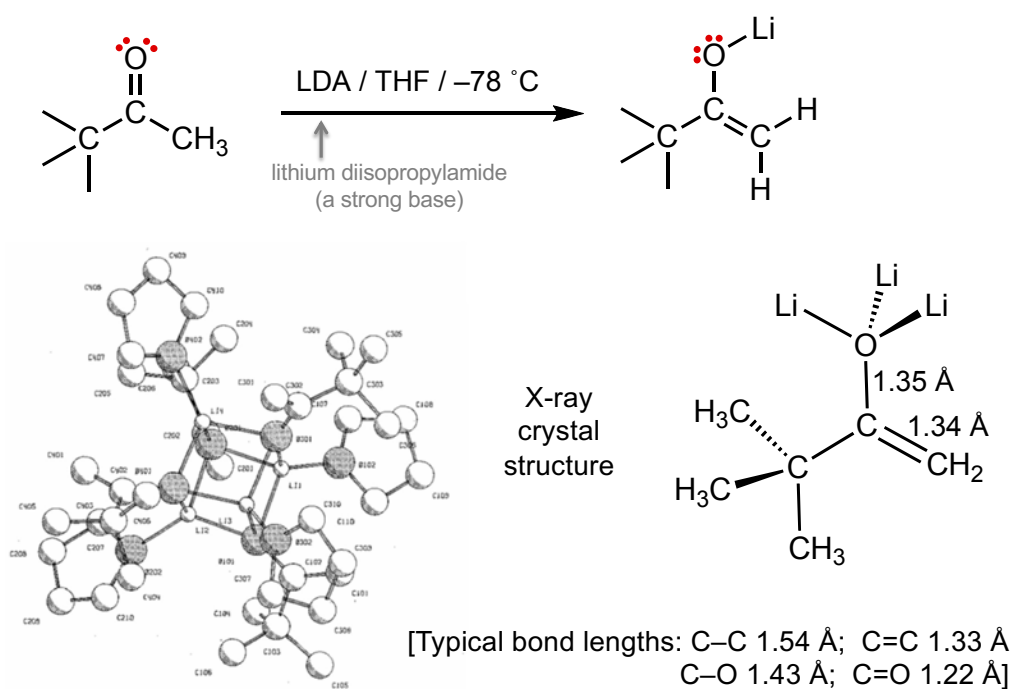
3.4 Enolate Anions

Conjugate base (**enolate anion**) is stabilised by resonance delocalisation through the π -electron system:



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3.4 Enolate Anions – Structure

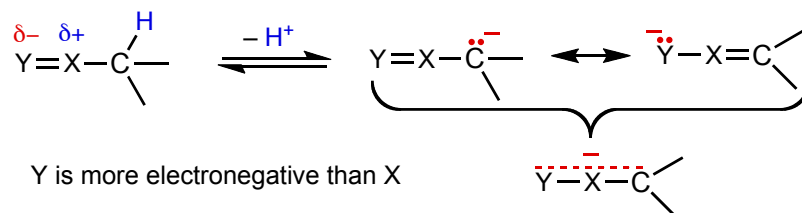


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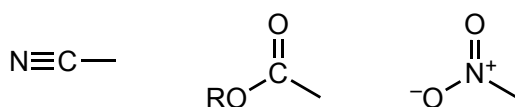
3.5 Carbon Acids

Generally, relatively strong carbon acids are noted if:

- X=Y is electron withdrawing
- can delocalise negative charge in the conjugate base



Other groups with similar properties:



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3.5 Carbon Acid Dissociation

Mono-functional/Carbonyl Carbon Acids	pK _a
$\text{H}_3\text{C}-\text{CH}_3 \rightleftharpoons \text{H}_3\text{C}-\text{CH}_2^- + \text{H}^+$	60
$\text{N}\equiv\text{C}-\text{C}(\text{H})-\text{R} \rightleftharpoons \left[\text{N}\equiv\text{C}-\text{C}(\text{H})^- \leftrightarrow \text{:}\ddot{\text{N}}=\text{C}=\text{C}(\text{H})-\text{R} \right] + \text{H}^+$	
$\text{R}-\text{O}-\text{C}(=\text{O})-\text{C}(\text{H})-\text{R}' \rightleftharpoons \left[\text{R}-\text{O}-\text{C}(=\text{O})-\text{C}(\text{H})^- \leftrightarrow \text{R}-\text{O}-\text{C}(\text{O}^-)=\text{C}(\text{H})-\text{R}' \right] + \text{H}^+$	
$\text{C}(=\text{O})-\text{C}(\text{H})-\text{R} \rightleftharpoons \left[\text{C}(=\text{O})-\text{C}(\text{H})^- \leftrightarrow \text{:}\ddot{\text{O}}=\text{C}-\text{C}(\text{H})-\text{R} \right] + \text{H}^+$	
$\text{H}-\text{C}(=\text{O})-\text{C}(\text{H})-\text{R} \rightleftharpoons \left[\text{H}-\text{C}(=\text{O})-\text{C}(\text{H})^- \leftrightarrow \text{:}\ddot{\text{O}}=\text{C}-\text{C}(\text{H})-\text{R} \right] + \text{H}^+$	
$\text{O}=\text{N}^+-\text{C}(\text{H})-\text{R} \rightleftharpoons \left[\text{O}=\text{N}^+-\text{C}(\text{H})^- \leftrightarrow \text{:}\ddot{\text{O}}=\text{N}^+=\text{C}(\text{H})-\text{R} \right] + \text{H}^+$	

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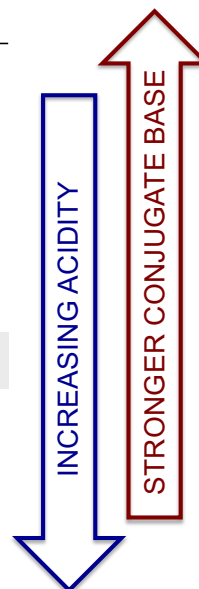
3.5 Carbon Acid Dissociation

β-Dicarbonyl Carbon Acids	pK _a
$\text{RO}-\text{C}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})-\text{OR} \rightleftharpoons \left[\text{RO}-\text{C}(=\text{O})-\text{CH}_2^- \leftrightarrow \text{RO}-\text{C}(\text{O}^-)=\text{CH}-\text{C}(=\text{O})-\text{OR} \leftrightarrow \text{RO}-\text{C}(=\text{O})-\text{CH}=\text{C}(\text{O}^-)-\text{OR} \right] + \text{H}^+$	
$\text{RO}-\text{C}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})-\text{R} \rightleftharpoons \left[\text{RO}-\text{C}(=\text{O})-\text{CH}_2^- \leftrightarrow \text{RO}-\text{C}(\text{O}^-)=\text{CH}-\text{C}(=\text{O})-\text{R} \leftrightarrow \text{RO}-\text{C}(=\text{O})-\text{CH}=\text{C}(\text{O}^-)-\text{R} \right] + \text{H}^+$	
$\text{C}(=\text{O})-\text{CH}_2-\text{C}(=\text{O})-\text{R} \rightleftharpoons \left[\text{C}(=\text{O})-\text{CH}_2^- \leftrightarrow \text{:}\ddot{\text{O}}=\text{C}-\text{CH}=\text{C}(=\text{O})-\text{R} \leftrightarrow \text{C}(=\text{O})-\text{CH}=\text{C}(\text{O}^-)-\text{R} \right] + \text{H}^+$	
<p>compare with</p> $\text{C}(=\text{O})-\text{C}(\text{H})-\text{R} \rightleftharpoons \left[\text{C}(=\text{O})-\text{C}(\text{H})^- \leftrightarrow \text{:}\ddot{\text{O}}=\text{C}-\text{C}(\text{H})-\text{R} \right] + \text{H}^+$	

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pK_as for Some Organic Compounds and Water

Compound type	Typical compound structure	pK _a
Alkane	CH ₃ CH ₃	60
Dialkylamine	HN(<i>i</i> -C ₃ H ₇) ₂	35
Ester	CH ₃ COOR	25
Ketone	CH ₃ COCH ₃	20
Aldehyde	CH ₃ CHO	17
Alcohol	CH ₃ CH ₂ OH	16
Water	H ₂ O	15.7
1,3-Diester	RCOOCH ₂ COOR	13
1,3-Keto ester	RCOOCH ₂ COCH ₃	11
1,3-Diketone	CH ₃ COCH ₂ COCH ₃	9
Carboxylic acid	CH ₃ COOH	5



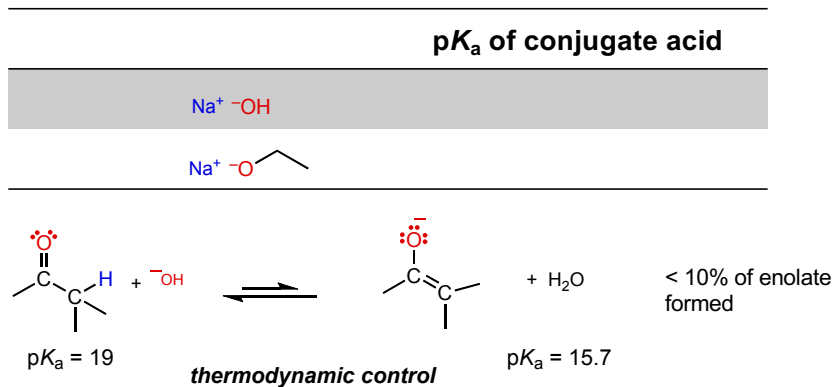
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3.6 Bases

The proton is removed from the carbon acid by a base which must be sufficiently strong. The choice of base depends on the acidity of the substrate and reversibility options.

The equilibrium of an acid-base reaction favours **reaction of the strong acid** and **formation of the weak acid**.

Reversible Bases

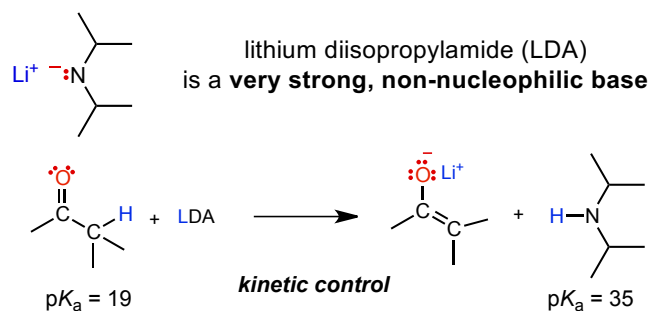


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3.6 Bases

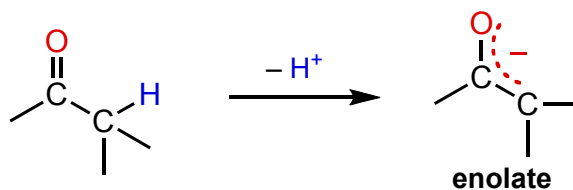
Irreversible Bases

base	pK_a of conjugate acid	conjugate acid
$Na^+ H^-$	35	$H-H$
$Li^+ R^-$		$H-R$
$MgX^+ R^-$		$H-R$
$Li^+ R_2N^-$		HNR_2



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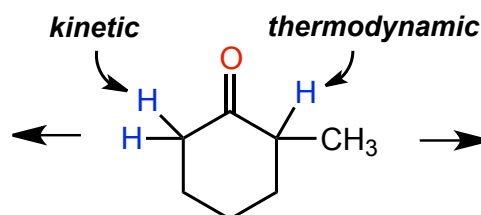
3.7 Formation of Enolates



Kinetic and thermodynamic **deprotonation** can give different enolates from unsymmetrical ketones:

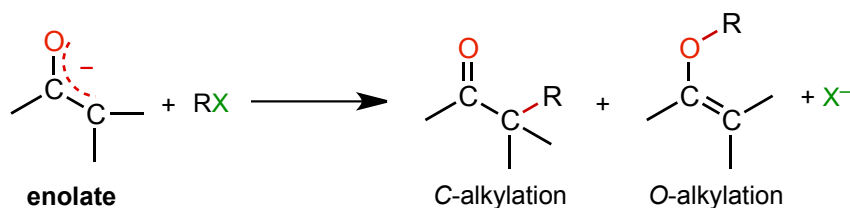
Kinetic → most accessible H removed

Thermodynamic → most substituted (stable) enolate formed



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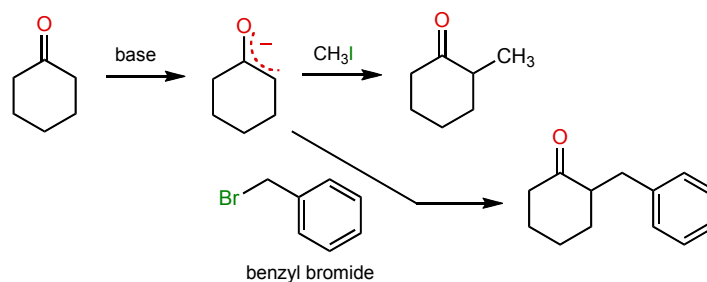
3.8 Reaction of Enolates with Alkyl Halides (RX)



➤ $\text{S}_{\text{N}}2$ mechanistic features

- reaction best if RX is $\text{S}_{\text{N}}2$ active
 - methyl, primary (1°) or secondary (2°)
 - X is a good leaving group

➤ reaction is irreversible (kinetic control)

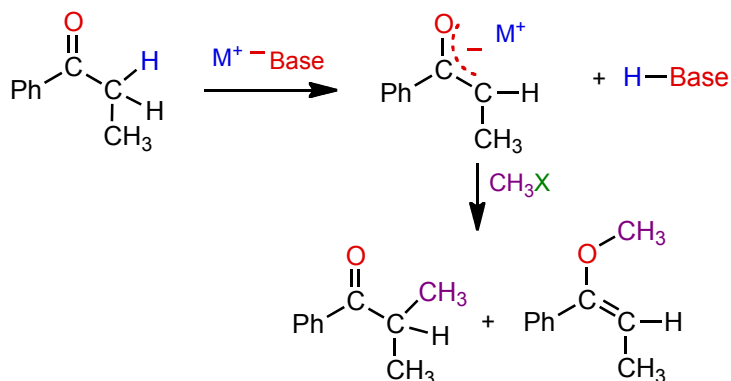


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3.8 Reaction of Enolates with Alkyl Halides (RX)

➤ issue of C- vs O-alkylation

- generally soft X in protic environments favors C-reaction

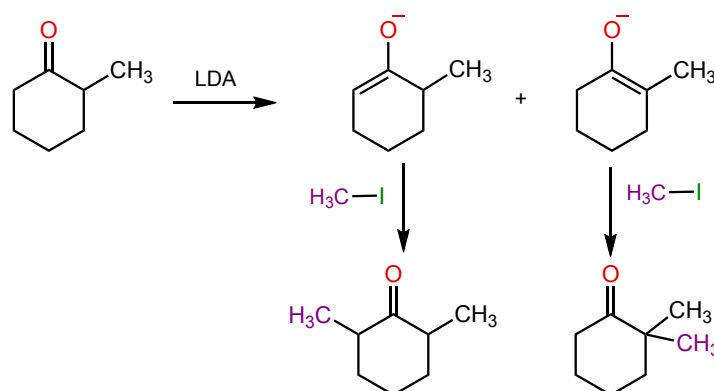


X	C-alkylation (%)	O-alkylation (%)
Cl	45	55
Br	61	39
I	81	19

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3.8 Reaction of Enolates with Alkyl Halides (RX)

- for unsymmetrical ketones, can control which product predominates by **choice of base and reaction conditions**

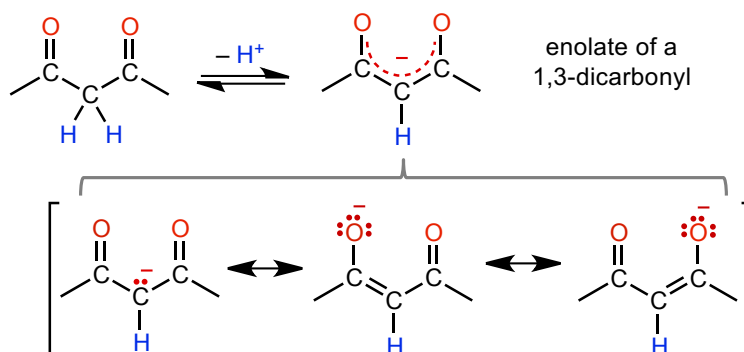


- **Kinetic** conditions (-78°C) irreversibly generates 2,6-dimethylcyclohexanone
- **Thermodynamic** conditions (higher temp, unhindered base e.g. NaOEt) reversibly generates the *more stable enolate*, and thus 2,2-dimethylcyclohexanone

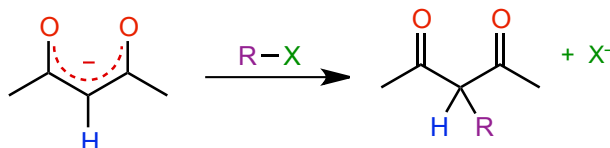
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3.9 1,3-Dicarbonyls

1,3-Dicarbonyls are relatively acidic molecules ($\text{p}K_{\text{a}}$ 9-13) as their conjugate base is extensively delocalised.



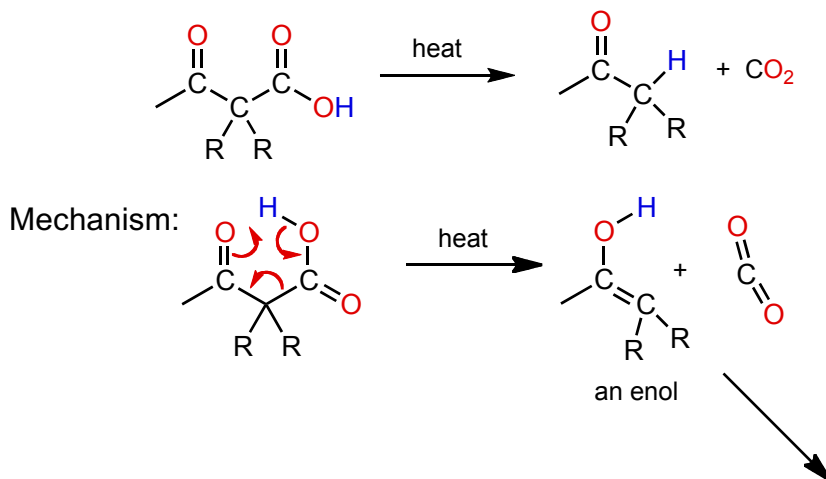
As with the mono-carbonyl compounds discussed earlier, 1,3-dicarbonyl enolates can be **alkylated**:



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3.9 Decarboxylation of 1,3-Dicarbonyls

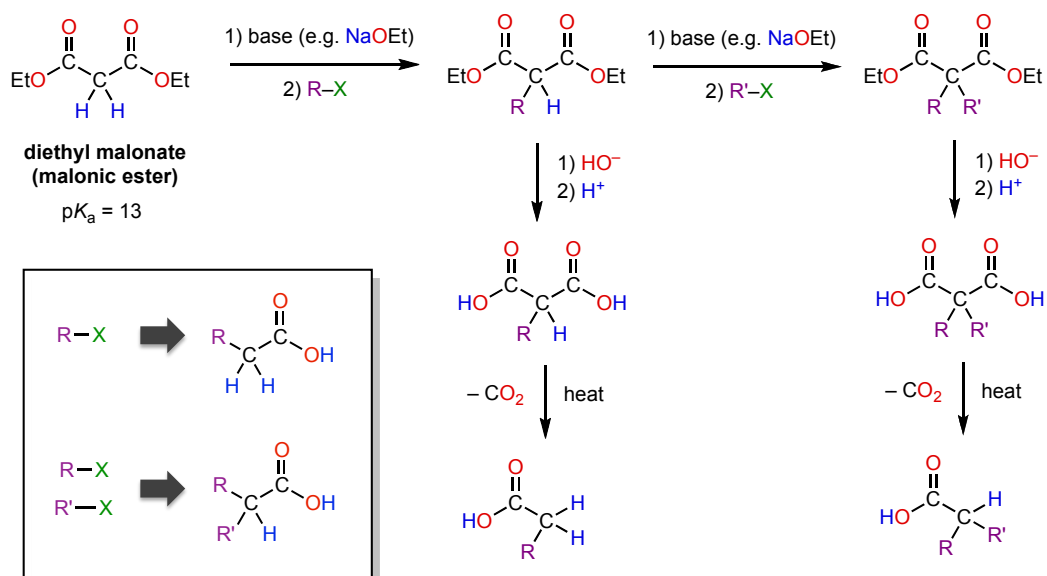
1,3-Dicarbonyls are useful in organic synthesis as they can be **decarboxylated** to generate new carbonyl compounds:



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3.10 Malonic Ester Synthesis

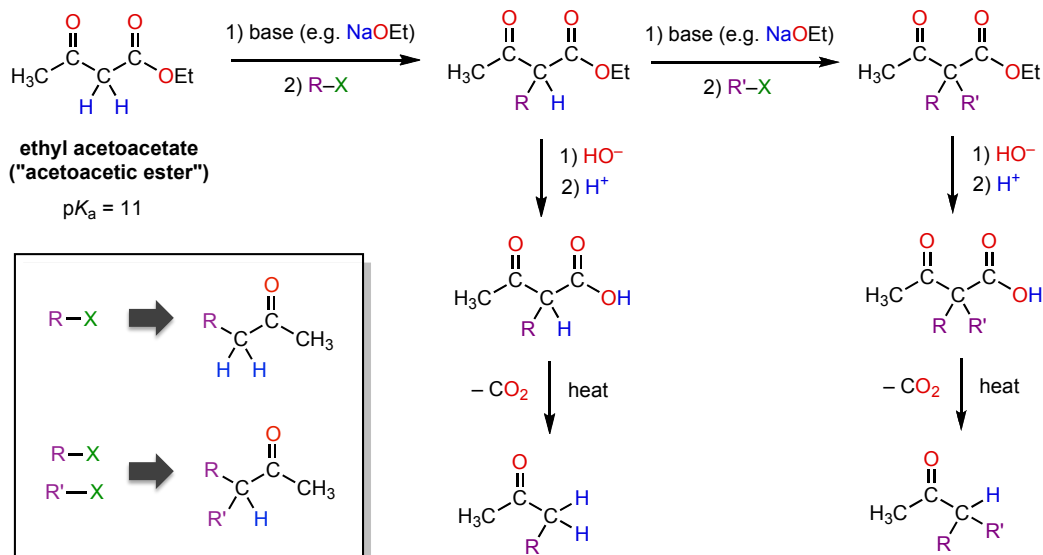
This is a combination of **alkylation** of an α -carbon and **decarboxylation** of a β -dicarboxylic acid



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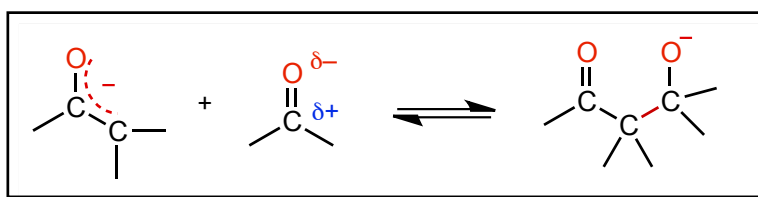
3.11 Acetoacetic Ester Synthesis

This is related to the malonic ester synthesis. An **alkylation** followed by **decarboxylation** gives a **methyl ketone** (rather than a carboxylic acid).



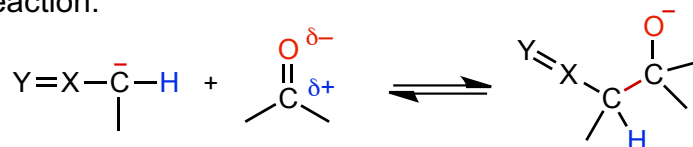
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3.12 Reaction of Enolates with Carbonyls

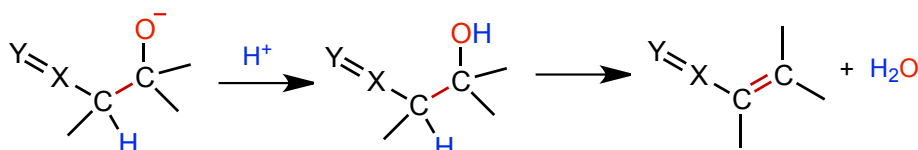


➤ Reversible reaction (thermodynamic control)

General reaction:



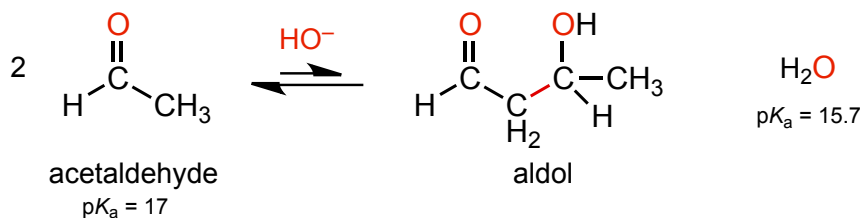
Addition step is often followed by **protonation** and **elimination**



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3.13 Aldol Reaction (Addition)

The enolate of acetaldehyde reversibly reacts with another molecule of acetaldehyde to give a β -hydroxyaldehyde known as **aldol**.



- catalytic in base
- carbonyl activates C–H for deprotonation and is also the site of nucleophilic attack
- pK_a of aldehyde = 17, pK_a of water = 15.7, so less than 10% of the aldehyde will be deprotonated to the enolate by hydroxide
- acid catalysis possible

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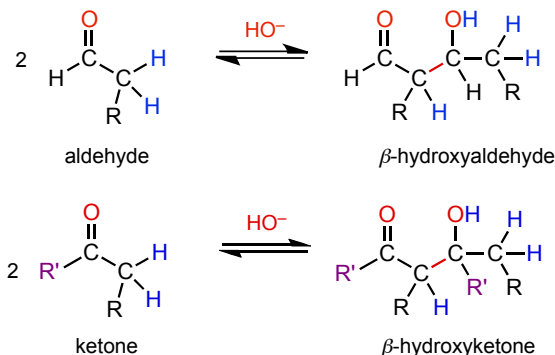
3.13 Aldol Reaction

Generally, aldol addition is the reaction between two molecules of an *aldehyde* or two molecules of a *ketone*.

- 2 x aldehyde \rightarrow β -hydroxyaldehyde
- 2 x ketone \rightarrow β -hydroxyketone

The aldehyde/ketone **must** have an α -hydrogen.

Good yields of the addition product are obtained only if it is removed from the solution as it is formed.

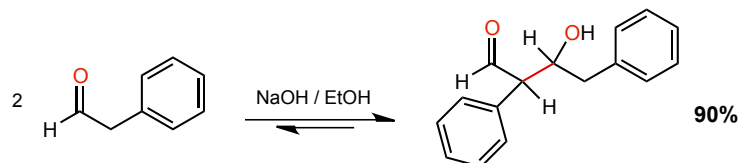


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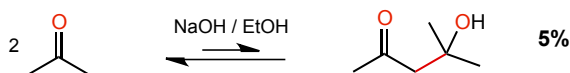
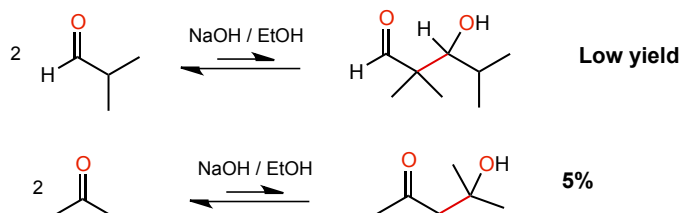
3.13 Aldol Reaction

The equilibrium for formation of the β -hydroxycarbonyl compound is:

- favourable only for **aldehydes** with **one α -substituent**
i.e. RCH_2CHO



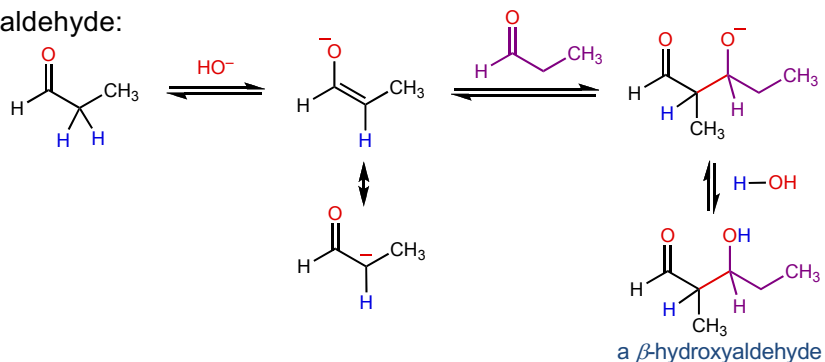
- favours starting materials for more substituted aldehydes and ketones



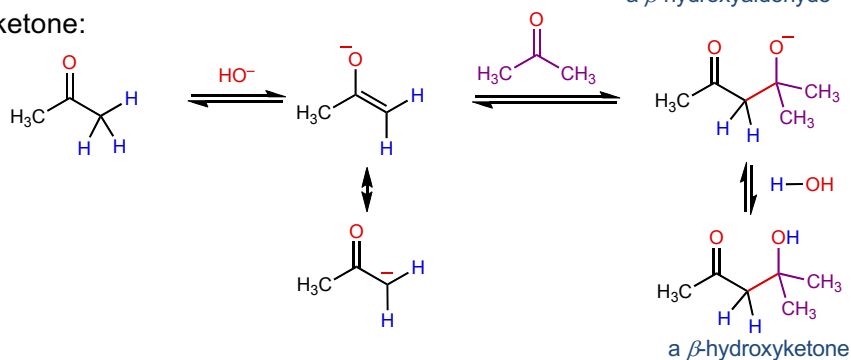
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3.13 Aldol Reaction – Examples & Mechanism

With an aldehyde:



With a ketone:



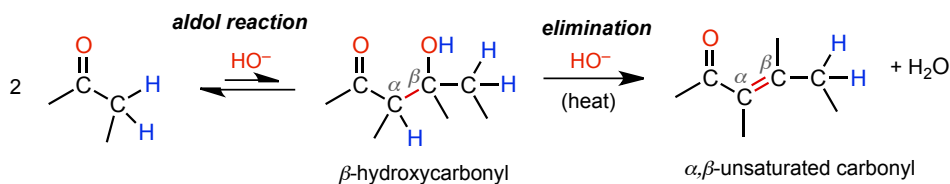
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3.14 Aldol Condensation

Recall: Alcohols can undergo dehydration in the presence of base (or acid).

Under forcing conditions, an aldol addition product may undergo dehydration/elimination of water ($E1_{cb}$ mechanism).

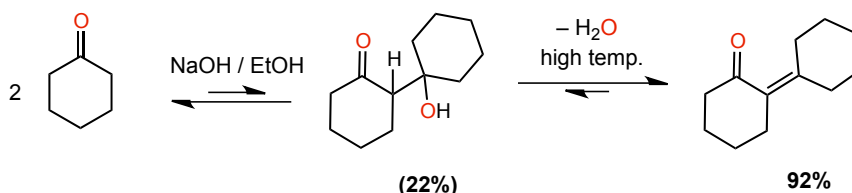
This process is known as **aldol condensation**.



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3.14 Aldol Condensation

Irrespective of the favourability for formation of the initial β -hydroxy aldehyde or ketone, under more forcing conditions which favour the elimination of water, the α,β -unsaturated aldehyde or ketone is usually obtained in good yield, e.g.

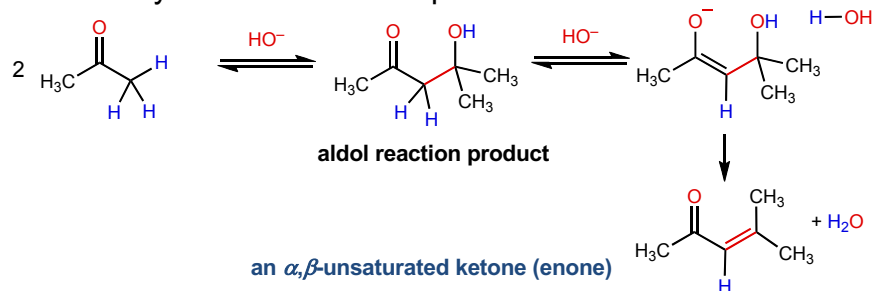


The product of the dehydration is a **conjugated enone**. It can be obtained directly from the aldol reaction without isolating the intermediate β -hydroxy carbonyl compound.

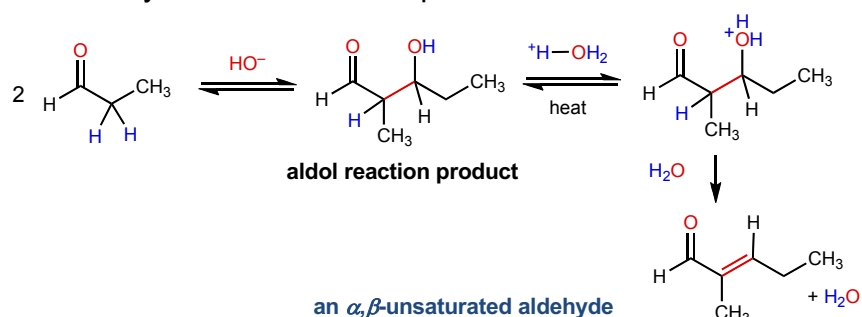
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3.14 Aldol Condensation – Examples & Mechanism

With base-catalysed elimination step:



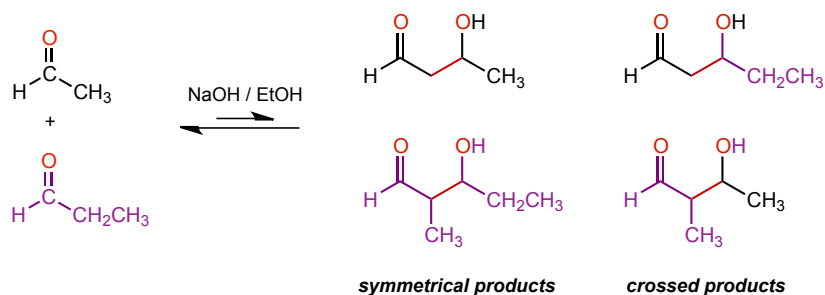
With acid-catalysed elimination step:



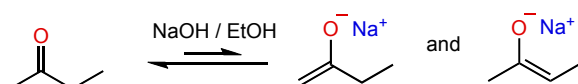
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3.15 Crossed (Mixed) Aldol Reaction

New C–C bond formed between α -carbon and carbonyl carbon of two **different** aldehydes/ketones. Without some “control”, a mixture of products can be obtained → not synthetically useful.



With ketones, the situation may be even more complex: recall that unsymmetrical ketones can generate two possible enolates.



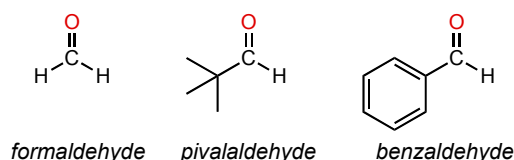
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3.15 Crossed (Mixed) Aldol Reaction

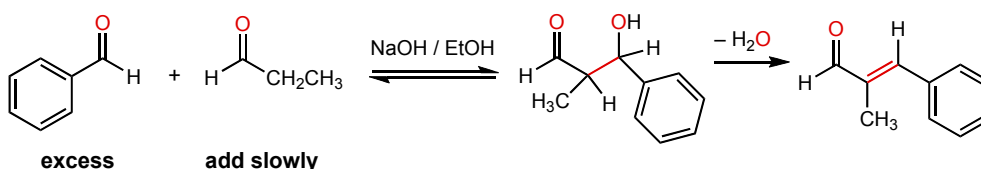
To obtain a single product from a crossed aldol reaction (under reversible conditions), the following conditions need to be met:

- *one partner only* must be *capable of enolisation*, and
- the other partner, as well as being incapable of enolisation, must be *more electrophilic* than the enolisable partner

Typical partners containing a highly reactive carbonyl group, but not being capable of enolisation, are aldehydes *without* α -hydrogens.



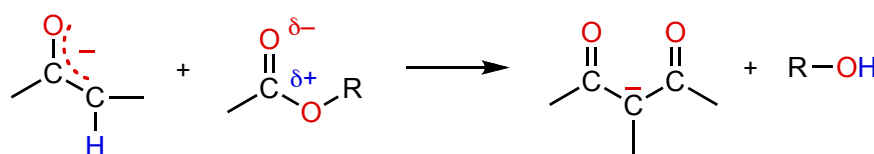
A single major crossed aldol reaction product may be obtained using an excess of an non-enolisable aldehyde and slowly adding a second aldehyde. The product can then undergo dehydration.



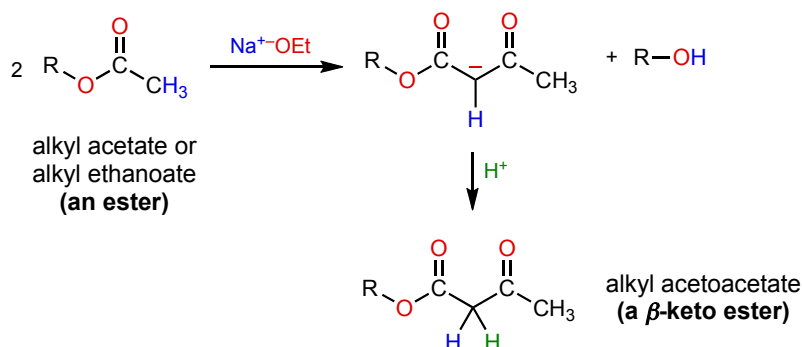
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3.16 Claisen Condensation

The **Claisen condensation** is the reaction of an (ester) enolate with an ester to give a 1,3-dicarbonyl compound.



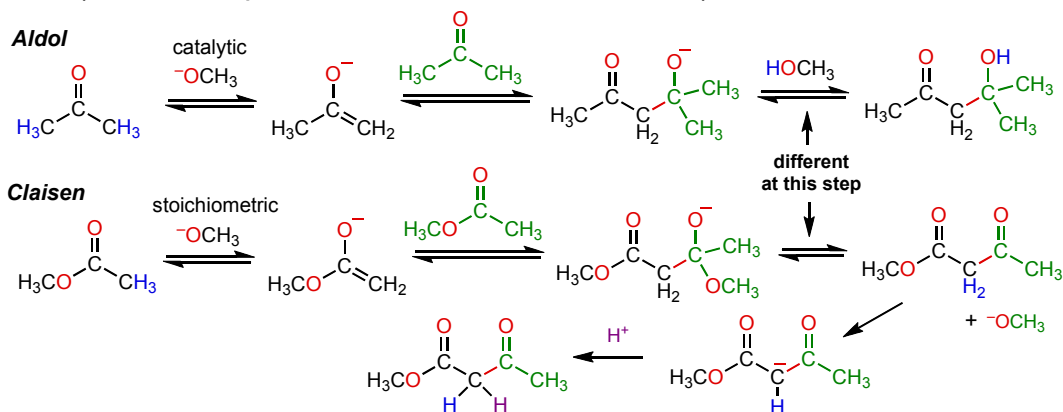
Initial addition of the enolate to the carbonyl group is followed by **extrusion** of RO^- .



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3.16 Claisen Condensation

- as in the aldol reaction/addition, one molecule of a carbonyl compound is converted into an enolate anion when a strong base removes a proton at an α -carbon
- the enolate attacks the carbonyl carbon of a second molecule of ester
- after nucleophilic attack, the C=O bond re-forms and ^-OR is *expelled* (this last step is different to the aldol reaction)

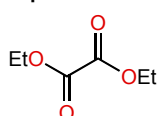


3.17 Crossed (Mixed) Claisen Condensations

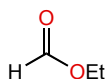
As with the crossed aldol condensation, two conditions need to be met for a successful crossed Claisen condensation:

- *one partner only* must be *capable of enolisation*, and
- the other partner, as well as being *incapable* of enolisation, should be *more electrophilic* than the enolisable partner

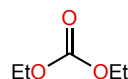
Typical partners containing a reactive carbonyl group, but not being capable of enolisation are:



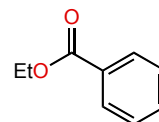
diethyl oxalate



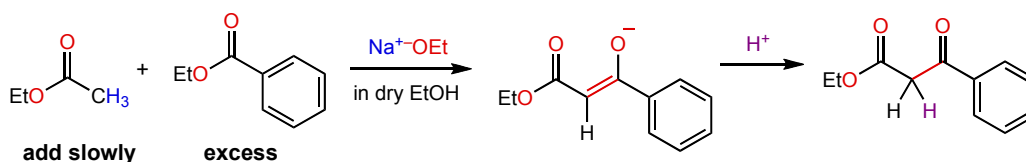
ethyl formate
(ethyl methanoate)



diethyl carbonate



ethyl benzoate



3.17 Crossed (Mixed) Claisen Condensations

Crossed Claisen condensation reactions are also possible with ketones (providing the enolate):

