ENOLATES IN ORGANIC SYNTHESIS
Recall

Enolate alkylation, Aldol addition and condensation can provide access to a wide variety of multi-functional compounds, which can lend themselves to further functionalization in multi-step organic synthesis.
Enolates in Organic Synthesis

Bases for Generation of Enolates

Inorganic bases: NaOH and KOH in aqueous solution can be employed
(Caution: Ester substrates may be hydrolysed)
Hydride bases: NaH and KH are also common
Alkoxide bases: NaOMe, NaOEt and KO-t-Bu are also effective
Nitrogenous bases: NaNH₂, LiNH₂, KNH₂ can also be employed.
The most effective nitrogenous base, however, is lithium diisopropylamidine (LDA). LDA is a secondary amine-derived base that is soluble in organic solvents.

\[
\text{Diisopropylamine} \quad \text{H} + n\text{-BuLi} \rightarrow \quad \text{LDA} \quad + \quad n\text{-BuH}
\]

LDA is a strong, relatively hindered band therefore non-nucleophilic base.
LDA is readily commercially available.
Its amine by-product (Diisopropylamine) is low-molecular weight, volatile and easily removed.
Bases for Generation of Enolates

Alternative nitrogenous bases that have attracted wide use include sodium hexamethyldisilazide (NaHMDS) or lithium hexamethyldisilazide (LiHMDS). These bases can be generated from the reaction of hexamethyldisilazane with an appropriate base.

\[
\begin{align*}
\text{Hexamethyldisilazane} & \quad \text{pKa} = 40 \\
\text{NaHMDS} & \\
\text{LiHMDS} & \quad \text{pKa} = 48
\end{align*}
\]
Generation of Enolates in Acyclic Systems: The Challenges

The generation of enolates in unsymmetrical acyclic enolizable carbonyl compounds has to address two issues of concern:

(i) The site of deprotonation (Regiochemical problem): Thermodynamic vs Kinetic enolate
(ii) Geometry of enolate formed (Stereochemical problem): E- vs Z-Enolate

Regiochemical Problem

The reaction of unsymmetrical ketones with bases provides regioisomeric enolates.

With judicious choice of a base and reaction conditions, one regioisomer can predominate. Whereas a strong base at low temperature favours the kinetic enolate, a weak base at high temperature allows for equilibration to occur to favour the thermodynamic enolate.
Regioselective Generation of Enolates in Cyclic Systems

Kinetic vs Thermodynamic Enolate: Depends on the base and the reaction conditions

<table>
<thead>
<tr>
<th>Base</th>
<th>Control</th>
<th>Enolate Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA</td>
<td>Kinetic</td>
<td>99</td>
</tr>
<tr>
<td>NaH</td>
<td>Thermodynamic</td>
<td>25</td>
</tr>
</tbody>
</table>

Regiospecific Generation of E-Enolates in Cyclic Systems: Dissolving metal conditions
Enolate Alkylation

Malonic Ester Synthesis

Diethyl malonate

Cheap and commercially available

CO₂ +

Various acids can be prepared

Example

Diethyl malonate

(1) NaOEt

(2) vinylBr

Ester hydrolysis and decarboxylation

Monoprotected succinic acid
Enolate Alkylation

Malonic Ester Synthesis

Example
Dialkylation of the malonic ester platform is possible leading to complex derivatives of synthetic relevance.
Aldol condensations involve the nucleophilic addition of an enolate of an aldehyde or ketone to another aldehyde or ketone with initial formation of a $\beta$-hydroxyaldehyde or ketone, which undergoes dehydration under the reaction conditions with eventual formation of an $\alpha,\beta$-unsaturated aldehyde or $\alpha,\beta$-unsaturated ketone. The product is commonly referred to as an “Aldol’ condensation product.

\[
\text{CH}_3\text{C}(\text{R}_1) + \text{R}(\text{C})\text{H} \xrightarrow{\text{Base}} \begin{array}{c}
\text{OH} \\
\text{O}
\end{array} \xrightarrow{\text{Heat}} \begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\]

The extra stabilization achieved from the conjugation in the $\alpha,\beta$-unsaturated product favours the dehydration step and particularly when the conjugation is further extended by an aromatic substituent. The $\alpha,\beta$-unsaturated aldehydes or ketones obtained in Aldol condensation reactions are very important in conjugate addition reactions (Michael addition reactions).
Mechanism of the Aldol Condensation

Base-Catalysed Aldol Condensation

(i) \[ \text{OH}^- + \text{H}^+ - \text{C} = \text{C} - \text{R}_1 \rightarrow \text{H}^+ - \text{C} = \text{C} - \text{R}_1 \rightarrow \text{H}^+ - \text{C} = \text{C} - \text{R}_1 + \text{H}_2\text{O} \]

(ii) \[ \text{R} - \text{C} - \text{H} + \text{OH}^- - \text{C} = \text{C} - \text{R}_1 \rightarrow \text{R} - \text{C} - \text{C} - \text{R}_1 \]

(iii) \[ \text{R} - \text{C} - \text{C} - \text{R}_1 + \text{H}_2\text{O} \rightarrow \text{R} - \text{C} - \text{C} - \text{R}_1 + \text{OH}^- \]

(iv) \[ \text{R} - \text{C} - \text{C} - \text{R}_1 + \text{OH}^- \rightarrow \text{R} - \text{C} - \text{C} - \text{R}_1 + \text{H}_2\text{O} \]

(v) \[ \text{R} - \text{C} - \text{C} - \text{C} - \text{R}_1 \rightarrow \text{R} - \text{C} = \text{C} - \text{C} - \text{R}_1 + \text{OH}^- \]
Stereochemistry of Aldol Condensation

In acyclic systems

\[
\begin{align*}
\text{Mechanism: } E_1\text{Cb: Unimolecular Elimination via Conjugate Base} \\
\text{E-Alkenes are the predominant products in Aldol condensation reactions.}
\end{align*}
\]
Aldol Condensation

The dehydration step in Aldol condensation reactions become even more facile when further conjugation can be achieved especially with the use of aromatic system, wherein additional conjugation to the aromatic nucleus serves to stabilize the $\alpha,\beta$-unsaturated condensation product further.

Consider the industrial synthesis of cinnamaldehyde, wherein only the Aldol condensation product is isolated since the conjugation in the product is further extended by the Ph substituent. No Aldol addition product is isolated.

\[
\begin{align*}
\text{PhCHO} + \text{CH}_3\text{CHO} \xrightarrow{\text{NaOH}} \text{PhCH=CHCOH} + \text{H}_2\text{O}
\end{align*}
\]

Cinnamaldehyde

*(A flavour in confectioneries and bakery goods)*

Cinnamaldehyde occurs naturally in the cinnamon plant
Conjugate Addition of Enolates

Enolates, by virtue of being resonance stabilized, are soft nucleophiles; consequently they undergo conjugate addition (1,4-addition or Michael addition) reactions to $\alpha,\beta$-unsaturated enones.

![Conjugate Addition of Enolates Diagram](image)

Enolates are stabilized by resonance so are soft electrophiles
Conjugate Addition of Enolates

1,4-Addition (Conjugate Addition or Michael Addition)

Soft nucleophile  Soft electrophile

\[ \text{Work-up} \]

1,5-Dicarbonyl generated

Conjugate additions of enolates generate 1,5-dicarbonyl products like those employed in intramolecular Aldol condensation reactions.

This conjugate addition is the first step in the Robinson annulation towards the synthesis of the Wieland Miescher ketone. This is followed by an intramolecular Aldol condensation.
Robinson Annulation

The Robinson annulation generates a cyclohexenone ring on top of a pre-existing ring thereby providing a 5-6 or 6-6 ring system. Robinson annulation involves the following basic steps:
(1) Michael addition \ conjugate addition \ 1,4-addition
(2) Aldol addition
(3) Dehydration (base-catalysed)
The Wieland Miescher ketone has been employed in the total synthesis of more than 50 natural products, predominantly steroids possessing possible biological properties including anticancer, antibacterial and immunodulatory activities.
Mannich Reaction

The Mannich reaction is the condensation of an enolizable carbonyl compound with an iminium ion leading to an $\alpha$-alkylation through introduction of a diakylaminomethyl substituent.

$$\text{Enolizable carbonyl} + \text{Iminium ion} \rightarrow \text{$\alpha$-Alkylated carbonyl compound}$$

The electrophilic (iminum) species is often generated in situ from the reaction of the parent dialkylamine and formaldehyde in a presence of an acid catalyst.

$$\text{HCHO} + \text{Parent dialkylamine} \rightarrow \text{Iminium ion} \quad \text{Eschenmoser salt}$$

Mechanism
Mannich Reaction

Thermal elimination of the dialkylaminomethyl ketones formed in the Mannich reaction provides $\alpha$-methylene carbonyl compounds.

\[ \text{CH}_3\text{N}^+\text{CH}_2\text{C}=\text{C} \quad \text{Heat} \quad \text{CH}_3\text{N}^-\text{CH}_2\text{C}=\text{C} \]

$\alpha$-Dimethylamino carbonyl compound $\quad \alpha$-Methylene carbonyl compound

Alternatively, the elimination to an $\alpha$-methylene can be accomplished through a two-step sequence involving the derived quarternary salts.

\[ \text{CH}_3\text{N}^+\text{CH}_2\text{C}=\text{C} \quad \text{CH}_3\text{I} \quad \text{CH}_3\text{N}^-\text{CH}_2\text{C}=\text{C} \]

\[ \text{CH}_3\text{N}^+\text{CH}_2\text{C}=\text{C} \quad \text{NaHCO}_3 \quad \text{CH}_3\text{N}^-\text{CH}_2\text{C}=\text{C} \]

$\alpha$-Methylene carbonyl compound
α-Methylene lactones are present in a number of natural products. The reaction of ester enolates with the Eschenmoser salt was used to introduce the α-methylene group in the synthesis of vernolepin, a compound with anti-leukemic activity.