Stereoselective reactions of enolates

• The stereoselectivity of reactions of enolates is dependent on:
  • Presence of stereogenic centres on $R^1$, $R^2$ or $E$ (obviously!)
  • Frequently on the geometry of the enolate (but not always)

• Use terms cis and trans with relation to O–M to avoid confusion
Enolate formation and geometry

- Enolate normally formed by **deprotonation**
- This is favoured when the C–H bond is perpendicular to C=O bond as this allows \( \sigma \) orbital to overlap \( \pi \) orbital
- \( \sigma \) C–H orbital ultimately becomes p orbital at C-\( \alpha \) of the enolate p bond

Two possible conformations which allow this
- First is given below and results in the formation of **cis enolate**
- Initial conformation (Newman projection) similar to transition state
- Little steric interaction between \( R^1 \) and \( R^2 \)
Enolate formation and geometry II

- Second conformation that places C–H perpendicular to C=O gives *trans*-enolate.
- Only differs by relative position of $R^1$ and $R^2$.
- The steric interaction of $R^1$ and $R^2$ results in the *cis*-enolate normally predominating.
- As results below demonstrate stereoselectivity is influenced by the size of $R$.

![Enolate formation diagram]

<table>
<thead>
<tr>
<th>R</th>
<th>cis (%)</th>
<th>trans (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>i-Pr</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>t-Bu</td>
<td>&gt;98</td>
<td>&lt;2</td>
</tr>
<tr>
<td>OMe</td>
<td>95</td>
<td>&lt;3</td>
</tr>
<tr>
<td>NEt$_2$</td>
<td>&gt;97</td>
<td></td>
</tr>
</tbody>
</table>
Enolate formation and geometry III

- The selectivity observed can be explained via chair-like transition state.
- In ketones cis-enolate favoured if R is large but trans-enolate favoured if R is small.

If R is large, this TS* is destabilised by R–Me interaction and cis predominates.

If R is small, 1,3-diaxial interaction is important as it destabilises this TS* and trans predominates.

With esters the R vs OMe interaction is alleviated and 1,3-diaxial interaction controls geometry - hence trans-enolate predominates.
Enolate formation and geometry IV

- Amides invariably give the *cis*-enolate; remember restricted rotation of C–N bond
- The previous arguments are good generalisations, many factors effect geometry
- Use of the additive HMPA (hexamethylphosphoric triamide) reduces coordination and favours the thermodynamically more stable enolate
Addition of an electrophile to an enolate

- Finally, need to know the trajectory of approach of the enolate and electrophile.
- Reaction is the overlap of the enolate HOMO and electrophile LUMO.
- Therefore, new bond is formed more or less perpendicular to carbonyl group.
- Above is simple S_N2 with X = leaving group.
Enolate alkylation

Simple alkylation of a chiral enolate can be very diastereoselective.

As we have a cis-enolate, diastereoselectivity can be explained in an analogous fashion to simple alkenes via $A^{1,3}$ strain.

Larger the substituent, $R$, greater the selectivity.

Note: minor diastereoisomer probably arises from electrophile passing by $R$ group.

Therefore, size does matter...
In this example enolate geometry is not important - both are cis-alkenes.
Therefore, selectivity the same in both cases.
If we want to reverse selectivity, change the electrophile to H.
This route far less selective as H is small so less interaction with substituents.
The aldol reaction

The aldol reaction is a valuable C–C forming reaction. In addition, it can form two new stereogenic centres in a diastereoselective manner. Most aldol reactions take place via a highly ordered transition state known as the Zimmerman–Traxler transition state. It will not come as much surprise that this is a 6-membered, chair-like transition state. Interestingly, enolate geometry effects diastereoselectivity.
The aldol reaction II

- Generally speaking the above guideline sums up aldol chemistry!
- To understand why this happens we need to examine Zimmerman-Traxler TS⁺
- You must learn to draw chair-like conformation of 6-membered rings
Zimmerman-Traxler transition state

- We only have one choice in the aldol reaction - the orientation of the aldehyde.
- Enolate substituents are fixed due to the double bond.
- Aldehyde substituent is pseudo-equatorial to avoid 1,3-diaxial interactions.

*re* face of enolate attacks *si* face of aldehyde.
Zimmerman-Traxler transition state II

- Attack via the enantiomeric transition state (re face of aldehyde) gives the enantiomeric aldol product.
- This differs only by the absolute stereochemistry - the relative stereochemistry is the same.
The opposite stereochemistry of enolate gives opposite relative stereochemistry.

Once again the enolate has no choice where the methyl group is placed.
Enolisation and the aldol reaction

- Hopefully, all the previous discussion highlights that selective enolisation is essential for diastereoselective aldol reaction
- Each geometry of enolate gives a different relative stereochemistry
- With the lithium enolates of ketones the size of the non-enolised substituent, R, is important

\[ \text{R} = \text{t-Bu} \quad 98\% \quad \text{R} = \text{Et} \quad 2\% \]

- With boron enolates we can select the geometry by altering the boron reagent used

\[ \text{bulk} \quad \text{substituents} \quad \text{forces enolate to adopt trans geometry} \]
Enolisation and the aldol reaction II

- 9-BBN (9-borabicyclononane) looks bulky
- But most of it is ‘tied-back’ behind boron thus allowing formation of the cis-enolate

![Chemical reaction diagram]

Ph\_Me + 9-BBN \(\rightarrow\) cis-enolate \(\rightarrow\) syn aldol (96% de)
Substrate control in total synthesis I

Chemical reactions and structures are shown, including the formation of products with indicated yields and diastereomeric excess (d.e.). The Oleandomycin aglycon (R=H but should be a sugar) is highlighted. The anti-aldol product is favored, with a re-face interaction.
Substrate control in total synthesis II

- Seen oleandomycin earlier
- Here see the opportunities offered by the aldol reaction
- It creates 1 C–C bond and 2 stereogenic centres per reaction