Handout 5: Diastereocontrol in Acyclic Systems (Part 2)
**Conformations of Propene: Stereoelectronic effects**

- The lowest energy conformation of propene is one in which a C–H bond eclipses the C=C group (the so-called ‘inside’ position, $\phi = 0^\circ$), because this gives the best orbital alignment for two stabilising $\sigma_{C-H} \rightarrow \pi^*_{C-O}$ hyperconjugative interactions [see handout 4 for related phenomenon in acetaldehyde].

- As the C=C bond in propene is electron-rich, another stabilising effect in this conformation is a $\pi_{C-C} \rightarrow \sigma^*_{C-H}$ ‘negative hyperconjugation’ interaction (similar to the anomeric effect).

- When the allylic hydrogen lies in the ‘outside’ position ($\phi = 180^\circ$), destabilising $\sigma_{C-H} \rightarrow \pi_{C-C}$ interactions occur between the C–H bonds and the $\pi$-orbital of the C=C group, putting the energy at a maximum.

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**Conformations of But-1-ene: 1,3-allylic strain**

For **but-1-ene**, the conformer with a hydrogen in the ‘inside’ position is lower in energy than that with a methyl, although the effect is rather small:

- This additional steric interaction is known as **1,3-allylic strain** \( (A^{1,3} \text{ strain}) \) - an energy-raising effect (but small in this case!).

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Conformations of (Z)-Pent-2-ene: 1,3-allylic strain

- Increasing the size of the eclipsing substituent on the alkene **massively increases the effect of 1,3-allylic strain.**
- For (Z)-pent-2-ene, the lowest energy conformer is one in which the C(1)-methyl group adopts a perpendicular position ($\phi = 90^\circ$):
Conformations of 2-Methyl-2-butene: 1,2-allylic strain

- Substituents at the C(2) position of the alkene can also cause severe steric clashing – this is called 1,2-allylic strain ($A^{1,2}$ strain):

  1,2-allylic strain severely destabilises this conformation

With an understanding of alkene conformations, we can now start to think about transition states for electrophilic additions.

As for the Felkin-Anh model for nucleophilic additions to C=O, we must consider approach trajectories and reactive conformations [see handout 4].
Approach Trajectories and Reactive Conformations

- Reactive conformations are **not necessarily** the same as ‘ground state’ conformations of the substrate – a general requirement is that a \( \sigma \)-bond at the ‘allylic’ position is aligned **anti** to the forming bond in order to stabilise the TS [see handout 3].

- Unlike C=O additions with (simple) nucleophiles, there is not a single TS model we can apply, as the approach trajectories (and thus reactive conformations) depend on the **nature of both the electrophile and the alkene**:

<table>
<thead>
<tr>
<th>( \pi )-species</th>
<th>carbonyl</th>
<th>simple alkene</th>
<th>simple alkene</th>
<th>highly ( \pi )-rich alkene (e.g. enolate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>attacking species</td>
<td>nucleophile</td>
<td>( \text{Br}_2 )</td>
<td>( \text{BH}_3 )</td>
<td>( \text{MeI} )</td>
</tr>
<tr>
<td>approach trajectory</td>
<td>obtuse ( (~107^\circ) )</td>
<td>acute</td>
<td>perpendicular</td>
<td>obtuse</td>
</tr>
<tr>
<td>relevant ( \pi )-orbital</td>
<td>( \pi^\text{c} ) (LUMO)</td>
<td>( \pi ) (HOMO)</td>
<td>( \pi ) (HOMO)</td>
<td>( \pi ) (HOMO)</td>
</tr>
<tr>
<td>relevant ( \sigma ) orbital for anti group</td>
<td>( \sigma^a )</td>
<td>( \sigma )</td>
<td>( \sigma )</td>
<td>( \sigma )</td>
</tr>
</tbody>
</table>

- Because the precise conformation at the allylic stereocentre will vary somewhat from system to system, two slightly different reactive conformations (below) are often used when drawing TS models.

- The left one is more accurate for additions via 3-membered TSs (e.g. brominations, epoxidations) and the right one is better for additions via 4- or 5-membered TSs (e.g. hydroborations, dihydroxylations) or enolate alkylations, but they are effective interchangeable.

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H C=C or H C=C

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"Theory and modeling of stereoselective organic reactions" *Science 1986*, 231, 1108 (Houk et al.)
**1,3-Allylic Strain as a Stereocontrol Feature: Epoxidation**

- We'll begin by focusing on electrophilic additions to alkenes in which **none of the allylic substituents are electronegative atoms.** This is akin in many ways to the simple Felkin-Anh (F-A) model for C=O additions, where **steric interactions** are the primary concern.
- The TS with the **least allylic strain and minimal steric interactions between the alkene and electrophile** will be the lowest in energy.
- Consider the following epoxidation, where **A\textsuperscript{1,3} strain** is operative as a stereocontrolling feature:

**Example:**

\[
\begin{array}{c}
\text{PhMe}_2\text{Si} \quad \text{H} \\
\text{Me} \quad \text{Me} \\
\end{array}
\quad m\text{-CPBA}
\quad \quad
\begin{array}{c}
\text{PhMe}_2\text{Si} \quad \text{O} \\
\text{Me} \quad \text{Me} \\
\end{array}
\]

| R = H, 61:39 dr | R = Me, 95:5 dr |

**Model:**

- Small group in 'inside' position (A\textsuperscript{1,3} strain minimised)
- peracid approaches *anti* to large group

**Application:**

- In general, a **(Z)-substituted alkene is generally required for high diastereoselectivity**, as the A\textsuperscript{1,3} strain is much more severe.

For a review on 1,3-allylic strain as a stereocontrol element, see: *Chem. Rev.* 1989, **89**, 1841
1,3-allylic Strain as a Stereocontrol Feature: Hydroboration

- **Hydroboration** is another classic electrophilic addition process; it is commonly to effect an (indirect) anti-Markovnikov hydration.
- In a classic case, Kishi used A\(^{1,3}\) strain-controlled hydroboration not once but twice in his landmark synthesis of **monensin**:

**Example:**

\[
\text{BH}_3 \quad \text{then H}_2\text{O}_2, \text{ OH}^- \quad \hspace{1cm} 89:11 \text{ dr} \]

**Model:**

- Large group in 'anti' position (avoid clash with electrophile)
- Small group in 'inside' position (A\(^{1,3}\) strain minimised)

**Application:**

For Kishi's monensin synthesis, see: *J. Am. Chem. Soc.* 1979, 101, 259. The steric difference between a furanyl and a methyl group is insufficient to explain the above selectivity, and a stabilising interaction between the furan lone pair and the alkene LUMO is likely; see: *Tetrahedron* 1984, 40, 2257
1,3-Allylic Strain as a Stereocontrol Feature: *Iodolactonisation*

Another example of A\(^{1,3}\) strain can be found in the following *iodolactonisation* reaction – a powerful transformation that has been heavily utilised in complex molecule synthesis (see *Tetrahedron* 1984, 40, 2317):

**Example:**

\[
\text{HO-} \quad \text{I}_2, \text{NaHCO}_3 \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\rightarrow \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{I} \\
\]

**Analysis 1:**
- Rapid and reversible iodonium ion formation (only productive when reacts on top face)
- Small group in 'inside' position (A\(^{1,3}\) strain minimised)
- Iodolactonisation via S\(_{N2}\) (6-ring forms faster than 7)

**Analysis 2 (reinforcing conformational effects):**
- A\(^{1,3}\) strain minimised
- Chair-like TS with all groups pseudoequatorial
1,3-Allylic Strain as a Stereocontrol Feature: Substrate-directed reactions

- We met hydroxyl-directed epoxidation of cyclic allylic alcohols in handout 3. The same process can also be used in acyclic systems, and a (Z)-substituted alkene is again generally required for high diastereoselectivity:

\[
\text{OH} \quad \begin{array}{c}
\text{R}^1 \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{R}^2 \\
\text{Me}
\end{array} \xrightarrow{\text{m-CPBA}} \quad \begin{array}{c}
\text{OH} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{R}^1 \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{R}^2 \\
\text{Me}
\end{array} \\
\text{O} \quad \text{Ar} \quad \text{O} \\
\text{O} \quad \text{R}^1 \quad \text{R}^2
\]

- Substrate-directed hydrogenations using cationic iridium or rhodium catalysts [see handout 3] have also been used to great effect in acyclic systems. A classic example is found in Evans’s synthesis of the polyether antibiotic ionomycin:

\[
\begin{array}{c}
\text{Me} \\
\text{OH} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{H}_2 (15 \text{ psi}) \\
\text{1 (5 mol%)}
\end{array} \quad \begin{array}{c}
\text{H} \\
\text{O} \\
\text{R} \\
\text{Rh} \\
\text{Ln}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array}
\]

\[
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{O}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
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\text{Me} \\
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\text{Me}
\end{array} \quad \begin{array}{c}
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\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array} \quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me}
\end{array}
\]

\[
R^1= \text{H}, R^2= \text{Me}, 64:36 \text{ dr} \\
R^1= \text{Me}, R^2= \text{H}, 95:5 \text{ dr}
\]

For Evans’ ionomycin synthesis, see: J. Am. Chem. Soc. 1990, 112, 5290
1,2-Allylic Strain as a Stereocontrol Feature: Hydroboration

- The aforementioned examples have focused on $A^{1,3}$ strain, but $A^{1,2}$ strain can also be effective as a stereocontrolling feature.

- For example, Still has shown that the diastereoselectivity of hydroboration of chiral allylic alcohols is reagent-dependent:

  - In the case of $BH_3$, the diastereoselectivity can be explained by a transition state which minimises $A^{1,2}$ strain by placing the medium-sized OH group in the ‘inside’ position [see later for stereoelectronic rationale of this choice]:

- In the case of 9-BBN, a different reagent, the diastereoselectivity can be explained by a transition state which minimises $A^{1,2}$ strain by placing the medium-sized OH group in the ‘inside’ position:

For Still’s study on the diastereodivergent hydroboration of allylic alcohols, see: *J. Am. Chem. Soc.* 1983, 105, 2487
1,2-Allylic Strain as a Stereocontrol Feature: Hydroboration

- With 9-BBN-H, the borane is so large that it encounters severe non-bonded steric interactions with the ‘inside’ substituent, so it is preferable to put the smallest group (H) in this position, despite the fact that this increases the $A_{1,2}$ strain:

- A striking example of diastereodivergent hydroboration can be found in Evans’ total synthesis of lonomycin A:

For Evans’ lonomycin A synthesis, see: J. Am. Chem. Soc. 1995, 117, 3448
**Influence of Polar Groups: Is there an equivalent to the 'polar' Felkin-Anh model?**

- Compared to *nucleophilic* additions to C=O (Felkin-Anh model), *electrophilic* additions to C=C display essentially **opposite stereoelectronic preferences** when it comes to donor/acceptor groups at the ‘allylic’ position:

**Nucleophilic additions to C=O**

![Diagram showing nucleophilic addition to C=O](image)

- **acceptor** groups prefer 'anti' position
- **donor** groups prefer 'outside' position*

**Electrophilic additions to C=C**

![Diagram showing electrophilic addition to C=C](image)

- **donor** groups prefer 'anti' position
- **acceptor** groups prefer 'inside' position**

* rarely need to worry about this effect

**the 'outside' position can be better for the acceptor group, depending on the electrophile approach trajectory and any steric interactions

- As electronegative groups (e.g. O, N, Hal) are much more common in organic molecules, the take-home message here is that **electronegative ‘allylic’ substituents in C=C electrophilic additions are (usually) best accommodated in the ‘inside’ position.**

- **Exceptions** to this generalisation can include some substrate-directed or intramolecular reactions, where conformational effects may override the above stereoelectronic preferences [see slide 9 on directed epoxidation for an example of OH in 'outside' position].

- Because of the wide variety of electrophilic additions to C=C, there is **no generally-applicable equivalent to the polar F-A model** for C=O, and different empirical ‘rules’ have often been devised for different reactions when polar groups are present.
Stereoelectronic Effects as a Stereocontrol Feature

- Consider the following alkene dihydroxylation reaction, which provides a single diastereoisomer despite the lack of either A\textsuperscript{1,2} or A\textsuperscript{1,3} strain effects:

![Reaction diagram showing the dihydroxylation of an alkene with OsO\textsubscript{4} and NMO, leading to a diastereomer with >99:1 dr.]

- The preference of allylic electronegative groups (i.e. oxygen-based functionalities) to occupy the ‘inside’ position of the allyl system so as to maximise the reactivity (HOMO energy) of the alkene is known as the ‘inside alkoxy effect’.
Conformational Stereocontrol: The ultimate in acyclic stereocontrol

- If a reaction involves formation of one or more 6-membered rings, then conformational stereocontrol can be operative.
- For 6-membered ring-formation, the most stable (favoured) TS of the reaction is one that is chair-like with as many substituents pseudoequatorial as possible.
- The ultimate example of this phenomenon is Nature’s synthesis of the steroid framework from a totally acyclic polyene. This is a cascade polycyclisation involving a carbocation-initiated formation of multiple rings in a single step.
- Remarkably, chemists have been able to mimic such cationic polycyclisations in the lab (see below). Syntheses of complex molecules which utilise bio-inspired cascade reactions are often referred to as biomimetic.

![Diagram of a chemical reaction](image)

- chair-like arrangements of forming rings gives lowest strain
- antiperiplanar C=C additions give best orbital interaction

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4 rings and 7 stereocentres formed in a single step!
Revision Checklist

Revised?

☐ Conformations of propene, but-1-ene, (Z)-pent-2-ene, and 2-methyl-2-butene; 1,3- and 1,2-allylic strain

☐ Approach trajectories and reactive conformations for alkene additions (e.g., bromination, epoxidation, hydroboration, dihydroxylation)

☐ 1,3-Allylic strain as a stereocontrol feature (e.g., epoxidation, hydroboration, iodolactonisation, directed reactions)

☐ 1,2-Allylic strain as a stereocontrol feature (e.g., diastereodivergent hydroboration of allylic alcohols with BH$_3$ and 9-BBN-H)

☐ Influence of polar groups on nucleophilic additions to C=O versus electrophilic additions to C=C; the 'inside alkoxy' effect

☐ Conformational stereocontrol in cation-polyolefin cyclisations
Questions

- Predict the relative configuration of the major diastereomer from the following reaction:

  ![Reaction Scheme 1](image)

- Provide a transition model to explain the diastereoselectivity observed in the following dihydroxylation reaction. Make note of any stabilising or destabilising steric/electronic interactions:

  ![Reaction Scheme 2](image)