Acyclic Stereocontrol

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Scope of Lecture

- halofunctionalization of olefins
- directed reaction of olefins
- Felkin-Anh vs. chelate model
- inside hydroxy conformation
- allylic strain in stereocontrol

Helpful References


Key Questions

1. How do allylic and homoallylic stereogenic centers influence the stereochemical outcome of these reactions?

2. How can we explain the following?

- $\text{Me}_2\text{O} + \text{OTMS} \xrightarrow{\text{BF}_3\text{OET}_2} \text{Me}_2\text{O} \xrightarrow{95:5 \text{ dr}}$ 
- $\text{Me}_2\text{OH} \xrightarrow{\text{NaBH(OAc)}_3} \text{Me}_2\text{OH} \xrightarrow{98:2 \text{ dr}}$

Lecture notes edited by Richard Liu
Acyclic Stereocontrol

Highly diastereoselective reactions controlled only by substrate stereochemistry have become an invaluable tool in organic synthesis. In 1965 before their prevalence, Woodward famously remarked that the total synthesis of the erythronolides, a family of macrocyclic antibiotic compounds, was "hopelessly complex" on account of its multiple contiguous stereocenters.

Only 34 years later, a recent synthesis of 6-deoxyerythronolide by the White group sets every stereocenter except one by acyclic stereocontrol, using reactions that have become standard in the field.

Hydroboration

Hydroboration used to be an important reaction for converting alkenes to alcohols. Nowadays, the intermediate organoboranes are highly useful in themselves and can participate in cross-couplings, addition-migration reactions and halogenations.

Sodium perborate oxidation/workup (milder alternative):
Kalbalka JOC 1989 54 5930
Regioselectivity is generally moderate with BH₃·THF, but good with bulkier reagents like 9-BBN:

<table>
<thead>
<tr>
<th></th>
<th>Bu</th>
<th>Ph</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH₃</td>
<td>94:6</td>
<td>81:19</td>
</tr>
<tr>
<td>9-BBN</td>
<td>99.9:0.1</td>
<td>98.5:1.5</td>
</tr>
</tbody>
</table>

Common hydroboration reagents:

- 9-BBN
- ThxBH₂ (Thexylborane)
- Sia₂BH (Disiamylborane)
- Catecholborane

General trend of the rate of hydroboration:

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{R} \\
\end{align*}
\]
Hydroboration controlled by A$_{1,3}$ strain

Houk *Tetrahedron* 1984 40 2257
Consider this reaction in Kishi's Monensin synthesis (*JACS* 1979 101, 260; *JACS* 1979, 101, 262.)

\[
\begin{align*}
\text{B}_2\text{H}_6/\text{THF} & \quad \text{H}_2\text{O}_2 & \quad 8:1 \text{ dr}
\end{align*}
\]

This result can be rationalized by conformational analysis. The reactive conformation of the starting material is the one in which A$_{1,3}$ strain is minimized. BH$_3$ then approaches from the face opposite to the larger substituent.

In this case the severe A$_{1,3}$ strain of the 1,1,2-trisubstituted olefin dictates the reactive conformation. What is your prediction for the stereochemistry of this reaction? (-OH does not direct normal boranes.)

Still, W. C. *JACS* 1983 105 2487

Hydroborations Controlled by A$_{1,2}$ Strain

Let’s look at a 1,1-disubstituted olefin. Still has reported a study on the hydroboration of allylic alcohols (*JACS* 1983 105 2487). He notes that BH$_3$ displays only poor diastereoselectivity. However, if 9-BBN is used, good selectivities are obtained and the stereoinduction is reversed. So what is going on here? Again, a conformational analysis is revealing.

\[
\begin{align*}
\text{Bu} & \quad \text{Me} & \quad \text{Bu} \\
\text{H} & \quad \text{Me} & \quad \text{Me} \\
\text{OH} & \quad \text{OH} & \quad \text{OH}
\end{align*}
\]

BH$_3$: d.r. 1:1.4
9-BBN: d.r. 11:1

*small boranes:*

A$_{1,2}$ strain

In E-1,1,2-trisubstituted olefins A$_{1,2}$ strain in conformer I will favor conformer II. A small borane reagent can now come in from either side and will have to pass either R$_M$ or R$_L$, which explains the poor selectivity. *In general, selecting between R$_M$ and R$_L$ is always much more difficult than selecting between R$_M$ and H.*
large boranes:
If large borane reagents are used conformer II will still be favored. However, severe steric clash between RM and the borane will prevent the reaction with rotamer II. Instead, the less stable rotamer becomes the reactive one, reversing the observed selectivity.

![Diagram of borane reaction](image)

Another instructive example was reported by Midland (JACS 1983, 105, 3725):

![Diagram of another reaction](image)

Competing A1,3 and A1,2 strain
In Z-1,1,2 substituted olefins both conformers I and II will suffer from A1,2- and A1,3-strain, respectively. The following experiment by Still shows that A1,3 strain dominates A1,2 strain and reactive conformer I is favored despite the A1,2 energy. Note that the steric clash with bulky borane reagents favors I as well; both effects work in concert to give pronounced stereoinduction. (JACS 1983 105 2487)

Directed Reactions: Epoxidation
Thus far, the substrate controlled-selectivity we have discussed has relied on repulsive steric interactions. However, substrate control can also derive from attractive non-covalent interactions such as hydrogen-bonding or Lewis acid/base complexation. The resulting association of the substrate and reagent induces a conformational bias in the ground state that translates to highly organized transition states, and hence, high selectivity. Interestingly, the substrate-reagent interaction can also increase the rate of reaction as well. For example, in hydroxyl-directed peracid epoxidations, the carbonyl oxygen becomes more negatively charged in the transition state. As a result, hydrogen bonding is stronger in the transition state than the ground state, and the overall rate is faster (J. Chem. Soc. 1957 1958; Proc. Chem. Soc. 1963 159; JACS 1997 119 3385).
Acyclic Stereocontrol

Sharpless carried out an instructive study of acyclic stereocontrol in the epoxidation of allylic alcohols. As you can see, we perform the same type of conformational analysis using allylic strain, but now the electrophile approaches from the hydroxyl side, rather than the least hindered side.

\[
\begin{align*}
\text{Me} & \quad \text{n-Bu} & \quad \text{OH} & \quad \text{Me} & \quad \text{n-Bu} \\
\text{via:} & \quad \text{H} & \quad \text{C} & \quad \text{H} & \quad \text{OH} & \quad \text{A}_{1,2} \text{ strain minimized} \\
\text{OH directs epoxidation} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} & \quad \text{Me} \\
\text{via:} & \quad \text{H} & \quad \text{C} & \quad \text{H} & \quad \text{OH} & \quad \text{A}_{1,3} \text{ strain minimized} \\
\text{OH directs epoxidation}
\end{align*}
\]

\[
\begin{align*}
\text{m-CPBA} & \quad \text{d.r.} = 59:41 \\
t\text{BuOOH, VO(acac)}_2 & \quad \text{d.r.} = 98:2 \\
\text{m-CPBA} & \quad \text{d.r.} = 95:5 \\
t\text{BuOOH, VO(acac)}_2 & \quad \text{d.r.} = 71:29
\end{align*}
\]

Sharpless model (Aldrichimica Acta 1979 63):

for VO(acac)$_2$:
- if $A_{1,2}$ strain dominates
- epoxidation $\rightarrow$ ca $50^\circ$

for peracids ($m$-CPBA):
- if $A_{1,2}$ strain dominates
- epoxidation $\rightarrow$ ca $120^\circ$

Stereoinduction using $m$-CPBA is highest if the dihedral angle is around $120^\circ$. In contrast, the V(V) species prefers to be directed by a hydroxy group that forms a dihedral angle of ca. $50^\circ$.

Homoallylic alcohols have as well been reported to react in highly diastereoselective epoxidation reactions. Direction of the metal reagent by the hydroxyl group in a cyclic transition structure was proposed, in which most substituents occupy the equatorial position (JACS 1981, 7690).

Cyclopropanation

Directed cyclopropanation of allylic alcohols can also be quite stereoselective, but the mechanism is not as well understood.

The cyclopropanation of *E*-allylic alcohols is highly dependant on the reaction conditions. Furukawa's conditions ($\text{Et}_2\text{Zn}, \text{CH}_2\text{I}_2$) generally give higher d.r. than the Simmons-Smith procedure or the samarium carbenoid.

\[
\begin{align*}
\text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{OH} & \quad \text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\begin{align*}
\text{Zn/Cu, CH}_2\text{I}_2, \text{Et}_2\text{O} & \quad 56:44 \\
\text{Et}_2\text{Zn, CH}_2\text{I}_2, \text{CH}_2\text{Cl}_2 & \quad 86:14 \\
\text{Sm(Hg), CH}_2\text{I}_2, \text{THF} & \quad 25:74
\end{align*}
\]

The fact that samarium carbenoids often give complementary stereoinduction to zinc carbenoids is difficult to explain.
On the other hand, **Z-allylic alcohols** or trisubstituted olefins react under a variety of conditions to give the syn-products in good selectivities, usually >9:1.

> R<sup>1</sup>OH → R<sup>1</sup>OH

Sm- or Zn-reagents

With a few exceptions, the directing effects of basic groups that do not reside on a stereogenic center is rather poor.

> R<sup>1</sup>OH → R<sup>1</sup>OH

Sm- or Zn-reagents

Since this directing effect relies on interaction with the metal center rather than hydrogen bonding, cyclopropanation is directed by many more Lewis basic functionalities than are useful for peroxide-promoted epoxidation. For instance, allylic silyl ethers and acetals can be viable directing groups.

Numerous chiral auxiliaries have been developed. A selection of these auxiliaries is depicted below, for a good overview, see: *Chem. Rev.* **2003** 977.

**Halofunctionalizations**

We conclude our discussion of stereoselective olefin functionalization with a discussion of reactions that proceed through halonium ions. First, we will need some background. Typically, the bromination of an olefin is trans-selective. In 1937, Roberts proposed (*JACS* **1937** 59 947) that bromonium ions are intermediates:

> H<sub>3</sub>C<sub>Br</sub> + Br<sub>2</sub> → H<sub>3</sub>C<sub>Br</sub> Br<sup>+</sup> → H<sub>3</sub>C<sub>Br</sub> Br<sup>+</sup> → H<sub>3</sub>C<sub>Br</sub> Br<sup>+</sup> → trapping by nucleophiles

However, this picture is gravely lacking in mechanistic detail. It now appears that, like in hydroboration, π-complexes are often important intermediates. The exact mechanism depends also on the solvent. **In aprotic solvents:**


**bromonium ion**


(Complexes of 3:1 stoichiometry or higher are possible.) Nucleophiles can attack any of these intermediates, giving rise to very complex mechanistic behavior. These π-complexes were examined by Mulliken (*Molecular Complexes*, 1969, Wiley Interscience).
Chamberlin and Hehre have noted that the stereoselectivity of trapping reactions on allylic alcohol-derived bromonium ions depends on whether the nucleophile is internal or external (JACS 1983 105 5819; JACS 1987 109 672)!

With internal nucleophiles, the product seems to derive from a conformer in which the allylic alcohol occupies the inside position:

\[
\text{HO-CH(Me)} \rightleftharpoons \text{Me-C(O)} \rightleftharpoons \text{H-OH} \quad 95:5 \text{ dr}
\]

With external nucleophiles, the product seems to derive from a conformer in which the allylic alcohol occupies the normal, outside position:

\[
\text{Bu-CH(Me)} \rightleftharpoons \text{Me-C(O)} \rightleftharpoons \text{H-OH} \quad 99:1 \text{ dr}
\]

This is rationalized by considering a change in the rate-determining step:

(1) when the nucleophile is internal, the more stable complex is trapped quickly.

(2) when the nucleophile is external, trapping is slow, and cannot occur directly via the π-complex, so the more iodonium is trapped.

(3) the "OH inside" complex is favored because I\(_2\) does not compete with σ\(_{CO}^*\) for the π\(_{CC}\) electron density.

(4) the left-hand iodonium ion is favored because the C-O inductively stabilizes the iodonium ion.

(5) evidently there is a considerable barrier to go from the π-complex to the iodonium ion (reactions in Et\(_2\)O)
**Configurational Stability of Halonium Ions**

Interestingly, one bromonium ion can exchange with another (Brown ACR 1997 30 131):

\[
\begin{align*}
\text{Br} & \quad + \\
= & \quad \leftrightarrow \\
\text{Br} & \quad \\
\end{align*}
\]

The barrier to exchange for Ad=Ad is very small and can be determined by NMR lineshape analysis. Apparently, there is an intermediate in this process:

\[
\begin{align*}
\text{Br} & \quad + \\
= & \quad \leftrightarrow \\
\text{Br} & \quad \\
\end{align*}
\]

*at -80 °C:*

\[\Delta H^\ddagger = 1.8 \text{ kcal/mol}\]

\[\Delta S^\ddagger = -21 \text{ eu}\]

The negative entropy of activation is to be expected from a highly organized bimolecular reaction of this type. Transfers from the Ad=Ad (Ad = 2-adamantylidene) bromonium ion to less hindered olefins like cyclohexene occur faster, but the rate of transfer between cyclohexene bromonium ions is unclear.

A very clever experiment by Denmark (JACS 2010 132 1232) shows that exchange definitely occurs for other olefins:

\[
\begin{align*}
\text{OTs}_{\text{nPr}} & \quad \text{nPr}_{\text{Br}} \\
& \quad \text{HCO}_2\text{Na} \quad \text{HCO}_2\text{H} \\
& \quad 5 \text{ h, rt} \quad 68\% \\
\end{align*}
\]

94% ee

\[
\begin{align*}
\text{C}_2 \text{ symmetric} & \quad \text{94% ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{OTs}_{\text{nPr}} & \quad \text{nPr}_{\text{Br}} \\
& \quad 2 \text{ equiv.} \\
& \quad \text{Bu}_4\text{NOAc} \\
\end{align*}
\]

94% ee

\[
\begin{align*}
\text{OCHO}_{\text{nPr}} & \quad \text{nPr}_{\text{Br}} \\
& \quad \text{62% ee} \\
\end{align*}
\]

**Carbonyl Additions**


**Stereochemistry of Reaction Paths...** Bürgi, H.B. ACIE 1975 14 460-473.

**Q: What is the trajectory of attack of a nucleophile on a carbonyl group?**

Unfortunately, there is no way to observe reactions as they occur (yet). The idea is to instead infer reaction trajectories from perturbations seen from crystal structures.

**Case 1: 1,8-Disubstituted Naphthalenes**

This is a highly strained system where the oxygen nucleophile is forced to be close to the ketone. The O-C=O angle in the crystal structures is 103°.

Note that the O-C distance is 2.60 A, which is in the ballpark for a typical transition state.
Case 2: Cyclic Aminoketones

Here, the N-C distance is 2.47 Å, which is a bit more advanced. The N-C=O angle is 111°.

Bürgi argues (JACS 1972 94 5805) that the relative rate of lactonization in various hydroxyacids is increased in substrates for which the O-C=O bond angle is close to 100°.

Of course, the structures shown above are not transition state energy maxima, but ground state energy minima because they are derived from crystals.

The Bürgi-Dunitz Trajectory

There are two approaches to this. In an ideal world, one could perform molecular dynamics simulations, where nucleophiles and electrophiles are initialized with random trajectories. The simulation would run, and one would examine the trajectories that lead to product and determine what their Nuc-C=O bond angles were. Unfortunately, with today's technology a picosecond's worth of simulation time corresponds to about a week's worth of computer (wall clock) time, so this is entirely impractical. Another way to look at it is that most collisions do not actually result in a collisions; reactions are such rare events that one would have to run a huge number of trajectories to accurately sample anything.

A less ideal approach is to simply constrain the Nuc...C=O distance and measure the electronic energy. This has been done at a relatively crude level (roughly Hartree-Fock):

\[ \text{H}^\ominus + \text{H} = \text{CH}_3\text{O}^\ominus \]

The "tightness" of the angle of attack depends on how far the hydride is from formaldehyde:
Thus, one should not think of a specific Bürgi-Dunitz angle, but rather a Bürgi-Dunitz cone:

1) At large distances, the nucleophile and electrophile don't have a significant bonding interaction. The nucleophile approaches along the H-C(O)-H bisector, consistent with an electrostatic view.

2) At medium distances, bond formation begins to develop and we are in the neighborhood of a transition state. Given the numbers here for C, which has a realistic TS bond forming distance of 2.0 Å, we guess that the H-C=O angle must be between 110 and 130°.

3) At close distances, we are essentially wiggling a H-C bond in a methoxide, and the curvature of the well simply reflects the normal modes of the product.

**Chelate-Controlled Carbonyl Additions**

"...Aspects of Chelation-Controlled Carbonyl Additions"

These are the easiest diastereoselective carbonyl additions to understand. Asymmetric induction is possible from both α- and β-stereocenters; in both cases, a metal chelate is formed, and the nucleophile comes in anti to the stereocenter:

1,2-induction

![1,2-induction diagram](image)

1,3-induction

![1,3-induction diagram](image)

If this model is right, then changing the nature of the protecting group on oxygen should change the stereochemical outcome. Indeed, this is exactly what is found (Elie, *JACS* **1992** 114 1778):

![Chemical reaction](image)

What is the evidence for this model, other than the stereochemistry? Just because a chelate is possible does not mean that it will speed up the reaction:
**Acyclic Stereocontrol**

**chelate speeds up reaction**

\[
\text{ketone} \rightleftharpoons \text{chelate} \rightarrow \text{product}
\]

**chelate slows down reaction**

\[
\text{chelate} \rightleftharpoons \text{ketone} \rightarrow \text{product}
\]

1. If the chelate is just an unproductive side equilibrium, then it will just stabilize the ground state and slow down the reaction.

2. Conversely, the chelate might just form in the transition state, lowering its energy and speeding up the reaction.

It is found that chelation **significantly accelerates** addition:

\[
\begin{align*}
\text{PhCOCH}_2\text{Me} & \xrightarrow{\text{Me}_2\text{Mg}} \text{PhCH}_2\text{OHMin}\text{Me} \\
\text{PhCOCH}_2\text{OR} & \xrightarrow{\text{Me}_2\text{Mg}} \text{PhCH}_2\text{ORMin}\text{Me}
\end{align*}
\]

\[
\text{rate (10}^2 \text{ M}^{-1} \text{ s}^{-1})
\]

<table>
<thead>
<tr>
<th>R</th>
<th>0.51 attenuation is not steric</th>
<th>1000 (R=Me)</th>
<th>0.45 (R=TIPS)</th>
</tr>
</thead>
</table>

3. \(\alpha\)-Alkoxyketones and magnesium bromide do not visibly coordinate by NMR. This is expected, since THF is quite a good ligand for magnesium. However, in \(\text{CD}_2\text{Cl}_2\), there is a substantial shift.

\[
\begin{align*}
\text{RO} & \text{O} + \text{MgBr}_2 \rightleftharpoons \text{Br}^+ \text{MgBr}_2 \\
\text{RO} & \text{O} \quad \text{R'} \text{O}
\end{align*}
\]

The extent of chelation in \(\text{CD}_2\text{Cl}_2\) depends on the protecting group.

4. The reaction is first order in ketone and \(\text{Me}_2\text{Mg}\).

This means that the scenario is:

\[
\text{ketone} \rightleftharpoons \text{chelate} \rightarrow \text{product}
\]

If we want to draw an energy diagram, we can compare the competing chelated and unchelated transition states:

There is no differentiation between forming major and minor products on this diagram. Thus, we have to think of each transition state as really representing a pair of transition states, one for the major and one for the minor product.

Interestingly, \(\beta\)-\(\alpha\)koxy ketones do not seem to experience any rate acceleration. This is consistent with other literature precedents, which suggest that 5-membered chelates are more reactive than 6-membered chelates. However, 6-membered chelates do give high selectivity (Evans JACS 2001 123 10840):

\[
\text{CH}_2\text{Cl}_2 \quad \text{Me}_2\text{AlCl} \text{ or TiCl}_4
\]

97:3 dr
Intrinsic vs Chelate Selectivity

Before analyzing the outcomes of these chelate-controlled additions in more detail, it is important to realize that there is an intrinsic selectivity that is being turned over when chelation occurs (Evans JACS 2001 123 10840):

"intrinsic selectivity"

\[
\begin{align*}
\text{H} & \text{O} \quad \text{Me} \\
\text{Me} & \text{OBn}
\end{align*}
\]

\[
\begin{align*}
\text{TiCl}_4 & \quad \text{CH}_2\text{Cl}_2, -78 \degree \text{C} \\
\text{TMS enolsilane} & \\
\rightarrow & \\
\text{Me}_3\text{C} & \text{OH} \quad \text{Me} \\
\text{Me} & \text{OTBS}
\end{align*}
\]

93:7 dr

"Cram chelate selectivity"

\[
\begin{align*}
\text{H} & \text{O} \quad \text{Me} \\
\text{Me} & \text{OBn}
\end{align*}
\]

\[
\begin{align*}
\text{TiCl}_4 & \quad \text{CH}_2\text{Cl}_2, -78 \degree \text{C} \\
\text{TMS enolsilane} & \\
\rightarrow & \\
\text{Me}_3\text{C} & \text{OH} \quad \text{Me} \\
\text{Me} & \text{OBn}
\end{align*}
\]

5:95 dr

The idea here is that going from a bulky protecting group, TBS, to a less hindered, coordinating protecting group, Bn, gives chelate control. But where does the intrinsic selectivity come from?

Felkin-Anh-Eisenstein Model

In the Felkin model, one assumes:

1. all ground state rotamers are accessible (Curtin-Hammett)

2. the transition states are very early (exothermic reaction)

3. both the major and minor transition states place the largest substituent anti to the incoming nucleophile

4. the major transition state minimizes torsional interactions between the C-R bond in the front and the C-M group in the back (L=large, M=medium, S=small):

major TS

- L is opposite Nuc
- the torsional interaction between C-R and C-S is small
- also could imagine that S/Nuc interactions are small

minor TS

- L is still opposite Nuc
- the C-R/C-M interaction is bad
- so is the Nuc/M interaction

This model works for the vast majority of aldehydes and ketones and is generally accepted. However, it does seem to fail in some pathological cases, such as stERICALLY unbiased ketones which are nonetheless slightly electronically biased.

Effect of Electronegative Substituents

In the above analysis, it was tacitly assumed that all three substituents were alkyl; i.e., not electronically biased. Anh and Eisenstein showed that polar substituents X can take the place of the large group:

major TS

\[
\begin{align*}
\text{O} & \text{M} \\
\text{S} & \text{L}
\end{align*}
\]

minor TS

\[
\begin{align*}
\text{S} & \text{O} \\
\text{L} & \text{Nuc}
\end{align*}
\]

\[
\begin{align*}
\text{Nuc} & \\
\text{M} & \text{R}
\end{align*}
\]
Effect of Electronegative Substituents

The work of Anh and Eisenstein (Nouv J Chem 1977 1 61) was seminal because it showed that computational chemistry could be a powerful tool for analyzing real problems in organic chemistry. Even though their work was, in today's terms, at a very crude level of theory (HF/STO-3G), it is telling that it gives the right predictions most of the time.

In their study, they analyzed the reduction of 2-chloropropanal with hydride. The distance between the hydride and the carbonyl carbon was fixed at 1.5 Å, and the Cl-C-C=O dihedral angle was varied. Bachrach (page 303 of his book) has recomputed their results at a more modern (B3LYP/6-31++g(d)) level of theory:

(1) The solid line (circles) represents configurations that lead to the major product; dashed (squares) lead to minor product.

(2) The minimum energy structures of the solid and dashed lines correspond to the rotamers depicted:

![major TS and minor TS diagrams]

(3) Notice that the nucleophile approaches at the Bürgi-Dunitz angle. Hydride is not a very realistic nucleophile, but the Bürgi-Dunitz constraint is still realized.

(4) Why does the C-X bond take the place of the large group?

Explanation 1. Donation from the forming \( \sigma(C-Nuc) \) into the \( \pi^*(C=O) \). However, this is a very early TS, so there is very little density in \( \sigma(C-Nuc) \); NBO analysis shows that this is not a very significant interaction.

Explanation 2. The \( \pi^*(C=O) \) and \( \sigma^*(C-Cl) \) combine to form a better acceptor:

![HOMO-LUMO gap diagram]

(5) The possibilities of asymmetric \( \pi^* \) lobes (i.e., bigger on one diastereofacial surface) and electrostatic minimization (Cornforth model) have been examined.
Practice with Stereochemical Models
From a practical standpoint, what is the stereochemical outcome of a Felkin-controlled 1,2-addition? Let's analyze the reaction from before:

\[
\text{H}^+ \text{O} + \text{CH}_2\text{OTBS} \rightarrow \text{Me}_3\text{C}^+ \text{OH} \rightarrow \text{Me}_3\text{C}^+ \text{OH} \rightarrow \text{Me}_3\text{C}^+ \text{OH} \rightarrow 93:7 \text{dr}
\]

The major TS positions the large CH$_2$OTBS group anti to the nucleophile, which comes over the smallest group:

\[
\text{TBSO} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{Nuc} \rightarrow \text{TBSO} \quad \text{Me} \quad \text{OH} \quad \text{Me} \quad \text{Nuc}
\]

Notice that in the product, we have the R and the CH$_2$OTBS in the "zig-zag." So the Me and the OH are syn, as is observed. (If the R and CH$_2$OTBS weren't anti to each other, then we would need to rotate the Newman projection first.)

\[
\begin{align*}
\text{H} & \quad \text{O} & \quad \text{Me} & \quad \text{L} & \quad \text{Felkin control} & \quad \text{OH} \quad \text{Me} & \quad \text{L} & \quad \text{Nuc} \quad \text{1,2-syn} \\
\end{align*}
\]

What is the expected Felkin product of this addition (Keck, *TL* 1984 25 265)?

\[
\text{H} \quad \text{O} \quad \text{TMS} \rightarrow \text{OH} \quad \text{TMS} \rightarrow 95:5 \text{dr}
\]

(When there's a polar group involved, we use the "polar Felkin-Anh(-Eisenstein) model.")

The OTBS takes the place of the large group (it is interesting that the electronegative substituent seems to override the bulkiness of the cyclohexyl group):

\[
\begin{align*}
\text{TBSO} & \quad \text{H} & \quad \text{Nuc} & \rightarrow & \text{TBSO} & \quad \text{H} & \quad \text{Nuc} \\
\end{align*}
\]

Notice that we need to have the allyl nucleophile and the cyclohexyl group anti to each other in the Newman projection to decide if the product is 1,2-syn or 1,2-anti:

\[
\begin{align*}
\text{TBSO} & \quad \text{H} & \quad \text{Nuc} & \rightarrow & \text{TBSO} & \quad \text{H} & \quad \text{OH} & \rightarrow \text{rotate} & \text{TBSO} & \quad \text{H} & \quad \text{OH} \\
\end{align*}
\]

So the OH and the OTBS are 1,2-anti:

\[
\begin{align*}
\text{H} & \quad \text{O} & \quad \text{TBS} \rightarrow \text{OH} \quad \text{TBS} \rightarrow 95:5 \text{dr} \\
\end{align*}
\]

A Half-Chair Model for Chelate Control
With 1,2-chelates, the nucleophile simply adds from the face opposite the $\alpha$-substituent:

\[
\begin{align*}
\text{RO} & \quad \text{M} & \quad \text{Nuc} & \rightarrow & \text{HO} & \quad \text{OH} & \quad \text{Nuc} \\
\end{align*}
\]

The kinetic data on this is unclear (Reetz, *ACR* 1993 26 462), and it is possible that nucleophile transfer can be either intra- or inter-molecular, depending on the situation. But this is still a useful model for predicting stereoselectivity.
For 1,3-chelate induction, a half chair model has been proposed by Evans (JACS 2001 123 10840). In some cases, a 2:1 bidentate chelate is observable in the ground state; in others, a monodentate 1:1 complex. So given the lack of kinetic data, it is unclear whether one can view all of these reactions as adding a nucleophile to a chelated complex. However, if one assumes this, then the performance of the stereochemical model is very good.

If one assumes a boat-like chelate, then the nucleophile comes in opposite the R group:

If it's a half-chair, the same prediction is obtained:

Directed Reductions
These are among the most useful of the chelate-controlled addition reactions. What happens in this reaction?

Chelate control wins out over Felkin control. What is the stereochemical outcome of this reaction?

Evans has also developed (JACS 1988 110 3560) reductions where chelation overrides Felkin selectivity:

Note that 1,3-diaxial interactions are much worse on the top than on the bottom, where $R_1$ is the only axial substituent. In contrast, when $R_2$ is axial in the disfavored TS, it interacts with the acetate and axial hydrogen on the top face.