Diastereoselective Attack of Electrophiles on Chiral Olefins

1. Diels Alder reactions
2. Halogenation and related electrophilic additions
3. Reactions of allylsilanes
4. Hydroborations
5. Osmylations

Mick Dart
Evans Group Seminar
Tues. Jan. 18, 1994

Diastereoselective Diels–Alder Reactions: Chiral Dienes

- Other dienophiles also give adducts derived from endo addition syn to the hydroxyl

- Hehre’s Proposal:
  Based solely on electrostatic considerations

- Electron Rich Substituents have lone pairs (OR, NR₂, SR, SO₂R)
- Electron Poor Substituents: SiR₃ (electropositive)


- Stereocontrol: A(1,3) strain
- Diastereoselection 91 : 9

Diastereoselective Diels–Alder Reactions: Chiral Dienes

Diastereoselection 82 : 18

Diastereoselection 12 : 88

Rationalization for diastereofacial selectivity:

Allylsilane

Dienophile

Dienophile

Allylic Ether

Dienophile

Dienophile


Iodolactonization

Conditions  
Kinetic  
NIS, CHCl₃, 25 °C  75 : 25
Thermodynamic  
3 equiv I₂, MeCN, O °C  9 : 91


Iodolactonization of allylic alcohols

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Major Product</th>
<th>Selectivity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO-CH₂=CH</td>
<td>HO-CH₂=CH</td>
<td>93 : 7</td>
<td>66</td>
</tr>
<tr>
<td>HO-CH₂=CH-CH₂</td>
<td>HO-CH₂=CH-CH₂</td>
<td>95 : 5</td>
<td>49</td>
</tr>
<tr>
<td>HO-CH₂=CH-R</td>
<td>HO-CH₂=CH-R</td>
<td>93 : 7</td>
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<td>95 : 5</td>
<td>49</td>
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</table>

Kinetic conditions: 3 equiv I₂, aq Na₂CO₃, Et₂O, 0 °C
Bartlett's "thermodynamic conditions" produced complex mixtures
Protection of the hydroxyl group (TBS or Ac) does not affect selectivity


How can the above results be rationalized?
**Iodo diol formation from allylic alcohols**

<table>
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<tr>
<th>Substrate</th>
<th>Major Product</th>
<th>Selectivity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu′−CH=CHMe</td>
<td>Bu′−CH=CHMe−OAc</td>
<td>98 : 2</td>
<td>78</td>
</tr>
<tr>
<td>Me′−CH=CHMe</td>
<td>Me′−CH=CHMe−OAc</td>
<td>95 : 5</td>
<td>90</td>
</tr>
<tr>
<td>OH−CH=CHMe</td>
<td>OH−CH=CHMe−OAc</td>
<td>94 : 6</td>
<td>85</td>
</tr>
<tr>
<td>OH−CH=CHMe</td>
<td>OH−CH=CHMe−I</td>
<td>80 : 20</td>
<td></td>
</tr>
</tbody>
</table>

- Prevost conditions: 2 equiv I₂, 2 equiv AgOAc, THF, −78 → 0 °C
- Other conditions: I₂, THF/phosphate buffer; I₂, THF, aq Na₂CO₃ provide 1,3-diols in very high selectivity
- High selectivities are also observed with allylic ethers (OME, OBn, OTBS)


**Cytovaricin Synthesis**

```
HO          H
R
C
Me
R'
OH
Bu
Me
OH
Bu
OAc
I
```

```
Bu′−CH=CHMe
```

```
TIPSÖ
```

```
Bu′−CH=CHMe
```

```
OH
```

```
Bu
```

```
OAc
```

```
I
```

```
Me
```

```
H
```

Diastereoselection 96 : 4


**Model for Stereoinduction?**

**Gauche B** is more energetically destabilizing than **gauche A**

```
HO
```

```
Bu
```

```
OAc
```

```
I
```

```
Me
```

```
Me
```

```
OH
```

```
Bu
```

```
OAc
```

```
H
```

```
R'N
```

```
R
```

Ratio 80 : 20

**Perfect regioselectivity**

**Gauche A** is now more destabilizing than **gauche B**

```
HO
```

```
Bu
```

```
OAc
```

```
I
```

```
Me
```

```
Me
```

```
OH
```

```
Bu
```

```
OAc
```

```
H
```

```
R'N
```

```
R
```

**Diastereoselection 96 : 4**


**Cytovaricin Synthesis**

```
TIPSÖ−CH−CH=CHMe
```

```
Bu′−CH−CHMe
```

```
I,
```

```
Me
```

```
OH
```

```
Bu
```

```
OAc
```

```
I
```

```
Me
```

Diastereoselection 96 : 4


**Place the medium size group (−OH) outside and the small group (−H) inside**

```
OH
```

```
R
```

```
I
```

```
HCO₃⁻
```

```
H₂O
```

Poor regioselectivity affords a mixture of products
A complete turnover in olefin diastereofacial selectivity is observed when adding *internal* and *external* nucleophiles.

General Observation:
For electrophiles that react via onium intermediates (I₂, Br₂, Hg(OAc)₂, PhSeCl), the major diastereomer from electrophile-induced cyclization is opposite to that observed in the analogous intermolecular electrophilic addition.

For a review of electrophilic induced olefin cyclization reactions see:

Chamberlin & Hehre's Rationalization

- "Facial preferences in electrophilic addition reactions are not invariant with respect to the location of the transition state along the reaction coordinate."

- Change in diastereoselectivity is a consequence of a change in the *rate-limiting step*

  - Addition reactions: Formation of an onium ion intermediate (subsequently trapped by a Nu from the medium)
  - Cyclization reactions: Intramolecular attack on a π-complex (not an onium ion)

- Analysis of the stereoselectivity of electrophilic addition to chiral olefins:
  1. Relative abundances of conformational minima
  2. Relative reactivities of the available forms
  3. Stereoselectivities of the individual conformers


Houk: Argument for the "inside alkoxy effect" in π-complex formation

- π-complex cyclizes if R contains a Nu and its formation is rate determining
- Onium ion formation is rate determining in the addition reactions
- "The presence or absence of an internal nucleophile acts to determine the stereochemical outcome of the reaction by modifying the nature (timing) of transition state."
**Diastereoselective Functionalization of (E) Allylic Alcohols**


- **Halogenation**
  
  \[
  \text{OH} \quad \text{R'} \quad \text{R'} \quad \text{I}_2, \text{AgOAc} \quad \text{H}\text{O}^+ + \text{Cl}^- \quad \text{HgOAc} \quad \text{R} \quad \text{R'} \quad \text{OH} \quad \text{R'} \quad \text{R'}
  \]

  **Gauche B** is more energetically destabilizing than **gauche A**

- **Oxymercuration**
  
  \[
  \text{OH} \quad \text{n-Bu} \quad \text{Me} \quad \text{Hg(OAc)}_2 \quad \text{OH} \quad \text{OH} \quad \text{Me} \quad \text{HgOAc} \quad \text{n-Bu} \quad \text{OH}
  \]


- **Sulfenylation**
  
  \[
  \text{MeO} \quad \text{Et} \quad \text{PhS–Cl} \quad \text{Me}_2\text{Zn} \quad \text{TiCl}_4 \quad \text{MeO} \quad \text{Me} \quad \text{Et} \quad \text{Me} \quad \text{MeO} \quad \text{Me} \quad \text{Et}
  \]


- **Hydroboration**
  
  \[
  \text{OH} \quad \text{n-Bu} \quad \text{Me} \quad \text{H}_2\text{O}_2 \quad \text{THexyLBH}_2 \quad \text{At least 3 major products}
  \]

---

**Oxymercuration of Acyclic allylic alcohols:**

Giese, *Tet. Lett.* 1985, 26, 1197

<table>
<thead>
<tr>
<th>R</th>
<th>R'OH</th>
<th>Ratio</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Et</td>
<td>HOH</td>
<td>76 : 24</td>
<td>65%</td>
</tr>
<tr>
<td>-Et</td>
<td>MeOH</td>
<td>93 : 07</td>
<td>72%</td>
</tr>
<tr>
<td>-Ph</td>
<td>HOH</td>
<td>88 : 12</td>
<td>66%</td>
</tr>
<tr>
<td>-tBu</td>
<td>HOH</td>
<td>98 : 02</td>
<td>70%</td>
</tr>
</tbody>
</table>

Iodohydroxylation of these substrates is not regioselective

*O-acetate participation will turn over the stereochemical course of the rxn*

- **Syn : anti = 80 : 20**

- **Syn : anti = 77 : 23**

Hehre's model could be invoked to explain turnover in \(\pi\)-facial selectivity
**Stereochemical Model For Electrophilic Attack on Allylsilanes**

Model assumes:
1. Electrophilic attack *anti* to the silyl moiety
2. The silyl group is the "large" substituent

- **Path A**
  - If $A \geq Me$, then Path A dominates due to $A(1,3)$ strain
  - If $A = H$, then Path B can compete

- **Path B**

**Electrophilic Attack on Allylsilanes**

- **Epoxidation**
  - $\text{PhMe}_2\text{Si} - \text{AllylSi}_3$ + mCPBA
  - The products on the left correspond to attack by Path A
  - $R$ Ratio
    - Me 61 : 39
    - $^i$Pr >95 : 05
    - PH 89 : 11

- **Cyclopropanation**
  - $\text{PhMe}_2\text{Si} - \text{AllylSi}_3$ + $\text{AlMe}_3$ + $\text{CH}_32$
  - $R$ Ratio
    - Me 58 : 42
    - $^i$Pr >95 : 05
    - PH 91 : 09

- **Osmylation**
  - $\text{PhMe}_2\text{Si} - \text{AllylSi}_3$ + $\text{OsO}_4$
  - $R$ Ratio
    - Me 34 : 66
    - $^i$Pr 67 : 33
    - PH 92 : 08

- Larger R groups result in higher selectivity
- The size of R is more important in locking the substrate into the conformation leading to Path A than in shielding the $\text{El}^+$

Paddon-Row, Rondan, and Houk *JACS* 1982 104, 7162.


A Model for Diastereoselective Hydroborations

Dave Evans, Chem 115, Lecture 22, Dec 14, 1993

A turnover in diastereofacial selectivity is sometimes observed using BH₃

Hydroboration of allylic alcohols (ethers)


Assume OH (OR') = R_m and results are consistent with the model


Diastereoselective Hydroborations

- **Erythronolide synthesis:** Annette Kim

  ![Erythronolide synthesis](image)

  A 2:1 mixture of the lactol:lactone was obtained. This mixture was oxidized to the keto-lactone in 73% overall yield from the olefin.

- **Lonomycin synthesis:** Andy Ratz

  ![Lonomycin synthesis](image)

  The sense of asymmetric induction is completely turned over in Andy's reaction when using \( R_2BH \leftrightarrow BH_3 \).

- **Anti-selective hydroborations with borane**

  ![Anti-selective hydroborations with borane](image)


<table>
<thead>
<tr>
<th>( R = H )</th>
<th>Diastereoselection</th>
<th>( R = OBn )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( (\text{Chx})_2BH )</td>
<td>82 : 18</td>
<td>80%</td>
</tr>
<tr>
<td>BH(_3)-DMS</td>
<td>17 : 83</td>
<td>99%</td>
</tr>
</tbody>
</table>

09-Hydroboration-2 3/19/02 2:02 PM
Olefin binding to metal is irreversible for 1,1-disubstituted allylic alcohol derivatives.

Olefin→catalyst complexation is the stereochemistry-determining step.


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**The Catalyzed Hydroboration**

**The Catalyzed vs Uncatalyzed Hydroboration Reactions**

\[
\text{OR} \xrightarrow{\text{THF}} \text{OR} \quad \text{Anti} \quad \text{OR} \xrightarrow{\text{THF}} \text{OR} \quad \text{Syn}
\]

\[
\begin{array}{|c|c|c|c|}
\hline
\text{R} & \text{Conditions} & \text{Anti : Syn} & \text{Yield (\%)}
\hline
\text{Si(t-Bu)Ph}_2 & 9-BBN & 95 : 5 & 75
\hline
& \text{Rh(PPh}_3\text{)}_3\text{Cl / CB} & 3 : 97 & 77
\hline
\text{Si(t-Bu)Me}_2 & 9-BBN & 95 : 5 & 72
\hline
& \text{Rh(PPh}_3\text{)}_3\text{Cl / CB} & 15 : 85 & 65
\hline
\text{H} & 9-BBN & 96 : 4 & 67
\hline
& \text{Rh(PPh}_3\text{)}_3\text{Cl / CB} & 50 : 50 & 68
\hline
\end{array}
\]

Complementary diastereoselectivity for the catalyzed and uncatalyzed reactions is observed for a wide range of substrates.

Evans, Fu, & Hoveyda  *JACS* 1988, 110, 6917 and  *JACS* 1992, 114, 6671.

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**Stereochemical Model**

- Complexation involves back-donation from a filled metal d orbital→π^*_{C=C}
- The EWG (alkoxy substituent) is aligned perpendicular to the olefin (π→σ^*_C−O)
- This stereoelectronic interaction lowers the energy of \( \pi^* \)
- The small group is placed “inside”, the most sterically congested site

**The uncatalyzed variant:**

**Diastereoselective Osmylations**

*(z) Olefins*

\[
\text{BnO} - \text{R} \quad \text{Me} \quad \text{OBn} \quad \text{selectivity} \quad 50 : 50 \quad 86 : 14
\]

**Kishi's Empirical Model:**

- Arrange olefin in the stable ground state conformer
- \(\text{OsO}_4\) attacks \textit{anti} to the allylic oxygen substituent
- Works for both (Z) and (E) allylic ethers (alcohols)

*(E) Olefins*

\[
\text{BnO} - \text{R} \quad \text{Me} \quad \text{OBn} \quad \text{selectivity} \quad 60 : 40 \quad 81 : 19
\]

**Allylic oxygen protecting group:**

- H, Bn, SiR\(_3\), acetonides→all work well
- Acetates give lower selectivity

- Addition occurs \textit{anti} to the allylic heteroatom functionality
- Vedejs argues that hyperconjugative effects are not important because both EDG and EWG provide the same sense of induction

**Vedejs Model**

\[
\text{X = OTBS, OAC} \quad \text{X = SR, SO}_2\text{R, SiR}_3
\]

**Kishi Model**

<table>
<thead>
<tr>
<th>X</th>
<th>selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>34 : 66</td>
</tr>
<tr>
<td>PhMe(_2)Si</td>
<td>22 : 78</td>
</tr>
<tr>
<td>PhSO(_2)</td>
<td>83 : 17</td>
</tr>
<tr>
<td>PhS</td>
<td>62 : 38</td>
</tr>
<tr>
<td>TBSO</td>
<td>61 : 39</td>
</tr>
<tr>
<td>AcO</td>
<td>70 : 30</td>
</tr>
</tbody>
</table>

Kishi & Co-workers

**Diastereoselective Osmylations**


Oxygen avoids "outside" position to avoid repulsive electrostatic interactions with the incoming OsO₄.

Vedejs model breaks down or iPr, Ph > Me₂PhSi.


**Houk Model: Staggered transition states**

- Oxygen avoids "outside" position to avoid repulsive electrostatic interactions with the incoming OsO₄.