5.37 Introduction to Organic Synthesis Laboratory
Spring 2009

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Chemistry 5.37
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The Diels-Alder Reaction
(Adapted from 2008 Lecture Given by Professor Rick Danheiser)

April 7, 2009

Strategies and Tactics in Organic Synthesis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Tactics</th>
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</thead>
<tbody>
<tr>
<td>overall plan to achieve the ultimate synthetic target</td>
<td>means by which plan is implemented</td>
</tr>
<tr>
<td>intellectual</td>
<td>experimental</td>
</tr>
<tr>
<td>retrosynthetic planning</td>
<td>synthetic execution</td>
</tr>
<tr>
<td>TRANSFORMS</td>
<td>REACTIONS</td>
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</tbody>
</table>

Target ➔ Precursor ➔ Target
Efficiency and Selectivity in Organic Synthesis

Selectivity
- Stereoselectivity
- Regioselectivity
- Chemoselectivity

Efficiency

Tactical Efficiency
- High Yield
- Atom Economy

Strategic Efficiency
- Minimum # Steps
- Convergence

The Power of Convergent Synthesis
Strategies for the Assembly of Cyclic Compounds

**Cyclization**

**Annulation**

Concerted Cycloadditions
Non-Concerted "Single-Operation" Annulations
Multistep Annulation Strategies

The first principle of retrosynthetic planning: **convergent strategies** are the most efficient strategies for the assembly of complex molecules.

Efficiency and Selectivity in Organic Synthesis

**Cycloaddition and Annulation Strategies**

**Efficiency**

**Strategic Efficiency**
- Minimum # Steps
- Convergence

**Tactical Efficiency**
- High Yield
- Atom Economy
The Diels-Alder Reaction

The single most powerful ring-forming reaction in the arsenal of organic chemistry!

The Diels-Alder Reaction

Reaction Conditions

"Tragt man in eine Suspension von 1 Mol. Maleinsäure-anhydrid in der 5 fachen Menge von reinem Benzol unter Kuhlung allmahlich 1 Mol. Cyclopentadien ein, so reagieren die Komponenten augenblicklich unter starker Warmentwicklung. Das Maleinsäure-anhydrid geht in Losung, und schon während des Prozesses scheidet sich das Anhydrid der neuen Säure in schneeweissen, glanzenden Krystallen ab. Die Ausbeute ist nahezu quantitativ."

Otto Diels and Kurt Alder  Justus Liebigs Annalen der Chemie 460, 98 (1928)
The Diels-Alder Reaction

Regiochemical Course of the Reaction (R= alkyl)

Stereochemical Course of the Reaction

**Intrinsic Stereoselectivity**
- Suprafacial with respect to the diene
- Suprafacial with respect to the dienophile
- Alder endo rule

**Asymmetric Induction**
- Substrate control by chiral dienophiles
- Substrate control by chiral dienes
- Stereocontrol via chiral auxiliaries

**Catalytic Asymmetric Cycloadditions**
Module 7 Catalytic Asymmetric Diels-Alder Reaction

The Diels-Alder Reaction
Stereochemical Course of the Reaction

Suprafacial with respect to the diene component
The Diels-Alder Reaction
Stereochemical Course of the Reaction

The Alder Endo Rule

The term "endo" originates in the terminology used to describe the stereochemistry of substituents on bicyclic ring systems. A substituent is said to be endo when it is trans to the smaller of the two bridges; an exo substituent is cis to the smaller bridge.

This is an endo Diels-Alder adduct
This is an exo Diels-Alder adduct
The Diels-Alder Reaction

Exceptions to the Alder Endo Rule

Intrinsic Stereoselectivity

Predict the products of these Diels-Alder cycloadditions.
The Diels-Alder Reaction
Intrinsic Stereoselectivity

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{CHO} \\
\text{MeO} & \quad + \quad \text{CHO} \\
\text{CHO} & \quad + \quad \text{MeO} \\
\text{MeO} & \quad + \quad \text{CHO} \\
\end{align*}
\]
The Diels-Alder Reaction
Intrinsic Stereoselectivity
The Diels-Alder Reaction
Stereochemical Course of the Reaction

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**Catalytic Asymmetric Cycloadditions**