Intramolecular Diels-Alder Reaction (IMDA)


Type I and Type II:
- Type I: tether is attached at the 4-position of the diene.

![Diels-Alder Reaction Diagram](image)

* Fused products usually have 3- or 4-atom tethers.
* Bridged products are rarely observed (tether must be >9 atoms)

- Syn vs. Anti Transition State:
  * To determine the stereochemistry of the IMDA, both steric and electronic factors should be considered.
  * Although the IMDA is concerted, bond formation is asynchronous in the transition state.
  * Effects of asynchronicity are less pronounced for decatriene systems.

- *E*-diene:

![E-diene Diagram](image)

* The representative example above with *E*-diene, *anti* T.S. is sterically favored, and *syn* T.S. experiences non-bonding interactions between C4-C7.
* Internal bond formation is more advanced in the T.S. -> *anti* T.S., *trans* product.
* External bond formation is more advanced in the T.S. -> *syn* T.S., *cis* product.

- *Syn vs. Anti Transition State of Z-diene:

![Z-diene Diagram](image)

* No matter the length or nature of the tether, *cis-fused* adduct is the only product.
Intramolecular Diels-Alder Reaction (IMDA)

• Type II: tether is attached at 3-position of diene:

* Type II IMDA is always cyclized to syn product not anti product (Bredt’s rule says that <4 atom tether won’t work).

• Diastereoselectivity of the IMDA Reactions:

* Diastereoselectivity in the IMDA reactions of conformationally mobile, monosubstituted 1,6,8-nonatrienes and 1,7,9-decatrienes: sterically favored T.S.

• Unactivated Trienes:

* The ratios of product can be improved or reversed by using substituents on the triene or additives such as Lewis acids.

* In both systems, some preference for cis-fused products.

• Terminally Activated Dienophiles:

* E-dienophiles, [4.3.0] and [4.4.0] bicycles

<table>
<thead>
<tr>
<th>Triene</th>
<th>Reaction Conditions</th>
<th>cis Product</th>
<th>trans Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,6,8-nonatriene</td>
<td>250 °C, 1-5 h</td>
<td>73%</td>
<td>27%</td>
</tr>
<tr>
<td>1,7,9-decatriene</td>
<td>220 °C, 7 h</td>
<td>55%</td>
<td>45%</td>
</tr>
</tbody>
</table>

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Intramolecular Diels-Alder Reaction (IMDA)

[4.4.0] system:

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

Terminally activated \text{E-dienophiles} are sterically and electronically favored to give \text{trans} products.

\* Z-dienophiles, [4.3.0] and [4.4.0] bicycles

[4.3.0] system:

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

Trans product is favored sterically and cis product is favored electronically with terminally activated Z-dienophiles.

\* Internally Activated Dienophiles [4.3.0] and [4.4.0] Bicycles:

[4.3.0] system:

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

Unless other steric factors intervene, internally activated trienes give \text{cis-fused} products.

[4.4.0] system:

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{MeO}_2\text{C} & \quad \text{MeO}_2\text{C}
\end{align*}
\]

Decatrienes with internal carbonyls adjacent to dienophile cyclized through boat T.S. to give \text{cis-fused} products.


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Intramolecular Diels-Alder Reaction (IMDA)

- Internally Substituted Dienes [4.3.0] and [4.4.0] Bicycles:
  - [4.3.0] system:

    ![Diels-Alder Reaction Diagram for [4.3.0] system]

    - 150 °C, 92%
    - Anti T.S. -> trans product
    - Syn T.S. -> no cis product

    Sakamura, S. J. Am. Chem. Soc. 1980, 102, 6353

  - [4.4.0] system:

    ![Diels-Alder Reaction Diagram for [4.4.0] system]

    - 160 °C, 95%
    - Anti T.S. -> trans product
    - Syn T.S. -> no cis product

    Roush, W. S. J. Am. Chem. Soc. 1978, 100, 6289

- Effects of Substitution on tether:
  - [4.3.0], α,α-disubstitution system

    ![Diels-Alder Reaction Diagram for [4.3.0], α,α-disubstitution system]

    - MeO
    - 170 °C, 98%
    - Anti T.S. -> trans product
    - 72:28, trans


  - Nonbonding interactions in anti T.S. give predominantly trans product.

- [4.3.0], β,β-disubstitution system

    ![Diels-Alder Reaction Diagram for [4.3.0], β,β-disubstitution system]

    - MeOC
    - 155 °C, 85%
    - Trans only


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Intramolecular Diels-Alder Reaction (IMDA)

[4.4.0], dialkyl substitution system

Thorpe-Ingold effect: Dialkyl substitution improved the reaction rates.

$A_{1,3}$ effect:
[4.3.0], stereocenter adjacent to dienophile

Transannular Intramolecular Diels-Alder Reactions (TADA):

Transannular intramolecular Diels-Alder reactions are a subgroup of IMDA reactions, and are often very chemo-, regio-, and stereo-selective processes in general.

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Intramolecular Diels-Alder Reaction (IMDA)

- Formation of Heterocycles via IMDA:
  - Heterodienes:
    
    ![Heterodiene Reaction](image)
    
    - Because of the stereocenter at the 3-position of the diene, the methyl is placed equatorial in a chair-like T.S. and promotes an anti T.S. to give the only product.

  - Heterodienophiles:
    - Acyl-amine dienophile:
      
      ![Acyl-Amine Reaction](image)
      
      - One diastereomer is obtained. It is usually the opposite diastereomer as when the all-carbon triene is used.

    - Imino dienophile:
      
      ![Imino Dienophile Reaction](image)
      
      - The diastereoselectivity of the substrates with diene heteroatoms follows the same rules as all-carbon dienes.
**Intramolecular Diels-Alder Reaction (IMDA)**

- **Other Heterodienophile:**

  ![Diene Reaction Diagram]

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>conditions</th>
<th>yield</th>
<th>selectivity (A:B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBz</td>
<td>Me</td>
<td>70 °C</td>
<td>63%</td>
<td>71:29</td>
</tr>
<tr>
<td>Se</td>
<td>Me</td>
<td>55 °C</td>
<td>70%</td>
<td>45:55</td>
</tr>
<tr>
<td>S</td>
<td>H</td>
<td>36 °C</td>
<td>71%</td>
<td>33:67</td>
</tr>
</tbody>
</table>


  * Heteroatom substituents at the dienophile terminus have a significant effect on diastereoselectivity.

- **Removable Tethers for IMDA Reactions:**
  - **Boron:**

    ![Boron Tether Diagram]

    * Notice that the diastereoselectivity was not the same when different chains were applied.

  - **Magnesium:**

    ![Magnesium Tether Diagram]


  - **Silicon:**

    ![Silicon Tether Diagram]

    * IMDA of silyl ether gave trans-fused product.

Intramolecular Diels-Alder Reaction (IMDA)

- **Transition Metal-Catalyzed IMDA:**

  ![Chemical structure](image)

  * The alternative thermal reaction to form the IMDA product required a temperature of 150 °C, which caused the cleavage of the Boc protecting group and lowered the yield to 45%.

- **The Application of IMDA in the Total Synthesis of Natural Products.**
  - **Type I IMDA reactions:**

    ![Chemical structure](image)

    * Ruthenium catalysts could act as a Lewis acid to promote Type I and Type II IMDA reactions.

  - **Type II IMDA reactions:**

    ![Chemical structure](image)

    * The key step in the total synthesis of (—)-Fusarisetin A used a type I IMDA to afford the trans-fused decalin core with a Lewis acid catalyst.

  * The IMDA product was formed via the exo transition state.
Intramolecular Diels-Alder Reaction (IMDA)

* After the IMDA reaction, upon exposure to TBAF, the TBS group was hydrolyzed, and the phenyl sulfone part spontaneously eliminated to give the pentacyclic core.

• Type II IMDA Reactions:

* The reaction underwent an IMDA reaction smoothly at room temperature, and the crude was used directly in the next step. The overall yield was 53%.

• Transannular Intramolecular Diels-Alder Reactions:

* Cationic oxazaborolidine catalysts have been applied to the synthesis of the dolabellane natural products. Simple achiral Lewis acids such as Me₂AlCl, MeAlCl₂, or EtAlCl₂ did not promote the reaction to give the racemic product.

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Intramolecular Diels-Alder Reaction (IMDA)

• Organocatalysts:

\[ \text{Catalyst} (20 \text{ mol\%}), \text{TfOH (20 mol\%)} \rightarrow 71\%, >20:1 \text{ d.r.} \]

\[ \begin{align*}
\text{1st generation catalyst} & \rightarrow \text{Solanapyrone D} \\
\text{2nd generation catalyst} & \\
\end{align*} \]


* The organocatalysts could react with aldehydes to form an iminium first, which lowered the energy of the LUMO.

* Other representative asymmetric IMDA reactions:

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