Steric and Electronic Controllers

- How do substrate **sterics** affect the reactivity/selectivity in ring-closing metathesis (RCM)?

- How do substrate **electronics** affect the reactivity/selectivity in ring-closing metathesis (RCM)?
Outline

- Introduction to RCM
- Catalysts
- RCM Mechanism
- Steric Controllers
- Electronic Controllers
- Conclusion
Introduction – Ring Closing Metathesis

- Driven primarily by entropy gained by release of ethylene or other volatile side products
- Very powerful method for the formation of unsaturated cyclic systems from acyclic dienes
- Proceeds via a sequence of formal [2+2] cycloadditions/cycloreversions

Acknowledgment:
Catalysts

- **Molybdenum alkylidene complex – Schrock**
  - Superior reactivity even toward highly substituted alkenes
  - Stable for long periods in an inert atmosphere
  - Sensitive to oxygen and moisture as well as protic compounds

- **Ruthenium alkylidene complex – Grubbs**
  - Most widely used catalyst in organic synthesis for RCM and CM reactions
  - Somewhat less active, but significantly more stable, easier to handle, and shows excellent compatibility with functional groups

- **2nd generation ruthenium alkylidene complex**
  - Allow the formation of tri- and tetra-substituted cycloalkenes
  - More robust than the original Grubbs carbene in solution as well as in the solid state

RCM Mechanism

Ulman, M.; Grubbs, R.H. Organometallics 1998, 17, 2484-2489
Steric Controllers

- Allylic substitution
- Alkene substitution
- Substrate branching
- Tuning substituent groups
- Conformational constraints
Sterics: Allylic Substitution

Sterics: Allylic Substitution

Increasing Reactivity

H O
Me Me
Me Me
linalool
Me Me
Me Me
citronellene
Me Me
Me Me

5x (80%)*
1.5x (50%)
8x (60%)
>200x (100%)

Pairwise competition experiments:
~0.02M of each substrate
4-10 mol% Grubbs catalyst
*90-100 mol% Grubbs catalyst

Sterics: Allylic Substitution

Sterics: Allylic Substitution

Sterics: Alkene Substitution

R = CO$_2$Et

Sterics: Substrate Branching

Callipeltoside A

Sterics: Substituent Groups

Double RCM Strategy

Sterics: Substituent Groups

\[
\text{Catalyst A} = \begin{array}{c}
\text{PCy}_3 \\
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\text{PCy}_3 \\
\text{Ru} \\
\text{Ph}
\end{array}
\]

Sterics: Substituent Groups


Catalyst A =

Sterics: Conformational Constraints

A: Yield = 100%
B: Yield = 96%

A, B: No RCM product

A: Yield = 96%
B: Yield = 25%

A, B: No RCM product

R = CO$_2$Et

Catalyst A =

Ar = 2,6-i-Pr$_2$C$_6$H$_3$

Catalyst B =

Sterics: Conformational Constraints

Catalyst A =

Electronic Controllers

- Allylic substitution
- Alkene substitution
Electronics: Allylic Substitution

Increasing Reactivity

Pairwise competition experiments:
~0.02M of each substrate
4-10 mol% Grubbs catalyst
*90-100 mol% Grubbs catalyst

Electronics: Allylic Substitution

Fukuda, Y; Shindo, M.; Shishido, K. Org. Lett. 2003, 5, 749-751
Electronics: Allylic Substitution

1) 10 mol% A
48h

2) Hydrolysis

R₁ = Bn, TMS, MOM, Bz
R₂ = Me, Et, Ph

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS</td>
<td>Et</td>
<td>84</td>
<td>86:14</td>
</tr>
</tbody>
</table>

Catalyst A =

Electronics: Allylic Substitution

\[
\begin{array}{ccc}
\text{Yield} \text{ (%) of 2} & \text{diastereomeric} & \\
\text{(recovered 1 (%))} & \text{ratio} & \\
\hline
H & 7 (81) & 59:41 \\
Bz & 95 (5) & 72:28 \\
MOM & 92 (5) & 85:14 \\
Bn & 94 (6) & 88:12 \\
TMS & \text{quantitative (0)} & 87:13 \\
\end{array}
\]

Catalyst A =

Fukuda, Y; Shindo, M.; Shishido, K. *Org. Lett.* **2003**, *5*, 749-751
Electronics: Allylic Substitution

Conduritol A

Conduritol B

Conduritol C

Conduritol D

Conduritol E

Conduritol F

Electronics: Allylic Substitution

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Mol%</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>60</td>
<td>32</td>
</tr>
<tr>
<td>C</td>
<td>5</td>
<td>2</td>
<td>89</td>
</tr>
<tr>
<td>B</td>
<td>20</td>
<td>120!</td>
<td>77</td>
</tr>
<tr>
<td>C</td>
<td>1</td>
<td>5</td>
<td>71</td>
</tr>
</tbody>
</table>

Catalyst A: \( \text{Ar} = 2,6-i\text{-Pr}_2\text{C}_6\text{H}_3 \)

Catalyst B: \( \text{R} = 2,4,6\text{-trimethylphenyl} \)

Electronics: Allylic Substitution

Catalyst A = \[
\begin{array}{c}
\text{POy}_{3} \\
\text{Cl} \\
\text{Cl} \\
\text{Cl} \\
\text{PCy}_{3} \\
\end{array}
\]

Catalyst B = \[
\begin{array}{c}
\text{PCy}_{3} \\
\text{Cl} \\
\text{Cl} \\
\text{R} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{N}
\end{array}
\]

\( R = 2,4,6\text{-trimethylphenyl} \)

**Electronics: Alkene Substitution**


Only Product!

Catalyst A =

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Yield</th>
<th>R² = Me</th>
<th>5 mol% A</th>
<th>R² = H</th>
</tr>
</thead>
<tbody>
<tr>
<td>R¹ = Me, R² = H</td>
<td>86%</td>
<td></td>
<td>5 h</td>
<td></td>
</tr>
<tr>
<td>R¹ = H, R² = Me</td>
<td>43%</td>
<td></td>
<td>23 h</td>
<td></td>
</tr>
</tbody>
</table>
Electronics: Alkene Substitution

\[
\text{Catalyst A} = \begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{PCy}_3 \\
\text{PCy}_3 \\
\text{Ru} = \text{Ph}
\end{array}
\]

Electronics: Alkene Substitution

Catalyst A =

<table>
<thead>
<tr>
<th>R</th>
<th>k (1/min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃O-</td>
<td>0.0062</td>
<td>85</td>
</tr>
<tr>
<td>CH₃CO-</td>
<td>0.0154</td>
<td>83</td>
</tr>
<tr>
<td>PhSO₂⁻</td>
<td>0.0178</td>
<td>86</td>
</tr>
<tr>
<td>HOCH₂⁻</td>
<td>0.0215</td>
<td>77</td>
</tr>
<tr>
<td>EtOOC-</td>
<td>0.0261</td>
<td>65</td>
</tr>
<tr>
<td>H⁻</td>
<td>0.0762</td>
<td>80</td>
</tr>
</tbody>
</table>

Electronics: Alkene Substitution

\[
\begin{align*}
R = \text{CO}_2\text{Et} \\
\text{Ph} & \quad 97 & 25 \\
\text{CO}_2\text{Me} & \quad 89 & 5 \\
\text{CH}_2\text{OH} & \quad \text{decomp.} & 98 \\
\text{CH}_2\text{OAc} & \quad 100 & 97
\end{align*}
\]

Catalyst A = \[
\text{Ar} = 2,6-i-\text{Pr}_2\text{C}_6\text{H}_3
\]

Catalyst B = \[
\text{Ar} = 2,6-i-\text{Pr}_2\text{C}_6\text{H}_3
\]

Allylic Hydroxyl Group Effects

- Hydroxyl Activating Effect
- Competing Mechanisms
- Catalyst Control
Hydroxyl Group: Activating Effect

Pairwise competition experiments:
~0.02M of each substrate
4-10 mol% Grubbs catalyst
*90-100 mol% Grubbs catalyst

Hydroxyl Group: Activating Effect

Possible Explanations

- Rapid and reversible ligand exchange
  - Alkoxy for chloride
  - Alcohol for phosphine
- Hydrogen bonding between hydroxy group and one of the chloride ligands

Hydroxyl Group: Allylic Substitution

1592U89
-potent inhibitor of HIV reverse transcriptase

Hydroxyl Group: Allylic Substitution

Hydroxyl Group: Mechanism

Hydroxyl Group: Mechanism

Hydroxyl Group: Mechanism

\[
\text{Catalyst A} = \begin{array}{c}
\text{OH} \\
\text{Me} \\
\text{Me} \\
\text{OPMB}
\end{array}
\]

\[
\text{Me} \\
\text{Me} \\
\text{OPMB}
\]

Hydroxyl Group: Mechanism

Hydroxyl Group: Mechanism

Two Competing Mechanisms

Hydroxyl Group: Catalyst Control

Catalyst B = R=2,4,6-trimethylphenyl

Hydroxyl Group: Catalyst Control

\[
\text{HO} \quad \text{R} \quad 5 \text{ mol\% B, 1h} \quad \text{HO} \quad \text{R}
\]

- \( R = \text{Me, Et, and Ph} \) gave the desired RCM products in 78, 75, and 92\% yield. However, no diastereoselectivity was observed.

Catalyst B = 

Hydroxyl Group: Catalyst Control

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Mol%</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>20</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>1.5</td>
<td>2</td>
<td>69</td>
</tr>
</tbody>
</table>

Conclusion: Steric Controllers

- Allylic substitution: How?
  - Fully substituted allylic centers
  - Steric bulk (i.e., OTES)

- Alkene substitution: How?
  - Less substituted alkenes

- Substrate branching: How?
  - Additional substrate branching

- Tuning Substituent Groups: How?
  - Introduction of an alkyl group

- Conformational constraints: How?
  - The lack of conformational constraints
Conclusion: Electronic Controllers

- Allylic substitution: How?
  - Alkyl-substituted olefins bearing electron-withdrawing substituents

- Alkene substitution: How?
  - Electron-donating groups
  - Electron-withdrawing groups
Conclusion: Allylic Hydroxyl Group

- Hydroxyl Activating Effect: How?
  - Allylic hydroxyl groups greatly accelerate the rate

- Competing Mechanisms: How?
  - Two competing mechanisms have been proposed

- Catalyst Control: How?
  - Schrock’s molybdenum catalyst
  - The second generation Grubbs ruthenium complex
Thank You

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- Dr. Navine Asthana
- Mike Shafer
- Lars Peereboom
Questions?
Background

- Olefin metathesis was first observed in the 1950’s by industrial chemists.

- In 1967, Nissim Calderon figured out that the unexpected products were due to cleavage and reformation of the olefins’ double bonds.

- In 1971, Yves Chauvin and Jean-Louis Herisson proposed a mechanism, which turned out to be correct.

- Many people credit Grubbs ruthenium carbene catalyst and Schrock’s molybdenum alkylidene with putting olefin metathesis in the forefront of organic synthesis.

Advantages and Applications of RCM

- Provides an elegant pathway for the formation of small, medium, and large-ring carbo- and heterocycles

- Instrumental in natural product syntheses, including those of *aspidosperma indole and bicyclic izidine alkaloids*, as well as Callipeltoside A and conduritol derivatives

- Aids in the synthesis of optically pure materials

- Used in synthesis of carbocyclic nucleosides for the development of new antitumor and antiviral therapeutic agents

Electronics: Allylic Substitution

Catalyst =