Lanthanum(III) Triflate-Catalyzed Cyclopropanation via Intramolecular Methylene Transfer

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*J. Am. Chem. Soc.* ASAP
Stereoselective Cycloropanation Reactions

\[ \text{Halomethylmatal (Zn, Sm, Al)-Mediated Cyclopropanation Reactions} \]

\[ \text{Transition Metal-Catalyzed Decomposition of Diazo Compounds} \]

\[ \text{Nucleophilic Addition-Ring Closure} \]

Synlett 1995, 1197.
Halomethylmetal-Mediated Cyclopropanation Reactions

• Emschwiller (1929): \( \text{CH}_2\text{I}_2 + \text{Zn} \rightarrow \text{IZnCH}_2\text{I} \)

• Simmons and Smith (1958):

\[
\begin{align*}
\text{Zn/Cu, CH}_2\text{I}_2 & \quad \text{Ether} \\
\left[ \begin{array}{c}
\text{I} \cdots \text{Zn} \cdots \text{I} \\
\text{H} & \text{R}_1 & \text{H} \\
\text{R}_1 & \text{H} & \text{H} \\
\text{H} & \text{R}_1 & \text{H}
\end{array} \right] & \quad \rightarrow \\
\text{R}_1 & \text{R}_2 & \text{R}_2
\end{align*}
\]

(5)

• Wittig (1961): \( \text{ZnI}_2 + \text{CH}_2\text{N}_2 \rightarrow \text{IZnCH}_2\text{I} \quad \text{(Zn(CH}_2\text{I})_2} \)

• Furukawa (1966): \( \text{ZnI}_2 + \text{Et}_2\text{Zn} \rightarrow \text{EtZnCH}_2\text{I} \)

• Molander, Yamamoto

\[
\begin{array}{c}
\text{"MCH}_2\text{X"} \\
\text{RZnCH}_2\text{I, RSmCH}_2\text{I} \\
\text{R}_2\text{AlCH}_2\text{I}
\end{array}
\]

Compt. Rend. 1929, 188, 1555.
Halomethylmetal-Mediated Cyclopropanation Reactions: Acyclic Alkenes

<table>
<thead>
<tr>
<th>conditions</th>
<th>ratio 31:32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zn/Cu, CH₂I₂, ether</td>
<td>56:44</td>
</tr>
<tr>
<td>Et₂Zn, CH₂I₂ (1:1), CH₂Cl₂</td>
<td>86:14</td>
</tr>
<tr>
<td>Et₂Zn, CH₂I₂ (1:1), ether</td>
<td>67:33</td>
</tr>
<tr>
<td>Zn(CH₂I)₂, CH₂Cl₂</td>
<td>67:33</td>
</tr>
<tr>
<td>Sm(Hg), CH₂I₂, THF</td>
<td>25:75</td>
</tr>
</tbody>
</table>
Transition Metal-Catalyzed Decomposition of Diazoalkanes

\[ R\equiv\text{N} = N_{R'} + \text{N}_2 \text{CHR}'' \xrightarrow{\text{Catalyst}} R\equiv\text{N} = N_{R''} \]

N\_2\equiv\text{H(TMS)} \quad \text{N}_2\equiv\text{H} \quad \text{EWG} \quad \text{EWG}^1 \quad \text{EWG}^2 \quad \text{EWG}

H, \text{(Ar)} \quad \text{H} \quad \text{EWG}

Metals: Cu, Rh, Ru, Os, Co, Fe, Pd, Pt, Cr

chiral auxilaries

\[ \text{L}_n\text{M} = \text{Cu}, \text{Rh}, \text{Ru}, \text{Co}, \text{etc.} \]

chiral catalysts

Title Paper: Cyclopropanation via Intramolecular Methylene Transfer

![Chemical Reaction Diagram]

**Table 1: Catalytic Cycle for Cyclopropanation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Base (0.05 equiv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mg(OTf)₂</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OTf)₂</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Al(OTf)₃</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Bi(OTf)₃</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)₃</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Eu(OTf)₃</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>La(OTf)₃</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>La(OTf)₃</td>
<td>NEt₃</td>
</tr>
<tr>
<td>9</td>
<td>La(OTf)₃</td>
<td>TMU</td>
</tr>
<tr>
<td>10</td>
<td>La(OTf)₃</td>
<td>Pyridine</td>
</tr>
<tr>
<td>11</td>
<td>La(OTf)₃</td>
<td>2,6-lutidine</td>
</tr>
<tr>
<td>12</td>
<td>La(OTf)₃</td>
<td>2,6-lutidine</td>
</tr>
<tr>
<td>13</td>
<td>La(OTf)₃</td>
<td>2,6-lutidine</td>
</tr>
<tr>
<td>14</td>
<td>La(ClO₄)₃</td>
<td>2,6-lutidine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LiClO₄ (equiv)</th>
<th>Time (h)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>&lt;5</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>0</td>
<td>12</td>
<td>40</td>
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<tr>
<td>0</td>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td>0.75</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>0.75</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>38</td>
</tr>
</tbody>
</table>

Reactions were run in the presence of 5 mol % Lewis acid at a concentration of 0.2 M in DCE at reflux.

*J. Am. Chem. Soc. 2009, ASAP.*
Sequential Stereocontrolled Cyclopropane formation – Semi-pinacol Rearrangement

- multiple equivalents of Lewis acid promoter were used
- methylene is transferred in a constrained system

Epoxy Alcohol Rearrangements: Hydroxyl-Mediated Delivery of Lewis Acid Promoters

\[
\begin{align*}
\text{erythro: } & R_1 = \text{CH}_3, \ R_2 = \text{OH} \\
\text{threo: } & R_1 = \text{OH}, \ R_2 = \text{CH}_3
\end{align*}
\]

\[
\begin{align*}
\text{VO(OEt)}_3, \text{CH}_2\text{Cl}_2 & \quad \text{rt, 10h} \\
\text{DCM, rt, 12h} & \quad \text{Ti(O-i-Pr)}_4 (1.4 \text{ equiv})
\end{align*}
\]

\[
\begin{align*}
\text{trans-diols not observed} & \quad \text{30-40\%} \\
\text{Threo-isomer decomposed} & \quad \text{30-40\%} \\
\text{Threo-isomer recovered}
\end{align*}
\]

- terminal olefins require reflux; internal olefins react at lower temperatures
- process is stereospecific
- substitution along the carbon chain is well tolerated
- chelating motif is necessary
- internal epoxides react in lower yield

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Title Paper: Proposed Mechanism for Methylene-Transfer Reaction

epoxide opening

semi-pinacol rearrangement

J. Am. Chem. Soc. 2009, ASAP.
Title Paper: Synthesis of an Enantioenriched Cyclopropane via Asymmetric Epoxydation/Methylene Transfer

\[
\begin{align*}
\text{8} & \quad \text{91\% yield, 90\% ee} \\
\text{BnO} \quad \text{10} & \quad \text{10 mol\% La(OTf)}_3 \\
\text{LiClO}_4 & \quad \text{2,6-lutidine, DCE, 40 °C} \\
\text{84\% yield} & \\
\end{align*}
\]

\[
\begin{align*}
\text{BnBr} & \quad \text{85\% yield} \\
\text{NaH} & \\
\text{90\% ee} & \\
\text{11 R = CH}_2\text{OBn} & \\
\text{12 R = OH} & \quad \text{H}_2, \text{Pd/C} \\
\text{76\% yield} & \quad \text{NaIO}_4, \text{MeCN/H}_2\text{O} \\
\end{align*}
\]

*J. Am. Chem. Soc. 2009, ASAP.*
Conclusions

• New cyclopropanation strategy based on intramolecular methylene transfer from epoxydes to olefines

• Optimal yields were obtained with LiClO$_4$ as an additive, though its role is not clear

• Both internal and terminal olefins react (internal olefins reacts faster at lower temperatures)

• The reaction is stereospecific

• Chelating group is necessary, but need not reside along the carbon backbone between the epoxide and olefin moieties

• The mechanism involves Lewis acid activation of the substrate followed by semi-pinacol rearrangement

• The methylene transfer reaction can be used for the synthesis of enantioenriched cyclopropanes