Selectivity in [5+2] Cycloadditions with Vinylcyclopropane (VCP)

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University of Illinois at Urbana-Champaign
Seven-Membered Rings In Natural Products

*(-)-cyathin B

(+)-frondosin A

ingenol

(+)-aphanamol

(+)-tremulenediol A

(+)-dictamnol

tropolone

guanacastepene A

guanacastepene G

(-)-scabronine G

(-)-scabronine A

prostratin

crotophorbolone
Diels-Alder Analog for Seven-Membered Rings

\[
\begin{align*}
\text{Diene} + \text{Diene} & \rightarrow \text{Diene} + \text{Diene} \\
\text{[4+3]} & \rightarrow \text{Cyclooctatetraene} \\
\text{[4+2]} & \rightarrow \text{Cyclooctane}
\end{align*}
\]
[4+3] Cycloadditions: Synthesis of Cycloheptenes

Oxygen Substituents needed to stabilize allyl cation

Diels-Alder Analog for Seven-Membered Rings

Neutral Analog

No Need for Oxygen Stabilizing Group
[5+2] Cycloadditions with VCPs

(+)-alloxyathin B₂
(+)-scaborine E
(+)-erinacrine A
(+)-tremulonolide A
(±)-rameswaralide
(+)-dictamnol
(+)-aphanamol

R = 1-β-D-xylose

(+)-alloxyathin B₂
(+)-tremulenediol A
(+)-frondosin A
Rhodium Catalyzed [5+2] Cycloaddition with VCP

[RhCl(PPh₃)₃] (10 mol%) in Toluene (0.05 to 0.10 M), 110 °C

1.5 h, 88% yield
1.25 h, 74% yield
3.5 h, 83% yield
2 d, 82% yield
16 h, 81% yield

Rhodium Catalyzed [5+2] Cycloaddition with VCP

\[
\text{[RhCl(PPh_3)_3] (10 mol\%)} \quad \text{Toluene (0.05 to 0.10 M), 110 °C}
\]


Ruthenium Catalyzed [5+2] Cycloaddition with VCP

\[
\text{[CpRu(CH_3CN)_3]PF_6 (10mol\%), Acetone (0.1-0.2M), rt, 2 h}
\]

83% yield  
82% yield  
77% yield  
84% yield

88% yield  
87% yield  
70% yield 1.5:1 d.r.

Two Possible Mechanisms

Mechanism depends on:
1. Metal (Rh vs Ru)
2. Ligand Environment
3. Molecularity
Determining the Selectivity of [5+2] Cycloadditions with VCP

π-Bond Insertion Controls:
1. Regioselectivity
2. Diastereoselectivity
Regiochemical Outcomes for Intermolecular [5+2] Cycloadditions with VCPs: Two Pathways

Controlling the Regiochemistry of Intermolecular [5+2] Cycloadditions with VCPs

Substrate-Substrate Steric Control:

Applies to ALL Ligands; More Prominent in SMALL Ligands

*Supported by B3LYP/SDD-6-31G*/CPCM(DCE) Free Energies of Activation

Controlling the Regiochemistry of Intermolecular [5+2] Cycloadditions with VCPs

Ligand-Substrate Steric Control:

Applies to BULKY Ligands Only

*Supported by B3LYP/SDD-6-31G**/CPCM(DCE) Free Energies of Activation
Utilizing Different Ligands to Control Regioselectivity

Controlling the Regiochemistry of Intermolecular [5+2] Cycloadditions with VCPs

Metal-Substrate Electronic Control:

*Supported by B3LYP/SDD-6-31G*/CPCM(DCE) Free Energies of Activation
Utilizing Different Ligands to Control Regioselectivity

TBSO + EWG + Rh\textsuperscript{I} cat (5 mol%) → Distal: Proximal

<table>
<thead>
<tr>
<th>EWG</th>
<th>Ratio (Regioselectivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMe</td>
<td>1:1.9 (91%)</td>
</tr>
<tr>
<td></td>
<td>1:&gt;20 (65%)</td>
</tr>
<tr>
<td></td>
<td>1:20 (96%)</td>
</tr>
<tr>
<td>CO\textsubscript{2}Me</td>
<td>3.0:1 (84%)</td>
</tr>
<tr>
<td></td>
<td>1.2:1 (73%)</td>
</tr>
<tr>
<td></td>
<td>1.7:1 (95%)</td>
</tr>
</tbody>
</table>

Effect of Competing Steric and Electronic Factors

Steric Controls Predominate over Electronics

Utilizing Different Ligands to Control Regioselectivity

TBSO + Ar $\xrightarrow{\text{Rh}^1 \text{cat} (5 \text{ mol})}$ DCE:TFE (95:5) (0.1 M) then $\text{H}^+$

<table>
<thead>
<tr>
<th>$\text{Ar}$</th>
<th>$\text{Distal}$</th>
<th>$\text{Proximal}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>7.7:1 (78%)</td>
<td>6.8:1 (68%)</td>
</tr>
<tr>
<td>$p$-OMe-Ph</td>
<td>5.9:1 (76%)</td>
<td>--</td>
</tr>
<tr>
<td>$p$-COMe-Ph</td>
<td>11:1 (66%)</td>
<td>--</td>
</tr>
</tbody>
</table>

Controlling the Regiochemistry of Intermolecular [5+2] Cycloadditions with VCPs

Substrate-Substrate Steric Control:

Ligand-Substrate Steric Control:

Metal-Substrate Electronic Control:

$\pi/\pi$ and C-H/$\pi$ Interactions:

*Supported by B3LYP/SDD-6-31G*/CPCM(DCE) Free Energies of Activation
Controlling the Diasteroselectivity of Intramolecular [5+2] Cycloadditions with VCPs

Utilizing the Alkoxy Effect to Control Diastereoselectivity

σ^* CO orbital overlap with C-C π orbital decreases nucleophilicity of alkene

Towards the Synthesis of (±)-Rameswaralide
Towards the Synthesis of (±)-Rameswaralide

Retrosynthetic Analysis of Tricyclic Core

Application of [5+2] cycloaddition with VCP

Towards the Synthesis of (±)-Rameswaralide

Retroynthetic Analysis of Tricyclic Core

Application of [5+2] cycloaddition with VCP

Alkoxy Effect

Substrate Controlled Diastereoselectivity

Substrate Controlled Diastereoselectivity

Rhodium inserts on opposite face of bulky $t$-Bu
Determining the Selectivity of [5+2] Cycloadditions with VCP

π-Bond Insertion Controls:
1. Regioselectivity
2. Diastereoselectivity
Determining the Selectivity of [5+2] Cycloadditions with VCP

Cyclopropane Cleavage Controls:
1. Regioselectivity

Diagram:
- **Cyclopropane Cleavage**: The reaction involves the cleavage of the cyclopropane bond.
- **8-Membered Metallacycle**: Formation of an eight-membered ring involving the metal and the substrate.
- **Reductive Elimination**: The process where a reductive elimination reaction occurs, forming a double bond.
- **π-Bond Insertion**: Insertion of a π bond into the metallacycle.
- **Exchange**: Exchange of ligands or groups during the reaction.
- **Cyclopropane Cleavage**: Further cyclopropane cleavage steps are indicated.

Chemical Structures:
- **Rhodium Complex**: Representation of the rhodium complex involved in the catalytic cycle.
- **Metallacyclopentene** and **Metallacyclohexene**: Intermediate compounds formed during the reaction process.
Regioselectivity in Cyclopropane Ring Opening

Regioselectivity in Cyclopropane Ring Opening

Favored with \( \text{EWG} \)
Favored with \( \text{R}^{\text{cis}} \) substituents

Distal

Proximal

**cis 1,2-disubstituted VCPs**

<table>
<thead>
<tr>
<th>Product</th>
<th>Rh(^i) catalyst</th>
<th>Time</th>
<th>Yield</th>
<th>Ratio Distal:Proximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^{cis} = \text{CH}_2\text{OTBS})</td>
<td>[Rh((\text{CO})_2\text{Cl})]_2</td>
<td>1 h</td>
<td>93%</td>
<td>1:0</td>
</tr>
<tr>
<td></td>
<td>Rh((\text{PPh}_3))_3\text{Cl}/AgOTf</td>
<td>2 h</td>
<td>96%</td>
<td>1:0</td>
</tr>
<tr>
<td>(R^{cis} = \text{CH}_2\text{OTIPS})</td>
<td>[CpRu((\text{CH}_3\text{CN}))_3]PF_6</td>
<td>2 h</td>
<td>85%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>(R^{cis} = \text{CO}_2\text{Me})</td>
<td>[Rh((\text{CO})_2\text{Cl})]_2</td>
<td>2 h</td>
<td>98%</td>
<td>1.5:1</td>
</tr>
<tr>
<td></td>
<td>Rh((\text{PPh}_3))_3\text{Cl}/AgOTf</td>
<td>2 h</td>
<td>95%</td>
<td>6.4:1</td>
</tr>
<tr>
<td></td>
<td>[CpRu((\text{CH}_3\text{CN}))_3]PF_6</td>
<td>2 h</td>
<td>90%</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>(R^{cis} = \text{COH})</td>
<td>[Rh((\text{CO})_2\text{Cl})]_2</td>
<td>55 °C, 15 h</td>
<td>92%</td>
<td>0:1</td>
</tr>
<tr>
<td></td>
<td>[CpRu((\text{CH}_3\text{CN}))_3]PF_6</td>
<td>0.5 h</td>
<td>83%</td>
<td>100% Epi-Proximal</td>
</tr>
</tbody>
</table>


Aldehyde Isomerization

## trans 1,2-disubstituted VCPs

<table>
<thead>
<tr>
<th>Product</th>
<th>Rh(^1) catalyst</th>
<th>Time</th>
<th>Yield</th>
<th>Ratio Distal:Proximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^{\text{trans}} = \text{CH}_2\text{OTBS})</td>
<td>([\text{Rh(CO)}_2\text{Cl}]_2)</td>
<td>1 h</td>
<td>85%</td>
<td>2.5:1</td>
</tr>
<tr>
<td></td>
<td>(\text{Rh(PPh}_3)_3\text{Cl}/\text{AgOTf})</td>
<td>1 h</td>
<td>92%</td>
<td>1:0</td>
</tr>
<tr>
<td>(R^{\text{trans}} = \text{CH}_2\text{OTIPS})</td>
<td>([\text{CpRu(CH}_3\text{CN)}_3]\text{PF}_6)</td>
<td>2 h</td>
<td>81%</td>
<td>3:1</td>
</tr>
<tr>
<td>(R^{\text{trans}} = \text{CO}_2\text{Me})</td>
<td>([\text{Rh(CO)}_2\text{Cl}]_2)</td>
<td>1 h</td>
<td>93%</td>
<td>1:11</td>
</tr>
<tr>
<td></td>
<td>(\text{Rh(PPh}_3)_3\text{Cl}/\text{AgOTf})</td>
<td>1 h</td>
<td>81%</td>
<td>20:1</td>
</tr>
<tr>
<td></td>
<td>([\text{CpRu(CH}_3\text{CN)}_3]\text{PF}_6)</td>
<td>2 h</td>
<td>90%</td>
<td>1:2</td>
</tr>
<tr>
<td>(R^{\text{trans}} = \text{COH})</td>
<td>([\text{Rh(CO)}_2\text{Cl}]_2)</td>
<td>55 °C, 8 h</td>
<td>98%</td>
<td>0:1</td>
</tr>
<tr>
<td></td>
<td>([\text{CpRu(CH}_3\text{CN)}_3]\text{PF}_6)</td>
<td>0.5 h</td>
<td>83%</td>
<td>1:12</td>
</tr>
</tbody>
</table>

Enantioselective Total Synthesis of Tremulenediiodol A and Tremulenolide A

Enantioselective Total Synthesis of Tremulenediols A and Tremulenolide A

Retrosynthetic Analysis

Application of [5+2] cycloaddition with VCP

85% yield

Towards the Synthesis of (+)-Frondosin A

Towards the Synthesis of (+)-Frondosin A

Retrosynthetic Analysis

Application of [5+2] cycloaddition with VCP

Determining the Selectivity of [5+2] Cycloadditions with VCP

Cyclopropane Cleavage Controls:
1. Regioselectivity
Determining the Selectivity of [5+2] Cycloadditions with VCP

Reductive Elimination Controls:
1. Periselectivity
Expanding the Scope of Cycloadditions with VCPs

(+)-alloxythain B$_2$

(+)-dictamnol

(+)-aphanamol

(+)-tremulenediol A

(+)-frondosin A

(+)-tremulenolide A
Expanding the Scope of Cycloadditions with VCPs
Expanding the Scope of Cycloadditions with VCPs
Selection Between [(5+2)+1] and [5+2]

Rh Catalyzed [(5+2)+1] Cycloadditons with VCPs

Selectively Achieving [(5+2)+1] Cycloadditions: Insight into Alkenes

Developing \( \pi \)-Rh coordination facilitates reductive elimination

\[
\Delta G^\ddagger = 29.3 \\
\Delta G^\ddagger = 20.0 \\
\Delta G^\ddagger = 14.5
\]

*B3LYP/SDD-6-31G*/LANL2DZ+ECP computational analysis
Preferential [(5+2)+1] Cycloadditions with Alkenes

More Favorable Reductive Elimination for [(5+2)+1]

Total Synthesis of (±)-hirsutene and (±)-1-desoxyhypnophilin

Total Synthesis of (±)-hirsutene and (±)-1-desoxyhypnophilin

Retrosynthetic Analysis

Application of [5+2] cycloaddition with VCP

Divergent Total Synthesis using [(5+2)+1] Cycloadditions

0.2 atm CO + 0.8 atm N₂
(5 mol%) [Rh(CO)₂Cl]₂,
dioxane (0.05 M),
90 °C, 48 h

(±)-pentalene
(±)-Asterica-3(15),6-diene
(±)-Hirsutene

65% yield
Total Synthesis of Cyantanthe Core

\[ \text{5 mol}\% [\text{Rh}(\text{CO})_2\text{Cl}]_2 \rightarrow \text{DCE (0.02M), 80°C, 3.5 h} \]

90% yield

(+)-allocyathin B₂

(+)-scaborine E

(+)-erinacrine A

\( R = 1-\beta\text{-D-xylose} \)

[5+2] Cycloadditions with VCPs

(±)-asterica-3(15),6-diene
(±)-hirsutic acid C
(±)-asteriscanolide
(±)-1-desoxyhypnophilin
(±)-pentalene
(+).allocyathin B₂
(+)dictamnol
(+)aphanamol
(+)tremulenediol A
(+)tremulenolide A
(+)frondosin A
Future Directions: Towards a Homologous Diels-Alder

- Delve deeper into the mechanism of [5+2] cycloadditions
  - To distinguish between metallacyclopentene and metallacyclohexene pathway
  - To understand the role of metal, ligands, and molecularity

- Expand the scope of the reaction to include:
  - Hetero-π components
  - Epoxides and Aziridines
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CHEM 535
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The Burke Group