Reductive Enolate Generation From Enones
- Application in C-C bond Formation


Group Presentation

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Nov 20, 2003
Catalytic Nucleophilic Activation of Enones

- Hydrometallative nucleophilic activation via conjugate reduction

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{PhSiH}_3 \\
\text{(dpm = dipivaloylmethane)}
\end{align*}
\]

* Co, Ni, Rh catalyst systems, silane, borane, alane, and stannane, H\textsubscript{2} as reductants

- Nucleophilic organocatalysis via reversible conjugate addition

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \text{Et} \\
\text{O} & \quad \text{O} \text{Et} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \text{Et} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{O} & \quad \text{O} \text{Et}
\end{align*}
\]

* Intramolecular Baylis-Hillman reaction, Intramolecular Rauhut-Currier reaction

Catalytic C-C bond Formation of Monoenone and Monoaldehyde

![Chemical reaction diagram]

- Proposed catalytic cycle:

  \[ \text{H}_2 \xrightarrow{\text{Rh(COD)}_2\text{OTf} (10\text{mol\%})} \xrightarrow{(p-\text{CF}_3\text{Ph})_3\text{P} (24\text{mol\%})} \text{Rh}^{(I)} \xrightarrow{\text{H}_2 (1\text{atm}), \text{KOAc} (30\text{mol\%})} \text{DCE, 25°C} \]

  - Enolate addition
  - Conjugate reduction

  - 89% yield of 1b; 0.1% yield of 1c; \( \text{syn:anti} = 10:1 \).

Catalytic C-C bond Formation of Monoenone and Monoaldehyde

- Hydrogenative aldol cycloreduction of aromatic, heteroaromatic, and aliphatic enone substrates to form 5- and 6-membered rings.

\[
\begin{align*}
\text{R} & - \text{O} - \text{O} \\
n & = 1 - 2 \\
\text{Rh} & (\text{COD})_2 \text{OTf} (10\text{mol}\%) \\
(p-\text{CF}_3\text{Ph})_3 \text{P} (24\text{mol}\%) \\
\text{H}_2 & (1\text{atm}), \text{KOAc} (30\text{mol}\%) \\
\text{DCE}, & 25^\circ\text{C} \\
\end{align*}
\]

**Table 1.** Rh-Catalyzed Hydrogenative Aldol Cycloreduction of Monoenone Monoaldehydes 1a-7a

<table>
<thead>
<tr>
<th>substrate</th>
<th>product (syn:anti)</th>
<th>1,4-reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, ( n = 2 ), ( R = \text{Ph} )</td>
<td>1b, 89% (10:1)</td>
<td>1c, 0.1%</td>
</tr>
<tr>
<td>2a, ( n = 2 ), ( R = p-\text{MeOPh} )</td>
<td>2b, 74% (5:1)</td>
<td>2c, 3%</td>
</tr>
<tr>
<td>3a, ( n = 2 ), ( R = 2\text{-naphthyl} )</td>
<td>3b, 90% (10:1)</td>
<td>3c, 1%</td>
</tr>
<tr>
<td>4a, ( n = 2 ), ( R = 2\text{-thiophenyl} )</td>
<td>4b, 76% (19:1)</td>
<td>4c, 2%</td>
</tr>
<tr>
<td>5a, ( n = 2 ), ( R = 2\text{-furyl} )</td>
<td>5b, 70% (6:1)</td>
<td>5c, 10%</td>
</tr>
<tr>
<td>6a, ( n = 1 ), ( R = \text{Ph} )</td>
<td>6b, 71% (24:1)</td>
<td>6c, 1%</td>
</tr>
<tr>
<td>7a, ( n = 2 ), ( R = \text{CH}_3 )</td>
<td>7b, 65% (1:5)</td>
<td></td>
</tr>
</tbody>
</table>

Intermolecular Hydrogenative Aldol Condensation

- Phenyl vinyl ketone as prenucleophile.

![Chemical Reaction]

\[
\text{Phenyl vinyl ketone + Harters' Aldol reagent} \xrightarrow{\text{Rh}(\text{COD})_2\text{OTf}(5\text{mol} \%), \text{PPh}_3(12\text{mol} \%)}
\]

\[
\text{H}_2(1\text{atm}), \text{KOAc}(50\text{mol} \%), \text{DCE, 25}^\circ\text{C}
\]

Table 2. Intermolecular Rh-catalyzed hydrogenative aldol condensation of phenyl vinyl ketone and various aldehydes

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Stereoisomers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92%</td>
<td>(1.8:1) syn:anti</td>
</tr>
<tr>
<td>2</td>
<td>75%</td>
<td>1.7:1</td>
</tr>
<tr>
<td>3</td>
<td>61%</td>
<td>(2.3:1)</td>
</tr>
<tr>
<td>4</td>
<td>65%</td>
<td>(2:1)</td>
</tr>
<tr>
<td>5</td>
<td>88%</td>
<td>(2.5:1)</td>
</tr>
<tr>
<td>6</td>
<td>44%</td>
<td>(2:1)</td>
</tr>
</tbody>
</table>

* Changes of conditions:
  Intramolecular: enone: 100mol%, catalyst: 10mol%, conc: 0.5mol/L.
  Intermolecular: enone: 150mol%, catalyst: 5mol%, conc: 0.1mol/L.

Propiophenone doesn’t result in aldolization; Ethyl acrylate exclusively give 1,4-reduction product; Methyl vinyl ketone works.

Ketone and dione partners as electrophiles

Catalytic Hydrogenative Cycloreduction of Keto-enones

Catalytic Hydrogenative Cycloreduction of Keto-enones

n = 2

1b, 72% (1c, 20%)  
d.e. >95:5

2b, 78% (2c, 18%)  
d.e. >95:5

3b, 78% (3c, 8%)  
d.e. >95:5

4b, 83% (4c, 8%)  
d.e. >95:5

5b, 82% (5c, 12%)  
d.e. >95:5

6b, 72% (6c, 17%)  
d.e. >95:5

n = 1

7b, 75% (7c, 8%)  
d.e. >95:5

8b, 74% (8c, 18%)  
d.e. >95:5

9b, 66% (9c, 24%)  
d.e. >95:5

10b, 70% (10c, 24%)  
d.e. >95:5

11b, 75% (11c, 11%)  
d.e. >95:5

12b, 74% (12c, 8%)  
d.e. >95:5

Cycloreduction of Dione-enones

Diastereoselective formation of 3-contiguous stereogenic centers, including 2-contiguous quaternary centers.

Monohydride-based Catalytic Cycle

Formal heterolytic activation of elemental hydrogen mitigates competitive conjugate reduction manifolds by enabling monohydride-based catalytic cycles.

Mechanism Study on the Conjugate Reduction

- Catalytic cycloreduction employing elemental deuterium

\[
\begin{align*}
\text{Rh(COD)₂OTf (10 mol\%)} & \quad \text{(Ph)₃P (24 mol\%)} \\
D₂ (1 \text{ atm}) & \quad K₂CO₃ (80 \text{ mol\%}) \\
\text{DCE, 80°C} & 
\end{align*}
\]

19a

19b, 83% Isolated Yield
No Conjugate Reduction

\[
\begin{align*}
R₁ = R₂ = H, & 11\% +/- 5\% \\
R₁ = D, R₂ = H, & 81\% +/- 5\% \\
R₁ = R₂ = D, & 8\% +/- 5\%
\end{align*}
\]

The enone hydrometalation is reversible. Such as β-hydride elimination of Rh-enolate.

Carbometallative Aldol Cycloreduction: Tandem Conjugate Addition Aldol Cyclization

* Rh-catalyzed conjugate addition is performed:
  1. Aqueous organic media $\Rightarrow$ adding water (5 equiv with respect to substrate)
  2. Avoid the addition of arylboronic acids to aldehyde $\Rightarrow$ methyl ketones

* Three contiguous stereogenic centers are created in one manipulation with high relative and absolute stereochemical control. A single diastereomer was obtained, no epimeric material detected.

* The stereochemical assignment was corroborated by X-ray analysis.

### Carbometallative Aldol Cycloreduction

#### Table. Catalytic diastereoselective carbometallative aldol cycloreduction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>1a, n = 1</td>
<td>1b</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>2a, n = 2</td>
<td>2b</td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>3a, n = 1</td>
<td>3b</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>4a, n = 2</td>
<td>4b</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>4a, R = CH₃</td>
<td>4c</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>2a, R = Ph</td>
<td>2c</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>84%</td>
</tr>
<tr>
<td></td>
<td>5a</td>
<td>5b</td>
<td>84%</td>
</tr>
</tbody>
</table>

Catalytic Enantioselective Carbometallative Aldol Cycloreduction

Optimization of the enantioselective carbometallative cycloreduction of 2a

\[ \begin{align*}
[\text{Rh(COD)Cl}]_2 & \text{ (2.5 mol\%)} \\
\text{Ligand} & \text{ (7.5 mol\%)} \\
\text{PhB(OH)}_2 & \text{ (200 mol\%)} \\
\text{H}_2\text{O} & \text{ (500 mol\%)} \\
\text{Dioxane} & \text{ (0.1 M), 95 °C}
\end{align*} \]

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (ee %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,S)-Josiphos</td>
<td>57% (0)</td>
</tr>
<tr>
<td>(R,R)-MeDuphos</td>
<td>67% (0)</td>
</tr>
<tr>
<td>(R)-Phanephos</td>
<td>79% (5)</td>
</tr>
<tr>
<td>(R)-Tol-BINAP</td>
<td>94% (62)</td>
</tr>
<tr>
<td>(R)-BINAP</td>
<td>90% (77)</td>
</tr>
<tr>
<td>(R)-BINAP\text{c}</td>
<td>80% (87)</td>
</tr>
<tr>
<td>(R)-BINAP\text{d,e}</td>
<td>88% (88)</td>
</tr>
</tbody>
</table>

**Table**. Catalytic enantioselective carbometallative aldol cycloreduction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield (ee%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a, n = 1</td>
<td>1b</td>
<td>78% (77)</td>
</tr>
<tr>
<td></td>
<td>2a, n = 2</td>
<td>2b</td>
<td>88% (88)</td>
</tr>
<tr>
<td>2</td>
<td>3a, n = 1</td>
<td>3b</td>
<td>88% (94)</td>
</tr>
<tr>
<td></td>
<td>4a, n = 2</td>
<td>4b</td>
<td>69% (95)</td>
</tr>
</tbody>
</table>

Proposed Mechanism

- Proposed catalytic cycle

- Model of Z-enolate and Zimmerman-Traxler type Transition state

Summary

- A catalytic C-C bond formation under hydrogenative conditions via selectively generate and transform transition metal enolates.

- A mild and economical hydrometallative method which circumvents 1,4-reduction byproduct.

- Aldehyde, ketone, and dione used as electrophiles in aldol cycloreduction to form 5- or 6- membered rings.

- The ability of creating three contiguous stereogenic centers in a single manipulation with high relative and absolute stereochemical control.