Chiral Supramolecular Catalyst for Asymmetric Reaction

2017/1/21 (Sat.)
Literature Seminar
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Introduction

Conventional Chiral Catalyst

Central metal atom

Fine tuned chiral ligands

Rational design of chiral ligands remains very difficult.

Numerous trial-and-error attempts are needed.

Conventional chiral ligands are constructed with covalent bonds.

Synthesis of chiral ligands require multi-step operation and can be complicated.

Optimizing ligands is time-and-energy consuming
These attributes are induced by small components of supramolecular catalyst.
Supramolecular Chiral Catalyst

What is the advantage of supramolecular chiral catalyst?

- Synthesis of each small component is much easier than complex conventional large ligand.
- The ligands can be tuned easily by changing each component.
- Combinatorial methods can be used for screening ligands.

To date, some strategies for supramolecular catalysts have been developed.
Supramolecular Catalysis Strategy 1

1) Zn-pyridine interactions

Zn-pyridine interaction is indeed **selective**

First example of supramolecular bidentate ligands

Supramolecular Catalyst Strategy 2

Achiral ligand upon chiral scaffold

1) ion-paired chiral ligands

$\text{Me}_2\text{N}^+ \text{C}_6\text{H}_4\text{R}$

![Chemical structure](image)

$\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (1.25 mol%)

ligand 1 (5 mol%)

mesitylene/ $\text{H}_2\text{O}$

0 $^\circ\text{C}$

$\text{Ph} = \text{p-Cl-C}_6\text{H}_4$

$\text{R} = \text{tBu}$

$\text{Me}$

$\text{CO}_2\text{tBu}$

$\text{O}_2\text{N}$

$\text{Ph}=\text{C}=\text{C}\text{Me}$

$\text{Me}$

$\text{CO}_2\text{Me}$

$\text{NO}_2$

97% yield

94% ee

Hydrogen bond is critical for enantioselectivity.

co-solvent system is efficient?
In situ generation of chiral ligands enables us to use combinatorial strategy much easier. Just mixing reagent is enough to evaluate ligand selectivity.

1a H H 4-Cl-C₆H₄
1b H H 4-MeO-C₆H₄
1c H H 4-F-C₆H₄
1d H H 4-CF₃-C₆H₄
1e H Me 4-Cl-C₆H₄
1f H Me 4-MeO-C₆H₄
1g H Me 4-F-C₆H₄
1h H Me 4-CF₃-C₆H₄
1i Me H 4-Cl-C₆H₄
1j Me H 4-MeO-C₆H₄
1k Me H 4-F-C₆H₄
1l Me H 4-CF₃-C₆H₄

Step 1

<table>
<thead>
<tr>
<th>2</th>
<th>Ar²</th>
</tr>
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<tbody>
<tr>
<td>2a</td>
<td>H8</td>
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<td>2b</td>
<td>H8</td>
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<tr>
<td>2c</td>
<td>H8</td>
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<tr>
<td>2d</td>
<td>H8</td>
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<tr>
<td>2e</td>
<td>H8</td>
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<td>2f</td>
<td>H8</td>
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<td>2g</td>
<td>B</td>
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<tr>
<td>2h</td>
<td>B</td>
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<tr>
<td>2i</td>
<td>B</td>
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<td>2j</td>
<td>B</td>
</tr>
<tr>
<td>2k</td>
<td>B</td>
</tr>
<tr>
<td>2l</td>
<td>B</td>
</tr>
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</table>

Step 2

<table>
<thead>
<tr>
<th>2a-2f</th>
<th>2g-2i</th>
<th>2j-2l</th>
</tr>
</thead>
<tbody>
<tr>
<td>71% ee (97%)</td>
<td>72% ee (99%)</td>
<td>75% ee (98%)</td>
</tr>
<tr>
<td>79% ee (99%)</td>
<td>74% ee (94%)</td>
<td></td>
</tr>
</tbody>
</table>

Values in parentheses are isolated yields of 8a.

Step 3

<table>
<thead>
<tr>
<th>Step 2</th>
<th>2g</th>
<th>2h</th>
<th>2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g</td>
<td>89% ee (95%)</td>
<td>78% ee (89%)</td>
<td>70% ee (90%)</td>
</tr>
<tr>
<td>1h</td>
<td>92% ee (89%)</td>
<td>94% ee (99%)</td>
<td>79% ee (86%)</td>
</tr>
</tbody>
</table>

Only 16 experiments were enough!
In order to get higher ee, the reaction field should be bulkier
dissymmetrical environment. But such catalysts are often very
complicated and the synthesis of the catalysts is very laborious.

Using hydrogen bond, Lewis acid-base pair and selective
molecules interaction is attractive strategy to make better
dissymmetrical environment based on chiral scaffold.
Transmission of the chiral scaffold to other molecules

Catalyst 1 is prepared from Yb(Otf)$_3$, (R)-BINOL, and a tertiary amine.

The axial chirality is transferred to the amine part, which work as a “wall” in the transition state to shield one side of the dienophile.

The Effect of Tertiary Amine

The amine strongly influenced the diastereo- and enantioselectivities.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>MS</th>
<th>MS</th>
<th>ΔΔ</th>
<th>Yield (%)</th>
<th>0 °C. 30 min endo/exo</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N</td>
<td></td>
<td></td>
<td></td>
<td>87</td>
<td>76/24</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>Bu₃N</td>
<td></td>
<td></td>
<td></td>
<td>quant.</td>
<td>83/17</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>Pr₂NEt</td>
<td></td>
<td></td>
<td></td>
<td>82</td>
<td>85/15</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>iPr₂NBU</td>
<td></td>
<td></td>
<td></td>
<td>77</td>
<td>84/16</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>iPr₂NH</td>
<td></td>
<td></td>
<td></td>
<td>67</td>
<td>82/18</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>Pr(c-C₆H₁₁)NH</td>
<td></td>
<td></td>
<td></td>
<td>90</td>
<td>82/18</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>(c-C₆H₁₁)₂NH</td>
<td></td>
<td></td>
<td></td>
<td>43</td>
<td>81/19</td>
<td>46</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>85</td>
<td>81/19</td>
<td>50</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71</td>
<td>76/24</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93</td>
<td>80/20</td>
<td>51</td>
</tr>
<tr>
<td>21</td>
<td>(cis)</td>
<td></td>
<td></td>
<td></td>
<td>96</td>
<td>85/15</td>
<td>71</td>
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<td>22</td>
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<td></td>
<td></td>
<td></td>
<td>96</td>
<td>85/15</td>
<td>69</td>
</tr>
</tbody>
</table>

The Existence of Weak Interaction

This table indicates that the existence of a weak interaction.

Table 6. Comparison of $^{13}$C NMR Chemical Shifts (CD$_2$Cl$_2$) of the Carbons of the N-Methyl Groups of cis-1,2,6-Trimethylpiperidine (TMP) and IR Wave Numbers (CH$_2$Cl$_2$) in the Region 930-1000 cm$^{-1}$

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta$ (ppm)</th>
<th>Wave Number (cm$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP</td>
<td>38.2</td>
<td>947</td>
</tr>
<tr>
<td>TMP + (R)-(+) -binaphtol (1:1)</td>
<td>35.1</td>
<td>989, 947</td>
</tr>
<tr>
<td>TMP + TfOH (1:1)</td>
<td>34.1</td>
<td>958</td>
</tr>
<tr>
<td>TMP + Yb(OTf)$_3$ + (R)-(+) -binaphtol + 3-acetyl-1,3-oxazolidin-2-one (Catalyst A)</td>
<td>37.5</td>
<td>997, 955</td>
</tr>
<tr>
<td>TMP + Yb(OTf)$_3$ + (R)-(+) -binaphtol + PAA (Catalyst B)</td>
<td>38.5</td>
<td>982, 935</td>
</tr>
</tbody>
</table>

Additive is also Important Factor


Additive are effective not only in stabilizing the catalyst, but also in controlling the enantiofacial selectivity.

Both enantiomers could be prepared by the same chiral source!!!!!

The enantioselectivities were controlled by the achiral ligands.
Mechanism

The substrate and additive are under equilibrium condition.

1) Hydrogen bond + ion pair catalyst

The chirality of aminophosphonium is relayed over two achiral phenols.
Analysis of Interaction

Single-crystal x-ray diffraction analysis

$^{31}$P NMR spectra of in situ generated molecular assemblies of catalysts at -98 °C in toluene
X-ray Crystal Analysis of Interaction

1
$^{31}$P NMR $\delta$ = 45.4 ppm

$1 \cdot [2]_1$
35.4 ppm

$1 \cdot [2]_2$
33.9 ppm

$1 \cdot [2]_3$
32.4 ppm
The Effect of Phenol Derivative

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conc (mM)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a·(PhO)$_3$H$_2$</td>
<td>1</td>
<td>6</td>
<td>99</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>1a'</td>
<td>1</td>
<td>2</td>
<td>99</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>1a' + 3PhOH</td>
<td>1</td>
<td>10</td>
<td>98</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>1a·2' + 3PhOH</td>
<td>1</td>
<td>16</td>
<td>87</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>1a·(4-Me–C$_6$H$_4$O)$_3$H$_2$</td>
<td>1</td>
<td>4</td>
<td>96</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>1a·(4-Cl–C$_6$H$_4$O)$_3$H$_2$</td>
<td>1</td>
<td>10</td>
<td>97</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>1a·(2-Cl–C$_6$H$_4$O)$_3$H$_2$</td>
<td>1</td>
<td>12</td>
<td>94</td>
<td>63</td>
</tr>
<tr>
<td>8</td>
<td>1a·(3-Cl–C$_6$H$_4$O)$_3$H$_2$</td>
<td>1</td>
<td>6</td>
<td>93</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>1a·(3,5-Cl$_2$–C$_6$H$_3$O)$_3$H$_2$</td>
<td>1</td>
<td>16</td>
<td>92</td>
<td>80</td>
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<tr>
<td>10*</td>
<td>1a·(3,5-Cl$_2$–C$_6$H$_3$O)$_3$H$_2$</td>
<td>2</td>
<td>24</td>
<td>99</td>
<td>85</td>
</tr>
<tr>
<td>11†</td>
<td>1a·(3,5-Cl$_2$–C$_6$H$_3$O)$_3$H$_2$</td>
<td>5</td>
<td>18</td>
<td>98</td>
<td>89</td>
</tr>
<tr>
<td>12‡</td>
<td>1a·(3,5-Cl$_2$–C$_6$H$_3$O)$_3$H$_2$</td>
<td>10</td>
<td>20</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>13§</td>
<td>1a·(3,5-Cl$_2$–C$_6$H$_3$O)$_3$H$_2$</td>
<td>10</td>
<td>4</td>
<td>99</td>
<td>87</td>
</tr>
<tr>
<td>14§</td>
<td>1b·(3,5-Cl$_2$–C$_6$H$_3$O)$_3$H$_2$</td>
<td>10</td>
<td>4</td>
<td>95</td>
<td>95</td>
</tr>
</tbody>
</table>
The Importance of Phenols

Less Selective Molecular Assembly

More Selective Molecular Assembly

Subcomponents (=2B(C6F5)3) act as a bulky functional group to make a **chiral cavity**. And at once, they increase the activity of catalyst center.

Chiral cavity which consists of subcomponents is effective for anomalous Diels-Alder reaction.

Enantio Selectivity VS endo/exo Selectivity

Covering the re or si face is enough to get enantiomer. Covering one of the faces doesn’t matter.

Completely different two strategies are necessary to get endo/exo-enantio-selectivity.
Prof. Ishihara’s Strategy

(a) Normal endo-control by substrate ($R_\alpha = H$)
- favored, endo
- disfavored, exo

(b) Normal exo-control by substrate ($R_\alpha \neq H$)
- disfavored, endo
- favored, exo

(a) Anomalous exo-control by catalyst ($R_\alpha = H$):
- Shallow and wide cavity
- disfavored, endo
- favored, anomalous exo

(b) Anomalous endo-control by catalyst ($R_\alpha \neq H$):
- Deep and narrow cavity
- favored, anomalous endo
- disfavored, exo
Kazuaki Ishihara was born in Aichi, Japan, in 1963, and received his PhD from Nagoya University in 1991 under the direction of Professor Hisashi Yamamoto. He had the opportunity to work under the direction of Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student for three months in 1988. He was a JSPS Fellow under the Japanese Junior Scientists Program from 1989 to 1991. After he completed his postdoctoral studies with Professor E. J. Corey at Harvard University (15 months beginning in 1991), he returned to Japan and joined Professor Hisashi Yamamoto’s group at Nagoya University as an assistant professor in 1992, and became associate professor in 1997. In 2002, he was appointed to his current position as a full professor at Nagoya University. His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis toward green and sustainable chemistry, acid–base combination chemistry, and designer supramolecular acid–base combined catalysts.
The First Anomalous Diels-Alder Reaction

Catalyst covers around carbonyl group and inhibit the “secondary orbital interactions”.

The First Enantio and *endo/exo* Control

1 + \[ \text{HCHO} \]

\[ \begin{align*}
5 \text{ (5 mol\%)} \quad & 2,6\text{-lutidine (5 mol\%)} \\
& \text{CH}_2\text{Cl}_2, -20^\circ\text{C} \\
& 88\% \text{ (endo:exo = 70:30)} \\
\end{align*} \]

\[ \begin{align*}
\text{endo-} (2S)-3a \\
70\% \text{ ee} \\
\text{exo-} (2S)-3a \\
\end{align*} \]

\[ \begin{align*}
6 \text{ (5 mol\%)} \quad & 2,6\text{-lutidine (5 mol\%)} \\
& \text{CH}_2\text{Cl}_2, -20^\circ\text{C} \\
& 84\% \text{ (endo:exo = 29:71)} \\
\end{align*} \]

\[ \begin{align*}
\text{endo-} (2R)-3a \\
85\% \text{ ee} \\
\text{exo-} (2R)-3a \\
\end{align*} \]

Heteroleptic complex covers carbonyl group and at once, makes enantiomeric reaction field.
The First Organic Catalyst

\[
C_6H_4(p-t-Bu) + C_6H_4(p-t-Bu) \xrightarrow{(12 \text{ mol\%})} \text{R}
\]

\[
\text{PhCF}_3, -20 ^\circ C, \text{p-TsOH} \cdot \text{H}_2\text{O (10 mol\%)}
\]

R= Ph: 160h, 80% (endo/exo= 7:93) 91% ee 92% ee
R= H: 45h, 93% (endo/exo= 34:66) 68% ee 86% ee

Mechanism

\[
\text{catalyst (12 mol\%)} \Rightarrow \text{exo: endo}
\]

<table>
<thead>
<tr>
<th>catalyst</th>
<th>yield</th>
<th>exo: endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99%</td>
<td>9.2: 1</td>
</tr>
<tr>
<td>2</td>
<td>12%</td>
<td>6.6: 1</td>
</tr>
<tr>
<td>3</td>
<td>13%</td>
<td>6.6: 1</td>
</tr>
</tbody>
</table>


M. P. Sibi, *et al.* *Synlett.* **2008**, *2655*.
Epimerization

B(C₆F₅)₃ Function as Bulky Groups and LLA

Catalytic anomalous end-selective enantioselective Diels-Alder reactions with α-substituted acroleins

P=O…B(C₆F₅)₃ moieties are critical not only for bulky functional group, but also for LLA catalyst.

What is LLA?

LLA= **Lewis acid assisted Lewis acid** catalyst
LLA is one of the combined acid catalysis strategies.

<table>
<thead>
<tr>
<th>Catalyst system</th>
<th>General structure</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brønsted acid assisted Lewis acid catalyst (BLA)</td>
<td><img src="image1" alt="BLA structure" /></td>
<td><img src="image2" alt="BLA examples" /></td>
</tr>
<tr>
<td>Enhancement of Lewis acidity by the combination with Brønsted acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewis acid assisted Lewis acid catalyst (LLA)</td>
<td><img src="image3" alt="LLA structure" /></td>
<td><img src="image4" alt="LLA examples" /></td>
</tr>
<tr>
<td>Enhancement of Lewis acidity by the combination with Lewis acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewis acid assisted Brønsted acid catalyst (LBA)</td>
<td><img src="image5" alt="LBA structure" /></td>
<td><img src="image6" alt="LBA examples" /></td>
</tr>
<tr>
<td>Enhancement of Brønsted acidity by the combination with Lewis acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brønsted acid assisted Brønsted acid catalyst (BBA)</td>
<td><img src="image7" alt="BBA structure" /></td>
<td><img src="image8" alt="BBA examples" /></td>
</tr>
<tr>
<td>Enhancement of Brønsted acidity by the combination with Brønsted acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In fact, the two flexible subcomponents could have a syn conformation. It is more stable than the anti conformation by 3.86 kcal/mol.

Precedent Works and Results


Catalyst

<table>
<thead>
<tr>
<th>X</th>
<th>catalyst</th>
<th>yield</th>
<th>endo:exo</th>
<th>ee</th>
<th>catalyst</th>
<th>endo:exo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>1</td>
<td>94%</td>
<td>93:7</td>
<td>&gt;99%</td>
<td>B(C₆F₅)₃</td>
<td>15:85</td>
</tr>
<tr>
<td>Cl</td>
<td>2</td>
<td>&gt;99%</td>
<td>88:12</td>
<td>&gt;99%</td>
<td>B(C₆F₅)₃</td>
<td>10:90</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>&gt;99%</td>
<td>82:18</td>
<td>98%</td>
<td>B(C₆F₅)₃</td>
<td>*49:51</td>
</tr>
</tbody>
</table>

Tuning for $\alpha$-halo-acrolein

1. Resonance effect?
2. Less selectivity
3. Is resonance effect important?

The Cavity can be Applied for Acrolein

Same strategy

\[
\text{catalyst (5 mol\%)} \quad \text{MS 4A, CH}_2\text{Cl}_2 \quad -78^\circ\text{C, 6h}
\]

- >99% yield
- endo/exo = 20/80

with \(\text{B(C}_6\text{F}_5)_3\)

- >99% yield
- endo/exo = 86/14

Molecular recognition

- acrolein:methacrolein = 1:1
- catalyst (5 mol\%)
  - >99
  - <1

Induced-fit

Mechanism

A chiral, narrow and deep cavity is assumed.

Theoretical calculations using Gaussian03 with B3LYP/6-31G* basis set.

**Endo-Selective Diels Alder**

What is the difference between *endo-* and *exo-* selective catalyst?

Acrolein-catalyst complex
A chiral, shallow and wide cavity.

Non-covalent amide-B\((C_6F_5)_3\) moiety
turn outside the complex.

The amide has a less-hindered planar structure.

Pseudo-tetrahedral phosphorus structure

Develop New Type Cavity

Excessive interaction between three bulky groups is the reason of low ee?

# Substrate Scope

\[
\text{catalyst} \quad \begin{array}{cccccc}
\text{R}_1 & \text{R}_2 & \text{yield} & \text{endo:exo} & \text{ee (major)} \\
1 & a & \text{Et} & H & >99 & 3:97 & 85 \\
2 & a & \text{Et} & H & >99 & 2:98 & 92 \\
1 & b & \text{Br} & H & 98 & 10:90 & 44 \\
2 & b & \text{Br} & H & 98 & 9:91 & 0 \\
1 & c & \text{Me} & \text{Me} & 80 & 1:>:99 & 91 \\
2 & c & \text{Me} & \text{Me} & 16 & 1:>:99 & 28 \\
1 & d & \text{H} & \text{H} & 89 & 76:24 & 86 \\
2 & d & \text{H} & \text{H} & 89 & 73:27 & 42 \\
1 & e & \text{H} & \text{CO}_2\text{Et} & 72 & 86:14 & 85 \\
2 & e & \text{H} & \text{CO}_2\text{Et} & 78 & 86:14 & 10 \\
\end{array}
\]

The Importance of Two B(C₆F₅)₃
Summary

Hydrogen bond, acid-base pair, selective interaction....
Deconvolution strategy....

Supramolecular strategy could develop a new field which conventional catalysts are useless in it.

Chiral cavity strategy
Future Prospect

Problems
Each component is still difficult to synthesize. The search for non-covalent interactions is an important task. To date, most supramolecular catalytic asymmetric reaction proceed even with conventional catalysts.

but!

Conformationally flexible catalysts are promising!
Induced-fit, tailor-made….

May supramolecular catalysis be beyond enzyme mimics?
**Scheme 1.** Preparation of Chiral Phosphoramides

$$\text{POCl}_3 \, (1.2 \text{ equiv}) \quad \text{DMAP} \, (2 \text{ equiv})$$

$$\text{Et}_3\text{N} \, (7 \text{ equiv})$$

$$\text{CH}_2\text{Cl}_2$$

$$0 \, ^\circ \text{C} \sim \text{r.t., } 2 \text{ h}$$

$$\text{EtCN}$$

$$\text{r.t.} \sim \text{reflux}$$

$$\text{TINH}_2 \, (2 \text{ equiv})$$

2 or 3

1: $\text{Ar} = \text{Ph}$

3: $\text{Ar} = 1,3,5-(\text{HPr})_3\text{C}_6\text{H}_2$

**Table 1.** Reactivity for the Diels–Alder Reactions

<table>
<thead>
<tr>
<th>entry</th>
<th>diene (equiv)</th>
<th>chiral Brønsted acid</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%) (config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>0</td>
<td>n.d</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>91</td>
<td>9 (S)</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>3</td>
<td>CH$_2$Cl$_2$</td>
<td>1</td>
<td>86</td>
<td>32 (R)</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1</td>
<td>toluene</td>
<td>3</td>
<td>&lt;10</td>
<td>n.d</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>2</td>
<td>toluene</td>
<td>3</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>3</td>
<td>toluene</td>
<td>3</td>
<td>95</td>
<td>92</td>
</tr>
</tbody>
</table>

$a$ Only endo product was observed by $^1$H NMR. $^b$ Enantiomeric excess was determined by GC analysis. $^c$ $(Z,E):(E,E) = 86:14$. $^d$ Mixture of olefin regio isomer; see Table 2.
using Chiral phosphoric acid for diels-alder

Scheme 1. Achiral Lewis Acid-Assisted Chiral Phosphoric Acid Catalysts as Chiral Acid–Base Cooperative Catalysts

PBP Rhodium Complex

\[
\begin{align*}
\text{BBr}_3 (10-15 \text{ mol\%}) & \quad \text{CH}_2\text{Cl}_2 \\
-78^\circ \text{C}, 3-5 \text{ h} & \quad \text{end}-4 + \text{exo}-4
\end{align*}
\]

Products 4, reaction time, yield, and enantioselectivity.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Endo:Exo</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>exo-4b</td>
<td>3 h, &gt;99% yield(^a)</td>
<td>endo:exo = 5:95</td>
<td>86% ee (exo)</td>
<td></td>
</tr>
<tr>
<td>endo-4c</td>
<td>4 h, 88% yield(^b)</td>
<td>endo:exo = 97:3</td>
<td>87% ee (endo)</td>
<td></td>
</tr>
<tr>
<td>endo-4d</td>
<td>3 h, &gt;99% yield(^a)</td>
<td>endo:exo = 94:6</td>
<td>91% ee (endo)</td>
<td></td>
</tr>
<tr>
<td>endo-4e</td>
<td>5 h, 88% yield(^a)</td>
<td>endo:exo = 94:6</td>
<td>94% ee (endo)</td>
<td></td>
</tr>
</tbody>
</table>

Product 10, reaction time, yield, and enantioselectivity.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Endo:Exo</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>endo-10a</td>
<td>3 h, 82% yield(^a)</td>
<td>endo:exo = \text{&gt;99:1}</td>
<td>95% ee (endo)</td>
<td></td>
</tr>
<tr>
<td>endo-10b</td>
<td>5 h, 63% yield(^b)</td>
<td>endo:exo = \text{&gt;99:1}</td>
<td>98% ee (endo)</td>
<td></td>
</tr>
<tr>
<td>endo-10c</td>
<td>5 h, 58% yield(^a)</td>
<td>endo:exo = \text{&gt;99:1}</td>
<td>92% ee (endo)</td>
<td></td>
</tr>
<tr>
<td>endo-10d</td>
<td>3 h, 96% yield(^a)</td>
<td>endo:exo = \text{99:1}</td>
<td>94% ee (endo)</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{CO}_2\text{Ph} + \text{CHO} \rightarrow \text{PhO}_2\text{C} \quad \text{Ni}\)
Table 1  Screening of Chiral Supramolecular Catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R)-3</th>
<th>Lewis acid</th>
<th>Yield (%)</th>
<th>endo-6a/exo-6a</th>
<th>ee (%) of exo-6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-3a</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>(R)-3a</td>
<td>BF$_3$Et$_2$O</td>
<td>&gt;99</td>
<td>7:93</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>(R)-3a</td>
<td>BBr$_3$</td>
<td>98</td>
<td>8:92</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>(R)-3a</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>98</td>
<td>8:92</td>
<td>-53$^b$</td>
</tr>
<tr>
<td>5$^c$</td>
<td>(R)-3a</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>&gt;99</td>
<td>8:92</td>
<td>-31$^b$</td>
</tr>
<tr>
<td>6$^d$</td>
<td>(R)-3a</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>20</td>
<td>19:81</td>
<td>-1$^b$</td>
</tr>
<tr>
<td>7</td>
<td>(R)-3b</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>(R)-3b</td>
<td>BF$_3$Et$_2$O</td>
<td>&gt;99</td>
<td>7:93</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>(R)-3b</td>
<td>BBr$_3$</td>
<td>&gt;99</td>
<td>5:95</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>(R)-3b</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>&gt;99</td>
<td>5:95</td>
<td>90</td>
</tr>
<tr>
<td>11$^c$</td>
<td>(R)-3b</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>62</td>
<td>11:89</td>
<td>8</td>
</tr>
<tr>
<td>12$^d$</td>
<td>(R)-3b</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>13</td>
<td>(R)-3c</td>
<td>–</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14</td>
<td>(R)-3c</td>
<td>BF$_3$Et$_2$O</td>
<td>98</td>
<td>6:94</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>(R)-3c</td>
<td>BBr$_3$</td>
<td>96</td>
<td>10:90</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>(R)-3c</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>&gt;99</td>
<td>8:92</td>
<td>90</td>
</tr>
<tr>
<td>17$^c$</td>
<td>(R)-3c</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>&gt;99</td>
<td>9:91</td>
<td>85</td>
</tr>
<tr>
<td>18$^d$</td>
<td>(R)-3c</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>19$^e$</td>
<td>–</td>
<td>B(C$_6$F$_5$)$_3$</td>
<td>&gt;99</td>
<td>7:93</td>
<td>–</td>
</tr>
</tbody>
</table>
PBP Cobalt Complex

\[
\begin{align*}
\text{inactive species} & \quad + \text{B(C}_6\text{F}_5)_3 \\
\text{achiral} & \quad \text{active species}
\end{align*}
\]

\[
\begin{align*}
\text{tight coordination at } -78 \degree C
\end{align*}
\]

\[
\begin{align*}
& (\text{R})-3c \text{ (1 equiv)} \\
& ^{31}\text{P NMR (CD}_2\text{Cl}_2): 4.0 \text{ ppm} \\
& + \text{B(C}_6\text{F}_5)_3 \text{ (2 equiv)} \\
& ^{19}\text{F NMR (CD}_2\text{Cl}_2): -130.2 \text{ (6F) ppm,} \\
& -147.1 \text{ (3F) ppm,} \\
& -161.4 \text{ (6F) ppm.}
\end{align*}
\]

\[
\begin{align*}
\text{CD}_2\text{Cl}_2 \\
r.t., 30 \text{ min}
\end{align*}
\]

\[
\begin{align*}
& ^{31}\text{P NMR (CD}_2\text{Cl}_2): 4.6 \text{ ppm} \\
& ^{19}\text{F NMR (CD}_2\text{Cl}_2): -137.0 \text{ (6F) ppm,} \\
& -159.5 \text{ (3F) ppm,} \\
& -166.3 \text{ (6F) ppm.}
\end{align*}
\]

ESI-MS (−): calcd for C_{14}H_{36}B_{2}F_{30}N_{2}O_{8}P^{−} \\
[M + 2H_{2}O − H^{+}] 1697.1463, found 1697.1459
### Table 2  Substrate Specificity with the Use of 2B(C₆F₅)₃-(R)-3c

<table>
<thead>
<tr>
<th>Entry</th>
<th>5 (R)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>endo-6/exo-6</th>
<th>ee (%) of exo-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5a (Me)</td>
<td>6a</td>
<td>&gt;99</td>
<td>8.92</td>
<td>90 (2S)</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>5a (Me)</td>
<td>6a</td>
<td>94 (40 °C, 3 h)</td>
<td>16.84</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>5b (Et)</td>
<td>6b</td>
<td>&gt;99</td>
<td>2.98</td>
<td>84 (2S)</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>5b (Et)</td>
<td>6b</td>
<td>73 (110 °C, 24 h)</td>
<td>24.76</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>5c (i-Pr)</td>
<td>6c</td>
<td>72</td>
<td>15.85</td>
<td>23 (2R)</td>
</tr>
<tr>
<td>6ᵇ</td>
<td>5c (i-Pr)</td>
<td>6c</td>
<td>&lt;5 (110 °C, 3 h)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>5d (Br)</td>
<td>6d</td>
<td>&gt;99</td>
<td>15.85</td>
<td>18 (2R)</td>
</tr>
<tr>
<td>8ᵇ</td>
<td>5d (Br)</td>
<td>6d</td>
<td>&gt;99 (r.t., 3 h)</td>
<td>15.85</td>
<td>–</td>
</tr>
</tbody>
</table>

![Diagram](image)

(a) 1 + 7 + (R)-3c (10 mol%) + B(C₆F₅)₃ (20 mol%) → endo-(2S,3R)-8 and exo-(2S,3R)-8

38% (endo-8/exo-8 = 1:99)

56% ee
Figure 4  Possible structures and chiral cavities of supramolecular catalysts ($Ar_r = C_6F_{14}$). (a) Syn-conformation for $2B(C_6F_5)_3-(R)-3c$. (b) Anti-conformation for $2B(C_6F_5)_3-(R)-3c$. (c) Anti-conformation for $2B(C_6F_5)_3-(R)-3c$-catecholborane.
TABLE 2. Enantioselective Diethylzinc Addition to Benzaldehyde with Conjugate Acid–Base BINOL–Zn(II) Catalysts

\[
\text{PhCHO} + \text{Et}_2\text{Zn (1.5 equiv.)} \underbrace{7-10 (3 \text{ mol\%})}_{\text{THF–toluene}} \rightarrow \text{PhCH(OH)Et (R)}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>temp</th>
<th>time (h)</th>
<th>yield (%)(^a)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-7</td>
<td>rt</td>
<td>72</td>
<td>77</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>(R)-8</td>
<td>rt</td>
<td>48</td>
<td>70</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>(R)-9</td>
<td>rt</td>
<td>48</td>
<td>81</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>(R)-10</td>
<td>rt</td>
<td>24</td>
<td>98</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>(R)-7</td>
<td>50 °C</td>
<td>12</td>
<td>60</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>(R)-8</td>
<td>50 °C</td>
<td>12</td>
<td>65</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>(R)-9</td>
<td>50 °C</td>
<td>12</td>
<td>76</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>(R)-10</td>
<td>50 °C</td>
<td>4</td>
<td>&gt;99</td>
<td>95</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield. \(^b\) Absolute configuration of product was R. The ee values were determined by chiral GC analysis.