Chiral Calcium Complexes as Brønsted Base Catalysts for Asymmetric Addition of α-Amino Acid Derivatives to α,β-Unsaturated Carbonyl Compounds

Strontium-Catalyzed Highly Enantioselective Michael Additions of Malonates to Enones

Scheidt Group Literature
Yasufumi Kawanaka, 2008.03.18
**Introduction**

Name: Shu Kobayashi  
Department of Chemistry, School of Science,  
The University of Tokyo,

**Recent Work**  
*Catalytic Aldol reaction of Amide with Aldehyde*

They developed the first highly anti-selective direct-type catalytic aldol reaction of amides ((N-Boc)acylanisidines) with aldehydes by using alkaline earth metal.

Chiral Calcium Complexes as Brønsted Base Catalysts for Asymmetric Addition of $\alpha$-Amino Acid Derivatives to $\alpha,\beta$-Unsaturated Carbonyl Compounds

\[
\begin{align*}
8 \quad &\text{(1.0 eq.)} \\
+ \quad &\text{Ph}-\text{N} \quad \text{MeO} \\
(1.1 - 1.2 \text{ eq.}) \\
\rightarrow \quad &\text{Ph} \quad \text{N} \\
\text{Metal (10 mol\%)} \\
\text{Ligand (10 mol\%)} \\
\text{Temp., THF (0.2 M)} \\
\text{MS 5A or MS 4A} \\
\rightarrow \quad &\text{Ph} \\
\text{O} \\
\text{to} \\
\text{OtBu} \\
\text{MeO} \\
\text{6a}
\end{align*}
\]

Metal: Mg(OEt)$_2$, Ca(Oi-Pr)$_2$, Sr(Oi-Pr)$_2$, Ba(Ot-Bu)$_2$

Ligand: 1, 2, 3, 4, 5

Temp.: -78°C to rt

**Optimized condition:**
Ca(Oi-Pr)$_2$ (10 mol%), Ligand 4 (10 mol%), -30°C, THF (0.2 M), MS 4A, 12 h
88% yield, 94%ee

Asymmetric [3+2] cycloaddition reactions

In case of crotonate or amidine, corresponding [3+2] cycloadduct (pyrrolidine derivative) was obtained as a single diastereomer

A plausible catalytic cycle

1) Deprotonation of the glycine derivative 1
2) 1,4 addition with α,β-unsaturated carbonyl compound to form 10
3) Protonation to give 6, or intramolecular cyclization to give 7

Summary

• They have developed novel Ca-Box catalysts prepared from Ca(Oi-Pr)_2 and bisoxazoline ligand.

• This catalyst effectively promoted two types of catalytic asymmetric additions of α-amino acid derivatives with α,β-unsaturated carbonyl compounds.

  1,4-addition reactions and [3+2] cycloaddition reactions

• This reaction system does not require an excess amount of electrophiles or the external addition of bases.
Strontium-Catalyzed Highly Enantioselective Michael Additions of Malonates to Enones

Some reports of catalytic asymmetric Michael addition

1

\[
\begin{align*}
\text{EtO}_2\text{C} + \text{ Ph}_2\text{C} &= \rightarrow \text{EtO}_2\text{C} \\
10 &+ 11 &\rightarrow &12a \ (\text{EtO}_2\text{C}) \\
& &\text{K}_2\text{CO}_3 &\rightarrow &\text{CO}_2\text{Et} \\
& &\text{toluene} &\rightarrow &99\% \text{ yield} \\
& &\text{-20 °C, 24h} &\rightarrow &90\% \text{ ee (R)} \\
\end{align*}
\]


2

\[
\begin{align*}
\text{MeO}_2\text{C} + \text{ Ph}_2\text{C} &= \rightarrow \text{MeO}_2\text{C} \\
13 &+ 11 &\rightarrow &12b \ (\text{MeO}_2\text{C}) \\
& &\text{VI} &\rightarrow &\text{CO}_2\text{Me} \\
& &\text{neat, rt} &\rightarrow &86\% \text{ yield} \\
& & &\rightarrow &84\% \text{ ee (S)} \\
\end{align*}
\]


Excess (>4 eq.) malonate is used both cases
These systems need long reaction time (max 5 d)
**Effect of metal Sources and chiral Ligands**

\[
\text{EtO}_2\text{C} + \text{Ph-\(\chi\text{-}CH=\text{-CHPh}} \xrightarrow{\text{Metal (x mol%), Ligand (1.2 x mol%)}} \text{EtO}_2\text{C}-\text{Ph-CO}_2\text{Et}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>metal ((x \text{ mol %}))</th>
<th>ligand</th>
<th>solvent</th>
<th>time ((h))</th>
<th>yield ((%)^b)</th>
<th>ee ((%)^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{d}</td>
<td>Ca(O-i-Pr\textsubscript{2}) (10%)</td>
<td>I</td>
<td>THF</td>
<td>24</td>
<td>47</td>
<td>4</td>
</tr>
<tr>
<td>2\textsuperscript{d}</td>
<td>Ca(O-i-Pr\textsubscript{2}) (10%)</td>
<td>II</td>
<td>THF</td>
<td>24</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>3\textsuperscript{d}</td>
<td>Ca(O-i-Pr\textsubscript{2}) (10%)</td>
<td>III</td>
<td>THF</td>
<td>24</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>4\textsuperscript{e}</td>
<td>Ca(O-i-Pr\textsubscript{2}) (5%)</td>
<td>III</td>
<td>toluene</td>
<td>18</td>
<td>58</td>
<td>65</td>
</tr>
<tr>
<td>5\textsuperscript{e}</td>
<td>Sr(O-i-Pr\textsubscript{2}) (5%)</td>
<td>III</td>
<td>toluene</td>
<td>18</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>6\textsuperscript{e}</td>
<td>Ba(O-i-Pr\textsubscript{2}) (5%)</td>
<td>III</td>
<td>toluene</td>
<td>18</td>
<td>80</td>
<td>76</td>
</tr>
<tr>
<td>7\textsuperscript{e}</td>
<td>Ba(O-t-Bu\textsubscript{2}) (5%)</td>
<td>III</td>
<td>toluene</td>
<td>18</td>
<td>82</td>
<td>70</td>
</tr>
<tr>
<td>8\textsuperscript{e}</td>
<td>Ba(O-t-Bu\textsubscript{2}) (5%)</td>
<td>III</td>
<td>THF</td>
<td>18</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>9\textsuperscript{d}</td>
<td>Mg(O-t-Bu\textsubscript{2}) (10%)</td>
<td>III</td>
<td>toluene</td>
<td>18</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>

Sr(Oi-Pr\textsubscript{2}) gave the desired product in high yield with high % ee

Conjugate Addition Reaction of Malonates 1a-1f and 2a

Di-\textit{n}-Pr malonate was an optimal Micheal donor. Even with 0.5mol\% of catalyst, the yield and \%ee was high.
Conjugate Addition Reaction of 1c and enone 2b-u

This system is effective for various enones

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>adduct</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-ClC₆H₄</td>
<td>Ph</td>
<td>3eb</td>
<td>76</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-ClC₆H₄</td>
<td>Ph</td>
<td>3ec</td>
<td>93</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>4-FC₆H₄</td>
<td>Ph</td>
<td>3ed</td>
<td>92</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>4-MeOC₆H₄</td>
<td>Ph</td>
<td>3ee</td>
<td>80</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>4-NO₂C₆H₄</td>
<td>Ph</td>
<td>3ef</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>3-NO₂C₆H₄</td>
<td>Ph</td>
<td>3eg</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>4-FC₆H₄</td>
<td>4-FC₆H₄</td>
<td>3ch</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>4-MeOC₆H₄</td>
<td>4-FC₆H₄</td>
<td>3ei</td>
<td>81</td>
<td>&gt;99</td>
</tr>
<tr>
<td>9</td>
<td>3,4-di-MeOC₅H₃</td>
<td>4-FC₆H₄</td>
<td>3ej</td>
<td>61</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>4-ClC₆H₄</td>
<td>4-FC₆H₄</td>
<td>3ek</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>2-ClC₆H₄</td>
<td>4-FC₆H₄</td>
<td>3el</td>
<td>80</td>
<td>93</td>
</tr>
<tr>
<td>12</td>
<td>4-FC₆H₄</td>
<td>4-MeC₆H₄</td>
<td>3cm</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>4-ClC₆H₄</td>
<td>3eu</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>14</td>
<td>Ph</td>
<td>4-FC₆H₄</td>
<td>3eo</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>15</td>
<td>Ph</td>
<td>4-MeOC₆H₄</td>
<td>3ep</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>16</td>
<td>2-thienyl</td>
<td>2-thienyl</td>
<td>3eq</td>
<td>73</td>
<td>97</td>
</tr>
<tr>
<td>17</td>
<td>5-methylfuran-2-yl</td>
<td>Ph</td>
<td>3er</td>
<td>71</td>
<td>96</td>
</tr>
<tr>
<td>18</td>
<td>Ph</td>
<td>1-pyrrolyl</td>
<td>3es</td>
<td>93</td>
<td>99</td>
</tr>
<tr>
<td>19</td>
<td>Ph</td>
<td>−CH==CHPh</td>
<td>3et</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>20</td>
<td>−CH==CHPh</td>
<td>Ph</td>
<td>3eu</td>
<td>62</td>
<td>97</td>
</tr>
</tbody>
</table>
NMR spectroscopic studies

Free $i$-PrOH peak was detected by $^{13}$C, $^1$H-NMR, after Sr(O$i$-Pr)$_2$ was reacted with L III.

After malonate was added, three new peaks resonating at $\delta$ 174.6, 64.6 and 49.7 was shown.
Summary

- They have developed a novel Sr based catalyst, prepared from Sr(Oi-Pr)$_2$ and bissulfonamide.

- This catalyst effectively promoted the conjugate addition of malonates to a wide variety of calcone derivatives.

- This reaction system does not require an excess amount of malonates or long reaction times.

- The reaction are performed at room temperature and the catalyst loading can be reduced to 0.5mol%.