Catalytic Enhancement Effect of a Chiral Ligand on the Asymmetric Mannich-Type Reactions of Menthyl Alkanoates with Aldimines

Seiji Hata, Tetsuo Iwasawa, Mayu Iguchi, Ken-ichi Yamada, Kiyoshi Tomioka*
Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
Fax +81(75)7534604; E-mail: tomioka@pharm.kyoto-u.ac.jp
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Abstract: The lithium enolate of menthyl acetate underwent the Mannich-type reaction with benzaldehyde PMP-imine in toluene to give the corresponding adduct with 70:30 dr. The diastereoselectivity was dramatically improved to 97:3 dr by the addition of chiral 1,2-diphenyl-1,2-dimethoxyethane. The reaction of menthyl isobutyrate with imines was also influenced by a catalytic amount (5 mol%) of a chiral tridentate aminodiether ligand to give the corresponding β-lactams in high enantioselectivities. Matching and mismatching phenomena were observed by the reaction of L- and D-menthyl isobutyrates.

Key words: addition reactions, asymmetric synthesis, asymmetric catalysis, imines, lithium

Lithium enolates of alkanoates are easily generated by treating alkanoates with lithium diisopropylamide and enable reactions at the α-position of the ester carbonyl group with a variety of electrophiles.1 Since alkanoates are shelf-stable chemical species, the lithium enolates thereof have more advantage than the corresponding silyl enol ethers that require special care for storing. It is also important to note that the lithium enolates have powerful reactivity higher than the silyl enol ethers that usually react with electrophiles through activation by Lewis acids. We describe herein that the chiral diether and aminodiether ligands enhance the reactivity and stereoselectivity of the lithium enolate of chiral menthyl alkanoates in the Mannich-type reaction with imines to give the corresponding 3-amino esters and β-lactams with excellent stereoselectivity.

The asymmetric Mannich-type reaction of lithium chiral alkanoates with imines is a powerful methodology for the synthesis of chiral 3-aminooalkanoates.2 Many efficient chiral auxiliaries have been developed for this purpose.3,4 We began our studies with an asymmetric reaction of menthyl alkanoates, because both enantiomers of menthol are commercially available as a chiral auxiliary.5 We studied our works with an asymmetric reaction of menthyl alkanoates, because both enantiomers of menthol are commercially available as a chiral auxiliary.5 Our idea is based on the enhancement of reactivity and enantioselectivity of a chiral lithium enolate by a chiral ligand.5,7

A lithium enolate of L-menthyl acetate (1), prepared from 1 with 2 equivalents of LDA in toluene, underwent a Mannich-type reaction with benzaldehyde PMP (para-methoxyphenyl)imine 3 at 0 °C for two hours to afford an addition product 4 in 16% yield (Scheme 1). The diastereoselectivity was determined to be 70:30 dr by 1H and 13C carbon NMR (Table 1, entry 1). Upon addition of a chiral diether ligand 6,6 enhancement effect was observed at −20 °C for two hours to afford 4 with 97:3 dr in 54% yield (entry 2) (Figure 1).9 Mismatching was observed in the reaction of ent-1 (D-menthyl acetate) with 6 to give ent-4 with 60:40 dr in 47% yield (entry 3). These results indicate that the chiral ligand 6 affects the reactivity and stereoselectivity of the lithium enolate of 1 in toluene. In THF the reaction of 1 with 3 at −30 °C for four hours gave 4 with 96:4 dr in 76% yield. It is important to note that no ligand effect was observed with THF as solvent.

Scheme 1 Asymmetric Mannich reaction of 1 and 2 with 3

Figure 1 Chiral ligands 6 and 7

The reaction of a lithium enolate of menthyl propanoate (2), prepared from 2 and 2.2 equivalents of LDA with 3 in THF at −30 °C for 30 minutes gave a 5:1 mixture of 5a and 5b with both >98:2 dr in 90% yield (entry 4). Stereochemistry including the absolute configuration was determined by converting 5a and 5b to trans-8a and cis-8b with both >96% optical purities in 90% yields (Scheme 2). It is interesting to find that the reaction of a lithium enolate of 2, prepared with 1.2 equivalents of LDA, at −78 °C for 30 minutes gave a reversed 5:1 mixture of 5a and 5b with both >88:12 dr in 90% yield. Since
the enantioselectivity of these reactions is so high, further studies to evaluate a chiral ligand effect in toluene were not carried out.

The reaction of methyl isobutyrate (9) is interesting (Scheme 3). The reaction of a lithium enolate of 9, prepared with 1.2 equivalents of LDA in THF, proceeded smoothly at −20 °C for two hours to give directly \( \beta \)-lactam with 92:8 er (enantiomeric ratio) quantitatively. In toluene the reaction took five hours at room temperature for completion to afford 10 with 75:25 er in 95% yield (Table 2, entry 1). Enantioselectivity enhancement was observed upon addition of 5 mol% of a chiral diether ligand 6 at −10 °C for eight hours to give 10 with 97:3 er in 93% yield (entry 2). Mismatching was observed for the reaction of \( \text{ent-9} \) under the effect of 5 mol% of 6 at –10 °C for 15 hours to afford 10 with 60:40 er in 95% yield (entry 3). Dramatic observation was the effect by a chiral aminodiether tridentate ligand 7 at −35 °C for twelve hours to give 10 with 97:3 er in 93% yield (entry 4). The reaction of \( \text{ent-9} \) in the presence of 5 mol% of 7 at −20 °C for four hours was the mismatching to give almost racemic 10 with 54:48 er in 95% yield (entry 5).

Matching and mismatching catalytic effects were also observed in the reaction of 9 with cinnamaldehyde PMP-imine 11 (Scheme 4). In the absence of a chiral ligand, 71% yield of \( \beta \)-lactam 12 with 88:12 er was obtained at 0 °C for two hours. A conjugate addition product 13 with 59:41 er was also obtained in 10% yield (Table 3, entry 1). Upon addition of 6 (5 mol%) to the reaction mixture at –20 °C for 20 hours, 12 with 96:4 er was obtained in 62% yield together with 10% of 13 with 65:35 er (entry 2). Reaction pathway was influenced by 7 (5 mol%) to give 12 with 95:5 er in 34% yield together with 28% of 13 with 73:27 er (entry 3). Mismatching was observed in the reaction of \( \text{ent-9} \) and 7 (5 mol%) to give \( \text{ent-12} \) with

### Table 1 Mannich Reaction of 1 and 2 with 3 in Toluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr</th>
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</thead>
<tbody>
<tr>
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<td>none</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<td>2</td>
<td>1</td>
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<td>−20</td>
<td>2</td>
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<td>54</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>( \text{ent-1} )</td>
<td>6</td>
<td>−20</td>
<td>2</td>
<td>( \text{ent-4} )</td>
<td>47</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>none</td>
<td>−30</td>
<td>0.5</td>
<td>5</td>
<td>90</td>
<td>98:2</td>
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</tbody>
</table>

* 1.2 Equiv of 6 was used. Entry 4 was carried out in THF. In entry 4, a 1:5 mixture of 5a and 5b was obtained.

### Table 2 Mannich Reaction of 9 with 3 in Toluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand*</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>er</th>
</tr>
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<tbody>
<tr>
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<td>none</td>
<td>r.t.</td>
<td>5</td>
<td>10</td>
<td>95</td>
<td>75:25</td>
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<tr>
<td>2</td>
<td>9</td>
<td>6</td>
<td>−10</td>
<td>8</td>
<td>10</td>
<td>99</td>
<td>88:12</td>
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<tr>
<td>3</td>
<td>( \text{ent-9} )</td>
<td>6</td>
<td>−10</td>
<td>15</td>
<td>( \text{ent-10} )</td>
<td>85</td>
<td>64:36</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>7</td>
<td>−35</td>
<td>12</td>
<td>10</td>
<td>93</td>
<td>97:3</td>
</tr>
<tr>
<td>5</td>
<td>( \text{ent-9} )</td>
<td>7</td>
<td>−20</td>
<td>4</td>
<td>10</td>
<td>95</td>
<td>54:48</td>
</tr>
</tbody>
</table>

* A catalytic amount (5 mol%) of 6 and 7 was used.
The reaction of 9 with 3-phenylpropanal PMP-imine 14 was also an example of catalytic ligand effects (Scheme 5). In the absence of a chiral ligand the reaction of the lithium enolate in toluene proceeded at 0 °C for two hours to give 15a with 71:29 er in 72% yield (Table 4, entry 1). Upon addition of 6 (5 mol%), the reaction proceeded at –20 °C for one hour to give 15 with 74:26 er in 74% yield (entry 2). The reaction of ent-9 in the presence of 6 at –20 °C for two hours gave ent-15 with 58:42 er in 76% yield (entry 3). The reactions of 9 and ent-9 in the presence of 7 (5 mol%) gave 15 with 76:24 er and 52:48 er, respectively (entries 4 and 5).

In conclusion, we have succeeded in the observation of the chiral ligand enhancement effects on the reactivity and stereoselectivity of lithium enolates of menthyl alkanoates in the Mannich-type addition reaction with imines. Full availability of the chiral ligands and L- and D-menthol auxiliaries guarantees complementary use thereof.

### Table 3: Mannich Reaction of 9 with 11 in Toluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product 12</th>
<th>Yield (%)</th>
<th>er</th>
<th>Product 13</th>
<th>Yield (%)</th>
<th>er</th>
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<tbody>
<tr>
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<td>0</td>
<td>2</td>
<td>12</td>
<td>71</td>
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<td>10</td>
<td>59:41</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>6</td>
<td>–20</td>
<td>20</td>
<td>12</td>
<td>62</td>
<td>96:4</td>
<td>13</td>
<td>10</td>
<td>65:35</td>
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<td>9</td>
<td>7</td>
<td>–20</td>
<td>16</td>
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<td>73:27</td>
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<tr>
<td>4</td>
<td>ent-9</td>
<td>7</td>
<td>–20</td>
<td>16</td>
<td>ent-12</td>
<td>24</td>
<td>84:16</td>
<td>ent-13</td>
<td>43</td>
<td>55:45</td>
</tr>
</tbody>
</table>

* A catalytic amount (5 mol%) of 6 and 7 was used.

Melting points are uncorrected. Specific rotations were taken with a Jasco DIP-370 digital polarimeter. IR spectra were taken with a Shimadzu IR-435 IR spectrometer and are expressed in cm⁻¹. ¹H and ¹³C NMR spectra were taken with a Jeol EX-500 spectrometer at 500 MHz (¹H) and 125 MHz (¹³C). Chemical shift values are expressed in ppm relative to internal tetramethylsilane. MS spectra were taken with a Shimadzu GCMS-QP5000 mass spectrometer. HPLC analysis was carried out using Daicel Chiralcel OD-H and Chiralpak AD. Column chromatography was carried out with silica gel, Fuji Silysia BW200. Reactions were performed in an oven-dried glassware under argon. Toluene and THF were purchased as anhydrous solvents from Kanto Chemicals Co. Inc.

### Table 4: Mannich Reaction of 9 with 14 in Toluene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>er</th>
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</thead>
<tbody>
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<td>0</td>
<td>2</td>
<td>15</td>
<td>72</td>
<td>71:29</td>
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<tr>
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<td>–20</td>
<td>2</td>
<td>15</td>
<td>74</td>
<td>74:26</td>
</tr>
<tr>
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<td>ent-9</td>
<td>6</td>
<td>–20</td>
<td>2</td>
<td>ent-15</td>
<td>76</td>
<td>58:42</td>
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<td>9</td>
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<td>–20</td>
<td>1</td>
<td>15</td>
<td>86</td>
<td>76:24</td>
</tr>
<tr>
<td>5</td>
<td>ent-9</td>
<td>7</td>
<td>–20</td>
<td>1</td>
<td>15</td>
<td>86</td>
<td>52:48</td>
</tr>
</tbody>
</table>

* A catalytic amount (5 mol%) of 6 and 7 was used.
1H NMR (CDCl₃): δ = 0.44 and 0.64 (each 3 H, d, J = 7.0 Hz), 0.79–0.92 (5 H, m), 1.01 (1 H, m), 1.11 (3 H, d, J = 7.0 Hz), 1.33 (1 H, m), 1.44 (1 H, m), 1.57–1.67 (3 H, m), 1.75 (1 H, m), 1.91 (1 H, m), 2.92 (1 H, m), 3.67 (3 H, s), 4.13 (1 H, br s), 4.65 (1 H, ddd, J = 11.0, 11.0, 4.3 Hz), 4.70 (1 H, d, J = 5.2 Hz), 6.42 and 6.65 (each 2 H, d, J = 8.9 Hz), 7.21 (1 H, m), 7.27–7.34 (4 H, m).

13C NMR (CDCl₃): δ = 15.4, 15.8, 20.6, 21.9, 23.1, 25.6, 31.3, 34.1, 40.8, 46.5, 47.0, 55.7, 61.2, 74.3, 114.4, 114.7, 127.0, 127.4, 128.5, 141.0, 141.4, 151.9, 173.9.

5b
IR (KBr): 1716, 3391 cm⁻¹.

1H NMR (CDCl₃): δ = 0.60 and 0.74 (each 3 H, d, J = 7.0 Hz), 0.79–0.92 (5 H, m), 1.01 (1 H, m), 1.11 (3 H, d, J = 7.0 Hz), 1.33 (1 H, m), 1.44 (1 H, m), 1.57–1.67 (3 H, m), 1.75 (1 H, m), 1.81 (1 H, m), 2.75 (1 H, m), 3.67 (3 H, s), 4.39 (1 H, d, J = 8.3 Hz), 4.45 (1 H, br s), 6.46 (1 H, d, J = 11.0, 11.0, 4.3 Hz), 6.45 and 6.65 (each 2 H, d, J = 8.9 Hz), 7.21 (1 H, m), 7.27–7.34 (4 H, m).

13C NMR (CDCl₃): δ = 15.3, 15.8, 20.6, 21.9, 23.1, 25.8, 31.3, 34.1, 40.8, 46.9, 47.5, 55.7, 61.2, 74.3, 114.4, 114.7, 127.1, 127.4, 128.5, 141.0, 141.4, 151.9, 174.8.

MS: m/z = 423 (M⁺).

(3S,4R)-1-(4-Methoxyphenyl)-3-methyl-4-phenylazetidin-2-one (8a)
Typical Procedure
A solution of LHMDS (0.15 mmol) in THF (0.44 mL) was added to a solution of 2a and 5b obtained above (55 mg, 0.13 mmol) in THF (1.4 mL) at –10 °C and stirred for 0.5 h. The reaction was quenched with aq. sat. NH₄Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried (Na₂SO₄). Concentration and silica gel column chromatography (hexane–EtOAc, 9:1) gave a 5:1 mixture of 5a and 5b (379 mg, 90%) as a solid. Recrystallization (380 mg) from EtOH gave a 1:4 mixture of 5a and 5b (56 mg) as colorless needles. Concentration of the mother liquor gave a 97:3 mixture of 5a and 5b (300 mg). The structures including absolute configurations were determined by converting to known 8a and 8b.⁷,

(3S,4R)-1-(4-Methoxyphenyl)-3-methyl-4-phenylazetidin-2-one (8b)
The same procedure for 8a gave, after silica gel column chromatography (hexane-acetone, 9:1), 8b of [α]D₂⁵ +57.3 (c = 1.00, CHCl₃) in 90% yield. The data are identical with those reported.⁸,¹⁰ The optical purity was determined to be over 99% by comparison of its specific rotation with that reported.

(5S)-1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenylazetidin-2-one (8c)
Typical Procedure
A solution of menthol isobutyrate (9, 453 mg, 2.0 mmol) and 7 (15.0 mg, 0.05 mmol) in toluene (4 mL) was added dropwise over 5 min to a solution of LDA (2.2 mmol) in toluene (3 mL) at –78 °C and the resulting mixture was stirred at –20 °C for 1.5 h. A solution of imine 3 (211 mg, 1.0 mmol) in toluene (3 mL) was added dropwise over 5 min to the mixture and stirred at –35 °C for 12 h. The reaction was quenched with 10% HCl (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H₂O (20 mL), aq. sat. NaHCO₃ (20 mL) and brine (20 mL), and then dried (Na₂SO₄). Concentration and silica gel column chromatography (hexane-acetone, 9:1) gave 10a (263 mg, 93%) as colorless needles; mp 97.0–101.0 °C; [α]D₂⁵ +129 (c = 1.01, CHCl₃). The er was determined to be 96:4 by HPLC analysis [Daicel Chiralcel OD-H, hexane–i-PrOH, 100:1, 1.0 mL/min, 254 nm, 17.2 min (3%, R): 19.9 min (97%, S)].

(4S,5R)-1-(4-Methoxyphenyl)-3,3-dimethyl-4-[(E)-2-phenylethenyl]azetidin-2-one (12)
Typical Procedure
A solution of 9 (453 mg, 2.0 mmol) and 6 (12.1 mg, 0.05 mmol) in toluene (4 mL) was added dropwise over 5 min to a solution of LDA (2.2 mmol) in toluene (20 mL) at –78 °C and the resulting mixture was stirred at –20 °C for 1.5 h. A solution of imine 11 (237 mg, 1.0 mmol) in toluene (9 mL) was added dropwise over 5 min to the mixture and stirred at –20 °C for 20 h. The reaction was quenched with 10% HCl (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H₂O (20 mL), aq. sat. NaHCO₃ (20 mL) and brine (20 mL), and then dried (Na₂SO₄). Concentration and silica gel column chromatography (hexane–EtOAc, 9:1) gave 12a (189 mg, 62%) as a yellow gum; [α]D₂⁵ +128.6 (c = 1.01, CHCl₃) and 12b (32 mg, 10%) as a yellow gum; [α]D₂⁵ +66.7 (c = 0.38, CHCl₃).

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The er was determined to be 96:4 by HPLC analysis [Daicel Chiralpak AD, hexane–i-PrOH, 20:1, 1.0 mL/min, 254 nm, 17.3 min (4%, R), 25.9 min (96%, S)].

IR (CHCl₃): 1730 cm⁻¹.

1H NMR (CDCl₃): δ = 1.25, 1.45 and 3.76 (each 3 H, s), 4.31 (1 H, d, J = 8.2 Hz), 6.24 (1 H, dd, J = 8.2, 16.2 Hz), 6.73 (1 H, d, J = 16.2 Hz), 6.84 (2 H, m), 7.26–7.40 (7 H, m).

13C NMR (CDCl₃): δ = 17.9, 22.5, 55.5, 65.5, 114.3, 118.3, 125.3, 126.6, 128.3, 128.7, 132.0, 135.0, 136.0, 155.9, 170.8.

MS: m/z = 307 (M⁺).
A Chiral Ligand Effect on Stereoselectivity Enhancement of Lithium Enolates

MS: m/z = 307 (M+).

(S)-1-(4-Methoxyphenyl)-3,3-dimethyl-4-phenethylazetidin-2-one (15) (Table 4, entry 4)
A solution of 9 (453 mg, 2.0 mmol) and 7 (15 mg, 0.05 mmol) in toluene (3 mL) was added dropwise over 5 min to a solution of LDA (2.2 mmol) in toluene (3 mL) at –78 °C and the resulting mixture was stirred at –20 °C for 1.5 h. A solution of imine 14 (239 mg, 1.0 mmol) in toluene (3 mL) was added dropwise over 5 min to the reaction mixture and stirred at –20 °C for 1 h. The reaction was quenched with 10% HCl (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with H2O (20 mL), aq sat. NaHCO3 (20 mL) and brine (20 mL), and then dried (Na2SO4). Concentration and silica gel column chromatography (hexane–EtOAc, 9:1) gave 15 (266 mg, 86%) as a yellow oil; [α]D25 +28.9 (c = 2.32, CHCl3). The er was determined to be 76:24 by HPLC analysis [Daicel Chiralcel OD-H, hexane–i-ProOH, 30:1, 1.0 mL/min, 254 nm, 19.0 min (24%, R), 23.8 min (76%, S)].

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References
(9) The absolute configuration was determined by converting into the known compound (See, Ref. 5).

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