Primary Amino Acid Lithium Salt-Catalyzed Asymmetric Michael Addition of Carbon Nucleophiles to Enones

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Abstract: Asymmetric Michael addition of carbon nucleophiles, nitroalkanes and a β-ketoester, to enones was investigated by using a primary amino acid lithium salt as a catalyst.

Keywords: amino acid; asymmetric synthesis; organocatalysis; michael addition

1. Introduction

Michael addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is one of the most important synthetic methodologies to create a new carbon-carbon bond at the β-position of the carbonyl group. In the case of obtaining a Michael adduct enantioselectively, organocatalytic asymmetric synthesis has been recognized as an important candidate, as a result of explosive growth of organocatalysis in the past decade [1–5]. As pioneering works in organocatalytic asymmetric Michael addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds, Yamaguchi’s group reported that Michael addition of malonates to enones could be catalyzed by a proline alkali metal salt [6–12]. They later succeeded in the asymmetric Michael addition of nitroalkanes to enones using a proline rubidium salt-catalyst [13–32]. We recently reported that an O-silylated L-serine lithium salt was an effective catalyst for asymmetric Michael addition of malonates to enones to give various 1,5-ketoesters in good yields with high enantioselectivity [33]. In this context, we planned employing various carbon nucleophiles as Michael donors to investigate the generality of a primary amino acid lithium salt-catalysis in asymmetric Michael addition reactions. In this report, we disclose the details
of Michael addition reactions of nitroalkanes to enones catalyzed by a primary amino acid lithium salt (Figure 1). Results obtained by employing a β-ketoester as a Michael donor are also described.

Figure 1. Catalysts used in the Michael addition of carbon nucleophiles to enones.

\[ \text{Figure 1.} \]

\[ \text{Catalysts used in the Michael addition of carbon nucleophiles to enones.} \]

\[ \text{NH}_2 \text{CO}_2\text{Li} \]

\[ \text{TBSO} \]

\[ \text{TBS} = \text{tert-Butyldimethylsilyl} \]

\[ \text{TIPS} = \text{Triisopropylsilyl} \]

\[ \text{TBDPS} = \text{tert-Butyldiphenylsilyl} \]

2. Results and Discussion

Initially, we attempted Michael addition of 2-nitropropane (2a) to 2-cyclohexen-1-one (3a) to optimize the reaction conditions. A brief solvent screen in the presence of O-tert-butyldimethylsilyl L-serine lithium salt, Ser(O-TBS)-OLi, (1a) as a catalyst indicated that the Michael addition reaction proceeds smoothly in a high polarity solvent such as DMSO or MeOH; however, a Michael adduct, 3-(2-nitropropan-2-yl)cyclohexanone (4a), was obtained with poor enantioselectivity (Table 1, entries 1 and 2). On the other hand, in a lower polarity solvent, much better enantioselectivity was observed, though the reaction was sluggish (Table 1, entries 3–7). Interestingly, in cyclohexane, which is a very low polarity solvent, the Michael addition reaction proceeded well to give γ-nitroketone 4a in a good yield (69%) with the best enantioselectivity (70% ee) (Table 1, entry 8). Therefore, cyclohexane was chosen as a solvent for further investigations.

Table 1. Solvent screen for the Michael addition of 2a to 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Conv. b (%)</th>
<th>Yield c (%)</th>
<th>ee d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMSO</td>
<td>100</td>
<td>72</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>100</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>11</td>
<td>11</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>AcOEt</td>
<td>24</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>27</td>
<td>22</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>41</td>
<td>28</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>60</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>Cyclohexane</td>
<td>94</td>
<td>69</td>
<td>70</td>
</tr>
</tbody>
</table>

a The reaction was carried out with 2a (0.6 mol), 3a (0.5 mmol) and 1a (0.15 mmol) in a solvent (1 mL) at 25 °C for 72 h; b Determined by GC; c Isolated yield based on 3a; d Determined by Chiral HPLC analysis. The absolute configuration of a major enantiomer of 4a was determined as S by comparison with the authentic sample synthesized according to the literature [14].
We then synthesized various siloxy amino acids and their alkali metal salts from L-serine, L-threonine (Thr) and L-tyrosine (Tyr) to perform a catalyst screen in cyclohexane (Table 2) [33–40]. Since L-serine derived catalyst 1a gave better results in both yield and enantioselectivity of 4a than did Thr(O-TBS)-OLi (1b) and Tyr(O-TBS)-OLi (1c), L-serine was selected as a basic amino acid and used for further modification of the catalyst (Table 2, entries 1–3). As for a silyl group, the trisopropylsilyl (TIPS) group was chosen as a protective group of the hydroxyl group of L-serine, since Ser(O-TIPS)-OLi (1d) gave a better enantioselectivity than did the TBS-protected catalyst 1a and also gave a much better yield of 4a than did a tert-butyldiphenylsilylated catalyst, Ser(O-TBDPS)-OLi (1e) (Table 2, entries 1, 4 and 5). Finally, we examined the effects of alkali metals of Ser(O-TIPS)-OM (1f–j) and found that the lithium salt catalyst 1d gave the best enantioselectivity as was found in our previous studies (Table 2, entries 4, 6–10) [33,41–44]. Since the Michael adduct 4a was obtained with high enantioselectivity in a moderate yield, catalyst 1d was chosen as a catalyst.

Table 2. Catalyst screen for the Michael addition of 2a to 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ser(O-TBS)-OLi, 1a</td>
<td>94</td>
<td>69</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Thr(O-TBS)-OLi, 1b</td>
<td>84</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>Tyr(O-TBS)-OLi, 1c</td>
<td>79</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>Ser(O-TIPS)-OLi, 1d</td>
<td>91</td>
<td>46</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>Ser(O-TBDPS)-OLi, 1e</td>
<td>96</td>
<td>28</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Ser(O-TIPS)-ONa, 1f</td>
<td>100</td>
<td>76</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>Ser(O-TIPS)-OK, 1g</td>
<td>100</td>
<td>64</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>Ser(O-TIPS)-ORb, 1h</td>
<td>100</td>
<td>65</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>Ser(O-TIPS)-OCs, 1i</td>
<td>100</td>
<td>66</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>Ser(O-TIPS)-OH, 1j</td>
<td>0</td>
<td>0</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

*The reaction was carried out with 2a (0.6 mol), 3a (0.5 mmol) and a catalyst 1 (0.15 mmol) in cyclohexane (1 mL) at 25 °C for 72 h; ‡ Determined by GC; § Isolated yield of 4a based on 3a; ¶ Determined by Chiral HPLC analysis.

Further optimization of the reaction conditions for the Michael addition of 2a to 3a was examined to improve the yield of 4a (Table 3). By increasing the amount of 2a, mass balance of the reaction was improved greatly to produce 4a in a higher yield, while the enantioselectivity was gradually decreased (Table 3, entries 1–3). It was found that the amount of solvent also affected both mass balance and enantioselectivity of the reaction, and a better result was obtained by carrying out the reaction in a diluted condition, though the reaction was slow (Table 3, entry 4).

Under the optimized reaction conditions, we examined substrate scope with various enones 3 and nitroalkanes 2 (Table 4). Reaction of 2a with 2-cyclopenten-1-one (3b), a smaller cyclic enone than 3a, gave a Michael adduct 4b in a moderate yield; however, the enantioselectivity was quite low (Table 4, entry 2) [45]. On the other hand, the reaction of 2a with 2-cyclohepten-1-one (3c), a larger cyclic enone than 3a, was sluggish and gave a Michael adduct 4c in a low yield with high enantioselectivity (Table 4, entry 3). Enone 3c might be too bulky to smoothly form an imine intermediate with
catalyst 1d, and enone 3b might be too small to control the geometry of the corresponding imine intermediate [46]. Then acyclic enones were also subjected to the reaction conditions. As a result, benzalacetone (3d) gave a Michael adduct 4d in a good yield with moderate enantioselectivity, although no reaction was observed when chalcone (3e) was employed as a substrate (Table 4, entries 4 and 5). As for nitroalkanes, nitroethane (2b) and nitromethane (2c) were also examined in the Michael addition reaction with 3a (Table 4, entries 6 and 7). While enone 3a was smoothly consumed to give the corresponding Michael adducts 4f and 4g, generation of high-polarity compounds reduced the yield of the Michael adducts [47].

Table 3. Optimization of reaction conditions for the Michael addition of 2a to 3a using catalyst 1d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2a (equiv.)</th>
<th>Conc. (M)</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>0.5</td>
<td>91</td>
<td>46</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>0.5</td>
<td>97</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>0.5</td>
<td>98</td>
<td>82</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>5.0</td>
<td>0.1</td>
<td>76</td>
<td>70</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>5.0</td>
<td>neat</td>
<td>59</td>
<td>48</td>
<td>70</td>
</tr>
</tbody>
</table>

*a* The reaction was carried out with 3a (0.5 mmol), 2a and 1d (0.15 mmol) in cyclohexane (1 mL: 0.5 M, 5 mL: 0.1 M) at 25 °C for 72 h; *b* Concentration of 3a in cyclohexane; *c* Determined by GC; *d* Isolated yield of 4a based on 3a; *e* Determined by Chiral HPLC analysis.

Table 4. Substrate scope in the Michael addition of nitroalkanes 2 to enones 3 catalyzed by 1d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2, R&lt;sup&gt;1&lt;/sup&gt;, R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>3, R&lt;sup&gt;3&lt;/sup&gt;, R&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Conv. (%)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a, Me, Me</td>
<td>3a, –(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;−</td>
<td>76</td>
<td>70, 4a</td>
<td>77</td>
</tr>
<tr>
<td>2</td>
<td>2a, Me, Me</td>
<td>3b, –(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;−</td>
<td>– e</td>
<td>53, 4b</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>2a, Me, Me</td>
<td>3c, –(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;−</td>
<td>44</td>
<td>20, 4c</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>2a, Me, Me</td>
<td>3d, Me, trans-Ph</td>
<td>73</td>
<td>69, 4d</td>
<td>51</td>
</tr>
<tr>
<td>5</td>
<td>2a, Me, Me</td>
<td>3e, Ph, trans-Ph</td>
<td>0</td>
<td>0, 4e</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>2b, Me, H</td>
<td>3a, –(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;−</td>
<td>100</td>
<td>70, 4f</td>
<td>50, 38 f</td>
</tr>
<tr>
<td>7</td>
<td>2c, H, H</td>
<td>3a, –(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;−</td>
<td>94</td>
<td>50, 4g</td>
<td>55</td>
</tr>
</tbody>
</table>

*a* The reaction was carried out with 3 (0.5 mmol), 2 (2.5 mmol) and 1d (0.15 mmol) in cyclohexane (5 mL) at 25 °C for 72 h; *b* Determined by GC; *c* Isolated yield of 4a based on 3a; *d* Determined by Chiral HPLC analysis; *e* The amount of recovered 3b could not be estimated by GC analysis due to the low boiling-point of 3b, though 3b was detected by TLC analysis after the reaction had been stopped; *f* Michael adduct 4g was obtained as a mixture of diastereomers (dr = 1.01:1).
Finally, we employed a β-ketoester, ethyl benzoylketacetate (5), as a Michael donor. Although Michael addition of β-ketoesters to enones is an attractive method to obtain 1,5-diketones, to the best of our knowledge, highly enantioselective Michael addition of 5 to 3a has never been reported [48–51]. After a series of solvent screening, catalysts, concentrations and molar ratios of reagents were examined, as in the case of the Michael addition of 2a to 3a, and the best reaction conditions were determined as shown in Equation 1. Under the best reaction conditions, a Michael adduct 6 was successfully obtained in 84% yield with 59% ee. Since the α-proton of the β-ketoester moiety is acidic, the Michael adduct 6 was obtained as a 1:1 mixture of diastereomers. Further optimization of the reaction conditions and investigation of substrate scope with various ketoesters and enones are underway by our group.

$$\text{Ph} - \text{COOEt} \text{  } 5, 2 \text{ equiv.} + \text{ 3a} \underset{\text{DMSO (0.1 M)}}{\xrightarrow{1e, 30 \text{ mol\%}}} \text{Ph} - \text{COOEt} \text{ 6} \text{ 84\%, 59\% ee}$$

(Eq. 1)

3. Experimental Section

3.1. General

IR spectra were recorded using a JASCO FT/IR-5300 spectrometer. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on JEOL JNM-A400II FT NMR and ECX-400P. Chemical shifts, δ are referred to TMS. Optical rotation was measured by JASCO P-2200. HPLC was carried out using a JASCO PU-2089 Plus intelligent pump and a UV-2075 Plus UV detector. Nitroalkanes 2, enones 3 and ethyl benzoyleacetate (5) were used after distillation. Catalysts 1 were synthesized according to the literatures [34–39].

3.2. Typical Procedure for the Michael Addition of Nitroalkanes to Enones

In a 10 mL vial, 2-nitropropane (2a) (223 mg, 2.5 mmol) was added to a mixture of Ser(O-TIPS)-OLi (1d) (40 mg, 0.15 mmol), 2-cyclohexen-1-one (3a) (48 mg, 0.5 mmol) and cyclohexane (5 mL) at 25 °C. After stirring for 72 h at 25 °C, the reaction mixture was filtered through a thin silica gel layer by washing a small amount of Et₂O. Obtained organic phase was then concentrated under reduced pressure. The Michael adduct, (S)-3-(2-nitropropan-2-yl)cyclohexanone (4a), was isolated by column chromatography (silica gel, hexane/Et₂O) in 70% yield (65 mg) as white solid. The enantioselectivity was determined by HPLC analysis (77% ee, Daicel CHIRALPAK AD-H, 5% isopropanol/hexane, 1.0 mL/min, 229 nm; $t_r$(major enantiomer) = 18.8 min, $t_r$(minor enantiomer) = 20.0 min). δ$(\text{CDCl}_3)$ 1.37–1.48 (1H, m), 1.53–1.69 (1H, m), 1.57 (3H, m), 1.58 (3H, s), 1.77–1.84 (1H, m), 2.09–2.18 (2H, m), 2.21–2.29 (1H, m), 2.34–2.46 (3H, m); δ$(\text{CDCl}_3)$ 22.6, 23.7, 24.5, 26.1, 40.9, 42.8, 46.7, 90.7, 209.1; ν(KBr)/cm⁻¹ 1724 (C=O), 1535 (NO₂); $\alpha$D$^{217}$ = 15.0 (c = 1.0, CHCl₃, 77% ee).

Spectroscopic data of γ-nitroketones 4 are in agreement with published data [13–32].
3.3. (S)-3-(2-Nitropropan-2-yl)cyclopentanone (4b)

HPLC (15% ee, Daicel CHIRALPAK AD-H, 5% isopropanol/hexane, 1.0 mL/min, 229 nm; 
*t*(major enantiomer) = 15.4 min, *t*(minor enantiomer) = 16.8 min). δ(CDCl3) 1.62–1.74 (1H, m), 
1.62 (3H, s), 1.63 (3H, s), 2.03–2.14 (2H, m), 2.20–2.44 (3H, m), 2.81–2.90 (1H, m); 
δ(CDCl3) 23.3, 23.5, 24.3, 38.5, 40.0, 45.5, 89.4, 215.6; ν(neat)/cm\(^{-1}\) 1747 (C=O), 1539 (NO\(_2\)); [α]\(_D\)\(^{23.1} \) − 13.7 (c = 1.0, CHCl\(_3\), 15% ee).

3.4. (S)-3-(2-Nitropropan-2-yl)cycloheptanone (4c)

HPLC (79% ee, Daicel CHIRALPAK AD-H, 15% isopropanol/hexane, 1.0 mL/min, 229 nm; 
*t*(major enantiomer) = 10.0 min, *t*(minor enantiomer) = 12.4 min). δ(CDCl3) 1.19–1.28 (1H, m), 
1.36–1.49 (1H, m), 1.51–1.61 (1H, m), 1.53 (3H, s), 1.55 (3H, s), 1.70–1.74 (1H, m), 1.95–2.04 
(2H, m), 2.38–2.40 (2H, m), 2.49–2.63 (3H, m); δ(CDCl3) 21.8, 23.9, 24.7, 38.9, 31.6, 43.3, 44.0, 
45.1, 92.1, 211.9; ν(KBr)/cm\(^{-1}\) 1704 (C=O), 1539 (NO\(_2\)); [α]\(_D\)\(^{21.9} \) − 53.6 (c = 1.0, CHCl\(_3\), 79% ee).

3.5. (S)-5-Methyl-5-nitro-4-phenylhexan-2-one (4d)

HPLC (51% ee, Daicel CHIRALPAK AD-H, 15% isopropanol/hexane, 1.0 mL/min, 229 nm; 
*t*(major enantiomer) = 18.1 min, *t*(minor enantiomer) = 10.3 min). δ(CDCl3) 1.48 (3H, s), 1.55 
(3H, s), 2.02 (3H, s), 2.71 (1H, dd, J 3.5, 17.0 Hz), 3.09 (1H, dd, J 10.7, 17.0 Hz), 3.93, (1H, dd, J 3.5, 
10.7 Hz), 7.18–7.20 (2H, m), 7.24–7.32 (3H, m); δ(CDC\(_1\)l) 22.4, 25.8, 30.3, 44.0, 48.7, 91.0, 127.8, 
128.5, 129.1, 137.6, 205.1; ν(KBr)/cm\(^{-1}\) 1704 (C=O), 1533 (NO\(_2\)); [α]\(_D\)\(^{22.9} \) − 18.7 (c = 1.0, CHCl\(_3\), 51% ee).

3.6. (1'R,3S)-3-(1'-Nitroethyl)cyclohexanone and (1'S,3S)-3-(1'-nitroethyl)cyclohexanone (4f)

HPLC (dr = 1.01:1, 50% ee, 38% ee, Daicel CHIRALPAK AD-H, 5% isopropanol/hexane, 1.0 mL/min, 229 nm; 
*t*(major diastereomer, major enantiomer) = 36.7 min, *t*(major diastereomer, minor enantiomer) = 31.9 min, *t*(minor diastereomer, major enantiomer) = 34.6 min, *t*(minor diastereomer, minor enantiomer) = 24.5 min). δ(CDC\(_1\)l) 1.42–1.52 (2H, m), 1.54 (3H, d, J 6.8 Hz), 
1.57 (3H, d, J 6.8 Hz), 1.60–1.74 (2H, m), 1.87–1.97 (2H, m), 2.10–2.18 (4H, m), 2.24–2.37 (4H, m), 
2.38–2.48 (4H, m), 4.47–4.55 (2H, m); δ(CDC\(_1\)l) 16.1, 16.2, 24.1, 24.3, 26.8, 27.4, 40.76, 40.79, 42.2, 
42.4, 43.2, 43.6, 86.87, 86.90, 208.5, 208.6; ν(KBr)/cm\(^{-1}\) 1715 (C=O), 1544 (NO\(_2\)); [α]\(_D\)\(^{22.5} \) − 4.6 
(c = 1.0, CHCl\(_3\), dr = 1.01:1, 50% ee, 38% ee).

3.7. (S)-3-Nitromethylcyclohexanone (4g)

HPLC (55% ee, Daicel CHIRALPAK AD-H, 5% isopropanol/hexane, 1.0 mL/min, 229 nm; 
*t*(major enantiomer) = 32.5 min, *t*(minor enantiomer) = 26.6 min). δ(CDC\(_1\)l) 1.47–1.57 (1H, m), 
1.69–1.80 (1H, m), 1.97–2.02 (1H, m), 2.10–2.18 (2H, m), 2.26–2.34 (1H, m), 2.42–2.53 (2H, m), 
2.60–2.71 (1H, m), 4.32–4.42 (2H, m); δ(CDC\(_1\)l) 24.1, 28.2, 37.1, 40.8, 44.4, 80.0, 208.2; 
ν(neat)/cm\(^{-1}\) 1714 (C=O), 1549 (NO\(_2\)); [α]\(_D\)\(^{22.4} \) − 2.0 (c = 1.0, CHCl\(_3\), 55% ee).
3.8. Michael Addition of Ethyl Benzoylacetate (5) to 2-cyclohexen-1-one (3a)

In a 10 mL vial, ethyl benzoylacetate (5) (192 mg, 1 mmol) was added to a mixture of Ser(O-TBDPS)-OLi (52.4 mg, 0.15 mmol), 2-cyclohexen-1-one (1a) (48 mg, 0.5 mmol) and DMSO (5 mL) at 25 °C. After the reaction mixture was stirred for 72 h at 25 °C, saturated aqueous NaCl (2 mL) was added to the vial and extracted with Et2O (1.5 mL × 4). The combined organic phase was dried over MgSO4, filtered and concentrated under reduced pressure. The Michael adduct, ethyl benzoyl-(3-oxocyclohexyl)acetate (6), was isolated by column chromatography (silica gel, hexanes/Et2O) in 84% yield (121 mg) as oil. HPLC {59% ee, Daicel CHIRALPAK AS-H, 30% isopropanol/hexane, 0.3 mL/min, 254 nm; tR(major enantiomer-1) = 42.9 min, tR(major enantiomer-2) = 82.3 min, tR(minor enantiomer-1) = 39.5 min, tR(minor enantiomer-2) = 54.2 min}. δH(CDCl3) 1.18 (3H, t, J 7.2 Hz), 1.36–1.80 (2H, m), 1.92–2.30 (4H, m), 2.40–2.49 (2H, m), 2.79–2.87 (1H, m), 4.11–4.19 (2H, m), 4.26–4.30 (1H, m), 7.47–7.63 (3H, m), 7.98–8.03 (2H, m); δc(CDCl3) 14.90, 14.10, 14.12, 24.65, 24.72, 28.8, 29.6, 38.25, 38.30, 41.3, 45.3, 45.8, 59.2, 59.7, 61.7, 61.8, 128.6, 128.7, 128.98, 129.01, 133.9, 134.0, 136.58, 136.60, 168.1, 168.4, 193.5, 193.6, 209.8, 209.9; v(neat)/cm⁻¹ 1734, 1713, 1682; [α]D²⁰ + 3.7 (c = 1.0, CHCl3, 59% ee). [HR EI-MS: Calc. for C₁₇H₂₀O₄ (M): 288.1362. Found: M⁺, 288.1360].

4. Conclusions

The Michael addition of nitroalkanes to enones could be catalyzed by a siloxy primary amino acid lithium salt, O-TIPS L-serine lithium salt, to give γ-nitroketones enantioselectively. Since the reaction conditions were optimized using 2-nitropropane and 2-cyclohexen-1-one, the Michael addition reaction between other nitroalkanes and enones would result in relatively poor yields and/or enantioselectivity. Using the present method, therefore, individual condition screening for each substrate may be required to obtain various γ-nitroketones in good yields with high enantioselectivity.

The Michael addition of ethyl benzoylacetate to 2-cyclohexen-1-one was also investigated by using a siloxy primary amino acid lithium salt as a catalyst, and the corresponding Michael adduct was obtained in a good yield with high enantioselectivity. We believe this is the first report on highly enantioselective Michael addition of ethyl benzoylacetate to 2-cyclohexen-1-one, since we could find no reports about the synthesis of the corresponding Michael adduct with high enantioselectivity.

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References and Notes


45. Imine-based catalytic asymmetric Michael addition of nitroalkanes to cyclopentenone 3b usually resulted in lower yields and selectivity than those in the case of cyclohexenone 3a. Organocatalytic Enantioselective Michael Additions of Malonates to 2-Cyclopentenone. (Mase, N.; Fukasawa, M.; Kitagawa, N.; Shibagaki, F.; Noshiro, N.; Takabe, K. *Synlett* 2010, 2340.) See also References 13, 14 and 20–22.
46. It is likely that the reaction mechanism is similar to that of the Michael addition of malonates to enoens. See Reference 33.
47. TLC tracing of the reactions indicated the generation of high-polarity compounds.

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