Highly enantioselective introduction of bis(alkoxycarbonyl)methyl group into the 2-position of piperidine skeleton

Matsumura, Yoshihiro; Minato, Daishiro; Onomura, Osamu


Copyright © 2007 Elsevier Ltd All rights reserved.
Highly enantioselective introduction of bis(alkoxycarbonyl)methyl group into the 2-position of piperidine skeleton

Yoshihiro Matsumura,* Daishiro Minato, and Osamu Onomura

Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

Abstract

Copper ion catalyzed carbon-carbon bond forming reaction of N-acyliminium ions with diaryl malonates was achieved with high enantioselectivity. The key intermediates in the method were 2-methoxy-3,4-didehydropiperidines, which were easily prepared through electrochemical oxidation of 1-(p-methoxybenzoyl)piperidine in methanol followed by the conversion of the oxidation product to didehydropiperidine derivative, which was subjected to a chiral Cu(II) catalyzed coupling reaction with diaryl malonates affording diaryl 2-piperidylmalonates. The maximum %e.e. (e.e., enantiomeric excess) was 97% when di-p-chlorophenyl malonate was used as a nucleophile.

Keywords: Optically active 2-alkylpiperidines; 2-Methoxy-3,4-didehydropiperidines; Electrochemical oxidation; Catalytic asymmetric reaction; Copper ion-catalyzed

1. Introduction

Asymmetric introduction of alkyl nucleophiles (NuH) to the 2-position of 1-protected piperidinium ions C (PG: protecting group) may be one of the most convenient and simple routes for optically active 2-alkylpiperidines D, key synthetic intermediates for a variety of chiral piperidine alkaloids since piperidinium ions C can be generated from easily available 1-protected piperidines A through electrochemical oxidation of A followed by acid treatment of the oxidation products B (Scheme 1) [1]. However, there
have been very few reports for such asymmetric introduction in such cases that piperidinium ions C have a chiral protecting group [2] or a chiral NuH is used [3].

![Scheme 1. Asymmetric introduction of alkyl nucleophile (NuH) onto the 2-position of 1-protected piperidinium ions C](image)

We have already found an asymmetric introduction of NuH onto the 2-position of 1-protected 3,4-didehydro-piperidinium ions F, which are also easily prepared from B through 1-protected 2-methoxy-3,4-didehydro-piperidines E (Scheme 2) [4].

![Scheme 2. Asymmetric introduction of alkyl nucleophile (NuH) onto the 2-position of 1-protected 3,4-didehydro-piperidinium ions F](image)

However, the highest enantioselectivity so far reported in our study was 71%e.e. in a case that dimethyl malonate (2p) as NuH was used toward F. Since then, we have surveyed both PG of E (R of 1a-e) and NuH (R' of 1p-w) to improve the %e.e. of G (3ap-ez) Eq. (1) and, as the result, succeeded in achieving 97%e.e. of G. This paper describes the detail of those results.
2. Results and discussion

2.1. Preparation of 1-protected 2-methoxy-3,4-didehydropiperidines 1a-e

Substrates 1a-e were prepared from 1-acylated piperidines 4a-e according to the procedures indicated in Eq. (2) [5], the first step of which was electrochemical oxidation of 1a-e in methanol to afford 2-methoxylated compounds 5a-e [6]. The conversion of 5a-e into 1a-e was achieved by elimination of methanol, bromomethoxylation followed by dehydrobromination according to the reported method [5]. In a case of 1a, the yields of 5a and 1a were 91% at 5F/mol and 70%, respectively.

2.2. Chiral ligands

Some known chiral bisoxazoline ligands L1-L6 (Fig. 1) [7] were examined in the coupling reaction of 1a-e with 2p-z.
2.3. Coupling reaction of 1a with dialkyl malonates 2p-s

First, the coupling reaction between 1a and dialkyl malonates 2p-s as NuH was examined in the presence of a chiral bisoxazoline ligand L1 Eq. (3).

\[
1a + 2p-s \text{ (1.5 equiv)} \xrightarrow{\text{Cu(OTf)}_2 \text{ (0.05 equiv)}} \text{chiral ligand L1 (0.06 equiv)}}\xrightarrow{\text{in THF, at rt, 12hrs}} 3ap-as
\]

The results are shown in Table 1. Although the reaction of 1a with dimethyl malonate (2p) gave the coupling product 3ap in good yield (Entry 1), using diethyl and di-tert-butyl malonates (2q) and (2r) in place of 2p did not afford the corresponding coupling products 3aq,ar (Entries 2 and 3). On the other hand, the coupling reaction of 1a with diphenyl malonate (2s) proceeded to give the 2-substituted piperidine 3as with higher enantioselectivity than that using 2p (Entry 4).
Table 1. Coupling reactions between 1a and some malonates 2p-s^a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Malonic acid ester</th>
<th>Product</th>
<th>R'</th>
<th>Yield (%)</th>
<th>[%e.e.]^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{CO}_2\text{Me} ) ( \text{CO}_2\text{Me} ) 2p</td>
<td>3ap</td>
<td>Me</td>
<td>78 [41]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>( \text{CO}_2\text{Et} ) ( \text{CO}_2\text{Et} ) 2q</td>
<td>3aq</td>
<td>Et</td>
<td>0 [-]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>( \text{CO}_2\text{t-Bu} ) ( \text{CO}_2\text{t-Bu} ) 2r</td>
<td>3ar</td>
<td>t-Bu</td>
<td>0 [-]</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>( \text{CO}_2\text{Ph} ) ( \text{CO}_2\text{Ph} ) 2s</td>
<td>3as</td>
<td>Ph</td>
<td>50 [89]</td>
<td></td>
</tr>
</tbody>
</table>

^a The reaction conditions: 1a (0.5 mmol), 2p-s (0.75 mmol), Cu(OTf)_2 (0.025 mmol), and L1 (0.03 mmol) in THF (2.5 mL) at RT for 12hrs under nitrogen atmosphere.  
^b Determined by chiral HPLC.

2.4. Coupling reaction of 1a with diaryl malonates 2s-z

On the basis of the results in Table 1, the coupling reaction of 1a with bis(monosubstituted phenyl) malonates 2s-z as NuH in the presence of a chiral bisoxazoline ligand L1 was examined Eq. (4).

\[
\begin{align*}
1a & \quad \overset{\text{2s-z (1.5 equiv)}}{\text{Cu(OTf)}_2} \quad \overset{\text{0.05 equiv}}{\text{chiral ligand L1}} \quad \overset{\text{in THF, at rt, 12hrs}}{\rightarrow} \\
& \quad \text{3as-az}
\end{align*}
\]

The results are shown in Table 2. Although using di-p-methoxyphenyl malonate (2t) did not afford the coupling product 3at (Entry 2), di-p-methylphenyl or di-p-bromophenyl malonate (2u) or (2v) afforded the corresponding 2-substituted piperidines 3au or 3av with high enantioselectivity (Entries 3 and 4) similar to that of using 2s (Entry 1). Di-p-chlorophenyl and di-p-fluorophenyl malonates (2w) and (2x), which were more acidic than 2s, coupled with 1a to give the carbon-carbon bond forming products 3aw and 3ax with higher enantioselectivity than 2s (Entries 5 and 6). However, di(m- and o-chlorophenyl) malonates (2y) and (2z), which seemed to be a more bulky than 2s, did not always work well (Entries 7 and 8).
### Table 2. Coupling reactions between 1a and diaryl malonates 2s-z<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diaryl malonate</th>
<th>Product</th>
<th>Yield (%)</th>
<th>%e.e.&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2s</td>
<td>50</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>p-MeOPh</td>
<td>2t</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>p-MePh</td>
<td>2u</td>
<td>57</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>p-BrPh</td>
<td>2v</td>
<td>56</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>p-ClPh</td>
<td>2w</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>6</td>
<td>p-FPh</td>
<td>2x</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>m-ClPh</td>
<td>2y</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>o-ClPh</td>
<td>2z</td>
<td>16</td>
<td>35</td>
</tr>
</tbody>
</table>

<sup>a</sup> The reaction conditions: 1a (0.5 mmol), 2s-z (0.75 mmol), Cu(OTf)<sub>2</sub> (0.025 mmol), and L1 (0.03 mmol) in THF (2.5 mL) at RT for 12 hrs under nitrogen atmosphere.  
<sup>b</sup> Determined by chiral HPLC.

2.5. Coupling reaction of 1-protected 2-methoxy-3,4-didehydropiperidines 1a-e with dimethyl or diaryl malonate (2p or 2s,w)

The effect of 1-protecting group of 2-methoxy-3,4-didehydropiperidines 1a-e on their asymmetric coupling reaction with malonates 2p,s,w in the presence of chiral ligand L1 was examined Eq. (5).

![Chemical structure](image)

\[
\text{1a-e} \xrightarrow{\text{Cu(OTf)\textsubscript{2} (0.05 equiv)}} \text{2p,s,w} \text{ (1.5 equiv)}} \xrightarrow{\text{chiral ligand L1 (0.06 equiv)}} \text{3ap-ew}
\]

The results are summarized in Table 3. Enhanced enantioselectivity by using diaryl malonates 2s,w in place of dimethyl malonate (2p) was observed in the reactions using 1-methoxycarbonylated, 1-benzoylated, and 1-p-chlorobenzoylated piperidines 1b-d. Although an asymmetric coupling reaction of 3,4-didehydro-2-methoxy-1-methoxycarbonylpiperidine (1b) with 2p, which was
prepared from 2-methoxy-1-methoxycarbonylpiperidine (5b) [8], proceeded with low efficiency (Entry 4), that of 1b with 2w afforded the coupling product 3bw in good enantioselectivity (Entry 6). Also, the reaction of 1-benzooylated and 1-p-chlorobenzooylated piperidines 1c and 1d with 2w as NuH gave the corresponding 2-substituted piperidines 3cw and 3dw in high enantioselectivities (Entries 8 and 10). The reaction of 1-phenoxy carbonylated piperidine 1e with 2w afforded the coupling product 3ew in a reasonable optical purity (Entry 11).

Table 3. Coupling reactions between 1a-e and malonates 2p,s,w a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R</th>
<th>Malonate R1</th>
<th>Product</th>
<th>Yield (%)</th>
<th>%e.e. b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-MeOPh 1a</td>
<td>Me 2p</td>
<td>3ap</td>
<td>78</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Ph 2s</td>
<td>3as</td>
<td>50</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>p-ClPh 2w</td>
<td>3aw</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>MeO 1b</td>
<td>Me 2p</td>
<td>3bp</td>
<td>36</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>1b</td>
<td>Ph 2s</td>
<td>3bs</td>
<td>48</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>p-ClPh 2w</td>
<td>3bw</td>
<td>86</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>Ph 1c</td>
<td>Me 2p</td>
<td>3cp</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td>p-ClPh 2w</td>
<td>3cw</td>
<td>51</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>p-ClPh 1d</td>
<td>Me 2p</td>
<td>3dp</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td>10</td>
<td>1d</td>
<td>p-ClPh 2w</td>
<td>3dw</td>
<td>71</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>PhO 1e</td>
<td>p-ClPh 2w</td>
<td>3ew</td>
<td>73</td>
<td>77</td>
</tr>
</tbody>
</table>

a The reaction conditions: 1a-e (0.5 mmol), 2p,s,w (0.75 mmol), Cu(OTf)2 (0.025 mmol), and L1 (0.03 mmol) in THF (2.5 mL) at RT for 12hrs under nitrogen atmosphere.  
b Determined by chiral HPLC.

2.6. Temperature effect on the coupling reaction of 1a,c with 2p,w

With having those data in hand, we then examined a temperature effect on an enantioselective carbon-carbon bond formation at the 2-position of 1a,c with 2p,w in the presence of chiral ligand L1 Eq. (6).
The results are summarized in Table 4. Although in a case of using dimethyl malonate (2p) (0.75 mmol) the coupling reaction of 1a (0.5 mmol) did not occurred at all at 0°C in THF (2.5 mL) (Entry 2), the reaction between 1a and di-p-chlorophenyl malonate (2w) proceeded well at 0°C to afford the coupling product 3aw in 95%e.e. (Entry 4). The reaction of 1a (5 mmol) with 2w (7.5 mmol) in the larger scale than Entry 4 at 0°C also gave 3aw in 97%e.e. (Entry 5), while the reactions of 1a (0.5 mmol) with 2w (0.75 mmol) at -20°C, and of 1c (0.5 mmol) with 2w (0.75 mmol) at 0°C proceeded slowly (Entries 6 and 8).

### Table 4. Temperature effect on coupling reactions between 1a,c and malonates 2p,w

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate R</th>
<th>Malonate R^1</th>
<th>Temperature</th>
<th>Product</th>
<th>Yield (%)</th>
<th>%e.e. b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>p-MeOPh 1a</td>
<td>Me 2p</td>
<td>RT</td>
<td>3ap</td>
<td>78</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2p</td>
<td>0°C</td>
<td>3ap</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>p-ClPh 2w</td>
<td>RT</td>
<td>3aw</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>2w</td>
<td>0°C</td>
<td>3aw</td>
<td>65</td>
<td>95</td>
</tr>
<tr>
<td>5^c</td>
<td>1a</td>
<td>2w</td>
<td>0°C</td>
<td>3aw</td>
<td>57</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>1a</td>
<td>2w</td>
<td>-20°C</td>
<td>3aw</td>
<td>23</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>Ph 1c</td>
<td>2w</td>
<td>RT</td>
<td>3cw</td>
<td>51</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>1c</td>
<td>2w</td>
<td>0°C</td>
<td>3cw</td>
<td>24</td>
<td>95</td>
</tr>
</tbody>
</table>

^a The reaction conditions: 1a,c (0.5 mmol), 2p,w (0.75 mmol), Cu(OTf)_2 (0.025 mmol), and L1 (0.03 mmol) in THF (2.5 mL) for 12hrs under nitrogen atmosphere. ^b Determined by chiral HPLC. ^c The reaction conditions: 1a (5 mmol), 2w (7.5 mmol), Cu(OTf)_2 (0.25 mmol), and L1 (0.3 mmol) in THF (25 mL) for 12hrs under nitrogen atmosphere.
2.7. Solvent effect on the coupling reaction of 1a with 2w

Solvent effect on the coupling reaction of 1a with 2w was examined in the presence of chiral ligand L1. The results are summarized in Table 5. THF afforded the best result (Entry 1), while dichloromethane, diethyl ether, toluene, ethyl acetate, and 1,2-dimethoxyethane were a little bit ineffective than THF (Entries 2–6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield (%) of 3aw</th>
<th>%e.e. a of 3aw</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>43</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>37</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>63</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>AcOEt</td>
<td>51</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>DME</td>
<td>45</td>
<td>75</td>
</tr>
</tbody>
</table>

a The reaction conditions: 1a (0.5 mmol), 2w (0.75 mmol), Cu(OTf)₂ (0.025 mmol), and L1 (0.03 mmol) in solvent (2.5 mL) at RT for 12hrs under nitrogen atmosphere. b Determined by chiral HPLC.

2.8. Effect of chiral ligand on the coupling reaction of 1a with 2w

The coupling reaction of 1a with 2w in THF was carried out in the presence of chiral bisoxazoline ligands L1-L6. The results are summarized in Table 6. Among the examined chiral ligands L1–L6 (Entries 1–4), L1 gave the best result for 1a to give 3aw with 93% e.e. (Entry 1). Ligand L2 showed almost similar effect to L1 (Entry 2), while ligands L3-L5 were a little ineffective than L1 (Entries 3-5). PyBOX L6 did not work at all (Entry 6).
Table 6. Effect of ligand on the coupling reaction of 1a with 2wa

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%) of 3aw</th>
<th>%e.e.b of 3aw</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>61</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>72</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>54</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>52</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>52</td>
<td>-65c</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

a The reaction conditions: 1a (0.5 mmol), 2w (0.75 mmol), Cu(OTf)2 (0.025 mmol), and L1-L6 (0.03 mmol) in THF (2.5 mL) at RT for 12hrs under nitrogen atmosphere. b Determined by chiral HPLC. c Antipode of 3aw was obtained.

2.9. Effect of Lewis acid on the coupling reaction of 1a with 2w

Next, we examined a variety of Lewis acid catalysts in the reaction of 1a with di-p-chlorophenyl malonate (2w) to disclose the counter ion effect. The results are shown in Table 7.
Among metal trifluoromethanesulphonates, Cu(OTf)$_2$ gave the best result (Entry 1), while Zn(OTf)$_2$, Mg(OTf)$_2$, and La(OTf)$_3$ were ineffective than Cu(OTf)$_2$ (Entries 1-3,6). Sc(OTf)$_3$ and Hf(OTf)$_4$ did not work as the catalyst (Entries 4 and 5). Also, examined copper salts did not give better result than Cu(OTf)$_2$. Namely, Cu(ClO$_4$)$_2$, Cu(BF$_4$)$_2$, and Cu(SbF$_6$)$_2$ were 6~26%ee less effective than Cu(OTf)$_2$ (Entries 8-10), while CuCl$_2$ and Cu(PF$_6$)$_2$ did not work at all (Entries 7 and 11).

2.10. Identification of absolute stereochemistry of the coupling products

In order to propose a reaction mechanism, the absolute configuration of the coupling products was identified as shown in Eq. (7). Thus, 3aw (95%e.e.) were easily converted by the reaction with NaOMe to 3ap (95%e.e.) in 85% yield. The comparison of the optical rotation of 3ap with authentic sample indicated that enantiomerically enriched isomer of 3aw had a R-configuration.
2.11. Reaction mechanism

The reaction mechanism for the coupling reaction of 1 with dialkyl malonates 2 is not clear, but it may be tentatively supposed as shown in Schemes 3-5 which are exemplified by the reaction of 1a with 2w. At the initiation step, a copper enolate Pw may be generated from 2w and Cu(OTf)$_2$ with a loss of a proton which attacks on 1a to generate an iminium ion 6a. The iminium ion is trapped with Pw to afford a coupling product 3aw with a regeneration of Cu(II). Thus, a catalytic cycle of Cu(II) for a formation of 3aw from 1a is achieved.

Scheme 3. A plausible reaction mechanism
The stereochemical outcome is hypothetically explainable using a mechanism described in Schemes 4 and 5, in which iminium ion 6a approaches on a copper enolate Pw through four paths 1–4. Paths 1 and 2 represent approaches with minimizing an overlap between the C5,6 methylene groups of 6a and Pw (Scheme 4), while paths 3 and 4 represent approaches in which the C5,6 methylene groups of 6a overlap Pw (Scheme 5).
Among those paths, path 1 seems more likely than the other paths because of a steric repulsion between Ph group of $\text{Pw}$ and an aryloyl group of $6a$ in path 2 and between the $C_{5,6}$ methylene groups of $6a$ and $\text{Pw}$ in paths 3 and 4.

The steric factor may be primarily important for the stereoselectivity, but the result is not always explained only by the steric factor since diaryl malonates $2s,u-x$ afforded the different %e.e. of the coupling products (Entries 1,3-6 in Table 2) and more bulky $L3$ gave a less stereoselective result than less bulky $L1, L2$ did (Entries 1-3 in Table 6). A strength of the coordination (a tightness) between copper ion and the carbonyl oxygen in $\text{Pw}$ may depend on $Ar$ group of diaryl malonates, and it may be responsible to some extent for the stereoselectivity. Also, a substituent on the 4-phenyl group of the oxazolidine ring may affect to the tightness by its electronic or steric reason.

3. Conclusion

We have presented a facile method for asymmetric introduction of bis(alkoxycarobonyl)methyl group into the 2-position of a piperidine skeleton. The key intermediates were 2-methoxy-3,4-didehydropiperidines $1a-e$, which were prepared through electrochemical oxidation of easily available 1-protected piperidines $4a-e$ in methanol. The highest enantioselectivity (97%e.e.) was observed in a coupling reaction between 1-(p-methoxybenzoyl)-3,4-didehydro-2-methoxypiperidine ($1a$) and di-p-chlorophenyl malonate ($2w$) with a catalytic amount of Cu(OTf)$_2$ and a chiral ligand $L1$ in THF at 0°C. Further study to improve the stereoselectivity is under investigation.

4. Experimental

4.1. General

HPLC analyses were achieved by using a LC-10AT $VP$ and a SPD-10A $VP$ of Shimadzu Seisakusho Inc. Specific rotations were measured with Jasco DIP-1000. $^1$H NMR spectra were measured on a Varian Gemini 300 spectrometer with TMS as an internal standard. IR spectra were obtained on a Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-700N instrument. Melting points are uncorrected.
All solvents were dried by standard techniques. The preparation of 2-methoxy-3,4-didehydropiperidines \(1a,c,d\) [4b], \(1b\) [3c] and chiral ligands \(L2,L3\) [4c] were already reported by us. Malonate \(2s\) [9], \(2u,w\) [10], \(2v\) [11], and \(2x\) [12] are known compounds. Malonates \(2p-r\), chiral ligands \(L1,L4-L6\), and Cu(OTf)\(_2\), Mg(OTf)\(_2\), Sc(OTf)\(_3\), La(OTf)\(_2\), Hf(OTf)\(_4\), Zn(OTf)\(_2\) were commercially available. Cu(PF\(_6\))\(_2\) and Cu(SbF\(_6\))\(_2\) were prepared according to the reported method [13].

4.2. Preparation of 1-phenoxycarbonyl-2-methoxy-3,4-didehydropiperidine (1e)

1-Phenoxycarbonyl-2-methoxy-3,4-didehydropiperidine (1e) was easily prepared by our reported procedure [3c,4b,5]. Namely, electrochemical oxidation of 1-phenoxycarbonylpiperidine (4e) in methanol afforded 2-methoxylated compound 5e [14], which was successively transformed into the corresponding enecarbamate [15] by acid-catalyzed elimination of methanol. Bromomethylation of the enecarbamate afforded 3-bromo-2-methoxylated compound [15], which was transformed into 1e by a base-catalyzed elimination of hydrobromic acid.

4.2.1. 1-phenoxycarbonyl-2-methoxy-3,4-didehydropiperidine (1e)

Colorless oil; IR (neat) 3044, 2936, 1736, 1651, 1593, 1424, 1368, 1235, 754 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.00-2.12 (m, 1H), 2.25-2.40 (m, 1H), 3.15-3.50 (m, 1H), 3.45 and 3.49 (2s, 3H), 4.18-4.28 (m, 1H), 5.50 and 5.60 (2br s, 1H), 5.80-5.88 (m, 1H), 6.00-6.15 (m, 1H), 7.12 (d, \(J = 8.1\) Hz, 2H), 7.22 (t, \(J = 8.1\) Hz, 1H), 7.38 (t, \(J = 8.1\) Hz, 2H); HRMS (M, EI) calcd for C\(_{13}\)H\(_{15}\)NO\(_3\) 233.1052 found 233.1042.

4.4. Preparation of diaryl malonates 2t-z

Diaryl malonates 2t-z were prepared from malonic acid and the corresponding phenols in the presence of POCl\(_3\) according to a reported method [9].

4.4.1. Di-p-methoxyphenyl malonate (2t)

Pale brown solid; mp 77-80°C; IR (neat) 2950, 2840, 1767, 1752, 1514, 1472, 1300, 1186, 1102, 1034 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 3.80 (s, 6H), 3.82 (s, 2H), 6.90 (d, \(J = 9.0\) Hz, 4H), 7.07 (d, \(J = 8.7\) Hz, 1H); HRMS (M, EI) calcd for C\(_{13}\)H\(_{16}\)O\(_6\) 316.0947. found 316.0929.

4.4.2. Di-m-chlorophenyl malonate (2y)

Pale brown solid; mp 67-69°C; IR (neat) 3073, 2940, 1773, 1752, 1590, 1474, 1431,
1197, 1134, 1070 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.86 (s, 2H), 7.07 (d, $J=8.0$Hz, 2H), 7.20 (s, 2H), 7.26 (d, $J=8.0$Hz, 2H), 7.35 (t, $J=8.1$Hz, 2H); HRMS (M, EI) calcd for C$_{15}$H$_{10}$Cl$_2$O$_6$ 323.9956 found 323.9937.

4.4.3. Di-o-chlorophenyl malonate (2z)
Colorless oil; IR (neat) 3073, 2950, 1782, 1763, 1584, 1478, 1217, 1063, 752 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.98 (s, 2H), 7.20-7.35 (m, 6H), 7.448 (d, $J=8.1$Hz, 2H); HRMS (M, EI) calcd for C$_{15}$H$_{10}$Cl$_2$O$_4$ 323.9956 found 323.9932.

4.5. Asymmetric coupling reaction of 1 with 2: a typical experimental procedure

A solution of di-p-chlorophenyl malonate (2w) (0.75 mmol), Cu(OTf)$_2$ (0.025 mmol) and L1 (0.03 mmol) in THF (1 mL) was stirred for 5 min at room temperature under a nitrogen atmosphere. Into the solution was added a solution of 1a (0.5 mmol) in THF. After stirring for 12 hrs, the resulting mixture was poured into aqueous NaHCO$_3$ (5 mL). The organic portion was extracted with AcOEt (10 mL × 3) and dried over MgSO$_4$. The resulting solution was concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt = 5/1) to afford 3aw (61% yield, 93% e.e.). The spectroscopic data of products 3ap,bp,cp,dp were also described in the report [4b].

4.5.1. Di-p-chlorophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3aw) (93% e.e.)
Colorless oil; $[\alpha]_D^{25} +53.7^\circ$ (c=0.5, CHCl$_3$); IR (neat) 2934, 2840, 1752, 1624, 1608, 1487, 1429, 1304, 1250, 1192, 1134, 1090, 1015 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 2.00-2.17 (m, 1H), 2.20-2.40 (m, 1H), 3.25-3.45 (m, 1H), 3.75-3.95 (m, 1H), 3.83 (s, 3H), 4.24 (d, $J=8.4$Hz, 1H), 5.75-5.90 (m, 1H), 6.00-6.20 (m, 2H), 6.90 (d, $J=8.7$Hz, 2H), 7.05-7.20 (m, 4H), 7.27-7.40 (m, 6H); HRMS (M, EI) calcd for C$_{28}$H$_{23}$Cl$_2$NO$_6$ 539.0902 found 539.0921.

The e.e. was obtained by DAICEL Chiralcel OD (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 9min for minor enantiomer and 24min for major enantiomer.

4.5.2. Diphenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3as) (89% e.e.)
Colorless oil; $[\alpha]_D^{22} +86.2^\circ$(c=0.5, CHCl$_3$); IR (neat) 3044, 2936, 2840, 1752, 1628, 1512, 1493, 1427, 1304, 1250, 1186, 1136, 1026 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 1.90-2.15 (m, 1H), 2.15-2.40 (m, 1H), 3.25-3.50 (m, 1H), 3.75-3.95 (m, 1H), 3.83 (s, 3H), 4.30 (d,
$J=7.8\text{Hz}, 1\text{H}$, $5.80-5.95$ (m, 1H), $6.00-6.20$ (m, 2H), $6.90$ (d, $J=9.0\text{Hz}, 2\text{H}$), $7.10-7.45$ (m, 12H); HRMS (M, El) calcd for $C_{28}H_{25}NO_6$ 471.1682 found 471.1664.

The e.e. was obtained by DAICEL Chiralcel OD ($\phi 4.6\text{mm, 250mm}$) [hexane/isopropanol (5/1) (v/v), $1.0\text{ml/min}$, detection at $210\text{nm}$, 25min for minor enantiomer and 39min for major enantiomer.

4.5.3. Di-p-methylphenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3au) (88%e.e.)
Colorless oil; $[\alpha]_D^{21}+70.9^\circ$ (c=0.5, CHCl$_3$); IR (neat) 2932, 2840, 1750, 1628, 1609, 1507, 1426, 1304, 1252, 1136, 843 cm$^{-1}$; $^1$$H$ NMR (CDCl$_3$) $\delta$ 1.95-2.15 (m, 1H), 2.15-2.40 (m, 1H), 2.33 (s, 3H), 2.35 (s, 3H), 3.30-3.45 (m, 1H), 3.75-3.95 (m, 1H), 3.82 (s, 3H), 4.27 (d, $J=8.1\text{Hz}, 1\text{H}$), 5.80-5.90 (m, 1H), 6.00-6.20 (m, 2H), 6.89 (d, $J=8.7\text{Hz}, 2\text{H}$), 7.03 and 7.06 (2d, $J=9.0\text{Hz}, 4\text{H}$), 7.16 and 7.19 (2d, $J=9.0\text{Hz}, 4\text{H}$), 7.36 (d, $J=8.7\text{Hz}, 2\text{H}$); HRMS (M, El) calcd for $C_{30}H_{29}NO_6$ 499.1995 found 499.1986.

The e.e. was obtained by DAICEL Chiralcel OD ($\phi 4.6\text{mm, 250mm}$) [hexane/isopropanol (5/1) (v/v), $1.0\text{mL/min}$, detection at $210\text{nm}$, 10min for minor enantiomer and 20min for major enantiomer.

4.5.4. Di-p-bromophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3av) (88%e.e.)
Colorless oil; $[\alpha]_D^{22}+38.6^\circ$ (c=0.5, CHCl$_3$), IR (neat) 2936, 2838, 2249, 1752, 1640, 1508, 1458, 1304, 1254, 1134, 1068, 1012 cm$^{-1}$; $^1$$H$ NMR (CDCl$_3$) $\delta$ 2.00-2.15 (m, 1H), 2.20-2.40 (m, 1H), 3.25-3.45 (m, 1H), 3.75-3.95 (m, 1H), 3.83 (s, 3H), 4.23 (d, $J=8.3\text{Hz}, 1\text{H}$), 5.75-5.90 (m, 1H), 6.00-6.15 (m, 2H), 6.90 (d, $J=8.5\text{Hz}, 2\text{H}$), 7.00-7.15 (m, 4H), 7.32 (d, $J=8.5\text{Hz}, 2\text{H}$), 7.45-7.55 (m, 4H); HRMS (M+H, FAB) calcd for $C_{28}H_{24}Br_2NO_6$ 627.9971 found 627.9985.

The e.e. was obtained by DAICEL Chiralcel OD ($\phi 4.6\text{mm, 250mm}$) [hexane/isopropanol (5/1) (v/v), $1.0\text{mL/min}$, detection at $210\text{nm}$, 10min for minor enantiomer and 26min for major enantiomer.

4.5.5. Di-p-fluorophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3ax) (92%e.e.)
Colorless oil; $[\alpha]_D^{22}+110.1^\circ$ (c=0.5, CHCl$_3$); IR (neat) 3078, 2936, 2840, 1754, 1628, 1611, 1507, 1429, 1306, 1254, 1136, 1030, 843 cm$^{-1}$; $^1$$H$ NMR (CDCl$_3$) $\delta$ 2.00-2.15 (m, 1H), 2.20-2.40 (m, 1H), 3.25-3.45 (m, 1H), 3.75-3.95 (m, 1H), 3.83 (s, 3H), 4.24 (d, $J=8.1\text{Hz}, 1\text{H}$), 5.80-5.95 (m, 1H), 6.00-6.20 (m, 2H), 6.90 (d, $J=8.7\text{Hz}, 2\text{H}$), 7.00-7.20
(m, 8H), 7.33 (d, J=8.7Hz, 2H); HRMS (M, EI) calcd for C_{28}H_{23}F_{2}NO_{6} 507.1493 found 507.1490.

The e.e. was obtained by DAICEL Chiralcel OD (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 9min for minor enantiomer and 22min for major enantiomer.

### 4.5.6. Di-m-chlorophenyl [1-(p-Methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3ay) (90%e.e.)

Colorless oil; [α]_{D}^{22} +61.6°(c=0.25, CHCl_{3}); IR (neat) 3069, 2934, 2838, 1754, 1624, 1591, 1512, 1471, 1427, 1304, 1248, 1192, 1129 cm^{-1}; \textsuperscript{1}H NMR (CDCl_{3}) δ 2.05-2.15 (m, 1H), 2.25-2.45 (m, 1H), 3.25-3.45 (m, 1H), 3.75-3.95 (m, 1H), 3.83 (s, 3H), 4.27 (d, J=8.0Hz, 1H), 5.75-5.90 (m, 1H), 6.00-6.20 (m, 2H), 6.91 (d, J=8.5Hz, 2H), 7.05-7.40 (m, 10H); HRMS (M, EI) calcd for C_{28}H_{23}Cl_{2}NO_{6} 539.0902 found 539.0912.

The e.e. was obtained by DAICEL Chiralcel OD (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 9min for minor enantiomer and 15min for major enantiomer.

### 4.5.7. Di-o-chlorophenyl [1-(p-Methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3az) (35%e.e.)

White solid; mp.143-144°C; [α]_{D}^{20} +38.8° (c=0.5, CHCl_{3}); IR (neat) 2936, 2840, 1759, 1628, 1609, 1512, 1478, 1428, 1304, 1254, 1136, 1061 cm^{-1}; \textsuperscript{1}H NMR (CDCl_{3}) δ 2.00-2.15 (m, 1H), 2.20-2.40 (m, 1H), 3.30-3.50 (m, 1H), 3.80-3.95 (m, 1H), 4.42 (d, J=8.7Hz, 1H), 5.85-6.00 (m, 1H), 6.00-6.25 (m, 2H), 6.90 (d, J=8.7Hz, 2H), 7.20-7.50 (m, 10H); HRMS (M, EI) calcd for C_{28}H_{23}Cl_{2}NO_{6} 539.0902 found 539.0920.

The e.e. was obtained by DAICEL Chiralcel OD (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 12min for minor enantiomer and 19min for major enantiomer.

### 4.5.8. Diphenyl (1-methoxycarbonyl-3,4-didehydro-2-piperidyl)malonate (3bs) (49%e.e.)

Colorless oil; [α]_{D}^{21} +88.1°(c=0.5, CHCl_{3}); IR (neat) 3044, 2955, 2840, 1752, 1701, 1591, 1491, 1447, 1410, 1300, 1188 cm^{-1}; \textsuperscript{1}H NMR (CDCl_{3}) δ 2.00-2.42 (m, 2H), 2.05-3.20 (m, 1H), 3.71 and 3.75 (2s, 3H), 4.10-4.42 (m, 2H), 5.25-5.42 (m, 1H), 5.98-6.10 (m, 2H), 7.14 (d, J=7.8Hz, 4H), 7.20-7.32 (m, 2H), 7.35-7.45 (m, 4H); HRMS (M, EI) calcd for C_{22}H_{21}NO_{6} 395.1369 found 395.1357.
The e.e. was obtained by DAICEL Chiralcel OD (φ4.6mm, 250mm) [hexane/isopropanol (10/1) (v/v), 1.0mL/min, detection at 210nm, 9min for minor enantiomer and 10min for major enantiomer.

4.5.9. Di-p-chlorophenyl (1-methoxycarbonyl-3,4-didehydro-2-piperidyl)malonate (3bw) (68%e.e.)

Colorless oil; [α]D$^2$ +82.2°(c=0.5, CHCl$_3$); IR (neat) 2955, 1754, 1701, 1487, 1300, 1200, 1196, 1092, 1015 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 2.00-2.12 (m, 1H), 2.20-2.38 (m, 1H), 3.00-3.15 (m, 1H), 3.68 and 3.72 (2s, 3H), 4.10-4.42 (m, 2H), 5.20-5.40 (m, 1H), 5.90-6.10 (m, 2H), 7.07 (d, J=8.8Hz, 4H), 7.30-7.40 (m, 4H); HRMS (M, EI) calcd for C$_{22}$H$_{19}$Cl$_2$NO$_6$ 463.0589 found 463.0570.

The e.e. was obtained by DAICEL Chiralcel OD (φ4.6mm, 250mm) [hexane/isopropanol (50/1) (v/v), 1.0mL/min, detection at 210nm, 12min for minor enantiomer and 16min for major enantiomer.

4.5.10. Di-p-chlorophenyl (1-benzoyl-3,4-didehydro-2-piperidyl)malonate (3cw) (94%e.e.)

White solid; mp.111-113°C; [α]D$^2$ +60.0°(c=0.25, CHCl$_3$); IR (neat) 2932, 1753, 1632, 1487, 1429, 1306, 1192, 1090, 1015 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 2.00-2.40 (m, 2H), 3.15-3.42 (m, 1H), 3.71 and 3.76 (2d, J=5.4 and 5.4Hz, 1H), 4.20 (d, J=8.4Hz, 1H), 5.85 (d, J=8.4Hz, 1H), 6.09 (br s, 2H), 7.10 (d, J=9.0Hz, 2H), 7.14 (d, J=9.0Hz, 2H), 7.20-7.52 (m, 8H); HRMS (M, EI) calcd for C$_{27}$H$_{21}$Cl$_2$NO$_5$ 509.0797 found 509.0786.

The e.e. was obtained by DAICEL Chiralcel OD (φ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 8min for minor enantiomer and 15min for major enantiomer.

4.5.11. Di-p-chlorophenyl [1-(p-chlorobenzoyl)-3,4-didehydro-2-piperidyl]malonate (3dw) (91%e.e.)

White solid; mp.31-33°C; [α]D$^1$ +40.3°(c=0.25, CHCl$_3$); IR (neat) 2930, 1750, 1632, 1487, 1431, 1306, 1194, 1090, 1015 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 2.00-2.40 (m, 2H), 3.15-3.42 (m, 1H), 3.71 and 3.76 (2d, J=5.4 and 5.4Hz, 1H), 4.20 (d, J=8.4Hz, 1H), 5.85 (d, J=8.4Hz, 1H), 6.09 (br s, 2H), 7.10 (d, J=9.0Hz, 2H), 7.14 (d, J=9.0Hz, 2H), 7.20-7.52 (m, 8H); HRMS (M, EI) calcd for C$_{27}$H$_{20}$Cl$_{25}$Cl$_{37}$ClNO$_5$ 545.0378 found 545.0394.

The e.e. was obtained by DAICEL Chiralcel OD (φ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 7min for minor
enantiomer and 12 min for major enantiomer.

4.5.12. Di-p-chlorophenyl (1-phenoxycarbonyl-3,4-didehydro-2-piperidyl)malonate (3ew) (77% ee)

Colorless oil; [α]D 24 +89.6° (c=0.7, CHCl3); IR (neat) 3046, 2936, 1755, 1719, 1489, 1424, 1209, 1092, 1015 cm−1; 1H NMR (CDCl3) δ 21.0-2.25 (m, 1H), 2.35-2.50 (m, 1H), 3.12-3.35 (m, 1H), 4.11 and 4.21 (2d, J=7.8 and 7.8 Hz, 1H), 4.35-4.45 (m, 1H), 5.38-5.56 (m, 1H), 6.00-6.18 (m, 2H), 6.98-7.42 (m, 13H); HRMS (M, EI) calcd for C27H21Cl2NO6 525.0746 found 525.0741.

The e.e. was obtained by DAICEL Chiralcel OD (φ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 7 min for minor enantiomer and 9 min for major enantiomer.

4.6. Transformation of 3aw into (R)-3ap

A solution of NaOMe (95 mg, 1.77 mmol) in MeOH (7 mL) was added into a solution of 3aw (95% ee, 318 mg, 0.59 mmol) in MeOH (3 mL), and the resulting solution was allowed to be stirred at 0°C to room temperature. After 12 hrs, solvent of the reaction mixture was removed in vacuo. Into the residue was added water. The organic portion was extracted with AcOEt (10 mL × 3) and dried over MgSO4. The resulting solution was concentrated in vacuo to afford a crude (R)-3ap [1], which was purified by silica gel chromatography (hexane/AcOEt = 5/1) to afford (R)-3ap (85% yield, 95% ee). [α]D 25 +172.4° (c=0.25, CHCl3).

The e.e. was obtained by DAICEL Chiralcel OD (φ4.6mm, 250mm) [hexane/isopropanol (9/1) (v/v), 1.0 mL/min, detection at 210 nm, 41 min for (S)-3ap and 53 min for (R)-3ap.

Acknowledgement

This study was supported by a Grant-in-Aid for Scientific Research on Priority Areas, (No. 420: Reaction Control of Dynamic Complexes) from the Ministry of Education, Science, Sports and Culture, Japan and by a Grant-in-Aid for Scientific Research (C) (No. 15550094) from Japan Society for the Promotion of Science.
References


   (b) Y. Kanda, O. Onomura, T. Maki, Y. Matsumura, Chirality 15 (2003), 89;
   (c) O. Onomura, Y. Kanda, E. Imai, Y. Matsumura, Electrochimica Acta 50 (2005), 4926.


   (c) N. Halland, T. Velgaard, K.A. Jorgensen, J. Org. Chem. 68 (2003), 5067;
   (f) V.K. Aggarwal, A.J. Belfield, Org. Lett. 5 (2003), 5075;
   (g) M.P. Sibi, G. Petrovic, J. Zimmerman, J. Am. Chem. Soc. 127 (2005), 2390;
15016.

    (b) T. Shono, Y. Matsumura, K. Tsubata, J. Am. Chem. Soc. 103 (1981), 1172;


