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

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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 % ee (ee, enantiomeric excess) was 97% when di-*p*-chlorophenyl malonate was used as a nucleophile.
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Keywords: Optically active 2-alkylpiperidines; 2-Methoxy-3,4-didehydropiperidines; Electrochemical oxidation; Catalytic asymmetric reaction; Copper ion-catalyzed
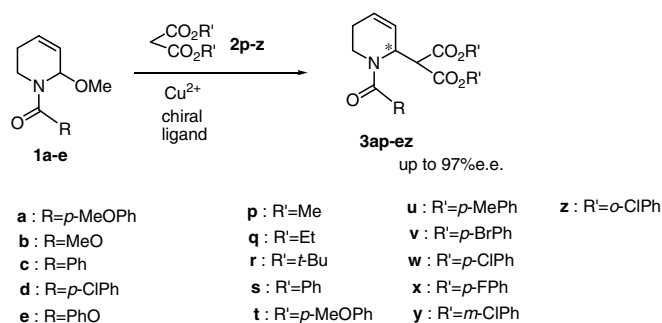
1. Introduction

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].

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

However, the highest enantioselectivity so far reported in our study was 71% ee 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 % ee of **G** (**3ap–ez**) Eq. (1) and, as the result, succeeded in achieving 97% ee of **G**. This paper describes the detail of those results.
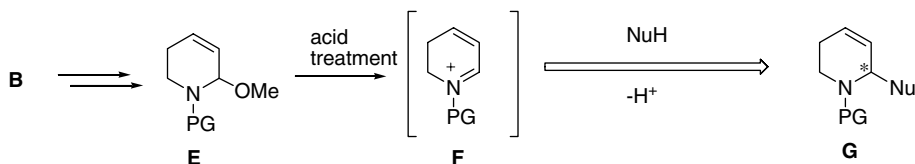

a : R=*p*-MeOPh
b : R=MeO
c : R=Ph
d : R=*p*-ClPh
e : R=PhO

p : R′=Me
q : R′=Et
r : R′=*t*-Bu
s : R′=Ph
t : R′=*p*-MeOPh

u : R′=*p*-MePh
v : R′=*p*-BrPh
w : R′=*p*-ClPh
x : R′=*p*-FPh
y : R′=*m*-ClPh

z : R′=*o*-ClPh

$$\tag{1}$$

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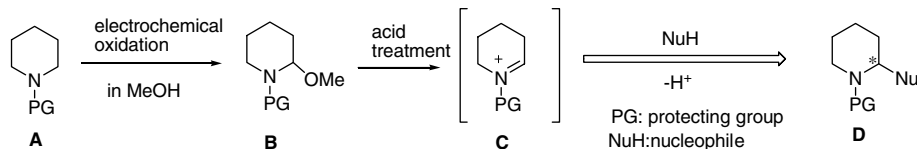
Scheme 1. Asymmetric introduction of alkyl nucleophile (NuH) onto the 2-position of 1-protected piperidinium ions **C**.

Scheme 2. Asymmetric introduction of alkyl nucleophile (NuH) onto the 2-position of 1-protected 3,4-dihydropiperidinium ions **F**.

2. Results and discussion

2.1. Preparation of 1-protected 2-methoxy-3,4-dihydropiperidines **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 5 F/mol and 70%, respectively.
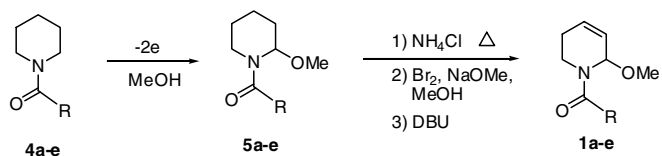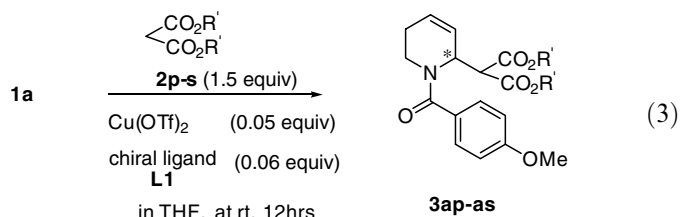
$$ (2) $$

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**.

$$ (3) $$

The results are shown in Table 1. Although the reaction of **1a** with dimethyl malonate (**2p**) gave the coupling product
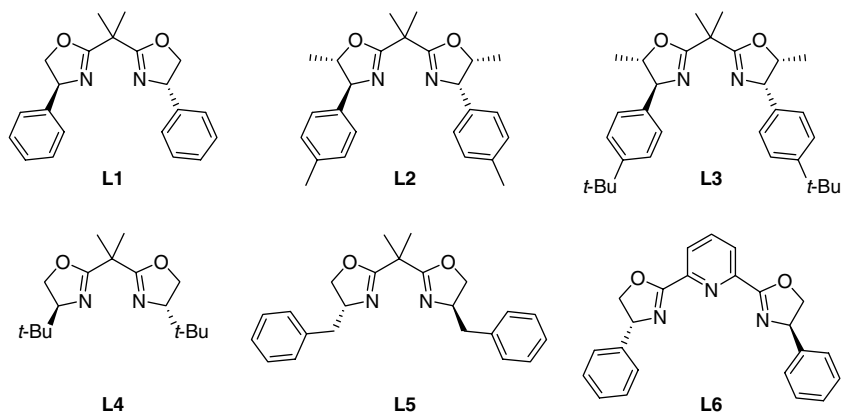
Fig. 1. Bisoxazolines as chiral ligands.

Table 1
Coupling reactions between **1a** and some malonates **2p–s**[a]

| Entry	Malonic acid	Ester	Product	R'	Yield (%) [% ee][b]
1	CO$_2$Me / CO$_2$Me	**2p**	**3ap**	Me	78 [41]
2	CO$_2$Et / CO$_2$Et	**2q**	**3aq**	Et	0 [–]
3	CO$_2$t-Bu / CO$_2$t-Bu	**2r**	**3ar**	t-Bu	0 [–]
4	CO$_2$Ph / CO$_2$Ph	**2s**	**3as**	Ph	50 [89]

[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 12 h under nitrogen atmosphere.
[b] Determined by chiral HPLC.

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).

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.

(4)
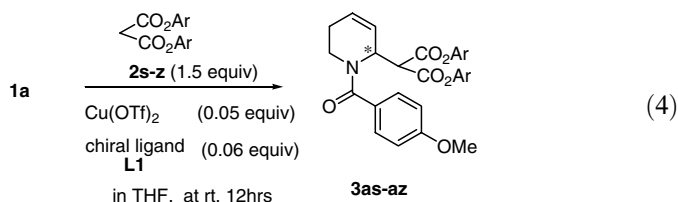
The results are shown in Table 2. Although using di-*p*-methoxyphenyl malonate (**2t**) did not afford the coupling product **3at** (entry 2), di-*p*-methylphenyl or di-*p*-bromo-

Table 2
Coupling reactions between **1a** and diaryl malonates **2s–z**[a]

| Entry	Diaryl malonate Ar		Product	Yield (%)	% Ee[b]
1	Ph	**2s**	**3as**	50	89
2	*p*-MeOPH	**2t**	**3at**	0	–
3	*p*-MePh	**2u**	**3au**	57	88
4	*p*-BrPh	**2v**	**3av**	56	88
5	*p*-ClPh	**2w**	**3aw**	61	93
6	*p*-FPh	**2x**	**3ax**	59	92
7	*m*-ClPh	**2y**	**3ay**	30	90
8	*o*-ClPh	**2z**	**3az**	16	35

[a] The reaction conditions: **1a** (0.5 mmol), **2s–z** (0.75 mmol), Cu(OTf)$_2$ (0.025 mmol), and **L1** (0.03 mmol) in THF (2.5 mL) at RT for 12 h under nitrogen atmosphere.
[b] Determined by chiral HPLC.

phenyl 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).

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-dide-hydropiperidines **1a–e** on their asymmetric coupling reaction with malonates **2p,s,w** in the presence of chiral ligand **L1** was examined.

(5)
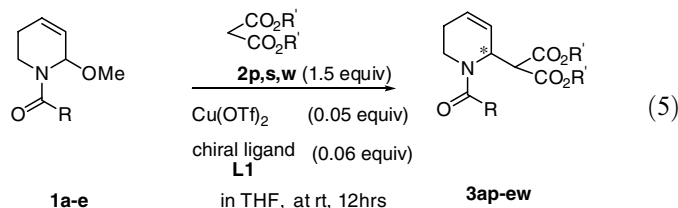
The results are summarized in Table 3. Enhanced enantioselectivity by using diaryl malonates **2s,w** in place of dimethyl malonate (**2p**) was observed in the reactions using 1-methoxycarbonylated, 1-benzoylated, and 1-*p*-chloro-benzoylated piperidines **1b–d**. Although an asymmetric coupling reaction of 3,4-didehydro-2-methoxy-1-methoxycarbonylpiperidine (**1b**) with **2p**, which was prepared from 2-methoxy-1-methoxycarbonylpiperidine (**5b**) [8],

Table 3
Coupling reactions between **1a–e** and malonates **2p,s,w**[a]

| Entry	Substrate R		Malonate R^1		Product	Yield (%)	% Ee[b]
1	*p*-MeOPh	**1a**	Me	**2p**	**3ap**	78	41
2		**1a**	Ph	**2s**	**3aa**	50	89
3		**1a**	*p*-ClPh	**2w**	**3aw**	61	93
4	MeO	**1b**	Me	**2p**	**3bp**	36	21
5		**1b**	Ph	**2s**	**3bs**	48	49
6		**1b**	*p*-ClPh	**2w**	**3bw**	86	68
7	Ph	**1c**	Me	**2p**	**3cp**	36	46
8		**1c**	*p*-ClPh	**2w**	**3cw**	51	94
9	*p*-ClPh	**1d**	Me	**2p**	**3dp**	38	49
10		**1d**	*p*-ClPh	**2w**	**3dw**	71	91
11	PhO	**1e**	*p*-ClPh	**2w**	**3ew**	73	77

[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 12 h under nitrogen atmosphere.
[b] Determined by chiral HPLC.

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-benzoylated and 1-*p*-chlorobenzoylated 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-phenoxycarbonylated piperidine **1e** with **2w** afforded the coupling product **3ew** in a reasonable optical purity (entry 11).

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**.

$$ (6) $$
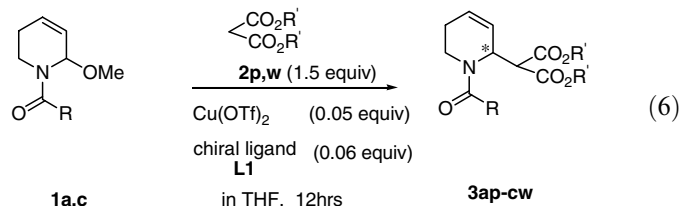
The results are summarized in Table 4. Although in a case of using dimethyl malonate (**2p**) (0.75 mmol) the coupling reaction of **1a** (0.5 mmol) did not occurred at all at 0 °C in THF (2.5 mL) (entry 2), the reaction between **1a** and di-*p*-chlorophenyl malonate (**2w**) proceeded well at 0 °C to afford the coupling product **3aw** in 95% ee (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% ee (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).

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).

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% ee (entry 1). Ligand

Table 5
Solvent effect on the coupling reaction of **1a** with **2w**[a]

Entry	Solvent	Yield (%) of **3aw**	% Ee[b] of **3aw**
1	THF	61	93
2	CH_2Cl_2	43	81
3	Et_2O	37	83
4	Toluene	63	88
5	AcOEt	51	82
6	DME	45	75

[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 12 h under nitrogen atmosphere.
[b] Determine by chiral HPLC.

Table 6
Effect of ligand on the coupling reaction of **1a** with **2w**[a]

Entry	Ligand	Yield (%) of **3aw**	% Ee[b] of **3aw**
1	**L1**	61	93
2	**L2**	72	92
3	**L3**	54	86
4	**L4**	52	71
5	**L5**	52	−65[c]
6	**L6**	0	–

[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 12 h under nitrogen atmosphere.
[b] Determined by chiral HPLC.
[c] Antipode of **3aw** was obtained.

Table 4
Temperature effect on coupling reactions between **1a,c** and malonates **2p,w**[a]

Entry	Substrate		Malonate		Temperature	Product	Yield (%)	% Ee[b]
	R		R^1					
1	*p*-MeOPh	**1a**	me	**2p**	RT	**3ap**	78	41
2		**1a**		**2p**	0 °C	**3ap**	0	–
3		**1a**	*p*-ClPh	**2w**	RT	**3aw**	61	93
4		**1a**		**2w**	0 °C	**3aw**	65	95
5[c]		**1a**		**2w**	0 °C	**3aw**	57	97
6		**1a**		**2w**	−20 °C	**3aw**	23	93
7	Ph	**1c**		**2w**	RT	**3cw**	51	94
8		**1c**		**2w**	0 °C	**3cw**	24	95

[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 12 h under nitrogen atmosphere.
[b] Determined by chiral HPLC.
[c] The reaction conditions: **1a** (7.5 mmol) $Cu(OTf)_2$ (0.025 mmol), and **L1** (0.03 mmol) in THF (25 mL) for 12 h under nitrogen atmosphere.

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).

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 trifluoromethanesulfonates, $Cu(OTf)_2$ 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, and 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% ee) were easily converted by the reaction with NaOMe to **3ap** (95% ee) 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.
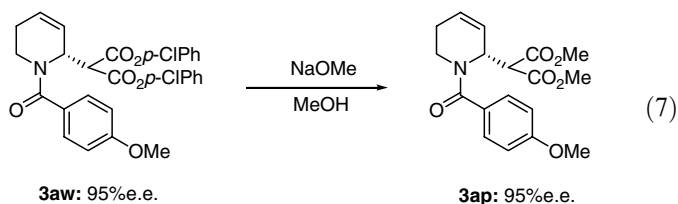

$$(7)$$

3aw: 95%e.e.   **3ap:** 95%e.e.

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.

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

Table 7
Effect of Lewis acid catalysts on the reaction of **1a** with **2w**[a]

Entry	Lewis acid	Yield (%) of 3aw	% Ee of 3aw[b]
1	$Cu(OTf)_2$	61	93
2	$Zn(OTf)_2$	68	24
3	$Mg(OTf)_2$	42	0
4	$Sc(OTf)_2$	Trace	8
5	$Hf(OTf)_2$	0	–
6	$La(OTf)_2$	78	–8[c]
7	$CuCl_2$	0	–
8	$Cu(ClO_4)_2$	58	87
9	$Cu(BF_4)_2$	54	84
10	$Cu(SbF_6)_2$	36	67
11	$Cu(PF_6)_2$	0	–

[a] The reaction conditions: **1a** (0.5 mmol), **2w** (0.75 mmol), Lewis acid (0.025 mmol), and **L1** (0.03 mmol) in THF (2.5 mL) at RT for 12 h under nitrogen atmosphere.
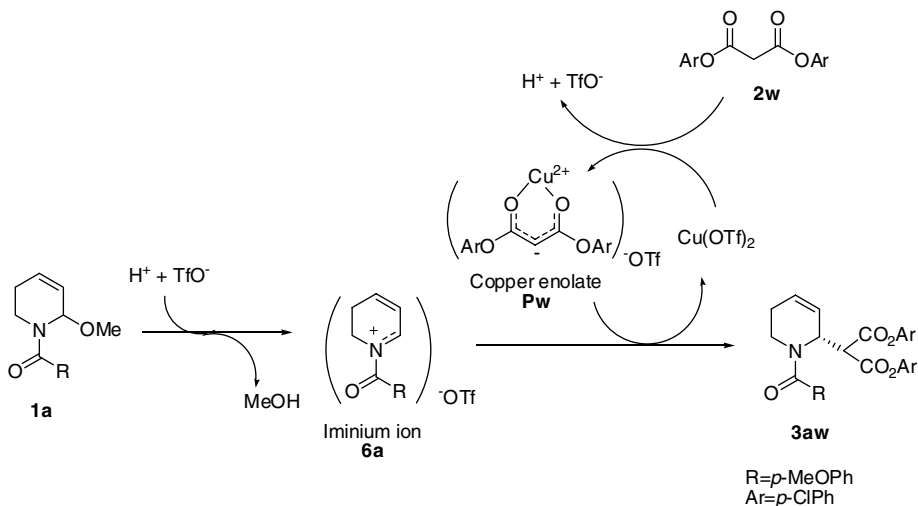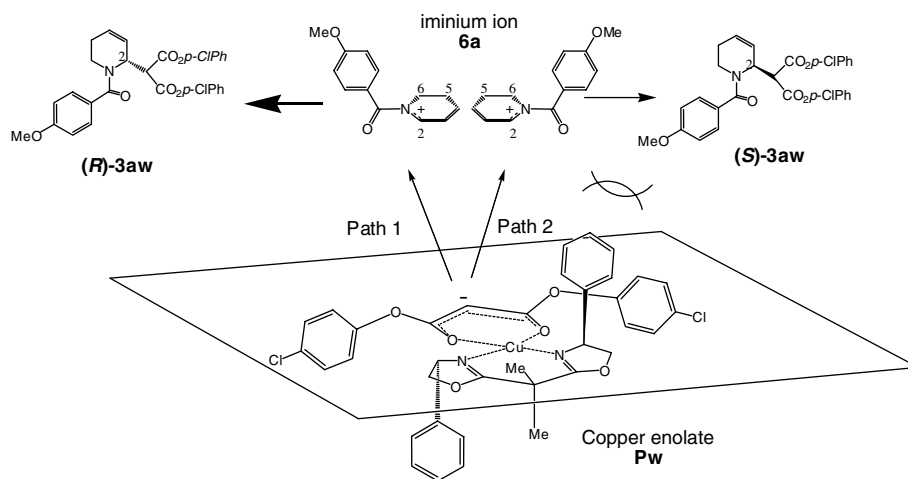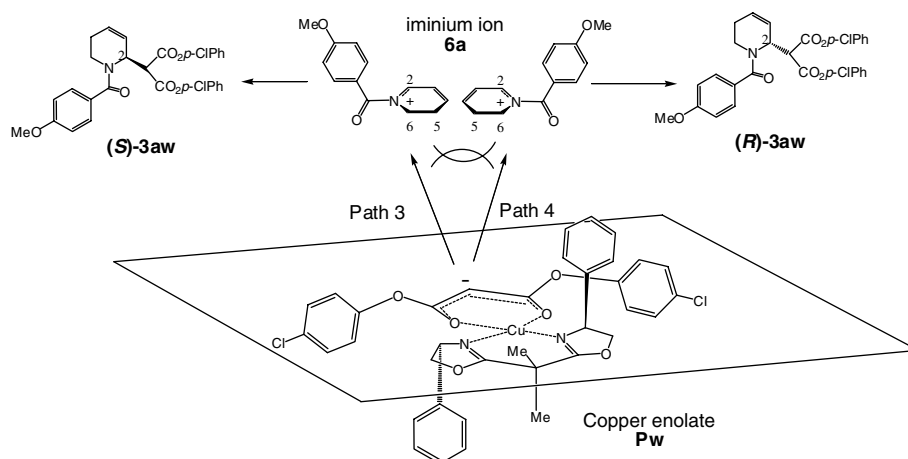[b] Determined by chiral HPLC.
[c] The reverse stereochemistry was observed.

Scheme 3. A plausible reaction mechanism.

Scheme 4. Stereochemical outcome **1**.

Scheme 5. Stereochemical outcome **2**.

approaches with minimizing an overlap between the $C_{5,6}$ methylene groups of **6a** and **Pw** (Scheme 4), while paths 3 and 4 represent approaches in which the $C_{5,6}$ 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 **Pw** and an aryloyl group of **6a** in path 2 and between the $C_{5,6}$ methylene groups of **6a** and **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 % ee 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 **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(alkoxycarbonyl)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% ee) 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–5]. Namely, electrochemical oxidation of 1-phenoxycarbonyl-piperidine (**4e**) in methanol afforded 2-methoxylated compound **5e** [14], which was successively transformed into the corresponding enecarbamate [15] by acid-catalyzed elimination of methanol. Bromomethoxylation 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$_3$) δ 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.

4.3. 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].

4.3.1. 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$_3$) δ 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$_{17}$H$_{16}$O$_6$ 316.0947; found 316.0929.

4.3.2. 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$_3$) δ 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.

4.3.3. Di-o-chlorophenyl malonate (2z)

Colorless oil; IR (neat) 3073, 2950, 1782, 1763, 1584, 1478, 1217, 1063, 752 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 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.

4.4. 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 h, 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% ee). The spectroscopic data of products **3ap**,**bp**,**cp**,**dp** were also described in the report [4b].

4.4.1. Di-p-chlorophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3aw) (93% ee)

Colorless oil; [α]$_D^{25}$ +53.7° ($c = 0.5$, CHCl$_3$); IR (neat) 2934, 2840, 1752, 1624, 1608, 1487, 1429, 1304, 1250, 1192, 1134, 1090, 1015 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 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 ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 9 min for minor enantiomer and 24 min for major enantiomer.

4.4.2. Diphenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3as) (89% ee)

Colorless oil; [α]$_D^{22}$ +86.2° ($c = 0.5$, CHCl$_3$); IR (neat) 3044, 2936, 2840, 1752, 1628, 1512, 1493, 1427, 1304, 1250, 1186, 1136, 1026 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 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, $J = 7.8$ Hz, 1H), 5.80–5.95 (m, 1H), 6.00–6.20 (m, 2H), 6.90 (d, $J = 9.0$ Hz, 2H), 7.10–7.45 (m, 12H); HRMS (M, EI) calcd for C$_{28}$H$_{25}$NO$_6$ 471.1682; found 471.1664.

The ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 ml/min, detection at 210 nm, 25 min for minor enantiomer and 39 min for major enantiomer.

4.4.3. Di-p-methylphenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3au) (88% ee)

Colorless oil; $[\alpha]_D^{21}$ +70.9° ($c = 0.5$, CHCl$_3$); IR (neat) 2932, 2840, 1750, 1628, 1609, 1507, 1426, 1304, 1252, 1136, 843 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 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, $J = 8.1$ Hz, 1H), 5.80–5.90 (m, 1H), 6.00–6.20 (m, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 7.03 and 7.06 (2d, $J = 9.0$ Hz, 4H), 7.16 and 7.19 (2d, $J = 9.0$ Hz, 4H), 7.36 (d, $J = 8.7$ Hz, 2H); HRMS (M, EI) calcd for C$_{30}$H$_{29}$NO$_6$ 499.1995; found 499.1986.

The ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 10 min for minor enantiomer and 20 min for major enantiomer.

4.4.4. Di-p-bromophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3av) (88% ee)

Colorless oil; $[\alpha]_D^{22}$ +38.6° ($c = 0.5$, CHCl$_3$), IR (neat) 2936, 2838, 2249, 1752, 1640, 1508, 1458, 1304, 1254, 1134, 1068, 1012 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 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, $J = 8.3$ Hz, 1H), 5.75–5.90 (m, 1H), 6.00–6.15 (m, 2H), 6.90 (d, $J = 8.5$ Hz, 2H), 7.00–7.15 (m, 4H), 7.32 (d, $J = 8.5$ Hz, 2H), 7.45–7.55 (m, 4H); HRMS (M+H, FAB) calcd for C$_{28}$H$_{24}$Br$_2$NO$_6$ 627.9971; found 627.9985.

The ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 10 min for minor enantiomer and 26 min for major enantiomer.

4.4.5. Di-p-fluorophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3ax) (92% ee)

Colorless oil; $[\alpha]_D^{22}$ +110.1° ($c = 0.5$, CHCl$_3$); IR (neat) 3078, 2936, 2840, 1754, 1628, 1611, 1507, 1429, 1306, 1254, 1136, 1030, 843 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 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, $J = 8.1$ Hz, 1H), 5.80–5.95 (m, 1H), 6.00–6.20 (m, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 7.00–7.20 (m, 8H), 7.33 (d, $J = 8.7$ Hz, 2H); HRMS (M, EI) calcd for C$_{28}$H$_{23}$F$_2$NO$_6$ 507.1493; found 507.1490.

The ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 9 min for minor enantiomer and 22 min for major enantiomer.

4.4.6. Di-m-chlorophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3ay) (90% ee)

Colorless oil; $[\alpha]_D^{22}$ +61.6° ($c = 0.25$, CHCl$_3$); IR (neat) 3069, 2934, 2838, 1754, 1624, 1591, 1512, 1471, 1427, 1304, 1248, 1192, 1129 cm^{-1}; ^{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, $J = 8.0$ Hz, 1H), 5.75–5.90 (m, 1H), 6.00–6.20 (m, 2H), 6.91 (d, $J = 8.5$ Hz, 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 ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 8 min for minor enantiomer and 15 min for major enantiomer.

4.4.7. Di-o-chlorophenyl [1-(p-methoxybenzoyl)-3,4-didehydro-2-piperidyl]malonate (3az) (35% ee)

White solid; mp 143–144 °C; $[\alpha]_D^{20}$ +38.8° ($c = 0.5$, CHCl$_3$); IR (neat) 2936, 2840, 1759, 1628, 1609, 1512, 1478, 1428, 1304, 1254, 1136, 1061 cm^{-1}; ^{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), 3.82 (s, 3H), 4.42 (d, $J = 8.7$ Hz, 1H), 5.85–6.00 (m, 1H), 6.00–6.25 (m, 2H), 6.90 (d, $J = 8.7$ Hz, 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 ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 12 min for minor enantiomer and 19 min for major enantiomer.

4.4.8. Diphenyl (1-methoxycarbonyl-3,4-didehydro-2-piperidyl)malonate (3bs) (49% ee)

Colorless oil; $[\alpha]_D^{21}$ +88.1° ($c = 0.5$, CHCl$_3$); IR (neat) 3044, 2955, 2840, 1752, 1701, 1591, 1491, 1447, 1410, 1300, 1188 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 2.00–2.42 (m, 2H), 3.05–3.20 (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, $J = 7.8$ Hz, 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 ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (10/1) (v/v), 1.0 mL/min, detection at 210 nm, 9 min for minor enantiomer and 10 min for major enantiomer.

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

Colorless oil; $[\alpha]_D^{21}$ +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, $J = 8.8$ Hz, 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 ee was obtained by DAICEL Chiralcel OD (∅4.6 mm, 250 mm) hexane/isopropanol (50/1) (v/v), 1.0 mL/min, detection at 210 nm, 12 min for minor enantiomer and 16 min for major enantiomer.

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

White solid; mp 111–113 °C; $[\alpha]_D^{22}$ +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 2.00–2.12 (m, 1H), 2.2.0–2.38 (m, 1H), 3.25–3.40 (m, 1H), 3.70–3.85 (m, 1H), 4.23 (d, $J = 8.4$ Hz, 1H), 5.88 (br d, $J = 6.9$ Hz, 1H), 6.05–6.15 (m, 2H), 7.09 (d, $J = 8.9$ Hz, 2H), 7.15 (d, $J = 8.9$ Hz, 2H), 7.30–7.45 (m, 9H); HRMS (M, EI) calcd for C$_{27}$H$_{21}$Cl$_2$NO$_5$ 509.0797; found 509.0786.

The ee was obtained by DAICEL Chiralcel OD ($\varnothing$4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 8 min for minor enantiomer and 15 min for major enantiomer.

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

White solid; mp 31–33 °C; $[\alpha]_D^{19}$ +40.3° ($c = 0.25$, CHCl$_3$); IR (neat) 2930, 1752, 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 5.4 Hz, 1H), 4.20 (d, $J = 8.4$ Hz, 1H), 5.85 (d, $J = 8.4$ Hz, 1H), 6.09 (br s, 2H), 7.10 (d, $J = 9.0$ Hz, 2H), 7.14 (d, $J = 9.0$ Hz, 2H), 7.20–7.52 (m, 8H); HRMS (M, EI) calcd for C$_{27}$H$_{20}$^{35}Cl$_2$^{37}ClNO$_5$ 545.0378; found 545.0394.

The ee was obtained by DAICEL Chiralcel OD ($\varnothing$4.6 mm, 250 mm) hexane/isopropanol (5/1) (v/v), 1.0 mL/min, detection at 210 nm, 7 min for minor enantiomer and 12 min for major enantiomer.

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

Colorless oil; $[\alpha]_D^{24}$ +89.6° ($c = 0.7$, CHCl$_3$); IR (neat) 3046, 2936, 1755, 1719, 1489, 1424, 1209, 1092, 1015 cm^{-1}; ^{1}H NMR (CDCl$_3$) 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 C$_{27}$H$_{21}$Cl$_2$NO$_6$ 525.0746; found 525.0741.

The ee was obtained by DAICEL Chiralcel OD ($\varnothing$4.6 mm, 250 mm) 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.

4.5. 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 h, 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 MgSO$_4$. 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). $[\alpha]_D^{25}$ +172.4° ($c = 0.25$, CHCl$_3$).

The ee was obtained by DAICEL Chiralcel OD ($\varnothing$4.6 mm, 250 mm) 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**.

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