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

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Abstract

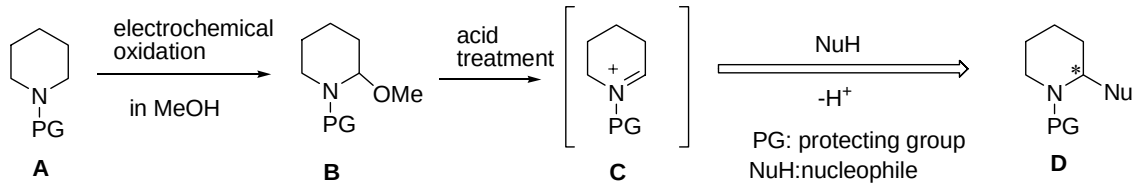
Copper ion catalyzed carbon-carbon bond forming reaction of *N*-acyliminium ions with diaryl malonates was achieved with high enantioselectivity. The key intermediates in the method were 2-methoxy-3,4-didehydropiperidines, which were easily prepared through electrochemical oxidation of 1-(*p*-methoxybenzoyl)piperidine 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 %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

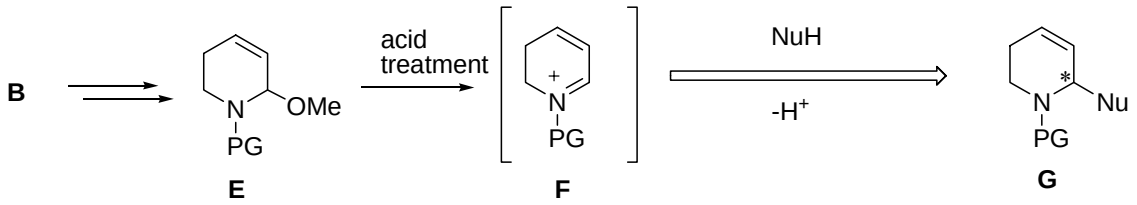
Asymmetric introduction of alkyl nucleophiles (NuH) to the 2-position of 1-protected piperidinium ions **C** (PG: protecting group) may be one of the most convenient and simple routes for optically active 2-alkylpiperidines **D,** key synthetic intermediates for a variety of chiral piperidine alkaloids 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].



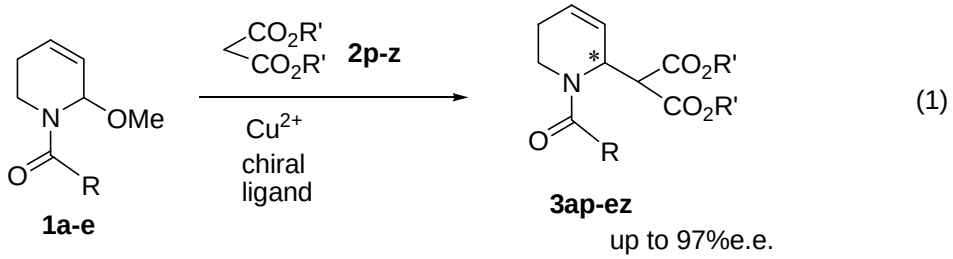
Scheme 1. Asymmetric introduction of alkyl nucleophile (NuH) onto the 2-position of 1-protected piperidinium ions **C**

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].



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

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.



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

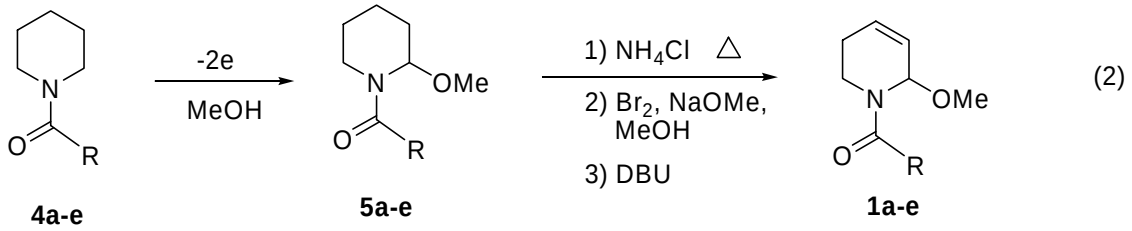
u : R'=*p*-MePh
v : R'=*p*-BrPh
w : R'=*p*-ClPh
x : R'=*p*-FPh
y : R'=*m*-ClPh

z : R'=*o*-ClPh

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 5*F*/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**.

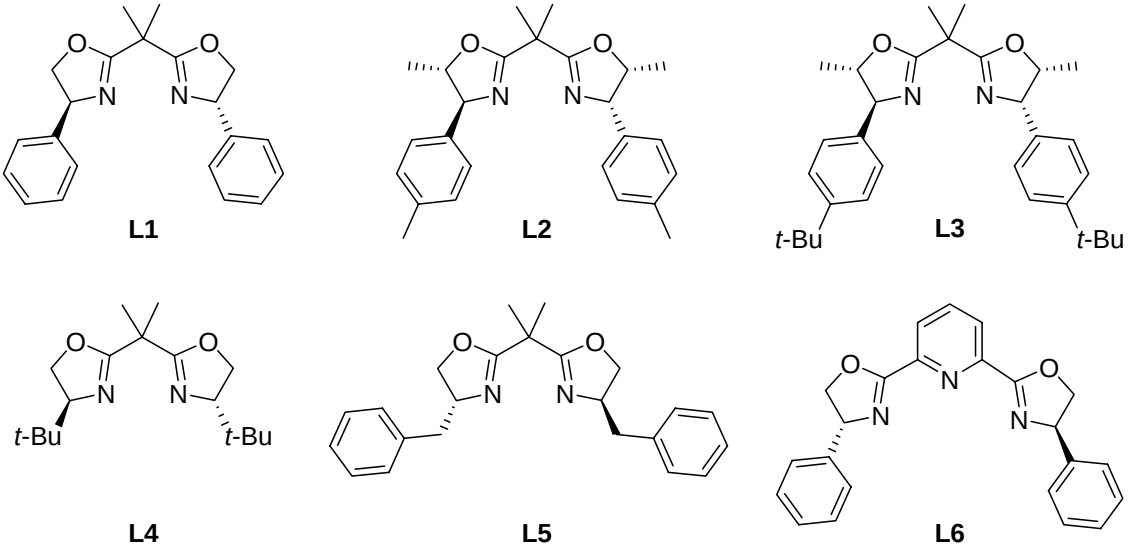
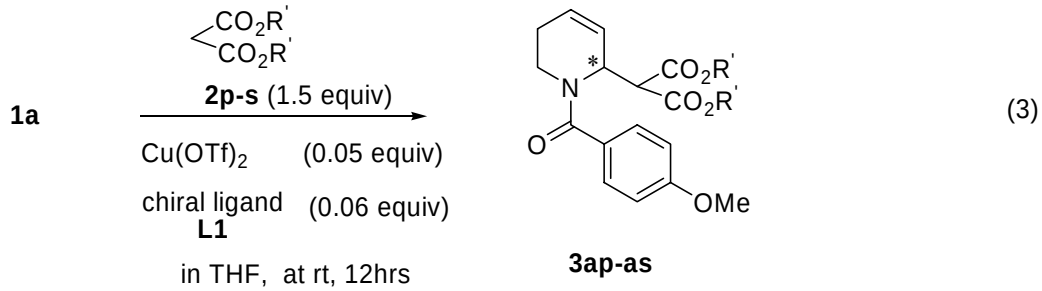


Figure 1. Bisoxazolines as chiral ligands

*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).



(3)

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).

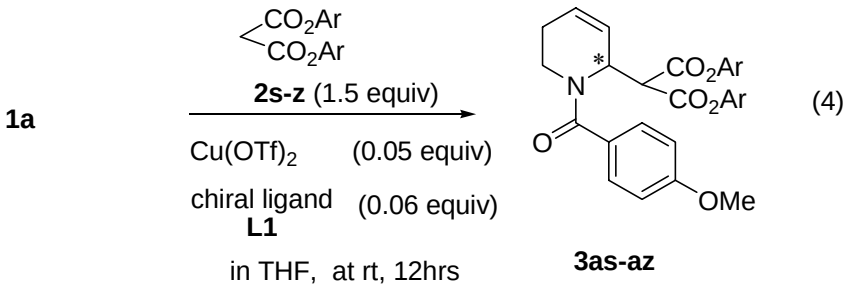
Table 1. Coupling reactions between **1a** and some malonates **2p-s**[a]

Entry	Malonic acid ester		Product	R'	Yield (%) [%e.e.][b]
1	CO_2Me / CO_2Me	**2p**	**3ap**	Me	78 [41]
2	CO_2Et / CO_2Et	**2q**	**3aq**	Et	0 [-]
3	CO_2t-Bu / CO_2t-Bu	**2r**	**3ar**	*t*-Bu	0 [-]
4	CO_2Ph / CO_2Ph	**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 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).



(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*-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).

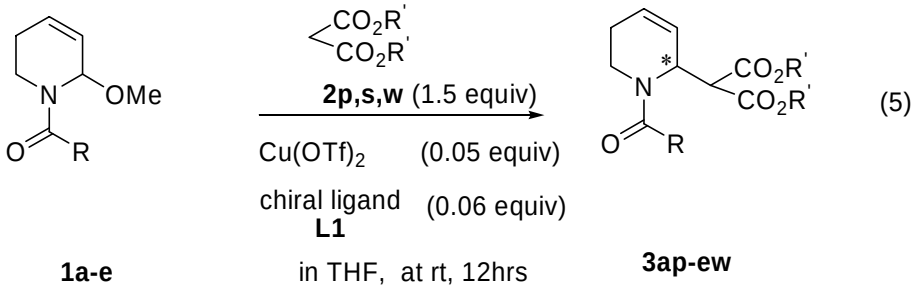
Table 2. Coupling reactions between **1a** and diaryl malonates **2s-z**[a]

Entry	Diaryl malonate Ar		Product	Yield (%)	%e.e.[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 12hrs under nitrogen atmosphere. [b] 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).



1a-e **3ap-ew** (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*-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-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).

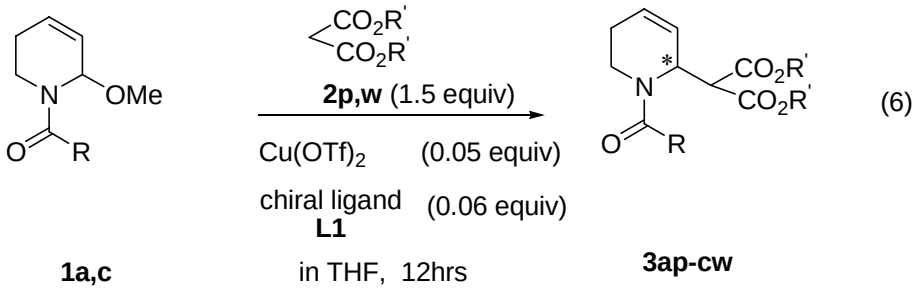
Table 3. Coupling reactions between **1a-e** and malonates **2p,s,w** [a]

Entry	Substrate R		Malonate R^1		Product	Yield (%)	%e.e. [b]
1	*p*-MeOPh	**1a**	Me	**2p**	**3ap**	78	41
2		**1a**	Ph	**2s**	**3as**	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 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).



(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**[a]

Entry	Substrate R		Malonate R^1		Temperature	Product	Yield (%)	%e.e. [b]
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 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 5. Solvent effect on the coupling reaction of **1a** with **2w**[a]

Entry	Solvent	Yield (%) of **3aw**	%e.e.[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 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 **L1–6** (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 **2w**[a]

Entry	Ligand	Yield (%) of **3aw**	%e.e.[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 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.

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

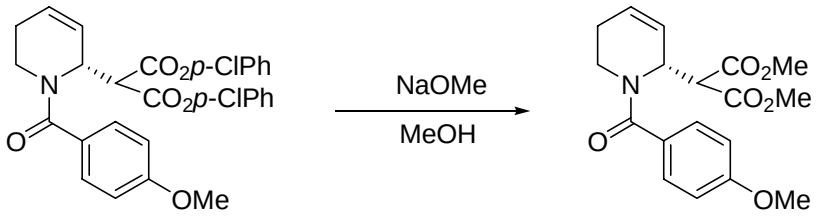
Entry	Lewis acid	Yield (%) of **3aw**	%e.e. of **3aw**[b]
1	$Cu(OTf)_2$	61	93
2	$Zn(OTf)_2$	68	24
3	$Mg(OTf)_2$	42	0
4	$Sc(OTf)_3$	trace	8
5	$Hf(OTf)_2$	0	-
6	$La(OTf)_2$	78	-8[c]
7	$CuCl_2$	0	-
8	$Cu(ClO_4)_2$	58	87
9	$Cu(BF_4)_2$	54	84
10	$Cu(SbF_6)_2$	36	67
11	$Cu(PF_6)_2$	0	-

[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 12hrs under nitrogen atmosphere. [b] Determined by chiral HPLC. c The reverse stereochemistry was observed.

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 1-3,6). $Sc(OTf)_3$ 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.

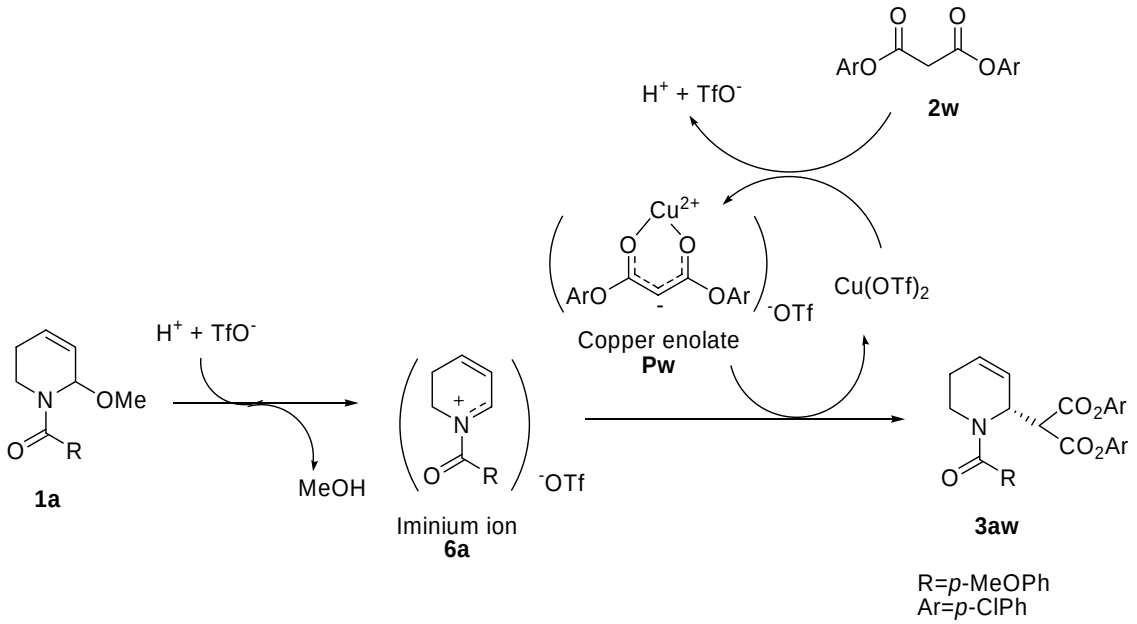


(7)

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

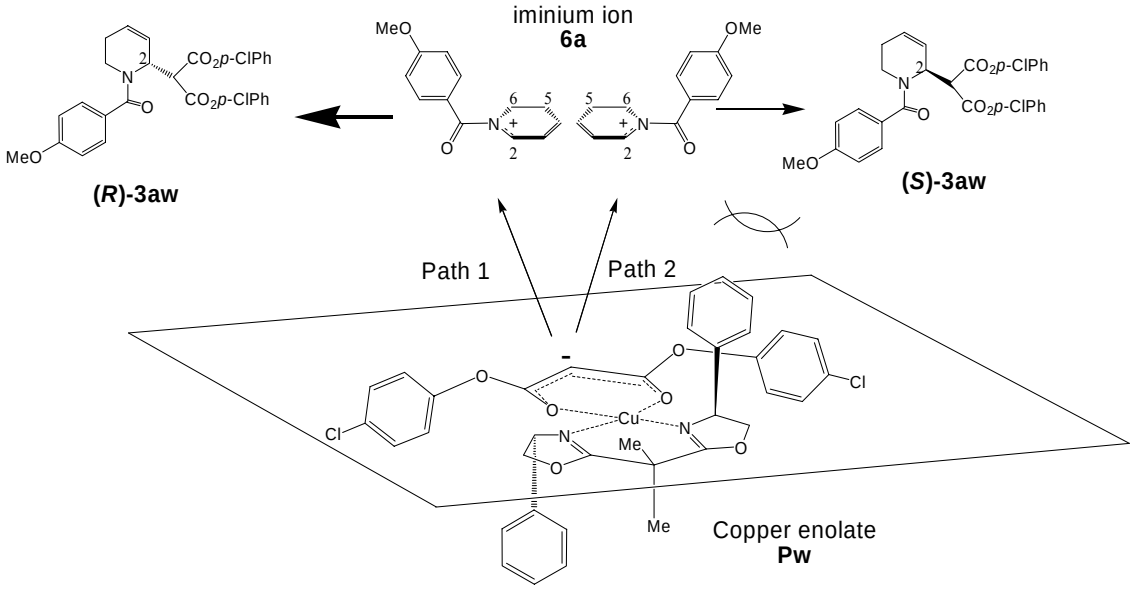
2.11. Reaction mechanism

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.

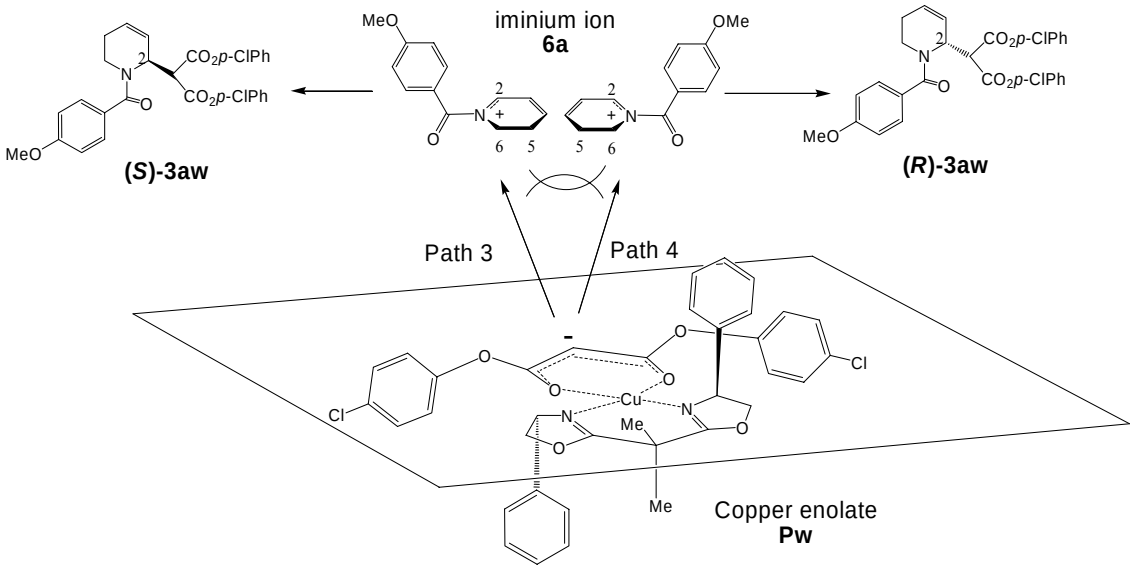


Scheme 3. A plausible reaction mechanism

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 $C_{5,6}$ 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).



Scheme 4. Stereochemical outcome 1



Scheme 5. Stereochemical outcome 2

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 %e.e. of the couling 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(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^oC. 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. ^1H 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. 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}; ^1H 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.

*4.4. 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^{o}C; IR (neat) 2950, 2840, 1767, 1752, 1514, 1472, 1300, 1186, 1102, 1034 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.80 (s, 6H), 3.82 (s, 2H), 6.90 (d, J=9.0Hz, 4H), 7.07 (d, J=8.7Hz, 1H); HRMS (M, EI) calcd for $C_{17}H_{16}O_6$ 316.0947. found 316.0929.

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

Pale brown solid; mp 67-69^{o}C; IR (neat) 3073, 2940, 1773, 1752, 1590, 1474, 1431,

1197, 1134, 1070 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 3.86 (s, 2H), 7.07 (d, *J*=8.0Hz, 2H), 7.20 (s, 2H), 7.26 (d, *J*=8.0Hz, 2H), 7.35 (t, J=8.1Hz, 2H); HRMS (M, EI) calcd for $C_{15}H_{10}Cl_2O_6$ 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}; ^1H NMR ($CDCl_3$) δ 3.98 (s, 2H), 7.20-7.35 (m, 6H), 7.448 (d, *J*=8.1Hz, 2H); HRMS (M, EI) calcd for $C_{15}H_{10}Cl_2O_4$ 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 for12 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° (c=0.5, $CHCl_3$); IR (neat) 2934, 2840, 1752, 1624, 1608, 1487, 1429, 1304, 1250, 1192, 1134, 1090, 1015 cm^{-1}; ^1H 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*=8.4Hz, 1H), 5.75-5.90 (m, 1H), 6.00-6.20 (m, 2H), 6.90 (d, *J*=8.7Hz, 2H), 7.05-7.20 (m, 4H), 7.27-7.40 (m, 6H); HRMS (M, EI) calcd for $C_{28}H_{23}Cl_2NO_6$ 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°(c=0.5, $CHCl_3$); IR (neat) 3044, 2936, 2840, 1752, 1628, 1512, 1493, 1427, 1304, 1250, 1186, 1136, 1026 cm^{-1}; ^1H 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=7.8Hz, 1H), 5.80-5.95 (m, 1H), 6.00-6.20 (m, 2H), 6.90 (d, *J*=9.0Hz, 2H), 7.10-7.45 (m, 12H); HRMS (M, EI) calcd for $C_{28}H_{25}NO_6$ 471.1682 found 471.1664.

The e.e. was obtained by DAICEL Chiralcel OD (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0ml/min, detection at 210nm, 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°(c=0.5, $CHCl_3$); IR (neat) 2932, 2840, 1750, 1628, 1609, 1507, 1426, 1304, 1252, 1136, 843 cm^{-1}; ^1H 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*=8.1Hz, 1H), 5.80-5.90 (m, 1H), 6.00-6.20 (m, 2H), 6.89 (d, *J*=8.7Hz, 2H), 7.03 and 7.06 (2d, *J*=9.0Hz, 4H), 7.16 and 7.19 (2d, *J*=9.0Hz, 4H), 7.36 (d, *J*=8.7Hz, 2H); HRMS (M, EI) calcd for $C_{30}H_{29}NO_6$ 499.1995 found 499.1986.

The e.e. was obtained by DAICEL Chiralcel OD (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 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°(c=0.5, $CHCl_3$), IR (neat) 2936, 2838, 2249, 1752, 1640, 1508, 1458, 1304, 1254, 1134, 1068, 1012 cm^{-1}; ^1H 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*=8.3Hz, 1H), 5.75-5.90 (m, 1H), 6.00-6.15 (m, 2H), 6.90 (d, *J*=8.5Hz, 2H), 7.00-7.15 (m, 4H), 7.32 (d, *J*=8.5Hz, 2H), 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 (ϕ4.6mm, 250mm) [hexane/isopropanol (5/1) (v/v), 1.0mL/min, detection at 210nm, 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°(c=0.5, $CHCl_3$); IR (neat) 3078, 2936, 2840, 1754, 1628, 1611, 1507, 1429, 1306, 1254, 1136, 1030, 843 cm^{-1}; ^1H 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*=8.1Hz, 1H), 5.80-5.95 (m, 1H), 6.00-6.20 (m, 2H), 6.90 (d, *J*=8.7Hz, 2H), 7.00-7.20

(m, 8H), 7.33 (d, *J*=8.7Hz, 2H); HRMS (M, EI) calcd for $C_{28}H_{23}F_2NO_6$ 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; $[\alpha]_D^{22}$ +61.6°(c=0.25, $CHCl_3$); IR (neat) 3069, 2934, 2838, 1754, 1624, 1591, 1512, 1471, 1427, 1304, 1248, 1192, 1129 cm^{-1}; ^1H 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 $C_{28}H_{23}Cl_2NO_6$ 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, 8min 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; $[\alpha]_D^{20}$ +38.8° (c=0.5, $CHCl_3$); IR (neat) 2936, 2840, 1759, 1628, 1609, 1512, 1478, 1428, 1304, 1254, 1136, 1061 cm^{-1}; ^1H 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*=8.7Hz, 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 $C_{28}H_{23}Cl_2NO_6$ 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; $[\alpha]_D^{21}$ +88.1°(c=0.5, $CHCl_3$); IR (neat) 3044, 2955, 2840, 1752, 1701, 1591, 1491, 1447, 1410, 1300, 1188 cm^{-1}; ^1H 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*=7.8Hz, 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; $[\alpha]_D^{21}$ +82.2°(c=0.5, $CHCl_3$); IR (neat) 2955, 1754, 1701, 1487, 1300, 1200, 1196, 1092, 1015 cm^{-1}; ^1H 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 $C_{22}H_{19}Cl_2NO_6$ 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; $[\alpha]_D^{22}$ +60.0°(c=0.25, $CHCl_3$); IR (neat) 2932, 1753, 1632, 1487, 1429, 1306, 1192, 1090, 1015 cm^{-1}; ^1H 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*=8.4Hz, 1H), 5.88 (br d, *J*=6.9Hz, 1H), 6.05-6.15 (m, 2H), 7.09 (d, *J*=8.9Hz, 2H), 7.15 (d, *J*=8.9Hz, 2H), 7.30-7.45 (m, 9H); HRMS (M, EI) calcd for $C_{27}H_{21}Cl_2NO_5$ 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; $[\alpha]_D^{19}$ +40.3°(c=0.25, $CHCl_3$); IR (neat) 2930, 1752, 1632, 1487, 1431, 1306, 1194, 1090, 1015 cm^{-1}; ^1H 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 $C_{27}H_{20}{}^{35}Cl_2{}^{37}ClNO_5$ 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 12min for major enantiomer.

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

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}; ^1H 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 7.8Hz, 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 $C_{27}H_{21}Cl_2NO_6$ 525.0746 found 525.0741.

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 9min 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 $MgSO_4$. 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%e.e.). $[\alpha]_D^{25}$ +172.4°(c=0.25, $CHCl_3$).

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

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