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Note

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The application of bidentate oxazoline-carbene ligands with planar and central chirality in asymmetric β-boration of α,β-unsaturated esters

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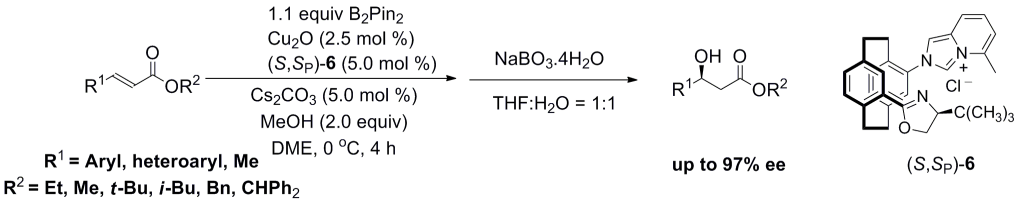


ABSTRACT:

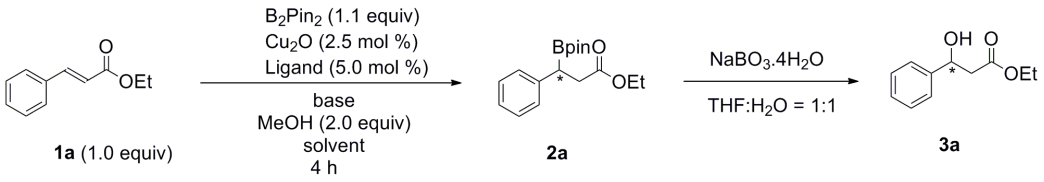
A series of new oxazoline substituted imidazolium salts based on [2.2]paracyclophane was synthesized and characterized. The new bidentate oxazoline-carbene precursor with planar and central chirality had significant advantage than the bicyclic 1,2,4-triazolium salt derived from [2.2]paracyclophane as a monodentate carbene ligand in Cu(I)-catalyzed asymmetric β-boration of α,β-unsaturated esters, giving the desired products in high enantioselectivities and yields.

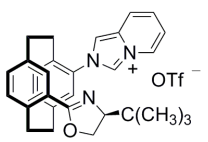
The asymmetric conjugate addition of diboron reagents to α,β-unsaturated compounds has been studied for a long time because the C−B bond can be converted into a wide variety of functional groups without loss of enantiopurity. [1] In recent years, many publications have focused on this transformation. [2] In 2008, the first attempt to catalyze the asymmetric β-boration of α,β-unsaturated esters was made by Yun et al. [3] Then copper-catalyzed asymmetric conjugate additions of diboron reagents to α,β- and α,β,γ,δ-unsaturated esters using different chiral bidentate phosphines as ligands have been developed. [4] In 2009, Fernández and co-workers firstly applied the monodentate NHC-copper complex to enantioselective boration of α,β-unsaturated esters. [5] Since then, catalysis mediated by NHC metal complexes has emerged as a powerful tool for this asymmetric transformation [6] because these catalysts have significant advantages over their phosphine counterparts. [7] Of course, the asymmetric conjugate addition of diboron reagents to α,β-unsaturated esters was also studied by Kobayashi and Nishiyama using chiral bidentate N-containing ligands. [8] On the other hand, Hoveyda first disclosed the metal-free catalytic β-boration of α,β-unsaturated esters and ketones.[9a] The NHC-catalyzed enantioselective boron conjugate additions were shown to be mechanistically unique, allowing them to be complementary to the more extensively examined copper-catalyzed variants.[9] Despite the fact that many exciting results have been achieved, the design of novel chiral ligands to enhance the enantioselectivity is still a challenge.

Planar chiral [2.2]paracyclophane-based ligands play an important role in asymmetric catalysis.[10] In 2003, the synthesis and application of chiral

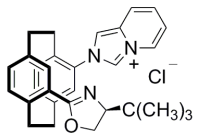
pseudo-ortho-disubstituted [2.2]paracyclophanyl bidentate oxazoline-carbene ligands were firstly reported by Bolm *et al*.[10a] Since then, our group identified both diastereoisomers of *pseudo-geminal* and *pseudo-ortho* oxazoline substituted [2.2]paracyclophanyl imidazo[1,5-*a*]pyridinium triflates and successfully applied them to copper(I)-catalyzed enantioselective boration of α,β-unsaturated ketones.[10n] Very recently, our group had synthesized and characterized a series of monodentate bicyclic triazolium ligands based on [2.2]paracyclophane which induced exceptional enantioselectivities in copper(I)-mediated β-boration of α,β-unsaturated N-acyloxazolidinones and α,β-unsaturated acyclic enones.[11] However, the above monodentate carbene-copper complexes induced β-boration of α,β-unsaturated esters in only low to moderate enantioselectivity. We therefore report a series of new *pseudo-ortho* oxazoline substituted [2.2]paracyclophanyl imidazo[1,5-*a*]pyridinium salts and their applications in copper(I)-catalyzed asymmetric β-boration of α,β-unsaturated esters.

Table 1. Screening of the reaction conditions[a]

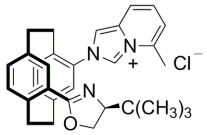




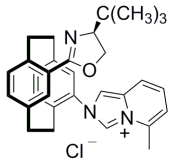
(*S*,*S*$_P$)-**4**



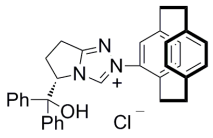
(*S*,*S*$_P$)-**5**



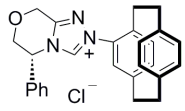
(*S*,*S*$_P$)-**6**



(*S*,*R*$_P$)-**6**



(*S*,*S*$_P$)-**7**



(*R*,*R*$_P$)-**8**

entry	ligand	solvent	T (^{o}C)	base	yield(%)[b]	ee(%)[c]
1[d]	(*S*,*S*$_P$)-**4**	THF	0	Cs_2CO_3 (5 mol %)	80	21 (*S*)
2	(*S*,*S*$_P$)-**5**	THF	0	Cs_2CO_3 (5 mol %)	86	85 (*S*)
3	(*S*,*S*$_P$)-**6**	THF	0	Cs_2CO_3 (5 mol %)	88	95 (*S*)
4	(*S*,*R*$_P$)-**6**	THF	0	Cs_2CO_3 (5 mol %)	80	58 (*R*)
5[e]	(*S*,*S*$_P$)-**6**	THF	0	Cs_2CO_3 (5 mol %)	81	93 (*S*)
6	(*S*,*S*$_P$)-**6**	dioxane	0	Cs_2CO_3 (5 mol %)	84	93 (*S*)
7	(*S*,*S*$_P$)-**6**	CH_2Cl_2	0	Cs_2CO_3 (5 mol %)	80	80 (*S*)
8	(*S*,*S*$_P$)-**6**	Et_2O	0	Cs_2CO_3 (5 mol %)	87	95 (*S*)
9	(*S*,*S*$_P$)-**6**	$PhCH_3$	0	Cs_2CO_3 (5 mol %)	85	91 (*S*)
10	(*S*,*S*$_P$)-**6**	DME	0	Cs_2CO_3 (5 mol %)	87	96 (*S*)
11	(*S*,*S*$_P$)-**6**	DME	25	Cs_2CO_3 (5 mol %)	85	94 (*S*)
12	(*S*,*S*$_P$)-**6**	DME	40	Cs_2CO_3 (5 mol %)	81	91 (*S*)
13	(*S*,*S*$_P$)-**6**	DME	-10	Cs_2CO_3 (5 mol %)	42	95 (*S*)
14	(*S*,*S*$_P$)-**6**	DME	0	Cs_2CO_3 (2.5 mol %)	80	40 (*S*)
15	(*S*,*S*$_P$)-**6**	DME	0	Cs_2CO_3 (7.5 mol %)	84	74 (*S*)
16	(*S*,*S*$_P$)-**6**	DME	0	Cs_2CO_3 (20 mol %)	86	66 (*S*)
17	(*S*,*S*$_P$)-**6**	DME	0	CsF (5 mol %)	84	80 (*S*)
18	(*S*,*S*$_P$)-**7**	DME	0	Cs_2CO_3 (5 mol %)	88	10 (*S*)
19	(*R*,*R*$_P$)-**8**	DME	0	Cs_2CO_3 (5 mol %)	90	71 (*R*)

[a]The reaction was carried out with ligand (5.0 mol %), Cu_2O (2.5 mol %), B_2Pin_2 (0.21 mmol), **1a** (0.19 mmol) and MeOH (0.38 mmol) in solvent (1.0 mL). [b]Yield of isolated product after oxidated by $NaBO_3.4H_2O$. [c]Determined by HPLC analysis using

a chiral stationary phase (Chiralpak IA column). [d]The carbene-Cu(I) was prepared by reaction of Cu_2O (2.5 mol %), (S,S_P)-**4** (5.0 mol %)and KI (5.0 mol %) in THF at 60 ^oC for 12 h. [e]Using the carbene-$CuCl_2$ as a catalyst.

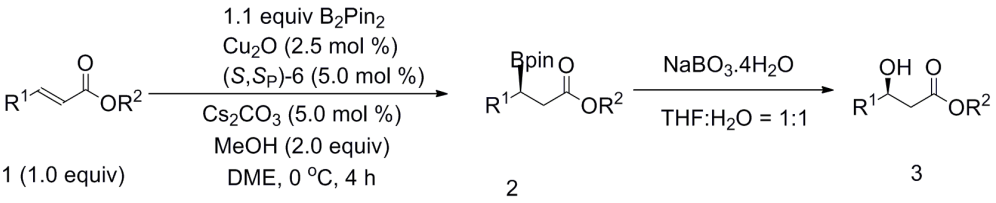
According to our previously reported procedure for the asymmetric boration of α,β-unsaturated ketones, [10n] ethyl cinnamate **1a** was selected as the model substrate. With 5.0 mol % of (S,S_P)-**4**, 2.5 mol % of Cu_2O, 5.0 mol % of KI, 5.0 mol % of Cs_2CO_3, 1.1 equiv of B_2Pin_2, 1.0 equiv of **1a**, and 2.0 equiv of MeOH in 1.0 mL THF, the boration reaction proceeded smoothly at 0 ^oC to provide, after the usual sodium perborate workup, the hydroxyl compound **3a** with high yield (80%) but low enantioselectivity (21% ee) (Table1, entry1). It is worth to note that the reaction of imidazo[1,5-*a*]pyridinium triflate (S,S_P)-**4** and Cu_2O failed to give any carbene-Cu complexes. However, in the presence of KI, a mixture of carbene copper complexes generated *in situ* by reaction of (S,S_P)-**4** and Cu_2O was not a good catalyst (Table 1, entry 1). Based on our previous research, [11] imidazo[1,5-*a*]pyridinium chloride (S,S_P)-**5** prepared by anion exchange of the (S,S_P)-**4** with an ion exchange resin [12] may be a suitable carbene precursor. To our delight, the reaction afforded improved enantioselectivity (85% ee) by using (S,S_P)-**5** as a ligand (Table 1, entry 2). Inspired by this result, we turned our attention to the preparation of new imidazo[1,5-*a*]pyridinium chlorides and investigation of new catalyst systems for the asymmetric boration reaction. We were interested to see whether the enantioselectivity could be enhanced by introducing a methyl group to the α-position of pyridinium. Hence imidazo[1,5-*a*]pyridinium chlorides (S,S_P)-**6** and (S,R_P)-**6** were

synthesized and examined in conjugate boration of ethyl cinnamate. Fortunately, the desired product **3a** was obtained in 88% yield and 95% ee with ligand (S,S_P)-**6** (Table 1, entry 3). However, its diastereomer (S,R_P)-**6** gave the corresponding product in 80% yield but in only 58% ee (Table 1, entry 4). The absolute configuration of the major enantiomer obtained with (S,S_P)-**6** was opposite to that obtained with (S,R_P)-**6** by comparing the sign of optical rotation of product **3a**, which revealed that the absolute configuration of product **3a** was determined by the planar chirality of the imidazolium salts. Moreover, the best result among them was obtained by using ligand (S,S_P)-**6**, in which the planar chirality and central chirality have the cooperative effect.

In order to optimize conditions with (S,S_P)-**6** as carbene precursor, a number of parameters were varied by using ethyl cinnamate **1a** as substrate. Carbene-Cu (II) displayed lower catalytic activity in this reaction in terms of either yield or enantioselectivity (Table 1, entry 5). Among the solvents screened (Table 1, entries 6-10), ethylene glycol dimethyl ether gave the best enantioselectivity (96% ee) and a good yield (87%), so it was chosen as the optimal solvent (Table 1, entry 10). The impact of temperature on the boration reaction was investigated next. The enantioselectivity could be increased by decreasing reaction temperature from 40 to 0 ^oC (Table 1, entries 10-12). However, there was no improvement in the enantiomeric excess of **3a** by a further decrease in temperature from 0 to -10 ^oC (Table 1, entry 13). These results suggested that the convenience of 0 ^oC made it the preferred temperature for the asymmetric reaction. The effect of the bases was also evaluated (Table 1, entries 14-17). The reduction of the amount of Cs_2CO_3 from 5 to 2.5 mol %

caused a significant decrease in the reaction rate and enantioselectivity (Table 1, entry 14), while increasing the amounts of Cs_2CO_3 resulted in low enantioselectivities (Table 1, entries 15-16). The enantioselectivity was not improved by using CsF instead of Cs_2CO_3 (Table 1, entries 17). As catalytic activity reached an acceptable level, we extensively screened triazolium ligands (S,S_P)-**7** and (R,R_P)-**8** which induced exceptional enantioselectivities in the copper(I)-mediated β-boration of α,β-unsaturated N-acyloxazolidinones and α,β-unsaturated acyclic enones. [10] However, the enantioselectivities dropped severely under the optimized conditions (Table 1, entries 18, 19). The screening indicated that imidazo[1,5-*a*]pyridinium chloride (S,S_P)-**6** was still the optimal ligand in terms of enantioselectivity and catalytic activity.

Table 2. Investigating the substrate scope of the reaction[a]



entry	R^1	R^2	yield [b](%)	ee[c] (%)
1	Ph	Et	87 (3a)	96 (*S*)
2	Ph	Me	84 (3b)	95 (*S*)
3	Ph	*t*-Bu	87 (3c)	96 (*S*)
4	Ph	*i*-Bu	82 (3d)	96 (*S*)
5	Ph	Bn	86(3e)	95 (*S*)
6	Ph	$CHPh_2$	95 (3f)	95 (*S*)
7	2-MeC_6H_4	Et	86 (3g)	94 (*S*)

8	3-MeC_6H_4	Et	95 (3h)	96 (*S*)
9	4-MeC_6H_4	Et	85 (3i)	88 (*S*)
10	2-ClC_6H_4	Et	92 (3j)	96 (*S*)
11	3-ClC_6H_4	Et	90 (3k)	90 (*S*)
12	4-ClC_6H_4	Et	87 (3l)	97 (*S*)
13	2-$MeOC_6H_4$	Et	89 (3m)	97 (*S*)
14	3-$MeOC_6H_4$	Et	86 (3n)	95 (*S*)
15	2-$CF_3C_6H_4$	Et	66 (3o)	96 (*S*)
16	3-$CF_3C_6H_4$	Et	68 (3p)	78 (*S*)
17	4-$CF_3C_6H_4$	Et	76 (3q)	97 (*S*)
18	1-Naphthyl	Et	85 (3r)	90 (*S*)
19	2-Naphthyl	Et	83 (3s)	96 (*S*)
20	2-Furyl	Et	80 (3t)	77 (*S*)
21	Me	$CHPh_2$	91 (3u)	70 (*R*)
22[d]	Cyclohexyl	Et	90 (3v)	92 (*S*)

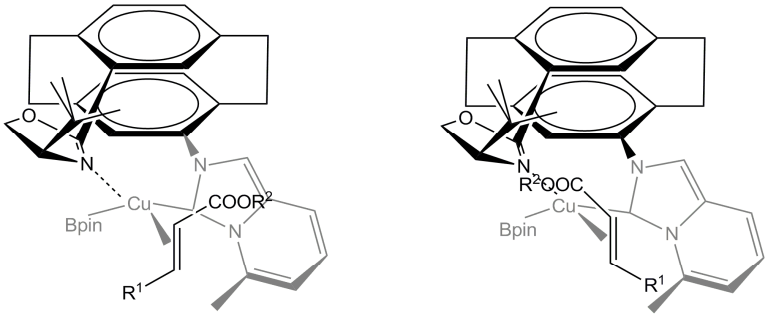
[a]The reaction was carried out with (S,S_P)-**6** (5.0 mol %), Cu_2O (2.5 mol %), Cs_2CO_3 (5.0 mol %), B_2Pin_2 (0.21 mmol), Substrate (0.19 mmol) and MeOH (0.38 mmol) in DME (1.0 mL) at 0 °C. [b]Yield of isolated product after oxidated by $NaBO_3.4H_2O$. [c]Determined by HPLC analysis using a chiral stationary phase (Chiralpak IB or IA column). [d]The ee value was determined as benzoylated compound.

Having established an optimal protocol, we then investigated the reaction with a variety of α,β-unsaturated esters. As shown in Table 2, the enantiomeric excess for the methyl cinnamate was similar to that obtained in the ethyl cinnamate case (Table 2,

entries 1-2). A further increase in the size of the ester moiety of the substrate to *i*-butyl as well as *t*-butyl could not alter the enantioselectivity by any appreciable amount (Table 2, entries 3-4). We also observed that the benzyl ester (95% ee) and the more bulky diphenyl methyl ester derivatives of cinnamic acid (95% ee) provided asymmetric inductions very similar to that found for **1a** (96% ee), although diphenyl methyl cinnamate showed an increase in yield to 95% (Table 2, entries 5-6). These results disclosed that the structures of different ester moieties do not significantly influence the enantioselectivity of the reaction. Then, we continued to evaluate various β-aryl substituted unsaturated ethyl esters in order to investigate the substituent effect. It is worthy to note that the electronic properties of the ethyl cinnamate derivatives have an important effect on both reactivity and enantioselectivity. When ethyl cinnamate derivatives having an electron-donating group in the phenyl ring were subjected to the boration reaction, high yields (85-95%) and enantioselectivities (94-97% ee) were observed except for the case of ethyl β-(4-methylphenyl)acrylate, in which the enantioselectivity was only 88% ee. The substrates bearing an electron-withdrawing group such as Cl and CF_3 at the 2 or 4-position in the aromatic ring provided the products with excellent enantioselectivity (96-97% ee), while, 3-position substitution at the phenyl ring lowered the ee value (Table 2, entries 11 and 16). On the other hand, when a trifluoromethyl group was introduced to the phenyl ring of ethyl cinnamate, lower yields were obtained (Table 2, entries 15-17). Moreover, 1- and 2-naphthyl substituted α,β-unsaturated esters were also tolerated and gave the corresponding products in good yields (83-85%) and

enantioselectivities (90-96% ee). However, the heteroaromatic furan-substituted substrate afforded the desired product with a lower enantioselectivity (77% ee). The scope was also extended to β-alkyl substituted unsaturated ester. The diphenylmethyl methylacrylate gave satisfactory conversion within the reaction time but yielded the product with poor enantioselectivity (70% ee). When ethyl β-(cyclohexyl)acrylate was used as a substrate for the reaction, the high yield and enantioselectivity were obtained again (Table 2, entry 22).

Based on the absolute configuration of the products, a postulated model of transition states is shown in Figure 1. The observed sense of chiral induction is in compliance with a proposed transition state model where the steric bulkiness of the *tert*-butyl group and the methyl group may give rise to an enantiofacial preference for the accessible *Si* face and as a result, lead to the major (*S*)-product (Figure 1, Favored). In contrast to reactions with the less sterically demanding *Si*-face attack, the activated C=C bond is approached by the boryl group at its *Re*-face to cause steric repulsion between the substituents on the oxazoline-carbene skeleton and the cinnamate substrate, leading to the minor (*R*)-product (Figure 1, Disfavored). Such a transition state model can provide a clear explanation of the high enantioselectivities observed for the asymmeric boration of α,β-unsaturated esters.



Si-face Favored

Re-face Disfavored

Figure 1. Postulated model of transition states for the asymmetric boration

In conclusion, we have developed a series of chiral bidentate oxazoline-carbene precursors based on [2.2]paracyclophane and demonstrated their utilization in copper-catalyzed enantioselective β-boration of α,β-unsaturated eaters. The new imidazo[1,5-*a*]pyridinium chloride is more efficient than the bicyclic triazolium salts derived from [2.2]paracyclophane with regard to both reactivity and enantioselectivity and affords the desired products with high yields and excellent enantiomeric excesses regardless of the structures of different ester moieties.

Experimental Section

imidazo[1,5-*a*]pyridinium triflate (S,S_P)-**4** was synthesized following a reported procedure. [10n]

General procedure for the synthesis of imidazo[1,5-*a*]pyridinium chloride.

A solution of 4-amino-12-oxazolinyl[2.2]paracyclophane[10n] (0.14 mmol) and 6-methyl-2-pyridine aldehyde (0.14 mmol) in toluene (2.0 mL) was stirred and refluxed overnight. The reaction mixture was concentrated in vacuum to give the corresponding imine as yellow oil, which was not stable enough for further purification and used to next step directly. To a suspension of AgOTf (62.5 mg, 0.24

mmol) in THF (1.0 mL) was added chloromethyl pivalate (0.036 mL, 0.24 mmol) and the resulting suspension was sealed and stirred for 30 min in the dark. Then the above imine in DCM (1.0 mL) was added and the mixture was stirred in a sealed tube in the dark at 40 °C for 12 h. After the reaction mixture was cooled to room temperature, EtOH (1.0 mL) was added and filtered. The filtrate was concentrated in vacuum and subjected to column chromatography on silica gel (DCM/MeOH = 30:1) to afford the desired imidazo[1,5-*a*]pyridinium triflate as a white solid. The corresponding imidazo[1,5-*a*]pyridinium chloride was obtained easily by anion exchange of its triflate analogue with an ion-exchange resin (chloride form) according the same method as described by McQuade.[12]

imidazolium salt (*S*,S_P)-**5.** White solid: 32.8 mg, 48.2% yield, mp171–173 °C, $[\alpha]_D^{25}$ = +180 (*c* 0.14 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.47 (s, 1H), 9.64 (d, *J* = 5.7Hz, 1H), 9.53 (s, 1H), 7.79 (d, *J* = 9.3 Hz, 1H), 7.23 (d, *J* = 2.7Hz, 1H), 7.09 – 7.05 (m, 1H), 6.91 – 6.77 (m, 6H), 4.40 – 4.33 (m, 1H), 4.00 (dd, *J* = 11.7, 3.0 Hz, 1H), 3.91 – 3.80 (m, 2H), 3.65 – 3.58 (m, 1H), 3.29 – 3.13 (m, 1H), 3.10 – 2.94 (m, 4H), 2.41 – 2.28 (m, 1H), 1.00 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 142.1, 140.2, 137.8, 136.8, 136.4, 136.0, 135.1, 134.9, 133.7, 133.0, 130.2, 128.9, 127.6, 126.7, 125.9, 125.1, 118.1, 117.5, 112.6, 59.4, 45.3, 35.3, 34.4, 33.6, 33.2, 26.8, 25.9. HRMS (ESI-TOF) m/z: $[M-Cl]^+$ calcd for $C_{30}H_{32}N_3O$ 450.2545; found 450.2573.

imidazolium salt (*S*,S_P)-**6.** White solid: 46.5 mg, 66.4% yield, mp 167–169 °C, $[\alpha]_D^{25}$ = +300 (*c* 0.17 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (s, 1H), 9.66 (s, 1H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.20 (d, *J* = 6.0 Hz, 1H), 7.17 (d, *J* = 6.9Hz, 1H), 6.95 (d, *J* =

0.9Hz, 1H), 6.89 (s, 1H), 6.86 (d, J = 8.1 Hz, 1H), 6.79 – 6.74 (m, 3H), 4.60 – 4.41 (m, 1H), 4.38 – 4.27 (m, 2H), 4.08 – 4.00 (m, 1H), 3.74 – 3.67 (m, 1H), 3.28 – 3.18 (m, 1H), 3.16 – 3.01 (m, 5H), 2.95 – 2.73 (m, 2H), 2.42 – 2.26 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 142.0, 140.7, 139.6, 137.8, 137.7, 136.2, 135.1, 133.8, 130.9, 130.5, 128.3, 126.8, 126.2, 125.3, 116.5, 115.8, 115.7, 114.3, 114.2, 75.3, 69.3, 35.8, 34.5, 34.1, 33.7, 33.6, 26.0, 19.9. HRMS (ESI-TOF) m/z: $[M\text{-}Cl]^+$ calcd for $C_{31}H_{34}N_3O$ 464.2702; found 464.2704.

imidazolium salt (S,R_P)-**6.** White solid: 20.4 mg, 29.1% yield, mp153–155 °C, $[\alpha]_D^{25}$ = +170 (c 0.17 CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.37 (d, J = 9.0 Hz, 1H), 9.77 (s, 1H), 7.71 (d, J = 9.3 Hz, 1H), 7.23 (dd, J = 9.3, 6.9 Hz, 1H), 7.11 (s, 1H), 6.93 (d, J = 6.6 Hz, 1H), 6.91 (d, J = 5.1 Hz, 1H), 6.81 – 6.76 (m, 4H), 4.56 – 4.50 (m, 1H), 4.31 – 4.19 (m, 2H), 3.88 (dd, J = 13.2, 9.6 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.27 – 3.16 (m, 1H), 3.16 – 3.03 (m, 5H), 2.98 – 2.88 (m, 1H), 2.82 – 2.71 (m, 1H), 2.30 – 2.24 (m, 1H), 1.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 141.9, 140.1, 139.7, 137.9, 136.1, 135.2, 135.1, 134.5, 134.2, 133.7, 131.1, 130.0, 128.3, 126.2, 125.9, 125.6, 117.0, 115.9, 114.2, 69.0, 35.1, 34.0, 33.8, 33.7, 33.5, 26.6, 19.6. HRMS (ESI-TOF) m/z: $[M\text{-}Cl]^+$ calcd for $C_{31}H_{34}N_3O$ 464.2702; found 464.2704.

General procedure for the copper-catalyzed β-boration of α,β-unsaturated esters. imidazolium salt (S,S_P)-**6** (4.74 mg, 9.5×10^{-3} mmol), Cu_2O (0.68 mg, 4.75×10^{-3} mmol) were added to 1.0 mL anhydrous THF in an oven dried Schlenk flask under an argon atmosphere. The mixture was stirred at 60 °C overnight to give a yellow solution of the Cu-complex. Then the solvent was evaporated under argon at 80 °C

and 1.0 mL anhydrous DME was added at room temperature. Cs_2CO_3 (3.1 mg, 9.5 × 10^{-3} mmol) and bis(pinacolato)diboron (53.1 mg, 0.209 mmol) were added consecutively. The mixture was stirred at room temperature for 10 minutes and cooled to 0 °C. Then α,β-unsaturated esters (0.19 mmol) and MeOH (15.2 μL, 0.38 mmol) were added simultaneously to the stirred mixture. After being stirred for 4h at 0 °C, the solvent was removed under the reduced pressure and the crude product was subjected to the oxidation with sodium peroxoborate (146 mg, 5.0 equiv) in THF (1.0 mL) and H_2O (1.0 mL) at room temperature for 1.5 h. The reaction mixture was concentrated in vacuum and the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate = 30:1 – 10:1), giving the corresponding alcohol **3**.

(*S*)-Ethyl 3-hydroxy-3-phenylpropanoate 3a. Colorless oil: 32.1 mg, 87% yield, 96% ee, $[\alpha]_D^{25}$ = -49.2 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (75:1, 220nm, 1.0 mL/min), retention time: 33.7 min (minor), 35.5 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.27 (m, 5H), 5.13 (dd, *J* = 8.3, 4.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.27 (s, 1H), 2.87 – 2.61 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Methyl 3-hydroxy-3-phenylpropanoate 3b. Colorless oil: 28.8 mg, 84% yield, 95% ee, $[\alpha]_D^{25}$ = -55.2 (*c* 0.15, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (75: 1, 220nm, 1.0 mL/min), retention time: 41.1 min (minor), 44.0 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.22 (m, 5H), 5.14 (dd, *J* = 8.4, 4.4 Hz, 1H), 3.73 (s, 3H), 3.17 (s, 1H), 2.87 –

2.62 (m, 2H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-*tert*-Butyl 3-hydroxy-3-phenylpropanoate 3c. Colorless oil: 36.7 mg, 87% yield, 96% ee, $[\alpha]_D^{25}$ = -41.6 (*c* 0.15, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (75: 1, 220nm, 1.0 mL/min), retention time: 22.9 min (minor), 25.0 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.26 (m, 5H), 5.09 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.37 (s, 1H), 2.75 – 2.58 (m, 2H), 1.45 (s, 9H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-*iso*-Butyl 3-hydroxy-3-phenylpropanoate 3d. Colorless oil: 34.6 mg, 82% yield, 96% ee, $[\alpha]_D^{25}$ = -40.5 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (200: 1, 220nm, 1.0 mL/min), retention time: 74.0 min (minor), 77.8 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 5H), 5.14 (dd, J = 8.2, 4.6 Hz, 1H), 3.91 (d, *J* = 6.7 Hz, 2H), 2.97 (s, 1H), 2.84 – 2.67 (m, 2H), 1.93 (dp, *J* = 13.4, 6.7 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 6H). Other spectra and properties data matched those reported in the literature.[6b]

(*S*)-Benzyl 3-hydroxy-3-phenylpropanoate 3e. Colorless oil: 41.9 mg, 86% yield, 95% ee, $[\alpha]_D^{25}$ = -25.1 (*c* 0.12, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (50: 1, 220nm, 1.0 mL/min), retention time: 40.8 min (minor), 47.6 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.17 (m, 10H), 5.56 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.19 – 5.09 (m, 2H), 3.17 (s, 1H), 3.00 – 2.61 (m, 2H). Other spectra and properties data matched those reported in the

literature.[8c]

(*S*)-Diphenyl methyl 3-hydroxy-3-phenylpropanoate 3f. white solid: 60.0 mg, 95% yield, 95% ee, $[\alpha]_D^{25}$ = -35.1 (*c* 0.15, $CHCl_3$); mp 63–65 ^oC The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (75: 1, 220nm, 1.0 mL/min), retention time: 71.4 min (major), 78.0 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 15H), 6.92 (s, 1H), 5.16 (dd, *J* = 8.4, 4.2 Hz, 1H), 3.11 (s, 1H), 2.95 – 2.80 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 142.4, 139.8, 139.7, 128.6, 128.5, 128.1, 128.0, 127.8, 127.1, 127.0, 125.7, 70.3, 43.6; HRMS (ESI-TOF) m/z: $[M+Na]^+$calcd for $C_{22}H_{20}NaO_3$ 355.1310; found 355.1319.

(*S*)-Ethyl 3-hydroxy-3-(2-methylphenyl)propanoate 3g. Colorless oil: 34.0 mg, 86% yield, 94% ee, $[\alpha]_D^{25}$ = -61.8 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 19.1 min (major), 23.0 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.44 (m, 1H), 7.27 – 7.10 (m, 3H), 5.34 (dd, *J* = 8.5, 4.2 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.11 (s, 1H), 2.76 – 2.57 (m, 2H), 2.34 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(3-methylphenyl)propanoate 3h. Colorless oil: 37.6 mg, 95% yield, 96% ee, $[\alpha]_D^{25}$ = -48.3 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 22.4 min (major), 25.2 min (minor); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.05 (m, 4H), 5.10 (dd, *J* = 8.5, 4.3 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H),

3.23 (s, 1H), 2.84 – 2.62 (m, 2H), 2.35 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(4-methylphenyl)propanoate 3i. Colorless oil: 33.6 mg, 85% yield, 88% ee, $[\alpha]_D^{25}$ = -41.5 (*c* 0.12, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (30: 1, 220nm, 1.0 mL/min), retention time: 35.4 min (major),40.2 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 5.09 (dd, J = 8.7, 4.1 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.18 (s, 1H), 2.84 – 2.58 (m, 2H), 2.34 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(2-chlorophenyl)propanoate 3j. Colorless oil: 40.0 mg, 92% yield, 96% ee, $[\alpha]_D^{25}$ = -74.8 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 17.6 min (major), 27.2 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.62 (m, 1H), 7.35 – 7.19 (m, 3H), 5.49 (dd, J = 9.6, 2.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.24 (s, 1H), 2.86 (dd, J = 16.6, 2.7 Hz, 1H), 2.69 – 2.51 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13a]

(*S*)-Ethyl 3-hydroxy-3-(3-chlorophenyl)propanoate 3k. Colorless oil: 39.1 mg, 90% yield, 90% ee, $[\alpha]_D^{25}$ = -35.5 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 21.8 min (major), 30.0 min (minor); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.40 (s, 1H), 7.33 – 7.21 (m, 3H), 5.11 (t, *J* = 6.3 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.39 (s, 1H), 2.71 (d, *J* = 6.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13b]

(*S*)-Ethyl 3-hydroxy-3-(4-chlorophenyl)propanoate 3l. Colorless oil: 37.8 mg, 87% yield, 97% ee, $[\alpha]_D^{25}$ = -39.5 (*c* 0.11, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (75: 1, 220nm, 1.0 mL/min), retention time: 73.1 min (minor), 76.6 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 4H), 5.10 (dd, *J* = 7.4, 5.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 1H), 2.72 – 2.67 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(2-methoxyphenyl)propanoate 3m. Colorless oil: 37.9 mg, 89% yield, 88% ee, $[\alpha]_D^{25}$ = -51.2 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (75: 1, 220nm, 0.5 mL/min), retention time: 61.2 min (major), 66.0 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 4.41 (m, 1H), 7.29 – 7.23 (m, 1H), 7.00 – 6.98 (m, 1H), 6.95 – 6.86 (m, 1H), 5.36 (dd, *J* = 9.0, 3.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 2.86 – 2.66 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13a]

(*S*)-Ethyl 3-hydroxy-3-(3-methoxyphenyl)propanoate 3n. Colorless oil: 36.6 mg, 86% yield, 95% ee, $[\alpha]_D^{25}$ = -33.4 (*c* 0.2, CHCl3); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 31.7 min (major), 35.2 min (minor); ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.29 – 7.23 (m, 1H), 6.95 – 6.92 (m, 2H), 6.84 – 6.80 (m, 1H), 5.11 (dd, *J* = 8.1, 4.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.29 (s, 1H), 2.81 – 2.63 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13a]

(*S*)-Ethyl 3-hydroxy-3-(2-trifluoromethylphenyl)propanoate 3o. Colorless oil: 33.0 mg, 66% yield, 96% ee, $[\alpha]_D^{25}$ = -42.0 (*c* 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (15: 1, 254nm, 0.5 mL/min), retention time: 11.2 min (major), 27.4 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.82 (m, 1H), 7.65 – 7.57 (m, 2H), 7.42 – 7.37 (m, 1H), 5.55 (d, *J* = 8.5 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.50 (d, *J* = 2.4 Hz, 1H), 2.78 – 2.55 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13c]

(*S*)-Ethyl 3-hydroxy-3-(3-trifluoromethylphenyl)propanoate 3p. Colorless oil: 33.9 mg, 68% yield, 78% ee, $[\alpha]_D^{25}$ = -27.5 (*c* 0.12, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 18.5 min (major), 28.6 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.59 – 7.45 (m, 3H), 5.19 (td, *J* = 6.3, 3.6 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.49 (d, *J* = 3.5 Hz, 1H), 2.74 (d, *J* = 6.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13d]

(*S*)-Ethyl 3-hydroxy-3-(4-trifluoromethylphenyl)propanoate 3q. Colorless oil: 38.0 mg, 76% yield, 95% ee, $[\alpha]_D^{25}$ = -39.5 (*c* 0.1, $CHCl_3$); The enantiomeric excess

was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (50: 1, 220nm, 1.0 mL/min), retention time: 24.6 min (major), 27.5 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 5.20 – 5.17 (m, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.54 (d, *J* = 3.0 Hz, 1H), 2.72 (d, *J* = 6.3 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(naphthalen-1-yl)propanoate 3r. Colorless oil: 39.4 mg, 85% yield, 90% ee, $[\alpha]_D^{25}$ = -65.2 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 254nm, 0.5 mL/min), retention time: 39.6 min (major), 46.8 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.70 (d, *J* = 7.1 Hz, 1H), 7.58 – 7.43 (m, 3H), 5.92 (dd, *J* = 9.1, 3.4 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 1H), 2.97 – 2.78 (m, 2H), 1.28 (t, *J* = 7.2 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(naphthalen-2-yl)propanoate 3s. Colorless oil: 38.5 mg, 83% yield, 96% ee, $[\alpha]_D^{25}$ = -27.5 (*c* 0.12, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 81.5 min (major), 84.5 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.78 (m, 4H), 7.52 – 7.42 (m, 3H), 5.30 (dd, *J* = 7.8, 4.9 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.40 (s, 1H), 2.94 – 2.71 (m, 2H), 1.26 (*t*, J = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[8c]

(*S*)-Ethyl 3-hydroxy-3-(furan-2-yl)propanoate 3t. Colorless oil: 28.0 mg, 80% yield,

77% ee, $[\alpha]_D^{25}$ = -17.5 (*c* 0.1, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (50: 1, 220nm, 1.0 mL/min), retention time: 32.6 min (minor), 35.5 min (major); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.34 – 6.32 (m, 1H), 6.29 – 6.27 (m, 1H), 5.14 (dd, *J* = 8.1, 4.4 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.27 (s, 1H), 2.95 – 2.79 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). Other spectra and properties data matched those reported in the literature.[13b]

(*R*)-Diphenyl methyl 3-hydroxy-3-methylpropanoate 3u. Colorless oil: 36.0 mg, 91% yield, 70% ee, $[\alpha]_D^{25}$ = -23.5 (*c* 0.2, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Chiralpak IB column, n-hexane/i-PrOH (30: 1, 220nm, 0.5 mL/min), retention time: 33.9 min (major), 36.0 min (minor); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 10H), 6.91 (s, 1H), 4.33 – 4.17 (m, 1H), 2.87 (s, 1H), 2.66 – 2.50 (m, 2H), 1.22 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 139.9, 139.8, 128.6, 128.5, 128.1, 128.0, 127.1, 127.0, 64.3, 43.1, 22.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{17}H_{18}NaO_3$ 293.1154; found 293.1142.

(*S*)-Ethyl 3-hydroxy-3-cyclohexylpropanoate 3v. Colorless oil: 34.2 mg, 90% yield, 92% ee, The enantiomeric excess value was determined as benzoylated compound by HPLC with a Chiralpak IA column, n-hexane/i-PrOH (75: 1, 220nm, 1.0 mL/min), retention time: 10.5 min (minor), 16.9 min (major); $[\alpha]_D^{25}$ = -56.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.81 – 3.75 (m, 1H), 2.90 (s, 1H), 2.51 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.41 (dd, *J* = 16.2, 9.3 Hz, 1H), 1.89 – 1.65 (m, 5H), 1.44 – 0.95 (m, 9H). Other spectra and properties data matched those reported in the

literature.[13e]

The synthesis of (*S*)-Ethyl 3-benzoyloxy-3-cyclohexylpropanoate 3v'.

To the oxidized product (0.17 mmol) in dichloromethane (1.0 mL) was added pyridine (67.2 mg, 0.85 mmol) and benzoyl chloride (47.8 mg, 0.34 mmol). After the reaction mixture was stirred for 1 h at 0 ^{o}C, the resulting mixture was quenched with 1.0 mL water. The obtained organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by preparative TLC (n-hexane/AcOEt = 75/1) to afford benzoylated product as a colorless oil: 33.0 mg, 64% yield, $[\alpha]_D^{25}$ = -85.9 (*c* 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 2H), 7.58 – 7.53 (m, 1H), 7.46 – 7.41 (m, 2H), 5.45 – 5.31 (m, 1H), 4.15 – 4.02 (m, 2H), 2.71 – 2.68 (m, 2H), 1.85 – 1.67 (m, 5H), 1.44 – 1.08 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 166.1, 133.1, 130.6, 129.9, 128.6, 74.9, 60.9, 41.7, 37.3, 29.0, 28.3, 26.5, 26.3, 26.2, 14.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{25}O_4$ 305.1753; found 305.1753.

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Supporting Information Available: Full compound characterization and detailed spectral data for products, this material is available free of charge via the Internet at http://pubs.acs.org.

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