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Synthesis of (*S*)-7-Amino-5-azaspiro[2.4]heptane via Highly Enantioselective Hydrogenation of Protected Ethyl 1-(2-Aminoaceto)cyclopropanecarboxylates

Ying Yao,[†] Weizheng Fan,[†] Wanfang Li,[†] Xin Ma,[†] Lvfeng Zhu,[‡] Xiaomin Xie,[†] and Zhaoguo Zhang[†,§,*]

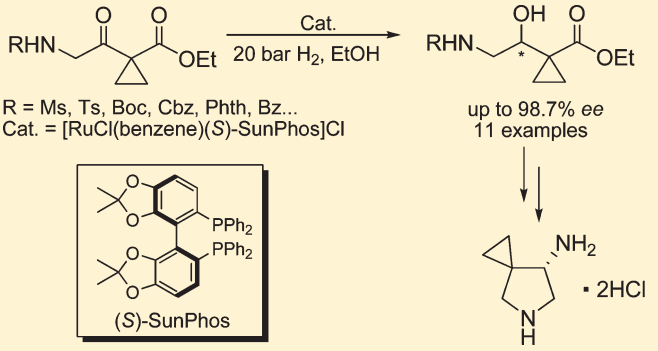
[†]School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China

[‡]School of Chemical Engineering, Nanjing University of Science & Technology, 200 Xiaolingwei, Nanjing 210094, China

[§]Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: Highly effective asymmetric hydrogenation of protected ethyl 1-(2-aminoaceto)cyclopropane carboxylates in the presence of [RuCl(benzene)(*S*)-SunPhos]Cl was realized, and high enantioselectivities (up to 98.7% ee) were obtained. This asymmetric hydrogenation provides a key intermediate for the enantioselective synthesis of (*S*)-7-amino-5-azaspiro[2.4]heptane moiety of quinolone antibacterial agents.



INTRODUCTION

Asymmetric reactions catalyzed by transition metals represent one of the most powerful tools for the synthesis of enantiomerically pure pharmaceuticals, agrochemicals, flavoring agents, and other fine chemicals.[1] In particular, asymmetric hydrogenation has attracted significant interest both in industry and in academia for its synthetic utility.[2] The therapeutic use of certain pyrido-[1,2-a]pyrimidine and quinolone antibacterial agents, such as Sitafloxacin and Olamufloxacin (Figure 1), are well-known.[3] Both molecules contain the (*S*)-7-amino-5-azaspiro[2.4]heptane moiety, which can be synthesized from an optically active tartrate ester intermediate or stereoselective microbial reduction of 5-benzyl-4,7-dioxo-5-azaspiro[2.4]heptane.[4] However, both synthetic routes suffer either low enantioselectivity or efficiency. Abbott reported a more efficient process for enantioselective synthesis of 3-aminopyrrolydine derivatives by using enantiomerically pure ethyl 1-(2-{[(benzyloxy)carbonyl]amino}-1-hydroxyethyl)cyclopropanecarboxylate as a key intermediate.[5] Accordingly, the search for effective, highly enantioselective, and practical approaches to optically synthesize pure ethyl 1-(2-amino-1-hydroxyethyl)cyclopropanecarboxylate is of significance.

Asymmetric hydrogenation of β-keto esters has been extensively studied, especially with ruthenium catalysts.[6] It has been proven that several Ru-BINAP complexes give high enantioselectivities for a wide variety of β-keto esters.[7] Ruthenium catalysts with structurally similar chiral atropisomeric biaryl ligands have also been examined intensively for the hydrogenation of β-keto esters.[8] In contrast, there are limited substrates being investigated, usually restricted to simple β-alkyl or aryl substituents. Since notably lower enantioselectivities were usually observed due to the competitive coordination to the catalyst, only a few investigations have been dedicated to the use of substrates bearing adjacent coordinating groups, such as a benzyloxyl group,[9] alkoxyl group,[10] halogen atoms,[8c,11] *tert*-butoxycarbonylamino group,[11d] or a double bond[11e] in the vicinity of the keto group. Consequently, asymmetric hydrogenation of β-ketoesters bearing adjacent functional coordinating groups is still a challenging work.

Recently we designed new biaryl phosphine ligands and exploited their applications in ruthenium-catalyzed asymmetric hydrogenation of simple β-keto esters,[12a,b] α-keto esters[12c−g] and β-keto sulfones[12h] with excellent enantioselectivities. In this paper, we disclose a highly enantioselective hydrogenation of ethyl 1-(2-aminoaceto)cyclopropanecarboxylates with a variety of amino-protecting groups.

RESULTS AND DISCUSSION

Subtle changes in geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations of reactivity and enantioselectivity.[8a,13] To test these effects, Ru-catalyzed

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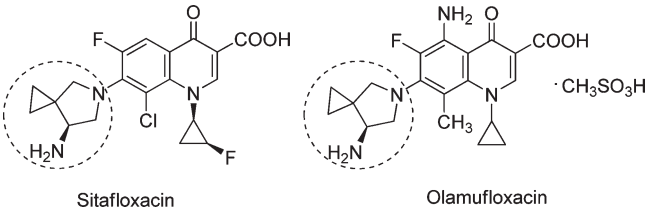


Figure 1. Structures of Sitafloxacin and Olamufloxacin.

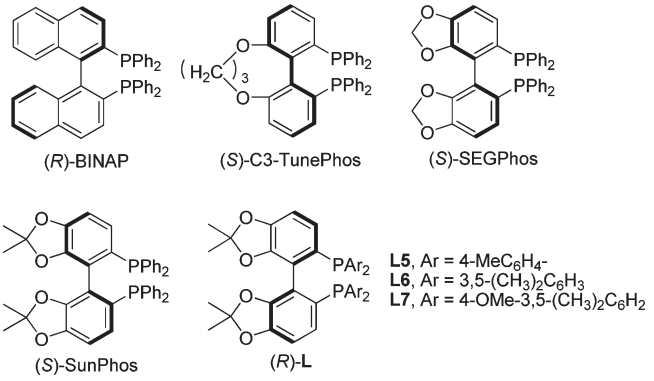
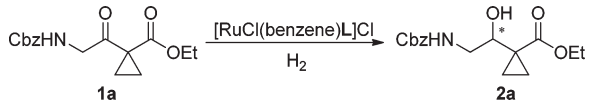


Figure 2. Strutures of chiral bidentate ligands.

Table 1. Catalytic Asymmetric Hydrogenation of 1a with [RuCl(benzene)L]Cl[a]

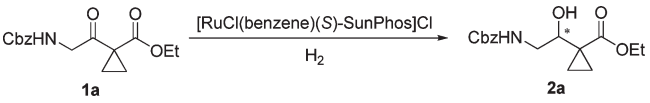


entry	ligand	ee (%)[b]
1	(*R*)-BINAP	92.5
2	(*S*)-C3-TunePhos	94.4
3	(*S*)-SEGPhos	95.3
4	(*S*)-SunPhos	97.1
5	**L5**	96.5
6	**L6**	95.2
7	**L7**	95.5

[a] All reactions were carried out with a substrate (0.5 mmol) concentration of 0.2 M in EtOH under 20 bar of H_2 for 18 h, substrate/[Ru(benzene)Cl_2]$_2$/ligand = 100/0.5/1.1. Conversion: 100%. No ring-opening product was detected. [b] ee values were determined by HPLC on a Chiralpak OD-H column.

asymmetric hydrogenation of ethyl 1-{2-[(benzyloxycarbonyl)-amino]acetyl}cyclopropanecarboxylate (**1a**) with the chiral bidentate ligands (*S*)-SunPhos, **L5**−**L7**, and three commercially available chiral bidentate phosphines, (*R*)-BINAP, (*S*)-SEGPhos, and (*S*)-C3-TunePhos (Figure 2), were performed under the same reaction conditions (Table 1). The catalyst was prepared from [Ru(benzene)Cl_2]$_2$ and a diphosphine ligand by refluxing them in degassed ethanol/dichloromethane for 1 h and then dried under reduced pressure.[12] The asymmetric hydrogenation was carried out under 20 bar of H_2, at 70 °C in EtOH for 18 h with 1 mol % of Ru(II) catalyst. While these ligands show similar reactivity, the enantioselectivity was greatly dependent on the ligand employed. As illustrated in Table 1, the

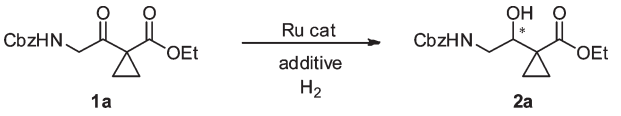
Table 2. Effects of Solvent and Temperature[a]



entry	solvent	*T* (°C)	convn (%)	ee (%)[b]
1	MeOH	70	100	95.1
2	EtOH	70	100	97.1
3	*i*-PrOH	70	100	95.0
4	DCM	70	100	29.7
5	THF	70	79.1	4.3
6	EtOH	50	100	95.9
7	EtOH	90	100	95.1

[a] All reactions were carried out with a substrate (0.5 mmol) concentration of 0.2 M in ethanol under 20 bar of H_2 for 18 h, substrate/[Ru(benzene)Cl_2]$_2$/(*S*)-SunPhos = 100/0.5/1.1. [b] ee values were determined by HPLC on a Chiralpak OD-H column.

Table 3. Effects of Additives on Catalytic Hydrogenation of 1a[a]



entry	additive	ee (%)[b]
1	1 M HCl	76.4
2	1 M HBr	85.3
3	1 M HI	89.6
4	1 M H_2SO_4	77.7
5	1 M CF_3COOH	85.0
6	1 M H_3BO_3	95.8
7	1 M CSA	81.4
8[c]	H_2O	93.9
9	$CeCl_3 \cdot 7H_2O$	96.1
10	I_2	83.2

[a] All reactions were carried out with a substrate (0.5 mmol) concentration of 0.2 M in EtOH under 20 bar of H_2 at 70 °C for 18 h, substrate/[Ru(benzene)Cl_2]$_2$/(*S*)-SunPhos/additive = 100/0.5/1.1/6. Conversion: 100%. [b] ee values were determined by HPLC on a Chiralpak OD-H column. [c] 0.03 mL of H_2O.

ee values of reduced product **2a** were increased with the reduction of the dihedral angles of the chiral ligands: (*R*)-BINAP (92.5% ee, dihedral angle:[13d] 86°), (*S*)-C3-TunePhos (94.4% ee, dihedral angle:[13b] 77°), (*S*)-SEGPhos (95.3% ee, dihedral angle:[13d] 67°). We were pleased to see that the highest ee was obtained with (*S*)-SunPhos (97.1%), which may because the bite angle of the [Ru((*S*)-SunPhos)(benzene)Cl]Cl (73°) was smaller than that of (*S*)-SEGPhos (75°).[12a] With **L5**−**L7** as ligands, the corresponding ee values of 96.5%, 95.2%, and 95.5% were achieved (Table 1), which revealed that the modifications of SunPhos on P atom did not impose a remarkable change in enantioselectivity in the asymmetric hydrogenation of **1a**.

Results of the optimization of solvents and reaction temperatures are summarized in Table 2. Solvent is important for the efficiency and enantioselectivity of the asymmetric hydrogenation (Table 2, entries 1−5). Protonic solvents resulted in high catalytic

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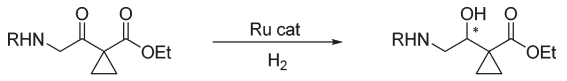
Table 4. Asymmetric Hydrogenation of 1 with [RuCl(benzene)(*S*)-SunPhos]Cl[a]



1 2

entry	R	ee (%)
1	Cbz (**1a**)	97.1[b]
2	Phth (**1b**)	84.7[b]
3	Bz (**1c**)	82.4[b]
4	Ms (**1d**)	97.5[c]
5	Ts (**1e**)	98.1[b]
6	Fmoc (**1f**)	98.3[b]
7	PhOCO (**1g**)	97.0[b]
8	Cl_3CCH_2OCO (**1h**)	94.8[c]
9	EtOCO (**1i**)	98.2[c]
10	*i*-BuOCO (**1j**)	96.6[c]
11	Boc (**1k**)	98.7[c]
12[d]	Cbz (**1a**)	96.2 (98.9)[e]

[a] All reactions were carried out with a substrate (0.5 mmol) concentration of 0.2 M in EtOH under 20 bar of H_2 at 70 °C for 18 h, substrate/[Ru(benzene)Cl_2]$_2$/(*S*)-SunPhos = 100/0.5/1.1. Conversion: 100%. [b] ee values were determined directly by HPLC. [c] ee values were determined through their corresponding *p*-nitrobenzoyl derivatives **3d, 3h, 3i, 3j, 3k** (see Experimental Section). [d] S/C = 500/1, 24 h. [e] The second ee value was examined after one recrystallization.

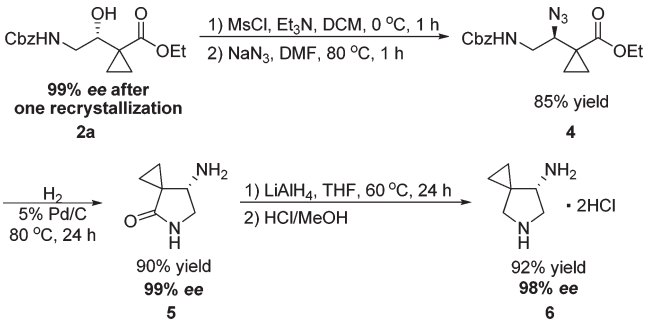
activities and enantioselectivities, providing complete conversions of **1a** to **2a** with ee values ranging from 95.0% (entry 3) to 97.1% (entry 2). Aprotonic solvents such as dichloromethane gave only 29.7% ee (entry 4), while THF gave even poorer ee of 4.3% and 79.1% conversion (entry 5). Temperatures can also influence the enantioselectivities (entry 2 vs 6, 7). Higher or lower the temperature may also slightly reduce the ee values.

It has been reported that additives play a crucial role in improving the reactivity and enantioselectivities in many asymmetric reactions.[14] In our preliminary work, we used aqueous solutions of Brønsted acids or Lewis acids as additives and achieved better results.[12] Accordingly, we evaluated a number of commonly used additives for the asymmetric hydrogenation of **1a** by using 1 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl as catalyst and 6 mol % of additives in an attempt to promote the enantioselectivity (Table 3). Unfortunately, the results did not turn out as we had expected. Using aqueous solutions of Brønsted acids as additives (entries 1−7), ee values decreased greatly, ranging from 76.4% to 89.6%, except for H_3BO_3, where the enantioselectivity remained. To find out what caused the enantioselectivity decrease, control test was performed (entry 8). The result showed that H_2O probably caused a slight decrease of ee value. Therefore, Brønsted acids were unfavorable for this reaction. Lewis acid, for example, $CeCl_3 \cdot 7H_2O$, was tried (entry 9), but the result was no better than those without additives. Using iodine as additive, the ee value decreased to 83.2% (entry 10).

On the basis of these results, the optimized reaction conditions were therefore set as the following: 1 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl as the catalyst, EtOH as the solvent with a substrate concentration of 0.2 M, and 20 bar of H_2 at 70 °C.

Under the optimized reaction conditions, a variety of protected ethyl 1-(2-aminoaceto)cyclopropanecarboxylates were

Scheme 1. Synthesis of (*S*)-7-Amino-5-azaspiro[2.4]heptane dihydrochloride



hydrogenated, as presented in Table 4. Noyori et al. had reported that using electron-withdrawing amino-protecting groups may reduce the competitive directing effects of the amino group versus the ester group within one molecule.[11d,15] Therefore we employ electron-withdarwing rather than electron-donating amino groups in our study (when dibenzyl was used as amino-protecting group, ee dropped to 11%; see Supporting Information). In all cases, complete conversions were obtained. The enantioselectivities were highly influenced by amino-protecting groups: phthaloyl-protected substrate (**1b**) and benzoyl-protected substrate (**1c**) gave moderate enantioselectivities: **2b** of 84.7% ee and **2c** of 82.4% ee were obtained, respectively (entries 2, 3). When sulfonyls were employed as amino-protecting groups, enantioselectivities for the hydrogenation turned out to be very high: product **2d** was obtained at 97.5% ee and **2e** at 98.1% ee (entries 4, 5). The presence of carbamate-protecting group gave even better ee values, ranging from 94.8% to 98.7% (entries 6−11). The employment of *tert*-butyloxycarbonyl group had accomplished the highest enantioselectivity (up to 98.7% ee). When **1a** was hydrogenated with [RuCl(benzene)(*S*)-SunPhos]Cl (S/C = 500/1) under the same reaction conditions, **2a** was also isolated in full conversion and 96.2% ee (entry 12), and via recrystallization, **2a** can be upgraded to 98.9% ee with 95% recovery.

(*S*)-7-Amino-5-azaspiro[2.4]heptane can be prepared from **2a** through a five-step transformation as outlined in Scheme 1. After methanesulfonation and azidation, compound **4** was produced in high yield. Reduction, deprotection, and cyclization of **4** was realized in one step and gave **5** in 90% yield and 98.9% ee, which was then converted to (*S*)-7-amino-5-azaspiro[2.4]heptane dihydrochloride (**6**) by reduction with LAH followed by salification in methanol in 92% yield over two steps.

CONCLUSION

In conclusion, we have developed a convenient protocol for highly enantioselective synthesis of protected ethyl 1-(2-amino-1-hydroxyethyl)cyclopropanecarboxylate by hydrogenation of protected ethyl 1-(2-aminoaceto)cyclopropanecarboxylate. This established a potentially practical mean for the synthesis of (*S*)-7-amino-5-azaspiro[2.4]heptane, which is a key intermediate of quinolone antibacterial agents.

EXPERIMENTAL SECTION

General. Commercially available reagents were used throughout without further purification other than those detailed below. Methylene

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chloride was distilled over calcium hydride. Ethanol was distilled over magnesium under nitrogen. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted. ^{1}H NMR spectra were recorded at 400 MHz, with TMS as internal standard. ^{13}C NMR spectra were obtained at 100 MHz and referenced to the central peak of 77.00 ppm for $CDCl_3$. Coupling constants (J) are reported in hertz and refer to apparent peak multiplications. Mass spectroscopy data were collected on an HRMS-EI instrument. Flash column chromatography was performed on silica gel (300−400 mesh). $[\alpha]_D$ values are given in deg cm^2 g^{-1} and were recorded at the D-line of sodium (589 nm) at 20 °C.

Preparation of Ethyl 1-Acetylcyclopropanecarboxylate (S1)[16]. A mixture of ethyl acetoacetate (66.0 g, 0.51 mol), 1,2-dibromoethane (141.0 g, 0.75 mol), and anhydrous K_2CO_3 (260.3 g, 1.88 mol) was stirred in 600 mL of DMSO at room temperature overnight, after which it was diluted with an equal volume of water and then extracted with ether (300 mL × 3). The ether extract was washed with water and dried with anhydrous Na_2SO_4. After removal of the ether by distillation, the residue was distilled in vacuo. Colorless product was obtained (65.0 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): 4.21 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 1.47 (s, 4H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 203.0, 170.9, 61.1, 34.9, 29.8, 19.0, 13.9.

Preparation of Ethyl 1-(2-Azidoacetyl)cyclopropanecarboxylate (S2). To a solution of ethyl 1-acetylcyclopropanecarboxylate (46.4 g, 0.30 mol) in EtOH (250 mL) was added Br_2 (22.8 mL, 0.45 mol) dropwise over 20 min in an ice bath. After the solution was warmed at 25−30 °C for 80 min, water (250 mL) was added and the lower layer (organic layer) was separated. The upper layer was concentrated in vacuo and extracted with AcOEt (100 mL × 3). The organic layers were combined and washed with aqueous 10% $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution, and brine. The washed organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give the product (52.0 g, 74.5%) as colorless oil, which was used for the next reaction without further purification.

A 250 mL three-necked flask was charged with ethyl 1-(2-bromoacetyl)cyclopropanecarboxylate (52.0 g, 221 mmol), acetonitrile (150 mL), and sodium azide (15.8 g, 243 mmol) in the flowing nitrogen gas and the mixture was stirred at room temperature for 20 h. The produced sodium salt was separated by filtration and the solvent was distilled under reduced pressure. The residue was dissolved into EtOAc (150 mL) and washed with saturated brine (80 mL). The washed organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to obtain 47.0 g of a crude product, which was purified by column chromatography (PE/EA = 20/1) to give the desired product (39.7 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): 4.52 (d, J = 2.2 Hz, 2H), 4.20 (q, J = 7.2 Hz, 2H), 1.63 (s, 4H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 199.9, 170.1, 61.4, 58.2, 33.3, 21.1, 14.0. HRMS: calcd for $C_8H_{11}N_3O_3$ $(M + H)^+$ 198.0879, found 198.0866.

Typical Procedure for the Preparation of 1. A 50 mL round flask was charged with ethyl 1-(2-azidoacetyl)cyclopropanecarboxylate (5.0 g, 25.4 mmol), EtOH (25 mL), 5 mL of 6 N aqueous hydrochloric acid, and 100 mg of 10% palladium−carbon, and then the flask was taken into an autoclave. The pressure of H_2 was set to 30 psi. The autoclave was stirred at room temperature for 2 h. After release of hydrogen, the autoclave was opened, the palladium−carbon was separated by filtration, and the solvent was distilled under reduced pressure.

The residue was dissolved into CH_2Cl_2 (40 mL) and pyridine (6.0 g, 76.1 mmol) was added, then CbzCl (5.2 g, 30.4 mmol) was added dropwise over 20 min in an ice bath. After the solution was stirred at 25−30 °C for 16 h, saturated aqueous $NaHCO_3$ solution (25 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (20 mL × 3). The organic layers were combined and washed with 1 M aqueous hydrochloric acid, saturated aqueous $NaHCO_3$ solution and brine. The washed organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 6.7 g of crude product, which was purified by column chromatography (PE/EA = 6/1) to give the compound ethyl 1-[2-(benzyloxycarbonylamino)acetyl]-cyclopropanecarboxylate (**1a**) (5.9 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.36−7.29 (m, 5H), 5.47 (s, 1H), 5.11 (s, 2H), 4.59 (d, J = 5.2 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.58 (s, 4H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.9, 170.1, 156.1, 136.3, 128.4, 128.0, 127.9, 66.8, 61.4, 50.9, 33.3, 20.9, 14.0. HRMS: calcd for $C_{16}H_{19}NO_5$ $(M + Na)^+$ 328.1161, found 328.1168.

Likewisely, compounds **1b**−**k** were prepared from the corresponding amino-protecting groups and ethyl 1-(2-aminoaceto)cyclopropanecarboxylate.

Ethyl 1-[2-(1,3-Dioxoisoindolin-2-yl)acetyl]cyclopropanecarboxylate (1b). ^{1}H NMR (400 MHz, $CDCl_3$): 7.88−7.84 (m, 2H), 7.75−7.70 (m, 2H), 5.09 (s, 2H), 4.26 (q, J = 7.2 Hz, 2H), 1.69−1.63 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 198.0, 170.3, 167.8, 134.0, 132.1, 123.4, 61.5, 47.4, 33.5, 22.0, 14.1. HRMS: calcd for $C_{16}H_{15}NO_5$ (M^+) 301.0950, found 301.0947.

Ethyl 1-(2-Benzamidoacetyl)cyclopropanecarboxylate (1c). ^{1}H NMR (400 MHz, $CDCl_3$): 7.83−7.80 (m, 2H), 7.54−7.42 (m, 3H), 6.95 (s, 1H), 4.86 (d, J = 4.8 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 1.67−1.60 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 201.1, 170.1, 167.2, 134.0, 131.6, 128.6, 127.0, 61.6, 50.0, 33.6, 21.1, 14.1. HRMS: calcd for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1156.

Ethyl 1-[2-(Methylsulfonamido)acetyl]cyclopropanecarboxylate (1d). ^{1}H NMR (400 MHz, $CDCl_3$): 5.12 (t, J = 4.8 Hz, 1H), 4.62 (d, J = 5.2 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 2.96 (s, 3H), 1.70−1.62 (m, 4H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.7, 167.0, 109.7, 61.6, 52.4, 40.7, 33.2, 21.9, 14.0. HRMS: calcd for $C_9H_{15}NO_5S$ $(M + Na)^+$ 272.0582, found 272.0572.

Ethyl 1-[2-(4-Methylphenylsulfonamido)acetyl]cyclopropanecarboxylate (1e). ^{1}H NMR (400 MHz, $CDCl_3$): 7.76−7.73 (m, 2H), 7.31−7.29 (m, 2H), 5.37 (t, J = 5.0 Hz, 1H), 4.42 (d, J = 5.0 Hz, 2H), 4.17 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.59−1.56 (m, 2H), 1.46−1.43 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 199.8, 169.8, 143.6, 136.2, 129.6, 127.2, 61.5, 52.1, 33.2, 21.9, 21.5, 14.0. HRMS: calcd for $C_{15}H_{19}NO_5S$ (M^+) 325.0984, found 325.0979.

Ethyl 1-(2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}acetyl)cyclopropanecarboxylate (1f). ^{1}H NMR (400 MHz, $CDCl_3$): 7.78−7.29 (m, 8H), 5.50 (s, 1H), 4.62 (d, J = 5.2 Hz, 2H), 4.39 (d, J = 7.2 Hz, 2H), 4.22 (q, J = 7.1 Hz, 3H), 1.62−1.60 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 201.0, 170.1, 156.1, 143.8, 141.2, 127.6, 127.0, 125.0, 119.9, 67.0, 61.4, 50.9, 47.1, 33.4, 21.0, 14.0. HRMS: calcd for $C_{23}H_{23}NO_5$ (M^+) 393.1576, found 393.1573.

Ethyl 1-[2-(Phenoxycarbonylamino)acetyl]cyclopropanecarboxylate (1g). ^{1}H NMR (400 MHz, $CDCl_3$): 7.37−7.33 (m, 2H), 7.22−7.12 (m, 3H), 5.74 (t, J = 4.0 Hz, 1H), 4.68 (d, J = 5.1 Hz, 2H), 4.23 (q, J = 7.1 Hz, 2H), 1.63 (s, 4H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.7, 170.1, 154.4, 150.8, 129.2, 125.3, 121.5, 61.5, 51.0, 33.4, 21.1, 14.0. HRMS: calcd for $C_{15}H_{17}NO_5$ $(M + H)^+$ 292.1185, found 292.1181.

Ethyl 1-{2-[(2,2,2-Trichloroethoxy)carbonylamino]acetyl}cyclopropanecarboxylate (1h). ^{1}H NMR (400 MHz, $CDCl_3$): 5.72 (s, 1H), 4.74 (s, 2H), 4.66 (d, J = 5.1 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 1.65−1.60 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 200.5, 170.1, 154.3, 95.3, 74.5, 61.5, 51.0, 33.3, 21.4, 14.0. HRMS: calcd for $C_{11}H_{14}Cl_3NO_5$ $(M + H)^+$ 346.0016, found 346.0007.

Ethyl 1-[2-(Ethoxycarbonylamino)acetyl]cyclopropanecarboxylate (1i). ^{1}H NMR (400 MHz, $CDCl_3$): 5.36 (s, 1H), 4.57 (d, J = 5.2 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 4.13 (q, J = 7.1 Hz, 2H),

1.62−1.56 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 201.1, 170.2, 156.4, 61.5, 61.1, 50.8, 33.4, 20.9, 14.5, 14.0. HRMS: calcd for $C_{11}H_{17}NO_5$ $(M + H)^+$ 244.1185, found 244.1173.

Ethyl 1-[2-(Isobutoxycarbonylamino)acetyl]cyclopropanecarboxylate (1j). ^{1}H NMR (400 MHz, $CDCl_3$): 5.41 (s, 1H), 4.57 (d, J = 5.3 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.85 (d, J = 6.7 Hz, 2H), 1.95−1.88 (m, 1H), 1.58 (s, 4H), 1.30 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 201.1, 170.2, 156.5, 71.2, 61.4, 50.8, 33.3, 27.9, 20.8, 18.9, 14.0. HRMS: calcd for $C_{13}H_{21}NO_5$ $(M + H)^+$ 272.1498, found 272.1498.

Ethyl 1-[2-(*tert*-Butoxycarbonylamino)acetyl)cyclopropanecarboxylate (1k):[17]**.** ^{1}H NMR (400 MHz, $CDCl_3$): 5.20 (s, 1H), 4.49 (d, J = 5.2 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 1.57 (s, 4H), 1.45 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 201.4, 170.2, 155.6, 79.6, 61.4, 50.5, 33.3, 28.2, 20.6, 14.0.

Typical Procedure for the Asymmetric Hydrogenation. To a 20 mL Schlenk tube were added $[Ru(benzene)Cl_2]_2$ (5 mg, 0.01 mmol) and (*S*)-SunPhos (15 mg, 0.022 mmol). The tube was vacuumed and purged with nitrogen three times before addition of freshly distilled and degassed EtOH/DCM (2 mL/2 mL). The resulting mixture was heated at 50 °C for 1 h and then cooled to room temperature. The solvent was removed under vacuum to give the catalyst. This catalyst was dissolved in degassed ethanol (10 mL) and distributed equally to four vials. The β-ketoesters (0.5 mmol) were added to these vials, respectively, and were transferred to an autoclave. The autoclave was purged three times with H_2, and the pressure of H_2 was set to 20 bar. Then the autoclave was stirred under specific reaction conditions. After 18 h, the autoclave was then cooled to room temperature and the H_2 was carefully released. The autoclave was opened and the ethanol was evaporated. The enantiomeric excess was determined by HPLC after passing the residue through a short pad of silica gel column with petroleum ether and ethyl acetate.

Ethyl 1-[2-(Benzyloxycarbonylamino)-1-hydroxyethyl]cyclopropanecarboxylate (2a). ^{1}H NMR (400 MHz, $CDCl_3$): 7.38−7.30 (m, 5H), 5.27 (s, 1H), 5.10 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 3.58−3.53 (m, 1H), 3.41−3.27 (m, 3H), 1.33−1.20 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.02−0.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.1, 156.9, 136.3, 128.4, 128.0, 127.9, 73.6, 66.6, 60.7, 45.2, 25.9, 14.1, 14.0, 12.4. HRMS: calcd for $C_{16}H_{21}NO_5$ $(M + Na)^+$ 330.1304, found 330.1317.

Ethyl 1-[2-(1,3-Dioxoisoindolin-2-yl)-1-hydroxyethyl]cyclopropanecarboxylate (2b). ^{1}H NMR (400 MHz, $CDCl_3$): 7.88−7.83 (m, 2H), 7.75−7.70 (m, 2H), 4.26−4.19 (m, 3H), 3.94 (dd, J = 14.1, 4.0 Hz, 1H), 3.38−3.35 (m, 1H), 3.29 (d, J = 10.3 Hz, 1H), 1.36−1.22 (m, 2H), 1.32 (t, J = 7.1, 3H), 1.01−0.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 173.7, 168.6, 134.0, 132.0, 123.3, 73.5, 61.0, 42.2, 25.9, 14.9, 14.1, 12.8. HRMS: calcd for $C_{16}H_{17}NO_5$ $(M + H)^+$ 304.1185, found 304.1179.

Ethyl 1-(2-Benzamido-1-hydroxyethyl)cyclopropanecarboxylate (2c). ^{1}H NMR (400 MHz, $CDCl_3$): 7.80−7.77 (m, 2H), 7.52−7.41 (m, 3H), 6.76 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.94−3.88 (m, 1H), 3.81 (d, J = 7.9 Hz, 1H), 3.58−3.46 (m, 2H), 1.36−1.24 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H),1.07−0.98 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.4, 168.4, 134.1, 131.5, 128.5, 126.9, 73.6, 60.8, 44.6, 26.1, 14.3, 14.0, 12.4. HRMS: calcd for $C_{15}H_{19}NO_4$ $(M + H)^+$ 278.1392, found 278.1382.

Ethyl 1-[1-Hydroxy-2-(methylsulfonamido)ethyl]cyclopropanecarboxylate (2d). ^{1}H NMR (400 MHz, $CDCl_3$): 5.07 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.45−3.33 (m, 4H), 3.00 (s, 3H), 1.36−1.26 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.05−1.00 (m, 1H), 0.96−0.91 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.1, 73.4, 60.9, 47.2, 40.3, 25.8, 14.3, 14.0, 12.7. HRMS: calcd for $C_9H_{17}NO_5S$ $(M + H)^+$ 252.0906, found 252.0905.

Ethyl 1-[1-Hydroxy-2-(4-methylphenylsulfonamido)ethyl]cyclopropanecarboxylate (2e). ^{1}H NMR (400 MHz, $CDCl_3$): 7.76−7.73 (m, 2H), 7.32−7.30 (m, 2H), 5.11 (dd, J = 8.6, 3.6 Hz, 1H), 4.12−4.04 (m, 2H), 3.29−3.22 (m, 2H), 3.27 (d, J = 3.5 Hz, 1H), 3.15−3.07 (m, 1H), 2.43 (s, 3H), 1.31−1.20 (m, 2H), 1.19 (t, J = 7.1 Hz, 3H), 0.97−0.92 (m, 1H), 0.87−0.82 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.1, 143.5, 136.9, 129.7, 127.0, 73.6, 60.9, 47.0, 25.8, 21.5, 14.9, 14.0, 12.7. HRMS: calcd for $C_{15}H_{21}NO_5S$ $(M + H)^+$ 328.1219, found 328.1223.

Ethyl 1-(2-{[(9*H*-Fluoren-9-yl)methoxy]carbonylamino}-1-hydroxyethyl)cyclopropanecarboxylate (2f). ^{1}H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.40 (t, J = 7.3 Hz, 2H), 7.31 (td, J = 7.5, 1.1 Hz, 2H), 5.27 (s, 1H), 4.39 (d, J = 7.0 Hz, 2H), 4.21 (t, J = 7.1 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.60−3.54 (m, 1H), 3.43−3.26 (m, 3H), 1.34−1.22 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.03−0.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.3, 157.0, 143.8, 141.2, 127.6, 127.0, 125.0, 120.0, 74.3, 66.7, 60.8, 47.1, 45.3, 25.9, 14.7, 14.1, 12.5. HRMS: calcd for $C_{23}H_{25}NO_5$ $(M + H)^+$ 396.1811, found 396.1807.

Ethyl 1-[1-Hydroxy-2-(phenoxycarbonylamino)ethyl]cyclopropanecarboxylate (2g). ^{1}H NMR (400 MHz, $CDCl_3$): 7.38−7.33 (m, 2H), 7.21−7.18 (m, 1H), 7.13−7.10 (m, 2H), 5.58 (s, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.66−3.59 (m, 1H), 3.47−3.29 (m, 3H), 1.38−1.25 (m, 2H), 1.25 (t, J = 7.1, 3H), 1.05−0.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.3, 155.2, 150.9, 129.2, 125.3, 121.6, 74.4, 60.9, 45.5, 25.9, 15.0, 14.1, 12.6. HRMS: calcd for $C_{15}H_{19}NO_5$ $(M + H)^+$ 294.1341, found 294.1346.

Ethyl 1-{1-Hydroxy-2-[(2,2,2-trichloroethoxy)carbonylamino]ethyl}cyclopropanecarboxylate (2h). ^{1}H NMR (400 MHz, $CDCl_3$): 5.52 (s, 1H), 4.72 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.62−3.56 (m, 1H), 3.44−3.29 (m, 3H), 1.39−1.27 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.04−0.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.2, 155.0, 95.5, 74.5, 74.1, 60.9, 45.3, 25.9, 14.7, 14.0, 12.5. HRMS: calcd for $C_{11}H_{16}Cl_3NO_5$ $(M + H)^+$ 348.0172, found 348.0158.

Ethyl 1-[2-(Ethoxycarbonylamino)-1-hydroxyethyl]cyclopropanecarboxylate (2i). ^{1}H NMR (400 MHz, $CDCl_3$): 5.16 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.11 (dd, J = 7.1, 14.2 Hz, 2H), 3.56−3.31 (m, 4H), 1.34−1.21 (m, 8H), 1.03−0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.3, 157.3, 74.0, 60.9, 60.7, 45.2, 25.9, 14.5, 14.4, 14.0, 12.5. HRMS calcd for $C_{11}H_{19}NO_5$ $(M + Na)^+$ 268.1145, found 268.1149.

Ethyl 1-[1-Hydroxy-2-(isobutoxycarbonylamino)ethyl]cyclopropanecarboxylate (2j). ^{1}H NMR (400 MHz, $CDCl_3$): 5.22 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.83 (d, J = 6.6 Hz, 2H), 3.56−3.47 (m, 2H), 3.37−3.30 (m, 2H), 1.93−1.86 (m, 1H), 1.34−1.21 (m, 2H), 1.24 (t, J = 7.1, 3H), 1.04−0.89 (m, 2H), 0.92 (d, J = 6.7, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.2, 157.4, 73.6, 71.0, 60.6, 45.2, 27.8, 25.8, 18.9, 14.0, 13.9, 12.4. HRMS: calcd for $C_{13}H_{23}NO_5$ $(M + Na)^+$ 296.1474, found 296.1465.

Ethyl 1-[2-(*tert*-Butoxycarbonylamino)-1-hydroxyethyl]cyclopropanecarboxylate (2k). ^{1}H NMR (400 MHz, $CDCl_3$): 5.01 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.59−3.20 (m, 4H), 1.44 (s, 9H), 1.31−1.20 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.02−0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.4, 156.7, 79.5, 74.1, 60.7, 45.0, 28.3, 25.9, 14.3, 14.1, 12.4. HRMS: calcd for $C_{13}H_{23}NO_5$ $(M + Na)^+$ 296.1474, found 296.1461.

Typical Procedure for the Preparation of 3. A 25 mL round flask was charged with **2d** (1 mmol), pyridine (0.4 mL, 5 mmol), 4-nitrobenzoyl chloride (278 mg, 1.5 mmol), DMAP (6 mg) and CH_2Cl_2 (10 mL). The mixture was stirred at 25−30 °C for 6 h, saturated aqueous $NaHCO_3$ solution (5 mL) was added and the organic layer was separated. The organic layer was washed with 1 M aqueous hydrochloric acid, saturated aqueous $NaHCO_3$ solution and brine. The washed organic solution was dried over anhydrous Na_2SO_4 and

concentrated in vacuo to obtain 410 mg of crude product, which was purified by column chromatography (PE/EA = 1/1) to give compound 1-[1-(ethoxycarbonyl)cyclopropyl]-2-(methylsulfonamido)ethyl 4-nitrobenzoate (**3d**) (341 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): 8.33−8.29 (m, 2H), 8.23−8.20 (m, 2H), 5.14 (dd, J = 7.8, 4.0 Hz, 1H), 4.81 (t, J = 6.3 Hz, 1H), 4.22- 4.14 (m, 2H), 3.84−3.71 (m, 2H), 2.96 (s, 3H), 1.46−1.34 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.19−1.34 (m, 1H), 1.07−1.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.1, 164.2, 150.6, 134.9, 130.9, 123.6, 75.4, 61.1, 45.2, 40.8, 24.9, 14.1, 13.9, 13.8. HRMS: calcd for $C_{16}H_{20}N_2O_8S$ $(M + Na)^+$ 423.0847, found 423.0838. HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 80/20, 0.5 mL/min, 254 nm): t_1 = 37.0 min, t_2 = 46.3 min.

Likewisely, **3h**−**k** were prepared from the corresponding alcohols and 4-nitrobenzoyl chloride.

1-[1-(Ethoxycarbonyl)cyclopropyl]-2-[(2,2,2-trichloroethoxy)carbonylamino]ethyl 4-Nitrobenzoate (3h). ^{1}H NMR (400 MHz, $CDCl_3$): 8.32−8.19 (m, 4H), 5.34 (t, J = 6.3 Hz, 1H), 5.16 (dd, J = 8.3, 3.6 Hz, 1H), 4.68 (dd, J = 28.0, 12.0 Hz, 2H), 4.23−4.11 (m, 2H), 3.96−3.89 (m, 1H), 3.83−3.77 (m, 1H), 1.44−1.33 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.19−1.14 (m, 1H), 1.06−1.00 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.1, 164.2, 154.6, 150.6, 135.0, 130.9, 123.5, 95.3, 75.4, 74.4, 61.0, 43.6, 24.9, 14.1, 13.9. HRMS: calcd for $C_{18}H_{19}N_2O_8Cl_3$ $(M + Na)^+$ 519.0090, found 519.0105. HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 254 nm): t_1 = 26.0 min, t_2 = 28.5 min.

1-[1-(Ethoxycarbonyl)cyclopropyl]-2-(ethoxycarbonylamino)ethyl 4-Nitrobenzoate (3i). ^{1}H NMR (400 MHz, $CDCl_3$): 8.31−8.20 (m, 4H), 5.12 (dd, J = 8.3, 3.3 Hz, 1H), 4.96 (t, J = 5.8 Hz, 1H), 4.24−4.12 (m, 2H), 4.05 (q, J = 6.8 Hz, 2H), 3.87−3.71 (m, 2H), 1.43−1.31 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.22−1.14 (m, 3H), 1.06−0.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 164.2, 156.6, 150.6, 135.2, 130.9, 123.5, 76.0, 60.9, 43.3, 25.0, 14.5, 14.2, 14.1, 13.8. HRMS: calcd for $C_{18}H_{22}N_2O_8$ $(M + Na)^+$ 417.1278, found 417.1274. HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 254 nm): t_1 = 27.0 min, t_2 = 31.0 min.

1-[1-(Ethoxycarbonyl)cyclopropyl]-2-(isobutoxycarbonylamino)ethyl 4-Nitrobenzoate (3j). ^{1}H NMR (400 MHz, $CDCl_3$): 8.31−8.10 (m, 4H), 5.13 (dd, J = 8.4, 3.4 Hz, 1H), 4.97 (t, J = 5.8 Hz, 1H), 4.24−4.12 (m, 2H), 3.88−3.70 (m, 4H), 1.85−1.79 (m, 1H), 1.41−1.31 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.19−1.02 (m, 2H), 0.84 (dd, J = 6.7, 1.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 164.3, 156.8, 150.6, 135.2, 130.9, 123.6, 76.0, 71.2, 61.0, 43.3, 27.9, 25.0, 18.9, 14.2 (2C), 13.9. HRMS: calcd for $C_{20}H_{26}N_2O_8$ $(M + Na)^+$ 445.1584, found 445.1587. HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 85/15, 0.5 mL/min, 254 nm): t_1 = 24.3 min, t_2 = 26.7 min.

2-(*tert*-Butoxycarbonylamino)-1-(1-(ethoxycarbonyl)cyclopropyl)ethyl 4-Nitrobenzoate (3k). ^{1}H NMR (400 MHz, $CDCl_3$): 8.31−8.21 (m, 4H), 5.16 (dd, J = 8.4, 3.3 Hz, 1H), 4.83 (t, J = 5.9 Hz, 1H), 4.24−4.12 (m, 2H), 3.82−3.62 (m, 2H), 1.36 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H), 1.21−1.14 (m, 2H), 1.05−1.00 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.2, 164.2, 155.8, 150.6, 135.3, 131.0, 123.5, 79.6, 75.8, 60.9, 42.8, 28.2, 24.9, 14.2, 14.0, 13.8. HRMS: calcd for $C_{20}H_{26}N_2O_8$ $(M + Na)^+$ 445.1584, found 445.1587. HPLC (Chiralcel AD-H column, hexane/*i*-PrOH = 90/10, 0.5 mL/min, 254 nm): t_1 = 36.8 min, t_2 = 47.1 min.

Preparation of (*S*)-Ethyl 1-(1-Azido-2-{[(benzyloxy)carbonyl]amino}ethyl)cyclopropanecarboxylate (4)[5]. To a solution of **2a** (4.8 g, 15.6 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (4.4 mL, 31.2 mmol). The mixture was stirred and cooled to 5 °C. MsCl (2.7 g, 23.4 mmol) was added via the addition funnel portionwise over a period of 5 min, while maintaining the internal temperature below 10 °C. The mixture was stirred at 5 °C for 1 h, and diluted with CH_2Cl_2 (50 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was dissolved into DMF (30 mL) and NaN_3 (1.1 g, 17.2 mmol) was added. The resulting mixture was heated at 80 °C for 1 h to effect a complete conversion. The reaction mixture was diluted with water, and the mixture was extracted with ethyl acetate. The extract was washed with brine and then dried over Na_2SO_4. Concentration of the solvent in vacuo gave an oily residue, which was purified by column chromatography (hexanes/ethyl acetate = 5/1) to give **4** (4.4 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39−7.23 (m, 5H), 5.15−5.07 (m, 3H), 4.15 (q, J = 7.0 Hz, 2H), 3.67−3.38 (m, 3H), 1.40−1.37 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.24−1.22 (m, 1H), 1.00−0.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 172.3, 156.3, 136.2, 128.5, 128.1, 128.0, 66.8, 64.4, 61.0, 43.3, 24.9, 14.0, 13.8, 13.6.

Preparation of (*S*)-7-Amino-5-azaspiro[2.4]heptan-4-one (5). A mixture of **4** (4.4 g, 13.2 mmol) and 5% palladium on carbon (30% wet) (1.0 g) in EtOH (50 mL) was hydrogenated at 75 °C under a hydrogen pressure of 4 bar for 24 h. After completion of the reaction, the catalyst was removed by filtration and the resulting filtrate was concentrated under a reduced pressure to obtain **5** (1.5 g, 90%) in the form of colorless crystals. $[\alpha]^{20}_D$ −99.5 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): 6.43 (bs, 1H), 3.77 (ddd, J = 9.8, 7.1, 0.7 Hz, 1H), 3.50 (dd, J = 7.1, 4.5 Hz, 1H), 3.13 (ddd, J = 9.8, 4.5, 0.7 Hz, 1H), 1.37 (bs, 2H), 1.20−1.17 (m, 1H), 0.99−0.97 (m, 2H), 0.82−0.77 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 179.2, 51.7, 50.0, 29.1, 12.1, 8.1. Then **5** was converted to *tert*-butyl (4-oxo-5-azaspiro[2.4]heptan-7-yl)carbamate (derivative of **5**) for chiral purity analysis by chiral HPLC. HPLC analysis indicated an enantiomeric excess of 98.9% (ChiralPak AD-H column, flow 0.5 mL/min, IPA/Hex =15/85, 210 nm, t_1 = 10.6 min, t_2 = 15.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): 6.08 (s, 1H), 4.84 (d, J = 6.8 Hz, 1H), 4.18 (t, J = 6.2 Hz, 1H), 3.81 (dd, J = 10.3, 6.9 Hz, 1H), 3.32 (dd, J = 10.2, 2.3 Hz, 1H), 1.44 (s, 9H), 1.21−0.95 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 178.4, 155.2, 79.9, 51.4, 47.9, 28.3, 27.3, 14.5, 8.7. HRMS: calcd for $C_{11}H_{18}N_2O_3$ $(M + Na)^+$ 249.1217, found 249.1215.

Preparation of (*S*)-7-Amino-5-azaspiro[2,4]heptane Dihydrochloride (6). $LiAlH_4$ (182 mg, 4.8 mmol) was charged into a 50 mL 3-necked round-bottom flask and THF (20 mL) was added. The resulting slurry was stirred and **5** (300 mg, 2.4 mmol) was added in portions. The reaction was heated to 60 °C for 24 h. Completion of the reaction was monitored by ^{1}H NMR. Water (0.3 mL) was added dropwise and stirred for 5 min. 15% NaOH solution (0.3 mL) was added and stirred for 5 min. Water (0.9 mL) was added dropwise and the white suspension stirred for 30 min, then filtered through a pad of Celite. The Celite pad was rinsed with hot THF, and the filtrate was concentrated to give an oily liquid. Then 1 M HCl in MeOH (3 mL) was added and stirred for 20 min to obtain **6** (407 mg, 92%) as white powder. $[\alpha]^{20}_D$ −44.7 (*c* = 1.0, H_2O) ($[\alpha]^{20}_D$ −41.5 in H_2O, *c* = 1.616).[3f] ^{1}H NMR (400 MHz, D_2O): 3.88 (dd, J = 13.8, 7.4 Hz, 1H), 3.59 (dd, J = 7.4, 3.2 Hz, 1H), 3.50 (d, J = 12.1 Hz, 1H), 3.45 (dd, J = 13.8, 3.2 Hz, 1H), 3.03 (d, J = 12.1 Hz, 1H), 1.01−0.76 (m, 4H). ^{13}C NMR (100 MHz, D_2O): 55.0, 51.0, 49.2, 23.3, 14.7, 5.0. Compound **6** was converted to *tert*-butyl 7-[(*tert*-butoxycarbonyl)amino]-5-azaspiro-[2.4]heptane-5-carboxylate (derivative of **6**). HPLC analysis indicated an enantiomeric excess of 98.9% (ChiralPak AD-H column, flow 0.5 mL/min, IPA/Hex =5/95, 210 nm, t_1 = 15.2 min, t_2 = 24.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): 4.69 (s, 1H), 3.68−3.43 (m, 4H), 3.12 (dd, J = 25.6, 10.8 Hz, 1H), 1.46 (s, 9H), 1.44 (s, 9H), 0.84−0.54 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 155.4, 154.5 (rotamer), 154.3, 79.7, 79.5, 56.2, 55.3 (rotamer), 53.0, 52.4 (rotamer), 52.1 (rotamer), 51.6, 28.4, 28.3, 25.8 (rotamer), 25.1, 13.1, 5.6. HRMS: calcd for $C_{16}H_{28}N_2O_4$ $(M + Na)^+$: 335.1953, found 335.1947.

■ ASSOCIATED CONTENT

Supporting Information. Details of the preparations and the NMR and/or HPLC data of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: zhaoguo@sjtu.edu.cn.

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REFERENCES

(1) (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008 and references therein. (b) Knowles, W. S. *Adv. Synth. Catal.* **2003**, *345*, 3. (c) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (d) Ojima, I. *Catalytic Asymmetric Synthesis*, 3rd ed.; Wiley: New York, 2010. (e) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (f) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993. (g) Jannes, G.; Dubois, V. In *Chiral Reaction in Heterogeneous Catalysis*; Plenum: New York, 1995. (h) Cornils, B.; Hermann, W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996; Vols. 1 and 2.

(2) (a) Ohkuma, T.; Noyori, R. In *Transition Metals for Organic Synthesis, Building Blocks and Fine Chemicals*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2. (b) Blaser, H.-U.; Pugin, B.; Spindler, F. *Applied Homogeneous Catalysis with Organometallic Compounds*, 2nd ed.; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 3.3.1. (c) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40. (d) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998. (e) Rossen, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4611. (f) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntyre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wüstenberg, B.; Zimmermann, N. *Adv. Synth. Catal.* **2003**, *345*, 33. (g) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.(h) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions*; Blaser, H.-U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004. (i) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912. (j) Knowles, W. S.; Noyori, R. *Acc. Chem. Res.* **2007**, *40*, 1238. (k) Fan, Q.-H.; Li, Y.-M.; Chan., A. S. C. *Chem. Rev.* **2002**, *102*, 3385. (l) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(3) (a) Chu, D. T.; Lee, C. M.; Li, Q.; Cooper, C. S.; Plattner, J. J. PCT Int. Appl. WO9116894A1, 1991. (b) Chu, D. T.; Li, Q.; Cooper, C. S.; Fung, A. K. L.; Lee, C. M.; Plattner, J. J. PCT Int. Appl. WO9510519A1, 1995. (c) Petersen, U.; Schenke, T.; Krebs, A.; Grohe, K.; Schriewer, M.; Haller, I.; Metzger, K. G.; Endermann, R.; Zeiler, H.-J. U.S. Pat. Appl. Publ. US4990517A, 1991. (d) Schriewer, M.; Grohe, K.; Krebs, A.; Petersen, U.; Schenke, T.; Haller, I.; Metzger, K. G.; Endermann, R.; Zeiler, H.-J. U.S. Pat. Appl. Publ. US5140033A, 1992. (e) Kim, W. J.; Park, T. H.; Kim, B. J.; Kim, M. H.; Pearson, N. PCT Int. Appl. WO9415938A1, 1994. (f) Hayakawa, I.; Atarashi, S.; Imamura, M.; Kimura, Y. Eur. Pat. Appl. EP357047A1, 1990.

(4) (a) Li, Q; Wang, W.-B; Chu, D. T.; Hasvold, L. A. U.S. Pat. Appl. Publ. US5703244A, 1997. (b) Satoh, K.; Imura, A.; Miyadera, A.; Kanai, K.; Yukimoto, Y. *Chem. Pharm. Bull.* **1998**, *46*, 587.

(5) Plata, D. J.; King, S. A.; Plagge, F. A.; Bailey, A. E.; Seif, L. U.S. Pat. Appl. Publ. US6197974B1, 2001.

(6) Ager, D. J.; Laneman, S. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3327.

(7) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163. (c) Shao, L.; Takeuchi, K.; Ikemoto, M.; Kawai, T.; Ogasawara, M.; Takeuchi, H.; Kawano, H.; Saburi, M. *J. Organomet. Chem.* **1992**, *435*, 133. (d) Genêt, J.-P.; Ratovelomanana-Vidal, V.; Caño De Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801. (e) Heiser, B.; Broger, E. A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51. (f) Kawano, H.; Ikariya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1571. (g) Ohta, T.; Tonomura, Y.; Nozaki, K.; Takaya, H.; Mashima, K. *Organometallics* **1996**, *15*, 1521. (h) Hoke, J. B.; Hollis, S.; Stern, E. W. *J. Organomet. Chem.* **1993**, *455*, 193.

(8) (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223. (b) Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 2501. (c) Zhou, Y.-G.; Tang, W.; Wang, W. B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952.

(9) (a) Labeeuw, O.; Blanc, D.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Eur. J. Org. Chem.* **2004**, *11*, 2352. (b) Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Ben Hassine, B.; Genêt, J.-P. *Adv. Synth. Catal.* **2003**, *345*, 261. (c) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.

(10) (a) Poupardin, O.; Greck, C.; Genêt, J.-P. *Synlett* **1998**, *11*, 1279. (b) Korostylev, A.; Andrushko, V.; Andrushko, N.; Tararov, V. I.; König, G.; Börner, A. *Eur. J. Org. Chem.* **2008**, *5*, 840. (c) Tararov, V. I.; Andrushko, N.; Andrushko, V.; König, G.; Spannenberg, A.; Börner, A. *Eur. J. Org. Chem.* **2006**, *24*, 5543.

(11) (a) Junge, K.; Hagemann, B.; Enthaler, S.; Oehme, G.; Michalik, M.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5066. (b) Karamé, I.; Bellur, E.; Rotzoll, S.; Langer, P.; Fischer, C.; Holz, J.; Börner, A. *Synth. Commun.* **2007**, *37*, 1067. (c) Pai, C.-C.; Lin, C.-W.; Lin, C.-C.; Chen, C.-C.; Chan, A. S. C.; Wong, W. T. *J. Am. Chem. Soc.* **2000**, *122*, 11513. (d) Nishi, T.; Kitamura., M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327. (e) Genêt, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Bischoff, L.; Caño De Andrade, M. C.; Darses, S.; Galopin, C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 675.

(12) (a) Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2185. (b) Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1070. (c) Sun, Y.; Wan, X.; Wang, J.; Meng, Q.; Zhang, H.; Jiang, L.; Zhang, Z. *Org. Lett.* **2005**, *7*, 5425. (d) Sun, X.; Zhou, L.; Li, W.; Zhang, X. *J. Org. Chem.* **2008**, *73*, 1143. (e) Meng, Q.; Sun, Y.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Zhang, Z. J. *Org. Chem.* **2008**, *73*, 3842. (f) Meng, Q.; Zhu, L.; Zhang, Z. J. *Org. Chem.* **2008**, *73*, 7209. (g) Zhu, L.; Meng, Q.; Fan, W.; Xie, X.; Zhang, Z. J. *Org. Chem.* **2010**, *75*, 6027. (h) Wan, X.; Zhang, H.; Sun, Y.; Fan, W.; Zhang, Z. *Org. Lett.* **2007**, *9*, 5613.

(13) (a) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, *10*, 1931. (b) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495. (c) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264. (d) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 320.

(14) (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Vogl, E. M.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570. (c) Spindler, F.; Blaser, H.-U. *Enantiomer* **1999**, *4*, 557. (d) Wang, C.; Xi, Z. *Chem. Soc. Rev.* **2007**, *36*, 1395. (e) Togni, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1475. (f) Xiao, D.; Zhang, X. *Angew. Chem., Int. Ed.* **2001**, *40*, 3425. (g) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (h) Chi, Y.; Zhou, Y.-G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (i) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564. (j) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (k) Hou, G.-H.; Xie, J.-H.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 11774. (l) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357.

(15) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555.

(16) (a) Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S. *Chem. Heterocycl. Compd.* **1983**, *19*, 644. (b) Inagaki, H.; Takeda, T.; Miyauchi, R. N.; Kawakami, K.; Takahashi, H.; Takemura, M. *Heterocycles* **2004**, *63*, 699.(c) Mitsuhashi, S.; Sumi, K.; Moroi, T.; Sotoguchi, T.; Miura, T. Eur. Pat. Appl. EP947505A2, 1999.

(17) Kazuaki, K., Makoto, M., Yasushi, S. Jpn. Kokai Tokkyo Koho. JP 11049750A, 1999.