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Asymmetric Synthesis of Chiral Heterocyclic Amino Acids via the Alkylation of the Ni(II) Complex of Glycine and Alkyl Halides

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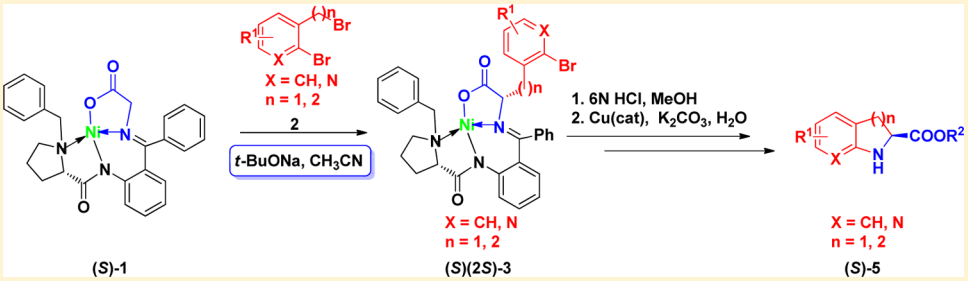
Supporting Information



ABSTRACT: An investigation into the reactivity profile of alkyl halides has led to the development of a new method for the asymmetric synthesis of chiral heterocyclic amino acids. This protocol involves the asymmetric alkylation of the Ni(II) complex of glycine to form an intermediate, which then decomposes to form a series of valuable chiral amino acids in high yields and with excellent diastereoselectivity. The chiral amino acids underwent a smooth intramolecular cyclization process to afford the valuable chiral heterocyclic amino acids in high yields and enantioselectivities. This result paves the way for the development of a new synthetic method for chiral heterocyclic amino acids.

INTRODUCTION

Enantiopure heterocyclic amino acids, especially those containing nitrogen, are the most important class of nonnatural amino acids in the pharmaceutical and agrochemical industries.[1] In particular, the indoline[2] and tetrahydroquinoline[3] ring systems are very common structural motifs that are found in numerous pharmacologically relevant therapeutic agents and biologically active natural products, including indolapril,[4] perindopril,[5] and virantmycin[6] (Figure 1). Because of the significance of these scaffolds in drug discovery and medicinal chemistry, the development of new methodologies for the asymmetric synthesis of enantiopure nitrogen-containing heterocyclic amino acids continues to be a very active field of research.

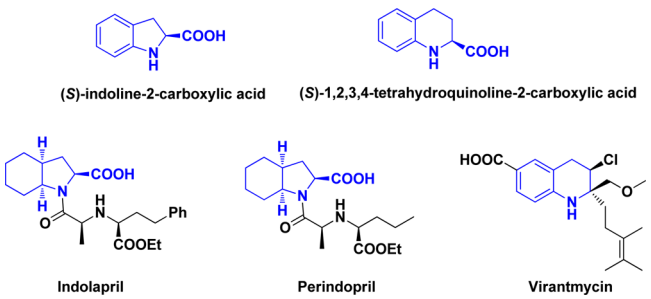


Figure 1. Examples of heterocyclic amino acids and related therapeutic agents and biologically active natural products.

The synthesis of (*S*)-indoline-2-carboxylic acid and (*S*)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives are generally achieved by the preparation of a racemic precursor, followed by classical or enzymatic reaction. The yields for these methods never exceed 50%. An asymmetric synthetic approach is much more appealing, and indeed, a number of potentially more economic routes have been considered. For example, de Vries and co-workers recently disclosed a protocol for the asymmetric synthesis of (*S*)-2-indolinecarboxylic acid by combining biocatalysis and homogeneous catalysis.[7] However, the homogeneous catalytic reaction requires the relatively exotic and expensive rhodium-MonoPhos catalyst, limiting the broad application of this synthetic method. In recent years, the Ni(II) complex of glycine has been widely applied as a nucleophilic reagent in numerous synthetic transformations due to its enhanced stereoselectivity when compared to the achiral glycine equivalent.[8−13] We herein report the development of a new method to access heterocyclic amino acids from alkyl halides by the asymmetric alkylation of the Ni(II) complex of glycine (Scheme 1).

RESULTS AND DISCUSSION

To initially explore the reaction process, the asymmetric alkylation of the Ni(II) complex of glycine (*S*)-**1** and 1-

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Scheme 1. Stereoselective Synthesis of Enantioenriched Nitrogen Heterocyclic Amino Acids via the Chiral Ni(II) Complex of Glycine with Alkyl Halides

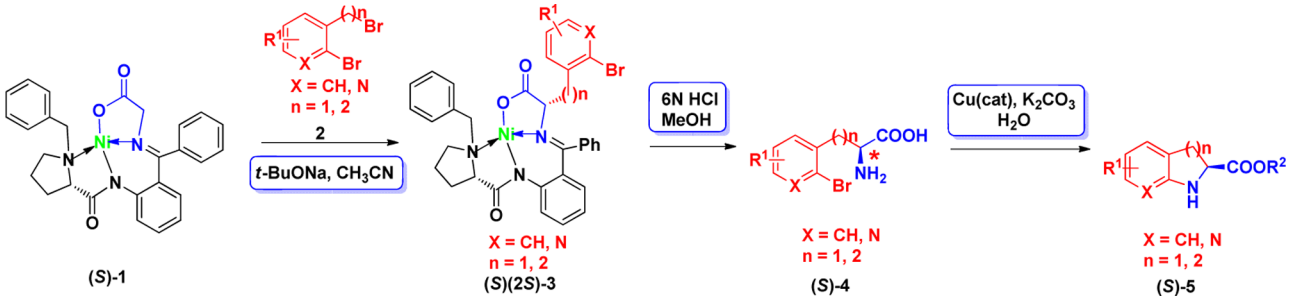
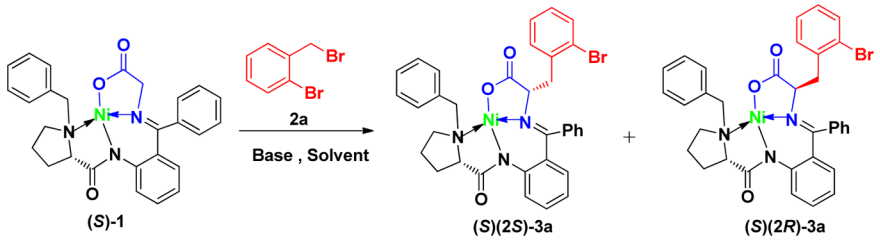


Table 1. Optimization of the Reaction Conditions for Alkylation of the Ni(II) Complex of Glycine



entry	base	solvent	temp (°C)	yield (%)[c]	dr[d]
1[a]	NaOH	DMF	rt	72	84:16
2[a]	NaH	DMF	rt	84	84:16
3[a]	KOH	DMF	rt	61	83:17
4[a]	*t*-BuOK	DMF	rt	53	82:18
5[a]	DBU	DMF	rt	14	94:6
6[a]	*t*-BuONa	DMF	rt	87	93:7
7[b]	*t*-BuONa	DMF	rt	87	97:3
8[b]	*t*-BuONa	DCM	rt	16	85:15
9[b]	*t*-BuONa	THF	rt	87	90:10
10[b]	*t*-BuONa	CH_3CN	rt	91	98:2
11[b]	*t*-BuONa	CH_3COCH_3	rt	81	95:5
12[b]	*t*-BuONa	CH_3CN	−20	70	92:8
13[b]	*t*-BuONa	CH_3CN	0	95	92:8
14[b]	*t*-BuONa	CH_3CN	40	93	97:3
15[b]	*t*-BuONa	CH_3CN	60	95	95:5

[a]Reactions were run with 0.20 mmol of (*S*)-**1**, 0.20 mmol of **2a** in 3 mL of solvent with 0.24 mmol of base for 1.5 h at rt. [b]Reactions were run with 0.20 mmol of (*S*)-**1**, 0.16 mmol of **2a** in 3 mL of solvent with 0.24 mmol of base for 1.5 h at rt. [c]Isolated yield of (*S*)(2*S*)-**3a** and (*S*)(2*R*)-**3a**. [d](*S*)(2*S*)-**3a**/(*S*)(2*R*)-**3a** determined by LC-MS analysis of the crude product.

bromo-2-(bromomethyl)benzene (**2a**) was selected as the benchmark reaction for our preliminary screening (Table 1). Under the standard reaction conditions reported by Soloshonok and co-workers[14] for the alkylation of alkyl halides by using NaOH as a base in DMF at room temperature for 1.5 h, the alkylation product **3a** was produced at 72% yield, with good diastereoselectivity (dr 84:16, entry 1). A moderate diastereoselectivity was observed with the use of NaH, KOH, and *t*-BuOK (entries 2−4). Subsequent optimization showed that *t*-BuONa was a suitable base (entries 5 and 6). The use of 0.8 equiv of the alkyl halide **2a** instead of the originally employed 1.0 equiv (entry 7) resulted in improved diastereoselectivity (dr 97:3). To identify the optimal conditions for this alkylation reaction, we screened a range of different solvents (entries 7−11). The use of CH_3CN led to the best results, and other solvents, such as DMF, DCM, THF, and CH_3COCH_3, furnished the target compound **3a** in lower yields and diastereoselectivities. The temperature had only a minor effect on the product yield and diastereoselectivity (entries 12−15). Under the optimal reaction conditions (using *t*-BuONa as the base in CH_3CN at room temperature for 1.5 h), alkylation product **3a** was obtained (from (*S*)-**1** and **2a**) at 91% yield with excellent diastereoselectivity (dr 98:2). The *S*-configuration of the newly created stereogenic center was established by X-ray crystal structure analysis of the Ni(II) complex **3a** (see the Supporting Information for details).[15]

To further investigate this process, a range of alkyl halides were then applied under the standard conditions (Table 2). Alkyl halides containing halide substituents worked well in this reaction process, producing the corresponding alkylation derivatives at good to excellent yield with high diastereoselectivity. Steric effects at the aryl ring had only a minor effect on the asymmetric alkylation reactions (entries 2−5). The presence of an electron-neutral methyl group at the *para*-position of the aryl ring (entry 6) did not significantly affect the product diastereoselectivity (dr 94:6) compared to the unsubstituted alkyl halide (dr 98:2). An electron-donating methoxy group attached to the *para*-position of the alkyl halide (entry 7)

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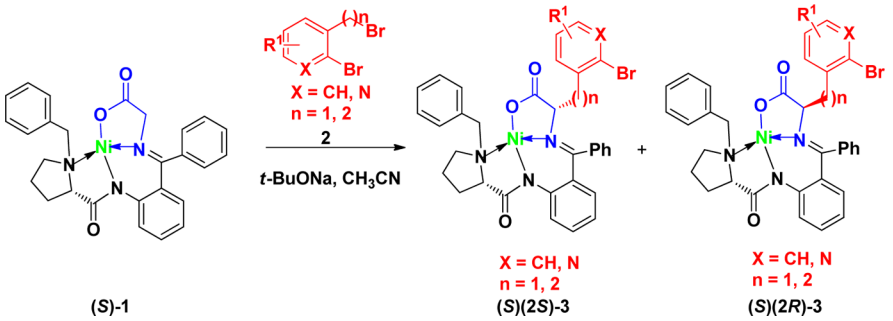
Table 2. Investigations into the Different Types of Alkyl Halides Applicable to This Reaction Process

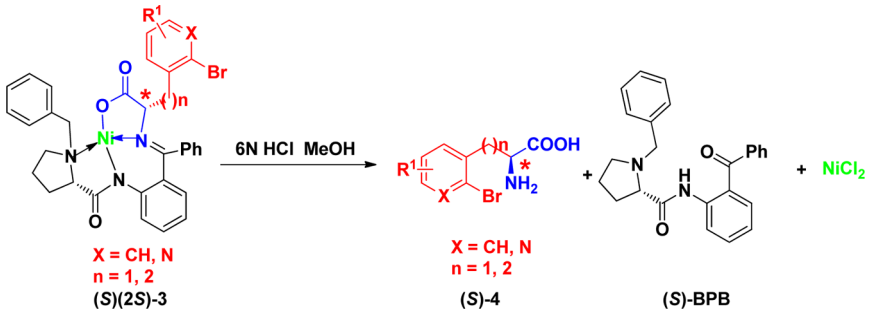


(*S*)-1 (*S*)(2*S*)-3 (*S*)(2*R*)-3

entry	3	X	*n*	R^1	yield (%)[d]	dr[e]
1[a]	**3a**	CH	1	H	91	98:2
2[a]	**3b**	CH	1	3-F	91	96:4
3[a]	**3c**	CH	1	4-F	90	95:5
4[a]	**3d**	CH	1	5-F	98	94:6
5[a]	**3e**	CH	1	6-F	99	93:7
6[a]	**3f**	CH	1	5-Me	95	94:6
7[a]	**3g**	CH	1	5-OMe	96	91:9
8[a]	**3h**	CH	1	5-CN	96	94:6
9[a]	**3i**	CH	1	5-NO_2	95	94:6
10[a]	**3j**	CH	1	5-Cl	99	95:5
11[a]	**3k**	CH	1	4,5-F_2	95	95:5
12[a]	**3l**	CH	1	4,5-OMe_2	99	91:9
13[a]	**3m**	N	1	H	99	93:7
14[b]	**3n**	CH	2	H	80	94:6
15[c]	**3o**	CH	2	5-Cl	66	91:9

[a]Reactions were run with 0.20 mmol of (*S*)-**1**, 0.16 mmol of **2** in 3 mL of CH_3CN with 0.24 mmol of *t*-BuONa for 1.5 h at rt. [b]Reactions were run with 2.01 mmol of (*S*)-**1**, 1.61 mmol of **2n** in 30 mL of CH_3CN with 2.41 mmol of *t*-BuONa for 3 h at 60 °C. [c]Reactions were run with 0.20 mmol of (*S*)-**1**, 0.16 mmol of **2o** in 3 mL of CH_3CN with 0.24 mmol of *t*-BuONa for 3 h at 60 °C. [d]Isolated yield of (*S*)(2*S*)-**3** and (*S*)(2*R*)-**3**. [e](*S*)(2*S*)-**3**/(*S*)(2*R*)-**3** determined by LC-MS analysis of the crude product.

Table 3. Decomposition of Ni(II) Complexes 3 to Release Amino Acids 4



(*S*)(2*S*)-3 (*S*)-4 (*S*)-BPB

					yield (%)[a]		
entry	4	X	*n*	R^1	(*S*)-4	(*S*)-BPB	ee (%)[b] (*S*)-4
1	**4a**	CH	1	H	82	93	>99
2	**4d**	CH	1	5-F	74	96	97
3	**4g**	CH	1	5-OMe	89	99	96
4	**4m**	N	1	H	96	96	98
5	**4n**	CH	2	H	77	99	99

[a]Isolated yield. [b]Determined by HPLC on a chiral stationary phase.

resulted in an excellent yield of the corresponding alkylation product **3g**. Substitution with an electron-withdrawing group, such as CN, NO_2, or Cl, at the *para*-position of the aromatic ring, led to a decrease in the selectivity (entries 8−10). 4,5-Difluoro- and 4,5-dimethoxy-substituted substrates also reacted well under these conditions, showing high diastereoselectivities (entries 11 and 12). It is worth mentioning that neither the position nor the electronic properties of the substituent on the aromatic ring had a significant impact on the diastereoselectivity of the reaction. Moreover, this reaction could be extended to heterocyclic compounds. The replacement of the aryl group with a pyridyl moiety (entry 13) resulted in excellent yield of the desired adduct with high stereoselectivity. Phenethyl alkyl

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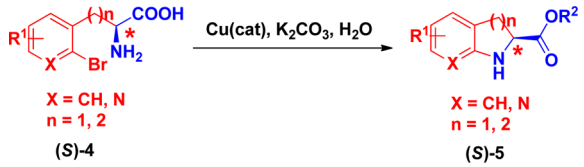
halides reacted with good to high stereoselectivity, although they provided low yields (entries 14 and 15).

Disassembly of enantiopure complex (*S*)(2*S*)-**3a** under an acidic condition (HCl/MeOH) afforded the target amino acid (*S*)-2-amino-3-(2-bromophenyl)propanoic acid ((*S*)-**4a**) in good yield (82%) with excellent enantioselectivity (>99% ee) (Table 3). Reactions bearing electron-withdrawing (5-F) and electron-donating (5-OMe) substituents proceeded well, and products (*S*)-**4d** and (*S*)-**4g** were isolated in good yields (74−89%) and excellent enantioselectivities (96−97% ee). Remarkably, the aryl group can be replaced by a pyridyl moiety. The pyridyl-substituted system was converted to the corresponding amino acid (*S*)-**4m** in high yield (96%) and excellent enantioselectivity (98%). Furthermore, (*S*)-**3n** was also a suitable substrate under the acidic treatment, affording the corresponding product in 77% yield. The chiral ligand (*S*)-**BPB** was recycled with high yields (93−99%) and used for the preparation of starting Ni(II) complex (*S*)-**1**.

Copper-catalyzed ring closure of (*S*)-*ortho*-bromophenylalanine derivatives could provide a fast access to the chiral heterocyclic amino acids. With the enantiopure amino acids (*S*)-**4** in hand, we then examined the intramolecular cyclization. As shown in Table 4, we were pleased to find that copper-catalyzed

Table 4. Intramolecular Cyclization and Methyl Esterification To Afford Chiral Heterocycle Amino Acids 5[a]



entry	5	X	*n*	R^1	R^2	yield (%)[c]	ee (%)[d]
1	**5a**	CH	1	H	H	83	>99
2	**5d**	CH	1	5-F	H	70	>99
3	**5g**	CH	1	5-OMe	H	65	>99
4	**5m**	N	1	H	H	77	>99
5[b]	**5n**	CH	2	H	Me	47	97

[a]Reactions were run with (*S*)-**4** (100 mg, 1 equiv), K_2CO_3 (1.05 equiv), and CuCl (0.5% mmol) in water (1 mL) at 95 °C for 1 h under nitrogen. [b]Reaction was run with 0.39 mmol of (*S*)-**4n**, 0.41 mmol of K_2CO_3, and 0.04 mmol of CuI in *i*PrOH/H_2O (v/v = 1/1, 5 mL) at 80 °C for 10 h under nitrogen. Then, the crude product was dissolved in MeOH (15 mL) under nitrogen and cooled to 0 °C, and $SOCl_2$ (112 μL, 1.55 mmol) was added dropwise. The mixture was refluxed at 70 °C for 4 h under nitrogen. [c]Isolated yield. [d]Determined by HPLC on a chiral stationary phase.

ring clousure was applicable to a broad substrate scope. Intramolecular cyclization of compound (*S*)-**4a** afforded the chiral heterocyclic amino acid (*S*)-**5a** in 83% yield with >99% ee value. Electronic effects on the reactions were limited. Both electron-rich and electron-poor substituted amino acids were tolerated (entries 2 and 3). Encouraged by this result, we further investigated the intramolecular cyclization reaction of heterocyclic amino acid (*S*)-**4m**. It was found that the pyridyl-substituted amino acid worked well, affording the corresponding product in good yield (77%) with excellent enantioselectivity (>99% ee). In addition, intramolecular cyclization and methyl esterification produced the chiral heterocyclic amino acid (*S*)-**5n** in 47% yield with 97% ee value, which is a potentially valuable intermediate in the synthesis of therapeutic agents and biologically active natural products.

CONCLUSIONS

In summary, we have developed a highly generalized, practical, and scalable alkylation of the Ni(II) complex of glycine to produce enantioenriched chiral heterocyclic amino acids with high yields and excellent diastereoselectivities. A broad range of alkyl halides could be employed under simple operational conditions. The chiral amino acids readily undergo transformations to generate highly functionalized heterocyclic amino acids that are potentially valuable intermediates in the synthesis of bioactive molecules.

EXPERIMENTAL SECTION

General Information. The reagents (chemicals) were purchased from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was performed on HSGF 254 (0.15−0.2 mm thickness). All products were characterized by their NMR and MS spectra. ^1H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) on 400, 500, and 600 MHz instruments. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on a spectrometer. Optical rotations were reported as follows: $[\alpha]_D^{25}$ (*c* g/100 mL, in solvent).

General Procedure for the Synthesis of (*S*)(2*S*)-3a and (*S*)(2*R*)-3a. (*S*)-**1a** (100 mg, 0.20 mmol) was dissolved in anhydrous CH_3CN (3 mL). After 1-bromo-2-(bromomethyl)benzene **2a** (40.1 mg, 0.16 mmol) and sodium *tert*-butoxide (23.2 mg, 0.24 mmol) were added successively, the reaction mixture was stirred for 1.5 h at room temperature. After the reaction was complete, as indicated by TLC, the reaction was quenched by pouring the crude reaction mixture over 5 mL of aq. sat. NH_4Cl. The suspension was extracted with ethyl acetate (2 times). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/4) to give (*S*)(2*S*)-**3a** and (*S*)(2*R*)-**3a** as a red solid (97 mg, yield 91%).

Procedure for the Synthesis of (*S*)(2*S*)-3n and (*S*)(2*R*)-3n. (*S*)-**1a** (1.0 g, 2.01 mmol) was dissolved in anhydrous CH_3CN (30 mL). After 1-bromo-2-(2-bromoethyl)benzene **2n** (423.9 mg, 1.61 mmol) and sodium *tert*-butoxide (231.5 mg, 2.41 mmol) were added successively, the reaction mixture was stirred for 3 h at 60 °C. After the reaction was complete, as indicated by TLC, the reaction was quenched by pouring the crude reaction mixture over 50 mL of aq. sat. NH_4Cl. The suspension was extracted with ethyl acetate (2 times). The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/4) to give (*S*)(2*S*)-**3n** and (*S*)(2*R*)-**3n** as a red solid (872 mg, yield 80%).

General Procedure for the Synthesis of (*S*)-4a. A solution of (*S*)(2*S*)-**3a** (1.64 g, 2.46 mmol) in MeOH (20 mL) was added to a stirring solution of 6 N HCl in MeOH (1:1, v/v) 40 mL at 70 °C. The mixture was gently heated under reflux for 45 min, the solution was evaporated to dryness, and the solid residue was dissolved in water (50 mL) and evaporated again to remove HCl. Water (50 mL) was added, and the resultant mixture was treated with an excess of concentrated NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated under vacuum to afford the free chiral ligand (882 mg, yield 93%). The aqueous phase was evaporated under vacuum and dissolved in a minimum amount of H_2O and loaded on a Dowex 50 × 2 100 ion-exchange column, which was washed with H_2O until neutral. The column was then washed with 10% aq NH_4OH. The first fraction (200 mL) was collected and evaporated under vacuum to afford the corresponding amino acid (*S*)-**4a** as a white solid (490 mg, yield 82%).

General Procedure for the Synthesis of (*S*)-5a. (*S*)-**4a** (100 mg, 0.41 mmol), K_2CO_3 (59.5 mg, 0.43 mmol), and CuCl (0.2 mg, 0.002 mmol) were dissolved in H_2O (1 mL) under nitrogen. After the mixture was stirred at 95 °C for 1 h under a nitrogen atmosphere, the

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reaction mixture was cooled to 25 °C. The pH of the solution was then acidified to pH 4 by addition of 6 N aqueous HCl and then concentrated in vacuo. (v/v = 1:1, 5 mL) was added to the residue to form a clear solution, and this solution was then separated by preparative HPLC [H_2O/(CH_3CN:MeOH = 1:1) = 90:10] to give (*S*)-**5a** as a white solid (55.7 mg, 83%), > 99% ee.

Procedure for the Synthesis of (*S*)-5n. (*S*)-**4n** (100 mg, 0.39 mmol), K_2CO_3 (56.2 mg, 0.41 mmol), and CuI (7.4 mg, 0.04 mmol) were dissolved in *i*PrOH/H_2O (v/v = 1/1, 5 mL) under nitrogen. After the mixture was stirred at 80 °C for 10 h under a nitrogen atmosphere, the reaction mixture was cooled to rt. The pH of the solution was then acidified to pH 4 by addition of 6 N aqueous HCl and then concentrated in vacuo. The crude product (68.5 mg, 0.39 mmol) was dissolved in methanol (15 mL) under nitrogen and cooled to 0 °C; then, $SOCl_2$ (112 μL, 1.55 mmol) was added dropwise. The mixture was refluxed at 70 °C for 4 h, and the solvent was removed by high vacuum distillation. The suspension was extracted with ethyl acetate (2 times). The combined organic layer was washed with aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to afford the (*S*)-**5n** as a light yellow oil (35 mg, yield 47%), 97% ee.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromophenyl)propanoic Acid Schiff Base Complex 3a. Red solid (97 mg, yield 91%, (*S*)(2*S*)/(*S*)(2*R*) = 98:2). (*S*)(2*S*)-**3a**: mp 153−155 °C; $[\alpha]_D^{25}$ +2362 (*c* 0.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.7 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 2H), 7.56 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.53−7.43 (m, 2H), 7.35−7.28 (m, 3H), 7.25−7.10 (m, 6H), 6.68−6.55 (m, 3H), 4.41−4.25 (m, 2H), 3.62−3.34 (m, 4H), 3.30−3.18 (m, 1H), 3.09−2.91 (m, 1H), 2.72−2.57 (m, 1H), 2.55−2.38 (m, 1H), 2.08−1.86 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 177.4, 170.8, 142.2, 135.3, 133.2, 132.7, 132.7, 132.1, 131.9, 131.0, 129.1, 128.5, 128.5, 128.4, 128.4, 127.4, 127.3, 127.1, 125.8, 125.4, 122.9, 120.1, 70.5, 70.0, 62.7, 56.6, 41.0, 30.4, 23.2. LRMS (ESI) *m*/*z*: [M + H]$^+$ found 666. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{34}H_{30}BrNaN_3NiO_3$ 688.0722; Found 688.0725. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.311 min, t_{minor} = 5.823 min, dr = 98:2.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-3-fluorophenyl)-propanoic Acid Schiff Base Complex 3b. Red solid (100 mg, yield 91%, (*S*)(2*S*)/(*S*)(2*R*) = 96:4). (*S*)(2*S*)-**3b**: mp 136−138 °C; $[\alpha]_D^{25}$ +2137 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 2H), 7.53−7.45 (m, 2H), 7.36−7.28 (m, 3H), 7.21−7.10 (m, 3H), 7.04 (td, *J* = 8.3, 1.5 Hz, 1H), 6.99 (d, *J* = 7 0.7 Hz, 1H), 6.67−6.62 (m, 1H), 6.61−6.56 (m, 1H), 6.56−6.51 (m, 1H), 4.42−4.28 (m, 2H), 3.66 (dd, *J* = 13.7, 5.8 Hz, 1H), 3.58−3.48 (m, 2H), 3.44 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.31 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.26−3.12 (m, 1H), 2.77−2.63 (m, 2H), 2.62−2.45 (m, 1H), 2.12−1.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 177.2, 170.8, 158.8 (d, *J* = 245.4 Hz), 142.2, 137.6, 133.2, 133.0, 132.7, 132.0, 131.0, 129.3, 128.5, 128.5, 128.4, 128.4, 128.1, 128.0, 127.2, 127.2, 127.1, 127.0, 125.8, 123.0, 120.2, 114.8 (d, *J* = 22.6 Hz), 112.4 (d, *J* = 20.4 Hz), 70.0, 70.0, 62.7, 56.7, 41.2, 30.4, 23.4. LRMS (ESI) *m*/*z*: [M + H]$^+$ found 684. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{34}H_{29}BrFNaN_3NiO_3$ 706.0627; Found 706.0609. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.166 min, t_{minor} = 5.610 min, dr = 96:4.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-4-fluorophenyl)-propanoic Acid Schiff Base Complex 3c. Red solid (99 mg, yield 90%, (*S*)(2*S*)/(*S*)(2*R*) = 95:5). (*S*)(2*S*)-**3c**: mp 88−91 °C; $[\alpha]_D^{25}$ +1885 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 7.4 Hz, 2H), 7.55−7.45 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.34−7.28 (m, 3H), 7.25 (d, *J* = 6.7 Hz, 1H), 7.19−7.09 (m, 3H), 6.95 (td, *J* = 8.3, 2.7 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.65 (t, *J* = 7.5 Hz, 1H), 6.61 (dd, *J* = 7.5, 1.5 Hz, 1H), 4.35 (d, *J* = 12.7 Hz, 1H), 4.29 (t, *J* = 6.2 Hz, 1H), 3.57−3.48 (m, 2H), 3.43 (dd, *J* = 10.6, 6.4 Hz, 1H), 3.37 (dd, *J* = 13.9, 6.7 Hz, 1H), 3.31−3.23 (m, 1H), 3.13−2.97 (m, 1H), 2.71−2.59 (m, 1H), 2.57−2.44 (m, 1H), 2.09−1.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 177.2, 170.9, 161.2 (d, *J* = 249.4 Hz), 142.2, 133.2, 132.7, 132.7, 132.0, 131.3, 131.3, 131.0, 129.2, 128.6, 128.5, 128.4, 127.2, 127.1, 125.8, 125.2, 125.1, 123.0, 120.2, 119.7 (d, *J* = 23.9 Hz), 114.5 (d, *J* = 20.8 Hz), 70.4, 70.0, 62.7, 56.7, 40.1, 30.4, 23.1. LRMS (ESI) *m*/*z*: [M + H]$^+$ found 684. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{34}H_{29}BrFNaN_3NiO_3$ 706.0627; Found 706.0637. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.815 min, t_{minor} = 6.630 min, dr = 95:5.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-5-fluorophenyl)-propanoic Acid Schiff Base Complex 3d. Red solid (108 mg, yield 98%, (*S*)(2*S*)/(*S*)(2*R*) = 94:6). (*S*)(2*S*)-**3d**: mp 109−111 °C; $[\alpha]_D^{25}$ +2134 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 2H), 7.57−7.48 (m, 3H), 7.38 (td, *J* = 7.4, 1.6 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.30−7.27 (m, 1H), 7.20−7.12 (m, 2H), 6.92−6.82 (m, 2H), 6.76 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.69−6.60 (m, 2H), 4.35 (d, *J* = 12.7 Hz, 1H), 4.28 (t, *J* = 6.3 Hz, 1H), 3.60−3.50 (m, 2H), 3.43 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.36−3.25 (m, 2H), 3.18−3.05 (m, 1H), 2.68−2.58 (m, 1H), 2.54−2.43 (m, 1H), 2.09−1.96 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 177.0, 171.0, 161.4 (d, *J* = 246.5 Hz), 142.2, 137.5, 137.4, 133.6, 133.6, 133.1, 133.1, 132.7, 132.1, 131.0, 129.3, 128.6, 128.6, 128.4, 128.4, 127.3, 127.1, 125.8, 123.0, 120.2, 119.3, 118.6 (d, *J* = 22.6 Hz), 115.8 (d, *J* = 22.4 Hz), 70.3,70.0, 62.7, 56.7, 40.7, 30.4, 23.2. LRMS (ESI) *m*/*z*: [M + H]$^+$ found 684. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{34}H_{29}BrFNaN_3NiO_3$ 706.0627; Found 706.0616. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.253 min, t_{minor} = 5.896 min, dr = 94:6.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-6-fluorophenyl)-propanoic Acid Schiff Base Complex 3e. Red solid (109 mg, yield 99%, (*S*)(2*S*)/(*S*)(2*R*) = 93:7). (*S*)(2*S*)-**3e**: mp 119−121 °C; $[\alpha]_D^{25}$ +2212 (*c* 0.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.14−8.07 (m, 3H), 7.52−7.42 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.29−7.27 (m, 2H), 7.23−7.14 (m, 2H), 7.11 (td, *J* = 7.5, 1.5 Hz, 1H), 7.08−7.00 (m, 1H), 6.91 (t, *J* = 8.7 Hz, 1H), 6.63 (t, *J* = 7.5 Hz, 1H), 6.54 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.34 (t, *J* = 7.9 Hz, 1H), 4.02−3.81 (m, 2H), 3.65 (dd, *J* = 12.4, 8.0 Hz, 1H), 3.57 (dd, *J* = 10.8, 6.4 Hz, 1H), 3.54−3.47 (m, 2H), 2.84−2.72 (m, 1H), 2.62−2.50 (m, 1H), 2.29−2.19 (m, 1H), 2.16−2.07 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.9, 177.1, 170.3, 161.4 (d, *J* = 247.0 Hz), 142.0, 133.1, 132.9, 132.8, 131.8, 131.1, 129.1, 129.0, 129.0, 128.6, 128.5, 128.4, 128.1, 128.0, 127.6, 127.4, 126.1, 125.4, 125.4, 123.3 (d, *J* = 17.4 Hz), 123.1, 120.2, 114.1 (d, *J* = 22.9 Hz), 70.0, 68.4, 62.6, 57.0, 35.3, 30.4, 23.6. LRMS (ESI) *m*/*z*: [M + H]$^+$ found 684. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{34}H_{29}BrFNaN_3NiO_3$706.0627; Found 706.0617. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.377 min, t_{minor} = 5.838 min, dr = 93:7.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-5-methylphenyl)-propanoic Acid Schiff Base Complex 3f. Red solid (104 mg, yield 95%, (*S*)(2*S*)/(*S*)(2*R*) = 94:6). (*S*)(2*S*)-**3f**: mp 88−90 °C; $[\alpha]_D^{25}$ +1766 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.6 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.53−7.46 (m, 2H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 3H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.19−7.10 (m, 2H), 6.96 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.90 (d, *J* = 2.1 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.68−6.58 (m, 2H), 4.33 (d, *J* = 12.7 Hz, 1H), 4.27 (t, *J* = 6.0 Hz, 1H), 3.52 (d, *J* = 12.7 Hz, 1H), 3.50−3.44 (m, 1H), 3.44−3.36 (m, 2H), 3.28−3.18 (m, 1H), 3.04−2.91 (m, 1H), 2.66−2.55 (m, 1H), 2.52−2.40 (m, 1H), 2.22−2.13 (s, 3H), 2.08−1.98 (m, 1H), 1.97−1.87 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.6, 177.5, 170.8, 142.3, 137.2, 135.0, 133.2, 133.1, 132.7, 132.7, 132.3, 131.9, 131.0, 129.4, 129.0, 128.4, 128.4, 128.3, 127.4, 127.0, 125.8, 122.9, 122.0, 120.0, 70.9, 70.1, 62.7, 56.6, 40.5, 30.4, 23.1, 20.3. LRMS (ESI) *m*/*z*: [M + H]$^+$ found 680. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{35}H_{32}BrNaN_3NiO_3$ 702.0878; Found 702.0889. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 5.398 min, t_{minor} = 7.645 min, dr = 94:6.

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Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-5-methoxyphenyl)-propanoic Acid Schiff Base Complex 3g. Red solid (107 mg, yield 96%, (*S*)(2*S*)/(*S*)(2*R*) = 91:9). (*S*)(2*S*)-**3g**: mp 236−238 °C; $[\alpha]_D^{25}$ +1992 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 2H), 7.52−7.43 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 7.35−7.28 (m, 3H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.18−7.09 (m,2H), 6.72 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.68−6.62 (m, 2H), 6.59 (dd, *J* = 8.8, 1.5 Hz, 2H), 4.34 (d, *J* = 12.7 Hz, 1H), 4.29 (dd, *J* = 6.9, 5.4 Hz, 1H), 3.61 (s, 3H), 3.58−3.47 (m, 3H), 3.42 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.33−3.25 (m, 1H), 3.18−3.08 (m, 1H), 2.70−2.59 (m, 1H), 2.55−2.43 (m, 1H), 2.09−1.94 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.6, 177.5, 170.7, 158.6, 142.3, 136.1, 133.2, 133.1, 133.1, 132.8, 131.9, 131.0, 129.1, 128.4, 128.4, 128.3, 127.5, 127.1, 125.8, 122.9, 120.1, 115.9, 115.7, 70.8, 70.1, 62.7, 56.7, 54.9, 41.2, 30.4, 23.2. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 696. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{35}H_{32}BrNaN_3NiO_4$ 718.0827; Found 718.0821. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.803 min, t_{minor} = 6.418 min, dr = 91:9.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-5-cyanophenyl)-propanoic Acid Schiff Base Complex 3h. Red solid (107 mg, yield 96%, (*S*)(2*S*)/(*S*)(2*R*) = 94:6). (*S*)(2*S*)-**3h**: mp 111−114 °C; $[\alpha]_D^{25}$ +2017 (*c* 0.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.61−7.54 (m, 2H), 7.45 (td, *J* = 7.4, 2.0 Hz, 1H), 7.39−7.30 (m, 4H), 7.21−7.13 (m, 2H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.71−6.62 (m, 2H), 4.38 (d, *J* = 12.7 Hz, 1H), 4.25 (t, *J* = 8.0 Hz, 1H), 3.74 (dd, *J* = 13.6, 8.0 Hz, 1H), 3.55 (d, *J* = 12.7 Hz, 1H), 3.47 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.39 (dd, *J* = 10.3, 6.5 Hz, 1H), 3.35−3.19 (m, 2H), 2.71−2.60 (m, 1H), 2.58−2.46 (m, 1H), 2.17−2.02 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.8, 176.6, 170.9, 142.1, 137.3, 134.4, 133.4, 133.1, 133.0, 132.7, 132.2, 131.3, 131.0, 130.2, 129.5, 128.9, 128.8, 128.5, 128.5, 127.2, 125.7, 123.2, 120.3, 117.2, 111.5, 69.8, 69.8, 62.8, 56.7, 40.5, 30.4, 23.5. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 691. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{35}H_{29}BrNaN_4NiO_3$ 713.0674; Found 713.0657. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 3.232 min, t_{minor} = 4.261 min, dr = 94:6.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-5-nitrophenyl)-propanoic Acid Schiff Base Complex 3i. Red solid (109 mg, yield 95%, (*S*)(2*S*)/(*S*)(2*R*) = 94:6). (*S*)(2*S*)-**3i**: mp 127−129 °C; $[\alpha]_D^{25}$ +1971 (*c* 0.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.6 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 2H), 7.91 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.62−7.55 (m, 2H), 7.52 (d, *J* = 2.7 Hz, 1H), 7.47−7.41 (m, 1H), 7.38−7.31 (m, 3H), 7.22−7.14 (m, 2H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.72−6.64 (m, 2H), 4.40 (d, *J* = 12.7 Hz, 1H), 4.25 (dd, *J* = 8.7, 5.9 Hz, 1H), 3.94 (dd, *J* = 13.5, 8.8 Hz, 1H), 3.62−3.52 (m, 2H), 3.52−3.44 (m, 2H), 3.33 (dd, *J* = 13.5, 5.9 Hz, 1H), 2.77−2.67 (m, 1H), 2.62−2.50 (m, 1H), 2.26−2.17 (m, 1H), 2.14−2.04 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.8, 176.5, 170.8, 146.7, 142.1, 137.3, 133.3, 133.0, 132.8, 132.8, 132.2, 131.8, 131.0, 129.7, 128.9, 128.7, 128.5, 128.5, 127.2, 127.1, 125.8, 125.5, 123.3, 122.8, 120.4, 69.8, 69.7, 62.8, 56.8, 41.0, 30.4, 23.6. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 711. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{34}H_{29}BrNaN_4NiO_5$ 733.0572; Found 733.0573. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 3.784 min, t_{minor} = 5.376 min, dr = 94:6.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-5-chlorophenyl)-propanoic Acid Schiff Base Complex 3j. Red solid (111 mg, yield 99%, (*S*)(2*S*)/(*S*)(2*R*) = 95:5). (*S*)(2*S*)-**3j**: mp 99−101 °C; $[\alpha]_D^{25}$ +1991 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.38 (t, *J* = 8.7 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.29−7.27 (m, 1H), 7.20−7.09 (m, 3H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.70−6.60 (m, 2H), 4.35 (d, *J* = 12.7 Hz, 1H), 4.26 (t, *J* = 6.2 Hz, 1H), 3.53 (dt, *J* = 13.7, 3.7 Hz, 2H), 3.43 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.33 (dd, *J* = 13.9, 5.8 Hz, 2H), 3.18−3.05 (m, 1H), 2.65−2.56 (m, 1H), 2.53−2.44 (m, 1H), 2.09−1.98 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 177.0, 171.0, 142.3, 137.2, 133.5, 133.3, 133.2, 133.1, 132.8, 132.1, 131.5, 131.0, 129.3, 128.6, 128.6, 128.4, 127.2, 127.1, 125.7, 123.0, 123.0, 120.2, 70.4, 70.0, 62.7, 56.7, 40.4, 30.4, 23.2. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 700. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{34}H_{29}BrClNaN_3NiO_3$ 722.0332; Found 722.0335. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 75/25, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 9.537 min, t_{minor} = 15.995 min, dr = 95:5.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-4,5-difluorophenyl)-propanoic Acid Schiff Base Complex 3k. Red solid (107 mg, yield 95%, (*S*)(2*S*)/(*S*)(2*R*) = 95:5). (*S*)(2*S*)-**3k**: mp 106−108 °C; $[\alpha]_D^{25}$ +2107 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 2H), 7.59−7.50 (m, 2H), 7.45−7.36 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.21−7.12 (m, 2H), 6.91 (d, *J* = 7.5 Hz, 1H), 6.80 (dd, *J* = 10.7, 8.1 Hz, 1H), 6.70−6.61 (m, 2H), 4.36 (d, *J* = 12.6 Hz, 1H), 4.24 (t, *J* = 6.4 Hz, 1H), 3.60−3.50 (m, 2H), 3.45 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.35 (dd, *J* = 9.1, 6.3 Hz, 1H), 3.26−3.13 (m, 2H), 2.71−2.59 (m, 1H), 2.58−2.46 (m, 1H), 2.12−2.01 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 176.9, 170.9, 142.2, 133.1, 132.7, 132.3, 132.2, 132.2, 132.1, 131.0, 129.4, 128.5, 128.4, 127.9 (dd, *J* = 187.1, 14.2 Hz), 125.7, 123.1, 120.4 (dd, *J* = 181.0, 19.5 Hz), 120.3, 118.3, 118.3, 118.3, 70.1, 69.9, 62.8, 56.7, 40.1, 30.4, 23.2. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 702. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{34}H_{28}BrF_2NaN_3NiO_3$ 724.0533; Found 724.0530. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 4.898 min, t_{minor} = 7.089 min, dr = 95:5.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromo-4,5-dimethoxy-phenyl)propanoic Acid Schiff Base Complex 3l. Red solid (115 mg, yield 99%, (*S*)(2*S*)/(*S*)(2*R*) = 91:9). (*S*)(2*S*)-**3l**: mp 93−95 °C; $[\alpha]_D^{25}$ +1662 (*c* 0.05, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 2H), 7.52−7.42 (m, 2H), 7.34−7.28 (m, 3H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.17−7.10 (m, 2H), 7.02 (s, 1H), 6.67−6.56 (m, 4H), 4.33 (d, *J* = 12.6 Hz, 1H), 4.26 (dd, *J* = 7.0, 4.9 Hz, 1H), 3.87 (s, 3H), 3.64 (s, 3H), 3.58−3.48 (m, 2H), 3.46−3.39 (m, 2H), 3.33−3.23 (m, 1H), 3.15−3.01 (m, 1H), 2.70−2.57 (m, 1H), 2.55−2.44 (m, 1H), 2.10−1.93 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.5, 177.7, 170.7, 148.4, 148.0, 142.3, 133.2, 133.2, 132.8, 131.9, 131.0, 129.0, 128.4, 128.3, 127.5, 127.1, 127.1, 125.8, 122.8, 120.1, 115.2, 114.8, 113.6, 71.0, 70.1, 62.8, 56.7, 55.7, 55.5, 40.5, 30.5, 23.0. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 726. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{36}H_{34}BrNaN_3NiO_5$ 748.0933; Found 748.0955. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 3.766 min, t_{minor} = 4.634 min, dr = 91:9.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-3-(2-bromopyridin-3-yl)propanoic Acid Schiff Base Complex 3m. Red solid (106 mg, yield 99%, (*S*)(2*S*)/(*S*)(2*R*) = 93:7). (*S*)(2*S*)-**3m**: mp 117−120 °C; $[\alpha]_D^{25}$ +2173 (*c* 0.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.31(dd, *J* = 4.7, 2.0 Hz, 1H), 8.23 (d, *J* = 8.7 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 2H), 7.57−7.47 (m, 2H), 7.43 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.38 (td, *J* = 7.4, 1.7 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.29−7.27 (m, 1H), 7.22−7.11 (m, 3H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.69−6.64 (m,1H), 6.61 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.42−4.27 (m, 2H), 3.61−3.48 (m, 2H), 3.43 (dd, *J* = 10.7, 6.3 Hz,1H), 3.34 (dd, *J* = 13.9, 6.7 Hz, 1H), 3.26 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.13−2.97 (m, 1H), 2.76−2.64 (m, 1H), 2.57−2.44 (m, 1H), 2.07−1.95 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.7, 177.0, 171.0, 148.4, 144.7, 142.2, 139.9, 133.2, 133.1, 133.0, 132.7, 132.1, 131.0, 129.4, 128.7, 128.7, 128.5, 128.4, 127.0, 125.7, 123.1, 122.6, 120.2, 70.0, 69.7, 62.7, 56.6, 40.1, 30.3, 23.3. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 667. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{33}H_{29}BrNaN_4NiO_3$ 689.0674; Found 689.0685. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) ($MeOH/H_2O$ = 80/20, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 2.674 min, t_{minor} = 3.096 min, dr = 93:7.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-4-(2-bromophenyl)butanoic Acid Schiff Base Complex 3n. Red solid (872 mg, yield 80%, (*S*)(2*S*)/(*S*)(2*R*) = 94:6). (*S*)(2*S*)-**3n**: mp 85−88 °C; $[\alpha]_D^{25}$ +2131 (*c* 0.06, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 9.1 Hz, 1H), 8.07

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(d, J = 7.2 Hz, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.39−7.33 (m, 5H), 7.23−7.17 (m, 2H), 7.17−7.10 (m, 3H), 7.02 (td, J = 7.7, 1.7 Hz, 1H), 6.95−6.90 (m, 1H), 6.64 (t, J = 7.5 Hz, 1H), 6.59 (dd, J = 8.0, 1.5 Hz, 1H), 4.45 (d, J = 12.6 Hz, 1H), 3.87 (dd, J = 9.2, 3.8 Hz, 1H), 3.68−3.42 (m, 5H), 2.95−2.84 (m, 1H), 2.83−2.71 (m, 1H), 2.58−2.41 (m, 2H), 2.22−2.12 (m, 1H), 2.13−2.03 (m, 1H), 1.97−1.88 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.9, 178.5, 170.1, 141.8, 139.3, 132.8, 132.8, 132.8, 132.4, 131.7, 131.1, 130.4, 129.1, 128.5, 128.5, 128.4, 128.1, 128.1, 127.5, 127.0, 126.9, 126.5, 126.4, 125.9, 123.8, 123.2, 120.3, 69.9, 68.9, 62.6, 56.6, 35.2, 31.4, 30.3, 23.4. LRMS (ESI) m/z: $[M + H]^+$ found 680. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{32}BrNaN_3NiO_3$ 702.0878; Found 702.0862. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 75/25, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 10.817 min, t_{minor} = 11.892 min, dr = 94:6.

Ni(II)-(*S*)-BPB/(*S*)-2-amino-4-(2-bromo-5-chlorophenyl)-butanoic Acid Schiff Base Complex 3o. Red solid (76 mg, yield 66%, (*S*)(2*S*)/(*S*)(2*R*) = 91:9). (*S*)(2*S*)-**3o**: mp 101−103 °C; $[\alpha]_D^{25}$ +2442 (c 0.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14−8.04 (m, 3H), 7.41−7.28 (m, 6H), 7.22−7.10 (m, 4H), 7.00 (dd, J = 8.5, 2.5 Hz, 1H), 6.91−6.84 (m, 1H), 6.67−6.61 (m, 1H), 6.58 (dd, J = 7.2, 1.2 Hz, 1H), 4.44 (d, J = 12.6 Hz, 1H), 3.85 (dd, J = 9.8, 3.7 Hz, 1H), 3.72−3.52 (m, 3H), 3.48 (dd, J = 11.1, 5.7 Hz, 1H), 3.39−3.27 (m, 1H), 2.88−2.68 (m, 2H), 2.61−2.46 (m, 2H), 2.26−2.15 (m, 1H), 2.15−2.03 (m, 1H), 1.94−1.79 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 180.4, 178.9, 170.6, 142.2, 141.5, 133.9, 133.3, 133.3, 133.3, 133.2, 132.2, 131.6, 130.7, 129.7, 129.0, 129.0, 128.9, 128.6, 128.1, 127.2, 126.9, 126.4, 123.8, 122.1, 120.8, 70.3, 68.9, 63.2, 57.2, 35.5, 31.7, 30.8, 24.1. LRMS (ESI) m/z: $[M + H]^+$ found 714. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{31}BrClNaN_3NiO_3$ 736.0488; Found 736.0494. The dr was determined by LC-MS with an Eclipse XDB-C18 column (150 mm × 4.6 mm, 5 μm) (MeOH/H_2O = 75/25, flow rate 1.0 mL/min, λ = 214 nm), t_{major} = 18.878 min, t_{minor} = 29.791 min, dr = 91:9.

(*S*)-2-Amino-3-(2-bromophenyl)propanoic Acid 4a. White solid (490 mg, yield 82%). mp 222−224 °C; $[\alpha]_D^{25}$ +5.9 (c 0.56, CH_3COOH). ^{1}H NMR (400 MHz, D_2O): δ 7.52 (d, J = 8.0 Hz, 1H), 7.26−7.17 (m, 2H), 7.15−7.06 (m, 1H), 4.27 (t, J = 8.6 Hz, 1H), 3.38 (dd, J = 14.4, 6.6 Hz, 1H), 3.14 (dd, J = 14.4, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, D_2O+10%CF_3COOD): δ 163.7, 126.2, 126.1, 124.7, 122.8, 121.1, 117.1, 45.5, 29.1. LRMS (ESI) m/z: $[M + H]^+$ found 244. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{11}BrNO_2$ 243.9973; Found 243.9972. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/H_2O = 70/30, λ = 214 nm, 1.0 mL/min). t_R (major enantiomer) = 8.002 min, >99% ee.

(*S*)-2-Amino-3-(2-bromo-5-fluorophenyl)propanoic Acid 4d. White solid (850 mg, yield 74%). mp 232−234 °C; $[\alpha]_D^{25}$ −2.5 (c 0.55, CH_3COOH). ^{1}H NMR (500 MHz, methanol-d_4 + 10% CF_3COOD) δ 7.65 (dd, J = 8.8, 5.3 Hz, 1H), 7.18 (dd, J = 9.2, 3.0 Hz, 1H), 7.04 (td, J = 8.4, 3.0 Hz, 1H), 4.31 (dd, J = 8.5, 6.7 Hz, 1H), 3.50 (dd, J = 14.3, 6.7 Hz, 1H), 3.22 (dd, J = 14.3, 8.5 Hz, 1H). ^{13}C NMR (125 MHz, methanol-d_4 + 10% CF_3COOD) δ 170.8, 163.5 (d, J = 245.0 Hz), 137.7 (d, J = 7.8 Hz), 135.9 (d, J = 8.3 Hz), 120.0, 119.8 (d, J = 23.5 Hz), 117.8 (d, J = 22.5 Hz), 53.3, 37.9. LRMS (ESI) m/z: $[M + H]^+$ found 261. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{10}BrFNO_2$ $[M + H]^+$ 261.9879; Found 261.9885. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/H_2O = 70/30, λ = 214 nm, 1.0 mL/min). t_R (major enantiomer) = 6.865 min, t_R (minor enantiomer) = 8.590 min, 97% ee.

(*S*)-2-Amino-3-(2-bromo-5-methoxyphenyl)propanoic Acid 4g. White solid (1.01 g, yield 89%). mp 246−247 °C; $[\alpha]_D^{25}$ −3.7 (c 0.57, CH_3COOH). ^{1}H NMR (500 MHz, methanol-d_4 + 10% CF_3COOD) δ 7.50 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 3.0 Hz, 1H), 6.82 (dd, J = 8.8, 3.0 Hz, 1H), 4.28 (dd, J = 8.9, 6.2 Hz, 1H), 3.79 (s, 3H), 3.49 (dd, J = 14.2, 6.2 Hz, 1H), 3.15 (dd, J = 14.2, 8.9 Hz, 1H). ^{13}C NMR (125 MHz, methanol-d_4 + 10% CF_3COOD) δ 171.1, 136.1, 135.1, 119.4, 118.7, 116.4, 115.7, 56.0, 53.6, 38.2. LRMS (ESI) m/z: $[M + H]^+$ found 274. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}BrNO_3$ 274.0079; Found 274.0083. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/H_2O = 70/30, λ = 214 nm, 1.0 mL/min). t_R (major enantiomer) = 7.898 min, t_R (minor enantiomer) = 11.349 min, 96% ee.

(*S*)-2-Amino-3-(2-bromopyridin-3-yl)propanoic Acid 4m. White solid (930 mg, yield 96%). mp 200−201 °C; $[\alpha]_D^{25}$ −0.2 (c 0.56, CH_3COOH). ^{1}H NMR (500 MHz, methanol-d_4 + 10% CF_3COOD) δ 8.30 (dd, J = 4.8, 1.9 Hz, 1H), 7.80 (dd, J = 7.6, 1.9 Hz, 1H), 7.42 (dd, J = 7.6, 4.8 Hz, 1H), 4.35 (t, J = 7.6 Hz, 1H), 3.49 (dd, J = 14.4, 7.3 Hz, 1H), 3.27 (dd, J = 14.4, 8.0 Hz, 1H). ^{13}C NMR (125 MHz, methanol-d_4 + 10% CF_3COOD) δ 170.8, 150.3, 145.0, 142.1, 133.9, 124.9, 53.1, 37.1. LRMS (ESI) m/z: $[M + H]^+$ found 244. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_8H_9BrNaN_2O_2$ 266.9745; Found 266.9746. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/H_2O = 70/30, λ = 214 nm, 1.0 mL/min). t_R (major enantiomer) = 7.394 min, t_R (minor enantiomer) = 8.742 min, 98% ee.

(*S*)-2-Amino-4-(2-bromophenyl)butanoic Acid 4n. White solid (690 mg, yield 76%). mp 162−164 °C; $[\alpha]_D^{25}$ +28.0 (c 0.55, CH_3COOH). ^{1}H NMR (400 MHz, D_2O): δ 7.43 (d, J = 7.9 Hz, 1H), 7.21−7.09 (m, 2H), 6.98 (t, J = 7.2 Hz, 1H), 3.98 (t, J = 6.0 Hz, 1H), 2.82−2.59 (m, 2H), 2.13−1.92 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD + 10%CF_3COOD) δ 172.1, 141.1, 134.6, 132.2, 130.2, 129.6, 125.5, 54.1, 33.2, 32.5. LRMS (ESI) m/z: $[M + H]^+$ found 258. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{13}BrNO_2$ 258.0130; Found 258.0127. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/H_2O = 70/30, λ = 214 nm, 1.0 mL/min). t_R (major enantiomer) = 7.368 min, t_R (minor enantiomer) = 11.098 min, 99% ee.

(*S*)-Indoline-2-carboxylic Acid 5a. White solid (55.7 mg, yield 83%). mp 148−150 °C; $[\alpha]_D^{25}$ +27.0 (c 0.46, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.00 (d, J = 7.1 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.63−6.47 (m, 2H), 4.26 (dd, J = 10.4, 5.6 Hz, 1H), 3.24 (dd, J = 16.0, 10.6 Hz, 1H), 3.07 (dd, J = 16.0, 5.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.9, 151.7, 127.7, 126.9, 124.5, 117.8, 108.9, 59.7, 33.7. LRMS (ESI) m/z: $[M + H]^+$ found 164. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{10}NO_2$ 164.0712; Found 164.0704. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/(0.1%HCOOH) H_2O = 70/30, λ = 254 nm, 1.0 mL/min). t_R (major enantiomer) = 8.510 min, > 99% ee.

(*S*)-5-Fluoroindoline-2-carboxylic Acid 5d. White solid (48.5 mg, yield 70%). mp 154−156 °C; $[\alpha]_D^{25}$ −1.5 (c 0.46, DMSO). ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.87 (d, J = 8.1 Hz, 1H), 6.73 (t, J = 8.1 Hz, 1H), 6.51 (dd, J = 8.5, 4.5 Hz, 1H), 4.27 (dd, J = 10.6, 5.7 Hz, 1H), 3.24 (dd, J = 16.4, 10.5 Hz, 1H), 3.07 (dd, J = 16.4, 5.7 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 175.2, 155.6 (d, J = 243.5 Hz), 147.63, 128.5 (d, J = 8.4 Hz), 113.0 (d, J = 22.7 Hz), 111.5 (d, J = 23.9 Hz), 108.6 (d, J = 7.9 Hz), 59.8, 33.4. LRMS (ESI) m/z: $[M + H]^+$ found 182. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_9FNO_2$ 182.0612; Found 182.0608. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/(0.1% HCOOH) H_2O = 70/30, λ = 254 nm, 1.0 mL/min). t_R (major enantiomer) = 7.004 min, >99% ee.

(*S*)-5-Methoxyindoline-2-carboxylic Acid 5g. White solid (46.1 mg, yield 65%). mp 144−146 °C; $[\alpha]_D^{25}$ +23.3 (c 0.40, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.69 (s, 1H), 6.51 (q, J = 8.6 Hz, 2H), 4.21 (dd, J = 10.3, 5.7 Hz, 1H), 3.62 (s, 3H), 3.21 (dd, J = 16.1, 10.4 Hz, 1H), 3.05 (dd, J = 16.3, 5.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.6, 152.4, 145.0, 128.1, 112.3, 111.0, 109.2, 59.8, 55.5, 33.8. LRMS (ESI) m/z: $[M + H]^+$ found 194. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}NO_3$ 194.0812; Found 194.0809. The ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/(0.1%HCOOH) H_2O = 70/30, λ = 254 nm, 1.0 mL/min). t_R (major enantiomer) = 17.154 min, >99% ee.

(*S*)-2,3-Dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic Acid 5m. White solid (51.4 mg, yield 77%). mp 210−212 °C; $[\alpha]_D^{25}$ −66.2 (c 0.40, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 7.54 (d, J = 7.0 Hz, 1H), 7.48 (d, J = 6.5 Hz, 1H), 6.69 (t, J = 6.8 Hz, 1H), 4.55 (dd, J = 10.8, 5.6 Hz, 1H), 3.51 (dd, J = 18.0, 11.0 Hz, 1H), 3.12 (dd, J = 17.9, 5.6 Hz, 1H). ^{13}C NMR (125 MHz, D_2O) δ 178.6, 156.3, 135.2, 131.6, 127.7, 112.4, 60.0, 30.8. LRMS (ESI) m/z: $[M + H]^+$ found 165. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_8H_9N_2O_2$ 165.0659; Found 165.0654. The

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ee was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (MeOH/(0.1%HCOOH) H_2O = 70/30, λ = 254 nm, 1.0 mL/min). t_R (major enantiomer) = 28.341 min, >99% ee.

(*S*)-Methyl-1,2,3,4-tetrahydroquinoline-2-carboxylate 5n. Light yellow oil (35.0 mg, yield 47%); $[\alpha]_D^{25}$ +28.8 (*c* 0.35, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (t, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 6.5, 1.3 Hz, 1H), 6.66 (td, *J* = 7.4, 1.2 Hz, 1H), 6.60 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.05 (dd, *J* = 8.8, 3.7 Hz, 1H), 3.79 (s, 3H), 2.90−2.70 (m, 2H), 2.34−2.24 (m, 1H), 2.08−1.95 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.7, 143.0, 129.1, 127.1, 120.5, 117.7, 114.6, 53.9, 52.4, 25.8, 24.7. LRMS (ESI) *m*/*z*: $[M + H]^+$ found 192. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{11}H_{13}NaNO_2$ 214.0844; Found 214.0850. The ee was determined by HPLC with a Chiralpak OD-H column (*n*-hexane/*i*-PrOH = 90/10, λ = 254 nm, 1.0 mL/min). t_R (major enantiomer) = 9.423 min, t_R (minor enantiomer) = 13.486 min, 97% ee.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystal structure of compound (*S*)(2*S*)-**3a**, copies of ^1H and ^{13}C NMR spectra, and chiral HPLC experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) CCDC 978847 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.