JOC The Journal of Organic Chemistry

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Enantioselective Synthesis of 2-Substitued-Tetrahydroisoquinolin-1-yl Glycine Derivatives via Oxidative Cross-Dehydrogenative Coupling of Tertiary Amines and Chiral Nickel(II) Glycinate

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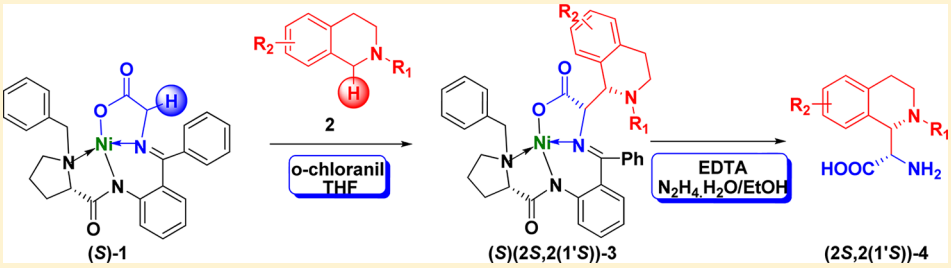
Supporting Information



ABSTRACT: The asymmetric synthesis of 2-substituted-tetrahydroisoquinolin-1-yl glycines was achieved by an oxidative cross-dehydrogenative coupling (CDC) reaction. This method for activation of the α-C-H bonds of amines with chiral nickel(II) glycinate using *o*-chloranil as the sole oxidant afforded highly diastereoselective coupling adducts. The decomposition of coupling adducts readily afforded 2-substituted-tetrahydroisoquinolin-1-yl glycine derivatives.

INTRODUCTION

Optically active non-proteinogenic amino acids have crucial roles in natural products, asymmetric chemical investigations, medicinal chemistry, and peptide/peptidomimetic agents due to their wide-ranging biological properties and versatility as synthetic building blocks.[1] Among numerous α,β-diamino acids,[2] substituted tetrahydroisoquinolin-1-yl glycine derivatives are important building blocks of many bioactive compounds and natural products, such as ecteinascidin,[3] PDE-II,[4] indolobenzazocin-8-ones,[5] and alkaloids.[6] Significant efforts have focused on the asymmetric preparation of α,β-diamino acids,[2] while few synthetic methods have been developed for substituted tetrahydroisoquinolin-1-yl glycine derivatives. These methods have mainly focused on conventional approaches using functional group chemistry including the reduction of azides[7] and nucleophilic substitution reactions of prefunctionalized tetrahydroisoquinoline derivatives,[4] but only racemic products were obtained. Asymmetric addition of glycine equivalents to (dihydro)isoquinolines have also been limited to few examples.[8] Accordingly, the development of a direct, efficient, and stereoselective synthetic method of substituted tetrahydroisoquinolin-1-yl glycine derivatives under mild conditions is of considerable interest in academia and industry.

Recently, cross-dehydrogenative coupling (CDC) has been a versatile strategy for C−C bond formations. Direct conversion of C−H bonds into C−C bonds by CDC allows for the most efficient synthesis of products.[9] Among these reactions, oxidative coupling of amines with various nucleophiles based on catalysis using simple metal salts has received considerable attention,[10] and progress has been made in this fascinating area since the pioneering studies of oxidative functionalization by Murahashi et al.[11] and CDC by Li et al.[12] However, development of the coupling reactions into a general and enantioselective process remains a great challenge.[13] In particular, an asymmetric oxidative reaction of tertiary amines and glycine equivalent has not been achieved.

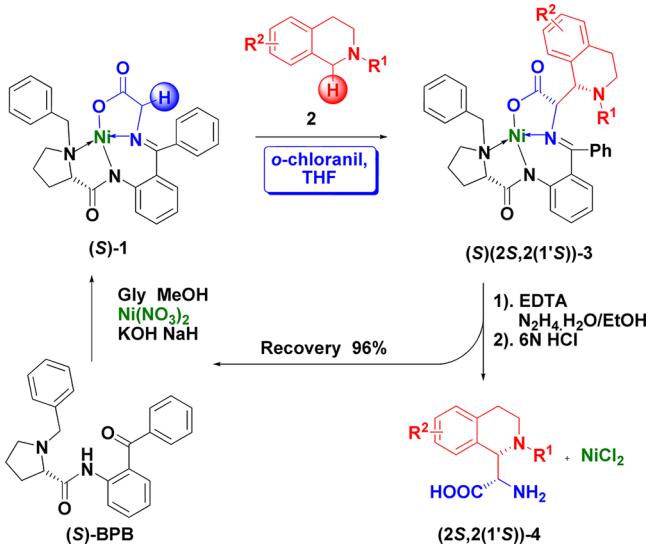
Very recently, Wang et al.[13a] used metals together with chiral bisoxazoline ligands to realize enantioselective reactions of activated carbonyl nucleophiles (such as 1,3-dicarbonyls and acetyl phosphates) to oxidatively generate iminiums or their analogues. Based on this work, they also used metals/Lewis acids with bifunctional cinchona alkaloids to realize asymmetric oxidative cross-coupling reaction of amines and olefins.[13b] In addition, Chi et al.[13c] reported an enantioselective oxidative reaction of aldehydes and tertiary amines under cooperative amine and metal catalysis. Despite the considerable enantioselectivities of these reactions, limitations remain: (i) Some existing problems (e.g., unsatisfactory control of reaction diastereomeric ratio and instability of coupling products) may limit their applications.[13c] (ii) Less reactive and stable nucleophiles, such as glycine equivalent, cannot react under these conditions. We describe here a novel oxidative CDC of tertiary amines with chiral nickel(II) glycinate with high diastereoselectivities.

Received: July 11, 2013
Published: October 11, 2013

   dx.doi.org/10.1021/jo401510b | J. Org. Chem. 2013, 78, 11204−11212

Chiral nickel(II) complexes of glycine Schiff bases have been used widely to synthesize enantiopure non-proteinogenic amino acids via aldol,[14] Michael addition,[15] Mannich,[16] and C-alkylation reactions.[17] Given our recent involvement in the asymmetric synthesis of optically active amino acids via the nucleophilic reactions of nickel(II) glycinate and electron-deficient substrates,[18] we sought to develop new synthetic protocols by C−H activation. Recently, we developed an asymmetric oxidative heterocoupling reaction of a nickel(II) glycinate and indoles.[19] Encouraged by these successful efforts and aiming to develop other unprecedented transformations, we describe here our contribution regarding diastereoselectively oxidative CDC of tertiary amines and chiral nickel(II) glycinate (Scheme 1). This method possesses four main advantages: (i) formation of C(sp^3)-C(sp^3) bonds by C(sp^3)-H activation avoiding prefunctionalization of the substrates; (ii) activation of the α-C-H bonds of amines using *o*-chloranil as the sole oxidant; (iii) achieving an asymmetric CDC reaction of amines with high diastereoselectivities through control of chiral nickel(II) complexes; (iv) generation of optically active and potential 2-substituted-tetrahydroisoquinolin-1-yl glycine derivatives in easy and convenient reaction procedures.

Scheme 1. Asymmetric Synthesis of 2-Substituted-Tetrahydroisoquinolin-1-yl Glycine Derivatives via Oxidative Cross-Dehydrogenative Coupling of Tertiary Amines and Chiral Nickel(II) Glycinate



RESULTS AND DISCUSSION

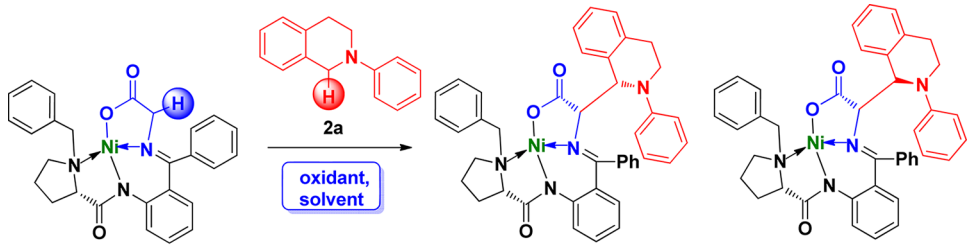
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been used in efficient oxidative coupling reactions involving C(sp^3)-H activation.[9f,d,13a] We focused initially on the DDQ-oxidized coupling reaction of chiral nickel(II) glycinate (*S*)-**1** with *N*-phenyl tetrahydroisoquinoline **2a** at ambient temperature. The reaction afforded moderate yield and a moderate *syn*/*anti* ratio but good diastereoselectivity (Table 1, entry 1). This suggested that chiral nickel(II) glycinate has excellent *si*-face-selectivity[16,18c,19] under oxidative conditions (stereochemistry analysis see Figure S1 in the Supporting Information). A survey of oxidants suggested that *o*-chloranil was a good oxidant for the nickel(II) glycinate CDC reaction. The reaction mediated by *o*-chloranil in dimethyl formamide (DMF) generated the desired product in 72% yield and in a *syn*/*anti* ratio of 2.5:1 with excellent diastereoselectivity (99%/85% de; Table 1, entries 2−6). The effect of the solvent was then investigated (Table 1, entries 7−14). Good diastereoselectivities could be achieved in 1,4-dioxane, chloroform ($CHCl_3$), and dichloromethane (CH_2Cl_2) but with moderate yields and a low *syn*/*anti* ratio (Table 1, entries 7−9). In acetonitrile (CH_3CN) and toluene, the reaction gave coupling products with an improved *syn*/*anti* ratio, but lower yields (Table 1, entries 10 and 11). Methanol (MeOH) and diethyl ether (Et_2O) were not appropriate solvents (Table 1, entries 12 and 13). The reaction in tetrahydrofuran (THF) afforded the product with good yield, a moderate *syn*/*anti* ratio, and excellent diastereoselectivity (Table 1, entry 14). Further optimization studies on the reaction undertaken with the oxidant *o*-chloranil in THF at various temperatures suggested that the *syn*/*anti* ratio decreased significantly with increase of temperature and that the desired product was not obtained at low temperature (Table 1, entries 15 and 16). Better results were not obtained by the screening of metal catalysts and the equivalent of reactants (see the Supporting Information for details). The relative and absolute configuration of major coupling compound **3a**-*syn* was determined to be (*S*)(2*S*,2(1′*S*)) by X-ray crystallography[20] (Figure S2 in the Supporting Information).

With the best reaction conditions established, the scope of substrates for the asymmetric oxidative coupling reactions was then studied. In general, the reaction proceeded well to afford the desired products in good yields with good to excellent diastereoselectivities. For the reaction with nickel(II) glycinate-(*S*)-**1**, initial investigation of the steric effect showed that substituents on the *para*- and *meta*- position of the phenyl ring of **2** were well tolerated in this reaction (Table 2, entries 1−3). Nevertheless, (*S*)-**1** and aromatic-substituted tetrahydroisoquinoline **2d** with substituent at the *ortho*- position of the phenyl ring did not afford the stable oxidative coupling product due to the larger steric hindrance. The *syn*/*anti* ratio and de values were not obtained owing to the instability of **3d** toward decompositions (Table 2, entry 4). When methyl group at the *ortho*- position of the phenyl ring, the corresponding coupling product was still obtained in a poor yield due to steric hindrance (Table 2, entry 5). Then, our focus shifted to evaluation of the electronic effects on the *para*- position of the phenyl ring. Coupling products were obtained in satisfactory yields of 55−88%, with moderate *syn*/*anti* ratio and excellent diastereoselectivities of 90−99% (Table 2, entries 6−11). The coupling products of (*S*)-**1** and aromatic-substituted tetrahydroisoquinolines **2** with double substituents on the *N*-aryl ring, respectively, were also isolated in good yields and high diastereoselectivities (45−59% yields, up to a 5:1 *syn*/*anti* ratio and 89−99% de; Table 2, entries 12−14). Substituents with methoxy or methylenedioxy on the 6,7-position of the tetrahydroisoquinoline ring did not influent reaction outcomes (Table 2, entries 15 and 16). *N*-benzyl tetrahydroisoquinoline and nickel(II) glycinate were used to obtain the corresponding coupling product in acceptable yield (Table 2, entry 17). The plausible reaction pathway is postulated to involve a single-electron transfer (SET) radical mechanism[9,13a,c] (See Scheme S1 in the Supporting Information). The relative and absolute configuration of minor coupling compound **3k**-*anti* was determined to be (*S*)(2*S*,2(1′*R*)) by X-ray crystallography[20] (Figure S3 in the Supporting Information).

The attempts to liberate 2-substituted-tetrahydroisoquinolin-1-yl glycine derivatives from coupling products **3** under acidic

dx.doi.org/10.1021/jo401510b | J. Org. Chem. 2013, 78, 11204−11212

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	yield (%)[b]	*syn*/*anti*[c]	de (%)[d] (*syn*/*anti*)
1	DDQ	DMF	50	2.2:1	98/80
2	TBHP	DMF	<5	nd	nd
3	DTBP	DMF	<5	nd	nd
4	*m*-CPBA	DMF	trace	nd	nd
5	$Cu(OAc)_2$	DMF	trace	nd	nd
6	*o*-chloranil	DMF	72	2.5:1	99/85
7	*o*-chloranil	1,4-dioxane	46	2.8:1	99/84
8	*o*-chloranil	$CHCl_3$	45	2.5:1	98/84
9	*o*-chloranil	CH_2Cl_2	35	2.2:1	99/85
10	*o*-chloranil	CH_3CN	25	4.2:1	99/80
11	*o*-chloranil	toluene	33	3.7:1	99/82
12	*o*-chloranil	MeOH	0	nd	nd
13	*o*-chloranil	Et_2O	0	nd	nd
14	*o*-chloranil	THF	64	4.6:1	99/88
15[e]	*o*-chloranil	THF	70	2.3:1	96/75
16[f]	*o*-chloranil	THF	<10	nd	nd

[a]Reaction conditions: (*S*)-**1** (0.1 mmol), **2a** (0.12 mmol), oxidant (0.12 mmol), and solvent (1.0 mL) at room temperature for 24 h unless otherwise noted. nd = not determined. [b]Combined yield of isolated **3** (*syn* and *anti*). [c]Determined by ^1H NMR spectroscopy. [d]Determined by HPLC on a chiral stationary phase. [e]60 °C, 8 h. [f]0 °C, 36 h.

conditions resulted in the generation of iminium intermediates by β-elimination. Next, the basic reaction conditions were examined. Fortunately, the complexes (*S*)(2*S*,2(1′*S*))-**3a** and (*S*)(2*S*,2(1′*S*))-**3i** were decomposed in a solution of $N_2H_4{\cdot}H_2O$ (85%)/EtOH (1/5) with ethylene diamine tetra-acetic acid (EDTA) under heat to afford the target amino acids **4a** and **4i** in 80−85% yields with 90−98% ee values (Scheme 2). The chiral ligand (*S*)-**BPB** was recovered readily in quantitative yield and could be reused via a simple procedure. The specific rotation of the recovered (*S*)-**BPB** was identical to that of freshly prepared (*S*)-**BPB**.

CONCLUSIONS

In summary, we developed a novel, direct, and highly enantioselective route to the synthesis of 2-substituted-tetrahydroisoquinolin-1-yl glycine derivatives via an asymmetric oxidative cross-dehydrogenative coupling reaction between tertiary amines and nickel(II) glycinate. This method provided an alternative approach for the construction of $C(sp^3)$-$C(sp^3)$ bonds under mild conditions using *o*-chloranil as the terminal oxidant with a moderate *syn*/*anti* ratio, moderate to good yields, and excellent diastereoselectivities (up to 99% de). We showed, for the first time, that the optically active target amino acids could be obtained by decomposition of nickel(II) complexes under basic reaction condition with satisfactory yields and excellent excess enantioselectivity. Moreover, the described method provided opportunities for the synthesis of various chiral non-proteinogenic amino acids via the CDC reaction of extensive sp^3 carbons oxidized fragilely and chiral nickel(II) glycinate.

EXPERIMENTAL SECTION

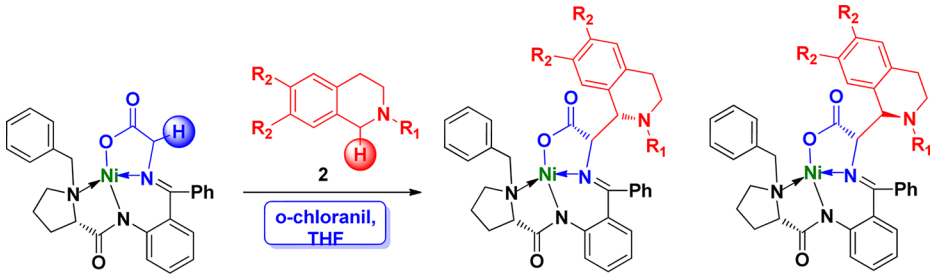
General Information. The reagents (chemicals) were purchased from commercial sources and used without further purification. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15−0.2 mm thickness). All products were characterized by their NMR and MS spectra. ^1H and ^{13}C NMR spectra were recorded in deuterochloroform ($CDCl_3$) on a 300 or 400 MHz instrument. 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). High-resolution mass spectra (HRMS) was measured on Micromass Ultra Q-TOF spectrometer. Optical rotations were reported as follows: $[\alpha]^{20}_D$ (*c* g/100 mL, in solvent).

General Procedure for the Synthesis of (*S*)(2*S*,2(1′*S*))-3a. The nickel(II) complex of glycine (*S*)-**1** (50 mg, 0.1 mmol) was dissolved in tetrahydrofuran (1.0 mL). After *N*-phenyl tetrahydroisoquinoline (**2a**) (26 mg, 0.12 mmol) and *o*-chloranil (30 mg, 0.12 mmol) were added successively, the reaction mixture was stirred for 24 h at room temperature. After the reaction was complete as indicated by TLC, the solvent was evaporated under vacuum. The residue was treated with saturated aqueous Na_2CO_3, and the mixture was extracted with dichloromethane (3 mL × 3). The combined organic layers were dried with $MgSO_4$, concentrated, and purified by column chromatography on silica gel (dichloromethane/ethyl acetate = 4/1) to give the desired coupling product **3a** (45 mg, yield 64%, *syn*/*anti* 4.6:1) as a red solid. In some cases, some pure *syn*-**3** or *anti*-**3** coupling products could be isolated by column.

Nickel(II)-(*S*)-BPB/2-Amino-2-((*S*)-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3a. Red solid (45 mg, yield 64%, *syn*/*anti* 4.6:1). Mp 224−226 °C; $[\alpha]^{20}_D$ = +2113 (*c* 0.15 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.32 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 7.6 Hz, 1H),

dx.doi.org/10.1021/jo401510b | J. Org. Chem. 2013, 78, 11204−11212

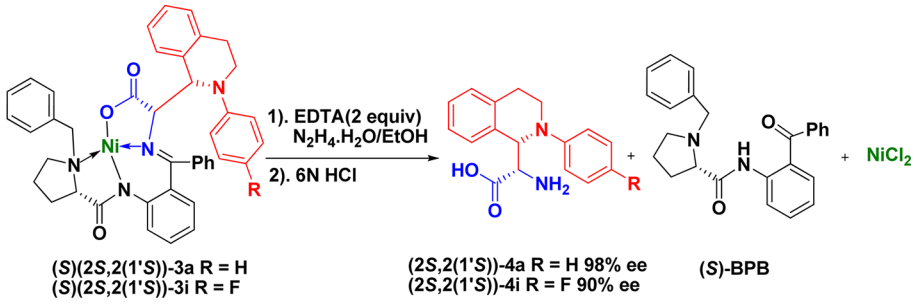
Table 2. Investigation of the Scope of the Procedure[a]



entry	2, R^1, R^2	yield (%)[b]	*syn*/*anti*[c]	de (%)[d] (*syn*/*anti*)
1	**2a**, Ph, H	64	4.6:1 (>10:1)[e]	99/88
2[f]	**2b**, 4-OMe-C_6H_4, H	45	3.6:1	96/97
3[f]	**2c**, 3-OMe-C_6H_4, H	58	2.3:1	98/98
4[f]	**2d**, 2-OMe-C_6H_4, H	20	nd	nd
5	**2e**, 2-Me-C_6H_4, H	21	nd	nd
6	**2f**, 4-Me-C_6H_4, H	55	2.3:1	98/98
7	**2g**, 4-*t*-Bu-C_6H_4, H	59	3.4:1	97/93
8	**2h**, 4-CF_3-C_6H_4, H	74	1.1:1	90/96
9	**2i**, 4-F-C_6H_4, H	70	3.6:1	99/98
10	**2j**, 4-Cl-C_6H_4, H	72	1.6:1	93/99
11	**2k**, 4-Br-C_6H_4, H	88	1.5:1	98/98
12[f]	**2l**, 3,4-di-Me-C_6H_3, H	52	5.0:1	>99/>99
13	**2m**, 3-Cl-4-Me-C_6H_3, H	45	3.0:1	89/96
14	**2n**, 3,5-di-CF_3-C_6H_3, H	59	1:1.2	99/98
15[g]	**2o**, 4-Br-C_6H_4, OCH_2O	45	1.3:1	97/97
16[g]	**2p**, 4-Br-C_6H_4, OMe	57	2.6:1	99/98
17	**2q**, Bn, H	25	<1:20	-/98

[a]Reaction conditions: (*S*)-**1** (0.1 mmol), **2** (0.12 mmol), *o*-chloranil (0.12 mmol), and THF (1.0 mL) at room temperature for 24 h. [b]Combined yield of isolated **3** (*syn* and *anti*). [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC on a chiral stationary phase. [e]Recrystallized with ethyl acetate. [f]12 h. [g]36 h.

Scheme 2. Disassembling of Nickel(II) Complexes To Release Amino Acids and Recovery of the Ligand (*S*)-BPB



7.29–7.26 (m, 2H), 7.18–7.05(m, 7H), 6.99–6.95 (m, 1H), 6.82–6.67 (m, 6H), 6.04 (s, 1H), 5.04 (d, J = 3.1 Hz, 1H), 4.69 (d, J = 3.3 Hz, 1H), 4.35 (d, J = 12.6 Hz, 1H), 3.77–3.66 (m, 2H), 3.43 (d, J = 12.6 Hz, 1H), 3.30–3.25 (m, 2H), 3.07–2.99 (m, 1H), 2.80–2.74 (m, 1H), 2.65–2.59 (m, 1H), 2.22–2.02 (m, 2H), 1.91–1.83 (m, 1H), 1.77–1.69 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.2, 177.2, 172.0, 149.7, 143.1, 136.3, 133.9, 133.8, 133.4, 132.7, 131.5, 129.4, 129.1, 128.9, 128.7, 127.9, 127.4, 126.2, 125.9, 123.2, 120.5, 118.6, 113.9, 75.5, 70.6, 66.1, 63.6, 57.4, 42.2, 30.2, 26.3, 23.2 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 727.8. HRMS (ESI) m/z calcd for $C_{42}H_{38}N_4NiO_3Na^+$ $[M + Na]^+$: 727.2195, found: 727.2152. The de was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 75/25, λ = 254 nm, 0.8 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 31.61 min, t_R (minor enantiomer) = 50.85 min, >99% de; for the *anti*-isomer: t_R (major enantiomer) = 143.18 min, t_R (minor enantiomer) = 43.91 min, 88% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3b. Red solid (33 mg, yield 45%, *syn*/*anti* 3.6:1). $[\alpha]^{20}_D$ = +1238 (*c* 0.16 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.31 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 7.2 Hz, 2H), 4.93 (d, J = 3.2 Hz, 1H), 4.61 (d, J = 3.3 Hz, 1H), 4.38 (d, J = 12.3 Hz, 1H), 3.70 (s, 3H); *anti*-isomer 8.22 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 7.4 Hz, 2H), 5.72 (d, J = 4.9 Hz, 1H), 4.62 (J = 4.9 Hz, 1H), 4.36 (d, J = 12.4 Hz, 1H), 3.71 (s, 3H). Other overlapped peaks: δ 7.58–7.36 (m), 7.34–7.23 (m), 7.19–6.91 (m), 6.82–6.06 (m), 3.74–3.60 (m), 3.48–3.30 (m), 3.15–2.96 (m), 2.63–2.45 (m), 2.31–2.21 (m), 2.13–2.04 (m), 1.84–1.75 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 179.9, 176.7, 171.3, 152.5, 144.1, 142.7, 120.0, 115.7, 114.4, 75.1, 70.1, 66.3, 63.0, 57.0, 55.4, 42.6, 30.0, 25.5, 22.8; *anti*-isomer 179.6, 177.5, 171.0, 152.1, 143.3, 142.4, 120.0, 115.2, 114.5, 74.9, 70.5, 66.2, 63.2, 57.0, 55.3, 43.0, 30.6, 25.0, 22.8. Other overlapped peaks: δ 135.8, 135.1, 133.6, 133.5, 133.4, 133.2, 133.1, 133.0, 132.2, 132.0, 131.1, 131.0, 128.9, 128.8,

dx.doi.org/10.1021/jo401510b | J. Org. Chem. 2013, 78, 11204–11212

128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.6, 127.5, 127.1, 126.9, 126.8, 126.0, 125.7, 125.5, 122.8, 122.5 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 756.8. HRMS (ESI) m/z calcd for $C_{43}H_{40}N_4NiO_4Na^+$ $[M + Na]^+$: 757.2301, found: 757.2289. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 33.68 min, t_R (minor enantiomer) = 12.14 min, 96% de; for the *anti*-isomer: t_R (major enantiomer) = 143.25 min, t_R (minor enantiomer) = 17.61 min, 97% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3c. Red solid (43 mg, yield 58%, *syn*/*anti* 2.3:1). $[\alpha]^{20}_D$ = +1325 (*c* 0.16 g/100 mL, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ *syn*-isomer 8.34 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 2H), 5.04 (d, *J* = 2.8 Hz, 1H), 4.66 (d, *J* = 3.2 Hz, 1H), 4.35 (d, *J* = 12.6 Hz, 1H), 3.60 (s, 3H); *anti*-isomer 8.24 (d, *J* = 8.6 Hz, 1H), 8.10 (d, *J* = 7.3 Hz, 2H), 5.94 (d, *J* = 5.4 Hz, 1H), 4.63 (d, *J* = 5.6 Hz, 1H), 4.39 (d, *J* = 12.6 Hz, 1H), 3.73 (s, 3H). Other overlapped peaks: δ 7.59−7.56 (m), 7.46−7.28 (m),7.20−6.92 (m), 6.83−6.66 (m), 6.59−6.42 (m), 6.32−6.02 (m), 3.76−3.57 (m), 3.48−3.41 (m), 3.30−3.27 (m), 3.06−2.70 (m), 2.63−2.58 (m), 2.52−2.46 (m), 2.25−1.95 (m), 1.86−1.76 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 177.9, 171.9, 160.9, 151.2, 143.2, 136.2, 126.2, 125.9, 123.2, 120.4, 106.8, 103.6, 100.5, 75.4, 70.6, 66.1, 63.5, 57.4, 55.2, 43.0, 30.4, 26.2, 23.2; *anti*-isomer 180.0, 177.7, 171.5, 161.0, 150.6, 142.9, 135.4, 126.4, 126.3, 122.9, 120.3, 107.1, 102.9, 100.7, 75.1, 70.9, 65.9, 63.6, 57.4, 55.2, 42.4, 30.9, 25.7, 23.4. Other overlapped peaks: δ 134.0, 133.9, 133.8, 133.7, 133.4, 132.7, 132.4, 131.5, 131.4, 130.2, 130.0, 129.4, 129.2, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.8, 127.5, 127.4, 127.3 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 756.8. HRMS (ESI) m/z calcd for $C_{43}H_{40}N_4NiO_4Na^+$ $[M + Na]^+$: 757.2301, found: 757.2313, The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 38.88 min, t_R (minor enantiomer) = 13.48 min, 98% de; for the *anti*-isomer: t_R (major enantiomer) = 164.17 min, t_R (minor enantiomer) = 12.01 min, 98% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3e. Red solid (15 mg, yield 21%). $[\alpha]^{20}_D$ = +2105 (*c* 0.15 g/100 mL, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ *syn*-isomer 8.29 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 7.2 Hz, 2H), 7.45−6.92 (m, 16H), 6.68−6.50 (m, 3H), 5.49 (s, 1H), 5.36 (s, 1H), 4.42 (d, *J* = 12.5 Hz, 1H), 4.25−3.98 (m, 1H), 3.55−3.21 (m, 6H), 2.79−2.49 (m, 5H), 2.20−1.98 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 177.4, 170.8, 150.3, 142.6, 136.9, 134.2, 134.0, 133.8, 133.7, 133.3, 132.4, 131.6, 131.3, 129.5, 129.4, 128.8, 128.7, 128.4, 128.0, 127.7, 127.4, 127.3, 126.7, 126.2, 126.0, 125.8, 123.7, 123.2, 122.7, 120.6, 74.0, 70.4, 63.2, 57.1, 44.3, 30.7, 24.2, 24.0, 18.6. LRMS (ESI) m/z $[M + Na]^+$ found: 741.2. HRMS (ESI) m/z calcd for $C_{43}H_{40}N_4NiO_3Na^+$ $[M + Na]^+$: 741.2352, found: 741.2346.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3f. Red solid (40 mg, yield 55%, *syn*/*anti* 2.3:1). $[\alpha]^{20}_D$ = +1412 (*c* 0.17 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.31 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.1 Hz, 2H), 4.97 (d, *J* = 3.1 Hz, 1H), 4.64 (d, *J* = 3.3 Hz, 1H), 4.37 (d, *J* = 12.4 Hz, 1H), 2.19 (s, 3H); *anti*-isomer 8.21 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 2H), 5.93 (d, *J* = 5.8 Hz, 1H), 4.61 (d, *J* = 5.8 Hz, 1H), 4.38 (d, *J* = 12.8 Hz, 1H), 2.18 (s, 3H). Other overlapped peaks: δ 7.59−7.27 (m), 7.20−7.04 (m), 7.02−6.84 (m), 6.78−6.48 (m), 3.77−3.66 (m), 3.52−3.27 (m), 3.07−2.93 (m), 2.70−2.41 (m), 2.22−1.75 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *syn*-isomer: δ 180.3, 177.2, 171.7, 147.9, 143.1, 136.2, 126.1, 126.0, 123.3, 120.5, 113.9, 75.6, 70.5, 66.4, 63.4, 57.3, 42.3, 30.3, 26.0, 23.1, 20.2; *anti*-isomer 180.0, 177.7, 171.3, 147.1, 142.8, 135.5, 126.4, 126.3, 123.0, 120.4, 114.4, 75.1, 70.9, 66.4, 63.6, 57.4, 42.7, 31.0, 25.6, 23.4, 20.2. Other overlapped peaks: δ 134.0, 133.8, 133.7, 133.5, 133.4, 132.6, 132.4, 131.6, 131.4, 130.0, 129.8, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 740.8. HRMS (ESI) m/z calcd for $C_{43}H_{40}N_4NiO_3Na^+$ $[M + Na]^+$: 741.2352, found: 741.2336. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 22.28 min, t_R (minor enantiomer) = 10.54 min, 98% de; for the *anti*-isomer: t_R (major enantiomer) = 72.41 min, t_R (minor enantiomer) = 14.63 min, 98% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-*tert*-butylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3g. Red solid (45 mg, yield 59%, *syn*/*anti* 3.4:1). $[\alpha]^{20}_D$ = +1260 (*c* 0.20 g/100 mL, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ *syn*-isomer 8.31 (d, *J* = 8.7 Hz, 1H), 8.05 (d, *J* = 7.2 Hz, 2H), 5.03 (d, *J* = 2.9 Hz, 1H), 4.68 (d, *J* = 3.2 Hz, 1H), 4.35 (d, *J* = 12.6 Hz, 1H), 1.24 (s, 9H); *anti*-isomer 8.26 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 5.68 (d, *J* = 4.6 Hz, 1H), 4.65 (d, *J* = 4.7 Hz, 1H), 4.35 (d, *J* = 12.6 Hz, 1H), 1.23 (s, 9H). Other overlapped peaks: δ 7.56−7.53 (m), 7.46−7.34 (m), 7.30−7.26 (m), 7.20−7.02 (m), 6.97−6.87 (m), 6.77−6.68 (m), 6.59−6.49 (m), 6.25−6.05 (m), 3.70−3.68 (m), 3.47−3.25 (m), 3.04−2.98 (m), 2.73−2.59 (m), 2.17−2.04 (m), 1.87−1.64 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.0, 177.2, 147.3, 143.2, 141.2, 136.4, 123.2, 120.4, 113.5, 75.6, 70.5, 66.1, 63.5, 57.4, 42.4, 33.8, 31.5, 30.1, 26.4, 23.2; *anti*-isomer 180.0, 178.1, 146.8, 143.0, 140.9, 135.6, 122.9, 120.3, 113.5, 75.2, 71.0, 65.4, 63.7, 57.4, 43.0, 33.7, 31.4, 31.2, 25.5, 23.0. Other overlapped peaks: δ 134.1, 133.9, 133.8, 133.7, 133.5, 133.2, 132.6, 132.4, 131.5, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.0, 127.9, 127.5, 127.4, 127.3, 127.2, 126.4, 126.3, 126.2, 126.1 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 782.8. HRMS (ESI) m/z calcd for $C_{46}H_{46}N_4NiO_3Na^+$ $[M + Na]^+$: 783.2821, found 783.2827. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 75/25, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 19.09 min, t_R (minor enantiomer) = 10.99 min, 97% de; for the *anti*-isomer: t_R (major enantiomer) = 72.15 min, t_R (minor enantiomer) = 25.54 min, 93% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3h. Red solid (57 mg, yield 74%, *syn*/*anti* 1.1:1). $[\alpha]^{20}_D$ = +1357 (*c* 0.21 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.38 (d, *J* = 8.6 Hz, 1H), 8.06 (d, *J* = 6.0 Hz, 2H), 5.25 (d, *J* = 3.5 Hz, 1H), 4.83 (d, *J* = 3.2 Hz, 1H), 4.25 (d, *J* = 12.6 Hz, 1H); *anti*-isomer 8.26 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 2H), 5.48 (d, *J* = 5.7 Hz, 1H), 4.67 (d, *J* = 5.8 Hz, 1H), 4.31 (d, *J* = 12.6 Hz, 1H). Other overlapped peaks: δ 7.59−7.56 (m), 7.50−7.28 (m), 7.25−7.04 (m), 6.90−6.83 (m), 6.70−6.45 (m), 3.62−3.22 (m), 3.08−2.91 (m), 2.64−2.60 (m), 2.13−2.03 (m), 1.75−1.67 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 176.8, 171.4, 151.0, 143.2, 136.6, 122.7, 120.5, 72.7, 70.8, 65.2, 64.0, 57.7, 43.4, 30.7, 27.3, 23.4; *anti*-isomer 179.9, 177.8, 171.4, 150.9, 143.0, 135.7, 123.0, 120.5, 74.1, 70.6, 63.8, 63.7, 57.1, 43.8, 30.8, 26.4, 23.1. Other overlapped peaks: δ 134.1, 134.0, 133.5, 133.4, 133.3, 133.1, 132.8, 131.4, 131.3, 129.7, 129.6, 129.1, 129.0, 128.8, 128.6, 128.2, 128.0, 127.8, 127.2, 126.9, 126.7, 126.4, 125.9, 125.7 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 794.8. HRMS (ESI) m/z calcd for $C_{43}H_{37}F_3N_4NiO_3Na^+$ $[M + Na]^+$: 795.2069, found: 795.2076. The de was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 80/20, λ = 254 nm, 0.8 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 31.64 min, t_R (minor enantiomer) = 23.18 min, 90% de; for the *anti*-isomer: t_R (major enantiomer) = 95.10 min, t_R (minor enantiomer) = 66.38 min, 96% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3i. Red solid (51 mg, yield 70%, *syn*/*anti* 3.6:1). $[\alpha]^{20}_D$ = +1171 (*c* 0.14 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.35 (d, *J* = 8.6 Hz, 1H), 8.06 (d, *J* = 7.1 Hz, 2H), 5.02 (d, *J* = 3.6 Hz, 1H), 4.68 (d, *J* = 3.7 Hz, 1H), 4.33 (d, *J* = 12.5 Hz, 1H); *anti*-isomer 8.23 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 7.5 Hz, 2H), 5.63 (d, *J* = 5.4 Hz, 1H), 4.63 (d, *J* = 5.3 Hz, 1H), 4.35 (d, *J* = 12.5 Hz, 1H). Other overlapped peaks: δ 7.53−7.37 (m), 7.33−7.22 (m), 7.18−6.96 (m), 6.87−6.84 (m), 6.73−6.65 (m), 6.62−6.49 (m), 6.35−6.31 (m), 3.64−3.53 (m), 3.48−3.40 (m), 3.36−3.29 (m), 3.25−3.19 (m), 3.01−2.41 (m), 2.31−2.23 (m), 2.12−2.05 (m), 1.80−1.72 (m) ppm. ^{13}C NMR (125 MHz,

$CDCl_3$): δ *syn*-isomer 180.2, 177.0, 157.3, 146.2, 143.1, 136.4, 123.0, 120.5, 115.7, 115.6, 114.9, 114.8, 75.0, 70.6, 66.4, 63.7, 57.5, 43.2, 30.6, 26.4, 23.3; *anti*-isomer 180.0, 177.9, 155.4, 145.7, 142.9, 135.5, 122.9, 120.4, 116.0, 115.8, 114.7, 74.6, 70.8, 65.8, 63.7, 57.4, 43.5, 30.9, 25.6, 23.2. Other overlapped peaks: δ 134.0, 133.9, 133.8, 133.7, 133.6, 133.4, 132.8, 132.6, 131.5, 131.4, 129.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.6, 127.4, 126.5, 126.4, 126.2, 125.8 ppm. LRMS (ESI) *m*/*z* $[M + Na]^+$ found: 745.8. HRMS (ESI) *m*/*z* calcd for $C_{42}H_{37}FN_4NiO_3Na^+$ $[M + Na]^+$: 745.2101, found: 745.2115. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 25.49 min, t_R (minor enantiomer) = 12.21 min, 99% de; for the *anti*-isomer: t_R (major enantiomer) = 147.17 min, t_R (minor enantiomer) = 14.68 min, > 98% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3j. Red solid (53 mg, yield 72%, *syn*/*anti* 1.6:1). $[\alpha]^{20}_D$ = +1114 (*c* 0.22 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.36 (d, *J* = 8.8 Hz, 1H), 8.06 (d, *J* = 6.9 Hz, 2H), 5.07 (d, *J* = 3.6 Hz, 1H), 4.72 (d, *J* = 3.7 Hz, 1H), 4.30 (d, *J* = 12.6 Hz, 1H); *anti*-isomer 8.23 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 6.0 Hz, 2H), 5.61 (d, *J* = 5.5 Hz, 1H), 4.64 (d, *J* = 5.6 Hz, 1H), 4.34 (d, *J* = 12.7 Hz, 1H). Other overlapped peaks: δ 7.51−7.46 (m), 7.37−7.19 (m), 7.16−6.99 (m), 6.83−6.41 (m), 3.57−3.16 (m), 3.00−2.91 (m), 2.77−2.24 (m), 2.12−2.05 (m), 1.76−1.69 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 176.9, 171.4, 147.6, 147.2, 136.4, 123.2, 122.9, 120.5, 114.4, 74.7, 70.7, 65.9, 63.8, 57.6, 43.4, 30.6, 25.9, 23.3; *anti*-isomer 179.9, 177.8, 172.6, 148.0, 142.9, 135.6, 123.0, 122.8, 120.5, 114.5, 73.9, 70.7, 63.7, 60.1, 57.4, 43.1, 30.9, 26.7, 23.3. Other overlapped peaks: δ 134.0, 133.6, 133.4, 132.9, 132.6, 131.4, 129.5, 129.3, 129.2, 129.0, 128.9, 128.8, 128.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.3, 126.6, 126.4, 126.2, 125.8 ppm. LRMS (ESI) *m*/*z* $[M + Na]^+$ found: 760.8. HRMS (ESI) *m*/*z* calcd for $C_{42}H_{37}ClN_4NiO_3Na^+$ $[M + Na]^+$: 761.1805, found: 761.1785. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 27.55 min, t_R (minor enantiomer) = 12.54 min, 93% de; for the *anti*-isomer: t_R (major enantiomer) = 100.13 min, t_R (minor enantiomer) = 18.98 min, > 99% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-bromophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3k. Red solid (69 mg, yield 88%, *syn*/*anti* 1.5:1). **3k**-*syn*: Mp 178−180 °C. $[\alpha]^{20}_D$ = +1429 (*c* 0.17 g/100 mL, $CHCl_3$). **3k**-*anti*: Mp 176−178 °C . $[\alpha]^{20}_D$ = +2088 (*c* 0.16 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.36 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.31−7.24 (m, 4H), 7.18−7.01 (m, 7H), 6.73−6.50 (m, 6H), 5.08 (d, *J* = 3.5 Hz, 1H), 4.73 (d, *J* = 3.7 Hz, 1H), 4.30 (d, *J* = 12.6 Hz, 1H), 3.59−3.46 (m, 2H), 3.39 (d, *J* = 12.6 Hz, 1H), 3.33−3.28 (m, 1H), 3.19−3.14 (m, 1H), 2.98−2.91 (m, 1H), 2.63−2.58 (m, 2H), 2.33−2.24 (m, 1H), 2.11−2.05 (m, 2H), 1.77−1.66 (m, 1H) ppm; *anti*-isomer 8.23 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 7.0 Hz, 2H), 7.53−7.47 (m, 2H), 7.33−7.27 (m, 2H), 7.25−7.07 (m, 8H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 9.1 Hz, 2H), 6.64−6.60 (m, 1H), 6.51 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 5.59 (d, *J* = 5.6 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 1H), 4.33 (d, *J* = 12.6 Hz, 1H), 3.53−3.39 (m, 3H), 3.34−3.28 (m, 1H), 3.24−3.18 (m, 1H), 3.00−2.93 (m, 1H), 2.81−2.72 (m, 2H), 2.54−2.38 (m, 2H), 2.12−2.05 (m, 1H), 1.82−1.73 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 176.9, 172.7, 148.4, 143.1, 136.4, 134.0, 133.6, 133.5, 133.4, 132.9, 131.8, 131.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.1, 127.9, 127.3, 126.6, 125.8, 122.9, 120.5, 115.0, 110.3, 74.6, 70.7, 65.8, 63.8, 57.6, 43.0, 30.6, 26.7, 23.3 ppm; *anti*-isomer 180.0, 177.8, 171.4, 148.0, 142.9, 135.6, 134.0, 133.5, 133.4, 132.7, 132.1, 131.4, 129.5, 128.8, 128.7, 128.6, 128.4, 127.8, 127.6, 126.5, 126.1, 123.0, 120.5, 114.8, 109.9, 73.7, 70.7, 64.9, 63.7, 57.4, 43.3, 30.9, 25.9, 23.3 ppm. LRMS (ESI) *m*/*z* $[M + Na]^+$ found: 804.7. HRMS (ESI) *m*/*z* calcd for $C_{42}H_{37}BrN_4NiO_3Na^+$ $[M + Na]^+$: 805.1300, found 805.1348. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 24.87 min, t_R (minor enantiomer) = 12.95 min, 98% de; for the *anti*-isomer: t_R (major enantiomer) = 80.08 min, t_R (minor enantiomer) = 19.35 min, 98% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(3,4-dimethylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3l. Red solid (38 mg, yield 52%, *syn*/*anti* 5.0:1). $[\alpha]^{20}_D$ = +1746 (*c* 0.14 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.34 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 7.4 Hz, 2H), 4.91 (s, 1H), 4.63 (s, 1H), 4.40 (d, *J* = 12.8 Hz, 1H), 2.10 (s, 3H), 1.89 (s, 3H); *anti*-isomer 8.26 (d, *J* = 8.7 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 2H), 6.05 (d, *J* = 5.4 Hz, 1H), 4.60 (d, *J* = 5.6 Hz, 1H), 4.40 (d, *J* = 12.8 Hz, 1H), 2.14 (s, 3H), 1.89 (s, 3H). Other overlapped peaks: δ 7.69−7.28 (m), 7.23−6.97 (m), 6.97−6.63 (m), 6.62−6.29 (m), 3.89−3.71 (m), 3.52−3.24 (m), 3.12−2.83 (m), 2.63−2.43 (m), 2.19−2.00 (m), 1.82−1.75 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 177.2, 171.2, 148.5, 143.3, 137.6, 123.4, 120.4, 117.0, 111.4, 75.9, 70.4, 66.6, 63.2, 57.1, 41.8, 30.1, 25.8, 23.0, 20.1, 18.5; *anti*-isomer 180.2, 177.6, 171.3, 147.6, 142.8, 137.6, 123.0, 120.4, 115.8, 111.8, 75.3, 70.9, 67.0, 63.5, 57.4, 42.2, 31.0, 25.4, 23.5, 20.3, 18.6. Other overlapped peaks: δ 136.0, 135.3, 134.2, 134.0, 133.7, 133.6, 133.3, 132.6, 132.4, 131.6, 131.4, 130.5, 130.3, 129.6, 129.5, 129.2, 129.1, 129.0, 128.8, 128.7, 128.4, 128.2, 127.9, 127.7, 127.6, 127.4, 127.3, 127.0, 126.7, 126.5, 126.4, 126.1, 125.9 ppm. LRMS (ESI) *m*/*z* $[M + Na]^+$ found: 754.8. HRMS (ESI) *m*/*z* calcd for $C_{44}H_{42}N_4NiO_3Na^+$ $[M + Na]^+$: 755.2508, found: 755.2512. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 14.83 min, t_R (minor enantiomer) = 7.97 min, > 99% de; for the *anti*-isomer: t_R (major enantiomer) = 49.99 min, t_R (minor enantiomer) = 8.70 min, > 99% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(3-chloro-4-methylphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3m. Red solid (34 mg, yield 45%, *syn*/*anti* 3.0:1). $[\alpha]^{20}_D$ = +1446 (*c* 0.16 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.36 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.7 Hz, 2H), 5.08 (d, *J* = 2.7 Hz, 1H), 4.67 (d, *J* = 3.3 Hz, 1H), 4.34 (d, *J* = 12.7 Hz, 1H), 2.21 (s, 3H); *anti*-isomer 8.25 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 7.9 Hz, 2H), 5.93 (d, *J* = 6.1 Hz, 1H), 4.59 (d, *J* = 6.0 Hz, 1H), 4.39 (d, *J* = 12.4 Hz, 1H), 2.18 (s, 3H). Other overlapped peaks: δ 7.56−7.26 (m), 7.23−6.99 (m), 6.93−6.81 (m), 6.73−6.50 (m), 6.37−6.29 (m), 3.62−3.59 (m), 3.50−3.42 (m), 3.34−3.26 (m), 3.01−2.85 (m), 2.60−2.54 (m), 2.32−2.05 (m), 1.85−1.80 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.3, 176.9, 172.1, 148.7, 143.2, 136.2, 123.0, 120.5, 114.4, 112.2, 70.6, 65.9, 63.5, 57.4, 42.6, 30.5, 26.4, 23.4, 18.7; *anti*-isomer 180.3, 177.4, 171.4, 148.3, 142.9, 135.2, 123.0, 120.4, 113.9, 112.6, 70.8, 66.1, 63.5, 57.4, 42.8, 30.9, 25.7, 23.6, 18.8. Other overlapped peaks: δ 135.1, 135.0, 134.0, 133.8, 133.5, 133.4, 133.3, 132.8, 132.6, 131.6, 131.5, 131.4, 131.2, 129.4, 129.3, 129.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.1, 128.0, 127.7, 127.6, 127.5, 126.4, 126.3, 126.2, 125.8, 125.4, 125.2 ppm. LRMS (ESI) *m*/*z* $[M + Na]^+$ found: 774.8. HRMS (ESI) *m*/*z* calcd for $C_{43}H_{39}ClN_4NiO_3Na^+$ $[M + Na]^+$: 775.1962, found: 775.1945. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 28.47 min, t_R (minor enantiomer) = 11.21 min, 89% de; for the *anti*-isomer: t_R (major enantiomer) = 132.25 min, t_R (minor enantiomer) = 13.93 min, 96% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(3,5-bis(trifluoromethyl)-phenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3n. Red solid (50 mg, yield 59%, *syn*/*anti* 1:1.2). **3n**-*syn*: Mp 164−166 °C. $[\alpha]^{20}_D$ = +1140 (*c* 0.10 g/100 mL, $CHCl_3$). **3n**-*anti*: Mp 157−159 °C. $[\alpha]^{20}_D$ = +1267 (*c* 0.21 g/100 mL, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.38 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 2H), 7.50−7.46 (m, 1H), 7.32−7.24 (m, 6H), 7.19−6.89 (m, 8H), 6.67−6.31 (m, 2H), 6.37 (s, 1H), 5.31 (d, *J* = 2.8 Hz 1H), 4.77 (d, *J* = 2 Hz, 1H), 4.30 (d, *J* = 12.2 Hz, 1H), 3.56 (s, 2H), 3.40 (d, *J* = 12.4 Hz, 1H), 3.32 (t, *J* = 8.6 Hz, 1H), 3.18 (s, 1H), 3.05−2.88 (m, 1H), 2.66−2.62 (m, 2H), 2.36−2.31 (m, 1H), 2.12−2.07 (m, 2H), 1.83 (s, 1H); *anti*-isomer 8.34 (d, *J* = 8.7 Hz, 1H), 8.09 (d, *J* = 7.4

Hz, 2H), 7.47−7.24 (m, 7H), 7.15−7.02 (m, 5H), 6.97−6.89 (m, 2H), 6.79 (d, J = 7.6 Hz, 1H), 6.59 (t, J = 7.4 Hz, 1H), 6.47 (d, J = 8.2 Hz, 1H), 6.03 (d, J = 7.5 Hz, 1H), 5.76 (d, J = 4.0 Hz, 1H), 4.74 (d, J = 4.2 Hz, 1H), 4.36 (d, J = 12.5 Hz, 1H), 3.87 (d, J = 13.3 Hz, 1H), 3.46−3.41 (m, 2H), 3.37−3.17 (m, 2H), 3.10−2.93 (m, 1H), 2.88−2.80 (m, 1H), 2.66−2.57 (m, 2H), 2.50−2.41 (m, 1H), 2.09−2.02 (m, 1H), 1.80−1.77 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 176.4, 172.8, 149.6, 143.4, 136.0, 134.0, 133.5, 133.4, 133.1, 133.0, 132.5, 132.2, 131.4, 129.3, 129.0, 128.9, 128.8, 128.7, 128.3, 128.0, 127.6, 126.8, 125.6, 124.5, 122.9, 122.3, 120.5, 112.2, 111.0, 73.5, 70.8, 65.2, 63.8, 57.6, 43.0, 30.7, 26.8, 23.5; *anti*-isomer 180.2, 177.1, 172.0, 149.7, 143.1, 136.3, 133.9, 133.8, 133.4, 132.7, 131.5, 129.4, 129.1, 128.9, 128.7, 127.8, 127.5, 127.4, 126.2, 125.9, 123.2, 120.5, 118.5, 113.9, 75.5, 70.6, 66.1, 63.6, 57.4, 42.2, 30.2, 26.3, 23.2 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 862.8. HRMS (ESI) m/z calcd for $C_{44}H_{36}F_6N_4NiO_3Na^+$ $[M + Na]^+$: 863.1943, found 863.1915. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 19.40 min, t_R (minor enantiomer) = 9.08 min, 99% de; for the *anti*-isomer: t_R (major enantiomer) = 17.52 min, t_R (minor enantiomer) = 6.98 min, 98% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-((6-(4-bromophenyl)-5,6,7,8-tetrahydro[1,3]dioxolo[4,5-*g*]isoquinolin-5-yl) Acetic Acid Schiff Base Complex 3o. Red solid (37 mg, yield 45%, *syn*/*anti* 1.3:1). $[\alpha]^{20}_D$ = +1331 (*c* 0.13 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.34 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 7.3 Hz, 2H), 5.89 (s, 1H), 5.85 (s, 1H), 4.77 (d, J = 2.5 Hz, 1H), 4.64 (d, J = 2.2 Hz, 1H), 4.33 (d, J = 12.5 Hz, 1H); *anti*-isomer 8.22 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 7.3 Hz, 2H), 5.90 (s, 1H), 5.82 (s, 1H), 5.47 (d, J = 4.3 Hz, 1H), 4.63 (d, J = 4.3 Hz, 1H), 4.34 (d, J = 12.6 Hz, 1H). Other overlapped peaks: δ 7.66−7.37 (m), 7.37−7.25 (m), 7.22−7.01 (m), 6.91−6.84 (m), 6.78−6.57 (m), 6.51−6.42 (m), 3.85−3.50 (m), 3.50−3.36 (m), 3.36−3.14 (m), 3.02−2.68 (m), 2.67−2.38 (m), 2.61−2.44(m), 2.16−1.94 (m), 1.80−1.75 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.1, 177.0, 171.8, 148.4, 147.1, 146.3, 143.2, 122.9, 120.5, 115.6, 110.4, 108.5, 107.2, 101.0, 74.9, 70.6, 65.6, 63.6, 57.4, 43.1, 30.4, 25.2, 23.0; *anti*-isomer 180.0, 178.0, 172.2, 148.7, 147.3, 146.2, 142.9, 123.0, 120.5, 115.4, 110.6, 108.1, 107.5, 100.9, 75.6, 70.9, 66.1, 63.8, 57.4, 42.7, 31.1, 26.3, 23.1. Other overlapped peaks: δ 134.1, 133.8, 133.7, 133.4, 132.9, 132.7, 132.2, 131.9, 131.4, 129.6, 129.4, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 128.0, 127.8, 127.4, 127.2, 126.7, 126.2, 126.1, 125.8 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 848.8. HRMS (ESI) m/z calcd for $C_{43}H_{37}BrN_4NiO_5Na^+$ $[M + Na]^+$: 849.1198, found: 849.1250. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 60/40, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 45.36 min, t_R (minor enantiomer) = 22.48 min, 97% de; for the *anti*-isomer: t_R (major enantiomer) = 57.83 min, t_R (minor enantiomer) = 28.42 min, 97% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-(4-bromophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3p. Red solid (48 mg, yield 57%, *syn*/*anti* 2.6:1). $[\alpha]^{20}_D$ = +1900 (*c* 0.12 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ *syn*-isomer 8.35 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 7.5 Hz, 2H), 5.12 (s, 1H), 4.66 (s, 1H), 4.31 (d, J = 12.5 Hz, 1H), 3.88 (s, 3H), 3.63 (s, 3H); *anti*-isomer 8.28 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 7.2 Hz, 2H), 5.33 (d, J = 2.6 Hz, 1H), 4.70 (d, J = 2.6 Hz, 1H), 4.31 (d, J = 12.5 Hz, 1H), 3.83 (s, 3H), 3.46 (s, 3H). Other overlapped peaks: δ 7.47−7.42 (m), 7.39−7.24 (m), 7.17−7.02 (m), 6.96−6.87 (m), 6.74−5.90 (m), 3.45−3.25 (m), 3.05−2.99 (m), 2.87−2.83 (m), 2.58−2.30 (m), 2.23−1.97 (m), 1.85−1.80 (m) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ *syn*-isomer 180.2, 177.0, 172.3, 148.7, 148.5, 147.5, 122.7, 120.5, 116.1, 111.2, 110.6, 110.5, 74.1, 70.8, 65.3, 63.8, 57.7, 56.2, 55.8, 43.1, 30.9, 29.7, 23.3; *anti*-isomer 180.0, 178.5, 172.3, 148.8, 148.3, 147.5, 122.8, 120.4, 115.2, 110.9, 110.4, 109.2, 75.6, 71.1, 65.5, 63.9, 57.4, 55.9, 55.3, 43.1, 31.1, 24.3, 22.7. Other overlapped peaks: δ 134.2, 134.0, 133.7, 133.6, 132.9, 132.7, 132.3, 131.8, 131.4, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.1, 127.3, 127.2, 126.9, 126.2, 125.9, 125.5, 125.0 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 864.8. HRMS (ESI) m/z calcd for $C_{44}H_{41}BrN_4NiO_5Na^+$ $[M + Na]^+$: 865.1511, found: 865.1505. The de was determined by HPLC with a Chiralpak AD-H column (*n*-hexane/*i*-PrOH = 75/25, λ = 254 nm, 1.0 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 80.42 min, t_R (minor enantiomer) = 39.52 min, 99% de; for the *anti*-isomer: t_R (major enantiomer) = 46.22 min, t_R (minor enantiomer) = 54.76 min, 98% de.

Nickel(II)-(*S*)-BPB/2-Amino-2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid Schiff Base Complex 3q. Red solid (18 mg, yield 25%, *syn*/*anti* < 1:20). Mp 124−126 °C. $[\alpha]^{20}_D$ = +1496 (*c* 0.14 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *anti*-isomer 8.34 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 7.1 Hz, 2H), 7.76 (d, J = 6.4 Hz, 2H), 7.55−7.45 (m, 3H), 7.37 (t, J = 7.6 Hz, 2H), 7.25−6.96 (m, 7H), 6.88−6.82 (m, 4H), 6.63 (t, J = 7.6 Hz, 1H), 6.42 (dd, J = 8.2, 1.4 Hz, 1H), 5.02 (d, J = 7.8 Hz, 1H), 4.56 (d, J = 12.7 Hz, 1H), 4.44−4.20 (m, 1H), 4.16 (d, J = 13.4 Hz, 1H), 4.07 (d, J = 3.9 Hz, 1H), 3.93−3.76 (m, 1H), 3.71 (d, J = 13.3 Hz, 1H), 3.64 (d, J = 4.8 Hz, 1H), 3.61 (d, J = 4.9 Hz, 1H), 3.58 (d, J = 12.6 Hz, 1H), 3.49−3.44 (m, 1H), 3.17−3.09 (m, 1H), 2.86−2.70 (m, 1H), 2.61−2.48 (m, 2H), 2.27−2.12 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.8, 177.4, 170.3, 150.0, 142.8, 138.7, 134.4, 134.0, 133.4, 133.0, 132.0, 131.8, 131.6, 129.3, 129.1, 129.0, 128.8, 128.7, 128.4, 127.6, 127.4, 127.2, 126.6, 126.3, 126.0, 123.5, 120.3, 75.0, 69.8, 62.9, 61.7, 59.1, 57.3, 45.9, 30.8, 23.5, 21.9 ppm. LRMS (ESI) m/z $[M + Na]^+$ found: 740.8. HRMS (ESI) m/z calcd for $C_{43}H_{40}N_4NiO_3Na^+$ $[M + Na]^+$: 741.2352, found: 741.2361. The de was determined by HPLC with a Chiralpak IA column (*n*-hexane/*i*-PrOH = 80/20, λ = 254 nm, 1.0 mL/min). For the *anti*-isomer: t_R (major enantiomer) = 32.57 min, t_R (minor enantiomer) = 19.99 min, 98% de.

Procedure for the Synthesis of (2*S*,2(1′*S*))-4a. The crystallized complex (*S*)(2*S*,2(1′*S*))-**3a** (1 g, 1.42 mmol) and EDTA (0.83 g, 2.82 mmol) were suspended in a mixture of aqueous N_2H_4 (85% in water, 5 mL) and EtOH (25 mL) and stirred at 80 °C for 4 h, until the red color of the solution disappeared. The reaction was cooled to room temperature and then evaporated to dryness. Water (20 mL) was added to the residue to form a clear solution, and the solution was extracted with CH_2Cl_2 (3 times). The aqueous layer was purified to give the desired amino acids, while the organic layer was evaporated to dryness and treated with 6 N HCl for recovering the ligand (*S*)-**BPB** (525 mg, 96%). The aqueous layer was adjusted pH to 7 with aqueous 6 N HCl and then evaporated to dryness. The residue was treated with MeOH (40 mL) and an amount of precipitation was produced. After filtering, the solution was concentrated and separated by column chromatography on C_{18}-reversed phase (230−400 mesh) silica gel. Water/MeOH (1:1) was used to obtain product **4a** (340 mg, yield 85%, *syn*:*anti* 9:1). The organic layer was evaporated to dryness, and MeOH (10 mL) and 6 N HCl (10 mL) were added and then stirred for 2 h at room temperature. After the reaction was complete as indicated by TLC, the solution was extracted with dichloromethane (20 mL × 3). The combined organic layers were dried with anhydrous Na_2SO_4, concentrated, and purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1) to give the ligand (*S*)-**BPB** (525 mg, yield 96%).

(*S*)-2-Amino-2-((*S*)-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid 4a. White solid (340 mg, yield 85%, *syn*/*anti* 9:1). Mp > 300 °C. $[\alpha]^{20}_D$ = +59 (*c* 0.30 g/100 mL, CH_3OH). ^{1}H NMR (400 MHz, D_2O) δ 7.32−7.21 (m, 3H), 7.19−7.16 (m, 3H), 7.06 (d, J = 8.0 Hz, 2H), 6.94 (t, J = 7.4 Hz, 1H), 5.30 (d, J = 5.3 Hz, 1H), 4.34 (d, J = 5.3 Hz, 1H), 3.65−3.55 (m, 1H), 3.34−3.28 (m, 1H), 2.89−2.76 (m, 2H) ppm. ^{13}C NMR (125 MHz, D_2O/MeOD) δ 171.3, 149.3, 137.3, 130.7, 130.3, 129.6, 128.3, 127.9, 122.7, 119.6, 60.1, 57.2, 46.8, 27.2 ppm. LRMS (ESI) m/z $[M + H]^+$ found: 283.0. HRMS (ESI) m/z calcd for $C_{17}H_{19}N_2O_2^+$ $[M + H]^+$: 283.1441, found: 283.1451. The enantiomeric excess was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (H_2O/MeOH = 60/40, λ = 254 nm, 0.5 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 15.32 min, t_R (minor enantiomer) = 18.13 min, 98% ee; for the *anti*-isomer: t_R (major enantiomer) = 12.68 min, t_R (minor enantiomer) = 13.68 min, 80% ee.

(*S*)-2-Amino-2-((*S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl) Acetic Acid 4i. White solid (332 mg, yield 80%, *syn*/

dx.doi.org/10.1021/jo401510b | *J. Org. Chem.* 2013, 78, 11204−11212

anti 3.6:1). Mp > 300 °C. $[\alpha]^{20}_{D}$ = +42 (*c* 0.20 g/100 mL, CH_3OH). ^1H NMR (500 MHz, MeOD): δ 7.43−6.91 (m, 8H), 5.40 (s, 1H), 3.95 (s, 1H), 3.75−3.65 (m 1H), 3.25−3.07 (m, 2H), 2.92−2.80 (m, 1H) ppm. ^{13}C NMR (125 MHz, MeOD): δ 172.6, 159.7 (d, $^1J_{CF}$ = 238 Hz), 147.7, 138.1, 132.5, 130.0, 129.2, 128.8, 127.7, 122.6 (d, $^3J_{CF}$ = 7.4 Hz), 116.9 (d, $^2J_{CF}$ = 22 Hz), 61.4, 59.5, 46.0, 25.6 ppm. LRMS (ESI) *m*/*z* $[M - H]^-$ found: 299.1. HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}FN_2O_2^-$ $[M - H]^-$: 299.1196, found: 299.1202. The enantiomeric excess was determined by HPLC with a Chirobiotic T column (25 cm × 4.6 mm, 5 μm) (H_2O/MeOH = 50/50, λ = 254 nm, 0.5 mL/min). For the *syn*-isomer: t_R (major enantiomer) = 19.59 min, t_R (minor enantiomer) = 21.73 min, 90% ee; for the *anti*-isomer: t_R (major enantiomer) = 16.17 min, t_R (minor enantiomer) = 16.94 min, 73% ee.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experiment details including X-ray crystal, product characterization, and NMR 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.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grants 21021063, 91229204, 81302633, and 81025017), National S&T Major Projects (2012ZX09103101-072 and 2012ZX09301001-005).

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