Asymmetric synthesis of α-(1-oxoisoindolin-3-yl)glycine: Synthetic and mechanistic challenges

Tingting Li,[a,b] Shengbin Zhou,[b] Jiang Wang,[b] José Luis Aceña,[c] Vadim A. Soloshonok,*[c,d] Hong Liu,*[a, b]

[a] *School of Pharmacy, China Pharmaceutical University, Jiangsu, Nanjing 210009, China*

[b] *Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China. E-mail: hliu@simm.ac.cn*

[c] *Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, Paseo Manuel Lardizábal 3, 20018 San Sebastián, Spain*

[d] *IKERBASQUE, Basque Foundation for Science, Alameda Urquijo 36-5, Plaza Bizkaia, 48011 Bilbao, Spain*

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(A) General Methods

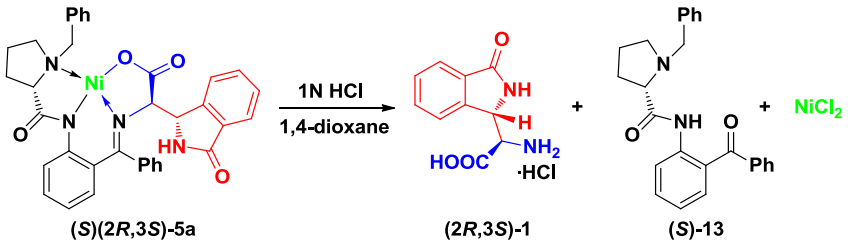
The reagents (chemicals) were purchased from commercial sources, and used without further purification. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). All products were characterized by their NMR and MS spectra. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz, 500 MHz, and 600 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) were measured on Micromass Ultra Q-TOF spectrometer. The determination of dr was performed via LC/MS analysis using Agilent 6120 spectrometer. Optical rotations were measured using a 1 mL cell with a 10 mm path length on an Auto pol V PLVS matic polarimeter and are reported as follows: $[\alpha]^{25}_{D}$ (*c*: g/100 mL, in solvent).

(B) General Procedure for the Asymmetric Reactions

General Procedure for the Synthesis of(*S*)(2*R*, 3*S*)-5a.

(*S*)-**4** (1 g, 2 mmol) was dissolved in anhydrous MeOH (20 mL) at ambient conditions, followed by 2-cyanobenzaldehyde **3a** (289 mg, 2.2 mmol) and sodium methoxide (5.4 M solution in methanol, 446 μL, 2.4 mmol). The solution was stirred at 80 ^{o}C. After 10 h, the reaction was cooled down and quenched by pouring into 50 mL aq. Sat. NH_4Cl. The suspension was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (CH_2Cl_2/acetone = 1/5) to give (*S*)(2*R*, 3*S*)-**5a** as a red solid (852 mg, yield 67.5%).

Disassembly of Ni(II) complex (*S*)(2*R*,3*S*)-5a



Scheme S1. Releasing of amino acid (2*R*,3*S*)-**1** and the recovery of chiral ligand (*S*)-**13**.

Synthesis of (2*R*, 3*S*)-1 HCl. To a stirring solution of (*S*)(2*R*, 3*S*)-**5a** (385 mg, 0.6 mmol) in 1,4-dioxane (10 mL), 1 *N* HCl (20 mL) was added at 70 ^{o}C for 20 min, the solution was evaporated and the solid residue was dissolved in water. Then the precipitation ((*S*)-BPB) was filtered and the filtrate was extracted with CH_2Cl_2 to recover extra (*S*)-BPB. The aqueous phase was concentrated. Water (5 mL) was added to the residue which was purified by reversed-phase preparative chromatography (MeOH/water, 5/95) resulting in optically pure product (2*R*, 3*S*)-**1** HCl as white solid (104 mg, 82.5%).

(C) Analytic Characterization Data of Products

Ni(II)-(*S*)-BPB/ (*R*)-2-amino-2-((*S*)-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5a. Red solid (75 mg, yield 62.4%). Mp 160-162 ℃; $[\alpha]^{25}_{D}$ = -1711 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.7 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 2H), 7.61 (s, 0H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.28 (m, 4H), 7.26 – 7.21 (m, 1H), 7.18 – 7.03 (m, 1H), 7.02 – 6.87 (m, 1H), 6.75 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 4.72 (d, *J* = 7.3 Hz, 1H), 4.18 – 4.08 (m, 2H), 4.04 (ddd, *J* = 11.6, 7.2, 4.1 Hz, 1H), 3.69 (dd, *J* = 9.6, 3.5 Hz, 1H), 3.59 (d, *J* = 13.6 Hz, 1H), 2.62 (ddd, *J* = 11.8, 9.2, 6.4 Hz, 1H), 2.44 – 2.27 (m, 1H), 2.12 (dq, *J* = 10.7, 4.1 Hz, 1H), 1.96 (s, 1H), 1.81 (ddt, *J* = 17.5, 13.1, 8.5 Hz, 1H), 1.76 – 1.67 (m, 1H) ppm. ^{13}C NMR (150MHz, $CDCl_3$) δ 181.9, 176.4, 173.1, 170.2, 143.8, 143.4, 134.5, 133.8, 133.1, 133.1, 132.1, 131.8, 131.3, 129.8, 129.1, 129.1, 129.0, 128.9, 128.5, 126.7, 125.8, 125.1, 124.1, 123.8, 121.0, 72.0, 69.7, 61.2, 58.0, 57.7, 31.1, 23.5 ppm. LRMS (ESI) $[M+H]^+$ found *m/z* 629.2. HRMS (ESI) calcd. for $C_{35}H_{30}N_4NiO_4Na^+$ $[M + Na]^+$ 651.1518, found 651.1509. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 39.347 min, t_R (minor diastereomers) = 33.207 min, 34.111 min respectively. dr = 6/1/0/93.

(*R*)-2-amino-2-((*S*)-1-oxoisoindolin-3-yl)acetic acid 1 HCl. White solid (104 mg, yield 82.5%). Mp 263-265 ℃; $[\alpha]^{25}_{D}$ = +105 (*c* 0.10 g/100 mL, H_2O). ^{1}H NMR (400 MHz, D_2O + CF_3COOH) δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 5.29 (d, *J* = 2.3 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, D_2O + CF_3COOH) δ 172.9, 168.8, 140.8, 133.2, 130.6, 129.7, 123.4, 122.9, 55.6, 53.6 ppm.LRMS (ESI) $[M+H]^+$ found *m/z* 206.9. HRMS (ESI) calcd. for $C_{10}H_{11}N_2O_3^+$ $[M+H]^+$ 207.0770, found 207.0771.

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-fluoro-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5b. Red solid (58.2 mg, yield 44.8%). Mp 174-176 ℃; $[\alpha]^{25}_{D}$ = -1312 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.83 – 7.63 (m, 3H), 7.42 – 7.34 (m, 3H), 7.33 – 7.29 (m, 1H), 7.29 – 7.22 (m, 3H), 7.18 – 7.13 (m, 1H), 7.03 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 6.70 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.68 – 6.61 (m, 1H), 4.65 – 4.56 (m, 1H), 4.11 (d, *J* = 13.6 Hz, 1H), 4.09 – 4.01 (m, 1H), 3.99 – 3.94 (m, 1H), 3.69 (dd, *J* = 9.7, 3.4 Hz, 1H), 3.57 (d, *J* = 13.6 Hz, 1H), 2.66 – 2.54 (m, 1H), 2.42 – 2.26 (m, 1H), 2.18 – 2.08 (m, 1H), 1.98 – 1.82 (m, 1H), 1.82 – 1.68 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 176.1, 173.0, 168.7, 168.7, 162.9 (d, *J* = 249.0 Hz), 142.9, 138.8, 138.8, 134.1, 133.4 (d, *J* = 8.9 Hz), 133.3, 133.1, 132.8, 130.6, 129.6, 129.4, 128.8, 128.7, 128.5, 128.4, 128.1, 126.2, 126.1, 125.4, 123.2, 120.6, 118.9 (d, *J* = 23.5 Hz), 110.2 (d, *J* = 23.4 Hz), 71.5, 69.5, 61.2, 58.0, 57.5, 30.7, 23.0. LRMS (ESI) $[M+H]^+$ found *m/z* 647.1. HRMS (ESI) calcd. for $C_{35}H_{29}FN_4NiO_4Na^+$ $[M + Na]^+$ 669.1424, found 669.1431. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min),t_R (major diastereomer) = 44.188 min, t_R (minor diastereomers) = 35.681 min, 37.454 min respectively. dr =5/1/0/94

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5-fluoro-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5c. Red solid (42 mg, yield 32.3%). Mp 175-177 ℃; $[\alpha]^{25}_{D}$ = -1212 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.52 (m, 1H), 7.76 – 7.71 (m, 2H), 7.66 (dd, *J* = 8.4, 5.0 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.43 – 7.36 (m, 2H), 7.34 – 7.30 (m, 1H), 7.30 – 7.22 (m, 3H), 7.18 – 7.12 (m, 1H), 7.07 – 7.03 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 6.70 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.67 – 6.62 (m, 1H), 6.57 (s, 1H), 4.58 (d, *J* = 6.8 Hz, 1H), 4.24 (d, *J* = 13.6 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.99 (d, *J* = 6.9 Hz, 1H), 3.73 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.61 (d, *J* = 13.5 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.45 – 2.30 (m, 1H), 2.20 – 2.08 (m, 1H), 1.99 – 1.87 (m, 1H), 1.82 – 1.71 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 176.1, 173.2, 168.9, 164.6 (d, *J* = 252.2 Hz) 145.9, 145.8, 143.0, 134.0, 133.3, 133.1, 132.8, 130.9, 130.6, 129.6, 129.3, 128.8, 128.7, 128.5, 128.4, 128.3, 128.3, 127.1, 126.2, 125.5 (d, *J* = 10.0 Hz), 125.3,

123.2, 120.6, 116.3 (d, *J* = 23.6 Hz), 111.8 (d, *J* = 25.3 Hz), 71.1, 69.5, 61.3, 58.0, 57.6, 30.6, 23.0. LRMS (ESI) $[M+H]^+$ found *m/z* 647.0. HRMS (ESI) calcd. for $C_{35}H_{29}N_4NiO_4Na^+$ $[M + Na]^+$ 669.1424, found 669.1433. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 43.179 min, t_R (minor diastereomers) = 35.988 min, 37.491 min respectively, dr = 1/5/0/94.

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-bromo-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5d. Red solid (35.2 mg, yield 24.7%). Mp 189-191 ℃; $[\alpha]^{25}_D$ = -1291 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.84 – 7.82 (m, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.68 (d, *J* = 1.1 Hz, 1H), 7.64 – 7.61 (m, 1H), 7.41 – 7.34 (m, 2H), 7.33 – 7.26 (m, 3H), 7.24 – 7.20 (m, 2H), 7.04 (d, *J* = 6.0 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 6.69 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.67 – 6.62 (m, 1H), 4.56 (dd, *J* = 7.4, 1.4 Hz, 1H), 4.09 – 4.04 (m, 1H), 4.03 – 4.00 (m, 1H), 3.99 (d, *J* = 7.4 Hz, 1H), 3.69 (dd, *J* = 9.7, 3.3 Hz, 1H), 3.55 (d, *J* = 13.6 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.39 – 2.24 (m, 1H), 2.16 – 2.06 (m, 1H), 1.92 – 1.81 (m, 1H), 1.79 – 1.69 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 175.9, 172.9, 168.3, 142.9, 142.0, 134.4, 134.1, 133.3, 133.2, 133.0, 132.8, 130.7, 129.6, 129.4, 128.8, 128.7, 128.5, 128.1, 126.7, 126.2, 125.3, 123.3, 122.9, 120.6, 71.3, 69.5, 61.2, 57.9, 57.5, 30.7, 23.0. LRMS (ESI) $[M+H]^+$ found *m/z* 707.0. HRMS (ESI) calcd. for $C_{35}H_{29}BrN_4NiO_4Na^+$ $[M + Na]^+$ 729.0623, found 729.0613. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 5 min, then sustained 5 min, rise to 70/30 in 5 min, sustained 15 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 39.544 min, t_R (minor diastereomers) = 36.894 min, 37.391 min respectively, dr = 6/1/0/93.

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-methoxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5e. Red solid (92.8 mg, yield 70.1%). Mp 178-180 ℃; $[\alpha]^{25}_D$ = -1651 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.59 – 7.52 (m, 2H), 7.46 – 7.40 (m, 3H), 7.40 – 7.34 (m, 3H), 7.31 – 7.27 (m, 2H), 7.19 (s, 1H), 6.99 (s, 1H), 6.80 (dd, *J* = 8.3, 1.9 Hz, 1H),

6.77 – 6.72 (m, 1H), 6.58 (s, 1H), 4.65 (dd, *J* = 7.2, 1.2 Hz, 1H), 4.16 (d, *J* = 7.3 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.95 (d, *J* = 13.7 Hz, 1H), 3.81 (s, 3H), 3.68 (dd, *J* = 9.5, 3.5 Hz, 1H), 3.56 (d, *J* = 13.6 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.38 – 2.28 (m, 1H), 2.14 – 2.03 (m, 1H), 1.77 – 1.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 175.6, 172.4, 169.6, 160.5, 142.8, 135.1, 133.9, 133.5, 133.3, 132.7, 132.3, 131.0, 129.5, 128.6, 126.0, 125.5, 123.4, 120.6, 119.7, 106.3, 71.7, 69.0, 60.5, 56.9, 55.3, 30.8, 23.1. LRMS (ESI) $[M+H]^+$ found *m/z* 659.1. HRMS (ESI) calcd. for $C_{36}H_{32}N_4NiO_5Na^+$ $[M + Na]^+$ 681.1624, found 681.1611. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 47.383 min, t_R (minor diastereomers) = 37.410 min, 39.032 min respectively. dr = 5/2/0/93.

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-methyl-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5f. Red solid (85.7 mg, yield 66.4%). Mp 166-168 ℃; $[\alpha]^{25}_D$ = -853 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 6.7, 1.7 Hz, 3H), 7.50 – 7.46 (m, 1H), 7.42 – 7.35 (m, 5H), 7.31 – 7.29 (m, 1H), 7.17 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 6.79 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.76 – 6.70 (m, 1H), 4.69 (d, *J* = 7.3 Hz, 1H), 4.14 (d, *J* = 7.3 Hz, 1H), 4.07 (d, *J* = 13.7 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.69 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.59 (d, *J* = 13.6 Hz, 1H), 2.63 – 2.59 (m, 1H), 2.43 (s, 3H), 2.41 – 2.30 (m, 2H), 2.17 – 2.07 (m, 1H), 1.86 – 1.77 (m, 1H), 1.76 – 1.67 (m, 1H). ^{13}C NMR (10 MHz, $CDCl_3$) δ 181.5, 175.8, 172.5, 169.7, 142.9, 140.3, 138.9, 134.0, 133.4, 132.8, 132.5, 132.4, 130.9, 129.4, 128.7, 128.7, 128.5, 126.3, 125.3, 124.6, 124.0, 123.3, 120.6, 71.7, 69.1, 60.7, 57.2, 57.1, 30.7, 23.1, 21.0. LRMS (ESI) $[M+H]^+$ found *m/z* 643.0. HRMS (ESI) calcd. for $C_{36}H_{32}N_4NiO_4Na^+$ $[M + Na]^+$ 665.1675, found 665.1676. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 48.372 min, t_R (minor diastereomers) = 38.175 min, 39.063 min respectively. dr = 6/2/0/92.

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5-methoxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5g. Red solid (79.6 mg, yield 60.1%). Mp 169-172 ℃; $[\alpha]^{25}_{D}$ = -1047 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.41 – 7.33 (m, 3H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.14 (s, 1H), 7.01 – 6.96 (m, 1H), 6.92 (s, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.34 (d, *J* = 13.6 Hz, 1H), 4.11 (d, *J* = 6.9 Hz, 1H), 4.05 – 3.98 (m, 1H), 3.80 (s, 3H), 3.75 – 3.65 (m, 2H), 2.64 – 2.55 (m, 1H), 2.50 – 2.39 (m, 1H), 2.23 – 2.13 (m, 1H), 1.96 – 1.84 (m, 1H), 1.82 – 1.72 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.1, 176.7, 173.3, 170.2, 163.0, 146.1, 143.4, 134.5, 133.8, 133.2, 133.1, 131.3, 129.8, 129.2, 128.9, 128.8, 128.7, 126.7, 125.6, 125.3, 124.2, 123.7, 121.0, 116.1, 109.3, 72.0, 69.6, 62.0, 61.4, 58.0, 57.7, 55.7, 31.0, 23.5. LRMS (ESI) $[M+H]^+$ found *m/z* 659.0. HRMS (ESI) calcd. for $C_{36}H_{32}N_4NiO_5Na^+$ $[M + Na]^+$ 681.1624, found 681.1623. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 41.788 min, t_R (minor diastereomers) = 34.712 min, 35.663 min respectively. dr = 6/1/0/93.

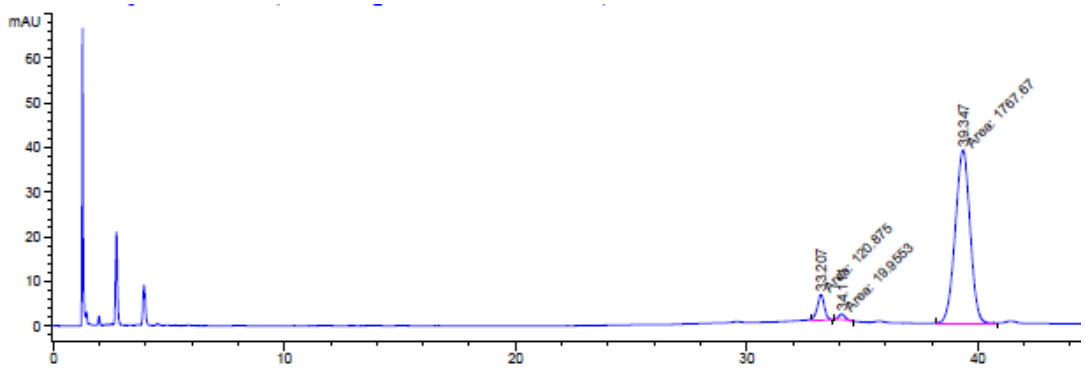
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5,6-dimethoxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5h. Red solid (98.0 mg, yield 70.8%), Mp 182-184 ℃; $[\alpha]^{25}_{D}$ = -936 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.7 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.40 – 7.31 (m, 3H), 7.26 (t, *J* = 1.9 Hz, 1H), 7.23 (s, 1H), 7.18 (s, 1H), 7.15 – 7.07 (m, 1H), 7.03 (s, 1H), 6.95 – 6.87 (m, 1H), 6.75 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.73 – 6.68 (m, 1H), 4.71 (d, *J* = 7.4 Hz, 1H), 4.23 (d, *J* = 13.7 Hz, 1H), 4.11 – 4.05 (m, 1H), 4.04 (d, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.71 (dd, *J* = 9.7, 3.5 Hz, 1H), 3.65 (d, *J* = 13.7 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.46 – 2.35 (m, 1H), 2.21 – 2.12 (m, 2H), 1.96 – 1.86 (m, 1H), 1.84 – 1.75 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 177.0, 173.1, 170.7, 152.7, 150.3, 143.4, 137.5, 134.5, 133.9, 133.3, 133.1, 131.2, 129.7, 129.2, 129.1, 125.7, 124.0, 123.6, 121.0, 106.9, 105.2, 72.5, 69.7, 61.5, 58.2, 58.0, 56.3, 56.3, 31.0, 23.4. LRMS (ESI) $[M+H]^+$

found *m/z* 688.9. HRMS (ESI) calcd. for $C_{37}H_{34}N_4NiO_6Na^+$ $[M + Na]^+$ 711.1730, found 711.1719. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 55/45 in 10 min, then 55/45 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 42.182 min, t_R (minor diastereomers) = 33.417 min, 35.411 min respectively. dr = 6/2/0/92.

Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5,6-methylenedioxy-1-oxoisoindolin-3-yl)aceti c acid Schiff Base Complex 5i. Red solid (93.2 mg, yield 69.0%), Mp 141-143 ℃; $[\alpha]^{25}_D$ = -977 (*c* 0.05 g/100 mL, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.59 – 7.54 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.40 (s, 1H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.28 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.12 (s, 1H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.76 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.72 – 6.68 (m, 1H), 6.00 (d, *J* = 1.3 Hz, 1H), 5.95 (d, *J* = 1.3 Hz, 1H), 4.58 (dd, *J* = 7.1, 1.4 Hz, 1H), 4.39 (d, *J* = 13.6 Hz, 1H), 4.10 – 4.03 (m, 1H), 4.00 (d, *J* = 7.0 Hz, 1H), 3.76 (dd, *J* = 9.9, 3.7 Hz, 1H), 3.72 (d, *J* = 13.7 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.49 – 2.38 (m, 1H), 2.26 – 2.14 (m, 1H), 2.04 – 1.92 (m, 1H), 1.84 – 1.77 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 176.8, 173.4, 170.0, 151.5, 148.8, 143.4, 139.4, 134.5, 133.9, 133.5, 133.2, 131.1, 130.1, 129.7, 129.2, 129.1, 128.9, 128.5, 126.6, 125.7, 125.7, 123.7, 121.0, 105.1, 103.4, 102.1, 72.1, 69.9, 61.8, 58.2, 58.2, 31.0, 23.4. LRMS (ESI) $[M+H]^+$ found *m/z* 673.0. HRMS (ESI) calcd. for $C_{36}H_{30}N_4NiO_6Na^+$ $[M + Na]^+$ 695.1417, found 695.1404. The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 38.591 min, t_R (minor diastereomers) = 33.349 min, 34.020 min respectively. dr = 5/1/0/94.

(D) HPLC Spectra for dr Determination

5a

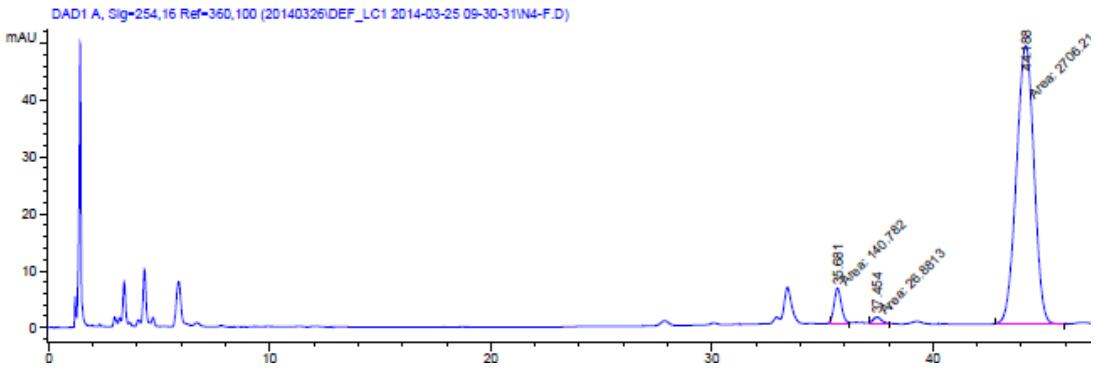


Signal 1: DAD1 A, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.207	MM	0.3536	120.87501	5.69732	6.3335
2	34.111	MM	0.2883	19.95530	1.15382	1.0456
3	39.347	MM	0.7572	1767.67053	38.90554	92.6209
Totals :				1908.50084	45.75668	

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 39.347 min, t_R (minor diastereomers) = 33.207 min, 34.111 min respectively. dr = 6/1/0/93.

5b

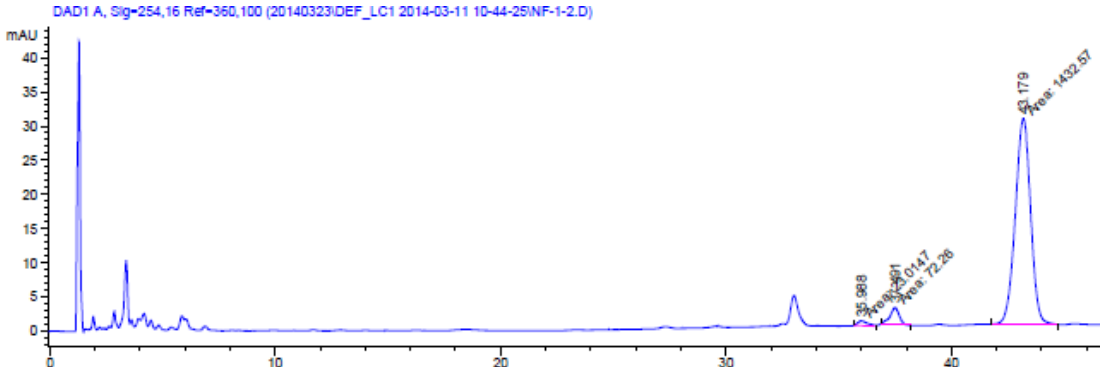


Signal 1: DAD1 A, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.681	MM	0.3835	140.78165	6.11814	4.8987
2	37.454	MM	0.4251	26.88131	1.05392	0.9354
3	44.188	MM	0.9219	2706.20898	48.92316	94.1660
Totals :				2873.87194	56.09521	

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min), t_R (major diastereomer) = 44.188 min, t_R (minor diastereomers) = 35.681 min, 37.454 min respectively. dr = 5/1/0/94.

5c

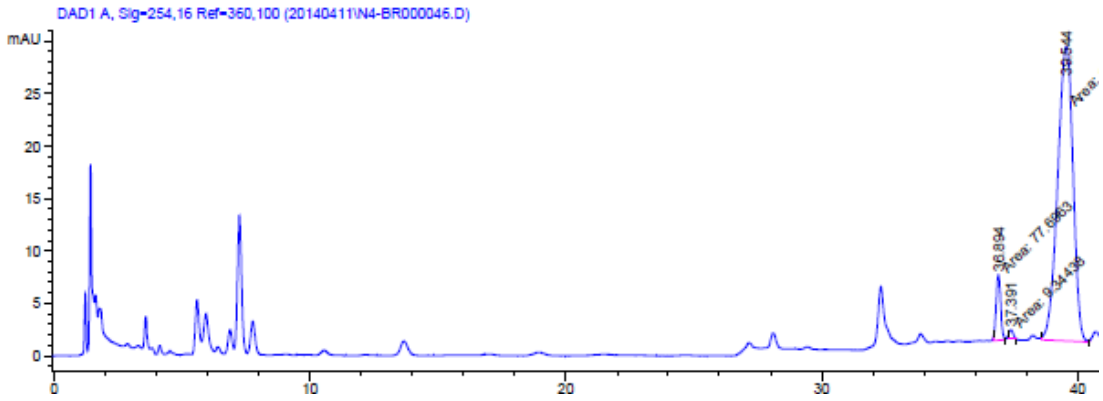


Signal 1: DAD1 A, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	35.988	MM	0.5421	23.01471	7.07614e-1	1.5063
2	37.491	MM	0.4803	72.25996	2.50764	4.7295
3	43.179	MM	0.7918	1432.57397	30.15405	93.7641
Totals :				1527.84865	33.36931	

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 43.179 min, t_R (minor diastereomers) = 35.988 min, 37.491 min respectively, dr = 1/5/0/94.

5d

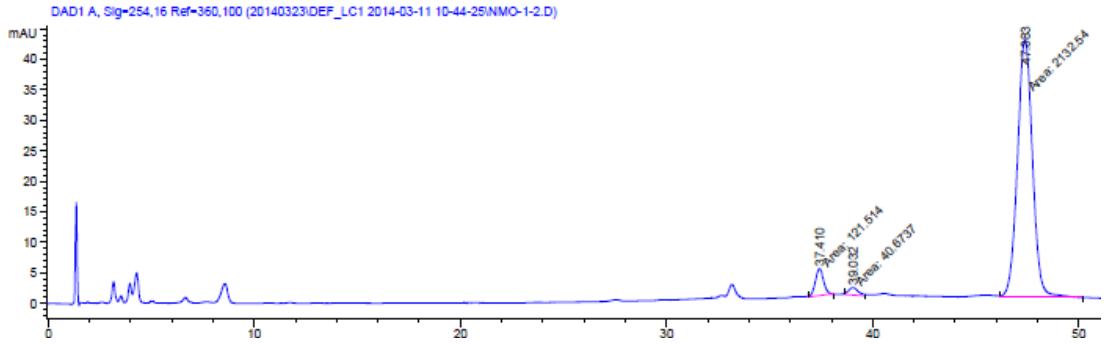


Signal 1: DAD1 A, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.894	MM	0.2059	77.69627	6.28854	6.1546
2	37.391	MM	0.1772	9.34438	8.78807e-1	0.7402
3	39.544	MM	0.6969	1175.37109	28.10924	93.1052
Totals :				1262.41175	35.27659	

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 5 min, then sustained 5 min, rise to 70/30 in 5 min, sustained 15 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 39.544 min, t_R (minor diastereomers) = 36.894 min, 37.391 min respectively, dr = 6/1/0/93.

5e

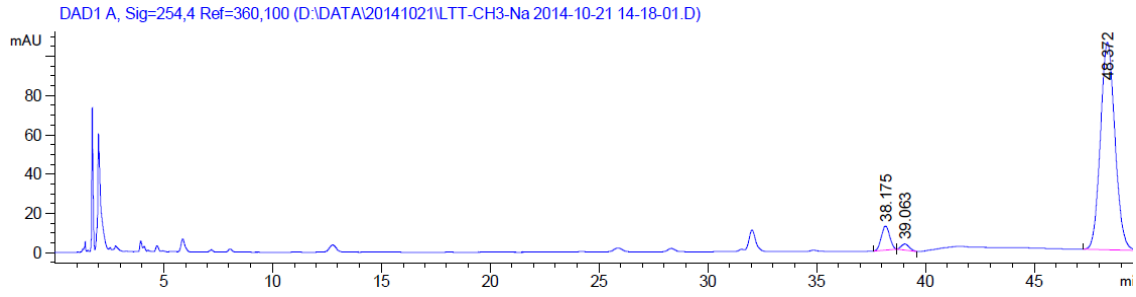


Signal 1: DAD1 A, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	37.410	MM	0.4629	121.51405	4.37469	5.2954
2	39.032	MM	0.5559	40.67367	1.21952	1.7725
3	47.383	MM	0.8421	2132.54028	42.20675	92.9322
Totals :				2294.72800	47.80096	

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 47.383 min, t_R (minor diastereomers) = 37.410 min, 39.032 min respectively. dr = 5/2/0/93.

5f

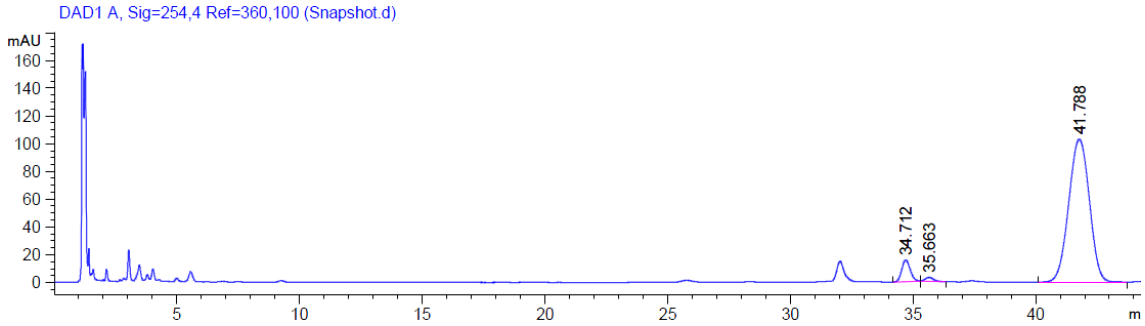


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	38.175	BB	0.4166	325.44675	12.26336	6.1274
2	39.063	BB	0.3783	77.54952	3.07426	1.4601
3	48.372	BBA	0.7183	4908.31885	105.78688	92.4125

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 48.372 min, t_R (minor diastereomers) = 38.175 min, 39.063 min respectively. dr = 6/2/0/92.

5g

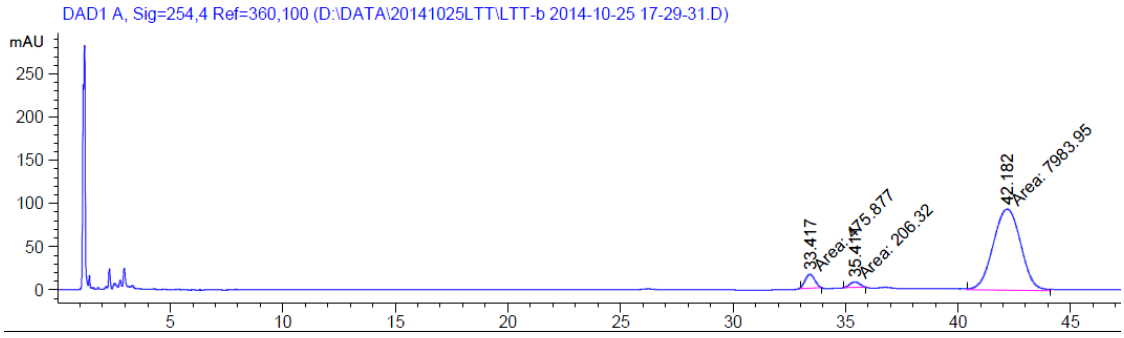


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.712	BB	0.3688	368.90973	15.54642	5.7278
2	35.663	BB	0.3434	63.72580	2.78037	0.9894
3	41.788	BB	0.9283	6008.06104	102.87830	93.2828

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 41.788 min, t_R (minor diastereomers) = 34.712 min, 35.663 min respectively. dr = 6/1/0/93.

5h

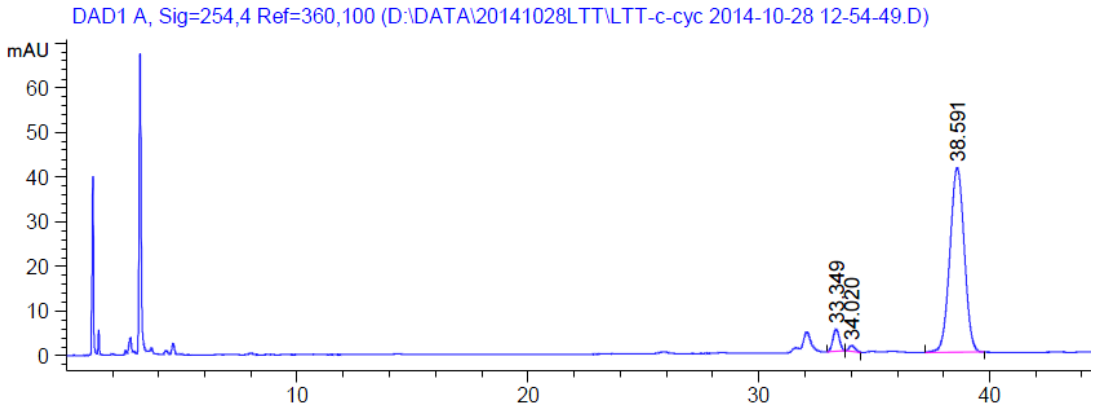


Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.417	MM	0.4941	475.87723	16.05355	5.4912
2	35.411	MM	0.5205	206.31976	6.60707	2.3808
3	42.182	MM	1.4215	7983.95020	93.61044	92.1280

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 55/45 in 10 min, then 55/45 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 42.182 min, t_R (minor diastereomers) = 33.417 min, 35.411 min respectively. dr = 6/2/0/92.

5i



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.349	BB	0.3032	97.26297	4.95040	5.0726
2	34.020	BB	0.2401	24.08734	1.28232	1.2562
3	38.591	BB	0.6684	1796.07373	41.37985	93.6712

The dr was determined by LC/MS with an Eclipse XDB-C18 column (5 μm, 4.6 × 150 mm) (MeOH/H_2O: 50/50 for 20 min, rise to 60/40 in 10 min, then 60/40 sustained 20 min, λ = 254 nm, 1.0 mL/min). t_R (major diastereomer) = 38.591 min, t_R (minor diastereomers) = 33.349 min, 34.020 min respectively. dr = 5/1/0/94.

(E) The Absolute Configuration of 5a

X-ray Single Crystal Structure Analysis of (*S*)(2*R*, 3*S*)-**5a**

X-ray crystallographic data of (*S*)(2*R*, 3*S*)-**5a** were solutions at T = 293(2) K: $C_{37}H_{38}N_4NiO_6$, Mr = 693.42, monoclinic. Space group *P2* (1), a = 8.2226(5) Å, b = 39.325(2) Å, c = 10.4346(7) Å, α = 90 °, β = 91.4940(10)°, γ = 90 °, *V* = 3373.0(4) $Å^3$, *Z* = 4.

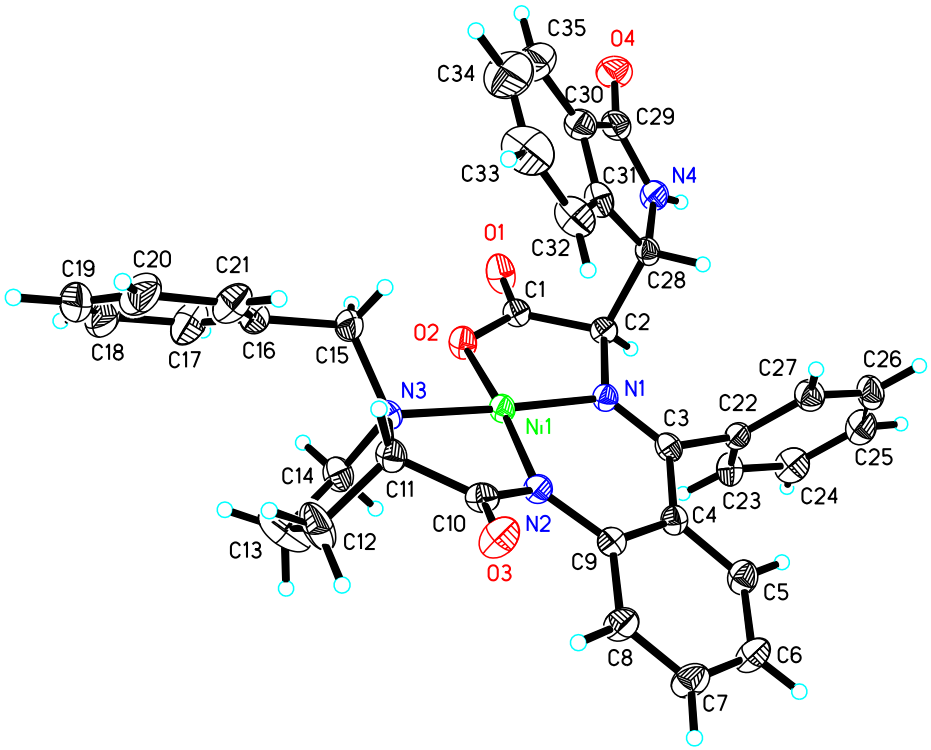


Figure S1. The crystal structure of (*S*)(2*R*, 3*S*)-**5a** by X-ray analysis. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif, the CCDC number is 1015197.

X-ray Single Crystal Structure Analysis of (*S*)(2*S*, 3*S*)-**5a**

X-ray crystallographic data of (*S*)(2*S*, 3*S*)-**5a** were solutions at T = 293(2) K: $C_{36}H_{34}N_4NiO_5$, Mr = 661.38, monoclinic. Space group *P2* (1), a = 11.0249(8) Å, b = 18.0900(14) Å, c = 15.8569(11) Å, α = 90 °, β = 91.288(2)°, γ = 90°, *V* = 3161.7(4) $Å^3$, *Z* = 4.

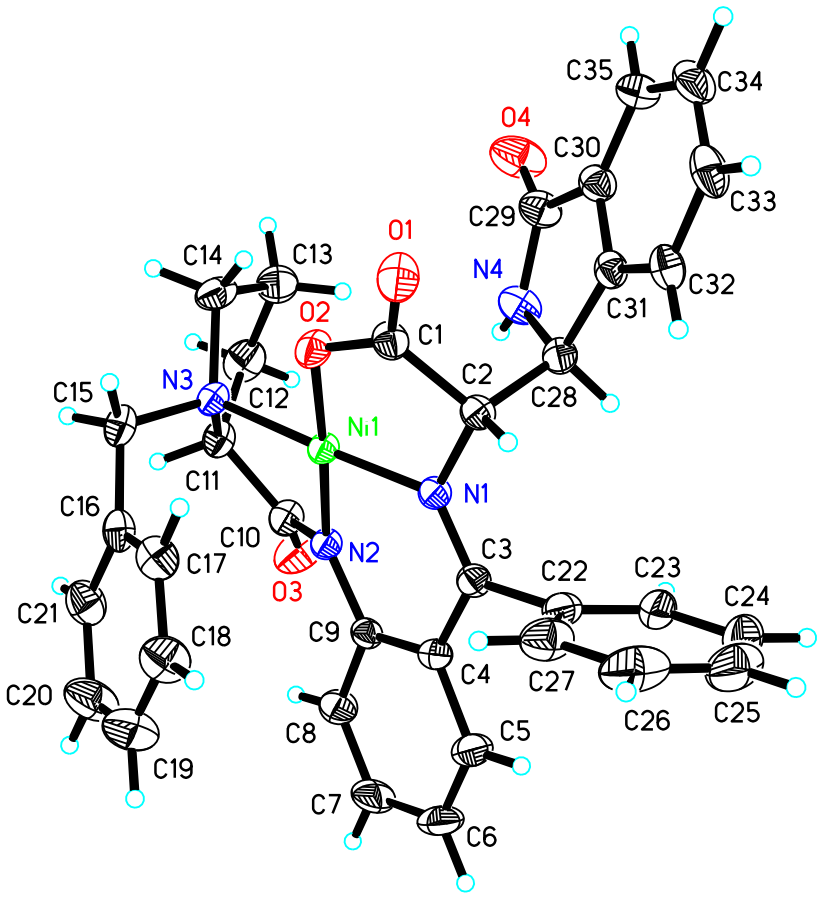


Figure S2. The crystal structure of (*S*)(2*S*, 3*S*)-**5a** by X-ray analysis. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif, the CCDC number is 1031123.

(F) Transformation of (*S*)(2*S*,3*S*)-5a to (*S*)(2*R*,3*S*)-5a

(*S*)(2*S*,3*S*)-**5a** (100 mg, 0.16 mmol) was dissolved in anhydrous MeOH (2 mL) at ambient conditions, followed by sodium methoxide (5.4 M solution in methanol, 35.3 μL, 0.19 mmol). Then the solution was stirred at 80 ^{o}C. The reaction was monitored over time and the equilibrium of these two diastereomers was reached after 2 h and the dr is 5/95 (Figure S3).

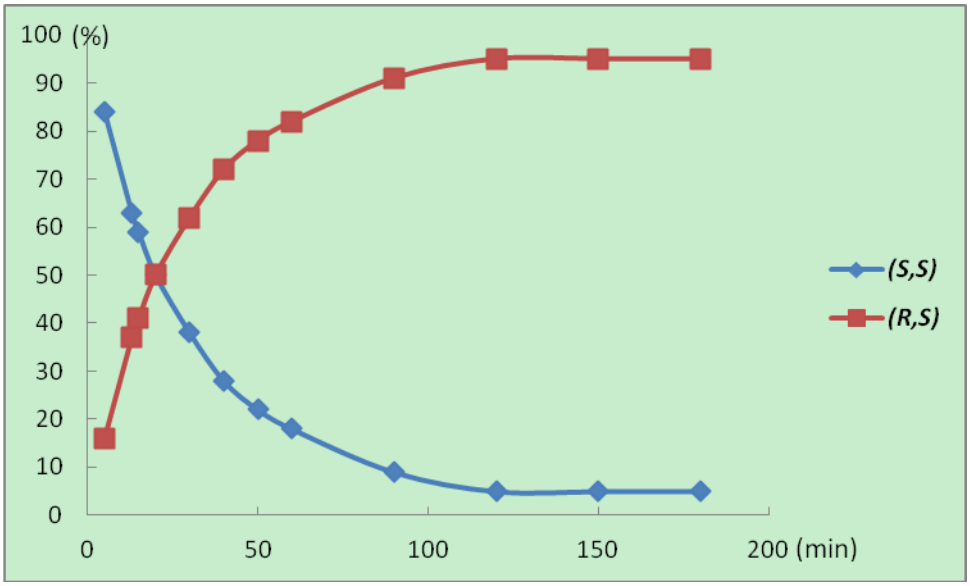
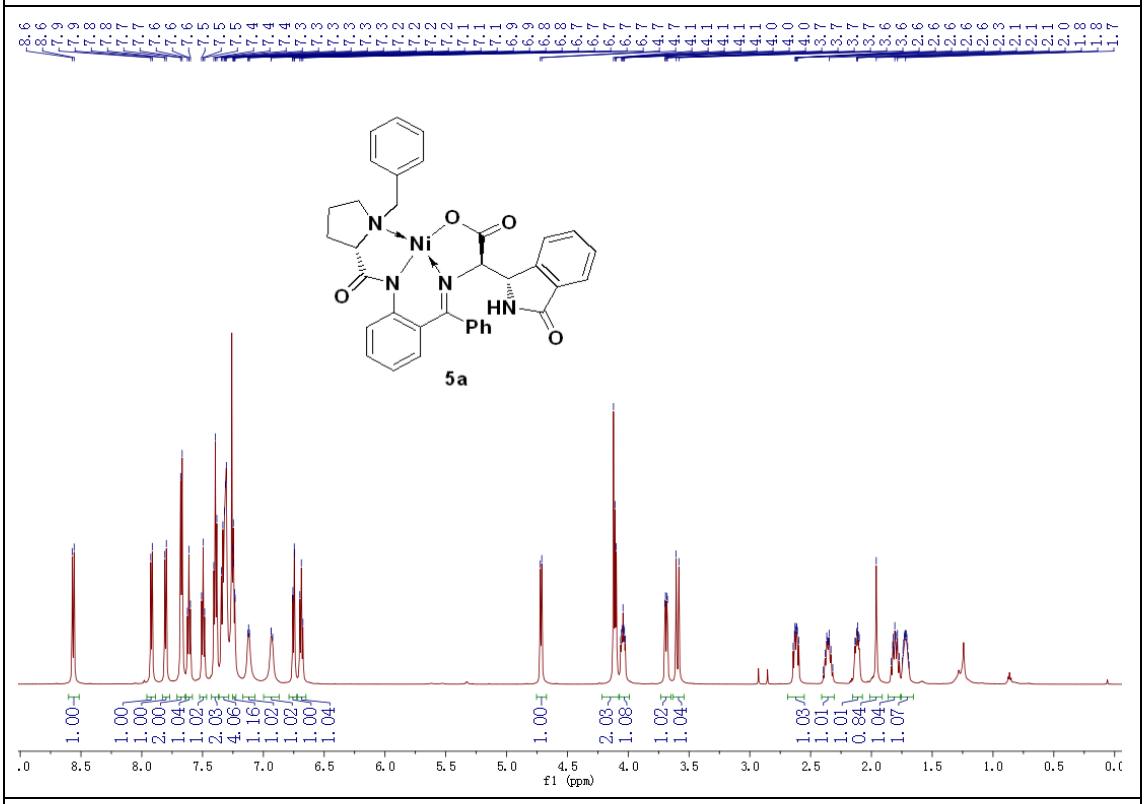
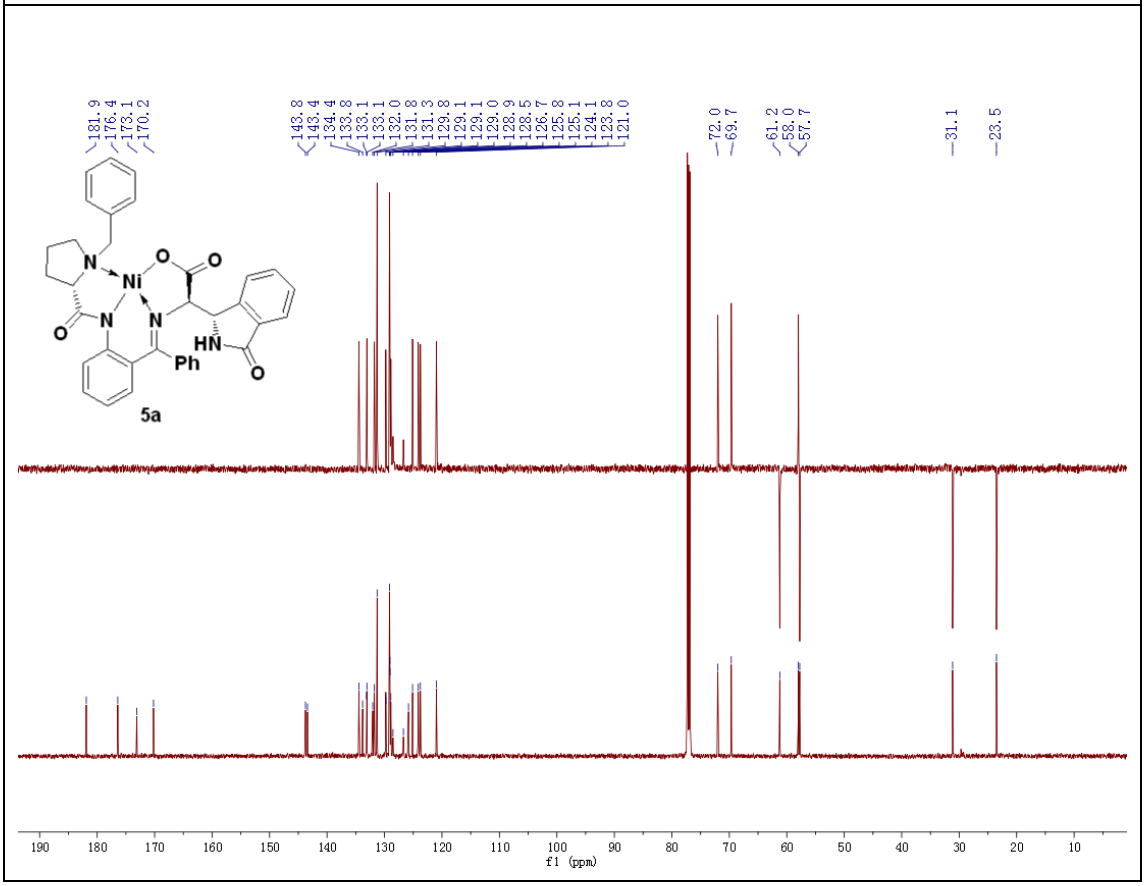


Figure S3. (*S*)(2*S*,3*S*)-**5a** to (*S*)(2*R*,3*S*)-**5a** transformation of Ni(II) complex of glycine Schiff base.

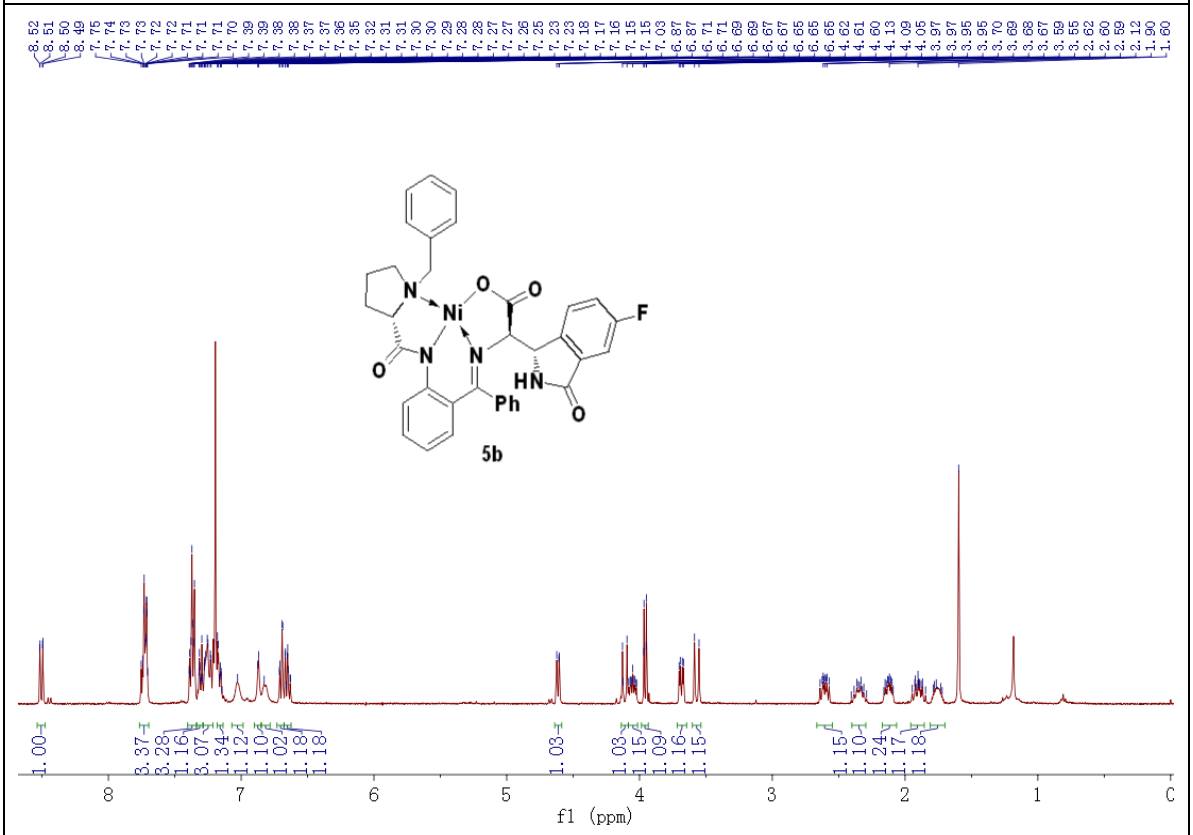
(G) Copies of ^{1}H NMR and ^{13}C NMR Spectra for the Products

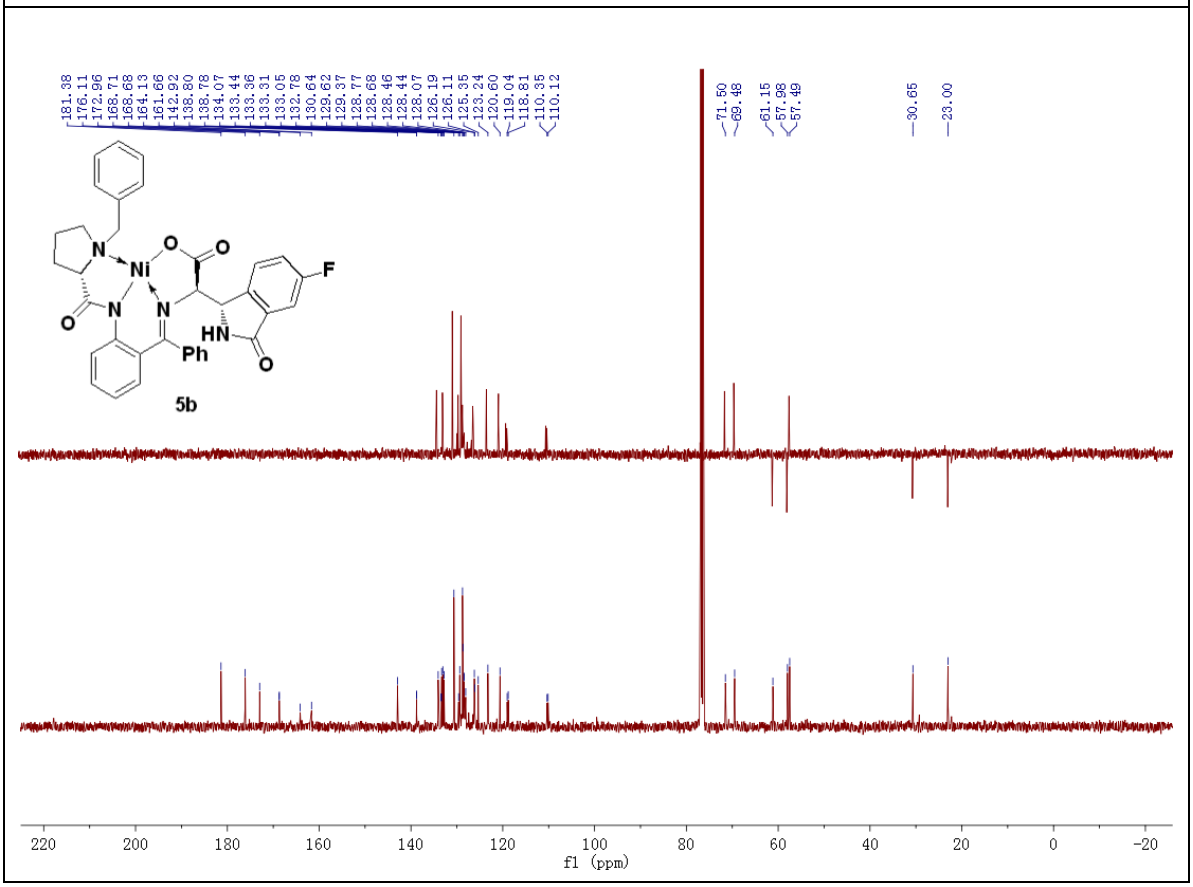
Ni(II)-(*S*)-BPB/ (*R*)-2-amino-2-((*S*)-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5a.



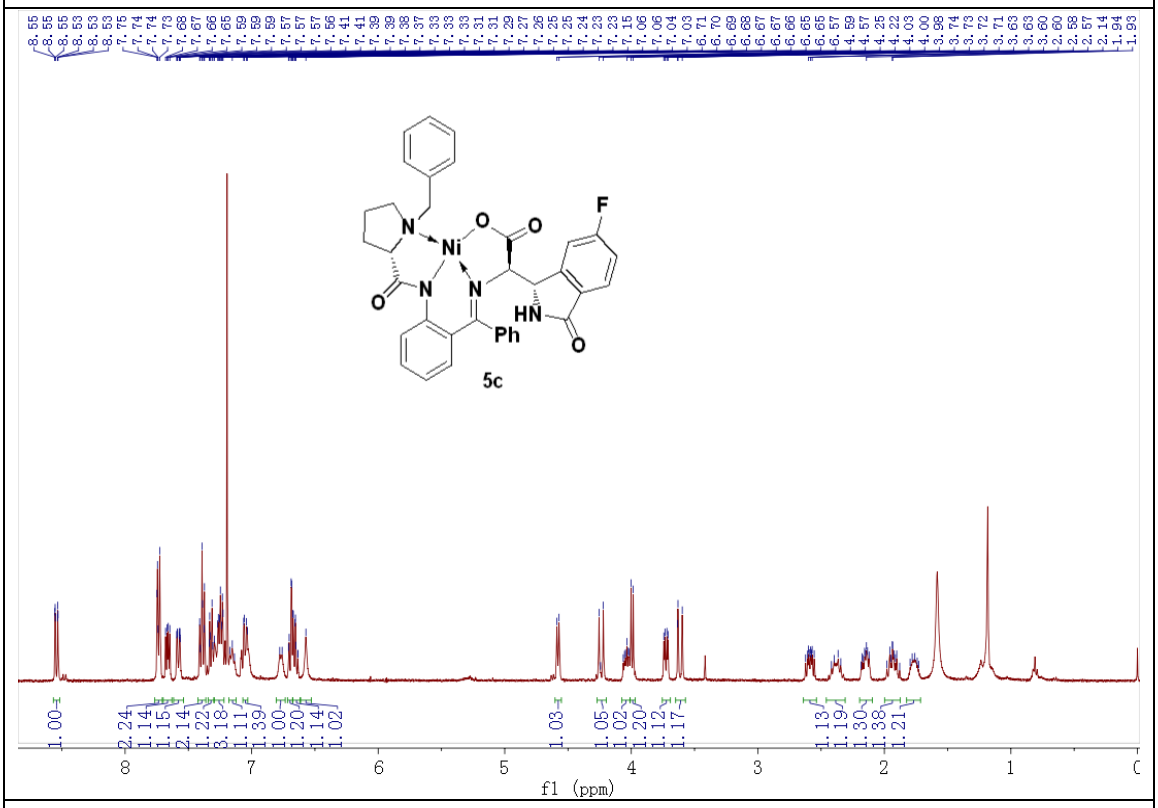


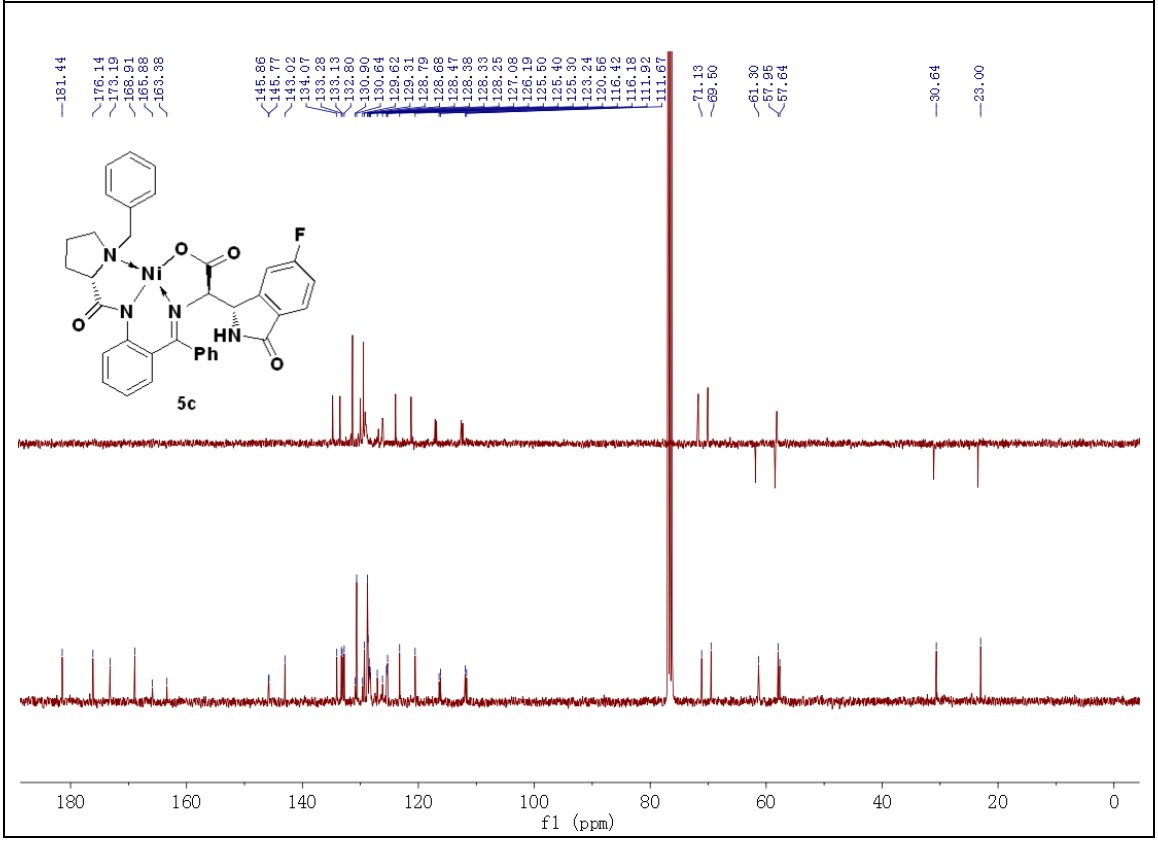
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-fluoro-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5b.



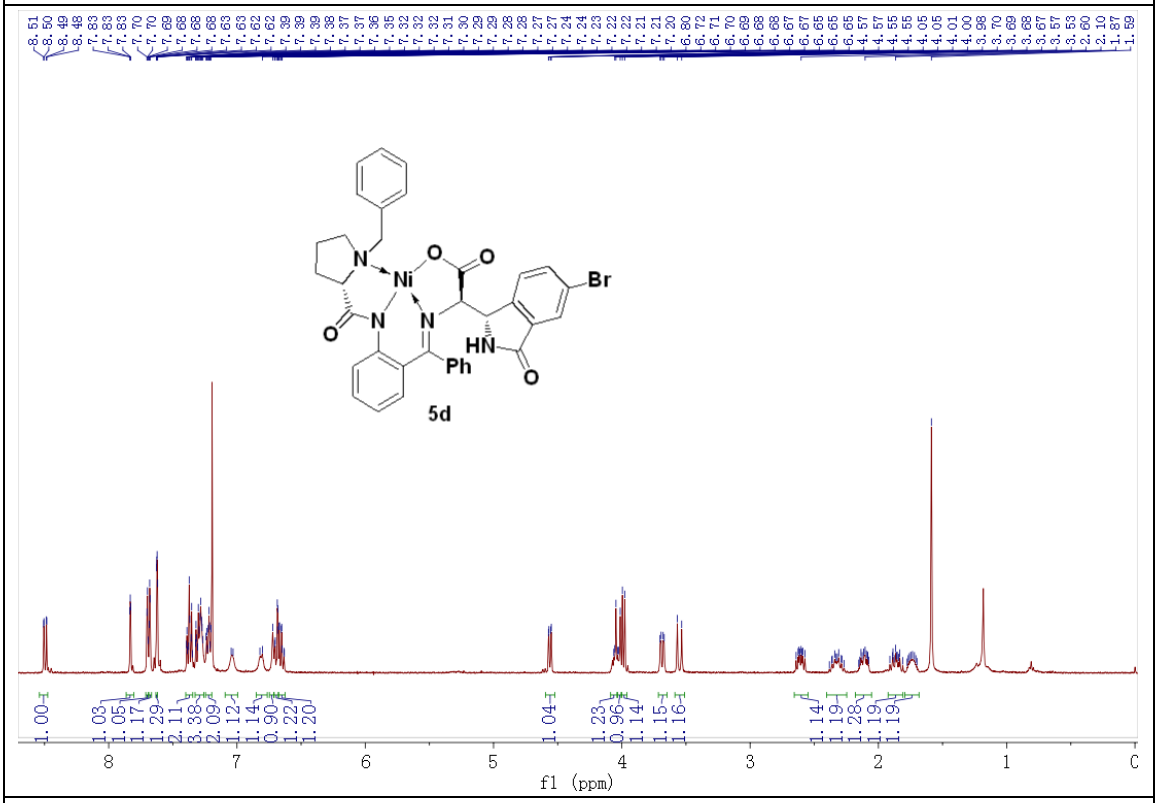


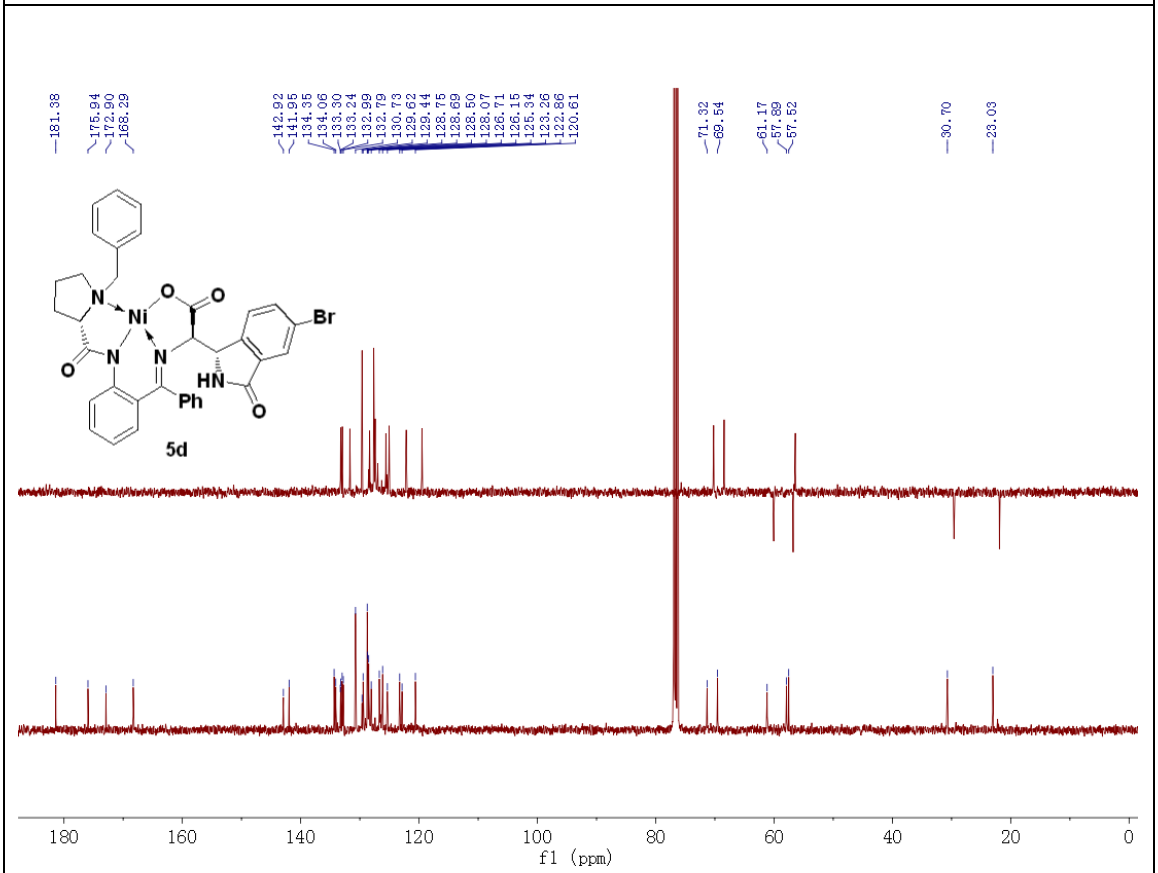
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5-fluoro-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5c.



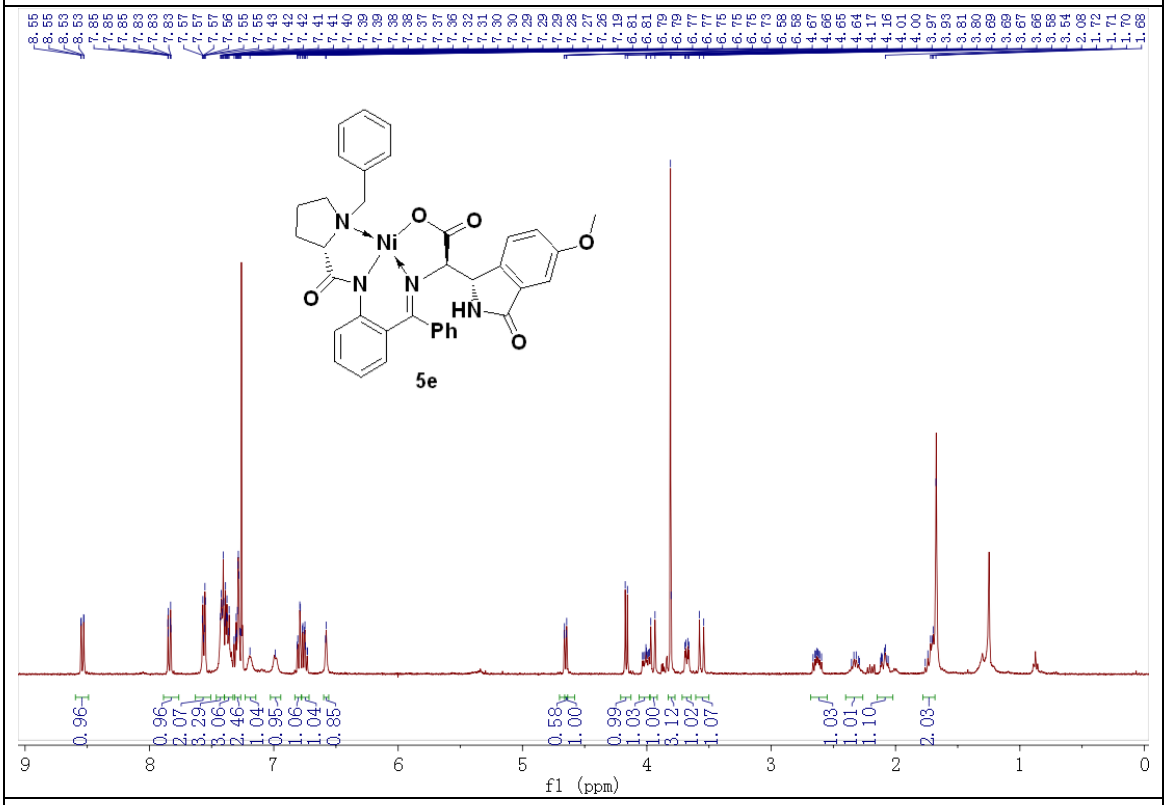


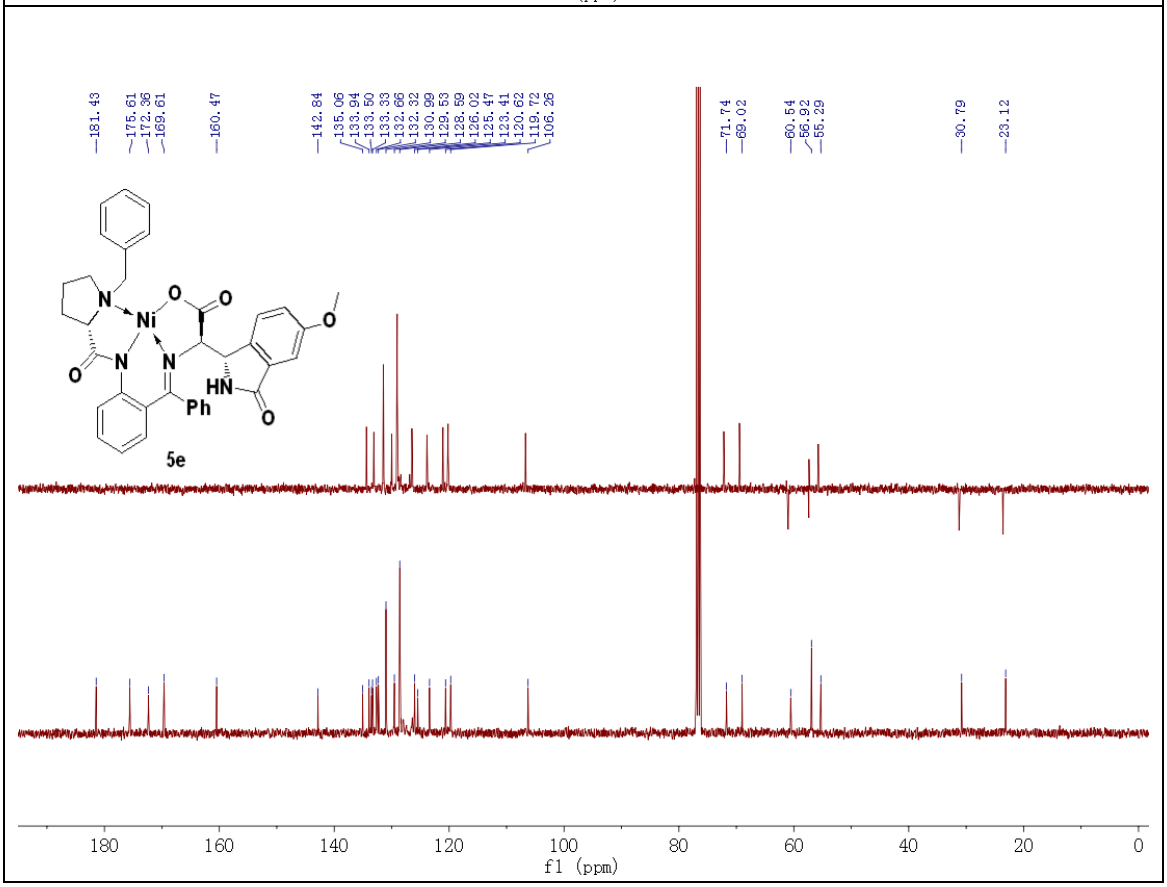
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-bromo-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5d.



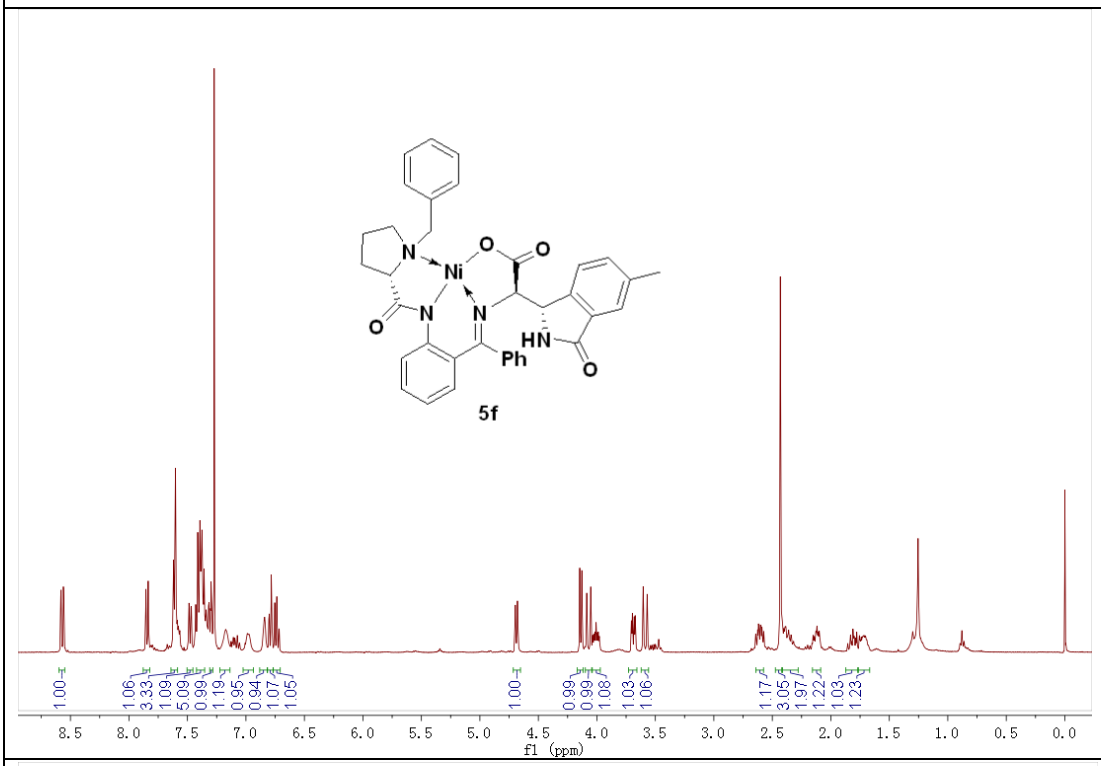


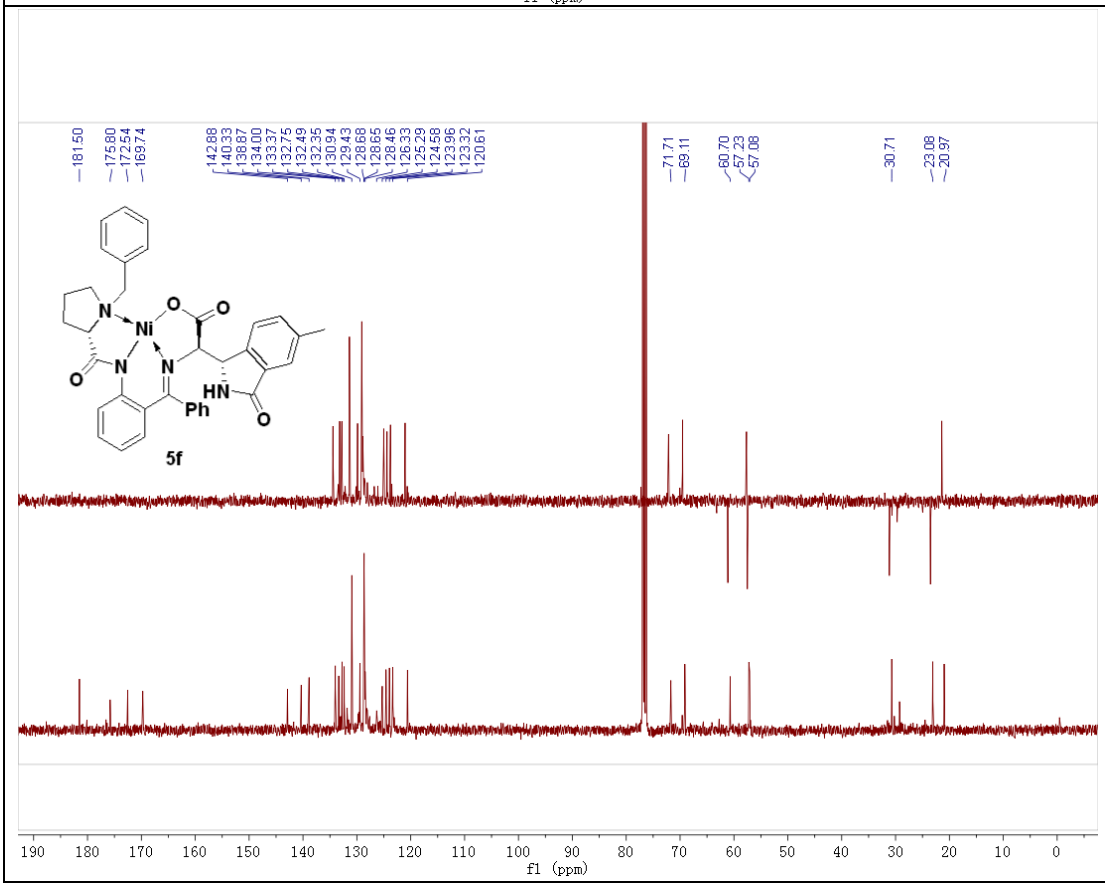
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-methoxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5e.



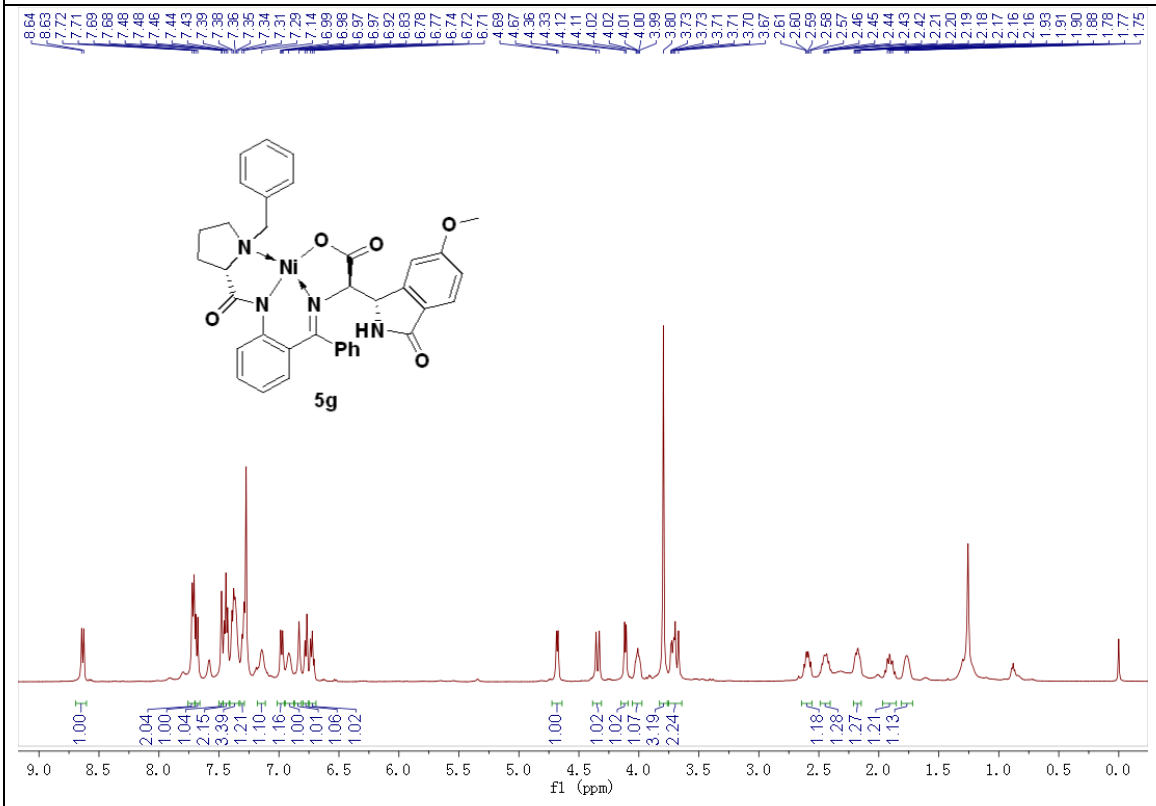


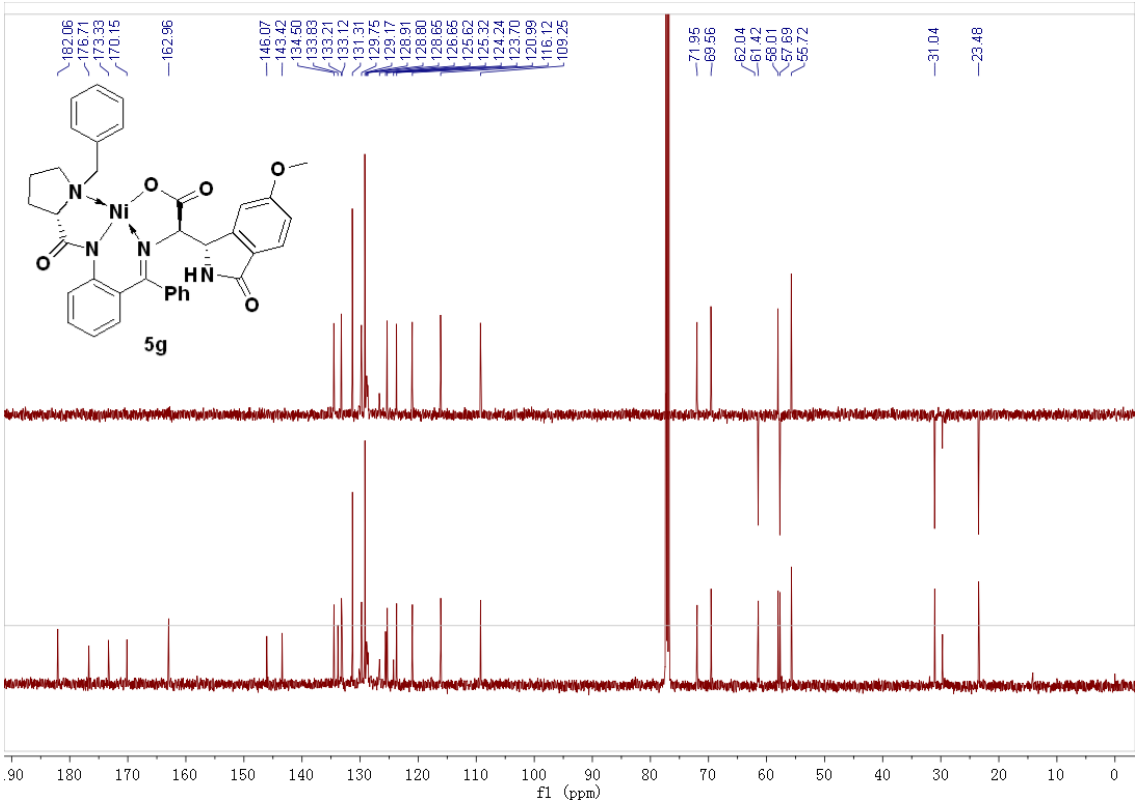
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-6-methyl-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5f.



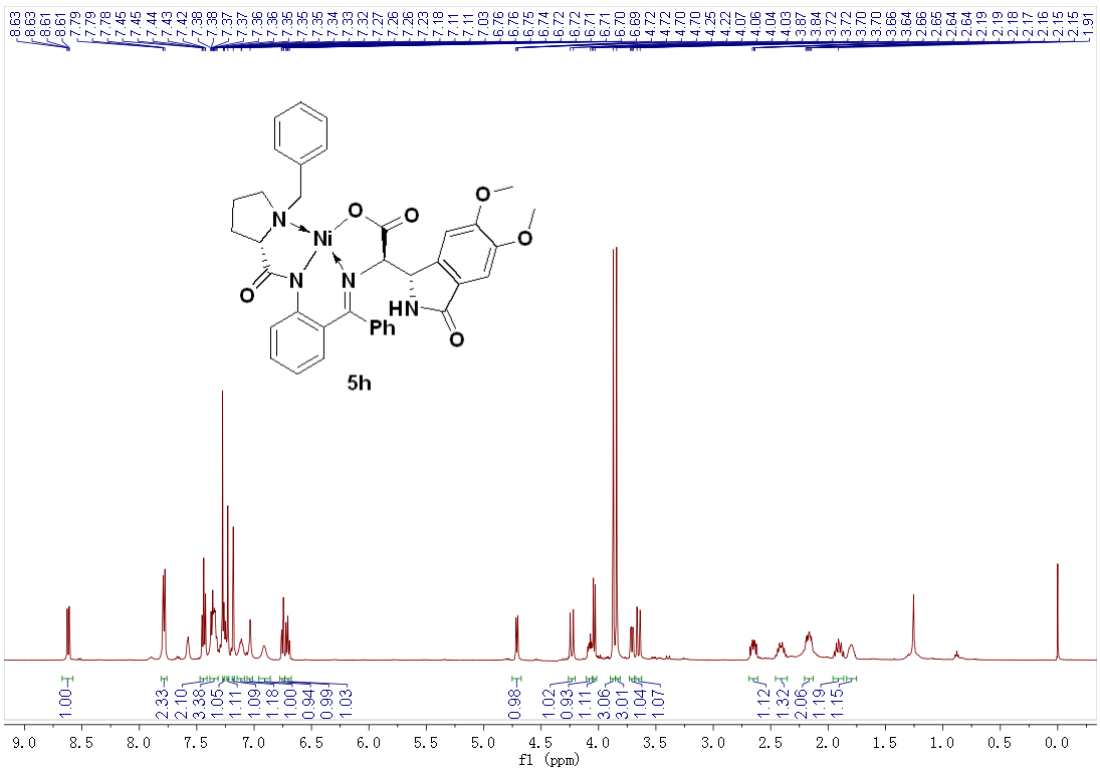


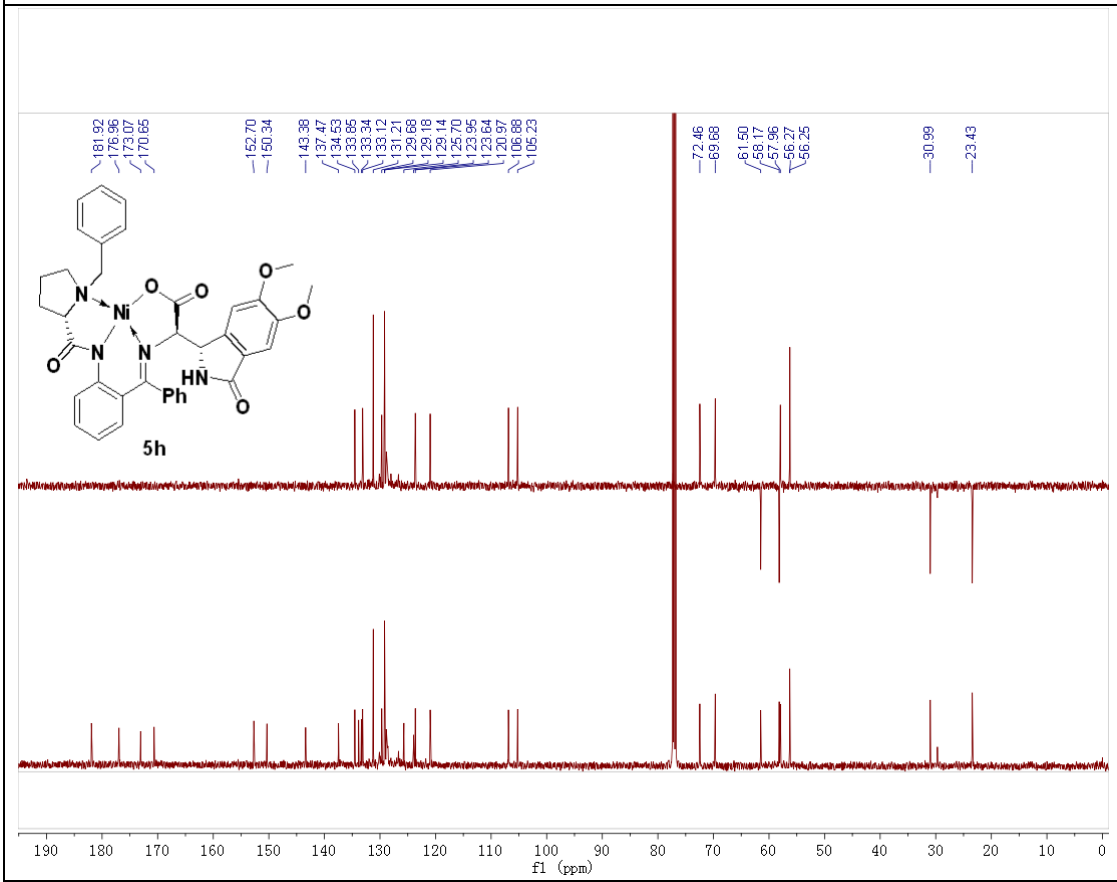
Ni(II)-(S)-BPB/(R)-2-amino-2-((S)-5-methoxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5g.



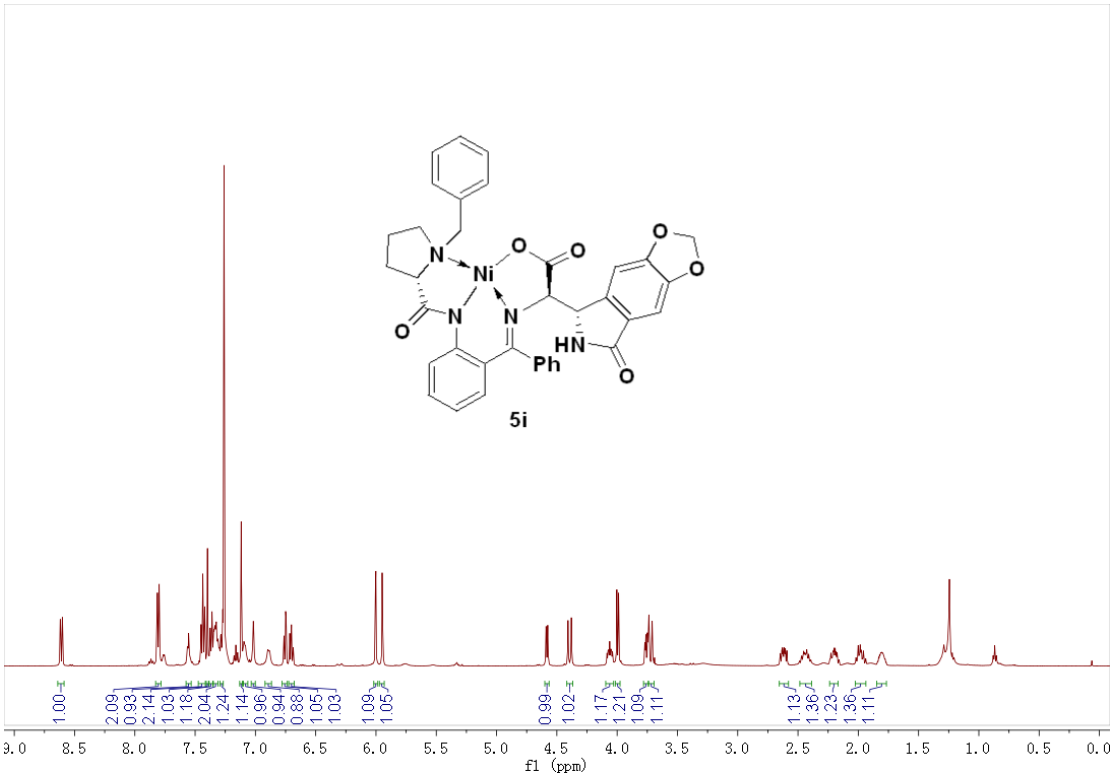


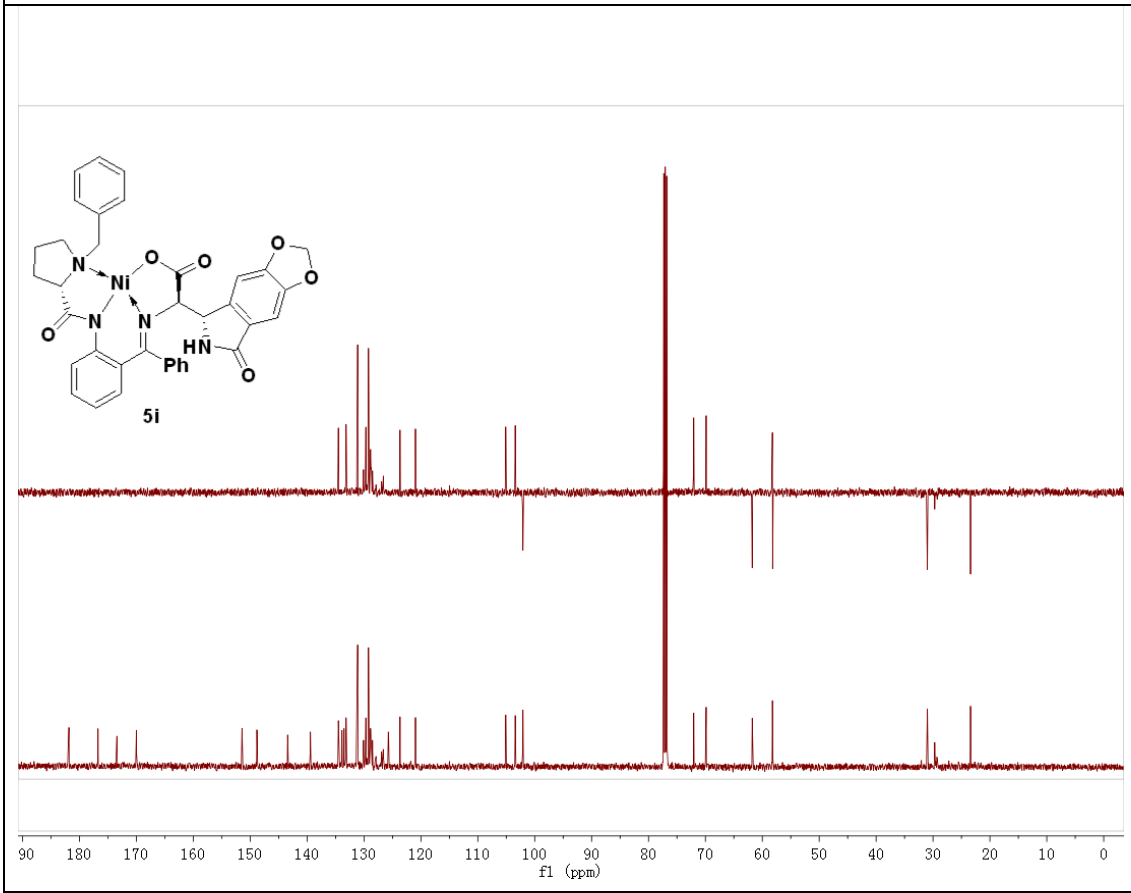
Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5,6-dimethoxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5h.





Ni(II)-(*S*)-BPB/(*R*)-2-amino-2-((*S*)-5,6-methylenedioxy-1-oxoisoindolin-3-yl)acetic acid Schiff Base Complex 5i.





(*R*)-2-amino-2-((*S*)-1-oxoisoindolin-3-yl)acetic acid 1 HCl.