Supporting Information

Enantioselective Addition of Vinylzinc Reagents to 3,4-Dihydroisoquinoline *N*-Oxide

Sa Wang and Christopher T. Seto*

Department of Chemistry, Brown University, 324 Brook Street Box H

Providence, Rhode Island 02912

Christopher_Seto@brown.edu

Table of Contents

Materials and Methods. Solvents were of reagent grade and were used as received except for CH_2Cl_2, which was purified by passage through a column of activated alumina. 1,2,3,4-Tetrahydroisoquinoline was distilled over calcium hydride under reduced pressure and phenyl acetylene was distilled prior to use. All other reagents were used as received. Vinylzinc reactions were conducted using oven-dried or flame-dried glassware and standard syringe techniques under a nitrogen atmosphere. Reactions were monitored using TLC. TLC plates were visualized using either a CAM (ceric ammonium molybdate) or ninhydrin staining solution, or UV at 254 nm. Racemic standards for allylic hydroxylamines were synthesized and analyzed by HPLC to confirm the peak assignments of the two enantiomers.

NMR spectra were recorded at either 300 MHz or 400 MHz using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm and were referenced to residual protonated solvent (^{1}H-NMR: δ 7.26 ppm for $CHCl_3$; ^{13}C-NMR: δ 77.16 ppm for $CDCl_3$). Data are represented as follows: chemical shift (multiplicity [br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet], integration, coupling constants in Hz). High-resolution mass spectra were obtained using electrospray, electron impact, or fast atom bombardment ionization methods. Enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column (0.46 cm i.d. × 25 cm) with UV detection at 219 and 254 nm. 2-Propanol and hexanes were used as solvents, and the flow rate was set at 1.0 mL/min. Optical rotations were obtained with a digital polarimeter at ambient temperature and at a wavelength of 589 nm (c = g/100 mL).

General Procedures for the Synthesis of the Ligands.[1a,b]

Step 1) The Boc-protected amino acid (1 equiv) was suspended or dissolved in dry

DMF. To this solution was added *N*,*N*-diisopropylethylamine (2 equiv) and HBTU (1.5 equiv). After stirring at rt for 5 min, the appropriate secondary amine (1.1 equiv) was added and the reaction was allowed to stir for 2 h. The reaction was quenched by the addition of 1 N HCl. The mixture was extracted with EtOAc three times and the organic phase was washed with 1 N HCl, brine and dried over $MgSO_4$. The solvent was removed and purification was performed by flash column chromatography (EtOAc:hexanes) to give amides **1a-f**.

Step 2) To a solution of the amide (1 equiv) dissolved in anhydrous THF was slowly added 1.0 M BH_3 in THF (4 equiv). The reaction was stirred at rt for 18 h, then cooled to 0°C and carefully quenched (evolution of H_2 gas!) with methanol. The solvent was removed and the residue was redissolved in methanol. To this solution was added ethylenediamine (4 equiv) and the solution was heated by microwave irradiation for 420 s at 100 °C. The methanol was removed and the residue was dissolved in water and extracted with CH_2Cl_2 three times. The organic phase was washed with water, dried over Na_2CO_3 and concentrated. The crude product was purified by flash column chromatography (30% aqueous NH_4OH:CH_3OH:CH_2Cl_2) to give diamine ligands **2a-f**.

Amide 1a. Amide **1a** was prepared as described above from Boc-Chg-OH (1.0 g, 2.3 mmol) and morpholine (0.22 mL, 2.5 mmol). Purification (EtOAc:hexanes 2:3) gave a white solid (0.69 g, 2.1 mmol, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.26 (d, 1H, J = 9.1 Hz), 4.40 (dd, 1H, J = 6.6, 9.1 Hz), 3.67-3.52 (m, 8H), 1.76-1.55 (m, 6H), 1.42 (s, 9H), 1.23-0.99 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 155.9, 79.7, 67.0, 66.9, 54.2, 46.5, 42.5, 41.5, 30.1, 28.5, 28.0, 26.2, 26.1; HRMS-ESI (M + H) calcd for $C_{17}H_{30}N_2O_4$ 327.2284, found 327.2292.

Ligand 2a. Amide **1a** (0.67 g, 2.05 mmol) was reduced as described above with 1.0 M BH_3-THF (8.20 mL, 8.20 mmol) followed by boron exchange with ethylenediamine (0.55 mL, 8.20 mmol). Purification (gradient of 0.1:0.9:150 to 0.1:0.9:45 30% aqueous NH_4OH:CH_3OH:CH_2Cl_2) gave a white solid (0.54 g, 1.73 mmol, 86%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44 (br s, 1H), 3.70-3.62 (m, 5H), 2.51-2.50 (m, 2H), 2.35-2.29 (m, 4H), 1.75-1.63 (m, 5H), 1.48 (m, 1H), 1.43 (s, 1H), 1.24-0.95 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 79.0, 67.2, 60.5, 54.0, 51.9, 40.9, 29.8, 28.6, 28.1, 26.6, 26.45, 26.43; HRMS-ESI (M + H) calcd for $C_{17}H_{32}N_2O_3$ 313.2491, found 313.2499.

Amide 1d. Amide **1d** was prepared as described above from Boc-Cys (Trt)-OH (1.55 g, 3.3 mmol) and morpholine (0.32 mL, 3.7 mmol). Purification (EtOAc:hexanes 2:3) gave a white solid (1.66 g, 3.1 mmol, 94%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, 6H, J = 7.6 Hz), 7.29-7.19 (m, 9H), 5.24 (d, 1H, J = 8.6 Hz), 4.44 (m, 1H), 3.58-3.54 (m, 5H), 3.42 (m, 1H), 3.24 (m, 1H), 3.10 (m, 1H), 2.49 (dd, 1H, J = 5.6, 12.4 Hz), 2.41 (dd, 1H, J = 7.5, 12.4), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 155.1, 144.6, 129.7, 128.1, 126.9, 80.0, 67.0, 66.8, 66.7, 49.3, 46.0, 42.6, 35.0, 28.4; HRMS-ESI (M + Na) calcd for $C_{31}H_{36}N_2O_4S$ 555.2294, found 555.2278.

Ligand 2d. Amide **2d** (1.63 g, 3.06 mmol) was reduced as described above with 1.0 M BH_3-THF (12.2 mL, 12.24 mmol) followed by boron exchange with ethylenediamine (0.82 mL, 12.24 mmol). Purification (gradient of 0.1:0.9:150 to 0.1:0.9:45 30% aqueous NH_4OH:CH_3OH:CH_2Cl_2) gave a white solid (1.25 g, 2.40 mmol, 79%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.43 (m, 6H), 7.32-7.22 (m, 9H), 4.62 (d, 1H, J = 7.1 Hz), 3.75 (m, 1H), 3.64-3.62 (m, 4H), 2.46-2.30 (m, 7H), 2.24-2.19 (m, 1H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 144.8, 129.8, 128.0, 126.8, 79.5, 67.2, 66.7, 61.3,

53.9, 35.3, 28.5; HRMS-ESI (M + H) calcd for $C_{31}H_{38}N_2O_3S$ 519.2681, found 519.2698.

Amide 1e. Amide **1e** was prepared as described above from Boc-Chg-OH (400 mg, 0.91 mmol) and piperidine (0.48 mL, 2.74 mmol). Purification (EtOAc:hexanes 1:4) gave a white solid (0.29 g, 0.89 mol, 96%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.32 (d, 1H, *J* = 9.0 Hz), 4.38 (dd, 1H, *J* = 6.1, 9.1 Hz), 3.48 (t, 2H, *J* = 5.6 Hz), 3.39 (m, 2H), 1.65-1.39 (m, 2H), 1.34 (s, 9H), 1.15-0.92 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 155.8, 79.1, 54.2, 46.9, 43.0, 41.4, 29.9, 28.3, 27.6, 26.5, 26.1, 26.04, 26.00, 25.6, 24.5; HRMS-FAB calcd for $C_{18}H_{32}N_2O_3$ [M+Na] 347.2311, found 347.2320.

Ligand 2e. Amide **2e** (0.27 g, 0.84 mmol) was reduced as described above with 1.0 M BH_3-THF (3.40 mL, 3.40 mmol) followed by boron exchange with ethylenediamine (0.23 mL, 3.40 mmol). Purification (0.1:0.9:45 30% aqueous NH_4OH:CH_3OH:CH_2Cl_2) gave a white solid (0.20 g, 0.64 mmol, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.57 (br s, 1H), 3.57 (br s, 1H), 2.41 (br s , 1H), 2.27 (br s, 1H), 2.25 (br s, 1H), 1.74-1.63 (m, 5H), 1.54-1.37 (m, 16H), 1.27-0.91 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 78.8, 60.3, 54.9, 52.2, 41.0, 29.6, 28.60, 28.58, 28.56, 28.1, 26.7, 26.5, 26.2, 24.6; HRMS-FAB calcd for $C_{18}H_{34}N_2O_2$ [M+Na] 333.2518, found 333.2529.

Amide 1f. Amide **1f** was prepared as described above from Boc-Chg-OH (400 mg, 0.91 mmol) and diethylamine (0.104 mL, 1.0 mmol). Purification (EtOAc:hexanes 1:5) gave a white solid (0.26 g, 0.83 mmol, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.20 (d, 1H, *J* = 9.4 Hz), 4.29 (dd, 1H, *J* = 7.2, 9.3 Hz), 3.52 (dq, 1H, *J* = 7.4, 13.6 Hz), 3.39 (dq, 1H, *J* = 7.0, 14.9 Hz), 3.27 (dq, 1H, *J* = 7.2, 14.8 Hz), 3.10 (dq, 1H, *J* = 7.3, 13.6 Hz), 1.69-1.48 (m, 6H), 1.34 (s, 9H), 1.18-0.93 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ

171.3, 155.6, 79.1, 54.4, 42.0, 41.7, 40.2, 29.8, 28.3, 28.1, 26.13, 26.09, 26.0, 14.6; 12.9; HRMS-FAB calcd for $C_{17}H_{32}N_2O_3$ [M+Na] 335.2320, found 335.2311.

Ligand 2f. Amide **2f** (0.26 g, 0.83 mmol) was reduced as described above with 1.0 M BH_3-THF (3.40 mL, 3.33 mmol) followed by boron exchange with ethylenediamine (0.22 mL, 3.33 mmol). Purification (gradient of 0.1:0.9:45 to 0.15:1.35:45 30% aqueous NH_4OH:CH_3OH:CH_2Cl_2) gave a pale yellow solid (0.13 g, 0.44 mmol, 53%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.52 (br s, 1H), 3.46 (br s, 1H), 2.54-2.28 (m, 6H), 1.72-1.45 (m, 6H), 1.40 (s, 9H), 1.24-0.87 (m, 5H), 0.94 (t, 6H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.3, 78.8, 54.2, 53.2, 47.2, 40.3, 29.8, 28.58, 28.55, 28.5, 27.9, 26.7, 26.5, 11.9; HRMS-FAB calcd for $C_{17}H_{34}N_2O_2$ [M+Na] 321.2518, found 321.2530.

Representative Procedures for the Addition of Vinylzinc Reagents to 3,4-Dihydro-isoquinoline *N*-oxide and HPLC Conditions for ee Determination of 3a-g.

1) To an oven-dried vial were added dry CH_2Cl_2 (2.80 mL) and neat BH_3•DMS complex (228 μL, 2.40 mmol). The solution was cooled to 0 °C, and cyclohexene (486 μL, 4.80 mmol) was added. The reaction was stirred for 2 h, during which time a white precipitate formed. After 2 h, 4-phenyl-1-butyne (337 μL, 2.40 mmol) was added, and the reaction was slowly warmed to rt and stirred for 2 h. The white precipitate dissolved and the mixture turned to a clear solution (Solution **A**).

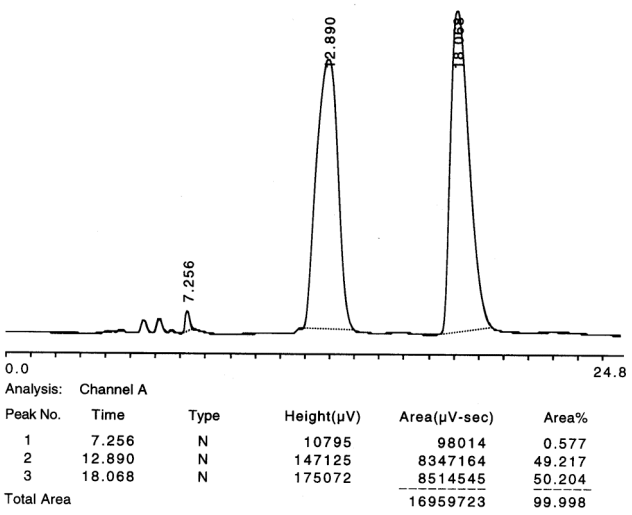
2) To another oven-dried vial pre-loaded with ligand **2a** (74.9 mg, 0.24 mmol), 3,4-dihydroisoquinoline *N*-oxide (29.4 mg, 0.20 mmol) and a magnetic stirring bar was added dry CH_2Cl_2 (1.20 mL). The solution was then cooled to -50°C and a 1 M solution of diethylzinc in CH_2Cl_2 was added (369 μL, 0.48 mmol) to give a clear solution **B**. An

aliquot of the solution **A** (385 μL) was transferred to the solution **B** using a syringe pump over 20 min at -48 °C, and the reaction was kept at -48 °C for 24 h. The reaction was then carefully quenched with sat. NH_4Cl solution. The mixture was extracted with CH_2Cl_2, and the organic phase was washed with sat. NH_4Cl and water. The product solution was filtered through a small silica plug and concentrated *in vacuo*. Flash column chromatography (EtOAc:hexanes 1:6) gave a purified product **3e** (41.2 mg, 0.15 mmol, 74%).

Hydroxylamine 3a. The general procedure was used with 3,3-dimethylbutyne (296 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:8), hydroxylamine **3a** was isolated (31.7 mg, 0.14 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16-7.06 (m, 4H), 5.86 (d, 1H, J = 15.6 Hz), 5.39 (dd, 1H, J = 15.2, 8.4 Hz), 4.21 (br s, 1H), 3.52-3.48 (m, 1H), 3.17-3.01 (m, 2H), 2.92-2.87 (m, 1H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 136.2, 133.4, 128.3, 127.9, 126.8, 126.1, 124.9, 72.4, 54.0, 33.5, 29.8; HRMS-FAB calcd for $C_{15}H_{21}NO$ [M+Na] 254.1521, found 254.1529; 93% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99.5:0.5) at 1.0 mL/min and detected at 219 nm), t_R = 13.8 min for (*S*) and t_R = 20.3 min for (*R*); $[\alpha]^{24}_D = +23.5^o$ (c = 1.0, $CHCl_3$).

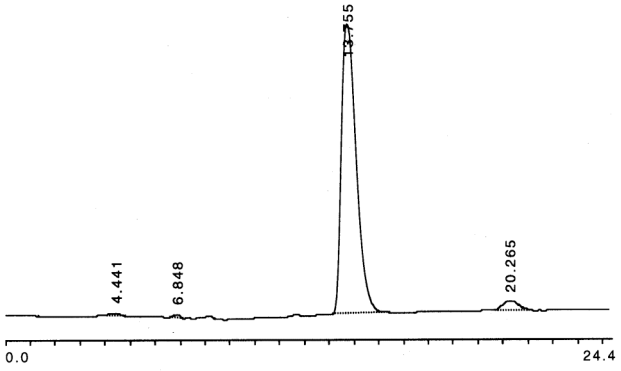
Hydroxylamine 3b. The general procedure was used with 1-hexyne (270 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:8), hydroxylamine **3b** was isolated (30.3 mg, 0.13 mmol, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19-7.10 (m, 4H), 5.87-5.78 (m, 1H), 5.52 (dd, 1H, J = 15.2, 8.3 Hz), 4.27 (d, 1H, J = 6.8 Hz), 3.53-3.49 (m, 1H), 3.18-3.03 (m, 2H), 2.96-2.90 (m, 1H), 2.21-2.14 (m, 2H), 1.51-1.29 (m, 4H), 0.94 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 136.0, 133.4,

129.8, 128.3, 128.1, 126.7, 126.1, 72.0, 53.7, 32.3, 31.6, 28.6, 22.5, 14.1; HRMS-FAB calcd for $C_{15}H_{21}NO$ [M+Na] 254.1521, found 254.1526; 94% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), t_R = 12.4 min for (*S*) and t_R = 16.4 min for (*R*); $[\alpha]^{25}_D = +34.6^o$ (c = 1.0, $CHCl_3$).



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	7.256	N	10795	98014	0.577
2	12.890	N	147125	8347164	49.217
3	18.068	N	175072	8514545	50.204
Total Area				16959723	99.998



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	4.441	N	2097	48613	0.420
2	6.848	N	2883	46962	0.405
3	13.755	N	284058	11094820	95.873
4	20.265	N	9257	381944	3.300
Total Area				11572339	99.998

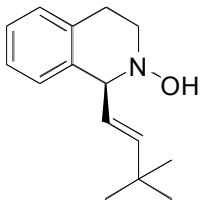
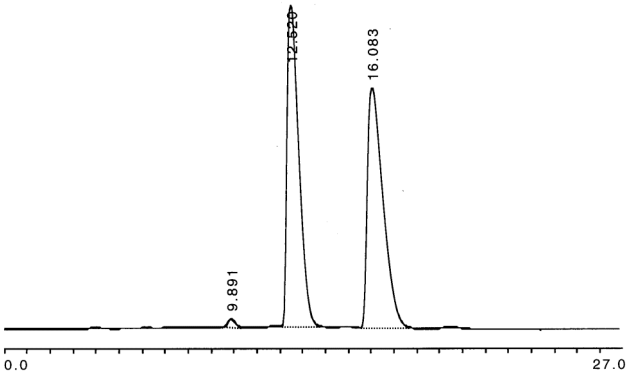


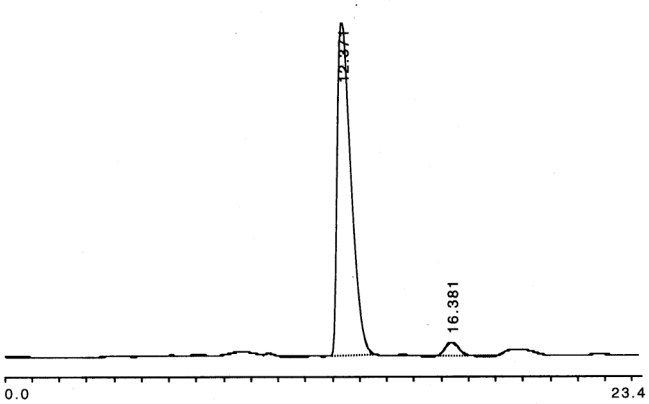
Figure S1. HPLC trace of hydroxylamine **3a**.

Top trace: racemic sample; bottom trace: enantiomerically enriched sample.



Analysis: Channel B

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	9.891	N	6941	127276	0.659
2	12.520	N	292836	9493290	49.160
3	16.083	N	218926	9690397	50.180
Total Area				19310963	99.999



Analysis: Channel B

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	12.371	N	236061	7604078	96.391
2	16.381	N	9138	284689	3.608
Total Area				7888767	99.999

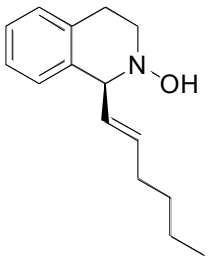
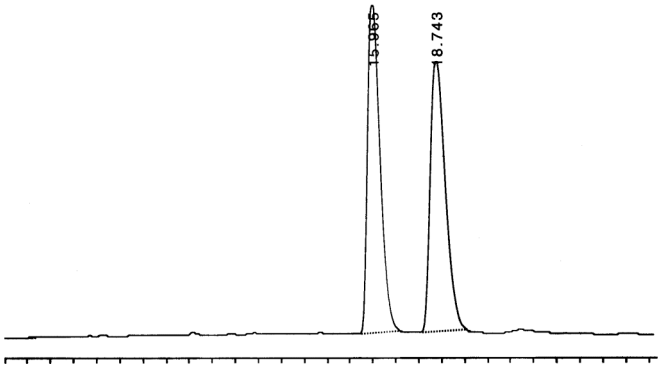


Figure S2. HPLC trace of hydroxylamine **3b**.

Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

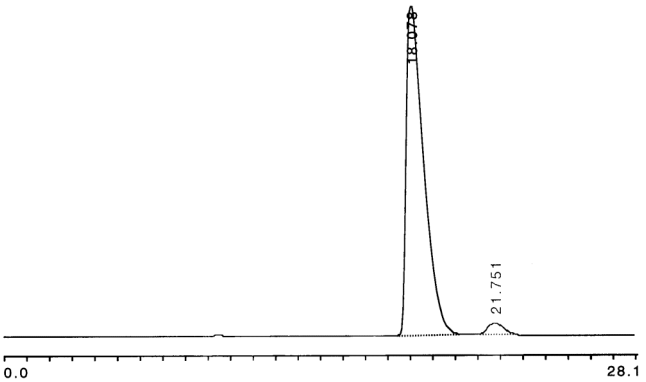
Hydroxylamine 3c. The general procedure was used with cyclopropyl acetylene (203 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:4), hydroxylamine **3c** was isolated (34.0 mg, 0.16 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.09 (m, 4H), 5.60 (dd, 1H, J = 14.2, 8.7 Hz), 5.35-5.29 (m, 1H), 4.31 (br

s, 1H), 3.55-3.51 (m, 1H), 3.14-3.08 (m, 2H), 2.96-2.92 (m, 1H), 1.53-1.47 (m, 1H), 0.79-0.74 (m, 2H), 0.48-0.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 135.3, 133.1, 128.4, 128.1, 127.0, 126.6, 126.2, 71.5, 53.1, 27.9, 13.9, 7.2, 7.1; HRMS-FAB calcd for $C_{14}H_{17}NO$ [M+H] 216.1388, found 216.1382; 94% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), t_R = 18.1 min for (*S*) and t_R = 21.8 min for (*R*); $[\alpha]^{25}_D$ = +69.6 ^{o} (c = 0.76, $CHCl_3$).



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	15.965	N	109953	3767739	49.762
2	18.743	N	90530	3803679	50.237
Total Area				7571418	99.999



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	18.078	N	259117	13019264	96.826
2	21.751	N	8884	426773	3.173
Total Area				13446037	99.999

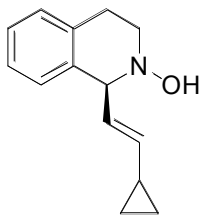
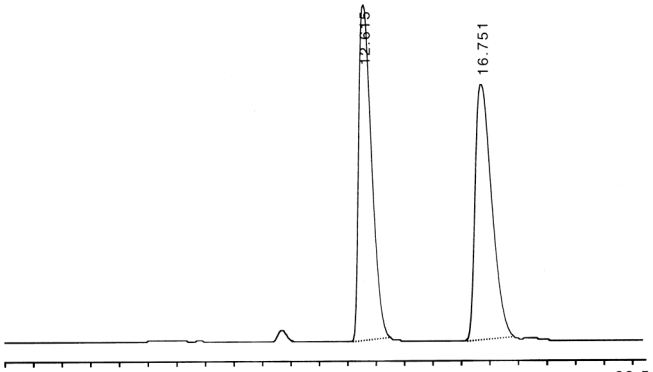


Figure S3. HPLC trace of hydroxylamine **3c**.

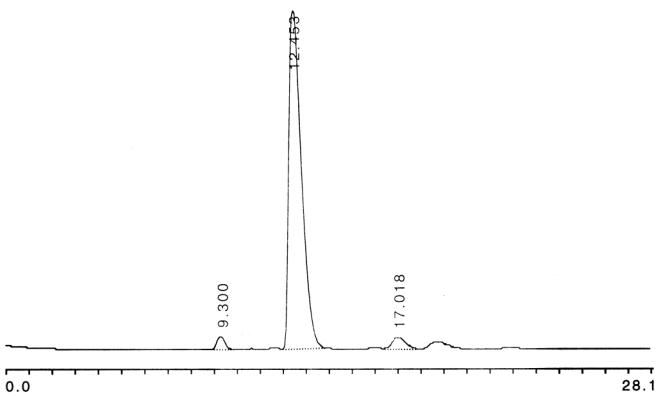
Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

Hydroxylamine 3d. The general procedure was used with cyclohexylacetylene (309 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:9), hydroxylamine **3d** was isolated (32.0 mg, 0.12 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.08 (m, 4H), 5.77 (dd, 1H, *J* = 15.5, 6.5 Hz), 5.45 (dd, 1H, *J* = 14.9, 8.4 Hz), 4.23 (br s, 1H), 3.51-3.48 (m, 1H), 3.16-3.02 (m, 2H), 2.92-2.88 (m, 1H), 2.12-2.05 (m, 1H), 1.82-1.65 (m, 5H), 1.35-1.11 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 136.0, 133.4, 128.2, 128.0, 127.3, 126.7, 126.0, 72.2, 53.7, 40.7, 33.1, 33.0, 28.6, 26.3, 26.1; HRMS-FAB calcd for $C_{17}H_{23}NO$ [M+Na] 280.1677, found 280.1685; 94% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), t_R = 12.5 min for (*S*) and t_R = 17.0 min for (*R*); $[\alpha]^{25}_D$ = +33.3 ^{o} (c = 0.64, $CHCl_3$).



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	12.615	N	148607	4234465	50.121
2	16.751	N	113128	4213879	49.878
Total Area				8448344	99.999



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	9.300	N	9372	193730	**2.124**
2	12.453	N	249940	8620965	**94.533**
3	17.018	N	8389	304834	**3.342**
Total Area				9119529	**99.999**

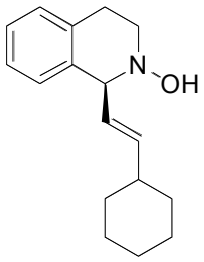
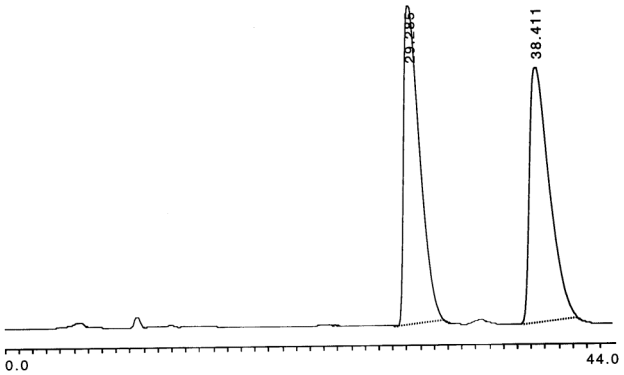


Figure S4. HPLC trace of hydroxylamine **3d**.

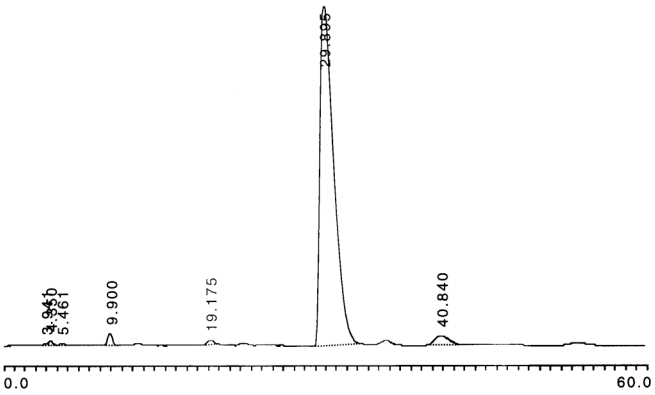
Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

Hydroxylamine 3e. The general procedure was used with 4-phenyl-1-butyne (337 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:6), hydroxylamine **3e** was isolated (41.2 mg, 0.15 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.10 (m, 8H), 6.94 (d, 1H, J = 7.4 Hz), 5.85-5.78 (m, 1H), 5.51-5.45 (m, 1H), 4.23 (br s, 1H), 3.49-3.47 (m, 1H), 3.13-3.01 (m, 2H), 2.93-2.80 (m, 3H), 2.56-2.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7 136.0, 135.7, 133.3, 130.9, 128.7, 128.5, 128.2, 128.0, 126.7, 126.05, 126.03, 71.9, 53.8, 35.6, 34.3, 28.6; HRMS-FAB calcd for $C_{19}H_{21}NO$ [M+Na] 302.1521, found 302.1516; 95% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (99:1) at 1.0 mL/min and detected at 219 nm), t_R = 29.9 min for (*R*) and t_R = 40.8 min for (*S*); $[\alpha]^{25}_D$ = +28.3 ^{o} (c = 1.0, $CHCl_3$).



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	29.285	N	85024	6323383	50.206
2	38.411	N	67728	6271409	49.793
Total Area				12594792	99.999



Analysis: Channel A

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	3.941	N1	881	15582	0.134
2	4.350	N2	1664	32526	0.281
3	5.461	N3	544	13270	0.114
4	9.900	N	4668	109914	0.951
5	19.175	N	1910	67102	0.580
6	29.895	N	134210	11021798	95.412
7	40.840	N	3464	291517	2.523
Total Area				11551709	99.995

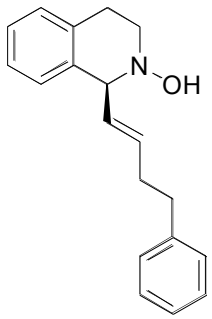
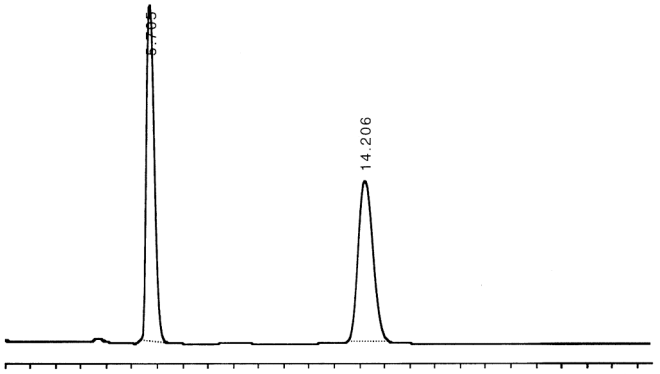


Figure S5. HPLC trace of hydroxylamine **3e**.

Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

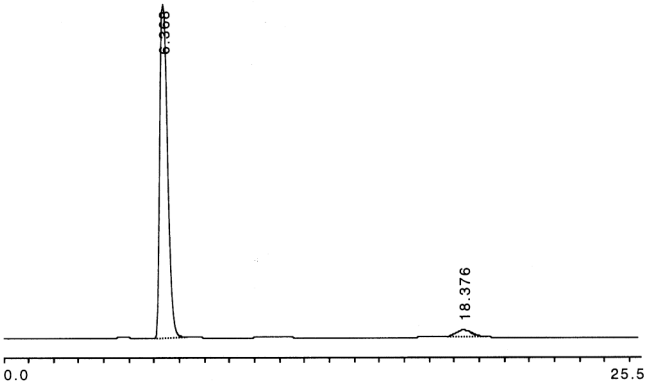
Hydroxylamine 3f. The general procedure was used with phenylacetylene (264 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:6), hydroxylamine **3f** was isolated (37.4 mg, 0.15 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.46 (m, 2H), 7.38-7.27 (m, 3H), 7.22-7.12 (m, 4H), 6.72 (d, 1H, J = 15.8

Hz), 6.30 (dd, 1H, J = 15.5, 8.5 Hz), 4.49 (d, 1H, J = 6.2 Hz), 3.54-3.51 (m, 1H), 3.17-3.08 (m, 2H), 2.92-2.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.5, 135.3, 133.4, 129.5, 128.7, 128.4, 128.1, 127.9, 127.0, 126.7, 126.2, 71.9, 53.9, 28.6; HRMS-FAB calcd for $C_{17}H_{17}NO$ [M+Na] 274.1208, found 274.1216; 90% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (80:20) at 1.0 mL/min



Analysis: Channel B

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	5.705	N	104382	1913746	50.452
2	14.206	N	49785	1879398	49.547
Total Area				3793144	99.999



Analysis: Channel B

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	6.368	N	906445	16580236	95.279
2	18.376	N	18713	821396	4.720
Total Area				17401632	99.999

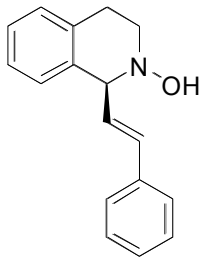
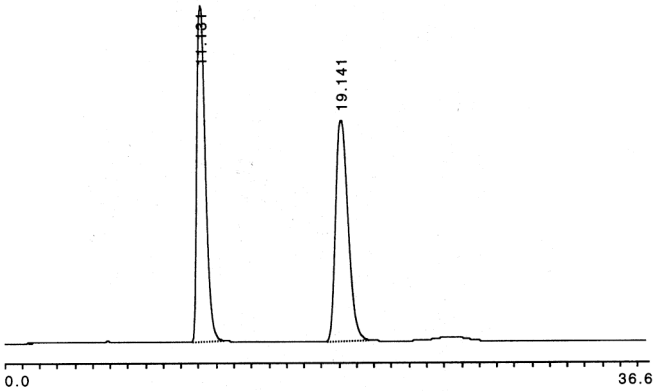


Figure S6. HPLC trace of hydroxylamine **3f**.

Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

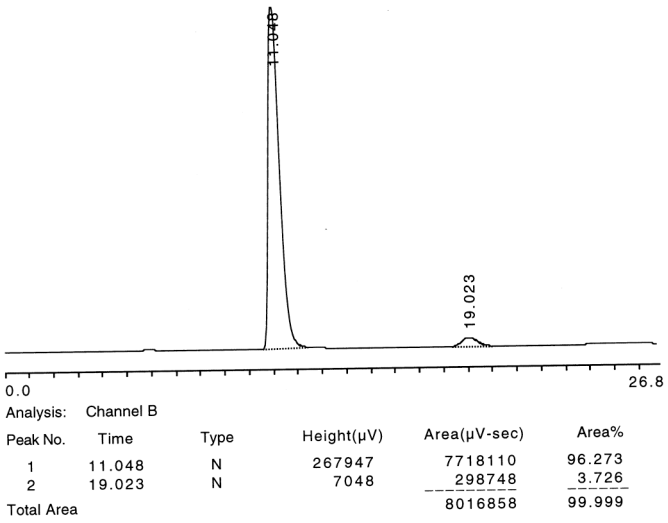
and detected at 219 and 254 nm), t_R = 6.4 min for (*R*) and t_R = 18.4 min for (*S*); $[\alpha]^{25}_D$ = +16.7 ^{o} (c = 1.0, $CHCl_3$).

Hydroxylamine 3g. The general procedure was used with 4-ethynylanisole (311 μL, 2.4 mmol). Following flash column chromatography (EtOAc:hexanes 1:5), hydroxylamine **3g** was isolated (47.7 mg, 0.17 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2H, *J* = 8.7 Hz), 7.18-7.09 (m, 4H), 6.87 (d, 2H, *J* = 8.7 Hz), 6.63 (d, 1H, *J* = 15.8 Hz), 6.13 (dd, 1H, *J* = 15.2, 8.3 Hz), 4.44 (br s, 1H), 3.51-3.48 (m, 1H), 3.14-3.05 (m, 2H), 2.88-2.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 135.6, 134.7, 133.4, 129.5, 128.3, 128.1, 127.8, 127.2, 126.8, 126.1, 114.1, 72.0, 55.4, 53.8, 28.6; HRMS-FAB calcd for $C_{18}H_{19}NO$ [M+Na] 304.1313, found 304.1321; 92% ee by HPLC analysis (Chiralcel OD-H column eluted with hexanes:2-propanol (90:10) at 1.0 mL/min and detected at 219 and 254nm), t_R = 11.0 min for (*R*) and t_R = 19.0 min for (*S*); $[\alpha]^{24}_D$ = +15.1 ^{o} (c = 0.86, $CHCl_3$).



Analysis: Channel B

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	11.131	N	188030	5414366	49.486
2	19.141	N	122948	5526747	50.513
Total Area				10941113	99.999



Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	11.048	N	267947	7718110	96.273
2	19.023	N	7048	298748	3.726
Total Area				8016858	99.999

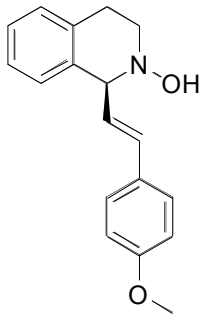
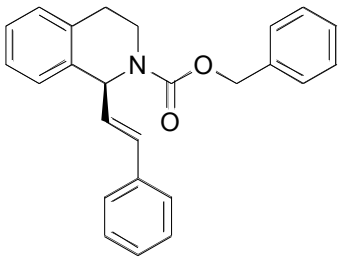


Figure S7. HPLC trace of hydroxylamine **3g**.

Top trace: racemic sample; bottom trace: enantiomerically enriched sample.

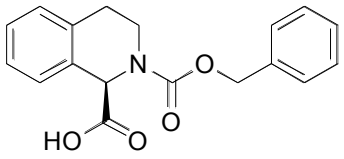
Preparation of *N*-Cbz–D-1,2,3,4-Tetrahydroisoquinoline-1-Carboxylic Acid.



Compound 4

Zn dust (471 mg, 7.20 mmol) was added into a solution of $Cu(OAc)_2$ (29 mg, 0.14 mmol) in acetic acid (4 mL), and the mixture was stirred at rt for 15 min under N_2. A solution of hydroxylamine **3f** (96% ee, 362 mg, 1.44 mmol) in acetic acid (4 mL) and water (2 mL) was then added. The mixture was heated at 70 °C for 2 h. After 2 h, the brown suspension was cooled to rt. EDTA (1.61 g, 4.32 mmol) was added, and the solution was basified to pH 10 by addition of 3 M NaOH. The solution was extracted with EtOAc four times, washed with sat. EDTA, brine and dried over $MgSO_4$. The

organic solution was concentrated *in vacuo* to give a white solid (305 mg, 1.30 mmol, 90%) which was directly used in the next step without further purification. The crude amine was dissolved in EtOAc (10 mL). Sat. $NaHCO_3$ aq (10 mL) was added. The biphasic solution was cooled to 0 °C and benzyl chloroformate (253 μL, 1.8 mmol) was added dropwise. The reaction was stirred overnight at rt, then the solution was extracted with EtOAc. The organic phase was washed with sat NH_4Cl, brine, dried over Na_2SO_4, and concentrated. Flash column chromatography (1:9 EtOAc:hexanes) gave a colorless oil (354 mg, 0.96 mmol, 74%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.26 (m, 14H), 6.43 (br s, 2H), 5.96-5.83 (m, 1H), 5.30-5.25 (m, 2H), 4.31-4.18 (m, 1H), 3.43 (br s, 1H), 3.01-2.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.8, 136.6, 134.9, 134.6, 131.6, 129.0, 128.6, 128.1, 127.8, 127.0, 126.6, 126.4, 67.4, 56.6, 38.7, 28.8; HRMS-FAB calcd for $C_{25}H_{23}NO_2$ [M+Na] 392.1626, found 392.1636; $[\alpha]^{25}_D = +155.7^o$ (c = 0.26, CH_3OH).

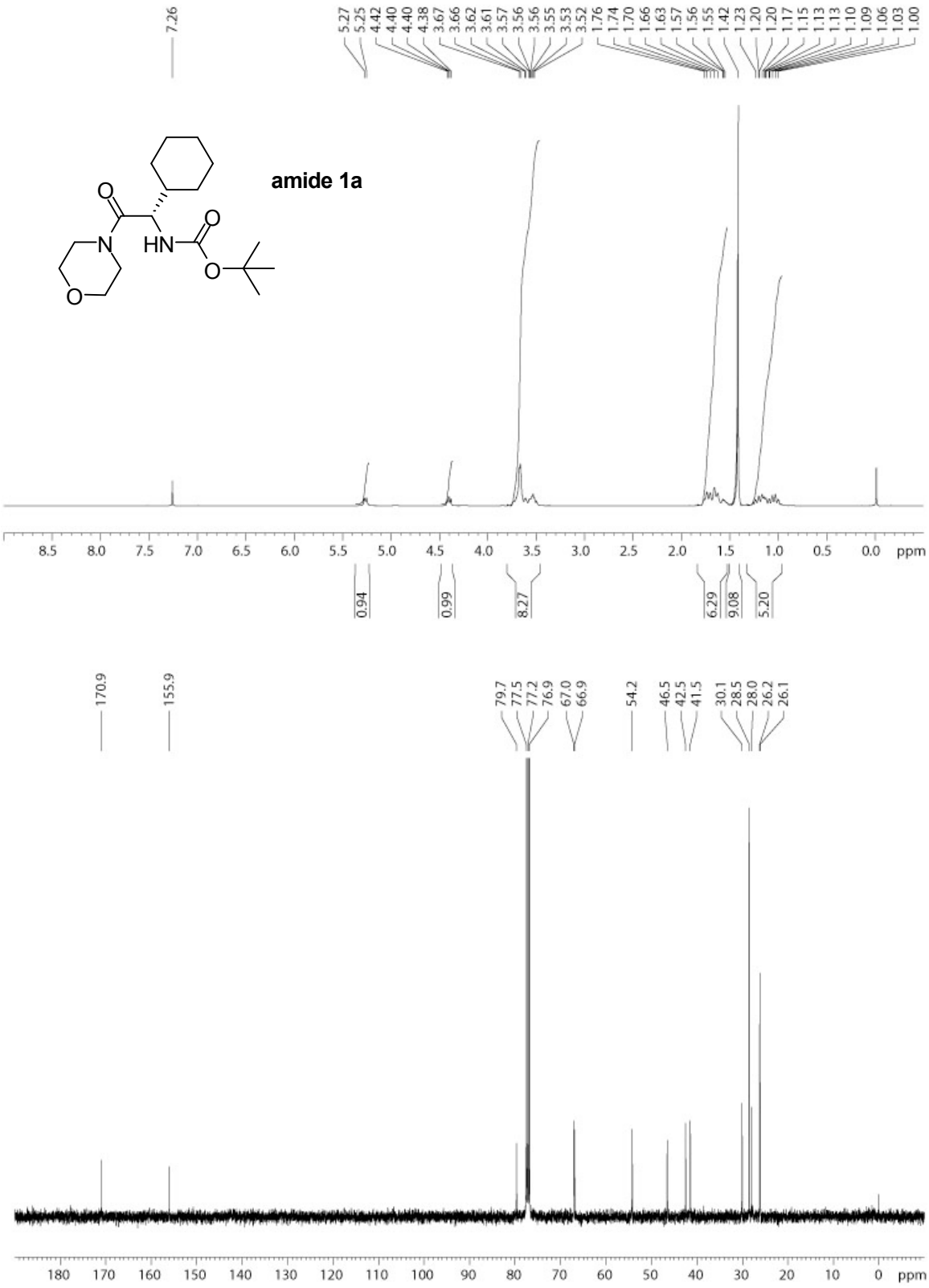


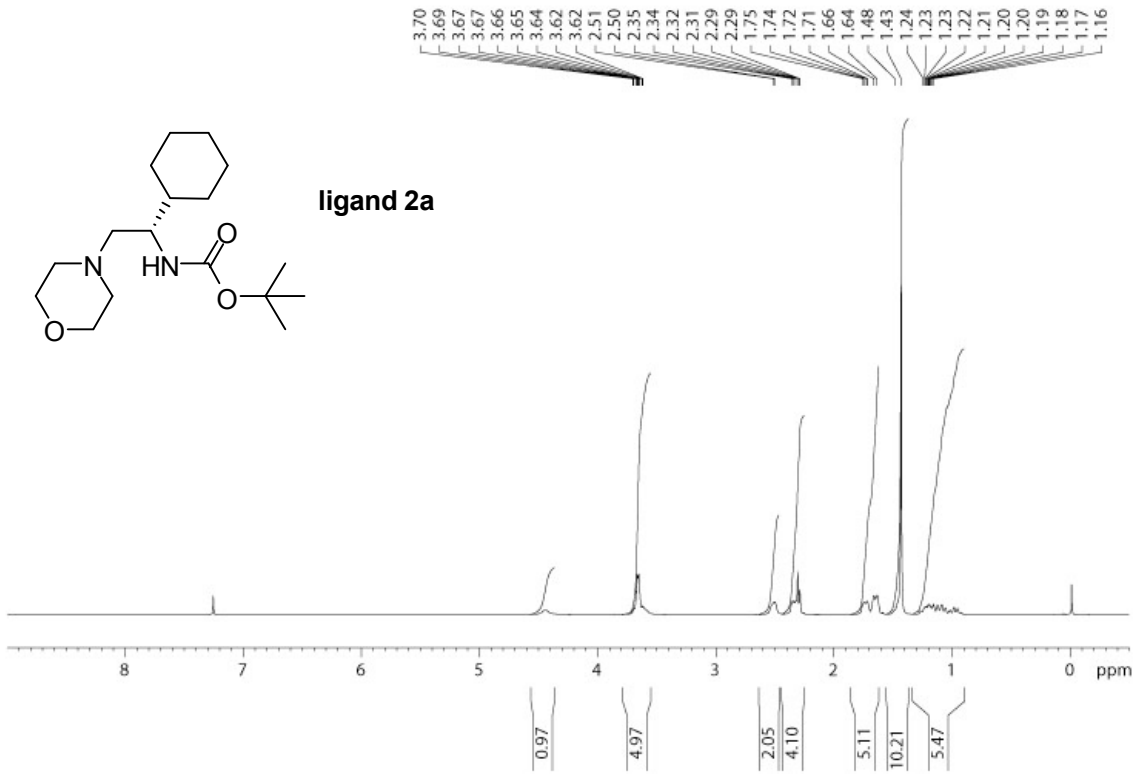
(*R*)-*N*-(Benzyloxycarbonyl)-1,2,3,4-Tetrahydroisoquinoline-1-Carboxylic Acid: 5

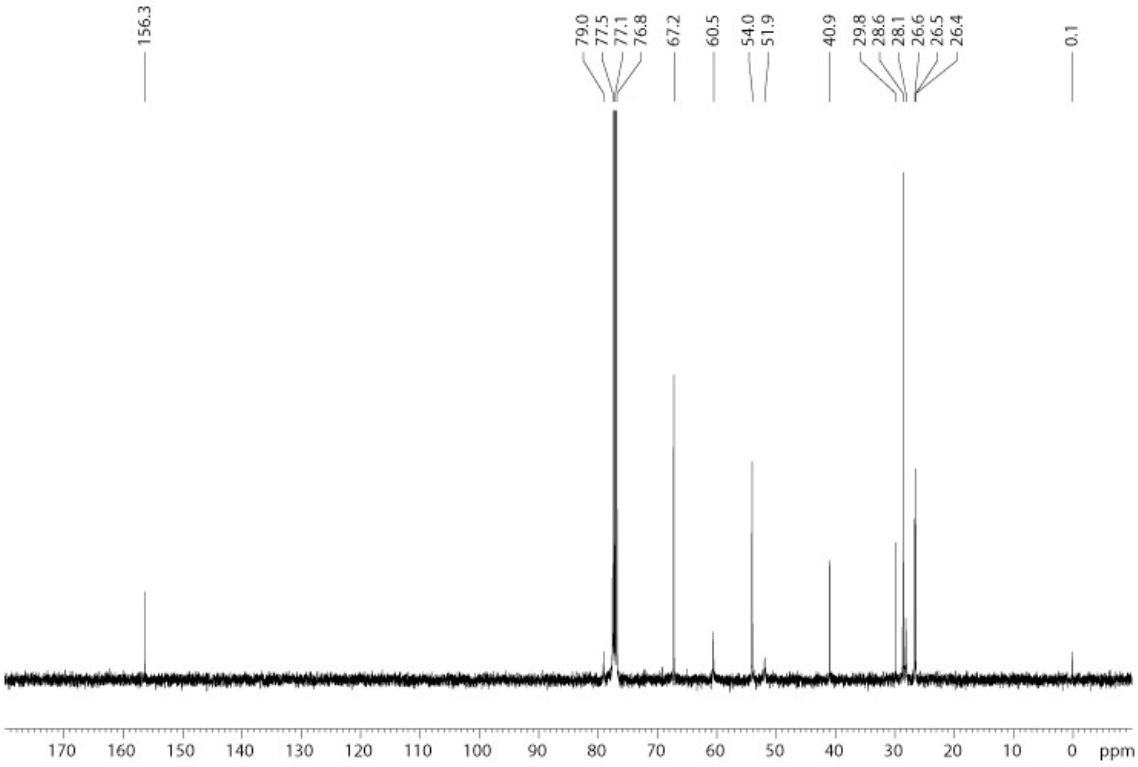
The alkene **4** (51 mg, 0.14 mmol) was dissolved in CCl_4-CH_3CN-H_2O (2:2:3). $NaIO_4$ (60 mg, 0.28 mmol) and $RuCl_3$ hydrate (0.004 mmol, 0.9 mg) were added. After 0.5 h, another equivalent of $NaIO_4$ (60 mg, 0.28 mmol) was added. The mixture was stirred vigorously at rt overnight. The solution was extracted with CH_2Cl_2 five times. The organic solutions were combined, dried over $MgSO_4$ and concentrated. Diethyl ether was then added to precipitate $RuCl_3$ and the solution was filtered though celite. The

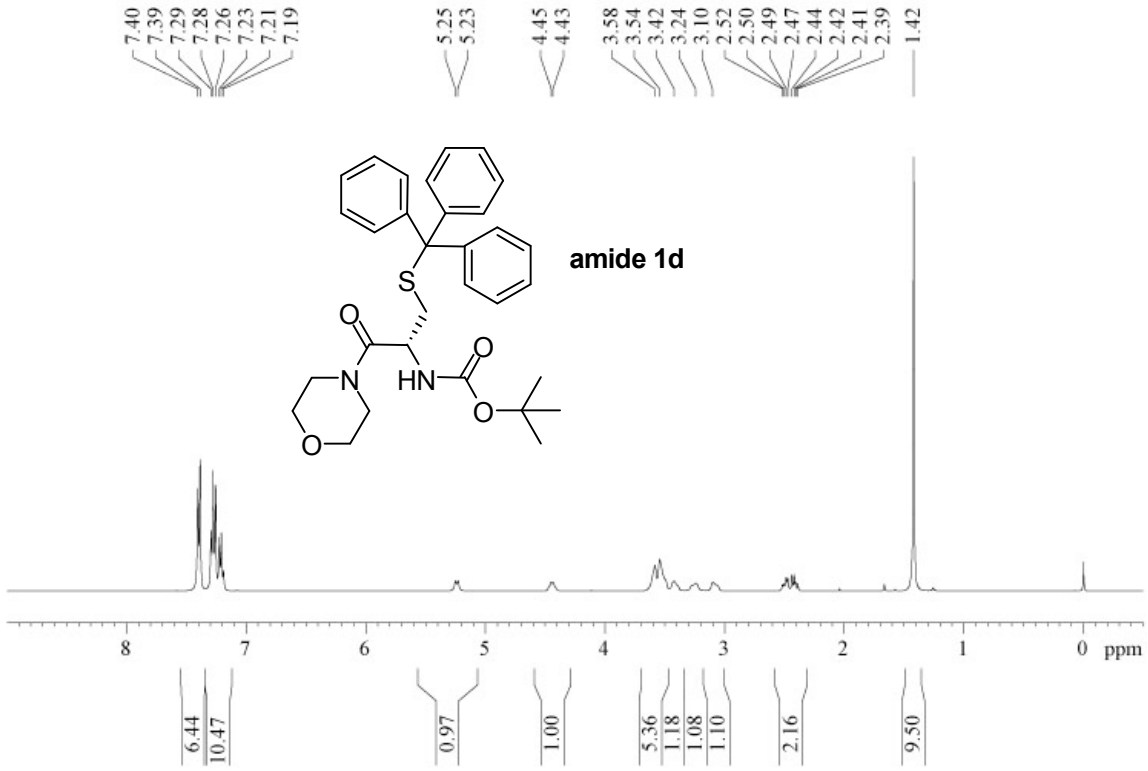
residue was purified by flash column chromatography (1:1 EtOAc:hexanes with 0.25% AcOH) to give a white oily solid (26 mg, 0.084 mmol, 61%) (existing as 5:4 *N*-invertomers as determined by ^{1}H NMR spectroscopy).[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.17 (m, 9H), 5.67 (s, 0.5H), 5.58 (s, 0.4H), 5.23-5.19 (m, 2H), 3.88-3.83 (m, 2H), 2.97-2.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 176.7, 156.4, 155.6, 136.5, 136.4, 135.7, 135.4, 130.0, 129.4, 128.9, 128.75, 128.67, 128.62, 128.56, 128.39, 128.36, 128.32, 128.2, 128.1, 127.0, 126.9, 68.0, 67.9, 58.2, 58.1, 41.0, 40.7, 28.7, 28.6; HRMS-FAB calcd for $C_{18}H_{17}NO_4$ [M+Na] 334.1055, found 334.1066; $[\alpha]^{24}_{D} = -24.8^{o}$ (c = 0.5, CH_3OH) {lit.[3] $[\alpha]^{20}_{D} = -40.1^{o}$ (c = 1.0, CH_3OH) for (*R*) enantiomer}.

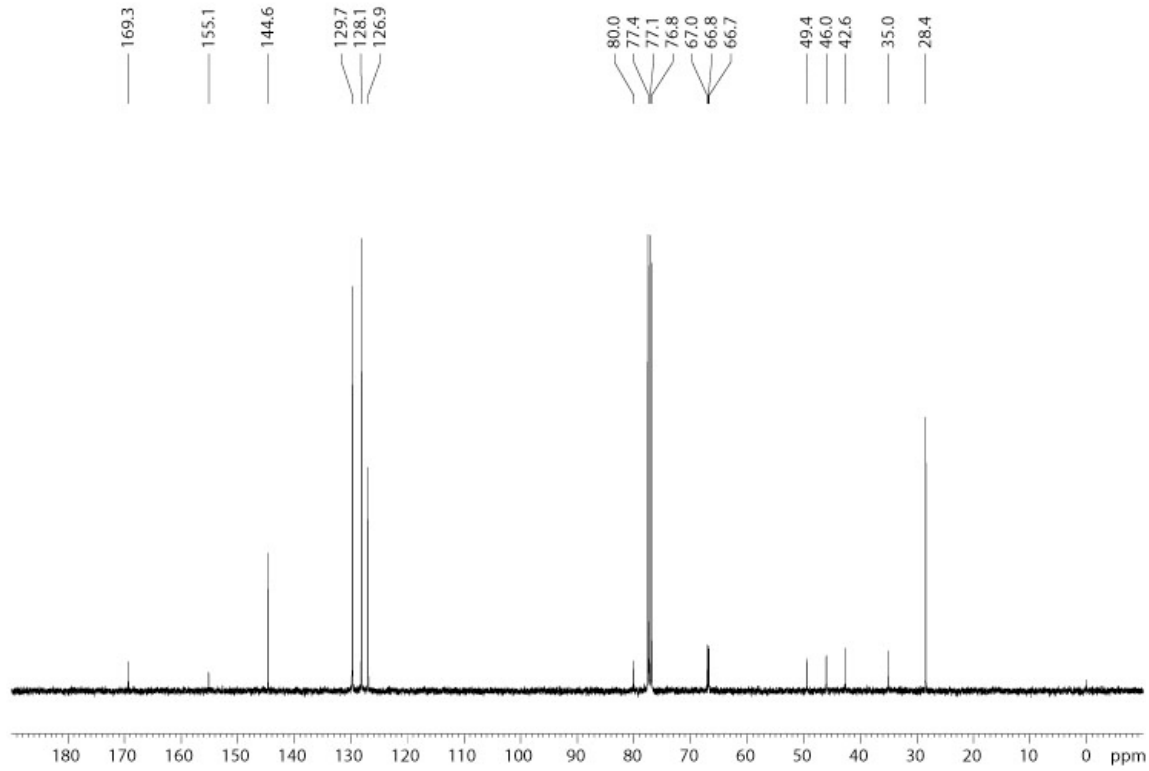
^{1}H and ^{13}C NMR Spectra for Compounds 1a, 2a, 1d-f, 2d-f

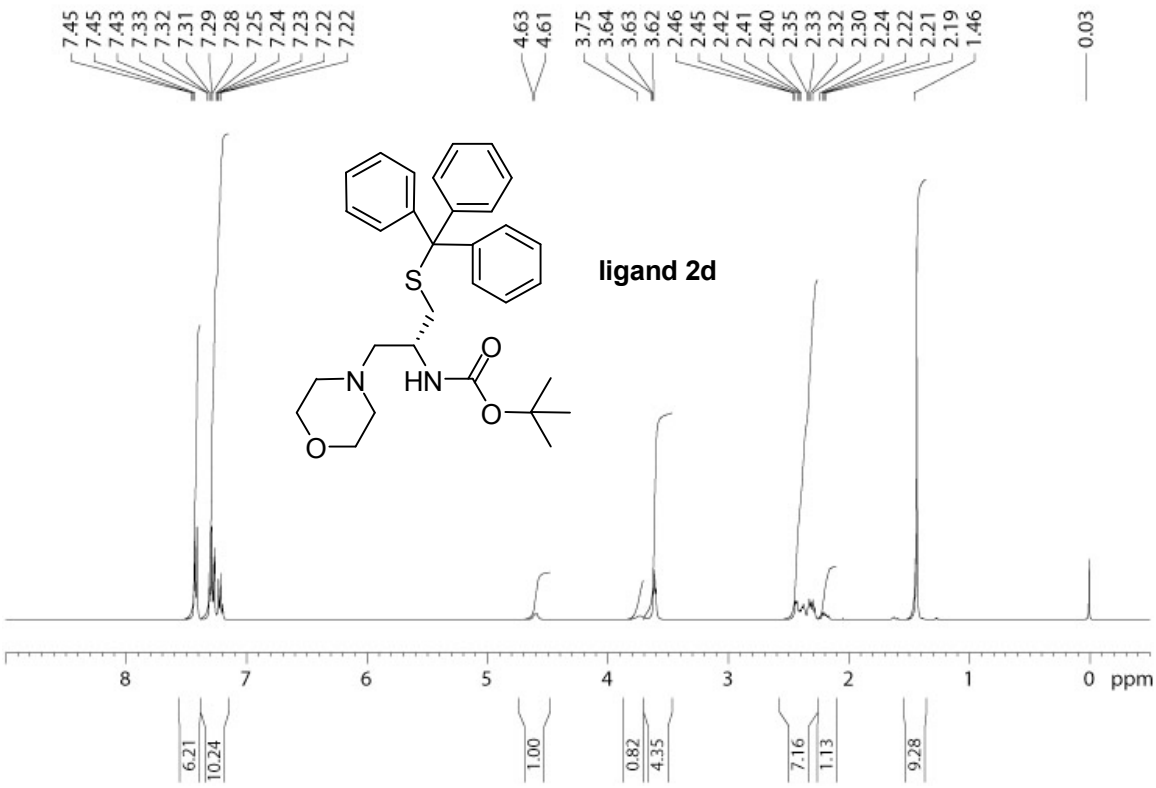


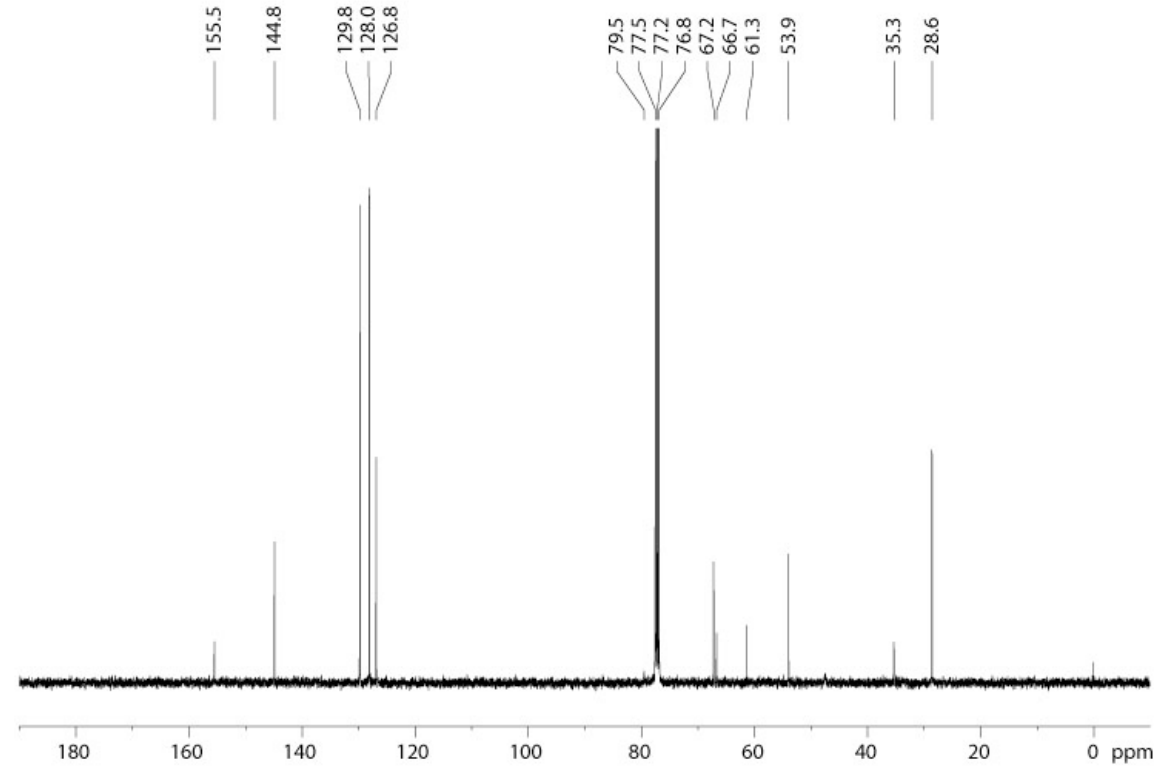

3.70
3.69
3.67
3.67
3.66
3.65
3.64
3.62
3.62
2.51
2.50
2.35
2.34
2.32
2.31
2.29
2.29
1.75
1.74
1.72
1.71
1.66
1.64
1.48
1.43
1.24
1.23
1.23
1.22
1.21
1.20
1.20
1.19
1.18
1.17
1.16
ligand 2a
N
HN
O
O
O
8
7
6
5
4
3
2
1
0
ppm
0.97
4.97
2.05
4.10
5.11
10.21
5.47

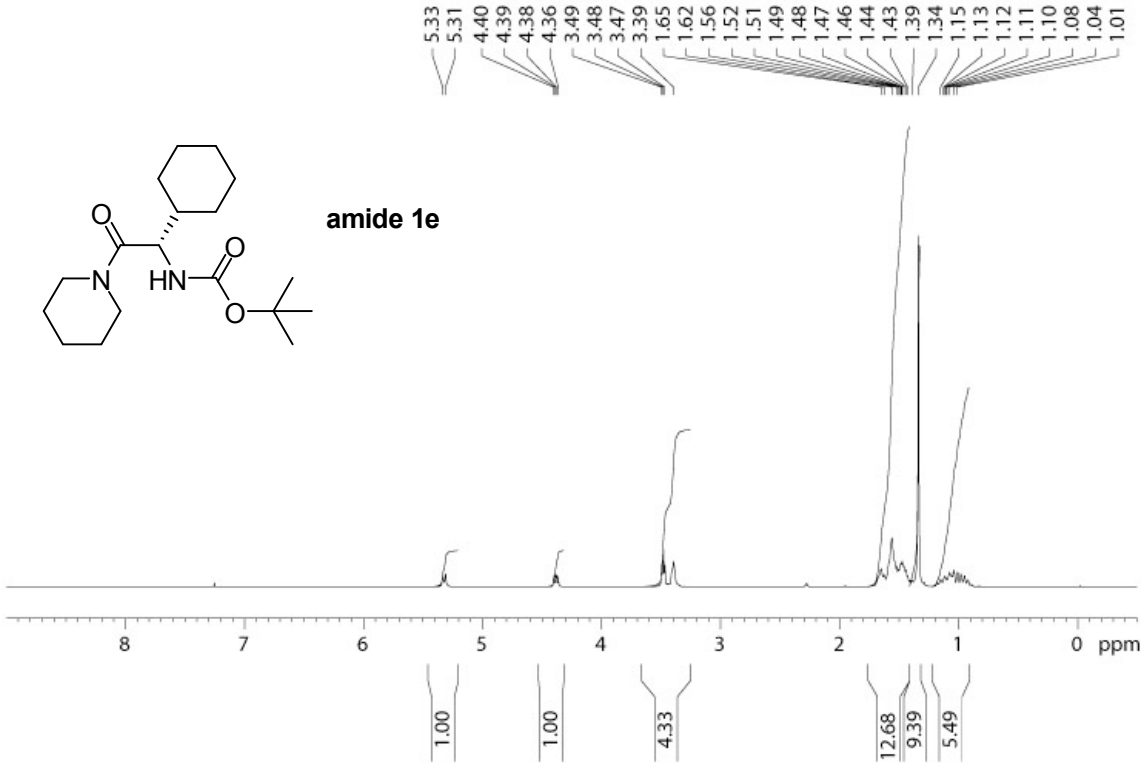

156.3
79.0
77.5
77.1
76.8
67.2
60.5
54.0
51.9
40.9
29.8
28.6
28.1
26.6
26.5
26.4
0.1
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

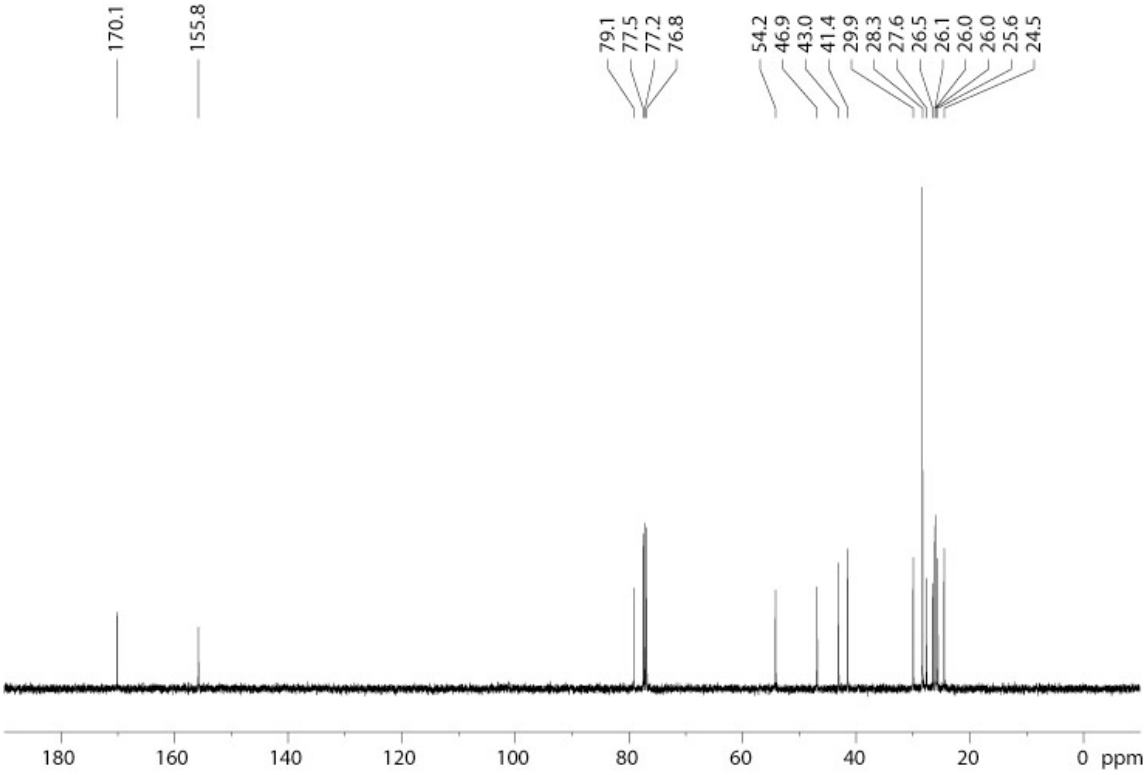

7.40
7.39
7.29
7.28
7.26
7.23
7.21
7.19
5.25
5.23
4.45
4.43
3.58
3.54
3.42
3.24
3.10
2.52
2.50
2.49
2.47
2.44
2.42
2.41
2.39
1.42
amide 1d
S
O
N
HN
O
O
O
8
7
6
5
4
3
2
1
0 ppm
6.44
10.47
0.97
1.00
5.36
1.18
1.08
1.10
2.16
9.50

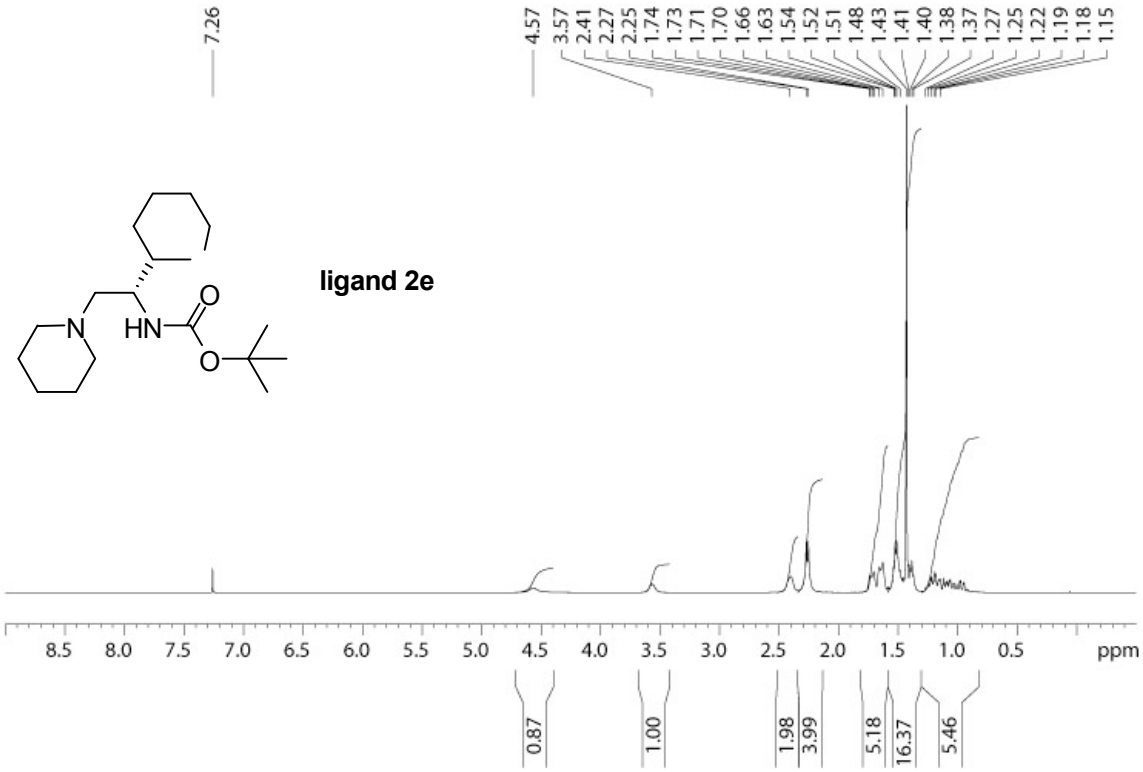

169.3
155.1
144.6
129.7
128.1
126.9
80.0
77.4
77.1
76.8
67.0
66.8
66.7
49.4
46.0
42.6
35.0
28.4
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


7.45
7.45
7.43
7.33
7.32
7.31
7.29
7.28
7.25
7.24
7.23
7.22
7.22
4.63
4.61
3.75
3.64
3.63
3.62
2.46
2.45
2.42
2.41
2.40
2.35
2.33
2.32
2.30
2.24
2.22
2.21
2.19
1.46
0.03
ligand 2d
S
N
HN
O
O
O
8
7
6
5
4
3
2
1
0 ppm
6.21
10.24
1.00
0.82
4.35
7.16
1.13
9.28

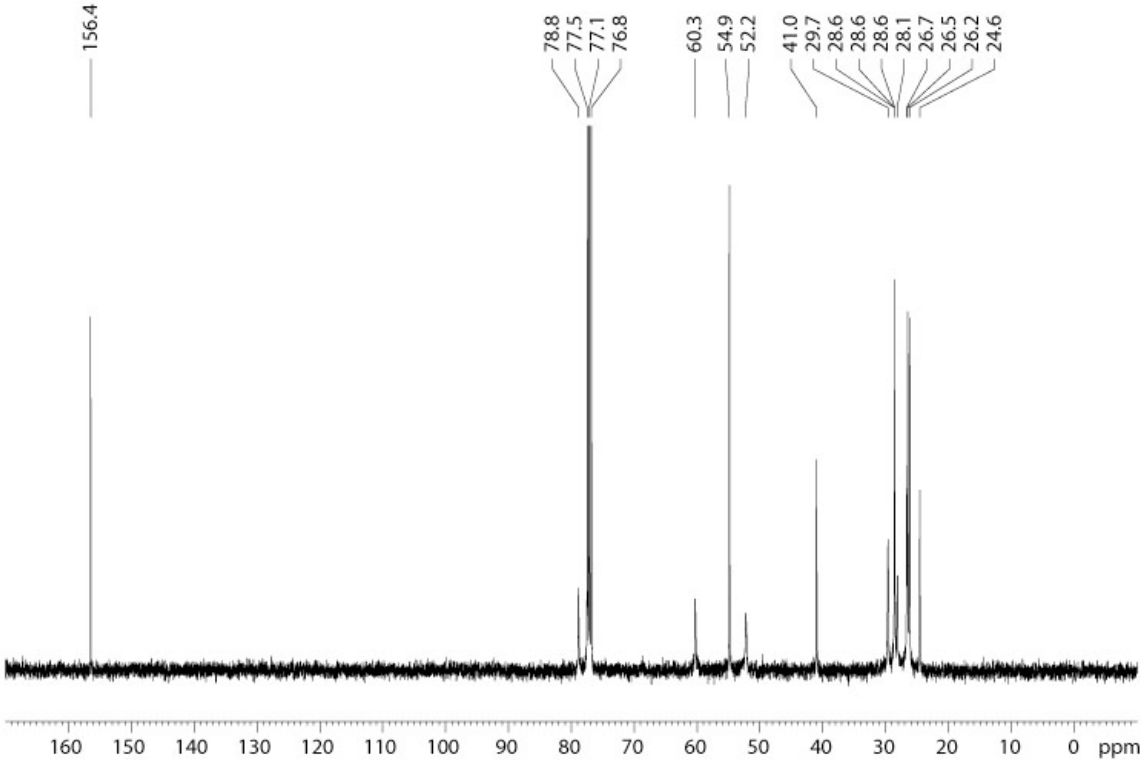

155.5
144.8
129.8
128.0
126.8
79.5
77.5
77.2
76.8
67.2
66.7
61.3
53.9
35.3
28.6
180
160
140
120
100
80
60
40
20
0 ppm

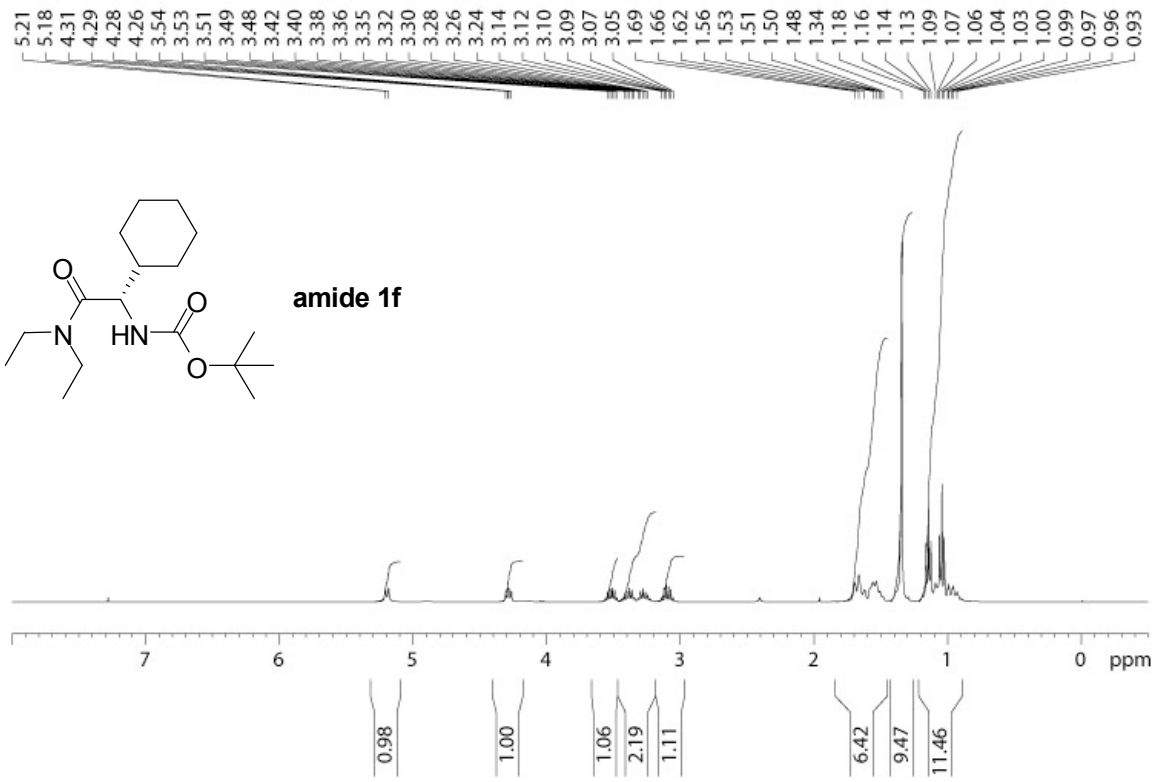

5.33
5.31
4.40
4.39
4.38
4.36
3.49
3.48
3.47
3.39
1.65
1.62
1.56
1.52
1.51
1.49
1.48
1.47
1.46
1.44
1.43
1.39
1.34
1.15
1.13
1.12
1.11
1.10
1.08
1.04
1.01
amide 1e
O
N
HN
O
O
8
7
6
5
4
3
2
1
0 ppm
1.00
1.00
4.33
12.68
9.39
5.49

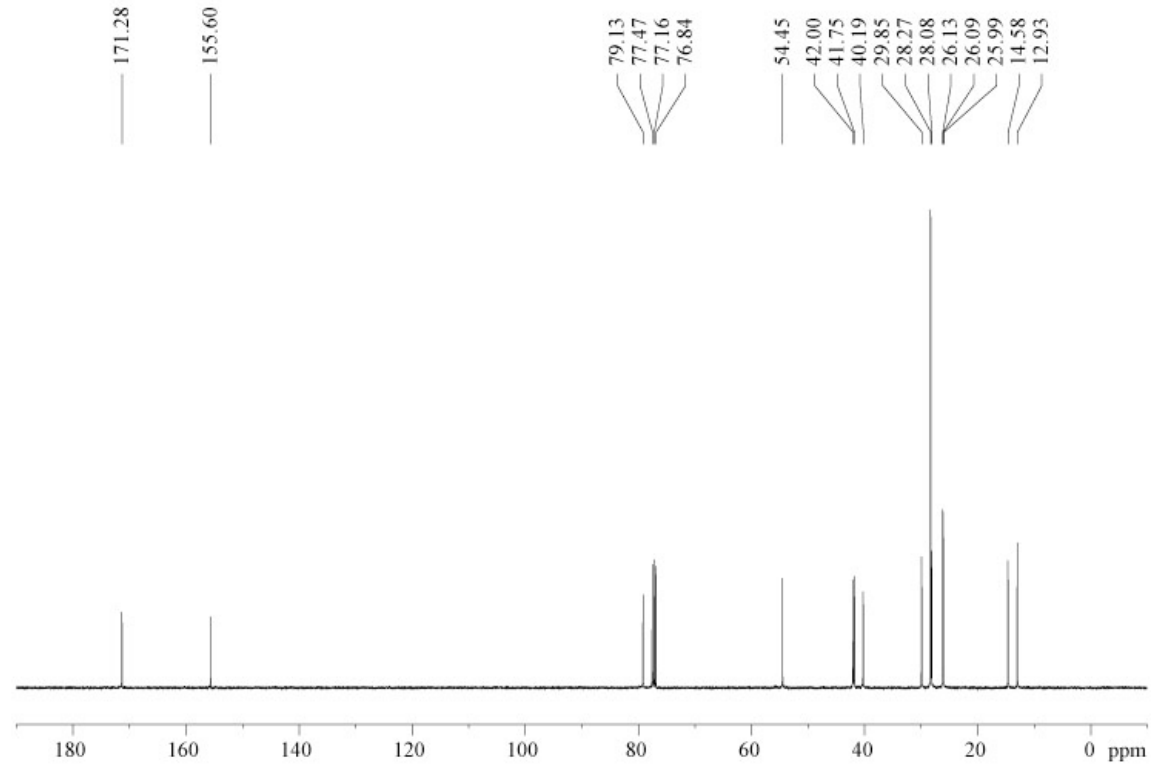

170.1
155.8
79.1
77.5
77.2
76.8
54.2
46.9
43.0
41.4
29.9
28.3
27.6
26.5
26.1
26.0
26.0
25.6
24.5
180
160
140
120
100
80
60
40
20
0 ppm

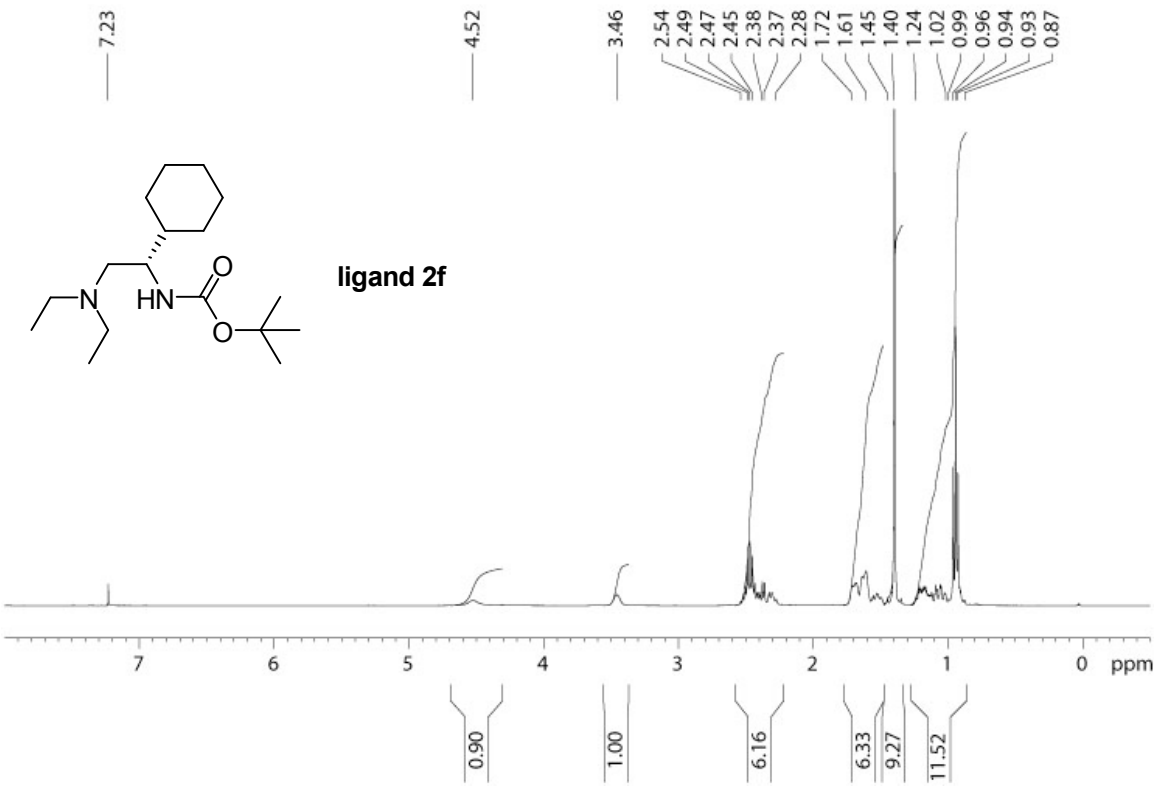

7.26
4.57
3.57
2.41
2.27
2.25
1.74
1.73
1.71
1.70
1.66
1.63
1.54
1.52
1.51
1.48
1.43
1.41
1.40
1.38
1.37
1.27
1.25
1.22
1.19
1.18
1.15
N
HN
O
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.87
1.00
1.98
3.99
5.18
16.37
5.46

ligand 2e

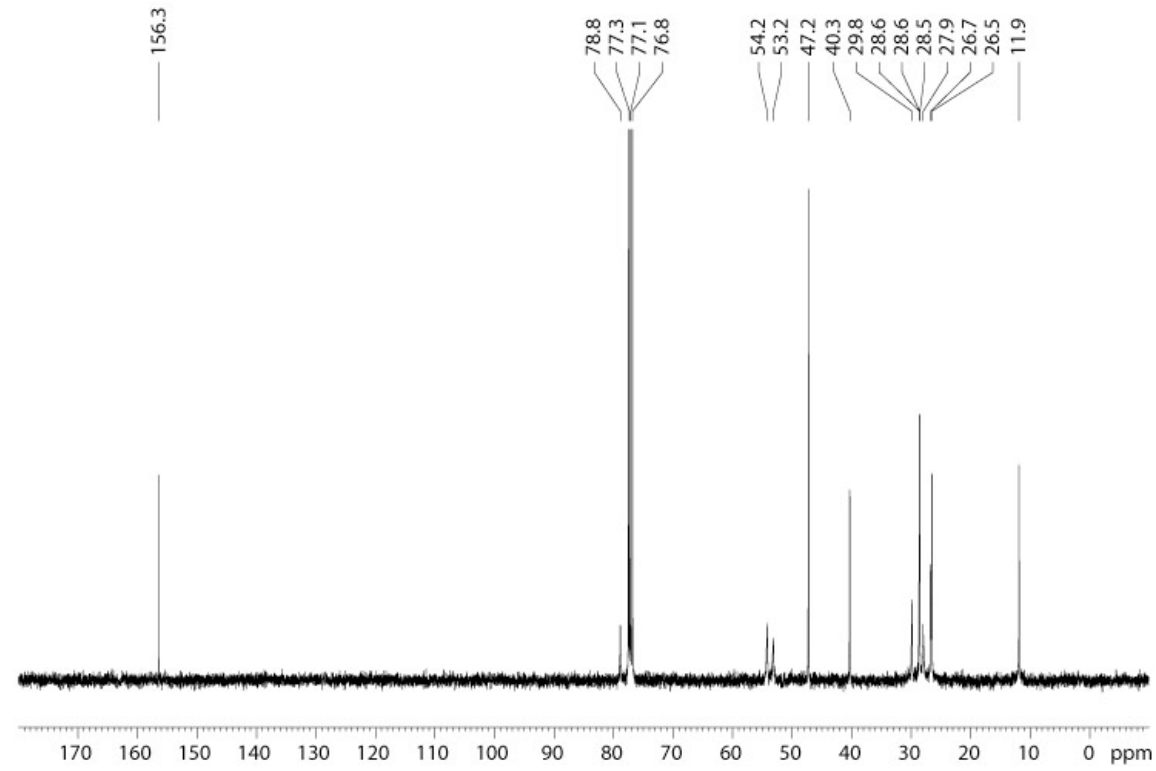

156.4
78.8
77.5
77.1
76.8
60.3
54.9
52.2
41.0
29.7
28.6
28.6
28.6
28.1
26.7
26.5
26.2
24.6
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


5.21
5.18
4.31
4.29
4.28
4.26
3.54
3.53
3.51
3.49
3.48
3.42
3.40
3.38
3.36
3.35
3.32
3.30
3.28
3.26
3.24
3.14
3.12
3.10
3.09
3.07
3.05
1.69
1.66
1.62
1.56
1.53
1.51
1.50
1.48
1.34
1.18
1.16
1.14
1.13
1.09
1.07
1.06
1.04
1.03
1.00
0.99
0.97
0.96
0.93
O
N
HN
O
O
amide 1f
7
6
5
4
3
2
1
0
ppm
0.98
1.00
1.06
2.19
1.11
6.42
9.47
11.46

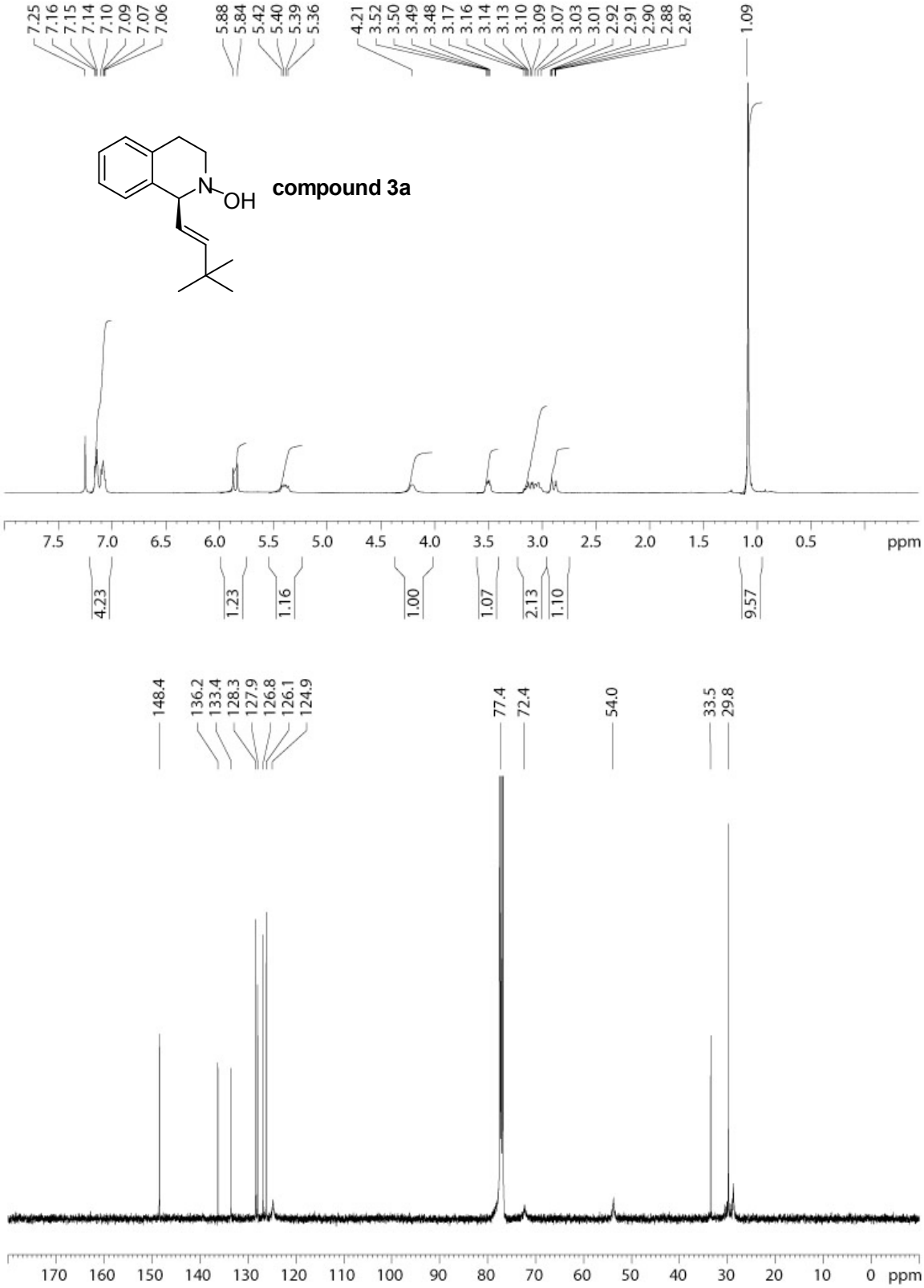

171.28
155.60
79.13
77.47
77.16
76.84
54.45
42.00
41.75
40.19
29.85
28.27
28.08
26.13
26.09
25.99
14.58
12.93
180
160
140
120
100
80
60
40
20
0
ppm

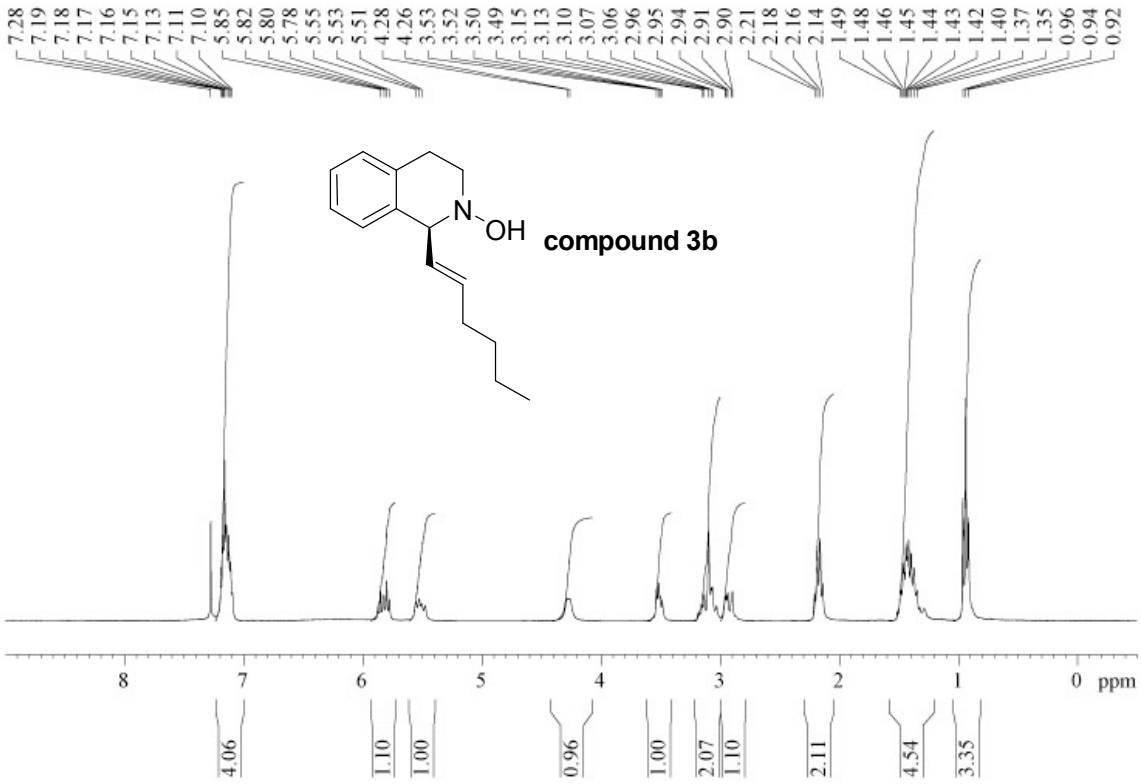

7.23
4.52
3.46
2.54
2.49
2.47
2.45
2.38
2.37
2.28
1.72
1.61
1.45
1.40
1.24
1.02
0.99
0.96
0.94
0.93
0.87
N
HN
O
O
7
6
5
4
3
2
1
0
ppm
0.90
1.00
6.16
6.33
9.27
11.52

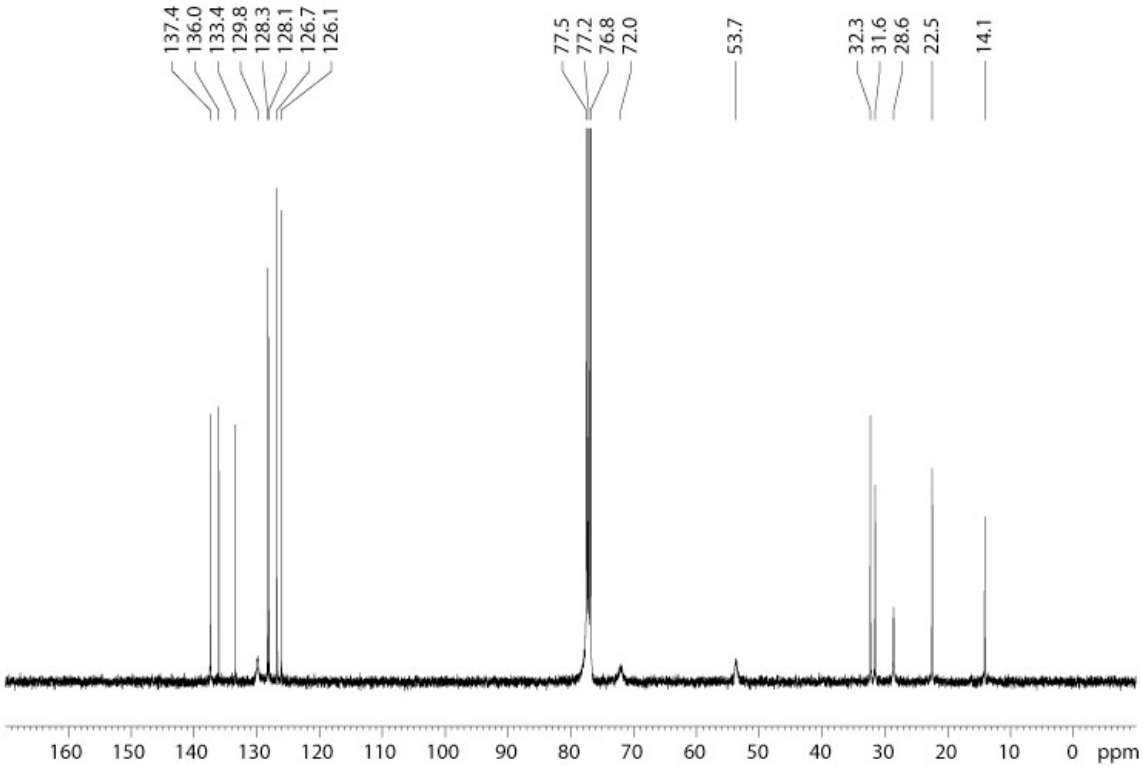
ligand 2f

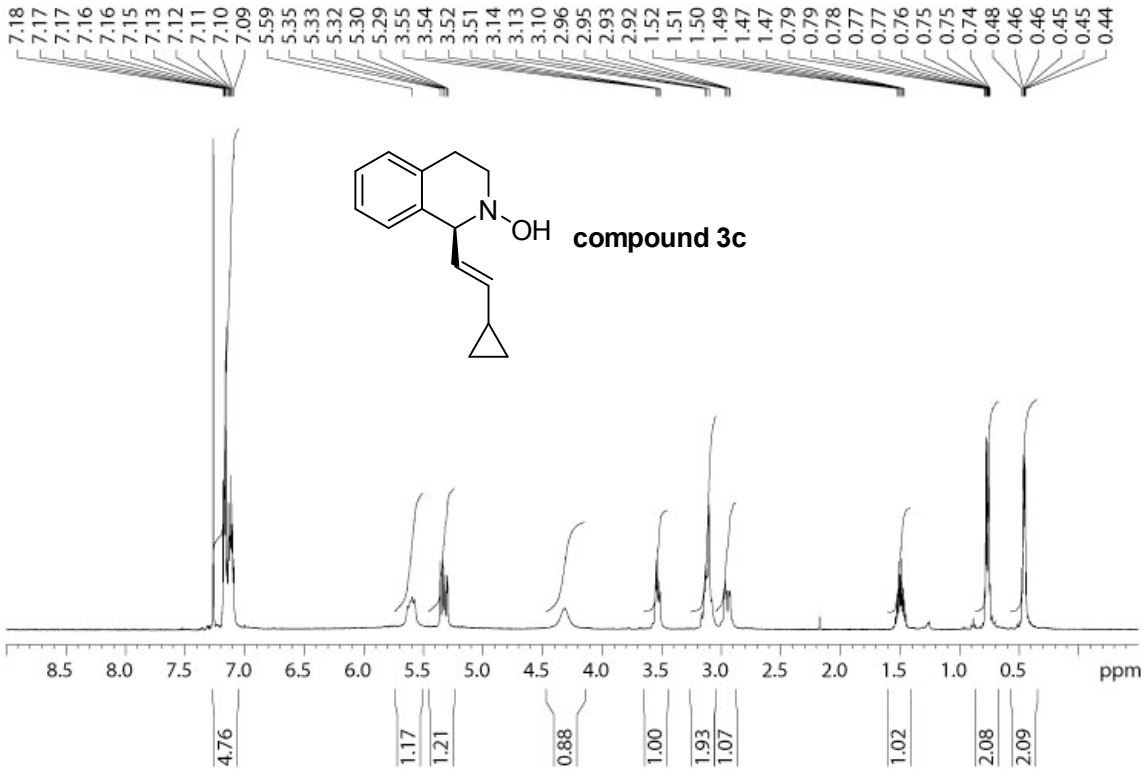

156.3
78.8
77.3
77.1
76.8
54.2
53.2
47.2
40.3
29.8
28.6
28.6
28.5
27.9
26.7
26.5
11.9
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

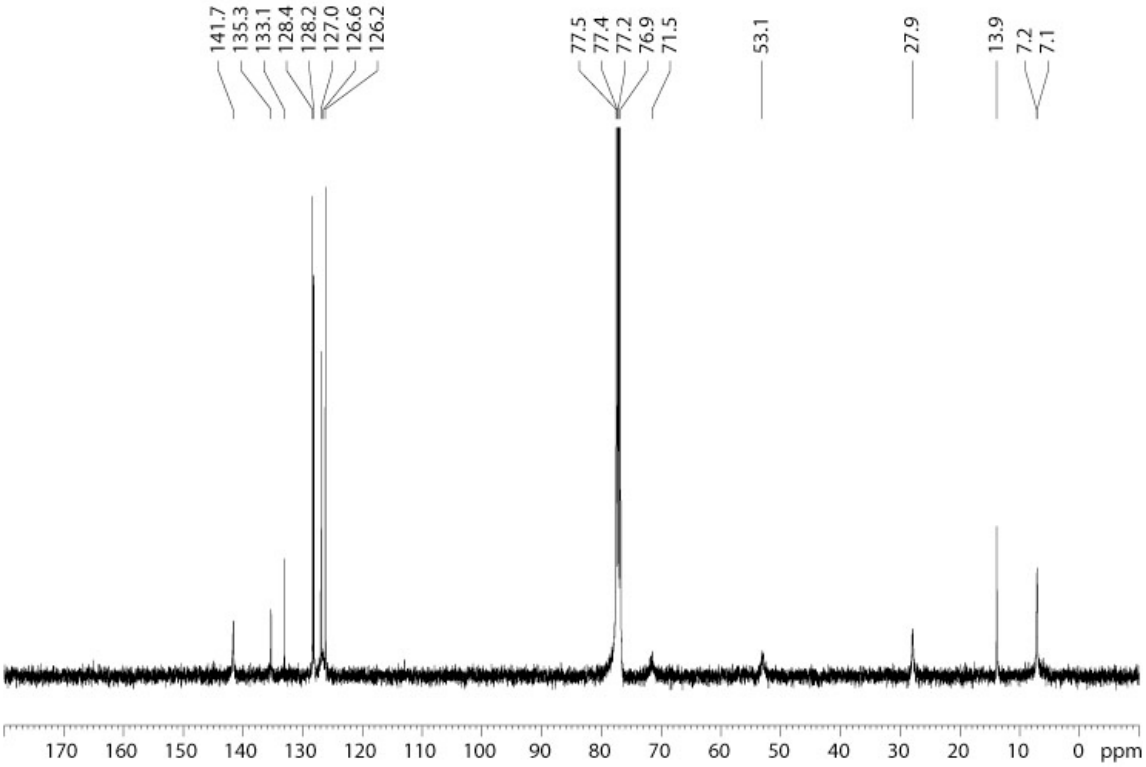
^{1}H and ^{13}C NMR Spectra for Compounds 3a-g, 4, 5

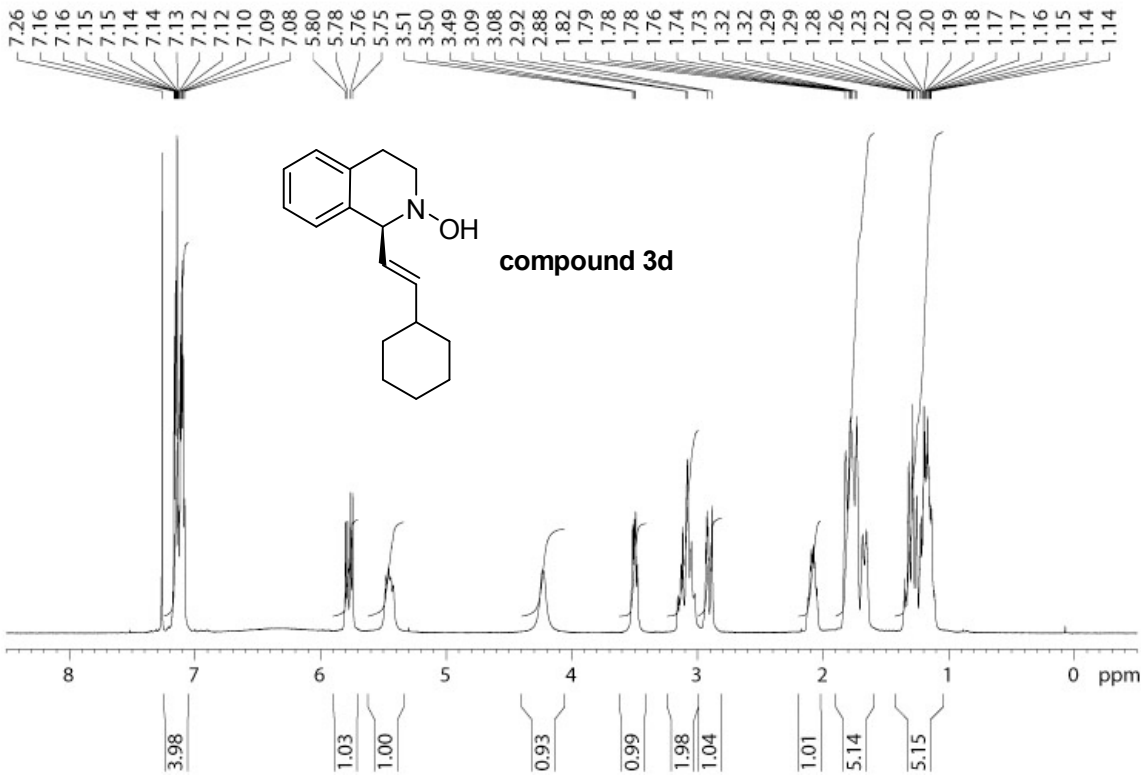


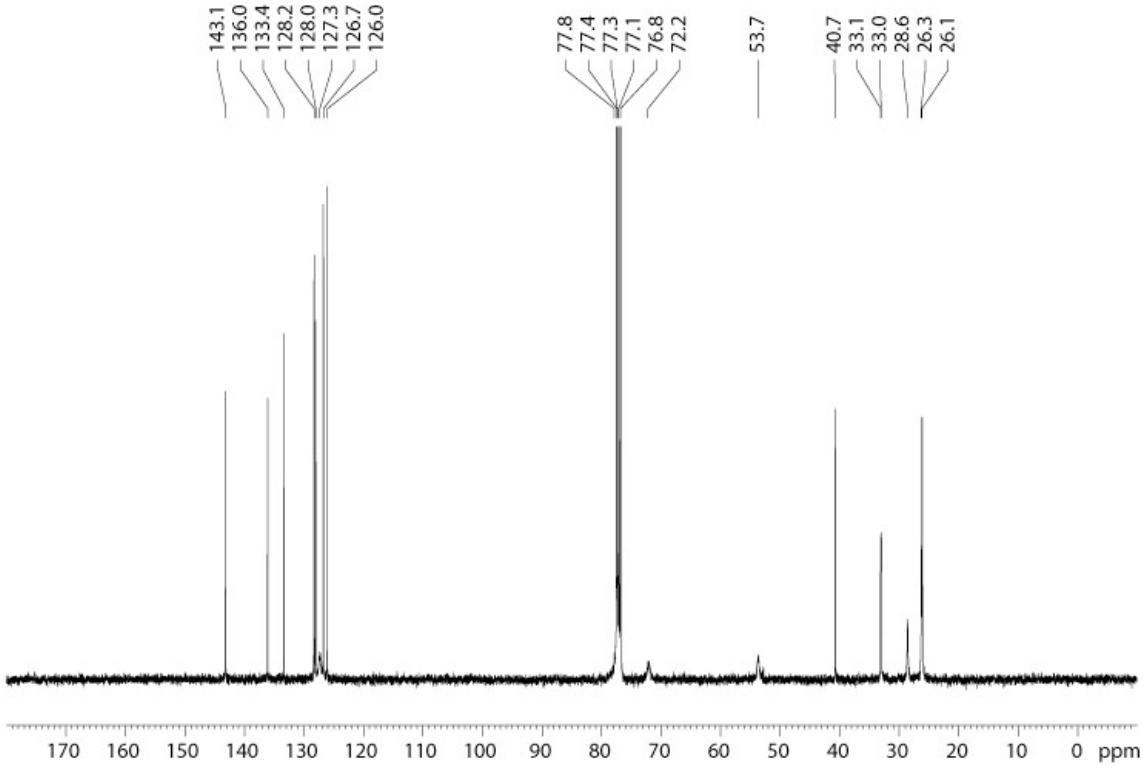

7.28
7.19
7.18
7.17
7.16
7.15
7.13
7.11
7.10
5.85
5.82
5.80
5.78
5.55
5.53
5.51
4.28
4.26
3.53
3.52
3.50
3.49
3.15
3.13
3.10
3.07
3.06
2.96
2.95
2.94
2.91
2.90
2.21
2.18
2.16
2.14
1.49
1.48
1.46
1.45
1.44
1.43
1.42
1.40
1.37
1.35
0.96
0.94
0.92
N
OH
compound 3b
8
7
6
5
4
3
2
1
0 ppm
4.06
1.10
1.00
0.96
1.00
2.07
1.10
2.11
4.54
3.35

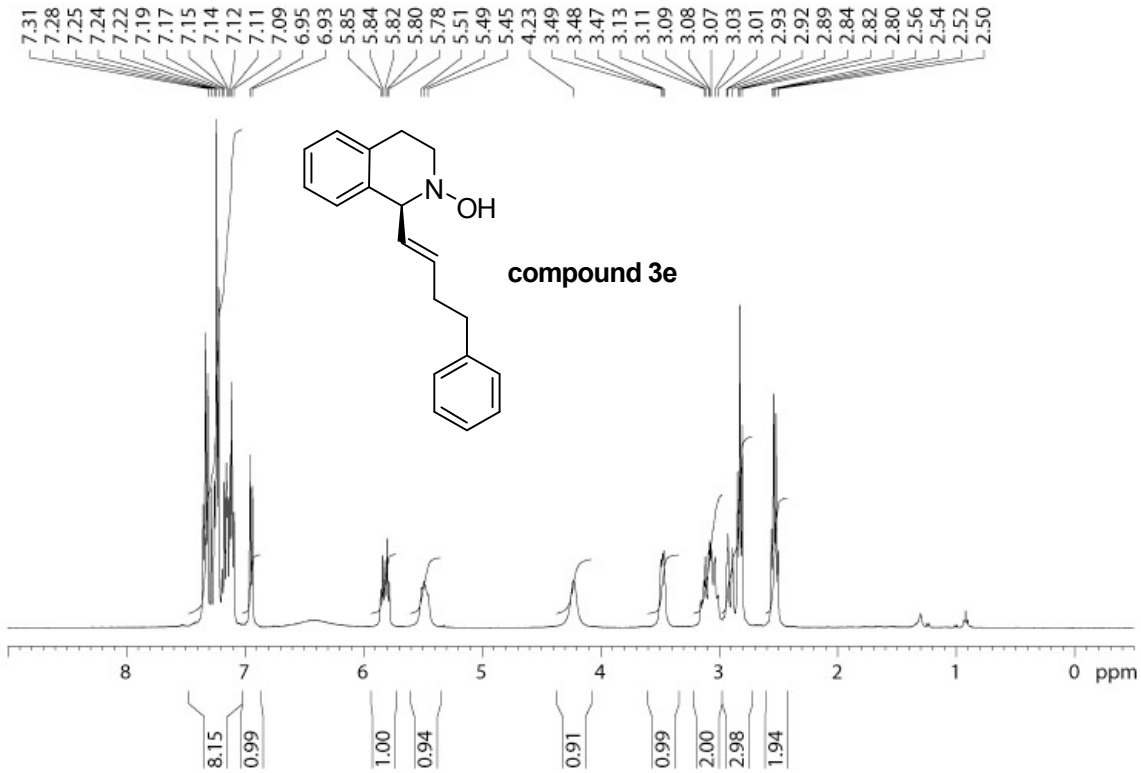

137.4
136.0
133.4
129.8
128.3
128.1
126.7
126.1
77.5
77.2
76.8
72.0
53.7
32.3
31.6
28.6
22.5
14.1
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

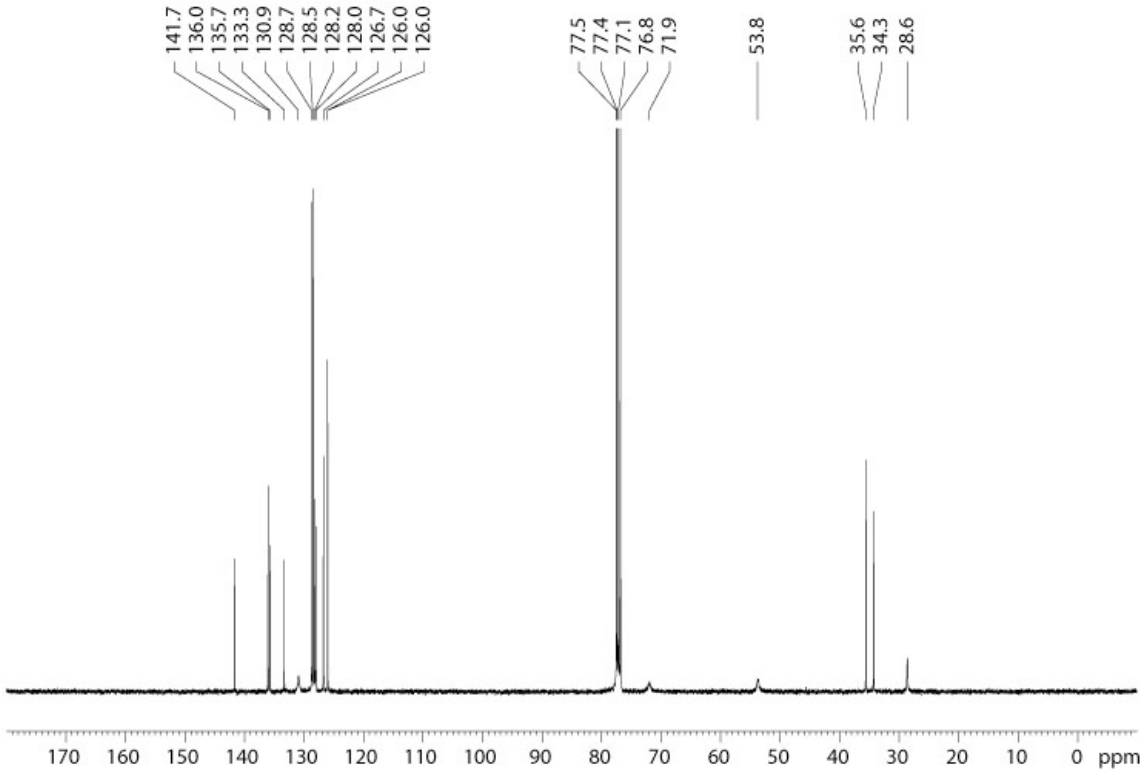

7.18 7.17 7.17 7.16 7.16 7.15 7.13 7.12 7.11 7.10 7.09
5.59 5.35 5.33 5.32 5.30 5.29 3.55 3.54 3.52 3.51 3.14 3.13 3.10 2.96 2.95 2.93 2.92 1.52 1.51 1.50 1.49 1.47 1.47 0.79 0.79 0.78 0.77 0.77 0.76 0.75 0.75 0.74 0.48 0.46 0.46 0.45 0.45 0.44
N OH
compound 3c
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.76 1.17 1.21 0.88 1.00 1.93 1.07 1.02 2.08 2.09

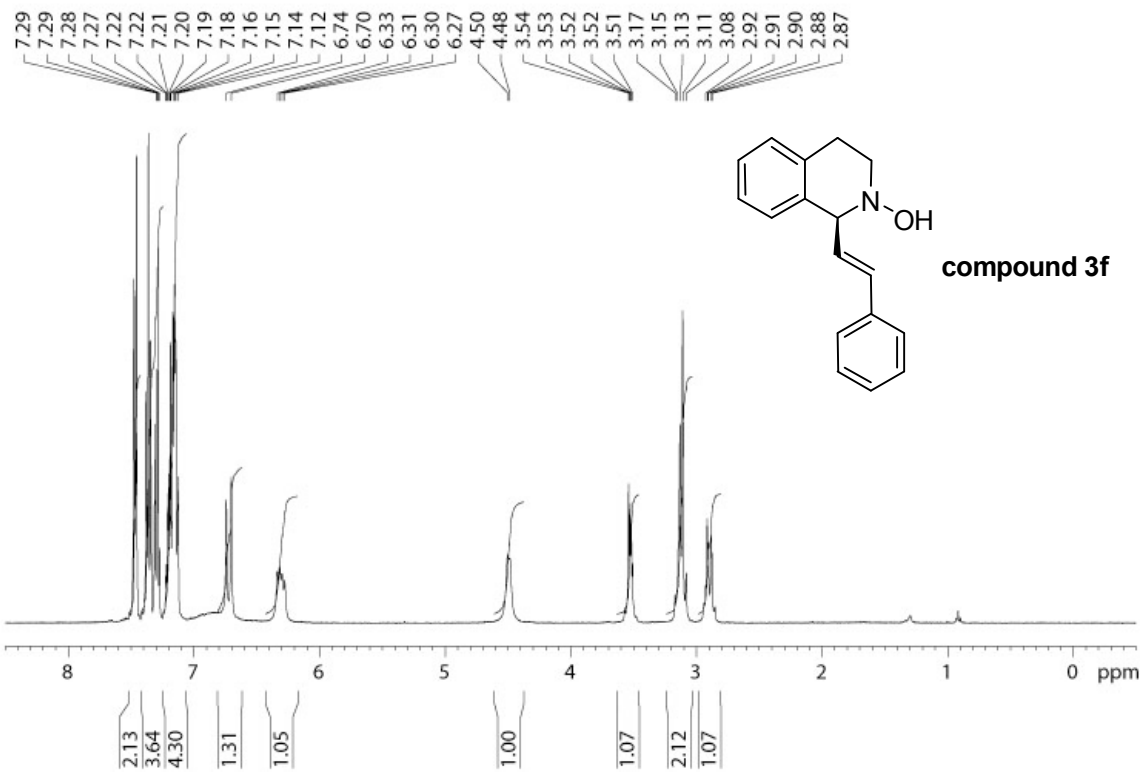

141.7 135.3 133.1 128.4 128.2 127.0 126.6 126.2
77.5 77.4 77.2 76.9 71.5
53.1
27.9
13.9 7.2 7.1
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

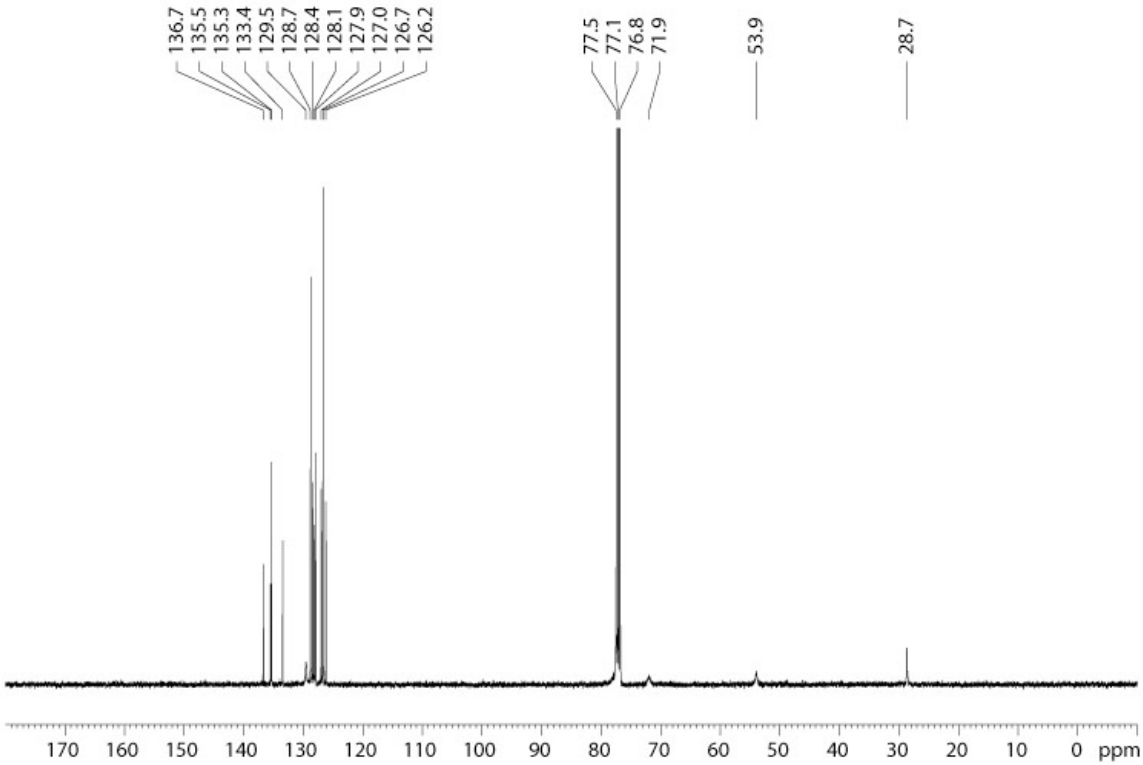

7.26 7.16 7.16 7.15 7.15 7.14 7.14 7.13 7.12 7.12 7.10 7.09 7.08 5.80 5.78 5.76 5.75 3.51 3.50 3.49 3.09 3.08 2.92 2.88 1.82 1.79 1.78 1.78 1.76 1.74 1.73 1.32 1.32 1.29 1.29 1.28 1.26 1.23 1.22 1.20 1.20 1.19 1.18 1.17 1.17 1.16 1.15 1.14 1.14
N
OH
compound 3d
8 7 6 5 4 3 2 1 0 ppm
3.98 1.03 1.00 0.93 0.99 1.98 1.04 1.01 5.14 5.15

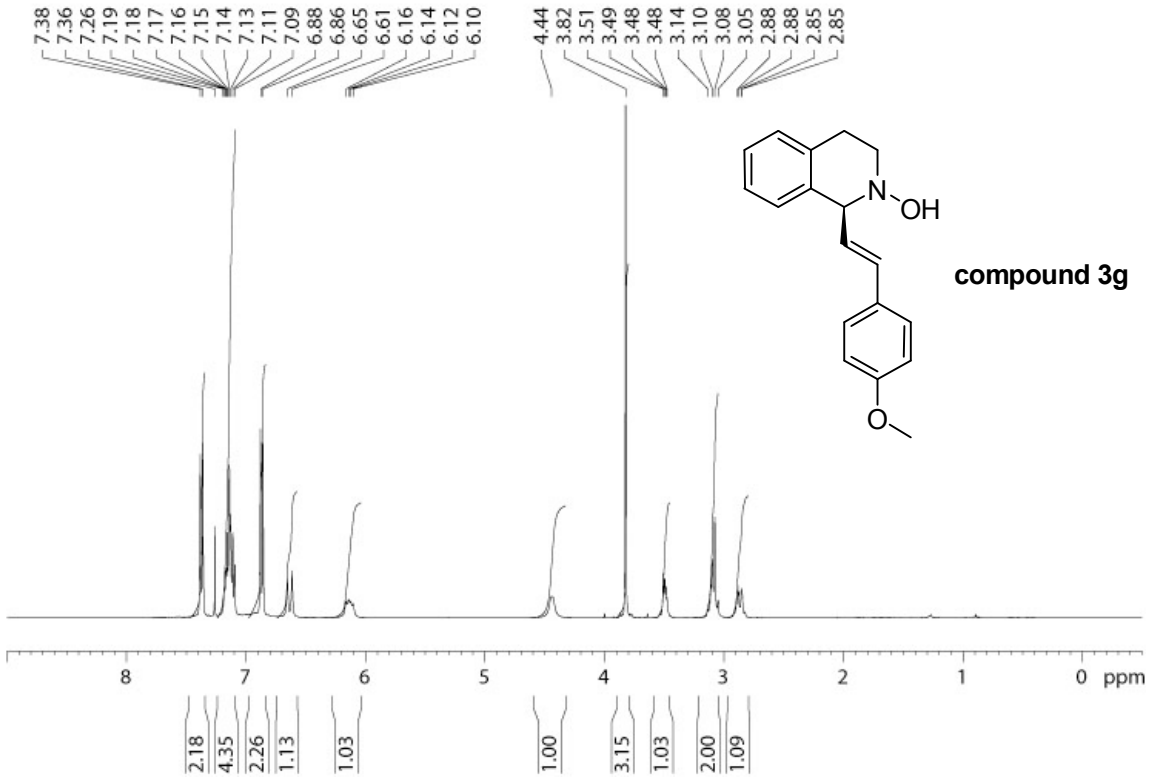

143.1 136.0 133.4 128.2 128.0 127.3 126.7 126.0
77.8 77.4 77.3 77.1 76.8 72.2
53.7
40.7 33.1 33.0 28.6 26.3 26.1
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.31
7.28
7.25
7.24
7.22
7.19
7.17
7.15
7.14
7.12
7.11
7.09
6.95
6.93
5.85
5.84
5.82
5.80
5.78
5.51
5.49
5.45
4.23
3.49
3.48
3.47
3.13
3.11
3.09
3.08
3.07
3.03
3.01
2.93
2.92
2.89
2.84
2.82
2.80
2.56
2.54
2.52
2.50
N
OH
compound 3e
8
7
6
5
4
3
2
1
0 ppm
8.15
0.99
1.00
0.94
0.91
0.99
2.00
2.98
1.94

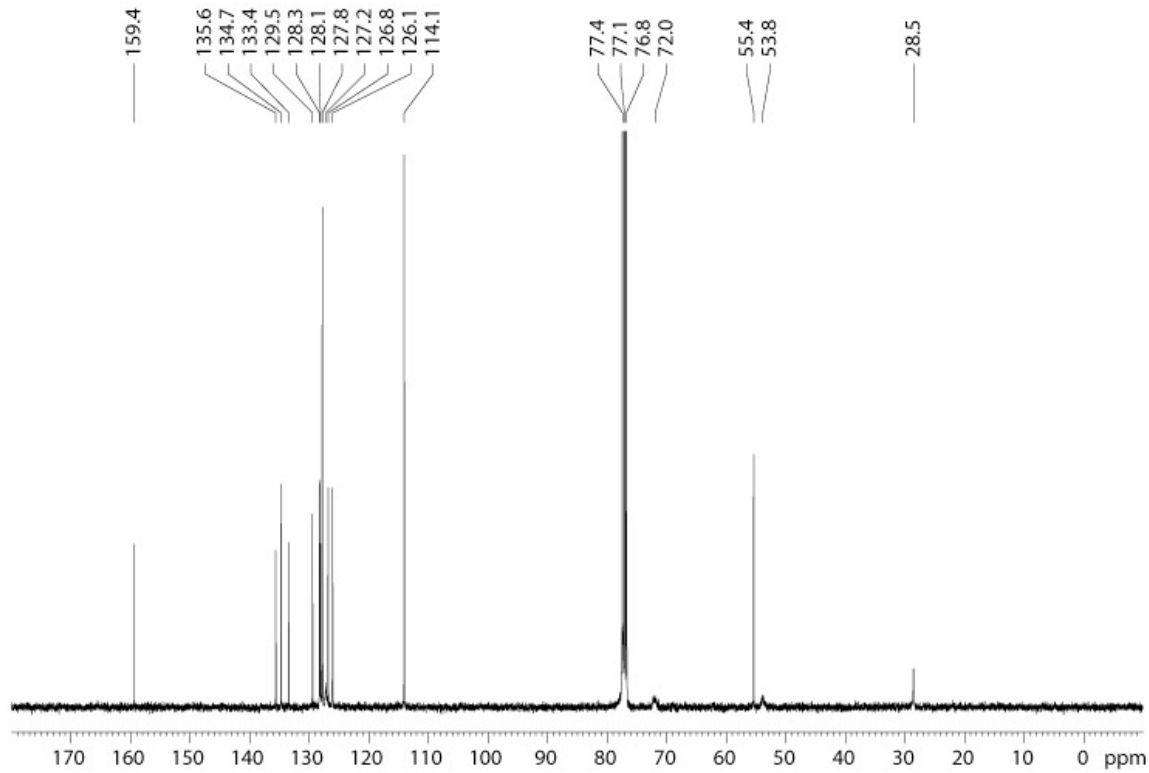

141.7
136.0
135.7
133.3
130.9
128.7
128.5
128.2
128.0
126.7
126.0
126.0
77.5
77.4
77.1
76.8
71.9
53.8
35.6
34.3
28.6
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

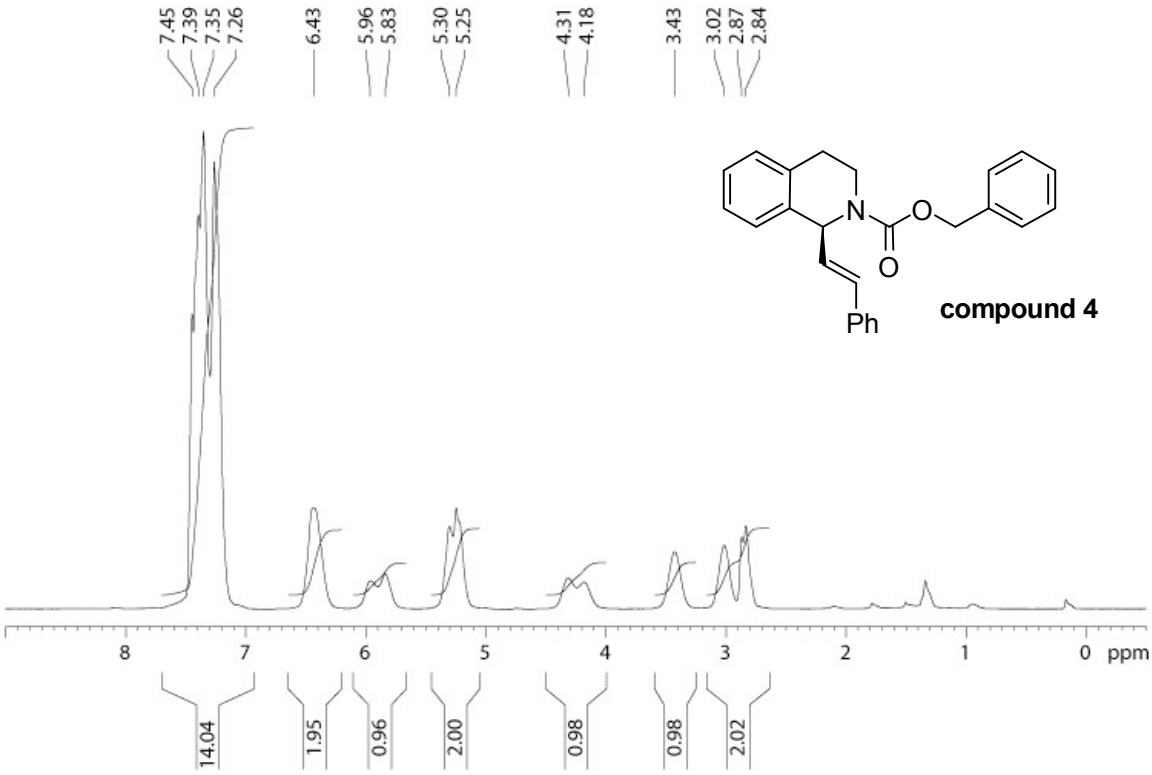

7.29
7.29
7.28
7.27
7.22
7.22
7.21
7.20
7.19
7.18
7.16
7.15
7.14
7.12
6.74
6.70
6.33
6.31
6.30
6.27
4.50
4.48
3.54
3.53
3.52
3.52
3.51
3.17
3.15
3.13
3.11
3.08
2.92
2.91
2.90
2.88
2.87
N
OH
compound 3f
8
7
6
5
4
3
2
1
0 ppm
2.13
3.64
4.30
1.31
1.05
1.00
1.07
2.12
1.07

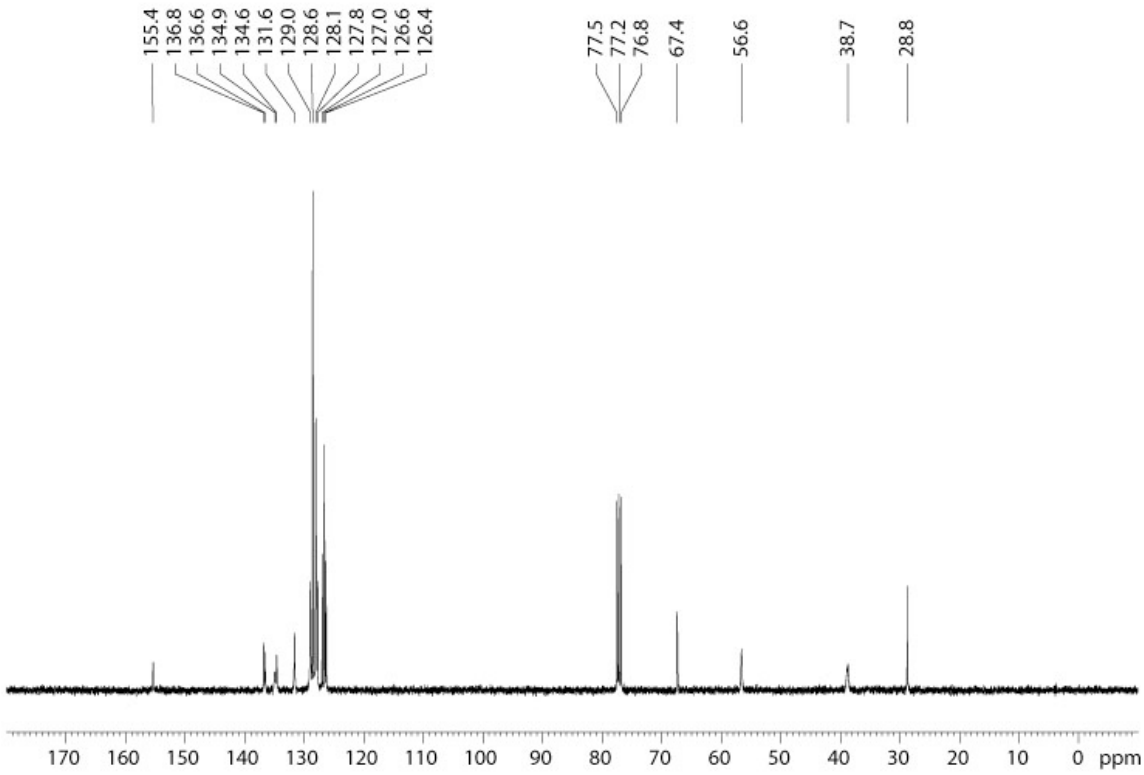

136.7
135.5
135.3
133.4
129.5
128.7
128.4
128.1
127.9
127.0
126.7
126.2
77.5
77.1
76.8
71.9
53.9
28.7
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

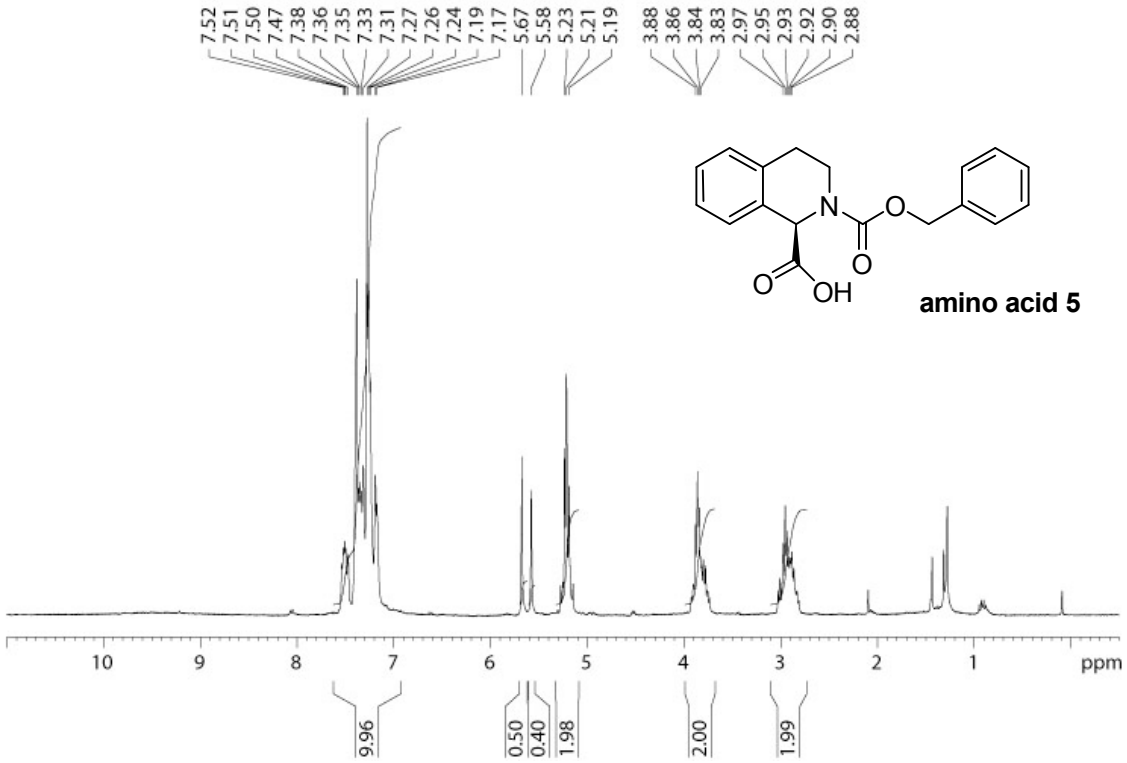

7.38
7.36
7.26
7.19
7.18
7.17
7.16
7.15
7.14
7.13
7.11
7.09
6.88
6.86
6.65
6.61
6.16
6.14
6.12
6.10
4.44
3.82
3.51
3.49
3.48
3.48
3.14
3.10
3.08
3.05
2.88
2.88
2.85
2.85
N
OH
O
8
7
6
5
4
3
2
1
0 ppm
2.18
4.35
2.26
1.13
1.03
1.00
3.15
1.03
2.00
1.09

compound 3g

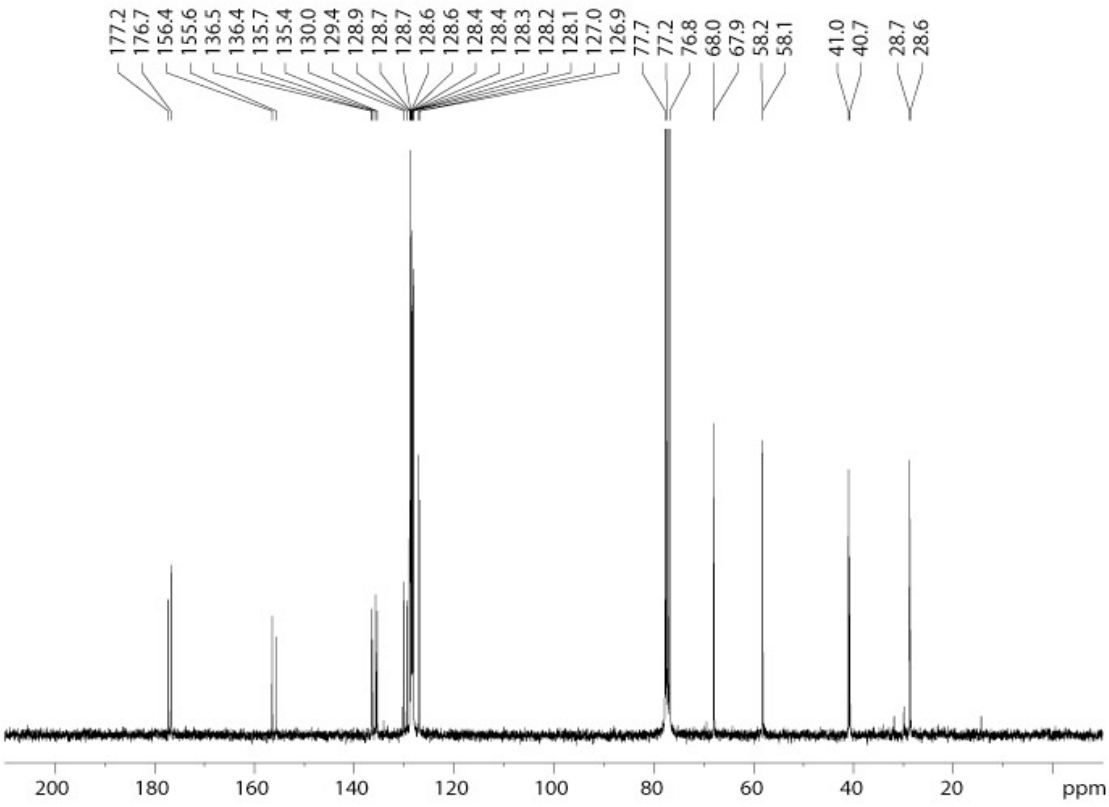

159.4
135.6
134.7
133.4
129.5
128.3
128.1
127.8
127.2
126.8
126.1
114.1
77.4
77.1
76.8
72.0
55.4
53.8
28.5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


7.45
7.39
7.35
7.26
6.43
5.96
5.83
5.30
5.25
4.31
4.18
3.43
3.02
2.87
2.84
N
O
O
Ph
compound 4
8
7
6
5
4
3
2
1
0 ppm
14.04
1.95
0.96
2.00
0.98
0.98
2.02


155.4
136.8
136.6
134.9
134.6
131.6
129.0
128.6
128.1
127.8
127.0
126.6
126.4
77.5
77.2
76.8
67.4
56.6
38.7
28.8
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm


7.52
7.51
7.50
7.47
7.38
7.36
7.35
7.33
7.31
7.27
7.26
7.24
7.19
7.17
5.67
5.58
5.23
5.21
5.19
3.88
3.86
3.84
3.83
2.97
2.95
2.93
2.92
2.90
2.88
N
O
O
O
OH
10
9
8
7
6
5
4
3
2
1
ppm
9.96
0.50
0.40
1.98
2.00
1.99

amino acid 5


177.2
176.7
156.4
155.6
136.5
136.4
135.7
135.4
130.0
129.4
128.9
128.7
128.7
128.6
128.6
128.4
128.4
128.3
128.2
128.1
127.0
126.9
77.7
77.2
76.8
68.0
67.9
58.2
58.1
41.0
40.7
28.7
28.6
200
180
160
140
120
100
80
60
40
20
ppm

References

1. (a) Richmond, M. L.; Seto, C. T. *J. Org. Chem*. **2003**, *68*, 7505-7508. (b) Richmond, M. L.; Seto, C. T. *J. Org. Chem*. **2005**, *70*, 8835-8840.
2. Belkacemi, D.; Malpass, J. R. *Tetrahedron* **1993**, *49*, 9105-9110.
3. Bajusz, S.; Mohai, L.; Feher, A.; Lavich, J.; Szell, G.; Veghelyi, B. PCT Int. Appl. WO 9312091 A1 930624, 1993 (36 pp).