Iridium-Catalyzed Asymmetric *trans*-Selective Hydrogenation of 1,3-Disubstituted Isoquinolines

Alexia N. Kim, Aurapat Ngamnithiporn, Michael D. Bartberger, and Brian M. Stoltz*

Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

stoltz@caltech.edu

Table of Contents:

Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[1] Reaction progress was monitored by thin-layer chromatography (TLC) or Agilent 1290 UHPLC-MS. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, with $KMnO_4$ or *p*-anisaldehyde staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 μm) was used for flash chromatography. ^{1}H NMR spectra were recorded on Bruker 400 MHz or Varian Mercury 300 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR spectra were recorded on Bruker 400 MHz spectrometer (100 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm). ^{19}F NMR spectra were recorded on Varian Mercury 300 MHz spectrometer (282 MHz). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Optical rotations were measured with a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in 10 mg/1 mL, solvent). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system utilizing Chiralpak (AD-H, AS-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source, or an Agilent 6230 TOF, in electrospray ionization (ESI+).

A crystal was mounted on a polyimide MiTeGen loop with STP Oil Treatment and placed under a nitrogen stream. Low temperature (100K) X-ray data (ϕ-and ω-scans) were collected with a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON II CPAD detector with Cu K_α radiation (λ = 1.54178 Å) from an IμS micro-source for the structure of compound V21097. The structure was solved by direct methods using SHELXS[2] and refined against F^2 on all data by full-matrix least squares with SHELXL-2017[3] using established refinement techniques.[4] All non-hydrogen atoms were refined using anisotropic displacement parameters. Hydrogen atoms were placed in idealized positions and the coordinates refined (each of the two disordered pairs were constrained to the same position). The isotropic displacement parameters of all hydrogen atoms were fixed at 1.2 times (1.5 times for methyl groups and alcohol) the U_{eq} value of the bonded atom.

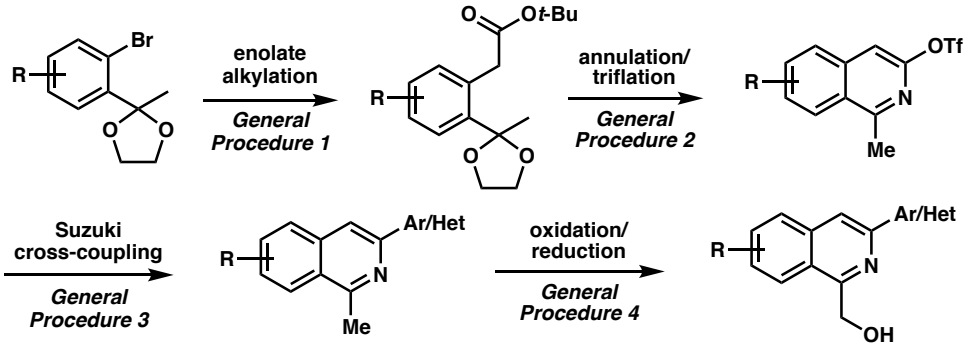
Reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated.

List of Abbreviations:

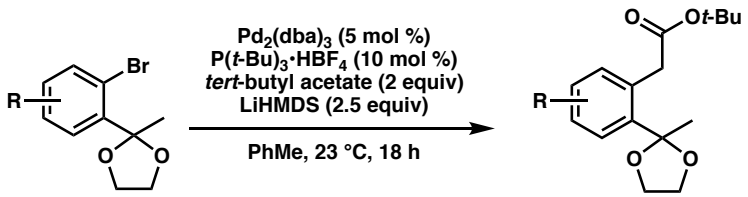
ee – enantiomeric excess, SFC – supercritical fluid chromatography, TLC – thin-layer chromatography, IPA – isopropanol, LiHMDS – lithium bis(trimethylsilyl)amide, dba – dibenzylideneacetone, RBF – round-bottom flask, TFA – trifluoroacetic acid, TBAI – tetrabutylammonium iodide, TBABr – tetrabutylammonium bromide, TBACl – tetrabutylammonium chloride, Boc_2O – di-*tert*-butyl dicarbonate, HPLC – high-performance liquid chromatography, DMAP – 4-dimethylaminopyridine, THF – tetrahydrofuran, BnBr – benzyl bromide, CDI – 1,1'-carbonyldiimidazole

Syntheses of Hydroxymethyl 1,3-Disubstituted Isoquinolines

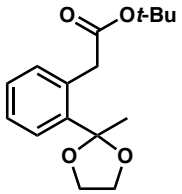
General sequence:



General procedure 1: Enolate alkylation of aryl bromide



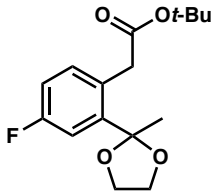
S1a–b *S2a–b*



S2a

***tert*-butyl 2-(2-(2-methyl-1,3-dioxolan-2-yl)phenyl)acetate (S2a):** To a Schlenk flask were added P(*t*-Bu)$_3$•HBF$_4$ (1.4 g, 4.8 mmol, 0.1 equiv), $Pd_2(dba)_3$ (2.2 g, 2.4 mmol, 0.05 equiv), a solution of 2-(2-bromophenyl)-2-methyl-1,3-dioxolane **(S1a)** (12 g, 48 mmol, 0.42 M in toluene), and *tert*-butyl acetate (11 g, 97 mmol, 2 equiv), respectively. The reaction mixture was cooled to –78 °C and sparged with N_2 for 15 min. A degassed solution of LiHMDS (20 g, 121

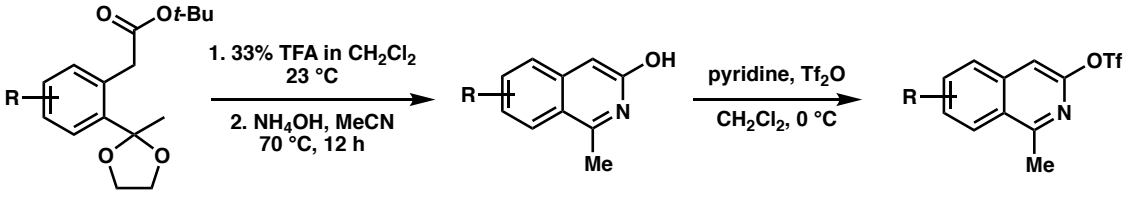
mmol, 1 M in toluene) was then added via syringe. The reaction mixture was sparged with N_2 for an additional 15 minutes at –78 °C, and allowed to slowly warm to room temperature. The reaction mixture was stirred at 23 °C for 18 h, and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O twice (2 x 100 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford **S2a** as a yellow oil (12.4 g, 44.5 mmol, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 1H), 7.20 – 7.06 (m, 3H), 3.96 – 3.83 (m, 2H), 3.71 (s, 2H), 3.68 – 3.55 (m, 2H), 1.60 (s, 3H), 1.39 (s, 9H); All characterization data match those reported in the literature.[5]



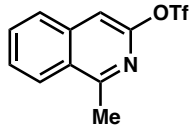
S2b

***tert*-butyl 2-(4-fluoro-2-(2-methyl-1,3-dioxolan-2-yl)phenyl)acetate (S2b):** Compound **S2b** was prepared using general procedure 1 and purified by column chromatography (10% EtOAc in hexanes) to provide a colorless solid (1.9 g, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, J = 10.3, 2.8 Hz, 1H), 7.15 (dd, J = 8.4, 5.7 Hz, 1H), 6.94 (td, J = 8.2, 2.9 Hz, 1H), 4.06 – 3.90 (m, 2H), 3.74 (s, 2H), 3.72 – 3.69 (m, 2H), 1.65 (s, 3H), 1.45 (s, 9H); All characterization data match those reported in the literature.[5]

General procedure 2: Isoquinoline annulation and triflation



S2a–b ***S3a–b***

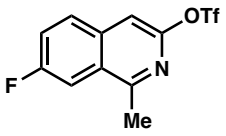


S3a

1-methylisoquinolin-3-yl trifluoromethanesulfonate (S3a): To a RBF was added ester **S2a** (12.4 g, 48 mmol), anhydrous CH_2Cl_2 (480 mL, 0.1 M), and TFA (160 mL, 33% volume of CH_2Cl_2), respectively. The reaction mixture was stirred at 23 °C for 2 h, and then concentrated in vacuo. The crude mixture was transferred to a Schlenk tube, and dissolved in MeCN (48 mL, 1 M) and aqueous NH_4OH (28–30%, 96 mL, 200% volume of MeCN). The tube was sealed with a Kontes valve to prevent loss of gaseous ammonia and stirred at 70 °C. Within 1 h, the yellow

solid of the 3-hydroxyisoquinoline began to precipitate from the solution. After stirring for 18 hours at 70 °C, the reaction mixture was cooled to room temperature and placed in a –20 °C freezer overnight, and the yellow solid was collected via vacuum filtration. This yellow powder was then washed with cold MeCN and dried under high vacuum to provide a 3-hydroxyisoquinoline intermediate (3.9 g, 24 mmol). If any starting material remains, the filtrate could be transferred to a flask and concentrated in vacuo to undergo a second condensation reaction.

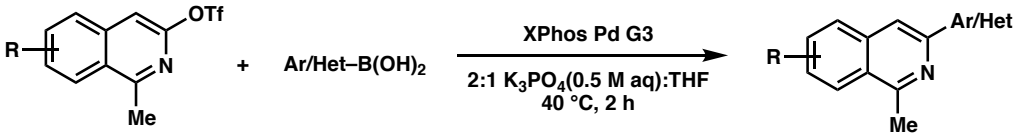
To a separate flame-dried RBF containing CH_2Cl_2 (120 mL, 0.2 M) and freshly distilled pyridine (19.6 mL, 242 mmol, 10 equiv), the collected intermediate (3.9 g, 24 mmol) was added, and the flask was cooled to 0 °C. Trifluoromethanesulfonic anhydride (8.2 mL, 48 mmol, 2 equiv) was then added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ at 0 °C, and then slowly warmed to room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 x 100 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (10% EtOAc in hexanes) to afford **S3a** as a pale yellow oil (5.0 g, 17 mmol, 36% yield over 3 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.88 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.76 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.67 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.42 (s, 1H), 2.97 (s, 3H); All characterization data match those reported in the literature.[5]



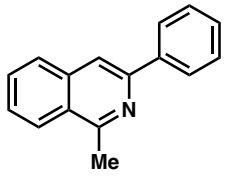
S3b

7-fluoro-1-methylisoquinolin-3-yl trifluoromethanesulfonate (S3b): Compound **S3b** was prepared using general procedure 2 and purified by column chromatography (10% EtOAc in hexanes) to provide a pale brown oil (1.3 g, 39% yield over 3 steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 9.0, 5.3 Hz, 1H), 7.76 (dd, *J* = 9.6, 2.5 Hz, 1H), 7.56 (ddd, *J* = 8.9, 8.0, 2.5 Hz, 1H), 7.43 (s, 1H), 2.92 (s, 3H); All characterization data match those reported in the literature.[5]

General procedure 3: Suzuki cross-coupling

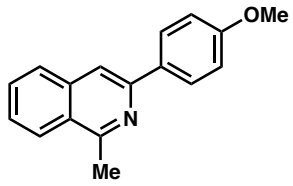


S3a–b ***3d, S4b–n***



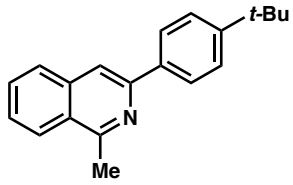
3d

1-methyl-3-phenylisoquinoline (3d): To a flame-dried 20-mL scintillation vial capped with a PTFE-lined silicone septum was added XPhos Pd G3 (50 mg, 0.05 mmol, 0.02 equiv) and phenyl boronic acid (548 mg, 3.8 mmol, 1.5 equiv). The reaction vial was then evacuated and backfilled with N_2 three times. The isoquinoline triflate **S3a** (720 mg, 2.5 mmol) in degassed THF (7 mL, 0.3 M) was then added to the vial, followed by degassed 0.5 M K_3PO_4 solution (13 mL, 0.2 M). The reaction was then stirred at 40 °C for 2 hours. Afterwards, the reaction was diluted with water and the aqueous layer was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, concentrated in vacuo, and purified by column chromatography (5% EtOAc in hexanes) to afford **3d** as a white solid (495 mg, 2.3 mmol, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.13 (m, 3H), 7.93 (s, 1H), 7.86 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.67 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.42 – 7.38 (m, 1H), 3.05 (s, 3H); All characterization data match those reported in the literature.[5]



S4b

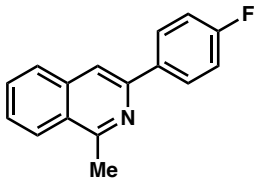
3-(4-methoxyphenyl)-1-methylisoquinoline (S4b): Compound **S4b** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a white solid (101 mg, 99% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.07 (m, 3H), 7.89 – 7.81 (m, 2H), 7.68 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.20 – 7.16 (m, 2H), 3.04 (s, 3H); All characterization data match those reported in the literature.[5]



S4c

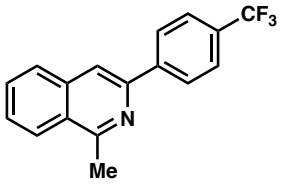
3-(4-(*tert*-butyl)phenyl)-1-methylisoquinoline (S4c): Compound **S4c** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a pale yellow oil (164 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 3H), 7.84 (s, 1H), 7.81 (d, *J* = 8.5, 1H), 7.64 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.53 (ddd, *J* = 8.2, 6.8, 1.3 Hz,

1H), 7.06 – 7.01 (m, 2H), 3.88 (s, 3H), 3.03 (s, 3H); All characterization data match those reported in the literature.[5]



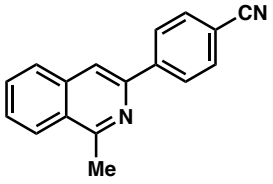
S4d

3-(4-fluorophenyl)-1-methylisoquinoline (S4d): Compound **S4d** was prepared using general procedure 3 and purified by column chromatography (10% EtOAc in hexanes) to provide a white solid (158 mg, 96% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.4 Hz, 1H) 8.06 (d, *J* = 8.5 Hz, 2H), 7.90 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.66 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.57 – 7.52 (m, 3H), 3.04 (s, 3H), 1.38 (s, 9H); All characterization data match those reported in the literature.[5]



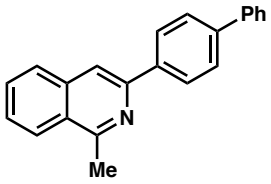
S4e

1-methyl-3-(4-(trifluoromethyl)phenyl)isoquinoline (S4e): Compound **S4e** was prepared using general procedure 3 and purified by column chromatography (2% to 3% EtOAc in hexanes) to provide a white solid (449 mg, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.1 Hz, 2H), 8.15 (d, *J* = 8.4, 1H), 7.96 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.73 (m, 2H), 7.73 – 7.67 (m, 1H), 7.63 – 7.59 (m, 1H), 3.05 (s, 3H); All characterization data match those reported in the literature.[5]



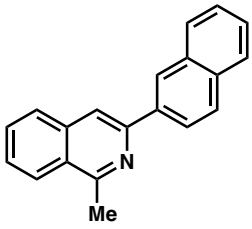
S4f

4-(1-methylisoquinolin-3-yl)benzonitrile (S4f): Compound **S4f** was prepared using general procedure 3 and purified by column chromatography (10% to 20% EtOAc in hexanes) to provide a white solid (122 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.22 (m, 2H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 8.3, 1H), 7.82 – 7.75 (m, 2H), 7.73 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.64 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 3.05 (s, 3H); All characterization data match those reported in the literature.[5]



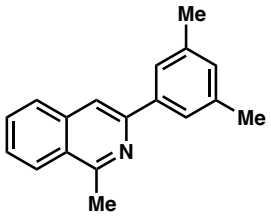
S4g

3-([1,1'-biphenyl]-4-yl)-1-methylisoquinoline (S4g): Compound **S4g** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a colorless solid (191 mg, 94% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 – 8.22 (m, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.98 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.75 – 7.73 (m, 2H), 7.70 – 7.67 (m, 3H), 7.58 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.39 – 7.37 (m, 1H), 3.06 (s, 3H); All characterization data match those reported in the literature.[5]



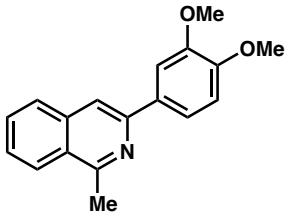
S4h

1-methyl-3-(naphthalen-2-yl)isoquinoline (S4h): Compound **S4h** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a white solid (142 mg, 77% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.27 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.16 (dq, *J* = 8.3, 1.0 Hz, 1H), 8.07 (s, 1H), 8.00 – 7.96 (m, 2H), 7.91 – 7.86 (m, 2H), 7.70 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.59 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.56 – 7.46 (m, 2H), 3.09 (s, 3H); All characterization data match those reported in the literature.[5]



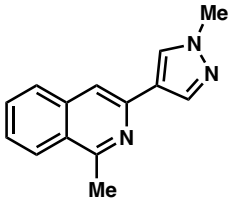
S4i

3-(3,5-dimethylphenyl)-1-methylisoquinoline (S4i): Compound **S4i** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a white solid (156 mg, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.90 (s, 1H), 7.85 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.75 (s, 2H), 7.66 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.05 (s, 1H), 3.05 (s, 3H), 2.43 (s, 6H); All characterization data match those reported in the literature.[5]



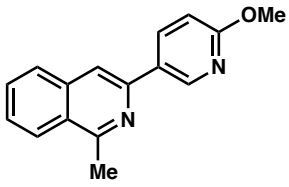
S4j

3-(3,4-dimethoxyphenyl)-1-methylisoquinoline (S4j): Compound **S4j** was prepared using general procedure 3 and purified by column chromatography (20% EtOAc in hexanes) to provide a white solid (248 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4, 1H), 7.89 – 7.81 (m, 2H), 7.77 (d, *J* = 2.1 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.55 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 4.04 (s, 3H), 3.95 (s, 3H), 3.04 (s, 3H); All characterization data match those reported in the literature.[5]



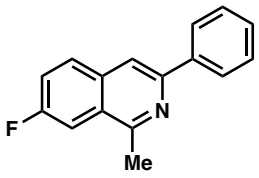
S4k

1-methyl-3-(1-methyl-1*H*-pyrazol-4-yl)isoquinoline (S4k): Compound **S4k** was prepared using general procedure 3 and purified by column chromatography (50% to 60% EtOAc in hexanes) to provide a white solid (124 mg, 64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 1H), 8.04 – 8.00 (m, 2H), 7.77 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.54 – 7.47 (m, 1H), 3.98 (s, 3H), 2.97 (s, 3H); All characterization data match those reported in the literature.[5]



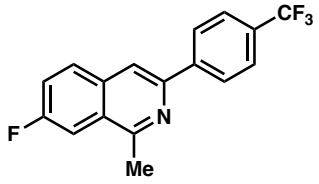
S4l

3-(6-methoxypyridin-3-yl)-1-methylisoquinoline (S4l): Compound **S4l** was prepared from triflate **S3a** using general procedure 3 and purified by column chromatography (15% EtOAc in hexanes) to afford a white solid (232 mg, 90% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, *J* = 2.5, 0.8 Hz, 1H), 8.36 (dd, *J* = 8.6, 2.5 Hz, 1H), 8.11 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.67 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 6.87 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.01 (s, 3H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 159.0, 147.7, 145.7, 137.6, 136.8, 130.3, 129.2, 127.6, 126.9, 126.6, 125.8, 114.5, 110.8, 53.8, 22.8; IR (Neat Film, NaCl) 2937, 2363, 1604, 1568, 1498, 1443, 1326, 1278, 1254, 1119, 1021, 831, 745; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{15}N_2O$ $[M+H]^+$: 251.1184, found 251.1185.



S4m

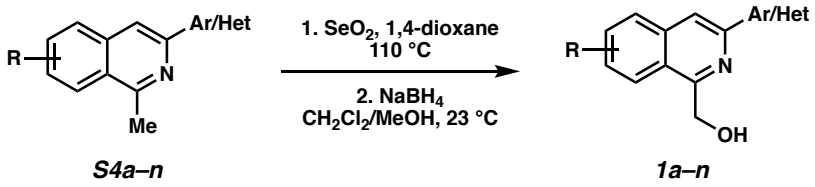
7-fluoro-1-methyl-3-phenylisoquinoline (S4m): Compound **S4m** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a white solid (254 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.11 (m, 2H), 7.90 (s, 1H), 7.85 (dd, *J* = 9.2, 5.7 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.54 – 7.48 (m, 2H), 7.48 – 7.38 (m, 2H), 2.99 (s, 3H); All characterization data match those reported in the literature.[5]



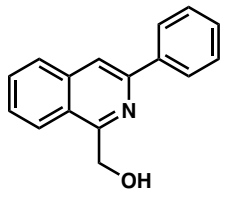
S4n

7-fluoro-1-methyl-3-(4-(trifluoromethyl)phenyl)isoquinoline (S4n): Compound **S4n** was prepared using general procedure 3 and purified by column chromatography (5% EtOAc in hexanes) to provide a white solid (349 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.0 Hz, 2H), 7.94 (s, 1H), 7.90 – 7.85 (m, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.71 – 7.69 (m, 1H), 7.53 – 7.43 (m, 1H), 2.99 (s, 3H); All characterization data match those reported in the literature.[5]

General procedure 4: Oxidation and reduction to hydroxymethyl isoquinoline



S4a–n ***1a–n***

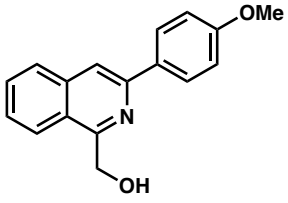


1a

(3-phenylisoquinolin-1-yl)methanol (1a): To a 20-mL microwave vial under N_2 containing a magnetic stir bar was added SeO_2 (375 mg, 3.4 mmol, 2 equiv), isoquinoline **S4a** (370 mg, 1.7 mmol), and 1,4-dioxane (17 mL, 0.1 M). The reaction vial was then sealed and heated to 110 °C while stirring for 2 hours. The reaction mixture was then cooled to 23 °C, filtered through celite,

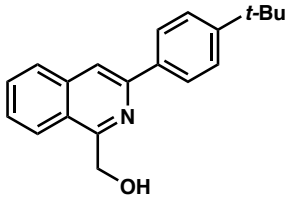
and rinsed with EtOAc. The filtrate was then concentrated in vacuo to afford the crude aldehyde intermediate that was used in the next step without further purification.

To a scintillation vial containing the crude aldehyde in 4:1 CH_2Cl_2:MeOH (0.1 M) was added sodium borohydride (96 mg, 2.5 mmol, 1.5 equiv) at 23 °C. The reaction mixture was stirred until no starting material remained by TLC, and then quenched by the addition of citric acid monohydrate (355 mg, 1.7 mmol, 1 equiv). The reaction mixture was stirred for an additional 10 minutes at 23 °C, then basified by the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (10% acetone in hexanes) to afford **1a** as a white solid (337 mg, 1.43 mmol, 85% yield over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.15 (d, J = 7.0 Hz, 2H), 8.03 (s, 1H), 7.94 – 7.92 (m, 2H), 7.73 (ddd, J = 8.3, 6.9, 1.1 Hz, 1H), 7.61 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.46 – 7.42 (m, 1H), 5.31 (s, 2H), 5.26 (br s, 1H, OH); All characterization data match those reported in the literature.[5]



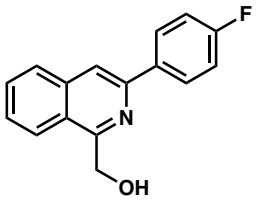
1b

(3-(4-methoxyphenyl)isoquinolin-1-yl)methanol (1b): Compound **1b** was prepared using general procedure 4 and purified by column chromatography (20% EtOAc in hexanes) to provide a white solid (148 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 2H), 7.93 (s, 1H), 7.91 – 7.85 (m, 2H), 7.69 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 7.56 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.06 – 7.03 (m, 2H), 5.28 (s, 3H), 3.89 (s, 3H); All characterization data match those reported in the literature.[5]



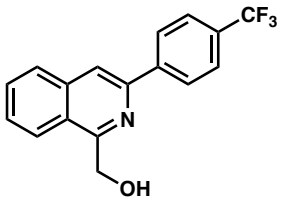
1c

((3-(4-(*tert*-butyl)phenyl)isoquinolin-1-yl)methanol (1c): Compound **1c** was prepared using general procedure 4 and purified by column chromatography (20% EtOAc in hexanes) to provide a white solid (135 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.06 (m, 2H), 8.00 (s, 1H), 7.97 – 7.85 (m, 2H), 7.72 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.58 – 7.52 (m, 2H), 5.30 (s, 3H), 1.40 (s, 9H); All characterization data match those reported in the literature.[5]



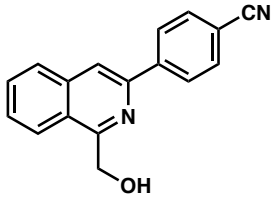
1d

(3-(4-fluorophenyl)isoquinolin-1-yl)methanol (1d): Compound **1d** was prepared using general procedure 4 and purified by column chromatography (20% EtOAc in hexanes) to provide a colorless solid (134 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.96 (s, 1H), 7.95 – 7.89 (m, 2H), 7.73 (ddd, *J* = 8.3, 6.9, 1.1 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.21 (dd, *J* = 8.9, 8.5 Hz, 2H), 5.30 (s, 2H), 5.17 (br s, 1H, OH); All characterization data match those reported in the literature.[5]



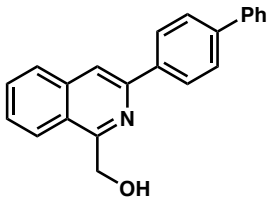
1e

(3-(4-(trifluoromethyl)phenyl)isoquinolin-1-yl)methanol (1e): Compound **1e** was prepared using general procedure 4 and purified by column chromatography (10% to 20% EtOAc in hexanes) to provide a white solid (302 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.8 Hz, 2H), 8.07 (s, 1H), 8.00 – 7.92 (m, 2H), 7.82 – 7.73 (m, 3H), 7.70 – 7.61 (m, 1H), 5.32 (s, 2H), 5.10 (br s, 1H, OH); All characterization data match those reported in the literature.[5]



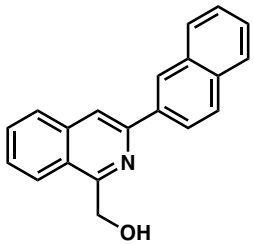
1f

4-(1-(hydroxymethyl)isoquinolin-3-yl)benzonitrile (1f): Compound **1f** was prepared using general procedure 4 and purified by column chromatography (30% EtOAc in hexanes) to provide a white solid (112 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.18 (m, 2H), 8.09 (s, 1H), 7.97 (m, 2H), 7.86 – 7.74 (m, 3H), 7.68 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 5.32 (s, 2H), 4.99 (s, 1H); All characterization data match those reported in the literature.[5]



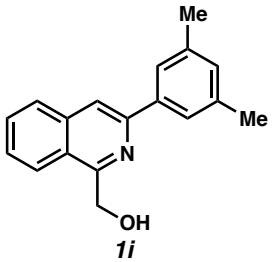
1g

(3-([1,1'-biphenyl]-4-yl)isoquinolin-1-yl)methanol (1g): Compound **1g** was prepared using general procedure 4 and purified by column chromatography (20% EtOAc in hexanes) to provide a colorless solid (79 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.20 (m, 2H), 8.07 (s, 1H), 7.98 – 7.88 (m, 2H), 7.81 – 7.66 (m, 5H), 7.62 (ddd, *J* = 8.4, 6.9, 1.2 Hz, 1H), 7.49 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.43 – 7.34 (m, 1H), 5.32 (s, 3H); All characterization data match those reported in the literature.[5]



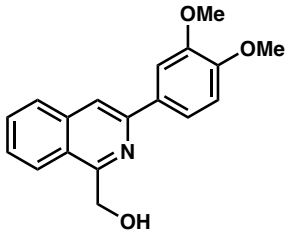
1h

(3-(naphthalen-2-yl)isoquinolin-1-yl)methanol (1h): Compound **1h** was prepared using general procedure 4 and purified by column chromatography (20% EtOAc in hexanes) to provide a white solid (124 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.27 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.16 (s, 1H), 8.05 – 7.93 (m, 4H), 7.91 – 7.89 (m, 1H), 7.75 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.62 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.58 – 7.47 (m, 2H), 5.34 (s, 3H); All characterization data match those reported in the literature.[5]



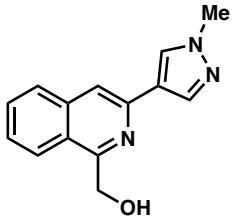
1i

(3-(3,5-dimethylphenyl)isoquinolin-1-yl)methanol (1i): Compound **1i** was prepared using general procedure 4 and purified by column chromatography (20% EtOAc in hexanes) to provide a white solid (155 mg, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.94 – 7.91 (m, 2H), 7.78 – 7.76 (m, 2H), 7.72 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.09 (s, 1H), 5.30 (s, 3H), 2.44 (s, 6H); All characterization data match those reported in the literature.[5]



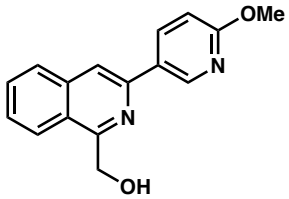
1j

(3-(3,4-dimethoxyphenyl)isoquinolin-1-yl)methanol (1j): Compound **1j** was prepared using general procedure 4 and purified by column chromatography (40% EtOAc in hexanes) to provide a white solid (168 mg, 64% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.93 – 7.90 (m, 2H), 7.77 – 7.67 (m, 3H), 7.58 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.03 – 7.01 (m, 1H), 5.30 (s, 2H), 5.26 (br s, 1H, OH), 4.03 (s, 3H), 3.97 (s, 3H); All characterization data match those reported in the literature.[5]



1k

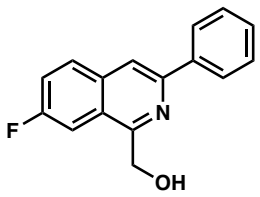
(3-(1-methyl-1*H*-pyrazol-4-yl)isoquinolin-1-yl)methanol (1k): Compound **1k** was prepared using general procedure 4 and purified by column chromatography (70% to 80% EtOAc in hexanes + 1% NEt_3) to provide a pale beige solid (93 mg, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.95 (m, 2H), 7.85 – 7.79 (m, 2H), 7.71 – 7.59 (m, 2H), 7.53 – 7.49 (m, 1H), 5.21 (s, 2H), 3.98 (s, 3H); All characterization data match those reported in the literature.[5]



1l

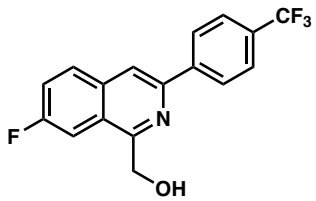
(3-(6-methoxypyridin-3-yl)isoquinolin-1-yl)methanol (1l): Compound **1l** was prepared from isoquinoline **S4l** using general procedure 4 and purified by column chromatography (20% to 30% EtOAc in hexanes) to provide a white solid (177 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 2.6, 0.7 Hz, 1H), 8.34 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.94 – 7.91 (m, 3H), 7.73 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 6.89 (dd, *J* = 8.7, 0.7 Hz, 1H), 5.30 (s, 2H), 5.10 (br s, 1H, OH), 4.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 157.7, 146.4, 145.7, 137.2, 137.0, 131.1, 128.2, 127.8, 127.6, 124.1, 123.3, 115.4, 111.1, 61.6, 53.9; IR (Neat Film, NaCl) 3380, 3058, 2948, 2363, 1624, 1606, 1573, 1504, 1447, 1380, 1326, 1286,

1088, 1024, 832, 747 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$: 267.1128, found 267.1131.



1m

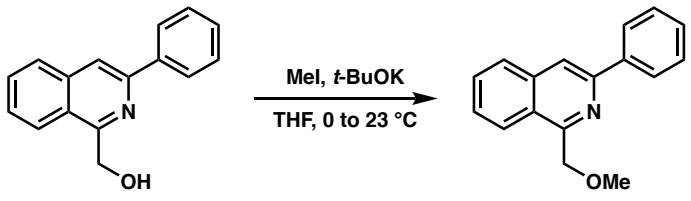
(7-fluoro-3-phenylisoquinolin-1-yl)methanol (1m): Compound **1m** was prepared using general procedure 4 and purified by column chromatography (10% EtOAc in hexanes) to provide a white solid (94 mg, 81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.0 Hz, 2H), 8.00 (s, 1H), 7.96 – 7.87 (m, 1H), 7.57 – 7.47 (m, 4H), 7.44 (td, *J* = 6.9, 6.4, 1.4 Hz, 1H), 5.21 (s, 2H), 5.11 (br s, 1H, OH); All characterization data match those reported in the literature.[5]



1n

(7-fluoro-3-(4-(trifluoromethyl)phenyl)isoquinolin-1-yl)methanol (1n): Compound **1n** was prepared using general procedure 4 and purified by column chromatography (10% EtOAc in hexanes) to provide a white solid (80 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.1 Hz, 2H), 8.02 (s, 1H), 7.95 (dd, *J* = 9.8, 5.4 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.58 – 7.47 (m, 2H), 5.21 (s, 2H), 4.94 (br s, 1H, OH); All characterization data match those reported in the literature.[5]

<u>Syntheses of 1,3-Disubstituted Isoquinolines with Different Directing Groups</u>



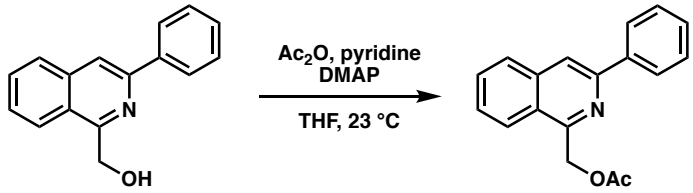
1a ***3a***

1-(methoxymethyl)-3-phenylisoquinoline (3a): To a scintillation vial containing a magnetic stir bar and isoquinoline **1a** (165 mg, 0.70 mmol) in THF (7 mL, 0.1 M) was added KO*t*-Bu (86 mg, 0.77 mmol, 1.1 equiv) at 23 °C. The resulting mixture was stirred for 5 minutes, then cooled to 0 °C, followed by the addition of MeI (0.05 mL, 0.77 mmol, 1.1 equiv). The reaction was allowed to slowly warm to 23 °C overnight and then was quenched with saturated aqueous NH_4Cl. The organic phase was collected and the aqueous phase was extracted with EtOAc (2 x 20 mL). The

organic phases were combined, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography (5% EtOAc in hexanes) to afford **3a** as a white solid (79 mg, 45% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.20 – 8.13 (m, 2H), 8.04 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.51 (td, *J* = 7.3, 6.5, 1.2 Hz, 2H), 7.45 – 7.37 (m, 1H), 5.14 (s, 2H), 3.51 (s, 3H); All characterization data match those reported in the literature.[5]

1a *3b*

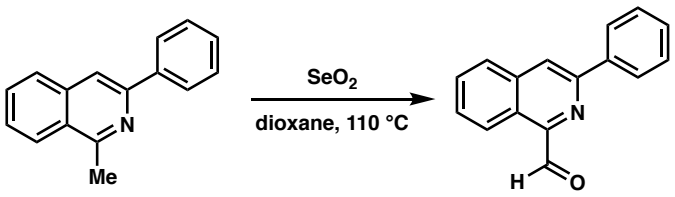
1-((benzyloxy)methyl)-3-phenylisoquinoline (3b): This procedure has been adapted from a previous report.[6] To a flame-dried RBF equipped with a magnetic stir bar was added NaH (36.4 mg, 60% w/w in mineral oil, 0.91 mmol, 1.3 equiv) and THF (7 mL, 0.1 M). To this suspension, isoquinoline **1a** (165 mg, 0.70 mmol) was added. After 5 minutes of stirring at room temperature, the reaction mixture was cooled to 0 °C and BnBr (0.91 mL, 0.91 mmol, 1.3 equiv) was added. The reaction was allowed to slowly warm to room temperature overnight. Silica (1 g) was then added and the solvent was evaporated under vacuum. The crude product was purified by column chromatography (5% EtOAc in hexanes) to afford **3b** as a colorless viscous oil (153 mg, 67% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.21 – 8.14 (m, 2H), 8.04 (s, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.8, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.3, 6.8, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.45 – 7.27 (m, 6H), 5.24 (s, 2H), 4.67 (s, 2H); All characterization data match those reported in the literature.[5]



1a *3c*

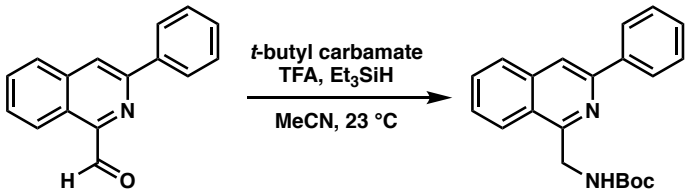
(3-phenylisoquinolin-1-yl)methyl acetate (3c): To a 20-mL scintillation vial containing a magnetic stir bar and isoquinoline **1a** (165 mg, 0.70 mmol) in THF (7 mL, 0.1 M) was added DMAP (8.6 mg, 0.07 mmol, 0.1 equiv) and pyridine (0.14 mL, 1.75 mmol, 2.5 equiv). Acetic anhydride (0.1 mL, 1.05 mmol, 1.5 equiv) was then added dropwise. The reaction mixture was stirred overnight at room temperature then diluted with Et_2O and washed with saturated aqueous NH_4Cl. The organic phase was collected, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (10% EtOAc in hexanes) to afford **3c** as a colorless viscous oil (194 mg, >99% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.13 (m, 2H), 8.11 (dd, *J* = 8.4, 1.0 Hz, 1H), 8.07 (s, 1H), 7.92 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.71 (ddd, *J* =

8.2, 6.8, 1.2 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.8, 1.3 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.45 – 7.38 (m, 1H), 5.79 (s, 2H), 2.20 (s, 3H); All characterization data match those reported in the literature.[5]



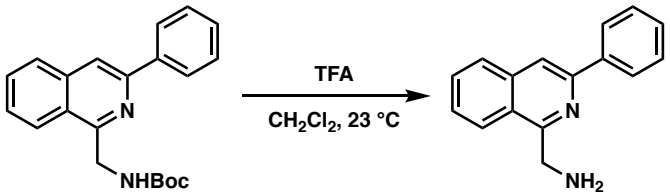
3d ***S5***

3-phenylisoquinoline-1-carbaldehyde (S5): To a Schlenk flask containing a magnetic stir bar was added SeO_2 (140 mg, 1.26 mmol, 2 equiv) and a solution of isoquinoline **3d** (138 mg, 0.63 mmol) in 1,4-dioxane (13 mL, 0.05 M). The reaction vial was then sealed and heated to 110 °C while stirring for 2 hours. The reaction mixture was then cooled to 23 °C and filtered through celite with EtOAc. The crude product was then purified by column chromatography (5% EtOAc in hexanes) to afford **S5** as a pale yellow solid (1.32 g, 96% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 9.32 (d, *J* = 8.2 Hz, 1H), 8.31 (s, 1H), 8.24 (d, *J* = 8.1 Hz, 2H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.84 – 7.67 (m, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.47 (t, *J* = 7.4 Hz, 1H); All characterization data match those reported in the literature.[5]



S5 ***3e***

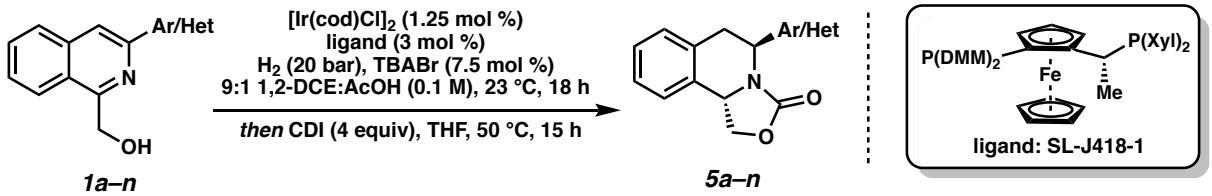
***tert*-butyl ((3-phenylisoquinolin-1-yl)methyl)carbamate (3e):** This procedure has been adapted from a previous report.[7] To a solution of aldehyde **S5** (196 mg, 0.84 mmol) and *t*-butyl carbamate (197 mg, 1.68 mmol, 2 equiv) in MeCN (8 mL, 0.1 M) were added trifluoroacetic acid (0.2 mL, 2.52 mmol, 3 equiv) and triethylsilane (1.3 mL, 8.4 mmol, 10 equiv). The reaction mixture was stirred at 23 °C overnight and then quenched with saturated aqueous Na_2CO_3 and extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (15% EtOAc in hexanes) to afford **3e** as a white solid (225 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.7 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.70 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.48 – 7.40 (m, 1H), 6.43 (br s, 1H), 5.03 (d, *J* = 4.4 Hz, 2H), 1.54 (s, 9H); All characterization data match those reported in the literature.[5]



3e *3f*

(3-phenylisoquinolin-1-yl)methanamine (3f): To a solution of carbamate **3e** (225 mg, 0.67 mmol) in CH_2Cl_2 (2.2 mL, 0.3 M) was added trifluoroacetic acid (1.03 mL, 13.48 mmol, 20 equiv). The reaction was stirred at 23 °C for 1 hour and then neutralized to neutral pH with 1M NaOH. The organic phase was washed with water and extracted with CH_2Cl_2 (2 x 20 mL), then dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (5% MeOH in CH_2Cl_2 with 1% NEt_3) to afford **3f** as a yellow solid (113 mg, 72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.18 (m, 2H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.97 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.68 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.44 – 7.39 (m, 1H), 4.56 (s, 2H), 2.31 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 149.5, 139.6, 137.1, 130.3, 128.9, 128.6, 128.0, 127.2, 127.0, 125.2, 124.1, 115.7, 44.6; IR (Neat Film, NaCl) 3276, 3054, 2968, 2924, 1622, 1574, 1501, 1456, 1439, 1365, 1326, 1201, 882, 784, 766, 694 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{15}N_2$ $[M+H]^+$: 235.1235, found 235.1231.

General Procedure 5: Hydrogenation Reactions



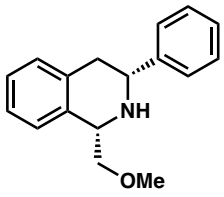
1a–n *5a–n*

An oven-dried 20-mL scintillation vial containing a magnetic stir bar and an isoquinoline substrate (0.2 mmol) was capped with a PTFE-lined septum and pierced with two 21-gauge needles. The vials were then placed in a Parr bomb and brought into a N_2-filled glovebox, with the exception of the pressure gauge. In a nitrogen-filled glovebox, a solution of the ligand (SL-J418-1) (4.53 mg, 0.006 mmol per reaction) and $[Ir(cod)Cl]_2$ (1.68 mg, 0.0025 mmol per reaction) in 1,2-DCE (1.8 mL per reaction) was prepared and allowed to stand for 10 minutes. Meanwhile, a solution of TBABr (4.83 mg, 0.015 mmol per reaction) in AcOH (0.2 mL per reaction) was prepared in a 1-dram vial, and 0.2 mL of the solution was added to each reaction vial by syringe. Afterwards, 1.8 mL of the homogeneous iridium catalyst solution was added to each reaction vial by syringe. After re-capping the vials with caps equipped with needles, the reaction vials were placed in the bomb and the top was covered tightly with plastic wrap secured by a rubber band. The bomb was then removed from the glovebox, and the pressure gauge was quickly screwed in place and tightened. The bomb was charged to 5-10 bar H_2 and slowly released. This process was repeated two more times, before charging the bomb to 20 bar of H_2 (or 60 bar H_2). The bomb was then left stirring at 200 rpm at 23 °C (or placed in an oil bath and

heated to 60 °C) for 18 hours. Then, the bomb was removed from the stir plate and the hydrogen pressure was vented. The reaction vials were removed from the bomb and each solution was basified by the addition of saturated aqueous K_2CO_3 (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 2 mL). The combined organics layers were then dried over Na_2SO_4 and concentrated in vacuo. The diastereoselectivity of the hydrogenation reaction was determined by crude ^{1}H NMR analysis.

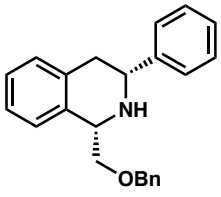
Then, to a scintillation vial containing the crude reaction mixture in THF (0.05 M) was added 1,1'-carbonyldiimidazole (CDI) (130 mg, 0.8 mmol, 4 equiv) and heated at 50 °C for 15 hours. The reaction mixture was then cooled to 23 °C, concentrated, and purified by column chromatography to separate the diastereomers and isolate the *trans*-product.

Please note that the NMR data listed is for the major diastereomer. The enantiomeric excess was determined by chiral SFC analysis of the *trans*-product (see Table S3). The absolute configuration was determined for compound **5a** via X-ray crystallographic analysis, and the absolute configuration for all other products has been inferred by analogy.



4a

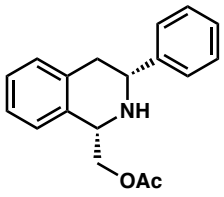
(1*S*,3*R*)-1-(methoxymethyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4a): Compound **4a** was prepared from isoquinoline **3a** using general procedure 5 and determined by ^{1}H NMR spectroscopy of the crude reaction mixture to consist of a mixture of diastereomers; (dr = 17:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 2H), 7.39 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.25 – 7.20 (m, 1H), 7.20 – 7.15 (m, 2H), 7.16 – 7.10 (m, 1H), 4.45 – 4.42 (m, 1H), 4.07 – 3.94 (m, 2H), 3.59 (t, *J* = 8.7 Hz, 1H), 3.43 (s, 3H), 3.06 (dd, *J* = 16.0, 11.1 Hz, 1H), 2.92 (dd, *J* = 16.0, 3.6 Hz, 1H); All characterization data match those reported in the literature.[5]



4b

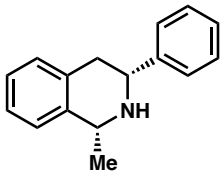
(1*S*,3*R*)-1-((benzyloxy)methyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4b): Compound **4b** was prepared from isoquinoline **3b** using general procedure 5 and determined by ^{1}H NMR spectroscopy of the crude reaction mixture to consist of a mixture of diastereomers; (dr = >20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.46 (m, 2H), 7.40 – 7.34 (m, 6H), 7.32 – 7.28 (m, 2H), 7.22 – 7.16 (m, 3H), 7.14 – 7.11 (m, 1H), 4.61 (s, 2H), 4.48 (dd, *J* = 8.7, 3.4 Hz, 1H), 4.12 (dd, *J*

= 9.0, 3.6 Hz, 1H), 4.04 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.67 (t, *J* = 8.7 Hz, 1H), 3.05 (dd, *J* = 15.9, 11.1 Hz, 1H), 2.91 (dd, *J* = 15.8, 3.5 Hz, 1H); All characterization data match those reported in the literature.[5]



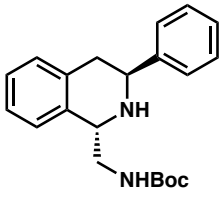
4c

((1*S*,3*R*)-3-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl acetate (4c): Compound **4c** was prepared from isoquinoline **3c** using general procedure 5 and determined by ^{1}H NMR spectroscopy of the crude reaction mixture to consist of a mixture of diastereomers; (dr = >20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 2H), 7.41 – 7.37 (m, 2H), 7.34 – 7.30 (m, 1H), 7.27 – 7.24 (m, 1H), 7.23 – 7.18 (m, 2H), 7.16 – 7.10 (m, 1H), 4.78 (dd, *J* = 10.8, 3.5 Hz, 1H), 4.54 – 4.51 (m, 1H), 4.14 (dd, *J* = 10.8, 8.7 Hz, 1H), 4.05 (dd, *J* = 11.1, 3.4 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.90 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.08 (s, 3H); All characterization data match those reported in the literature.[5]



4d

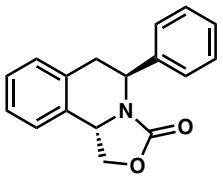
(1*R*,3*R*)-1-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline (4d): Compound **4d** was prepared from isoquinoline **3d** using general procedure 5 and determined by ^{1}H NMR spectroscopy of the crude reaction mixture to consist of a mixture of diastereomers; (dr = >20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 2H), 7.41 – 7.37 (m, 2H), 7.33 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.23 – 7.14 (m, 2H), 7.11 (d, *J* = 6.9 Hz, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.08 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.12 – 3.01 (m, 1H), 2.96 (dd, *J* = 16.2, 4.1 Hz, 1H), 1.55 (d, *J* = 6.5 Hz, 3H); All characterization data match those reported in the literature.[5]



4e

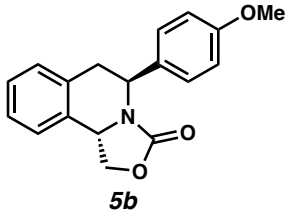
***tert*-butyl (((1*S*,3*R*)-3-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)carbamate (4e):** Compound **4e** was prepared from isoquinoline **3e** using general procedure 5 and determined by ^{1}H NMR spectroscopy of the crude reaction mixture as a mixture of diastereomers; (dr = 1.4:1);

25% ee for major diastereomer; $[\alpha]_D^{25}$ –1.3 (*c* 0.53, $CHCl_3$); Major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2H), 7.40 – 7.36 (m, 2H), 7.32 – 7.28 (m, 1H), 7.20 – 7.18 (m, 3H), 7.14 – 7.12 (m, 1H), 5.12 (br s, 1H), 4.18 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.59 – 3.54 (m, 1H), 3.39 (ddd, *J* = 14.2, 10.7, 4.9 Hz, 1H), 3.02 (dd, *J* = 16.3, 4.2 Hz, 1H), 2.94 (dd, *J* = 16.3, 10.8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 142.8, 134.5, 134.3, 128.2, 127.6, 126.4, 126.0, 125.7, 125.7, 125.1, 55.2, 50.1, 43.6, 36.1, 28.9, 27.4; IR (Neat Film, NaCl) 3733, 3330, 2924, 2368, 2335, 1699, 1492, 1394, 1366, 1268, 1258, 1171, 754 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{27}N_2O_2$ $[M+H]^+$: 339.2073, found 339.2075; SFC Conditions: 30% IPA, 2.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 1.95, minor = 4.28.



5a

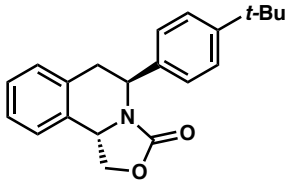
(5*S*,10b*S*)-5-phenyl-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5a): Compound **5a** was prepared from isoquinoline **1a** using general procedure 5 and purified by column chromatography (20% to 40% to 60% EtOAc in hexanes) to provide a clear solid (33 mg, 63% yield); 91% ee; $[\alpha]_D^{25}$ +124.3 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.19 (m, 8H), 6.91 (d, *J* = 7.3 Hz, 1H), 5.31 (dd, *J* = 6.7, 2.8 Hz, 1H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.69 – 4.66 (m, 1H), 4.29 (dd, *J* = 7.8, 5.9 Hz, 1H), 3.41 (dd, *J* = 16.8, 6.7 Hz, 1H), 3.22 (dd, *J* = 16.7, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 138.8, 134.4, 133.2, 129.4, 128.8, 128.1, 127.9, 127.2, 127.2, 124.4, 68.7, 51.7, 51.5, 31.4; IR (Neat Film, NaCl) 2910, 1751, 1601, 1494, 1452, 1402, 1221, 1114, 1066, 1030, 758, 701 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1176, found 266.1177; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): major = 2.61, minor = 2.41.



5b

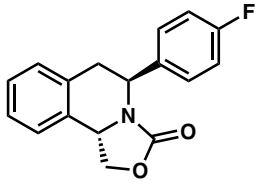
(5*S*,10b*S*)-5-(4-methoxyphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5b): Compound **5b** was prepared from isoquinoline **1b** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a pale yellow oil (38 mg, 64% yield); 96% ee; $[\alpha]_D^{25}$ +150.4 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 3H), 7.22 – 7.20 (m, 2H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.82 – 6.78 (m, 2H), 5.32 (dd, *J* = 6.7, 2.4 Hz, 1H), 4.77 (t, *J* = 8.0 Hz, 1H), 4.71 – 4.67 (m, 1H), 4.30 (dd, *J* = 8.0, 6.2 Hz, 1H), 3.75 (s, 3H), 3.44 (dd, *J* = 16.6, 6.8 Hz, 1H), 3.23 (dd, *J* = 16.7, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.4, 134.4, 133.2, 130.7, 129.4, 128.4, 128.1, 127.2, 124.5, 114.1, 68.8,

55.3, 51.6, 50.8, 31.4; IR (Neat Film, NaCl) 2907, 2836, 1750, 1610, 1513, 1402, 1304, 1251, 1178, 1066, 1030, 828, 756 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1281, found 296.1280; SFC Conditions: 10% MeOH, 3.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): major = 8.66, minor = 7.52.



5c

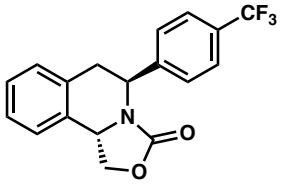
(5*S*,10b*S*)-5-(4-(*tert*-butyl)phenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5c): Compound **5c** was prepared from isoquinoline **1c** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a clear oil (43 mg, 67% yield); 95% ee; $[\alpha]_D^{25}$ +115.6 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 4H), 7.24 – 7.22 (m, 1H), 7.21 – 7.19 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 5.31 (dd, *J* = 6.8, 2.5 Hz, 1H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.72 – 4.68 (m, 1H), 4.29 (dd, *J* = 7.3, 5.3 Hz, 1H), 3.42 (dd, *J* = 16.6, 6.9 Hz, 1H), 3.23 (dd, *J* = 16.7, 2.6 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.8, 135.7, 134.5, 133.4, 129.4, 128.1, 127.1, 126.9, 125.7, 124.5, 68.7, 51.6, 51.1, 34.6, 31.4, 31.3; IR (Neat Film, NaCl) 3010, 2962, 1754, 1455, 1401, 1267, 1215, 1115, 1068, 1026, 828, 757 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{24}NO_2$ $[M+H]^+$: 322.1802, found 322.1801; SFC Conditions: 20% MeOH, 3.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 5.04, minor = 5.44.



5d

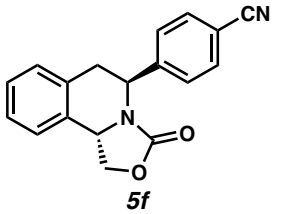
(5*S*,10b*S*)-5-(4-fluorophenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5d): Compound **5d** was prepared from isoquinoline **1d** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a clear oil (40 mg, 70% yield); 95% ee; $[\alpha]_D^{25}$ +150.5 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.21 (m, 5H), 6.96 – 6.91 (m, 3H), 5.29 (dd, *J* = 6.8, 2.8 Hz, 1H), 4.76 (t, *J* = 8 Hz, 1H), 4.67 (ddd, *J* = 8.7, 6.2, 1.1 Hz, 1H), 4.30 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.42 (ddd, *J* = 16.7, 6.6, 1.3 Hz, 1H), 3.19 (dd, *J* = 16.7, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, *J* = 246.8 Hz), 157.5, 134.6 (d, *J* = 3.3 Hz), 134.3, 132.9, 129.4, 129.0 (d, *J* = 8.1 Hz), 128.3, 127.4, 124.5, 115.7 (d, *J* = 21.5 Hz), 68.7, 51.6, 50.9, 31.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ –114.4 – –114.5 (m); IR (Neat Film, NaCl) 2910, 1753, 1605, 1510, 1402, 1223, 1161, 1068, 1043, 1029, 885, 828, 758, 745 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{15}FNO_2$ $[M+H]^+$: 284.1081, found 284.1078; SFC

Conditions: 35% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 2.39, major = 2.58.



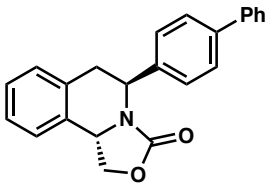
5e

(5*S*,10b*S*)-5-(4-(trifluoromethyl)phenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5e): Compound **5e** was prepared from isoquinoline **1e** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a white solid (43 mg, 64% yield); 91% ee; $[\alpha]_D^{25}$ +118.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.26 (m, 3H), 7.00 – 6.97 (m, 1H), 5.35 (dd, *J* = 6.7, 3.4 Hz, 1H), 4.82 (t, *J* = 8.0 Hz, 1H), 4.76 – 4.72 (m, 1H), 4.38 (dd, *J* = 8.1, 5.9 Hz, 1H), 3.47 (ddd, *J* = 16.6, 6.6, 1.2 Hz, 1H), 3.24 (dd, *J* = 16.6, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 143.0, 143.0, 134.2, 132.7, 130.2 (q, *J* = 32.6 Hz), 129.3, 128.4, 127.5, 125.9 (q, *J* = 3.8 Hz), 124.4, 124.0 (q, *J* = 271.0 Hz), 68.6, 51.8, 51.5, 31.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ 62.7; IR (Neat Film, NaCl) 2916, 1753, 1620, 1402, 1326, 1225, 1162, 1114, 1068, 1017, 889, 829, 757 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{15}F_3NO_2$ $[M+H]^+$: 334.1049, found 334.1048; SFC Conditions: 25% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 2.22, major = 2.37.



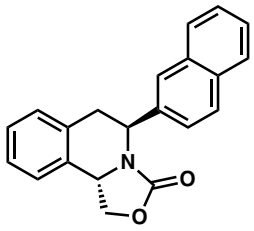
5f

4-((5*S*,10b*S*)-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-5-yl)benzonitrile (5f): Compound **5f** was prepared from isoquinoline **1f** using general procedure 5 and purified by column chromatography (25% to 35% to 50% EtOAc in hexanes) to provide a white solid (27 mg, 47% yield); 83% ee; $[\alpha]_D^{25}$ +112.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.58 (m, 2H), 7.46 – 7.43 (m, 2H), 7.32 – 7.27 (m, 3H), 7.01 – 6.99 (m, 1H), 5.31 (dd, *J* = 6.5, 3.8 Hz, 1H), 4.83 (t, *J* = 8.4 Hz, 1H), 4.76 – 4.72 (m, 1H), 4.40 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.45 (dd, *J* = 16.5, 6.4 Hz, 1H), 3.20 (dd, *J* = 16.6, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 144.5, 134.1, 132.7, 132.5, 129.3, 128.5, 127.9, 127.7, 124.3, 118.6, 111.9, 68.5, 51.9, 51.8, 31.7; IR (Neat Film, NaCl) 2909, 2228, 1747, 1679, 1608, 1402, 1224, 1160, 1114, 1043, 1031, 829, 764, 733 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{15}N_2O_2$ $[M+H]^+$: 291.1134, found 291.1137; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 3.97, major = 4.48.



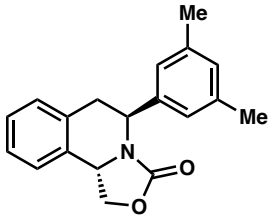
5g

(5*S*,10b*S*)-5-([1,1'-biphenyl]-4-yl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5g): Compound **5g** was prepared from isoquinoline **1g** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a white solid (38 mg, 56% yield); 75% ee; $[\alpha]_D^{25}$ +108.5 (*c* 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 4H), 7.44 – 7.37 (m, 4H), 7.36 – 7.31 (m, 3H), 7.30 – 7.25 (m, 1H), 6.98 (d, *J* = 7.1 Hz, 1H), 5.40 (dd, *J* = 6.7, 2.8 Hz, 1H), 4.83 – 4.76 (m, 2H), 4.39 – 4.32 (m, 1H), 3.49 (dd, *J* = 16.7, 6.7 Hz, 1H), 3.31 (dd, *J* = 16.7, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 140.8, 140.6, 137.8, 134.4, 133.2, 129.4, 128.9, 128.2, 127.6, 127.6, 127.5, 127.3, 127.1, 124.5, 68.7, 51.7, 51.3, 31.5; IR (Neat Film, NaCl) 3028, 2908, 1751, 1487, 1454, 1402, 1220, 1162, 1070, 1042, 886, 830, 760 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{23}H_{20}NO_2$ $[M+H]^+$: 342.1489, found 342.1501; SFC Conditions: 45% MeOH, 3.5 mL/min, Chiralcel OJ-H column, λ = 210 nm, t_R (min): minor = 5.72, major = 6.80.



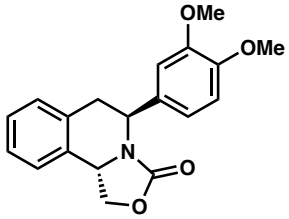
5h

(5*S*,10b*S*)-5-(naphthalen-2-yl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5h): Compound **5h** was prepared from isoquinoline **1h** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a pale white solid (34 mg, 54% yield); 89% ee; $[\alpha]_D^{25}$ +91.3 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.79 (m, 2H), 7.73 – 7.70 (m, 1H), 7.68 (s, 1H), 7.50 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.38 – 7.30 (m, 2H), 7.27 – 7.23 (m, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 5.52 (dd, *J* = 6.5, 3.2 Hz, 1H), 4.79 (t, *J* = 8.0 Hz, 1H), 4.74 – 4.70 (m, 1H), 4.35 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.54 (dd, *J* = 16.7, 6.6 Hz, 1H), 3.41 (dd, *J* = 16.8, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 136.1, 134.4, 133.2, 133.1, 132.9, 129.4, 128.8, 128.2, 128.1, 127.7, 127.2, 126.4, 126.3, 125.9, 125.4, 124.5, 68.8, 51.8, 51.6, 31.3; IR (Neat Film, NaCl) 3017, 1750, 1454, 1401, 1327, 1215, 1070, 1030, 818, 756 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{21}H_{18}NO_2$ $[M+H]^+$: 316.1332, found 316.1332; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min):, minor = 4.21, major = 4.61.



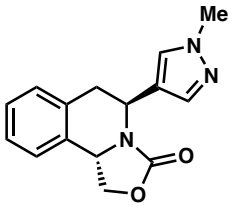
5i

(5*S*,10b*S*)-5-(3,5-dimethylphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5i): Compound **5i** was prepared from isoquinoline **1i** using general procedure 5 and purified by column chromatography (10% to 20% to 30% to 40% EtOAc in hexanes) to provide a pale white solid (36 mg, 61% yield); 86% ee; $[\alpha]_D^{25}$ +125.3 (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 3H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.92 (s, 2H), 6.89 (s, 1H), 5.26 (dd, *J* = 6.7, 3.2 Hz, 1H), 4.82 – 4.75 (m, 2H), 4.39 – 4.32 (m, 1H), 3.42 (dd, *J* = 16.6, 6.7 Hz, 1H), 3.24 (dd, *J* = 16.6, 3.2 Hz, 1H), 2.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 138.9, 138.3, 134.5, 133.4, 129.5, 129.3, 128.1, 127.1, 124.8, 124.3, 68.5, 51.8, 51.5, 31.7, 21.5; IR (Neat Film, NaCl) 3010, 2916, 1752, 1606, 1454, 1402, 1265, 1220, 1070, 1043, 1030, 758, 747 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO_2$ $[M+H]^+$: 294.1489, found 294.1489; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 2.47, major = 2.71.



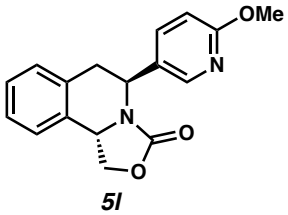
5j

(5*S*,10b*S*)-5-(3,4-dimethoxyphenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5j): Compound **5j** was prepared from isoquinoline **1j** using general procedure 5 and purified by column chromatography (40% to 50% to 75% EtOAc in hexanes) to provide a pale yellow oil (33 mg, 51% yield); 87% ee; $[\alpha]_D^{25}$ +120.9 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.28 (m, 2H), 7.27 – 7.23 (m, 1H), 6.95 (d, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 5.32 (d, *J* = 6.7, 2.3 Hz, 1H), 4.78 (t, *J* = 8.0 Hz, 1H), 4.70 – 4.66 (m, 1H), 4.30 (dd, *J* = 8.1, 6.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.45 (dd, *J* = 16.8, 6.5 Hz, 1H), 3.24 (dd, *J* = 16.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 149.2, 148.7, 134.4, 133.3, 131.1, 129.3, 128.1, 127.2, 124.5, 119.1, 111.0, 110.9, 68.9, 56.0, 56.0, 51.6, 51.1, 31.4; IR (Neat Film, NaCl) 2929, 2836, 1748, 1592, 1516, 1403, 1259, 1237, 1142, 1026, 758, 749 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{19}H_{20}NO_4$ $[M+H]^+$: 326.1387, found 326.1385; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): major = 2.13, minor = 2.74.



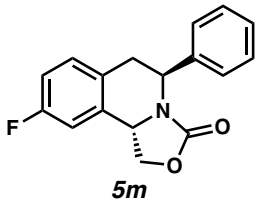
5k

(5*S*,10b*S*)-5-(1-methyl-1*H*-pyrazol-4-yl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5k): Compound **5k** was prepared from isoquinoline **1k** using general procedure 5 and purified by column chromatography (80% to 90% to 100% EtOAc in hexanes) to provide a pale yellow oil as a mixture of diastereomers (47 mg, 88% overall yield) (dr = 3.0:1); 97% ee for major diastereomer; $[\alpha]_D^{25}$ +113.6 (*c* 1.00, $CHCl_3$); Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.27 – 7.21 (m, 3H), 7.17 (s, 1H), 6.96 – 6.94 (m, 1H), 5.34 (dd, *J* = 6.6, 2.0 Hz, 1H), 4.77 – 4.74 (m, 2H), 4.29 – 4.23 (m, 1H), 3.78 (s, 3H), 3.42 (dd, *J* = 16.5, 6.7 Hz, 1H), 3.03 (dd, *J* = 16.4, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 138.1, 134.1, 132.8, 129.7, 128.8, 128.0, 127.3, 124.7, 119.7, 69.1, 51.5, 44.2, 39.1, 32.3; IR (Neat Film, NaCl) 2930, 1750, 1444, 1401, 1276, 1216, 1070, 1021, 988, 761, 751 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{15}H_{16}N_3O_2$ $[M+H]^+$: 270.1237, found 270.1238; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 2.24, major = 2.67.



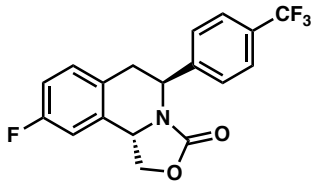
5l

(5*S*,10b*S*)-5-(6-methoxypyridin-3-yl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5l): Compound **5l** was prepared from isoquinoline **1l** using general procedure 5 and purified by column chromatography (25% to 35% to 50% EtOAc in hexanes) to provide a pale yellow oil (38 mg, 64% yield); 95% ee; $[\alpha]_D^{25}$ +124.9 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.6 Hz, 1H), 7.54 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.29 – 7.27 (m, 2H), 7.25 – 7.23 (m, 1H), 6.95 (dd, *J* = 6.9 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 1H), 5.31 (dd, *J* = 6.7, 2.5 Hz, 1H), 4.78 (t, *J* = 8.0 Hz, 1H), 4.69 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.31 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.86 (s, 3H), 3.45 (dd, *J* = 16.7, 6.8 Hz, 1H), 3.21 (dd, *J* = 16.8, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 157.4, 145.4, 138.3, 134.1, 132.6, 129.5, 128.3, 127.4, 126.9, 124.6, 111.3, 68.9, 53.5, 51.6, 49.3, 31.1; IR (Neat Film, NaCl) 2945, 1752, 1608, 1494, 1400, 1288, 1262, 1068, 1027, 827, 758, 742 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234, found 297.1236; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak AD-H column, λ = 210 nm, t_R (min): minor = 2.80, major = 3.30.



5m

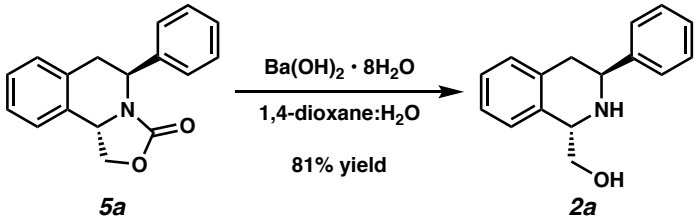
(5*S*,10b*S*)-9-fluoro-5-phenyl-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5m): Compound **5m** was prepared from isoquinoline **1m** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a white solid (38 mg, 67% yield); 95% ee; $[\alpha]_D^{25}$ +163.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 6H), 6.98 (td, *J* = 8.6, 2.5 Hz, 1H), 6.65 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.33 (dd, *J* = 6.6, 2.7 Hz, 1H), 4.74 (t, *J* = 8.5 Hz, 1H), 4.67 – 4.63 (m, 1H), 4.28 (dd, *J* = 8.2, 5.9 Hz, 1H), 3.38 (dd, *J* = 16.6, 6.4 Hz, 1H), 3.22 (dd, *J* = 16.6, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7 (d, J = 246.6 Hz), 157.4, 138.4, 136.1 (d, *J* = 6.6 Hz), 131.0 (d, *J* = 7.8 Hz), 128.9, 128.8 (d, *J* = 3.3 Hz), 128.0, 127.1, 115.4 (d, *J* = 21.3 Hz), 111.4 (d, *J* = 22.1 Hz), 68.4, 51.7 (d, *J* = 2.2 Hz), 51.4, 30.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ –114.3 – –114.4 (m); IR (Neat Film, NaCl) 3061, 2914, 1752, 1613, 1593, 1499, 1450, 1430, 1402, 1327, 1241, 1216, 1162, 1069, 1034, 868, 814, 756 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{15}FNO_2$ $[M+H]^+$: 284.1081, found 284.1083; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 2.09, major = 2.53.



5n

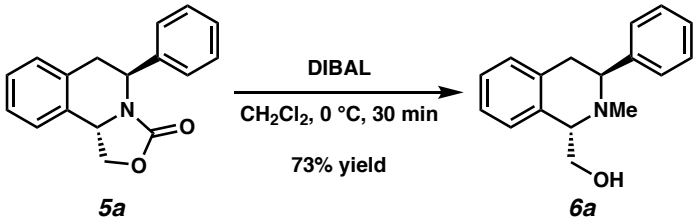
(5*S*,10b*S*)-9-fluoro-5-(4-(trifluoromethyl)phenyl)-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-3-one (5n): Compound **5n** was prepared from isoquinoline **1n** using general procedure 5 and purified by column chromatography (20% to 30% to 40% EtOAc in hexanes) to provide a pale yellow oil (38 mg, 54% yield); 92% ee; $[\alpha]_D^{25}$ +115.7 (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.29 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.02 (td, *J* = 8.4, 2.5 Hz, 1H), 6.71 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.35 (dd, *J* = 6.6, 3.4 Hz, 1H), 4.80 (t, *J* = 8.5, 1H), 4.69 (dd, *J* = 8.6, 5.9 Hz, 1H), 4.35 (dd, *J* = 8.4, 5.8 Hz, 1H), 3.42 (dd, *J* = 16.6, 6.3 Hz, 1H), 3.22 (dd, *J* = 16.6, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (d, *J* = 247.2 Hz), 157.5, 142.7, 136.0 (d, *J* = 6.8 Hz), 131.0 (d, *J* = 7.9 Hz), 130.3 (q, *J* = 32.6 Hz), 128.4 (d, *J* = 3.3 Hz, 1H), 127.5, 125.9 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 271.0 Hz), 115.7 (d, J = 21.3 Hz), 111.5 (d, *J* = 22.4 Hz), 68.3, 51.9 (d, *J* = 2.2 Hz), 51.5, 30.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.7, –113.7 – –113.8 (m); IR (Neat Film, NaCl) 2921, 1754, 1620, 1594, 1500, 1402, 1326, 1241, 1162, 1115, 1068, 1018, 839, 759 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{18}H_{14}F_4NO_2$ $[M+H]^+$: 352.0955, found 352.0954; SFC Conditions: 40% MeOH, 3.5 mL/min, Chiralpak IC column, λ = 210 nm, t_R (min): minor = 1.43, major = 1.60.

Experimental Procedure for Product Transformations:



5a *2a*

This procedure has been adapted from a previous report.[8] To a 1-dram vial equipped with a stir bar was added a solution of tetrahydroisoquinoline **5a** (4.4 mg, 0.02 mmol) in 1:1 1,4-dioxane:H_2O (0.4 mL total, 0.05 M). Barium hydroxide octahydrate (24 mg, 4.1 equiv, 0.07 mmol) was then added and the vial was capped with a PTFE-lined septum and sealed with electrical tape. The reaction mixture was heated to 120 °C and stirred for 3 hours until TLC analysis indicated complete consumption of the starting material. The reaction was then diluted with H_2O, extracted with EtOAc, and the collected organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (50% EtOAc in hexanes + 1% NEt_3) to afford **2a** as a white solid (3.2 mg, 81% yield): $[\alpha]_D^{25}$ –8.3 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.42 – 7.38 (m, 2H), 7.33 – 7.29 (m, 1H), 7.22 – 7.18 (m, 2H), 7.17 – 7.13 (m, 2H), 4.23 (dd, *J* = 10.6, 4.8 Hz, 1H), 4.15 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.80 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.71 (t, *J* = 10.7 Hz, 1H), 3.07 (dd, *J* = 16.4, 3.9 Hz, 1H), 2.95 (dd, *J* = 16.3, 11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 135.5, 134.7, 129.5, 128.8, 127.5, 127.0, 126.7, 126.6, 126.4, 63.8, 57.4, 50.7, 36.8; IR (Neat Film, NaCl) 3411, 2357, 2086, 1733, 1716, 1700, 1652, 1558, 1540, 1457, 678 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{16}H_{18}NO$ $[M+H]^+$: 240.1388, found 240.1387.



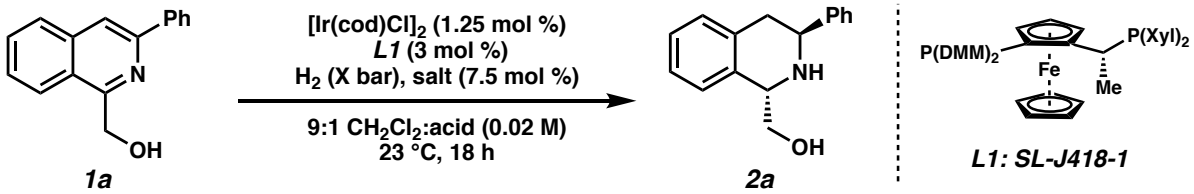
5a *6a*

This procedure has been adapted from a previous report.[9] To a 1-dram vial equipped with a stir bar was added a solution of tetrahydroisoquinoline **5a** (5.0 mg, 0.02 mmol) in CH_2Cl_2 (0.4 mL, 0.05 M). The reaction mixture was cooled to 0 °C, and a solution of DIBAL (1.0 M in THF, 0.38 mL, 0.2 mmol) was added dropwise. After stirring for 1 hour, the reaction mixture showed complete consumption of starting material by TLC, and was quenched with MeOH, H_2O, and saturated aqueous Rochelle's salt and stirred for an additional hour. The reaction was then diluted with H_2O, extracted with CH_2Cl_2 (2 x 5 mL), and the collected organic layers were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (30% EtOAc in hexanes) to afford **6a** as a clear oil (3.5 mg, 73% yield): $[\alpha]_D^{25}$ +115.8 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2H), 7.42 – 7.38 (m, 2H),

7.33 – 7.29 (m, 1H), 7.25 – 7.22 (m, 3H), 7.17 – 7.13 (m, 1H), 4.34 (dd, *J* = 12.2, 4.0 Hz, 1H), 3.93 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.81 (dd, *J* = 10.8, 5.3 Hz, 1H), 3.72 (t, *J* = 10.6 Hz, 1H), 3.37 (dd, *J* = 16.5, 12.2 Hz, 1H), 2.92 (dd, *J* = 16.5, 4.0 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 134.5, 133.7, 129.5, 128.5, 127.9, 127.8, 127.4, 126.9, 126.7, 65.8, 63.4, 53.2, 35.7, 25.1; IR (Neat Film, NaCl) 3423, 3058, 3024, 2918, 2854, 2366, 1496, 1450, 1406, 1222, 1130, 1044, 774, 752, 699 cm^{-1}; HRMS (MM:ESI-APCI+) *m/z* calc'd for $C_{17}H_{20}NO$ $[M+H]^+$: 254.1545, found 254.1543.

Additional Optimization Results

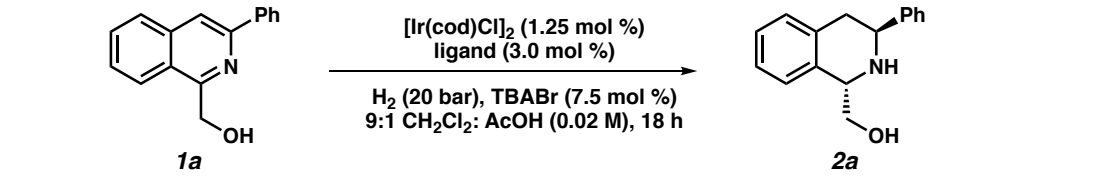
Table S1. Additional Optimization Studies[a]

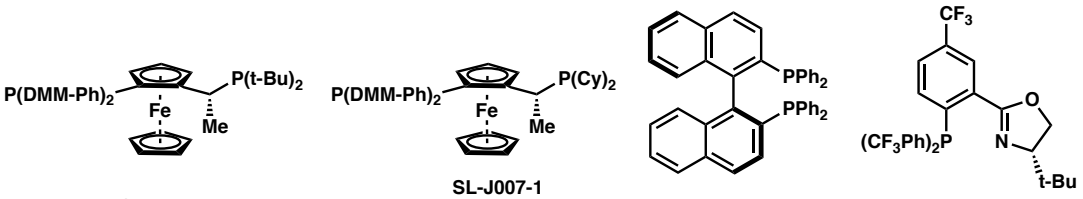


entry	salt additive	acid	pressure	% conversion[b]	cis:trans[b]	% ee of trans[c]
1	TBACl	AcOH	20 bar	75	1:2.3	90
2	TBAI	AcOH	20 bar	>95	1.5:1	97
3	$TBAPF_6$	AcOH	20 bar	<10	–	–
4	$TBABF_4$	AcOH	20 bar	<10	–	–
5	$TBABPh_4$	AcOH	20 bar	<10	–	–
6	LiBr	AcOH	20 bar	>95	1:2.3	91
7	NaBr	AcOH	20 bar	90	1:2.3	89
8	KBr	AcOH	20 bar	35	1:2.4	86
9	TBABr	TFA	20 bar	<10	–	–
10	TBABr	MsOH	20 bar	<10	–	–
11	TBABr	AcOH	10 bar	>95	1:2.3	91
12	TBABr	AcOH	60 bar	>95	1:2.6	93

[a]Conditions: 0.04 mmol *1a*, 1.25 mol % $[Ir(cod)Cl]_2$, 3 mol % ligand, 7.5 mol % salt additive, 20 bar H_2 in 0.5 mL 9:1 CH_2Cl_2:acid. [b]Determined from crude ^{1}H NMR using trimethoxybenzene as a standard. [c]Determined by chiral SFC analysis of Cbz-protected product.

Table S2. Additional Ligand Screen[a]





SL-J013-1
<10% conversion

SL-J007-1
15% conversion
2:1 cis:trans, ee ND

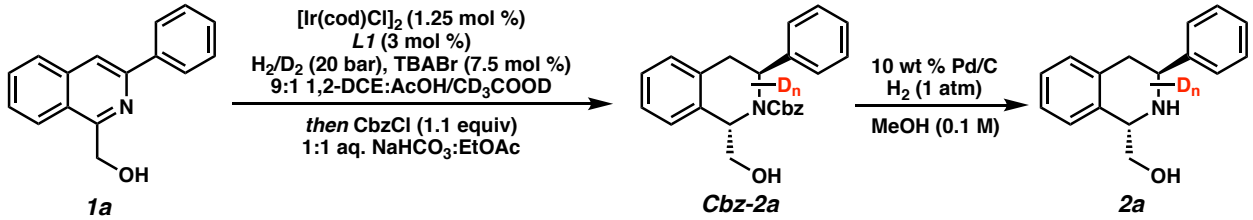
62% conversion
>20:1 cis:trans, ee ND

<10% conversion

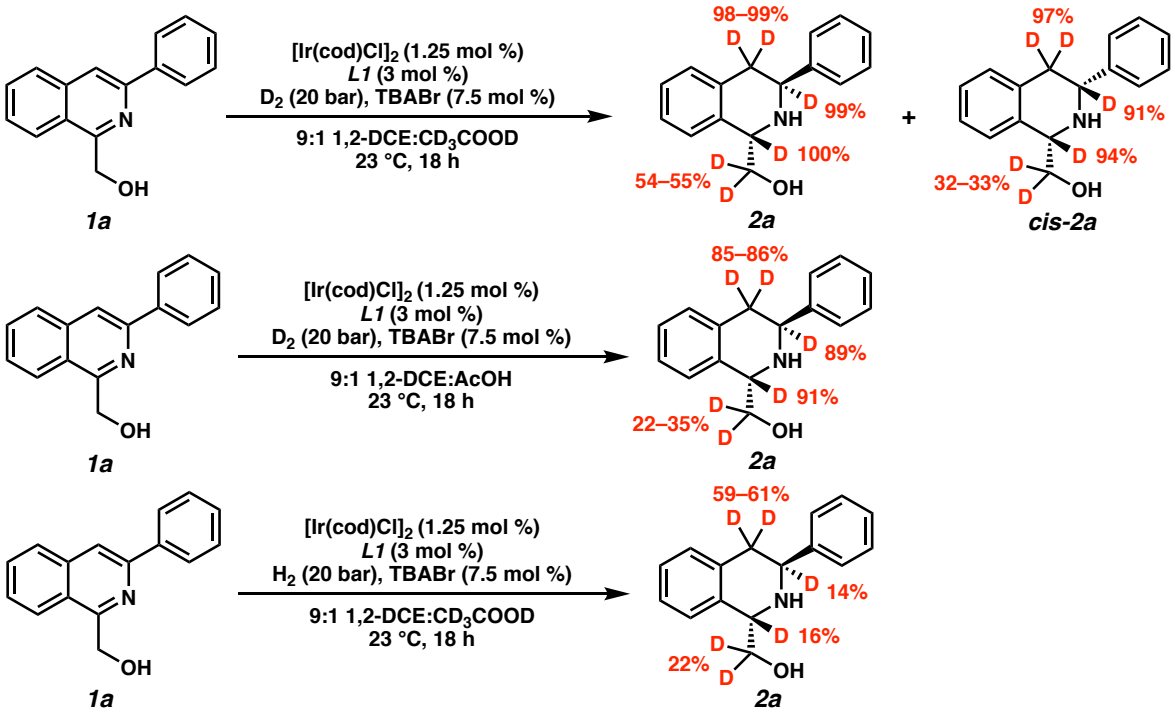
[a]Conditions: 0.04 mmol *1a*, 1.25 mol % $[Ir(cod)Cl]_2$, 3 mol % ligand, 7.5 mol % TBABr, 20 bar H_2 in 0.5 mL 9:1 CH_2Cl_2:AcOH. Determined from crude ^1H NMR using trimethoxybenzene as a standard.

Deuterium Incorporation Experiments

Deuterium experiments were conducted according to general procedure 5 for the hydrogenation of isoquinoline **1a** using deuterium gas instead of hydrogen gas, and/or d_4-AcOH instead of protio acetic acid.



Due to the inseparable nature of the *cis*- and *trans*-diastereomers, the hydrogenated products were subsequently protected with benzyl chloroformate (6.3 µL, 0.044 mmol, 1.1 equiv) in 1:1 saturated aq. $NaHCO_3$ and EtOAc (1 mL total). After the reaction showed full conversion of the hydrogenated product, the crude reaction mixture was washed with ethyl acetate and the collected organic layers were dried over Na_2SO_4 and concentrated under vacuum. Both the *cis*- and *trans*-isomers were isolated by preparative TLC (40% EtOAc in hexanes) of the Cbz-protected THIQ, then subsequently deprotected using 10 wt% Pd/C catalyst (1 mg) under a H_2 balloon in MeOH (0.1 M) to afford deuterium-labelled **2a**. The major *trans*-isomer was analyzed by ^1H and ^2H NMR spectroscopy.


[Ir(cod)Cl]2 (1.25 mol %)
L1 (3 mol %)
D2 (20 bar), TBABr (7.5 mol %)
9:1 1,2-DCE:CD3COOD
23 °C, 18 h
1a
2a
cis-2a
98–99%
99%
100%
54–55%
97%
91%
94%
32–33%
[Ir(cod)Cl]2 (1.25 mol %)
L1 (3 mol %)
D2 (20 bar), TBABr (7.5 mol %)
9:1 1,2-DCE:AcOH
23 °C, 18 h
85–86%
89%
91%
22–35%
[Ir(cod)Cl]2 (1.25 mol %)
L1 (3 mol %)
H2 (20 bar), TBABr (7.5 mol %)
9:1 1,2-DCE:CD3COOD
23 °C, 18 h
59–61%
14%
16%
22%

Proposed Catalytic Cycle

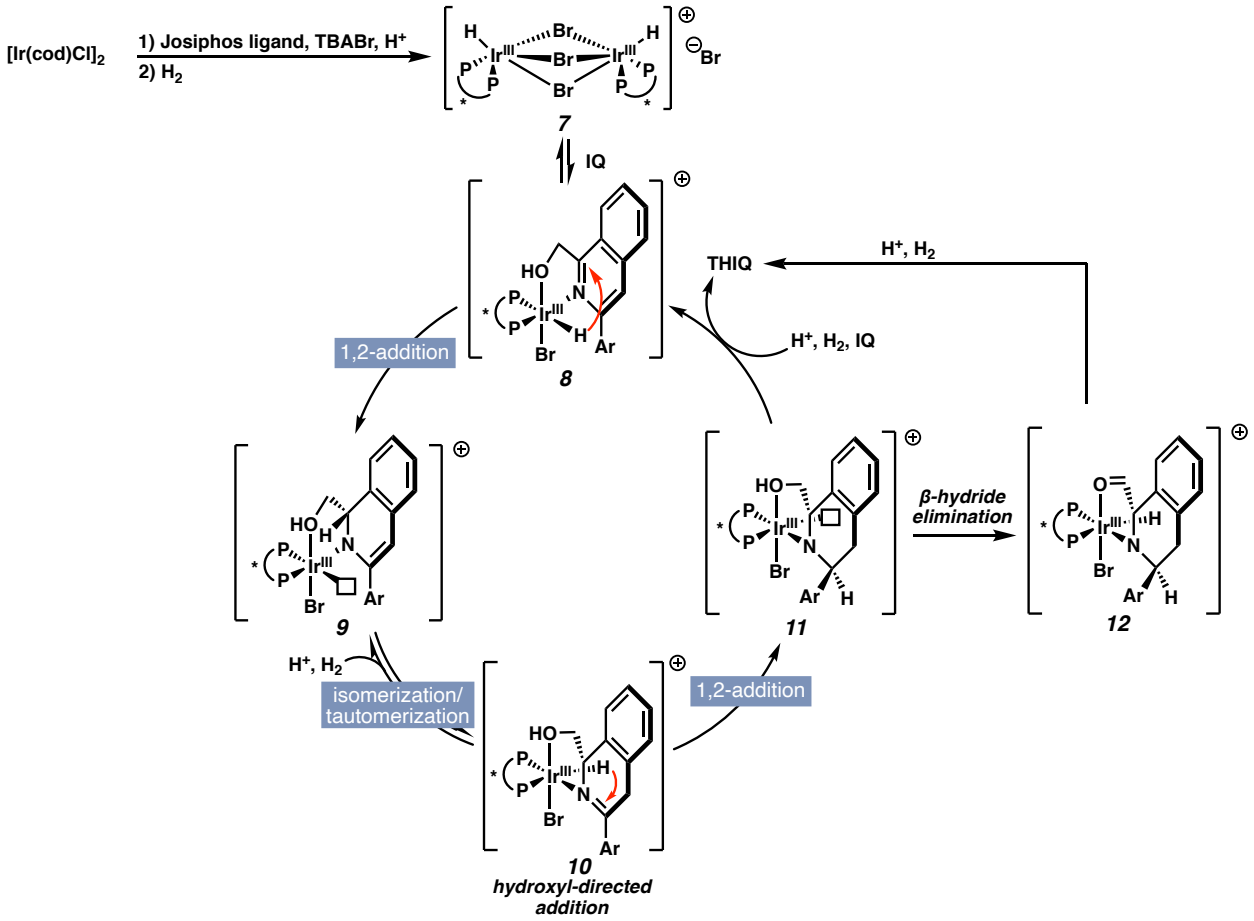
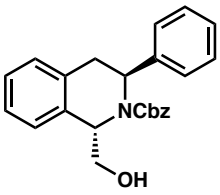
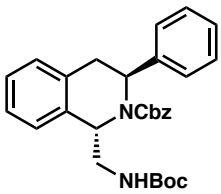
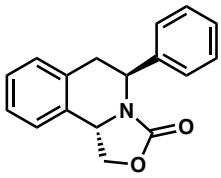
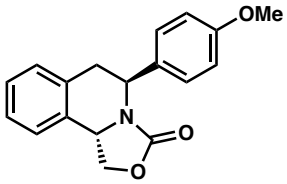
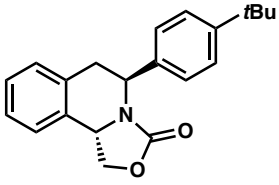
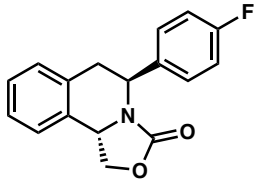
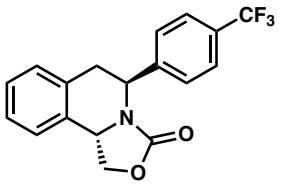
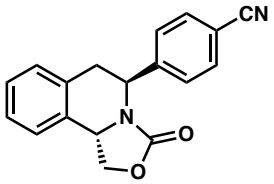
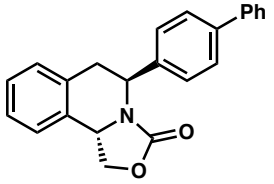
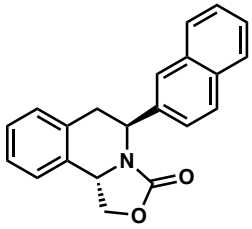
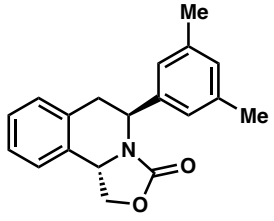
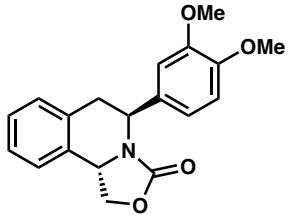
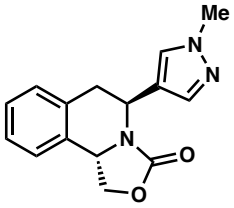
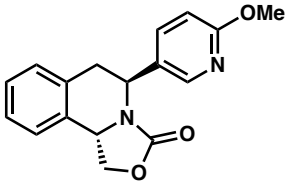
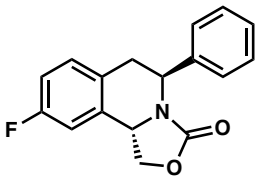
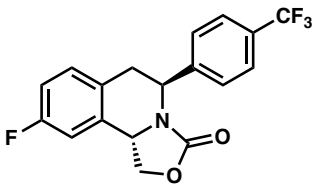


Figure S1. Based on preliminary mechanistic studies and literature precedent, a proposed catalytic cycle for the *trans*-selective asymmetric hydrogenation is described. Pre-formation of the chiral catalyst using $[Ir(cod)Cl]_2$, chiral ligand, and TBABr, followed by oxidative addition with H_2 delivers the halogen-bridged dinuclear Ir^{III} catalyst complex **7**. Without the halide, the iridium bisphosphane catalysts tend to irreversibly form dimeric iridium hydride complexes that are catalytically inactive.[10] Addition of the isoquinoline substrate then undergoes bidentate coordination to the metal to generate the corresponding mononuclear Ir^{III} complex **8**, followed by a 1,2-hydride addition to establish the C1-stereocenter (**9**).[11] Isomerization and tautomerization of the substrate then enables a directed hydrogenation (**10**) guided by the hydroxymethyl group to deliver the hydride on the opposite face of the molecule. The addition of H_2 in the presence of acid regenerates the catalyst species and liberates the enantioenriched *trans*-THIQ product. Alternatively, based on our deuterium experiments, β-hydride elimination can also proceed from intermediate **11** to generate aldehyde intermediate **12**, which is subsequently reduced to provide the same THIQ product. However, the possibility of β-hydride elimination occurring at other intermediates still cannot be ruled out, and further investigations of the mechanism are currently underway.

Table S3. Determination of Enantiomeric Excess

entry	compound	SFC analytic conditions	ee (%)
1	 ***2a·Cbz***	**Chiralpak AD-H, λ = 210 nm 45% IPA/CO_2, 3.5 mL/min t_R (min) major 1.69, minor 2.04**	**92**
2	 ***3e·Cbz***	**Chiralpak AD-H, λ = 210 nm 30% IPA/CO_2, 2.5 mL/min t_R (min) major 1.95, minor 4.28**	**25**
3	 ***5a***	**Chiralpak IC, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.41, major 2.61**	**91**
4	 ***5b***	**Chiralcel OJ-H, λ = 210 nm 10% MeOH/CO_2, 3.5 mL/min t_R (min) minor 7.52, major 8.66**	**96**
5	 ***5c***	**Chiralpak AD-H, λ = 210 nm 20% MeOH/CO_2, 3.5 mL/min t_R (min) major 5.04, minor 5.44**	**95**
6	 ***5d***	**Chirapak IC, λ = 210 nm 35% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.39, major 2.58**	**95**

entry	compound	SFC analytic conditions	ee (%)
7	 *5e*	Chiralpak IC, λ = 210 nm 25% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.22, major 2.37	91
8	 *5f*	Chiralpak IC, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 3.97, major 4.48	83
9	 *5g*	Chiralcel OJ-H, λ = 210 nm 45% MeOH/CO_2, 3.5 mL/min t_R (min) minor 5.72, major 6.80	75
10	 *5h*	Chiralpak IC, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 4.21, major 4.61	89
11	 *5i*	Chirapak IC, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.47, major 2.71	86
12	 *5j*	Chiralpak AD-H, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) major 2.13, minor 2.74	87

entry	compound	SFC analytic conditions	ee (%)
13	 ***5k***	Chiralpak AD-H, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.24, major 2.67	97
14	 ***5l***	Chiralpak AD-H, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.80, minor 3.30	95
15	 ***5m***	Chiralpak IC, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 2.09, major 2.53	95
16	 ***5n***	Chiralpak IC, λ = 210 nm 40% MeOH/CO_2, 3.5 mL/min t_R (min) minor 1.43, major 1.60	92

X-Ray Crystal Structure Data for Hydrogenated Product 5a

The tetrahydroisoquinoline product **5a** (91% ee) was crystallized by slow evaporation from chloroform at 23 °C to provide crystals suitable for X-ray analysis.

Compound V21097 crystallizes in the orthorhombic space group $P2_12_12_1$ with one molecule in the asymmetric unit.

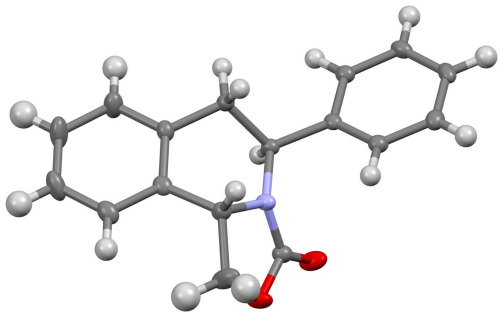


Table S4. Crystal data and structure refinement for V21097.

Identification code	V21097	
Empirical formula	C17 H15 N O2	
Formula weight	265.30	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 6.5620(8) Å	a= 90°.
	b = 14.2320(17) Å	b= 90°.
	c = 14.4563(19) Å	g = 90°.
Volume	1350.1(3) $Å^3$	
Z	4	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.687 mm^{-1}	
F(000)	560	
Crystal size	0.300 x 0.150 x 0.150 mm^3	
Theta range for data collection	4.359 to 79.624°.	
Index ranges	-8<=h<=8, -17<=k<=18, -18<=l<=18	
Reflections collected	23786	

Independent reflections	2903 [R(int) = 0.0368]
Completeness to theta = 67.679°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7543 and 0.6141
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2903 / 0 / 181
Goodness-of-fit on F^2	1.106
Final R indices [I>2sigma(I)]	R1 = 0.0314, wR2 = 0.0806
R indices (all data)	R1 = 0.0317, wR2 = 0.0807
Absolute structure parameter	0.04(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.157 and -0.228 e.$Å^{-3}$

Table S5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for V21097. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	5632(2)	5374(1)	8245(1)	20(1)
O(1)	7103(2)	4818(1)	8618(1)	26(1)
O(2)	3839(2)	5236(1)	8370(1)	30(1)
C(2)	9070(3)	5142(1)	8341(2)	39(1)
C(3)	8729(2)	6082(1)	7842(1)	20(1)
C(4)	9357(2)	6972(1)	8337(1)	18(1)
C(5)	10846(3)	7016(1)	9020(1)	24(1)
C(6)	11296(3)	7867(2)	9444(1)	32(1)
C(7)	10246(3)	8669(2)	9192(1)	35(1)
C(8)	8766(3)	8632(1)	8500(1)	28(1)
C(9)	8329(2)	7787(1)	8060(1)	19(1)
C(10)	6807(2)	7701(1)	7288(1)	19(1)
C(11)	5305(2)	6893(1)	7469(1)	16(1)
C(12)	3921(2)	6716(1)	6645(1)	16(1)
C(13)	4020(3)	5903(1)	6111(1)	20(1)
C(14)	2681(3)	5771(1)	5375(1)	22(1)
C(15)	1261(3)	6451(1)	5150(1)	23(1)

C(16)	1180(3)	7277(1)	5665(1)	22(1)
C(17)	2487(2)	7401(1)	6413(1)	19(1)
N(1)	6496(2)	6060(1)	7731(1)	19(1)

Table S6. Bond lengths [Å] and angles [°] for V21097.

C(1)-O(2)	1.206(2)
C(1)-N(1)	1.352(2)
C(1)-O(1)	1.360(2)
O(1)-C(2)	1.428(2)
C(2)-C(3)	1.536(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-N(1)	1.474(2)
C(3)-C(4)	1.512(2)
C(3)-H(3)	1.0000
C(4)-C(5)	1.391(2)
C(4)-C(9)	1.401(2)
C(5)-C(6)	1.389(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.383(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.395(3)
C(7)-H(7)	0.9500
C(8)-C(9)	1.390(2)
C(8)-H(8)	0.9500
C(9)-C(10)	1.503(2)
C(10)-C(11)	1.537(2)
C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900
C(11)-N(1)	1.4693(19)
C(11)-C(12)	1.518(2)
C(11)-H(11)	1.0000
C(12)-C(13)	1.392(2)
C(12)-C(17)	1.395(2)
C(13)-C(14)	1.393(2)

C(13)-H(13)	0.9500
C(14)-C(15)	1.382(3)
C(14)-H(14)	0.9500
C(15)-C(16)	1.391(2)
C(15)-H(15)	0.9500
C(16)-C(17)	1.391(2)
C(16)-H(16)	0.9500
C(17)-H(17)	0.9500

O(2)-C(1)-N(1)	127.52(16)
O(2)-C(1)-O(1)	122.54(15)
N(1)-C(1)-O(1)	109.93(14)
C(1)-O(1)-C(2)	110.03(13)
O(1)-C(2)-C(3)	106.31(14)
O(1)-C(2)-H(2A)	110.5
C(3)-C(2)-H(2A)	110.5
O(1)-C(2)-H(2B)	110.5
C(3)-C(2)-H(2B)	110.5
H(2A)-C(2)-H(2B)	108.7
N(1)-C(3)-C(4)	109.86(13)
N(1)-C(3)-C(2)	100.27(13)
C(4)-C(3)-C(2)	117.83(15)
N(1)-C(3)-H(3)	109.5
C(4)-C(3)-H(3)	109.5
C(2)-C(3)-H(3)	109.5
C(5)-C(4)-C(9)	120.26(15)
C(5)-C(4)-C(3)	124.42(15)
C(9)-C(4)-C(3)	115.32(14)
C(6)-C(5)-C(4)	120.11(17)
C(6)-C(5)-H(5)	119.9
C(4)-C(5)-H(5)	119.9
C(7)-C(6)-C(5)	119.90(17)
C(7)-C(6)-H(6)	120.1
C(5)-C(6)-H(6)	120.1
C(6)-C(7)-C(8)	120.27(17)
C(6)-C(7)-H(7)	119.9

C(8)-C(7)-H(7)	119.9
C(9)-C(8)-C(7)	120.30(17)
C(9)-C(8)-H(8)	119.9
C(7)-C(8)-H(8)	119.9
C(8)-C(9)-C(4)	119.13(15)
C(8)-C(9)-C(10)	123.21(15)
C(4)-C(9)-C(10)	117.66(14)
C(9)-C(10)-C(11)	111.16(13)
C(9)-C(10)-H(10A)	109.4
C(11)-C(10)-H(10A)	109.4
C(9)-C(10)-H(10B)	109.4
C(11)-C(10)-H(10B)	109.4
H(10A)-C(10)-H(10B)	108.0
N(1)-C(11)-C(12)	112.78(13)
N(1)-C(11)-C(10)	107.82(12)
C(12)-C(11)-C(10)	111.92(12)
N(1)-C(11)-H(11)	108.0
C(12)-C(11)-H(11)	108.0
C(10)-C(11)-H(11)	108.0
C(13)-C(12)-C(17)	118.59(15)
C(13)-C(12)-C(11)	122.95(14)
C(17)-C(12)-C(11)	118.46(14)
C(12)-C(13)-C(14)	120.40(15)
C(12)-C(13)-H(13)	119.8
C(14)-C(13)-H(13)	119.8
C(15)-C(14)-C(13)	120.71(15)
C(15)-C(14)-H(14)	119.6
C(13)-C(14)-H(14)	119.6
C(14)-C(15)-C(16)	119.42(15)
C(14)-C(15)-H(15)	120.3
C(16)-C(15)-H(15)	120.3
C(15)-C(16)-C(17)	119.92(15)
C(15)-C(16)-H(16)	120.0
C(17)-C(16)-H(16)	120.0
C(16)-C(17)-C(12)	120.94(15)
C(16)-C(17)-H(17)	119.5

C(12)-C(17)-H(17)	119.5
C(1)-N(1)-C(11)	120.07(13)
C(1)-N(1)-C(3)	111.82(13)
C(11)-N(1)-C(3)	122.70(12)

Symmetry transformations used to generate equivalent atoms:

Table S7. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for V21097. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(1)	19(1)	20(1)	2(1)	2(1)	2(1)
O(1)	22(1)	23(1)	34(1)	12(1)	1(1)	5(1)
O(2)	20(1)	26(1)	43(1)	11(1)	7(1)	0(1)
C(2)	20(1)	28(1)	68(1)	18(1)	-9(1)	-2(1)
C(3)	14(1)	21(1)	25(1)	2(1)	1(1)	1(1)
C(4)	14(1)	25(1)	16(1)	1(1)	5(1)	0(1)
C(5)	16(1)	36(1)	20(1)	0(1)	2(1)	4(1)
C(6)	20(1)	49(1)	26(1)	-11(1)	-6(1)	6(1)
C(7)	27(1)	39(1)	39(1)	-21(1)	-7(1)	3(1)
C(8)	23(1)	28(1)	35(1)	-10(1)	-6(1)	4(1)
C(9)	16(1)	24(1)	18(1)	-3(1)	1(1)	0(1)
C(10)	19(1)	17(1)	19(1)	2(1)	-1(1)	-1(1)
C(11)	16(1)	17(1)	16(1)	2(1)	1(1)	1(1)
C(12)	13(1)	19(1)	15(1)	3(1)	2(1)	-2(1)
C(13)	20(1)	20(1)	18(1)	2(1)	2(1)	1(1)
C(14)	25(1)	24(1)	18(1)	0(1)	3(1)	-6(1)
C(15)	21(1)	32(1)	16(1)	5(1)	-2(1)	-8(1)
C(16)	16(1)	27(1)	22(1)	8(1)	0(1)	1(1)
C(17)	17(1)	20(1)	20(1)	2(1)	2(1)	0(1)
N(1)	14(1)	20(1)	22(1)	6(1)	0(1)	0(1)

Table S8. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for V21097.

	x	y	z	U(eq)
H(2A)	9723	4683	7921	47
H(2B)	9959	5231	8888	47
H(3)	9391	6060	7219	24
H(5)	11557	6463	9197	29
H(6)	12322	7897	9906	38
H(7)	10535	9249	9491	42
H(8)	8054	9187	8328	34
H(10A)	7534	7586	6698	22
H(10B)	6043	8297	7227	22
H(11)	4430	7072	8007	20
H(13)	5007	5436	6250	24
H(14)	2744	5208	5024	27
H(15)	348	6356	4649	28
H(16)	234	7755	5505	26
H(17)	2402	7959	6770	22

Table S9. Torsion angles [°] for V21097.

O(2)-C(1)-O(1)-C(2)	179.11(18)
N(1)-C(1)-O(1)-C(2)	-0.1(2)
C(1)-O(1)-C(2)-C(3)	8.0(2)
O(1)-C(2)-C(3)-N(1)	-11.7(2)
O(1)-C(2)-C(3)-C(4)	107.34(18)
N(1)-C(3)-C(4)-C(5)	138.89(15)
C(2)-C(3)-C(4)-C(5)	25.0(2)
N(1)-C(3)-C(4)-C(9)	-41.39(18)
C(2)-C(3)-C(4)-C(9)	-155.28(15)
C(9)-C(4)-C(5)-C(6)	1.2(2)
C(3)-C(4)-C(5)-C(6)	-179.11(16)
C(4)-C(5)-C(6)-C(7)	0.6(3)
C(5)-C(6)-C(7)-C(8)	-1.3(3)

C(6)-C(7)-C(8)-C(9)	0.2(3)
C(7)-C(8)-C(9)-C(4)	1.6(3)
C(7)-C(8)-C(9)-C(10)	-177.85(17)
C(5)-C(4)-C(9)-C(8)	-2.3(2)
C(3)-C(4)-C(9)-C(8)	178.00(15)
C(5)-C(4)-C(9)-C(10)	177.19(14)
C(3)-C(4)-C(9)-C(10)	-2.5(2)
C(8)-C(9)-C(10)-C(11)	-130.25(17)
C(4)-C(9)-C(10)-C(11)	50.33(18)
C(9)-C(10)-C(11)-N(1)	-48.40(16)
C(9)-C(10)-C(11)-C(12)	-172.99(12)
N(1)-C(11)-C(12)-C(13)	-9.5(2)
C(10)-C(11)-C(12)-C(13)	112.26(16)
N(1)-C(11)-C(12)-C(17)	170.44(13)
C(10)-C(11)-C(12)-C(17)	-67.77(18)
C(17)-C(12)-C(13)-C(14)	-1.4(2)
C(11)-C(12)-C(13)-C(14)	178.59(14)
C(12)-C(13)-C(14)-C(15)	1.3(2)
C(13)-C(14)-C(15)-C(16)	0.3(2)
C(14)-C(15)-C(16)-C(17)	-1.7(2)
C(15)-C(16)-C(17)-C(12)	1.5(2)
C(13)-C(12)-C(17)-C(16)	0.0(2)
C(11)-C(12)-C(17)-C(16)	-179.99(14)
O(2)-C(1)-N(1)-C(11)	17.7(3)
O(1)-C(1)-N(1)-C(11)	-163.14(14)
O(2)-C(1)-N(1)-C(3)	172.42(17)
O(1)-C(1)-N(1)-C(3)	-8.43(19)
C(12)-C(11)-N(1)-C(1)	-80.48(17)
C(10)-C(11)-N(1)-C(1)	155.43(14)
C(12)-C(11)-N(1)-C(3)	127.63(15)
C(10)-C(11)-N(1)-C(3)	3.6(2)
C(4)-C(3)-N(1)-C(1)	-112.36(15)
C(2)-C(3)-N(1)-C(1)	12.38(19)
C(4)-C(3)-N(1)-C(11)	41.6(2)
C(2)-C(3)-N(1)-C(11)	166.32(16)

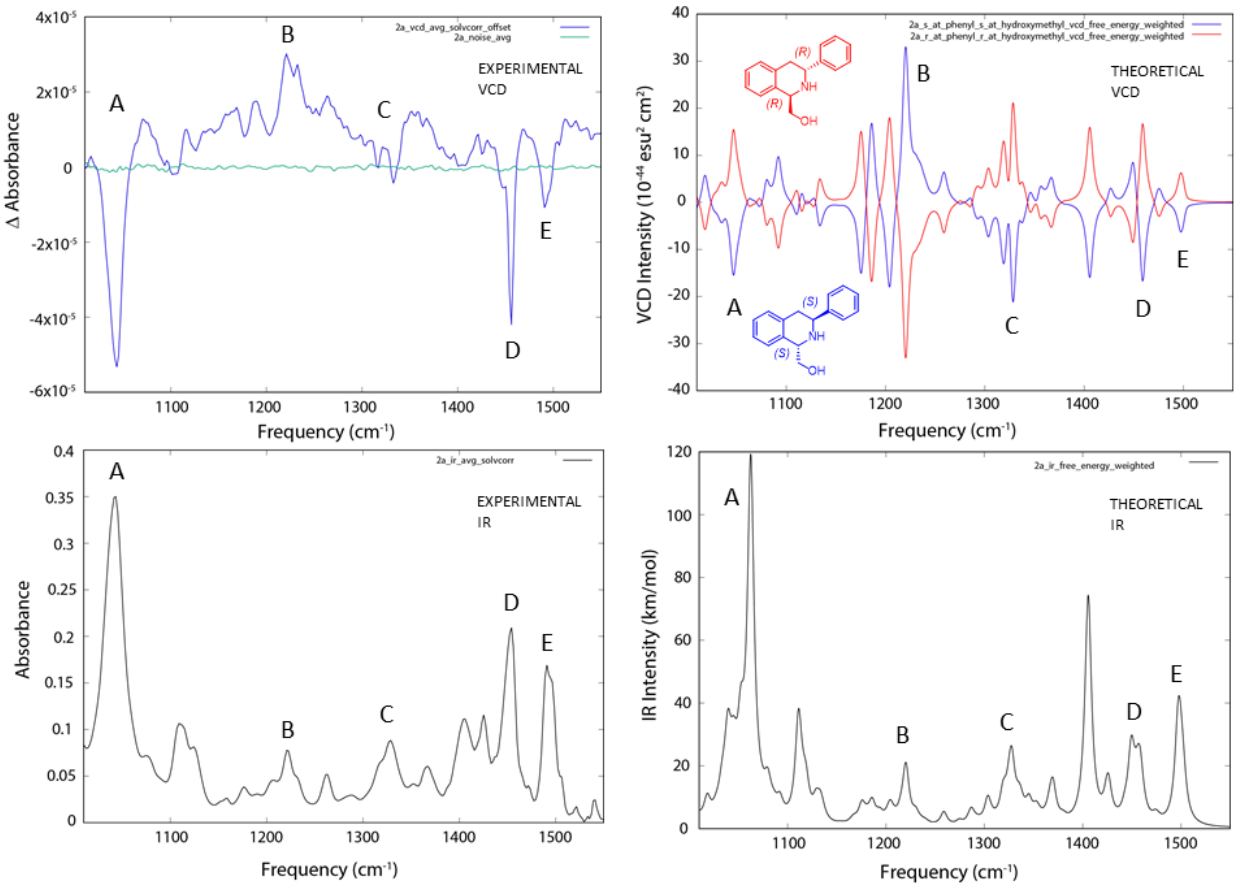
Symmetry transformations used to generate equivalent atoms:

Determination of Relative and Absolute Configuration of 2a by Vibrational Circular Dichroism (VCD):

Experimental Protocol. A solution of the isolated *trans* isomer of **2a** (11 mg) was prepared in $CDCl_3$ (225 μL; 49 mg/mL) and loaded into a front-loading SL-4 cell (International Crystal Laboratories) possessing BaF_2 windows and 100 μm path length. Infrared (IR) and VCD spectra were acquired on a BioTools ChiralIR-2X VCD spectrometer as a set of 30 one-hour blocks (30 blocks, 3120 scans per block) at 4 cm^{-1} resolution in dual PEM mode. A 15-minute acquisition of neat (–)-α-pinene control (separate 75 μm BaF_2 cell) yielded a VCD spectrum in agreement with literature spectra and identical to those previously acquired on the same instrument. IR and VCD spectra were background corrected using a 30-minute block IR acquisition of the empty instrument chamber under gentle N_2 purge, and were solvent corrected using a 6-hour (6 blocks, 3120 scans per block) IR/VCD acquisition of $CDCl_3$ in the same 100 μm BaF_2 cell as used for **2a**. The reported spectra represent the result of block averaging. The baseline of the resultant VCD spectrum (top left panel below) was vertically offset by a constant such that that the y-value was zero at a frequency of 1000 cm-1 for ease of viewing and assignment.

Computational Protocol. The arbitrarily chosen *(R,R)* enantiomer of **2a** (ultimately corresponding to ***ent*-2a**) was subjected to an initial exhaustive stochastic molecular mechanics-based conformational search (MMFF94 force field, 0.06 Å geometric RMSD cutoff, and 30 kcal/mol energy window) as implemented in MOE 2019.0102 (Chemical Computing Group, Montreal, CA). All conformers retained the *(R,R)* configuration and were subjected to geometry optimization, harmonic frequency calculation, and VCD rotational strength evaluation using density functional theory utilizing the B3PW91 functional, cc-pVTZ basis, and implicit IEFPCM chloroform solvation model. All calculations were performed with the *Gaussian 16* program system (Rev. C.01; Frisch *et al*., Gaussian, Inc., Wallingford, CT). Resultant IEFPCM-B3PW91/cc-pVTZ harmonic frequencies were scaled by 0.98. All structurally unique conformers possessing all positive Hessian eigenvalues were Boltzmann weighted by relative free energy at 298.15 K. The predicted IR and VCD frequencies and intensities of the retained conformers were convolved using Lorentzian line shapes (γ = 4 cm^{-1}) and summed using the

respective Boltzmann weights to yield the final predicted IR and VCD spectra. The predicted VCD spectrum of the *(S,S)* enantiomer (ultimately agreeing with the experimentally measured spectrum of isolated **2a**) was generated by inversion of sign. From alignment of the experimentally measured and theoretical IR spectra, in particular regions **A-E** corresponding to unambiguous regions of the experimental VCD spectrum (see below) the absolute configuration of the isolated and measured **2a** could be confidently assigned as *(S,S)*.



Experimental (left) and theoretical (right) IR and VCD spectra of **2a**.

References:

(1) Pangborn, A. M.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics.* **1996**, *15*, 1518–1520.

(2) Sheldrick, G. M. *Acta Cryst.* **1990**, A46, 467-473.

(3) Sheldrick, G. M. *Acta Cryst.* **2015**, C71, 3-8.

(4) Müller, P. *Crystallography Reviews* **2009**, *15*, 57-83.

(5) Kim, A. N.; Ngamnithiporn, A.; Welin, E. R.; Daiger, M. T.; Grünanger, C. U.; Bartberger, M. D.; Virgil, S. C.; Stoltz, B. M. *ACS Catal.* **2020**, *10*, 3241–3248.

(6) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966–8967.

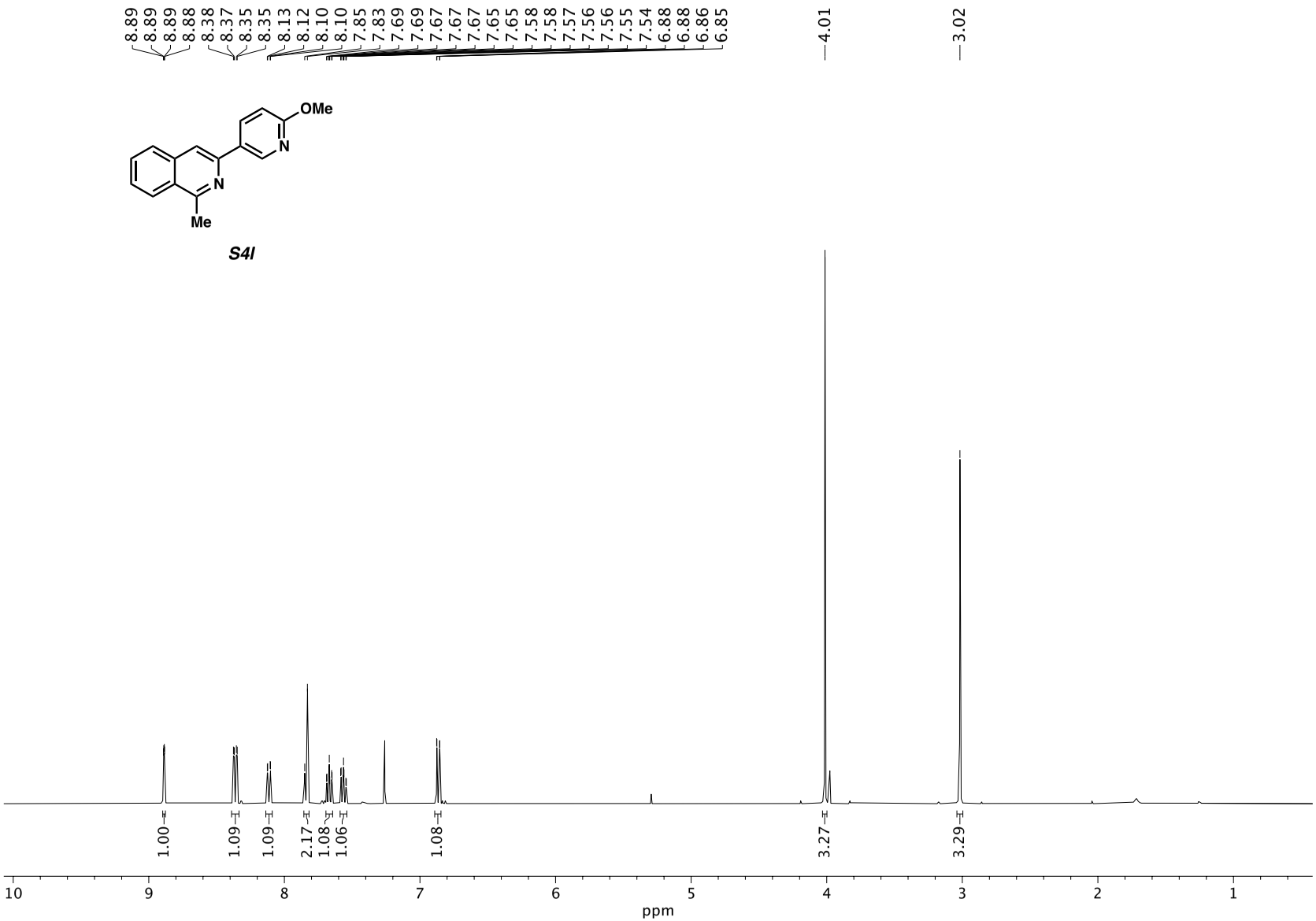
(7) Xu, Z.; Xu, X.; O'Laoi, R.; Ma, H.; Zheng, J.; Chen, S.; Luo, L.; Hu, Z.; He, S.; Li, J.; Zhang, H.; Zhang, X. *Bioorg. Med. Chem.* **2016**, *24,* 5861–5872.

(8) Liu, C.-Y.; Angamuthu, V.; Chen, W.-C.; Hou, D.-R. *Org. Lett.* **2020**, *22*, 2246–2250.

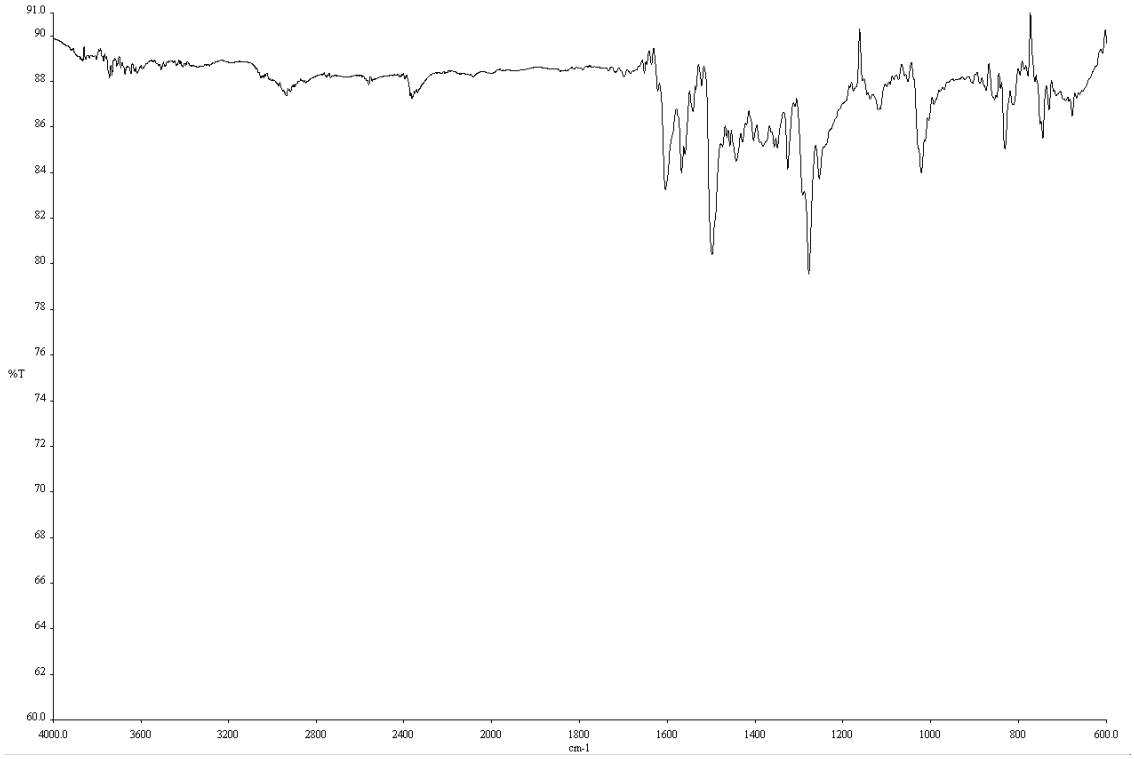
(9) Butora, G.; Hudlicky, T.; Fearnley, S. P.; Gum, A. G.; Stabile, M. R.; Abboud, K. *Tetrahedron Lett.* **1996**, *37*, 8155–8158.

(10) Kita, Y.; Yamaji, K.; Higashida, K.; Sathaiah, K.; Iimuro, A.; Mashima, K. *Chem. Eur. J.* **2015**, *21*, 1915–1927.

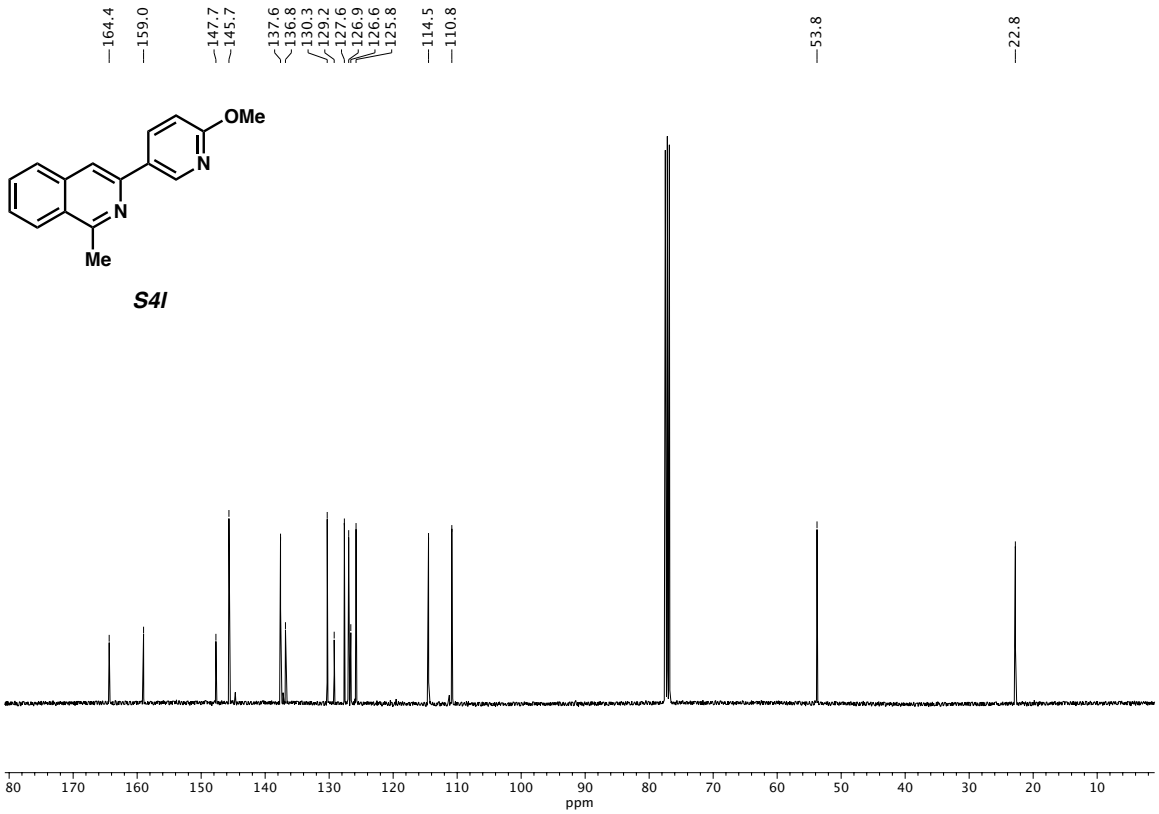
(11) Dorta, R.; Broggini, D.; Stoop, R.; Rüegger, H.; Spindler, F.; Togni, A. *Chem. Eur. J.* **2004**, *10*, 267–278.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **S4l**.

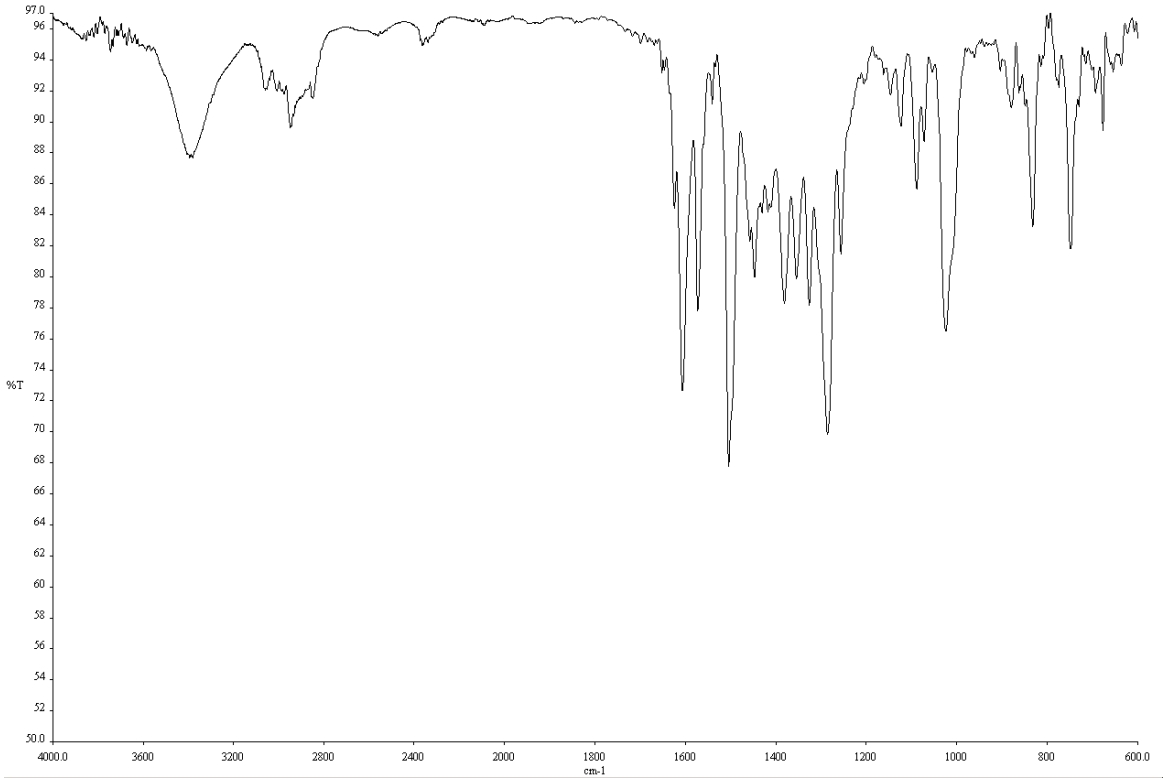


Infrared spectrum (Thin Film, NaCl) of compound **S4l**.

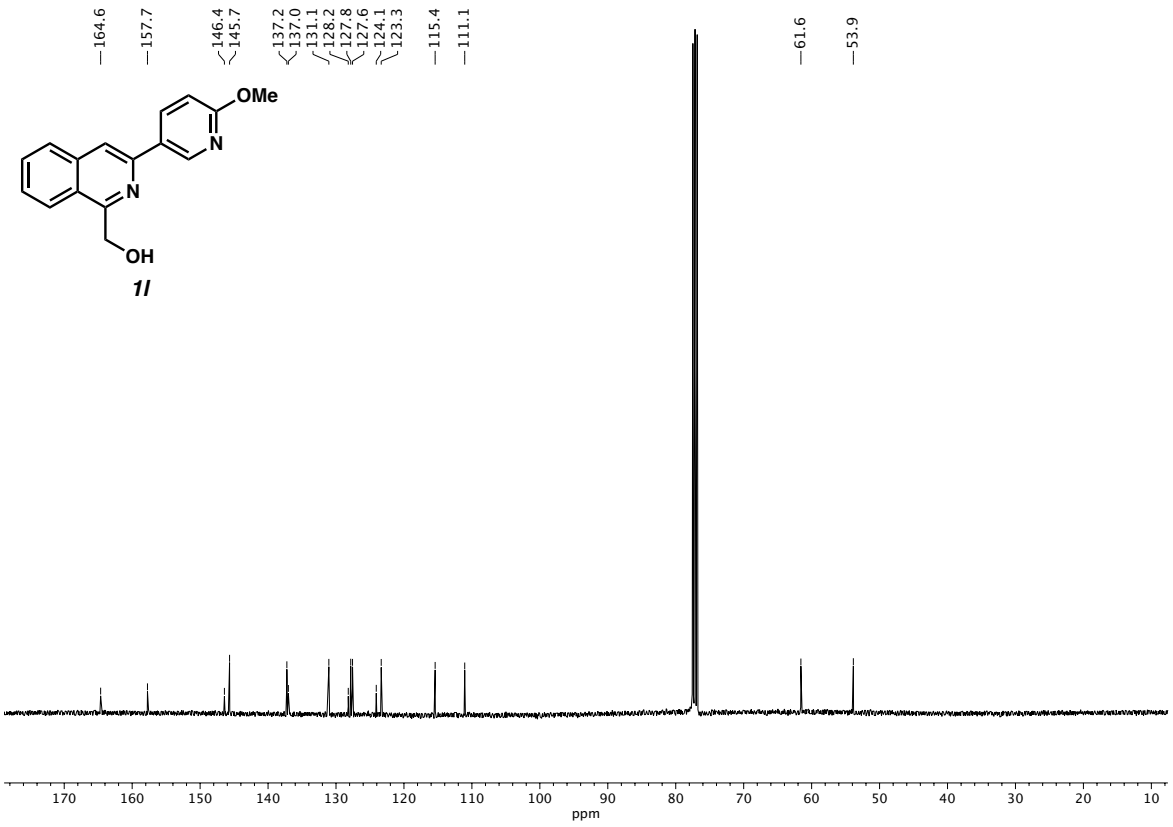


^{13}C NMR (100 MHz, $CDCl_3$) of compound **S4l**.

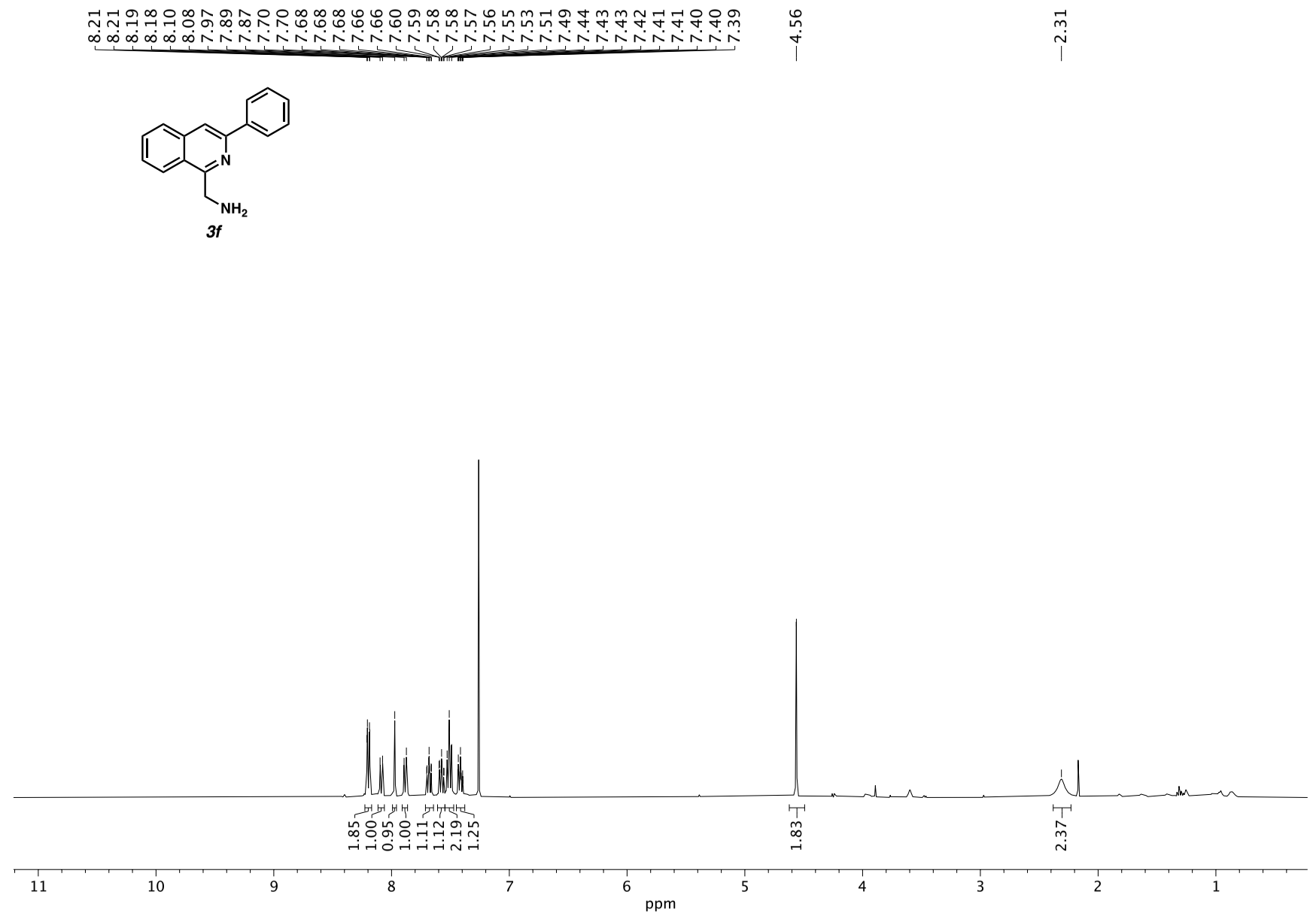
^{1}H NMR (400 MHz, $CDCl_3$) of compound **11**.



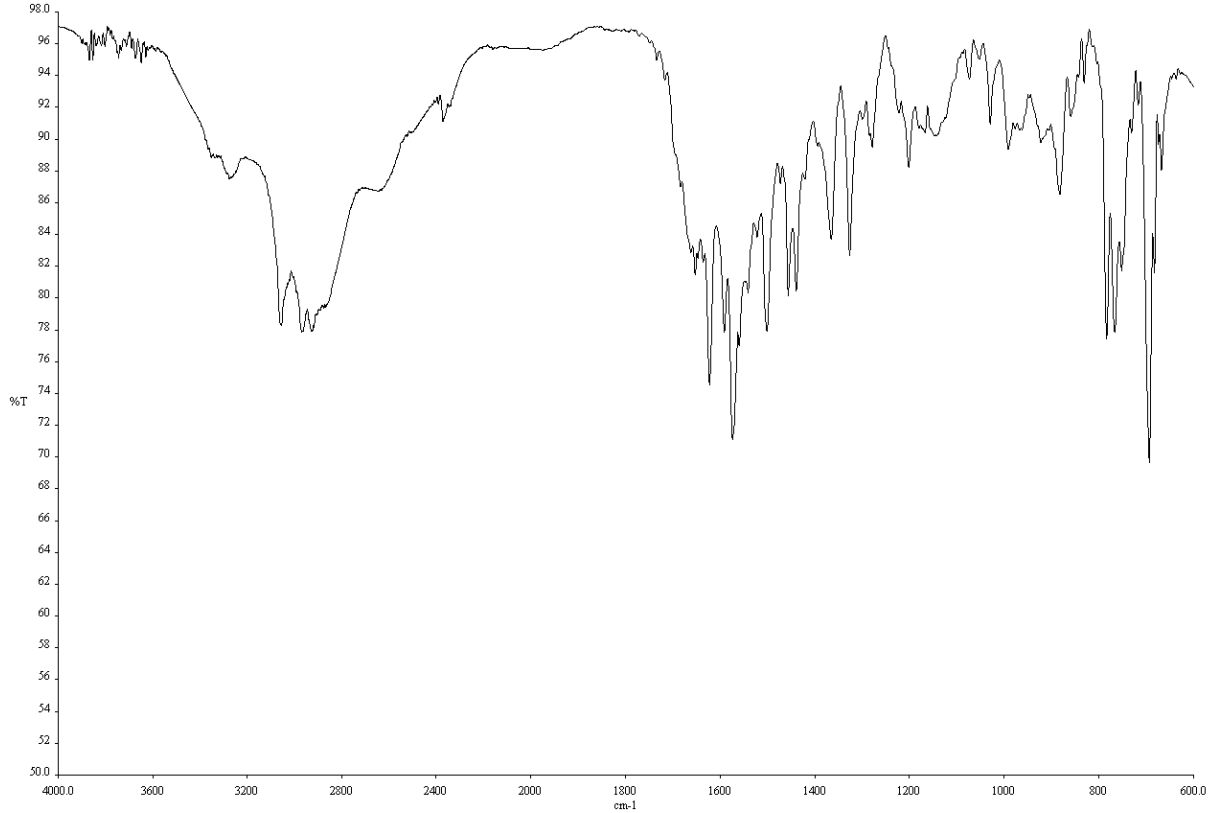
Infrared spectrum (Thin Film, NaCl) of compound **1l**.



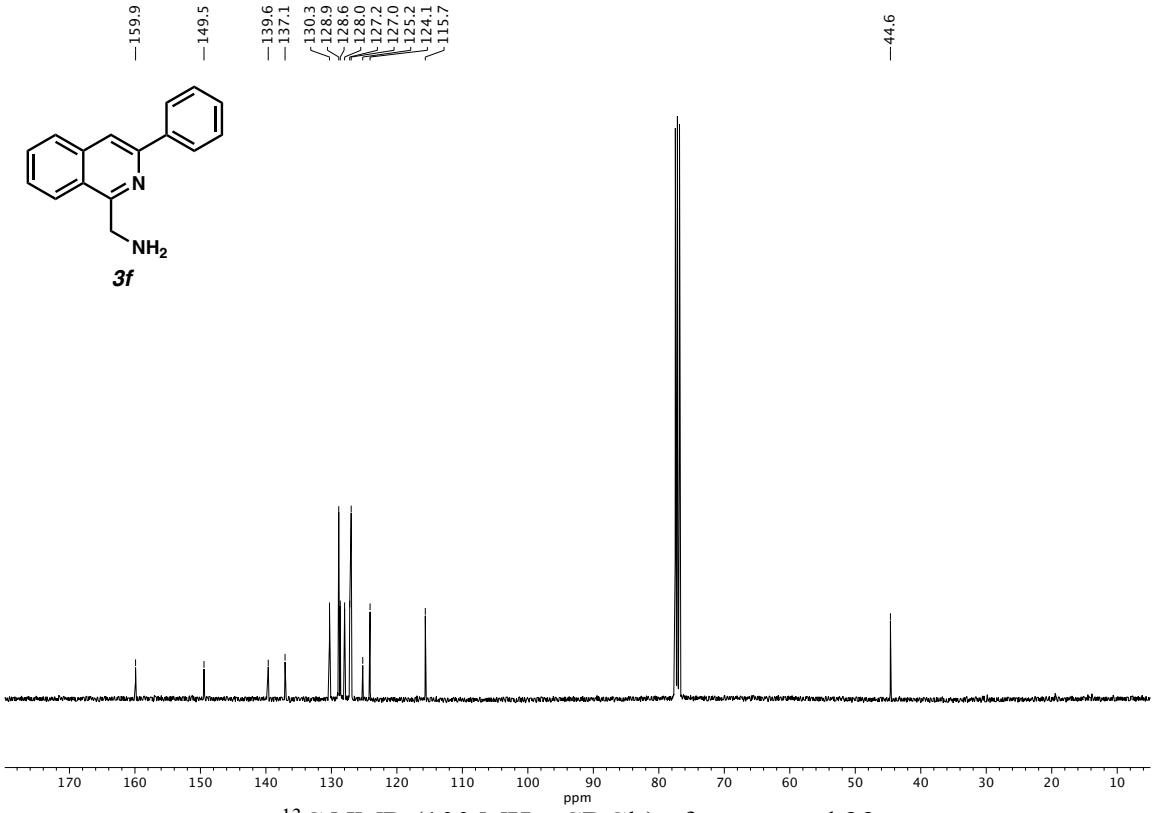
^{13}C NMR (100 MHz, $CDCl_3$) of compound **1l**.



^{1}H NMR (400 MHz, $CDCl_3$) of compound **3f**.

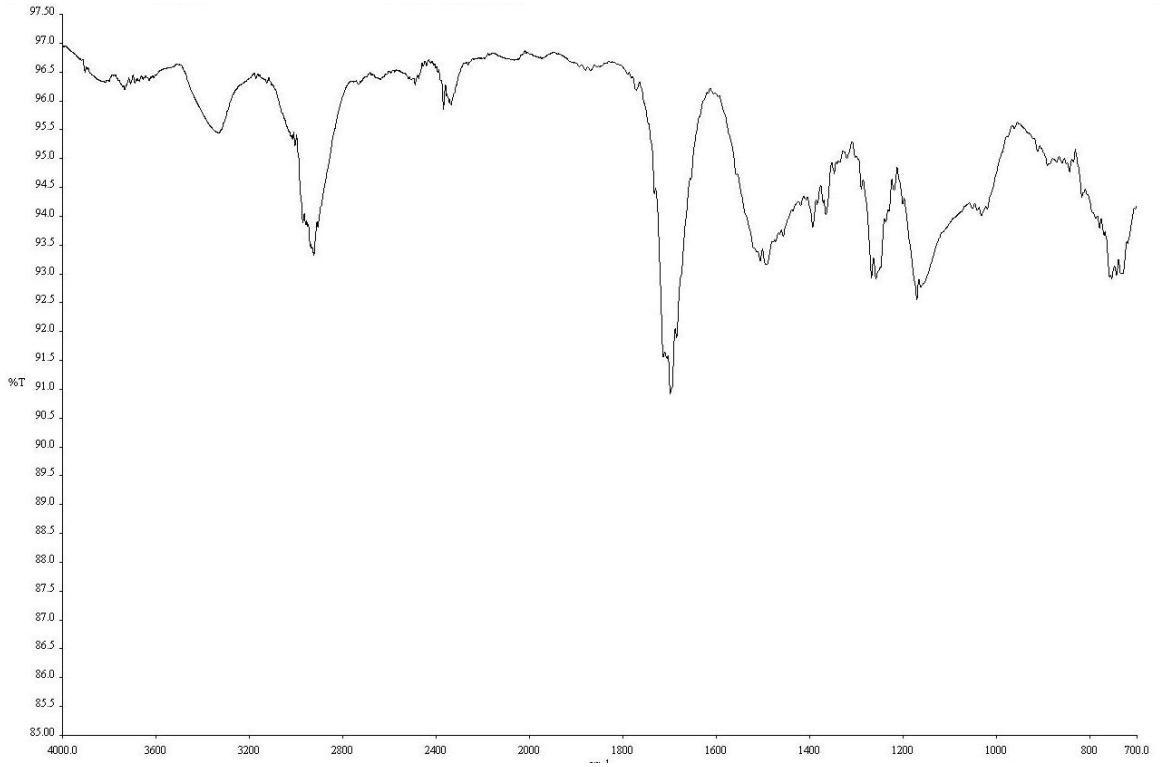


Infrared spectrum (Thin Film, NaCl) of compound **3f**.

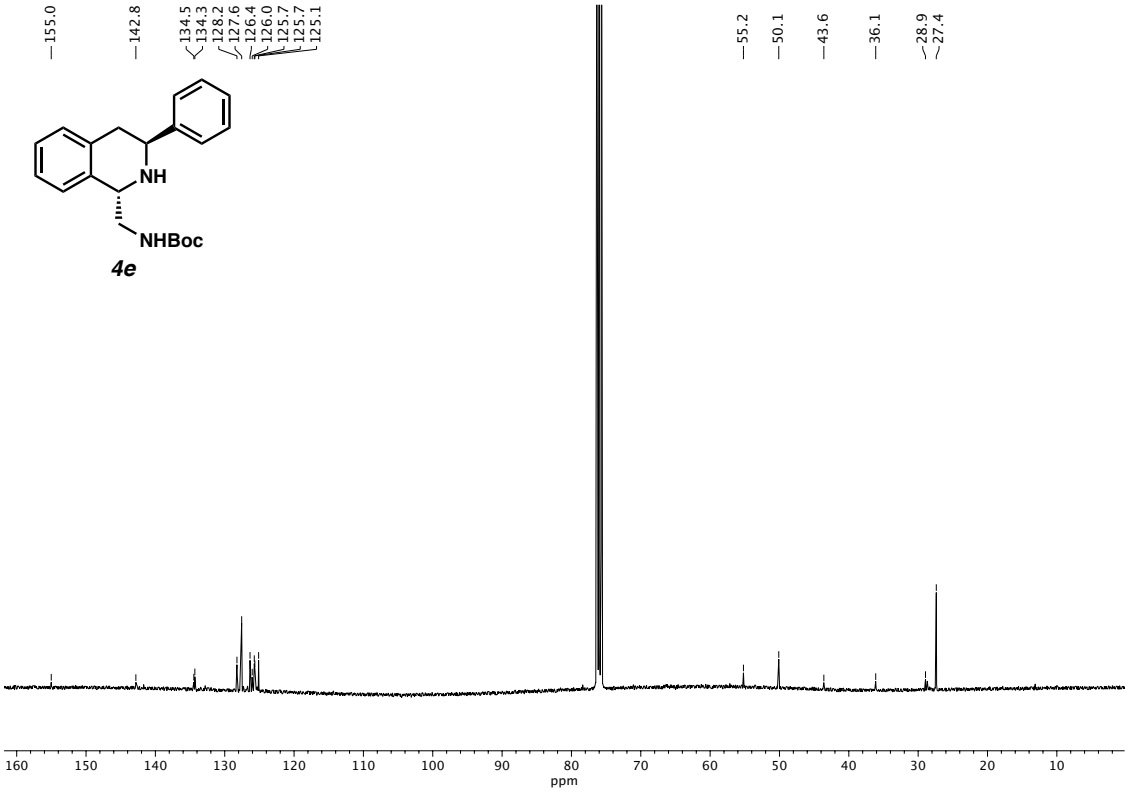


^{13}C NMR (100 MHz, $CDCl_3$) of compound **3f**.

^{1}H NMR (400 MHz, $CDCl_3$) of compound **4e**.

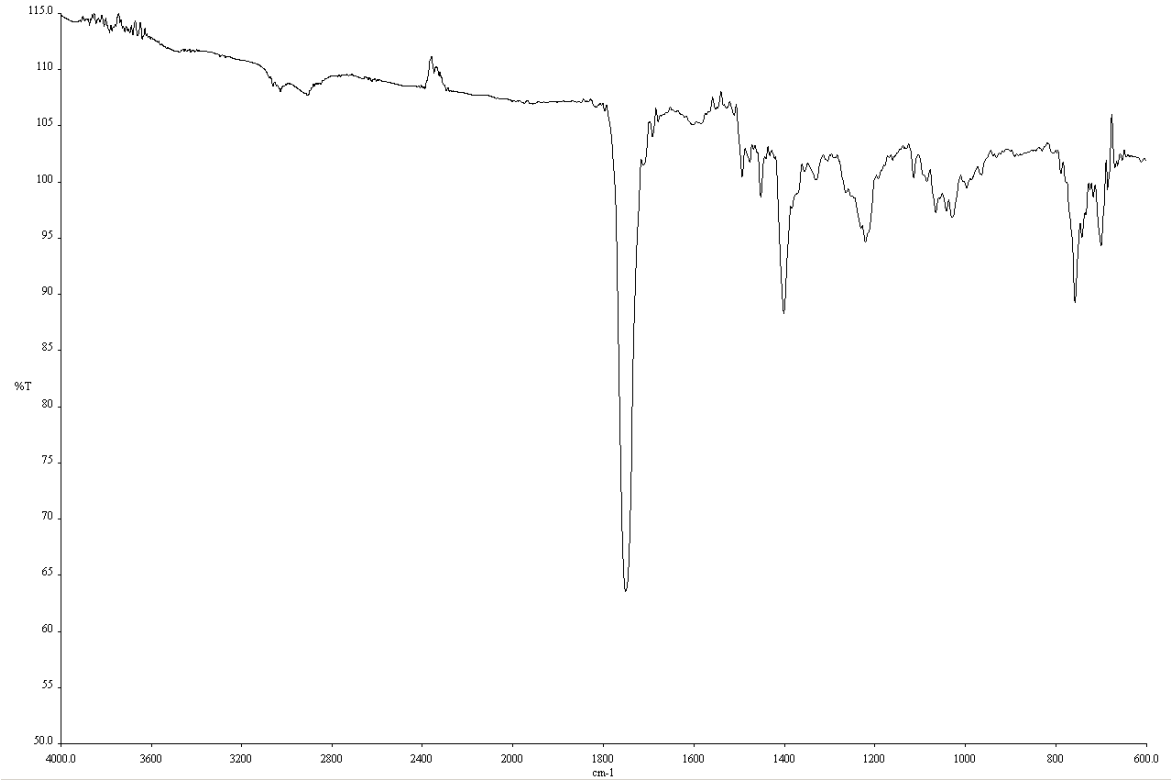


Infrared spectrum (Thin Film, NaCl) of compound **4e**.

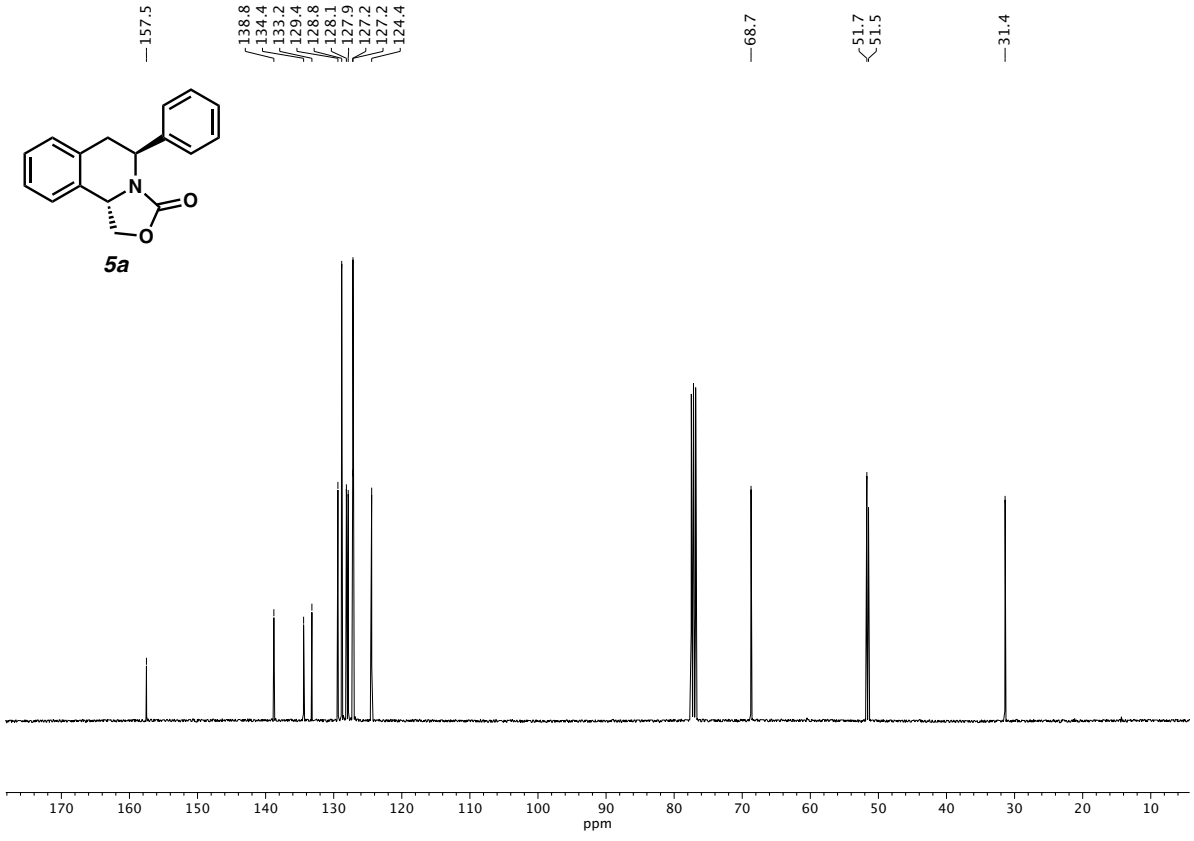


^{13}C NMR (100 MHz, $CDCl_3$) of compound **4e**.

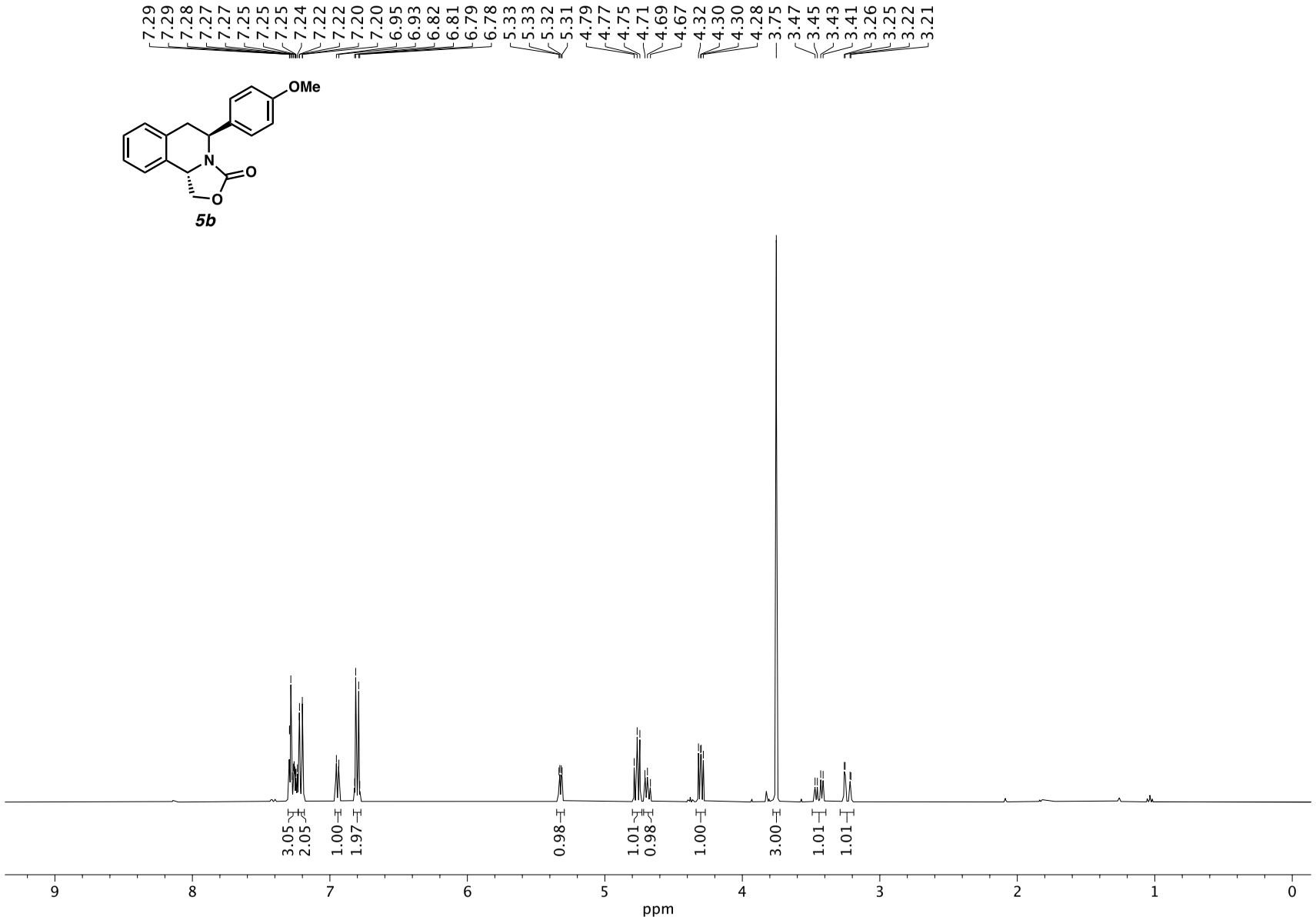
^{1}H NMR (400 MHz, $CDCl_3$) of **5a**.



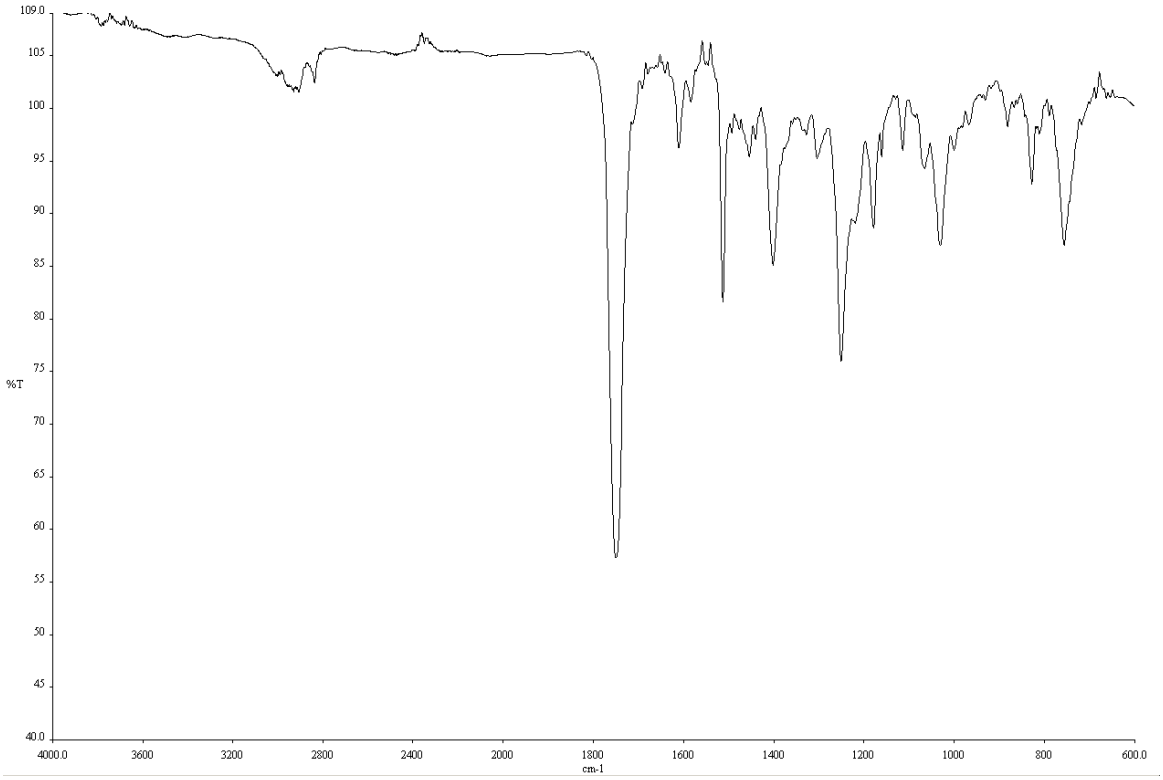
Infrared spectrum (Thin Film, NaCl) of **5a**.



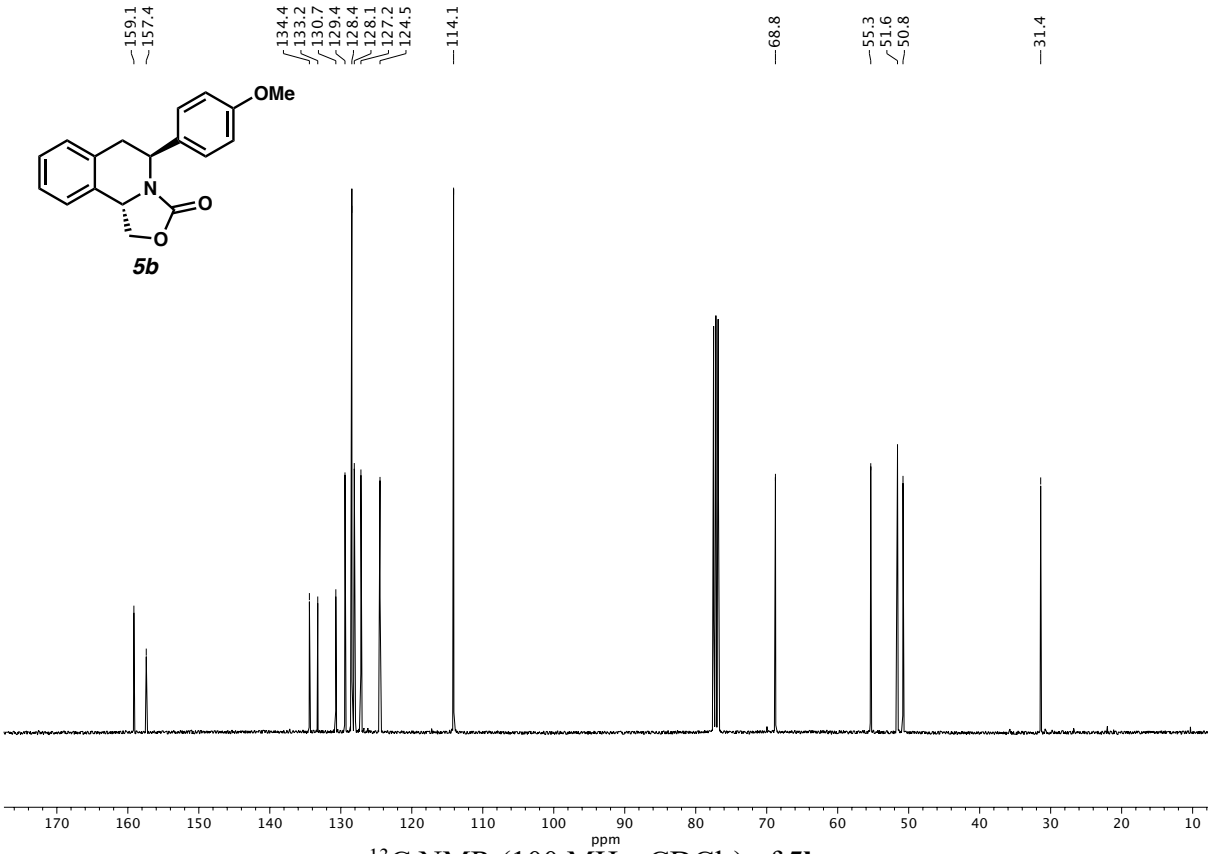
^{13}C NMR (100 MHz, $CDCl_3$) of **5a**.



^{1}H NMR (400 MHz, $CDCl_3$) of **5b**.

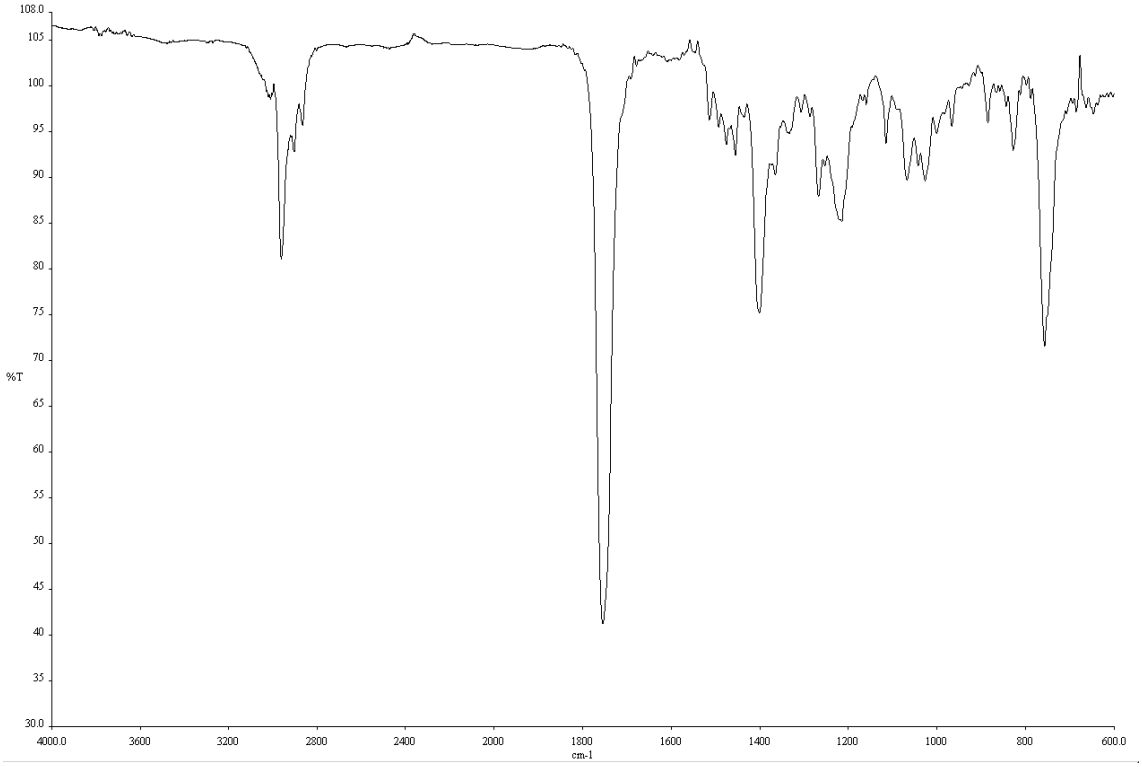


Infrared spectrum (Thin Film, NaCl) of **5b**.

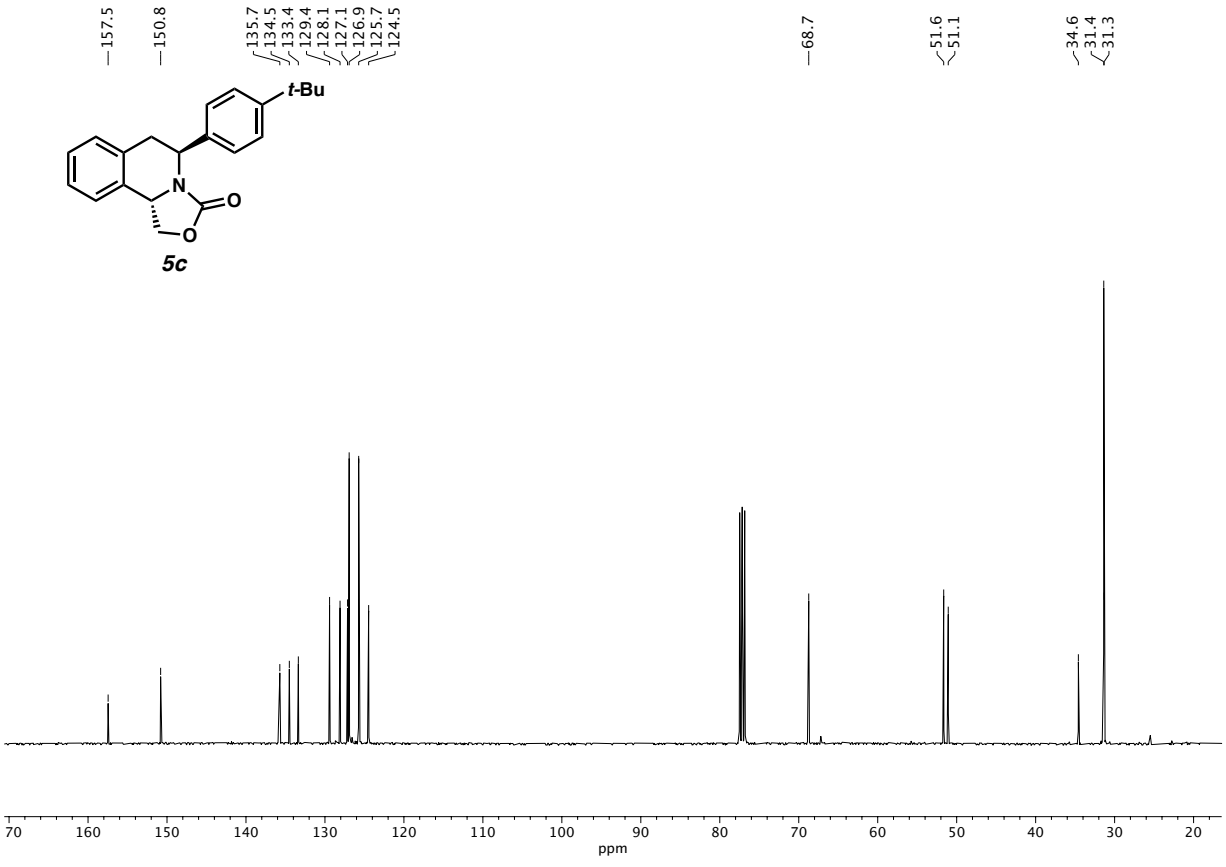


^{13}C NMR (100 MHz, $CDCl_3$) of **5b**.

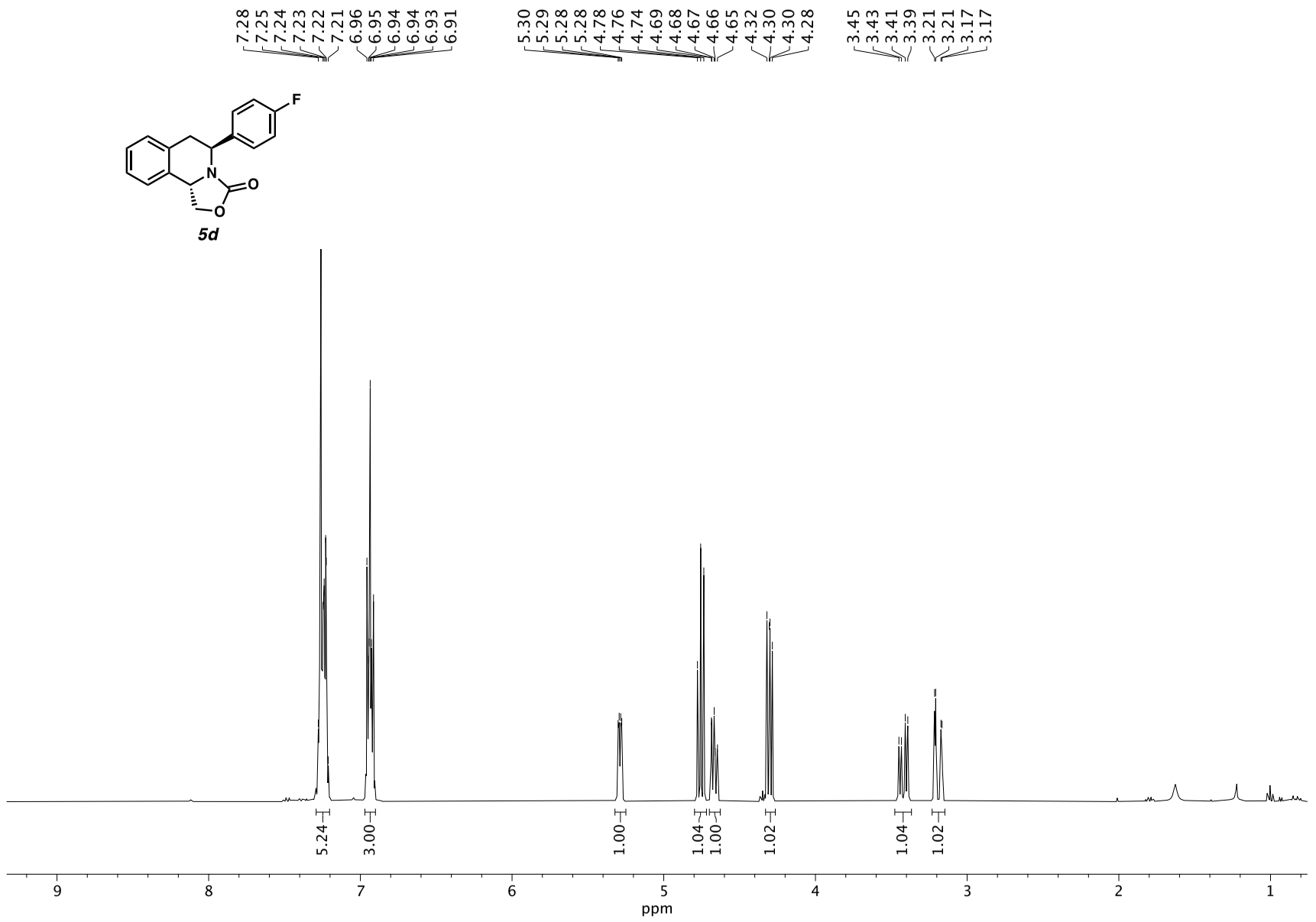
^{1}H NMR (400 MHz, $CDCl_3$) of **5c**.



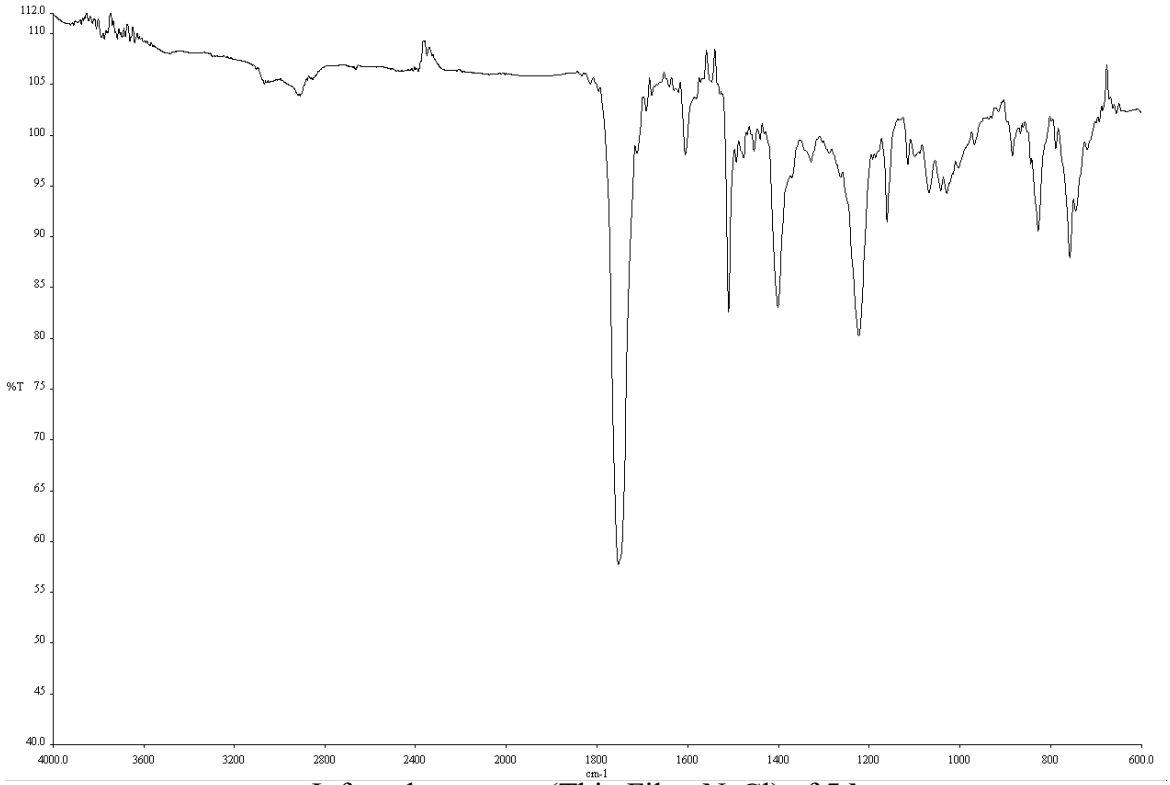
Infrared spectrum (Thin Film, NaCl) of **5c**.



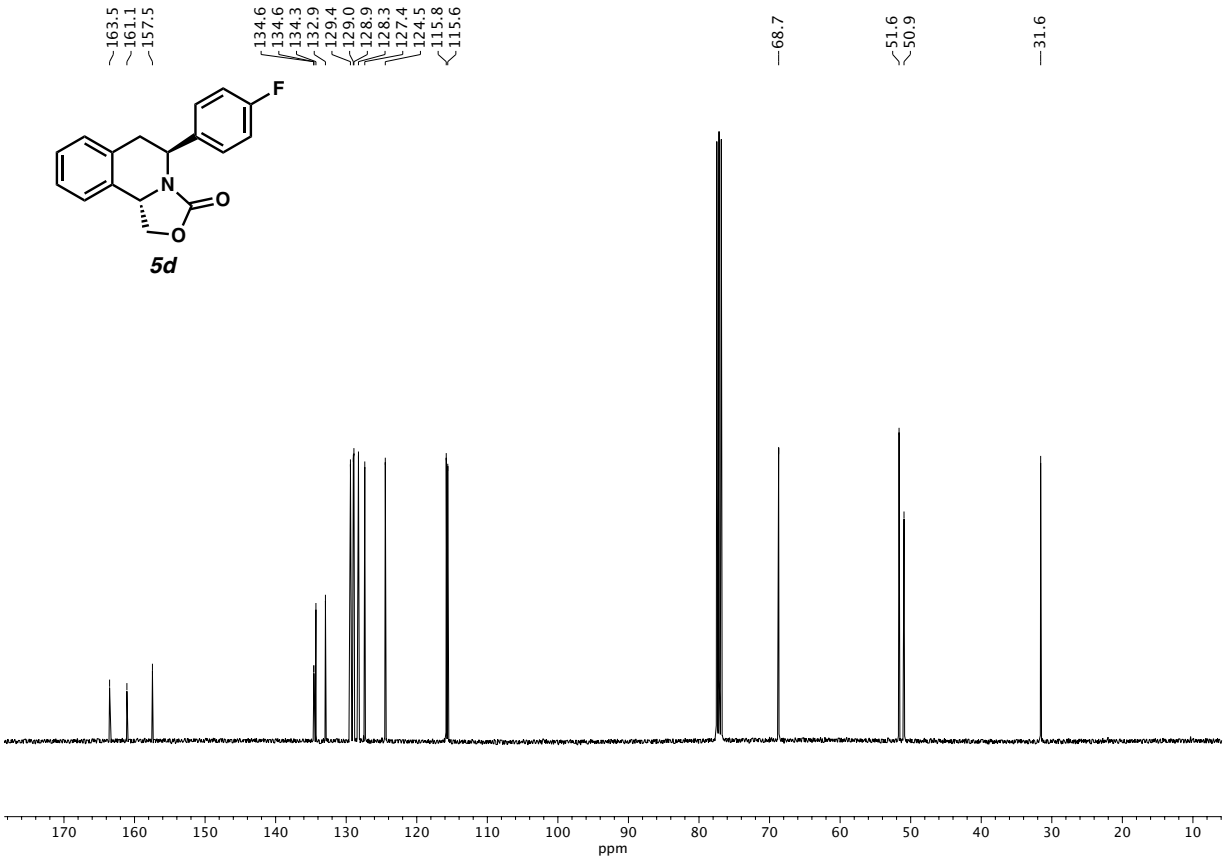
^{13}C NMR (100 MHz, $CDCl_3$) of **5c**.



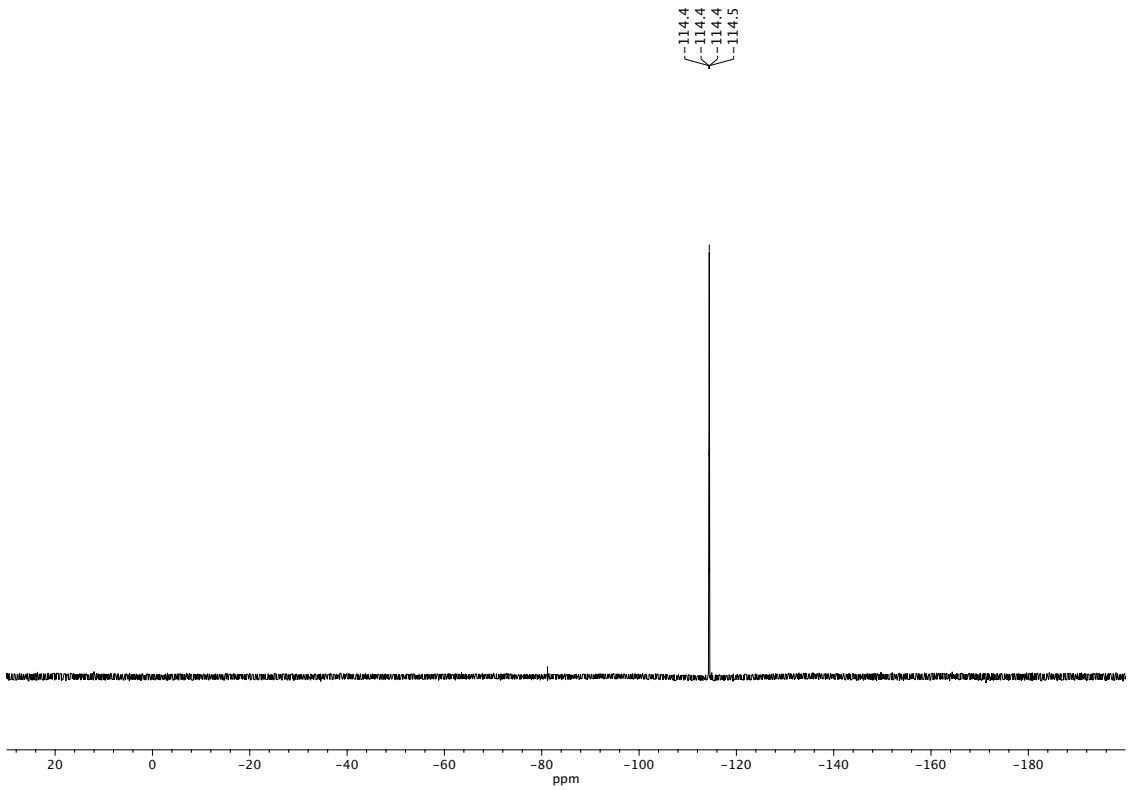
^{1}H NMR (400 MHz, $CDCl_3$) of **5d**.



Infrared spectrum (Thin Film, NaCl) of **5d**.

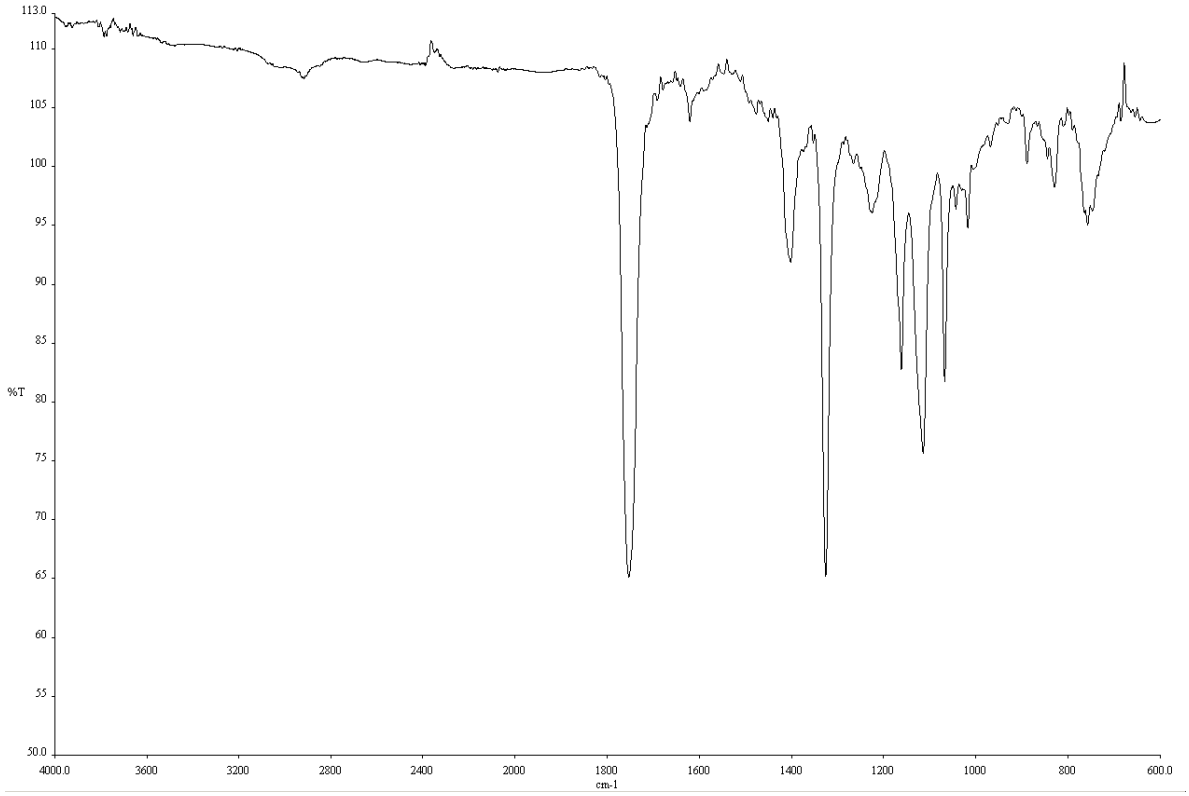


^{13}C NMR (100 MHz, $CDCl_3$) of **5d**.

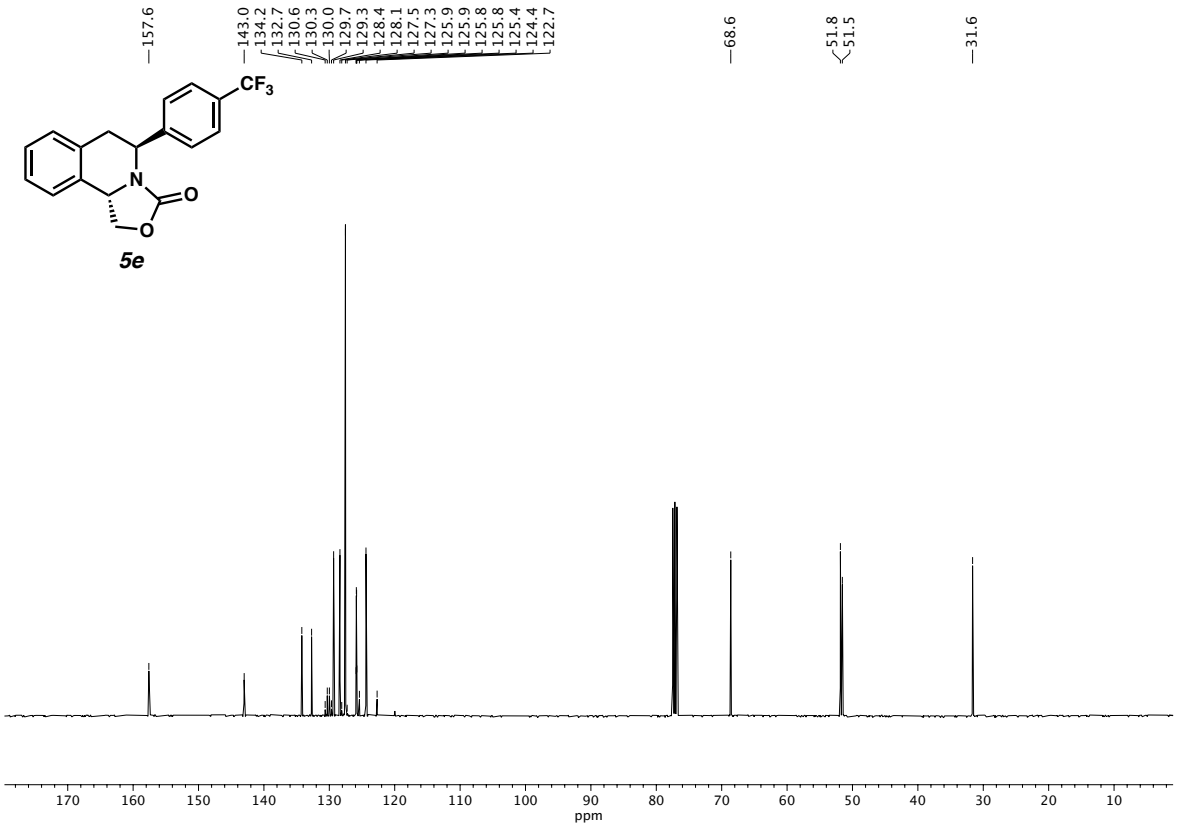


^{19}F NMR (282 MHz, $CDCl_3$) of **5d**.

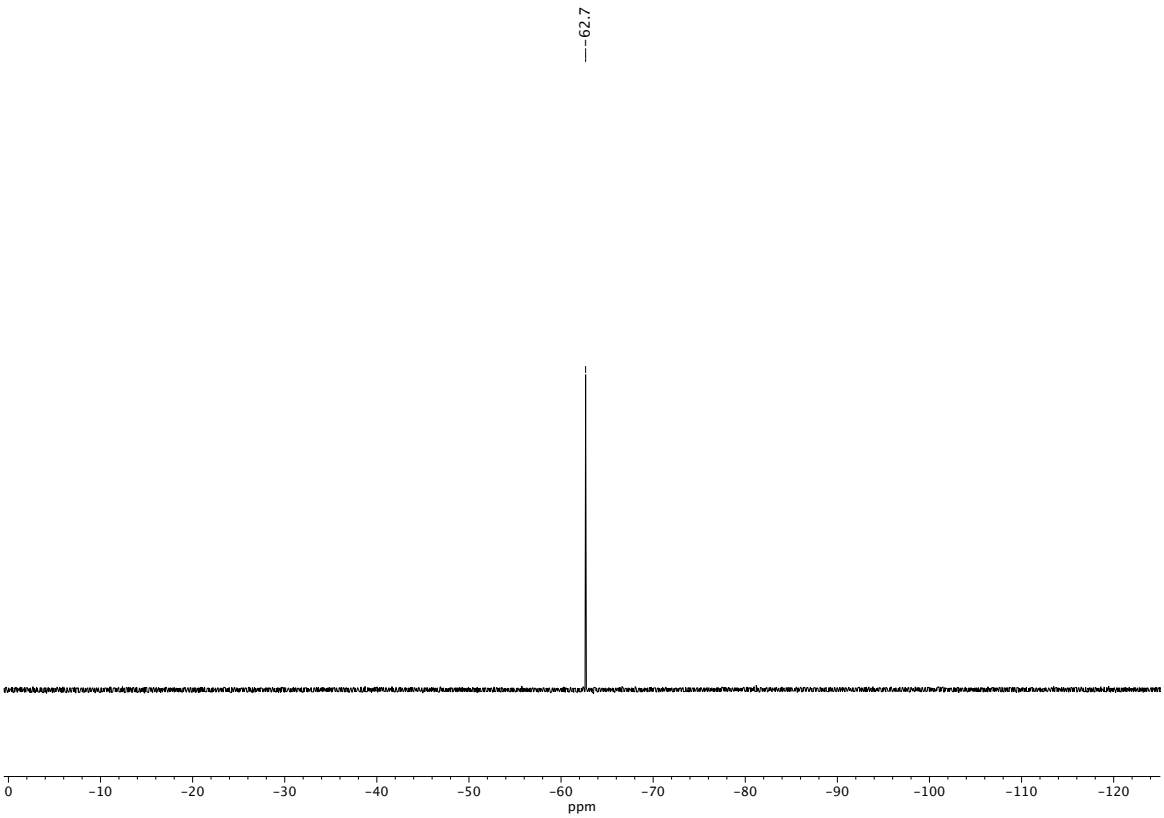
^{1}H NMR (400 MHz, $CDCl_3$) of **5e**.



Infrared spectrum (Thin Film, NaCl) of **5e**.

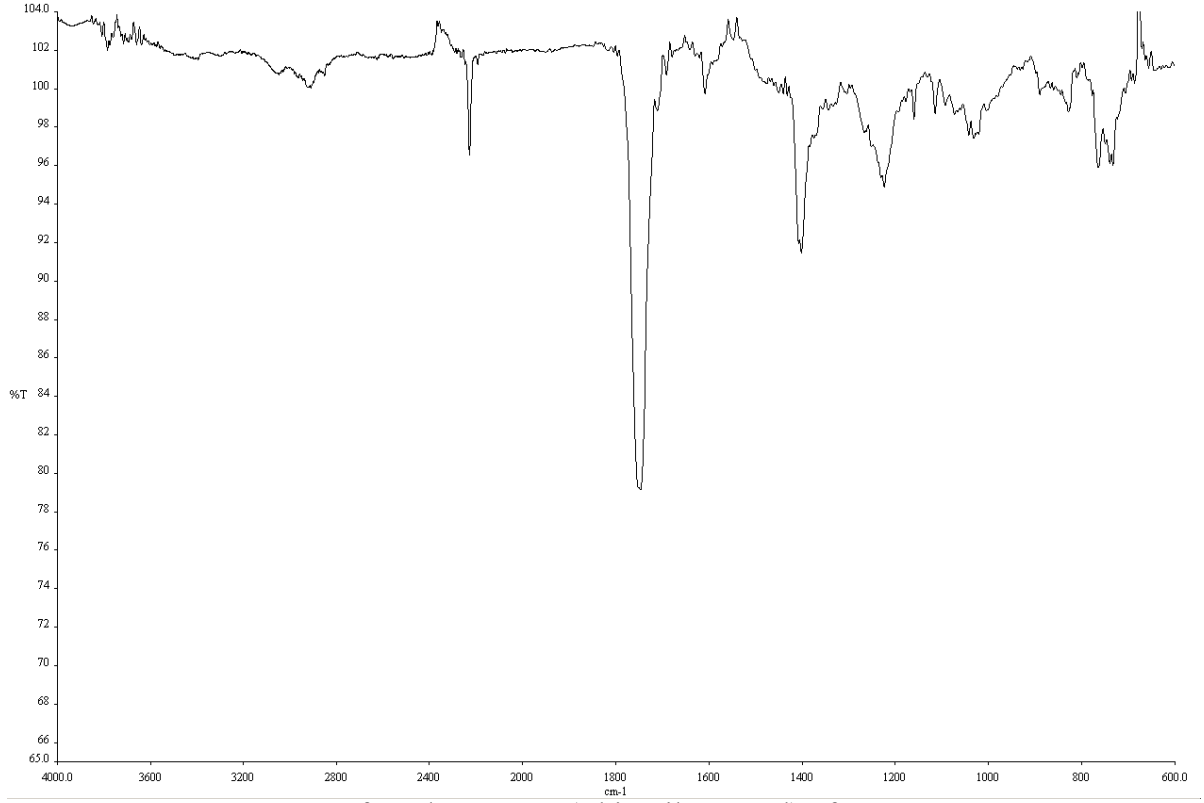


^{13}C NMR (100 MHz, $CDCl_3$) of **5e**.

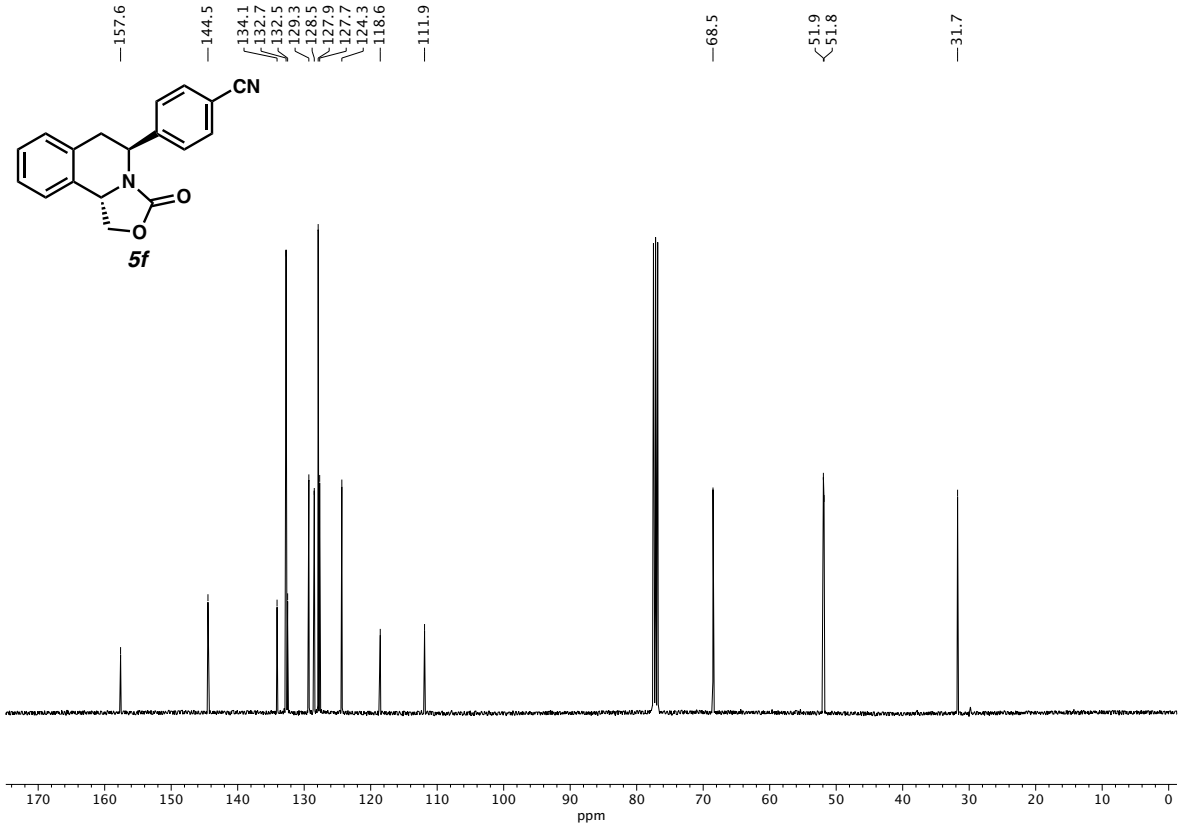


^{19}F NMR (282 MHz, $CDCl_3$) of **5e**.

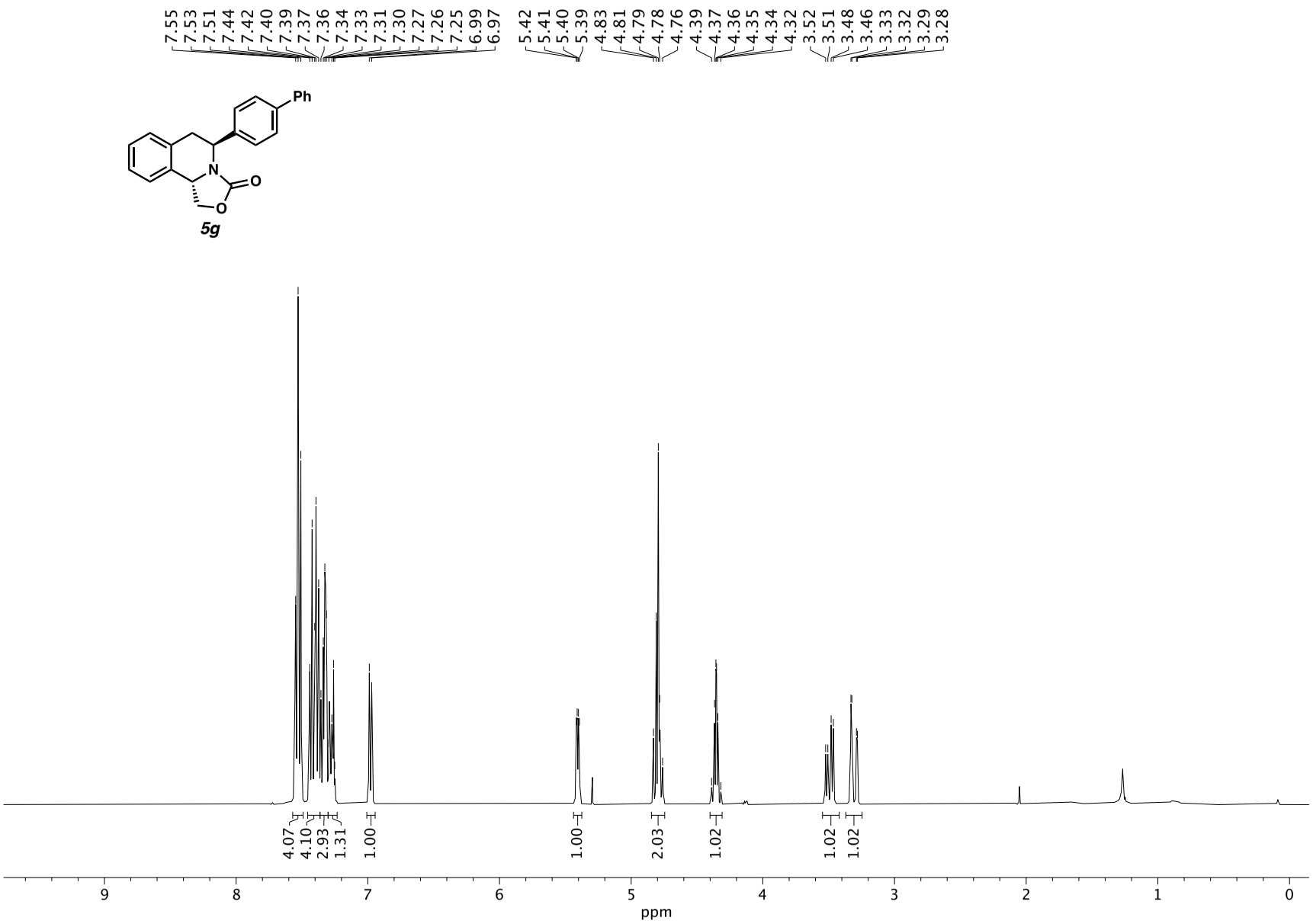
^{1}H NMR (400 MHz, $CDCl_3$) of **5f**.



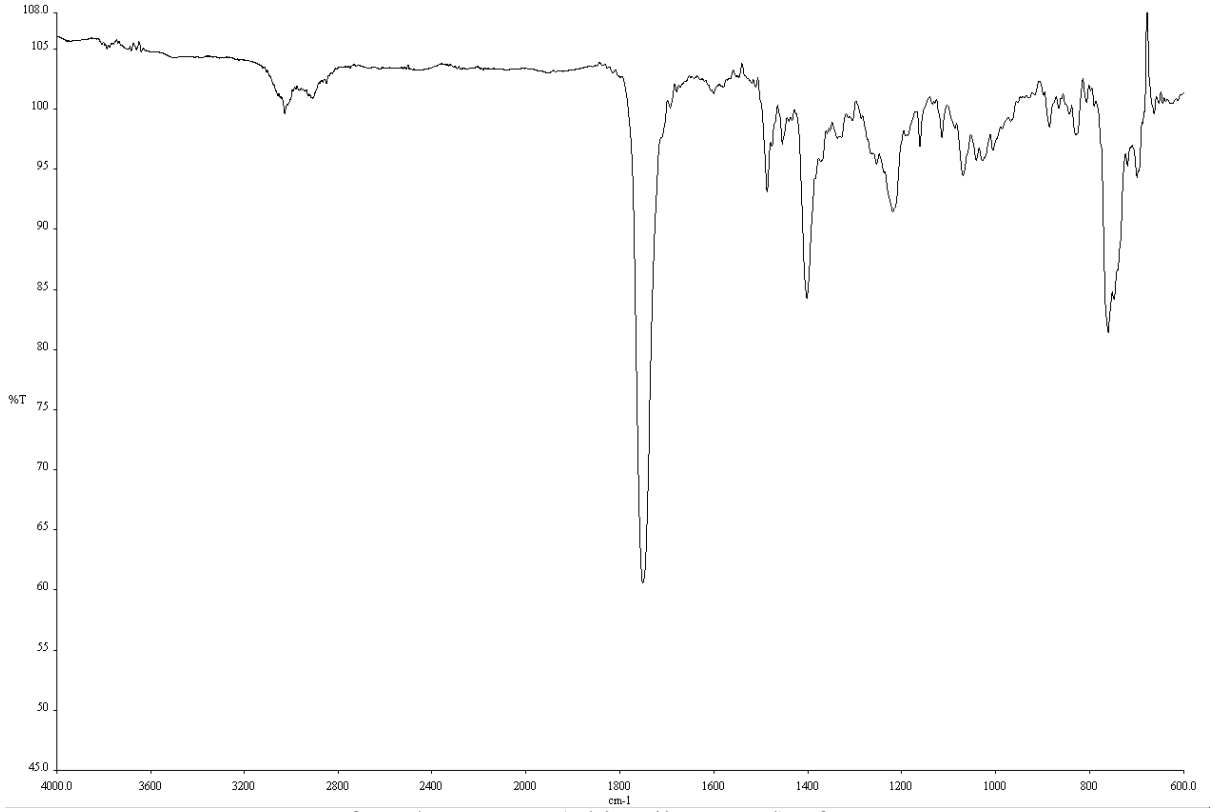
Infrared spectrum (Thin Film, NaCl) of **5f**.



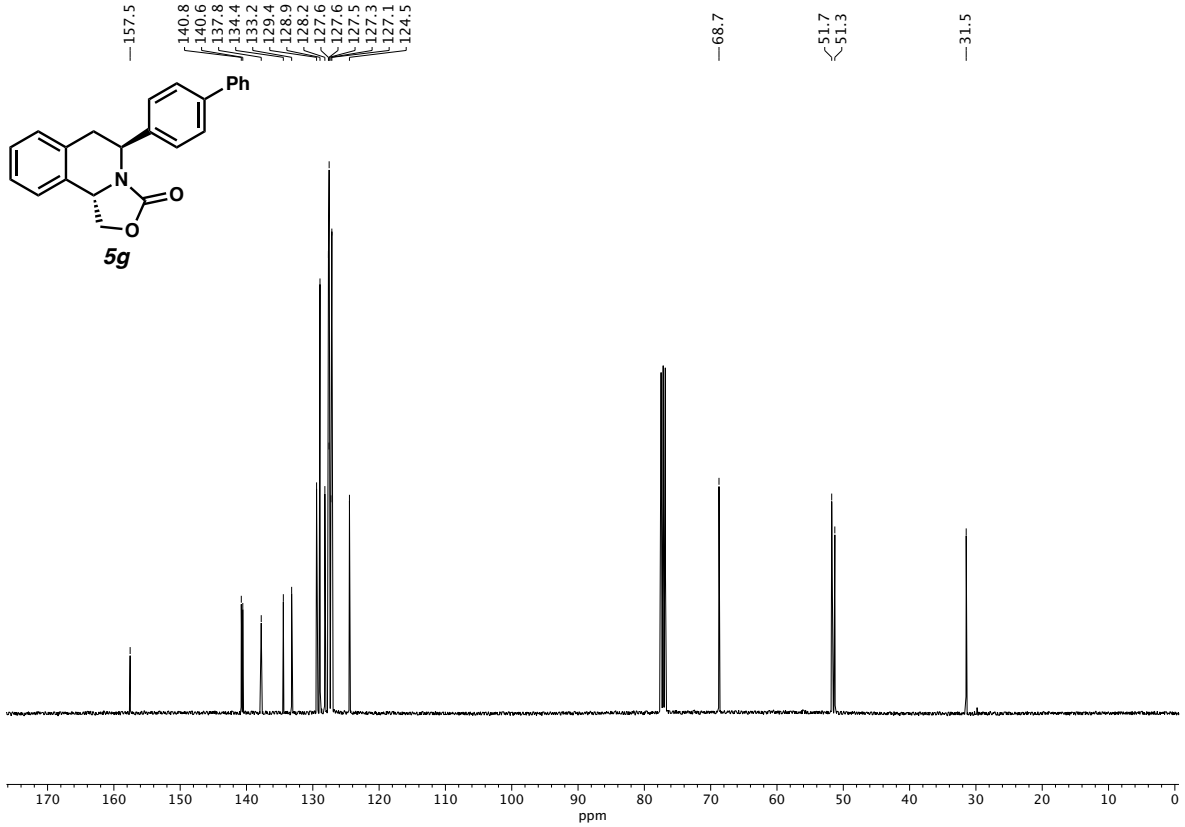
^{13}C NMR (100 MHz, $CDCl_3$) of **5f**.



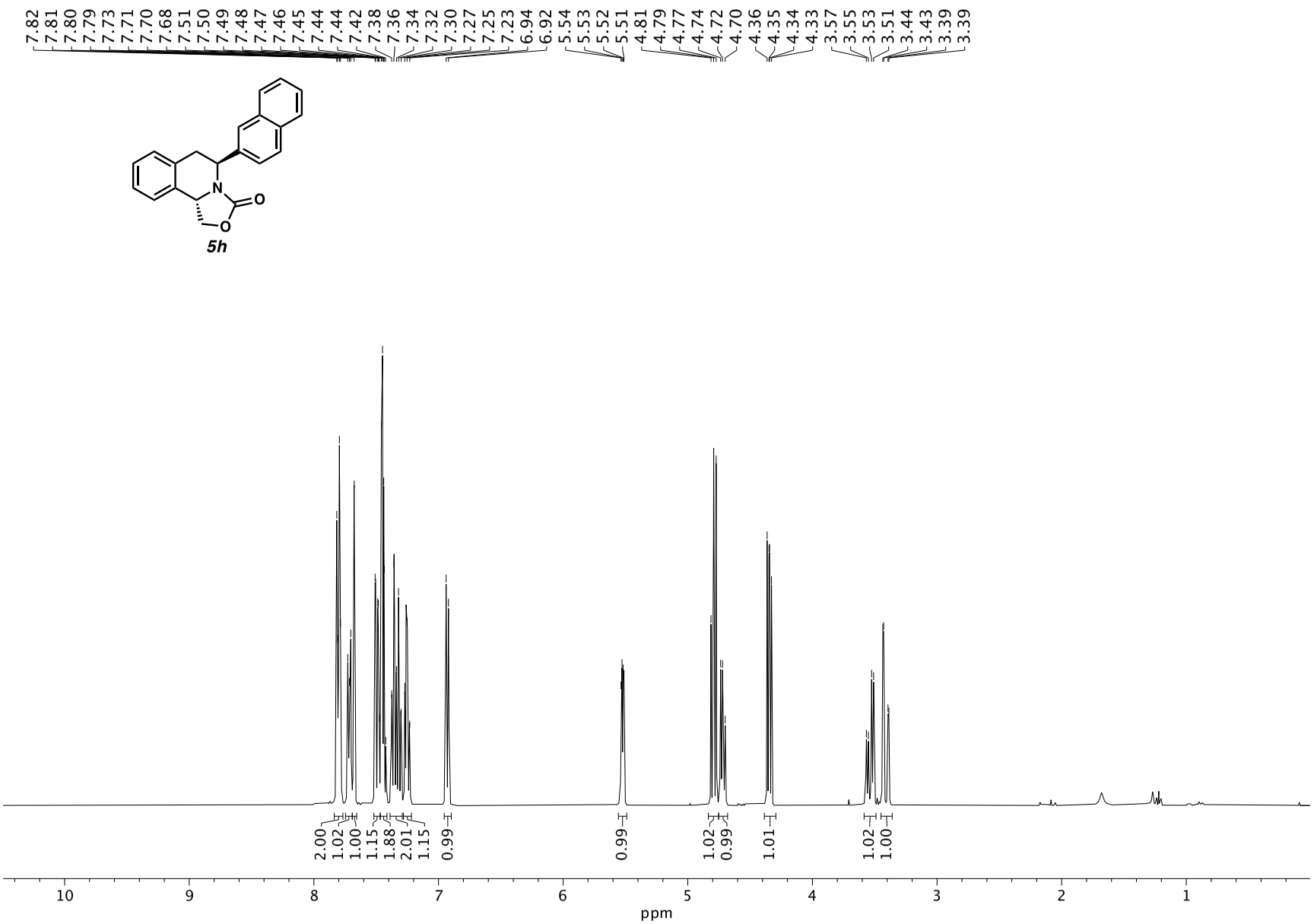
^{1}H NMR (400 MHz, $CDCl_3$) of **5g**.



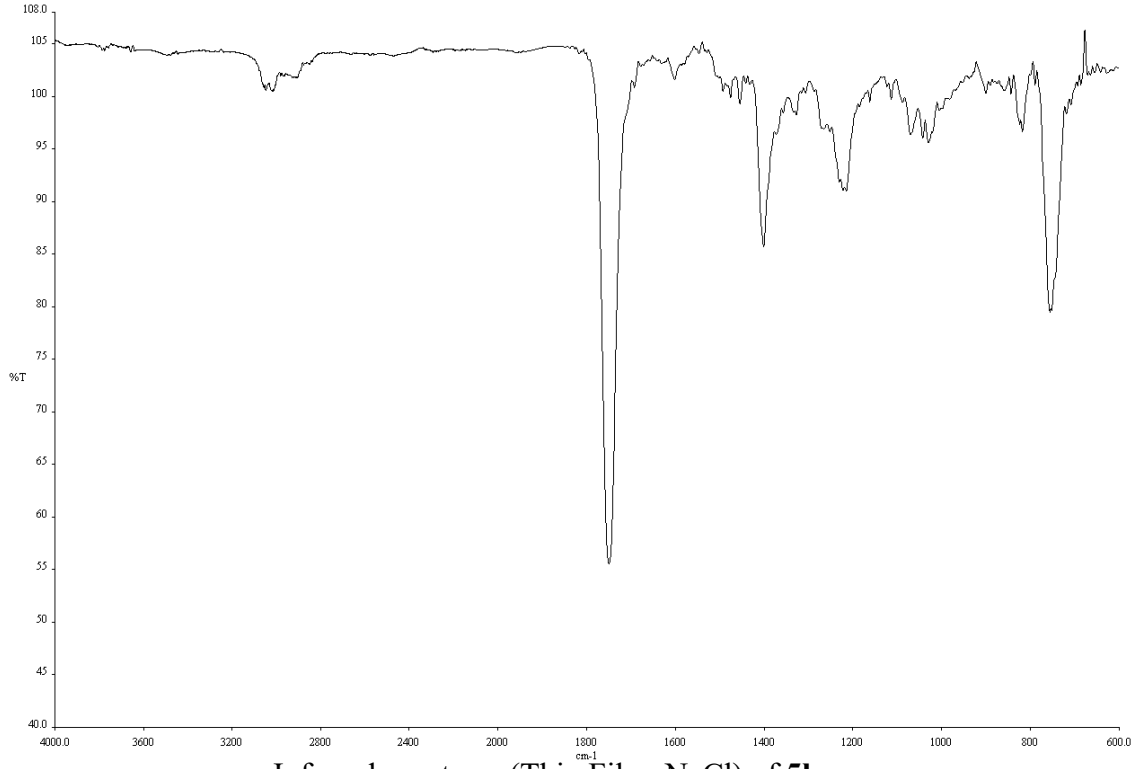
Infrared spectrum (Thin Film, NaCl) of **5g**.



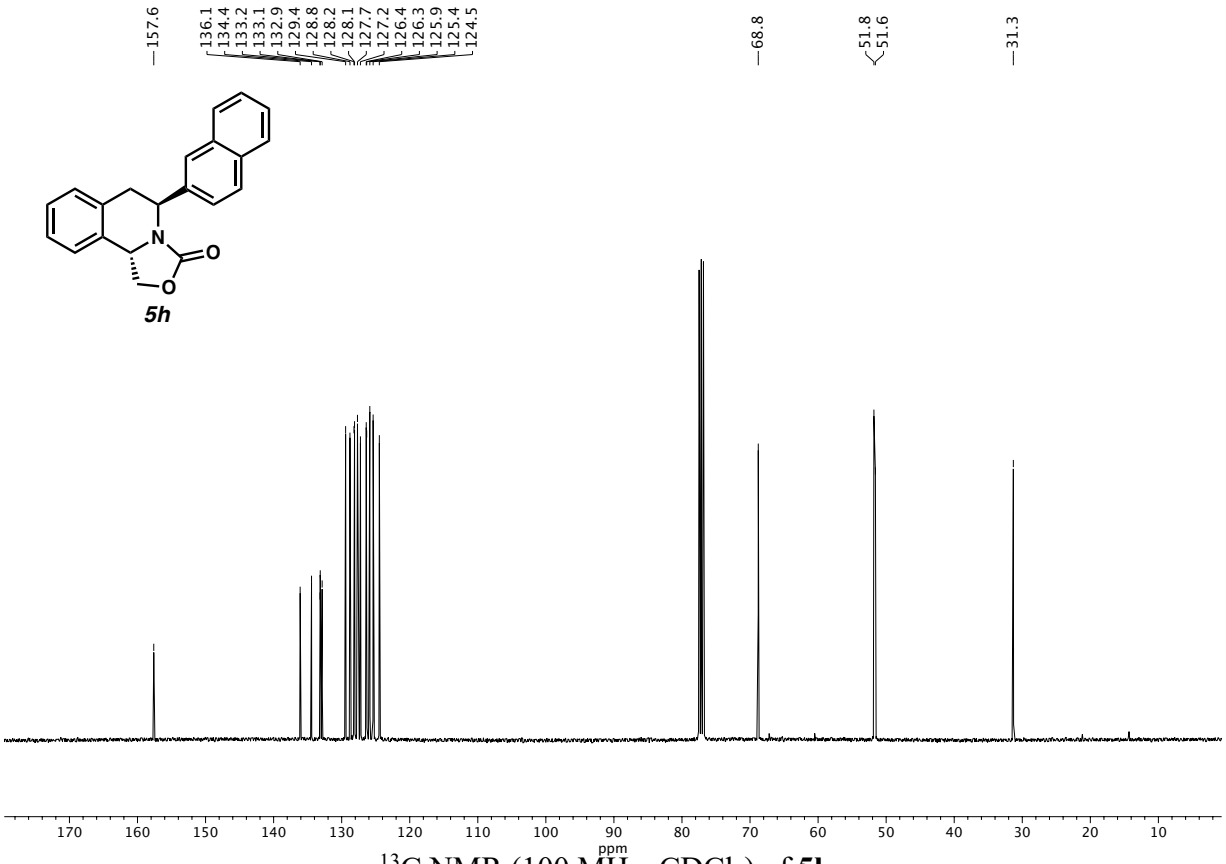
^{13}C NMR (100 MHz, $CDCl_3$) of **5g**.



^{1}H NMR (400 MHz, $CDCl_3$) of **5h**.

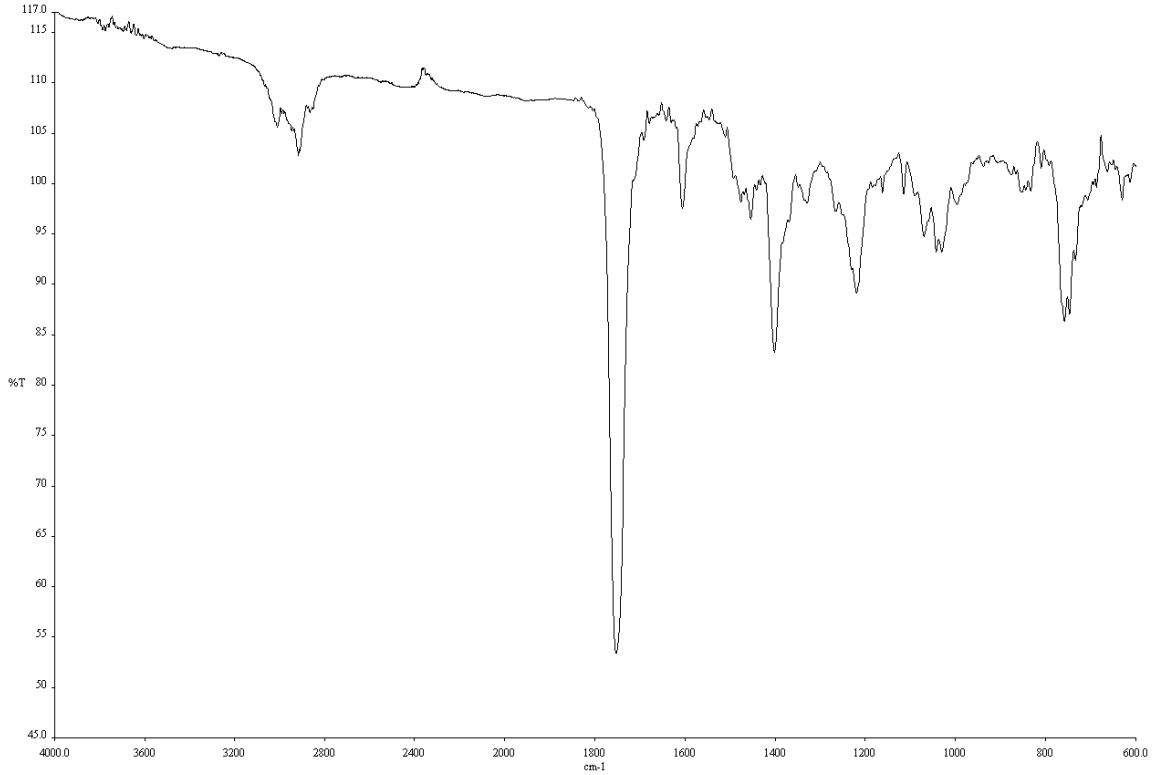


Infrared spectrum (Thin Film, NaCl) of **5h**.

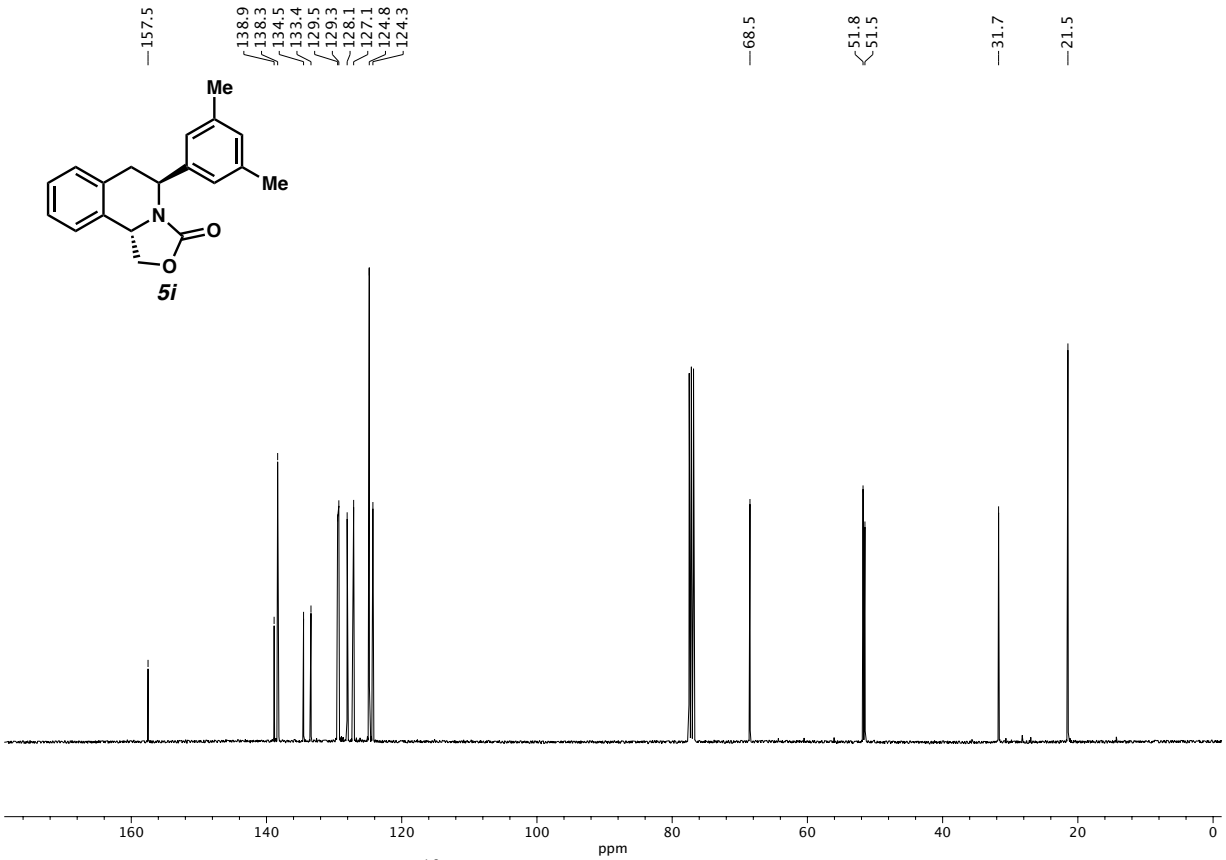


^{13}C NMR (100 MHz, $CDCl_3$) of **5h**.

^{1}H NMR (400 MHz, $CDCl_3$) of **5i**.

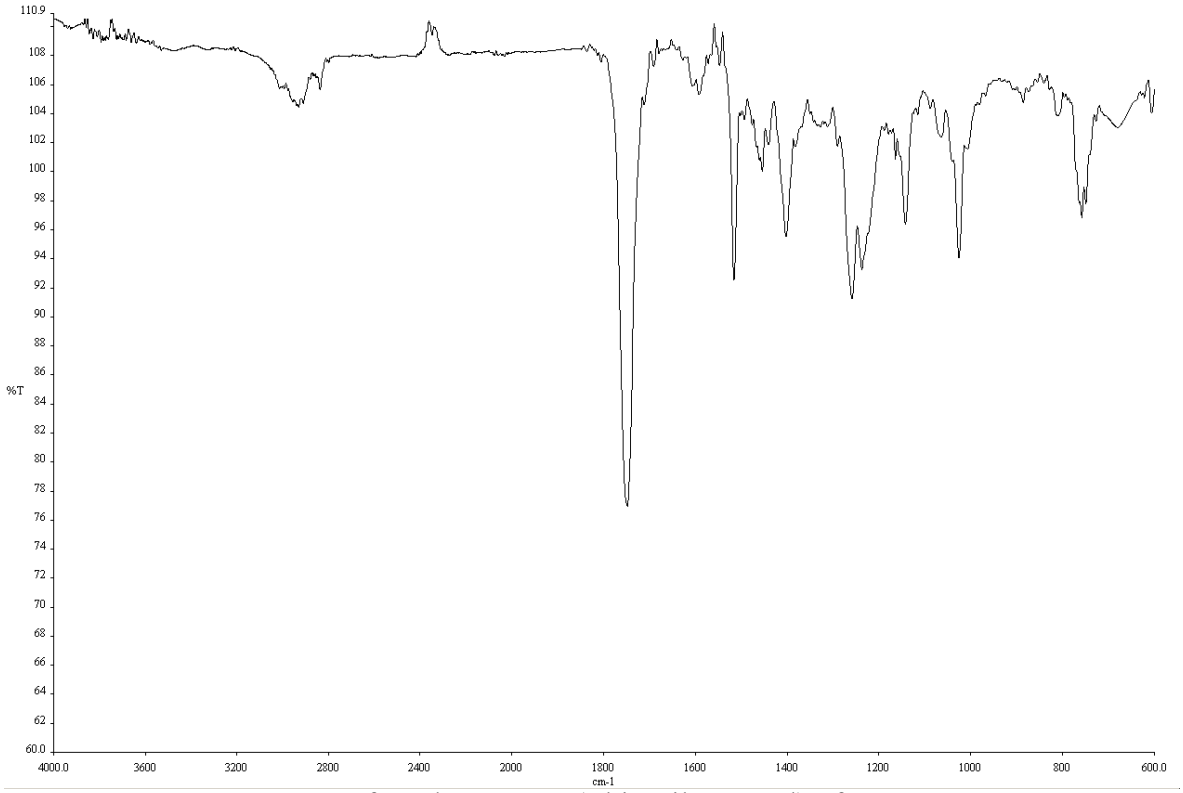


Infrared spectrum (Thin Film, NaCl) of **5i**.

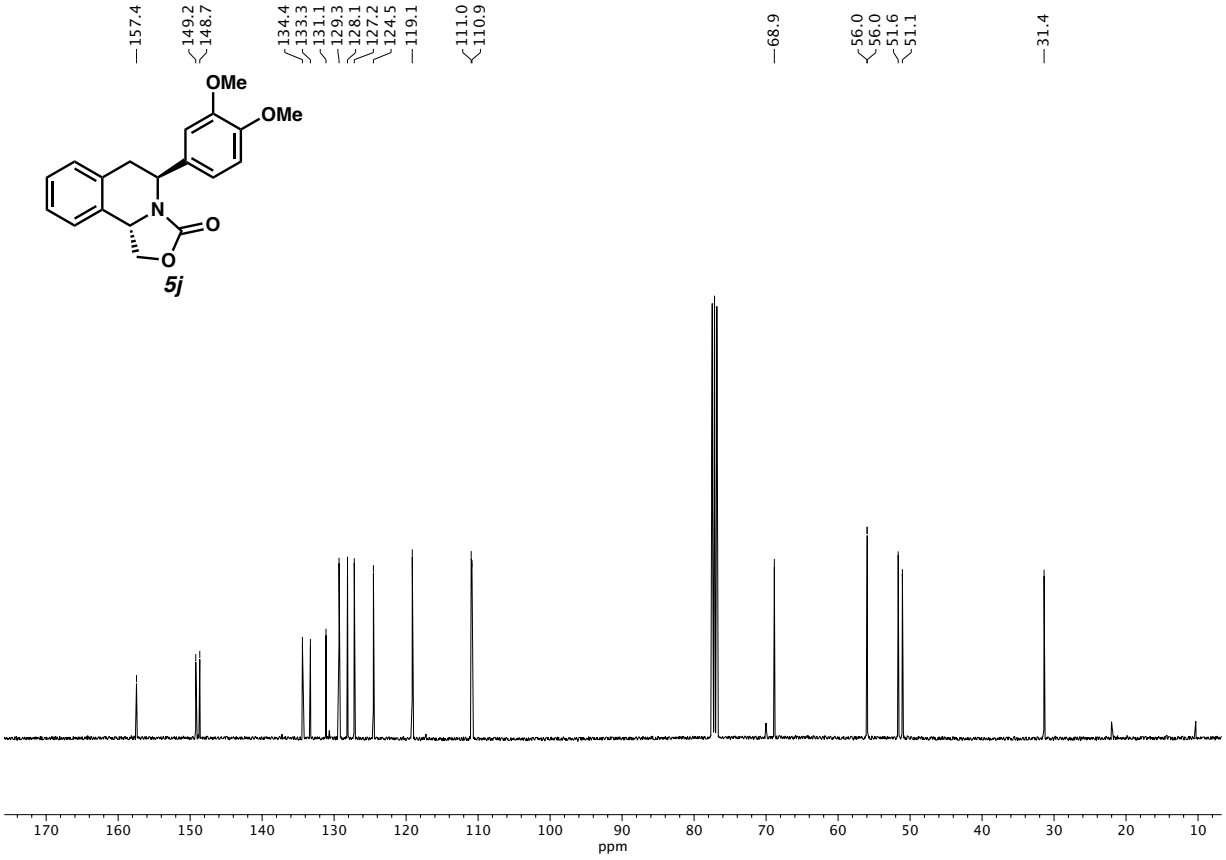


^{13}C NMR (100 MHz, $CDCl_3$) of **5i**.

^{1}H NMR (400 MHz, $CDCl_3$) of **5j**.

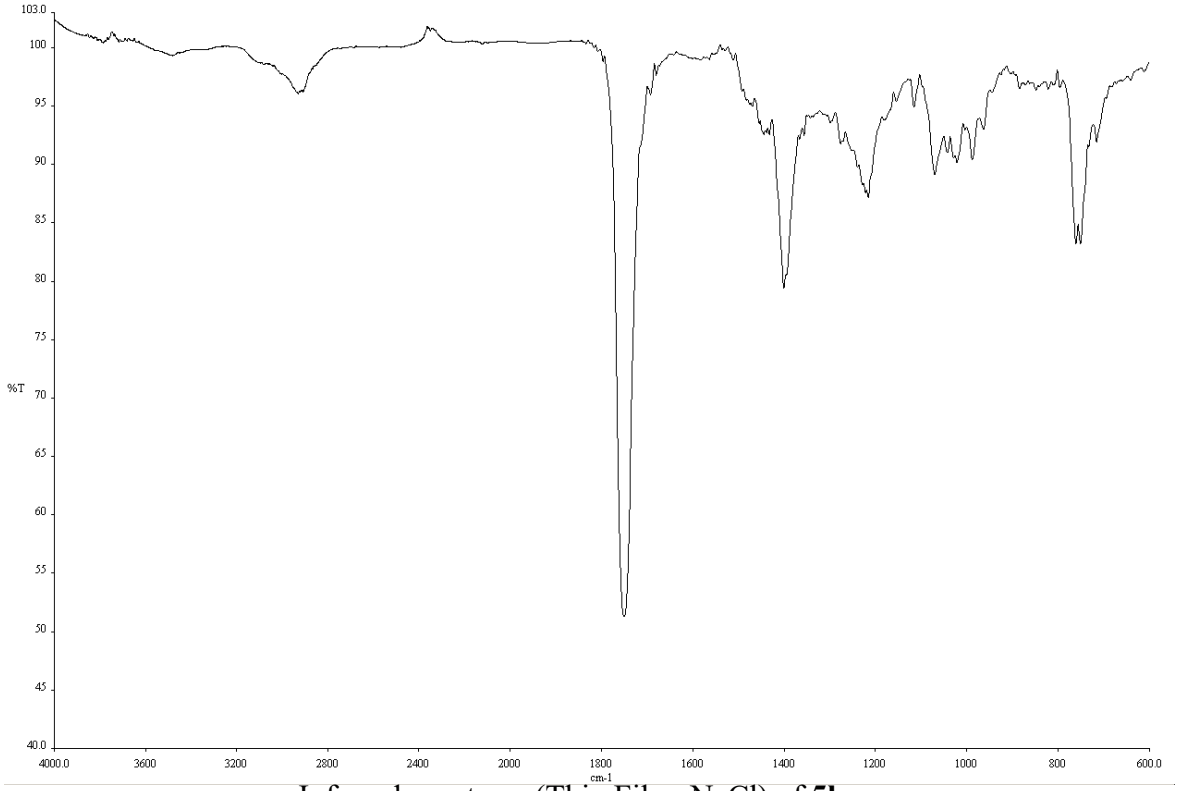


Infrared spectrum (Thin Film, NaCl) of **5j**.

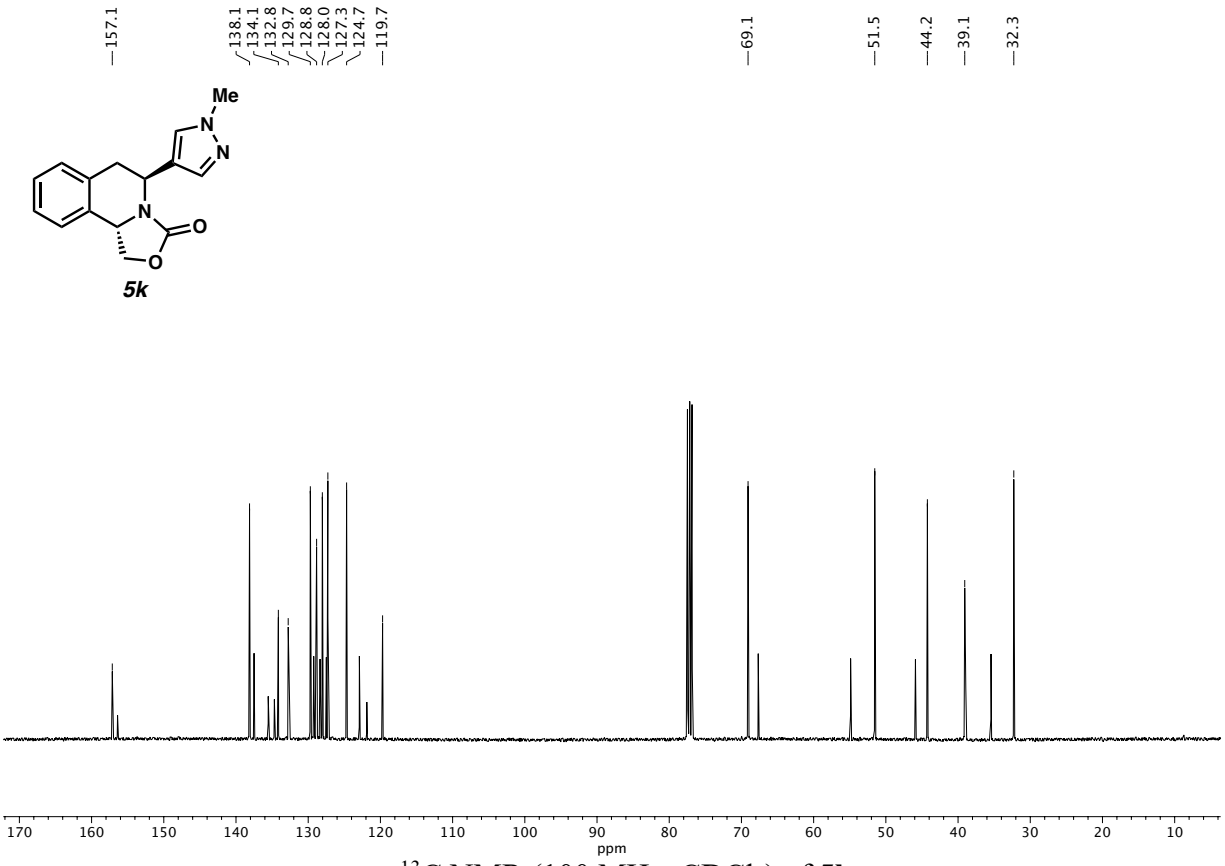


^{13}C NMR (100 MHz, $CDCl_3$) of **5j**.

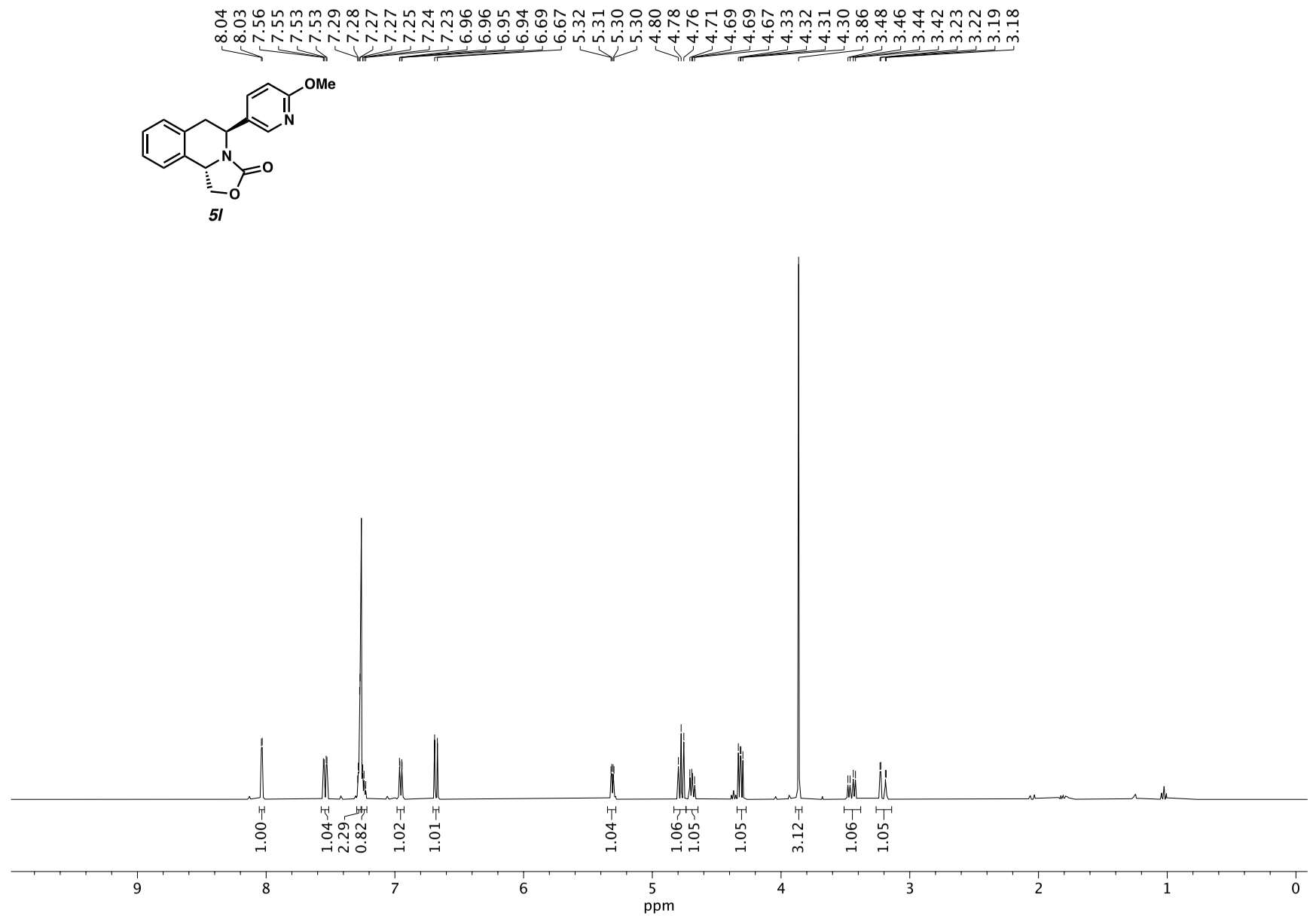
^{1}H NMR (400 MHz, $CDCl_3$) of **5k**.



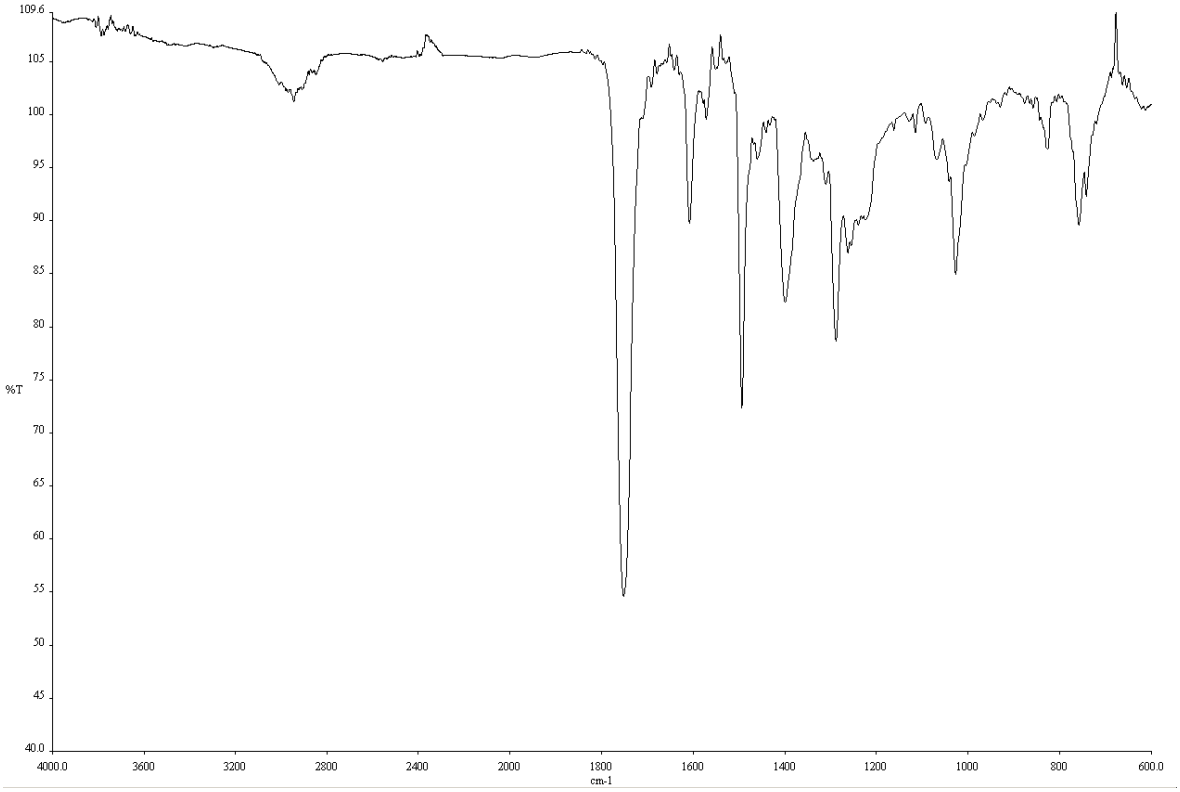
Infrared spectrum (Thin Film, NaCl) of **5k**.



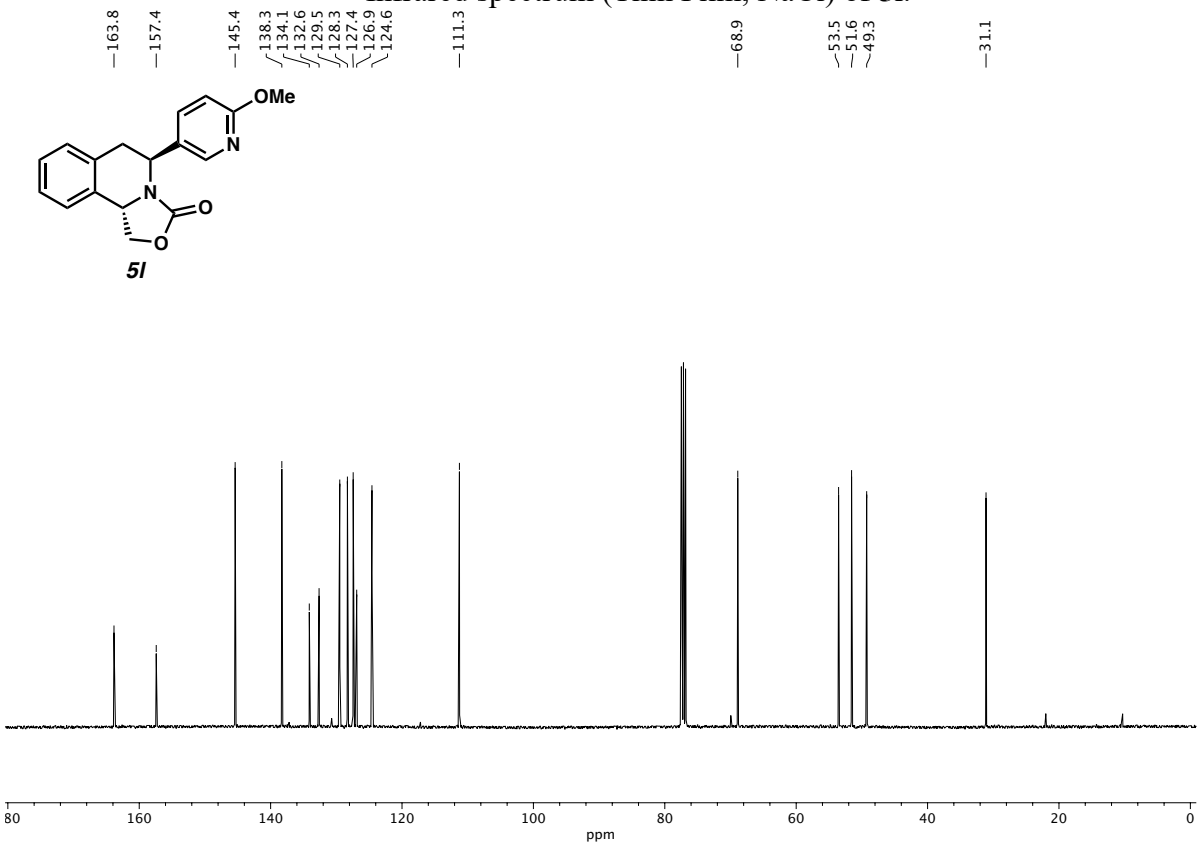
^{13}C NMR (100 MHz, $CDCl_3$) of **5k**.



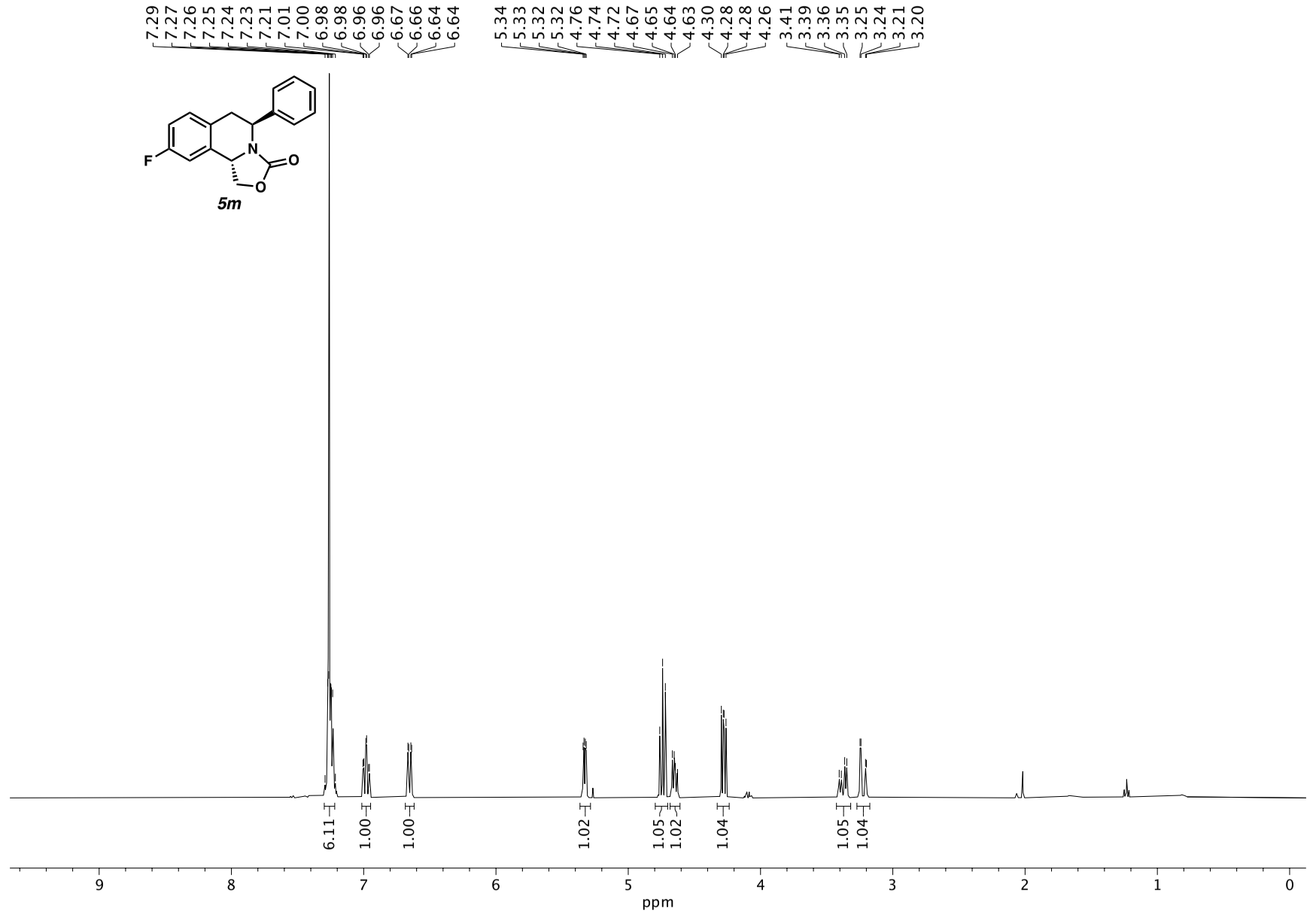
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5l**.



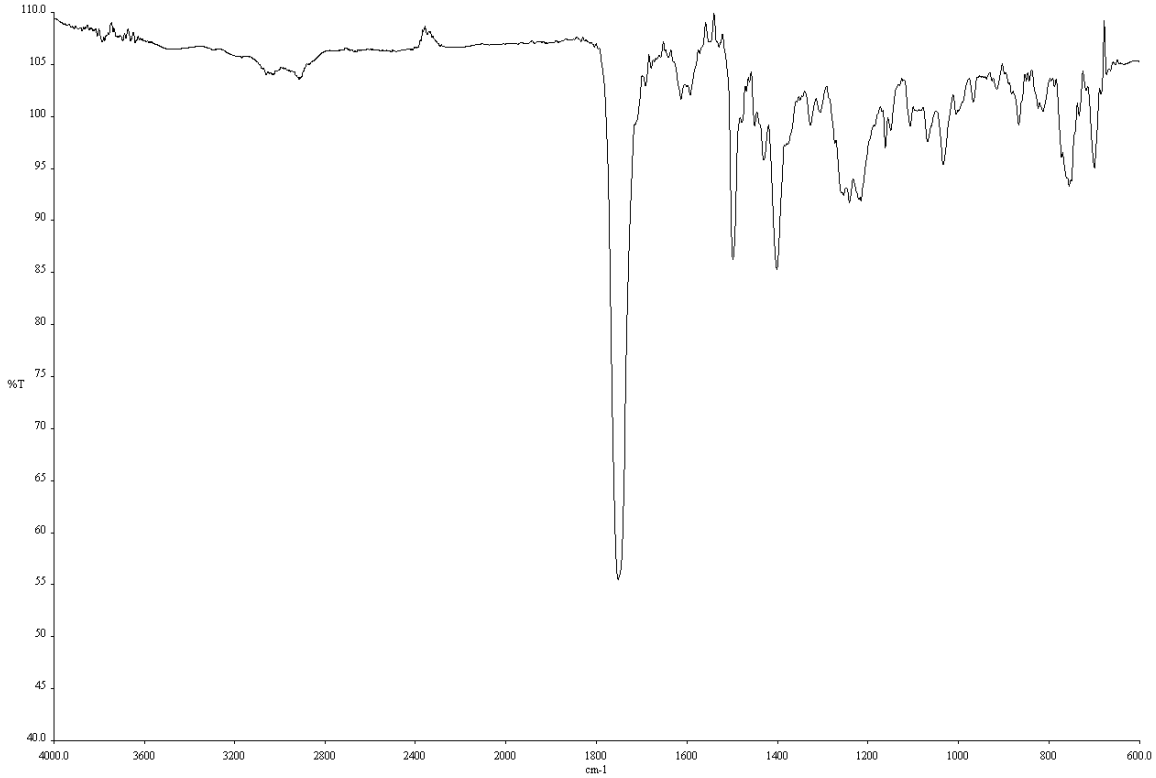
Infrared spectrum (Thin Film, NaCl) of **5l**.



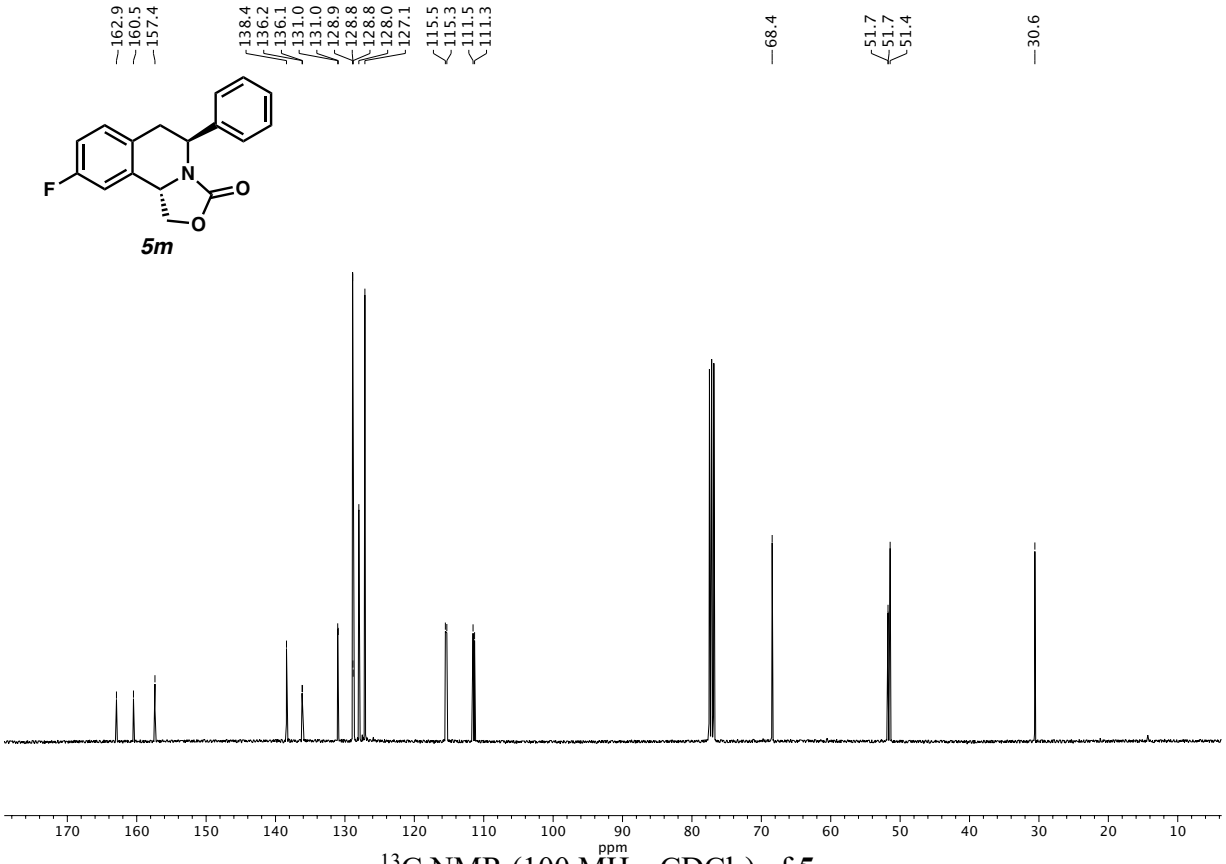
^{13}C NMR (100 MHz, $CDCl_3$) of **5l**.



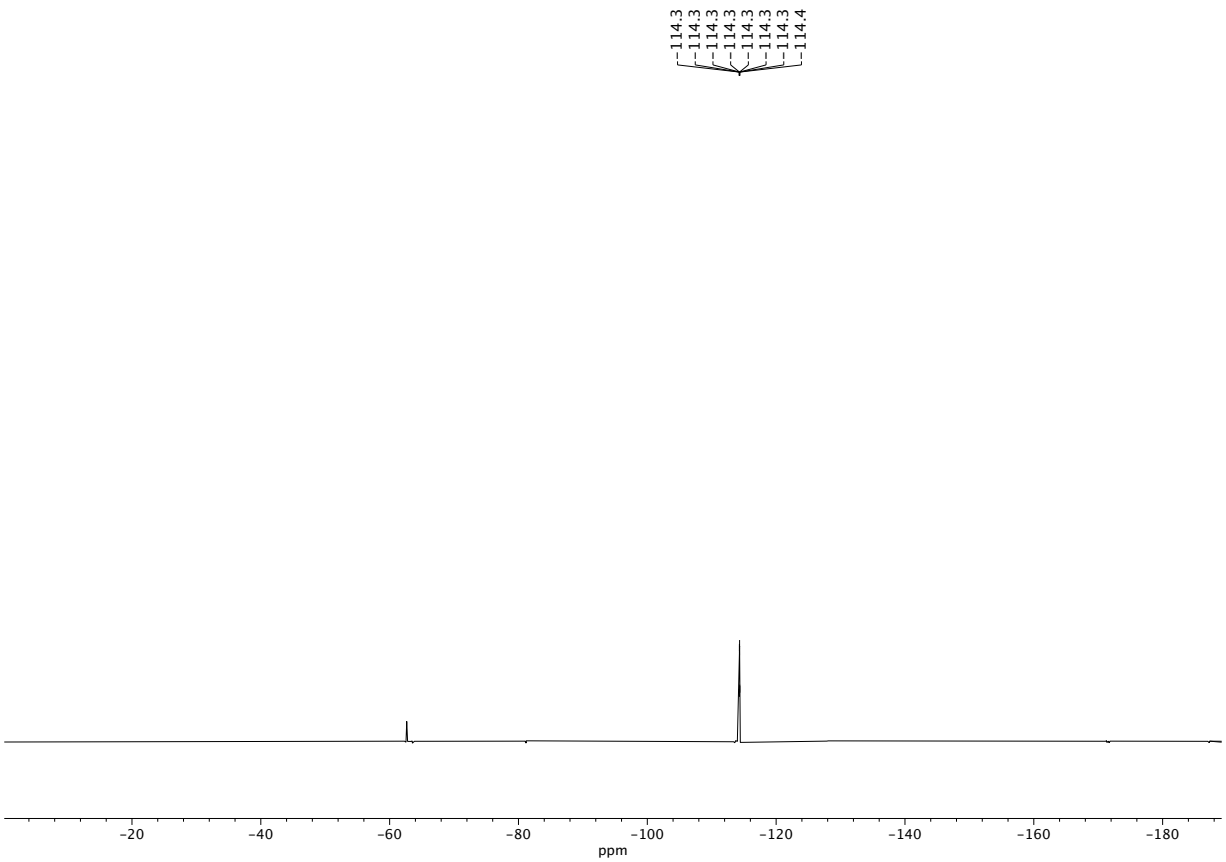
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5m**.



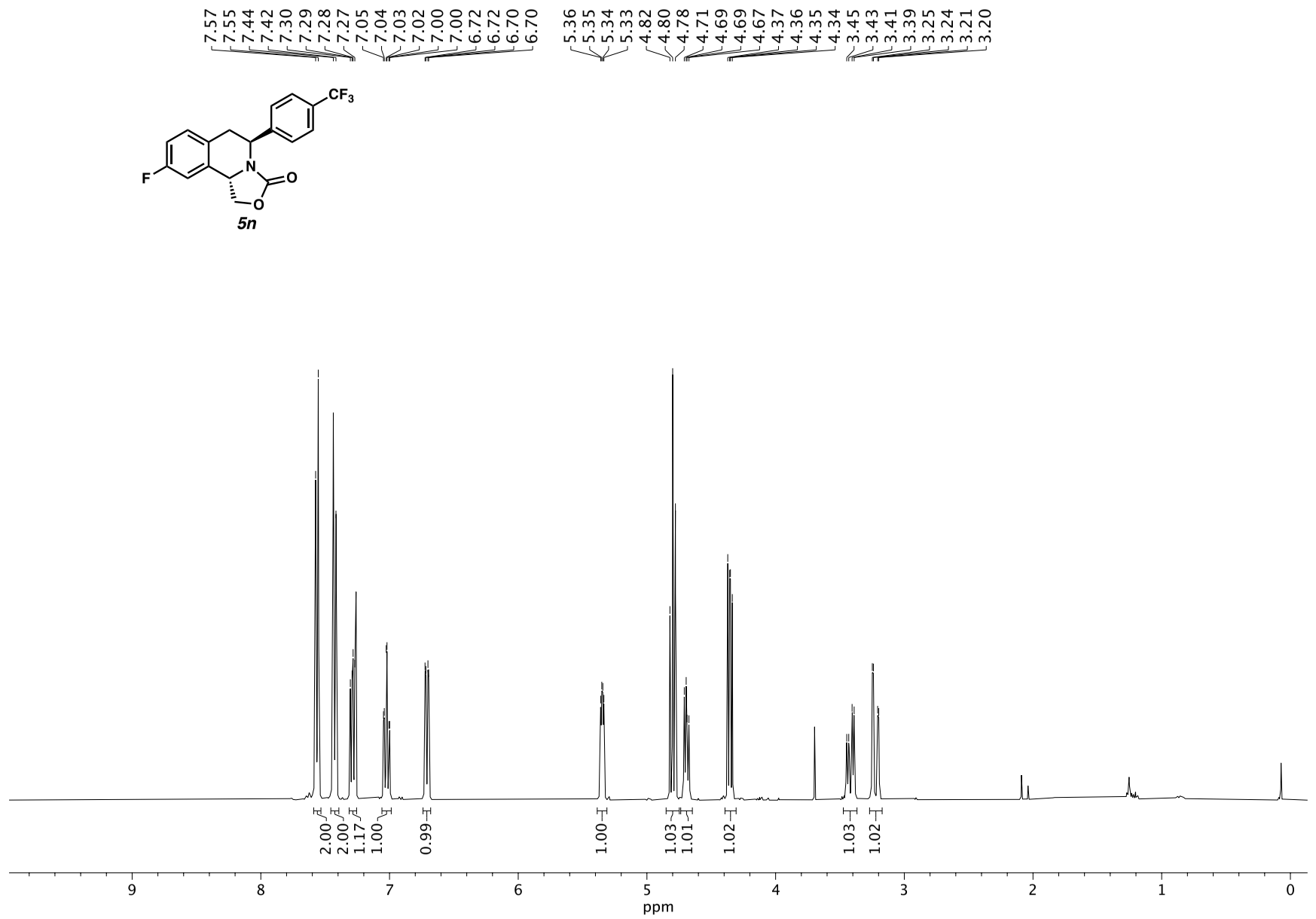
Infrared spectrum (Thin Film, NaCl) of **5m**.



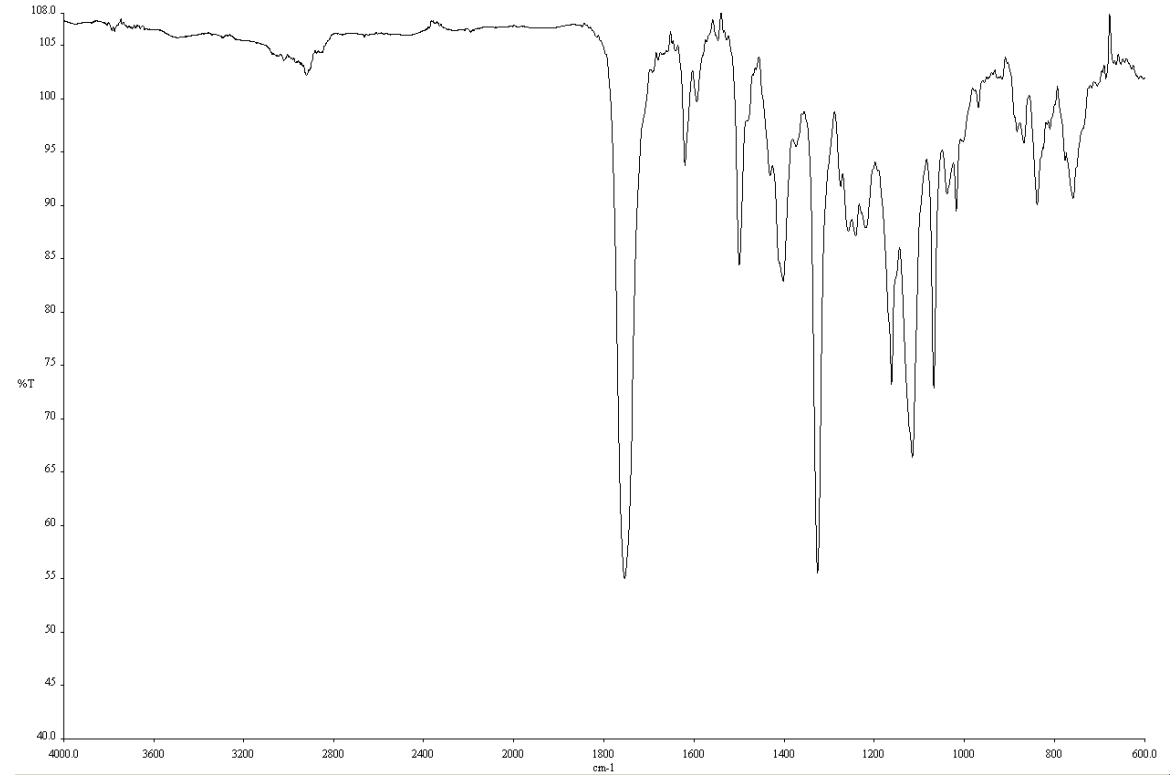
^{13}C NMR (100 MHz, $CDCl_3$) of **5m**.



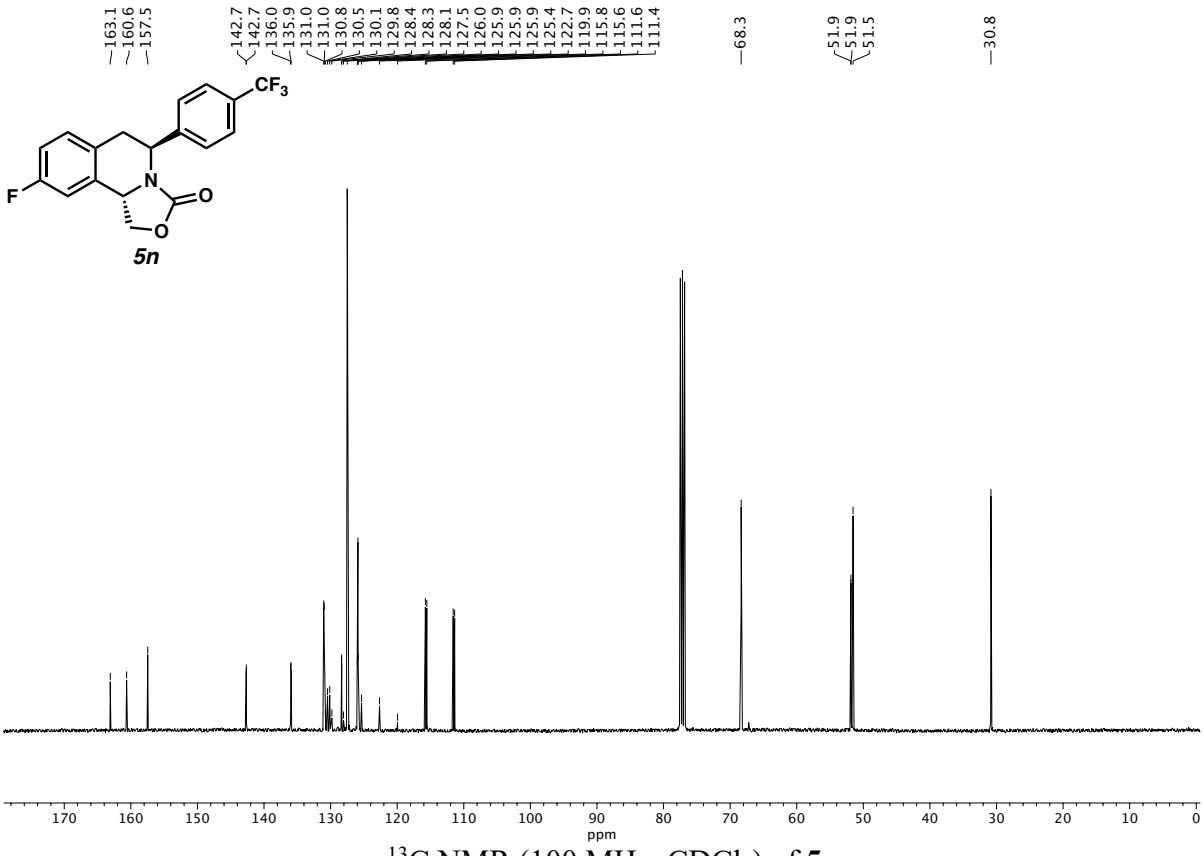
^{19}F NMR (282 MHz, $CDCl_3$) of **5m**.



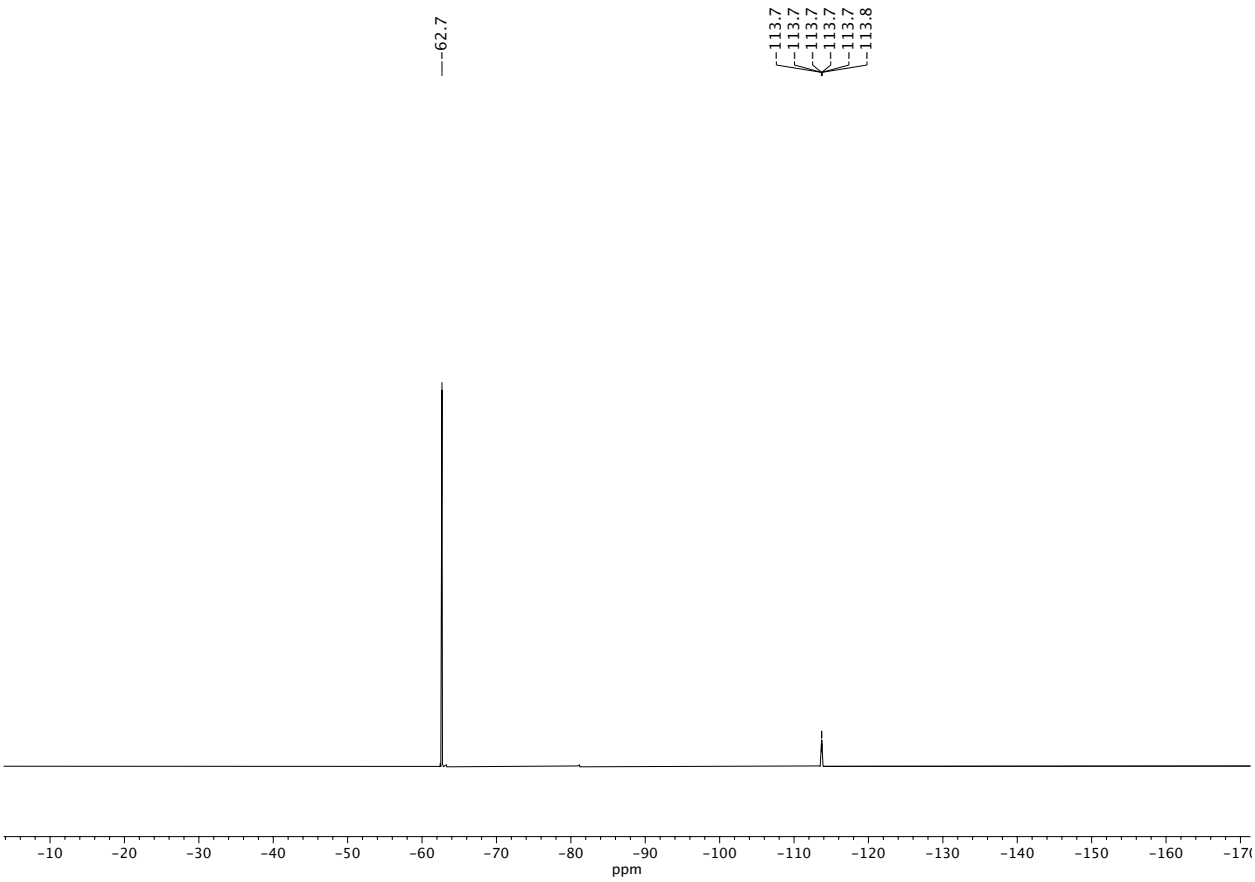
^{1}H NMR (400 MHz, $CDCl_3$) of compound **5n**.



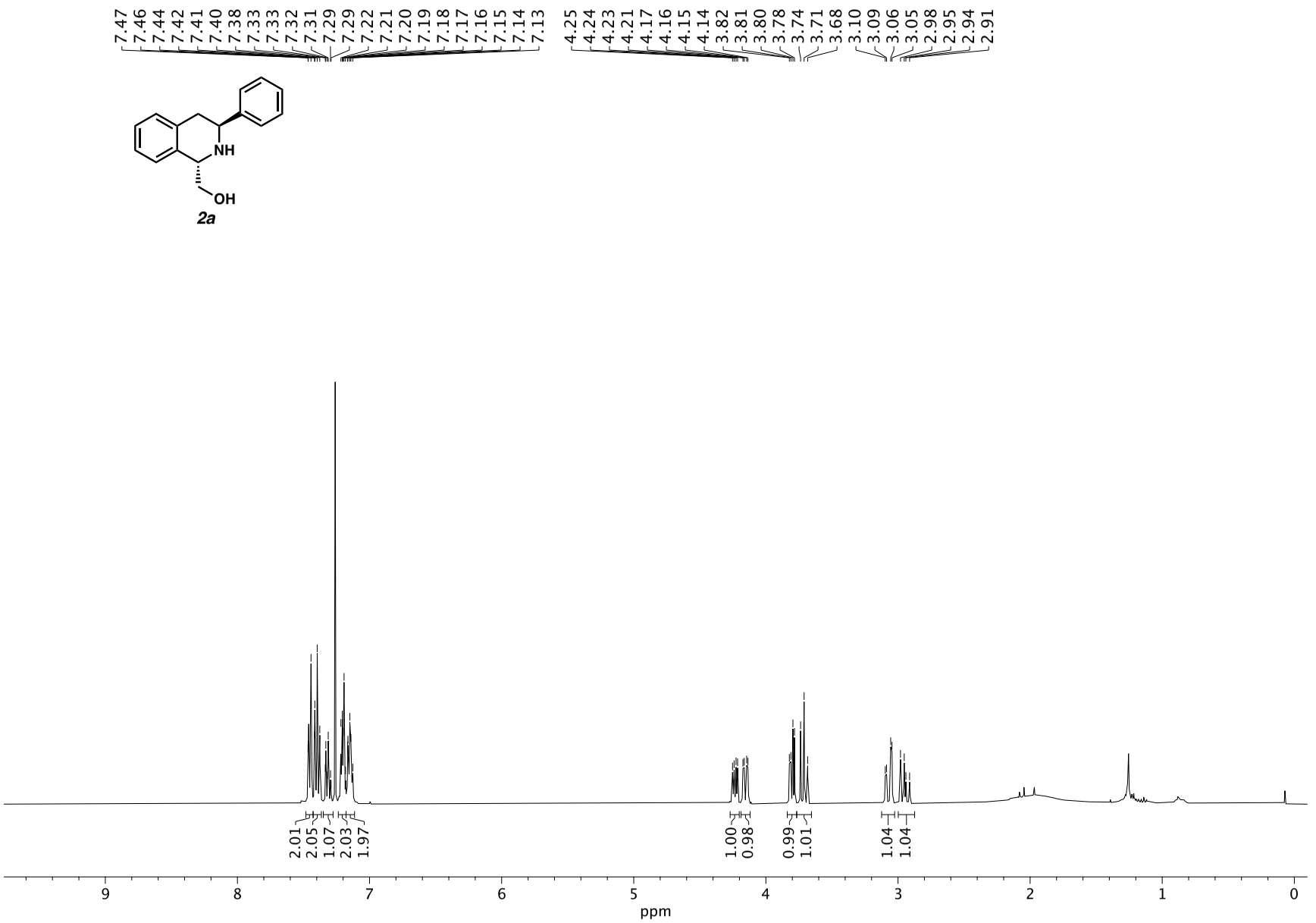
Infrared spectrum (Thin Film, NaCl) of **5n**.



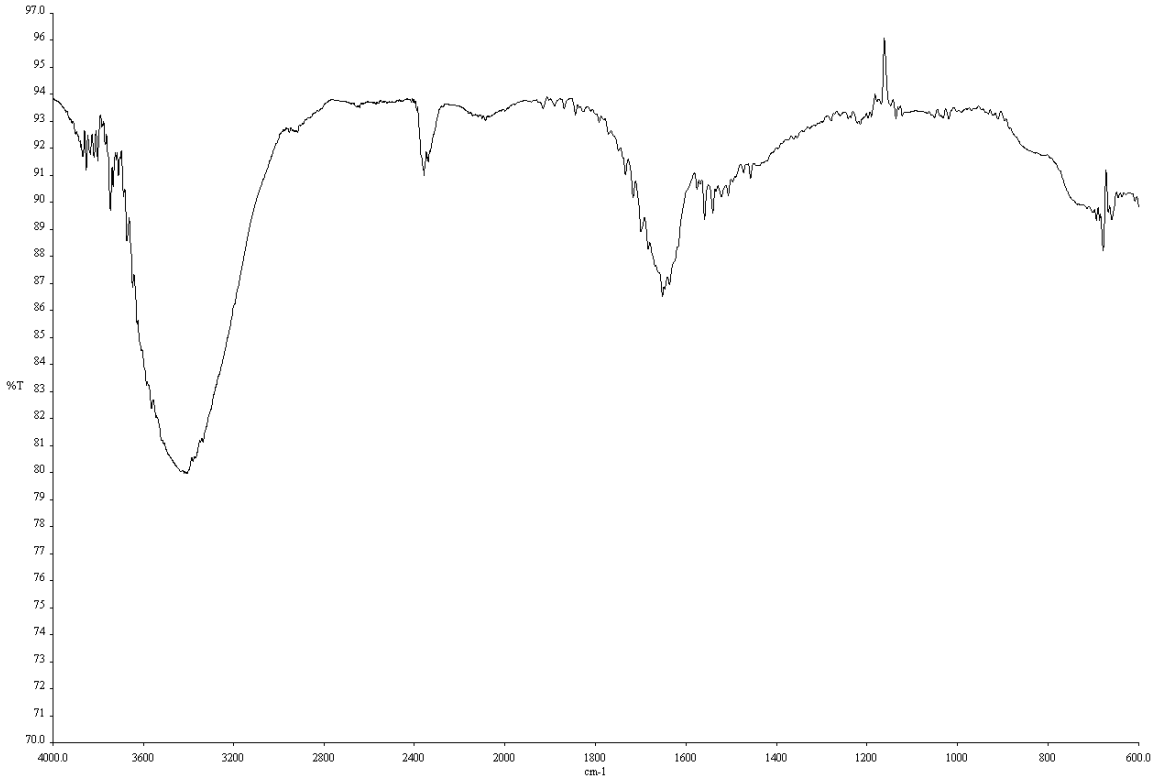
^{13}C NMR (100 MHz, $CDCl_3$) of **5n**.



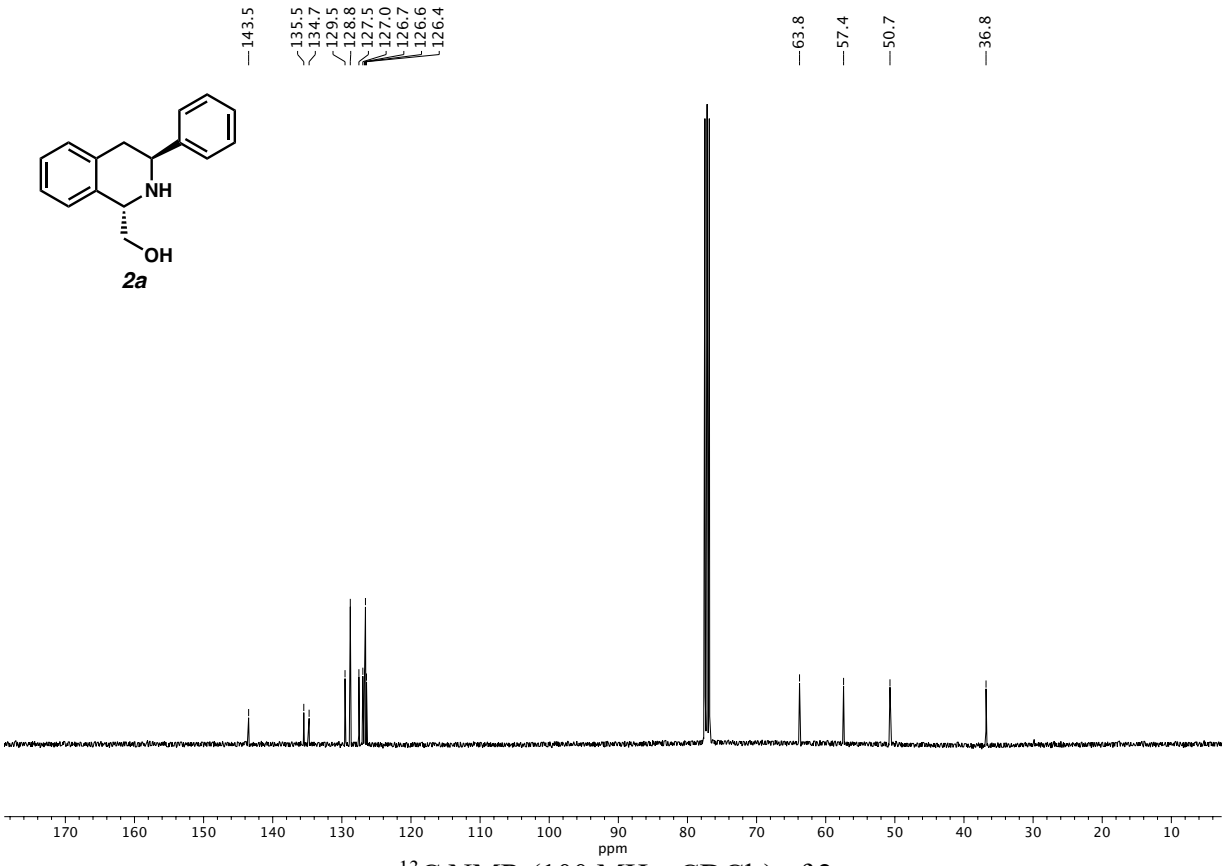
^{19}F NMR (282 MHz, $CDCl_3$) of **5n**.



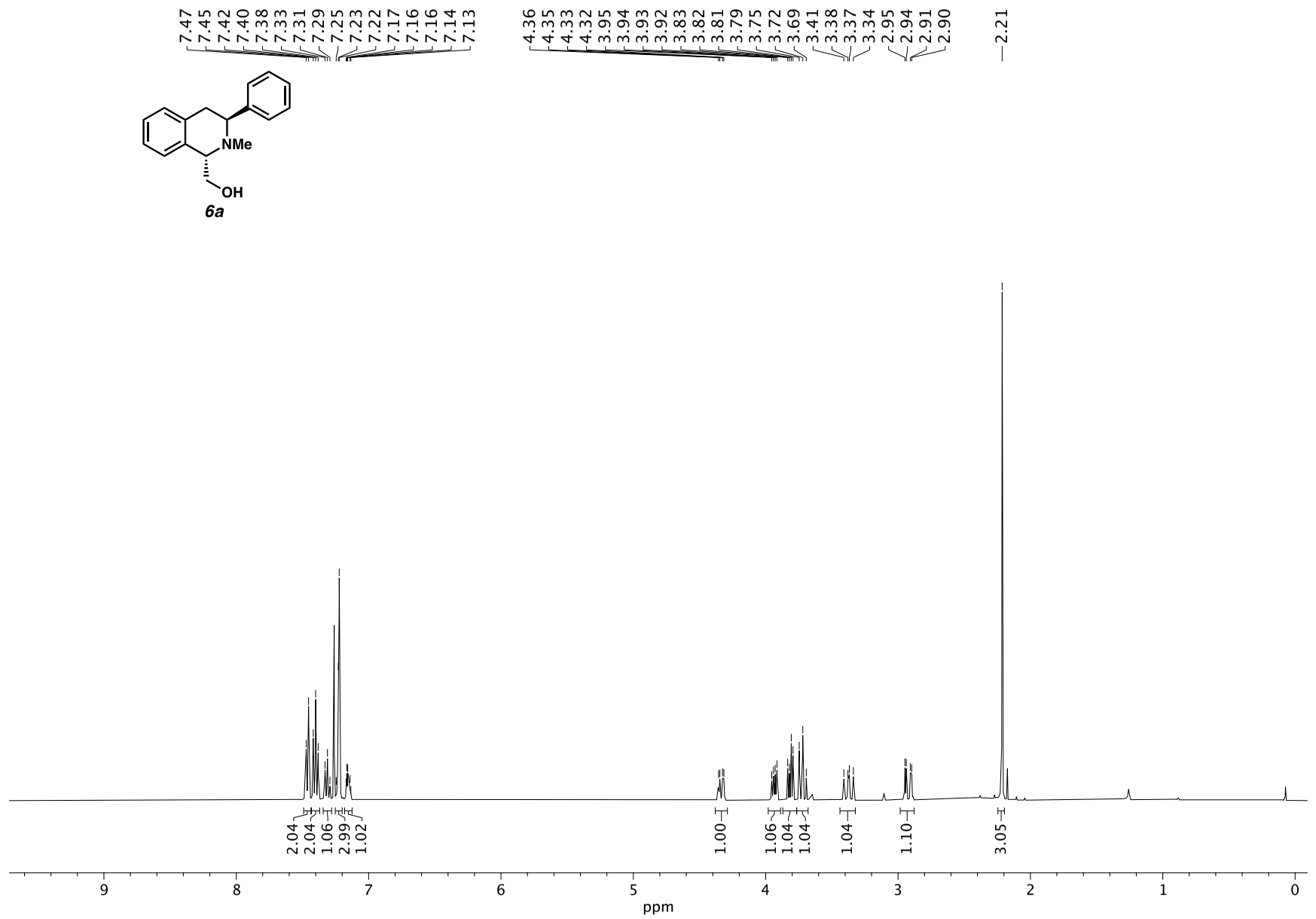
^{1}H NMR (400 MHz, $CDCl_3$) of compound **2a**.



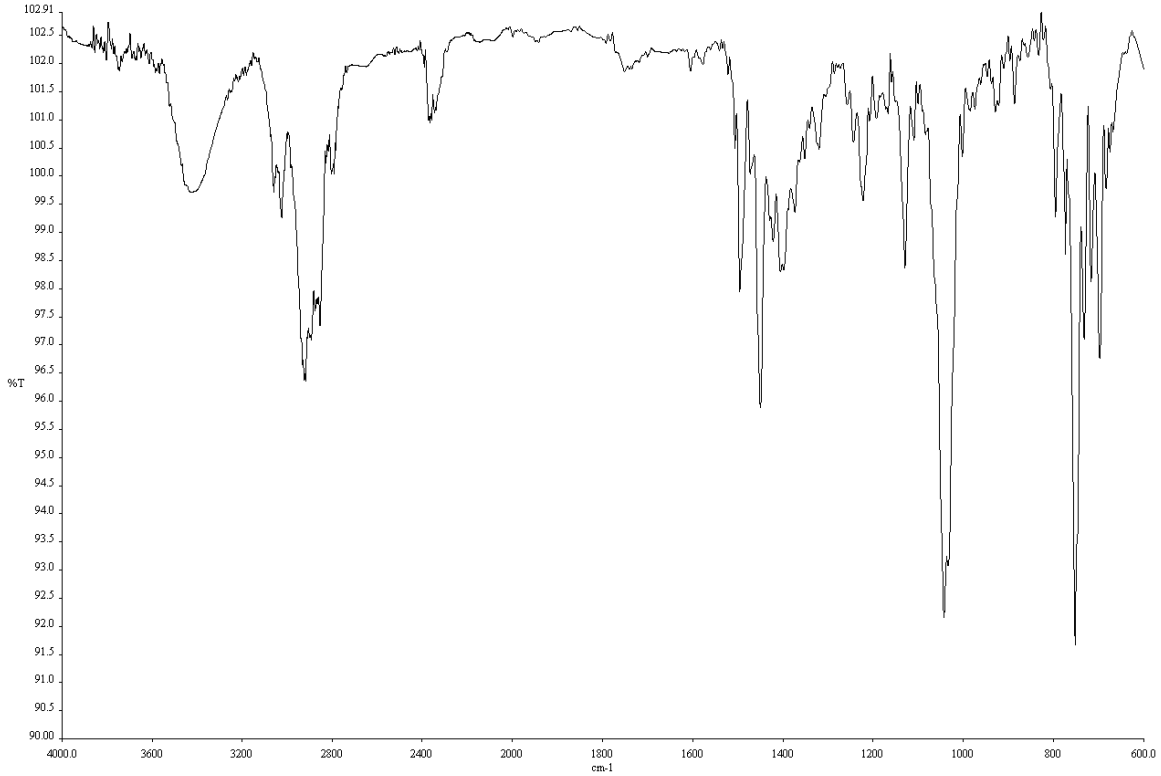
Infrared spectrum (Thin Film, NaCl) of **2a**.



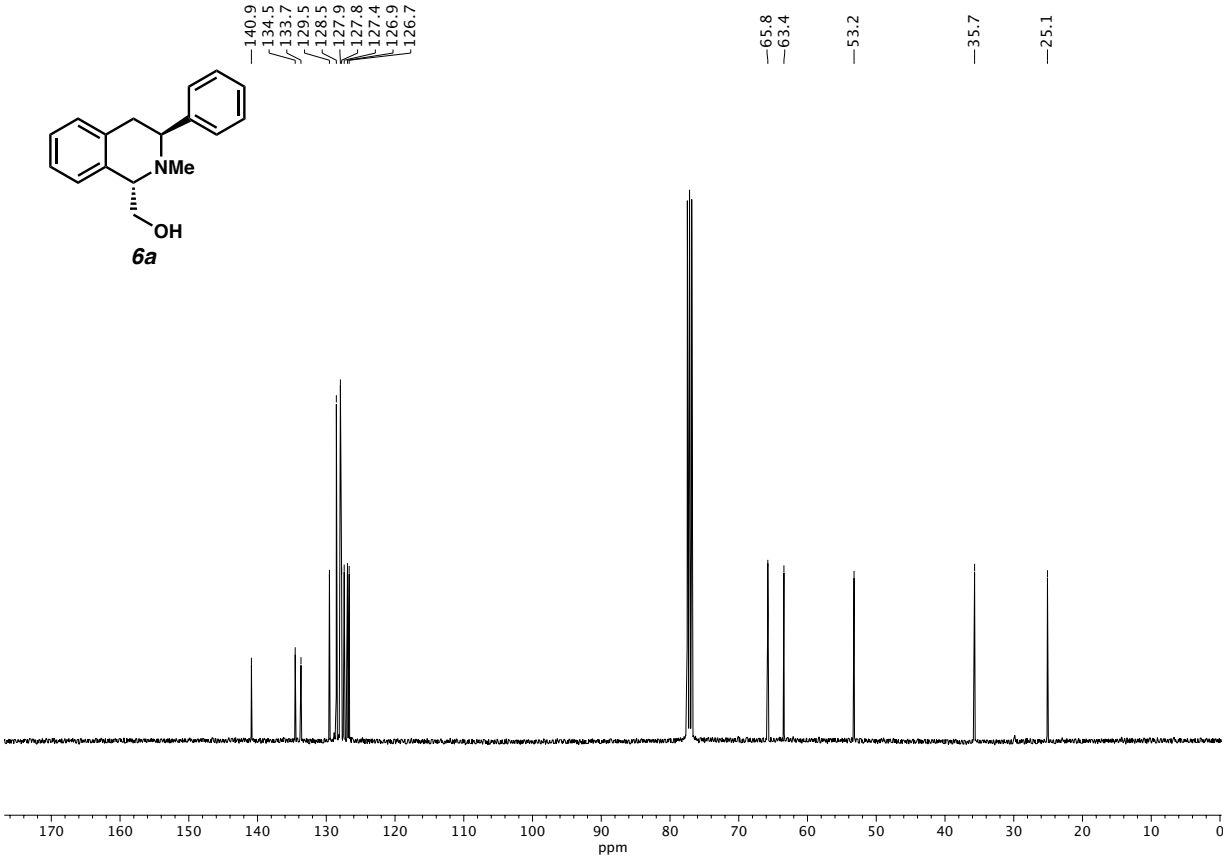
^{13}C NMR (100 MHz, $CDCl_3$) of **2a**.



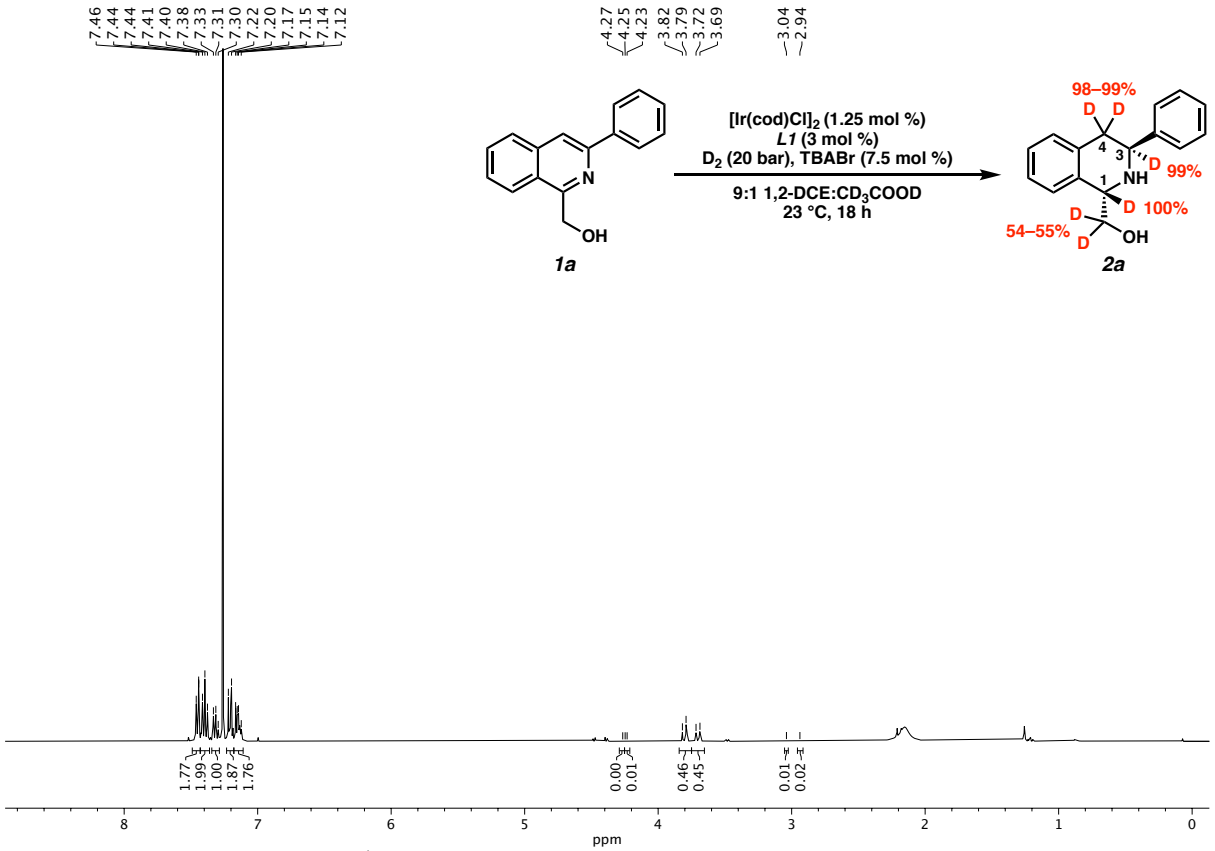
^{1}H NMR (400 MHz, $CDCl_3$) of compound **6a**.



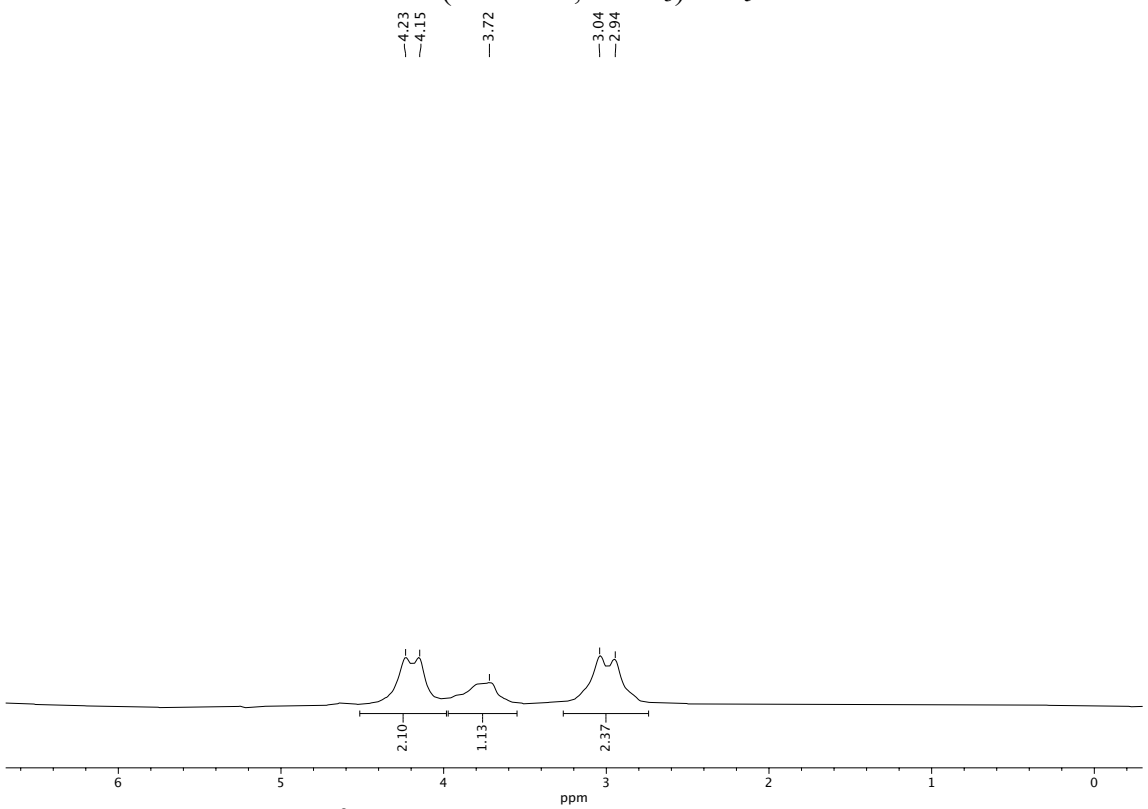
Infrared spectrum (Thin Film, NaCl) of **6a**.



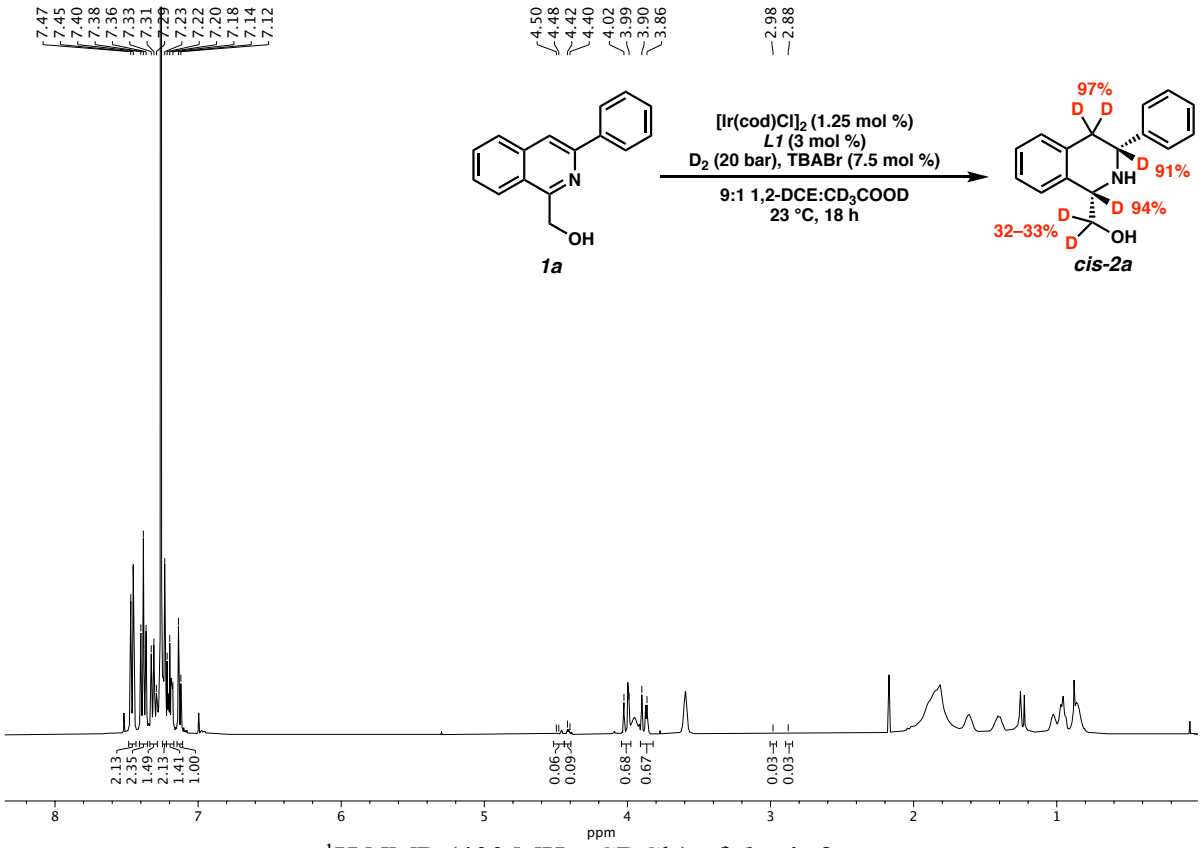
^{13}C NMR (100 MHz, $CDCl_3$) of **6a**.



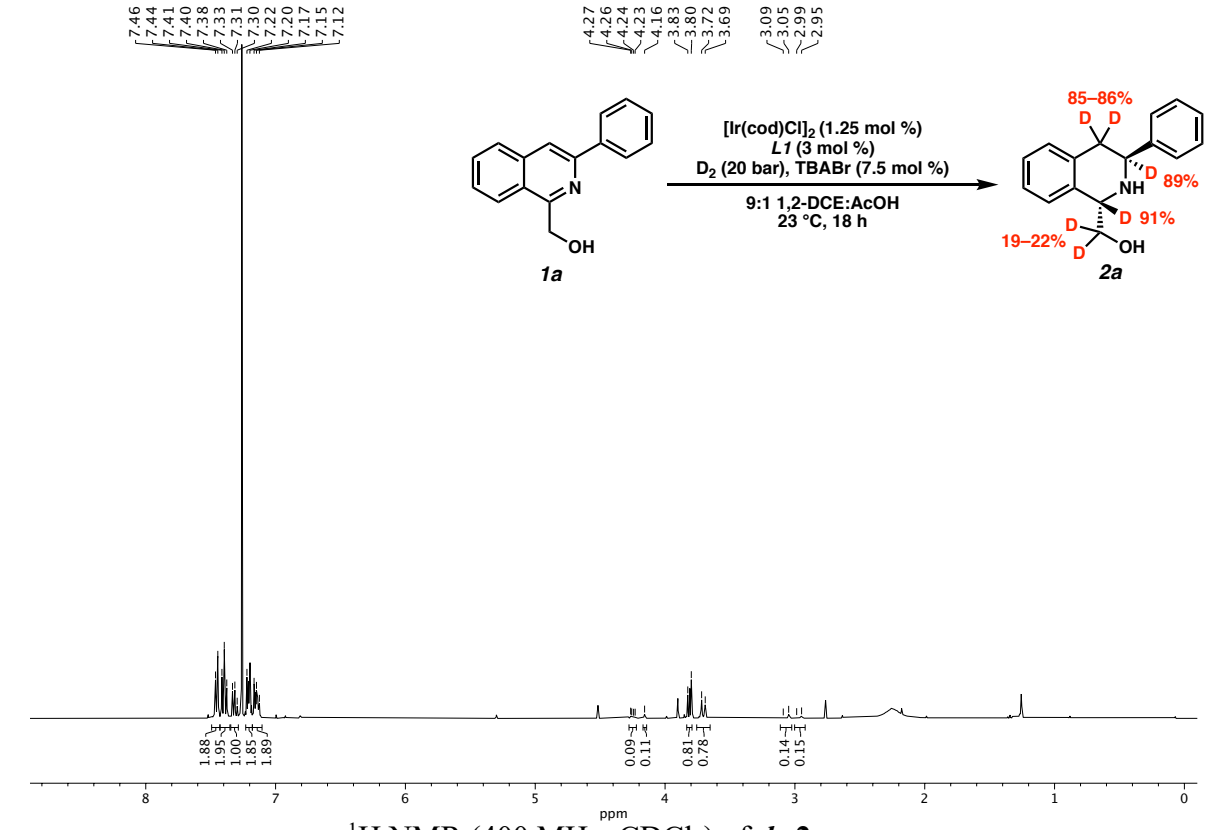
^{1}H NMR (400 MHz, $CDCl_3$) of ***d*$_5$-2a**.



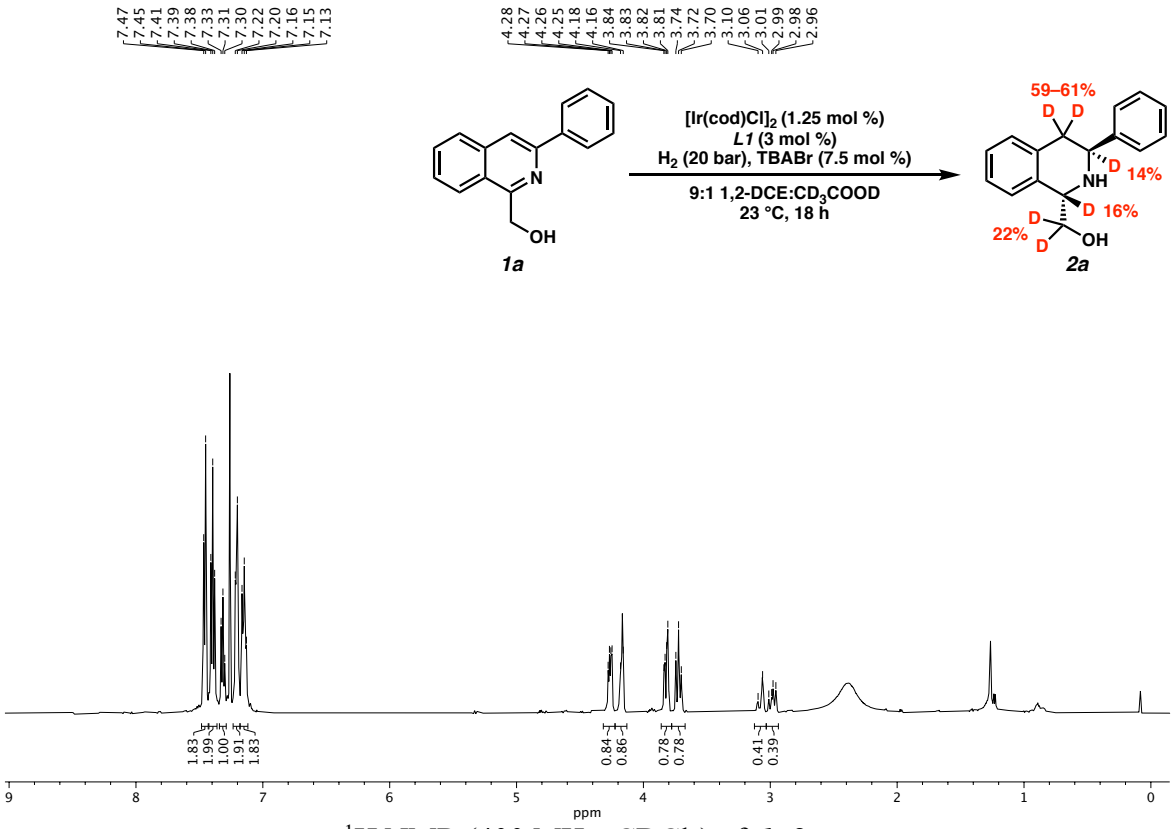
^{2}H NMR (61 MHz, $CDCl_3$) of ***d*$_5$-2a**.



^{1}H NMR (400 MHz, $CDCl_3$) of ***d$_n$-cis*-2a**.



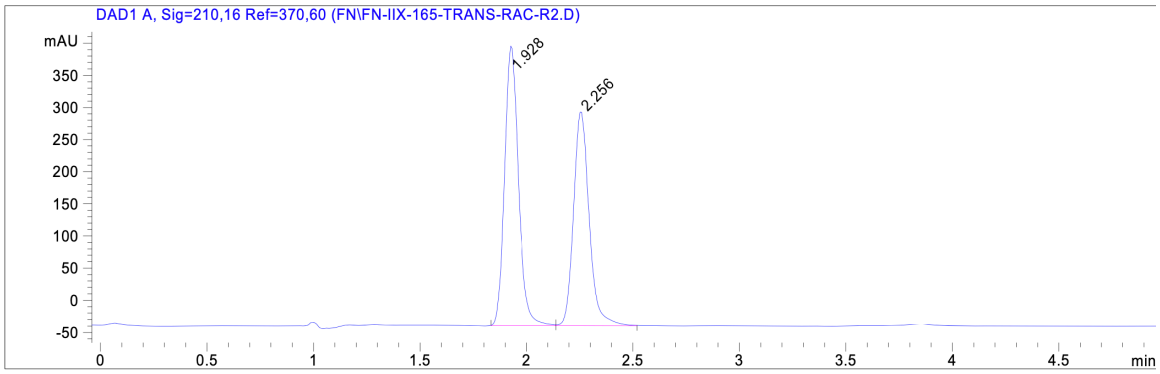
^{1}H NMR (400 MHz, $CDCl_3$) of ***d$_n$*-2a**.



^{1}H NMR (400 MHz, $CDCl_3$) of ***d*$_n$-2a**.

SFC Traces of Racemic and Enantioenriched Compounds

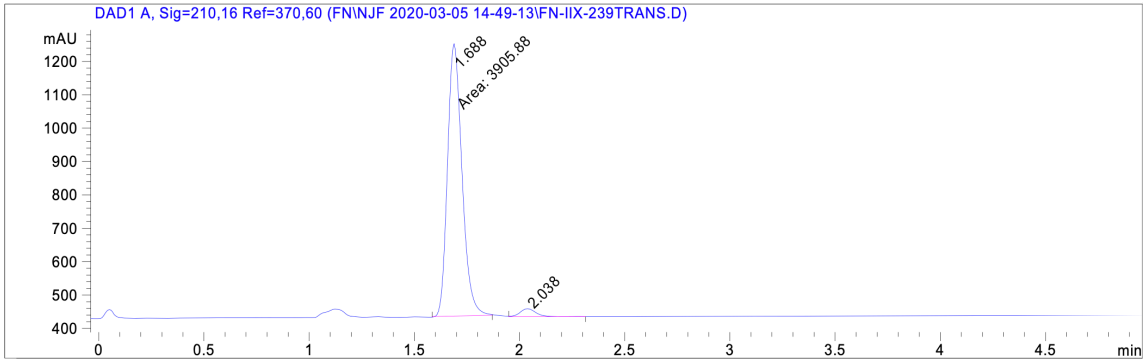
Racemic **2a•Cbz**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.928	BV	0.0710	1980.20166	435.95096	53.8603
2	2.256	VB	0.0792	1696.34778	334.17471	46.1397

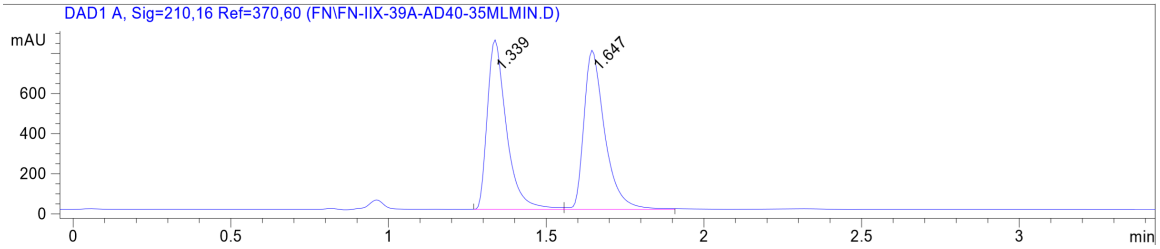
Enantioenriched **2a•Cbz**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.688	MM	0.0796	3905.88330	817.43951	96.8437
2	2.038	VB	0.0815	127.29790	24.16609	3.1563

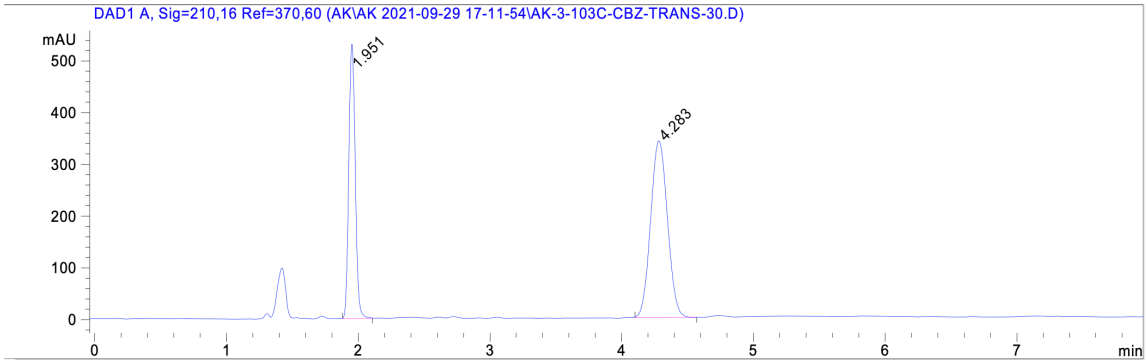
Racemic **4e•Cbz**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.339	BV	0.0654	3562.84033	841.34003	49.4402
2	1.647	VB	0.0697	3643.52856	791.14252	50.5598

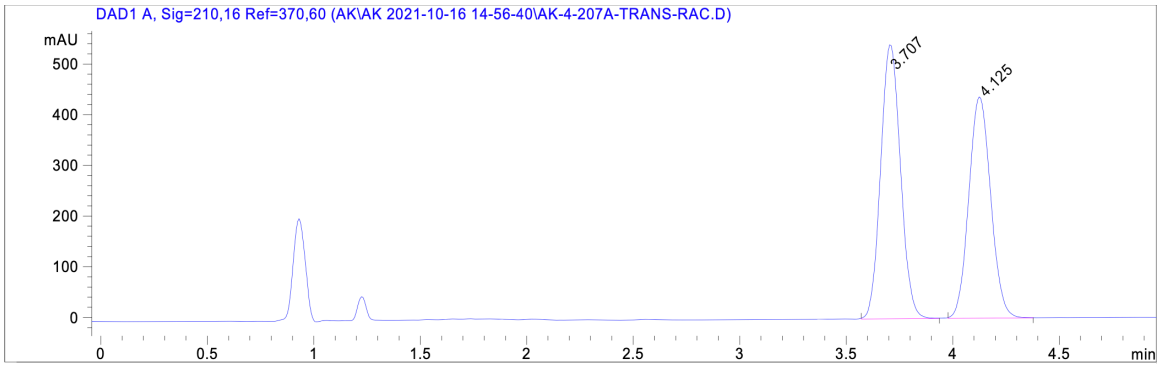
Enantioenriched **4e•Cbz**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.951	BB	0.0532	1799.63599	535.01355	37.2214
2	4.283	BB	0.1396	3035.31348	341.70935	62.7786

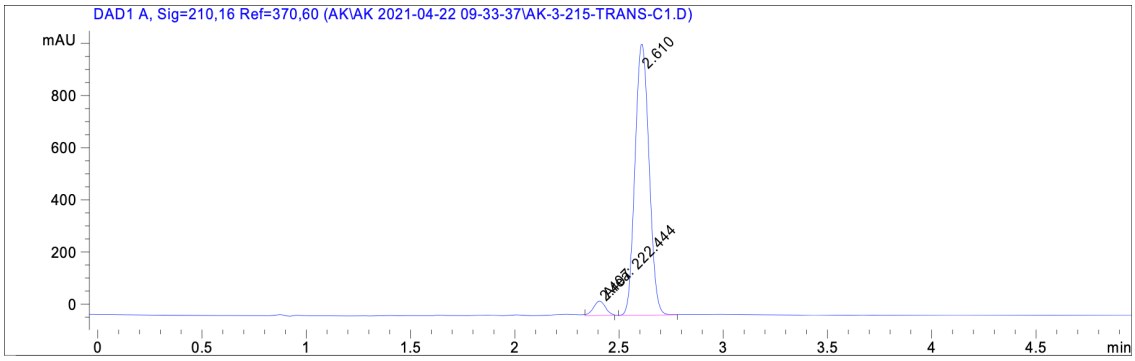
Racemic **5a**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.707	BB	0.1015	3502.39062	541.37115	52.8660
2	4.125	BB	0.1114	3122.64380	436.64725	47.1340

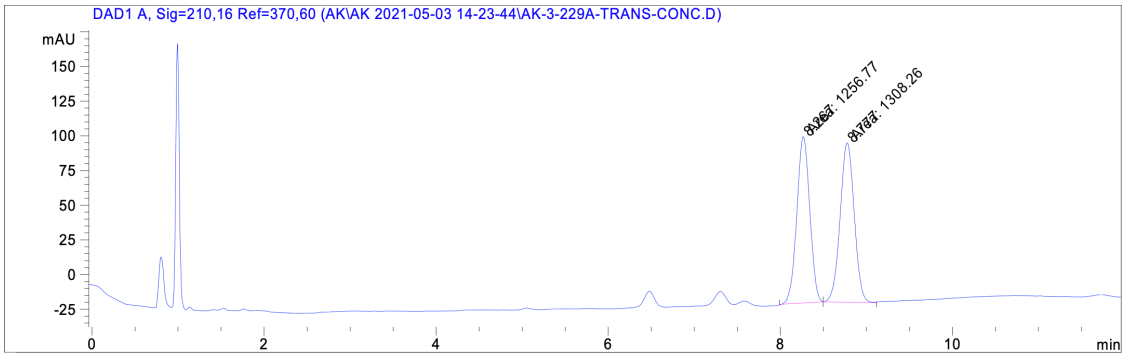
Enantioenriched **5a**




```
Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   2.407 MM    0.0668  222.44351   55.51492   4.3600
   2   2.610 VB    0.0746 4879.43848 1043.11670  95.6400
```

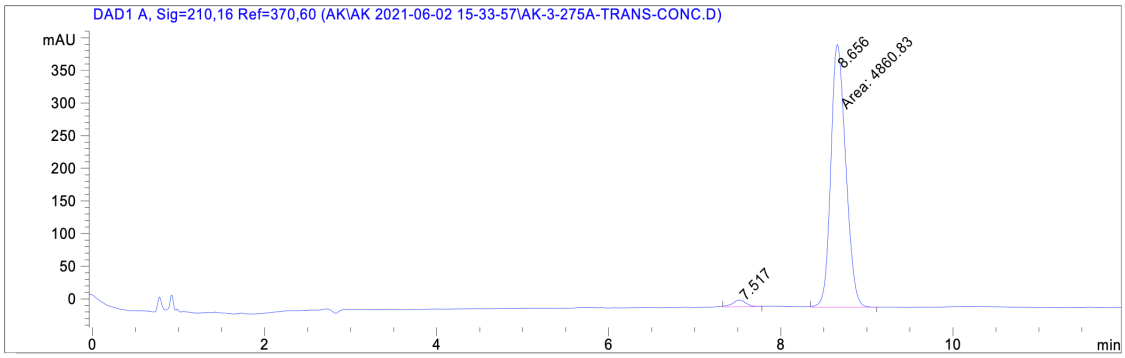
Racemic **5b**




```
Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.267 MM    0.1746 1256.77405  119.94225  48.9963
   2   8.777 MM    0.1897 1308.26367  114.92722  51.0037
```

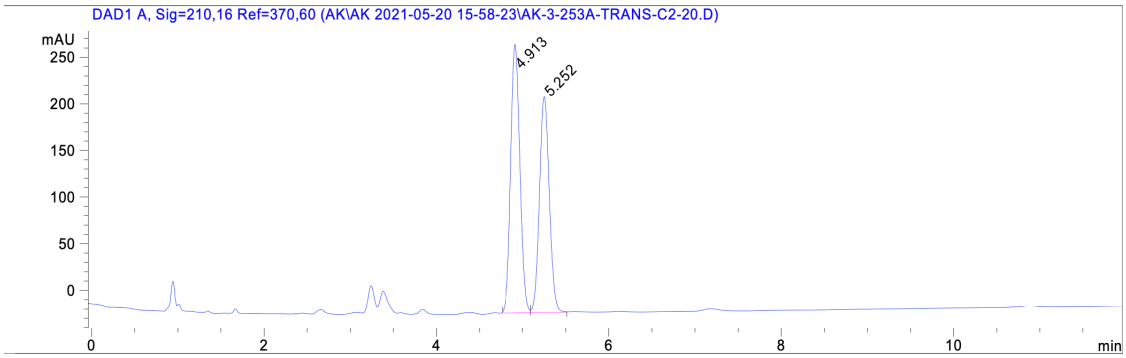
Enantioenriched **5b**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.517	BB	0.1605	109.86375	10.29189	2.2102
2	8.656	MM	0.2012	4860.83008	402.59357	97.7898

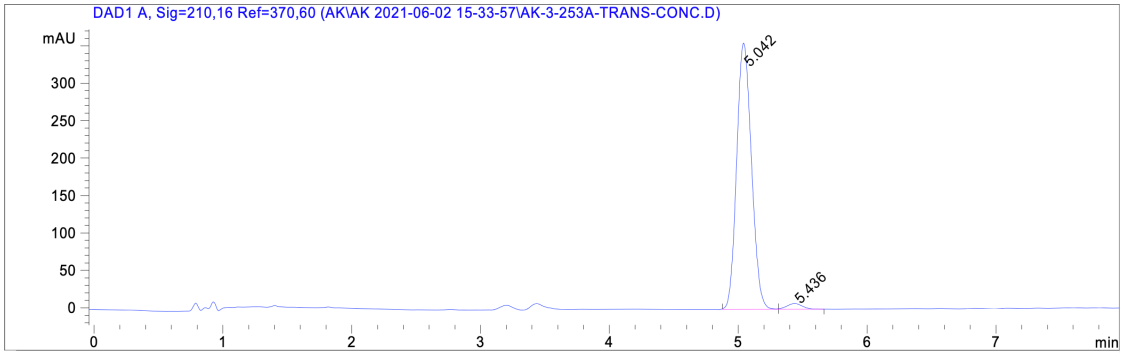
Racemic **5c**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.913	BV	0.1173	2155.09814	287.93854	53.9109
2	5.252	VB	0.1248	1842.42236	231.71597	46.0891

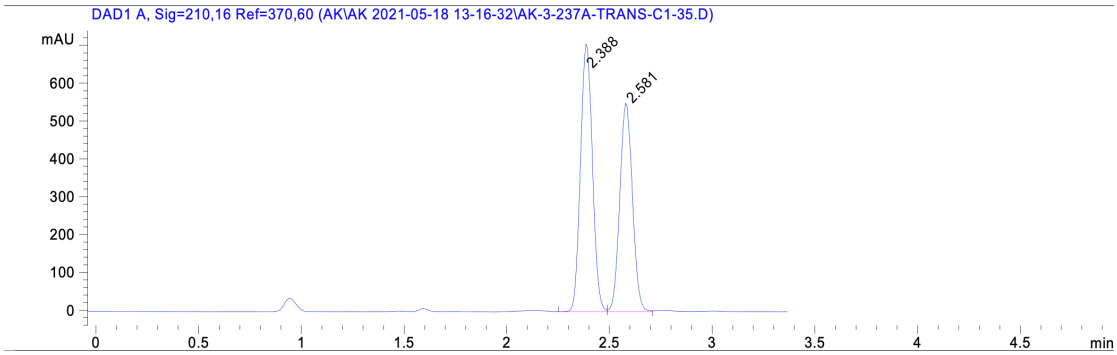
Enantioenriched **5c**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.042	BB	0.1251	2841.96826	356.06854	97.7926
2	5.436	BB	0.1298	64.14865	7.64981	2.2074

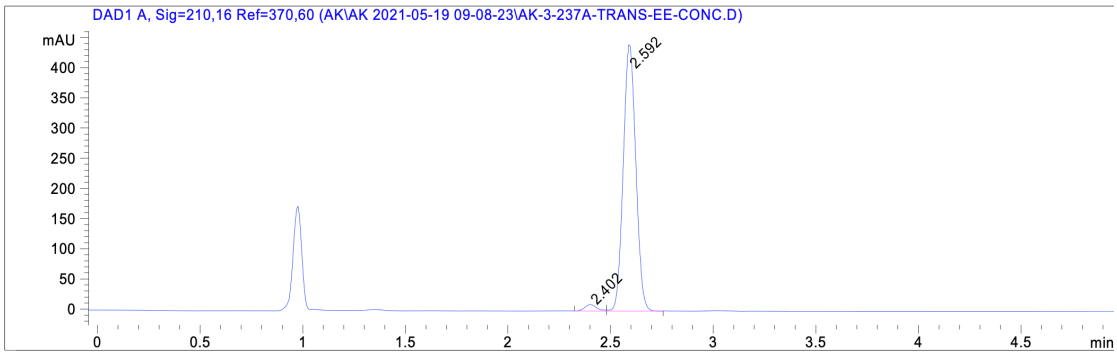
Racemic **5d**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.388	VV	0.0630	2858.31030	709.17267	54.7573
2	2.581	VV	0.0679	2361.65356	551.95624	45.2427

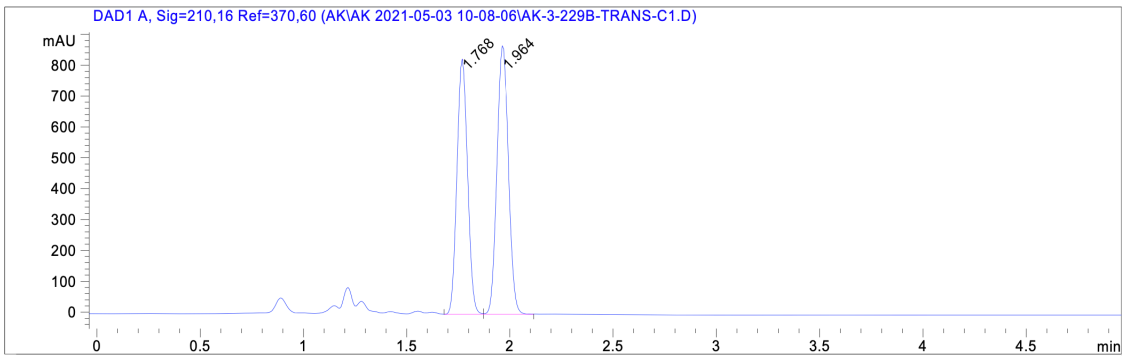
Enantioenriched **5d**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.402	BV	0.0636	44.24749	10.85165	2.3018
2	2.592	VB	0.0654	1878.07214	443.49234	97.6982

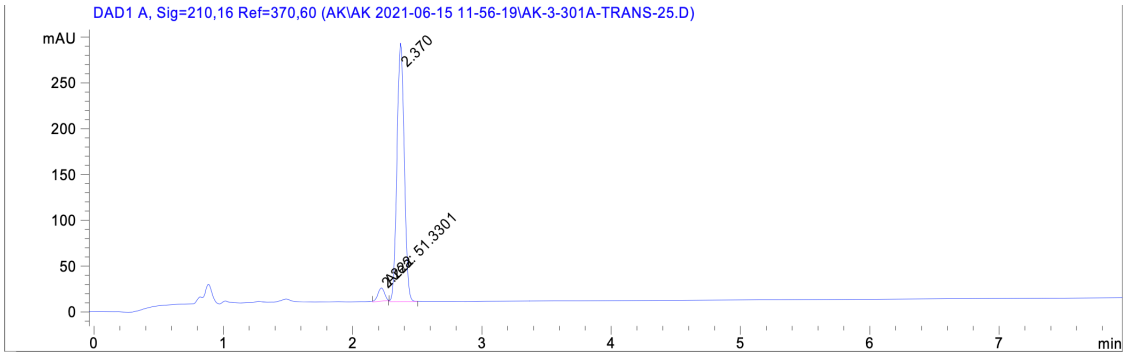
Racemic **5e**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.768	VV	0.0557	2954.45508	827.37811	46.4989
2	1.964	VB	0.0614	3399.35913	872.99890	53.5011

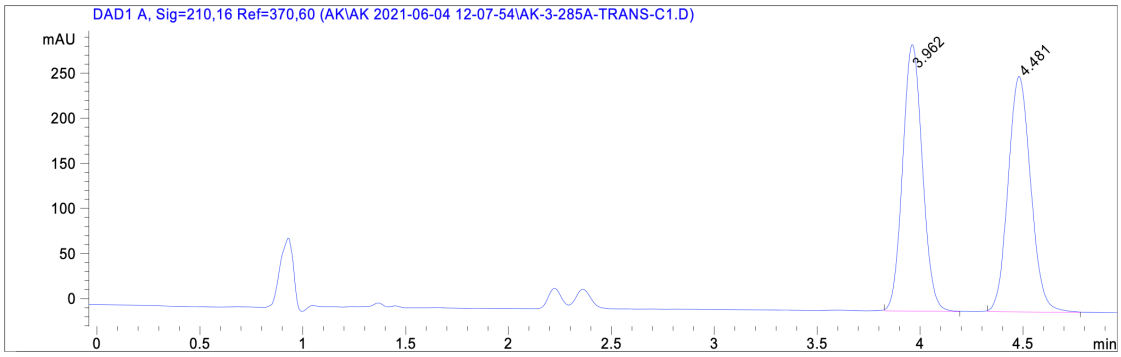
Enantioenriched **5e**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.222	MM	0.0589	51.33008	14.52952	4.4192
2	2.370	VB	0.0618	1110.19238	282.54547	95.5808

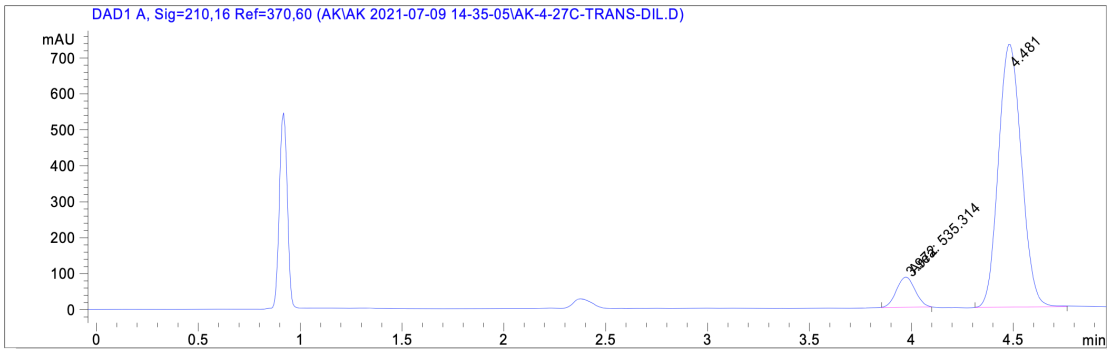
Racemic **5f**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.962	BB	0.1038	1974.61340	296.26938	49.6855
2	4.481	BB	0.1192	1999.60779	261.47470	50.3145

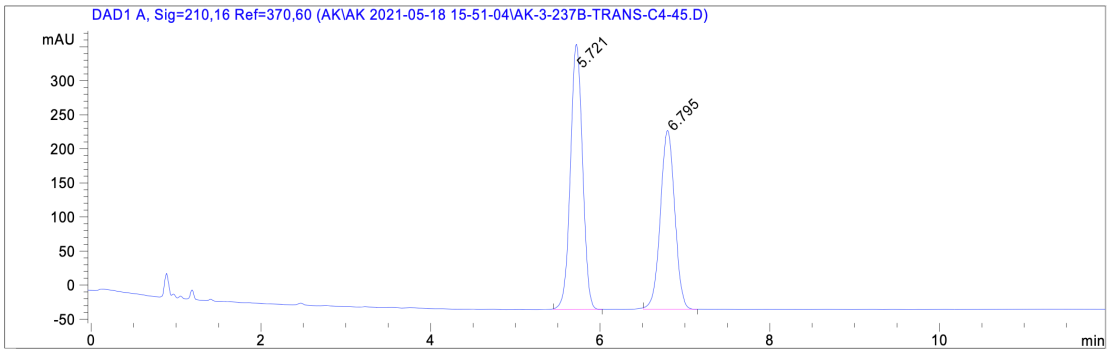
Enantioenriched **5f**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.972	MM	0.1059	535.31372	84.21969	8.5046
2	4.481	BB	0.1237	5759.05176	732.42853	91.4954

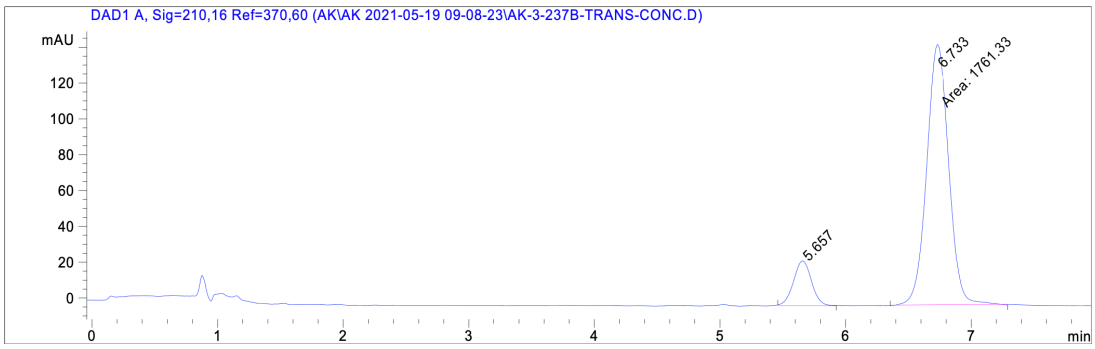
Racemic **5g**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.721	BB	0.1560	3871.54150	389.45190	55.6158
2	6.795	BB	0.1833	3089.68970	262.50827	44.3842

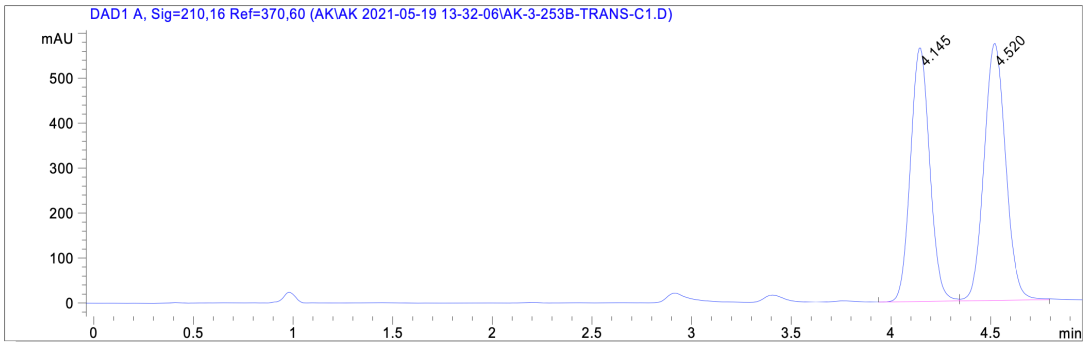
Enantioenriched **5g**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.657	BB	0.1548	250.86575	25.05193	12.4672
2	6.733	MM	0.2019	1761.33459	145.37187	87.5328

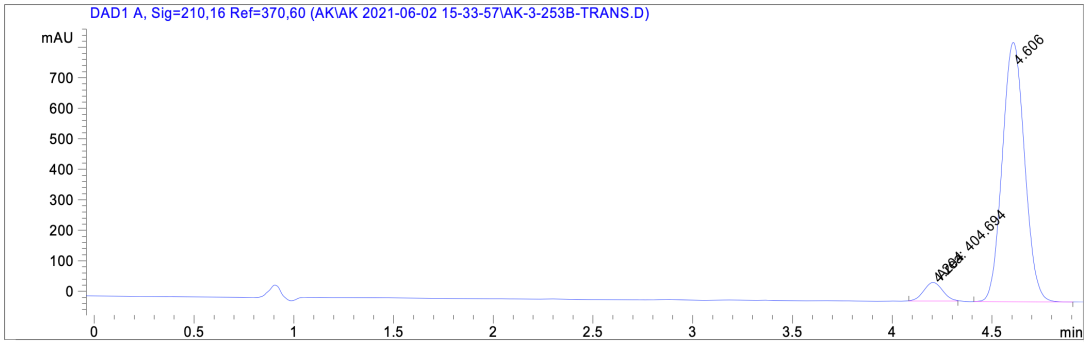
Racemic **5h**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.145	VV	0.1063	3792.93726	565.46350	46.8336
2	4.520	VB	0.1178	4305.81396	572.19220	53.1664

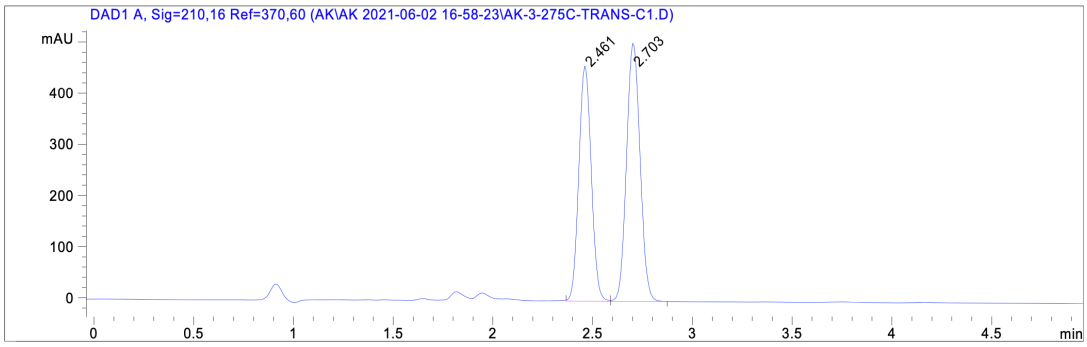
Enantioenriched **5h**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.204	MM	0.1100	404.69440	61.30987	5.7254
2	4.606	VB	0.1253	6663.66309	851.73578	94.2746

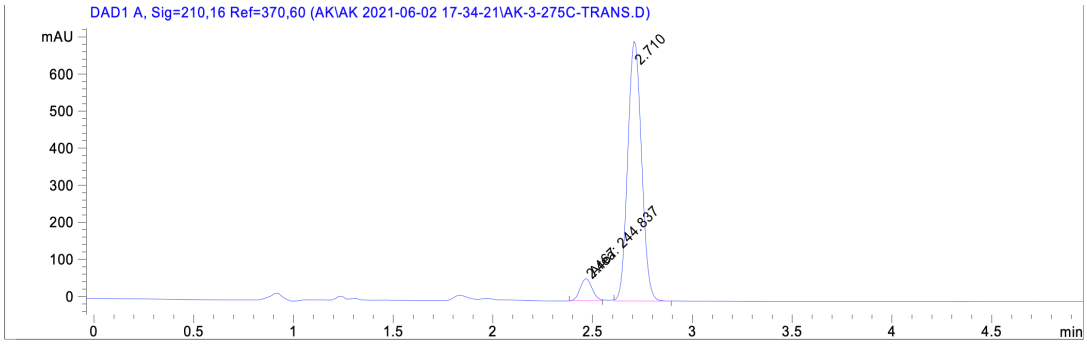
Racemic **5i**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.461	BV	0.0685	1989.77161	459.68130	45.4962
2	2.703	VB	0.0750	2383.71631	505.36072	54.5038

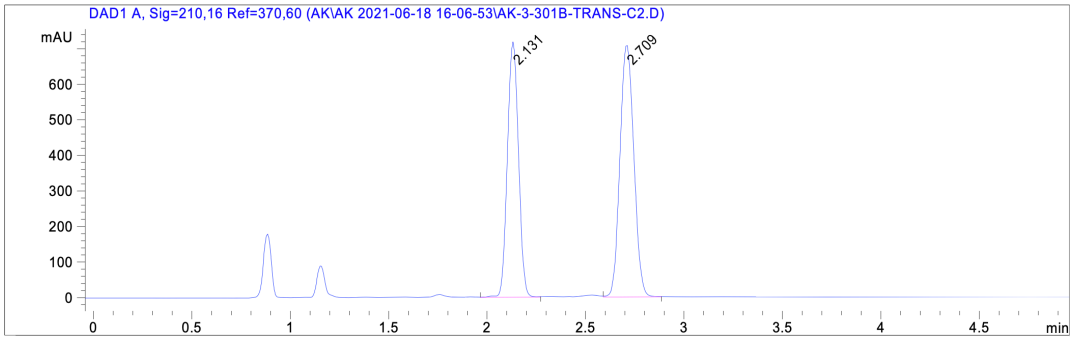
Enantioenriched **5i**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.467	MM	0.0691	244.83684	59.04865	6.7569
2	2.710	BB	0.0762	3378.64526	701.71271	93.2431

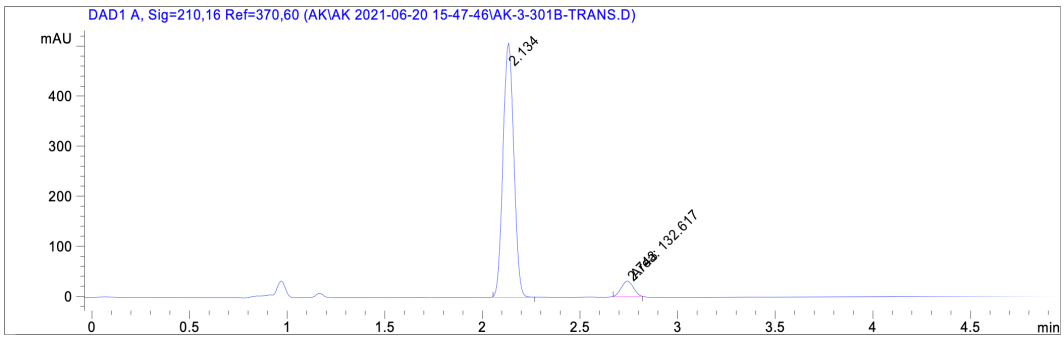
Racemic **5j**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.131	VB	0.0637	2812.75122	717.95227	44.7721
2	2.709	VB	0.0771	3469.62817	709.34265	55.2279

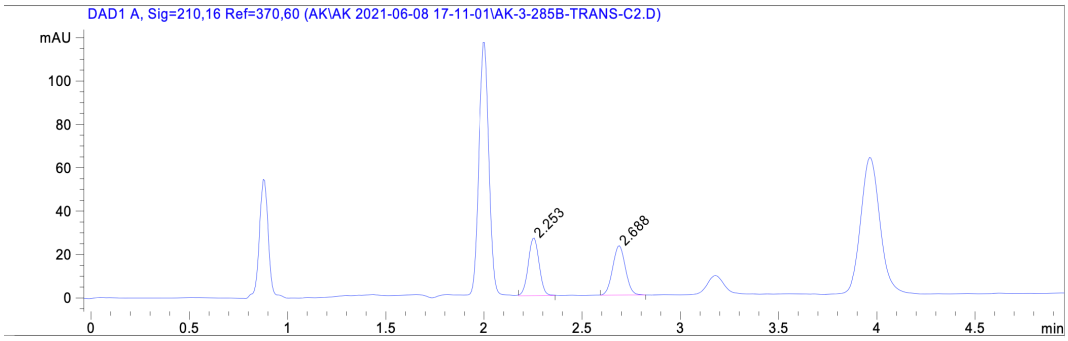
Enantioenriched **5j**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.134	BB	0.0607	1950.11230	508.64514	93.6326
2	2.743	MM	0.0713	132.61661	31.00001	6.3674

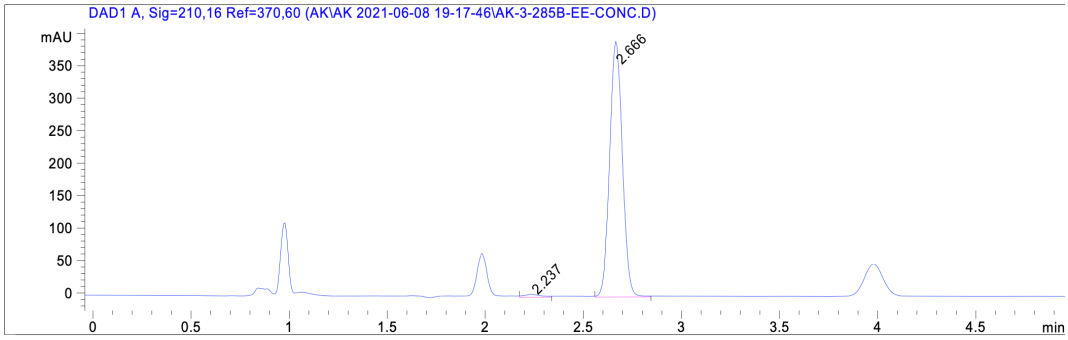
Racemic **5k**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.253	BB	0.0608	102.34369	26.65138	49.9903
2	2.688	BB	0.0704	102.38338	22.78030	50.0097

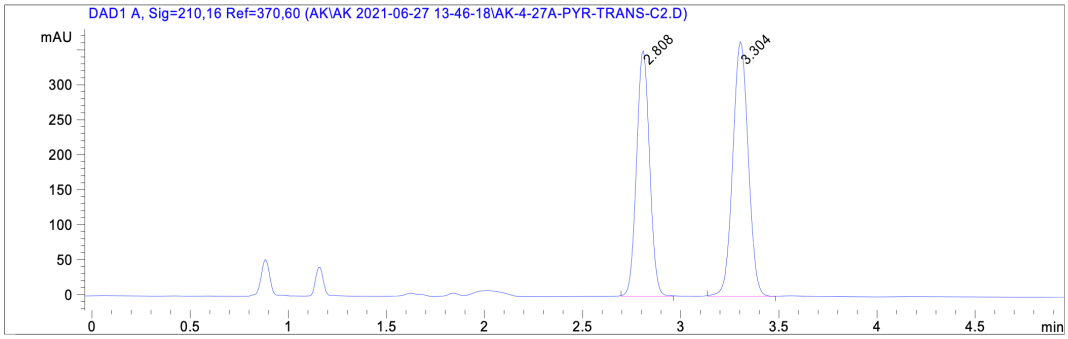
Enantioenriched **5k**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.237	BB	0.0852	28.60090	4.68965	1.5821
2	2.666	BB	0.0707	1779.20972	393.78354	98.4179

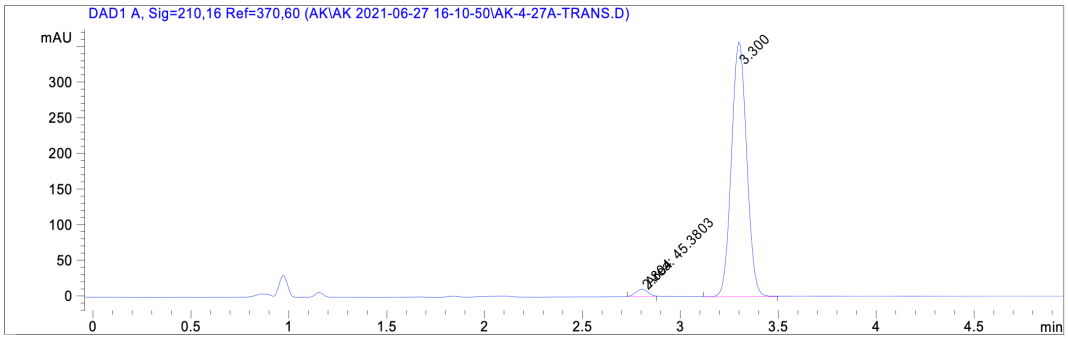
Racemic **5l**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.808	BB	0.0721	1630.49646	351.82343	44.9502
2	3.304	BB	0.0859	1996.83997	364.45786	55.0498

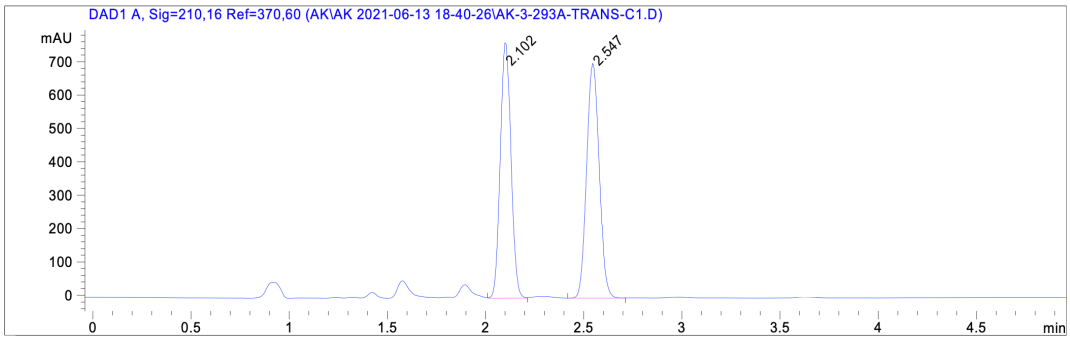
Enantioenriched **5l**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.804	MM	0.0740	45.38032	10.21401	2.2827
2	3.300	BB	0.0853	1942.64270	357.85828	97.7173

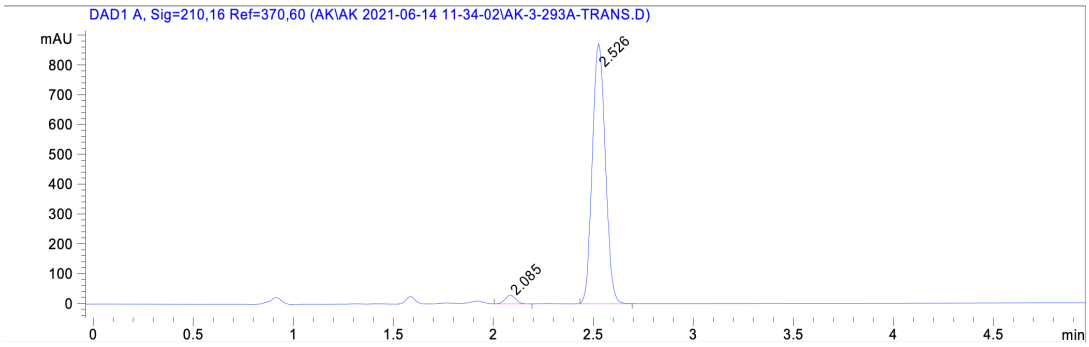
Racemic **5m**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.102	VV	0.0601	2910.37720	769.22076	48.1925
2	2.547	VB	0.0699	3128.68921	703.73804	51.8075

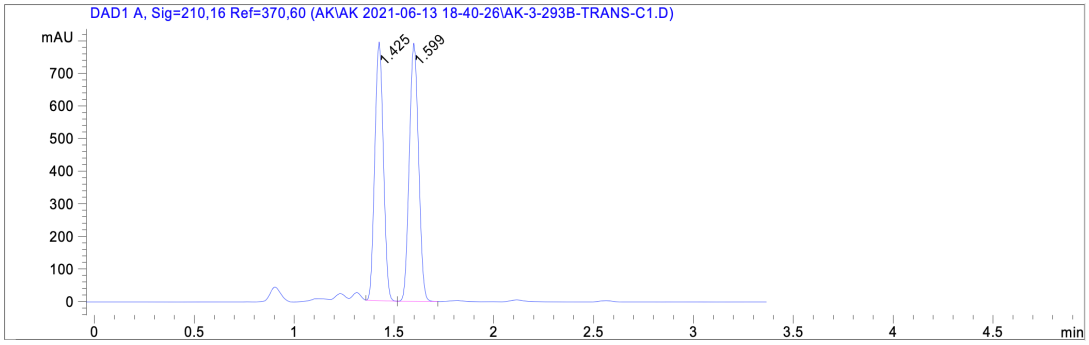
Enantioenriched **5m**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.085	VB	0.0584	106.31534	29.28596	2.6213
2	2.526	BB	0.0708	3949.48437	872.81018	97.3787

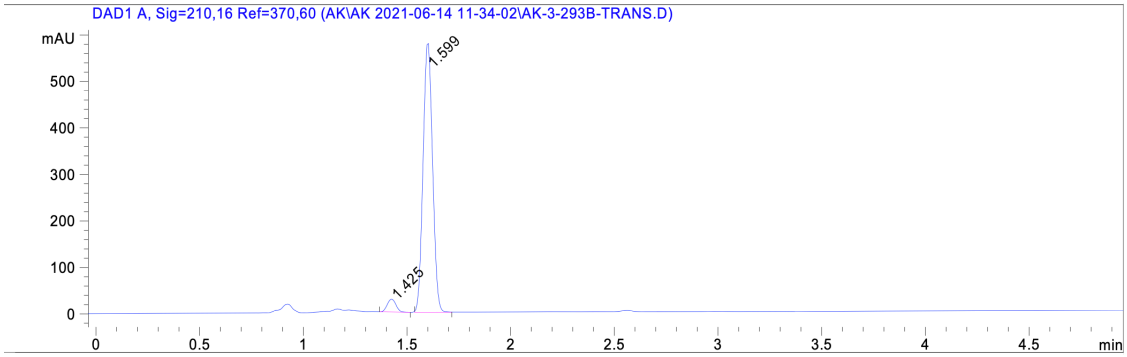
Racemic **5n**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.425	VV	0.0489	2372.91919	793.90009	48.1444
2	1.599	VB	0.0516	2555.83887	792.44293	51.8556

Enantioenriched **5n**



Signal 1: DAD1 A, Sig=210,16 Ref=370,60

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.425	BB	0.0455	79.36908	27.67383	4.1301
2	1.599	BB	0.0489	1842.37402	583.17084	95.8699