

Supporting Information

Synthesis of Bridged Bi-cyclic Amines by Intramolecular Amination of Remote C–H Bonds: Synergistic Activation by Light and Heat

Michaelyn C. Lux,^{§‡} Justin Jurczyk,^{||‡} Yu-hong Lam,^{¥†} Zhiguo J. Song,^{±†} Chao Ma,^β Jose B. Roque,^{||} Jin Su Ham,^{||} Nunzio Sciammetta,^Δ Donovan Adpressa,^{*ε} Richmond Sarpong,^{*||} Charles S. Yeung^{*†}

[†]Disruptive Chemistry Fellow, Department of Discovery Chemistry, Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115

[§]MRL Postdoctoral Fellow, Department of Discovery Chemistry, Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115

^{||}Department of Chemistry, University of California, Berkeley, CA 94720

^ε Department of Analytical Research & Development, Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115

[¥] Department of Computational and Structural Chemistry, Merck & Co., Inc., 126 E. Lincoln Avenue, Rahway, NJ 07065

[±]External Discovery Process Chemistry, Department of Process Research & Development, Merck & Co., 126 E. Lincoln Avenue, Rahway, NJ 07065

^βWuXi Aptec Co., Ltd. 168 Nanhai Road, Tianjin Economic-Technological Development Area (TDEA), Tianjin 330457, China

^ΔDepartment of Discovery Chemistry, Merck & Co., Inc., 33 Avenue Louis Pasteur, Boston, MA 02115

Email: donovon.adpressa@merck.com, rsarpong@berkeley.edu, charles.yeung@merck.com

Table of Contents

1.	General Considerations	S2
2.	Sulfonylation of Primary Amines	S4
3.	Intramolecular C–H Bond Amination	S11
4.	Characterization of Alkyl Iodide Intermediates and Kinetic Data	S19
5.	Second Generation Approach and Scale-up Procedures	S21
6.	¹ H and ¹³ C Spectra	S22
7.	Computational Details and Cartesian Coordinates	S68

1. General Considerations

Methods:

All reactions were performed in scintillation or microwave vials under a nitrogen atmosphere unless otherwise specified. Reactions were monitored by liquid chromatography/mass spectrometry (LCMS) or by thin layer chromatography (TLC) on Silica Gel 60 F₂₅₄ plates (EMD) and visualized with UV light (254 nm). Flash chromatography was performed using pre-packed RediSep R_f silica gel columns on a Teledyne Isco CombiFlash R_f automated chromatography system. Organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator. Reversed-phase high-performance liquid chromatography was carried out using an Agilent 1100 HPLC-MSD system consisting of a 6130B single quadrupole mass-selective detector (MSD), G1315B diode array detector, G2258A autosampler, two G1361A preparative pumps, one G1379A quaternary pump with degasser, one G1312A binary pump, and three G1364B fraction collectors from Agilent Technologies. System control and data analysis was performed using Agilent's ChemStation software, revision B.03.01-SR.1. A Waters XBridge C18 OBD Prep Column, 100 Å, 5 µm, 19 mm × 150 mm column was used as the stationary phase (Waters Corporation). Gradient elution was carried out using water and acetonitrile as the mobile phase. An aqueous 10% trifluoroacetic acid or 10% ammonium hydroxide solution was teed into the mobile phase as a modifier using a static mixer prior to the column, pumped at 1% of the total mobile phase flow rate. ESI mass-triggered fraction collected was employed using positive ion polarity scanning to monitor for the target mass. Aqueous fractions were concentrated using a SP Industries, Inc. Genevac HT-12 Series 3i instrument. SFC purifications were performed with either a Waters ACQUITY UPC² system or a Sepiatec Prep SFC 100.

Materials and Reagents:

All reagents and solvents were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Strem, Acros, Enamine, etc.) and used without further purification unless otherwise specified. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used without further purification unless otherwise specified. CDCl₃ was treated with and stored over K₂CO₃.

Instrumentation:

Proton nuclear magnetic resonance (¹H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian 500 (500 MHz) NMR spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm). Proton resonances are referenced to residual protium in the NMR solvent. Carbon resonances are referenced to the carbon resonances of the NMR solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) in Hertz (Hz), integration.

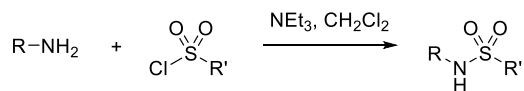
LCMS samples were run on an Agilent 1100 or 1200 system. High-resolution mass spectrometry (HRMS) data were recorded on a Waters Xevo G2 QToF instrument in either ESI⁺ or ESI⁻ (electrospray) ionization mode.

Optical rotations were taken using a Perkin-Elmer 241 Polarimeter.

Abbreviations Used:

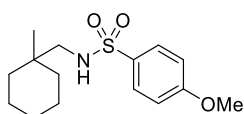
aq = aqueous, b.r.s.m. = based on recovered starting materials, Calcd = calculated, h = hours, min = minutes, s = seconds, rt = room temperature

2. Sulfonylation of Primary Amines

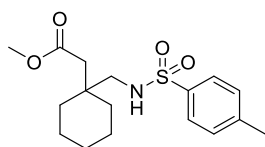


General Procedure: To a 40 mL scintillation vial was added amine or ammonium salt (2–4 mmol), CH₂Cl₂ (20 mL, 0.1–0.2 M), triethylamine (1.2 equiv, with an additional 1 equiv per ammonium salt). To the resulting solution was added sulfonyl chloride (1 equiv), and the reaction mixture was stirred at rt until complete as determined by LCMS analysis. The reaction mixture was diluted with EtOAc, and then washed with sat'd NH₄Cl (aq). The layers were separated, and the organic layer was washed twice more with sat'd NH₄Cl (aq). Finally, the separated organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel to afford analytically pure product.

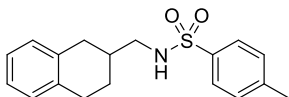
4-Methyl-N-((1-methylcyclohexyl)methyl)benzenesulfonamide (1a): 3.3 g, 82% yield. 0–25% EtOAc/hexanes. White solid. ¹H NMR (600 MHz, CDCl₃) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.27 (s, 1H), 2.72 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.49 – 1.35 (m, 5H), 1.24 (dt, *J* = 20.3, 6.2 Hz, 5H), 0.85 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 143.5, 137.3, 129.9, 127.3, 53.6, 35.4, 33.9, 26.3, 21.8, 21.7 (two C's are overlapping). HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₃NO₂S 282.1527; Found 282.1536.



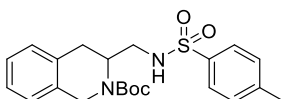
4-Methoxy-N-((1-methylcyclohexyl)methyl)benzenesulfonamide (1b): 666 mg, 62% yield. 0–20% EtOAc/hexanes. White solid. ¹H NMR (700 MHz, CDCl₃) δ 7.80 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.51 (t, *J* = 6.9 Hz, 1H), 3.87 (s, 3H), 2.70 (d, *J* = 6.9 Hz, 2H), 1.45 – 1.36 (m, 5H), 1.27 – 1.19 (m, 5H), 0.85 (s, 3H). ¹³C NMR (176 MHz, CDCl₃): δ 162.9, 131.9, 129.3, 114.3, 55.7, 35.3, 33.8, 26.2, 21.7, 21.5 (two C's are overlapping). HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₄NO₃S 298.1471; Found 298.1475.



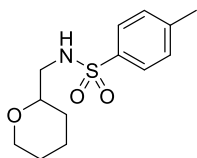
Methyl 2-(1-(((4-methylphenyl)sulfonamido)methyl)cyclohexyl)acetate (1c): 735 mg, 83% yield. 0–35% EtOAc/hexanes. White solid. ¹H NMR (499 MHz, CDCl₃) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.14 (t, *J* = 7.2 Hz, 1H), 3.61 (s, 3H), 2.85 (d, *J* = 7.3 Hz, 2H), 2.43 (s, 3H), 2.31 (s, 2H), 1.48 – 1.32 (m, 10H). ¹³C NMR (126 MHz, CDCl₃) δ 173.2, 143.4, 137.5, 129.9, 127.2, 53.6, 51.8, 37.2, 34.2, 26.0, 21.7, 21.5 (two C's are overlapping). HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₇H₂₅NO₄S 340.1582; Found 340.1588.



(±)-4-Methyl-N-((1,2,3,4-tetrahydronaphthalen-2-yl)methyl)benzenesulfonamide (1d): 725 mg, 90% yield. 0–25% EtOAc/Hexanes. White solid. ¹H NMR (600 MHz, CDCl₃) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.15 – 6.97 (m, 4H), 4.44 (s, 1H), 2.96 (t, *J* = 6.6 Hz, 2H), 2.78 (dddt, *J* = 33.1, 16.7, 11.2, 5.1 Hz, 3H), 2.43 (s, 4H), 1.98 – 1.84 (m, 2H), 1.38 (dtd, *J* = 13.3, 11.2, 5.8 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 143.7, 137.2, 136.4, 135.3, 129.9, 129.3, 129.0, 127.3, 126.0, 125.9, 48.7, 34.8, 33.6, 28.6, 26.9, 21.7. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₈H₂₂NO₂S 316.1371; Found 316.1366.

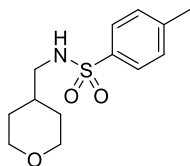


(±)-tert-Butyl 3-(((4-methylphenyl)sulfonamido)methyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (1e): Material was isolated as a mixture of rotamers. 257 mg, 24% yield. 0–45% EtOAc/hexanes. White solid. ¹H NMR (500 MHz, 85 °C, DMSO-*d*₆) δ 7.63 (d, *J* = 7.9 Hz, 2H), 7.47 – 7.30 (m, 3H), 7.21 – 7.06 (m, 4H), 4.62 (d, *J* = 16.8 Hz, 1H), 4.37 (s, 1H), 4.17 (d, *J* = 16.8 Hz, 1H), 3.05 (s, 1H), 2.91 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.65 (dd, *J* = 12.7, 7.8 Hz, 1H), 2.38 (s, 3H), 1.44 (s, 9H). ¹³C NMR (126 MHz, DMSO) δ 154.8, 142.9, 138.6, 133.7, 133.0, 129.9, 129.4, 127.0, 126.9, 126.6, 126.3, 79.8, 50.0, 44.2, 43.2, 30.3, 28.6, 21.3. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₂₂H₂₈N₂O₄S 417.1848; Found 417.1837.

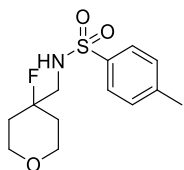


(±)-4-Methyl-N-((tetrahydro-2H-pyran-2-yl)methyl)benzenesulfonamide (1f): 940 mg, 70% yield. 0–40% EtOAc/hexanes. White solid. ¹H NMR (600 MHz, CDCl₃) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.83 (d, *J* = 5.1 Hz, 1H), 3.94 – 3.87 (m, 1H), 3.34 (qd, *J* = 11.1, 9.6, 3.3 Hz, 2H), 3.07 (ddd, *J* = 11.9, 8.4, 3.2 Hz, 1H), 2.77 (ddd, *J* = 12.1, 8.3, 3.6 Hz, 1H), 2.42 (s, 3H), 1.85 – 1.76 (m, 1H), 1.57 (s, 3H), 1.46 (dddt, *J* =

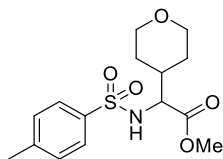
16.2, 12.3, 8.1, 4.2 Hz, 4H), 1.30 – 1.21 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 143.5, 137.1, 129.9, 127.3, 75.9, 68.5, 48.1, 29.0, 25.9, 23.0, 21.7. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₃H₁₉NO₃S 270.1164; Found 270.1179.



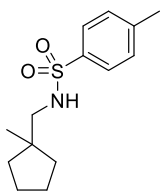
4-Methyl-N-((tetrahydro-2H-pyran-4-yl)methyl)benzenesulfonamide (1g): 1.19 g, 92% yield. 0–55% EtOAc/hexanes. White solid. ¹H NMR (600 MHz, CDCl₃) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.39 (s, 1H), 3.94 (dd, *J* = 10.9, 3.7 Hz, 2H), 3.32 (td, *J* = 11.9, 2.0 Hz, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.69 (ddh, *J* = 15.2, 7.0, 3.6 Hz, 1H), 1.61 – 1.56 (m, 2H), 1.22 (qd, *J* = 12.1, 4.6 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 143.5, 137.0, 129.8, 127.1, 67.4, 48.9, 35.4, 30.4, 21.5. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₃H₂₀NO₃S 270.1164; Found 270.1158.



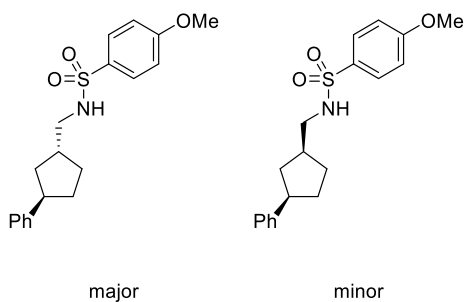
N-((4-Fluorotetrahydro-2H-pyran-4-yl)methyl)-4-methylbenzenesulfonamide (1h): 0.68 g, 90% yield. 0–40% EtOAc/hexanes. Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.62 (s, 1H), 3.79 (ddd, *J* = 11.6, 4.8, 2.7 Hz, 2H), 3.67 (td, *J* = 11.5, 2.2 Hz, 2H), 3.09 (dd, *J* = 20.6, 6.7 Hz, 2H), 2.44 (s, 3H), 1.88 – 1.77 (m, 2H), 1.76 – 1.60 (m, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 143.9, 137.0, 130.0, 127.2, 92.9 (d, *J* = 173.5 Hz), 63.5 (d, *J* = 1.9 Hz), 51.0 (d, *J* = 21.9 Hz), 33.4 (d, *J* = 21.1 Hz), 21.7. HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₃H₁₈FNNaO₃S 310.0889; Found 310.0884.



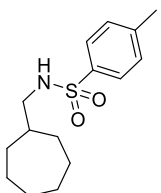
(±)-Methyl 2-((4-methylphenyl)sulfonamido)-2-(tetrahydro-2H-pyran-4-yl)acetate (1i): 0.71 g, 84% yield. 0–60% EtOAc/hexanes. White solid. ¹H NMR (600 MHz, CDCl₃) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.05 (d, *J* = 10.1 Hz, 1H), 3.96 (t, *J* = 11.7 Hz, 2H), 3.75 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.46 (s, 3H), 3.36 – 3.24 (m, 2H), 2.42 (s, 3H), 1.88 (tdd, *J* = 12.0, 6.7, 3.7 Hz, 1H), 1.54 – 1.48 (m, 1H), 1.39 (ddd, *J* = 25.2, 11.8, 4.2 Hz, 2H). ¹³C NMR (151 MHz, CDCl₃) δ 171.4, 144.0, 136.7, 129.8, 127.5, 67.7, 67.5, 60.3, 52.5, 38.8, 29.1, 28.5, 21.7. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₂NO₅S 328.1219; Found 328.1213.



4-Methyl-N-((1-methylcyclopentyl)methyl)benzenesulfonamide (1j): 1.5 g, 89% yield. 0–20% EtOAc/hexanes. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.74 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 4.37 (s, 1H), 2.77 (d, $J = 6.7$ Hz, 2H), 2.43 (s, 3H), 1.71 – 1.50 (m, 5H), 1.37 (dt, $J = 13.5, 7.2$ Hz, 2H), 1.29 (dq, $J = 13.0, 7.8, 6.1$ Hz, 2H), 0.94 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 143.5, 137.3, 129.9, 127.3, 53.1, 42.7, 37.4, 25.1, 24.8, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{S}$ 268.1371; Found 268.1378.

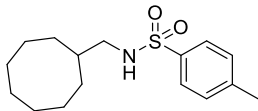


(±)-4-Methyl-N-((3-phenylcyclopentyl)methyl)benzenesulfonamide, inseparable ~3:1 mixture of *anti*- to *syn*-isomers, peaks solely attributable to the minor diastereomer are marked with an asterisk (1k): 0.64 g, 83% yield. 0–20% EtOAc/hexanes. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.85 – 7.74 (m, 2H), 7.28 (d, $J = 7.8$ Hz, 2H), 7.16 (dd, $J = 7.1, 3.3$ Hz, 3H), 6.99 (d, $J = 8.9$ Hz, 2H), 4.33 (s, 1H), 3.87 (s, 3H), 3.03 (dt, $J = 16.9, 8.8$ Hz, 1H), 2.98 – 2.88 (m, 2H), 2.26 (dp, $J = 15.5, 7.7$ Hz, 1H), 2.21 – 2.14 (m, 0.33H),* 2.08 (ddt, $J = 14.3, 9.2, 4.7$ Hz, 1H), 1.97 (dtd, $J = 12.7, 7.6, 2.5$ Hz, 1H), 1.86 (dd, $J = 12.8, 8.5$ Hz, 0.33H),* 1.76 (ddt, $J = 21.5, 13.3, 8.4$ Hz, 2H), 1.63 (dtd, $J = 12.5, 10.3, 7.7$ Hz, 1H), 1.44 (s, 0.33H),* 1.28 (ddt, $J = 12.8, 10.5, 7.6$ Hz, 1H), 1.22 – 1.17 (m, 0.33H).* ^{13}C NMR (151 MHz, CDCl_3) δ 162.9, 145.5, 131.6, 129.2, 128.3, 127.0, 126.0, 114.3, 55.6, 48.4, 44.3, 38.7, 37.7, 34.5, 30.6. HRMS (ESI) m/z Calcd: $[\text{M}+\text{H}]^+$ for $\text{C}_{19}\text{H}_{24}\text{NO}_3\text{S}$ 346.1477; Found 346.1471.

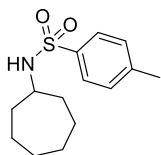


N-(Cycloheptylmethyl)-4-methylbenzenesulfonamide (1l): 0.75 g, 88% yield. 0–5% EtOAc/ CH_2Cl_2 . Light yellow solid. ^1H NMR (600 MHz, CDCl_3) δ 7.73 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 4.28 (t, $J = 6.7$ Hz, 1H), 2.76 (t, $J = 6.6$ Hz, 2H), 2.43 (s, 3H), 1.62 (dddd, $J = 34.4, 13.5, 9.8, 6.9, 3.2$ Hz, 6H), 1.52 (dd, $J = 6.8, 3.6$ Hz, 1H), 1.48 – 1.41 (m, 2H), 1.40 – 1.32 (m, 2H), 1.12 (dtd, $J = 12.5, 9.7, 2.9$ Hz, 2H). ^{13}C NMR (151 MHz,

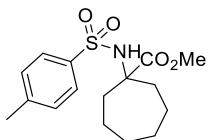
CDCl_3) δ 143.5, 137.3, 129.9, 127.3, 49.8, 39.5, 32.0, 28.5, 26.4, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_2\text{S}$ 282.1527; Found 282.1530.



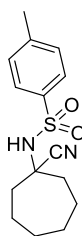
***N*-(Cyclooctylmethyl)-4-methylbenzenesulfonamide (1m)**: 769 mg, 97% yield. 0–25% EtOAc/hexanes. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.74 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.34 (s, 1H), 2.75 (t, J = 6.5 Hz, 2H), 2.43 (s, 3H), 1.70 – 1.33 (m, 14H), 1.23 – 1.16 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 143.5, 137.3, 129.9, 127.3, 50.2, 37.6, 30.3, 27.0, 26.4, 25.4, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{25}\text{NO}_2\text{S}$ 296.1684; Found 296.1682.



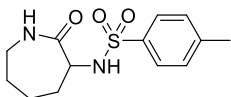
***N*-Cycloheptyl-4-methylbenzenesulfonamide (1n)**: 0.93 g, 98% yield. 0–20% EtOAc/hexanes. Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 7.75 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 4.30 (d, J = 6.8 Hz, 1H), 3.34 (ddq, J = 13.0, 8.7, 4.5 Hz, 1H), 2.43 (s, 3H), 1.81 – 1.70 (m, 2H), 1.55 – 1.30 (m, 10H). ^{13}C NMR (151 MHz, CDCl_3) δ 143.3, 138.4, 129.8, 127.2, 55.0, 36.1, 28.1, 23.7, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{S}$ 268.1371; Found 268.1373.



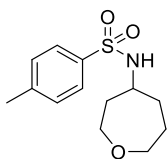
Methyl 1-((4-methylphenyl)sulfonamido)cycloheptane-1-carboxylate (1o): 0.32 g, 44% yield. 0–30% EtOAc/hexanes. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.74 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 4.81 (s, 1H), 3.59 (s, 3H), 2.42 (s, 3H), 2.18 – 2.01 (m, 2H), 1.84 (dd, J = 14.9, 9.0 Hz, 2H), 1.53 – 1.43 (m, 6H), 1.42 – 1.33 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 175.0, 143.5, 139.0, 129.6, 127.5, 65.5, 52.6, 36.6, 29.8, 22.2, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4\text{S}$ 326.1426; Found 326.1427.



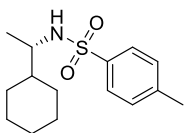
***N*-(1-Cyanocycloheptyl)-4-methylbenzenesulfonamide (1p)**: 2.6 g, 24% yield. 80–90% EtOAc/petroleum ether. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.82 (d, $J = 8.3$ Hz, 2H), 7.34 (d, $J = 8.1$ Hz, 2H), 4.68 (s, 1H), 2.44 (s, 3H), 2.22 (dd, $J = 14.5, 8.1$ Hz, 2H), 2.02 – 1.94 (m, 2H), 1.62 (ddt, $J = 37.9, 20.9, 9.2$ Hz, 8H). ^{13}C NMR (151 MHz, CDCl_3) δ 144.4, 137.6, 130.0, 127.8, 120.0, 57.4, 40.0, 27.9, 21.8, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{O}_2\text{S}$ 293.1324; Found 293.1318.



(±)-4-Methyl-*N*-(2-oxoazepan-3-yl)benzenesulfonamide (1q): 0.37 g, 51% yield. 100% EtOAc. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.73 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 6.14 (d, $J = 5.0$ Hz, 1H), 5.82 (s, 1H), 3.86 – 3.78 (m, 1H), 3.17 (dt, $J = 13.0, 6.4$ Hz, 1H), 3.07 (ddd, $J = 15.6, 11.7, 5.1$ Hz, 1H), 2.41 (s, 3H), 2.17 (d, $J = 14.7$ Hz, 1H), 2.01 (d, $J = 14.7$ Hz, 1H), 1.85 – 1.75 (m, 1H), 1.72 – 1.60 (m, 2H), 1.40 – 1.30 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 174.3, 143.6, 137.1, 129.9, 127.2, 55.6, 42.5, 33.6, 28.9, 28.2, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ 283.1116; Found 283.1122.

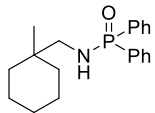


(±)-4-Methyl-*N*-(oxepan-4-yl)benzenesulfonamide (1r): 0.54 g, 46% yield. 0–50% EtOAc/hexanes. White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.77 (d, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 7.9$ Hz, 2H), 4.79 (d, $J = 8.8$ Hz, 1H), 3.75 (dt, $J = 11.1, 5.0$ Hz, 1H), 3.67 (ddd, $J = 18.4, 12.4, 7.5$ Hz, 2H), 3.58 – 3.45 (m, 2H), 2.43 (s, 3H), 1.85 – 1.77 (m, 1H), 1.70 (tt, $J = 13.2, 6.9$ Hz, 3H), 1.66 – 1.58 (m, 2H). ^{13}C NMR (151 MHz, CDCl_3) δ 143.5, 138.5, 129.9, 127.1, 69.4, 65.7, 52.6, 36.1, 33.9, 26.1, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_3\text{S}$ 270.1164; Found 270.1170.



(*S*)-*N*-(1-Cyclohexylethyl)-4-methylbenzenesulfonamide (1s): 706 mg, 95% yield. 0–20% EtOAc/hexanes. White solid. $[\alpha]_D^{25} -0.18$ (c 0.66, CHCl_3). ^1H NMR (499 MHz, CDCl_3) δ 7.74 (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.0$ Hz, 2H), 4.14 (d, $J = 8.7$ Hz, 1H), 3.15 (dq, $J = 13.4, 6.7$ Hz, 1H), 2.42 (s, 3H), 1.76 – 1.59 (m, 4H), 1.52 (d, $J = 9.5$ Hz, 1H), 1.24 (ddt, $J = 11.8, 5.3, 2.8$ Hz, 1H), 1.20 – 1.03 (m, 3H), 0.97 (td, $J = 12.3, 3.2$ Hz, 1H), 0.93 (d, $J = 6.7$ Hz, 3H), 0.88 – 0.76 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.3, 138.5, 129.8, 127.2, 54.6, 43.7,

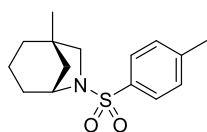
28.8, 28.7, 26.5, 26.3, 26.2, 21.7, 18.7. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{15}H_{14}NO_2S$ 282.1528; Found 282.1522.



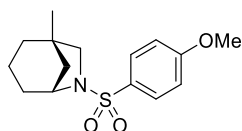
***N*-((1-Methylcyclohexyl)methyl)-*P,P*-diphenylphosphinic amide (1t):** Synthesized using General Procedure indicated above but with phosphinic chloride instead of sulfonyl chloride. 0.64 g, 71% yield. 0–100% EtOAc/hexanes. White solid. 1H NMR (600 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 4H), 7.56 – 7.51 (m, 2H), 7.50 – 7.44 (m, 4H), 2.78 (d, $J = 6.7$ Hz, 2H), 1.79 (s, 1H), 1.51 – 1.46 (m, 1H), 1.43 (p, $J = 6.3$ Hz, 4H), 1.33 – 1.28 (m, 4H), 1.26 (dd, $J = 12.5, 6.3$ Hz, 1H), 0.96 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.2 (d, $J = 9.4$ Hz), 131.9 (app d, $J = 2.3$ Hz), 128.6 (d, $J = 12.6$ Hz), 51.2, 35.4, 35.1, 34.2, 34.1, 26.3, 21.7, 21.5. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{20}H_{26}NOP^+$ 328.1830; Found 328.1840.

3. Intramolecular C–H Amination

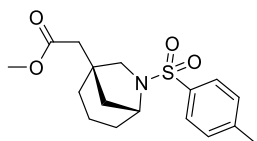
General Procedure: To a 20 mL scintillation vial was added sulfonamide (0.2 mmol), 1,3-diiodo-5,5-dimethylhydantoin (304 mg, 0.8 mmol, 4 equiv), and MeCN (4 mL, 0.05 M). The resulting suspension was stirred at rt for 5 min, and then heated to 80 °C for 24 h using an aluminum heating block. The mixture was diluted with CH₂Cl₂, and then quenched with sat'd Na₂S₂O₃ (aq). The organic layer was separated using a phase separator. The aqueous layer was extracted twice with CH₂Cl₂. Finally, the combined organic layers were concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel to afford analytically pure product.



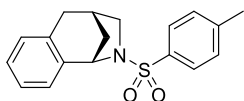
(±)-(1*S*,5*R*)-1-Methyl-6-tosyl-6-azabicyclo[3.2.1]octane (2a): 25.6 mg, 46% yield. 0–5% EtOAc/CH₂Cl₂. Orange solid. ¹H NMR (600 MHz, DMSO-*d*₆) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 4.01 (t, *J* = 5.1 Hz, 1H), 3.12 (d, *J* = 9.5 Hz, 1H), 2.78 – 2.73 (m, 1H), 2.38 (s, 3H), 1.64 – 1.58 (m, 1H), 1.52 – 1.39 (m, 3H), 1.33 – 1.23 (2H), 1.21 (d, *J* = 11.0 Hz, 1H), 0.93 – 0.88 (m, 1H), 0.86 (s, 3H). ¹³C NMR (151 MHz, DMSO-*d*₆) δ 143.5, 135.6, 130.1, 127.2, 59.2, 57.7, 43.5, 40.3, 36.9, 31.0, 24.6, 21.3, 19.2. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₅H₂₂NO₂S 280.1371; Found 280.1362.



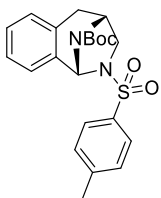
(±)-6-((4-Methoxyphenyl)sulfonyl)-1-methyl-6-azabicyclo[3.2.1]octane (2b): 35.4 mg, 60% yield. 0–20% EtOAc/hexanes. White solid. ¹H NMR (700 MHz, CDCl₃) δ 7.77 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.11 (t, *J* = 5.2 Hz, 1H), 3.86 (s, 3H), 3.19 (d, *J* = 9.4 Hz, 1H), 2.86 (dd, *J* = 9.4, 1.8 Hz, 1H), 1.83 (dt, *J* = 12.4, 5.9 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.57 (dt, *J* = 13.4, 5.8 Hz, 1H), 1.50 – 1.45 (m, 1H), 1.30 (qd, *J* = 13.4, 4.9 Hz, 2H), 1.23 – 1.14 (m, 2H), 0.94 (s, 3H). ¹³C NMR (176 MHz, CDCl₃) δ 162.7, 131.1, 129.2, 114.2, 59.5, 57.9, 55.7, 44.3, 40.6, 37.7, 31.4, 24.8, 19.4. HRMS (ESI) *m/z*: [M+Na]⁺ Calcd for C₁₅H₂₁NNaO₃S 318.1134; Found 318.1135.



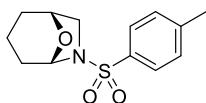
(±)-**Methyl 2-((1S,5R)-6-tosyl-6-azabicyclo[3.2.1]octan-1-yl)acetate (2c)**: 27.9 mg, 41%. 0-35%. Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.15 (t, *J* = 5.2 Hz, 1H), 3.60 (s, 3H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.08 (dd, *J* = 9.9, 1.6 Hz, 1H), 2.42 (s, 3H), 2.33 – 2.19 (m, 2H), 1.91 – 1.83 (m, 1H), 1.71 – 1.58 (m, 3H), 1.43 – 1.27 (m, 3H), 1.27 – 1.21 (m, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 171.5, 143.3, 136.2, 129.8, 127.3, 58.8, 56.4, 51.7, 43.4, 42.9, 42.4, 35.1, 31.4, 21.7, 19.1. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₇H₂₄NO₄S 338.1426; Found 338.1425.



(±)-**(1S,4S)-2-Tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[c]azepine (2d)**: 26.4 mg, 42% yield. 0–15% EtOAc/hexanes. Colorless oil. ¹H NMR (600 MHz, CD₃CN) δ 7.62 – 7.58 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.15 (d, *J* = 10.0 Hz, 1H), 3.07 (dd, *J* = 17.5, 5.0 Hz, 1H), 2.73 (d, *J* = 17.9 Hz, 1H), 2.70 (d, *J* = 5.3 Hz, 1H), 2.39 (s, 3H), 1.69 (d, *J* = 11.4 Hz, 1H), 1.53 – 1.47 (m, 1H). ¹³C NMR (151 MHz, CD₃CN) δ 144.4, 140.4, 136.6, 135.1, 130.5, 130.4, 128.8, 128.1, 127.6, 126.6, 61.1, 55.0, 36.6, 34.8, 34.4, 21.4. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₈H₂₀NO₂S 314.1215; Found 314.1215.

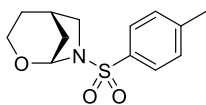


(±)-**tert-Butyl (1R,4R)-2-tosyl-2,3,4,5-tetrahydro-1H-1,4-epiminobenzo[c]azepine-10-carboxylate (2e)**: 55 mg, 66% yield. 0–60% EtOAc/hexanes. White solid. ¹H NMR (600 MHz, CDCl₃) δ 7.69 (d, *J* = 7.7 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.26 – 7.24 (m, 2H), 7.22 (td, *J* = 7.4, 1.6 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.27 (s, 1H), 4.65 (s, 1H), 3.58 (t, *J* = 8.7 Hz, 1H), 3.36 (dd, *J* = 17.6, 4.9 Hz, 1H), 3.21 (d, *J* = 10.0 Hz, 1H), 2.64 (d, *J* = 17.0 Hz, 1H), 2.40 (s, 3H), 1.33 (s, 9H). ¹³C NMR (151 MHz, CDCl₃) δ 152.2, 143.8, 137.1, 135.6, 131.5, 129.8, 129.6, 128.7, 128.1, 126.7, 126.0, 81.2, 72.1, 53.0, 52.1, 34.6, 28.3, 21.6. HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₂₂H₂₇N₂O₄S 415.1691; Found 415.1697.

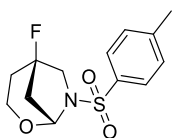


(±)-**(1R,5S)-6-Tosyl-8-oxa-6-azabicyclo[3.2.1]octane (2f)**: 31.2 mg, 58% yield. 0–30% EtOAc/hexanes. Colorless oil. ¹H NMR (600 MHz, CD₃CN) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.48 (s, 1H), 4.39 – 4.30 (m, 1H), 3.33 (d, *J* = 9.6 Hz, 1H), 3.22 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.42 (s, 3H), 1.91 – 1.82 (m, 1H), 1.76 –

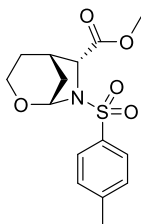
1.69 (m, 2H), 1.66 – 1.59 (m, 2H), 1.45 (dd, $J = 14.1, 4.9$ Hz, 1H). ^{13}C NMR (151 MHz, CD_3CN) δ 145.2, 135.1, 130.7, 128.7, 89.8, 76.3, 50.9, 32.4, 29.3, 21.5, 16.2. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3\text{S}$ 268.1007; Found 268.1008.



(±)-(1R,5S)-7-Tosyl-2-oxa-7-azabicyclo[3.2.1]octane (2g): 46.4 mg, 87% yield. 0–30% EtOAc/hexanes. Colorless oil. ^1H NMR (600 MHz, CD_3CN) δ 7.73 (d, $J = 8.2$ Hz, 2H), 7.38 (d, $J = 8.1$ Hz, 2H), 5.44 (d, $J = 3.1$ Hz, 1H), 3.52 (dd, $J = 11.8, 6.9$ Hz, 1H), 3.32 – 3.24 (m, 3H), 2.54 (s, 1H), 2.41 (s, 3H), 1.83 – 1.76 (m, 1H), 1.73 (d, $J = 11.4$ Hz, 1H), 1.42 – 1.36 (m, 2H). ^{13}C NMR (151 MHz, CD_3CN) δ 144.7, 137.5, 130.6, 127.9, 87.3, 60.0, 51.8, 39.3, 33.3, 31.0, 21.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3\text{S}$ 268.1007; Found 268.0994.

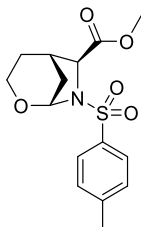


(±)-(1R,5R)-5-Fluoro-7-tosyl-2-oxa-7-azabicyclo[3.2.1]octane (2h): 26.9 mg, 47% yield. 0–40% EtOAc/hexanes. Colorless oil. Prolonged exposure to ambient light leads to decomposition. ^1H NMR (600 MHz, CDCl_3) δ 7.77 (d, $J = 8.2$ Hz, 2H), 7.33 (d, $J = 8.1$ Hz, 2H), 5.66 (t, $J = 3.8$ Hz, 1H), 3.75 (ddd, $J = 11.3, 7.0, 3.7$ Hz, 1H), 3.51 – 3.35 (m, 2H), 3.14 (td, $J = 12.2, 4.6$ Hz, 1H), 2.44 (s, 3H), 2.13 (dtd, $J = 14.9, 8.1, 7.6, 4.2$ Hz, 2H), 1.92 (d, $J = 10.3$ Hz, 1H), 1.82 (ddt, $J = 12.0, 8.0, 3.9$ Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 144.0, 136.0, 129.8, 127.2, 94.7 (d, $J = 202.6$ Hz), 87.0 (d, $J = 7.7$ Hz), 59.7 (d, $J = 10.5$ Hz), 52.2 (d, $J = 30.8$ Hz), 43.6 (d, $J = 16.3$ Hz), 36.0 (d, $J = 19.7$ Hz), 21.6. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{17}\text{FNO}_3\text{S}$ 286.0913; Found 286.0905.

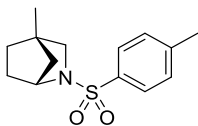


(±)-Methyl (1R,5S,6R)-7-tosyl-2-oxa-7-azabicyclo[3.2.1]octane-6-carboxylate (2i, major diastereomer): 37.2 mg, 57% yield. 0–25% EtOAc/hexanes. Colorless oil. ^1H NMR (600 MHz, CD_3CN) δ 7.78 (d, $J = 8.3$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 2H), 5.42 (d, $J = 3.6$ Hz, 1H), 4.32 (d, $J = 4.7$ Hz, 1H), 4.07 (td, $J = 12.0, 4.7$ Hz, 1H), 3.73 (s, 3H), 3.59 (dd, $J = 11.5, 7.4$ Hz, 1H), 2.81 – 2.76 (m, 1H), 2.42 (s, 3H), 1.91 – 1.84 (m, 1H), 1.74 (d, $J = 11.4$ Hz, 1H), 1.37 (dq, $J = 13.9, 3.8$ Hz, 1H), 1.26 (dq, $J = 11.2, 4.2$ Hz, 1H). ^{13}C NMR (151 MHz, CD_3CN) δ

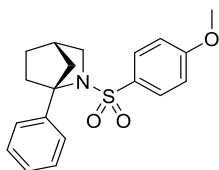
170.8, 145.2, 137.3, 130.6, 128.2, 88.3, 65.4, 60.0, 52.8, 39.1, 37.4, 28.0, 21.5. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{15}H_{20}NO_5S$ 326.1062; Found 326.1065.



(±)-Methyl (1R,5S,6S)-7-tosyl-2-oxa-7-azabicyclo[3.2.1]octane-6-carboxylate (2i, minor diastereomer): 13.6 mg, 21% yield. 0–25% EtOAc/hexanes. Colorless oil. 1H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 5.60 (d, $J = 3.1$ Hz, 1H), 4.17 (s, 1H), 3.71 (s, 3H), 3.53 – 3.46 (m, 1H), 2.99 (td, $J = 12.4, 4.5$ Hz, 1H), 2.69 – 2.61 (m, 1H), 2.43 (s, 4H), 2.21 – 2.13 (m, 1H), 1.93 – 1.84 (m, 1H), 1.76 (d, $J = 11.4$ Hz, 1H), 1.60 (s, 1H), 1.55 – 1.49 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 144.0, 136.9, 129.7, 127.9, 87.1, 63.1, 58.9, 52.7, 38.8, 37.3, 31.1, 21.8. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{15}H_{20}NO_5S$ 326.1062; Found 326.1059.

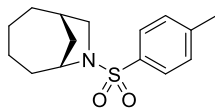


(±)-(1R,4S)-4-Methyl-2-tosyl-2-azabicyclo[2.2.1]heptane (2j): 23.1 mg, 44% yield. 0–15% EtOAc/hexanes. Colorless oil. 1H NMR (600 MHz, $DMSO-d_6$) δ 7.68 (d, $J = 8.2$ Hz, 2H), 7.42 (d, $J = 8.0$ Hz, 2H), 4.04 (s, 1H), 2.93 (d, $J = 8.7$ Hz, 1H), 2.77 (dd, $J = 8.8, 2.8$ Hz, 1H), 2.40 (s, 3H), 1.68 – 1.55 (m, 2H), 1.41 – 1.30 (m, 2H), 1.12 (d, $J = 9.7$ Hz, 1H), 1.04 (s, 3H), 0.68 – 0.59 (m, 1H). ^{13}C NMR (151 MHz, $DMSO-d_6$) δ 143.2, 135.2, 129.8, 127.2, 61.0, 59.1, 44.7, 42.4, 33.6, 31.7, 21.0, 17.7. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{14}H_{20}NO_2S$ 266.1515; Found 266.1519.

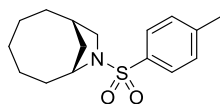


(±)-(1R,4S)-2-((4-Methoxyphenyl)sulfonyl)-1-phenyl-2-azabicyclo[2.2.1]heptane (2k): 44.1 mg, 64% yield. 0–20% EtOAc/hexanes. Yellow oil. 1H NMR (600 MHz, CD_3CN) δ 7.44 – 7.40 (m, 2H), 7.37 (dd, $J = 6.5, 3.2$ Hz, 2H), 7.28 – 7.21 (m, 3H), 6.92 – 6.88 (m, 2H), 3.83 (s, 3H), 3.53 – 3.46 (m, 2H), 2.54 (s, 1H), 2.38 (tq, $J = 9.0, 3.3$ Hz, 1H), 2.20 (d, $J = 10.0$ Hz, 2H), 2.10 (td, $J = 12.4, 5.3$ Hz, 2H), 1.91 – 1.84 (m, 1H), 1.68 – 1.63 (m, 1H), 1.56 – 1.49 (m, 1H). ^{13}C NMR (151 MHz, CD_3CN) δ 163.5, 139.6, 134.5, 130.0, 129.2, 128.5, 128.3,

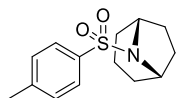
114.74.8, 58.0, 56.4, 48.4, 37.6, 33.3, 28.9. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{19}H_{22}NO_3S$ 344.1320; Found 344.1312.



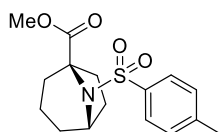
(±)-(1S,6R)-7-Tosyl-7-azabicyclo[4.2.1]nonane (**2l**): 23.2 mg, 42% yield. 0–20% EtOAc/hexanes. Colorless oil. 1H NMR (600 MHz, CD_3CN) δ 7.69 (d, $J = 8.3$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H), 3.98 (ddd, $J = 8.7, 4.4, 2.1$ Hz, 1H), 3.13 (dd, $J = 9.5, 6.9$ Hz, 1H), 3.08 (d, $J = 9.6$ Hz, 1H), 2.41 (s, 3H), 2.38 (tt, $J = 7.1, 3.9$ Hz, 1H), 1.92 – 1.86 (m, 1H), 1.71 – 1.62 (m, 3H), 1.61 (d, $J = 12.6$ Hz, 1H), 1.59 – 1.53 (m, 2H), 1.50 – 1.38 (m, 3H). ^{13}C NMR (151 MHz, CD_3CN) δ 144.5, 135.5, 130.5, 128.3, 60.5, 55.1, 37.0, 35.4, 35.2, 33.8, 25.3, 24.3, 21.4. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{15}H_{22}NO_2S$ 280.1371; Found 280.1363.



(±)-(1S,7R)-8-Tosyl-8-azabicyclo[5.2.1]decane (**2m**): 9.8 mg, 17% yield. 0–15% EtOAc/hexanes. Yellow oil. 1H NMR (600 MHz, CD_3CN) δ 7.71 – 7.66 (m, 2H), 7.40 (d, $J = 7.9$ Hz, 2H), 3.66 (ddt, $J = 11.5, 6.1, 2.0$ Hz, 1H), 3.36 (d, $J = 9.7$ Hz, 1H), 3.04 (dd, $J = 9.6, 7.3$ Hz, 1H), 2.42 (s, 3H), 2.17 – 2.13 (m, 1H), 2.02 – 1.96 (m, 1H), 1.88 – 1.82 (m, 1H), 1.81 – 1.70 (m, 4H), 1.69 – 1.65 (m, 1H), 1.60 – 1.53 (m, 2H), 1.52 – 1.45 (m, 2H), 1.27 – 1.20 (m, 1H). ^{13}C NMR (151 MHz, CD_3CN) δ 144.6, 134.1, 130.5, 128.7, 58.5, 54.6, 37.9, 36.7, 35.5, 35.1, 27.9, 26.6, 26.0, 21.4. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{16}H_{24}NO_2S$ 294.1527; Found 294.1531.

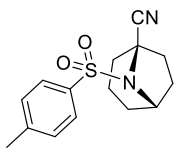


(±)-(1R,5S)-8-Tosyl-8-azabicyclo[3.2.1]octane (**2n**): 15.8 mg, 30% yield. 0–15% EtOAc/hexanes. 1H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H), 4.19 (s, 2H), 2.41 (s, 3H), 1.81 (ddd, $J = 20.7, 8.6, 2.7$ Hz, 2H), 1.62 – 1.54 (m, 2H), 1.53 – 1.50 (m, 4H), 1.50 – 1.45 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3, 137.8, 129.7, 127.5, 57.3, 32.6, 28.2, 21.7, 16.8. HRMS (ESI) m/z : $[M+H]^+$ Calcd for $C_{14}H_{20}NO_2S$ 266.1215; Found 266.1209.

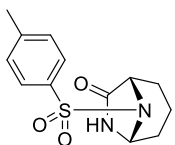


(±)-Methyl (1R,5S)-8-tosyl-8-azabicyclo[3.2.1]octane-1-carboxylate (**2o**): 30.6 mg, 47% yield. 0–30% EtOAc/hexanes. White solid. 1H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, $J = 8.2$ Hz, 2H), 7.26 (d, $J = 8.0$ Hz, 2H),

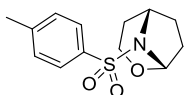
4.18 – 4.08 (m, 1H), 3.70 (s, 3H), 2.41 (s, 3H), 2.30 (qd, $J = 13.9, 13.4, 6.6$ Hz, 2H), 2.22 (td, $J = 12.4, 11.1, 5.3$ Hz, 1H), 1.96 (dt, $J = 14.2, 9.4, 5.4$ Hz, 2H), 1.91 – 1.85 (m, 1H), 1.77 (td, $J = 12.2, 11.3, 5.4$ Hz, 2H), 1.65 (ddd, $J = 13.1, 9.4, 3.0$ Hz, 1H), 1.48 – 1.38 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 172.1, 143.0, 139.5, 129.4, 127.2, 69.3, 59.4, 52.5, 34.4, 33.4, 29.8, 28.21.7, 17.3. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{S}$ 324.1269; Found 324.1276.



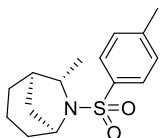
(±)-(1R,5S)-8-Tosyl-8-azabicyclo[3.2.1]octane-1-carbonitrile (2p): 22.6 mg, 39% yield. 0–30% EtOAc/hexanes. Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 7.86 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 4.52 (dd, $J = 7.0, 3.0$ Hz, 1H), 2.43 (s, 3H), 2.38 (td, $J = 12.5, 6.7$ Hz, 1H), 2.18 (qt, $J = 13.0, 7.3$ Hz, 2H), 2.08 – 1.90 (m, 2H), 1.87 – 1.82 (m, 1H), 1.76 (dt, $J = 10.5, 4.5$ Hz, 2H), 1.67 (ddd, $J = 13.3, 9.1, 5.0$ Hz, 1H), 1.56 – 1.51 (m, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 144.1, 137.8, 129.8, 127.9, 118.7, 58.9, 57.6, 36.9, 35.9, 30.7, 27.6, 21.8, 17.0. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ 293.1324; Found 293.1318.



(±)-(1S,5R)-8-Tosyl-6,8-diazabicyclo[3.2.1]octan-7-one (2q): 11.9 mg, 21% yield. Purified via reverse phase chromatography (eluent: 2–55% ACN in water with 0.1% NH_4OH modifier). ^1H NMR (600 MHz, CDCl_3) δ 7.68 (d, $J = 8.2$ Hz, 2H), 7.31 (d, $J = 8.1$ Hz, 2H), 5.32 (s, 1H), 5.25 (s, 1H), 4.04 (t, $J = 3.1$ Hz, 1H), 2.42 (s, 3H), 2.13 – 1.88 (m, 4H), 1.83 – 1.65 (m, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 174.1, 144.9, 134.3, 130.3, 128.0, 69.6, 59.2, 29.4, 26.1, 21.9, 16.6. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{17}\text{N}_2\text{O}_3\text{S}$ 281.0960; Found 281.0951.

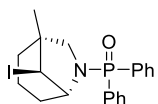
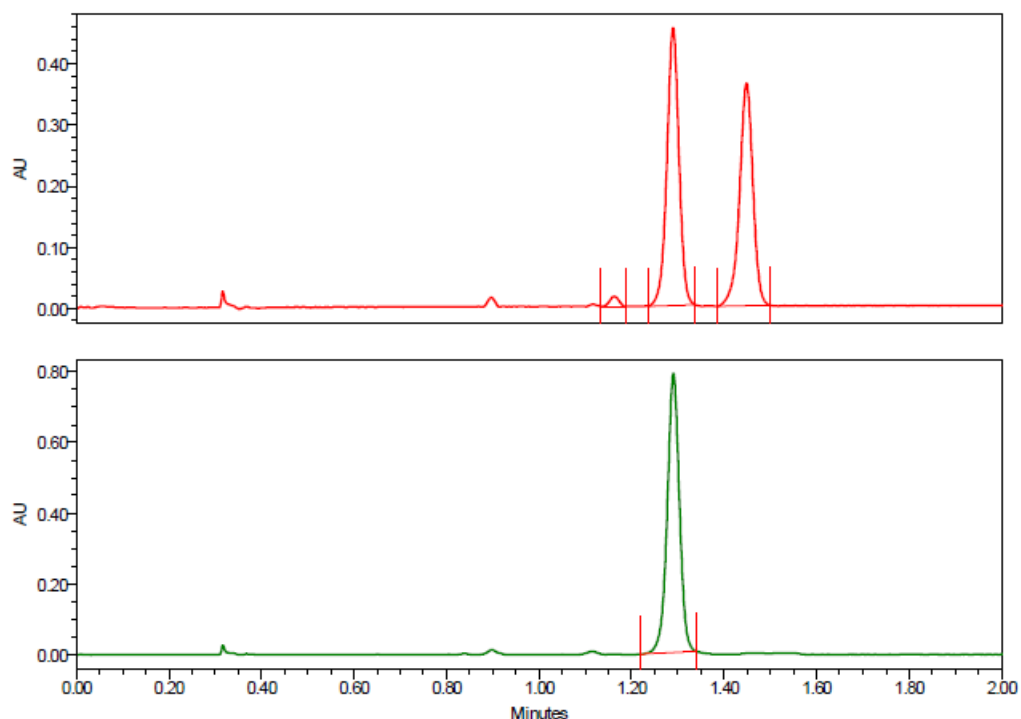


(±)-(1S,5S)-8-Tosyl-2-oxa-8-azabicyclo[3.2.1]octane (2r): 29.3 mg, 55% yield. 0–35% EtOAc/hexanes. Yellow solid. ^1H NMR (600 MHz, CDCl_3) δ 7.83 (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 8.1$ Hz, 2H), 5.61 (d, $J = 4.1$ Hz, 1H), 4.32 – 4.23 (m, 1H), 3.87 (td, $J = 12.3, 4.2$ Hz, 1H), 3.62 (dd, $J = 12.1, 6.5$ Hz, 1H), 2.42 (s, 4H), 2.16 – 2.00 (m, 4H), 1.93 (tdd, $J = 12.7, 6.5, 3.0$ Hz, 1H), 1.76 – 1.69 (m, 1H), 1.08 (dt, $J = 13.2, 3.2$ Hz, 1H). ^{13}C NMR (151 MHz, CDCl_3) δ 143.5, 138.5, 129.7, 127.9, 86.3, 58.9, 55.6, 29.9, 29.8, 28.1, 21.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_3\text{S}$ 268.1007; Found 268.1010.



(1R,5S,7S)-7-Methyl-6-tosyl-6-azabicyclo[3.2.1]octane (2s): 15.6 mg, 28% yield. 0–15% EtOAc/hexanes. Colorless oil. $[\alpha]_D^{25} -0.09$ (c 0.18, CHCl_3). ^1H NMR (499 MHz, CDCl_3) δ 7.73 (d, $J = 8.2$ Hz, 2H), 7.30 (d, $J = 8.1$ Hz, 2H), 4.06 (t, $J = 5.0$ Hz, 1H), 3.52 – 3.41 (m, 1H), 2.42 (s, 3H), 2.01 (d, $J = 3.0$ Hz, 1H), 1.93 – 1.67 (m, 3H), 1.65 – 1.54 (m, 2H), 1.48 (d, $J = 6.6$ Hz, 3H), 1.41 – 1.33 (m, 1H), 1.23 (d, $J = 11.1$ Hz, 1H), 1.01 (dtd, $J = 11.0, 6.1, 5.4, 3.5$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 143.2, 135.1, 129.7, 127.7, 60.2, 59.8, 39.6, 37.1, 31.8, 25.9, 21.7, 18.7, 16.0. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2\text{S}$ 280.1371; Found 280.1386.

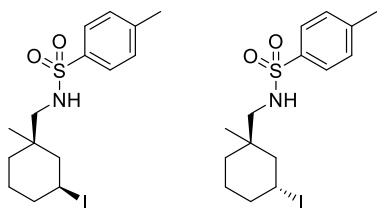
A chiral SFC trace of **2s** (bottom trace) in comparison to a racemic standard (top trace) using a (*R,R*)-Whelk-01 4.6 mm x 100 mm column on a Sepiatec instrument (eluent: 20% MeOH w/ 0.1% NH_4OH in CO_2).



(±)-((1R,2S,5S)-2-Iodo-6-azabicyclo[3.2.1]octan-6-yl)diphenylphosphine oxide (2t): 16.1 mg, 18% yield. 0–100% EtOAc/hexanes. White solid. ^1H NMR (600 MHz, CDCl_3) δ 8.02 – 7.86 (m, 4H), 7.47 (dddd, $J = 16.9, 8.5, 7.1, 5.2, 1.6$ Hz, 6H), 4.28 (d, $J = 5.0$ Hz, 1H), 3.71 (dt, $J = 8.9, 4.7$ Hz, 1H), 3.07 – 2.97 (m, 2H), 2.06 – 1.99 (m, 1H), 1.94 (ddt, $J = 19.3, 12.7, 6.0$ Hz, 1H), 1.74 (td, $J = 12.9, 5.0$ Hz, 1H), 1.60 (dt, $J = 11.8, 5.3$ Hz, 1H), 1.51 (dt, $J = 12.6, 4.5$ Hz, 1H), 1.34 (dd, $J = 13.5, 5.7$ Hz, 1H), 0.95 (s, 3H). ^{13}C NMR (151 MHz, CDCl_3) δ 132.6 (d, $J = 9.2$ Hz), 132.5 (d, $J = 9.2$ Hz), 132.3 (app. t, $J = 2.6$ Hz), 131.9 (d, $J = 9.1$ Hz), 131.0 (d, $J = 8.2$

Hz), 129.0 (d, $J = 12.3$ Hz), 128.8 (d, $J = 12.5$ Hz), 59.9, 52.8, 42.34, 34.44, 27.0, 23.8, 18.7. HRMS (ESI) m/z :
[M+H]⁺ Calcd for C₂₀H₂₄INOP 452.0640; Found 452.0645.

4. Characterization of Alkyl Iodide Intermediates and Kinetic Data



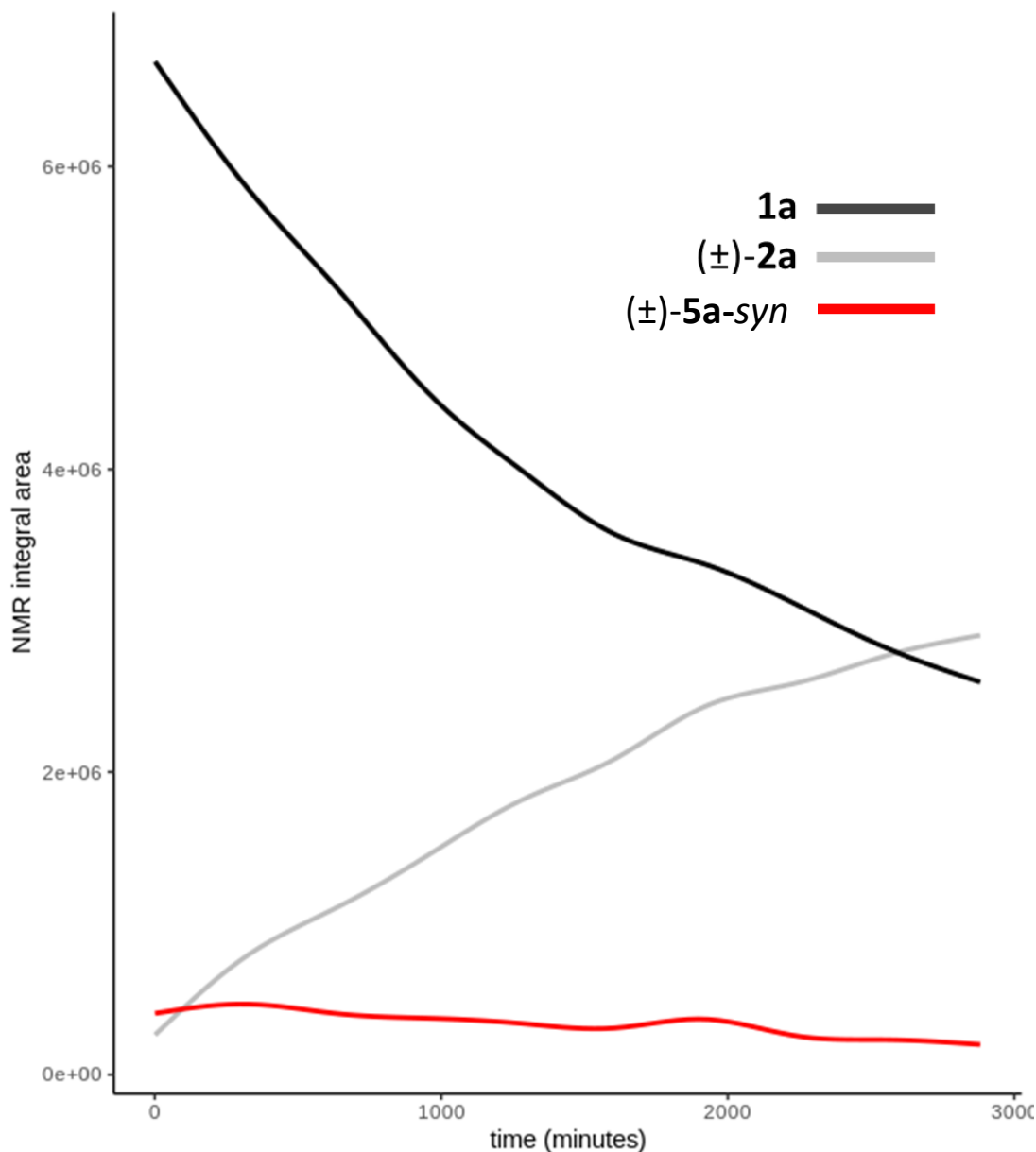
(±)-N-(((1R,3S)-3-Iodo-1-methylcyclohexyl)methyl)-4-methylbenzenesulfonamide ((±)-5a-syn) and (±)-N-(((1R,3R)-3-iodo-1-methylcyclohexyl)methyl)-4-methylbenzenesulfonamide ((±)-5a-anti): 9.4 mg, 23% yield. 10% EtOAc/hexanes (preparative TLC plate). Off-white solid. The molecular formula of **5a** was determined to be C₁₅H₂₁NO₂I by analysis of HRESIMS data (m/z : [M+Na]⁺ Calcd for C₁₅H₂₁NO₂INa 430.0314; Found 430.0308). Analysis of COSY, TOCSY, HSQC, HMBC, and ROESY allowed for the full assignment of carbon and proton signals of (±)-**5a** within the mixture of *cis* and *trans*. Briefly, COSY and TOCSY revealed the presence of a coupling system containing four methylenes and a methine (H-2a/b to H-3, H-3 to H-4a/b, H4a/4b to H-5a/b, and H-5a/b to H-6a/b) and another comprised of the sulfonamide and remaining methylene (NH to H-7a/b) in addition to the aromatic tosylate spin system. HSQC revealed the lone methine to possess chemical shifts indicative of an iodo substituent effect (¹H -4.41 ppm, ¹³C -28.5 ppm).¹ HMBC correlations from CH₃-16 to C-1, C-7, C-6 established the rest of the planar structure about the cyclohexyl ring. For (±)-**5a-syn**, a ROESY correlation from H-3 to CH₃-16 sets the relative configuration, while in (±)-**5a-anti** a ROESY correlation between H-3 and H-7a/b set the relative configuration.

((±)-5a-syn): ¹H NMR (600 MHz, CD₃CN) δ 7.70 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 5.57 (t, J = 7.4 Hz, 1H), 4.41 (tt, J = 12.6, 4.1 Hz, 1H), 2.56 (d, J = 7.2 Hz, 2H), 2.41 (s, 3H), 2.04 (dt, J = 12.9, 4.1, 2.1 Hz, 1H), 1.79 (dd, J = 25.3, 4.1 Hz, 1H), 1.79 (p, 1H), 1.53 (qt, J = 13.3, 3.7 Hz, 1H), 1.49 – 1.41 (m, 1H), 1.37 – 1.33 (m, 1H), 1.24 – 1.17 (m, 1H), 0.88 (s, 3H). ¹³C NMR (151 MHz, CD₃CN) δ 144.4, 138.9, 130.7, 127.8, 56.0, 49.8, 41.5, 39.3, 33.9, 28.4, 24.7, 21.6, 20.4.

((±)-5a-anti): ¹H NMR (600 MHz, CD₃CN) δ 7.73 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 7.4 Hz, 2H), 5.53 (t, J = 6.9 Hz, 1H), 4.33 (tt, J = 12.5, 4.1 Hz, 1H), 2.84 (dd, J = 13.2, 7.4 Hz, 1H), 2.69 – 2.64 (m, 1H), 2.42 (s, 3H), 2.38 – 2.28 (m, 1H), 1.77 – 1.72 (m, 1H), 1.59 – 1.56 (m, 1H), 1.38 – 1.35 (m, 1H), 0.83 (s, 3H). ¹³C NMR (151 MHz, CD₃CN) δ 144.4, 138.8, 130.7, 127.8, 49.5, 48.4, 41.0, 39.0, 34.6, 24.7, 21.6.

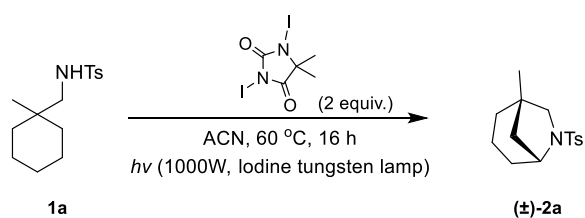
¹ Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. Nature of substituent effects in nuclear magnetic resonance spectroscopy. 1. Factor analysis of carbon-13 chemical shifts in aliphatic halides. *J. Org. Chem.* **1980**, *45*, 4936–4947

^1H NMR time course of the reaction of substrate **1a** with *N*-iodohydantoin (**3**) at 70 °C

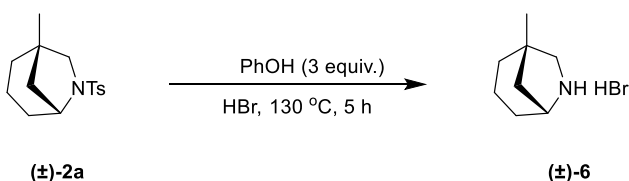


The reaction was performed at 70 °C in CD_3CN with sample rotation at 120 Hz. Proton spectra were recorded with the following parameters for approximately two days. Carbon decoupled proton spectra with a 30° flip angle were acquired for 8 scans across a sweep width of 7462.7 Hz for 2 s of acquisition with a 1.6 s relaxation delay providing for a 29 s total acquisition time per experiment, allowing for one acquisition to be acquired every 30 s. The amine proton of the starting material was integrated from 5.390 to 5.184 ppm, the product on the methine proton alpha to the amine from 4.210 to 4.074 ppm, and the iodo-intermediate was integrated on the iodo-methine proton from 4.563 to 4.417 ppm. Experiments were performed on a 500 MHz spectrometer equipped with a Bruker Avance NEO console and a Bruker Iprobe SmartProbe. The smoothed line plot was generated in R utilizing the ggplot2 package.

5. Second Generation Approach and Scale-up Procedures

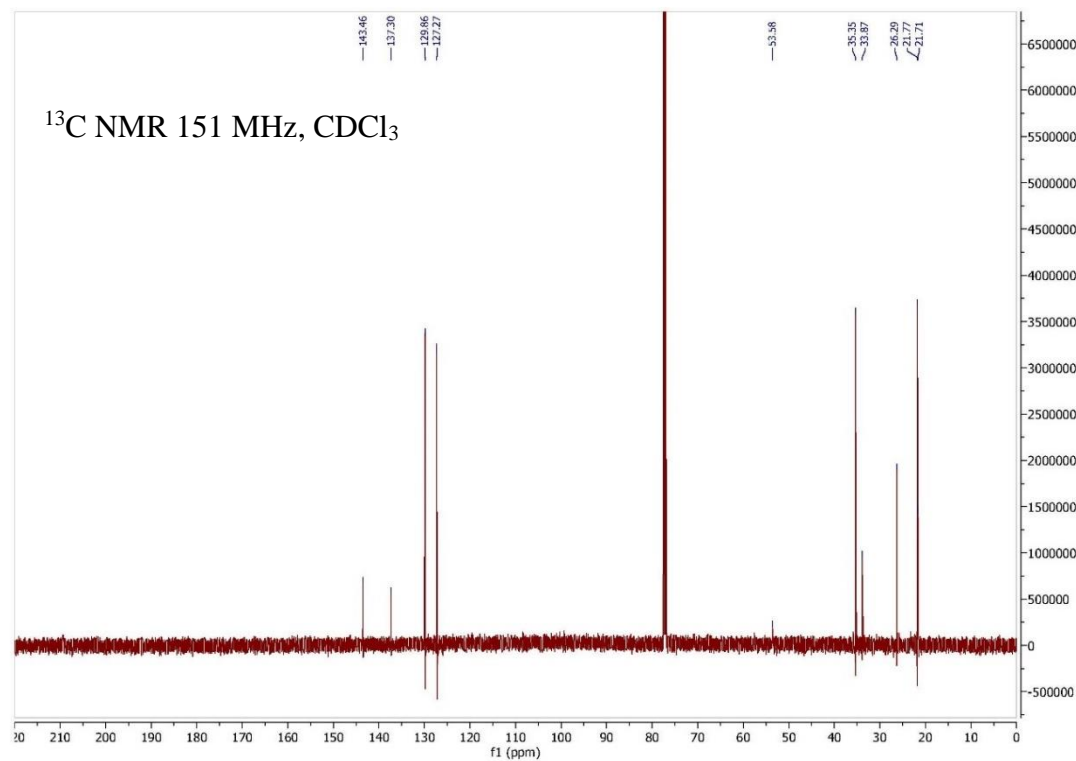
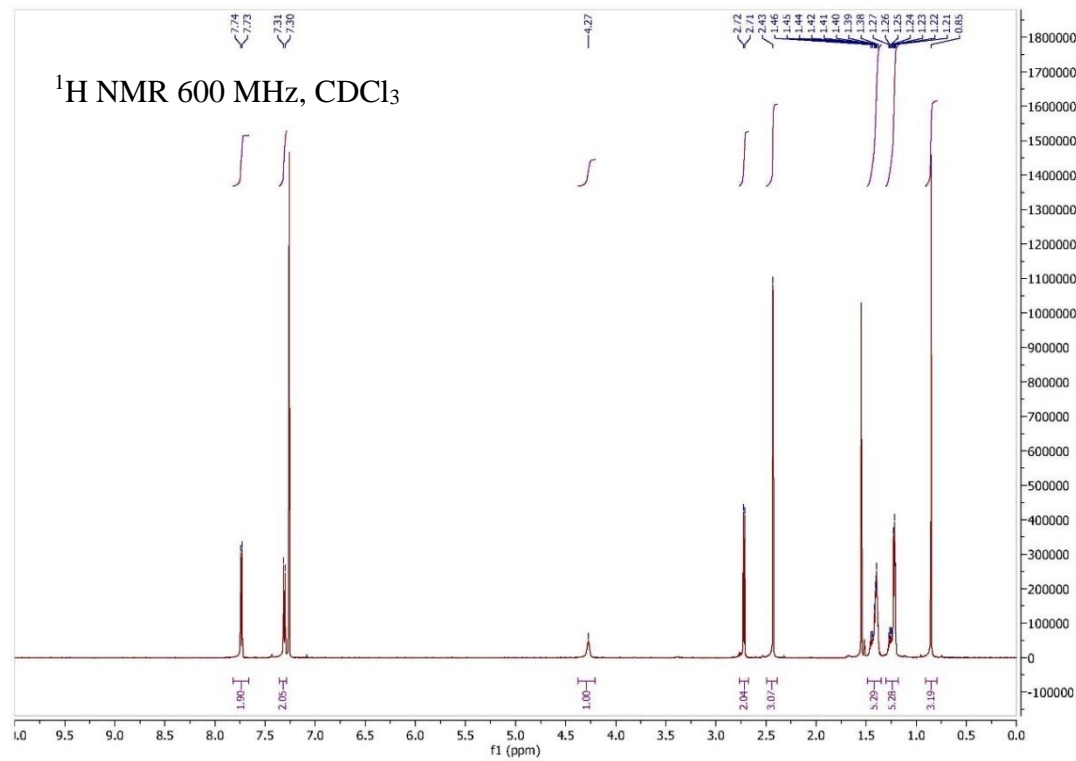
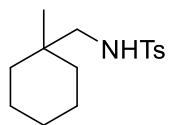


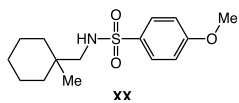
Tosylated amine **1a** (2 g, 7.2 mmol) and 1,3-diiodo-5,5-dimethylhydantoin (5.5 g, 14.4 mmol, 2 equiv) were charged in a 100 mL round bottom flask under nitrogen. Acetonitrile (36 mL, 0.2 M) was added to the reaction and the reaction was then stirred at 60 °C using an oil bath and illuminated with an iodine tungsten lamp (1000 W, broadband source, no filter) within 10 inches of the reaction vessel (borosilicate glass) for 6 h. The material was diluted with CH₂Cl₂ (15 mL). The reaction was quenched with sat'd Na₂S₂O₃ (aq) (25 mL). The organic phase was separated from the aqueous phase and then the aqueous phase was washed with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered and then concentrated *in vacuo*. The crude residue was purified by column chromatography (2–10% EtOAc/petroleum ether) to obtain a crude product that was further purified by reverse phase chromatography (eluent: 50%–70% MeOH in water with 0.075% TFA modifier). Bi-cyclic amine **(±)-2a** was obtained as a white solid (600 mg, 2.1 mmol, 30% yield). Spectral data matches that of compound **(±)-2a** above.



The tosylated bi-cyclic amine **(±)-2a** (0.5 g, 1.8 mmol) was charged into a 25 mL round bottom flask. Phenol (0.5 g, 5.4 mmol, 3 equiv) and HBr (48 wt% in water, 6 mL) were added. The reaction was stirred at 130 °C for 5 h using an oil bath and the reaction was monitored by LCMS analysis. The reaction was cooled to 25 °C, and diluted with CH₂Cl₂ (10 mL). The phases were separated, and the aqueous phase was washed with CH₂Cl₂ (3 x 10 mL). The aqueous phase was concentrated *in vacuo* and then lyophilized to provide HBr salt **(±)-11** as a light brown oil (280 mg, 1.4 mmol, 76% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.03 (br s, 1H), 8.59 (br s, 1H), 3.86-3.94 (m, 1H), 3.08-3.17 (m, 1H), 2.71-2.81 (m, 1H), 1.78 (br d, *J* = 12.0 Hz, 1H), 1.36-1.69 (m, 7H), 1.05 (s, 3H). ¹³C NMR (151 MHz, CD₃CN) δ 59.02, 53.89, 43.64, 40.55, 37.22, 28.06, 23.86, 19.27. HRMS (ESI) *m/z* Calcd for C₈H₁₆N⁺ [M+H]: 126.1283; Found 126.1277.

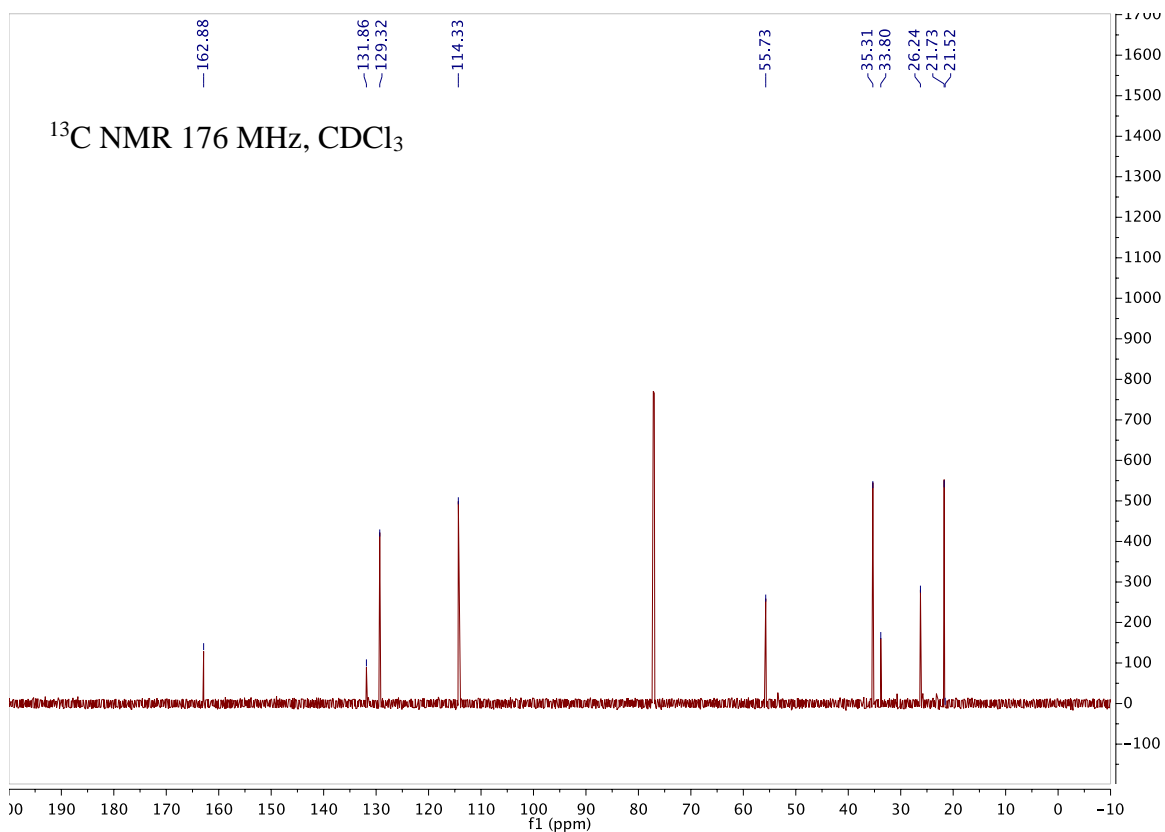
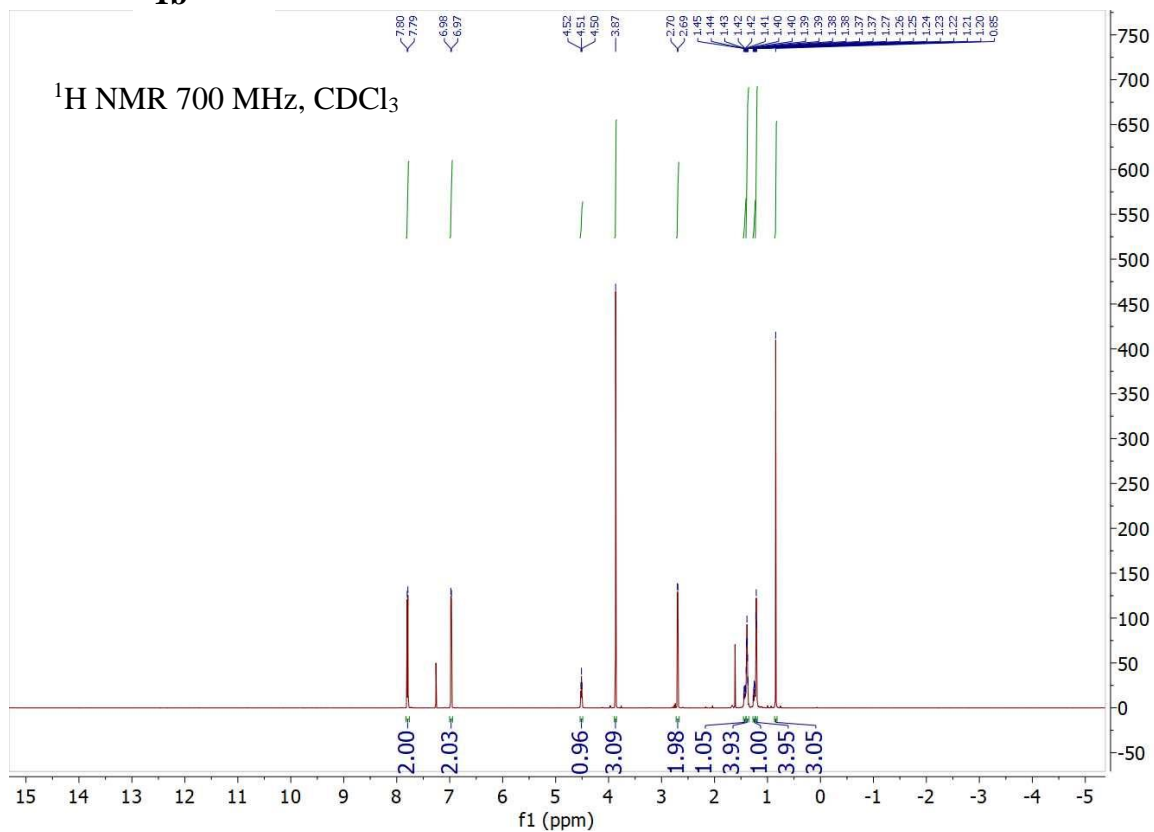
5. ^1H and ^{13}C Spectra of New Products

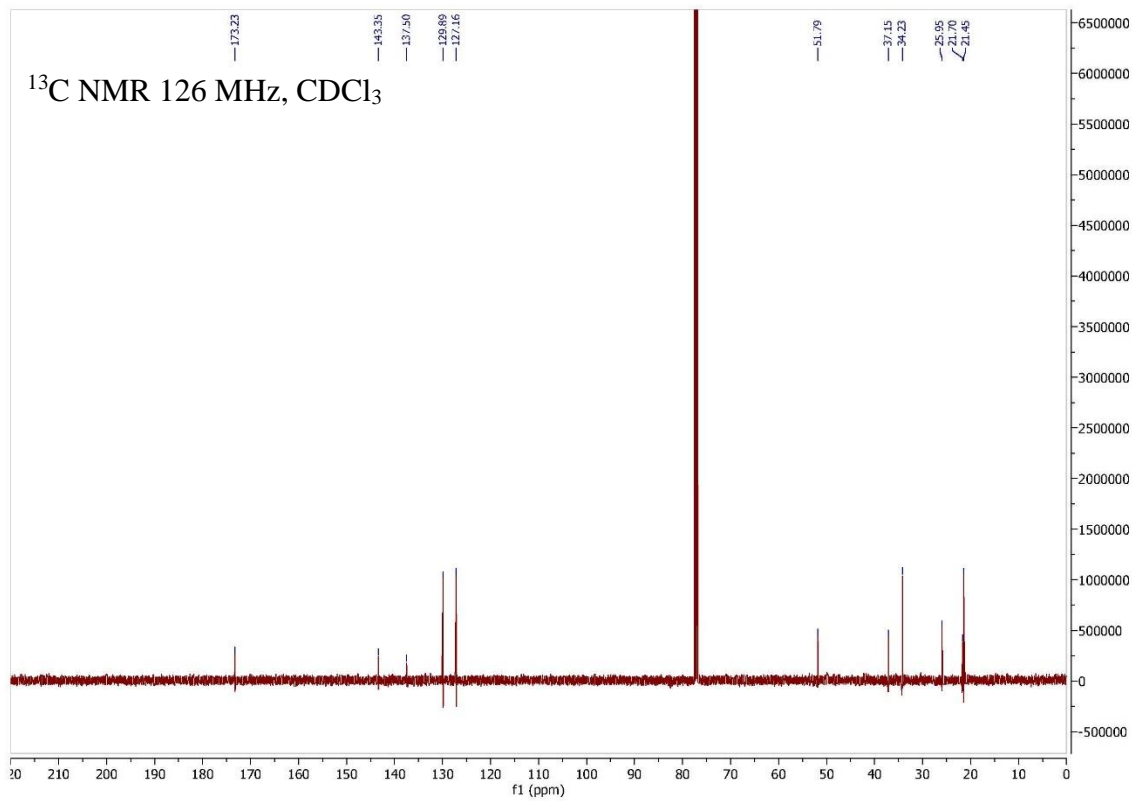
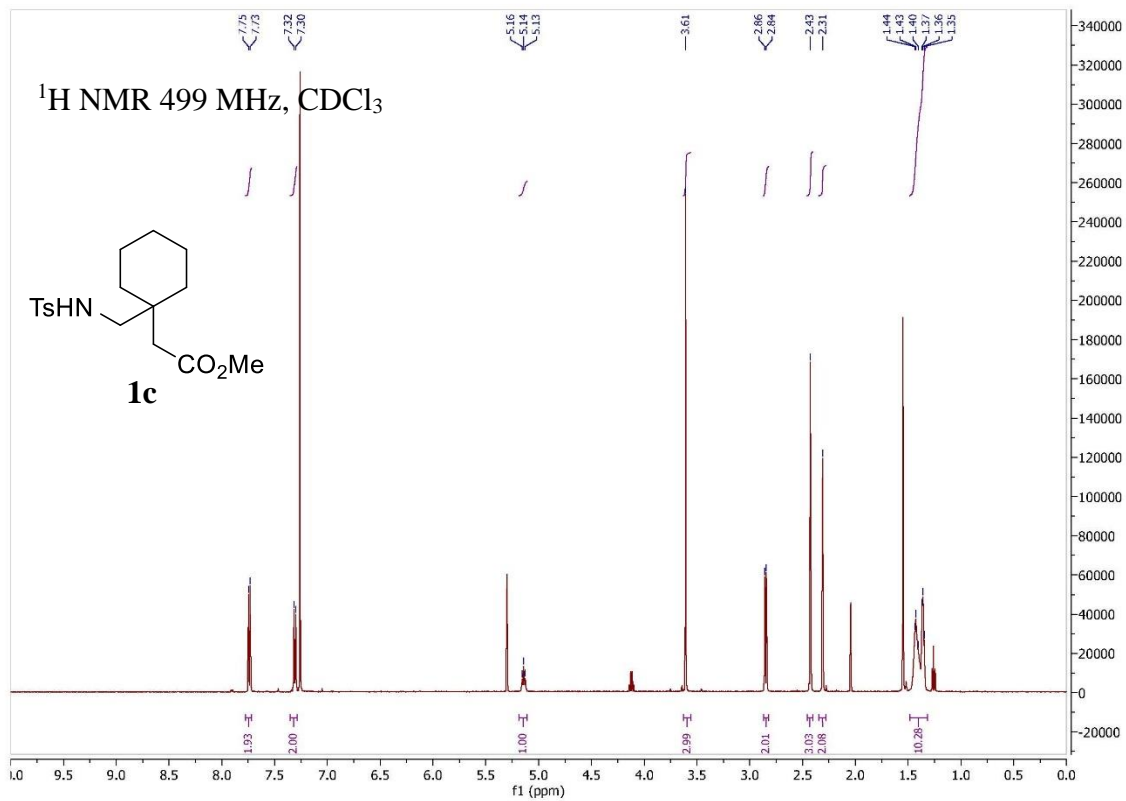


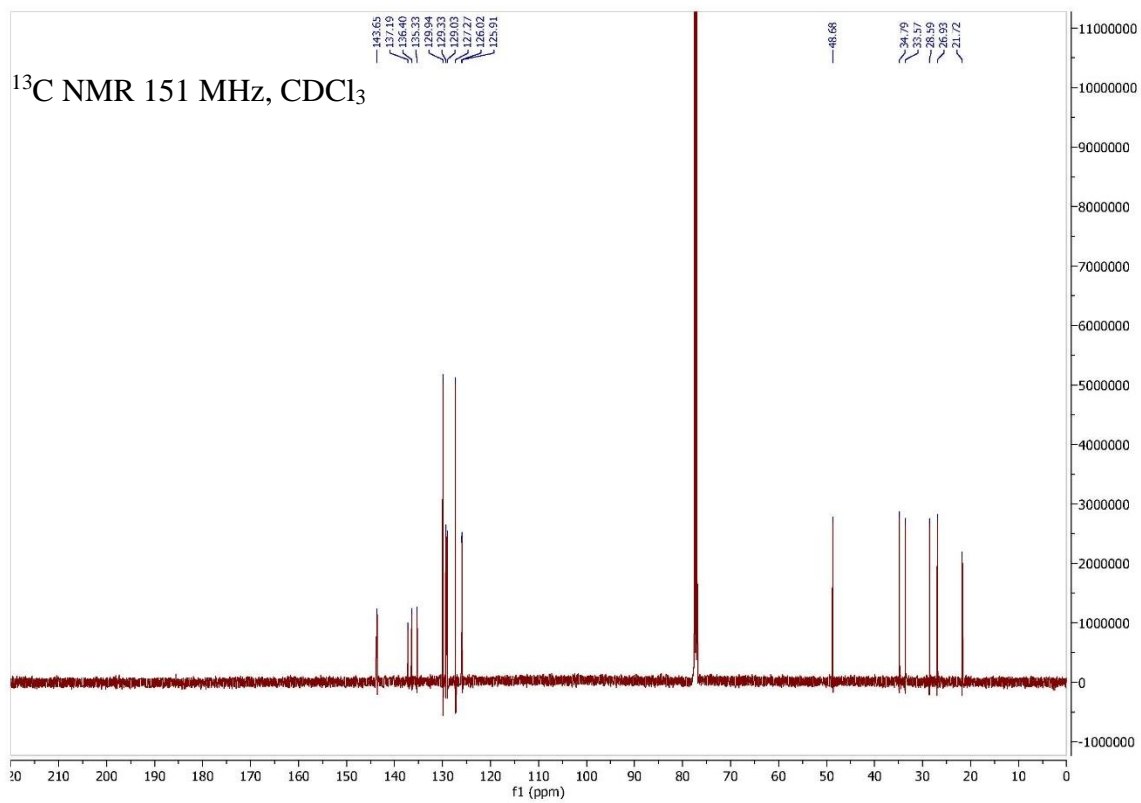
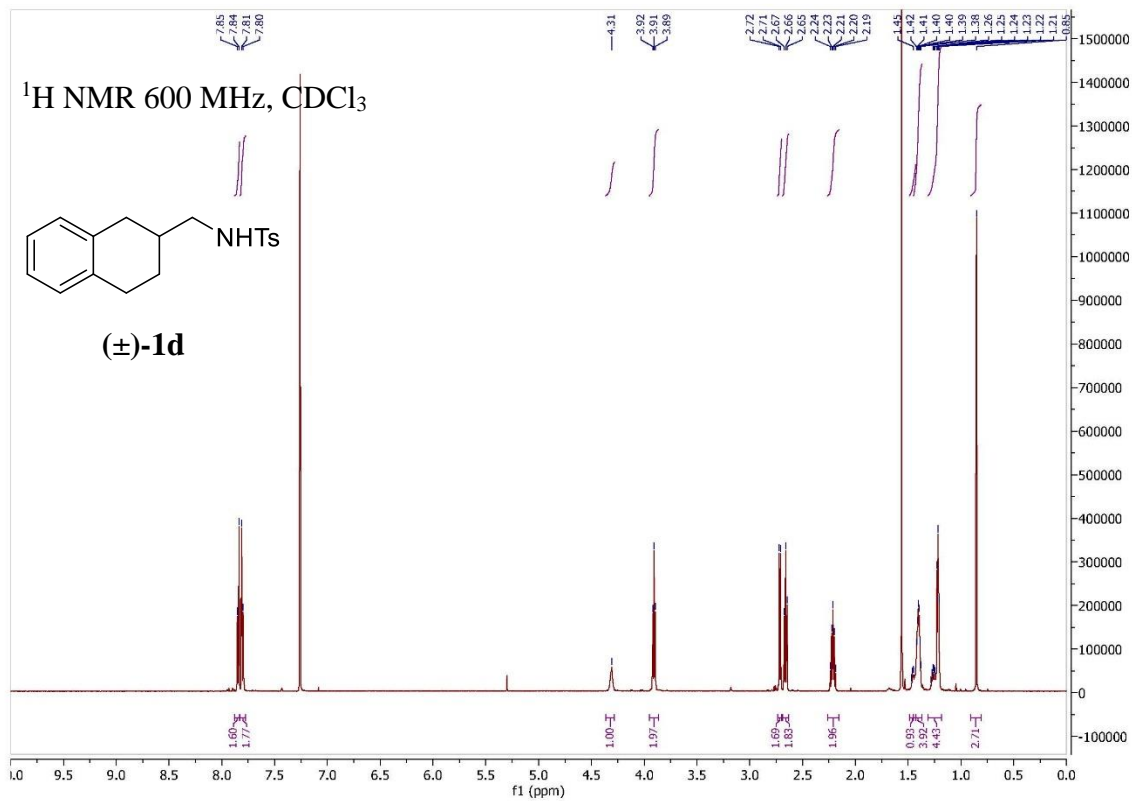


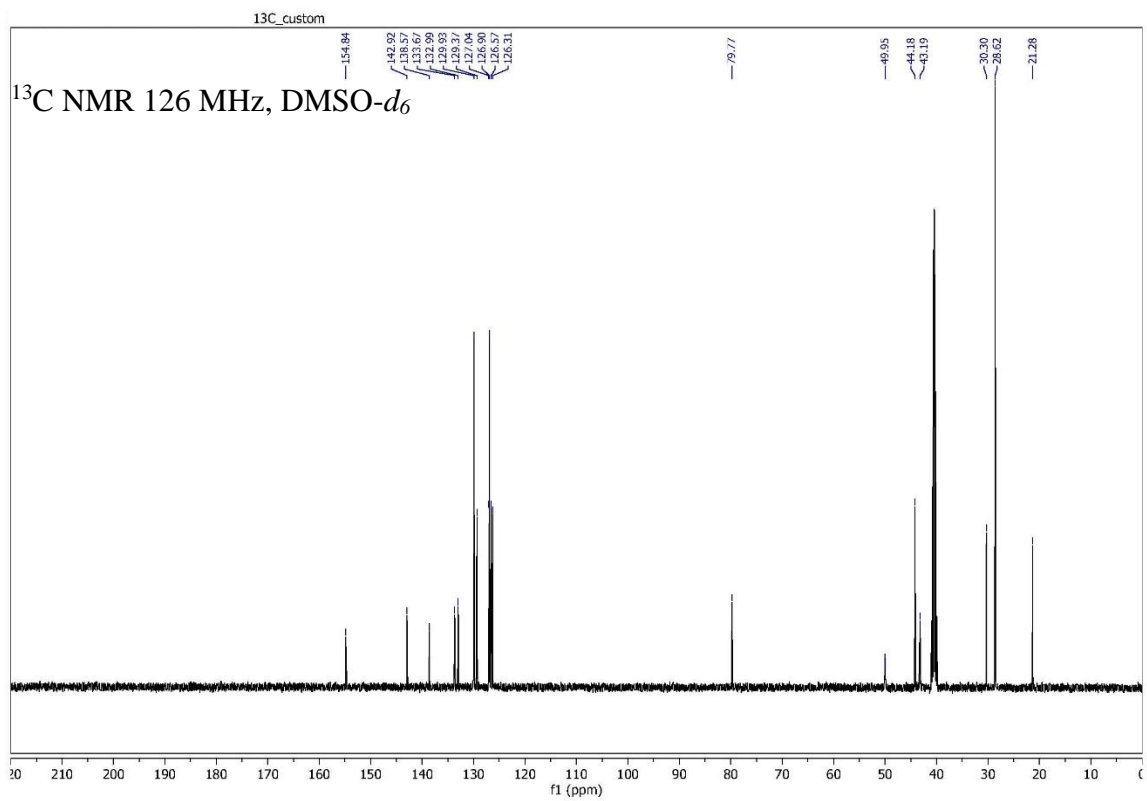
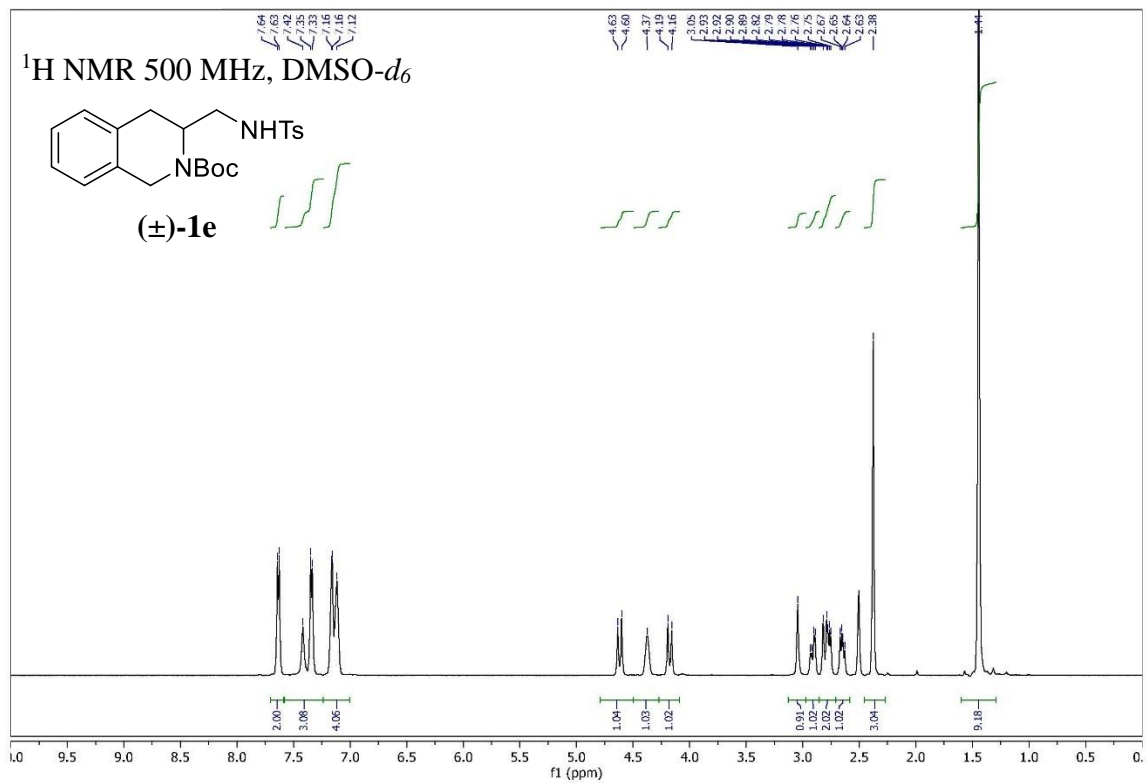
xx

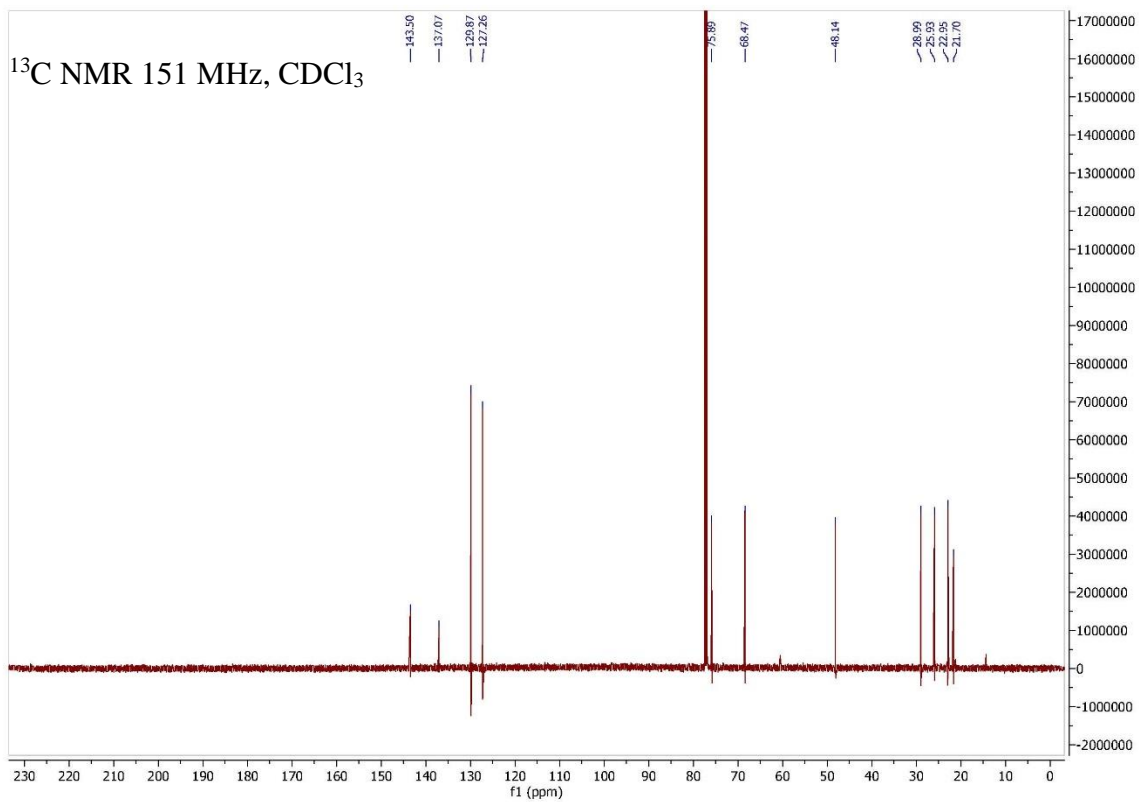
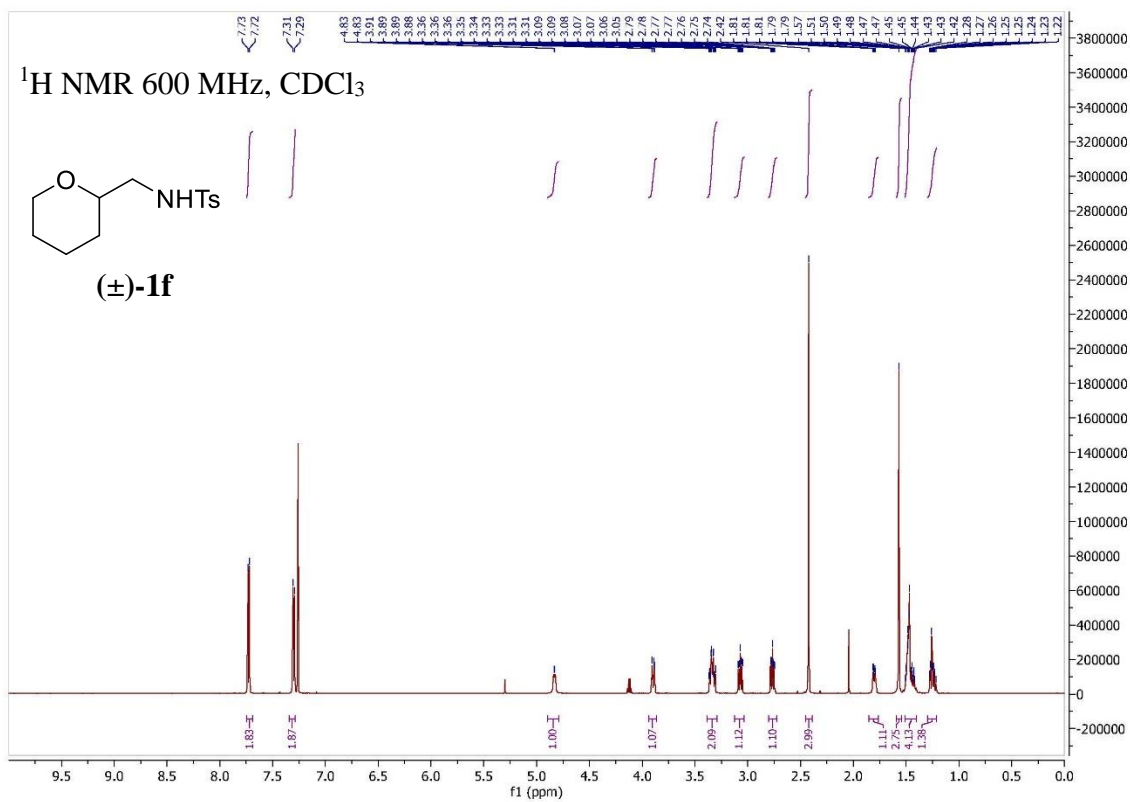
1b

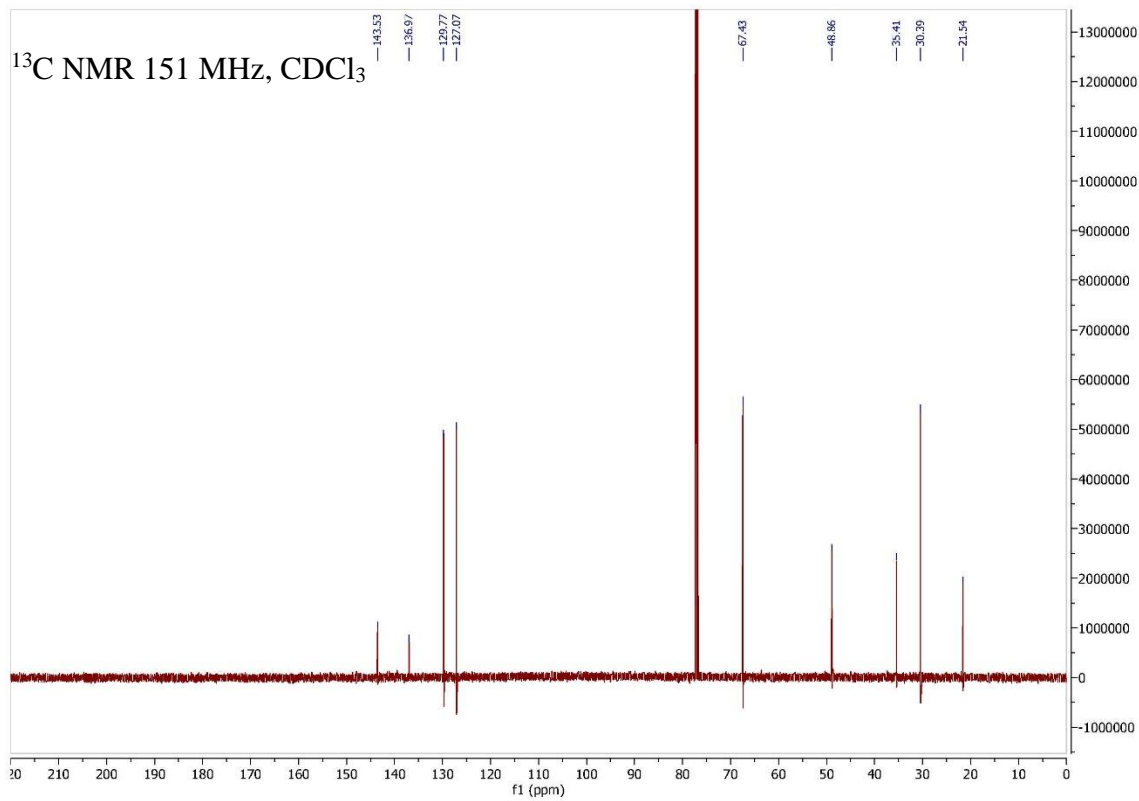
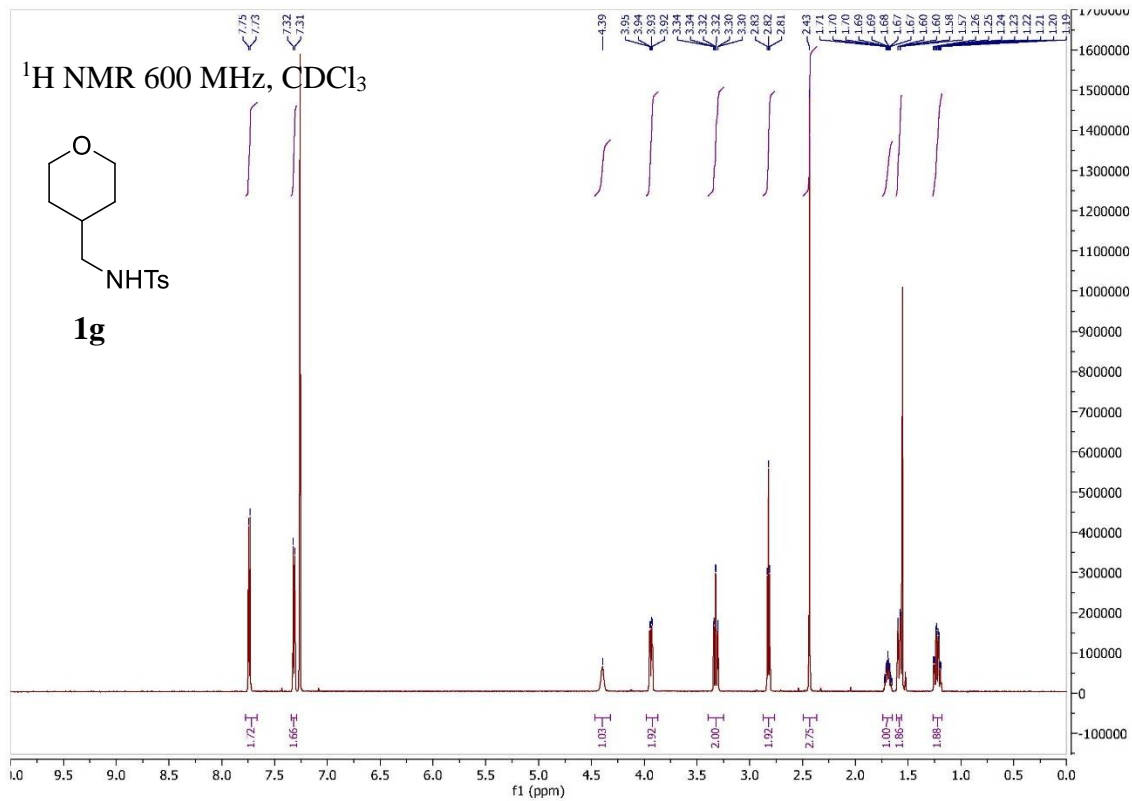


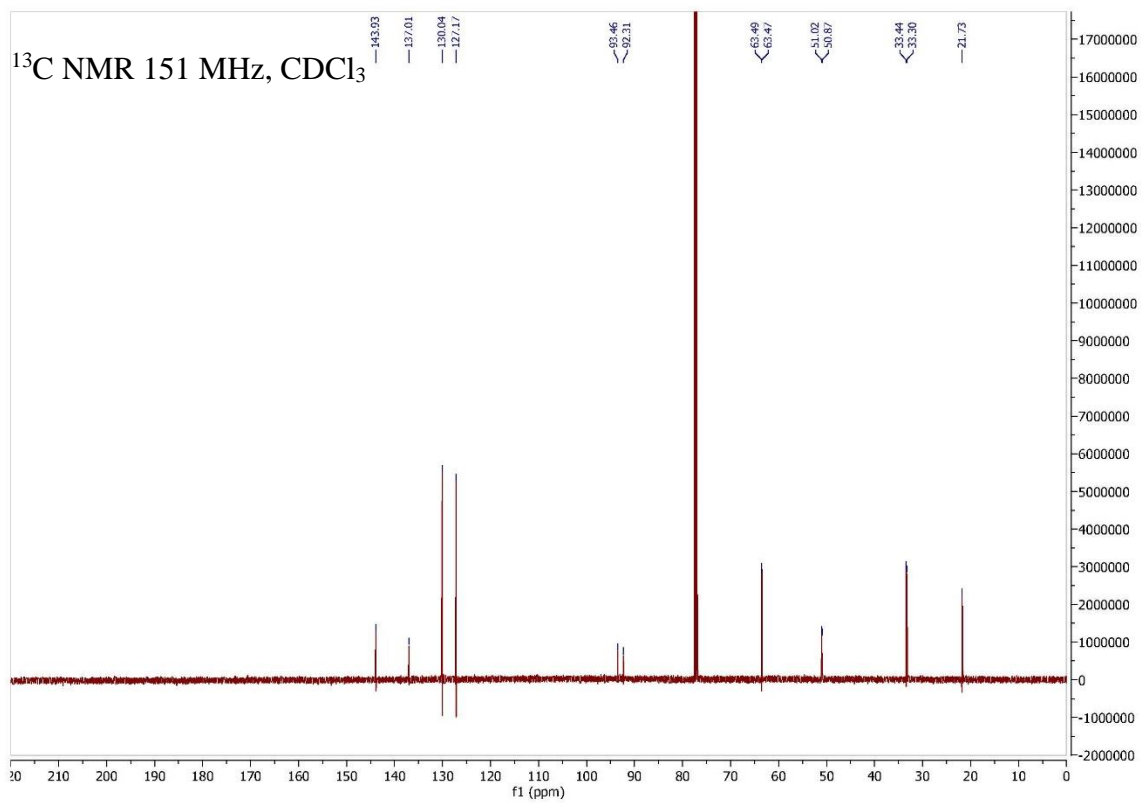
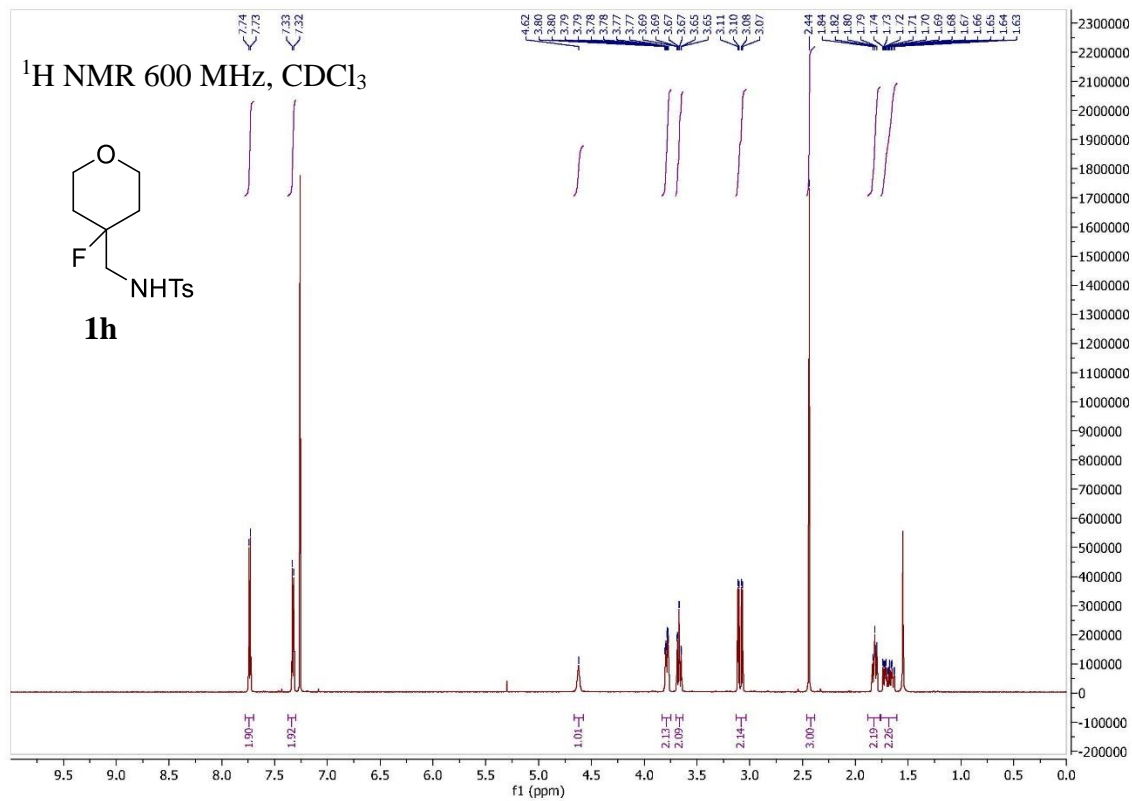


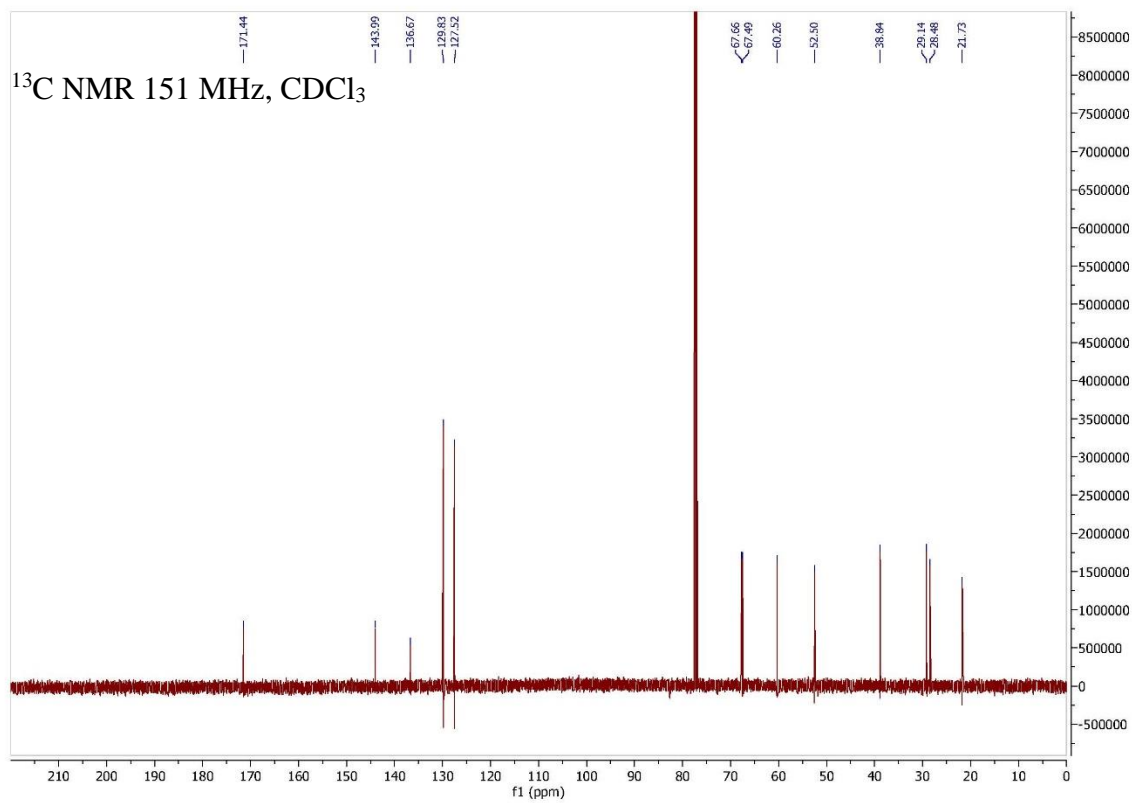
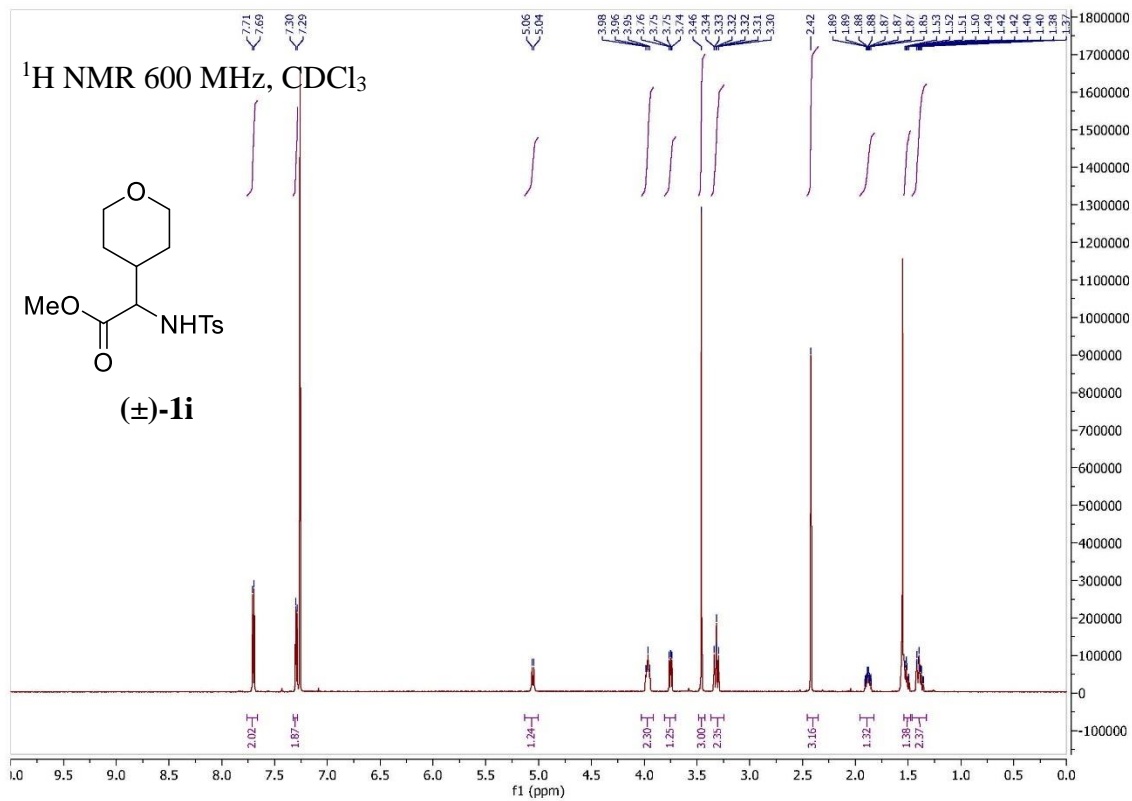


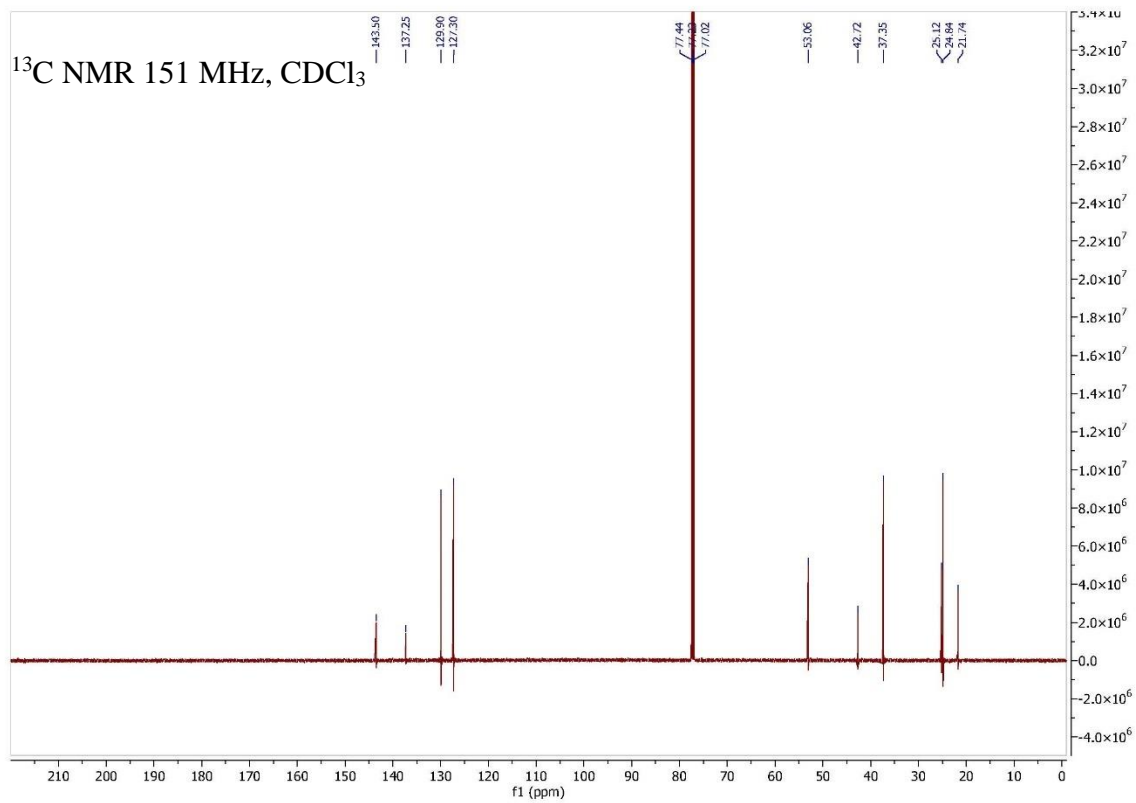
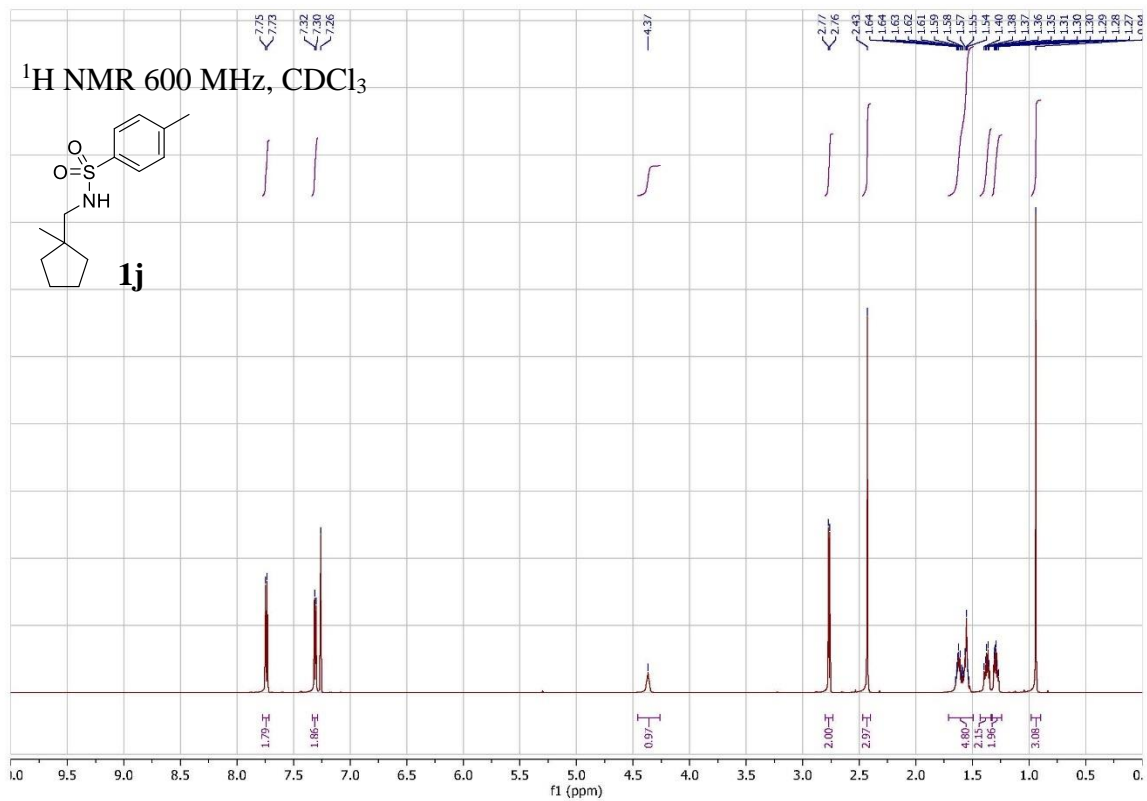


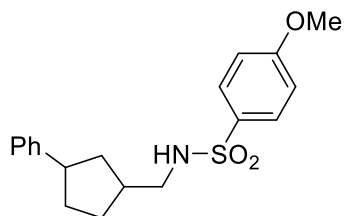




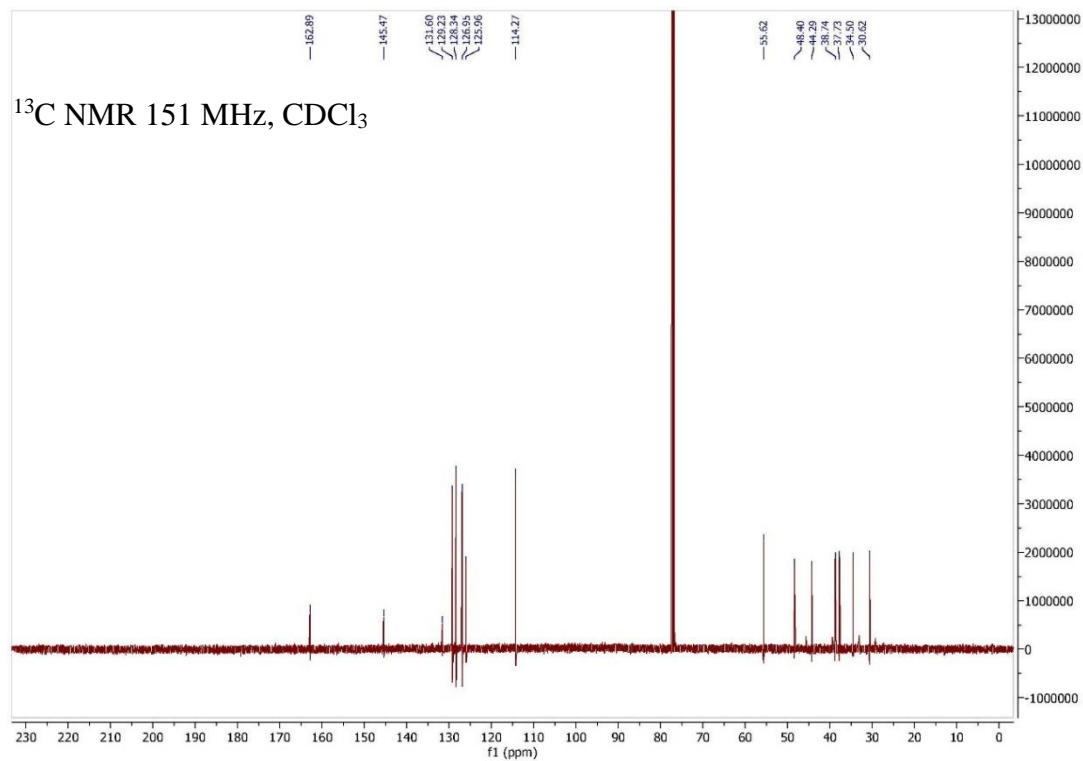
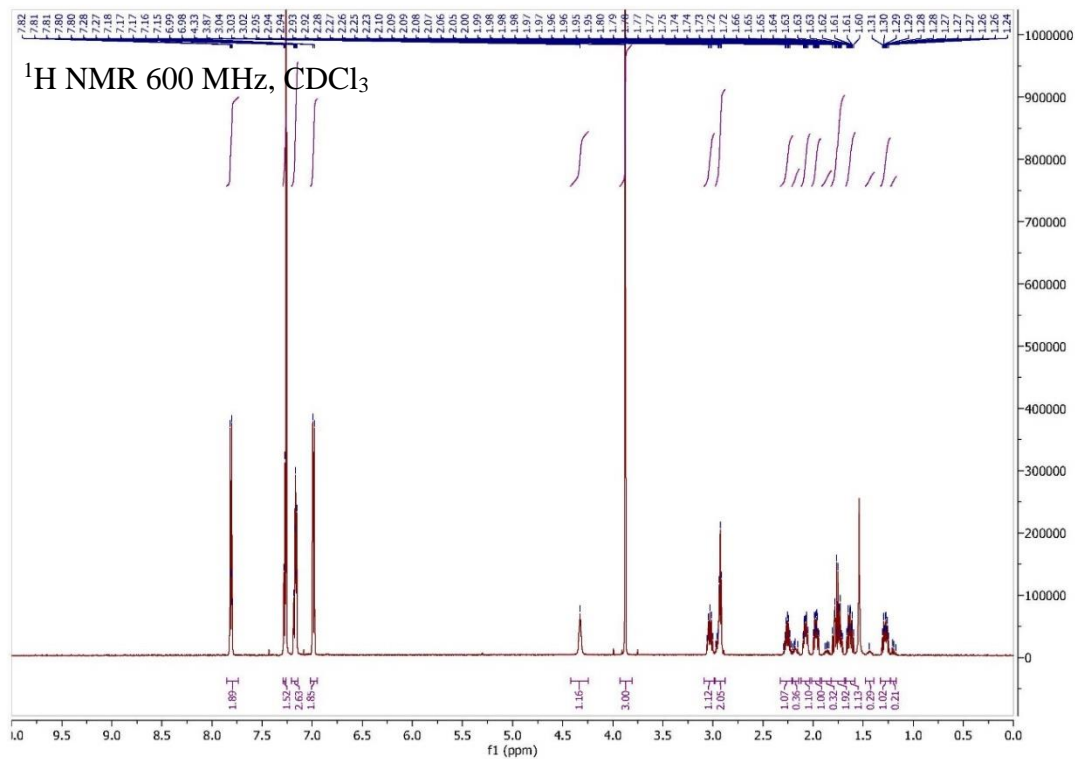


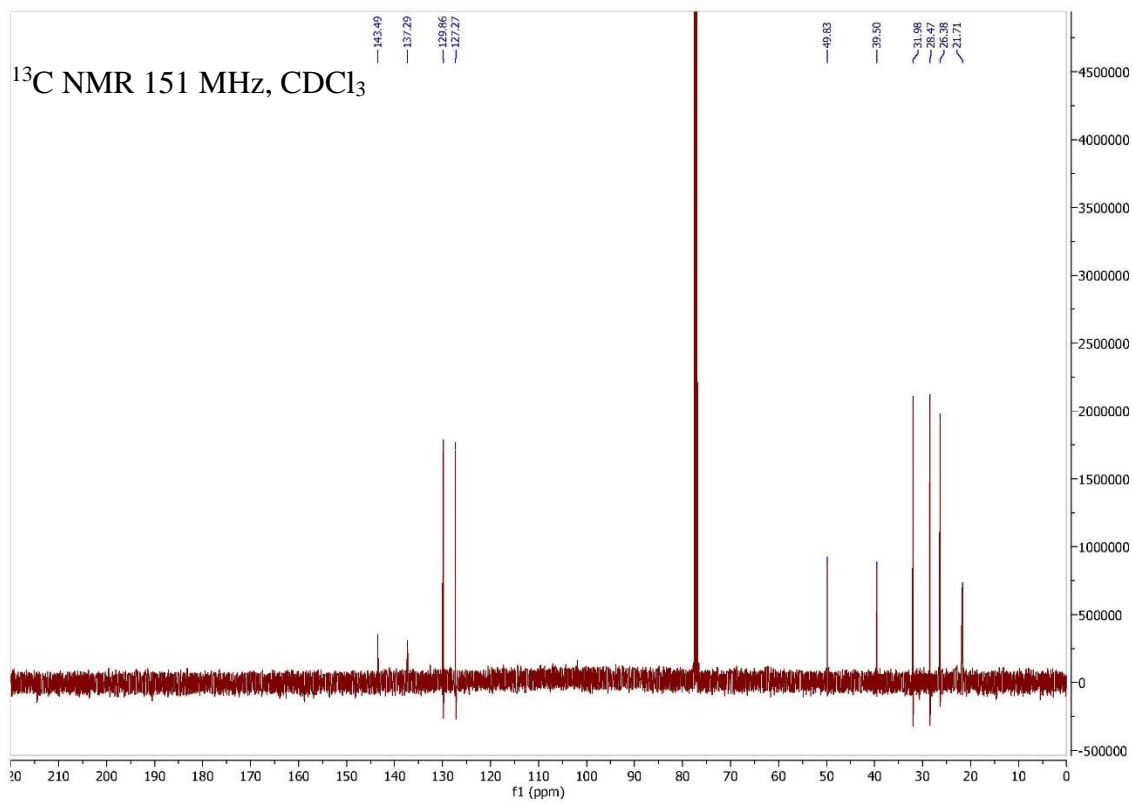
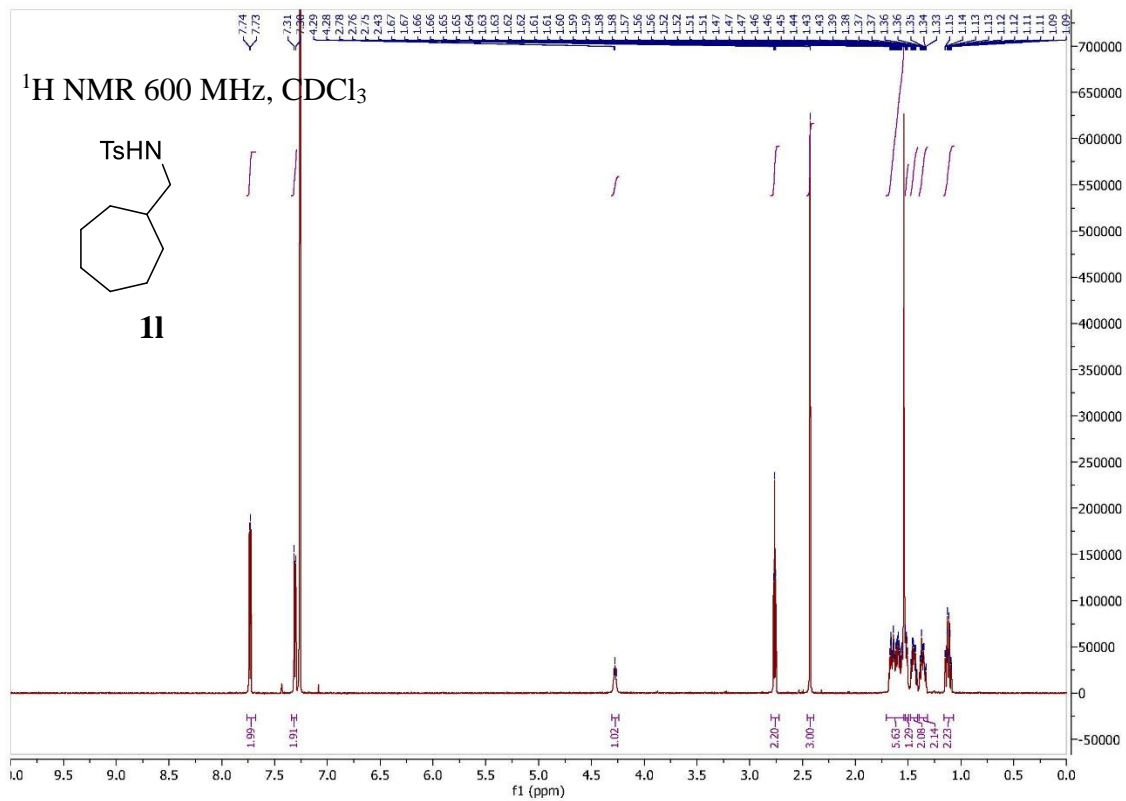


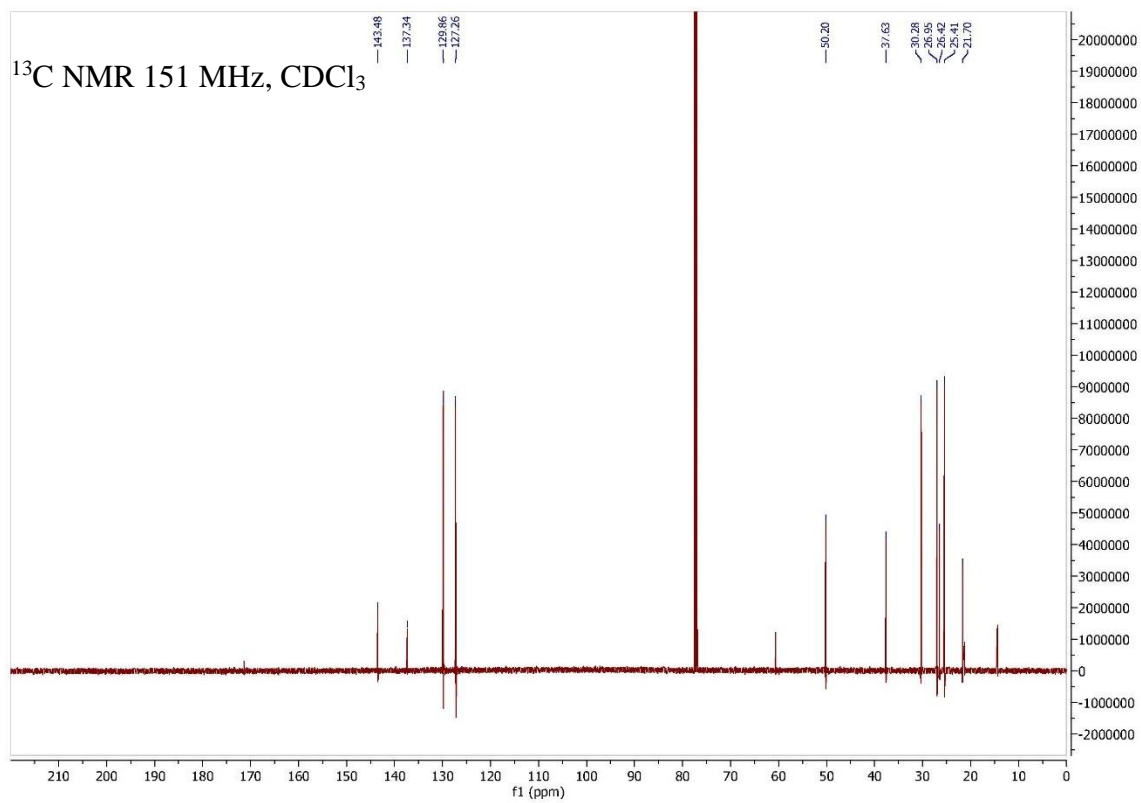
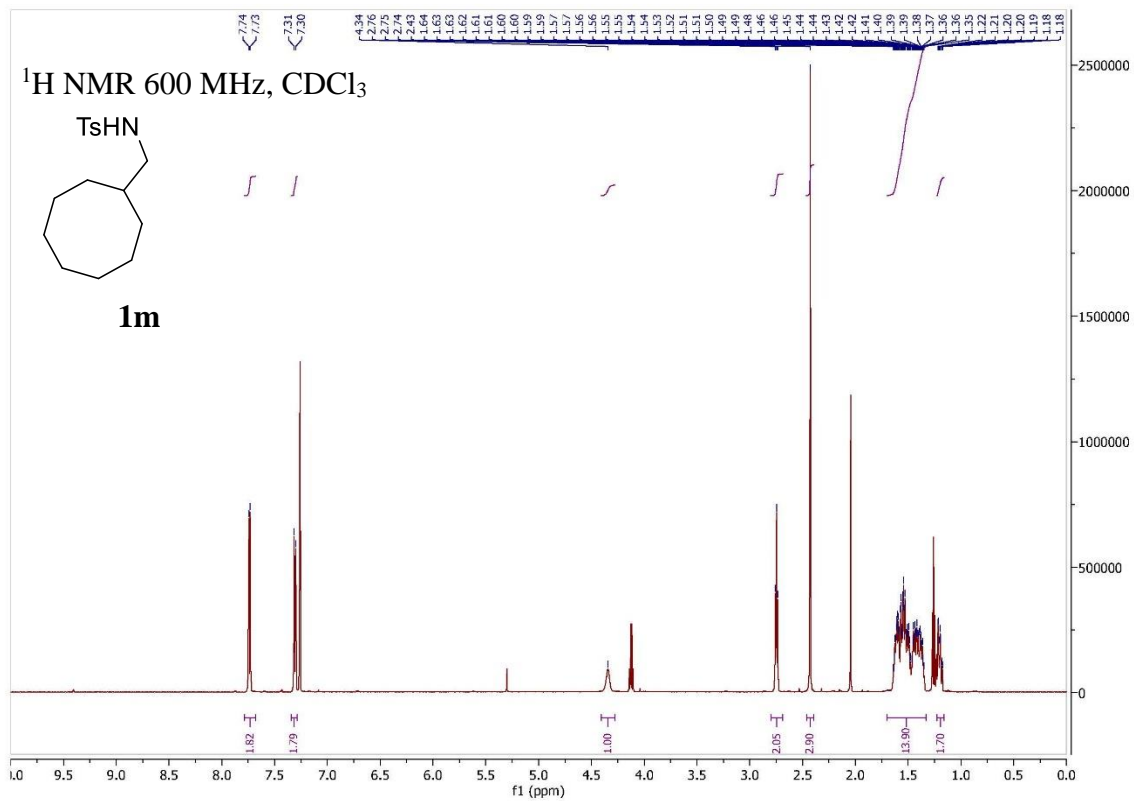


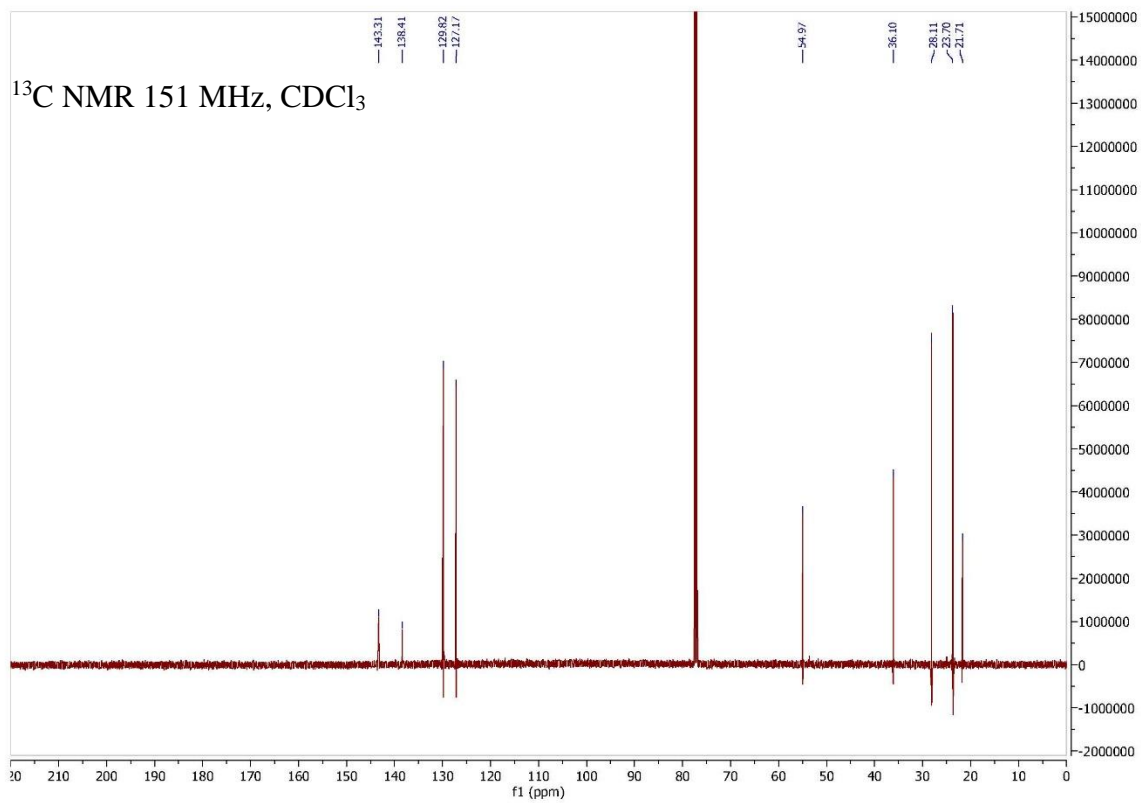
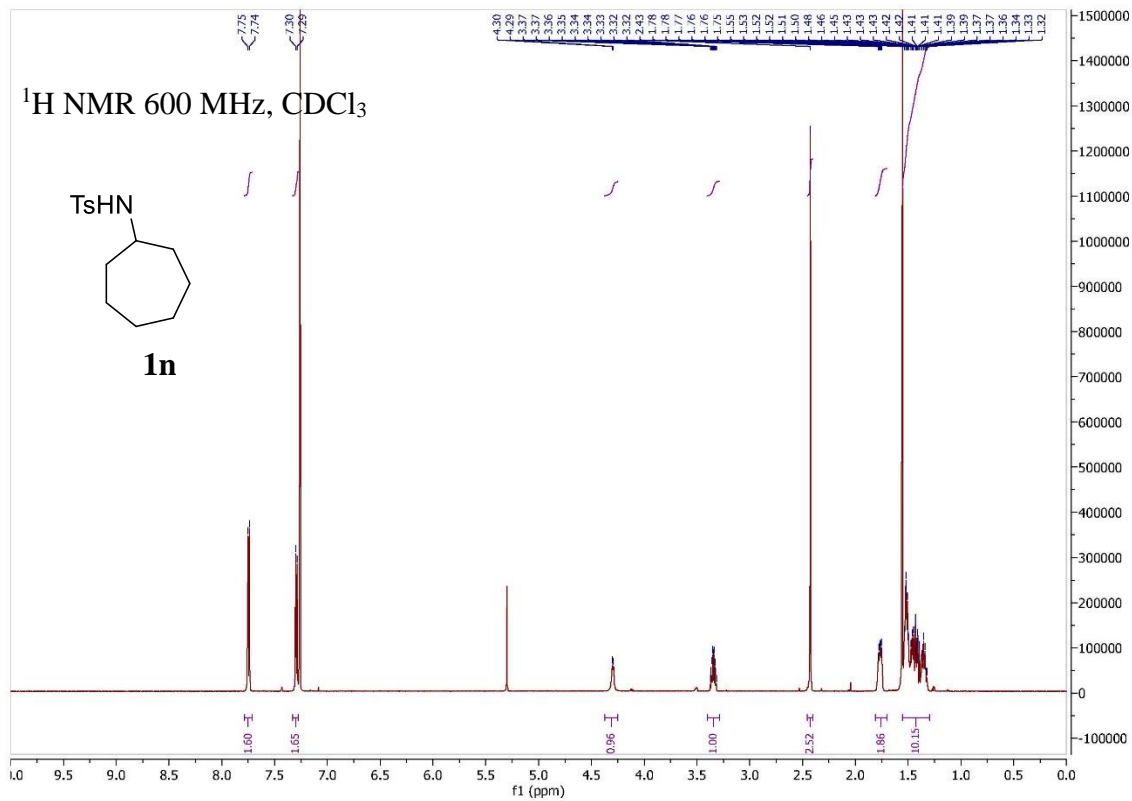


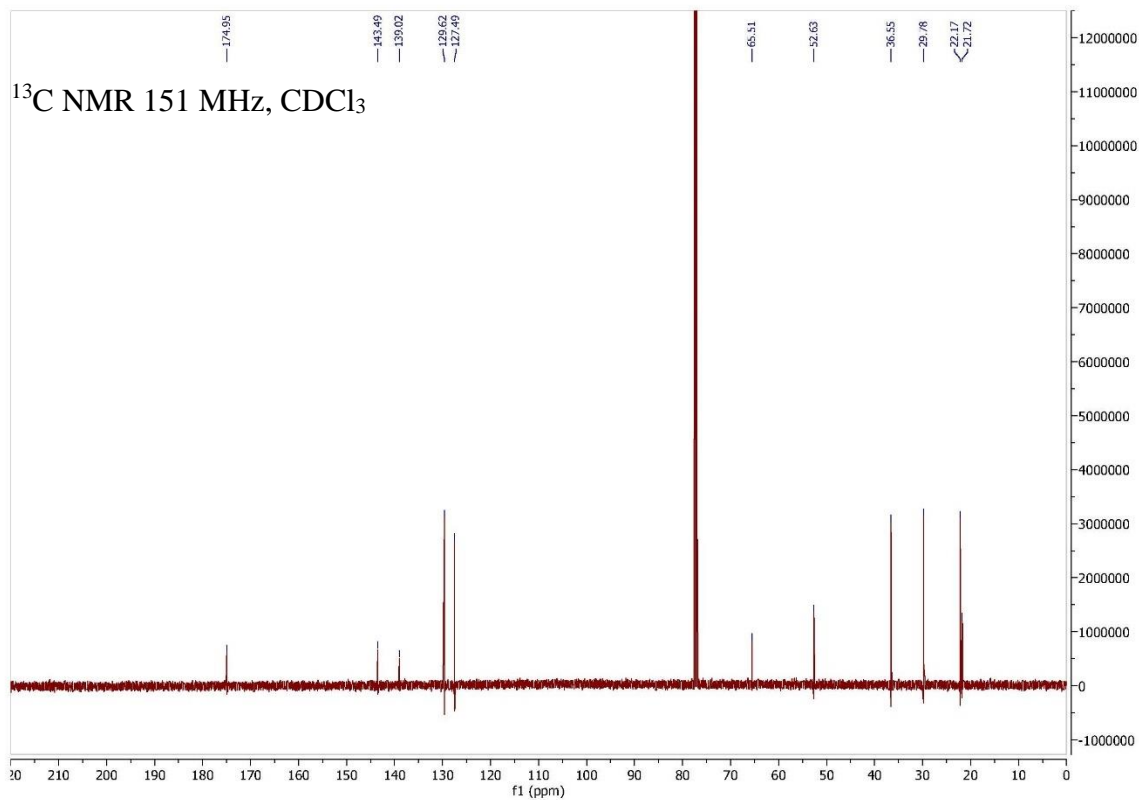
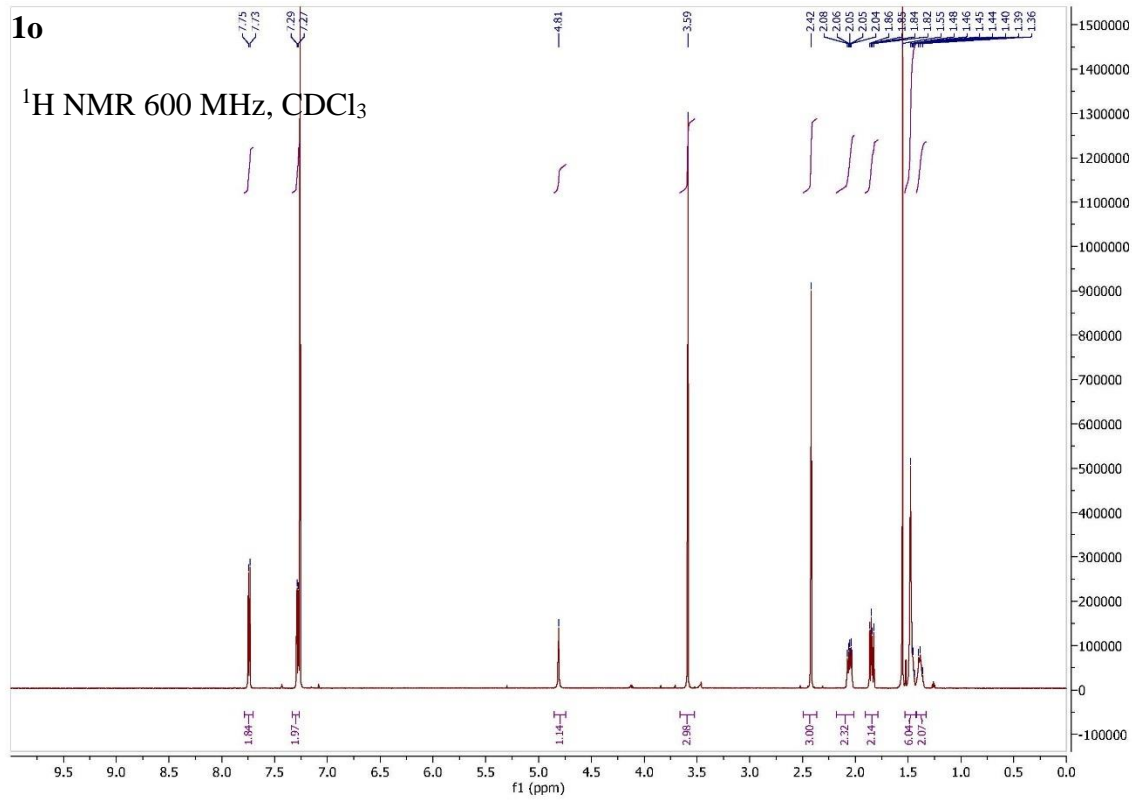
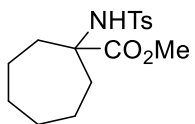
(±)-1k

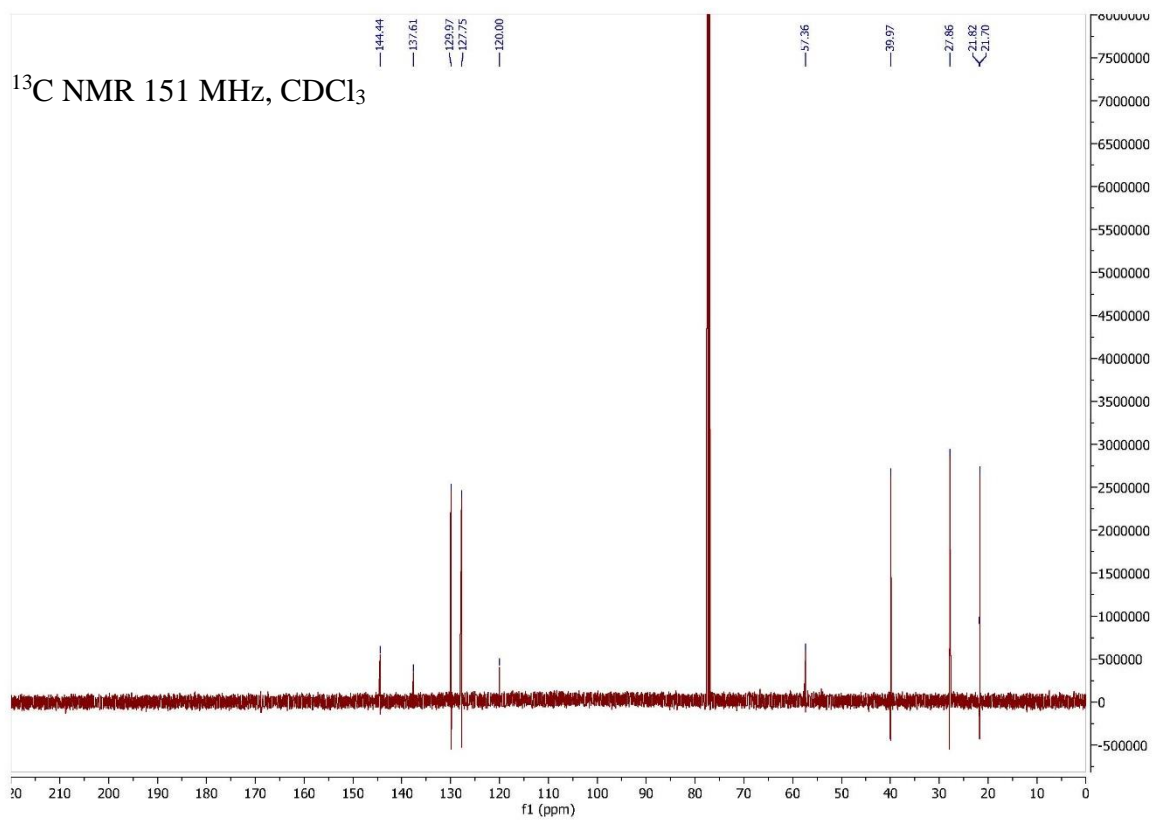
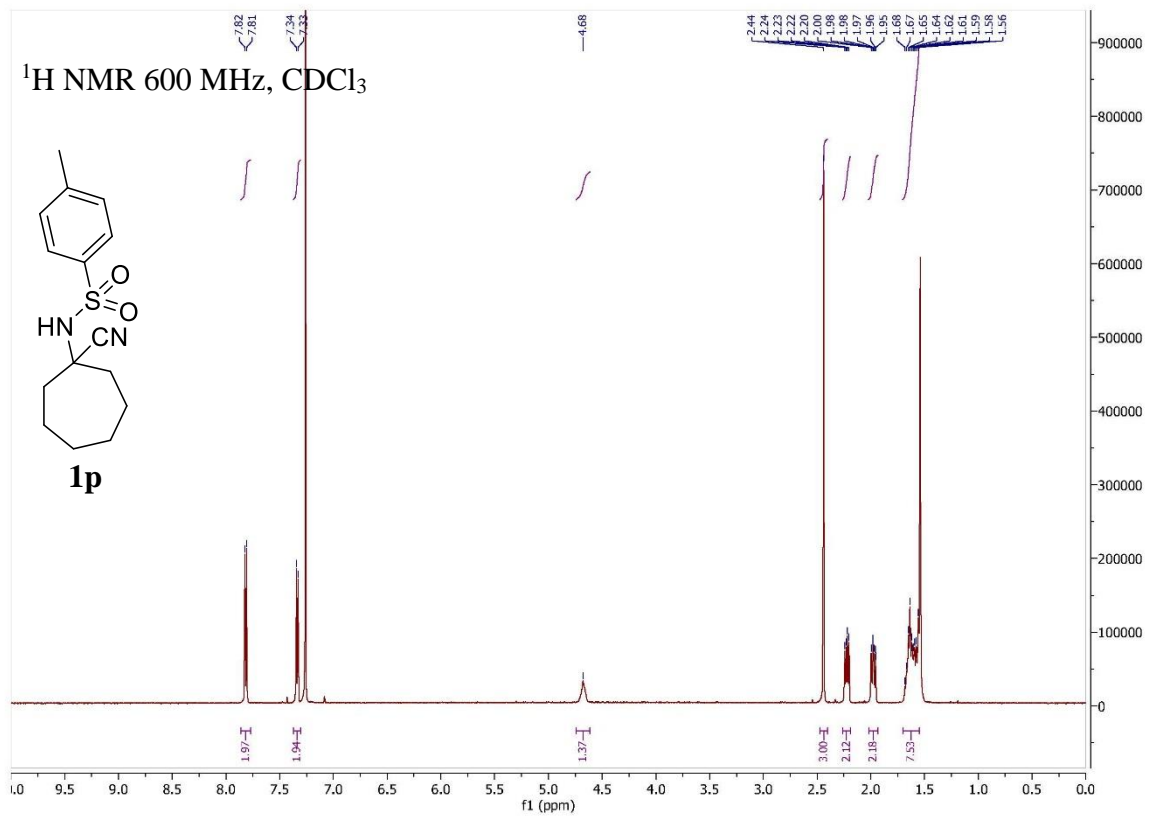


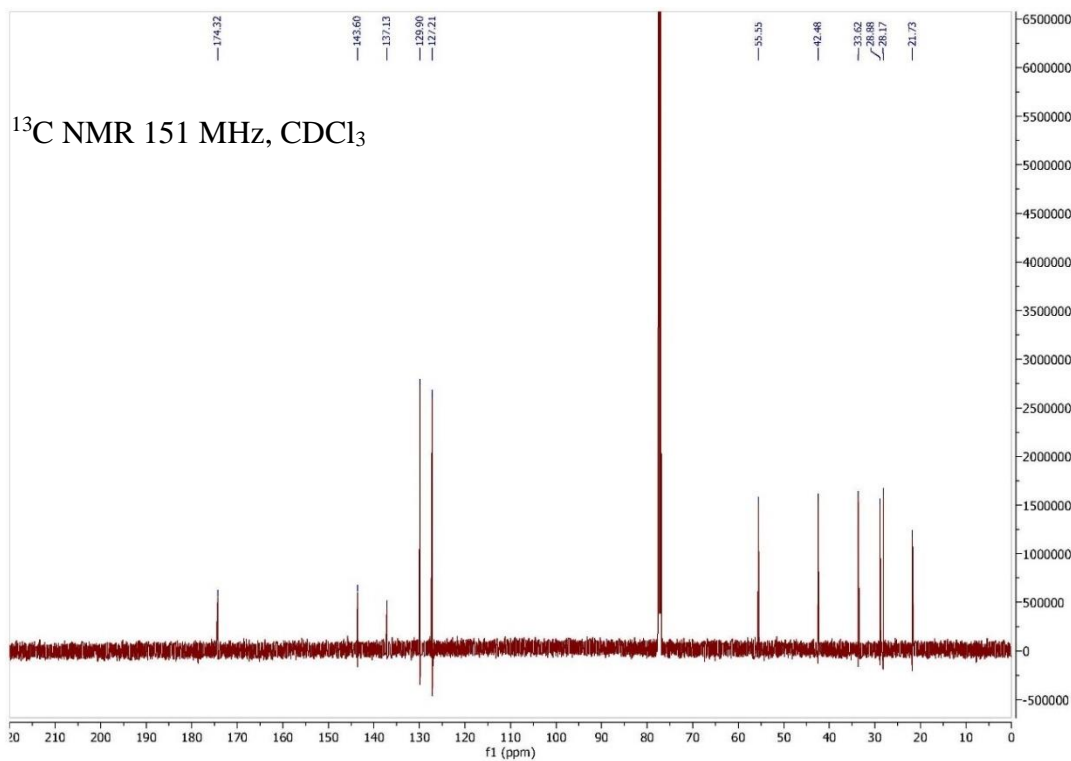
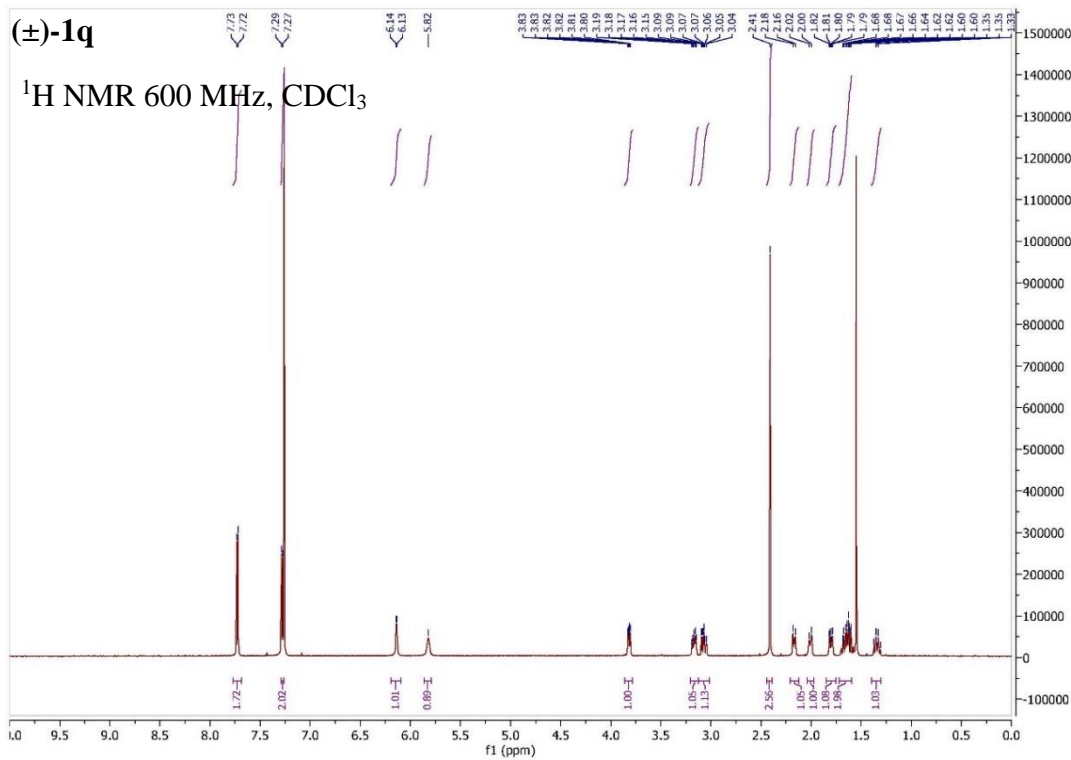
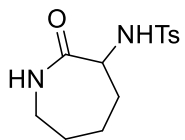


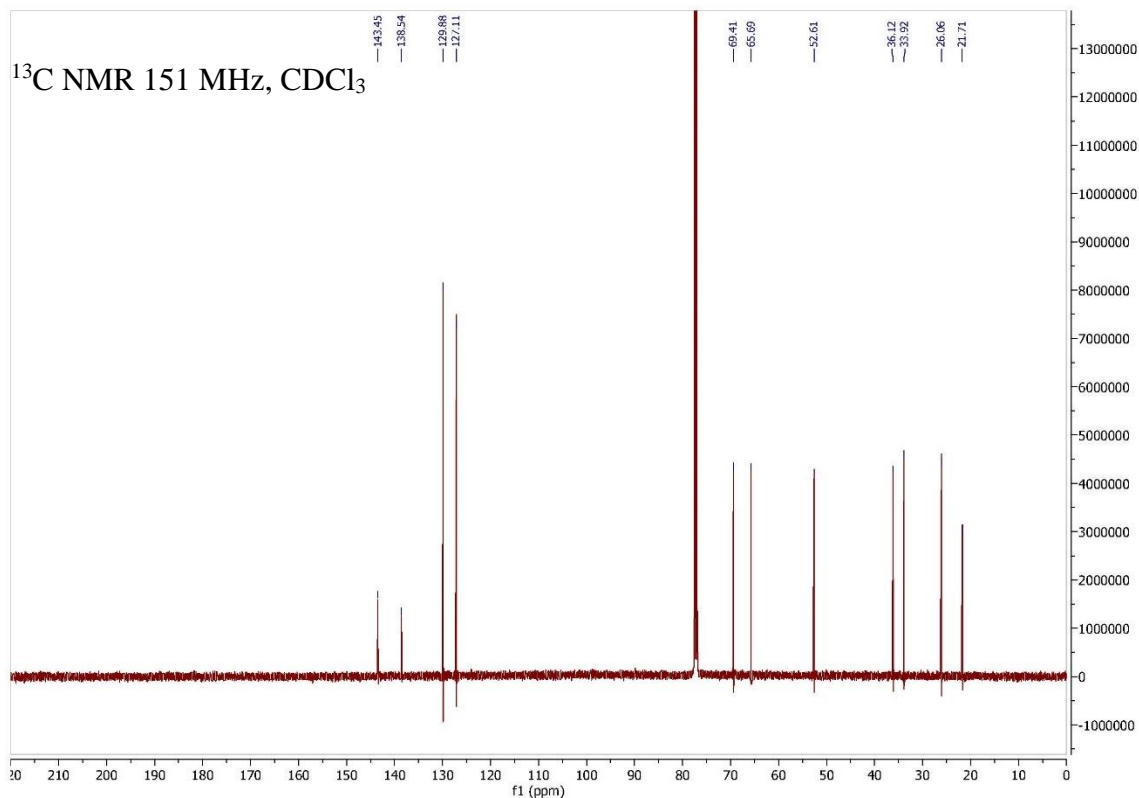
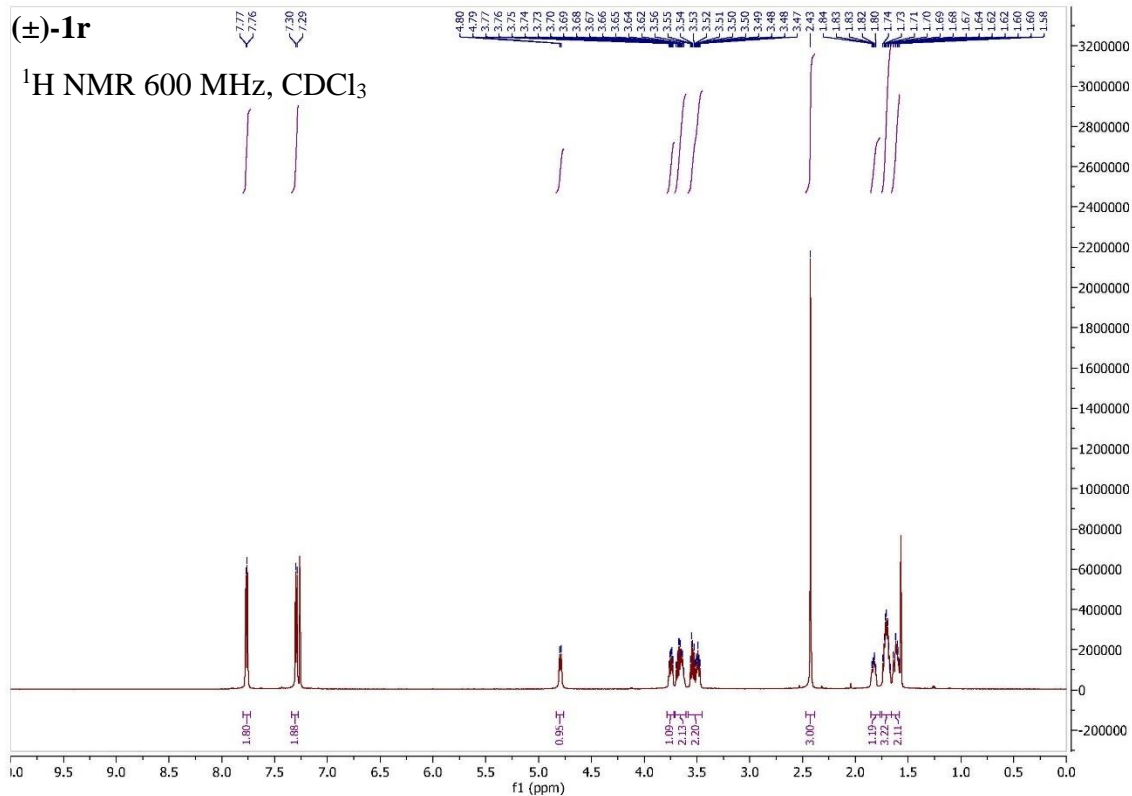
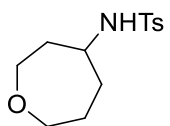


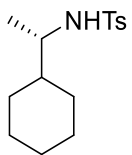




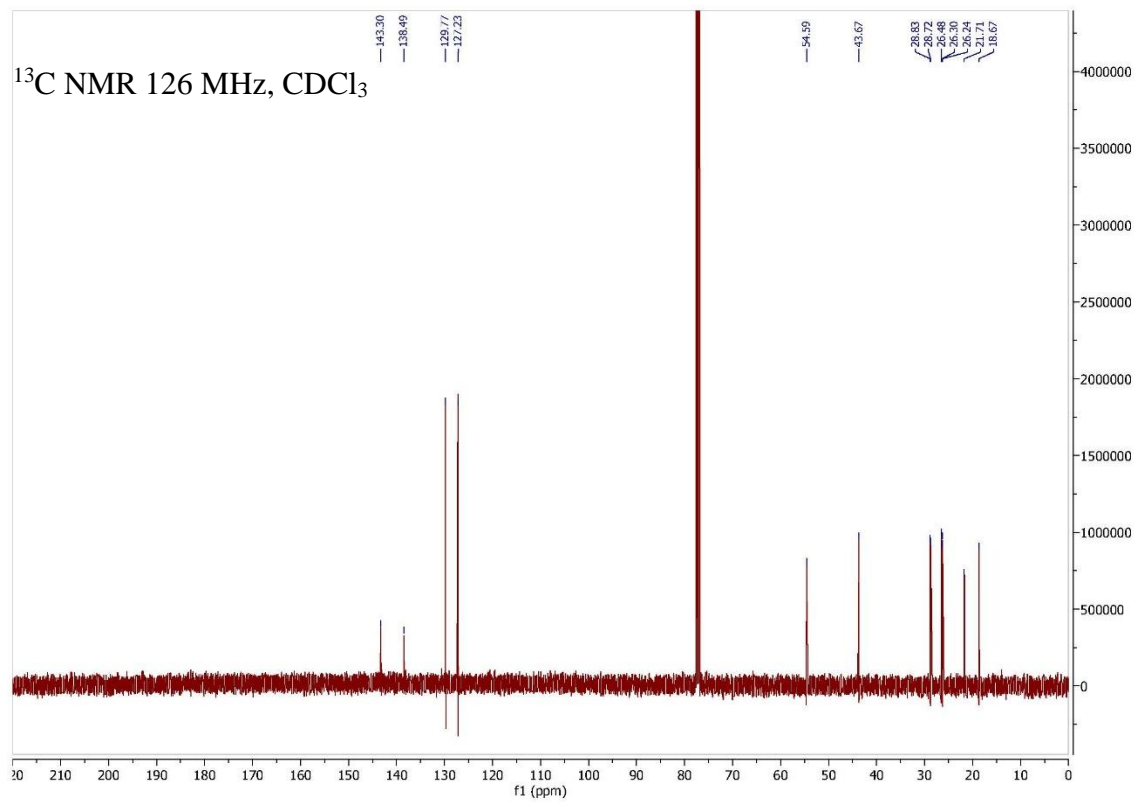
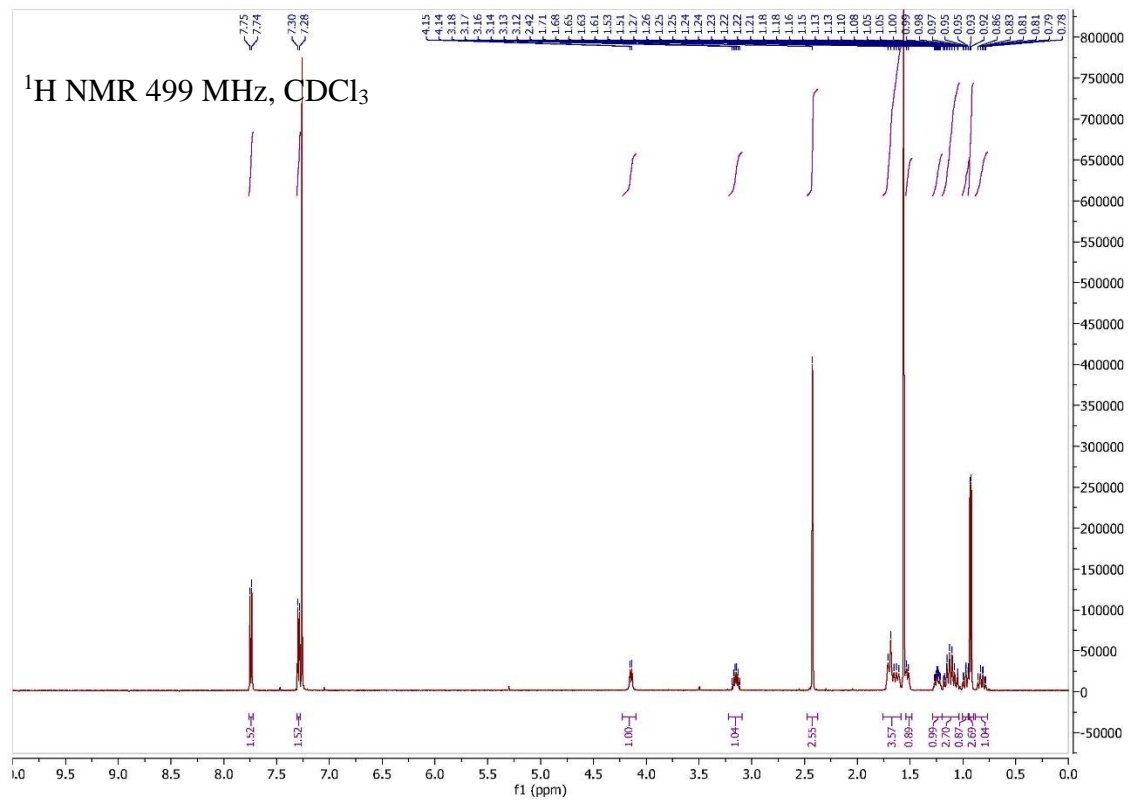


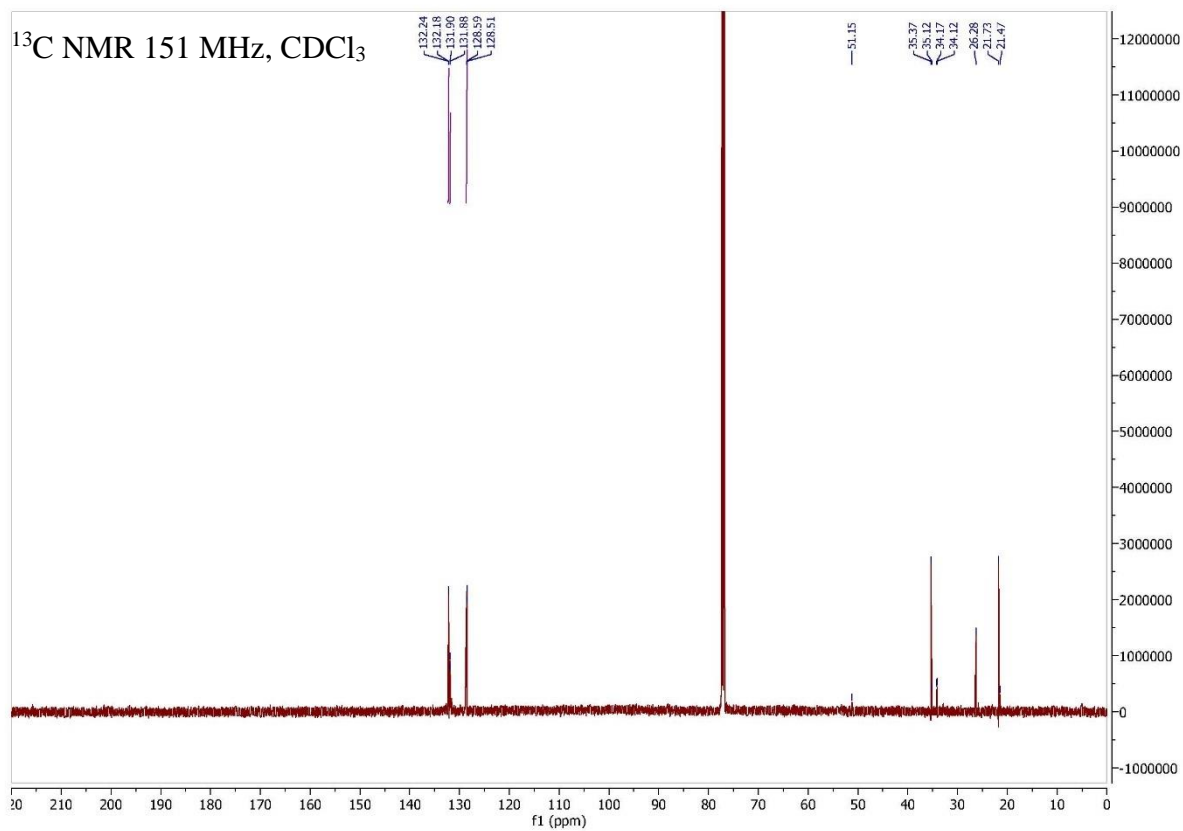
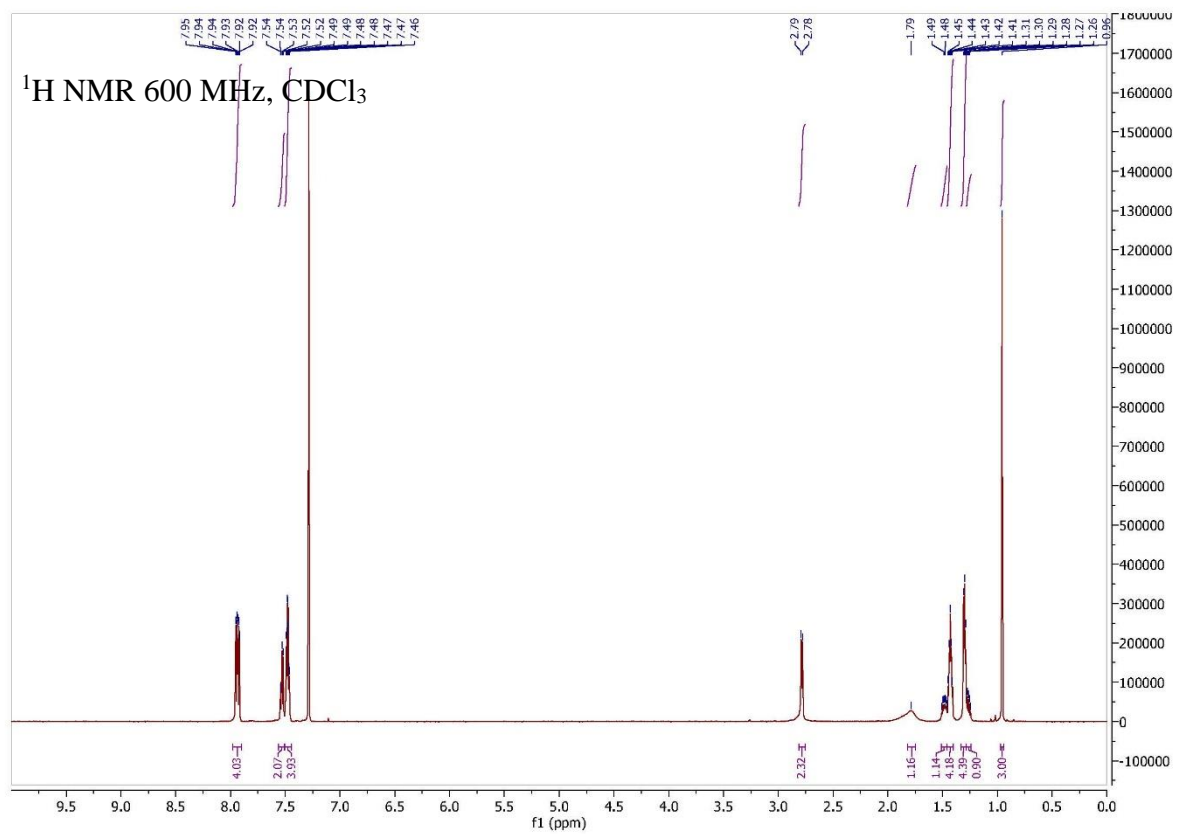
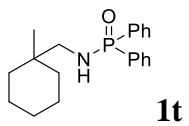


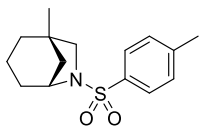




1s

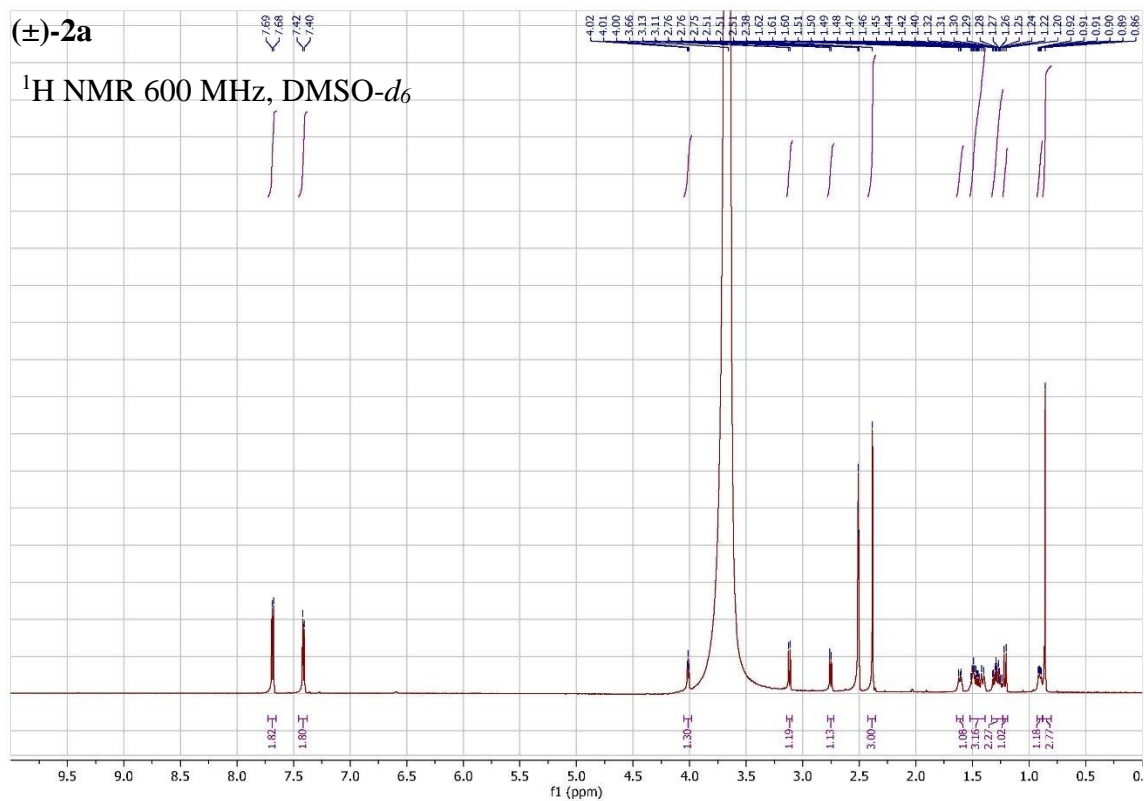




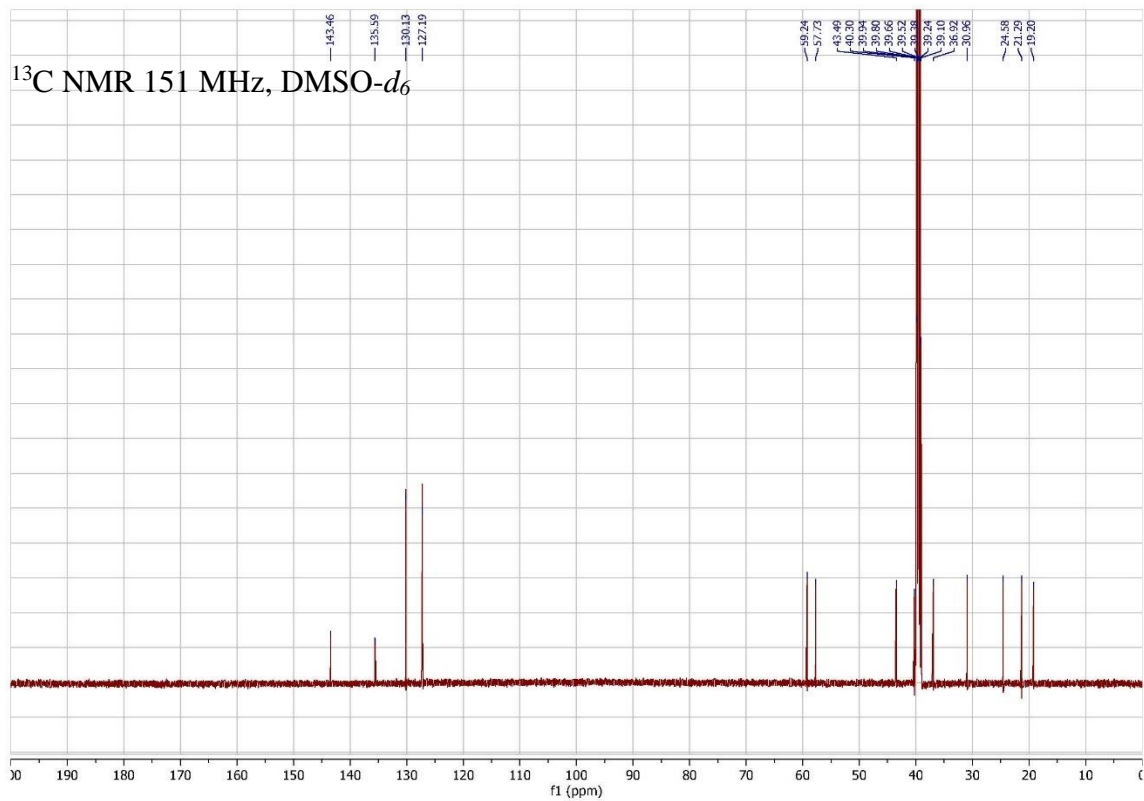


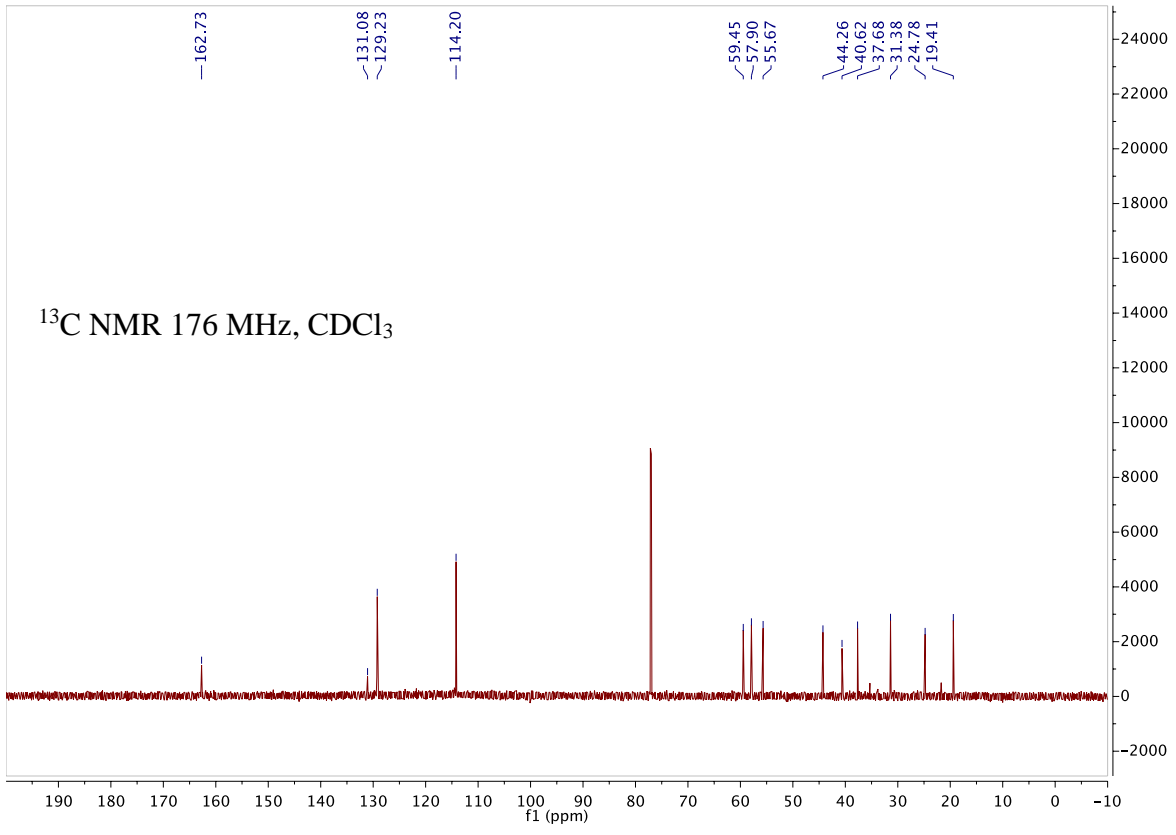
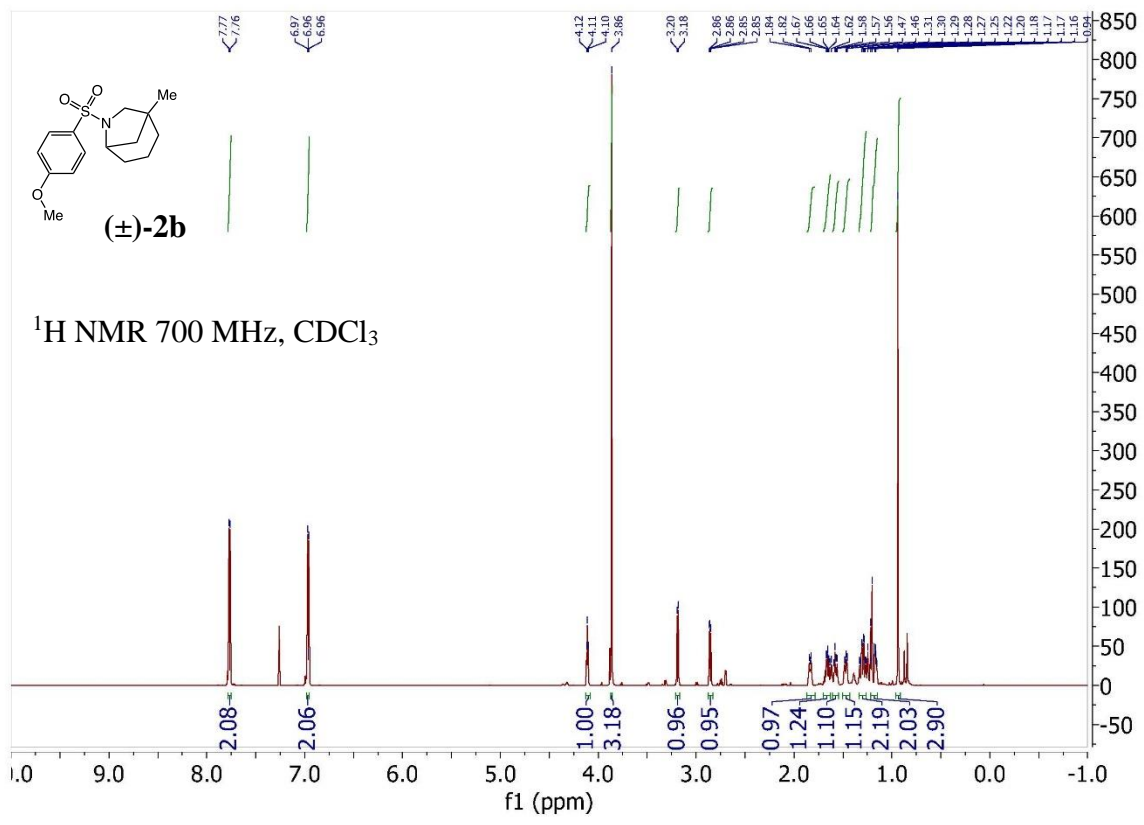
(±)-2a

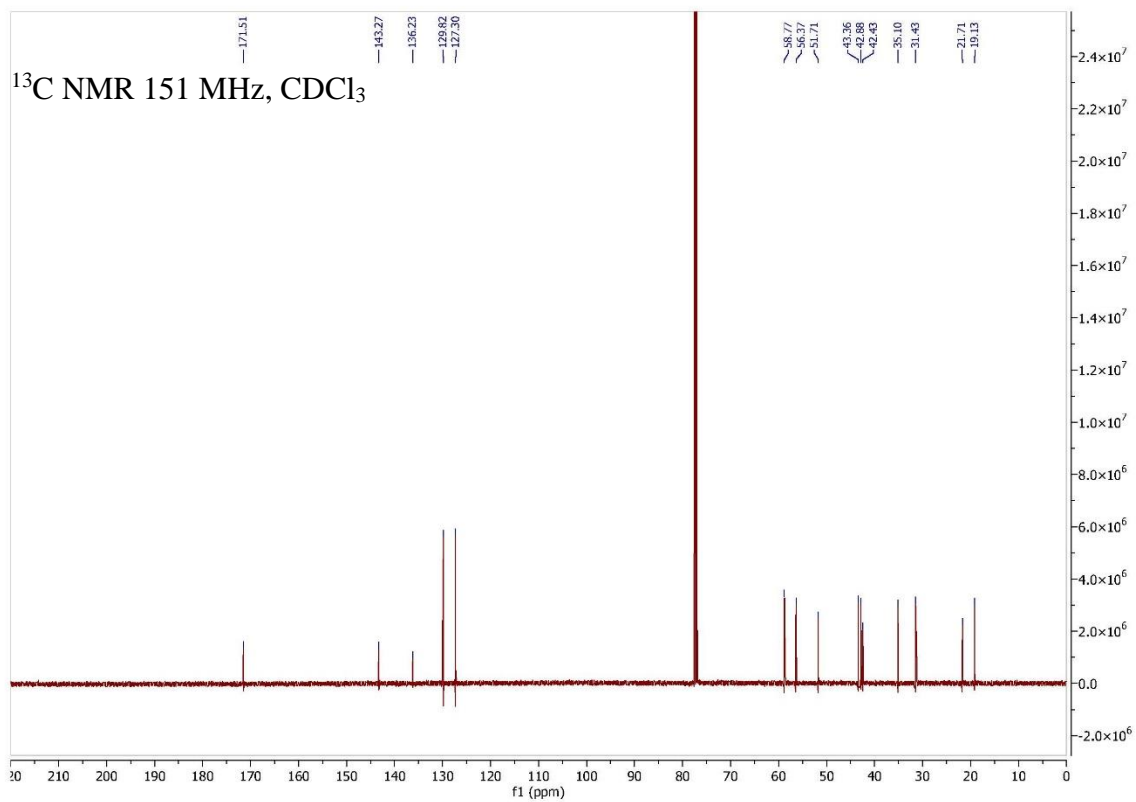
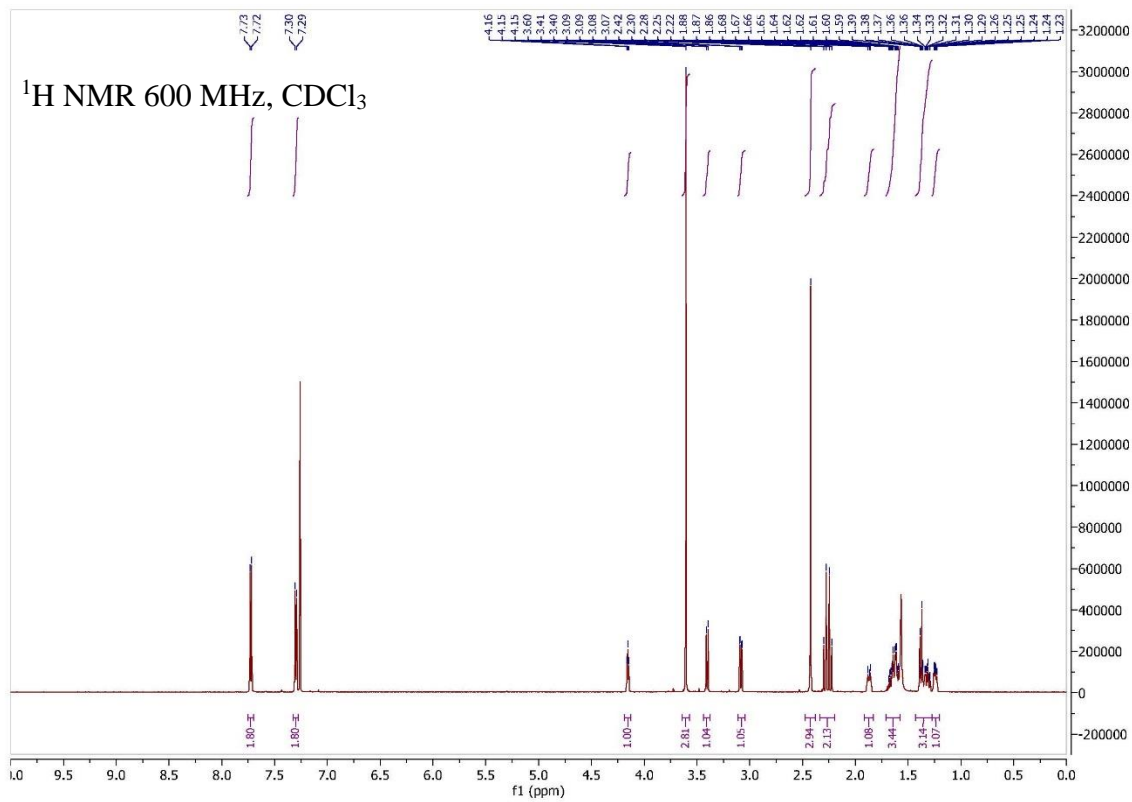
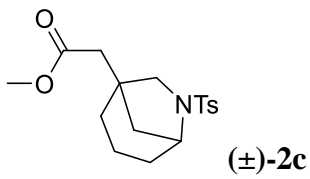
^1H NMR 600 MHz, $\text{DMSO}-d_6$

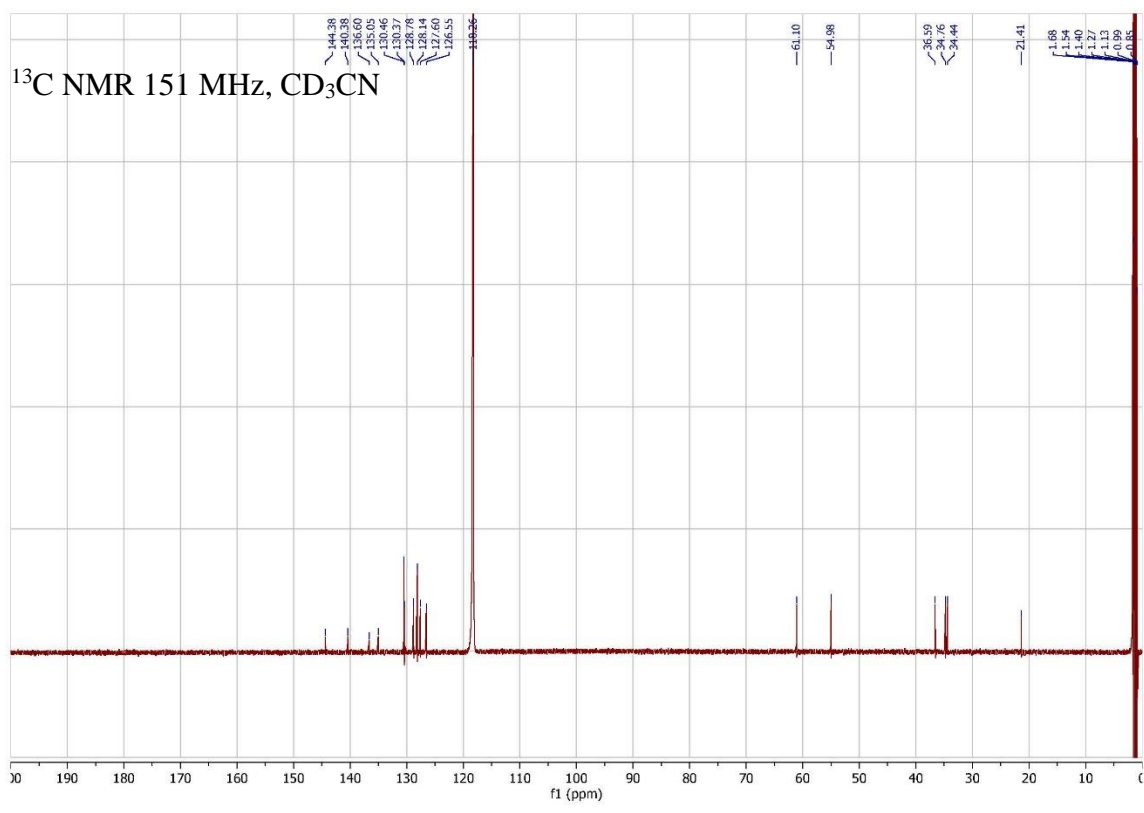
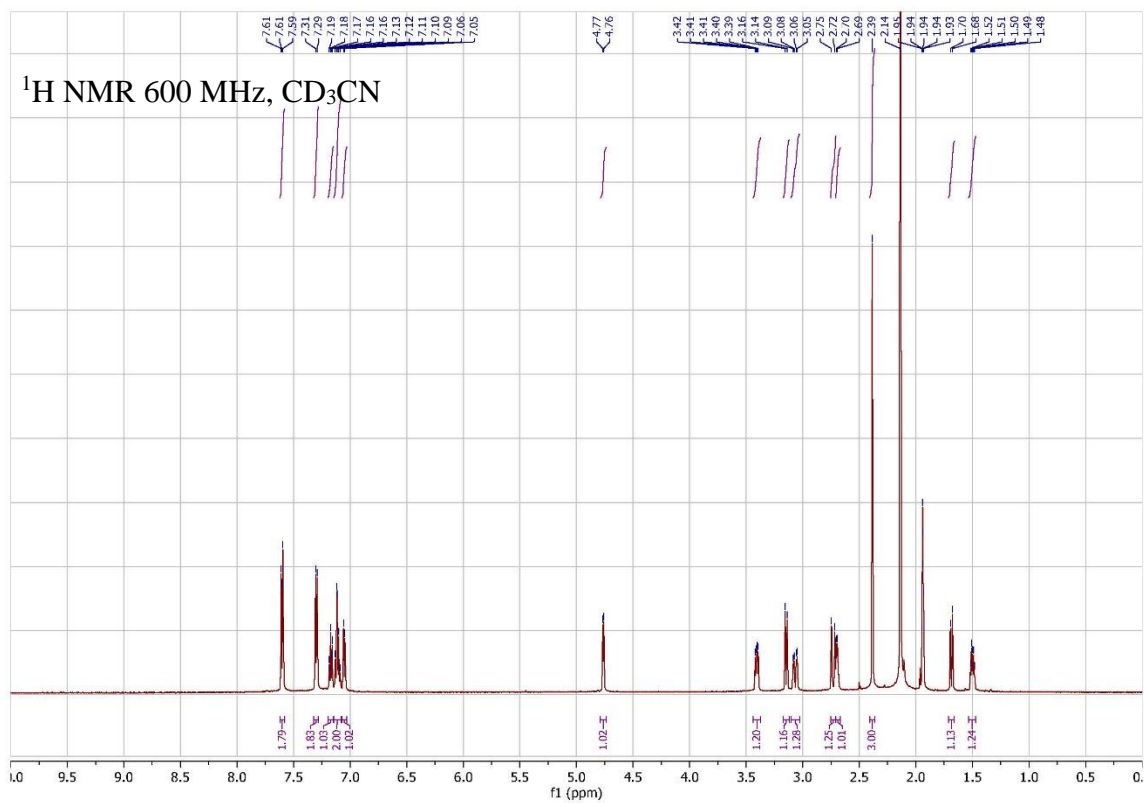
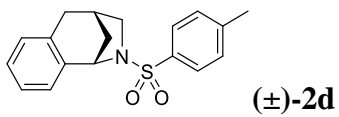


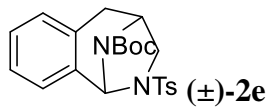
^{13}C NMR 151 MHz, $\text{DMSO}-d_6$



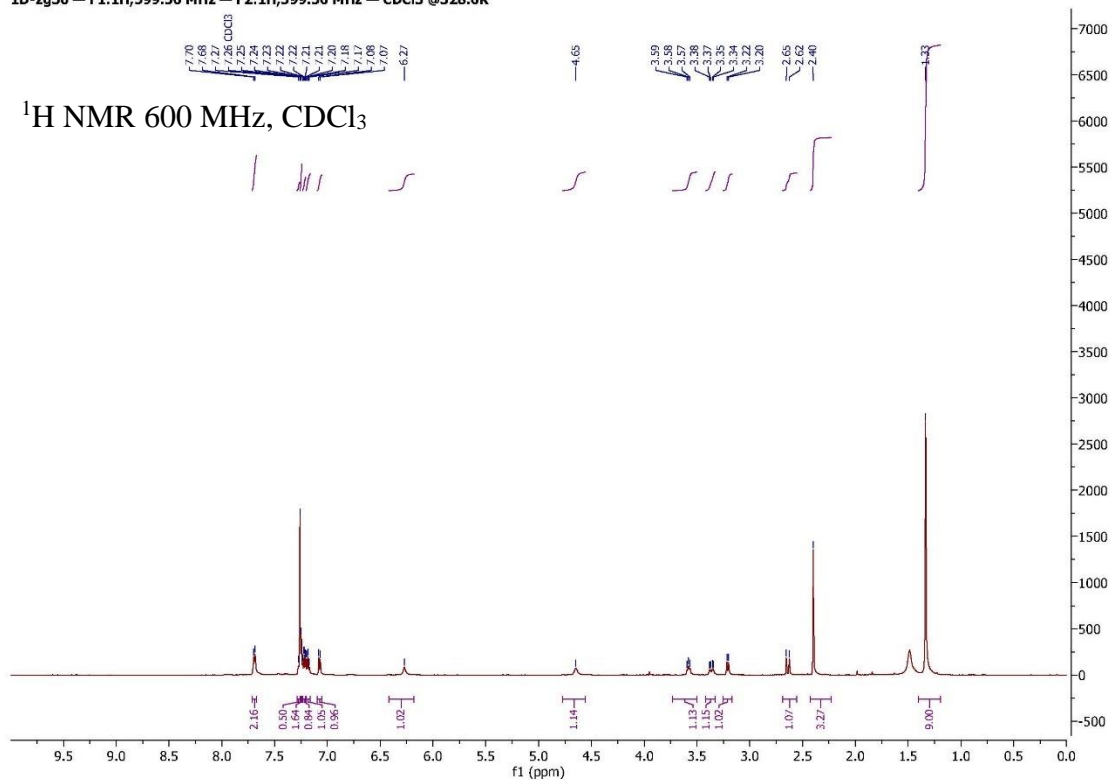




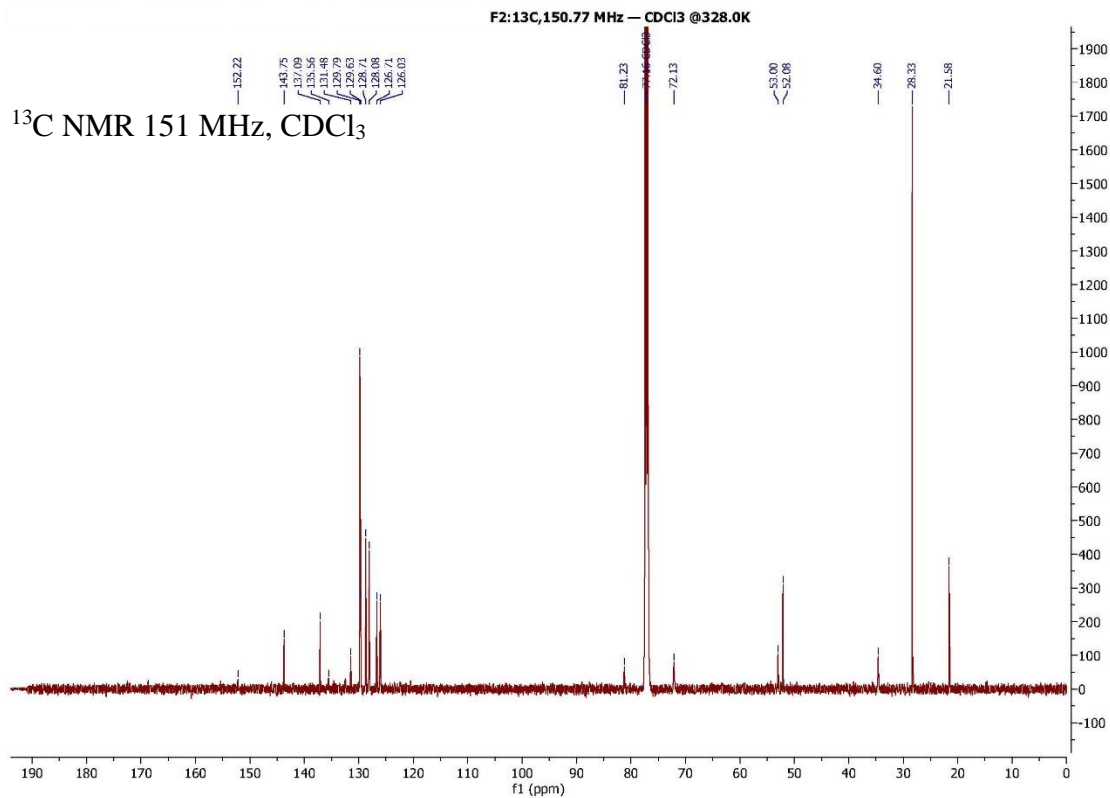


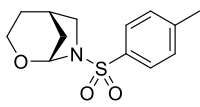


1D-zg30 — F1:1H,599.56 MHz — F2:1H,599.56 MHz — CDCl₃ @328.0K

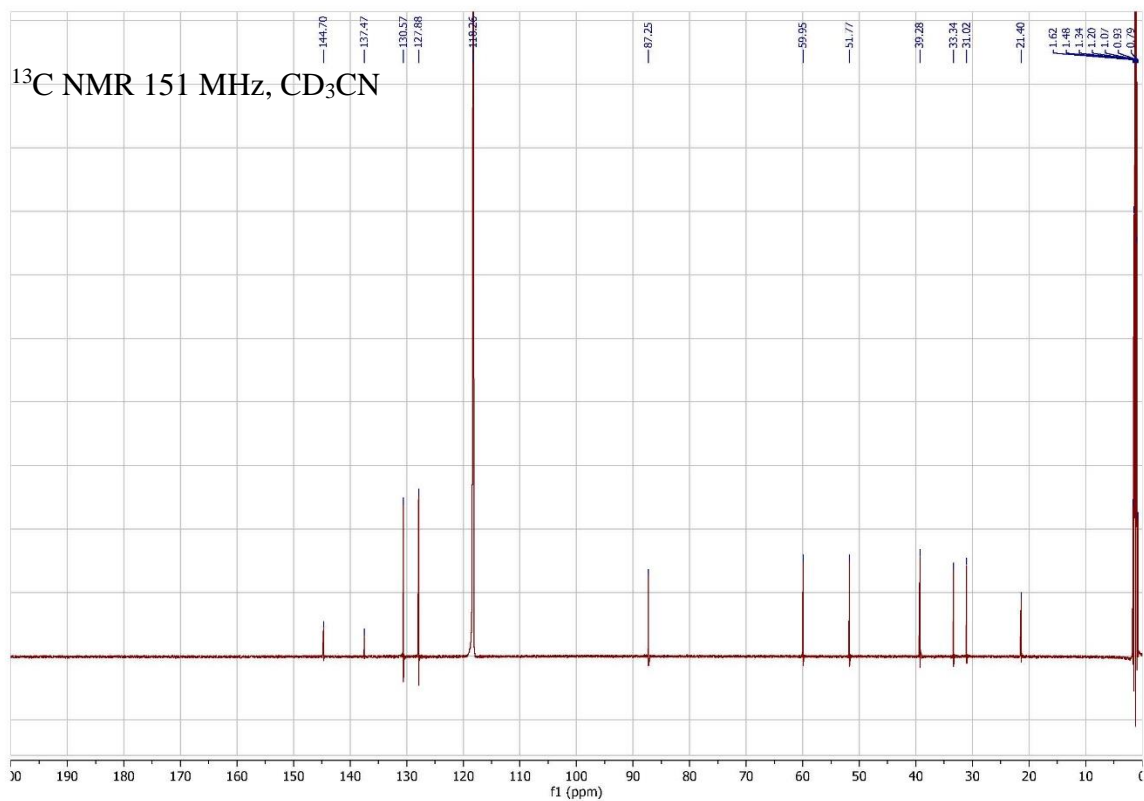
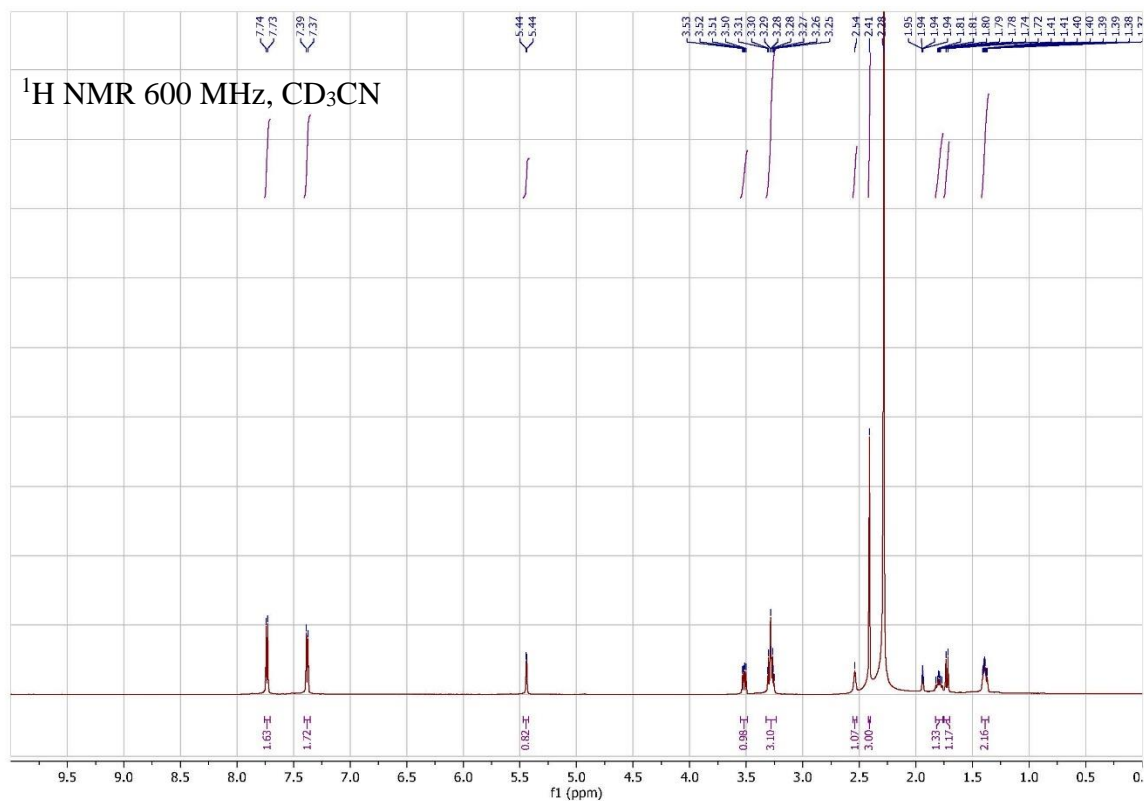


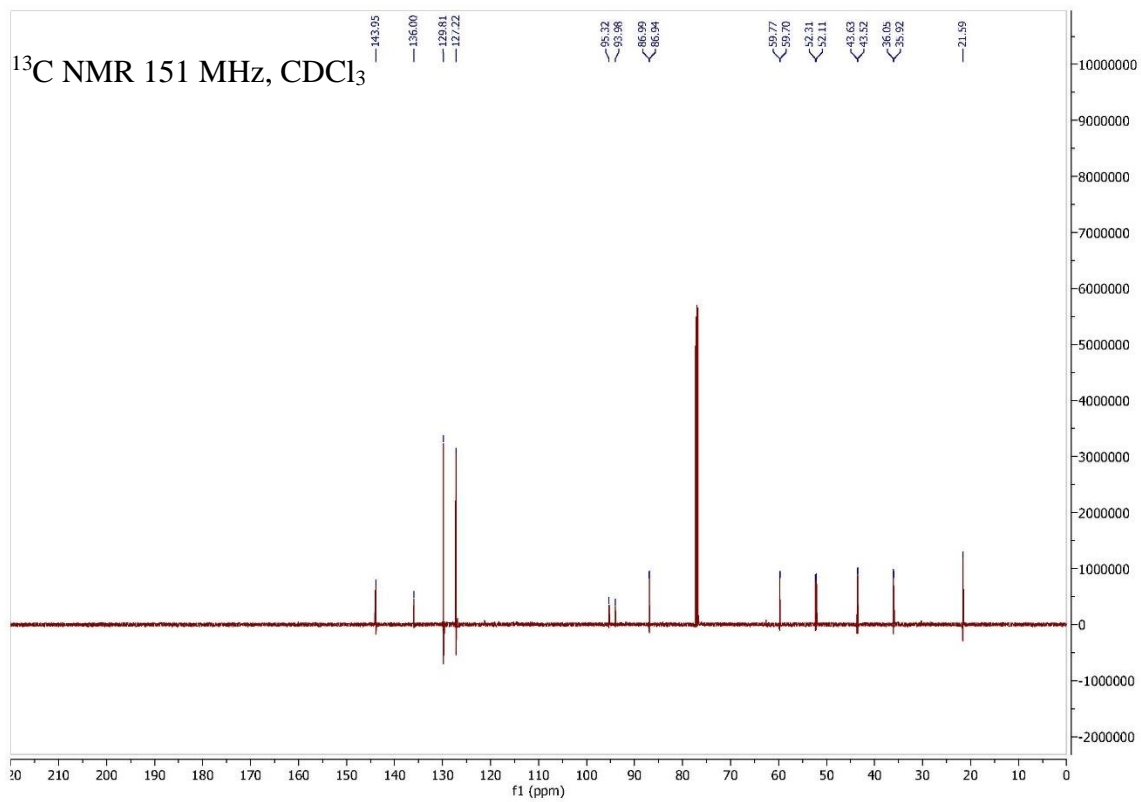
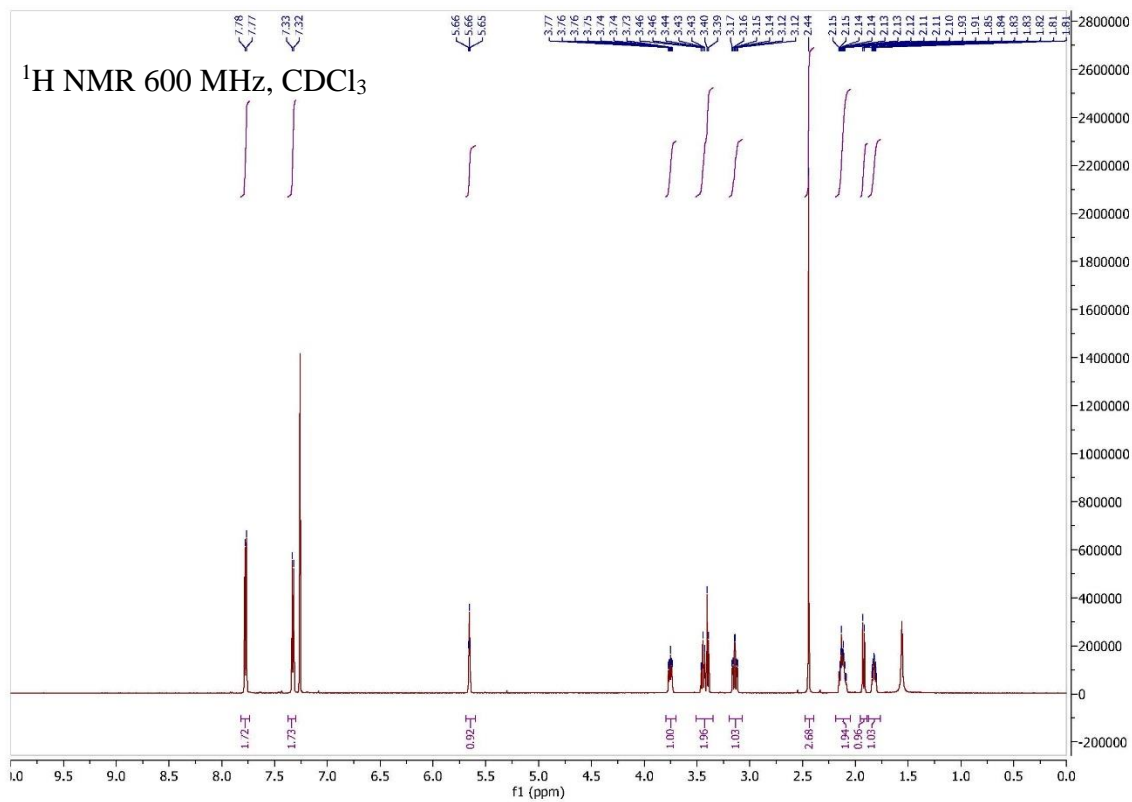
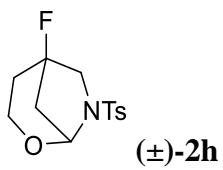
F2:13C,150.77 MHz — CDCl₃ @328.0K

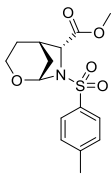




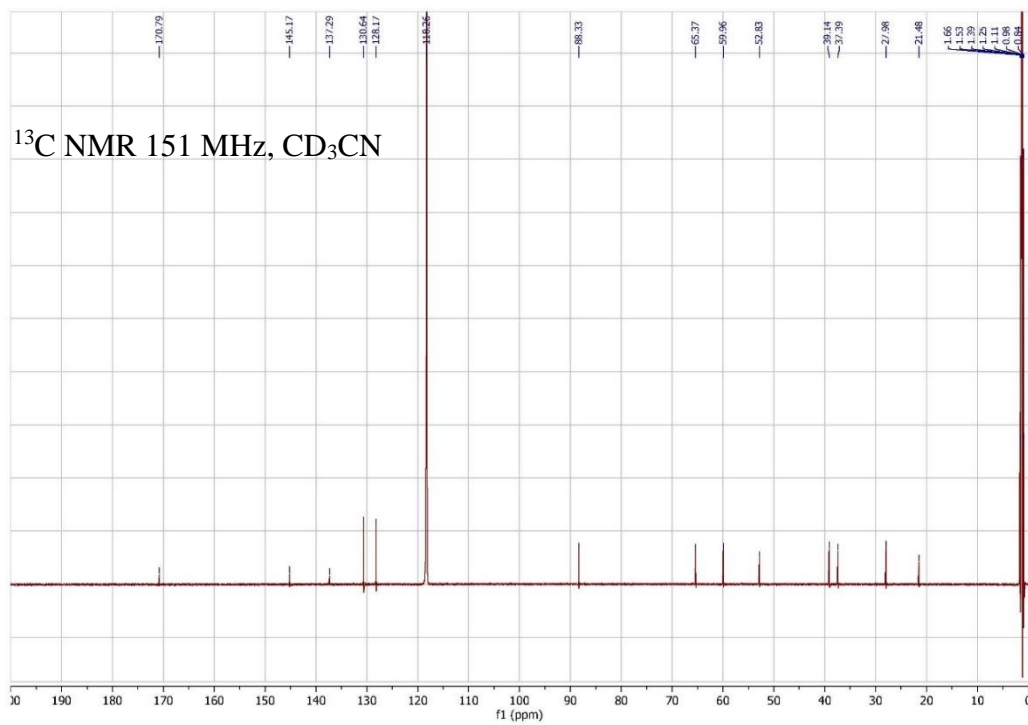
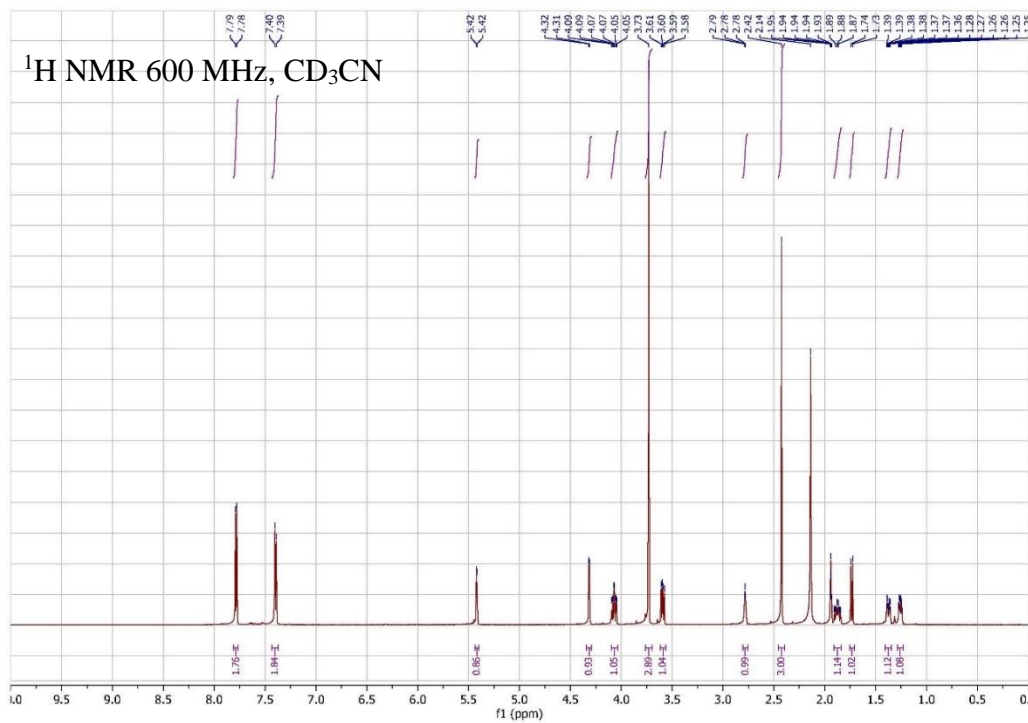
(±)-2g



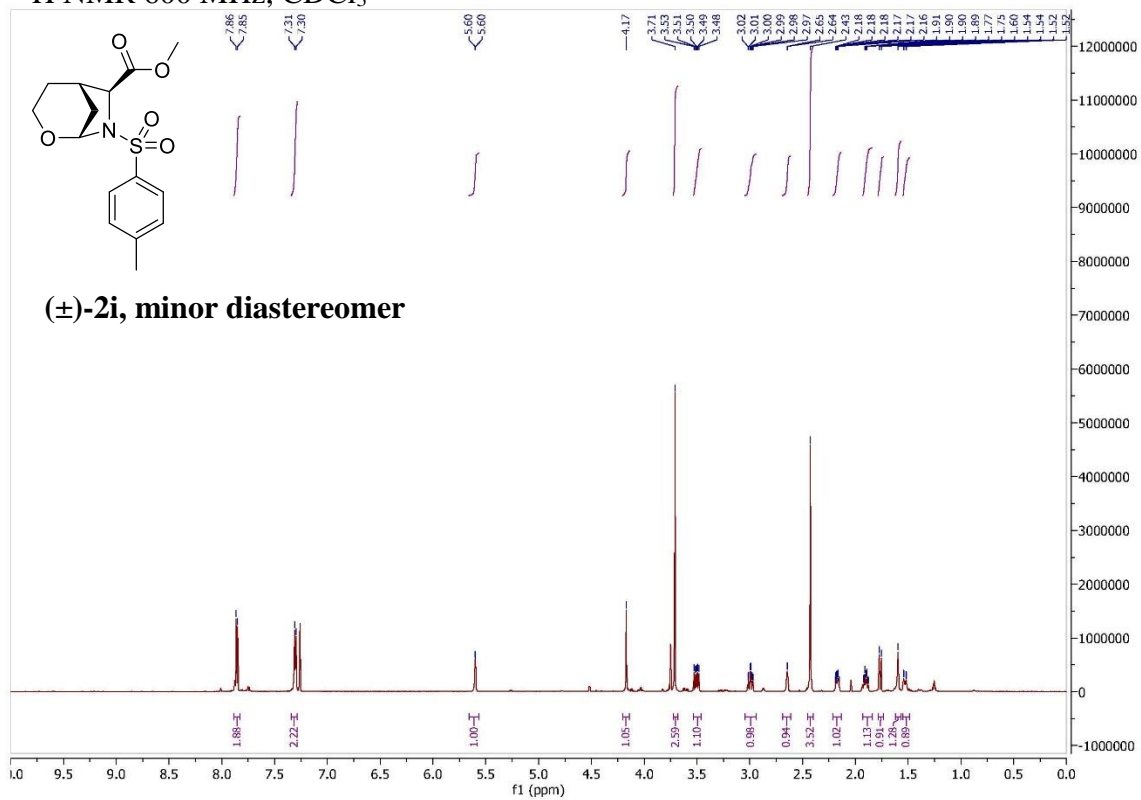




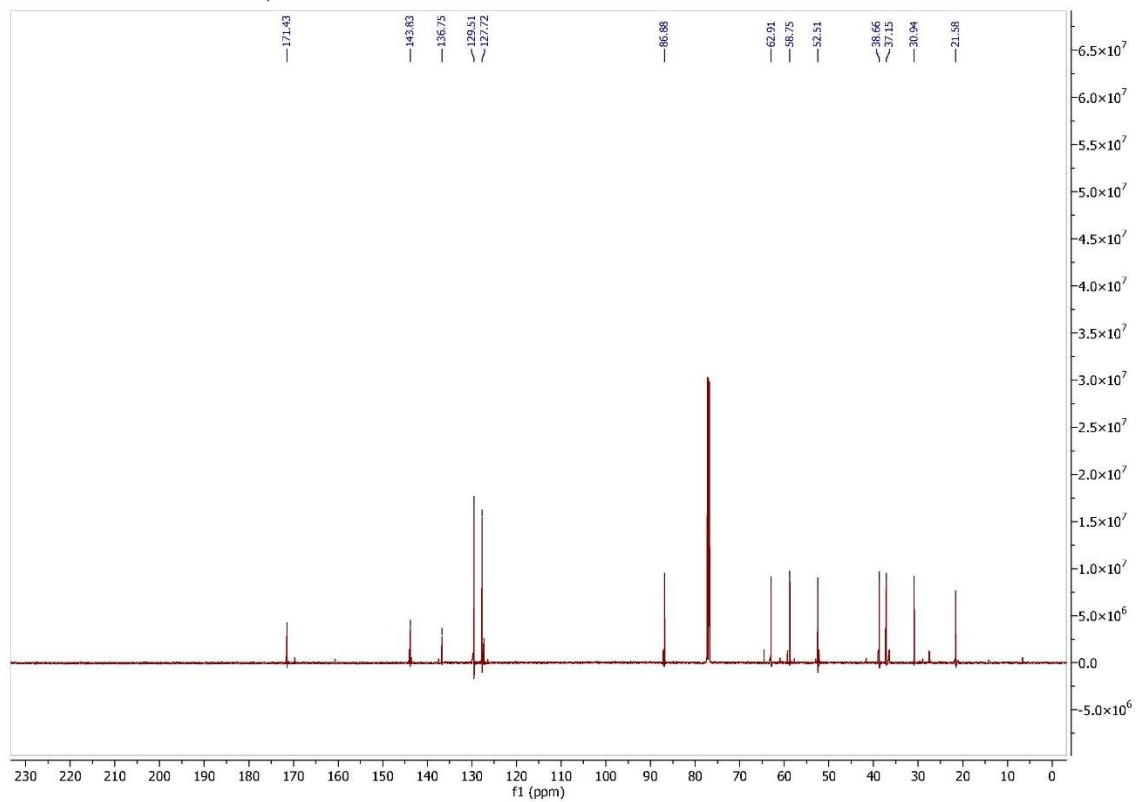
(±)-2i, major diastereomer

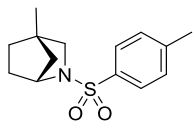


¹H NMR 600 MHz, CDCl₃

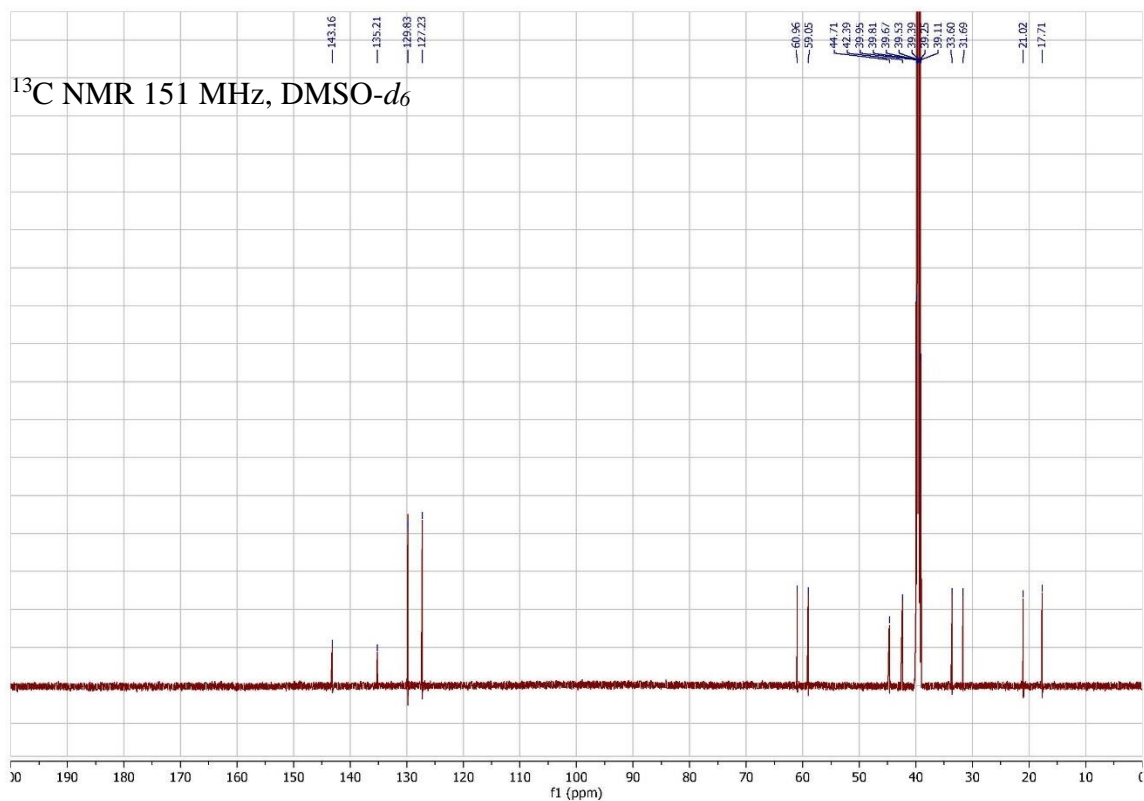
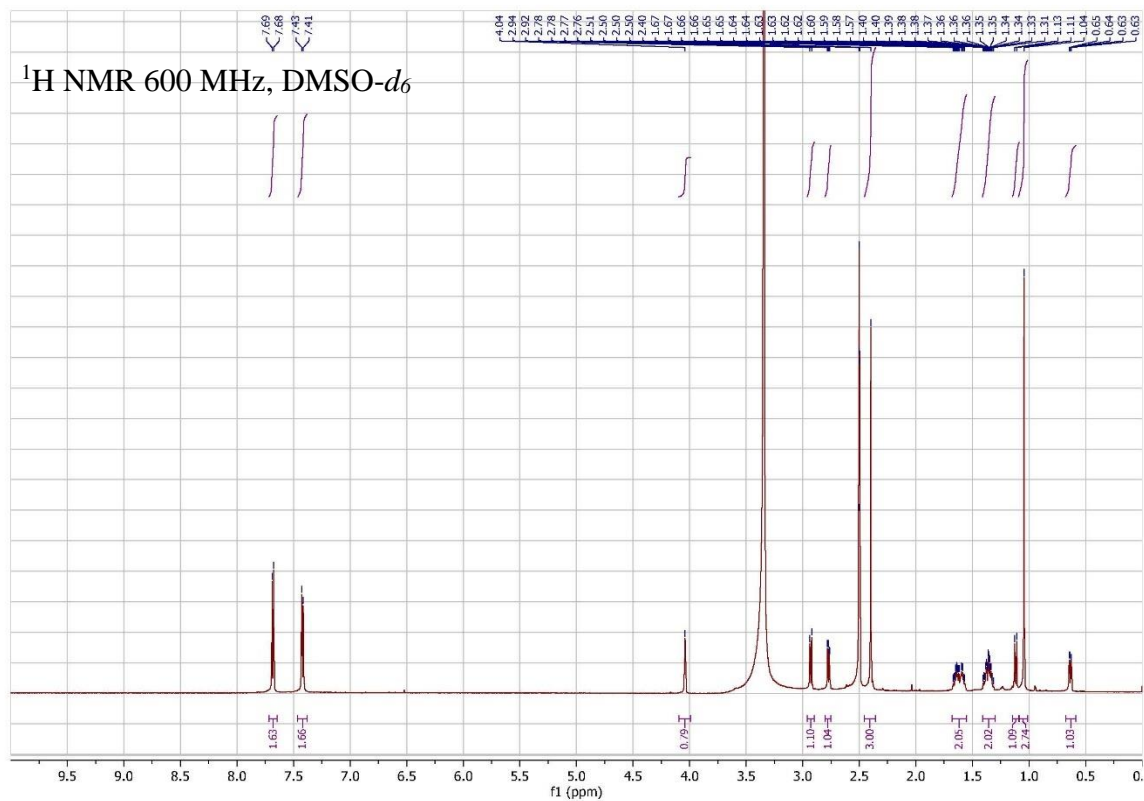


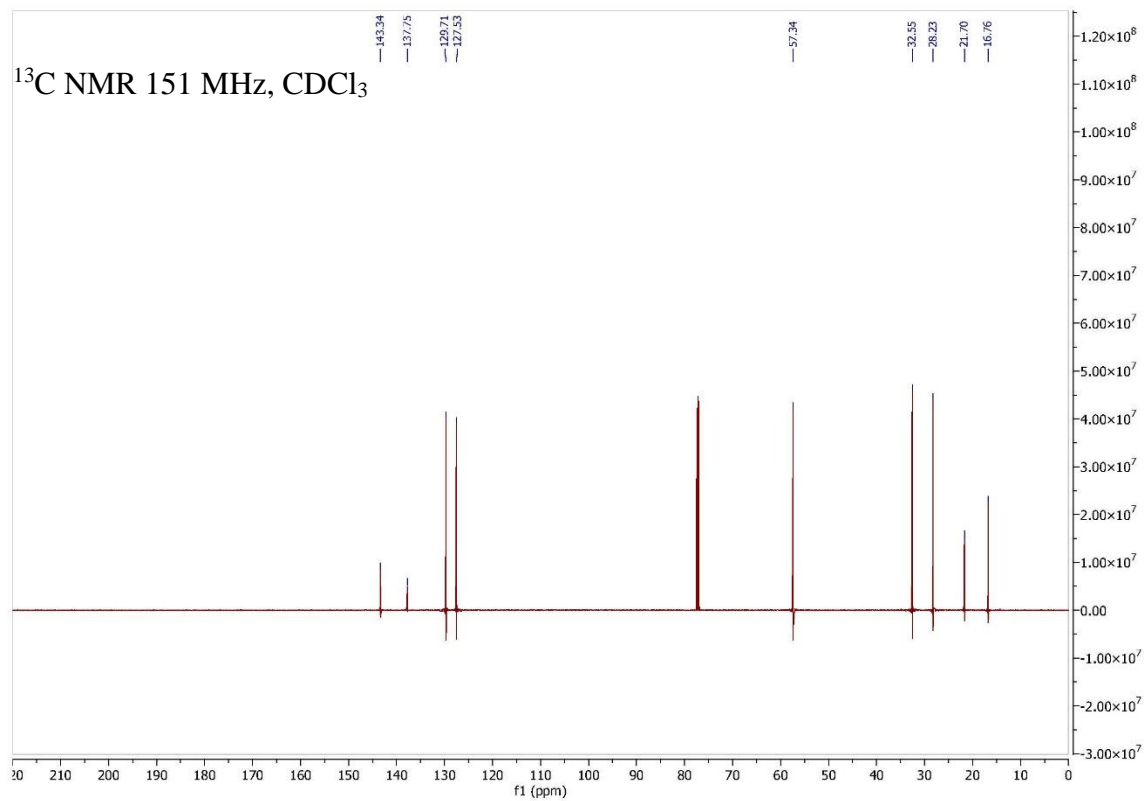
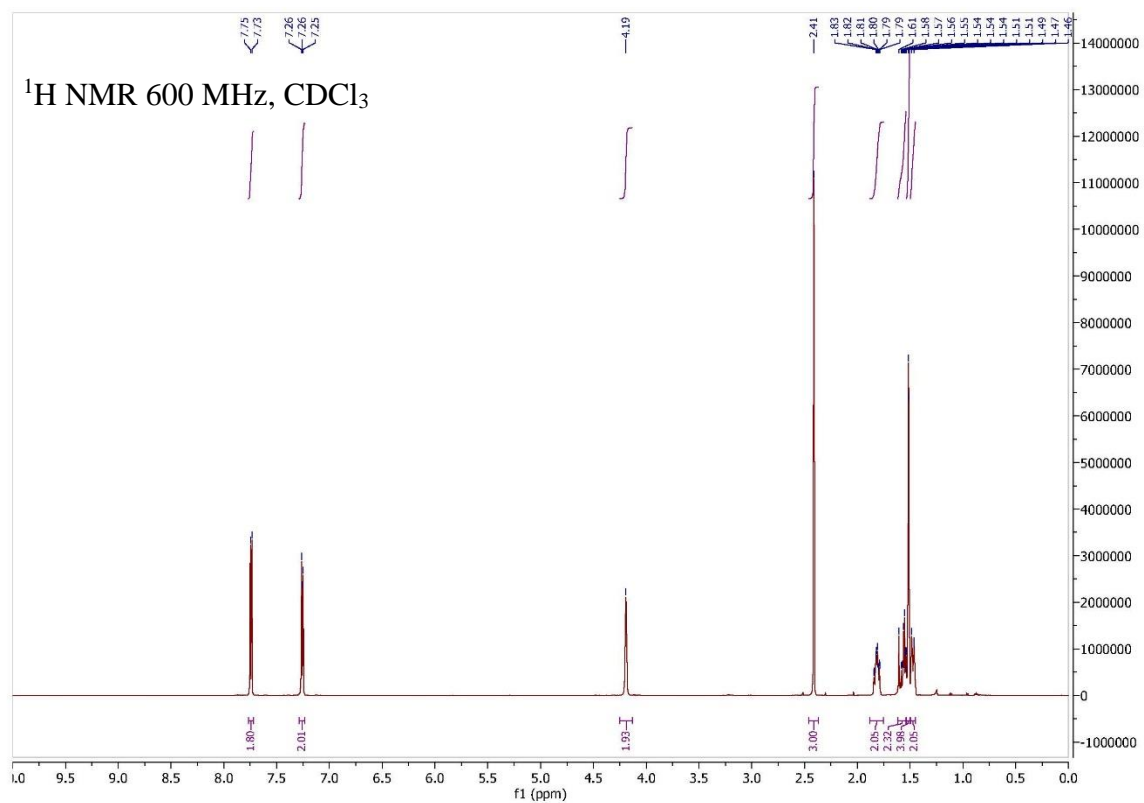
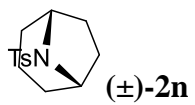
¹³C NMR 151 MHz, CDCl₃

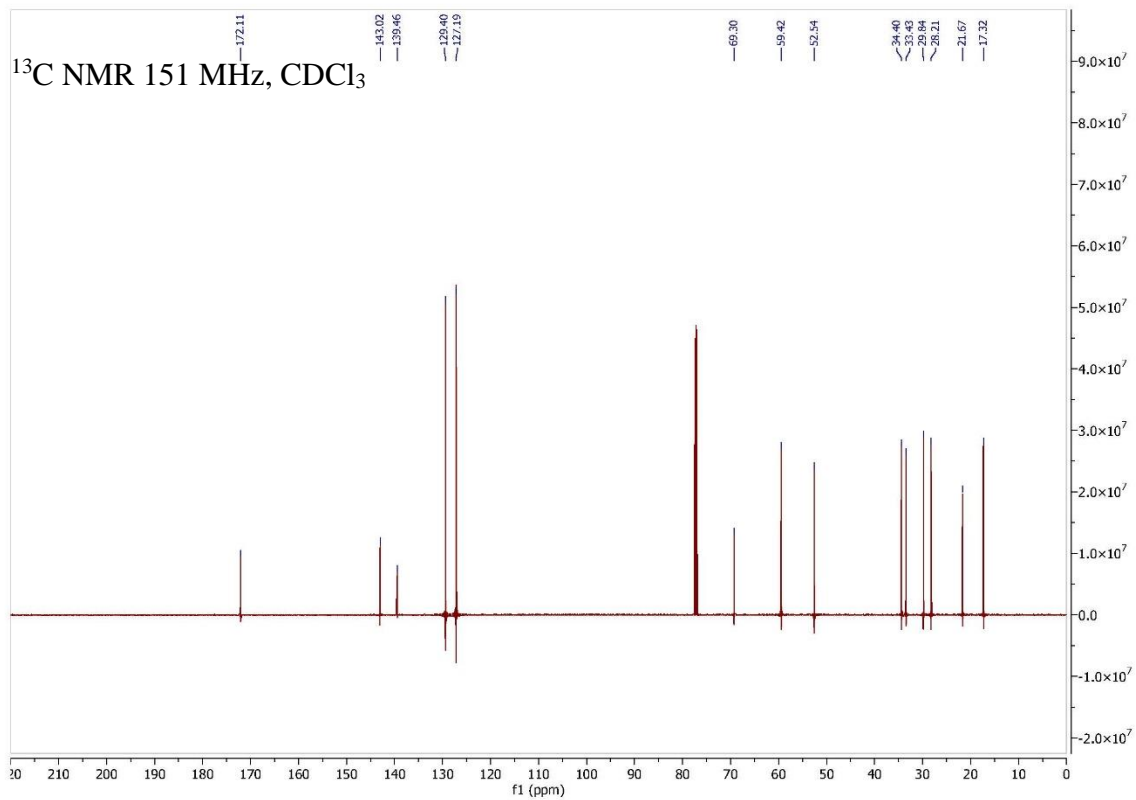
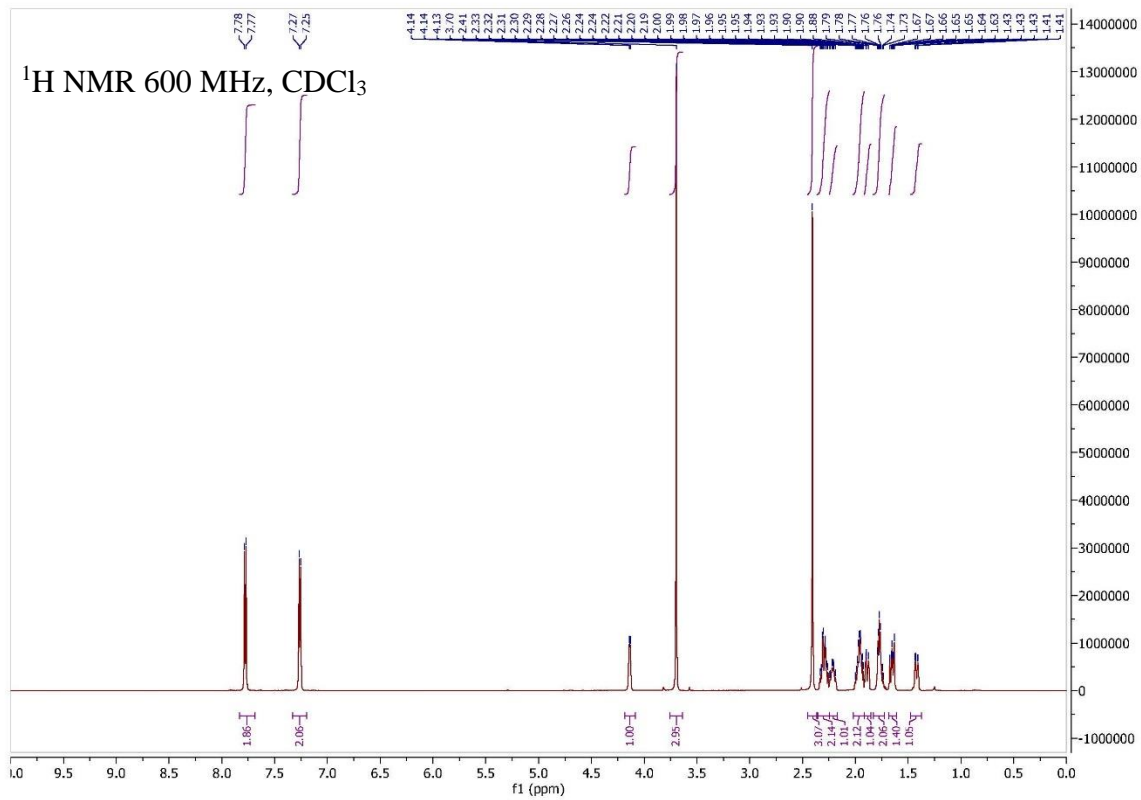
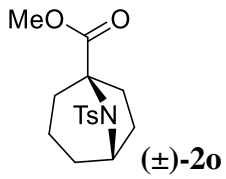


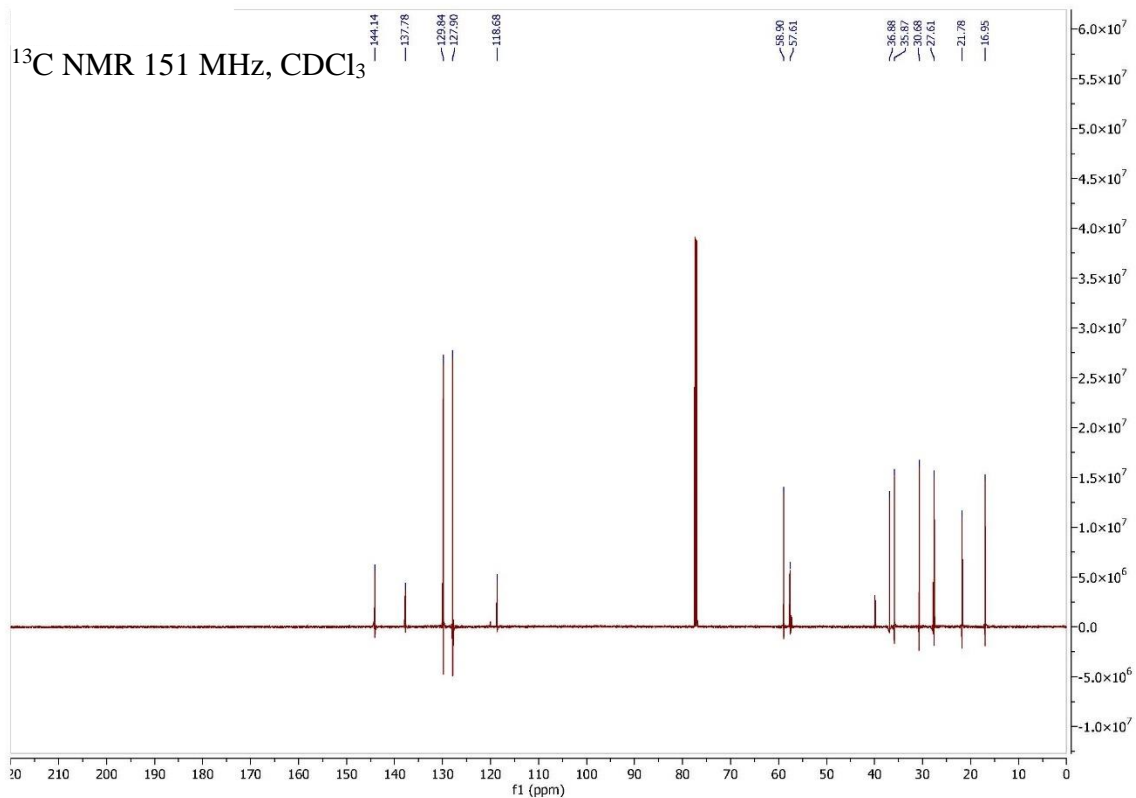
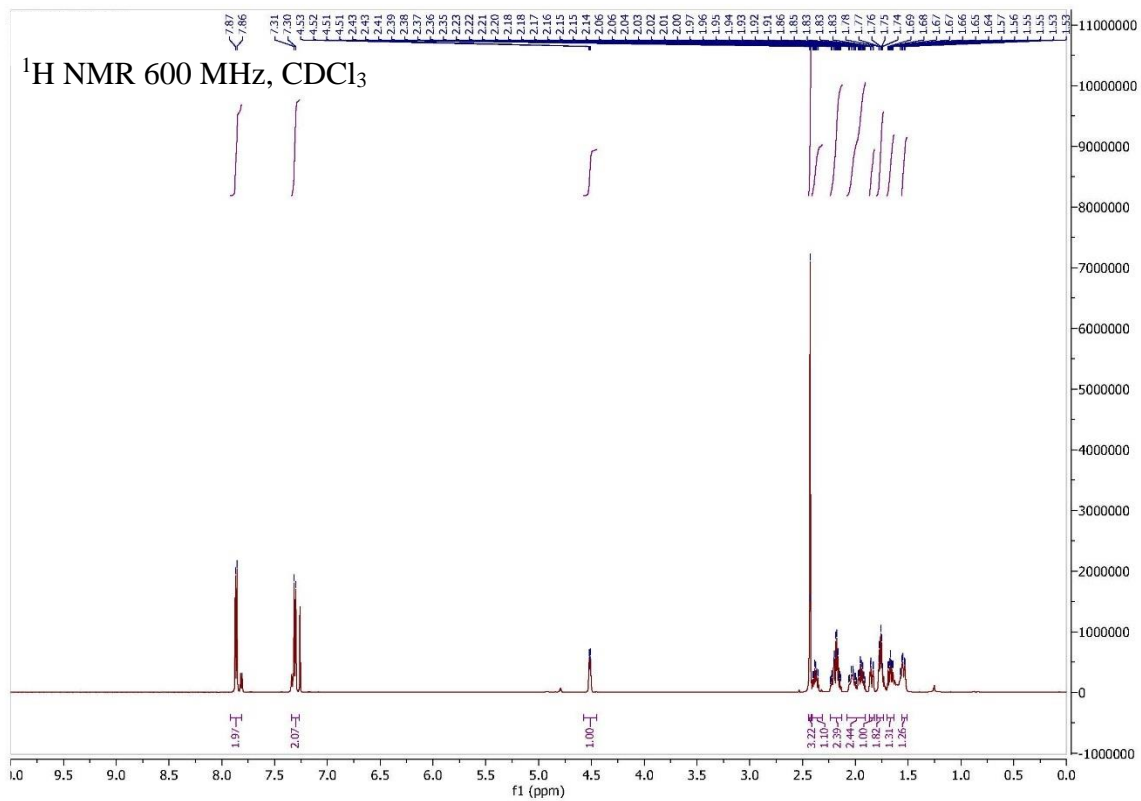
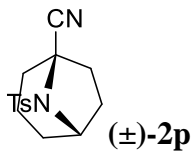


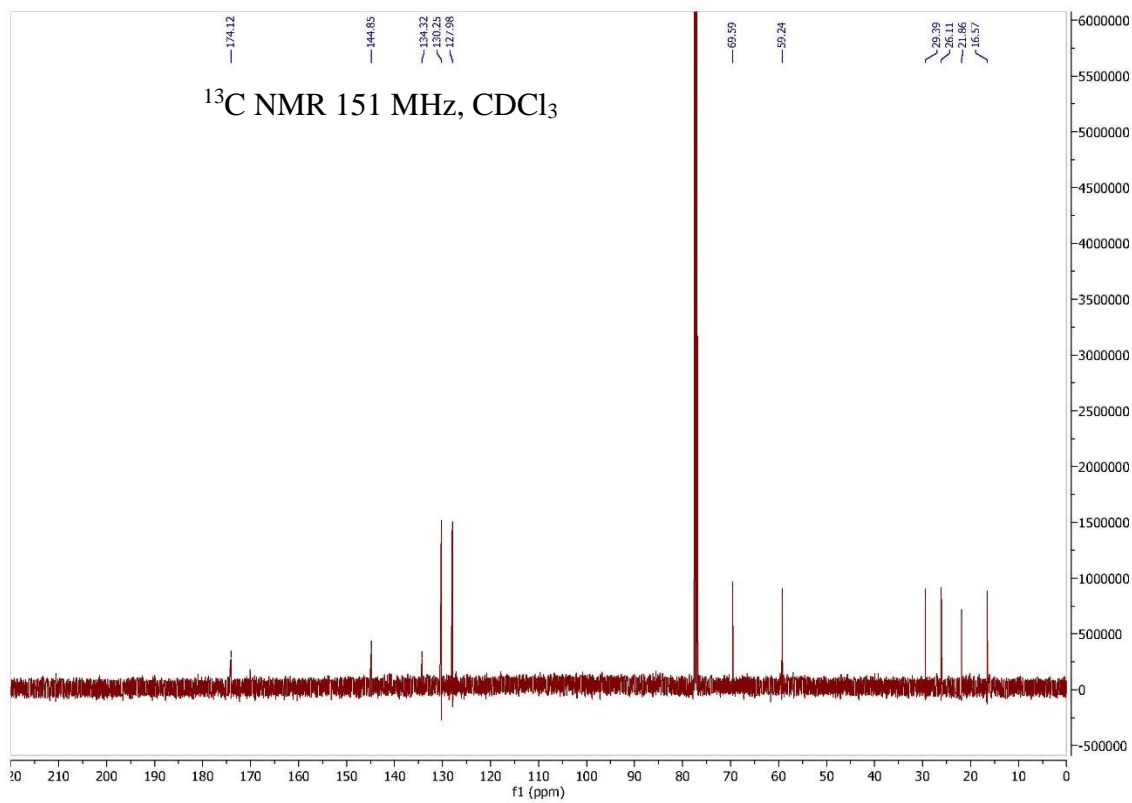
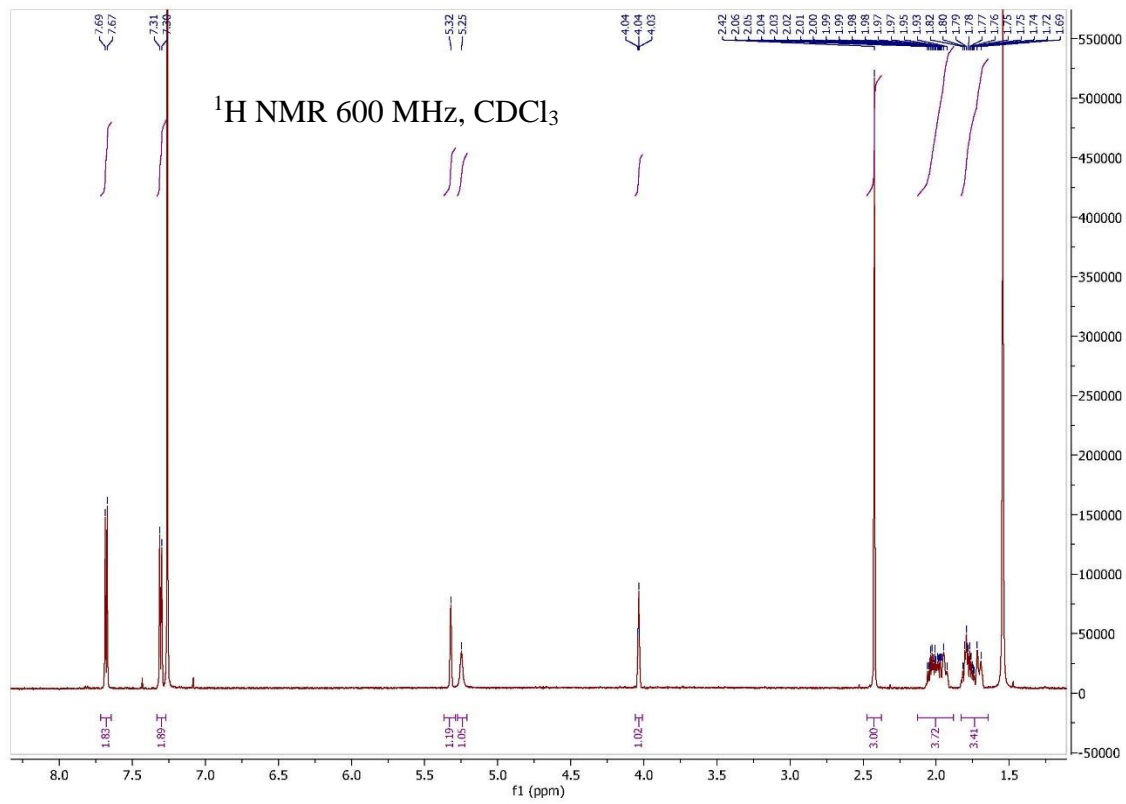
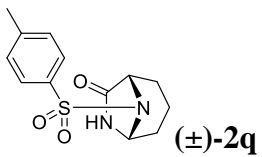
(±)-2j

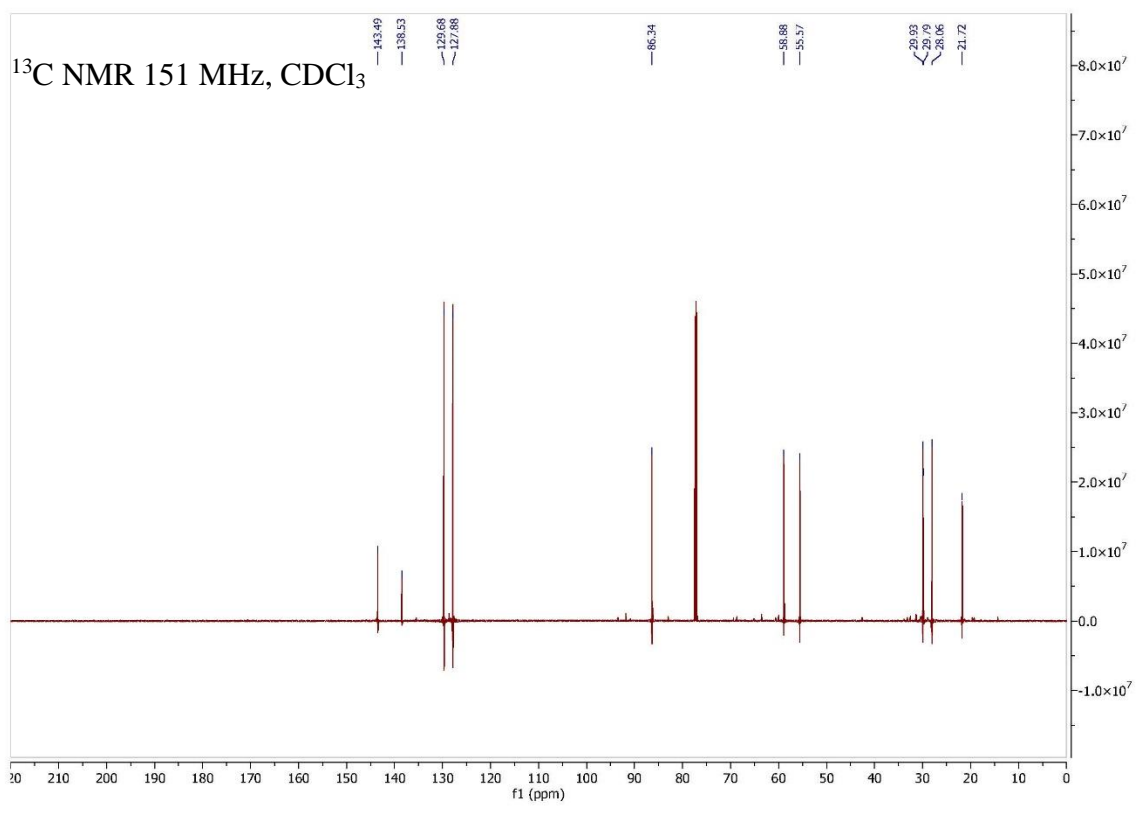
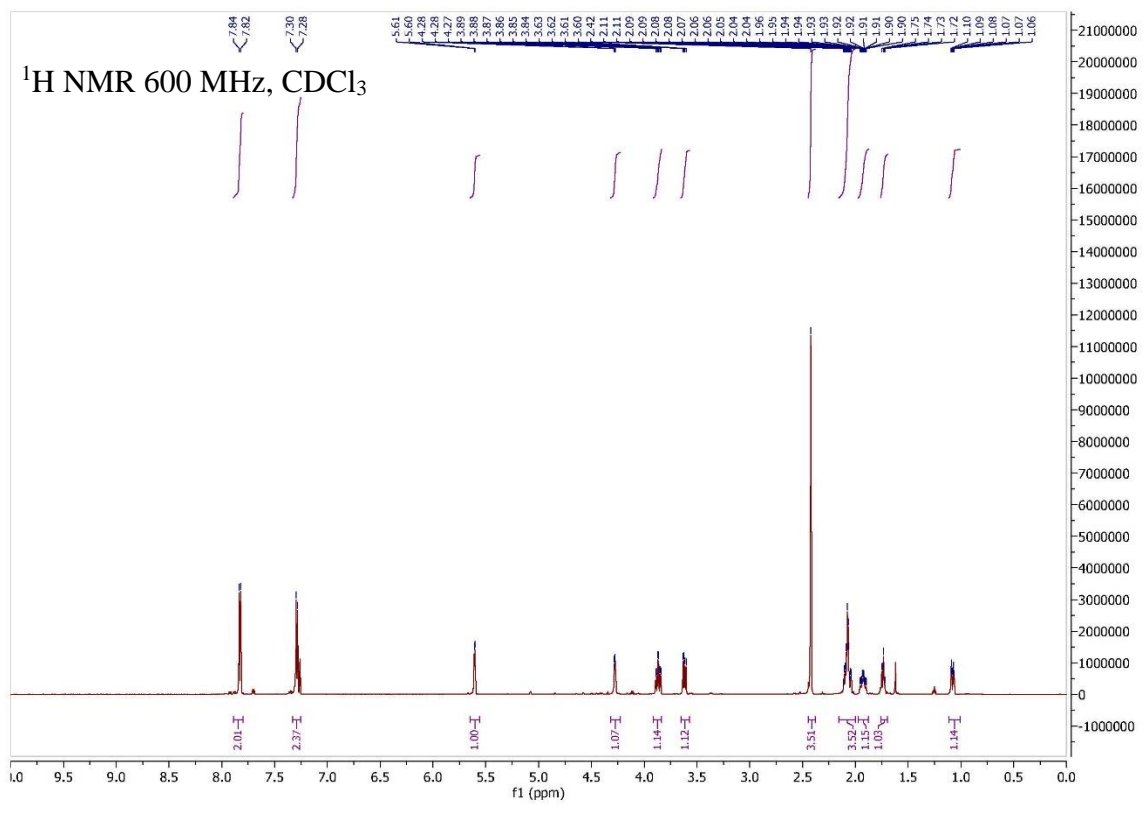
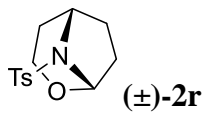


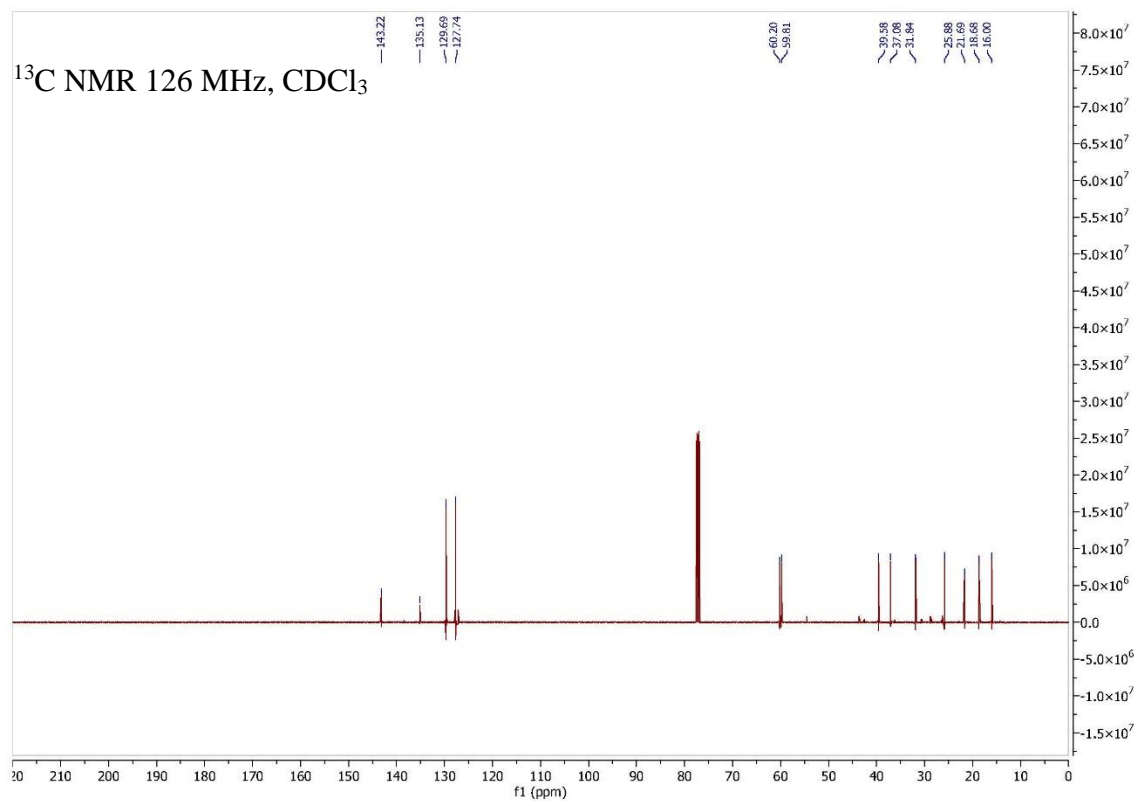
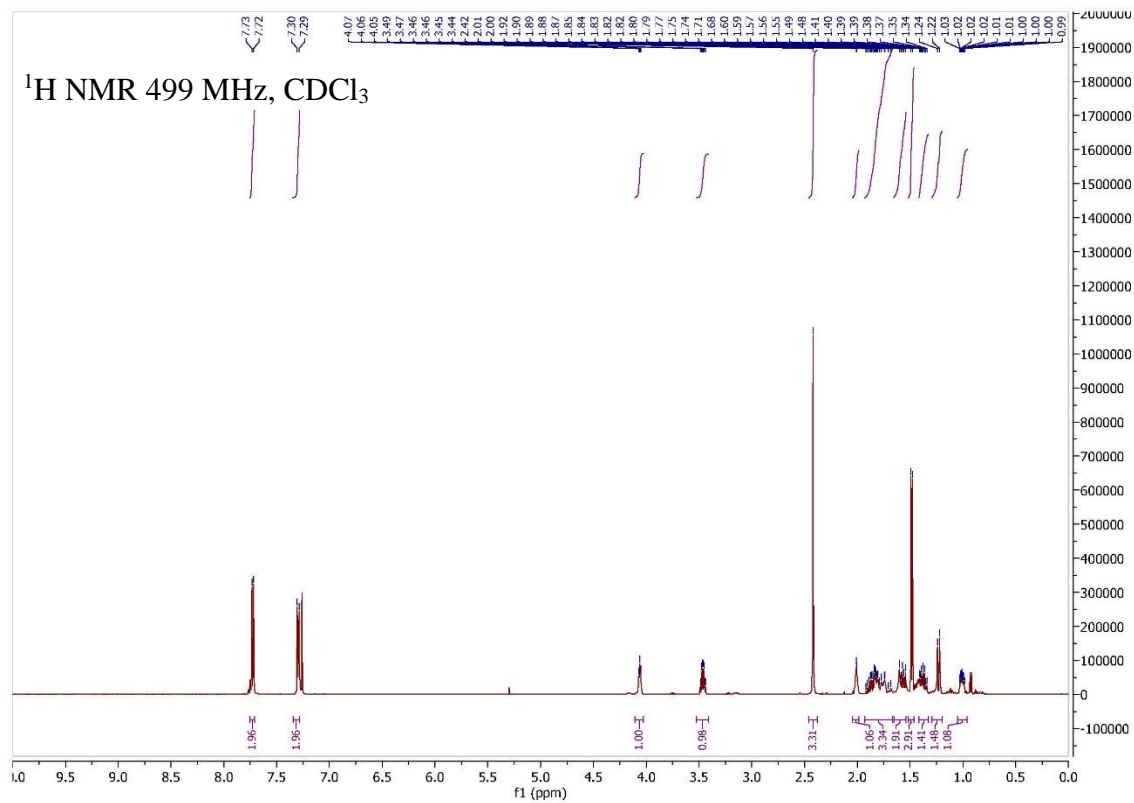
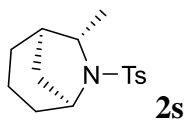


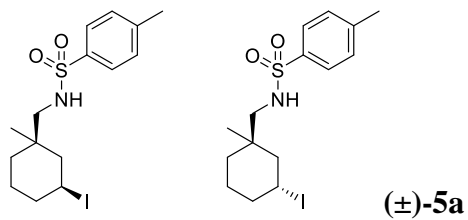




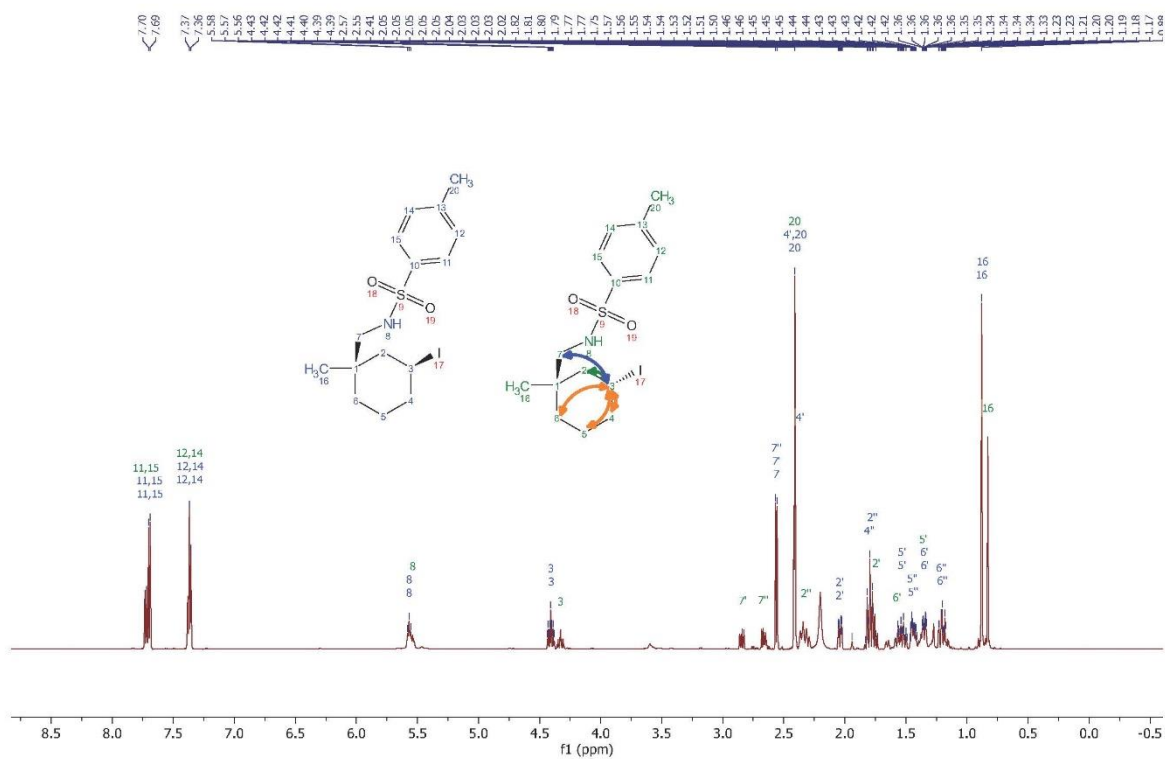




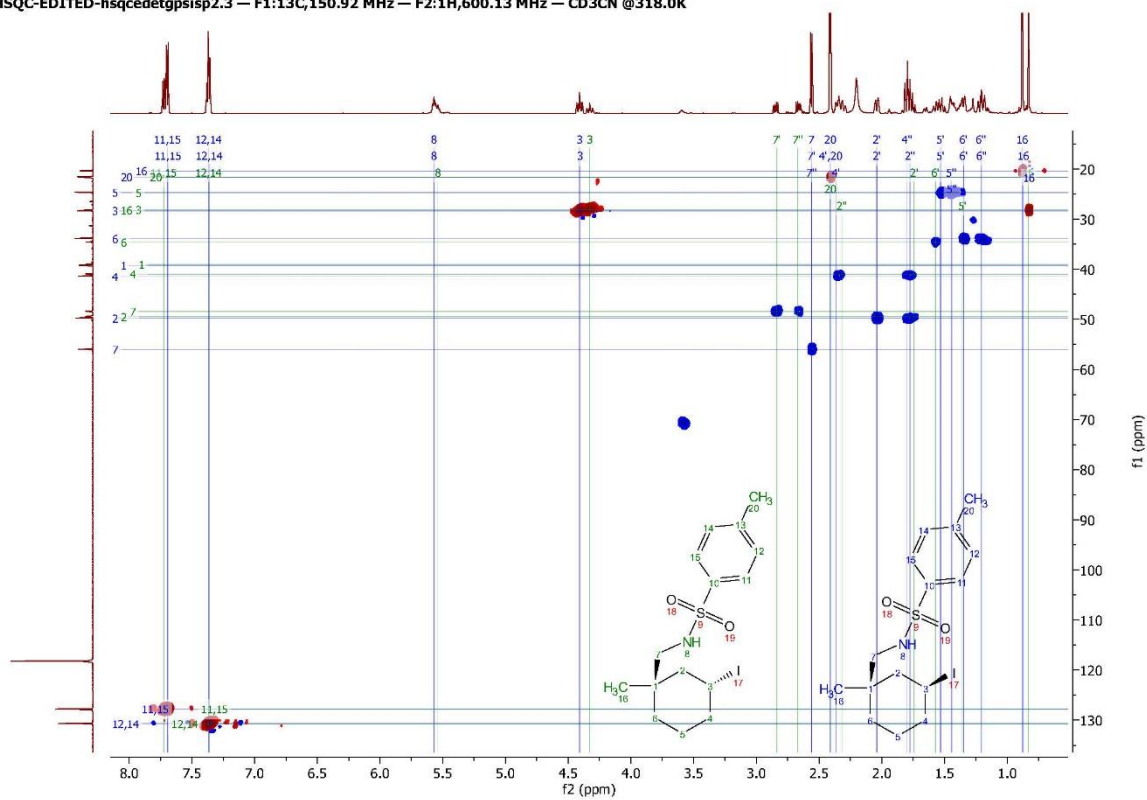




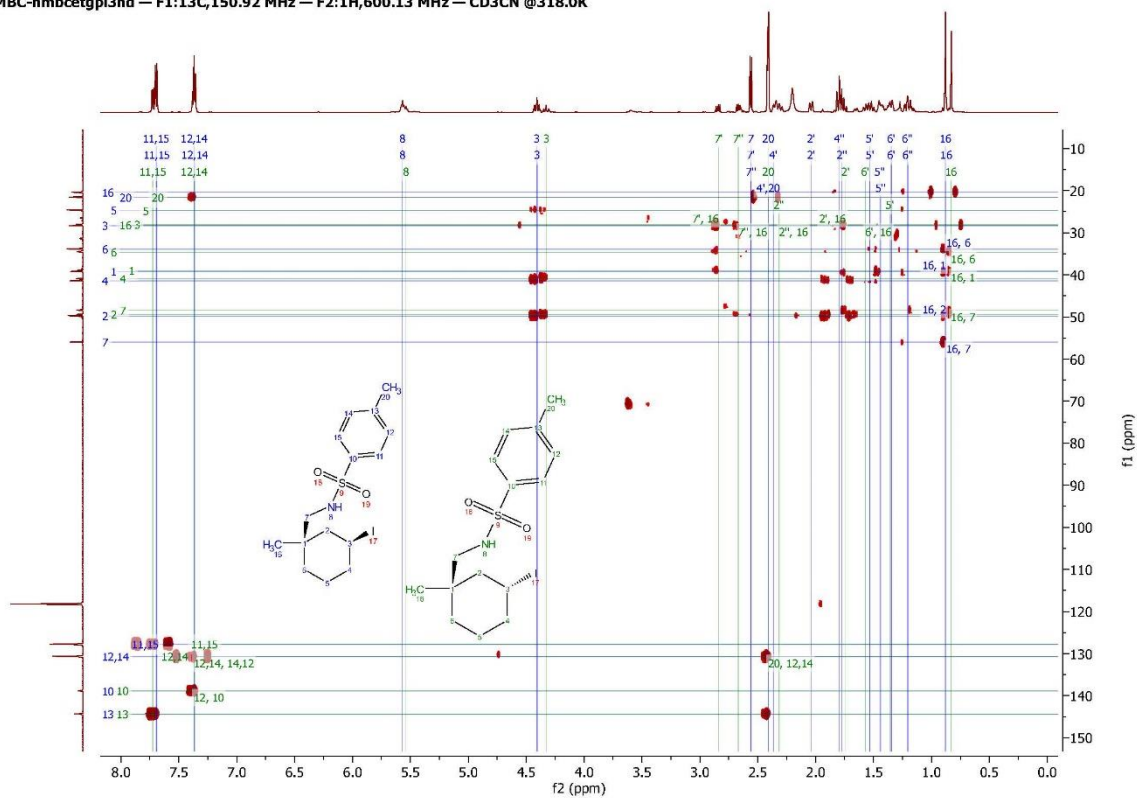
1D-zg30 — 1H,600.13 MHz — CD3CN @318.0K

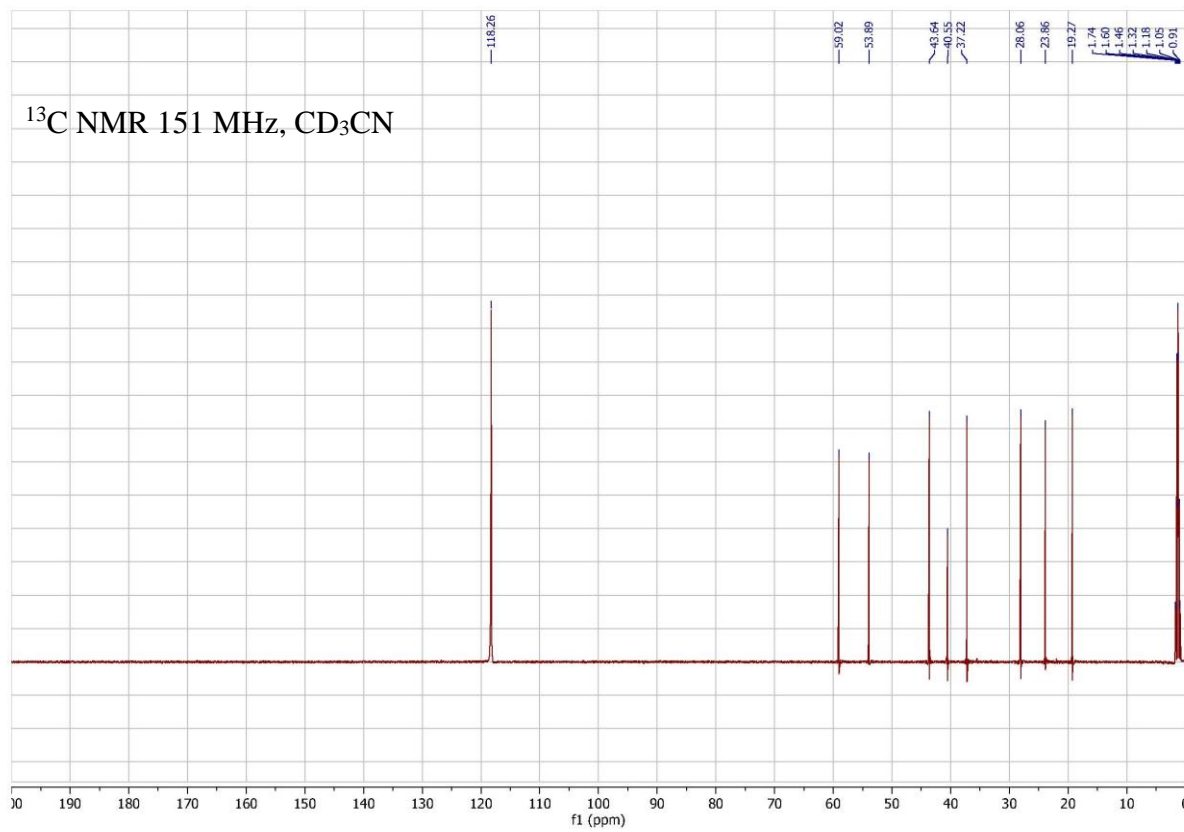
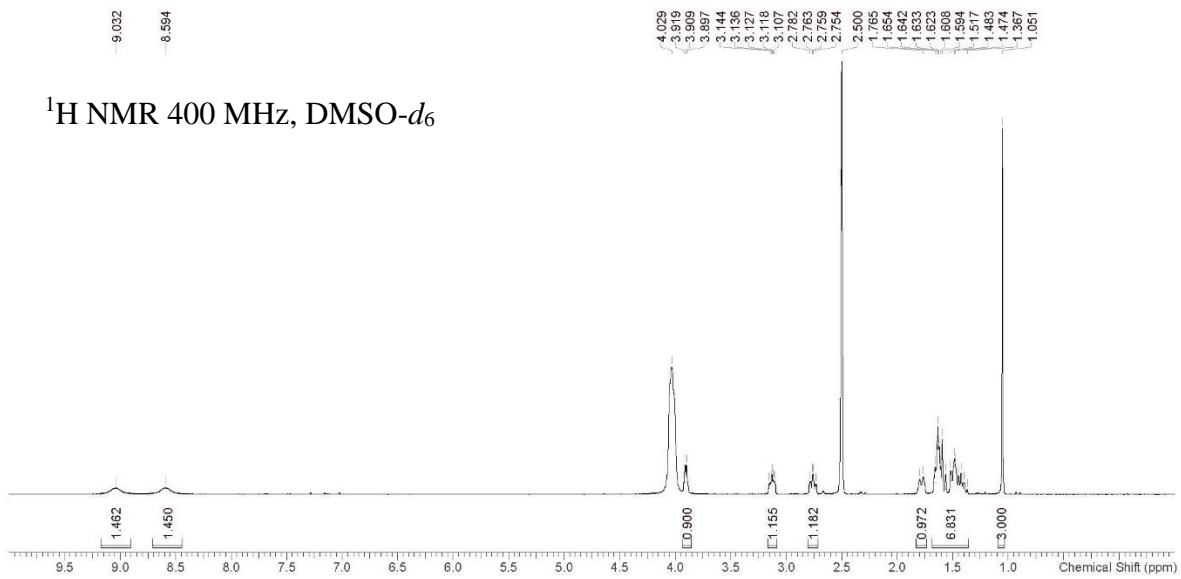
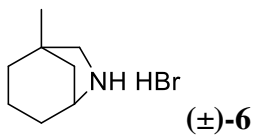


HSQC-EDITED-hsqcedetgpsisp2.3 — F1:13C,150.92 MHz — F2:1H,600.13 MHz — CD3CN @318.0K



HMBC-hmbcetgp13nd — F1:13C,150.92 MHz — F2:1H,600.13 MHz — CD3CN @318.0K





7. Computational Details and Cartesian Coordinates

A. Computational results

For substrate **1g**, on the basis of DFT calculations, the 1,5-HAT, which features an α -heteroatom, has a lower energy barrier (by 4.6 kcal mol⁻¹) as compared to a 1,5-HAT, on the carbocycle **1a** (Fig. S2).

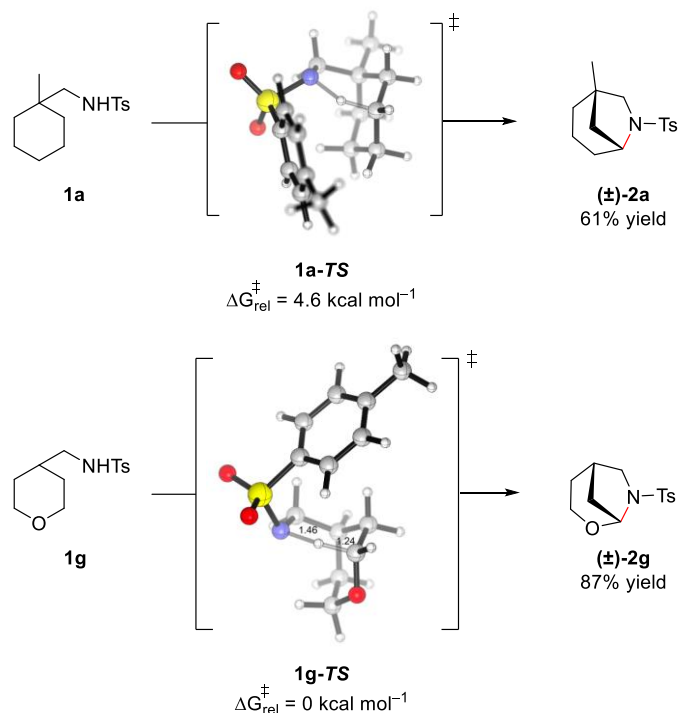


Figure S2. 1,5-HAT transition states for carbocycle **1a** and heterocycle **1g**, modeled at the M06-2X/6-311++G**–SMD(CH₃CN)//M06-2X/6-31G**–SMD(CH₃CN) level of theory.

For substrate **1s**, on the basis of DFT calculations, the 1,5-HAT, which features the methyl group pointing out, has a lower energy barrier (by 3.1 kcal mol⁻¹) as compared to a 1,5-HAT, with the methyl group sterically occluding with the cyclohexane ring (Fig. S3).

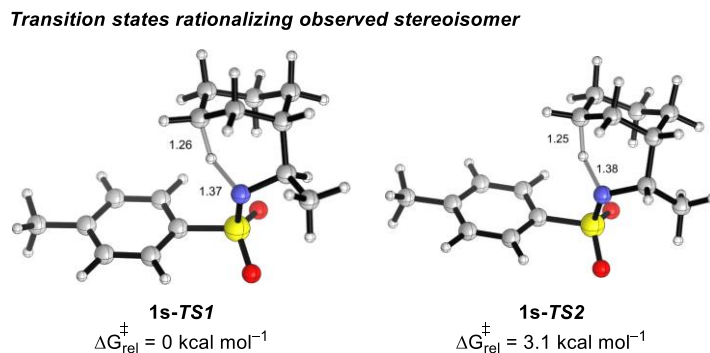


Figure S3. Chirality transfer in C–N bi-cyclization. The transition states were modeled at the M06-2X/6-311++G**–SMD(CH₃CN)//M06-2X/6-31G**–SMD(CH₃CN) level.

B. Computational methods, Cartesian coordinates, and energies

All of the quantum chemical calculations were performed using the *Gaussian 16* program.² Geometry optimizations and frequency calculations were performed at the M06-2X³/6-31G** level of theory with the SMD model⁴ for implicit solvation by acetonitrile.⁵ Single-point (SP) energies were then computed on the optimized geometries at the M06-2X/6-311++G** level with the same SMD model. An “ultrafine” integration grid and a two-electron integral accuracy of 10^{-14} (int=(Acc2E=14,ultrafine)) were used. The stationary points were characterized as minima or transition structures by the presence of only positive eigenvalues or a single negative eigenvalue of the Hessian, respectively. The free energies were calculated for 298.15 K and 1 atm using the quasi-harmonic approximation proposed by Cramer and Truhlar,⁴ in which all of the real vibrational frequencies lower than 100 cm^{-1} were set to 100 cm^{-1} before the thermal corrections were computed with the usual harmonic oscillator model. The illustrations of the optimized geometries in the main text were prepared using *CYLVView*.⁶

² Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. *Gaussian 16*. Gaussian, Inc.: Wallingford, CT.

³ Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Function. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

⁴ Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

⁵ Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Use of Solution-Phase Vibrational Frequencies in Continuum Models for the Free Energy of Solvation. *J. Phys. Chem. B* **2011**, *115*, 14556–14562.

⁶ Legault, C. Y. *CYLVView*, 1.0b. *Université de Sherbrooke*. 2009.

Structure: N-centered radical derived from 1a

Charge = 0, Multiplicity = 2

SCF Energy: -1187.789624 hartree

SCF Energy + ZPVE: -1187.438394 hartree

Enthalpy: -1187.418645 hartree

Free Energy: -1187.485909 hartree

Free Energy with quasiharmonic correction: -1187.483149 hartree

SCF Energy (SP): -1188.01233877 hartree

6 -3.486060 -0.646756 1.285594
6 -2.523720 0.143173 0.397181
6 -1.662424 -0.845294 -0.413503
7 -0.903930 -1.703982 0.464341
16 0.525018 -2.313302 -0.223104
6 1.549713 -0.881448 -0.095047
6 1.912855 -0.194434 -1.249599
6 2.671306 0.965583 -1.122545
6 3.045823 1.446846 0.136115
6 3.829868 2.722179 0.274095
6 2.660547 0.732376 1.280079
6 1.915415 -0.433463 1.176613
8 0.993419 -3.349134 0.688466
8 0.319067 -2.640311 -1.633031
6 -3.331678 1.015329 -0.582844
6 -2.480555 2.004216 -1.386019
6 -1.631578 2.877631 -0.460141
6 -0.765393 2.015540 0.460575
6 -1.625966 1.041890 1.269640
1 -2.944043 -1.282848 1.991812
1 -4.118479 0.038072 1.859549
1 -4.138567 -1.286589 0.680527
1 -1.025422 -0.338336 -1.150192
1 -2.327380 -1.512012 -0.992648
1 1.610577 -0.566167 -2.223287
1 2.972983 1.508376 -2.013398
1 4.654432 2.598919 0.981383
1 3.186655 3.520971 0.658625
1 4.235087 3.044984 -0.686831
1 2.953853 1.096573 2.260536
1 1.624694 -0.989331 2.063137
1 -4.060622 1.584724 0.009951
1 -3.908592 0.367193 -1.254943
1 -3.135971 2.628390 -2.002867
1 -1.822127 1.466762 -2.080697
1 -2.296271 3.501069 0.153898
1 -1.005455 3.558162 -1.047038
1 -0.186347 2.647323 1.143707
1 -0.035624 1.459923 -0.144053
1 -2.279467 1.619381 1.937885
1 -0.995499 0.410509 1.909573

Structure: 1a-TS

Charge = 0, Multiplicity = 2

SCF Energy: -1187.762105 hartree

SCF Energy + ZPVE: -1187.415738 hartree

Enthalpy: -1187.396608 hartree

Free Energy: -1187.463622 hartree

Free Energy with quasiharmonic correction: -1187.459450 hartree

SCF Energy (SP): -1187.98545166 hartree

16	0.118318	1.733017	0.335065
8	0.327048	3.066663	-0.235154
8	-0.300566	1.668127	1.739515
6	3.862620	-0.792130	-0.217938
6	3.101003	-0.898731	0.949824
6	1.963372	-0.118372	1.137404
6	1.595115	0.776540	0.138215
6	2.333769	0.907983	-1.036527
6	3.463768	0.118768	-1.205496
6	5.104883	-1.619280	-0.406478
6	-3.126305	-1.059720	0.957644
6	-1.756926	-1.429022	1.533066
6	-0.937239	-2.260236	0.541272
6	-4.493715	-0.155194	-0.928423
1	-2.520759	1.433345	0.614132
1	-2.797146	1.638907	-1.134032
1	3.401689	-1.600980	1.721925
1	1.370418	-0.198835	2.043237
1	2.027838	1.615092	-1.801286
1	4.048962	0.207450	-2.116421
1	5.102003	-2.492986	0.248739
1	5.198536	-1.955842	-1.442084
1	5.995777	-1.026774	-0.172162
1	-3.659351	-0.395672	1.649270
1	-3.732088	-1.971240	0.860980
1	-1.887483	-1.980508	2.469756
1	-1.204198	-0.514843	1.780256
1	-1.383360	-3.262385	0.441982
1	0.085992	-2.402164	0.903512
1	-0.204565	-2.009425	-1.535650
1	-2.876607	-2.264926	-1.495950
1	-2.233330	-0.874307	-2.386140
1	-4.491033	0.239268	-1.949866
1	-5.065654	-1.088435	-0.921404
1	-5.012281	0.564947	-0.285677
6	-0.935114	-1.614395	-0.825617
6	-2.308738	-1.328348	-1.391401
6	-3.068912	-0.396836	-0.432289
6	-2.346582	0.990216	-0.374705
7	-0.911846	0.916841	-0.691900
1	-0.591374	-0.411605	-0.677044

Structure: N-radical derived from 1g

Charge = 0, Multiplicity = 2

SCF Energy: -1184.376852 hartree

SCF Energy + ZPVE: -1184.077425 hartree

Enthalpy: -1184.059093 hartree

Free Energy: -1184.125452 hartree

Free Energy with quasiharmonic correction: -1184.121010 hartree

SCF Energy (SP): -1184.60924012 hartree

6 2.402758 3.937603 -0.265072

1 1.888924 4.451234 0.551721

1 3.470583 4.162361 -0.172112

1 2.052233 4.345850 -1.214958

16 1.453110 -2.021052 0.068737

8 2.257797 -2.619023 1.126331

8 1.469919 -2.613329 -1.267689

6 2.175397 2.453398 -0.192716

6 1.886047 1.715097 -1.345480

6 1.688304 0.339715 -1.283962

6 1.794958 -0.294362 -0.048034

6 2.084285 0.413530 1.120813

6 2.272381 1.785456 1.036658

6 -3.383623 -0.642498 -0.760093

6 -4.393457 0.381147 -0.253397

8 -3.787935 1.642792 -0.029132

1 -2.606660 -1.210170 1.165147

1 -1.591249 -2.695456 -0.538747

1 -0.748072 -1.324174 -1.273276

1 1.812505 2.224778 -2.301456

1 1.463663 -0.235728 -2.176264

1 2.160523 -0.103624 2.072301

1 2.498681 2.352381 1.935111

1 -2.996246 -0.307455 -1.730965

1 -3.878681 -1.608066 -0.911177

1 -4.853841 0.018373 0.680523

1 -5.189310 0.542157 -0.985412

1 -3.210576 1.218780 1.911279

1 -0.898948 0.559472 1.327021

1 -1.169024 1.012912 -0.364598

6 -2.774065 1.561062 0.958232

6 -1.656488 0.614847 0.536404

6 -2.224962 -0.774438 0.231411

6 -1.147282 -1.707879 -0.324139

7 -0.131772 -1.946133 0.674881

1 -2.395616 2.576556 1.102066

Structure: 1g-TS

Charge = 0, Multiplicity = 2

SCF Energy: -1184.357340 hartree

SCF Energy + ZPVE: -1184.061230 hartree

Enthalpy: -1184.043969 hartree

Free Energy: -1184.106603 hartree

Free Energy with quasiharmonic correction: -1184.103859 hartree

SCF Energy (SP): -1184.59006498 hartree

6	4.509096	-2.075563	-0.127567
1	5.411558	-1.679504	0.350164
1	4.753977	-2.312007	-1.165135
1	4.244024	-3.000458	0.391296
16	-0.030253	1.930507	0.234324
8	0.114723	2.916431	-0.838244
8	-0.133540	2.380862	1.619141
6	3.391198	-1.072277	-0.046265
6	2.687214	-0.894670	1.153065
6	1.667093	0.041893	1.251442
6	1.345531	0.811654	0.132594
6	2.033907	0.663776	-1.068286
6	3.053489	-0.281651	-1.148279
6	-3.431054	-1.230723	-0.976726
6	-3.718335	-0.873289	0.476882
8	-2.783989	-1.463222	1.390309
1	-1.799241	-1.426905	-2.362042
1	-0.538855	0.474442	-1.936760
1	-2.227201	1.019053	-1.986945
1	2.947662	-1.497227	2.018796
1	1.127836	0.182422	2.183365
1	1.782564	1.286067	-1.921205
1	3.596613	-0.405171	-2.080760
1	-3.686324	-2.283346	-1.141959
1	-4.081479	-0.627481	-1.618631
1	-4.700922	-1.236209	0.784375
1	-3.689977	0.214132	0.619614
1	-0.818422	-1.594057	1.858540
1	-0.028543	-1.642241	-0.521074
1	-1.306730	-2.873182	-0.395371
6	-1.464701	-1.285009	1.034428
6	-1.098497	-1.797536	-0.342498
6	-1.956511	-1.033513	-1.353512
6	-1.497895	0.441970	-1.405562
7	-1.411822	1.059965	-0.074044
1	-1.320491	-0.069138	0.844916

Structure: 1s-TS1

Charge = 0, Multiplicity = 2

SCF Energy: -1187.762728 hartree

SCF Energy + ZPVE: -1187.415973 hartree

Enthalpy: -1187.396811 hartree

Free Energy: -1187.464393 hartree

Free Energy with quasiharmonic correction: -1187.459816 hartree

SCF Energy (SP): -1187.98537965 hartree

16 0.046905 1.464088 0.646748
8 -0.033848 2.895525 0.339955
8 0.456032 1.096901 2.007107
6 -3.913752 -0.566479 -0.295671
6 -3.098465 -1.042147 0.736826
6 -1.895578 -0.414802 1.045789
6 -1.512455 0.698739 0.304210
6 -2.300875 1.196304 -0.730685
6 -3.499505 0.557227 -1.022266
6 -5.227228 -1.230910 -0.606079
6 3.346419 -1.415928 0.634397
6 2.042917 -1.869646 1.298222
6 1.110415 -2.559234 0.296253
1 4.088253 -0.340627 -1.069719
6 3.015569 1.914532 -1.201628
1 2.662486 1.048429 0.747601
1 -3.410602 -1.912840 1.306212
1 -1.263353 -0.778216 1.850313
1 -1.980830 2.068010 -1.292739
1 -4.126004 0.932904 -1.826311
1 -5.244605 -2.260528 -0.242354
1 -5.422098 -1.233299 -1.681387
1 -6.049641 -0.691442 -0.124083
1 3.955221 -0.852771 1.350883
1 3.930704 -2.298522 0.342725
1 2.264920 -2.543930 2.131594
1 1.527921 -0.999139 1.722992
1 1.532257 -3.536040 0.011225
1 0.131946 -2.755574 0.746416
1 0.156598 -2.039789 -1.634982
1 2.814350 -2.264801 -1.926689
1 2.082134 -0.772744 -2.536759
6 0.961746 -1.734207 -0.962509
6 2.267683 -1.358700 -1.630443
6 3.113696 -0.566025 -0.623807
6 2.452093 0.813349 -0.304764
7 0.989839 0.762806 -0.532598
1 0.648881 -0.563231 -0.622930
1 2.870923 1.653609 -2.254879
1 4.085970 2.038835 -1.013458
1 2.511659 2.864794 -1.007016

Structure: 1s-TS2

Charge = 0, Multiplicity = 2

SCF Energy: -1187.758280 hartree

SCF Energy + ZPVE: -1187.411230 hartree

Enthalpy: -1187.392238 hartree

Free Energy: -1187.459153 hartree

Free Energy with quasiharmonic correction: -1187.454913 hartree

SCF Energy (SP): -1187.98083212 hartree

16	0.020845	1.474269	-0.369399
8	-0.072129	2.857294	0.112168
8	0.456613	1.279982	-1.757285
6	-3.999652	-0.607826	0.126968
6	-3.172960	-0.907122	-0.959807
6	-1.948222	-0.266210	-1.126310
6	-1.554191	0.679478	-0.185879
6	-2.354868	0.998713	0.909097
6	-3.574408	0.351290	1.056452
6	-5.335377	-1.281077	0.288426
6	3.543295	-1.119528	-0.408590
6	2.398592	-1.483503	-1.357864
6	1.389225	-2.423783	-0.689069
1	3.953907	-0.437281	1.580738
6	3.016406	1.781985	-0.013939
1	2.443359	1.180214	1.956170
1	-3.492662	-1.649097	-1.685714
1	-1.307614	-0.491190	-1.973098
1	-2.026078	1.741483	1.629255
1	-4.209531	0.589791	1.904974
1	-5.384653	-2.205482	-0.290902
1	-5.534073	-1.512171	1.338082
1	-6.138526	-0.622840	-0.059916
1	4.214662	-0.398360	-0.885031
1	4.143622	-2.017544	-0.211203
1	2.802195	-1.949454	-2.262780
1	1.877140	-0.572521	-1.673682
1	1.841752	-3.419662	-0.560356
1	0.504710	-2.556737	-1.320330
1	0.131332	-2.404063	1.134129
1	2.731350	-2.570288	1.771697
1	1.802558	-1.300796	2.586962
6	0.995568	-1.913704	0.679545
6	2.159880	-1.645553	1.610749
6	3.067725	-0.595143	0.956141
6	2.344389	0.792007	0.935074
7	0.880186	0.624461	0.762344
1	0.641127	-0.720087	0.552195
1	2.930379	1.472030	-1.057278
1	2.574919	2.776323	0.089319
1	4.077028	1.849844	0.245715