Photochemical formal (4+2)-cycloaddition of imine-substituted bicyclo[1.1.1]pentanes and alkenes

Supporting Information

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I. General Methods

Unless otherwise noted, all reactions were run under a nitrogen or argon atmosphere in flame-dried or oven-dried glassware. Reactions were stirred using Teflon-coated magnetic stir bars. Reactions were monitored by ^{1}HNMR or by thin layer chromatography (TLC) using glass-backed plates pre-coated with 230–400 mesh silica gel (250 μm thickness) with fluorescent indicator F_{254}, available from EMD Millipore (cat. #: 1.05715.0001). Plates were visualized by irradiation with UV light and with $KMnO_4$ stain (with gentle heating). Products were purified by flash column chromatography using the solvent systems indicated. Column flash chromatography was performed manually or via automated column chromatography using Biotage Selekt or Biotage Isolera purification systems. Silica gel was purchased from SiliCycle, specifically using SiliaFlash P60, 40-63 μm, 230-400 mesh (cat. #: R12030B).

Organic solvents (acetonitrile, dichloromethane, diethyl ether, dimethylformamide, dimethyl sulfoxide, methanol, tetrahydrofuran, toluene) and amine bases (triethylamine) were purified prior to use using a Phoenix Solvent Drying System (for organic solvents, available from JC-Meyer Solvent Systems) or PureSolv Micro amine drying columns (for amine bases, available from Innovative Technology/Inert) under positive argon pressure. Ethyl acetate used as a reaction solvent was distilled before use and stored over activated 4Å molecular sieves. All solvents were supplied by Fisher Scientific. Unless otherwise noted, all other reagents were used as received from commercial suppliers, typically Sigma-Aldrich, Ambeed, Inc., Synthonix, Inc., or Enamine, Ltd.

NMR spectra were measured on a Varian MR400 (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{19}F at 376 MHz), a Varian Vnmrs 700 MHz (^{1}H at 700 MHz, ^{13}C at 176 MHz), or Bruker Ascend 500 (^{1}H at 500 MHz, ^{13}C at 126 MHz) magnetic resonance spectrometer, as noted. ^{1}H chemical shifts are reported relative to the residual solvent peak (chloroform = 7.26 ppm, DMSO = 2.50 ppm, methanol = 3.31 ppm) as follows: chemical shift (δ) (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, bs = broad singlet, app. = apparent], integration, coupling constant(s) in Hz. ^{13}C chemical shifts are reported relative to the deuterated solvent ^{13}C signals ($CDCl_3$ = 77.16 ppm, DMSO-d_6 = 39.52 ppm, methanol-d_4 = 49.00). ^{19}F chemical shifts are reported relative to an internal standard (α,α,α-trifluorotoluene = -63.72 ppm).

Infrared spectra were recorded using a PerkinElmer Frontier FT-IR spectrometer equipped with the PerkinElmer universal ATR sampling accessory. Peaks are reported in wavenumbers (cm^{-1}).

High resolution mass spectra were recorded with an Agilent 1290 Infinity II UPLC with a TOF 6230B Dual AJS Ion source utilizing either positive or negative mode electrospray ionization (ESI), or at the Mass Spectrometry Facility at the Department of Chemistry of the University of Michigan in Ann Arbor, MI either on an Agilent Q-TOF HPLC-MS with positive or negative ion mode electrospray ionization (ESI) or on a Micromass AutoSpec Ultima magnetic sector mass spectrometer utilizing either positive ion mode ESI or electron impact ionization (EI). We thank Dr. James Windak and Dr. Hye Kyong Kweon at the University of Michigan Department of Chemistry instrumentation facility for collecting some of the mass spectra. UV/VIS measurements were obtained on a Varian Cary-50 spectrophotometer.

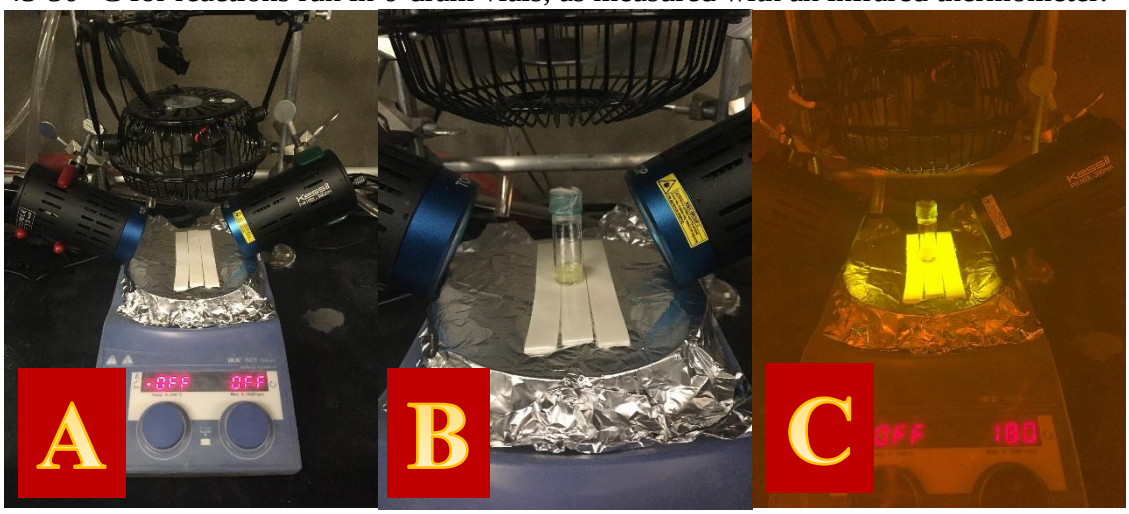
II. Equipment for Photochemistry

II.A. Lighting and Safety Materials

The standard photochemical procedure utilizes two 390 nm LED lamps available from Kessil (PR160L-390nm; https://www.kessil.com/science/PR160L.php). Alternative wavelengths tested were chosen from the remaining Kessil PR160L series (370 nm, 456 nm) or PR160 series (427 nm, 440 nm, 525 nm). Reactions were cooled with a fan (Westpointe, 4-inch personal fan https://www.hardwareandtools.com/westpointe-fe10-cd-homepointe-hi-velocity-4-inch-fan-ucgb-9511.html). Reactions were performed behind plastic guards (provided by Ann Arbor Plastics) wrapped in orange film to provide eye protection during prolonged irradiation (film purchased from UV Process Supply, Amber UV filter film; https://www.uvprocess.com/c3/1785-amber-uv-filter-films.html).

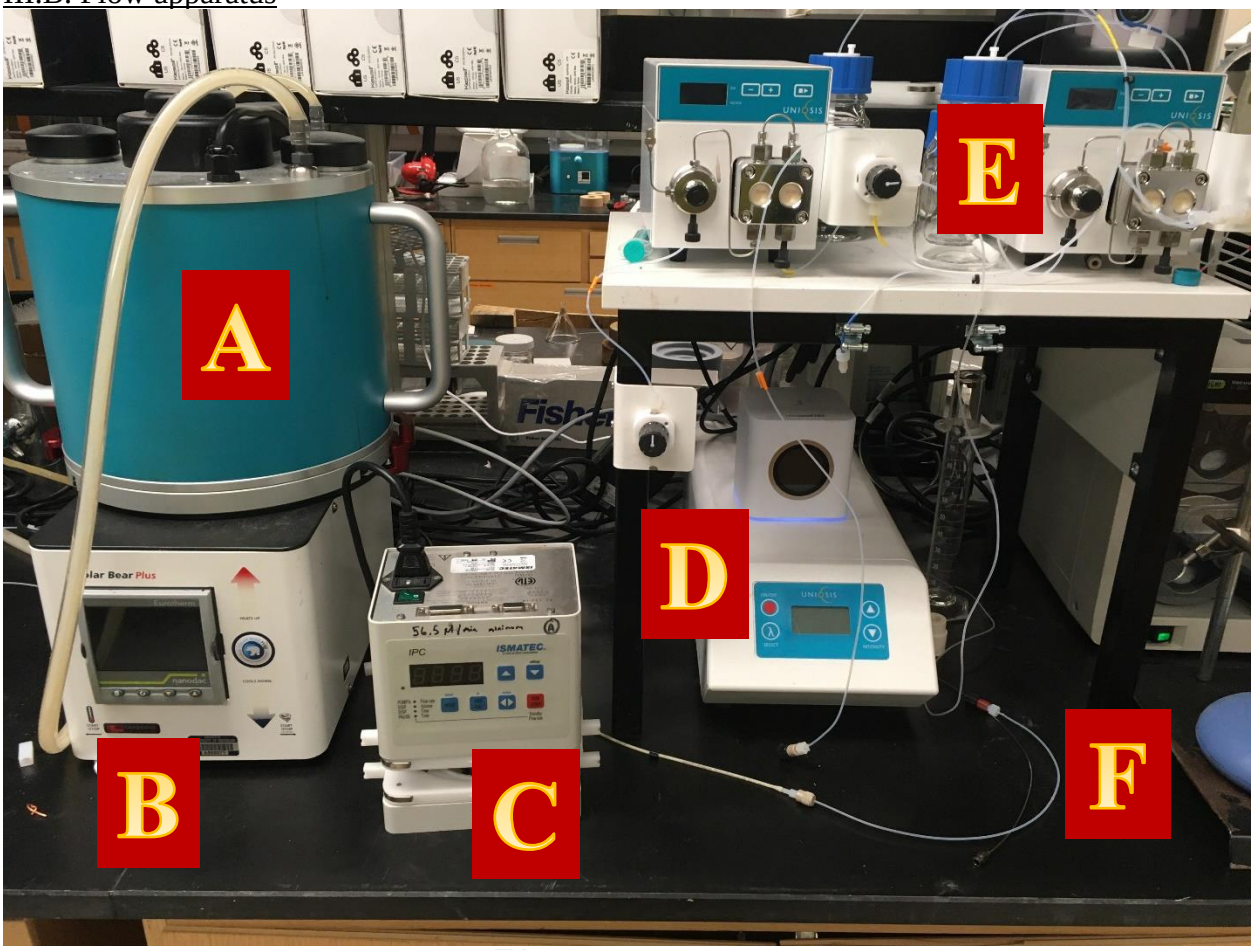
II.B. Batch apparatus

Reactions were performed on a magnetic heat-stir plate covered in aluminum foil and double-sided foam tape. Lamps were placed ~4 cm away from the vial on opposite sides and angled toward the bottom of the vial. Cooling was provided by a fan placed ~3 cm above the top of the reaction vial. The entire apparatus was placed behind an amber plastic shield and the lamps were turned to their maximum intensity (100%) for the entirety of the reaction time. Under these conditions, external vial temperature stabilized between 35-40 °C for reactions run in 1-dram vials or 2-dram vials and 45-50 °C for reactions run in 6-dram vials, as measured with an infrared thermometer.



SI Figure 1: A. Photochemical reaction setup. B. Reaction before irradiation. C. Reaction during irradiation behind amber safety film.

III.B. Flow apparatus



SI Figure 2: A. Uniqsis PhotoSyn™ LED housing with water cooling lines. B. Uniqsis PolarBearPlus Flow™ reactor base. C. Ismatec IPC-04 peristaltic pump. D. Uniqsis PhotoSyn™ LED controller unit. E. Uniqsis pumps (not used). F. Pump intake tube with Luer-Lok fitting for needles.

Flow reactions were performed using components purchased from Uniqsis and Ismatec. Specifically, the Uniqsis PhotoSyn™ LED Photoreactor was used in conjunction with the Uniqsis PolarBearPlus Flow™ reactor base (for precise temperature control). The PolarBearPlus Flow™ was controlled using Uniqsis Flow Lab software. The LEDs of the Photosyn reactor were cooled by a constant flow of tap water. A 10 mL Uniqsis PFA coil reactor (part number UQ2503; PFA coil dimensions were 1.0 mm inner diameter and 1/16” inch outer diameter) was used as the reaction vessel. Material was drawn through a needle and pumped through the system by an IPC-04 Ismatec peristaltic pump (Model No.: ISM930C, 4 channel pump).

III. Reaction Optimization

General procedure for optimization: To an oven-dried 1-dram vial was added the specified amount of imine **2a**, 2,2'-dipyridyldisulfide (1 mol %) (when applicable), the specified amount of styrene (**3**), and the specified amount of solvent (when applicable). The vial was sealed with cap containing a Teflon-lined septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles (when applicable). The cap was further sealed with Parafilm and was either heated in the absence of light or subjected to irradiation with the specified light source in the batch apparatus configuration for the specified amount of time (for full apparatus details, see the above section II. Equipment for Photochemistry). The crude reaction mixture was diluted with $CDCl_3$ and a known amount of 1,3,5-trimethoxybenzene was added. The amounts of **2a**, **4a**, and **5** present in the samples were determined by ^{1}HNMR. A T_1 relaxation delay of 25 seconds was used during data acquisition to ensure meaningful integrations.

Specifically, the following peaks were considered for analysis:

1,3,5-trimethoxybenzene: ~6.08 (s, 3H)
4a: 3.48 (app. t, J = 7.3 Hz, 1H)
2a: 2.61 (s, 1H)
5: 3.11 (d, J = 6.6 Hz, 2H)

The 1,3,5-trimethoxybenzene internal standard was assumed to be 100% pure by mass.

IV. General Comments and Additional Experiments

IV.A. NMR/Structure determination

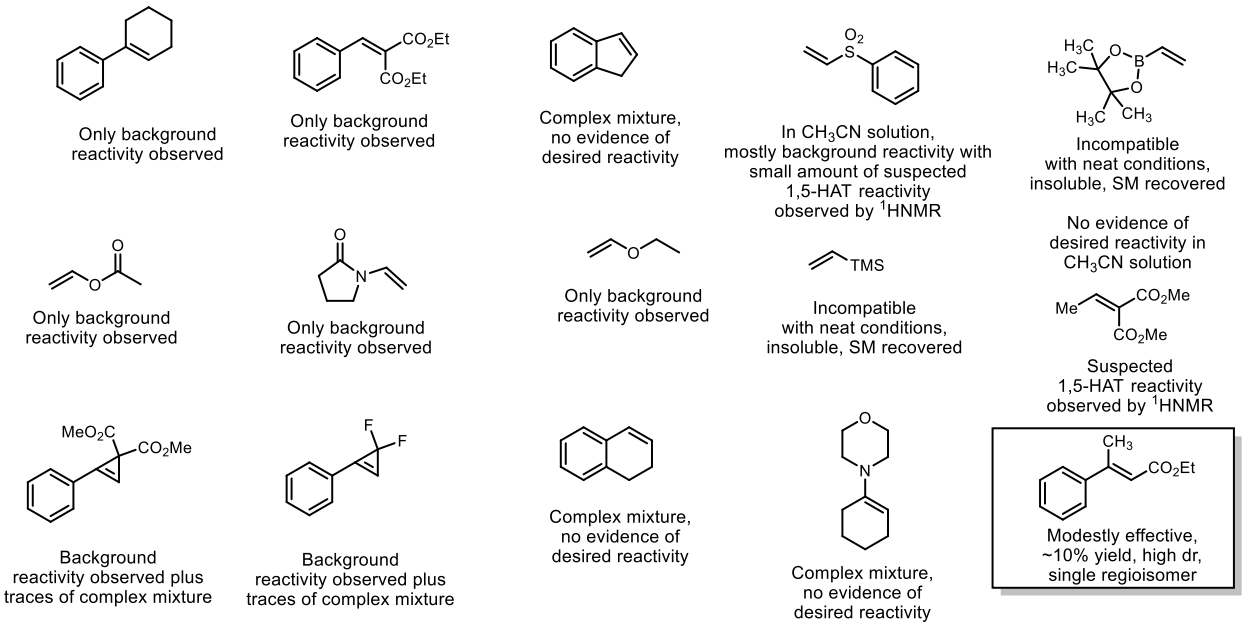
Complete assignments of the ^{1}H and ^{13}C signals were made for selected compounds (**SI-1**, **4h**, **4u**, **7c**, **8b**, **17, and 4af**) on the basis of ^{1}H, ^{13}C, HSQC, HMBC, COSY, and NOESY experiments and are tabulated below the corresponding experimental procedures. Images of the relevant spectra are also included herein. All other structural assignments were made by analogy and the corresponding peaks were not explicitly assigned. In the case of styrene-derived cycloadducts and derivatives thereof, strong correlation is observed between the benzylic hydrogen (diagnostic peak, apparent triplet ~3+ ppm) and the inward-facing hydrogen of the nearby bridging methylene in the NOESY experiment. Consideration of NOESY and HSQC experiments allow the assignment of the remaining methylene bridge proton signals. The benzylic hydrogen is also visibly correlated with the hydrogens of an adjacent methylene in the COSY experiment. In the case of cycloadducts and their derivatives derived from 1,2-disubstituted alkenes, a characteristic doublet and apparent quartet are observed, corresponding to the two formerly olefinic hydrogens contributed by the alkene. The assignment of *trans* stereochemistry was made on the basis of NOESY experiments (the two aforementioned peaks are correlated to *different* methylene bridges). The full set of NMR experiments for each completely assigned compound is consistent with the structure assigned. Notably, the COSY spectra of the cycloadducts and derivatives are rather correlation-dense in the "methylene window" containing the majority of the Csp^3-H peaks, a factor likely attributable to the rigid and densely packed nature of the bicyclo[3.1.1]heptan-1-amine ring system. Zoomed-in views of the spectra are superimposed on the full spectra throughout this SI for the reader's benefit.

IV.B. Scope screening strategy

Identification of promising alkene substrates is straightforward. Since the imines are excellent at ionizing via protonation, mass spectrometric analysis of crude reaction mixtures (positive ion mode ESI) easily shows whether intramolecular reactivity occurred. However, since the formal (4+2)-cycloaddition product and the 1,5-HAT product for a particular reaction are isomeric, crude NMR analysis is a more valuable tool in assessing reaction outcome. The rotational symmetry of the bicyclo[1.1.1]pentane ring system leads the starting materials for cycloaddition to have very simple NMR spectra in the region below 100 ppm. The symmetry-breaking from formal cycloaddition leads to highly diagnostic set of ^{13}C peaks corresponding to the bicyclo[3.1.1]heptane ring system that span a range from ~70 to ~20 ppm. Particularly diagnostic is the change in chemical shift for the bridge-head carbon bearing the imine functionality, which moves from ~60 ppm to ~70 ppm upon successful formal (4+2)-cycloaddition. The symmetry breaking is also notable in the crude ^{1}HNMR spectrum, particularly in the case of styrene-derived cycloadducts, which show a characteristic apparent triplet at ~3.5 ppm. The 1,5-HAT products have characteristic olefinic signals in both ^{1}H and ^{13}CNMR. TLC analysis was not especially valuable in assessing reaction performance due to the formation of many highly absorbing byproducts of R_f values comparable to species of interest. Of all the above strategies for reaction outcome determination, crude ^{13}C NMR analysis on a high-field instrument proved the most useful in assessing reaction performance (in our hands).

IV.C. Alkenes showing poor performance

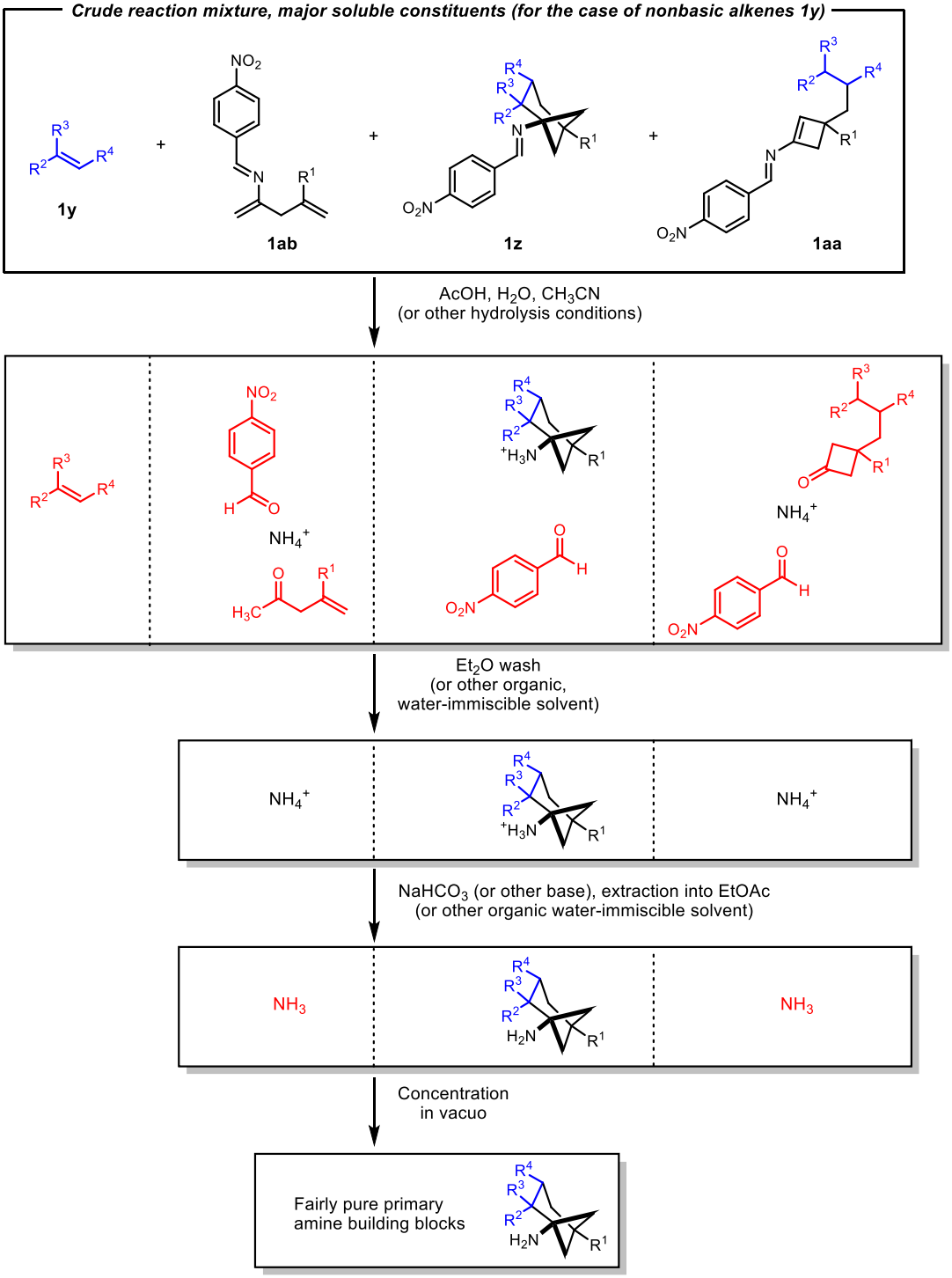
Substrates that failed to showed little to no desired reactivity



SI Figure 3: Some alkenes were poor performers due to slow radical trapping, competitive side reactions, or poor solubility.

Only alkenes that react rapidly with nucleophilic radicals are capable of trapping the short-lived radical intermediate we propose is formed upon bicyclo[1.1.1]pentane opening. Electron-rich monosubstituted alkenes such as N-vinyl pyrrolidone, vinyl acetate, and ethyl vinyl ether were not effective, with their crude reaction mixtures showing only unimolecular background reactivity. 1,2-Disubstituted alkenes also show relatively poor performance when compared to monosubstituted alkenes. We attribute this to steric effects. Nonetheless, cinnamates were modestly effective radical traps, giving synthetic useful yields and high diastereoselectivity, as detailed in the manuscript. Tri-substituted, similarly activated alkenes predictably showed even worse performance. We examined several cyclopropenes, that in principle are activated for radical addition by strain, but nonetheless observed only trace amounts of products indicative of radical capture. Notably, we are confident we *have* observed the desired reactivity with a single tri-substituted alkene, namely, ethyl trans-beta-methyl cinnamate. However, we have been unable to separate the cycloadduct or its corresponding product from significant impurities, preventing inclusion of a proper procedure and characterization in this manuscript. Several solid alkenes, particularly vinyl N-heterocycles, also showed low yields that we attribute to poor solubility in the limited selection of solvents examined. Substrate-specific solvent screening may be appropriate in such cases. Further studies interrogating the scope of the formal cycloaddition will be reported in due course.

IV.D. Hydrolysis strategy



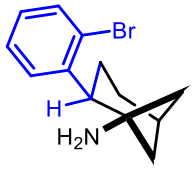
SI Figure 4: Differing carbon atom oxygen states between the formal cycloadducts **1z** and byproducts **1aa** and **1ab** allow for convenient extractive purifications (as long as alkene **1y** is non-basic). *Note:* the *optional* additive 2,2'-dipyridyl disulfide (Aldrithiol^{TM}) is basic and may not be effectively purged by this work-up. In future applications of this chemistry where chromatography is undesirable, exclusion of 2,2'-dipyridyl disulfide may be preferred.

IV.E. Synthesis of pyrazole carboxamide SDHI analogue library

IV.E.1: 2-bromostyrene case

Though initially successful, we encountered reproducibility and isolation challenges when repeating the formal (4+2)-cycloaddition with 2-bromostyrene. However, we were able to obtain primary amine **SI-1** by the following procedure involving a chromatographic purification and hydrolysis of the slightly impure imine intermediate. A complete 2D NMR analysis was performed, and all proton and carbon peaks were assigned (vide infra).

Compound (±)-**SI-1**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 1-dram vial equipped with a stir bar was added **2a** (432 mg, 2.00 mmol, 1 equiv), 2,2'-dipyridyldisulfide (4.4 mg, 0.02 mmol, 0.01 equiv), and 2-bromostyrene (1.88 mL, 15.0 mmol, 5 equiv). The vial was sealed with a cap containing a Teflon-lined septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 16 hours with two 390 nm PR160L Kessil lamps at maximum intensity positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. The mixture was diluted with chloroform and concentrated onto celite (3 g), which was dry-loaded atop a silica column that was pre-neutralized (with 3 column volumes of 5% ethyl acetate : 94% hexanes : 1% Et_3N). Elution with 5-40% ethyl acetate in hexanes gave an intractable mixture containing predominantly the desired formal cycloadduct as a yellow oil. This yellow oil was transferred to a 4-dram vial equipped with a magnetic stir bar and was sequentially diluted with acetonitrile (6 mL), water (2 mL), and acetic acid (2 mL). The headspace was flushed with argon, the vial was capped, and the mixture was allowed to stir at room temperature for 48 hours. The reaction mixture was diluted with 0.5 M aqueous hydrochloric acid (40 mL) and washed with diethyl ether (4 x 33 mL). The aqueous layer was neutralized with saturated aqueous sodium bicarbonate (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined ethyl acetate fractions were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (±)-**SI-1** (136.6 mg, 0.513 mmol, 26%) as a yellow oil.

Appearance: yellow oil

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.55 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.28 (app. t, *J* = 7.5 Hz, 1H), 7.07-7.03 (m, 1H), 3.68 (dd, *J* = 9.8, 7.6 Hz, 1H), 2.37 (app. t, *J* = 8.8 Hz, 1H), 2.30-2.25 (m, 1H), 2.15-2.06 (m, 2H), 1.94-1.88 (m, 1H), 1.85-1.77 (m, 1H), 1.76-1.70 (m, 1H), 1.67 (dd, *J* = 9.2, 6.7 Hz, 1H), 1.64 (app. t, *J* = 10.6 Hz, 1H), 1.56 (bs, 2H) ppm

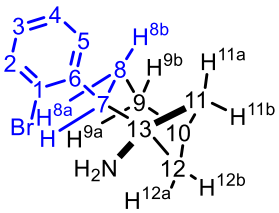
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 144.0, 133.3, 127.8, 127.8, 127.6, 125.9, 58.6, 49.6, 48.0, 36.2, 28.5, 27.5, 27.0 ppm

IR (neat): 3377, 3062, 2941, 2857, 1606, 1565, 1520, 1467, 1451, 1435, 1344, 1318, 1256, 1212, 1181, 1162, 1117, 1074, 1048, 1020, 964, 929, 885, 858, 746, 726, 692, 666 cm^{-1}

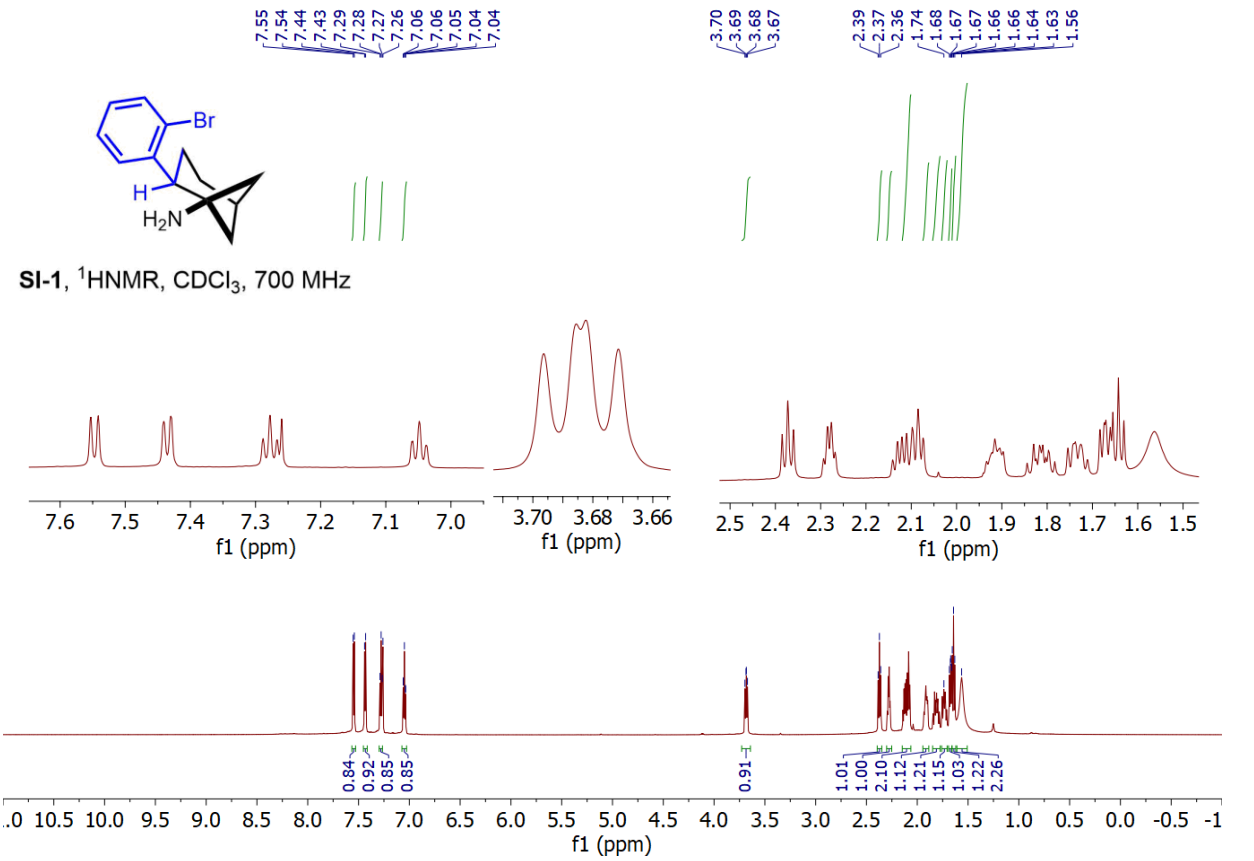
HRMS (ES+, m/z) calculated for $C_{13}H_{17}BrN^{+}$: 266.0539, Found: 266.0540

R_f = 0.55 (50% ethyl acetate : 49% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV-active

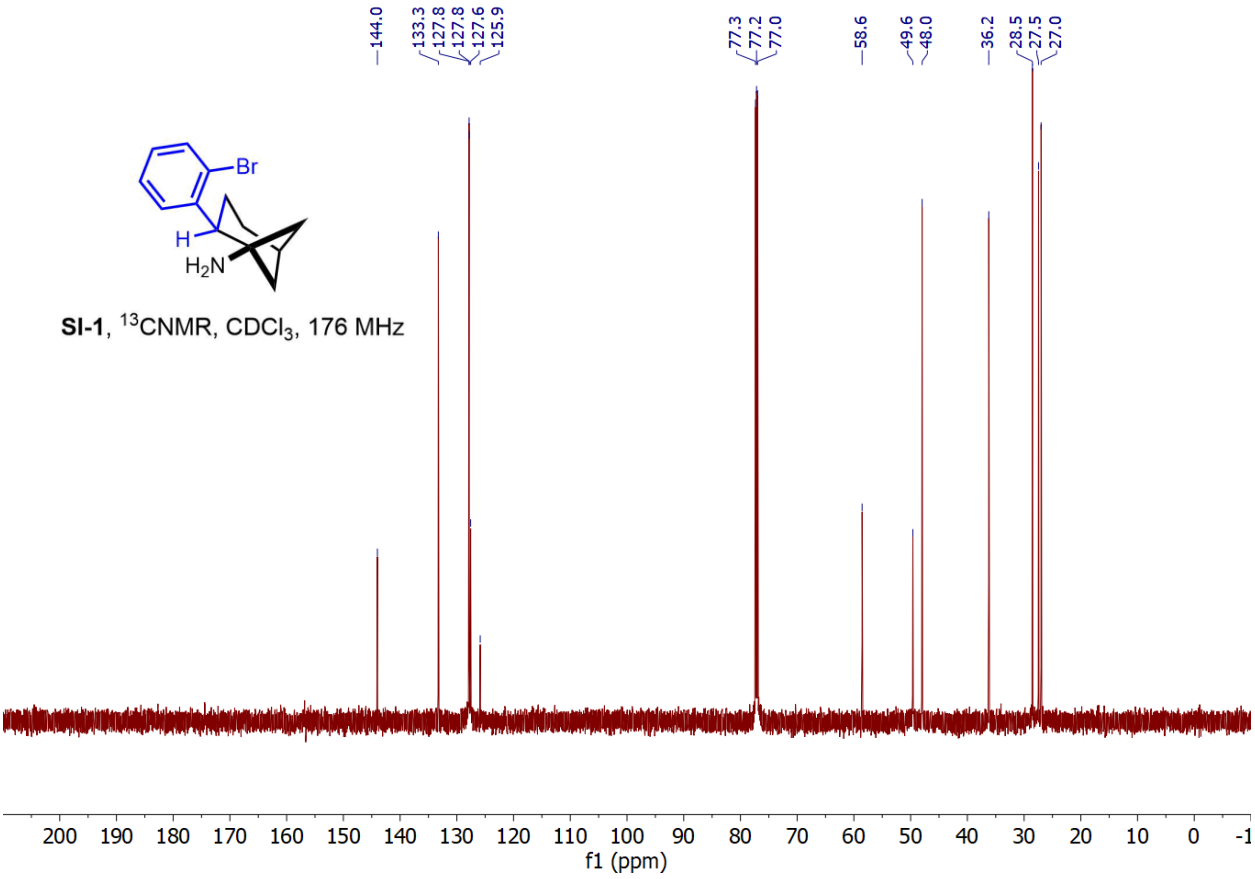
Complete assignment of ^{1}H and ^{13}C NMR signals



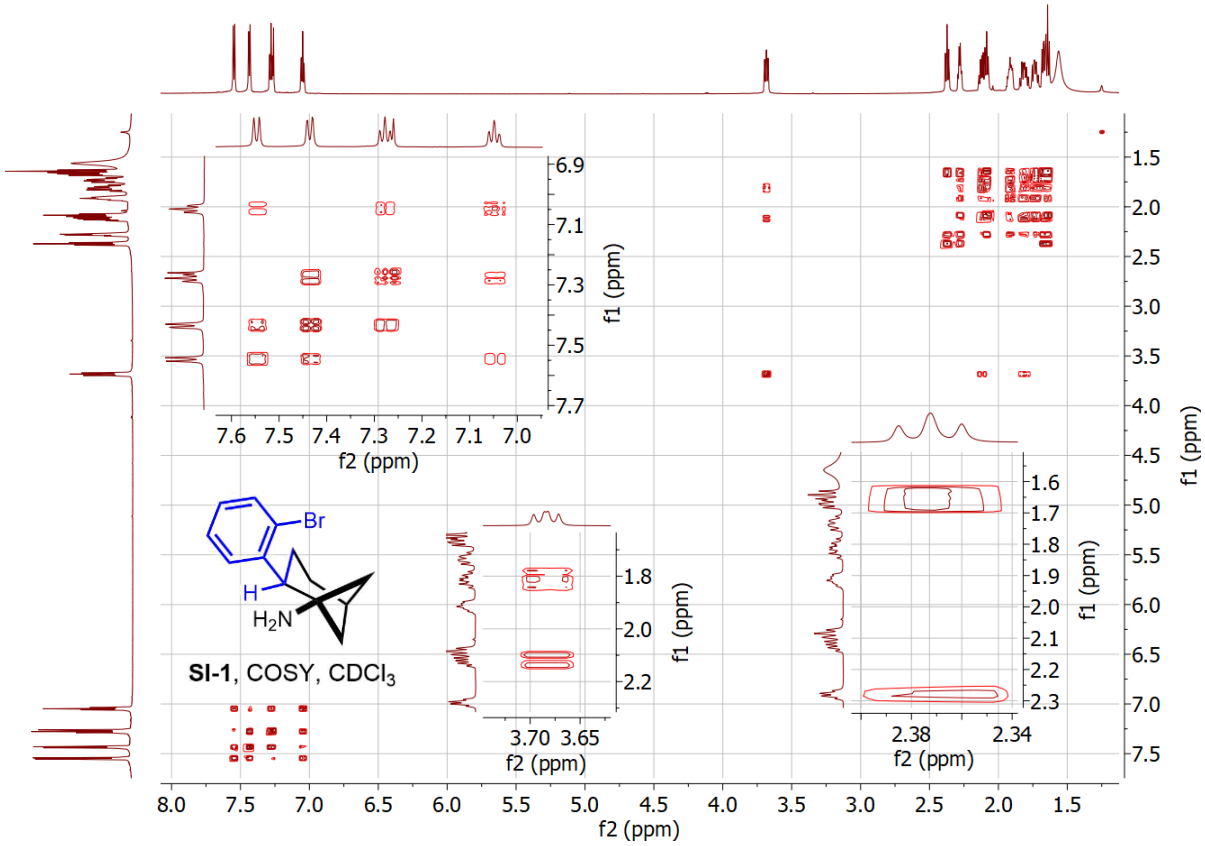
Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	125.9		2	7.55 (d, J = 8.0 Hz, 1H)
2	133.3		3	7.07-7.03 (m, 1H)
3	127.8		4	7.28 (app. t, J = 7.5 Hz, 1H)
4	127.8		5	7.44 (d, J = 7.2 Hz, 1H)
5	127.6		7	3.68 (dd, J = 9.8, 7.6 Hz, 1H)
6	144		8a	one of 2.15-2.06 (m, 2H)
7	49.6		8b	1.85-1.77 (m, 1H)
8	27.5		9a	1.76-1.70 (m, 1H)
9	28.5		9b	1.94-1.88 (m, 1H)
10	27		10	2.30-2.25 (m, 1H)
11	36.2		11a	2.37 (app. t, J = 8.8 Hz, 1H)
12	48		11b	1.67 (dd, J = 9.2, 6.7 Hz, 1H)
13	58.6		12a	1.64 (app. t, J = 10.6 Hz, 1H)
			12b	one of 2.15-2.06 (m, 2H)
			NH2	1.56 (bs, 2H)

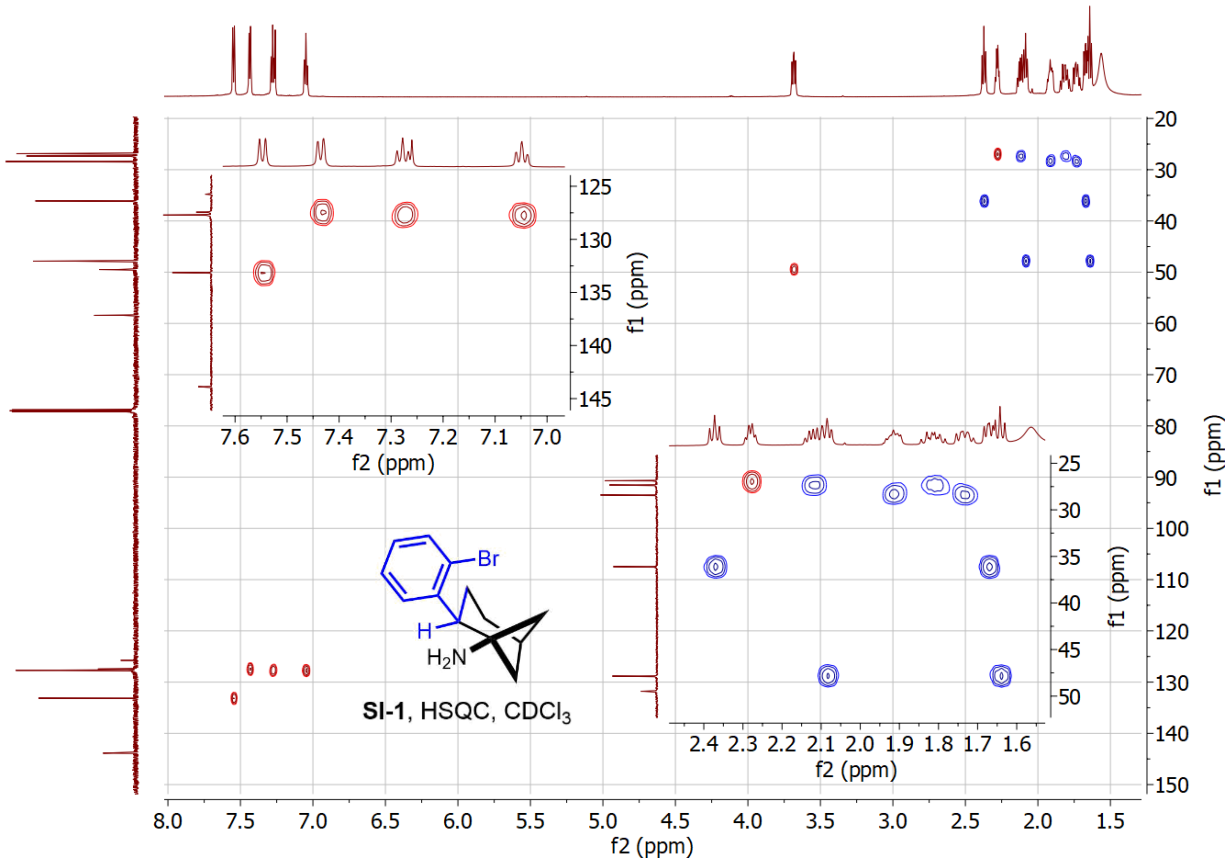


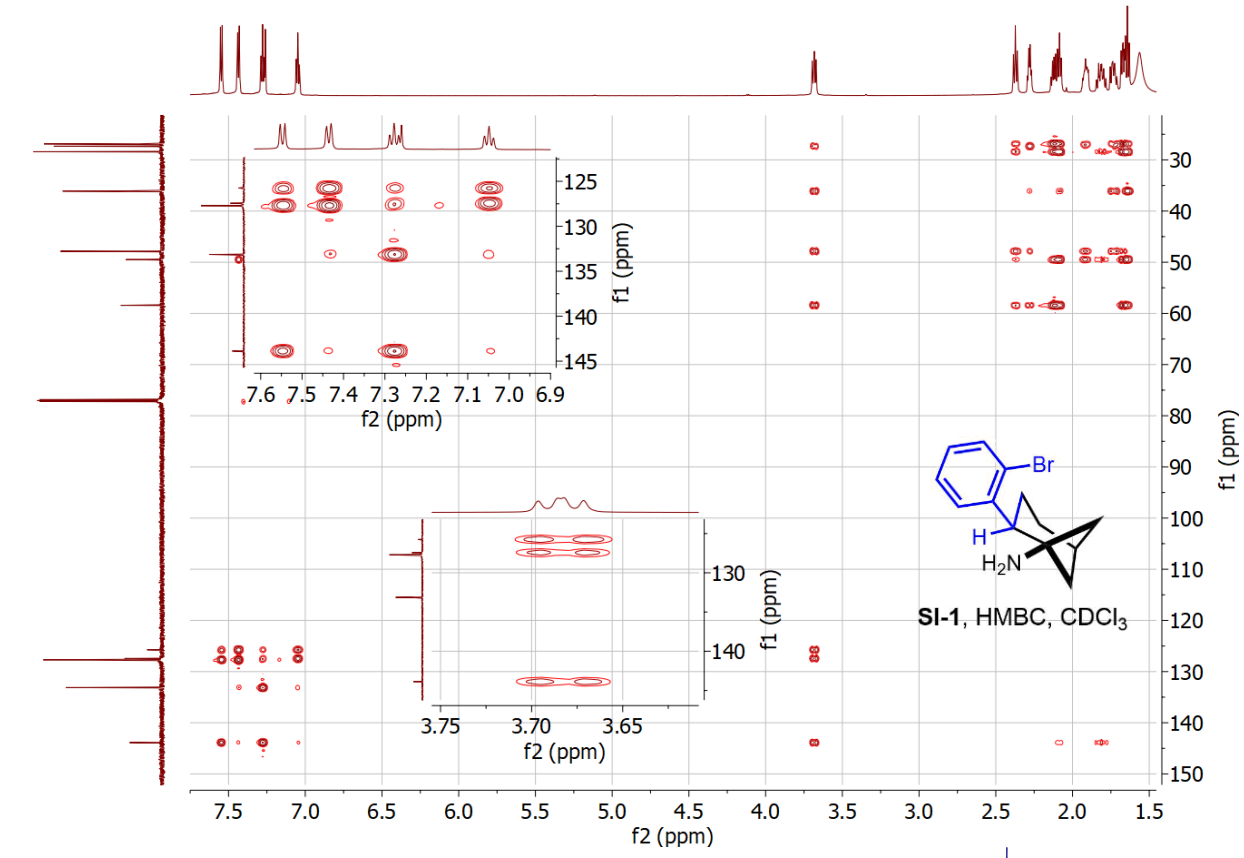
SI-1, ^{1}HNMR, $CDCl_3$, 700 MHz

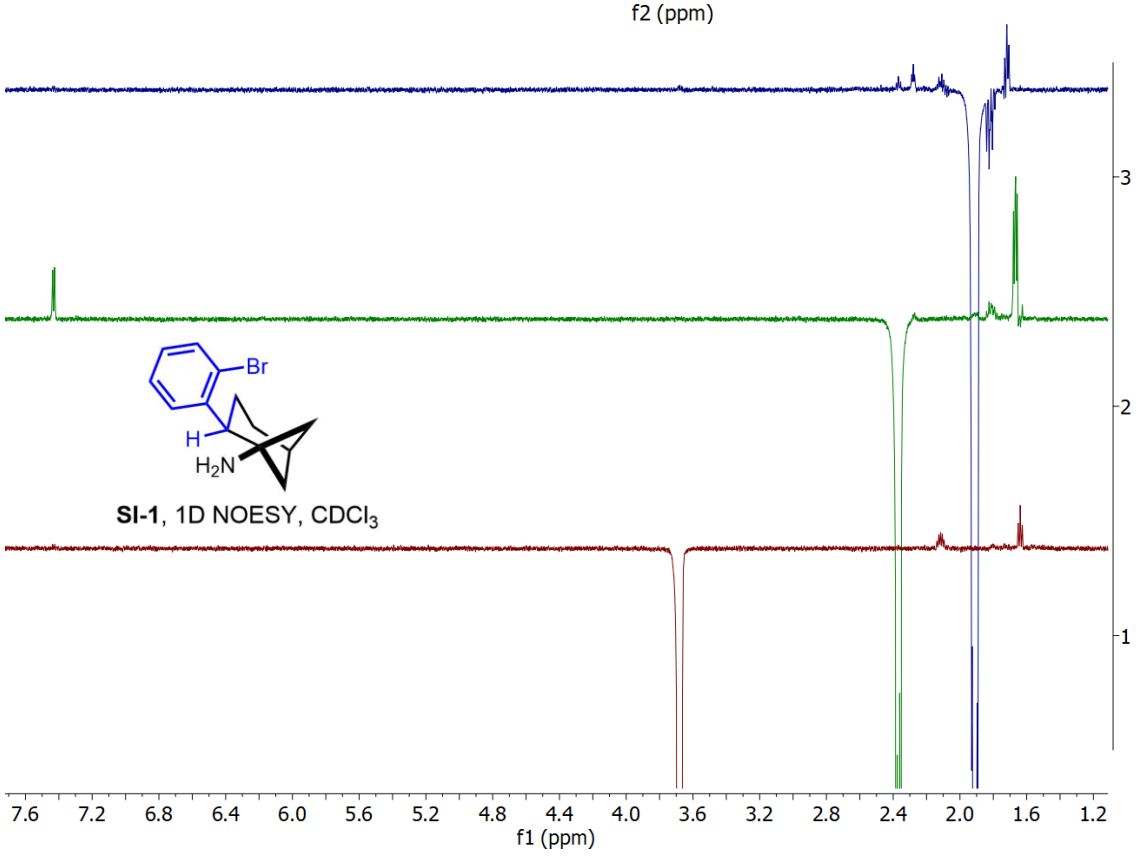


SI-1, ^{13}CNMR, $CDCl_3$, 176 MHz


Br
H
H2N
SI-1, COSY, CDCl3
f1 (ppm)
f2 (ppm)


Br
H
H2N
SI-1, HSQC, CDCl3
f1 (ppm)
f2 (ppm)

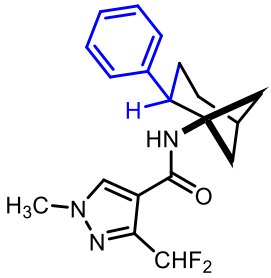

f2 (ppm)
f1 (ppm)
Br
H
H2N
SI-1, HMBC, CDCl3


f1 (ppm)
Br
H
H2N
SI-1, 1D NOESY, CDCl3

IV.E.2: Pyrazole-carboxamide succinate dehydrogenate inhibitor (SDHI) analogue library

We prepared a small library of pyrazole carboxamides (**SI-2**, **SI-3**, **SI-4**, **SI-5**, **SI-6**, and **SI-7**) from the primary amines reported herein to support studies in the use of sp^3-rich primary amines in the synthesis of SDHI fungicide candidates.

Compound (±)-**SI-2**:



EXPERIMENTAL PROCEDURE:
To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7d** (50.0 mg, 0.267 mmol, 1 equiv). To the vial containing (±)-**7d**, dichloromethane (5.34 mL), 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (70.5 mg, 0.400 mmol, 1.5 equiv), DMAP (52.2 mg, 0.427 mmol, 1.6 equiv) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (81.9 mg, 0.427 mmol, 1.6 equiv) were sequentially added. The headspace was flushed with argon, the vial was capped, and the reaction mixture was allowed to stir at room temperature for 20 hours. The crude reaction mixture was concentrated onto celite (3 g). The powdery residue was loaded atop a silica column (that had been pre-neutralized with 15% ethyl acetate : 84% hexanes : 1% triethylamine) and eluted with 15%-100% strong solvent in hexanes (where strong solvent was 1% triethylamine in ethyl acetate), giving (±)-**SI-2** (54.9 mg, 0.172 mmol, 64%) as a faintly yellow solid.

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.51 (s, 1H), 7.27-7.23 (m, 4H), 7.21-7.16 (m, 1H), 6.55 (app. t, *J* = 54.2 Hz, 1H), 5.92 (s, 1H), 3.83 (s, 3H), 3.75 (app. t, *J* = 8.2 Hz, 1H), 2.63-2.57 (m, 1H), 2.52-2.47 (m, 1H), 2.27-2.18 (m, 2H), 2.15-2.09 (m, 2H), 2.09-2.05 (m, 1H), 2.02-1.96 (m, 1H), 1.88-1.81 (m, 1H) ppm

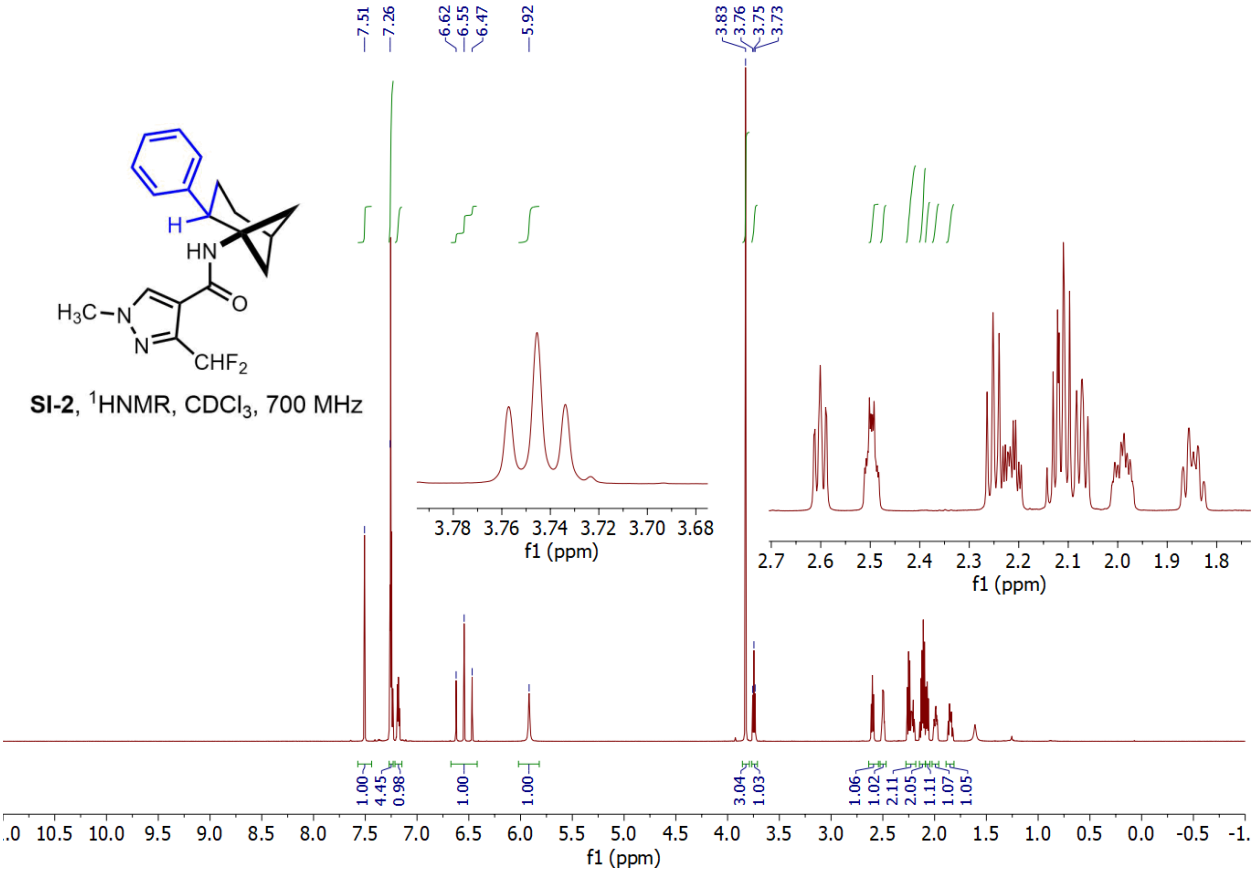
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 160.2, 144.2, 143.2 (app. t, *J* = 27.1 Hz), 133.9, 128.4, 128.3, 126.6, 117.6, 111.0 (app. t, *J* = 234.3 Hz), 59.5, 48.4, 43.7, 39.5, 32.5, 29.7, 28.4, 26.5 ppm

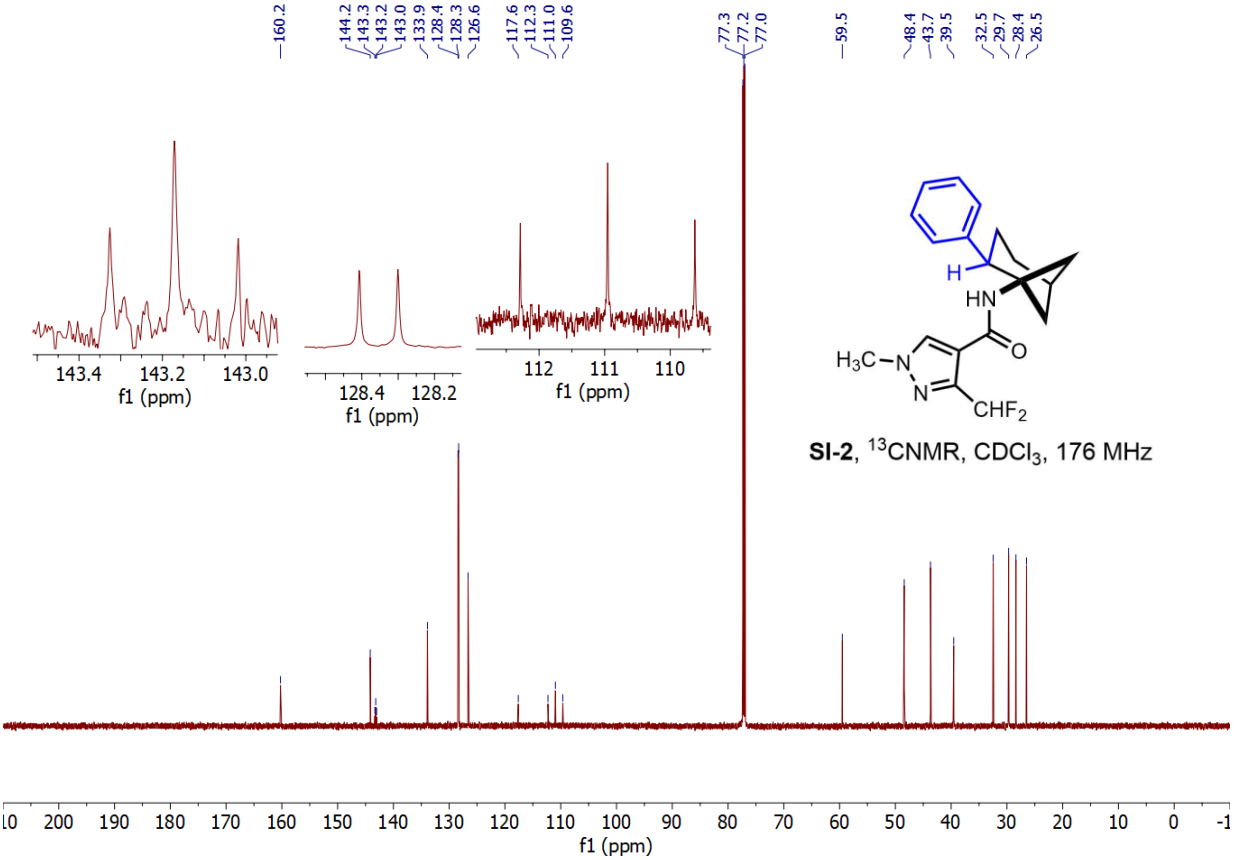
^{19}F NMR ($CDCl_3$, 376 MHz): *NOTE:* The difluoromethyl group appears as a so-called AB quartet of doublets (with an additional level of "doublet" splitting visible for one of the fluorine atoms with small coupling constant). The F-H coupling shows normal doublet behavior not impacted by AB considerations, whereas the F-F coupling contributes the AB quartet nature to the signals. δ = -110.6 (ddd, *J* = 307.0, 54.4, 3.1 Hz), -113.6 (dd, *J* = 307.0, 53.9 Hz) ppm

IR (neat): 3448, 3316, 2945, 1632, 1554, 1521, 1491, 1452, 1338, 1278, 1177, 1129, 1067, 1026, 885, 857, 810, 761, 701 cm^{-1}

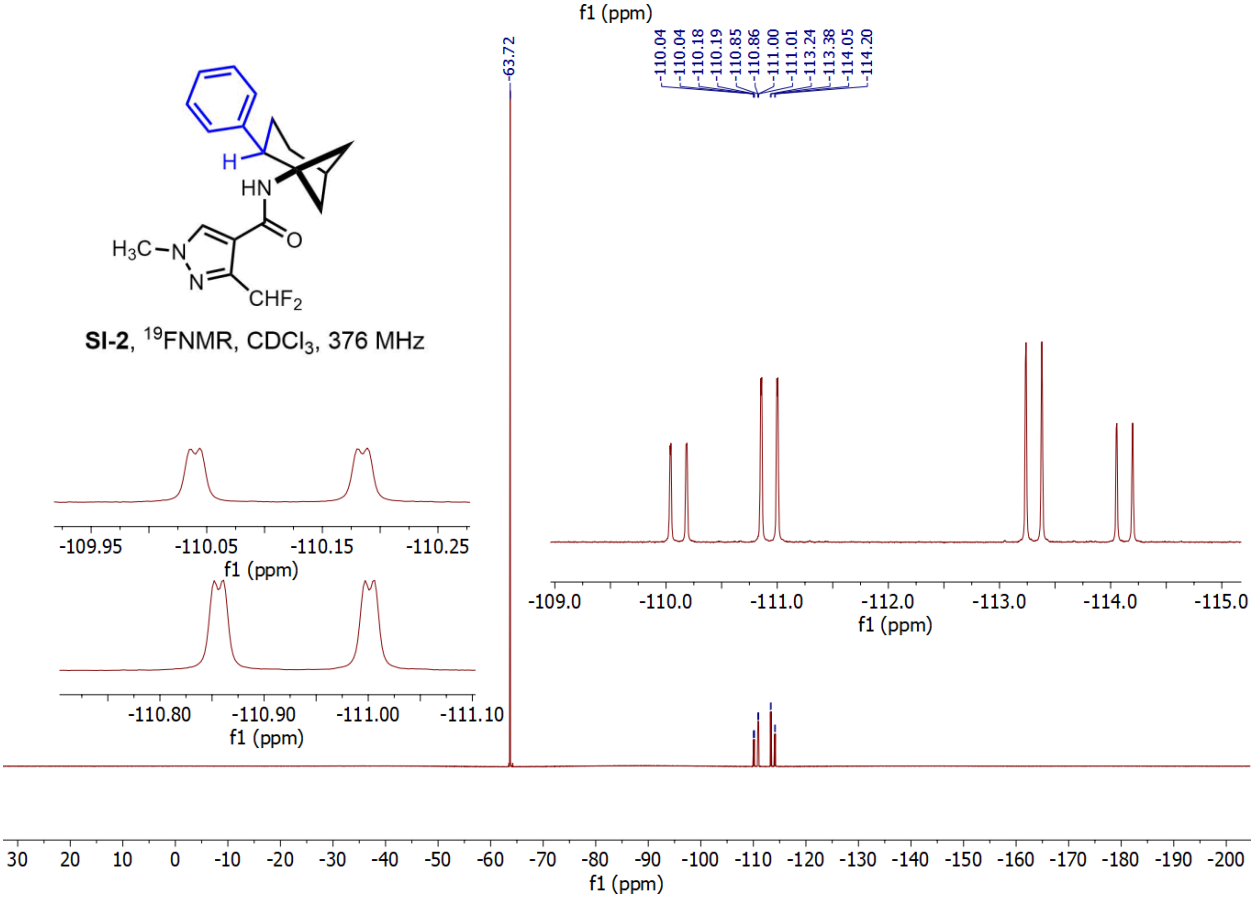
HRMS (ES+, m/z) calculated for $C_{19}H_{22}F_2N_3O^+$: 346.1725, Found: 346.1721

R_f = 0.53 (60% ethyl acetate : 39% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



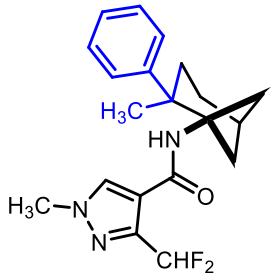


SI-2, ^{13}CNMR, $CDCl_3$, 176 MHz



SI-2, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound **SI-3**:



EXPERIMENTAL PROCEDURE:
To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7e** (56.4 mg, 0.280 mmol, 1 equiv). To the vial containing (±)-**7e**, dichloromethane (5.60 mL), 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (74.0 mg, 0.420 mmol, 1.5 equiv), DMAP (54.8 mg, 0.448 mmol, 1.6 equiv) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (85.9 mg, 0.448 mmol, 1.6 equiv) were sequentially added. The headspace was flushed with argon, the vial was capped, and the reaction mixture was allowed to stir at room temperature for 22 hours. The crude reaction mixture was concentrated onto celite (3 g). The powdery residue was loaded atop a silica column (that had been pre-neutralized with 15% ethyl acetate : 84% hexanes : 1% triethylamine) and eluted with 15%-100% strong solvent in hexanes (where strong solvent was 1% triethylamine in ethyl acetate), giving (±)-**SI-3** (80.9 mg, 0.225 mmol, 80%) as a white solid.

Appearance: white solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.78 (s, 1H), 7.46 (d, *J* = 7.7 Hz, 2H), 7.30 (app. t, *J* = 7.7 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.80 (app. t, *J* = 54.2 Hz, 1H), 3.91 (s, 3H), 2.51 (dd, *J* = 9.9, 8.5 Hz, 1H), 2.47-2.43 (m, 1H), 2.43-2.39 (m, 1H), 2.38-2.32 (m, 1H), 2.12-2.05 (m, 1H), 2.05-1.99 (m, 1H), 1.99-1.92 (m, 2H), 1.64 (app. t, *J* = 8.7 Hz, 1H), 1.50 (s, 3H) ppm

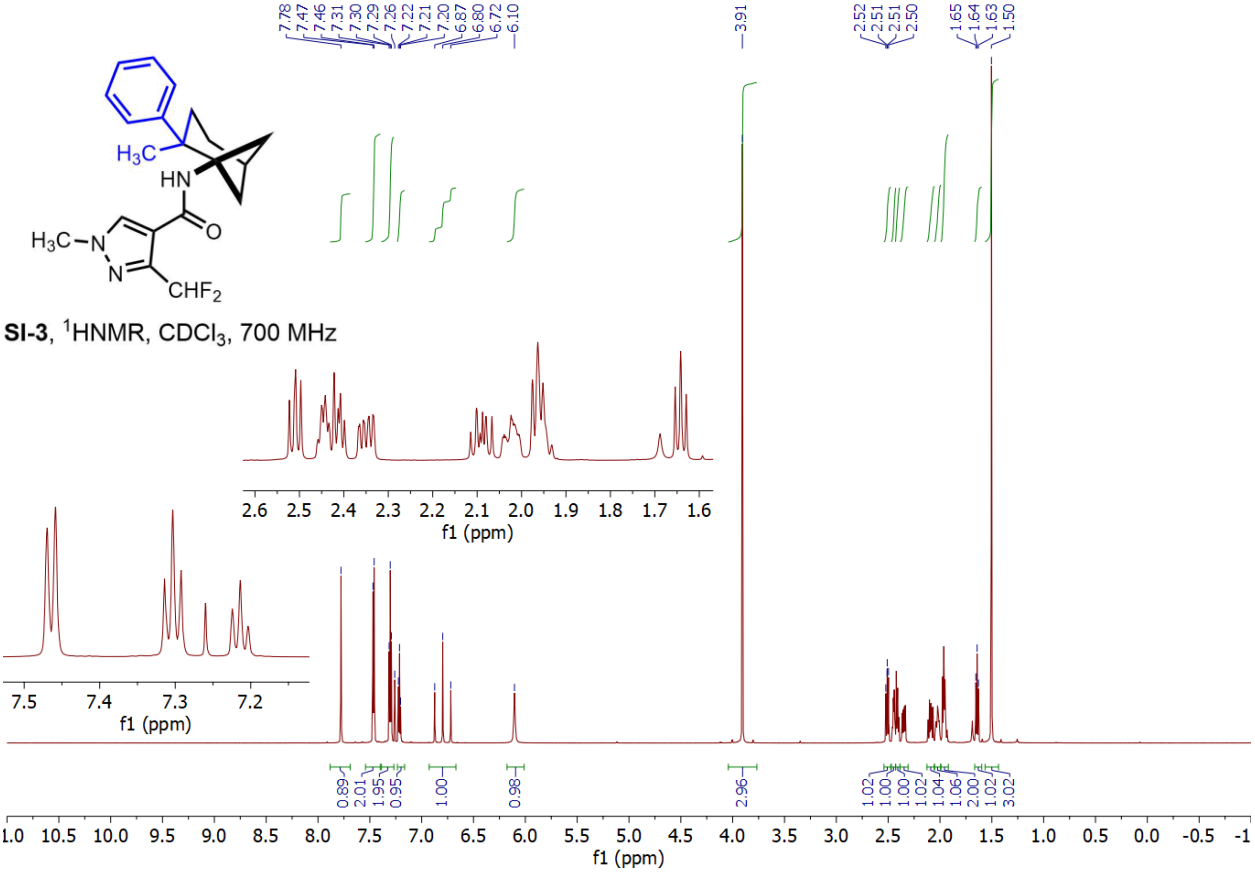
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 160.0, 146.4, 142.9 (app. t, *J* = 28.1 Hz), 134.8, 128.0, 127.7, 126.2, 118.1, 111.6 (app. t, *J* = 233.4 Hz), 62.7, 47.1, 39.6, 38.9, 34.8, 33.4, 30.3, 28.6, 25.6 ppm

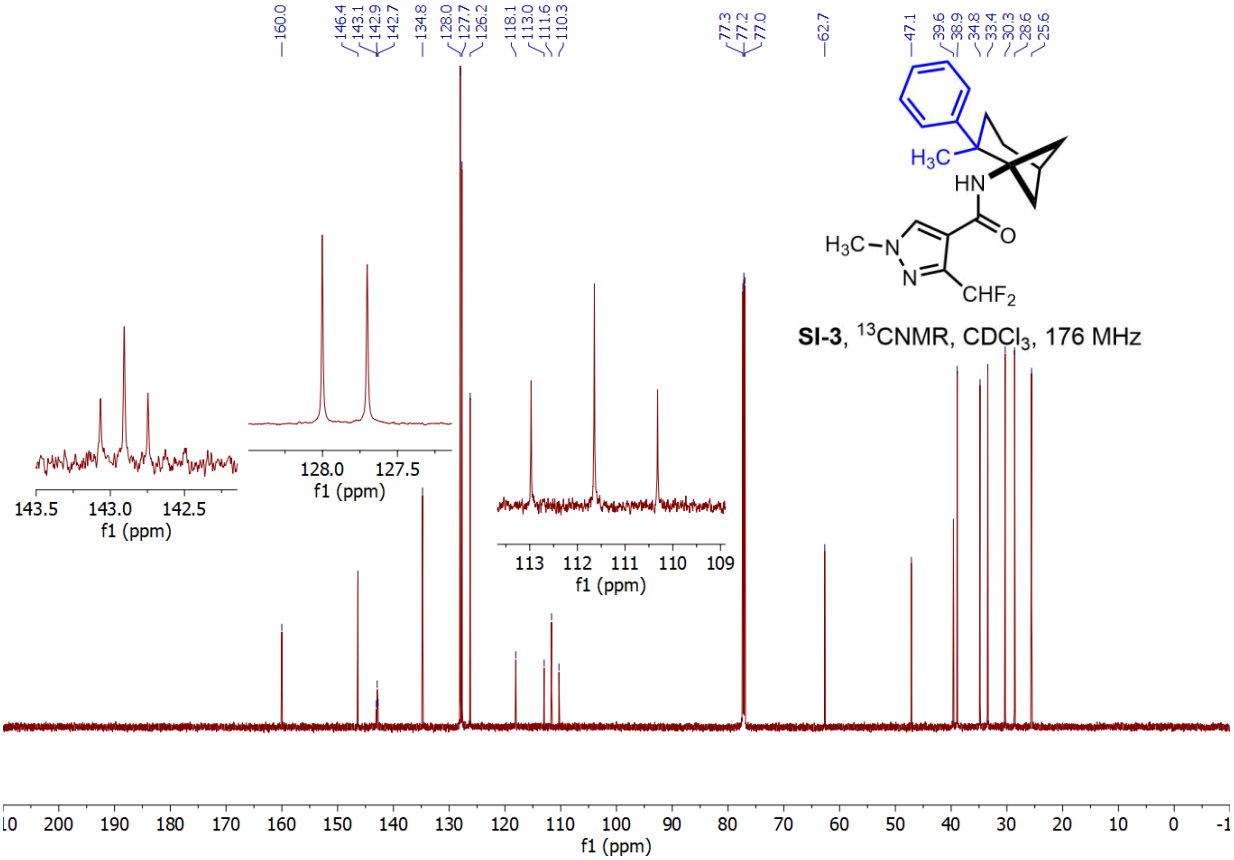
^{19}F NMR ($CDCl_3$, 376 MHz): *NOTE:* The difluoromethyl group appears as a so-called AB quartet of doublets. The F-H coupling shows normal doublet behavior not impacted by AB considerations, whereas the F-F coupling contributes the AB quartet nature to the signals. δ = -109.2 (dd, *J* = 306.3, 54.2 Hz), -111.2 (dd, *J* = 306.3, 54.1 Hz) ppm

IR (neat): 3439, 3326, 2951, 2865, 1666, 1642, 1549, 1512, 1483, 1456, 1389, 1341, 1267, 1244, 1231, 1171, 1124, 1065, 1049, 1009, 943, 871, 826, 804, 773, 763, 736, 709, 673 cm^{-1}

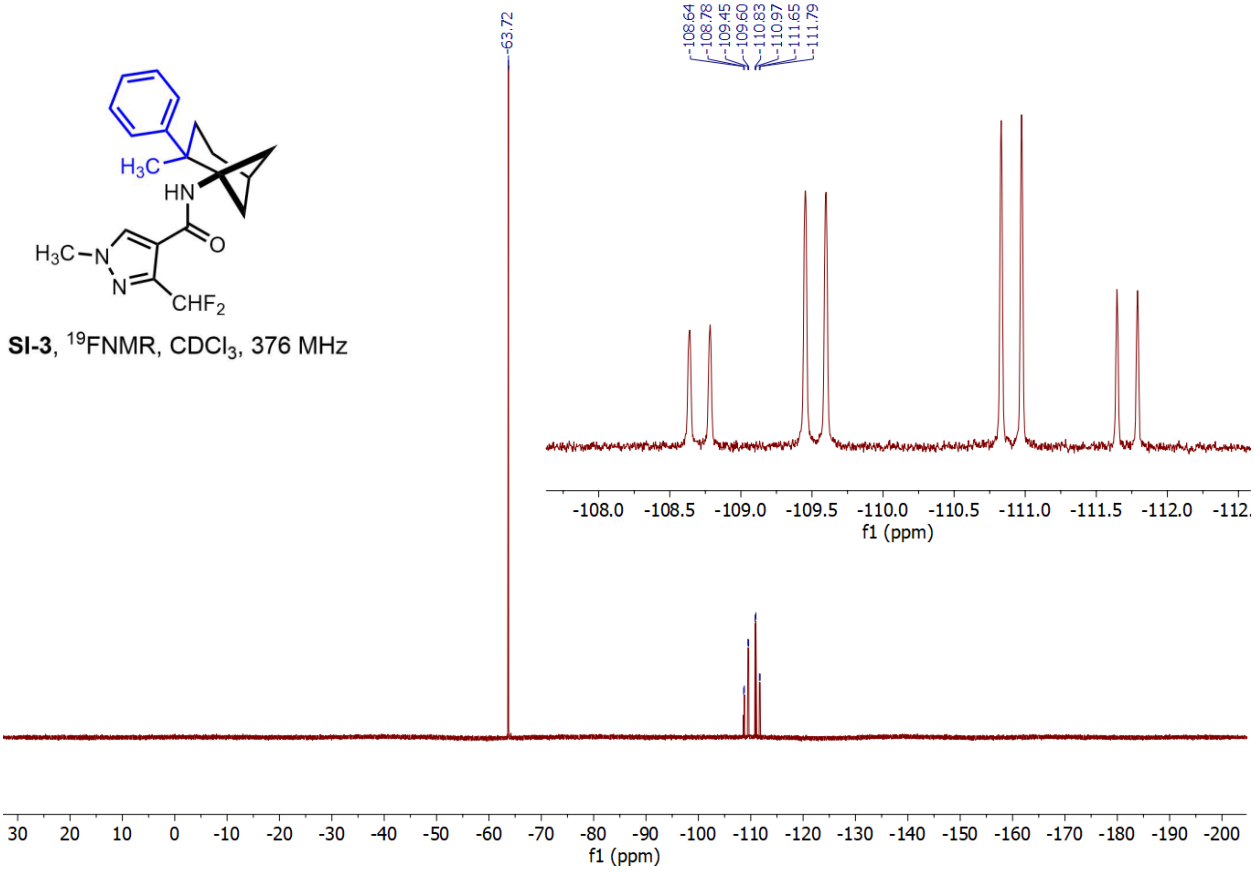
HRMS (ES+, m/z) calculated for $C_{20}H_{24}F_2N_3O^+$: 360.1882, Found: 360.1878

R_f = 0.58 (60% ethyl acetate : 39% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



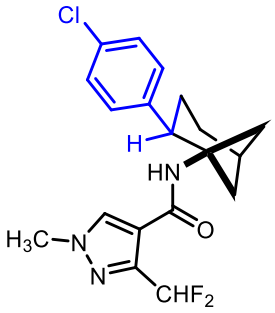


SI-3, ^{13}CNMR, $CDCl_3$, 176 MHz



SI-3, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound (±)-**SI-4**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7a** (104.5 mg, 0.471 mmol, 1 equiv). To the vial containing (±)-**7a**, dichloromethane (4.71 mL), 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (124.5 mg, 0.707 mmol, 1.5 equiv), DMAP (92.1 mg, 0.754 mmol, 1.6 equiv) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (144.6 mg, 0.754 mmol, 1.6 equiv) were sequentially added. The headspace was flushed with argon, the vial was capped, and the reaction mixture was allowed to stir at room temperature for 23 hours. The crude reaction mixture was concentrated onto celite (3 g). The powdery residue was loaded atop a silica column (that had been pre-neutralized with 15% ethyl acetate : 84% hexanes : 1% triethylamine) and eluted with 15%-100% strong solvent in hexanes (where strong solvent was 1% triethylamine in ethyl acetate), giving (±)-**SI-4** (109.1 mg, 0.287 mmol, 61%) as a faintly yellow solid.

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.57 (s, 1H), 7.21-7.15 (m, 4H), 6.63 (app. t, *J* = 54.3 Hz), 6.05 (s, 1H), 3.83 (s, 1H), 3.79 (app. t, *J* = 8.1 Hz), 2.52-2.46 (m, 2H), 2.23-2.16 (m, 2H), 2.16-2.11 (m, 1H), 2.07-1.94 (m, 3H), 1.87-1.81 (m, 1H) ppm

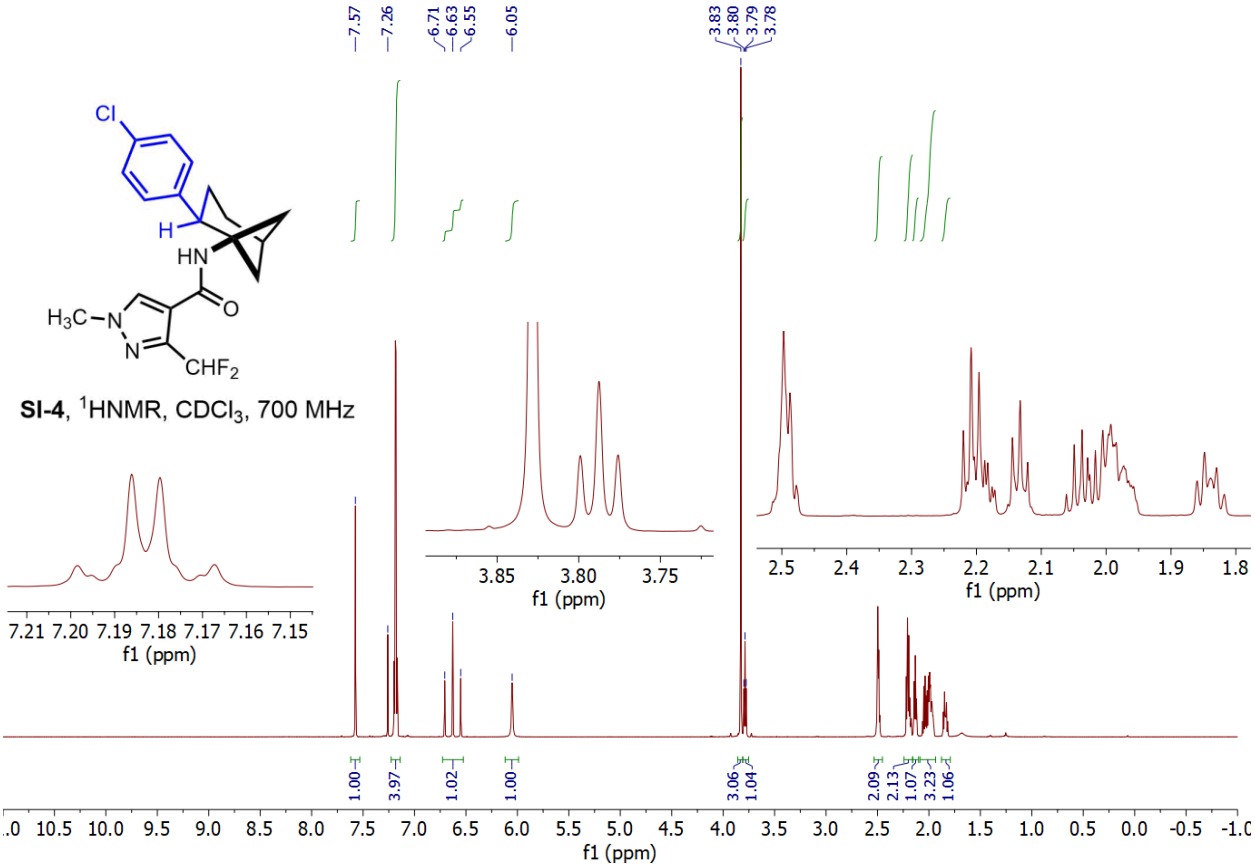
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 160.1, 142.9 (app. t, *J* = 27.9 Hz), 142.7, 134.4, 132.2, 129.6, 128.4, 117.3, 111.3 (app. t, *J* = 233.7 Hz), 59.4, 47.7, 43.8, 39.5, 32.5, 29.7, 28.3, 26.5 ppm

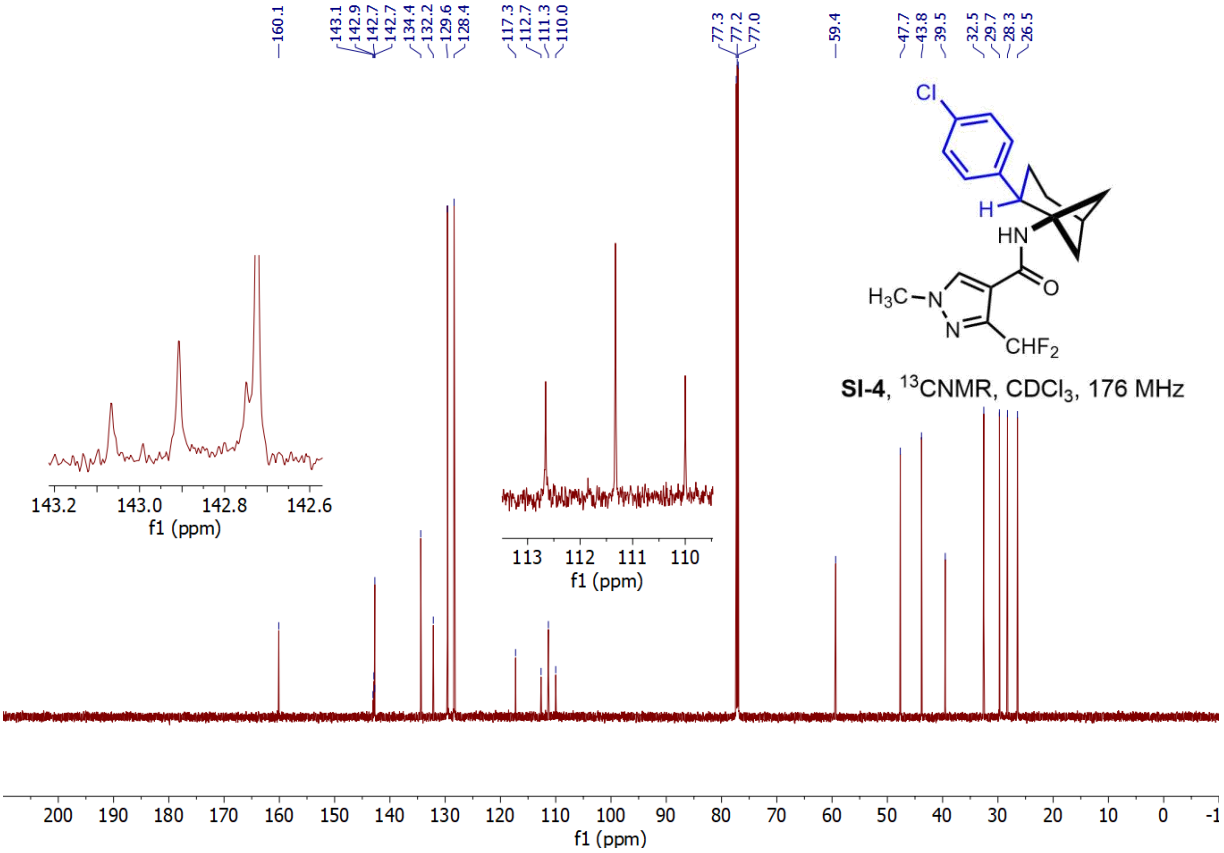
^{19}F NMR ($CDCl_3$, 376 MHz): *NOTE:* The difluoromethyl group appears as a so-called AB quartet of doublets. The F-H coupling shows normal doublet behavior not impacted by AB considerations, whereas the F-F coupling contributes the AB quartet nature to the signals. δ = -110.2 (dd, *J* = 306.6, 54.3 Hz), -112.1 (dd, *J* = 306.6, 54.2 Hz) ppm

IR (neat): 3448, 3301, 2947, 2864, 1634, 1552, 1522, 1491, 1451, 1414, 1339, 1314, 1277, 1256, 1178, 1130, 1089, 1071, 1028, 1013, 886, 858, 830, 808, 768, 753, 703, 678 cm^{-1}

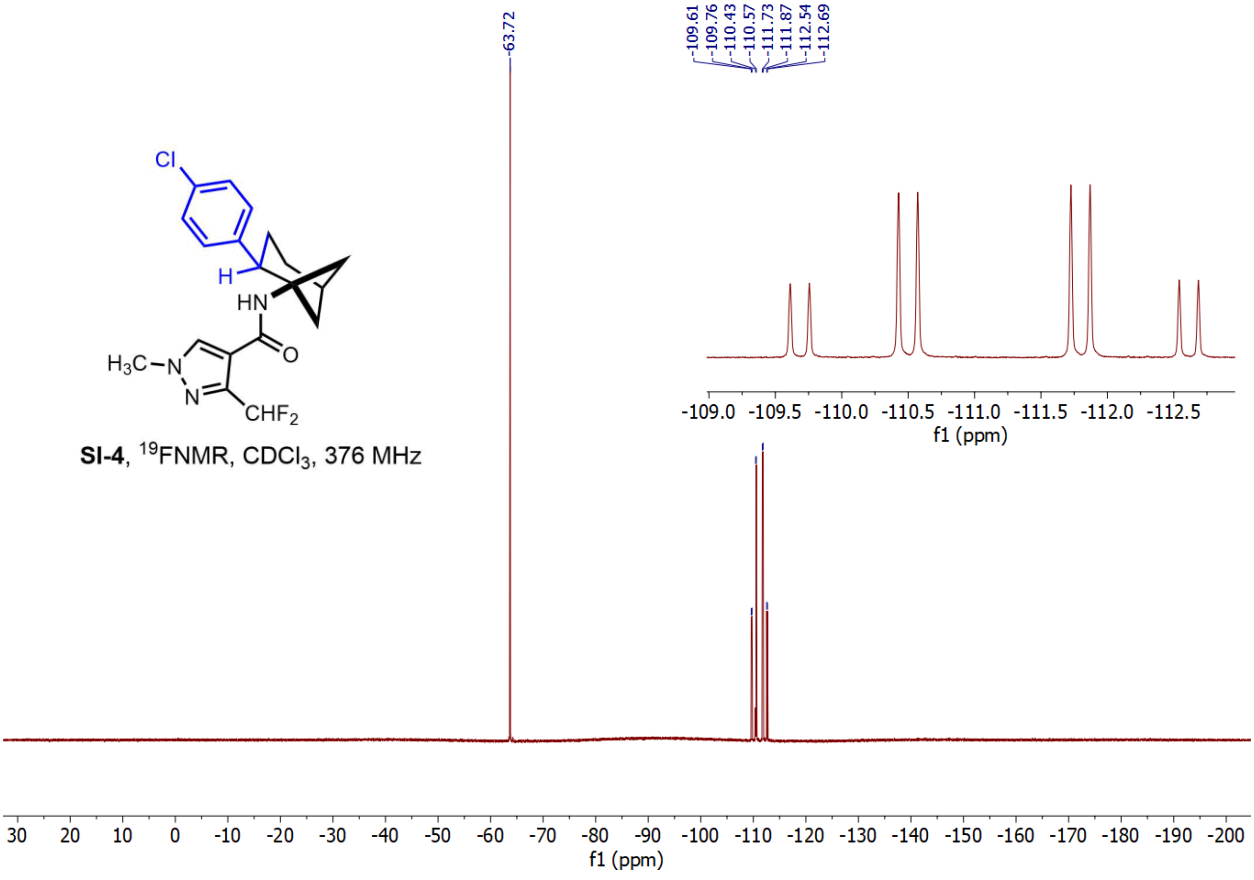
HRMS (ES+, m/z) calculated for $C_{19}H_{21}ClF_2N_3O^+$: 380.1336, Found: 380.1333

R_f = 0.56 (60% ethyl acetate : 39% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



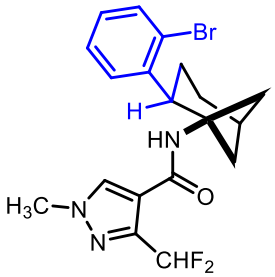


SI-4, ^{13}CNMR, $CDCl_3$, 176 MHz



SI-4, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound (±)-**SI-5**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**SI-1** (56.9 mg, 0.214 mmol, 1 equiv). To the vial containing (±)-**SI-1**, dichloromethane (4.28 mL), 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (56.5 mg, 0.321 mmol, 1.5 equiv), DMAP (41.8 mg, 0.342 mmol, 1.6 equiv) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (65.6 mg, 0.342 mmol, 1.6 equiv) were sequentially added. The headspace was flushed with argon, the vial was capped, and the reaction mixture was allowed to stir at room temperature for 24 hours. The crude reaction mixture was concentrated onto celite (3 g). The powdery residue was loaded atop a silica column (that had been pre-neutralized with 15% ethyl acetate : 84% hexanes : 1% triethylamine) and eluted with 15%-100% strong solvent in hexanes (where strong solvent was 1% triethylamine in ethyl acetate), giving two impure portions which were individually resubjected to the chromatography conditions, giving clean (±)-**SI-5** (31.2 mg, 0.0735 mmol, 34%) as a faintly yellow solid.

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.52-7.46 (m, 2H), 7.41 (d, *J* = 7.8 Hz), 7.23 (app. t, *J* = 7.5 Hz, 1H), 7.00 (app. t, *J* = 7.6 Hz, 1H), 6.63 (app. t, *J* = 54.3 Hz, 1H), 6.14 (s, 1H), 4.16 (app. t, *J* = 8.5 Hz, 1H), 3.76 (s, 3H), 2.78 (app. t, *J* = 8.0 Hz, 1H), 2.52-2.46 (m, 1H), 2.46-2.39 (m, 3H), 2.29-2.20 (m, 1H), 2.02-1.92 (m, 2H), 1.92-1.74 (m, 2H) ppm

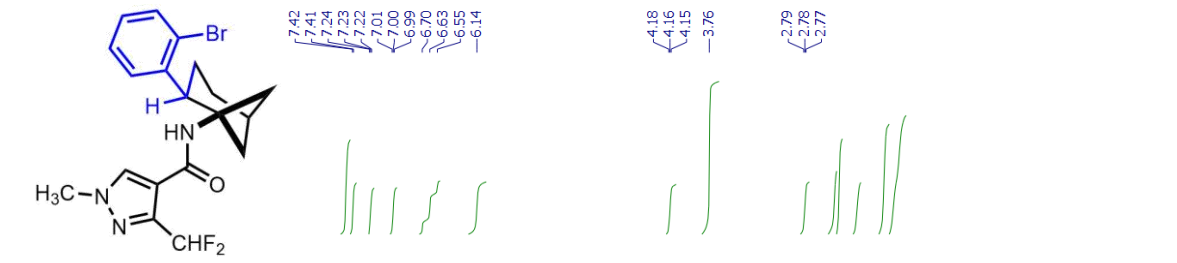
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 160.1, 143.4, 142.9 (app. t, *J* = 27.4 Hz), 134.2, 133.1, 128.2, 127.9, 127.7, 125.4, 117.6, 111.1 (app. t, *J* = 233.9 Hz), 59.1, 47.7, 44.8, 39.4, 31.8, 29.2, 28.3, 27.1 ppm

^{19}F NMR ($CDCl_3$, 376 MHz): *NOTE:* The difluoromethyl group appears as a so-called AB quartet of doublets. The F-H coupling shows normal doublet behavior not impacted by AB considerations, whereas the F-F coupling contributes the AB quartet nature to the signals. δ = -111.0 (dd, *J* = 306.6, 54.4 Hz), -111.8 (dd, *J* = 306.6, 54.3 Hz) ppm

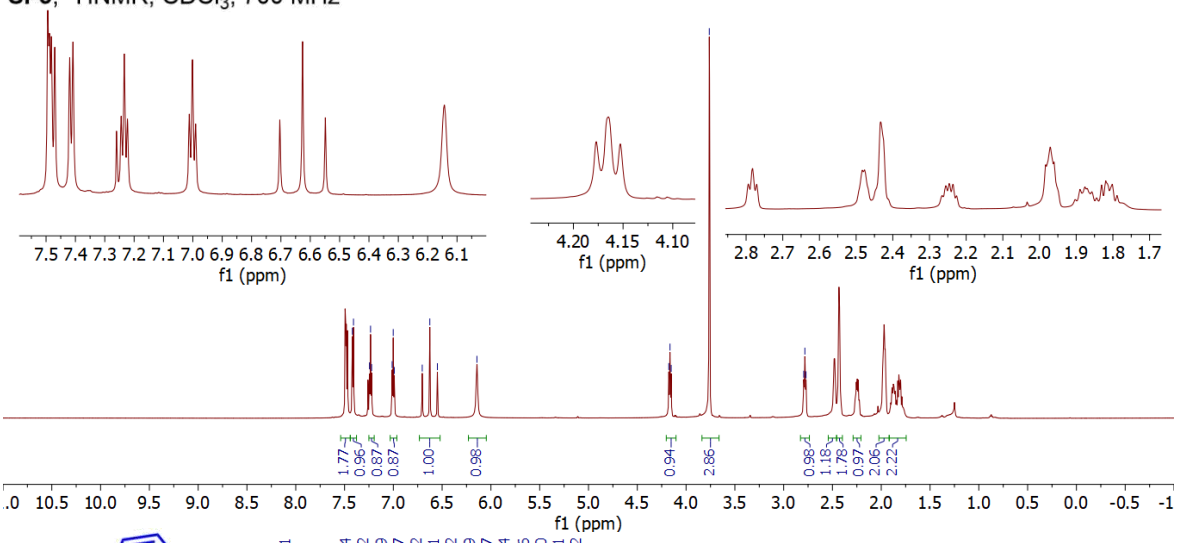
IR (neat): 3245, 2938, 2865, 1631, 1553, 1496, 1470, 1433, 1343, 1319, 1293, 1251, 1207, 1181, 1167, 1133, 1077, 1036, 1019, 946, 889, 860, 837, 820, 765, 739, 703, 668 cm^{-1}

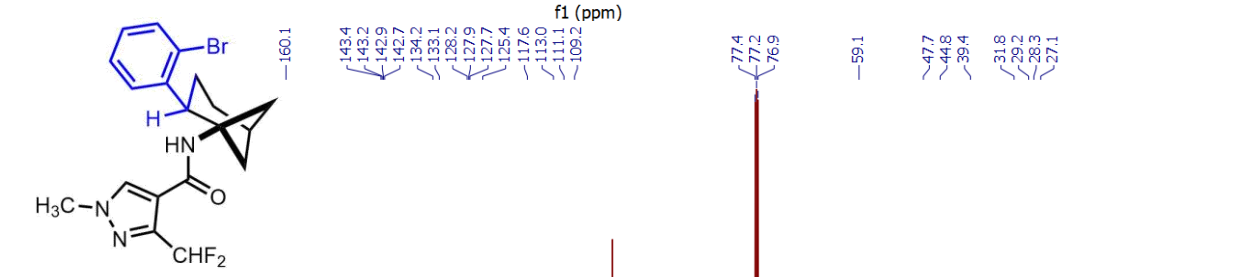
HRMS (ES+, m/z) calculated for $C_{19}H_{21}BrF_2N_3O^+$: 424.0831, Found: 424.0823

R_f = 0.46 (60% ethyl acetate : 39% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

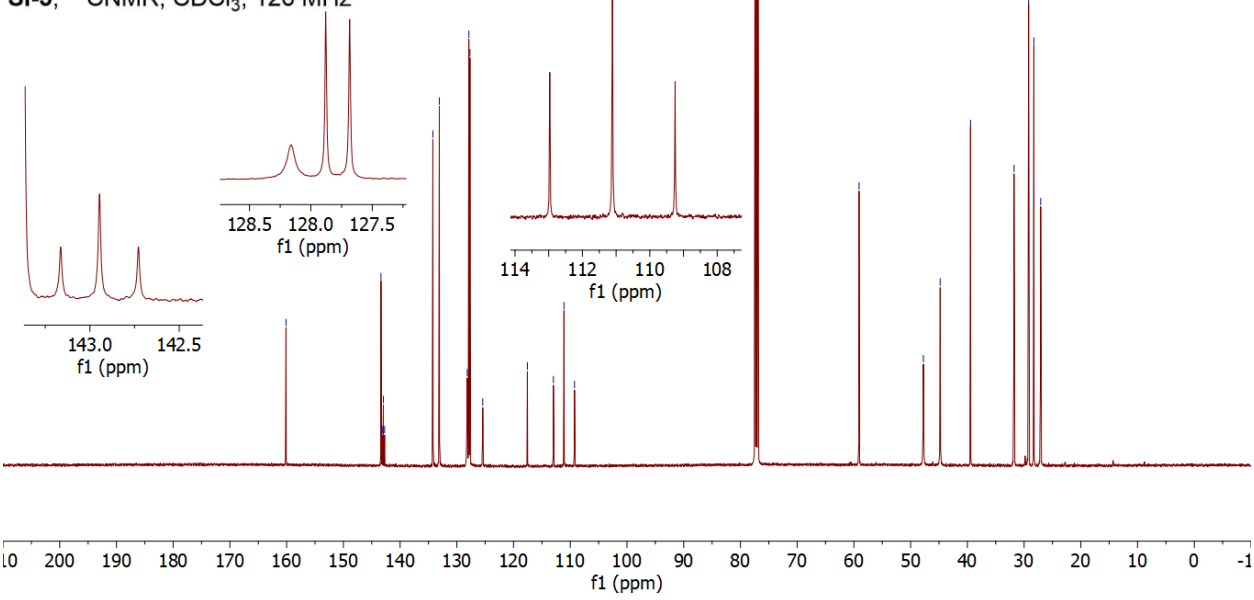


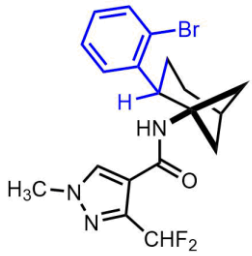
SI-5, ^{1}HNMR, $CDCl_3$, 700 MHz





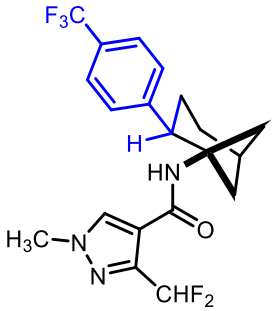
SI-5, ^{13}CNMR, $CDCl_3$, 126 MHz





SI-5, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound (±)-**SI-6**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7c** (39.0 mg, 0.153 mmol, 1 equiv). To the vial containing (±)-**7c**, dichloromethane (3.06 mL), 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (40.4 mg, 0.229 mmol, 1.5 equiv), DMAP (29.9 mg, 0.244 mmol, 1.6 equiv) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (46.9 mg, 0.244 mmol, 1.6 equiv) were sequentially added. The headspace was flushed with argon, the vial was capped, and the reaction mixture was allowed to stir at room temperature for 25 hours. The crude reaction mixture was concentrated onto celite (3 g). The powdery residue was loaded atop a silica column (that had been pre-neutralized with 15% ethyl acetate : 84% hexanes : 1% triethylamine) and eluted with 15%-100% strong solvent in hexanes (where strong solvent was 1% triethylamine in ethyl acetate), giving (±)-**SI-6** (38.5 mg, 0.0931 mmol, 61%) as a white solid.

Appearance: white solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.62 (s, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.58 (app. t, *J* = 54.3 Hz, 1H), 6.05 (s, 1H), 3.91 (app. t, *J* = 8.1 Hz, 1H), 3.84 (s, 3H), 2.55-2.50 (m, 1H), 2.50-2.45 (m, 1H), 2.27-2.15 (m, 3H), 2.07 (app. dq, *J* = 14.7, 8.4 Hz, 1H), 2.03-1.97 (m, 2H), 1.91-1.84 (m, 1H) ppm

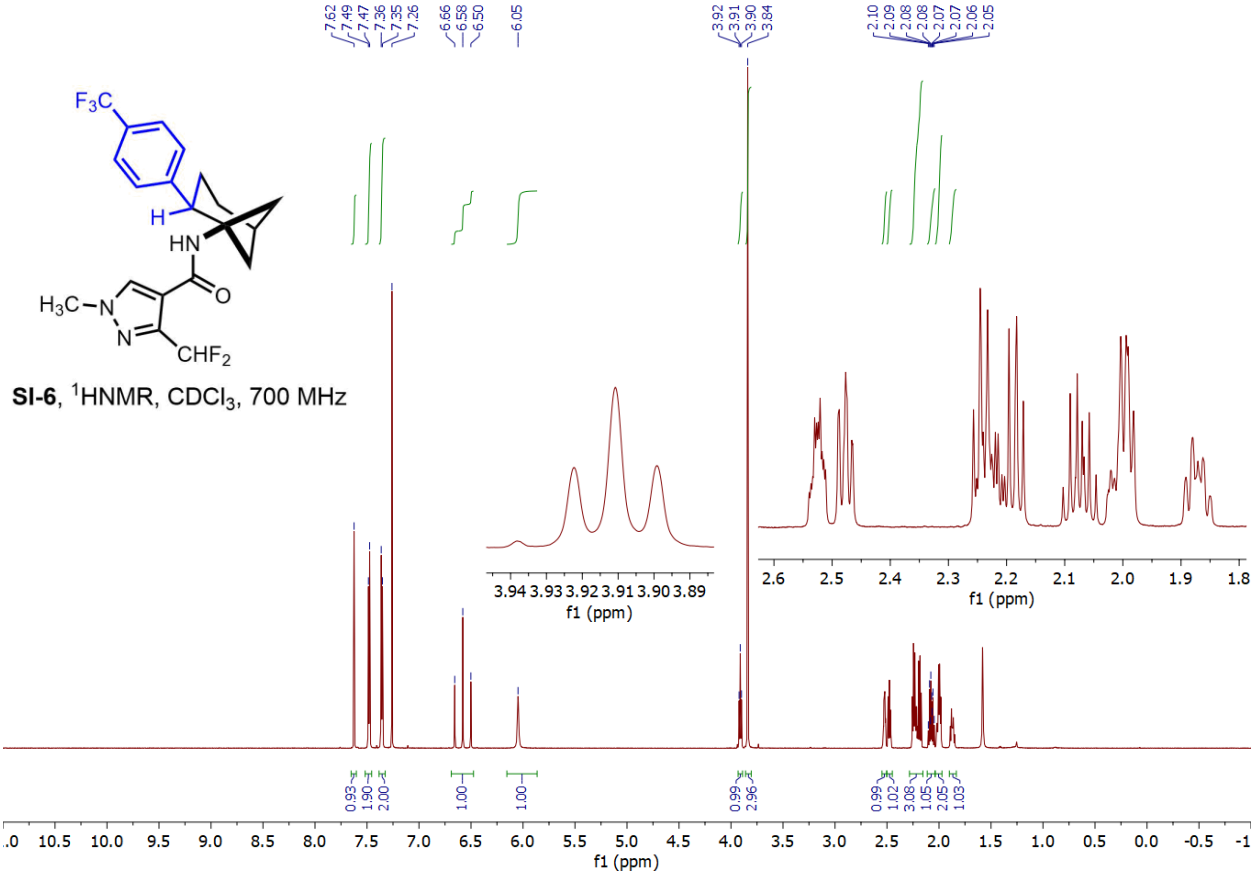
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 160.1, 148.4, 142.7 (app. t, *J* = 28.3 Hz), 134.7, 128.7 (q, *J* = 32.3 Hz), 128.5, 125.2 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.9 Hz), 117.2, 111.4 (app. t, *J* = 233.5 Hz), 59.4, 48.0, 43.9, 39.5, 32.7, 29.8, 28.2, 26.3 ppm

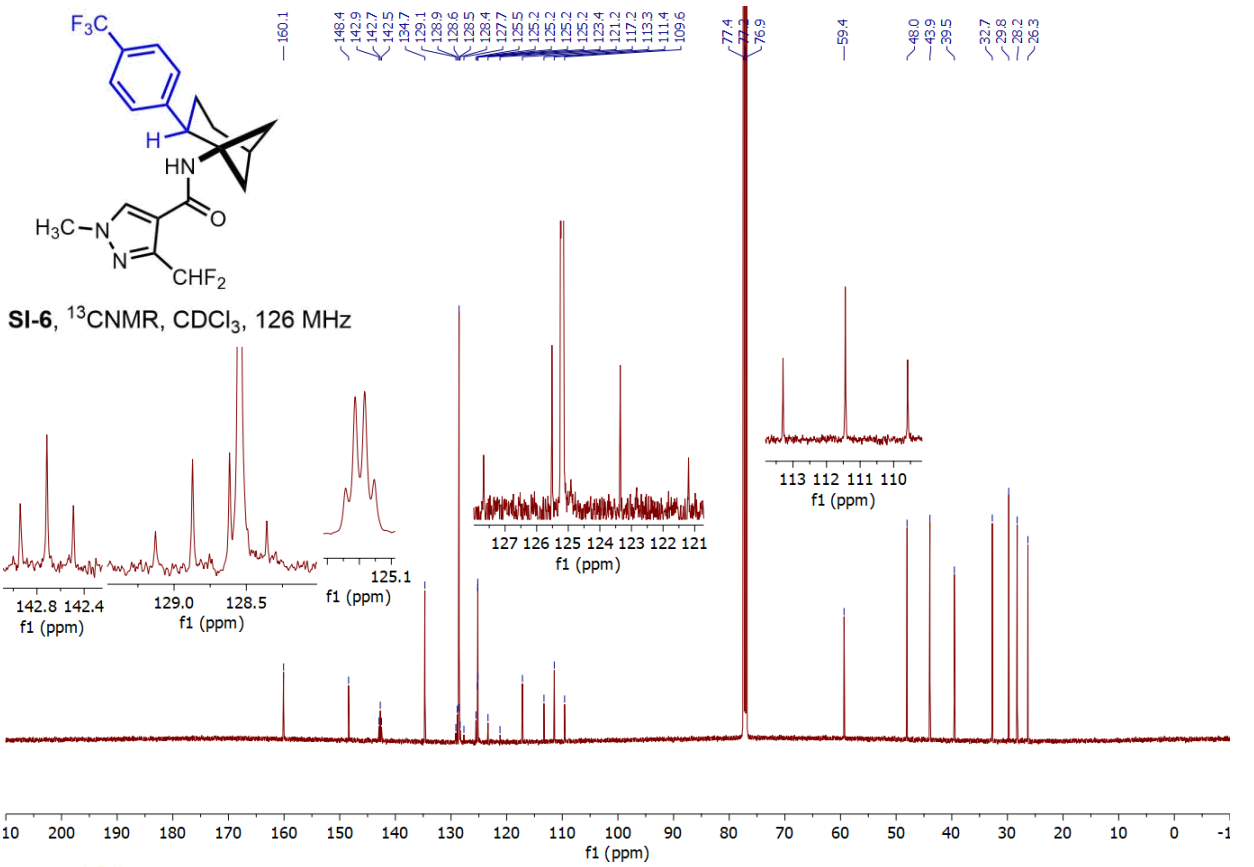
^{19}F NMR ($CDCl_3$, 376 MHz): *NOTE:* The difluoromethyl group appears as a so-called AB quartet of doublet of doublets. The F-H coupling shows normal doublet of doublet behavior not impacted by AB considerations, whereas the F-F coupling contributes the AB quartet nature to the signals. δ = -63.4 (s), -110.2 (dd, *J* = 306.6, 54.3, 3.4 Hz), -112.1 (dd, *J* = 306.6, 54.2, 3.6 Hz) ppm

IR (neat): 3449, 3299, 2950, 2867, 1636, 1555, 1523, 1487, 1422, 1326, 1280, 1164, 1114, 1069, 1017, 887, 841, 812, 769 cm^{-1}

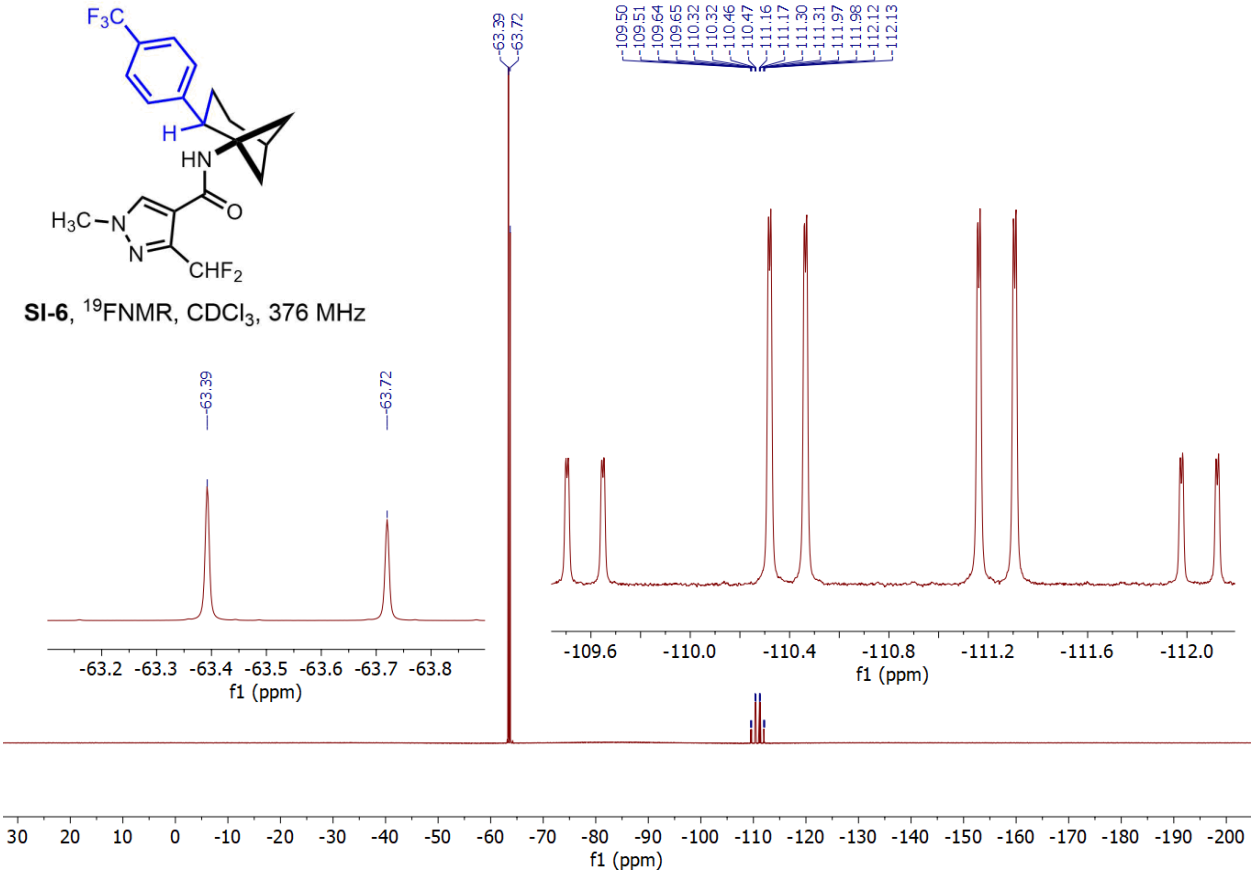
HRMS (ES+, m/z) calculated for $C_{20}H_{21}F_5N_3O^+$: 414.1599, Found: 414.1595

R_f = 0.61 (60% ethyl acetate : 39% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



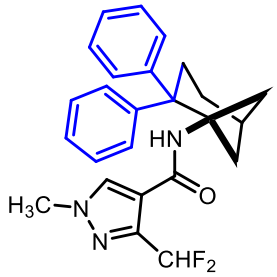


SI-6, ^{13}CNMR, $CDCl_3$, 126 MHz



SI-6, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound **SI-7**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added **7f** (42.4 mg, 0.161 mmol, 1 equiv). To the vial containing **7f**, dichloromethane (3.22 mL), 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (42.5 mg, 0.241 mmol, 1.5 equiv), DMAP (31.5 mg, 0.258 mmol, 1.6 equiv) and N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (49.4 mg, 0.258 mmol, 1.6 equiv) were sequentially added. The headspace was flushed with argon, the vial was capped, and the reaction mixture was allowed to stir at room temperature for 26 hours. The crude reaction mixture was concentrated onto celite (3 g). The powdery residue was loaded atop a silica column (that had been pre-neutralized with 15% ethyl acetate : 84% hexanes : 1% triethylamine) and eluted with 15%-100% strong solvent in hexanes (where strong solvent was 1% triethylamine in ethyl acetate), giving **SI-7** (55.7 mg, 0.132 mmol, 82%) as a white solid.

Appearance: white solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.49 (s, 1H), 7.31-7.27 (m, 8H), 7.25-7.21 (m, 2H), 6.83 (app. t, *J* = 54.2 Hz, 1H), 6.35 (s, 1H), 3.86 (s, 3H), 3.20-3.14 (m, 2H), 2.48 (t, *J* = 7.0 Hz, 1H), 2.45-2.41 (m, 1H), 2.18-2.11 (m, 2H), 2.05-1.98 (m, 2H) ppm

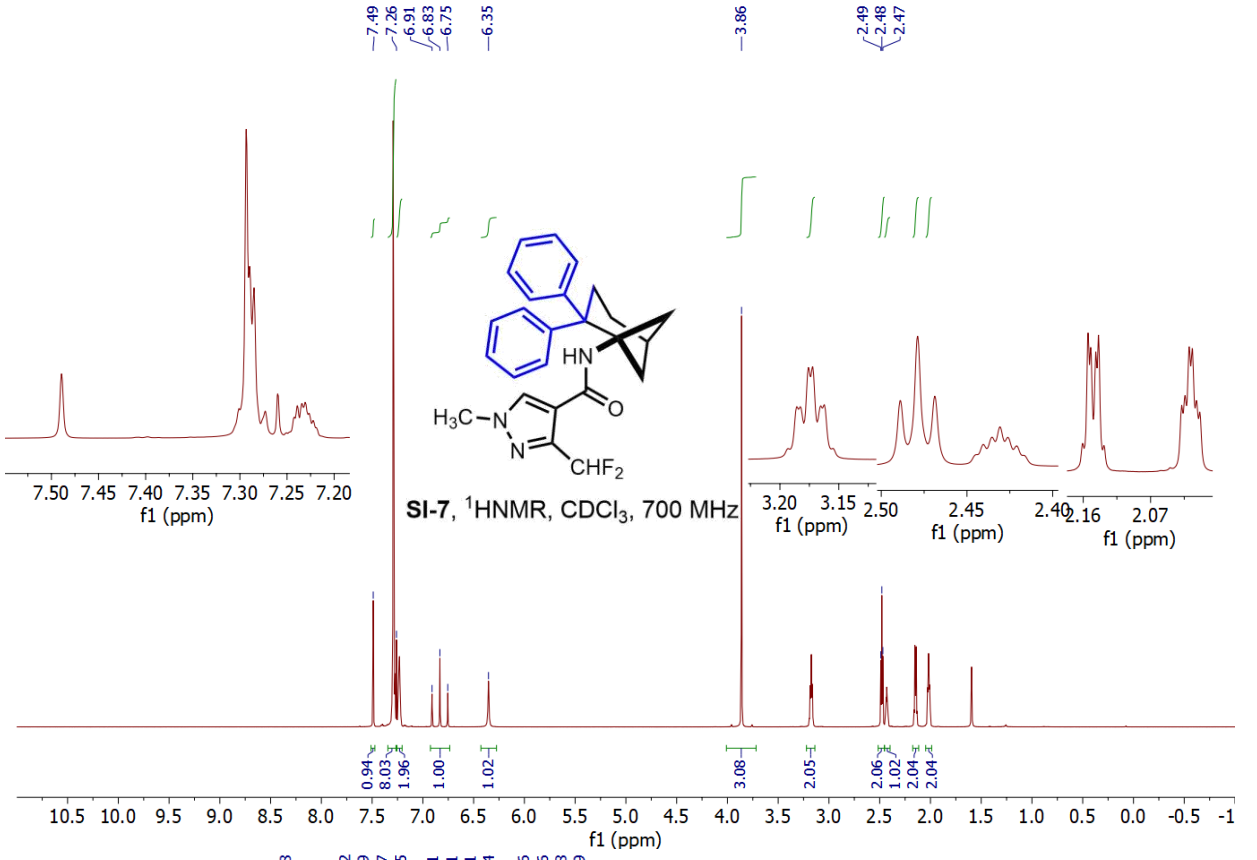
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 160.8, 147.2, 143.7 (app. t, *J* = 26.8 Hz), 133.1, 129.1, 128.1, 126.4, 118.6, 110.8 (app. t, *J* = 234.6 Hz), 62.8, 56.5, 39.6, 36.5, 36.2, 29.1, 28.5 ppm

^{19}F NMR ($CDCl_3$, 376 MHz): δ = -112.1 (app. d, *J* = 54.2 Hz) ppm

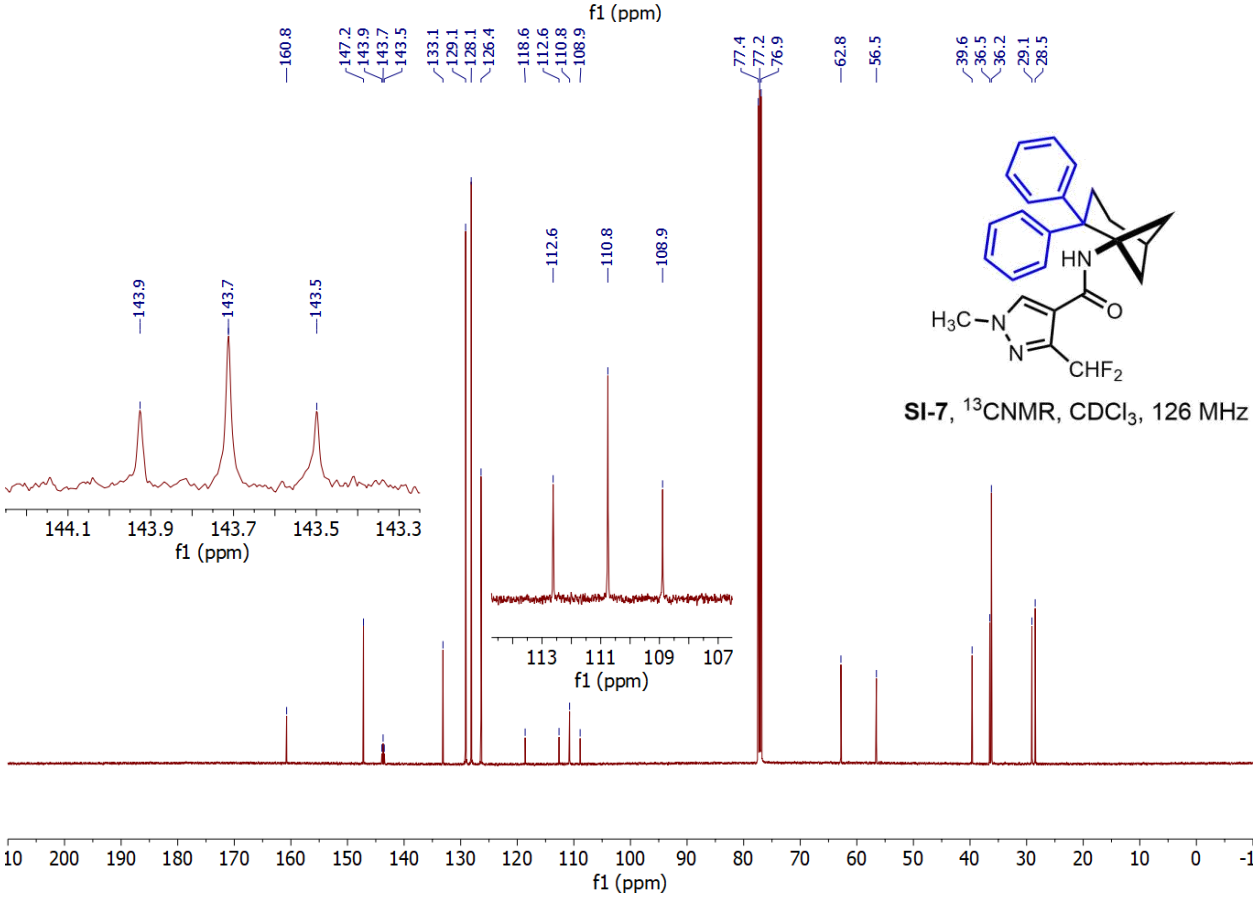
IR (neat): 3434, 2952, 2865, 1658, 1545, 1514, 1493, 1444, 1335, 1273, 1175, 1128, 1072, 1016, 890, 862, 809, 782, 765, 751, 704 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{25}H_{26}F_2N_3O^+$: 422.2038, Found: 422.2028

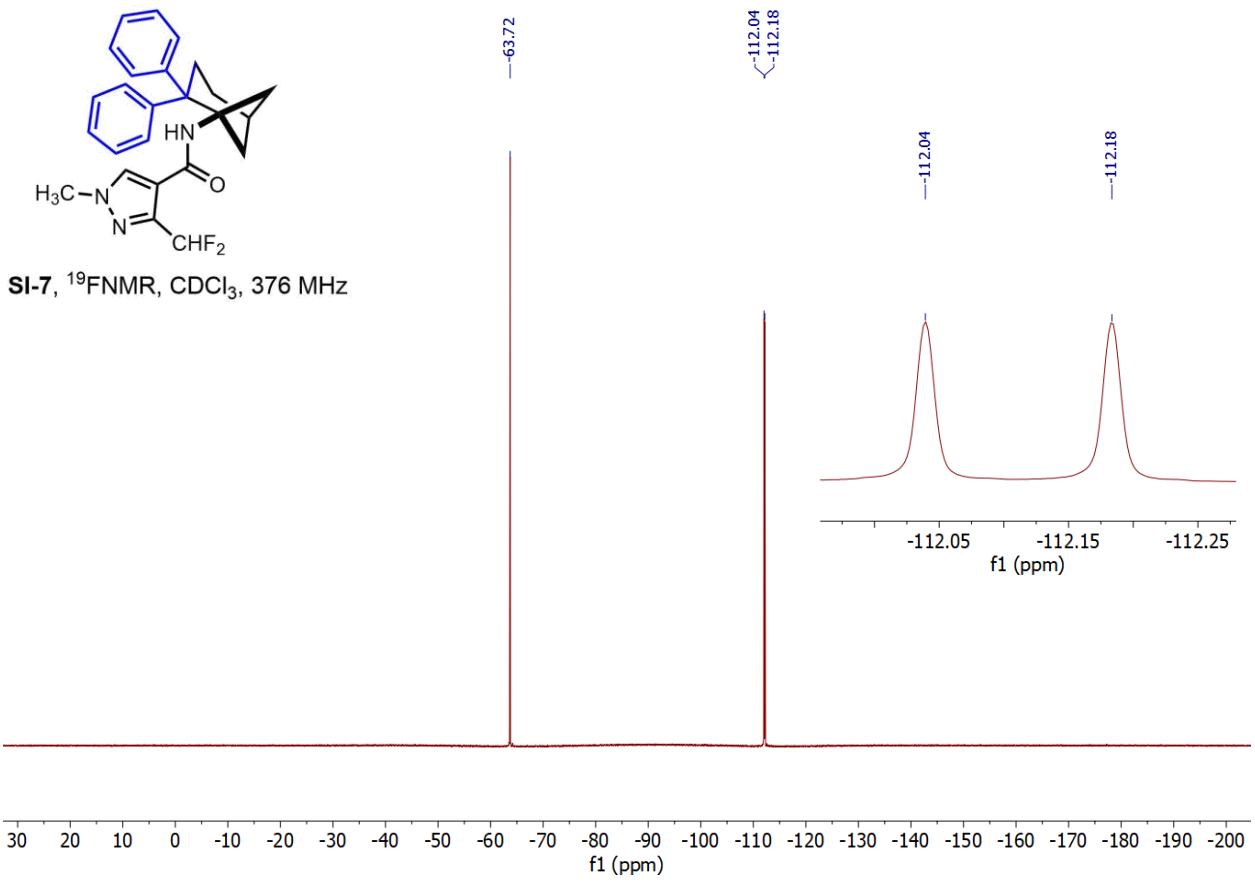
R_f = 0.75 (60% ethyl acetate : 39% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



SI-7, ^{1}HNMR, $CDCl_3$, 700 MHz



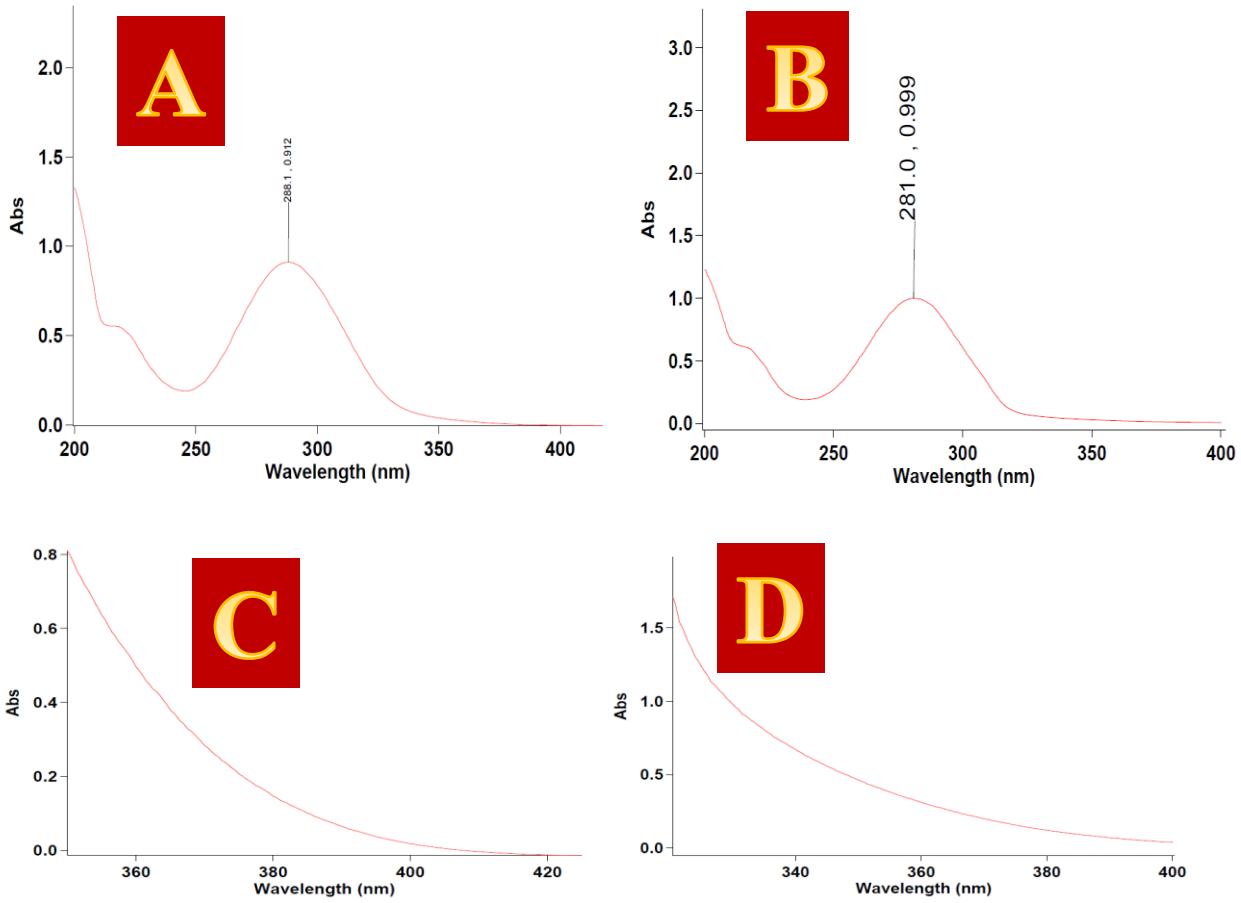
SI-7, ^{13}CNMR, $CDCl_3$, 126 MHz



SI-7, ^{19}FNMR, $CDCl_3$, 376 MHz

IV.F. UV-Vis Spectra

In our previous studies of the UV-Vis spectra of 4-nitrobenzimines, we have observed a strong absorbance (extinction coefficient ~1.7 x 10^4 $M^{-1}cm^{-1}$) around 300 nm, a weak absorbance (extinction coefficient ~200 $M^{-1}cm^{-1}$) around 380 nm, the latter of which corresponds to the transition we believe leads to the formal cycloaddition reactivity. The latter peak is poorly resolved from the tail of the former peak but appeared as a well-defined shoulder with a local maximum. We attributed the peak at lower wavelength to the pi-to-pi star transition, and the peak at longer wavelength to the n-to-pi star transition, consistent with many examples in the imine literature.[1] However, it is sometimes observed that the n-to-pi star transition of aryl imines is convoluted by or covered by the pi-to-pi star transition. This would appear to be the case with **2a**, as a large peak was observed in the expected position for the pi-to-pi star transition (SI Figure 5A, 5B) but no defined peak or significant shoulder was observed in the range consistent with the observed reactivity (SI Figure 5C, 5D). Similar results were observed in CH_3CN and hexanes.



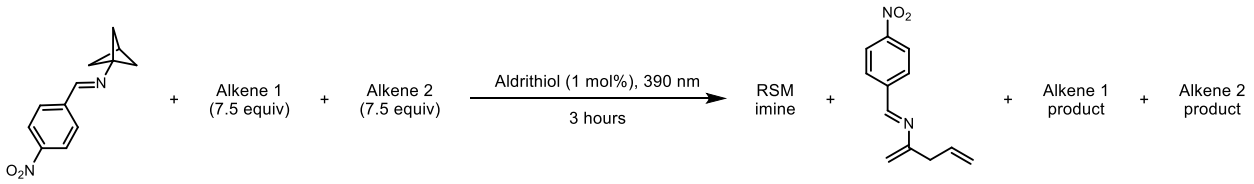
SI Figure 5: A. 50 µM solution of **2a** in CH_3CN in a 1 cm path length quartz cuvette, showing an absorption maximum at 288 nm with an extinction coefficient of 1.8 x 10^4 $M^{-1}cm^{-1}$, values comparable to those of similar imines studied in our previous work.[2] B. 50 µM solution of **2a** in hexanes in a 1 cm path length quartz cuvette, showing an absorption maximum at 281 nm with an extinction coefficient of 2.0 x 10^4 $M^{-1}cm^{-1}$, comparable to those values for acetonitrile. C. 1 mM solution of **2a** in in CH_3CN a 1 cm path length quartz cuvette, showing no obvious peak or shoulder in the range corresponding to the radiation that effects the desired chemistry. D. 1 mM solution of **2a** in in hexanes a 1 cm path length quartz cuvette, showing no obvious peak or shoulder in the range corresponding to the radiation that effects the desired chemistry.

IV.G. Competition experiments

We performed a competition experiment study to gauge the relative radical trapping aptitudes of several alkenes that were effective substrates for the formal (4+2)-cycloaddition. The alkenes chosen for the study did not form significant amounts of the cyclobutene-containing byproducts shown in the main text, making the comparison of the relative concentrations of the corresponding formal cycloadducts a fair metric for establishing relative rates of radical capture. Based on our study, the relative aptitude of trapping the relevant diradical intermediate (ignoring minor side reactivity) followed the following trend:

2-chloroacrylonitrile >>> 2-vinylpyridine >> 4-CF_3-styrene > styrene > 4-OMe-styrene >> ethyl cinnamate

This trend is fairly consistent with the trends observed in isolated and assay yields when employing each of the alkenes under the standard conditions (at longer reaction times, ~16 hours). Based on this competition study and our scope study, 2-substituted acrylonitriles and other captodative olefins appear to be an exceptionally effective class of substrates for the formal (4+2)-cycloaddition.[3] While the relatively low yield of (±)-**4af** may appear at first glance to violate this trend, one would expect the bicyclic system to lock the nitrogen lone pair in **19** perpendicular to the pi system, rendering **19** a non-captodative olefin.



0.4 mmol

Alkene 1	Alkene 2	RSM imine	ByPdt	Alkene 1 pdt	Alkene 2 pdt
Styrene	Ethyl cinnamate	0.94	1.13	1.00	0.52
Styrene	4-CF_3-styrene	0.68	1.00	0.88	0.99
Styrene	4-OMe-styrene	1.30	1.00	1.00	0.80
Styrene	2-vinylpyridine	1.03	1.00	1.29	2.11
2-chloroacrylonitrile	2-vinylpyridine	--	--	>10	1

SI Figure 6: Competition experiments were performed, and the molar ratios are reported here in tabular format. Molar ratios were determined using ^{1}HNMR with a relaxation delay of T_1 = 25 seconds to ensure meaningful integrations. In the case where Alkene 1 = 2-chloroacrylonitrile and Alkene 2 = 2-vinylpyridine, the starting material imine and diene byproduct were not identified in the reaction mixture (denoted with --).

IV.G. Simplified cost/accessibility analysis (prices as of 07/23/2021)

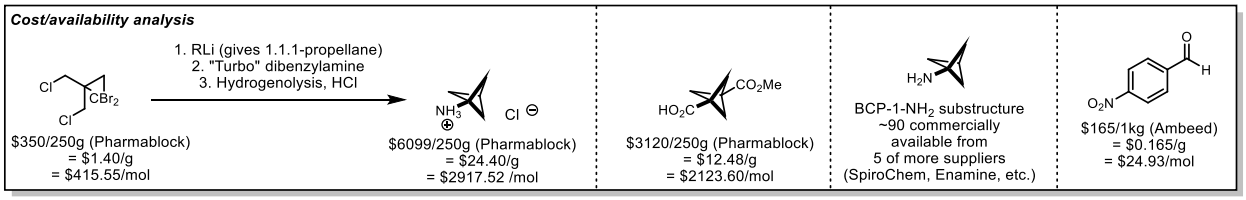
Synthesis of BCP-containing species typically proceeds through bridge-head functionalization reactions of [1.1.1]propellane, an unstable, polymerization-prone species (furthermore, a species synthesized from pyrophoric alkyl lithium reagents) that laboratories focused on medicinal chemistry may not wish to generate and handle.[4] Fine chemical companies have responded to this reality by developing scalable procedures for the synthesis of [1.1.1]propellane and commercializing a number of BCP-containing building blocks.[5] Two of the most affordable BCP-containing precursors to BCP-1-NH_2-derived imines are bicyclo[1.1.1]pentan-1-amine hydrochloride and 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid, the former of which can be condensed with 4-nitrobenzaldehyde to give **2a** in quantitative yield without the need for column chromatography (SI Figure 7). Despite their relatively high cost, BCP-1-NH_2 compounds are increasingly commercially available, with approximately 90 such compounds being available from 5 or more suppliers. Additional BCP-1-NH_2 compounds are available from 4 or fewer suppliers.

At the time of the writing of this document, the price of 4-nitrobenzaldehyde, the "photo-auxiliary" employed in this study to form the reactive imine for cycloaddition, is negligible compared to the cost of bicyclo[1.1.1]pentane-containing building blocks (SI Figure 7).

The commercial alkenes employed in this study were used as received. For many of these alkenes, the commercial samples include a small amount of a (typically phenolic) polymerization inhibitor. These inhibitors were tolerated and likely beneficial to reaction outcome by slowing the formation of solids.

The wavelengths of light employed in this work (wavelength maxima from 370 nm to 456 nm were effective) are accessible with affordable LED lights (no specialized photoreactor required) and easy to use safely. Lights/lamps with ~390 nm emission maxima are routinely sold to the general public at low cost as "black lights."

The chemistry described in this manuscript does not require the use of a glovebox or refined Schlenk techniques. While an inert atmosphere may be somewhat beneficial to reaction yield, degassing is unnecessary to achieve useful yields. The reactions may be conducted effectively in a "dump, stir, and irradiate" fashion.



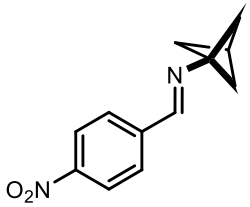
SI Figure 7: Costs of relevant starting materials at 250+ gram scale from several low-cost vendors and general availability of primary bicyclo[1.1.1]pentan-1-amines (based on SciFinder® search conducted on 07/23/2021)

V. Experimental procedures; Characterization and Spectroscopic Data (Pertaining to the Main Text)

General Procedure A (Wittig reaction for alkene synthesis): Methyltriphenylphosphonium bromide (1.5 equiv) was dissolved in tetrahydrofuran (0.05 M concentration). The solution was then cooled in a -78 °C dry ice/acetone bath and *n*-BuLi (2.6 M in hexanes, 1.3 equiv) was added dropwise over 10 minutes. The reaction mixture was allowed to stir at -78 °C for an hour. Ketone (1.0 equiv) in THF (0.05 M concentration) was then added to the reaction mixture dropwise over 10 minutes. The reaction mixture was stirred at -78 °C for 2 hours before being allowed to warm to room temperature and stirring for a further 14 hours. The reaction was then quenched with saturated aqueous ammonium chloride solution (200 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude material was then purified via column chromatography (100% hexanes to 100% ethyl acetate using a gradient).

General Procedure B (formal (4+2)-cycloaddition): To an oven-dried 1-dram vial was added bicyclopentan-1-amine-derived imine (0.4 mmol), 2,2'-dipyridyldisulfide (1 mol %), and alkene (7.5 equivalents). The vial was sealed with a cap containing a Teflon-lined septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The cap was further sealed with Parafilm and was irradiated with 390 nm lamps in the batch apparatus configuration (for full apparatus details, see the above section II. Equipment for Photochemistry) for the specified amount of time (~16 hours). The crude reaction mixture was purified by column chromatography.

Compound **2a**:



Method involving chromatography: To a flame-dried 250 mL round bottom flask equipped with a 3 cm egg-shaped magnetic stir bar was added bicyclo[1.1.1]pentan-1-amine hydrochloride (2.50 g, 20.9 mmol, 1 equiv) and dichloromethane (124 mL). The flask was capped with a rubber septum and the reaction mixture was put under argon atmosphere. The flask was wrapped in aluminum foil to shield the reaction mixture from light. Triethylamine (2.91 mL, 20.9 mmol, 1.0 equiv) was added with stirring in one portion via syringe. 4-Nitrobenzaldehyde (3.16 g, 20.9 mmol, 1 equiv) was added in one portion by briefly removing the septum, pouring in the solid, and replacing the septum. The reaction mixture was stirred at room temperature for two hours. Celite (30 g) was then added to the flask and the reaction mixture was concentrated onto the celite in vacuo. The resulting powder was loaded onto a silica column that was neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine. The reaction mixture was chromatographed eluting with 6-27% ethyl acetate in hexanes to give **2a** (4.24 g, 19.6 mmol, 94%) as a faintly yellow crystalline solid.

Method not involving chromatography (small scale): To an oven-dried 50 mL round bottom flask equipped with a 3 cm oval magnetic stir bar was added bicyclo[1.1.1]pentan-1-amine hydrochloride (218 mg, 1.82 mmol, 1.1 equiv) and dichloromethane (12.4 mL). The flask was capped with a rubber septum and the reaction mixture was put under argon atmosphere. The flask was wrapped in aluminum foil to shield the reaction mixture from light. Triethylamine (0.277 mL, 1.99 mmol, 1.2 equiv) was added with stirring in one portion via syringe. 4-Nitrobenzaldehyde (250 mg, 1.65 mmol, 1 equiv) was added in one portion by briefly removing the septum, pouring in the solid, and replacing the septum. The reaction mixture was stirred at room temperature for 24 hours (not rigorously monitored). The mixture was diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and the layers separated. The aqueous layer was further extracted with dichloromethane (2 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give **2a** as a faintly yellow solid (349.2 mg, 1.62 mmol, 98%).

Method not involving chromatography (large scale): To an oven-dried 500 mL round bottom flask equipped with a 3 cm oval magnetic stir bar was added bicyclo[1.1.1]pentan-1-amine hydrochloride (6.093 g, 50.95 mmol, 1.1 equiv) and dichloromethane (200 mL). The flask was capped with a rubber septum and the reaction mixture was put under argon atmosphere. The flask was wrapped in aluminum foil to shield the reaction mixture from light. Triethylamine (12.9 mL, 92.6 mmol, 2 equiv) was added with stirring in one portion via syringe. 4-Nitrobenzaldehyde (7.00 g, 46.3 mmol, 1 equiv) was added in one portion by briefly removing the septum, pouring in the solid, and replacing the septum. The reaction mixture was stirred at room temperature for 16 hours (not rigorously monitored). The mixture was diluted with saturated aqueous $NaHCO_3$ solution (50 mL) and the layers separated. The aqueous layer was further extracted with dichloromethane (2 x 25 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give **2a** as a faintly yellow solid (9.97 g, 46.1 mmol, 99.5%).

Note: **2a** crystallizes from conveniently from boiling hexanes. Concentration from hexanes/ethyl acetate solution also typically provides crystalline material. Concentration from dichloromethane solution typically provides amorphous solid material. We have not observed any difference in performance between the crystalline and amorphous forms of **2a** in the formal (4+2)-cycloaddition chemistry reported herein.

Appearance: faintly yellow solid

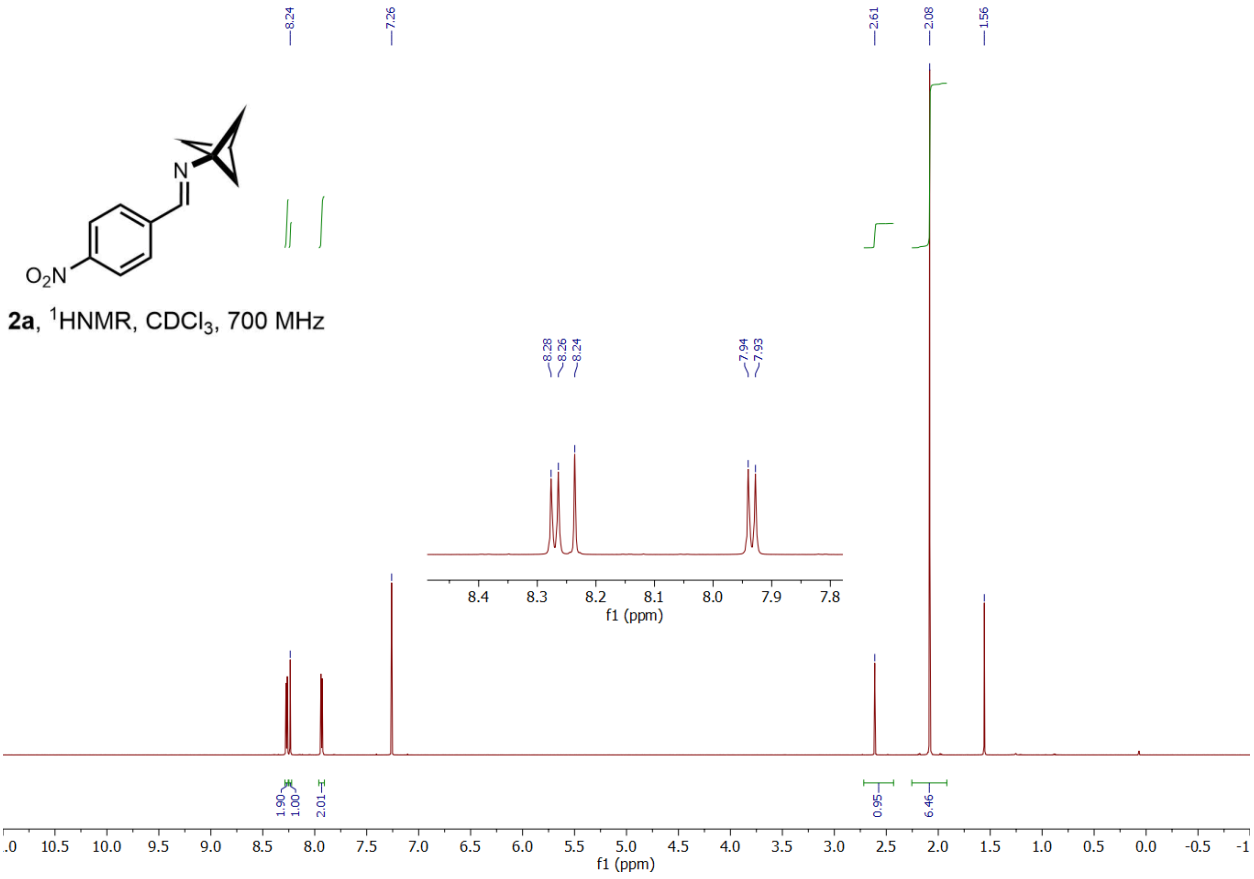
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.29-8.25 (m, 2H), 8.24 (s, 1H), 7.95-7.91 (m, 2H), 2.61 (s, 1H), 2.08 (s, 6H) ppm

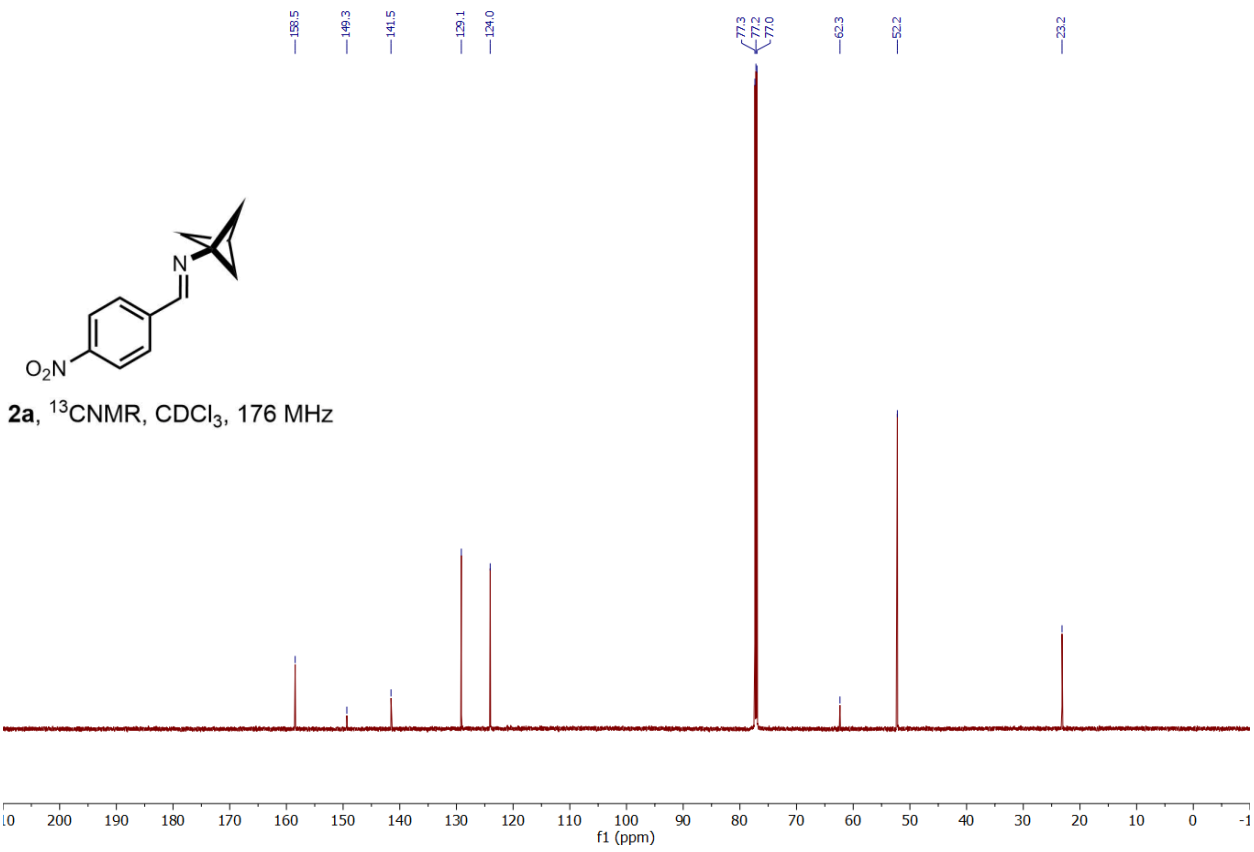
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 158.5, 149.3, 141.5, 129.1, 124.0, 62.3, 52.2, 23.2 ppm

IR (neat): 3109, 3011, 2975, 2871, 1728, 1635, 1601, 1520, 1424, 1341, 1315, 1290, 1253, 1208, 1112, 1063, 1012, 962, 927, 861, 841, 792, 745, 688 cm^{-1}

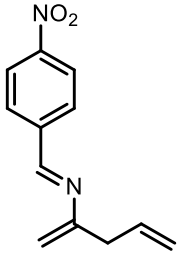
HRMS (ES+, m/z) calculated for $C_{12}H_{13}N_2O_2^+$: 217.0972, Found: 217.0965

R_f = 0.53 (25% ethyl acetate: 74% hexanes : 1% aqueous NH_4OH), one yellow spot, $KMnO_4$, UV





Compound **5**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added **2a** (216 mg, 1.00 mmol, 1 equiv) and dichloromethane (5 mL). The vial was sealed with a cap containing a Teflon-lined septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 20 hours with two 390 nm PR160L Kessil lamps positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. External vial temperature stabilized at ~35-40 °C. After cooling to room temperature, the reaction mixture was concentrated onto celite (3 g) and loaded atop a silica column (that had been pre-neutralized with 3 column volumes of 5% dichloromethane : 94% hexanes : 1% Et_3N). The mixture was chromatographed eluting with 6-27% ethyl acetate in hexanes to give **5** (84.9 mg, 0.393 mmol, 39%) as a faintly yellow oil. *Note:* after ~2 days on the bench in a vial sealed under air, **5** shows substantial decomposition by ^{1}HNMR.

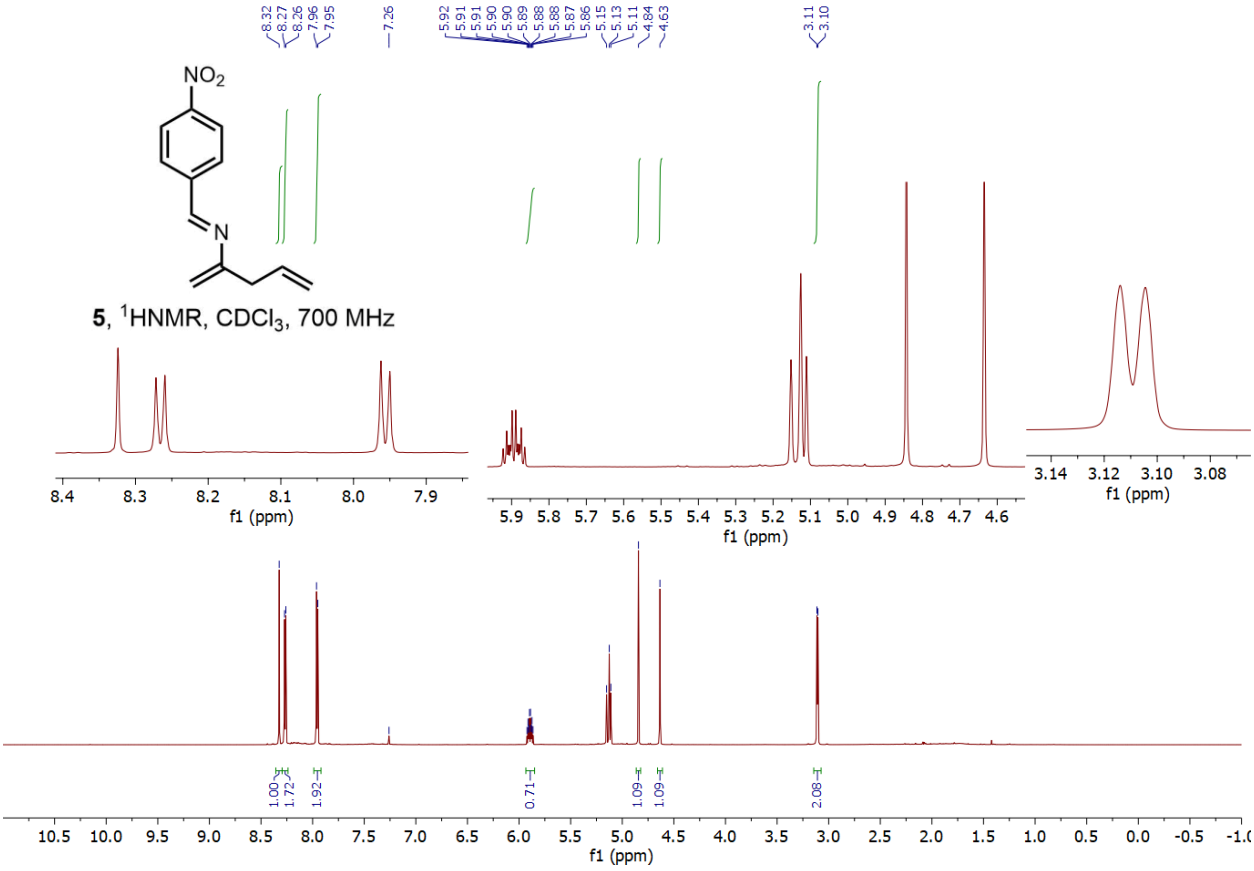
Appearance: faintly yellow oil

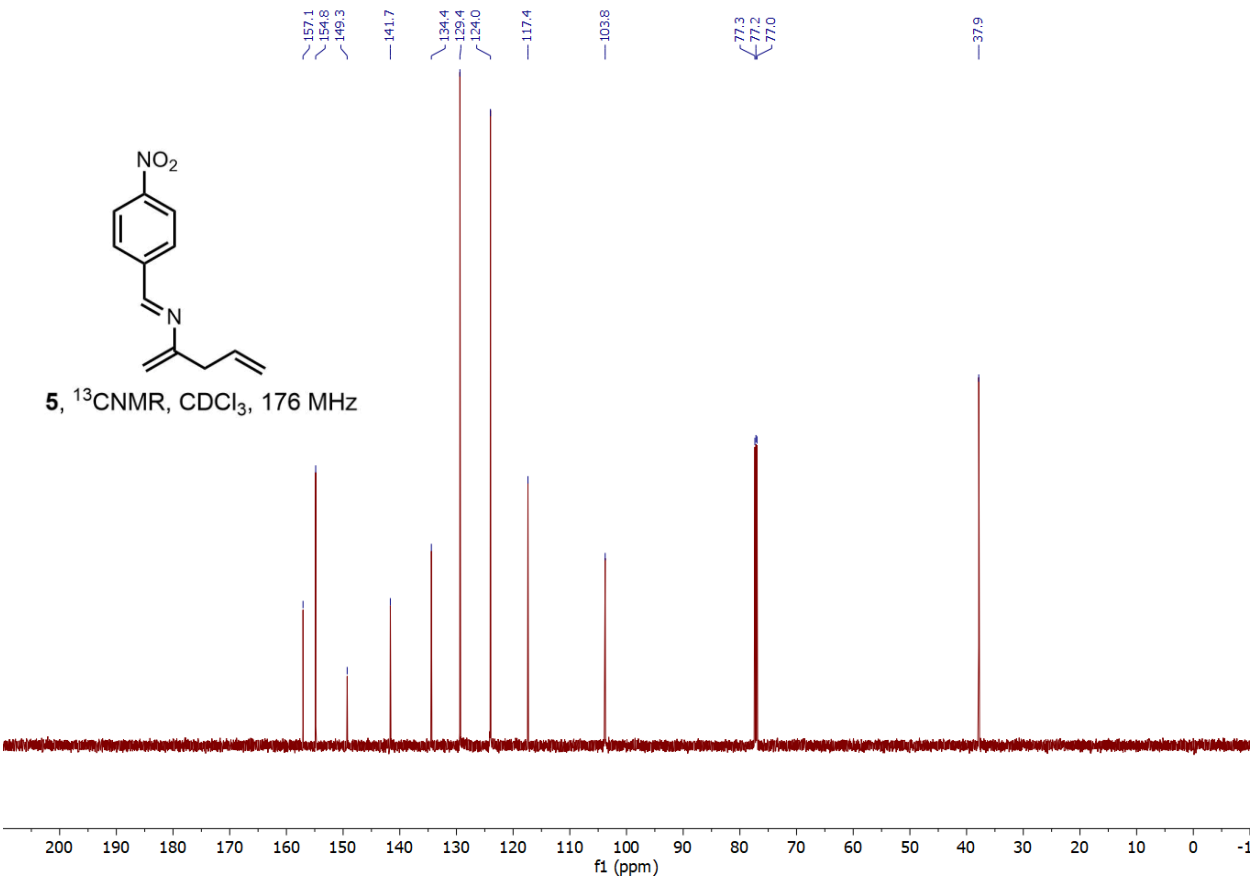
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.32 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 5.89 (qt, *J* = 10.2, 6.7 Hz, 1H), 5.16-5.10 (m, 2H) 4.84 (s, 1H), 4.63 (s, 1H), 3.11 (d, *J* = 6.6 Hz, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 157.1, 154.8, 149.3, 141.7, 134.4, 129.4, 124.0, 117.4, 103.8, 37.9 ppm

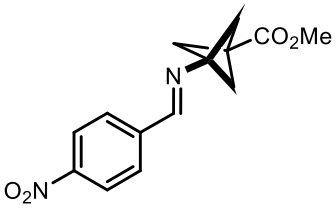
HRMS (ES+, m/z) calculated for $C_{12}H_{13}N_2O_2^+$: 217.0972, Found: 217.0964

R_f = 0.36 (10% ethyl acetate : 89% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV





Compound **2b**:



To a flame-dried 500 mL round bottom flask equipped with a 3 cm egg-shaped magnetic stir bar was added 3-(Methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (7.00 g, 41.1 mmol, 1 equiv) followed by *tert*-butanol (175 mL). The mixture was stirred and triethylamine (6.31 mL, 45.3 mmol, 1.1 equiv) was added in one portion via syringe. Diphenyl phosphoryl azide (9.75 mL, 45.3 mmol, 1.1 equiv) was added dropwise via syringe over 5 minutes with stirring.

CAUTION: Diphenyl phosphoryl azide is toxic and must be handled with special care during reaction set-up and reaction workup/waste management.

The headspace was flushed with nitrogen, the flask was sealed with a rubber septum with a nitrogen inlet, and the mixture was stirred at room temperature under nitrogen atmosphere for 1 hour. The rubber septum was then replaced with a reflux condenser topped with a rubber septum with a nitrogen inlet. The reaction apparatus was placed behind a blast shield and was heated to reflux in a 100 °C aluminum heating block for 6 hours.

CAUTION: The reaction evolves nitrogen gas upon heating.
The reaction mixture was allowed to cool to room temperature. The solvent was removed in vacuo to give a pasty white solid. This residue was diluted with ethyl acetate (250 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 125 mL) and brine (125 mL). The aqueous fractions were discarded (azide-containing aqueous waste stream) and the organic fraction was dried over sodium sulfate, filtered, and dried in vacuo in a 500 mL round bottom flask to a white solid, which was used without further purification.

A stir bar was added to the flask along with dichloromethane (140 mL). The flask was sealed with a rubber septum and the headspace was flushed with nitrogen. Trifluoroacetic acid (35 mL) was added dropwise over 15 minutes. The mixture was allowed to stir at room temperature under nitrogen for 5 hours. The solvent was carefully removed in vacuo to give a yellow oil, which was used without further purification.

CAUTION: Trifluoroacetic acid is corrosive. The rotary evaporator trap was loaded with saturated aqueous sodium bicarbonate solution to neutralize the condensing trifluoroacetic acid as it came over.

The residue was taken up in dichloromethane (210 mL), the flask was equipped with a rubber septum, and the reaction mixture was put under argon. The flask was shielded from light with aluminum foil. Triethylamine (17.2 mL, 123 mmol, 3.0 equiv) was added dropwise over 5 minutes with stirring. The septum was briefly removed and 4-nitrobenzaldehyde (6.22 g, 41.1 mmol, 1.0 equiv) was added in one portion. The septum was replaced, and the mixture was stirred under argon at room temperature for 7 hours. Celite (25 g) was added to the flask and the reaction mixture was concentrated onto the celite in vacuo. The resulting pasty solid mass was loaded onto a silica column that was neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine. The reaction mixture was chromatographed eluting with 3-58% ethyl acetate in hexanes to give ~9.5 grams of fairly pure **2b**. This material was recrystallized from hot hexanes/ethyl acetate to give **2b** (7.26 g, 26.5 mmol, 64%) as a faintly yellow solid.

Appearance: faintly yellow solid

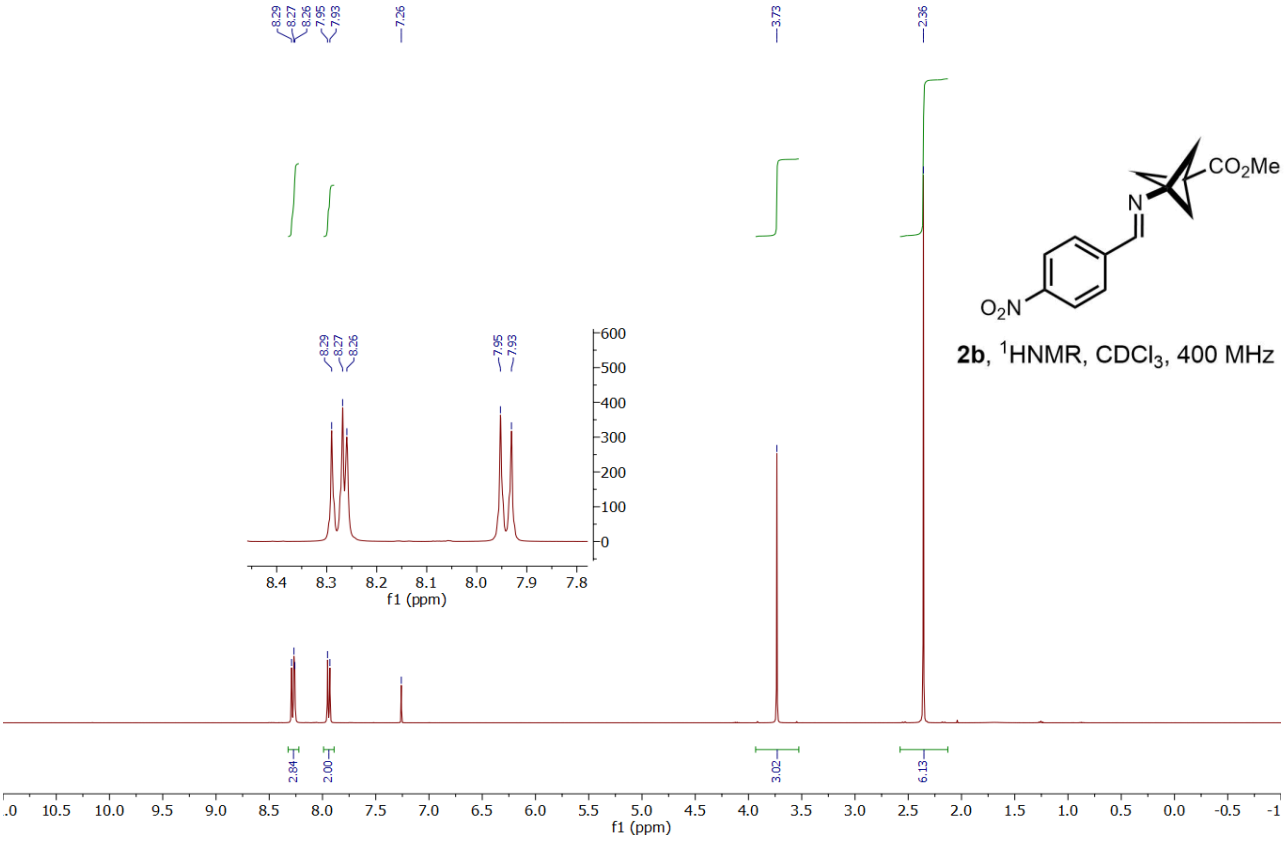
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.30-8.24 (m, 3H), 7.97-7.91 (m, 2H), 3.73 (s, 3H), 2.36 (s, 6H) ppm

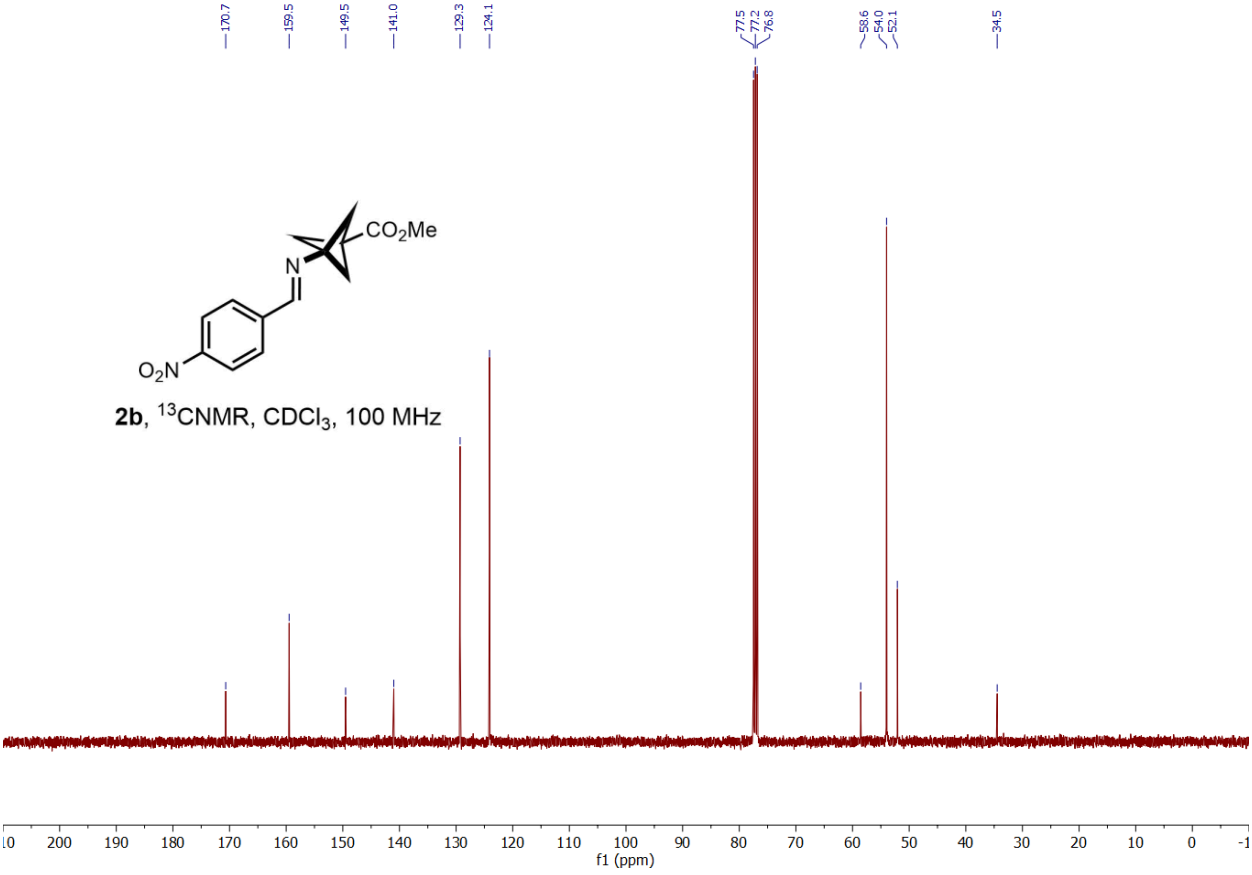
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 159.5, 149.5, 141.0, 129.3, 124.1, 58.6, 54.0, 52.1, 34.5 ppm

IR (neat): 3104, 3007, 2956, 2915, 2862, 1727, 1635, 1598, 1505, 1443, 1425, 1338, 1314, 1289, 1258, 1201, 1107, 1094, 1061, 1004, 970, 953, 914, 862, 846, 833, 790, 750, 735, 711, 689 cm^{-1}

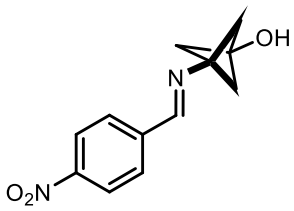
HRMS (ES+, m/z) calculated for $C_{14}H_{15}N_2O_4^+$: 275.1026, Found: 275.1021

R_f = 0.23 (20% ethyl acetate : hexanes + 0.1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


8.29
8.27
8.26
7.95
7.93
7.26
3.73
2.36
CO2Me
N
O2N
2b, 1HNMR, CDCl3, 400 MHz
f1 (ppm)


170.7
159.5
149.5
141.0
129.3
124.1
77.5
77.2
76.8
58.6
54.0
52.1
34.5
CO2Me
N
O2N
2b, 13CNMR, CDCl3, 100 MHz
f1 (ppm)

Compound **2c**:



EXPERIMENTAL PROCEDURE:

To an oven-dried 4-dram vial equipped with a 2 cm oval magnetic stir bar was sequentially added 3-aminobicyclo[1.1.1]pentan-1-ol hydrochloride (100 mg, 0.738 mmol, 1 equiv), dichloromethane (7.4 mL), deuterated chloroform (3.7 mL), triethylamine (0.308 mL, 2.21 mmol, 3 equiv), and 4-nitrobenzaldeyde. The headspace of the vial was flushed with nitrogen and the reaction mixture was allowed to stir at room temperature for 1.5 hours. The reaction mixture was concentrated onto 1 gram of celite. The resulting powdery residue was dry-loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-60% ethyl acetate in hexanes to give **2c** (100.7 mg, 0.434 mmol, 59%) as a faintly yellow solid.

Appearance: faintly yellow solid

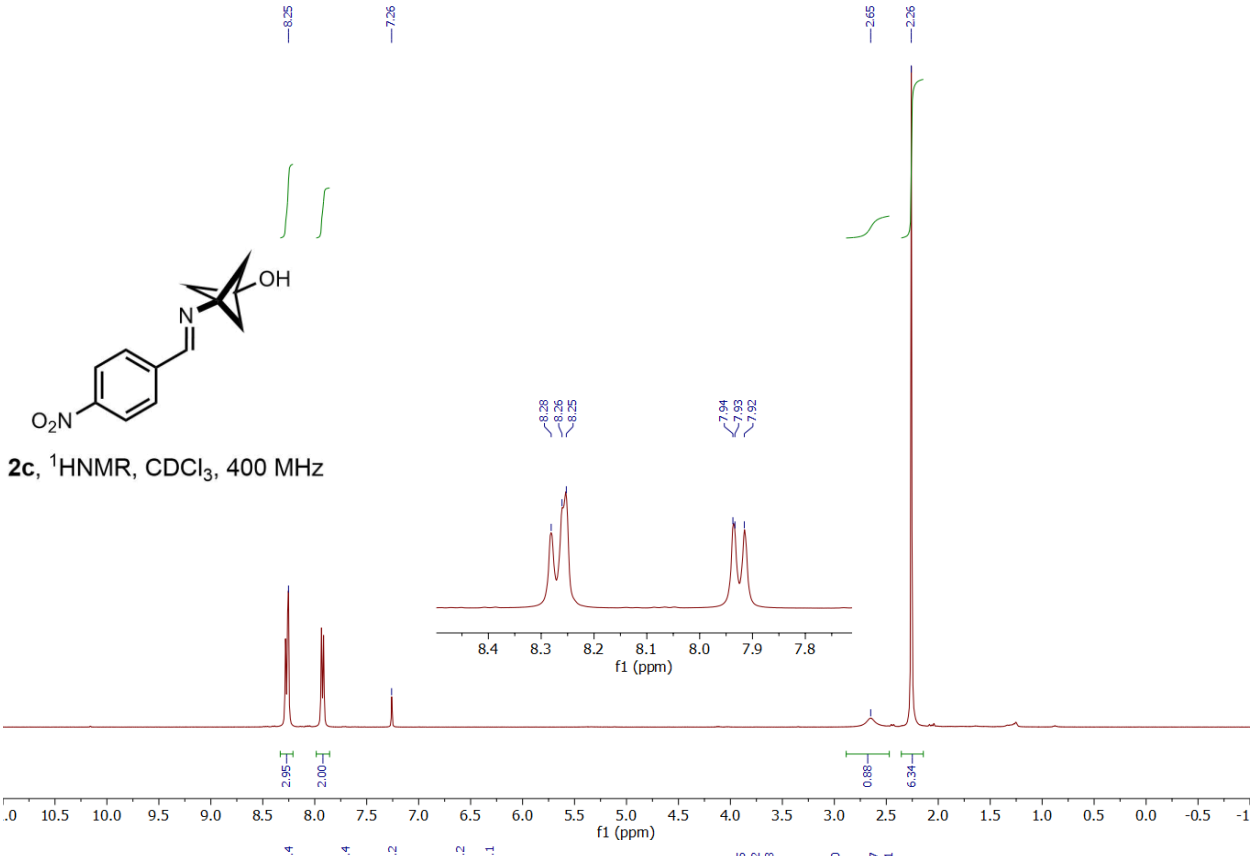
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.32-8.22 (m, 3H), 7.97-7.86 (m, 2H), 2.65 (bs, 1H), 2.26 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.4, 149.4, 141.2, 129.2, 124.1, 63.0, 55.7, 54.1 ppm

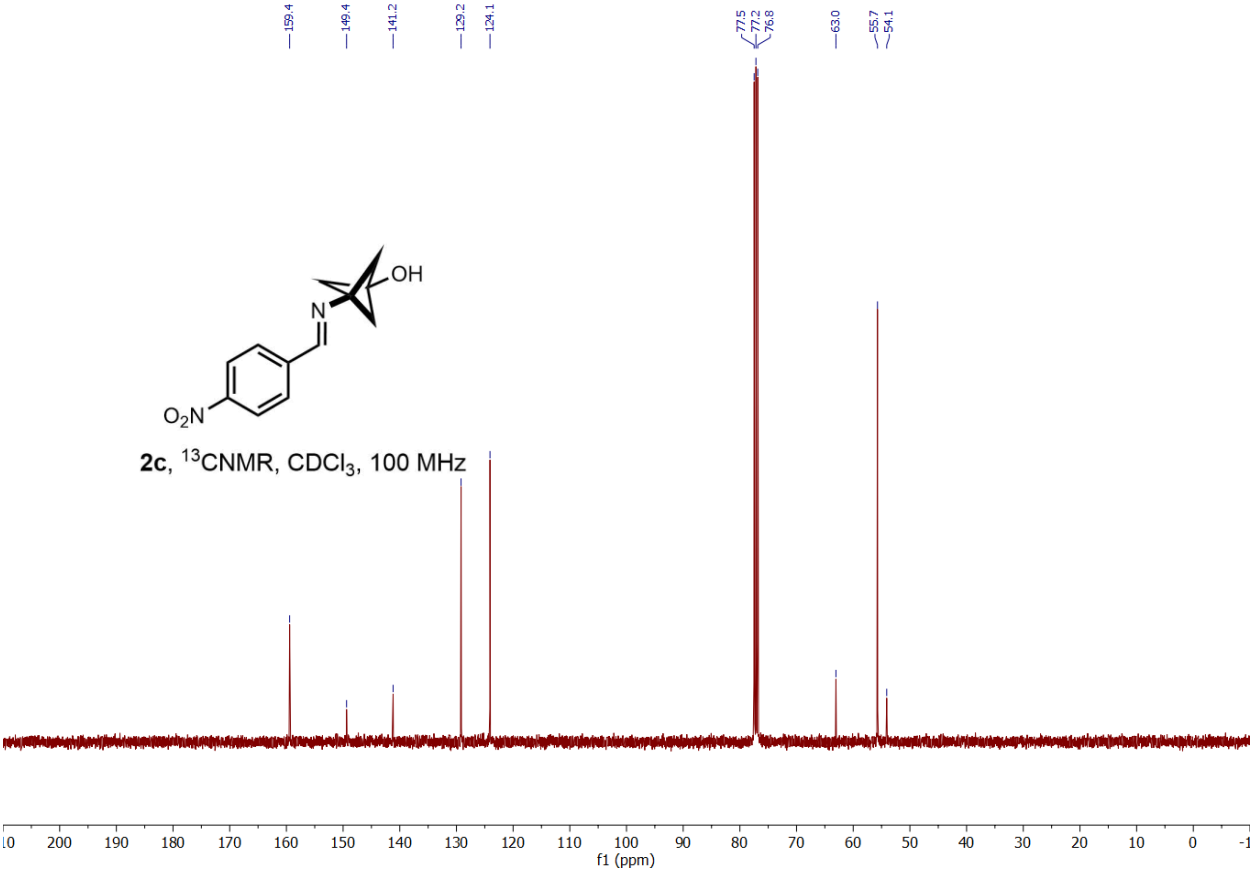
IR (neat): 3106 (broad), 2981, 2910, 2872, 1633, 1601, 1517, 1445, 1383, 1346, 1312, 1241, 1211, 1109, 1087, 1041, 1017, 994, 850, 775, 745, 690 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{12}H_{13}N_2O_3^+$: 233.0921, Found: 233.0928

R_f = 0.15 (50% ethyl acetate : 49% hexanes + 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

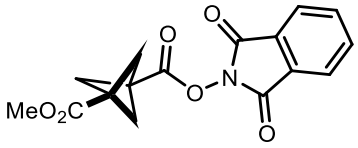


2c, ^{1}HNMR, $CDCl_3$, 400 MHz



2c, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound **SI-8**:



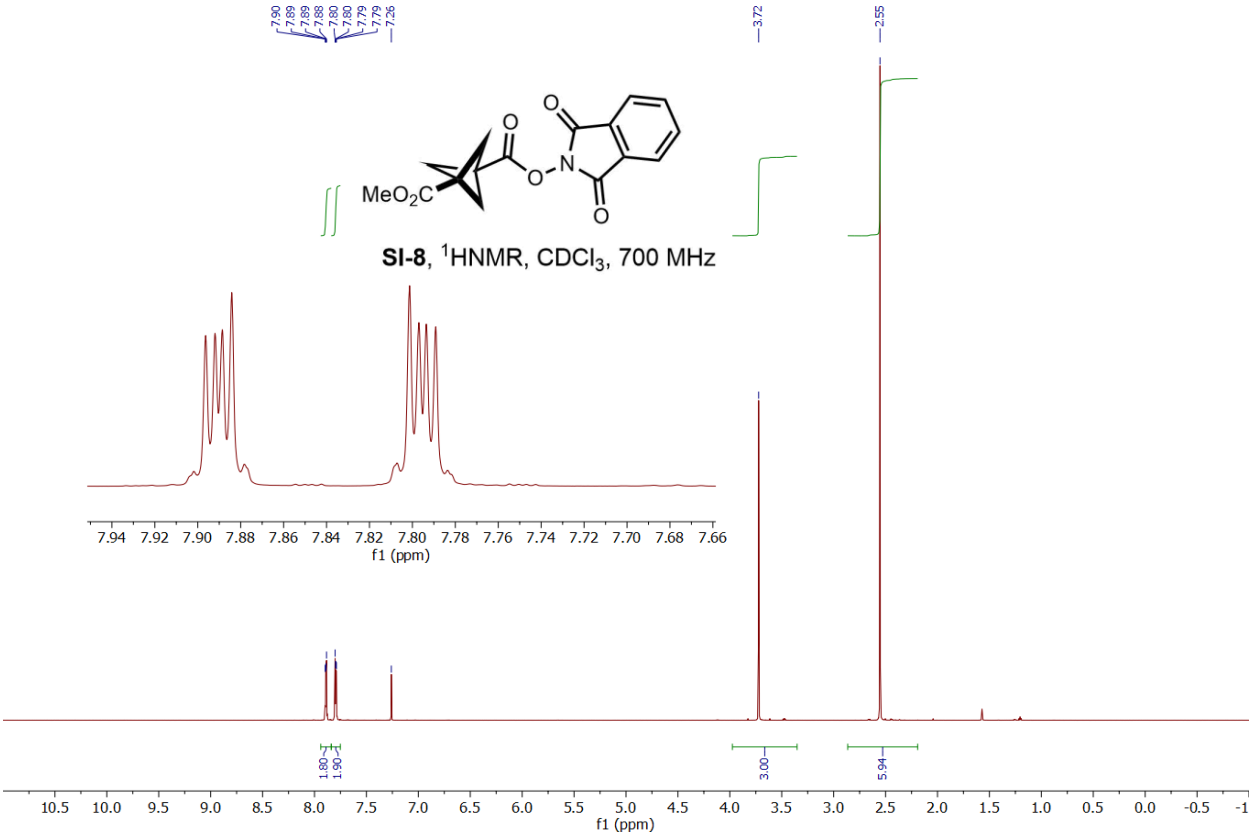
EXPERIMENTAL PROCEDURE:

The procedure drawn from published work.[6] To an oven-dried 250 mL round-bottom flask equipped with an egg-shaped stir bar were added 3-(Methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (3.00 g, 17.6 mmol, 1 equiv), *N*-Hydroxyphthalimide (2.88 g, 17.6 mmol, 1.00 equiv), and 4-(dimethylamino)pyridine (215 mg, 1.76 mmol, 0.100 equiv). The mixture was put under nitrogen atmosphere and dichloromethane (117 mL) was added and vigorous stirring was initiated. *N,N'*-Diisopropylcarbodiimide (273 mL, 17.6 mmol, 1.00 equiv) was added dropwise over 5 minutes. The mixture was allowed to stir at room temperature for 19 hours. The mixture was filtered through a pad of celite and the celite was rinsed with an additional 400 mL dichloromethane. The filtrate was concentrated onto 25 g of celite and dry loaded onto a silica gel column and eluted with 5-100 % ethyl acetate in hexanes to give **SI-8** (4.31 g, 13.7 mmol, 78%) as a white solid and its ^{1}H and ^{13}C NMR spectra match those reported in the literature.[6]

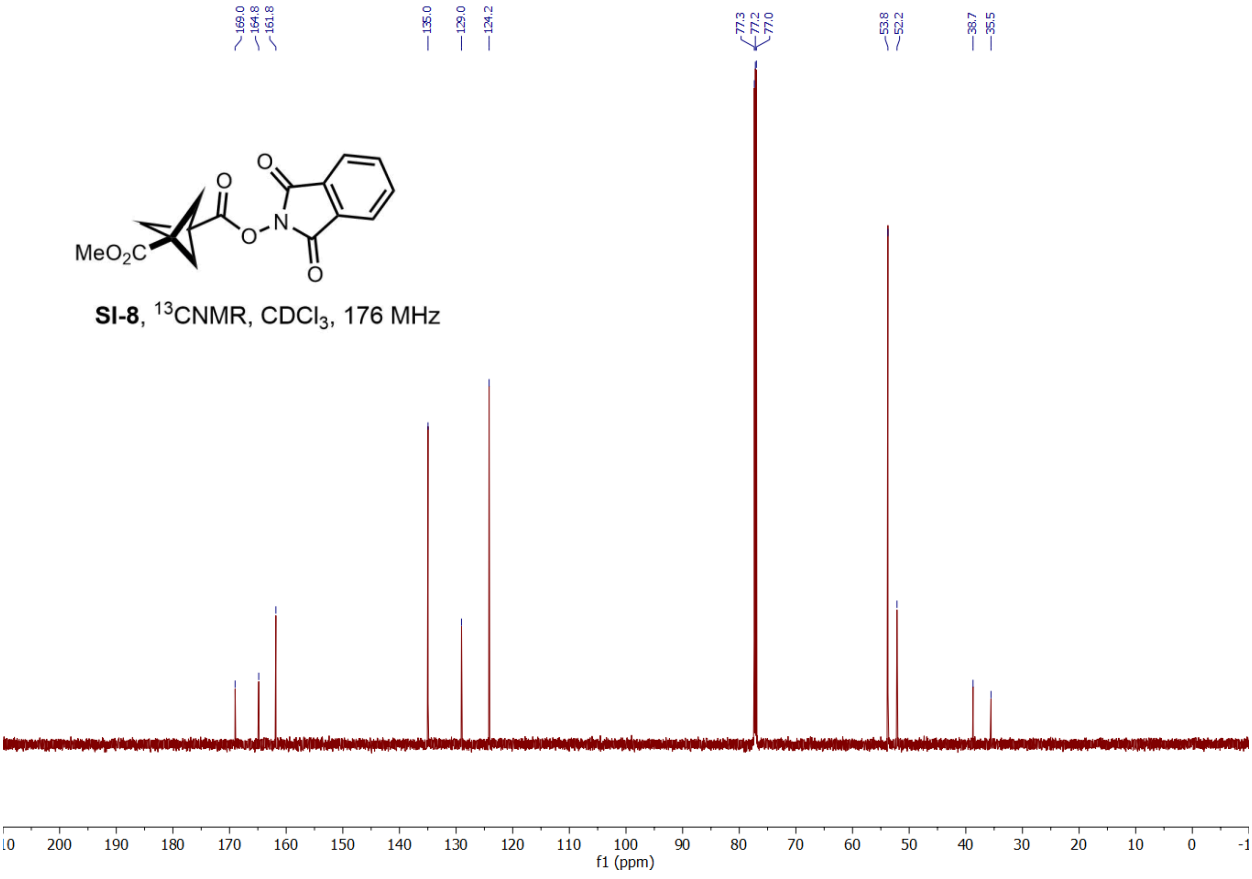
Appearance: white solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.91-7.87 (m, 2H), 7.82-7.78 (m, 2H), 3.72 (s, 3H), 2.55 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 169.0, 164.8, 161.8, 135.0, 129.0, 124.2, 53.8, 52.2, 38.7, 35.5 ppm



SI-8, ^{1}HNMR, $CDCl_3$, 700 MHz



SI-8, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound **SI-9**:

EXPERIMENTAL PROCEDURE:

The procedure was modified from a published procedure for synthesizing a related compound.[7] To an oven dried 50 mL round-bottom flask equipped with a magnetic stir bar were added .sequentially sodium benzene sulfinate (521 mg, 3.17 mmol, 2.00 equiv), **SI-8** (500 mg, 1.59 mmol, 1 equiv), copper(II) triflate (115 mg, 0.317 mmol, 0.200 equiv), and the photocatalyst 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene, 2,4,5,6-Tetrakis(9H-carbazol-9-yl) isophthalonitrile (4CzIPN) (25.0 mg, 0.0317 mmol, 0.02 equiv). Acetonitrile (8 mL) and 1,2-dimethoxyethane (8 mL) were the added. The flask was sealed with a rubber septum and the reaction mixture was sparged with argon for 15 minutes (~1 L of argon). Trifluoroacetic acid (0.244 mL, 3.17 mmol, 2.00 equiv) was then added in one portion via syringe. The flask was kept under argon atmosphere with a balloon and was irradiated for 48 hours with two 456 nm lamps, one on each side of the reaction vessel located ~6 cm away from the flask. A cooling fan was placed 10 cm above the reaction vessel. After irradiation, the mixture was concentrated onto celite (5 g) and was dry loaded atop a silica column. Elution with 7-60% ethyl acetate in hexanes gave impure **SI-9**. Repeating the same chromatographic purification two addition times gave pure **SI-9** (155.6 mg, 0.584 mmol, 37%) as a faintly yellow solid.

Appearance: faintly yellow solid

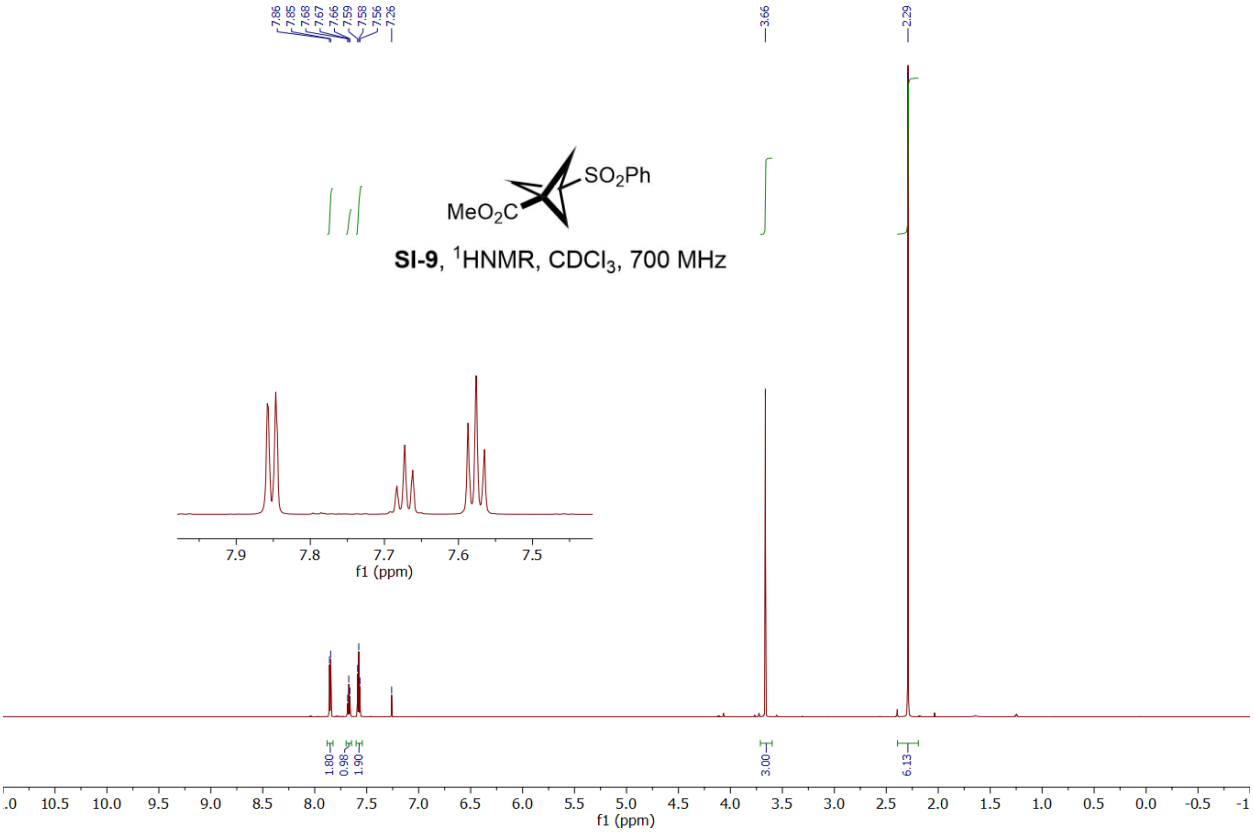
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.75 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.8 Hz, 2H), 3.66 (s, 3H), 2.29 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 168.4, 136.5, 134.1, 129.4, 128.7, 52.3, 52.0, 51.6, 36.8 ppm

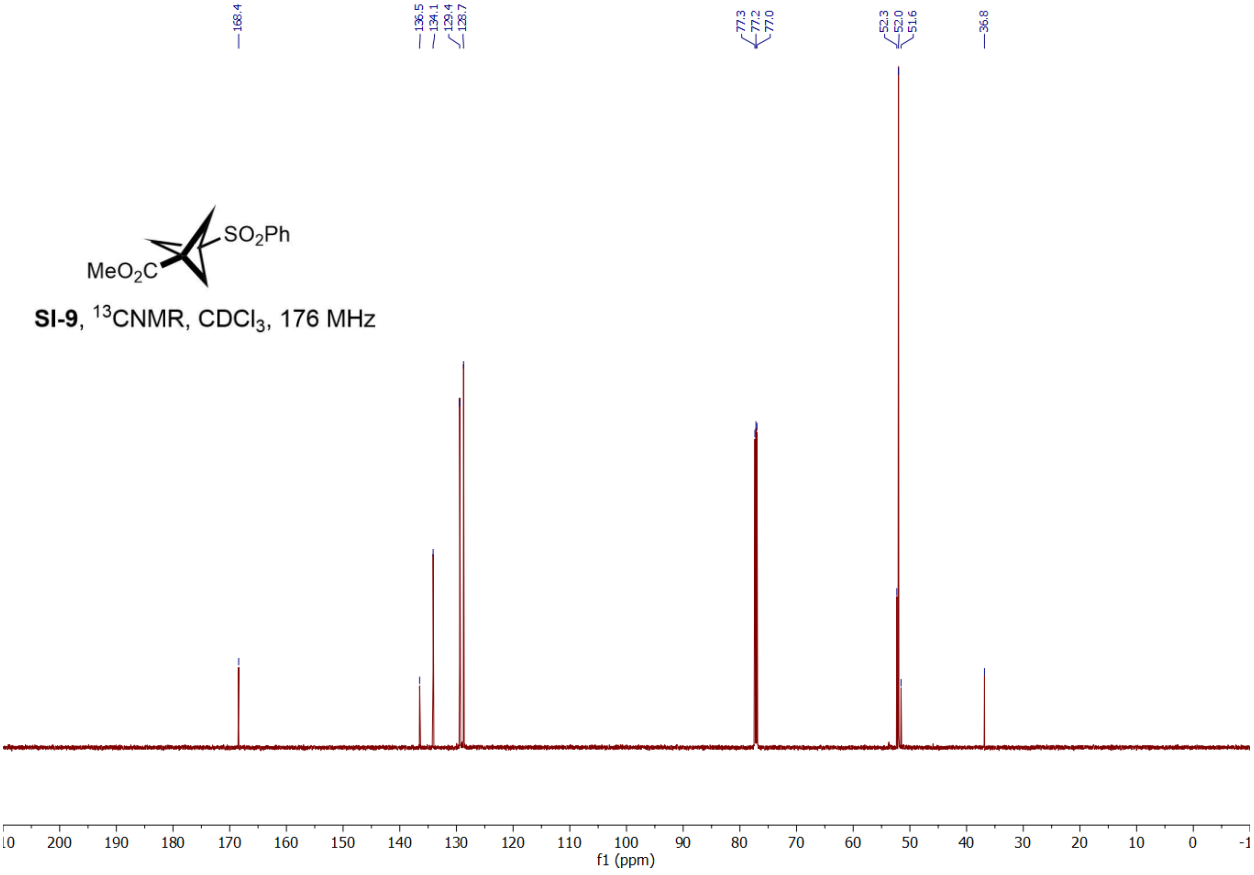
IR (neat): 2954, 1724, 1584, 1447, 1437, 1331, 1303, 1212, 1197, 1175, 1140 1089, 1073, 1028, 1014, 999, 935, 827, 795, 761, 723, 690 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{13}H_{18}NO_4S^+$ (ammonium adduct): 284.0951, Found: 284.0952

R_f = 0.36 (50% ethyl acetate: 50% hexanes), yellow spot, $KMnO_4$, UV



SI-9, ^{1}HNMR, $CDCl_3$, 700 MHz



SI-9, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound **SI-10**:

EXPERIMENTAL PROCEDURE:

To a 2-dram vial equipped with a magnetic stir bar was added **SI-9** (100.0 mg, 0.3755 mmol, 1 equiv) followed by tetrahydrofuran (4 mL), methanol (1.3 mL), and water (1.3 mL). To this stirred solution was added lithium hydroxide monohydrate (78.8 mg, 1.88 mmol, 5 equiv). The headspace was flushed with argon and the vial was sealed with a Teflon-lined cap and placed in a pre-heated aluminum block at 60 °C for 18.5 hours. The reaction mixture was then diluted with water (20 mL) and washed with dichloromethane (3 x 10 mL). The organic washes were discarded, and the aqueous phase was acidified to pH = 1 with 4N hydrochloric acid and was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to give **SI-10** (94.7 mg, 0.375 mmol, 100%) as a faintly yellow solid.

Appearance: Faintly yellow solid

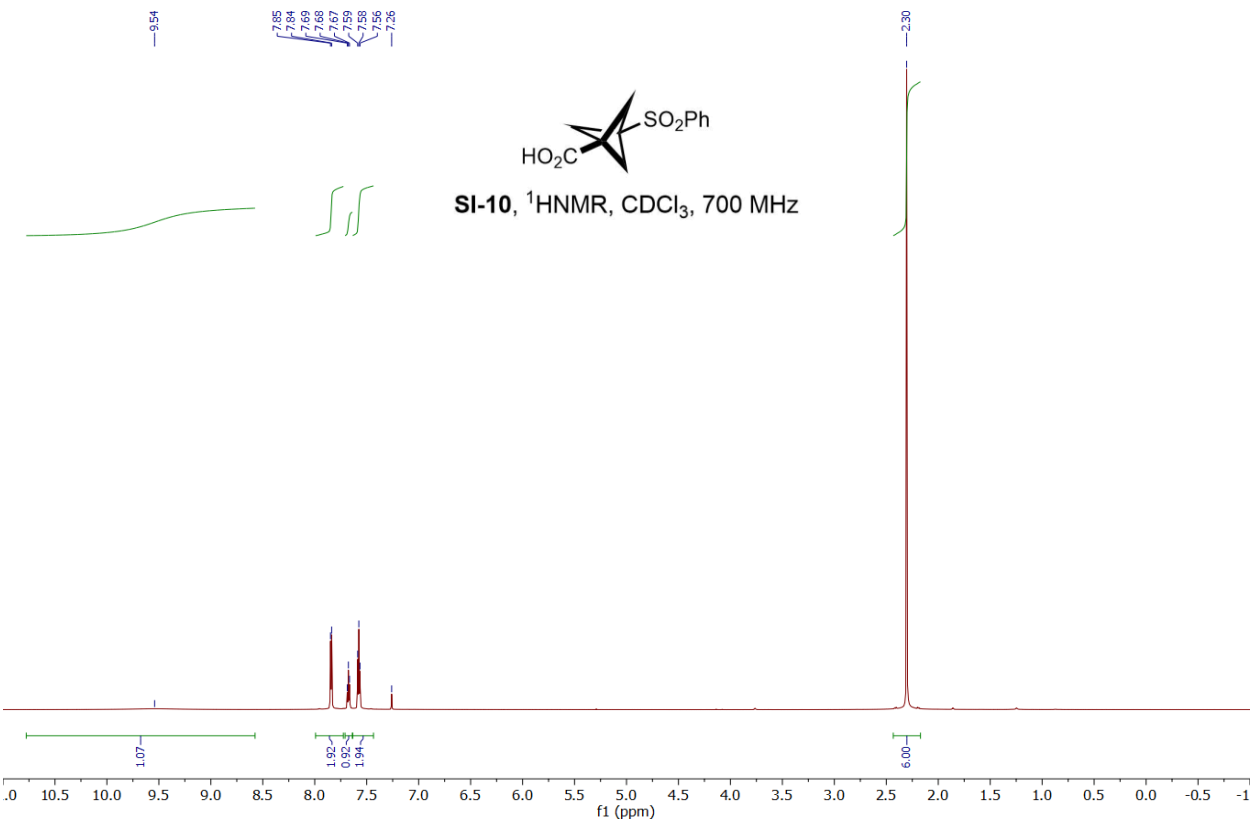
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 9.54 (bs, 1H), 7.86-7.82 (m, 2H), 7.70-7.65 (m, 1H), 7.60-7.55 (m, 2H), 2.30 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 173.4, 136.3, 134.2, 129.5, 128.7, 52.0, 51.5, 36.7 ppm

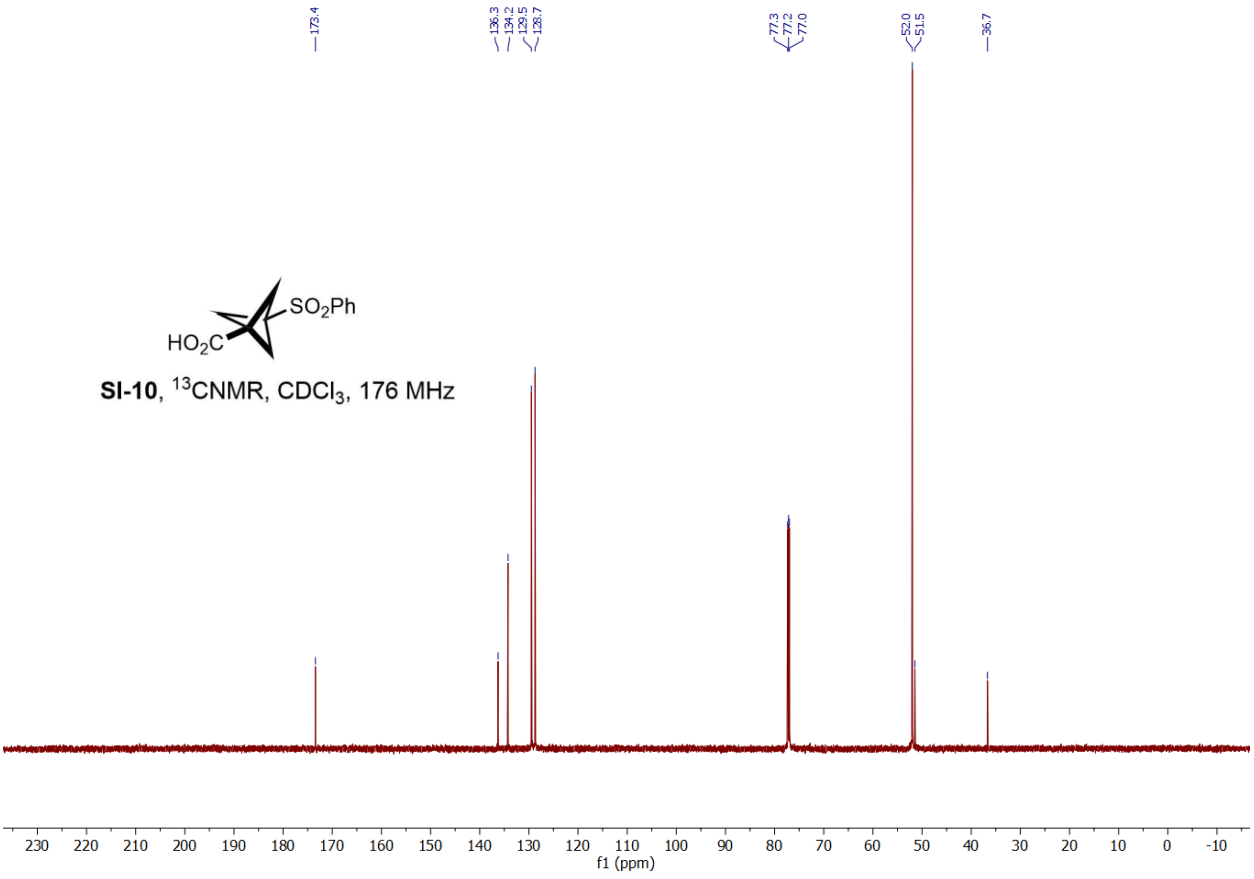
IR (neat): 3300-2300 (broad), 2890, 2606, 1700, 1446, 1303, 1289, 1220, 1199, 1144, 1089, 1028, 996, 946, 833, 757, 723, 688 cm^{-1}

HRMS (ES-, m/z) calculated for $C_{12}H_{11}O_4S^-$: 251.0384, Found: 251.0383

R_f = baseline (100% ethyl acetate), yellow spot, $KMnO_4$, UV

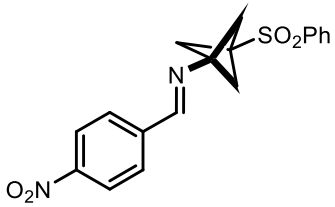


SI-10, ^{1}HNMR, $CDCl_3$, 700 MHz



SI-10, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound **2d**:



EXPERIMENTAL PROCEDURE:

To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **SI-10** (70.0 mg, 0.277 mmol, 1 equiv) and tert-butanol (10 mL). Triethylamine (0.0387 mL, 1.00 mmol, 1.00 equiv) and diphenylphosphoryl azide (0.0598 mL, 1.00 mmol, 1.00 equiv) were added sequentially via syringe. The headspace was flushed with argon and the reaction mixture was stirred for 1 hour at room temperature. Next, the flask was equipped with a reflux condenser and brought to reflux for 6 hours (heating in an aluminum block at 100 °C). The mixture was concentrated to near dryness then taken up in ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 20 mL) then brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo in a 100 mL round-bottom flask. A magnetic stir bar was added, and the residue was taken up in dichloromethane (6 mL). Trifluoroacetic acid (2 mL) was added. The mixture was allowed to stir at room temperature under air for 2 hours. The solvent was then removed in vacuo and the residue taken up in dichloromethane (10 mL). Triethylamine (0.387 mL, 2.77 mmol, 10.0 equiv) was added followed by 4-nitrobenzaldehyde (49.1 mg, 0.277 mmol, 1.00 equiv). The headspace of the flask was flushed with argon and the flask was sealed with a rubber septum and stirred at room temperature for 12 hours. The mixture was concentrated onto 4 grams of celite and chromatographed silica (neutralized with 5% ethyl acetate, 94% hexanes, and 1% triethylamine) eluting with 5-60% ethyl acetate in hexanes to give **2d** (52.2 mg, 0.146 mmol, 53%) as a faintly yellow solid.

Appearance: faintly yellow solid

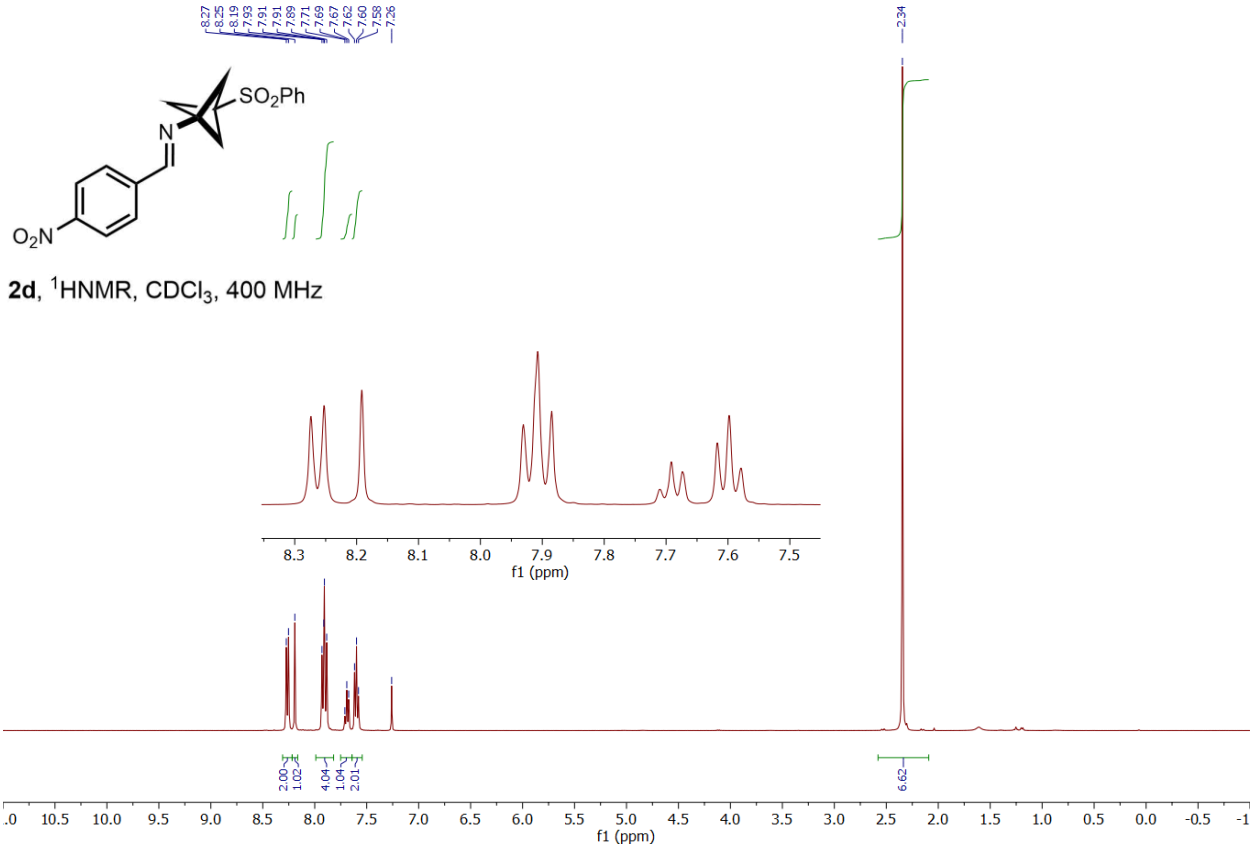
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.26 (d, *J* = 8.5 Hz, 2H), 8.19 (s, 1H), 7.96-7.84 (m, 4H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 160.3, 149.7, 140.6, 137.1, 134.1, 129.4 (2 carbons), 128.7, 124.1, 58.3, 53.1, 49.5 ppm

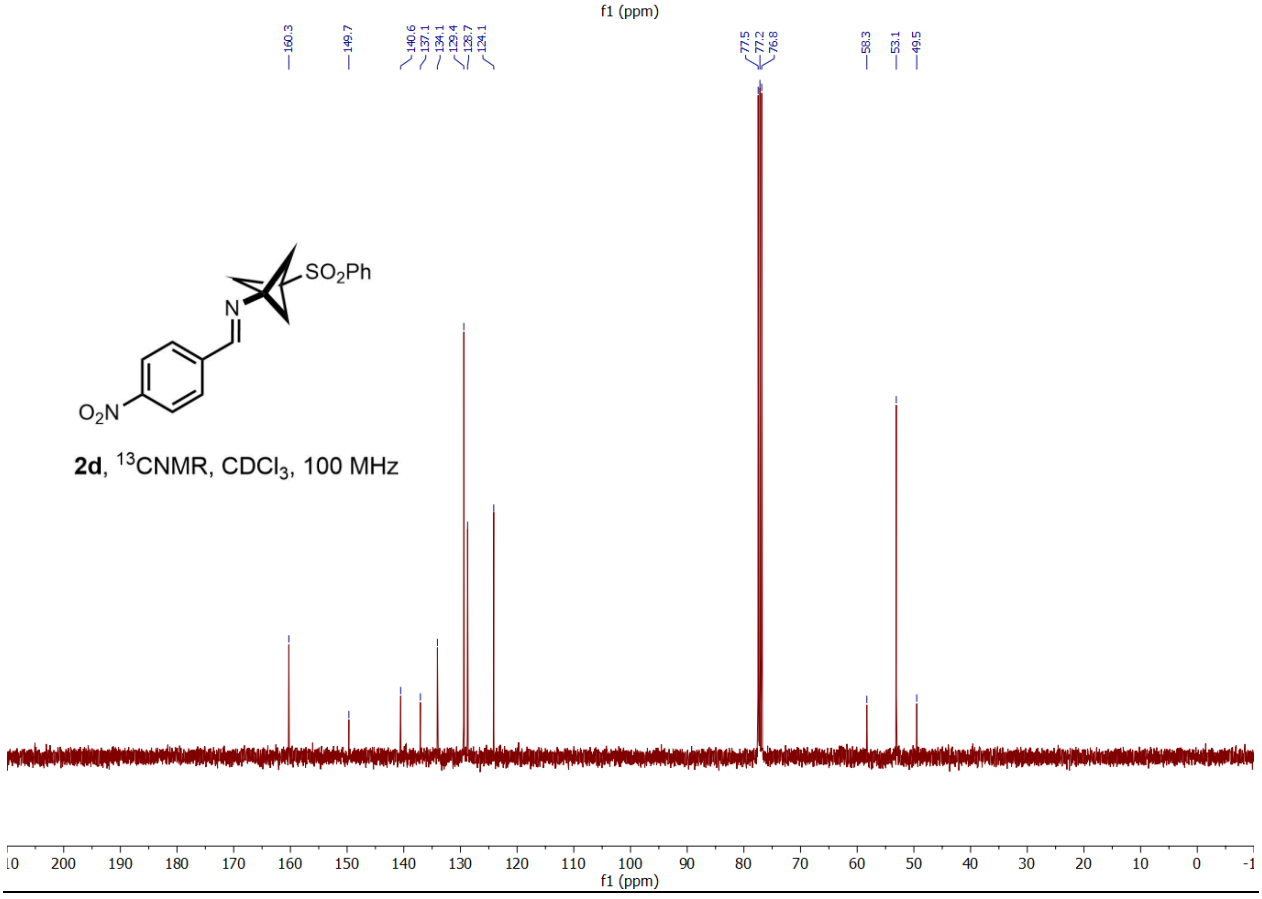
IR (neat): 3002, 2914, 1637, 1601, 1515, 1443, 1344, 1299, 1263, 1214, 1148, 1109, 1090, 1018, 970, 951, 848, 829, 787, 760, 746, 733, 719, 685 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{18}H_{17}N_2O_4S^+$: 357.0904, Found: 357.0898

R_f = 0.35 (50% ethyl acetate: 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



2d, ^{1}HNMR, $CDCl_3$, 400 MHz



2d, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound **SI-11**:

EXPERIMENTAL PROCEDURE:

The procedure was modified from a published procedure for synthesizing a related compound.[8] To an oven-dried 50 mL round-bottom flask equipped with a magnetic stir bar were added sequentially CuCl (39.6 mg, 0.400 mmol, 0.100 equiv), $Cu(acac)_2$ (105 mg, 0.400 mmol, 0.100 equiv), **SI-8** (1.89 g, 6.00 mmol, 1.50 equiv), triethylamine (1.39 mL, 10.0 mmol, 2.5 equiv), phenylacetylene (0.439 mL, 4.00 mmol, 1 equiv), and tetrahydrofuran (20 mL). The flask was sealed with a rubber septum and the mixture was sparged with argon for 15 minutes (~1 liter of argon). The flask was kept under argon atmosphere with a balloon and irradiated for 48 hours with two 456nm kessil lamps, one on each side ~6 cm away from the reaction vessel. Cooling was provided by a fan placed ~10 cm above the reaction vessel. Following irradiation, the reaction mixture was concentrated onto celite (5 g) and dry loaded atop a silica column. Elution with 2-20% ethyl acetate in hexanes gave **SI-11** (672.2 mg, 2.97 mmol, 74%) as a white solid.

Appearance: white solid

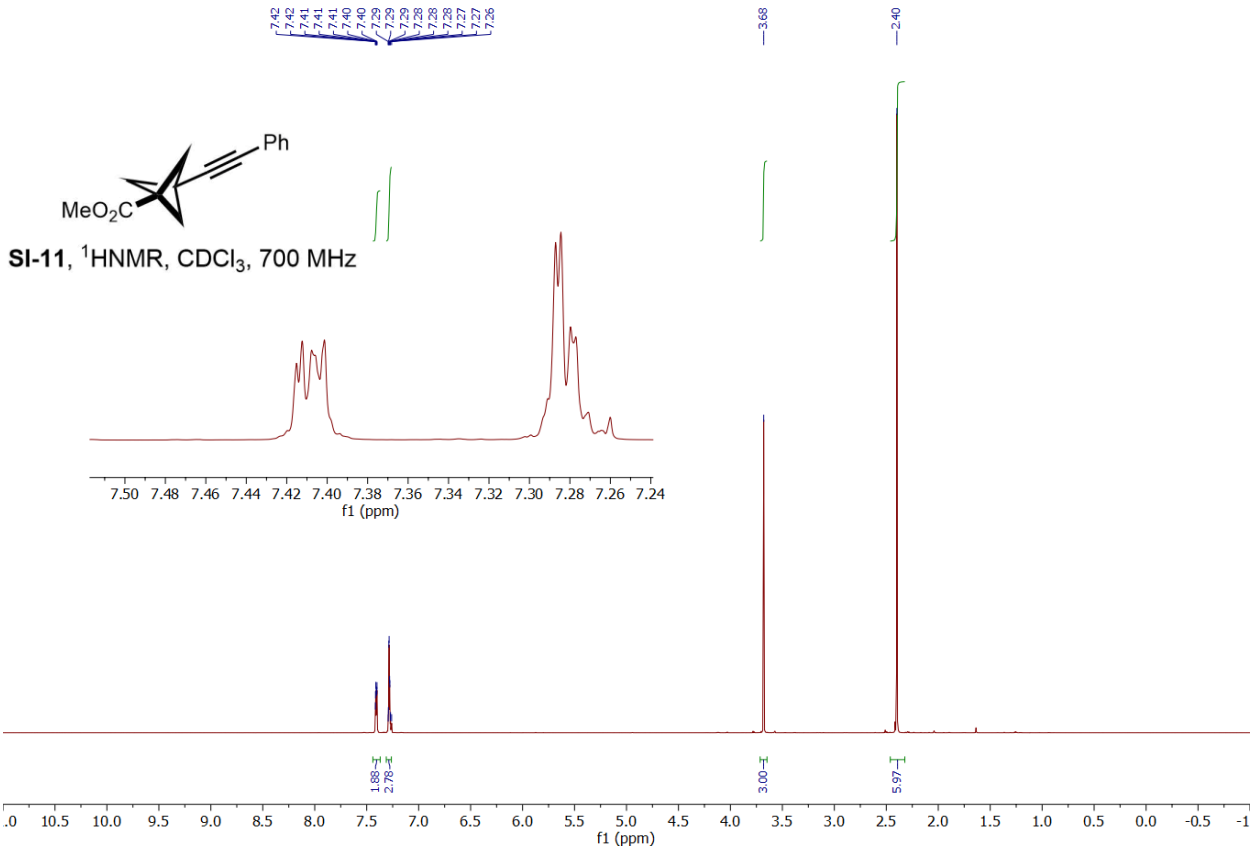
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.43-7.39 (m, 2H), 7.30-7.26 (m, 3H), 3.68 (s, 3H), 2.40 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 169.9, 131.9, 128.4, 128.3, 122.9, 87.8, 80.7, 56.0, 51.8, 39.9, 29.0 ppm

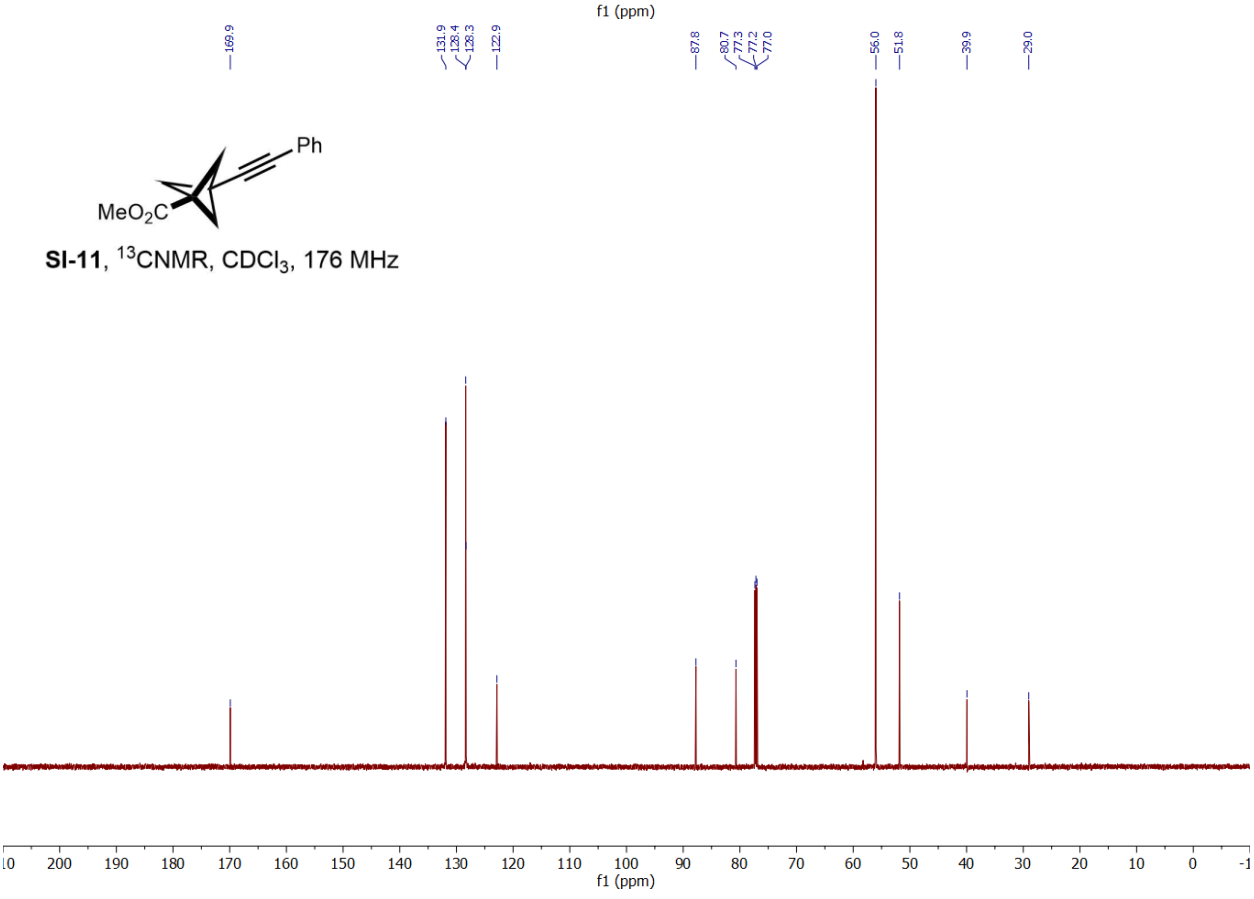
IR (neat): 2995, 2970, 2949, 2918, 2880, 1725, 1600, 1572, 1506, 1490, 1439, 1358, 1299, 1210, 1180, 1166, 1140, 1103, 1072, 1052, 999, 951, 912, 823, 797, 754, 717, 690 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{15}H_{15}O_2^+$: 227.1067, Found: 227.1062

R_f = 0.39 (10% ethyl acetate : 90% hexanes), yellow spot, $KMnO_4$, UV



SI-11, ^{1}HNMR, $CDCl_3$, 700 MHz



SI-11, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound **SI-12**:

EXPERIMENTAL PROCEDURE:

To a 2-dram vial equipped with a magnetic stir bar was added **SI-11** (300.0 mg, 1.326 mmol, 1 equiv) followed by tetrahydrofuran (4 mL), methanol (1.3 mL), and water (1.3 mL). To this stirred solution was added lithium hydroxide monohydrate (278.2 mg, 6.629 mmol, 5 equiv). The headspace was flushed with argon and the vial was sealed with a Teflon-lined cap and placed in a pre-heated aluminum block at 60 °C for 18.5 hours. The reaction mixture was then diluted with water (40 mL) and washed with dichloromethane (3 x 20 mL). The organic washes were discarded, and the aqueous phase was acidified to pH = 1 with 4N hydrochloric acid and was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo to give **SI-12** (271.0 mg, 1.277 mmol, 96%) as a white solid.

Appearance: White solid

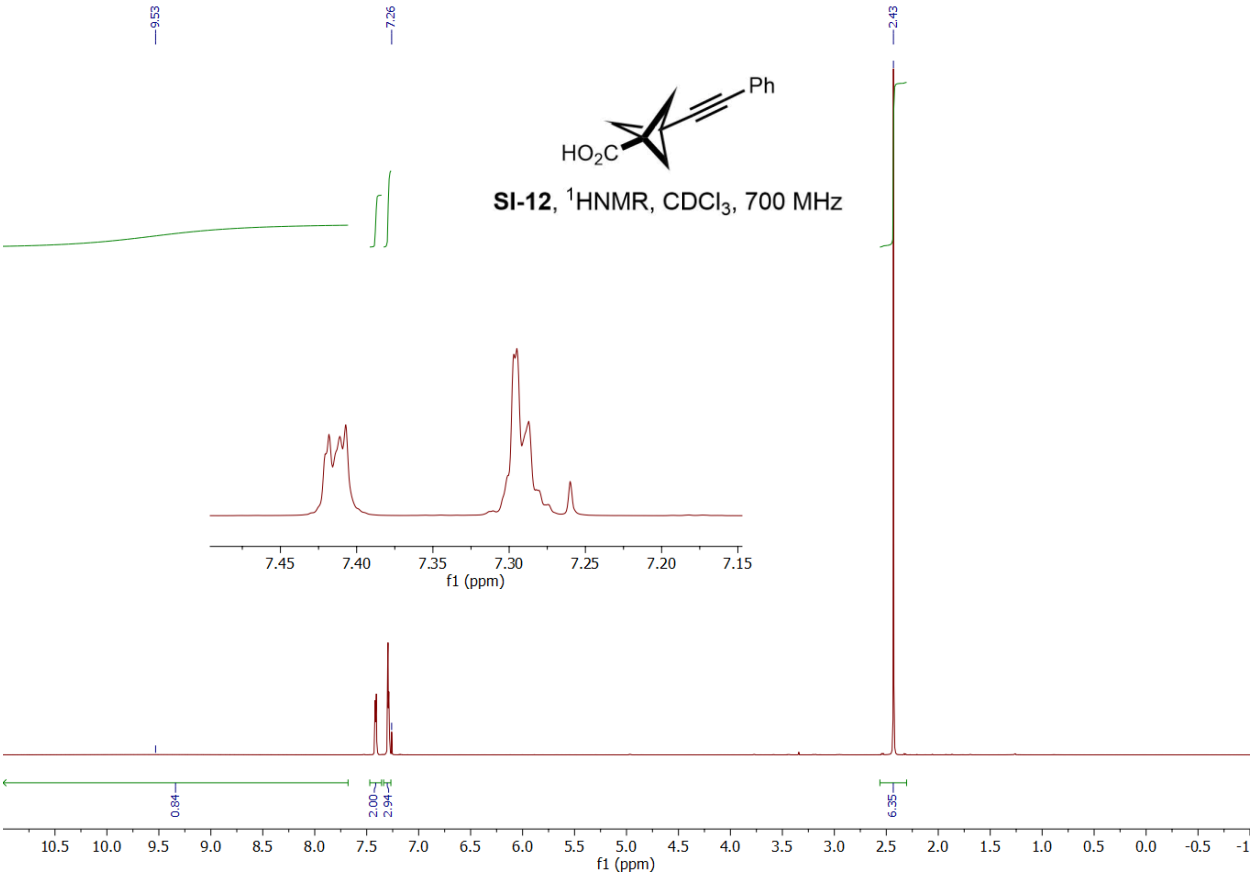
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 9.53 (bs, 1H), 7.44-7.38 (m, 2H), 7.32-7.26 (m, 3H), 2.43 (s, 6H) ppm

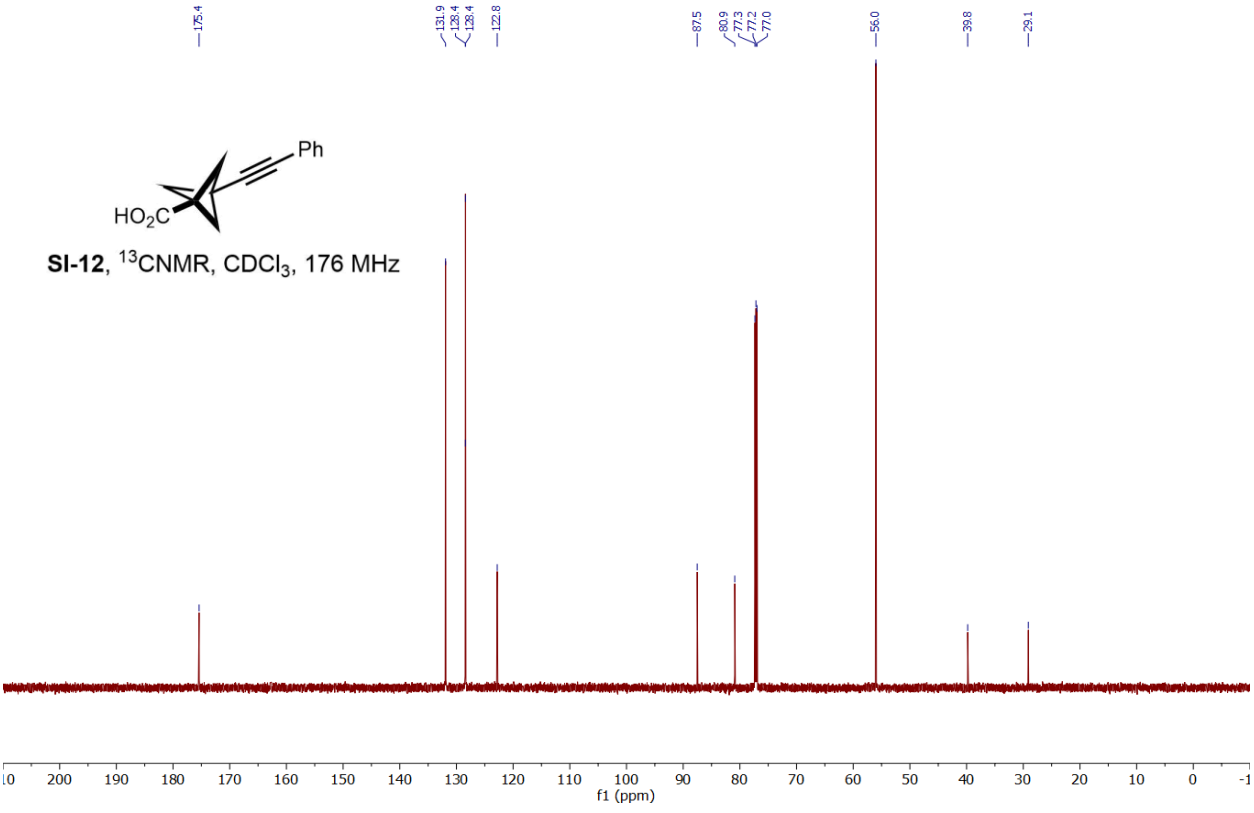
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.4, 131.9, 128.4, 128.4, 122.8, 87.5, 80.9, 56.0, 39.8, 29.1 ppm

IR (neat): 3300-2300 (broad), 3002, 2921, 2587, 1683, 1600, 1510, 1490, 1428, 1341, 1297, 1219, 1189, 1151, 1072, 1021, 943, 790, 752, 690 cm^{-1}

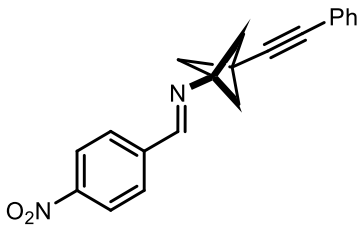
HRMS (ES-, m/z) calculated for $C_{14}H_{11}O_2^-$: 211.0765, Found: 211.0762

R_f = 0.13 (100% ethyl acetate), yellow spot, $KMnO_4$, UV


9.53
7.26
2.43
Ph
HO2C
SI-12, 1HNMR, CDCl3, 700 MHz
7.45 7.40 7.35 7.30 7.25 7.20 7.15
f1 (ppm)
0.84
2.00
2.94
6.35
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


175.4
131.9
128.4
128.4
122.8
87.5
80.9
77.3
77.2
77.0
56.0
39.8
29.1
Ph
HO2C
SI-12, 13CNMR, CDCl3, 176 MHz
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

Compound **2e**:



EXPERIMENTAL PROCEDURE:

To a 50 mL round-bottom flask equipped with a magnetic stir bar was added **SI-12** (212 mg, 1.00 mmol, 1 equiv) and tert-butanol (10 mL). Triethylamine (0.139 mL, 1.00 mmol, 1.00 equiv) and diphenylphosphoryl azide (0.216 mL, 1.00 mmol, 1.00 equiv) were added sequentially via syringe. The headspace was flushed with argon and the reaction mixture was stirred for 1 hour at room temperature. Next, the flask was equipped with a reflux condenser and brought to reflux for 6 hours (heating in an aluminum block at 100 °C). The mixture was concentrated to near dryness then taken up in ethyl acetate (30 mL) and washed with saturated aqueous $NaHCO_3$ (3 x 20 mL) then brine (2 x 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo in a 100 mL round-bottom flask. A magnetic stir bar was added, and the residue was taken up in dichloromethane (6 mL). Trifluoroacetic acid (2 mL) was added. The mixture was allowed to stir at room temperature under air for 2 hours. The solvent was then removed in vacuo and the residue taken up in dichloromethane (10 mL). Triethylamine (1.39 mL, 10.0 mmol, 10 equiv) was added followed by 4-nitrobenzaldehyde (151 mg, 1.00 mmol, 1.00 equiv). The headspace of the flask was flushed with argon and the flask was sealed with a rubber septum and stirred at room temperature for 12 hours. The mixture was concentrated onto 4 grams of celite and chromatographed silica (neutralized with 5% ethyl acetate, 94% hexanes, and 1% triethylamine) eluting with 5-60% ethyl acetate in hexanes to give **2ed** (146.7 mg, 0.464 mmol, 46%) as a faintly yellow solid.

Appearance: faintly yellow solid

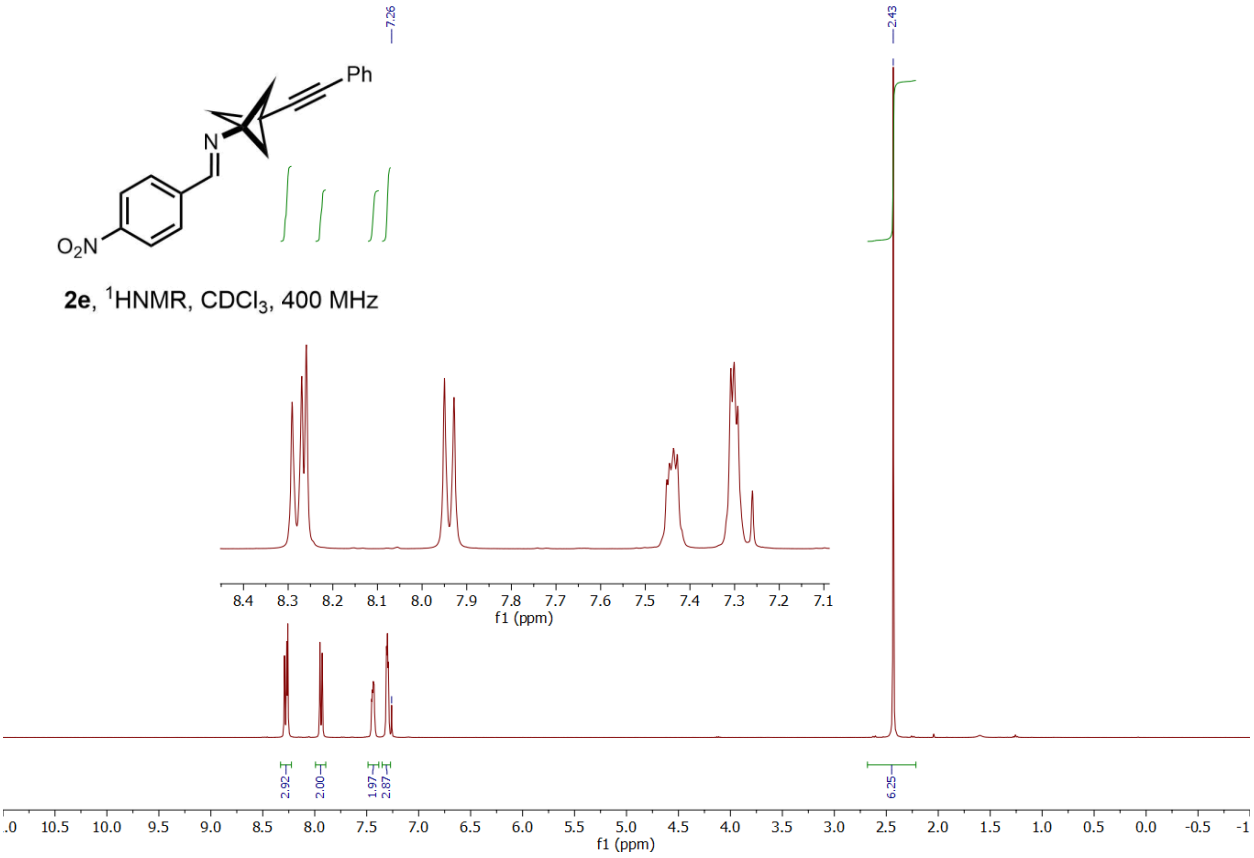
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.32-8.22 (m, 3H), 7.99-7.89 (m, 2H), 7.48-7.38 (m, 2H), 7.35-7.25 (m, 3H), 2.43 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.1, 149.5, 141.2, 131.9, 129.2, 128.4, 128.3, 124.1, 123.1, 87.6, 82.2, 60.3, 57.0, 25.6 ppm

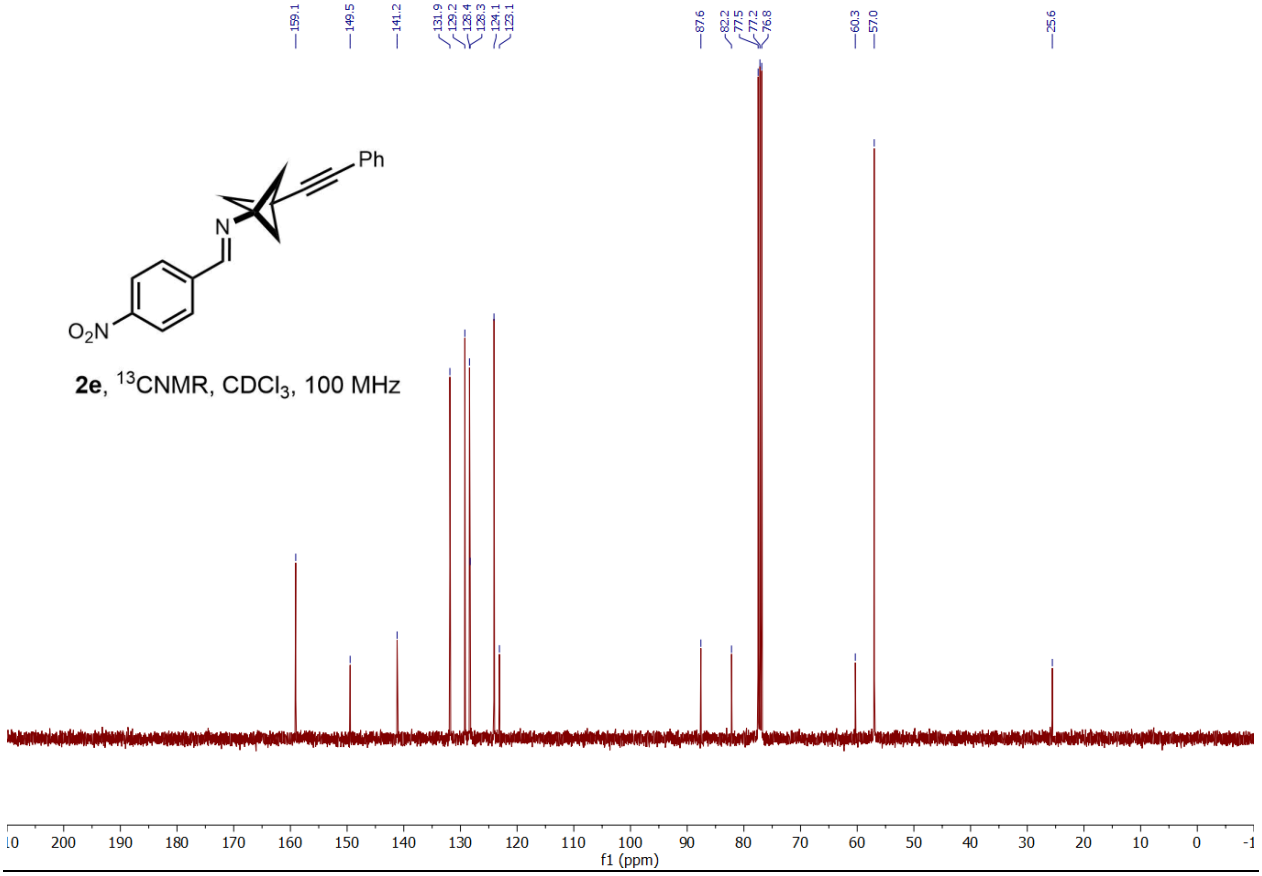
IR (neat): 2993, 2911, 2874, 2449, 1988, 1637, 1603, 1515, 1489, 1442, 1416, 1379, 1346, 1317, 1295, 1261, 1213, 1174, 1107, 1070, 1028, 1015, 970, 951, 917, 848, 786, 761, 744, 731, 688 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{17}N_2O_2^+$: 317.1285, Found: 317.1282

R_f = 0.67 (50% ethyl acetate: 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

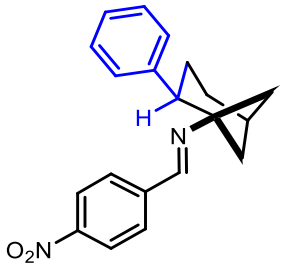


2e, ^{1}HNMR, $CDCl_3$, 400 MHz



2e, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound (±)-**4a**:



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), styrene (0.345 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was combined with celite (2 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-50% ethyl acetate in hexanes to give (±)-**4a** (40.0 mg, 0.125 mmol, 31%) as a faintly yellow solid.

Appearance: faintly yellow solid

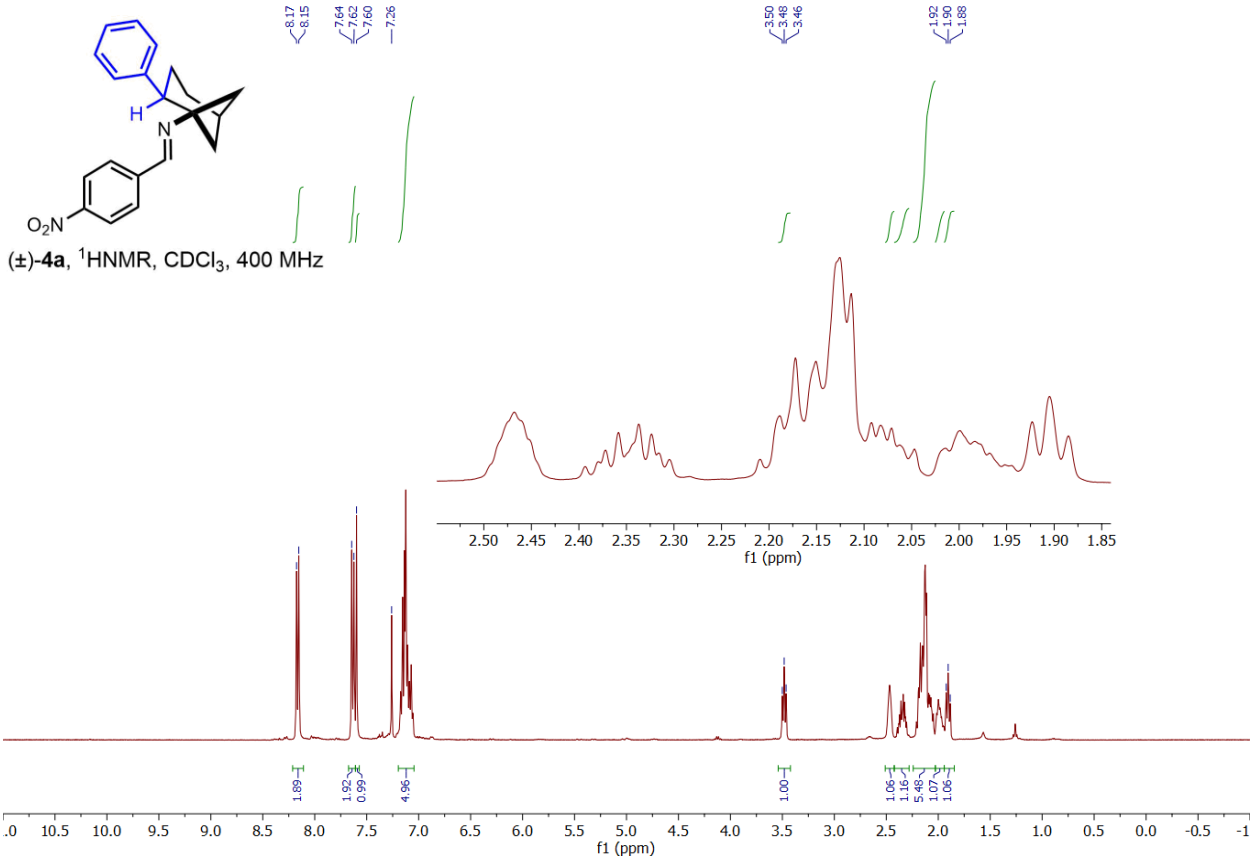
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.16 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.60 (s, 1H), 7.19-7.04 (m, 5H), 3.48 (app. t, *J* = 7.3 Hz, 1H), 2.51-2.42 (m, 1H), 2.40-2.28 (m, 1H), 2.22-2.03 (m, 5H), 1.03-1.94 (m, 1H), 1.90 (app. t, *J* = 7.7 Hz, 1H), ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.8, 148.9, 143.7, 142.0, 128.8, 128.5, 127.8, 126.3, 123.9, 71.0, 50.4, 42.7, 33.1, 28.5, 27.6, 25.2 ppm

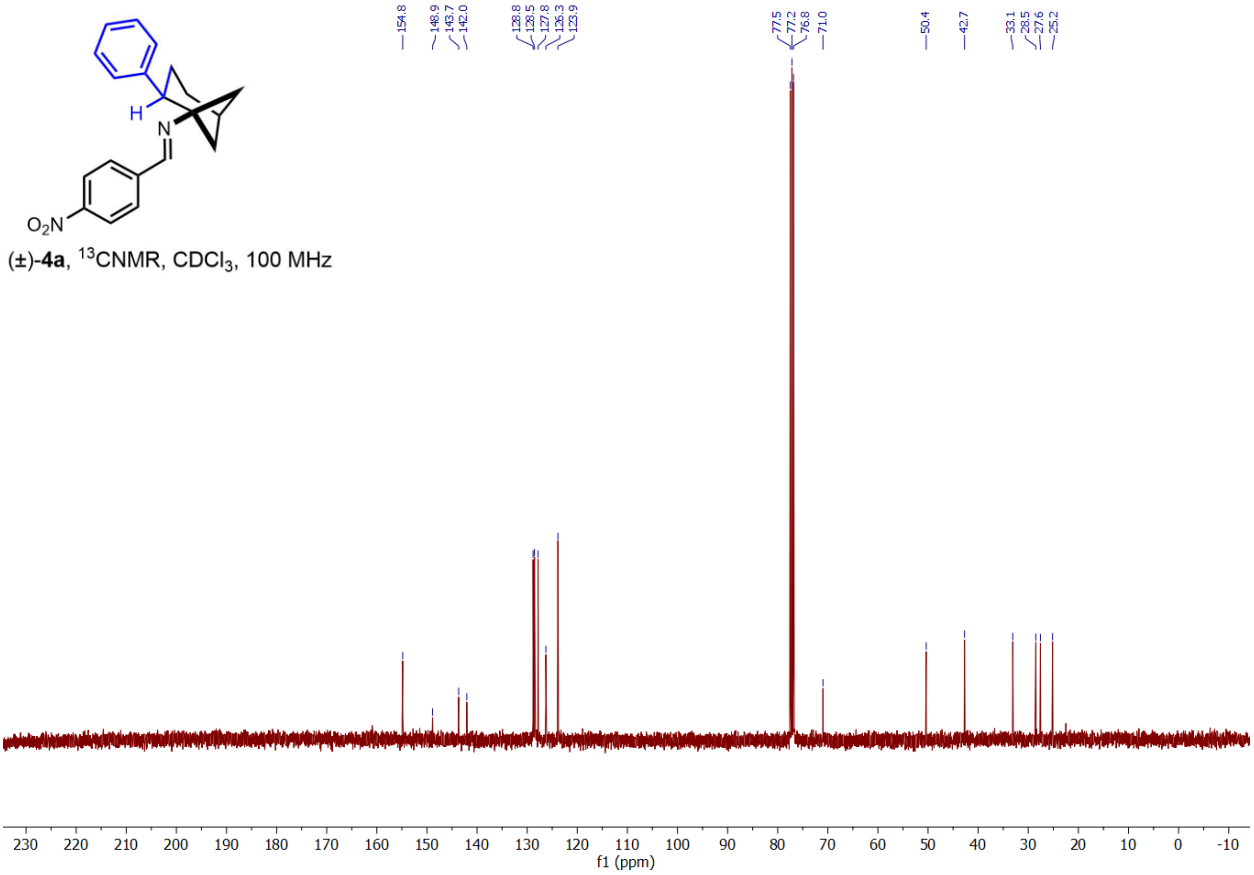
IR (neat): 2961, 2939, 2861, 1638, 1600, 1516, 1495, 1450, 1339, 1315, 1294, 1254, 1204, 1168, 1107, 1072, 1048, 1032, 1012, 996, 972, 958, 934, 926, 904, 852, 839, 818, 766, 749, 737, 701, 690, 658 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{21}N_2O_2^+$: 321.1598, Found: 321.1590

R_f = 0.36 (20% ethyl acetate : 80% hexanes), yellow spot, $KMnO_4$, UV

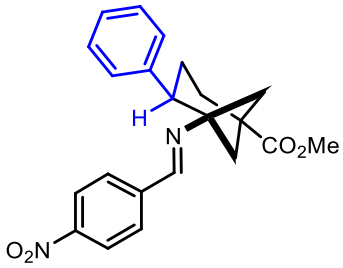


(±)-**4a**, ^{1}HNMR, $CDCl_3$, 400 MHz



(±)-**4a**, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound (±)-**4b** :



EXPERIMENTAL PROCEDURE:
A modification of general procedure B (modification = 10.0 mmol of imine used rather than the standard 0.400 mmol) was performed using **2b** (2.743 g, 10.0 mmol, 1 equiv), styrene (8.62 mL, 75.0 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (22.0 mg, 0.100 mmol, 0.01 equiv) and irradiating for 36 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 5 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 2-30% ethyl acetate in hexanes to give (±)-**4b** (1.56 g, 4.12 mmol, 41%) as a thick, faintly yellow oil.

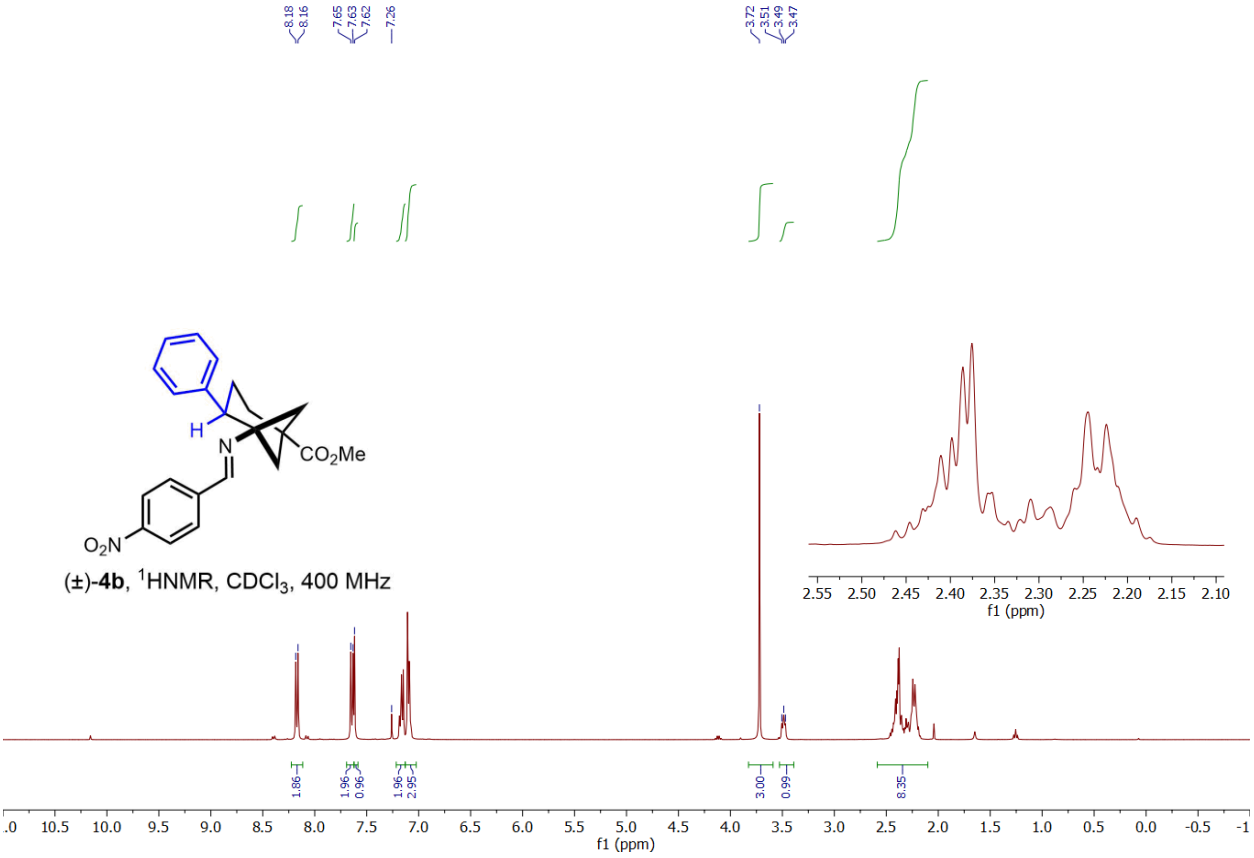
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.62 (s, 1H), 7.21-7.13 (m, 2H), 7.13-7.05 (m, 3H), 3.72 (s, 3H), 3.49 (app. t, *J* = 7.0 Hz, 1H), 2.51-2.14 (m, 8H) ppm

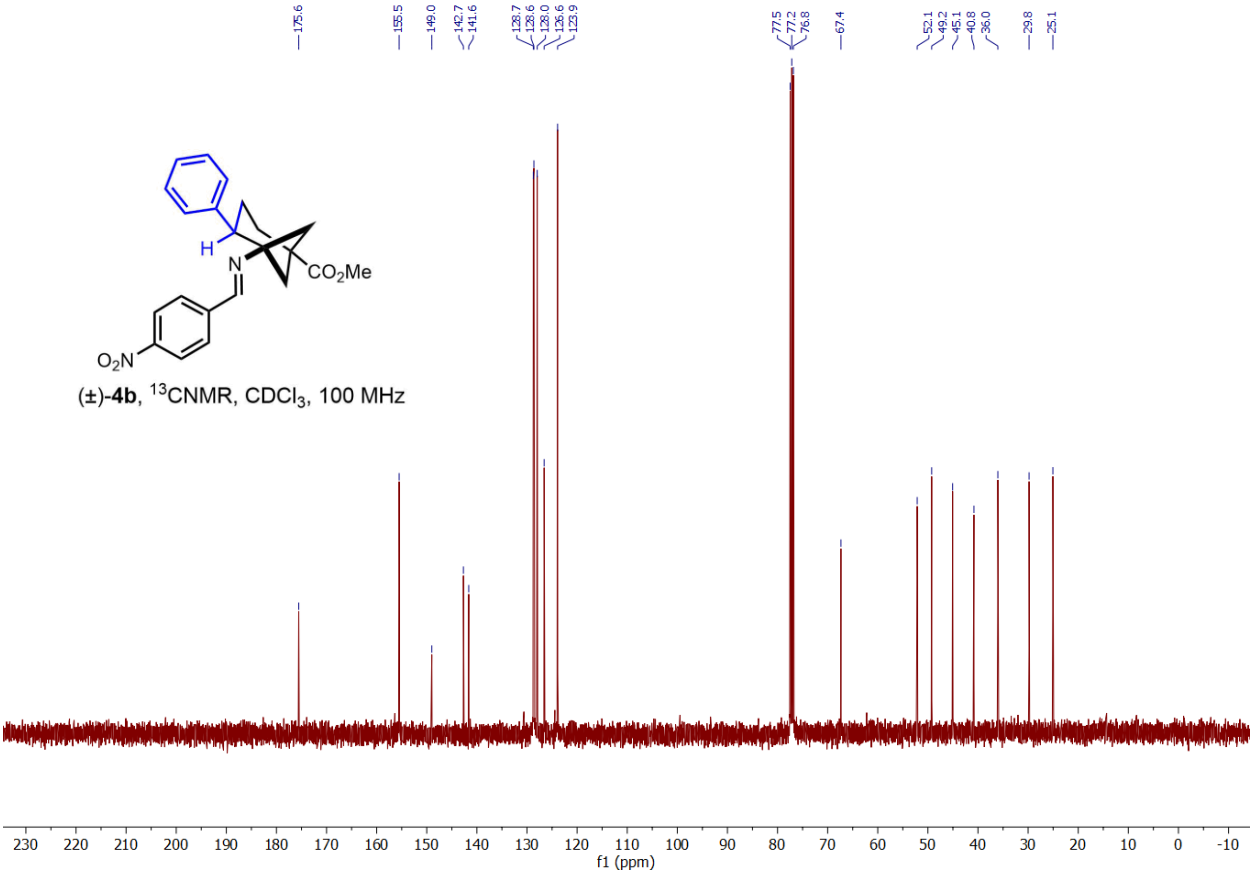
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.6, 155.5, 149.0, 142.7, 141.6, 128.7, 128.6, 128.0, 126.6, 123.9, 67.4, 52.1, 49.2, 45.1, 40.8, 36.0, 29.8, 25.1 ppm

IR (neat): 3029, 2951, 2871, 1727, 1642, 1601, 1520, 1495, 1452, 1435, 1414, 1343, 1315, 1294, 1254, 1213, 1153, 1107, 1077, 1047, 1012, 975, 957, 913, 887, 853, 836, 789, 767, 749, 732, 701, 690, 662 cm^{-1}

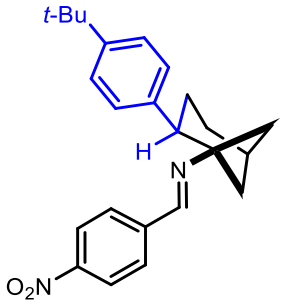
HRMS (ES+, m/z) calculated for $C_{22}H_{23}N_2O_4^+$: 379.1652, Found: 379.1645

R_f = 0.45 (30% ethyl acetate : 69 % hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


8.18
8.16
7.65
7.63
7.62
7.26
3.72
3.51
3.49
3.47
H
N
CO2Me
O2N
(±)-4b, 1HNMR, CDCl3, 400 MHz
1.86
1.96
0.96
1.96
2.95
3.00
0.99
8.35
f1 (ppm)


175.6
155.5
149.0
142.7
141.6
128.7
128.6
128.0
126.6
123.9
77.5
77.2
76.8
67.4
52.1
49.2
45.1
40.8
36.0
29.8
25.1
H
N
CO2Me
O2N
(±)-4b, 13CNMR, CDCl3, 100 MHz
f1 (ppm)

Compound (±)-**4c** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-*tert*-butylstyrene (0.549 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 20 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 2-16% ethyl acetate in hexanes to give (±)-**4c** (43.9 mg, 0.117 mmol, 29%) as a yellow oil.

The reaction was repeated as above 2 times. To the crude reaction mixtures were added known amounts of 1,3,5-trimethoxybenzene. Q^{1}HNMR analysis was performed. A T_1 relaxation delay of 25 seconds was used during data acquisition to ensure meaningful integrations.

Trial 1: (±)-**4c** (27%), **5** (13%)
Trial 2: (±)-**4c** (27%), **5** (11%)

Appearance: yellow oil

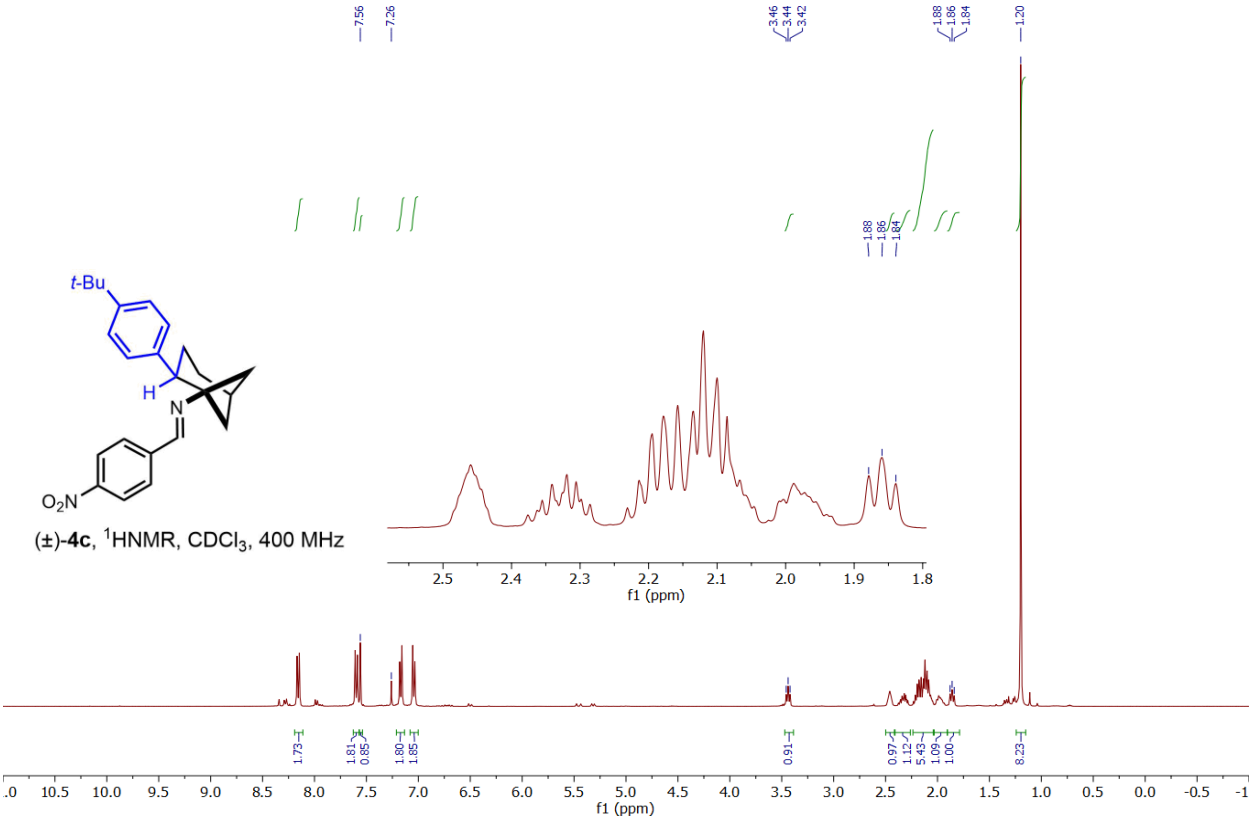
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.19-8.12 (m, 2H), 7.63-7.57 (m, 2H), 7.56 (s, 1H), 7.20-7.13 (m, 2H), 7.08-7.01 (m, 2H), 3.44 (app. t, *J* = 7.4 Hz, 1H), 2.50-2.42 (m, 1H), 2.39-2.27 (m, 1H), 2.24-2.04 (m, 5H), 2.03-1.92 (m, 1H), 1.86 (app. t, *J* = 7.9 Hz, 1H), 1.20 (s, 9H) ppm

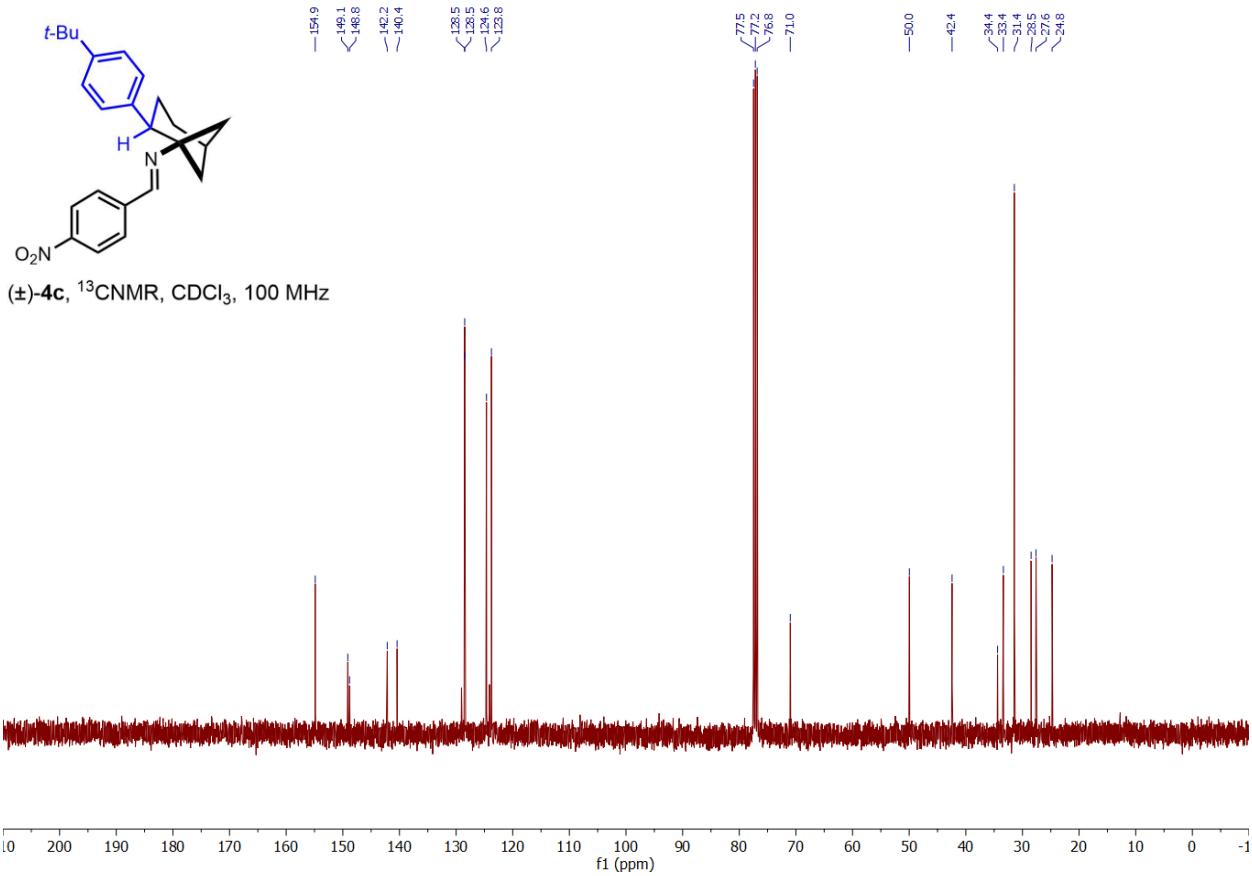
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 154.9, 149.1, 148.8, 142.2, 140.4, 128.5, 128.5, 124.6, 123.8, 71.0, 50.0, 42.4, 34.4, 33.4, 31.4, 28.5, 27.6, 24.8 ppm

IR (neat): 2956, 2864, 1640, 1601, 1520, 1475, 1454, 1412, 1342, 1316, 1293, 1269, 1255, 1202, 1163, 1107, 1048, 1014, 999, 971, 956, 930, 909, 852, 832, 797, 748, 731, 690 cm^{-1}

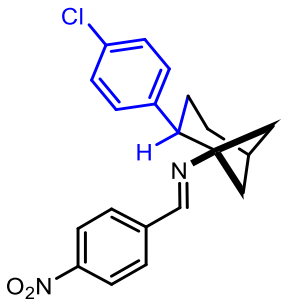
HRMS (ES+, m/z) calculated for $C_{24}H_{29}N_2O_2^+$: 377.2224, Found: 377.2221

R_f = 0.63 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


t-Bu
H
N
O2N
(±)-4c, 1HNMR, CDCl3, 400 MHz
f1 (ppm)


t-Bu
H
N
O2N
(±)-4c, 13CNMR, CDCl3, 100 MHz
f1 (ppm)

Compound (±)-**4d** :



EXPERIMENTAL PROCEDURE:
General procedure B was followed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-chlorostyrene (0.360 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was mixed with celite (2 g) to give a powdery mixture, which was dry-loaded atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-60% ethyl acetate in hexanes to give (±)-**4d** (48.6 mg, 0.137 mmol, 34%) as a faintly yellow solid.

Appearance: faintly yellow solid

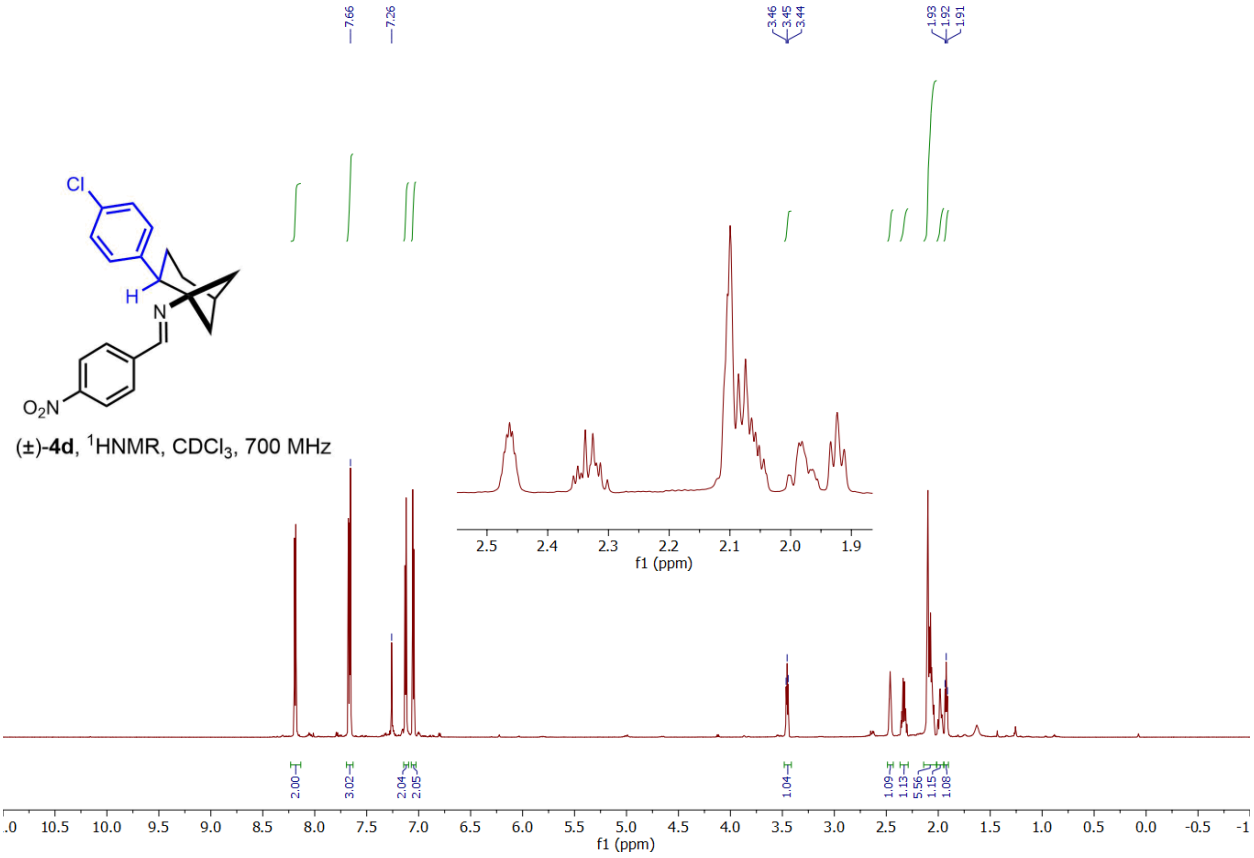
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.21-8.17 (m, 2H), 7.69-7.64 (m, 3H), 7.14-7.10 (m, 2H), 7.07-7.03 (m, 2H), 3.45 (app. t, *J* = 6.9 Hz, 1H), 2.48-2.43 (m, 1H), 2.36-2.29 (m, 1H), 2.14-2.03 (m, 5H), 2.02-1.95 (m, 1H), 1.92 (app. t, *J* = 7.9 Hz, 1H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 154.9, 149.0, 142.3, 141.8, 131.9, 130.1, 128.6, 127.9, 124.0, 70.8, 49.8, 42.5, 33.0, 28.3, 27.5, 25.2 ppm

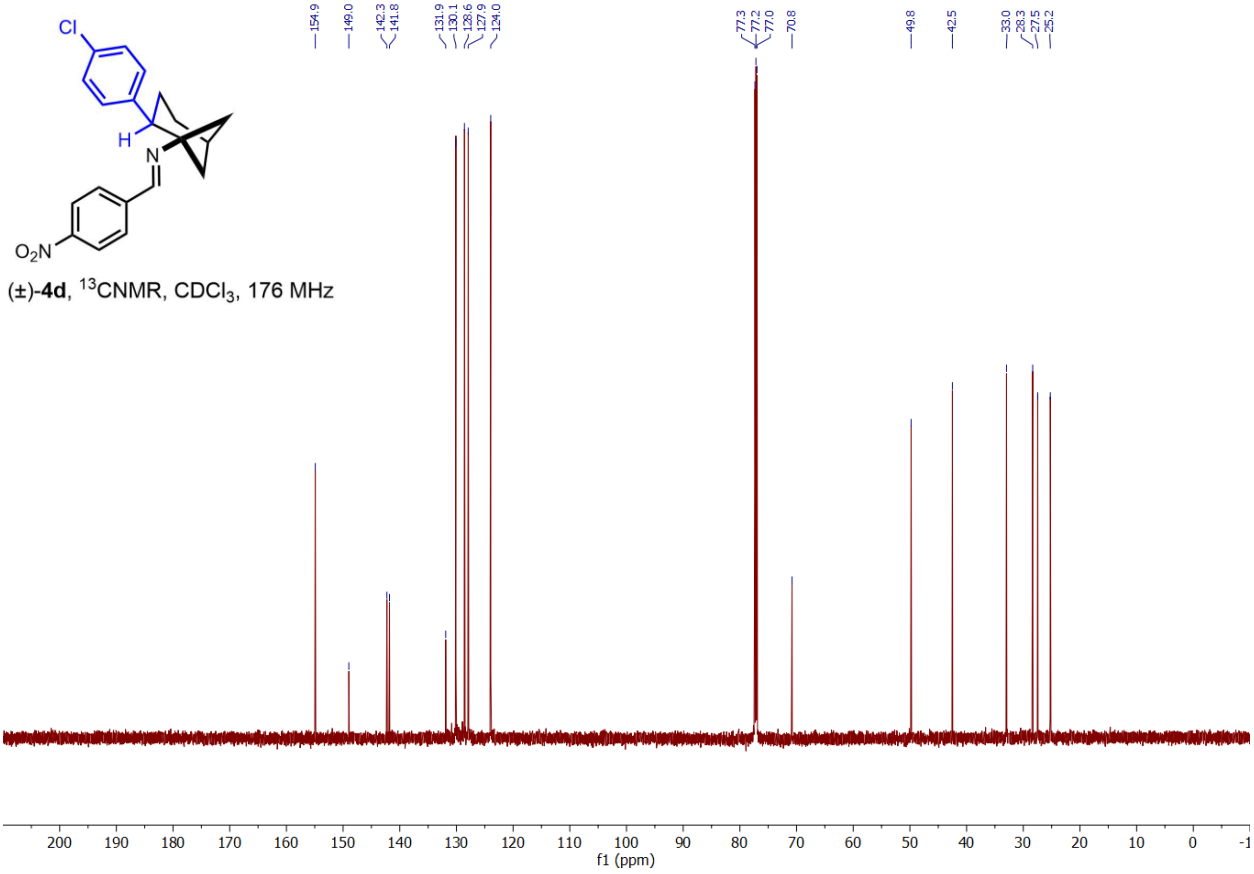
IR (neat): 2944, 2863, 1640, 1601, 1517, 1490, 1454, 1410, 1342, 1315, 1294, 1254, 1203, 1162, 1107, 1091, 1013, 971, 957, 930, 852, 827, 749, 718, 689 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{20}ClN_2O_2^+$: 355.1208, Found: 355.1213

R_f = 0.44 (30% ethyl acetate: 69% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

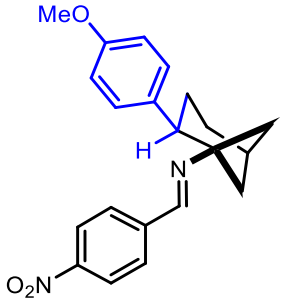


(±)-**4d**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4d**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4e** :



EXPERIMENTAL PROCEDURE:
General procedure B was followed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-methoxystyrene (399 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 15.5 hours. The crude mixture was loaded with toluene atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-50% ethyl acetate in hexanes to give 36.6 mg of a yellow oil that consisted primarily of (±)-**4e** . This mixture was loaded with toluene atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine) and chromatographed eluting on a gradient from 2-20% ethyl acetate in hexanes to give a clean sample of (±)-**4e** (11.2 mg, 0.0320 mmol, 8%) as a faintly yellow solid.

Due to the large material losses encountered during isolation, it was determined that an assay yield would provide a more meaningful reflection of the reactivity.

Procedure for determining assay yields: For two identical trials, general procedure B was followed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-vinylanisole (0.399 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixtures were diluted with $CDCl_3$ and a known amount of 1,3,5-trimethoxybenzene was added to each. The amount of (±)-**4e** present in the samples was determined by ^{1}HNMR. A T_1 relaxation time of 25 seconds was used during data acquisition to ensure meaningful integrations.

Specifically, the following peaks were considered for analysis:

1,3,5-trimethoxybenzene: ~6.08 (s, 3H)
(±)-**4e** : 3.44 (app. t, J = 7.2 Hz, 1H)

The 1,3,5-trimethoxybenzene internal standard was assumed to be 100% pure by mass.

Trial 1: 24% assay yield
Trial 2: 27% assay yield

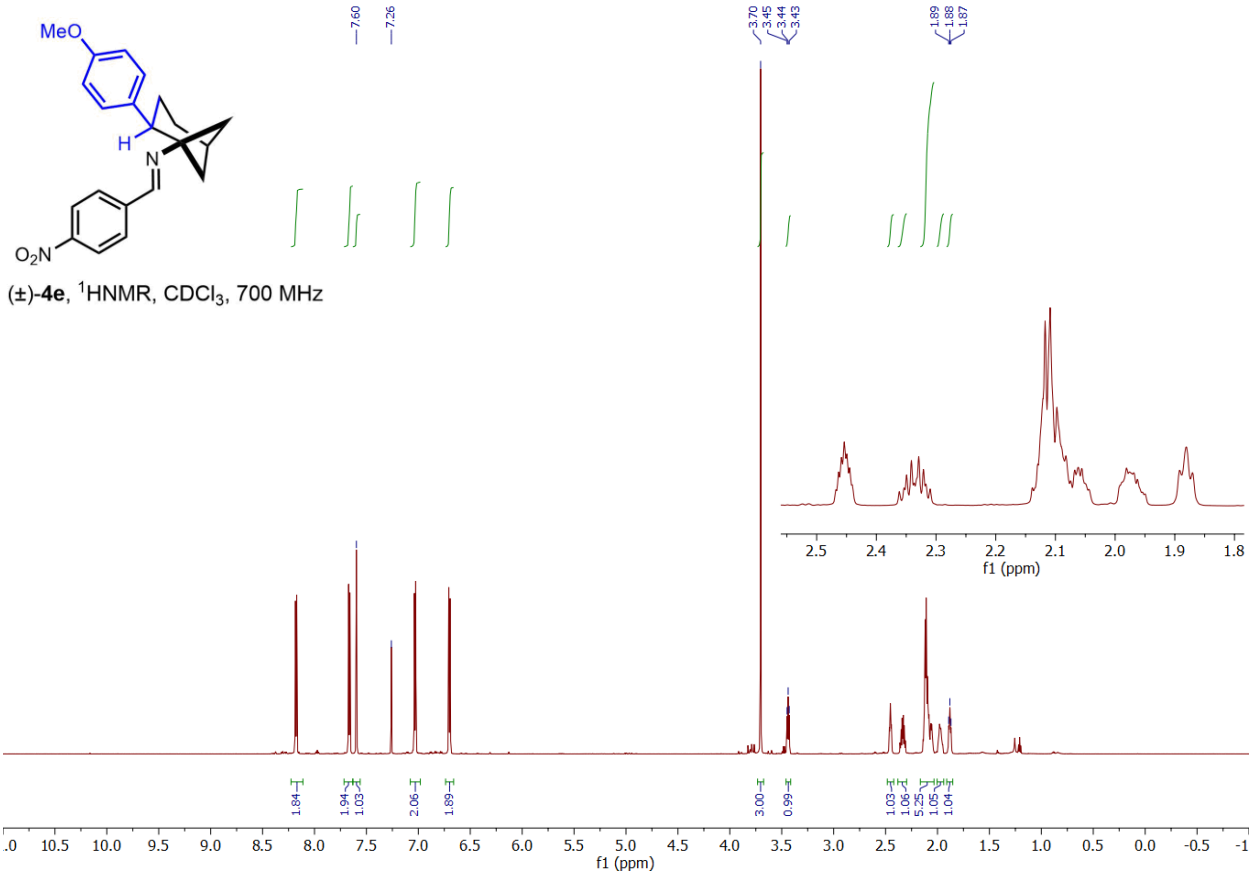
Appearance: faintly yellow solid

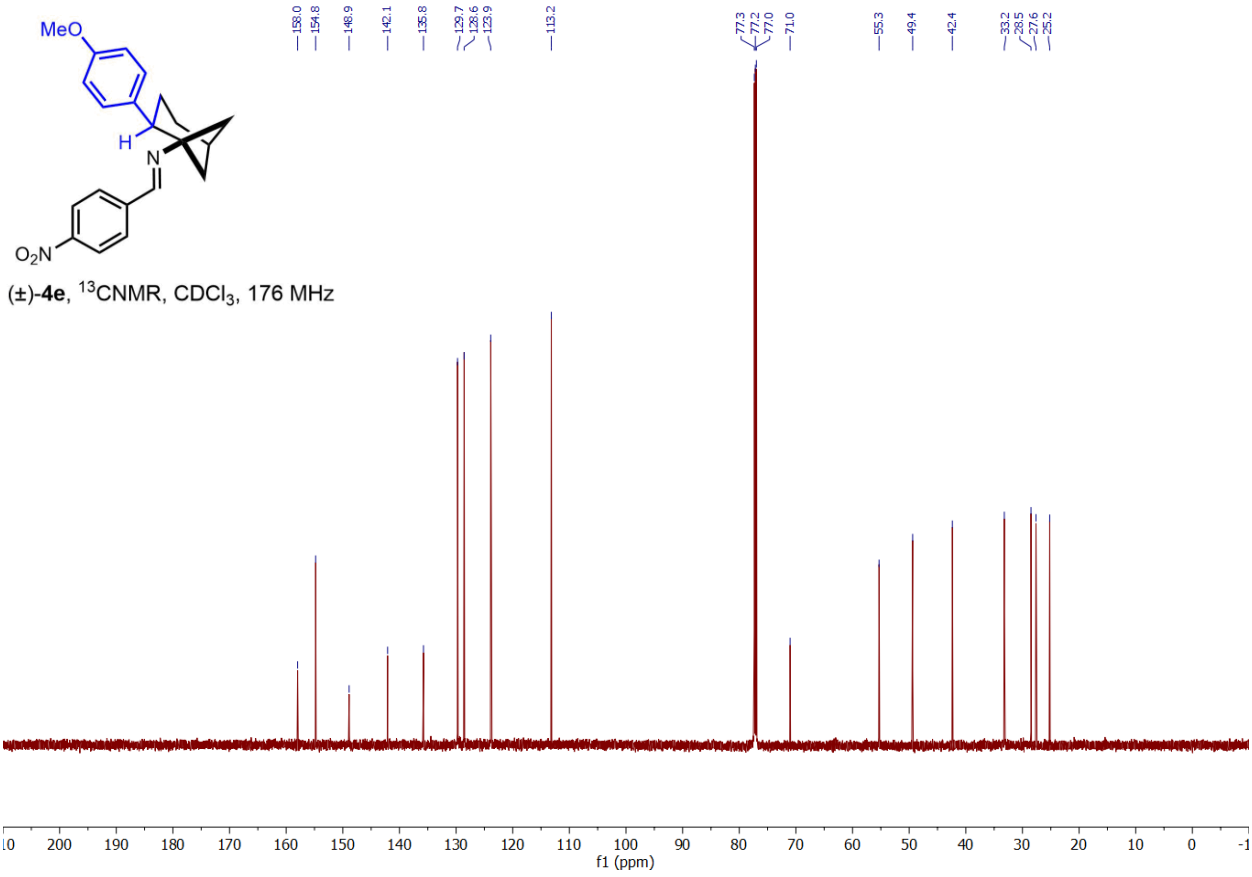
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.20-8.16 (m, 2H), 7.68-7.64 (m, 2H), 7.60 (s, 1H), 7.06-7.01 (m, 2H), 6.72-6.67 (m, 2H), 3.70 (s, 3H), 3.44 (app. t, *J* = 7.2 Hz, 1H), 2.47-2.43 (m, 1H), 2.37-2.20 (m, 1H), 2.15-2.03 (m, 5H), 2.00-1.94 (m, 1H), 1.88 (app. t, *J* = 7.6 Hz, 1H) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 158.0, 154.8, 148.9, 142.1, 135.8, 129.7, 128.6, 123.9, 113.2, 71.0, 55.3, 49.4, 42.4, 33.2, 28.5, 27.6, 25.2 ppm

IR (neat): 2998, 2941, 2871, 2838, 1637, 1604, 1513, 1466, 1457, 1444, 1383, 1345, 1317, 1307, 1291, 1278, 1243, 1211, 1203, 1180, 1163, 1142, 1110, 1096, 1034, 1013, 996, 970, 956, 928, 870, 852, 838, 825, 812, 783, 749, 728, 691, 656 cm^{-1}

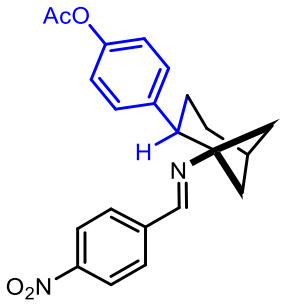
HRMS (ES+, m/z) calculated for $C_{21}H_{23}N_2O_3^+$: 351.1703, Found: 351.1699

R_f = 0.54 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV





Compound (±)-**4f** :



EXPERIMENTAL PROCEDURE:
General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-acetoxystyrene (0.459 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-50% ethyl acetate in hexanes to give (±)-**4f** (34.0 mg, 0.0898 mmol, 22%) as a faintly yellow solid.

Appearance: faintly yellow solid

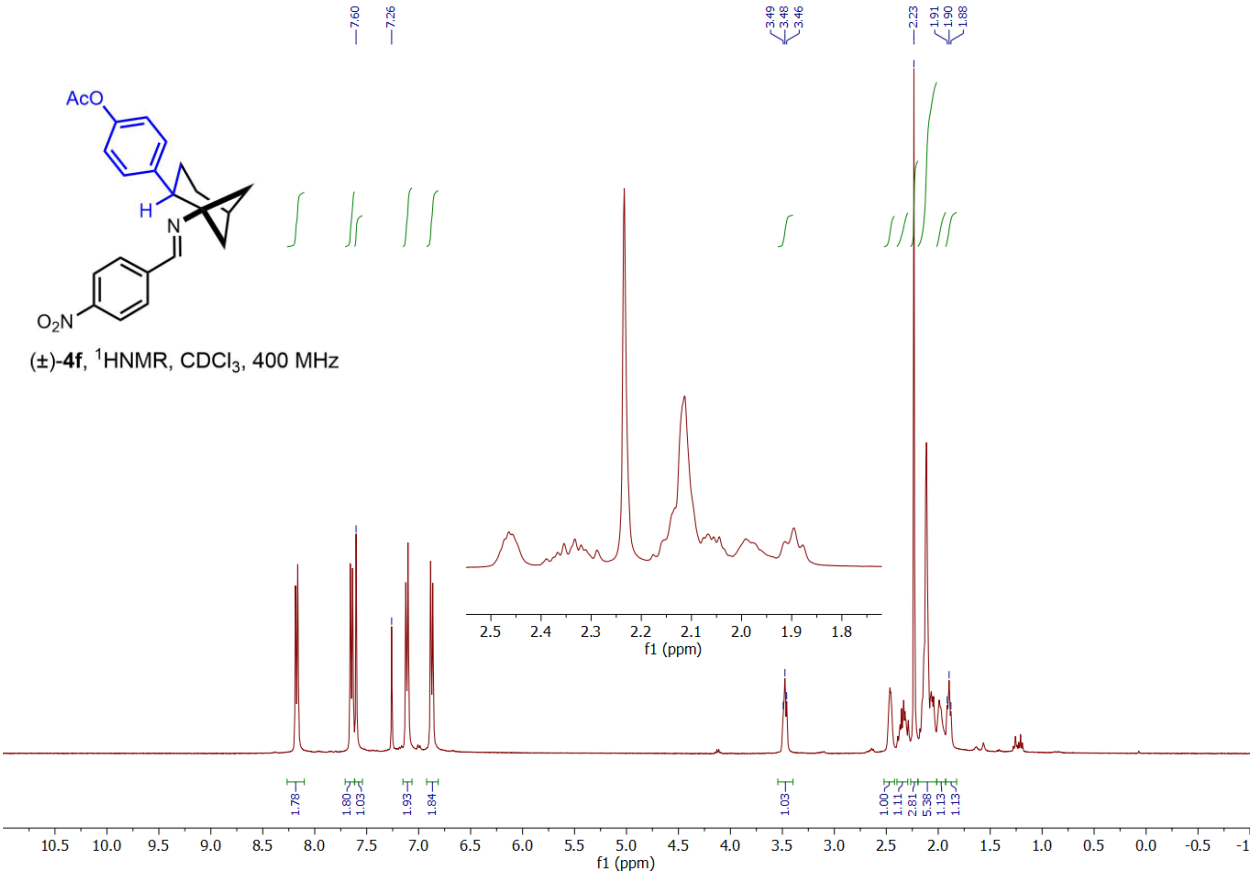
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.21-8.13 (m, 2H), 7.68-7.61 (m, 2H), 7.60 (s, 1H), 7.14-7.07 (m, 2H), 6.91-6.83 (m, 2H), 3.48 (app. t, *J* = 6.6 Hz, 1H), 2.51-2.41 (m, 1H), 2.40-2.27 (m, 1H), 2.23 (s, 3H), 2.19-2.01 (m, 5H), 2.02-1.93 (m, 1H), 1.90 (app. t, *J* = 7.0 Hz, 1H) ppm

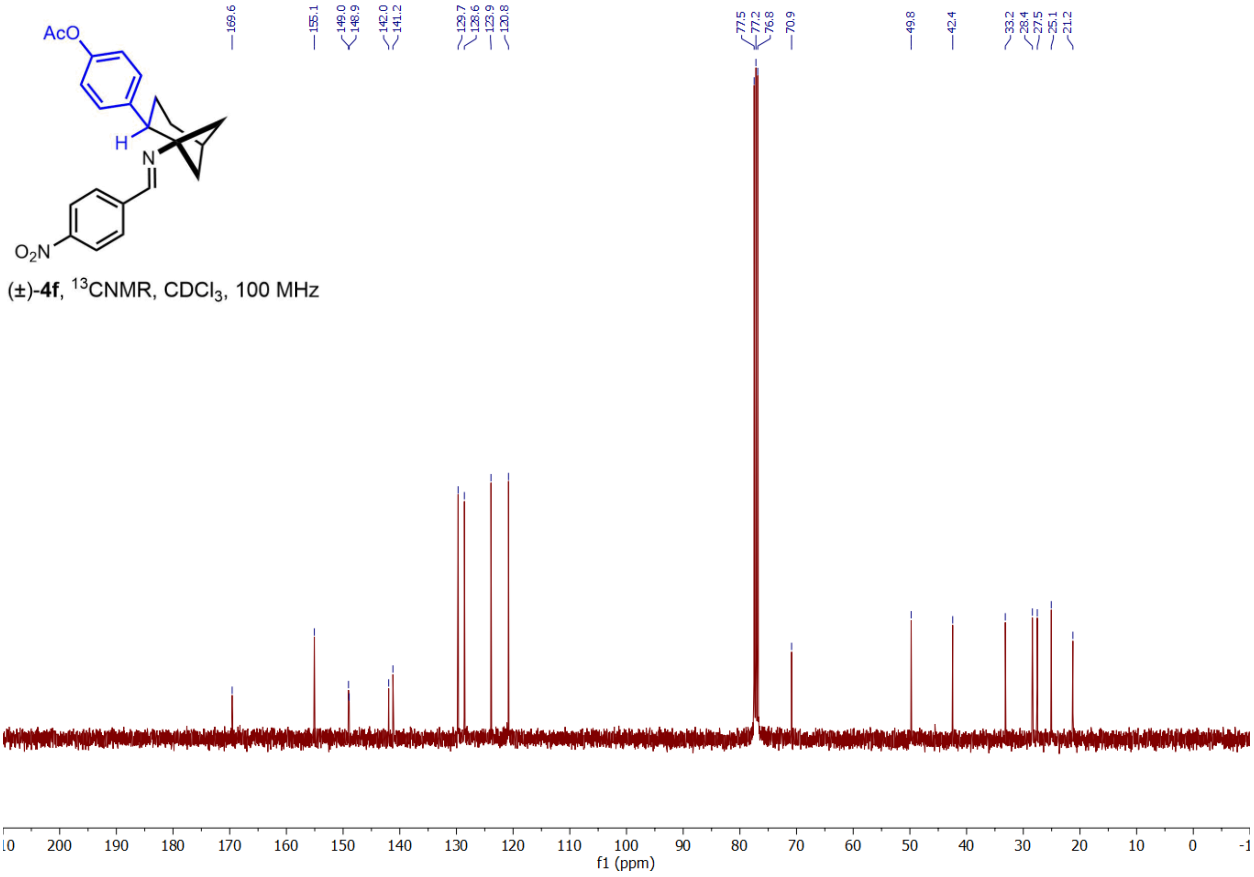
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.6, 155.1, 149.0, 148.9, 142.0, 141.2, 129.7, 128.6, 123.9, 120.8, 70.9, 49.8, 42.4, 33.2, 28.4, 27.5, 25.1, 21.2 ppm

IR (neat): 2966, 2936, 2887, 2865, 1753, 1637, 1601, 1519, 1508, 1472, 1451, 1432, 1372, 1343, 1316, 1295, 1254, 1220, 1199, 1187, 1169, 1107, 1048, 1018, 969, 955, 925, 911, 849, 833, 821, 796, 752, 735, 686, 669 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{22}H_{23}N_2O_4^+$: 379.1652, Found: 379.1655

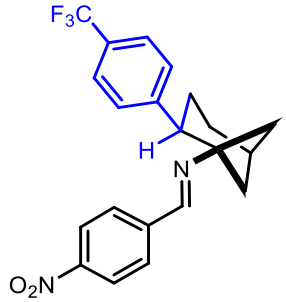
R_f = 0.33 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV





(±)-**4f**, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound (±)-**4g** :



EXPERIMENTAL PROCEDURE:

General procedure B was followed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-(trifluoromethyl)styrene (0.443 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude mixture was concentrated onto celite and loaded atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-60% ethyl acetate in hexanes to give an (±)-**4g** as an intractable mixture with trace impurities. A small amount (<5% yield) of pure (±)-**4g** was obtained as a faintly yellow solid by trituration from ethyl acetate/hexanes.

Due to the large material losses encountered during isolation, it was determined that an assay yield would provide a more meaningful reflection of the reactivity.

Procedure for determining assay yield: General procedure B was followed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-(trifluoromethyl)styrene (0.443 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixtures were diluted with $CDCl_3$ and a known amount of 1,3,5-trimethoxybenzene was added. The amount of (±)-**4g** present in the sample was determined by ^{1}HNMR. A T_1 relaxation delay of 25 seconds was used during data acquisition to ensure meaningful integrations.

Specifically, the following peaks were considered for analysis:

1,3,5-trimethoxybenzene: ~3.7 (s, 9H)
(±)-**4g** : 3.53 (app. t, J = 6.9 Hz, 1H)

The 1,3,5-trimethoxybenzene internal standard was assumed to be 100% pure by mass. The assay yield of (±)-**4g** was 38%..

Appearance: faintly yellow solid

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J = 8.7 Hz), 7.69 (s, 1H), 7.65 (d, J = 8.7 Hz), 7.42 (d, J = 8.1 Hz), 7.24 (d, J = 8.3 Hz), 3.53 (app. t, J = 6.9 Hz, 1H), 2.53-2.45 (m, 1H), 2.40-2.30 (m, 1H), 2.18-2.05 (m, 5H), 2.05-1.92 (m, 2H) ppm

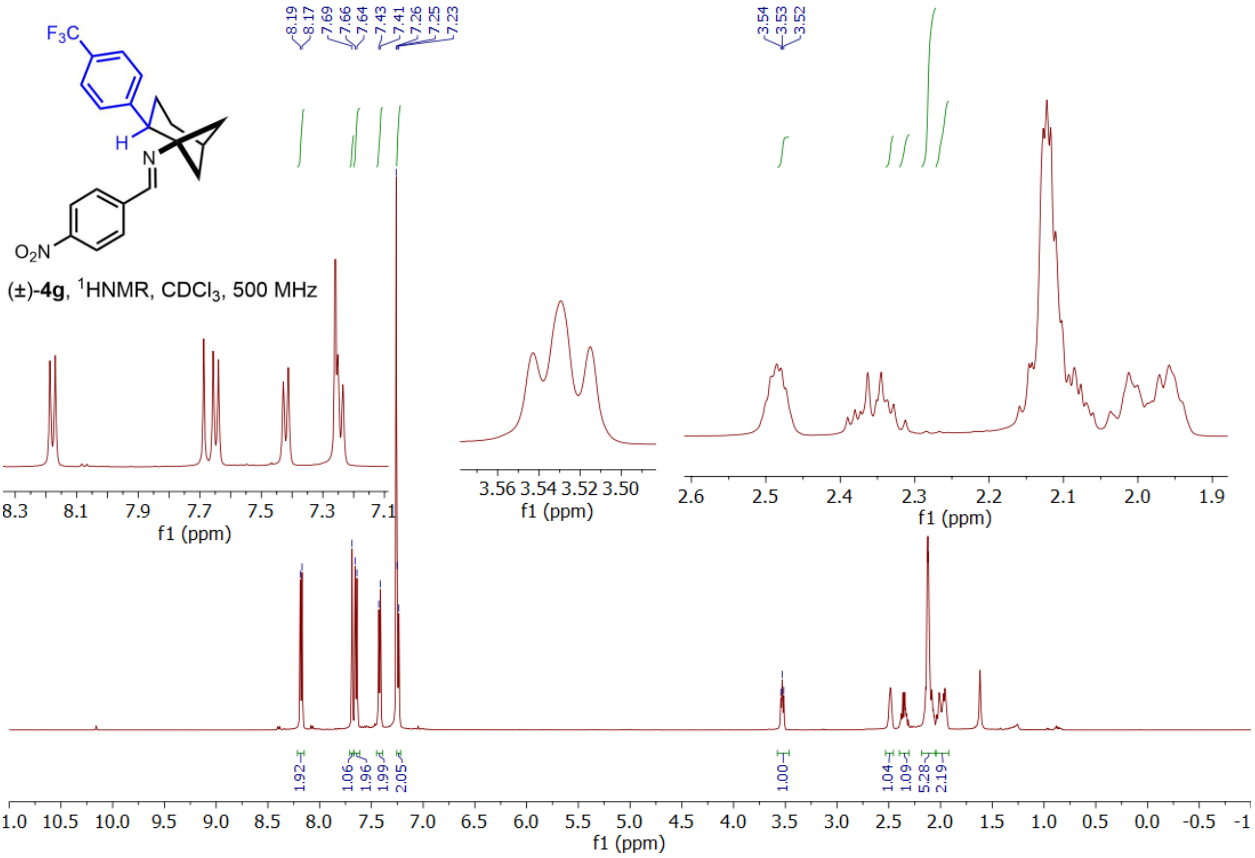
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.0, 149.0, 148.0 (q, J = 1.4 Hz), 141.7, 129.1, 128.6, 128.5 (q, J = 32.4 Hz), 124.7 (q, J = 3.7 Hz), 124.3 (q, J = 271.8 Hz), 123.9, 70.8, 50.4, 42.5, 33.0, 28.3, 27.4, 25.2 ppm

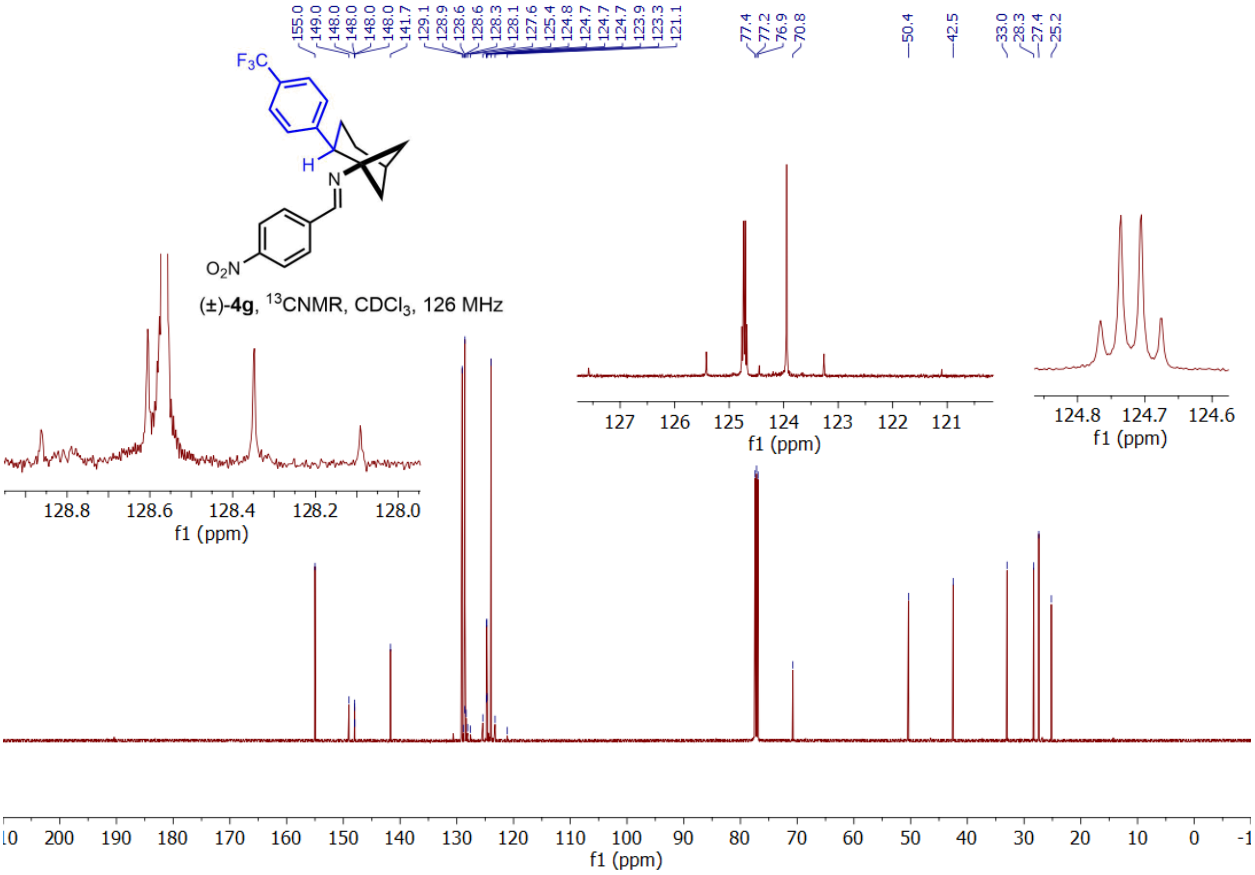
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -63.4 (s) ppm

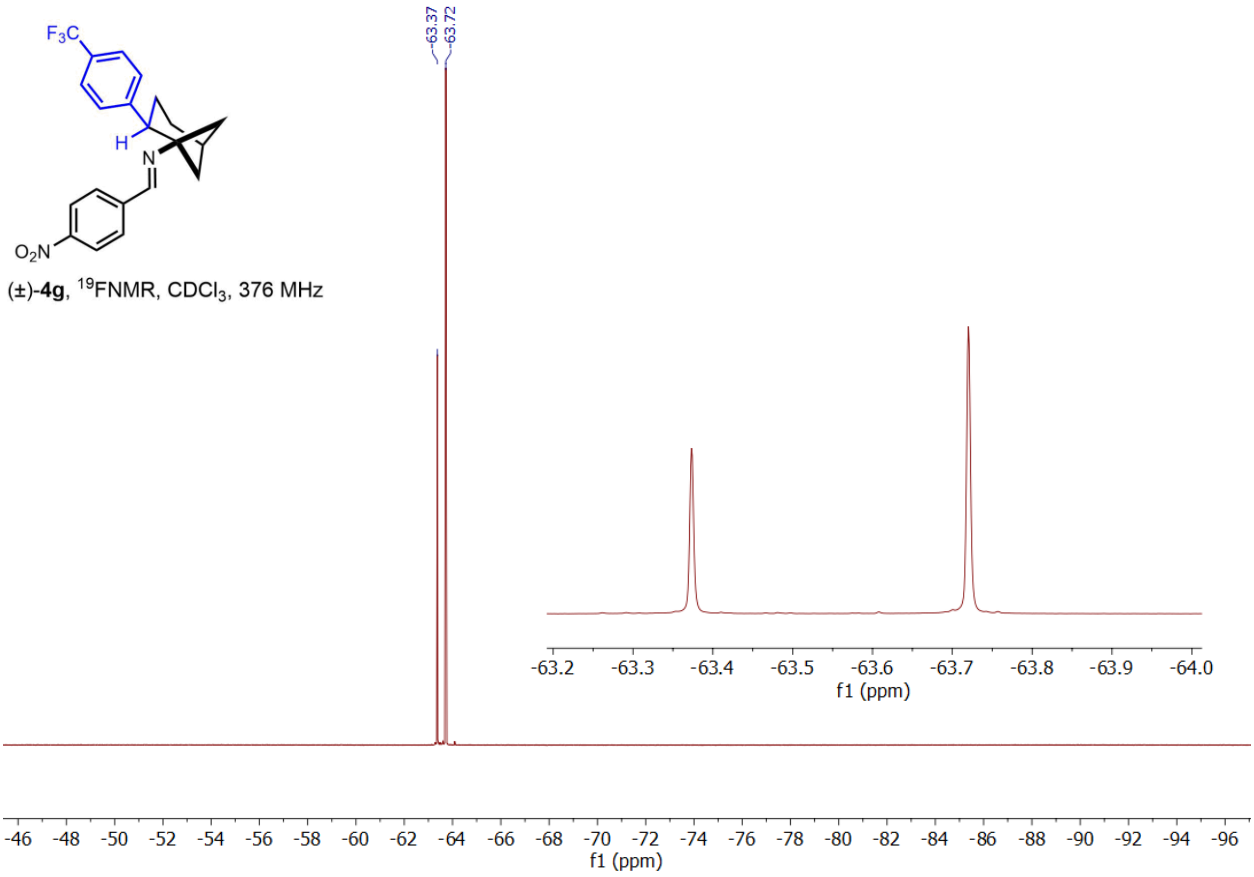
IR (neat): 2963, 2940, 2866, 1639, 1617, 1600, 1521, 1474, 1454, 1420, 1353, 1324, 1296, 1254, 1203, 1158, 1110, 1068, 1015, 998, 969, 955, 931, 894, 851, 839, 823, 814, 751, 735, 694, 663 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{21}H_{20}F_3N_2O_2^+$: 389.1471, Found: 389.1471

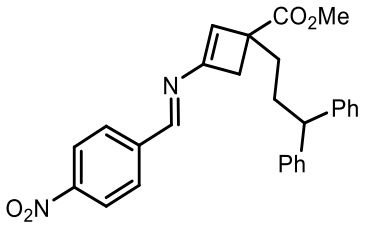
R_f = 0.19 (10% ethyl acetate : 90% hexanes), yellow spot, $KMnO_4$, UV


(±)-4g, 1HNMR, CDCl3, 500 MHz
f1 (ppm)


(±)-4g, 13CNMR, CDCl3, 126 MHz
f1 (ppm)



Compound **6**:



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), 1,1-diphenylethylene (0.530 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16.5 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% dichloromethane, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 12-100% dichloromethane in hexanes to give **6** (20.5 mg, 0.0451 mmol, 11%) as a very thick yellow oil and **4h** (56.7 mg, 0.125 mmol, 31%) as a faintly yellow solid.

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.28 (d, *J* = 8.4 Hz, 2H), 8.14 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.30-7.26 (m, 4H), 7.25-7.21 (m, 4H), 7.19-7.15 (m, 2H), 6.29 (s, 1H), 3.89 (app. t, *J* = 7.8 Hz,

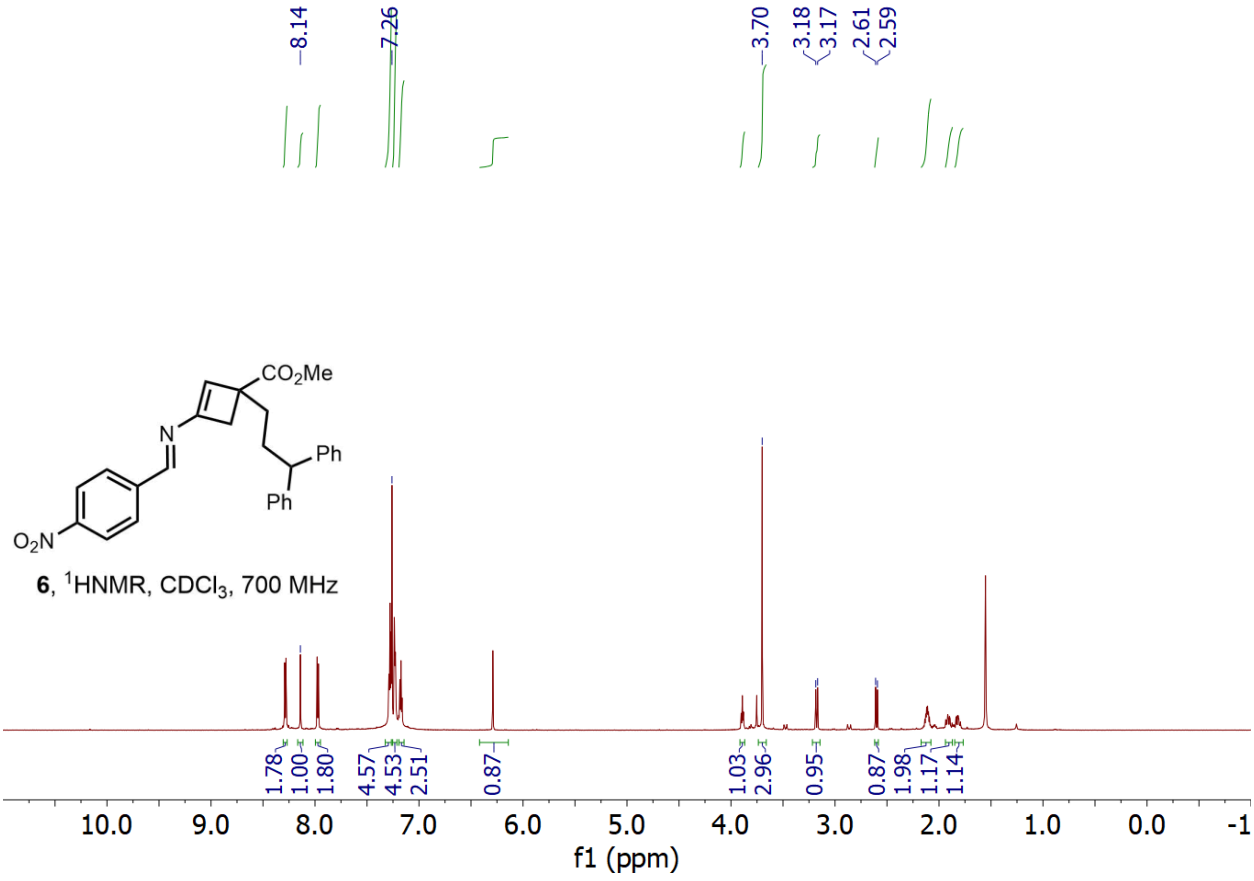
1H), 3.70 (s, 3H), 3.18 (d, *J* = 12.4 Hz, 1H), 2.60 (d, *J* = 12.5 Hz, 1H), 2.16-2.07 (m, 2H), 1.95-1.88 (m, 1H), 1.85-1.78 (m, 1H) ppm

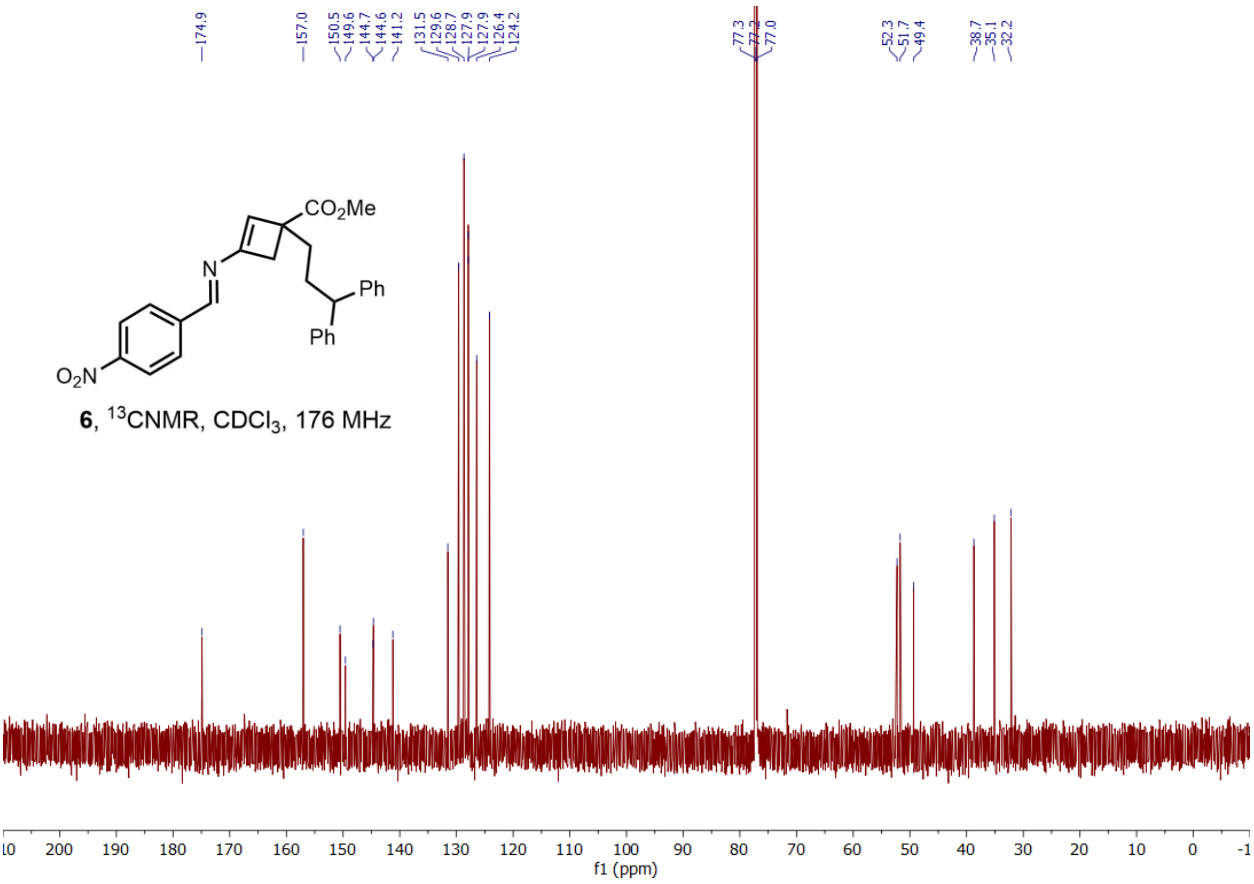
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 174.9, 157.0, 150.5, 149.6, 144.7, 144.6, 141.2, 131.5, 129.6, 128.7, 127.9, 127.9, 126.4, 124.2, 52.3, 51.7, 49.4, 38.7, 35.1, 32.2 ppm (Note: 2 additional aromatic peaks expected but not observed due to signal overlap; phenyl groups are diastereotopic)

IR (neat): 3061, 3027, 2948, 2862, 1949, 1726, 1596, 1571, 1519, 1494, 1451, 1434, 1342, 1319, 1297, 1260, 1236, 1192, 1165, 1138, 1107, 1094, 1070, 1031, 1012, 972, 956, 910, 854, 839, 748, 731, 699, 689 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{28}H_{27}N_2O_4^+$: 455.1965, Found: 455.1961

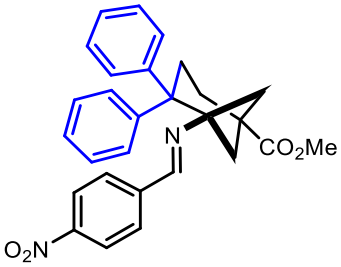
R_f = 0.45 (30% ethyl acetate : hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV





6, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound **4h**:



Experimental procedure: See above procedure on page S74

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.24-8.20 (m, 2H), 7.99-7.75 (m, 2H), 7.61 (s, 1H), 7.27-7.23 (m, 4H overlapping with $CHCl_3$), 7.21-7.18 (m, 4H), 7.18-7.15 (m, 2H), 3.71 (s, 3H), 2.60 (t, *J* = 7.2 Hz, 2H), 2.53-2.48 (m, 2H), 2.43-2.38 (m, 2H), 2.36 (t, *J* = 7.2 Hz, 2H) ppm

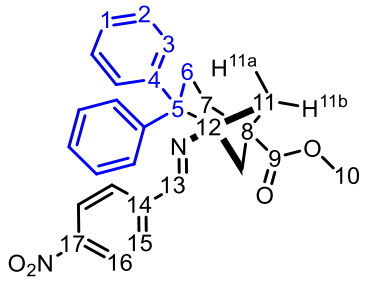
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.4, 157.0, 149.1, 147.5, 141.8, 129.8, 129.0, 127.4, 126.0, 124.0, 68.8, 56.5, 52.1, 41.0, 40.9, 36.2, 30.7 ppm

IR (neat): 2946, 2877, 1732, 1641, 1602, 1517, 1494, 1453, 1444, 1434, 1343, 1316, 1294, 1281, 1258, 1213, 1179, 1152, 1105, 1094, 1064, 1048, 1012, 970, 958, 941, 917, 875, 853, 835, 786, 767, 749, 699, 661 cm^{-1}

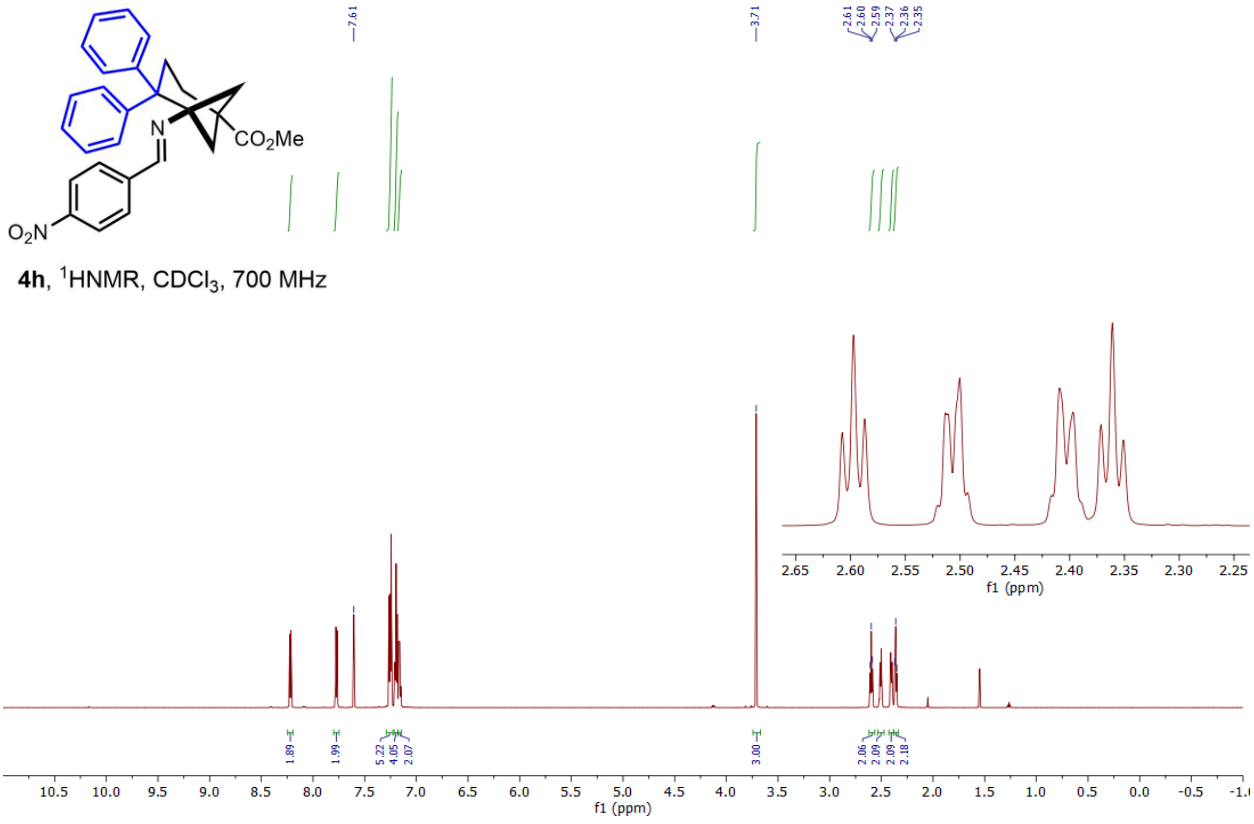
HRMS (ES+, m/z) calculated for $C_{28}H_{27}N_2O_4^+$: 455.1965, Found: 455.1960

R_f = 0.47 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

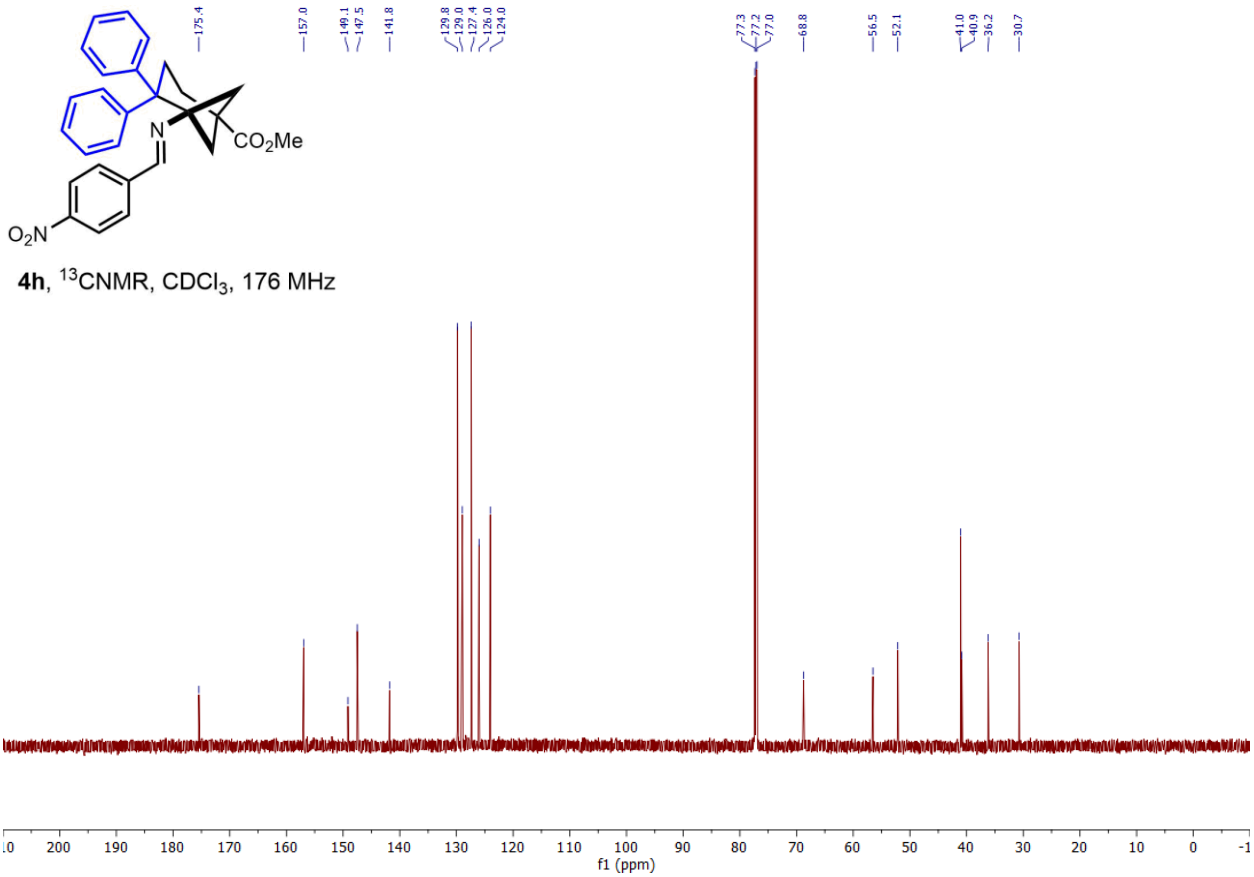
Complete assignment of ^1H and ^{13}C NMR signals



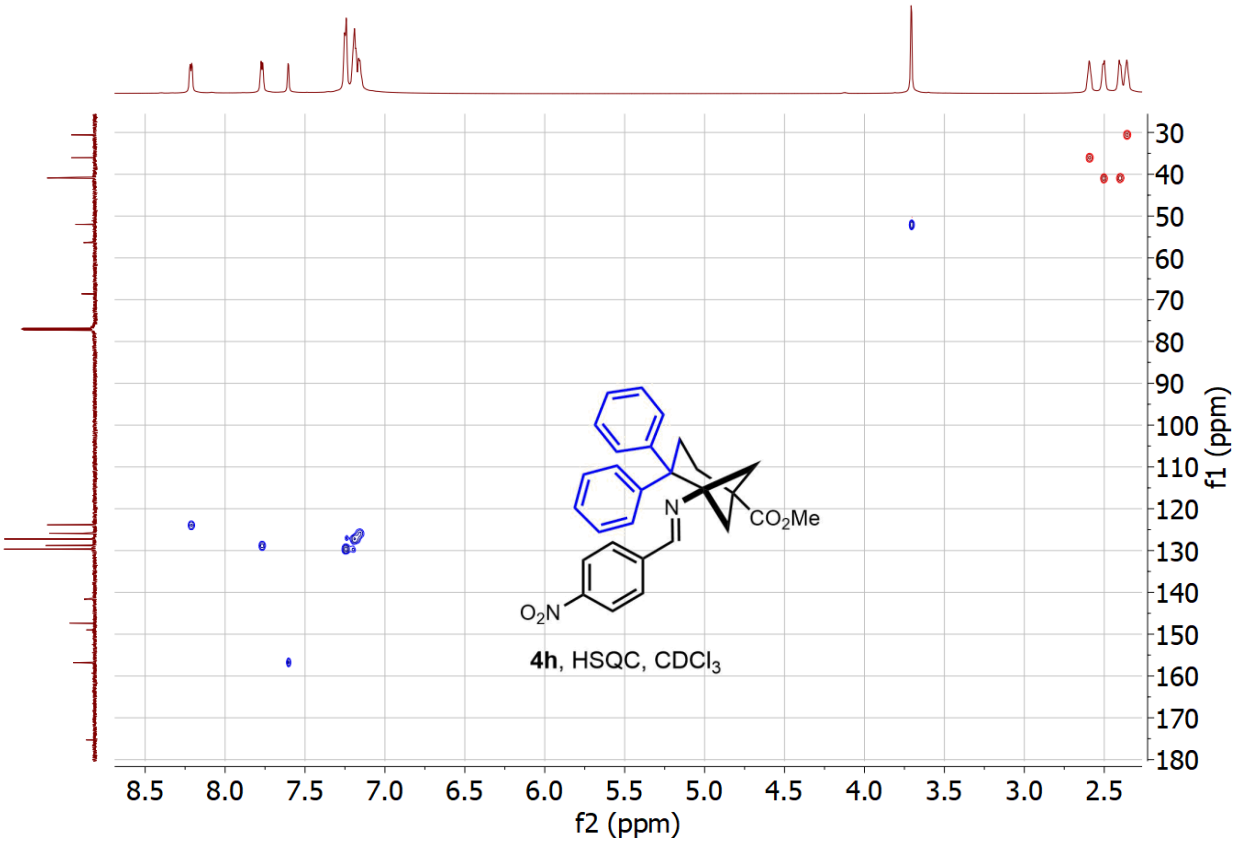
Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	126		1	7.18-7.15 (m, 2H)
2	127.4		2	7.21-7.18 (m, 4H)
3	129.8		3	7.27-7.23 (m, 4H)
4	147.5		6	2.60 (t, *J* = 7.2 Hz, 2H)
5	56.5		7	2.36 (t, *J* = 7.2 Hz, 2H)
6	36.2		10	3.71 (s, 3H)
7	30.7		11a	2.53-2.48 (m, 2H)
8	40.9		11b	2.43-2.38 (m, 2H)
9	175.4		13	7.61 (s, 1H)
10	52.1		15	8.24-8.20 (m, 2H)
11	41		16	7.99-7.75 (m, 2H)
12	68.8			
13	157			
14	141.8			
15	124			
16	129			
17	149.1			

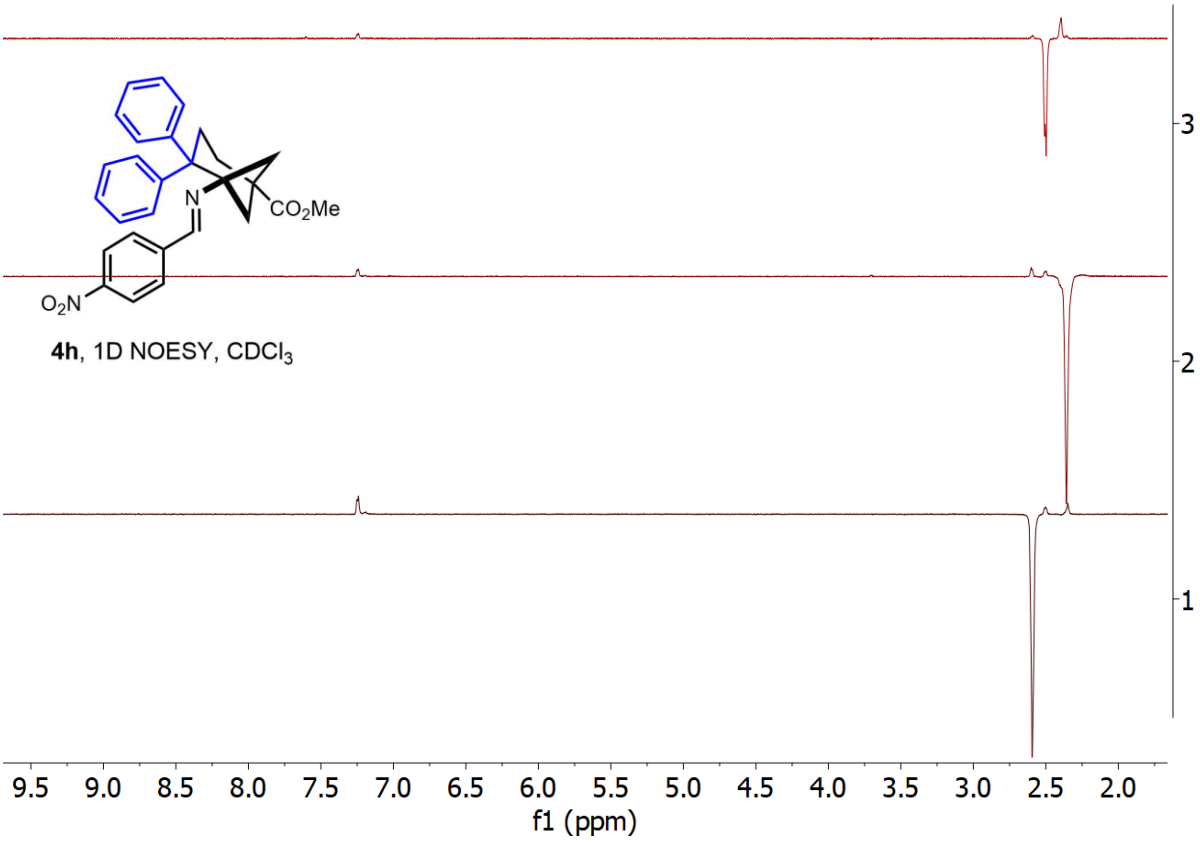


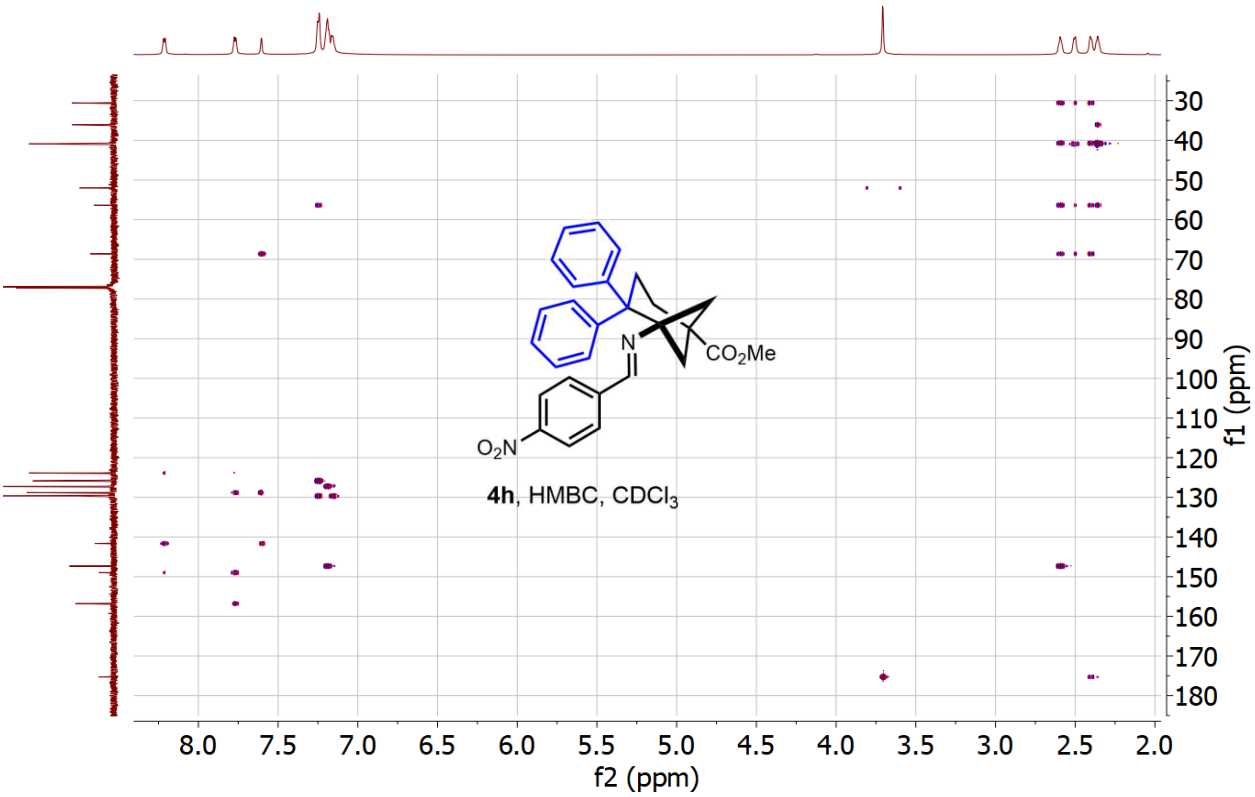
4h, ^{1}HNMR, $CDCl_3$, 700 MHz

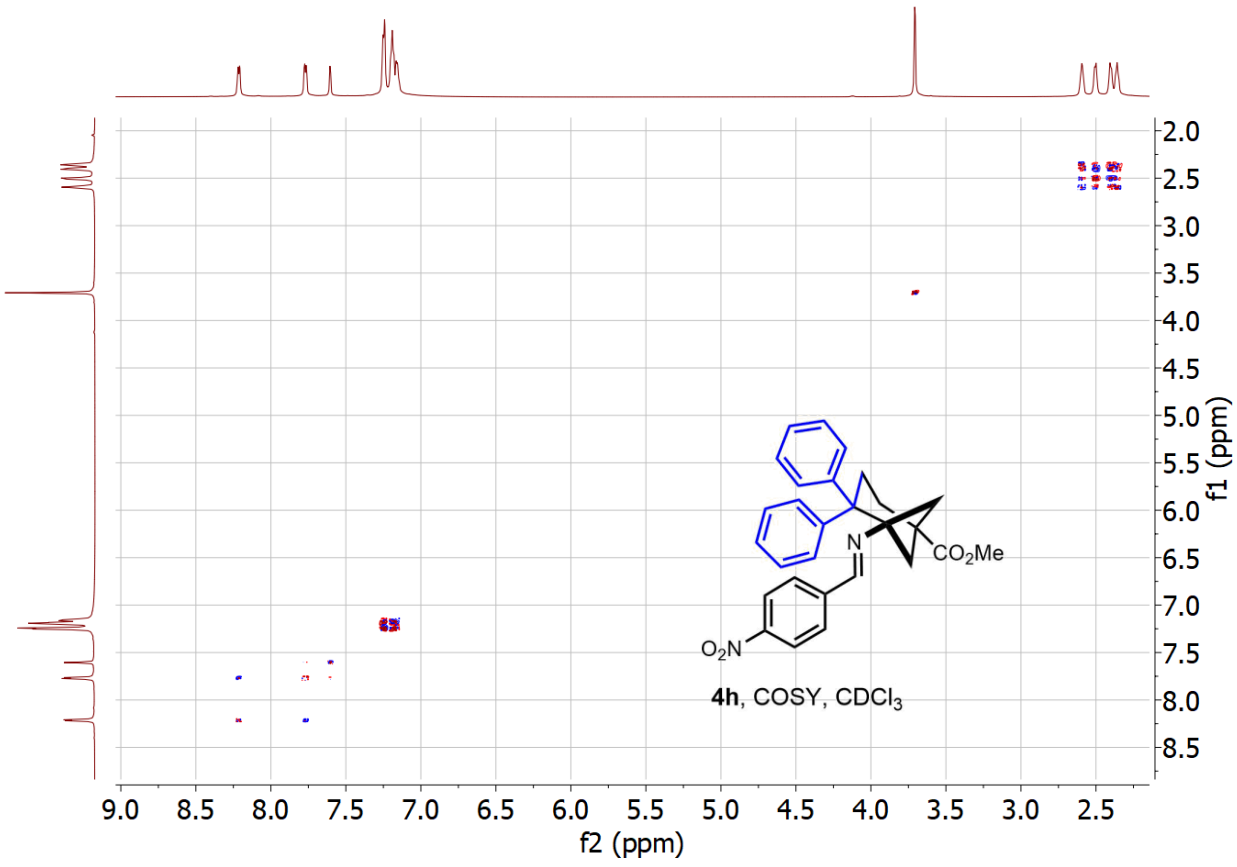


4h, ^{13}CNMR, $CDCl_3$, 176 MHz

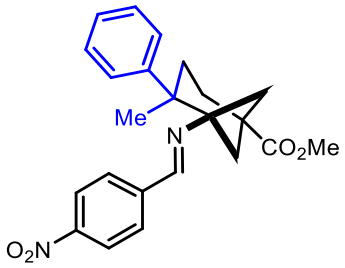

N
CO2Me
O2N
4h, HSQC, CDCl3
f2 (ppm)
f1 (ppm)


N
CO2Me
O2N
4h, 1D NOESY, CDCl3
f1 (ppm)


CO2Me
N
O2N
4h, HMBC, CDCl3
f2 (ppm)
f1 (ppm)


CO2Me
N
O2N
4h, COSY, CDCl3
f2 (ppm)
f1 (ppm)

Compound (±)-**4i** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), isopropenylbenzene (0.390 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 13 hours. The crude reaction mixture was loaded with toluene atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-50% ethyl acetate in hexanes. Fractions containing (±)-**4i** were combined and chromatographed over basic alumina eluting with 0-20% ethyl acetate in hexanes to give (±)-**4i** (50.8 mg, 0.129 mmol, 32%) as a yellow oil.

Appearance: yellow oil

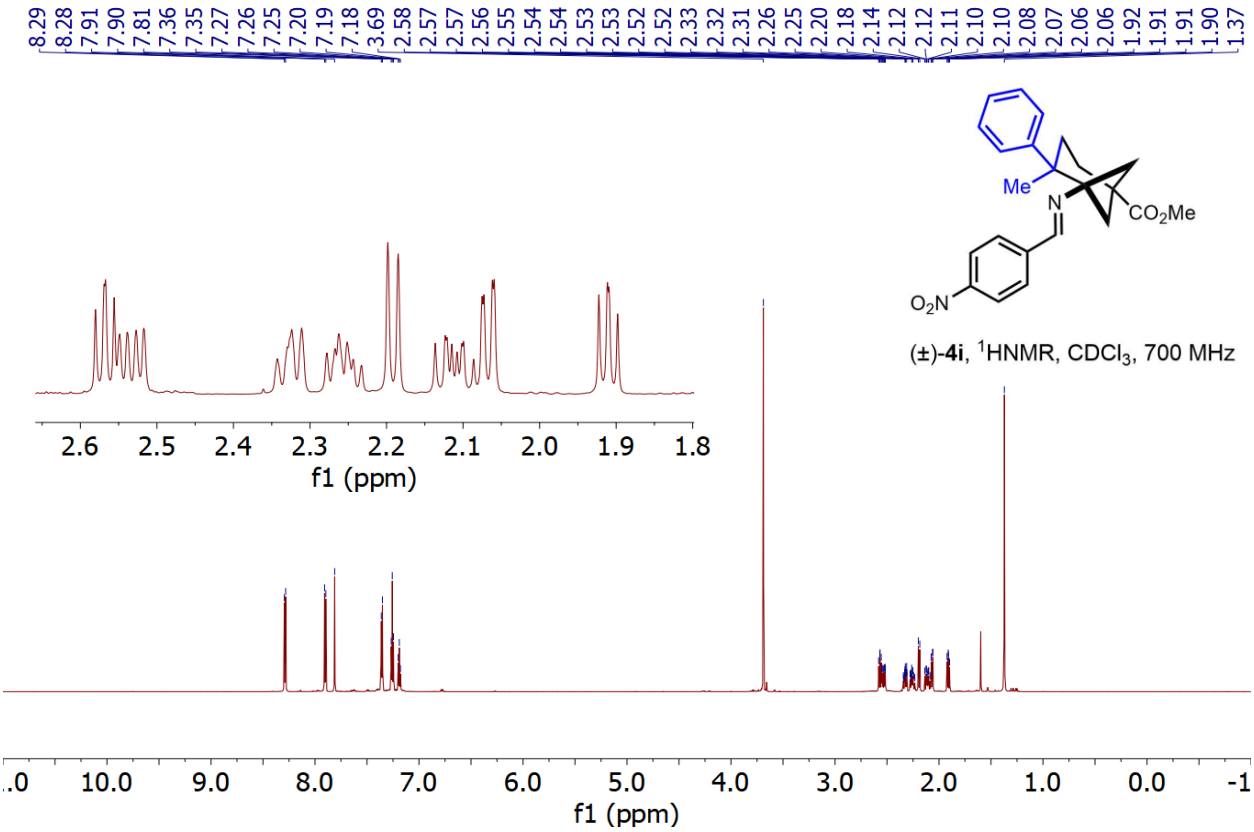
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.31-8.27 (m, 2H), 7.92-7.88 (m, 2H), 7.81 (s, 1H), 7.38-7.34 (m, 2H), 7.28-7.24 (m, 2H), 7.21-7.17 (m, 1H), 3.69 (s, 3H), 2.57 (dd, *J* = 9.4, 7.7 Hz, 1H), 2.54 (dd, *J* = 15.2, 7.2 Hz, 1H), 2.36-2.30 (m, 1H), 2.29-2.24 (m, 1H), 2.24-2.17 (m, 1H), 2.15-2.08 (m, 1H), 2.07 (dd, *J* = 9.5, 1.7 Hz, 1H), 1.91 (dd, *J* = 9.3, 7.8 Hz, 1H), 1.37 (s, 3H) ppm

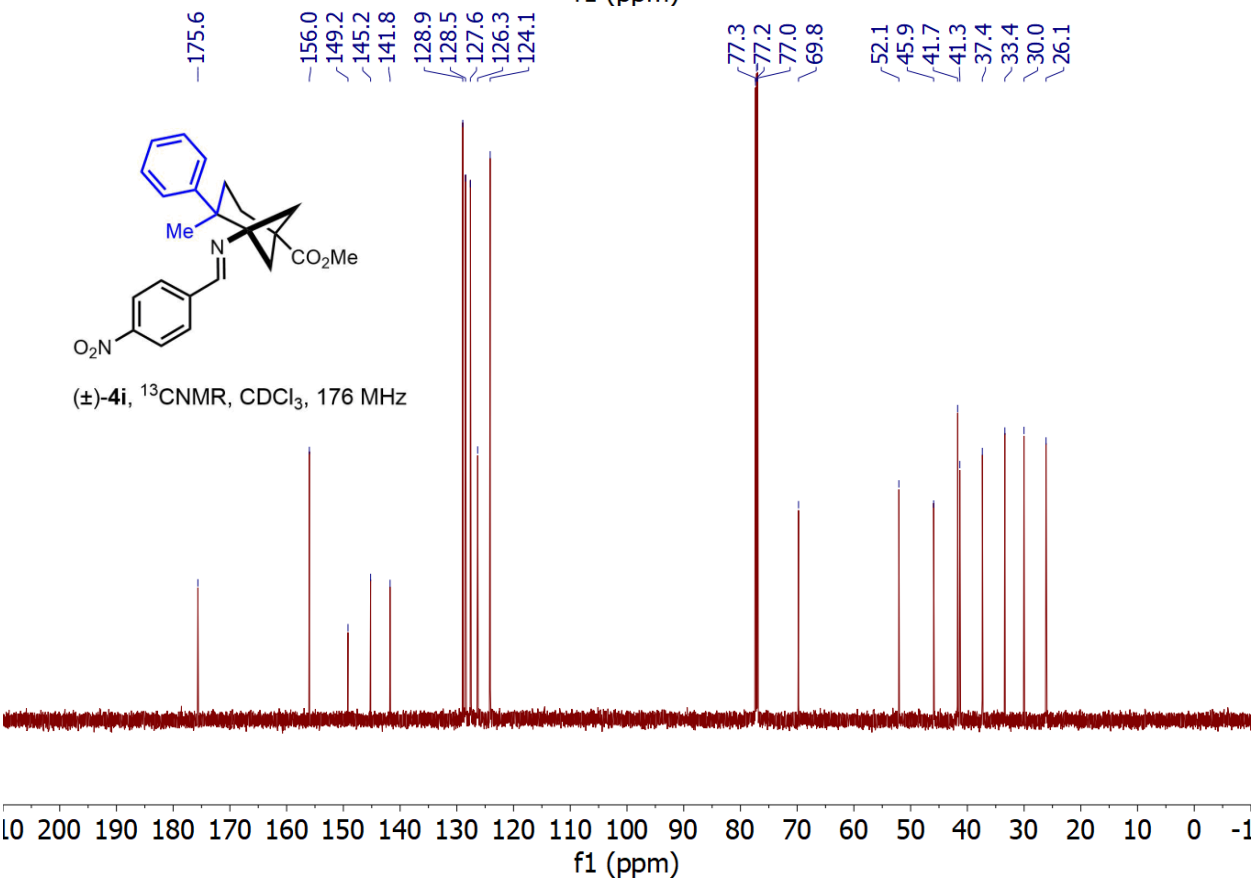
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.6, 156.0, 149.2, 145.2, 141.8, 128.9, 128.5, 127.6, 126.3, 124.1, 69.8, 52.1, 45.9, 41.7, 41.3, 37.4, 33.4, 30.0, 26.1 ppm

IR (neat): 3058.8, 2952, 2872, 1726, 1641, 1601, 1520, 1497, 1455, 1435, 1414, 1375, 1343, 1292, 1267, 1242, 1216, 1193, 1164, 1139, 1108, 1094, 1047, 1012, 977, 957, 928, 853, 835, 791, 772, 748, 700, 688 cm^{-1}

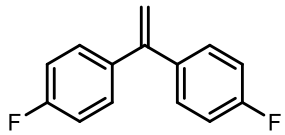
HRMS (ES+, m/z) calculated for $C_{23}H_{25}N_2O_4^+$: 393.1809, Found: 393.1815

R_f = 0.47 (30% ethyl acetate: 69% hexanes : 1% aqueous NH_4OH), one yellow spot, $KMnO_4$, UV


8.29 8.28 7.91 7.90 7.81 7.36 7.35 7.27 7.26 7.25 7.20 7.19 7.18 3.69 2.58 2.57 2.57 2.56 2.55 2.54 2.54 2.53 2.53 2.52 2.52 2.33 2.32 2.31 2.26 2.25 2.20 2.18 2.14 2.12 2.12 2.11 2.10 2.10 2.08 2.07 2.06 2.06 1.92 1.91 1.91 1.90 1.37
Me
N
CO2Me
O2N
(±)-4i, 1HNMR, CDCl3, 700 MHz
2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)


175.6
156.0 149.2 145.2 141.8 128.9 128.5 127.6 126.3 124.1
77.3 77.2 77.0 69.8
52.1 45.9 41.7 41.3 37.4 33.4 30.0 26.1
Me
N
CO2Me
O2N
(±)-4i, 13CNMR, CDCl3, 176 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Compound **SI-13**:



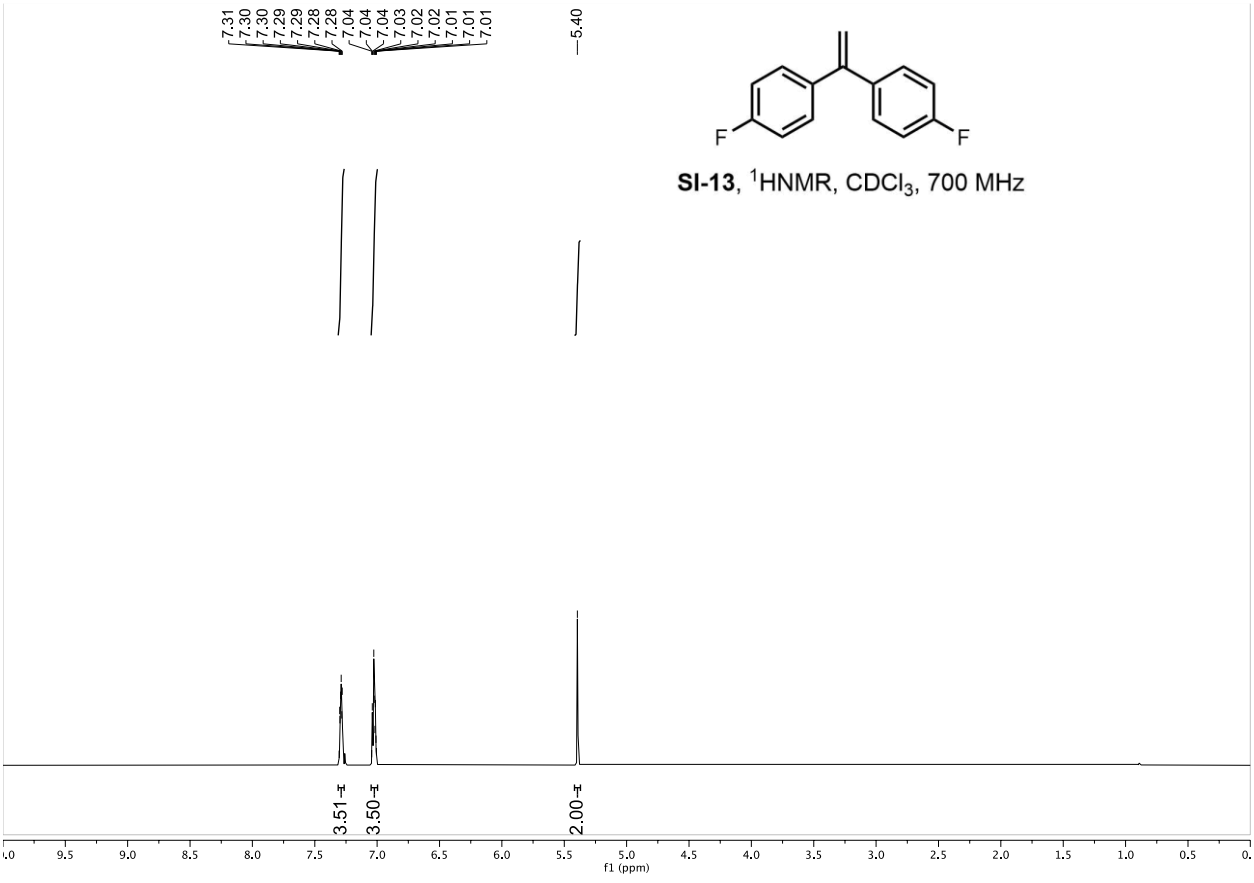
EXPERIMENTAL PROCEDURE:

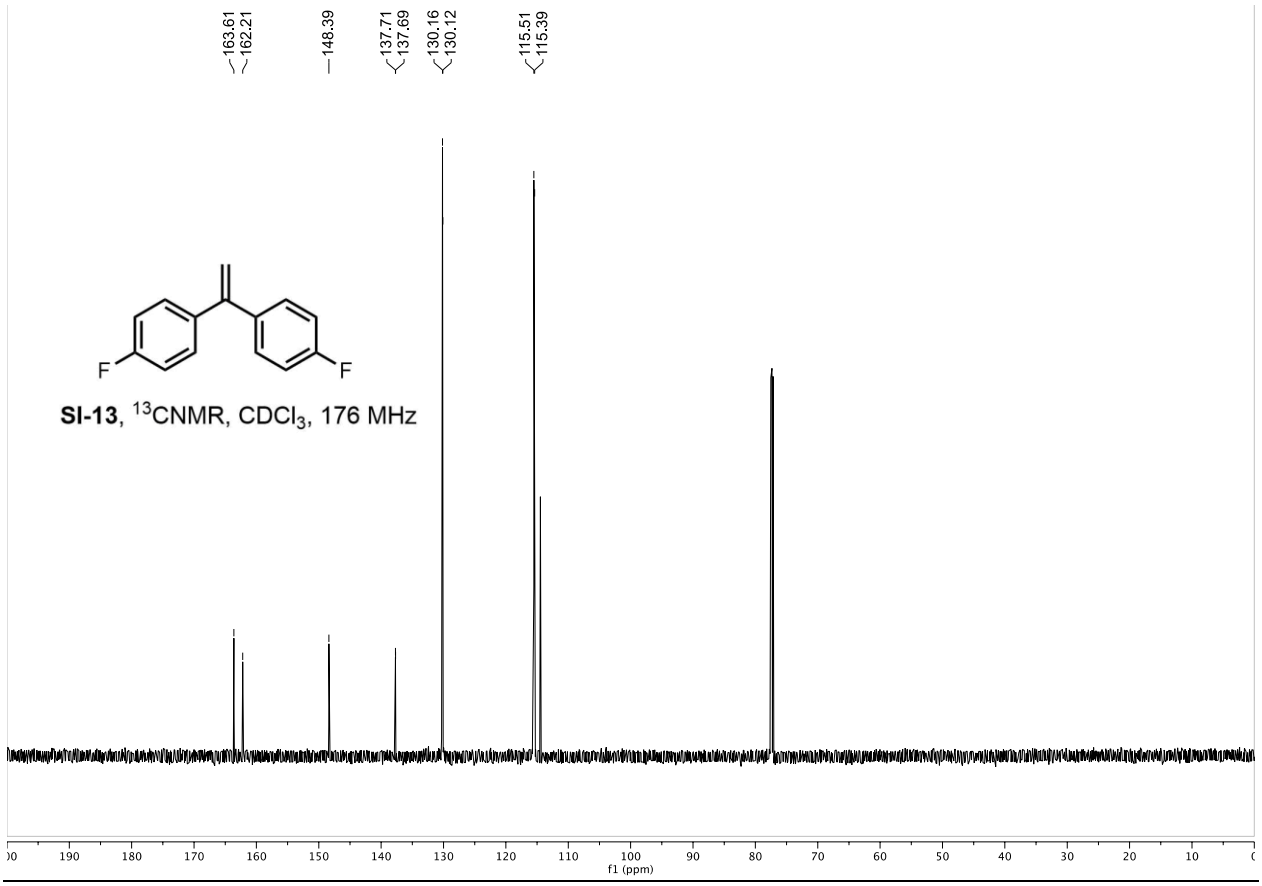
This compound was synthesized via general procedure A, from 4,4′-difluorobenzophenone (2.00 g, 9.17 mmol, 1.0 mol equiv) to give **SI-13** (870 mg, 4.02 mmol, 44% yield) as a colorless oil. ^{1}H and ^{13}C NMR match those previously reported.[9]

Appearance: colorless oil

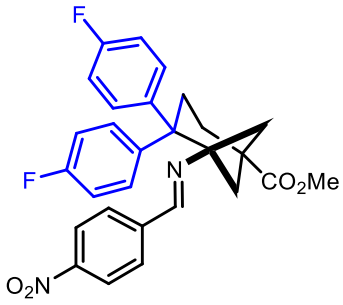
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.32-7.27 (m, 4H), 7.06-7.00 (m, 4H), 5.40 (s, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz, $CDCl_3$ referenced to 77.00 ppm instead of 77.16 ppm): δ = 162.9 (d, *J* = 247.0 Hz), 148.39, 137.7 (d, *J* = 3.3 Hz), 130.1 (d, *J* = 7.9 Hz), 115.5 (d, *J* = 21.5 Hz), 114.46 ppm





Compound **4j**:



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), **SI-13** (649 mg, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 13 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 3-30% ethyl acetate in hexanes to give **4j** (48.0 mg, 0.0979 mmol, 24%) as a faintly yellow solid.

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.25-8.21 (m, 2H), 7.79-7.75 (m, 2H), 7.64 (s, 1H), 7.21-7.17 (m, 4H), 6.89 (app. t, *J* = 8.6 Hz, 4H), 3.71 (s, 3H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.45-2.38 (m, 4H), 2.33 (t, *J* = 7.2 Hz, 2H) ppm

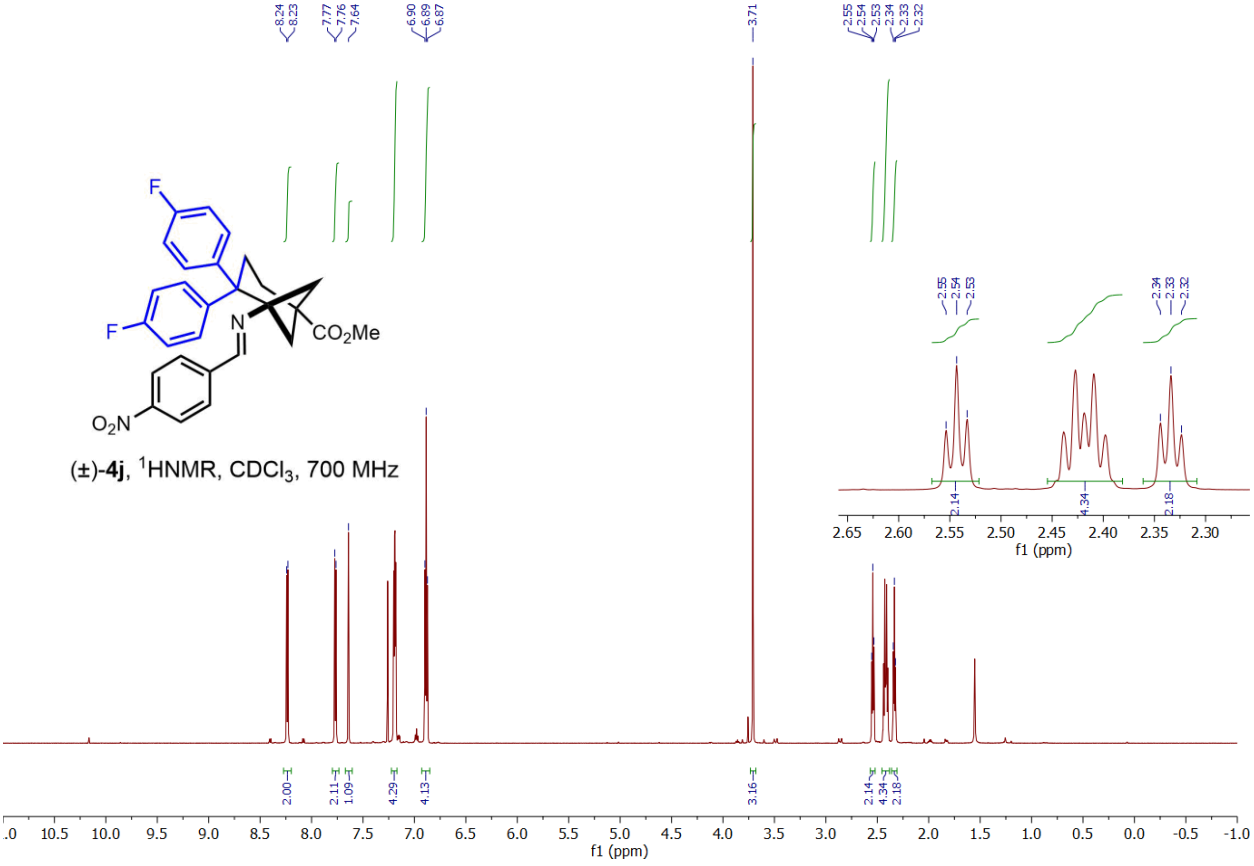
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.2, 161.2 (d, *J* = 245.6 Hz), 157.2, 149.3, 143.0 (d, *J* = 3.4 Hz), 141.5, 131.2 (d, *J* = 7.6 Hz), 129.0, 124.1, 114.3 (d, *J* = 20.8 Hz), 68.6, 55.5, 52.2, 40.9, 40.8, 36.5, 30.6 ppm

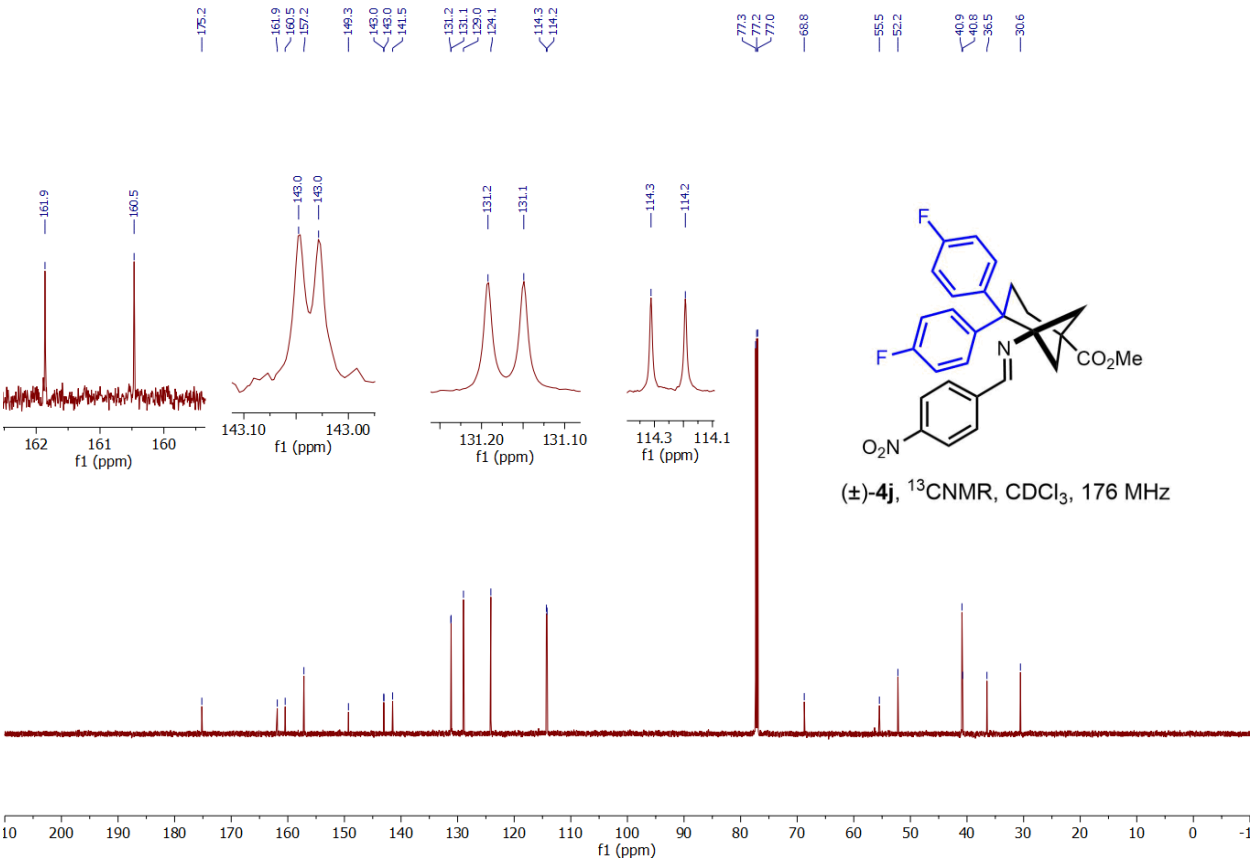
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -117.8 (m) ppm

IR (neat): 2949, 1726, 1643, 1603, 1525, 1507, 1455, 1436, 1346, 1278, 1257, 1227, 1176, 1163, 1150, 1108, 1068, 1047, 1015, 950, 914, 834, 810, 791, 750, 742, 689 cm^{-1}

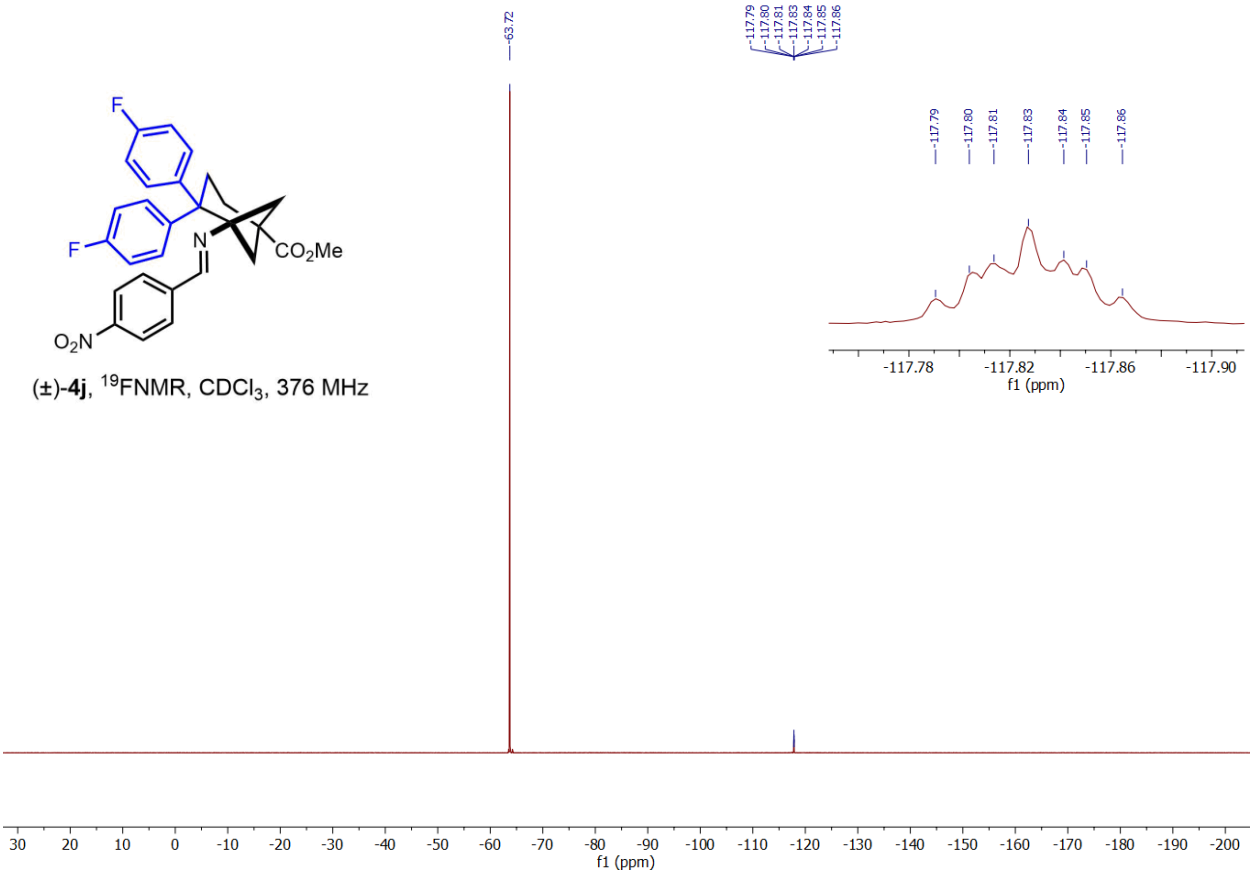
HRMS (ES+, m/z) calculated for $C_{28}H_{25}F_2N_2O_4^+$: 491.1777, Found: 491.1768

R_f = 0.43 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), one yellow spot, $KMnO_4$, UV



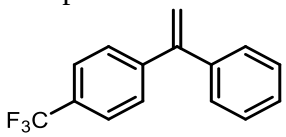


(±)-**4j**, ^{13}CNMR, $CDCl_3$, 176 MHz



(±)-**4j**, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound **SI-14**:



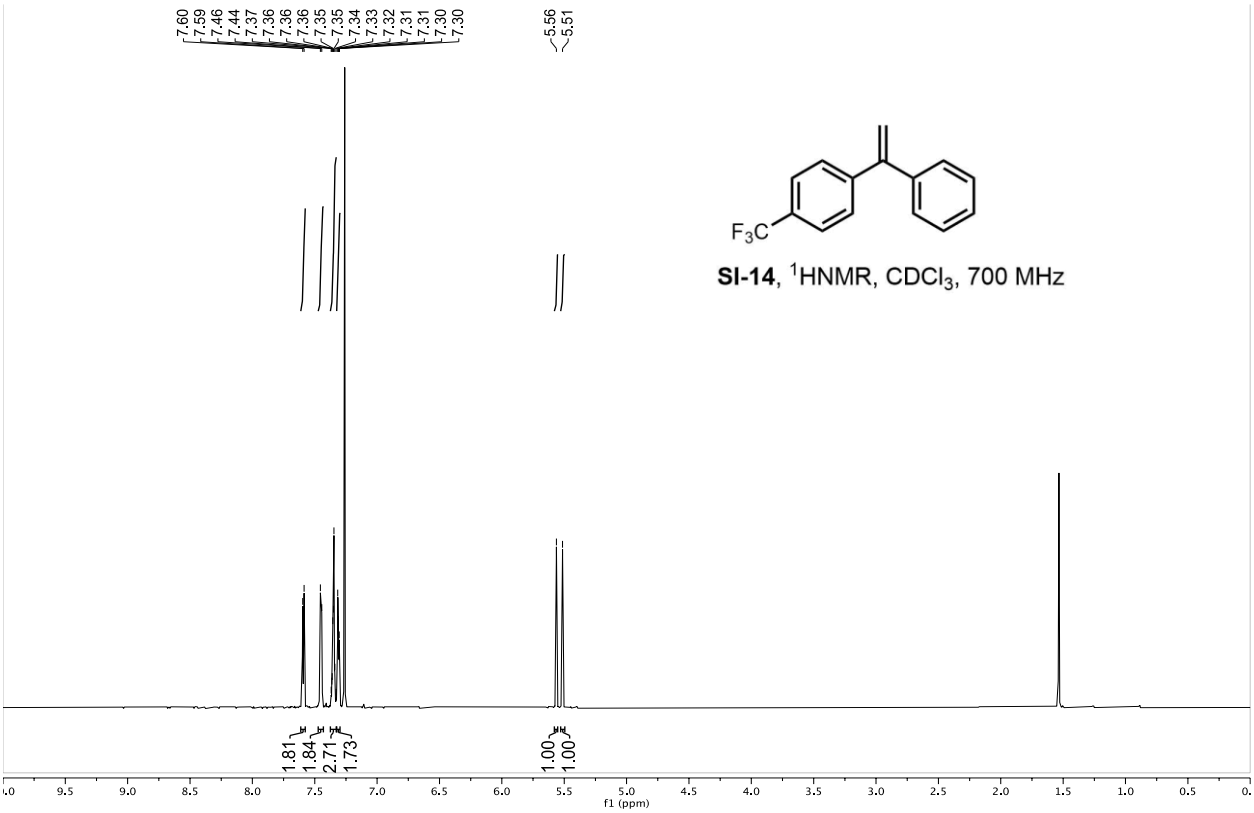
EXPERIMENTAL PROCEDURE:

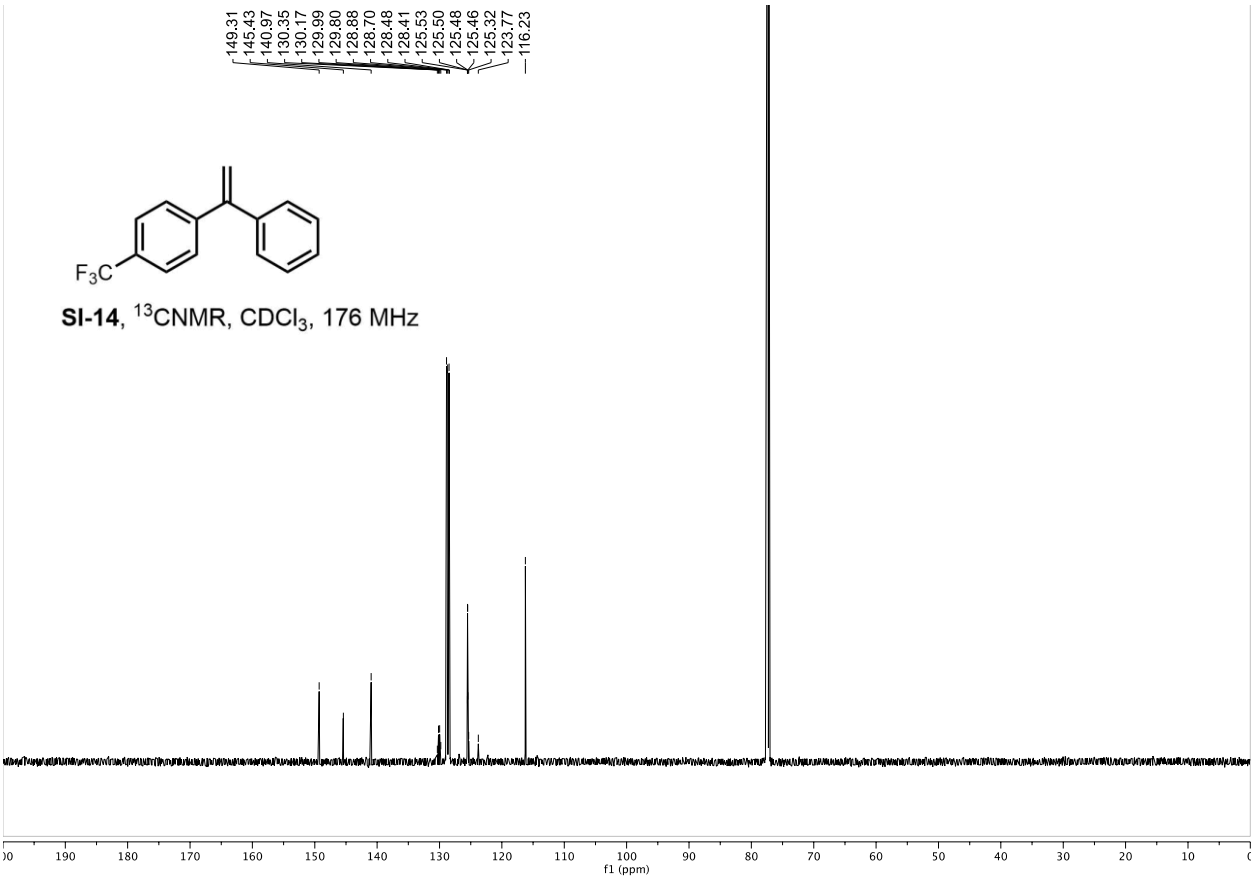
This compound was synthesized via standard procedure A, from 4-(trifluoromethyl)benzophenone (2.00 g, 7.99 mmol, 1.0 equiv) to give **SI-14** (900 mg, 3.63 mmol, 45% yield) as a colorless oil. ^{1}H and ^{13}C NMR match those previously reported.[10]

Appearance: colorless oil

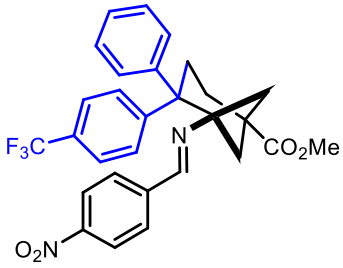
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.59 (d, *J* = 8.1 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.38-7.32 (m, 3H), 7.33-7.28 (m, 2H), 5.56 (s, 1H), 5.51 (s, 1H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz, $CDCl_3$ referenced to 77.00 ppm instead of 77.16 ppm): δ = 149.3, 145.4, 141.0, 130.1 (q, *J* = 32.2 Hz), 128.9, 128.7, 128.5, 128.4, 125.5 (q, *J* = 3.9 Hz), 124.5 (q, *J* = 271.8), 116.2 ppm





Compound (±)-**4k** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), **SI-14** (745 mg, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 13 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 3-30% ethyl acetate in hexanes to give (±)-**4k** (56.6 mg, 0.108 mmol, 27%) as a faintly yellow solid.

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.26-8.22 (m, 2H), 7.79-7.75 (m, 2H), 7.65 (s, 1H), 7.46 (m, 4H), 7.21-7.16 (m, 3H), 7.15-7.11 (m, 2H), 3.71 (s, 3H), 2.65 (app. dt, *J* = 15.5, 6.5Hz, 1H), 2.59-2.55 (m, 1H), 2.53-2.44 (m, 2H), 2.42-2.33 (m, 4H) ppm

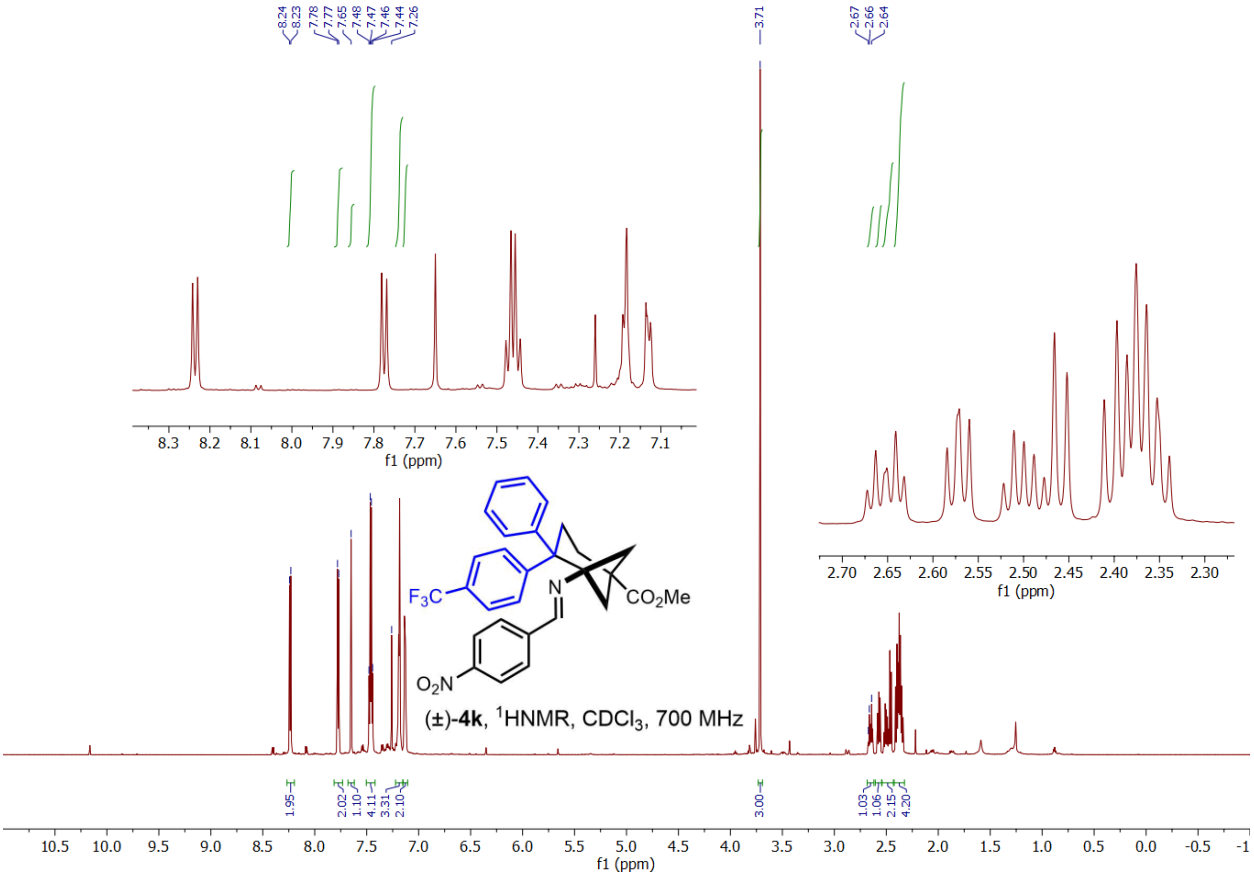
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.2, 157.3, 152.2, 149.2, 146.1, 141.5, 129.9, 129.8, 129.0, 128.1 (q, *J* = 32.3 Hz), 127.5, 126.5, 124.4 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.9 Hz), 124.1, 68.5, 56.4, 52.2, 40.9, 40.8, 40.7, 36.0, 30.6 ppm

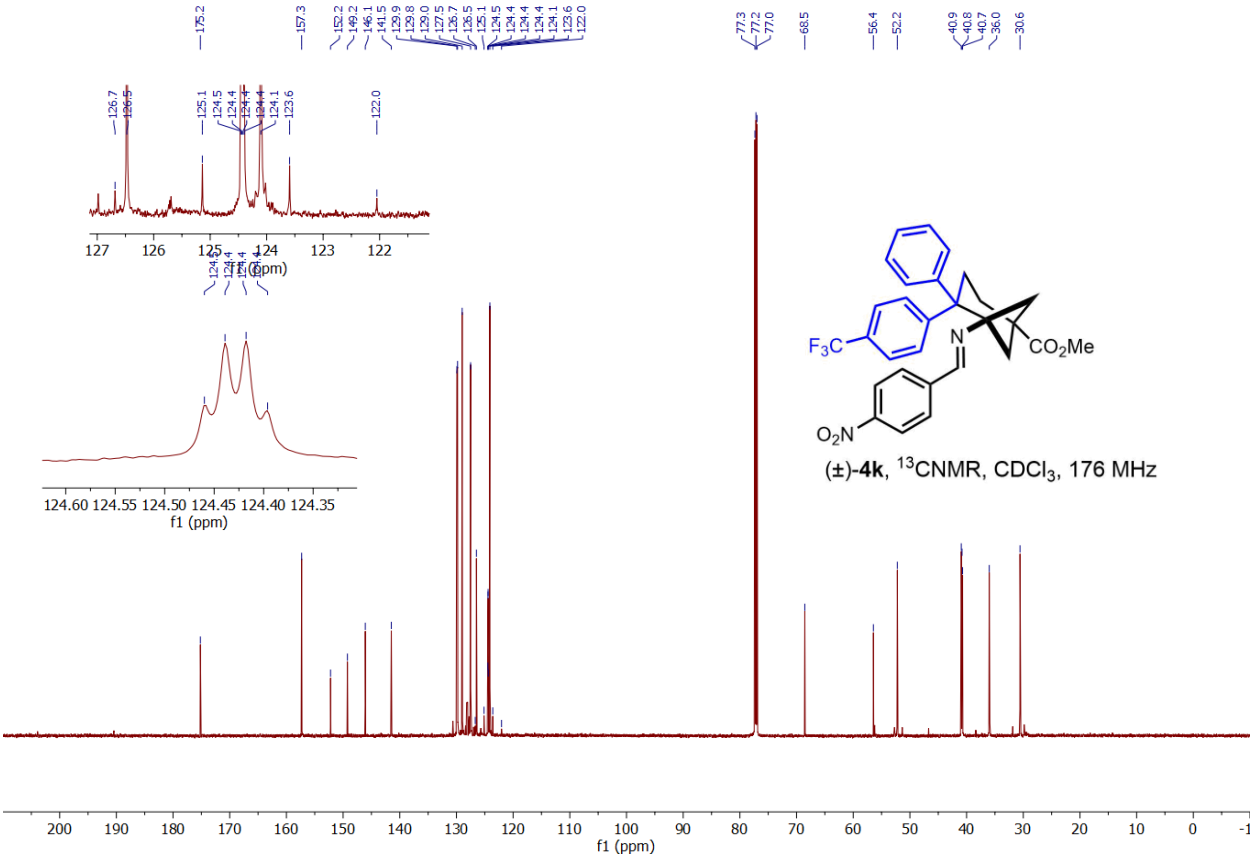
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -63.3 (s) ppm

IR (neat): 2952, 1794, 1734, 1641, 1617, 1601, 1522, 1494, 1453, 1435, 1410, 1345, 1327, 1292, 1256, 1217, 1164, 1147, 1108, 1067, 1046, 1017, 981, 912, 874, 856, 834, 790, 748, 738, 703, 670 cm^{-1}

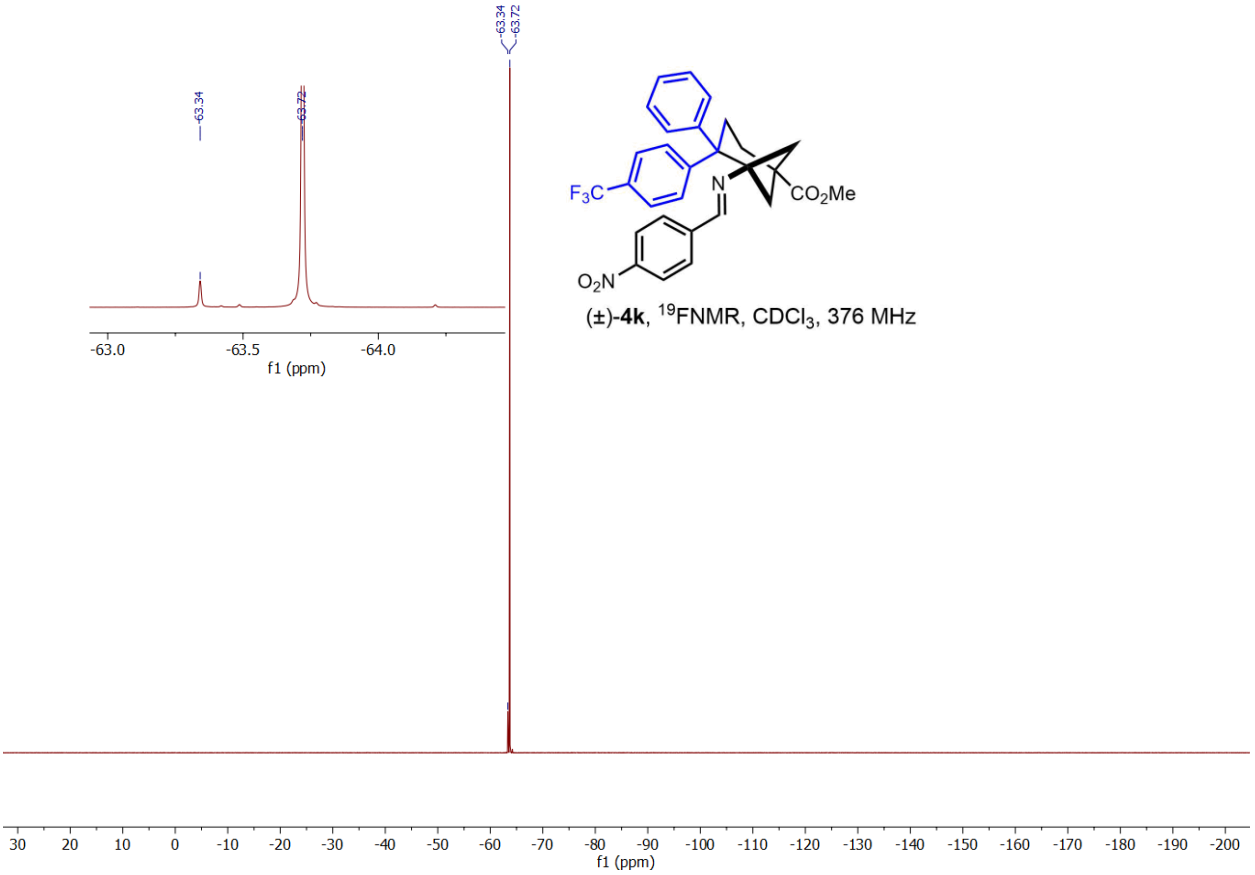
HRMS (ES+, m/z) calculated for $C_{29}H_{26}F_3N_2O_4^+$: 523.1839, Found: 523.1834

R_f = 0.41 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



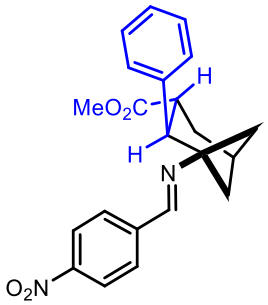


(±)-**4k**, ^{13}CNMR, $CDCl_3$, 176 MHz



(±)-**4k**, ^{19}FNMR, $CDCl_3$, 376 MHz

Compound (±)-**4l** :



EXPERIMENTAL PROCEDURE:
A modification of general procedure B (modification = 0.200 mL acetonitrile used) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), methyl cinnamate (487 mg, 3.00 mmol, 7.5 equiv), 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv), acetonitrile (0.200 mL), and irradiating for 17 hours. The crude reaction mixture was mixed diluted with chloroform and concentrated onto celite (3 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-50% ethyl acetate in hexanes to give (±)-**4l** (24.5 mg, 0.0647 mmol, 16%) as a yellow oil. The reaction was repeated as above and analyzed by crude ^{1}HNMR. Only the major, *trans* diastereomer was identified. The mixture was then concentrated into a 4-dram vial and a magnetic stir bar was added, followed by acetonitrile (3 mL), water (1 mL), and acetic acid (1 mL). The headspace was flushed with nitrogen, the vial was capped, and the mixture was stirred at room temperature for 18 hours. The mixture was diluted with 1 M aqueous hydrochloric acid (40 mL) and washed with diethyl ether (3 x 20 mL). The aqueous layer was neutralized with saturated aqueous sodium bicarbonate (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined ethyl acetate fractions were washed with brine (50 mL) and concentrated in vacuo to give a brown oil. ^{1}HNMR analysis did not show the minor, *cis* diastereomer of the primary amine. On these bases, the d.r.is >20:1 for the formal cycloaddition.

Appearance: yellow oil

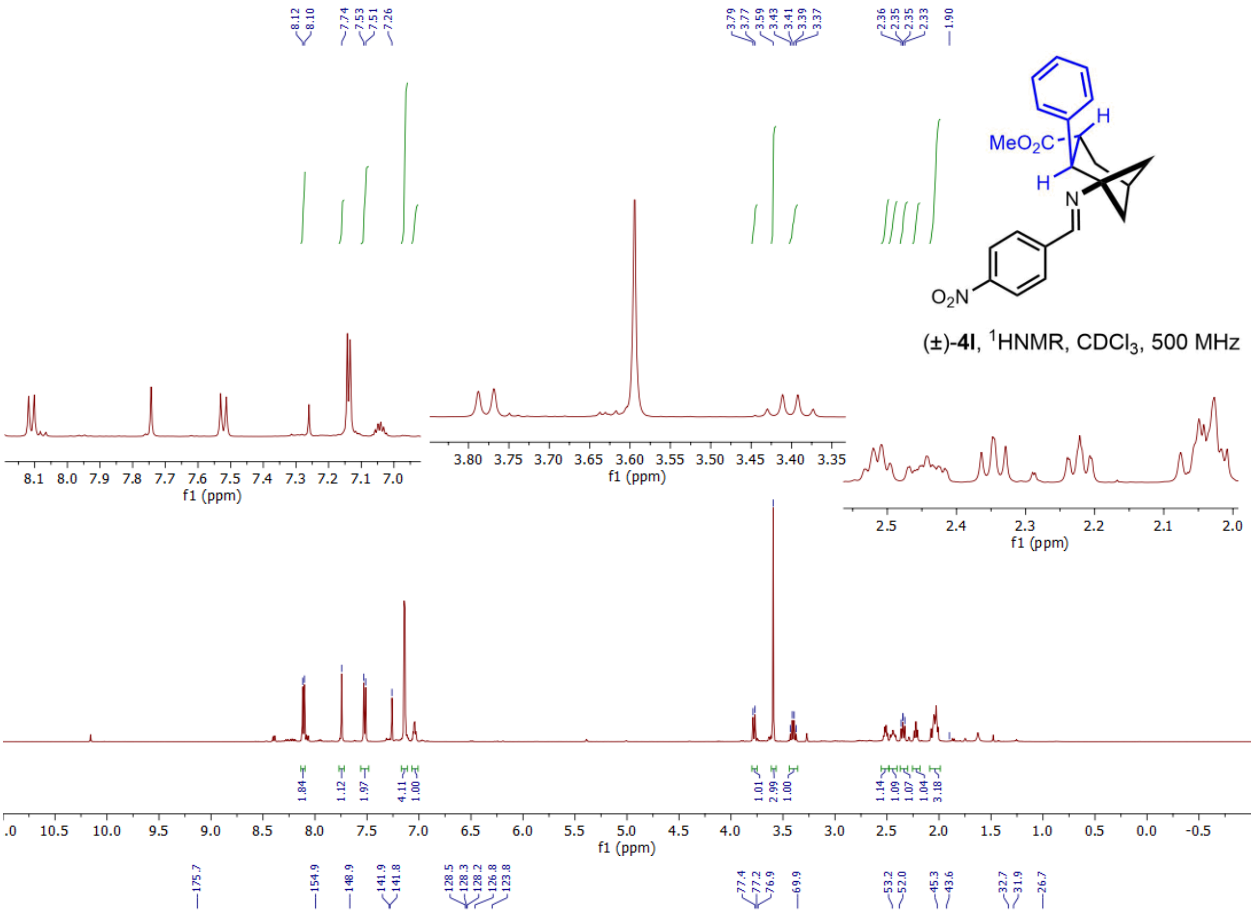
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.11 (d, *J* = 8.7 Hz, 2H), 7.74 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.17-7.10 (m, 4H), 7.07-7.01 (m, 1H), 3.78 (d, *J* = 9.7 Hz, 1H), 3.59 (s, 3H), 3.40 (app. q, *J* = 9.4 Hz, 1H), 2.55-2.48 (m, 1H), 2.48-2.40 (m, 1H), 2.38-2.31 (dd, *J* = 9.2, 8.2 Hz, 1H), 2.26-2.18 (m, 1H), 2.09-1.99 (m, 3H) ppm

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 175.7, 154.9, 148.9, 141.9, 141.8, 128.5, 128.3, 128.2, 126.8, 123.8, 69.9, 53.2, 52.0, 45.3, 43.6, 32.7, 31.9, 26.7 ppm

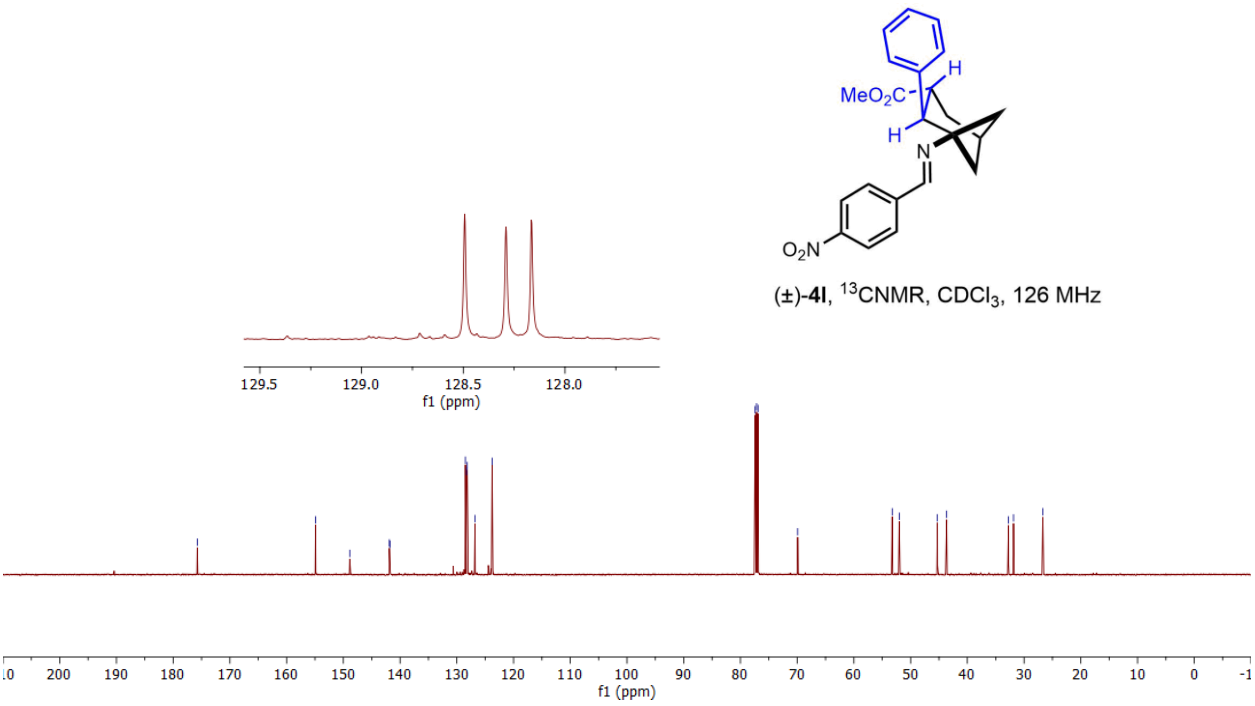
IR (neat): 3030, 2950, 2868, 1731, 1642, 1601, 1519, 1496, 1453, 1435, 1343, 1316, 1295, 1270, 1226, 1194, 1171, 1157, 1107, 1084, 1050, 1030, 1012, 978, 933, 914, 853, 834, 765, 748, 700, 691, 665 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{22}H_{23}N_2O_4^+$: 379.1652, Found: 379.1648

R_f = 0.52 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

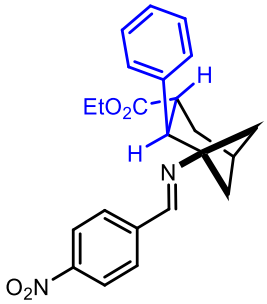


(±)-**4l**, ^{1}HNMR, $CDCl_3$, 500 MHz



(±)-**4l**, ^{13}CNMR, $CDCl_3$, 126 MHz

Compound (±)-**4m** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 15 equiv alkene used rather than the standard 7.5 equiv) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), ethyl cinnamate (1.01 mL, 6.00 mmol, 15 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 17 hours. The crude reaction mixture was mixed with celite (3 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 6-54% ethyl acetate in hexanes to give (±)-**4m** (24.6 mg, 0.0627 mmol, 16%) as a yellow oil. The reaction was repeated as above and analyzed by crude ^{1}HNMR. Only the major, *trans* diastereomer was identified. The mixture was then concentrated into a 4-dram vial and a magnetic stir bar was added, followed by acetonitrile (3 mL), water (1 mL), and acetic acid (1 mL). The headspace was flushed with nitrogen, the vial was capped, and the mixture was stirred at room temperature for 18 hours. The mixture was diluted with 1 M aqueous hydrochloric acid (40 mL) and washed with diethyl ether (3 x 20 mL). The aqueous layer was neutralized with saturated aqueous sodium bicarbonate (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined ethyl acetate fractions were washed with brine (50 mL) and concentrated in vacuo to give a brown oil. ^{1}HNMR analysis did not show the minor, *cis* diastereomer of the primary amine. On these bases, the d.r.is >20:1 for the formal cycloaddition.

Appearance: yellow oil

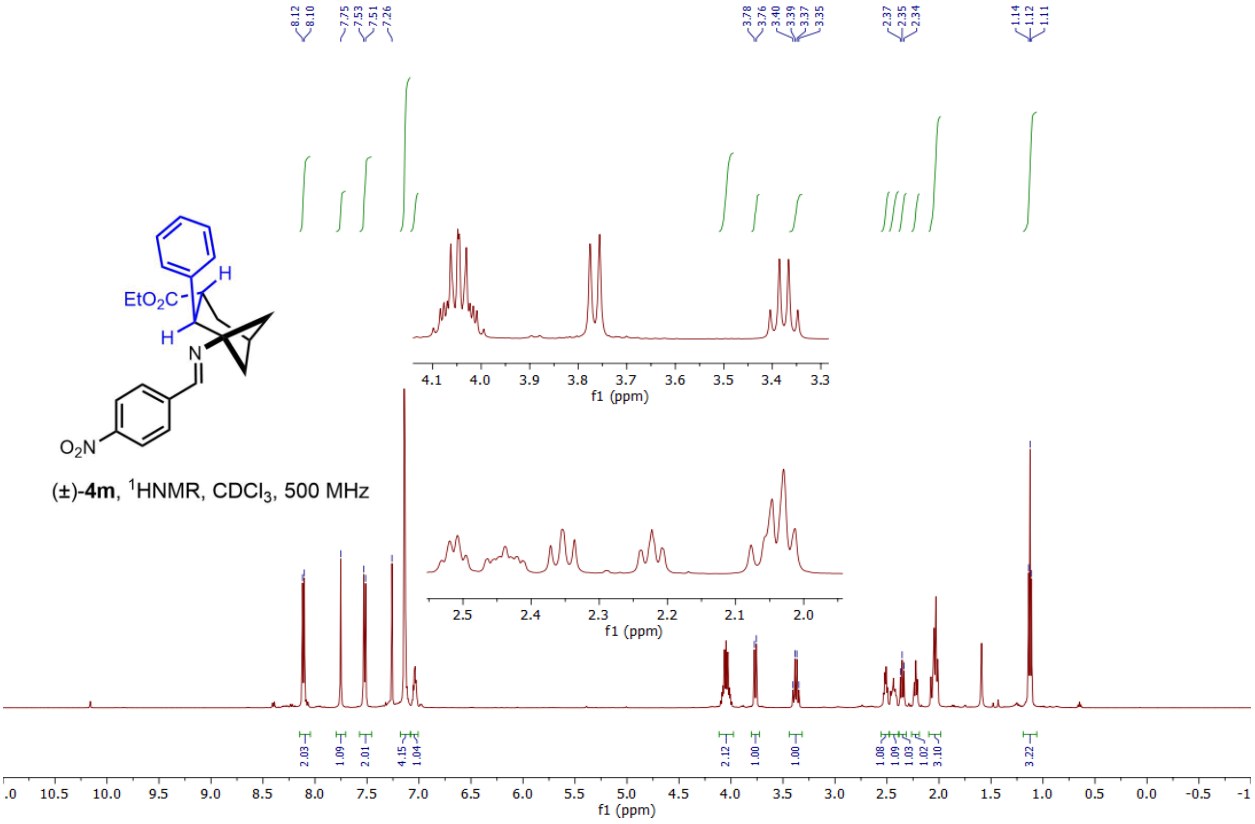
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.11 (d, *J* = 8.6 Hz, 2H), 7.75 (s, 1H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.17-7.08 (m, 4H), 7.08-7.00 (m, 1H), 4.11-3.98 (m, 2H), 3.77 (d, *J* = 9.7 Hz, 1H), 3.38 (app. q, *J* = 9.5 Hz, 1H), 2.55-2.48 (m, 1H), 2.48-2.39 (m, 1H), 2.26-2.19 (m, 1H), 2.35 (app. t, *J* = 8.7 Hz, 1H), 2.10-1.98 (m, 3H), 1.12 (app. t, *J* = 7.1 Hz, 3H) ppm

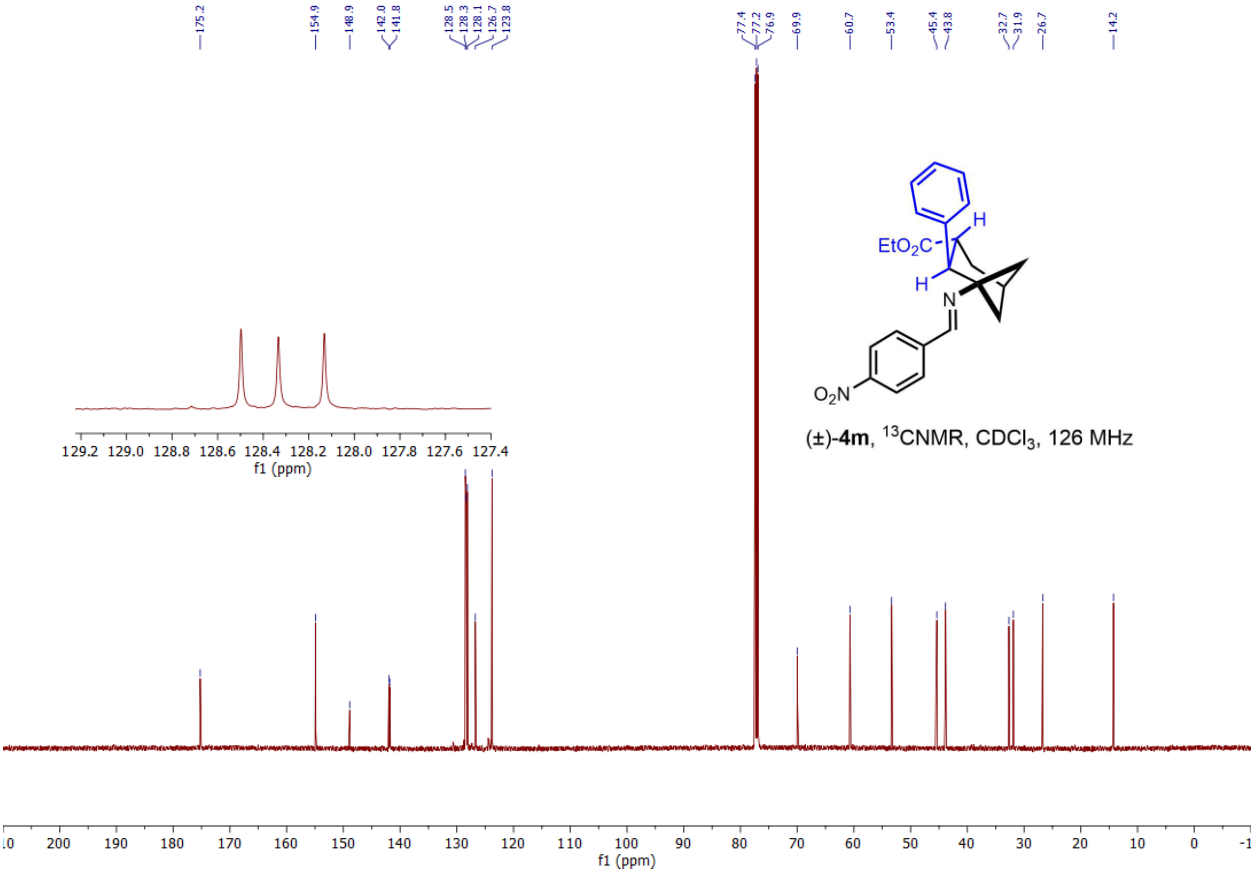
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 175.2, 154.9, 148.9, 142.0, 141.8, 128.5, 128.3, 128.1, 126.7, 123.8, 69.9, 60.7, 53.4, 45.4, 43.8, 32.7, 31.9, 26.7, 14.2 ppm

IR (neat): 3031, 2940, 2869, 1727, 1643, 1602, 1520, 1495, 1453, 1413, 1374, 1343, 1316, 1295, 1270, 1226, 1179, 1157, 1128, 1107, 1097, 1085, 1032, 1014, 979, 943, 921, 854, 835, 749, 700, 692, 664 cm^{-1}

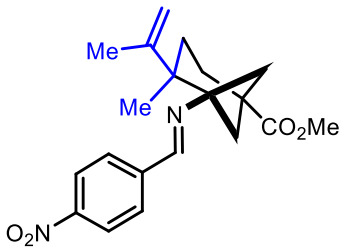
HRMS (ES+, m/z) calculated for $C_{23}H_{25}N_2O_4^+$: 393.1809, Found: 393.1806

R_f = 0.57 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, U


EtO2C
H
H
N
O2N
(±)-4m, 1HNMR, CDCl3, 500 MHz
f1 (ppm)


EtO2C
H
H
N
O2N
(±)-4m, 13CNMR, CDCl3, 126 MHz
f1 (ppm)

Compound (±)-**4n** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 15 equivalents of alkene used rather than the standard 7.5) was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), 2,3-dimethylbutadiene (0.679 mL, 6.00 mmol, 15 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 18 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-60% ethyl acetate in hexanes to give (±)-**4n** (31.2 mg, 0.0875 mmol, 22%) as a yellow oil.

Appearance: yellow oil

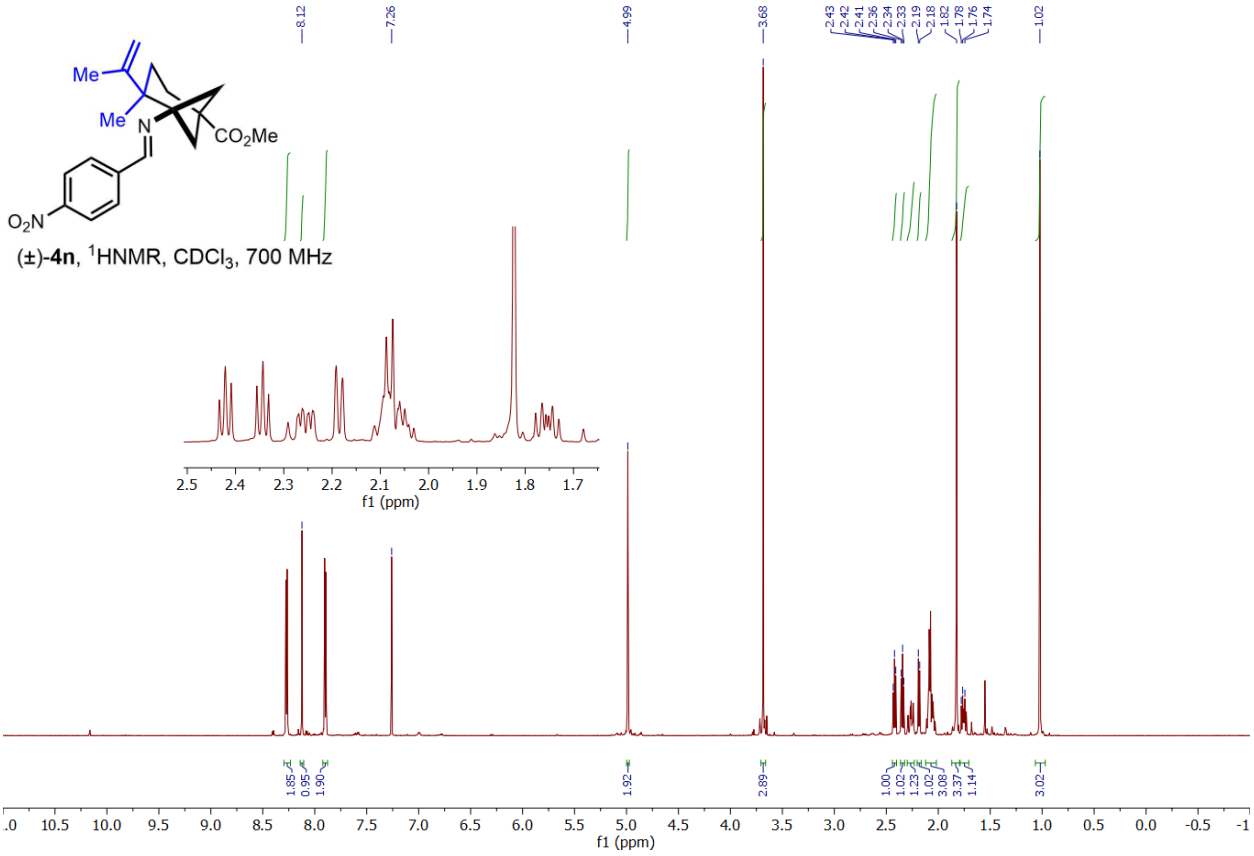
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.29-8.25 (m, 2H), 8.12 (s, 1H), 7.92-7.88 (m, 2H), 4.99 (app. s, 2H), 3.68 (s, 3H), 2.42 (app. t, *J* = 8.5 Hz, 1H), 2.34 (app. t, *J* = 8.4 Hz, 1H), 2.30-2.23 (m, 1H), 2.19 (app. d, *J* = 9.2 Hz, 1H), 2.12-2.02 (m, 3H), 1.82 (s, 3H), 1.75 (dt, *J* = 15.0, 9.3 Hz, 1H), 1.02 (s, 3H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.8, 154.7, 149.8, 149.1, 142.0, 128.9, 124.1, 112.9, 69.6, 52.0, 46.5, 42.1, 41.2, 37.0, 32.5, 29.1, 23.6, 23.3 ppm

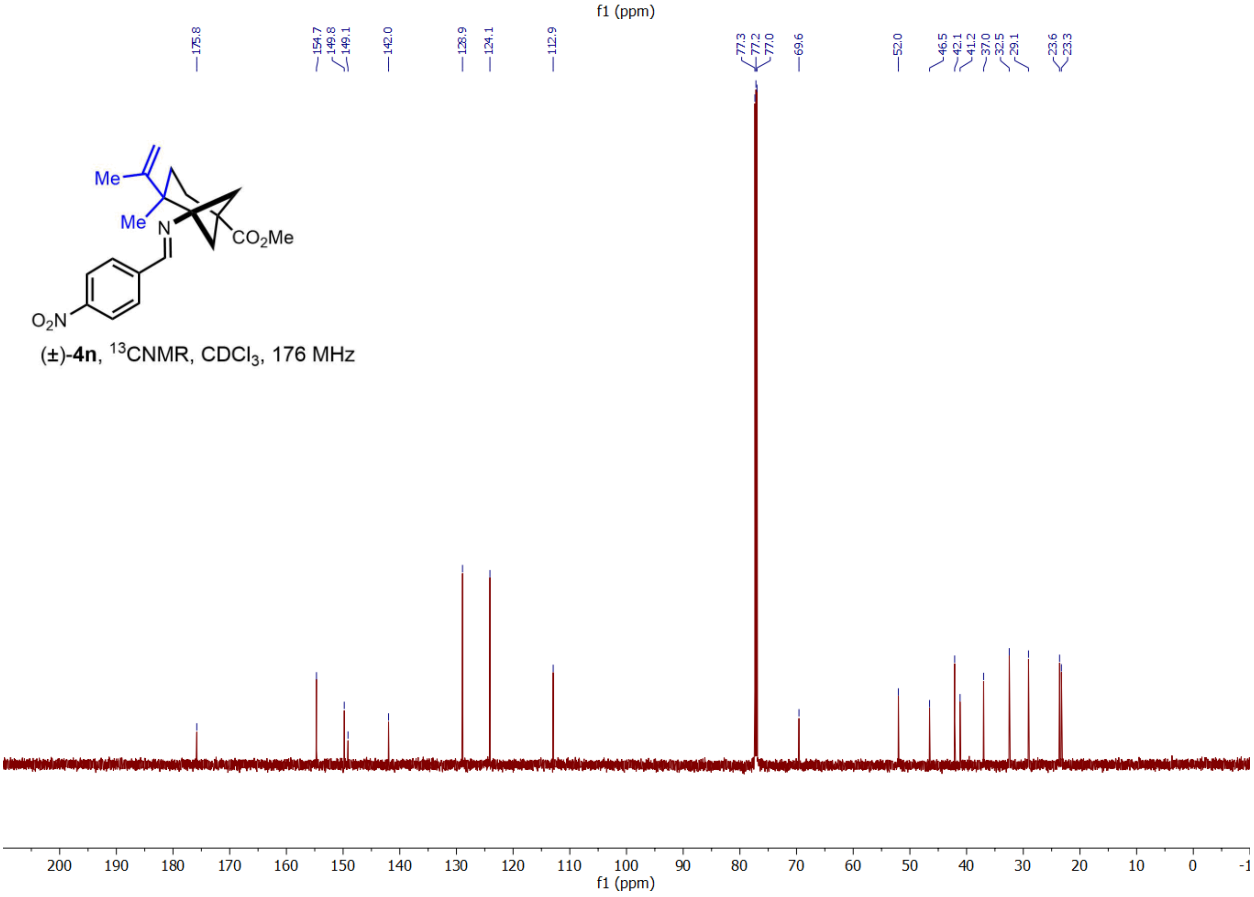
IR (neat): 3087, 2953, 2872, 1727, 1641, 1601, 1521, 1456, 1435, 1371, 1343, 1293, 1279, 1246, 1215, 1192, 1164, 1136, 1108, 1090, 1047, 1012, 978, 951, 896, 853, 834, 791, 748, 733, 693 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{25}N_2O_4^+$: 357.1809, Found: 357.1806

R_f = 0.53 (30% ethyl acetate: 69% hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

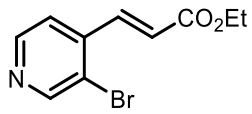


(±)-**4n**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4n**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound **SI-15**:



EXPERIMENTAL PROCEDURE:

To a 500 mL flask equipped with an egg-shaped stirrer was added 3,4-dibromopyridine (3.55 g, 15.0 mmol, 1 equiv), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (1.22 g, 1.50 mmol, 0.100 equiv), and dimethylformamide (300 mL). The flask was sealed with a rubber septum and the reactants put under nitrogen atmosphere. Ethyl (E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (3.39 g, 15.0 mmol, 1.00 equiv) was then added in one portion via syringe. 1M aqueous K_3PO_4 (45 mL) was added by briefly removing the septum, pouring the K_3PO_4 solution into the flask using a funnel, and replacing the septum. The reaction mixture was sparged with nitrogen for 15 minutes then placed in an aluminum heating block at 60 °C for 6 hours. After cooling to room temperature, the reaction mixture was diluted with water (1 L) and ethyl acetate (1 L) and the layers were separated. The organic layer was washed with brine (3 x 500 mL), washed with 10% solution of aqueous lithium chloride (3 x 10 mL), dried over sodium sulfate, filtered, concentrated onto celite (20 g), and loaded atop a silica column. Elution with 100% dichloromethane gave **SI-15** (323 mg, 1.26 mmol, 8%) as a faintly yellow solid.

Appearance: faintly yellow solid

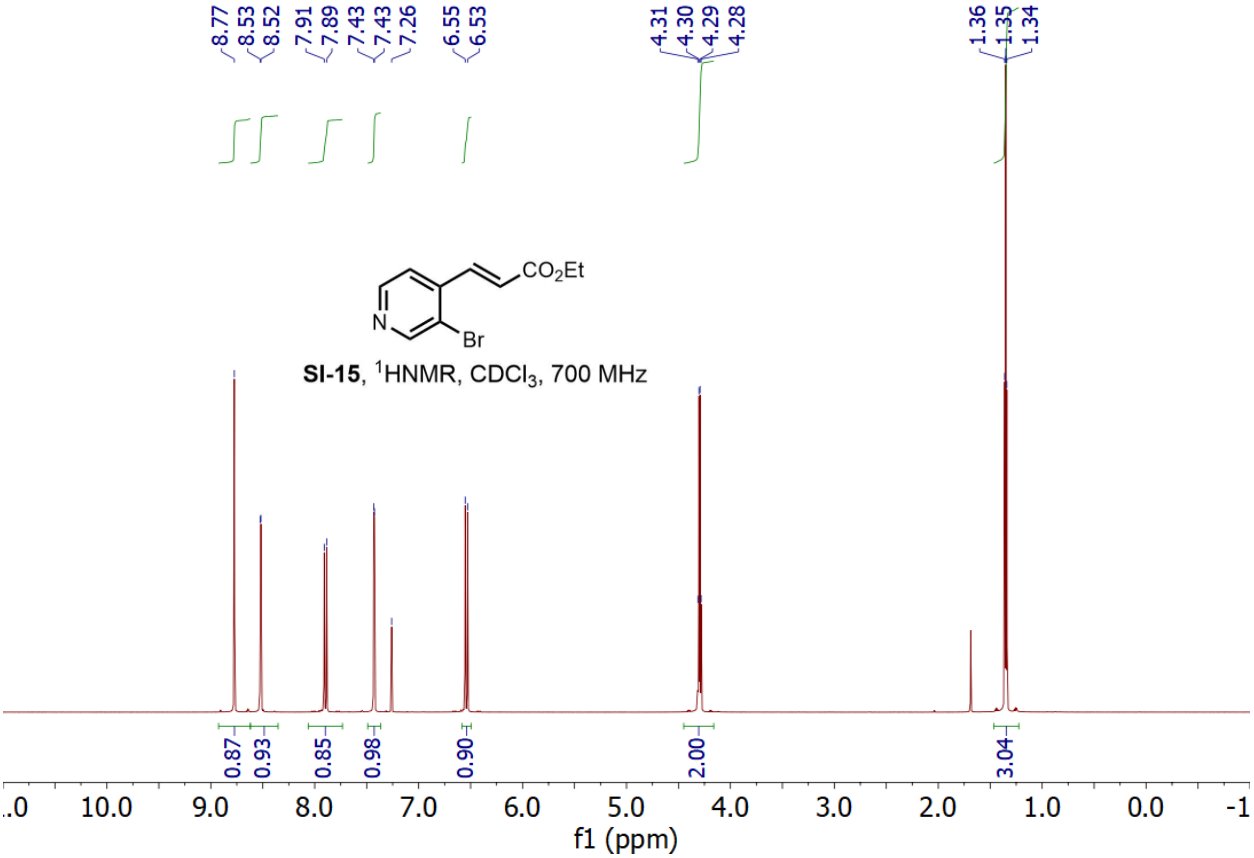
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.77 (s, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 7.90 (d, *J* = 16.0 Hz, 1H), 7.43 (d, *J* = 5.0 Hz, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 165.7, 153.1, 148.7, 141.9, 140.2, 125.1, 122.5, 121.5, 61.3, 14.4 ppm

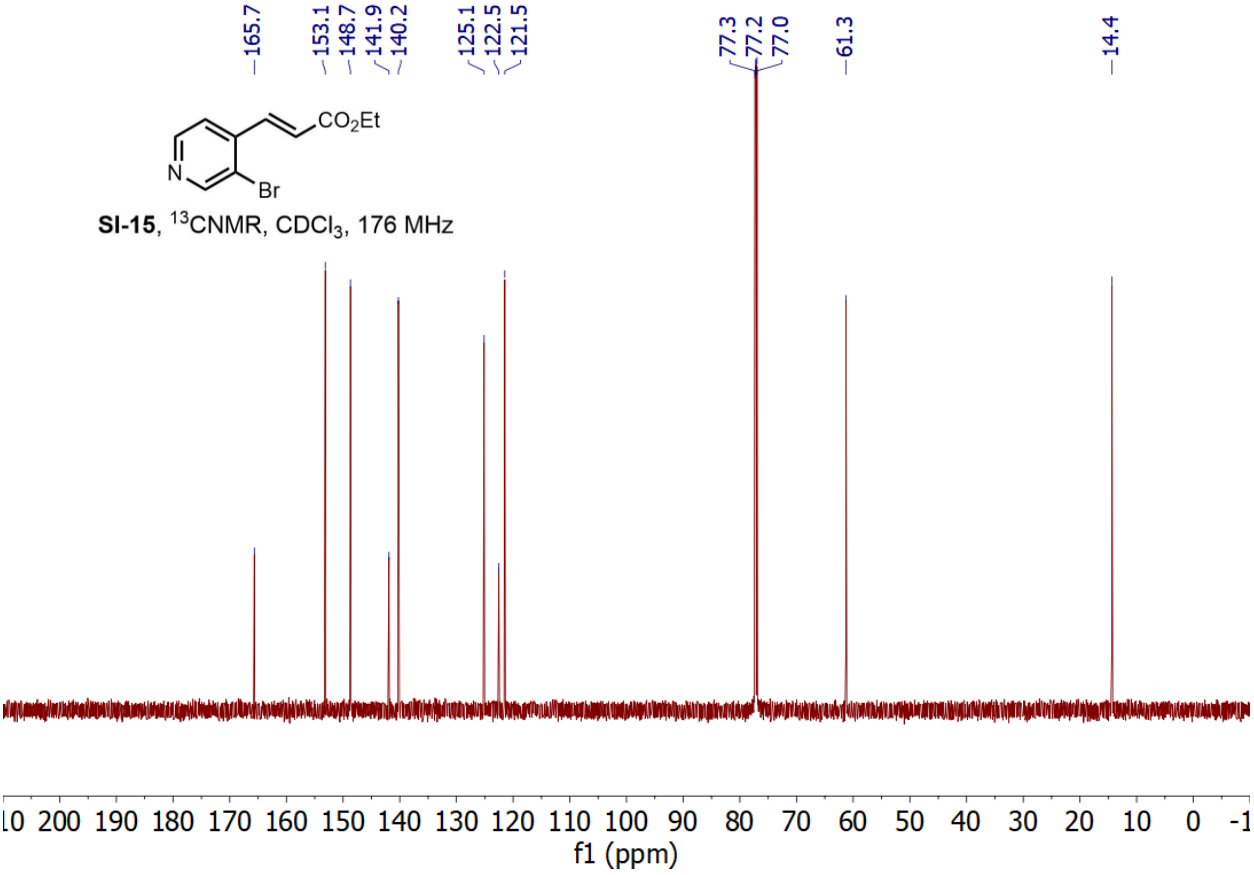
IR (neat): 2956, 1716, 1637, 1580, 1448, 1404, 1369, 1303, 1169, 1097, 1047, 1023, 983, 882, 841, 810, 753, 731, 702 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{10}H_{11}BrNO_2^+$: 255.9968, Found: 255.9968

R_f = 0.79 (50% ethyl acetate : 49 % hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

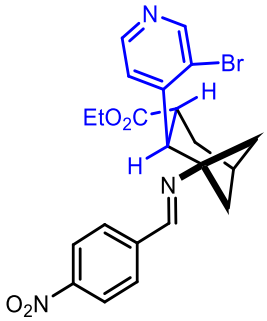


SI-15, ^{1}HNMR, $CDCl_3$, 700 MHz



SI-15, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4o** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 3 equiv alkene used rather than the standard 7.5 equiv and acetonile + ethyl acetate used as cosolvents) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), **SI-15** (307 mg, 1.20 mmol, 3 equiv), 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv), acetonitrile (0.400 mL), and ethyl acetate (0.400 mL) and irradiating for 23 hours. The crude reaction mixture was concentrated onto celite (3 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-100% ethyl acetate in hexanes to give (±)-**4o** (28.5 mg, 0.0603 mmol, 15%) as a faintly yellow oil. The reaction was repeated as above and analyzed by crude ^{1}HNMR. Only the major, *trans* diastereomer was identified. The mixture was concentrated into a 4-dram vial. A magnetic stir bar, acetonitrile (3 mL), water (1 mL), and acetic acid (1 mL) were added. The headspace was flushed with nitrogen, the vial was capped, and the mixture was stirred at room temperature for 18 hours. The mixture was diluted with 1 M aqueous HCl (40 mL) and washed with diethyl ether (3 x 20 mL). The aqueous layer was neutralized with saturated aqueous $NaHCO_3$ (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined ethyl acetate extracts were washed with brine (50 mL) and concentrated in vacuo. ^{1}HNMR analysis did not show the minor, *cis* diastereomer of the primary amine. On these bases, d.r.is >20:1 for the formal cycloaddition.

Appearance: faintly yellow oil

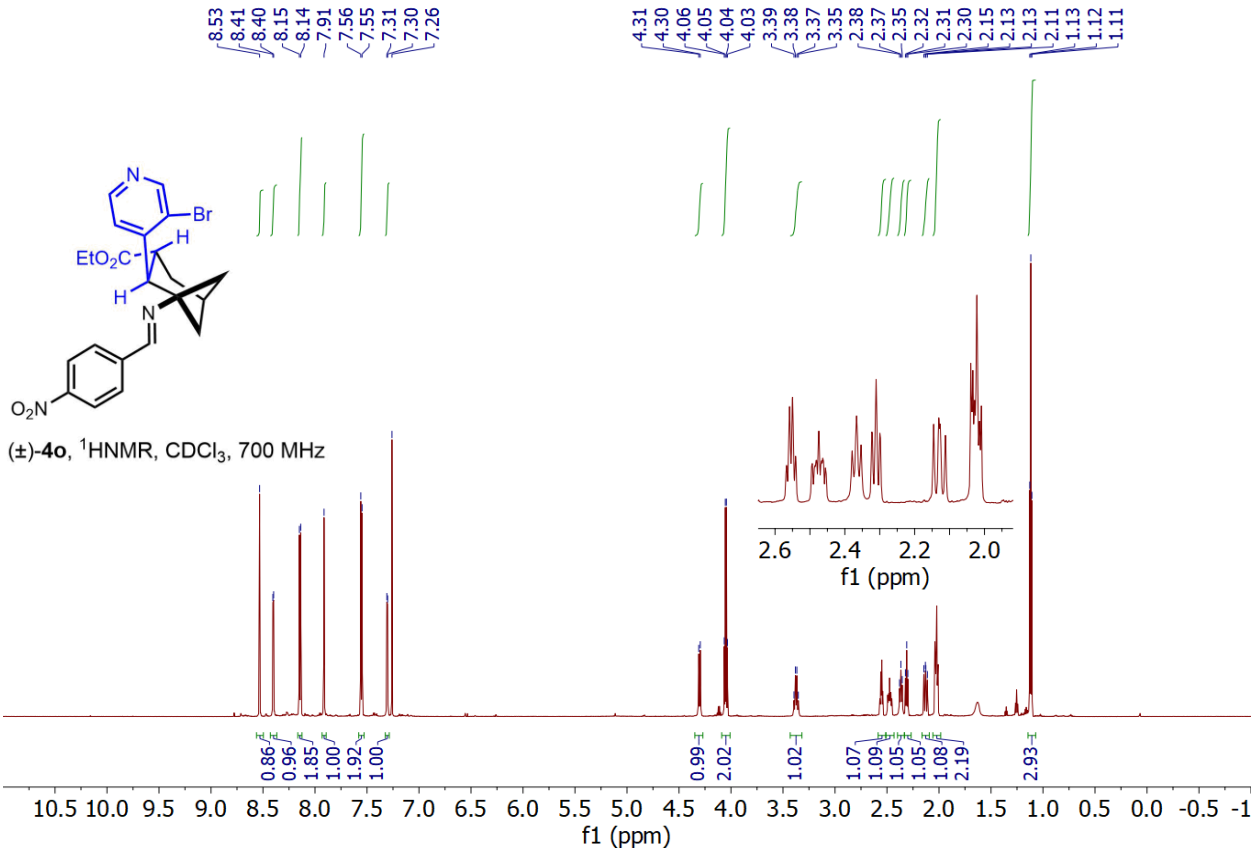
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.53 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.91(s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 5.1 Hz, 1H), 4.30 (d, *J* = 10.2 Hz, 1H), 4.05 (app. q, *J* = 7.1 Hz, 2H), 3.37 (app. q, *J* = 9.7 Hz, 2H), 2.58-2.53 (m, 1H), 2.51-2.44 (m, 1H), 2.37 (app. t, *J* = 8.9 Hz, 1H), 2.31 (app. t, *J* = 8.1 Hz, 1H), 2.13 (dd, *J* = 13.2, 10.3 Hz, 1H), 2.05-2.00 (m, 2H), 1.12 (app. t, *J* = 7.1 Hz, 3H) ppm

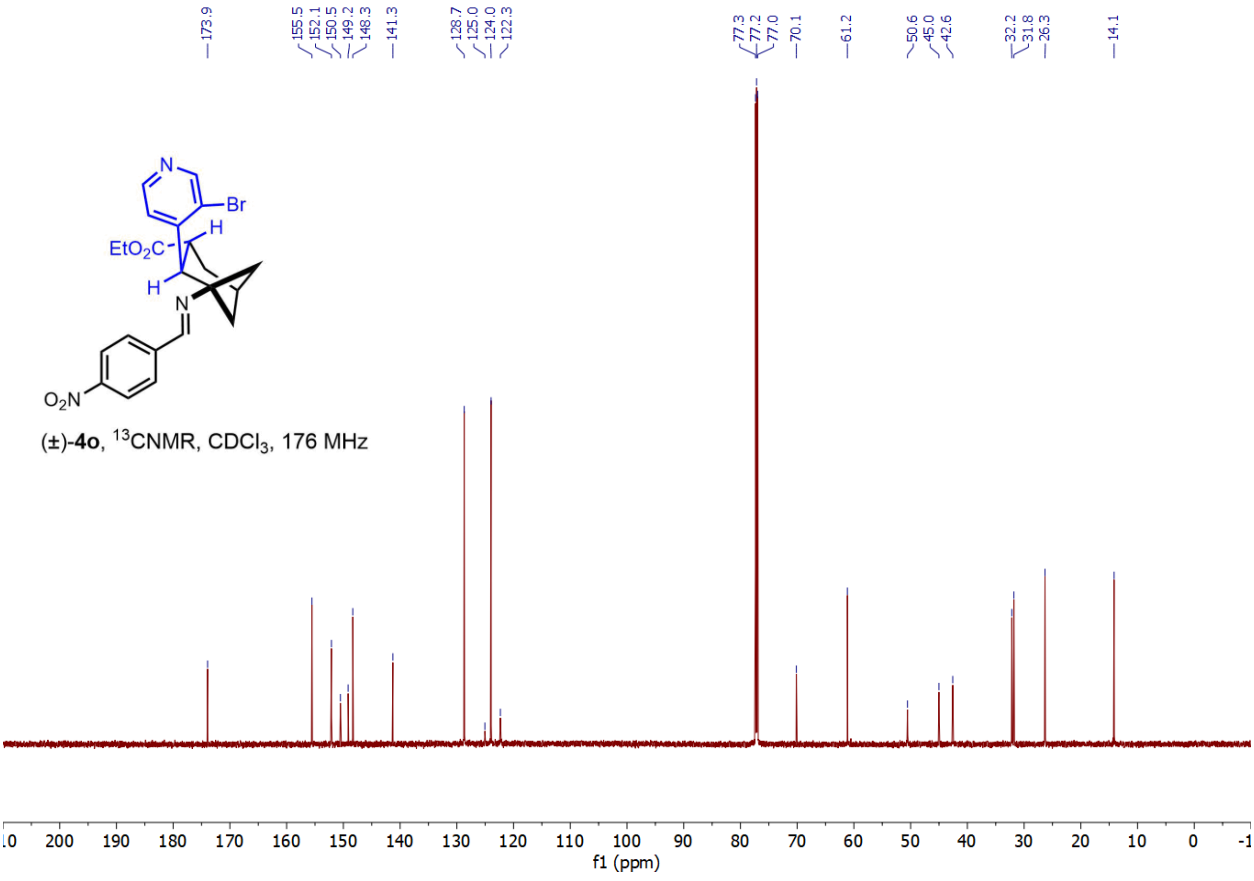
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 173.9, 155.5, 152.1, 150.5, 149.2, 148.3, 141.3, 128.7, 125.0, 124.0, 122.3, 70.1, 61.2, 50.6, 45.0, 42.6, 32.2, 31.8, 26.3, 14.1 ppm

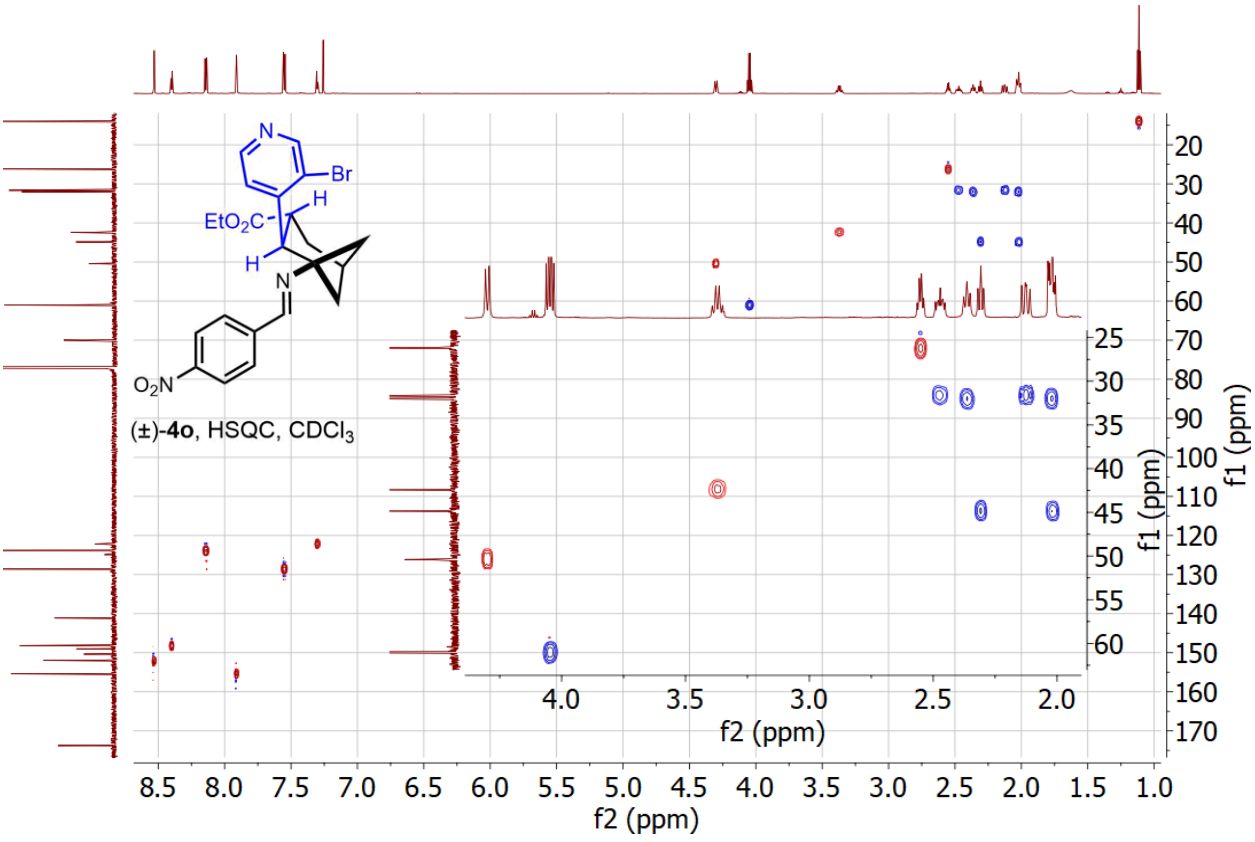
IR (neat): 2963, 2871, 1726, 1642, 1602, 1582, 1519, 1474, 1454, 1398, 1372, 1343, 1315, 1295, 1270, 1209, 1184, 1160, 1107, 1091, 1076, 1050, 1018, 980, 944, 913, 854, 836, 748, 729, 702, 690 cm^{-1}

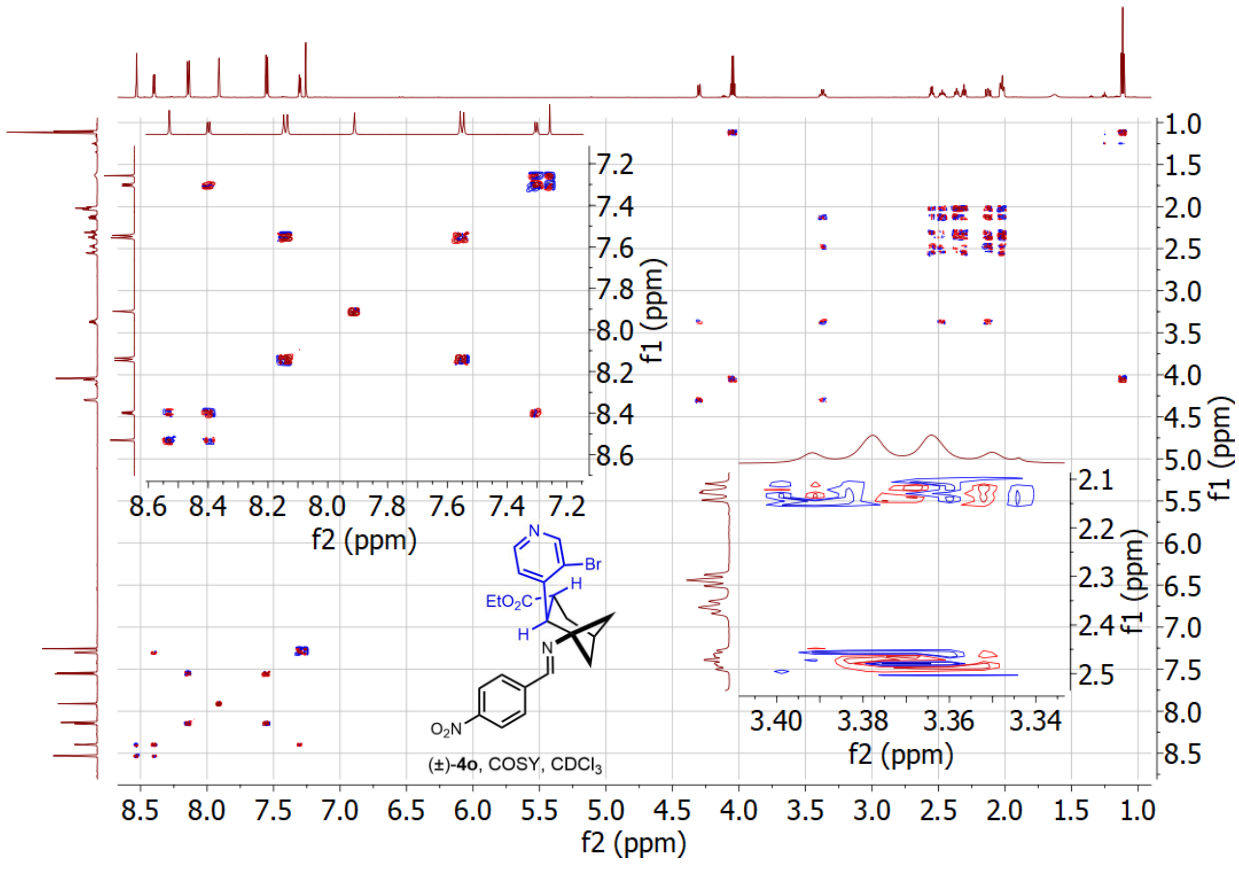
HRMS (ES+, m/z) calculated for $C_{22}H_{23}BrN_3O_4^+$: 472.0866, Found: 472.0860

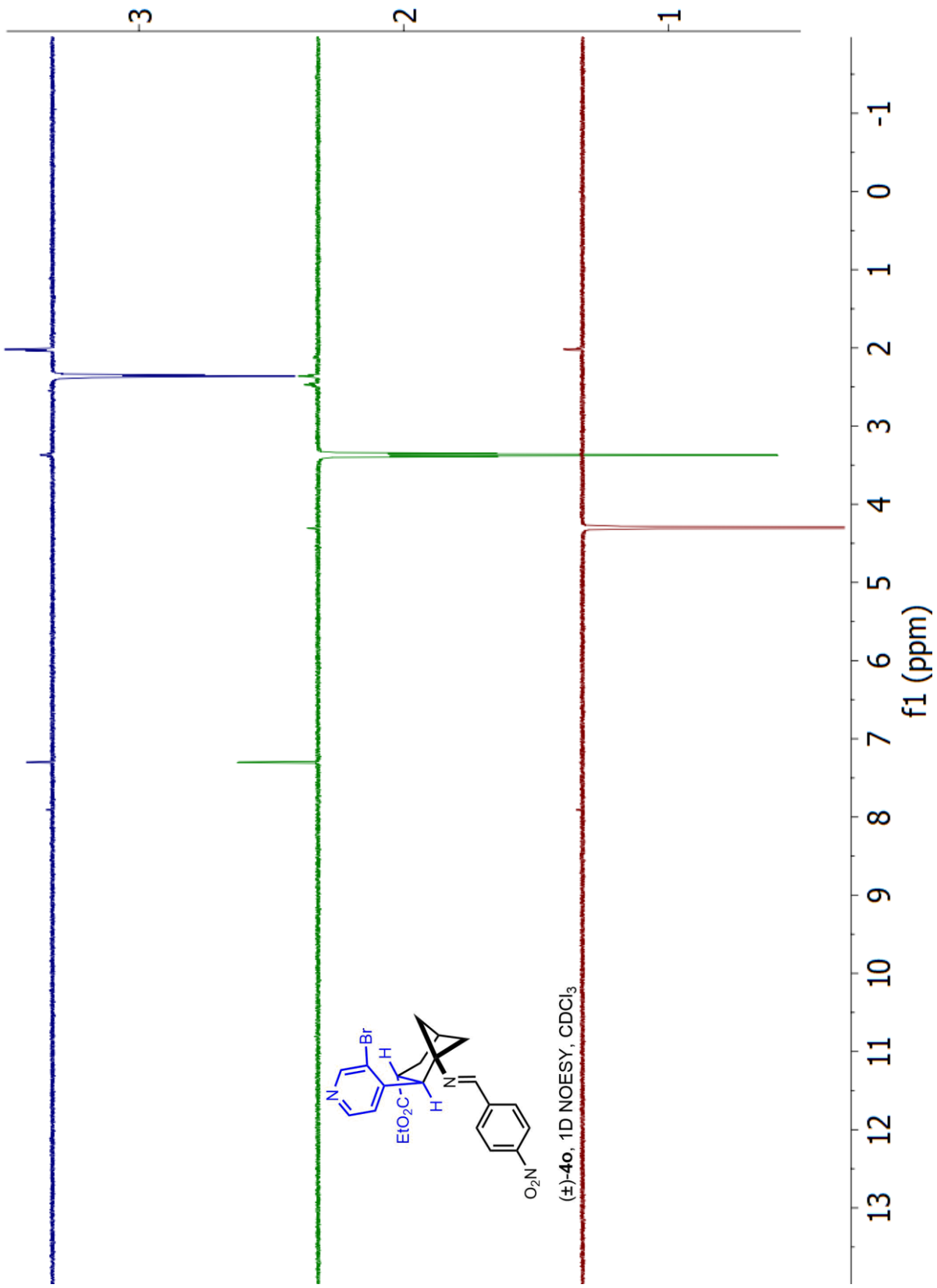
R_f = 0.46 (50% ethyl acetate : 49 % hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


8.53 8.41 8.40 8.15 8.14 7.91 7.56 7.55 7.31 7.30 7.26
4.31 4.30 4.06 4.05 4.04 4.03 3.39 3.38 3.37 3.35 2.38 2.37 2.35 2.32 2.31 2.30 2.15 2.13 2.13 2.11 1.13 1.12 1.11
Br
EtO2C
H
H
N
O2N
(±)-4o, 1HNMR, CDCl3, 700 MHz
2.6 2.4 2.2 2.0
f1 (ppm)
0.86 0.96 1.85 1.00 1.92 1.00 0.99 2.02 1.02 1.07 1.09 1.05 1.05 1.08 2.19 2.93
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

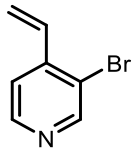

173.9
155.5 152.1 150.5 149.2 148.3 141.3 128.7 125.0 124.0 122.3
77.3 77.2 77.0 70.1 61.2 50.6 45.0 42.6 32.2 31.8 26.3 14.1
Br
EtO2C
H
H
N
O2N
(±)-4o, 13CNMR, CDCl3, 176 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


(±)-4o, HSQC, CDCl3
f2 (ppm)
f1 (ppm)


(±)-4o, COSY, CDCl3
f2 (ppm)
f1 (ppm)


(±)-4o, 1D NOESY, CDCl3
f1 (ppm)

Compound **SI-16**:



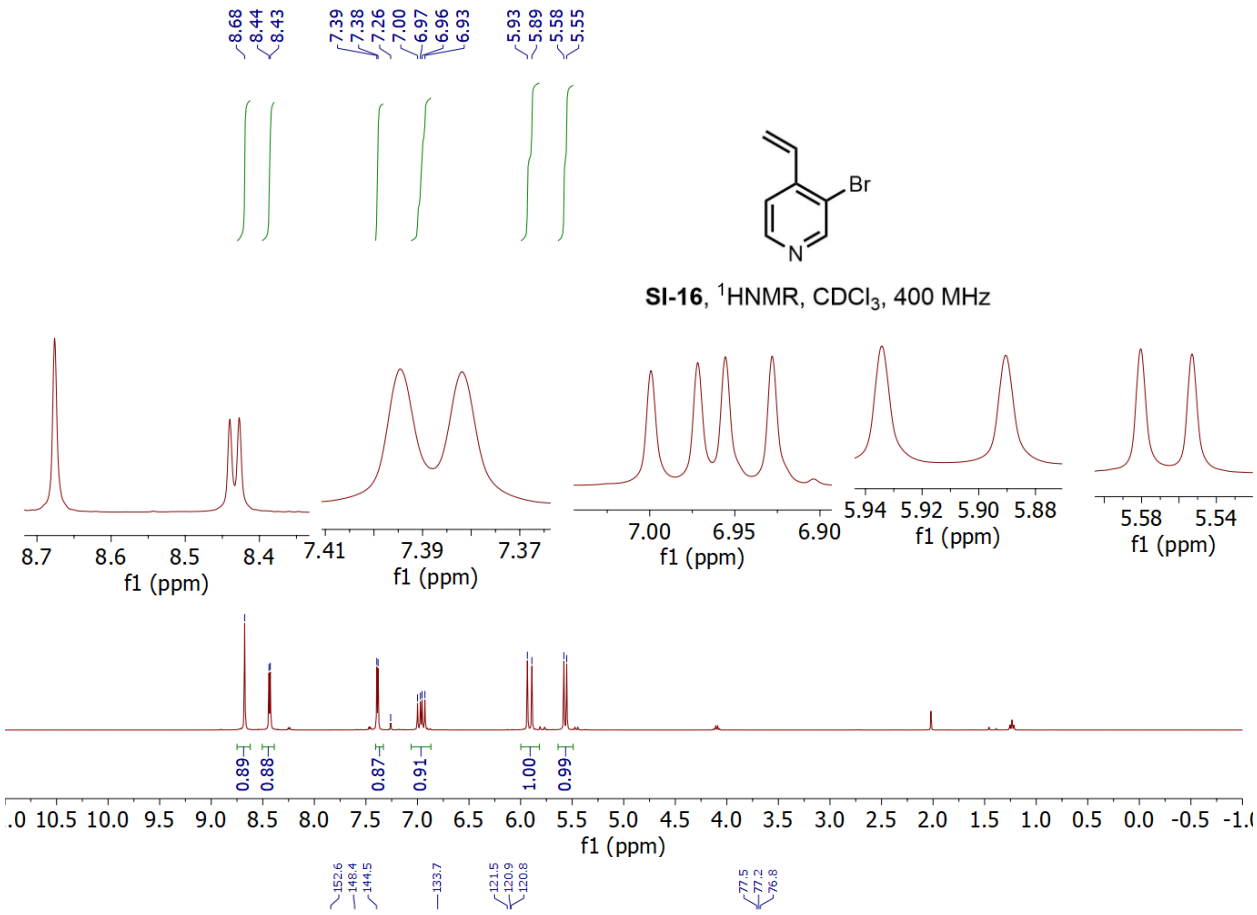
EXPERIMENTAL PROCEDURE:

The procedure drawn from published work.[11] To a 1 L round-bottom flask equipped with an egg-shaped magnetic stir bar was added 3,4-dibromopyridine (7.11 g, 30.0 mmol, 1 equiv), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (2.45 g, 3.00 mmol, 0.100 equiv), and dimethylformamide (300 mL). The flask was sealed with a rubber septum and the reactants put under argon atmosphere. Vinyl boronic acid pinacol ester (5.09 mL, 30.0 mmol, 1.00 equiv) was then added in one portion via syringe. 1M aqueous K_3PO_4 (90 mL) was added by briefly removing the septum, pouring the K_3PO_4 solution into the flask using a funnel, and replacing the septum. The reaction mixture was sparged with argon for 15 minutes then placed in an aluminum heating block at 60 °C for 4.5 hours. After cooling to room temperature, the reaction mixture was diluted with water (1000 mL) and extracted with ethyl acetate (3 x 250 mL). The combined organic fractions were washed with water (3 x 300 mL) and brine (3 x 200 mL), dried over Na_2SO_4, and filtered through a 5 cm silica plug, which was then flushed with ethyl acetate (500 mL). The filtrate was concentrated onto celite (15 g), dry-loaded onto a silica gel column, and eluted with 2-50% ethyl acetate in hexanes to provide **SI-16** (2.32 g, 12.6 mmol, 42%) as a yellow oil and **SI-17** (281 mg, 2.14 mmol, 7% based on 3,4-dibromopyridine) as a yellow oil. The spectral information for **SI-16** matched reported values.[11]

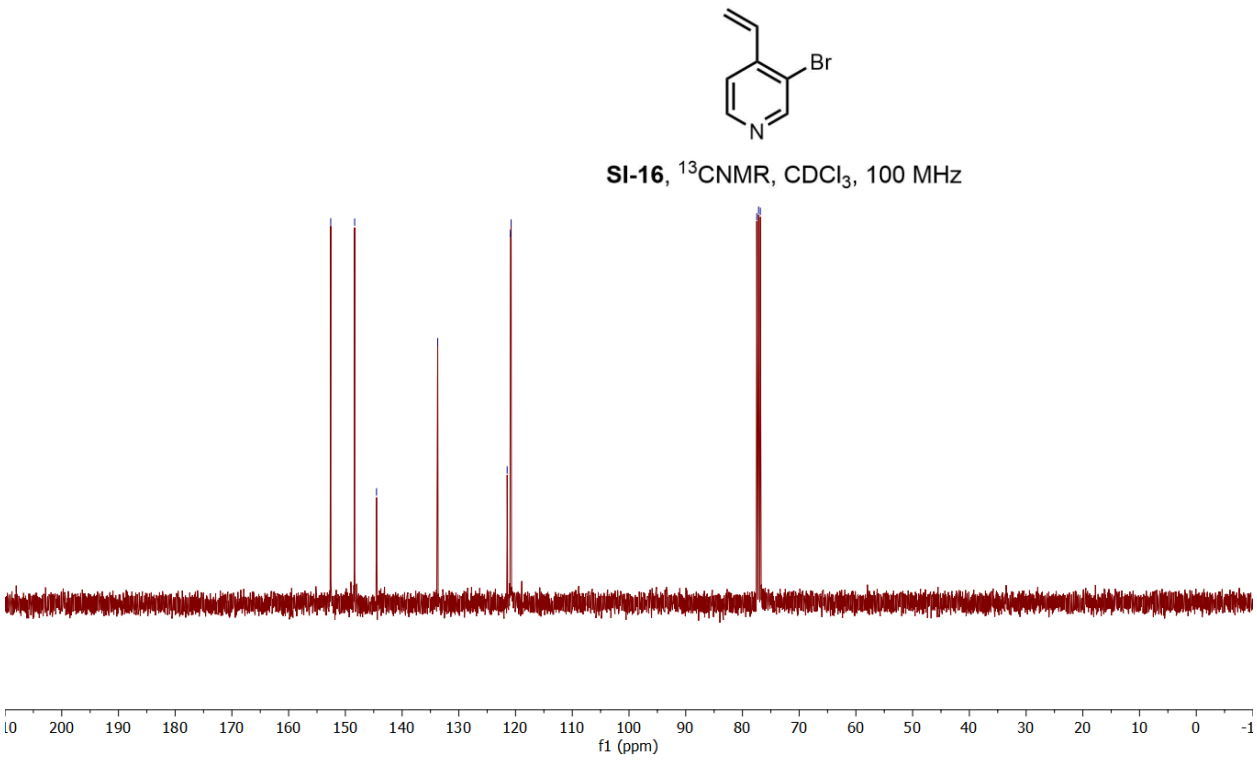
Appearance: yellow oil

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.68 (s, 1H), 8.43 (d, *J* = 5.1 Hz, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 6.96 (dd, *J* = 17.4, 11.0 Hz, 1H), 5.91 (d, *J* = 17.5 Hz, 1H), 5.57 (d, *J* = 11.0 Hz, 1H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.6, 148.4, 144.5, 133.7, 121.5, 120.9, 120.8 ppm

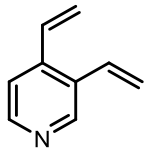


SI-16, ^{1}HNMR, $CDCl_3$, 400 MHz



SI-16, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound **SI-17**:



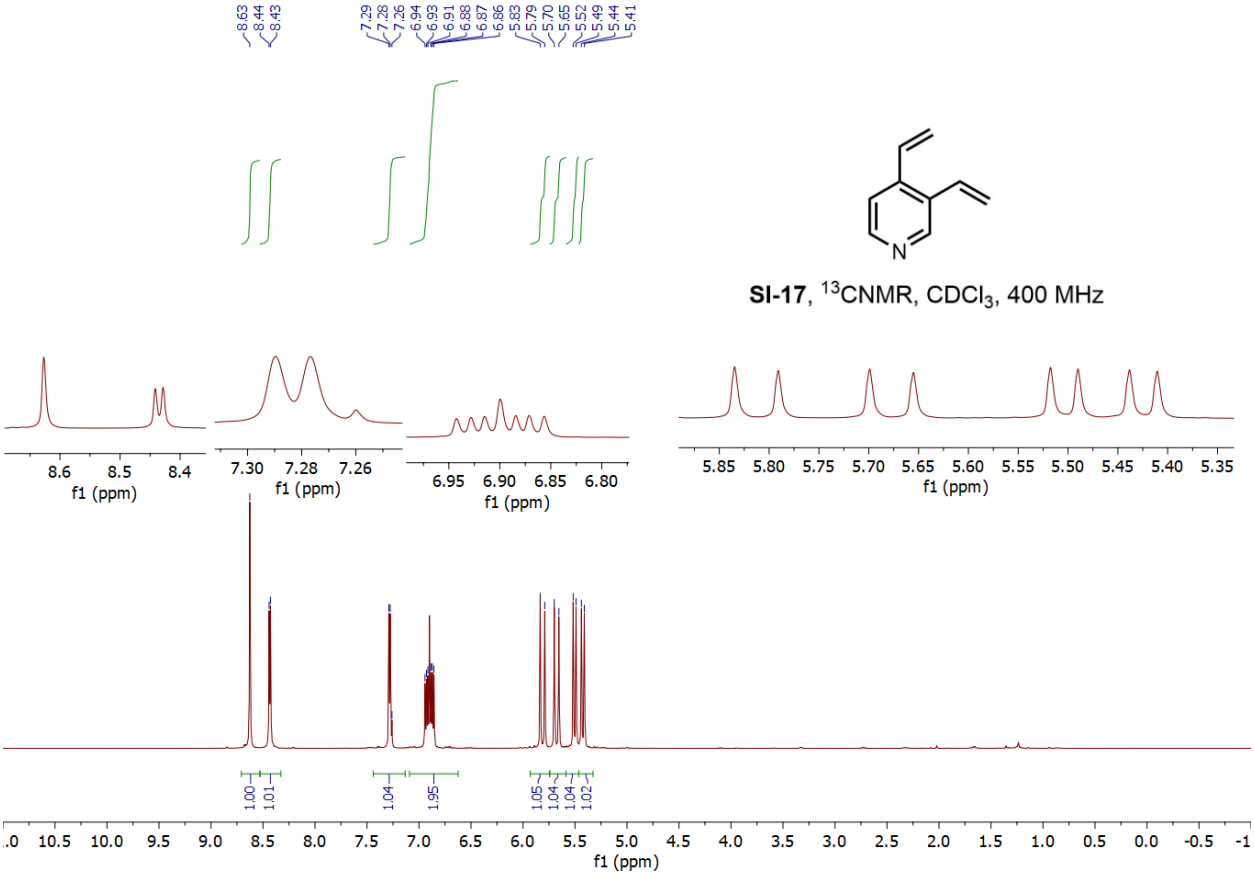
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.63 (s, 1H), 8.43 (d, *J* = 5.2 Hz, 1H), 7.28 (d, *J* = 5.2 Hz, 1H), 6.91 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.89 (dd, *J* = 17.5, 11.1 Hz, 1H), 5.81 (d, *J* = 17.3 Hz, 1H), 5.68 (d, *J* = 17.5 Hz, 1H), 5.50 (d, *J* = 11.0 Hz, 1H), 5.42 (d, *J* = 11.2 Hz, 1H) ppm

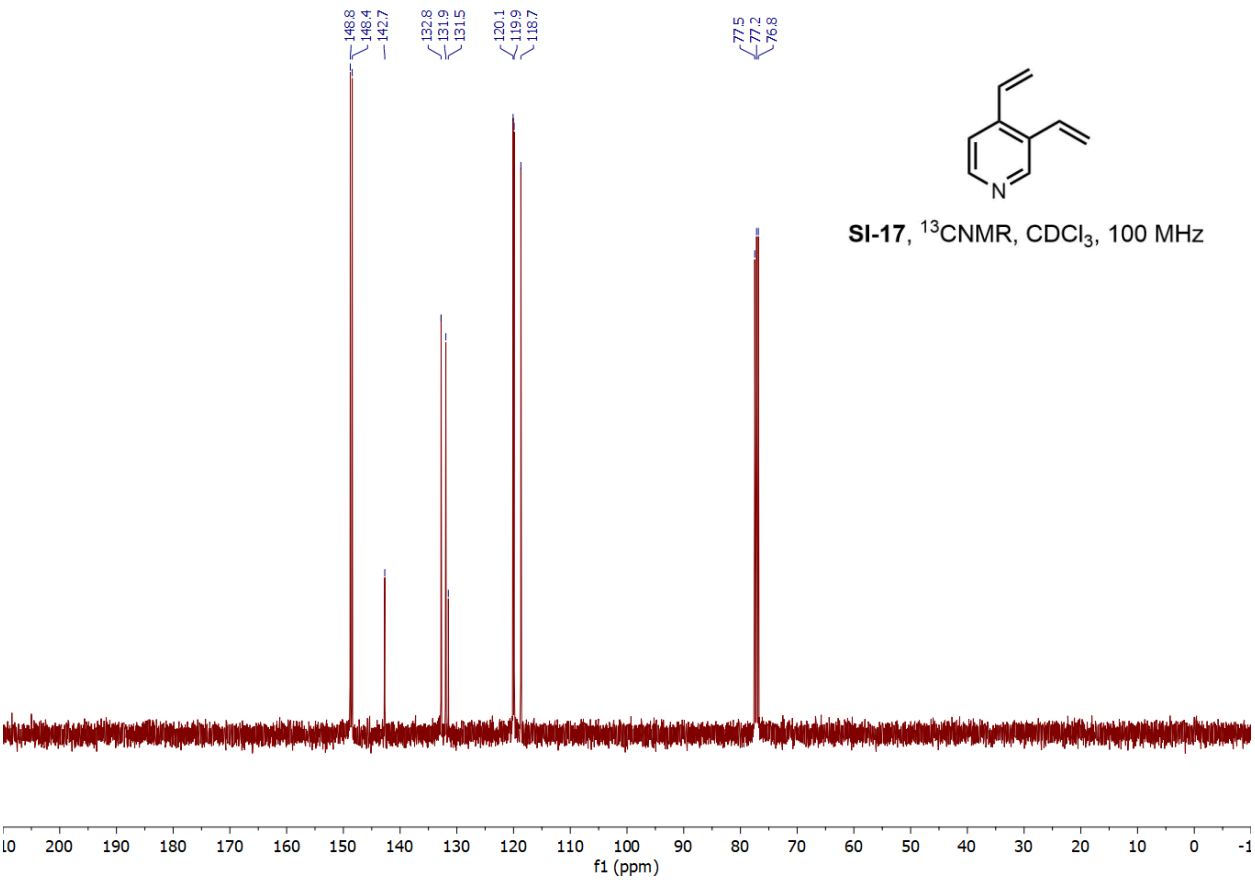
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.8, 148.4, 142.7, 132.8, 131.9, 131.5, 120.1, 119.9, 118.7 ppm

IR (neat): 3089, 3036, 1854, 1626, 1586, 1539, 1480, 1416, 1310, 1292, 1233, 1200, 1076, 1022, 984, 920, 835, 793, 752, 670 cm^{-1}

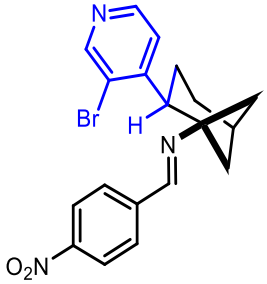
HRMS (ES+, m/z) calculated for $C_9H_{10}N^+$: 132.0808, Found: 132.0807

R_f = 0.29 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), one yellow spot, $KMnO_4$, UV





Compound (±)-**4p** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), **SI-16** (552 mg, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-50% ethyl acetate in hexanes to give (±)-**4p** (58.5mg, 0.146 mmol, 37%) as a yellow oil

Appearance: yellow oil

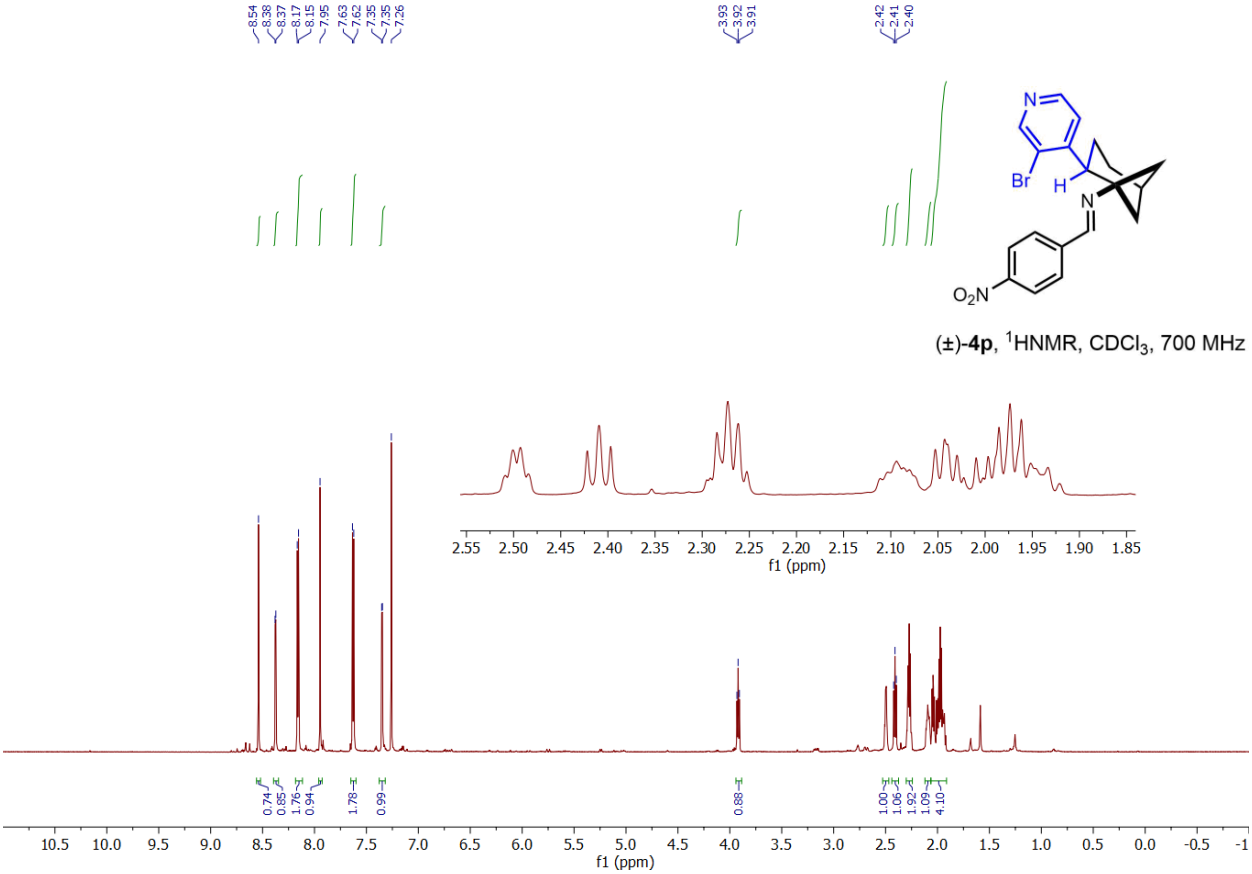
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.54 (s, 1H), 8.38 (d, *J* = 5.1 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.95 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 5.1 Hz, 1H), 3.92 (app. t, *J* = 8.3 Hz, 1H), 2.52-2.47 (m, 1H), 2.41 (app. t, *J* = 8.7 Hz, 1H), 2.30-2.24 (m, 2H), 2.12-2.06 (m, 1H), 2.06-1.91 (m, 4H) ppm

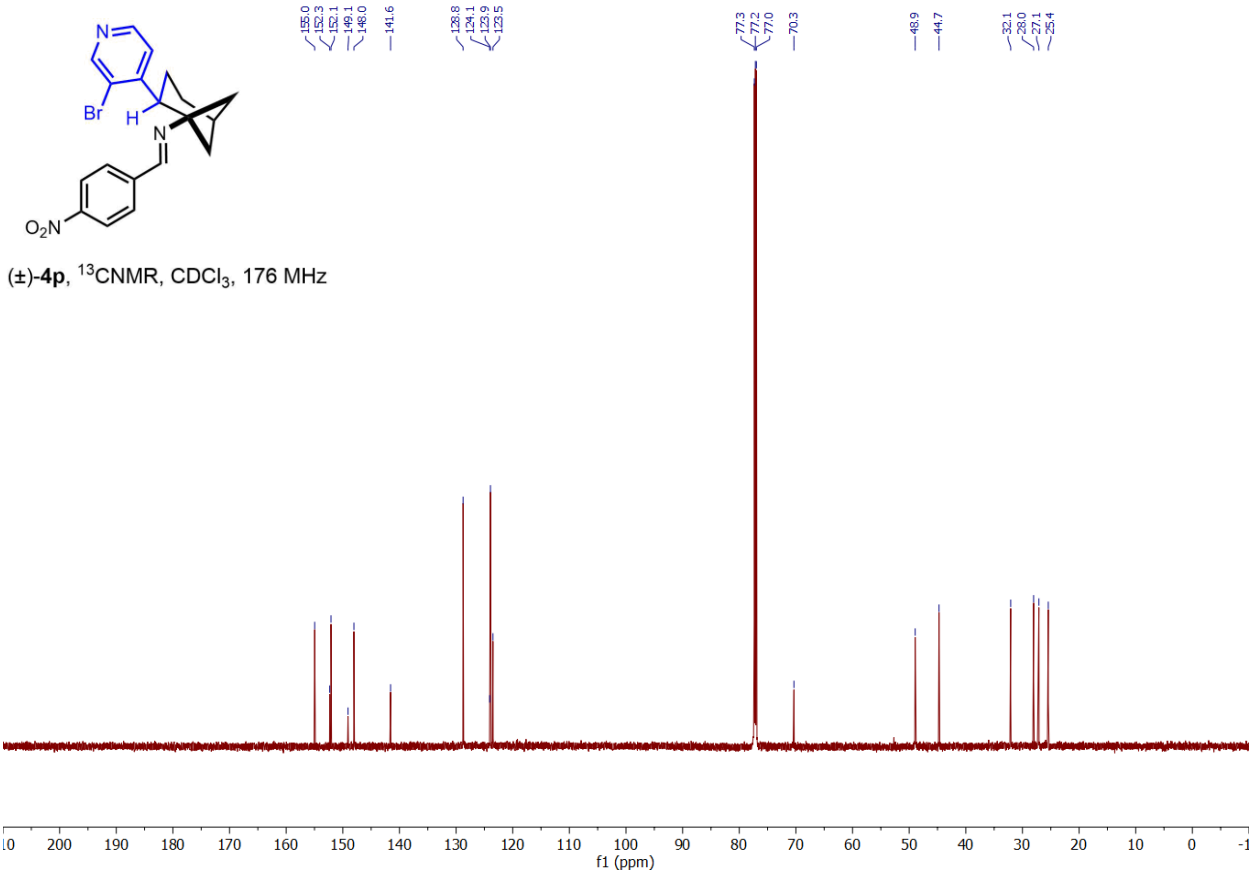
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 155.0, 152.3, 152.1, 149.1, 148.0, 141.6, 128.8, 124.1, 123.9, 123.5, 70.3, 48.9, 44.7, 32.1, 28.0, 27.1, 25.4 ppm

IR (neat): 2944, 2862, 1641, 1602, 1581, 1518, 1468, 1453, 1398, 1342, 1316, 1293, 1255, 1222, 1207, 1197, 1163, 1107, 1090, 1076, 1045, 1015, 973, 931, 853, 835, 812, 748, 729, 700, 690, 657 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{19}H_{19}BrN_3O_2^+$: 400.0655, 402.0635, Found: 400.0656, 402.0636

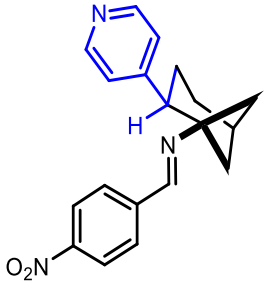
R_f = 0.46 (50% ethyl acetate : 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV





(±)-**4p**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4q** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 4-vinylpyridine (0.324 mL, 3.0 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture diluted with chloroform, concentrated onto celite (3g), and loaded atop a pre-neutralized (3 column volumes of 5% ethyl acetate: 94% hexanes : 1% Et_3N) silica gel column. The mixture was chromatographed eluting on a gradient from 7-100% ethyl acetate in hexanes to give (±)-**4q** (46.2 mg, 0.144 mmol, 36%) as a faintly yellow solid.

Appearance: faintly yellow solid

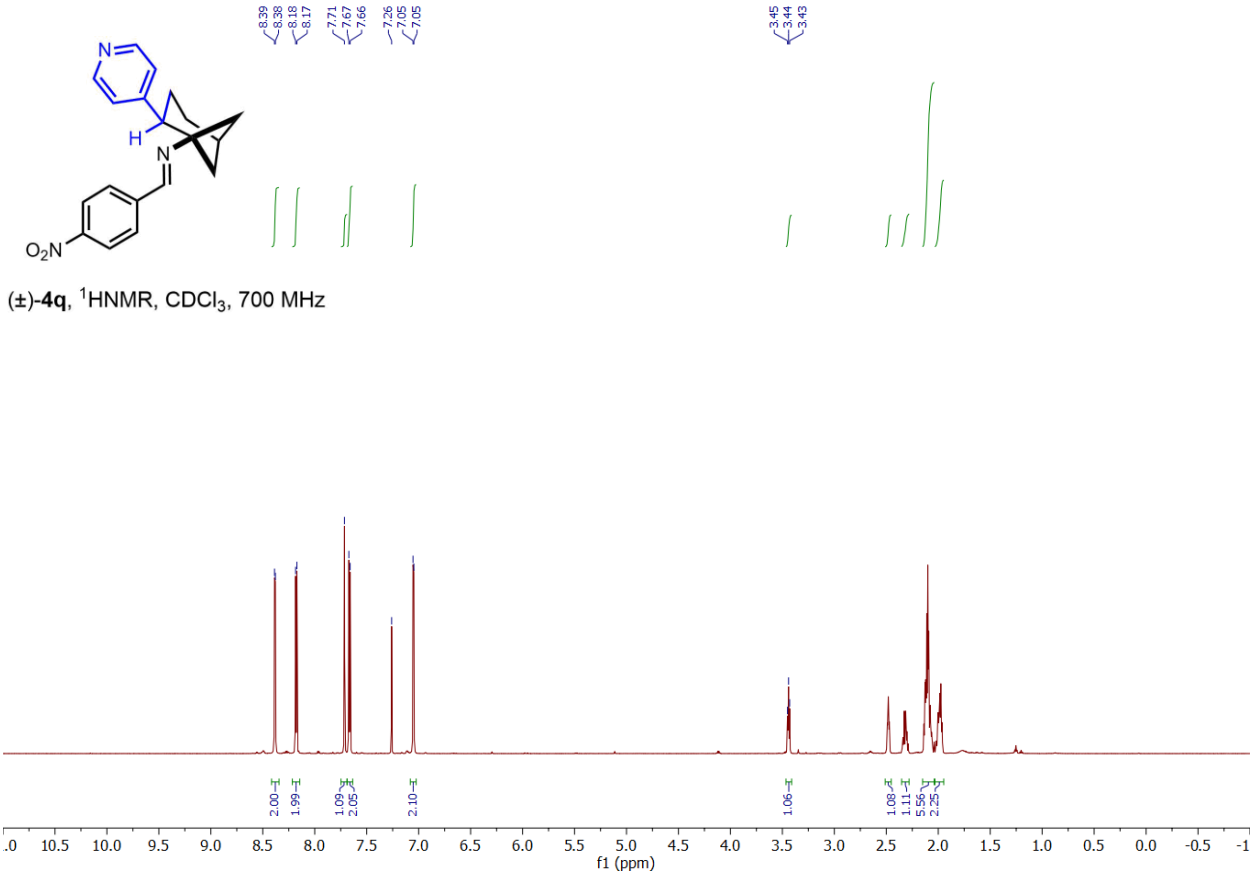
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.38 (d, *J* = 5.6 Hz, 2H), 8.18 (d, *J* = 8.6 Hz, 2H), 7.71 (s, 1H), 7.67 (d, *J* = 8.6 Hz, 2H), 7.05 (d, *J* = 5.6 Hz, 2H), 3.44 (app. t, *J* = 7.1 Hz, 1H), 2.50-2.46 (m, 1H), 2.36 – 2.28 (m, 1H), 2.17 – 2.05 (m, 5H), 2.02 – 1.95 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 155.1, 152.8, 149.4, 149.1, 141.6, 128.6, 124.1, 124.0, 70.5, 50.1, 42.7, 32.8, 28.2, 27.3, 24.7 ppm

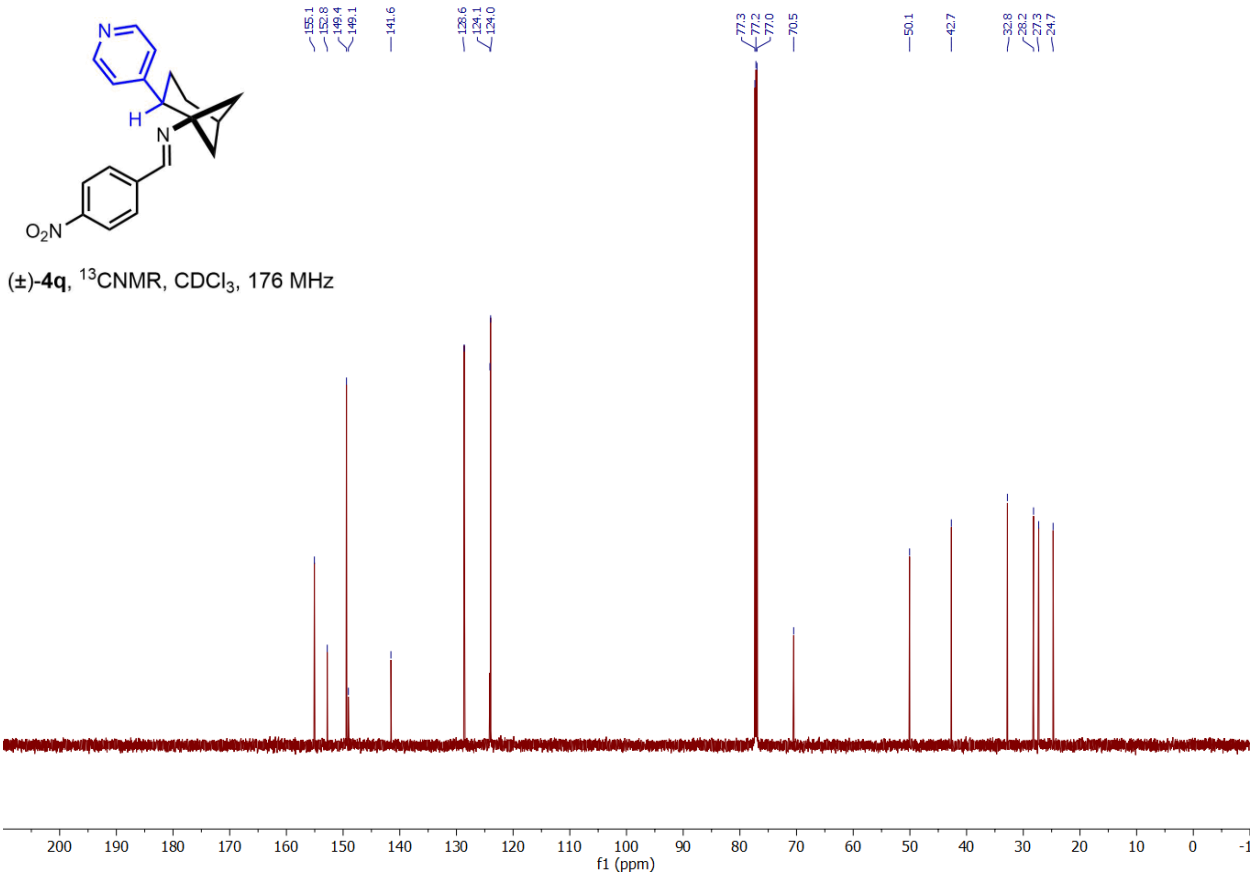
IR (neat): 2960, 2864, 1634, 1599, 1552, 1516, 1456, 1416, 1345, 1314, 1293, 1261, 1249, 1221, 1152, 1107, 1068, 995, 959, 930, 892, 848, 836, 827, 799, 764, 747, 687 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{19}H_{20}N_3O_2^+$: 322.1550, Found: 322.1547

R_f = 0.10 (30% ethyl acetate : 69% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

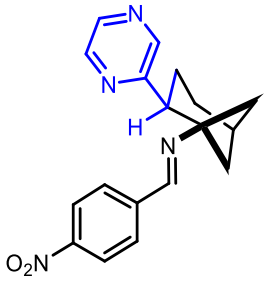


(±)-**4q**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4q**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4r** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 2-vinylpyrazine (0.306 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 21 hours. The crude reaction mixture was diluted with chloroform and concentrated onto celite (1 g), which was dry-loaded atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 10-100% ethyl acetate in hexanes to give (±)-**4r** (58.0 mg, 0.180 mmol, 45%) as a faintly yellow solid.

Appearance: faintly yellow solid

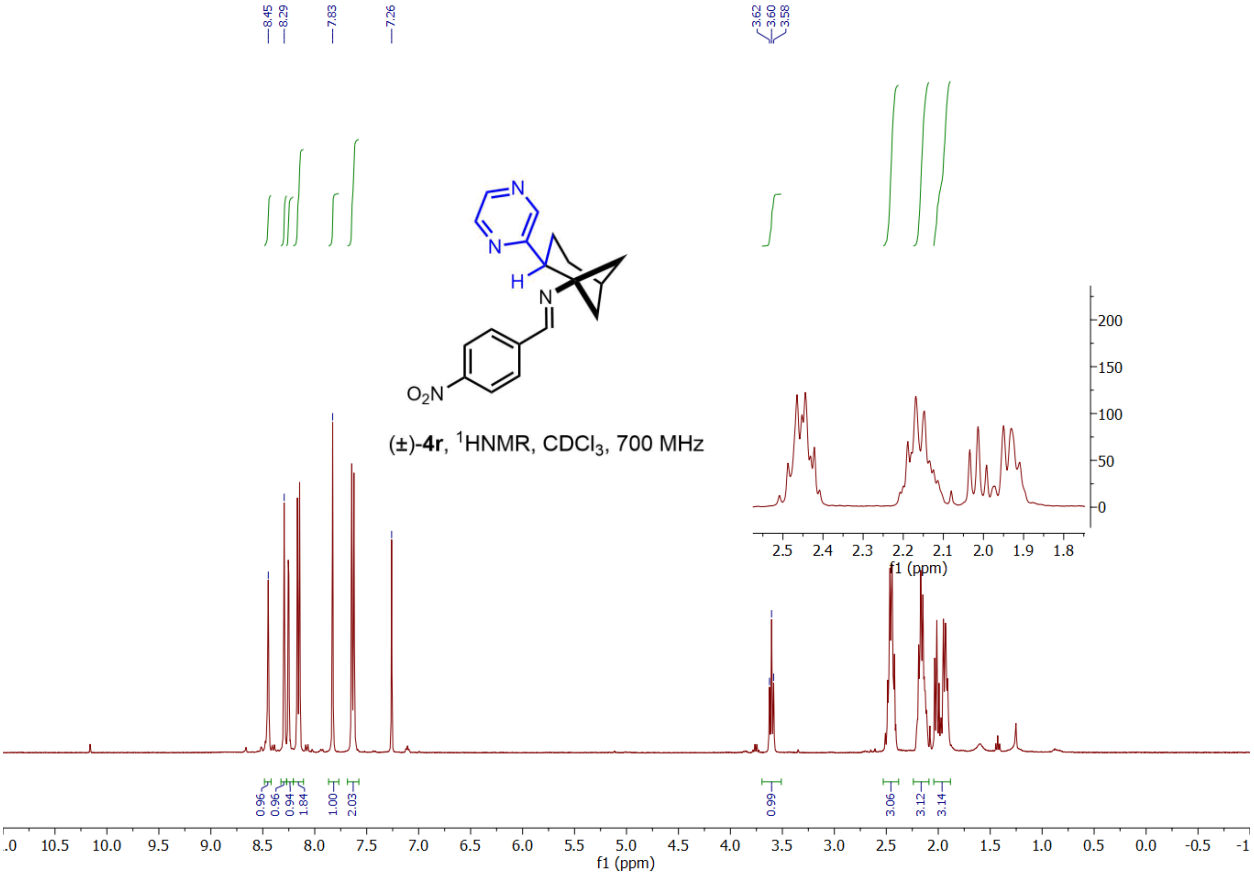
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.45 (s, 1H), 8.29 (s, 1H), 8.27-8.23 (m, 1H), 8.19-8.13 (m, 2H), 7.83 (s, 1H), 7.67-7.60 (m, 2H), 3.60 (app. t, *J* = 7.9 Hz, 1H), 2.52-2.38 (m, 3H), 2.22-2.09 (m, 3H), 2.05-1.88 (m, 3H) ppm

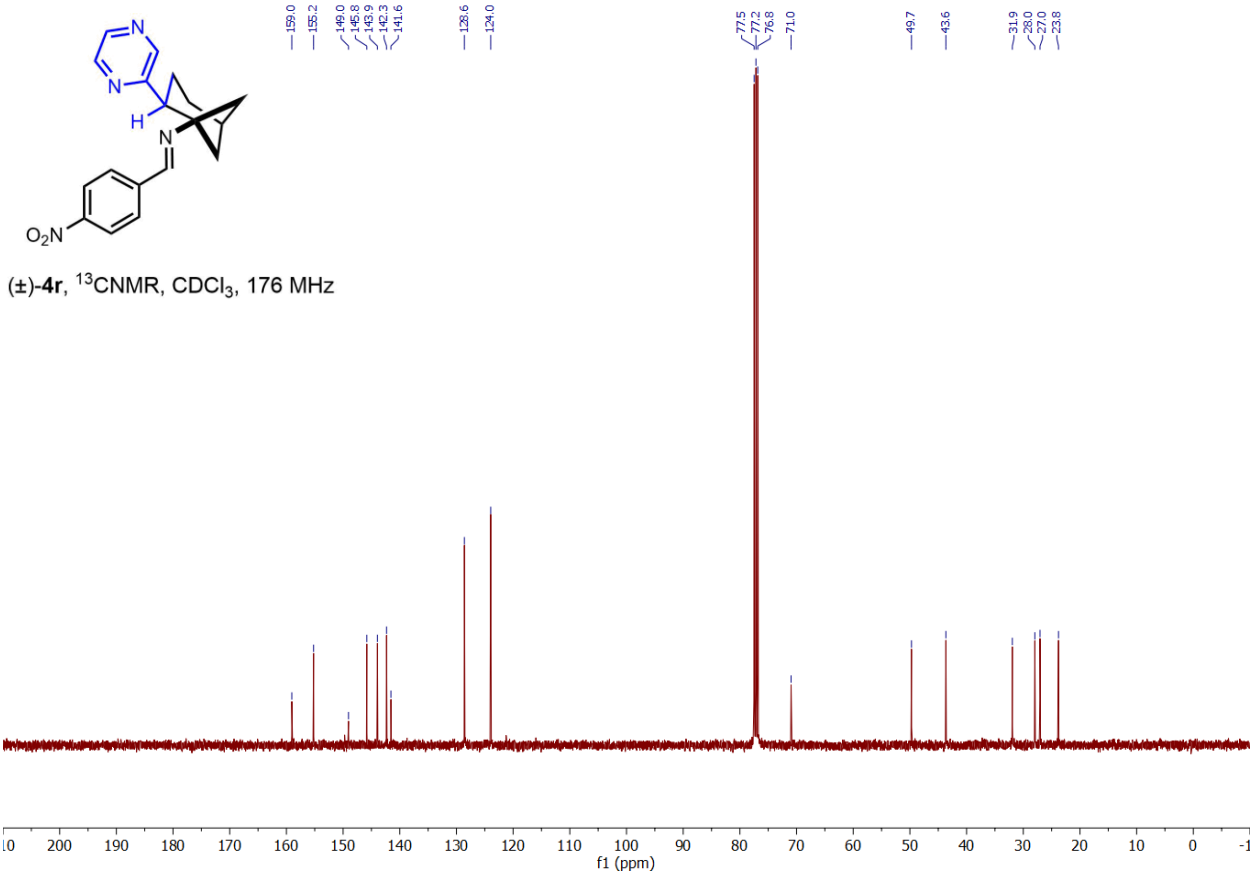
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 159.0, 155.2, 149.0, 145.8, 143.9, 142.3, 141.6, 128.6, 124.0, 71.0, 49.7, 43.6, 31.9, 28.0, 27.0, 23.8 ppm

IR (neat): 3045, 2947, 2863, 1635, 1599, 1512, 1476, 1450, 1405, 1380, 1341, 1317, 1286, 1258, 1222, 1195, 1153, 1136, 1107, 1070, 1054, 1034, 1025, 1014, 985, 963, 932, 912, 895, 853, 842, 811, 773, 748, 690 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{18}H_{19}N_4O_2^+$: 323.1503, Found: 323.1498

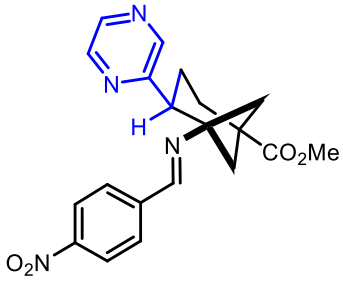
R_f = 0.73 (99% ethyl acetate + 1% NH_4OH), one yellow spot, $KMnO_4$, UV





(±)-**4r**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4s** :



EXPERIMENTAL PROCEDURE:

General procedure B was followed using **2b** (110 mg, 0.400 mmol, 1 equiv), 2-vinylpyrazine (0.306 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 21 hours. The crude reaction mixture was diluted with chloroform and concentrated onto celite (1 g), which was dry-loaded atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 10-100% ethyl acetate in hexanes to give (±)-**4s** (50.6 mg, 0.133 mmol, 33%) as a faintly yellow solid.

Appearance: faintly yellow solid

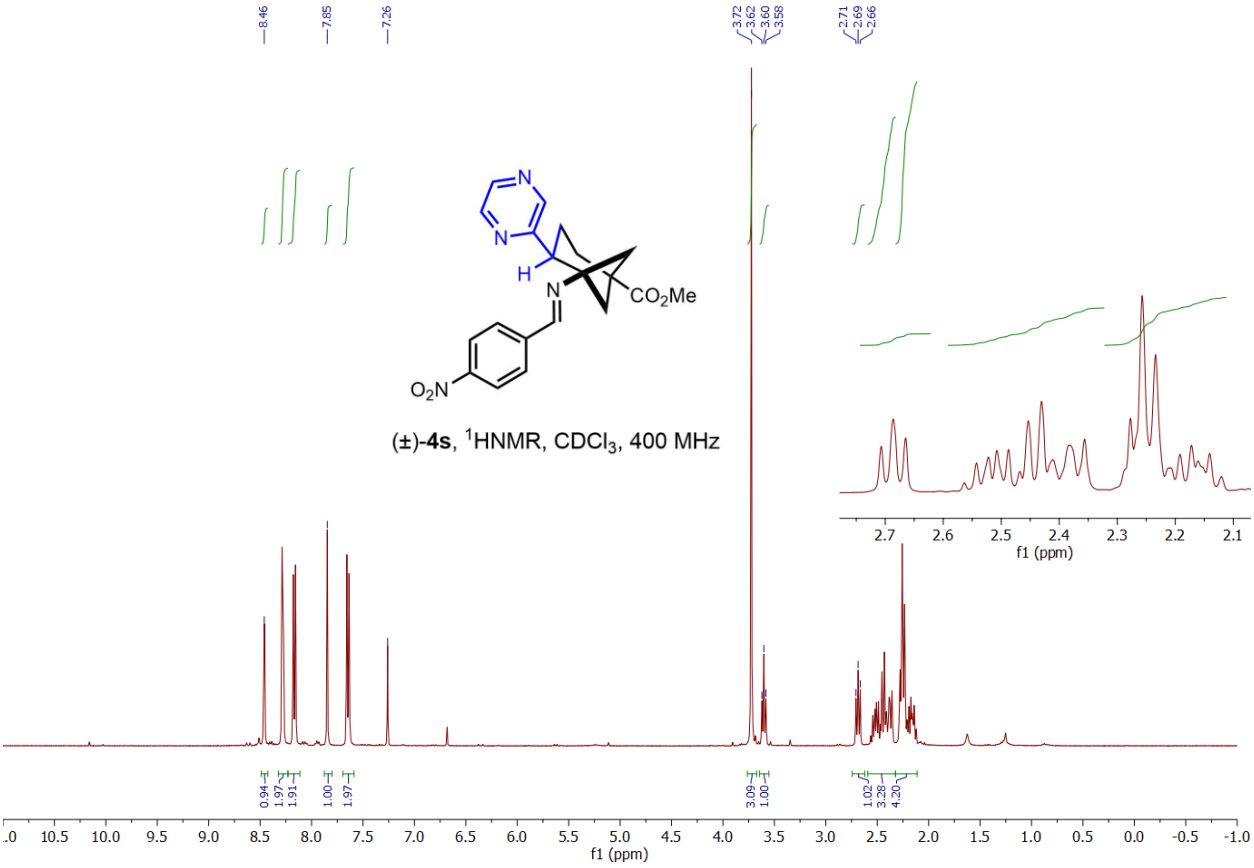
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.46 (s, 1H), 8.31-8.26 (m, 2H), 8.20-8.13 (m, 2H), 7.85 (s, 1H), 7.68-7.61 (m, 2H), 3.72 (s, 3H), 3.60 (app. t, *J* = 7.8 Hz, 1H), 2.69 (app. t, *J* = 8.4 Hz, 1H), 2.58-2.33 (m, 3H), 2.31-2.10 (m, 4H) ppm

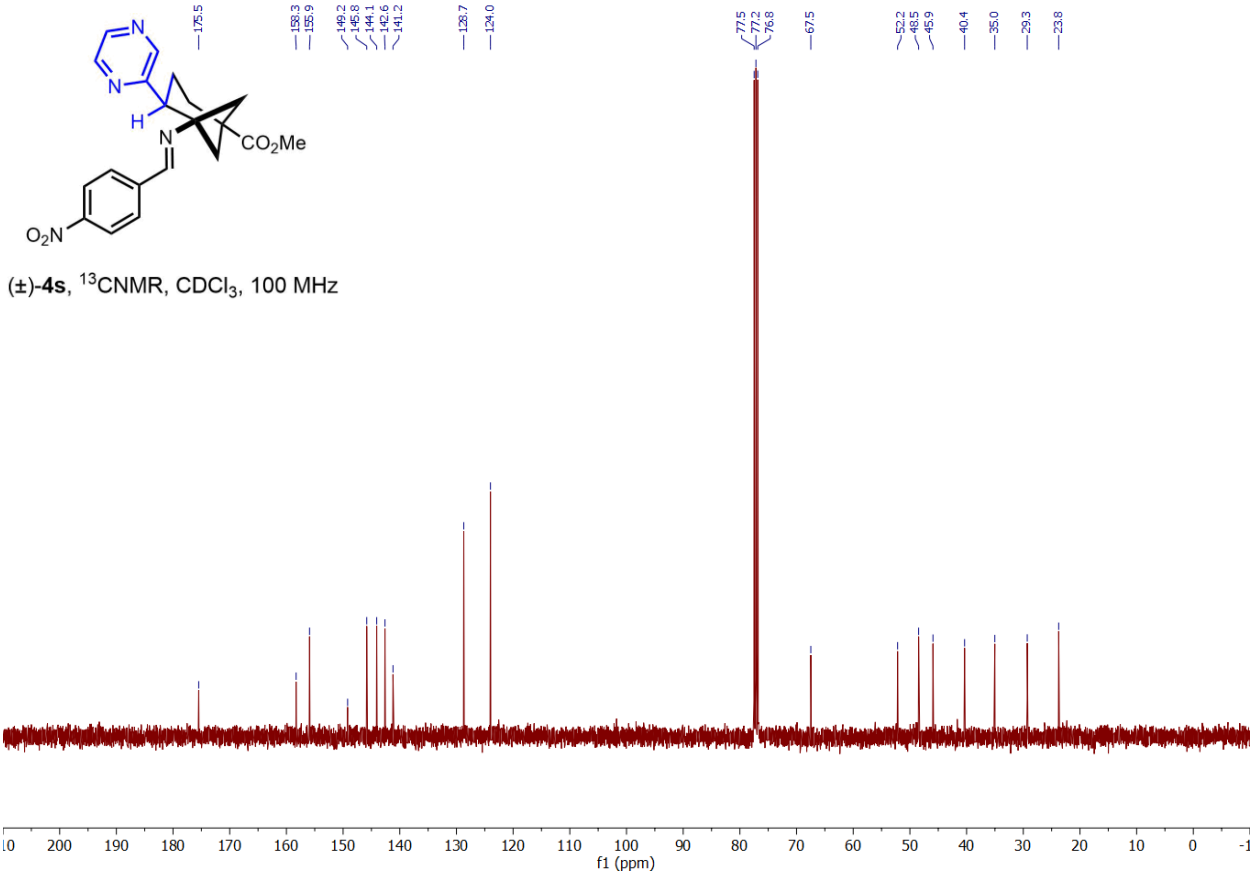
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 175.5, 158.3, 155.9, 149.2, 145.8, 144.1, 142.6, 141.2, 128.7, 124.0, 67.5, 52.2, 48.5, 45.9, 40.4, 35.0, 29.3, 23.8 ppm

IR (neat): 2950, 2871, 1726, 1641, 1601, 1519, 1476, 1452, 1435, 1407, 1343, 1316, 1286, 1257, 1214, 1156, 1145, 1107, 1078, 1047, 1017, 978, 913, 852, 837, 790, 771, 749, 731, 690, 661 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{21}N_4O_4^+$: 381.1557, Found: 381.1566

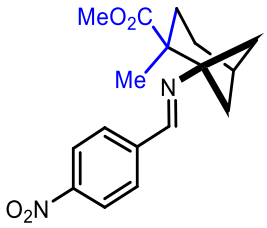
R_f = 0.67 (99% ethyl acetate + 1% NH_4OH), one yellow spot, $KMnO_4$, UV





(±)-**4s**, ^{13}CNMR, $CDCl_3$, 100 MHz

Compound (±)-**4t** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 0.8 mmol imine vs typical 0.4 mmol imine) was performed using **2a** (173 mg, 0.800 mmol, 1 equiv), methyl methacrylate (0.642 mL, 6.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (1.8 mg, 0.0080 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was loaded with toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-24% ethyl acetate in hexanes to give (±)-**4t** (43.8 mg, 0.138 mmol, 17%) as a yellow oil.

Appearance: yellow oil

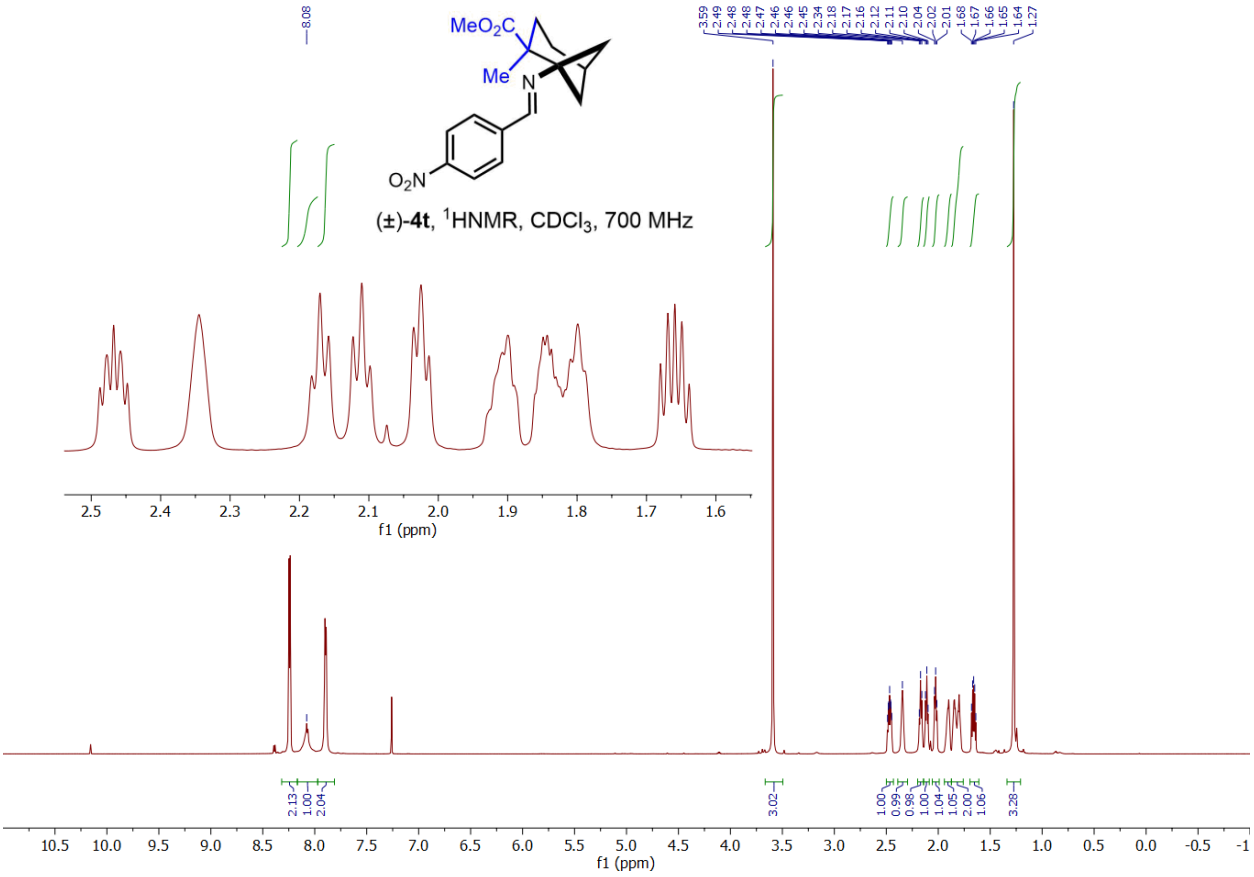
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.28-8.21 (m, 2H), 8.08 (bs, 1H), 7.93-7.85 (m, 2H), 3.59 (s, 3H), 2.47 (ddd, *J* = 13.9, 8.0, 5.6 Hz, 1H), 2.34 (bs, 1H), 2.17 (t, *J* = 8.5 Hz, 1H), 2.11 (t, *J* = 8.6 Hz, 1H), 2.02 (t, *J* = 7.6 Hz, 1H), 1.94-1.88 (m, 1H), 1.87-1.77 (m, 2H), 1.66 (dt, *J* = 14.2, 7.3 Hz, 1H), 1.27 (s, 3H) ppm

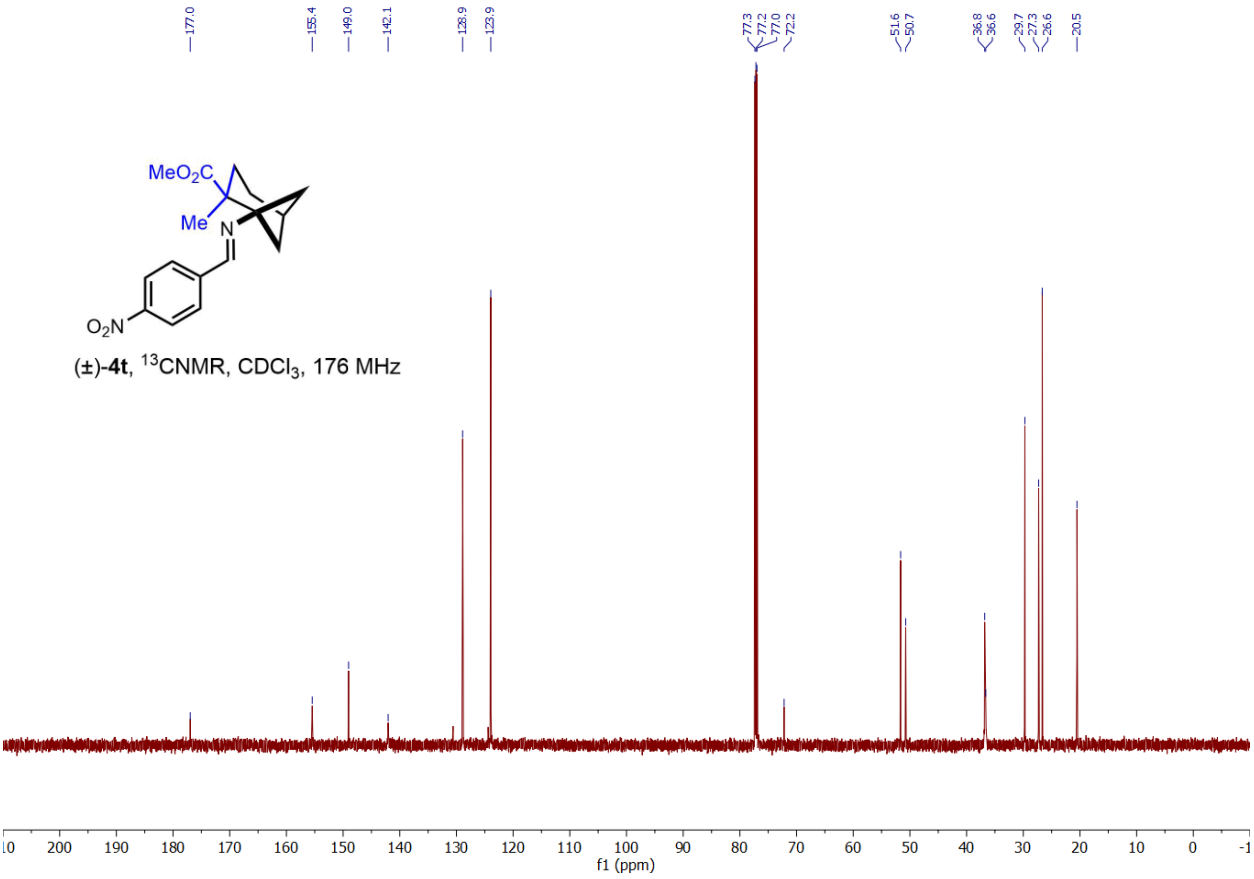
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 177.0, 155.4, 149.0, 142.1, 128.9, 123.9, 72.2, 51.6, 50.7, 36.8, 36.6, 29.7, 27.3, 26.6, 20.5 ppm

IR (neat): 2986, 2936, 2860, 1722, 1650, 1600, 1513, 1451, 1428, 1377, 1350, 1341, 1318, 1270, 1246, 1220, 1202, 1178, 1150, 1107, 1064, 1033, 1012, 997, 975, 957, 934, 916, 898, 880, 853, 838, 821, 811, 780, 748, 737, 689, 667 cm^{-1}

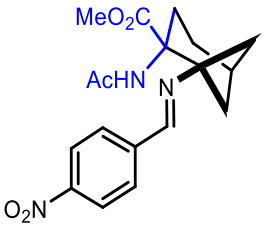
HRMS (ES+, m/z) calculated for $C_{17}H_{21}N_2O_4^+$: 317.1496, Found: 317.1495

R_f = 0.76 (50% ethyl acetate: 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV





Compound (±)-**4u** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 0.400 mL acetonitrile used as solvent instead of typical neat conditions) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), methyl 2-acetamidoacrylate (429 mg, 3.00 mmol, 7.5 equiv), 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv), and acetonitrile (0.400 mL) and irradiating for 16 hours. The crude reaction mixture was diluted with chloroform, concentrated onto celite (2 g), and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 10-100% ethyl acetate in hexanes to give (±)-**4u** (66.5 mg, 0.185 mmol, 46%) as a faintly yellow solid. Recrystallization from ethyl acetate / chloroform gave (±)-**4u** as a faintly yellow solid of excellent purity.

Repeating the procedure with the deviations specified below gave the isolated yields shown:

None: (±)-**4u** (66.7 mg, 0.186 mmol, 46%)

methyl acetamidoacrylate (115 mg, 0.800 mmol, 2.00 equiv): (±)-**4u** (73.0 mg, 0.203 mmol, 51%)

acetonitrile (0.800 mL): (±)-**4u** (53.1 mg, 0.148 mmol, 37%)

methyl acetamidoacrylate (115 mg, 0.800 mmol, 2.00 equiv), acetonitrile (0.200 mL): (±)-**4u** (74.5 mg, 0.207 mmol, 52%)

methyl acetamidoacrylate (57.3 mg, 0.400 mmol, 1.00 equiv), acetonitrile (0.200 mL): (±)-**4u** (38.3 mg, 0.107 mmol, 27%)

methyl acetamidoacrylate (63.0 mg, 0.440 mmol, 1.10 equiv), acetonitrile (0.200 mL): (±)-**4u** (63.3 mg, 0.176 mmol, 44%) (This example shown in main text)

methyl acetamidoacrylate (68.7 mg, 0.480 mmol, 1.20 equiv), acetonitrile (0.200 mL): (±)-**4u** (64.1 mg, 0.178 mmol, 45%)

methyl acetamidoacrylate (85.9 mg, 0.600 mmol, 1.50 equiv), acetonitrile (0.200 mL): (±)-**4u** (69.2 mg, 0.193 mmol, 48%)

Repeating the procedure with the deviations specified below gave the assay yields shown, determined using Q^{1}HNMR with 1,3,5-trimethoxybenzene as internal standard:

methyl acetamidoacrylate (63.0 mg, 0.440 mmol, 1.10 equiv), dichloromethane (0.200 mL): (±)-**4u** (61%)

methyl acetamidoacrylate (63.0 mg, 0.440 mmol, 1.10 equiv), dichloromethane (0.400 mL): (±)-**4u** (39%)

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.28 (d, *J* = 8.7 Hz, 2H), 8.00 (s, 1H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.07 (s, 1H), 3.53 (s, 3H), 3.07 (ddd, *J* = 14.8, 7.9, 3.6 Hz, 1H), 2.43-2.39 (m, 1H), 2.35 (dd, *J* = 9.3, 8.3 Hz, 1H), 2.22-2.14 (m, 2H), 2.02 (s, 3H), 1.99-1.90 (m, 2H), 1.88 (dd, *J* = 9.4, 8.2 Hz, 1H), 1.77 (dd, *J* = 9.2, 6.5 Hz, 1H) ppm

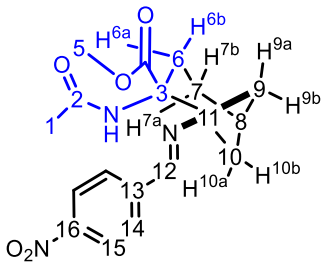
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 172.5, 170.9, 156.6, 149.4, 141.1, 129.1, 124.1, 70.1, 66.7, 52.1, 37.3, 34.0, 28.6, 27.1, 26.3, 23.6 ppm

IR (neat): 3265, 2937, 2869, 1719, 1645, 1600, 1526, 1512, 1432, 1371, 1348, 1319, 1297, 1267, 1249, 1229, 1158, 1107, 1073, 1034, 1017, 985, 960, 935, 915, 859, 840, 829, 800, 749, 726, 710, 691 cm^{-1}

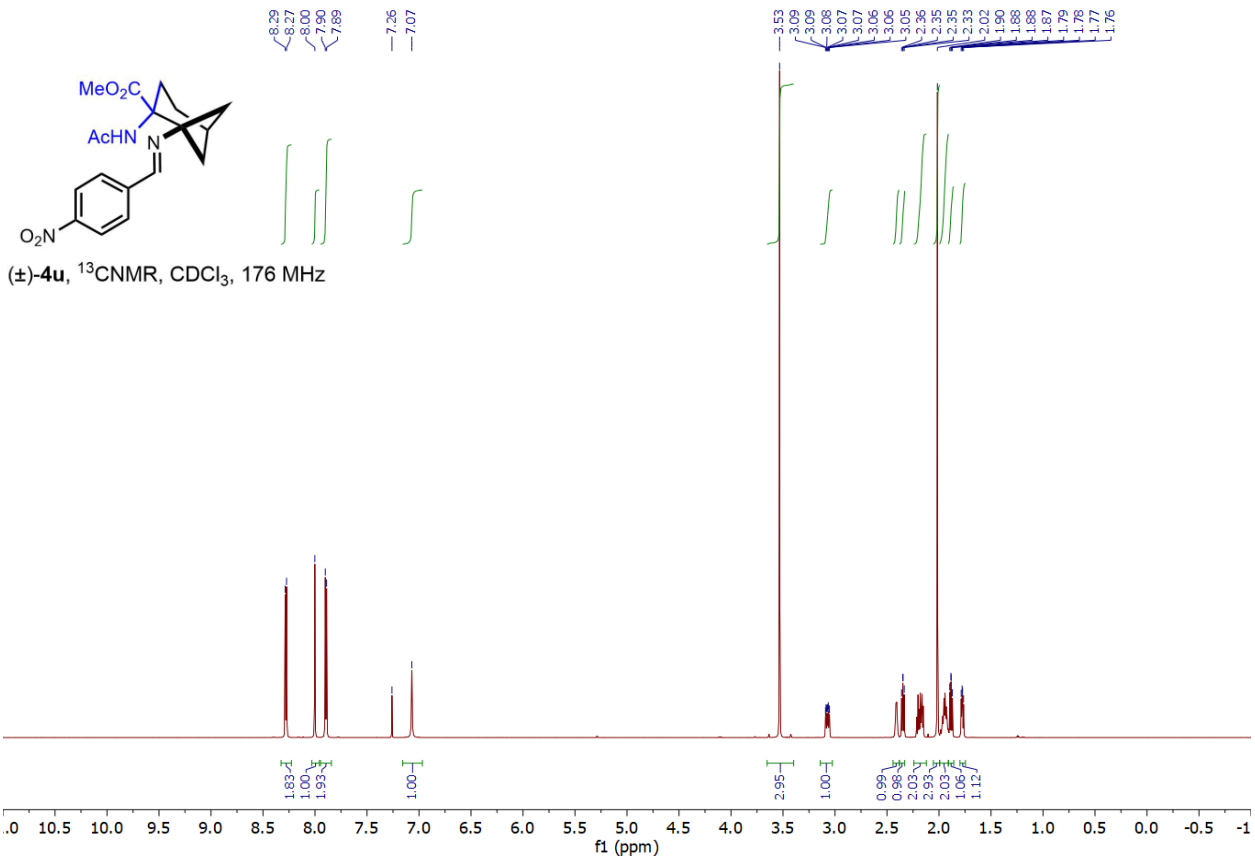
HRMS (ES+, m/z) calculated for $C_{18}H_{22}N_3O_5^+$: 360.1554, Found: 360.1553

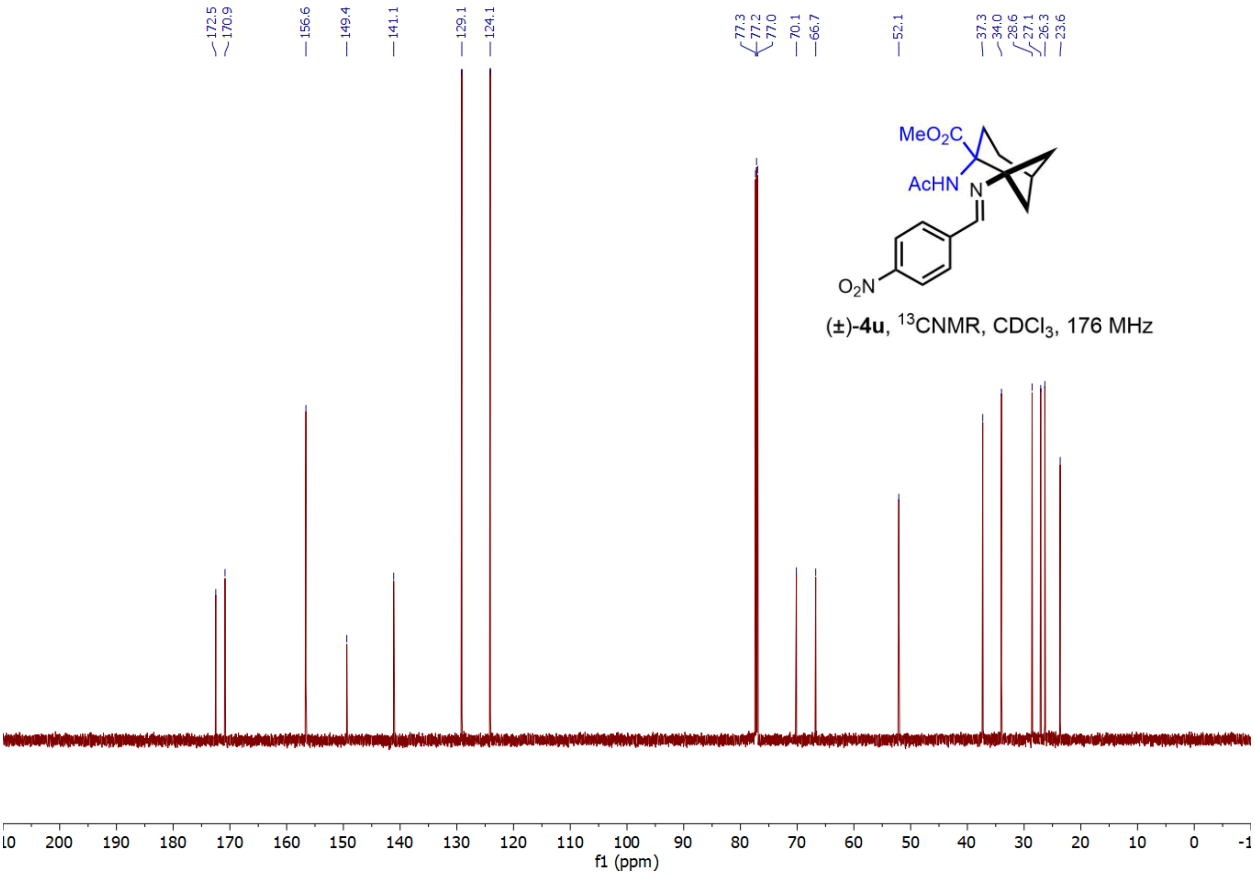
R_f = 0.23 (50% ethyl acetate : 49% hexanes : 1% Et_3N), yellow spot, $KMnO_4$, UV

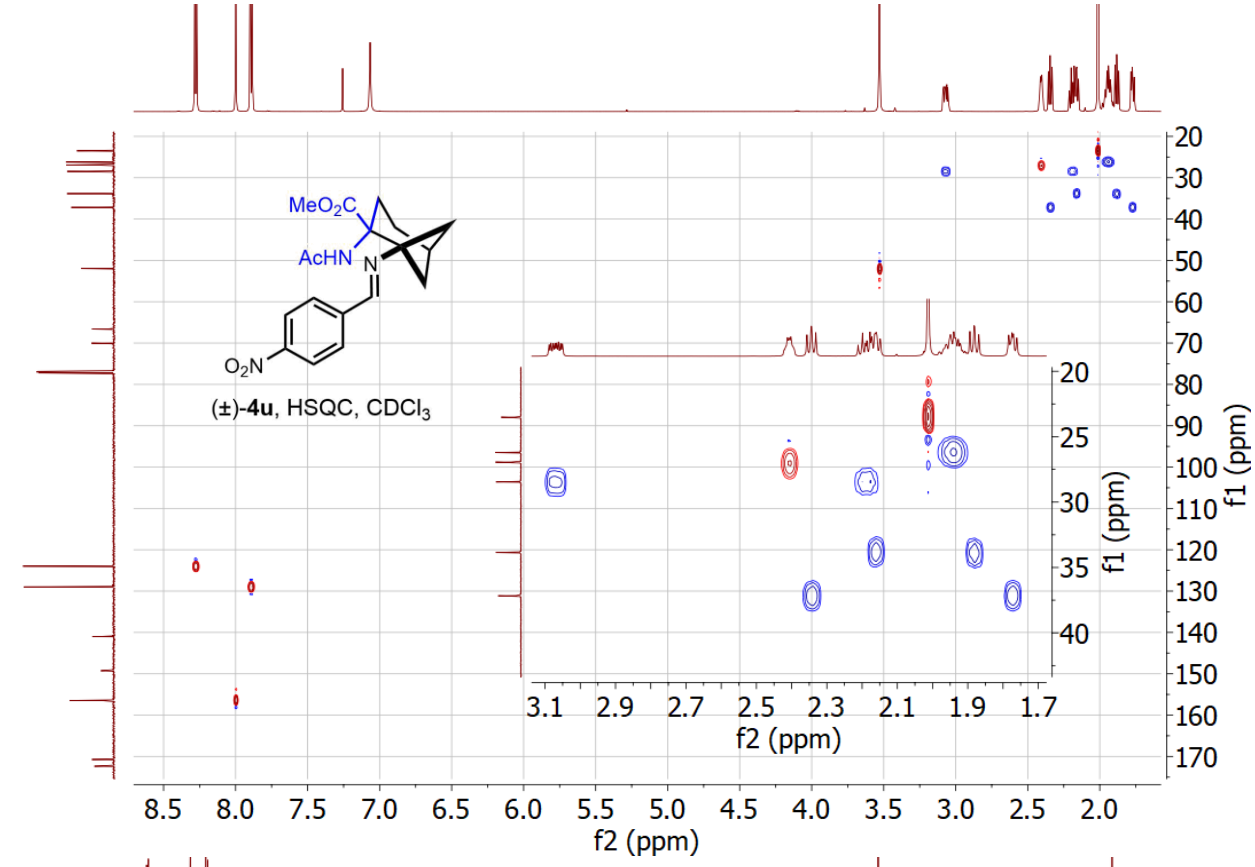
Complete assignment of ^1H and ^{13}C NMR signals

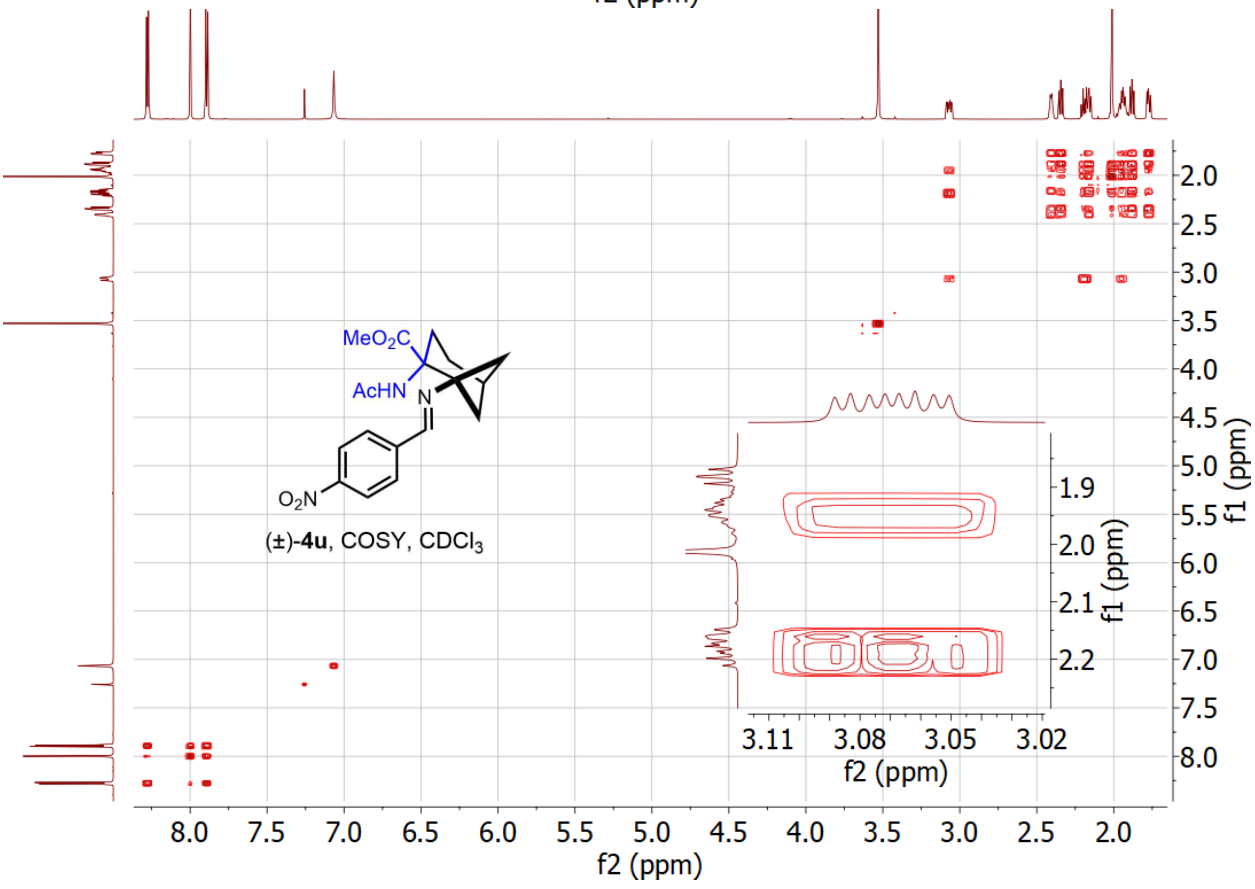


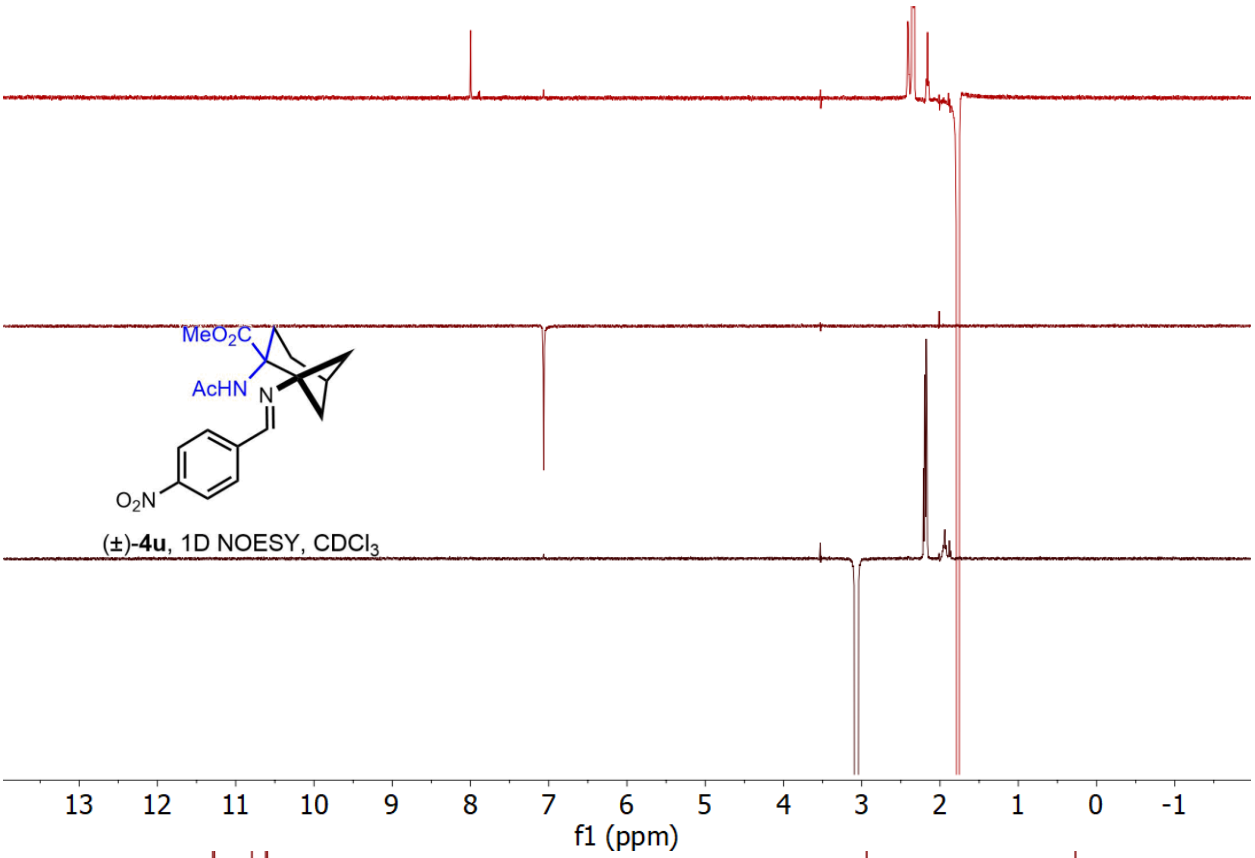
Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	23.6		1	2.02 (s, 3H)
2	170.9		N-H	7.07 (s, 1H)
3	66.7		5	3.53 (s, 3H)
4	172.5		6a	one of 2.22-2.14 (m, 2H)
5	52.1		6b	3.07 (ddd, J = 14.8, 7.9, 3.6 Hz, 1H)
6	28.6		7a	one of 1.99-1.90 (m, 2H)
7	26.3		7b	one of 1.99-1.90 (m, 2H)
8	27.1		8	2.43-2.39 (m, 1H)
9	34		9a	one of 2.22-2.14 (m, 2H)
10	37.3		9b	2.22-2.14 (m, 2H)
11	70.1		10a	2.35 (dd, J = 9.3, 8.3 Hz, 1H)
12	156.6		10b	1.77 (dd, J = 9.2, 6.5 Hz, 1H)
13	141.1		12	8.00 (s, 1H)
14	124.1		14	8.28 (d, J = 8.7 Hz, 2H)
15	129.1		15	7.89 (d, J = 8.7 Hz, 2H)
16	149.4			

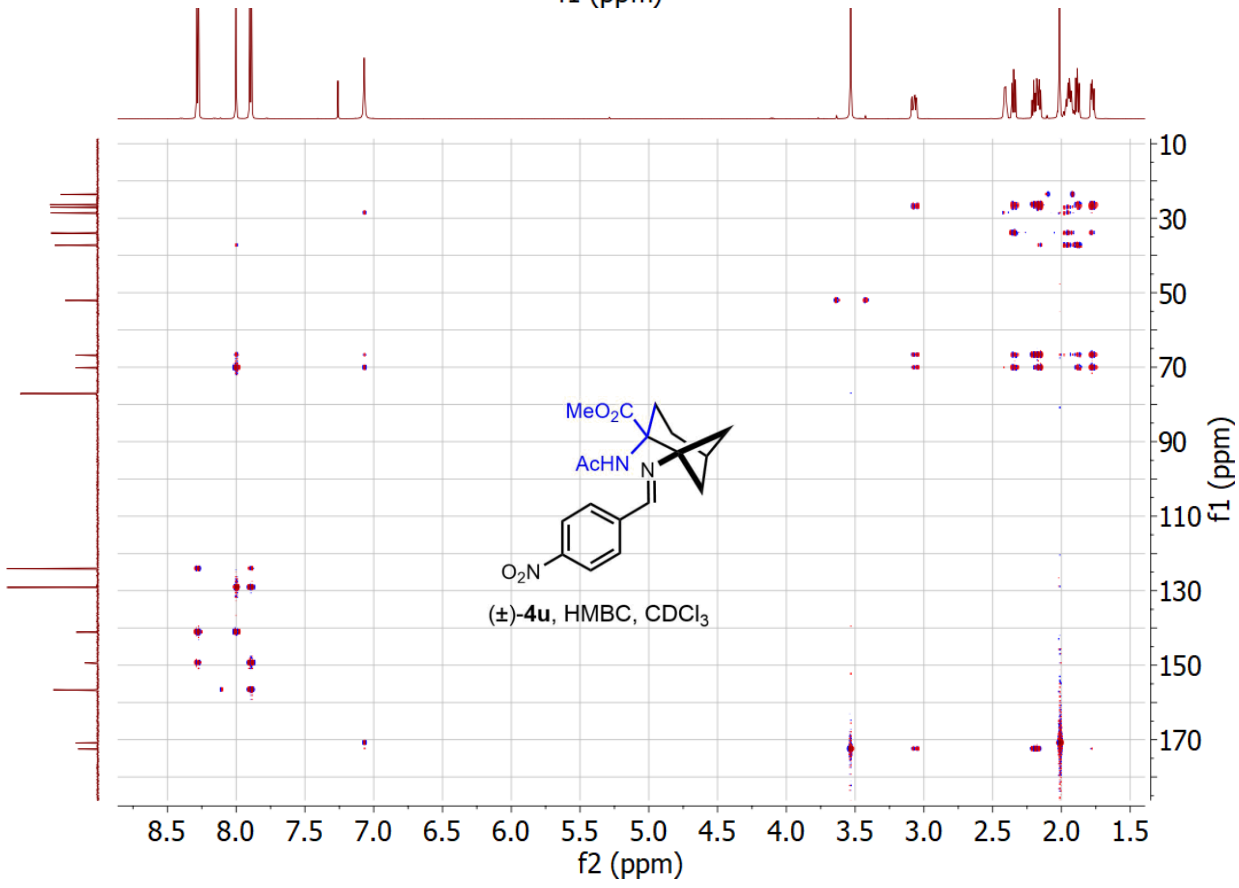

MeO2C
AcHN
N
O2N
(±)-4u, 13CNMR, CDCl3, 176 MHz
f1 (ppm)


MeO2C
AcHN
N
O2N
(±)-4u, 13CNMR, CDCl3, 176 MHz
f1 (ppm)

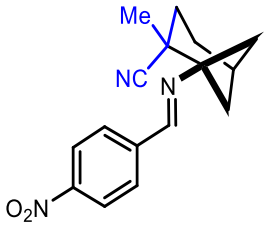

MeO2C
AcHN
N
O2N
(±)-4u, HSQC, CDCl3
f2 (ppm)
f1 (ppm)


MeO2C
AcHN
N
O2N
(±)-4u, COSY, CDCl3
f2 (ppm)
f1 (ppm)


MeO2C
AcHN
N
O2N
(±)-4u, 1D NOESY, CDCl3
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


MeO2C
AcHN
N
O2N
(±)-4u, HMBC, CDCl3
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
f2 (ppm)
10 30 50 70 90 110 130 150 170
f1 (ppm)

Compound (±)-**4v**:



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), methacrylonitrile (0.252 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was diluted with chloroform, concentrated onto celite (3 g), and loaded atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-60% ethyl acetate in hexanes to give (±)-**4v** (62.5 mg, 0.221 mmol, 55%) as a faintly yellow solid.

Appearance: faintly yellow solid

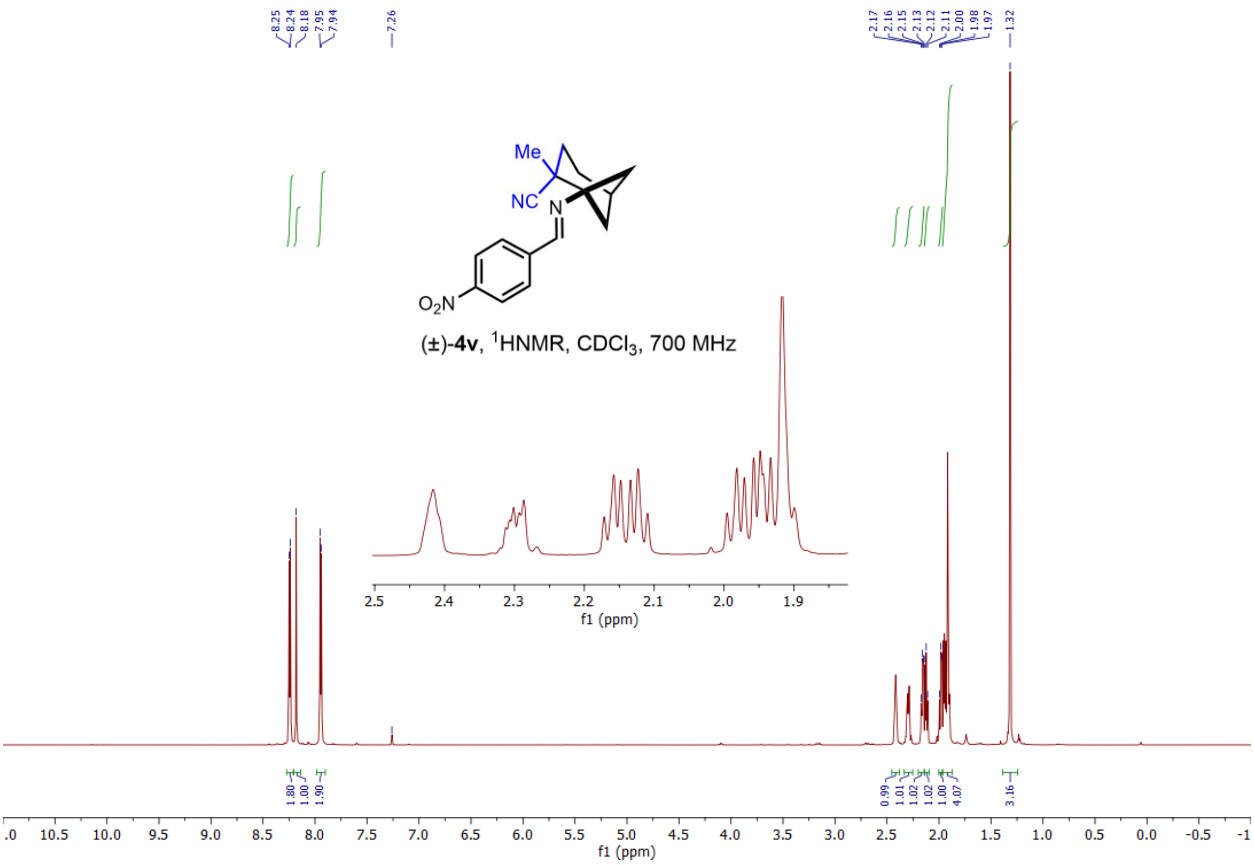
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.24 (d, *J* = 7.9 Hz, 2H), 8.18 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 2H), 2.45-2.39 (m, 1H), 2.33-2.25 (m, 1H), 2.16 (app. t, *J* = 8.3 Hz, 1H), 2.12 (app. t, *J* = 8.6 Hz, 1H), 1.98 (app. t, *J* = 8.6 Hz, 1H), 1.96-1.87 (m, 4H), 1.32 (s, 1H) ppm

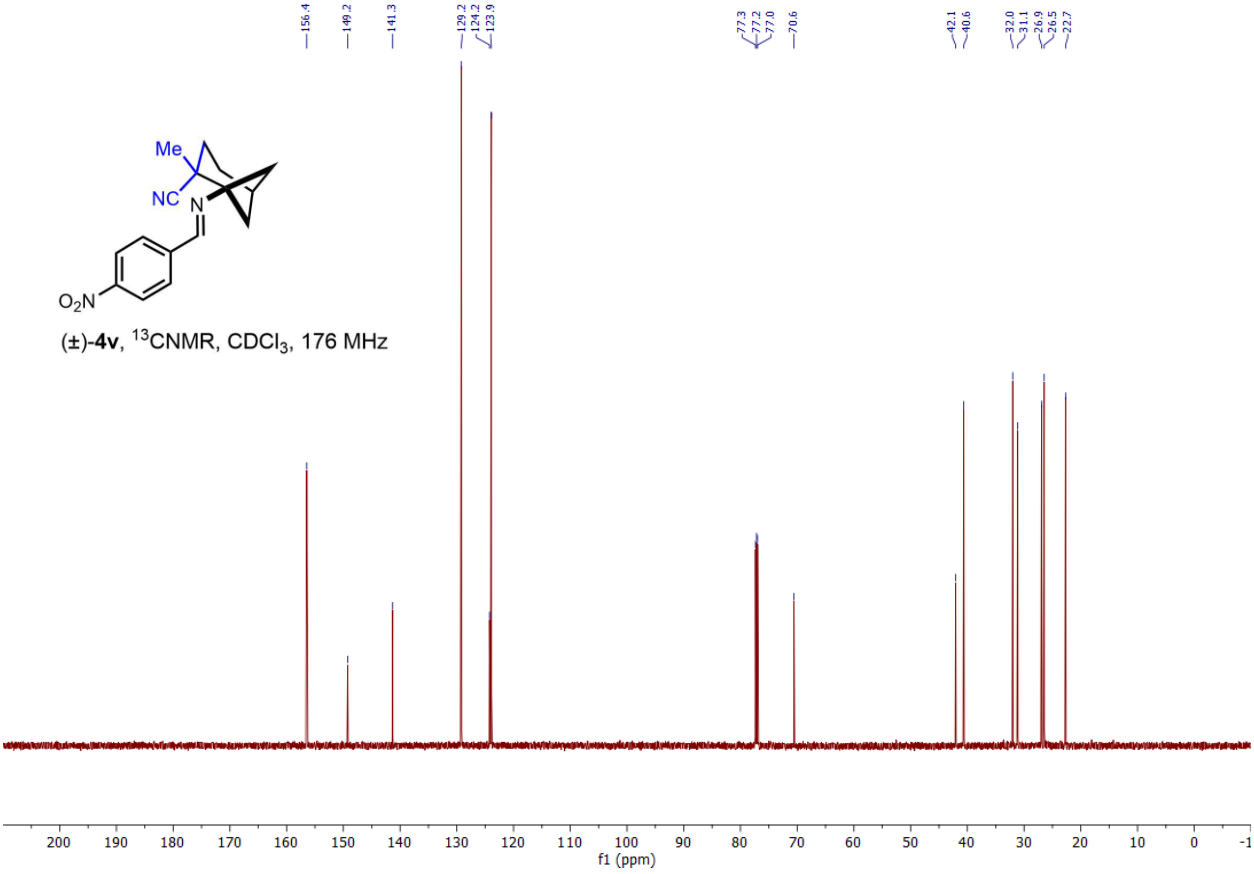
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 156.4, 149.2, 141.3, 129.2, 124.2, 123.9, 70.6, 42.1, 40.6, 32.0, 31.1, 26.9, 26.5, 22.7 ppm

IR (neat): 2957, 2870, 2226, 1646, 1598, 1519, 1445, 1414, 1376, 1343, 1313, 1291, 1265, 1217, 1182, 1129, 1108, 1044, 1010, 982, 974, 953, 931, 853, 838, 747, 686 cm^{-1}

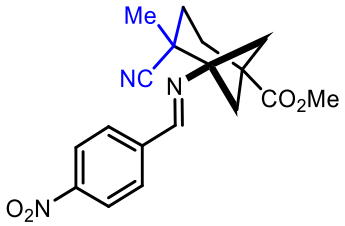
HRMS (ES+, m/z) calculated for $C_{16}H_{18}N_3O_2^+$: 284.1394, Found: 284.1394

R_f = 0.17 (20% ethyl acetate : 80% hexanes), yellow spot, $KMnO_4$, UV


Me
NC
N
O_2N
(±)-**4v**, ^{1}HNMR, $CDCl_3$, 700 MHz
f1 (ppm)


Me
NC
N
O_2N
(±)-**4v**, ^{13}CNMR, $CDCl_3$, 176 MHz
f1 (ppm)

Compound (±)-**4w** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 15 equivalents of alkene used rather than the standard 7.5) was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), methacrylonitrile (0.503 mL, 6.00 mmol, 15 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 18 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-60% ethyl acetate in hexanes to give (±)-**4w** (92.3 mg, 0.270 mmol, 68%) as a faintly yellow solid.

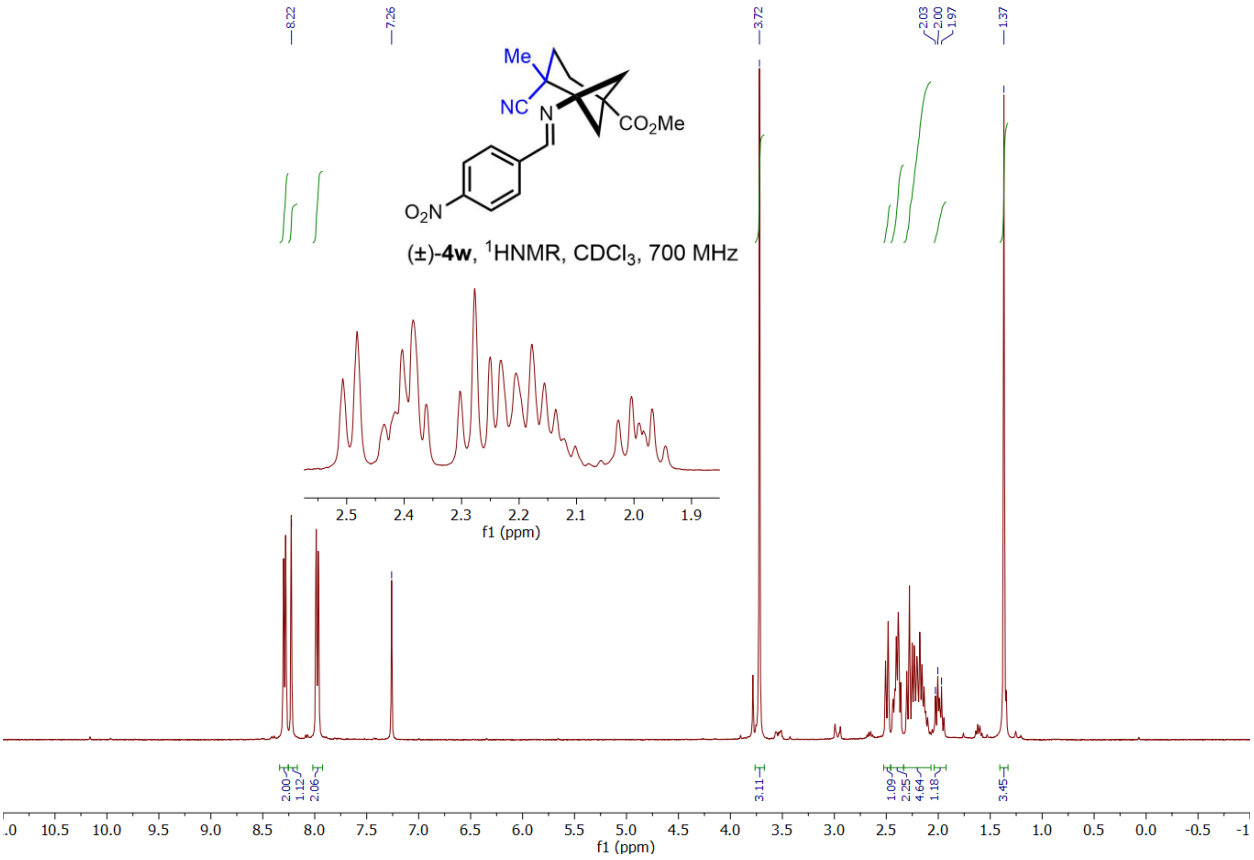
Appearance: faintly yellow solid

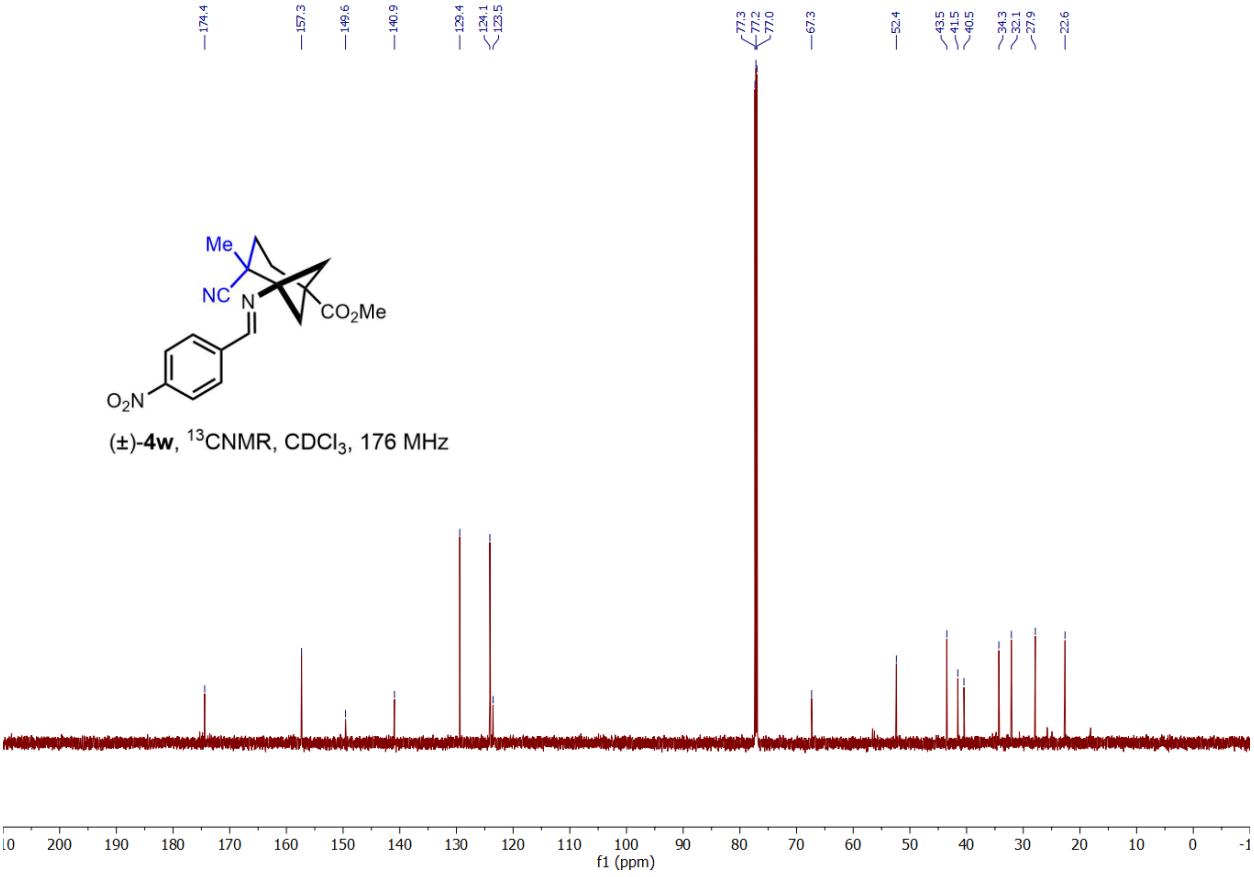
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.33-8.25 (m, 2H), 8.22 (s, 1H), 8.01-7.93 (m, 2H), 3.72 (s, 3H), 2.52-2.46 (m, 1H), 2.46-2.35 (m, 2H), 2.33-2.08 (m, 4H), 1.99 (app. dt, *J* = 14.5, 9.1 Hz, 1H), 1.37 (s, 3H) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 174.4, 157.3, 149.6, 140.9, 129.4, 124.1, 123.5, 67.3, 52.4, 43.5, 41.5, 40.5, 34.3, 32.1, 27.9, 22.6 ppm

IR (neat): 3106, 2987, 2954, 2879, 2226, 1792, 1732, 1641, 1600, 1519, 1438, 1417, 1382, 1344, 1292, 1259, 1217, 1202, 1194, 1164, 1134, 1108, 1053, 1012, 988, 965, 943, 920, 872, 855, 838, 791, 760, 747, 690 cm^{-1}

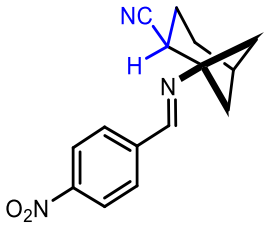
HRMS (ES+, m/z) calculated for $C_{18}H_{20}N_3O_4^+$: 342.1448, Found: 342.1444

R_f = 0.17 (30% ethyl acetate: 69% hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV


Me
NC
N
CO2Me
O2N
(±)-4w, 1HNMR, CDCl3, 700 MHz
f1 (ppm)


Me
NC
N
CO2Me
O2N
(±)-4w, 13CNMR, CDCl3, 176 MHz
f1 (ppm)

Compound (±)-**4x** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 15 equivalents of alkene used rather than the standard 7.5) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), acrylonitrile (0.393 mL, 6.00 mmol, 15 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was concentrated in a fume hood to near dryness under a gentle stream of nitrogen. The residue was dissolved in chloroform, concentrated onto celite (3 g), and loaded atop a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 7-60% ethyl acetate in hexanes to give (±)-**4x** (40.3 mg, 0.150 mmol, 37%) as a faintly yellow solid.

Appearance: faintly yellow solid

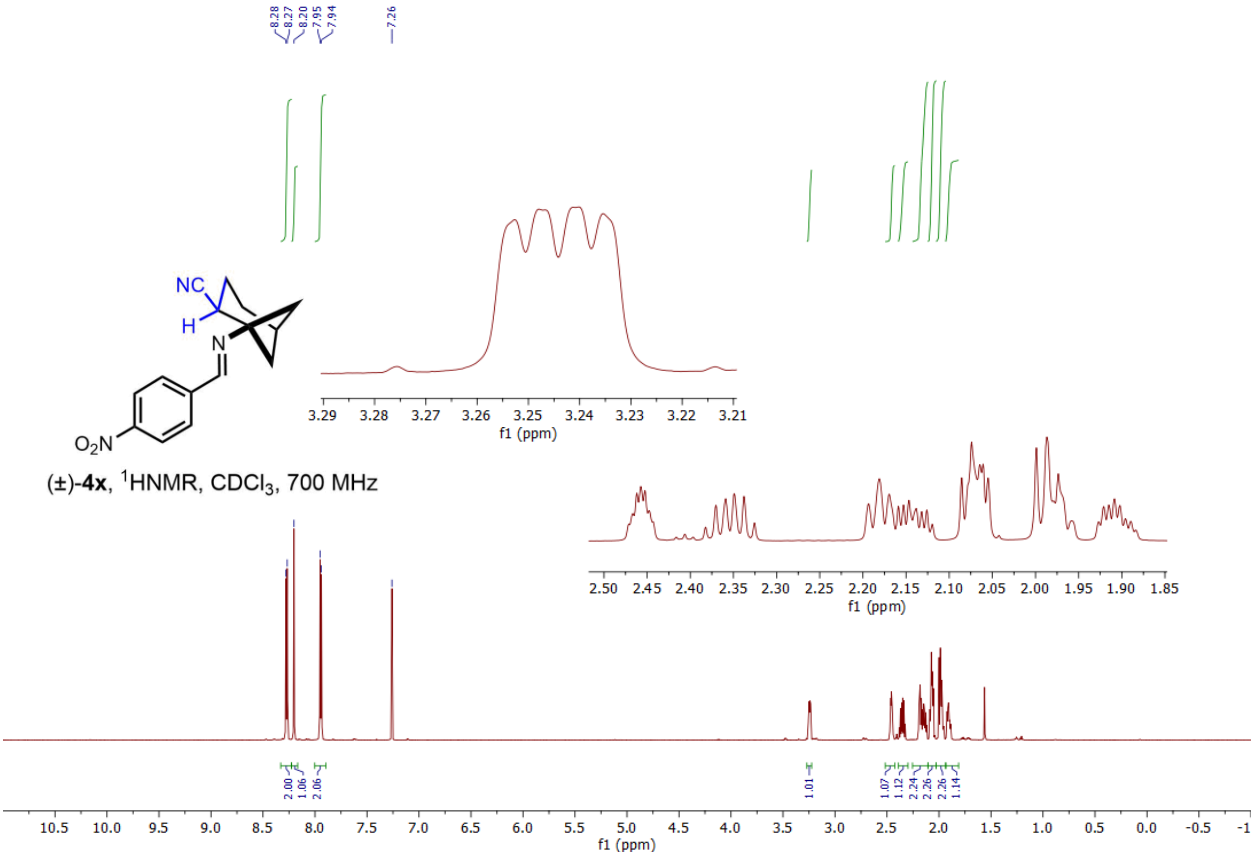
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.27 (d, *J* = 8.6 Hz, 2H), 8.20 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 2H), 3.27-3.22 (m, 1H), 2.48-2.43 (m, 1H), 2.39-2.32 (m, 1H), 2.20-2.11 (m, 2H), 2.10-2.04 (m, 2H), 2.01-1.95 (m, 2H), 1.94-1.87 (m, 1H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 156.9, 149.4, 141.3, 129.3, 124.0, 121.3, 68.0, 37.3, 37.0, 36.0, 26.6, 26.2, 21.6 ppm

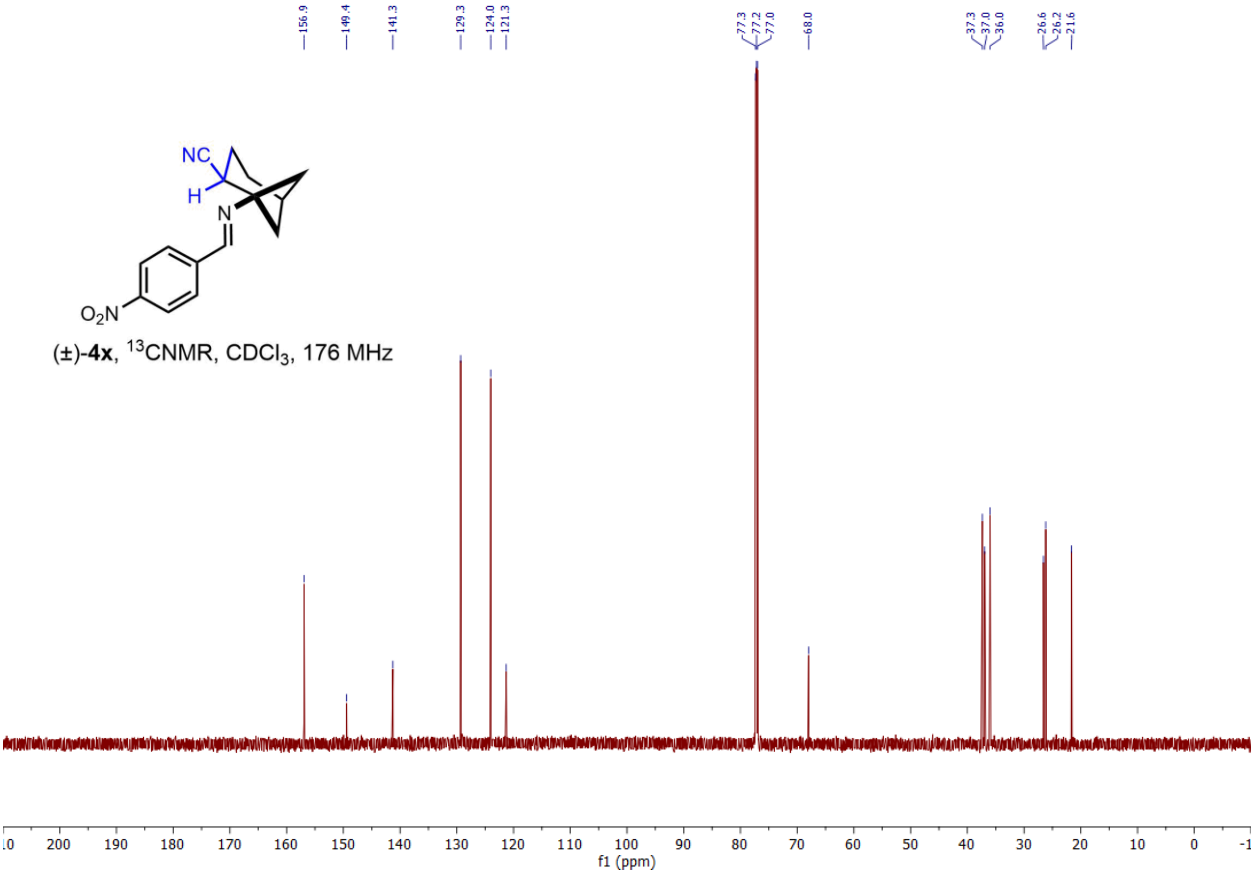
IR (neat): 2926, 2866, 2231, 1642, 1600, 1519, 1450, 1375, 1344, 1294, 1277, 1219, 1158, 1108, 1002, 986, 933, 853, 841, 747, 690 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{15}H_{16}N_3O_2^+$: 270.1237, Found: 270.1240

R_f = 0.26 (30% ethyl acetate : 69% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

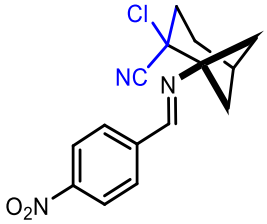


(±)-**4x**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4x**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4y** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 2-chloroacrylonitrile (0.240 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was diluted with chloroform, concentrated onto celite (2 g), and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-40% ethyl acetate in hexanes to give (±)-**4y** (76.8 mg, 0.253 mmol, 63%) as a faintly yellow solid.

Appearance: faintly yellow solid

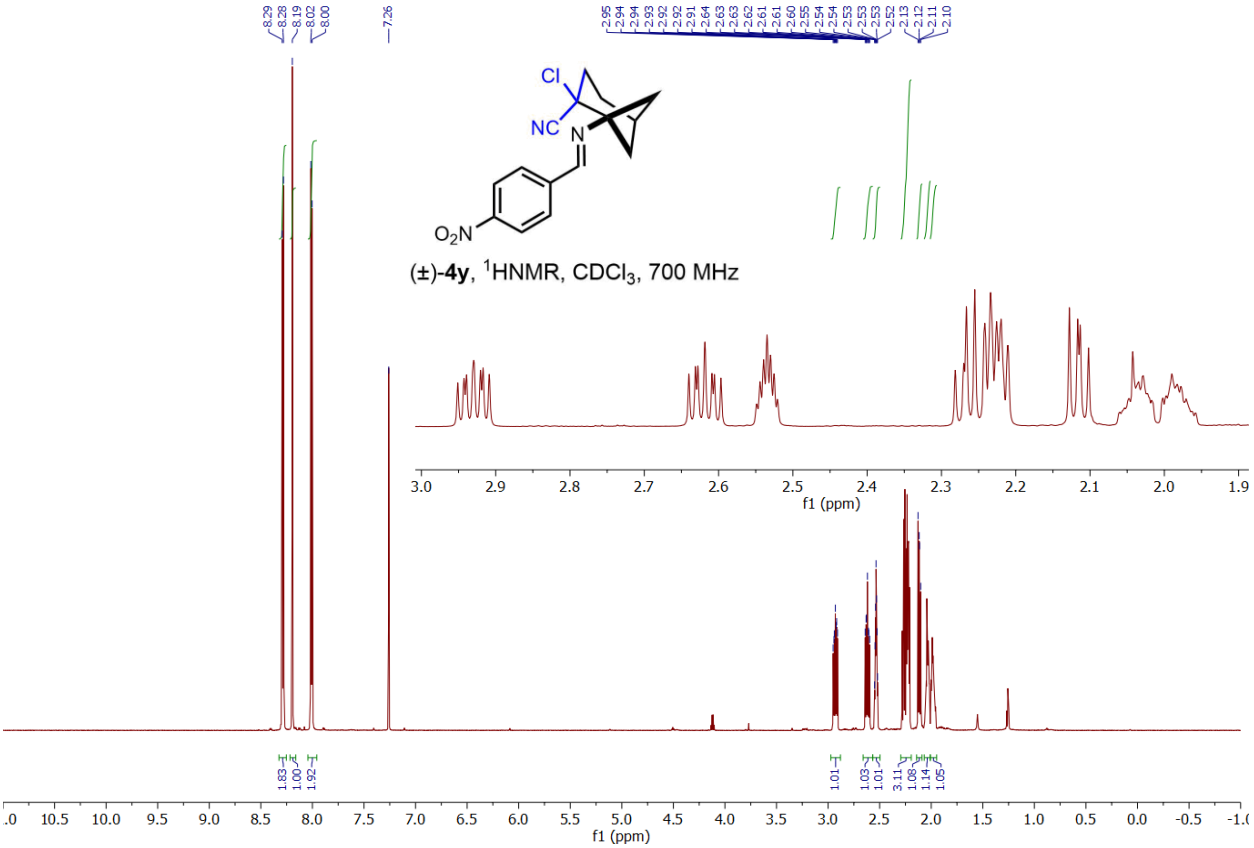
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.30–8.27 (m, 2H), 8.19 (s, 1H), 8.02–7.99 (m, 2H), 2.93 (ddd, *J* = 15.1, 8.3, 5.9 Hz, 1H), 2.62 (ddd, *J* = 15.1, 8.5, 6.2 Hz, 1H), 2.53 (tt, *J* = 6.6, 3.2 Hz, 1H), 2.29–2.20 (m, 3H), 2.14–2.09 (m, 1H), 2.07–2.01 (m, 1H), 2.01–1.95 (m, 1H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 158.3, 149.6, 140.9, 129.6, 124.1, 118.9, 72.7, 64.5, 38.8, 36.2, 32.8, 26.8, 26.0 ppm

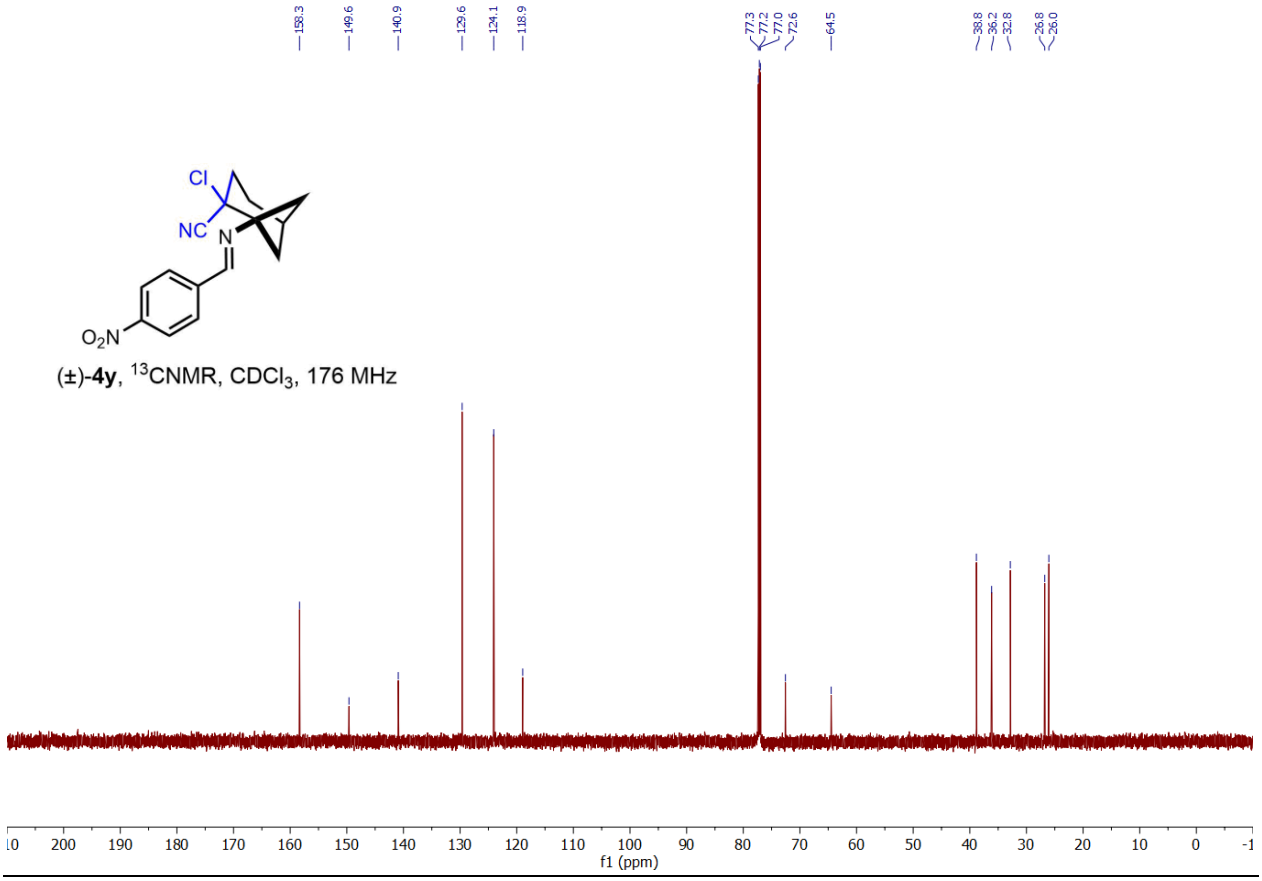
IR (neat): 2955, 2241, 1646, 1602, 1520, 1447, 1413, 1343, 1314, 1291, 1250, 1220, 1182, 1160, 1106, 1042, 1021, 1011, 972, 946, 928, 903, 871, 852, 838, 822, 744, 690, 673 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{15}H_{15}ClN_3O_2^+$: 304.0847, Found: 304.0842

R_f = 0.21 (20% ethyl acetate : 80% hexanes), yellow spot, $KMnO_4$, UV

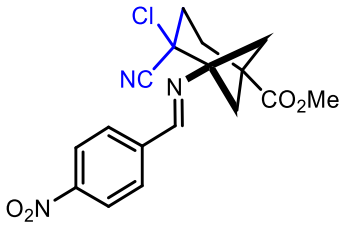


(±)-**4y**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4y**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4z** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), 2-chloroacrylonitrile (0.240 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 13 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-50% ethyl acetate in hexanes to give (±)-**4z** (105 mg, 0.290 mmol, 73%) as a thick yellow oil.

Appearance: thick yellow oil

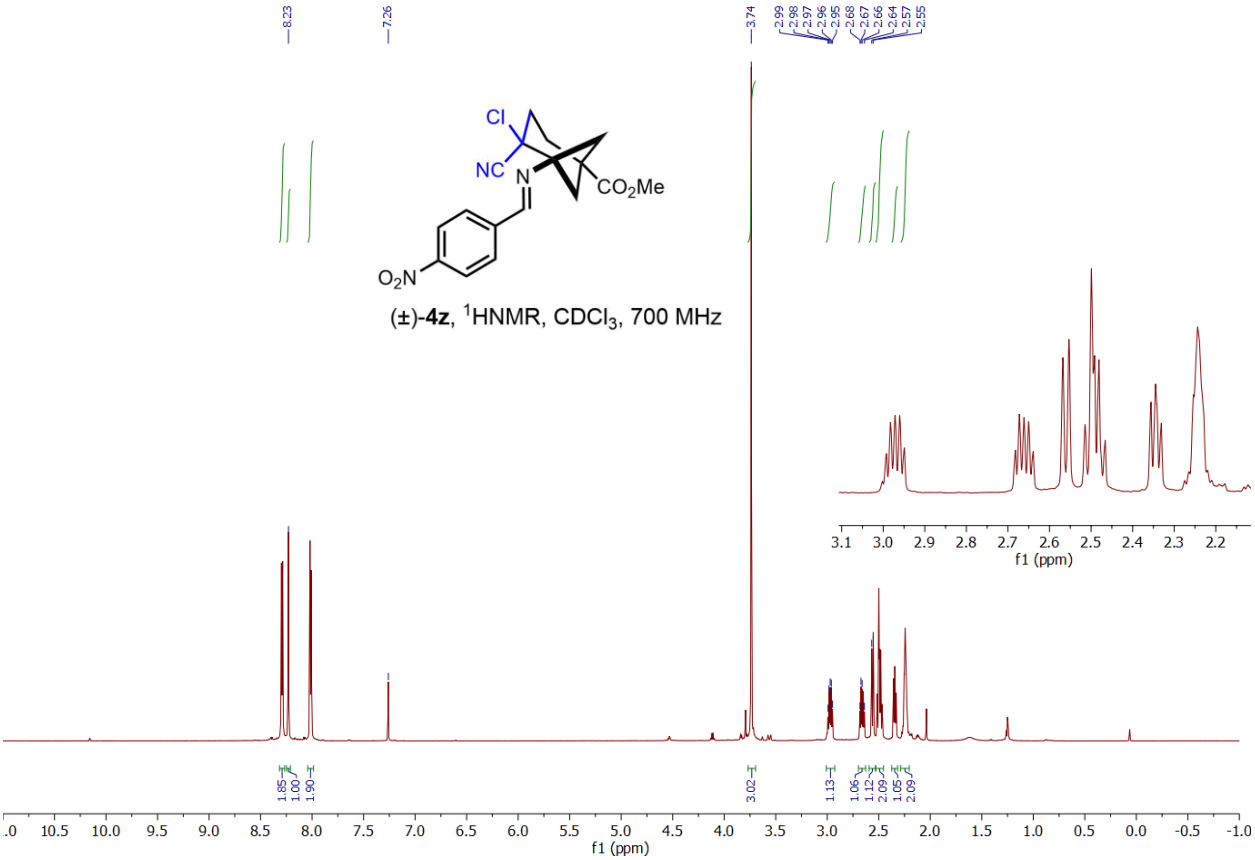
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.31-8.27 (m, 2H), 8.23 (s, 1H), 8.03-7.99 (m, 2H), 3.74 (s, 3H), 2.97 (dt, *J* = 15.1, 7.6 Hz, 1H), 2.66 (dt, *J* = 14.9, 7.5 Hz, 1H), 2.56 (d, *J* = 9.9 Hz, 1H), 2.53-2.45 (m, 2H), 2.37-2.32 (m, 1H), 2.28-2.20 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 173.6, 159.1, 149.8, 140.5, 129.7, 124.1, 118.3, 69.5, 63.4, 52.6, 41.2, 40.2, 36.2, 36.1, 27.2 ppm

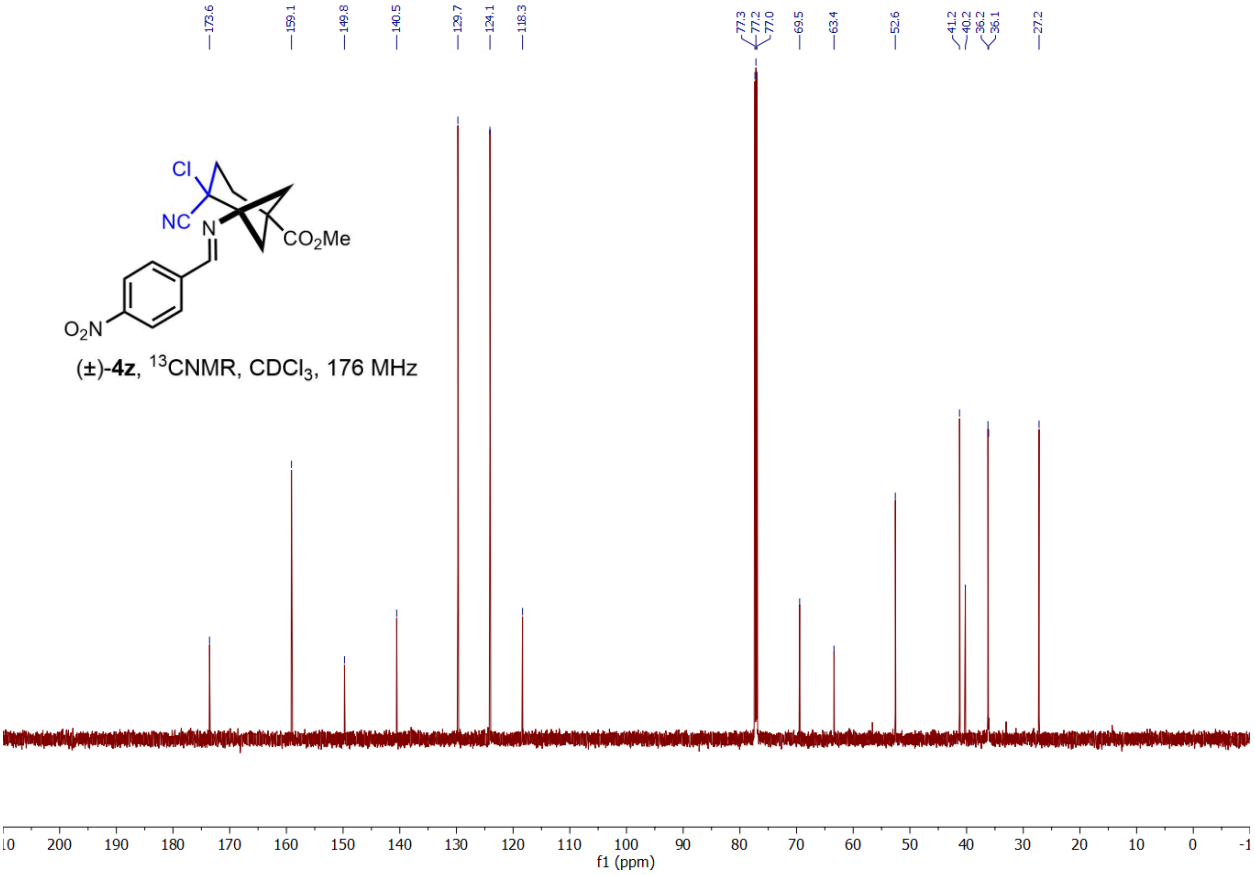
IR (neat): 2954, 2255, 1794, 1729, 1646, 1603, 1521, 1451, 1436, 1415, 1344, 1294, 1262, 1217, 1200, 1167, 1127, 1108, 1084, 1053, 1013, 978, 957, 913, 850, 837, 792, 748, 731, 691 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{17}H_{17}ClN_3O_4^+$: 362.0902, Found: 362.0900

R_f = 0.19 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

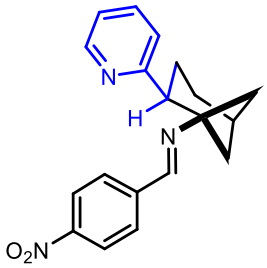


(±)-**4z**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4z**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4aa** :



EXPERIMENTAL PROCEDURE:

General procedure B was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), 2-vinylpyridine (0.324 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was combined with celite (2 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 5-40% ethyl acetate in hexanes to give (±)-**4aa** (48.6 mg, 0.151 mmol, 38%) as a faintly yellow solid.

Due to the surprisingly low isolated yield, the reaction was repeated as above 2 times but with only 3 hours of irradiation and either 7.5 or 15 equivalents of 2-vinylpyridine. To the crude reaction mixtures were added known amounts of 1,3,5-trimethoxybenzene. Q^1HNMR analysis was performed. A T_1 of 25 seconds was used during data acquisition to ensure meaningful integrations. These data are more reflective of 2-vinylpyridine's radical capturing aptitude.

Case of 15 equiv 2-vinylpyridine: (±)-**4aa** (52%), **5** (7%), remaining **2a** (10%)
Case of 7.5 equiv 2-vinylpyridine: (±)-**4aa** (48%), **5** (7%), remaining **2a** (14%)

Appearance: faintly yellow solid

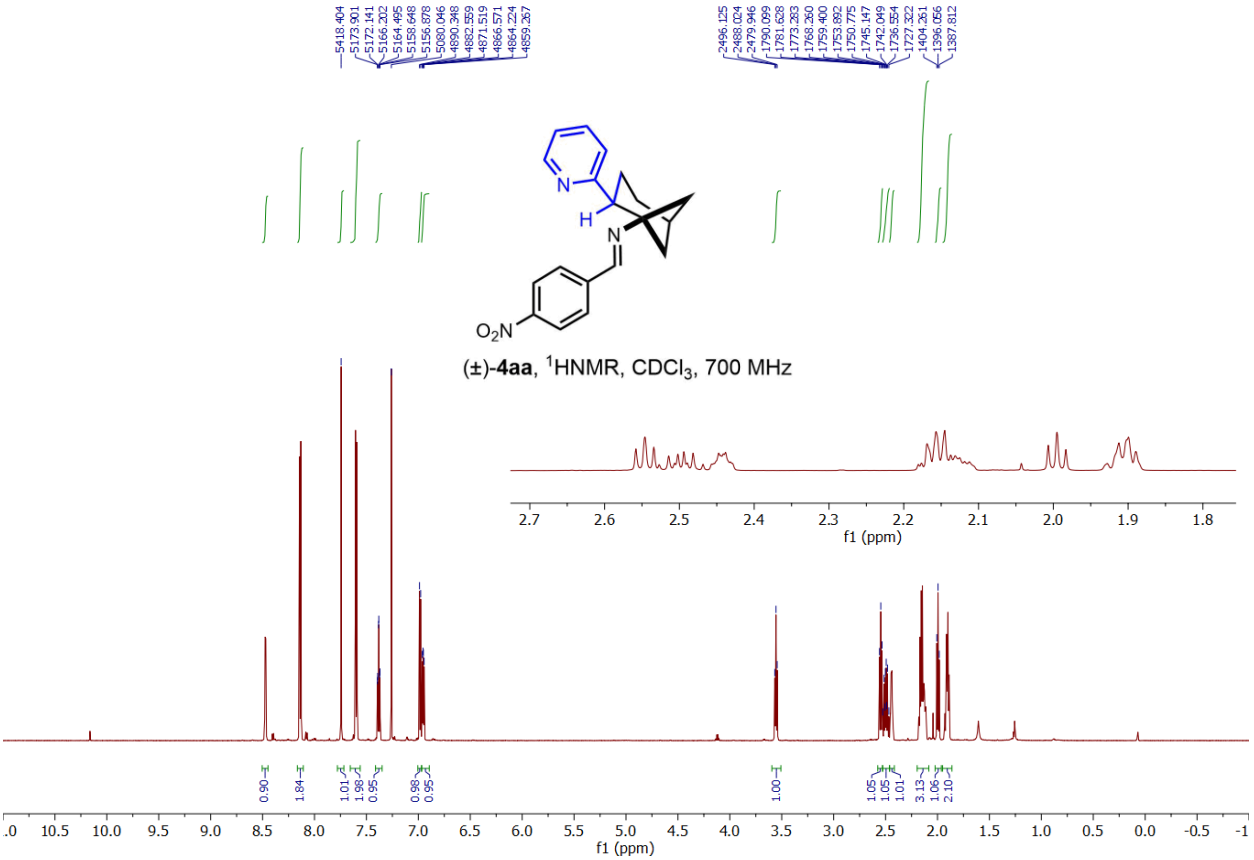
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.49 – 8.46 (m, 1H), 8.16 – 8.12 (m, 2H), 7.74 (s, 1H), 7.62 – 7.57 (m, 2H), 7.38 (td, *J* = 7.7, 1.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.95 (dd, *J* = 7.3, 4.9 Hz, 1H), 3.56 (app. t, *J* = 8.1 Hz, 1H), 2.55 (app. t, *J* = 8.4 Hz, 1H), 2.50 (app. dq, *J* = 14.4, 8.9 Hz, 1H), 2.46-2.42 (m, 1H), 2.19-2.10 (m, 3H), 2.00 (app. t, *J* = 8.2 Hz, 1H), 1.94-1.88 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 163.3, 155.0, 149.1, 148.9, 142.0, 135.4, 128.5, 124.3, 123.8, 121.3, 71.0, 52.5, 44.3, 32.0, 28.2, 27.3, 24.3 ppm

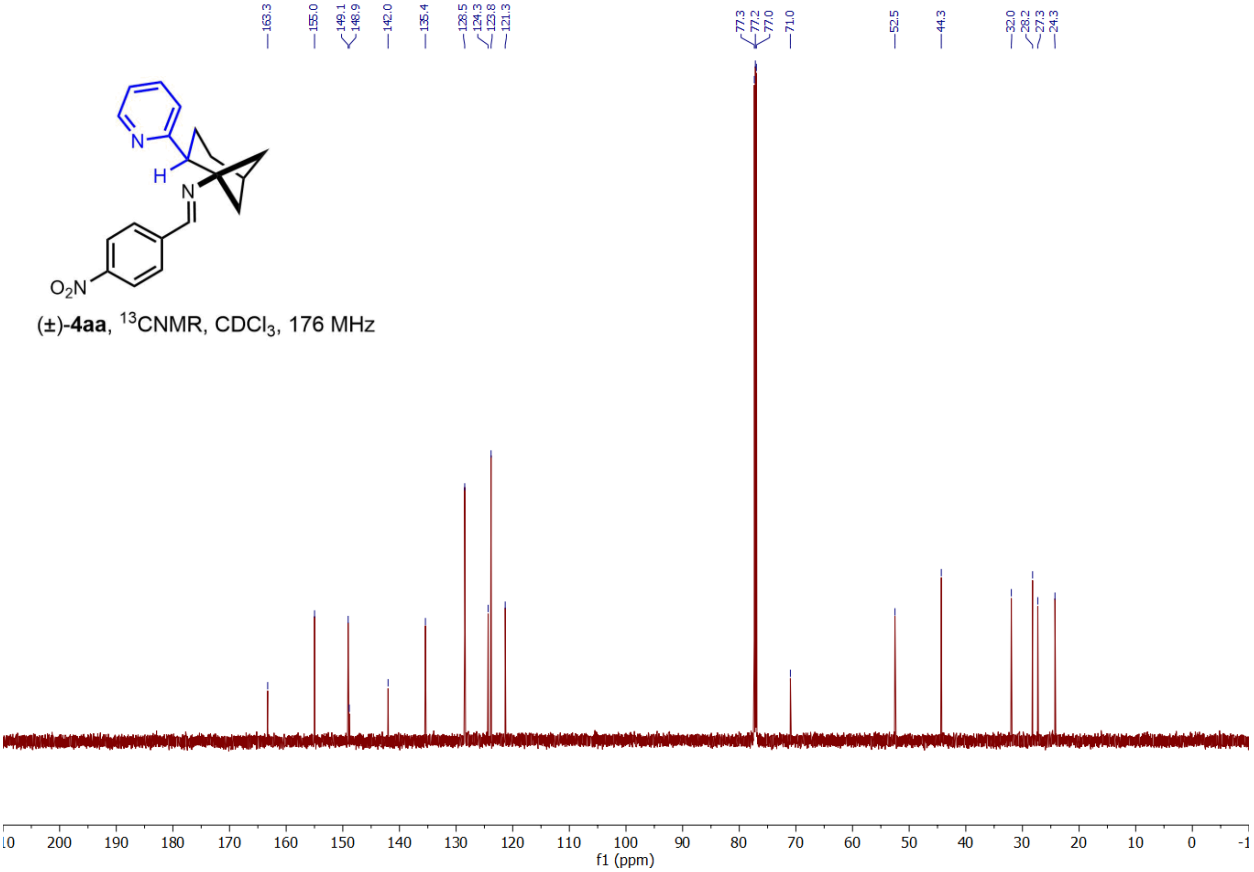
IR (neat): 3006, 2961, 2932, 2860, 1709, 1639, 1602, 1591, 1570, 1517, 1472, 1450, 1434, 1343, 1319, 1298, 1258, 1208, 1165, 1150, 1106, 1099, 1051, 1012, 996, 976, 961, 931, 858, 840, 825, 791, 760, 746, 691, 661 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{19}H_{20}N_3O_2^+$: 322.1550, Found: 322.1545

R_f = 0.14 (20% ethyl acetate : 80% hexanes), yellow spot, $KMnO_4$, UV

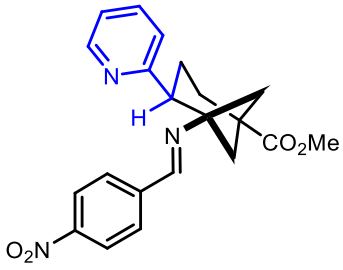


(±)-**4aa**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4aa**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4ab** :



EXPERIMENTAL PROCEDURE:
General procedure B was performed using **2b** (110 mg, 0.400 mmol, 1 equiv), 2-vinylpyridine (0.323 mL, 3.00 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv) and irradiating for 13 hours. The crude reaction mixture was directly loaded using toluene onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 12-97% ethyl acetate in hexanes to give (±)-**4ab** (98.4 mg, 0.259 mmol, 65%) as a faintly yellow solid.

Appearance: faintly yellow solid

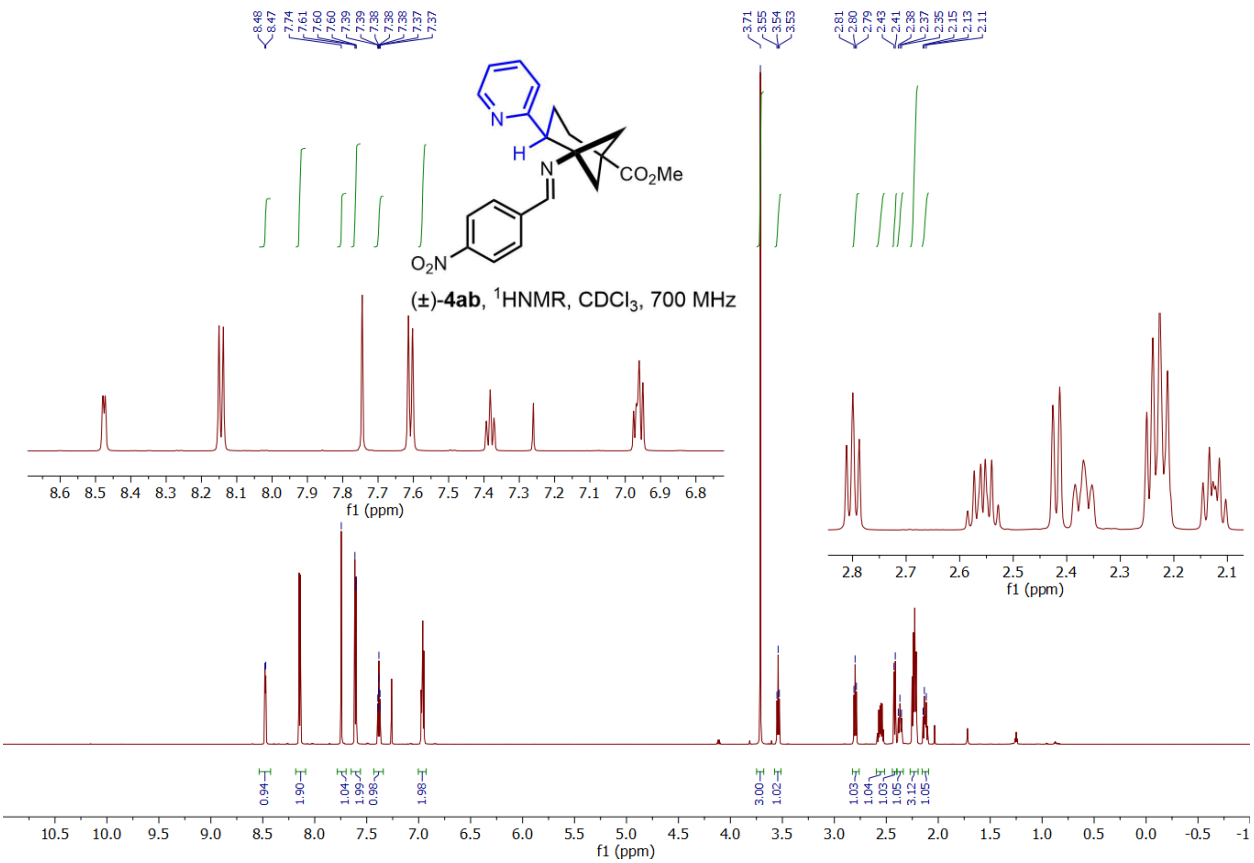
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.48 (d, *J* = 5.7 Hz, 1H), 8.16-8.12 (m, 2H), 7.74 (s, 1H), 7.63-7.59 (m, 2H), 7.40-7.36 (m, 1H), 6.99-6.94 (m, 2H), 3.71 (s, 3H), 3.54 (t, *J* = 8.0 Hz, 1H), 2.80 (t, *J* = 8.2 Hz, 1H), 2.60-2.52 (m, 1H), 2.42 (d, *J* = 8.9 Hz, 1H), 2.37 (t, *J* = 10.7 Hz, 1H), 2.26-2.19 (m, 3H), 2.16-2.09 (m, 1H) ppm

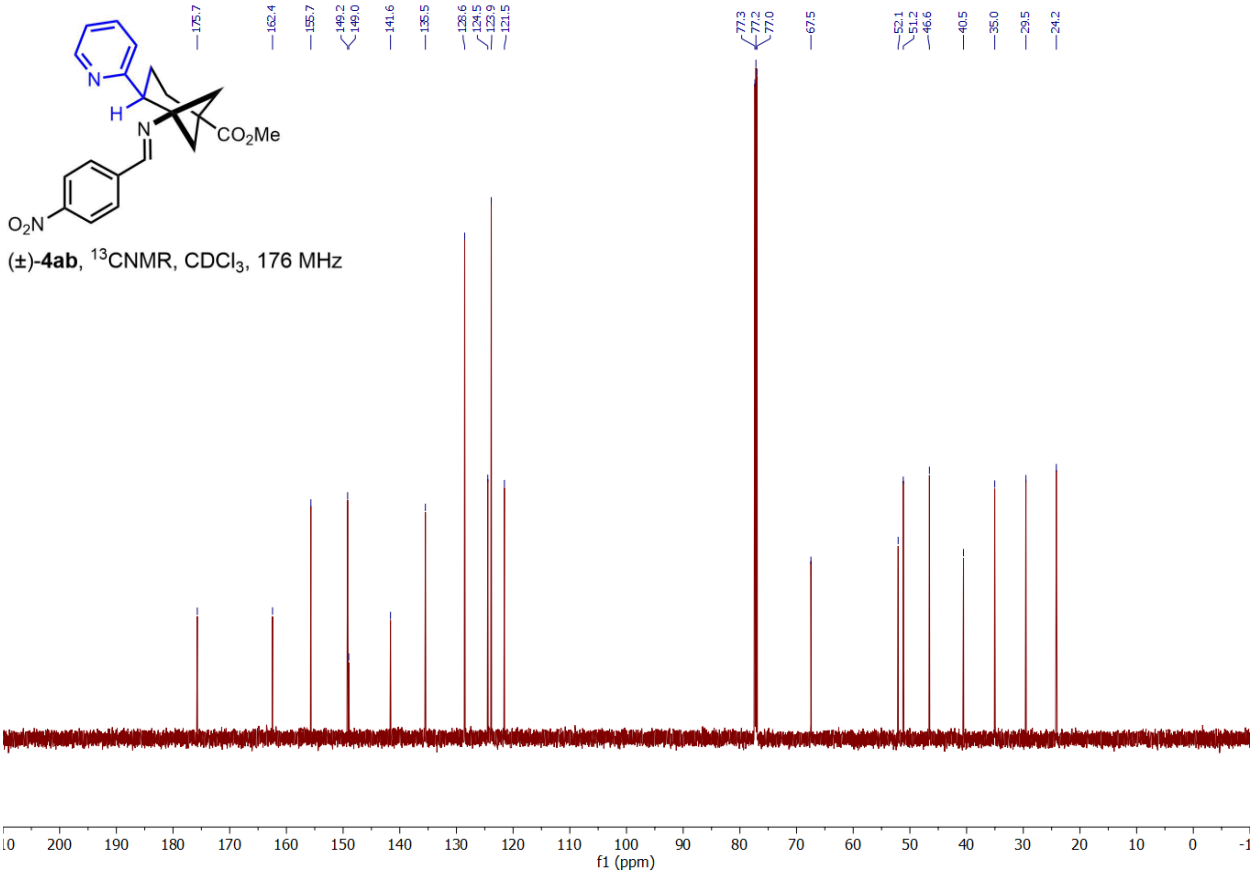
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.7, 162.4, 155.7, 149.2, 149.0, 141.6, 135.5, 128.6, 124.5, 123.9, 121.5, 67.5, 52.1, 51.2, 46.6, 40.5, 35.0, 29.5, 24.2 ppm

IR (neat): 2956, 2870, 1724, 1638, 1603, 1590, 1570, 1532, 1475, 1455, 1435, 1343, 1317, 1301, 1288, 1258, 1213, 1159, 1108, 1078, 1050, 1012, 995, 957, 928, 902, 887, 865, 838, 795, 757, 750, 691, 664 cm^{-1}

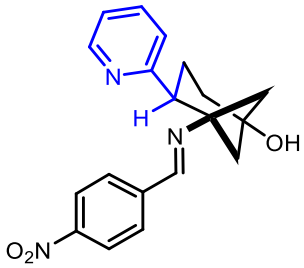
HRMS (ES+, m/z) calculated for $C_{21}H_{22}N_3O_4^+$: 380.1605, Found: 380.1602

R_f = 0.20 (30% ethyl acetate : 79% hexanes + 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


(±)-4ab, 1HNMR, CDCl3, 700 MHz
f1 (ppm)


(±)-4ab, 13CNMR, CDCl3, 176 MHz
f1 (ppm)

Compound (±)-**4ac**:



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 0.2 mmol imine vs typical 0.4 mmol imine) was performed using **2c** (46.4 mg, 0.200 mmol, 1 equiv), 2-vinylpyridine (0.162 mL, 1.50 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.4 mg, 0.002 mmol, 0.01 equiv) and irradiating for 18 hours. The crude reaction mixture was diluted with chloroform and concentrated onto celite (2 grams) and was dry loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 10-100% ethyl acetate in hexanes to give (±)-**4ac** (38.0 mg, 0.113 mmol, 56%) as a yellow oil.

Appearance: faintly yellow solid

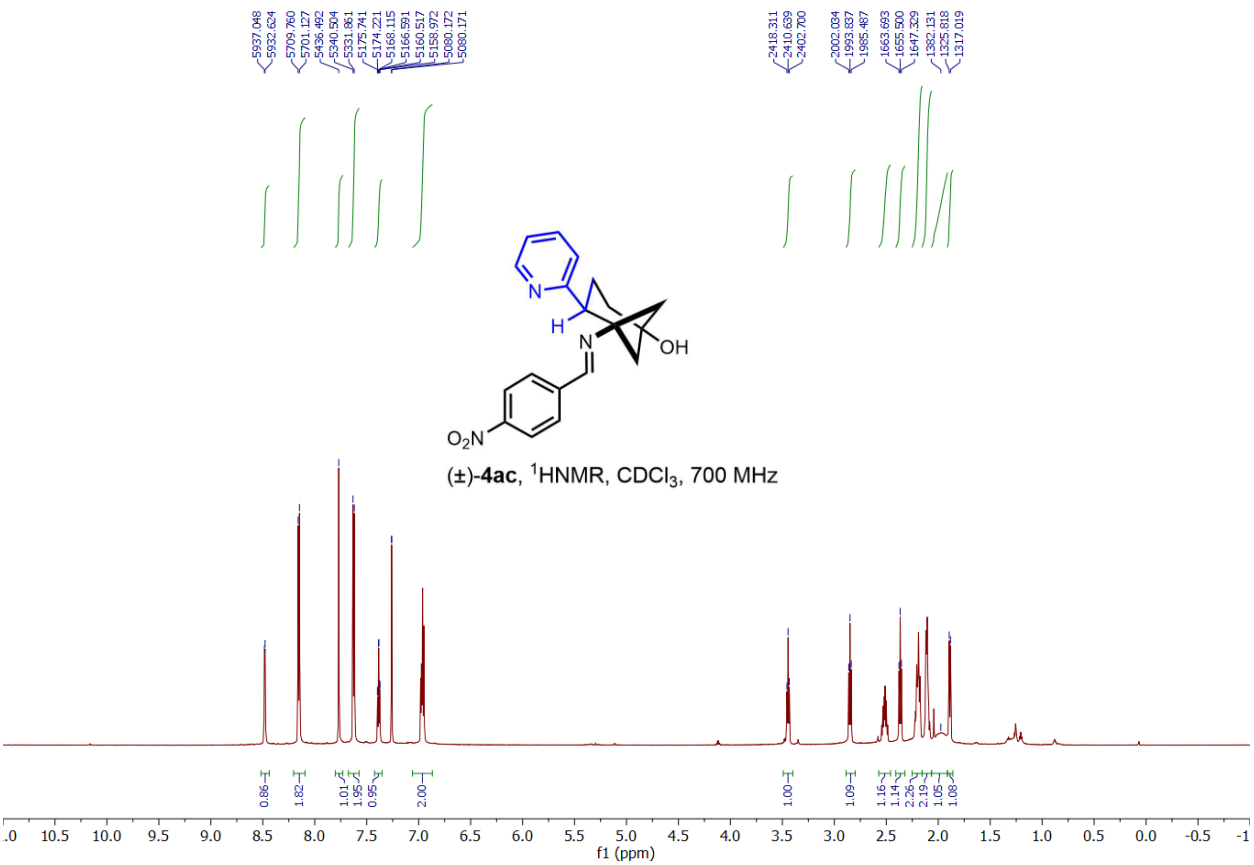
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.48 (d, *J* = 4.4 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 2H), 7.77 (s, 1H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.38 (td, *J* = 7.1, 1.5 Hz, 1H), 7.00-6.92 (m, 2H), 3.45 (app. t, *J* = 7.8 Hz, 1H), 2.85 (app. t, *J* = 8.3 Hz, 1H), 2.55-2.48 (m, 1H), 2.37 (app. t, *J* = 8.2 Hz, 1H), 2.25-2.16 (m, 2H), 2.15-2.06 (m, 2H), 1.98 (bs, 1H), 1.89 (d, *J* = 8.8 Hz, 1H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 162.6, 155.9, 149.2, 149.0, 141.7, 135.5, 128.6, 124.6, 123.9, 121.5, 69.7, 64.4, 51.4, 50.7, 40.4, 35.5, 24.6 ppm

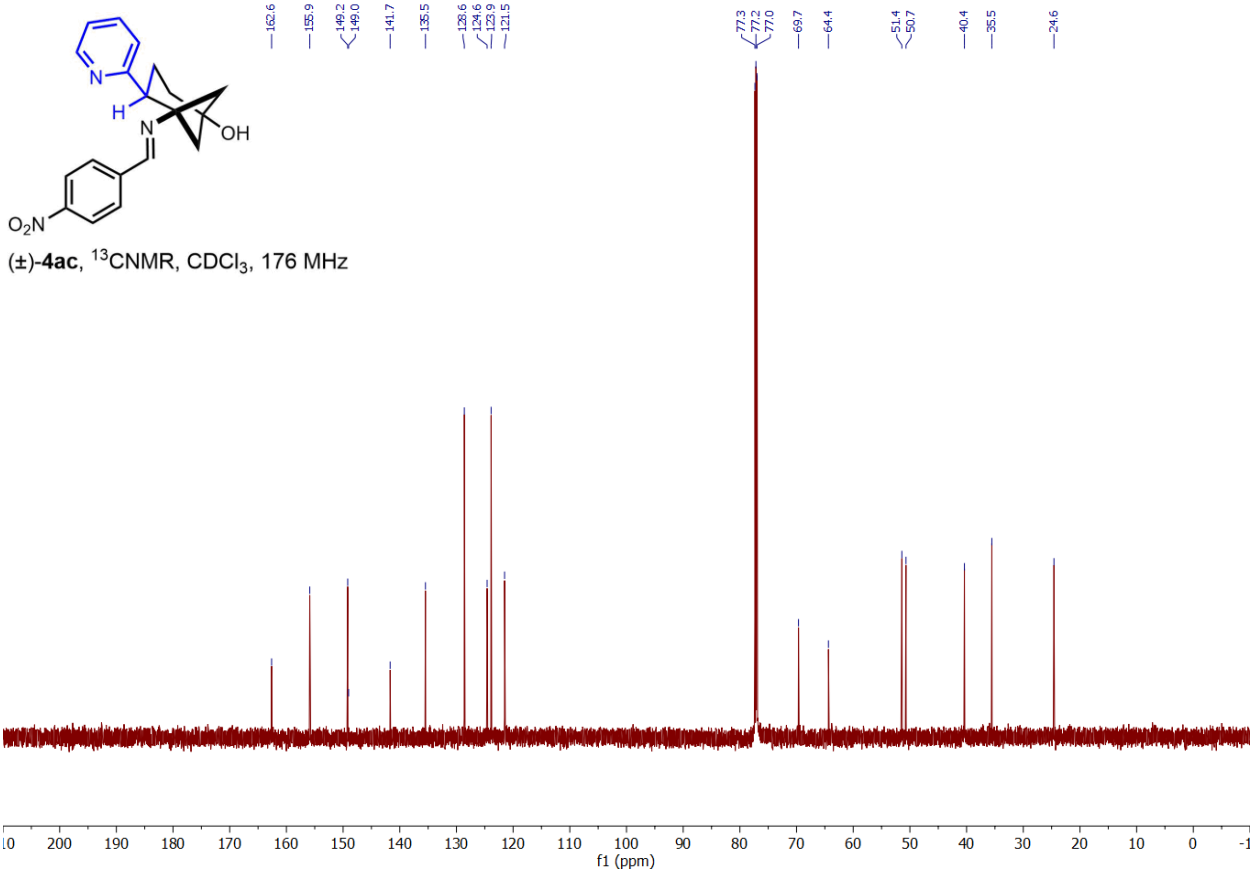
IR (neat): 3330, 2937, 2862, 1641, 1600, 1592, 1569, 1519, 1472, 1452, 1435, 1343, 1294, 1260, 1211, 1178, 1108, 1054, 1012, 995, 973, 949, 909, 853, 838, 786, 748, 727, 690 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{19}H_{20}N_3O_3^+$: 338.1499, Found: 338.1495

R_f = 0.08 (50% ethyl acetate: 49% hexanes : 1% aqueous NH_4OH), one yellow spot, $KMnO_4$, UV

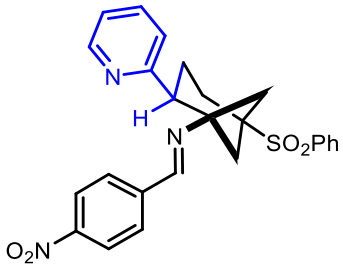


(±)-**4ac**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**4ac**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**4ad** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 0.087 mmol imine used rather than the standard 0.4 mmol) was performed using **2d** (31.0 mg, 0.087 mmol, 1 equiv), 2-vinylpyridine (0.0703 mL, 0.652 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.2 mg, 0.001 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was mixed with celite (2 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 10% ethyl acetate, 89% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 12-100% ethyl acetate in hexanes to give (±)-**4ad** (8.5 mg, 0.018 mmol, 21%) as a colorless oil.

Appearance: colorless oil

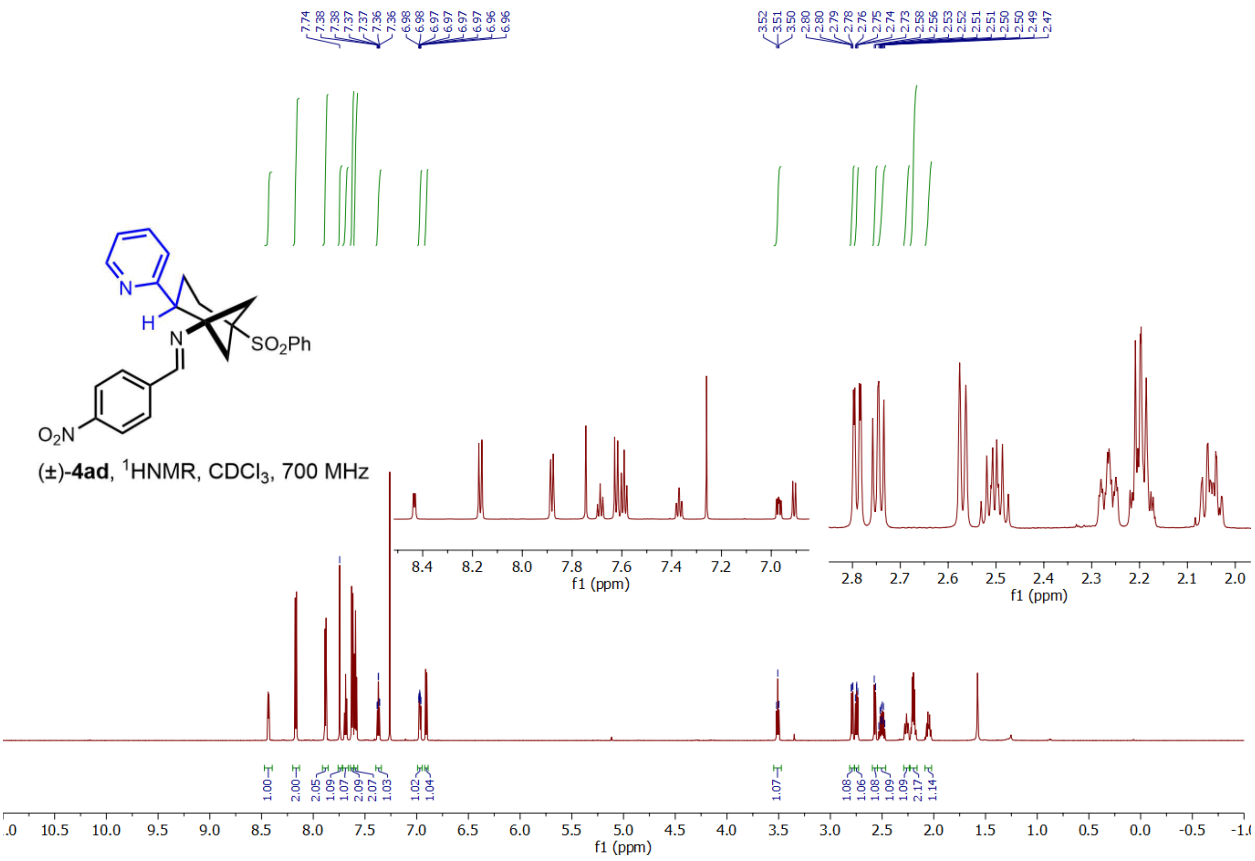
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.45-8.41 (m, 1H), 8.19-8.15 (m, 2H), 7.90-7.86 (m, 2H), 7.74 (s, 1H), 7.71-7.67 (m, 1H), 7.64-7.61 (m, 2H), 7.61-7.57 (m, 2H), 7.37 (td, *J* = 7.6, 1.8 Hz, 1H), 6.97 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H), 6.92-6.89 (m, 1H), 3.51 (app. t, *J* = 7.9 Hz, 1H), 2.79 (dd, *J* = 8.9, 2.1 Hz, 1H), 2.75 (dd, *J* = 8.9, 7.4 Hz, 1H), 2.57 (app. d, *J* = 9.0 Hz, 1H), 2.50 (dq, *J* = 14.5, 8.4 Hz, 1H), 2.29-2.24 (m, 1H), 2.23-2.16 (m, 2H), 2.08-2.02 (m, 1H) ppm

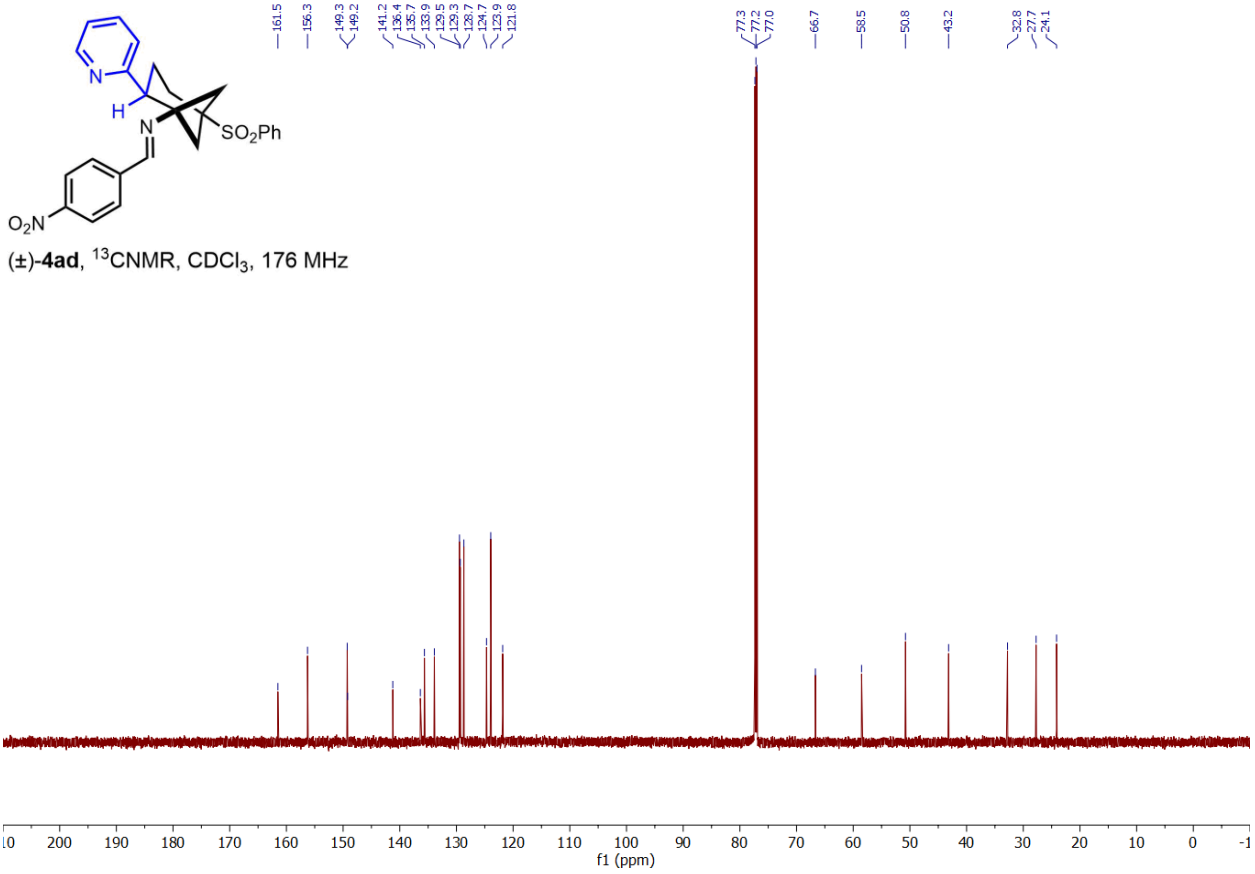
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.5, 156.3, 149.3, 149.2, 141.2, 136.4, 135.7, 133.9, 129.5, 129.3, 128.7, 124.7, 123.9, 121.8, 66.7, 58.5, 50.8, 43.2, 32.8, 27.7, 24.1 ppm

IR (neat): 2947, 1641, 1592, 1520, 1474, 1447, 1345, 1299, 1258, 1141, 1087, 995, 915, 854, 838, 787, 749, 722, 690 cm^{-1}

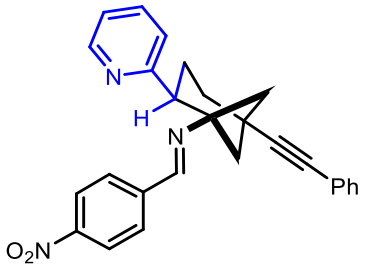
HRMS (ES+, m/z) calculated for $C_{25}H_{24}N_3O_4S^+$: 462.1482, Found: 462.1480

R_f = 0.15 (30% ethyl acetate : 69% hexanes : 1% aqueous NH4OH), yellow spot, $KMnO_4$, UV


(±)-4ad, ^{1}HNMR, CDCl$_3$, 700 MHz
f1 (ppm)


(±)-4ad, ^{13}CNMR, CDCl$_3$, 176 MHz
f1 (ppm)

Compound (±)-**4ae** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modification = 0.200 mmol imine used rather than the standard 0.400 mmol) was performed using **2e** (63.3 mg, 0.200 mmol, 1 equiv), 2-vinylpyridine (0.162 mL, 1.50 mmol, 7.5 equiv), and 2,2-dipyridyl disulfide (0.4 mg, 0.002 mmol, 0.01 equiv) and irradiating for 16 hours. The crude reaction mixture was mixed with celite (2 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 10% ethyl acetate, 89% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 10-100% ethyl acetate in hexanes. The impure material was resubjected to the same chromatographic conditions. Remaining impure material was mixed with celite (2 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 25% ethyl acetate, 74% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 50-100% dichloromethane in hexanes. In total, these purifications gave (±)-**4ae** (27.6 mg, 0.0655 mmol, 33%) as a yellow oil.

Appearance: yellow oil

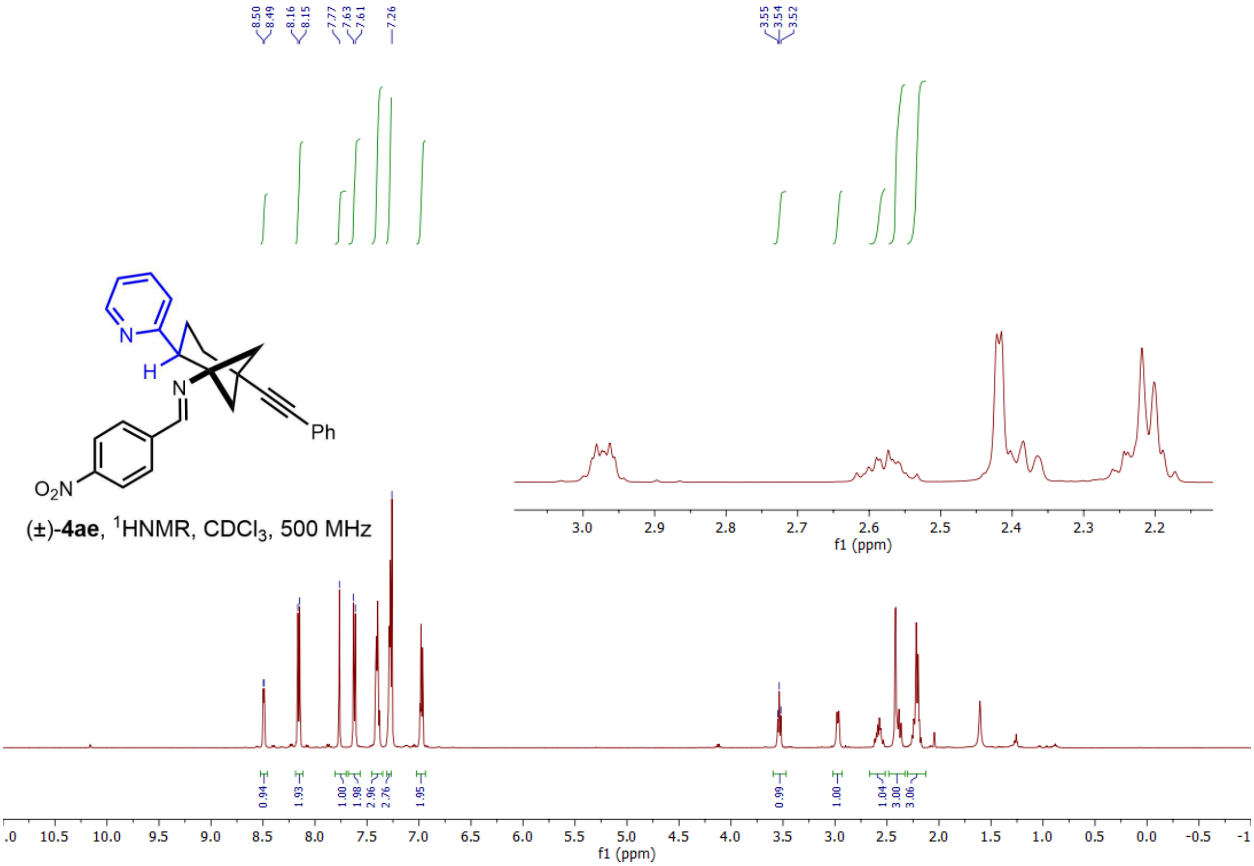
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.49 (d, *J* = 4.2 Hz, 1H), 8.16 (d, *J* = 8.7 Hz, 2H), 7.77 (s, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.44-7.36 (m, 3H), 7.31-7.26 (m, 3H), 7.01-6.94 (m, 2H), 3.54 (app. t, *J* = 7.6 Hz, 1H), 3.02-2.93 (m, 1H), 2.64-2.52 (m, 1H), 2.48-2.33 (m, 3H), 2.30-2.14 (m, 3H) ppm

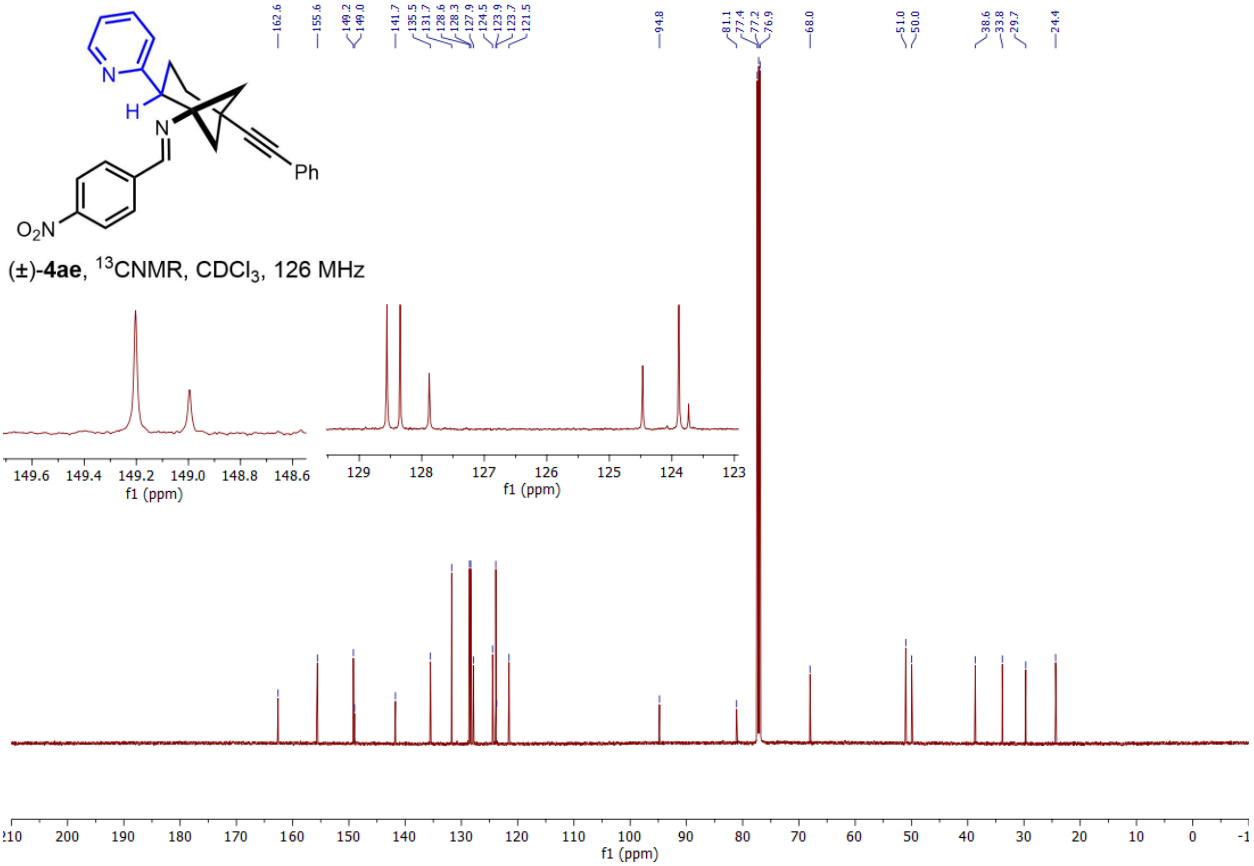
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 162.6, 155.6, 149.2, 149.0, 141.7, 135.5, 131.7, 128.6, 128.3, 127.9, 124.5, 123.9, 123.7, 121.5, 94.8, 81.1, 68.0, 51.0, 50.0, 38.6, 33.8, 29.7, 24.4 ppm

IR (neat): 2942, 2221, 1641, 1591, 1569, 1520, 1491, 1474, 1435, 1344, 1293, 1257, 1217, 1170, 1108, 1050, 1012, 995, 913, 853, 838, 790, 749, 691cm^{-1}

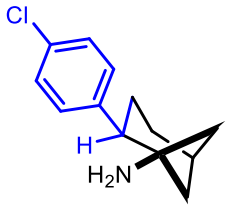
HRMS (ES+, m/z) calculated for $C_{27}H_{24}N_3O_2^+$: 422.1863, Found: 422.1861

R_f = 0.60 (30% ethyl acetate : 69% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


8.50
8.49
8.16
8.15
7.77
7.63
7.61
7.26
3.55
3.54
3.52
N
H
N
Ph
O2N
(±)-4ae, 1HNMR, CDCl3, 500 MHz
f1 (ppm)


162.6
155.6
149.2
149.0
141.7
135.5
131.7
128.6
128.3
127.9
124.5
123.9
123.7
121.5
94.8
81.1
77.4
77.2
76.9
68.0
51.0
50.0
38.6
33.8
29.7
24.4
N
H
N
Ph
O2N
(±)-4ae, 13CNMR, CDCl3, 126 MHz
f1 (ppm)

Compound (±)-**7a** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a stir bar was added **2a** (1.08 g, 5.00 mmol, 1 equiv), 2,2'-dipyridyldisulfide (11.0 mg, 0.050 mmol, 0.01 equiv), and 4-chlorostyrene (4.50 mL, 37.5 mmol, 7.5 equiv). The vial was sealed with a cap containing a Teflon-lined septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated with 2 390 nm Kessil lamps positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. The reaction mixture was allowed to cool to room temperature, then was transferred to a 250 mL round-bottom flask and sequentially diluted with acetonitrile (30 mL), water (10 mL), and acetic acid (10 mL) (with stirring). The headspace was flushed with argon and the mixture was stirred at room temperature for 24 hours. The mixture was then diluted with 1M aqueous HCl (100 mL) and extracted with diethyl ether (3 x 50 mL). The ethereal extracts (containing 4-chlorostryene, 4-nitrobenzaldehyde, acetic acid, and non-basic byproducts) were discarded. The aqueous layer was brought to pH ~ 12 with 3M aqueous NaOH and was extracted with diethyl ether (4 x 50 mL). The combined ethereal extracts were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give (±)-**7a** as a tan solid (451.6 mg, 2.04 mmol, 41%).

Appearance: Tan solid

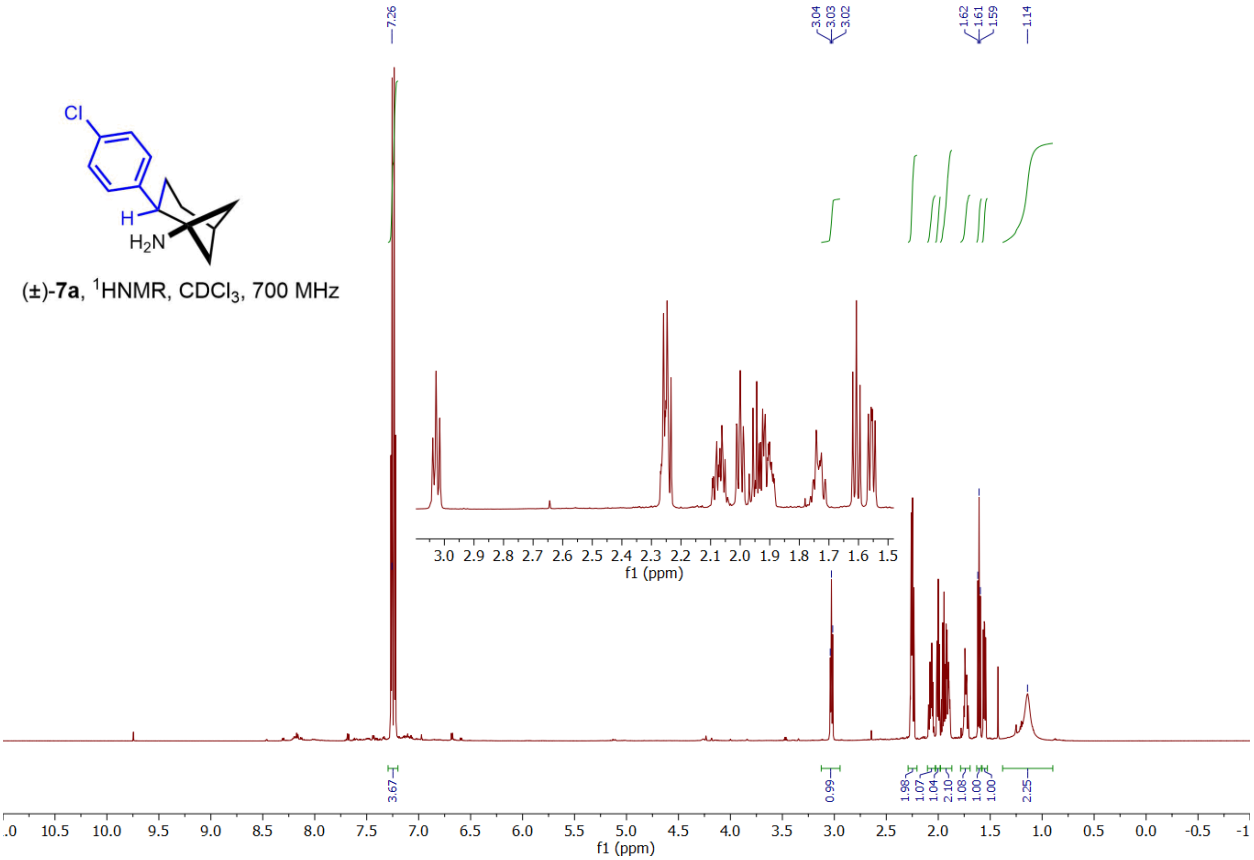
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.28-7.21 (m, 4H), 3.03 (app. t, *J* = 8.2 Hz, 1H), 2.28-2.21 (m, 2H), 2.10-2.03 (m, 1H), 2.02-1.98 (m, 1H), 1.98-1.88 (m, 2H), 1.78-1.70 (m, 1H), 1.61 (app. t, *J* = 8.6 Hz, 1H), 1.58-1.53 (m, 1H), 1.14 (bs, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 143.2, 132.2, 129.6, 128.6, 58.4, 51.3, 46.5, 37.4, 28.5, 27.6, 26.7 ppm

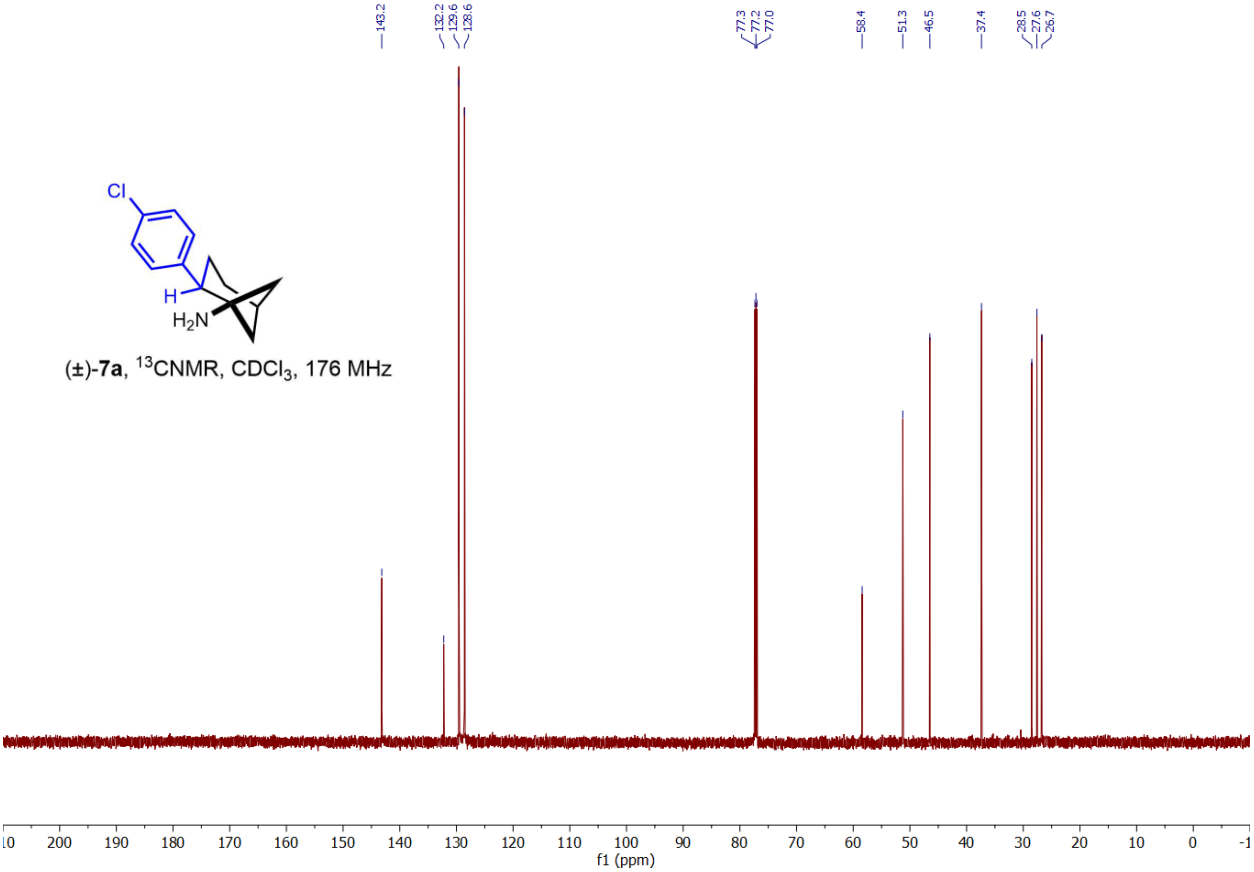
IR (neat): 3367, 2941, 2858, 1598, 1518, 1489, 1452, 1411, 1345, 1308, 1280, 1267, 1213, 1186, 1173, 1108, 1087, 1028, 1009, 963, 947, 932, 887, 863, 825, 810, 753, 723, 696, 670 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{13}H_{17}ClN^+$: 222.1044, Found: 222.1051

R_f = 0.50 (99% ethyl acetate + 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

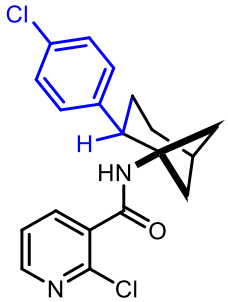


(±)-**7a**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**7a**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**8a** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7a** (62.1 mg, 0.280 mmol, 1 equiv) and the vial was capped and put under argon. Triethylamine (0.195 mL, 1.40 mmol, 5 equiv) and and dichloromethane (4.4 mL) were sequentially added. Next, a mixture of 2-Chloronicotinoyl chloride (73.9 mg, 0.420 mmol, 1.5 equiv) in dichloromethane (0.9 mL) was added to the vial over 2 minutes via syringe at room temperature. Some smoking was observed during the addition. The vial was sealed shut under argon, the cap being wrapped with parafilm, then placed in an aluminum heating block at 40 °C and allowed to stir for 2 hours. The reaction mixture was transferred to a round-bottom flask and concentrated onto celite (3 grams). The resulting solid mixture was dry-loaded atop a silica column and eluted with 12-100% ethyl acetate in hexanes to give (±)-**8a** (76.7 mg, 0.212 mmol, 76%) as a faintly yellow solid.

Note: The reaction was repeated as above but run instead at room temperature for 2.5 hours and gave a comparable yield of (±)-**8a** (75.2 mg, 0.208 mmol, 74%) as a faintly yellow solid.

Appearance: Faintly yellow solid

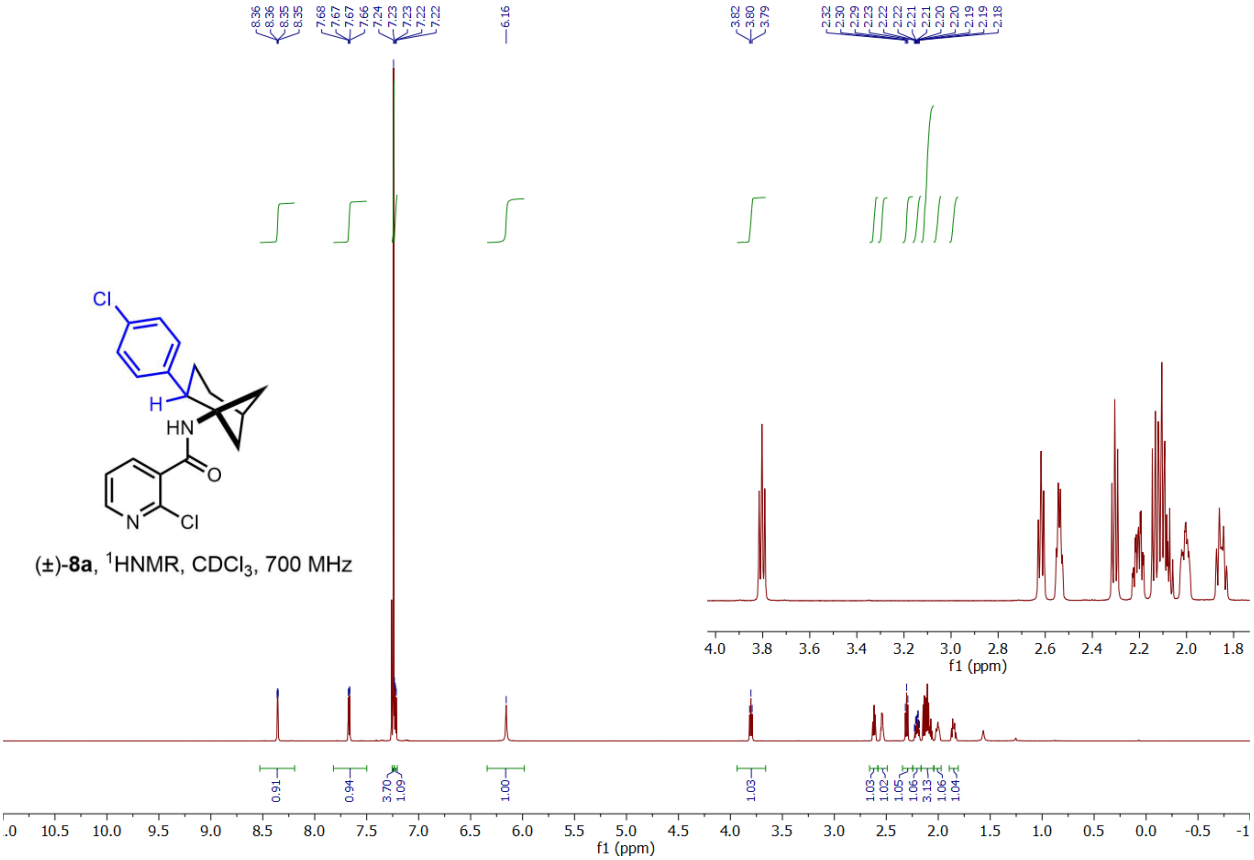
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.36 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.67 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.24 (s, 4H), 7.22 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.16 (s, 1H) 3.80 (app. t, *J* = 8.4 Hz, 1H), 2.64-2.59 (m, 1H), 2.56-2.51 (m, 1H), 2.30 (app. t, *J* = 8.5 Hz, 1H), 2.21 (dtd, *J* = 14.4, 7.8, 2.7 Hz, 1H), 2.16-2.05 (m, 3H), 2.04-1.97 (m, 1H), 1.88-1.82 (m, 1H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 163.4, 150.8, 147.1, 142.6, 139.3, 132.6, 131.5, 129.7, 128.6, 122.8, 59.9, 48.0, 44.4, 32.1, 29.6, 28.2, 26.7 ppm

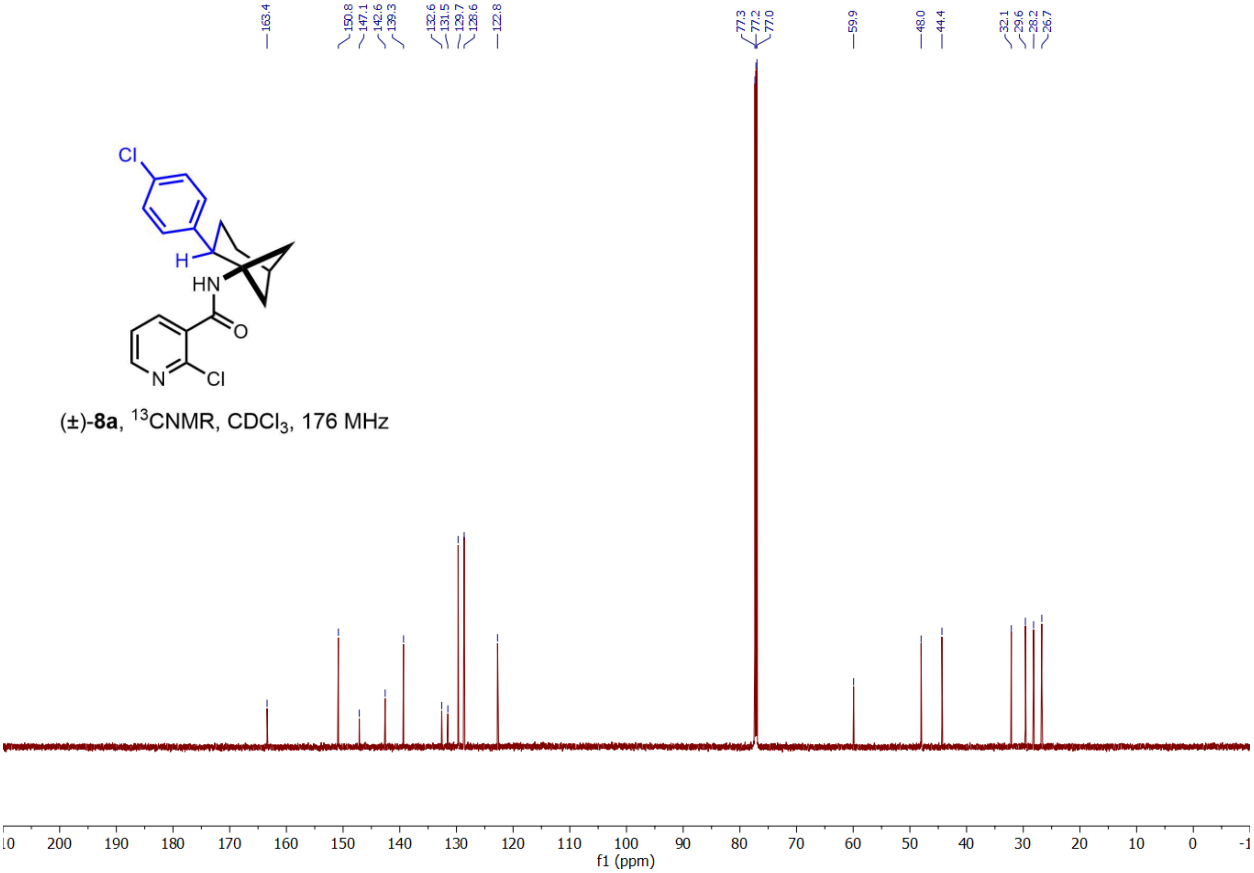
IR (neat): 3230, 3053, 2947, 2863, 1634, 1582, 1537, 1492, 1452, 1397, 1314, 1290, 1256, 1179, 1153, 1125, 1089, 1072, 1014, 959, 897, 876, 847, 829, 811, 770, 750, 694, 679 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{19}H_{19}Cl_2N_2O^+$: 361.0869, Found: 361.0873

R_f = 0.13 (30% ethyl acetate in hexanes), one yellow spot, $KMnO_4$, UV

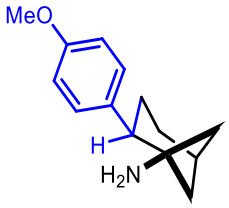


(±)-**8a**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**8a**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**7b** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a stir bar was added **2a** (216 mg, 1.00 mmol, 1 equiv), 2,2'-dipyridyldisulfide (2.20 mg, 0.010 mmol, 0.01 equiv), and 4-methoxystyrene (0.997 mL, 7.50 mmol, 7.5 equiv). The vial was sealed with a Teflon-lined cap and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 18 hours with 2 390 nm Kessil PR160L lamps positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. The reaction mixture was allowed to cool to room temperature, then was sequentially diluted with acetonitrile (3 mL), water (1 mL), and acetic acid (1 mL) (with stirring). The headspace was flushed with argon and the mixture was stirred at room temperature for 20 hours. The mixture was then diluted with 0.5 M aqueous HCl (20 mL) and extracted with diethyl ether (3 x 25 mL). The ethereal extracts (containing styrene, 4-nitrobenzaldehyde, acetic acid, and non-basic byproducts) were discarded. The aqueous layer was brought to pH ~ 12 with 2M aqueous NaOH and was extracted with ethyl acetate (4 x 25 mL). The combined ethyl acetate extracts were washed with brine (2 x 25 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude (±)-**7b** (~90 mg) as a dark brown solid. ^{1}HNMR analysis showed significant impurities. The mixture was concentrated onto celite and loaded atop a silica column (that had been pre-neutralized by eluting with 3 column volumes of 50% ethyl acetate : 49% hexanes : 1% Et_3N). Elution with 100% ethyl acetate gave (±)-**7b** (52.7 mg, 0.243 mmol, 24%) as a beige solid.

Appearance: beige solid

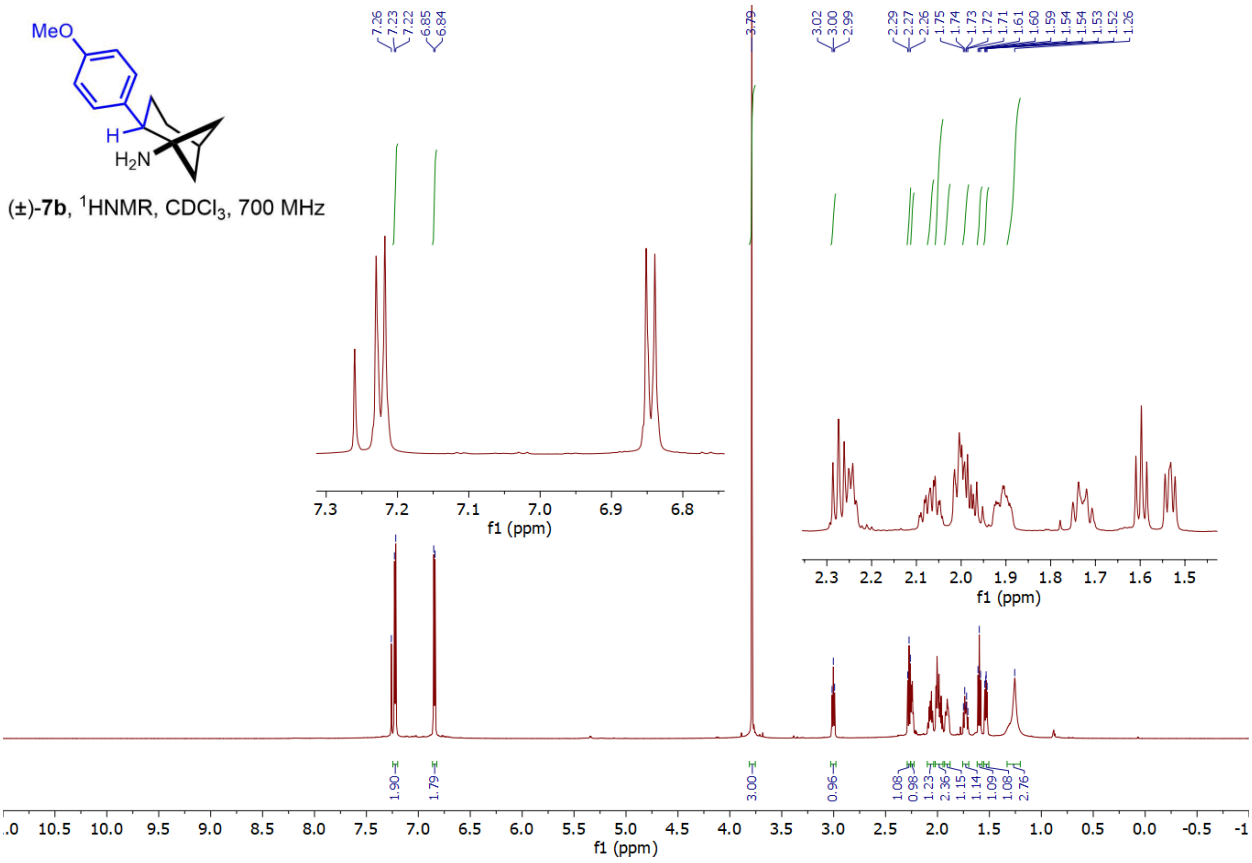
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.24-7.21 (m, 2H), 6.86-6.83 (m, 2H), 3.79 (s, 3H), 3.00 (app. t, *J* = 8.4 Hz, 1H), 2.27 (app. t, *J* = 8.8 Hz, 1H), 2.26-2.23 (m, 1H), 2.10-2.04 (m, 1H), 2.02-1.94 (m, 2H), 1.93-1.88 (m, 1H), 1.73 (dt, *J* = 12.6, 8.8 Hz, 1H), 1.60 (app. t, *J* = 8.5 Hz, 1H), 3.00 (dd, *J* = 9.1, 6.6 Hz, 1H), 1.26 (bs, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 158.3, 136.7, 129.2, 113.9, 58.5, 55.4, 51.0, 46.5, 37.5, 28.7, 27.7, 26.8 ppm

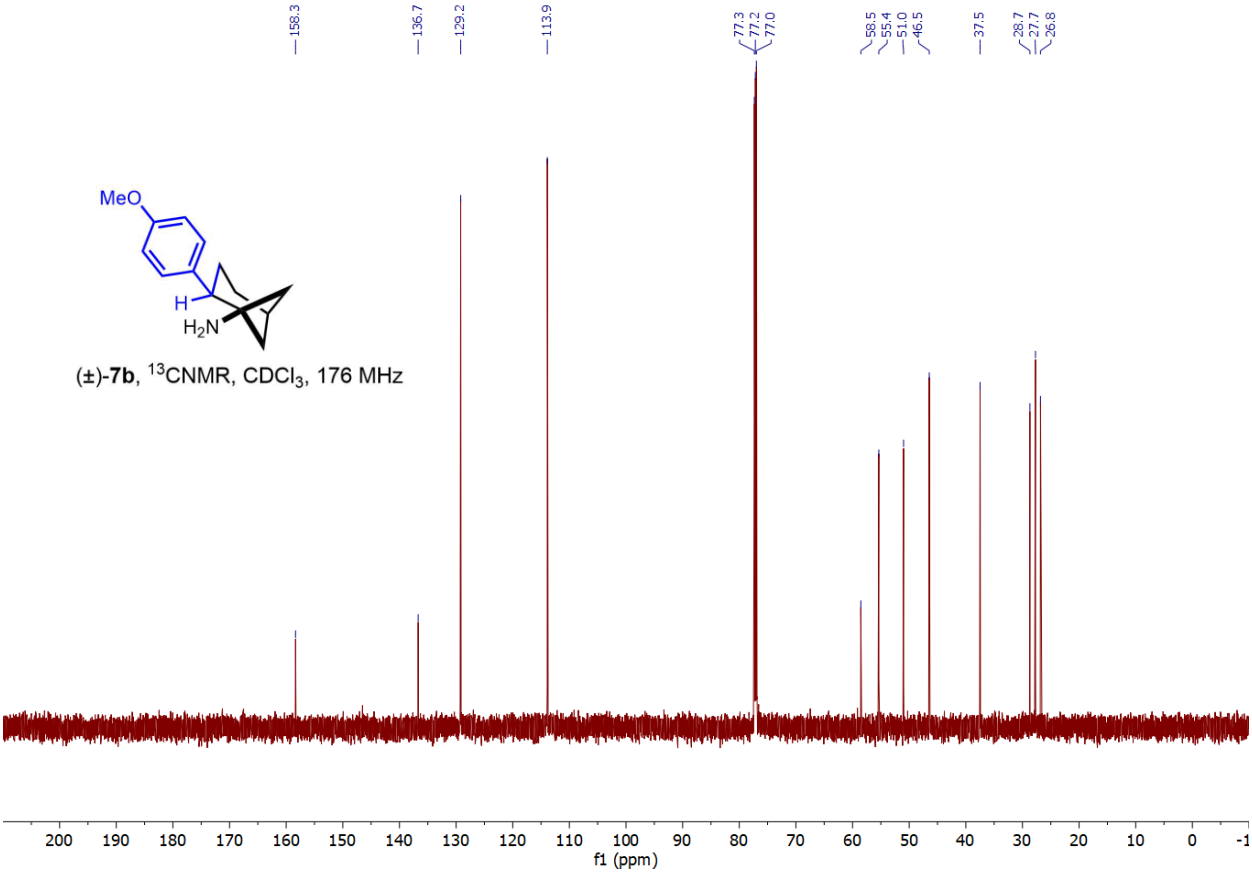
IR (neat): 3357, 2947, 2857, 1608, 1511, 1455, 1442, 1345, 1302, 1277, 1249, 1213, 1173, 1149, 1110, 1032, 976, 942, 927, 892, 867, 827, 810, 783, 739, 724, 685 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{14}H_{20}NO^+$: 218.1539, Found: 218.1534

R_f = 0.31 (99% ethyl acetate : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

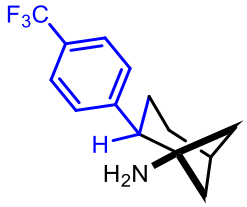


(±)-**7b**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**7b**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**7c** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial was added **2a** (432.0 mg, 2.00 mmol, 1 equiv), 4-(trifluoromethyl)styrene (2.21 mL, 15 mmol, 7.5 equiv), and 2,2'-dipyridyldisulfide (0.9 mg, 0.02 mmol, 0.01 equiv). The vial was sealed with a cap containing a Teflon-lined septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 36 hours with two 390 nm Kessil PR160L lamps positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. Following irradiation, the mixture was transferred to a 100 mL round-bottom flask equipped with a magnetic stir bar and diluted with acetonitrile (15 mL), water (5 mL), and acetic acid (5 mL). The headspace was flushed with argon, the flask sealed with a rubber septum, and the mixture was stirred at room temperature for 20 hours under argon (atmosphere maintained by balloon). The mixture was then diluted with aqueous 1M HCl (40 mL) and washed with diethyl ether (3 x 50 mL).The organic layer was neutralized with saturated sodium bicarbonate solution (200 mL) and extracted with diethyl ether (4 x 100 mL). The combined ethereal fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The sample was diluted with ethyl acetate and was concentrated onto 3 grams celite and loaded atop a silica column that had been pre-neutralized (by eluting with 3 column volumes of 10% ethyl acetate : 89% hexanes : 1% triethylamine). Elution with 12-100% ethyl acetate in hexanes gave (±)-**7c** (123.4 mg, 0.483 mmol, 24%) as a beige solid.

Appearance: beige solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.55 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 3.12 (app. t, *J* = 8.2 Hz, 1H), 2.30-2.25 (m, 2H), 2.12-2.06 (m, 1H), 2.01 (app. t, *J* = 8.1 Hz, 1H), 1.99-1.90 (m, 2H), 1.78-1.72 (m, 1H), 1.64 (app. t, *J* = 8.6 Hz, 1H), 1.59 (dd, *J* = 9.3, 6.6 Hz, 1H), 1.29 (bs, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 148.9, 128.8 (q, *J* = 32.3 Hz), 128.5, 125.4 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.8 Hz), 58.5, 51.7, 46.5, 37.3, 28.4, 27.5, 26.7 ppm

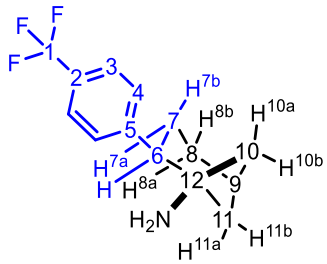
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -63.4 (s) ppm

IR (neat): 3375, 3315, 2943, 2867, 1616, 1520, 1451, 1420, 1324, 1282, 1262, 1213, 1187, 1163, 1107, 1065, 1010, 961, 937, 921, 889, 862, 838, 803, 749, 692 cm^{-1}

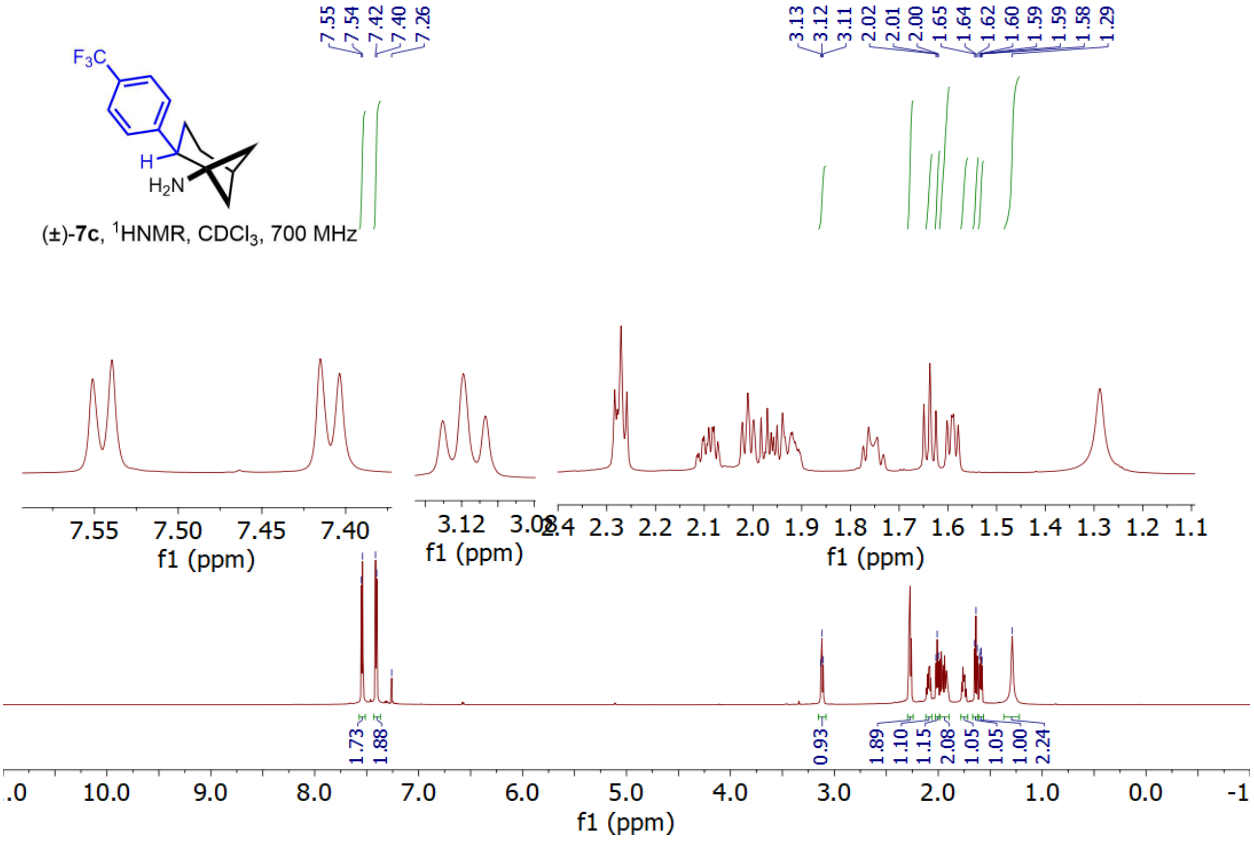
HRMS (ES+, m/z) calculated for $C_{14}H_{17}F_3N^+$: 256.1308, Found: 256.1310

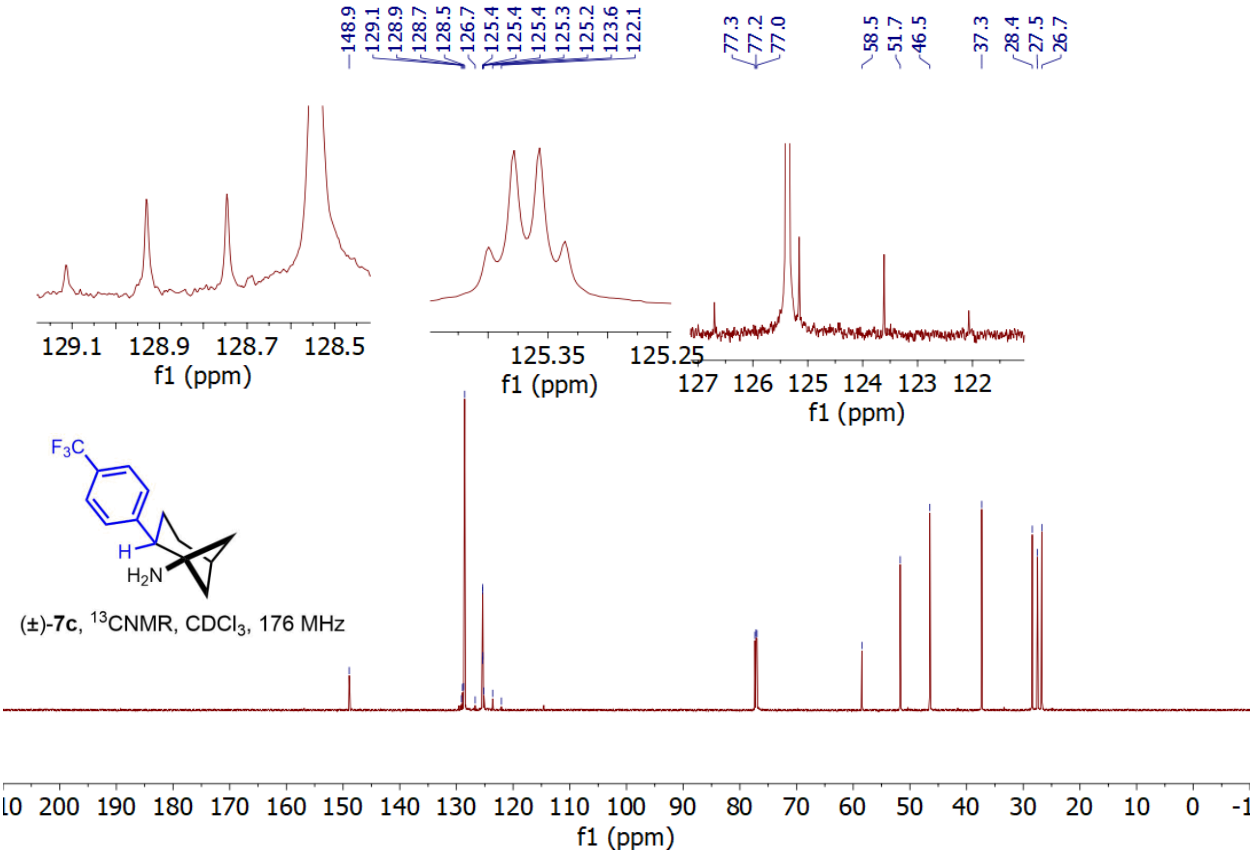
R_f = 0.11 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

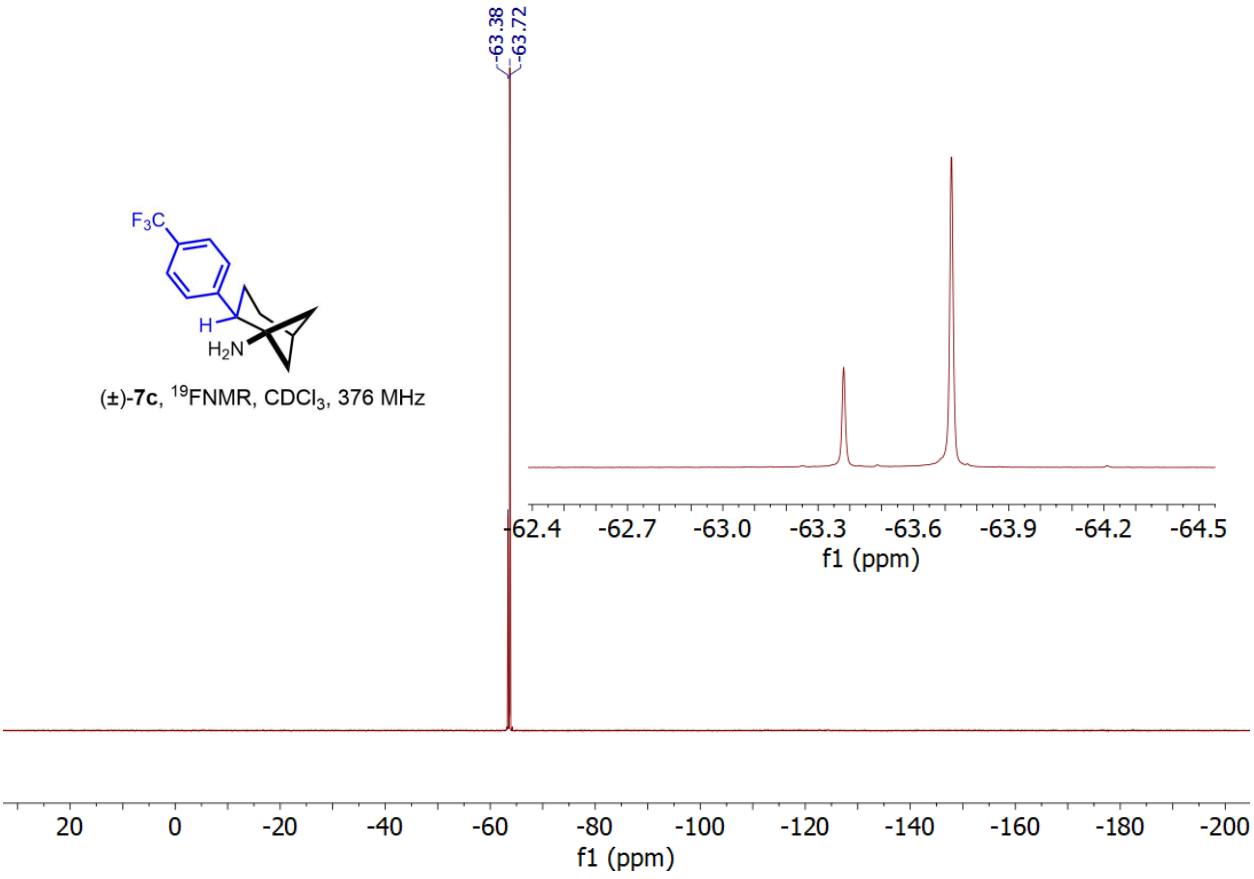
Complete assignment of ^{1}H and ^{13}C NMR signals

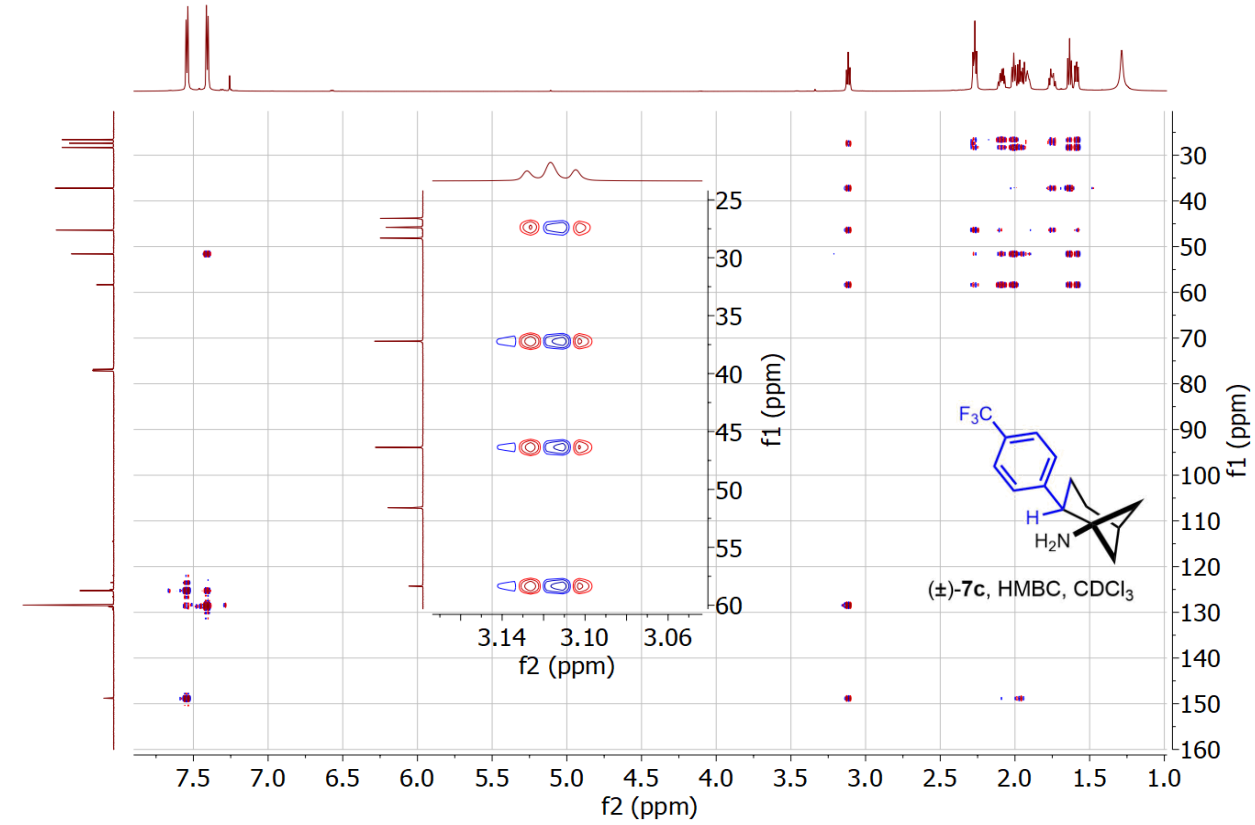


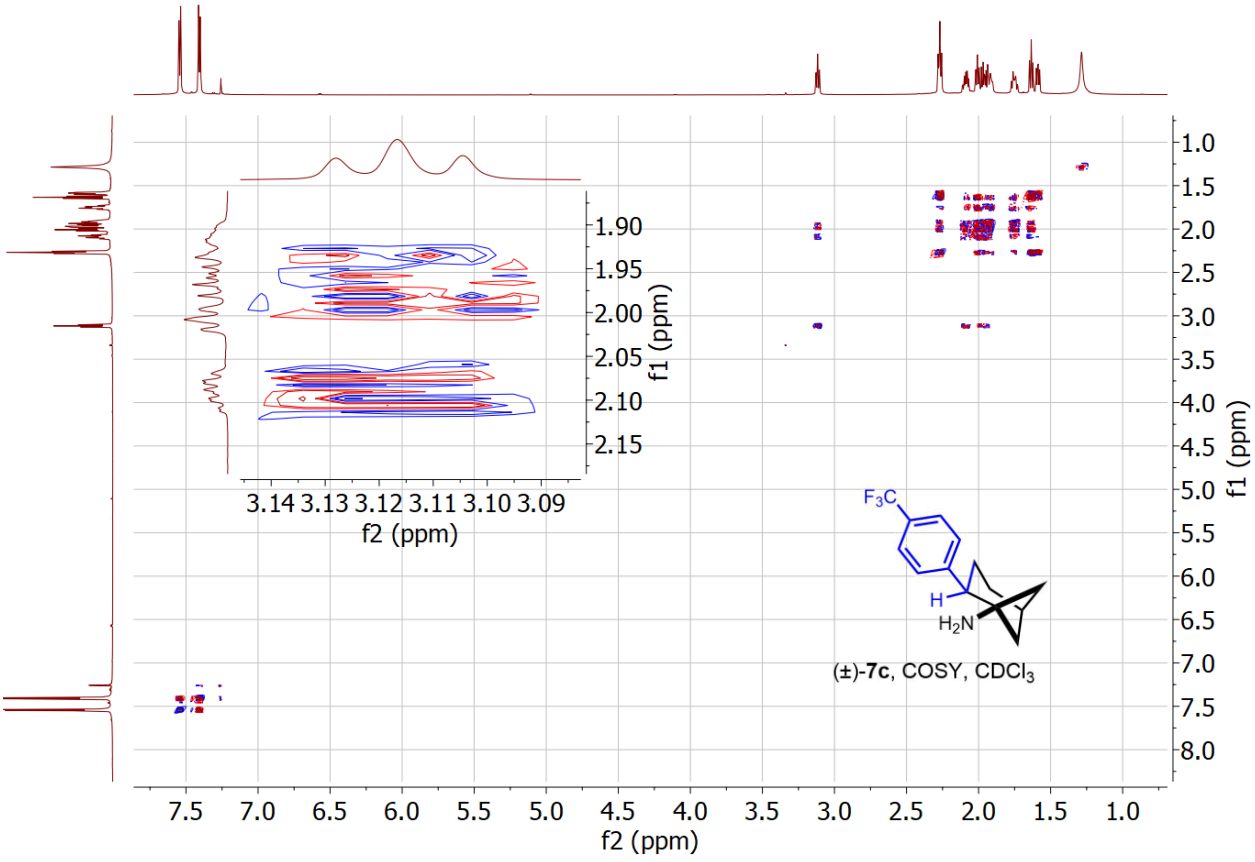
Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	124.4 (q, J = 271.8 Hz)		3	7.55 (d, J = 8.1 Hz, 2H)
2	128.8 (q, J = 32.3 Hz)		4	7.41 (d, J = 8.0 Hz, 2H)
3	125.4 (q, J = 3.8 Hz)		6	3.12 (app. t, J = 8.2 Hz, 1H)
4	128.5		7a	2.12-2.06 (m, 1H)
5	148.9		7b	one of 1.99-1.90 (m, 2H)
6	51.7		8a	1.78-1.72 (m, 1H)
7	27.5		8b	one of 1.99-1.90 (m, 2H)
8	28.4		9	one of 2.30-2.25 (m, 2H)
9	26.7		10a	one of 2.30-2.25 (m, 2H)
10	37.3		10b	1.59 (dd, J = 9.3, 6.6 Hz, 1H)
11	46.5		11a	1.64 (app. t, J = 8.6 Hz, 1H)
12	58.5		11b	2.01 (app. t, J = 8.1 Hz, 1H)
			NH2	1.29 (bs, 2H)

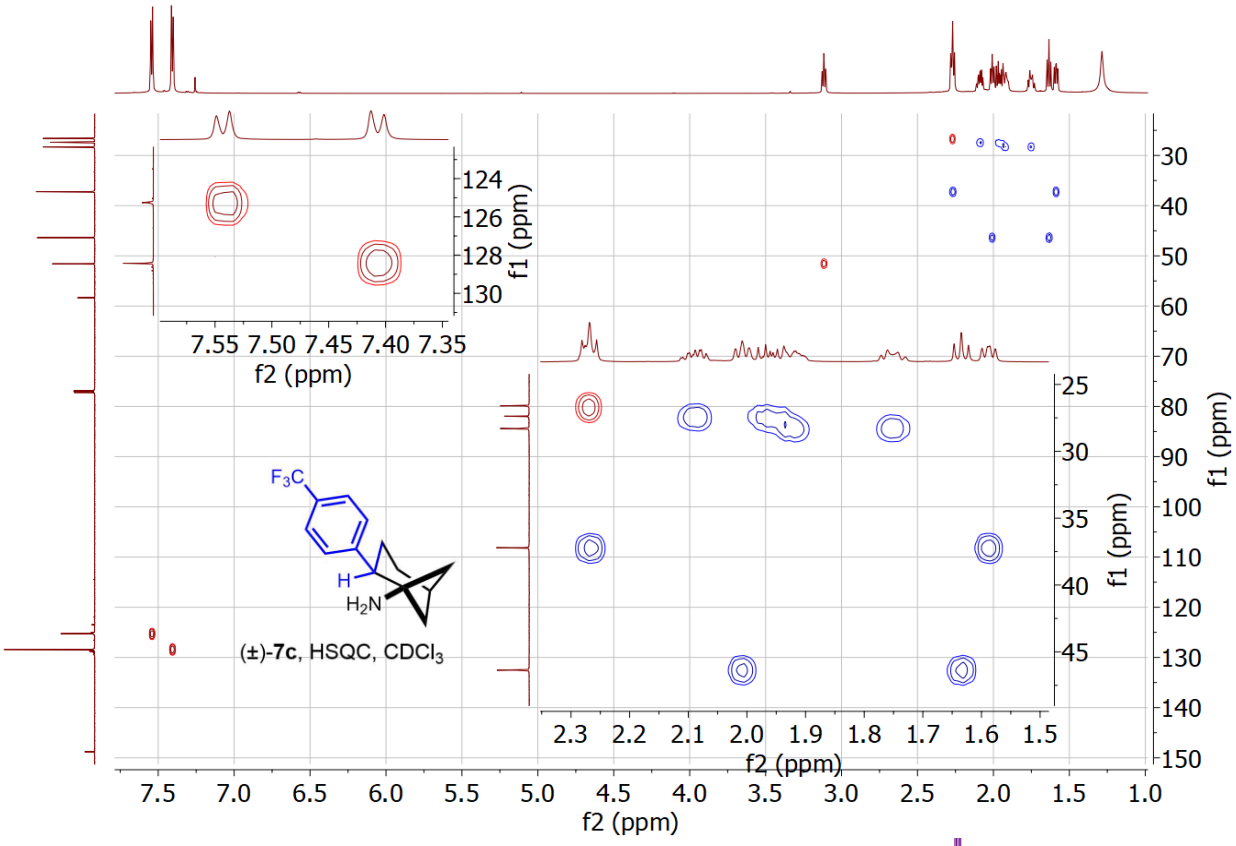


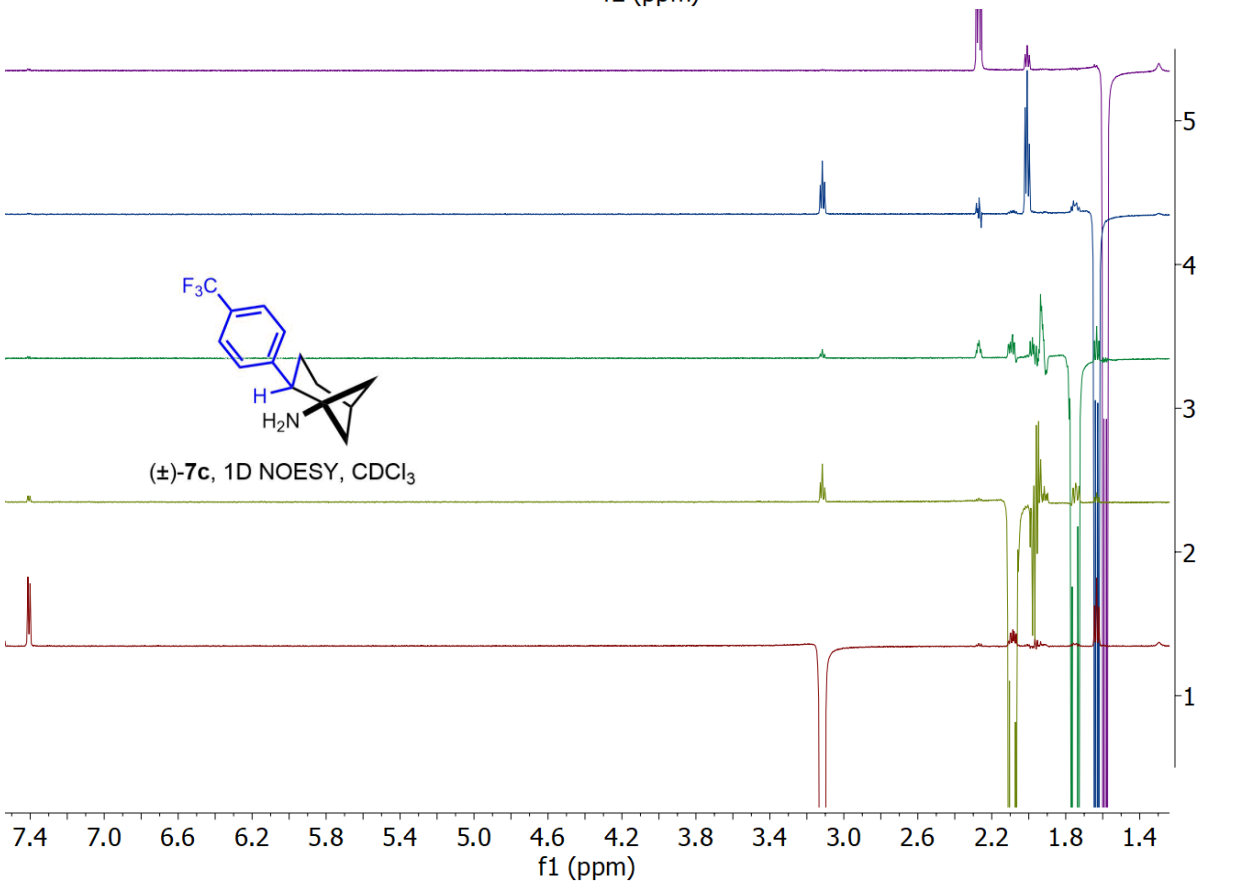

148.9
129.1
128.9
128.7
128.5
126.7
125.4
125.4
125.4
125.3
125.2
123.6
122.1
77.3
77.2
77.0
58.5
51.7
46.5
37.3
28.4
27.5
26.7
129.1 128.9 128.7 128.5
f1 (ppm)
125.35 125.25
f1 (ppm)
127 126 125 124 123 122
f1 (ppm)
F3C
H
H2N
(±)-7c, 13CNMR, CDCl3, 176 MHz
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


-63.38
-63.72
F3C
H
H2N
(±)-7c, 19FNMR, CDCl3, 376 MHz
-62.4 -62.7 -63.0 -63.3 -63.6 -63.9 -64.2 -64.5
f1 (ppm)
20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200
f1 (ppm)

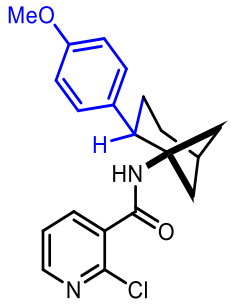

f2 (ppm)
f1 (ppm)
(±)-7c, HMBC, CDCl3


f2 (ppm)
f1 (ppm)
(±)-7c, COSY, CDCl3


F3C
H
H2N
(±)-7c, HSQC, CDCl3
f2 (ppm)
f1 (ppm)


F3C
H
H2N
(±)-7c, 1D NOESY, CDCl3
f1 (ppm)

Compound (±)-**8b** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7b** (30.0 mg, 0.138 mmol, 1 equiv) and the vial was capped and put under argon atmosphere with a balloon. Triethylamine (0.0698 mL, 0.690 mmol, 5 equiv) and dichloromethane (2.2 mL) were sequentially added to the reaction vial. In a separate vial, 2-chloronicotinoyl chloride (36.4 mg, 0.207 mmol, 1.5 equiv) was dissolved in dichloromethane (0.5 mL). This solution was transferred to the reaction vial in one portion via syringe. The argon balloon was removed, and the reaction vial was further sealed with Parafilm over the cap. The vial was placed in a pre-heated aluminum block at 40 °C for 40 minutes. After cooling to room temperature, the reaction mixture was concentrated onto celite (3 g), loaded atop a silica column, and chromatographed eluting with 25-50% ethyl acetate in hexanes to give (±)-**8b** (41.8 mg, 0.117 mmol, 85%) as a white solid.

Appearance: white solid

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.32 (dd, *J* = 4.6, 1.8 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.24-7.20 (m, 2H), 7.19 (dd, *J* = 7.6, 4.7 Hz, 1H), 6.83-6.79 (m, 2H), 6.16 (s, 1H), 3.76 (s, 3H), 3.68 (app. t, *J* = 8.5 Hz, 1H), 2.75 (app. t, *J* = 8.1 Hz, 1H), 2.53-2.49 (m, 1H), 2.30 (app. t, *J* = 8.4 Hz, 1H), 2.23-2.15 (m, 2H), 2.16-2.08 (m, 1H), 2.05 (app. t, *J* = 8.5 Hz, 1H), 2.02-1.96 (m, 1H), 1.86-1.79 (m, 1H) ppm

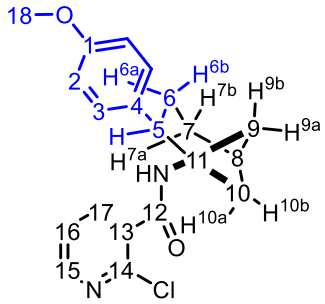
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 163.5, 158.6, 150.6, 147.2, 139.3, 135.9, 131.8, 129.3, 122.6, 114.0, 60.0, 55.4, 48.0, 44.1, 31.7, 29.5, 28.3, 27.0 ppm

IR (neat): 3224, 3066, 2950, 2857, 2834, 1635, 1610, 1584, 1555, 1511, 1475, 1463, 1399, 1332, 1306, 1279, 1260, 1241, 1182, 1154, 1124, 1113, 1098, 1073, 1034, 1017, 959, 896, 874, 846, 831, 809, 774, 755, 700 cm^{-1}

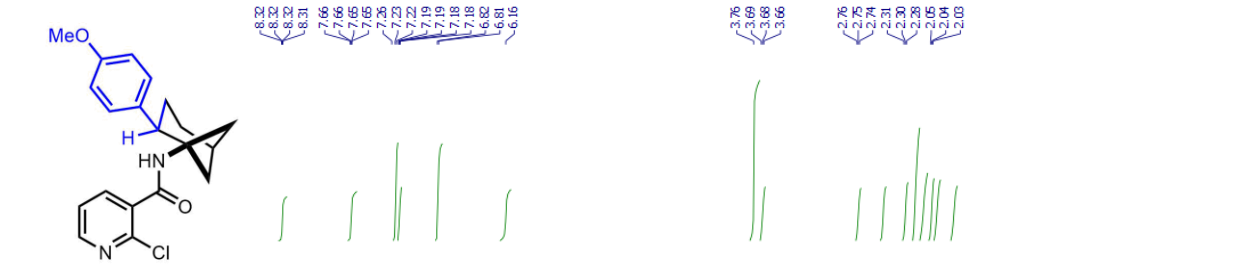
HRMS (ES+, m/z) calculated for $C_{20}H_{22}ClN_2O_2^+$: 357.1364, Found: 357.1361

R_f = 0.19 (50% ethyl acetate : 50% hexanes), yellow spot, $KMnO_4$, UV

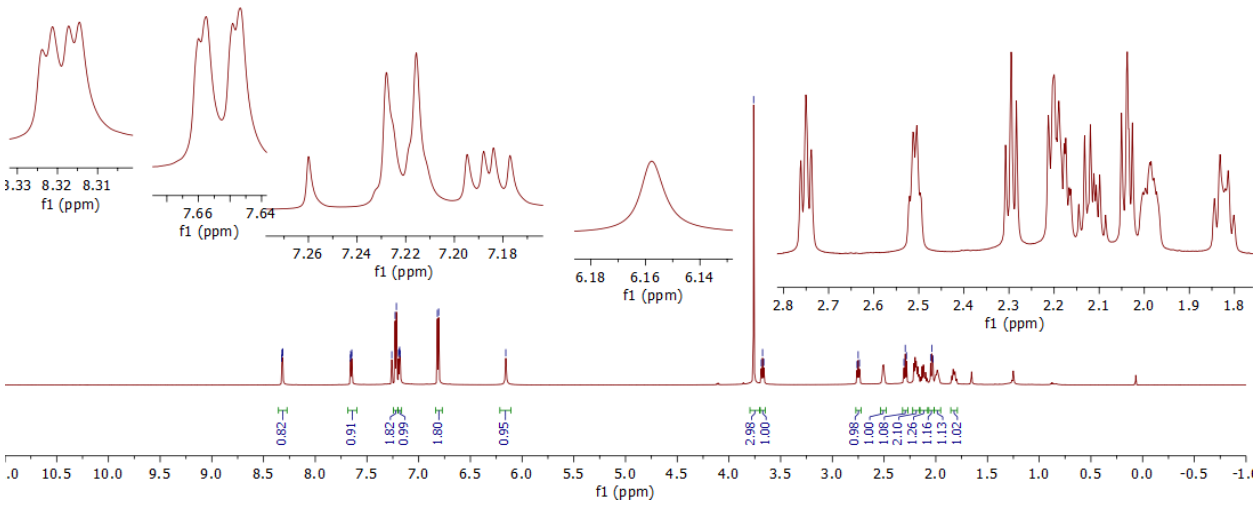
Complete assignment of ^{1}H and ^{13}C NMR signals

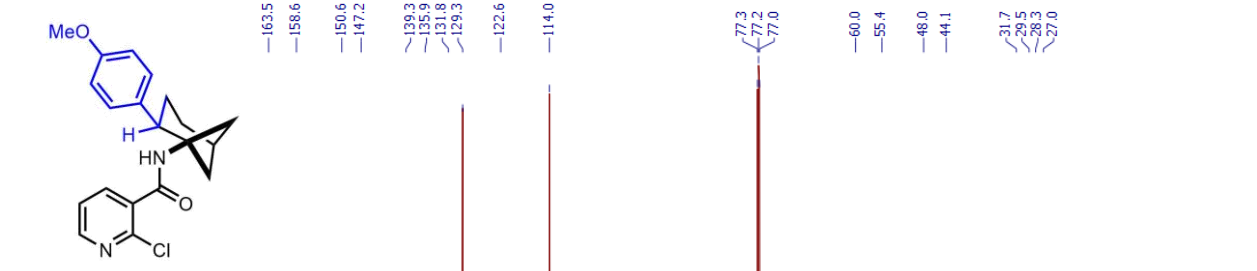


Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	158.6		2	6.83-6.79 (m, 2H)
2	114		3	7.24-7.20 (m, 2H)
3	129.3		5	3.68 (app. t, J = 8.5 Hz, 1H)
4	135.9		6a	one of 2.23-2.15 (m, 2H)
5	48		6b	2.16-2.08 (m, 1H)
6	27		7a	1.86-1.79 (m, 1H)
7	28.3		7b	2.02-1.96 (m, 1H)
8	29.5		8	2.53-2.49 (m, 1H)
9	31.7		9a	one of 2.23-2.15 (m, 2H)
10	44.1		9b	2.30 (app. t, J = 8.4 Hz, 1H)
11	60		10a	2.05 (app. t, J = 8.5 Hz, 1H)
12	163.5		10b	2.75 (app. t, J = 8.1 Hz, 1H)
13	131.8		N-H	6.16 (s, 1H)
14	147.2		15	8.32 (dd, J = 4.6, 1.8 Hz, 1H)
15	150.6		16	7.19 (dd, J = 7.6, 4.7 Hz, 1H)
16	122.6		17	7.65 (dd, J = 7.6, 1.7 Hz, 1H)
17	139.3		18	3.76 (s, 3H)
18	55.4			

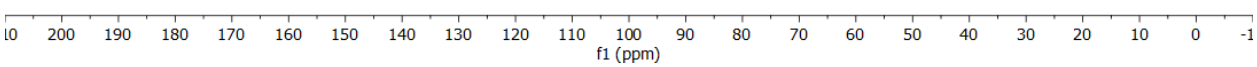


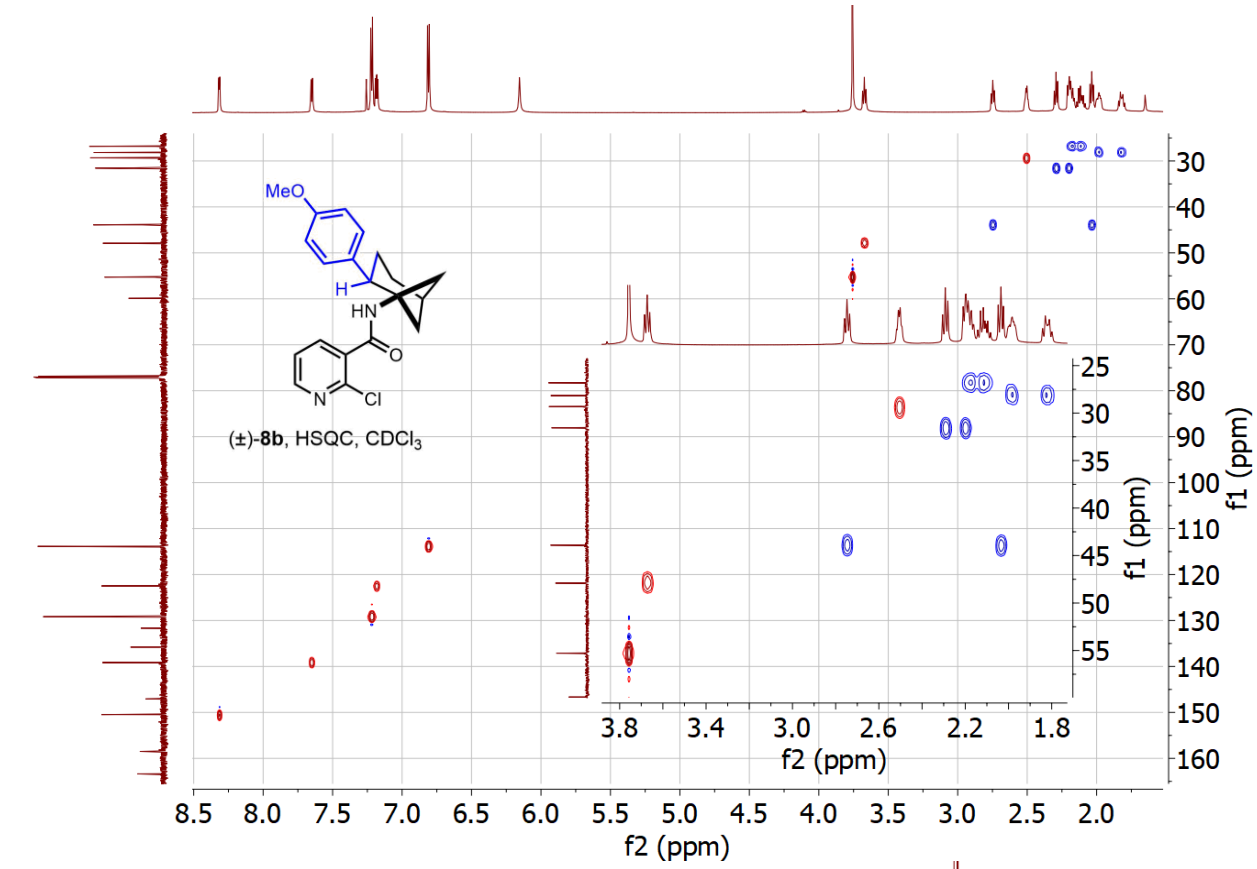
(±)-**8b**, ^{1}HNMR, $CDCl_3$, 700 MHz

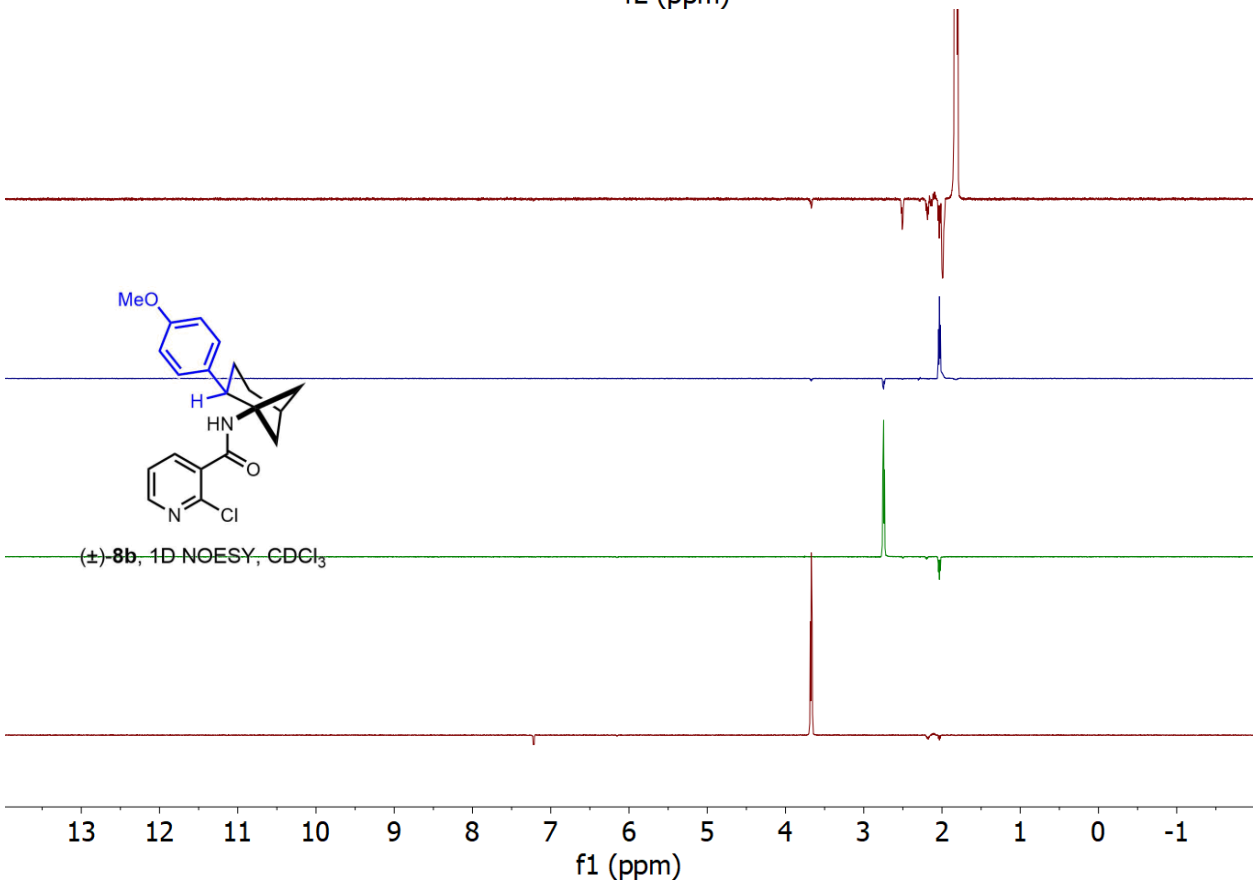


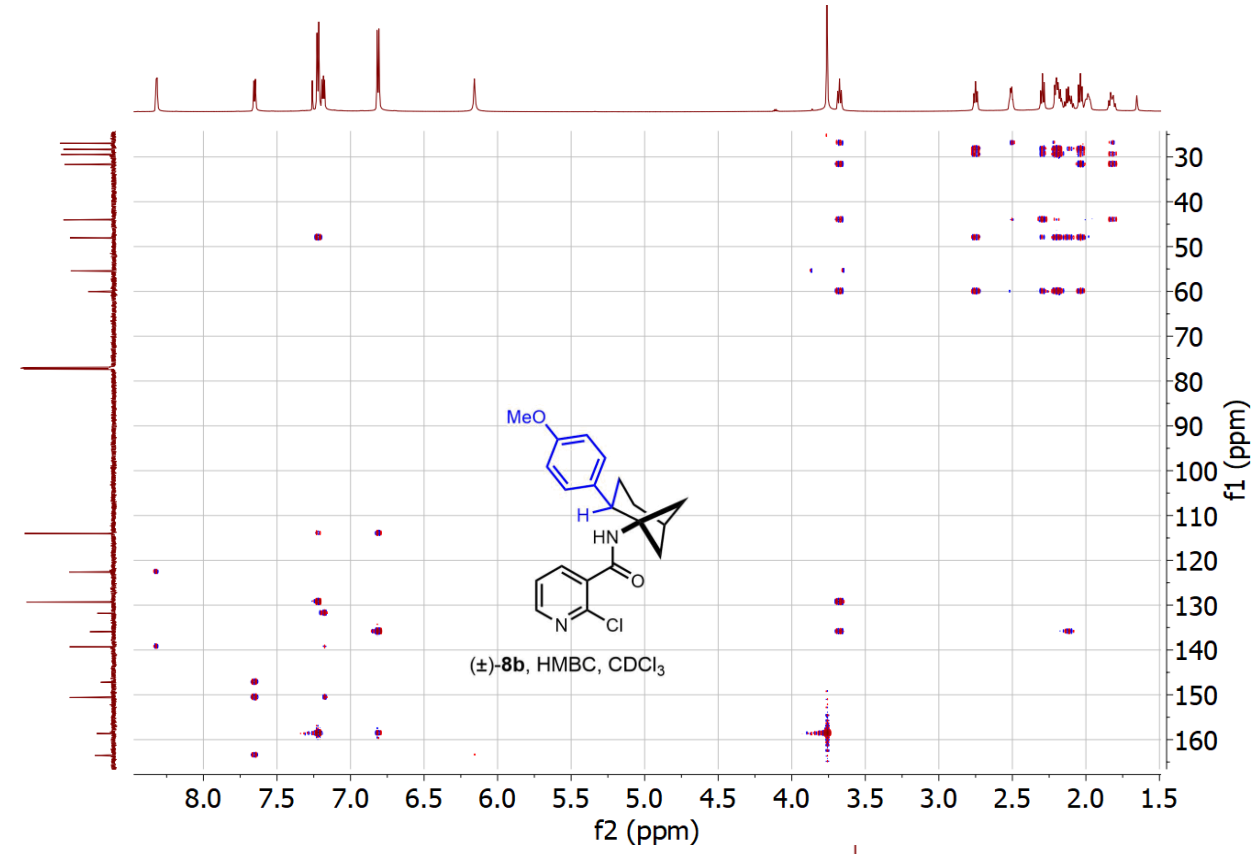


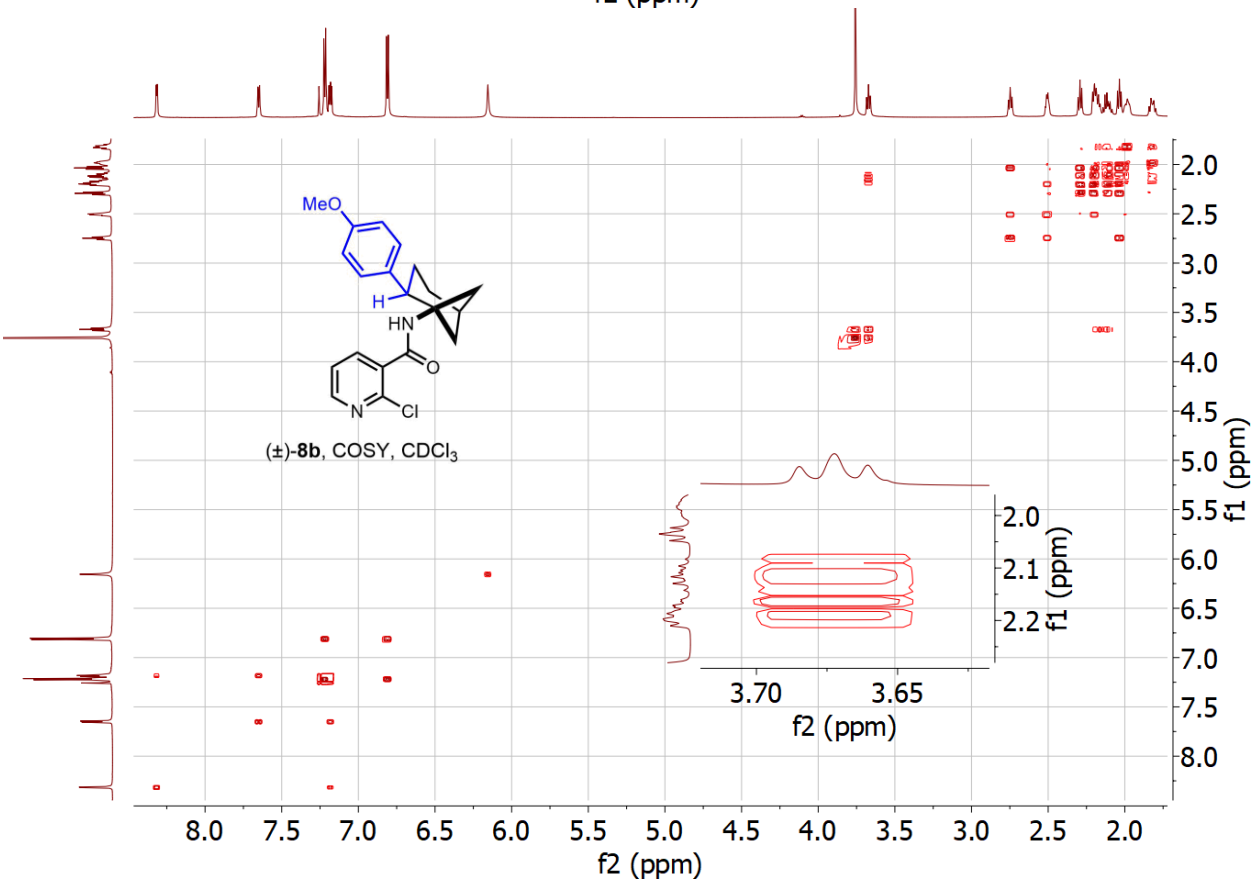
(±)-**8b**, ^{13}CNMR, $CDCl_3$, 176 MHz



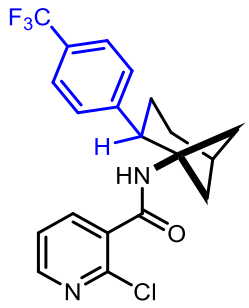

MeO
H
HN
O
N
Cl
(±)-8b, HSQC, CDCl3
f2 (ppm)
f1 (ppm)


MeO
H
HN
O
N
Cl
(±)-8b, 1D NOESY, CDCl3
f1 (ppm)


MeO
H
HN
O
N
Cl
(±)-8b, HMBC, CDCl3
f1 (ppm)
f2 (ppm)


MeO
H
HN
O
N
Cl
(±)-8b, COSY, CDCl3
3.70
3.65
f2 (ppm)
f1 (ppm)

Compound (±)-**8c** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7c** (50.0 mg, 0.196 mmol, 1 equiv) and the vial was sealed with a cap containing a Teflon-lined septum and put under argon atmosphere. Triethylamine (0.136 mL, 0.979 mmol, 5 equiv) and dichloromethane (3 mL) were sequentially added. Next, a mixture of 2-chloronicotinoyl chloride (51.7 mg, 0.294 mmol, 1.5 equiv) in dichloromethane (1 mL) was added to the vial over 2 minutes via syringe at room temperature. The mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was then concentrated onto celite (3 g), loaded atop a silica column, and eluted with 10-81% ethyl acetate in hexanes to afford (±)-**8c** (70.2 mg, 0.178 mmol, 91%) as a white solid.

Appearance: white solid

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.28 (d, *J* = 3.1 Hz, 1H), 7.55-7.47 (m, 3H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.15 (dd, *J* = 7.5, 4.8 Hz, 1H), 6.26 (s, 1H), 3.91 (app. t, *J* = 8.4 Hz, 1H), 2.59-2.50 (m, 2H), 2.33 (app. t, *J* = 8.6 Hz, 1H), 2.26-1.97 (m, 5H), 1.86 (dt, *J* = 12.8, 8.4 Hz, 1H) ppm

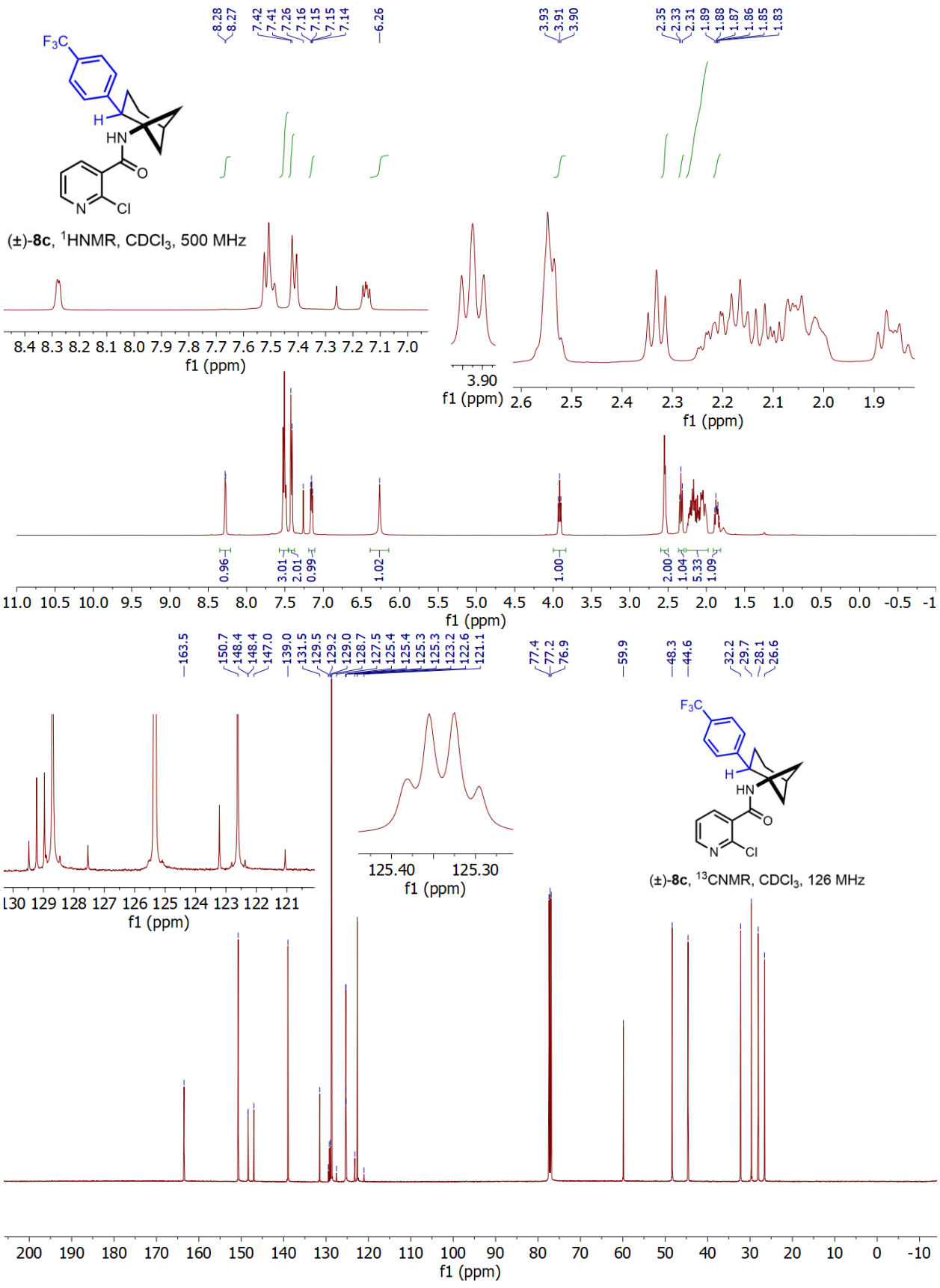
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 163.5, 150.7, 148.4 (d, *J* = 0.8 Hz), 147.0, 139.0, 131.5, 129.1 (q, *J* = 32.4 Hz), 128.7, 125.3 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 271.9 Hz), 122.6, 59.9, 48.3, 44.6, 32.2, 29.7, 28.1, 26.6 ppm

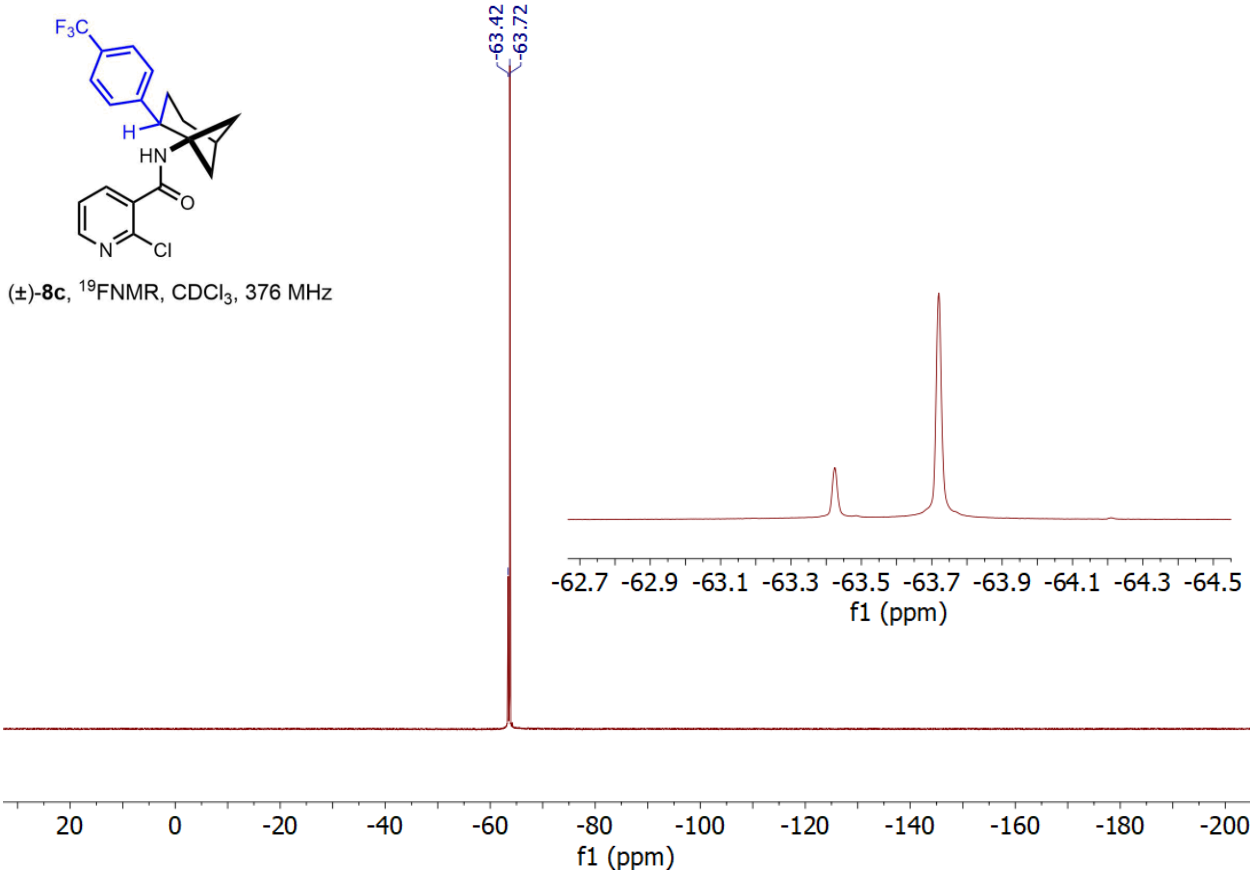
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -63.4 (s) ppm

IR (neat): 3232, 3067, 2948, 2857, 1637, 1619, 1586, 1553, 1477, 1453, 1424, 1399, 1327, 1293, 1260, 1230, 1151, 1110, 1068, 1018, 958, 928, 900, 880, 842, 812, 775, 751, 733, 701, 655 cm^{-1}

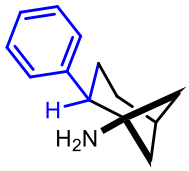
HRMS (ES+, m/z) calculated for $C_{20}H_{19}ClF_3N_2O^+$: 395.1133, Found: 395.1134

R_f = 0.61 (70% ethyl acetate : 30% hexanes), yellow spot, $KMnO_4$, UV-active


F3C
H
HN
O
N
Cl
(±)-8c, 1HNMR, CDCl3, 500 MHz
8.28 8.27 7.42 7.41 7.26 7.16 7.15 7.15 7.14 6.26 3.93 3.91 3.90 2.35 2.33 2.31 1.89 1.88 1.87 1.86 1.85 1.83
0.96 3.01 2.01 0.99 1.02 1.00 2.00 1.04 5.33 1.09
f1 (ppm)
3.90
(±)-8c, 13CNMR, CDCl3, 126 MHz
163.5 150.7 148.4 148.4 147.0 139.0 131.5 129.5 129.2 129.0 128.7 127.5 125.4 125.4 125.3 125.3 123.2 122.6 121.1 77.4 77.2 76.9 59.9 48.3 44.6 32.2 29.7 28.1 26.6
125.40 125.30



Compound (±)-**7d** :



EXPERIMENTAL PROCEDURE:
To an oven-dried 1-dram vial equipped with a stir bar was added **2a** (216 mg, 1.00 mmol, 1 equiv), 2,2'-dipyridyldisulfide (2.20 mg, 0.010 mmol, 0.01 equiv), and styrene (0.862 mL, 7.50 mmol, 7.5 equiv). The vial was sealed with a Teflon-lined cap and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 40 hours with 2 390 nm Kessil lamps at maximum intensity positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. The reaction mixture was allowed to cool to room temperature, then was transferred to a 50 mL round-bottom flask and sequentially diluted with acetonitrile (3 mL), water (1 mL), and acetic acid (1 mL) (with stirring). The headspace was flushed with argon and the mixture was stirred at room temperature for 43 hours. The mixture was then diluted with 1M aqueous HCl (20 mL) and extracted with diethyl ether (3 x 25 mL). The ethereal extracts (containing styrene, 4-nitrobenzaldehyde, acetic acid, and non-basic byproducts) were discarded. The aqueous layer was brought to pH ~ 12 with 3M aqueous NaOH and was extracted with diethyl

ether (4 x 25 mL). The combined ethereal extracts were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude (±)-**7d** as a dark brown solid (91.2 mg, 0.487 mmol, 49%), which was sufficiently pure for most purposes.

Note: A portion of crude material from another run was chromatographed on silica gel (that had been pre-neutralized with 3 column volumes of 5% ethyl acetate: 94% hexanes: 1% triethylamine) eluting with 12-100% ethyl acetate in hexanes to give (±)-**7d** as a beige solid. NMR spectra are provided of both the crude and chromatographed materials, with the minor impurity peaks emphasized for the crude material. The listed analytical data was collected on the chromatographed sample.

Appearance: dark brown solid crude and beige solid after chromatography

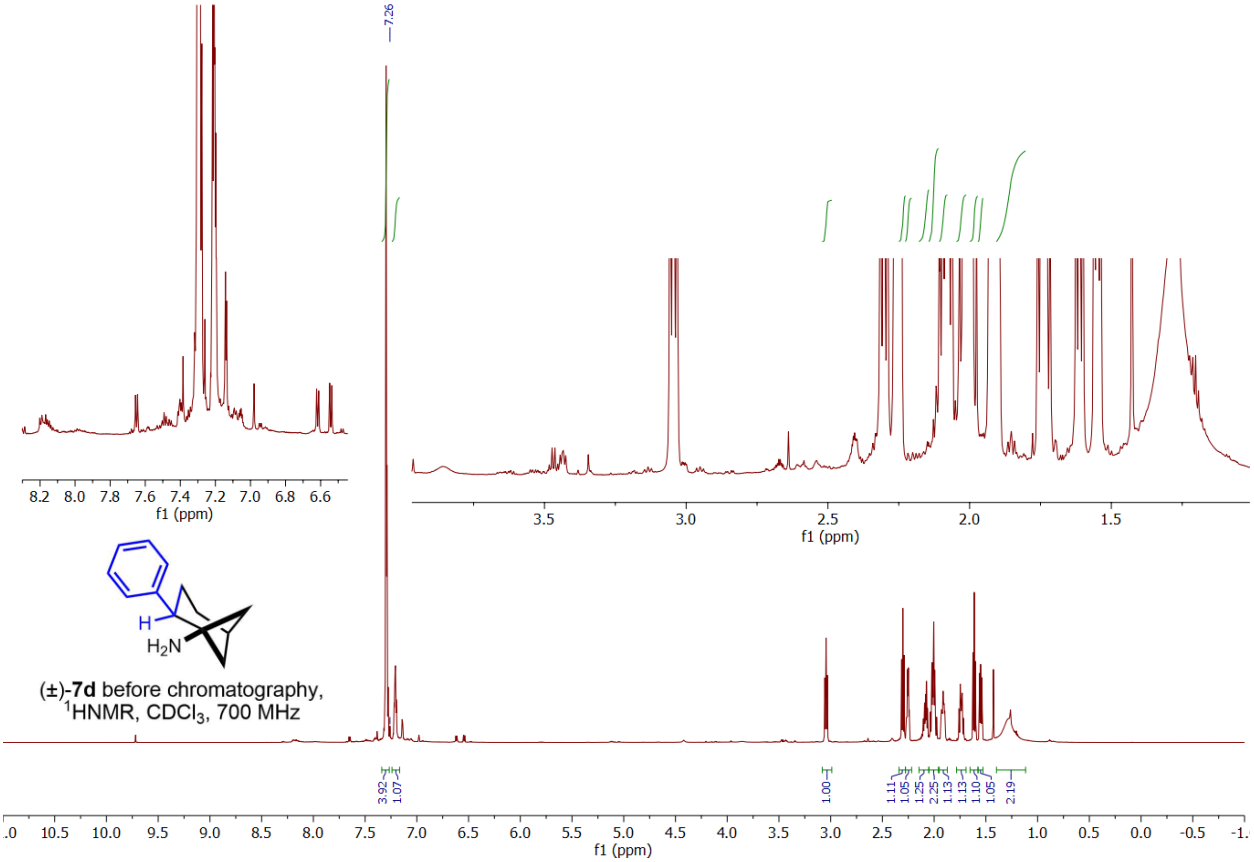
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.33-7.28 (m, 4H), 7.24-7.19 (m, 1H), 3.05 (app. t, *J* = 8.5 Hz, 1H), 2.31 (app. t, *J* = 8.7 Hz, 1H), 2.28-2.24 (m, 1H), 2.13-2.06 (m, 1H), 2.05-1.98 (m, 2H), 1.96-1.89 (m, 1H), 1.75 (dt, *J* = 13.1, 8.6 Hz, 1H), 1.62 (app. t, *J* = 8.5 Hz, 1H), 1.56 (dt, *J* = 9.5, 6.5 Hz, 1H), 1.20 (bs, 2H) ppm

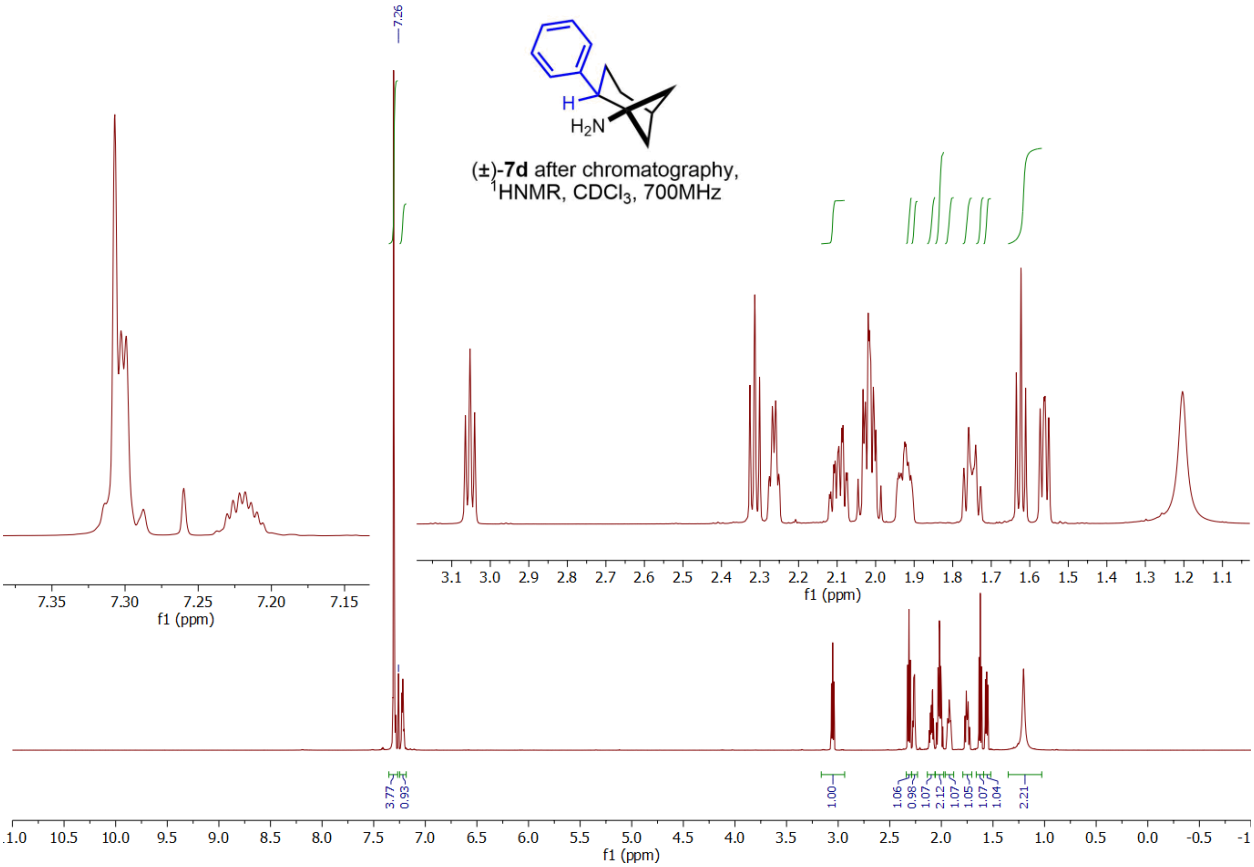
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 144.7, 128.5, 128.3, 126.6, 58.5, 51.9, 46.5, 37.6, 28.7, 27.7, 26.8 ppm

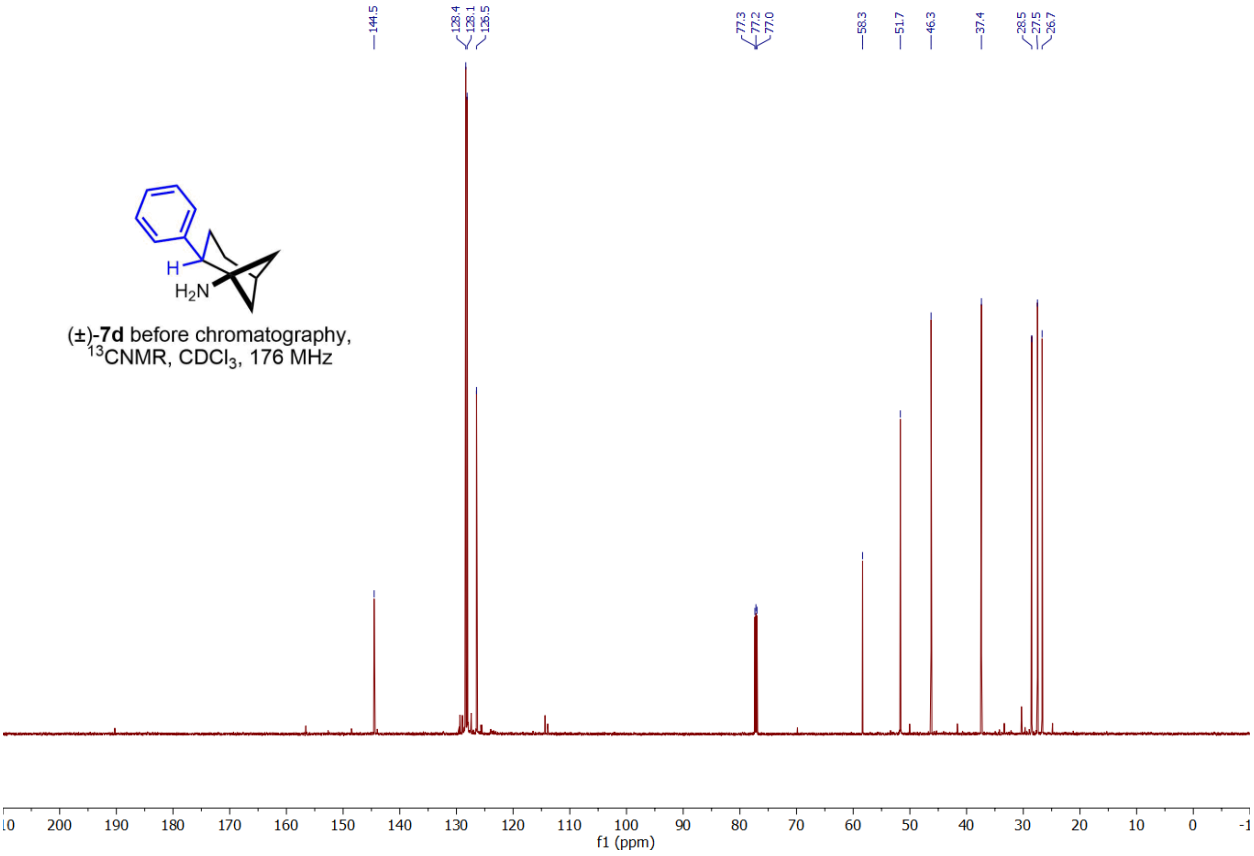
IR (neat): 3361, 3283, 3023, 2954, 2906, 2859, 1599, 1491, 1470, 1451, 1285, 1257, 1212, 1176, 1148, 1088, 1065, 1028, 975, 941, 924, 890, 866, 839, 761, 742, 699 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{13}H_{18}N^+$: 188.1434, Found: 188.1434

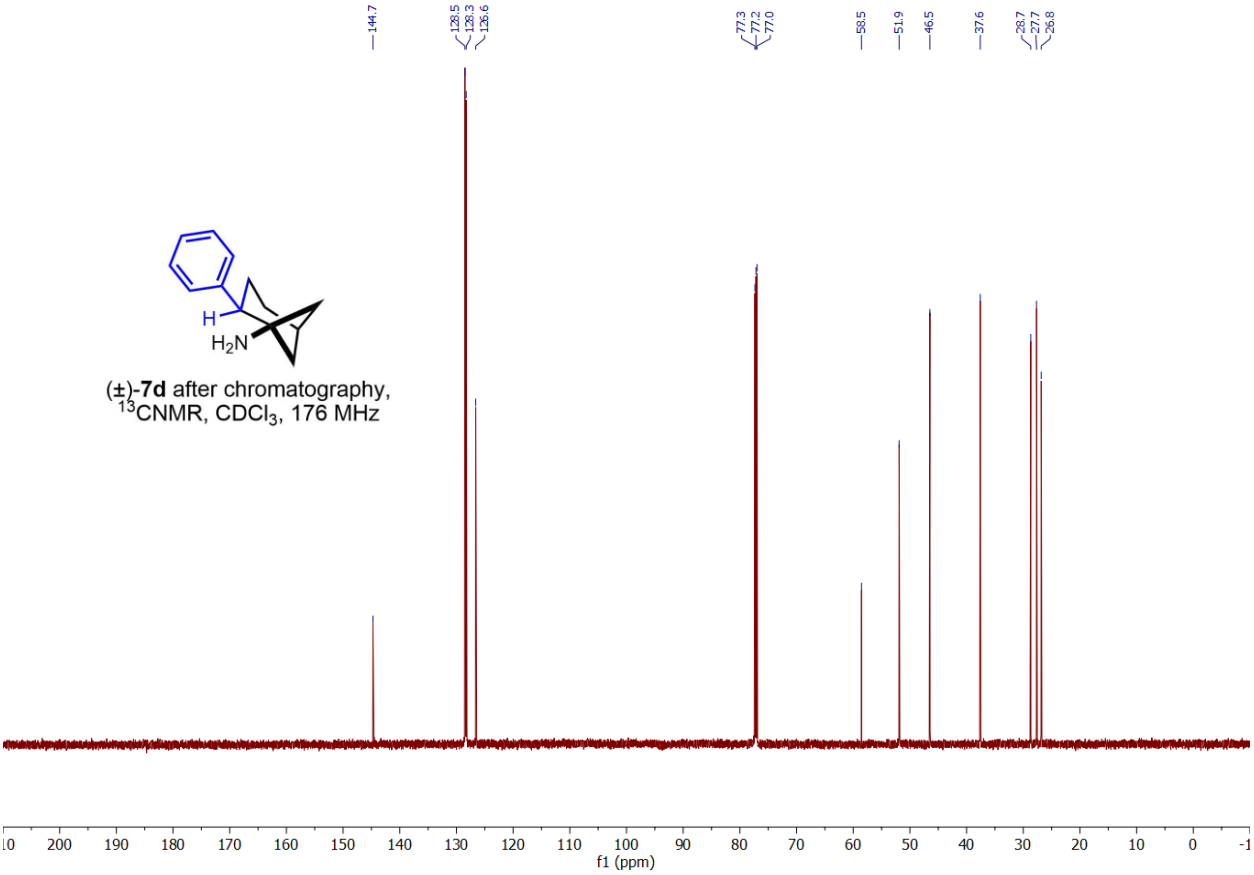
R_f = 0.25 (50% ethyl acetate: 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


7.26
8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6
f1 (ppm)
3.5 3.0 2.5 2.0 1.5
f1 (ppm)
H
H2N
(±)-7d before chromatography,
1HNMR, CDCl3, 700 MHz
3.92
1.07
1.00
1.11
1.05
1.25
2.25
1.13
1.10
1.05
2.19
f1 (ppm)


7.26
H
H2N
(±)-7d after chromatography,
1HNMR, CDCl3, 700MHz
7.35 7.30 7.25 7.20 7.15
f1 (ppm)
3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1
f1 (ppm)
3.77
0.93
1.00
1.06
0.98
1.07
2.12
1.05
1.07
1.07
1.04
2.21
f1 (ppm)

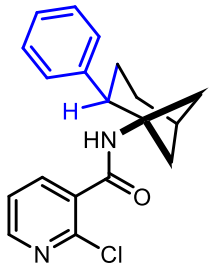


(±)-**7d** before chromatography,
^{13}CNMR, $CDCl_3$, 176 MHz



(±)-**7d** after chromatography,
^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**8d** :



EXPERIMENTAL PROCEDURE:
To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7d** (52.4 mg, 0.280 mmol, 1 equiv) and the vial was capped and put under argon. Triethylamine (0.195 mL, 1.40 mmol, 5 equiv) and and dichloromethane (4.4 mL) were sequentially added. Next, a mixture of 2-Chloronicotinoyl chloride (73.9 mg, 0.420 mmol, 1.5 equiv) in dichloromethane (0.9 mL) was added to the vial over 2 minutes via syringe at room temperature. Some smoking was observed during the addition. The vial was sealed shut under argon, the cap being wrapped with parafilm, then placed in an aluminum heating block at 40 °C and allowed to stir for 3 hours. The reaction mixture was transferred to a round-bottom flask and concentrated onto celite (3 grams). The resulting solid mixture was dry-loaded atop a silica column and eluted with 12-100% ethyl acetate in hexanes to give (±)-**8d** (88.7 mg, 0.271 mmol, 97%) as a faintly yellow solid.

Appearance: Faintly yellow solid

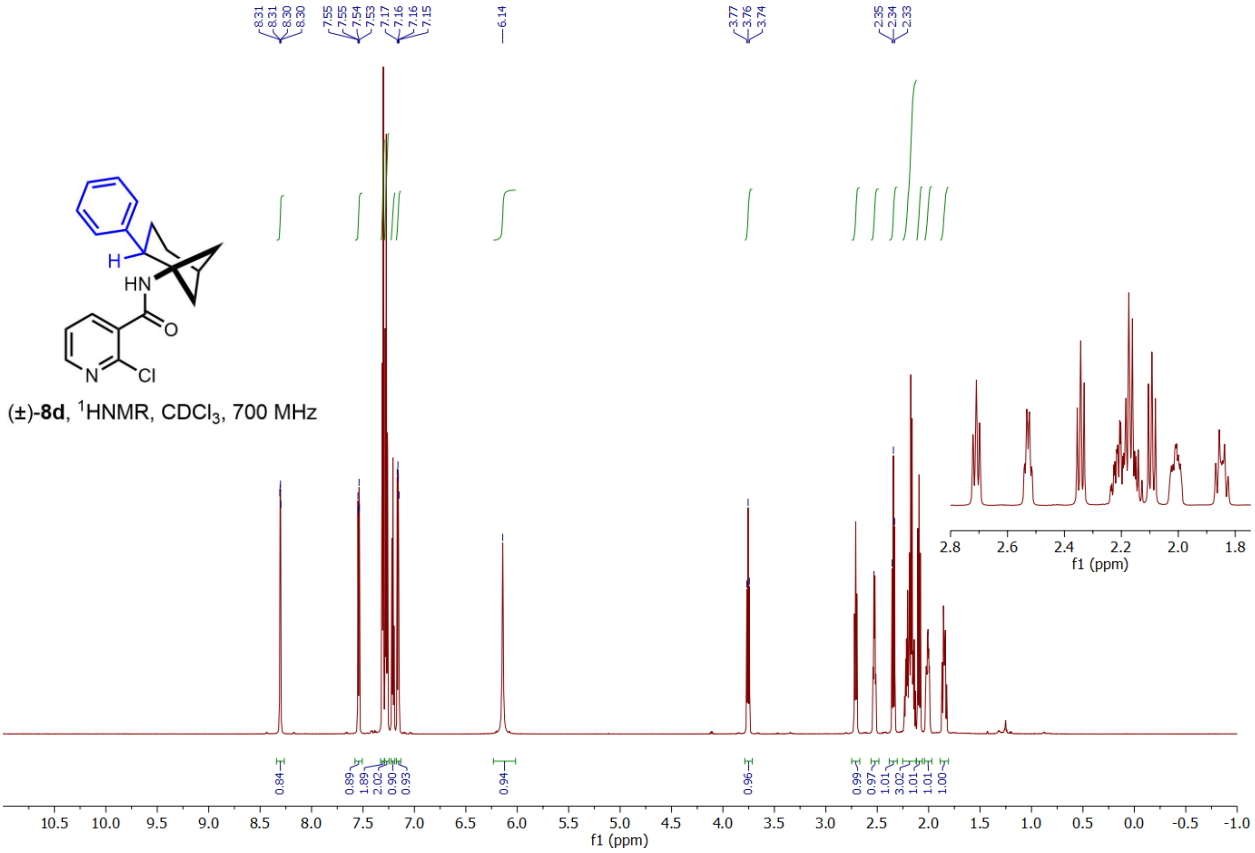
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.30 (dd, *J* = 4.8, 2.0 Hz, 1H), 7.54 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.33-7.29 (m, 2H), 7.29-7.25 (m, 2H), 7.23-7.19 (m, 1H), 7.16 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.14 (s, 1H) 3.76 (app. t, *J* = 8.5 Hz, 1H), 2.74-2.68 (m, 1H), 2.56-2.50 (m, 1H), 2.34 (app. t, *J* = 8.5 Hz, 1H), 2.25-2.12 (m, 3H), 2.11-2.07 (m, 1H), 2.04-1.97 (m, 1H), 1.88-1.81 (m, 1H) ppm

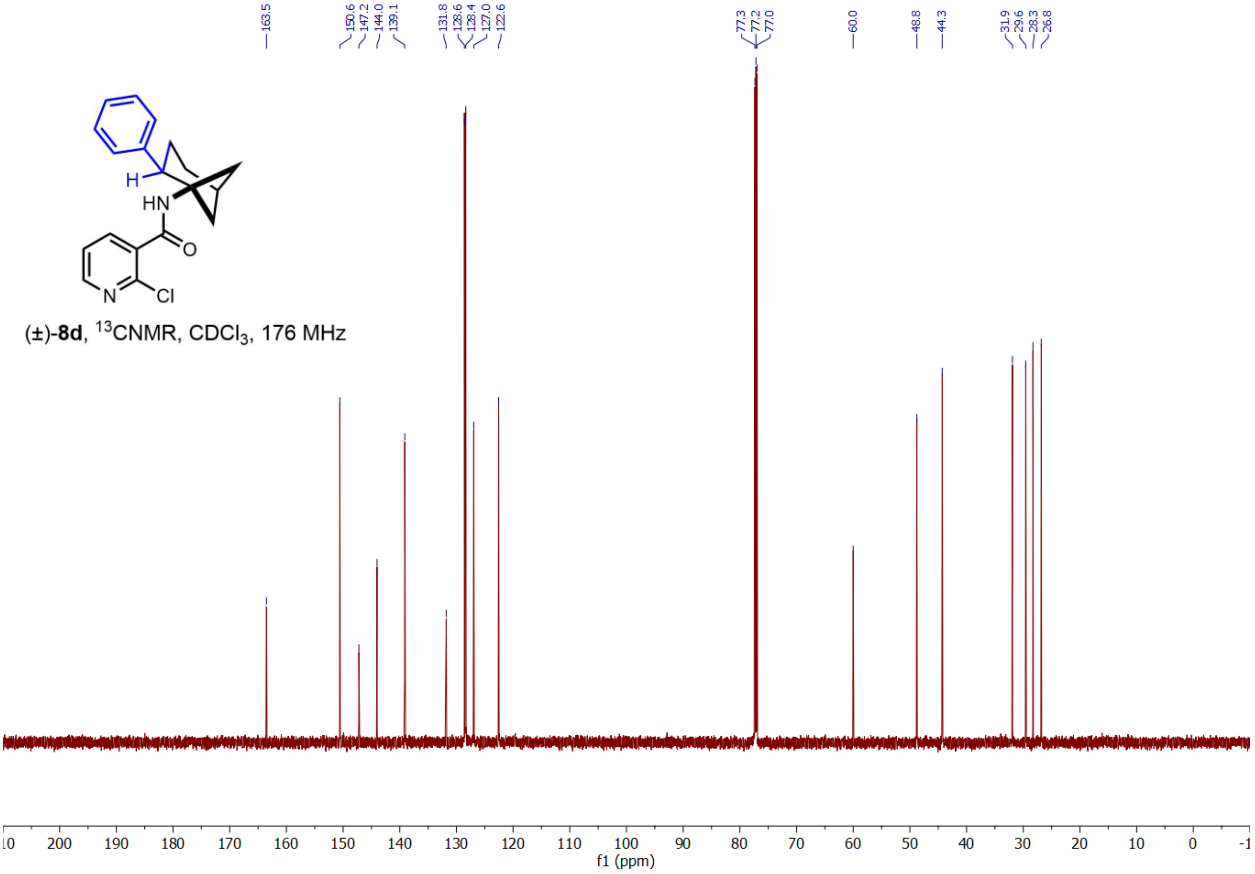
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 163.5, 150.6, 147.2, 144.0, 139.1, 131.8, 128.6, 128.4, 127.0, 122.6, 60.0, 48.8, 44.3, 31.9, 29.6, 28.3, 26.8 ppm

IR (neat): 3224, 3058, 2944, 2862, 1637, 1582, 1543, 1494, 1452, 1399, 1316, 1291, 1259, 1182, 1152, 1124, 1070, 1031, 907, 879, 846, 817, 760, 736, 696 cm^{-1}

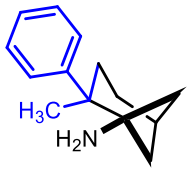
HRMS (ES+, m/z) calculated for $C_{19}H_{20}ClN_2O^+$: 327.1259, Found: 327.1267

R_f = 0.29 (50% ethyl acetate in hexanes), one yellow spot, $KMnO_4$, UV


8.31
8.31
8.30
8.30
7.55
7.55
7.54
7.53
7.17
7.16
7.16
7.15
6.14
3.77
3.76
3.74
2.35
2.34
2.33
H
HN
O
N
Cl
(±)-8d, 1HNMR, CDCl3, 700 MHz
0.84
0.89
1.89
2.02
0.90
0.93
0.94
0.96
0.99
0.97
1.01
3.02
1.01
1.01
1.00
f1 (ppm)


163.5
150.6
147.2
144.0
139.1
131.8
128.6
128.4
127.0
122.6
77.3
77.2
77.0
60.0
48.8
44.3
31.9
29.6
28.3
26.8
H
HN
O
N
Cl
(±)-8d, 13CNMR, CDCl3, 176 MHz
f1 (ppm)

Compound (±)-**7e** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 6-dram vial equipped with a stir bar was added **2a** (2.16 g, 10.0 mmol, 1 equiv), 2,2'-dipyridyldisulfide (22.0 mg, 0.100 mmol, 0.01 equiv), and isopropenylbenzene (9.75 mL, 75.0 mmol, 7.5 equiv). The vial was sealed with a rubber septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 76 hours with 2 390 nm Kessil lamps at maximum intensity positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. The reaction mixture was allowed to cool to room temperature, then was transferred to a 250 mL round-bottom flask and sequentially diluted with acetonitrile (60 mL), water (20 mL), and acetic acid (20 mL) (with stirring). The headspace was flushed with argon and the mixture was stirred at room temperature for 24 hours. The mixture was then diluted with 1M aqueous HCl (200 mL) and extracted with diethyl ether (3 x 100 mL). The ethereal extracts (containing isopropenylbenzene, 4-nitrobenzaldehyde, acetic acid, and non-basic byproducts) were discarded. The aqueous layer was brought to pH ~ 12 with 3M aqueous NaOH and was extracted with diethyl ether (4 x 100 mL). The combined ethereal extracts were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give crude (±)-**7e** as a brown oil (920.1 mg, 4.57 mmol, 46%), which was sufficiently pure for most purposes.

Note: A portion of this material was chromatographed on silica gel (that had been pre-neutralized with 3 column volumes of 10% ethyl acetate: 89% hexanes: 1% triethylamine) eluting with 24-100% ethyl acetate in hexanes to give (±)-**7e** as a thick brown oil. Spectra are provided of both the crude and chromatographed materials, with the minor impurity peaks emphasized for the crude material. The listed analytical data was collected on the chromatographed sample.

Appearance: brown oil crude and brown oil after chromatography

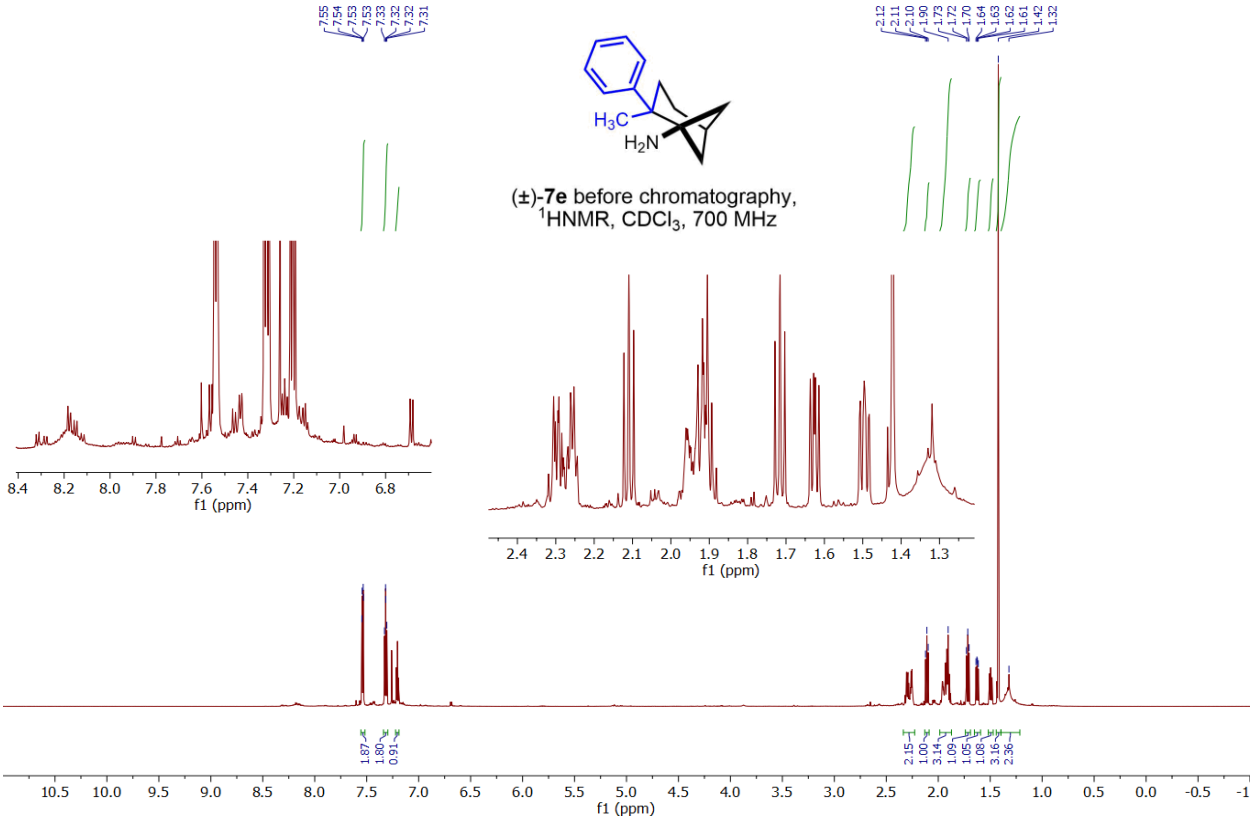
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.55-7.52 (m, 2H), 7.34-7.30 (m, 2H), 7.22-7.19 (m, 1H), 2.33-2.28 (m, 1H), 2.28-2.24 (m, 1H), 2.11 (app. t, *J* = 8.8 Hz, 1H), 1.99-1.87 (m, 3H), 1.72 (app. t, *J* = 8.9 Hz, 1H), 1.63 (dd, *J* = 9.3, 6.3 Hz, 1H), 1.52-1.48 (m, 1H), 1.43 (s, 3H), 1.34 (bs, 2H) ppm

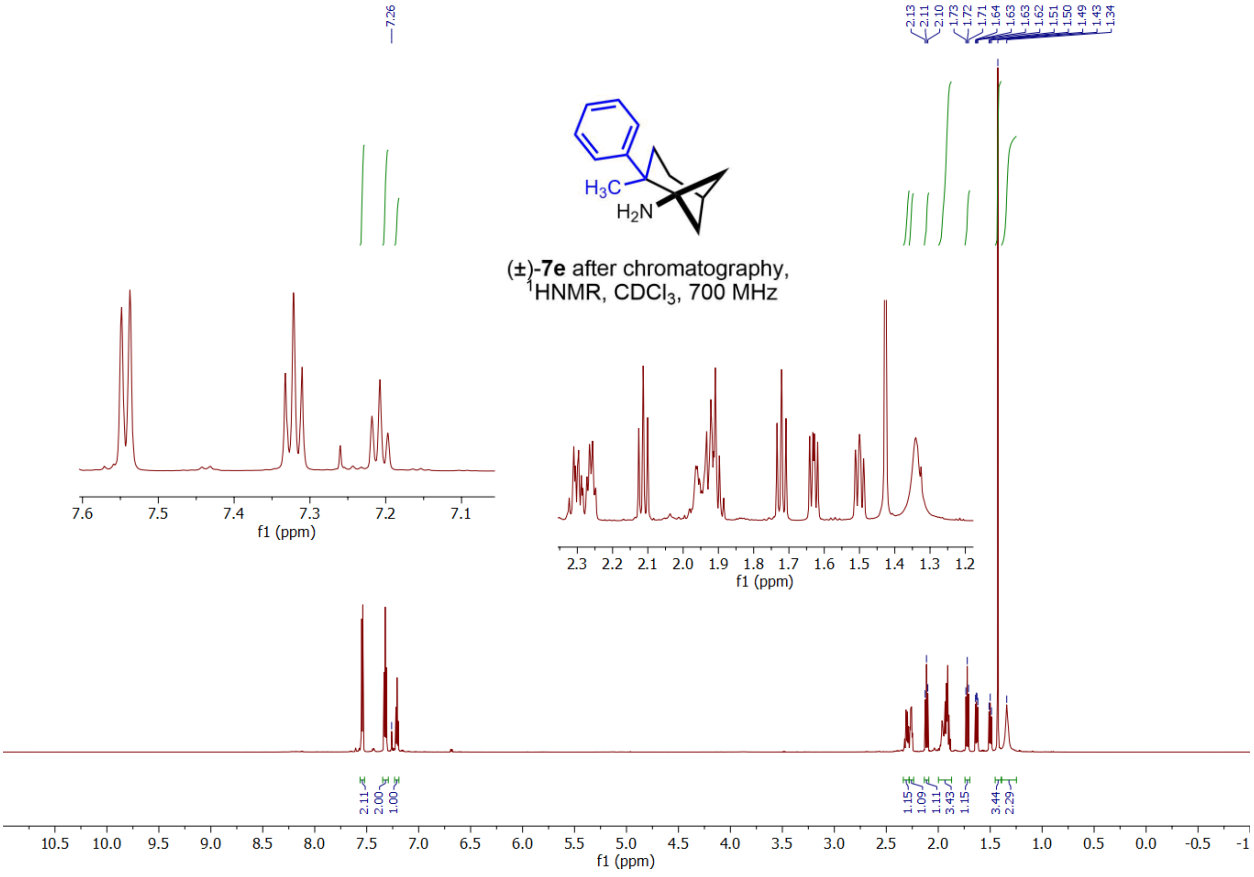
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 147.0, 128.0, 127.7, 125.9, 61.7, 45.7, 41.9, 38.6, 34.0, 29.2, 27.9, 24.3 ppm

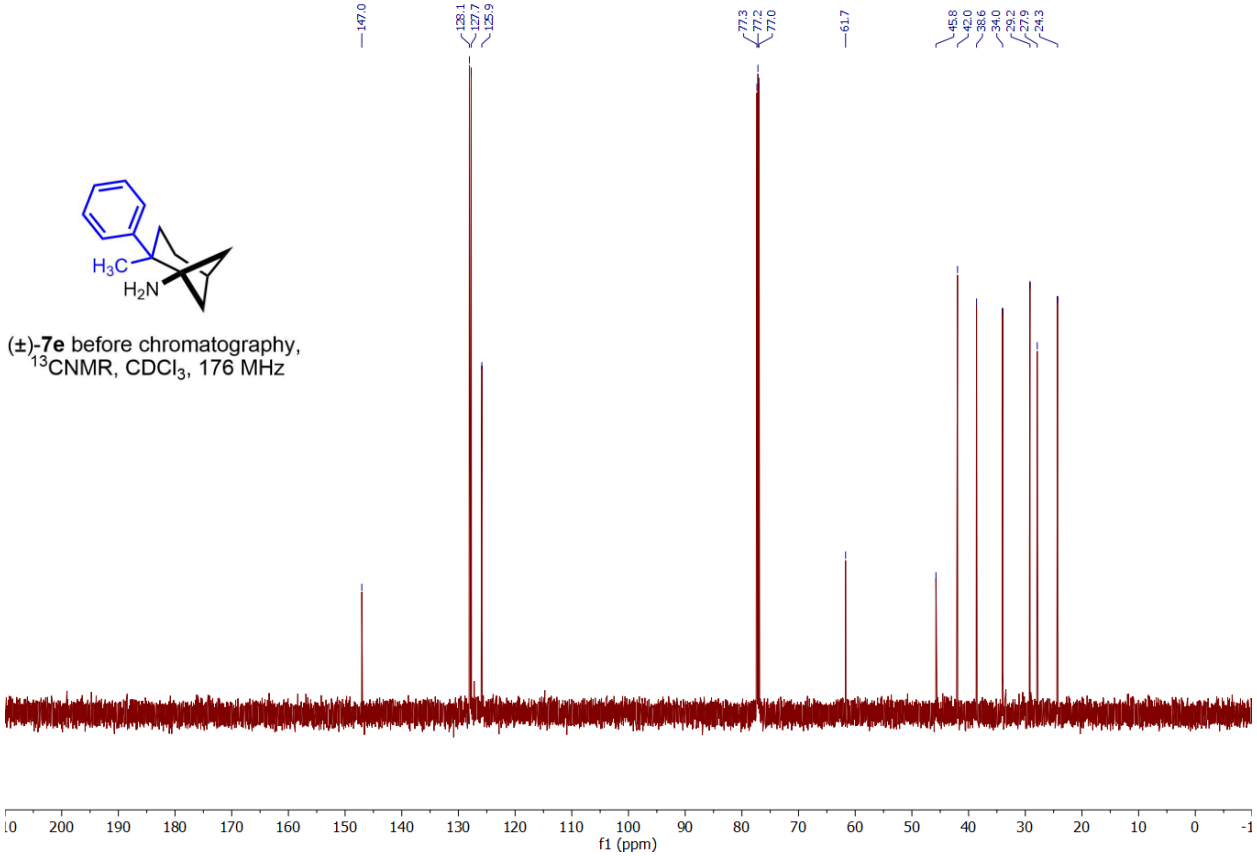
IR (neat): 3376, 3089, 3056, 2941, 2861, 1602, 1578, 1520, 1496, 1480, 1456, 1443, 1374, 1346, 1317, 1271, 1253, 1217, 1156, 1092, 1068, 1032, 998, 966, 931, 910, 809, 767, 753, 720, 699, 655 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{14}H_{20}N^+$: 202.1590, Found: 202.1583

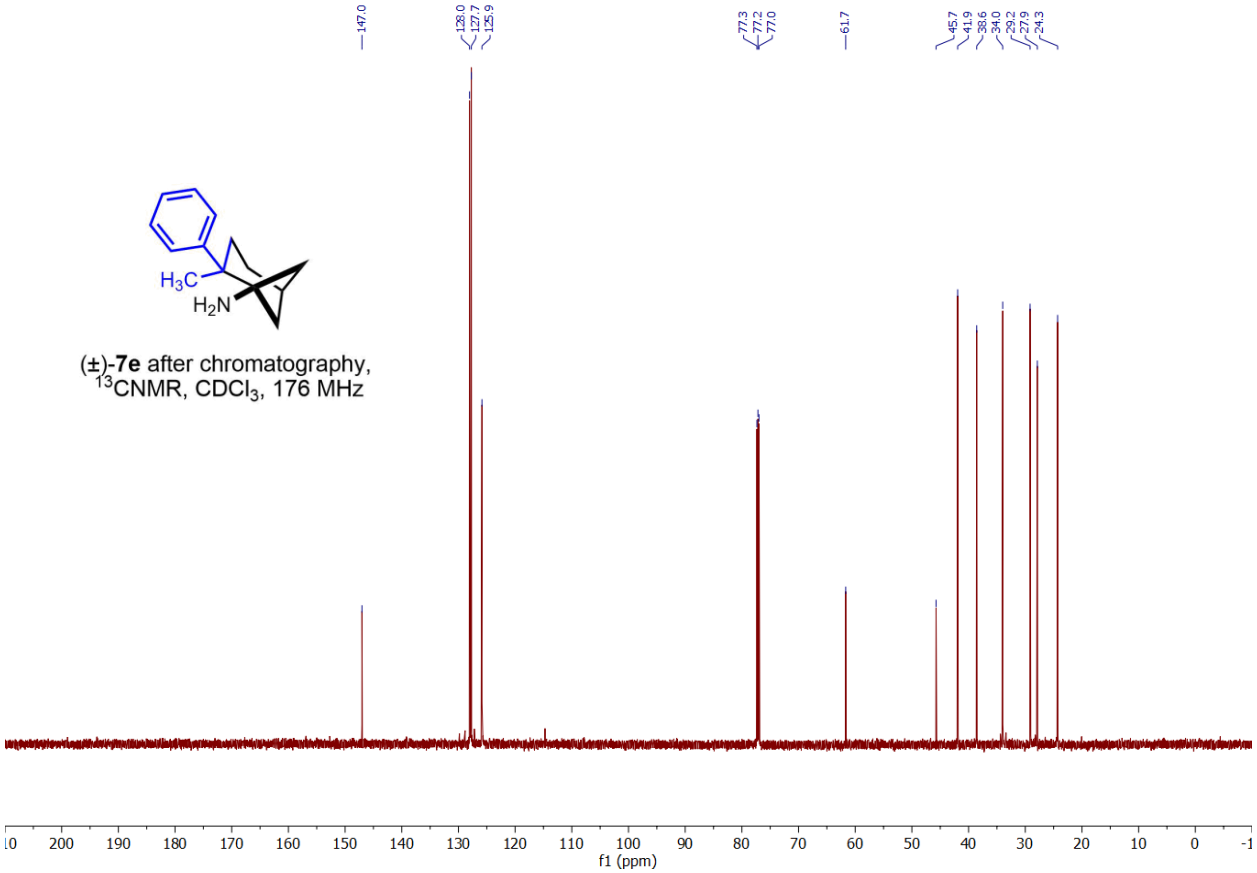
R_f = 0.25 (50% ethyl acetate: 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


H3C
H2N
(±)-7e before chromatography,
1HNMR, CDCl3, 700 MHz
f1 (ppm)


H3C
H2N
(±)-7e after chromatography,
1HNMR, CDCl3, 700 MHz
f1 (ppm)

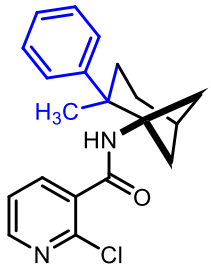


(±)-**7e** before chromatography,
^{13}CNMR, $CDCl_3$, 176 MHz



(±)-**7e** after chromatography,
^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**8e** :



EXPERIMENTAL PROCEDURE:
To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7e** (56.4 mg, 0.280 mmol, 1 equiv) and the vial was capped and put under argon. Triethylamine (0.195 mL, 1.40 mmol, 5 equiv) and and dichloromethane (4.4 mL) were sequentially added. Next, a mixture of 2-Chloronicotinoyl chloride (73.9 mg, 0.420 mmol, 1.5 equiv) in dichloromethane (0.9 mL) was added to the vial over 2 minutes via syringe at room temperature. Some smoking was observed during the addition. The vial was sealed shut under argon, the cap being wrapped with parafilm, then placed in an aluminum heating block at 40 °C and allowed to stir for 3 hours. The reaction mixture was transferred to a round-bottom flask and concentrated onto celite (3 grams). The resulting solid mixture was dry-loaded atop a silica column and eluted with 12-100% ethyl acetate in hexanes to give (±)-**8e** (74.2 mg, 0.218 mmol, 78%) as a faintly yellow oil.

Appearance: Faintly yellow oil

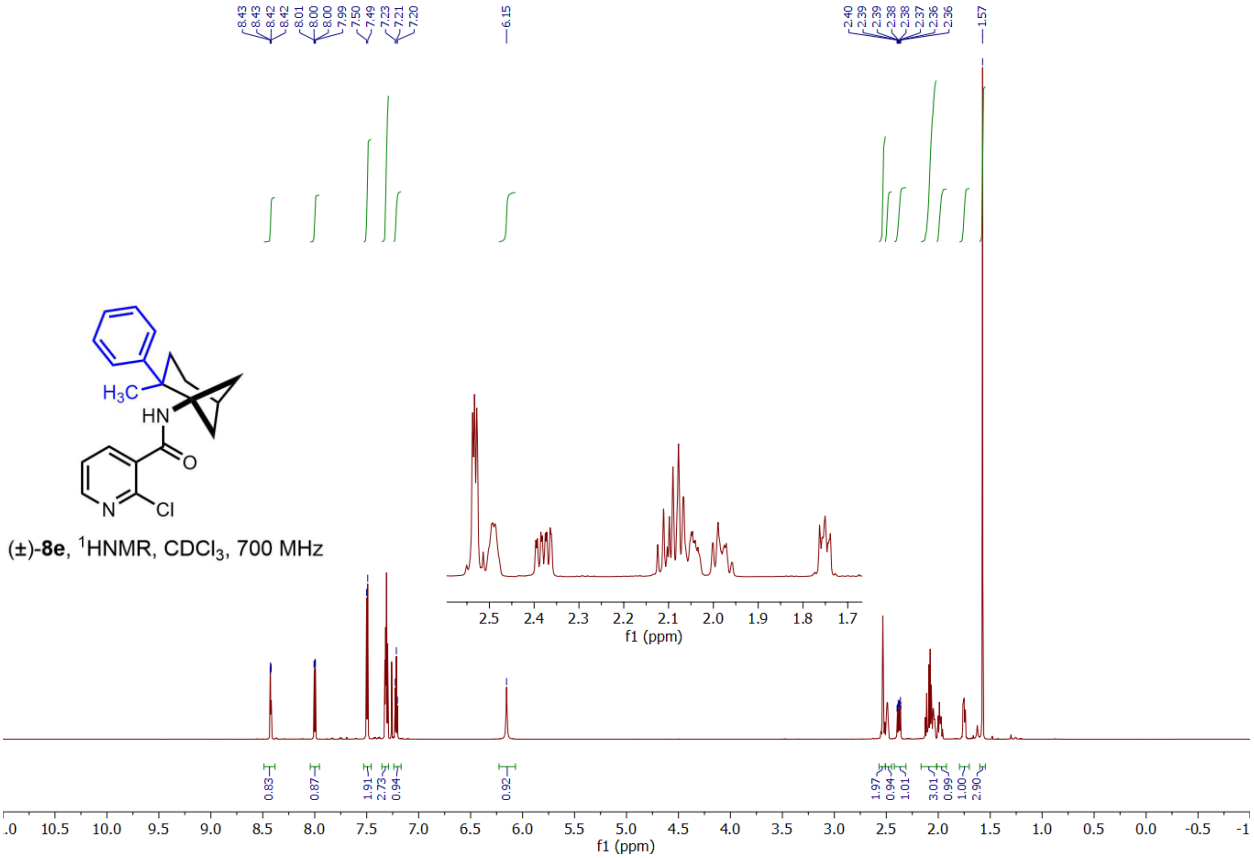
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.42 (dd, *J* = 4.8, 2.0 Hz, 1H), 8.00 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 2H), 7.34-7.29 (m, 3H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.15 (s, 1H), 2.56-2.51 (m, 2H), 2.51-2.47 (m, 1H), 2.38 (ddd, *J* = 14.8, 7.9, 2.6 Hz, 1H), 2.14-2.02 (m, 3H), 2.01-1.94 (m, 1H), 1.78-1.72 (m, 1H), 1.57 (s, 3H) ppm

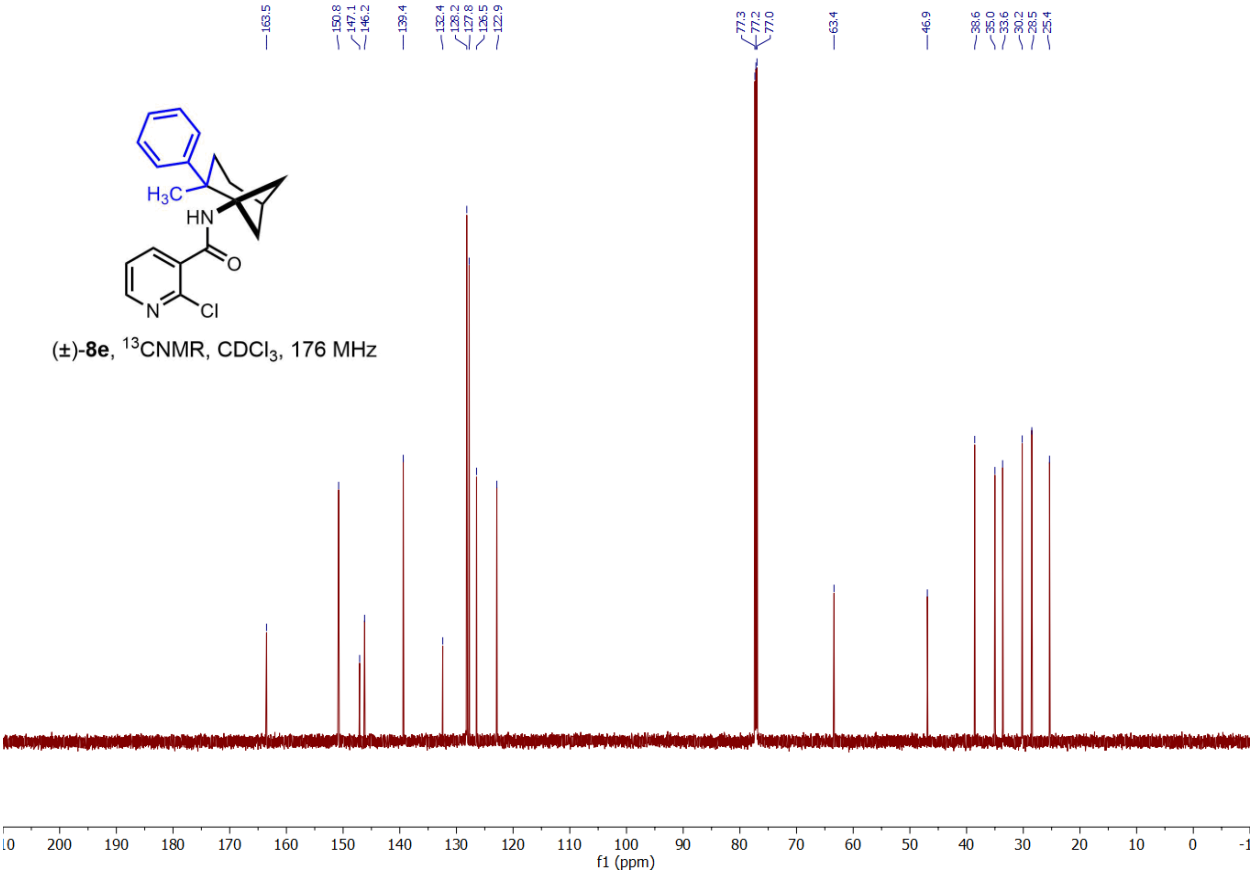
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 163.5, 150.8, 147.1, 146.2, 139.4, 132.4, 128.2, 127.8, 126.5, 122.9, 63.4, 46.9, 38.6, 35.0, 33.6, 30.2, 28.5, 25.4 ppm

IR (neat): 3268, 2944, 2864, 1651, 1581, 1519, 1497, 1455, 1397, 1306, 1271, 1244, 1229, 1185, 1156, 1126, 1095, 1071, 1033, 975, 910, 882, 844, 812, 775, 751, 721, 702, 672 cm^{-1}

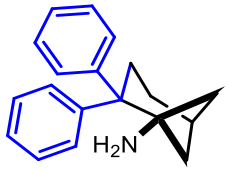
HRMS (ES+, m/z) calculated for $C_{20}H_{22}ClN_2O^+$: 341.1415, Found: 341.1432

R_f = 0.29 (50% ethyl acetate in hexanes), one yellow spot, $KMnO_4$, UV


8.43
8.43
8.42
8.42
8.01
8.00
8.00
7.99
7.50
7.49
7.23
7.21
7.20
6.15
2.40
2.39
2.39
2.38
2.38
2.37
2.36
2.36
1.57
H3C
HN
O
N
Cl
(±)-8e, 1HNMR, CDCl3, 700 MHz
f1 (ppm)
0.83
0.87
1.91
2.73
0.94
0.92
1.97
0.94
1.01
3.01
0.99
1.00
2.90
f1 (ppm)


163.5
150.8
147.1
146.2
139.4
130.4
128.2
127.8
126.5
122.9
77.3
77.2
77.0
63.4
46.9
38.6
35.0
33.6
30.2
28.5
25.4
H3C
HN
O
N
Cl
(±)-8e, 13CNMR, CDCl3, 176 MHz
f1 (ppm)

Compound **7f** :



EXPERIMENTAL PROCEDURE:
To an oven-dried 6-dram vial equipped with a stir bar was added **2a** (1.08 g, 5.00 mmol, 1 equiv), 2,2'-dipyridyldisulfide (11.0 mg, 0.050 mmol, 0.01 equiv), and 1,1-diphenylethylene (6.62 mL, 37.5 mmol, 7.5 equiv). The vial was sealed with a rubber septum and the reaction mixture was degassed through 3 freeze-pump-thaw cycles. The vial was further sealed with parafilm and irradiated for 76 hours with 2 390 nm Kessil lamps at maximum intensity positioned ~4 cm away from the vial on opposite sides and angled towards the bottom of the vial. Temperature was controlled using a fan positioned ~3 cm above the vial. The reaction mixture was allowed to cool to room temperature, then was transferred to a 250 mL round-bottom flask and sequentially diluted with acetonitrile (60 mL), water (20 mL), and acetic acid (20 mL) (with stirring). The headspace was flushed with argon and the mixture was stirred at room temperature for 24 hours. The mixture was then diluted with 1M aqueous HCl (200 mL) and extracted with diethyl ether (3 x 100 mL). The ethereal extracts (containing 1,1-diphenylethylene, 4-nitrobenzaldehyde, acetic acid, and non-basic byproducts) were discarded. The aqueous layer was brought to pH ~ 12 with 3M aqueous NaOH and was extracted with diethyl ether (4 x 100 mL). The combined ethereal extracts were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **7f** as a brown oil (492.4 mg, 1.87 mmol, 37%), which was pure enough for most purposes.

Note: A portion of this material was chromatographed on silica gel (that had been pre-neutralized with 3 column volumes of 10% ethyl acetate: 89% hexanes: 1% triethylamine) eluting with 24-100% ethyl acetate in hexanes to give **7f** as an extremely thick yellow oil (Note: strongly retains ethyl acetate). Spectra are provided of both the crude and chromatographed materials, with the minor impurity peaks emphasized for the crude material. The listed analytical data was collected on the chromatographed sample.

Appearance: brown oil when crude, yellow oil after chromatography on silica gel

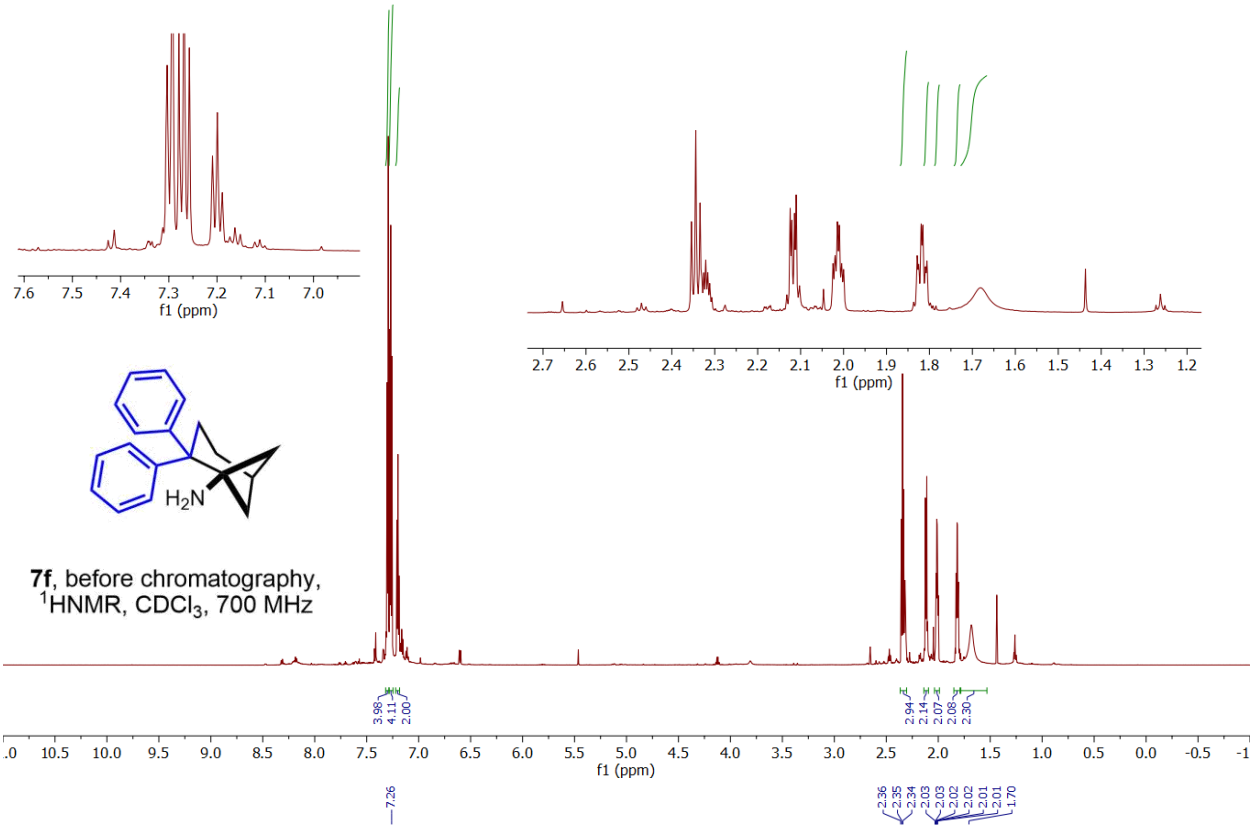
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.33-7.29 (m, 4H), 7.29-7.25 (m, 4H), 7.22-7.19 (m, 2H), 2.35 (app. t, *J* = 7.1 Hz, 2H), 2.34-2.31 (m, 1H), 2.15-2.10 (m, 2H), 2.02 (td, *J* = 7.0, 3.2 Hz, 2H) 1.70 (s, 2H) ppm

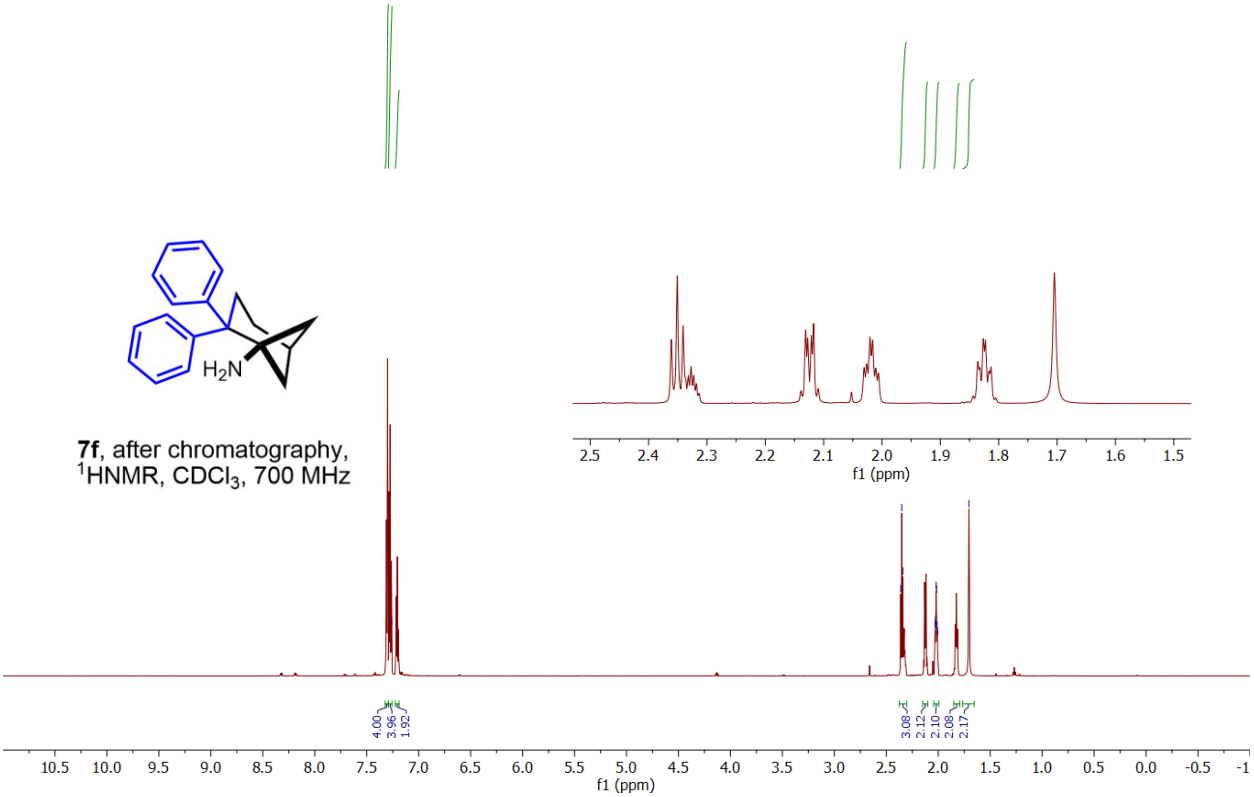
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 148.3, 129.2, 127.7, 125.8, 61.2, 57.0, 41.4, 36.5, 30.0, 28.1 ppm

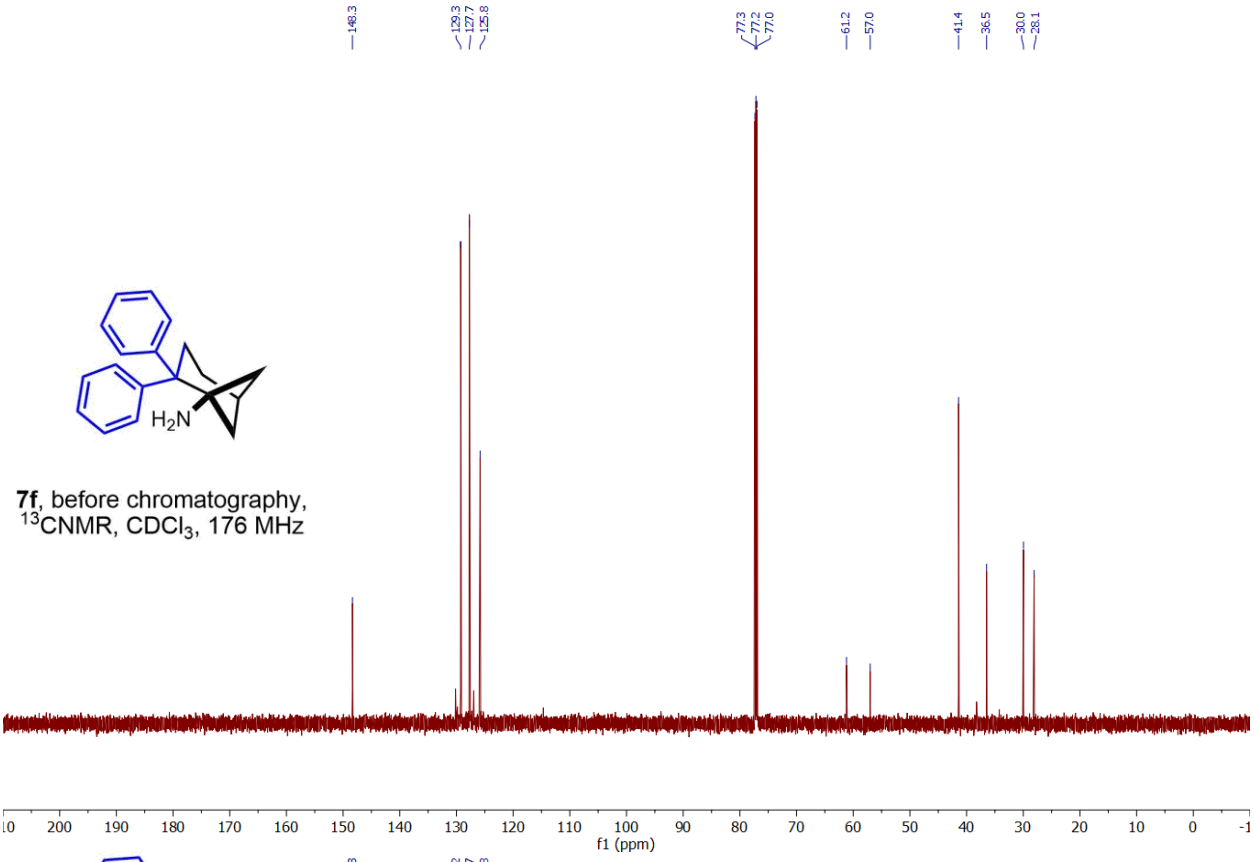
IR (neat): 3387, 3085, 3054, 3030, 2943, 2860, 1600, 1520, 1493, 1455, 1443, 1346, 1319, 1263, 1232, 1209, 1190, 1157, 1088, 1076, 1028, 1021, 1001, 949, 925, 904, 865, 852, 796, 778, 763, 748, 723, 699, 667 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{19}H_{22}N^+$: 264.1747, Found: 264.1746

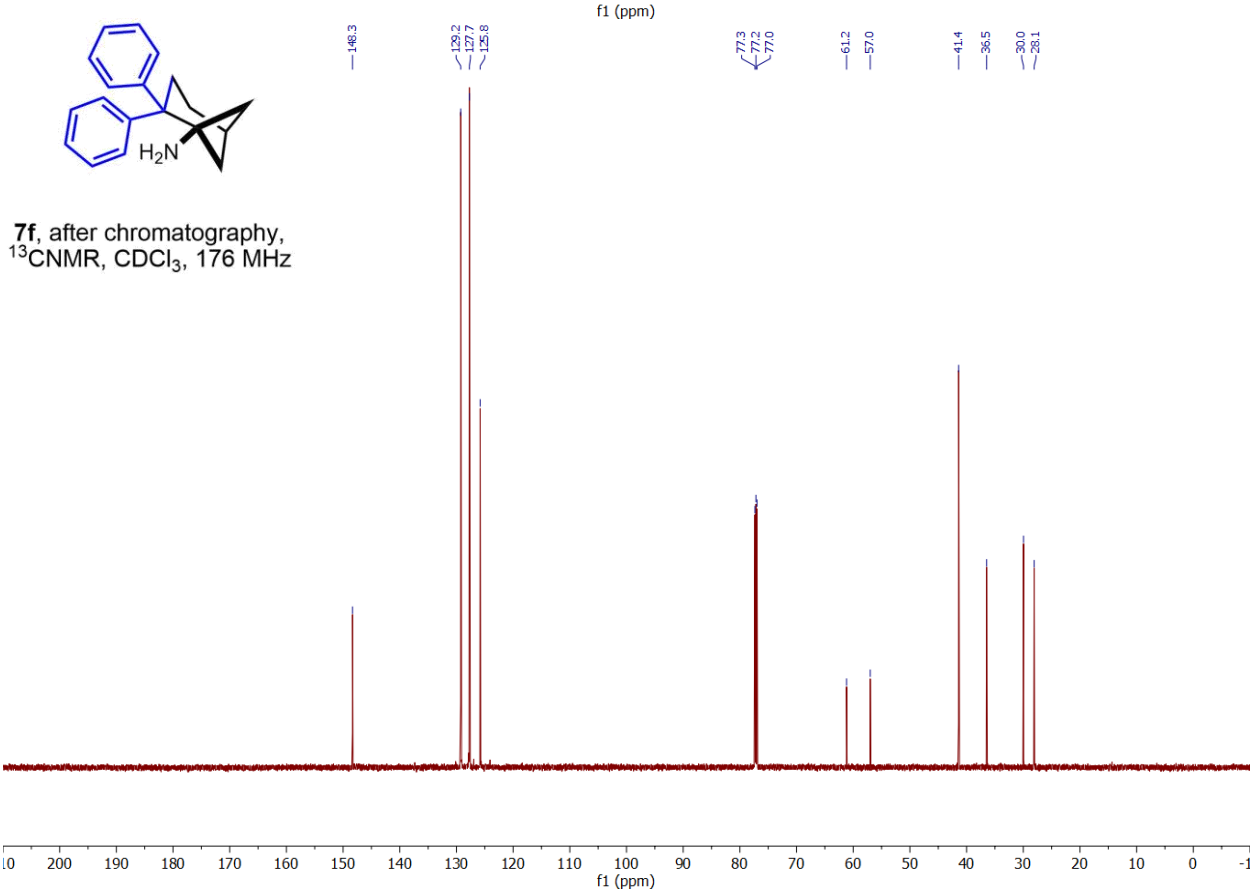
R_f = 0.50 (50% ethyl acetate: 49% hexanes: 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


H2N
7f, before chromatography,
1HNMR, CDCl3, 700 MHz
f1 (ppm)
7.26


H2N
7f, after chromatography,
1HNMR, CDCl3, 700 MHz
f1 (ppm)

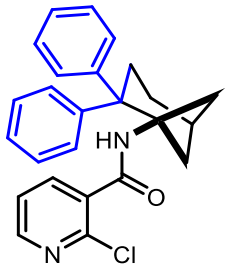


7f, before chromatography,
^{13}CNMR, $CDCl_3$, 176 MHz



7f, after chromatography,
^{13}CNMR, $CDCl_3$, 176 MHz

Compound **8f** :



EXPERIMENTAL PROCEDURE:
To an oven-dried 2-dram vial equipped with a magnetic stir bar was added **7f** (73.7 mg, 0.280 mmol, 1 equiv) and the vial was capped and put under argon. Triethylamine (0.195 mL, 1.40 mmol, 5 equiv) and and dichloromethane (4.4 mL) were sequentially added. Next, a mixture of 2-Chloronicotinoyl chloride (73.9 mg, 0.420 mmol, 1.5 equiv) in dichloromethane (0.9 mL) was added to the vial over 2 minutes via syringe at room temperature. Some smoking was observed during the addition. The vial was sealed shut under argon, the cap being wrapped with parafilm, then placed in an aluminum heating block at 40 °C and allowed to stir for 3 hours. The reaction mixture was transferred to a round-bottom flask and concentrated onto celite (3 grams). The resulting solid mixture was dry-loaded atop a silica column and eluted with 12-100% ethyl acetate in hexanes to give **8f** (65.9 mg, 0.164 mmol, 58%) as a faintly yellow solid.

Appearance: Faintly yellow solid

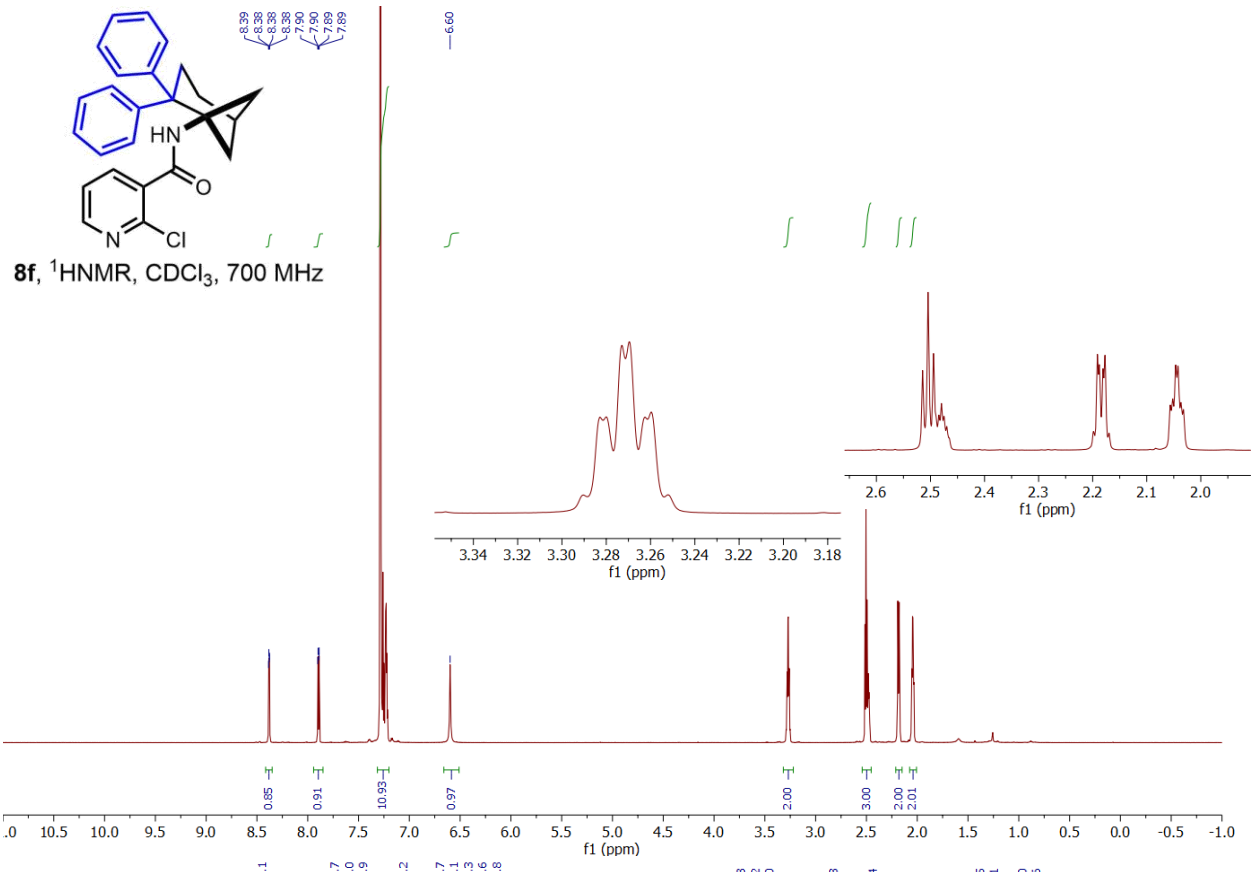
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.38 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.89 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.31-7.20 (m, 11H), 6.60 (s, 1H), 3.30-3.24 (m, 2H), 2.53-2.45 (m, 3H), 2.21-2.16 (m, 2H), 2.07-2.01 (m, 2H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 164.1, 150.7, 147.0, 146.9, 139.2, 132.7, 129.1, 128.3, 126.6, 122.8, 63.3, 56.4, 36.5, 36.1, 29.0, 28.6 ppm

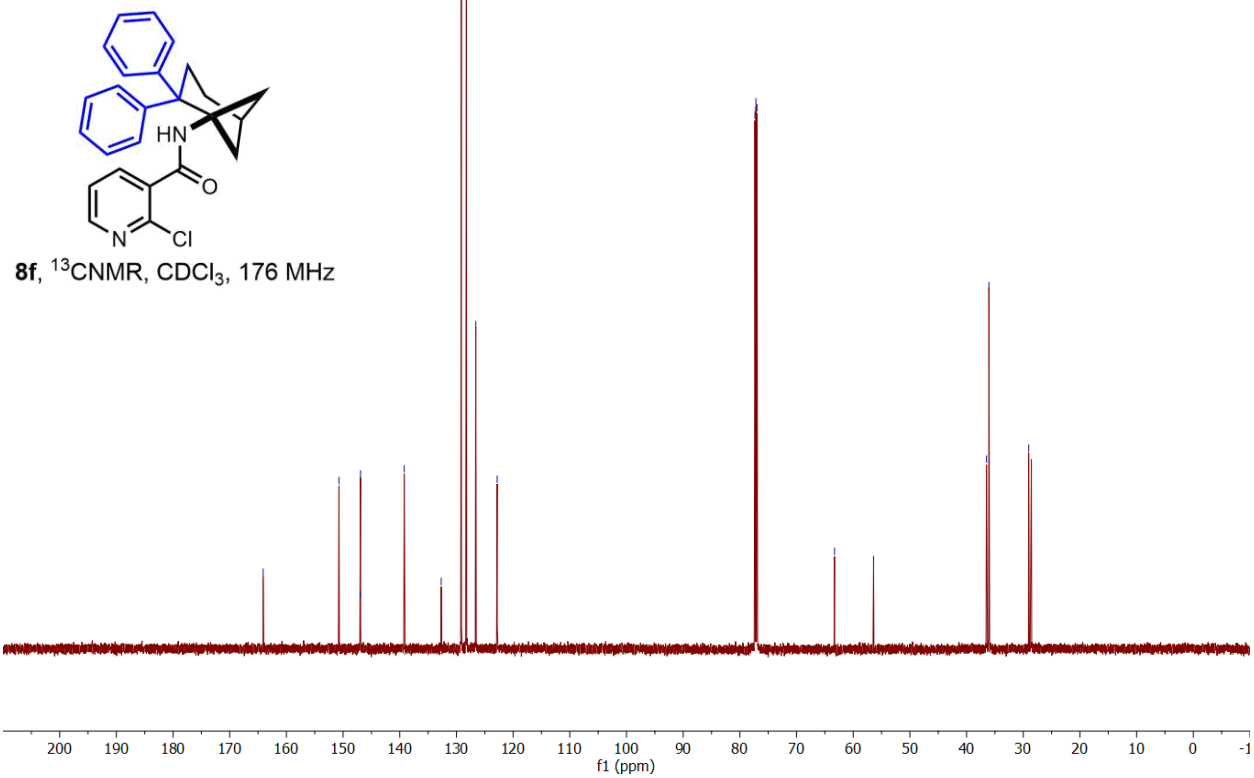
IR (neat): 3398, 2964, 1668, 1578, 1494, 1444, 1400, 1301, 1263, 1220, 1203, 1185, 1132, 1067, 1003, 951, 916, 876, 819, 786, 767, 757, 716, 702, 678 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{25}H_{24}ClN_2O^+$: 403.1572, Found: 403.1589

R_f = 0.41 (50% ethyl acetate in hexanes), one yellow spot, $KMnO_4$, UV

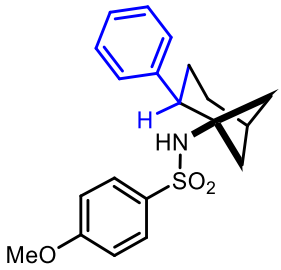


8f, ^{1}HNMR, $CDCl_3$, 700 MHz



8f, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**10** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7d** (50.0 mg, 0.267 mmol, 1 equiv) and triethylamine (0.0447 mL, 0.320 mmol, 1.2 equiv) followed by acetonitrile (2.67 mL). 4-Methoxybenzenesulfonyl chloride (55.2 mg, 0.259 mmol, 1 equiv) was then added in one portion. The headspace was flushed with argon and the vial was sealed with a Teflon-lined cap. The cap was further sealed with parafilm and the vial was placed in a preheated aluminum block at 100 °C and stirred for 18 hours. The reaction mixture was then concentrated onto 3 grams of celite which was loaded atop a silica column. Elution with 7-60% ethyl acetate in hexanes afforded (±)-**10** (92.7 mg, 0.259 mmol, 97%) as a white solid.

Appearance: white solid

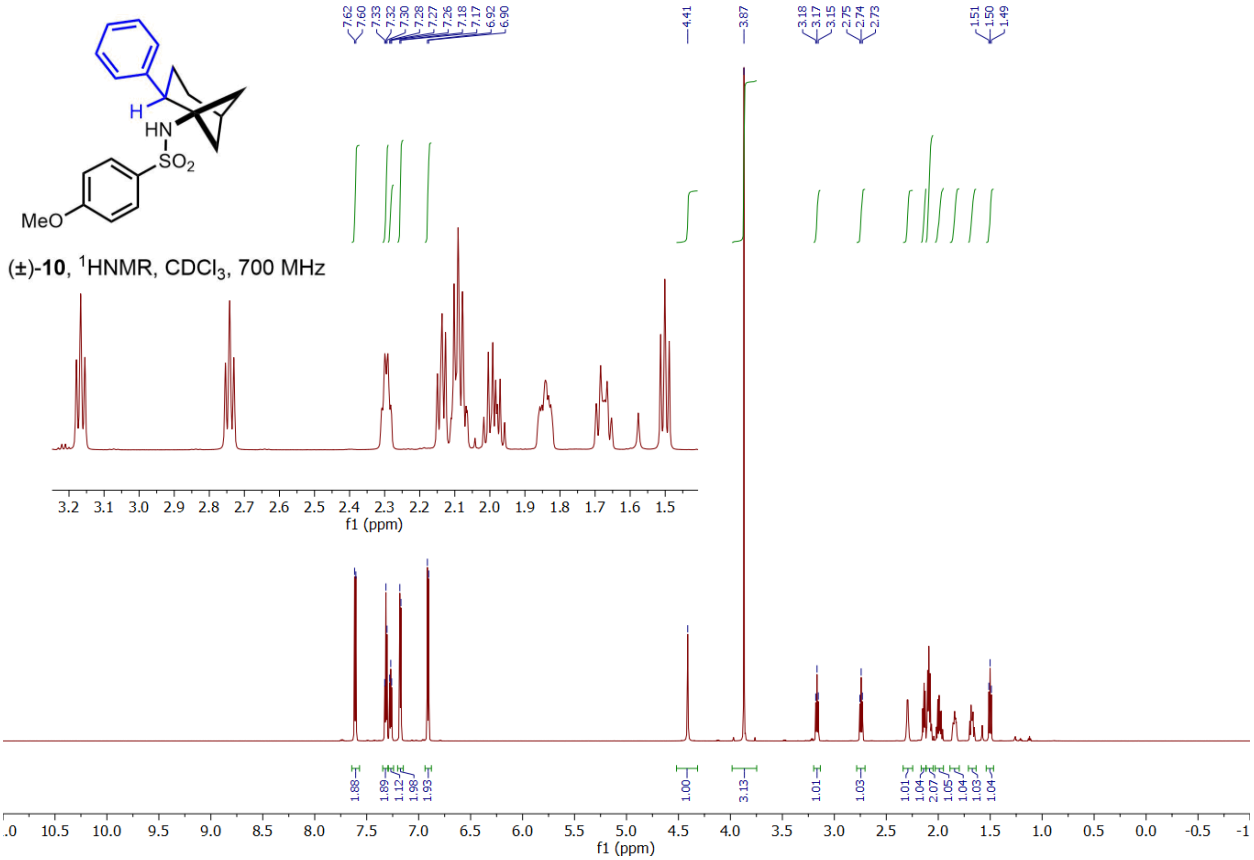
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.63-7.59 (m, 2H), 7.33-7.29 (m, 2H), 7.29-7.25 (m, 1H), 7.19-7.16 (m, 2H), 6.93-6.89 (m, 2H), 4.41 (s, 1H), 3.87 (s, 3H), 3.17 (app. t, *J* = 8.5 Hz, 1H), 2.74 (app. t, *J* = 8.4 Hz, 1H), 2.32-2.27 (m, 1H), 2.16-2.12 (m, 1H), 2.12-2.05 (m, 2H), 2.03-1.95 (m, 1H), 1.88-1.81 (m, 1H), 1.71-1.64 (m, 1H), 1.50 (app. t, *J* = 8.5 Hz, 1H) ppm

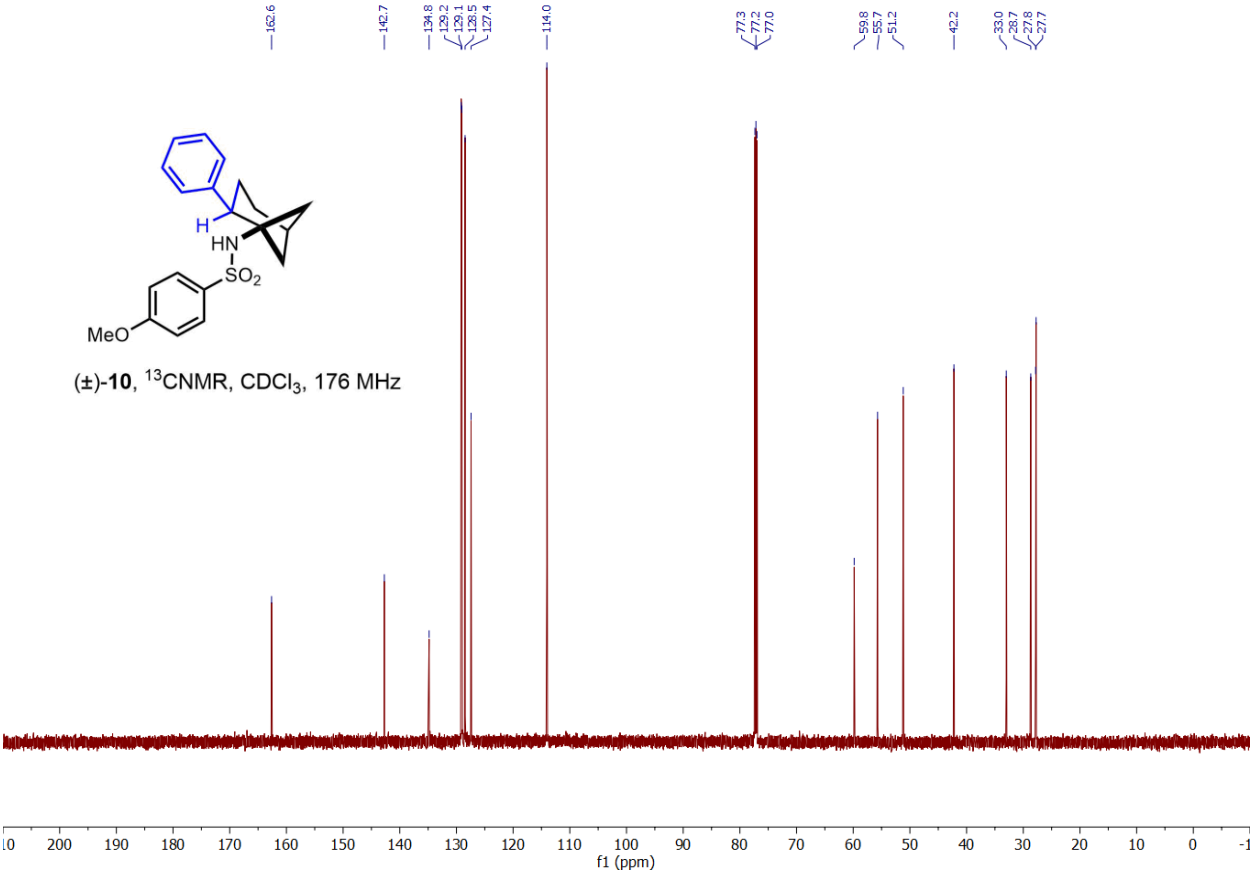
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 162.6, 142.7, 134.8, 129.2, 129.1, 128.5, 127.4, 114.0, 59.8, 55.7, 51.2, 42.2, 33.0, 28.7, 27.8, 27.7 ppm

IR (neat): 3249, 2947, 2870, 1596, 1579, 1499, 1456, 1442, 1417, 1319, 1292, 1259, 1186, 1139, 1116, 1095, 1030, 997, 955, 904, 883, 834, 811, 802, 767, 701, 668 cm^{-1}

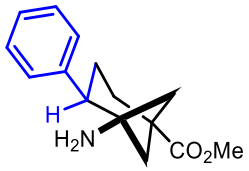
HRMS (EI+, m/z) calculated for $[C_{20}H_{23}NO_3S]^{\bullet+}$: 357.1393, Found: 357.1393

R_f = 0.26 (30% ethyl acetate : 70% hexanes), yellow spot, $KMnO_4$, UV


H
HN
SO2
MeO
(±)-10, 1HNMR, CDCl3, 700 MHz
f1 (ppm)


H
HN
SO2
MeO
(±)-10, 13CNMR, CDCl3, 176 MHz
f1 (ppm)

Compound (±)-**7g** :



EXPERIMENTAL PROCEDURE:

To a 250 mL round bottom flask equipped with a magnetic stir bar was added (±)-**4b** (1.55 g, 4.10 mmol, 1 equiv) and acetonitrile (24 mL) and the mixture was put under argon atmosphere. Stirring gave a yellow solution. Water (8 mL) and acetic acid (8 mL) were added via syringe and the mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with 0.5 M hydrochloric acid (50 mL) and extracted with diethyl ether (3 x 50 mL) to remove the 4-nitrobenzaldehyde by-product. The aqueous layer was then diluted with saturated aqueous sodium bicarbonate solution (400 mL) and extracted with diethyl ether (5 x 100 mL). The combined organic fractions were washed with brine (100 mL), dried over sodium sulfate, filtered, and dried in vacuo to give (±)-**7g** (832 mg, 3.39 mmol, 83%) as a white solid.

Appearance: white solid

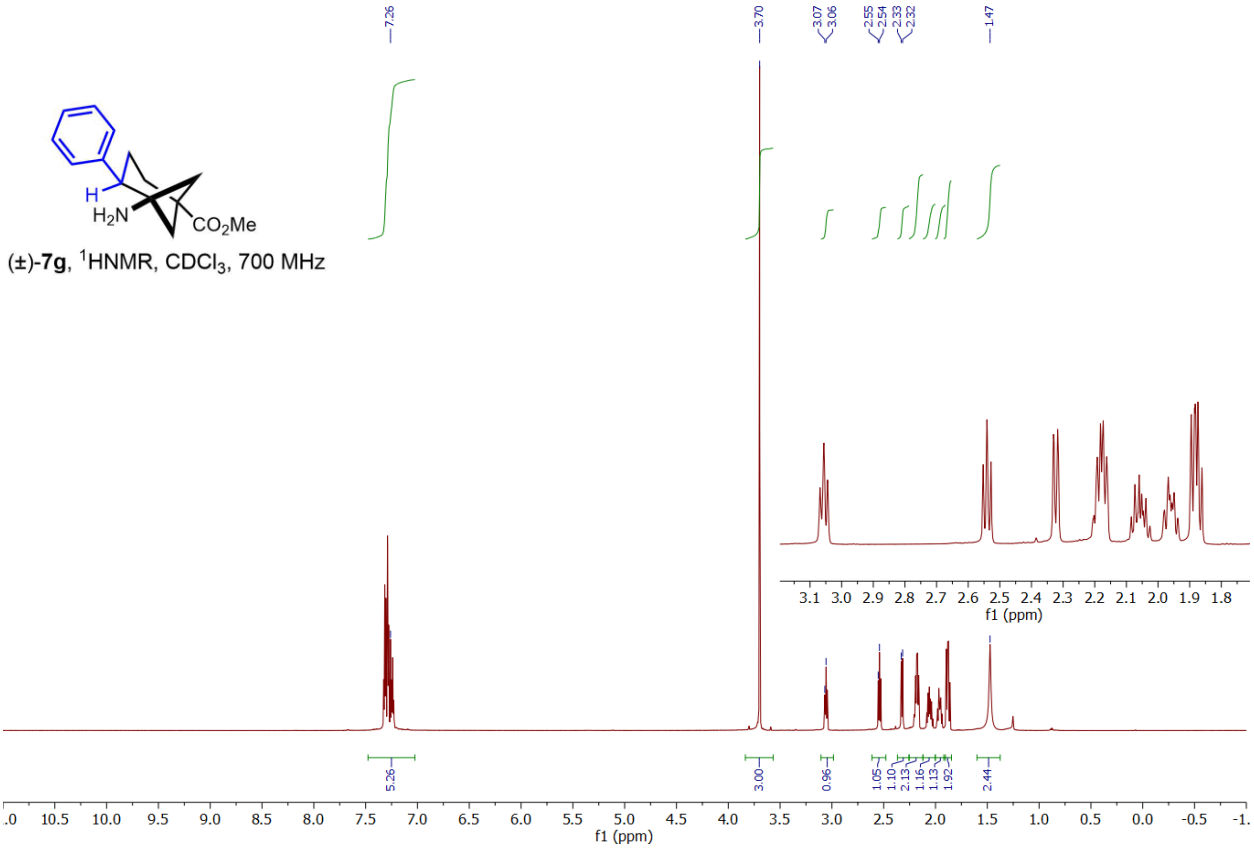
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.35-7.20 (m, 5H), 3.70 (s, 3H), 3.06 (app. t, *J* = 8.4 Hz, 1H), 2.54 (app. t, *J* = 8.2 Hz, 1H), 2.32 (app. d, *J* = 9.1 Hz, 1H), 2.21-2.15 (m, 2H), 2.10-2.02 (m, 1H), 2.00-1.93 (m, 1H), 1.91-1.85 (m, 2H), 1.47 (bs, 2H), ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.8, 143.6, 128.7, 128.3, 127.0, 55.3, 52.0, 50.6, 48.8, 40.4, 39.9, 29.8, 27.3 ppm

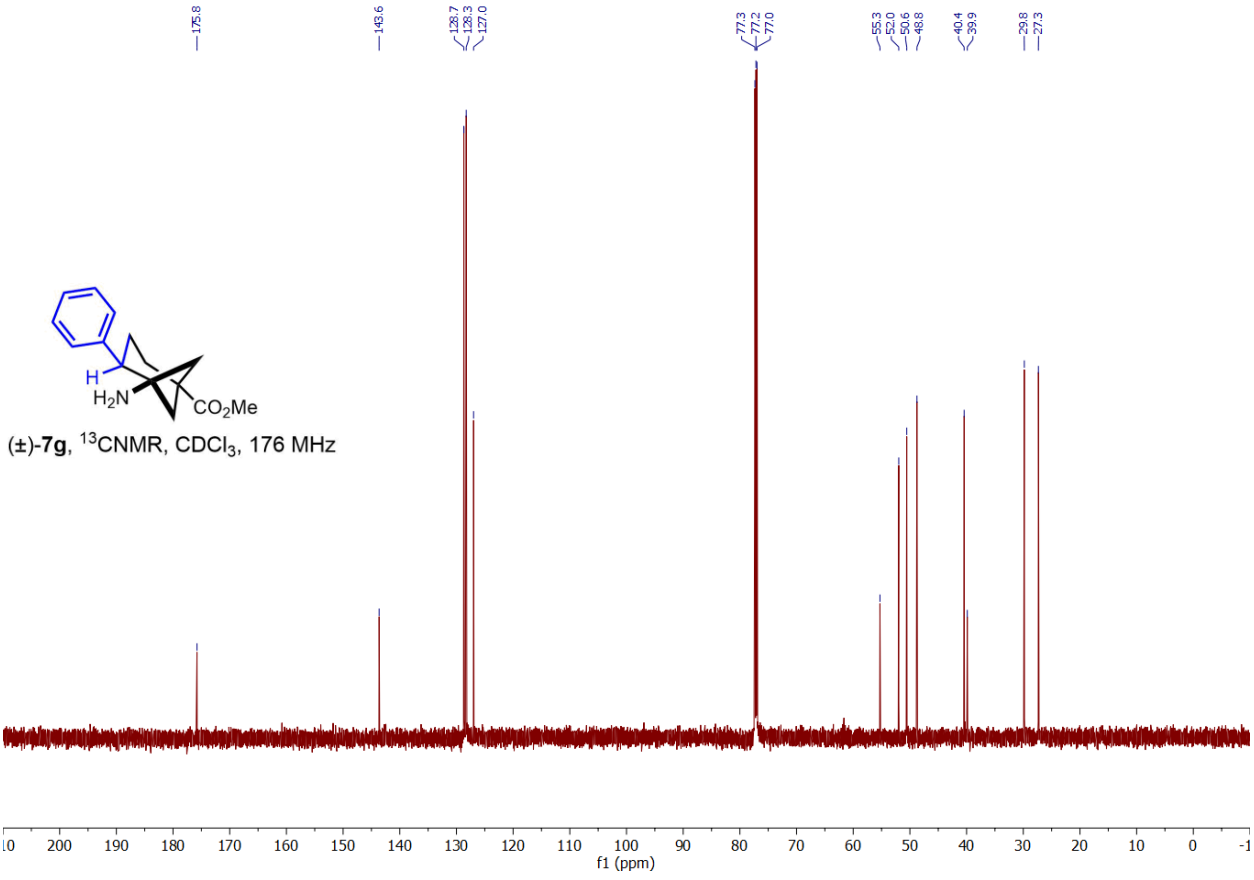
IR (neat): 3390, 3327, 3059, 3030, 2963, 2947, 2911, 2865, 1719, 1602, 1495, 1474, 1451, 1431, 1341, 1298, 1264, 1235, 1217, 1206, 1172, 1155, 1114, 1074, 1050, 1031, 993, 980, 958, 944, 921, 887, 808, 788, 769, 751, 705, 691 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{15}H_{20}NO_2^+$: 246.1489, Found: 246.1486

R_f = 0.42 (99% ethyl acetate : 1% NH_4OH), one yellow spot, $KMnO_4$, UV

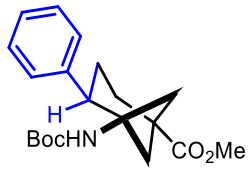


(±)-**7g**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**7g**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**13** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with stir bar was added (±)-**7g** (100 mg, 0.41 mmol, 1 equiv), CH_2Cl_2 (3 mL), and Et_3N (63 µL, 0.45 mmol, 1.1 equiv). The headspace was flushed with argon and kept under argon atmosphere with a balloon. Boc_2O (98 mg, 0.45 mmol, 1.1 equiv) in CH_2Cl_2 (1.1 mL) was added in one portion and the mixture was stirred at room temperature for 18 hours. The reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (1 mL) and partitioned with saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and dried in vacuo. The crude material was purified by flash column chromatography on silica eluting with 5-40% ethyl acetate in hexanes to afford (±)-**13** (117 mg, 0.34 mmol, 83%) as a colorless oil that solidified upon standing to give a white solid.

Appearance: white solid

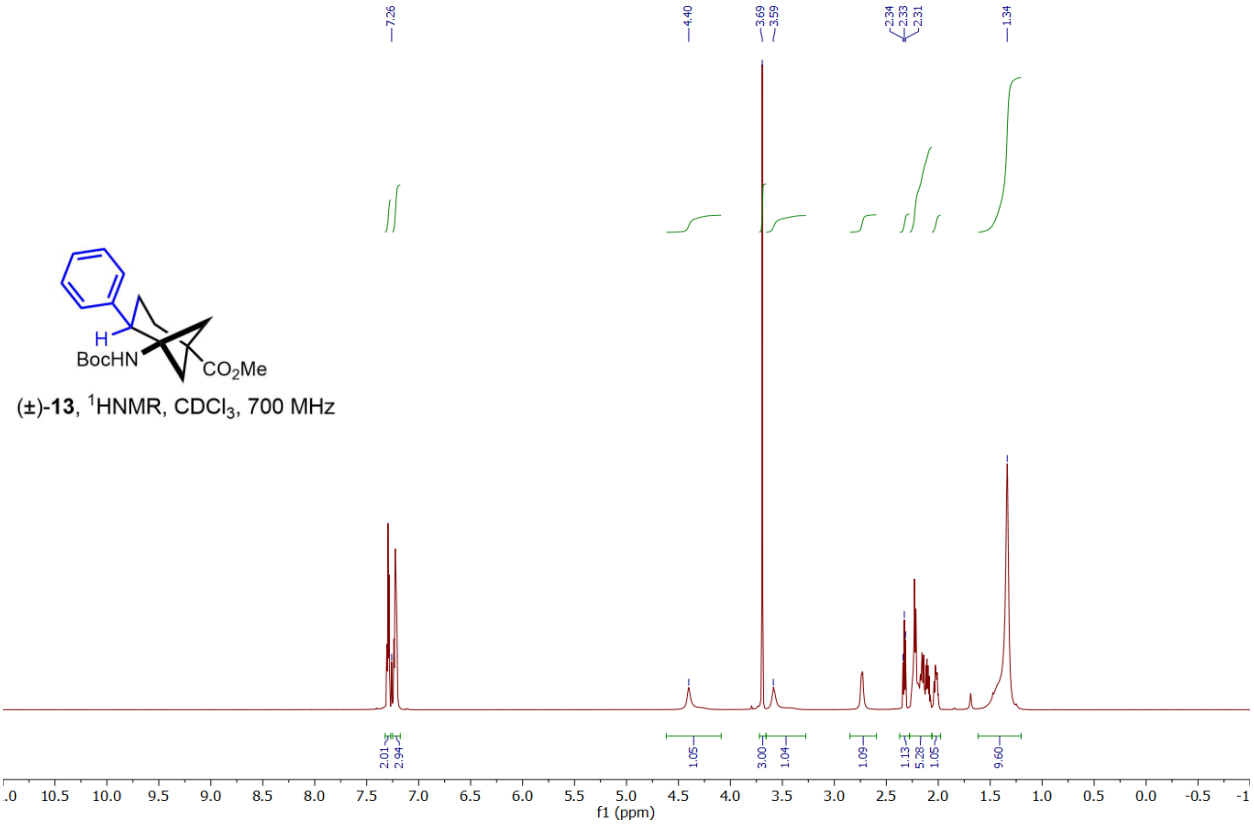
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.32-7.27 (2, 3H), 7.25-7.19 (m, 3H), 4.40 (bs with up-field shoulder, 1H), 3.69 (s, 3H), 3.59 (bs with up-field shoulder, 1H), 2.33 (app. t, *J* = 8.6 Hz, 1H), 2.28-2.07 (m, 5H), 2.06-1.98 (m, 1H), 1.34 (bs with down-field shoulder, 9H) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 175.3, 154.3, 143.2, 128.5, 128.4, 126.8, 79.1, 54.8, 52.0, 47.4, 45.5, 42.3, 35.1, 29.8, 28.5, 25.9 ppm

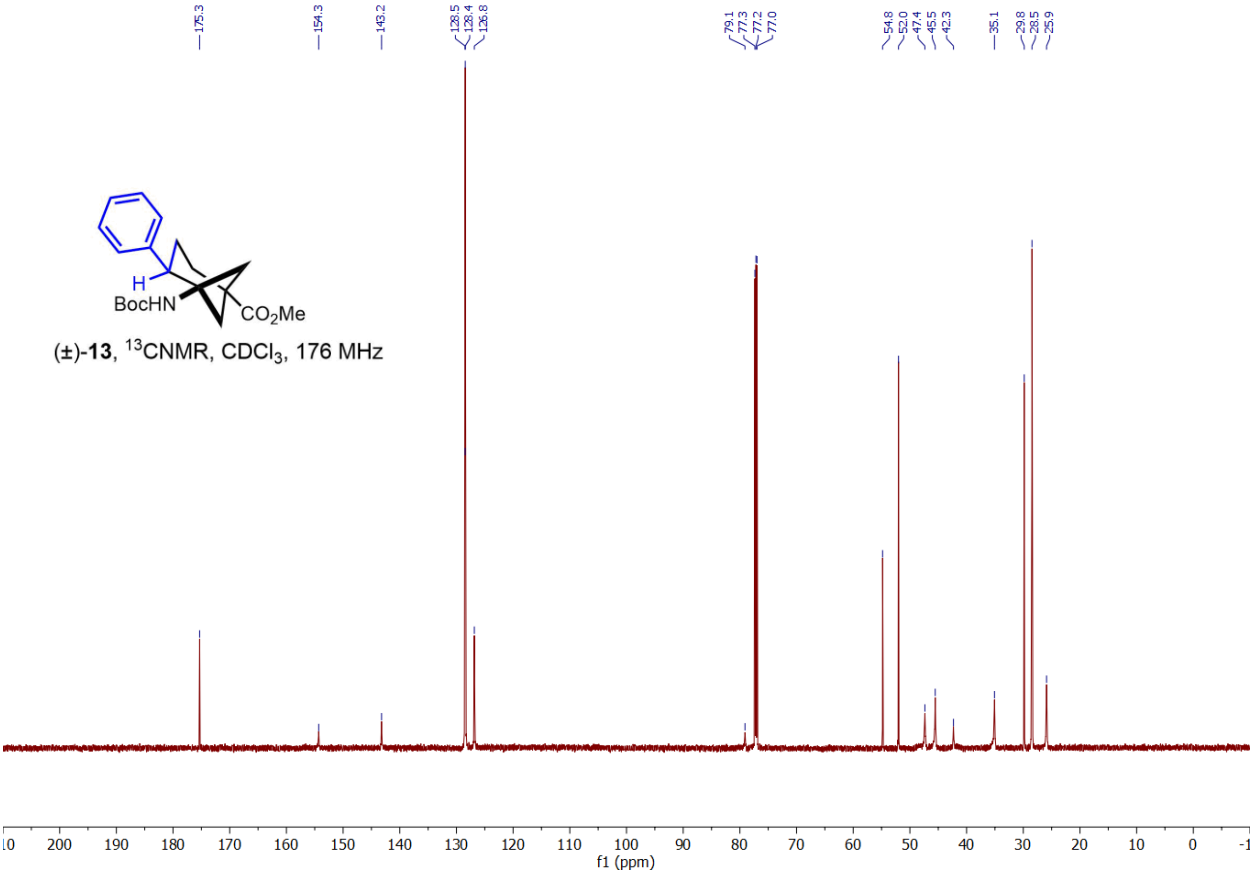
IR (neat): 3368, 3030, 2977, 2952, 2871, 1708, 1603, 1495, 1454, 1435, 1391, 1365, 1345, 1279, 1258, 1243, 1214, 1163, 1121, 1086, 1041, 1026, 1012, 973, 917, 873, 778, 753, 736, 700 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{27}NNaO_4^+$: 368.1832, Found: 368.1831

R_f = 0.21 (20% ethyl acetate : 80% hexanes), yellow spot, $KMnO_4$, UV

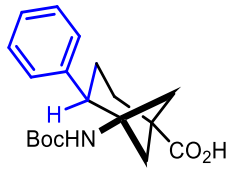


(±)-**13**, ^{1}HNMR, $CDCl_3$, 700 MHz



(±)-**13**, ^{13}CNMR, $CDCl_3$, 176 MHz

Compound (±)-**14** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial equipped with a magnetic stir bar was added (±)-**13** (87.1 mg, 0.252 mmol, 1 equiv) followed by a 4:1:1 mixture of THF/methanol/water. To the resulting solution was added lithium hydroxide hydrate (15.9 mg, 0.378 mmol, 1.50 equiv) in one portion. The vial was sealed with a Teflon-lined cap and the mixture was stirred at room temperature for 18 hours. The mixture was then diluted with water (20 mL) and washed with diethyl ether (2 x 10 mL). The aqueous layer was carefully acidified to pH ~4 using 2M aqueous hydrochloric acid and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate fractions were dried over sodium sulfate, filtered, and concentrated in vacuo to give (±)-**14** (83.0 mg, 0.250 mmol, 99%) as a white solid.

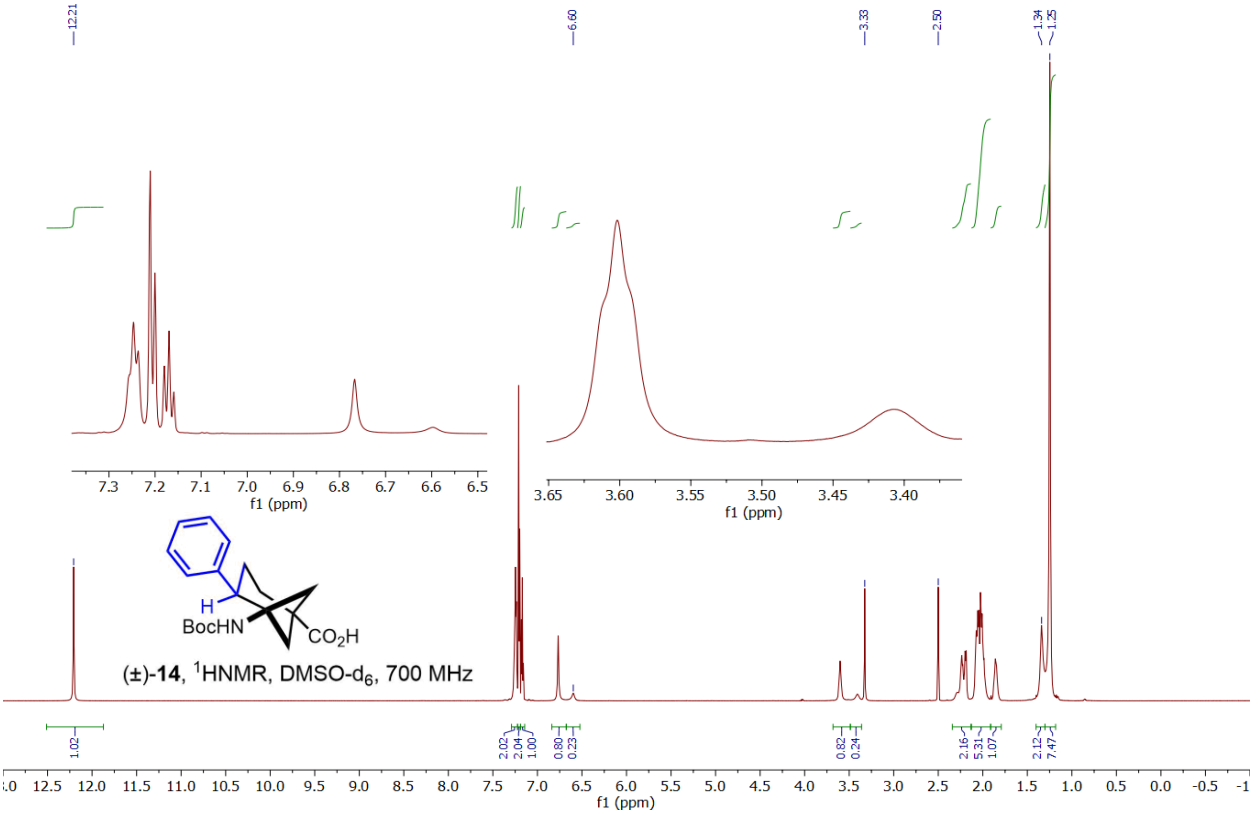
Appearance: white solid

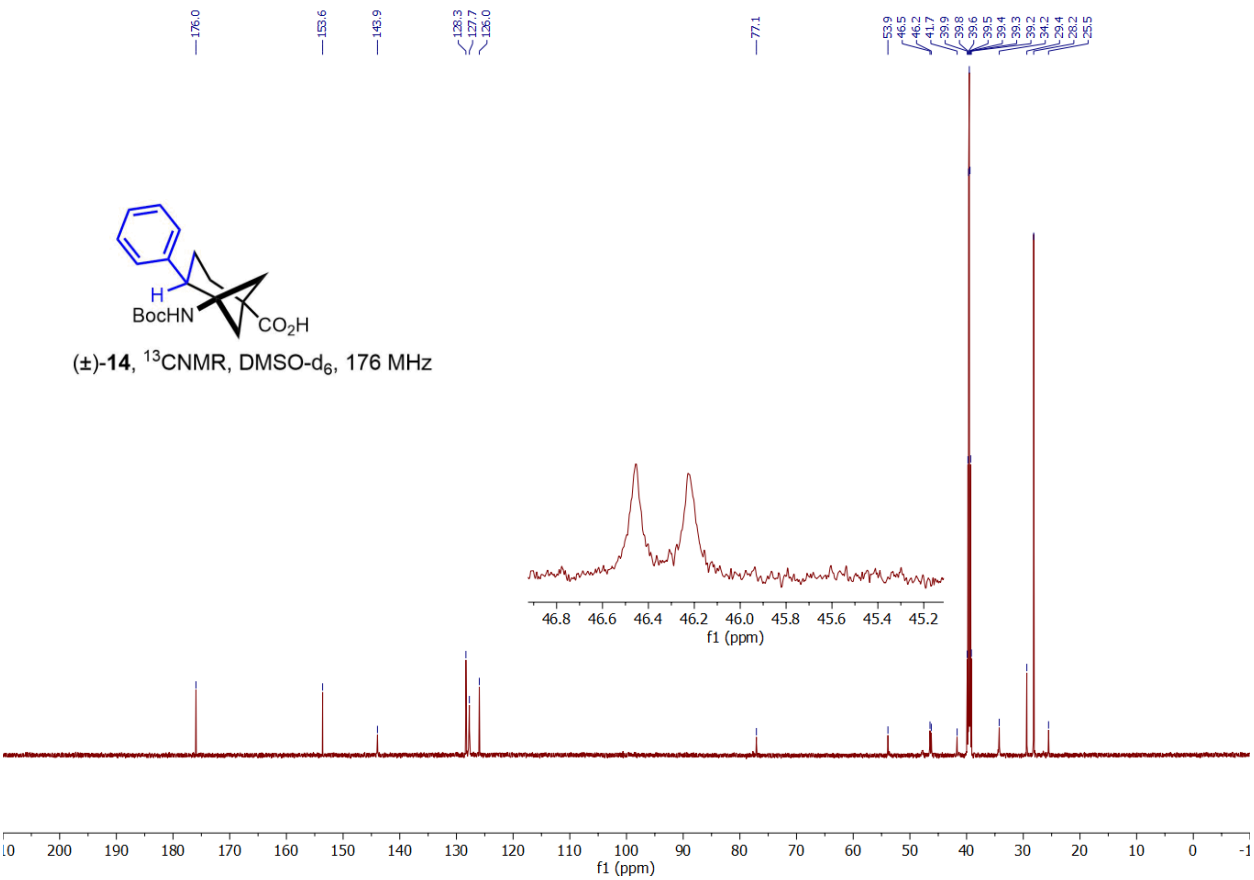
^{1}H NMR (DMSO-d_6, 700 MHz): Note: observed an approximately ~4:1 mixture of rotamers δ = 12.21 (s, 1H), 7.29-7.22 (m, 2H), 7.22-7.19 (m, 2H), 7.19-7.14 (m, 1H), 6.77 (bs, ~0.8H), 6.60 (bs, ~0.2H), 3.67-3.49 (m, ~0.8H), 3.49-3.36 (m, ~0.2H), 2.34-2.13 (m, 2H), 2.13-1.91 (m, 5H), 1.91-1.79 (m, 1H), 1.34 (bs, ~2H), 1.25 (bs, ~7H) ppm

^{13}C NMR (DMSO-d_6, 176 MHz): Major rotamer: δ = 176.0, 153.6, 143.9, 128.3, 127.7, 126.0, 77.1, 53.9, 46.5, 46.2, 41.7, 34.2, 29.4, 28.2, 25.5 ppm

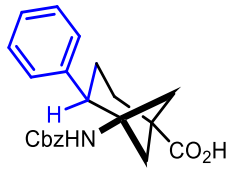
IR (neat): 3500-2200 (broad), 3409, 2979, 1696, 1496, 1454, 1419, 1391, 1364, 1296, 1270, 1238, 1201, 1169, 1091, 1043, 1008, 951, 910, 894, 875, 844, 779, 763, 742, 704, 656 cm^{-1}

HRMS (ES-, m/z) calculated for $C_{19}H_{24}NO_4^-$: 330.1711, Found: 330.1718


12.21
6.60
3.33
2.50
1.34
1.25
7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5
f1 (ppm)
3.65 3.60 3.55 3.50 3.45 3.40
f1 (ppm)
H
BocHN
CO2H
(±)-14, 1HNMR, DMSO-d6, 700 MHz
1.02
2.02
2.04
1.00
0.80
0.23
0.82
0.24
2.16
5.31
1.07
2.12
7.47
f1 (ppm)


176.0
153.6
143.9
128.3
127.7
126.0
77.1
53.9
46.5
46.2
41.7
39.9
39.8
39.6
39.5
39.4
39.3
39.2
34.2
29.4
28.2
25.5
H
BocHN
CO2H
(±)-14, 13CNMR, DMSO-d6, 176 MHz
46.8 46.6 46.4 46.2 46.0 45.8 45.6 45.4 45.2
f1 (ppm)
f1 (ppm)

Compound (±)-**12** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 2-dram vial was added (±)-**7g** (100 mg, 0.408 mmol, 1 equiv) and sodium bicarbonate (86.4 mg, 0.815 mmol, 2.00 equiv). To this mixture were added dioxane (1.5 mL) and water (0.5 mL). The headspace was flushed with argon and the mixture was maintained under argon atmosphere with a balloon. Benzyl chloroformate (0.0683 mL, 0.448 mmol, 1.10 equiv) was added dropwise over 5 minutes with stirring and the mixture was allowed to stir at room temperature for 19 hours. The reaction mixture was then partitioned between ethyl acetate (20 mL) and water (10 mL) and the layers were separated. The organic layer was washed with brine (1 x 10 mL), dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was chromatographed on silica eluting with 5-40% ethyl acetate in hexanes. All fractions containing spot with Rf = 0.15 (20% ethyl acetate : 80% hexanes) were combined and concentrated in 4-dram vial. The impure residue was dissolved in a 4:1:1 mixture of THF/methanol/water (4.08 mL) and lithium hydroxide hydrate (34.2 mg, 0.815 mmol, 2.00 equiv) was added in one portion. The mixture was stirred at room temperature for 18 hours. The mixture was then diluted with water (20 mL) and washed with diethyl ether (2 x 20 mL). The aqueous layer was acidified to pH ~2 with 2M aqueous HCl and extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate fractions were dried over sodium sulfate, filtered, and concentrated in vacuo to give (±)-**12** (144.9 mg, 0.397 mmol, 97%) as a white solid.

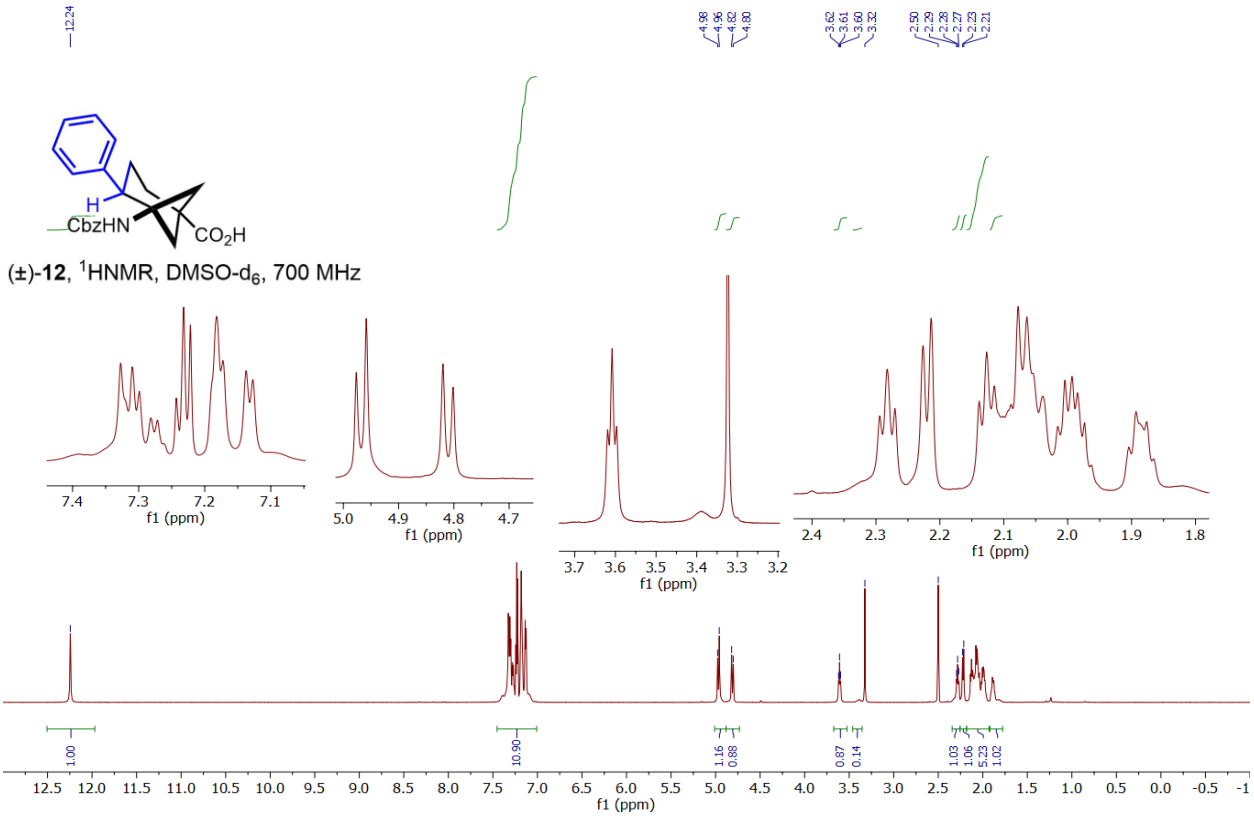
Appearance: white solid

^{1}H NMR (DMSO-d_6, 700 MHz): δ = Note: observed an approximately ~7:1 mixture of rotamers 12.24 (s, 1H), 7.45-7.01 (m, 10H), 4.99-4.94 (m, ~1.16H), 4.84-4.78 (m, ~0.88H) (the former 2 peaks should appear as an AB quartet but the signals are convoluted by the presence of rotamers), 3.61 (app. t, *J* = 7.6 Hz, ~0.87H), 3.45-3.35 (m, ~0.14H), 2.28 (app. t, *J* = 8.3 Hz, 1H), 2.22 (app. t, *J* = 9.0 Hz, 1H), 2.18-1.92 (m, 5H), 1.92-1.78 (m, 1H) ppm

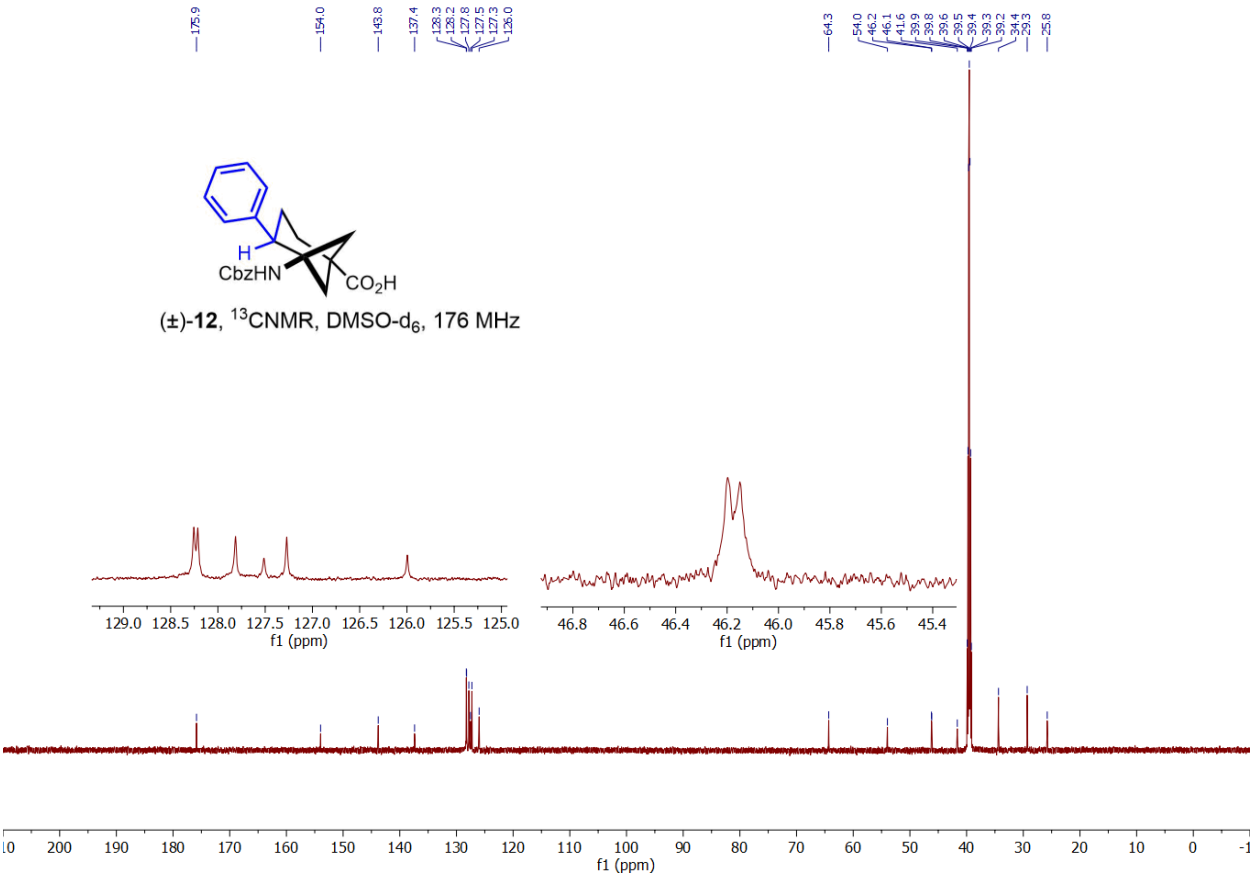
^{13}C NMR (DMSO-d_6, 176 MHz): Major rotamer: δ = 175.9, 154.0, 143.8, 137.4, 128.3, 128.2, 127.8, 127.5, 127.3, 126.0, 64.3, 54.0, 46.2, 46.1, 41.6, 34.4, 29.3, 25.8 ppm

IR (neat): 3500-2100 (broad), 3399, 3030, 2953, 2875, 1699, 1685, 1604, 1512, 1495, 1463, 1453, 1420, 1376, 1295, 1259, 1232, 1198, 1095, 1040, 1020, 954, 907, 844, 788, 778, 762, 743, 733, 711, 704, 697, 656 cm^{-1}

HRMS (ES-, m/z) calculated for $C_{22}H_{22}NO_4^-$: 364.1554, Found: 364.1567

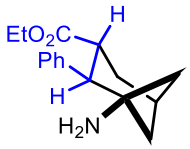


(±)-**12**, ^{1}HNMR, DMSO-d_6, 700 MHz



(±)-**12**, ^{13}CNMR, DMSO-d_6, 176 MHz

Compound (±)-**7h** :



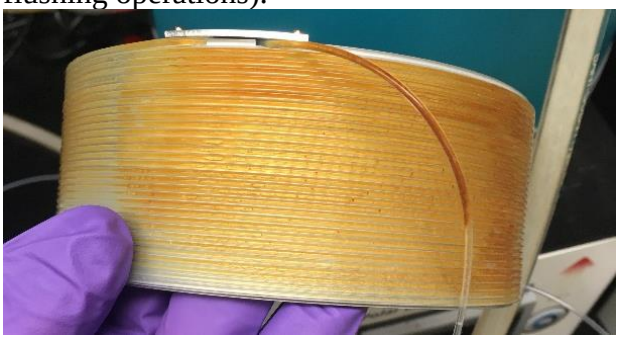
EXPERIMENTAL PROCEDURE:

Batch procedure: To an oven dried 6-dram vial equipped with a stir bar was added **2a** (684 mg, 3.16 mmol, 1.0 equiv.), and ethyl cinnamate (7.97 mL, 47.4 mmol, 15 equiv). The vial was sealed with a rubber septum and the mixture was subjected to three freeze-pump-thaw cycles. Two 390 nm kessil PR160L lamps were placed 5 cm from the center of the stir plate and the vial was irradiated for 36 hours at the highest lamps' intensity (100%). A fan was added over the reaction to help control the temperature. When all starting material was consumed, the reaction mixture was transferred to a 100 mL round-bottom flask equipped with a magnetic stir bar. Acetonitrile (37 mL), acetic acid (12 mL), and water (12 mL) were added, and the mixture was stirred for 4 hours at room temperature. The reaction mixture was diluted with water and 2M aqueous HCl was added until solution reached pH of zero, then washed with diethyl ether. A saturated solution of aqueous sodium bicarbonate was added until bubbling ceased, indicating full neutralization. The aqueous layer was then extracted twice with ethyl acetate. The combined ethyl acetate fractions were dried over Na_2SO_4 and concentrated. The crude mixture was dissolved in dichloromethane and then concentrated onto celite and loaded onto a silica column. Elution with 5-60% ethyl acetate in hexanes (hexanes doped with 1-3% triethylamine) gave (±)-**7h** (127 mg, 0.490 mmol, 16%) as a tan solid.

Flow procedure: To a 6-dram vial equipped with a magnetic stir bar was added **2a** (2.16 g, 10.0 mmol, 1 equiv) and ethyl cinnamate (16.8 mL, 100 mmol, 10 equiv). The mixture was stirred to give a yellow solution. No effort was made to exclude oxygen or moisture from the reactants vial. The Uniqsis Flow System (as described in section II.C. Flow apparatus) was equipped with a 10 mL PFA coil reactor and was primed with acetonitrile (20 mL). No back-pressure regulator was used. The outflow was placed into a 125 mL Erlenmeyer flask. The reaction mixture was fed at 0.167 mL/min through the 10 mL PFA coil reactor (residence time 60 minutes). The temperature of the reactor was maintained at 20.0 °C using the Polar Bear Plus. The mixture was irradiated at maximum intensity using the system's 385 nm LEDs. When the effluent leaving the reactor began to show orange color, the outflow was removed from the Erlenmeyer flask and placed into a 250 mL round bottom flask equipped with a magnetic stir bar. No effort was made to exclude oxygen or moisture from the collection vessel. Once the reaction mixture vial was emptied, it was rinsed with acetonitrile (2 x 20 mL). Once the full mixture was flushed through the system (collection flask containing reaction solution + 40 mL acetonitrile), the pump and Uniqsis flow system were shut off. To the collection flask were sequentially added acetonitrile (20 mL), water (20 mL), and acetic acid (20 mL). The mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with 0.5 M aqueous HCl (200 mL) and washed with diethyl ether (4 x 100 mL). The aqueous layer was neutralized with saturated aqueous sodium bicarbonate solution (500 mL) and extracted with ethyl acetate (4 x 100 mL). The combined ethyl acetate extracts were washed with brine (2 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give

671.2 mg of a brown oil that was mostly desired product (based on crude NMR) but requiring further purification. The mixture was concentrated onto celite and loaded atop a silica column (that had been pre-neutralized with 3 column volumes of 5% ethyl acetate : 94% hexanes : 1% triethylamine). Elution with 12-100% mixture of strong solvent in hexanes (where strong solvent is 1% Et_3N in ethyl acetate) gave (±)-**7h** (451.2 mg, 1.74 mmol, 17%) as a tan solid.

Note: As with the batch reactions, substantial reactor fouling was observed in the continuous flow reaction (SI Figure 8). Nevertheless, comparable yields were obtained in batch and flow modes, with continuous flow processing increasing material throughput. The total reaction time for the photochemical step in flow was <2 hours for 10.0 mmol of **2a** (>5 mmol/h, excluding priming and flushing operations).



SI Figure 8: Reactor coil showing solid deposits

Appearance: tan solid

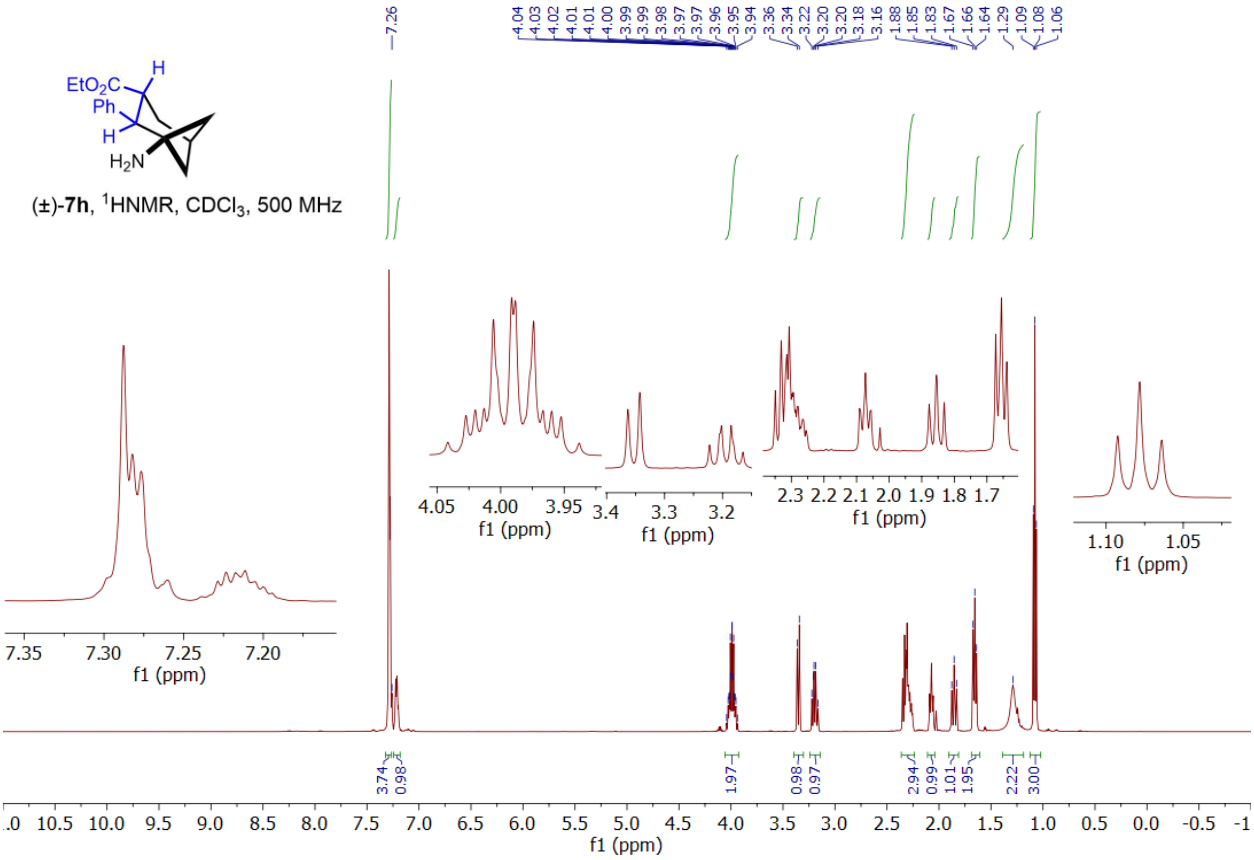
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 4H), 7.24-7.18 (m, 1H), 4.05-3.93 (m, 2H), 3.35 (d, *J* = 10.2 Hz, 1H), 3.19 (app. td, *J* = 10.3, 8.8 Hz, 1H), 2.37-2.24 (m, 3H), 2.11-2.05 (m, 1H), 1.85 (app t, *J* = 11.5 Hz, 1H), 1.66 (app. t, *J* = 8.5 Hz, 2H), 1.29 (bs, 2H), 1.08 (app. t, *J* = 7.1 Hz, 3H) ppm

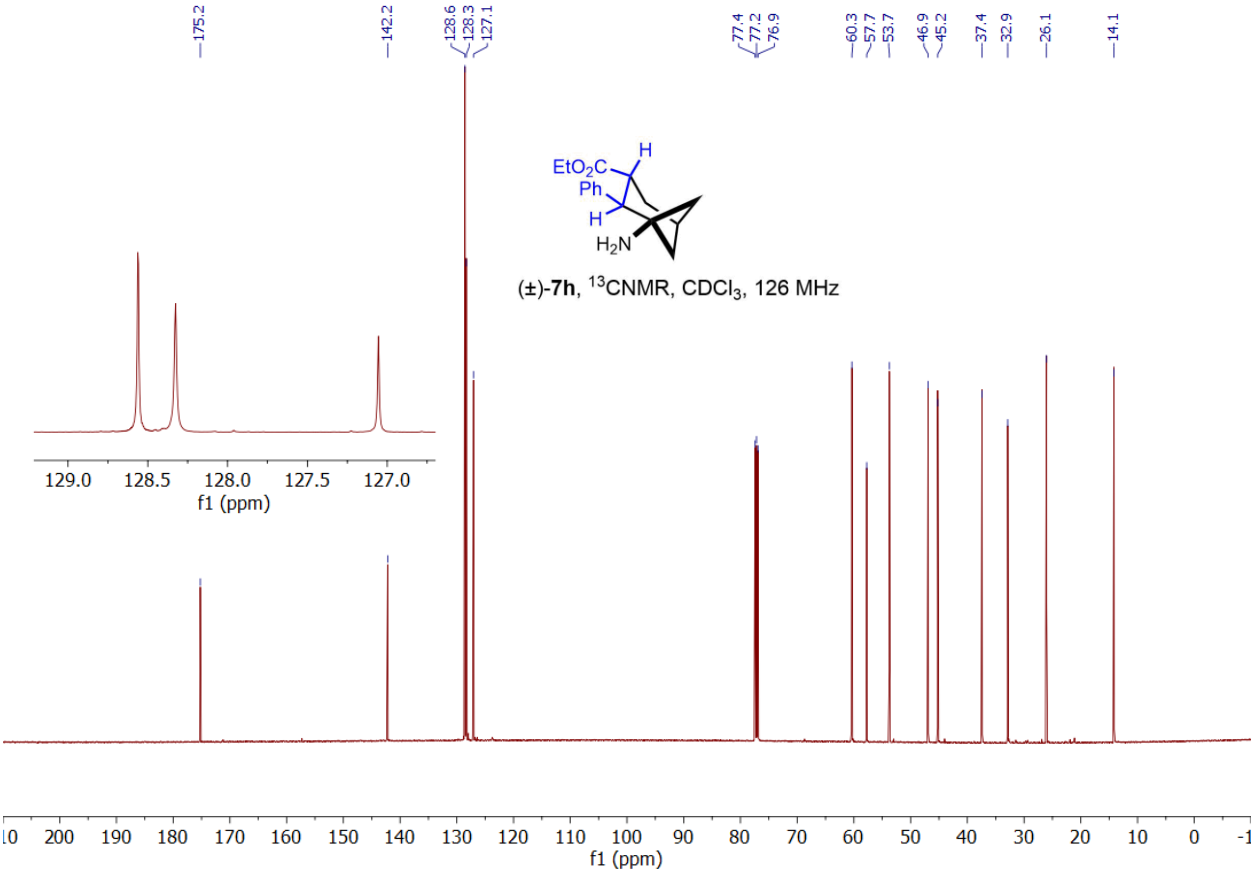
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 142.2, 128.6, 128.3, 127.1, 60.3, 57.7, 53.7, 46.9, 45.2, 37.4, 32.9, 26.1, 14.1 ppm

IR (neat): 2933, 2864, 1725, 1601, 1520, 1497, 1454, 1382, 1346, 1277, 1176, 1141, 1087, 1041, 968, 898, 873, 826, 758, 706 cm^{-1}

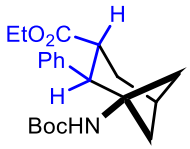
HRMS (ES+, m/z) calculated for $C_{16}H_{22}NO_2^+$: 260.1645, Found: 260.1646

R_f = 0.70 (99% ethyl acetate : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV


EtO2C
Ph
H
H2N
(±)-7h, 1HNMR, CDCl3, 500 MHz
f1 (ppm)


EtO2C
Ph
H
H2N
(±)-7h, 13CNMR, CDCl3, 126 MHz
f1 (ppm)

Compound (±)-**15** :



EXPERIMENTAL PROCEDURE:

To an oven dried 2-dram vial equipped with a magnetic stir bar was added (±)-**7h** (127 mg, 0.490 mmol, 1.0 equiv) the vial was sealed, and the headspace flushed with nitrogen. Dichloromethane (4.0 mL), and triethylamine (0.0819 mL, 0.588 mmol, 1.2 equiv) were added via syringe. Di-tert-butyl dicarbonate (0.135 mL, 0.588 mmol, 1.2 equiv) was added as a solution in dichloromethane (0.9 mL) and the reaction was stirred for 6 hours. When all starting material was consumed, reaction was quenched with a saturated solution of sodium bicarbonate. Aqueous layer was extracted three times with dichloromethane and organic layers were combined and washed with water, then brine. The organic layer was then dried over sodium sulfate and concentrated to afford crude (±)-**15** as faintly orange off-white solid. The material was carried forward into the following saponification step assuming a quantitative yield.

A pure sample of (±)-**15** isolated as a white solid was obtained by analogous procedure from a different run was used for characterization.

Appearance: white solid

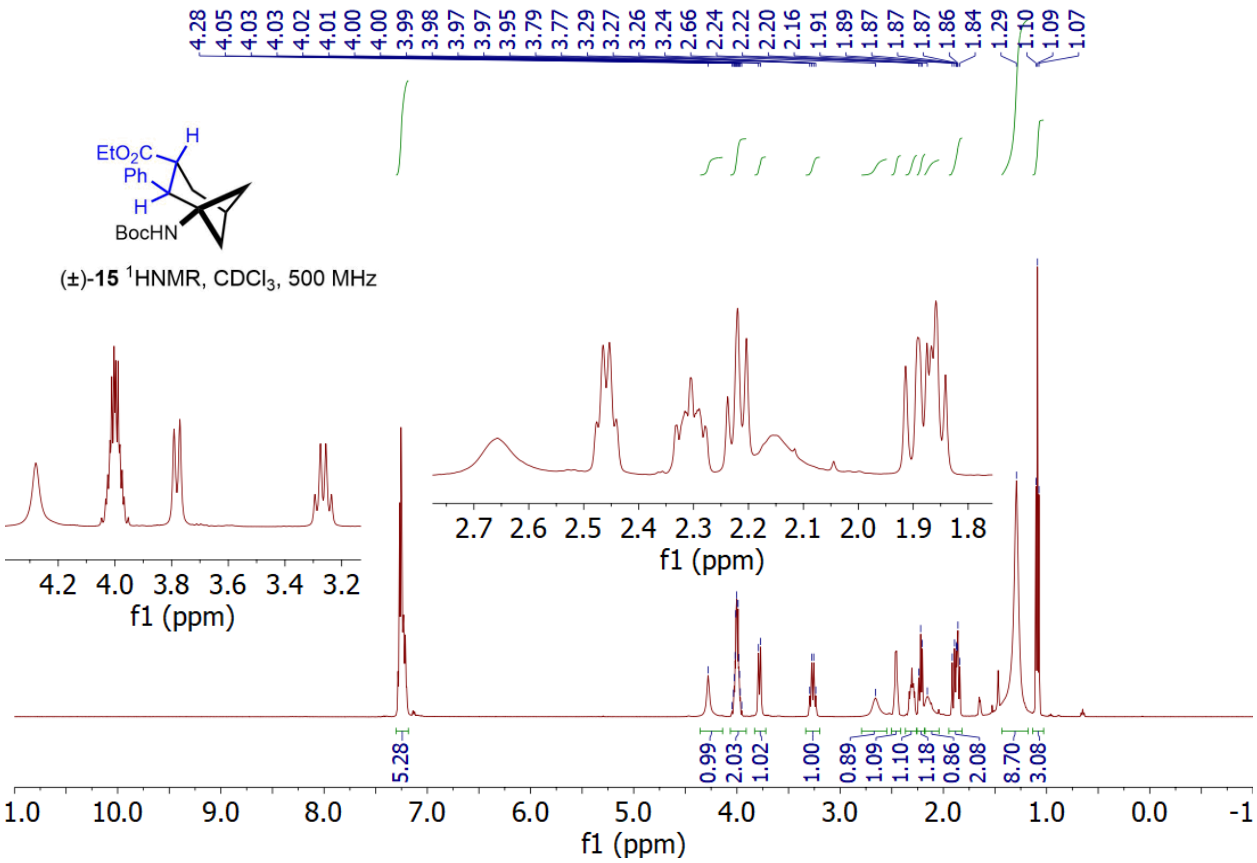
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H), 4.28 (s, 1H), 4.05-3.94 (m, 2H), 3.78 (d, *J* = 10.2 Hz, 1H), 3.26 (app. q, *J* = 9.7 Hz, 1H), 2.66 (bs, 1H), 2.49-2.43 (m, 1H), 2.35-2.26 (m, 1H), 2.22 (app. t, *J* = 8.6 Hz, 1H), 2.16 (bs, 1H), 1.89 (dd, *J* = 12.4, 11.1 Hz, 1H), 1.86 (app. t, *J* = 8.8 Hz, 1H), 1.29 (bs, 9H), 1.09 (app. t, *J* = 7.1 Hz, 3H) ppm

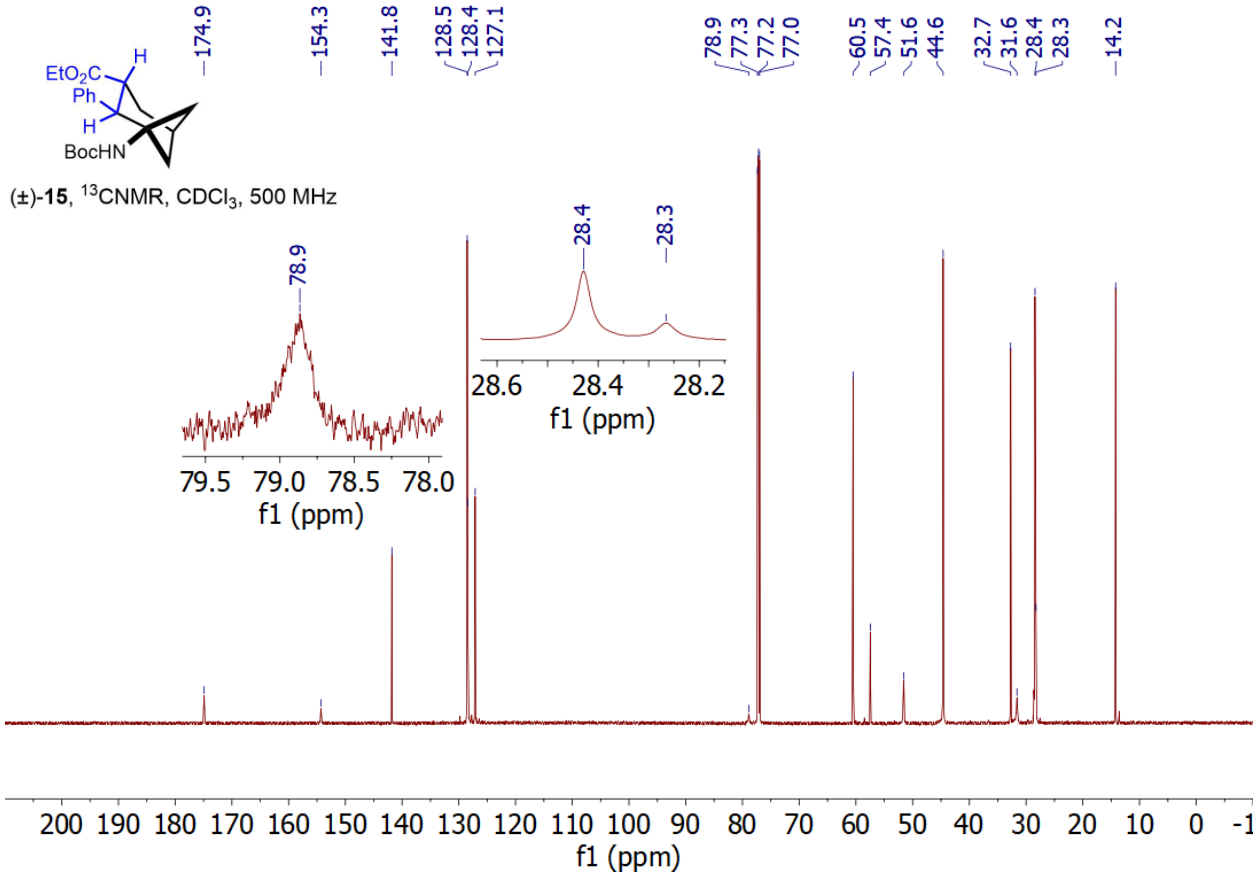
^{13}C NMR (176 MHz, $CDCl_3$) δ 174.9, 154.3, 141.8, 128.5, 128.4, 127.1, 78.9, 60.5, 57.4, 51.6, 44.6 (two overlapping carbon signals based on HSQC), 32.7, 31.6, 28.4, 28.3, 14.2 ppm

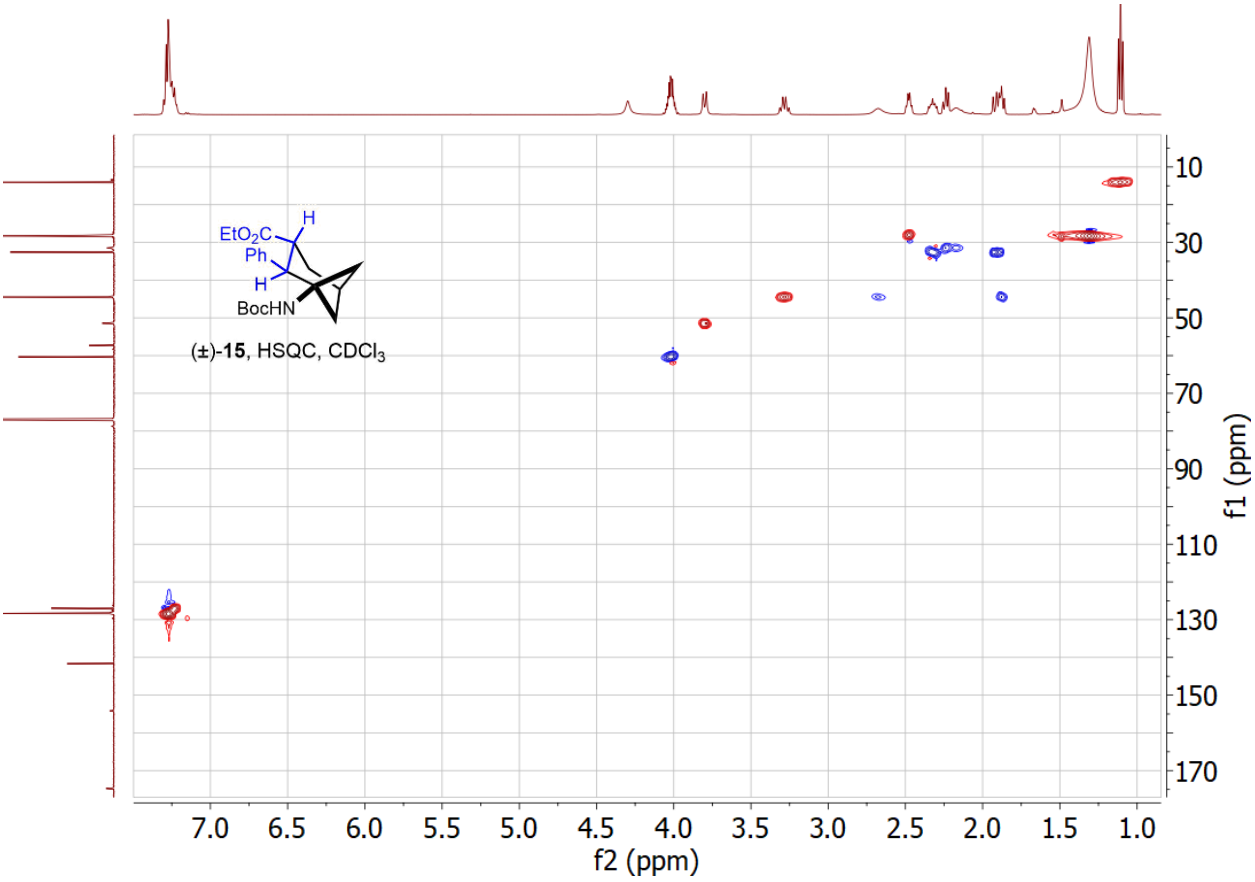
IR (neat): 3341, 2971, 2945, 2872, 2360, 1724, 1698, 1673, 1603, 1514, 1455, 1389, 1367, 1287, 1272, 1247, 1228, 1167, 1071, 1054, 1030, 993, 955, 930, 913, 883, 856, 835, 783, 756, 709, 691 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{21}H_{29}NNaO_4^+$: 382.1989, Found: 382.2031

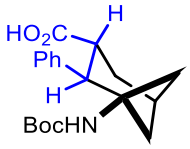
R_f = 0.57 (20% ethyl acetate : 80% hexanes), slightly paler purple spot, $KMnO_4$, UV


4.28 4.05 4.03 4.03 4.02 4.01 4.00 4.00 3.99 3.98 3.97 3.97 3.95 3.79 3.77 3.29 3.27 3.26 3.24 2.66 2.24 2.22 2.20 2.16 1.91 1.89 1.87 1.87 1.87 1.86 1.84 1.29 1.10 1.09 1.07
EtO2C
Ph
H
H
BocHN
(±)-15 1HNMR, CDCl3, 500 MHz
4.2 4.0 3.8 3.6 3.4 3.2
f1 (ppm)
2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8
f1 (ppm)
5.28 0.99 2.03 1.02 1.00 0.89 1.09 1.10 1.18 0.86 2.08 8.70 3.08
1.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0 -1
f1 (ppm)


174.9 154.3 141.8 128.5 128.4 127.1 78.9 77.3 77.2 77.0 60.5 57.4 51.6 44.6 32.7 31.6 28.4 28.3 14.2
EtO2C
Ph
H
H
BocHN
(±)-15, 13CNMR, CDCl3, 500 MHz
78.9
79.5 79.0 78.5 78.0
f1 (ppm)
28.4 28.3
28.6 28.4 28.2
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)


EtO2C
H
Ph
H
BocHN
(±)-15, HSQC, CDCl3
10
30
50
70
90
110
130
150
170
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f2 (ppm)

Compound (±)-**16** :



EXPERIMENTAL PROCEDURE:

To a 2-dram vial equipped with a magnetic stir bar was added intermediate (±)-**15** and lithium hydroxide monohydrate (30.8 mg, 0.734 mmol, 1.5 equiv based on assumed quantitative yield of (±)-**15**). Tetrahydrofuran (2 mL), water (0.5 mL), and methanol (0.5 mL) were added. The vial was capped, and the reaction mixture was allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with 20 mL of water and extracted with three times with diethyl ether. Aqueous layer was then acidified carefully to pH 4 with 1M aqueous citric acid, then the aqueous layer was extracted with ethyl acetate 3 times. The combined ethyl acetate extracts were dried over sodium sulfate and concentrated to give (±)-**16** (68 mg, 0.21 mmol, 42%) as a white solid.

Appearance: white solid

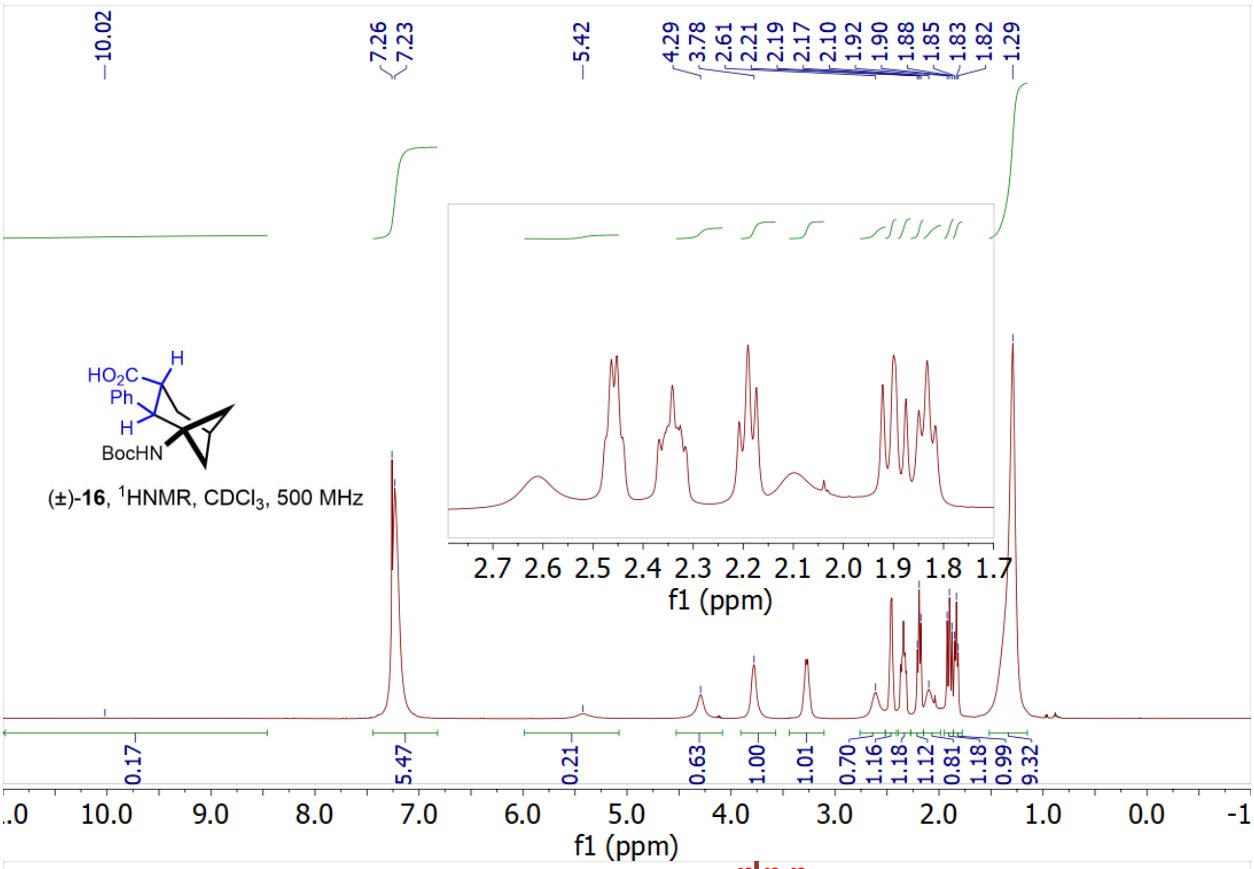
^{1}H NMR (500 MHz, $CDCl_3$) A mixture of rotamers was observed. Peak broadening was observed, particularly with peaks corresponding to protons near the carbamate functionality. δ 10.02 (bs, 1H but integrating low), 7.23 (bs, 5H), 1.29 (bs, 1.29H), 5.42 (0.2 H), 4.29 (bs, 0.6H), 3.78 (bs, 1H), 3.35-3.15 (m, 1H), 2.61 (bs, 0.7 H), 2.50-2.41 (m, 1H), 2.39-2.29 (m, 1H), 2.19 (app. t, *J* = 8.6 Hz, 1H), 2.10 (bs, 0.8 H), 1.90 (app. t, *J* = 11.6 Hz, 1H), 1.83 (app. t, *J* = 8.3 Hz, 1H), 1.29 (bs with downfield shoulder, 9H) ppm

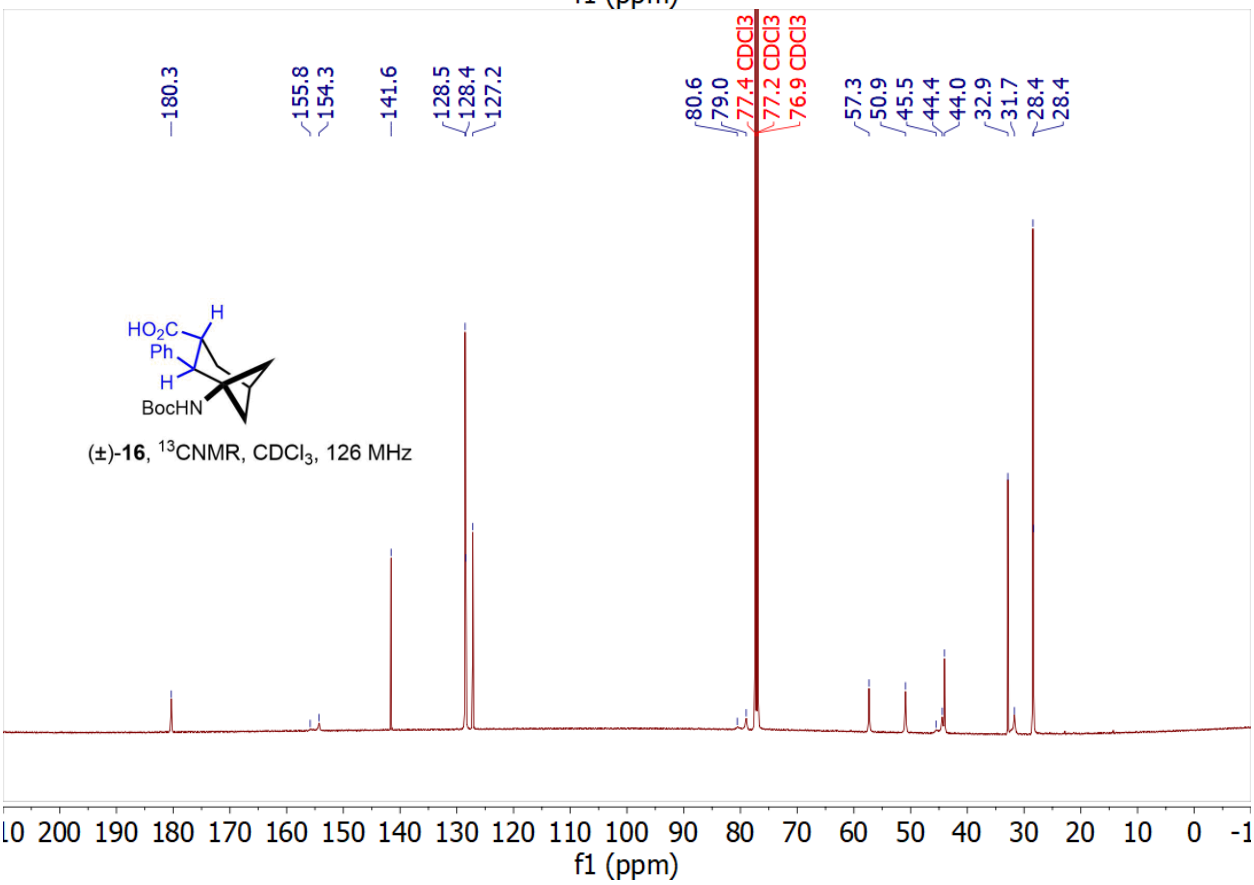
^{13}C NMR (126 MHz, $CDCl_3$) Peaks of the major rotamer are reported (on the basis of HSQC): δ 180.3, 154.3, 141.6, 128.5, 128.4, 127.2, 79.0, 57.3, 50.9, 44.4, 44.0, 32.9, 31.7, 28.4, 28.4 ppm

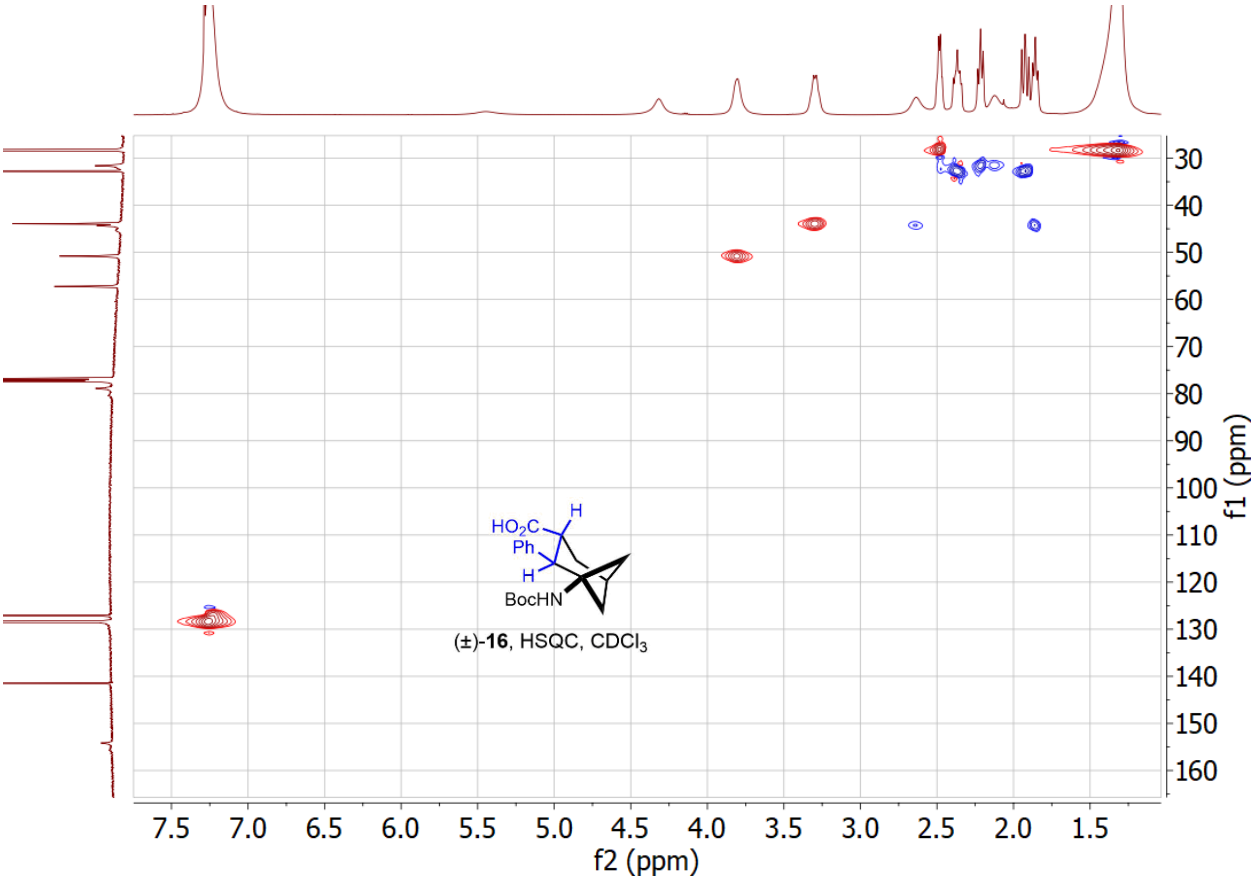
IR (neat): 3421, 3300-2300 (broad), 2966, 1722, 1700, 1486, 1455, 1391, 1367, 1276, 1258, 1237, 1219, 1155, 1131, 1063, 1006, 952, 878, 779, 758, 738, 702, 678 cm^{-1}

HRMS (ES-, m/z) calculated for $C_{19}H_{24}NO_4^-$: 330.1711, Found: 330.1703

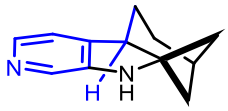
R_f = 0.16 (30% ethyl acetate : 70% hexanes), yellow spot, $KMnO_4$, UV


10.02
7.26
7.23
5.42
4.29
3.78
2.61
2.21
2.19
2.17
2.10
1.92
1.90
1.88
1.85
1.83
1.82
1.29
HO2C
H
Ph
H
BocHN
(±)-16, 1HNMR, CDCl3, 500 MHz
2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7
f1 (ppm)
0.17
5.47
0.21
0.63
1.00
1.01
0.70
1.16
1.18
1.12
0.81
1.18
0.99
9.32
10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)


180.3
155.8
154.3
141.6
128.5
128.4
127.2
80.6
79.0
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
57.3
50.9
45.5
44.4
44.0
32.9
31.7
28.4
28.4
HO2C
H
Ph
H
BocHN
(±)-16, 13CNMR, CDCl3, 126 MHz
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



Compound (±)-**17** :



EXPERIMENTAL PROCEDURE:

To an oven-dried 4-dram vial equipped with a magnetic stir bar was added (±)-**4p** (244.8 mg, 0.612 mmol, 1 equiv) followed sequentially by acetonitrile (3 mL), water (1 mL), and acetic acid (1 mL). The headspace was flushed with argon and the vial was sealed with a Teflon-lined cap. The mixture was allowed to stir at room temperature for 168 hours. The reaction mixture was diluted with 0.5 M aqueous hydrochloric acid (20 mL) and washed with diethyl ether (3 x 20 mL). The aqueous layer was brought to pH ~11 using 1 M aqueous NaOH and was extracted with ethyl acetate (4 x 30 mL). The combined ethyl acetate extracts were washed with brine (2 x 50 mL), dried over sodium sulfate, filtered, and concentrated into an oven-dried 2-dram vial. To the vial containing the resulting brown oily residue was added a magnetic stir bar, copper (I) iodide (11.7 mg, 0.0612 mmol, 0.1 equiv), L-proline (mg, 0.122 mmol, 0.2 equiv), and potassium phosphate (259.6 mg, 1.22 mmol, 2 equiv). The vial was sealed with a cap containing a Teflon-lined septum and the mixture was put under nitrogen atmosphere. Dimethyl sulfoxide (2 mL) was added in one portion via syringe. A vent needle was pieced through the septum and the mixture was then degassed by sparging with nitrogen for 15 minutes. The vent needle and nitrogen line were removed, and the cap further sealed with Parafilm. The vial was then placed in a preheated

aluminum block at 95 °C and allowed to stir for 1 hour. After cooling to room temperature, the mixture was diluted with saturated aqueous sodium bicarbonate (40 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine (5 x 20 mL), dried over sodium sulfate, and concentrated onto 3 grams of celite. The resulting powdery mixture was loaded atop a silica column (pre-neutralized with 3 column volumes of 25% ethyl acetate : 74% hexanes : 1% Et_3N) and was chromatographed eluting with 25%-100% strong solvent in weak solvent (where the strong solvent was 1% Et_3N in ethyl acetate and the weak solvent was hexanes) to give (±)-**17** (65.2 mg, 0.350 mmol, 57%) as a faintly yellow solid.

Note: Trituration with acetonitrile purged a minor, colored impurity, leaving (±)-**17** as a white solid. The acetonitrile wash containing slightly impure (±)-**17** was allowed to sit in a vial on the bench under air for ~48 hours, at which time orange crystals were visible on the bottom of the vial. The remaining acetonitrile was decanted from the crystals (>10 mg) and they were analyzed and assigned to be hydroperoxide **SI-18**, which had not previously been identified in the sample of purified (±)-**17** . **SI-18** was also observed to form upon prolonged storage of previously pure NMR samples of (±)-**17** **in** DMSO-d_6 or $CDCl_3$. The mechanism of this auto-oxidation is the subject of ongoing research in our laboratory.

Appearance: faintly yellow to white solid

^{1}H NMR (DMSO-d_6, 700 MHz): δ = 7.84 (d, *J* = 3.9 Hz, 1H), 7.77 (s, 1H), 7.00 (d, *J* = 4.3 Hz, 1H), 6.00 (s, 1H), 3.09 (dd, *J* = 11.0, 7.1 Hz, 1H), 2.33 (app. t, *J* = 7.6 Hz, 1H), 2.25-2.19 (m, 1H), 2.19-2.14 (m, 1H), 1.91 (app. t, *J* = 8.5 Hz, 1H), 1.89-1.82 (m, 1H), 1.82-1.76 (m, 1H), 1.70-1.62 (m, 1H), 1.58 (app. t, *J* = 8.3 Hz, 1H), 1.42 (dd, *J* = 8.3, 6.8 Hz, 1H) ppm

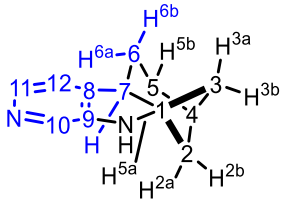
^{13}C NMR (DMSO-d_6, 176 MHz): δ = 147.4, 140.2, 139.4, 129.6, 118.3, 68.0, 47.1, 44.9, 30.7, 26.4, 25.6, 19.8 ppm

IR (neat): 3158, 3068, 2938, 2860, 2822, 1741, 1604, 1577, 1456, 1402, 1318, 1290, 1249, 1219, 1202, 1185, 1173, 1101, 1088, 1036, 1014, 996, 933, 904, 858, 794, 738, 708 cm^{-1}

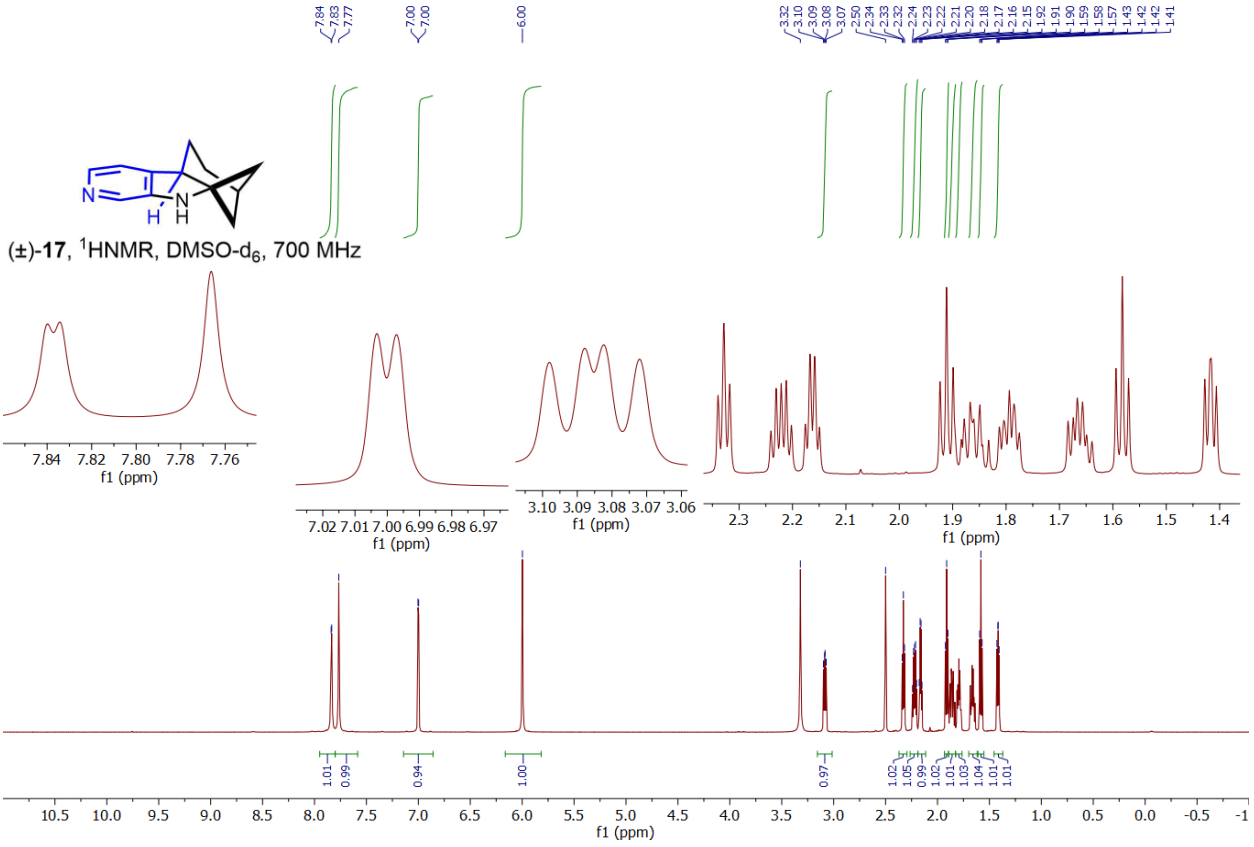
HRMS (ES+, m/z) calculated for $C_{12}H_{15}N^+$: 187.1230, Found: 187.1229

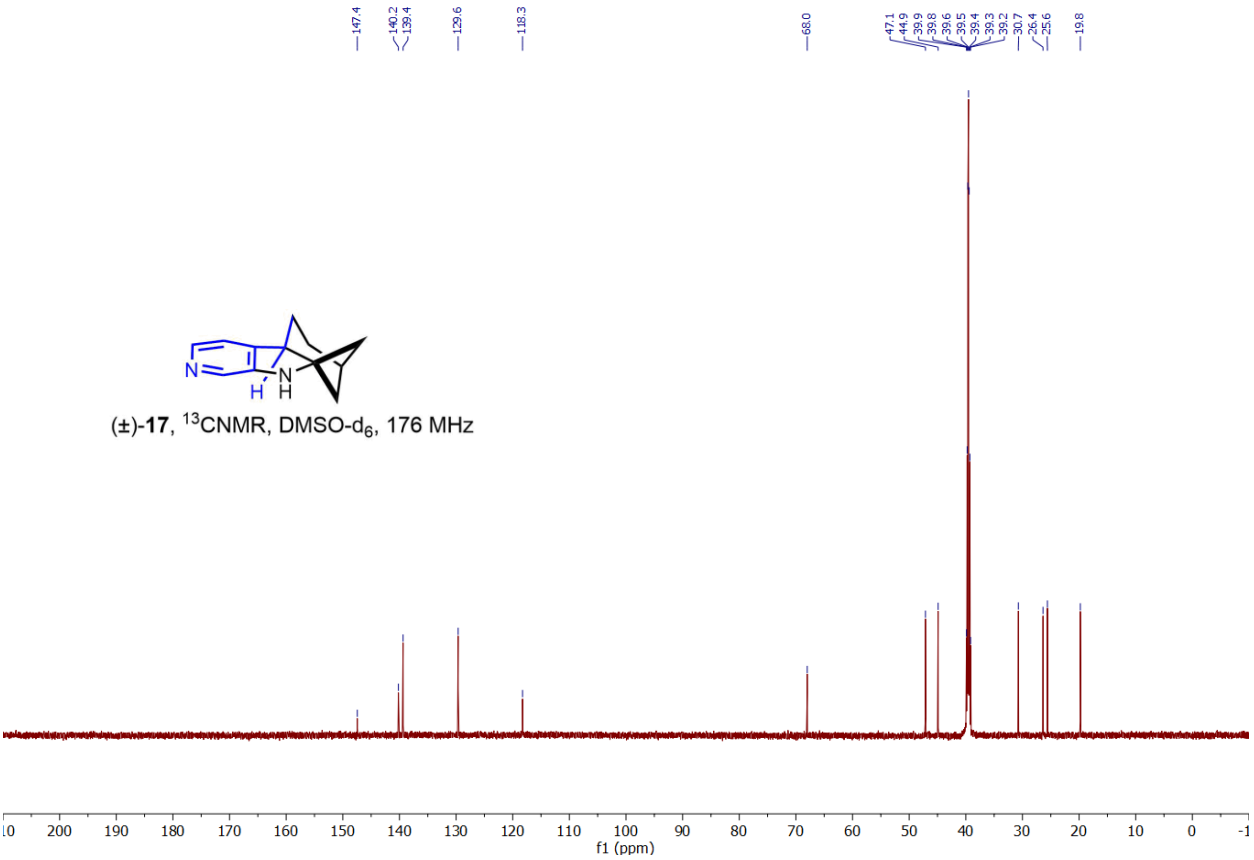
R_f = 0.36 (99% ethyl acetate : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

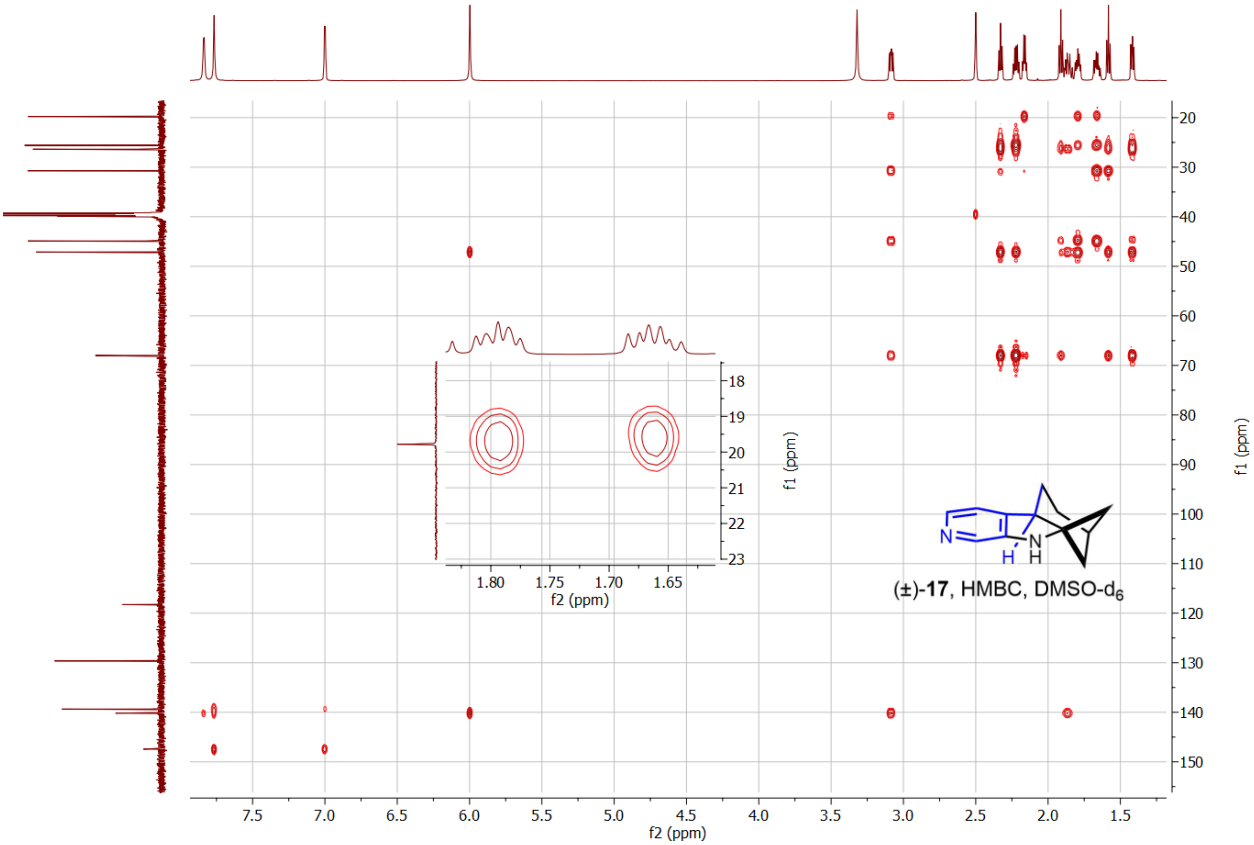
Complete assignment of ^{1}H and ^{13}C NMR signals

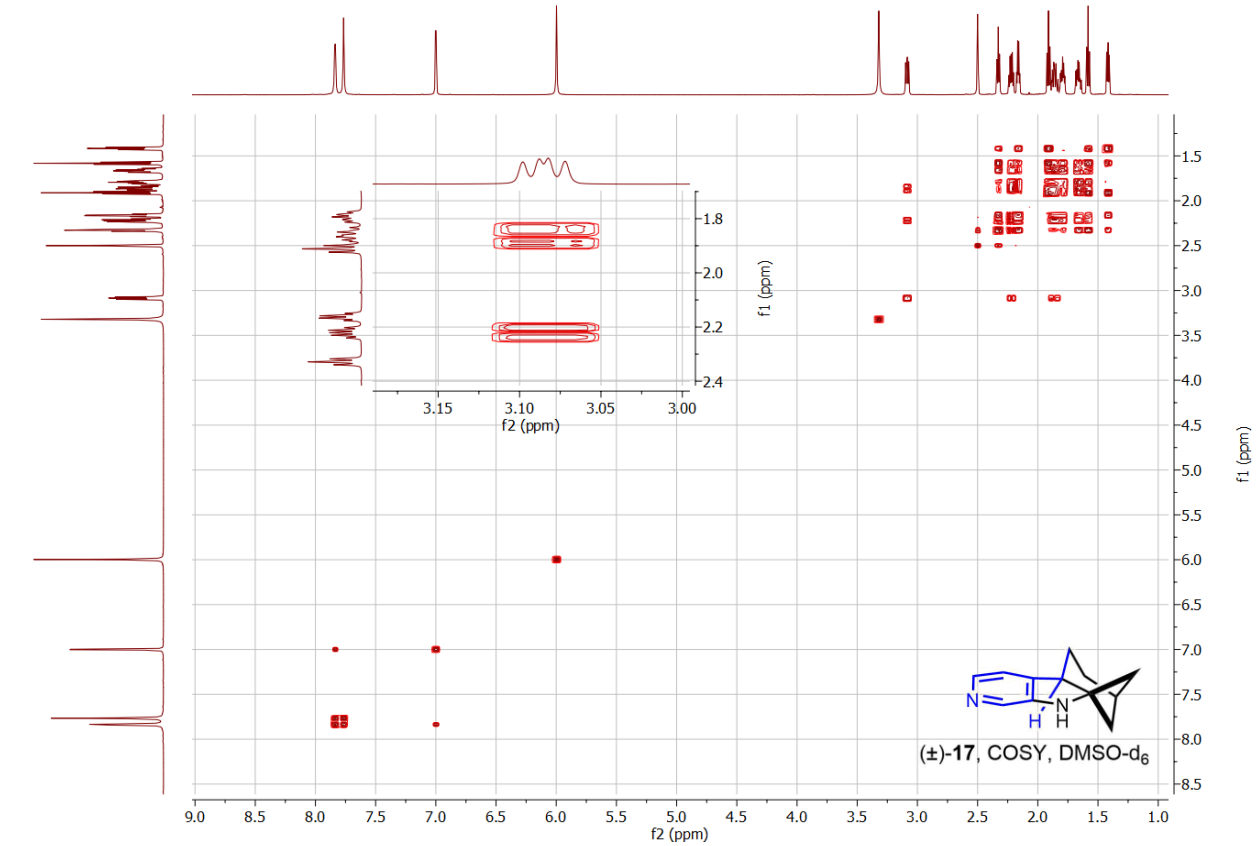


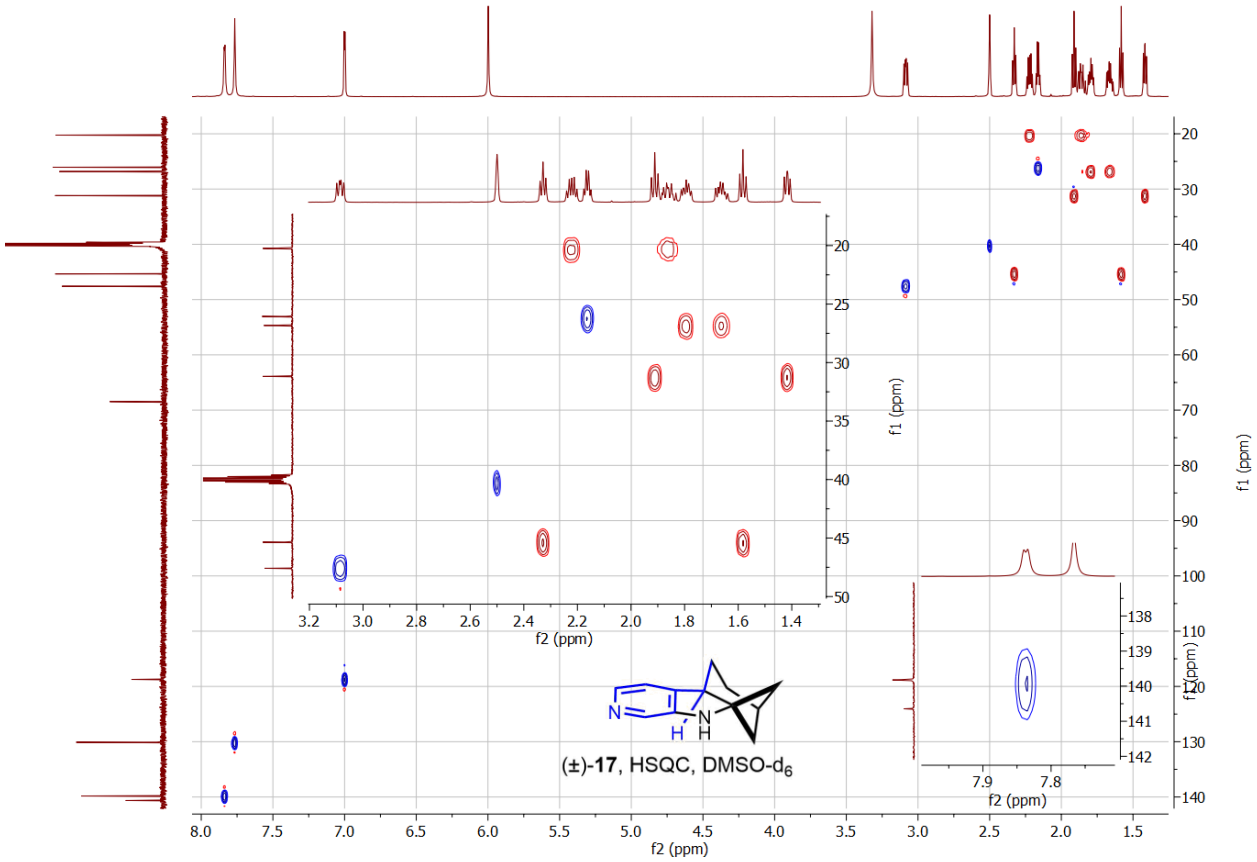
Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	68		N-H	6.00 (s, 1H)
2	44.9		2a	1.58 (app. t, J = 8.3 Hz, 1H)
3	30.7		2b	2.33 (app. t, J = 7.6 Hz, 1H)
4	25.6		3a	1.91 (app. t, J = 8.5 Hz, 1H)
5	26.4		3b	1.42 (dd, J = 8.3, 6.8 Hz, 1H)
6	19.8		4	2.19-2.14 (m, 1H)
7	47.1		5a	1.70-1.62 (m, 1H)
8	140.2		5b	1.82-1.76 (m, 1H)
9	147.4		6a	2.25-2.19 (m, 1H)
10	129.6		6b	1.89-1.82 (m, 1H)
11	139.4		7	3.09 (dd, J = 11.0, 7.1 Hz, 1H)
12	118.3		10	7.77 (s, 1H)
			11	7.84 (d, J = 3.9 Hz, 1H)
			12	7.00 (d, J = 4.3 Hz, 1H)

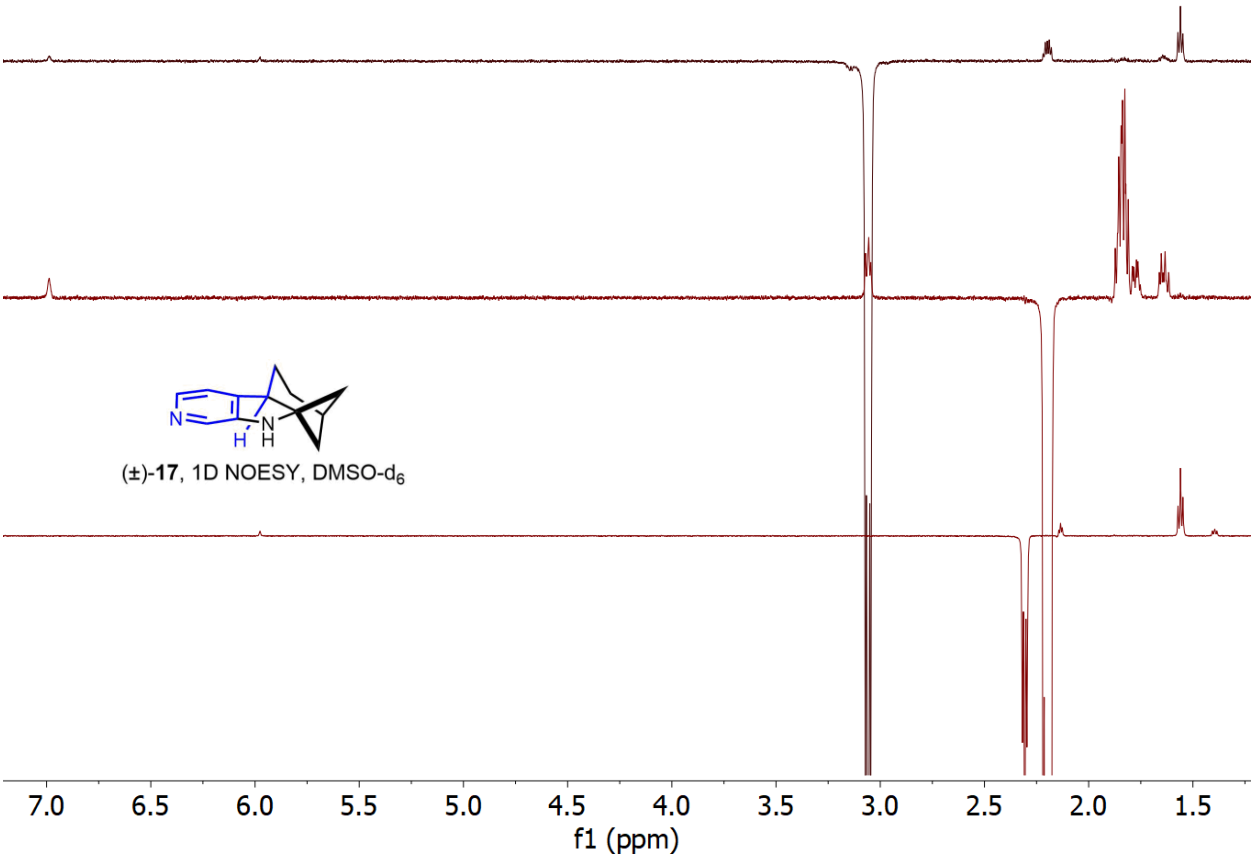



147.4
140.2
139.4
129.6
118.3
68.0
47.1
44.9
39.9
39.8
39.6
39.5
39.4
39.3
39.2
30.7
26.4
25.6
19.8
(±)-17, 13CNMR, DMSO-d6, 176 MHz
f1 (ppm)

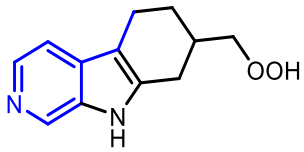

f2 (ppm)
f1 (ppm)
(±)-17, HMBC, DMSO-d6


f2 (ppm)
f1 (ppm)
(±)-17, COSY, DMSO-d6


f2 (ppm)
f1 (ppm)
(±)-17, HSQC, DMSO-d6



Compound **SI-18**:

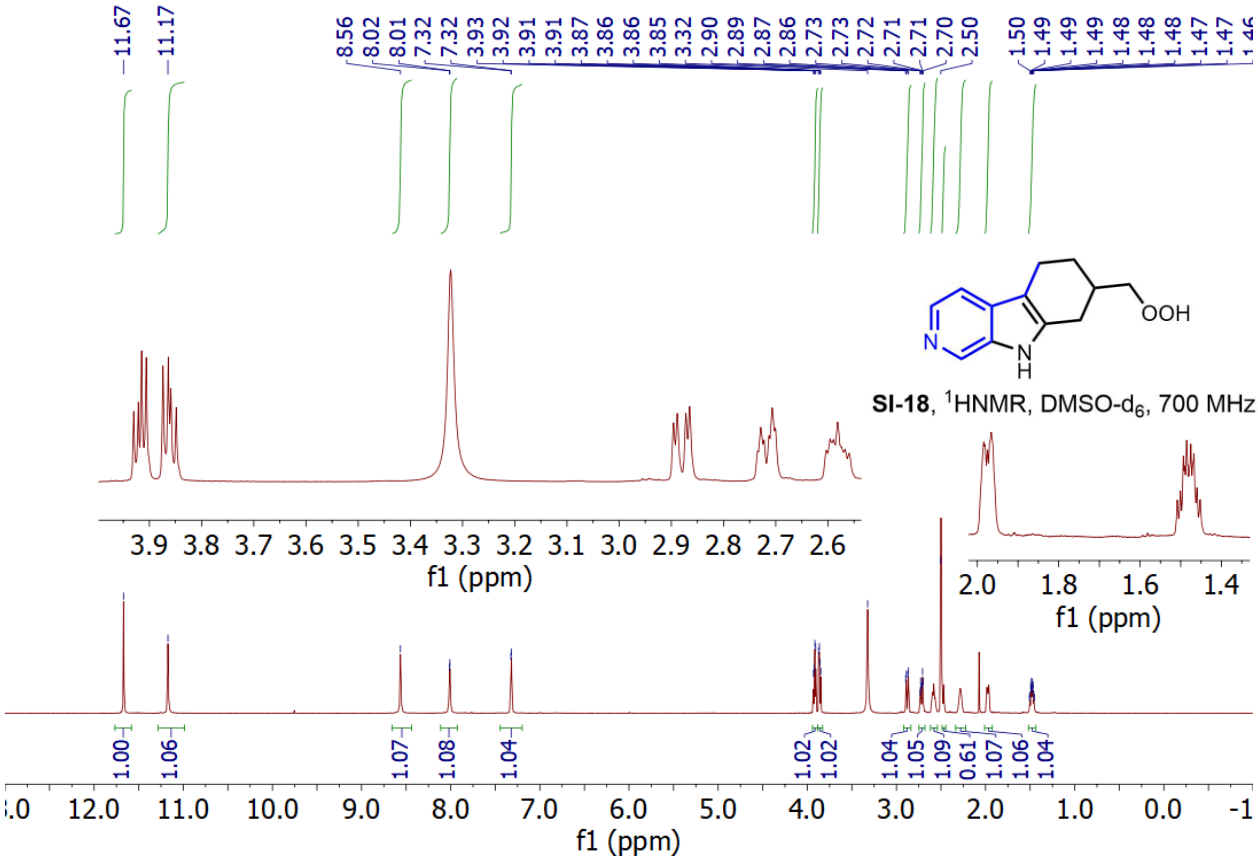


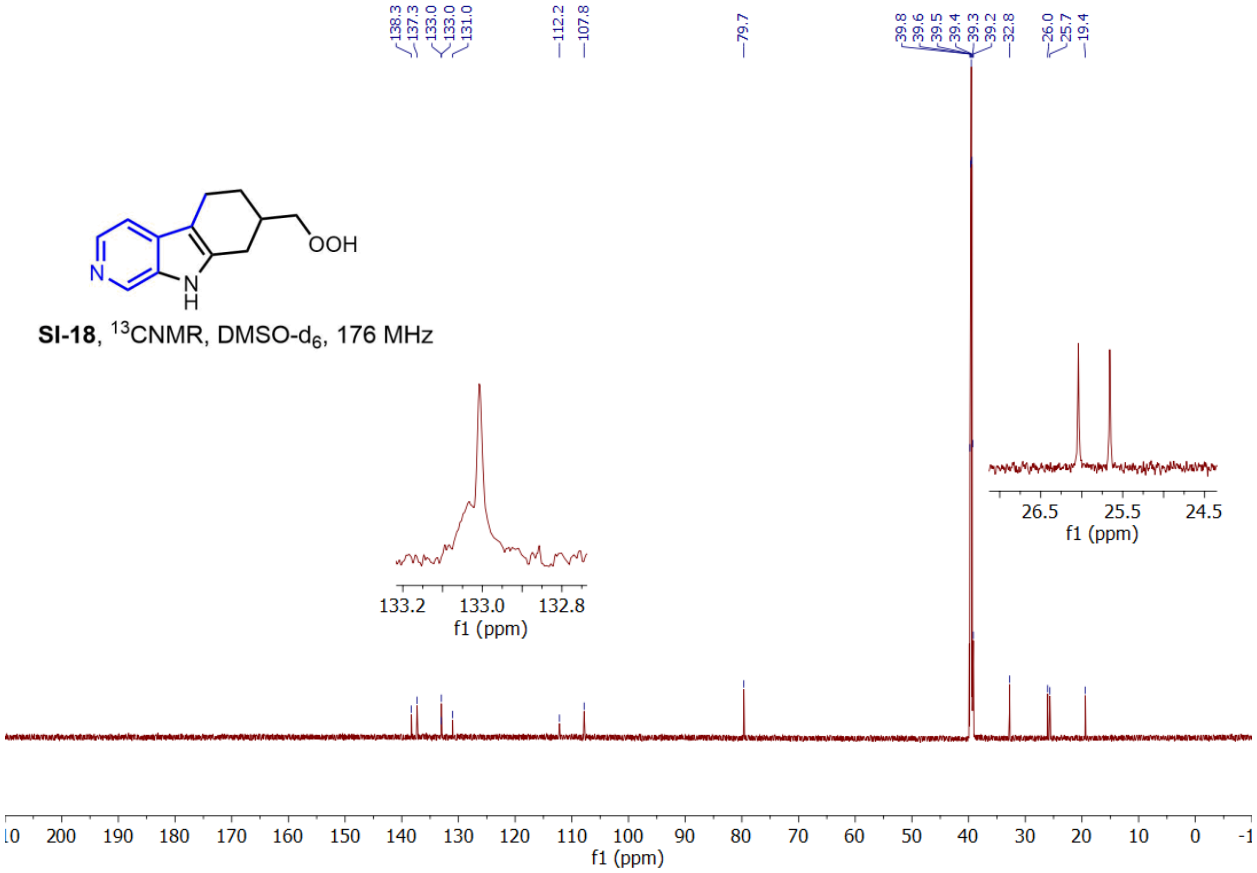
Appearance: orange crystalline solid

^{1}H NMR (DMSO-d_6, 700 MHz): Note: the dd signals at 3.92 and 3.86 correspond to the methylene adjacent to the hydroperoxide and show AB behavior. δ = 11.67 (s, 1H), 11.17 (s, 1H), 8.56 (s, 1H), 8.01 (d, *J* = Hz, 1H), 7.32 (d, *J* = Hz, 1H), 3.92 (dd, *J* = 10.6, 6.2 Hz, 1H), 3.86 (dd, *J* = 10.6, 7.2 Hz, 1H), 2.88 (dd, *J* = 16.6, 5.1 Hz, 1H), 2.72 (app. dt, *J* = 15.4, 4.1 Hz, 1H), 2.61-2.55 (m, 1H), 2.50-2.46 (m, 1H), 2.32-2.24 (m, 1H), 2.01-1.93 (m, 1H), 1.48 (app. dtd, *J* = 12.7, 10.4, 5.5 Hz, 1H) ppm

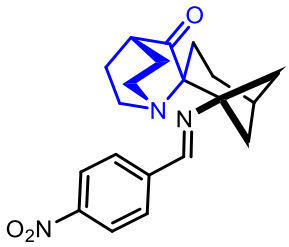
^{13}C NMR (DMSO-d_6, 176 MHz): δ = 138.3, 137.3, 133.0, 133.0, 131.0, 112.2, 107.8, 79.7, 32.8, 26.0, 25.7, 19.4 ppm

HRMS (ES+, m/z) calculated for $C_{12}H_{15}N_2O_2^+$: 219.1128, Found: 219.1126


11.67
11.17
8.56
8.02
8.01
7.32
7.32
3.93
3.92
3.91
3.91
3.87
3.86
3.86
3.85
3.32
2.90
2.89
2.87
2.86
2.73
2.73
2.72
2.71
2.71
2.70
2.50
1.50
1.49
1.49
1.49
1.48
1.48
1.48
1.47
1.47
OOH
N
H
SI-18, 1HNMR, DMSO-d6, 700 MHz
3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6
f1 (ppm)
2.0 1.8 1.6 1.4
f1 (ppm)
1.00
1.06
1.07
1.08
1.04
1.02
1.02
1.04
1.05
1.09
0.61
1.07
1.06
1.04
12.0 11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)


138.3
137.3
133.0
133.0
131.0
112.2
107.8
79.7
39.8
39.6
39.5
39.4
39.3
39.2
32.8
26.0
25.7
19.4
OOH
N
H
SI-18, 13CNMR, DMSO-d6, 176 MHz
133.2 133.0 132.8
f1 (ppm)
26.5 25.5 24.5
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Compound (±)-**4af** :



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (modifications = 5 equiv alkene used rather than the standard 7.5 equiv, and 0.2 mL dichloromethane added as solvent) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), **19** (274 mg, 2.00 mmol, 5 equiv), 2,2-dipyridyl disulfide (0.9 mg, 0.004 mmol, 0.01 equiv), dichloromethane (0.2 mL), and irradiating for 13.5 hours. The crude reaction mixture was diluted with chloroform and concentrated onto celite (3 g) and loaded onto a silica gel column (that was pre-neutralized by eluting with 3 column volumes of a mobile phase consisting of 5% ethyl acetate, 94% hexanes, and 1% triethylamine). The mixture was chromatographed eluting on a gradient from 10-100% ethyl acetate in hexanes to give impure (±)-**4af** . Fractions containing (±)-**4af** were combined and chromatographed on small plug of basic alumina eluting with 10-30% ethyl acetate in hexanes to give (±)-**4af** (16.0 mg, 0.0453 mmol, 11%) as a faintly yellow solid.

Appearance: faintly yellow solid

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.24 (d, *J* = 8.6 Hz, 2H), 8.18 (s, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 3.75-3.64 (m, 1H), 3.49-3.39 (m, 1H), 2.92-2.79 (m, 2H), 2.71 (app. t, *J* = 8.9 Hz, 1H), 2.52 (app. t, *J* = 8.5 Hz, 1H), 2.38-2.32 (m, 1H), 2.32-2.25 (m, 1H), 2.19 (app. p, *J* = 3.0 Hz, 1H), 2.10 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.01 (app. t, *J* = 7.9 Hz, 1H), 1.99-1.93 (m, 1H), 1.93-1.80 (m, 4H), 1.79-1.69 (m, 2H) ppm

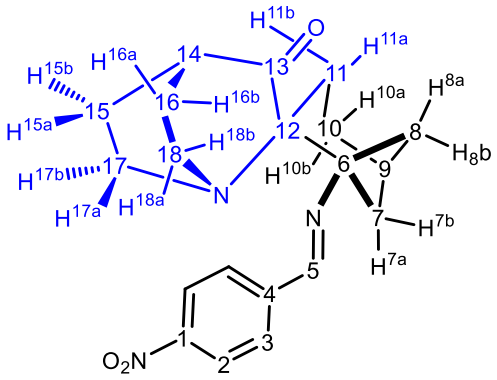
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 223.1, 157.0, 149.1, 142.0, 128.9, 124.1, 74.9, 74.5, 46.0, 45.4, 41.6, 39.5, 36.2, 27.3, 27.1, 25.9, 25.2, 24.1 ppm

IR (neat): 2970, 2931, 2860, 1709, 1638, 1601, 1512, 1475, 1462, 1447, 1343, 1292, 1259, 1243, 1221, 1202, 1177, 1157, 1107, 1056, 1037, 1015, 997, 965, 947, 909, 853, 842, 827, 808, 773, 749, 691 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{20}H_{24}N_3O_3^+$: 354.1812, Found: 354.1804

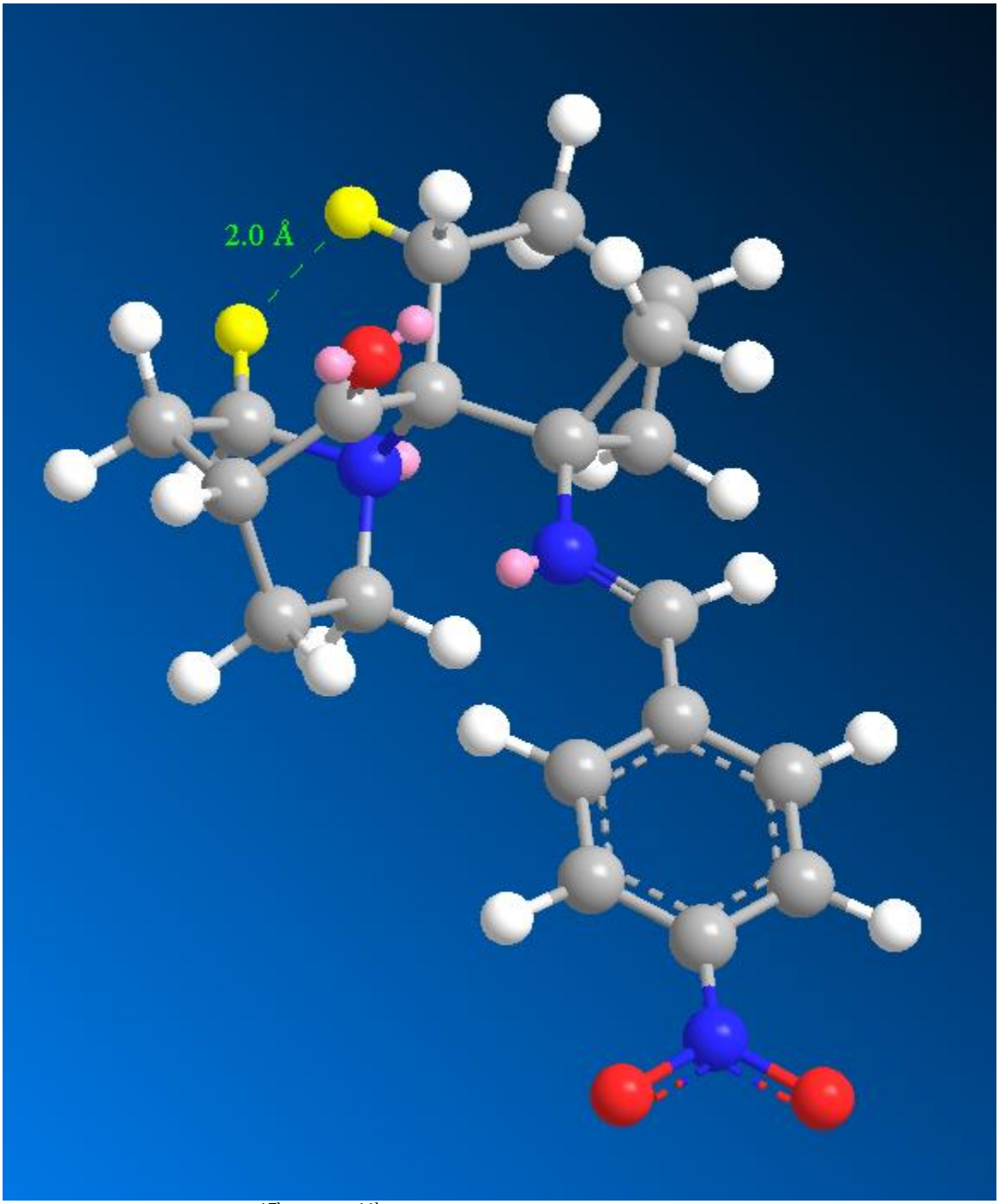
R_f = 0.33 (50% ethyl acetate : 49% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV

Complete assignment of ^{1}H and ^{13}C NMR signals

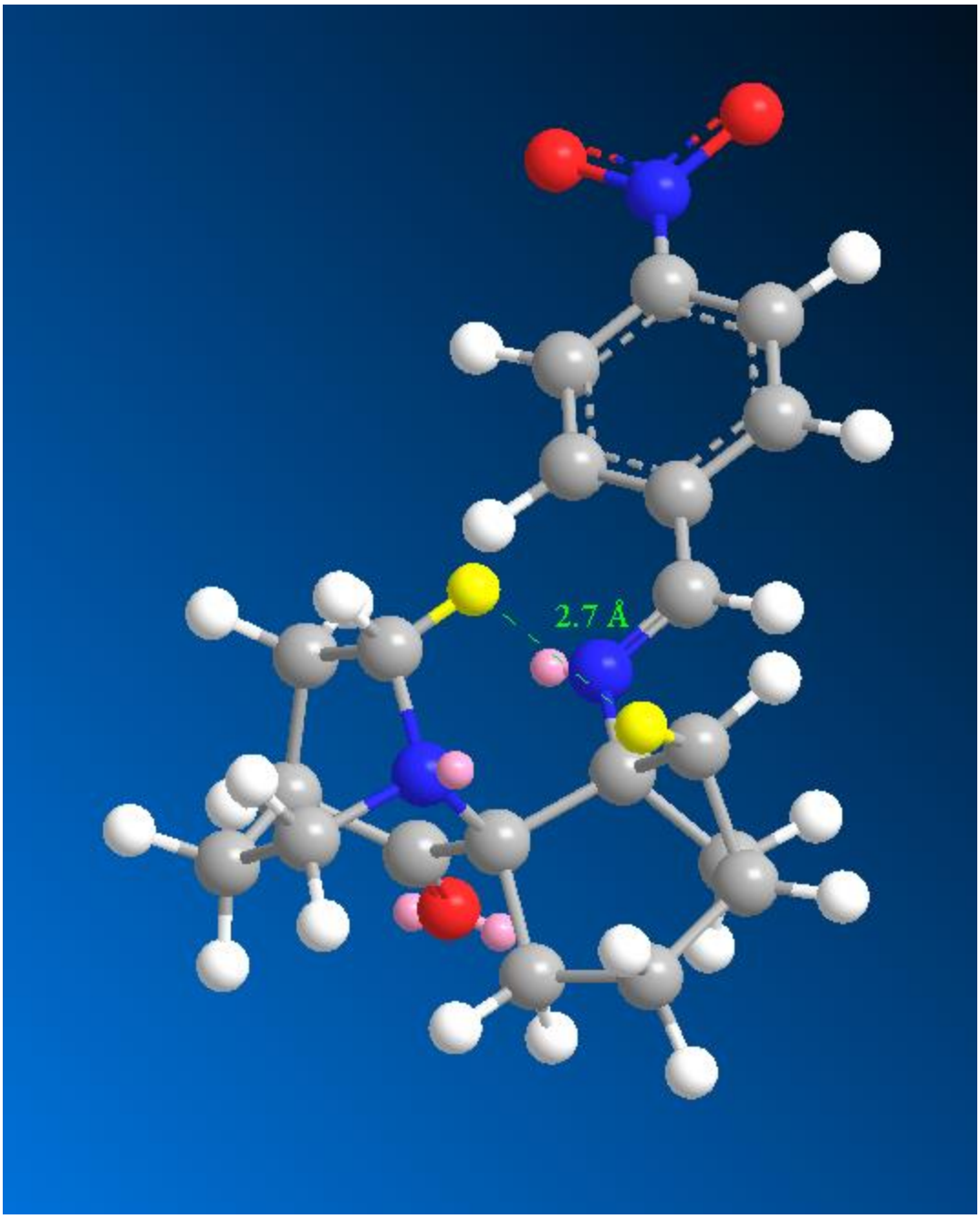


Carbon	Chemical shift (ppm)		Proton(s)	Chemical shift (ppm)
1	149.1		2	8.24 (d, J = 8.6 Hz, 2H)
2	124.1		3	7.85 (d, J = 8.7 Hz, 2H)
3	128.9		5	8.18 (s, 1H)
4	142		7a	2.52 (app. t, J = 8.5 Hz, 1H)
5	157		7b	2.01 (app. t, J = 7.9 Hz, 1H)
6	74.5		8a	2.71 (app. t, J = 8.9 Hz, 1H)
7	39.5		8b	one of 1.93-1.80 (m, 4H)
8	36.2		9	2.38-2.32 (m, 1H)
9	27.1		10a	one of 1.93-1.80 (m, 4H)
10	25.2		10b	one of 1.93-1.80 (m, 4H)
11	25.9		11a	2.32-2.25 (m, 1H)
12	74.9		11b	2.10 (dd, J = 14.5, 5.3 Hz, 1H)
13	223.1		14	2.19 (app. p, J = 3.0 Hz, 1H)
14	41.6		15a	1.99-1.93 (m, 1H)
15	27.3		15b	one of 1.93-1.80 (m, 4H)
16	24.1		16a	one of 1.79-1.69 (m, 2H)
17	45.4		16b	one of 1.79-1.69 (m, 2H)
18	46		17a	one of 2.92-2.79 (m, 2H)
			17b	3.49-3.39 (m, 1H)
			18a	one of 2.92-2.79 (m, 2H)
			18b	3.75-3.64 (m, 1H)

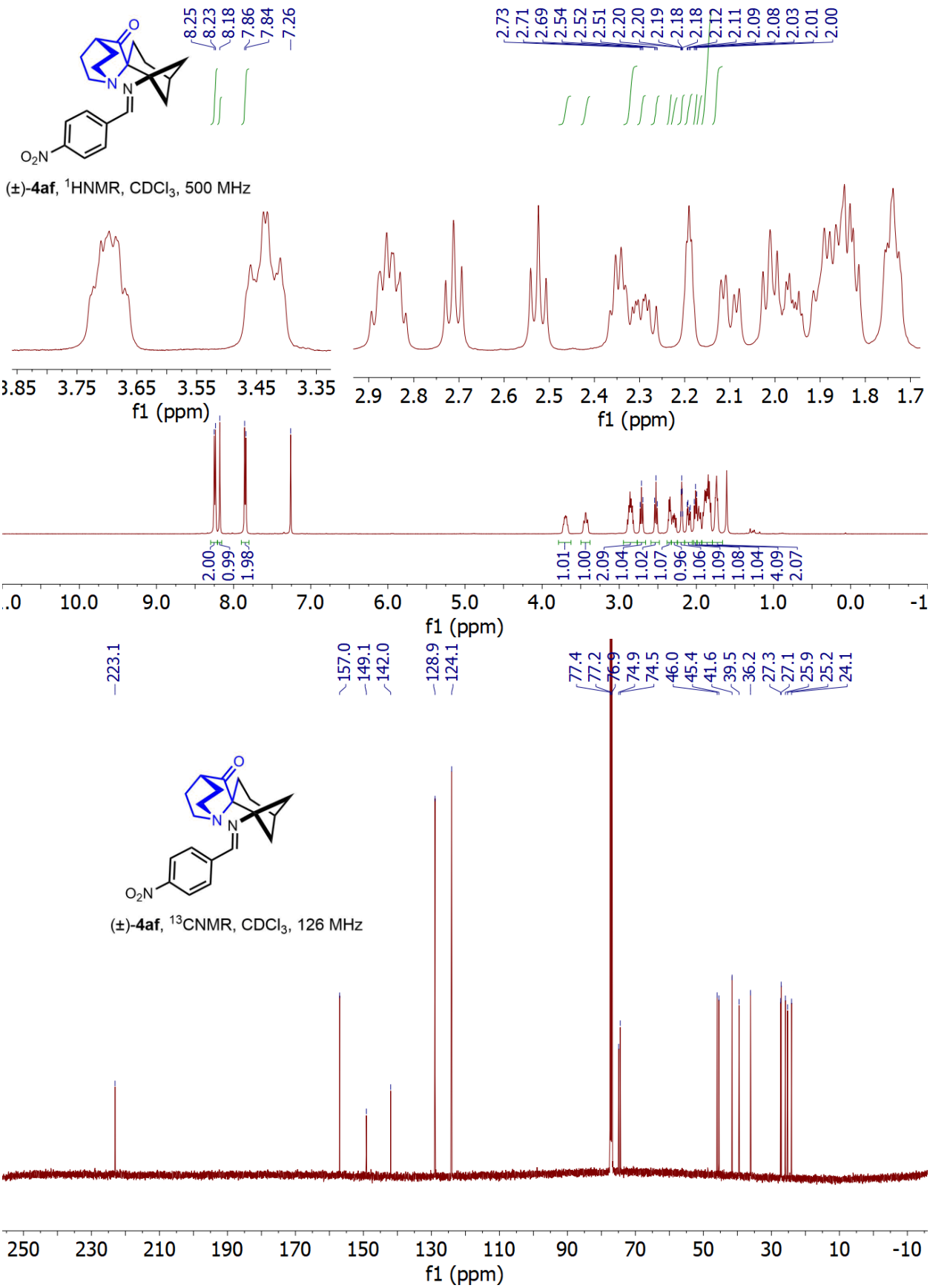
The atom-labeled structure of (±)-**4af** presented on the previous page is a bit challenging to interpret in 3-dimensions. Therefore, (±)-**4af** was constructed in Perkin-Elmer's Chem3D software and the MM2 minimized conformation is depicted from several angles below to highlight close contacts relevant to the interpretation of the NOESY spectra. Notably, this conformation doesn't capture the rotation about the C^6-N bond and C^4-C^5 bond, which are necessary to achieve conformations that explain the observed NOESY correlations between H^{18b} and both H^5 and H^3.

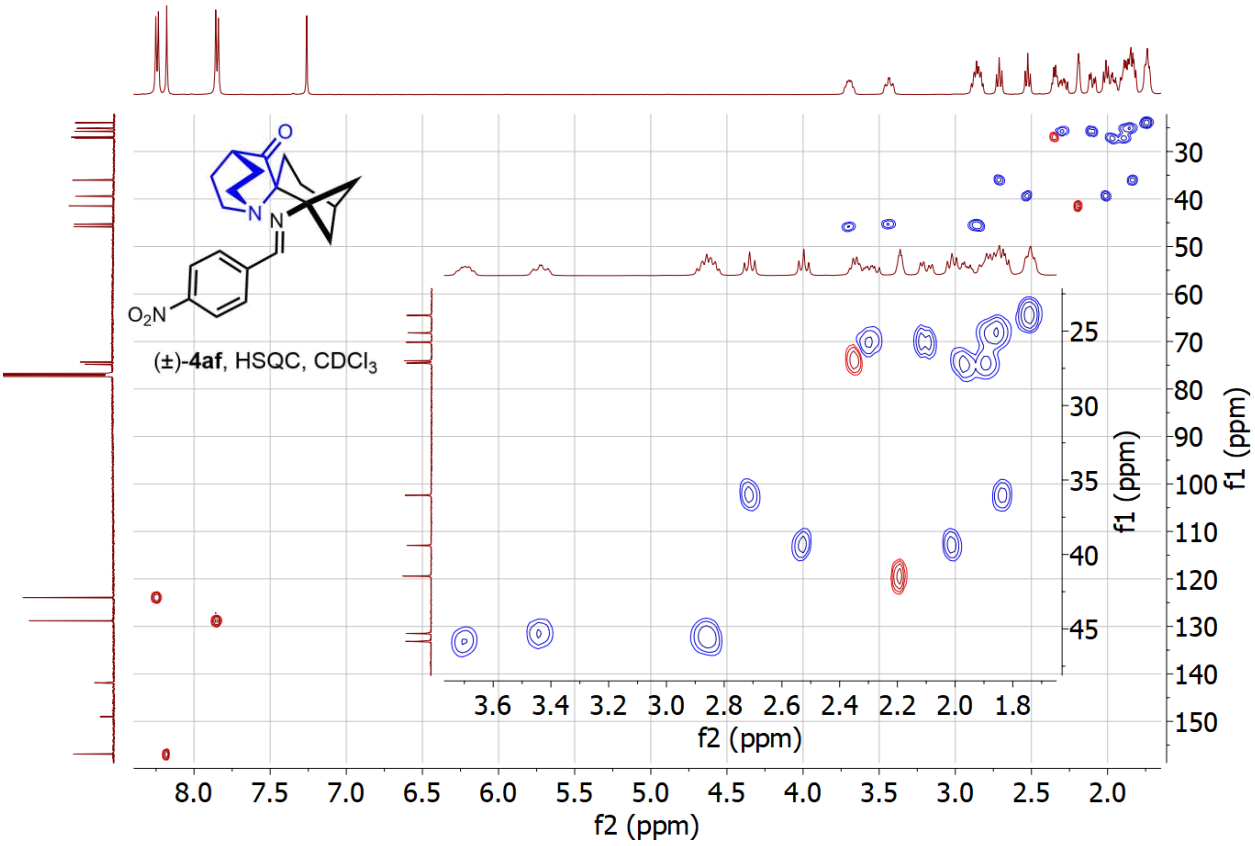


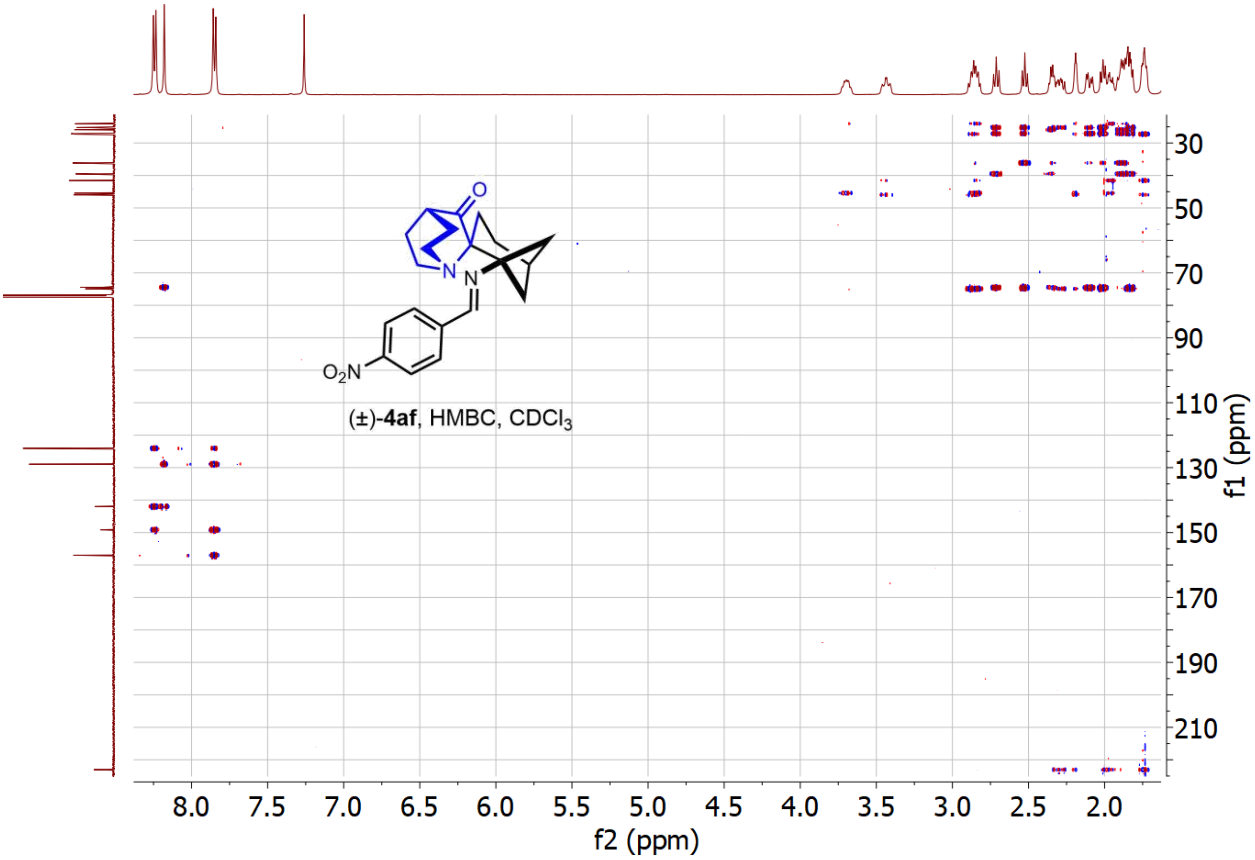
SI Figure 9: Protons H^{17b} and H^{11b} are in close proximity

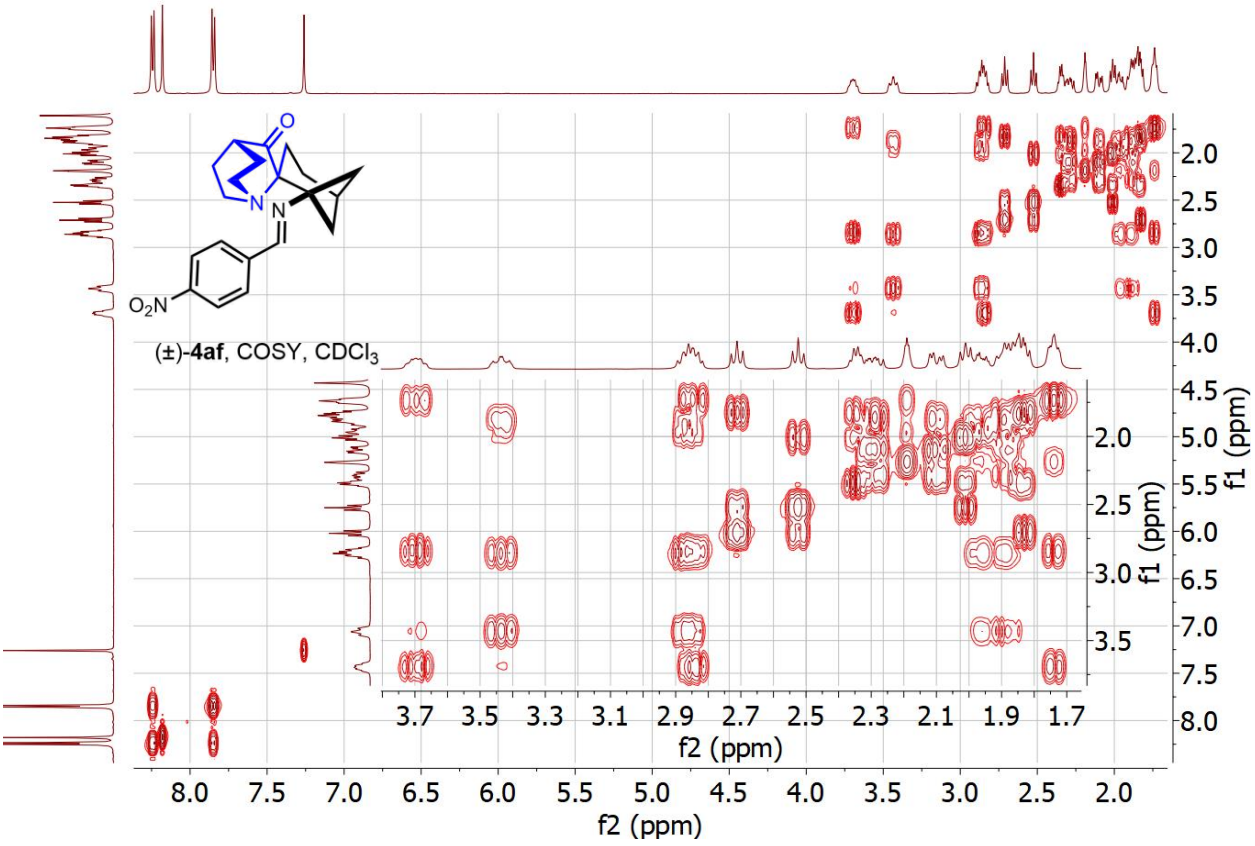


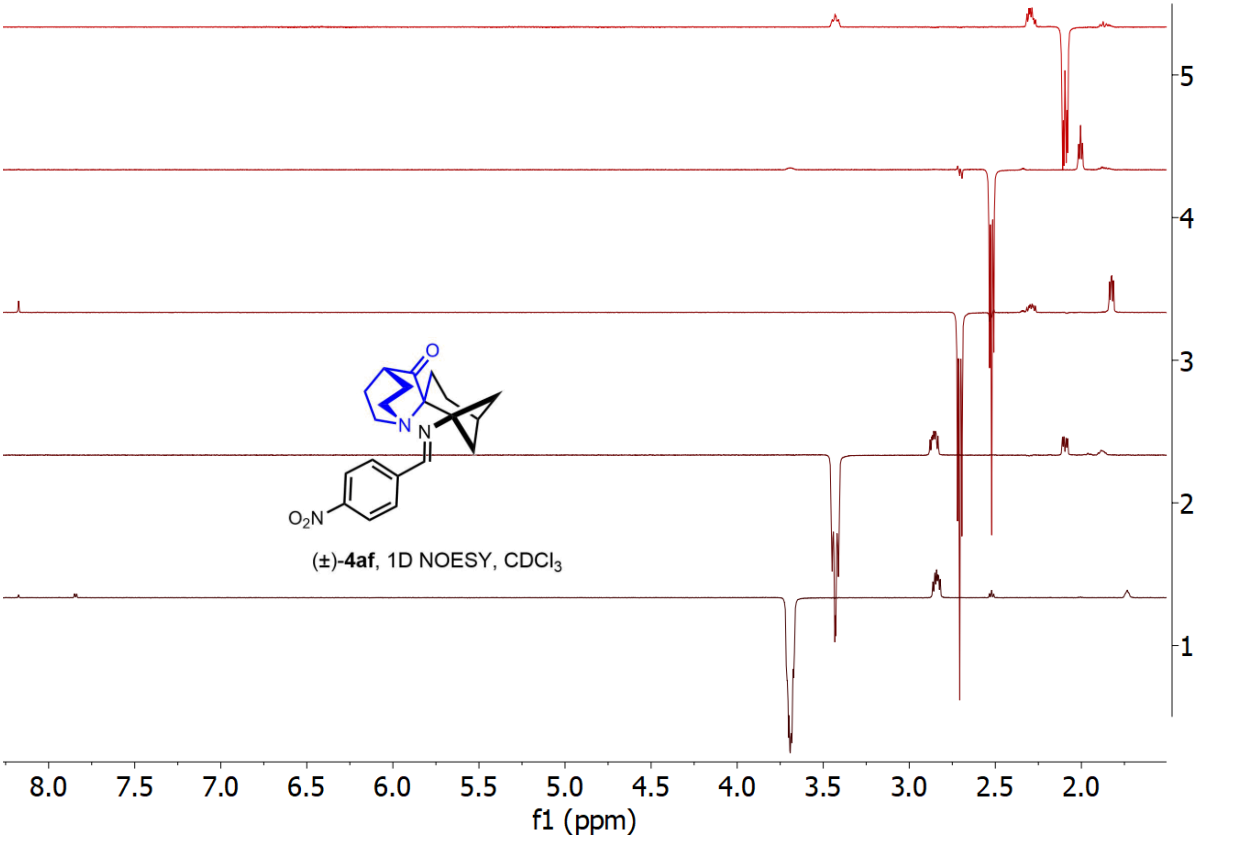
SI Figure 10: Protons H^{18b} and H^{7a} are in close proximity


8.25
8.23
8.18
7.86
7.84
7.26
2.73
2.71
2.69
2.54
2.52
2.51
2.20
2.20
2.19
2.18
2.18
2.12
2.11
2.09
2.08
2.03
2.01
2.00
O2N
(±)-4af, 1HNMR, CDCl3, 500 MHz
f1 (ppm)
f1 (ppm)
2.00
0.99
1.98
1.01
1.00
2.09
1.04
1.02
1.07
0.96
1.06
1.09
1.08
1.04
4.09
2.07
f1 (ppm)
223.1
157.0
149.1
142.0
128.9
124.1
77.4
77.2
76.9
74.9
74.5
46.0
45.4
41.6
39.5
36.2
27.3
27.1
25.9
25.2
24.1
O2N
(±)-4af, 13CNMR, CDCl3, 126 MHz
f1 (ppm)

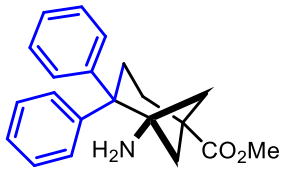

(±)-4af, HSQC, CDCl3
f2 (ppm)
f1 (ppm)


(±)-4af, HMBC, CDCl3
f2 (ppm)
f1 (ppm)


O
N
N
O_2N
(±)-**4af**, COSY, $CDCl_3$
f2 (ppm)
f1 (ppm)


O
N
N
O_2N
(±)-**4af**, 1D NOESY, $CDCl_3$
f1 (ppm)

Compound **SI-19**:



EXPERIMENTAL PROCEDURE:

To a 100 mL round-bottom flask equipped with a magnetic stir bar was added **4h** (200.2 mg, 0.440 mmol, 1 equiv). Acetonitrile (36 mL), water (4 mL), and acetic acid (8 mL) were sequentially added. Stirring gave a colorless solution. The headspace was flushed with nitrogen and the flask was sealed with a rubber septum. The reaction mixture was allowed to stir at room temperature for 96 hours. The reaction mixture was diluted with 1M aqueous hydrochloric acid (40 mL) and extracted with diethyl ether (3 x 30 mL). The aqueous phase was neutralized with saturated sodium bicarbonate solution (100 mL) and was extracted with ethyl acetate (4 x 40 mL). The combined ethyl acetate extracts were washed with brine (2 x 50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give **SI-19** (131.3 mg, 0.409 mmol, 93%) as a white solid.

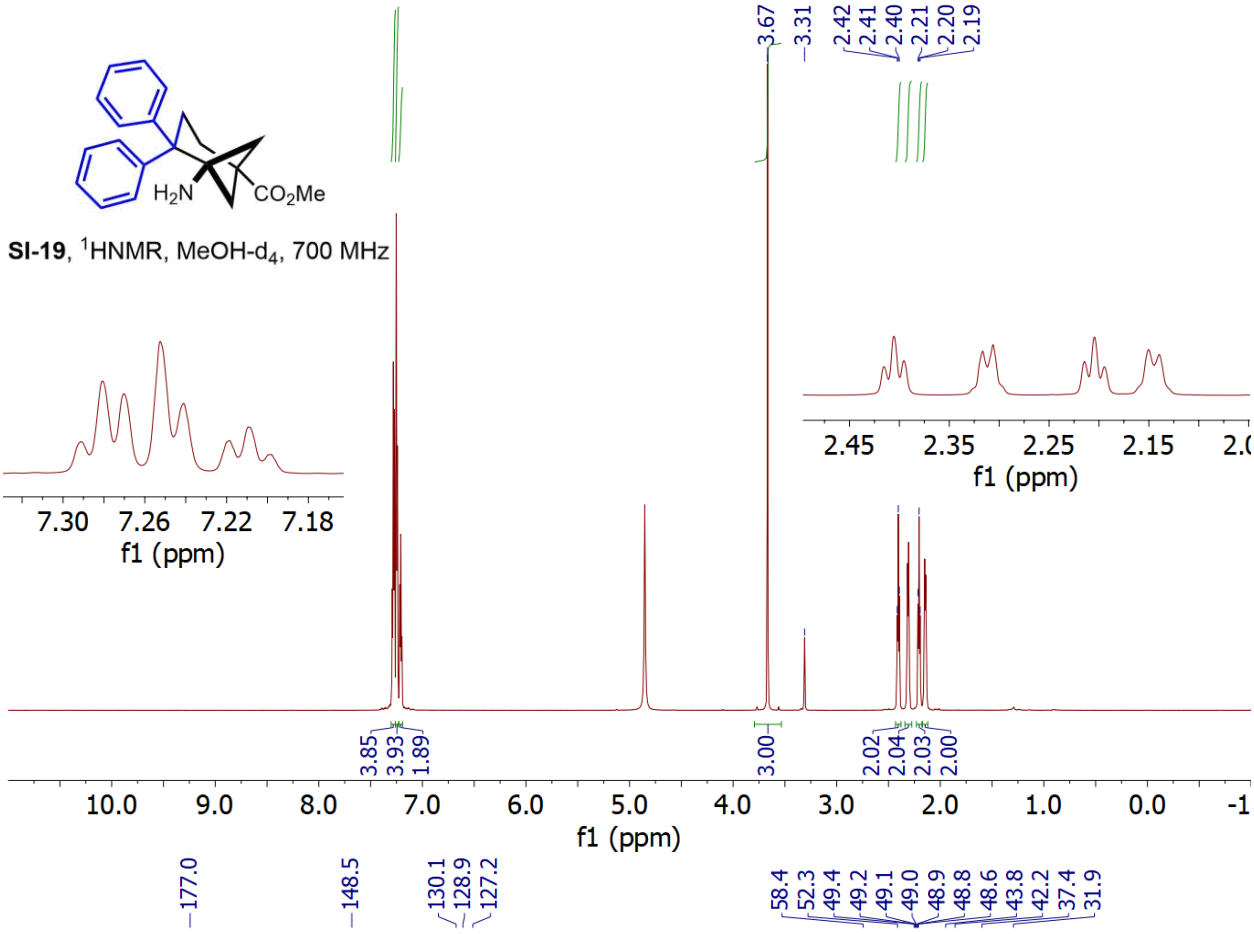
Appearance: white solid

^{1}H NMR (methanol-d_4, 700 MHz): δ = 7.30-7.26 (m, 4H), 7.26-7.23 (m, 4H), 7.23-7.19 (m, 2H), 3.67 (s, 3H), 2.41 (t, *J* = 6.9 Hz, 2H), 2.34-2.28 (m, 2H), 2.20 (t, *J* = 7.0 Hz, 2H), 2.17-2.12 (m, 2H) ppm

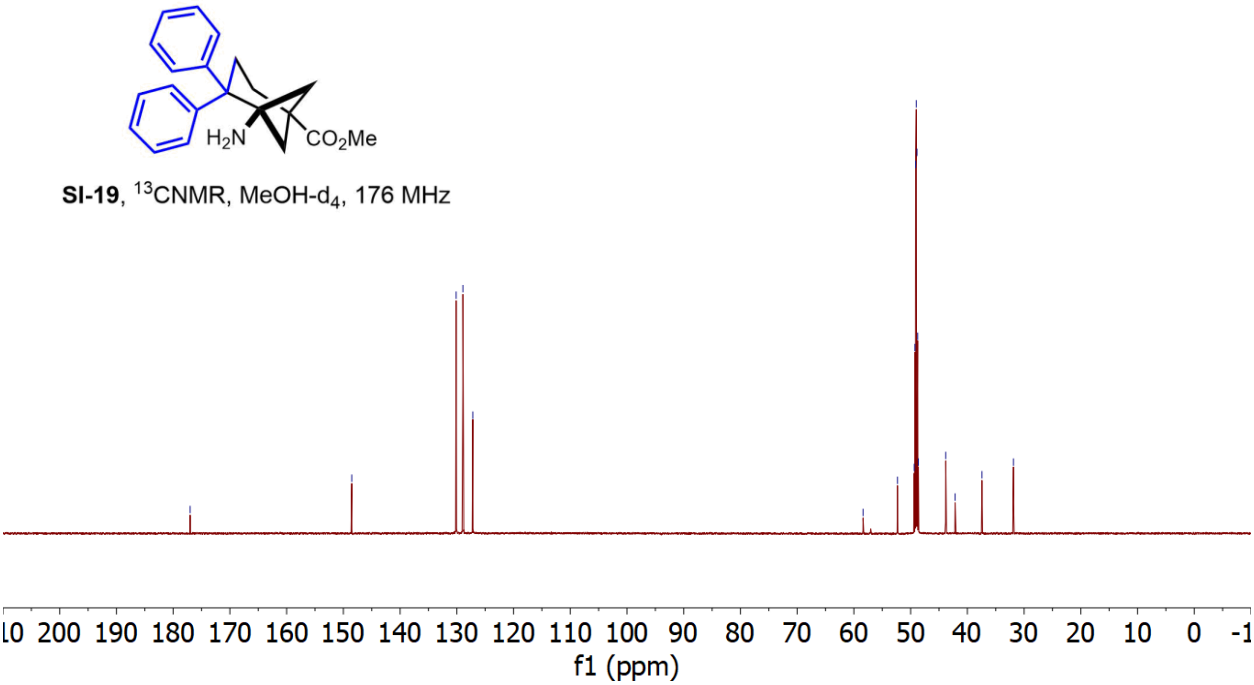
^{13}C NMR (methanol-d_4, 176 MHz): δ = 177.0, 148.5, 130.1, 128.9, 127.2, 58.4, 52.3, 43.8, 43.8, 42.2, 37.4, 31.9 ppm

IR (neat): 3374, 3028, 2950, 2868, 1722, 1601, 1492, 1476, 1435, 1349, 1296, 1282, 1268, 1237, 1189, 1168, 1103, 1086, 1046, 1034, 1009, 979, 920, 901, 862, 807, 791, 769, 751, 731, 709, 700, 671 cm^{-1}

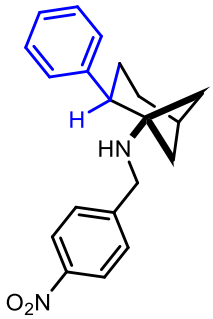
HRMS (ES+, m/z) calculated for $C_{21}H_{24}NO_2^+$: 322.1802, Found: 322.1800


H2N
CO2Me
SI-19, 1HNMR, MeOH-d4, 700 MHz
3.67
3.31
2.42
2.41
2.40
2.21
2.20
2.19
7.30
7.26
7.22
7.18
f1 (ppm)
2.45
2.35
2.25
2.15
f1 (ppm)
3.85
3.93
1.89
3.00
2.02
2.04
2.03
2.00
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

177.0
148.5
130.1
128.9
127.2
58.4
52.3
49.4
49.2
49.1
49.0
48.9
48.8
48.6
43.8
42.2
37.4
31.9


H2N
CO2Me
SI-19, 13CNMR, MeOH-d4, 176 MHz
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Compound **SI-20**:



EXPERIMENTAL PROCEDURE:

A modification of general procedure B (no 2,2'-dipyridyl disulfide was used, alternative workup used) was performed using **2a** (86.5 mg, 0.400 mmol, 1 equiv), styrene (0.345 mL, 3.00 mmol, 7.5 equiv), and irradiating for 17 hours. The crude reaction mixture was transferred to an oven-dried 50 mL round bottom flask equipped with an egg-shaped magnetic stir bar using absolute ethanol (10 mL) and dichloromethane (5 mL). The flask was capped with a rubber septum and mixture was put under nitrogen atmosphere and cooled to 0 °C in an ice bath. $NaBH_4$ (151 mg, 4.00 mmol, 10 equiv) was added in one portion by briefly removing the septum and pouring in the solid. The mixture was allowed to stir in the ice bath. All the ice melted over the course of 1 hour. The bath was then removed, and the mixture was allowed to warm to room temperature and stir for 2 hours. Then, the mixture was transferred to a separatory funnel with ethyl acetate (50 mL). 1 M HCl (80 mL) was slowly added to quench the excess $NaBH_4$ and to protonate basic amines. The funnel was shaken, and the layers were separated. The aqueous layer was washed with ethyl acetate (2 x 50 mL) and the organic washes were combined and set aside. Then, the acidic aqueous phase was neutralized with saturated aqueous $NaHCO_3$ (150 mL). The cloudy aqueous suspension was extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The organic layer from the original extraction showed evidence of **SI-20**, so another series of extractions were performed. The organic wash was further extracted with 0.5 M HCl (4 x 50 mL). These combined acidic aqueous fractions were neutralized with saturated aqueous $NaHCO_3$ (200 mL). The cloudy aqueous suspension was extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, combined with the earlier ethyl acetate extract, and concentrated onto celite. The mixture was loaded atop a pre-neutralized (3 column volumes of 5% Et_3N in hexanes) silica gel column and eluted with 7-60% ethyl acetate in hexanes to give **SI-20** (16.5 mg, 0.0512 mmol, 13%) as a faintly yellow oil.

Appearance: faintly yellow oil

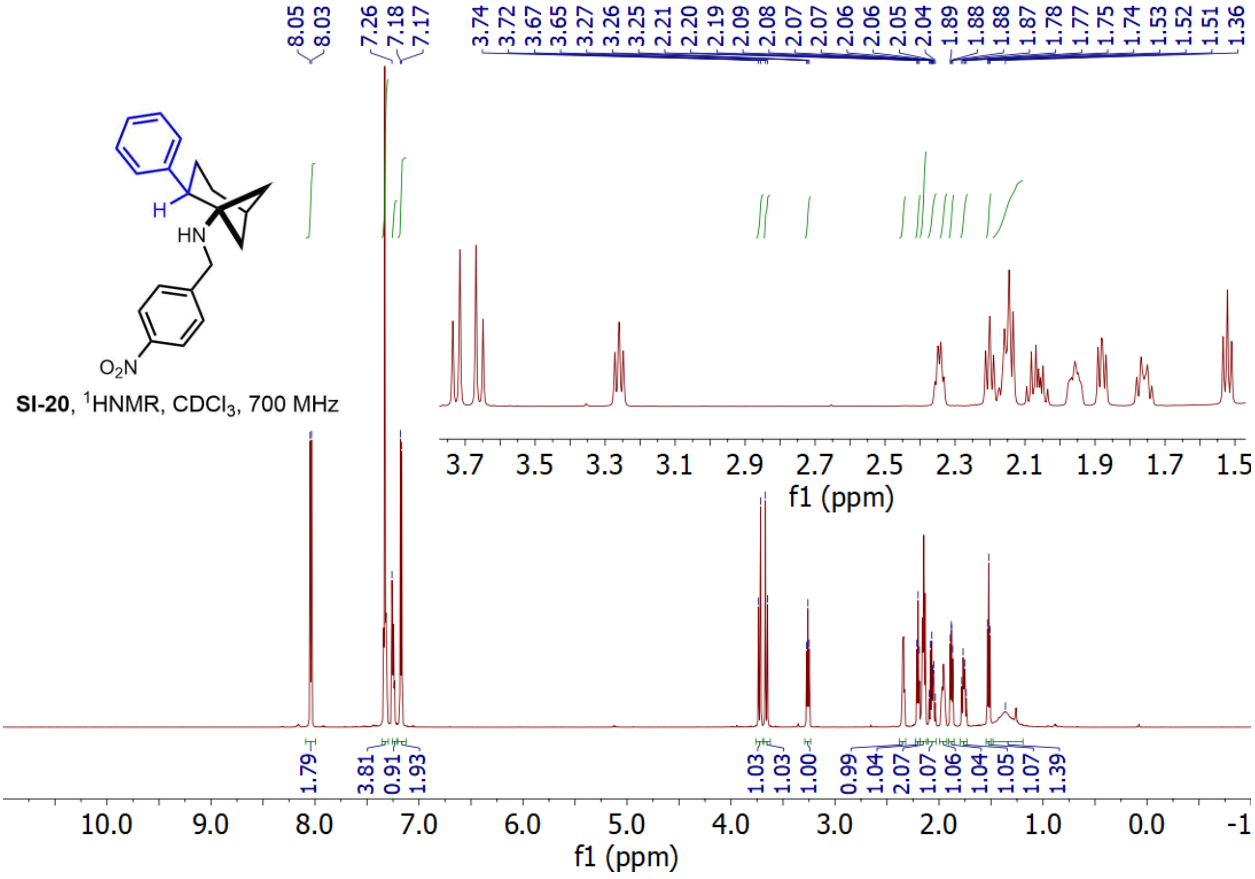
^{1}H NMR ($CDCl_3$, 700 MHz): Note that the doublets at chemical shifts of 3.72 and 3.66 ppm are an AB quartet. δ = 8.04 (d, *J* = 8.5 Hz, 2H), 7.35-7.30 (m, 4H), 7.26-7.23 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.72 (d, *J* = 14.2 Hz, 1H), 3.66 (d, *J* = 14.2 Hz, 1H), 3.26 (app. t, *J* = 8.5 Hz, 1H), 2.37-2.32 (m, 1H), 2.20 (app. t, *J* = 8.0 Hz, 1H), 2.18-2.12 (m, 2H), 2.06 (app. dq, *J* = 14.3, 9.1Hz, 1H), 1.99-1.93 (m, 1H), 1.88 (dd, *J* = 8.6, 7.0 Hz, 1H), 1.76 (app. dt, *J* = 12.8, 8.6 Hz, 1H), 1.52 (app. t, *J* = 8.4 Hz, 1H), 1.36 (bs, 1H) ppm

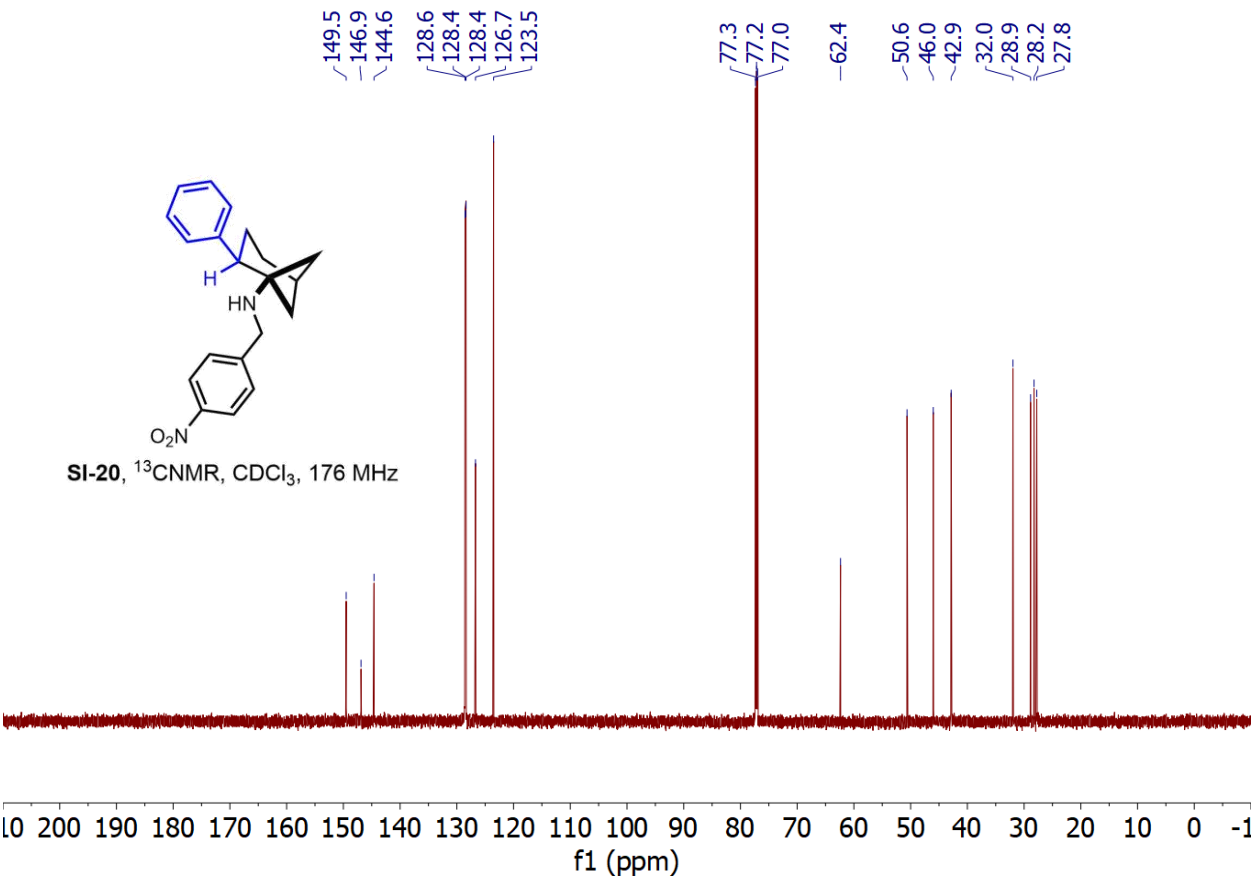
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 149.5, 146.9, 144.6, 128.6, 128.4, 128.4, 126.7, 123.5, 62.4, 50.6, 46.0, 42.9, 32.0, 28.9, 28.2, 27.8 ppm

IR (neat): 3060, 3028, 2941, 2859, 1600, 1516, 1492, 1451, 1341, 1318, 1294, 1256, 1212, 1175, 1108, 1087, 1030, 1015, 982, 953, 902, 853, 760, 738, 700 cm^{-1}

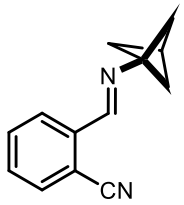
HRMS (ES+, m/z) calculated for $C_{20}H_{23}N_2O_2^+$: 323.1754, Found: 323.1755

R_f = 0.64 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV





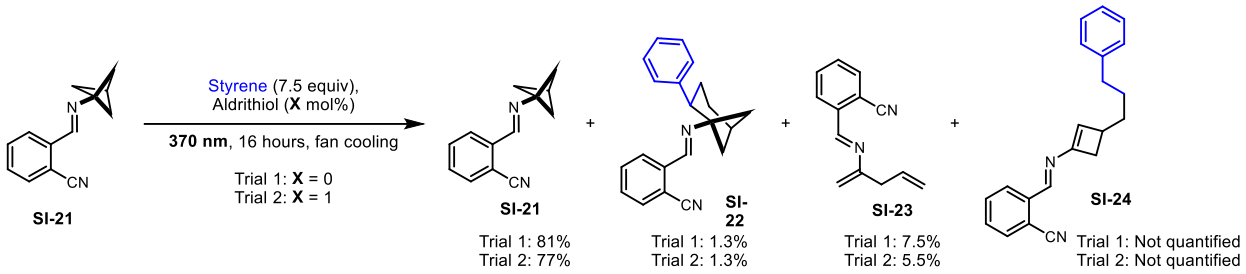
Compound **SI-21**:



EXPERIMENTAL PROCEDURE:

To a 50 mL recovery flask equipped with an egg-shaped magnetic stir bar were sequentially added bicyclo[1.1.1]pentan-1-amine hydrochloride (251 mg, 2.10 mmol, 1.1 equiv), 2-formylbenzonitrile (0.250 g, 1.91 mmol, 1 equiv), dichloromethane (20 mL), and triethylamine (797 µL, 5.72 mmol, 3 equiv), giving an orange solution. The headspace was flushed with argon and flask was capped with a rubber septum. An argon balloon was attached via needle through the septum and the flask was covered in aluminum foil to shield the reaction mixture from light. The mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was diluted with saturated aqueous sodium bicarbonate (50 mL) and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 x 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo to give SI-21 (345.2 mg, 1.76 mmol, 92%) as a faintly tan solid.

Compound **SI-21** did not undergo photochemical reaction at a practical rate when using desirable UV-A or visible LED lamps (370+ nm) and simple modifications of general procedure B. Insufficient amounts of the BCP-activation products (**SI-22**, **SI-23**, and **SI-24**) were produced to allow for isolation and characterization. The yields in the figure below are based on analogy to diagnostic peaks of the corresponding products of **2a**'s photoactivation in the presence of styrene.



SI Figure 11: Replacing the para-nitrophenyl group with a meta-cyanophenyl group led to drastically decreased reactivity and a higher amount of azadiene byproduct, even at 370 nm

Appearance: faintly tan solid

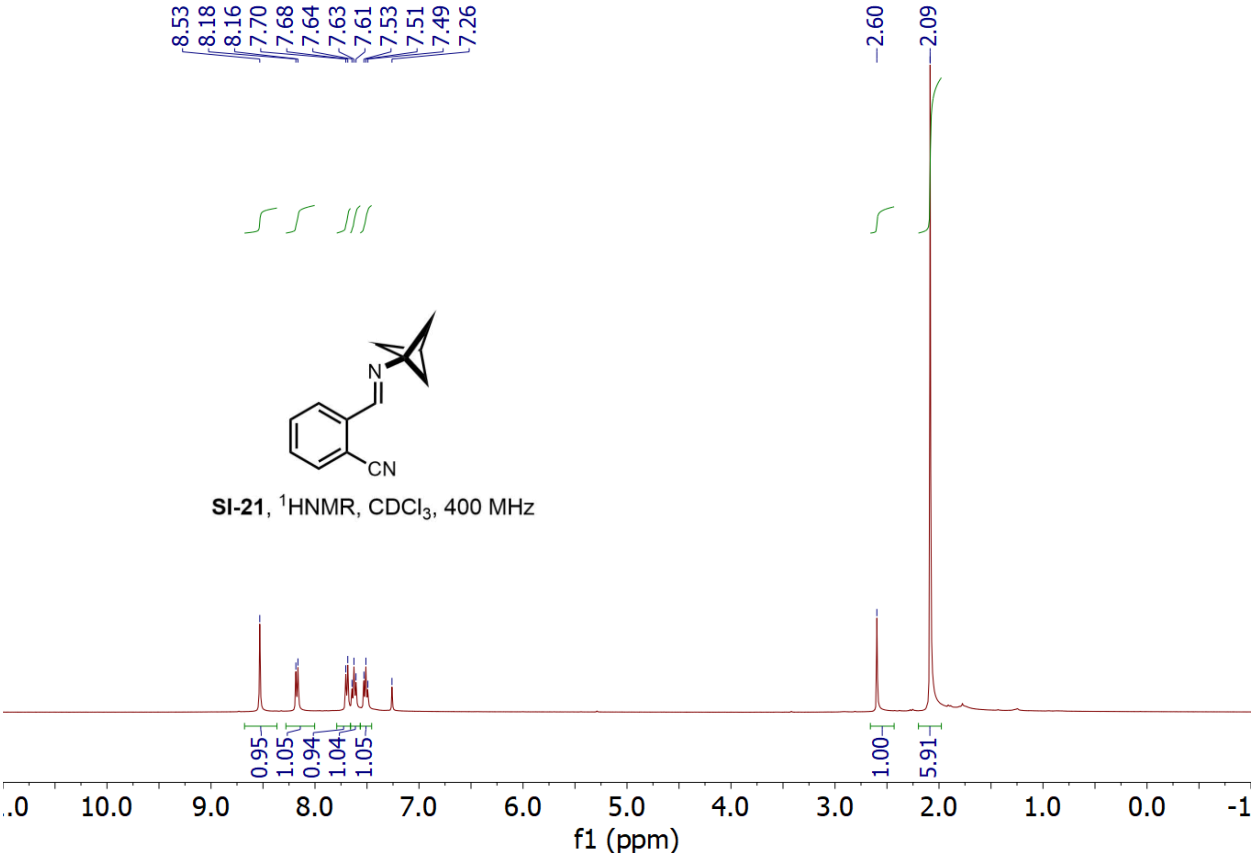
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.53 (s, 1H), 8.17 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 2.60 (s, 1H), 2.09 (s, 6H) ppm

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.7, 138.1, 133.1, 133.0, 131.0, 127.3, 117.0, 113.3, 62.3, 52.2, 23.1 ppm

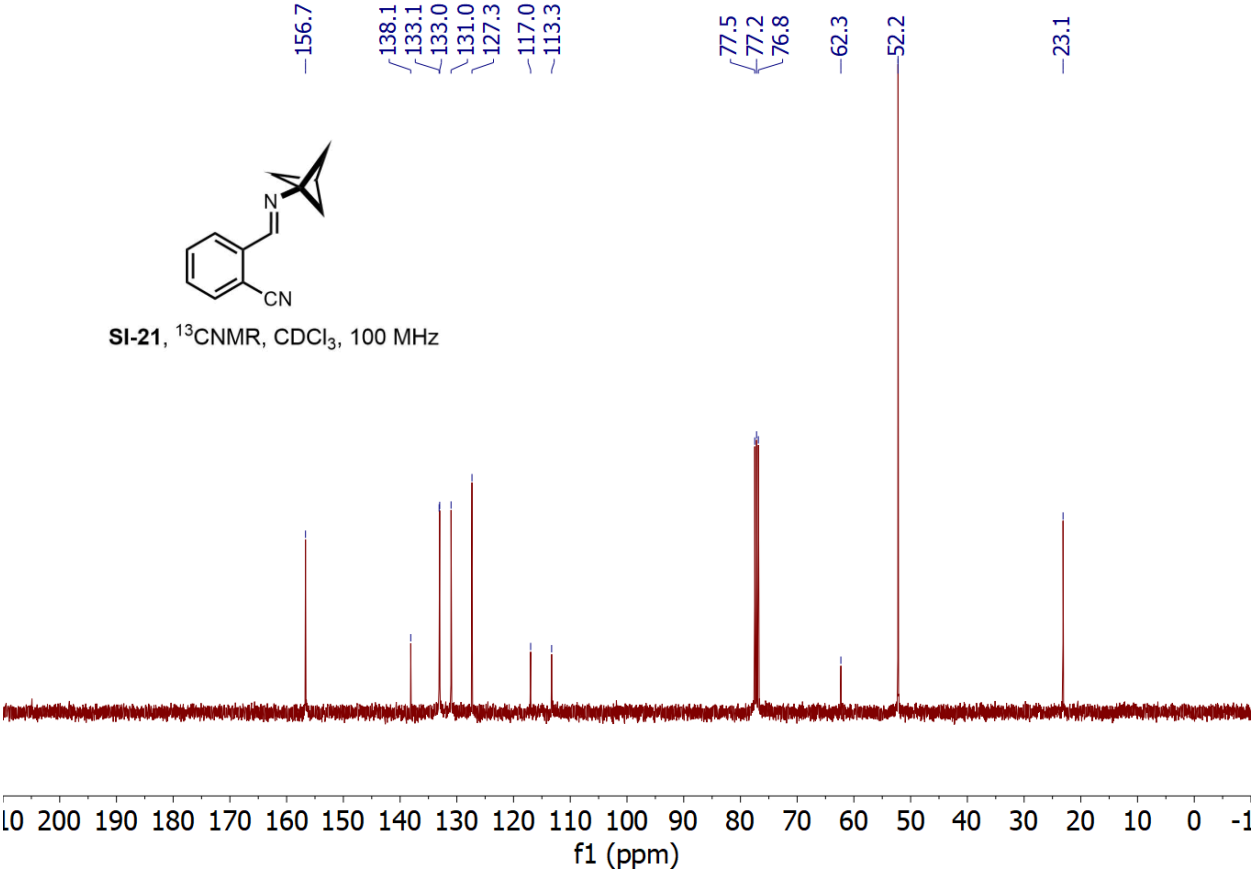
IR (neat): 3066, 3009, 2975, 2910, 2871, 2229, 1961, 1658, 1630, 1592, 1568, 1505, 1481, 1447, 1369, 1302, 1284, 1253, 1215, 1195, 1143, 1089, 1040, 978, 961, 938, 925, 876, 860, 781, 767, 698 cm^{-1}

HRMS (ES+, m/z) calculated for $C_{13}H_{13}N_2^+$: 197.1073, Found: 197.1075

R_f = 0.50 (20% ethyl acetate : 79% hexanes : 1% aqueous NH_4OH), yellow spot, $KMnO_4$, UV



SI-21, ^{1}HNMR, $CDCl_3$, 400 MHz



SI-21, ^{13}CNMR, $CDCl_3$, 100 MHz

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