Direct Deaminative Functionalization

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I. Material and Methods

Unless noted otherwise, all reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry N_2. CH_3CN, THF, Et_2O, CH_2Cl_2, toluene, and Et_3N were dried by passing these previously degassed solvents through a PPT Solvent Purification System, and all other solvents were dried over molecular sieves (4 Å) and degassed prior to use or purchased anhydrous and sealed under N_2 (e.g. VWR Dri-solv or equivalent). Reaction temperatures were reported as the temperatures of the bath surrounding the flasks or vials. Sensitive reagents and solvents were transferred under nitrogen into a nitrogen-filled glovebox with standard techniques. Unless otherwise noted, all reagents were used as received. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254) and visualized by UV irradiation or staining as indicated. Flash chromatography was accomplished using an automated system (monitoring at 254 nm and 280 nm as well as an ELS detector for non-chromaphoric species) with silica cartridges (60 Å porosity, 20-40 µm). High resolution mass spectra were recorded on either an Agilent 6224 TOF High Resolution Accurate MS with electrospray ionization or an Agilent 7200B QTOF High Resolution Accurate Mass GCMS using an Agilent HP-5MS column with a gradient of 50 °C to 200 °C over 15 minutes and electron impact ionization. LCMS data was recorded on an Acquity I-Class UPLC-MS system from Waters running with both acidic (TFA) and basic (NH_4OH) modifiers. All mass spectra were processed with Agilent MassHunter or Virscidian Analytical Studio. NMR spectra (^1H, ^{13}C, ^{19}F) were obtained at 298 K. ^1H NMR spectra were referenced to residual, nondeuterated chloroform (δ 7.26) in $CDCl_3$, residual DMSO-d_5 (δ 2.50) in DMSO-d_6, acetone-d_5 (δ 2.09) in acetone-d_6, and residual MeCN-d_2 (δ 1.94) in MeCN-d_3. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ 77.16), DMSO-d_6 (δ 39.5), the carbonyl carbon of acetone (δ 205.9), or the nitrile carbon of MeCN-d_3 (δ 118.3), respectively. ^{19}F NMR spectra are run with C-F/C-H decoupling (δ –161.64 in $CDCl_3$). Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant *J* (Hz) and integration. Anomeric amide reagent **1** was prepared according to our previously published protocol[1] or purchased from commercial suppliers.

Safety Note: While we have not encountered any issues with routine handling of the anomeric amide reagent, **1**, we note that it does have a mildly exothermic decomposition (114 °C).[2] Moreover, the title reaction occurs rapidly and releases gas, so proper venting and temperature control is important especially as the scale is increased.

Additionally, Many members of this class of compounds have been experimentally demonstrated to behave as direct-acting mutagens in bacteria (as ascertained by Ames tests using the *S. typhimurium* TA100 strain).[3] A QSAR Model developed by Glover predicts a mutagenicity for **1** of log(TA100) = 2.6, corresponding to 400 predicted revertants at a dose of 1 μmol/plate.[4]

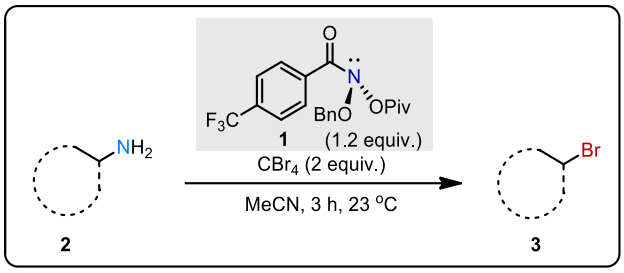
We have conducted Ames II testing of compound **1**, which uses a different set of *S. typhimurium* strains (TA Mix, a mixture of TA7001-7006 which collectively test for point mutations, and TA98, which tests for frameshift mutations). While no biologically significant activity was observed in the TA98 strain in the absence of metabolic activation, we did observe activity in the TA Mix strains as well as in both strains with S9 metabolic activation. With the caveat that TA100 and Ames II tests cannot be directly compared unambiguously, the response in this latter test can be expressed in analogous units; at a dose equivalent to 1 μmol/plate we interpolate an activity of 13 revertants, or a log(TA Mix) = 1.11.

This is meaningfully less mutagenic activity than predicted by QSAR analysis of the original members of this compound family studied by Glover, which vary with $2 < \log(TA100) < 4$. Common laboratory reagents are known to be mutagenic at similar or higher levels to **1**, e.g. dibromoethane (log(TA100) = 1.96)[5], glutaraldehyde (log(TA100) = 1.98)[6], and benzyl chloride (log(TA100) = 1.68)[7]. These data are of course in addition to the many known carcinogenic and mutagenic reagents that are routinely handled in the laboratory for which raw revertant data is not readily available.[8]

The relationship between mutagenicity in *Salmonella* and human carcinogenicity is complex, but positive Ames results can preclude medicinal uses of compounds (i.e., ingestion). We therefore advise appropriate caution in the handling of **1**: standard chemical safety protocols to minimize exposure and prevent accidental ingestion, inhalation, or dermal contact, including proper ventilation and personal protective equipment.

I. General Procedures

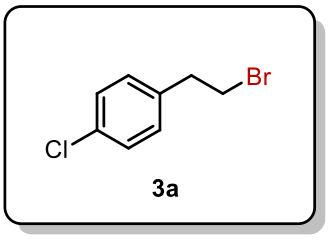
IIA. General Procedure for Deaminative Bromination of Aliphatic Amines



To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the amine (1 equiv.). The anomeric amide, **1**, (1.2 equiv.) and carbon tetrabromide (2 equiv.) were added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe. Dissolved amine was then added dropwise to vial containing mixture of **1** and CBr_4 over the period of 5 min. The total volume of solvent is such that the concentration of amine in the reaction is 0.1 M. The reaction was stirred at room temperature for 3 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude product was purified by silica gel chromatography.

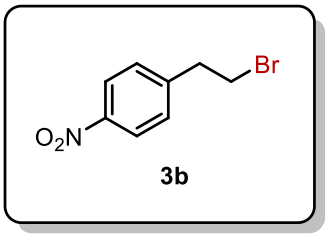
Note: *In case, where the aliphatic amine is not completely soluble in acetonitrile, a solution of* **1** *in MeCN was added dropwise to the mixture of amine and* CBr_4.

1-(2-bromoethyl)-4-chlorobenzene (3a):



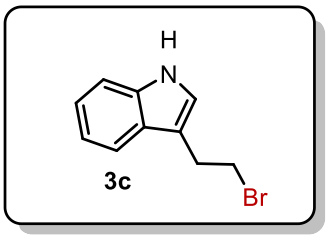
Synthesized according to **General Procedure IIA** from 2-(4-chlorophenyl)ethan-1-amine (50 mg, 0.32 mmol). The title compound was obtained in 78% yield (55.0 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 5% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 3.54 (t, *J* = 7.4 Hz, 1H), 3.13 (t, *J* = 7.4 Hz, 1H). Spectroscopic data are in agreement with the literature.[9]

1-(2-bromoethyl)-4-nitrobenzene (3b):



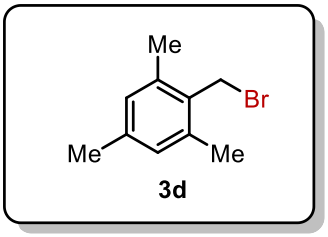
Synthesized according to **General Procedure IIA** from 2-(4-nitrophenyl)ethan-1-amine (50 mg, 0.30 mmol). The title compound was obtained in 67% yield (46.3 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 15% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 3.61 (t, *J* = 7.1 Hz, 3H), 3.28 (t, *J* = 7.1 Hz, 3H). Spectroscopic data are in agreement with the literature.[10]

3-(2-bromoethyl)-1*H*-indole (3c):



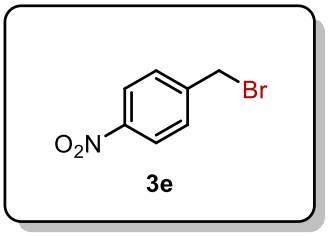
Synthesized according to **General Procedure IIA** from tryptamine (50 mg, 0.31 mmol). The title compound was obtained in 55% yield (38.6 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 20% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.58-7.60 (dd, *J* =8.0, 0.4 Hz, 1H), 7.36-7.38 (d, *J* = 8.4 Hz, 1H), 7.19-7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.12-7.16 (d, *J* = 8.4, 1.0 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 3.61 (t, *J* =7.8 Hz, 2H), 3.31 (t, *J* = 7.6 Hz, 2H) ppm. Spectroscopic data are in agreement with the literature.[11]

2-(bromomethyl)-1,3,5-trimethylbenzene (3d):



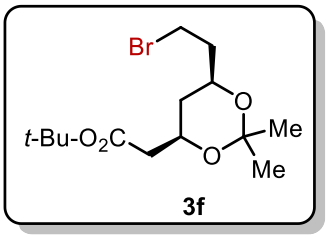
Synthesized according to **General Procedure IIA** from mesitylmethanamine (40 mg, 0.27 mmol). The title compound was obtained in 67% NMR yield. R_f = 0.80 (silica gel, 5% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.90 (s, 2H), 4.60 (s, 2H), 2.42 (s, 6H), 2.31 (s, 3H). Spectroscopic data are in agreement with the literature.[12]

1-(bromomethyl)-4-nitrobenzene (3e):



Synthesized according to **General Procedure IIA** from (4-nitrophenyl)methanamine (40 mg, 0.26 mmol). The title compound was obtained in 59% yield (33.5 mg) after purification by silica gel chromatography. R_f = 0.6 (silica gel, 10% EtOAc in hexanes). Formation of 7% of deamination product nitrobenzene was observed. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.23 – 8.06 (m, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 4.45 (s, 2H). Spectroscopic data are in agreement with the literature.[13]

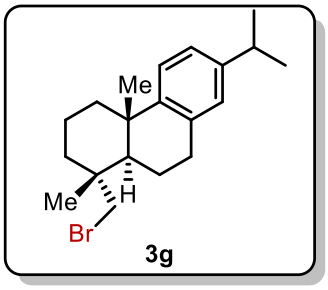
***tert*-butyl 2-((4*R*,6*S*)-6-(2-bromoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (3f):**



3f

Synthesized according to **General Procedure IIA** from *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (60 mg, 0.22 mmol). The title compound was obtained in 64% yield (47.3 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 20% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.27 (dtd, *J* = 11.5, 6.5, 2.4 Hz, 1H), 4.13 – 4.01 (m, 1H), 3.61 – 3.41 (m, 2H), 2.43 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.30 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.06 – 1.85 (m, 2H), 1.56 (dt, *J* = 12.6, 2.5 Hz, 1H), 1.46 (s, 3H), 1.44 (s, 9H), 1.35 (s, 3H), 1.24 (td, *J* = 5.4, 2.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 99.1, 80.8, 66.7, 66.3, 42.8, 39.2, 36.2, 30.1, 29.7, 28.2, 19.8. **HRMS** (ESI-TOF) calcd 359.0828 and 361.0808 for $C_{14}H_{25}BrNaO_4^+$ $[M+Na]^+$, found 359.0825 and 361.0806.

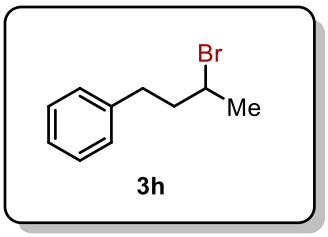
(1*R*,4a*S*,10a*R*)-1-(bromomethyl)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (3g):



3g

Synthesized according to **General Procedure IIA** from leelamine (60 mg, 0.21 mmol). The title compound was obtained in 61% yield (45.0 mg) after purification by silica gel chromatography. R_f = 0.5 (silica gel, 2% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.2 Hz, 1H), 7.01 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 3.50 (d, *J* = 10.2 Hz, 1H), 3.30 (d, *J* = 10.1 Hz, 1H), 2.92 (dd, *J* = 9.8, 6.1 Hz, 2H), 2.84 (p, *J* = 6.9 Hz, 1H), 2.29 (ddt, *J* = 12.9, 4.3, 2.1 Hz, 1H), 1.86 – 1.64 (m, 5H), 1.54 (td, *J* = 13.2, 4.4 Hz, 1H), 1.48 – 1.37 (m, 2H), 1.25 (s, 3H), 1.23 (d, *J* = 1.5 Hz, 6H), 1.07 (s, 3H). Spectroscopic data are in agreement with the literature.[14]

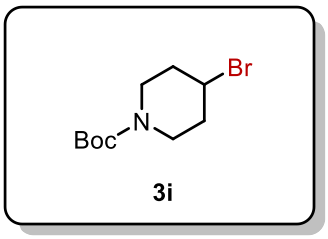
(3-bromobutyl)benzene (3h):



3h

Synthesized according to the **General Procedure IIA** from 4-phenylbutan-2-amine (30 mg, 0.201 mmol). The title compound was obtained (28.0 mg, 0.132 mmol, 66% yield) after purification by silica gel preparative TLC. R_f = 0.76 (silica gel, 10% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 – 7.10 (m, 5H), 4.06 – 3.96 (m, 1H), 2.86 – 2.63 (m, 2H), 2.09 – 1.93 (m, 2H), 1.66 (d, *J* = 6.8 Hz, 3 H). Spectroscopic data are in agreement with the literature.[15]

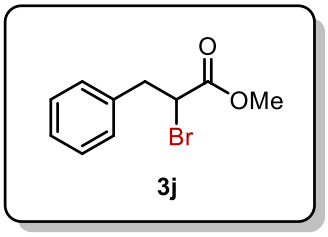
***tert*-butyl 4-bromopiperidine-1-carboxylate (3i):**



3i

Synthesized according to **General Procedure IIA** from *tert*-butyl 4-aminopiperidine-1-carboxylate (60 mg, 0.3 mmol). The title compound was obtained in 63% yield (50.0 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 20% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.34 (tt, *J* = 7.6, 3.8 Hz, 1H), 3.68 (ddd, *J* = 13.7, 7.1, 3.8 Hz, 2H), 3.32 (ddd, *J* = 13.7, 7.7, 3.7 Hz, 2H), 2.14 – 2.02 (m, 2H), 2.00 – 1.80 (m, 2H). Spectroscopic data are in agreement with those in the literature.[16]

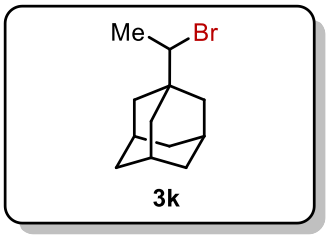
Methyl 2-bromo-3-phenylpropanoate (3j):



3j

Synthesized according to **General Procedure IIA** from methyl L-phenylalaninate (50 mg, 0.28 mmol) with the following modifications: The amine was slowly added a solution of **1** over the period of 1 h (instead of 5 min) using syringe pump. The title compound was obtained in 58% yield (39.3 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 10% EtOAc in hexanes). 8% Deamination product formation was observed. **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.17-7.29 (m, 5H), 4.39 (t, *J* = 8.3 Hz, 1H), 3.71 (s, 3H), 3.45 (dd, *J* = 8.3 Hz, 14.1 Hz, 1H), 3.22 (dd, *J* = 7.1 Hz, 13.9 Hz, 1H). Spectroscopic data are in agreement with the literature.[17]

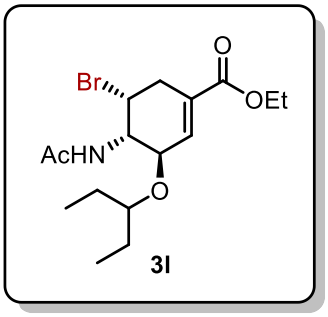
(3*r*,5*r*,7*r*)-1-(1-bromoethyl)adamantane (3k):



3k

Synthesized according to **General Procedure IIA** from rimantadine (50 mg, 0.28 mmol). The title compound was obtained in 54% yield (36.3 mg) after purification by silica gel chromatography. R_f = 0.7 (silica gel, 2% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.93 (q, *J* = 6.9 Hz, 1H), 2.00 (p, *J* = 3.2 Hz, 3H), 1.74 – 1.56 (m, 11H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 65.8, 39.3, 37.2, 36.9, 28.5, 20.0. **HRMS** (ESI-TOF) calcd 265.0562 for $C_{12}H_{19}BrNa^+$ $[M+Na]^+$, found 265.0585.

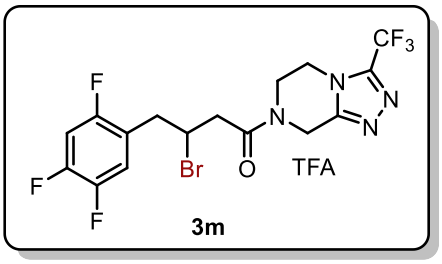
Ethyl (3*R*,4*S*,5*R*)-4-acetamido-5-bromo-3-(pentan-3-yloxy)cyclohex-1-ene-1-carboxylate (3l):



3l

Synthesized according to **General Procedure IIA** from oseltamivir (60 mg, 0.19 mmol). The title compound was obtained in 65% yield (47.0 mg) after purification by silica gel chromatography (d.r. = 9:1). R_f = 0.3 (silica gel, 50% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.97 – 6.80 (m, 1H), 5.66 (d, *J* = 7.9 Hz, 1H), 4.63 (td, *J* = 4.8, 2.7 Hz, 1H), 4.29 – 4.05 (m, 4H), 3.40 (p, *J* = 5.8 Hz, 1H), 3.17 – 3.06 (m, 1H), 2.93 – 2.80 (m, 1H), 2.02 (s, 3H), 1.59 – 1.45 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.2, 165.8, 136.4, 128.9, 82.4, 74.1, 61.2, 53.1, 33.4, 26.5, 26.1, 23.5, 14.3, 9.6, 9.5. **HRMS** (ESI-TOF) calcd 376.1118 and 378.1098 for $C_{16}H_{27}BrNO_4^+$ $[M+H]^+$, found 376.1120 and 378.1101.

3-bromo-1-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-4-(2,4,5-trifluorophenyl)butan-1-one TFA (3m):

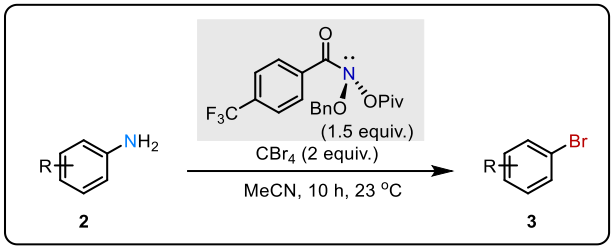


3m

Synthesized according to the **General Procedure IIA** from sitagliptin (300 mg, 0.7365 mmol). The title compound TFA salt was obtained as a clear residue in 58% yield (249.4 mg) after purification by reverse-phase preparative HPLC with an Agilent 5 Prep C18 column using water (TFA pH 3.5.)/acetonitrile. **^{1}H NMR** (400 MHz, CD_3CN) δ 7.34 – 7.26 (m, 1H), 7.16 – 7.07 (m, 1H), 4.92 (s, 2H), 4.70 – 4.61 (m, 1H), 4.20 – 3.88 (m, 4H), 3.36 – 3.14 (m, 3H), 3.08 – 2.98 (m, 1H). **^{13}C NMR** (101 MHz, CD_3CN) δ 169.9, 159.4 (q, $J_{C\text{-}F}$ = 40.8 Hz, TFA), 158.2 (dd, $J_{C\text{-}F}$ = 9.7 Hz, 2.5 Hz), 156.3 (dd, $J_{C\text{-}F}$ = 9.9 Hz, 2.7 Hz), 152.3, 151.9, 151.0 (d, $J_{C\text{-}F}$ = 12.9 Hz), 150.9 (d, $J_{C\text{-}F}$ = 12.9 Hz), 149.0 (d, $J_{C\text{-}F}$ = 13.0 Hz), 148.9 (d, $J_{C\text{-}F}$ = 12.8 Hz), 148.4 (dd, $J_{C\text{-}F}$ = 13.1 Hz, 3.4 Hz), 146.2 (dd, $J_{C\text{-}F}$ = 12.8 Hz, 3.3 Hz), 144.2 (q, $J_{C\text{-}F}$ = 40.0 Hz), 123.3 (d, $J_{C\text{-}F}$ = 20.0 Hz), 120.3 (dd, $J_{C\text{-}F}$ = 18.4 Hz, 5.4 Hz), 116.2 (q, $J_{C\text{-}F}$ = 288 Hz), 106.6 (d, $J_{C\text{-}F}$ = 21.3 Hz), 106.3 (d, $J_{C\text{-}F}$ = 21.3 Hz), 50.0 (*major*), 45.0 (*major*), 44.4 (*minor*), 42.9 (*minor*), 42.3 (*minor*), 42.2 (*minor*), 42.1 (*major*), 42.0 (*major*), 39.6 (*major*), 38.7 (*minor*), 37.9 (*major*). **^{19}F NMR** (376 MHz, CD_3CN) δ -63.78, -76.83 (TFA), -119.96 (t, J = 19.7 Hz), -137.56 (d, J = 22.2 Hz), -145.01 – -145.13 (m). **HRMS** (ESI-TOF) calculated 470.0177 for $C_{16}H_{13}BrF_6N_4O$, found 470.0175.

This major/minor conformer pattern is analogous to the carbon NMR of the starting material in CD_3CN.[18]

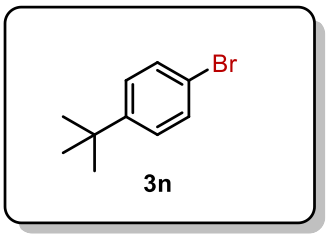
IIB. General Procedure for Deaminative Bromination of Aromatic Amines



To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the aniline (1 equiv.). The anomeric amide, **1**, (1.5 equiv.) and carbon tetrabromide (2 equiv.) were added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe. Dissolved amine was then added dropwise to a vial containing the mixture of **1** and CBr_4 over the period of 5 min. The total volume of solvent is such that the concentration of amine in the reaction is 0.1 M. The reaction was stirred at room temperature for 10 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude product was purified by silica gel chromatography.

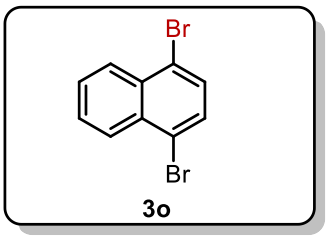
Note: *In case where the aromatic amine is not completely soluble in acetonitrile, a solution of* ***1*** *in MeCN was added dropwise to the mixture of amine and* CBr_4.

1-bromo-4-(*tert*-butyl)benzene (3n):



Synthesized according to **General Procedure IIB** from 4-(*tert*-butyl)aniline (50 mg, 0.34 mmol). The title compound was obtained in 84% yield (60.0 mg) after purification by silica gel chromatography. R_f = 0.8 (silica gel, 3% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz,2H), 7.26 (d, *J* = 8.4 Hz,2H), 1.30 (s, 9H). Spectroscopic data are in agreement with the literature.[19]

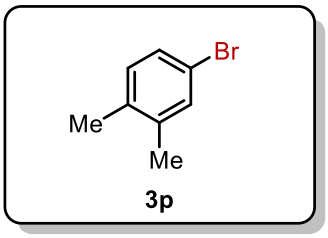
1,4-dibromonaphthalene (3o):



3o

Synthesized according to **General Procedure IIB** from 4-bromonaphthalen-1-amine (50 mg, 0.22 mmol). The title compound was obtained in 83% yield (54.0 mg) after purification by silica gel chromatography. R_f = 0.7 (silica gel, 2% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 – 8.20 (m, 2H), 7.70 – 7.56 (m, 4H). Spectroscopic data are in agreement with the literature.[20]

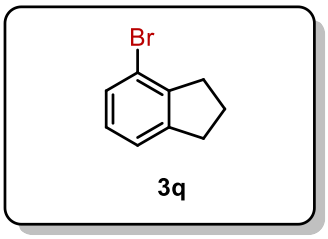
4-bromo-1,2-dimethylbenzene (3p):



3p

Synthesized according to **General Procedure IIB** from 3,4-dimethylaniline (40 mg, 0.33 mmol). The title compound was obtained in 80% NMR yield. **^{1}H NMR** ($CDCl_3$) δ (ppm) = 7.27 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 2.23 (s, 3H), 2.20 (s, 3H). Spectroscopic data are in agreement with the literature.[21]

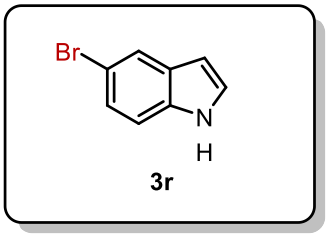
4-bromo-2,3-dihydro-1*H*-indene (3q):



3q

Synthesized according to **General Procedure IIB** from 2,3-dihydro-1*H*-inden-4-amine (50 mg, 0.38 mmol). The title compound was obtained in 86% yield (63.6 mg) after purification by silica gel chromatography. R_f = 0.7 (silica gel, 2% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.13 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.03 – 6.94 (m, 1H), 3.07 – 2.92 (m, 4H), 2.09 (dp, *J* = 9.1, 7.6 Hz, 2H). Spectroscopic data are in agreement with the literature.[22]

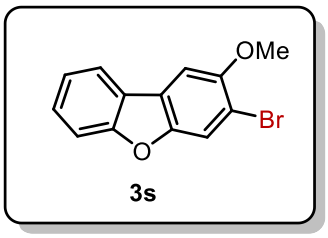
5-bromo-1*H*-indole (3r):



3r

Synthesized according to **General Procedure IIB** from 5-aminoindole (50 mg, 0.38 mmol). The title compound was obtained in 67% yield (50.0 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 15% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.77 (s, 1H), 7.28-7.23 (m, 2H), 7.23-7.20 (m, 1H), 6.49 (dd, *J* = 3.2, 2.0 Hz, 1H). Spectroscopic data are in agreement with the literature.[19]

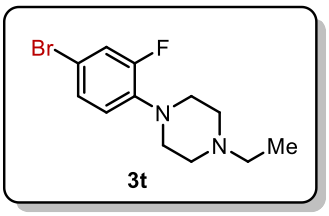
3-bromo-2-methoxydibenzo[*b*,*d*]furan (3s):



3s

Synthesized according to **General Procedure IIB** from 2-methoxydibenzo[b,d]furan-3-amine (60 mg, 0.28 mmol). The title compound was obtained in 57% yield (44.3 mg) after purification by silica gel chromatography. R_f = 0.7 (silica gel, 4% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (ddd, *J* = 7.8, 1.4, 0.7 Hz, 1H), 7.78 (d, *J* = 0.9 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.47 (tt, *J* = 8.2, 1.1 Hz, 1H), 7.41 (s, 1H), 7.38 – 7.30 (m, 1H), 4.01 (d, *J* = 0.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.9, 152.4, 150.7, 127.6, 124.1, 124.1, 122.9, 120.6, 116.6, 112.1, 111.2, 102.9, 57.1. **HRMS** (EI-TOF) calcd 275.9786 and 277.9765 for $C_{13}H_9BrO_2^+$ $[M]^+$, found 275.9775 and 277.9756.

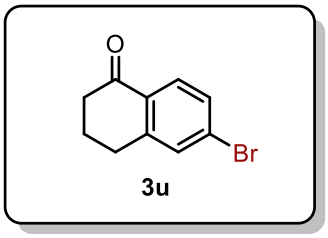
1-(4-bromo-3-fluorophenyl)-4-ethylpiperazine (3t):



3t

Synthesized according to **General Procedure IIB** from 4-(4-ethylpiperazin-1-yl)-3-fluoroaniline (50 mg, 0.22 mmol). The title compound was obtained in 74% yield (47.5 mg) after purification by silica gel chromatography. R_f = 0.2 (silica gel, 100% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 – 7.11 (m, 2H), 6.85-6.79 (m, 1H), 3.30 – 2.97 (m, 4H), 2.63 (t, *J* = 4.9 Hz, 4H), 2.49 (q, *J* = 7.2 Hz, 2H), 1.13 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.5 (d, *J* = 250.8 Hz), 139.6 (d, *J* = 8.7 Hz), 127.6 (d, *J* = 3.6 Hz), 120.2 (d, *J* = 3.7 Hz), 119.7 (d, *J* = 24.2 Hz), 113.7 (d, *J* = 9.3 Hz), 52.7, 52.4, 50.3, 50.3, 27.6, 11.8. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -119.68. **HRMS** (ESI-TOF) calcd 287.0554 and 289.0534 for $C_{12}H_{17}BrFN_2^+$ $[M+H]^+$, found 287.0558 and 289.0535.

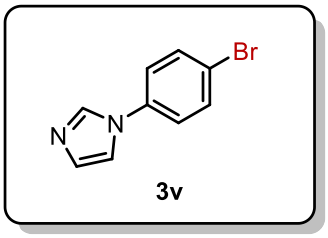
6-bromo-3,4-dihydronaphthalen-1(2H)-one (3u):



3u

Synthesized according to **General Procedure IIB** from 6-amino-3,4-dihydronaphthalen-1(2*H*)-one (50 mg, 0.31 mmol). The title compound was obtained in 62% yield (43.0 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 10% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.9 Hz, 1H), 7.52 – 7.37 (m, 2H), 2.94 (t, *J* = 6.1 Hz, 3H), 2.65 (dd, *J* = 7.3, 5.8 Hz, 3H), 2.14 (ddd, *J* = 12.6, 6.9, 5.6 Hz, 2H). Spectroscopic data are in agreement with the literature.[23]

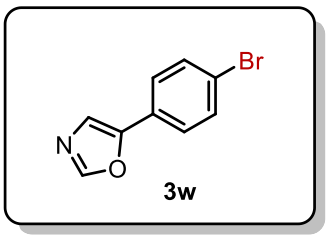
1-(4-bromophenyl)-1*H*-imidazole (3v):



3v

Synthesized according to **General Procedure IIB** from 4-(1*H*-imidazol-1-yl)aniline (50 mg, 0.31 mmol). The title compound was obtained in 63% yield (44.0 mg) after purification by silica gel chromatography. R_f = 0.2 (silica gel, 100% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.65 – 7.56 (m, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 7.25 (s, 1H), 7.22 (s, 1H). Spectroscopic data are in agreement with the literature.[24]

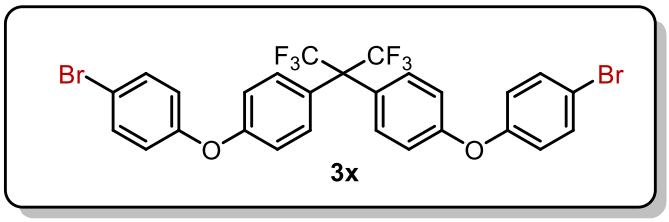
5-(4-bromophenyl)oxazole (3w):



3w

Synthesized according to **General Procedure IIB** from 4-(oxazol-5-yl)aniline (50 mg, 0.31 mmol). The title compound was obtained in 60% yield (42.0 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 20% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.36 (s, 1H). Spectroscopic data are in agreement with the literature.[25]

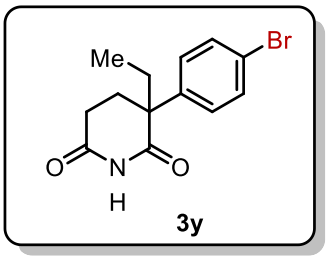
4,4'-(perfluoropropane-2,2-diyl)bis((4-bromophenoxy)benzene) (3x):



3x

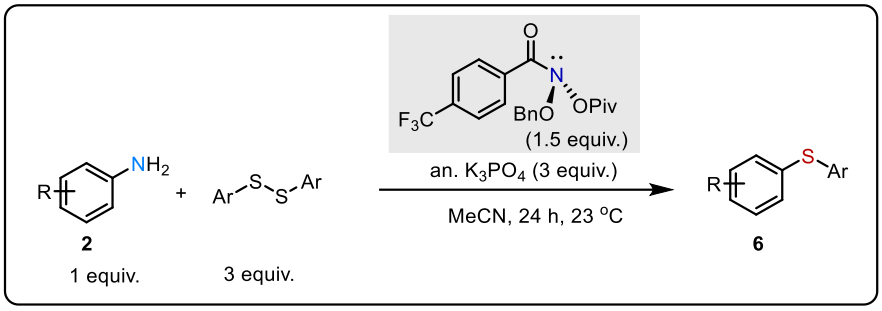
Synthesized according to **General Procedure IIB** from 4,4'-(((perfluoropropane-2,2-diyl)bis(4,1-phenylene))bis(oxy))dianiline (100 mg, 0.19 mmol). The title compound was obtained in 56% yield (69.4 mg) after purification by silica gel chromatography. R_f = 0.6 (silica gel, 5% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 – 7.42 (m, 4H), 7.35 (d, *J* = 8.5 Hz, 4H), 7.03 – 6.78 (m, 8H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 155.2, 133.0, 131.8, 127.9, 124.2 (d, *J* = 284.8 Hz), 121.5, 117.6, 116.8, 63.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -64.03. **HRMS** (EI-TOF) calcd 643.9423, 645.9413 and 647.9395 for $C_{27}H_{16}Br_2F_6O_2^+$ $[M]^+$, found 643.9421, 645.9401 and 647.9383.

3-(4-bromophenyl)-3-ethylpiperidine-2,6-dione (3y):



Synthesized according to **General Procedure IIB** from aminoglutethimide (50 mg, 0.22 mmol) with the following modification: The reaction was stirred for 24 h. The title compound was obtained in 77% yield (49.0 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 50% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.56 – 7.44 (m, 2H), 7.20 – 7.04 (m, 2H), 2.71 – 2.53 (m, 1H), 2.45 – 2.31 (m, 2H), 2.24 (dd, *J* = 14.0, 4.6 Hz, 1H), 2.04 (dq, *J* = 14.8, 7.5 Hz, 1H), 1.89 (dq, *J* = 14.8, 7.5 Hz, 1H), 0.86 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9, 172.2, 138.0, 132.3, 128.1, 121.9, 50.9, 32.9, 29.3, 27.1, 9.1. **HRMS** (ESI-TOF) calcd 296.0281 and 298.0261 for $C_{13}H_{15}BrNO_2^+$ $[M+H]^+$ 296.0270, found 298.0254.

IIC. General Procedure for Deaminative Thiolation of Aromatic Amines

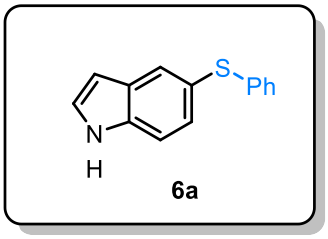


To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the aniline (1 equiv.). The anomeric amide (1.5 equiv.), aryl disulfide (3 equiv.) and anhydrous, coarse K_3PO_4 (3 equiv.)* were added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe. Dissolved amine was then added dropwise to a vial containing mixture of anomeric amide and disulfide over the period of 5 min. The total volume of solvent is such that the concentration of amine in the reaction is 0.1 M. The reaction was stirred at room temperature for 24 hours. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulphate. The volatiles were removed *in vacuo* and the crude product was purified by silica gel chromatography.

**Note: Coarse K_3PO_4 is crucial for the reaction (see the picture below). Diminished yields were obtained with powdered K_3PO_4.*

Anhydrous, coarse K_3PO_4

5-(phenylthio)-1*H*-indole (6a):

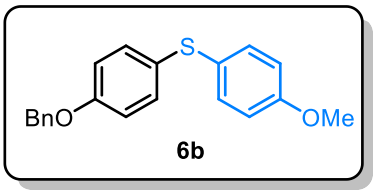


6a

Synthesized according to **General Procedure IIC** from 5-aminoindole (50 mg, 0.38 mmol). The title compound was obtained in 63% yield (54.0 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 20% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.84 (dd, *J* = 0.8 Hz, 1H), 7.30-7.39 (m, 2H), 7.06-7.23 (m, 6H), 6.53 (m, 1H). Spectroscopic data are in agreement with the literature.[26]

***Note:** In the case of 6a, formation of 20% deamination product (indole) was observed.*

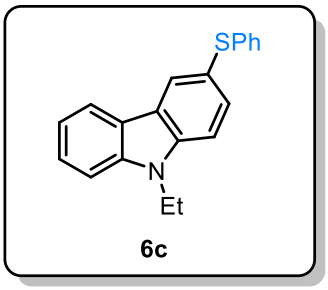
(4-(benzyloxy)phenyl)(4-methoxyphenyl)sulfane (6b):



6b

Synthesized according to **General Procedure IIC** from 4-(benzyloxy)aniline (60 mg, 0.3 mmol). The title compound was obtained in 53% yield (51.0 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 5% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 7.27 – 7.17 (m, 4H), 6.89 – 6.84 (m, 2H), 6.83 – 6.77 (m, 2H), 5.00 (s, 2H), 3.75 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 158.3, 136.9, 133.1, 132.6, 128.8, 128.2, 128.1, 127.6, 127.3, 115.8, 114.9, 70.3, 55.5. **HRMS** (ESI-TOF) calcd 323.1100 for $C_{20}H_{19}O_2S^+$ $[M+H]^+$, found 323.1098.

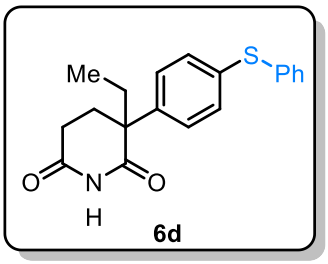
3-(benzylthio)-9-ethyl-9*H*-carbazole (6c):



6c

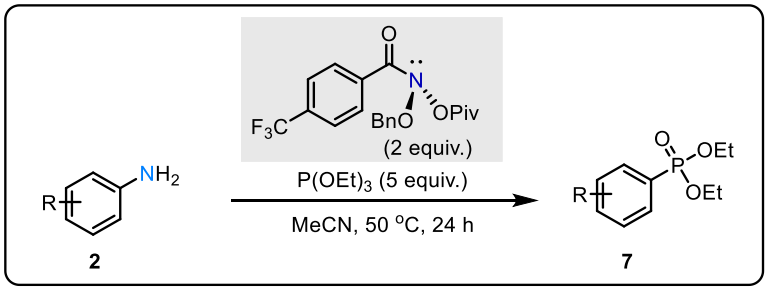
Synthesized according to **General Procedure IIC** from 9-ethyl-9*H*-carbazol-3-amine (55 mg, 0.26 mmol). The title compound was obtained in 57% yield (45.0 mg) after purification by silica gel chromatography. R_f = 0.6 (silica gel, 5% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 1.8 Hz, 1H), 8.07 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.62 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.50 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.43 (dd, *J* = 8.4, 5.4 Hz, 2H), 7.27 – 7.14 (m, 5H), 7.13 – 7.07 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 140.1 (2C), 132.4, 129.0, 127.5, 127.5, 126.4, 125.4, 124.2, 122.5, 121.6, 120.8, 119.5, 109.6, 108.9, 37.9, 14.0. **HRMS** (ESI-TOF) calcd 304.1154 for $C_{20}H_{18}NS^+$ $[M+H]^+$, found 304.1156.

3-ethyl-3-(4-(phenylthio)phenyl)piperidine-2,6-dione (6d):



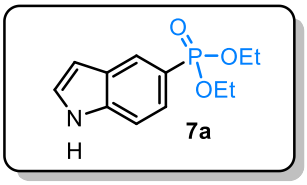
Synthesized according to **General Procedure IIC** from aminoglutethimide (60 mg, 0.26 mmol) with the following modification: The reaction was heated to 50 °C. The title compound was obtained in 56% yield (47.0 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 50% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.42 – 6.96 (m, 9H), 2.62 – 2.45 (m, 1H), 2.42 – 2.22 (m, 2H), 2.14 (td, *J* = 13.4, 4.3 Hz, 1H), 1.97 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.82 (dq, *J* = 14.5, 7.4 Hz, 1H), 0.80 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.0, 172.3, 137.4, 136.4, 134.5, 132.2, 130.6, 129.5, 127.8, 127.1, 51.0, 33.0, 29.4, 27.1, 9.2. **HRMS** (ESI-TOF) calcd 326.1209 for $C_{19}H_{20}NO_2S^+$ $[M+H]^+$, found 326.1210.

IID. General Procedure for Deaminative Phosphorylation of Aromatic Amines



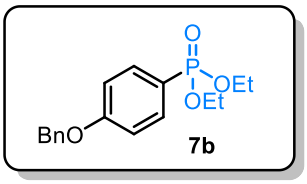
To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the aniline (1 equiv.). The anomeric amide, **1**, (2 equiv.) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Triethyl phosphite was added to the second vial (containing **1**) (5 equiv.). Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe. Dissolved amine was then added dropwise to vial containing **1** and $P(OEt)_3$ for the period of 5 min. The total volume of solvent is such that the concentration of amine in the reaction is 0.1 M. The reaction was stirred at 50 °C for 24 hours. The solvents were removed *in vacuo*. Excess triethyl phosphite was removed by co-distillation using toluene. The crude product was purified by silica gel chromatography.

Diethyl (1*H*-indol-5-yl)phosphonate (7a):



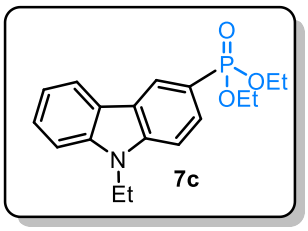
Synthesized according to **General Procedure IID** from 5-aminoindole (50 mg, 0.38 mmol). The title compound was obtained in 59% yield (56.3 mg) after purification by silica gel chromatography. R_f = 0.25 (silica gel, 100% EtOAc in hexanes). **^{1}H NMR** (400 MHz, DMSO-*d6*) δ 11.44 (s, 1H), 8.05 – 7.87 (m, 1H), 7.50 (ddt, *J* = 8.4, 3.5, 0.9 Hz, 1H), 7.45 (t, *J* = 2.8 Hz, 1H), 7.36 (ddd, *J* = 11.8, 8.4, 1.4 Hz, 1H), 6.55 (ddd, *J* = 3.0, 1.9, 0.9 Hz, 1H), 4.22 – 3.65 (m, 3H), 1.18 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO-*d6*) δ 137.8 (d, *J* = 2.8 Hz), 127.2 (d, *J* = 17.7 Hz), 127.0, 125.0 (d, *J* = 11.2 Hz), 123.3 (d, *J* = 11.9 Hz), 117.3 (d, *J* = 189.7 Hz), 111.8 (d, *J* = 16.2 Hz), 102.1 (d, *J* = 1.6 Hz), 61.2 (d, *J* = 5.3 Hz), 16.2 (d, *J* = 6.2 Hz). **^{31}P NMR** (162 MHz, DMSO-*d6*) δ 21.5. **HRMS** (ESI-TOF) calcd 254.0941 for $C_{12}H_{17}NO_3P^+$ $[M+H]^+$, found 254.0941.

Diethyl (4-(benzyloxy)phenyl)phosphonate (7b):



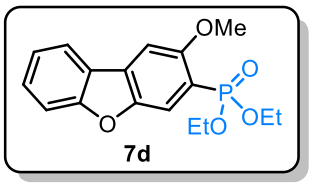
Synthesized according to **General Procedure IID** from 4-(benzyloxy)aniline (50 mg, 0.25 mmol). The title compound was obtained in 78% yield (62.5 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 60% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.64 (m, 2H), 7.48 – 7.30 (m, 5H), 7.04 (dd, *J* = 8.7, 3.2 Hz, 2H), 5.11 (s, 2H), 4.40 – 3.73 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, CDCl3) δ 162.2 (d, *J* = 2.9 Hz), 136.4, 133.9 (d, *J* = 11.2 Hz), 128.8, 128.4, 127.6, 120.0 (d, *J* = 194.7 Hz),115.0 (d, *J* = 15.8 Hz), 70.2, 62.1 (d, *J* = 4.9 Hz), 16.5 (d, *J* = 6.2 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 19.59. **HRMS** (ESI-TOF) calcd 321.1250 for $C_{17}H_{22}O_4P^+$ $[M+H]^+$, found 321.1253.

Diethyl (9-ethyl-9*H*-carbazol-3-yl)phosphonate (7c):



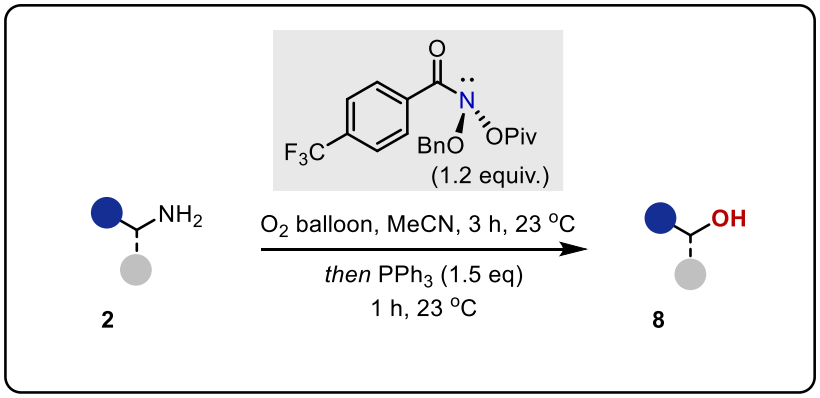
Synthesized according to **General Procedure IID** from 9-ethyl-9*H*-carbazol-3-amine (50 mg, 0.24 mmol). The title compound was obtained in 61% yield (48.0 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 100% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 13.9, 1.5 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 7.99 – 7.73 (m, 1H), 7.64 – 7.39 (m, 3H), 7.34 – 7.27 (m, 1H), 4.40 (q, *J* = 7.3 Hz, 2H), 4.28 – 4.01 (m, 4H), 1.45 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2, 140.5, 128.9 (d, *J* = 11.9 Hz), 125.6 (d, *J* = 11.6 Hz), 123.0, 122.9, 122.8, 120.9, 120.0, 117.1 (d, *J* = 192.7 Hz), 109.0, 108.7 (d, *J* = 16.5 Hz), 62.1 (d, *J* = 5.1 Hz), 37.9, 16.5 (d, *J* = 6.7 Hz), 13.9. **^{31}P NMR** (162 MHz, $CDCl_3$) δ 21.76. **HRMS** (ESI-TOF) calcd 332.1410 for $C_{18}H_{23}NO_3P^+$ $[M+H]^+$, found 332.1410.

Diethyl (2-methoxydibenzo[*b*,*d*]furan-3-yl)phosphonate (7d):



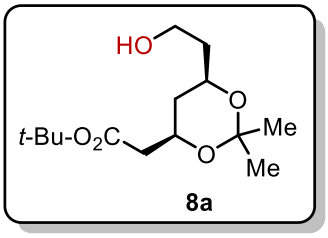
Synthesized according to **General Procedure IID** from 2-methoxydibenzo[*b*,*d*]furan-3-amine (50 mg, 0.34 mmol). The title compound was obtained in 58% yield (45.3 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 100% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 and 7.95 (s, 1H, *rotameric proton*), 7.88 and 7.86 (s, 1H, *rotameric proton*), 7.50 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.38 (d, *J* = 6.4 Hz, 1H), 7.28 (td, *J* = 7.5, 1.1 Hz, 1H), 4.22 – 4.04 (m, 4H), 3.95 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.7, 157.6 (d, *J* = 2.9 Hz), 149.8 (d, *J* = 21.2 Hz), 129.0 (d, *J* = 2.4 Hz), 128.5, 123.7, 122.8, 121.1, 118.0 (d, *J* = 8.1 Hz), 116.2 (d, *J* = 189.1 Hz), 112.1, 102.7 (d, *J* = 11.4 Hz), 62.4 (d, *J* = 5.6 Hz), 56.6, 16.4 (d, *J* = 6.5 Hz). **^{31}P NMR** (162 MHz, $CDCl_3$) δ 16.55. **HRMS** (ESI-TOF) calcd 335.1043 for $C_{17}H_{20}O_5P^+$ $[M+H]^+$, found 335.1046.

IIE. General Procedure for Deaminative Hydroxylation of Aliphatic Amines



To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the anomeric amide (1.2 equiv.) and dry acetonitrile. The clear anomeric amide solution was saturated with oxygen (by sparging oxygen from balloon for 5 min). Aliphatic amine (1 equiv.) and dry acetonitrile were added to a second vial. Dissolved amine was then added dropwise to the vial containing anomeric amide (with active oxygen sparging) for the period of 1 h using syringe pump. The total volume of solvent is such that the concentration of amine in the reaction is 0.1 M. After additional 2 h, oxygen sparging stopped and triphenyl phosphine (1.5 equiv.) was added to the reaction mixture and stirring was continued for one more hour. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulphate. The volatiles were removed *in vacuo* and the crude product was purified by silica gel chromatography.

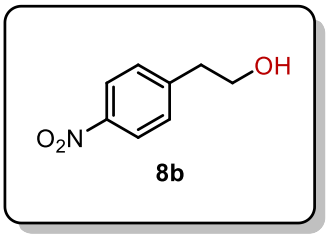
***tert*-butyl 2-((4*R*,6*R*)-6-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (8a):**



8a

Synthesized according to **General Procedure IIE** from *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (60 mg, 0.22 mmol). The title compound was obtained in 70% yield (42.0 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 50% EtOAc in hexanes). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 4.26 (dtd, *J* = 11.7, 6.5, 2.4 Hz, 1H), 4.11 (dddd, *J* = 9.6, 7.1, 4.8, 2.5 Hz, 1H), 3.82 – 3.67 (m, 2H), 2.48 (s, 1H), 2.41 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.28 (dd, *J* = 15.2, 6.1 Hz, 1H), 1.71 (ddd, *J* = 7.3, 5.8, 4.0 Hz, 2H), 1.54 (dt, *J* = 12.9, 2.5 Hz, 1H), 1.46 (s, 3H), 1.43 (s, 9H), 1.35 (s, 3H), 1.29 (dt, *J* = 12.8, 11.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.3, 98.9, 80.8, 69.2, 66.3, 60.8, 42.7, 38.2, 36.4, 30.2, 28.2, 19.9. **HRMS** (ESI-TOF) calcd 275.1853 for $C_{14}H_{27}O_5^+$ $[M+H]^+$, found 275.1887.

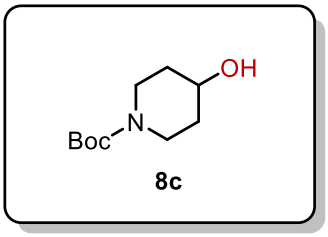
2-(4-nitrophenyl)ethan-1-ol (8b):



8b

Synthesized according to **General Procedure IIE** from 2-(4-nitrophenyl)ethan-1-amine (40 mg, 0.24 mmol). The title compound was obtained in 64% yield (25.7 mg) after purification by silica gel chromatography. R_f = 0.25 (silica gel, 50% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 2.96 (t, *J* = 6.4 Hz, 2H), 1.78 (br s, 1H). Spectroscopic data are in agreement with the literature.[27]

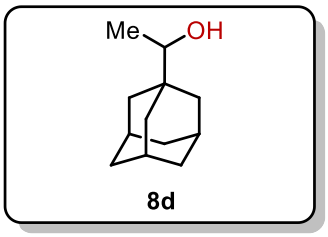
***tert*-butyl 4-hydroxypiperidine-1-carboxylate (8c):**



8c

Synthesized according to **General Procedure IIE** from *tert*-butyl 4-aminopiperidine-1-carboxylate (50 mg, 0.25 mmol). The title compound was obtained in 67% yield (33.6 mg) after purification by silica gel chromatography. R_f = 0.25 (silica gel, 60% EtOAc in hexanes). **^{1}H NMR** (400 MHz, CDCl3) δ 3.90 – 3.76 (m, 3H), 3.01 (ddd, J = 13.3, 9.7, 3.3 Hz, 2H), 1.90 – 1.75 (m, 3H), 1.50 – 1.37 (m, 11H). Spectroscopic data are in agreement with the literature.[28]

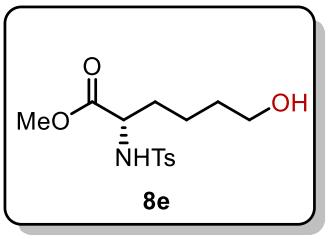
1-((3*r*,5*r*,7*r*)-adamantan-1-yl)ethan-1-ol (8d):



8d

Synthesized according to **General Procedure IIE** from rimantadine (50 mg, 0.28 mmol). The title compound was obtained in 66% NMR yield. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.28 (q, *J* = 6.4 Hz, 1H), 2.01-1.95 (m, 3H), 1.74 – 1.55 (m, 9H), 1.51 – 1.43 (m, 3H), 1.09 (d, *J* = 6.5 Hz, 3H). Spectroscopic data are in agreement with the literature.[29]

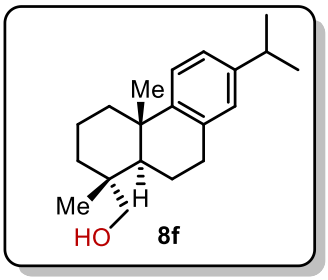
Methyl (*S*)-6-hydroxy-2-((4-methylphenyl)sulfonamido)hexanoate (8e):



8e

Synthesized according to **General Procedure IIE** from methyl tosyl-L-lysinate (60 mg, 0.19 mmol). The title compound was obtained in 69% yield (41.5 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 100% EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 5.35 (br s, 1H), 3.84 (dd, *J* = 7.8, 5.1 Hz, 1H), 3.53 (t, *J* = 6.3 Hz, 2H), 3.41 (s, 3H), 2.34 (s, 3H), 1.67 (ddd, *J* = 13.2, 9.4, 5.3 Hz, 1H), 1.57 (dt, *J* = 14.2, 7.5 Hz, 1H), 1.51 – 1.41 (m, 2H), 1.37 (q, *J* = 7.0 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.3, 143.8, 136.8, 129.7, 127.4, 62.4, 55.7, 52.5, 33.1, 31.9, 21.6, 21.4. **HRMS** (ESI-TOF) calcd 316.1213 for $C_{14}H_{22}NO_5S^+$ $[M+H]^+$, found 316.1213.

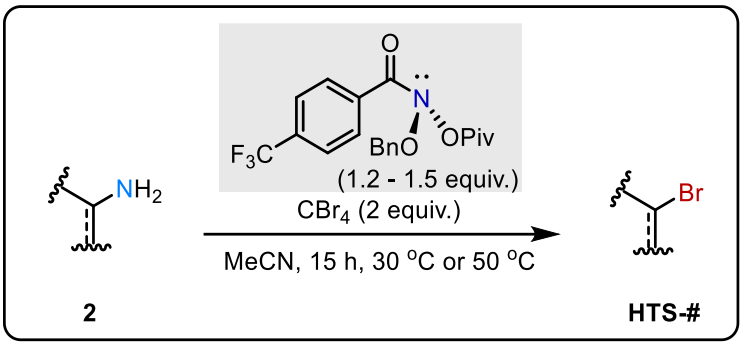
Dehydroabietic alcohol (8f):



8f

Synthesized according to **General Procedure IIE** from leelamine (60 mg, 0.21 mmol). The title compound was obtained in 68% yield (41.0 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 20% EtOAc in hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 3.48 (d, *J* = 10.9 Hz, 1H), 3.24 (d, *J* = 10.9 Hz, 1H), 2.97 – 2.65 (m, 3H), 2.43 – 2.26 (m, 1H), 1.88 – 1.59 (m, 5H), 1.51 – 1.36 (m, 3H), 1.24 (dd, *J* = 4.0, 3.0 Hz, 9H), 0.90 (s, 3H). Spectroscopic data are in agreement with the literature.[30]

III. High Throughput Evaluation of Deaminative Bromination



To 1-dram vials containing the appropriate amine substrate (0.1 mmol) was added MeCN (0.5 mL) and, in the case of amine HCl salts, triethylamine (34.8 uL, 0.25 mmol) (Note 1). To the resulting mixtures was added a solution of CBr_4 (2 equiv.) and anomeric amide **1** (1.2 -1.5 equiv.) in MeCN (0.5 mL) dropwise (Notes 2 and 3). The plate was sealed and stirred at either 30 °C (aliphatic substrates) or 50 °C (aromatic substrates) for 15 h. The plates were unsealed and concentrated under reduced pressure in a Genevac EZ-2. The crude product mixtures were dissolved in DMSO and purified by high throughput, reverse phase HPLC (see next page for details). Data regarding the success or failure of the 75 scaffolds evaluated can be seen in **Figure S1** and **Figure S2**. An analysis of trends seen with aromatic and aliphatic amines can be seen in **Figure S3** and **S4 respectively**.

Note 1: Reactions were carried out in a N_2 purge box with O_2 < 20 ppm.
Note 2: In the case of primary amines, the reagent solution was dosed to six vials at a time using the Unchained Labs Junior liquid handling robot over 5 minutes (see below for images). In the case of aromatic amines, the reagent solution was dosed dropwise by pipette one at a time.

Note 3: For aromatic amines, 1.5 equivalents of **1** were used, while for aliphatic amines, 1.2 equivalents of **1** were used.

Details Regarding High Throughput Mass Directed Purification

Pre- and post-purification characterization completed on an Acquity I-Class UPLC-MS system from Waters running with both acidic (TFA) and basic (NH_4OH) modifiers.

Purification processes were done on an Autopurification Waters UV/MS system, with Auto Blend Technology capable to auto-generate gradients, and to monitor the elution of each targeted compound. The autopurification platform consists of: 2545 binary gradient module (HPLC pump), 2767 injector/collector, 2-515 analytical HPLC pumps for At Column Dilution sample loading and MS make-up flow, Waters static flow splitters, 2996 photodiode Array UV detector, and SQD2 mass spectrometer. High throughput purification is based on both UV absorbance and MS signal to trigger collection.

Waters Autopurification System

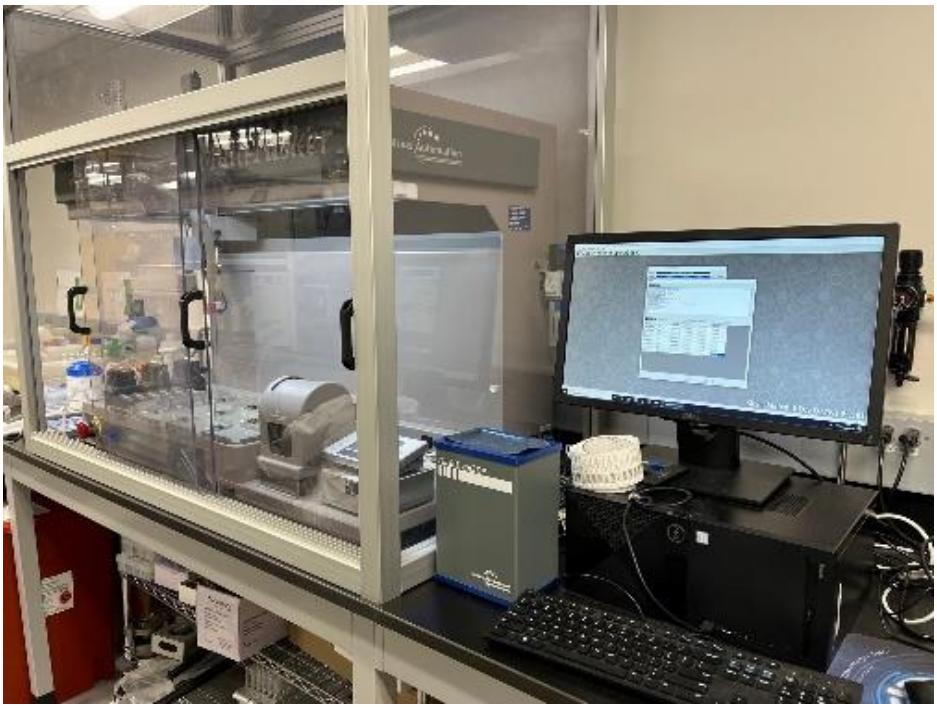
To validate this purification process, a standard mixture composed of commercially available compounds were subjected to purification. Generic purification methods were used, each separated peak was dried and weighed to validate robust instrument performance. Fractions were collected in vials that can hold up to 20 mL. Recoveries were consistently above 90%.

All HTS compounds were purified using TFA as a modifier. The primary stationary phase was a XSelect CSH C18 5um OBD 19x150mm column. Purification was done with appropriate linear gradients of increasing concentration of acetonitrile in water, 0.1% TFA, flow rate 25 mL/min. A few sample gradient examples are shown below:

TFA_25mL_15_50_8m_V3_C3
TFA_25mL_8_30_8m_V3_C3
TFA_25mL_10_40_8m_V3_C3

Fractions containing the desired product were combined and dried on a Genevac.

Post purification processes include post-QC plate creation and analysis of every compound, solvent evaporation, and weighing.



Sirius Automated Weigher

The fraction QC plate is dried and submitted to High Throughput NMR for structure validation.

Figure S1. Results of HTS screen with Aromatic Amines

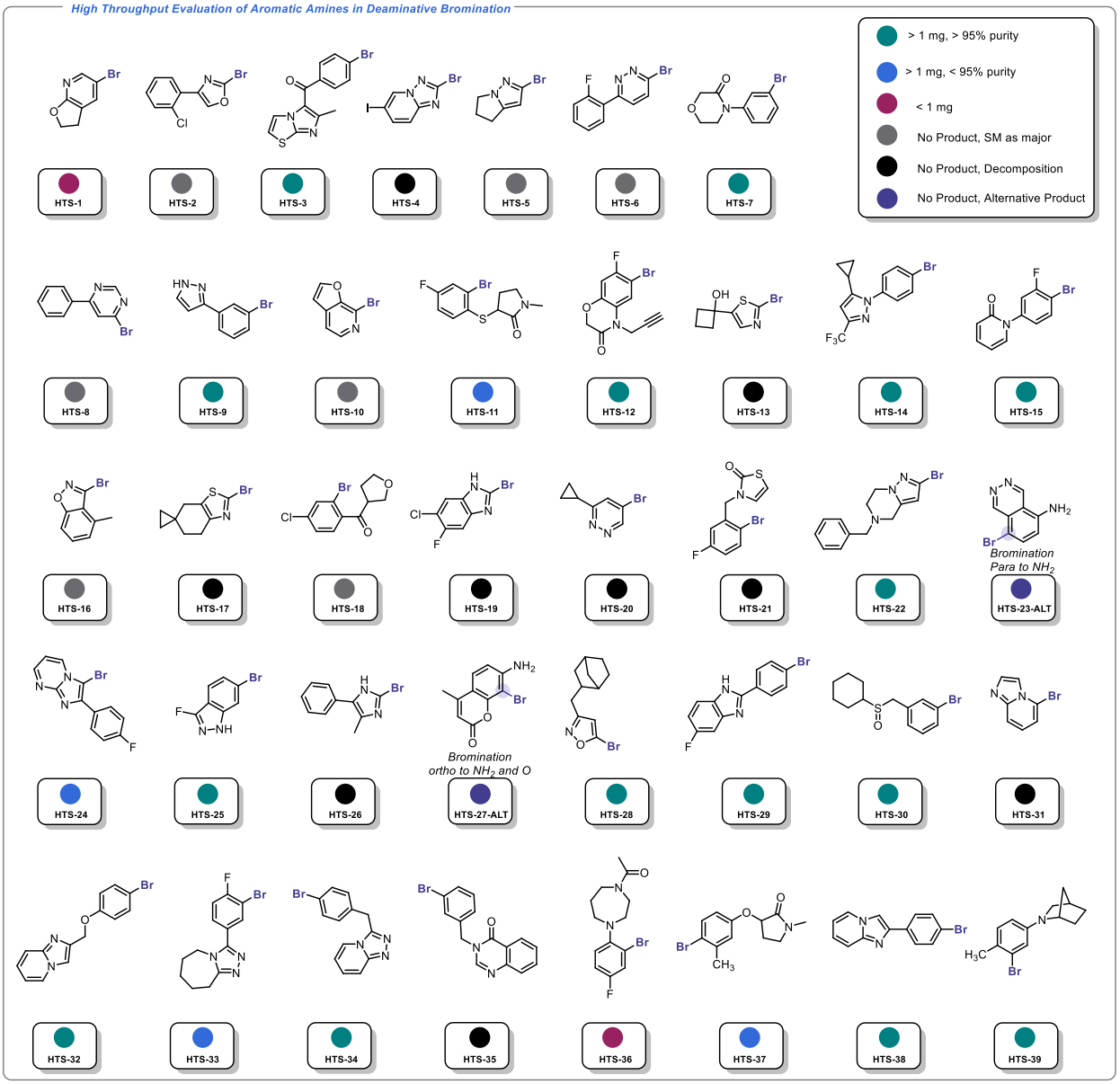


Figure S2. Results of HTS screen with Aliphatic Amines

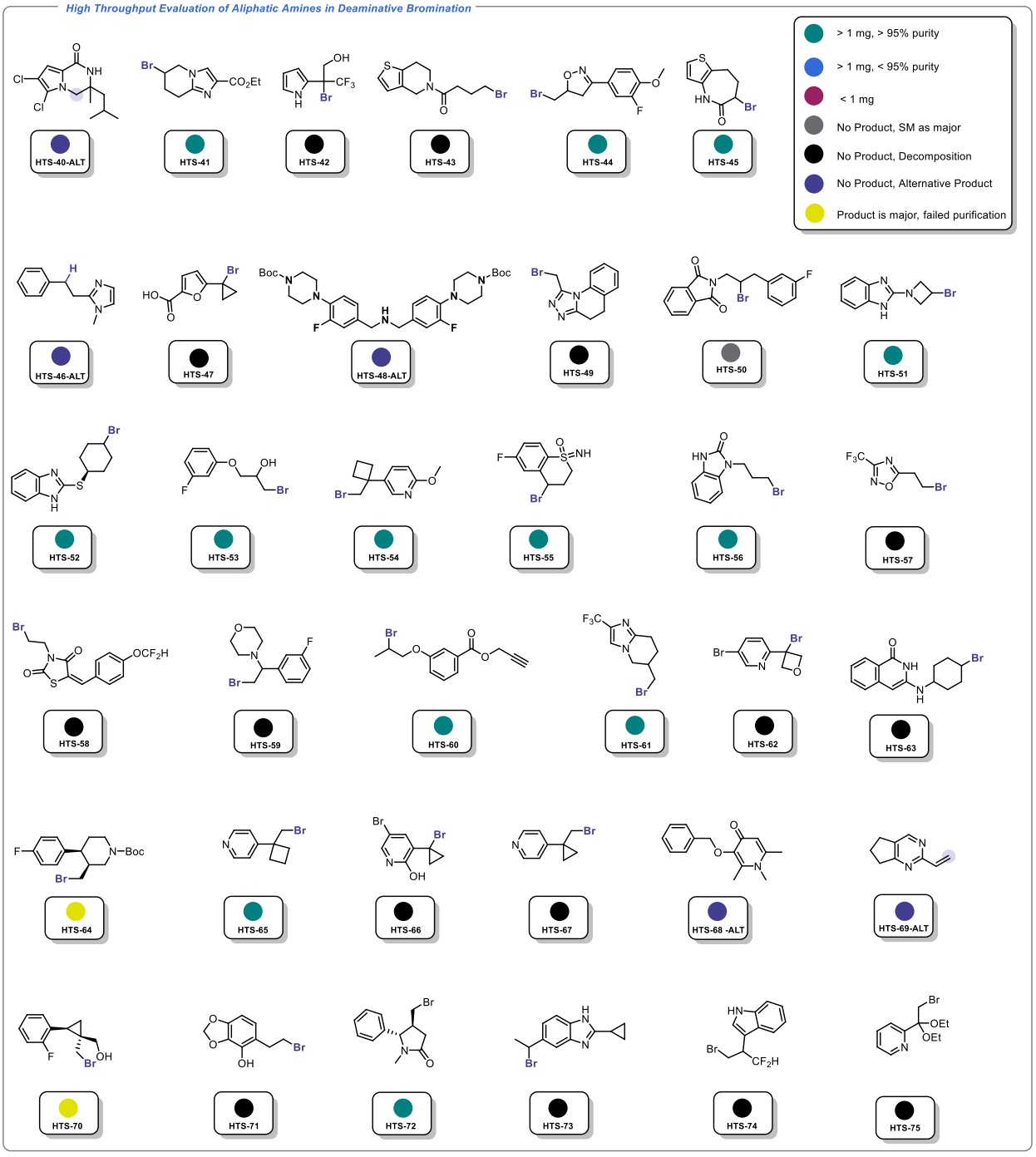
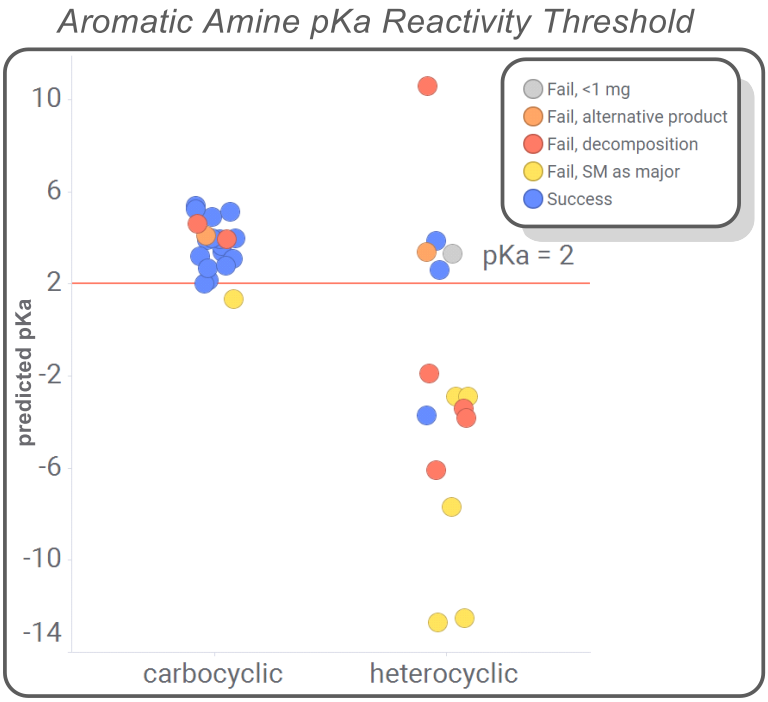


Figure S3. Impact of aromatic amine pK_a on reaction success



ACD/Percepta was used to calculate pKa values for amines. These values are included in the .csv file under the header, “Combined pKa prediction.” Each row contains data from one of two methodologies: ACD/pKa GALAS or ACD/pKa Classic. The ACD/pKa GALAS methodology was used unless it failed to predict a pKa value for the reactive nitrogen (usually because of electron-deficiency and the presence of more basic heteroatoms), in which case ACD/pKa Classic was used.

Figure S4. Impact of aliphatic amine structure on reaction success

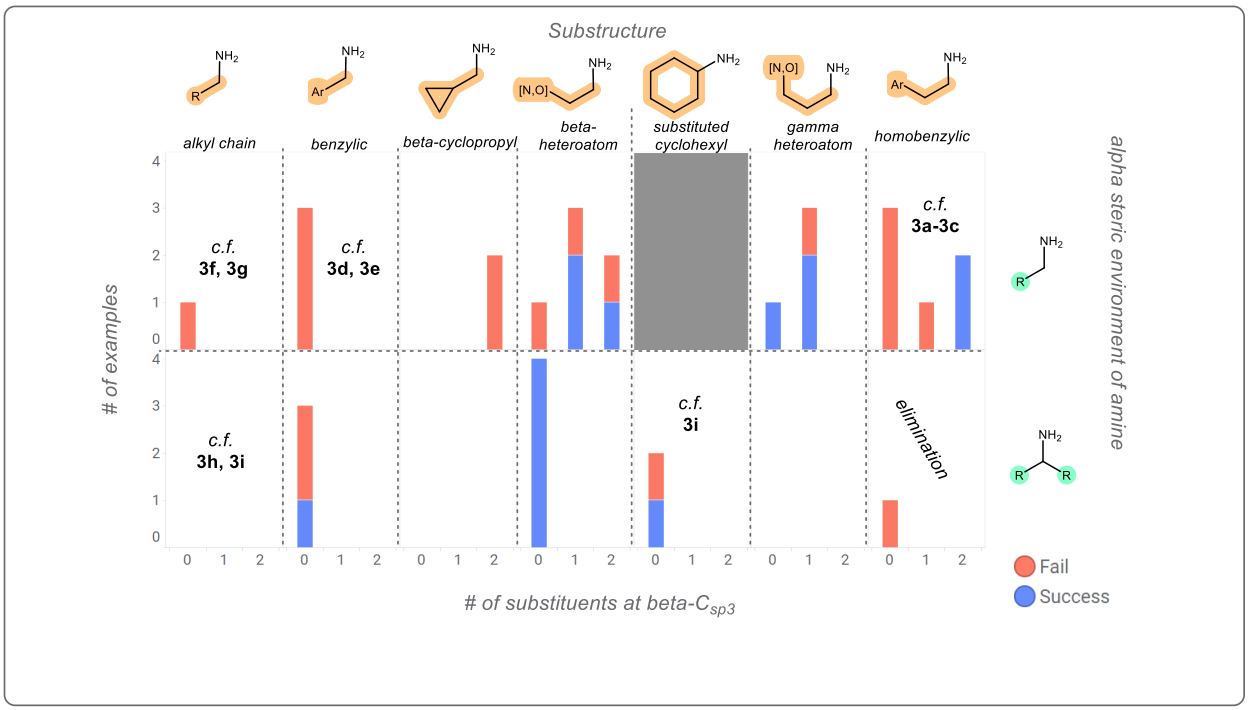
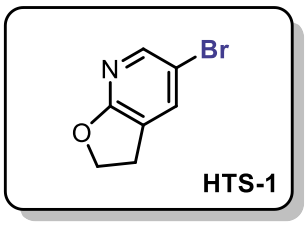


Figure S4 breaks down the aliphatic amine results in terms of steric environment (i.e. number of alpha and beta substituents) and amine substructure. A range of steric environments were tolerated including primary, secondary, and branching beta to the reactive center. Proximal inductively withdrawing groups were also tolerated. Tertiary benzylic amines did not yield bromides under the reaction conditions tested, a result which may be driven by electronic effects as well as sterics. In contrast to **3d** and **3e**, benzylic amines explored in this high-throughput study largely provided undesired products (elimination, dimerization, or reductive deamination). This finding highlights the usefulness of rapidly expanding the reaction scope via high throughput methods, as the additional benzylic amines were differentiated from **3d** and **3e** - they contain electron-rich aromatics, which promote elimination/dimerization and/or hydrodeamination. Bromides derived from beta cyclopropyl amines, HTS-67 and HTS-70, were not successfully isolated. For HTS-67, two peaks with the desired mass were observed in the crude LCMS, suggesting radical rearrangement. For HTS-70, the ^{1}H NMR suggested that the desired product was isolated in about a 1:1 ratio with a by-product derived from the anomeric amide. Note: RDKit was used to calculate a range of molecular properties for the amine starting materials, and these data are included in the .csv file.

Characterization Data for HTS Compounds

Below is data for compounds prepared in library format (high throughput screen) and isolated via high-throughput purification techniques. Unless otherwise indicated, mass quantities indicate compounds isolated at >95% purity by LCMS. Proof of structure is supported via high-throughput LCMS trace data and high-throughput NMR data (with water/solvent suppression). In certain cases, suppression in this manner led to difficulties with improper integration and/or absence of peaks. In these cases, spectral images of the non-suppressed spectra are given (indicated where applicable). Data is also given for instances where a clear alternative major product was observed and isolated via mass-directed high throughput purification.

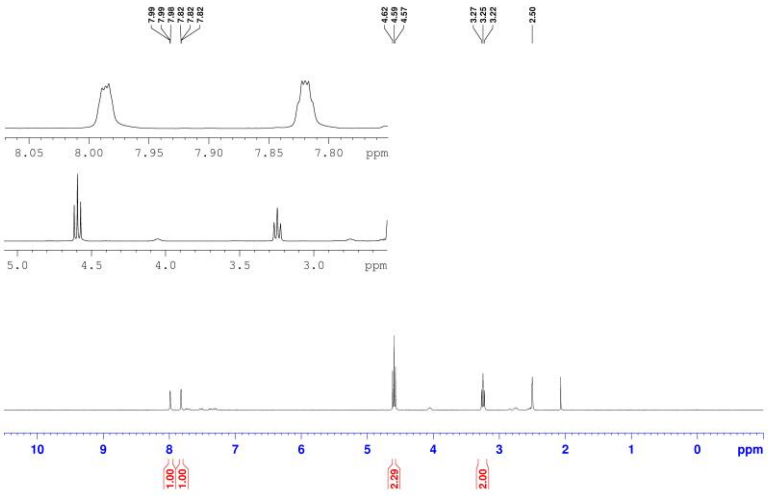


5-bromo-2,3-dihydrofuro[2,3-b]pyridine (HTS-1)

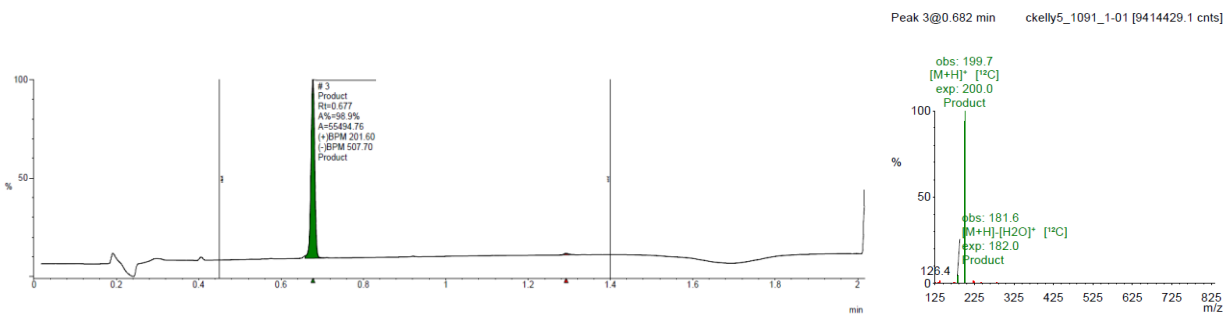
Quantity Obtained: 0.21 mg (99% purity by LC)

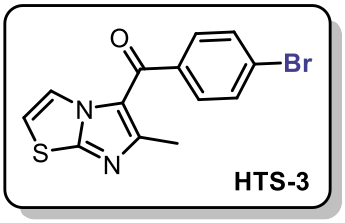
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1H) 7.84 (s, 1H) 4.61 (t, J = 8.6 Hz, 2H) 3.26 (t, J = 8.6 Hz, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.677 min; **MS ES+** ([M+H]$^+$): 199.7.



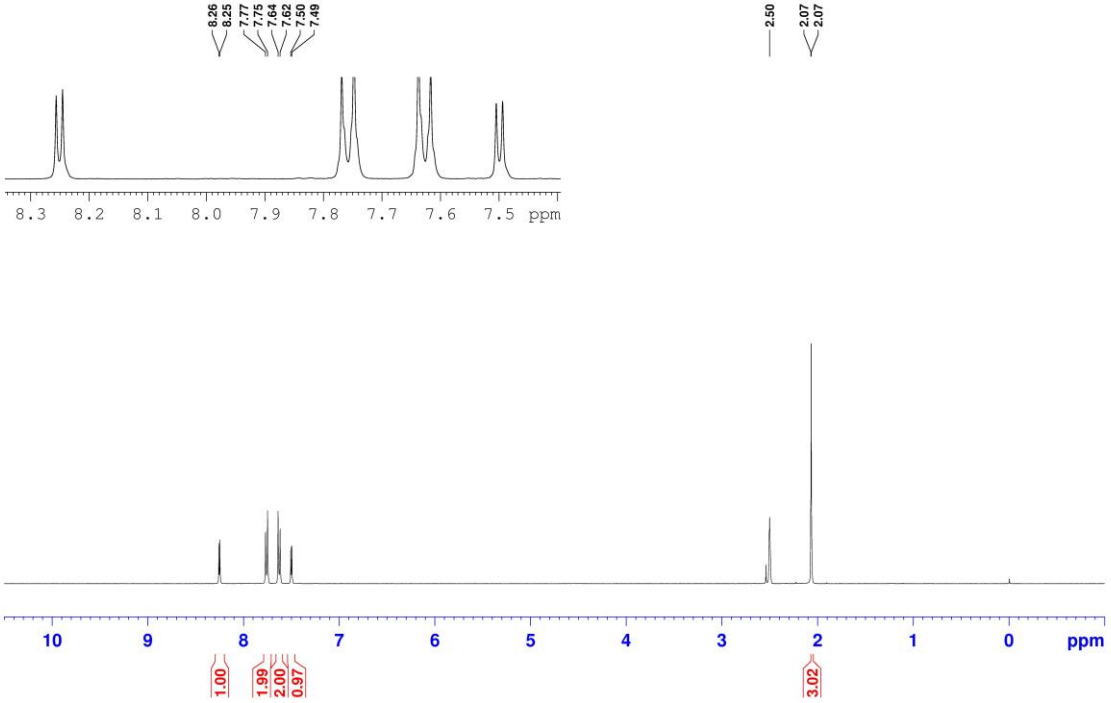


(4-bromophenyl)(6-methylimidazo[2,1-b]thiazol-5-yl)methanone (HTS-3)

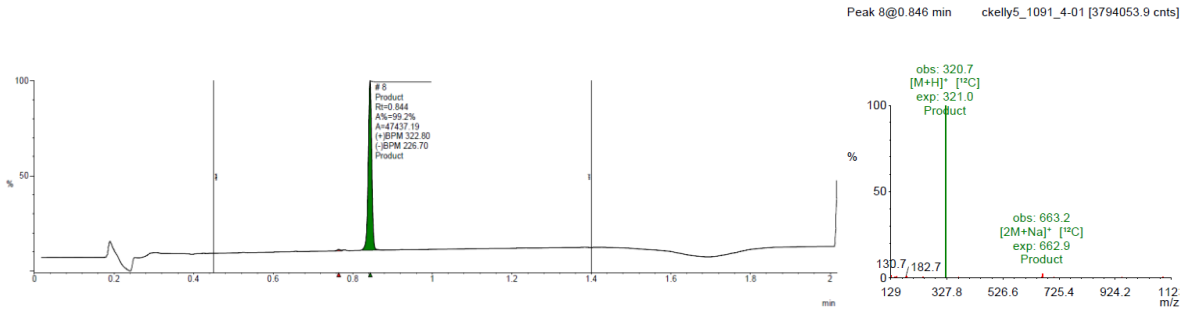
Quantity Obtained: 5.0 mg

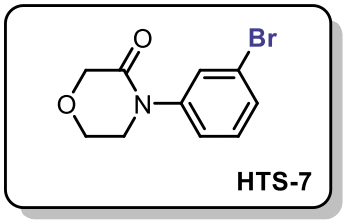
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (d, *J*=4.4 Hz, 1H) 7.76 (d, *J* = 8.3 Hz, 2H) 7.63 (d, *J* = 8.3 Hz, 2H) 7.50 (d, *J* = 4.4 Hz, 1H) 2.07 (s, 3H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.844 min; **MS ES+** ([M+H]$^+$): 320.7.



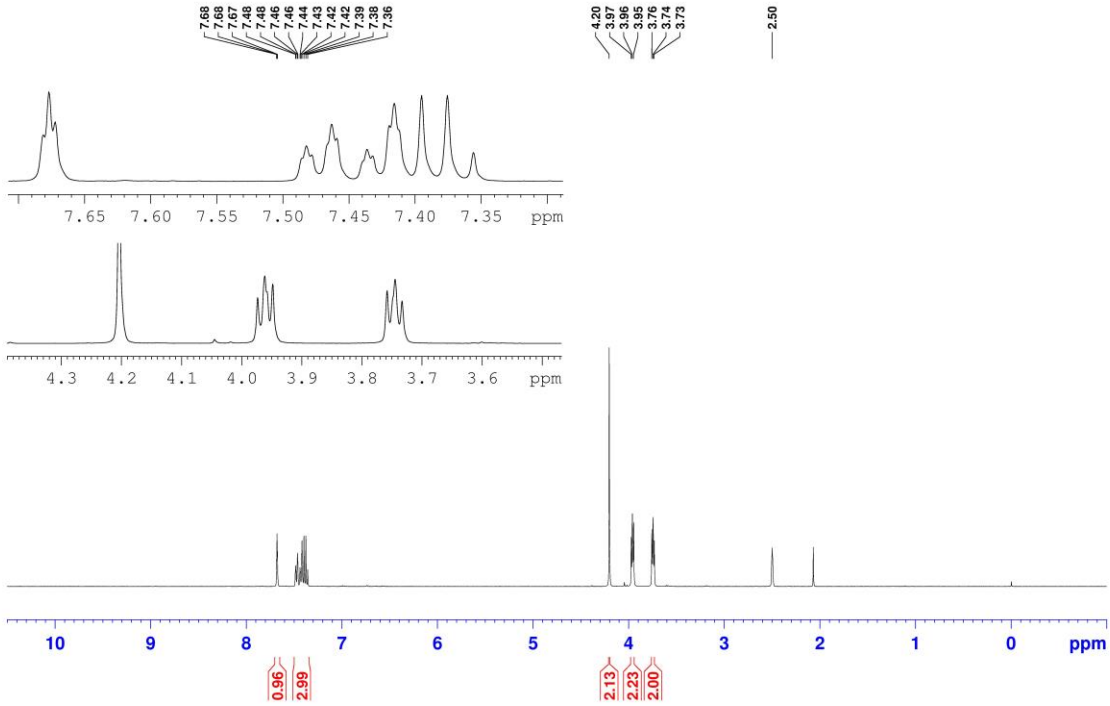


4-(3-bromophenyl)morpholin-3-one (HTS-7)

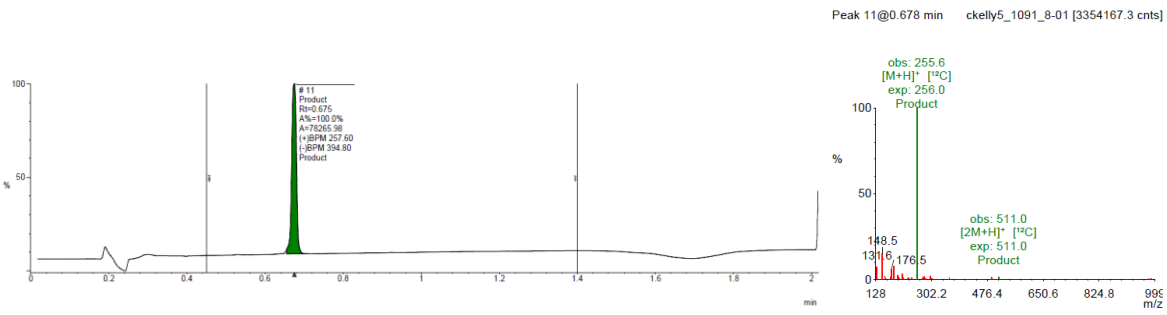
Quantity Obtained: 8.4 mg

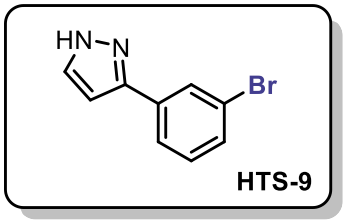
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 - 7.70 (m, 1H), 7.45 - 7.50 (m, 1H), 7.35 - 7.45 (m, 2H), 4.21 (s, 2H), 3.96 (dd, J = 6.4, 4.40 Hz, 2H), 3.75 (dd, J = 5.4, 3.9 Hz, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.675 min; **MS ES+** ([M+H]$^+$): 255.6.



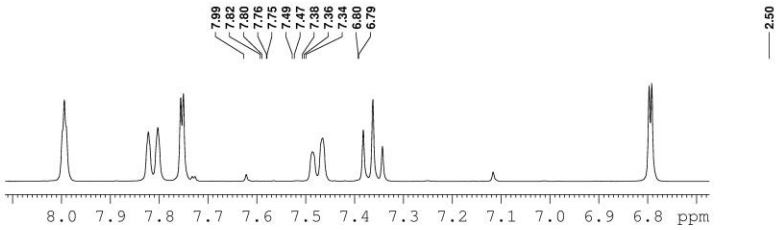


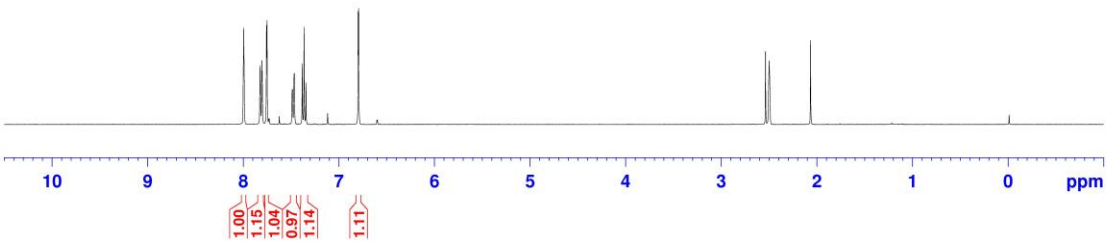
3-(3-bromophenyl)-1H-pyrazole (HTS-9)

Quantity Obtained: 10.0 mg

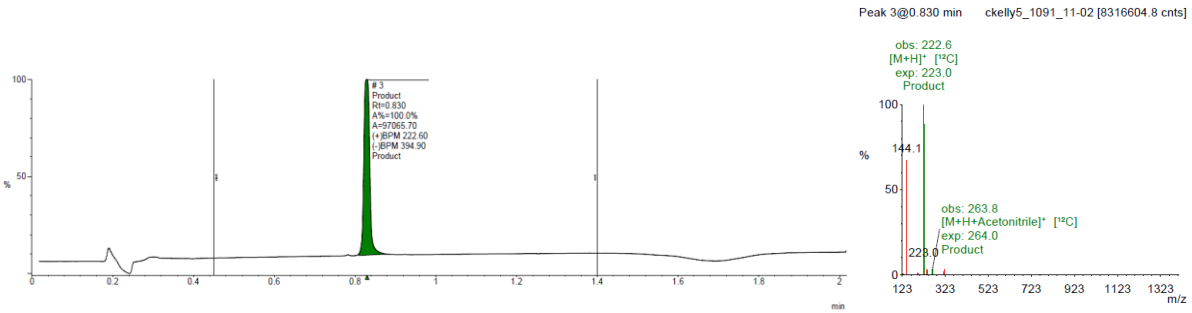
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (s, 1H), 7.81 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.30 - 7.41 (m, 1H), 6.79 (d, J = 2.2 Hz, 1H)

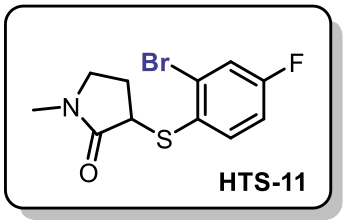
^{1}H NMR Spectra (with suppression):





LCMS Data: Retention Time: 0.830 min; **MS ES+** ([M+H]$^+$): 222.6.



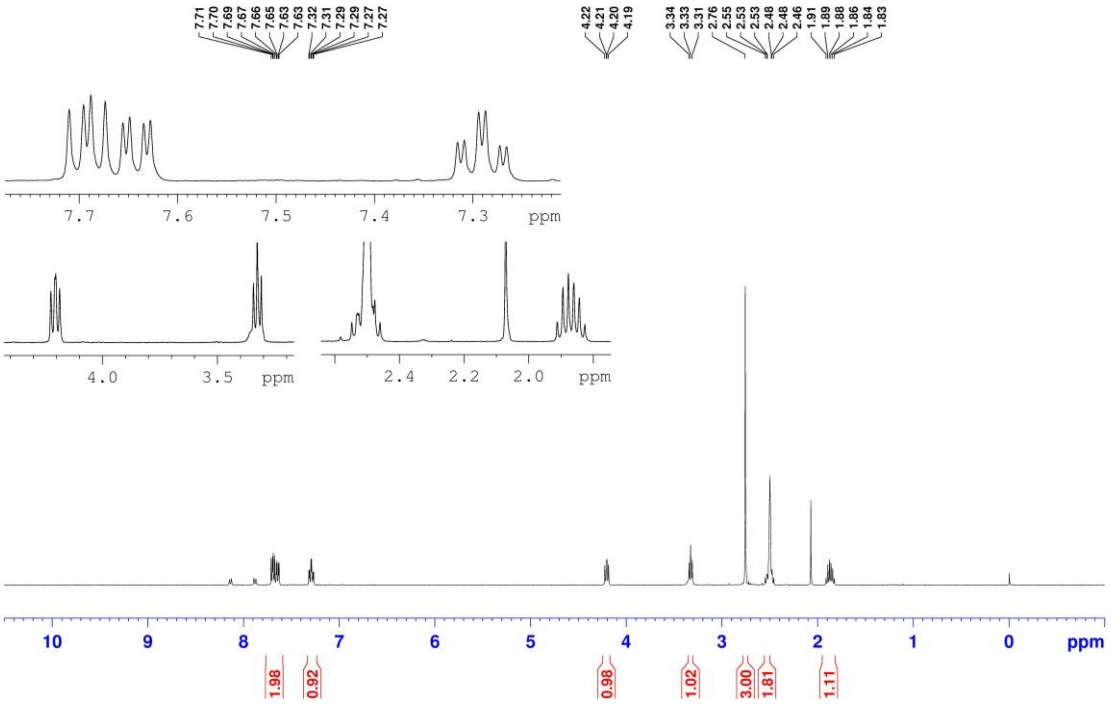


3-((2-bromo-4-fluorophenyl)thio)-1-methylpyrrolidin-2-one (HTS-11)

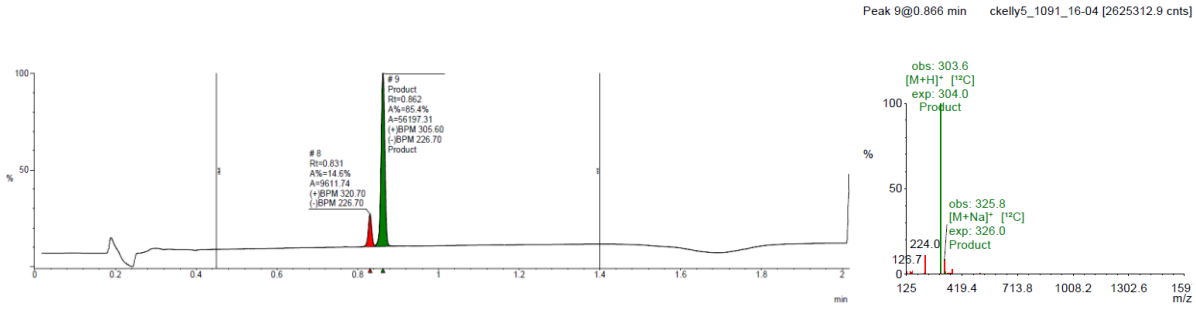
Quantity Obtained: 3.1 mg (90% purity by NMR, 85% purity by LC)

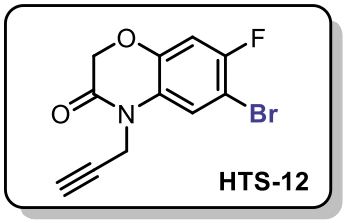
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69 (dd, J = 8.8, 5.9 Hz, 1H), 7.64 (dd, J = 8.4, 2.8 Hz, 1H), 7.29 (td, J = 8.6, 2.7 Hz, 1H), 4.20 (dd, J = 8.4, 6.7 Hz, 1H), 3.33 (dd, J = 7.5, 5.9 Hz, 1H), 2.76 (s, 3H), 2.45 - 2.56 (m, 3H), 1.87 (dq, J = 13.5, 6.8 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.862 min; **MS ES+** ([M+H]$^+$): 303.6.



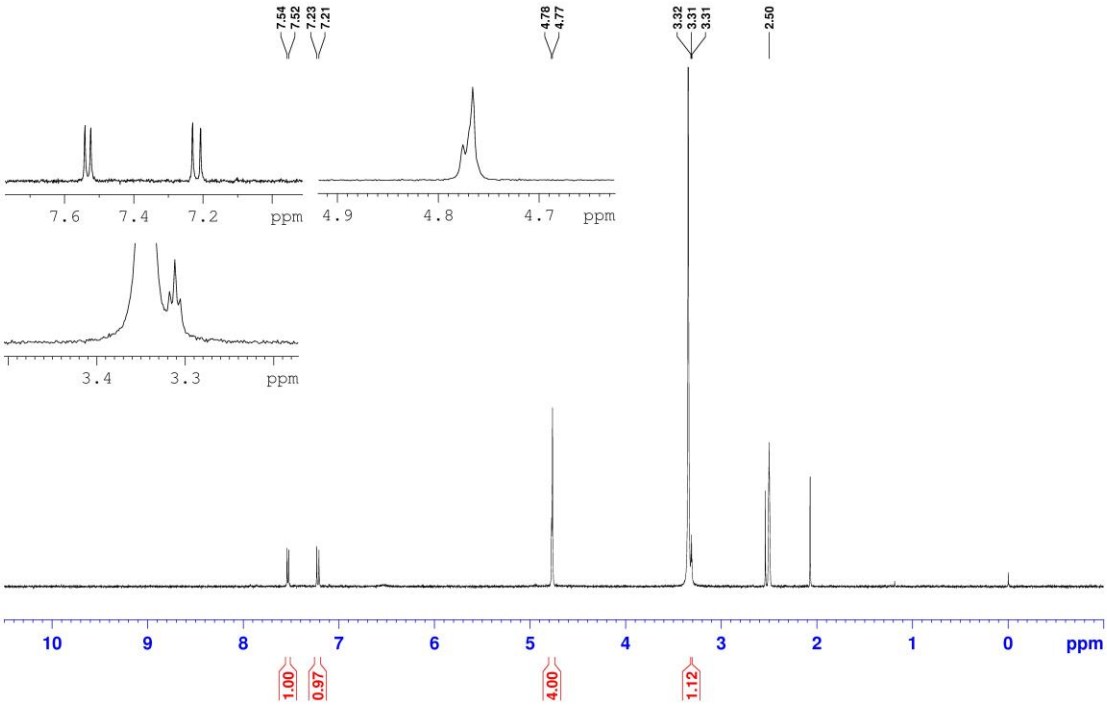


6-bromo-7-fluoro-4-(prop-2-yn-1-yl)-2H-benzo[b][1,4]oxazin-3(4H)-one (HTS-12)

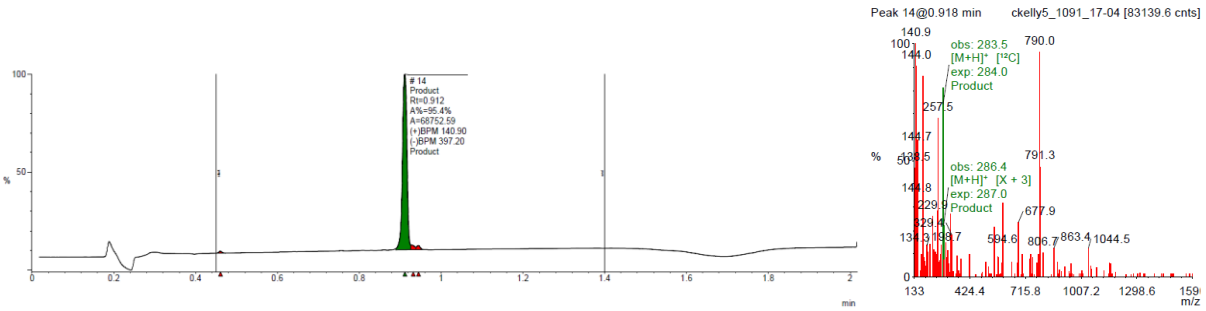
Quantity Obtained: 2.7 mg

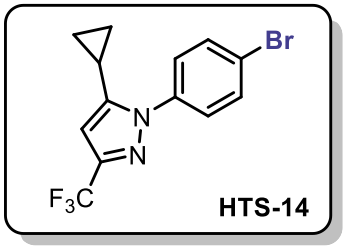
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (d, J = 6.9 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 4.73 - 4.82 (m, 4H), 3.31 (t, J = 2.5 Hz, 1H)

^{1}H NMR Spectra (without suppression):



LCMS Data: Retention Time: 0.912 min; **MS ES+** ([M+H]$^+$): 283.5.



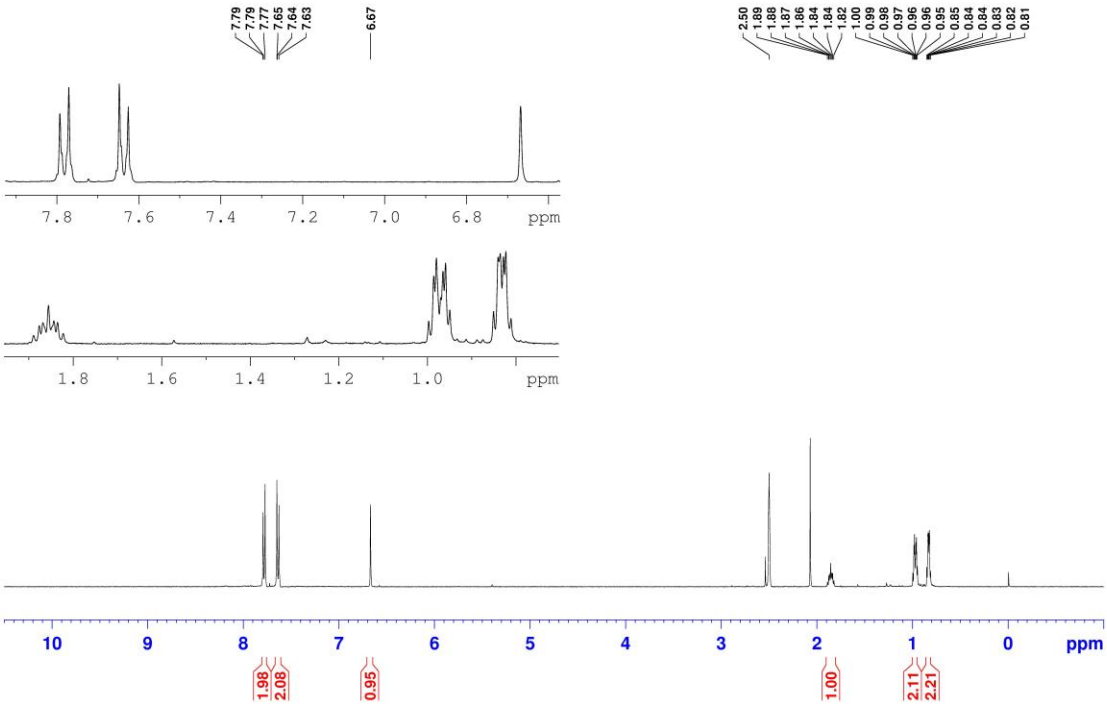


1-(4-bromophenyl)-5-cyclopropyl-3-(trifluoromethyl)-1*H*-pyrazole (HTS-14)

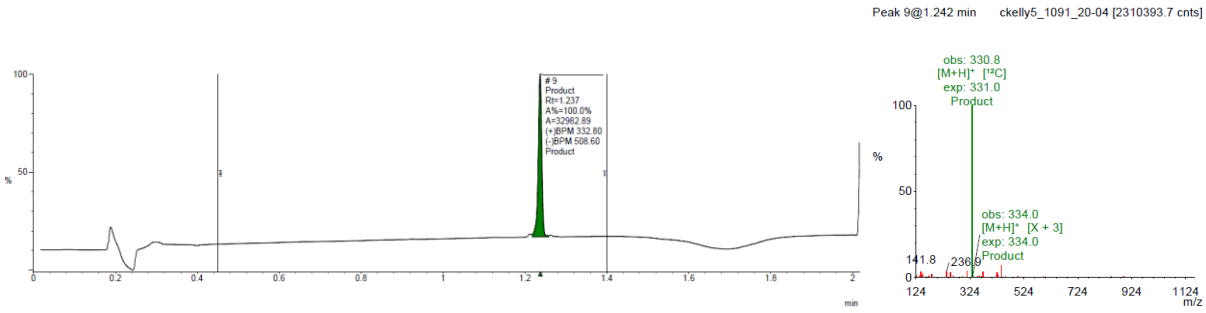
Quantity Obtained: 3.8 mg

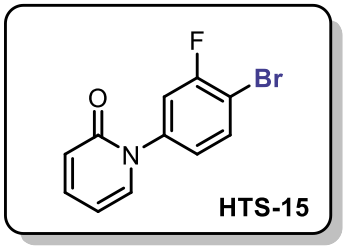
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.6 Hz, 2H), 6.67 (s, 1H), 1.86 (tt, J = 8.3, 5.1 Hz, 1H), 0.94 - 1.01 (m, 2H), 0.79 - 0.86 (m, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 1.237 min; **MS ES+** ([M+H]$^+$): 330.8.



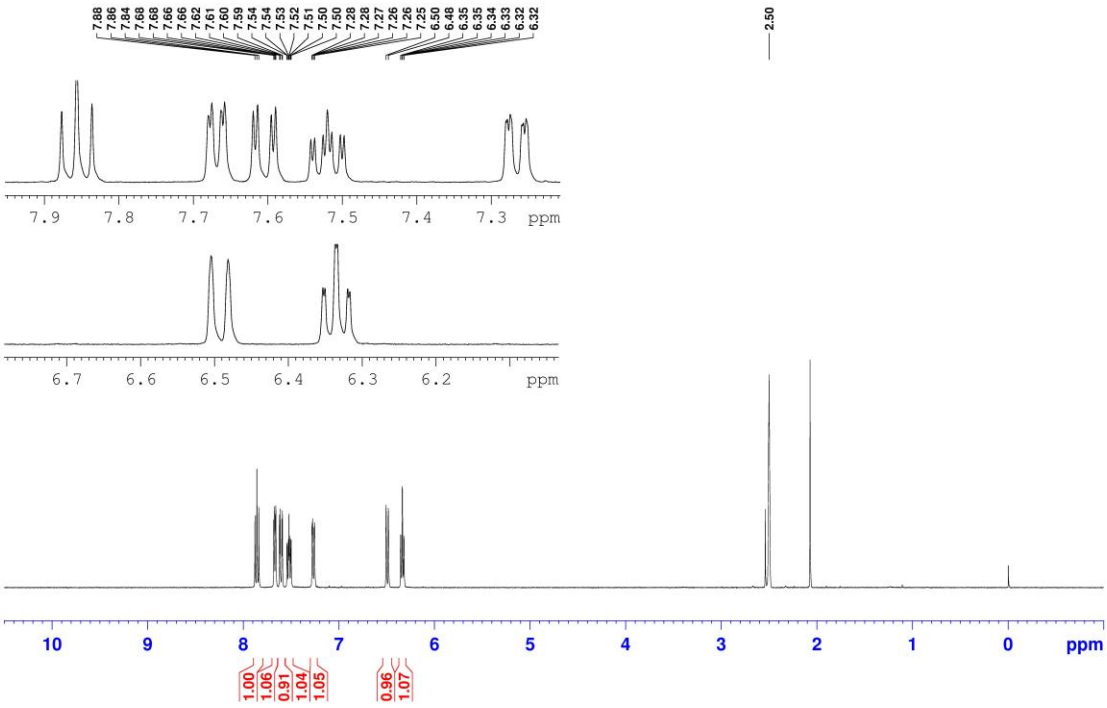


1-(4-bromo-3-fluorophenyl)pyridin-2(1*H*)-one (HTS-15)

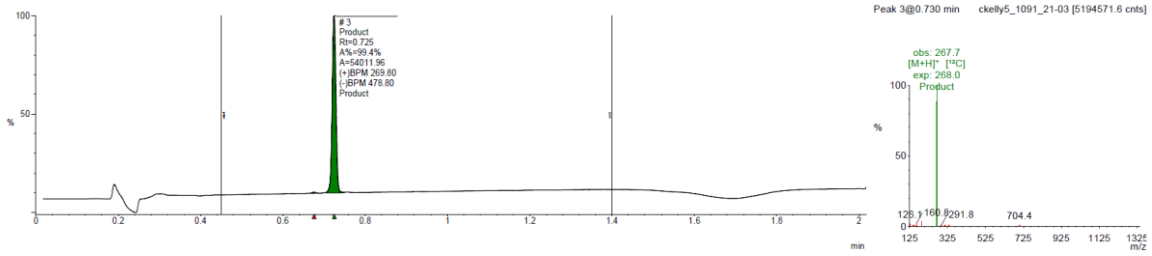
Quantity Obtained: 3.0 mg

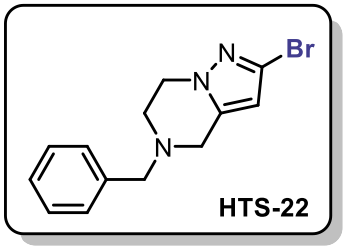
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (t, *J* = 8.19 Hz, 1H), 7.67 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.60 (dd, *J* = 9.7, 2.3 Hz, 1H), 7.52 (ddd, *J* = 9.1, 6.8, 2.0 Hz, 1H), 7.27 (ddd, *J* = 8.6, 2.2, 0.7 Hz, 1H), 6.49 (d, *J* = 9.3 Hz, 1H), 6.33 (td, *J* = 6.7, 1.0 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.726 min; **MS ES+** ([M+H]$^+$): 267.7.



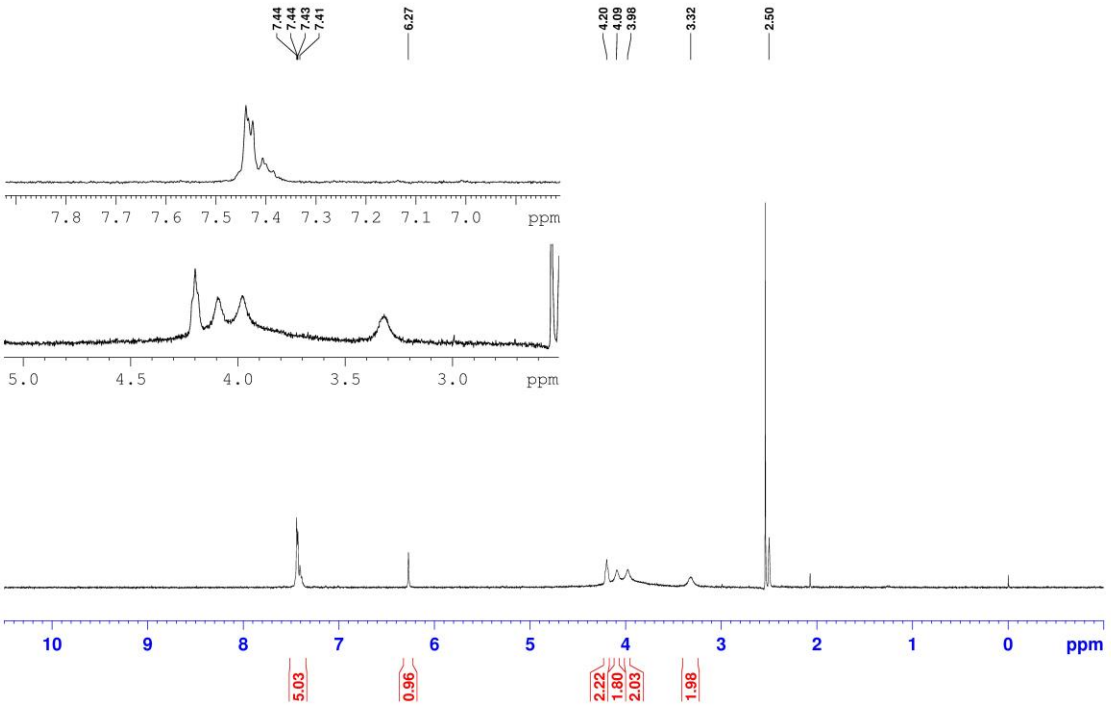


5-benzyl-2-bromo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (HTS-22)

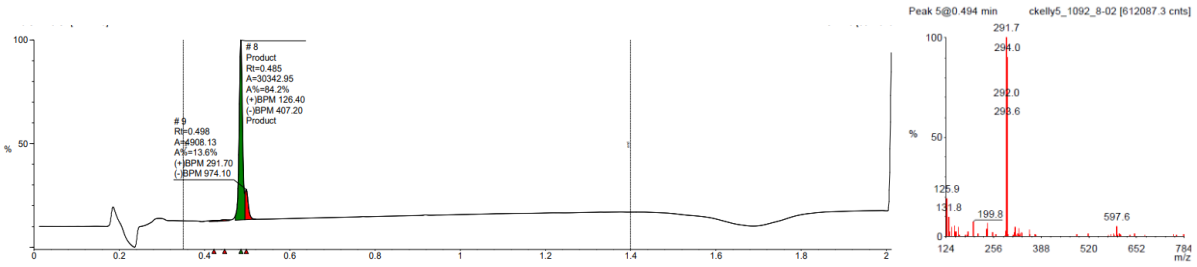
Quantity Obtained: 4.3 mg (85% purity by LCMS)

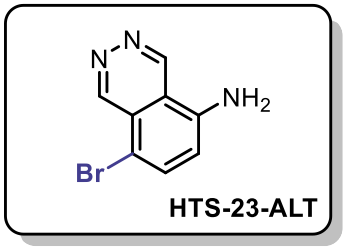
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 - 7.49 (m, 5H), 6.27 (s, 1H), 4.20 (t, J = 5.9 Hz, 2H), 4.06 - 4.13 (m, 2H), 3.93 - 4.01 (m, 3H), 3.24 - 3.39 (m, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.494 min; **MS ES+** ([M+H]$^+$): 291.7.



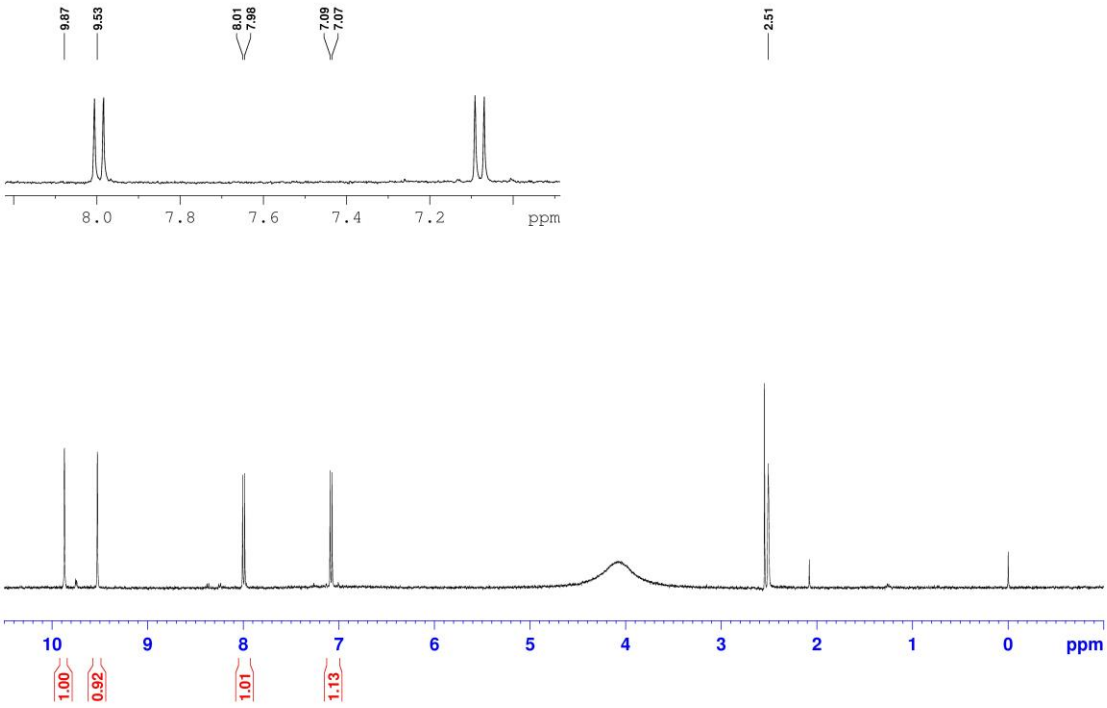


8-bromophthalazin-5-amine (HTS-23-ALT)

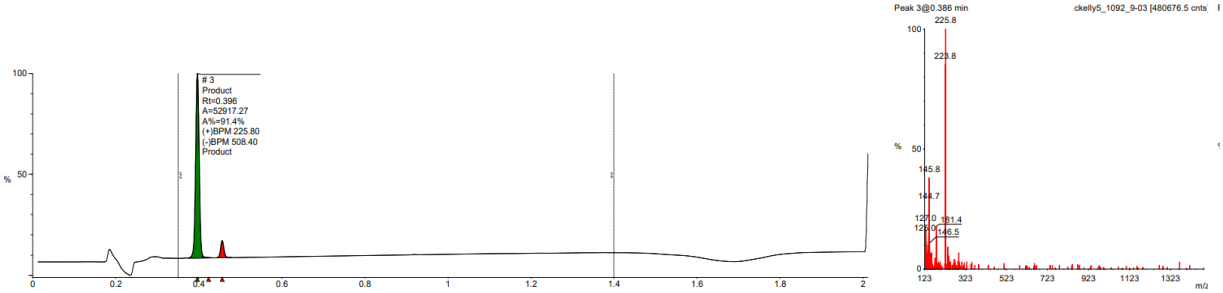
Quantity Obtained: 5.4 mg

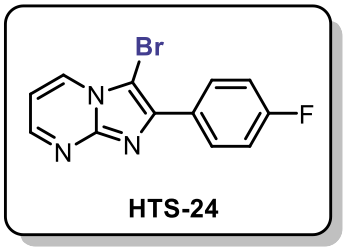
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.53 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H)

^{1}H NMR Spectra (without suppression):



LCMS Data: Retention Time: 0.396 min; **MS ES+** ([M+H]$^+$): 225.8.



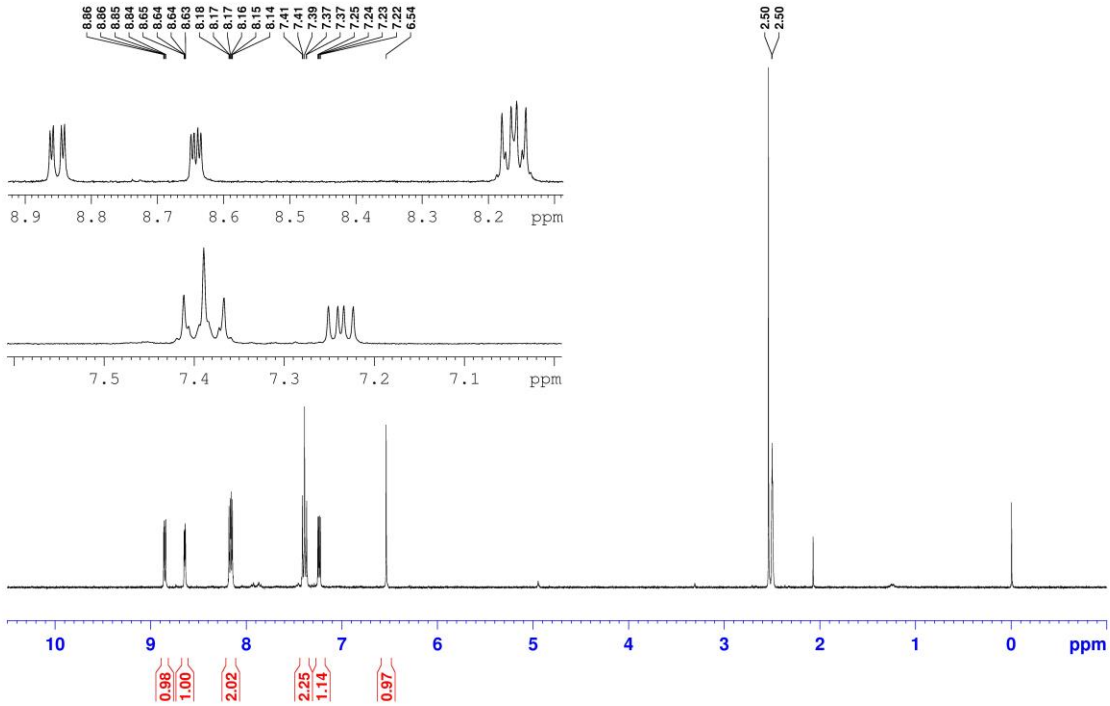


2-(4-fluorophenyl)imidazo[1,2-a]pyrimidine (HTS-24)

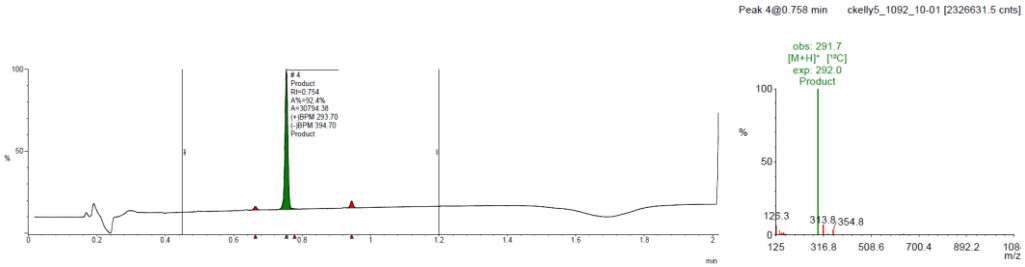
Quantity Obtained: 1.0 mg (92% purity by LCMS)

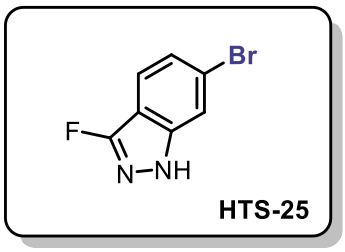
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (dd, *J* = 6.8, 2.0 Hz, 1H), 8.65 (dd, *J* = 3.9, 2.0 Hz, 1H), 8.17 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.39 (t, *J* = 8.8 Hz, 2H), 7.24 (dd, *J* = 6.8, 3.9 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.758 min; **MS ES+** ([M+H]$^+$): 291.7.



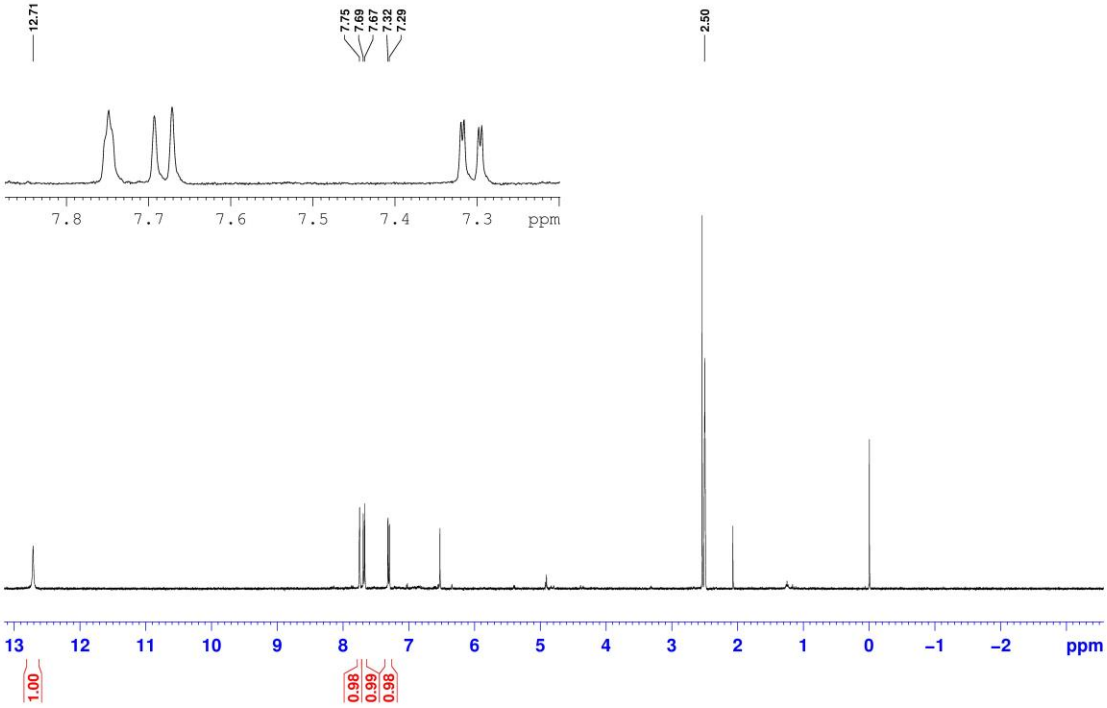


6-bromo-3-fluoro-1H-indazole (HTS-25)

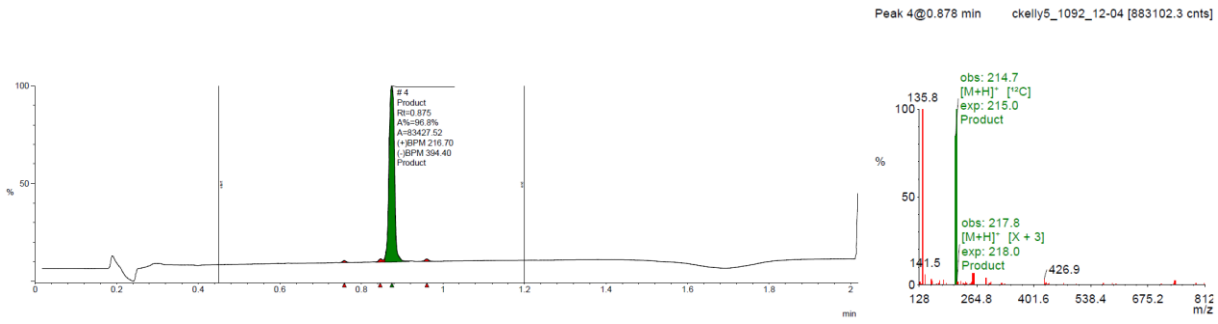
Quantity Obtained: 3.4 mg

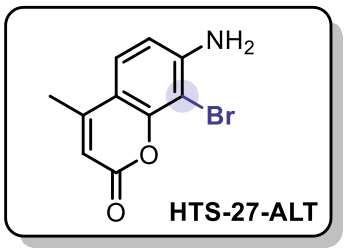
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.71 (s, 1H), 7.75 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 8.3, 1.5 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.875 min; **MS ES+** ([M+H]$^+$): 214.7.



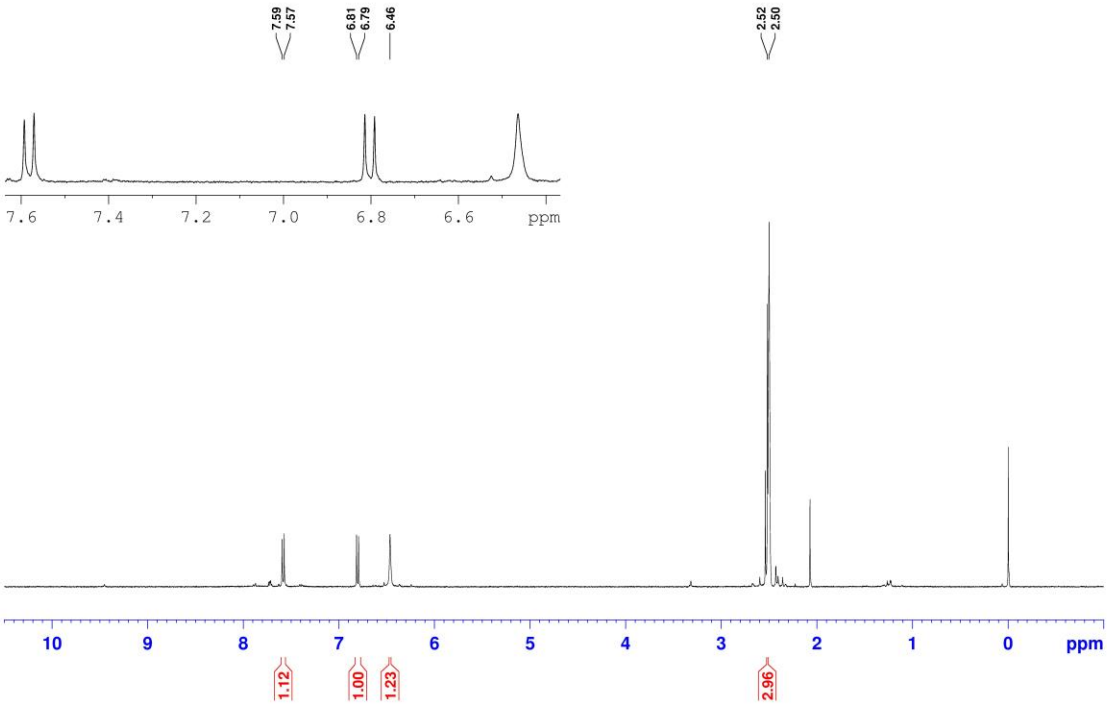


7-amino-8-bromo-4-methyl-2*H*-chromen-2-one (HTS-27-ALT)

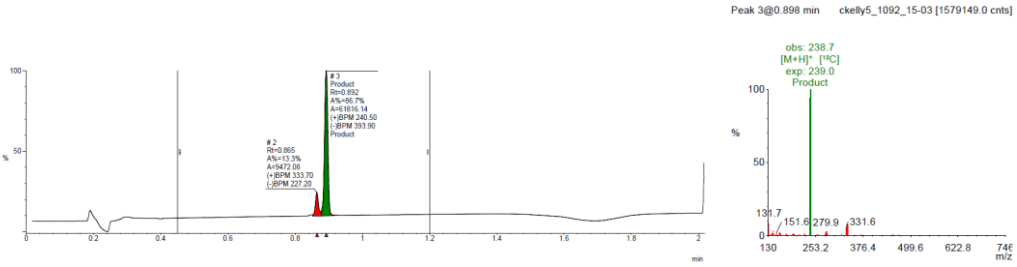
Quantity Obtained: 4.0 mg

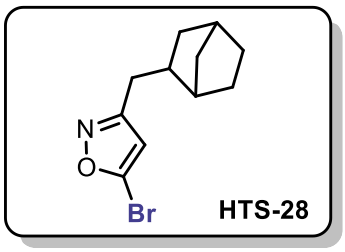
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (d, J = 9.0 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 6.46 (s, 1H), 2.52 (s, 3H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.898 min; **MS ES+** ([M+H+DMSO]$^+$): 331.6.



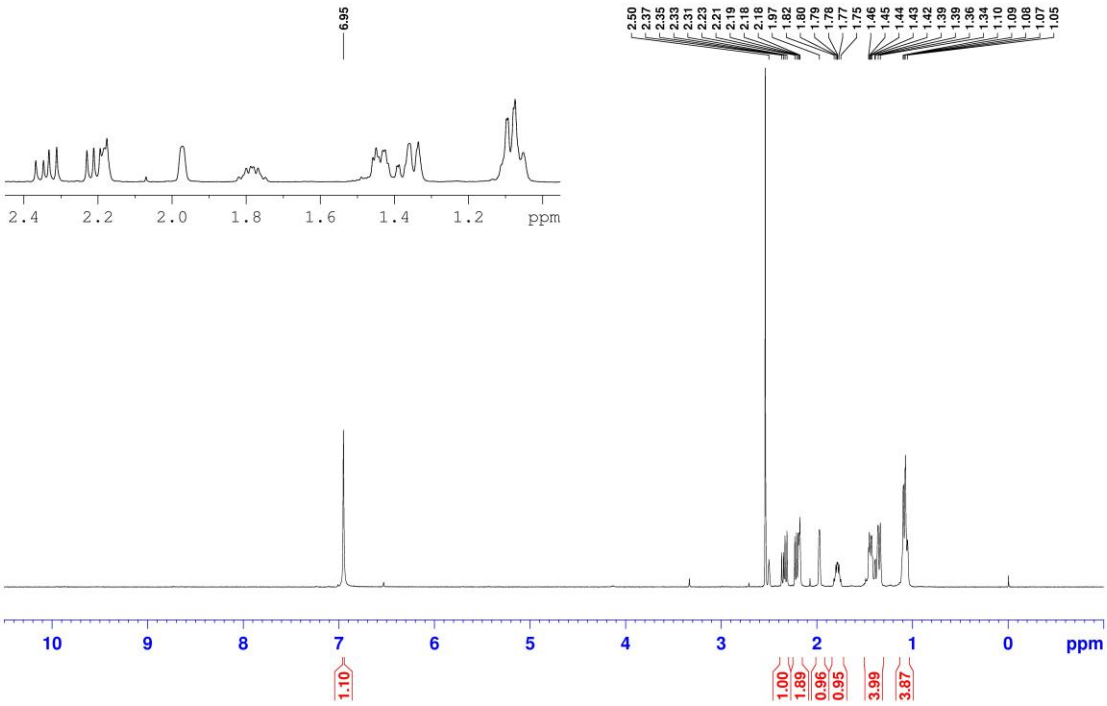


3-(bicyclo[2.2.1]heptan-2-ylmethyl)-5-bromoisoxazole (HTS-28)

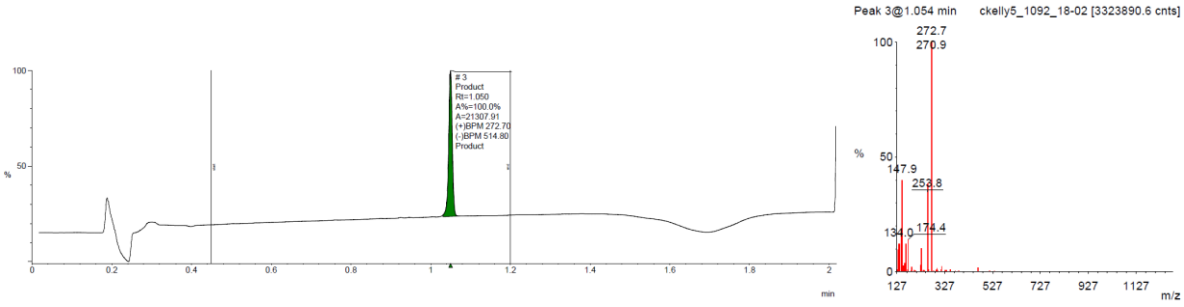
Quantity Obtained: 2.0 mg

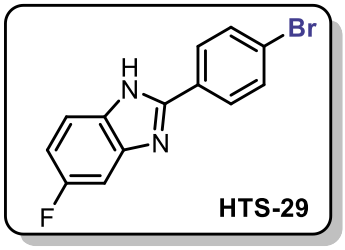
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.95 (s, 1H), 2.34 (dd, J = 14.2, 8.3 Hz, 1H), 2.16 - 2.24 (m, 2H), 1.97 (br. s., 1H), 1.78 (dq, J = 9.0, 7.0 Hz, 1H), 1.30 - 1.49 (m, 4H), 1.00 - 1.14 (m, 4H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 1.05 min; **MS ES+** ([M+NH$_4$]$^+$): 272.7



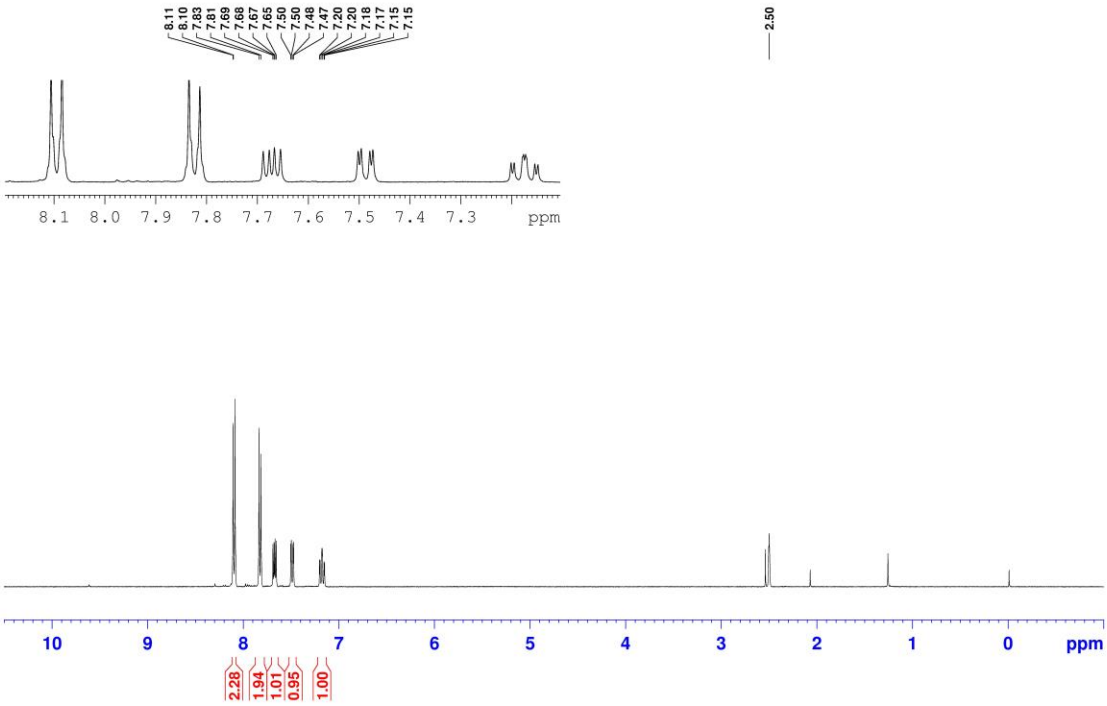


2-(4-bromophenyl)-5-fluoro-1H-benzo[d]imidazole (HTS-29)

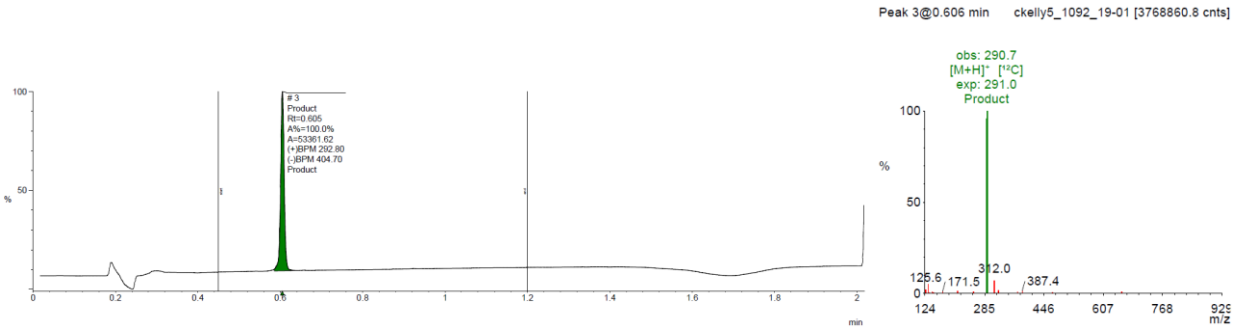
Quantity Obtained: 11.7 mg

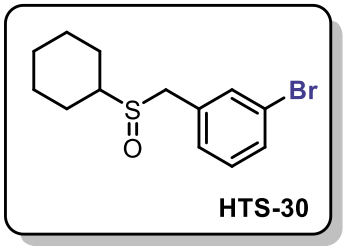
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.6 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.67 (dd, J = 8.9, 4.8 Hz, 1H), 7.49 (dd, J = 9.0, 2.4 Hz, 1H), 7.17 (td, J = 9.4, 2.4 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.605 min; **MS ES+** ([M+H]$^+$): 290.7



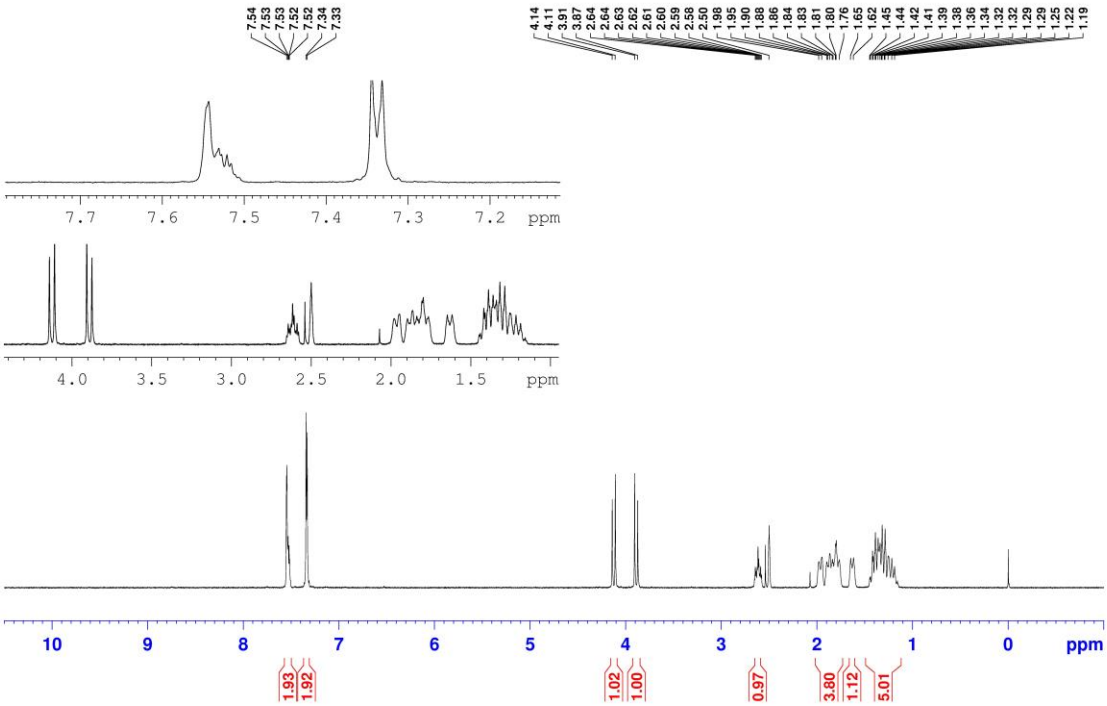


1-bromo-3-((cyclohexylsulfinyl)methyl)benzene (HTS-30)

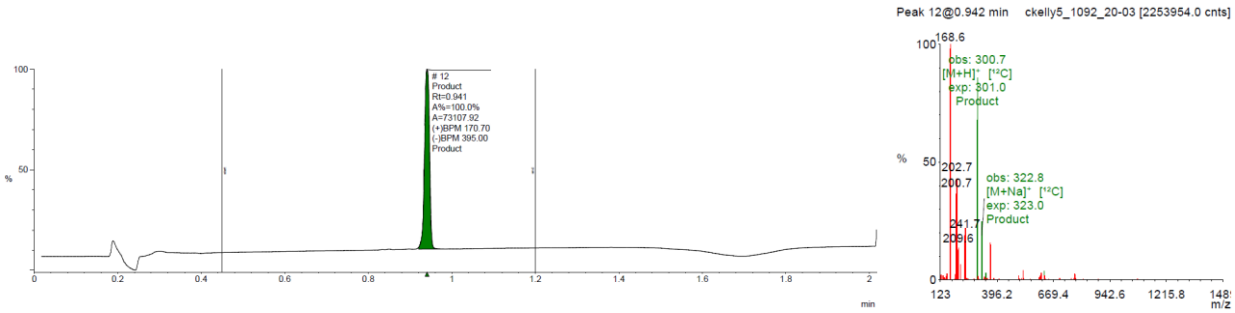
Quantity Obtained: 14.0 mg

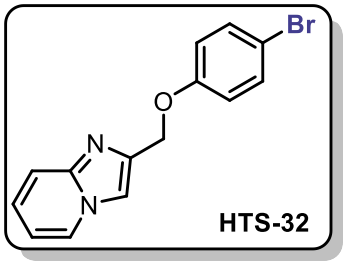
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 - 7.57 (m, 2H), 7.28 - 7.38 (m, 2H), 4.12 (d, J = 13.0 Hz, 1H), 3.89 (d, J = 13.0 Hz, 1H), 2.62 (tt, J = 11.0, 3.4 Hz, 1H), 1.96 (d, J =12.0 Hz, 1H), 1.83 (dt, J = 26.9, 13.0 Hz, 3H), 1.63 (d, J = 11.7 Hz, 1H), 1.14 - 1.47 (m, 5H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.941 min; **MS ES+** ([M+H]$^+$): 300.7



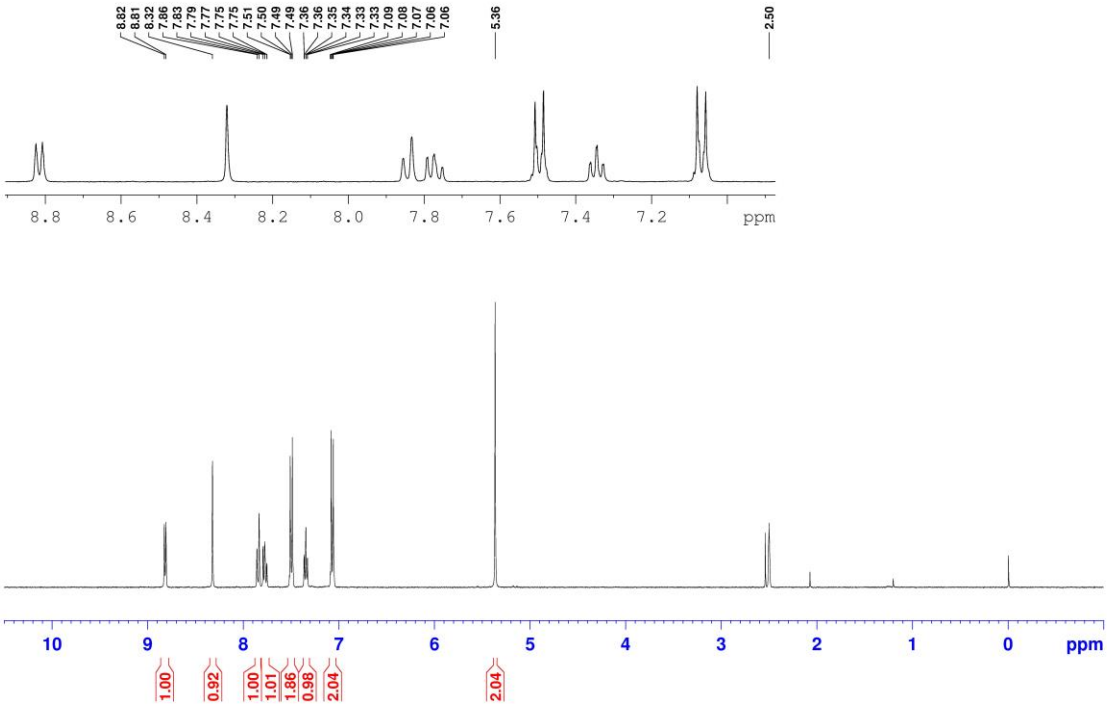


2-((4-bromophenoxy)methyl)imidazo[1,2-a]pyridine (HTS-32)

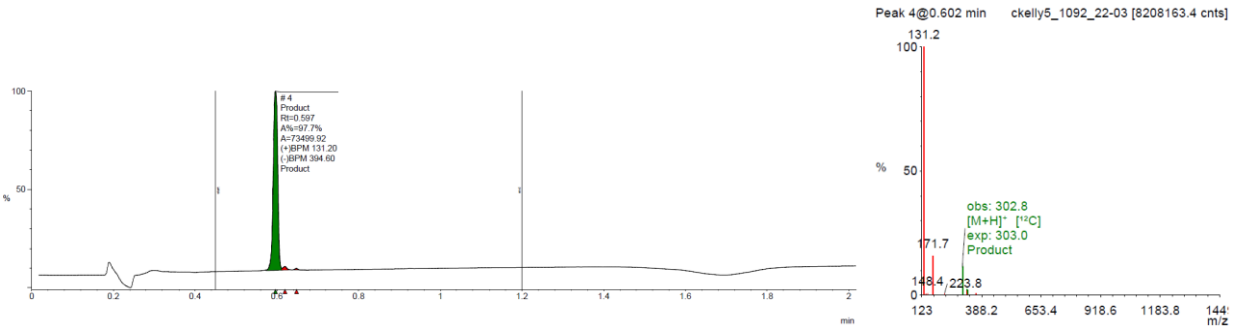
Quantity Obtained: 14.0 mg

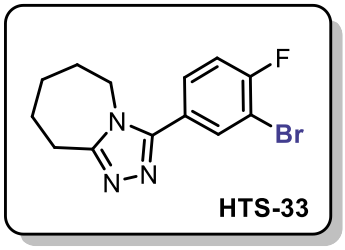
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (d, J = 6.8 Hz, 1H), 8.32 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.77 (dd, J = 9.0, 6.8 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.34 (td, J = 6.8, 1.0 Hz, 1H), 7.07 (d, J = 9.0 Hz, 2H), 5.36 (s, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.597 min; **MS ES+** ([M+H]$^+$): 302.8



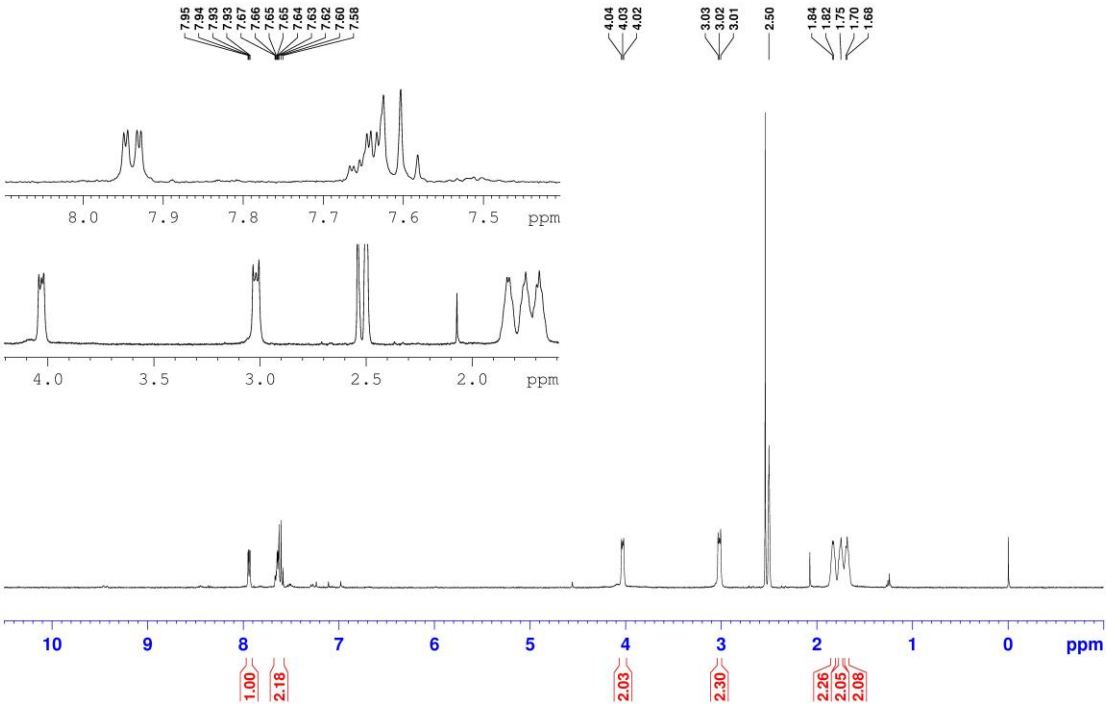


3-(3-bromo-4-fluorophenyl)-6,7,8,9-tetrahydro-5*H*-[1,2,4]triazolo[4,3-a]azepine (HTS-33)

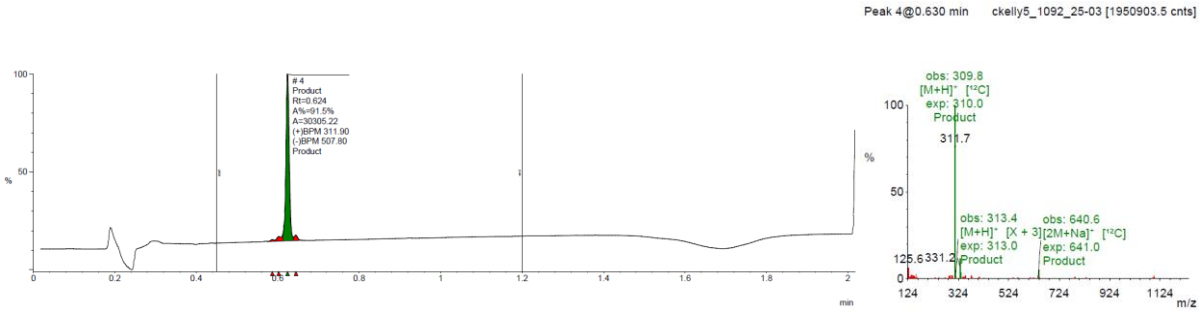
Quantity Obtained: 3.3 mg (92% purity by LC)

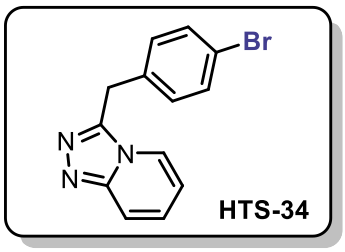
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (dd, J = 6.6, 2.0 Hz, 1H), 7.54 - 7.68 (m, 2H), 4.01 - 4.05 (m, 2H), 2.99 - 3.05 (m, 2H), 1.79 - 1.87 (m, 2H), 1.71 - 1.78 (m, 3H), 1.64 - 1.70 (m, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.624 min; **MS ES+** ([M+H]$^+$): 309.8



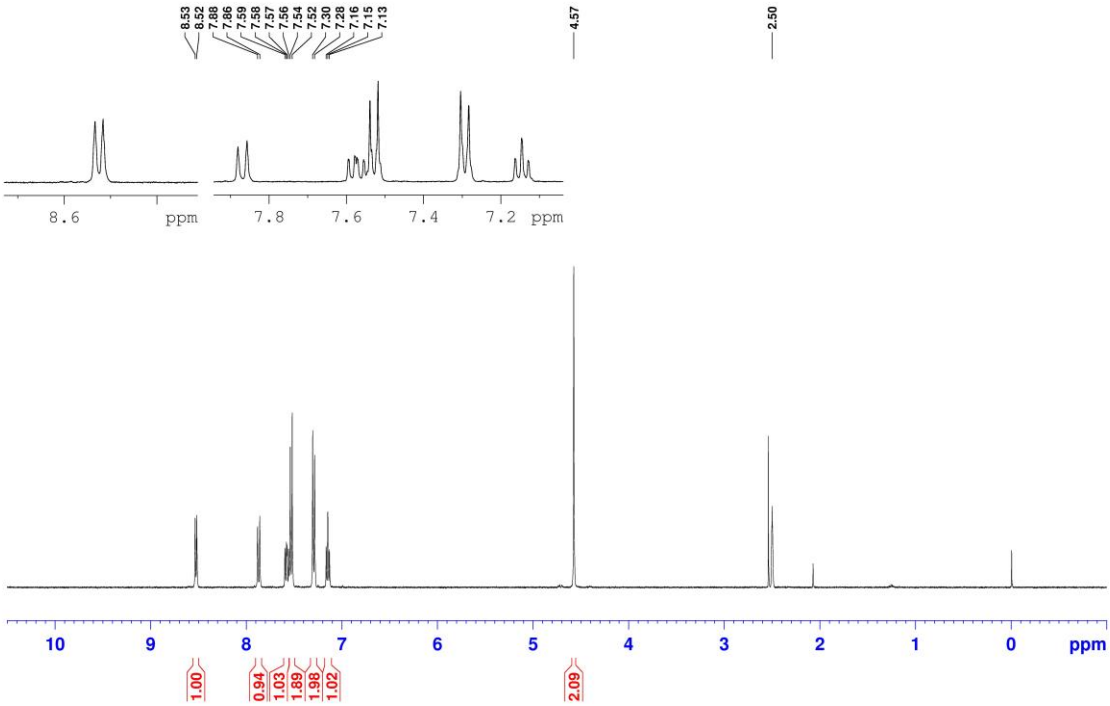


3-(4-bromobenzyl)-[1,2,4]triazolo[4,3-a]pyridine (HTS-34)

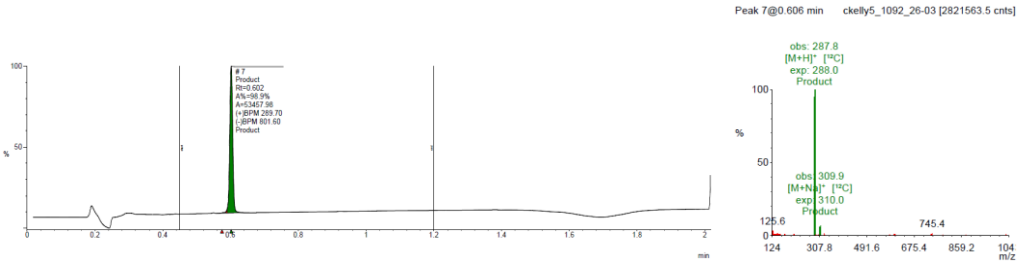
Quantity Obtained: 8.1 mg

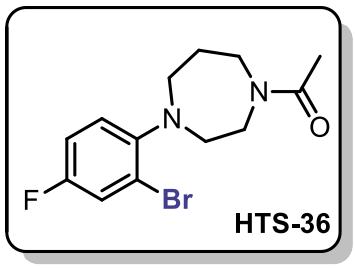
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (d, J = 7.1 Hz, 1H), 7.87 (d, J = 9.3 Hz, 1H), 7.57 (dd, J =9.0, 6.6 Hz, 1H), 7.53 (d, J =8.3 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.15 (t, J = 6.7 Hz, 1H), 4.57 (s, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.602 min; **MS ES+** ([M+H]$^+$): 287.8.



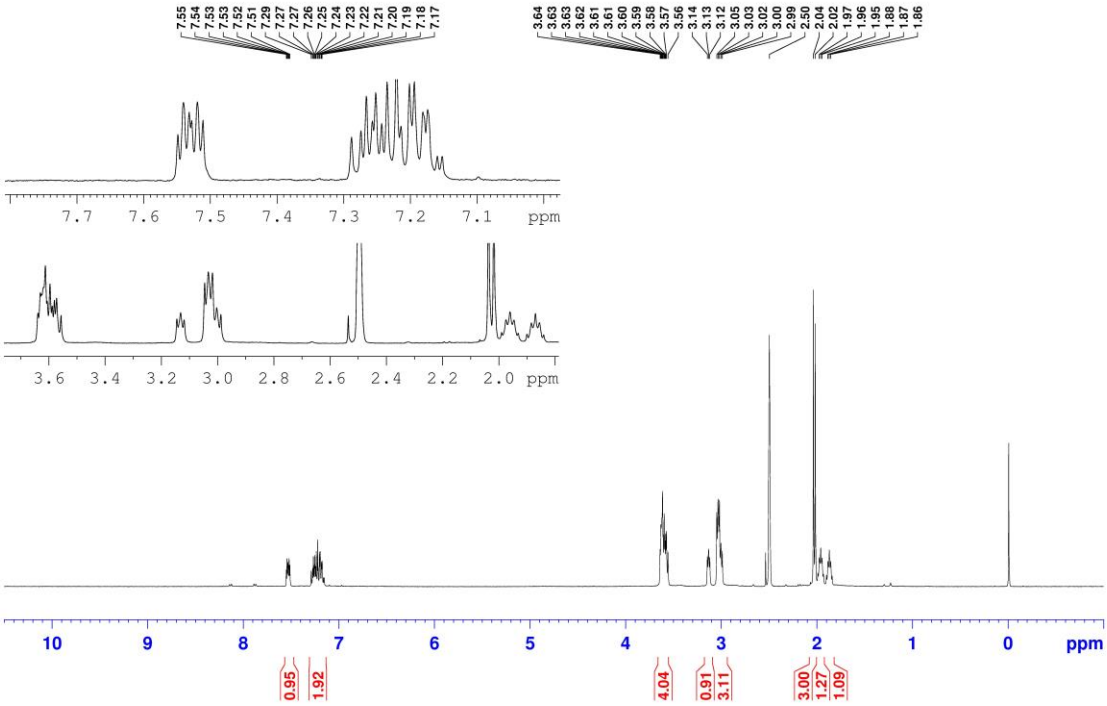


1-(4-(2-bromo-4-fluorophenyl)-1,4-diazepan-1-yl)ethan-1-one (HTS-36)

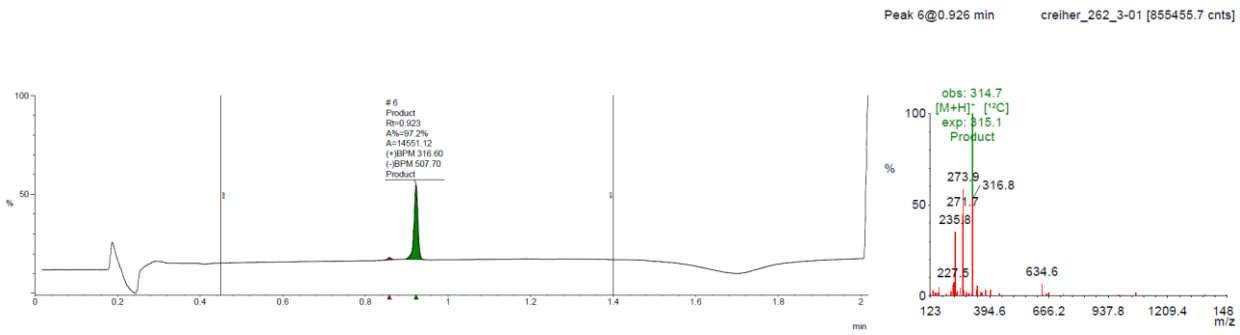
Quantity Obtained: 0.9 mg (97% purity by LC)

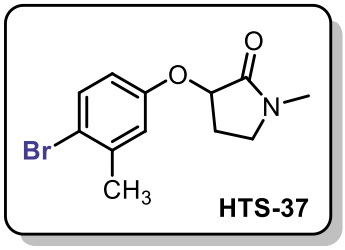
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.53 (dt, *J* =8.3, 3.4 Hz, 1H), 7.12 - 7.30 (m, 2H), 3.54 - 3.65 (m, 4H), 3.13 (dd, *J* = 6.6, 3.9 Hz, 1H), 2.97 - 3.06 (m, 3H), 2.03 (d, *J* = 7.6 Hz, 3H), 1.96 (dt, *J* = 11.7, 6.0 Hz, 1H), 1.87 (dt, *J* = 11.8, 6.0 Hz, 1H).

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.923 min; **MS ES+** ([M+H]$^+$): 314.7



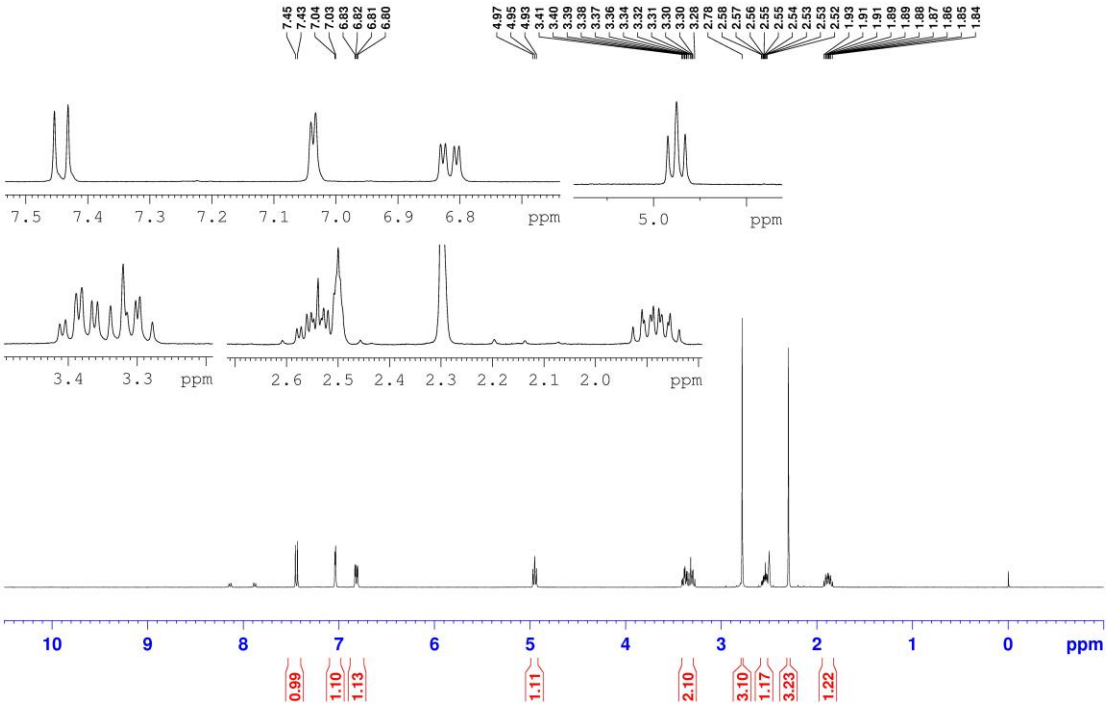


3-(4-bromo-3-methylphenoxy)-1-methylpyrrolidin-2-one (HTS-37)

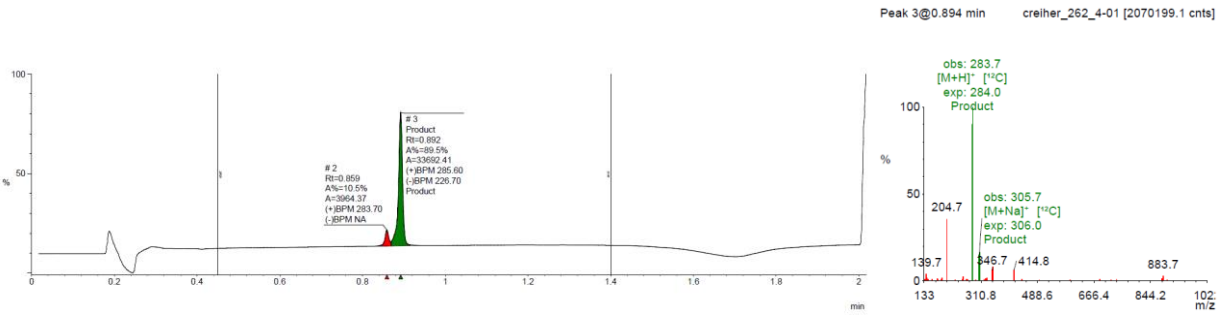
Quantity Obtained: 9.0 mg (90% purity by LCMS)

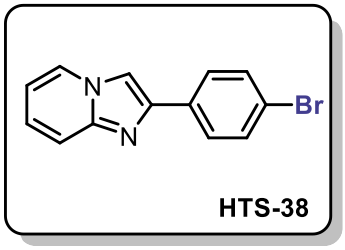
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.9 Hz, 1H), 6.82 (dd, *J* = 8.7, 3.1 Hz, 1H), 4.95 (t, *J* = 7.3 Hz, 1H), 3.38 (td, *J* = 9.0, 3.4 Hz, 1H), 3.27 - 3.34 (m, 1H), 2.78 (s, 3H), 2.49 - 2.59 (m, 2H), 2.30 (s, 3H), 1.88 (ddt, *J* = 13.3, 8.8, 6.9, 6.9 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.892 min; **MS ES+** ([M+H]$^+$): 283.7



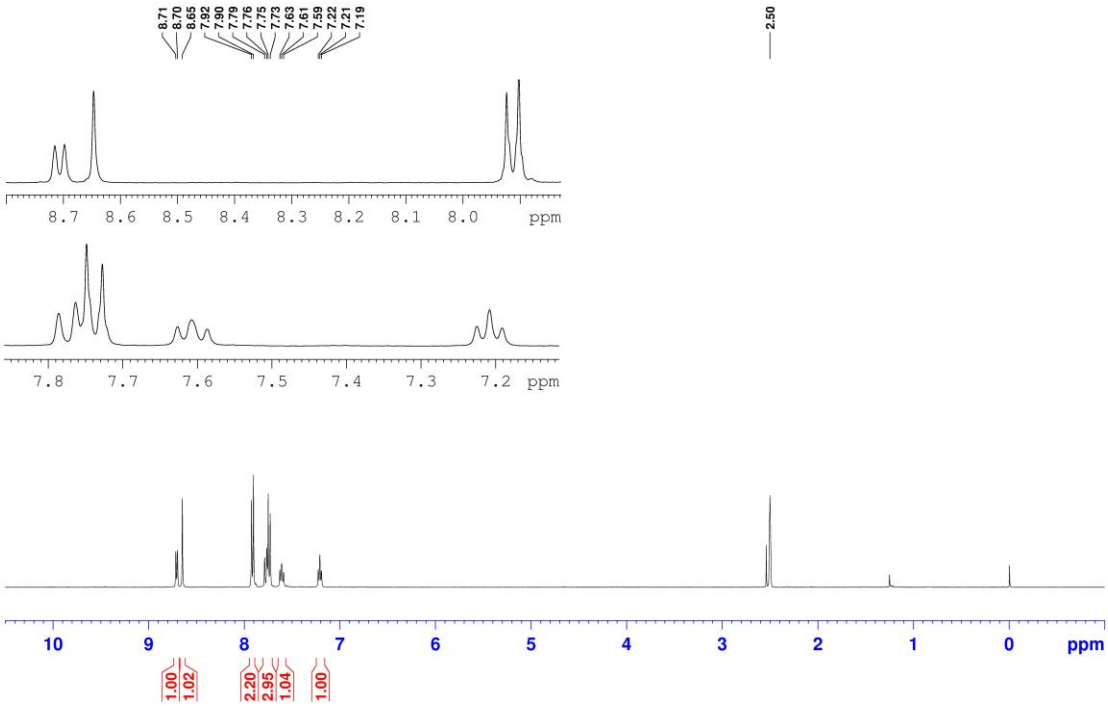


2-(4-bromophenyl)imidazo[1,2-a]pyridine (HTS-38)

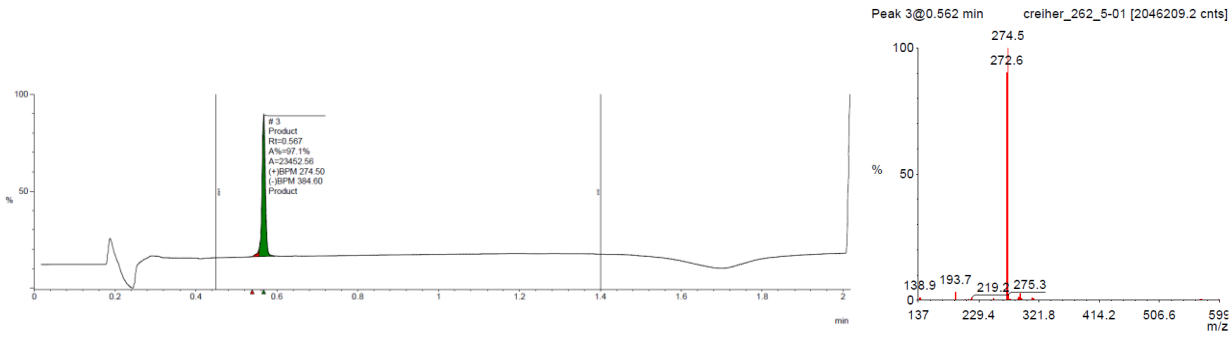
Quantity Obtained: 3.3 mg

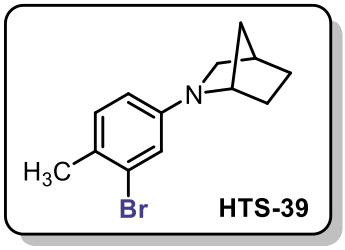
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, *J* = 6.6 Hz, 1H), 8.65 (s, 1H), 7.91 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 9.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 6.8 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.567 min; **MS ES+** ([M+H]$^+$): 274.5



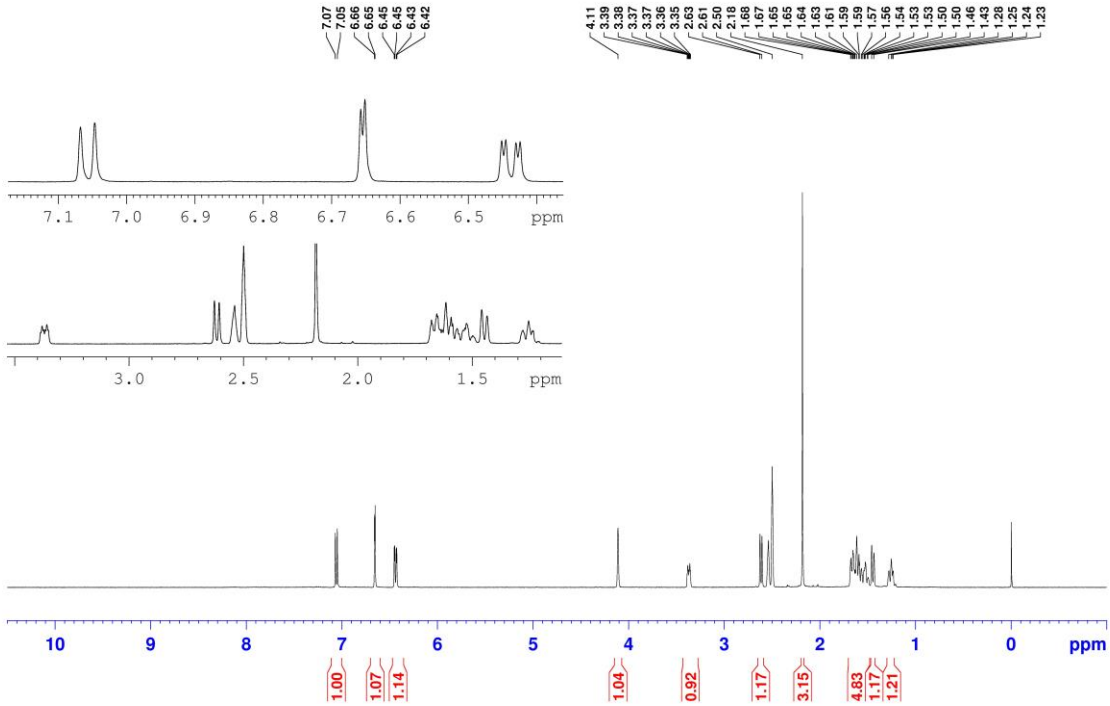


2-(3-bromo-4-methylphenyl)-2-azabicyclo[2.2.1]heptane (HTS-39)

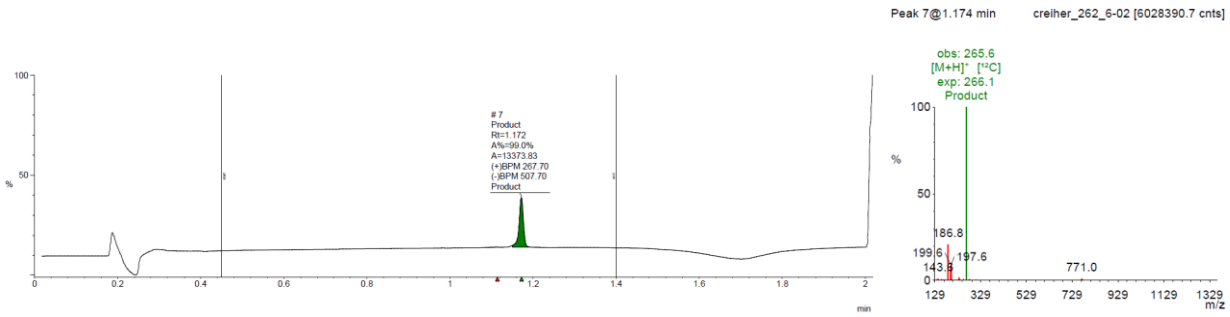
Quantity Obtained: 2.3 mg

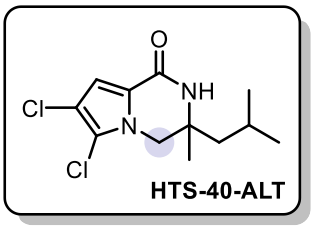
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.06 (d, *J* = 8.3 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.44 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.11 (s, 1H), 3.37 (dt, *J* = 8.3, 2.4 Hz, 1H), 2.62 (d, *J* = 8.6 Hz, 1H), 2.18 (s, 3H), 1.48 - 1.69 (m, 5H), 1.45 (d, *J* = 9.5 Hz, 1H), 1.22 - 1.30 (m, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 1.172 min; **MS ES+** ([M+H]$^+$): 265.6.



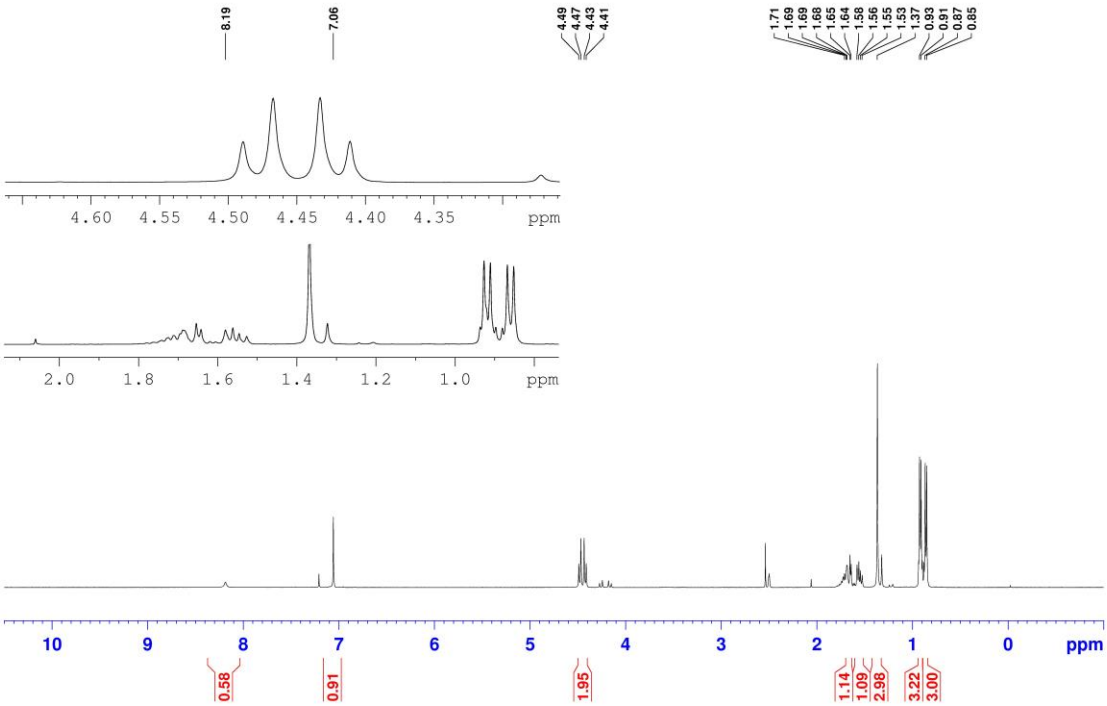


6,7-dichloro-3-isobutyl-3-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (HTS-40-ALT)

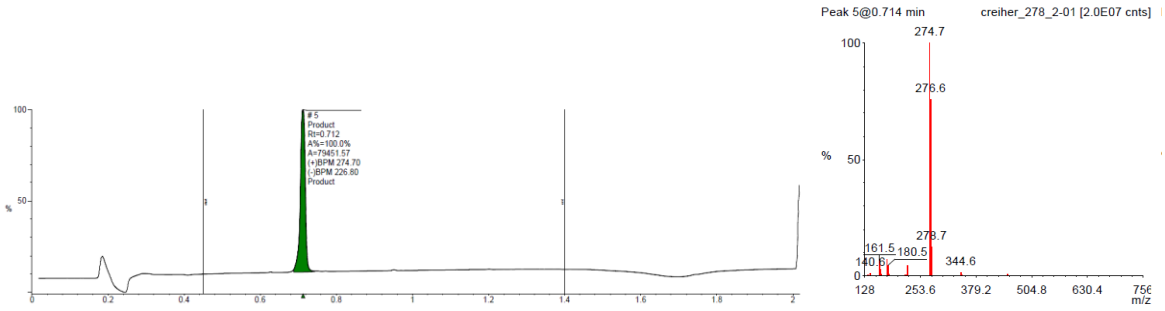
Quantity Obtained: 3.3 mg

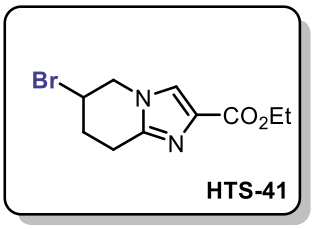
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (br. s., 1H), 7.08 (s, 1H), 4.50 (d, *J* = 9.0 Hz, 1H), 4.44 (d, *J* = 8.6 Hz, 1H), 1.65 - 1.81 (m, 1H), 1.58 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.39 (s, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.712 min; **MS ES+** ([M+H]$^+$): 276.6.



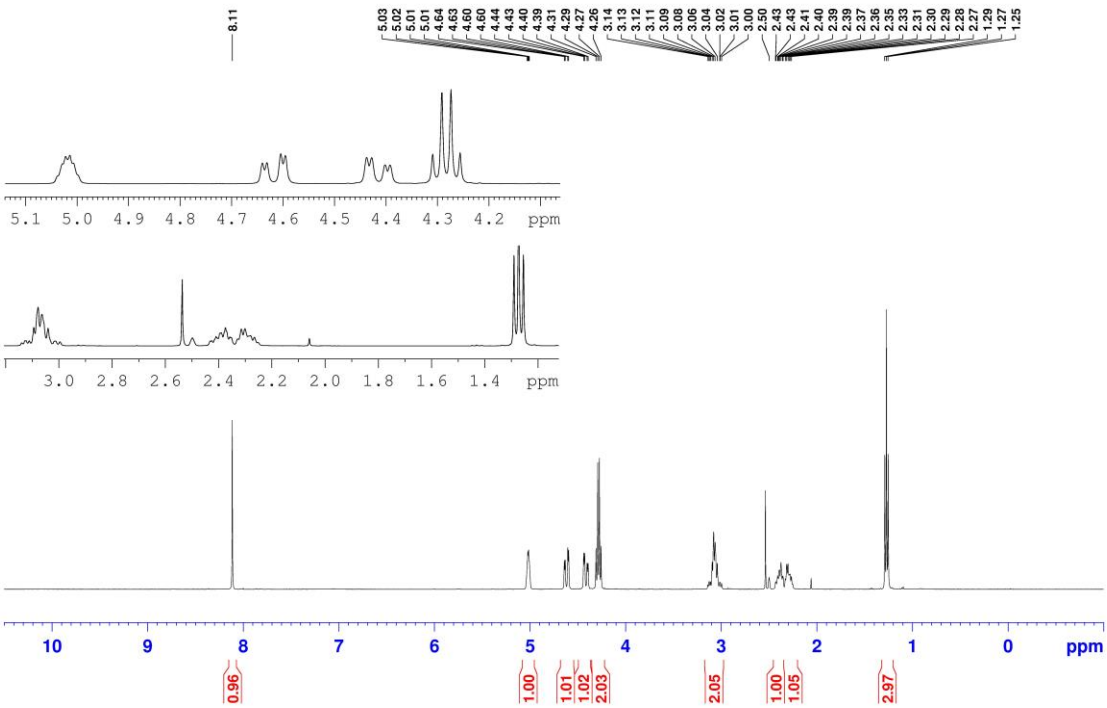


ethyl 6-bromo-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine-2-carboxylate (HTS-41)

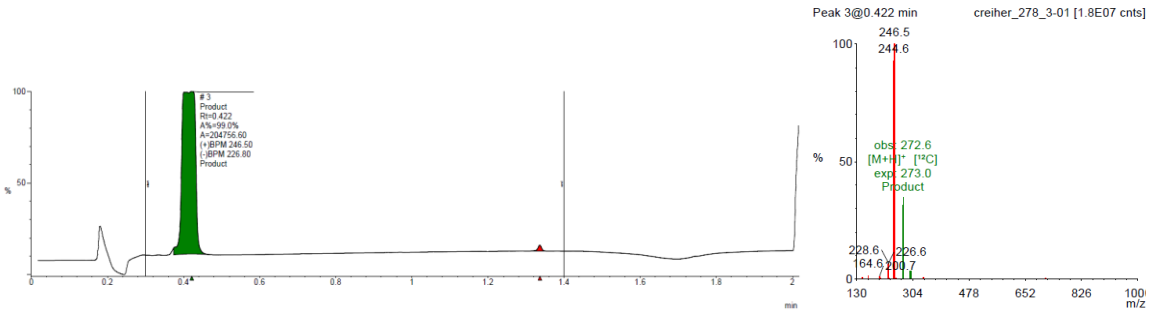
Quantity Obtained: 11.5 mg

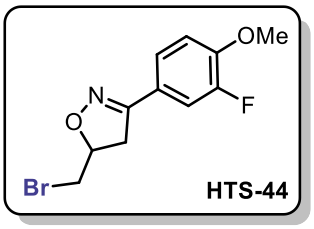
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.14 (s, 1H), 5.04 (sxt, *J* = 3.2 Hz, 1H), 4.64 (dd, *J* = 14.3, 3.5 Hz, 1H), 4.44 (dd, *J* =14.3, 4.1 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.99 - 3.18 (m, 2H), 2.37 - 2.46 (m, 1H), 2.26 - 2.36 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.422 min; **MS ES+** ([M+H]$^+$): 272.6.



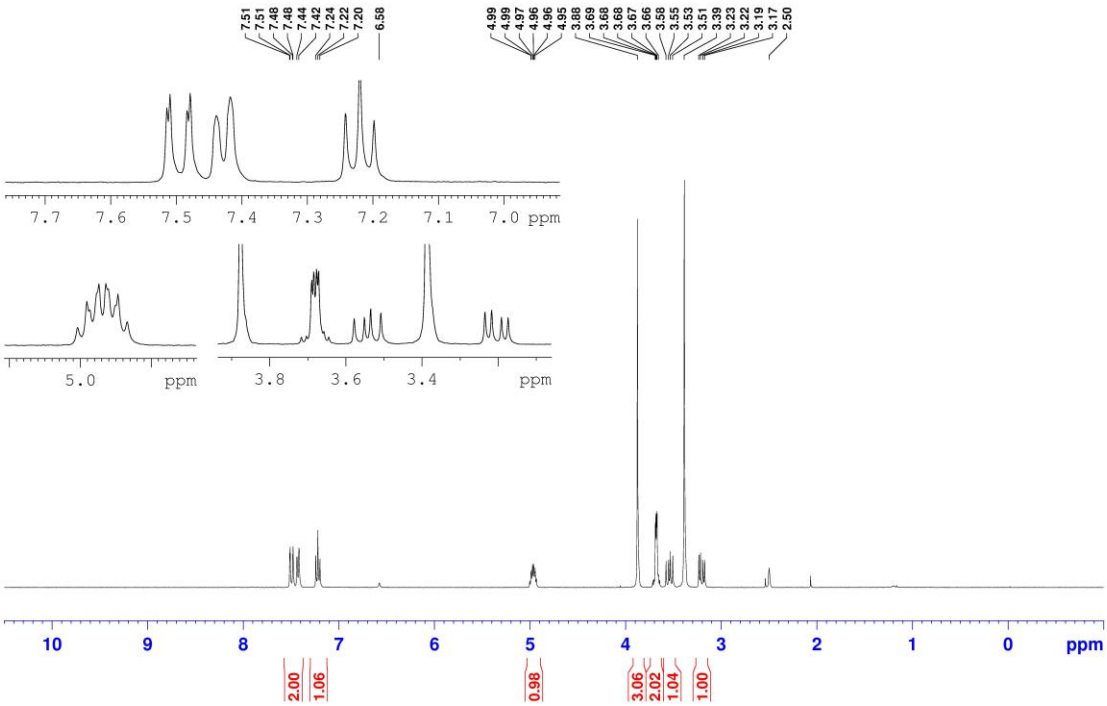


5-(bromomethyl)-3-(3-fluoro-4-methoxyphenyl)-4,5-dihydroisoxazole (HTS-44)

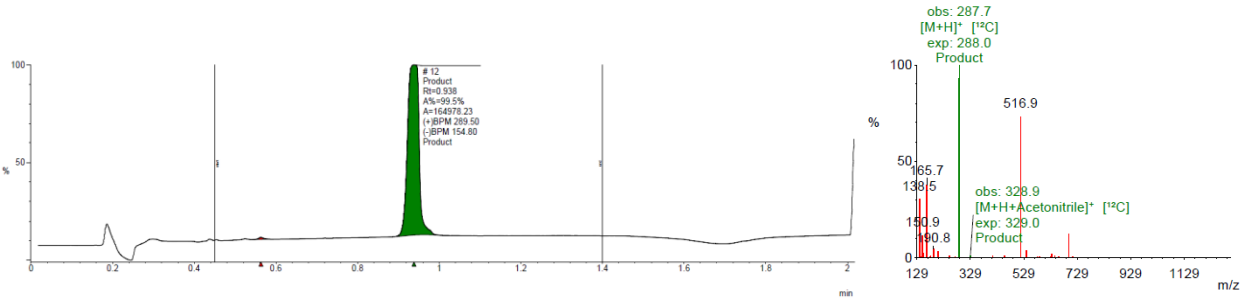
Quantity Obtained: 9.4 mg

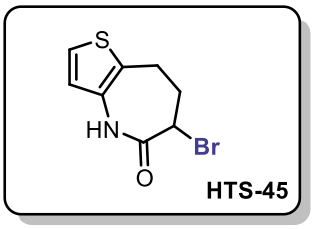
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (dd, *J* = 12.2, 2.0 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.24 (t, *J* = 8.8 Hz, 1H), 4.99 (sxt, *J* = 5.5 Hz, 1H), 3.89 (s, 3H), 3.66 - 3.74 (m, 2H), 3.56 (dd, *J* = 17.6, 10.8 Hz, 1H), 3.22 (dd, *J* = 17.1, 6.8 Hz, 1H)

^{1}H NMR Spectra (without suppression):



LCMS Data: Retention Time: 0.938 min; **MS ES+** ([M+H]$^+$): 287.7.



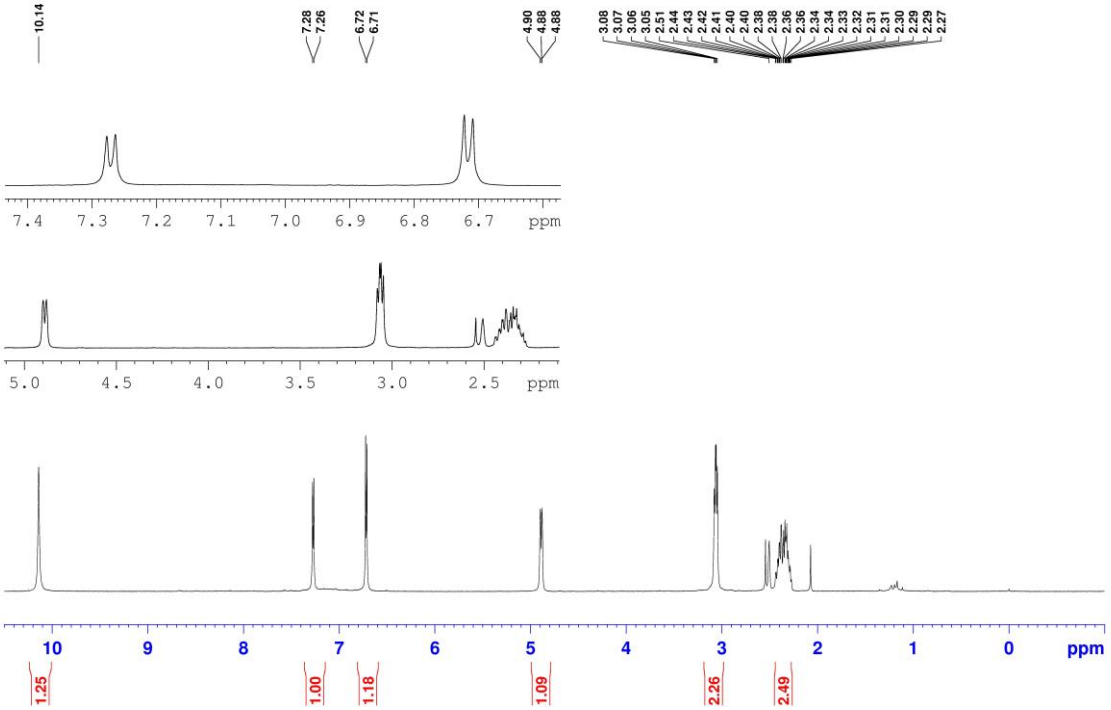


6-bromo-7,8-dihydro-4H-thieno[3,2-b]azepin-5(6H)-one (HTS-45)

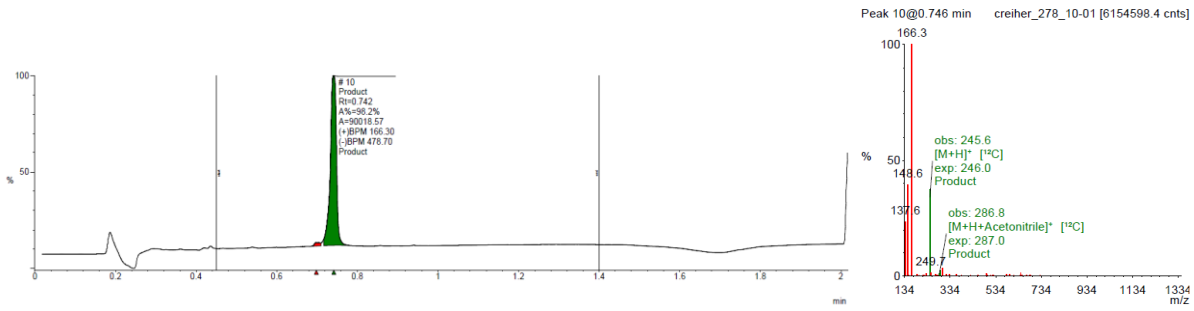
Quantity Obtained: 8.9 mg

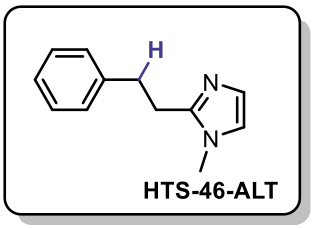
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (br. s., 1H), 7.27 (d, J = 5.1 Hz, 1H), 6.72 (d, J = 5.4 Hz, 1H), 4.89 (d, J = 7.1 Hz, 1H), 3.06 (dd, J = 8.1, 4.9 Hz, 2H), 2.24 - 2.47 (m, 3H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.742 min; **MS ES+** ([M+H]$^+$): 245.6.



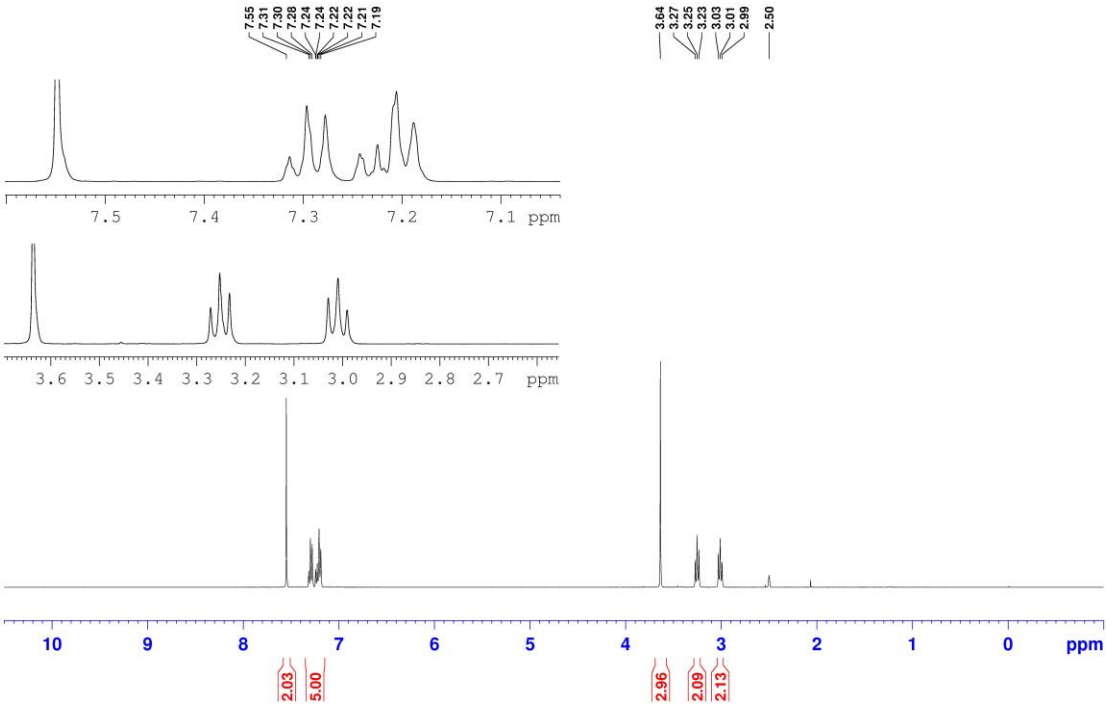


1-methyl-2-phenethyl-1H-imidazole (HTS-46-ALT)

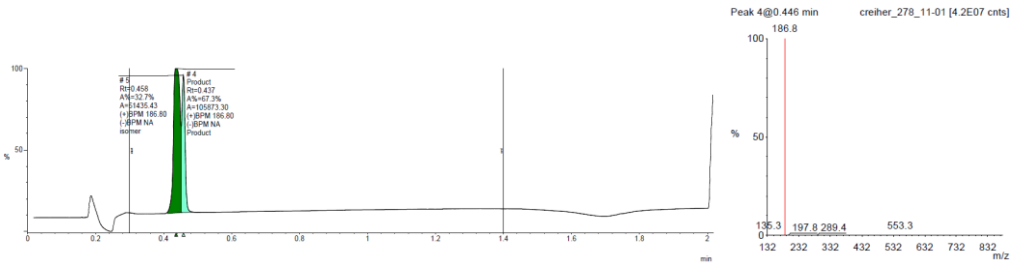
Quantity Obtained: 2.5 mg

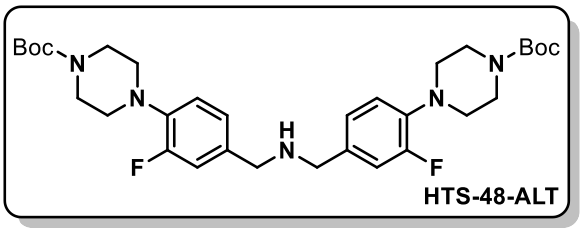
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (s, 2H), 7.30 (t, J = 7.3 Hz, 2H), 7.13 - 7.26 (m, 3H), 3.64 (s, 3H), 3.26 (t, J = 7.8 Hz, 2H), 3.02 (t, J = 7.8 Hz, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.437 min; **MS ES+** ([M+H]$^+$): 186.8.



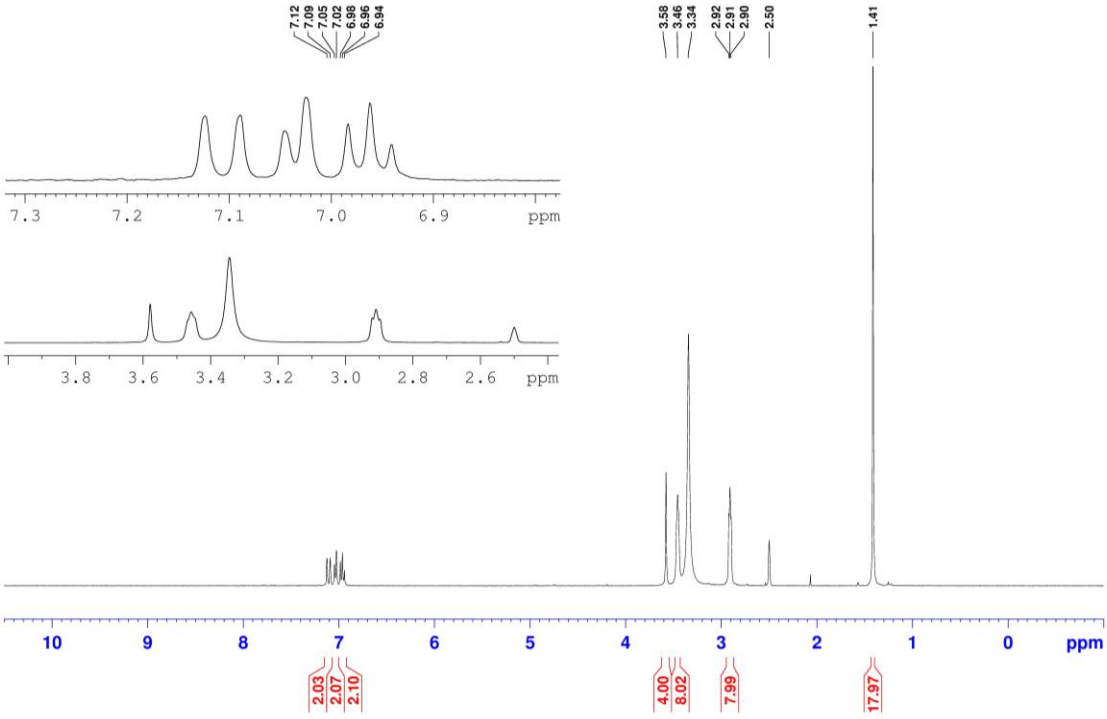


di-*tert*-butyl 4,4'-((azanediylbis(methylene))bis(2-fluoro-4,1-phenylene))bis(piperazine-1-carboxylate) (HTS-48-ALT)

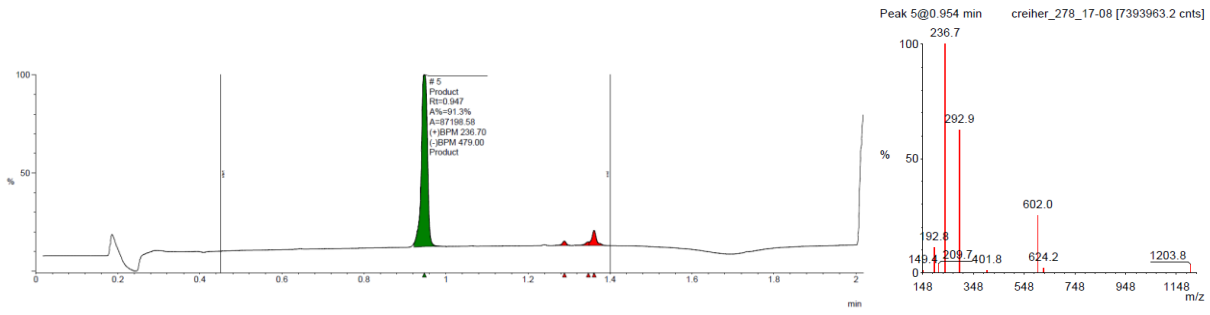
Quantity Obtained: 3.7 mg (91% purity by LCMS)

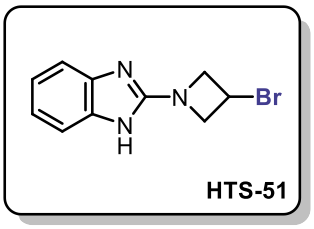
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.11 (d, *J* = 13.7 Hz, 2H), 7.01 - 7.06 (m, 2H), 6.97 (d, *J* = 8.3 Hz, 2H), 3.58 (s, 4H), 3.43 - 3.49 (m, 8H), 2.86 - 2.94 (m, 8H), 1.41 (s, 18H)

^{1}H NMR Spectra (without suppression):



LCMS Data: Retention Time: 0.947 min; **MS ES+** ([M+H]$^+$): 602.0.



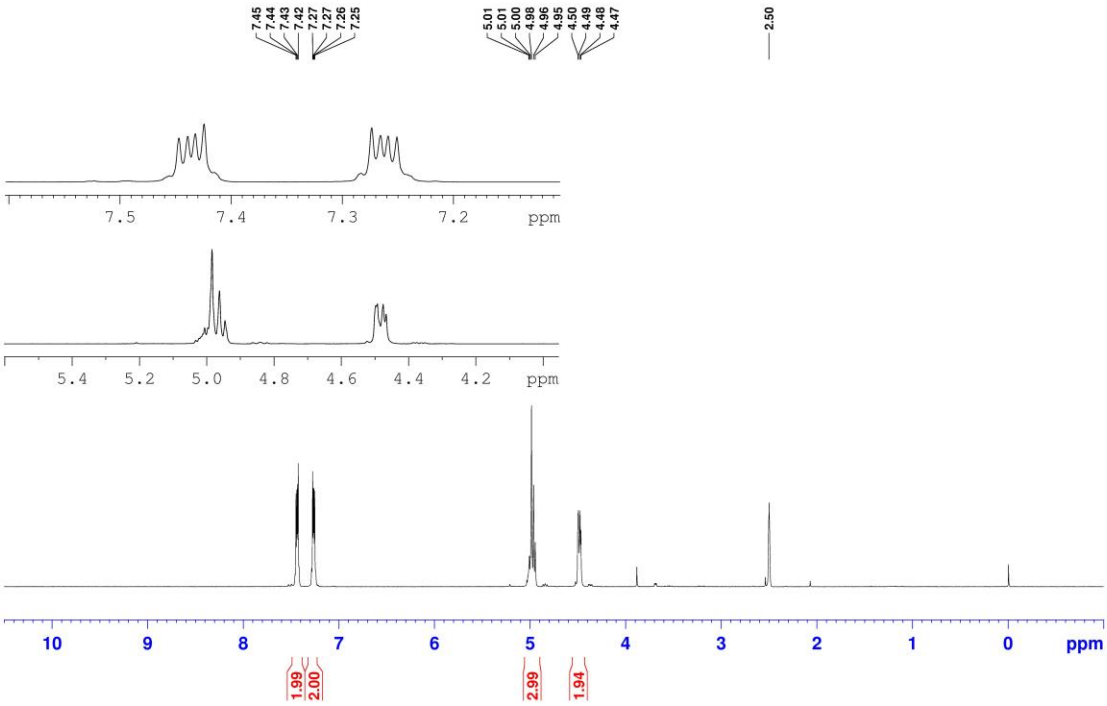


2-(3-bromoazetidin-1-yl)-1H-benzo[d]imidazole (HTS-51)

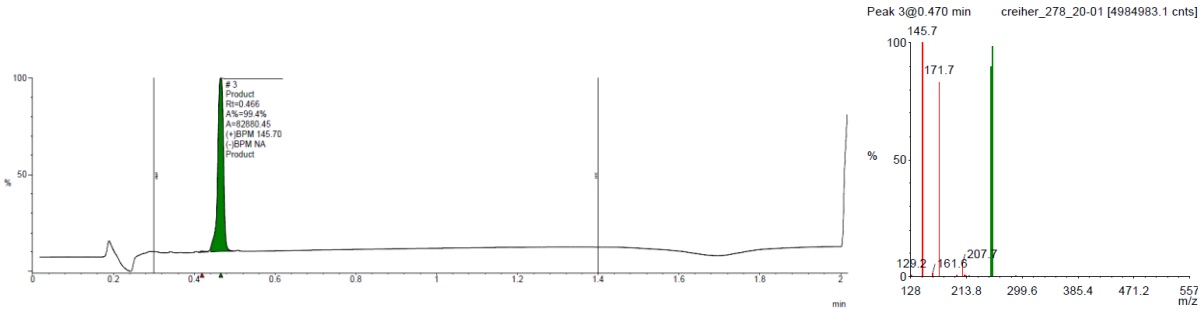
Quantity Obtained: 3.1 mg

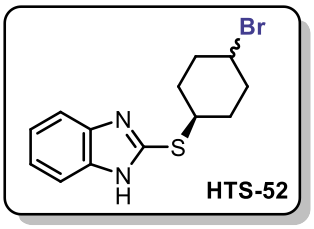
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 - 7.49 (m, 2H), 7.21 - 7.31 (m, 2H), 4.93 - 5.05 (m, 3H), 4.45 - 4.52 (m, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.466 min; **MS ES+** ([M+H]$^+$): 265.5.



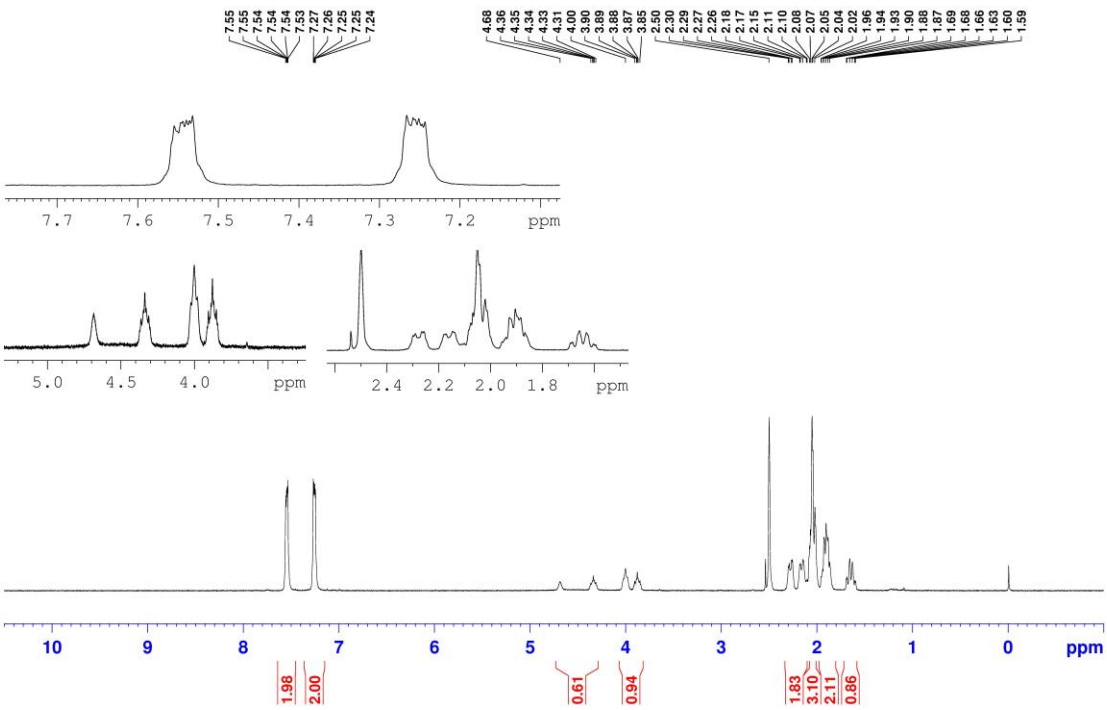


2-((4-bromocyclohexyl)thio)-1H-benzo[d]imidazole (HTS-52)

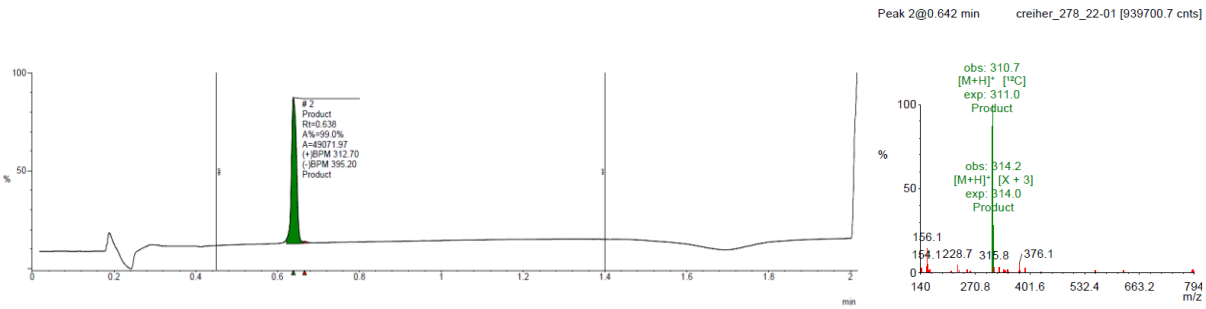
Quantity Obtained: 10.4 mg (*d.r.*: ~1.5:1 *trans:cis*)

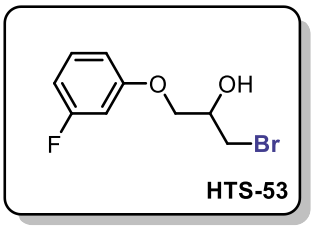
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 - 7.61 (m, 2H), 7.18 - 7.33 (m, 2H), 4.63 - 4.74 (m, 1H, *cis*), 4.34 (tt, *J* = 10.6, 3.7 Hz, 1H, *cis*), 3.94 - 4.05 (m, 1H, *trans*), 3.88 (tt, *J* = 10.8, 3.7 Hz, 1H, *trans*), 2.28 (dq, *J* = 13.2, 3.2 Hz, 1H), 2.16 (d, *J* = 10.5 Hz, 1H), 1.99 - 2.11 (m, 3H), 1.84 - 1.97 (m, 2H), 1.65 (qd, *J* = 12.0, 2.7 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.638 min; **MS ES+** ([M+H]$^+$): 310.7.



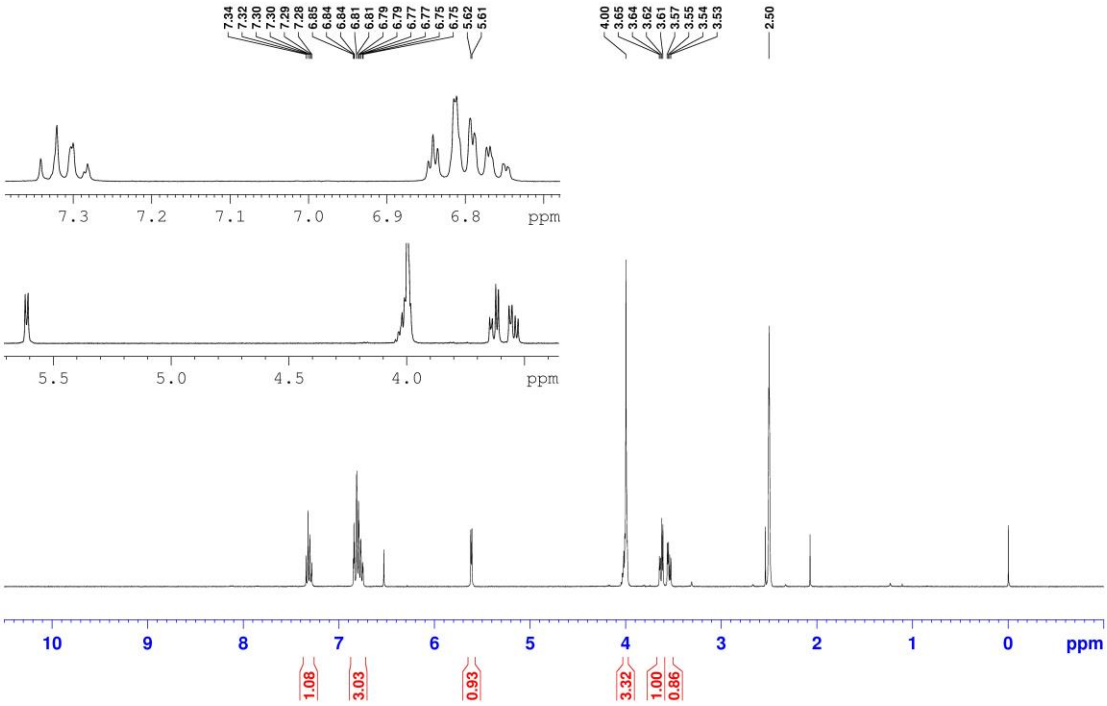


1-bromo-3-(3-fluorophenoxy)propan-2-ol (HTS-53)

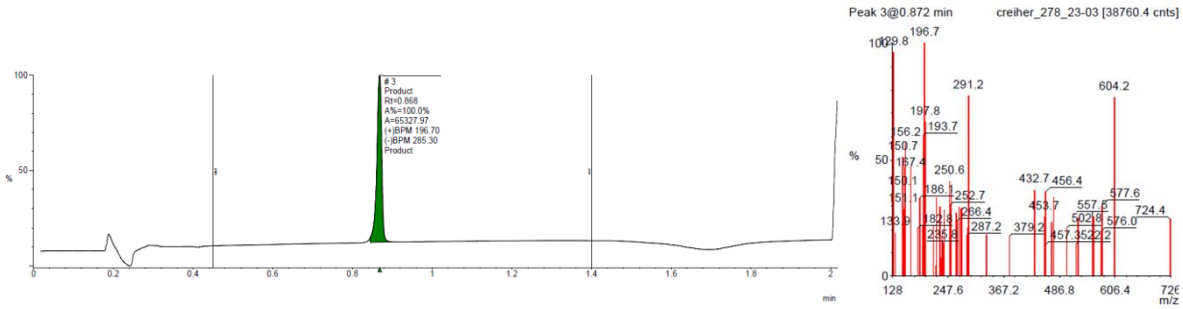
Quantity Obtained: 2.3 mg

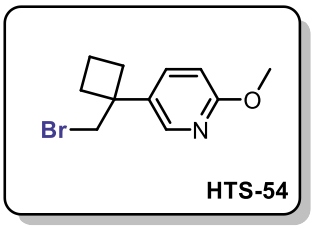
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.25 - 7.37 (m, 1H), 6.71 - 6.88 (m, 3H), 5.61 (d, J = 4.9 Hz, 1H), 3.96 - 4.05 (m, 3H), 3.63 (dd, J = 10.3, 4.4 Hz, 1H), 3.55 (dd, J = 10.3, 5.1 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.868 min; **MS ES+** ([M+H+MeCN]$^+$): 291.2.



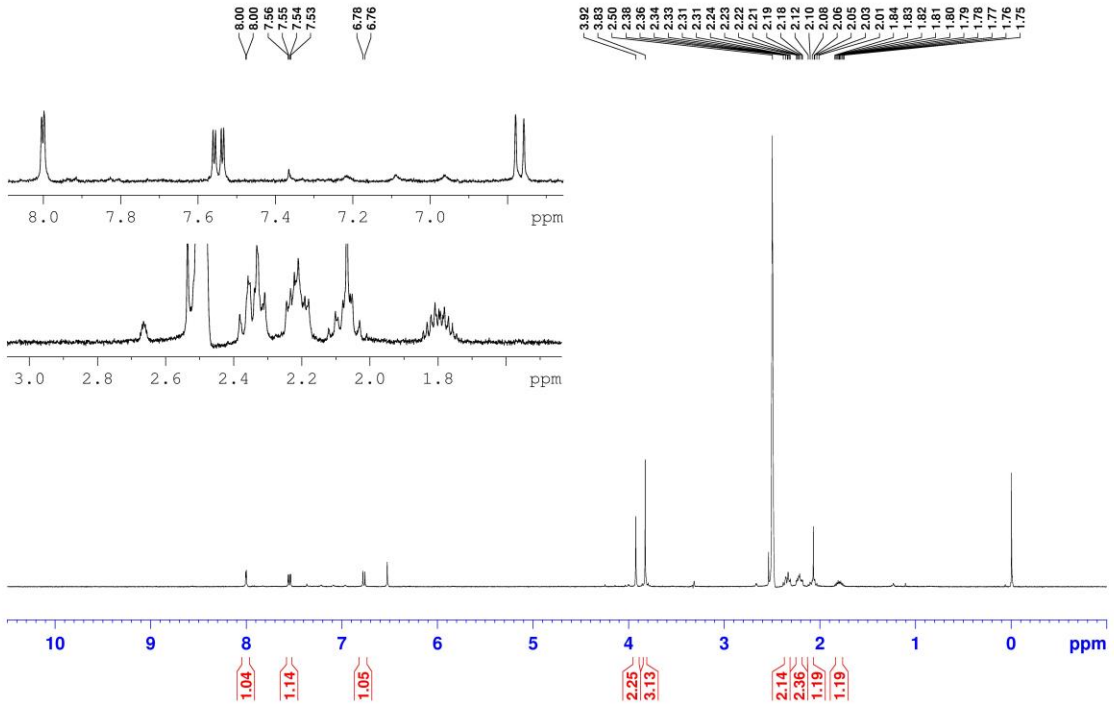


5-(1-(bromomethyl)cyclobutyl)-2-methoxypyridine (HTS-54)

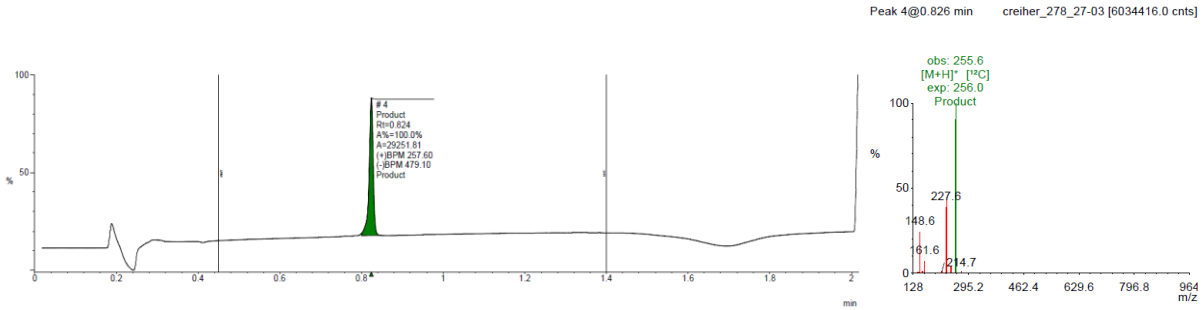
Quantity Obtained: 3.5 mg

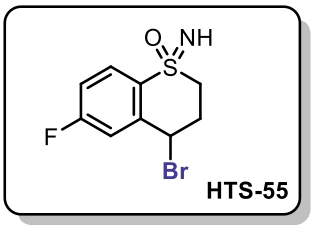
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.6, 2.4 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 3.93 (s, 2H), 3.83 (s, 3H), 2.30 - 2.40 (m, 2H), 2.16 - 2.26 (m, 2H), 2.03 - 2.13 (m, 1H), 1.73 - 1.87 (m, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.824 min; **MS ES+** ([M+H]$^+$): 255.6.



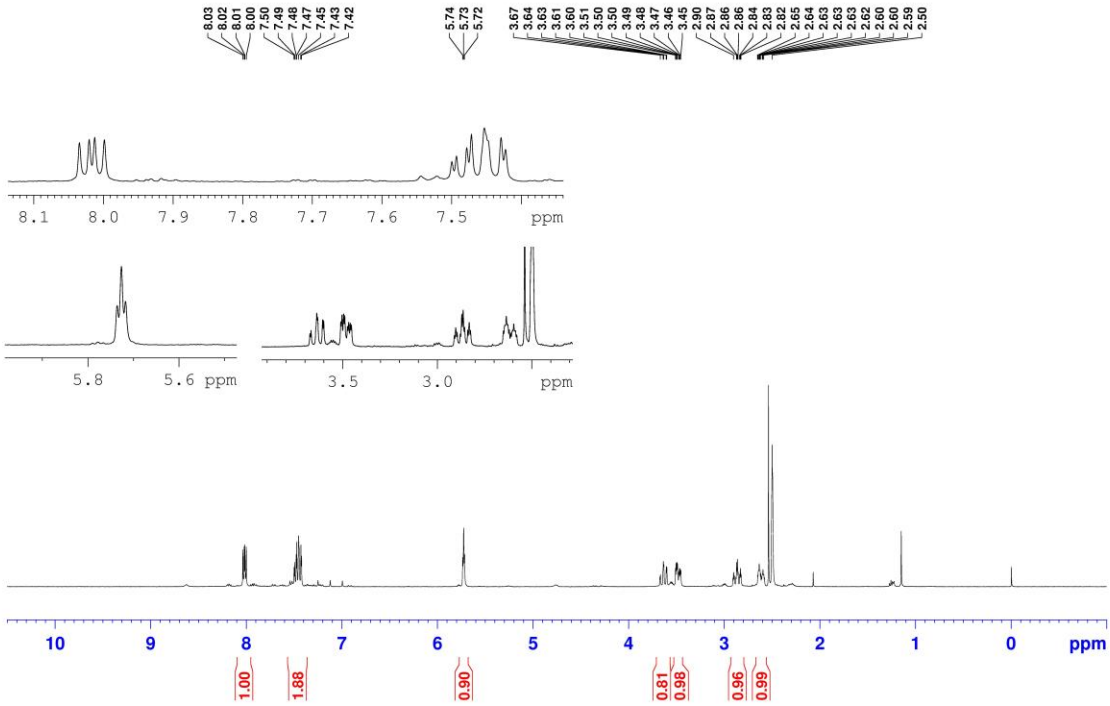


4-bromo-6-fluoro-1-iminothiochroman 1-oxide (HTS-55)

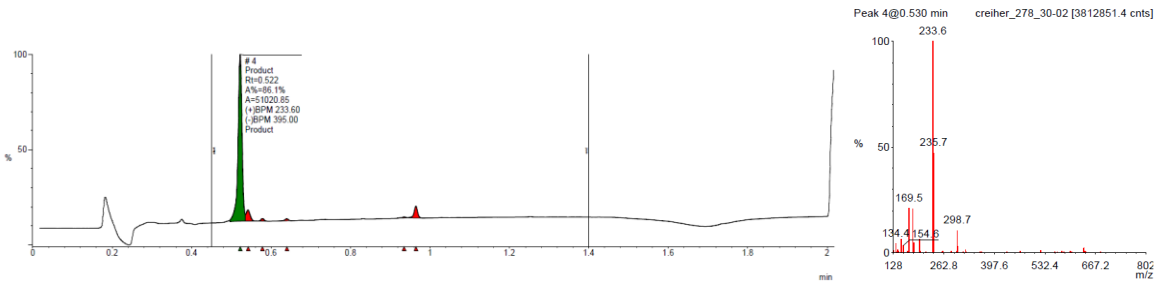
Quantity Obtained: 3.0 mg (86% purity by LCMS)

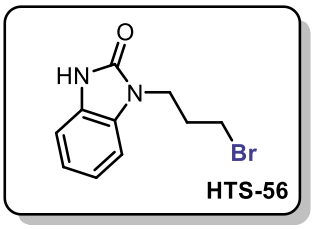
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (dd, J = 8.8, 5.6 Hz, 1H), 7.47 (ddd, J = 19.0, 8.6, 2.7 Hz, 2H), 5.73 (t, J = 3.8 Hz, 1H), 3.64 (td, J = 13.5, 2.4 Hz, 1H), 3.49 (ddd, J = 14.2, 5.6, 2.2 Hz, 1H), 2.87 (ddt, J = 15.7, 12.7, 2.9Hz, 1H), 2.62 (dtt, J=15.9, 3.7, 2.7Hz, 1 H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.522 min; **MS ES+** ([M+Na]$^+$): 298.7



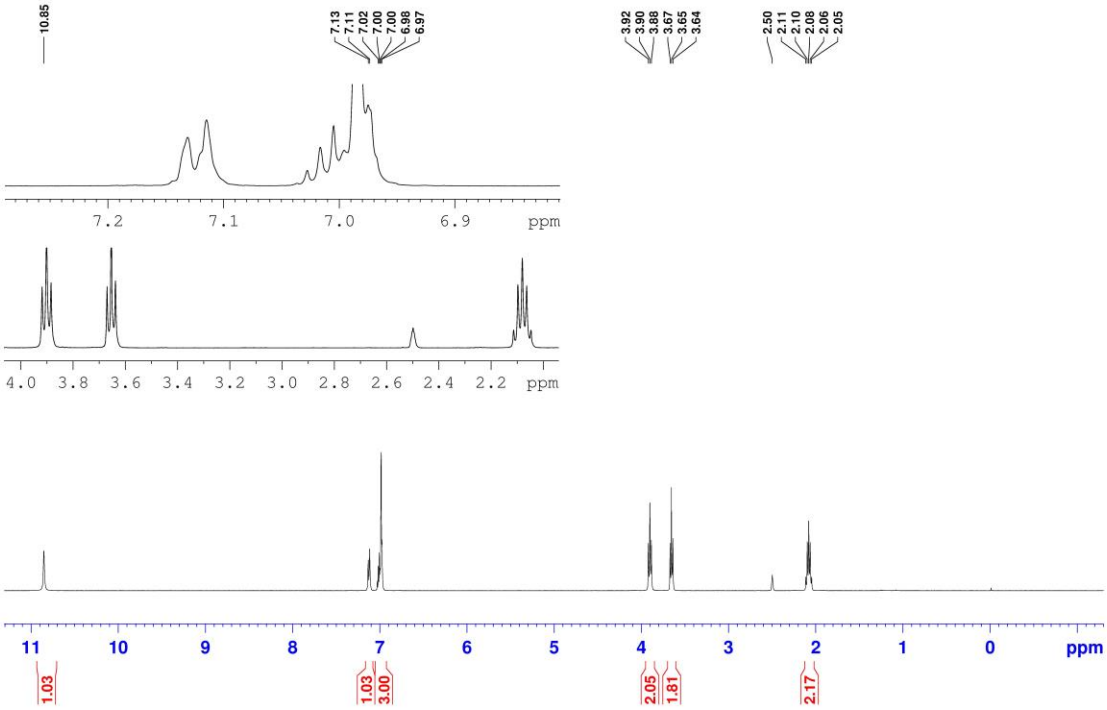


1-(3-bromopropyl)-1H-benzo[d]imidazol-2(3H)-one (HTS-56)

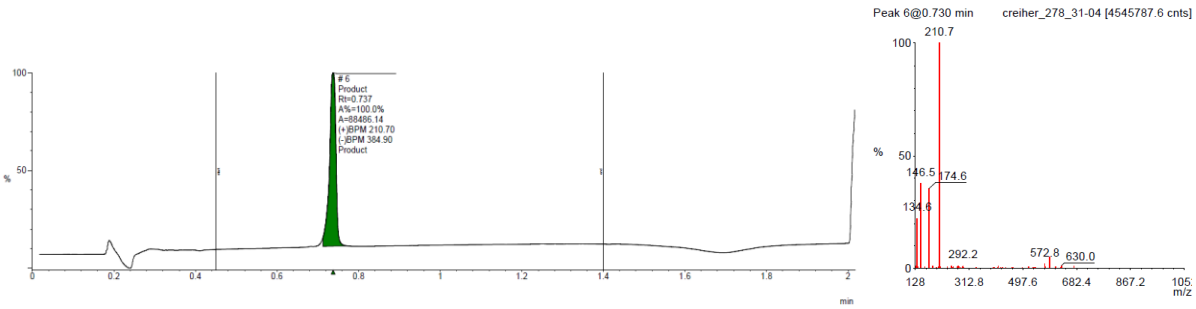
Quantity Obtained: 2.2 mg

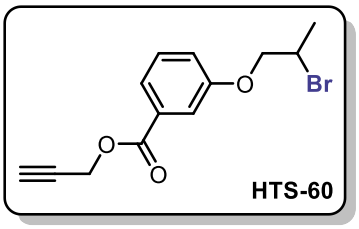
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.86 (s, 1H), 7.13 (d, J = 6.6 Hz, 1H), 6.93 - 7.06 (m, 3H), 3.91 (t, J = 6.8 Hz, 2H), 3.67 (t, J = 6.5 Hz, 2H), 2.09 (quin, J = 6.7 Hz, 2H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.737 min; **MS ES+** ([M-Br]$^+$): 174.6.



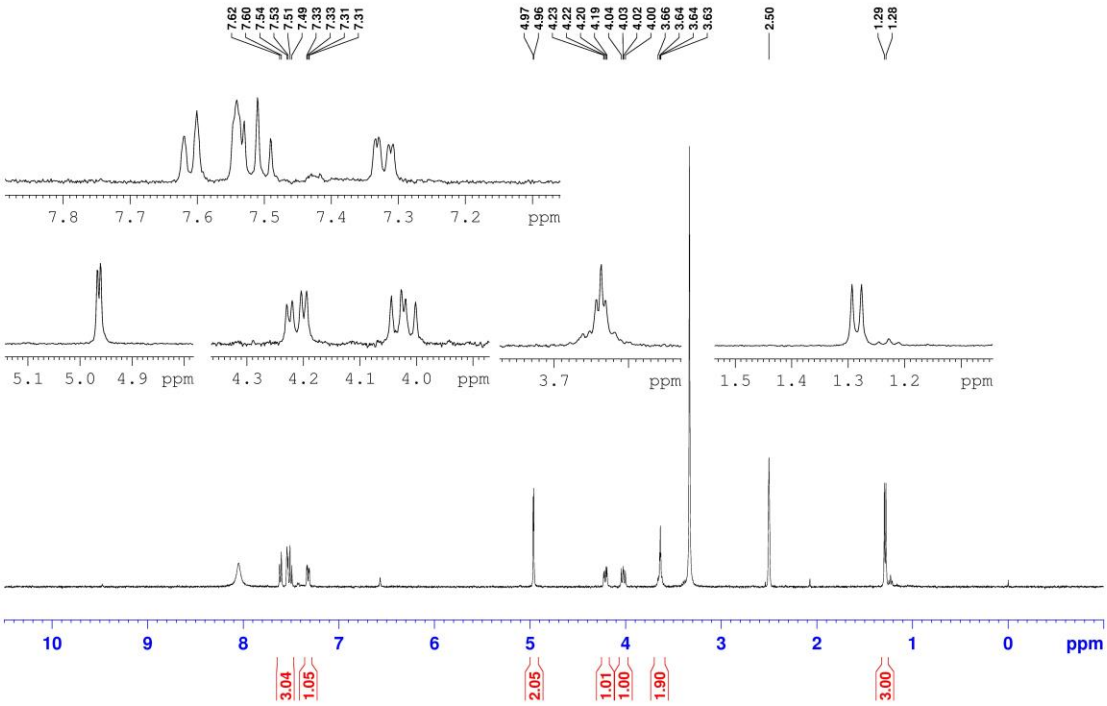


prop-2-yn-1-yl 3-(2-bromopropoxy)benzoate (HTS-60)

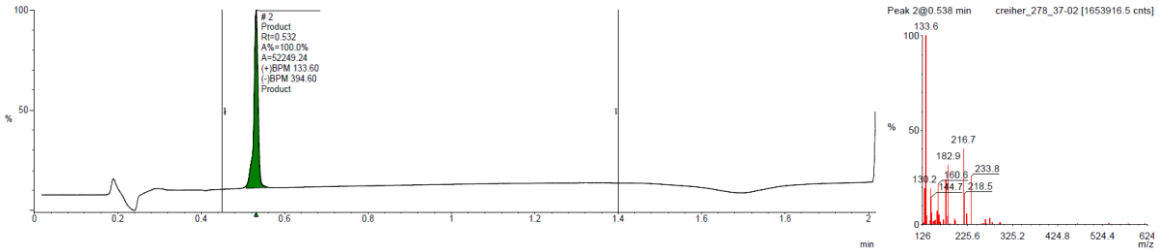
Quantity Obtained: 5.9 mg

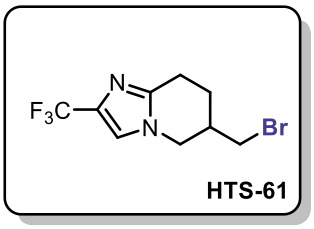
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 7.6 Hz, 1H), 7.48 - 7.56 (m, 2H), 7.32 (dd, J = 8.1, 2.0 Hz, 1H), 4.97 (d, J = 2.4 Hz, 2H), 4.21 (dd, J = 10.1, 3.8 Hz, 1H), 4.03 (dd, J = 10.0, 7.1 Hz, 1H), 3.57 - 3.70 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H)

^{1}H NMR Spectra (without suppression):



LCMS Data: Retention Time: 0.532 min; **MS ES+** ([M-Br]$^+$): 216.7.



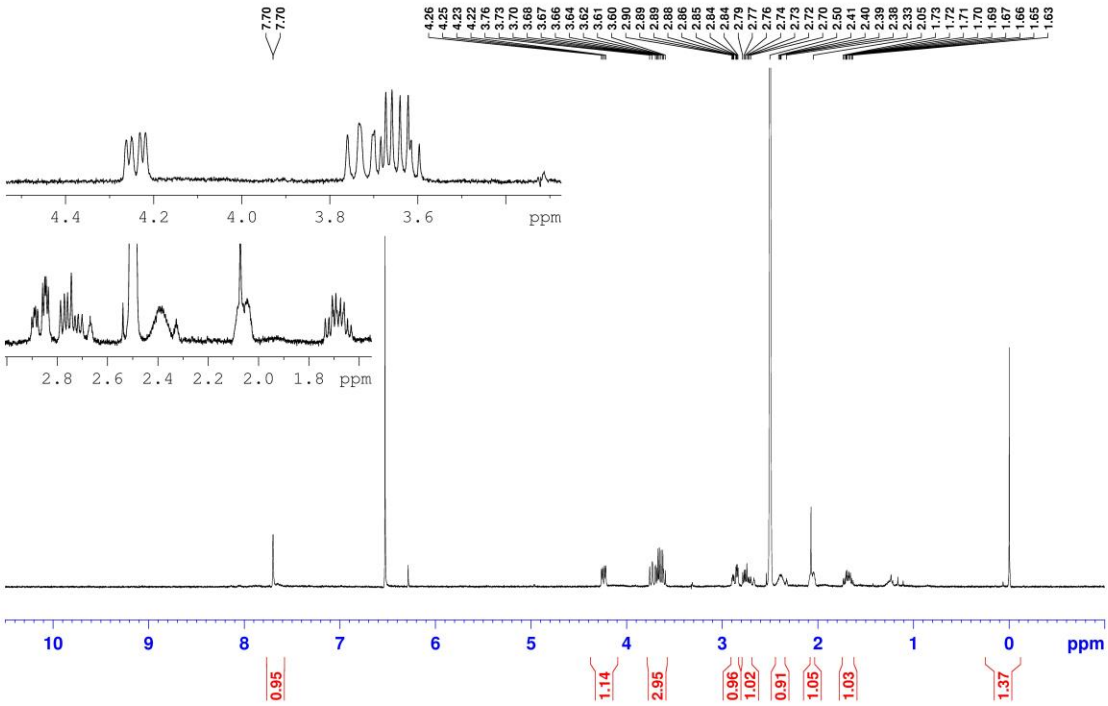


6-(bromomethyl)-2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (HTS-61)

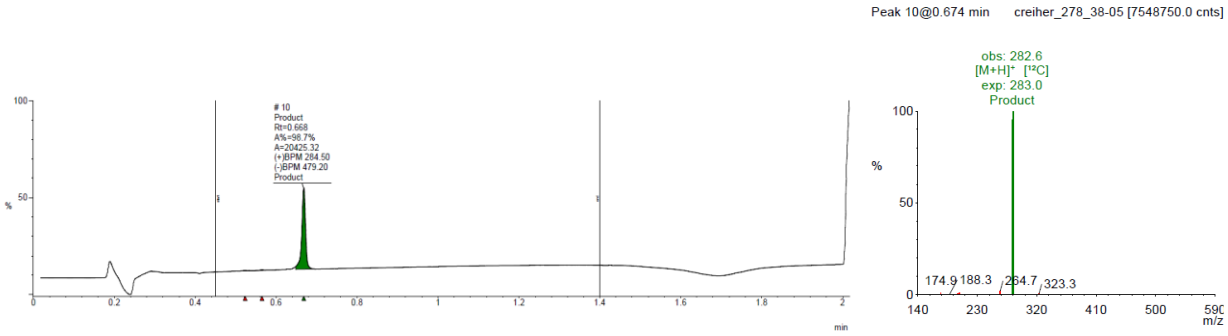
Quantity Obtained: 2.7 mg

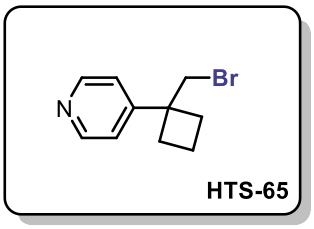
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (s, 1H), 4.24 (dd, J = 12.5, 5.6 Hz, 1H), 3.57 - 3.78 (m, 3H), 2.87 (dq, J = 16.9, 2.2 Hz, 1H), 2.74 (s, 1H), 2.34 - 2.44 (m, 1H), 1.68 (qd, J = 11.5, 5.6 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.668 min; **MS ES+** ([M+H]$^+$): 282.6.



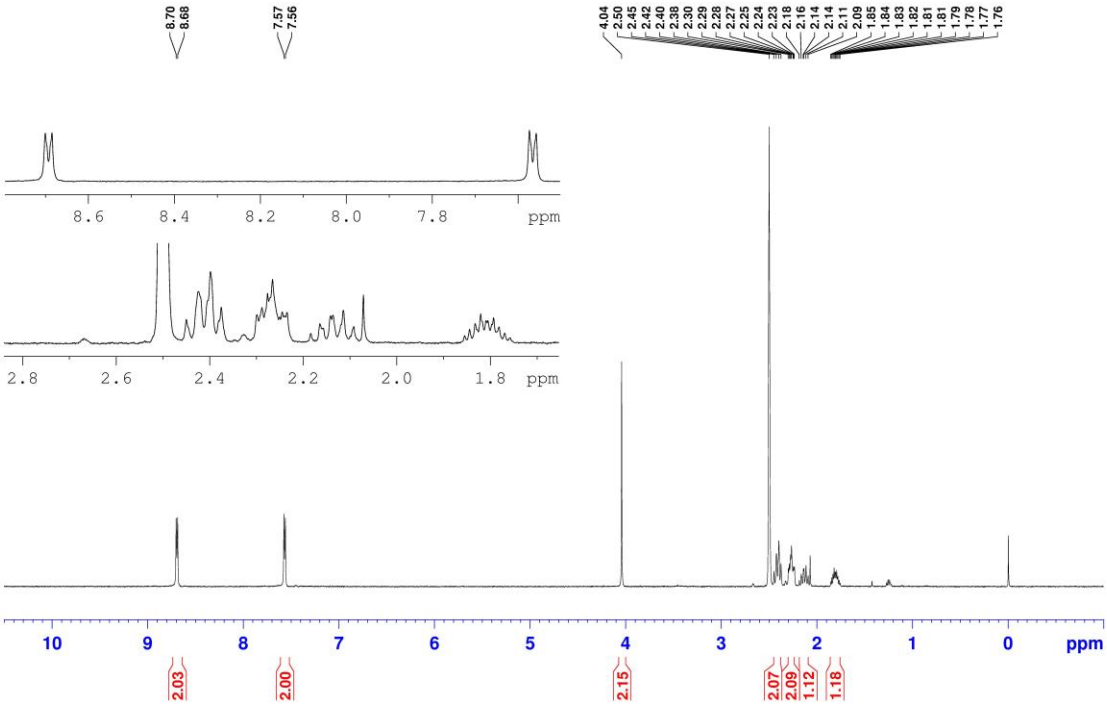


4-(1-(bromomethyl)cyclobutyl)pyridine (HTS-65)

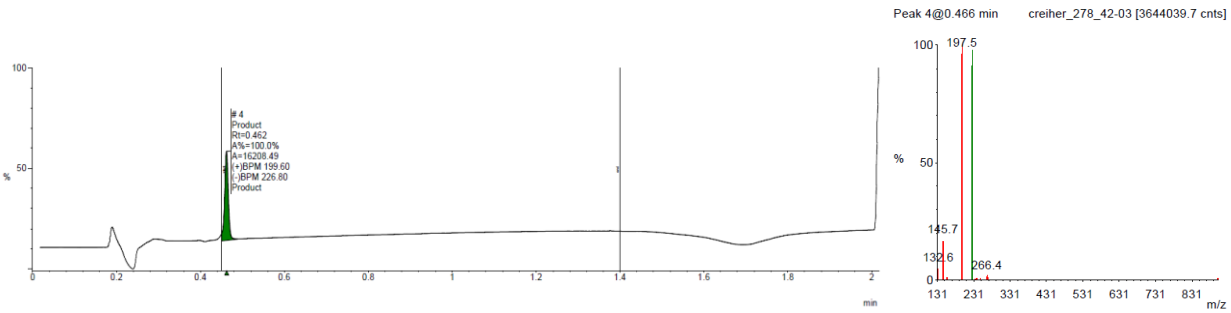
Quantity Obtained: 2.1 mg

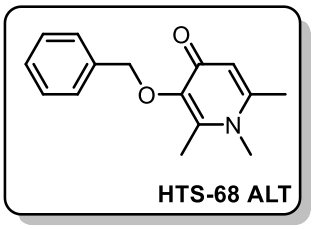
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 6.4 Hz, 2H), 7.57 (d, J = 6.4 Hz, 2H), 4.04 (s, 2H), 2.37 - 2.46 (m, 2H), 2.22 - 2.31 (m, 2H), 2.08 - 2.19 (m, 1H), 1.81 (dt, J = 10.9, 4.7 Hz, 1H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.462 min; **MS ES+** ([M+H+MeCN]$^+$): 266.4.



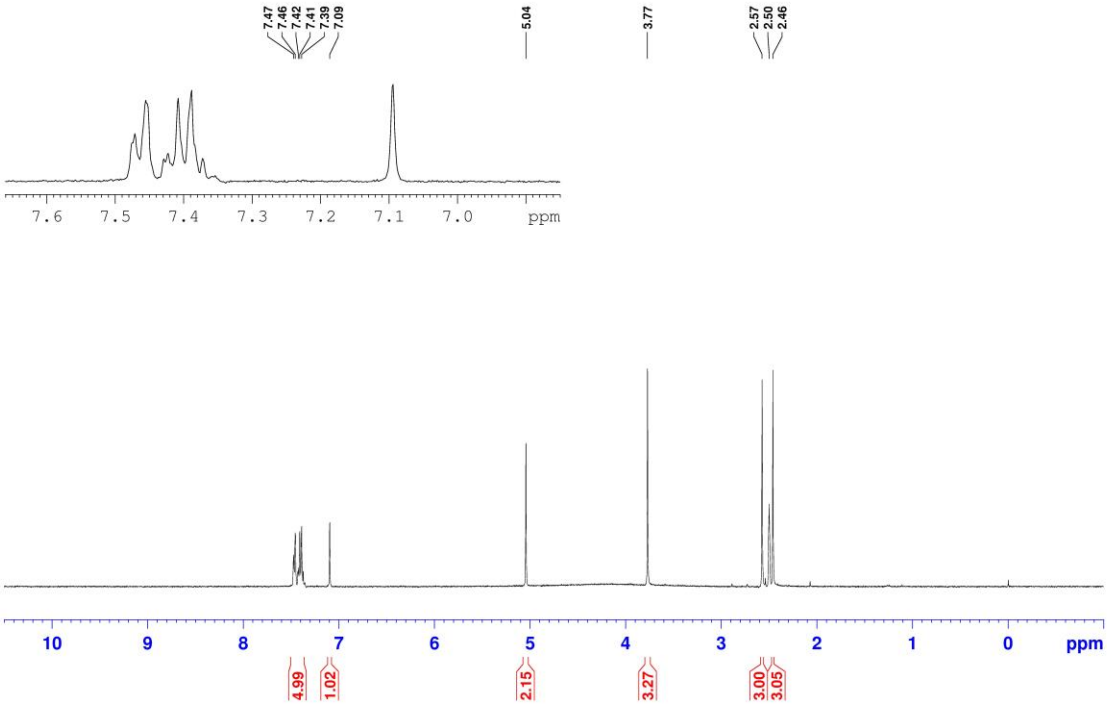


3-(benzyloxy)-1,2,6-trimethylpyridin-4(1H)-one (HTS-68 ALT)

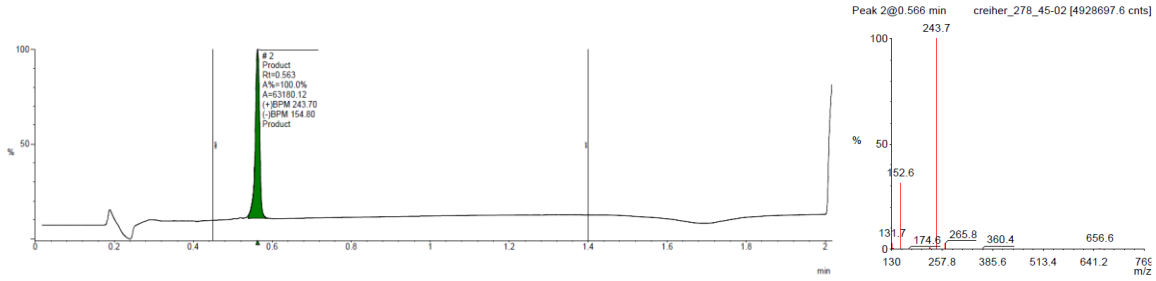
Quantity Obtained: 6.9 mg

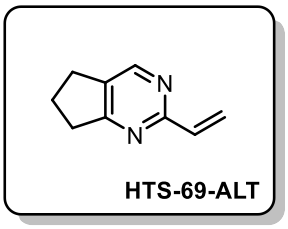
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 - 7.49 (m, 2H), 7.36 - 7.43 (m, 3H), 7.09 (s, 1H), 5.04 (s, 2H), 3.77 (s, 3H), 2.57 (s, 3H), 2.46 (s, 3H)

^{1}H NMR Spectra (with suppression):



LCMS Data: Retention Time: 0.563 min; **MS ES+** ([M+H]$^+$): 243.7.



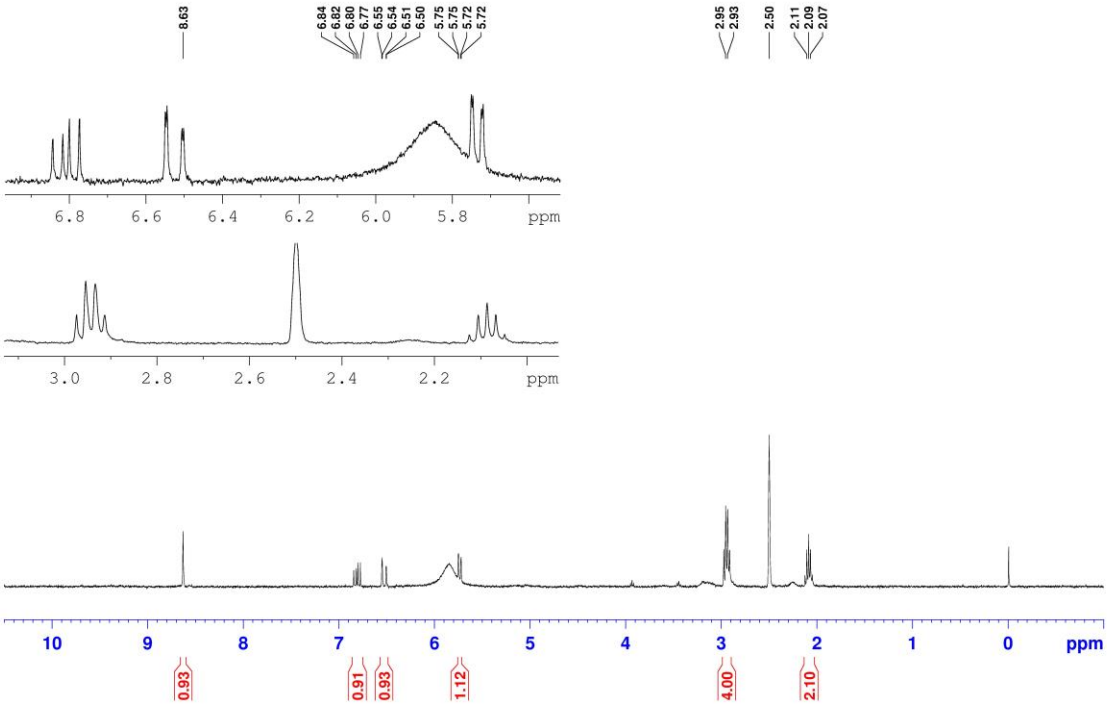


2-vinyl-6,7-dihydro-5*H*-cyclopenta[d]pyrimidine (HTS-69-ALT)

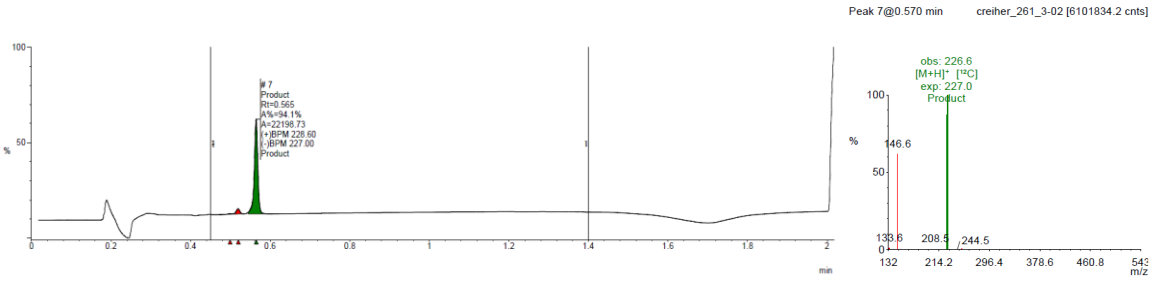
Quantity Obtained: 5.2 mg

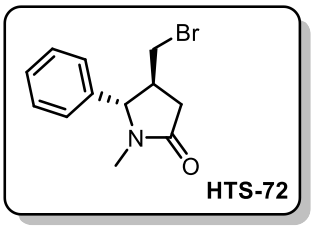
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 6.81 (dd, J = 17.4, 10.5 Hz, 1H), 6.53 (dd, J = 17.4, 1.7 Hz, 1H), 5.74 (dd, J = 10.6, 1.8 Hz, 1H), 2.95 (q, J = 8.2 Hz, 4H), 2.09 (quin, J = 7.6 Hz, 2H)

^{1}H NMR Spectra (without suppression):



LCMS Data: Retention Time: 0.565 min; **MS ES+** ([M+H]$^+$): 146.6.



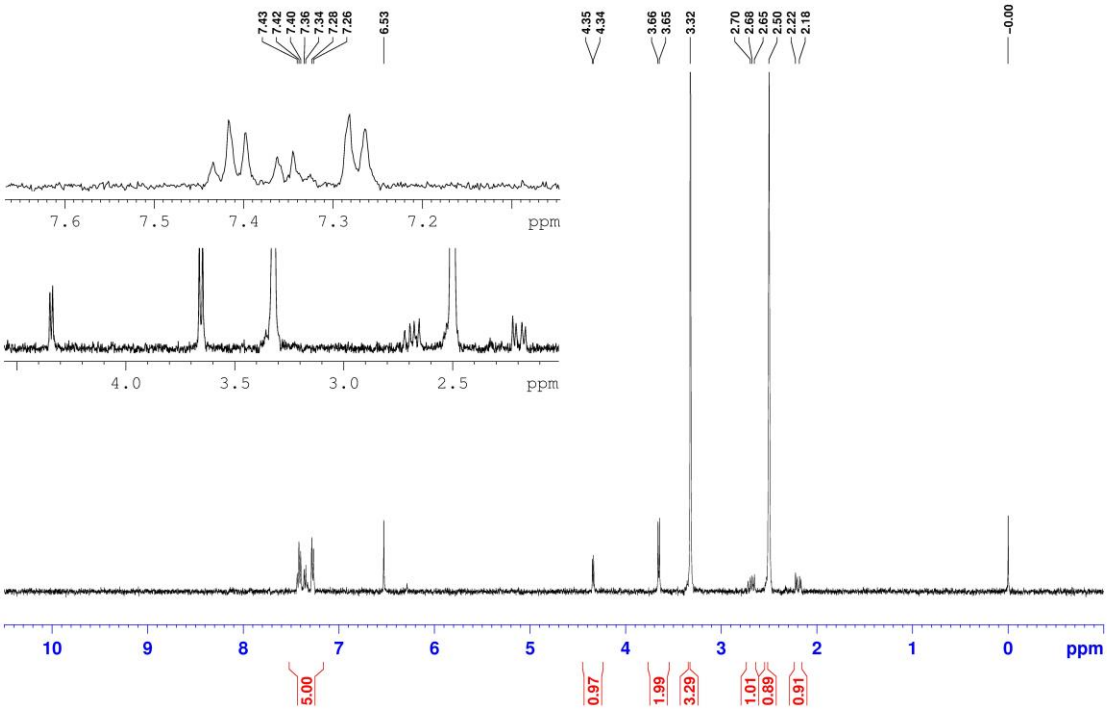


***trans*-4-(bromomethyl)-1-methyl-5-phenylpyrrolidin-2-one (HTS-72)**

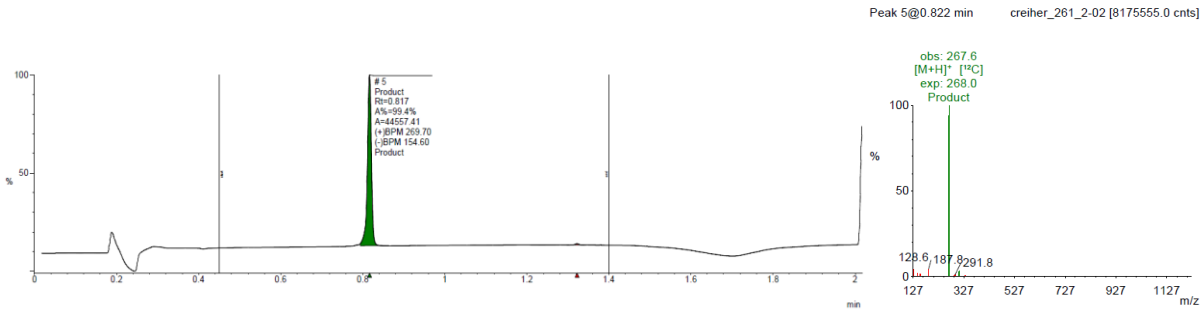
Quantity Obtained: 9.4 mg

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 6.4 Hz, 1H), 7.27 (d, J = 6.8 Hz, 2H), 4.34 (d, J = 4.9 Hz, 1H), 3.66 (d, J = 6.4 Hz, 2H), 3.32 (s, 3H), 2.69 (dd, J = 17.1, 8.8 Hz, 1H), 2.45 - 2.55 (m, 1H), 2.20 (dd, J = 17.1, 6.4 Hz, 1H)

^{1}H NMR Spectra (with suppression):

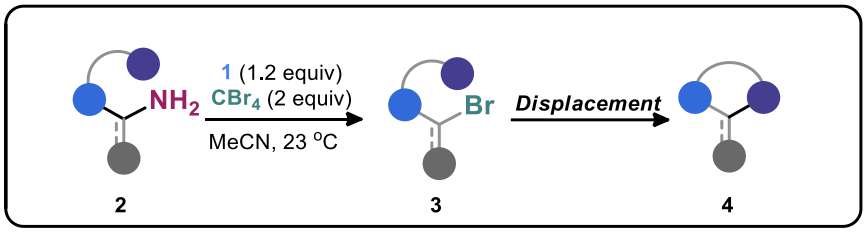


LCMS Data: Retention Time: 0.817 min; **MS ES+** ([M+H]$^+$): 267.6.

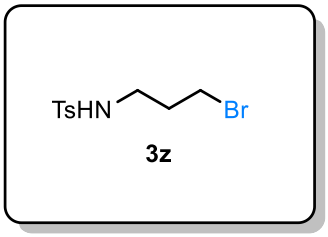


IV. Tandem Reactions Involving Deaminative Bromination

VI.A. Bromination/Cyclization



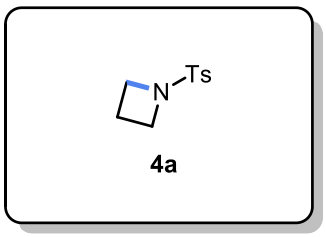
N-(3-bromopropyl)-4-methylbenzenesulfonamide (3z)



Synthesized according to **General Procedure IIA** from *N*-(3-aminopropyl)-4-methylbenzenesulfonamide (70 mg, 0.31 mmol). The title compound was obtained in 75% yield (67 mg) after purification by silica gel chromatography. R_f = 0.25 (silica gel, 30% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 4.70 (t, *J* = 6.4 Hz, 1H), 3.42 (t, *J* = 6.3 Hz, 2H), 3.11 (q, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.03 (p, *J* = 6.4 Hz, 2H). Spectroscopic data are in agreement with the literature.[31]

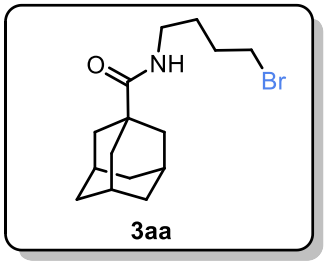
1-tosylazetidine (4a)



To a stirred solution of *N*-(3-bromopropyl)-4-methylbenzenesulfonamide (50 mg, 0.71 mmol, 1.0 equiv.) in DMF (1 mL) at 23 °C was added NaO-*t*-Bu (49 mg, 0.51 mmol, 3.0 equiv.), and the reaction mixture was stirred at same temperature. After 2 h, the reaction mixture was quenched by saturated aq. NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained in 82% yield (29.6 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 40% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.61 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 3.77 (t, *J* = 7.6 Hz, 4H), 2.46 (s, 3H), 2.06 (p, *J* = 7.6 Hz, 2H). Spectroscopic data are in agreement with the literature.[32]

(3*r*,5*r*,7*r*)-*N*-(4-bromobutyl)adamantane-1-carboxamide (3aa)



3aa

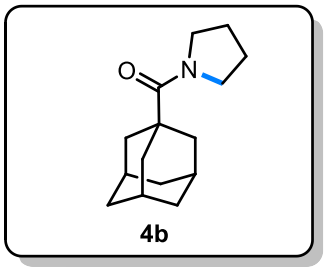
Synthesized according to **General Procedure IIA** from (3*r*,5*r*,7*r*)-*N*-(4-aminobutyl)adamantane-1-carboxamide (100 mg, 0.4 mmol). The title compound was obtained in 72% yield (90 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 50% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (s, 1H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.29 (td, *J* = 7.0, 5.8 Hz, 2H), 2.06 (p, *J* = 3.2 Hz, 3H), 1.93 – 1.79 (m, 8H), 1.77 – 1.60 (m, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 40.7, 39.4, 38.4, 36.6, 33.5, 30.1, 28.4, 28.2.

HRMS (ESI-TOF) calcd 314.1114 and 316.1094 for $C_{15}H_{25}BrNO^+$ $[M+H]^+$ 314.1119, found 316.1101.

((3*r*,5*r*,7*r*)-adamantan-1-yl)(pyrrolidin-1-yl)methanone (4b)

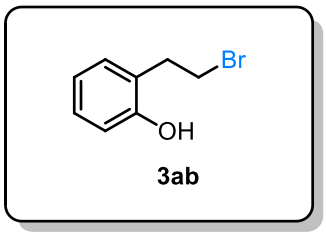


4b

To a stirred solution of (3*r*,5*r*,7*r*)-*N*-(4-bromobutyl)adamantane-1-carboxamide (80 mg, 0.25 mmol, 1.0 equiv.) in DMF (1 mL) at 23 °C was added NaO-*t*-Bu (49 mg, 0.51 mmol, 3.0 equiv.), and the reaction mixture was stirred at same temperature. After 2 h, the reaction mixture was quenched by saturated aq. NH_4Cl (3 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained in 87% yield (51.6 mg) after purification by silica gel chromatography. R_f = 0.4 (silica gel, 50% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.57 (br s, 4H), 2.05-1.93 (m, 9H), 1.82 (br s, 4H), 1.71 (br s, 6H). Spectroscopic data are in agreement with the literature.[33]

2-(2-bromoethyl)phenol (3ab)

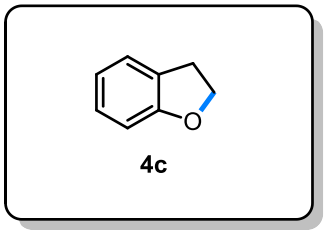


3ab

Synthesized according to **General Procedure IIA** from 2-(2-aminoethyl)phenol (70 mg, 0.51 mmol). The title compound was obtained in 65% yield (66.2 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 10% EtOAc in hexanes).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-6.99 (m, 2H), 6.91 (td, *J* = 7.4, 1.2 Hz, 1H), 6.75 (dd, *J* = 8.4, 1.3 Hz, 1H), 3.62 (t, *J* = 7.6 Hz, 2H), 3.20 (t, *J* = 7.6 Hz, 2H). Spectroscopic data are in agreement with the literature.[34]

2,3-dihydrobenzofuran (4c)

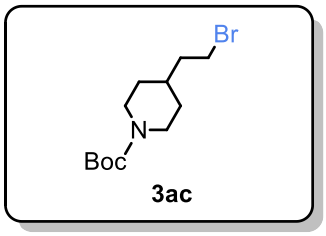


4c

To a stirred solution of 2-(2-bromoethyl)phenol (50 mg, 0.25 mmol, 1.0 equiv.) in DMF (1 mL) at 23 °C was added K_2CO_3 (103 mg, 0.75 mmol, 3.0 equiv.), NaI (27 mg, 0.25 mmol, 1.0 equiv.) and the reaction mixture was heated to 60 °C. After 8 h, the reaction mixture was allowed to cool to 23 °C and quenched by the addition of cold water (3 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained in 77% yield (22.4 mg) after purification by silica gel chromatography. R_f = 0.6 (silica gel, 10% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dq, *J* = 7.5, 1.3 Hz, 1H), 7.10 (tdd, *J* = 8.1, 1.5, 0.7 Hz, 1H), 6.84 (td, *J* = 7.4, 1.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 4.56 (t, *J* = 8.7 Hz, 2H), 3.21 (t, *J* = 8.7 Hz, 2H). Spectroscopic data are in agreement with the literature.[35]

4-(2-bromoethyl)piperidine (3ac)

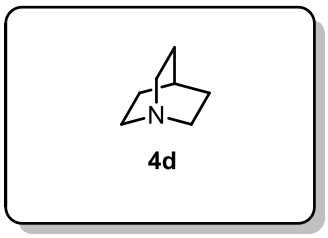


3ac

Synthesized according to **General Procedure IIA** from *tert*-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (80 mg, 0.35 mmol). The title compound was obtained in 73% yield (74.4 mg) after purification by silica gel chromatography. R_f = 0.25 (silica gel, 10% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (br s, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.67 (t, *J* = 12.7 Hz, 2H), 1.77 (q, *J* = 6.8 Hz, 2H), 1.71 – 1.56 (m, 3H), 1.42 (s, 9H), 1.07 (dtd, *J* = 13.5, 11.8, 4.3 Hz, 2H). Spectroscopic data are in agreement with the literature.[36]

Quinuclidine (4d)



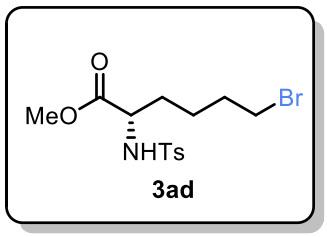
4d

Step I: To a stirred solution of *tert*-butyl 4-(2-bromoethyl)piperidine-1-carboxylate (50 mg, 0.17 mmol, 1.0 equiv.) in CH_2Cl_2 (1.5 mL) at 0 °C was added trifluoroacetic acid (0.13 mL, 0.17 mmol, 10.0 equiv.). After 5 minutes, reaction was warmed to 23 °C and stirred for 2 h. After completion of reaction, reaction mixture was concentrated in vacuo to afford corresponding amine trifluoroacetic acid salt, which was advanced to next step without further purification.

Step II: To a stirred solution of above crude compound in water (0.2 mL) and EtOAc (2 mL) at 0 °C was heated at 70 °C and 20 wt% sodium hydroxide aqueous solution (prepared from 41 mg sodium hydroxide, 1 mmol, 6 equiv.) was added and reacted at 70 °C for 6 hours. After completion of the reaction, volatiles were removed under vacuo and crude product submitted for ^{1}H NMR spectroscopy confirmed the formation of title compound in 72% NMR yield (for 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 – 2.8 (m, 6H), 1.74 (p, *J* = 3.2 Hz, 1H), 1.54 (dq, *J* = 8.4, 3.5 Hz, 6H). Spectroscopic data are in agreement with the literature.[37]

Methyl (*S*)-6-bromo-2-((4-methylphenyl)sulfonamido)hexanoate (3ad)



3ad

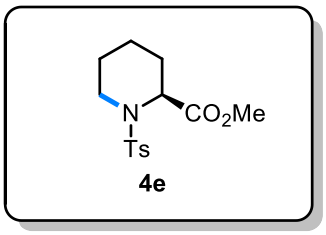
Synthesized according to **General Procedure IIA** from methyl tosyl-L-lysinate (100 mg, 0.32 mmol). The title compound was obtained in 76% yield (91 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 25% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.67 (m, 2H), 7.32 – 7.27 (m, 2H), 5.23 (d, *J* = 9.1 Hz, 1H), 3.90 (ddd, *J* = 9.1, 7.6, 5.1 Hz, 1H), 3.50 (s, 3H), 3.33 (t, *J* = 6.7 Hz, 2H), 2.41 (s, 3H), 1.84 – 1.57 (m, 4H), 1.52 – 1.41 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 143.9, 136.7, 129.8, 127.4, 55.5, 52.6, 33.1, 32.5, 32.0, 23.6, 21.6.

HRMS (ESI-TOF) calcd 378.0369 and 380.0349 for $C_{14}H_{21}BrNO_4S^+$ $[M+H]^+$, found 378.0373 and 380.0353.

Methyl (*S*)-1-tosylpiperidine-2-carboxylate (4e)

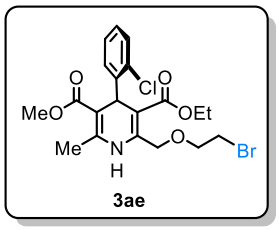


4e

To a stirred solution of methyl (*S*)-6-bromo-2-((4-methylphenyl)sulfonamido)hexanoate (80 mg, 0.21 mmol, 1.0 equiv.) in DMF (0.5 mL) at 23 °C was added K_2CO_3 (88 mg, 0.63 mmol, 3.0 equiv.), and the reaction mixture was heated to 70 °C. After 8 h, the reaction mixture was allowed to cool to 23 °C and quenched by the addition of cold water (3 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained in 85% yield (53.5 mg) after purification by silica gel chromatography. R_f = 0.5 (silica gel, 20% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.76 – 4.69 (m, 1H), 3.79 – 3.71 (m, 1H), 3.53 (s, 3H), 3.19 (td, *J* = 12.7, 3.0 Hz, 1H), 2.41 (s, 3H), 2.16 – 2.06 (m, 1H), 1.73 (dtd, *J* = 13.6, 6.8, 3.6 Hz, 1H), 1.64 (dtd, *J* = 15.6, 7.9, 3.8 Hz, 2H), 1.46 (dtq, *J* = 16.8, 8.2, 4.1 Hz, 1H), 1.34 – 1.20 (m, 1H). Spectroscopic data are in agreement with the literature.[38]

3-ethyl 5-methyl 2-((2-bromoethoxy)methyl)-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate (3ae)



3ae

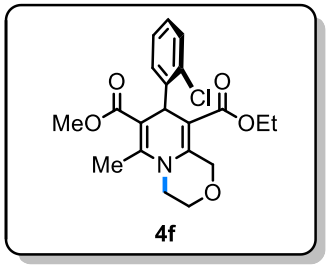
Synthesized according to the **General Procedure IIA** from amlodipine (100 mg, 0.245 mmol). The title compound was obtained as a yellow solid (84.9 mg, 0.1796 mmol, 73% yield) after purification by silica gel chromatography. R_f = 0.82 (silica gel, 50% Ethyl acetate in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.3 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.15 (t, J = 7.3 Hz, 1H), 7.05 (t, J = 7.1 Hz, 1H), 5.42 (s, 1H), 4.81 (q, J = 16.6 Hz, 2H), 4.10 – 4.01 (m, 2H), 3.90 (nonet, J = 5.6 Hz, 2H), 3.63 (s, 3H), 3.60 (t, J = 5.2 Hz, 2H), 2.37 (s, 3H), 1.19 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 167.3, 145.8, 145.1, 144.1, 132.5, 131.6, 129.4, 127.5, 127.0, 104.1, 101.8, 71.1, 67.9, 60.0, 50.9, 37.4, 31.3, 19.6, 14.4.

HRMS (ESI): calculated 472.0526 for $C_{20}H_{24}BrClNO_5$ $[M+H]^+$, found 742.0508.

9-ethyl 7-methyl 8-(2-chlorophenyl)-6-methyl-1,3,4,8-tetrahydropyrido[2,1-*c*][1,4]oxazine-7,9-dicarboxylate (4f):



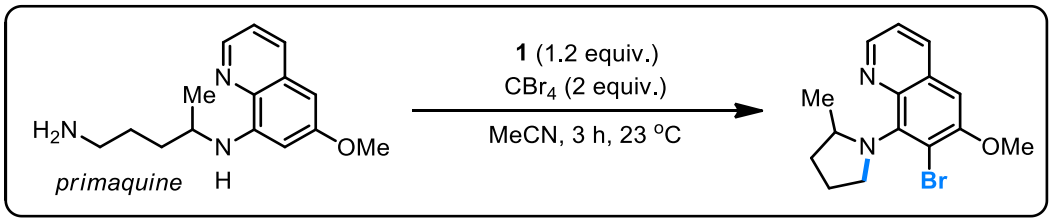
To a stirred solution of amlodipine (80 mg, 0.17 mmol, 1.0 equiv.) in DMF (0.5 mL) at 23 °C was added K_2CO_3 (70 mg, 0.71 mmol, 3.0 equiv.), and the reaction mixture was heated to 70 °C. After 8 h, the reaction mixture was allowed to cool to 23 °C and quenched by the addition of cold water (3 mL). The aqueous layer was extracted with EtOAc (3 × 2 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The title compound was obtained in 86% yield (57 mg) after purification by silica gel chromatography. R_f = 0.3 (silica gel, 30% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 3H), 7.13 (td, *J* = 7.5, 1.4 Hz, 1H), 7.06 (td, *J* = 7.5, 1.8 Hz, 1H), 5.43 (s, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 4.92 (d, *J* = 17.3 Hz, 1H), 4.11-4.00 (m, 3H), 3.90 (ddd, *J* = 11.4, 9.4, 4.5 Hz, 1H), 3.79 (ddd, *J* = 11.5, 9.5, 3.2 Hz, 1H), 3.66 (s, 3H), 3.51 (dt, *J* = 11.3, 3.4 Hz, 1H), 2.41 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 166.9, 146.7, 146.3, 144.6, 132.6, 130.7, 129.8, 127.7, 127.1, 107.9, 102.1, 68.0, 63.9, 60.1, 51.4, 44.7, 36.8, 15.7, 14.4.

HRMS (ESI-TOF) calcd 392.1259 for $C_{20}H_{23}ClNO_5^+$ $[M+H]^+$, found 392.1258.

7-bromo-6-methoxy-8-(2-methylpyrrolidin-1-yl)quinoline:



Synthesized according to **General Procedure IIA** from primaquine (60 mg, 0.23 mmol). The title compound was obtained in 34% yield (25 mg) after purification by silica gel chromatography. R_f = 0.25 (silica gel, 10% EtOAc in hexanes).

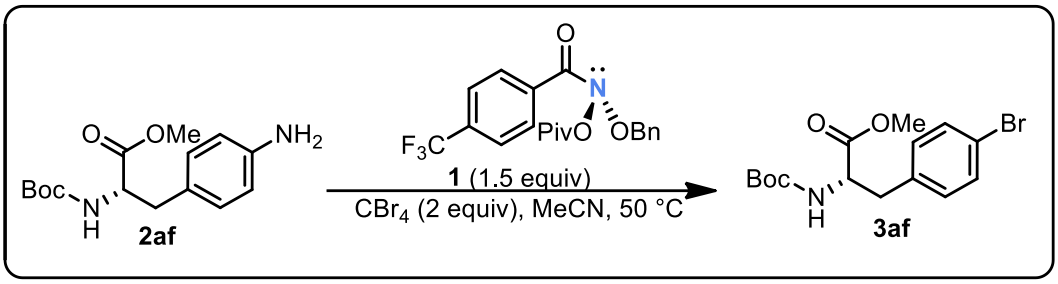
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.44 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.37 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.63 (s, 1H), 4.71 (h, *J* = 6.3 Hz, 1H), 4.14 – 3.97 (m, 4H), 3.45 (ddd, *J* = 10.7, 7.9, 3.5 Hz, 1H), 2.29 (dtd, *J* = 11.7, 7.2, 4.3 Hz, 1H), 2.05 (dtt, *J* = 11.2, 7.4, 3.9 Hz, 1H), 1.99 – 1.85 (m, 1H), 1.75 (ddt, *J* = 12.0, 9.1, 7.1 Hz, 1H), 1.12 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5, 147.6, 144.4, 138.6, 134.2, 129.4, 122.2, 100.6, 95.0, 56.9, 55.9, 53.0, 34.0, 24.1, 19.4.

HRMS (ESI-TOF) calcd 321.0597 and 323.0577 for $C_{15}H_{18}BrN_2O^+$ $[M+H]^+$, found 321.0587 and 323.0576.

VI.B. Bromination/Functionalization

*Deaminative Bromination of **2af***



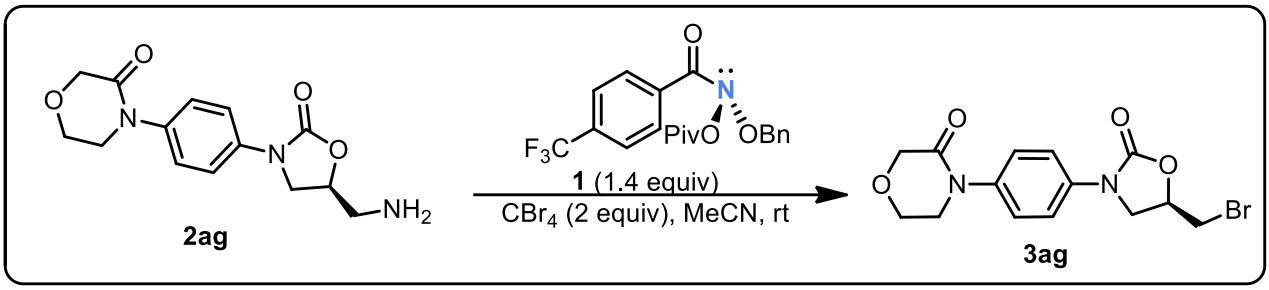
(S)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate (3af)[39]

To an 8 mL vial equipped with a stir bar was added methyl (*S*)-3-(4-aminophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **2af**, (0.147 g, 0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2.5 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.297 g, 0.75 mmol, 1.5 equiv) and CBr_4 (0.332 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the aniline. Once addition was complete, the reaction mixture was heated to 50 °C and allowed to stir at this temperature overnight. After this time, the reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (Heptane to 7:3 Heptane/EtOAc). The desired brominated amino acid derivative was obtained as an off-white powder (0.115 g, 64%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 4.86 - 5.06 (m, 1H), 4.56 (br. s., 1H), 3.71 (s, 3H), 3.09 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.99 (dd, *J* = 14.2, 5.9 Hz, 1H), 1.42 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 155.1, 135.2, 131.7, 131.1, 121.1, 80.2, 54.3, 52.4, 37.9, 28.4.

*Deaminative Bromination of **2ag***



(*R*)-4-(4-(5-(bromomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one (3ag)

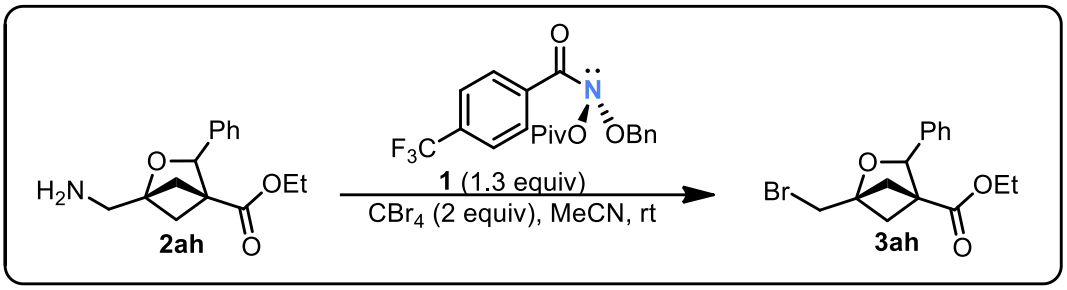
To a 50 mL round bottom flask equipped with a stir bar was added (*S*)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one, **2ag**, (0.437 g, 1.5 mmol, 1 equiv). The flask was sealed with a rubber septum and the atmosphere was exchanged with Ar. The flask was then charged with half the volume of the reaction solvent, MeCN (7.5 mL). In a vial equipped with a stir bar, was added the anomeric amide **1** (0.830 g, 2.1 mmol, 1.4 equiv) and CBr_4 (1.00 g, 3 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (7.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the amine. Once addition was complete, the reaction mixture was allowed to stir at room temperature overnight. After this time, the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (100% Heptane to 100% EtOAc). The desired bromide was obtained as a white powder (0.411 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 4.83 - 4.93 (m, 1 H), 4.34 (s, 2H), 4.18 (t, *J* = 9.0 Hz, 1H), 4.04 (t, *J* = 5.1 Hz, 2H), 3.93 (dd, *J* = 9.3, 5.9 Hz, 1H), 3.76 (t, *J* = 4.9 Hz, 2H), 3.65 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.57 (dd, *J* = 10.8, 7.3 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.0, 137.5, 136.6, 126.4, 119.2, 70.7, 68.7, 64.2, 49.8, 49.4, 32.7.

HRMS (ESI+) calcd for $C_{14}H_{16}BrN_2O_4$ $[M+H]^+$: 355.0293, found: 355.0300.

*Deaminative Bromination of **2ah***



(1r,4r)-ethyl 1-(bromomethyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate (3ah)

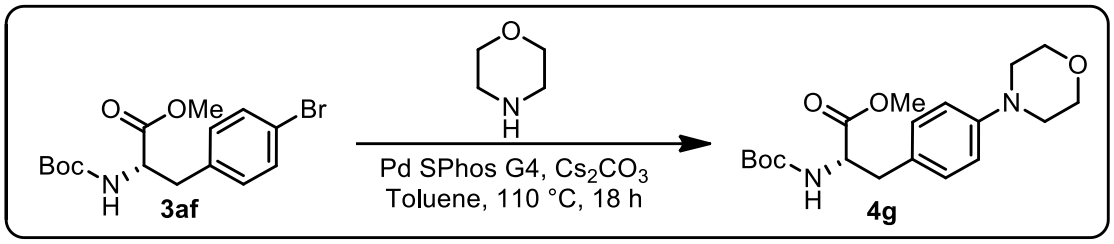
To an 8 mL vial equipped with a stir bar was added ethyl (1r,4r)-1-(aminomethyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate, **2ah**, (0.131 g, 0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.256 g, 0.65 mmol, 1.3 equiv) and CBr_4 (0.332 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the aniline. Once addition was complete, the reaction mixture was heated to 50 °C and allowed to stir at this temperature overnight. After this time, the reaction mixture was allowed to cool to room temperature and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (Heptane to 95:5 to 9:1 Heptane/EtOAc). The desired brominated bicyclic compound was obtained as an clear colorless oil (0.103 g, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 5.39 (s, 1H), 4.17 (qq, *J* = 6.8, 2.9 Hz, 2H), 3.63 - 3.76 (m, 2H), 2.34 (dd, *J* = 9.8, 6.8 Hz, 1H), 2.26 (d, *J* = 6.8 Hz, 1H), 2.08 (dd, *J* = 10.0, 8.1 Hz, 1H), 1.93 (d, *J* = 7.8 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 139.0, 128.1, 127.9, 126.6, 84.4, 80.9, 61.0, 54.3, 49.1, 38.1, 30.8, 14.2.

HRMS (ESI+) calcd for $C_{15}H_{18}BrO_3$ $[M+H]^+$: 325.0439, found: 325.0432.

*Buchwald-Hartwig Coupling of **3af***



(*S*)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-morpholinophenyl)propanoate (4g)

Stepwise Process

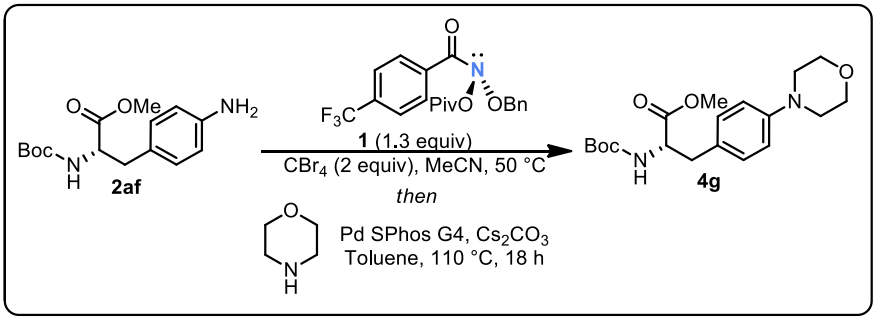
To a 20 mL vial equipped with a stir bar was added (*S*)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **3af**, (0.358 g, 1 mmol, 1 equiv) followed by XPhos Pd G4 (0.086 g, 0.1 mmol, 0.1 equiv) and Cs_2CO_3 (0.652 g, 2 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with a solution of morpholine (0.218 g, 0.22 mL, 2.5 mmol, 2.5 equiv) in toluene (10 mL). The vial was then heated to 110 °C overnight. After this time, the reaction was cooled to rt and the solvent was removed *in vacuo*. Further purification was accomplished by FCC (Heptane to 7:3 Heptane/EtOAc). The desired product was obtained as thick yellow oil (0.290 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.53 (q, *J* = 7.3 Hz, 1H), 3.82 - 3.89 (m, 4H), 3.71 (s, 3H), 3.10 - 3.17 (m, 4H), 2.94 - 3.07 (m, 2H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 155.1, 150.0, 130.0, 127.4, 115.8, 79.7, 66.8, 54.5, 52.1, 49.4, 37.3, 28.3

HRMS (ESI+) calcd for $C_{14}H_{16}BrN_2O_4$ $[M+H]^+$: 365.2076, found: 365.2072.

*Telescoped Process from **2af***



To an 20 mL vial equipped with a stir bar was added methyl (*S*)-3-(4-aminophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **2af**, (0.147 g, 0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2.5 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.257 g, 0.65 mmol, 1.3 equiv) and CBr_4 (0.332 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the aniline. Once addition was complete, the reaction mixture was heated to 50 °C and allowed to stir at this temperature overnight. After this time, the vial was cooled to rt and diluted with an equal volume of pentane (~5 mL). The contents of the vial was rigorously stirred for two minutes and the layers were allowed to separate. The pentane layer was removed using a pipette. This liquid-liquid extractive process was repeated two additional times. The solvent was then removed from the vial in vacuo via rotary evaporation.

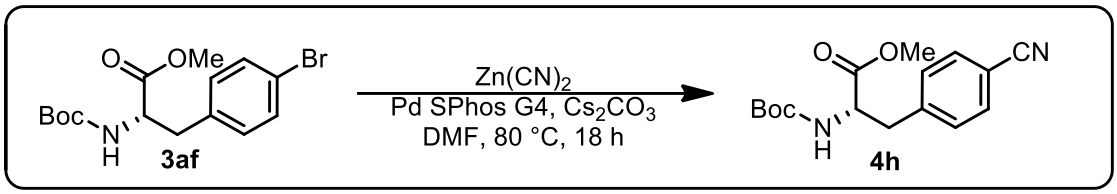
The vial was then charged with XPhos Pd G4 (0.043 g, 0.05 mmol, 0.1 equiv) and Cs_2CO_3 (0.325 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with a solution of morpholine (0.108 g, 0.11 mL, 1.25 mmol, 2.5 equiv) in toluene (5 mL). The vial was then heated to 110 °C overnight. After this time, the reaction was cooled to rt and the solvent was removed *in vacuo*. Further purification was accomplished by FCC (Heptane to 7:3 Heptane/EtOAc). The desired product was obtained as thick yellow oil (0.080 g, 44% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 7.8 Hz, 2H), 4.93 (d, *J* = 7.8 Hz, 1H), 4.53 (q, *J* = 7.3 Hz, 1H), 3.82 - 3.89 (m, 4H), 3.71 (s, 3H), 3.10 - 3.17 (m, 4H), 2.94 - 3.07 (m, 2H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 155.1, 150.0, 130.0, 127.4, 115.8, 79.7, 66.8, 54.5, 52.1, 49.4, 37.3, 28.3

HRMS (ESI+) calcd for $C_{14}H_{16}BrN_2O_4$ $[M+H]^+$: 365.2076, found: 365.2072.

Cyanation of 3af



(S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-cyanophenyl)propanoate (4h)[40]

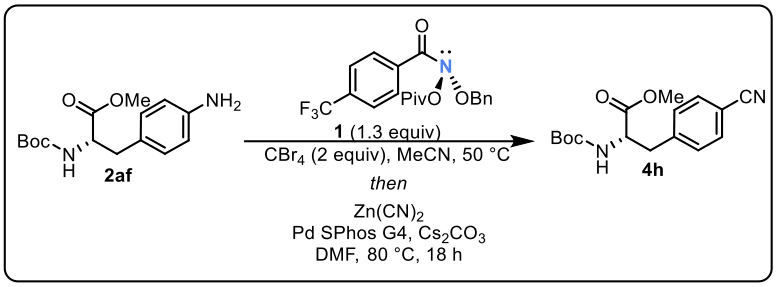
Stepwise Process

To a 20 mL vial equipped with a stir bar was added (*S*)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **3af**, (0.358 g, 1 mmol, 1 equiv) followed by SPhos Pd G4 (0.079 g, 0.1 mmol, 0.1 equiv), $Zn(CN)_2$ (0.235 g, 2 mmol, 2 equiv), and Cs_2CO_3 (0.652 g, 2 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged DMF (10 mL). The vial was then heated to 80 °C overnight. After this time, the reaction was cooled to rt and diluted with EtOAc and deionzed water. The layers were separated and the aq layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with deionzed water (50 mL) and then brine (50 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (Heptane to 7:3 Heptane/EtOAc). The desired product was obtained as an off-white solid (0.215 g, 71%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.61 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J* = 13.7, 5.9 Hz, 1H), 3.06 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.9, 142.0, 132.1, 130.1, 118.6, 110.8, 80.0, 54.0, 52.3, 38.4, 28.1

*Telescoped Process from **2af***



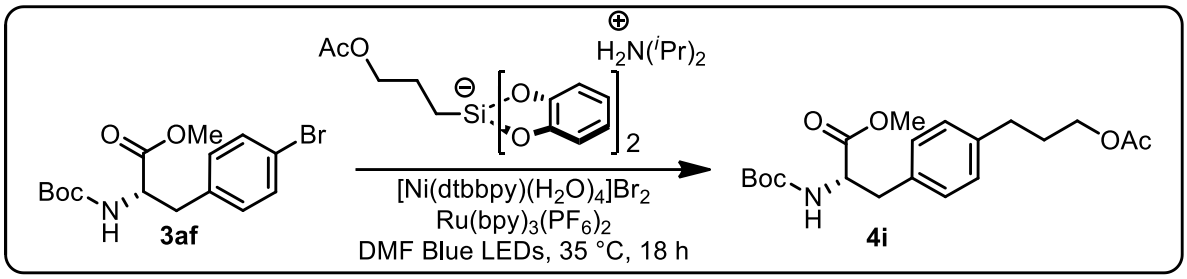
To an 20 mL vial equipped with a stir bar was added methyl (*S*)-3-(4-aminophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **2af**, (0.147 g, 0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2.5 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.257 g, 0.65 mmol, 1.3 equiv) and CBr_4 (0.332 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the aniline. Once addition was complete, the reaction mixture was heated to 50 °C and allowed to stir at this temperature overnight. After this time, the vial was cooled to rt and diluted with an equal volume of pentane (~5 mL). The contents of the vial was rigorously stirred for two minutes and the layers were allowed to separate. The pentane layer was removed using a pipette. This liquid-liquid extractive process was repeated two additional times. The solvent was then removed from the vial *in vacuo* via rotary evaporation.

The vial was then charged with SPhos Pd G4 (0.040 g, 0.1 mmol, 0.1 equiv), $Zn(CN)_2$ (0.176 g, 1.5 mmol, 3 equiv), and Cs_2CO_3 (0.325 g, 2 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged DMF (5 mL). The vial was then heated to 80 °C overnight. After this time, the reaction was cooled to rt and diluted with EtOAc and deionzed water. The layers were separated and the aq layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with deionzed water (50 mL) and then brine (50 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (Heptane to 7:3 Heptane/EtOAc). The desired product was obtained as an off-white solid (0.061 g, 40% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.61 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J* = 13.7, 5.9 Hz, 1H), 3.06 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.9, 142.0, 132.1, 130.1, 118.6, 110.8, 80.0, 54.0, 52.3, 38.4, 28.1

*Ni/Photoredox Cross-Coupling of **3af***



(S)-methyl 3-(4-(3-acetoxypropyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate (4i)

Stepwise Process

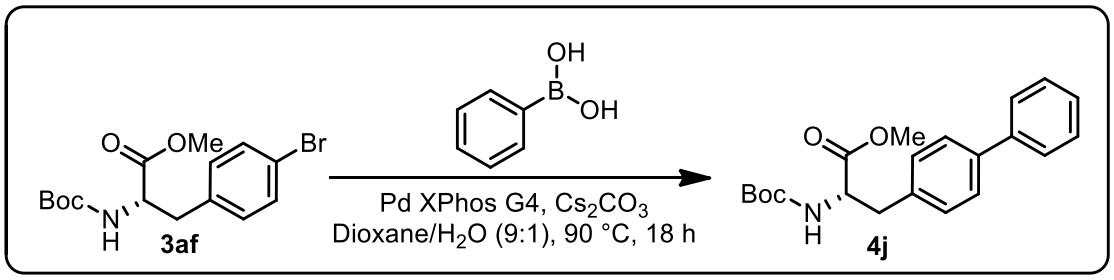
To a 20 mL vial equipped with a stir bar was added (*S*)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **3af**, (0.358 g, 1 mmol, 1 equiv) followed by diisopropylammonium bis(catecholato)(3-acetoxypropyl)silicate[41] (0.581 g, 1.3 mmol, 1.3 equiv), $Ni(dtbbpy)Br_2•4H_2O$[42] (0.056 g, 0.1 mmol, 0.1 equiv), and $Ru(bpy)_3(PF_6)_2$ (0.043 g, 0.05 mmol, 0.05 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged DMF (10 mL) and placed in a blue LED reactor identical as described in previous publication.[43] The reaction was irradiated overnight (reaction vessel temperature was ~35 °C). After this time, the reaction mixture was diluted with EtOAc (20 mL) and 2 M aq NaOH (20 mL). Note that the reaction mixture became dark brown upon addition of the aq base. The layers were separated and the aq layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with additional 2 M NaOH (50 mL), 2 M HCl (50 mL), deionzed water (50 mL) and finally brine (100 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation. Further purification by FCC (Heptane to 8:2 Heptane/EtOAc). The desired coupled product was isolated as an off white solid (0.305 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.8 Hz, 2H), 7.03 (d, *J* = 8.3 Hz, 2H), 4.95 (d, *J* = 7.8 Hz, 1H), 4.56 (q, *J* = 7.3 Hz, 1H), 4.07 (t, *J* = 6.6 Hz, 2H), 3.70 (s, 3H), 3.04 (qd, *J* = 14.7, 5.9 Hz, 2H), 2.64 (t, *J* = 7.8 Hz, 2H), 2.04 (s, 3H), 1.93 (quin, *J* = 7.3 Hz, 2H), 1.40 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 171.2, 155.2, 140.0, 133.7, 129.4, 128.6, 79.9, 63.9, 54.5, 52.2, 38.0, 31.8, 30.2, 28.4, 21.0

HRMS (ESI+) calcd for $C_{15}H_{22}NO_4$ $[M\text{-}Boc+2H]^+$: 280.1549, found: 280.1555.

*Suzuki Cross Coupling of **3af***



(S)-methyl 3-([1,1'-biphenyl]-4-yl)-2-((tert-butoxycarbonyl)amino)propanoate (4j)[44]

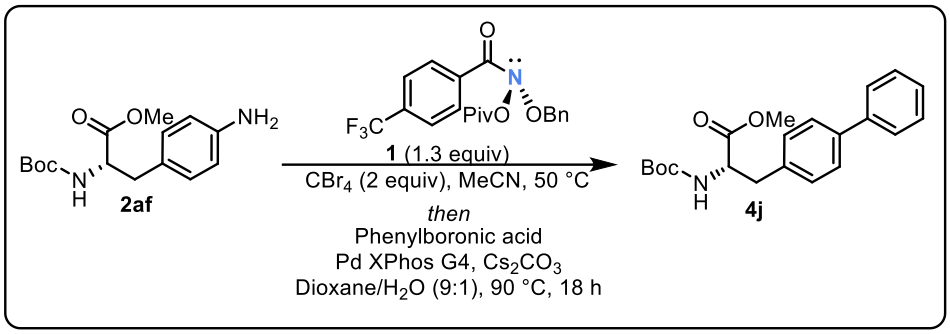
Stepwise Process

To a 20 mL vial equipped with a stir bar was added (*S*)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **3af**, (0.358 g, 1 mmol, 1 equiv) followed by XPhos Pd G4 (0.086 g, 0.1 mmol, 0.1 equiv), phenylboronic acid (0.243 g, 2 mmol, 2 equiv), and Cs_2CO_3 (0.652 g, 2 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged 9:1 by volume mixture of 1,4 dioxane to H_2O (10 mL). The vial was then heated to 90 °C overnight. After this time, the reaction was cooled to rt and diluted with EtOAc and deionzed water. The layers were separated and the aq layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with deionzed water (50 mL) and then brine (50 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (Heptane to 9:1 Heptane/EtOAc). The desired product was obtained as an off-white solid (0.355 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.61 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J* = 13.7, 5.9 Hz, 1H), 3.06 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.9, 142.0, 132.1, 130.1, 118.6, 110.8, 80.0, 54.0, 52.3, 38.4, 28.1

*Telescoped Process from **2af***



To an 20 mL vial equipped with a stir bar was added methyl (*S*)-3-(4-aminophenyl)-2-((tert-butoxycarbonyl)amino)propanoate, **2af**, (0.147 g, 0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2.5 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.257 g, 0.65 mmol, 1.3 equiv) and CBr_4 (0.332 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the aniline. Once addition was complete, the reaction mixture was heated to 50 °C and allowed to stir at this temperature overnight. After this time, the vial was cooled to rt and diluted with an equal volume of pentane (~5 mL). The contents of the vial was rigorously stirred for two minutes and the layers were allowed to separate. The pentane layer was removed using a pipette. This liquid-liquid extractive process was repeated two additional times. The solvent was then removed from the vial *in vacuo* via rotary evaporation.

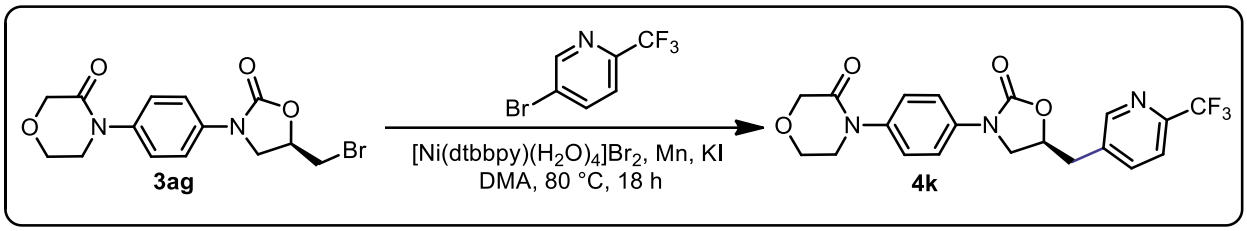
The vial was then charged with XPhos Pd G4 (0.043 g, 0.1 mmol, 0.1 equiv), phenylboronic acid (0.152 g, 2 mmol, 2 equiv), and Cs_2CO_3 (0.326 g, 2 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged 9:1 by volume mixture of 1,4 dioxane to H_2O (5 mL). The vial was then heated to 90 °C overnight. After this time, the reaction was cooled to rt and diluted with EtOAc and deionzed water. The layers were separated and the aq layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with deionzed water (50 mL) and then brine (50 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation.

Further purification was accomplished by FCC (Heptane to 9:1 Heptane/EtOAc). The desired product was obtained as a tan solid (0.097 g, 55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 5.01 (d, *J* = 8.3 Hz, 1H), 4.61 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, *J* = 13.7, 5.9 Hz, 1H), 3.06 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.41 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 154.9, 142.0, 132.1, 130.1, 118.6, 110.8, 80.0, 54.0, 52.3, 38.4, 28.1

*Ni-Mediated Cross-Electrophile Coupling of **3ag***



(S)-4-(4-(2-oxo-5-((6-(trifluoromethyl)pyridin-3-yl)methyl)oxazolidin-3-yl)phenyl)morpholin-3-one (4k)

To a 8 mL vial equipped with a stir bar was added (*R*)-4-(4-(5-(bromomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one, **4k**, (0.098 g, 0.275 mmol, 1 equiv), Ni(dtbbpy)Br_2•$4H_2O$[35] (0.015 g, 0.028 mmol, 0.1 equiv), KI (0.114 g, 0.688 mmol, 2.5 equiv), Mn dust (0.045 g, 0.825 mmol, 3 equiv) and 5-bromo-2-(trifluoromethyl)pyridine (0.093 mg, 0.413 mmol, 1.5 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged DMA (3 mL) and heated to 75 °C overnight. After this time, the reaction was cooled to rt and diluted with EtOAc (10 mL). The heterogeneous mixture was filtered through a pad of Celite® eluting with EtOAc (30 mL). The filtrate was transferred to a separatory funnel and diluted with additional EtOAc (10 mL) and sat aq NH_4Cl (50 mL). The layers were separated and the aq layer waqs extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with additional sat aq NH_4Cl (50 mL) followed by deionized water (50 mL) and finally brine (100 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation. Further purification was accomplished by FCC (100% heptane to 100% EtOAc) to give the desired cross-coupled product as a white solid (0.072 g, 62%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.5 Hz, 1H), 7.89 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 9.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 4.92 (quint, *J* = 6.8, 1.5 Hz, 1H),

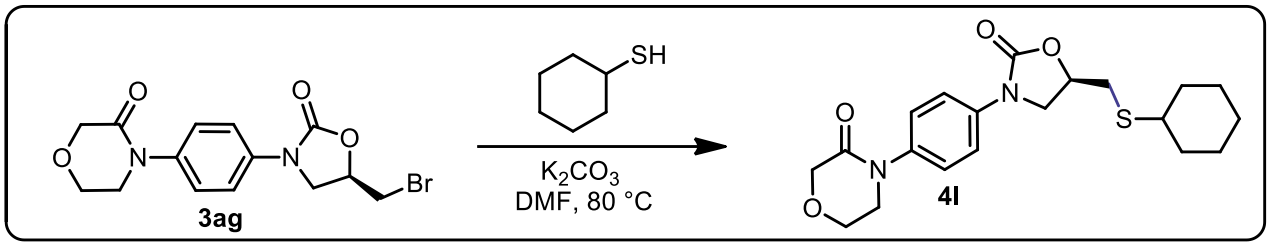
4.34 (s, 2H), 4.16 (t, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 6.4, 4.9 Hz, 2H), 3.75 (tt, *J* = 5.4, 2.4 Hz, 3H), 3.14 - 3.28 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.1, 150.6, 147.4 (q, $J_{C\text{-}C\text{-}F}$ = 35.2 Hz, C), 138.6, 137.5, 136.6, 134.4, 126.3, 120.6, 119.1, 121.6 (q, $J_{C\ F}$ = 274.4 Hz, CF_3), 72.3, 68.6, 64.2, 49.7, 49.7, 37.8

^{19}F NMR (101 MHz, $CDCl_3$) δ -67.83 (s, 3F)

HRMS (ESI+) calcd for $C_{20}H_{19}F_3N_3O_4$ $[M+H]^+$: 422.1328, found: 391.1327.

*Nucleophilic Subsitution of **3ag***



(R)-4-(4-(5-((cyclohexylthio)methyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one (4l)

Stepwise Process

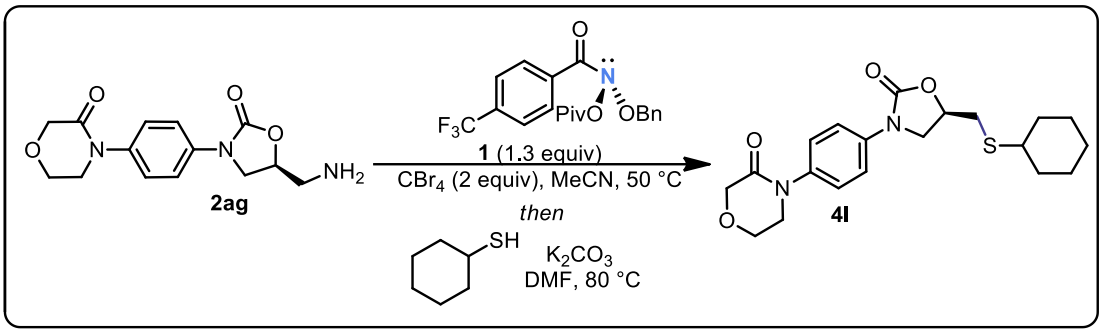
To a 4 mL vial equipped with a stir bar was added K_2CO_3 (0.114 g, 0.825 mmol, 3 equiv). To this vial was added a solution of (*R*)-4-(4-(5-(bromomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one, **3ag**, (0.098 g, 0.275 mmol, 1 equiv) and cyclohexanethiol (0.096 g, 0.10 mL, 0.825 mmol, 3 equiv) in DMF (2 mL). The reaction mixture was then heated to 80 °C and allowed to stir overnight. After this time, the reaction was diluted with EtOAc (40 mL) and 2 M HCl (20 mL). The layers were separated and the aq layer was extracted twice with EtOAc (2 × 20 mL). The combined organic layers were washed with additional 2 M HCl (20 mL), deionzied water (50 mL), and finally brine (100 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation to give a crude orange solid which was washed with a 9:1 mixture of pentane/Et_2O (2 × 25 mL) followed by pentane (50 mL) to give the pure substitution product as a tan solid (0.082 g, 76%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 9.3 Hz, 2H), 4.77 (tdt, *J* = 8.4, 8.4, 4.2, 2.0, 2.0 Hz, 1H), 4.34 (s, 2H), 4.13 (t, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 5.6, 4.2 Hz, 2H), 3.87 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.75 (t, *J* = 5.4 Hz, 2H), 3.02 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.82 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.71 - 2.80 (m, 1H), 1.92 - 2.05 (m, 2H), 1.79 (br. s., 2H), 1.59 - 1.66 (m, 1H), 1.16 - 1.42 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.4, 137.1, 137.0, 126.2, 119.0, 72.0, 68.6, 64.2, 49.7, 49.7, 44.4, 33.9, 33.7, 33.7, 26.0, 26.0, 25.7.

HRMS (ESI+) calcd for $C_{20}H_{27}N_2O_4S$ $[M+H]^+$: 391.1692, found: 391.1690.

*Telescoped Process from **2ag***



To an 20 mL vial equipped with a stir bar was added (S)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one, **2ag**, (0.146 g, 0.5 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2.5 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.257 g, 0.65 mmol, 1.3 equiv) and CBr_4 (0.332 g, 1 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the amine. Once addition was complete, the reaction mixture allowed to stir at room temperature overnight. After this time, the solvent was removed from the vial *in vacuo* via rotary evaporation. Note, although liquid-liquid extraction was not performed in this case, it may be beneficial for related substitution reactions to purge residual CBr_4 assuming the product is reasonably polar.

The vial was then charged with a stir bar was added K_2CO_3 (0.114 g, 2 mmol, 4 equiv). To this vial was added a solution of cyclohexanethiol (0.232 g, 0.24 mL, 2 mmol, 4 equiv) in DMF (4 mL). The reaction mixture was then heated to 80 °C and allowed to stir overnight. After this time, the reaction was diluted with EtOAc (40 mL) and 2 M HCl (20 mL). The layers were separated and the aq layer was extracted twice with EtOAc (2 × 20 mL). The combined organic layers were washed with additional 2 M HCl (20 mL), deionzied water (50 mL), and finally brine (100 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation to give a crude orange solid. Further purification was accomplished by FCC (100% heptane to

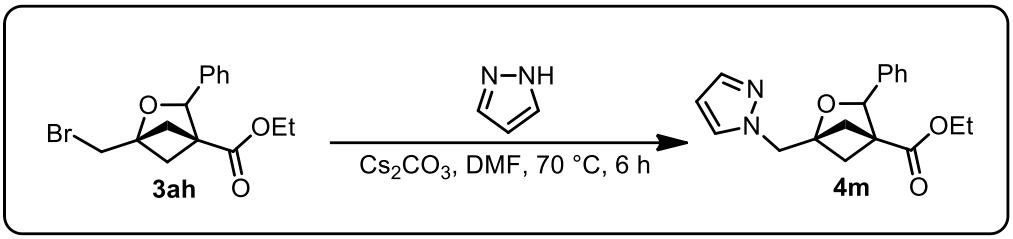
100% EtOAc) to give the desired substitution product as a white solid (0.101 g, 52% over two steps)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 9.3 Hz, 2H), 4.77 (tdt, *J* = 8.4, 8.4, 4.2, 2.0, 2.0 Hz, 1H), 4.34 (s, 2H), 4.13 (t, *J* = 8.8 Hz, 1H), 4.04 (dd, *J* = 5.6, 4.2 Hz, 2H), 3.87 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.75 (t, *J* = 5.4 Hz, 2H), 3.02 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.82 (dd, *J* = 13.7, 8.3 Hz, 1H), 2.71 - 2.80 (m, 1H), 1.92 - 2.05 (m, 2H), 1.79 (br. s., 2H), 1.59 - 1.66 (m, 1H), 1.16 - 1.42 (m, 5H)

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.4, 137.1, 137.0, 126.2, 119.0, 72.0, 68.6, 64.2, 49.7, 49.7, 44.4, 33.9, 33.7, 33.7, 26.0, 26.0, 25.7.

HRMS (ESI+) calcd for $C_{20}H_{27}N_2O_4S$ $[M+H]^+$: 391.1692, found: 391.1690.

*Nucleophilic Subsitution of **3ah***



(1r,4r)-ethyl 1-((1H-pyrazol-1-yl)methyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate (4m)

Stepwise Process

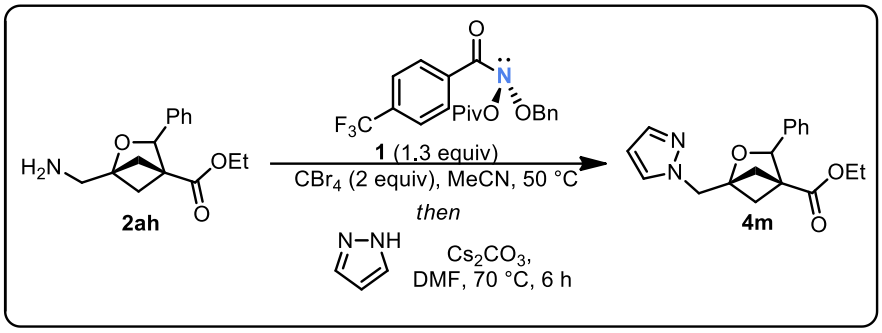
To a 4 mL vial equipped with a stir bar was added Cs_2CO_3 (0.305 g, 0.938 mmol, 1.25 equiv). To this vial was added a solution of (1r,4r)-ethyl 1-(bromomethyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate, **3ah**, (0.244 g, 0.75 mmol, 1 equiv) and pyrazole (0.102 g, 1.5 mmol, 2 equiv) in DMF (7.5 mL). The reaction mixture was then heated to 70 °C and allowed to stir for 6 h. After this time, the reaction was cooled to rt and diluted with EtOAc (40 mL) and deionized water (20 mL). The layers were separated and the aq layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with deionzied water (40 mL), and then brine (80 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo* by rotary evaporation to give the crude displacement product. Further purification was accomplished by FCC (100% heptane to 7:3 heptane/EtOAc) to give the desired substitution product as a thick, clear, colorless oil (0.195 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.4 Hz, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.19 - 7.33 (m, 5H), 6.30 (t, *J* = 2.0 Hz, 1H), 5.32 (s, 1H), 4.56 (s, 2H), 4.11 (qd, *J* = 6.8, 1.0 Hz, 2H), 2.12 - 2.27 (m, 2H), 1.88 (dt, *J* = 18.6, 8.3 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 139.6, 139.1, 130.3, 128.1, 127.9, 126.5, 106.0, 85.0, 80.6, 60.9, 54.9, 52.8, 48.6, 37.6, 14.2

HRMS (ESI+) calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$: 313.1552, found: 313.1557.

*Telescoped Process from **2ah***



To an 20 mL vial equipped with a stir bar was added (1r,4r)-1-(aminomethyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate, **2ah**, (0.243 g, 0.75 mmol, 1 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. The vial was then charged with half the volume of the reaction solvent, MeCN (2 mL). In a separate vial equipped with a stir bar, was added the anomeric amide **1** (0.386 g, 0.975 mmol, 1.3 equiv) and CBr_4 (0.498 g, 1.5 mmol, 2 equiv). The vial was sealed with a cap containing a PTFE lined septum and the atmosphere was exchanged with Ar. This vial was then charged with the remaining half the volume of MeCN (2.5 mL). After stirring for ~5 min, the **1**/CBr_4 solution was added dropwise over five minutes to the solution of the amine. Once addition was complete, the reaction mixture allowed to stir at room temperature overnight. After this time, the solvent was removed from the vial *in vacuo* via rotary evaporation. Note that liquid-liquid extraction was not performed in this case.

The vial was then charged with a stir bar was added Cs_2CO_3 (0.305 g, 0.938 mmol, 1.25 equiv) and pyrazole (0.204 g, 1.5 mmol, 2 equiv) in DMF (7.5mL). The reaction mixture was then heated to 70 °C and allowed to stir for 6 h. After this time, the reaction was cooled to rt and diluted with EtOAc (40 mL) and deionized water (20 mL). The layers were separated and the aq layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with deionzied water (40 mL), and then brine (80 mL). The organic layer was dried with Na_2SO_4 and the solvent

was removed *in vacuo* by rotary evaporation to give the crude displacement product. Further purification was accomplished by FCC (100% heptane to 7:3 heptane/EtOAc) to give the desired substitution product as a thick, clear, colorless oil (0.106 g, 45% over two steps).

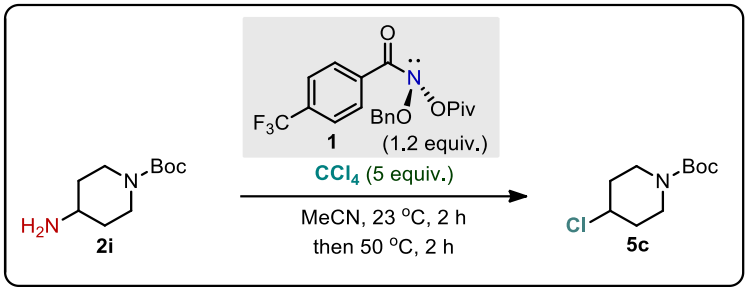
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 2.4 Hz, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.19 - 7.33 (m, 5H), 6.30 (t, *J* = 2.0 Hz, 1H), 5.32 (s, 1H), 4.56 (s, 2H), 4.11 (qd, *J* = 6.8, 1.0 Hz, 2H), 2.12 - 2.27 (m, 2H), 1.88 (dt, *J* = 18.6, 8.3 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 139.6, 139.1, 130.3, 128.1, 127.9, 126.5, 106.0, 85.0, 80.6, 60.9, 54.9, 52.8, 48.6, 37.6, 14.2

HRMS (ESI+) calcd for $C_{18}H_{21}N_2O_3$ $[M+H]^+$: 313.1552, found: 313.1557.

V. Deaminative Chlorination and Iodination

Chlorination

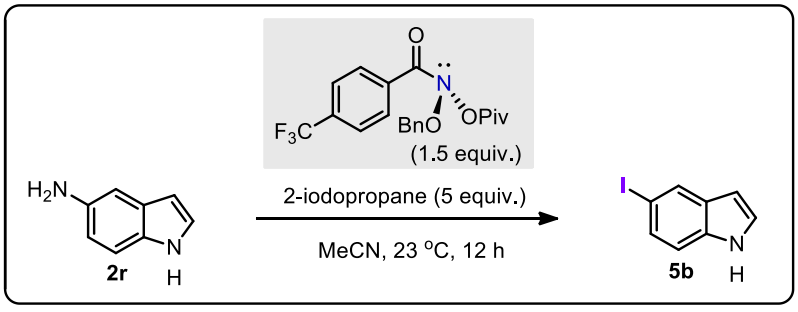


***Tert*-butyl 4-chloropiperidine-1-carboxylate (5c)**

To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the *tert*-butyl 4-aminopiperidine-1-carboxylate, **2i**, (40 mg, 0.2 mmol). The anomeric amide (95 mg, 0.24 mmol) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (1.0 mL each). Carbon tetrachloride (96 µL, 1.0 mmol) was added to a vial containing **1**. Dissolved amine from another vial was then added dropwise to a vial containing **1** and CCl_4 over the period of 5 min. The reaction was stirred at room temperature for 2 hours and at 50 °C for 2 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude product was submitted for ^{1}H NMR spectroscopy confirmed the formation of title compound in 66% NMR yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (dq, *J* = 7.7, 3.8 Hz, 1H), 3.72 (ddd, *J* = 13.7, 7.1, 3.7 Hz, 2H), 3.31 (ddd, *J* = 13.7, 7.8, 3.6 Hz, 2H), 2.05-1.99 (m, 2H), 1.80 (dtd, *J* = 13.3, 7.7, 3.7 Hz, 2H), 1.48 (s, 9H). Spectroscopic data are in agreement with the literature.[45]

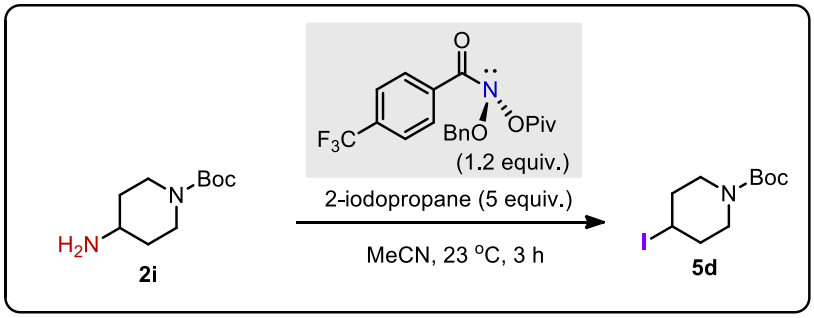
Iodination



5-Iodoindole (5b)

To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the 5-aminoindole, **2r**, (35 mg, 0.26 mmol). The anomeric amide, **1**, (157 mg, 0.4 mmol) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (1.3 mL each). 2-iodopropane (132 µL, 1.3 mmol) was added to a vial containing **1**. Dissolved amine from another vial was then added dropwise to a vial containing a mixture of **1** and 2-iodopropane over the period of 5 min. The reaction was stirred at room temperature for 12 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4 and purified by silica gel column chromatography to afford title compound in 68% yield (48 mg). R_f = 0.3 (silica gel, 20% EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 15.8 Hz, 1H), 7.99 (dt, *J* = 1.5, 0.7 Hz, 1H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.22 – 7.14 (m, 2H), 6.48 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H). Spectroscopic data are in agreement with the literature.[46]

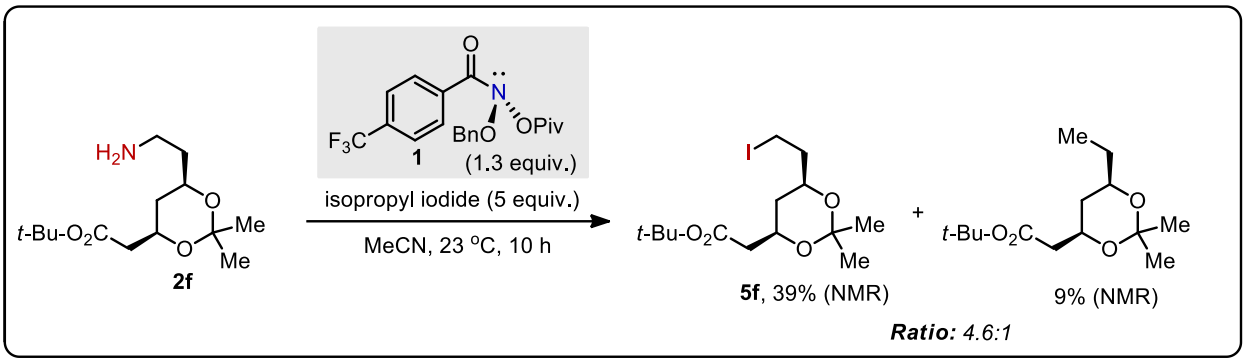


***Tert*-butyl 4-iodopiperidine-1-carboxylate (5d)**

To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the *tert*-butyl 4-aminopiperidine-1-carboxylate, **2i**, (40 mg, 0.2 mmol). The anomeric amide, **1**, (95 mg, 0.24 mmol) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (1.0 mL each). 2-iodopropane (100 µL, 1.0 mmol) was added to a vial containing **1**. Dissolved amine from another vial was then added dropwise to a vial containing a mixture of **1** and 2-iodopropane over the period of 5 min. The reaction was stirred at room temperature for 3 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and

extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude product was submitted for ^{1}H NMR spectroscopy confirmed the formation of title compound in 64% NMR yield.

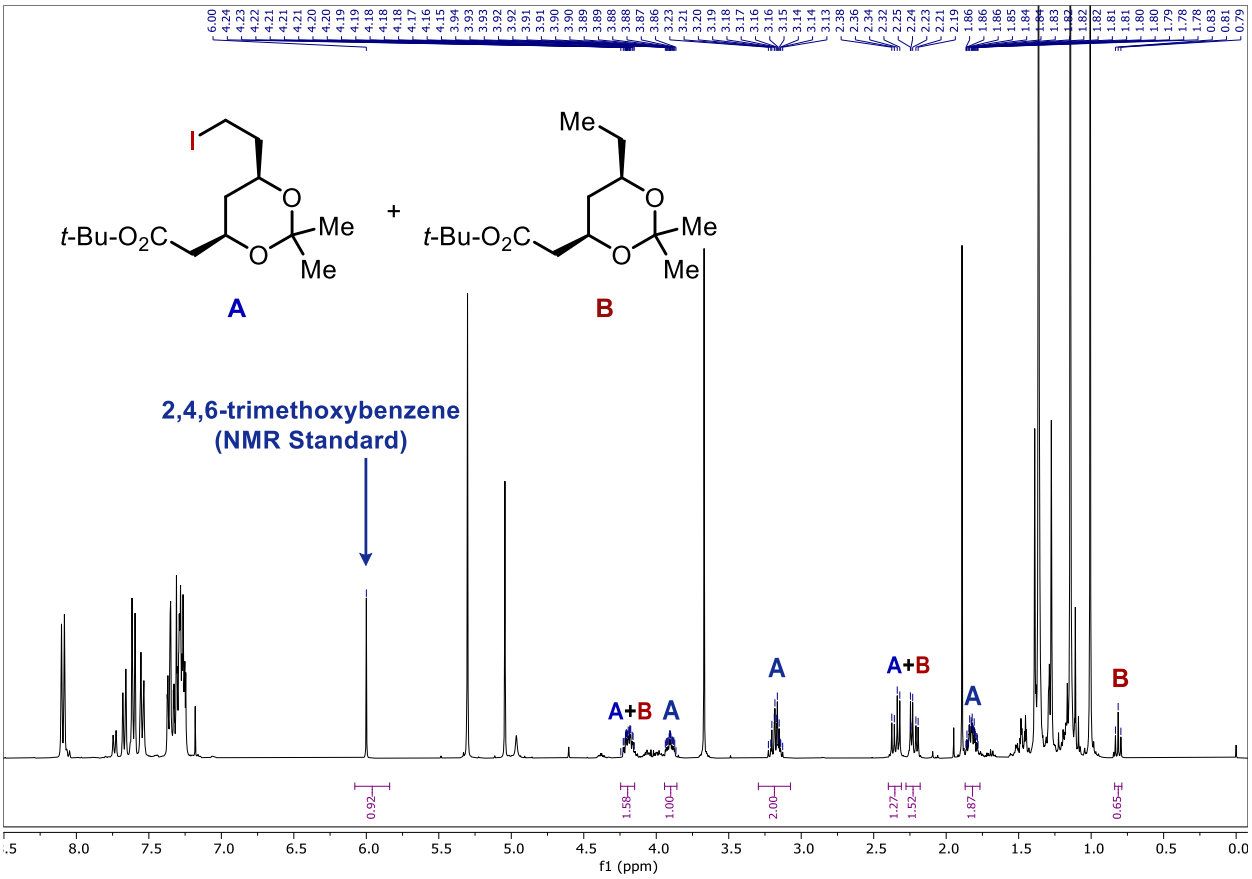
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (p, *J* = 6.0 Hz, 1H), 3.57 (dt, *J* = 13.7, 5.2 Hz, 2H), 3.26 (dt, *J* = 13.7, 5.8 Hz, 2H), 1.99 (q, *J* = 5.7 Hz, 4H), 1.44 (d, *J* = 1.3 Hz, 13H). Spectroscopic data are in agreement with the literature.[47]



***Tert*-butyl 2-((4*R*,6*S*)-6-(2-iodoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (5f)**

To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, **2f**, (50 mg, 0.183 mmol). The anomeric amide, **1**, (94 mg, 0.23 mmol) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (1.0 mL each). Isopropyl iodide (91 µL, 0.91 mmol) was added to a vial containing **1**. Dissolved amine from another vial was then added dropwise to a vial containing **1** and isopropyl iodide over the period of 10 min. The reaction was stirred at room temperature for 10 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. The volatiles were removed *in vacuo* and the crude reaction mixture was submitted for ^{1}H NMR spectroscopy confirmed the formation of corresponding iodo compound **5f** and deamination product in 39 and 9% NMR yield and 4.6:1 ratio respectively. Formation of compound **5f** was further confirmed by HRMS.

HRMS (ESI-TOF) calcd 407.0690 for $C_{14}H_{25}INaO_4^+$ $[M+Na]^+$, found 407.0690.


I
t-Bu-O2C
O
Me
Me
O
A
+
Me
t-Bu-O2C
O
Me
Me
O
B
2,4,6-trimethoxybenzene
(NMR Standard)
A+B
A
A
A+B
A
B
0.92
1.58
1.00
2.00
1.27
1.52
1.87
0.65
f1 (ppm)

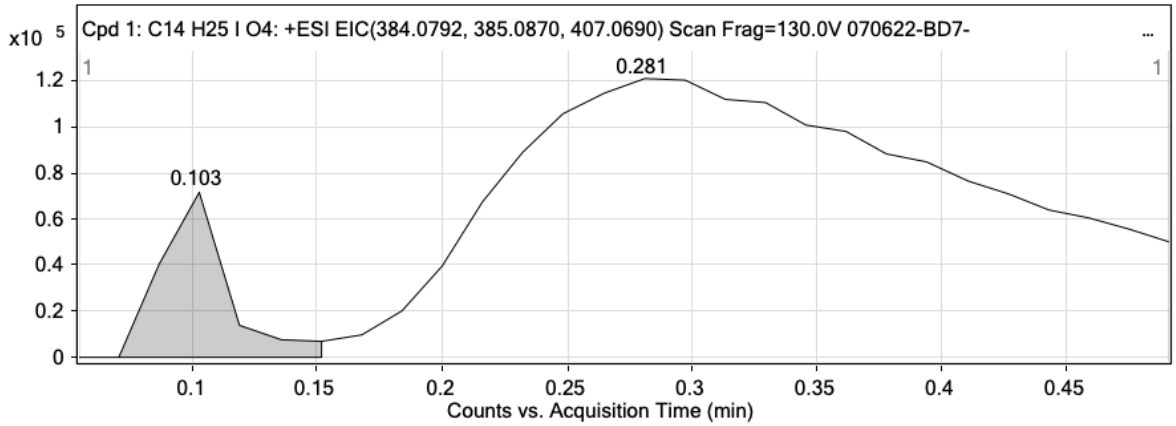
HRMS of 5f

Compound Table

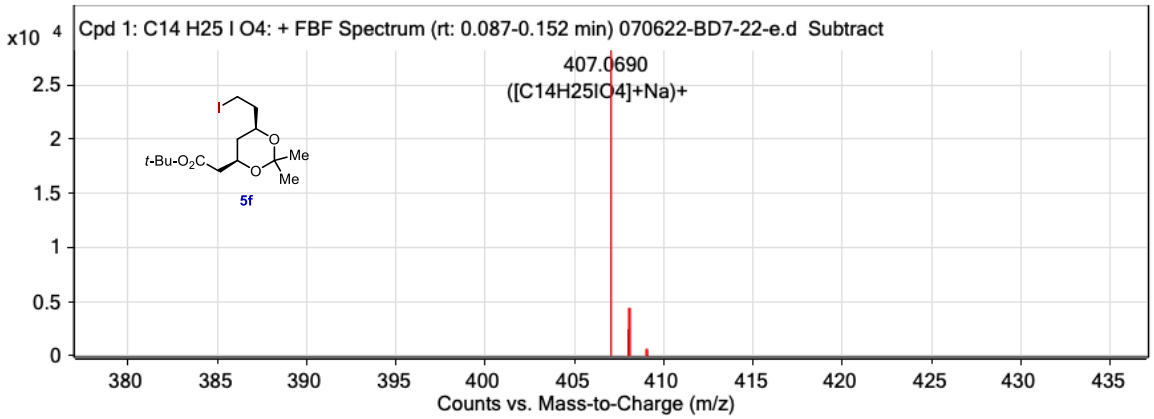
Label	Tgt Score	Mass Error (ppm)	Tgt Formula	Obs. RT	Ref. Mass	Obs. Mass
Cpd 1: C14 H25 I O4	87.33	-0.25	C14 H25 I O4	0.103	384.0798	384.0797

Obs. *m/z*	Obs. RT	Obs. Mass	Tgt Formula	Tgt Mass	Tgt Mass Error (ppm)	RT Diff.	Find Cpds Algorithm
407.069	0.103	384.0797	C14 H25 I O4	384.0798	-0.25	Find By Formula	

Compound Chromatograms

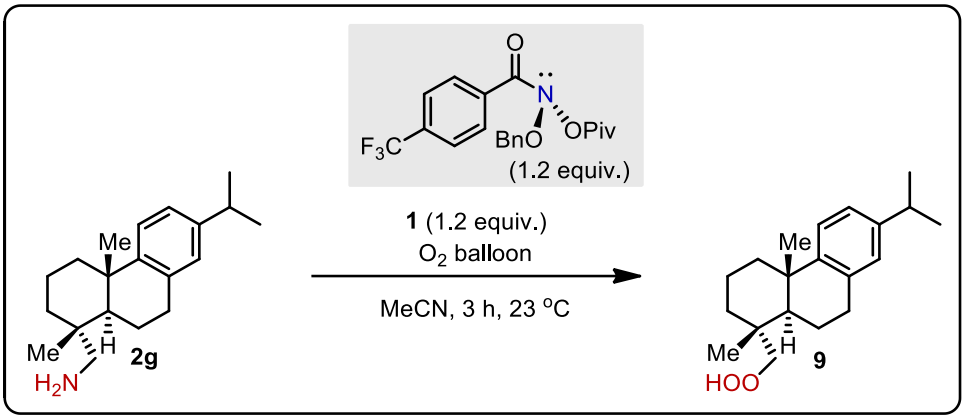


MS Zoomed Spectrum



VI. Mechanistic Experiments

VI.A. Isolation of Hydroperoxide 9



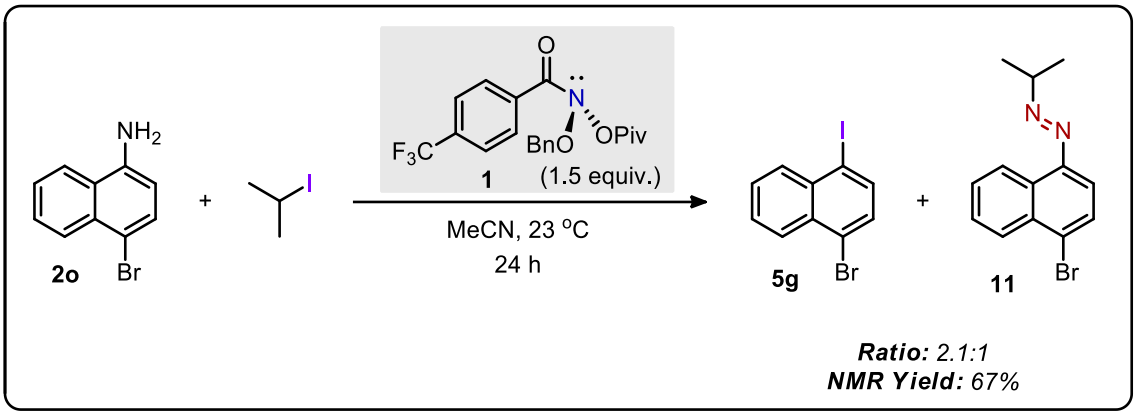
To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the anomeric amide, **1**, (83 mg, 0.21 mmol) and dry acetonitrile (1 mL). The clear solution of **1** was saturated with oxygen (by sparging oxygen from balloon for 5 min). Leelamine, **2g**, (50 mg, 0.17 mmol) and dry acetonitrile (0.7 mL) were added to a second vial. Dissolved amine was then added dropwise to vial containing **1** (with active oxygen sparging) for the period of 1 h using syringe pump. After additional 2 h, oxygen sparging stopped and the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude product was purified by silica gel chromatography to afford titled hydroperoxide in 60% yield (32 mg). R_f = 0.5 (silica gel, 5% EtOAc in hexanes).

^{1}H NMR (400 MHz, C_6D_6) δ 7.19 (s, 1H), 7.03 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.54 (d, *J* = 9.4 Hz, 1H), 2.92 – 2.69 (m, 3H), 2.24 – 2.07 (m, 1H), 1.72 (ddd, *J* = 11.5, 6.7, 3.4 Hz, 1H), 1.67 – 1.45 (m, 4H), 1.39 – 1.27 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.13 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ 147.6, 145.8, 135.0, 127.2, 124.7, 124.2, 86.0, 45.1, 38.7, 38.2, 37.7, 36.4, 34.1, 30.5, 25.6, 24.4, 24.4, 19.7, 19.0, 17.9.

HRMS (ESI-TOF) calcd 303.2319 for $C_{20}H_{31}O_2^+$ $[M+H]^+$, found 303.2310.

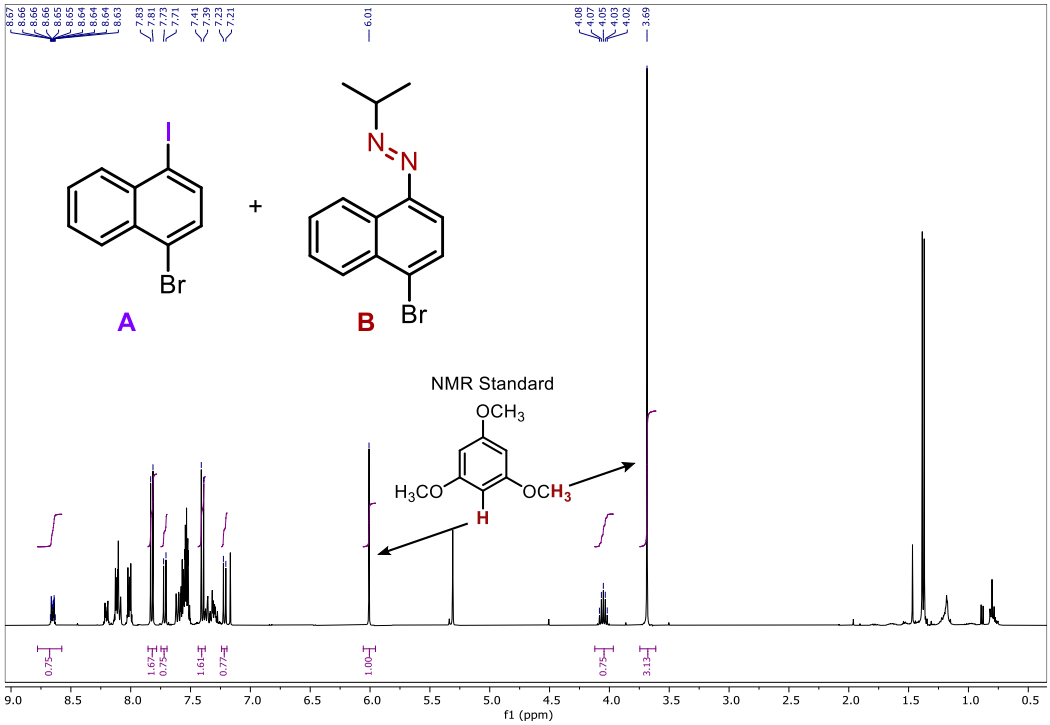
V.B. Isodiazene trapping



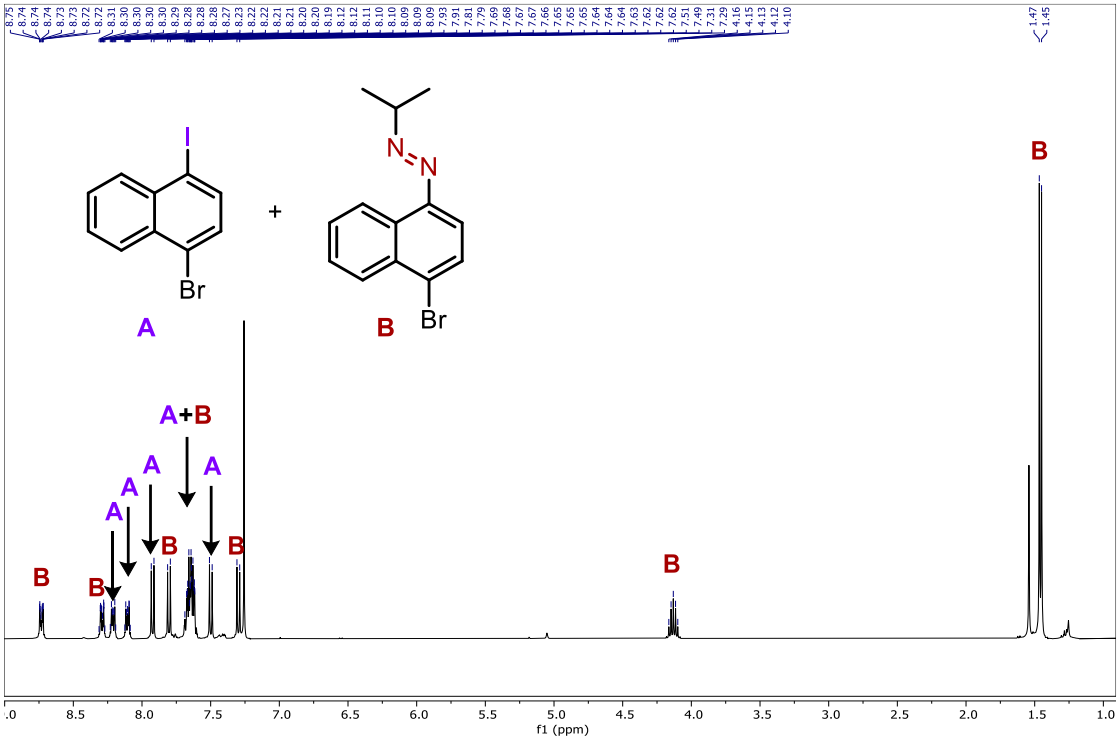
To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the 1-amino-4-bromonaphthalene, **2o**, (25 mg, 0.11 mmol). The anomeric amide, **1**, (67 mg, 0.17 mmol) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (0.55 mL each). Isopropyl iodide (34 µL, 0.34 mmol) was added to vial containing **1**. Dissolved amine was then added dropwise to vial containing **1** and isopropyl iodide over the period of 5 min. The reaction was stirred at 23 °C for 12 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude product was submitted for ^1H NMR spectroscopy confirmed the formation of mixture of compounds iodide **5g** and diazene **11** in 67% yield in a **2.1:1** ratio. Formation of diazene **11** was further confirmed by HRMS.

HRMS (ESI-TOF) calcd 277.0335 and 279.0315 for $C_{13}H_{14}BrN_2^+$ $[M+H]^+$, found 277.0333 and 279.0314.

Crude ^{1}H NMR spectrum



^{1}H NMR spectrum after purification: mixture of A and B



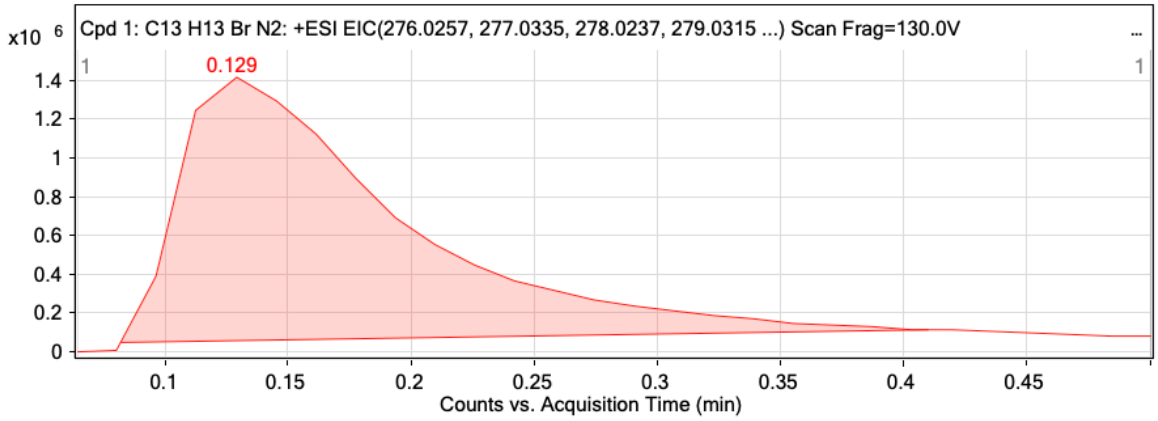
HRMS spectrum of diazene 11.

Compound Table

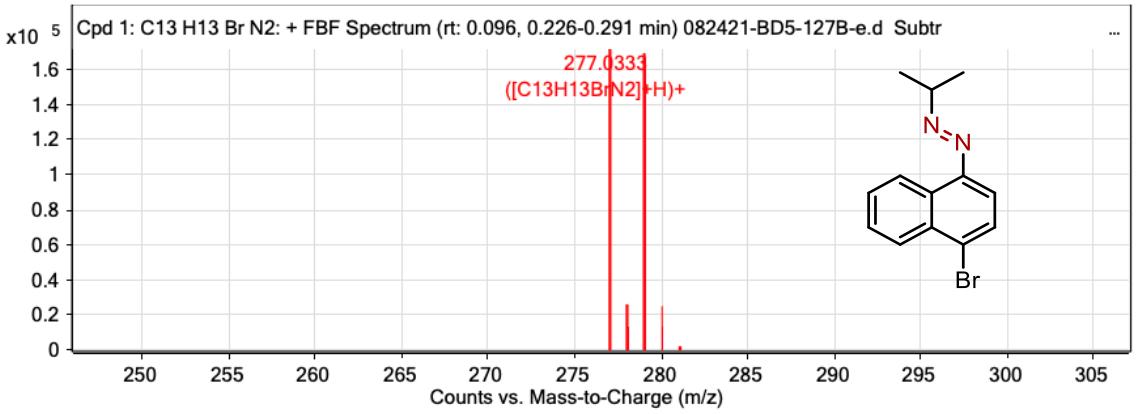
Label	Tgt Score	Mass Error (ppm)	Tgt Formula	Obs. RT	Ref. Mass	Obs. Mass
Cpd 1: C13 H13 Br N2	89.55	-0.88	C13 H13 Br N2	0.129	276.0262	276.026

Obs. *m/z*	Obs. RT	Obs. Mass	Tgt Formula	Tgt Mass	Tgt Mass Error (ppm)	RT Diff.	Find Cpds Algorithm
277.0333	0.129	276.026	C13 H13 Br N2	276.0262	-0.88	Find By Formula	

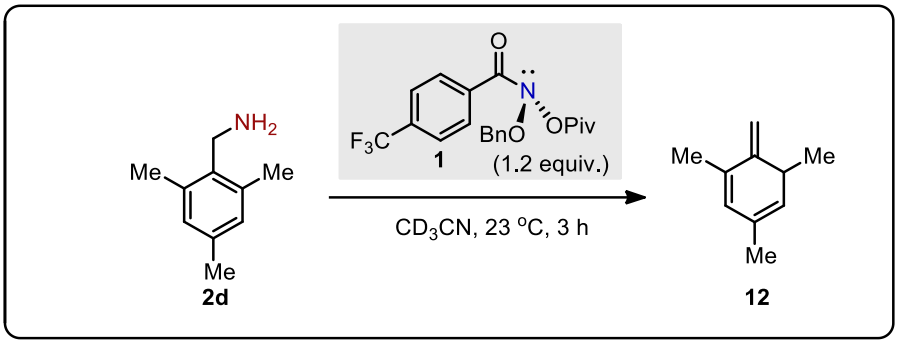
Compound Chromatograms



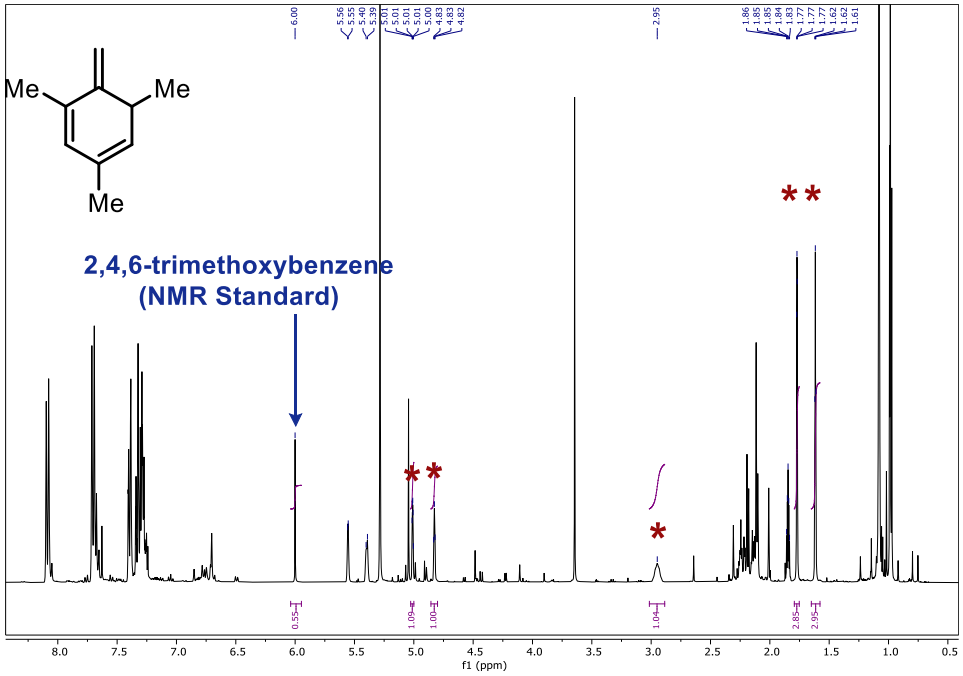
MS Zoomed Spectrum



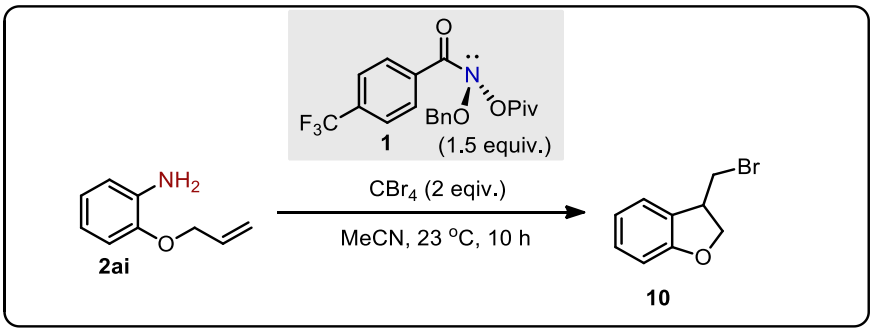
VI.C. Detection of Isotoluene 12



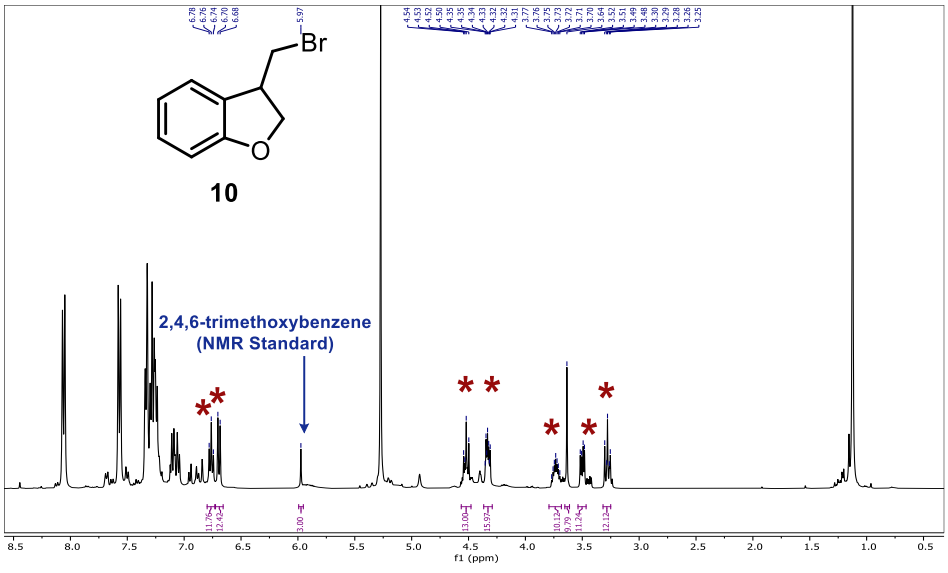
To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the mesitylmethanamine, **3d**, (16.6 mg, 0.11 mmol). The anomeric amide, **1**, (52 mg, 0.132 mmol) was added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry CD_3CN (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (0.6 mL each). Dissolved amine was then added dropwise to vial containing **1** over the period of 5 min. The reaction was stirred at room temperature for 3 hours. After completion, the crude reaction mixture was directly submitted for ^1H NMR spectroscopy confirmed the formation of product **12** in 50% yield.



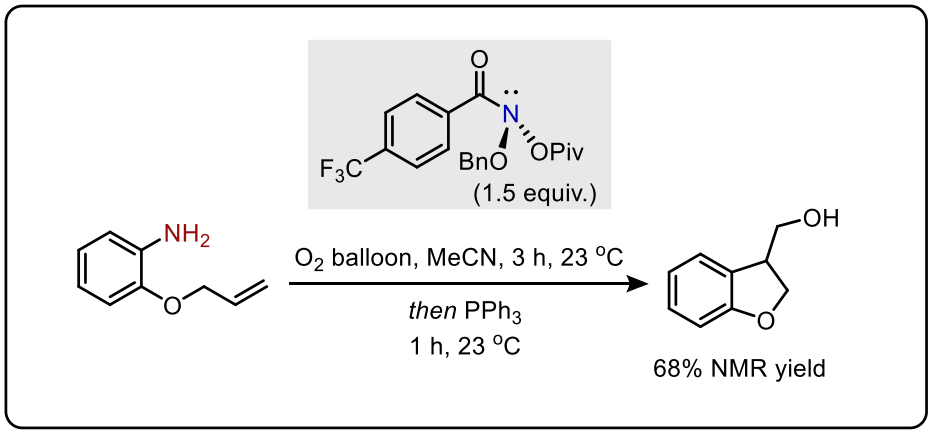
VI.D. Radical Clock Experiment



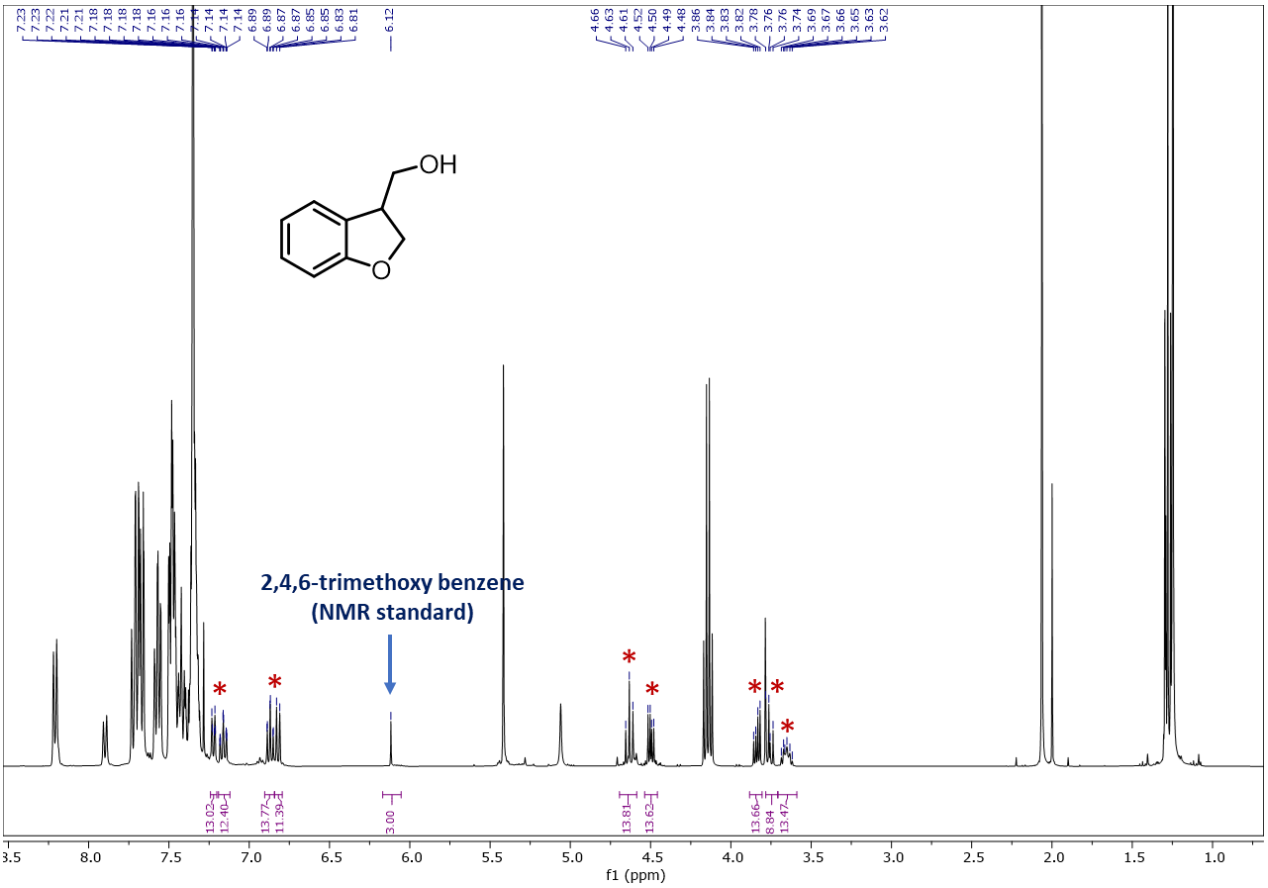
To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the 2-(allyloxy)aniline, **2ai**, (27 mg, 0.18 mmol). The anomeric amide, **1**, (107 mg, 0.27 mmol) and carbon tetrabromide (119 mg, 0.36 mmol) were added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry acetonitrile (degassed by sparging with N_2 for 10 minutes) was added to both vials via syringe (0.9 mL each). Dissolved amine was then added dropwise to vial containing mixture of **1** and CBr_4 over the period of 5 min. The reaction was stirred at room temperature for 10 hours. After completion, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The volatiles were removed *in vacuo* and the crude reaction mixture was submitted for ^1H NMR spectroscopy confirmed the formation of product **10** in 62% yield.



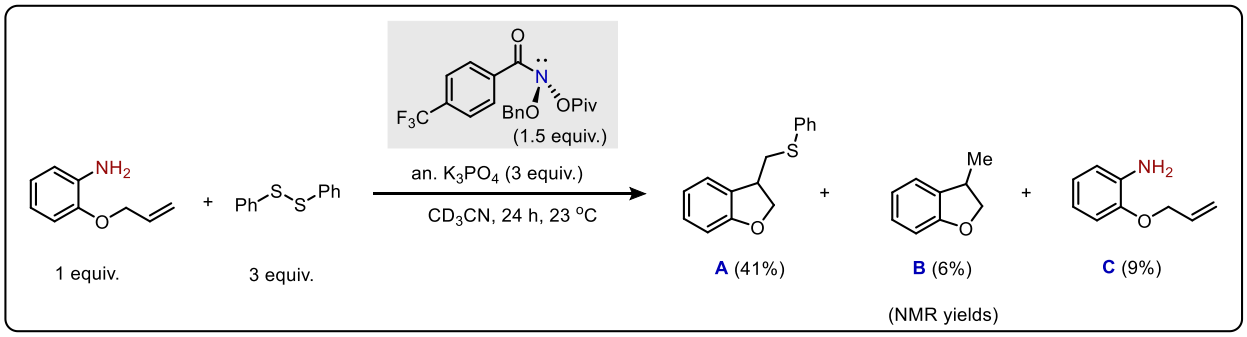
Radical clock experiment using oxygen as a trapping agent



To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the anomeric amide (119 mg, 0.3 mmol) and dry acetonitrile (1 mL). The clear anomeric amide solution was saturated with oxygen (by sparging oxygen from the balloon for 5 min). 2-(allyloxy)aniline (30 mg, 0.2 mmol) and dry acetonitrile (1 mL) were added to a second vial. Dissolved aniline was then added dropwise to the vial containing anomeric amide (with active oxygen sparging) for a period of 1 h using a syringe pump. After an additional 2 h, oxygen sparging stopped and triphenyl phosphine (105 mg, 0.4 mmol) was added to the reaction mixture and stirring was continued for one more hour. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were washed with brine and dried over sodium sulfate. The volatiles were removed *in vacuo* and the crude reaction mixture was submitted for ^1H NMR spectroscopy confirmed the formation of (2,3-dihydrobenzofuran-3-yl)methanol in 68% yield (using 2,4,6-trimethoxybenzene as internal NMR standard).

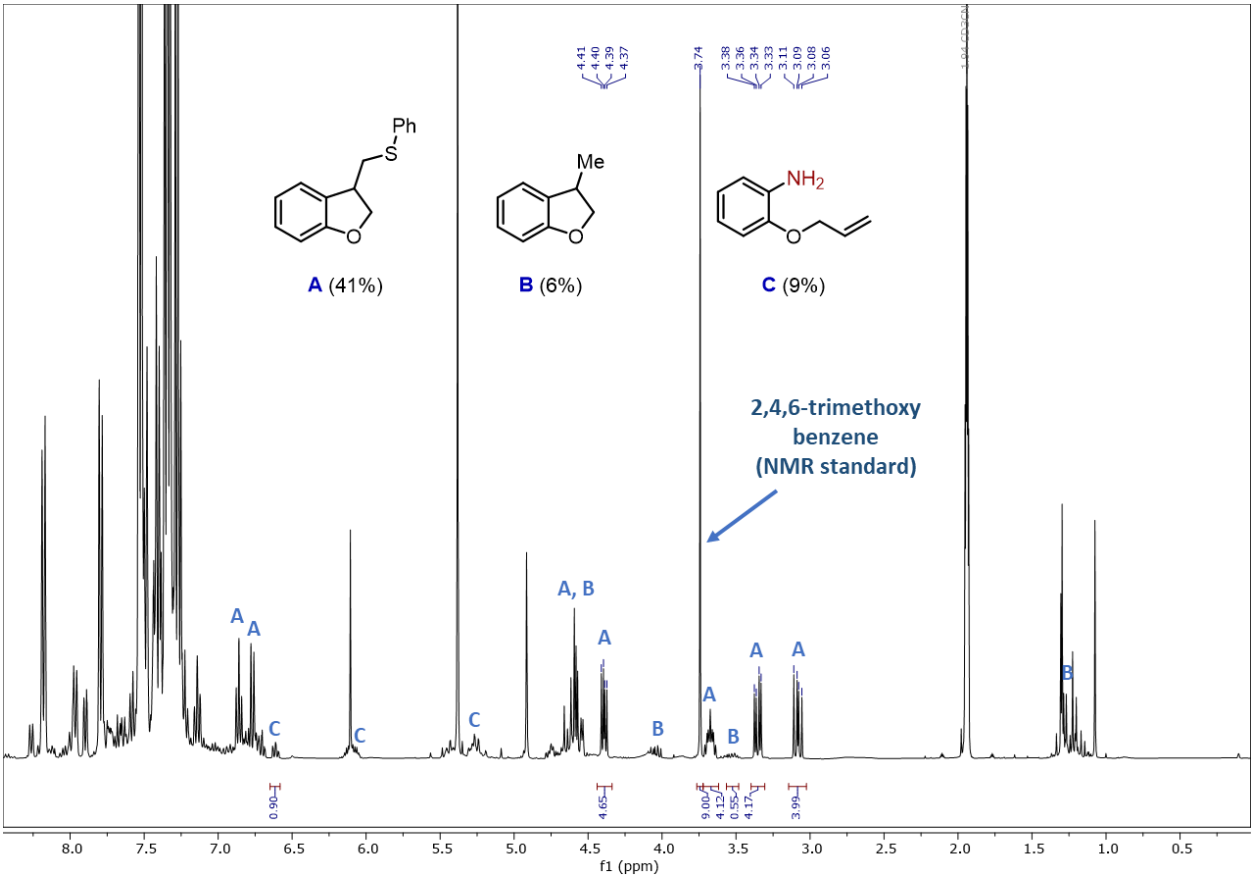


Radical clock experiment using phenyldisulfide as a trapping agent



To a 2-dram screw cap vial equipped with a stir bar and PTFE/white silicone septum was added the 2-(allyloxy)aniline (15 mg, 0.1 mmol). The anomeric amide (59 mg, 1.5 mmol), phenyldisulfide (66 mg, 0.3 mmol) and anhydrous K_3PO_4 (64 mg, 0.3 mmol) were added to a second vial and both vials were evacuated and backfilled with nitrogen twice. Dry CD_3CN (degassed by sparging with N_2 for 10 minutes) was added to both vials (0.5 mL each) via syringe. Dissolved amine was then added dropwise to a vial containing a mixture of anomeric amide and disulfide over a period of 5 min. The reaction was stirred at room temperature for 24 hours. The reaction mixture was

filtered through PTFE 0.2 µm filter and submitted for ^{1}H NMR, confirming the formation product A (41% NMR yield) and B (6% NMR yield) along with 9% starting material.



VII. Computational Methods and Analyses

Computational Methods

Structural optimizations of molecule were conducted at the B3LYP[48,49]-D3[50]/def2-SVP[51,52] level of theory in MeCN solvent using the SMD implicit solvent model[53] with "opt=noeigen" keyword as implemented in Gaussian16 (version C.01)[54]. Frequency calculations were performed at the same level to get thermal corrections to enthalpy and Gibbs free energy (at 298 K; noted as H_{corr} and G_{corr}, correspondingly), and to characterize the identity of obtained stationary points as transition states (with one and only one imaginary frequency) or minima (with zero imaginary frequency). Intrinsic reaction coordinate (IRC) calculations were performed for all transition states to ensure they are connected to the corresponding intermediates. To compare energetics, we also carried out single-point energy calculations using B3LYP-D3/def2-TZVPP-SMD(MeCN) and domain based local pair natural orbital coupled cluster method with single-, double-, and perturbative triple

excitations[55,56] [noted as DLPNO-CCSD(T), with def2-TZVPP basis set and def2-TZVPP/C as auxiliary basis set] with ORCA (version 4.1.1).[57,58] All structural figures were generated using CYLview20.[59]

Since DLPNO-CCSD(T)/def2-TZVPP generates electronic energy, solvation energies and thermal corrections need to be added in order to obtain the enthalpies and Gibbs free energies in solution [noted as DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN]. In this case, solvation energies were calculated as:

$$\Delta E_{soln} = E[\text{B3LYP-D3/def2-SVP-SMD(MeCN)}] - E[\text{B3LYP-D3/def2-SVP-gas}]$$

With solvation energies computed, enthalpies and Gibbs free energies at the DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN) level of theory can be calculated as:

$$H[\text{DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN)}] = E[\text{DLPNO-CCSD(T)/def2-TZVPP}] + \Delta E_{soln} + H_{corr}$$

$$G[\text{DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN)}] = E[\text{DLPNO-CCSD(T)/def2-TZVPP}] + \Delta E_{soln} + G_{corr}$$

Computational Results

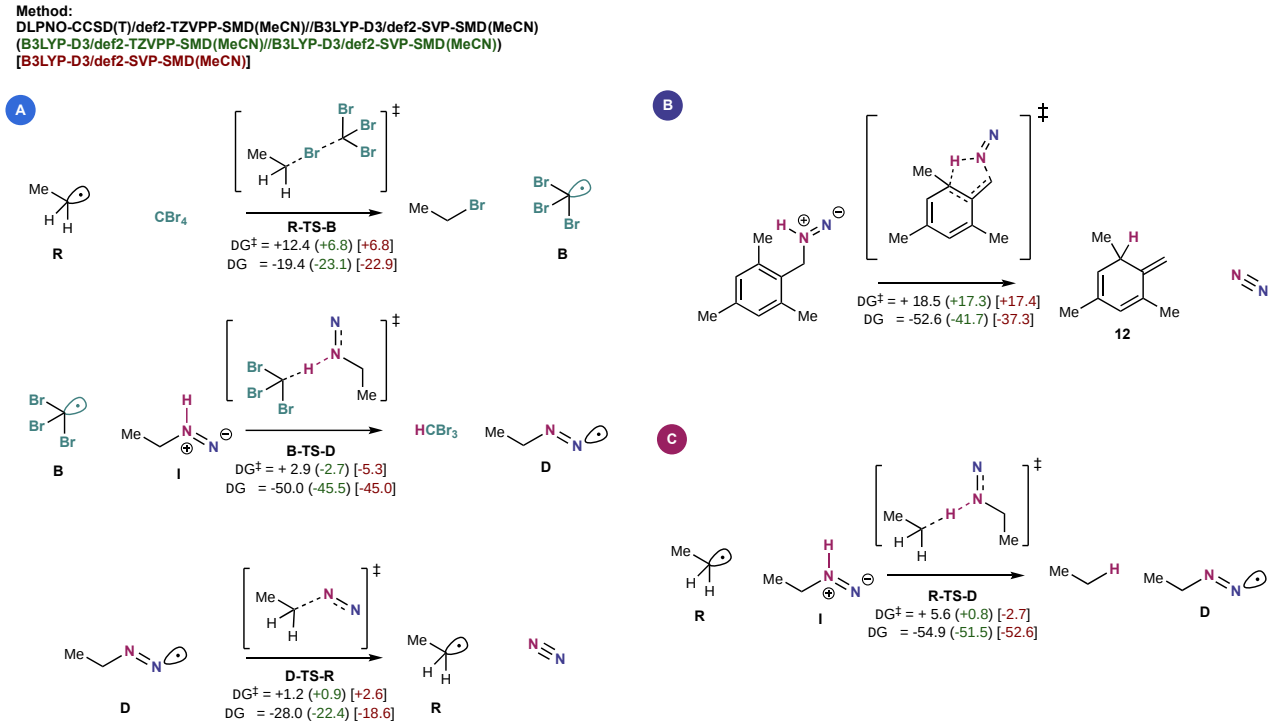


Figure S5: Thermodynamic drive and barrier for (A) chain propagation steps with CBr_3• as chain carrier (B) [2,3]-sigmatropic rearrangement/N_2 extrusion of isodiazene intermediate (C) HAT of isodiazene intermediate from ethyl radical. Gibbs free energies (kcal/mol; 298 K) were computed at the DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN) (black), B3LYP-D3/def2-TZVPP-SMD(MeCN) (green) and B3LYP-D3/def2-SVP-SMD(MeCN) (red) levels of theory.

Comparing the energetics of C–N homolytic cleavage (**Figure S6A**) and [2,3]-sigmatropic rearrangement (**Figure S5B**), the difference of barrier for these two processes was small (only 1.3 kcal/mol). Considering that the generation of benzylic radical $\mathbf{R^{tol}}$ was endergonic (by 6.3 kcal/mol), in the absence of CBr_4, [2,3]-sigmatropic rearrangement was more favorable, resulting in the formation of isotoluene **12** that agrees with the experimental observation. However, when CBr_4 is present, benzylic radical $\mathbf{R^{tol}}$ could undergo Br abstraction to generate the more effective chain carrier CBr_3• **B** (**Figure S6B**, barrier of 16.7 kcal/mol, exergonic by 7.7 kcal/mol).

Comparing the HAT reactivity of benzylic radical $\mathbf{R^{tol}}$ and CBr_3• radical **B**, consistent with the reactivity of ethyl radical versus CBr_3• (**Figure 6D**), HAT with CBr_3• was faster (via $\mathbf{B\text{-}TS\text{-}D^{tol}}$, $\Delta\Delta G^{‡}$ = 5.7 kcal/mol compared to $\mathbf{R\text{-}TS\text{-}D^{tol}}$). Considering the much higher barrier for Br abstraction from CBr_4 with benzylic radical $\mathbf{R^{tol}}$ (**Figure S6D**, 16.7 kcal/mol) versus HAT from isodiazene intermediate (9.8 kcal/mol), the much higher concentration of CBr_4 over isodizene makes the former species a better radical trapping agent.

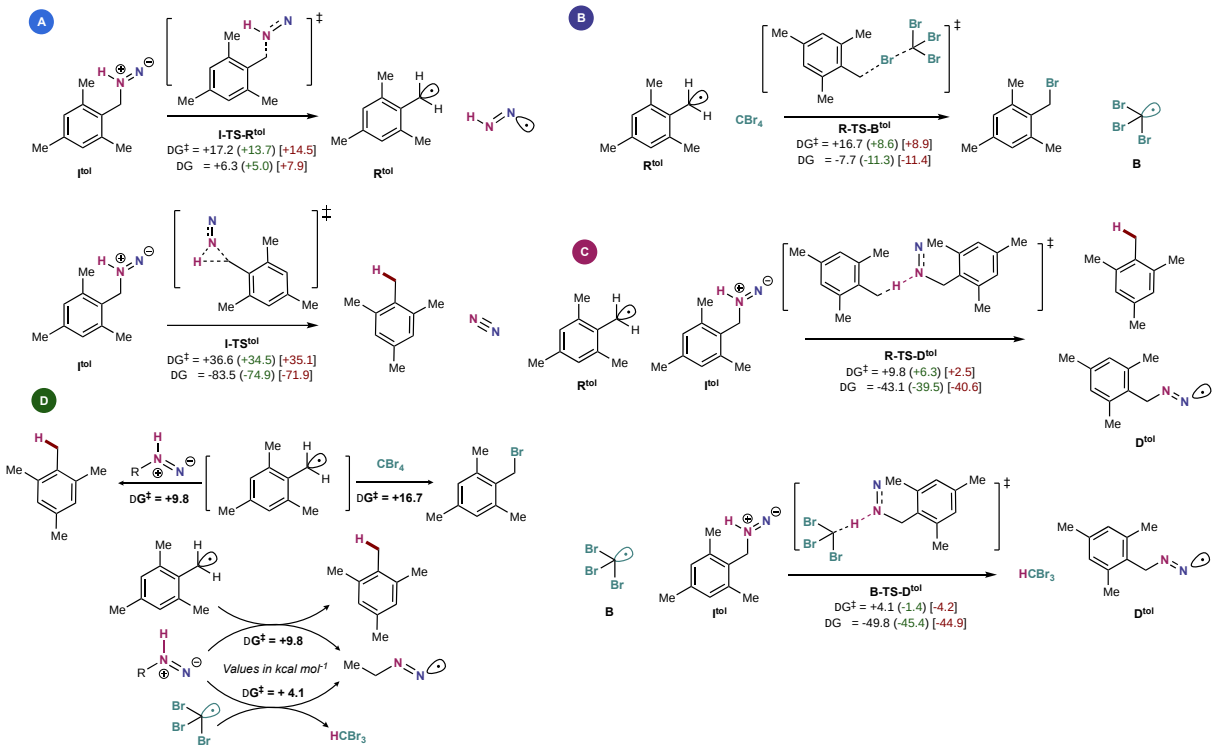


Figure S6: Thermodynamic drive and barrier for tolyl system (A) initiation of radical chain and direct C–H formation from tolyl isodiazene intermediate (B) Br abstraction of CBr_4 with tolyl benzylic radical (C) HAT of isodiazene intermediate from tolyl benzylic radical (D) summary of the divergent reactivity of tolyl benzylic and CBr_3• radical. Gibbs free energies (kcal/mol; 298 K) were computed at the DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN) (black), B3LYP-D3/def2-TZVPP-SMD(MeCN) (green) and B3LYP-D3/def2-SVP-SMD(MeCN) (red) levels of theory.

Reactivity of HAT from H-NN-Et Isodiazene: Thermodynamic (BDE) and Polarity Effect

1. Summary of Computed HAT Thermodynamics, Barrier, BDE and Radical Polarity (kcal/mol unless indicated)

Table S1. Summary of DFT energetics.

Radical		B3LYP-D3/def2-SVP-SMD			B3LYP-D3/def2-TZVPP-SMD		
		E	*H*	*G*	*E*	*H*	*G*
CBr_3•	rxn[c]	-45.1	-45.1	-45.0	-45.5	-45.5	-45.5
	barrier	-13.5	-15.8	-5.3	-10.9	-13.1	-2.7
	BDE[a]	97.5	91.2	82.6	99.0	92.7	84.1
	χ (eV)		/			4.63	
CCl_3•	rxn	-46.4	-46.2	-46.2	-46.4	-46.2	-46.3
	barrier	-9.8	-12.2	-1.4	-6.3	-8.7	2.1
	BDE	98.8	92.4	83.8	99.9	93.5	84.9
	χ (eV)		/			4.68	
iPr•	rxn	-50.8	-49.3	-48.3	-50.0	-48.4	-47.5
	barrier	-3.5	-5.2	5.4	-0.2	-1.9	8.7
	BDE	103.3	95.4	85.9	103.5	95.6	86.1
	χ (eV)		/			3.30	
OMe•	rxn	-53.7	-51.9	-52.4	-54.6	-52.9	-53.3
	barrier	-8.5	-10.3	0.2	-5.5	-7.3	3.2
	BDE	106.1	98.1	90.0	108.1	100.1	92.0
	χ (eV)		/			6.45	
PhS•	rxn	-28.9	-30.8	-31.7	-39.2	-41.0	-41.9
	barrier	-20.9	-23.5	-13.4	-27.9	-30.5	-20.4
	BDE	96.0	90.5	82.7	92.6	88.2	80.5
	χ (eV)		/			5.30	
Et•	rxn	-54.8	-53.2	-52.6	-53.7	-52.1	-51.5
	barrier	-11.2	-12.6	-2.7	-7.7	-9.1	0.8
	BDE	107.2	99.3	90.2	107.1	99.3	90.2
	χ (eV)		/			3.79	
Et-NN•[b]	BDE	52.4	46.2	37.6	53.5	47.2	38.6
	χ (eV)		/			3.76	

[a] BDE of corresponding radical X• was calculated as (X–H → X• + H•)

[b] BDE was calculated as (Et–N=N–H → Et–NN• + H•)

[b] Thermodynamics of HAT reaction was the same as the difference between BDE of reagents and products, i.e., ΔH of reaction (A–H + B• → A• + B–H) = BDE(A–H) – BDE(B–H). Therefore, correlation between the barrier and the BDE can be represented as correlation between the barrier and the reaction thermodynamics.

Table S2. Summary of DLPNO energetics.

Radical		DLPNO-CCSD(T) (gas phase)	DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN) [a]		
		E	*E*	*H*	*G*
CBr_3•	rxn	-52.5	-50.0	-50.0	-50.0
	barrier	-7.6	-5.3	-7.6	2.9
	χ (eV)		4.56		
CCl_3•	rxn	-52.2	-50.9	-50.7	-50.8
	barrier	-1.3	0.7	-1.7	9.1
	χ (eV)		4.54		
iPr•	rxn	-58.6	-54.3	-52.7	-51.8
	barrier	0.6	4.0	2.3	12.9
	χ (eV)		3.35		
OMe•	rxn	-64.1	-60.2	-58.5	-58.9
	barrier	0.0	2.3	0.6	11.1
	χ (eV)		6.62		
PhS•	rxn	-36.1	-22.6	-24.5	-25.3
	barrier	-18.9	-7.1	-9.7	0.4
	χ (eV)		5.27		
Et•	rxn	-61.0	-57.0	-55.4	-54.9
	barrier	-5.8	-2.9	-4.3	5.6
	χ (eV)		3.78		
Et-NN•[b]	χ (eV)		3.38		

[a] BDE with DLPNO-CCSD(T) method was not computed because of issue calculating H• atom energy, but the comparison of BDE of starting and end species

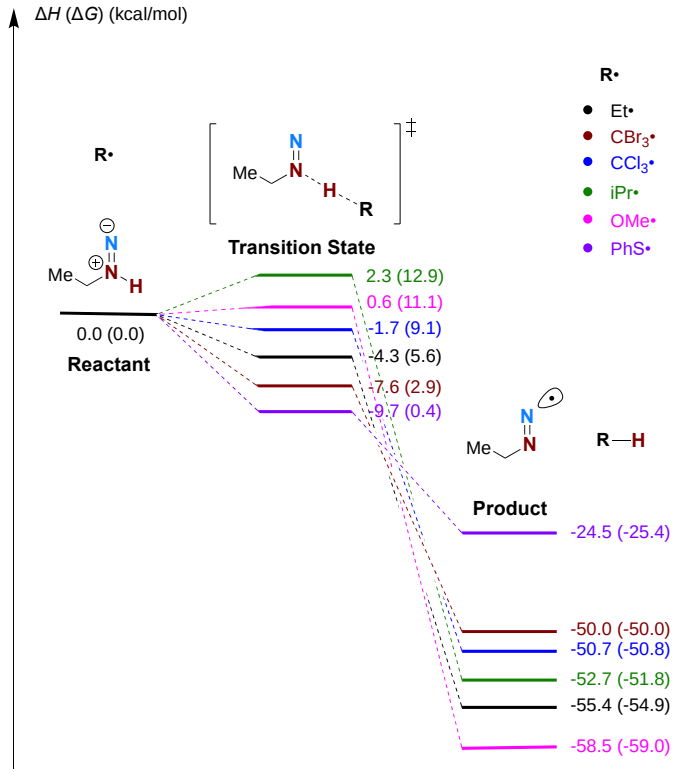


Figure S7. Energy profile of barrier and thermodynamic drive of N–H HAT from ethyl-isodiazene with different chain carrier radicals **R**•. Enthalpies and Gibbs free energies were calculated at the DLPNO-CCSD(T)/def2-TZVPP-SMD(MeCN) level of theory.

HAT of N–H bond with different proposed chain-carrier radicals are explored, including Et•, CBr_3•, CCl_3•, iPr•, OMe• and PhS• radicals. From **Figure S7**, the HAT of N–H bond from isodiazene have large thermodynamic drive due to the weak BDE of N–H in isodiazene (~ 46 kcal/mol) compared to other R–H bonds (> 90 kcal/mol). Consistent with Hammond's postulate, HAT thus have early transition states with low barriers. To avoid the systematic error of calculating entropy in different systems, enthalpies are discussed herein.

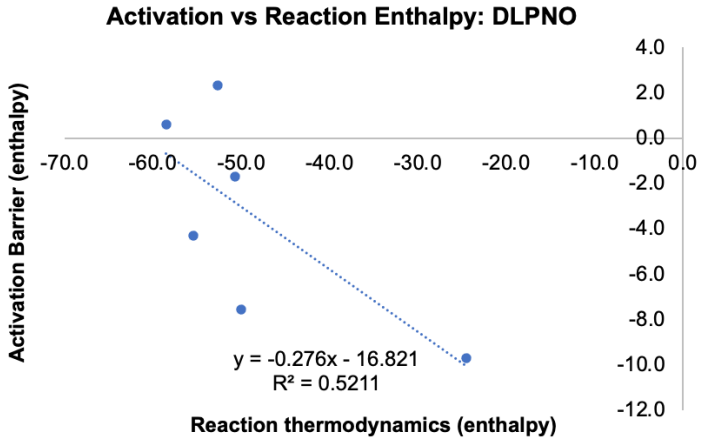


Figure S8. Plot of activation enthalpy vs reaction thermodynamics of HAT based on DLPNO energies.

From **Figure S8**, the correlation between activation $\Delta H^{\ddagger}$ and thermodynamic enthalpies ΔH of HAT reaction is poor (R^2 = 0.5211) based on linear regression. This indicates that thermodynamic effect is not the only affecting factor in the investigated HAT reaction. Considering the different identity of involved radical species, the potential influence of polarity effect is being explored.

Inspired by Houk's work (*JACS* **2022**, *144*, 6802−6812) on exploring the thermodynamic and polarity effect in HAT of C–H bonds, the Mulliken-type electronegativity (χ, eV) was calculated to account for the polarity properties of studied radicals (**Table 1**). Next, the difference in χ between the studied radical and Et–N=N• radical was calculated, i.e., the difference in χ between reactant and product of HAT.

Mulliken-type electronegativity was calculated as

$$\chi_R = (IE_R + EA_R) / 2,$$

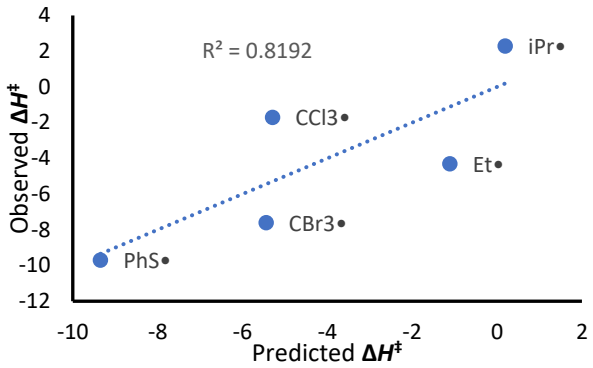
where IE and EA are the vertical ionization energy [$E(R^+)$ - E(R•)] and vertical electron affinity [E(R•) - $E(R^-)$] of radical R•. Next, $\Delta\chi$ was calculated compared to the χ of Et–N=N• radical (3.38, **Table S2**).

Table S3. Comparison of activation, thermodynamic enthalpy and electronegativity based on DLPNO energies.

	Activation $\Delta H^{\ddagger}$	Thermodynamics ΔH	$\Delta\chi$ (eV)	$(\Delta\chi)^2$
CBr_3•	-7.6	-50.0	1.18	1.38
CCl_3•	-1.7	-50.7	1.15	1.33
iPr•	2.3	-52.7	-0.03	0.00
OMe•	0.6	-58.5	3.23	10.46
PhS•	-9.7	-24.5	1.89	3.57
Et•	-4.3	-55.4	0.39	0.16

After obtaining the polarity data, linear regression was performed on the new set of data (**Table S3**). Similar to Houk's work,[60] a simplied Robert's relationship was applied containing the thermodynamic (ΔH) and polarity effects ($\Delta\chi$) of HAT reaction. As a results, the following equation was obtained, with much improved R^2 (0.8192).

$$\Delta H^{\ddagger} = 0.23\Delta H + (-4.5)(\Delta\chi)^2 + 12.4$$



This analysis excludes the alkoxy radical, given its much larger electronegativity than any of the other radicals examined. Overall, based on the much larger coefficient of $(\Delta\chi)^2$ compared to ΔH (0.23 and -4.50), the polarity effect plays an important role than thermodynamic effect in the HAT reaction of N–H from isodiazene. This is likewise in line with a qualitative analysis of polarity effects – the isodiazene hydrogen is hydridic, such that electrophilic radicals undergo faster HAT thanks to polarity effects.

When the alkoxy radical is included, the following equation was obtained.

$$\Delta H^{\ddagger} = 0.40\Delta H + (-6.10)(\Delta\chi)^2 + 22.37$$

Complete regression results from Excel are attached below.

Regression Statistics								
Multiple R	0.905532356							
R Square	**0.819988848**							
Adjusted R Square	0.699981413							
Standard Error	3.454208142							
Observations	6							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	2	163.0522497	81.52612483	6.83281705	0.07637463			
Residual	3	35.79466167	11.93155389					
Total	5	198.8469113						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	**22.37430682**	13.34686108	1.676372196	0.19225859	-20.10136192	64.84997556	-20.10136192	64.84997556
ΔH	**0.404328006**	0.231362046	1.747598675	0.17885828	-0.331969284	1.140625296	-0.331969284	1.140625296
$(\Delta\chi)^2$	**-6.103660403**	1.829695415	-3.335888779	0.04452348	-11.92656782	-0.28075299	-11.92656782	-0.28075299

Coordinates and Energies

Figure S1.A

R

C	1.96256600	1.07471700	-0.17121700
H	1.88510600	0.42301000	0.70520900
H	1.32604900	1.96521800	-0.19755600
C	2.72576800	0.64727500	-1.37316500
H	2.10898600	0.01935900	-2.05368900
H	3.06662800	1.50652400	-1.97644300
H	3.60687200	0.03636500	-1.11036300

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -79.1028939

Zero-point correction= 0.058522 (Hartree/Particle)

Thermal correction to Energy= 0.062493

Thermal correction to Enthalpy= 0.063438

Thermal correction to Gibbs Free Energy= 0.034382

Sum of electronic and zero-point Energies= -79.044372

Sum of electronic and thermal Energies= -79.040400

Sum of electronic and thermal Enthalpies= -79.039456

Sum of electronic and thermal Free Energies= -79.068512

B3LYP-D3/def2-SVP-gas

HF= -79.1021298

Solvent Correction ΔE_{soln} = -0.0007641

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -79.1964283

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -79.003070030481

CBr_4

C	1.78632700	0.90772700	-0.19944100
Br	0.63419100	-0.60864500	0.28019900
Br	0.68769600	2.35392100	-0.94677700
Br	2.71792500	1.55490400	1.40373900
Br	3.10557400	0.33078600	-1.53501100

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -10333.531475

Zero-point correction= 0.006686 (Hartree/Particle)

Thermal correction to Energy= 0.013579

Thermal correction to Enthalpy= 0.014523

Thermal correction to Gibbs Free Energy= -0.028581

Sum of electronic and zero-point Energies= -10333.524789

Sum of electronic and thermal Energies= -10333.517896

Sum of electronic and thermal Enthalpies= -10333.516952

Sum of electronic and thermal Free Energies= -10333.560056

B3LYP-D3/def2-SVP-gas

HF= -10333.5222467

Solvent Correction ΔE_{soln} = -0.0092283

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -10334.8296547

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -10328.8218518214

R-TS-B

C	2.36958600	0.65963800	-1.11124700
H	1.76044700	0.62259300	-2.02080200
H	3.06580700	-0.17517600	-0.97646800
Br	0.58339700	-0.28513000	0.39604200
C	-0.93249900	-1.03225000	1.69909600
Br	-0.96851800	0.07999100	3.30746700
Br	-0.49962800	-2.88373200	2.15763100
Br	-2.65003300	-0.94246900	0.76759500
C	2.71986400	1.98312700	-0.53855000
H	3.12926500	1.90121800	0.48064600
H	3.50794700	2.44959300	-1.16750700
H	1.86258700	2.67464300	-0.53290900

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -10412.6424662

Zero-point correction= 0.068040 (Hartree/Particle)

Thermal correction to Energy= 0.079374

Thermal correction to Enthalpy= 0.080318

Thermal correction to Gibbs Free Energy= 0.024775

Sum of electronic and zero-point Energies= -10412.574426

Sum of electronic and thermal Energies= -10412.563093

Sum of electronic and thermal Enthalpies= -10412.562148

Sum of electronic and thermal Free Energies= -10412.617691

B3LYP-D3/def2-SVP-gas

HF= -10412.6296694

Solvent Correction ΔE_{soln} = -0.0127968

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -10414.0342264

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -10407.8213833117

Et–Br

C	1.80852500	0.91463500	-0.21577900
H	2.27895900	1.25098100	0.71770800
H	1.15153800	1.70919700	-0.59393500
Br	0.58499700	-0.56101200	0.32104200
C	2.82122700	0.46169100	-1.24431900
H	3.46105600	-0.34499600	-0.85475700
H	2.33263700	0.10827800	-2.16529800
H	3.46788700	1.31738300	-1.50530300

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -2653.0504357

Zero-point correction= 0.065483 (Hartree/Particle)

Thermal correction to Energy= 0.069638

Thermal correction to Enthalpy= 0.070582

Thermal correction to Gibbs Free Energy= 0.038071

Sum of electronic and zero-point Energies= -2652.984953

Sum of electronic and thermal Energies= -2652.980798

Sum of electronic and thermal Enthalpies= -2652.979854

Sum of electronic and thermal Free Energies= -2653.012365

B3LYP-D3/def2-SVP-gas

HF= -2653.0441435

Solvent Correction ΔE_{soln} = -0.0062922

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -2653.4581475

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -2651.78241034637

B

C	1.59712200	0.99026200	-0.00851800
Br	0.70396700	-0.65636700	0.20471100
Br	0.75794700	2.33211100	-1.03305200
Br	2.80333200	1.52607300	1.33792800

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -7759.6247542

Zero-point correction= 0.005346 (Hartree/Particle)

Thermal correction to Energy= 0.010575

Thermal correction to Enthalpy= 0.011519

Thermal correction to Gibbs Free Energy= -0.027950

Sum of electronic and zero-point Energies= -7759.619408

Sum of electronic and thermal Energies= -7759.614180

Sum of electronic and thermal Enthalpies= -7759.613235

Sum of electronic and thermal Free Energies= -7759.652705

B3LYP-D3/def2-SVP-gas

HF= -7759.618559

Solvent Correction ΔE_{soln} = -0.0061952

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -7760.6090514

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -7756.07533072845

I

N	0.90330100	-0.26362100	0.14068900
N	0.01418300	-0.31733500	0.95935100
H	1.17313100	-1.08491800	-0.46158500
C	1.77579900	0.92205400	-0.18254100
H	1.64933200	1.10787900	-1.26276900
H	2.81549900	0.58549800	-0.03035500
C	1.43188200	2.13283400	0.65583500
H	2.09348400	2.96935700	0.38308300
H	0.38869100	2.44511300	0.49454800
H	1.55811700	1.92279300	1.72904100

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -189.1146504

Zero-point correction= 0.084465 (Hartree/Particle)

Thermal correction to Energy= 0.089329

Thermal correction to Enthalpy= 0.090273

Thermal correction to Gibbs Free Energy= 0.057428

Sum of electronic and zero-point Energies= -189.030186

Sum of electronic and thermal Energies= -189.025321

Sum of electronic and thermal Enthalpies= -189.024377

Sum of electronic and thermal Free Energies= -189.057222

B3LYP-D3/def2-SVP-gas

HF= -189.1038628

Solvent Correction ΔE_{soln} = -0.0107876

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -189.3383711

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -188.923853588782

B-TS-D

C	2.76520600	-2.12781200	-0.43923600
Br	0.82399100	-1.92623100	-0.55530200
Br	3.34720800	-2.49149000	1.39485000
Br	3.42639500	-3.48678200	-1.68213500
N	3.93815700	0.50905900	-1.25661800

N	3.38304200	1.27121400	-1.95993600
H	3.41012500	-0.63036800	-0.92063000
C	5.29470600	0.65055300	-0.61400300
H	5.08548700	0.70787600	0.46537000
H	5.71064300	1.60565400	-0.96209400
C	6.16196300	-0.54656200	-0.95989300
H	6.32272000	-0.62027200	-2.04631200
H	7.13979400	-0.42144200	-0.47014800
H	5.71887900	-1.48755900	-0.60048600

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -7948.7609525

Zero-point correction= 0.085651 (Hartree/Particle)

Thermal correction to Energy= 0.097283

Thermal correction to Enthalpy= 0.098227

Thermal correction to Gibbs Free Energy= 0.042585

Sum of electronic and zero-point Energies= -7948.675301

Sum of electronic and thermal Energies= -7948.663670

Sum of electronic and thermal Enthalpies= -7948.662725

Sum of electronic and thermal Free Energies= -7948.718367

B3LYP-D3/def2-SVP-gas

HF= -7948.7475667

Solvent Correction ΔE_{soln} = -0.0133858

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -7949.9647609

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -7945.01128321985

$HCBr_3$

C	1.75540200	0.92120000	-0.16861500
Br	0.65480400	-0.63627000	0.25368500
Br	0.70850400	2.35412500	-0.98515300
Br	2.75726600	1.54708100	1.38731500
H	2.49148400	0.59933400	-0.91327900

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -7760.280888

Zero-point correction= 0.017721 (Hartree/Particle)

Thermal correction to Energy= 0.022917

Thermal correction to Enthalpy= 0.023861

Thermal correction to Gibbs Free Energy= -0.014894

Sum of electronic and zero-point Energies= -7760.263167

Sum of electronic and thermal Energies= -7760.257971

Sum of electronic and thermal Enthalpies= -7760.257027

Sum of electronic and thermal Free Energies= -7760.295782

B3LYP-D3/def2-SVP-gas

HF= -7760.2720736

Solvent Correction ΔE_{soln} = -0.0036532

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -7761.2685339

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -7756.73365492158

D

N	0.94435200	-0.29194900	0.10128600
N	0.07595500	-0.34588900	0.88854700
C	1.79345400	0.92238800	-0.17936800
H	1.67504800	1.10180700	-1.25960200
H	2.82891200	0.58126000	-0.02262300
C	1.44186500	2.13687000	0.65937200
H	2.10476800	2.97387500	0.38954000
H	0.39987300	2.44957900	0.48703700
H	1.56641700	1.92703500	1.73345300

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -188.5303372

Zero-point correction= 0.072105 (Hartree/Particle)

Thermal correction to Energy= 0.077001

Thermal correction to Enthalpy= 0.077945

Thermal correction to Gibbs Free Energy= 0.044445

Sum of electronic and zero-point Energies= -188.458232

Sum of electronic and thermal Energies= -188.453337

Sum of electronic and thermal Enthalpies= -188.452392

Sum of electronic and thermal Free Energies= -188.485892

B3LYP-D3/def2-SVP-gas

HF= -188.5261721

Solvent Correction ΔE_{soln} = -0.0041651

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -188.7514046

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -188.349252778873

D-TS-R

N	0.73414700	-0.13316100	0.51415500
N	0.86864500	-1.21916500	0.20440000
C	1.86144300	1.18369600	-0.22048500
H	2.28054100	1.58282400	0.71069500
H	1.09512200	1.83553200	-0.65622300
C	2.80986400	0.52027500	-1.16536500
H	3.43532900	-0.22835800	-0.65265000
H	2.27712900	0.02324200	-1.99215700
H	3.48625800	1.27427200	-1.60828400

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -188.521917

Zero-point correction= 0.068708 (Hartree/Particle)

Thermal correction to Energy= 0.073950

Thermal correction to Enthalpy= 0.074895

Thermal correction to Gibbs Free Energy= 0.040155

Sum of electronic and zero-point Energies= -188.453209

Sum of electronic and thermal Energies= -188.447967

Sum of electronic and thermal Enthalpies= -188.447022

Sum of electronic and thermal Free Energies= -188.481762

B3LYP-D3/def2-SVP-gas

HF= -188.5207498

Solvent Correction ΔE_{soln} = -0.0011672

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -188.7456472

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -188.346119007306

N_2

N	0.92631100	-0.22751400	0.15637700
N	0.27497800	-0.16523700	1.04056100

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -109.4342155

Zero-point correction= 0.005683 (Hartree/Particle)

Thermal correction to Energy= 0.008043

Thermal correction to Enthalpy= 0.008987

Thermal correction to Gibbs Free Energy= -0.012758

Sum of electronic and zero-point Energies= -109.428533

Sum of electronic and thermal Energies= -109.426172

Sum of electronic and thermal Enthalpies= -109.425228

Sum of electronic and thermal Free Energies= -109.446973

B3LYP-D3/def2-SVP-gas

HF= -109.4392209

Solvent Correction ΔE_{soln} = 0.0050054

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -109.567901

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -109.37643781953

Figure S1.B

Starting Reagent

N	0.89347700	-0.27511400	0.14435000
N	0.00809300	-0.34702500	0.96029700
H	1.17338300	-1.08352600	-0.47052200
C	1.77834600	0.92899500	-0.18097200
H	1.65071100	1.09544300	-1.26003900
H	2.80867000	0.57609000	-0.03111200
C	1.44200600	2.13303800	0.64548600
C	2.06030200	2.32501300	1.90023800
C	0.45943100	3.04808000	0.19865800
C	1.72163200	3.45157200	2.66626200
C	0.14886400	4.15927800	0.99258000
C	0.77410900	4.38465200	2.22824000
H	2.20770400	3.59824800	3.63553600
H	-0.60870100	4.86720200	0.64178600

C	3.06318300	1.33100800	2.43648600
H	2.63423500	0.31656300	2.48500100
H	3.96038000	1.26953100	1.79718800
H	3.39315100	1.60653000	3.44885400
C	-0.26837700	2.83269400	-1.10720700
H	0.41946200	2.86414300	-1.96943900
H	-0.76550300	1.84891000	-1.12998600
H	-1.03717800	3.60317800	-1.26512500
C	0.42024300	5.59724300	3.05274500
H	0.94759100	5.60244200	4.01856200
H	0.67975800	6.52803400	2.51954800
H	-0.66355200	5.63914200	3.25400000

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -498.6019922

Zero-point correction= 0.219841 (Hartree/Particle)

Thermal correction to Energy= 0.232605

Thermal correction to Enthalpy= 0.233549

Thermal correction to Gibbs Free Energy= 0.179963

Sum of electronic and zero-point Energies= -498.382152

Sum of electronic and thermal Energies= -498.369388

Sum of electronic and thermal Enthalpies= -498.368443

Sum of electronic and thermal Free Energies= -498.422030

B3LYP-D3/def2-SVP-gas

HF= -498.5828927

Solvent Correction ΔE_{soln} = -0.0190995

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -499.1584045

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -498.024515385686

Transition State

N	1.40929300	-1.02157200	-0.12393500
N	0.62224300	-1.77018700	0.22090300
H	2.36728300	-1.10191500	-0.78958100
C	1.76881700	1.15989900	-0.22076200
H	2.22526700	1.17895500	0.76954500
H	0.80724500	1.66997300	-0.30087300
C	2.53741300	0.87386800	-1.36821800
C	2.05893100	1.16753600	-2.69862200
C	3.65957600	-0.02688700	-1.23294500
C	2.73649600	0.66574600	-3.79473700
C	4.32789000	-0.48544700	-2.40614600
C	3.88518200	-0.16561900	-3.67656300
H	2.37740600	0.91739800	-4.79809800
H	5.21694400	-1.11217500	-2.28629400
C	0.83332100	2.02398000	-2.88673300
H	-0.06513100	1.53056900	-2.47582900
H	0.92815900	2.98976000	-2.36258200

H	0.64712500	2.22703600	-3.95161600
C	4.35191900	-0.20120400	0.10777600
H	4.76535500	0.76209500	0.45585900
H	3.68264100	-0.55756200	0.90770800
H	5.18236800	-0.91785600	0.02754300
C	4.57503400	-0.66706700	-4.91903000
H	3.89277800	-1.28236500	-5.53144400
H	4.90209000	0.17073400	-5.55892700
H	5.45855100	-1.27728000	-4.67774100

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -498.5695308

Zero-point correction= 0.213159 (Hartree/Particle)

Thermal correction to Energy= 0.225605

Thermal correction to Enthalpy= 0.226549

Thermal correction to Gibbs Free Energy= 0.175304

Sum of electronic and zero-point Energies= -498.356371

Sum of electronic and thermal Energies= -498.343926

Sum of electronic and thermal Enthalpies= -498.342982

Sum of electronic and thermal Free Energies= -498.394227

B3LYP-D3/def2-SVP-gas

HF= -498.5629103

Solvent Correction ΔE_{soln} = -0.0066205

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -499.1262441

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -498.002847462924

12

H	3.06949000	-1.34890500	-0.64893600
C	1.25742100	0.57771500	-0.43385900
H	1.32025000	-0.02526000	0.47795300
H	0.41221000	1.26578000	-0.50721200
C	2.18836700	0.45839800	-1.40531200
C	2.12062700	1.22518600	-2.66420000
C	3.40211700	-0.44757200	-1.19213700
C	2.93997400	0.88209800	-3.69384500
C	4.08149800	-0.87499800	-2.46780700
C	3.89555600	-0.22923100	-3.63778900
H	2.87041200	1.43658100	-4.63581800
H	4.80501400	-1.69414500	-2.39452600
C	1.10977700	2.33135200	-2.80483900
H	0.07827300	1.94369600	-2.73555300
H	1.21740800	3.07848200	-1.99969400
H	1.21224800	2.84576200	-3.77182200
C	4.43898200	0.26125600	-0.28531700
H	4.79985000	1.18858000	-0.75957400
H	3.98578000	0.52252200	0.68471700
H	5.30893200	-0.39004300	-0.10007200

C	4.62412700	-0.58588800	-4.90647400
H	3.91459800	-0.85169300	-5.71001700
H	5.20806500	0.27459400	-5.27866400
H	5.31305700	-1.43169100	-4.76053400

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -389.2091889

Zero-point correction= 0.209747 (Hartree/Particle)

Thermal correction to Energy= 0.220135

Thermal correction to Enthalpy= 0.221079

Thermal correction to Gibbs Free Energy= 0.174746

Sum of electronic and zero-point Energies= -388.999442

Sum of electronic and thermal Energies= -388.989054

Sum of electronic and thermal Enthalpies= -388.988110

Sum of electronic and thermal Free Energies= -389.034443

B3LYP-D3/def2-SVP-gas

HF= -389.201312

Solvent Correction ΔE_{soln} = -0.0078769

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -389.6389339

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -388.730189302025

Figure S1.C

R-TS-D

N	-0.89921600	2.48753100	-6.05806400
C	-0.93955500	1.49808800	-7.19067700
H	-0.05830100	0.85339500	-7.03975600
H	-1.83211100	0.88020500	-6.99926600
N	-0.88579900	3.67303600	-6.12023400
C	-0.88310800	1.41031200	-3.60472400
H	-1.62466800	0.59889600	-3.55053200
H	0.14474000	1.04439600	-3.45604400
C	-0.96052600	2.16214300	-8.54966700
H	-0.99062000	1.38913400	-9.33300700
H	-1.84532700	2.80759400	-8.66262700
H	-0.06221900	2.77985800	-8.70370000
C	-1.23388800	2.67894900	-2.87203500
H	-2.28037900	2.97846100	-3.05538500
H	-1.11100700	2.59338500	-1.77266500
H	-0.59411100	3.52119900	-3.19523800
H	-0.88815500	1.92315400	-5.04856000

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -268.2354478

Zero-point correction= 0.141361 (Hartree/Particle)

Thermal correction to Energy= 0.150604

Thermal correction to Enthalpy= 0.151548

Thermal correction to Gibbs Free Energy= 0.105357

Sum of electronic and zero-point Energies= -268.094087

Sum of electronic and thermal Energies= -268.084844

Sum of electronic and thermal Enthalpies= -268.083899

Sum of electronic and thermal Free Energies= -268.130090

B3LYP-D3/def2-SVP-gas

HF= -268.2285227

Solvent Correction ΔE_{soln} = -0.0069251

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -268.5470861

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -267.936219550181

Et-H

C	1.73995500	0.89956100	-0.21966400
H	2.08467600	0.77429300	0.82087700
H	1.48083000	1.96334700	-0.35490800
H	0.81016100	0.31632600	-0.33103400
C	2.80431600	0.45175200	-1.21825900
H	3.73429900	1.03441800	-1.10662900
H	3.06397600	-0.61174900	-1.08274400
H	2.46057300	0.57659600	-2.25896700

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -79.7744617

Zero-point correction= 0.073875 (Hartree/Particle)

Thermal correction to Energy= 0.077348

Thermal correction to Enthalpy= 0.078292

Thermal correction to Gibbs Free Energy= 0.050770

Sum of electronic and zero-point Energies= -79.700586

Sum of electronic and thermal Energies= -79.697113

Sum of electronic and thermal Enthalpies= -79.696169

Sum of electronic and thermal Free Energies= -79.723692

B3LYP-D3/def2-SVP-gas

HF= -79.7734399

Solvent Correction ΔE_{soln} = -0.0010218

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -79.8688983

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -79.674892495728

Figure S2.A

I-TS-R^{tol}

N	0.64586900	1.52145200	-0.46625700
C	-1.13172200	1.61525900	-1.66736900
H	-0.69452400	1.30175100	-2.61652100
H	-1.70095900	0.83820700	-1.15497800
N	1.38378000	0.65097600	-0.24725000
H	0.67899600	2.52138400	-0.10743300
C	-1.45823300	3.00125000	-1.45174100
C	-0.89549800	4.01853500	-2.28461900

C	-2.22929200	3.39640100	-0.31725200
C	-1.16979800	5.36161700	-2.01367900
C	-2.47556300	4.75581700	-0.08790300
C	-1.96793500	5.75727900	-0.92741200
H	-0.74308700	6.13007900	-2.66629400
H	-3.07958400	5.04324700	0.77833600
C	-2.26007000	7.21594300	-0.68280200
H	-1.33700800	7.81936300	-0.70254600
H	-2.92170800	7.62468400	-1.46705000
H	-2.75425300	7.37602000	0.28752200
C	-2.78032400	2.36354500	0.63406000
H	-3.46097900	1.66058200	0.12343500
H	-1.97465400	1.75298200	1.07686700
H	-3.33778200	2.83599400	1.45613500
C	-0.00794600	3.65194600	-3.44784400
H	0.87539500	3.08027000	-3.11474800
H	-0.53541300	3.01527700	-4.17888900
H	0.34826900	4.54863600	-3.97595100

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -498.575225

Zero-point correction= 0.215561 (Hartree/Particle)

Thermal correction to Energy= 0.228352

Thermal correction to Enthalpy= 0.229296

Thermal correction to Gibbs Free Energy= 0.176236

Sum of electronic and zero-point Energies= -498.359664

Sum of electronic and thermal Energies= -498.346873

Sum of electronic and thermal Enthalpies= -498.345929

Sum of electronic and thermal Free Energies= -498.398989

B3LYP-D3/def2-SVP-gas

HF= -498.5651157

Solvent Correction ΔE_{soln} = -0.0101093

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -499.1328273

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -498.002356749287

R^{tol}

C	1.87877500	0.97289200	-0.25483000
H	2.09555200	0.93715600	0.81349700
H	0.90301200	1.36763600	-0.54063900
C	2.80808400	0.53373600	-1.21299300
C	2.50497400	0.58858200	-2.62479700
C	4.09864600	0.01297000	-0.81469300
C	3.44878700	0.14668100	-3.55051500
C	4.99759700	-0.41260000	-1.78592400
C	4.70308000	-0.35861500	-3.16410900
H	3.20455400	0.19486200	-4.61629600
H	5.97025500	-0.80414700	-1.47068000

C	1.17782900	1.11920000	-3.10102000
H	0.33609700	0.53242000	-2.69405100
H	1.01760600	2.16245800	-2.77786200
H	1.10925900	1.09143700	-4.19844600
C	4.46979800	-0.06940100	0.64314900
H	4.44958800	0.92395900	1.12392400
H	3.76430200	-0.70445700	1.20641400
H	5.47883600	-0.48733600	0.77335400
C	5.71216700	-0.83132700	-4.17662100
H	5.33719100	-0.73088200	-5.20628800
H	6.65283600	-0.25848200	-4.09880800
H	5.97609700	-1.89056600	-4.01136600

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -388.6138331

Zero-point correction= 0.196765 (Hartree/Particle)

Thermal correction to Energy= 0.207261

Thermal correction to Enthalpy= 0.208205

Thermal correction to Gibbs Free Energy= 0.160329

Sum of electronic and zero-point Energies= -388.417068

Sum of electronic and thermal Energies= -388.406572

Sum of electronic and thermal Enthalpies= -388.405628

Sum of electronic and thermal Free Energies= -388.453504

B3LYP-D3/def2-SVP-gas

HF= -388.6053172

Solvent Correction ΔE_{soln} = -0.0085159

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -389.0405704

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -388.127113488738

diazenyl radical

N	2.63806900	-0.30573600	-2.10924700
H	3.32545200	-0.18542400	-2.90977500
N	2.04815400	-1.31795200	-2.02560500

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -109.9478687

Zero-point correction= 0.013523 (Hartree/Particle)

Thermal correction to Energy= 0.016383

Thermal correction to Enthalpy= 0.017327

Thermal correction to Gibbs Free Energy= -0.008141

Sum of electronic and zero-point Energies= -109.934345

Sum of electronic and thermal Energies= -109.931486

Sum of electronic and thermal Enthalpies= -109.930542

Sum of electronic and thermal Free Energies= -109.956010

B3LYP-D3/def2-SVP-gas

HF= -109.9462523

Solvent Correction ΔE_{soln} = -0.0016164

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -110.0820337

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -109.868579496508

I-TS^{tol}

N	0.40467800	0.40241000	0.57766300
N	-0.55974100	0.93325500	0.86550800
H	1.27340800	-0.05815900	0.29759400
C	1.99164100	1.85041500	-0.49890700
H	2.35855700	1.29054400	-1.36284100
H	2.69631200	1.92870500	0.33262500
C	0.96067800	2.81573900	-0.65226900
C	0.53893700	3.62052100	0.45697200
C	0.17757700	2.89333400	-1.85792600
C	-0.53714100	4.51330000	0.31271000
C	-0.88628700	3.78830100	-1.94522500
C	-1.26143800	4.62804700	-0.87636400
H	-0.81758900	5.13629200	1.16888300
H	-1.45495500	3.83917400	-2.88046800
C	1.29353500	3.57026400	1.76281100
H	1.32168300	2.55346100	2.18979900
H	2.34720500	3.87780500	1.63314700
H	0.84081600	4.23608300	2.51307500
C	0.50849400	2.00172100	-3.02765600

H	1.54596200	2.14968800	-3.37600200
H	0.42401700	0.93392600	-2.75607700
H	-0.16414100	2.18671000	-3.87878600
C	-2.41538400	5.58885000	-1.02341300
H	-3.35257300	5.06136100	-1.27525500
H	-2.59053300	6.15905100	-0.09781300
H	-2.23733500	6.31526500	-1.83614300

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -498.5410391

Zero-point correction= 0.214112 (Hartree/Particle)

Thermal correction to Energy= 0.227300

Thermal correction to Enthalpy= 0.228244

Thermal correction to Gibbs Free Energy= 0.174926

Sum of electronic and zero-point Energies= -498.326927

Sum of electronic and thermal Energies= -498.313739

Sum of electronic and thermal Enthalpies= -498.312795

Sum of electronic and thermal Free Energies= -498.366114

B3LYP-D3/def2-SVP-gas

HF= -498.5238177

Solvent Correction ΔE_{soln} = -0.0172214

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -499.0983882

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -497.96303101806

Tolyl Bz-H product

C	1.75655900	0.89276600	-0.21919500
H	2.07982500	0.77635200	0.82247300
H	1.48683300	1.95295400	-0.36584200
C	2.80281000	0.45237300	-1.21572700
C	2.51493700	0.55049500	-2.60013800
C	4.05685400	-0.05406400	-0.80782900
C	3.47147400	0.14668300	-3.53999400
C	4.99103200	-0.44909000	-1.78206700
C	4.72180400	-0.35782400	-3.15211000
H	3.23580500	0.22752000	-4.60628000
H	5.95953600	-0.84027600	-1.45495600
C	1.18259900	1.08702900	-3.06290900
H	0.34511000	0.48080900	-2.67683500
H	1.01145800	2.11522500	-2.70031900
H	1.11299400	1.09954400	-4.16078700
C	4.42094600	-0.18386100	0.65416900
H	4.39274800	0.79002600	1.17154800
H	3.72430200	-0.84881100	1.19222100
H	5.43413700	-0.59553400	0.77405600
C	5.73403400	-0.77934600	-4.18919600
H	5.31796600	-1.54437400	-4.86668700
H	6.03517900	0.07335200	-4.82207100

H	6.64308600	-1.19352800	-3.72710600
H	0.82151500	0.31932000	-0.34214400

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -389.2630715

Zero-point correction= 0.209663 (Hartree/Particle)

Thermal correction to Energy= 0.220582

Thermal correction to Enthalpy= 0.221526

Thermal correction to Gibbs Free Energy= 0.173440

Sum of electronic and zero-point Energies= -389.053409

Sum of electronic and thermal Energies= -389.042489

Sum of electronic and thermal Enthalpies= -389.041545

Sum of electronic and thermal Free Energies= -389.089632

B3LYP-D3/def2-SVP-gas

HF= -389.2539373

Solvent Correction ΔE_{soln} = -0.0091342

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -389.6906471

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -388.776844848959

Figure S2.B

R-TS-B^{tol}

C	2.16401200	1.78495100	-0.38114100
H	2.59513400	2.15522000	0.54955300

H	1.40099900	2.43262400	-0.81425200
C	2.95594600	0.96202100	-1.24168500
C	2.53772400	0.71201400	-2.59180300
C	4.15360200	0.34550200	-0.75249800
C	3.33564400	-0.08030500	-3.41187500
C	4.91517500	-0.43986800	-1.61770600
C	4.53363400	-0.66056000	-2.95209400
H	3.02024200	-0.26497000	-4.44301000
H	5.83249900	-0.90374300	-1.24429800
C	1.24252800	1.27645700	-3.11245800
H	0.39136400	0.94689500	-2.49282900
H	1.24139500	2.37948500	-3.09527400
H	1.05754600	0.95468200	-4.14729000
C	4.57959200	0.51968000	0.68101400
H	4.77893000	1.57760500	0.92182500
H	3.78972300	0.17873000	1.37160200
H	5.49278600	-0.05354200	0.89558800
C	5.37645600	-1.49131900	-3.87988000
H	4.76320700	-2.23459300	-4.41578900
H	5.84575100	-0.85457000	-4.65082700
H	6.17879100	-2.01964400	-3.34413800
Br	0.58948100	0.29926600	0.69383700
C	-0.99138900	-0.98445200	1.78480200
Br	-2.27773700	-1.57117000	0.44650300

Br	-1.83126500	0.13066100	3.14001900
Br	-0.05463100	-2.49307400	2.58274000

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -10722.1489139

Zero-point correction= 0.204969 (Hartree/Particle)

Thermal correction to Energy= 0.224004

Thermal correction to Enthalpy= 0.224948

Thermal correction to Gibbs Free Energy= 0.149515

Sum of electronic and zero-point Energies= -10721.943945

Sum of electronic and thermal Energies= -10721.924910

Sum of electronic and thermal Enthalpies= -10721.923966

Sum of electronic and thermal Free Energies= -10721.999398

B3LYP-D3/def2-SVP-gas

HF= -10722.1290927

Solvent Correction ΔE_{soln} = -0.0198212

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -10723.8742324

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -10716.9380631566

Bz-Br product

C	1.81727400	0.92730200	-0.21998800
H	2.26261500	1.25156500	0.72503700
H	1.13784400	1.70434200	-0.58270900

C	2.81589000	0.48206900	-1.23288400
C	2.50951400	0.56285900	-2.61341900
C	4.06161700	-0.04647500	-0.81582400
C	3.46623000	0.14797300	-3.54862400
C	4.98920800	-0.44977900	-1.78553000
C	4.71570100	-0.35449700	-3.15734500
H	3.22723300	0.21280800	-4.61451600
H	5.95154200	-0.85641200	-1.46012500
C	1.16868600	1.07032200	-3.08513600
H	0.34160400	0.50492900	-2.62467900
H	1.01753200	2.13036700	-2.81834400
H	1.07339700	0.98411400	-4.17727300
C	4.39384000	-0.19623600	0.64889000
H	4.44861700	0.78194400	1.15665300
H	3.62578100	-0.78628500	1.17598600
H	5.36250400	-0.69819800	0.78667200
C	5.74269700	-0.75939300	-4.18431700
H	5.26914000	-1.14929900	-5.09900600
H	6.35904600	0.10759400	-4.48283900
H	6.42854600	-1.52643200	-3.79237900
Br	0.57469400	-0.57603000	0.32913500

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -2962.540516

Zero-point correction= 0.201212 (Hartree/Particle)

Thermal correction to Energy= 0.213135

Thermal correction to Enthalpy= 0.214079

Thermal correction to Gibbs Free Energy= 0.161554

Sum of electronic and zero-point Energies= -2962.339304

Sum of electronic and thermal Energies= -2962.327381

Sum of electronic and thermal Enthalpies= -2962.326437

Sum of electronic and thermal Free Energies= -2962.378962

B3LYP-D3/def2-SVP-gas

HF= -2962.5278338

Solvent Correction ΔE_{soln} = -0.0126822

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -2963.2809895

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -2960.88663064634

Figure S2.C

R-TS-D^{tol}

C	2.77208800	1.66299600	0.34206200
H	3.27485000	1.54706500	1.30297400
H	2.21554000	2.59251400	0.20753700
C	3.15400800	0.87364800	-0.77778800
C	2.61512700	1.12996500	-2.08527900
C	4.03957100	-0.25102700	-0.61473100
C	2.98839900	0.31727000	-3.15846700

C	4.37185700	-1.03101300	-1.71894500
C	3.86634300	-0.76774600	-3.00760900
H	2.57396200	0.52999300	-4.14896300
H	5.04916600	-1.88027000	-1.58098600
C	1.64526700	2.26292800	-2.30014700
H	0.73900700	2.12720100	-1.68592200
H	2.08064500	3.23643400	-2.01577300
H	1.33336400	2.32674500	-3.35308800
C	4.59634900	-0.58505500	0.74464300
H	5.20939500	0.23985900	1.14765300
H	3.79270400	-0.76242400	1.47678900
H	5.22496900	-1.48695800	0.70894400
C	4.26395000	-1.63373300	-4.17458000
H	3.73531000	-1.34588700	-5.09598600
H	5.34849100	-1.56475700	-4.37164200
H	4.04860200	-2.69776800	-3.97539100
H	1.35075200	0.70570200	0.68398700
N	0.51778700	-0.03651800	0.65207400
N	0.13672100	-0.50519700	-0.38152700
C	0.06191300	-0.41328100	2.05135300
H	-0.41396000	0.48557800	2.46292100
H	-0.70038000	-1.18957800	1.91584500
C	1.25102800	-0.86089300	2.86018000
C	1.94209100	0.05263600	3.68910300

C	1.72288300	-2.18991900	2.72612300
C	3.08525100	-0.38244600	4.37650400
C	2.86377600	-2.58348500	3.43642900
C	3.56376800	-1.69407300	4.26419700
H	3.61876000	0.32717900	5.01583100
H	3.22467800	-3.61107900	3.33096100
C	1.02347600	-3.17937000	1.82553300
H	-0.01507800	-3.35967900	2.15160800
H	0.96663800	-2.81597500	0.78675600
H	1.54694300	-4.14638300	1.81796500
C	4.81931400	-2.13231600	4.97474500
H	4.72746200	-3.16063400	5.35939600
H	5.68046700	-2.12369000	4.28304500
H	5.06562000	-1.46677900	5.81610400
C	1.47676800	1.48096100	3.85142200
H	0.47627100	1.52917900	4.31445900
H	2.16812200	2.05006600	4.48971300
H	1.40603400	2.00185900	2.88371500

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -887.2322968

Zero-point correction= 0.416021 (Hartree/Particle)

Thermal correction to Energy= 0.440040

Thermal correction to Enthalpy= 0.440984

Thermal correction to Gibbs Free Energy= 0.360759

Sum of electronic and zero-point Energies= -886.816276

Sum of electronic and thermal Energies= -886.792257

Sum of electronic and thermal Enthalpies= -886.791312

Sum of electronic and thermal Free Energies= -886.871538

B3LYP-D3/def2-SVP-gas

HF= -887.2107785

Solvent Correction ΔE_{soln} = -0.0215183

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -888.2093841

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -886.162621111193

D^{tol}

N	0.93478200	-0.30902400	0.10551200
N	0.06648100	-0.37555700	0.88511000
C	1.79972500	0.93589900	-0.17984200
H	1.67178900	1.09156300	-1.25846300
H	2.82416000	0.57420600	-0.02607000
C	1.45410500	2.13853700	0.64846300
C	2.06949900	2.33085600	1.90561500
C	0.46599500	3.04747900	0.19863600
C	1.72055300	3.45377800	2.67171500
C	0.14664100	4.15419300	0.99468800
C	0.76734700	4.38086000	2.23265100

H	2.20439100	3.60326700	3.64159600
H	-0.61330000	4.85889300	0.64275600
C	3.08106000	1.34494200	2.44045800
H	2.66459800	0.32502900	2.48475100
H	3.98022700	1.29591400	1.80282400
H	3.40560400	1.62095600	3.45431000
C	-0.25226700	2.83318500	-1.11271600
H	0.44090200	2.87807400	-1.97012000
H	-0.74014500	1.84507500	-1.14776000
H	-1.02713400	3.59764200	-1.26946600
C	0.40317300	5.58937300	3.05823200
H	0.93478300	5.60126100	4.02156700
H	0.64917300	6.52253200	2.52288200
H	-0.68017000	5.61846700	3.26411200

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -498.0181456

Zero-point correction= 0.207486 (Hartree/Particle)

Thermal correction to Energy= 0.220216

Thermal correction to Enthalpy= 0.221160

Thermal correction to Gibbs Free Energy= 0.167595

Sum of electronic and zero-point Energies= -497.810659

Sum of electronic and thermal Energies= -497.797930

Sum of electronic and thermal Enthalpies= -497.796985

Sum of electronic and thermal Free Energies= -497.850550

B3LYP-D3/def2-SVP-gas

HF= -498.0070228

Solvent Correction ΔE_{soln} = -0.0111228

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -498.5720311

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -497.451646921297

B-TS-D^{tol}

C	3.10150400	-2.32283800	-0.74089600
Br	1.28613100	-2.75208500	-1.31841600
Br	3.35655400	-2.65901500	1.16847800
Br	4.44469500	-3.25267600	-1.82162500
N	3.70300300	0.56180700	-1.24869800
N	3.08648500	1.31013800	-1.90948800
H	3.32501200	-0.66132600	-1.02271400
C	5.03549600	0.78136200	-0.52045400
H	5.57003300	-0.16415100	-0.67137400
H	4.73632900	0.82543200	0.53543800
C	5.78167500	1.98784900	-0.99859000
C	5.57745300	3.24068800	-0.37880300
C	6.66505300	1.86976200	-2.09958600
C	6.28786800	4.35385900	-0.85262000
C	7.35160700	3.00703400	-2.53935400

C	7.18065600	4.25846000	-1.92726000
H	6.13384100	5.32343100	-0.37026700
H	8.03711600	2.91785600	-3.38756300
C	4.60949100	3.40268900	0.76890100
H	3.59327600	3.07920700	0.48817300
H	4.90917000	2.79835300	1.64198000
H	4.55105700	4.45178600	1.09261200
C	6.86732400	0.54922600	-2.80397900
H	7.30071000	-0.20893900	-2.12946200
H	5.91533500	0.13508300	-3.17551500
H	7.54447200	0.65889500	-3.66320700
C	7.94146000	5.45964600	-2.42843700
H	7.67562300	6.37268000	-1.87510000
H	9.02968800	5.30569800	-2.33071800
H	7.74125900	5.63611200	-3.49876100

B3LYP-D3/def2-SVP-SMD(MeCN)

HF= -8258.2488775

Zero-point correction= 0.221151 (Hartree/Particle)

Thermal correction to Energy= 0.240600

Thermal correction to Enthalpy= 0.241544

Thermal correction to Gibbs Free Energy= 0.167399

Sum of electronic and zero-point Energies= -8258.027727

Sum of electronic and thermal Energies= -8258.008277

Sum of electronic and thermal Enthalpies= -8258.007333

Sum of electronic and thermal Free Energies= -8258.081478

B3LYP-D3/def2-SVP-gas

HF= -8258.2290785

Solvent Correction ΔE_{soln} = -0.019799

B3LYP-D3/def2-TZVPP-SMD(MeCN)

HF= -8259.7851285

DLPNO-CCSD(T)/def2-TZVPP-gas

HF= -8254.11417655505

VIII. References

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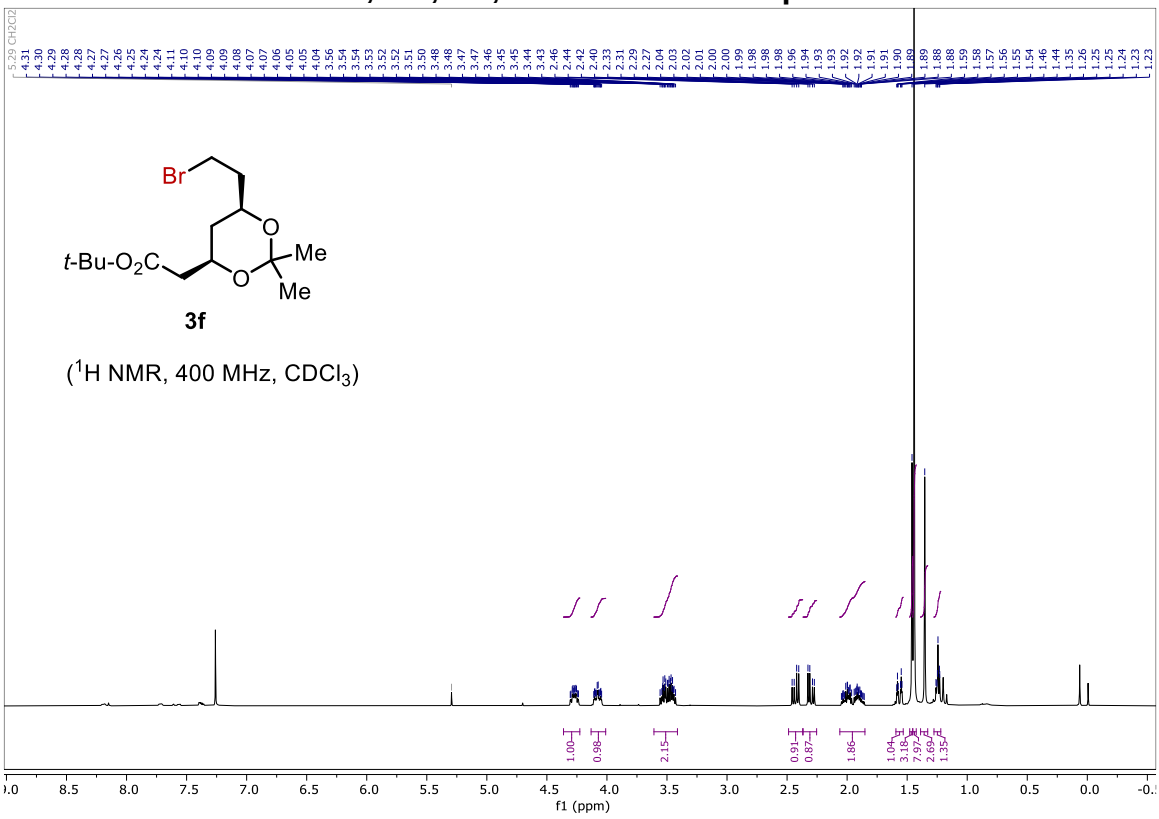
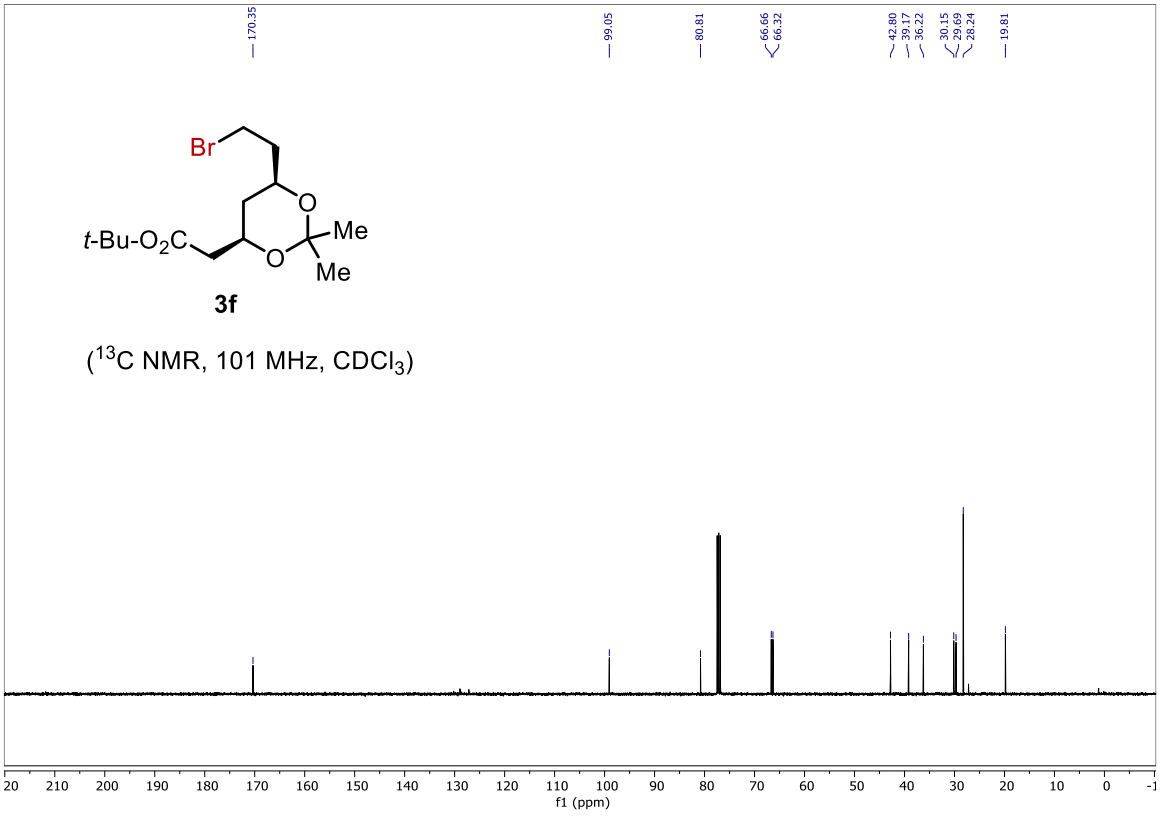
IX. ^{1}H, ^{13}C, ^{19}F, ^{31}P and 2D NMR Spectra



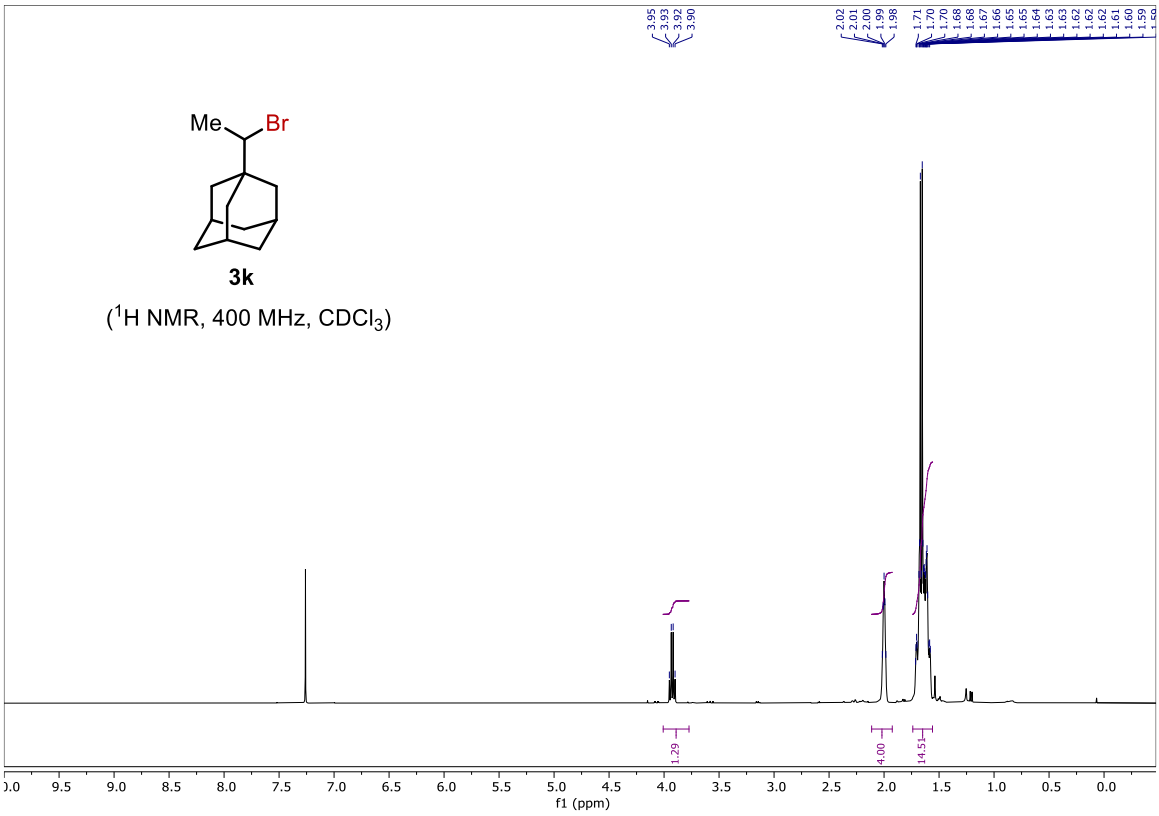
3f

(^{1}H NMR, 400 MHz, $CDCl_3$)



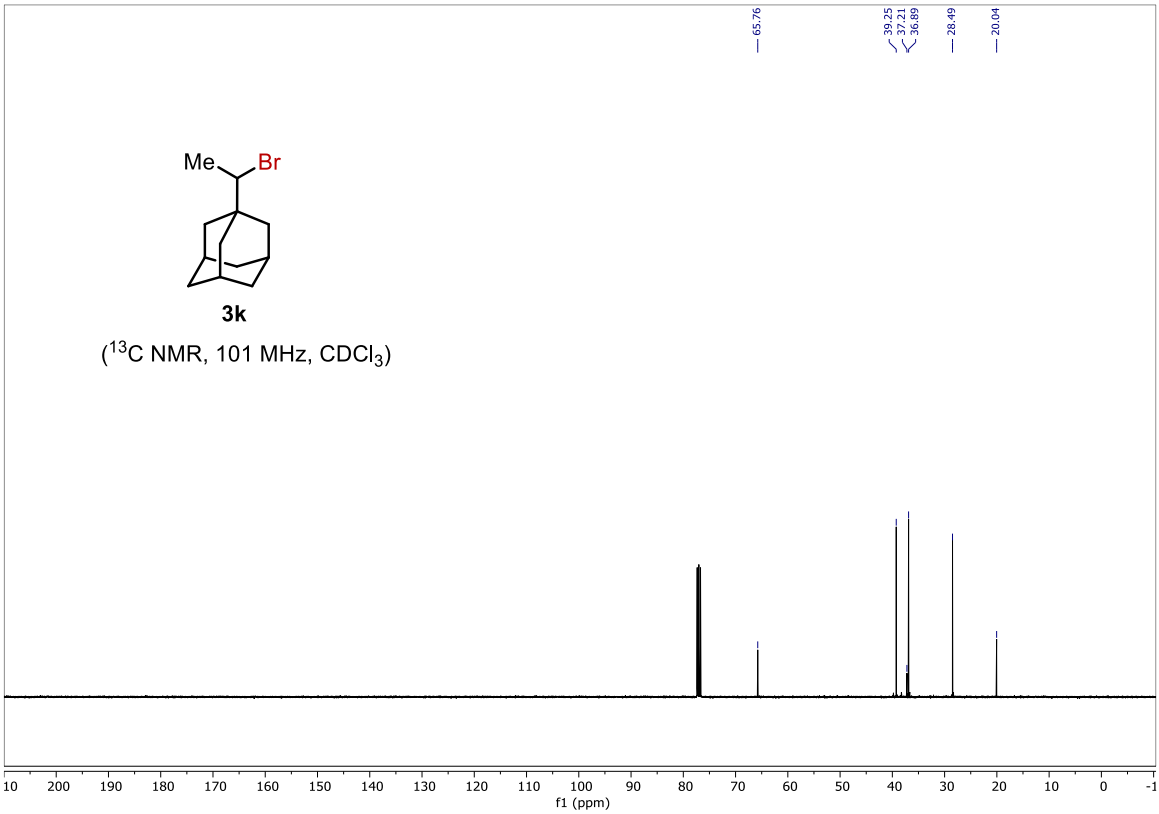
3f

(^{13}C NMR, 101 MHz, $CDCl_3$)



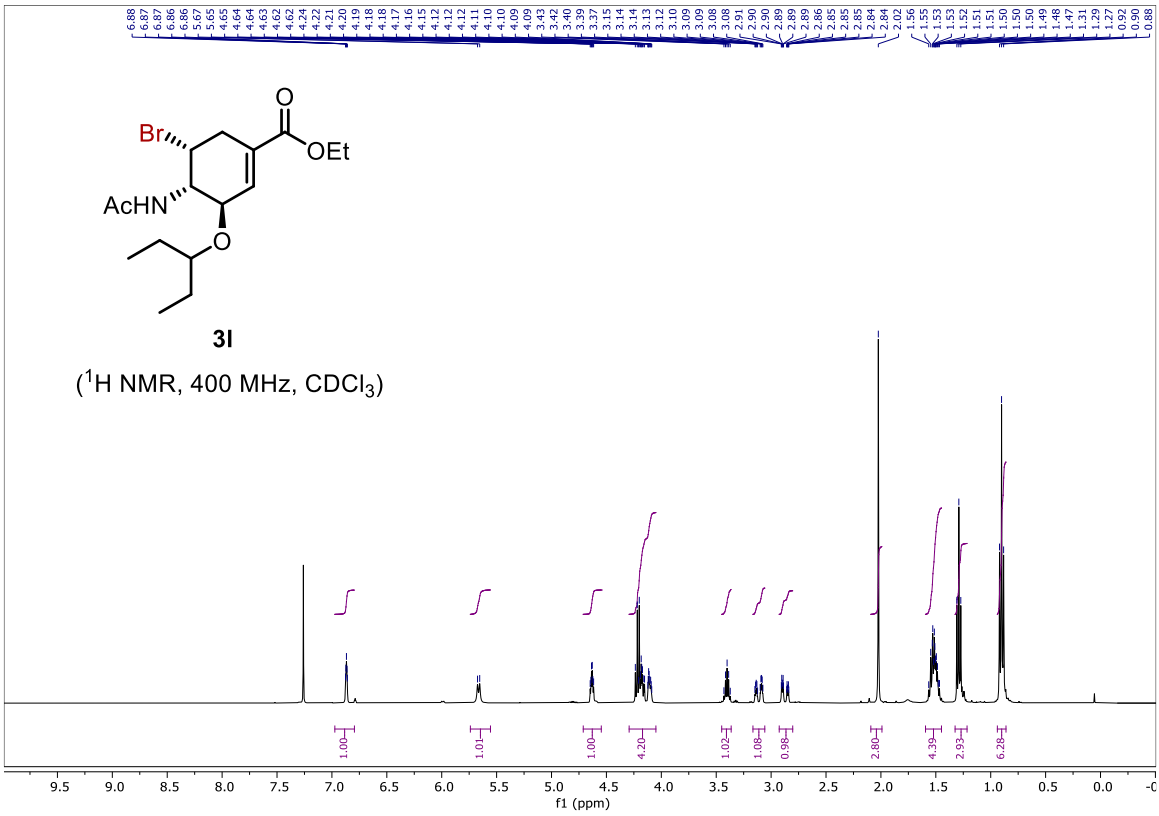
3k

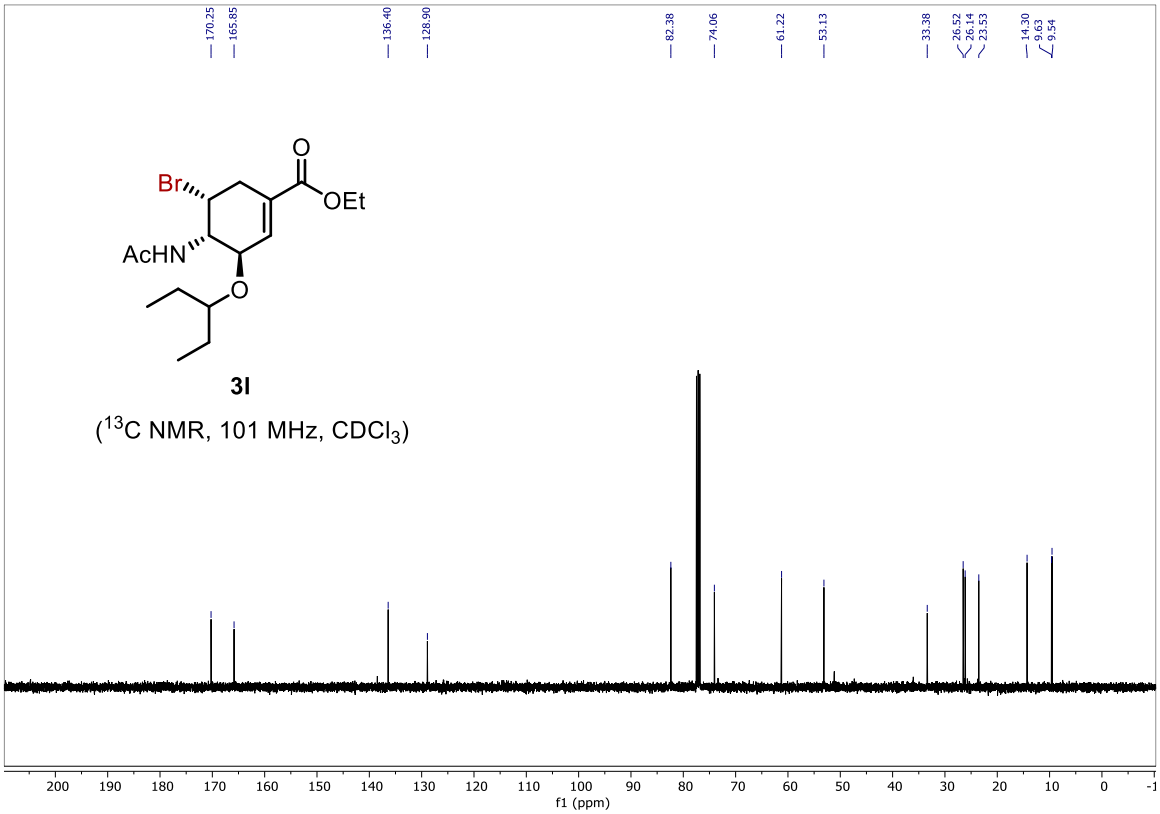
(^{1}H NMR, 400 MHz, $CDCl_3$)

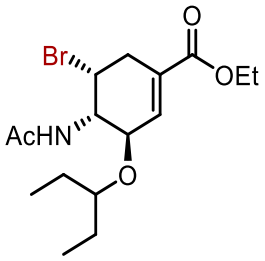


3k

(^{13}C NMR, 101 MHz, $CDCl_3$)

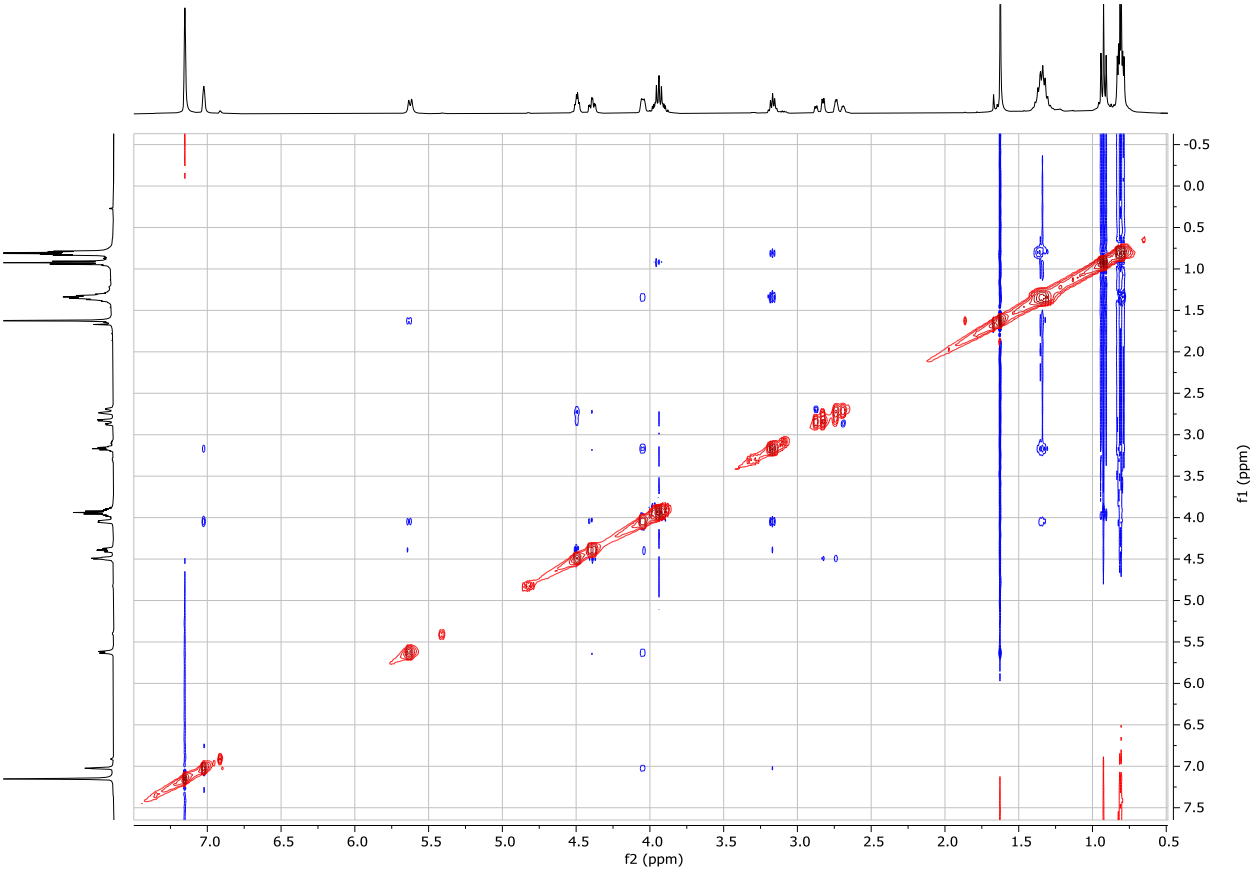

Br
OEt
AcHN
O
O
3l
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)

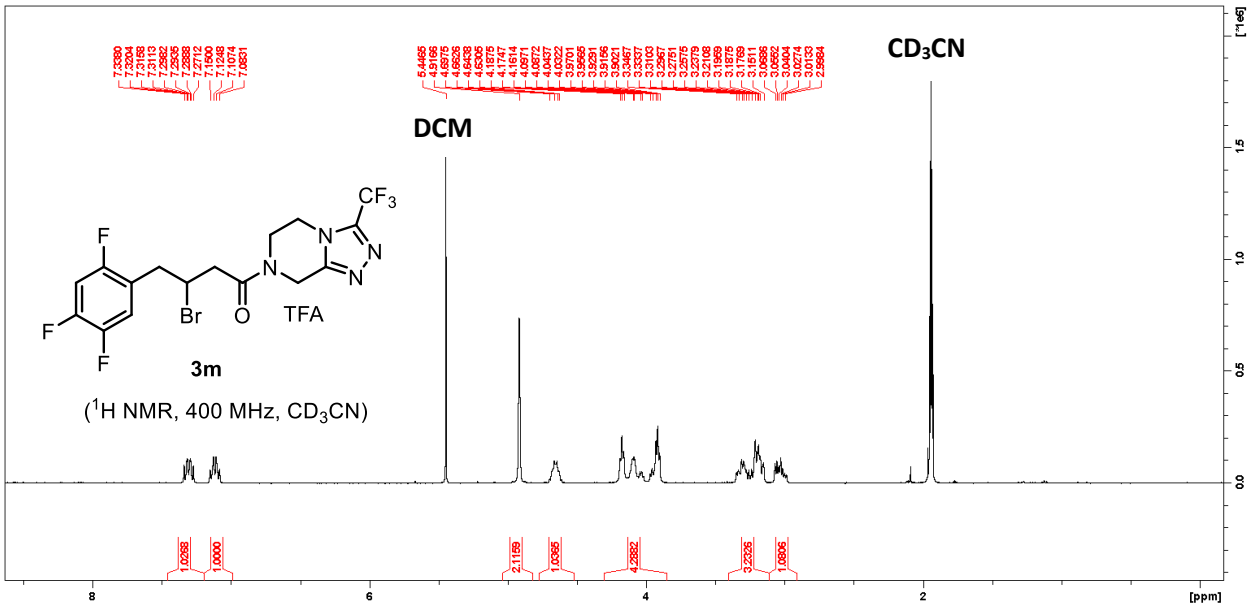

Br
OEt
AcHN
O
O
3l
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)

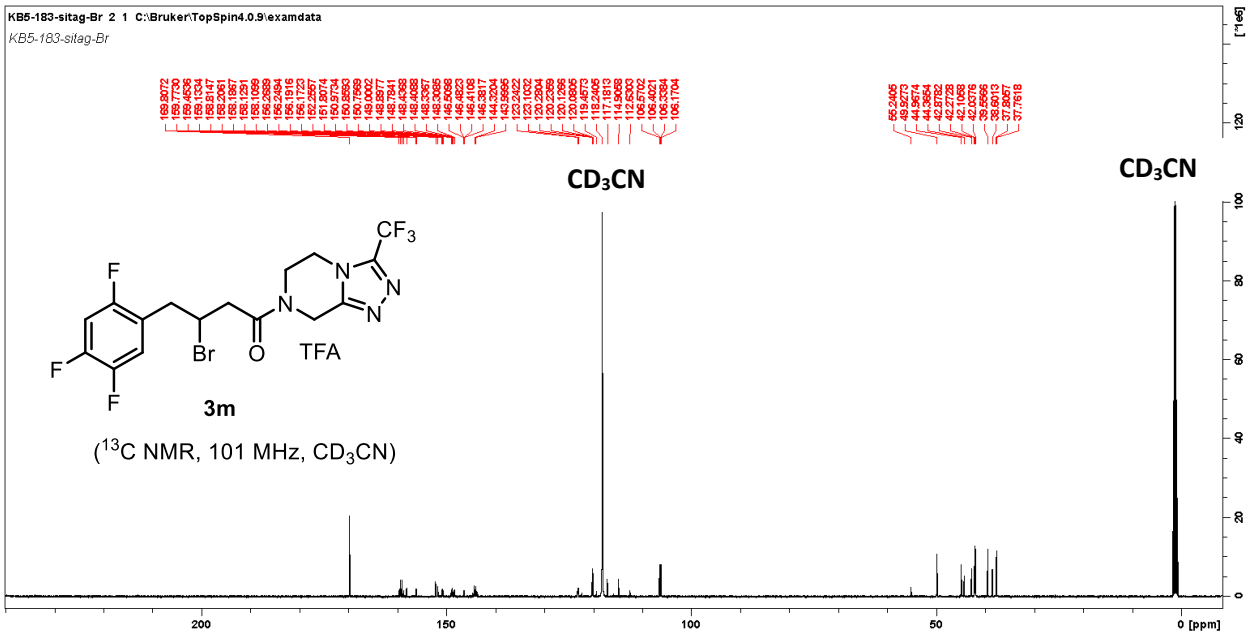


3l

(NOESY, 400 MHz, C_6D_6)




CD3CN
DCM
CF3
F
F
F
N
N
N
N
Br
O
TFA
3m
(1H NMR, 400 MHz, CD3CN)
8
6
4
2
[ppm]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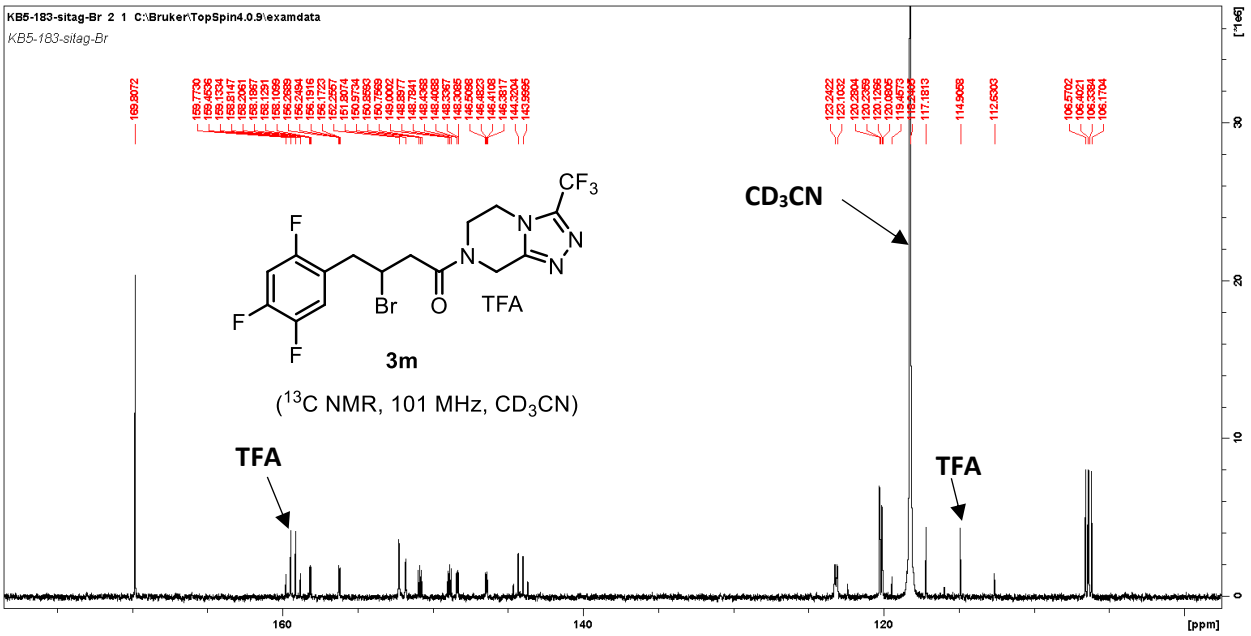
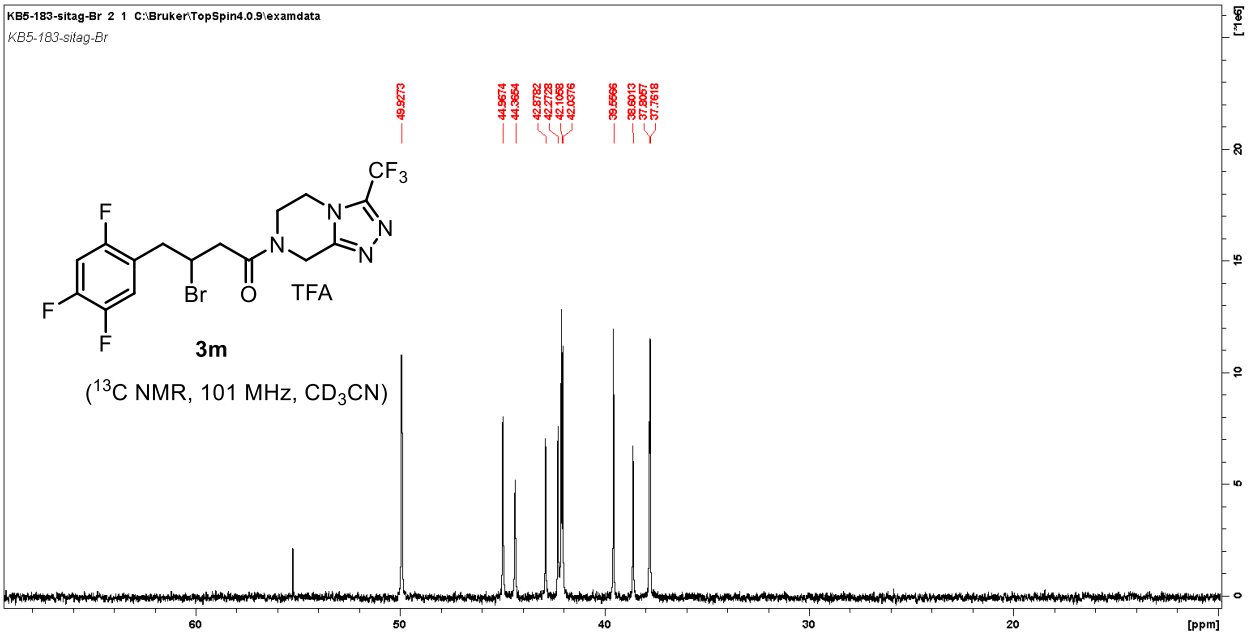
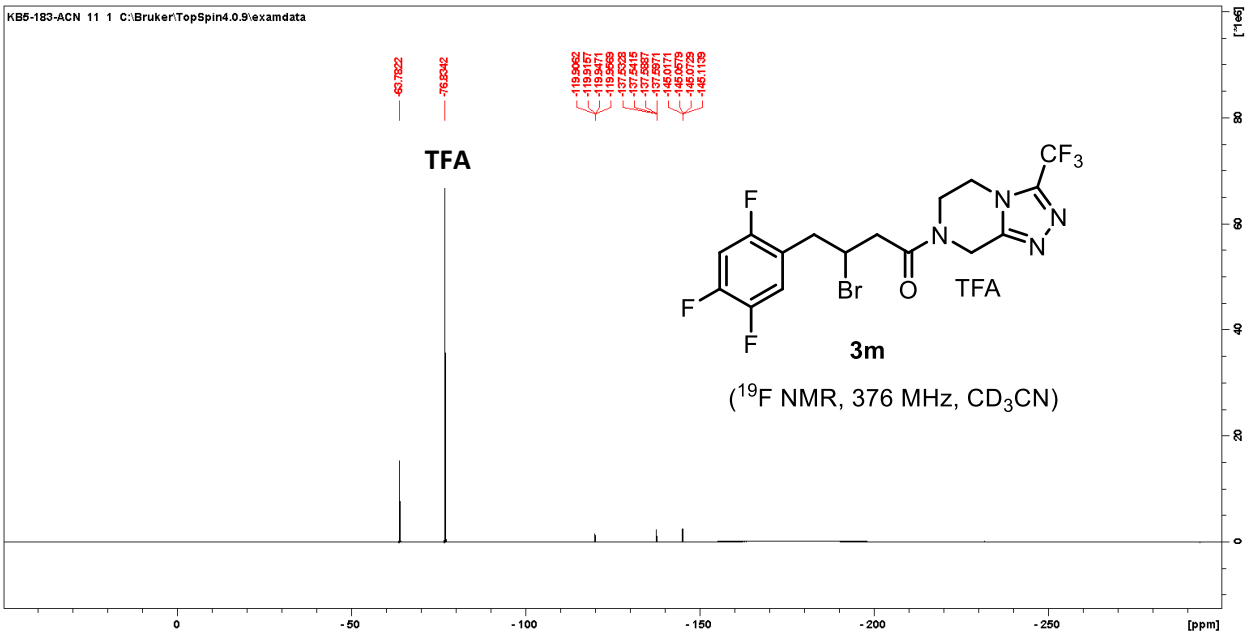
KB5-183-sitag-Br
CD3CN
CD3CN
CF3
F
F
F
N
N
N
N
Br
O
TFA
3m
(13C NMR, 101 MHz, CD3CN)
200
150
100
50
0 [ppm]

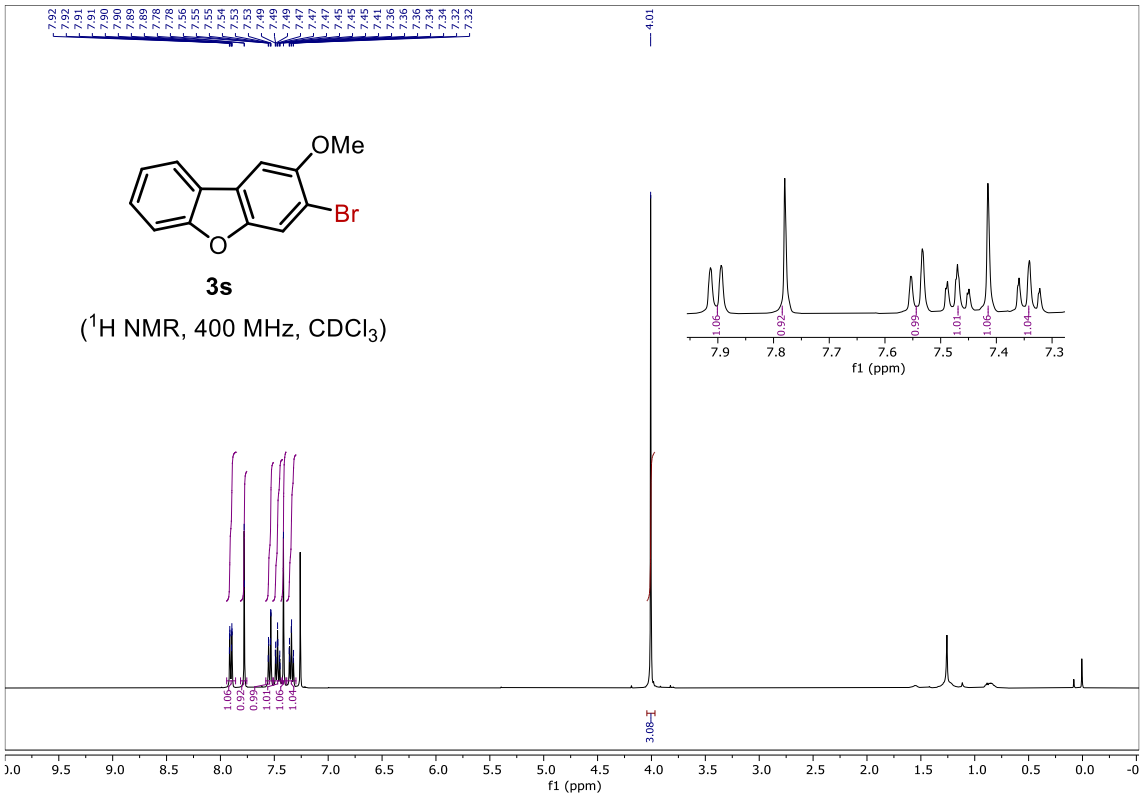
^{13}C spectrum – zoom into aromatic region

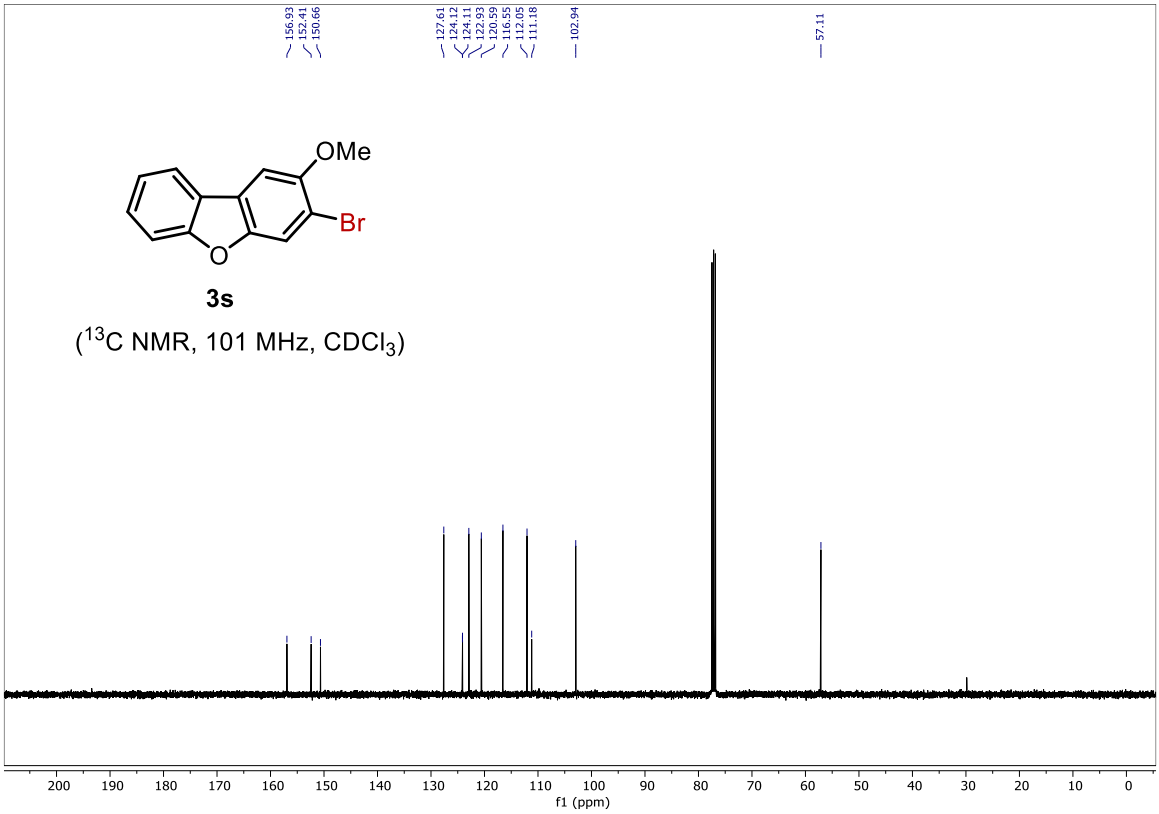


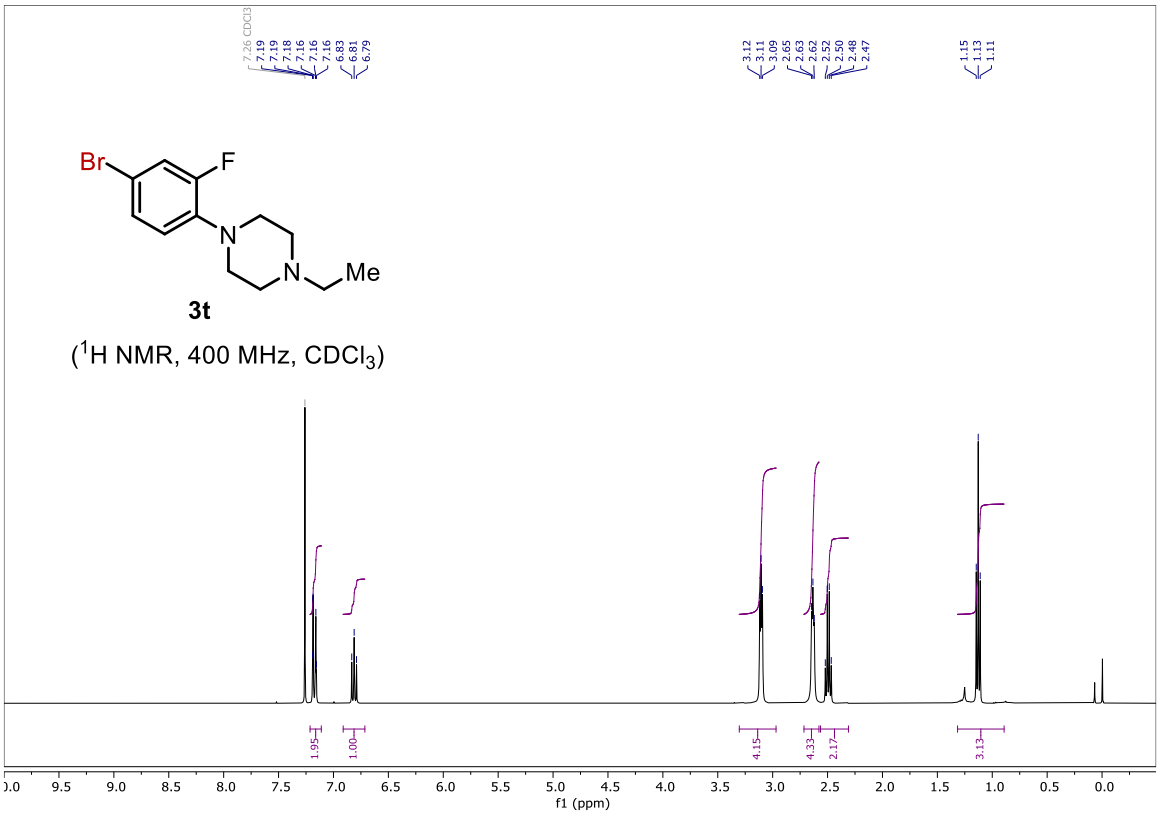
^{13}C spectrum – zoom into aliphatic region

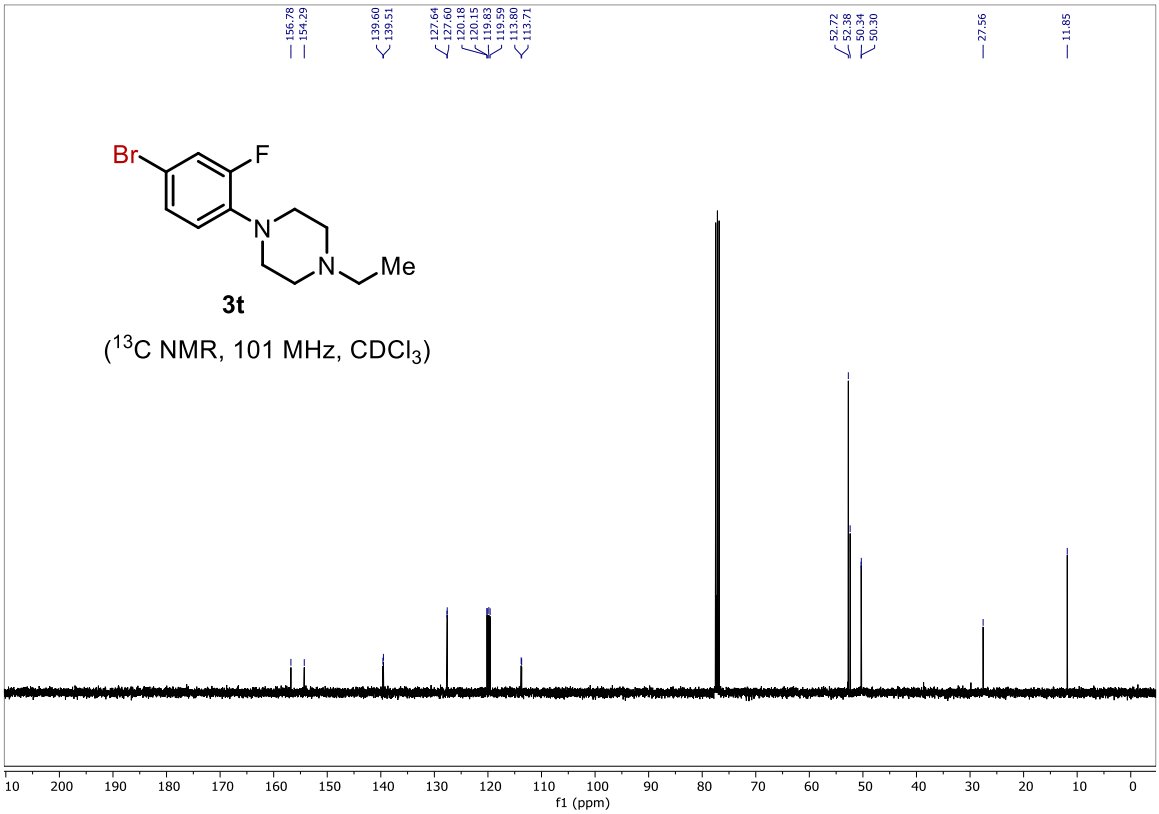


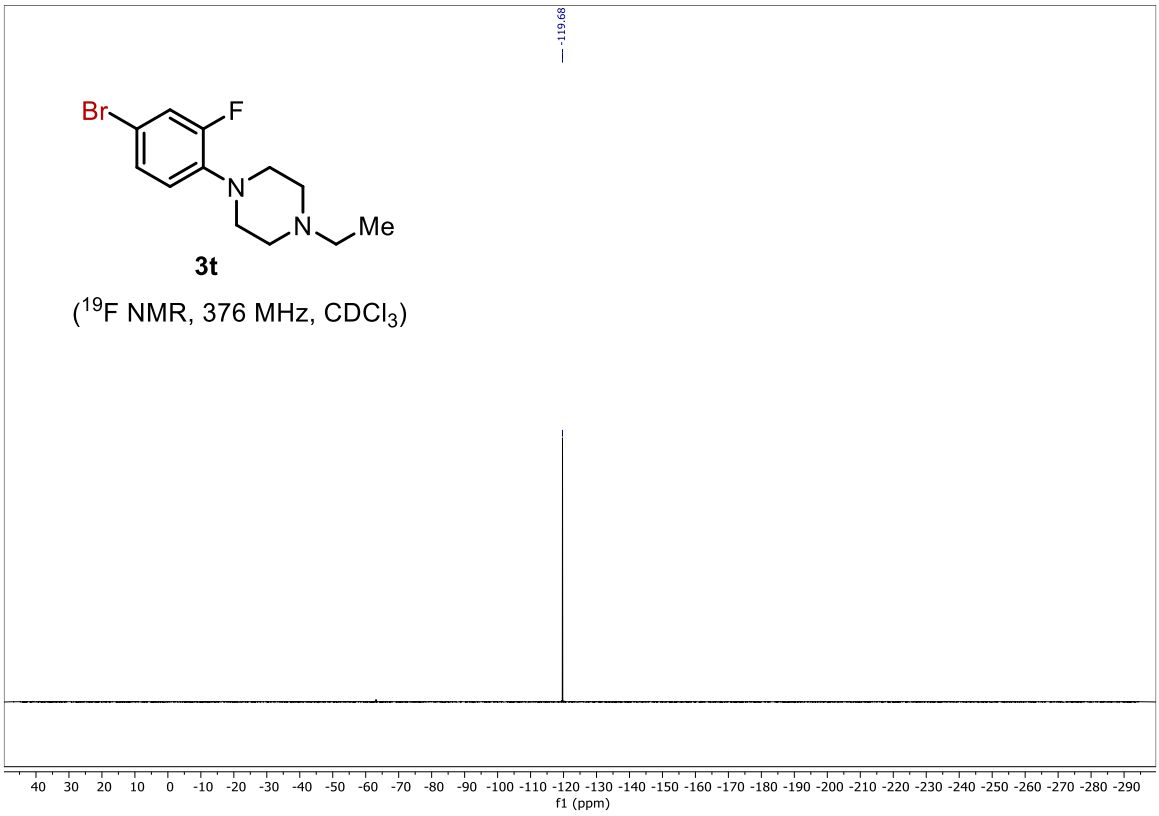

KB5-183-ACN 11 1 C:\Bruker\TopSpin4.0.9\examdata
-63.7822
-76.5342
-119.9062
-119.9157
-119.9471
-119.9569
-137.4228
-137.5415
-137.8887
-137.8971
-145.0171
-145.0279
-145.0729
-145.1139
TFA
CF3
F
F
F
N
N
N
N
Br
O
TFA
3m
(19F NMR, 376 MHz, CD3CN)
0
-50
-100
-150
-200
-250
[ppm]


OMe
Br
O
3s
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)


OMe
Br
O
3s
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)

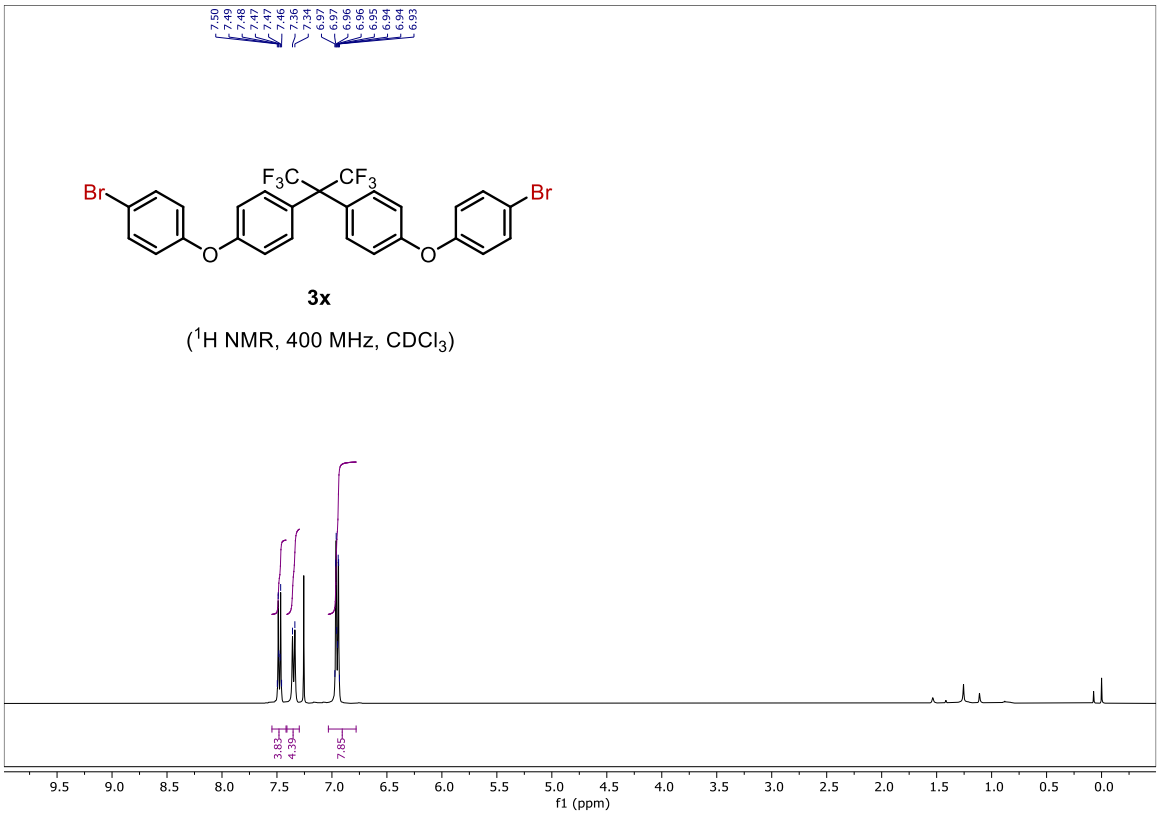

Br
F
N
N
Me
3t
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)


Br
F
N
N
Me
3t
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)



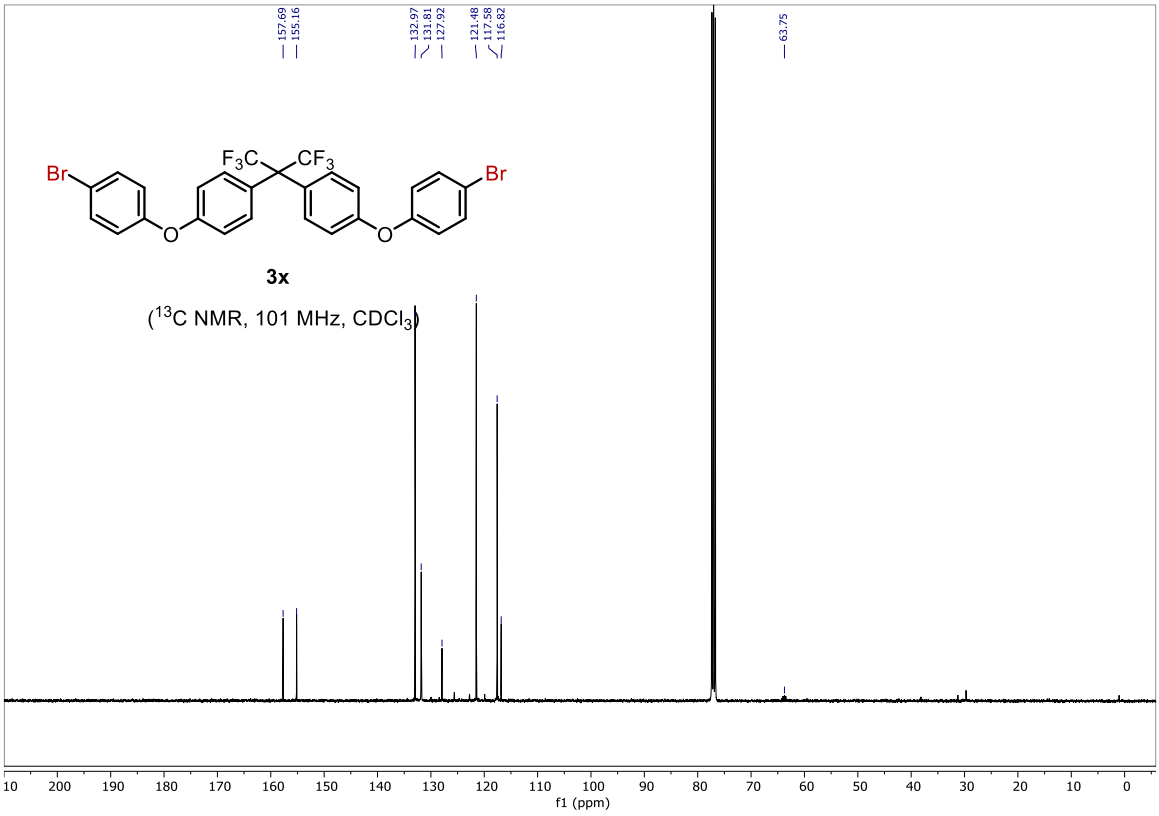
3t

(^{19}F NMR, 376 MHz, $CDCl_3$)



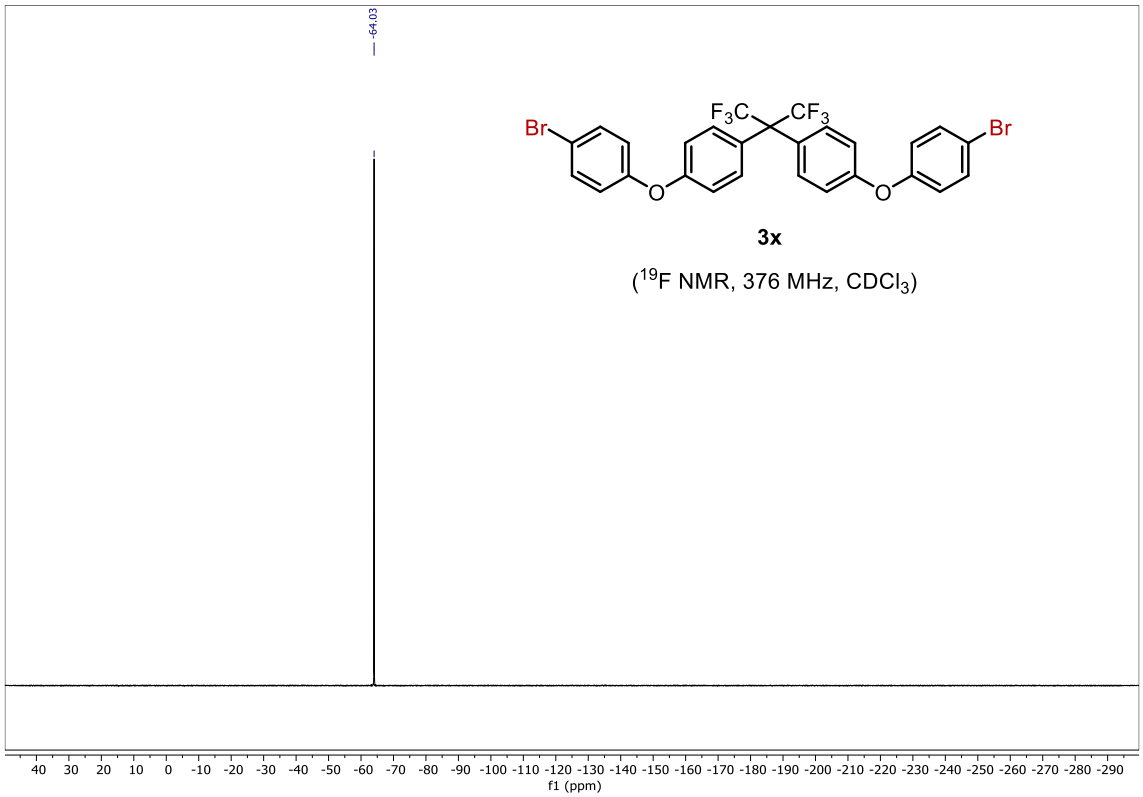
3x

(^{1}H NMR, 400 MHz, $CDCl_3$)



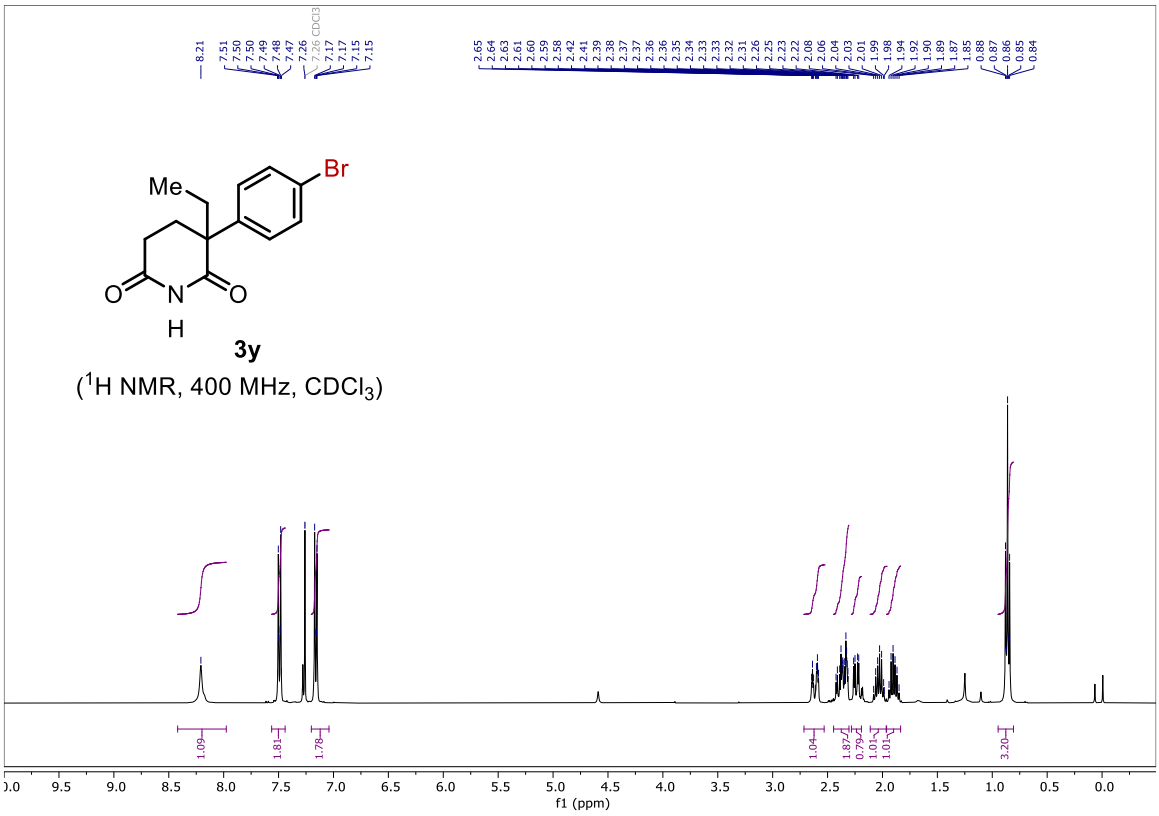
3x

(^{13}C NMR, 101 MHz, $CDCl_3$)



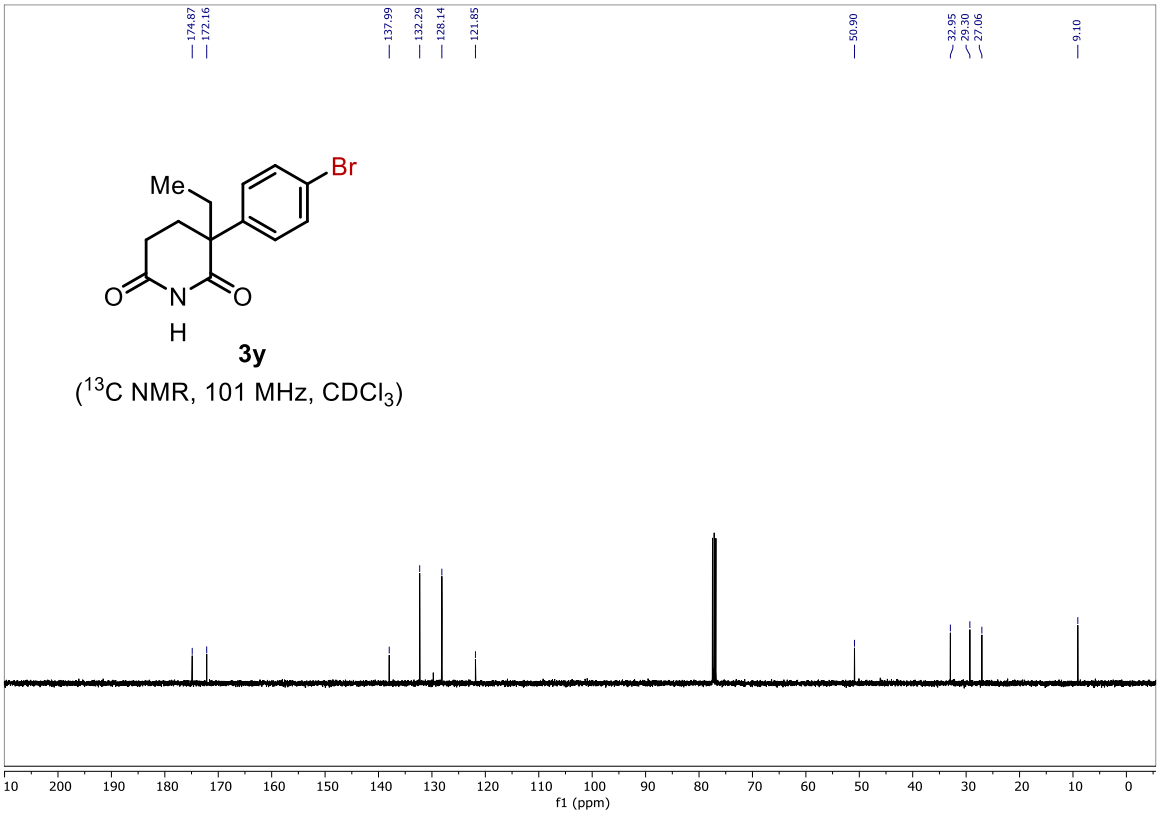
3x

(^{19}F NMR, 376 MHz, $CDCl_3$)



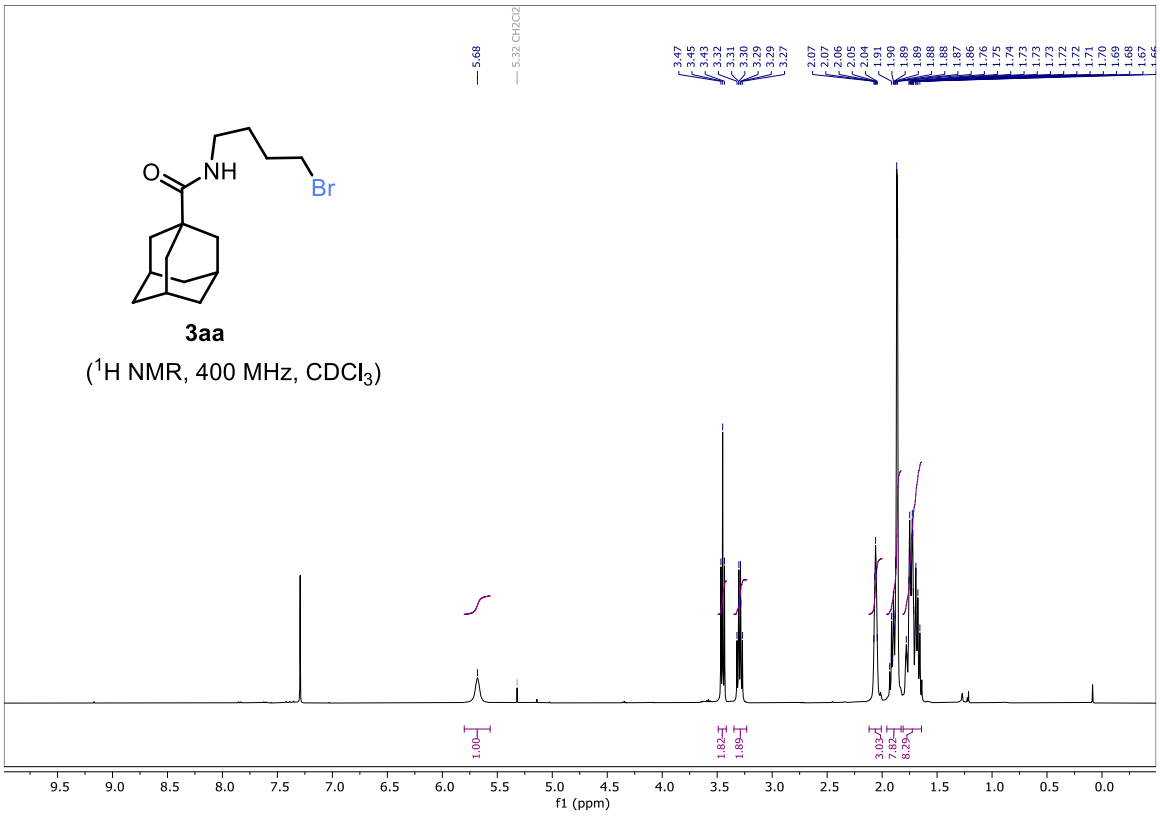
3y

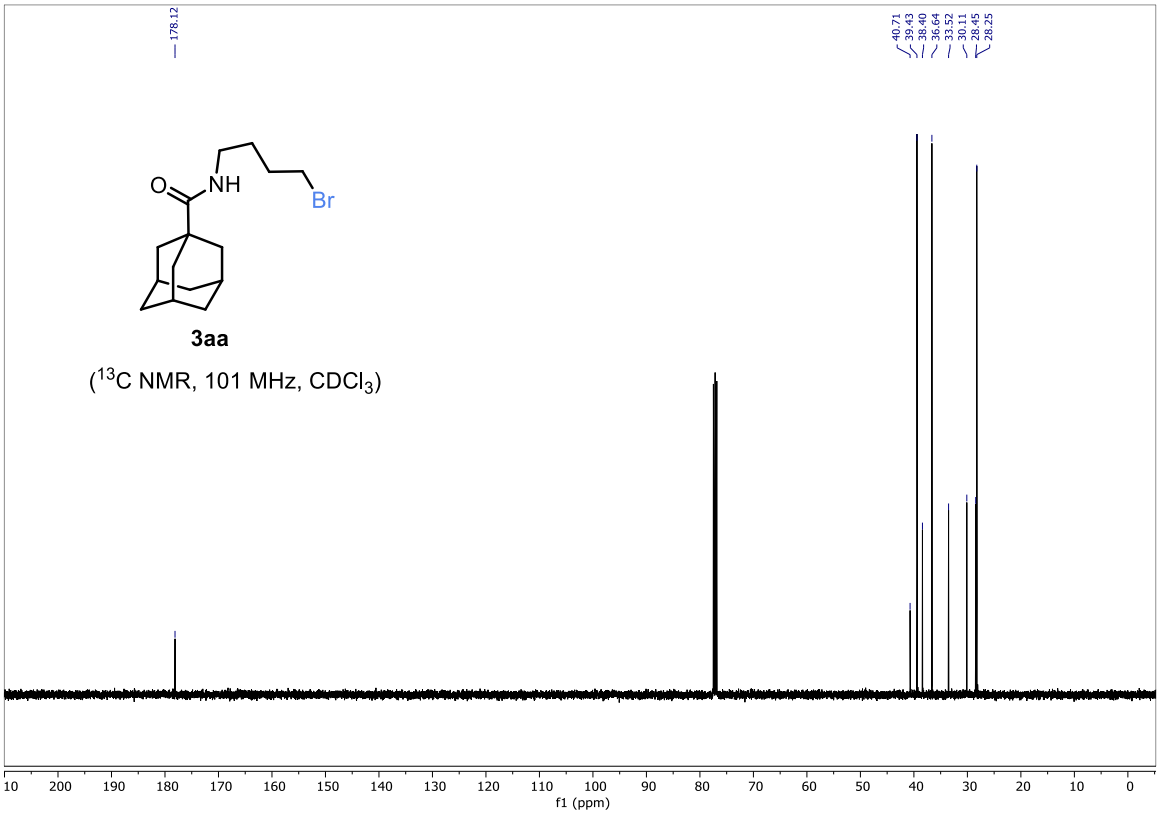
(^{1}H NMR, 400 MHz, $CDCl_3$)

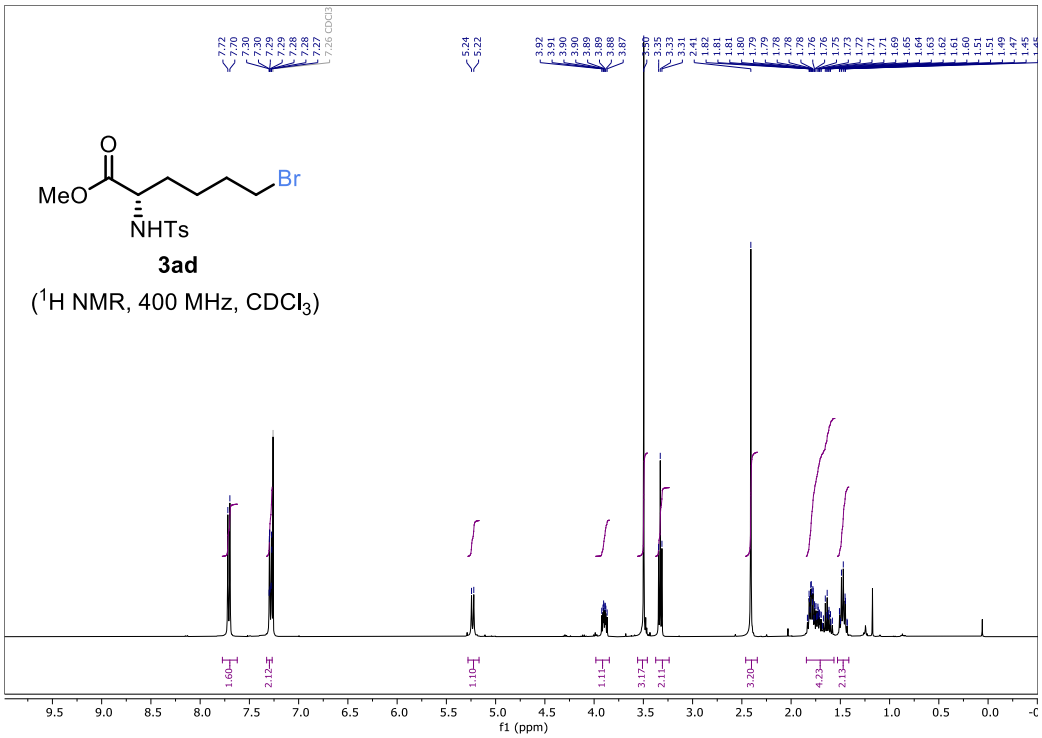


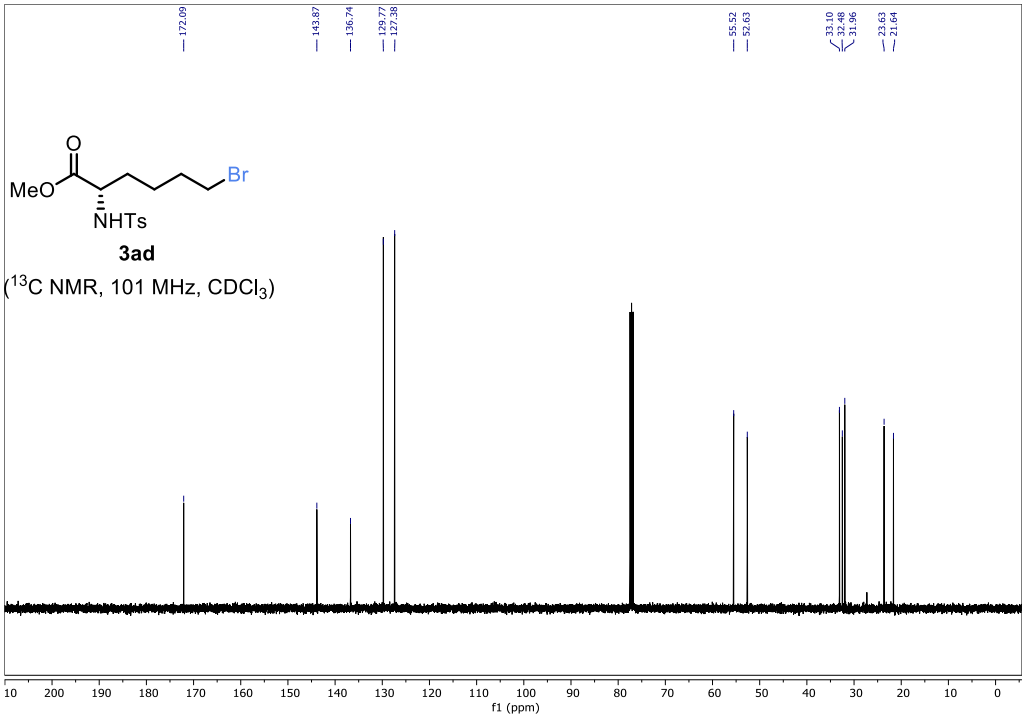
3y

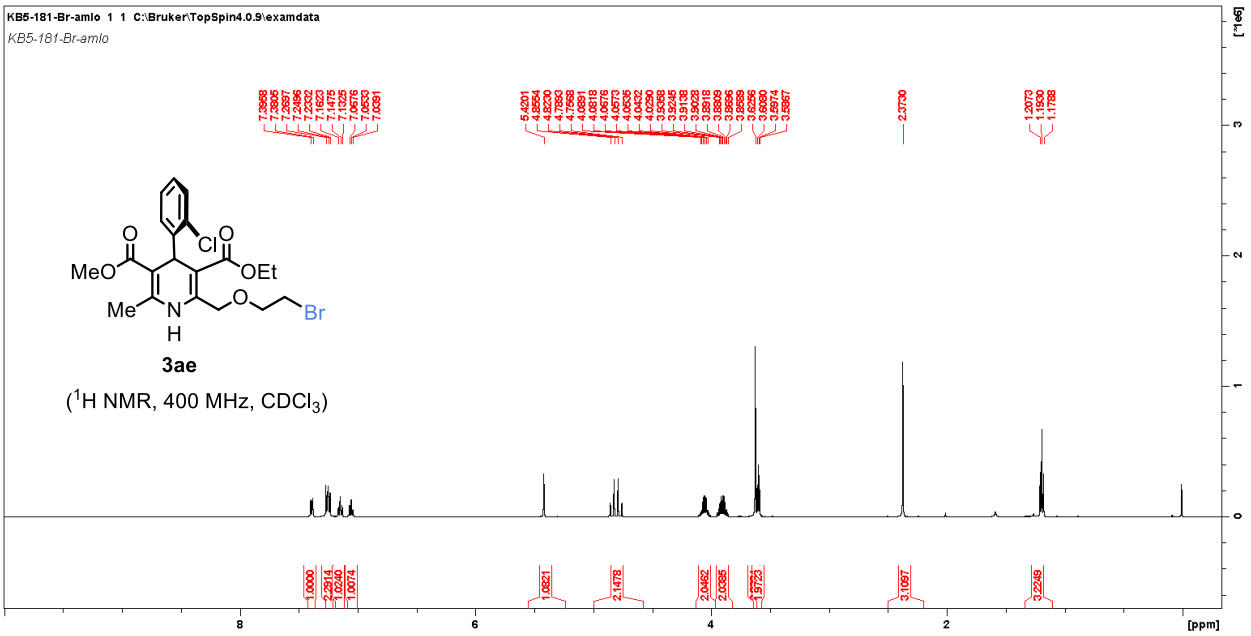
(^{13}C NMR, 101 MHz, $CDCl_3$)

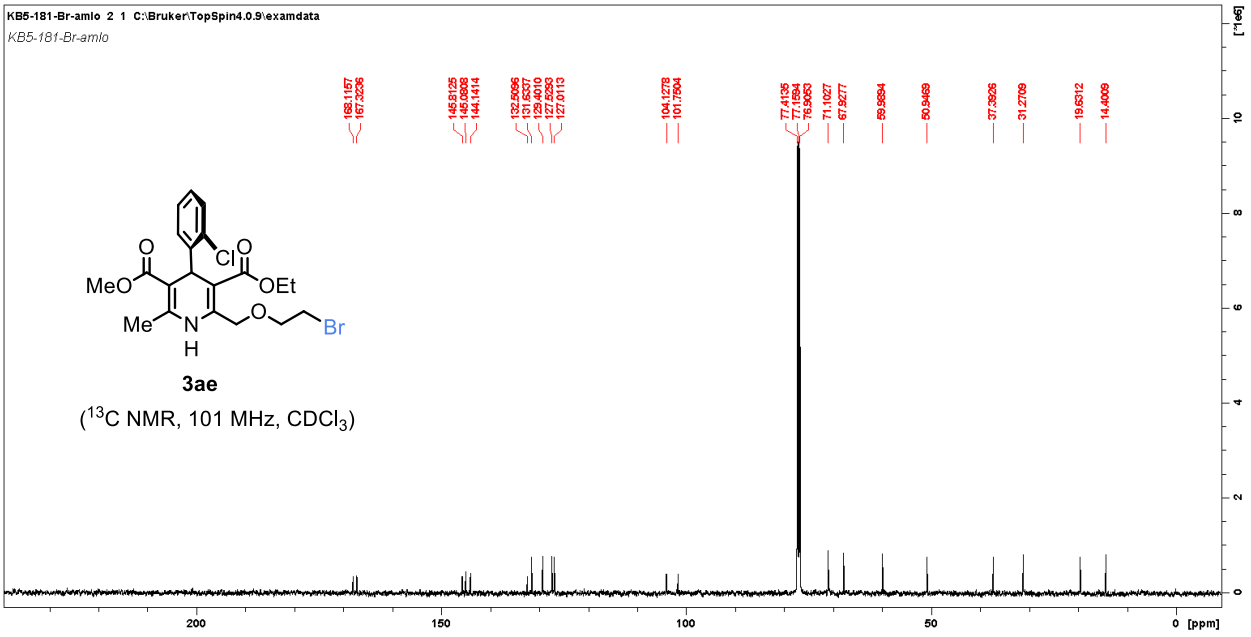

O
NH
Br
3aa
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)


O
NH
Br
3aa
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)


MeO
O
NHTs
Br
3ad
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)

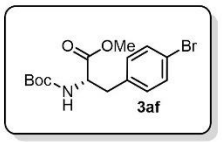

MeO
O
NHTs
Br
3ad
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)

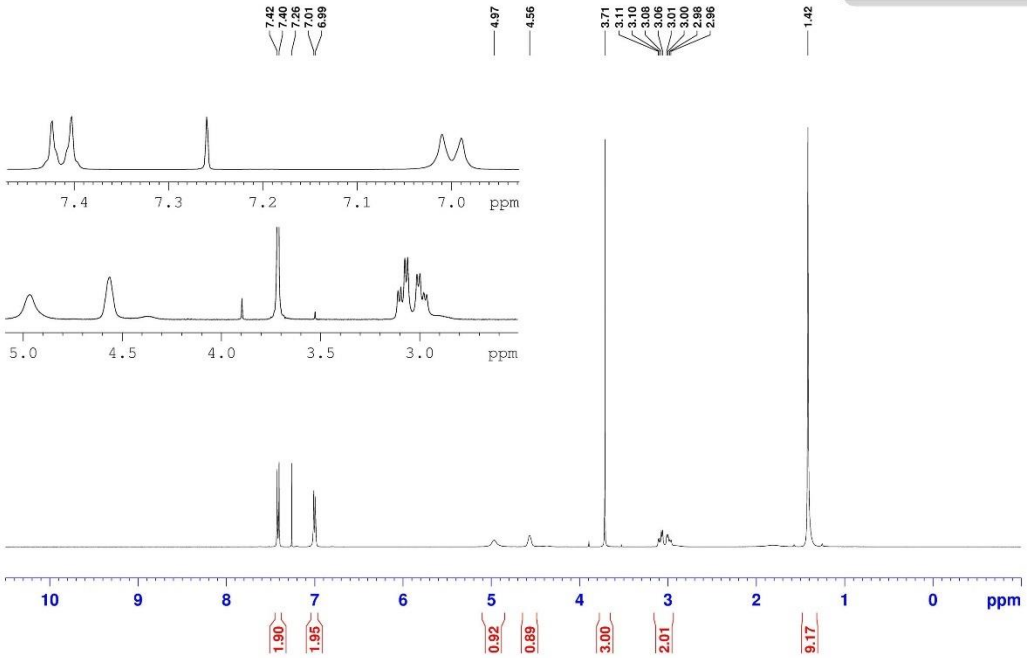

KB5-181-Br-amlo 1 1 C:\Bruker\TopSpin4.0.9\examdata
KB5-181-Br-amlo
MeO
OEt
Me
N
H
Cl
O
O
O
Br
3ae
(1H NMR, 400 MHz, CDCl3)
[ppm]


KB5-181-Br-amlo 2 1 C:\Bruker\TopSpin4.0.9\examdata
KB5-181-Br-amlo
MeO
OEt
Me
N
H
Cl
O
O
O
Br
3ae
(13C NMR, 101 MHz, CDCl3)
[ppm]

(*S*)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate
400 MHz, $CDCl_3$

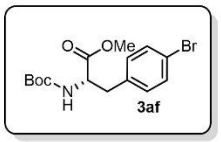
^{1}H NMR

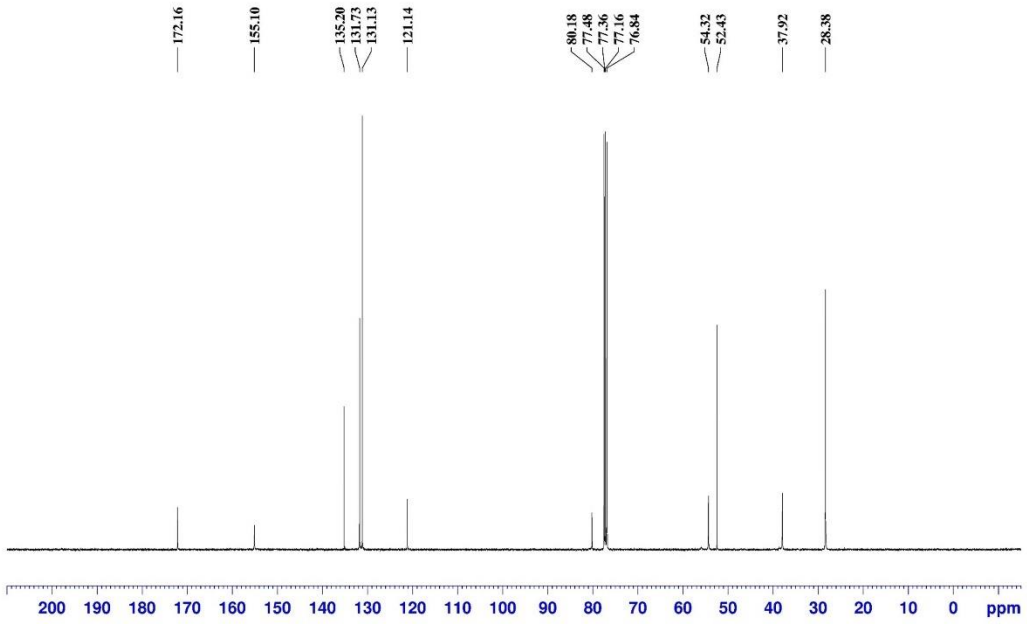




(*S*)-methyl 3-(4-bromophenyl)-2-((tert-butoxycarbonyl)amino)propanoate
125 MHz, $CDCl_3$

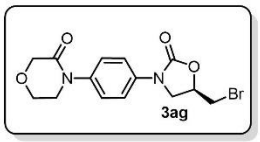
^{13}C NMR

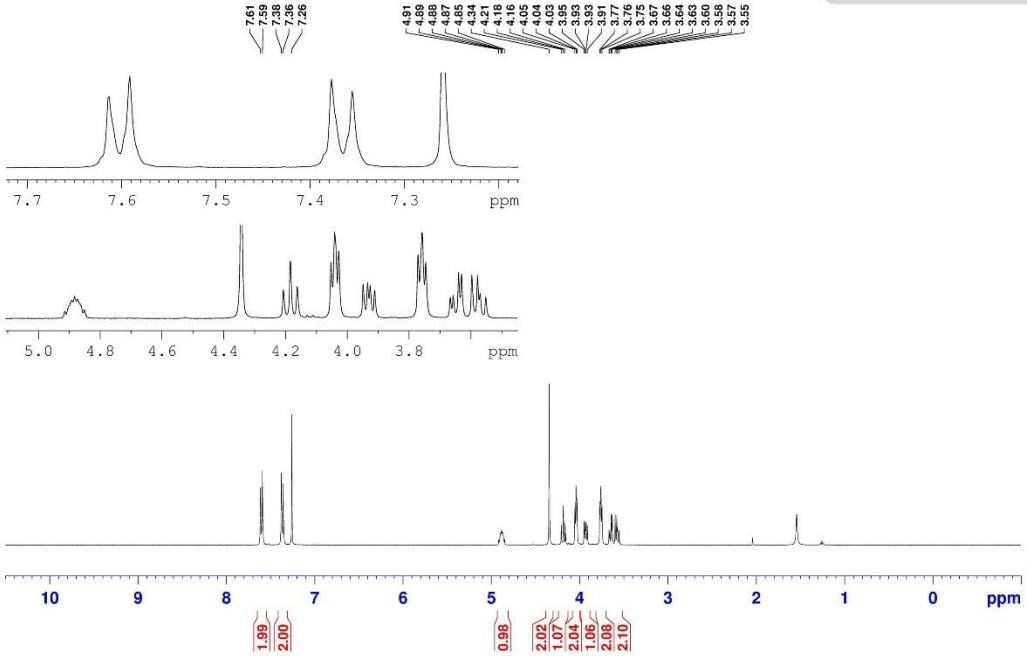




(R)-4-(4-(5-(bromomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one
400 MHz, $CDCl_3$

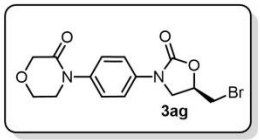
^{1}H NMR



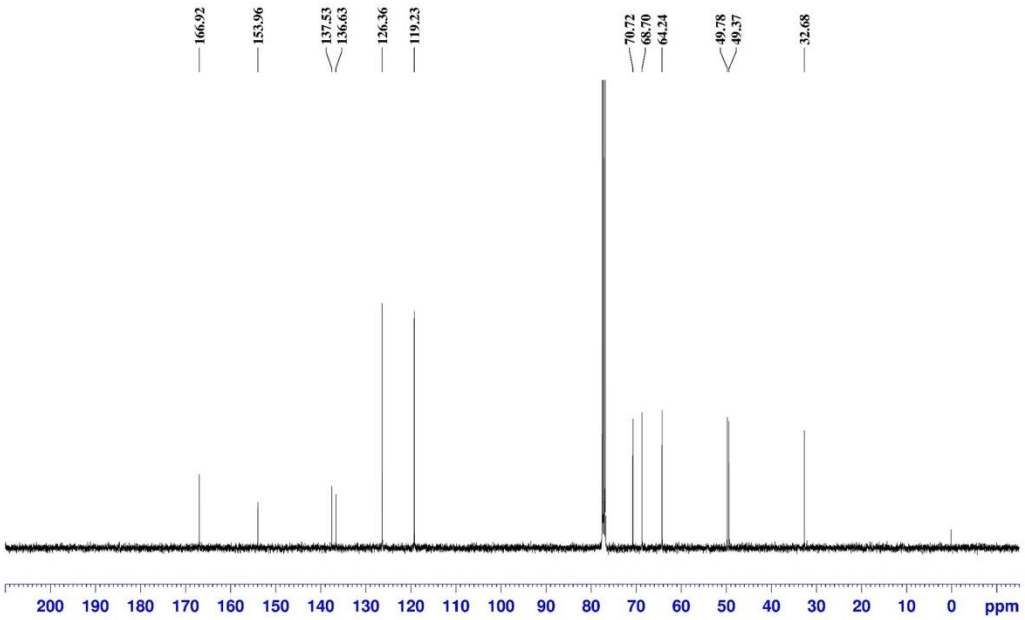


(R)-4-(4-(5-(bromomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one
125 MHz, $CDCl_3$

^{13}C NMR

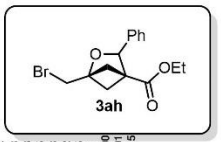


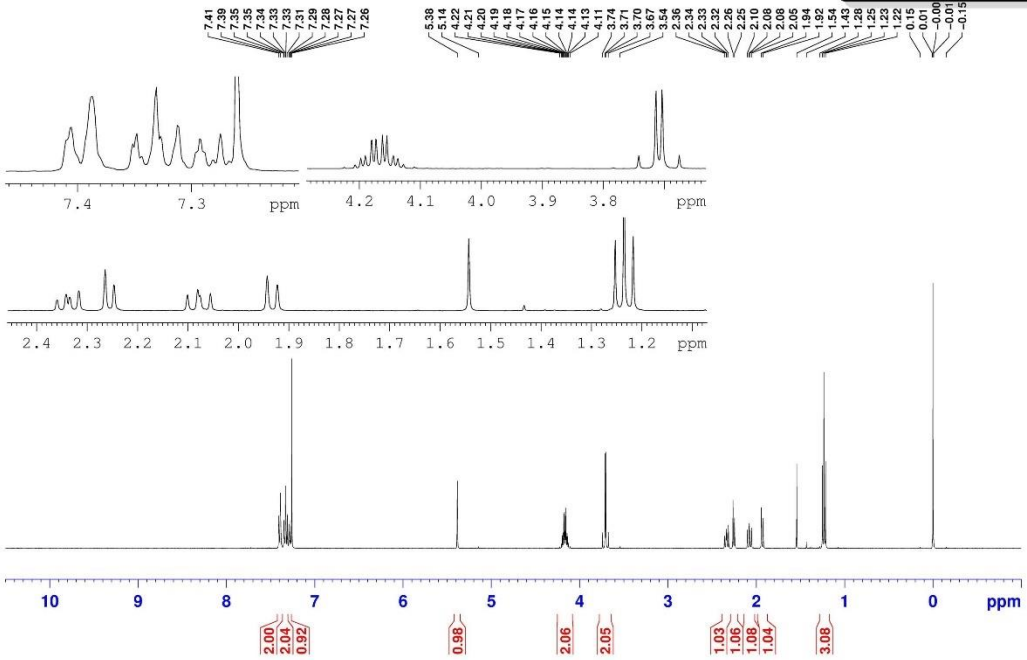
3ag

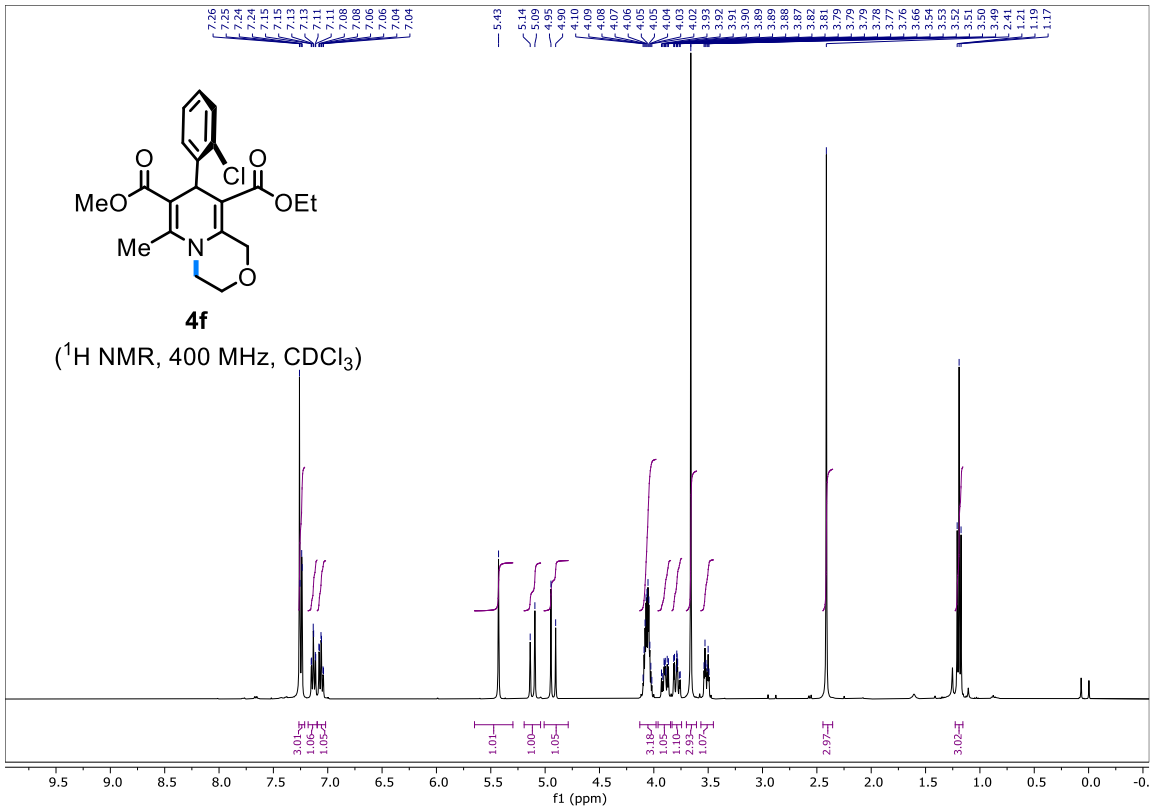


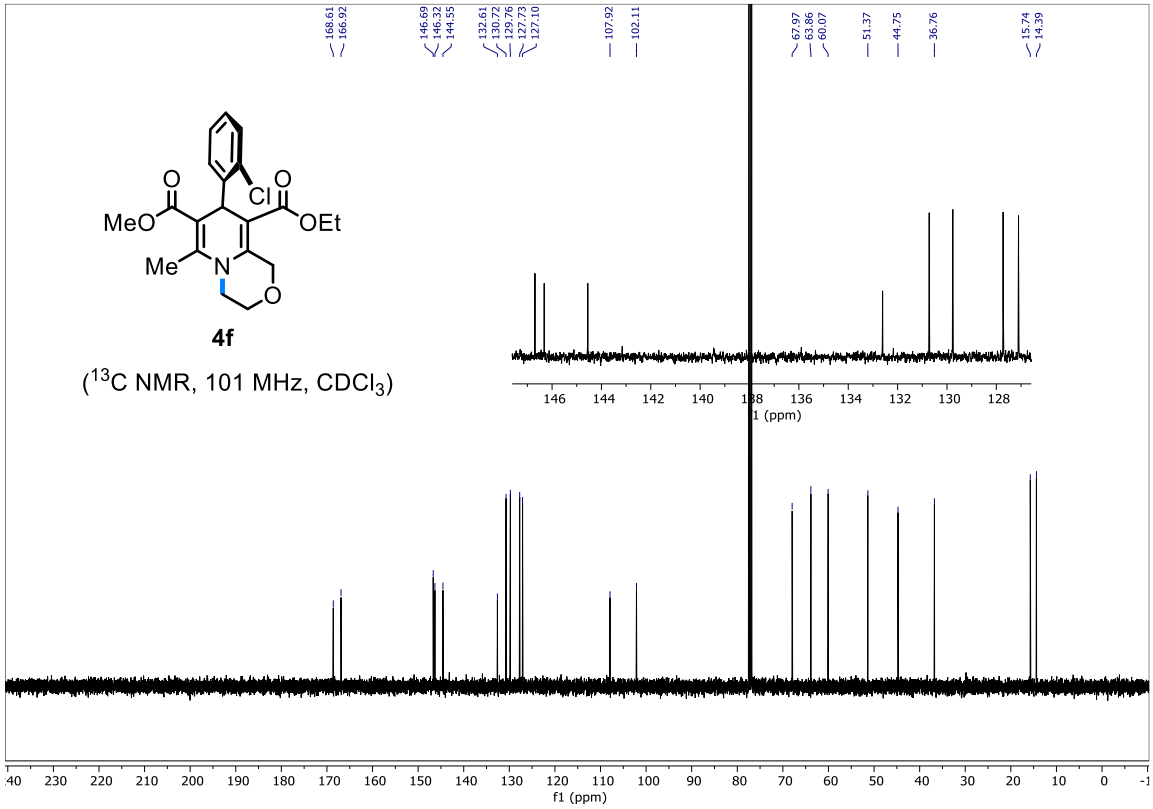
^1H NMR

(1r,4r)-ethyl 1-(bromomethyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate
400 MHz, $CDCl_3$



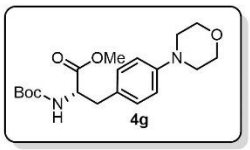



MeO
Cl
OEt
Me
N
O
4f
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)

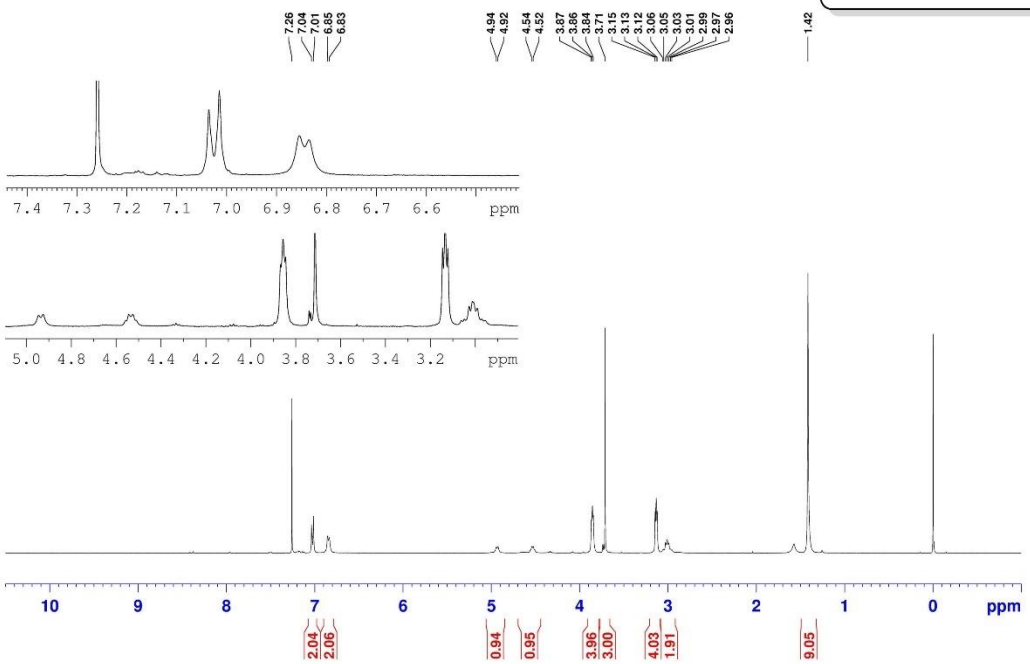

MeO
Cl
OEt
Me
N
O
4f
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)

^1H NMR

(S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-morpholinophenyl)propanoate
400 MHz, $CDCl_3$

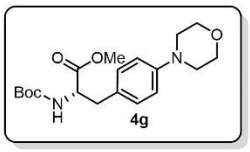


4g

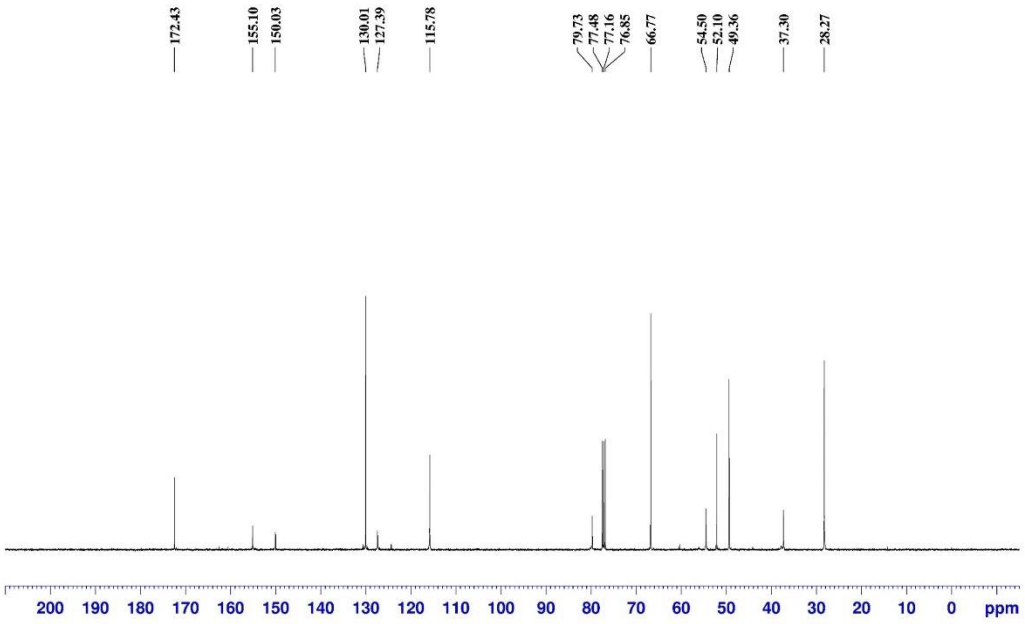


^{13}C NMR

(S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-morpholinophenyl)propanoate
125 MHz, $CDCl_3$

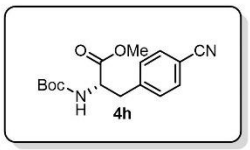


4g

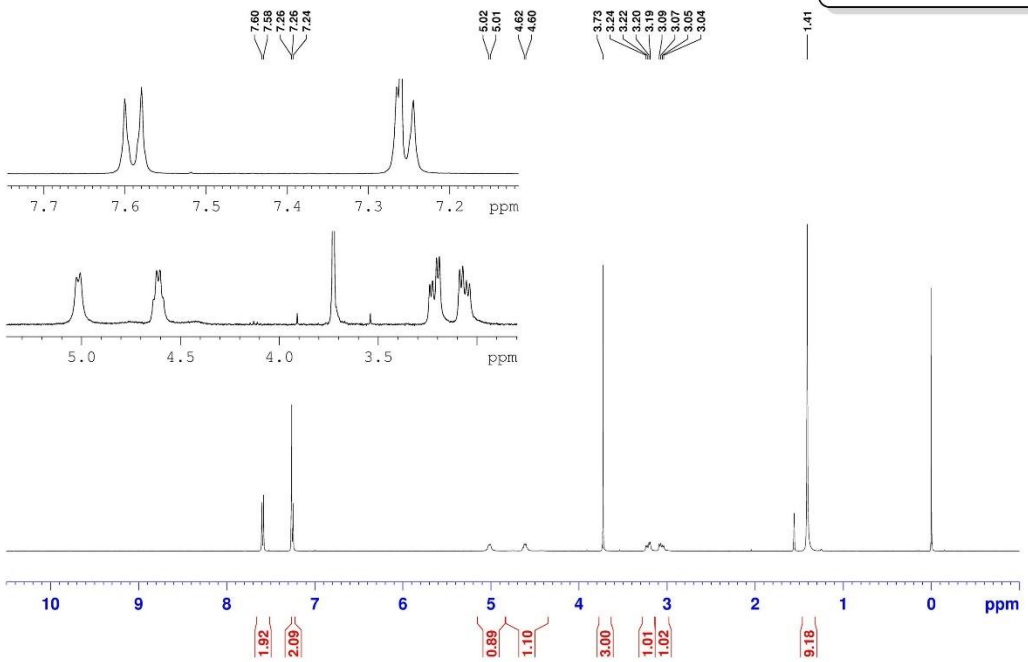


(S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-cyanophenyl)propanoate
400 MHz, $CDCl_3$

^{1}H NMR

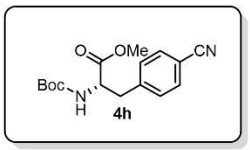


4h

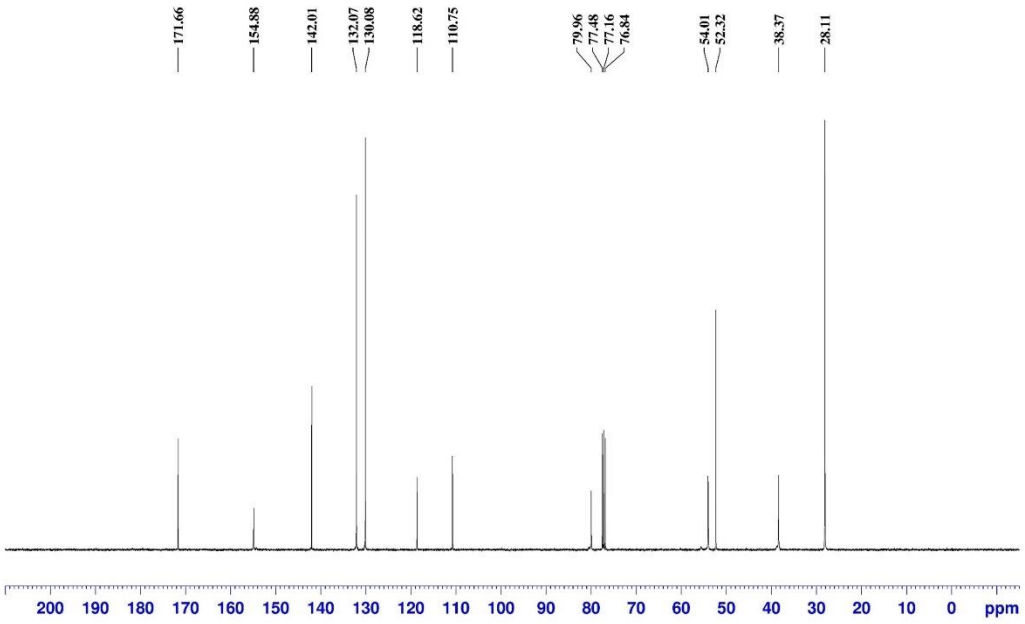


(S)-methyl 2-((tert-butoxycarbonyl)amino)-3-(4-cyanophenyl)propanoate
125 MHz, $CDCl_3$

^{13}C NMR

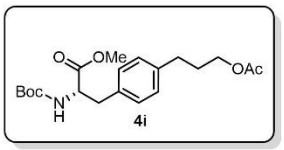


4h

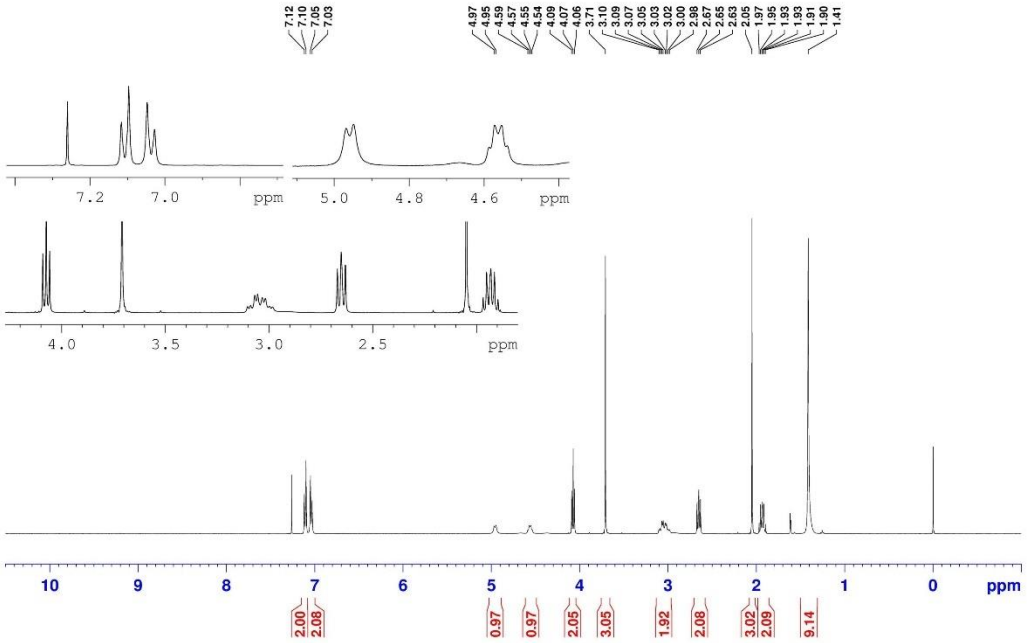


^{1}H NMR

(S)-methyl 3-(4-(3-acetoxypropyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate
400 MHz, $CDCl_3$

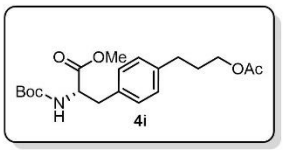


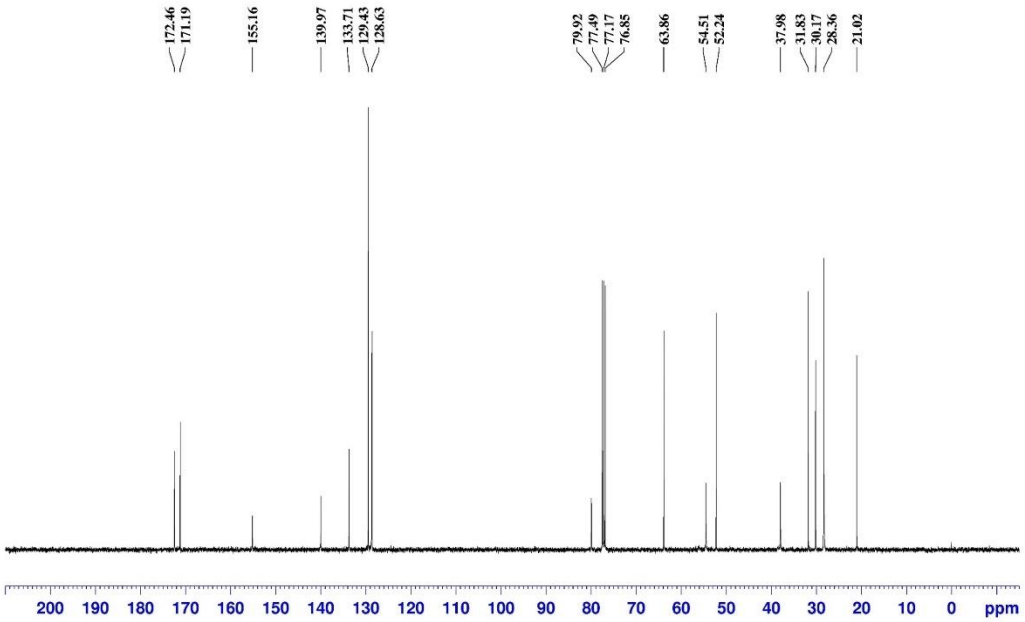
4i



^{13}C NMR

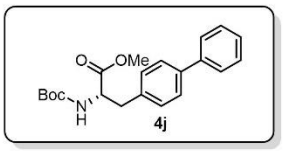
(S)-methyl 3-(4-(3-acetoxypropyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate
125 MHz, $CDCl_3$



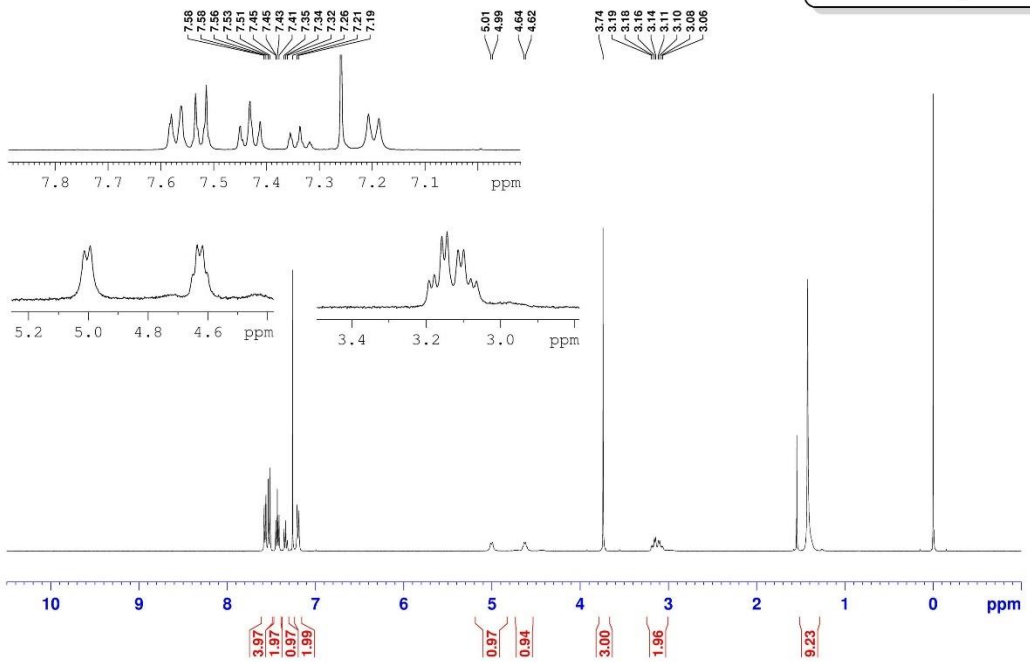


^{1}H NMR

(S)-methyl 3-([1,1'-biphenyl]-4-yl)-2-((tert-butoxycarbonyl)amino)propanoate
400 MHz, $CDCl_3$

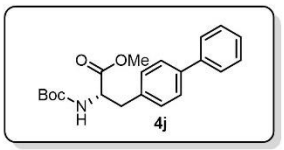


4j

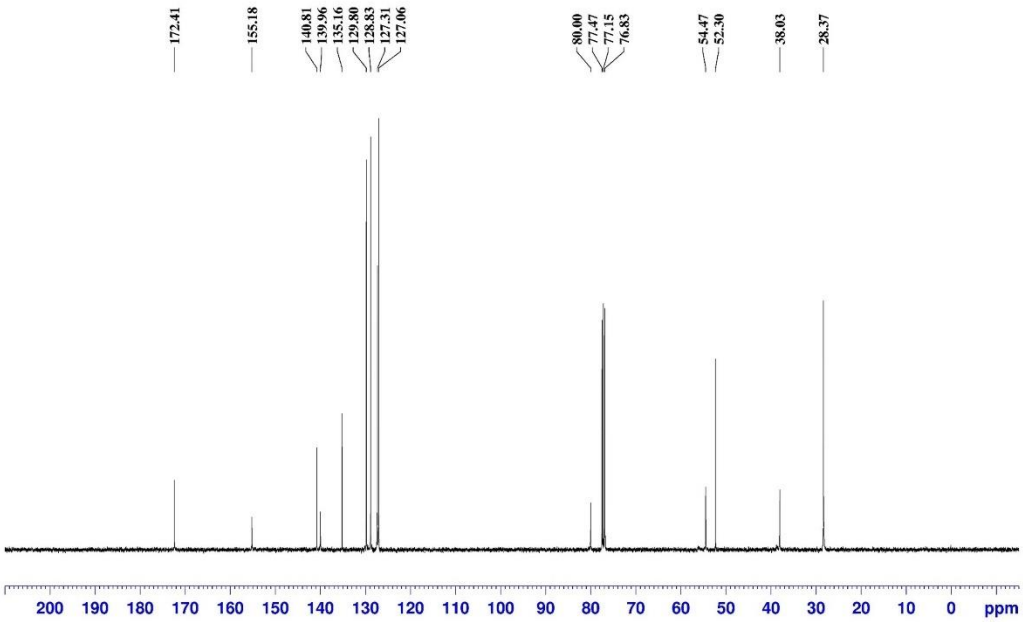


^{13}C NMR

(S)-methyl 3-([1,1'-biphenyl]-4-yl)-2-((tert-butoxycarbonyl)amino)propanoate
125 MHz, $CDCl_3$

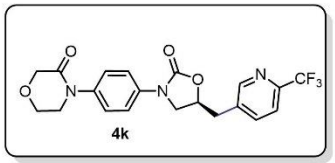


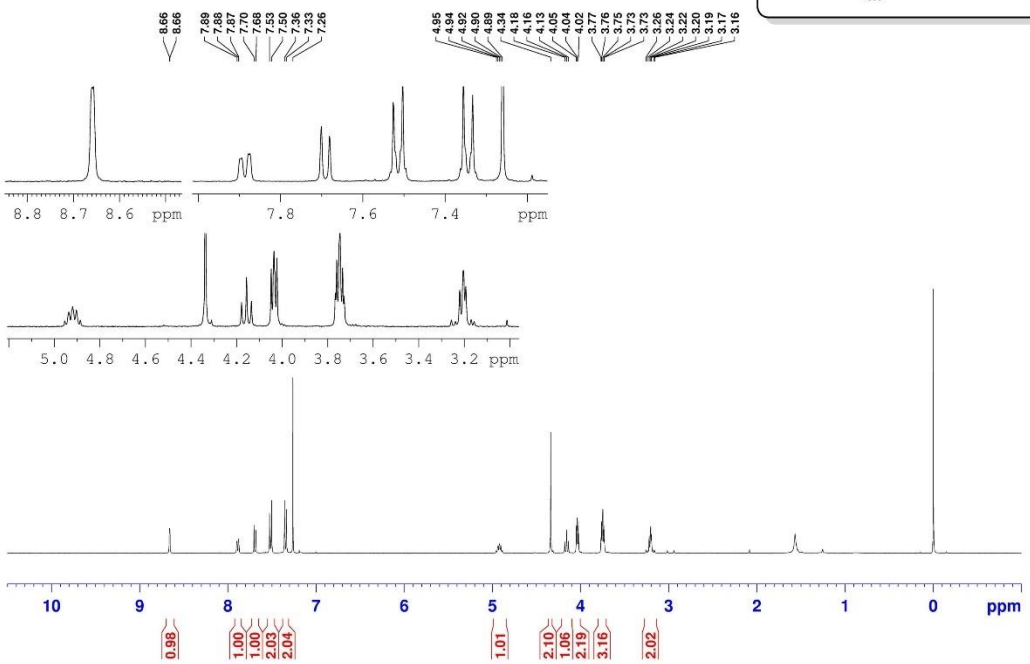
4j



^1H NMR

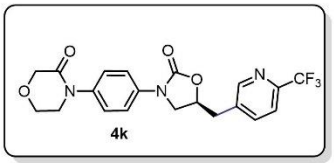
(*S*)-4-(4-(2-oxo-5-((6-(trifluoromethyl)pyridin-3-yl)methyl)oxazolidin-3-yl)phenyl)morpholin-3-one
400 MHz, $CDCl_3$

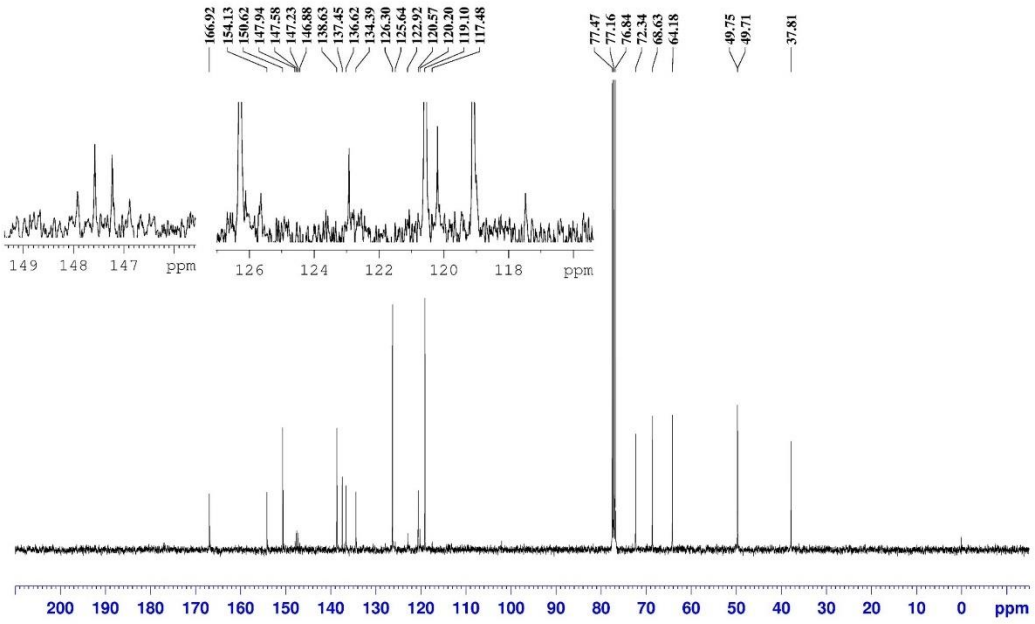




^{13}C NMR

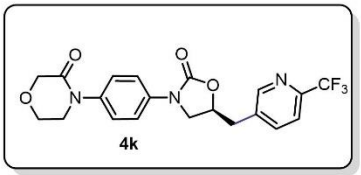
(*S*)-4-(4-(4-(2-oxo-5-((6-(trifluoromethyl)pyridin-3-yl)methyl)oxazolidin-3-yl)phenyl)morpholin-3-one
125 MHz, $CDCl_3$



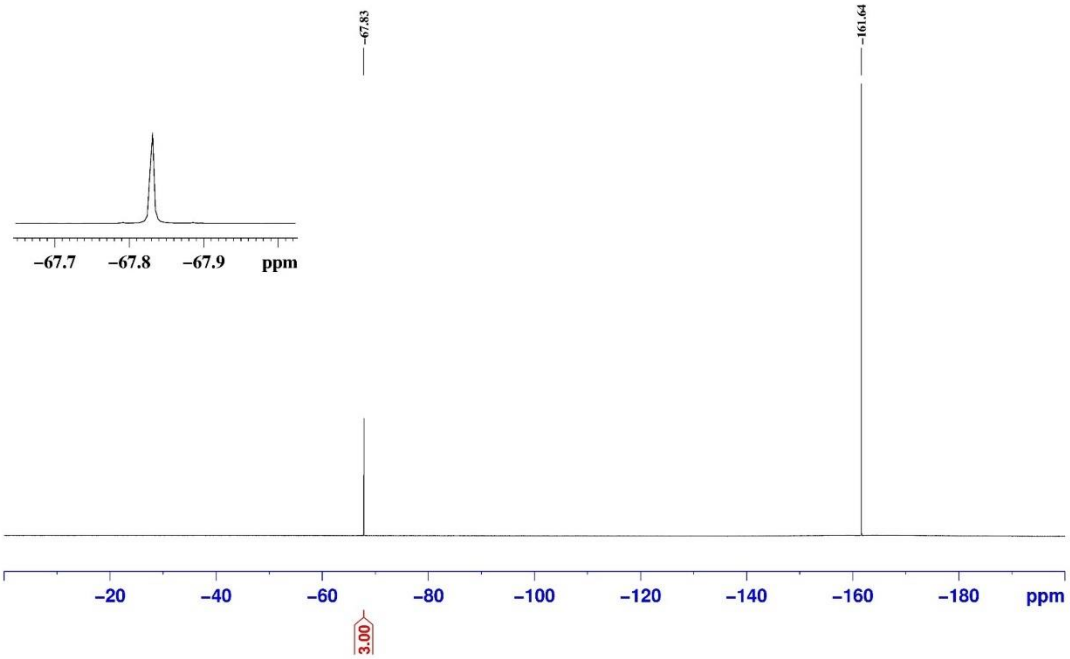


^{19}F NMR

(*S*)-4-(4-(2-oxo-5-((6-(trifluoromethyl)pyridin-3-yl)methyl)oxazolidin-3-yl)phenyl)morpholin-3-one
376 MHz, $CDCl_3$

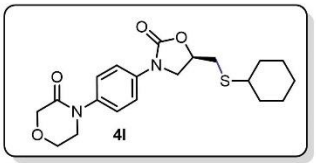


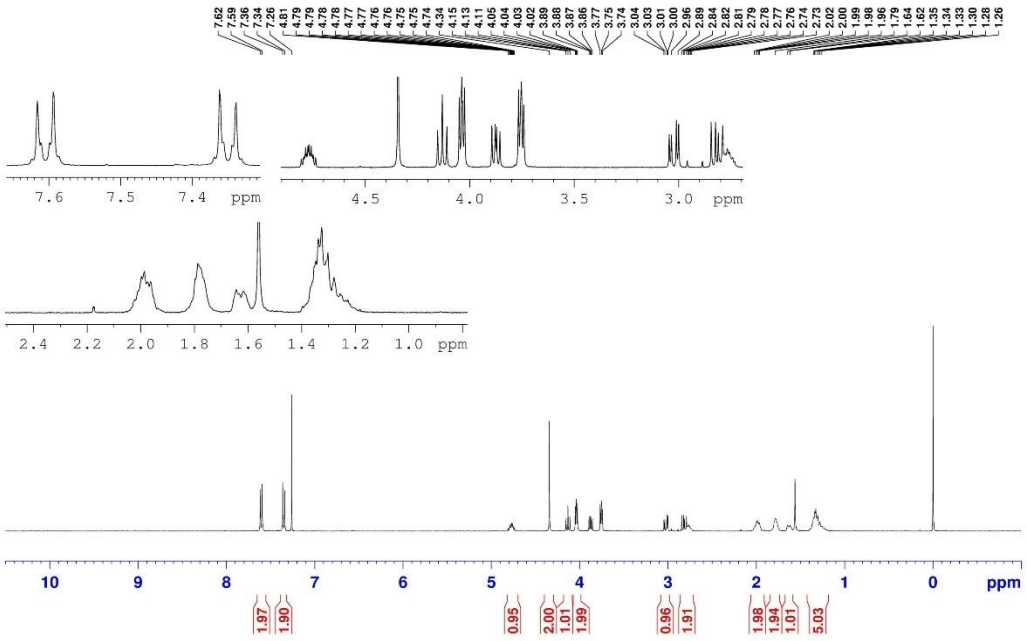
4k



^{1}H NMR

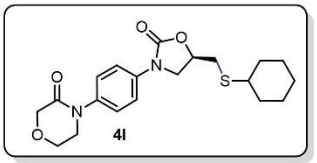
(*R*)-4-(4-(5-((cyclohexylthio)methyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one
400 MHz, $CDCl_3$

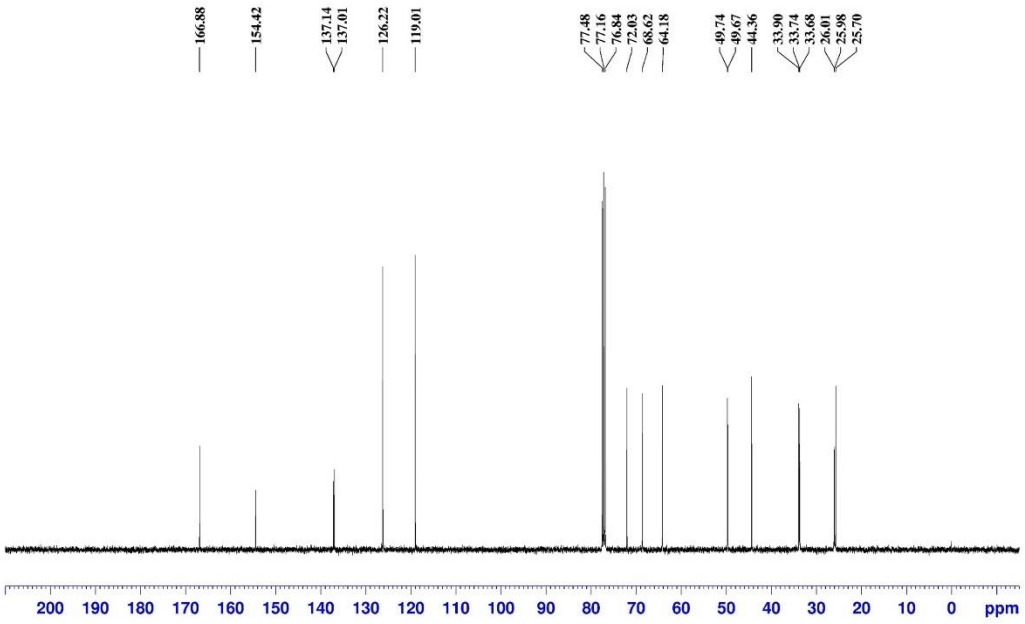




^{13}C NMR

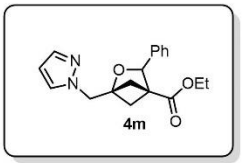
(*R*)-4-(4-(5-((cyclohexylthio)methyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one
125 MHz, $CDCl_3$

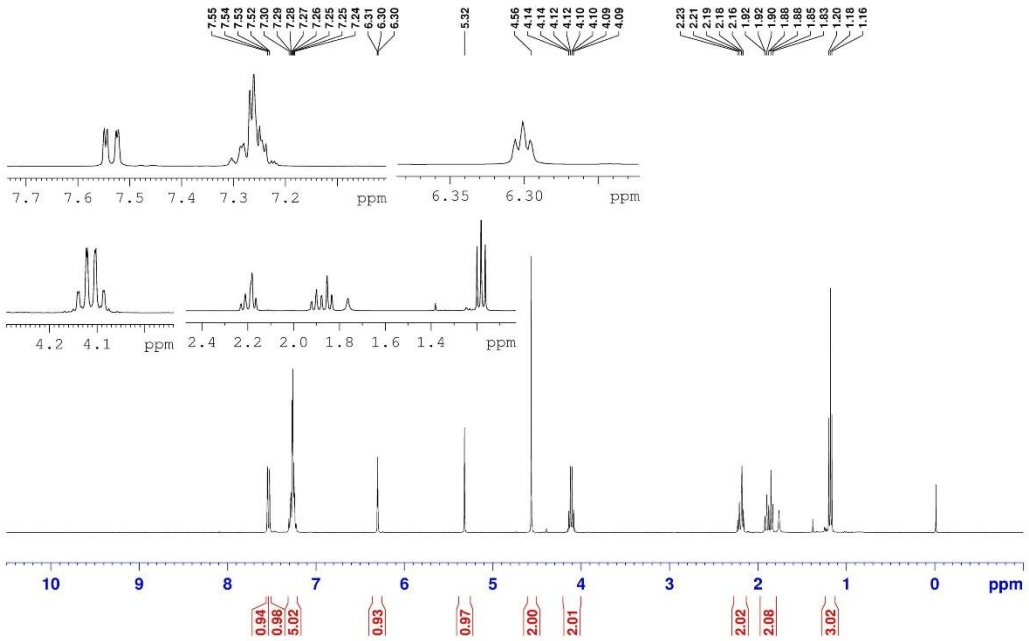




^{1}H NMR

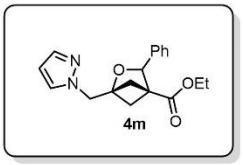
(1r,4r)-ethyl 1-((1H-pyrazol-1-yl)methyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate
400 MHz, $CDCl_3$



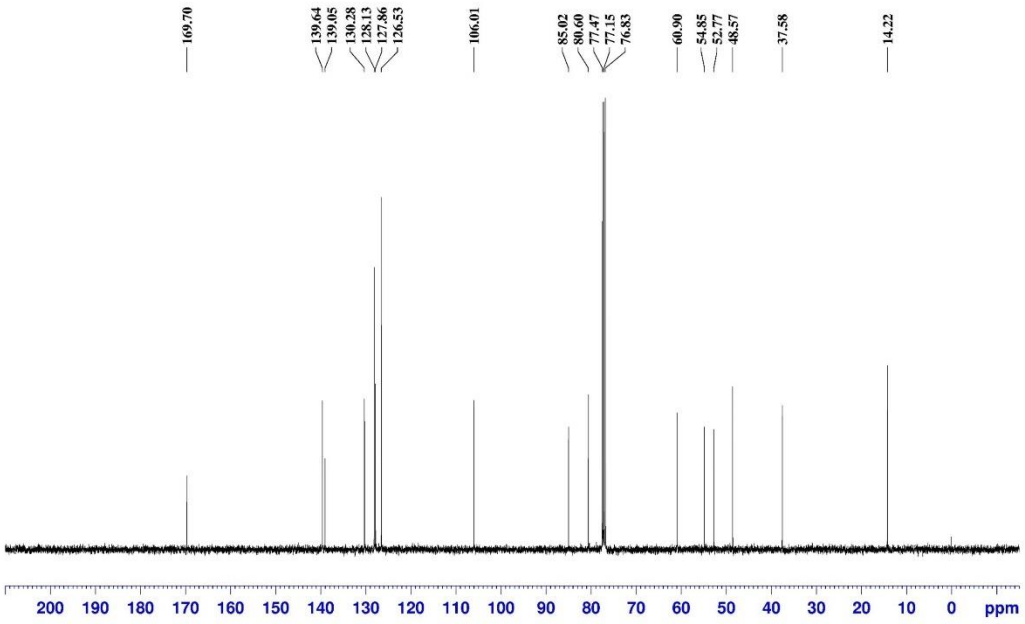


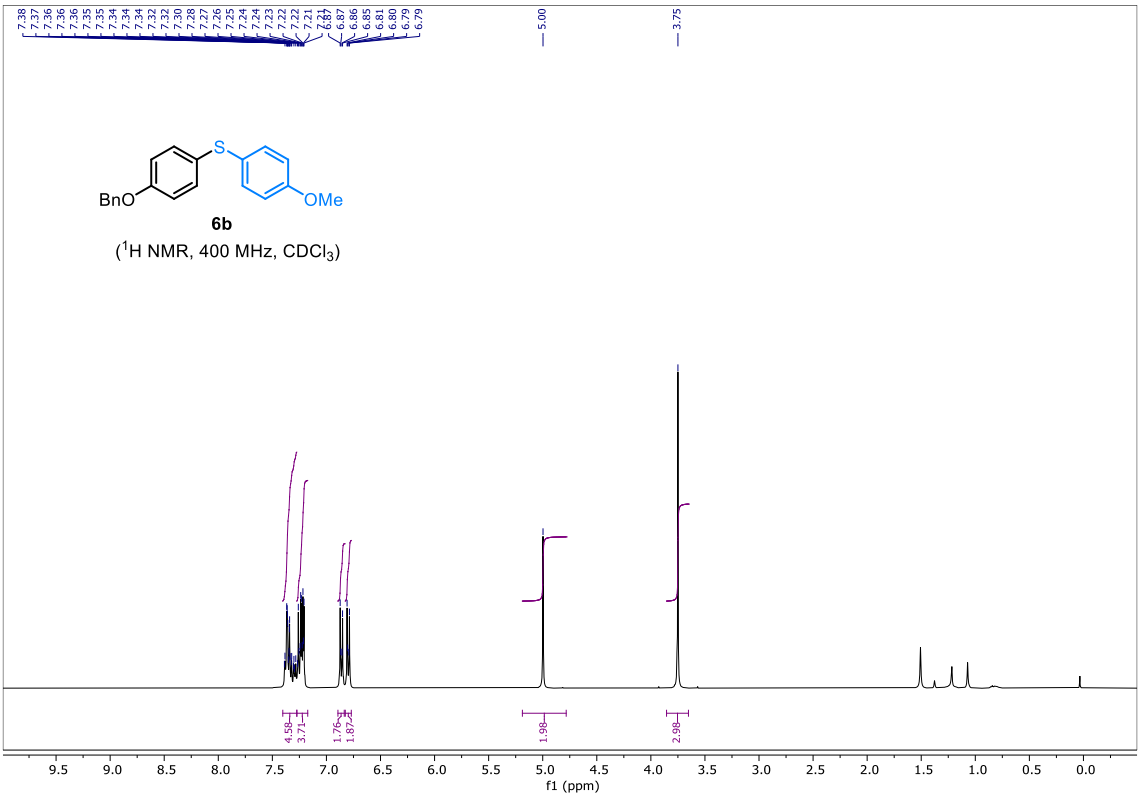
^{13}C NMR

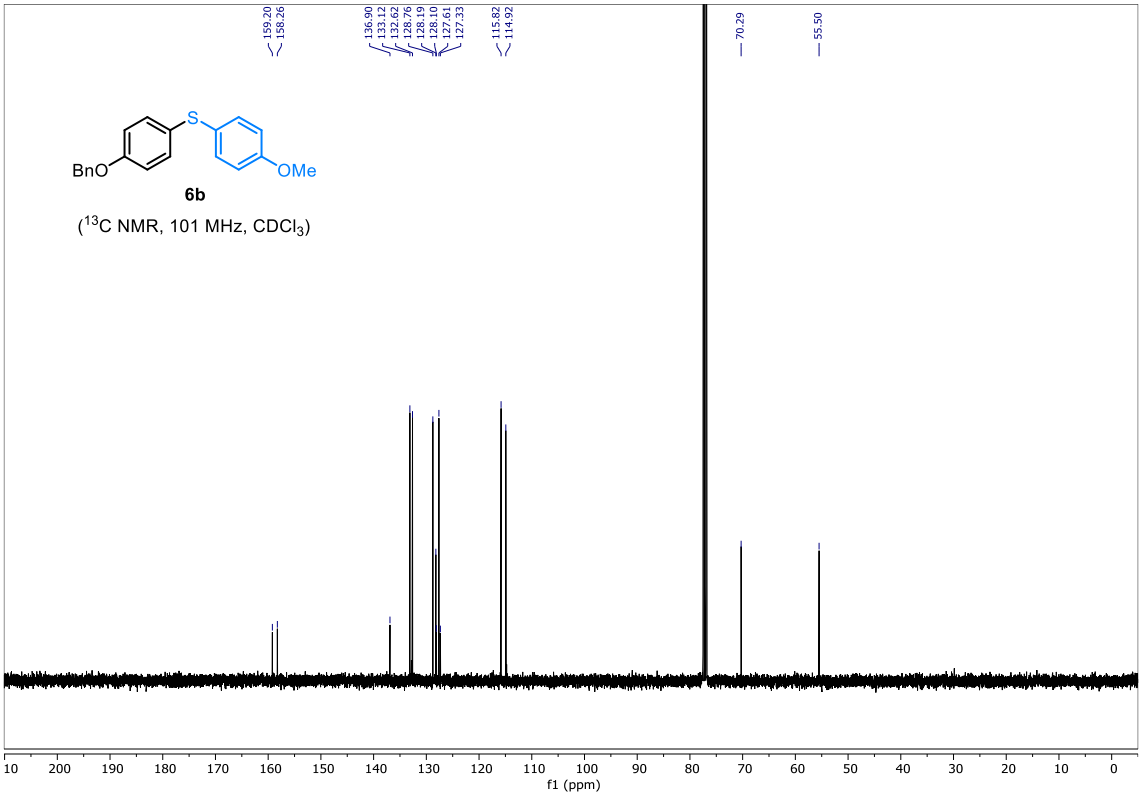
(1r,4r)-ethyl 1-((1H-pyrazol-1-yl)methyl)-3-phenyl-2-oxabicyclo[2.1.1]hexane-4-carboxylate
125 MHz, $CDCl_3$

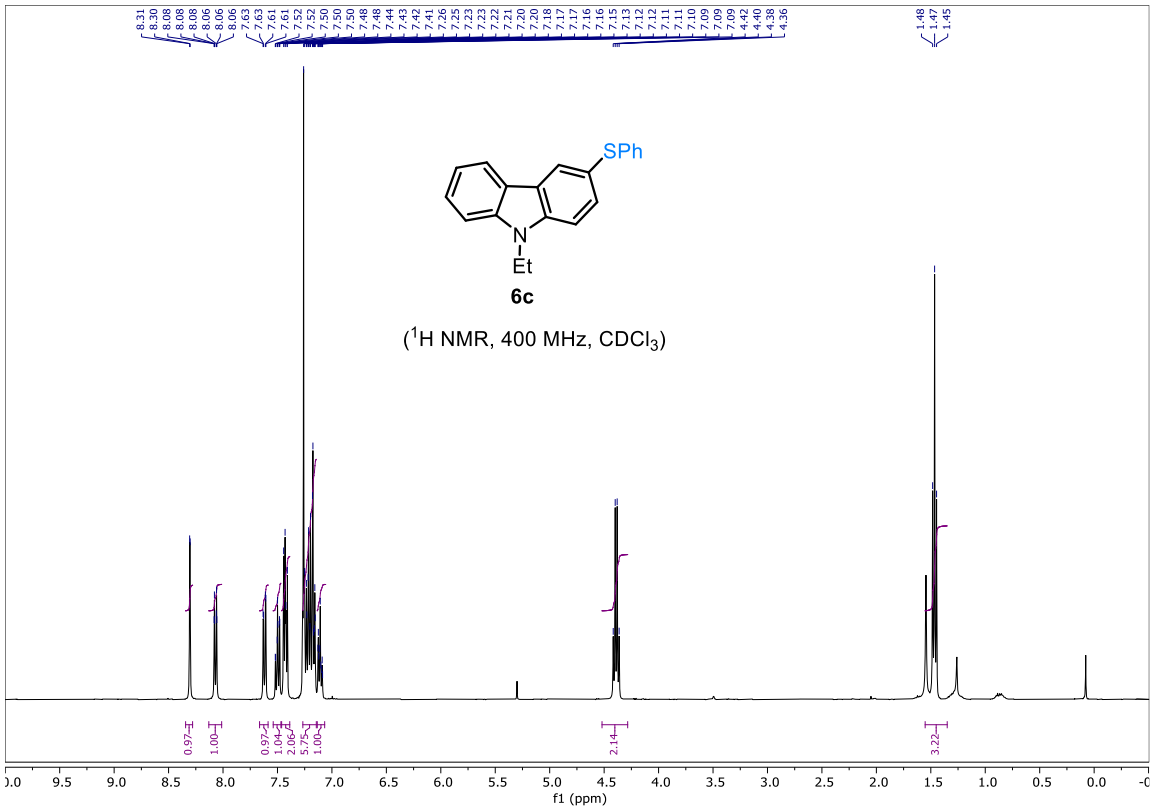


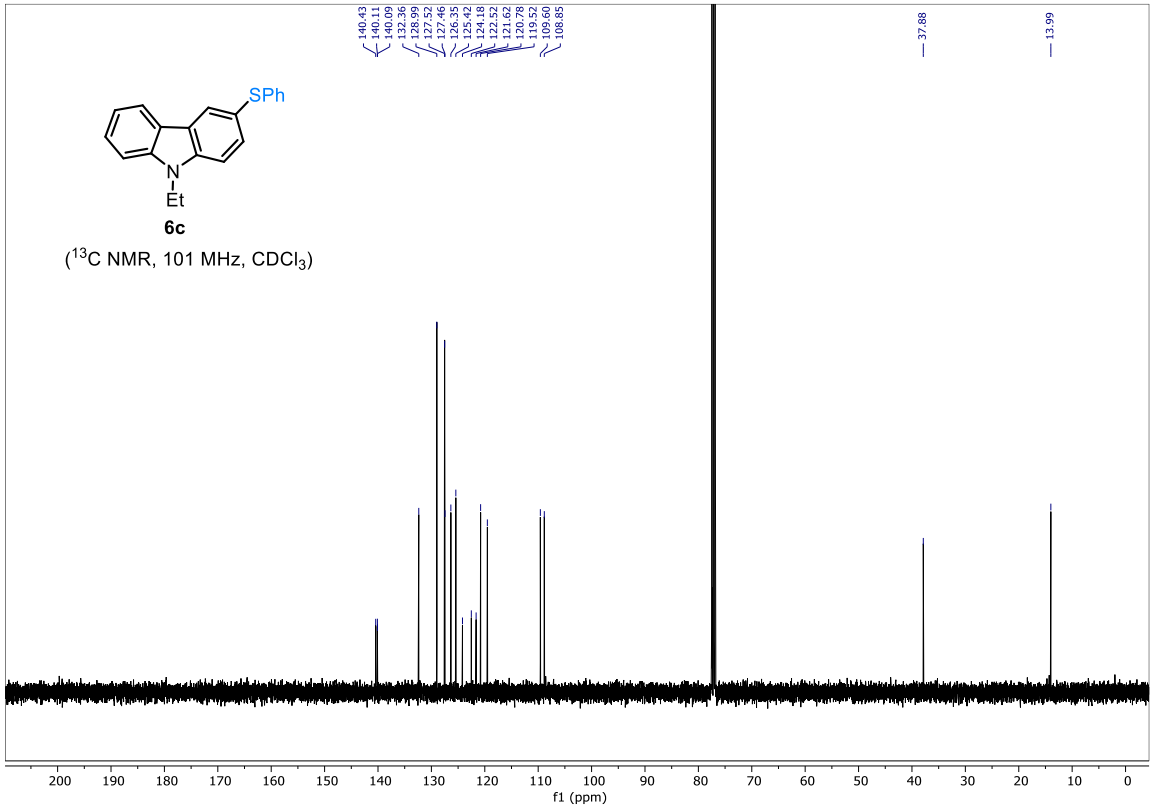
4m

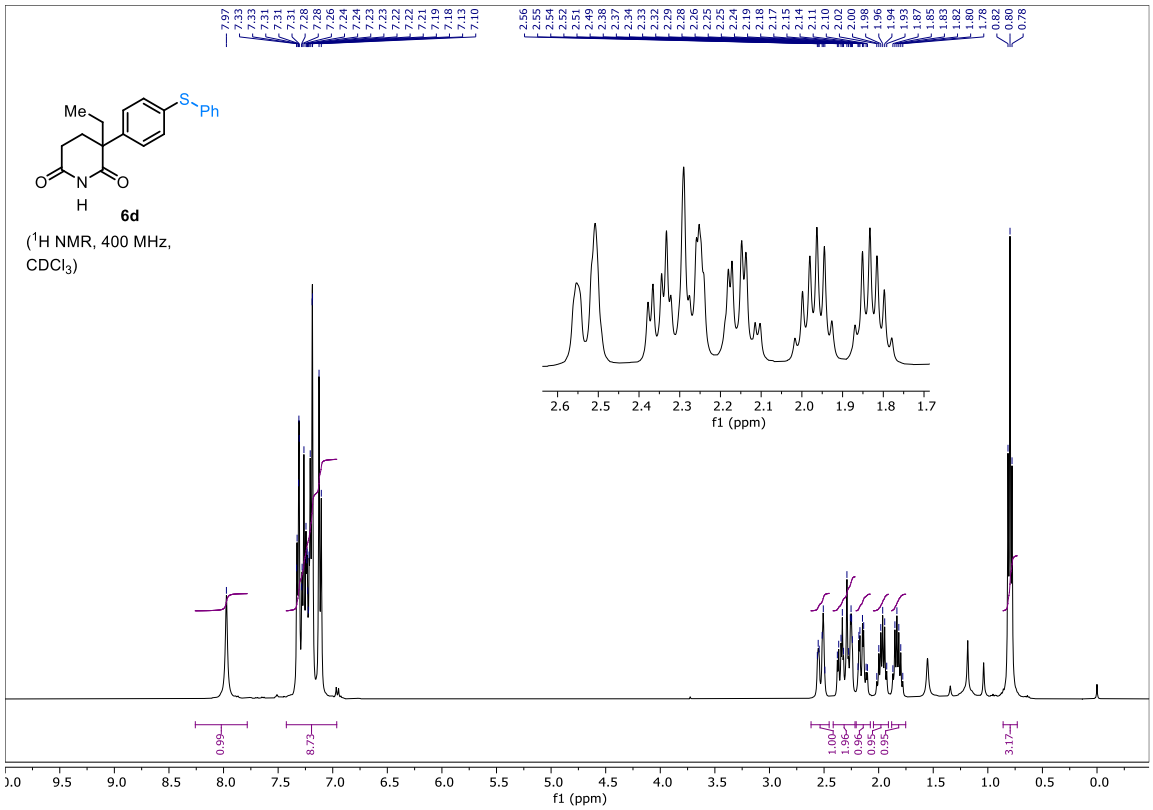


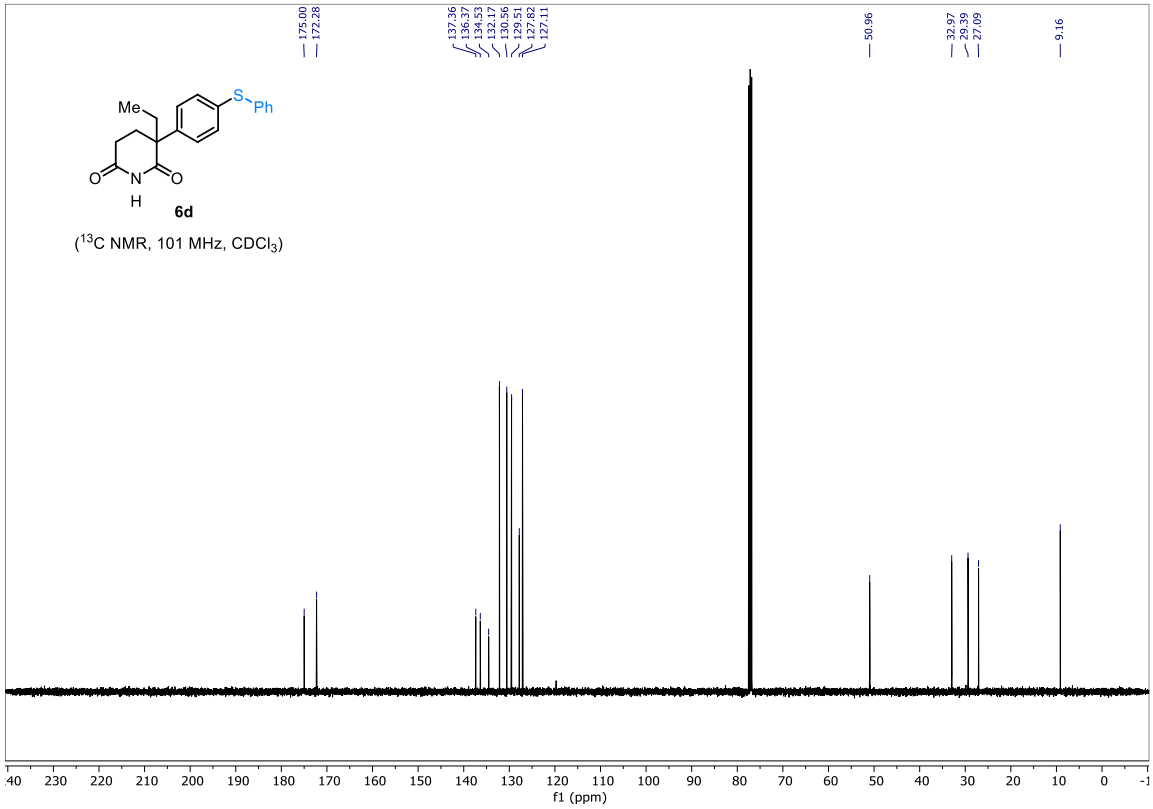

BnO
S
OMe
6b
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)

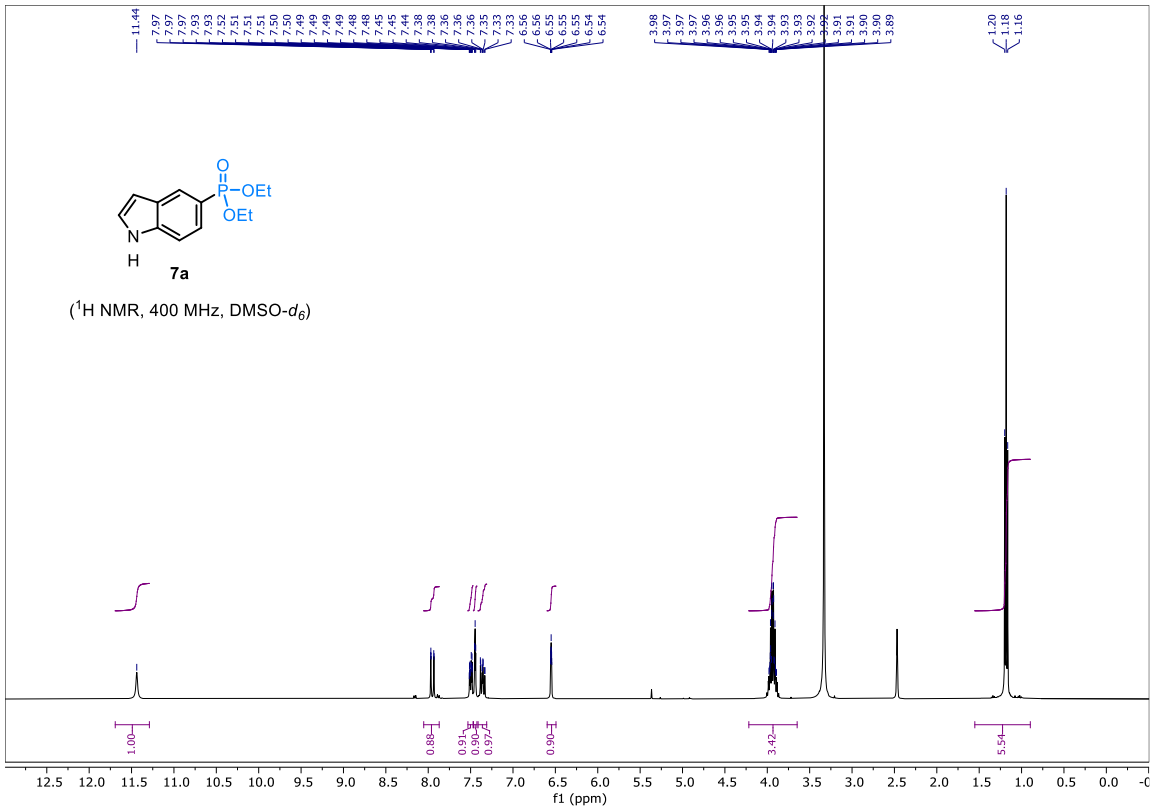

BnO
S
OMe
6b
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)

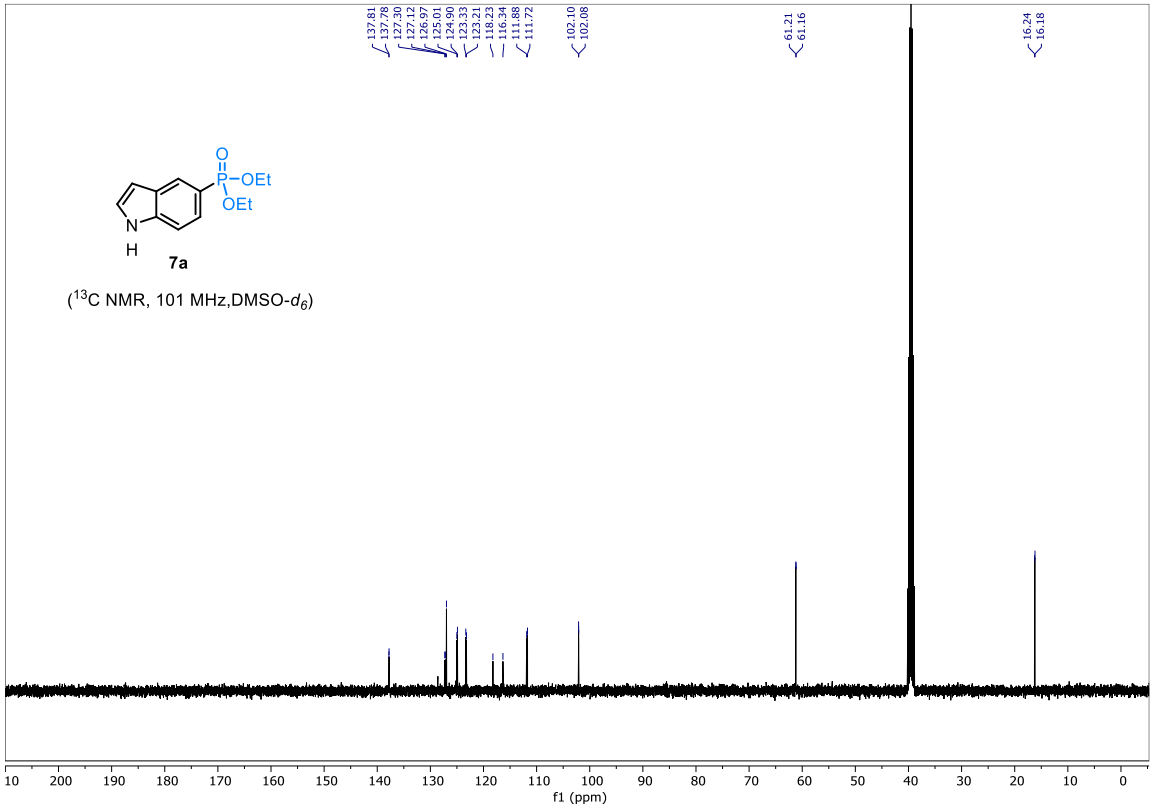

SPh
N
Et
6c
(^{1}H NMR, 400 MHz, $CDCl_3$)
f1 (ppm)

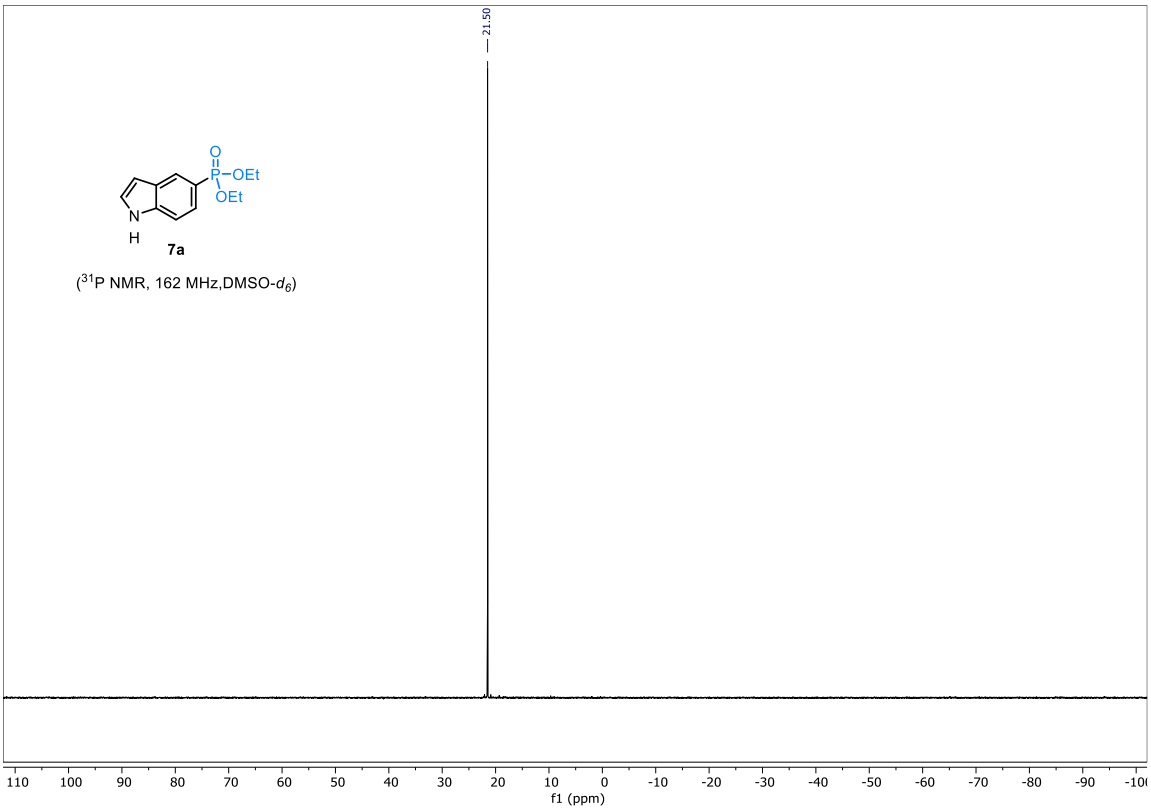

SPh
N
Et
6c
(^{13}C NMR, 101 MHz, $CDCl_3$)
f1 (ppm)


Me
S
Ph
O
N
O
H
6d
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)


Me
S
Ph
O
N
O
H
6d
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)

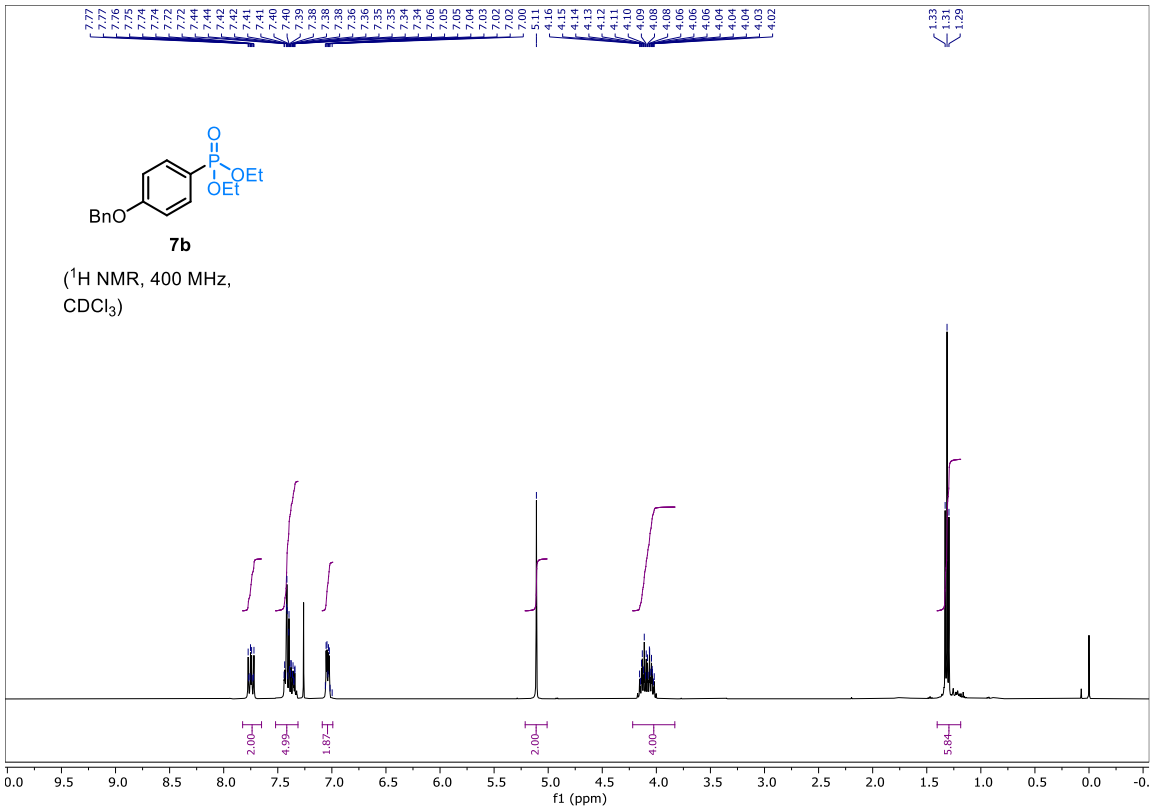

11.44
7.97
7.97
7.97
7.93
7.52
7.51
7.51
7.51
7.50
7.50
7.49
7.49
7.49
7.49
7.48
7.48
7.45
7.44
7.38
7.36
7.36
7.35
7.33
7.33
6.56
6.56
6.55
6.55
6.54
6.54
3.98
3.97
3.97
3.97
3.96
3.96
3.95
3.95
3.94
3.94
3.93
3.93
3.92
3.91
3.91
3.90
3.90
3.89
1.20
1.18
1.16
O
P–OEt
OEt
N
H
7a
(1H NMR, 400 MHz, DMSO-d6)
1.00
0.88
0.91
0.90
0.97
0.90
3.42
5.54
12.5 12.0 11.5 11.0 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
f1 (ppm)

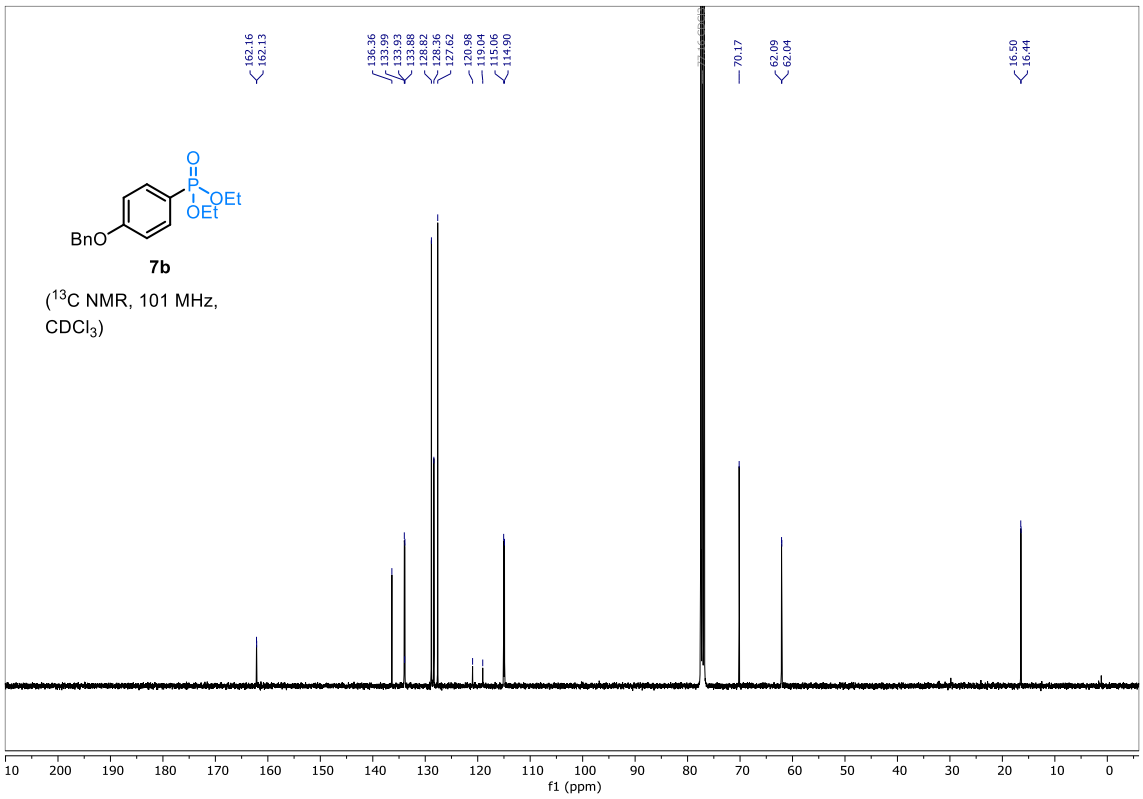

137.81
137.78
127.30
127.12
126.97
125.01
124.90
123.33
123.21
118.23
116.34
111.88
111.72
102.10
102.08
61.21
61.16
16.24
16.18
O
P–OEt
OEt
N
H
7a
(13C NMR, 101 MHz,DMSO-d6)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

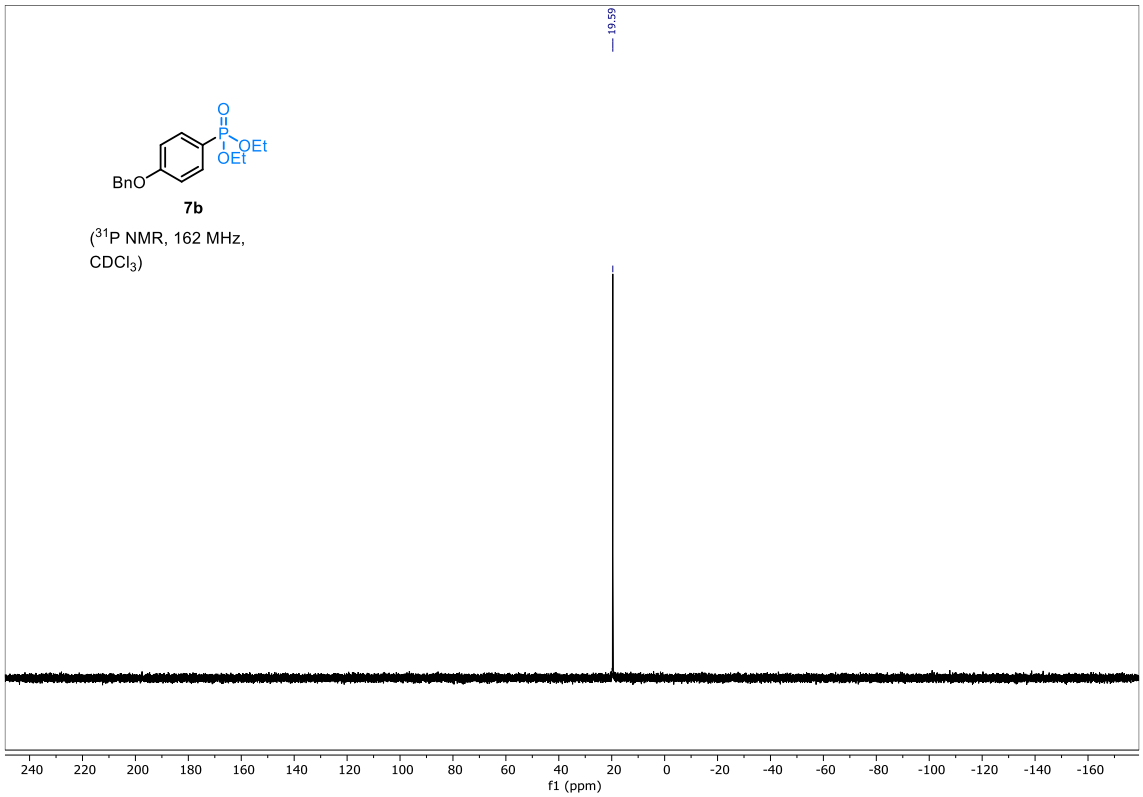


7a

(^{31}P NMR, 162 MHz,DMSO-d_6)

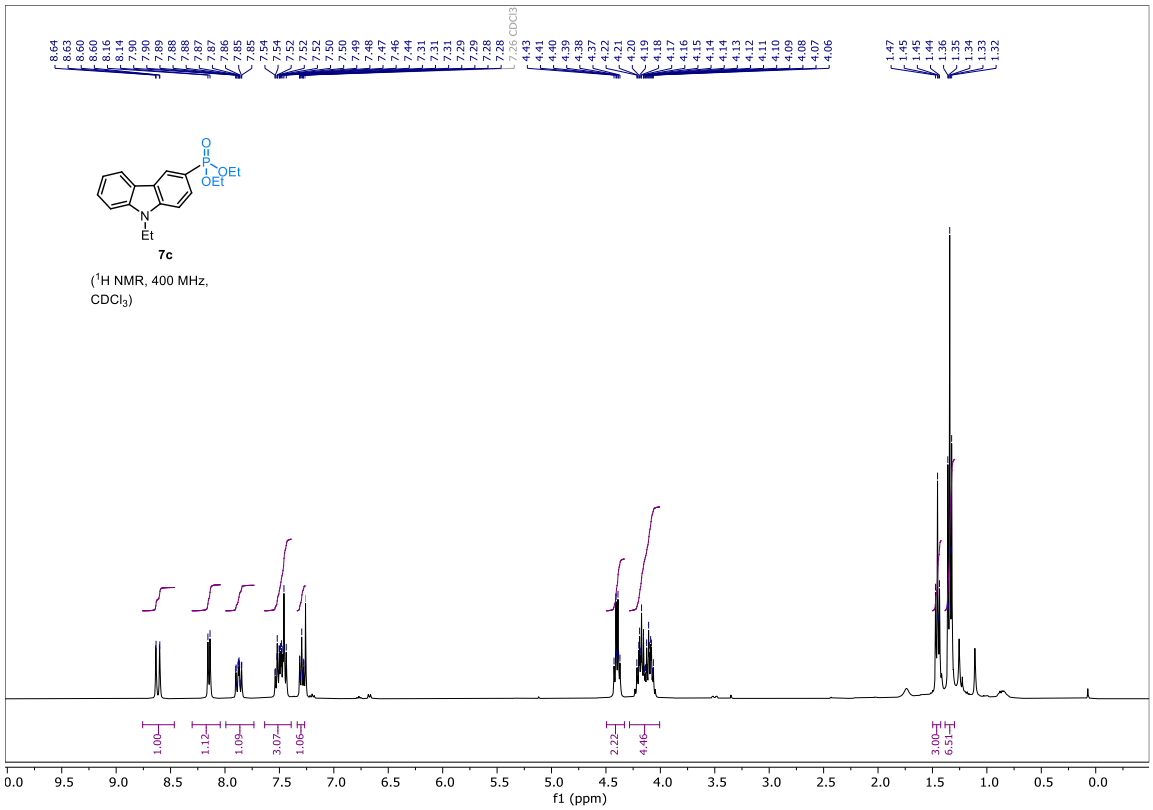

7.77 7.77 7.76 7.75 7.74 7.74 7.72 7.72 7.44 7.44 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.38 7.36 7.36 7.35 7.35 7.34 7.34 7.06 7.05 7.05 7.04 7.03 7.02 7.02 7.00 5.11 4.16 4.15 4.14 4.13 4.12 4.11 4.10 4.09 4.08 4.08 4.06 4.06 4.06 4.04 4.04 4.04 4.03 4.02 1.33 1.31 1.29
O
P
OEt
OEt
BnO
7b
(1H NMR, 400 MHz, CDCl3)
2.00 4.99 1.87 2.00 4.00 5.84
0.0 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.
f1 (ppm)

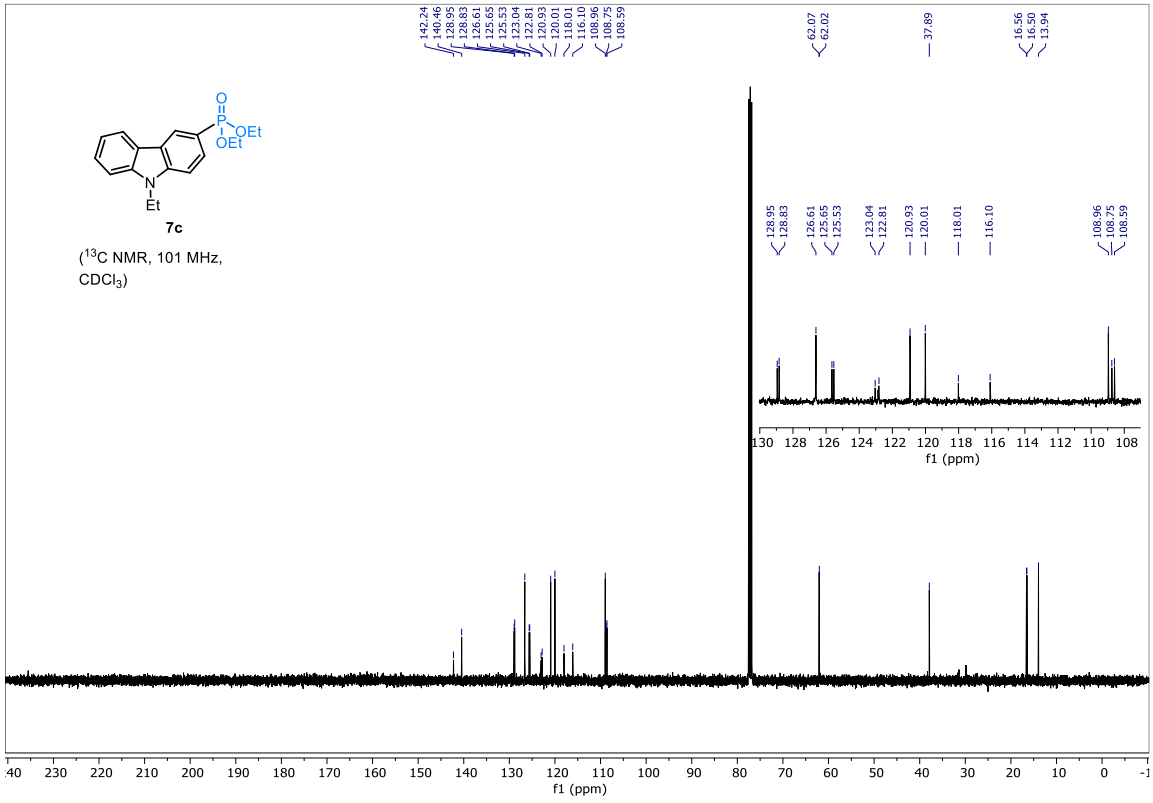

162.16 162.13 136.36 133.99 133.93 133.88 128.82 128.36 127.62 120.98 119.04 115.06 114.90 70.17 62.09 62.04 16.50 16.44
O
P
OEt
OEt
BnO
7b
(13C NMR, 101 MHz, CDCl3)
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

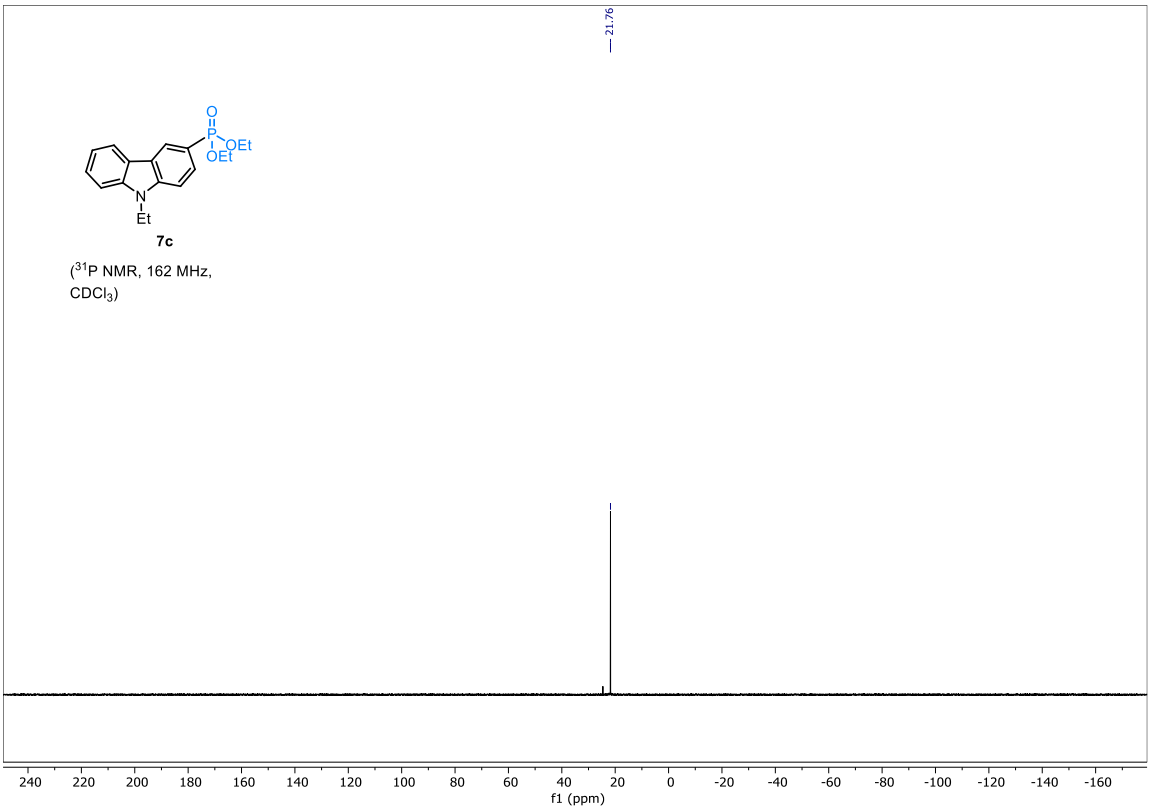


7b

(^{31}P NMR, 162 MHz, $CDCl_3$)

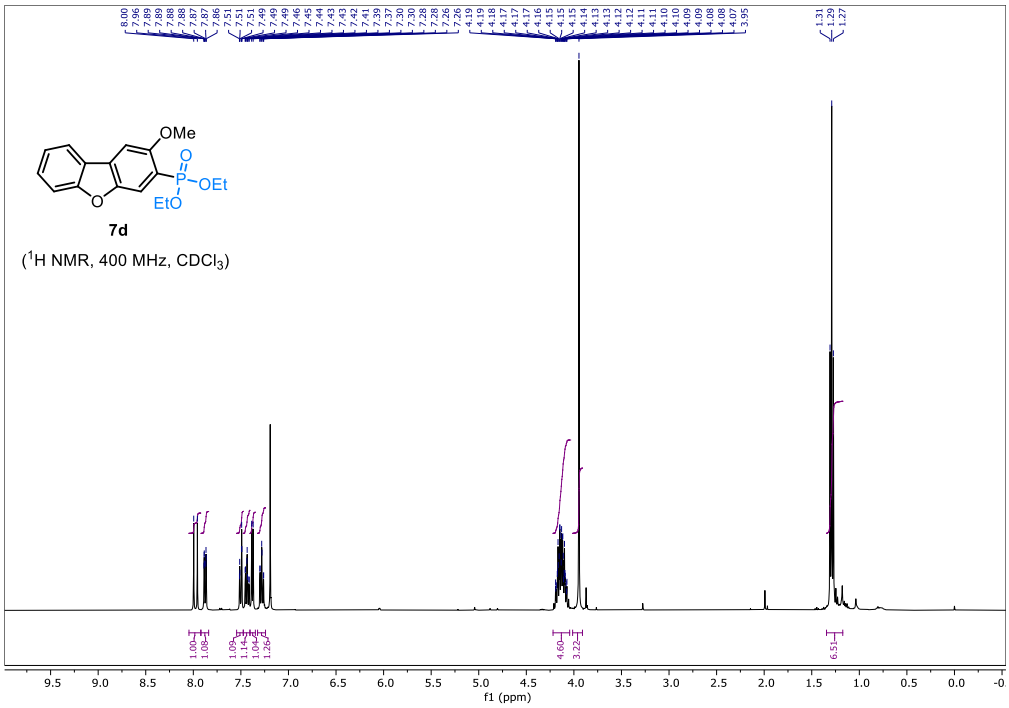

7c
(1H NMR, 400 MHz, CDCl3)
f1 (ppm)


7c
(13C NMR, 101 MHz, CDCl3)
f1 (ppm)



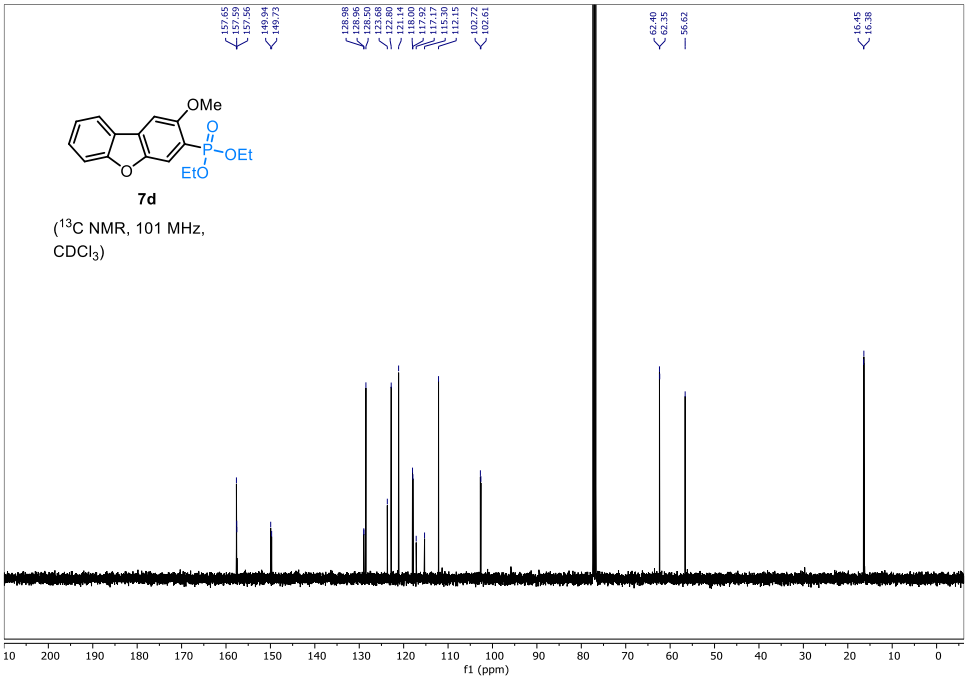
7c

(^{31}P NMR, 162 MHz, $CDCl_3$)



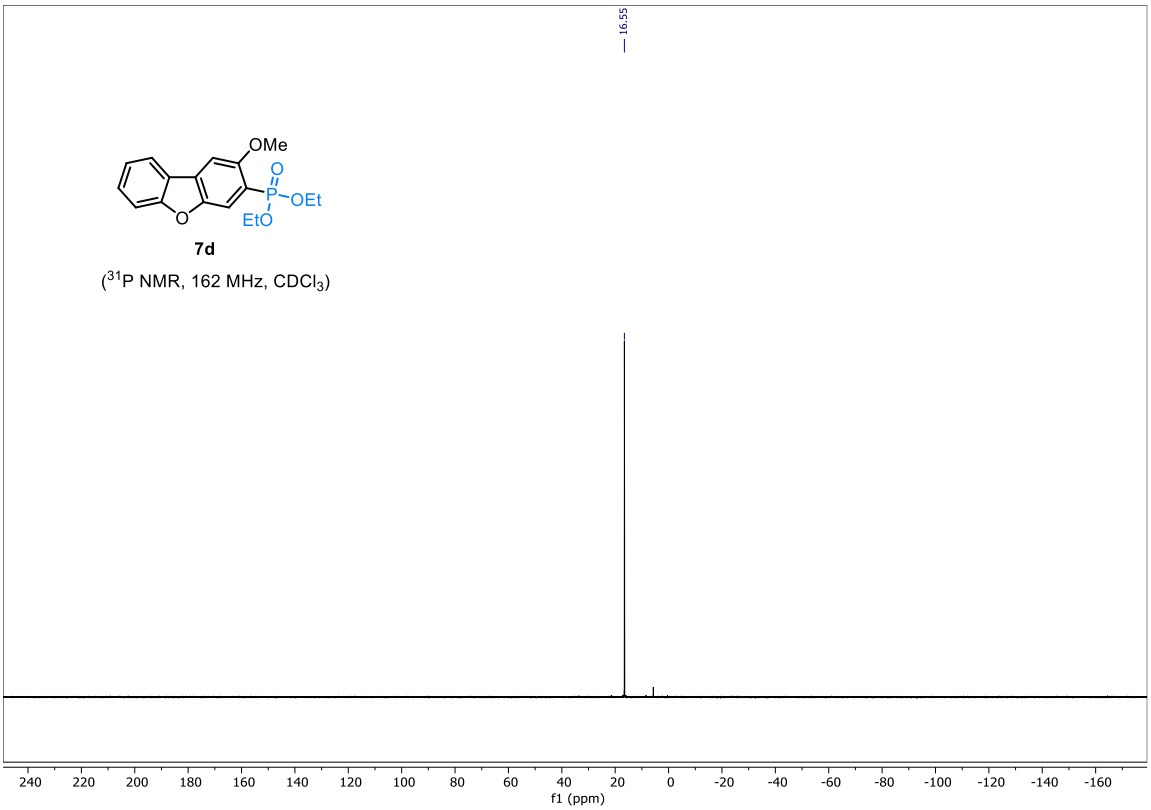
7d

(^{1}H NMR, 400 MHz, $CDCl_3$)



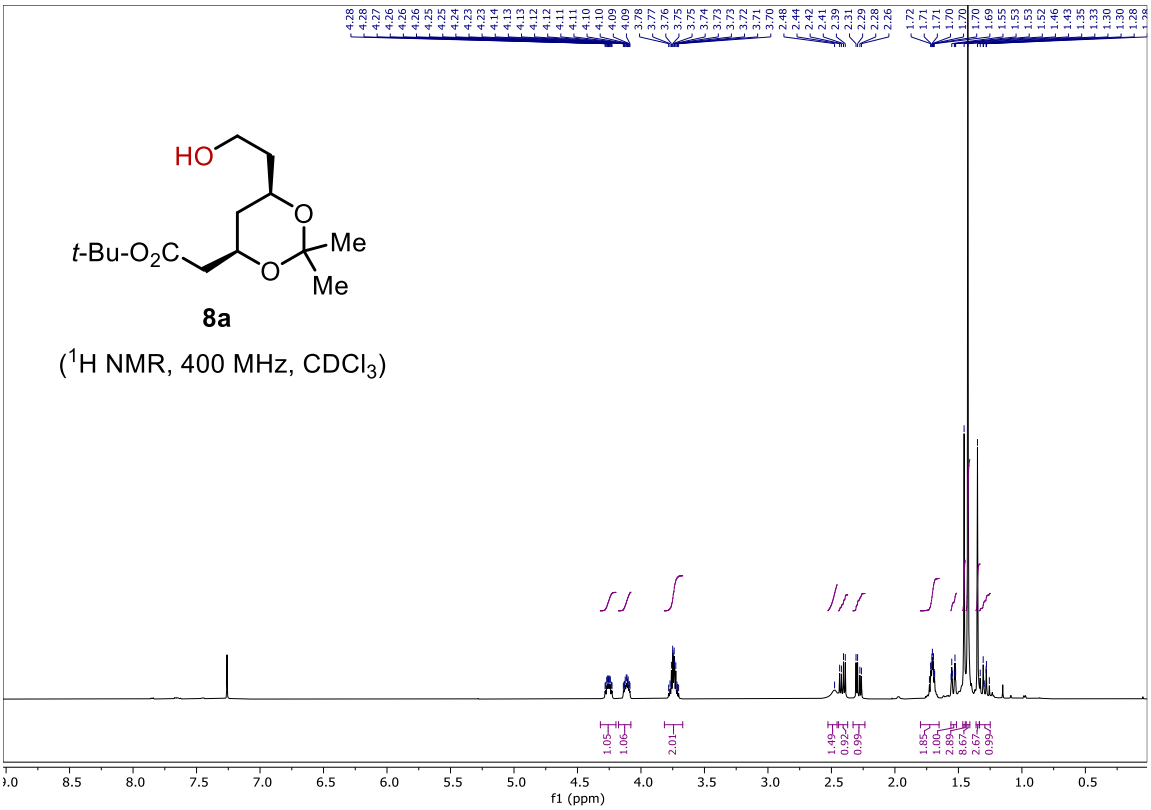
7d

(^{13}C NMR, 101 MHz, $CDCl_3$)



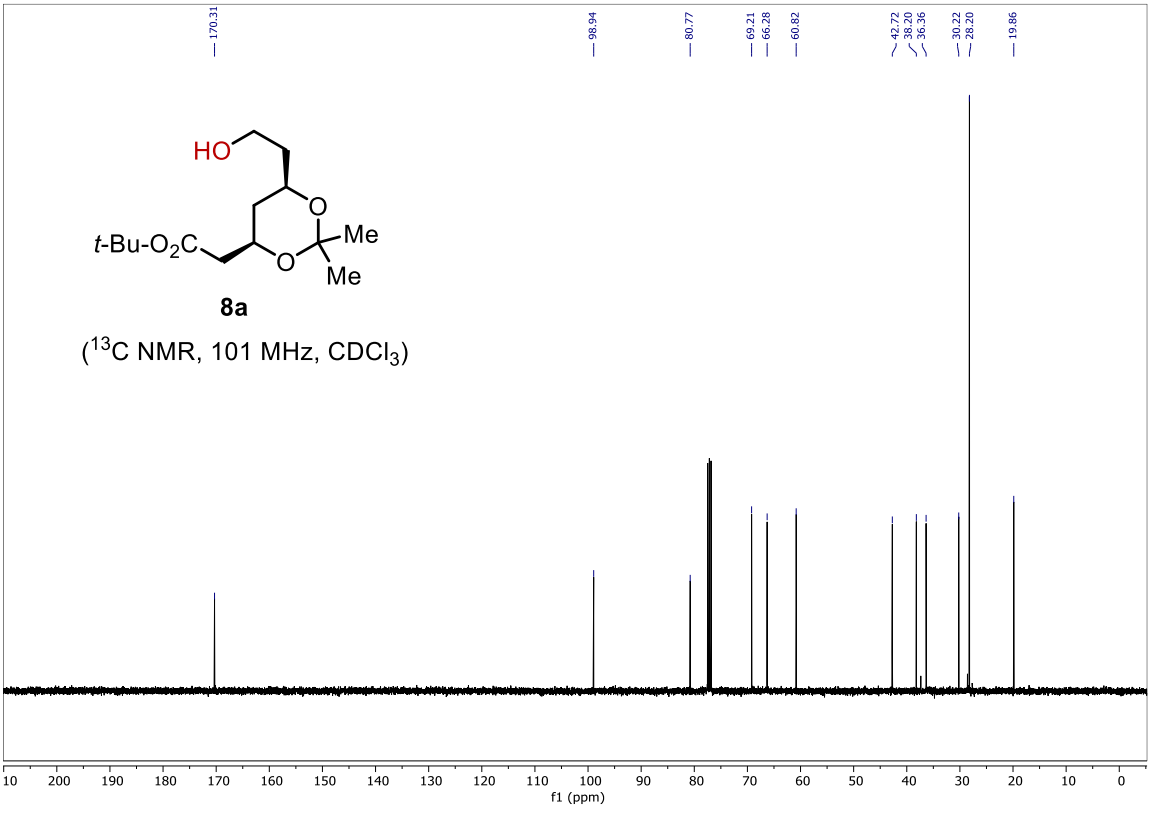
7d

(^{31}P NMR, 162 MHz, $CDCl_3$)



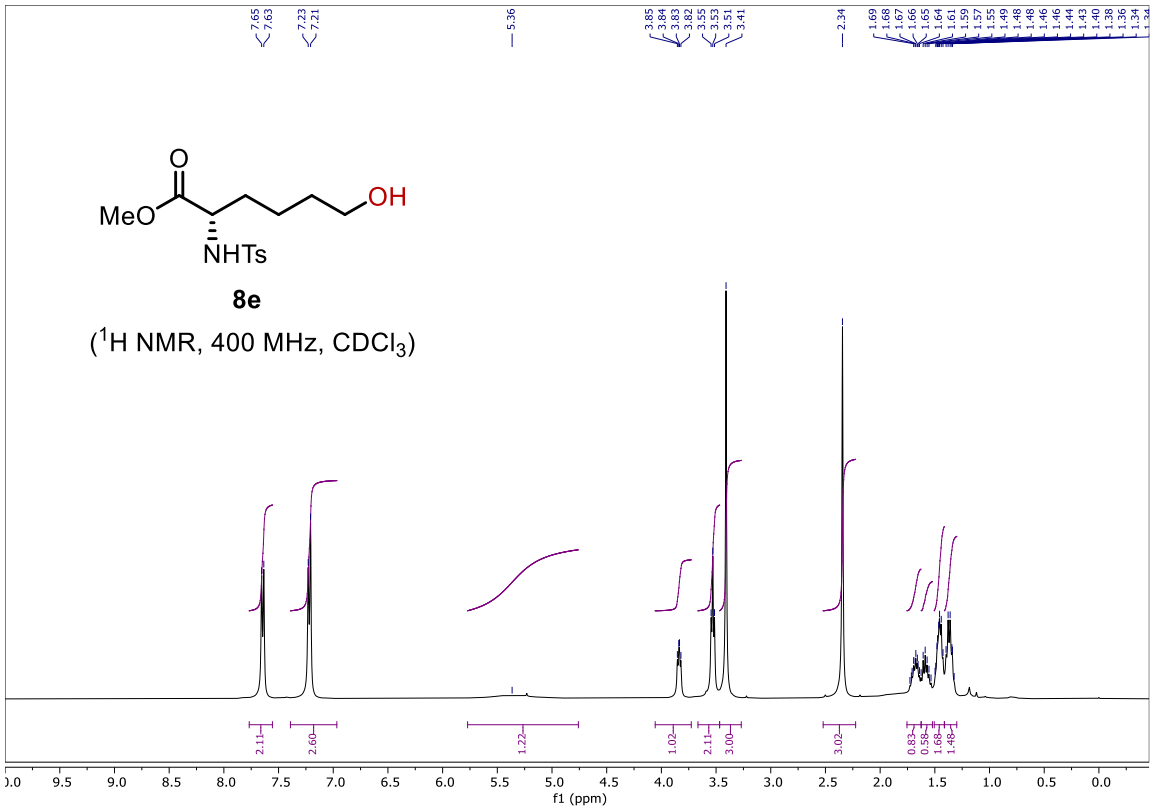
8a

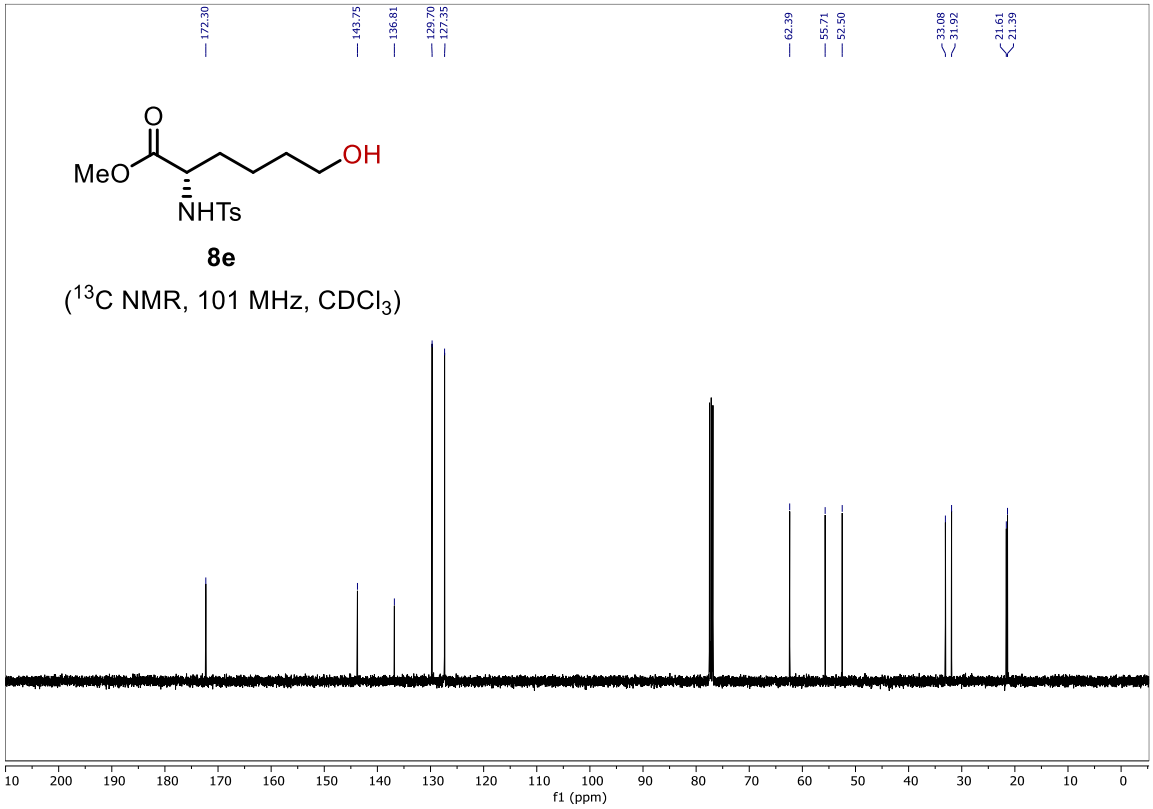
(^{1}H NMR, 400 MHz, $CDCl_3$)

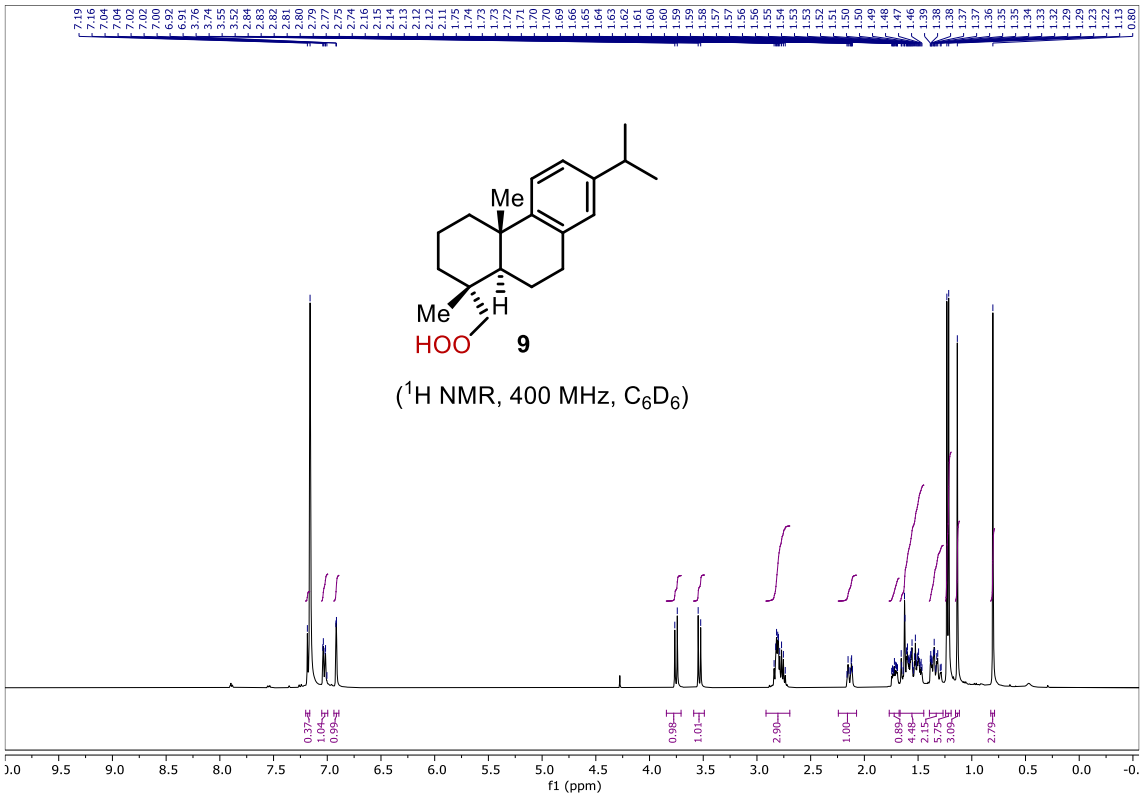


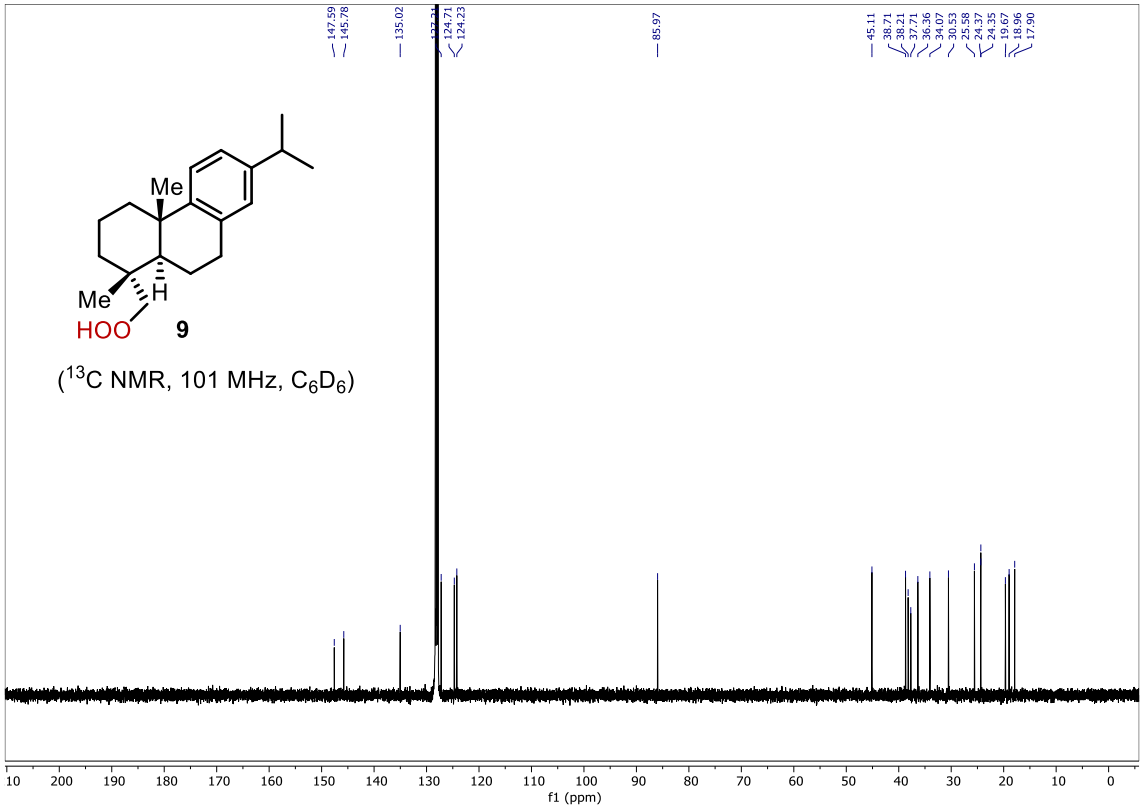
8a

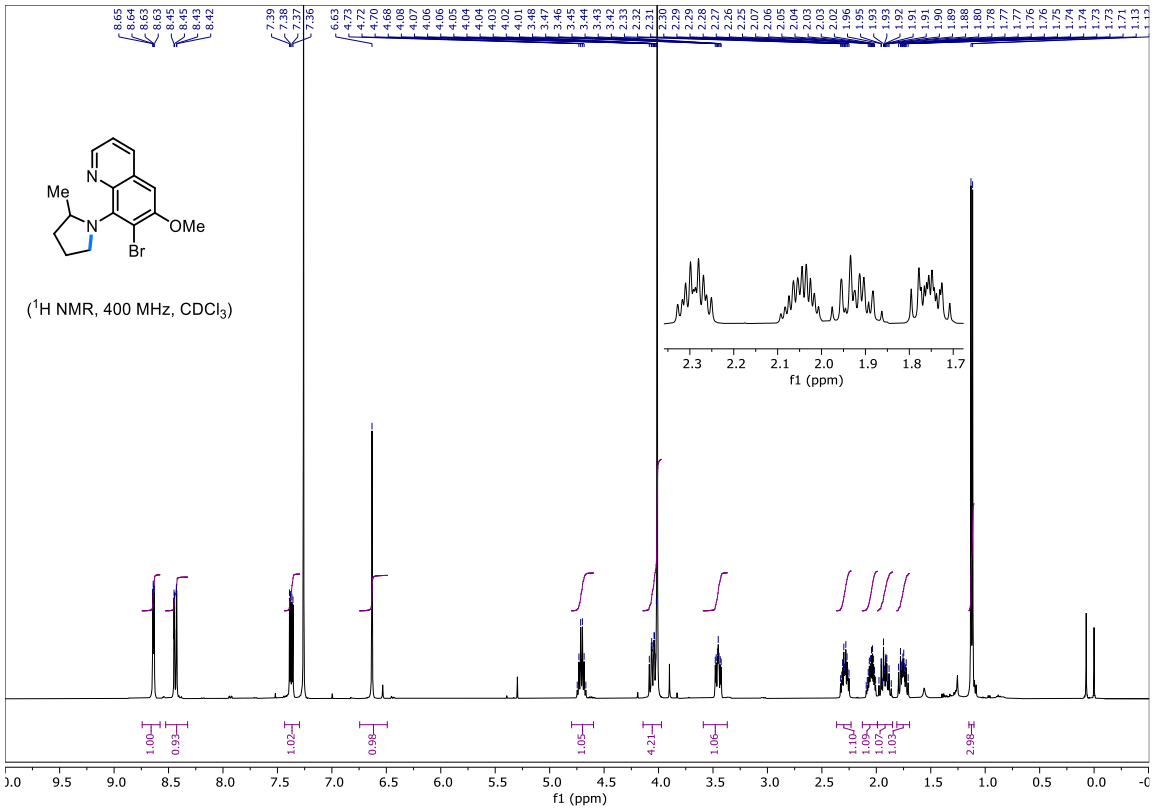
(^{13}C NMR, 101 MHz, $CDCl_3$)

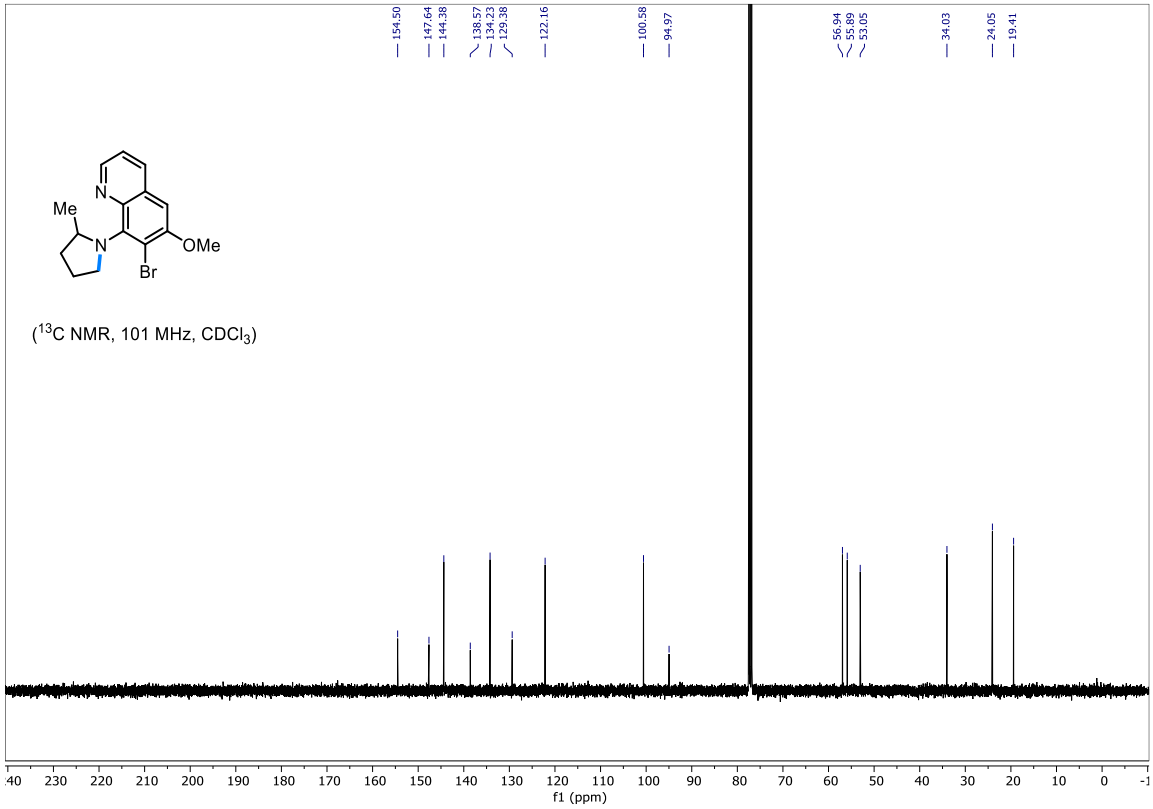

MeO
O
OH
NHTs
8e
(^{1}H NMR, 400 MHz, $CDCl_3$)
f1 (ppm)


MeO
O
OH
NHTs
8e
(^{13}C NMR, 101 MHz, $CDCl_3$)
f1 (ppm)


Me
Me
H
HOO
9
(1H NMR, 400 MHz, C6D6)
f1 (ppm)


Me
Me
H
HOO
9
(13C NMR, 101 MHz, C6D6)
f1 (ppm)


Me
N
N
OMe
Br
(^{1}H NMR, 400 MHz, $CDCl_3$)
f1 (ppm)


Me
N
N
OMe
Br
(^{13}C NMR, 101 MHz, $CDCl_3$)
f1 (ppm)