Photoredox activation of carbon dioxide for amino acid synthesis in continuous flow

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Contents

1. General Information

General Procedures

All reactions were performed under an inert atmosphere of argon with the exclusion of moisture from reagents and glassware unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm coated Science silica gel (EM 60 F_{254}) plates. Visualization was accomplished with UV light (254 nm) and exposure to either ceric ammonium molybdate (CAM), *para*-anisaldehyde, or potassium permanganate solution followed by heating. Column chromatography was carried out on a Biotage Isolera flash chromatography system using SNAP KP-Sil or Ultra-Sil columns (silica gel, average particle size 50 µm and 25 µm spherical respectively).

Material

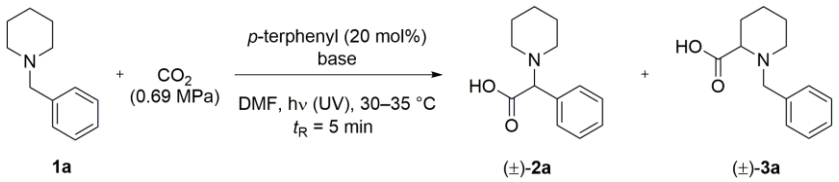
Potassium trifluoroacetate ($KOCOCF_3$) was purchased from Alfa Aesar and purified prior to use following the guidelines of Perrin and Armarego[1]. Methyl benzoate (99%, Sigma-Aldrich) was used as an internal standard for quantification. Commercially available chemicals were purchased from Sigma-Aldrich Chemical Company (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Acros Organics (Pittsburgh, PA), or TCI America (Portland, OR). All solvents were degassed by sparging with nitrogen and dried by passage through a column of activated alumna on an SG Water solvent purification system. Distilled water was obtained from an in-house supply.

Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a Bruker 400 MHz NMR instrument (400 and 101 MHz, respectively). Chemical shifts for proton are reported in parts per million (ppm) downfield from tetramethylsilane (δ = 0.00 ppm) and are referenced to residual protium in the NMR solvent ($CDCl_3$, 7.26 ppm; CD_3OD, 3.31 ppm; DMSO-*d*6, 2.50 ppm). Chemical shifts for carbon are reported in ppm downfield from tetramethylsilane (δ = 0.00 ppm) and are referenced to residual carbon in the NMR solvent ($CDCl_3$, 77.0 ppm; CD_3OD, 49.0 ppm; DMSO-*d*6, 39.5 ppm). Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were recorded on a Bruker 400 MHz (376 MHz) spectrometer; chemical shifts are reported in ppm and are referenced to α,α,α-trifluorotoluene (δ = –63.7 ppm). The following designations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were obtained on an Agilent Cary 630 FT-IR spectrometer equipped with an ATR (attenuated total reflectance) accessory. The following designations are used to describe intensities: s (strong), m (medium), w (weak), br (broad). High-resolution mass spectrometry data were acquired in the Department of Chemistry Instrumentation Facility, Massachusetts Institute of Technology on a Bruker Daltonics APEXIV 4.7 Tesla FT-ICR Mass Spectrometer. Gas chromatography (GC) was performed on an Agilent 5870 GC (HP-5 column) with a flame ionization detector. The mass flow controller (C101-DD-1-OV1-PA1-PV2-V3-S3-C10) was purchased from Sierra Instruments (Monterey, CA) and was calibrated for carbon dioxide by the vendor before using.

2. Additional Reaction Optimization Tables

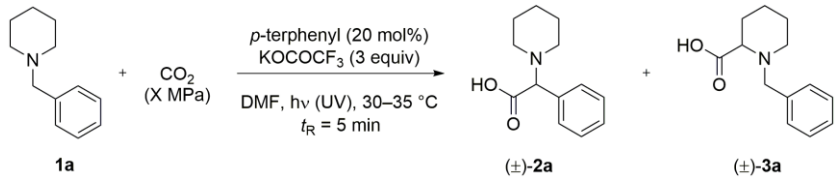
Supplementary Table 1. Base evaluation.



entry*	base	yield (%) **2a**+**3a**†	**2a**/**3a**†
1	TMP (1 equiv)	25	3.7:1
2	pyridine (1 equiv)	9	5.9:1
3	2,6-lutidine (1 equiv)	14	12:1
4	DABCO (1 equiv)	19	3.8:1
5	DBU (1 equiv)	33	2.9:1
6	*n*-Bu_4NOAc (1 equiv)	32	4.5:1
7	$NaOCOCF_3$ (2 equiv)	46	34:1
8	$LiOCOCF_3$ (2 equiv)	48	43:1
9	$CsOCOCF_3$ (2 equiv)	46	31:1
10	$KOCOCF_3$ (2 equiv)	57	35:1
11	**$KOCOCF_3$ (3 equiv)**	**59**	**27:1**
12	KDCA (2 equiv)	18	9:1
13	$KOCOCF_3$ (0.2 equiv)	42	23:1
14	TFA (0.2 equiv)	38	21:1
15	KOtBu (0.2 equiv)	30	4.4:1
16	KOTf (0.2 equiv)	26	6.1:1
17	none	21	6.6:1

*Reactions were carried out with the original continuous flow photochemistry system (Supplementary Fig. 1). †Calculated by gas chromatography (GC) after esterification with (trimethylsilyl)diazomethane ($TMSCHN_2$) using methyl benzoate as an internal standard. DMF, dimethylformamide; t_R, residence time; TMP, 2,2,6,6-tetramethylpiperidine; DABCO, 4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TFA, trifluoroacetic acid; KDCA, potassium dichloroacetate; KOTf, potassium trifluoromethanesulfonate.

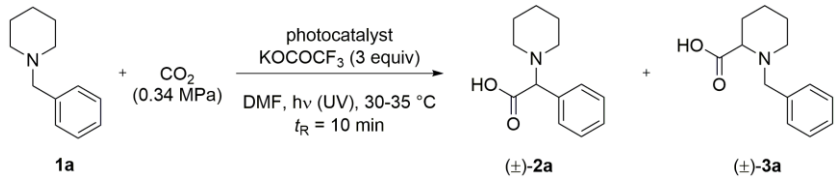
Supplementary Table 2. Pressure evaluation.



entry*	pressure† (MPa)	conversion‡ (%)	yield (%) **2a**+**3a**‡	**2a**/**3a**‡
1	0.69	72	59	27:1
2	**0.34**	**90**	**72**	**30:1**
3	0.10	87	58	17:1

*Reactions were carried out with the original continuous flow photochemistry system (Supplementary Fig. 1). †Pressure of back pressure regulator. 0.69 MPa is equivalent to 7.3 equiv of CO_2, 0.34 MPa to 3.6 equiv, and 0.10 MPa to 1.1 equiv[2]. ‡Calculated by GC after esterification with $TMSCHN_2$, using methyl benzoate as an internal standard.

Supplementary Table 3. Photoredox catalyst and UV filter evaluation.



1a (±)-**2a** (±)-**3a**

entry	photoredox catalyst	light source	UV filter	conversion (%)*	yield (%) **2a**+**3a***	**2a**/**3a***
1[†]	$Ir(ppy)_3$	blue LED	-	0	N/A	N/A
2[†]	acridine	blue LED	-	0	N/A	N/A
3[†]	phenazine	blue LED	-	0	N/A	N/A
4[‡]	*p*-terphenyl	UV (450W)	none	90	72	30:1
5[‡]	*p*-terphenyl	UV (450W)	Vycor®	90	90	26:1
6[‡]	*p*-terphenyl	UV (450W)	Pyrex®	28	28	24:1
7[‡,§]	*p*-terphenyl	UV (450W)	ethyl acetate	93	93	41:1
8[‖]	*p*-terphenyl	UV (500W)	no filter	87	83	45:1
9[‖]	*p*-terphenyl	UV (500W)	FGL 280[⊥]	20	20	43:1
10[‖]	***p*-terphenyl**	**UV (500W)**	**10CGA-280**[¶]	**92**	**92**	**52:1**

*Calculated by GC after esterification with $TMSCHN_2$, using methyl benzoate as an internal standard. [†]Reactions were carried out with the original continuous flow photochemistry system (Supplementary Fig. 1) using an array of blue LEDs instead of a UV lamp, 2.5 mol% of catalyst and 2 equiv of $KOCOCF_3$ were used. [‡]Reactions were carried out with the original continuous flow photochemistry system using 20 mol% catalyst and t_R = 5 min. [§]Reaction was carried out with the original setup with cooling bath filled with ethyl acetate instead of water. [‖]Reactions were carried out using Beeler's photochemistry system (Supplementary Fig. 2). [⊥]Purchased from Thorlabs (Newton, NJ), [¶]Purchased from Newport (Irvine, CA). $Ir(ppy)_3$, tris[2-phenylpyridinato-C^2,N]iridium(III); N/A, not applicable.

3. Reaction Setup

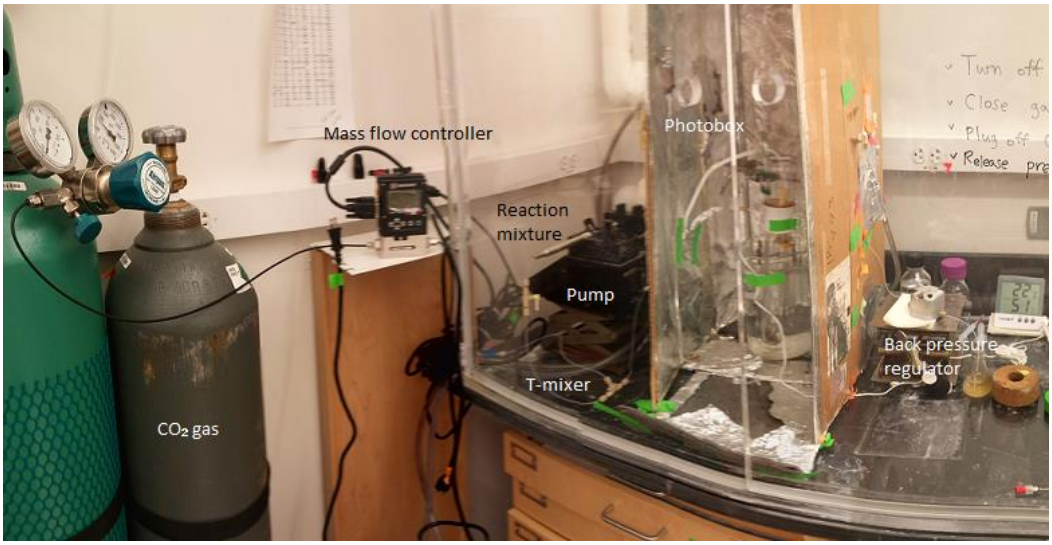
General Material Information for Continuous Flow setups

1. Harvard Apparatus PHD 2000 syringe pump was purchased from Harvard Apparatus (Holliston, MA).
2. Stainless steel syringes were purchased from Harvard Apparatus (Holliston, MA).
3. SGE gas-tight syringes were purchased from SGE analytical science (Austin, TX).
4. Tefzel® tubings and fluorinated ethylene propylene (FEP) tubings were purchased from IDEX health & science (Oak Harbor, WA).
5. Quartz tubing reactor was fabricated by James Glass Inc. (Hanover, MA)
6. PEEK™ T-mixers and unions were purchased from Upchurch Scientific®
7. Super Flangeless fittings (include nuts and ferrules) were purchased from Upchurch Scientific®
8. Mass flow controller was purchased from Sierra Instruments (Monterey, CA) and was calibrated for carbon dioxide by the vendor before using.
9. Back pressure regulator was purchased from Zaiput Flow Technologies (Cambridge, MA).
10. 450W Hg UV lamp, immersion well, and a power supply were purchased from Ace Glass (Vineland, NJ).
11. Cone-shaped frame was machined from aluminum 6061 by Proto Labs (Maple Plain, MN).
12. Research Arc Lamp Source, 500W Hg (Xe) arc lamp, and a power supply were purchased from Newport Corporation (Irvine, CA).
13. UV Hot Mirror was purchased from Edmund Optics (Barrington, NJ).
14. UV filter was purchased from Newport Corporation (Irvine, CA).
15. Blackout materials were purchased from Thorlabs (Newton, NJ).

Original continuous flow photochemistry system:

As shown in Supplementary Figure 1, a Harvard Apparatus PHD2000 syringe pump was used to deliver the reagent solution from either a stainless steel syringe or a SGE gas-tight syringe which were connected to Tefzel® tubing (OD 1/16", ID 0.04") at a shutoff valve (thru hole 0.04"). The CO_2 gas cylinder was connected to Tefzel® tubing (OD 1/8", ID 1/16"), and its stream was metered by a mass flow controller (MFC). The outlet of the MFC was connected to Tefzel® tubing (OD 1/16", ID 0.04"). The CO_2 stream was mixed with the solution phase at a T-mixer (thru hole 0.04"), and the combined stream was introduced to a quartz tubing reactor (OD 1/8", ID 0.04", volume = 2 mL). The tubing reactor was wrapped around an immersion well, inside which a 450W Hg lamp was placed, and immersed in a water bath. The tubing segments in front of and following the reactor were covered with aluminum foil. The entire reactor was placed in a cardboard box and the inside was covered with aluminum foil. The end of the quartz tubing reactor was connected to Tefzel® tubing (OD 1/16", ID 0.04"). At the distal end of the tubing system, a back pressure regulator (BPR) was installed. The final exiting stream from the BPR was collected into a flask.

a



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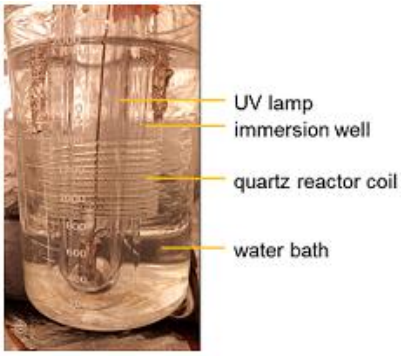
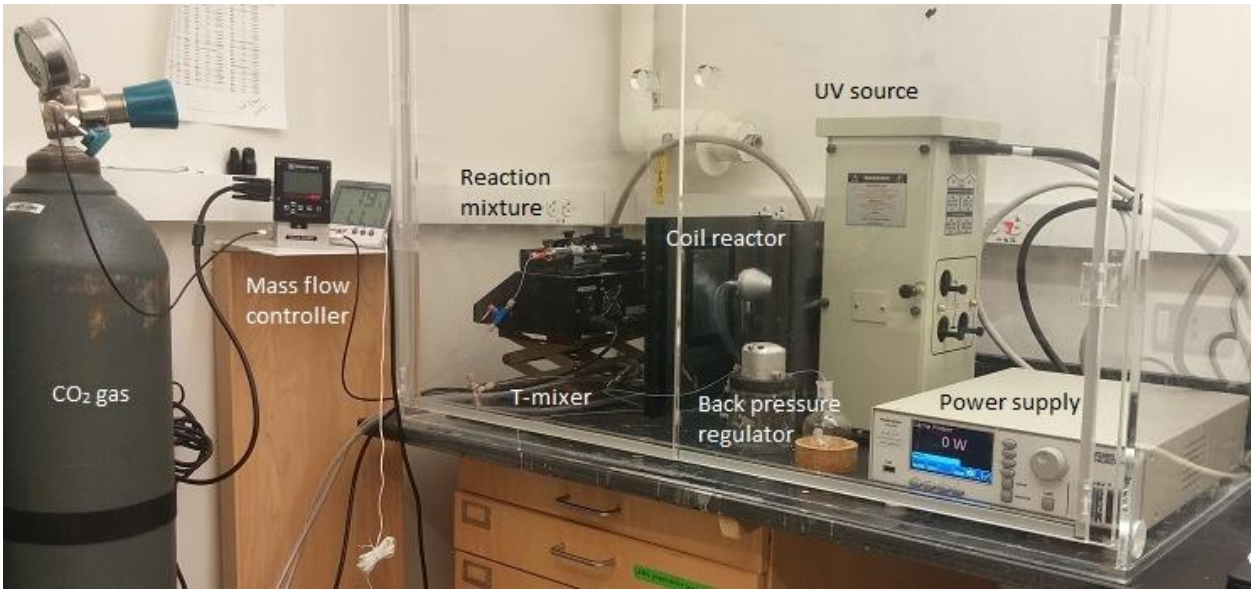


Supplementary Figure 1. Setup of the original continuous flow photochemistry system: a, The full setup. **b,** Close-up of the reactor.

Beeler's continuous flow photochemistry system:

As shown in Supplementary Figure 2, a Harvard Apparatus PHD2000 syringe pump was used to deliver the reagent solution from a SGE gas-tight syringe, which was connected to the fluorinated ethylene propylene (FEP) tubing at a shutoff valve (thru hole 0.03"). The CO_2 gas cylinder was connected to Tefzel® tubing (OD 1/8", ID 1/16"), and its stream was metered by a mass flow controller (MFC). The outlet of MFC was connected to FEP tubing (OD 1/16", ID 0.03"). The CO_2 stream was mixed with the solution phase at a T-mixer (thru hole 0.02"), and the combined stream was introduced to a FEP coil reactor (OD 1/16", ID 0.03", volume = 1.5 mL). The tubing reactor was wrapped within the helical grooves around a cone-shaped frame. The cone reactor was cooled by circulating water at room temperature. The cone reactor was irradiated by collimated light beam of 500W Hg (Xe) arc lamp. A UV Hot Mirror and wavelength filter were placed between the UV source and the cone reactor. The entire reactor was covered by black cardboard. At the distal end of the tubing system, a back pressure regulator (BPR) was installed. The final exiting stream from the BPR was collected into a flask.

a



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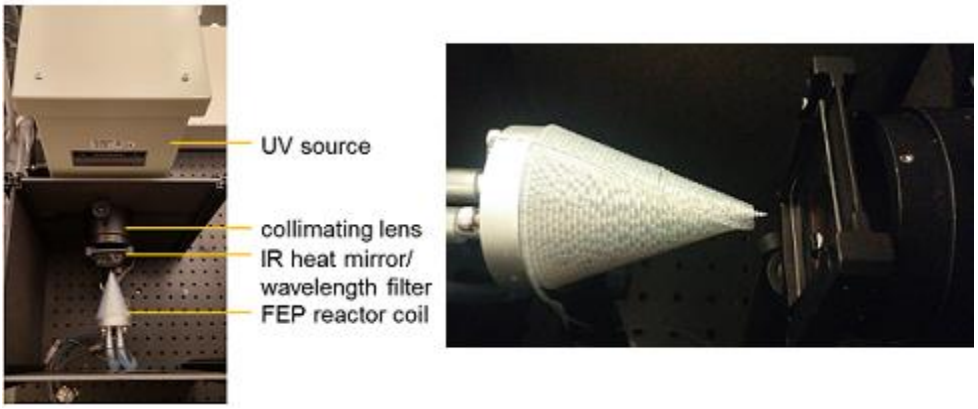
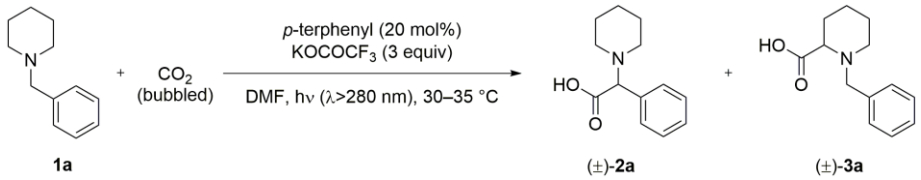


Supplementary Figure 2. Setup of the continuous flow Beeler's photochemistry system: a, The full setup. **b**, Close-up of the reactor.

4. Reaction in Batch

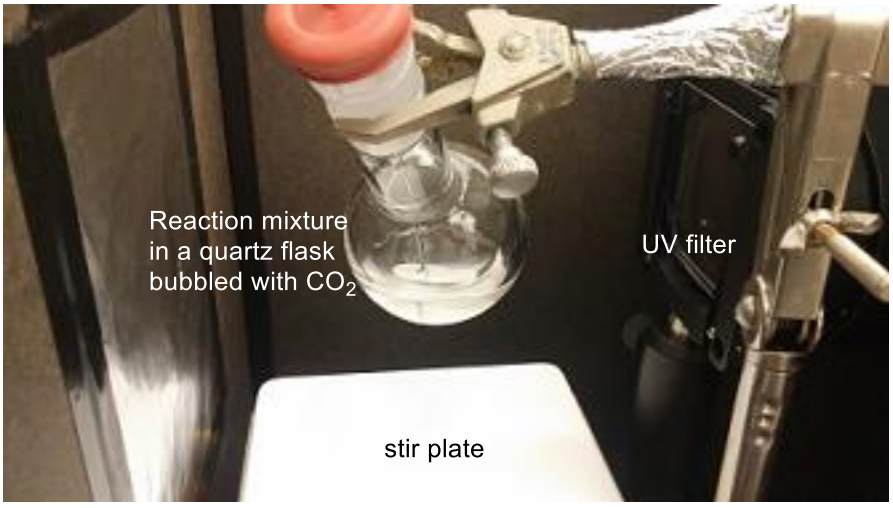
An oven-dried 50 mL Schlenk flask was charged with the appropriate tertiary amine (1.4 mmol, 1.0 equiv), *p*-terphenyl (0.28 mmol, 20 mol%), potassium trifluoroacetate (4.2 mmol, 3.0 equiv), and dimethylformamide (9.3 mL). The resulting homogeneous solution was degassed via three freeze-pump-thaw cycles. After the mixture was thoroughly degassed, the reaction mixture was transferred to a 50 mL quartz flask and the flask was placed in front of the collimated beam of UV light (Supplementary Figure 3). The reaction mixture was allowed to stir and the CO_2 gas was bubbled into the reaction mixture while the reaction proceeded. The results are summarized in the Supplementary Table 4.

Supplementary Table 4. Reaction in batch.



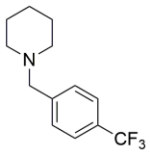
entry	reaction time (min)	conversion (%)*	yield **2a**+**3a** (%)*	**2a**/**3a***
1	10	<5	trace	-
2	60	55	20	10:1
3	120	73	30	12:1

*Calculated by GC after esterification with $TMSCHN_2$, using methyl benzoate as an internal standard.



Supplementary Figure 3. Setup of the photochemical reaction in batch.

5. Examples of Unsuccessful Substrates



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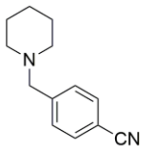

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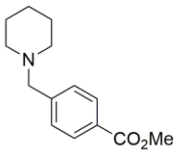

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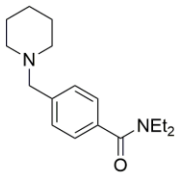

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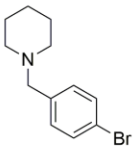

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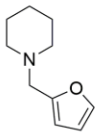

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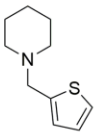

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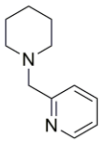

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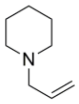

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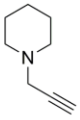

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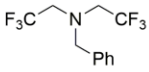

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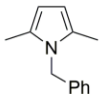


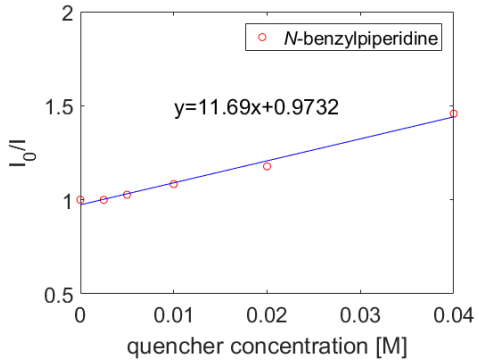
trace product

6. Mechanistic Studies

Stern-Volmer emission quenching experiments

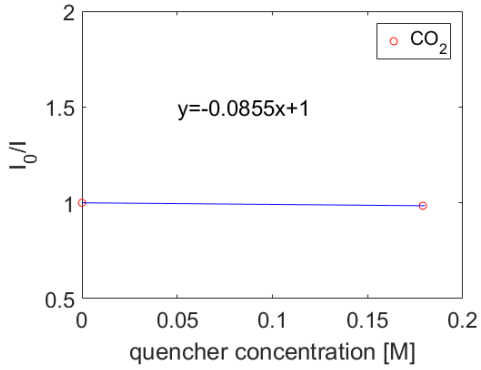
Emission intensities were recorded on a Horiba Jobin Yvon FluoroLog F13-21 Spectrophotometer. *p*-Terphenyl solutions were excited at λ_{max} = 283 nm and the emission was measured at 341 nm (emission maximum). In a typical experiment, a 2.5 μM solution of *p*-terphenyl in DMF was degassed with three freeze-pump-thaw cycles. Then, the appropriate amount of *N*-benzyl piperidine was added to the solution (along with $KOCOCF_3$ as appropriate), or the solution was bubbled with CO_2 for 20 min. After transferring the solution to a 10.0 mm quartz cuvette, the emission of the sample was collected.

a



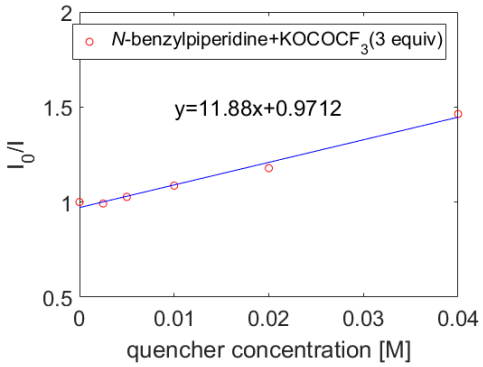
quencher concentration [M]	emission intensity	I_0/I
0	9395708	1
0.0025	9399376	0.999610
0.005	9149672	1.026890
0.01	8673632	1.083250
0.02	7978796	1.177585
0.04	6443348	1.458203

b



quencher concentration [M]	emission intensity	I_0/I
0	9049496	1
0.179	9190176	0.984692

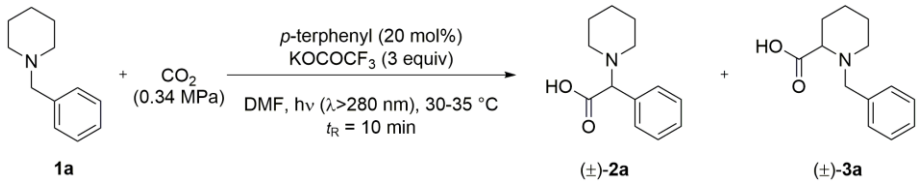
Supplementary Figure 4. *p*-Terphenyl emission quenching a, *N*-Benzylpiperidine as a quencher. **b**, Saturated CO_2 solution as a quencher.



quencher concentration [M]	$KOCOCF_3$ Concentration [M]	emission intensity	I_0/I
0	0	9049496	1
0.0025	0.0075	9117288	0.992564
0.005	0.015	8809416	1.027253
0.01	0.03	8329304	1.086465
0.02	0.06	7680268	1.178279
0.04	0.12	6182980	1.463614

Supplementary Figure 5. *p*-Terphenyl emission quenching with a mixture of *N*-benzylpiperidine and $KOCOCF_3$.

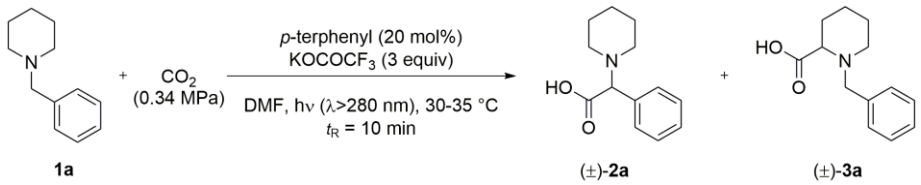
Supplementary Table 5. Control experiments.



entry*	omitted reagent	conversion (%)†	yield (%) **2a**+**3a**†	**2a**/**3a**†
1	CO_2	26	0	N/A
2	*p*-terphenyl	16	0	N/A
3	$KOCOCF_3$	94	44	5.4:1
4	light	0	0	N/A
5	none	92	92	52:1

*Reactions were carried out under optimized conditions using Beeler's photochemistry system (Supplementary Fig. 2). †Calculated by GC after esterification with $TMSCHN_2$, using methyl benzoate as an internal standard. N/A, not applicable.

Supplementary Table 6. Radical quenching experiments with TEMPO and 1,1-diphenylethylene.



1a (±)-**2a** (±)-**3a**

entry*	radical scavenger	Yield (%) **2a**+**3a**†	**2a**/**3a**†
1	TEMPO (2.5 equiv)	0	N/A
2	TEMPO (1.0 equiv)	9	>50:1
3	TEMPO (0.2 equiv)	60	40:1
4	1,1-diphenylethylene (2.5 equiv)	13	8.5:1
5	1,1-diphenylethylene (1.0 equiv)	14	9.1:1
6	1,1-diphenylethylene (0.2 equiv)	70	>50:1

*Reactions were carried out using Beeler's photochemistry system (Supplementary Fig. 2). †Calculated by GC after esterification with $TMSCHN_2$, using methyl benzoate as an internal standard. TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; N/A, not applicable.

Calculation of apparent quantum efficiency

In principle, it takes one photon to excite one *p*-terphenyl molecule and generate one CO_2 radical anion. The mean value of energy of a photon (E_{photon}) with wavelength range of 280–310 nm is calculated using the following equation:

$$E_{\text{photon}} = \frac{hc}{\lambda_{inc}} = \frac{1}{30}\int_{280}^{310} \frac{6.63 \times 10^{-34}\text{J} \cdot \text{s} \times 3 \times 10^{8}\text{m} \cdot \text{s}^{-1}}{\lambda_{inc}} \text{d}\lambda = 6.75 \times 10^{-19}\ \text{J}$$

where h (J·s) is Planck's constant, c (m·s^{-1}) is the speed of light and λ_{inc} (m) is the wavelength of the incident light. The total energy of the collimated beam (E_{total}) through lenses/filters is estimated at given wavelength range using the following equation:

$$\begin{aligned} E_{\text{total}} &= P(\lambda_1 - \lambda_2)F_{conv}F_{reflector}T_{hotmirror}T_{filter}t \\ &= 400\ \text{mWm}^{-2}\text{nm}^{-1} \times 30\ \text{nm} \times 0.13\ \text{m}^2 \times 1.6 \times 0.75 \times 0.9 \times 3780\ \text{s} \\ &= 6.37 \times 10^3\ \text{J} \end{aligned}$$

where P (mW·m^{-2}·nm^{-1}) is the irradiance of the collimated beam, F_{conv} is the conversion factor for the collimating lens given by Newport Corporation, $F_{\text{reflector}}$ is the factor when using the rear reflector to reflect backwards emitted radiation, $T_{\text{hotmirror}}$ is the transmission of the UV hot mirror in the given wavelength range, T_{filter} is the transmission of the wavelength filter, and t (s) is the photoreaction time. The total number of incident photons can be obtained through the following equation:

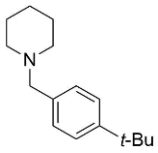
$$\text{Number of photons} = \frac{E_{total}}{E_{photon}} = \frac{6.37 \times 10^3\ \text{J}}{6.75 \times 10^{-19}\ \text{J}} = 9.44 \times 10^{21} = 14.2\ \text{mmol}$$

Since it is difficult to directly determine the number of reacted electrons via experimental methods[3], the apparent quantum efficiency (AQE) is defined for *N*-benzylamine (**1a**) as follows:

$$\text{AQE} = \frac{Number\ of\ product}{Number\ of\ photons} = \frac{0.7 \times 0.92\ \text{mmol}}{14.2\ \text{mmol}} = 0.045$$

This number indicates that radical chain processes are unlikely, but an apparent quantum efficiency less than 1 does not guarantee that no chain reaction is involved.

7. Synthesis of Starting Material Tertiary Amines

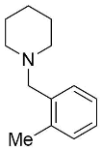


1-(4-(*tert*-butyl)benzyl)piperidine (**1b**)[4]

To a solution of 4-*tert*-butylbenzyl bromide (3.7 mL, 20 mmol, 1.0 equiv) in dichloromethane was added piperidine (7.9 mL, 80 mmol, 4.0 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring overnight at room temperature, 1N sodium hydroxide solution (40 mL) was added to the reaction mixture, and the aqueous portion was extracted with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g KP-sil, 5–60% EtOAc in hexanes) to afford **1b** (4.35 g, 18.8 mmol, 94% yield) as a colorless oil. IR (neat, cm^{-1}) 2934 (s), 2858 (m), 2790 (m), 2753 (m), 1513 (m), 1466 (m), 1441 (m), 1411 (w), 1391 (w), 1364 (m), 1342 (m), 1314 (w), 1299 (w), 1268 (m), 1249 (w), 1201 (w), 1153 (m), 1090 (s), 1039 (m), 1019 (w), 995 (m), 862 (m), 832 (m), 809 (w), 784 (m), 732 (w), 680 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 7.9 Hz, 2H), 3.49 (s, 2H), 2.42 (br s, 4H), 1.69–1.56 (m, 4H), 1.52–1.43 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 135.5, 128.8, 124.9, 63.5, 54.5, 34.3, 31.4, 25.9, 24.4. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{26}N$, 232.2060; found, 232.2053.

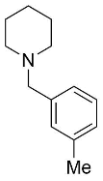
General procedure A for the synthesis of tertiary amines 1c–1e and 1h–1j.[5]

To a solution of *N*-formyl piperidine (4.4 mL, 40 mmol, 2.0 equiv) and potassium hydroxide (3.4 g, 60 mmol, 3.0 equiv) in water (15 mL) was added the appropriate benzyl halide (20 mmol, 1.0 equiv) at room temperature. After the reaction mixture was stirred at 50 °C for 3 h, the aqueous mixture was extracted with diethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage KP-sil) to provide the tertiary amine product.



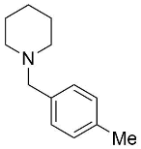
1-(2-methylbenzyl)piperidine (**1c**)

This compound was prepared via general procedure A, using 2-methylbenzyl bromide (2.7 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 5–25% EtOAc in hexanes) to afford **1c** (2.23 g, 11.8 mmol, 59% yield) as a colorless oil. IR (neat, cm^{-1}) 2933 (m), 2853 (w), 2796 (w), 2753 (w), 1492 (w), 1441 (w), 1343 (m), 1152 (w), 1118 (m), 1100 (m), 1038 (m), 992 (m), 861 (w), 790 (m), 739 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 1H), 7.17–7.11 (m, 3H), 3.41 (s, 2H), 2.39–2.37 (m, 7H), 1.59–1.53 (m, 4H), 1.47–1.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.3, 137.0, 130.0, 129.6, 126.6, 125.3, 61.5, 54.6, 26.1, 24.5, 19.2. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{20}N$, 190.1590; found, 190.1595.



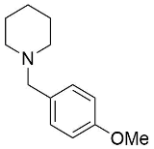
1-(3-methylbenzyl)piperidine (**1d**)

This compound was prepared via general procedure A, using 3-methylbenzyl bromide (2.7 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 5–25% EtOAc in hexanes) to afford **1d** (1.54 g, 8.14 mmol, 41% yield) as a yellow oil. IR (neat, cm^{-1}) 3021 (w), 2933 (m), 2854 (w), 2791 (w), 2753 (w), 1609 (w), 1489 (w), 1442 (m), 1389 (w), 1368 (w), 1342 (m), 1301 (w), 1269 (w), 1248 (w), 1197 (w), 1167 (w), 1112 (m), 1090 (w), 1039 (m), 993 (w), 887 (w), 859 (w), 794 (m), 769 (s), 743 (w), 696 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 9.5 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 3.48 (s, 2H), 2.42–2.38 (m, 7H), 1.62 (m, 4H), 1.50–1.44 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 137.5, 129.9, 127.9, 127.5, 126.3, 63.9, 54.5, 25.9, 24.3, 21.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{20}N$, 190.1590; found, 190.1589.



1-(4-methylbenzyl)piperidine (**1e**)

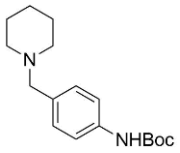
This compound was prepared via general procedure A, using 4-methylbenzyl bromide (2.7 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 5–25% EtOAc in hexanes) to afford **1e** (3.07 g, 16.2 mmol, 81% yield) as a colorless oil. IR (neat, cm^{-1}) 2932 (s), 2854 (m), 2790 (m), 2753 (m), 1514 (m), 1441 (m), 1390 (w), 1368 (w), 1342 (m), 1290 (m), 1268 (w), 1247 (w), 1152 (m), 1113 (m), 1101 (m), 1038 (m), 994 (m),962 (w), 862 (m), 839 (w), 806 (s), 777(s), 752 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.7 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 3.49 (s, 2H), 2.42–2.38 (m, 7H), 1.64–1.60 (m, 4H), 1.50–1.45 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 135.4, 129.1, 128.6, 63.5, 54.3, 25.9, 24.3, 21.0. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{20}N$, 190.1590; found, 190.1587.



1-(4-methoxybenzyl)piperidine (**1f**)[5]

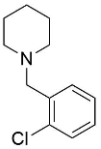
To a solution of *N*-formyl piperidine (0.89 mL, 8.0 mmol, 2.0 equiv) and potassium hydroxide (673 mg, 12 mmol, 3.0 equiv) in water (3 mL) was added 4-methoxybenzyl chloride (0.54 mL, 4.0 mmol, 1.0 equiv) at room temperature. After the reaction mixture was stirred at 50 °C for 3 h, the aqueous portion was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 25 g Ultra-sil, 2–40% EtOAc in hexanes) to afford **1f** (537 mg, 2.62 mmol, 65% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6, 2H), 3.79 (s, 3H), 3.42 (s, 2H), 2.36 (br s, 4H), 1.60–1.55 (m, 4H), 1.50–1.39 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 130.5, 130.2, 113.3, 63.1, 55.0, 54.2, 25.9, 24.3.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[6].



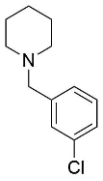
***tert*-butyl (4-(piperidin-1-ylmethyl)phenyl)carbamate (1g)**[7]

To a solution of piperidine (1.1 mL, 11 mmol, 1.1 equiv), 4-(Boc-amino)benzaldehyde (0.88 mL, 10 mmol, 1.0 equiv), and sodium triacetoxyborohydride (3.18 g, 15 mmol, 1.5 equiv) in dichloroethane (50 mL) was added acetic acid (0.57 mL, 10 mmol, 1.0 equiv) at room temperature. After the suspension was stirred overnight, saturated aqueous sodium bicarbonate was added to the reaction mixture, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g KP-sil, 5–25% EtOAc in hexanes) to afford **1g** (1.07 g, 3.70 mmol, 84% yield) as a white solid.
IR (neat, cm^{-1}) 3328 (w), 2978 (w), 2933 (m), 2854 (w), 2784 (w), 2756 (w), 1725 (m), 1701 (m), 1597 (w), 1522 (s), 1455 (w), 1411 (m), 1391 (w), 1366 (m), 1343 (w), 1312 (m), 1235 (m), 1157 (s), 1117 (w), 1103 (w), 1051 (m), 993 (w), 903 (w), 835 (w), 757 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.52 (s, 1H), 3.41 (s, 2H), 2.34 (br s, 4H), 1.58–1.53 (m, 4H), 1.51 (s, 9H), 1.44–1.39 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 137.0, 133.1, 129.9, 118.3, 80.3, 63.3, 54.3, 28.3, 25.9, 24.4. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{27}N_2O_2$, 291.2067; found, 291.2073.



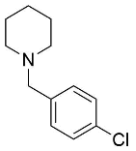
1-(2-chlorobenzyl)piperidine (1h)

This compound was prepared via general procedure A, using 2-chlorobenzyl bromide (2.6 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 2–10% EtOAc in hexanes) to afford **1h** (3.86 g, 18.5 mmol, 92% yield) as a colorless oil.
IR (neat, cm^{-1}) 3061 (w), 2933 (m), 2852 (w), 2793 (w), 2757 (w), 1572 (w), 1467 (w), 1441 (m), 1391 (w), 1367 (w), 1345 (m), 1301 (w), 1265 (w), 1198 (w), 1153 (w), 1113 (w), 1036 (m), 994 (w), 862 (w), 843 (w), 905 (w), 863 (w), 788 (w), 747 (s), 684 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.23 (td, *J* = 7.5, 1.5 Hz, 1H), 7.16 (td, *J* = 7.6, 1.8 Hz, 1H), 3.59 (s, 2H), 2.46 (t, *J* = 4.8 Hz, 4H), 1.63–1.57 (m, 4H), 1.49–1.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 134.1, 130.5, 129.2, 127.7, 126.4, 59.9, 54.6, 26.0, 24.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{17}ClN$, 210.1044; found, 210.1031.



1-(3-chlorobenzyl)piperidine (**1i**)

This compound was prepared via general procedure A, using 3-chlorobenzyl bromide (2.6 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 3–15% EtOAc in hexanes) to afford **1i** (3.09 g, 14.8 mmol, 74% yield) as a colorless oil. IR (neat, cm^{-1}) 2934 (m), 2854 (w), 2792 (w), 2754 (w), 1598 (w), 1575 (w), 1473 (w), 1431 (w), 1390 (w), 1369 (w), 1342 (m), 1301 (w), 1289 (w), 1244 (w), 1197 (w), 1154 (w), 1111 (m), 1075 (m), 996 (m), 963 (w), 870 (m), 791 (m), 769 (s), 698 (m), 682 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.0 Hz, 1H), 7.24–7.15 (m, 3H), 3.43 (s, 2H), 2.36 (s, 4H), 1.61–1.55 (m, 4H), 1.46–1.40 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 134.0, 129.2, 128.9, 127.1, 126.9, 63.2, 54.4, 25.9, 24.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{17}ClN$, 210.1044; found, 210.1034.



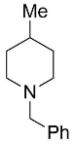
1-(4-chlorobenzyl)piperidine (**1j**)

This compound was prepared via general procedure A, using 4-chlorobenzyl bromide (2.6 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 20–45% EtOAc in hexanes) to afford **1j** (1.74 g, 8.32 mmol, 42% yield) as a colorless oil.

IR (neat, cm^{-1}) 2934 (s), 2853 (w), 2789 (m), 2755 (m), 2634 (w), 1895 (w), 1597 (w), 1490 (m), 1440 (w), 1407 (w), 1369 (w), 1342 (m), 1298 (w), 1246 (w), 1197 (w), 1152 (m), 1113 (m), 1096 (w), 1039 (m), 1015 (w), 995 (m), 907 (w), 862 (m), 834 (m), 804 (s), 780 (m), 710 (w), 667 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.22 (m, 4H), 3.42 (s, 2H), 2.35 (br s, 4H), 1.60–1.54 (m, 4H), 1.46–1.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 132.4, 130.3, 128.1, 63.0, 54.4, 25.9, 24.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{17}ClN$, 210.1044; found, 210.1035.

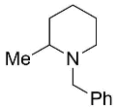
General procedure B for the synthesis of tertiary amines 1k and 1l[8].

To a solution of piperidine (22 mmol, 1.1 equiv) and potassium carbonate (1.4 g, 10 mmol, 0.5 equiv) in acetonitrile (15 mL) was added benzyl bromide (2.4 mL, 20 mmol, 1.0 equiv) dropwise at 0 °C. The reaction mixture was allowed to stir at reflux overnight. After cooling to room temperature, the reaction mixture was quenched with water, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage KP-sil) to provide the tertiary amine product.



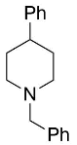
1-benzyl-4-methylpiperidine (**1k**)

This compound was prepared via general procedure B, using 4-methylpiperidine (2.6 mL, 22 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 5–70% EtOAc in hexanes) to afford **1k** (3.04 g, 16.1 mmol, 80% yield) as a colorless oil. IR (neat, cm^{-1}) 3064 (w), 3027 (w), 2949 (2), 2920 (m), 2870 (w), 2798 (w), 2757 (w), 1495 (w), 1454 (m), 1393 (w), 1367 (m), 1341 (w), 1315 (w), 1271 (w), 1254 (w), 1151 (w), 1118 (m), 1081 (m), 1029 (w), 978 (m), 906 (w), 821 (m), 777 (w), 733 (s), 696 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.34 (m, 4H), 7.30–7.26 (m, 1H), 3.54 (s, 2H), 2.90 (d, *J* = 11.8 Hz, 2H), 1.99 (t, *J* = 11.3 Hz, 2H), 1.65 (d, *J* = 12.5 Hz, 2H), 1.46–1.27 (m, 3H), 1.00–0.96 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 129.0, 128.0, 126.7, 63.4, 53.8, 34.3, 30.7, 21.9. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{20}N$, 190.1590; found, 190.1586.



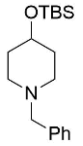
1-benzyl-2-methylpiperidine (**1l**)

This compound was prepared via general procedure B, using 2-methylpiperidine (2.6 mL, 22 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 5–40% EtOAc in hexanes) to afford **1l** (3.18 g, 16.8 mmol, 84% yield) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.29–7.25 (m, 1H), 4.06 (d, *J* = 13.4 Hz, 1H), 3.25 (d, *J* = 13.4 Hz, 1H), 2.80 (d, *J* = 11.4 Hz, 1H), 2.36 (br s, 1H), 2.01 (m, 1H), 1.70 (d, *J* = 9.9 Hz, 2H), 1.56–1.29 (m, 4H), 1.23 (dd, *J* = 6.2, 2.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.5, 129.0, 127.9, 126.5, 58.4, 56.3, 52.1, 34.7, 26.0, 24.0, 19.5.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[9].



1-benzyl-4-phenylpiperidine (**1m**)[8]

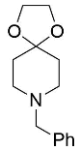
To a solution of 4-phenylpiperidine (2.7 g, 16.5 mmol, 1.1 equiv) and potassium carbonate (1.0 g, 7.5 mmol, 1.5 equiv) in acetonitrile (12 mL) was added benzyl bromide (1.8 mL, 15 mmol, 1.0 equiv) dropwise at 0 °C. The reaction mixture was allowed to stir at reflux overnight. After cooling to room temperature, the reaction mixture was quenched with water, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g Ultra-sil) to afford **1m** (3.26 g, 13.0 mmol, 86% yield) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.18 (m, 10H), 3.57 (s, 2H), 3.03 (d, *J* = 11.8 Hz, 2H), 2.51 (tt, *J* = 9.2, 6.2 Hz, 1H), 2.14–2.07 (m, 2H), 1.85–1.80 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5, 138.4, 129.2, 128.3, 128.1, 126.9, 126.8, 126.0, 63.5, 54.3, 42.7, 33.5.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[10].



1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)piperidine (**1n**)

To a solution of 1-benzyl-4-hydroxypiperidine (3.8 g, 20 mmol, 1.0 equiv) in dimethylformamide (60 mL) were added *tert*-butyldimethylsilyl chloride (3.3 g, 22 mmol, 1.1 equiv) and imidazole (2.7 g, 40 mmol, 2.0 equiv) at room temperature. The reaction mixture was allowed to stir for 1.5 h at room temperature. The reaction mixture was quenched by saturated aqueous ammonium chloride, and the aqueous portion was extracted with diethylether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g KP-sil, 0–40% EtOAc in hexanes) to afford **1n** (5.39 g, 17.6 mmol, 88% yield) as a colorless oil.

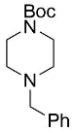
IR (neat, cm^{-1}) 2929 (m), 2888 (w), 2856 (w), 2801 (w), 1494 (w), 1471 (w), 1353 (w), 1251 (m), 1091 (s), 1054 (s), 1025 (w), 1005 (w), 972 (w), 938 (w), 905 (w), 873 (s), 832 (s), 772 (s), 733 (s), 697 (s), 670 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 4H), 7.29–7.24 (m, 1H), 3.75 (br s, 1H), 3.52 (s, 2H), 2.73–2.68 (m, 2H), 2.22 (t, J = 10.1 Hz, 2H), 1.86–1.72 (m, 2H), 1.63 (m, 2H), 0.93 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 129.0, 128.1, 126.8, 68.1, 63.1, 50.7, 34.7, 25.8, 18.1, –4.7. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{32}NOSi$, 306.2248; found, 306.2260.



8-benzyl-1,4-dioxa-8-azaspiro[4.5]decane (**1o**)

To a solution of 1,4-dioxa-8-azaspiro[4.5]decane (1.9 mL, 15 mmol, 1.0 equiv) and potassium carbonate (3.1 g, 23 mmol, 1.5 equiv) in acetonitrile (12 mL) was added benzyl bromide (1.8 mL, 15 mmol, 1.0 equiv) dropwise at 0 °C. The reaction mixture was allowed to stir at reflux overnight. After cooling to room temperature, the reaction mixture was quenched with water, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g Ultra-sil, 5–60% EtOAc in hexanes) to afford **1o** (2.71 g, 11.6 mmol, 77% yield) as a colorless oil.

IR (neat, cm^{-1}) 3028 (w), 2953 (w), 2929 (w), 2880 (w), 2808 (w), 2771 (w), 1495 (w), 1453 (w), 1393 (w), 1363 (w), 1339 (w), 1305 (m), 1243 (w), 1206 (w), 1140, m), 1088 (s), 1039 (m), 1005 (w), 963 (w), 945 (m), 915 (m), 799 (w), 771 (w), 736 (s), 698 (s), 667 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 4H), 7.25 (m, 1H), 3.92 (d, J = 8.0 Hz, 4H), 3.52 (s, 2H), 2.53 (br s, 4H), 1.74 (t, J = 4.5 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 128.8, 128.0, 126.7, 107.1, 63.9, 62.5, 51.1, 34.7. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1492.

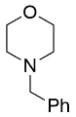


***tert*-butyl 4-benzylpiperazine-1-carboxylate** (**1p**)

To a solution of 1-boc-piperazine (2.8 g, 15 mmol, 1.0 equiv) and potassium carbonate (6.2 g, 45 mmol, 3.0 equiv) in dichloromethane (50 mL) was added benzyl bromide (2.7 mL, 22.5 mmol, 1.5 equiv) dropwise at 0 °C. The reaction mixture was allowed to stir at reflux overnight. After cooling to room temperature, the reaction mixture was quenched with water, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g Ultra-sil, 5–40% EtOAc in hexanes) to afford **1p** (3.08 g, 11.2 mmol, 75% yield) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.30 (m, 4H), 7.28–7.22 (m, 1H), 3.50 (s, 2H), 3.42 (t, J = 5.1 Hz, 4H), 2.38 (t, J = 5.0 Hz, 4H), 1.45 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 137.8, 129.1, 128.2, 127.1, 79.5, 63.0, 52.8, 44.1, 28.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[11].

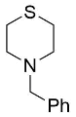


4-benzylmorpholine (**1q**)

To a solution of 4-formylmorpholine (0.80 mL, 8.0 mmol, 2.0 equiv) and potassium hydroxide (673 mg, 12 mmol, 3.0 equiv) in water (3 mL) was added benzyl bromide (0.48 mL, 4.0 mmol, 1.0 equiv) at room temperature. After the reaction mixture was stirred at 60 °C for 3h, the aqueous mixture was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 25 g Ultra-sil, 5–40% EtOAc in hexanes) to afford **1q** (680 mg, 3.84 mmol, 96% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.30 (m, 4H), 7.29–7.25 (m, 1H), 3.72 (t, J = 4.6 Hz, 4H), 3.51 (s, 2H), 2.51–2.40 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 128.9, 128.0, 126.9, 66.7, 63.2, 53.4.

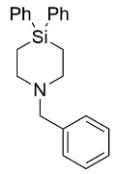
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[12].



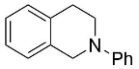
4-benzylthiomorpholine (**1r**)

To a solution of thiomorpholine (0.48 mL, 4.8 mmol, 1.2 equiv) and potassium carbonate (663 mg, 4.8 mmol, 1.2 equiv) in dimethylformamide (6 mL) was added benzyl bromide (0.48 mL, 4.0 mmol, 1.0 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and was allowed to stir overnight. The reaction mixture was quenched by water, and the aqueous portion was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 25 g KP-sil, 20–50% EtOAc in hexanes) to afford **1r** (772 mg, 4.00 mmol, 100% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.31 (m, 4H), 7.27 (m, 1H), 3.54 (s, 2H), 2.74–2.68 (m, 8H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 128.9, 128.2, 127.0, 63.6, 54.8, 28.0.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[13].

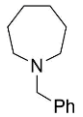


1-benzyl-4,4-diphenyl-1,4-azasilinane (**1s**)[14]
To a solution of 2,2'-(diphenylsilanediyl)bis(ethan-1-ol) (1.22 g, 4.48 mmol, 1.0 equiv) in dichloromethane (20 mL) was added triethylamine (2.5 mL, 18 mmol, 4.0 equiv) and methanesulfonyl chloride (1.0 mL, 13 mmol, 3.0 equiv) dropwise at 0 °C. After stirring for 20 min at 0 °C, the reaction mixture was quenched with water, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure.
To this crude residue in dimethylformamide (3 mL) was added triethylamine (2.5 mL, 18 mmol, 4.0 equiv) and benzylamine (0.98 mL, 9.0 mmol, 2.0 equiv) at room temperature. After stirring for 4h at room temperature, the mixture was quenched with water, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by colomn chromatography (Biotage 25 g Ultra-sil, 20–50% EtOAc in hexanes) to afford **1s** (826 mg, 2.41 mmol, 54% yield) as a colorless oil.
IR (neat, cm^{-1}) 3067 (w), 3044 (w), 2923 (w), 2899 (w), 2797 (w), 2760 (w), 1879 (w), 1813 (w), 1735 (w), 1590 (w), 1493 (w), 1452 (w), 1427 (m), 1389 (w), 1364 (w), 1343 (w), 1318 (w), 1249 (w), 1227 (w), 1186 (w), 1166 (w), 1111 (m), 1067 (w), 1028 (w), 997 (w), 970 (w), 926 (w), 904 (w), 866 (m), 754 (m), 725 (s), 695 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.61 (m, 4H), 7.53–7.38 (m, 10H), 7.34 (m, 1H), 3.69 (s, 2H), 2.97–2.83 (m, 4H), 1.53–1.40 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 135.8, 134.6, 129.3, 128.7, 128.1, 127.9, 126.7, 62.7, 52.2, 11.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{23}H_{26}NSi$, 344.1829; found, 344.1822.



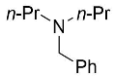
2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1t**)[15]
To a solution of 1,2,3,4-tetrahydroisoquinoline (3.8 mL, 30 mmol, 1.5 equiv), iodobenzene (2.2 mL, 20 mmol, 1.0 equiv), potassium phosphate (8.5 g, 40 mmol, 2.0 equiv), and ethylene glycol (2.2 mL, 40 mmol, 2.0 equiv) in isopropyl alcohol (30 mL) was added copper(I) iodide (381 mg, 2.0 mmol, 0.1 equiv) at room temperature. The reaction mixture was heated to 85 °C and was allowed to stir for 2 d. After cooling to room temperature, the reaction mixture was quenched with water, and the aqueous portion was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g KP-sil, 5–20% EtOAc in hexanes) to afford **1t** (3.58 g, 17.1 mmol, 86% yield) as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 2H), 7.25–7.15 (m, 4H), 7.02 (dt, *J* = 7.8, 1.1 Hz, 2H), 6.87 (tt, *J* = 7.3, 1.1 Hz, 1H), 4.45 (s, 2H), 3.60 (t, *J* = 5.9 Hz, 2H), 3.02 (t, *J* = 5.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 134.8, 134.4, 129.2, 128.5, 126.5, 126.3, 126.0, 118.6, 115.1, 50.7, 46.5, 29.1.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[15].



1-benzylazepane (**1u**)
To a solution of benzyl bromide (2.4 mL, 20 mmol, 1.0 equiv) in dichloromethane (3 mL) was added azepane (5.5 mL, 50 mmol, 2.5 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and was allowed to stir overnight. The reaction mixture was quenched by saturated aqueous sodium bicarbonate, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g Ultra-sil, 5–40% EtOAc in hexanes) to afford **1u** (3.15 g, 16.7 mmol, 83% yield) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 2H), 2.70 (s, 4H), 1.71 (s, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 128.6, 128.0, 126.6, 62.7, 55.5, 28.2, 27.0.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[16].

***N*-benzyl-*N*-ethylethanamine** (**1v**)
To a solution of benzyl bromide (0.48 mL, 4.0 mmol, 1.0 equiv) in dichloromethane (3 mL) was added diethylamine (1.0 mL, 10 mmol, 2.5 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and was allowed to stir overnight. The reaction mixture was quenched by saturated aqueous sodium bicarbonate, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 25 g KP-sil, 5–40% EtOAc in hexanes) to afford **1v** (497 mg, 3.05 mmol, 76% yield) as a colorless oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.32 (m, 4H), 7.30–7.26 (m, 1H), 3.63 (s, 2H), 2.62–2.56 (m, 4H), 1.13–1.09 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 128.8, 128.0, 126.5, 57.5, 46.6, 11.7.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[17].



***N*-benzyl-*N*-propylpropan-1-amine** (**1w**)
To a solution of benzyl bromide (2.4 mL, 20 mmol, 1.0 equiv) in dichloromethane (12 mL) was added dipropylamine (6.9 mL, 50 mmol, 2.5 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature and was allowed to stir overnight. The reaction mixture was quenched by saturated aqueous sodium bicarbonate, and the aqueous portion was extracted with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate,

filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage 50 g KP-sil, 5–30% EtOAc in hexanes) to afford **1w** (3.00 g, 15.7 mmol, 78% yield) as a colorless oil.

IR (neat, cm^{-1}) 3028 (w), 2959 (m), 2934 (w), 2873 (w), 2796 (w), 1494 (w), 1453 (m), 1367 (w), 1188 (w), 1162 (w), 1067 (m), 1027 (m), 969 (w), 844 (w), 731 (s), 696 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.34 (m, 4H), 7.34–7.28 (m, 1H), 3.64 (s, 2H), 2.48 (t, J = 7.4 Hz, 4H), 1.58 (m, 4H), 0.97 (t, J = 7.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 128.7, 128.0, 126.5, 58.7, 55.9, 20.2, 11.9. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{22}N$, 192.1747; found, 192.1744.

8. α-Carboxylation of Amines in Continuous Flow

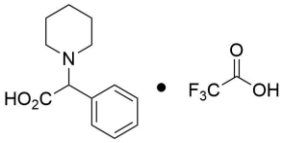
General Procedure C for α-carboxylation of amines with CO_2

An oven-dried 50 mL Schlenk flask was charged with the appropriate tertiary amine (1.5 mmol, 1.0 equiv), *p*-terphenyl (69 mg, 0.3 mmol, 20 mol%), potassium trifluoroacetate (684 mg, 4.5 mmol, 3.0 equiv), and dimethylformamide (10 mL). The resulting homogeneous solution was degassed via three freeze-pump-thaw cycles. After the mixture was thoroughly degassed, the solution was taken up in a SGE gas-tight syringe and connected to Beeler's photochemistry system (as described in Supplementary Figure 2). After the flow system is pressurized by CO_2 (1.86 sccm) and all the air expelled prior to the start of the reaction, a Harvard Apparatus PHD2000 syringe pump was used to pump the reaction mixture into the system. Once a steady 1:1 segmented flow of solution and CO_2 was observed, the system was equilibrated for 20 minutes. The product solution was then collected for 63 min (for the consumption of 0.7 mmol amine reactant). The collected reaction mixture was concentrated under reduced pressure. The crude mixture was purified by column chromatography (Biotage KP-sil) to afford the desired product. The collected residue was then diluted with ethyl acetate and filtered through a syringe filter (13 mm syringe filter w/ 0.45 μm PTFE membrane).

General Procedure for Optimization Reactions

For reaction optimization and mechanistic studies (Supplementary Tables 1–5), the above procedure was followed and the product solution was collected for 10 min. After transferring 0.2 mL of the collected mixture to a 10 mL vial, methanol (0.2 mL) and (trimethylsilyl)diazomethane (2M in diethyl ether, 0.1 mL, 0.2 mmol, 6.7 equiv) were added at 0 °C. The reaction mixture was allowed to warm to room temperature. After stirring for 30 min at room temperature, the reaction mixture was quenched with acetic acid solution in water (v/v 1:1), and methyl benzoate was added as an internal standard. Conversion, yield, and regioselectivity were determined by GC using a HP-5 column (a response factor was calculated using ^{1}H NMR).

Characterization of Products

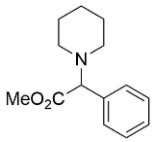


2-phenyl-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2a**)

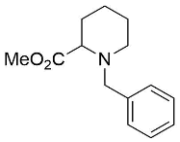
The general procedure C was followed using *N*-benzylpiperidine (263 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2a** (217 mg, 0.653 mmol, 92% yield) as a white solid. The regioselectivity was determined to be 52:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3387 (br), 2958 (w), 1674 (s), 1636 (s), 1433 (m), 1379 (m), 1182 (s), 1130 (s), 1025 (m), 941 (w), 839 (w), 801 (m), 725 (m), 701 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.50 (dd, *J* = 7.4, 2.3 Hz, 2H), 7.36 (dd, *J* = 5.0, 2.2 Hz, 3H), 4.36 (s, 1H), 3.10–2.91 (m, 2H), 2.77–2.72 (m, 2H), 1.82–1.56 (m, 4H), 1.55–1.41 (m, 2H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 168.8, 158.4 (q, *J* = 31.3 Hz), 134.1, 129.3, 128.7, 128.6, 117.3 (q, *J* = 299.4 Hz), 74.2, 51.5, 43.6, 22.7,

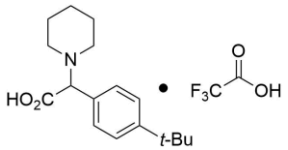
22.2, 22.1, 21.8. ^{19}F NMR (376 MHz, CD_3OD) δ –76.93. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$, 220.1332; found, 220.1323.
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-phenyl-2-(piperidin-1-yl)acetate (**S1**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.39 (m, 2H), 7.36–7.27 (m, 3H), 3.97 (s, 1H), 3.66 (s, 3H), 2.41–2.35 (m, 4H), 1.61–1.55 (m, 4H), 1.48–1.35 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 136.1, 128.7, 128.4, 128.1, 74.9, 52.3, 51.8, 25.7, 24.3.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[18].

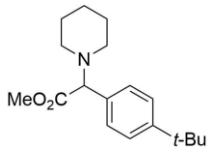


methyl 1-benzylpiperidine-2-carboxylate (**S2**)
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.18 (m, 5H), 3.78 (d, *J* = 13.3 Hz, 1H), 3.72 (s, 3H), 3.41 (d, *J* = 13.3 Hz, 1H), 3.17 (dd, *J* = 7.6, 4.6 Hz, 1H), 2.94 (dt, *J* = 10.4, 4.7 Hz, 1H), 2.15 (ddd, *J* = 11.6, 7.2, 4.9 Hz, 1H), 1.86–1.76 (m, 2H), 1.66–1.47 (m, 3H), 1.40–1.32 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 138.0, 129.0, 128.0, 126.9, 64.2, 60.5, 51.3, 50.0, 29.4, 25.1, 22.4.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[19].



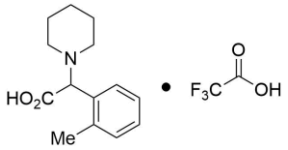
2-(4-(*tert*-butyl)phenyl)-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2b**)
The general procedure C was followed using **1b** (347 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–15% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2b** (237 mg, 0.609 mmol, 87% yield) as a white solid. The regioselectivity was determined to be 28:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.
IR (neat, cm^{-1}) 2968 (m), 2869 (w), 1684 (s), 1643 (s), 1418 (m), 1364 (m), 1205 (s), 1180 (m), 11334 (m), 1028 (w), 939 (w), 837 (w), 801 (w), 721 (w). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.40–7.36 (m, 4H), 4.17 (s, 1H), 3.04–2.79 (m, 2H), 2.70–2.64 (m, 2H), 1.76–1.55 (m, 4H), 1.53–1.36 (m, 2H), 1.27 (s, 9H).^{13}C NMR (101 MHz, CD_3OD) δ 171.9, 163.1 (q, *J* = 34.4 Hz), 154.1, 130.6, 130.0, 127.0, 118.2 (q, *J* = 292.8 Hz), 75.5, 49.9, 45.5, 35.5, 31.6, 23.7, 23.6, 23.0, 22.8. ^{19}F NMR (376 MHz, DMSO-*d*6) δ –73.53. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{26}NO_2$, 276.1958; found, 276.1961.

Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(4-(tert-butyl)phenyl)-2-(piperidin-1-yl)acetate (**S3**)

IR (neat, cm^{-1}) 2936 (m), 2861 (w), 2805 (w), 2758 (w), 1746 (s), 16685 (w), 1604 (w), 1506 (w), 1434 (m), 1393 (w), 1363 (w), 1335 (w), 1302 (w), 1267 (m), 1224 (m), 1191 (m), 1152 (s), 1109 (s), 1067 (w), 1017 (m), 925 (w), 878 (w), 841 (w), 810 (w), 754 (m), 720 (w), 667 (w). ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 4H), 3.94 (s, 1H), 3.67 (s, 3H), 2.41–2.34 (m, 4H), 1.61–1.56 (m, 4H), 1.48–1.36 (m, 2H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 151.0, 133.0, 128.3, 125.3, 74.7, 52.4, 51.8, 34.5, 31.3, 25.7, 24.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{28}NO_2$, 290.2115; found, 290.2097.

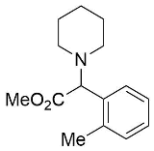


2-(piperidin-1-yl)-2-(*o*-tolyl)acetic acid, trifluoroacetate salt (**2c**)

The general procedure C was followed using **1c** (284 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2c** (243 mg, 0.700 mmol, 99% yield) as a white solid. The regioselectivity was determined to be 52:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

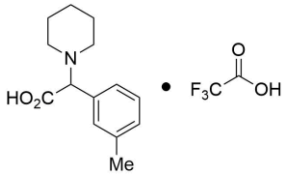
IR (neat, cm^{-1}) 3412 (br), 2956 (w), 2845 (w), 1674 (s), 1636 (s), 1432 (s), 1370 (s), 1202 (s), 1178 (s), 1127 (s), 1025 (m), 940 (w), 838 (w), 801 (m), 744 (w), 722 (m). ^1H NMR (400 MHz, DMSO-*d*6) δ 7.63 (d, *J* = 6.8 Hz, 1H), 7.25–7.12 (m, 3H), 4.57 (s, 1H), 3.16 (br s, 2H), 2.86–2.81 (m, 2H), 2.43 (s, 3H), 1.79–1.56 (m, 4H), 1.50–1.38 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.9, 163.0 (q, *J* = 34.3 Hz), 139.5, 132.2, 132.0, 130.5, 128.5, 127.9, 118.2 (q, *J* = 292.9 Hz), 71.8, 49.9, 45.5, 23.8, 23.6, 23.0, 22.8, 20.1. ^{19}F NMR (376 MHz, CD_3OD) δ –76.83. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1486.

Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(piperidin-1-yl)-2-(*o*-tolyl)acetate (**S4**)

IR (neat, cm^{-1}) 2933 (m), 2853 (w), 2802 (w), 2758 (w), 1735 (w), 1434 (m), 1393 (w), 1337 (w), 1259 (w), 1281 (w), 1192 (m), 1151 (w), 1122 (m), 1068 (w), 1036 (w), 1014 (m), 880 (w), 877 (w), 814 (w), 740 (s), 667 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.50 (m, 1H), 7.22–7.11 (m, 3H), 4.26 (s, 1H), 3.65 (s, 3H), 2.45–2.41 (m, 7H), 1.59–1.54 (m, 4H), 1.50–1.37 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 137.3, 134.7, 130.4, 128.3, 127.6, 126.0, 70.4, 52.0, 51.6, 25.9, 24.4, 19.6. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$, 248.1645; found, 248.1637.

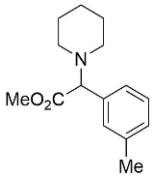


2-(piperidin-1-yl)-2-(*m*-tolyl)acetic acid, trifluoroacetate salt (**2d**)

The general procedure C was followed using **1d** (284 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2d** (225 mg, 0.648 mmol, 93% yield) as a white solid. The regioselectivity was determined to be 45:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3440 (br), 2960 (w), 2870 (w), 1673 (s), 1636 (s), 1433 (m), 1370 (m), 1202 (s), 1176 (s), 1124 (s), 1030 (w), 945 (w), 882 (w), 837 (m), 800 (m), 741 (w), 722 (s). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.32 (s, 1H), 7.31–7.21 (m, 2H), 7.16 (m, 1H), 4.32 (s, 1H), 3.11–2.93 (m, 2H), 2.79–2.72 (m, 2H), 2.28 (s, 3H), 1.77–1.57 (m, 4H), 1.56–1.37 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.8, 163.1 (q, J = 34.4 Hz), 140.3, 133.0, 131.5, 131.2, 130.1, 127.8, 118.2 (q, J = 293.0 Hz), 75.9, 49.9, 45.5, 23.7, 23.6, 23.1, 22.8, 21.3. ^{19}F NMR (376 MHz, CD_3OD) δ –76.88. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1487.

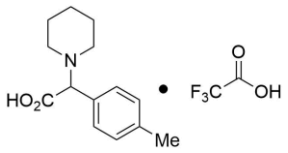
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(piperidin-1-yl)-2-(*m*-tolyl)acetate (**S5**)

IR (neat, cm^{-1}) 2933 (m), 2851 (w), 2801 (w), 2758 (w), 1736 (w), 1607 (w), 1487 (w), 1434 (m), 1392 (w), 1335 (w), 1306 (w), 1286 (w), 1224 (m), 1190 (m), 1152 (w), 1117 (m), 1067 (w), 1016 (m), 943 (w), 913 (w), 871 (w), 782 (w), 741 (m), 696 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.23–7.20 (m, 2H), 7.12 (m, 1H), 3.92 (s, 1H), 3.68 (s, 3H), 2.43–2.27 (m, 7H), 1.62–1.57 (m, 4H), 1.46–1.40 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 138.2, 136.0, 129.3, 129.0,

128.3, 126.0, 75.1, 52.5, 51.9, 25.7, 24.3, 21.4. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{22}NO_2$, 248.1645; found, 248.1630.

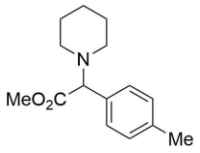


2-(piperidin-1-yl)-2-(*p*-tolyl)acetic acid, trifluoroacetate salt (**2e**)

The general procedure C was followed using **1e** (284 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2e** (237 mg, 0.683 mmol, 98% yield) as a white solid. The regioselectivity was determined to be 60:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3396 (br), 2956 (w), 2868 (w), 1673 (s), 1634 (s), 1517 (w), 1433 (m), 1203 (s), 1176 (s), 1123 (s), 1033 (w), 940 (w), 871 (w), 837 (m), 801 (m), 750 (w), 722 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.39 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.40 (s, 1H), 3.09–2.95 (m, 2H), 2.81–2.76 (m, 2H), 2.28 (s, 3H), 1.77–1.59 (m, 4H), 1.48–1.34 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.9, 163.1 (q, *J* = 34.4 Hz), 141.1, 130.7, 130.0, 118.2 (q, *J* = 292.9 Hz), 75.6, 49.9, 45.5, 23.7, 23.6, 23.0, 22.8, 21.2. ^{19}F NMR (376 MHz, CD_3OD) δ –76.83. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1487.

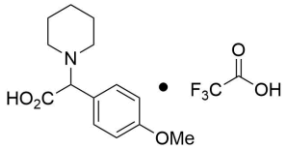
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(piperidin-1-yl)-2-(*p*-tolyl)acetate (**S6**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 3.93 (s, 1H), 3.67 (s, 3H), 2.44–2.33 (m, 7H) 1.63–1.52 (m, 4H), 1.47–1.38 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 137.9, 133.1, 129.1, 128.7, 74.7, 52.4, 51.9, 25.7, 24.3, 21.1.

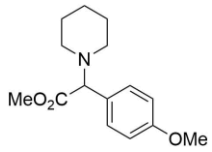
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[20].



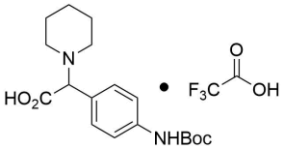
2-(4-methoxyphenyl)-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2f**)

The general procedure C was followed using **1f** (308 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2f** (228 mg, 0.628 mmol, 90% yield) as a white solid. The regioselectivity was determined to be 35:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3364 (br), 2947 (w), 2836 (w), 2521 (br), 1676 (s), 1637 (m), 1516 (m), 1407 (m), 1308 (w), 1258 (w), 1204 (s), 1180 (s), 1134 (s), 1025 (s), 980 (w), 941 (w), 837 (m), 800 (m), 754 (w), 722 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.44 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 1H), 3.74 (s, 3H), 3.15–2.94 (m, 2H), 2.86–2.73 (m, 2H), 1.76–1.56 (m, 4H), 1.45–1.41 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 172.1, 163.0 (q, *J* = 34.6 Hz), 162.2, 132.3, 124.6, 118.1 (q, *J* = 292.7 Hz), 115.4, 75.3, 55.8, 49.9, 45.5, 23.7, 23.6, 23.0, 22.8. ^{19}F NMR (376 MHz, CD_3OD) δ –76.80. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_3$, 250.1438; found, 250.1439.
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:

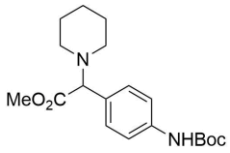


methyl 2-(4-methoxyphenyl)-2-(piperidin-1-yl)acetate (**S7**)
IR (neat, cm^{-1}) 2935 (m), 2837 (w), 2804 (w), 2759 (w), 1745 (w), 1675 (w), 1610 (m), 1510 (s), 1440 (m), 1392 (w), 1333 (w), 1303 (w), 1244 (s), 1223 (w), 1160 (s), 1116 (m), 1607 (w), 1032 (m), 941 (w), 876 (w), 834 (m), 793 (m), 754 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.89 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H), 2.43–2.27 (m, 4H), 1.63–1.49 (m, 4H), 1.46–1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 159.4, 129.9, 128.2, 113.8, 74.3, 55.1, 52.3, 51.8, 25.7, 24.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{22}NO_3$, 264.1594; found, 264.1595
Spectral data were not in agreement with literature values (one peak in the ^{13}C NMR spectrum appears to have been misassigned)[20], but the identity of the compound was confirmed through the above characterization.

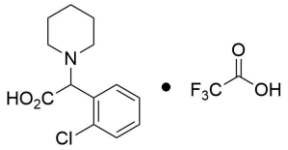


2-(4-((*tert*-butoxycarbonyl)amino)phenyl)-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2g**)
The general procedure C was followed using **1g** (435 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2g** (308 mg, 0.687 mmol, 98% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions. IR (neat, cm^{-1}) 3358 (br), 2980 (w), 2874 (w), 1671 (s), 1637 (s), 1524 (w), 1434 (m), 1370 (m), 1321 (w), 1174 (s), 1120 (s), 1056 (w), 1030 (w), 939 (w), 838 (m), 801 (m), 774 (w), 722 (s). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.48 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.35 (s, 1H), 3.13–2.94 (m, 2H), 2.83–2.75 (m, 2H), 1.77–1.57 (m, 4H), 1.46–1.40 (m, 11H). ^{13}C NMR (101 MHz, CD_3OD) δ 172.0, 163.1 (q, *J* = 34.3 Hz), 155.0, 142.2, 131.4, 126.5, 119.9, 118.2

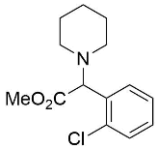
(q, J = 292.7 Hz), 81.2, 75.3, 49.8, 45.5, 28.6, 23.7, 23.6, 23.0, 22.8. ^{19}F NMR (376 MHz, CD_3OD) δ –76.87. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{18}H_{27}N_2O_4$, 335.1965; found, 334.1975.
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(4-((tert-butoxycarbonyl)amino)phenyl)-2-(piperidin-1-yl)acetate (**S8**)
IR (neat, cm^{-1}) 2959 (w), 1730 (s), 1596 (m), 1527 (s), 1457 (w), 1415 (w), 1367 (w), 1318 (w), 1234 (m), 1153 (s), 1054 (w), 1026 (w), 772 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (s, 4H), 6.71 (s, 1H), 3.88 (s, 1H), 3.63 (s, 3H), 2.43–2.24 (m, 4H), 1.56–1.53 (m, 4H), 1.47 (s, 9H), 1.43–1.33 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 152.7, 138.3, 130.4, 129.4, 118.4, 80.4, 74.3, 52.3, 51.8, 28.2, 25.6, 24.2. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{19}H_{29}N_2O_4$, 349.2122; found, 349.2105.

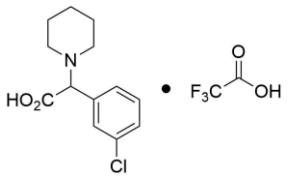


2-(2-chlorophenyl)-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2h**)
The general procedure C was followed using **1h** (314 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2h** (150 mg, 0.409 mmol, 58% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions. IR (neat, cm^{-1}) 3363 (br), 2959 (w), 2866 (w), 1674 (s), 1637 (s), 1437 (m), 1179 (s), 1126 (s), 1033 (w), 942 (w), 839 (w), 800 (m), 758 (w), 722 (m). ^{1}H NMR (400 MHz, CD_3OD) δ 7.76 (dd, J = 7.5, 2.0 Hz, 1H), 7.50 (dd, J = 7.9, 1.6 Hz, 1H), 7.38 (dtd, J = 17.5, 7.3, 1.6 Hz, 2H), 5.05 (s, 1H), 3.08 (t, J = 5.7 Hz, 2H), 3.04–2.93 (m, 2H), 1.84–1.70 (m, 4H), 1.68–1.54 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.8, 163.0 (q, J = 34.5 Hz), 136.9, 132.4, 131.3, 131.3, 131.2, 129.1, 118.2 (q, J = 292.8 Hz), 71.3, 49.9, 45.6, 23.9, 23.6, 23.1, 22.7. ^{19}F NMR (376 MHz, CD_3OD) δ –76.89. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{17}ClNO_2$, 254.0942; found, 254.0952.
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(2-chlorophenyl)-2-(piperidin-1-yl)acetate (**S9**)

IR (neat, cm^{-1}) 2935 (m), 2853 (w), 2805 (w), 2759 (w), 1739 (s), 1593 (w), 1468 (m), 1441 (m), 1393 (w), 1335 (w), 1263 (w), 1221 (m), 1194 (m), 1161 (s), 1114 (m), 1036 (m), 1014 (m), 864 (w), 814 (w), 749 (s), 692 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.32–7.17 (m, 2H), 4.61 (s, 1H), 3.68 (s, 3H), 2.51 (dt, *J* = 11.0, 5.4 Hz, 2H), 2.41 (dt, *J* = 11.0, 5.4 Hz, 2H), 1.62–1.58 (m, 4H), 1.47–1.43 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 134.6, 134.2, 130.0, 129.5, 129.0, 126.9, 69.6, 52.2, 51.9, 25.9, 24.3. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{19}ClNO_2$, 268.1099; found, 268.1081.

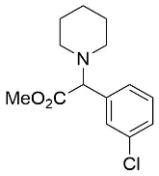


2-(3-chlorophenyl)-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2i**)

The general procedure C was followed using **1i** (314 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2i** (218 mg, 0.594 mmol, 85% yield) as a white solid. The regioselectivity was determined to be 76:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

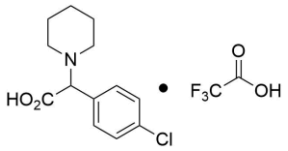
IR (neat, cm^{-1}) 3355 (br), 2943 (w), 2832 (w), 1679 (m), 1424 (br), 1204 (w), 1186 (w), 1140 (w), 1021 (s), 839 (w), 801 (w), 722 (w). ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (m, 1H), 7.48 (dt, *J* = 6.8, 1.8 Hz, 1H), 7.43–7.35 (m, 2H), 4.50 (s, 1H), 3.07 (t, *J* = 5.6 Hz, 2H), 3.01–2.89 (m, 2H), 1.87–1.69 (m, 4H), 1.66–1.60 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.0, 163.1 (q, *J* = 34.2 Hz), 136.0, 135.5, 131.7, 130.9, 130.5, 129.3, 118.2 (q, *J* = 293.0 Hz), 75.2, 66.8, 49.9, 45.5, 23.7, 23.6, 23.1, 22.8. ^{19}F NMR (376 MHz, CD_3OD) δ –76.91. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{17}ClNO_2$, 254.0942; found, 254.0946.

Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(3-chlorophenyl)-2-(piperidin-1-yl)acetate (**S10**)

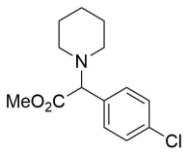
IR (neat, cm^{-1}) 2947 (m), 2851 (w), 2804 (w), 2761 (w), 1736 (s), 1669 (w), 1594 (m), 1574 (m), 1474 (m), 1432 (m), 1392 (w), 1335 (w), 1259 (w), 1223 (m), 1193 (m), 1153 (s), 1115 (m), 1078 (w), 1039 (w), 1015 (m), 941 (w), 887 (m), 871 (m), 814 (w), 753 (s), 725 (w), 693 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 2.1 Hz, 1H), 7.35–7.24 (m, 3H), 3.96 (s, 1H), 3.69 (s, 3H), 2.47–2.30 (m, 4H), 1.62–1.57 (m, 4H), 1.47–1.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 138.4, 134.4, 129.7, 128.8, 128.4, 126.9, 74.4, 52.3, 52.1, 25.8, 24.2. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{19}ClNO_2$, 268.1099; found, 268.1094.



2-(4-chlorophenyl)-2-(piperidin-1-yl)acetic acid, trifluoroacetate salt (**2j**)

The general procedure C was followed using **1j** (314 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2j** (244 mg, 0.655 mmol, 95% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions. IR (neat, cm^{-1}) 3011 (w), 2957 (w), 2757 (w), 1677 (s), 1494 (m), 1438 (m), 1385 (m), 1205 (s), 1182 (s), 1134 (s), 947 (w), 839 (m), 801 (m), 759 (m). ^{1}H NMR (400 MHz, CD_3OD) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 4.50 (s, 1H), 3.08 (t, *J* = 5.6 Hz, 2H), 2.97–2.86 (m, 2H), 1.84–1.68 (m, 4H), 1.68–1.47 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.5, 163.1 (q, *J* = 34.6 Hz), 136.8, 132.4, 132.0, 130.2, 118.2 (q, *J* = 292.8 Hz), 75.1, 49.9, 45.5, 23.8, 23.6, 23.0, 22.8. ^{19}F NMR (376 MHz, CD_3OD) δ –76.90. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{17}ClNO_2$, 254.0942; found, 254.0936.

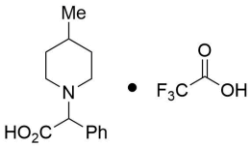
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 2-(4-chlorophenyl)-2-(piperidin-1-yl)acetate (**S11**)

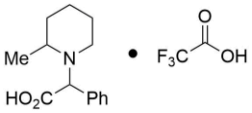
IR (neat, cm^{-1}) 2936 (m), 2851 (w), 2809 (w), 2760 (w), 1736 (s), 1595 (w), 1489 (m), 1435(m), 1409 (w), 1336 (w), 1255 (w), 1224 (w), 1197 (m), 1152 (s), 1115 (m), 1088 (s), 1038 (w), 1015 (s), 877 (w), 833 (m), 808 (w), 765 (m), 730 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 3.95 (s, 1H), 3.68 (s, 3H), 2.38–2.35 (m, 4H), 1.63–1.54 (m,

4H), 1.46–1.41 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 134.8, 134.0, 130.1, 128.6, 74.2, 52.3, 52.0, 25.8, 24.2. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{19}ClNO_2$, 268.1099; found, 268.1091.



2-(4-methylpiperidin-1-yl)-2-phenylacetic acid, trifluoroacetate salt (**2k**)

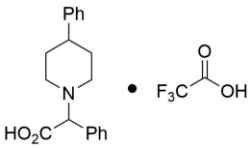
The general procedure C was followed using **1k** (284 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2k** (166 mg, 0.478 mmol, 68% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions. IR (neat, cm^{-1}) 3355 (br), 2943 (w), 2832 (w), 1677 (s), 1636 (s), 1457 (m), 1405 (m), 1376 (m), 1202 (s), 1180 (s), 1134 (s), 1024 (s), 953 (w), 933 (w), 835 (w), 800 (w), 740 (m), 721 (m), 701 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.54–7.47 (m, 2H), 7.40–7.32 (m, 3H), 4.32 (s, 1H), 3.42 (br s, 1H), 2.88–2.64 (m, 2H), 2.55 (m, 1H), 1.71–1.53 (m, 2H), 1.52–1.14 (m, 3H), 0.89–0.81 (m, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.8, 163.0 (q, *J* = 34.6 Hz), 133.4, 130.8, 130.7, 130.2, 118.2 (q, *J* = 292.9 Hz), 76.4, 51.7, 45.1, 31.8, 29.9, 21.7, 21.2. ^{19}F NMR (376 MHz, CD_3OD) δ –76.86. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1484.



2-(2-methylpiperidin-1-yl)-2-phenylacetic acid, trifluoroacetate salt (**2l**)

The general procedure C was followed using **1l** (284 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2l** (133 mg, 0.383 mmol, 55% yield) as a white solid. The diastereomeric ratio was determined to be 1.3:1 and the regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

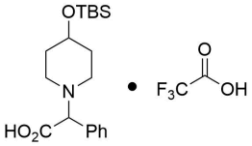
IR (neat, cm^{-1}) 3385 (br), 2952 (w), 2870 (w), 1676 (s), 1627 (s), 1381 (s), 1201 (s), 1174 (s), 1126 (s), 1031 (m), 978 (w), 936 (w), 832 (m), 800 (m), 738 (m), 720 (m), 701 (m). ^{1}H NMR (400 MHz, DMSO-*d*6, minor diastereomer indicated by *) δ 7.60–7.53 (m, 2H), 7.53–7.49 (m, 2H*), 7.41–7.29 (m, 3H, 3H*), 4.61 (s, 1H), 4.54 (s, 1H*), 3.47 (s, 1H), 3.14–2.93 (m, 2H), 2.93–2.79 (m, 1H*), 2.75–2.65 (m, 2H*), 2.03 (m, 1H), 1.80 (m, 1H*), 1.87–1.29 (m, 5H, 5H*), 1.26 (d, *J* = 6.7 Hz, 3H), 1.19 (d, *J* = 6.7 Hz, 3H*). ^{13}C NMR (101 MHz, CD_3OD, minor diastereomer indicated by *) δ 171.7*, 171.4, 162.9 (q, *J* = 34.4 Hz), 162.9* (q, *J* = 34.4 Hz), 133.4, 132.9*, 131.0, 131.0*, 130.8, 130.7*, 130.2, 130.2*, 118.2 (q, *J* = 293.1 Hz), 118.2* (q, *J* = 293.1 Hz), 71.9, 71.9*, 57.9*, 53.9, 46.8*, 45.5, 31.6*, 30.1, 29.1, 29.1*, 23.2*, 23.1, 23.1*, 19.5. ^{19}F NMR (376 MHz, CD_3OD) δ –76.74. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1482.



2-phenyl-2-(4-phenylpiperidin-1-yl)acetic acid, trifluoroacetate salt (**2m**)

The general procedure C was followed using **1m** (377 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2m** (209 mg, 0.511 mmol, 73% yield) as a white solid. The regioselectivity was determined to be 66:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

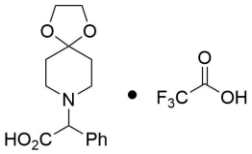
IR (neat, cm^{-1}) 3010 (w), 2865 (w), 1654 (s), 1495 (w), 1407 (m), 1202 (s), 1179 (s), 1132 (s), 1071 (w), 958 (w), 945 (w), 897 (w), 832 (w), 800 (w), 748 (s). ^{1}H NMR (400 MHz, CD_3OD) δ 7.60–7.57 (m, 2H), 7.40–7.30 (m, 3H), 7.28–7.19 (m, 2H), 7.18–7.09 (m, 3H), 4.48 (s, 1H), 3.85 (br s, 1H), 3.10–2.85 (m, 2H), 2.84–2.60 (m, 2H), 2.07–1.88 (m, 2H), 1.87–1.69 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 172.5, 162.9 (q, J = 34.5 Hz), 145.4, 145.3, 133.8, 130.7, 130.2, 129.7, 129.6, 127.8, 127.8, 127.7, 127.6, 118.2 (q, J = 292.9 Hz), 76.4, 52.0, 45.4, 41.1, 31.0. ^{19}F NMR (376 MHz, CD_3OD) δ –76.36. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{19}H_{22}NO_2$, 296.1645; found, 296.1642.



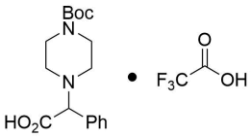
2-(4-((*tert*-butyldimethylsilyl)oxy)piperidin-1-yl)-2-phenylacetic acid, trifluoroacetate salt (**2n**)

The general procedure C was followed using **1n** (458 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 1–10% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2n** (234 mg, 0.505 mmol, 72% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

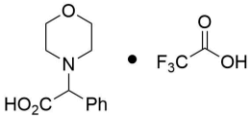
IR (neat, cm^{-1}) 3387 (br), 2954 (m), 2931 (m), 2889 (w), 2858 (m), 1678 (s), 1637 (s), 1385 (m), 1255 (m), 1201 (s), 1179 (m), 1129 (s), 1053 (m), 1024 (m), 980 (w), 945 (w), 881 (m), 834 (s), 800 (w), 776 (m), 741 (w), 703 (m), 678 (w). ^{1}H NMR (400 MHz, CD_3OD) δ 7.74–7.55 (m, 2H), 7.42 (d, J = 6.7 Hz, 3H), 4.61 (s, 1H), 4.97 (s, 1H), 3.24–3.06 (m, 2H), 3.06–2.88 (m, 2H), 2.09–1.87 (m, 2H), 1.83–1.59 (m, 2H), 0.88 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.9, 162.9 (q, J = 34.7 Hz), 133.1, 130.9, 130.8, 130.1, 118.1 (q, J = 293.0 Hz), 75.5, 64.9, 41.4, 32.0, 31.8, 26.2, 18.8, –4.8. ^{19}F NMR (376 MHz, CD_3OD) δ –76.60. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{19}H_{32}NO_3Si$, 350.2146; found, 350.2152.



2-phenyl-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)acetic acid, trifluoroacetate salt (**2o**)
The general procedure C was followed using **1o** (350 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–15% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2o** (240 mg, 0.614 mmol, 88% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.
IR (neat, cm^{-1}) 2889 (w), 1681 (s), 1418 (m), 1381 (m), 1206 (s), 1135 (s), 1051 (w), 976 (w), 941 (w), 838 (w), 801 (w), 754 (w). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.43 (d, *J* = 6.8 Hz, 2H), 7.31 (dt, *J* = 11.1, 6.9 Hz, 3H), 4.01 (s, 1H), 3.84 (s, 4H), 2.65 (s, 2H), 2.50 (s, 2H), 1.65 (s, 4H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.3, 163.2 (q, *J* = 34.6 Hz), 134.4, 130.8, 130.3, 130.3, 118.3 (q, *J* = 292.6 Hz), 105.8, 105.5, 76.0, 65.9, 65.8, 51.5, 43.9, 33.5, 33.2. ^{19}F NMR (376 MHz, DMSO-*d*6) δ –73.57. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{20}NO_4$, 278.1376; found, 278.1376.

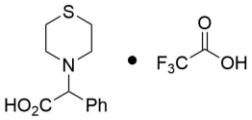


2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)-2-phenylacetic acid, trifluoroacetate salt (**2p**)
The general procedure C was followed using **1p** (414 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 1–10% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2p** (174 mg, 0.401 mmol, 57% yield) as a white solid. The regioselectivity was determined to be 25:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.
IR (neat, cm^{-1}) 3417 (br), 2980 (w), 2937 (w), 1676 (s), 1577 (m), 1420 (s), 1368 (m), 1283 (w), 1249 (m), 1203 (m), 1174 (s), 1135 (s), 1042 (w), 1003 (w), 856 (w), 800 (w), 741 (w), 721 (w), 701 (w). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.46–7.41 (m, 2H), 7.30–7.17 (m, 3H), 3.69 (s, 1H), 3.37 (s, 2H), 3.26 (br s, 2H), 2.46–2.35 (m, 2H), 2.30–2.26 (m, 2H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 176.6, 157.8 (q, *J* = 30.8 Hz), 153.8, 139.3, 128.8, 127.7, 126.8, 117.30 (q, *J* = 300.4 Hz), 78.6, 76.5, 50.4, 48.6, 43.9, 43.0, 28.1. ^{19}F NMR (376 MHz, DMSO-*d*6) δ –73.54. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{25}N_2O_4$, 321.1809; found, 321.1814.



2-morpholino-2-phenylacetic acid, trifluoroacetate salt (**2q**)
The general procedure C was followed using **1q** (266 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2q** (227 mg, 0.677 mmol, 97% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

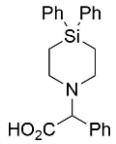
IR (neat, cm^{-1}) 3408 (br), 1673 (s), 1435 (m), 1389 (m), 1319 (w), 1179 (s), 1124 (s), 1021 (w), 952 (w), 911 (w), 886 (w), 838 (m), 801 (m), 743 (w). ^{1}H NMR (400 MHz, CD_3OD) δ 7.54–7.51 (m, 2H), 7.34–7.33 (m, 3H), 4.27 (s, 1H), 3.79–3.68 (m, 4H), 3.19–2.96 (m, 2H), 2.74–2.69 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 173.6, 163.1 (q, J = 34.4 Hz), 134.4, 130.6, 130.4, 130.0, 118.2 (q, J = 292.7 Hz), 77.3, 65.5, 64.8, 52.7, 44.4. ^{19}F NMR (376 MHz, CD_3OD) δ –76.88. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{16}NO_3$, 222.1125; found, 222.1123.



2-phenyl-2-thiomorpholinoacetic acid, trifluoroacetate salt (**2r**)

The general procedure C was followed using **1r** (290 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2r** (193 mg, 0.550 mmol, 79% yield) as a white solid. The regioselectivity was determined to be 20:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

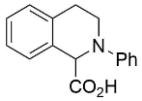
IR (neat, cm^{-1}) 3390 (br), 1681 (s), 1419 (br), 1207 (s), 1135 (s), 842 (w), 801 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.44–7.23 (m, 5H), 4.06 (s, 1H), 3.23 (m, 1H), 2.78 (m, 1H), 2.75–2.69 (m, 3H), 2.62–2.57 (m, 3H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 172.8, 158.7 (q, J = 31.1 Hz), 136.7, 129.3, 128.7, 128.3, 117.6 (q, J = 299.3 Hz), 74.1, 52.7, 45.1, 27.3, 24.1. ^{19}F NMR (376 MHz, CD_3OD) δ –76.95. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{16}NO_2S$, 238.0896; found, 238.0894.



2-(4,4-diphenyl-1,4-azasilinan-1-yl)-2-phenylacetic acid (**2s**)

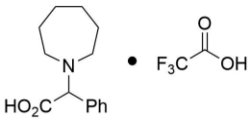
The general procedure C was followed using **1s** (515 mg, 1.50 mmol) under the atmospheric pressure of CO_2 with t_R = 5 min. The residue was purified by column chromatography (Biotage 25 g KP-sil, 1–10% methanol in dichloromethane) to afford an α-amino acid **2s** (157 mg, 0.406 mmol, 58% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3397 (br), 2942 (w), 2831 (w), 2355 (w), 1673 (s), 1637 (s), 1457 (w), 1428 (m), 1397 (m), 1202 (s), 1180 (s), 1117 (s), 1027 (m), 909 (w), 875 (w), 838 (m), 799 (m), 730 (s), 699 (s). ^{1}H NMR (400 MHz, CD_3OD) δ 7.57–7.51 (m, 4H), 7.49–7.29 (m, 11H), 4.39 (s, 1H), 3.09–2.93 (m, 4H), 1.50–1.36 (m, 4H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.8, 135.6, 135.6, 133.6, 131.4, 130.8, 130.7, 130.3, 129.5, 75.0, 53.1, 45.4, 9.6, 9.2. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{24}H_{26}NO_2Si$, 388.1727; found, 388.1726.

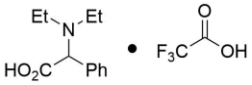


2-phenyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**2t**)

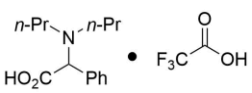
The general procedure C was followed using **1t** (314 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 1–5% methanol in dichloromethane) to afford an α-amino acid **2t** (81.4 mg, 0.322 mmol, 46% yield) as a white solid.
IR (neat, cm^{-1}) 3421 (br), 3026 (w), 2919 (w), 1682 (s), 1596 (s), 1492 (s), 1458 (w), 1387 (m), 1322 (m), 1297 (w), 1226 (m), 1156 (w), 1051 (s), 1033 (s), 992 (w), 942 (m), 904 (m). ^{1}H NMR (400 MHz, CD_3OD) δ 7.45–7.43 (m, 1H), 7.24–7.13 (m, 5H), 6.88–6.80 (m, 2H), 6.70 (tt, *J* = 7.2, 1.0 Hz, 1H), 5.21 (s, 1H), 3.79 (ddd, *J* = 11.2, 6.3, 5.0 Hz, 1H), 3.48 (ddd, *J* = 11.1, 8.1, 4.8 Hz, 1H), 3.12 (m, 1H), 2.92 (m, 1H). ^{13}C NMR (101 MHz, CD_3OD) δ 176.6, 150.5, 137.1, 133.8, 130.1, 129.1, 128.9, 128.7, 127.4, 118.9, 114.5, 63.3, 44.4, 29.7. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{16}H_{14}NO_2$, 252.1030; found, 252.1038.



2-(azepan-1-yl)-2-phenylacetic acid, trifluoroacetate salt (**2u**)
The general procedure C was followed using **1u** (284 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2u** (141 mg, 0.406 mmol, 58% yield) as a white solid. The regioselectivity was determined to be 22:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.
IR (neat, cm^{-1}) 3300 (br), 2939 (w), 2968 (w), 1673 (s), 1637 (s), 1438 (m), 1411 (m), 1376 (m), 1179 (s), 1127 (s), 1019 (w), 952 (w), 929 (w), 840 (m), 800 (m), 722 (m), 702 (m). ^{1}H NMR (400 MHz) δ 7.59–7.53 (m, 2H), 7.40–7.37 (m, 3H), 4.64 (s, 1H), 3.22–2.96 (m, 4H), 1.90–1.71 (m, 4H), 1.68–1.61 (m, 4H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 169.1, 158.3 (q, *J* = 31.4 Hz), 134.6, 129.3, 128.5, 117.3 (q, *J* = 299.3 Hz), 73.9, 52.9, 45.1, 26.3, 26.2, 24.5, 23.8.^{19}F NMR (376 MHz, CD_3OD) δ –76.90. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$, 234.1489; found, 234.1481.



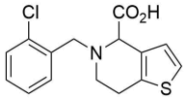
2-(diethylamino)-2-phenylacetic acid, trifluoroacetate salt (**2v**)
The general procedure C was followed using **1v** (245 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2v** (196 mg, 0.610 mmol, 87% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.
IR (neat, cm^{-1}) 3346 (br), 2945 (m), 2832 (m), 1679 (s), 1641 (m), 1409 (m), 1381 (m), 1203 (m), 1185 (m), 1140 (m), 1022 (s), 838 (w), 801 (w). ^{1}H NMR (400 MHz, CD_3OD) δ 7.60–7.54 (m, 2H), 7.39–7.37 (m, 3H), 4.59 (s, 1H), 3.25–2.70 (m, 4H), 1.44–0.93 (br s, 6H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.8, 163.0 (q, *J* = 34.5 Hz), 133.4, 130.8, 130.5, 130.2, 118.2 (q, *J* = 292.9 Hz), 72.9, 45.9, 8.7. ^{19}F NMR (376 MHz, CD_3OD) δ –76.82. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{18}NO_2$, 208.1332; found, 208.1324.



2-(dipropylamino)-2-phenylacetic acid, trifluoroacetate salt (**2w**)

The general procedure C was followed using **1w** (287 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **2w** (161 mg, 0.461 mmol, 66% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions..

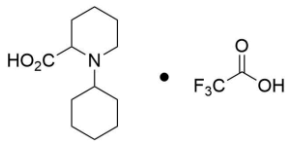
IR (neat, cm^{-1}) 3316 (br), 2976 (w), 2883 (w), 2828 (w), 1676 (s), 1635 (s), 1458 (m), 1368 (m), 1201 (s), 1178 (s), 1129 (s), 1030 (m), 980 (w), 952 (w), 833 (w), 800 (m), 738 (m), 719 (m), 700 (m). ^{1}H NMR (400 MHz, CD_3OD) δ 7.58–7.55 (m, 2H), 7.41–7.39 (m, 3H), 4.62 (s, 1H), 3.05 (s, 2H), 2.95–2.58 (m, 2H), 1.78–1.53 (m, 4H), 0.81 (s, 6H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 169.6, 158.4 (q, *J* = 31.6 Hz), 134.6, 129.3, 128.6, 128.5, 117.3 (q, *J* = 298.5 Hz), 70.9, 52.0, 17.4, 11.2. ^{19}F NMR (376 MHz, CD_3OD) δ –76.42. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{14}H_{22}NO_2$, 236.1645; found, 236.1642.



5-(2-chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-4-carboxylic acid (**5**)

The general procedure C was followed using ticlopidine (395 mg, 1.50 mmol). The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford an α-amino acid **5** (112 mg, 0.266 mmol, 38% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3328 (br), 3066 (w), 2927 (m), 2848 (w), 1670 (s), 1594 (m), 1475 (m), 1442 (s), 1386 (m), 1364 (m), 1200 (m), 1173 (m), 1127 (w), 1053 (m), 1037 (m), 958 (w), 828 (w), 800 (w), 755 (s), 705 (m). ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (m, 1H), 7.43 (m, 1H), 7.37–7.29 (m, 2H), 7.18 (d, *J* = 5.2 Hz, 1H), 7.04 (d, *J* = 5.3 Hz, 1H), 4.57 (s, 1H), 4.32 (d, *J* = 14.1 Hz, 1H), 4.23 (d, *J* = 13.8 Hz, 1H), 3.58 (m, 1H), 3.13 (m, 1H), 3.00–2.90 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 172.3, 134.7, 132.4, 132.1, 131.6, 130.0, 129.9, 129.5, 127.2, 125.8, 123.1, 65.8, 55.1, 55.1, 22.4. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{15}ClNO_2S$, 308.0507; found, 308.0519.

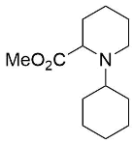


1-(piperidin-1-yl)cyclohexane-1-carboxylic acid, trifluoroacetate salt (**7**)

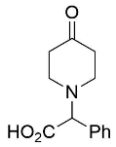
The general procedure was followed using *N*-cyclohexylpiperidine (251 mg, 1.50 mmol) under the atmospheric pressure of CO_2 with t_R = 6 min. The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a trifluoroacetate salt of α-amino acid **7** (99.0 mg, 0.304 mmol, 43% yield) as a white solid. The regioselectivity was determined to be >100:1 by GC analysis after derivatization of the crude reaction mixture with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions.

IR (neat, cm^{-1}) 3372 (br), 2948 (w), 2869 (w), 1675 (s), 1447 (m), 1204 (s), 1137 (s), 844 (m), 801 (m), 725 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 3.63–2.59 (m, 4H), 2.24–0.91 (m, 16H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 171.0, 158.7 (q, *J* = 31.7 Hz), 117.3 (q, *J* = 298.7 Hz), 65.0, 62.8, 45.4,

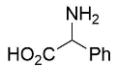
28.5, 27.9, 25.1, 25.0, 25.0, 24.7, 24.1, 22.4, 21.4. ^{19}F NMR (376 MHz, CD_3OD) δ –77.01. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{22}NO_2$, 212.1645; found, 212.1649.
Additional, unexpected peaks were present in the ^{13}C NMR spectrum (likely due to chemical and/or conformational equilibria), so the identity of the compound was confirmed by derivatization to the methyl ester with (trimethylsilyl)diazomethane, as in the procedure for optimization reactions:



methyl 1-(piperidin-1-yl)cyclohexane-1-carboxylate (**S12**)
IR (neat, cm^{-1}) 2930 (s), 2855 (m), 1739 (s), 1449 (m), 1376 (w), 1282 (w), 1280 (w), 1192 (m), 1162 (m), 1125 (w), 1068 (w), 1032 (w), 842 (w), 760 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 3.43 (m, 1H), 2.98 (m, 1H), 2.37 (m, 2H), 1.90–1.52 (m, 9H), 1.46–0.99 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 62.3, 61.5, 51.6, 44.9, 31.4, 31.3, 30.1, 29.7, 26.3, 26.0, 25.7, 23.0. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{24}NO_2$, 226.1802; found, 226.1785.



2-(4-oxopiperidin-1-yl)-2-phenylacetic acid (**S13**)
To a solution of the trifluoroacetate salt of **2o** (280 mg, 0.716 mmol, 1.0 equiv) in tetrahydrofuran (2 mL) was added concentrated hydrochloric acid (37% in H_2O, 1.4 mL, 14 mmol, 20 equiv) at room temperature. The reaction mixture was stirred overnight and then neutralized by 3N sodium hydroxide solution. The aqueous portion was extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (Biotage 25 g KP-sil, 2–20% methanol in dichloromethane) to afford a piperidone **S13** (133 mg, 0.571 mmol, 80% yield) as a white solid.
IR (neat, cm^{-1}) 3365 (br), 2960 (w), 2851 (w), 1674 (s), 1436 (m), 1380 (m), 1185 (s), 1131 (s), 1019 (m), 941 (w), 841 (m), 801 (m), 723 (m). ^{1}H NMR (400 MHz, DMSO-*d*6) δ 7.58–7.42 (m, 2H), 7.39–7.24 (m, 3H), 4.11 (s, 1H), 2.71 (t, *J* = 6.2 Hz, 4H), 2.31 (t, *J* = 6.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-*d*6) δ 208.4, 173.8, 138.1, 128.6, 128.1, 127.5, 73.1, 50.0, 40.7. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{16}NO_3$, 234.1125; found, 234.1116.



2-amino-2-phenylacetic acid (**8**)
To a solution of **S13** (80.7 mg, 0.346 mmol, 1.0 equiv) in ethanol (4 mL) were added ammonium chloride (18.5 mg, 0.346 mmol, 1.0 equiv) and JandaJel–NH_2 (519 mg, 0.519 mmol, 1.5 equiv) at room temperature. The reaction mixture was heated to 95 °C and allowed to stir at this temperature overnight. After cooling to room temperature, the residue was filtered and washed with methanol and water. The filtrate was concentrated under reduced pressure and recrystallized twice in water to provide **8** (45 mg, 0.30 mmol, 87% yield) as an off-white solid.

^{1}H NMR (400 MHz, D_2O + DCl) δ 7.40–7.34 (m, 5H), 5.08 (s, 1H). ^{13}C NMR (101 MHz, D_2O + DCl) δ 170.57, 131.17, 130.28, 129.60, 127.97, 56.34.
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature[21].

9. References

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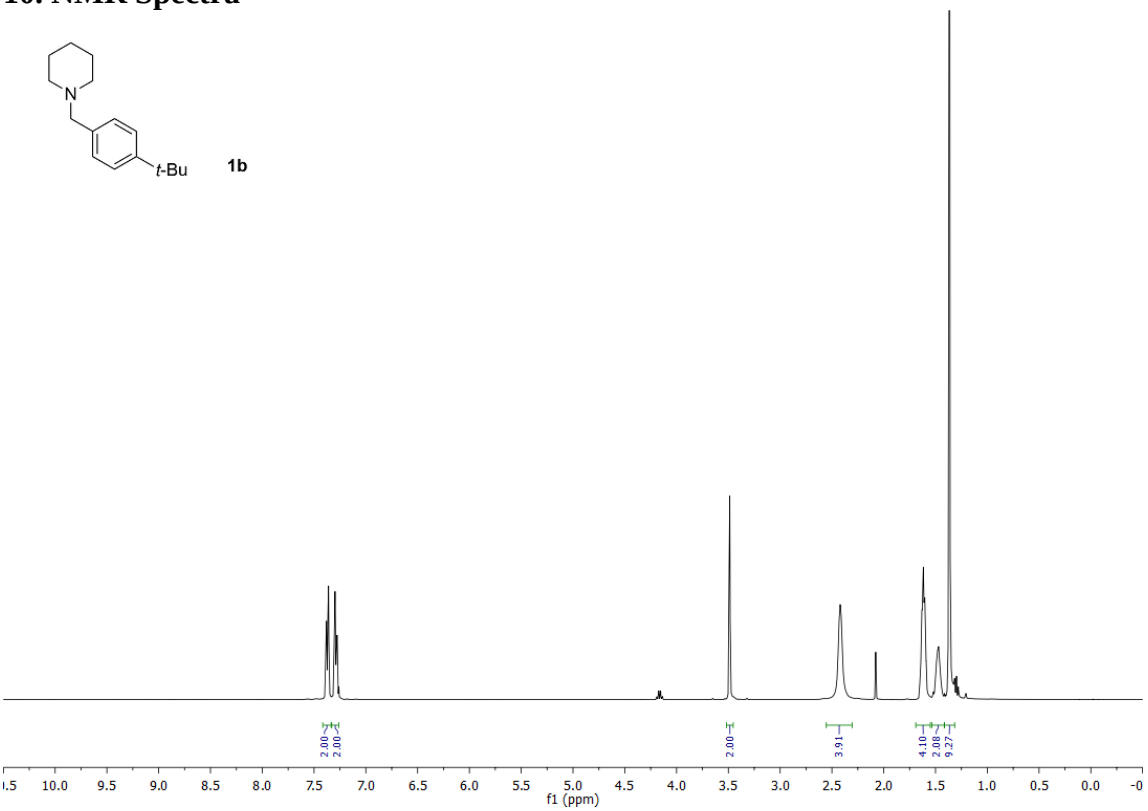
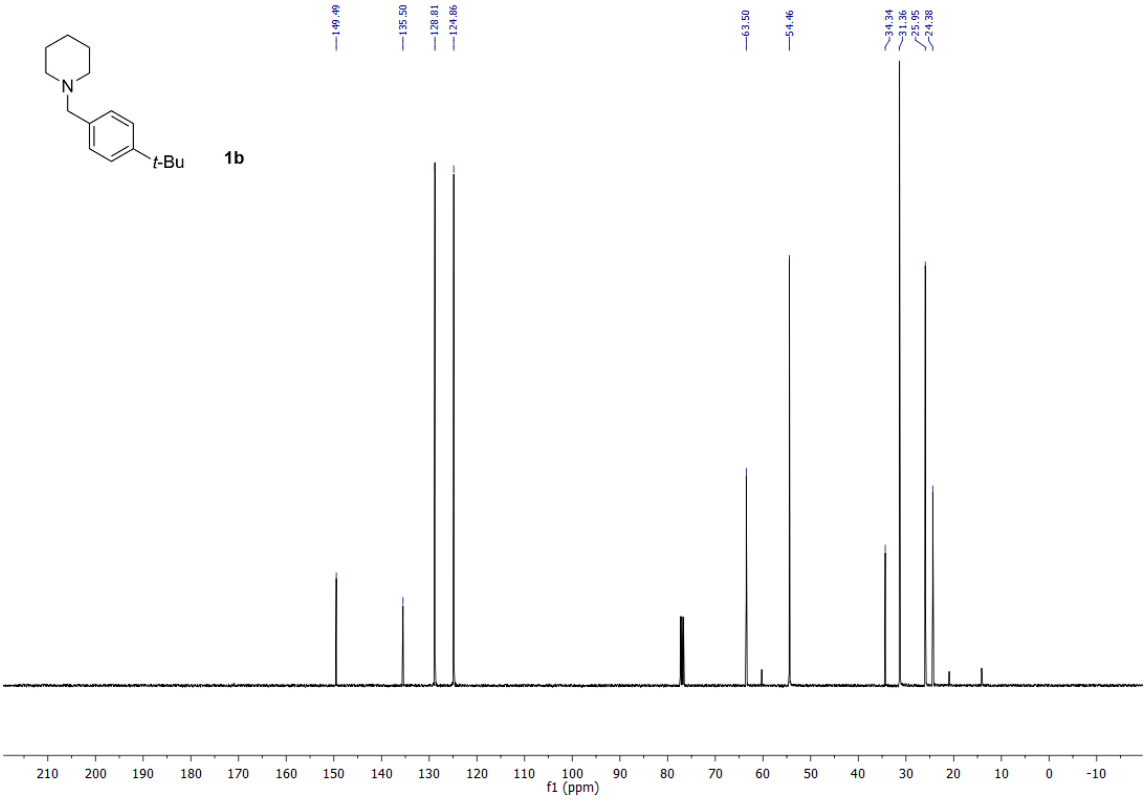
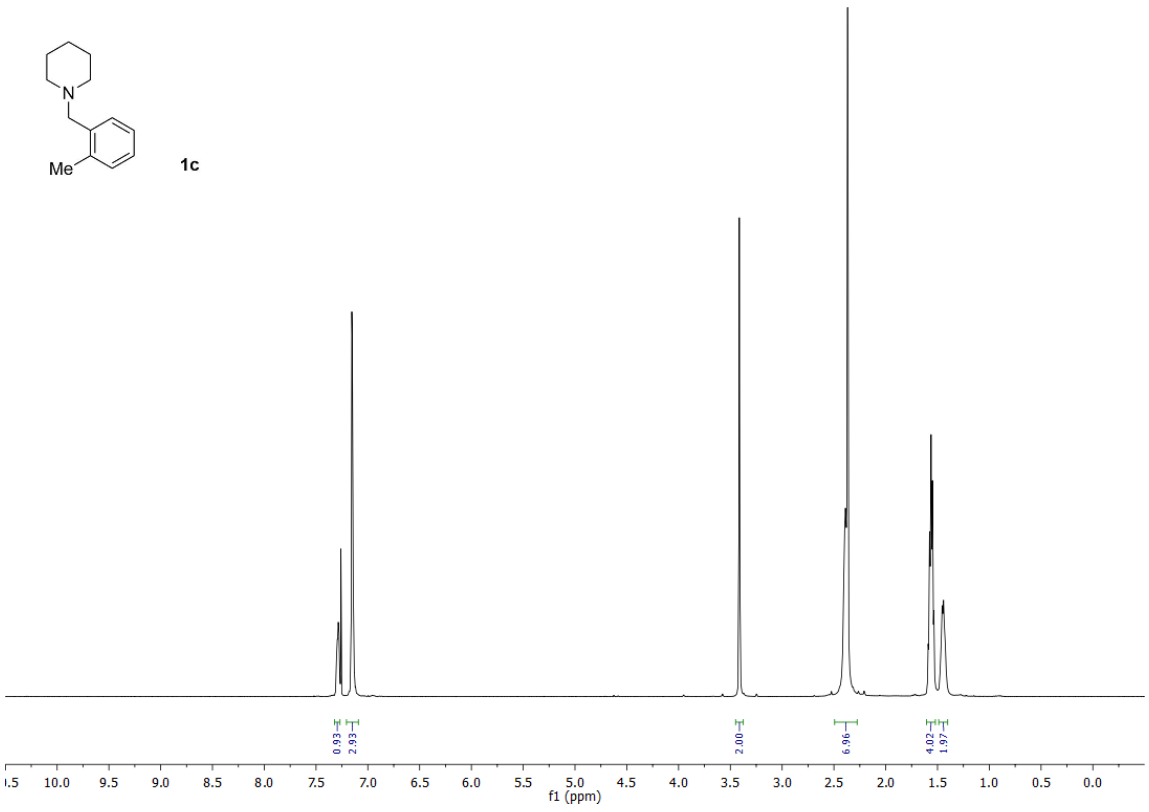
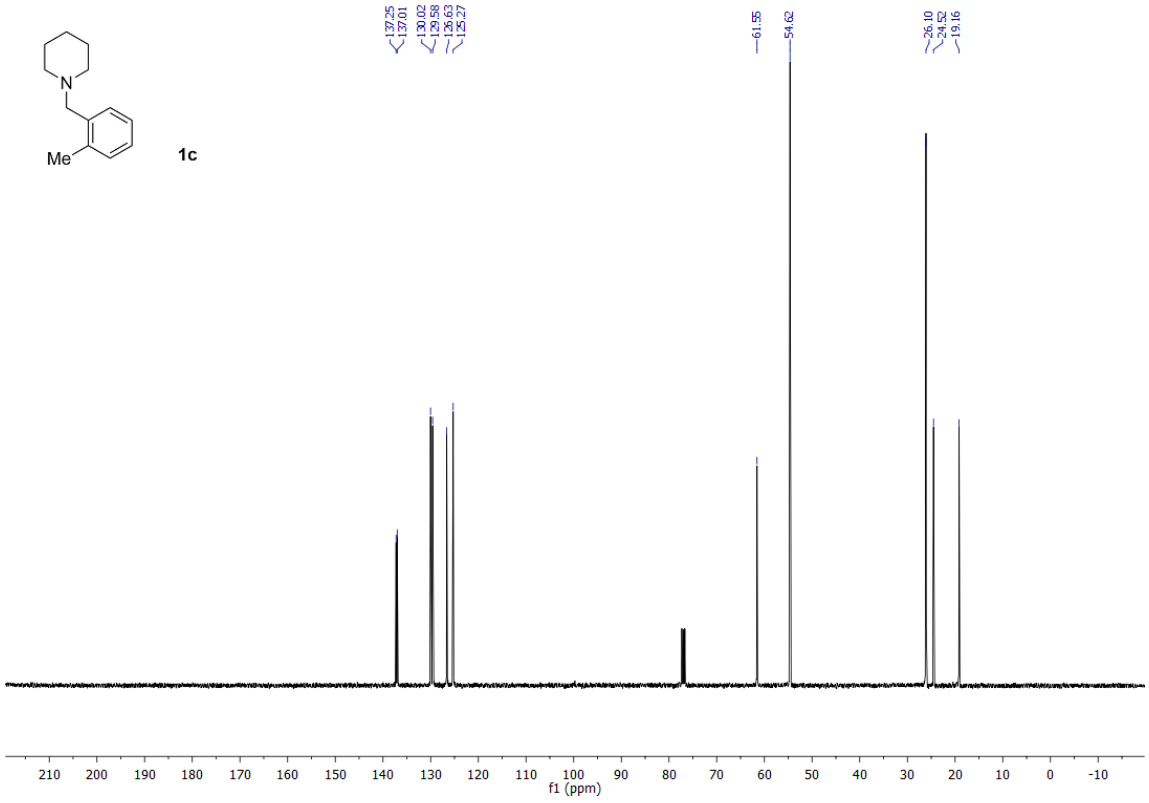
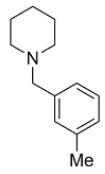
10. NMR Spectra





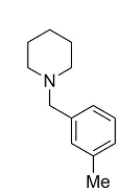

N
Me
1c
0.93
2.93
2.00
6.96
4.02
1.97
f1 (ppm)


137.25
137.01
130.02
129.58
126.63
125.27
61.55
54.62
26.10
24.52
19.16
N
Me
1c
f1 (ppm)


N
Me

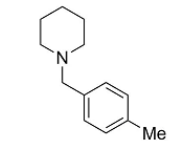
1d

1.02
1.96
0.94
2.00
6.77
4.04
2.09
f1 (ppm)


N
Me

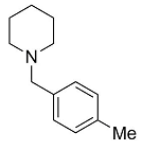
1d

138.38
137.53
129.87
127.85
127.49
126.27
63.87
54.46
25.89
24.34
21.31
f1 (ppm)


N
Me

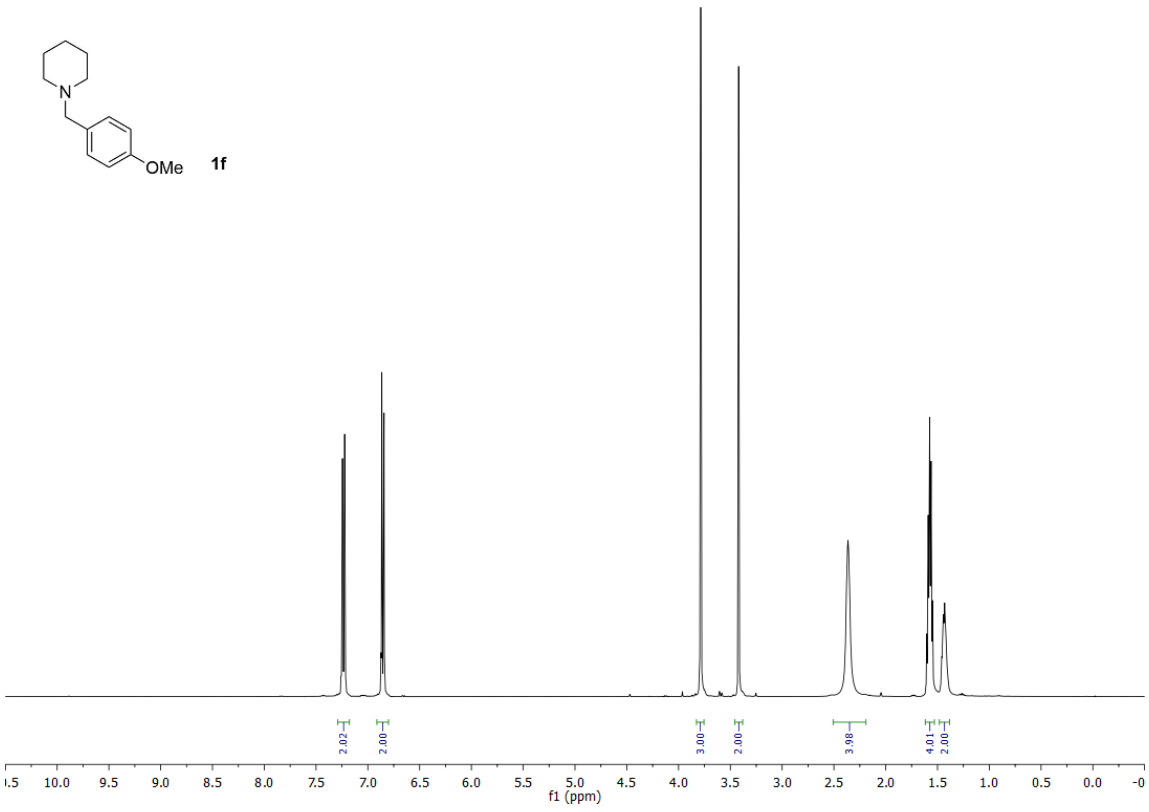
1e

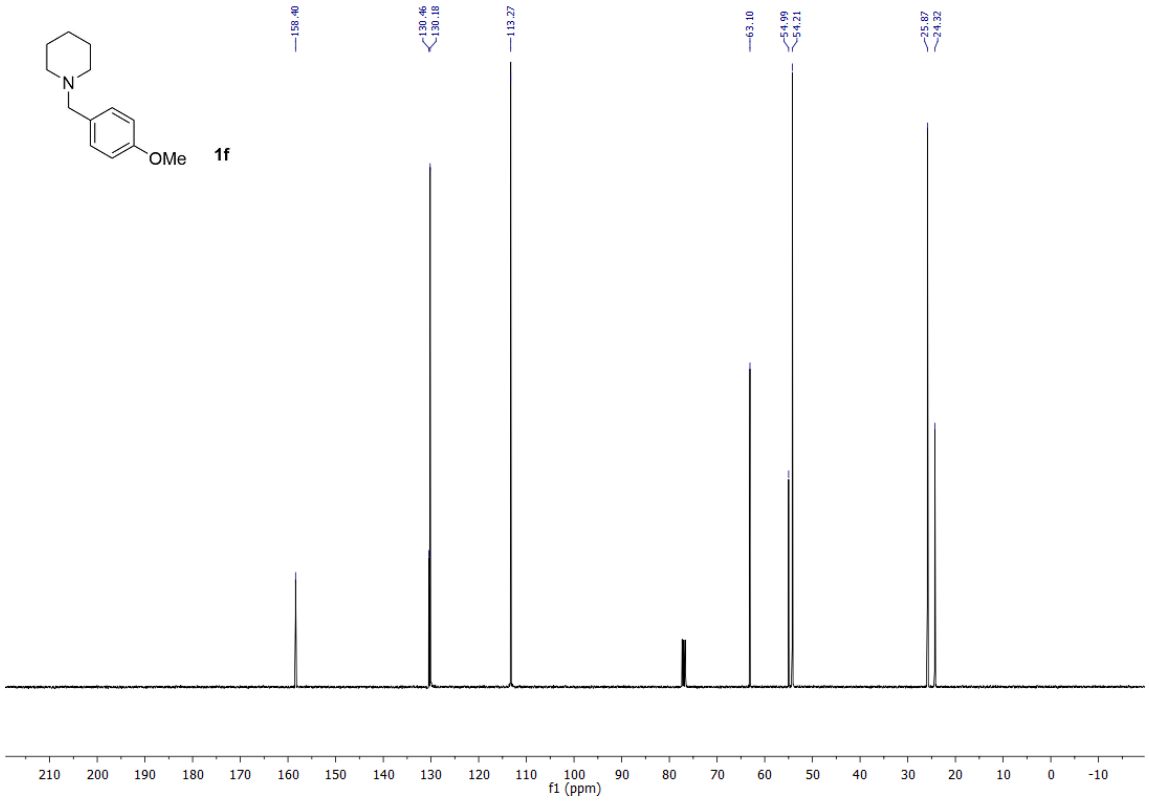
1.97
1.90
2.00
6.89
4.05
2.14
f1 (ppm)

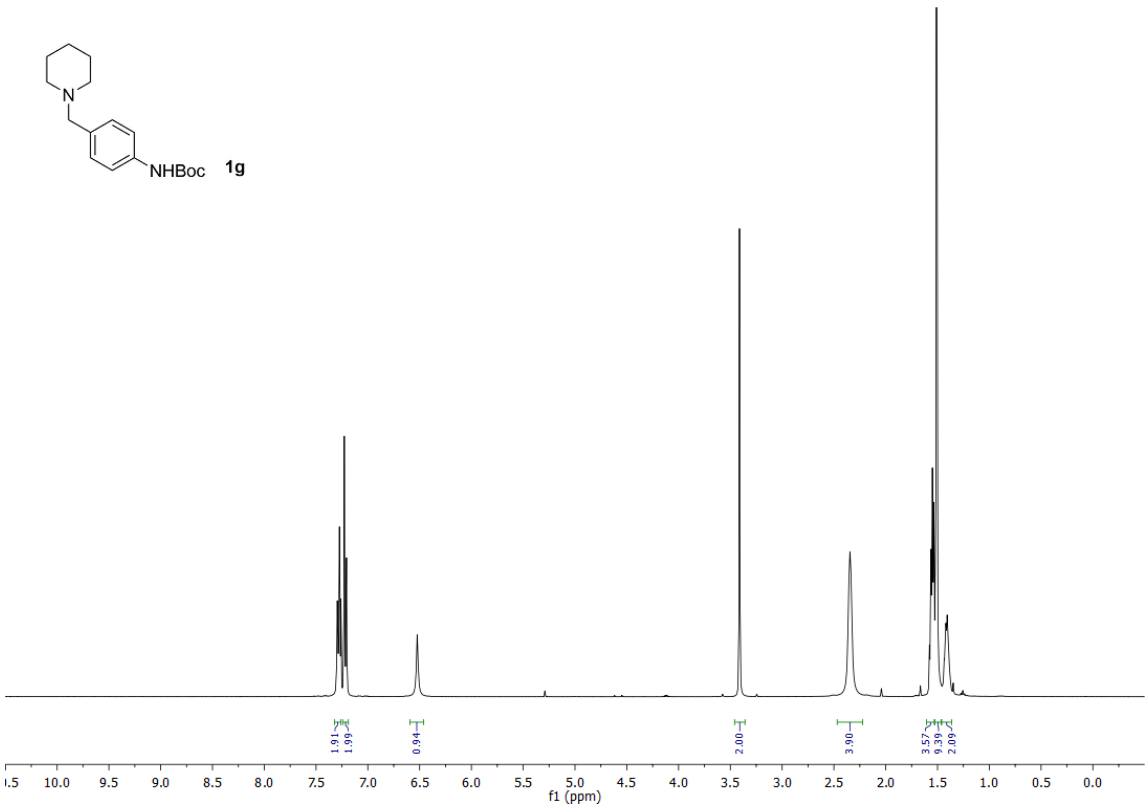

N
Me

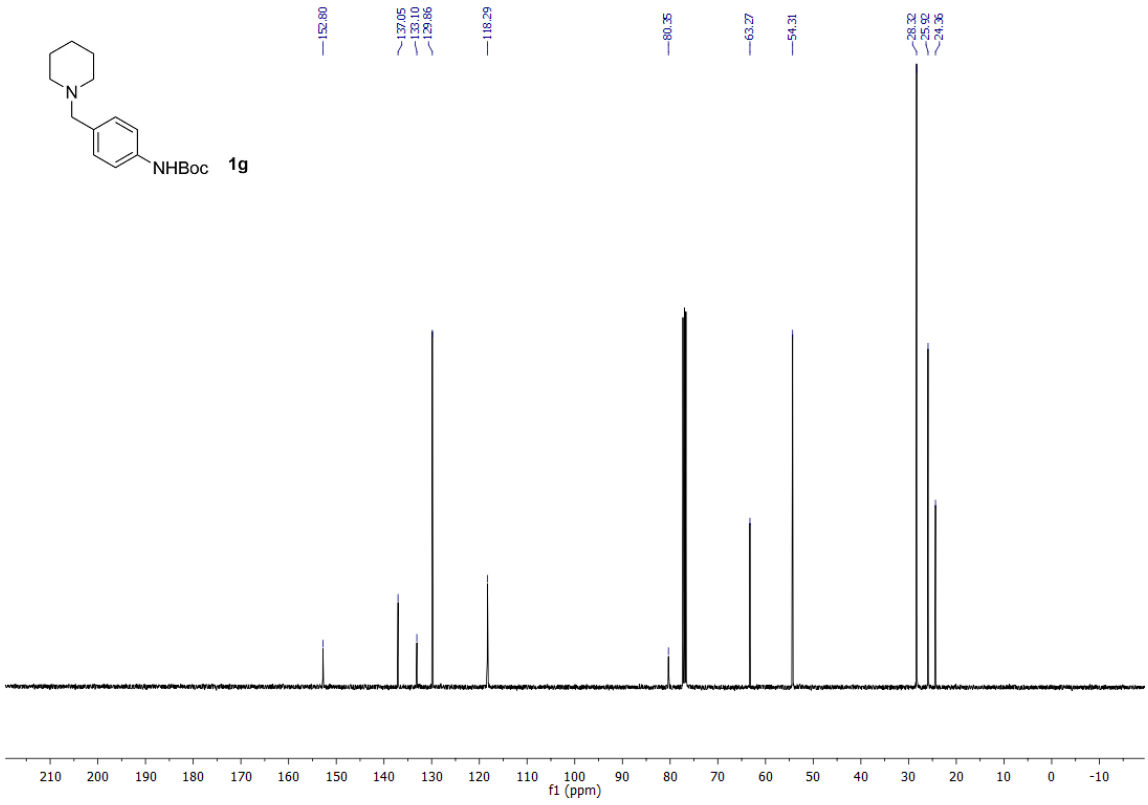
1e

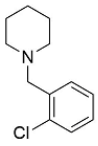
136.16
135.39
129.07
128.65
63.51
54.32
25.91
24.34
20.99
f1 (ppm)


N
OMe
1f
2.02
2.00
3.00
2.00
3.98
4.01
2.00
f1 (ppm)


N
OMe
1f
158.40
130.46
130.18
113.27
63.10
54.99
54.21
25.87
24.32
f1 (ppm)

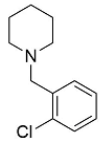

NHBoc
1g
1.91
1.99
0.94
2.00
3.90
3.57
9.39
2.09
f1 (ppm)


152.80
137.05
133.10
129.86
118.29
80.35
63.27
54.31
28.32
25.92
24.36
NHBoc
1g
f1 (ppm)


N
Cl

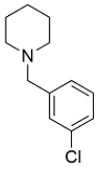
1h

1.00
0.96
1.04
1.01
2.11
4.08
4.25
2.12
f1 (ppm)


N
Cl

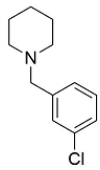
1h

136.50
134.11
130.51
129.21
127.72
126.43
59.90
54.61
26.04
24.31
f1 (ppm)


N
Cl

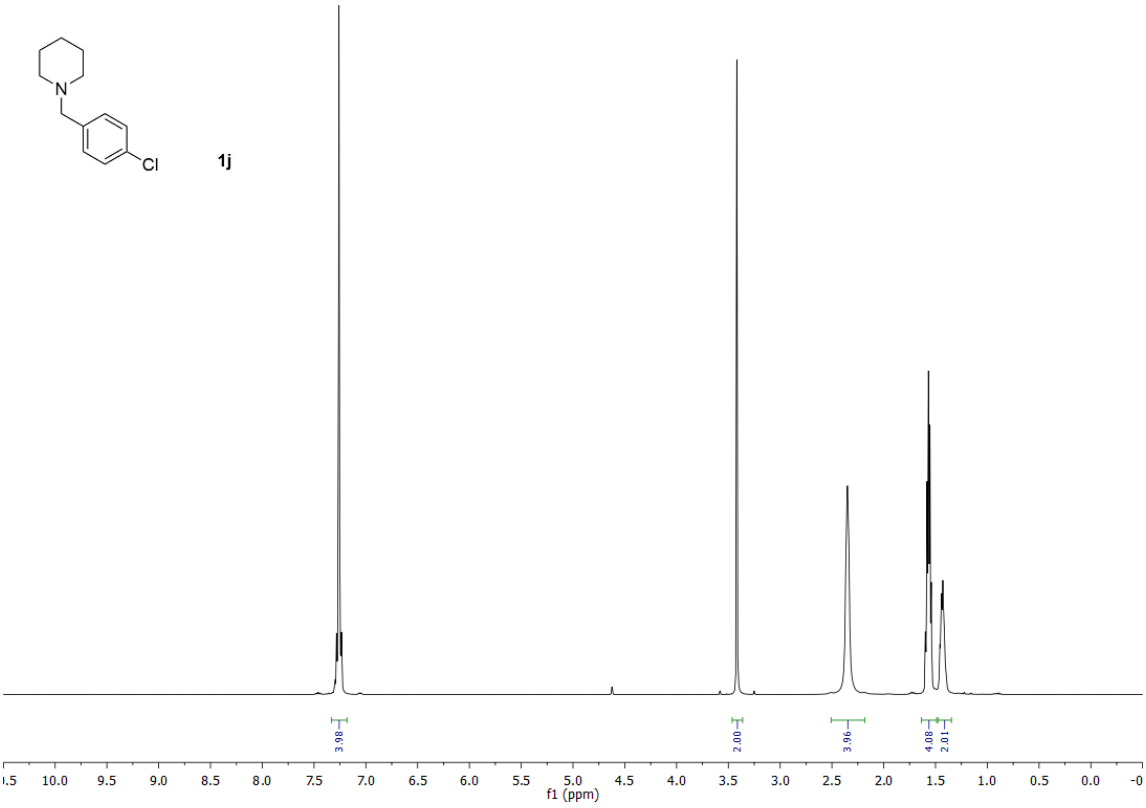
1i

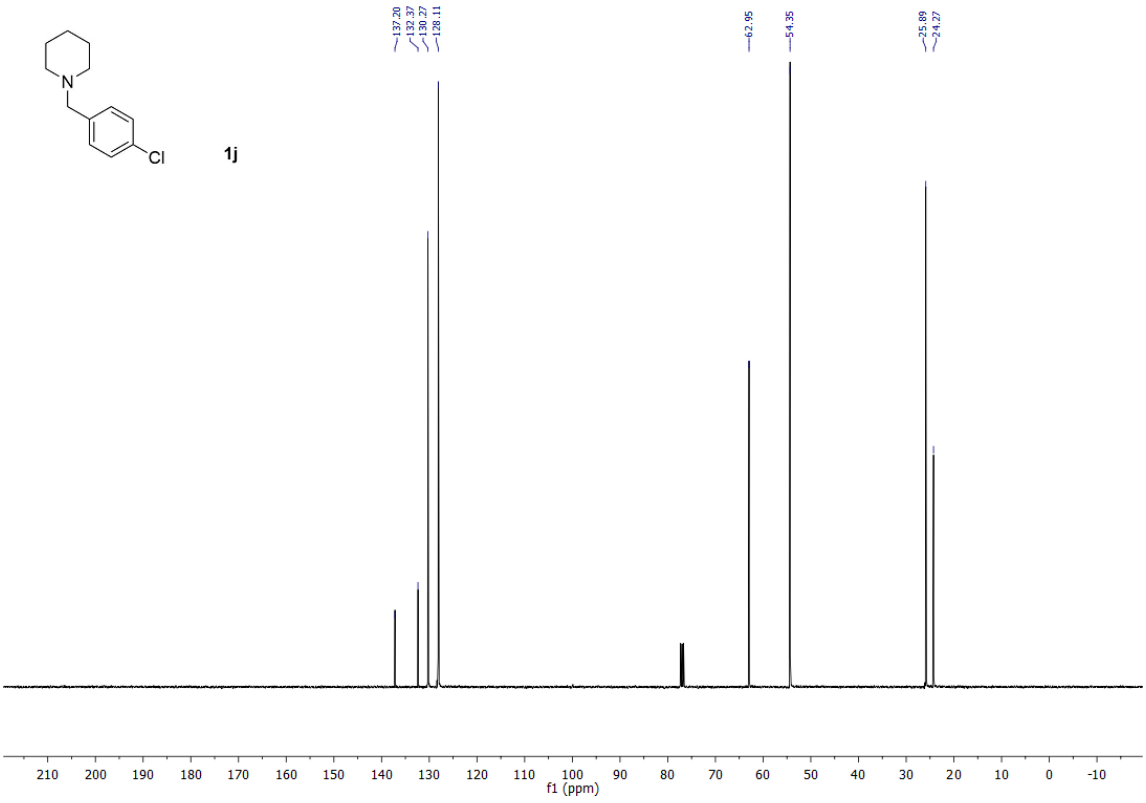
0.92
2.81
2.00
3.85
4.02
1.99
f1 (ppm)

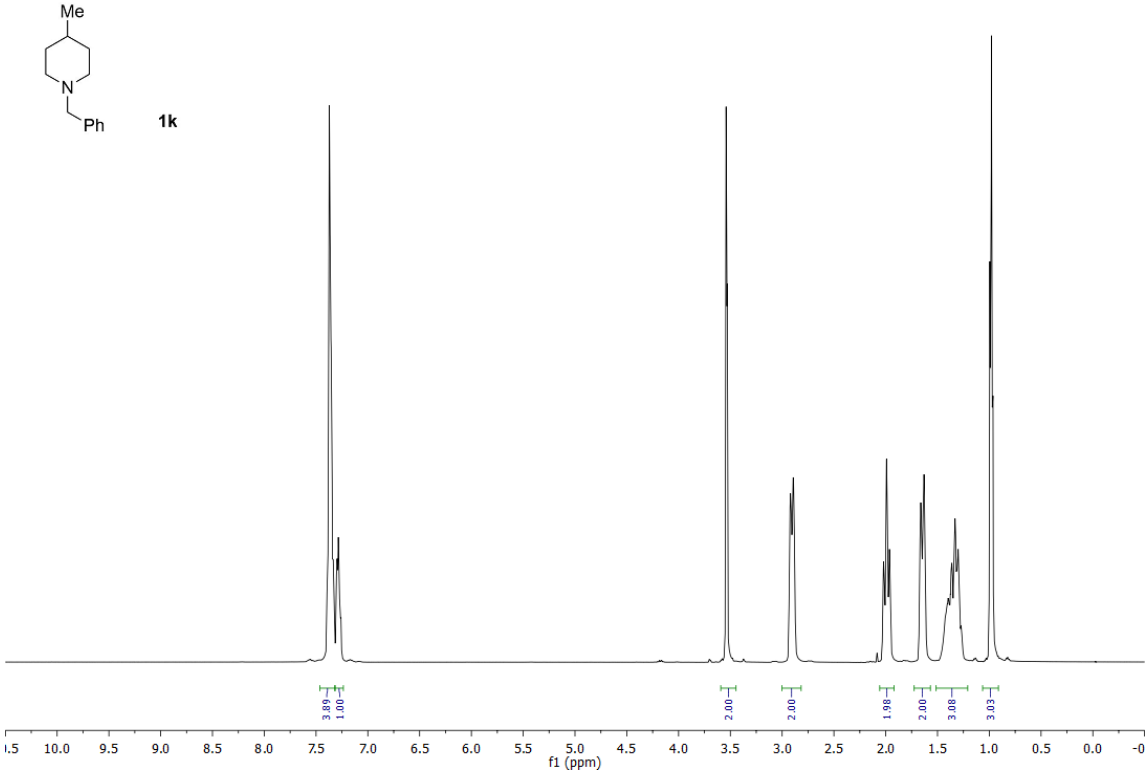

N
Cl

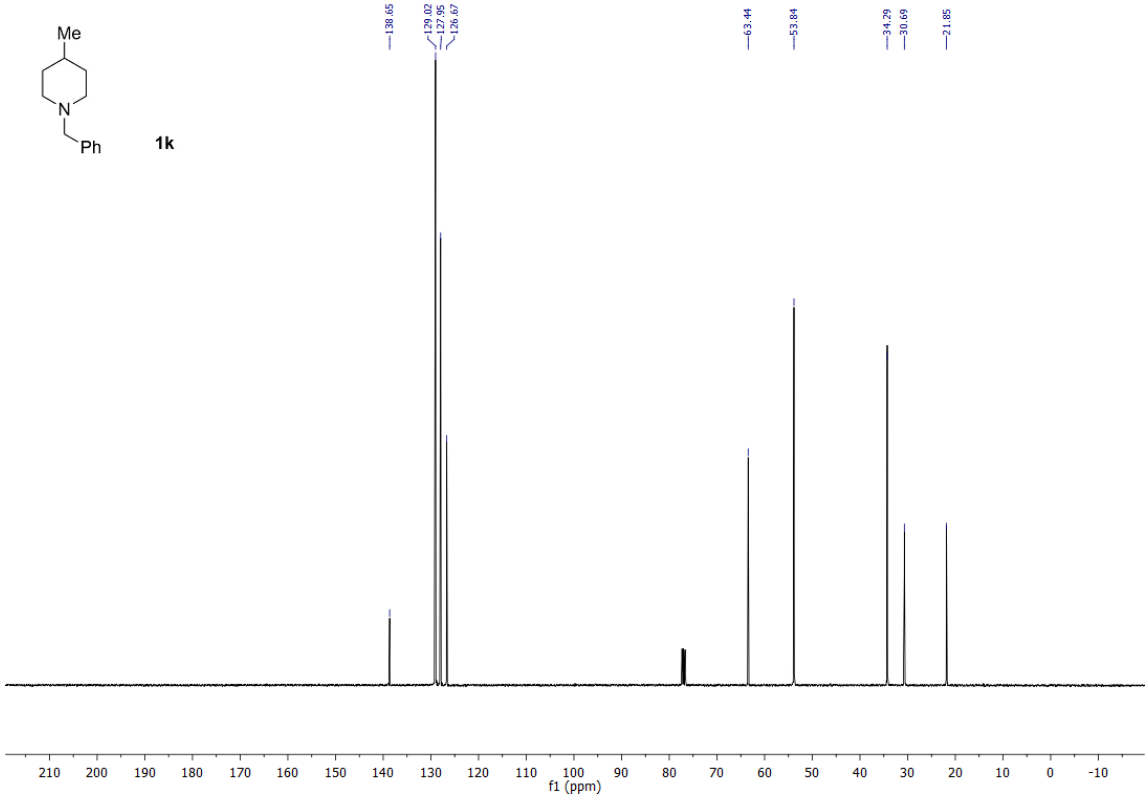
1i

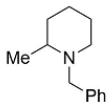
140.99
133.97
129.25
128.94
127.07
126.89
63.16
54.44
25.92
24.27
f1 (ppm)


N
Cl
1j
3.98
2.00
3.96
4.08
2.01
f1 (ppm)

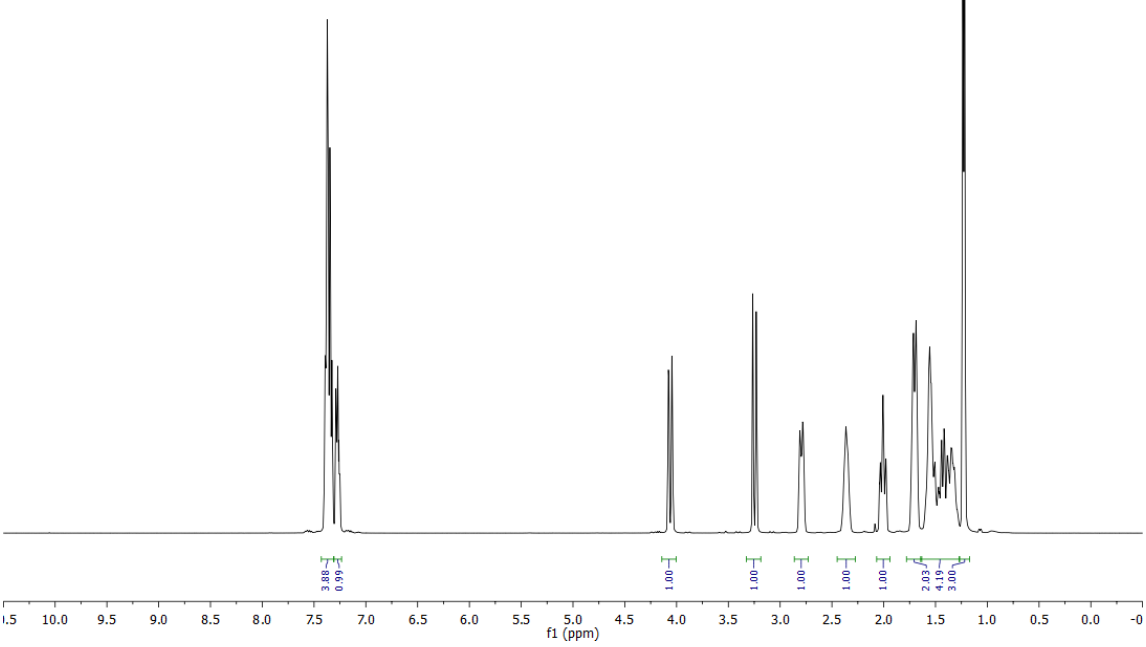

N
Cl
1j
137.20
132.37
130.27
128.11
62.95
54.35
25.89
24.27
f1 (ppm)

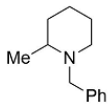

Me
N
Ph
1k
3.89
1.00
2.00
2.00
1.98
2.00
3.08
3.03
f1 (ppm)


Me
N
Ph
1k
138.65
129.02
127.95
126.67
63.44
53.84
34.29
30.69
21.85
f1 (ppm)


Me
N
Ph

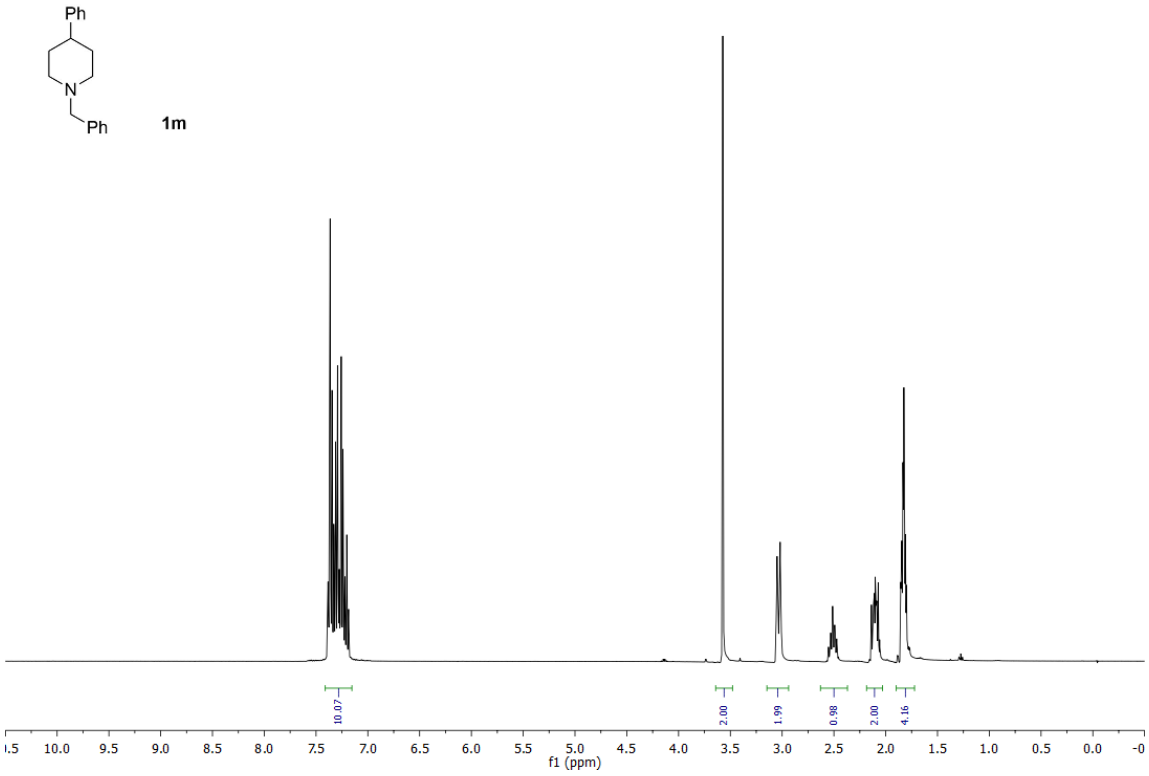
1l

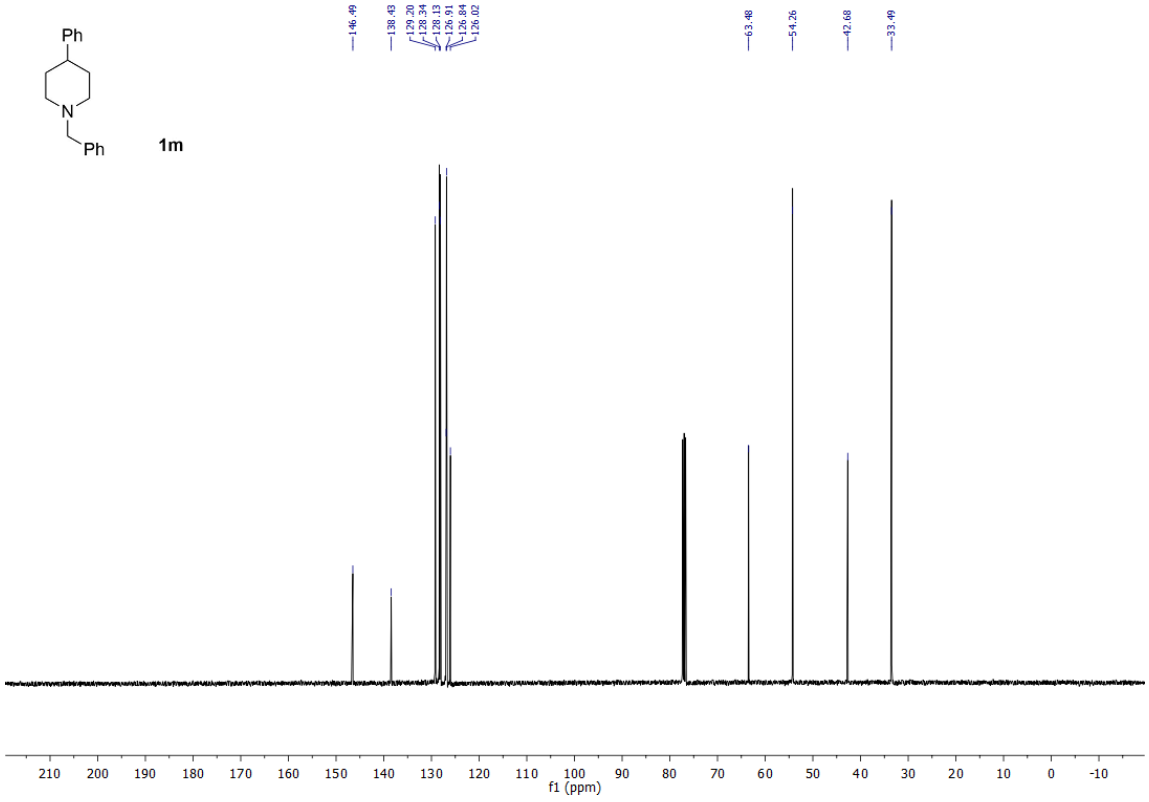

3.88
0.99
1.00
1.00
1.00
1.00
1.00
2.03
4.19
3.00
f1 (ppm)

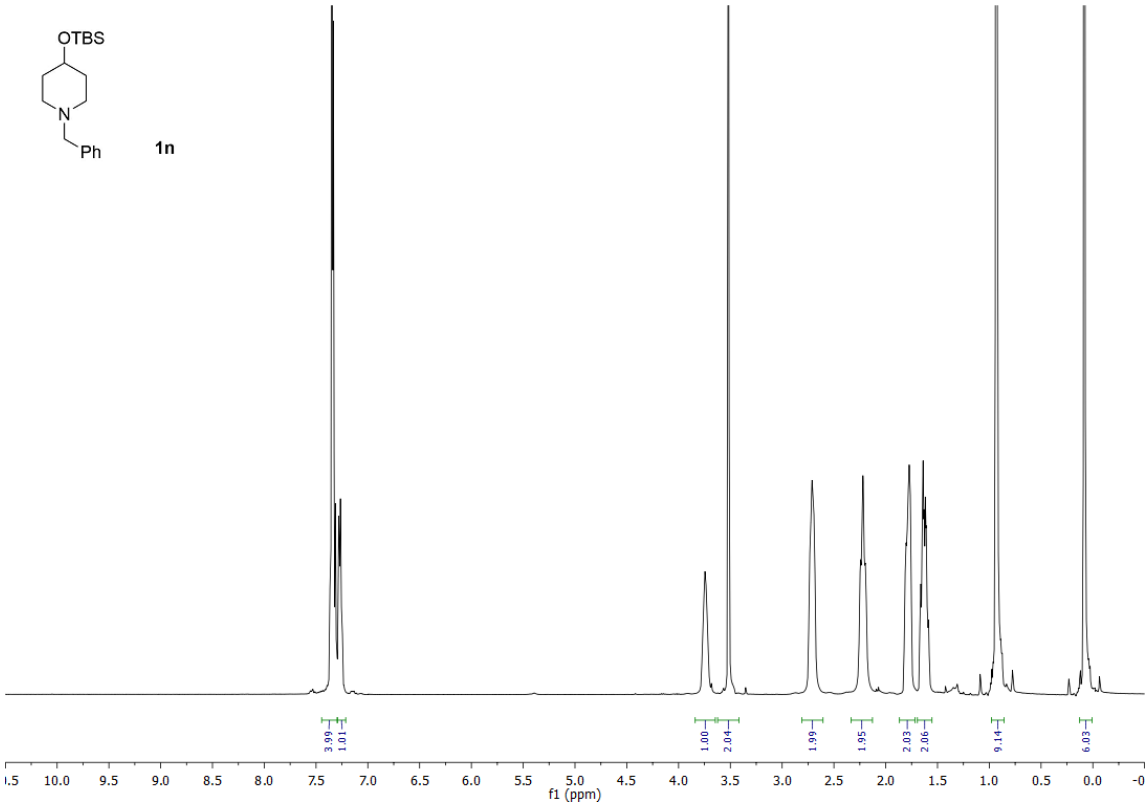

Me
N
Ph

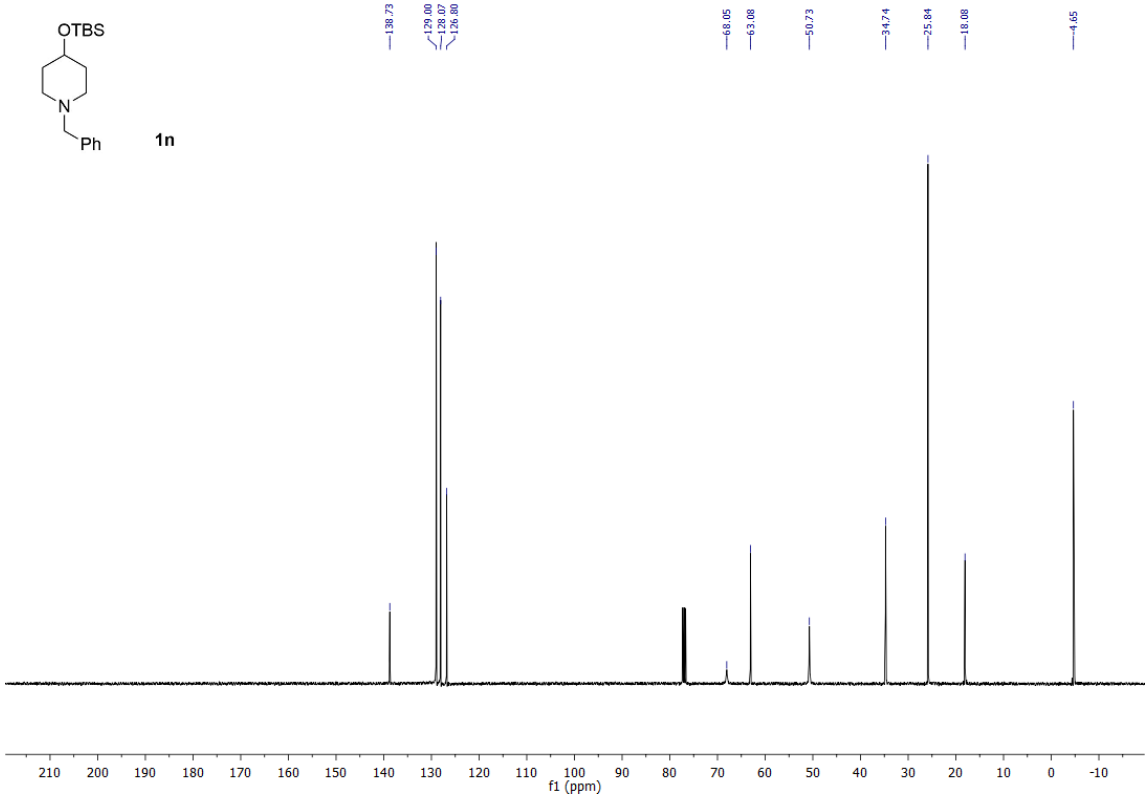
1l

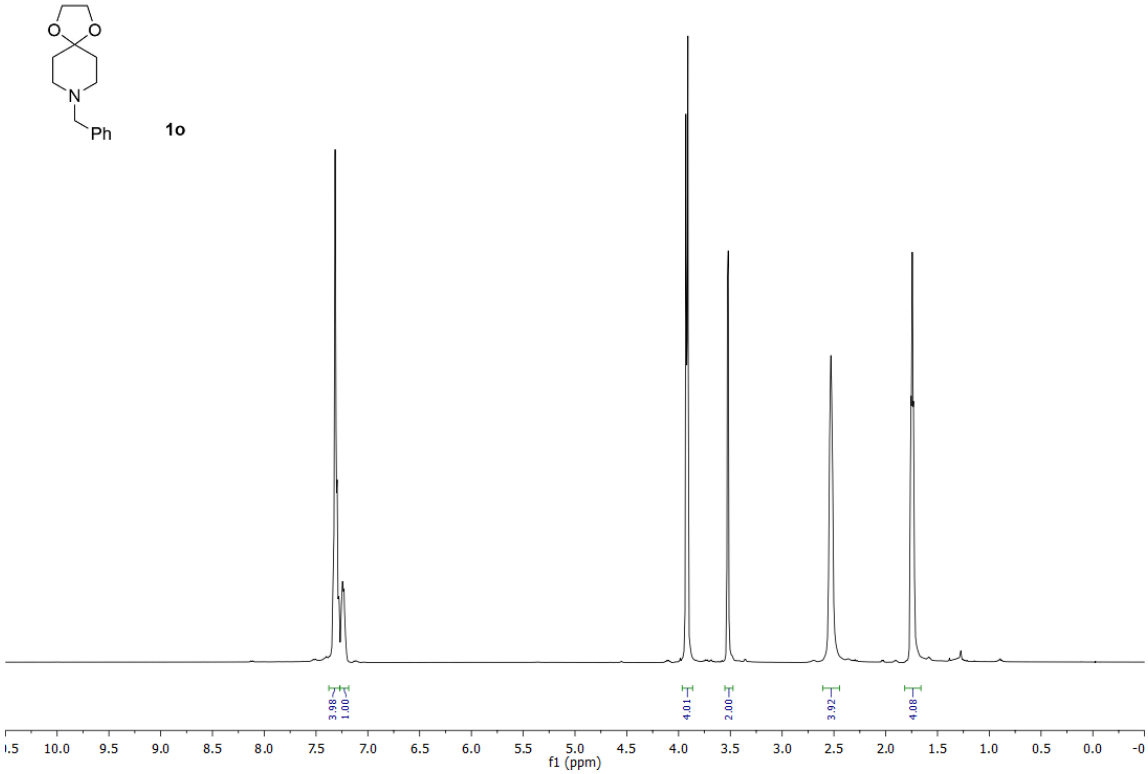
139.48
128.98
127.94
126.49
58.44
56.29
52.08
34.69
26.01
23.97
19.48
f1 (ppm)

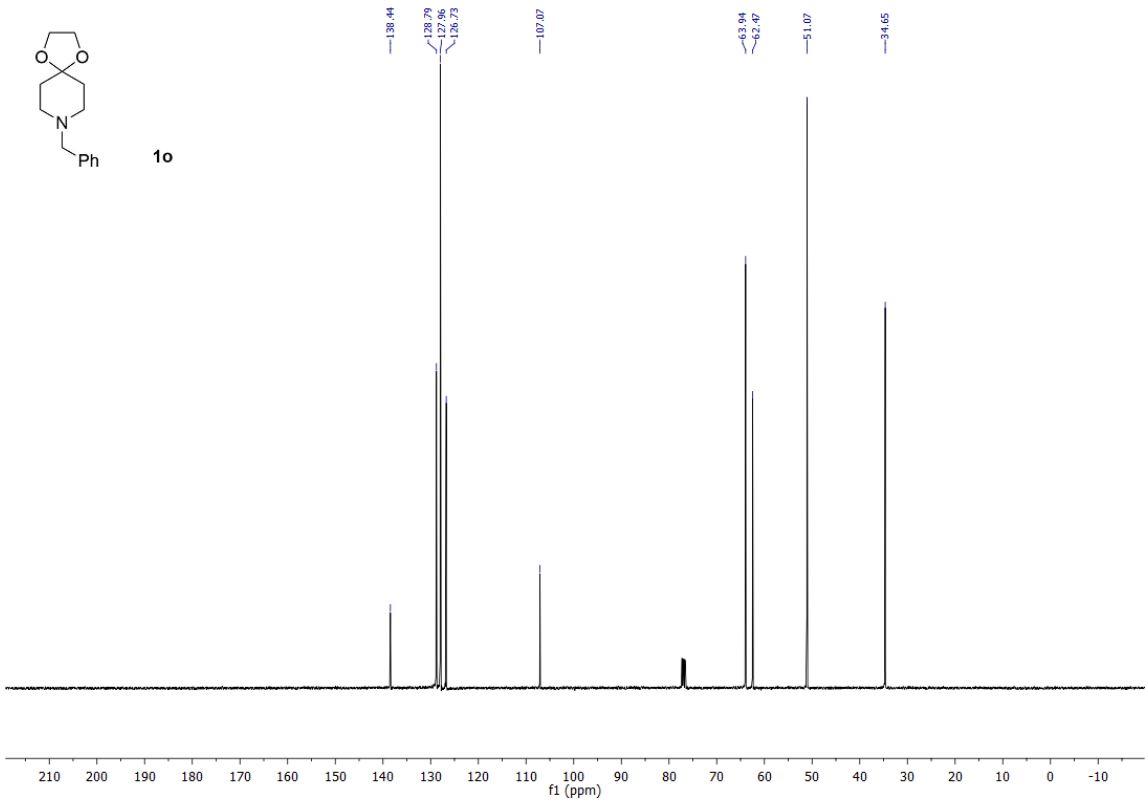

Ph
N
Ph
1m
10.07
2.00
1.99
0.88
2.00
4.16
f1 (ppm)

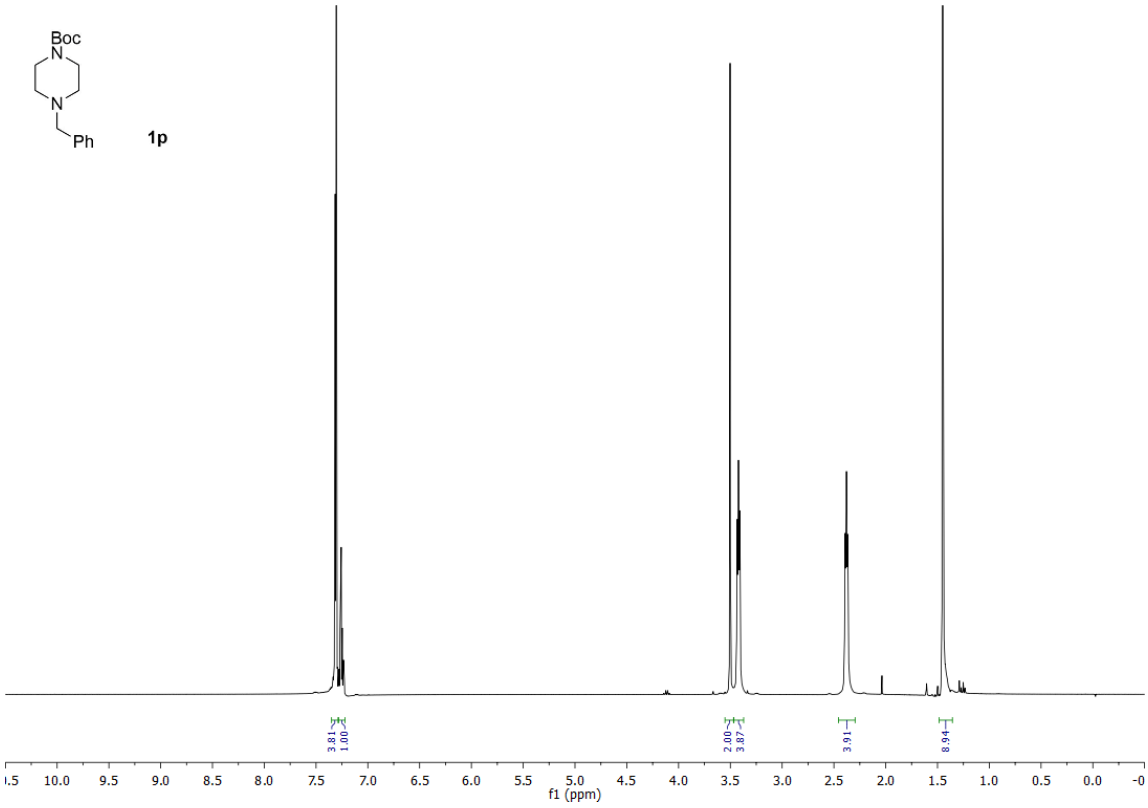

146.49
138.43
129.20
128.34
128.13
126.91
126.84
126.02
63.48
54.26
42.68
33.49
Ph
N
Ph
1m
f1 (ppm)

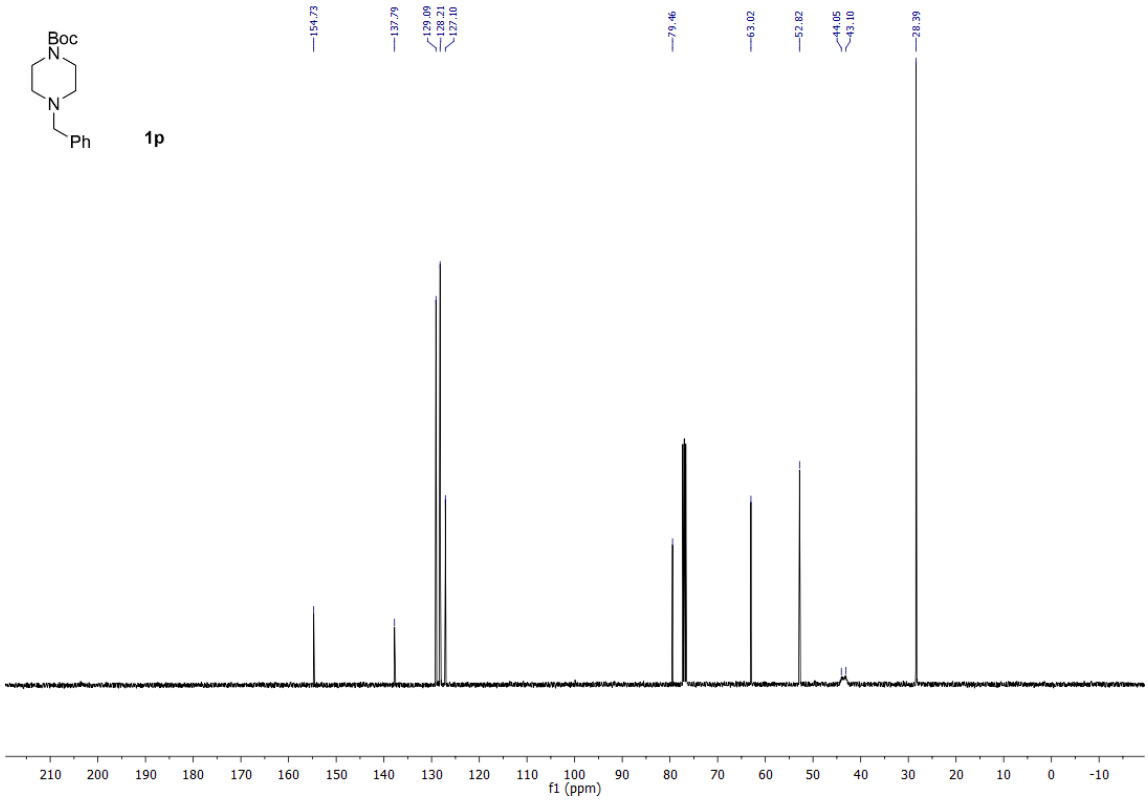

OTBS
N
Ph
1n
3.99
1.01
1.00
2.04
1.99
1.95
2.03
2.06
9.14
6.03
f1 (ppm)

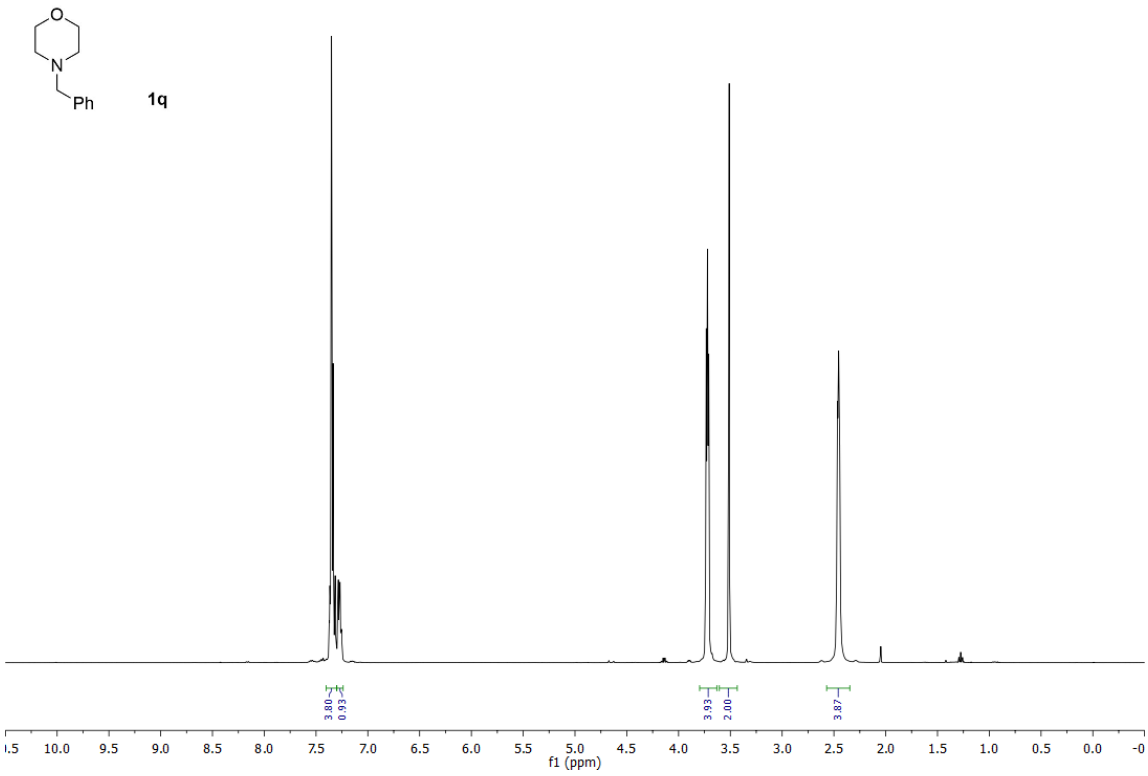

OTBS
N
Ph
1n
138.73
129.00
128.07
126.80
68.05
63.08
50.73
34.74
25.84
18.08
-4.65
f1 (ppm)

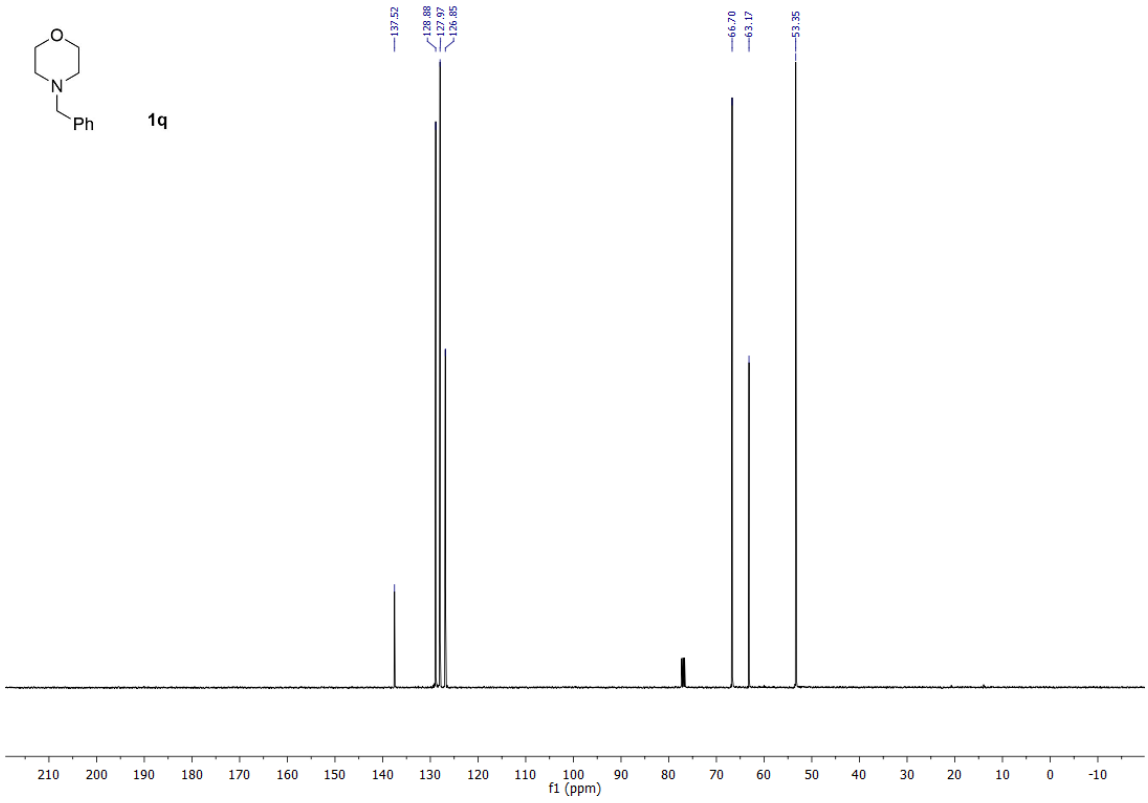

O
O
N
Ph
1o
3.98
1.00
4.01
2.00
3.92
4.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

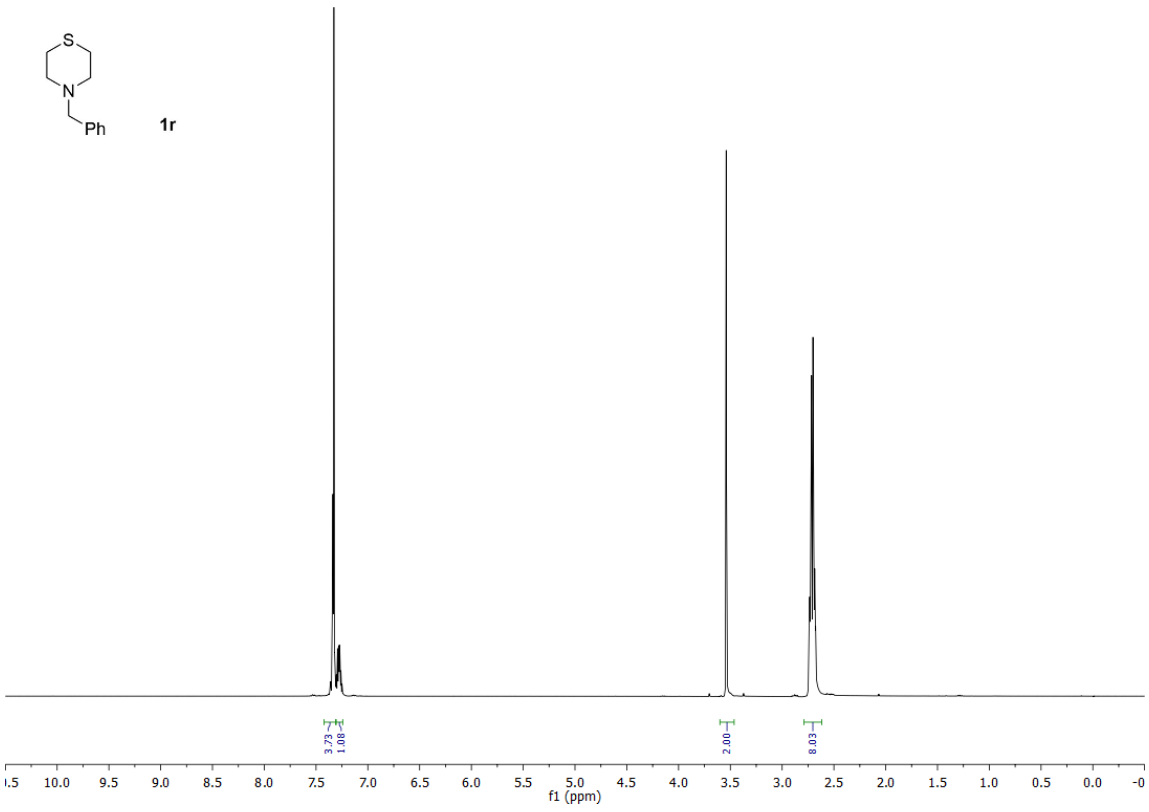

O
O
N
Ph
1o
138.44
128.79
127.96
126.73
107.07
63.94
62.47
51.07
34.65
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

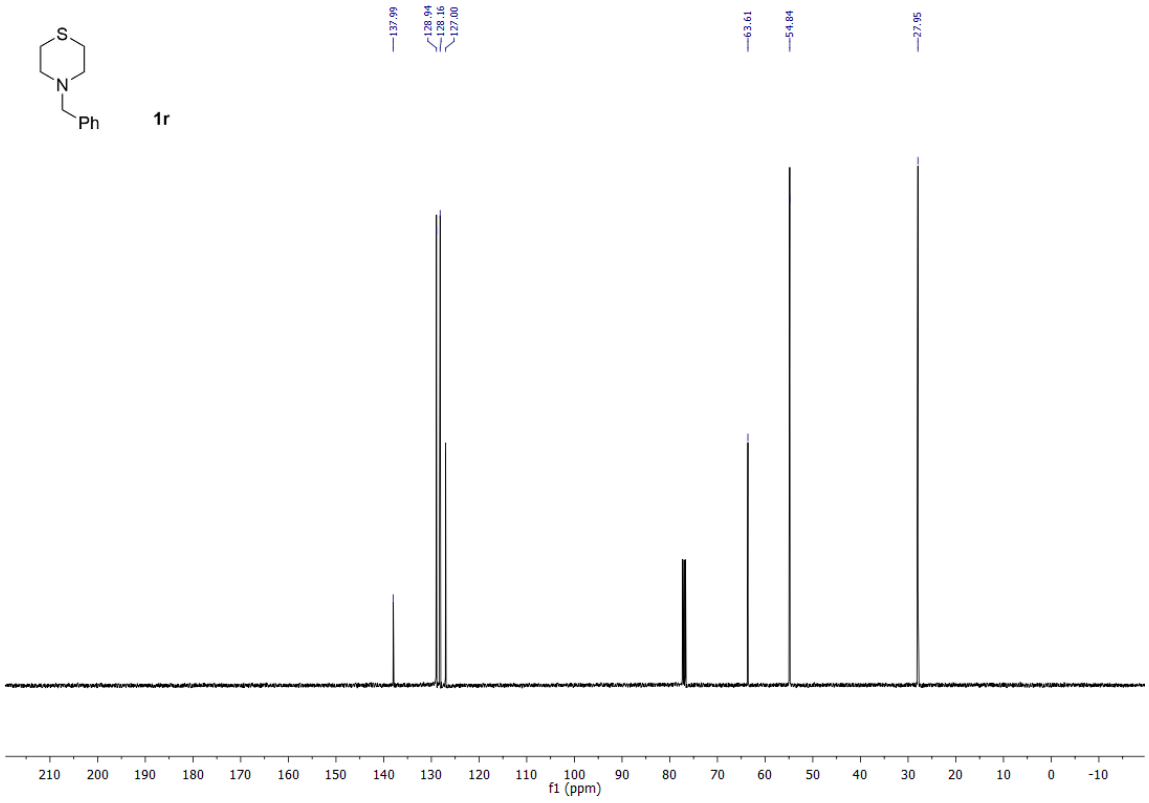

Boc
N
N
Ph
1p
3.81
1.00
2.00
3.87
3.91
8.94
f1 (ppm)

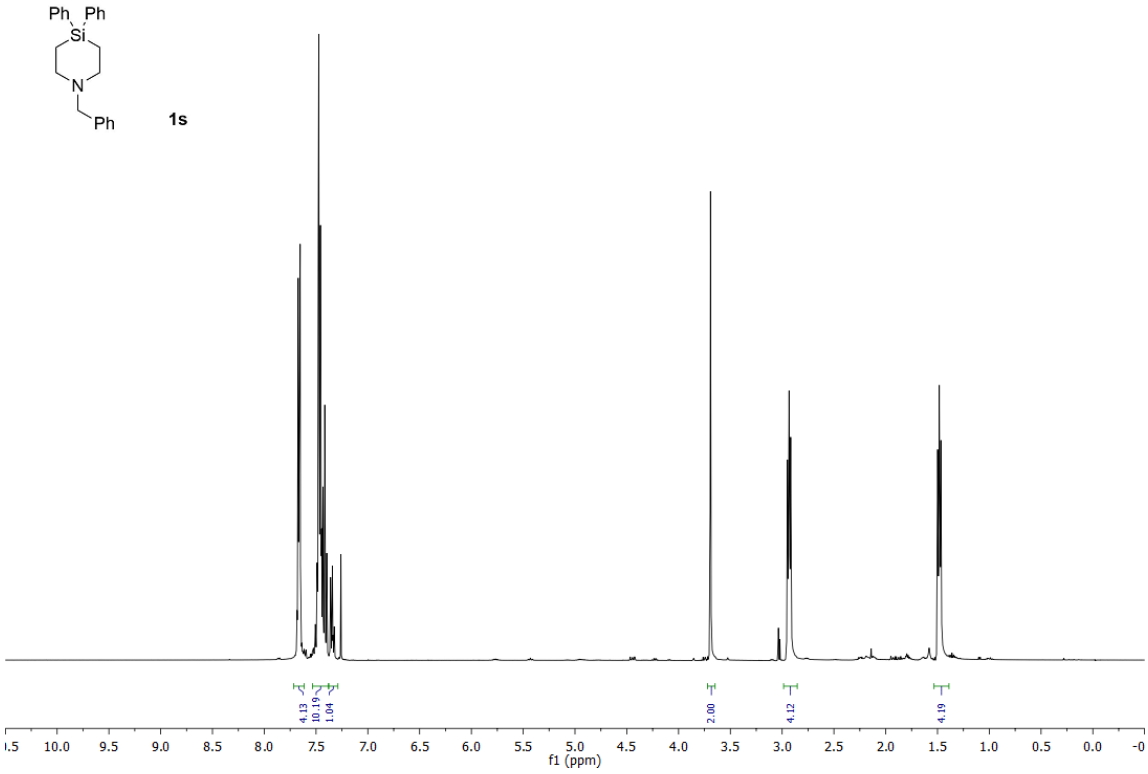

Boc
N
N
Ph
1p
154.73
137.79
129.09
128.21
127.10
79.46
63.02
52.62
44.05
43.10
28.39
f1 (ppm)

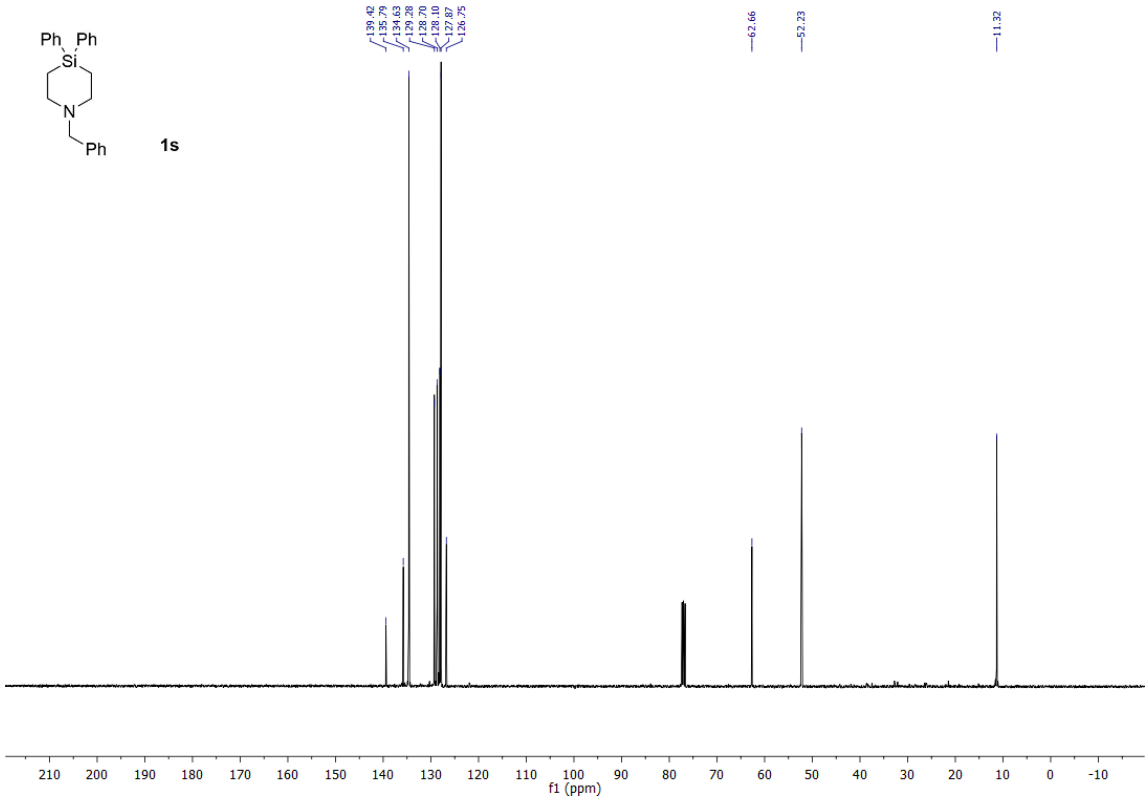

1q
3.80
0.93
3.93
2.00
3.87
f1 (ppm)

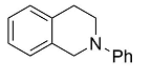

1q
137.52
128.88
127.97
126.85
66.70
63.17
53.35
f1 (ppm)


S
N
Ph
1r
3.73
1.08
2.00
8.03
f1 (ppm)


S
N
Ph
1r
137.99
128.94
128.16
127.00
63.61
54.84
27.95
f1 (ppm)

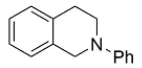

Ph
Ph
Si
N
Ph
1s
4.13
10.19
1.04
2.00
4.12
4.19
f1 (ppm)


Ph
Ph
Si
N
Ph
1s
139.42
135.79
134.63
129.28
128.70
128.10
127.87
126.75
62.66
52.23
11.32
f1 (ppm)


N
Ph

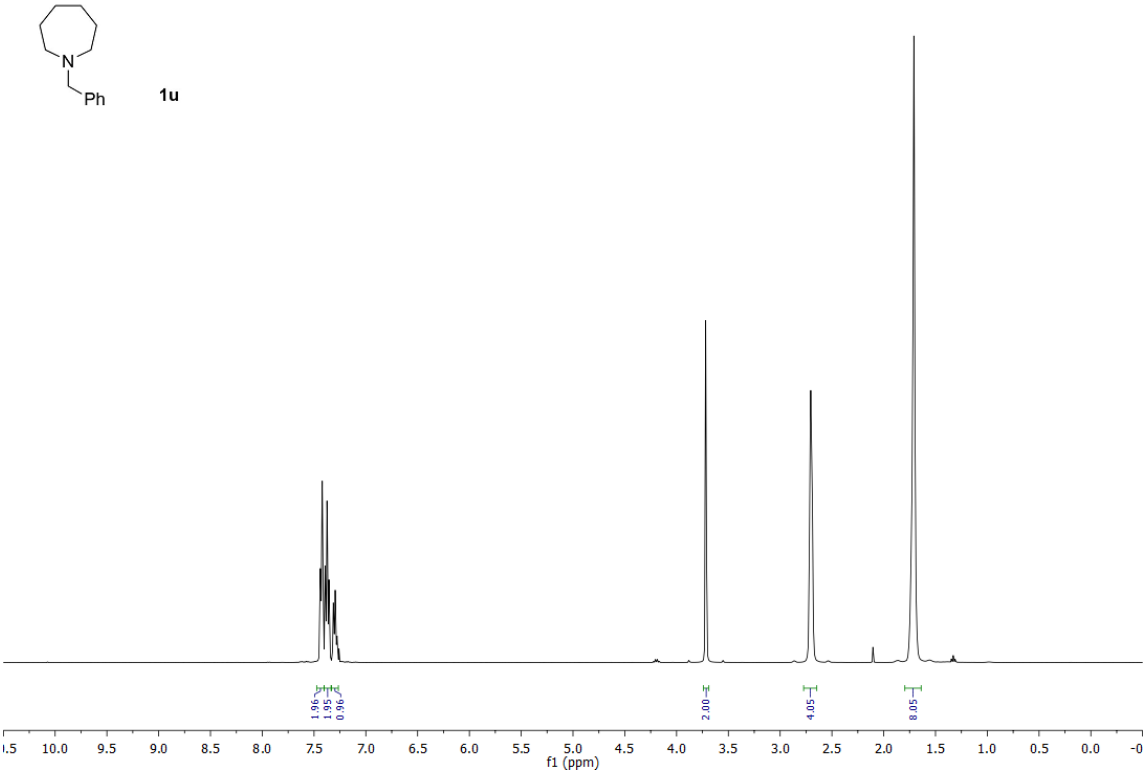
1t

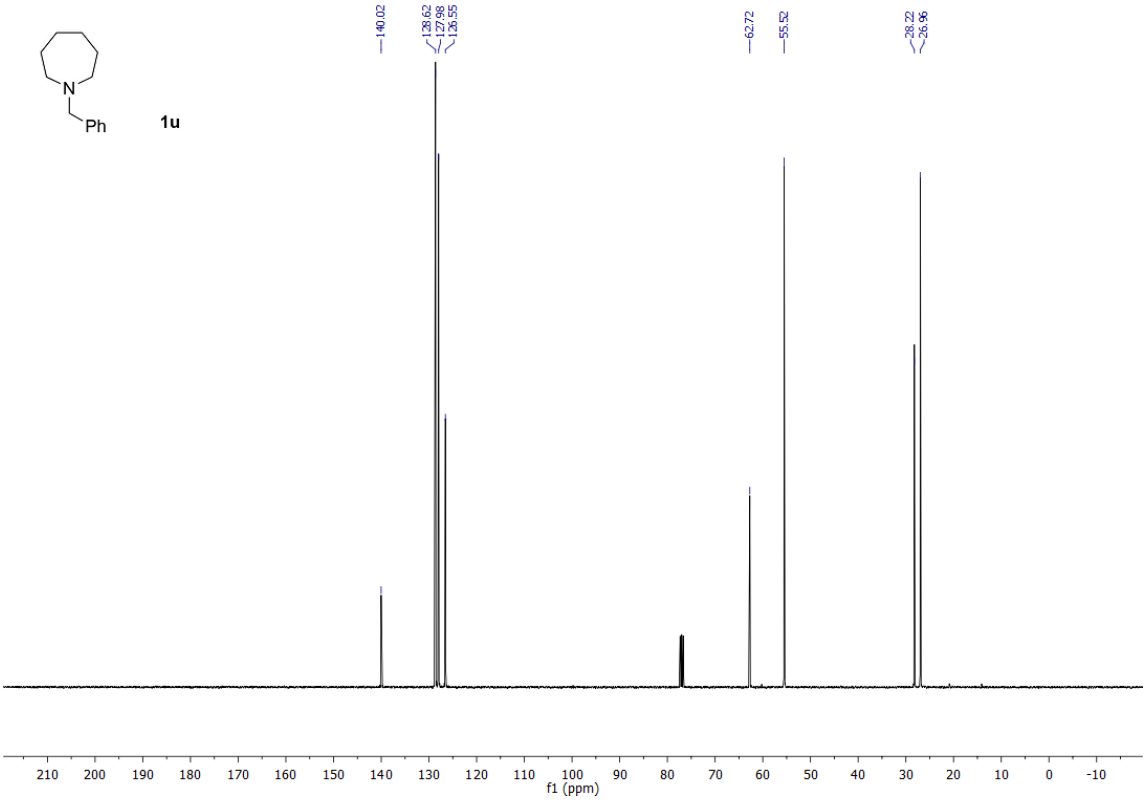
1.90
3.94
1.99
0.97
2.00
2.00
2.00
f1 (ppm)

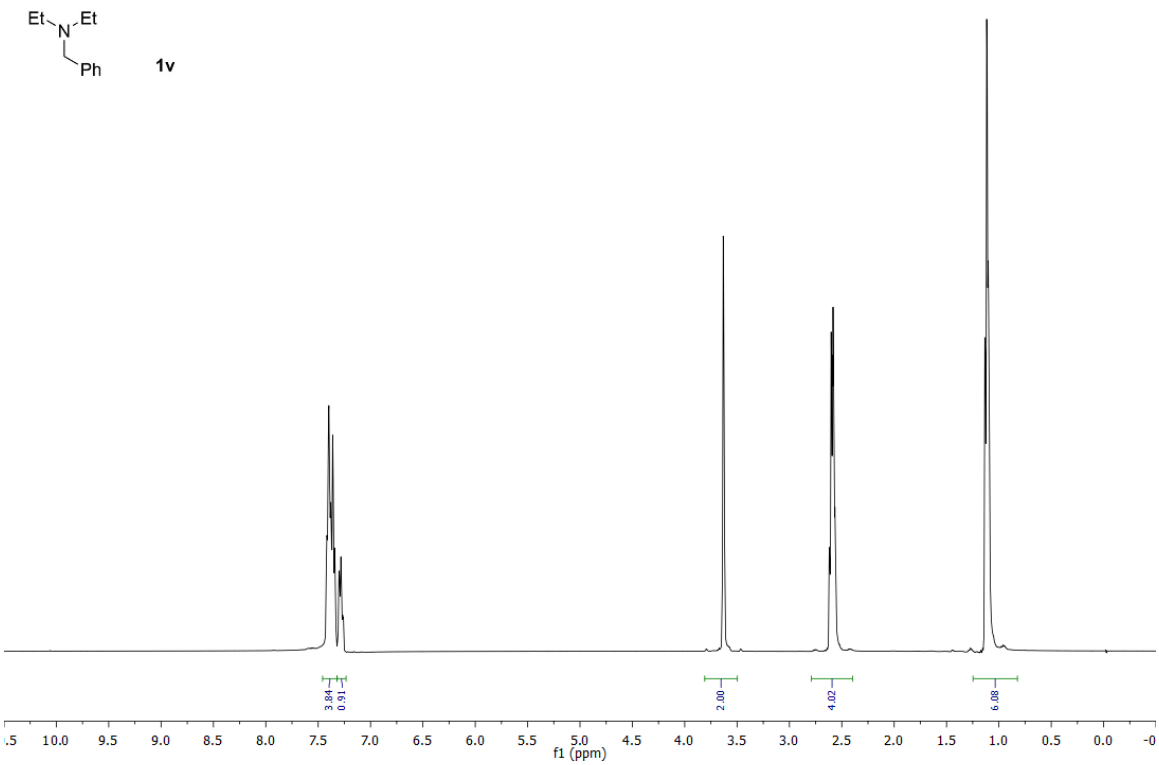

N
Ph

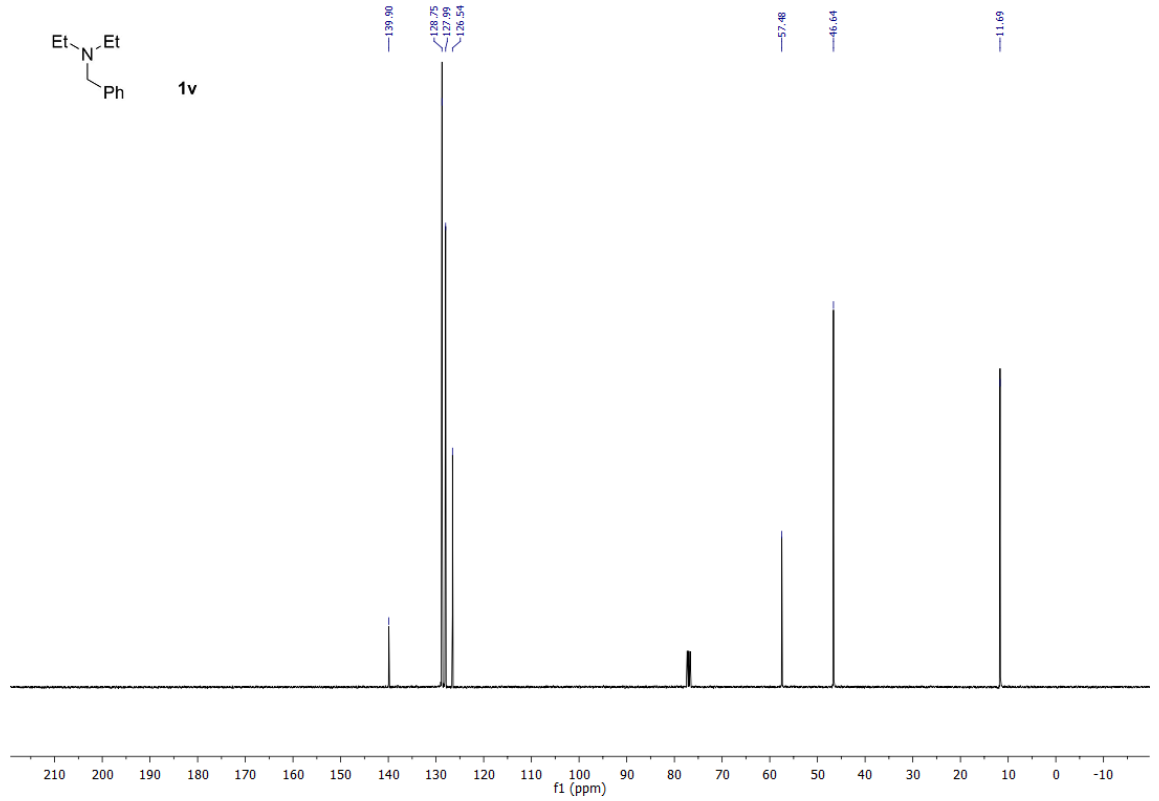
1t

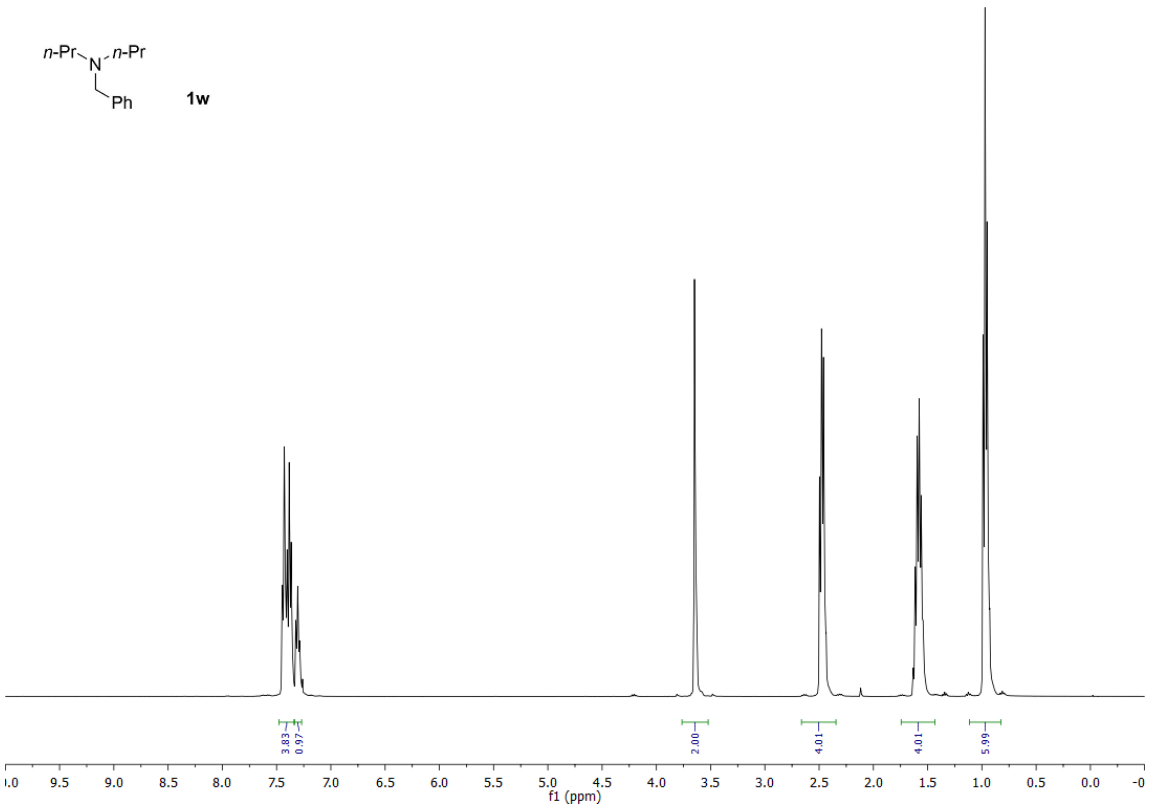
150.50
134.83
134.42
129.16
128.48
126.50
126.29
125.99
118.64
115.11
50.71
46.50
29.09
f1 (ppm)

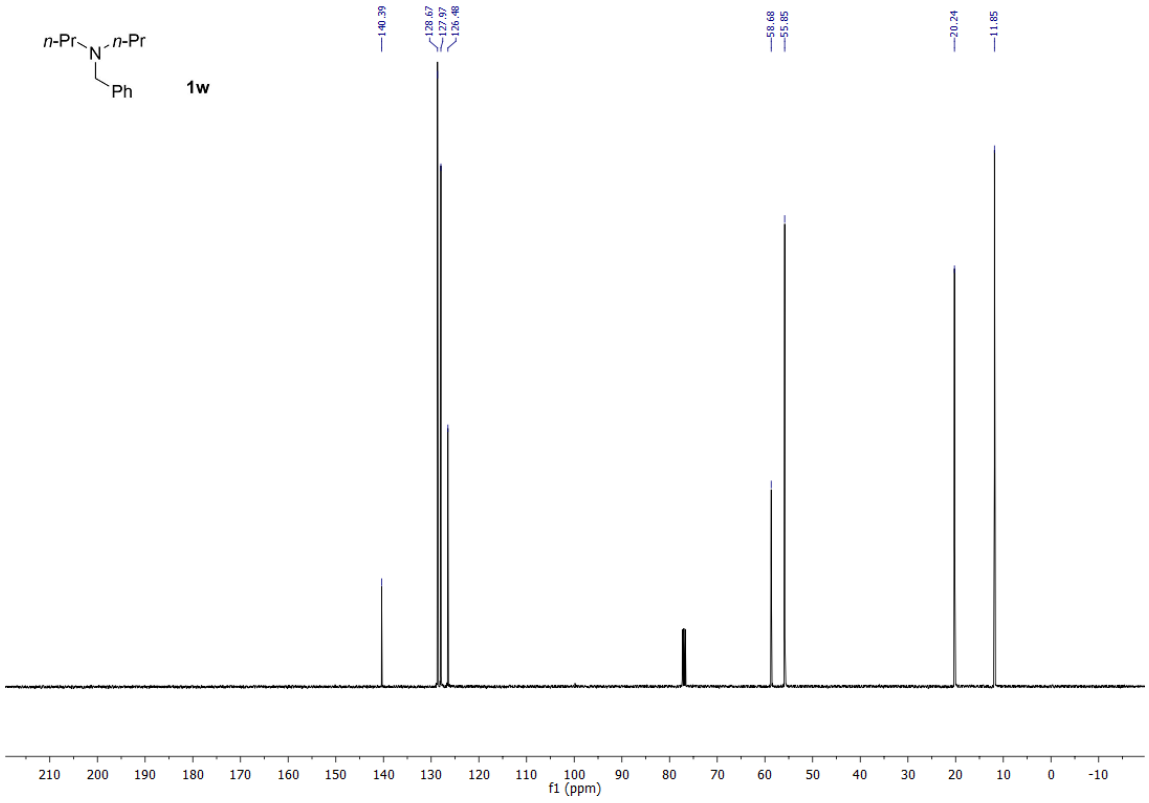

N
Ph
1u
1.96
1.95
0.96
2.00
4.05
8.05
f1 (ppm)

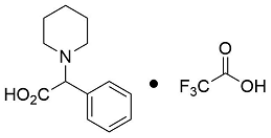

N
Ph
1u
140.02
128.62
127.98
126.55
62.72
55.52
28.22
26.96
f1 (ppm)


Et
N
Et
Ph
1v
3.84
0.91
2.00
4.02
6.08
f1 (ppm)

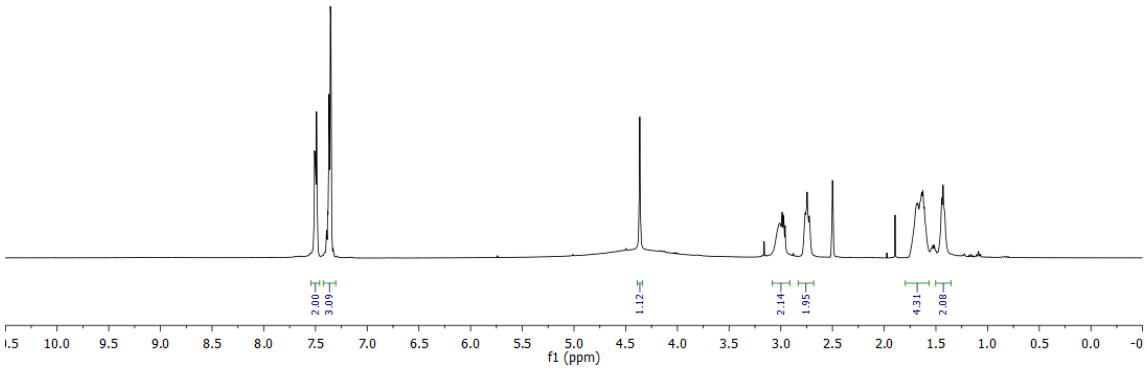

Et
N
Et
Ph
1v
139.90
128.75
127.99
126.54
57.48
46.64
11.69
f1 (ppm)

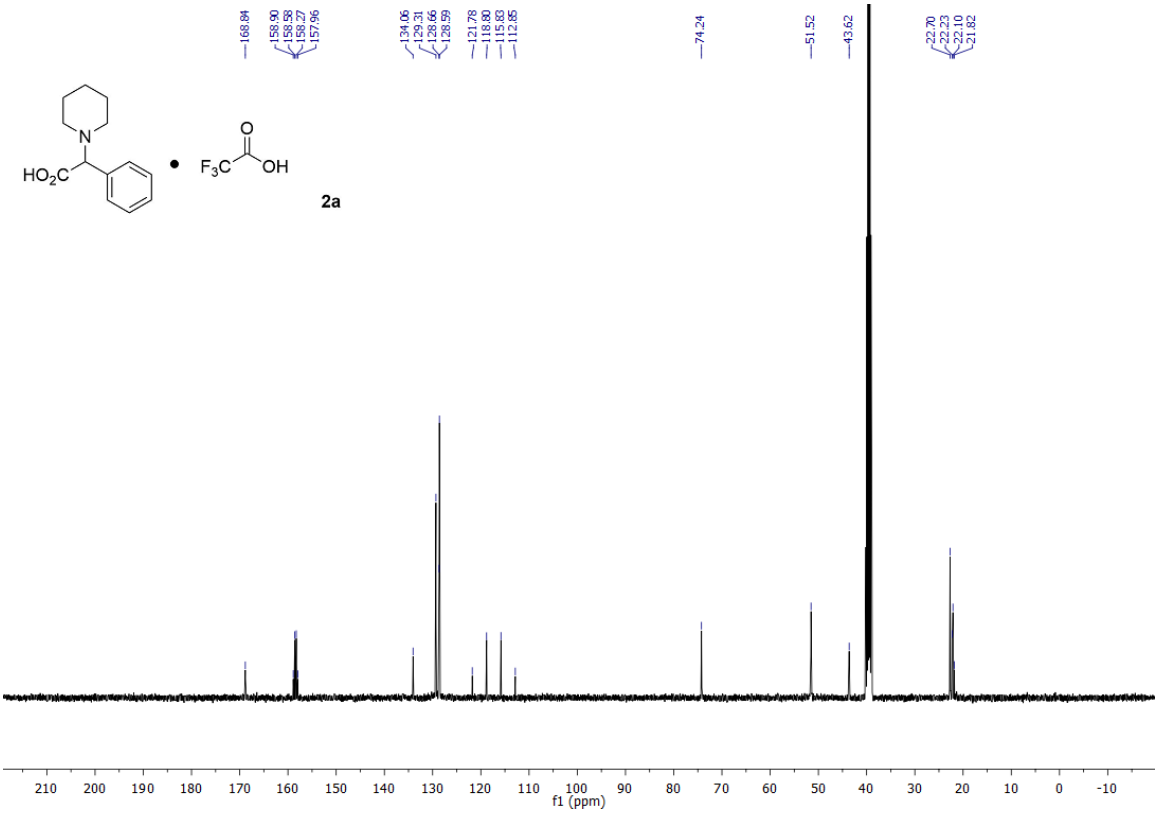

n-Pr
N
n-Pr
Ph
1w
3.83
0.97
2.00
4.01
4.01
5.99
f1 (ppm)


n-Pr
N
n-Pr
Ph
1w
140.39
128.67
127.97
126.48
58.68
55.85
20.24
11.85
f1 (ppm)

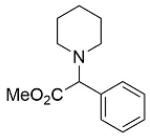


2a


2.00
3.09
1.12
2.14
1.95
4.31
2.08
f1 (ppm)

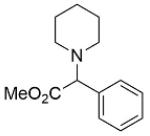

168.84
158.90
158.58
158.27
157.96
134.06
129.31
128.66
128.59
121.78
118.80
115.83
112.85
74.24
51.52
43.62
22.70
22.23
22.10
21.82
f1 (ppm)

2a


N
MeO2C

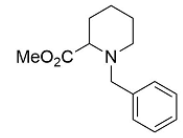
S1

2.06
3.10
1.00
3.10
4.15
4.31
2.21
f1 (ppm)


N
MeO2C

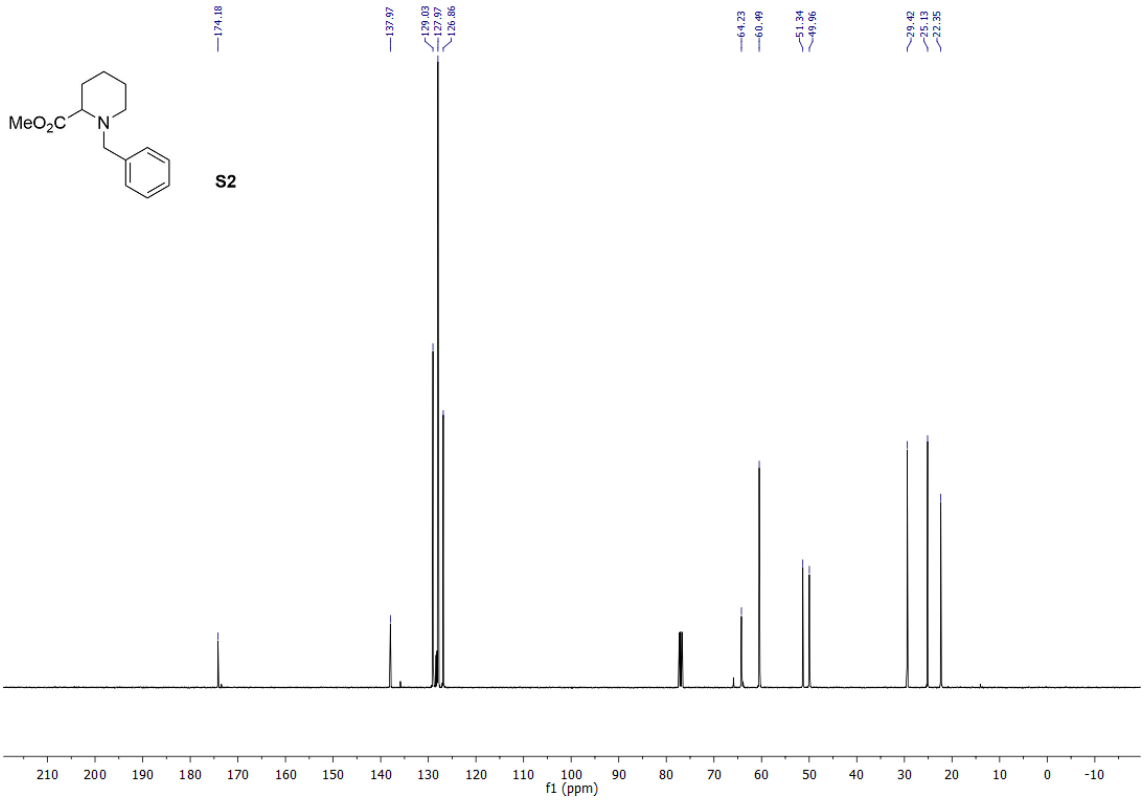
S1

172.24
136.12
128.72
128.36
128.07
74.91
52.34
51.80
25.70
24.25
f1 (ppm)


MeO2C
N

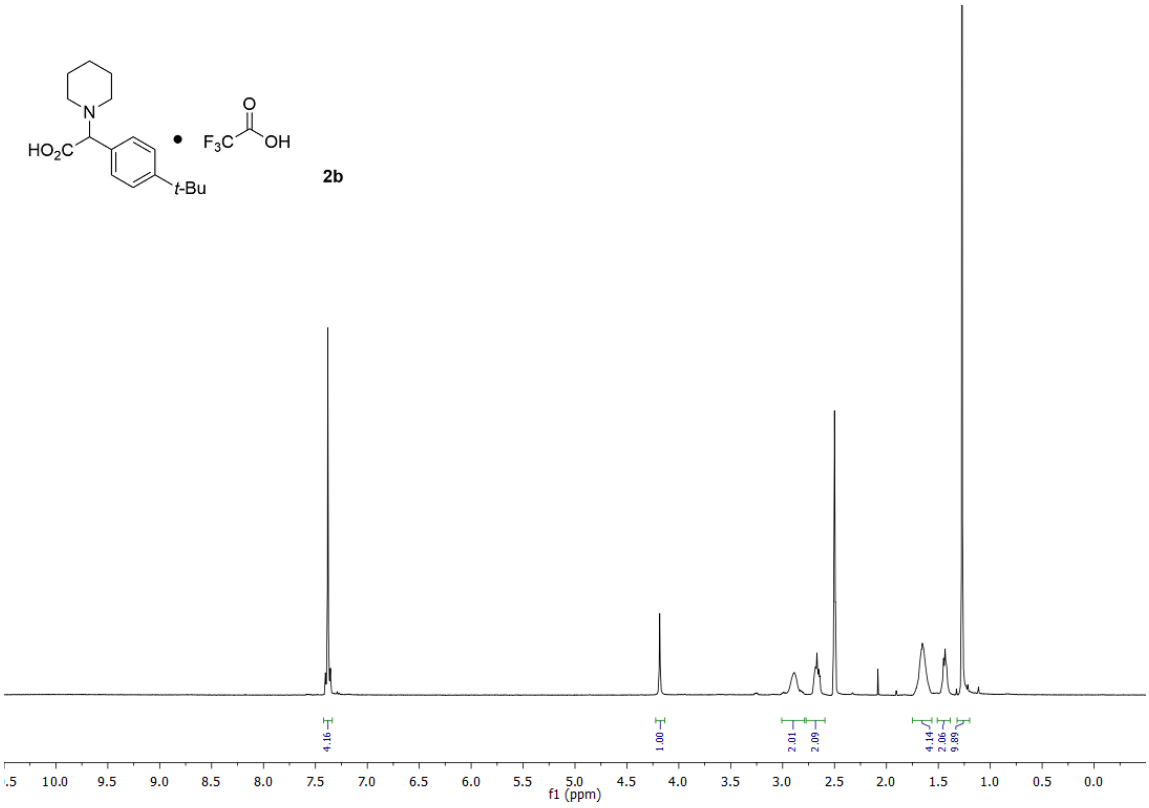
S2

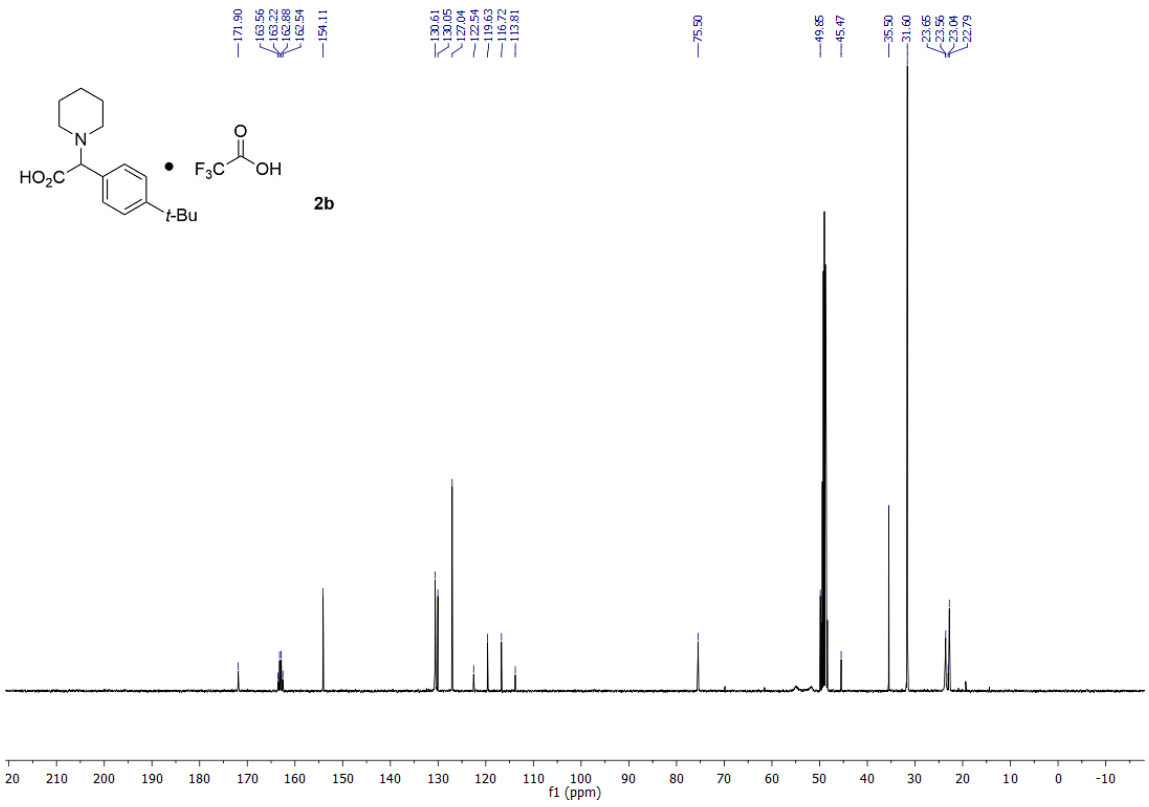
5.16
1.00
2.75
0.98
0.92
0.99
0.97
1.99
2.98
1.02
f1 (ppm)

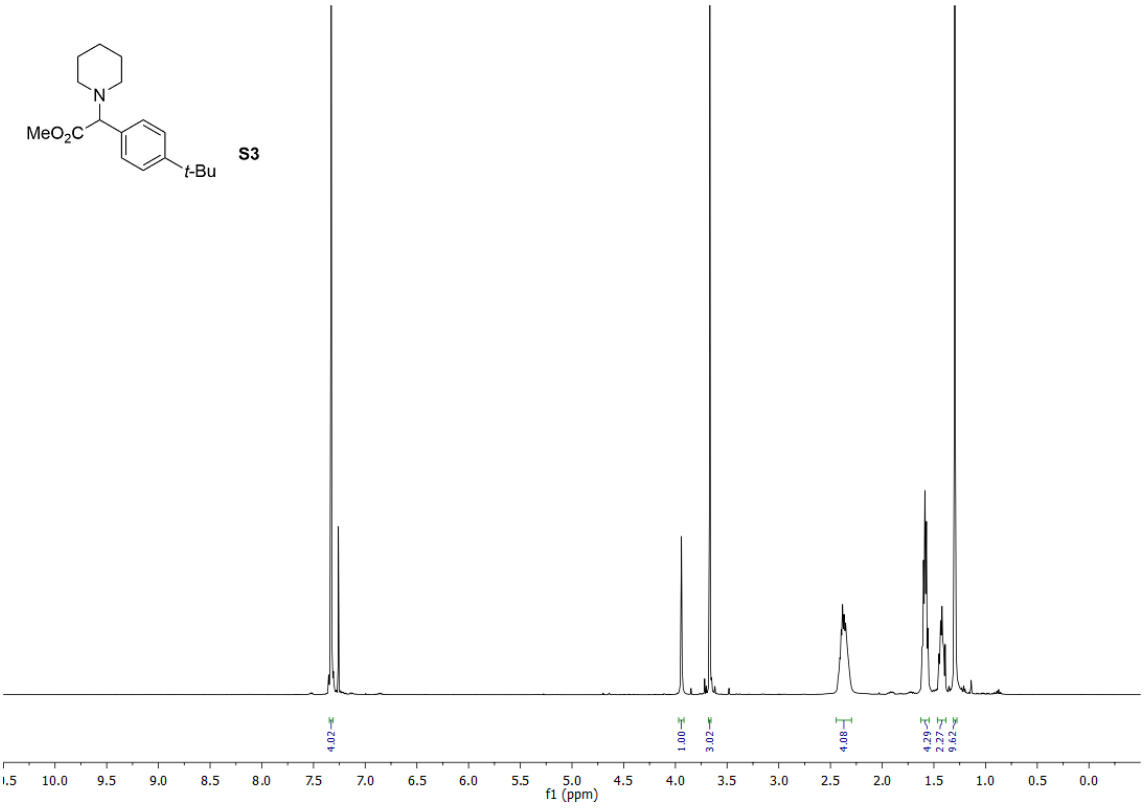

174.18
137.97
129.03
127.97
126.86
64.23
60.49
51.34
49.96
29.42
25.13
22.35
f1 (ppm)

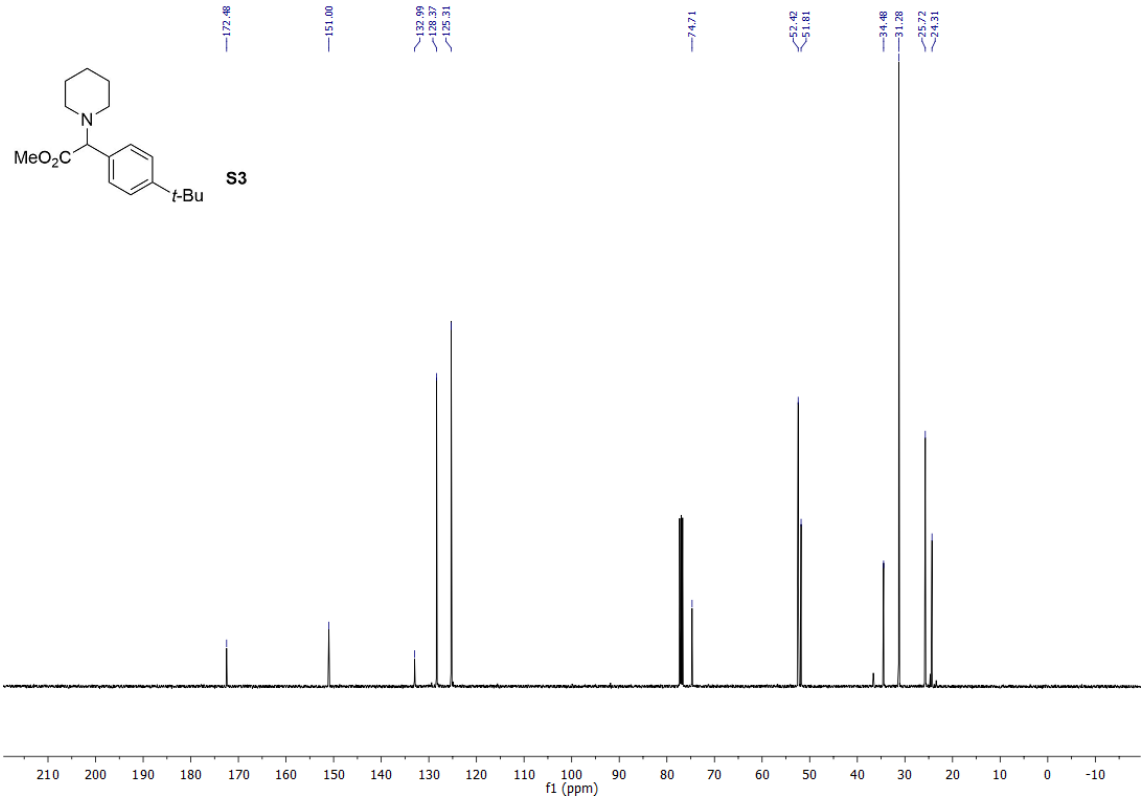
MeO2C
N

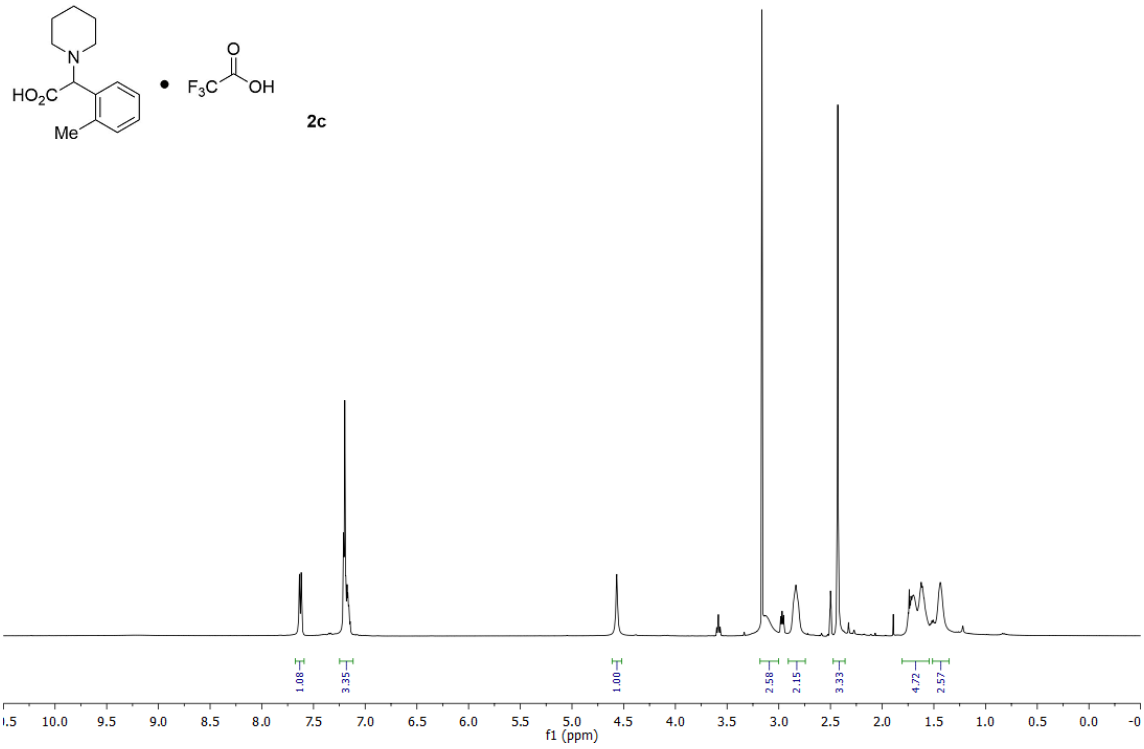
S2

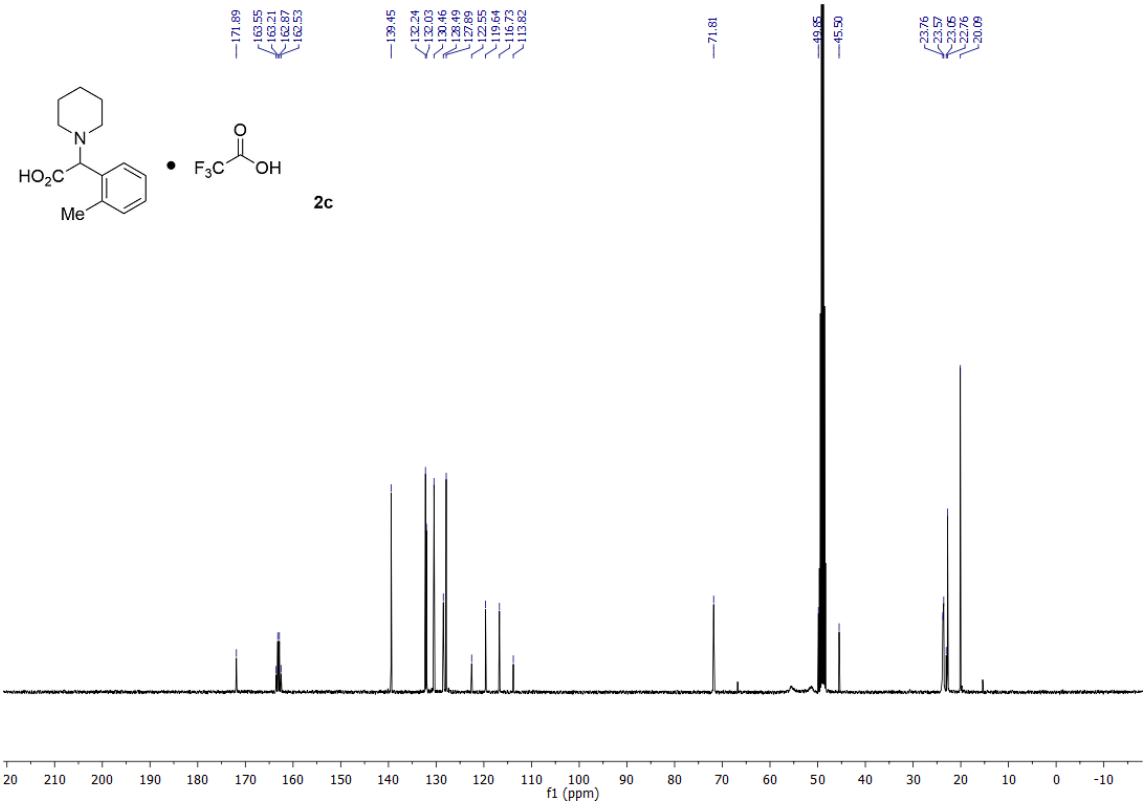

HO2C
F3C
OH
t-Bu
2b
4.16
1.00
2.01
2.09
4.14
2.06
9.89
f1 (ppm)

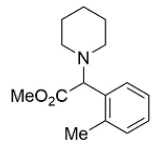

171.90
163.56
163.22
162.88
162.54
154.11
130.61
130.05
127.04
122.54
119.63
116.72
113.81
75.50
49.85
45.47
35.50
31.60
23.65
23.56
23.04
22.79
HO2C
F3C
OH
t-Bu
2b
f1 (ppm)


MeO2C
t-Bu
S3
4.02
1.00
3.02
4.08
4.29
2.27
9.62
f1 (ppm)


172.48
151.00
132.99
128.37
125.31
74.71
52.42
51.01
34.48
31.28
25.72
24.31
MeO2C
t-Bu
S3
f1 (ppm)

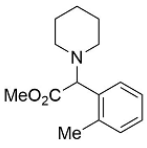

HO2C
Me
F3C
OH
2c
1.08
3.35
1.00
2.58
2.15
3.33
4.72
2.57
f1 (ppm)


171.89
163.55
163.21
162.87
162.53
139.45
132.24
132.03
130.46
128.49
127.89
122.55
119.64
116.73
113.82
71.81
49.85
45.50
23.76
23.57
23.05
22.76
20.09
HO2C
Me
F3C
OH
2c
f1 (ppm)


N
MeO2C
Me

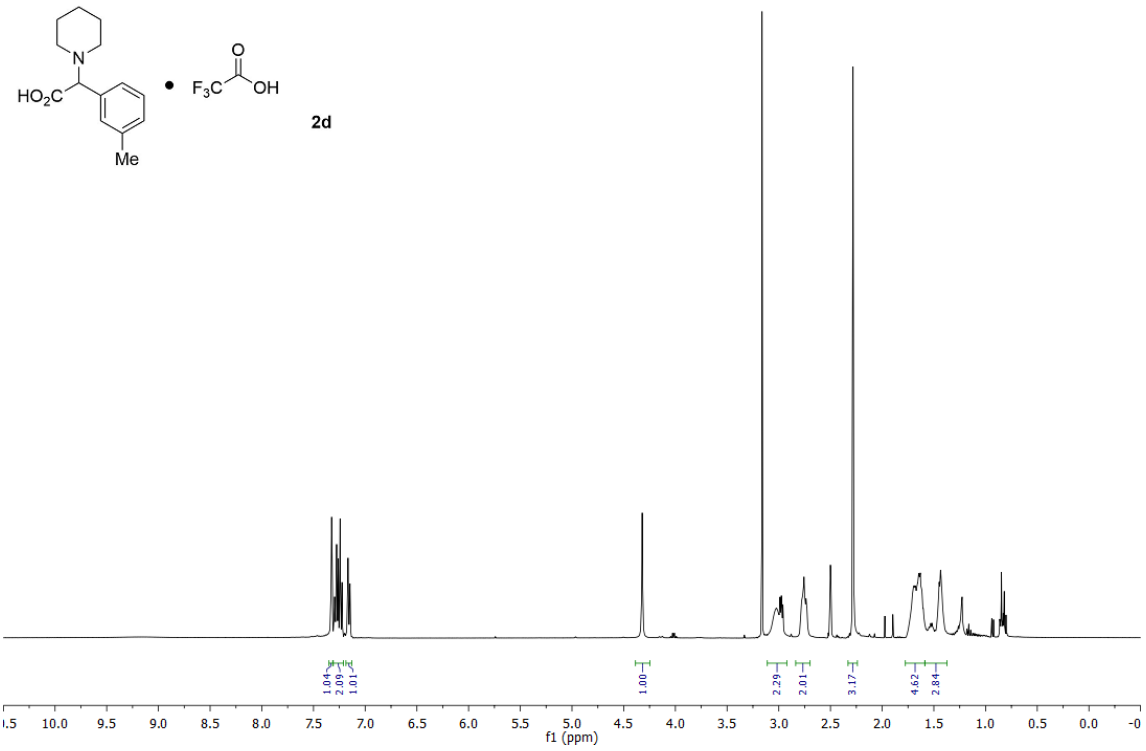
S4

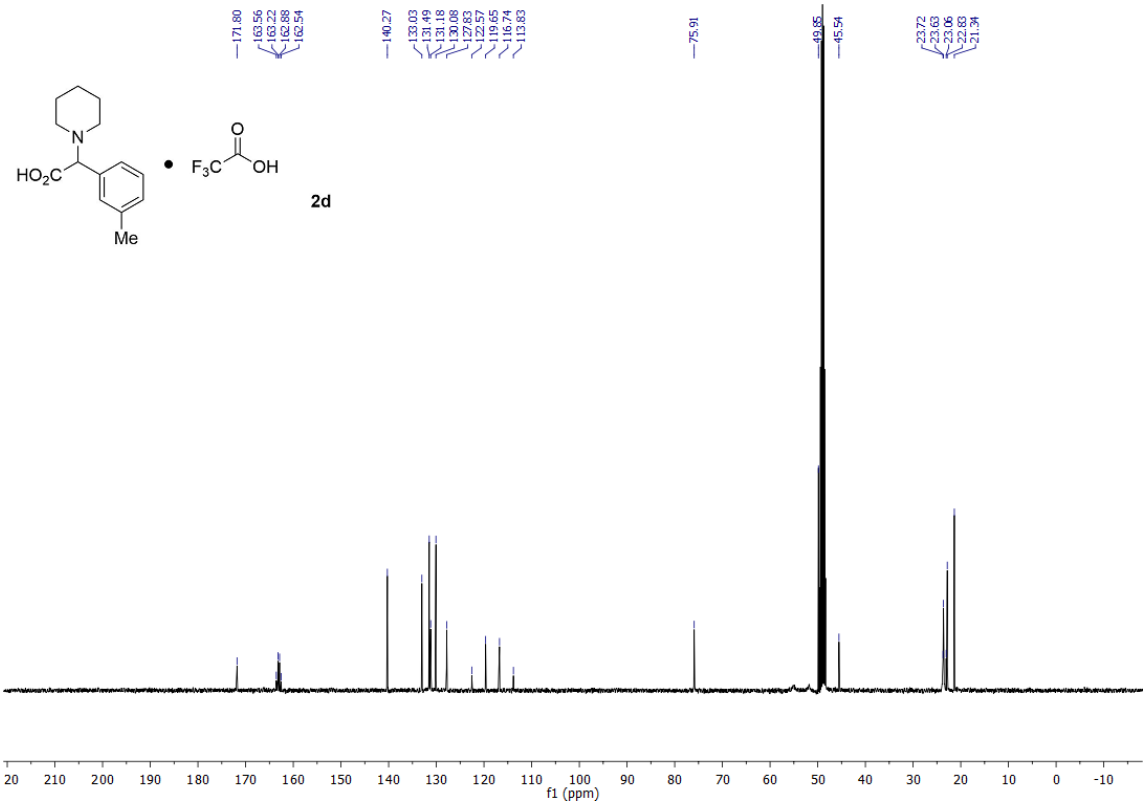
0.98
3.04
1.00
3.07
7.22
4.28
2.33
f1 (ppm)

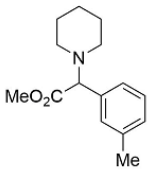

N
MeO2C
Me

S4

172.38
137.26
134.70
130.44
128.30
127.62
126.05
70.37
51.98
51.64
25.90
24.44
19.61
f1 (ppm)

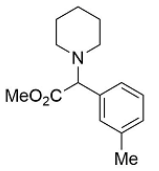

HO2C
N
Me
F3C
OH
O
2d
1.04
2.09
1.01
1.00
2.29
2.01
3.17
4.62
2.84
f1 (ppm)


171.80
163.56
163.22
162.88
162.54
140.27
133.03
131.49
131.18
130.08
127.83
122.57
119.65
116.74
113.83
75.91
49.85
45.54
23.72
23.63
23.06
22.83
21.34
HO2C
N
Me
F3C
OH
O
2d
f1 (ppm)


N
MeO2C
Me

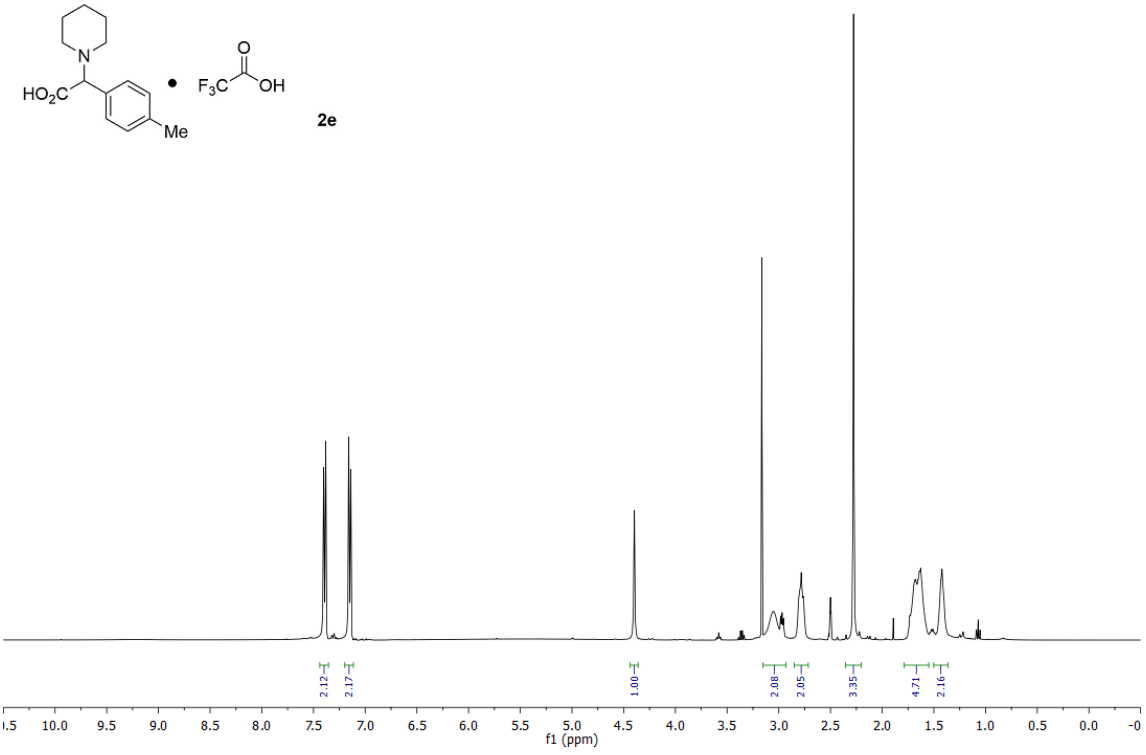
S5

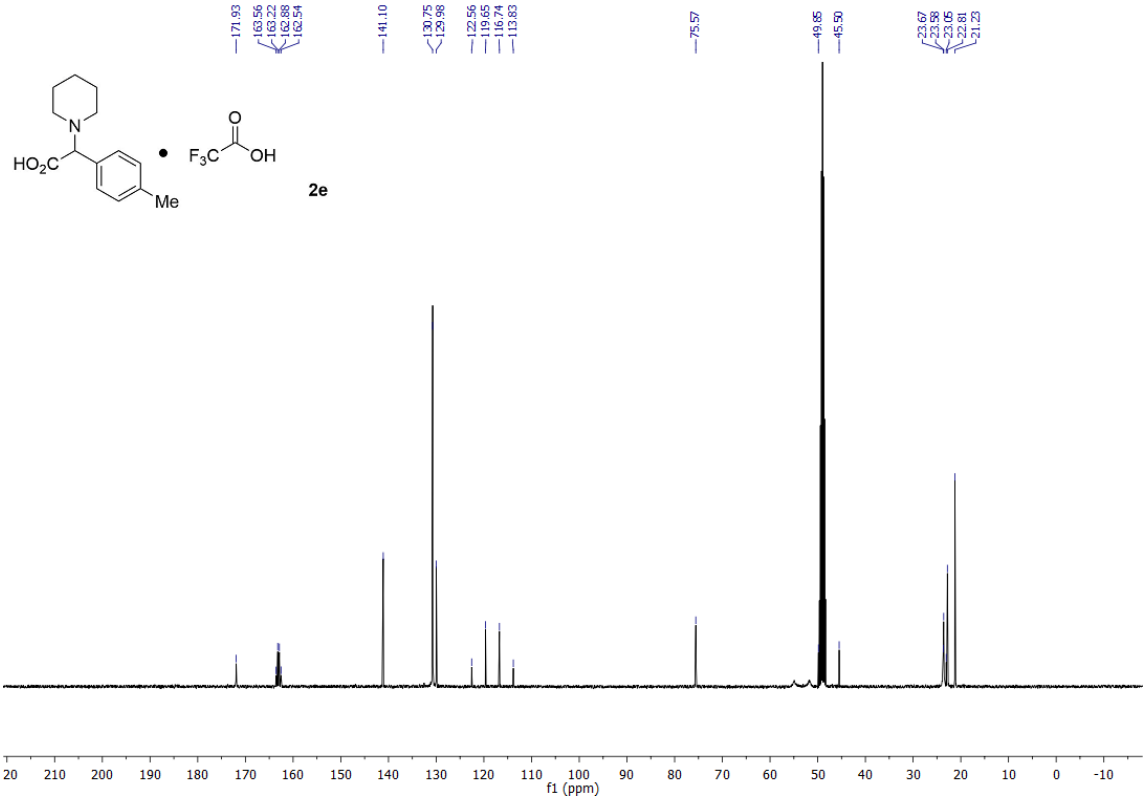
1.00
2.07
1.08
1.00
3.08
7.41
4.36
2.37
f1 (ppm)

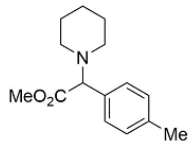

N
MeO2C
Me

S5

172.42
138.17
136.04
129.32
128.96
128.28
125.99
75.13
52.52
51.92
25.72
24.31
21.36
f1 (ppm)

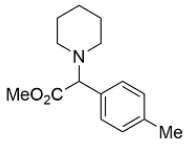

HO2C
N
Me
F3C
OH
O
2e
2.12
2.17
1.00
2.08
2.05
3.35
4.71
2.16
f1 (ppm)


171.93
163.56
163.22
162.88
162.54
141.10
130.75
129.98
122.56
119.65
116.74
113.83
75.57
49.85
45.50
23.67
23.58
23.05
22.81
21.23
HO2C
N
Me
F3C
OH
O
2e
f1 (ppm)


N
MeO2C
Me

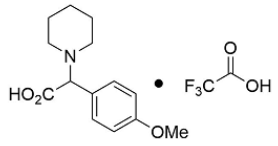
S6

2.10
2.15
1.00
3.04
7.57
4.45
2.29
f1 (ppm)

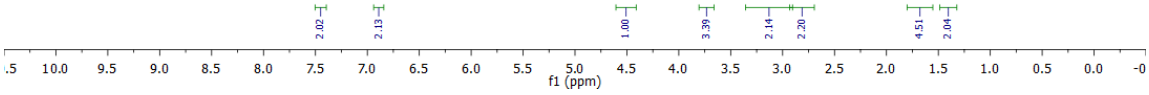

N
MeO2C
Me

S6

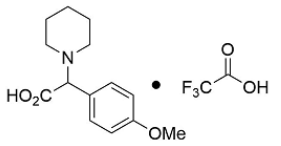
172.48
137.91
133.13
129.13
128.70
77.73
52.42
51.86
25.75
24.32
21.11
f1 (ppm)


HO2C
N
OMe
F3C
O
OH

2f

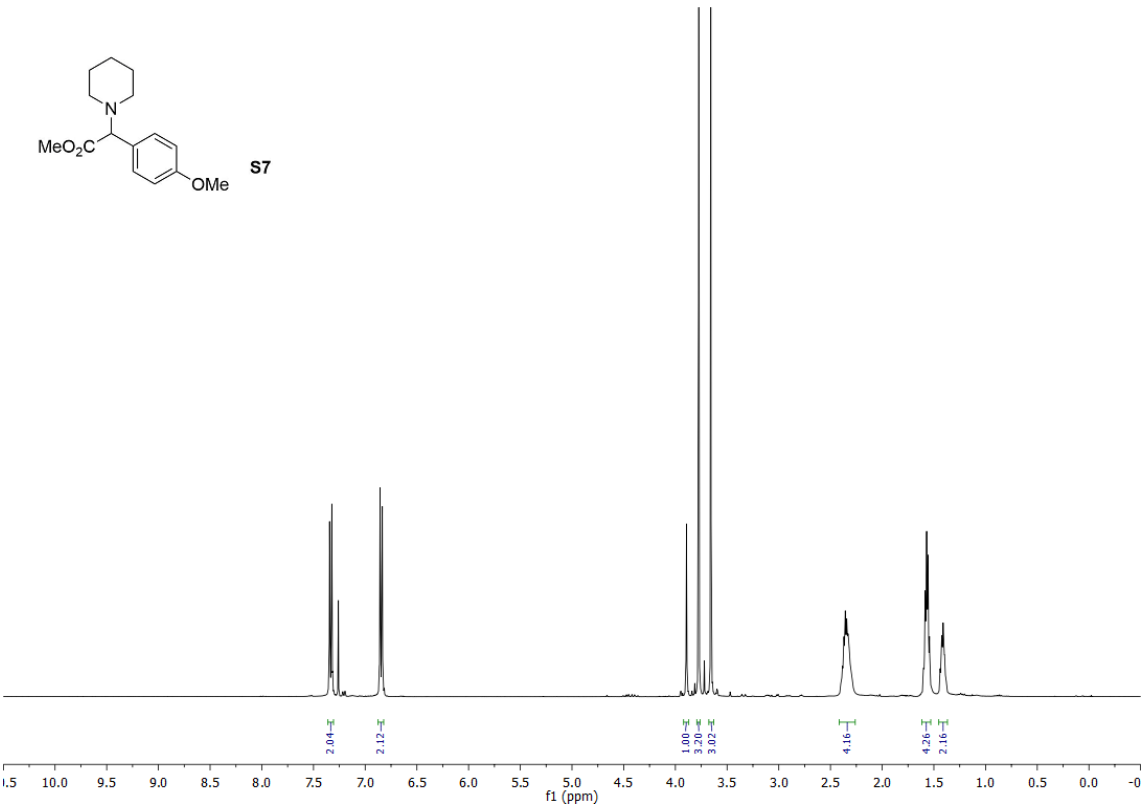

2.02
2.13
1.00
3.39
2.14
2.20
4.51
2.04
f1 (ppm)

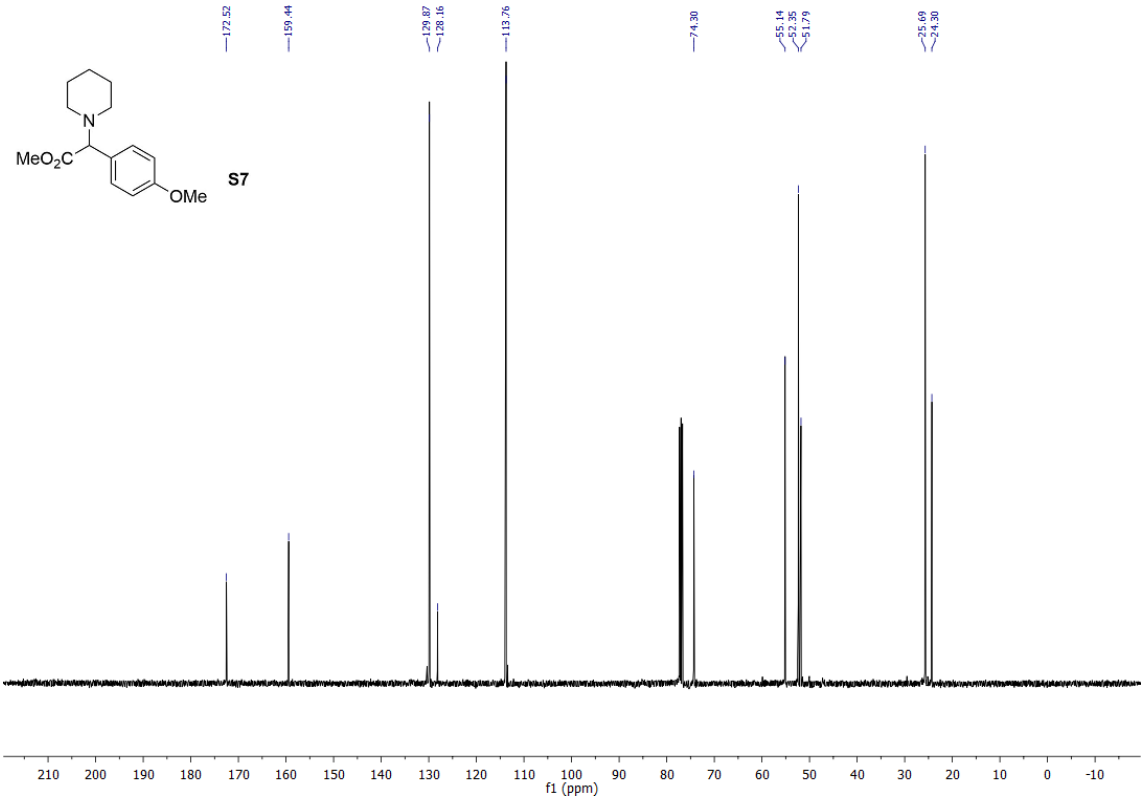
172.15
163.53
163.18
162.84
162.50
162.18
132.28
124.58
122.50
119.59
116.68
115.40
113.77
75.25
55.82
49.85
45.49
23.68
23.56
23.03
22.80

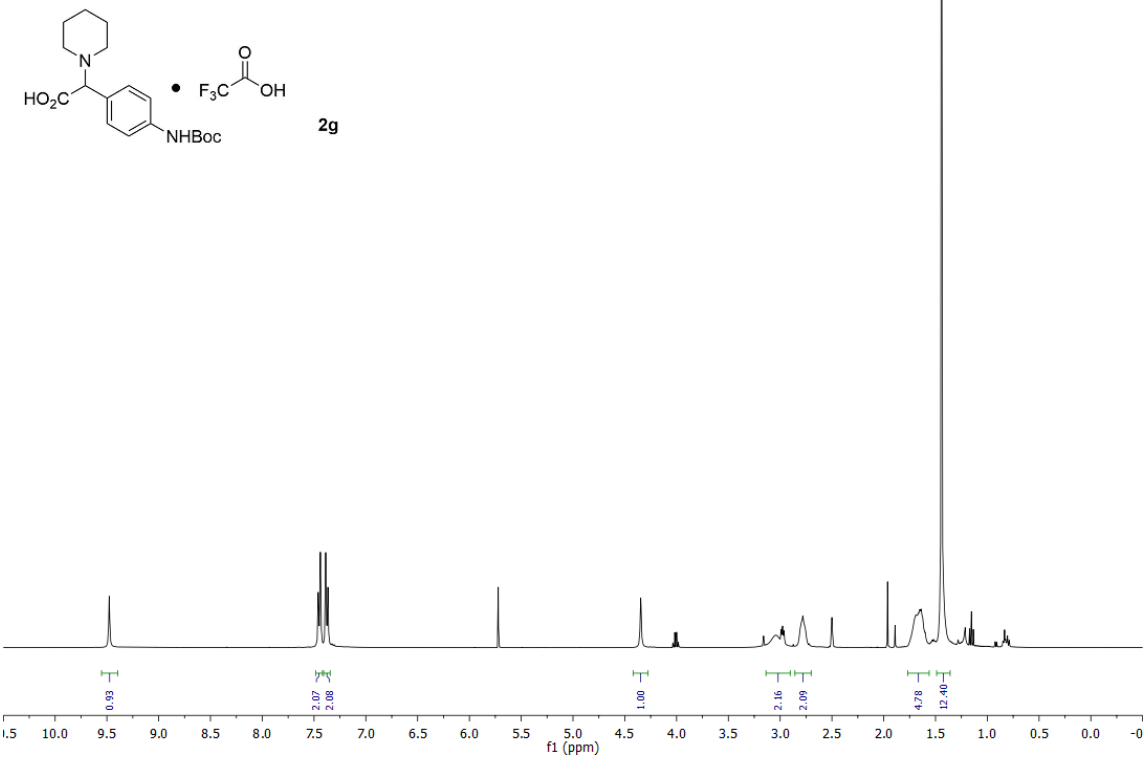

HO2C
N
OMe
F3C
O
OH

2f

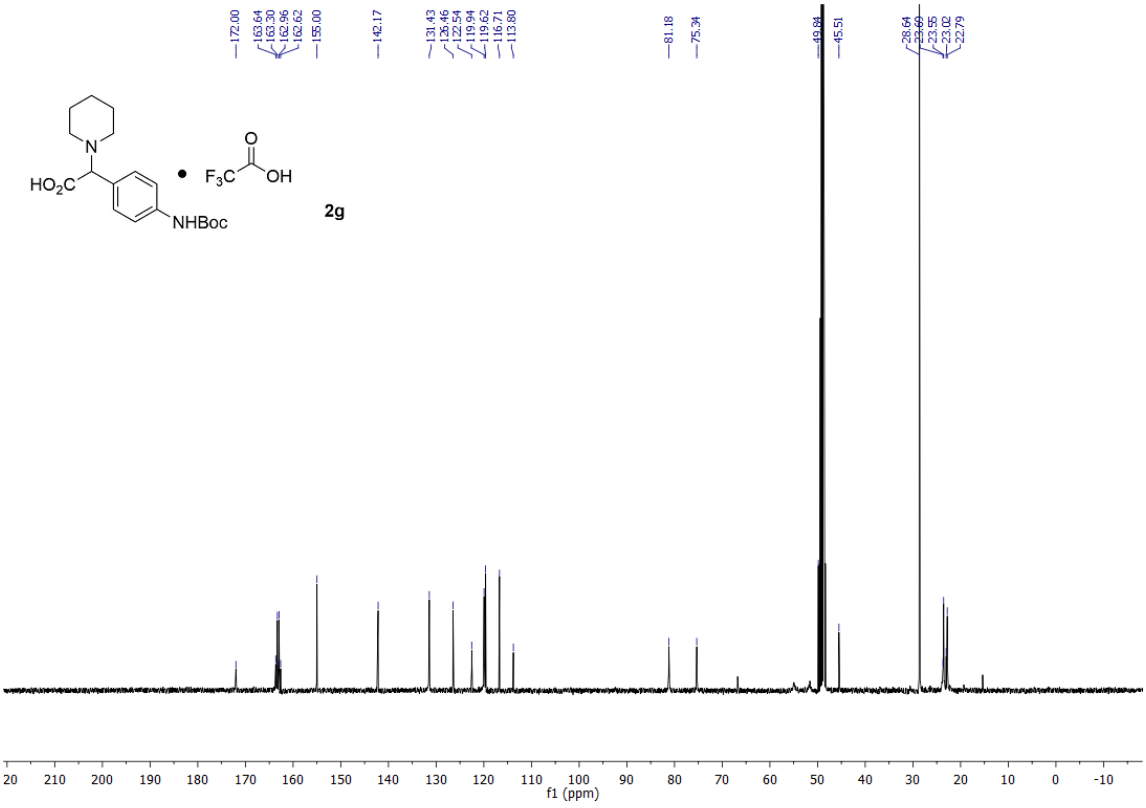
f1 (ppm)


MeO2C
OMe
S7
2.04
2.12
1.00
3.20
3.02
4.16
4.26
2.16
f1 (ppm)

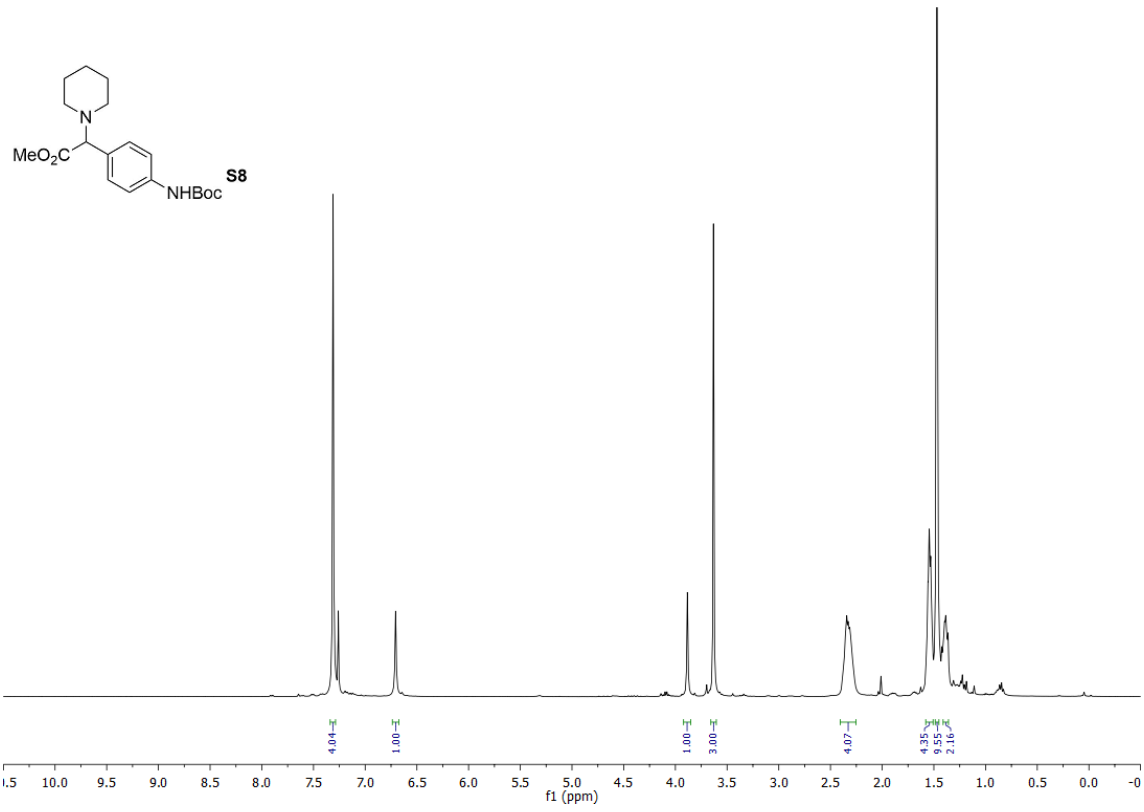

172.52
159.44
129.87
128.16
113.76
74.30
55.14
53.35
51.79
25.69
24.30
MeO2C
OMe
S7
f1 (ppm)

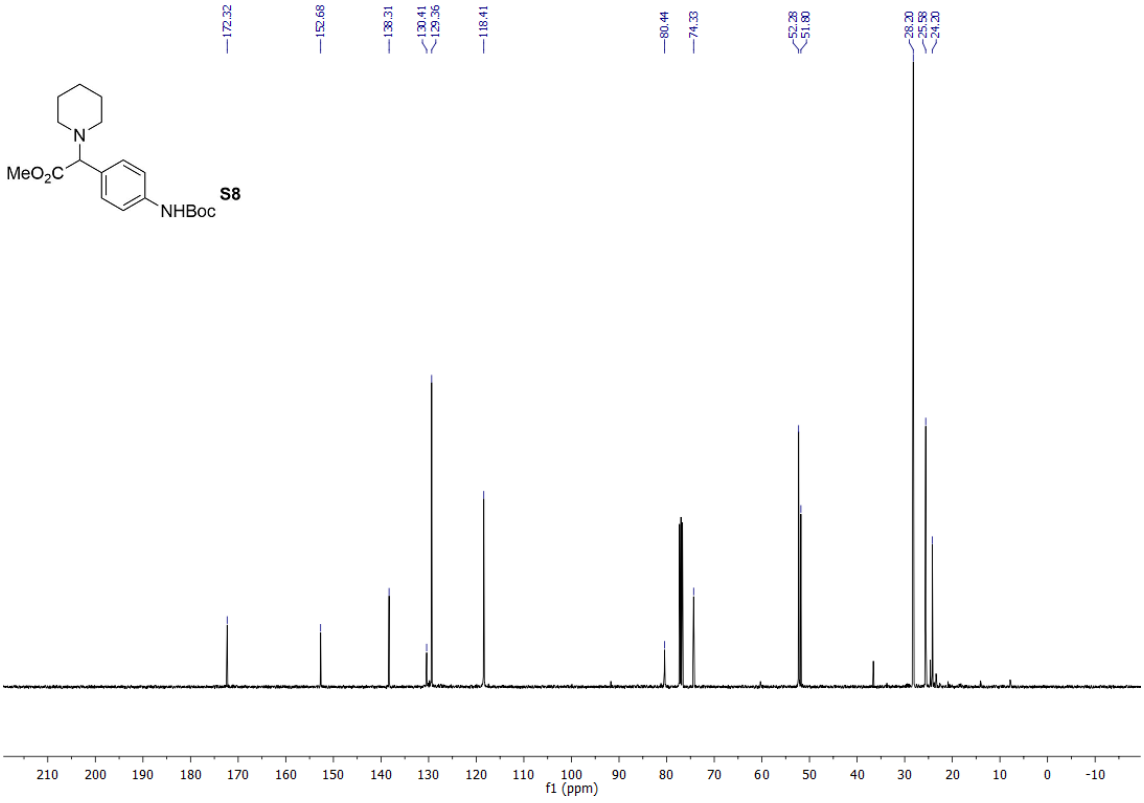

HO2C
F3C
OH
NHBoc
0.93
2.07
2.08
1.00
2.16
2.09
4.78
12.40
f1 (ppm)

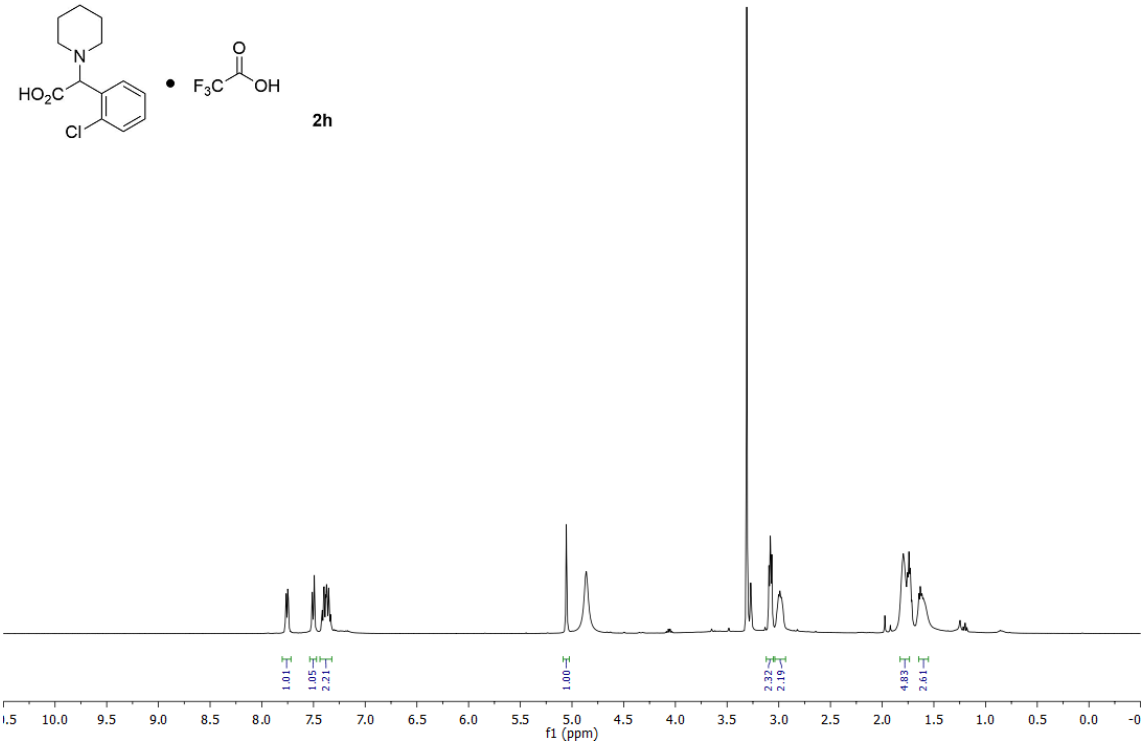
2g

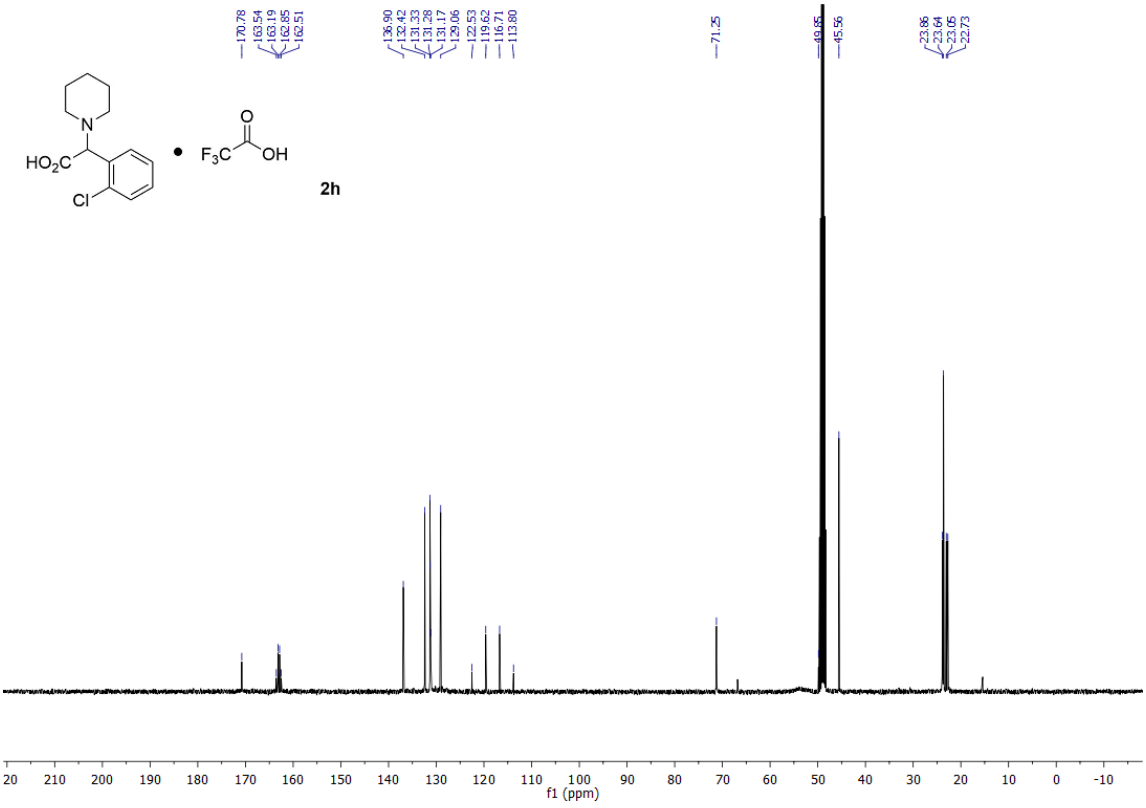

172.00
163.64
163.30
162.96
162.62
155.00
142.17
131.43
126.46
123.54
122.94
119.62
116.71
113.80
81.18
75.34
49.84
45.51
28.64
28.60
23.95
23.70
22.79
f1 (ppm)

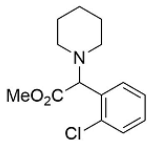
2g


MeO2C
N
NHBoc
S8
4.04
1.00
1.00
3.00
4.07
4.35
9.55
2.16
f1 (ppm)


172.32
152.68
138.31
130.41
129.36
118.41
80.44
74.33
52.28
51.80
28.20
25.58
24.20
MeO2C
N
NHBoc
S8
f1 (ppm)

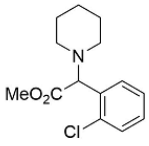

HO2C
Cl
F3C
OH
2h
1.01
1.05
2.21
1.00
2.32
2.19
4.83
2.61
f1 (ppm)


170.78
163.54
163.19
162.85
162.51
136.90
132.42
131.33
131.28
131.17
129.06
122.53
119.62
116.71
113.80
71.25
49.85
45.56
23.86
23.64
23.05
22.73
HO2C
Cl
F3C
OH
2h
f1 (ppm)


N
MeO2C
Cl

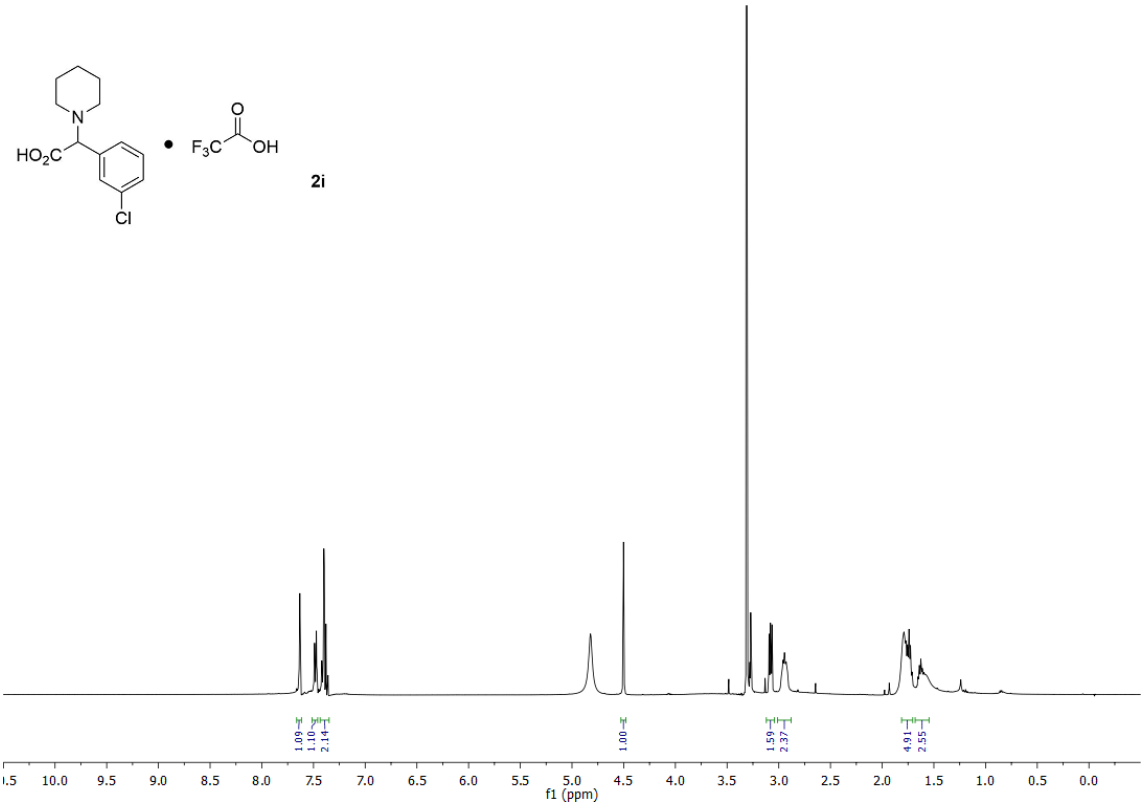
S9

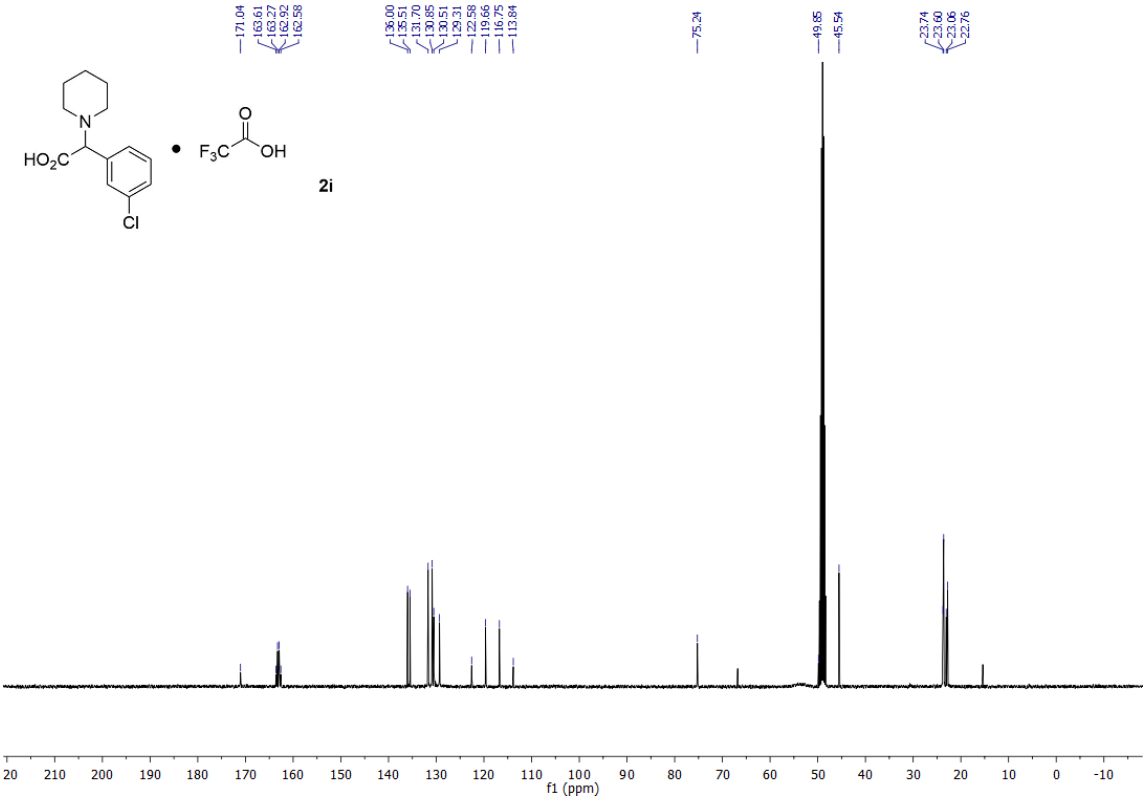
1.00
1.01
2.51
1.00
3.19
2.08
2.18
4.41
2.28
f1 (ppm)

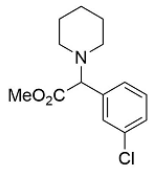

N
MeO2C
Cl

S9

171.51
134.60
134.20
129.96
129.54
129.00
126.92
69.60
52.19
51.93
25.92
24.28
f1 (ppm)

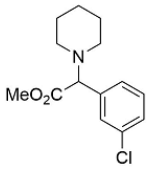

HO2C
Cl
F3C
OH
2i
1.09
1.10
2.14
1.00
1.59
2.37
4.91
2.55
f1 (ppm)


171.04
163.61
163.27
162.92
162.58
136.00
135.51
131.70
130.85
130.51
129.31
122.58
119.66
116.75
113.84
75.24
49.85
45.54
23.74
23.60
23.06
22.76
HO2C
Cl
F3C
OH
2i
f1 (ppm)


N
MeO2C
Cl

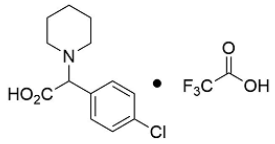
S10

1.11
3.48
1.00
3.17
4.13
4.31
2.24
f1 (ppm)

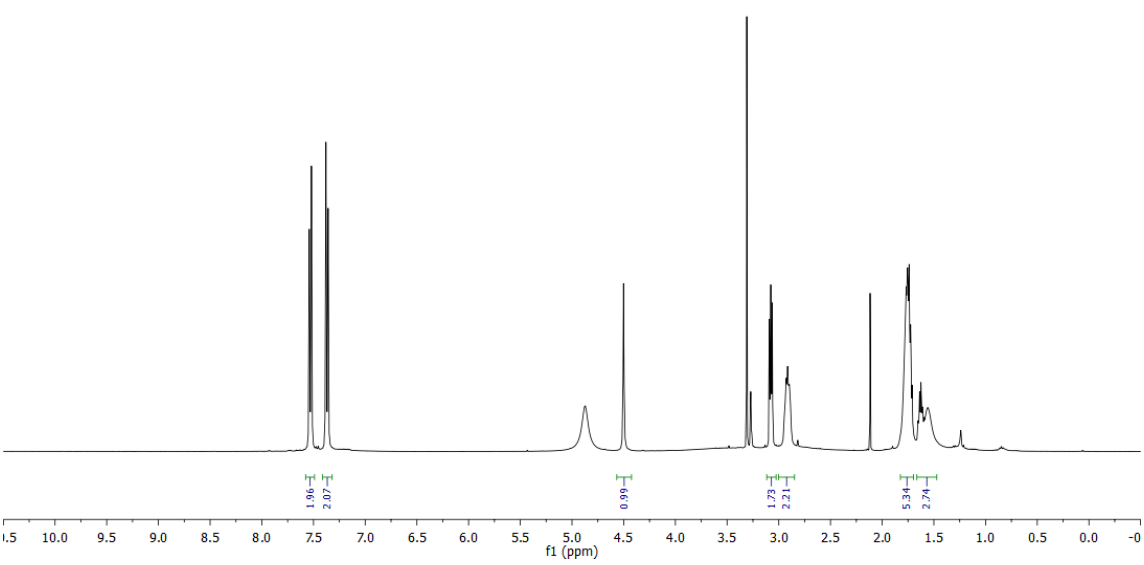

N
MeO2C
Cl

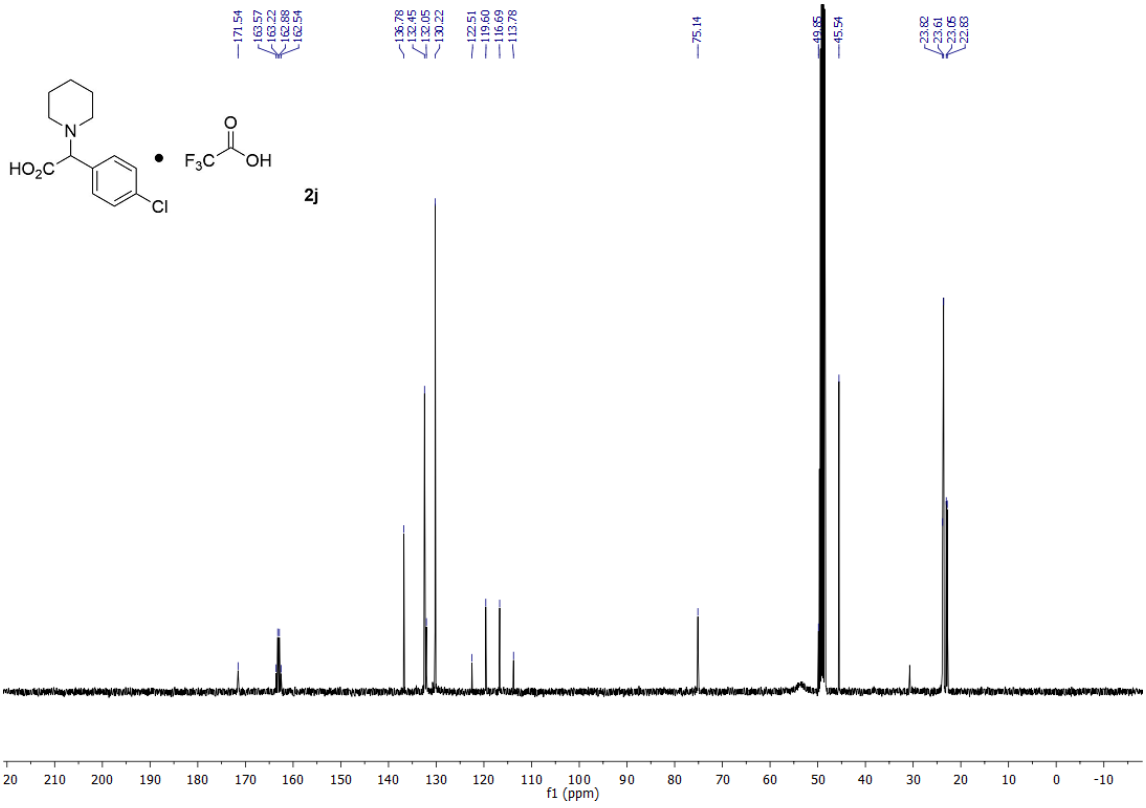
S10

171.71
138.38
134.40
129.66
128.79
128.38
126.94
74.36
52.33
52.05
25.77
24.24
f1 (ppm)



2j


1.96
2.07
0.99
1.73
2.21
5.34
2.74
f1 (ppm)


171.54
163.57
163.22
162.88
162.54
136.78
132.45
132.05
130.22
122.51
119.60
116.69
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75.14
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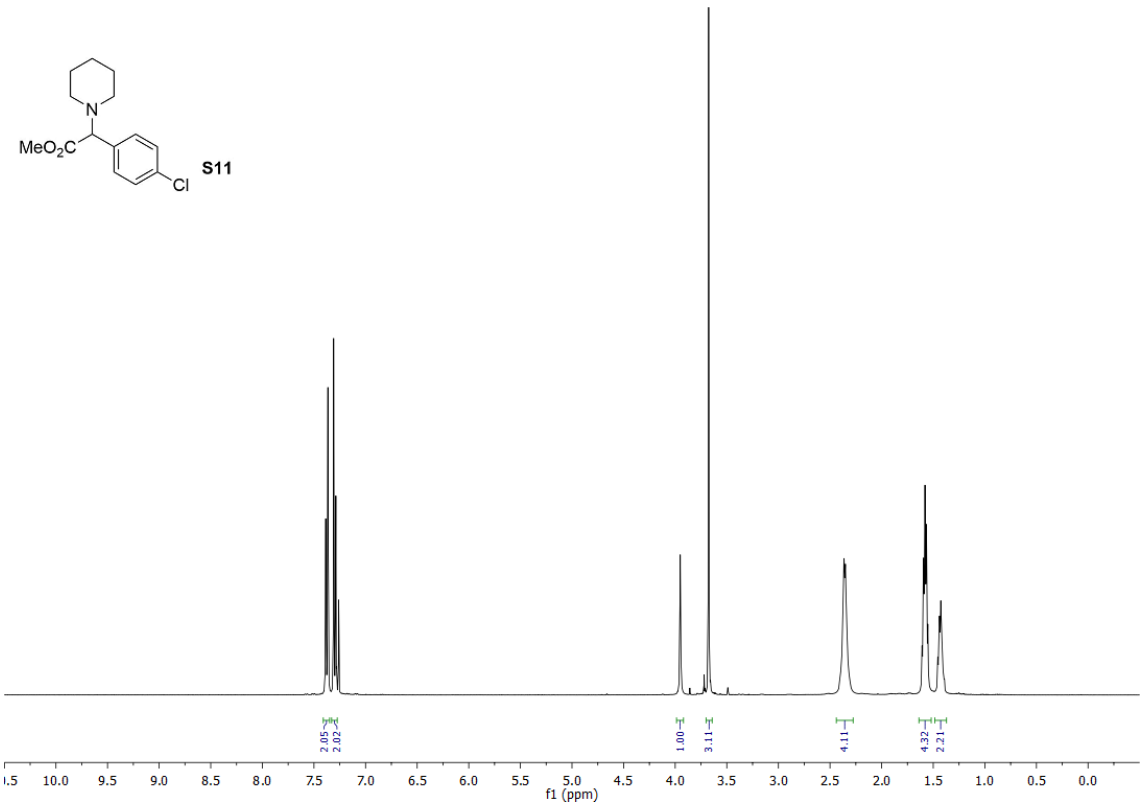
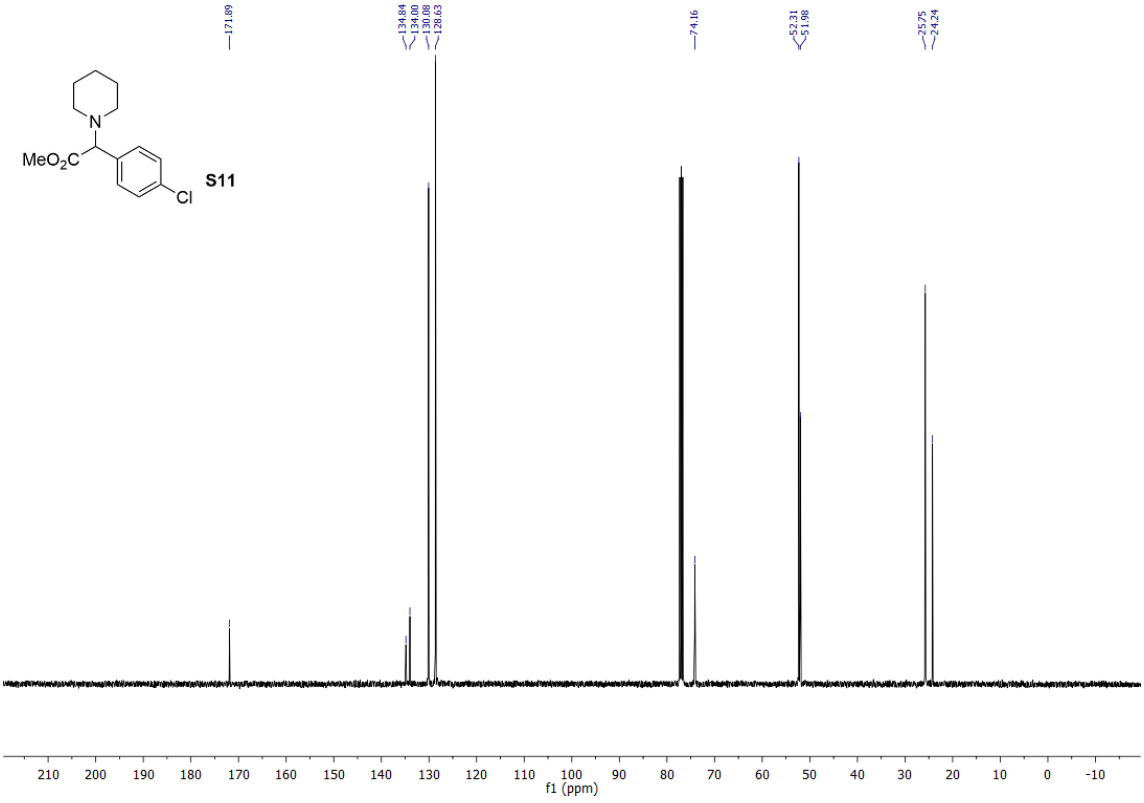
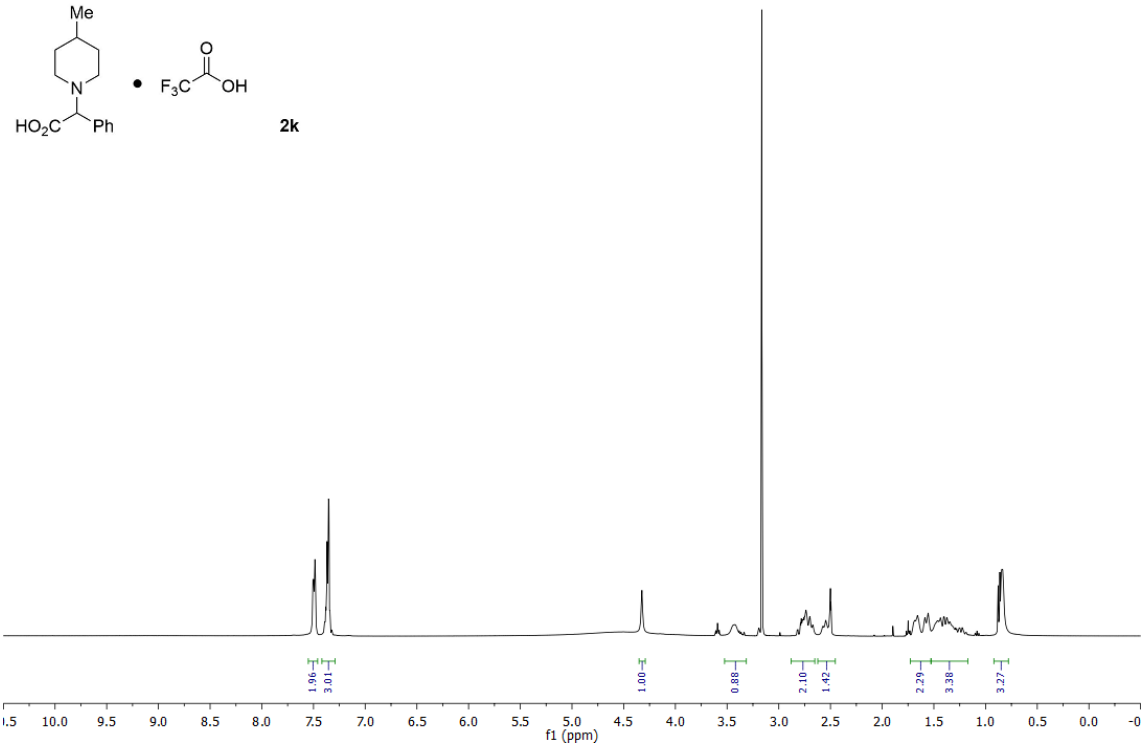
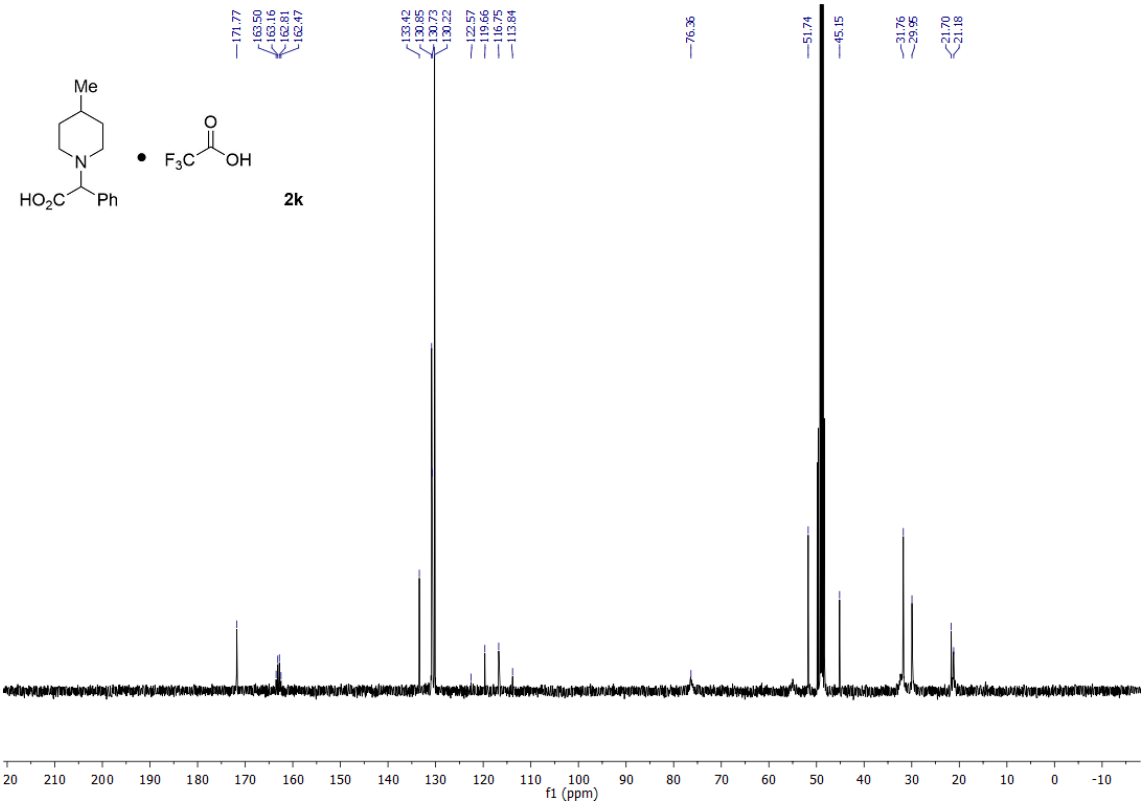
45.54
23.82
23.61
23.05
22.83
f1 (ppm)

2j


MeO2C
Cl
S11
2.05
2.02
1.00
3.11
4.11
4.32
2.21
f1 (ppm)


171.89
134.84
134.00
130.08
128.63
74.16
52.31
51.98
25.75
24.24
MeO2C
Cl
S11
f1 (ppm)


Me
N
HO2C
Ph
F3C
OH
2k
1.96
3.01
1.00
0.88
2.10
1.42
2.29
3.38
3.27
f1 (ppm)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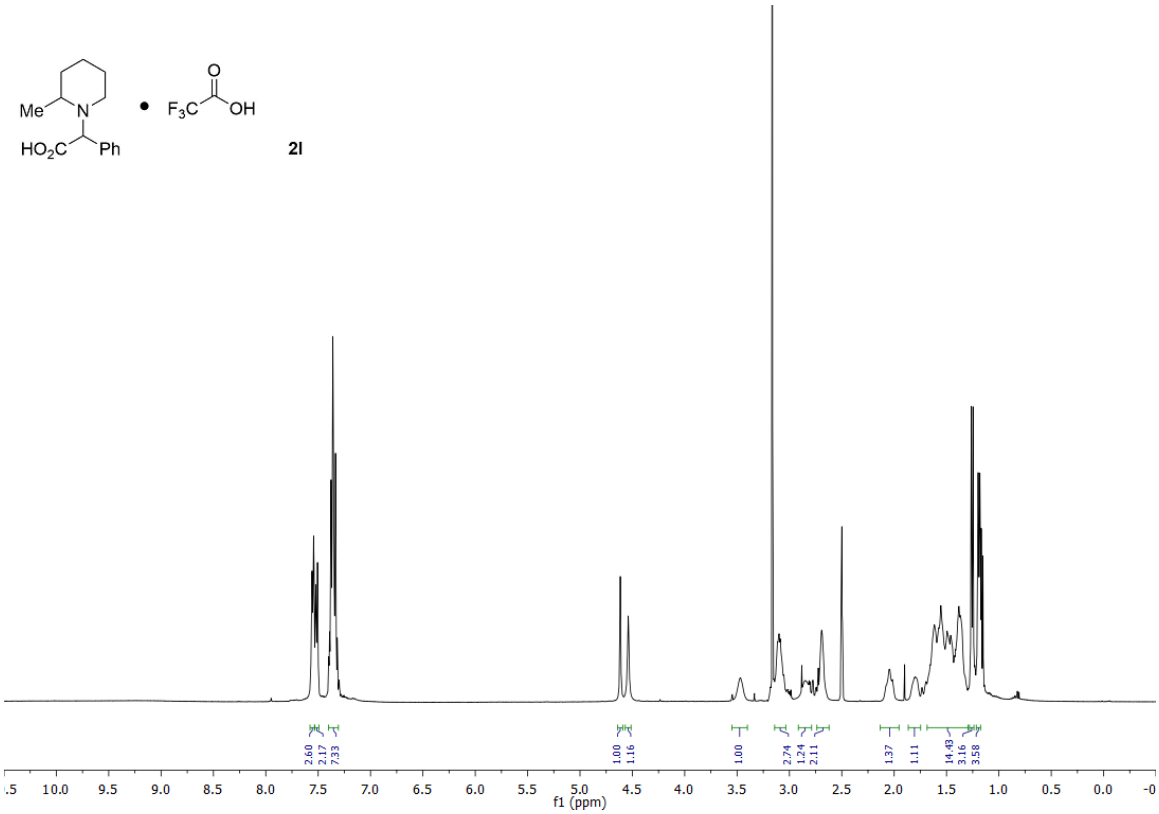
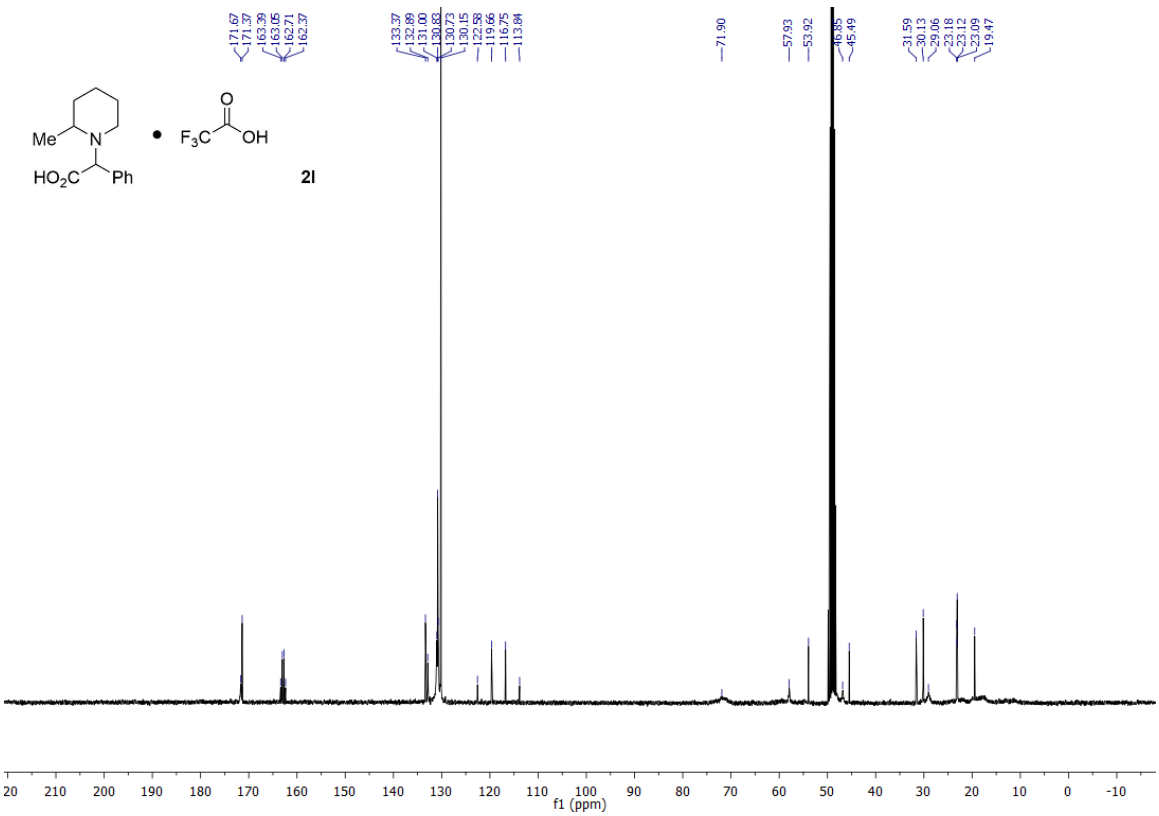
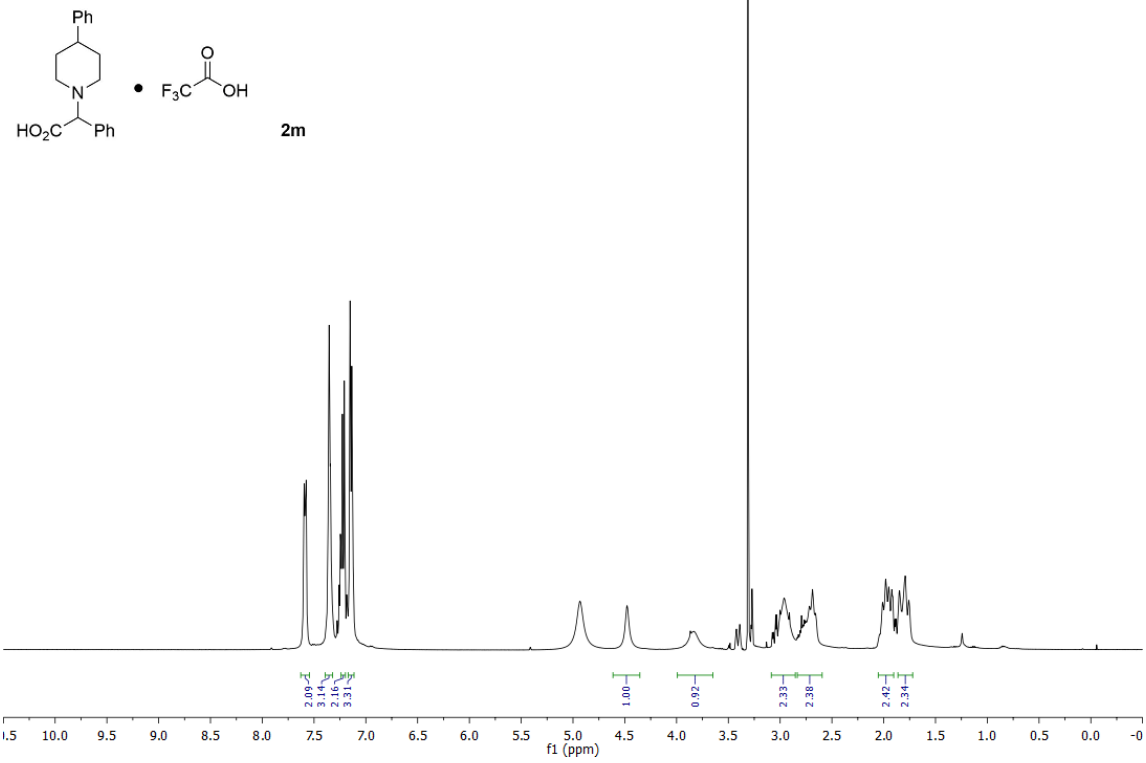
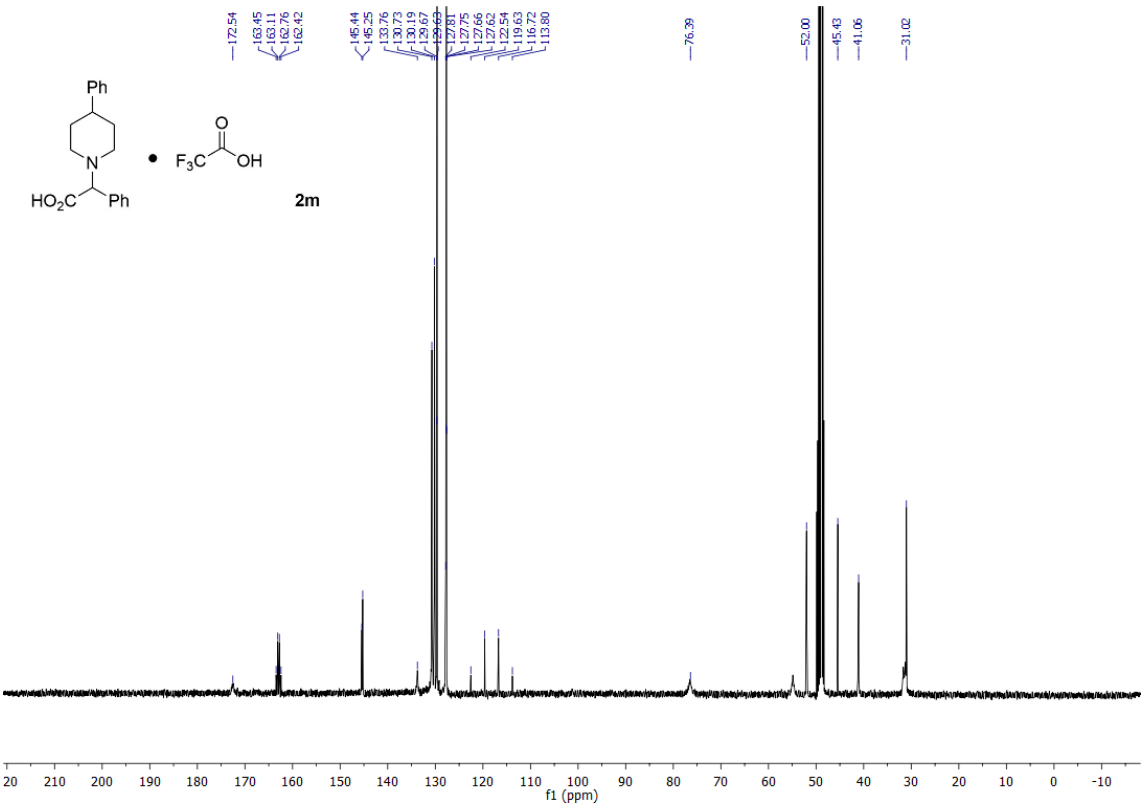
163.50
163.16
162.81
162.47
133.42
130.85
130.73
130.22
122.57
119.66
116.75
113.84
76.36
51.74
45.15
31.76
29.95
21.70
21.18
Me
N
HO2C
Ph
F3C
OH
2k
f1 (ppm)


Me
N
HO2C
Ph
F3C
OH
2l
2.60
2.17
7.33
1.00
1.16
1.00
2.74
1.24
2.11
1.37
1.11
14.48
3.16
3.58
f1 (ppm)


171.67
171.37
163.39
163.05
162.71
162.37
133.37
132.89
131.00
130.82
130.73
130.15
122.58
119.66
116.75
113.84
71.90
57.93
53.92
46.85
45.49
31.59
30.13
29.06
23.18
23.12
23.09
19.47
Me
N
HO2C
Ph
F3C
OH
2l
f1 (ppm)


Ph
N
HO2C
Ph
F3C
O
OH
2m
2.09
3.14
2.16
3.31
1.00
0.92
2.33
2.38
2.42
2.34
f1 (ppm)


172.54
163.45
163.11
162.76
162.42
145.44
145.25
133.76
130.73
130.19
129.67
129.63
127.81
127.75
127.66
127.62
122.54
119.63
116.72
113.80
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31.02
Ph
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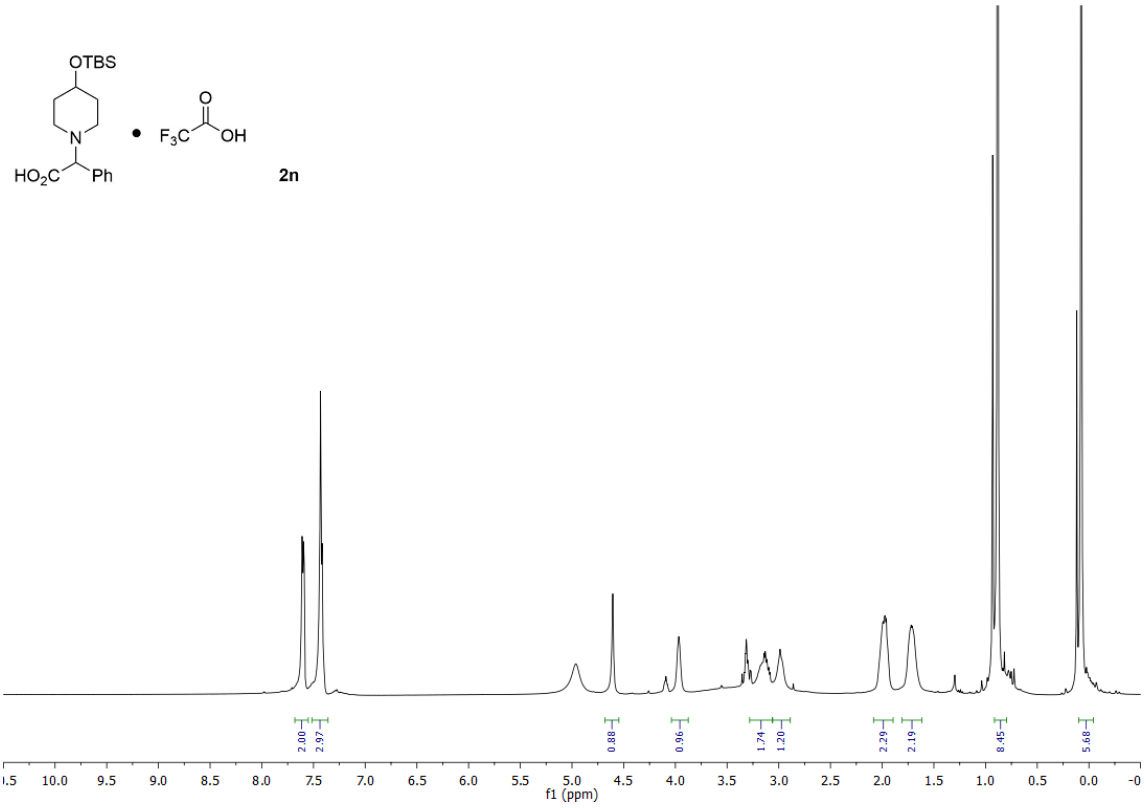
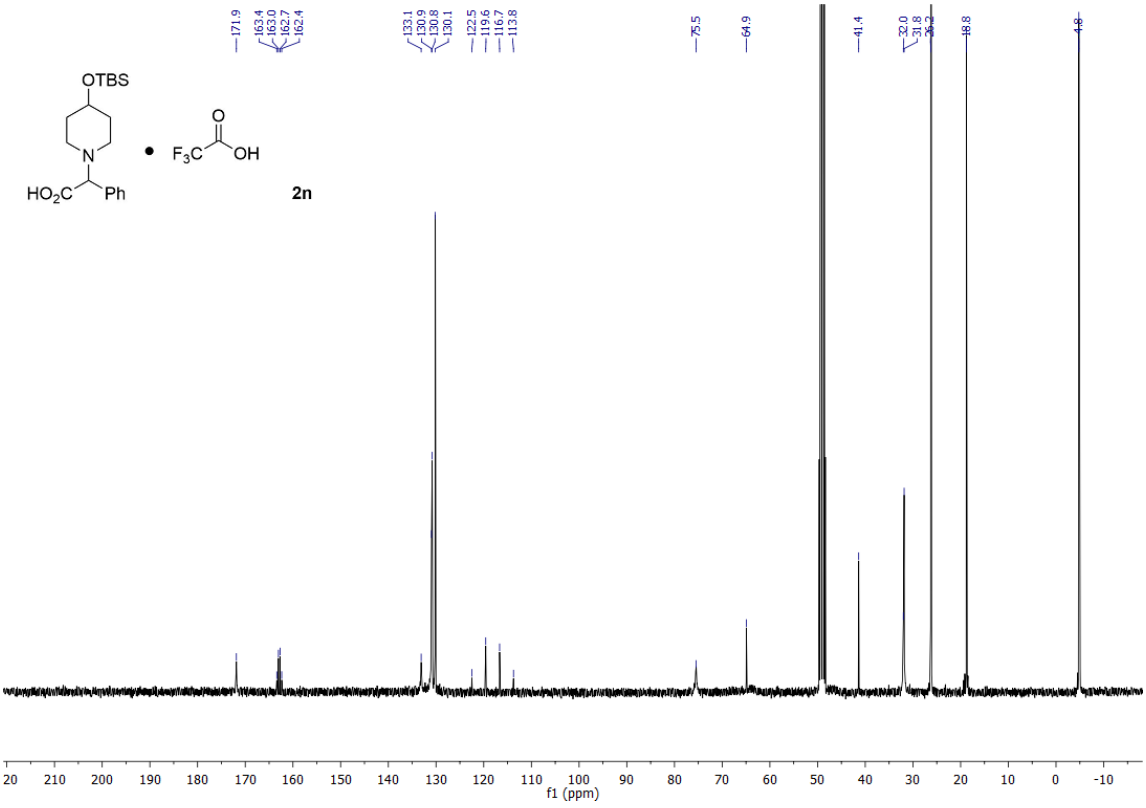
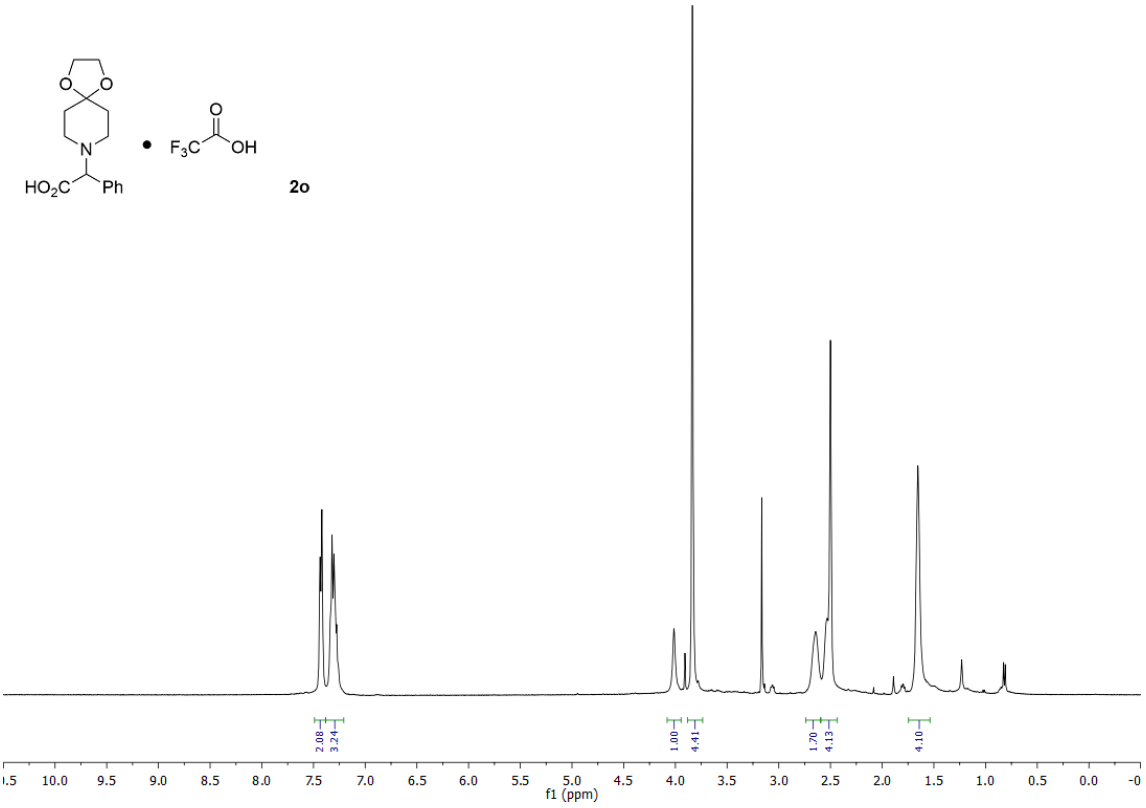
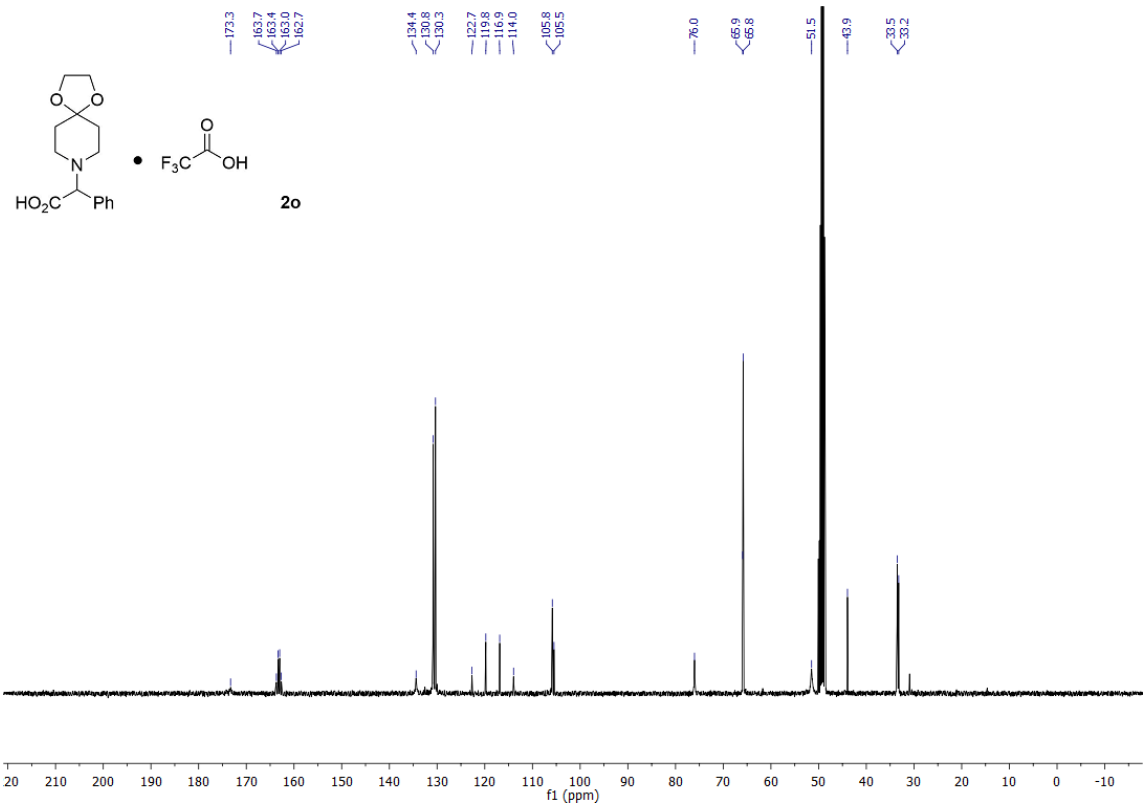
HO2C
Ph
F3C
O
OH
2m
f1 (ppm)


OTBS
N
HO2C
Ph
F3C
O
OH
2n
2.00
2.97
0.88
0.96
1.74
1.20
2.29
2.19
8.45
5.68
f1 (ppm)

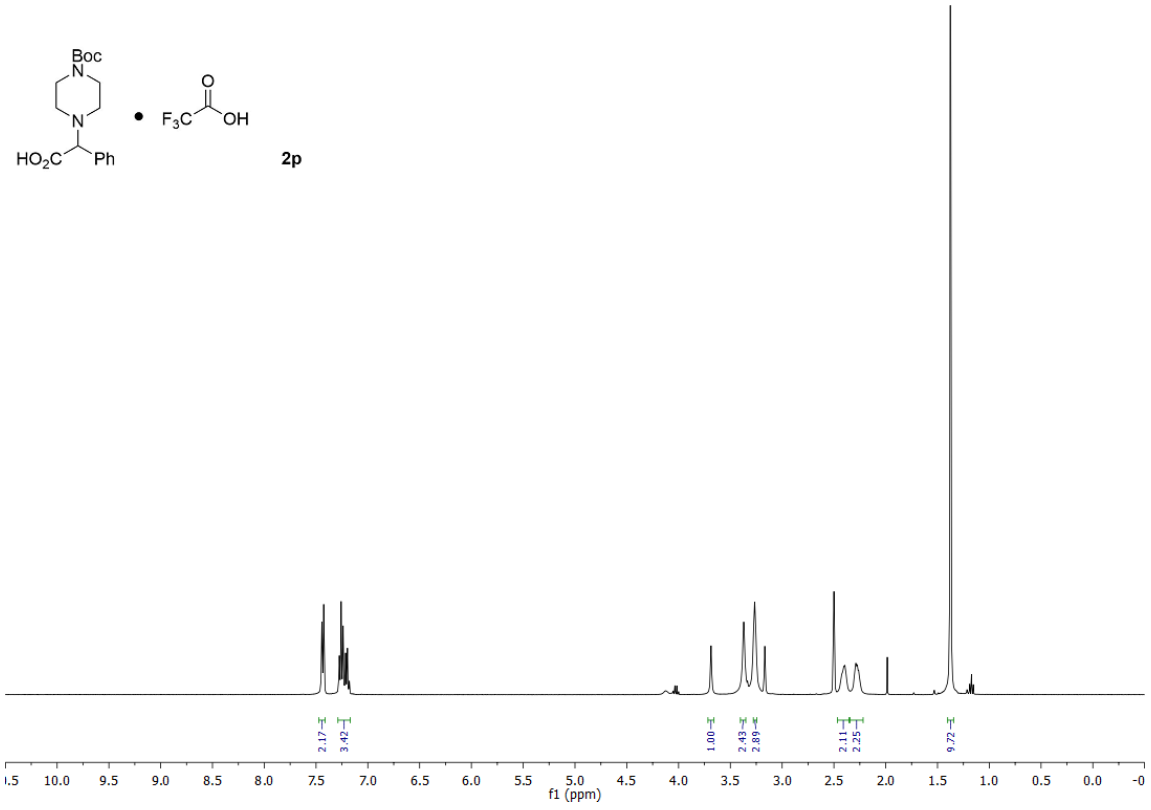

171.9
163.4
163.0
162.7
162.4
133.1
130.9
130.8
130.1
122.5
119.6
115.7
113.8
75.5
64.9
41.4
32.0
31.8
26.2
18.8
-4.8
OTBS
N
HO2C
Ph
F3C
O
OH
2n
f1 (ppm)

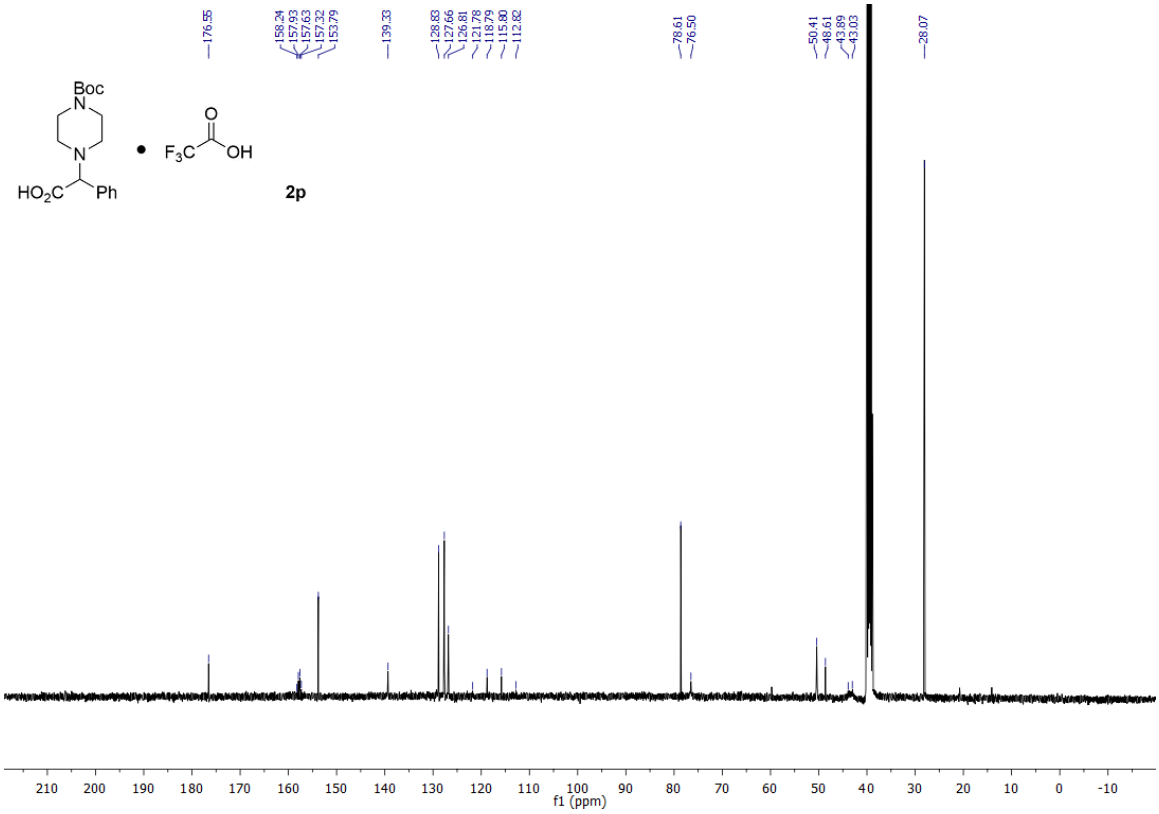

2.08
3.24
1.00
4.41
1.70
4.13
4.10
f1 (ppm)

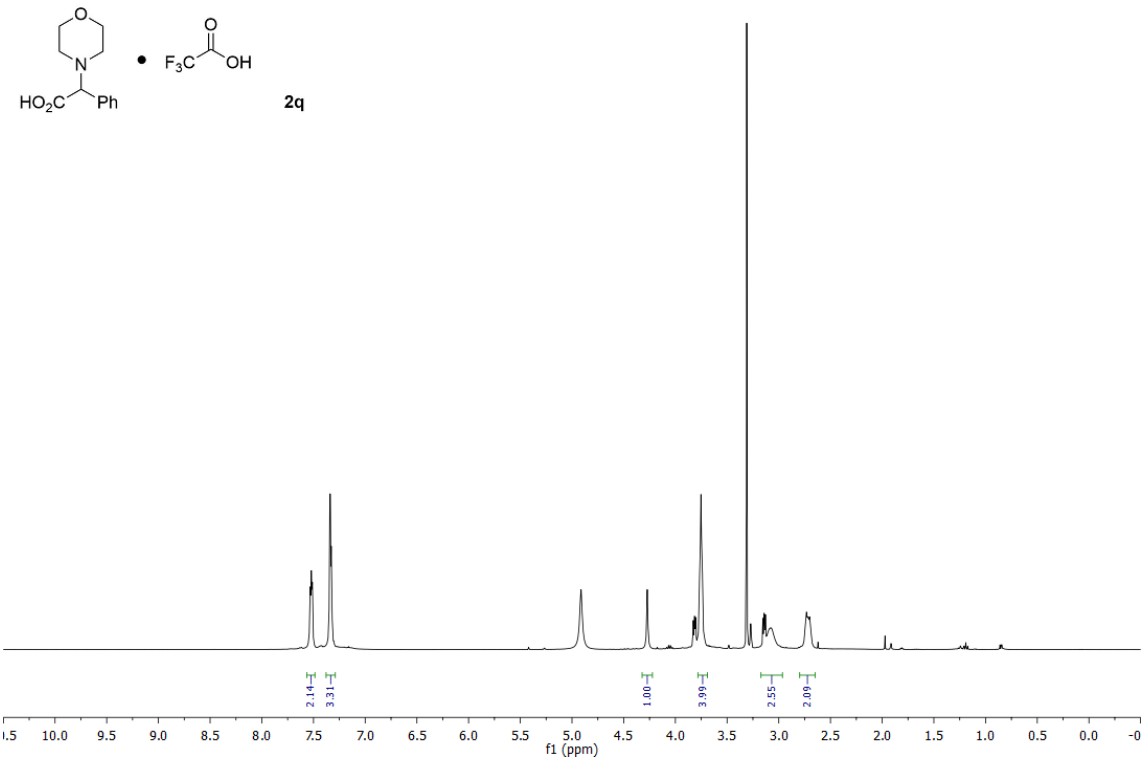
2o

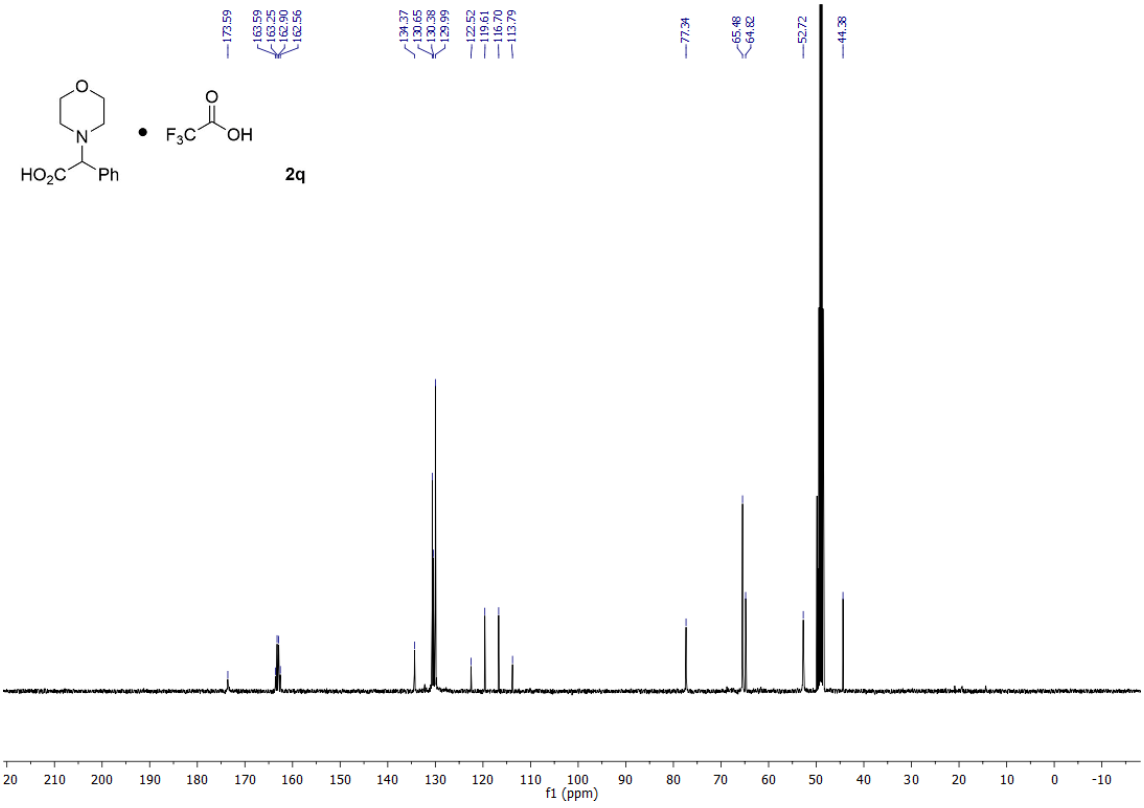

173.3
163.7
163.4
163.0
162.7
134.4
130.8
130.3
122.7
119.8
116.9
114.0
105.8
105.5
76.0
65.9
65.8
51.5
43.9
33.5
33.2
f1 (ppm)

2o


Boc
N
N
HO2C
Ph
F3C
OH
2p
2.17
3.42
1.00
2.43
2.89
2.11
2.25
9.72
f1 (ppm)


176.55
158.24
157.93
157.63
157.32
153.79
139.33
128.83
127.66
126.81
121.78
118.79
115.80
112.82
78.61
76.50
50.41
48.61
43.89
43.03
28.07
Boc
N
N
HO2C
Ph
F3C
OH
2p
f1 (ppm)


2q
2.14
3.31
1.00
3.99
2.55
2.09
f1 (ppm)


173.59
163.59
163.25
162.90
162.56
134.37
130.65
130.38
129.99
122.52
119.61
116.70
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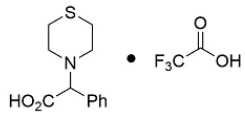
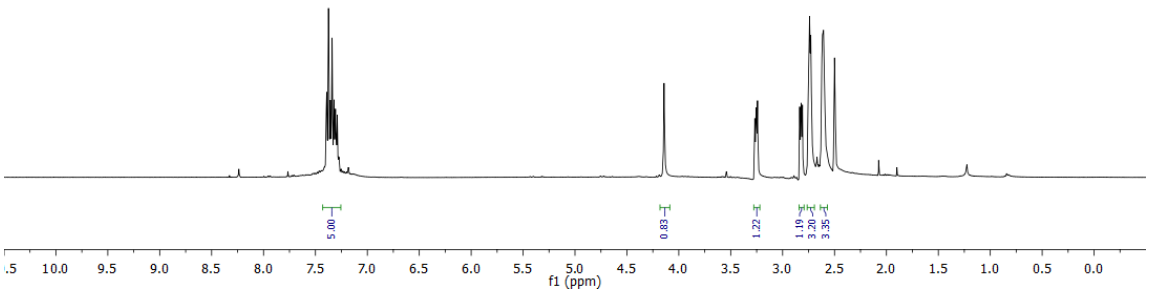
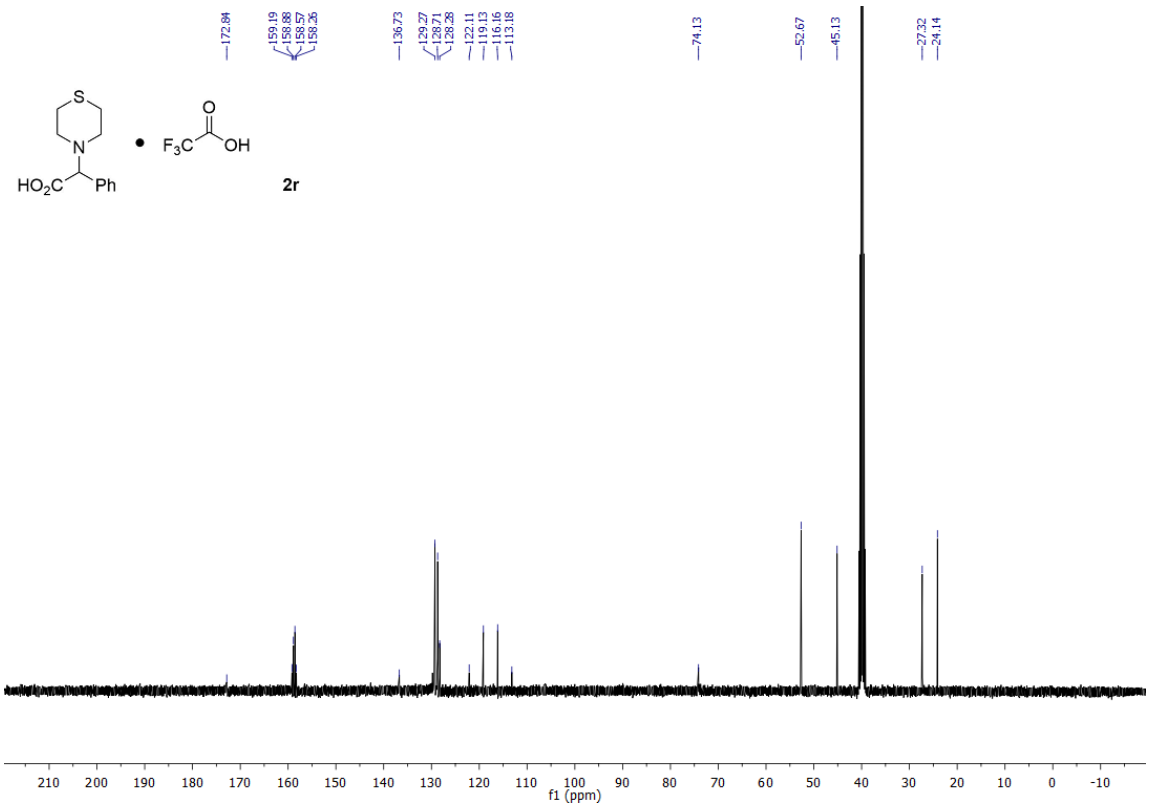
64.82
52.72
44.38
2q
f1 (ppm)


S
N
HO2C
Ph
F3C
O
OH

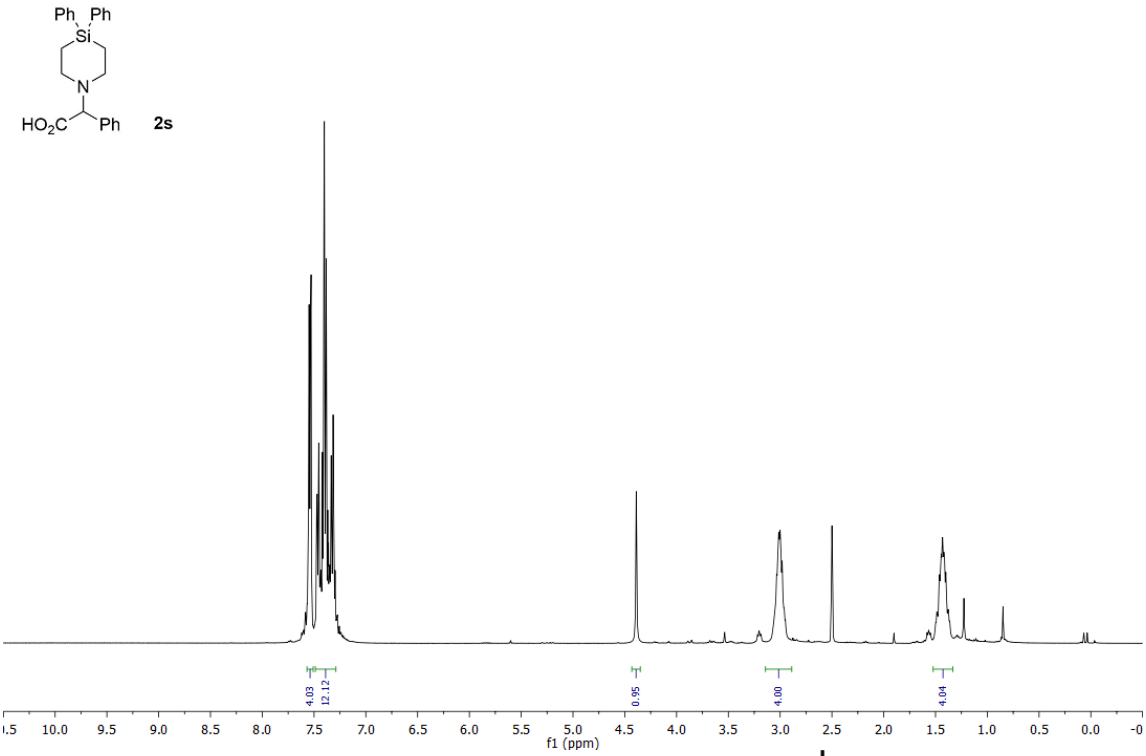
2r

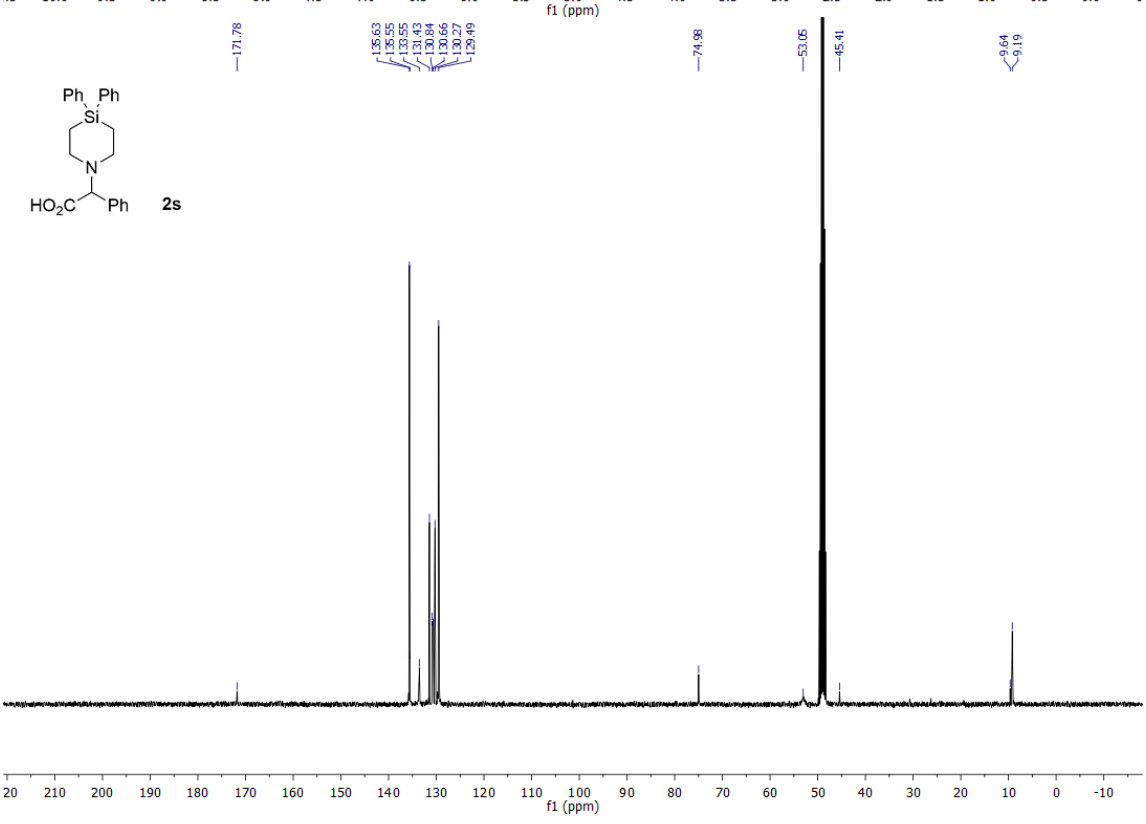

5.00
0.83
1.22
1.19
3.20
3.35
f1 (ppm)

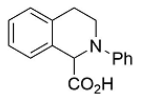

172.84
159.19
158.88
158.57
158.26
136.73
129.27
128.71
128.28
122.11
119.13
116.16
113.18
74.13
52.67
45.13
27.32
24.14
f1 (ppm)

S
N
HO2C
Ph
F3C
O
OH

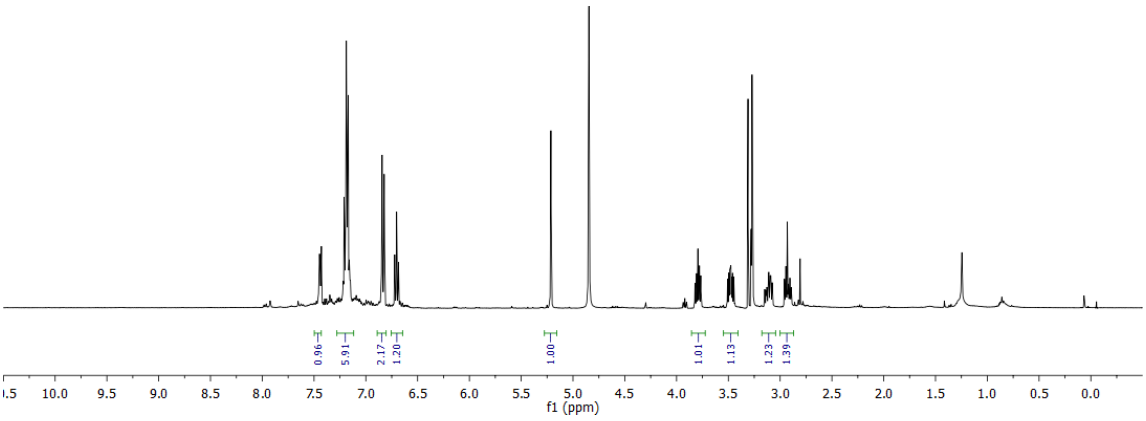
2r

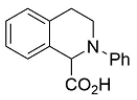

Ph
Ph
Si
N
HO2C
Ph
2s
4.03
12.12
0.95
4.00
4.04
f1 (ppm)


171.78
135.63
135.55
133.55
131.43
130.84
130.66
130.27
129.49
74.98
53.05
45.41
9.64
9.19
Ph
Ph
Si
N
HO2C
Ph
2s
f1 (ppm)


N
Ph
CO2H

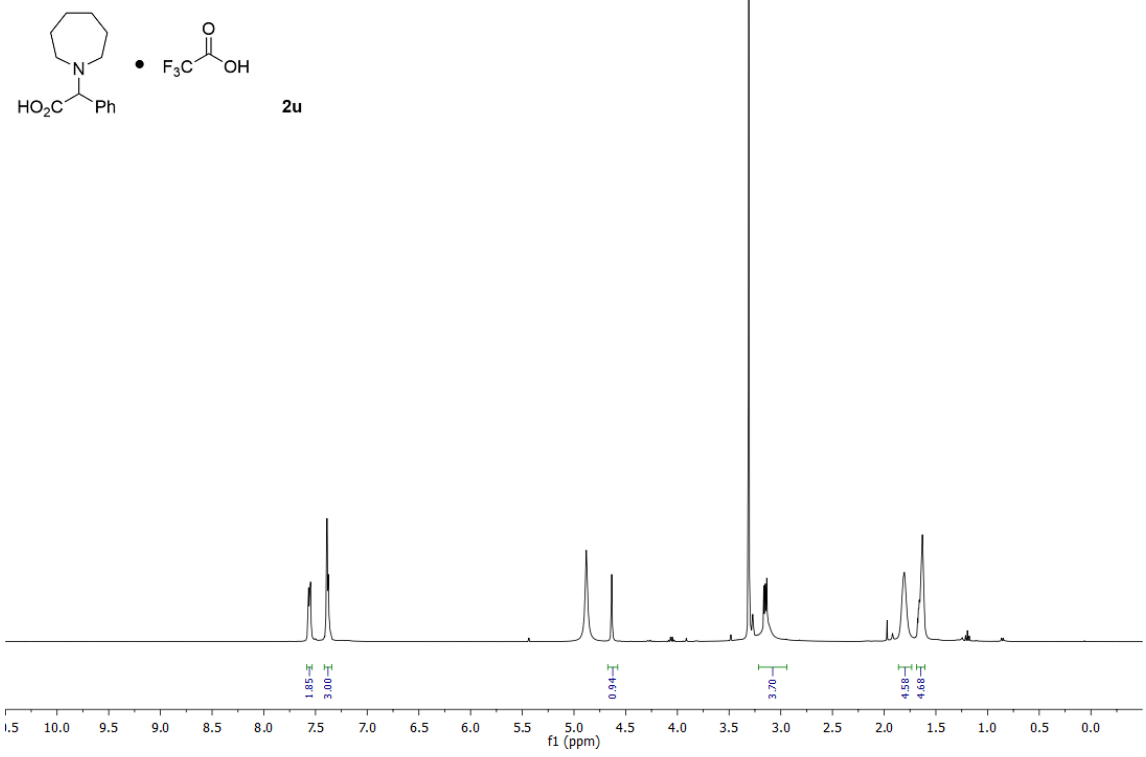
2t

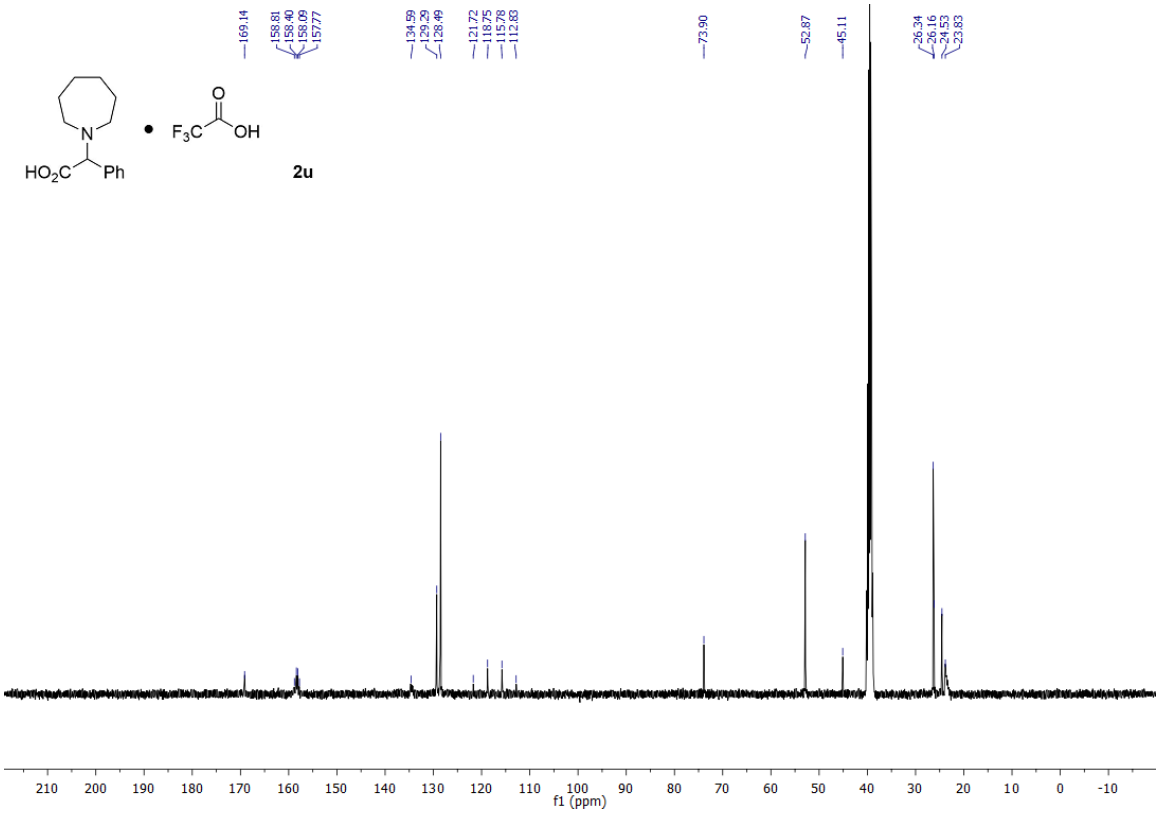

0.96
5.91
2.17
1.20
1.00
1.01
1.13
1.23
1.39
f1 (ppm)

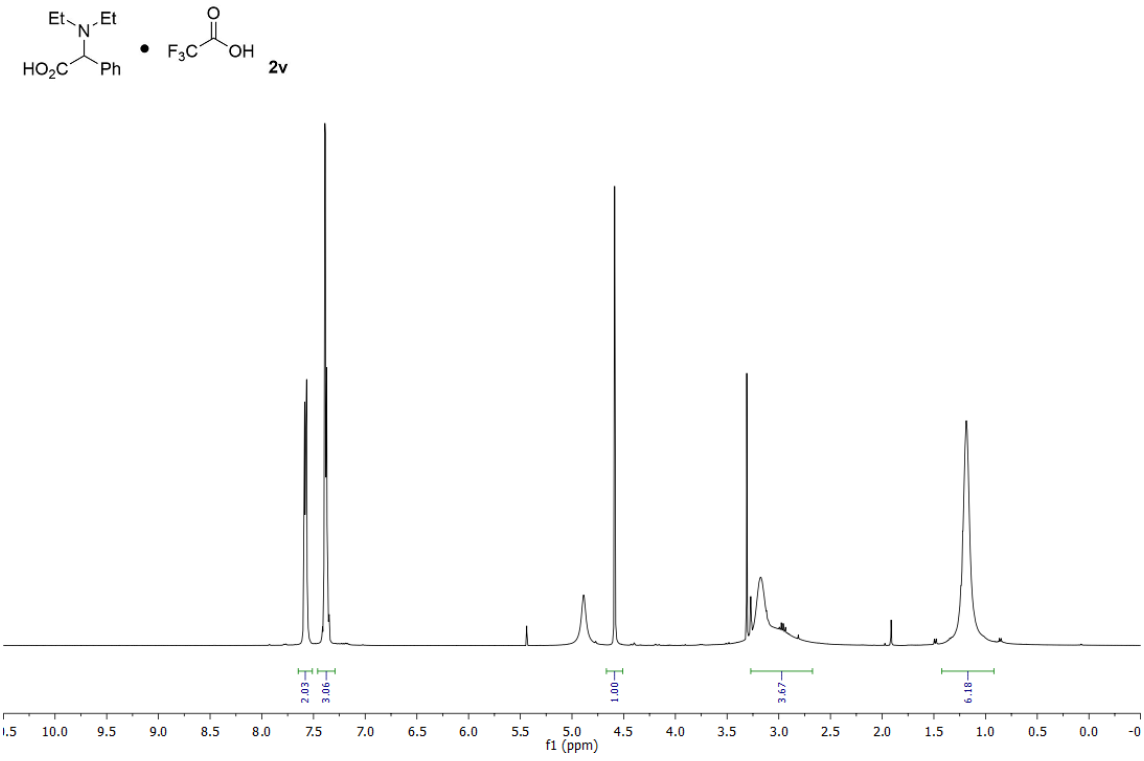

N
Ph
CO2H

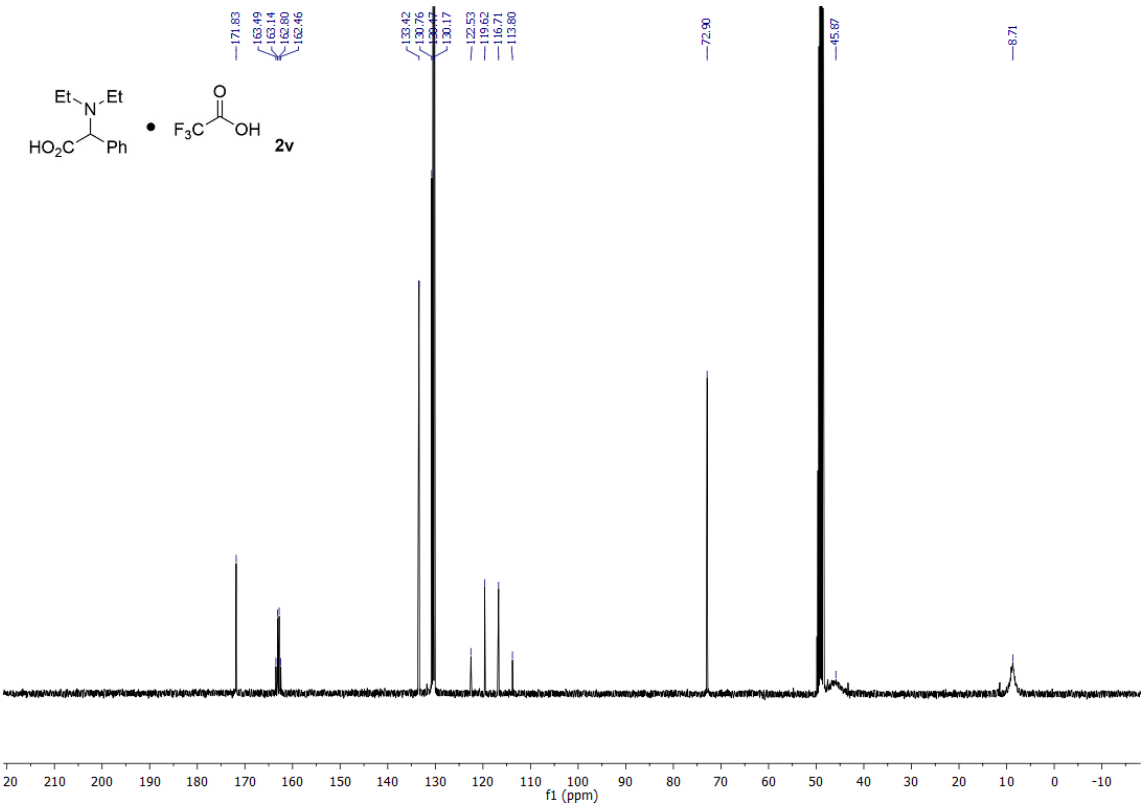
2t

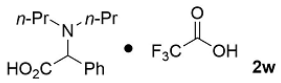
176.61
150.52
137.13
133.78
130.14
129.11
128.94
128.74
127.36
118.92
114.47
63.31
44.37
29.73
f1 (ppm)


HO2C
N
Ph
F3C
OH
2u
1.85
3.00
0.94
3.70
4.58
4.68
f1 (ppm)

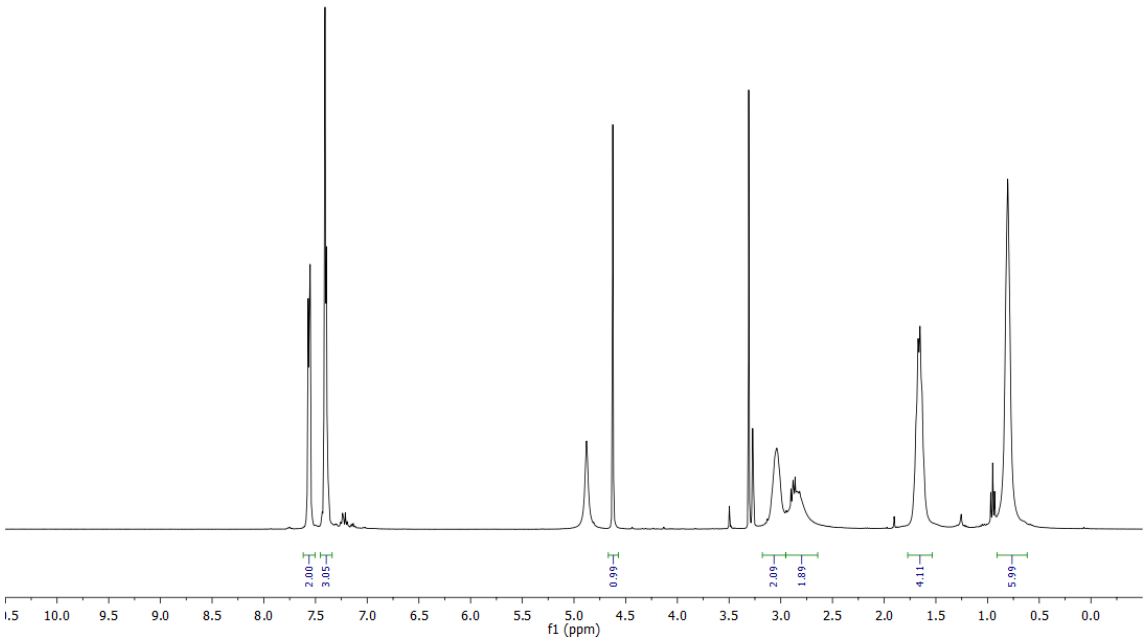

169.14
158.81
158.40
158.09
157.77
134.59
129.29
128.49
121.72
118.75
115.78
112.83
73.90
52.87
45.11
26.34
26.16
24.53
23.83
HO2C
N
Ph
F3C
OH
2u
f1 (ppm)


Et
N
Et
HO2C
Ph
F3C
OH
2v
2.03
3.06
1.00
3.67
6.18
f1 (ppm)

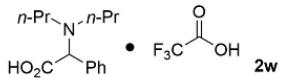

171.83
163.49
163.14
162.80
162.46
133.42
130.76
130.42
130.17
122.53
119.62
116.71
113.80
72.90
45.87
8.71
Et
N
Et
HO2C
Ph
F3C
OH
2v
f1 (ppm)


n-Pr
N
n-Pr
HO2C
Ph
F3C
OH

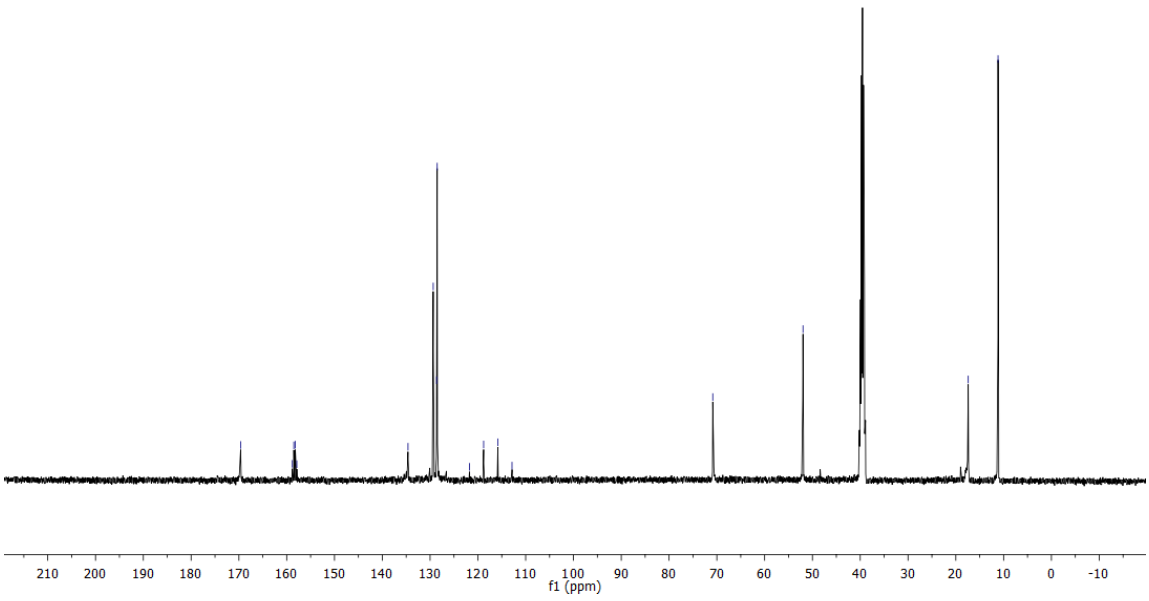
2w

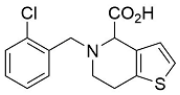

2.00
3.05
0.99
2.09
1.89
4.11
5.99
f1 (ppm)


169.63
158.83
158.51
158.20
157.88
134.62
129.34
128.63
128.51
121.77
118.80
115.83
112.86
70.86
51.97
17.40
11.16

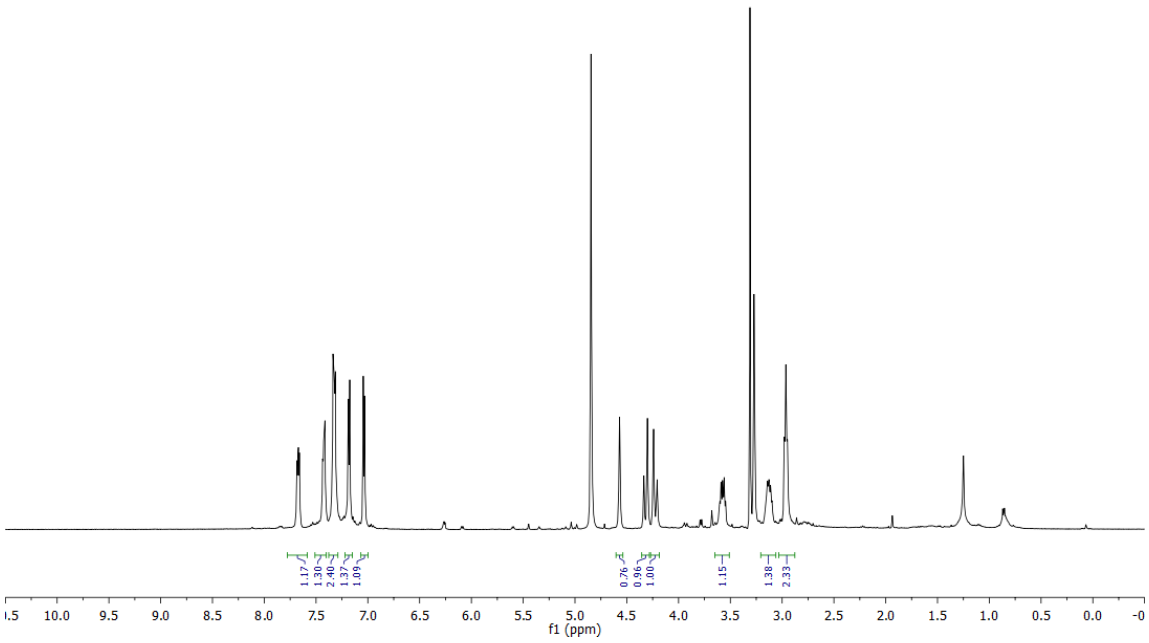

n-Pr
N
n-Pr
HO2C
Ph
F3C
OH

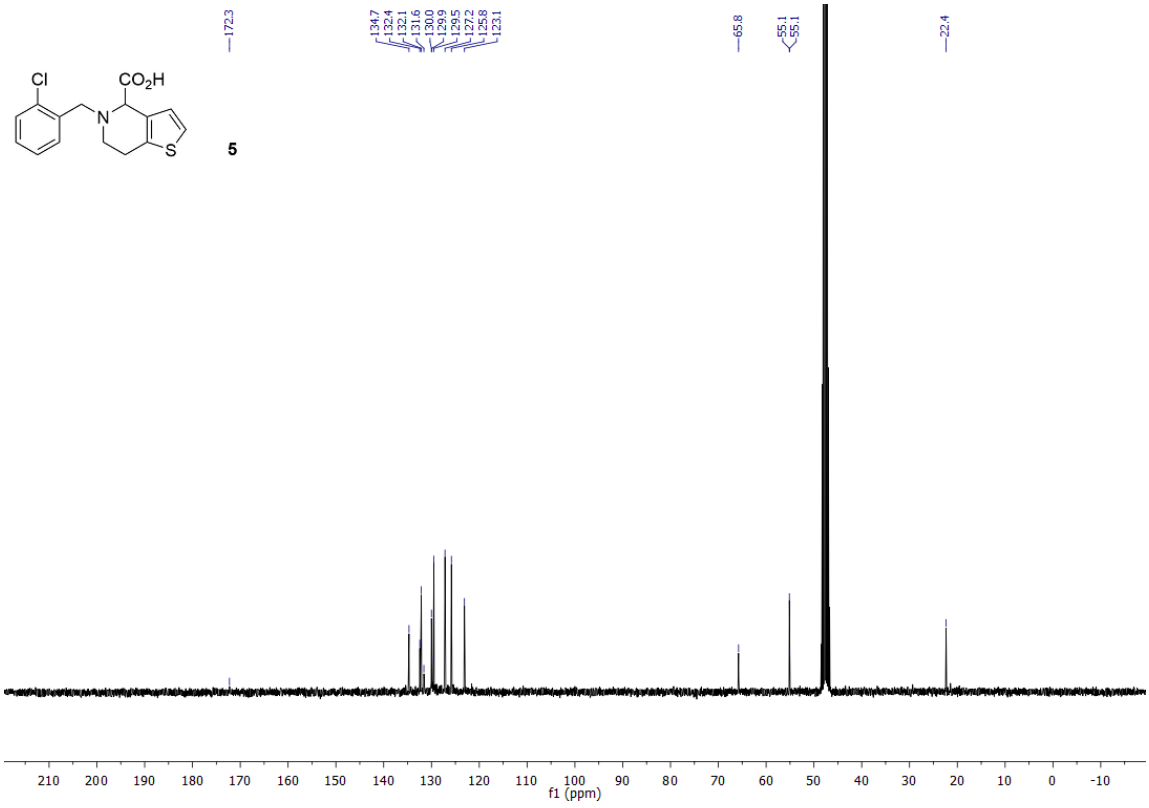
2w


f1 (ppm)


Cl
CO2H
N
S

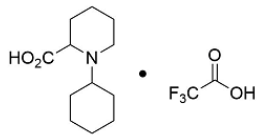
5


1.17
1.30
2.40
1.37
1.09
0.76
0.96
1.00
1.15
1.38
2.33
f1 (ppm)

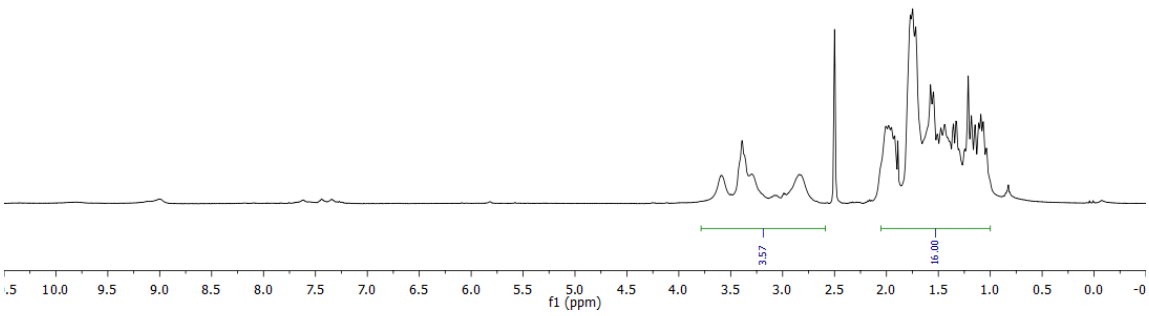

172.3
134.7
132.4
132.1
131.6
130.0
129.9
129.5
127.2
125.8
123.1
65.8
55.1
55.1
22.4
f1 (ppm)

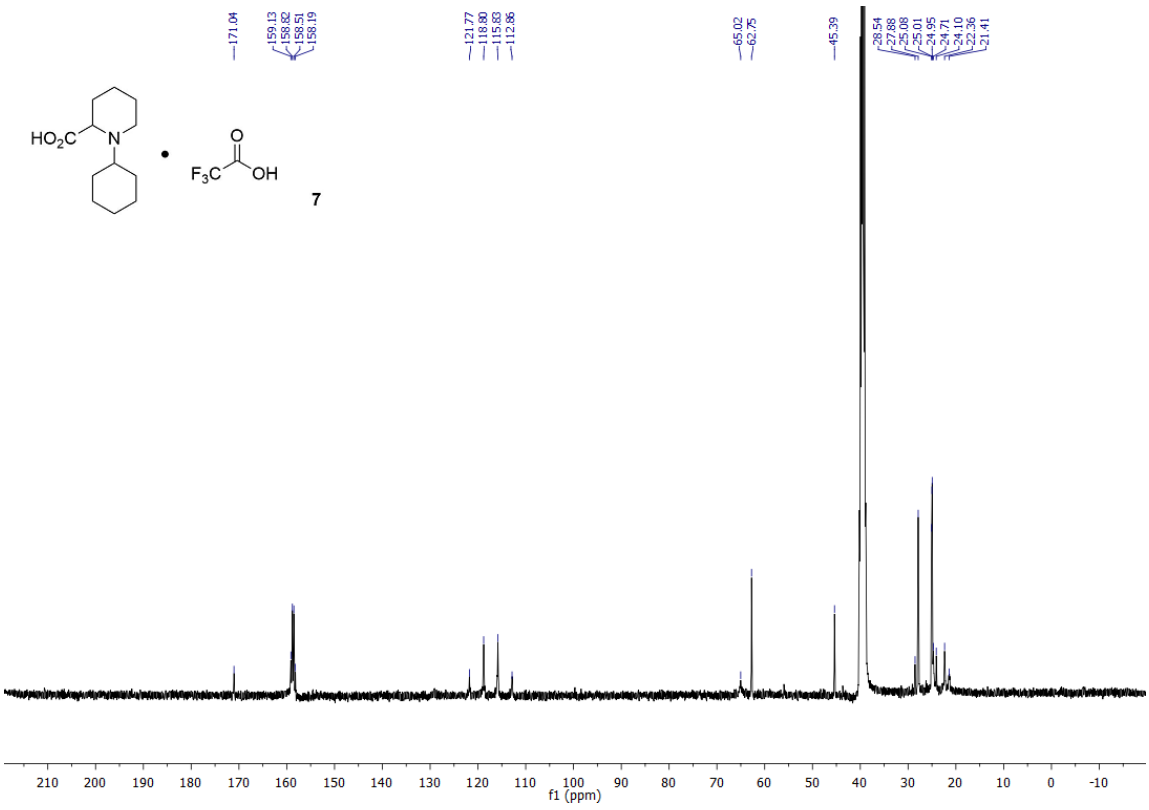
Cl
CO2H
N
S

5

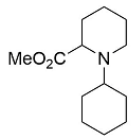


7

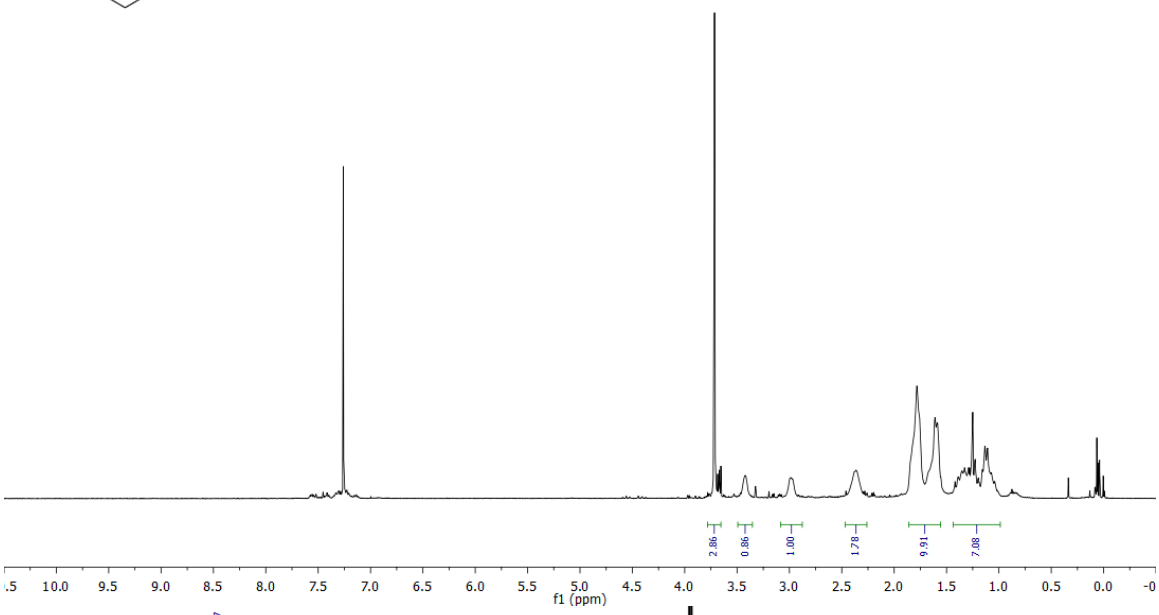

3.57
16.00
f1 (ppm)

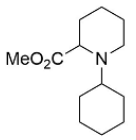

171.04
159.13
158.82
158.51
158.19
121.77
118.80
115.83
112.86
65.02
62.75
45.39
28.54
27.88
25.08
25.01
24.95
24.71
24.10
22.36
21.41
f1 (ppm)

7



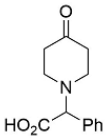
S12


2.86
0.86
1.00
1.78
9.91
7.08
f1 (ppm)

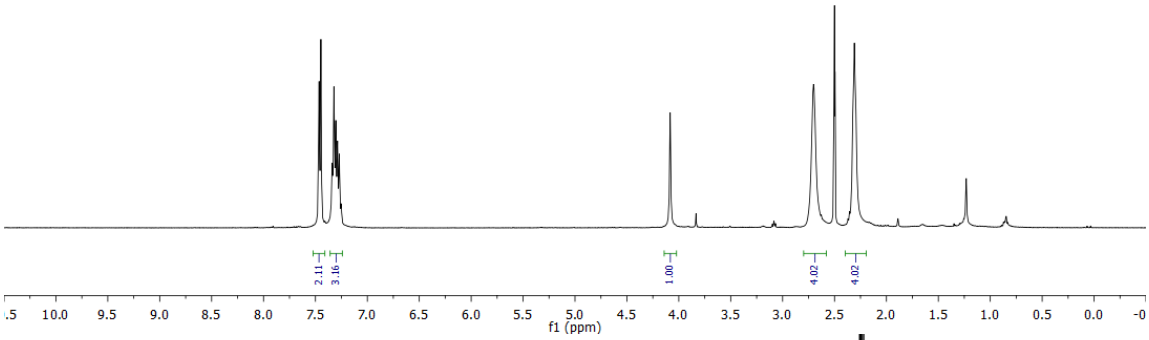


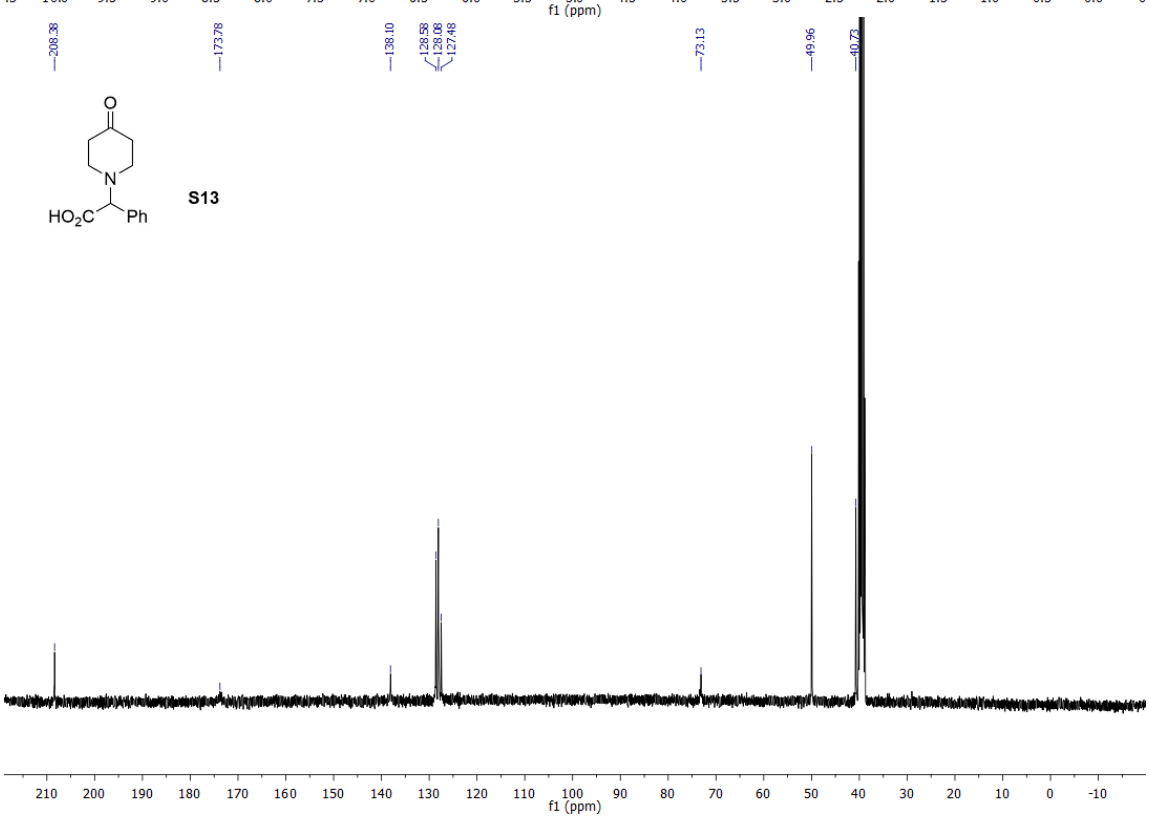
S12

174.77
62.28
61.45
51.63
44.87
31.41
31.27
30.09
29.69
26.27
25.98
25.71
22.99
f1 (ppm)


O
N
HO2C
Ph

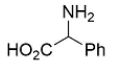
S13


2.11
3.16
1.00
4.02
4.02
f1 (ppm)


208.38
173.78
138.10
128.58
128.08
127.48
73.13
49.96
40.72
f1 (ppm)

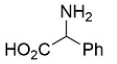
O
N
HO2C
Ph

S13


NH2
HO2C
Ph

8

4.81
1.00
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)


NH2
HO2C
Ph

8

170.57
131.17
130.28
129.60
127.97
56.34
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)