Direct β-Selective Hydrocarboxylation of Styrenes with CO_2 Enabled by Continuous Flow Photoredox Catalysis

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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, potassium permanganate, or bromocresol green 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

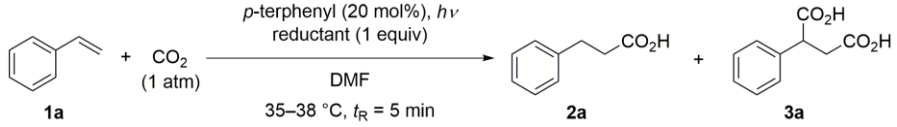
Methyl benzoate (99%, Sigma-Aldrich) was used as an internal standard for quantification. Commercially available chemicals were purchased from Sigma-Aldrich Chemical Company (Milwaukee, WI), Alfa Aesar (Ward Hill, MA), Acros Organics (Pittsburgh, PA), or TCI America (Portland, OR). Commercial styrene derivatives containing 4-*tert*-butylcatechol as an inhibitor were purified by passing them through a column of activated basic aluminum oxide. 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; DMSO, 2.50 ppm; D_2O, 4.79 ppm; C_6D_6, 7.16 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; DMSO, 39.5 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

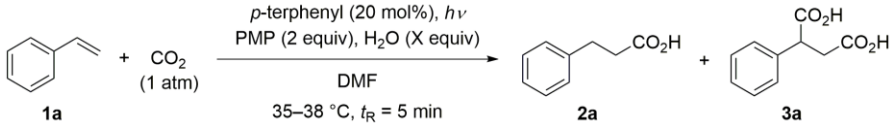
Table S1. Electron donor evaluation.[a]



entry	reductant	yield **2a**[b]	yield **3a**[b]	**2a**/**3a**[b]
1	triethylamine	12	4.9	2.4:1
2	*N*-benzylpiperidine	7.7	6.4	1.2:1
3	*N*,*N*-diisopropylethylamine	5	trace	-
4	*N*,*N*-diisopropylbenzylamine	0	0	-
5	*N*,*N*-dicyclohexylmethylamine	9.5	13.9	0.7:1
6	DIPEA	10	5.9	1.7:1
7	TMEDA	0	0	-
8	DABCO	0	0	-
9	TMP	0	0	-
10	Proton sponge	0	0	-
11	*N*,*N*-dimethylaniline	5	trace	-
12	*N*,*N*-diethylaniline	3	trace	-
13	triphenylamine	0	0	-
14	2,6-lutidine	0	0	-
15	2,4,6-collidine	0	0	-
16	1,2,5-trimethylpyrrole	0	0	-
17	Hantzsch ester	0	0	-
18	Sodium ascorbate	0	0	-
19	Thiophenol	0	0	-
20	Thioanisole	0	0	-
21	DBU	34	3.2	11:1
22	DBN	23	3.9	5.9:1
23	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene	20	1.6	13:1
24	2-*tert*-Butyl-1,1,3,3-tetramethylguanidine	0	0	-
25	1,2,2,6,6-pentamethylpiperidine (0.2 equiv)	4.7	4.3	1.1:1
26	1,2,2,6,6-pentamethylpiperidine (1 equiv)	31	29	1.1:1
27	1,2,2,6,6-pentamethylpiperidine (2 equiv)	26	32	0.8:1

[a]Reactions were carried out using a continuous flow photochemistry system developed by Beeler.
[b]Calculated by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

Table S2. Water equivalent evaluation.[a]



entry	H_2O equivalent	yield **2a**[b]	yield **3a**[b]	**2a**/**3a**[b]
1	0	26	32	0.8:1
2	1	41	25	1.6:1
3	2	54	12	4.5:1
4	5	67	8.2	8.2:1
5	10	75	4.8	16:1
6	19	87	3.0	29:1

[a]Reactions were carried out using a continuous flow photochemistry system developed by Beeler.
[b]Calculated by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

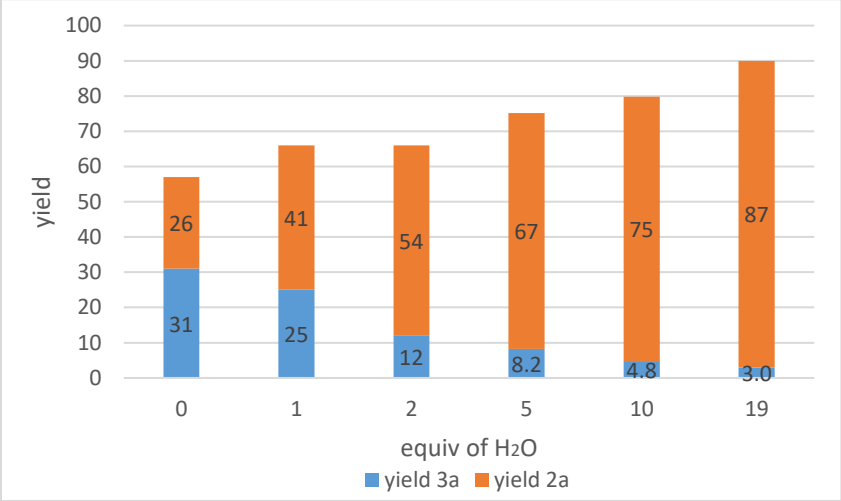
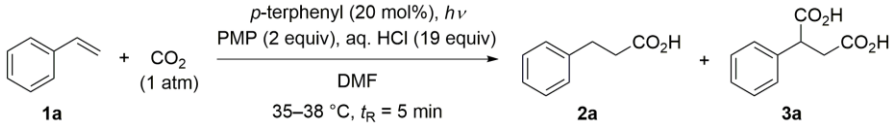


Table S3. Acidic condition evaluation.[a]



entry	aq. HCl	yield **2a**[b]	yield **3a**[b]	**2a**/**3a**[b]
1	1 M	68	3.6	19:1
2	3 M	51	3.0	17:1
3	5 M	32	2.2	15:1

[a]Reactions were carried out using a continuous flow photochemistry system developed by Beeler.
[b]Calculated by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

3. Reaction Setup

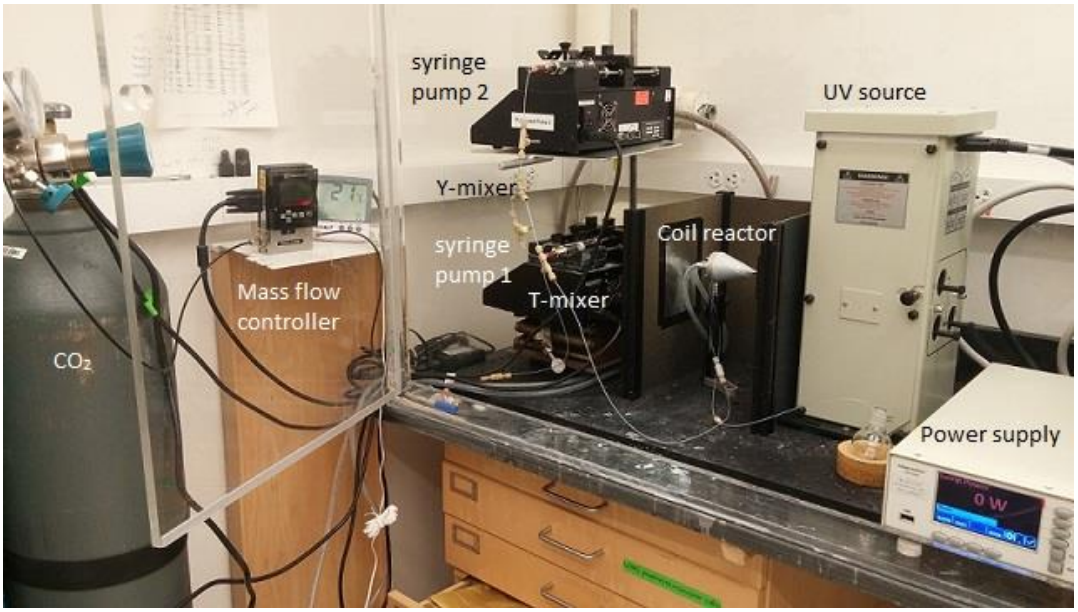
General Material Information for Continuous Flow setups

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. PEEK™ T-mixers, Y-mixers and unions were purchased from Upchurch Scientific®
6. Super Flangeless fittings (include nuts and ferrules) were purchased from Upchurch Scientific®
7. Mass flow controller was purchased from Sierra Instruments (Monterey, CA) and was calibrated for carbon dioxide by the vendor before using.
8. Cone-shaped frame was machined from aluminum 6061 by Proto Labs (Maple Plain, MN).
9. Research Arc Lamp Source, 500W Hg (Xe) arc lamp, and a power supply were purchased from Newport Corporation (Irvine, CA).
10. UV Hot Mirror was purchased from Edmund Optics (Barrington, NJ).
11. UV filter was purchased from Newport Corporation (Irvine, CA).
12. Blackout materials were purchased from Thorlabs (Newton, NJ).

Beeler's continuous flow photochemistry system:

As shown in Figure S1, a Harvard Apparatus PHD2000 syringe pump was used to deliver the reagent solution (syringe 1) and hexanes (syringe 2) 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 solution phase was mixed with hexanes at a Y-mixer (thru hole 0.3"). 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 0.03"), 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 longpass filter were placed between the UV source and the cone reactor. The entire reactor was covered by black cardboard. The final exiting stream was collected into a flask.

a



b

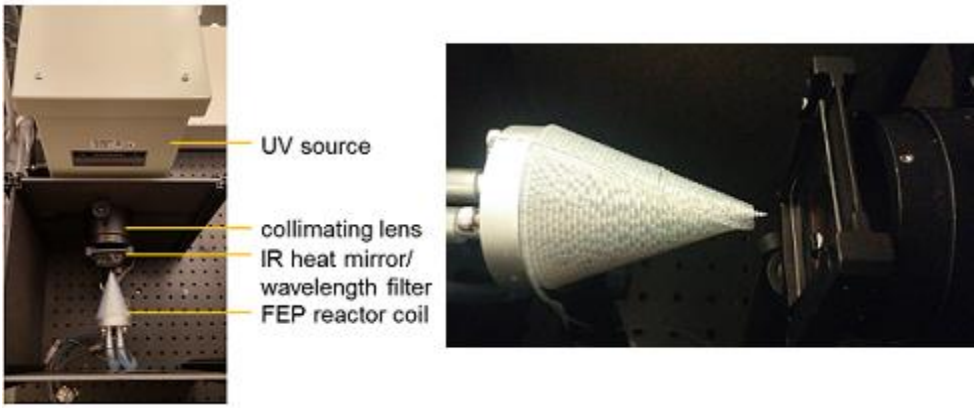
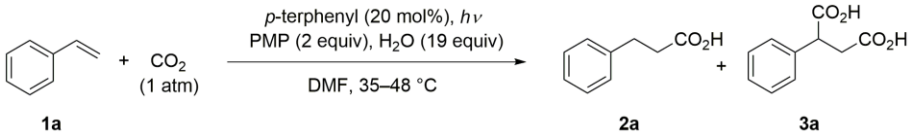


Figure S1. Setup of the continuous flow Beeler's photochemistry system: a, The full setup. **b**, Close-up of the reactor.

Photochemistry setup in batch

An oven-dried 50 mL Schlenk flask was charged with the styrene (1.05 mmol, 1.0 equiv), *p*-terphenyl (0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine (2.10 mmol, 2.0 equiv), water (20.0 mmol, 19 equiv) and dimethylformamide (7.0 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 (Figure S2). 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 Table S4.

Table S4. Reaction in batch.[a]



entry	reaction time (min)	conversion (%)[b]	yield **2a** (%)[b]	Yield **3a** (%)[b]	**2a**/**3a**[b]
1	8	42	9.2	trace	-
2	30	81	22	trace	-
3	60	100	36	0.78	46:1

[a]Reactions were carried out using a continuous flow photochemistry system developed by Beeler.
[b]Calculated by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

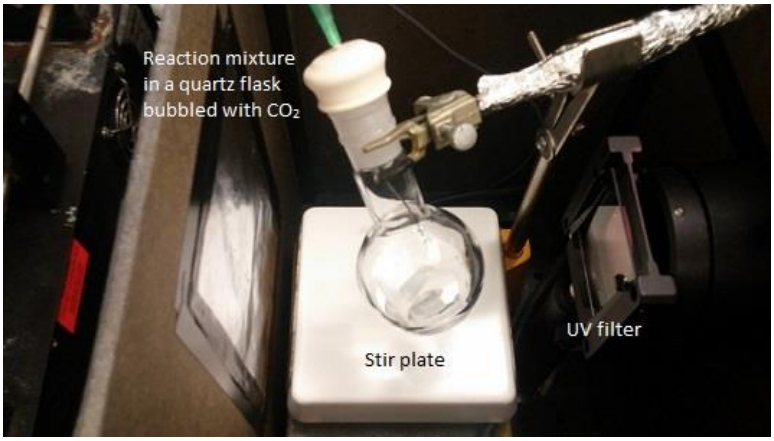


Figure S2. Setup of the photochemical reaction in batch.

4. 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 1,2,2,6,6-pentamethylpiperidine, water, or styrene was added to the solution. After transferring the solution to a 10.0 mm quartz cuvette, the emission of the sample was collected.

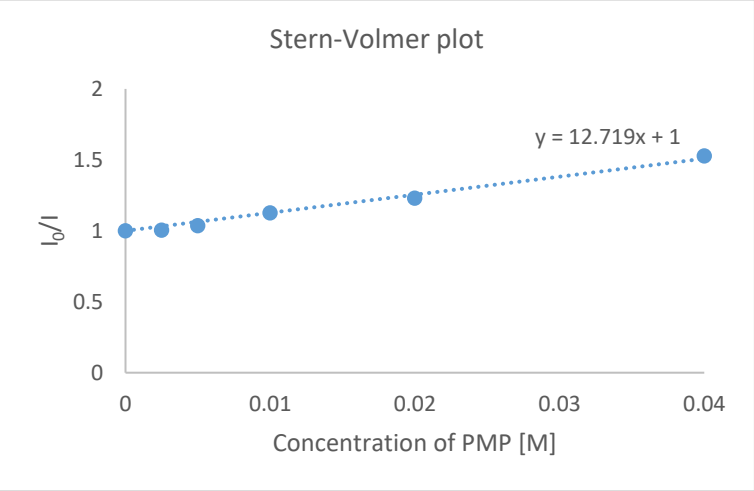


Figure S3. *p*-Terphenyl emission quenching by PMP.

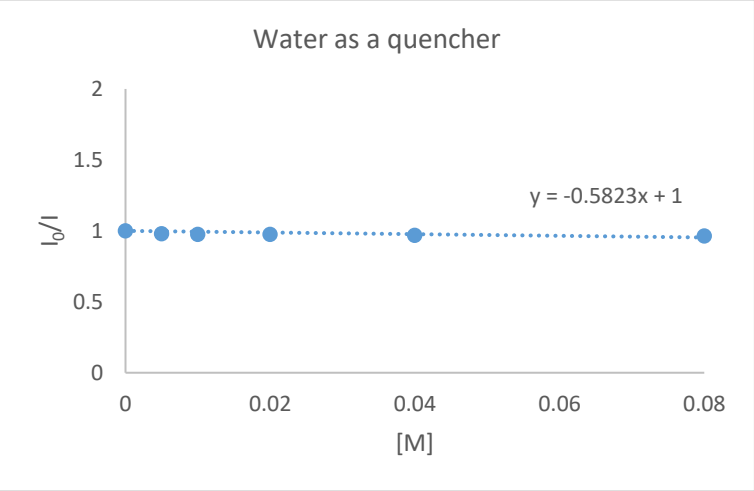
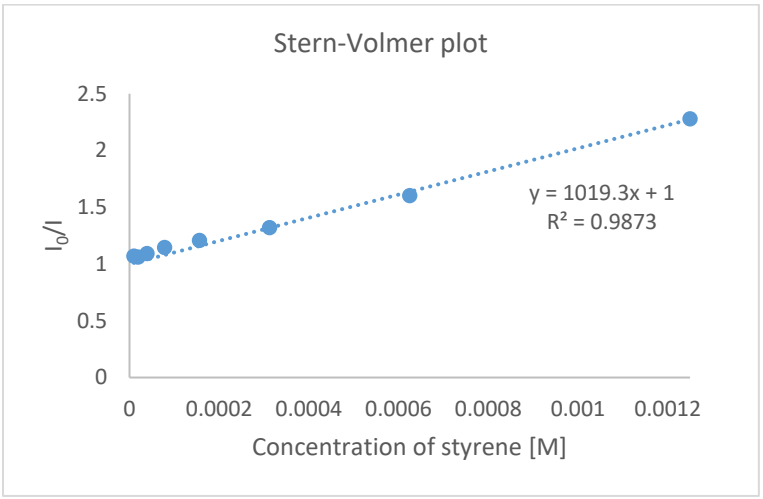


Figure S4. *p*-Terphenyl emission quenching by water.

(a)



(b)

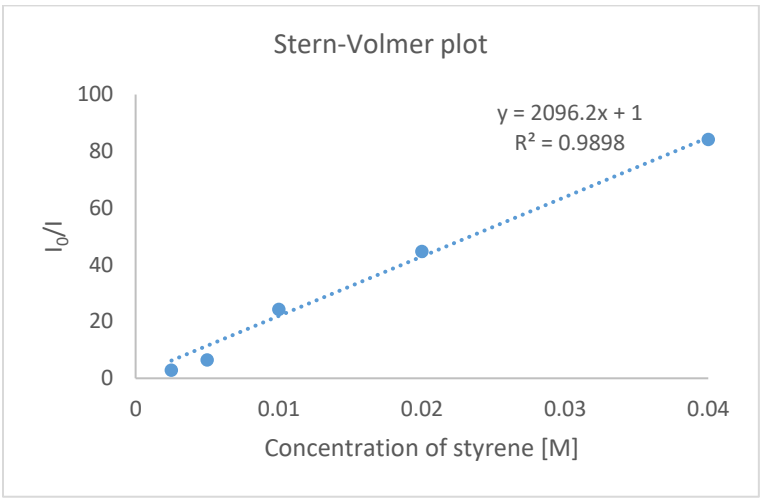
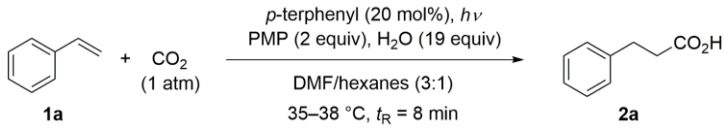


Figure S5. *p*-Terphenyl emission quenching by styrene. (**a**) At lower concentration of styrene. (**b**) At higher concentration of styrene. The emission intensities were normalized by subtracting those from styrene fluorescence.

Although *p*-terphenyl fluorescence quenching by styrene was observed in Stern-Volmer experiments, styrene might not be directly oxidized by the excited *p*-terphenyl in the optimized hydrocarboxylation conditions. The oxidation potential ($E_{p/2}$ = 1.97 V vs SCE in acetonitrile)[1] of styrene is much higher than that of PMP (E_p = 0.73 V vs SCE in acetonitrile)[2]. We assume aggregations between *p*-terphenyl and styrene might affect the excitation-emission properties.

Table S5. Control experiments.[a]

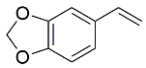


entry	omitted reagent	conversion (%)[b]	yield **2a** (%)[b]	notes
1	CO_2	88	0	ethylbenzene was detected
2	*p*-terphenyl	91	0	
3	PMP	<5	0	
4	light	<5	0	
5	hexanes	100	87	clogged in 20 min

[a]Reactions were carried out using a continuous flow photochemistry system developed by Beeler.
[b]Calculated by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard.

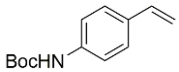
5. Synthesis of Starting Material

General procedure A for the synthesis of styrenes 1e, S1, and 4b.
To a solution of methyltriphenylphosphonium bromide (9.14 g, 25.6 mmol, 1.28 equiv) in THF (50 mL) was slowly added potassium *tert*-butoxide (2.91 g, 26 mmol, 1.30 equiv) at 0 °C. The resulting yellow suspension was stirred for 20 min at 0 °C. A solution of aldehyde (20 mmol, 1.0 equiv) in THF (10 mL) was added dropwise to the suspension and the reaction mixture was stirred for 1 h at 0 °C. 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.

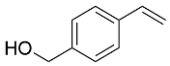


5-vinylbenzo[d][1,3]dioxole (**1e**)
This compound was prepared via general procedure A, using piperonal (3.00 g, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, straight hexanes) to afford **1e** (1.02 g, 6.89 mmol, 34% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 1.7 Hz, 1H), 6.84 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.63 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.96 (s, 2H), 5.58 (dd, *J* = 17.5, 0.7 Hz, 1H), 5.13 (dd, *J* = 10.8, 0.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.0, 147.3, 136.3, 132.1, 121.0, 111.9, 108.1, 105.4, 101.0.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[3]



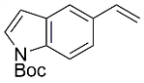
***tert*-butyl (4-vinylphenyl)carbamate** (**1f**)
To a solution of 4-vinylaniline (795 mg, 6.68 mmol, 1.0 equiv) in H_2O (8 mL) was added di-*tert*-butyl dicarbonate (1.60 g, 7.34 mmol, 1.1 equiv) at room temperature. After stirring for 8 h, the crude mixture was extracted with ethyl acetate. The combined 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 25 g KP-sil, straight hexanes) to afford **1g** (1.40 g, 6.37 mmol, 95% yield) as a white solid. IR (neat, cm^{-1}) 3377 (m), 2987 (m), 2938 (w), 1802 (w), 1701 (s), 1611 (w), 1586 (m), 1505 (s), 1459 (m), 1421 (m), 1404 (m), 1366 (m), 1320 (m), 1232 (m), 1156 (s), 1056 (m), 1026 (w), 985 (m), 899 (m), 837 (s), 773 (m), 720 (w). 1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 6.66 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.47 (s, 1H), 5.65 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.16 (dd, *J* = 10.9, 1.0 Hz, 1H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.6, 137.9, 136.2, 132.5, 126.8, 118.4, 112.4, 80.6, 28.3. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{13}H_{17}NO_2$, 218.1187; found, 218.1190.



(4-vinylphenyl)methanol (**1h**)[4]

To a solution of 4-vinylbenzyl chloride (2.8 mL, 20 mmol, 1.0 equiv) in H_2O (150 mL) was added sodium hydroxide (800 mg, 20 mmol, 1.0 equiv) and tetrabutylammonium bromide (25.8 g, 80 mmol, 4.0 equiv) at room temperature. The reaction mixture was heated to 125 °C and was allowed to stir for 2 h. After cooling to room temperature, the crude mixture was extracted with ethyl acetate. 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, 10–30% ethyl acetate in hexanes) to afford **1h** (1.54 g, 11.5 mmol, 57% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.75 (d, *J* = 17.6 Hz, 1H), 5.25 (d, *J* = 10.9 Hz, 1H), 4.68 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 137.0, 136.4, 127.2, 126.4, 113.9, 65.1.

The ^{1}H NMR spectra are in agreement with those reported in the literature**.**[4]



***tert*-butyl 5-vinyl-1H-indole-1-carboxylate** (**1k**)

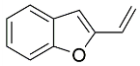
Step 1 (Wittig olefination) 5-vinyl-1*H*-indole (**S1**) was prepared via general procedure A, using 1*H*-indole-5-carbaldehyde (2.90 g, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 50 g KP-sil, 5-20% ethyl acetate in hexanes) to afford **S1** (857 mg, 5.99 mmol, 30% yield) as a yellow solid. IR (neat, cm^{-1}) 3408 (s, br), 3084 (w), 3050 (w), 3005 (w), 2977 (w), 2922 (w), 1717 (w), 1627 (s), 1510 (w), 1472 (s), 1449 (m), 1416 (s), 1344 (m), 1324 (s), 1287 (m), 1249 (m), 1226 (w), 1154 (w), 1129 (w), 1090 (m), 1066 (m), 990 (s), 884 (s), 809 (s), 766 (m), 723 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.66 (s, 1H), 7.35 (d, *J* = 1.4 Hz, 2H), 7.19 (t, *J* = 2.8 Hz, 1H), 6.85 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.60 – 6.52 (m, 1H), 5.71 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.15 (dd, *J* = 10.9, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 138.1, 135.8, 128.3, 127.7, 125.8, 119.0, 118.6, 111.5, 110.3, 101.4. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_{10}N$, 144.0808; found, 144.0809.

Step 2 (Boc protection) To a solution of **S1** (330 mg, 2.31 mmol, 1.0 equiv) in acetonitrile (8 mL) were added di-*tert*-butyl dicarbonate (604 mg, 2.77 mmol, 1.2 equiv) and 4-(dimethylamino)pyridine (2.4 mg, 0.02 mmol, 0.01 equiv) at room temperature. After stirring overnight, the reaction mixture was quenched with water, and the aqueous portion was extracted with ethyl acetate. 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 10 g KP-sil, straight hexanes) to afford **1k** (524 g, 2.16 mmol, 94% yield) as a colorless oil. IR (neat, cm^{-1}) 2979 (w), 2934 (w), 1730 (s), 1610 (w), 1576 (w), 1537 (w), 1470 (m), 1441 (m), 1367 (s), 1334 (s), 1286 (m), 1253 (m), 1215 (m), 1157 (s), 1128 (s), 1082 (s), 1022 (s), 990 (m), 890 (m), 854 (m), 822 (m), 799 (w), 766 (m), 730 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.6 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.41 (dd, *J* = 8.6, 1.7

Hz, 1H), 6.81 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.55 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.75 (dd, *J* = 17.6, 1.0 Hz, 1H), 5.21 (dd, *J* = 10.9, 0.9 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.6, 137.1, 134.9, 132.4, 130.8, 126.4, 122.4, 118.8, 115.1, 112.5, 107.4, 83.7, 28.2. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{18}NO_2$, 244.1332; found, 244.1391.

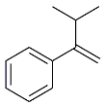
General procedure B for the synthesis of styrenes 1l, 4d, and 4e.

To a solution of methyltriphenylphosphonium bromide (7.86 g, 22 mmol, 1.1 equiv) in THF (80 mL) was slowly added *n*-butyllithiurm (2.5 M solution in hexanes, 8.8 mL, 22 mmol, 1.1 equiv) at room temperature. The resulting yellow suspension was stirred for 2 h at room temperature. A solution of aldehyde (20 mmol, 1.0 equiv) in THF (20 mL) was added dropwise to the suspension and the reaction mixture was stirred for 2 h at 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.



2-vinylbenzofuran (**1l**)

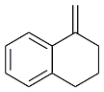
This compound was prepared via general procedure B in 13.7 mmol scale of starting material, using benzofuran-2-carbaldehyde (2.0 g, 13.7 mmol) as the starting material. The residue was purified by column chromatography (Biotage 25 g Ultra-sil, straight hexanes) to afford **1l** (1.60 g, 11.1 mmol, 81% yield) as a colorless oil. IR (neat, cm^{-1}) 3057 (w), 1685 (w), 1639 (w), 1613 (w), 1547 (m), 1451 (s), 1418 (w), 1345 (w), 1324 (w), 1283 (m), 1254 (s), 1194 (m), 1174 (m), 1150 (w), 1130 (w), 1108 (w), 1019 (m), 979 (m), 942 (s), 911 (m), 884 (m), 804 (s), 739 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.45 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.27 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.20 (td, *J* = 7.4, 1.1 Hz, 1H), 6.65 (dd, *J* = 17.5, 11.2 Hz, 1H), 6.60 (s, 1H), 5.97 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.39 (dd, *J* = 11.2, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 154.7, 128.8, 125.2, 124.6, 122.8, 120.9, 115.6, 111.0, 104.7. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_9O$, 145.0648; found, 145.0662.



(3-methylbut-1-en-2-yl)benzene (**4b**)

This compound was prepared via general procedure A, using isobutyrophenone (3.0 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 25 g Ultra-sil, straight hexanes) to afford **4b** (1.43 g, 9.75 mmol, 49% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 5H), 7.37 – 7.31 (m, 1H), 5.26 – 5.21 (m, 1H), 5.15 – 5.11 (m, 1H), 2.93 (hept, *J* = 6.9 Hz, 1H), 1.23 – 2.15 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 142.8, 128.1, 127.0, 126.6, 109.9, 32.3, 22.0.

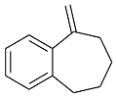
The ^{1}H NMR spectra are in agreement with those reported in the literature.[5]



1-methylene-1,2,3,4-tetrahydronaphthalene (**4d**)

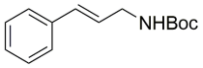
This compound was prepared via general procedure B, using α-tetralone (2.66 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 25 g Ultra-sil, straight hexanes) to afford **4d** (1.44 g, 10.0 mmol, 50% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 1H), 7.22 – 7.13 (m, 2H), 7.13 – 7.08 (m, 1H), 5.48 (d, *J* = 1.4 Hz, 1H), 4.96 (d, *J* = 1.5 Hz, 1H), 2.86 (t, *J* = 6.3 Hz, 2H), 2.55 – 2.52 (m, 2H), 1.90 – 1.84 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 135.8, 132.2, 127.3, 126.6, 126.3, 125.4, 122.7, 28.3, 23.2, 19.3.

The ^{1}H NMR spectra are in agreement with those reported in the literature.[6]



5-methylene-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene (**4e**)

This compound was prepared via general procedure B, using 1-benzosuberone (3.0 mL, 20 mmol) as the starting material. The residue was purified by column chromatography (Biotage 25 g Ultra-sil, straight hexanes) to afford **4e** (1.84 g, 11.6 mmol, 58% yield) as a colorless oil. IR (neat, cm^{-1}) 3072 (w), 3018 (w), 2921 (m), 2851 (m), 1629 (m), 1569 (w), 1485 (m), 1440 (m), 1347 (w), 1300 (w), 1269 (w), 1205 (w), 1176 (w), 1118 (w), 1089 (w), 1042 (m), 940 (m), 896 (s), 817 (w), 768 (s), 747 (s), 701 (m). 1H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 1H), 7.21 – 7.16 (m, 2H), 7.15 – 7.09 (m, 1H), 5.17 – 5.11 (m, 1H), 5.05 – 5.00 (m, 1H), 2.86 – 2.76 (m, 2H), 2.49 – 2.38 (m, 2H), 1.88 (p, *J* = 5.9 Hz, 2H), 1.78 (p, *J* = 5.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 144.1, 140.2, 128.9, 128.1, 127.1, 126.0, 113.7, 36.5, 36.3, 31.5, 27.4. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{15}$, 159.1168; found, 159.1163.



***tert*-butyl cinnamylcarbamate** (**4h**)[7]

To a solution of phenylboronic acid (975 mg, 8 mmol, 1.0 equiv) in acetone (25 mL) was added *tert*-butyl *N*-allylcarbamate (2.52 g, 16 mmol, 2.0 equiv), palladium acetate (90 mg, 0.4 mmol, 0.05 equiv), silver acetate (2.67 g, 16 mmol, 2.0 equiv) and potassium hydrogen difluoride (625 mg, 8 mmol, 1.0 equiv) at room temperature. The reaction mixture was heated to 60 °C and was allowed to stir for 8 h in sealed tube. After cooling to room temperature, the aqueous mixture was extracted with ethyl acetate. 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% ethyl acetate in hexanes) to afford **4h** (2.71 g, 7.33 mmol, 92% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 4H), 7.26 – 7.20 (m, 1H), 6.51 (dt, *J* = 15.8, 1.6 Hz, 1H), 6.20 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.71 (br s, 1H), 3.91 (d, *J* = 6.0 Hz, 2H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 136.7, 131.4, 128.6, 127.6, 126.4, 79.5, 42.8, 28.4.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[7]

6. Hydrocarboxylation of Styrenes in Continuous Flow

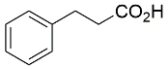
General Procedure C for hydrocarboxylation of styrenes

An oven-dried 50 mL Schlenk flask was charged with the appropriate styrene (1.05 mmol, 1.0 equiv), *p*-terphenyl (48 mg, 0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine (326 mg, 2.1 mmol, 2.0 equiv), water (0.4 mL, 20.0 mmol, 19 equiv) and dimethylformamide (7.0 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 a continuous flow photochemistry system (as described in Figure S1). After the flow system is filled by CO_2 (0.41 sccm) and all the air expelled prior to the start of the reaction, Harvard Apparatus PHD2000 syringe pumps were used to pump the reaction mixture and hexanes into the system. Once a steady 1:1 segmented flow of solution and CO_2 was observed, the system was equilibrated for 16 minutes. The product solution was then collected for 73 min (for the consumption of 0.70 mmol styrene reactant). The collected reaction mixture was concentrated under reduced pressure. The crude mixture was dissolved in ethyl acetate and added water and the pH was adjusted to pH 1 by adding aq. HCl. The aqueous portion was extracted with ethyl acetate. 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 to afford the desired product.

General Procedure for Optimization Reactions

For reaction optimization and mechanistic studies (Tables S1–5), the above procedure was followed and the product solution was collected for 5 min. After transferring 0.2 mL of the collected mixture to a 10 mL vial, methanol (0.2 mL) and (trimethylsilyl)diazomethane (2 M 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 mono/di carboxylation selectivity were determined by GC using a HP-5 column (a response factor was calculated using ^{1}H NMR).

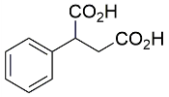
Characterization of Products



Hydrocinnamic acid (**2a**)

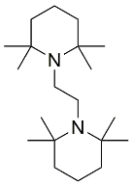
The general procedure C was followed using styrene **1a** (109 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a hydrocinnamic acid **2a** (91 mg, 0.61 mmol, 87% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 27:1 by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 2H), 7.30 – 7.23 (m, 3H), 3.02 (t, *J* = 7.8 Hz, 2H), 2.74 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 140.1, 128.5, 128.2, 126.3, 35.6, 30.5.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[8]



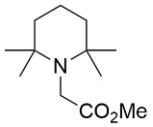
2-phenylsuccinic acid (**3a**)

IR (neat, cm^{-1}) 2881 (m, br), 2744 (m) 2636 (m, br), 1689 (s), 1600 (w), 1497 (w), 1419 (m), 1319 (m), 1240 (s), 1205 (s), 1070 (w), 1000 (m), 926 (s, br), 849 (m), 767 (m), 726 (s), 699 (s), 671 (m). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H), 7.37 – 7.22 (m, 5H), 3.89 (dd, J = 10.2, 5.1 Hz, 1H), 2.95 (dd, J = 16.9, 10.3 Hz, 1H), 2.54 (dd, J = 17.1, 5.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.0, 172.6, 138.7, 128.6, 127.7, 127.1, 46.8, 37.4. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{10}H_9O_4$, 193.0506; found, 193.0532.



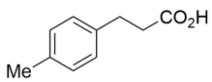
1,2-bis(2,2,6,6-tetramethylpiperidin-1-yl)ethane (**S2**)

IR (neat, cm^{-1}) 2999 (m), 2955 (m), 2920 (s), 2872 (m), 1476 (m), 1374 (m), 1354 (m), 1291 (m), 1253 (m), 1230 (w), 1204 (w), 1172 (m), 1130 (m), 1099 (m), 1024 (m), 976 (w), 949 (w), 919 (w), 873 (w), 780 (w), 716 (w). ^{1}H NMR (400 MHz, D_2O-DCl) δ 3.42 (s, 4H), 1.77 – 1.66 (m, 10H), 1.57 – 1.45 (m, 2H), 1.34 (s, 12H), 1.27 (s, 12H). ^{13}C NMR (101 MHz, D_2O-DCl) δ 67.6, 44.1, 36.7, 29.2, 20.0, 15.0. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_9O_2$, 309.3264; found, 309.3250.



methyl 2-(2,2,6,6-tetramethylpiperidin-1-yl)acetate (**S3**)

Compound **S3** was isolated after methylation following the general procedure for optimization reactions with 0.5 mmol scale. The yield was determined to 1.7% by GC analysis after esterification with (trimethylsilyl)diazomethane, using methyl benzoate as an internal standard. IR (neat, cm^{-1}) 2932 (s), 2873 (w), 1757 (s), 1729 (m), 1461 (m), 1435 (m), 1380 (m), 1361 (m), 1299 (m), 1267 (m), 1235 (m), 1192 (m), 1165 (s), 1135 (m), 1090 (w), 1064 (w), 1032 (w), 1063 (w), 976 (w), 951 (w), 928 (w), 908 (w), 885 (w), 852 (w), 805 (w), 723 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.28 (s, 2H), 1.56 – 1.54 (m, 2H), 1.51 – 1.46 (m, 4H), 1.00 (s, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 54.4, 51.6, 46.5, 40.5, 26.9, 17.6. HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{12}H_{23}NO_2$, 214.1802; found, 214.1810.

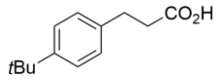


3-(*p*-tolyl)propanoic acid (**2b**)

The general procedure C was followed using styrene **1b** (124 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2b** (80 mg, 0.49 mmol, 70% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 18:1 by ^{1}H NMR analysis. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.10 (s, 4H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 137.1, 135.9, 129.2, 128.1, 35.4, 30.2, 21.0.

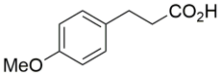
The ^1H and ^{13}C NMR spectra are in agreement with those reported in the literature.[9]



3-(4-(*tert*-butyl)phenyl)propanoic acid (**2c**)

The general procedure C was followed using styrene **1c** (168 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2c** (80 mg, 0.39 mmol, 55% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 16:1 by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 2.94 (t, *J* = 7.9 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 149.2, 137.1, 127.9, 125.4, 35.3, 34.4, 31.4, 30.0.

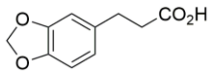
The ^1H and ^{13}C NMR spectra are in agreement with those reported in the literature.[10]



3-(4-methoxyphenyl)propanoic acid (**2d**)

The general procedure C was followed using styrene **1d** (128 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2d** (82 mg, 0.45 mmol, 65% yield) as a yellow solid. The selectivity of mono/di carboxylation was determined to be >40:1 by ^1H NMR analysis. ^1H NMR (400 MHz, $CCDl_3$) δ 10.15 (br s, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.9, 158.0, 132.3, 129.2, 129.1, 113.9, 113.7, 55.2, 35.9, 29.7.

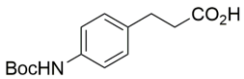
The ^1H and ^{13}C NMR spectra are in agreement with those reported in the literature.[11]



3-(benzo[*d*][1,3]dioxol-5-yl)propanoic acid (**2e**)

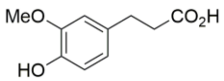
The general procedure C was followed using styrene **1e** (155 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2e** (50 mg, 0.26 mmol, 37% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be >40:1 by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 – 6.61 (m, 3H), 5.92 (s, 2H), 2.88 (t, *J* = 7.7 Hz, 2H), 2.63 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 147.6, 146.0, 134.0, 121.1, 108.7, 108.3, 100.8, 35.9, 30.3.

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



3-(4-((*tert*-butoxycarbonyl)amino)phenyl)propanoic acid (**2f**)

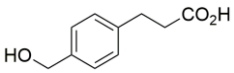
The general procedure C was followed using styrene **1f** (230 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2f** (129 mg, 0.48 mmol, 70% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 10:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3328 (w), 2977 (w), 2933 (w), 1706 (s), 1596 (w), 1524 (s), 1454 (w), 1413 (m), 1392 (m), 1368 (m), 1316 (m), 1238 (m), 1180 (s), 1054 (m), 903 (w), 835 (w), 773 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.68 (br s, 1H), 2.89 (t, *J* = 7.7 Hz, 1H), 2.61 (t, *J* = 7.9 Hz, 1H), 1.51 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.0, 153.0, 136.6, 134.9, 128.8, 118.9, 80.6, 35.6, 30.0, 28.3. HRMS (*m*/*z*) [M – H]$^-$ calcd for $C_{14}H_{18}NO_4$, 264.1241; found, 264.1256.



Dihydroferulic acid (**2g**)

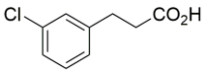
The general procedure C was followed using styrene **1g** (158 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–100% ethyl acetate in hexanes) to afford a propanoic acid **2g** (53 mg, 0.27 mmol, 38% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 10:1 by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, *J* = 7.8 Hz, 1H), 6.74 – 6.66 (m, 2H), 5.59 (br s, 1H), 3.86 (s, 3H), 2.89 (t, *J* = 7.7 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 146.4, 144.1, 132.1, 120.8, 114.4, 110.9, 55.8, 35.9, 30.3.

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



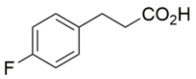
3-(4-(hydroxymethyl)phenyl)propanoic acid (**2h**)

The general procedure C was followed using styrene **1h** (141 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–100% ethyl acetate in hexanes) to afford a propanoic acid **2h** (61 mg, 0.34 mmol, 48% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 11:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3371 (m, br), 3031 (w), 2919 (m), 2709 (w), 1690 (s), 1517 (w), 1414 (m), 1343 (w), 1304 (m), 1223 (m), 1111 (w), 1014 (m), 942 (w), 827 (m), 755 (w), 674 (w). ^{1}H NMR (400 MHz, CD_3OD) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 4.56 (s, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 176.7, 141.3, 140.5, 129.3, 128.3, 65.0, 36.8, 31.7. HRMS (*m*/*z*) [M – H]$^-$ calcd for $C_{10}H_{12}O_3$, 179.0714; found, 179.0716.



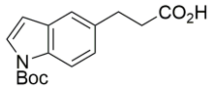
3-(3-chlorophenyl)propanoic acid (**2i**)

The general procedure C was followed using styrene **1i** (145 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2i** (42 mg, 0.23 mmol, 33% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 15:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3030 (w), 2961 (w), 2930 (w), 1707 (s), 1596 (m), 1572 (m), 1476 (m), 1430 (m), 1283 (w), 1208 (m), 1165 (m), 1080 (m), 1035 (w), 999 (w), 879 (w), 832 (w), 785 (m), 698 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 3H), 7.14 – 7.05 (m, 1H), 2.93 (t, *J* = 7.8 Hz, 2H), 2.67 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.6, 142.1, 134.3, 129.8, 128.5, 128.5, 126.6, 126.5, 35.1, 30.2. HRMS (*m*/*z*) [M – H]$^-$ calcd for $C_9H_8ClO_2$, 183.0218; found, 183.0221.



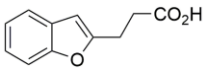
3-(4-fluorophenyl)propanoic acid (**2j**)

The general procedure C was followed using styrene **1j** (128 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford a propanoic acid **2j** (95 mg, 0.57 mmol, 81% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 18:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 2928 (w), 1707 (s), 1602 (w), 1509 (s), 1412 (w), 1292 (w), 1219 (s), 1158 (m), 1095 (w), 1016 (w), 934 (w), 830 (s), 765 (w), 727 (w), 700 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (br s, 1H), 7.16 (dd, *J* = 8.5, 5.5 Hz, 2H), 7.02 – 6.93 (m, 2H), 2.93 (t, *J* = 7.7 Hz, 2H), 2.66 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 162.7, 160.3, 135.7, 135.7, 129.7, 129.7, 115.4, 115.2, 35.6, 29.8. HRMS (*m*/*z*) [M – H]$^-$ calcd for $C_9H_8FO_2$, 167.0514; found, 167.0522.



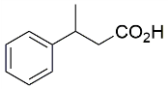
3-(1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl)propanoic acid (**2k**)

The general procedure C was followed using vinyl indole **1k** (255 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **2k** (115 mg, 0.40 mmol, 57% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 7:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 2976 (w), 2932 (w), 1729 (s), 1708 (s), 1582 (w), 1536 (w), 1470 (m), 1443 (m), 1370 (s), 1349 (s), 1297 (m), 1255 (m), 1219 (m), 1161 (s), 1122 (s), 1083 (m), 1041 (w), 1023 (m), 884 (w), 834 (w), 819 (w), 766 (m), 726 (m), 700 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H), 7.57 (d, *J* = 3.7 Hz, 1H), 7.41 – 7.37 (m, 1H), 7.16 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.51 (dd, *J* = 3.7, 0.8 Hz, 1H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.72 (t, *J* = 7.8 Hz, 2H), 1.67 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 149.7, 134.5, 130.9, 126.2, 124.7, 120.3, 115.1, 107.1, 83.6, 35.9, 30.6, 28.2. HRMS (*m*/*z*) [M – H]$^-$ calcd for $C_{16}H_{18}NO_4$, 288.1241; found, 288.1235.



3-(benzofuran-2-yl)propanoic acid (**2l**)

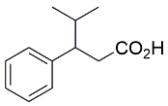
The general procedure C was followed using vinyl benzofuran **1l** (151 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **2l** (69 mg, 0.36 mmol, 52% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 7:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 2931 (w), 1709 (s), 1602 (w), 1587 (w), 1454 (s), 1390 (w), 1251 (s), 1167 (m), 1105 (w), 1009 (w), 944 (w), 881 (w), 806 (w), 758 (s), 700 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 1H), 7.43 – 7.39 (m, 1H), 7.25 – 7.15 (m, 2H), 6.45 (s, 1H), 3.13 (t, *J* = 7.5 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 123.5, 122.6, 120.4, 110.8, 102.6, 100.0, 31.6, 23.6. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{11}H_9O_3$, 189.0557; found, 189.0555.



3-phenylbutanoic acid (**5a**)

The general procedure C was followed using styrene **4a** (124 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5a** (72 mg, 0.44 mmol, 63% yield) as a white solid. Exclusive formation of monocarboxylated product was observed by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (br s, 1H), 7.36 – 7.28 (m, 2H), 7.25 – 7.19 (m, 3H), 3.28 (dq, *J* = 13.8, 7.1 Hz, 1H), 2.68 (dd, *J* = 15.5, 6.8 Hz, 1H), 2.58 (dd, *J* = 15.5, 8.3 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 145.4, 128.5, 126.7, 126.5, 42.5, 36.1, 21.8.

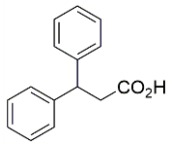
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[13]



4-methyl-3-phenylpentanoic acid (**5b**)

The general procedure C was followed using styrene **4b** (153 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5b** (82 mg, 0.43 mmol, 61% yield) as a white solid. Exclusive formation of monocarboxylated product was observed by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (br s, 1H), 7.31 – 7.25 (m, 2H), 7.23 – 7.17 (m, 1H), 7.17 – 7.12 (m, 2H), 2.88 (ddd, *J* = 9.5, 7.3, 5.5 Hz, 1H), 2.80 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.62 (dd, *J* = 15.5, 9.5 Hz, 1H), 1.89 – 1.80 (m, 6.8 Hz, 1H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.0, 142.5, 128.2, 128.1, 126.4, 48.4, 38.1, 33.1, 20.5, 20.1.

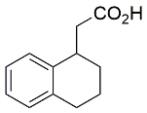
The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature.[13]



3,3-diphenylpropanoic acid (**5c**)

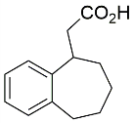
The general procedure C was followed using styrene **4c** (189 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5c** (101 mg, 0.45 mmol, 64% yield) as a white solid. Exclusive formation of monocarboxylated product was observed by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 10H), 4.58 (t, *J* = 7.9 Hz, 1H), 3.14 (d, *J* = 7.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 143.2, 128.6, 127.6, 126.6, 46.6, 40.2.

The ^{1}H and ^{13}C NMR spectra are in agreement with those reported in the literature**.**[14]



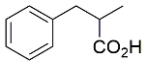
2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetic acid (**5d**)

The general procedure C was followed using styrene **4d** (151 mg, 1.05 mmol) and the crude mixture was collected for 63 min (0.6 mmol scale). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5d** (75 mg, 0.40 mmol, 67% yield) as a white solid. Exclusive formation of monocarboxylated product was observed by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3060 (w), 3017 (w), 2930 (m), 2863 (w), 1704 (s), 1602 (w), 1491 (m), 1451 (m), 1409 (m), 1338 (w), 1296 (m), 1240 (w), 1205 (w), 1173 (w), 1074 (w), 939 (w), 761 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.06 (m, 5H), 3.37 (dq, *J* = 9.9, 5.0 Hz, 1H), 2.84 – 2.74 (m, 3H), 2.60 (dd, *J* = 15.6, 10.0 Hz, 1H), 2.03 – 1.91 (m, 1H), 1.89 – 1.71 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.5, 138.9, 137.1, 129.3, 128.2, 126.1, 125.9, 41.7, 34.3, 29.5, 28.1, 19.5. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{12}H_{13}O_2$, 189.0921; found, 189.0919.



2-(6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-yl)acetic acid (**5e**)

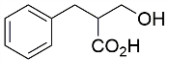
The general procedure C was followed using styrene **4e** (166 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5e** (79 mg, 0.39 mmol, 56% yield) as a white solid. Exclusive formation of monocarboxylated product was observed by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3063 (w), 3020 (w), 2919 (m), 2852 (m), 1702 (s), 1490 (m), 1445 (m), 1410 (m), 1283 (m), 1216 (m), 1134 (w), 939 (m), 756 (m), 679 (w). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.45 (br s, 1H), 7.20 – 7.06 (m, 4H), 3.55 – 3.42 (m, 1H), 3.02 – 2.71 (m, 4H), 1.97 – 1.67 (m, 4H), 1.65 – 1.50 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 143.6, 142.5, 129.8, 126.3, 126.2, 40.2, 38.4, 36.0, 33.4, 29.1, 27.7. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{13}H_{15}O_2$, 203.1078; found, 203.1081.



2-methyl-3-phenylpropanoic acid (**5f**)

The general procedure C was followed using *trans*-β-methylstyrene **4f** (124 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5f** (53 mg, 0.29 mmol, 42% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be >40:1 by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (br s, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.21 (m, 1H), 7.21 – 7.17 (m, 2H), 3.09 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.68 (dd, *J* = 13.3, 8.0 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 182.3, 139.0, 129.0, 128.4, 126.4, 41.2, 39.3, 16.5.

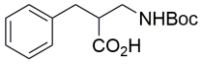
The ^{1}H NMR spectra are in agreement with those reported in the literature**.**[15]



2-benzyl-3-hydroxypropanoic acid (**5g**)

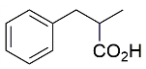
The general procedure C was followed using styrene **4g** (141 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5g** (64 mg, 0.35 mmol, 50% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 10:1 by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 2H), 7.18 – 7.10 (m, 3H), 3.74 – 3.68 (m, 1H), 3.67 – 3.61 (m, 1H), 3.06 – 2.96 (m, 1H), 2.87 – 2.75 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.3, 138.2, 128.9, 128.6, 126.7, 61.9, 48.7, 34.0.

The ^{1}H NMR spectra are in agreement with those reported in the literature**.**[16]



2-benzyl-3-((*tert*-butoxycarbonyl)amino)propanoic acid (**5h**)

The general procedure C was followed using styrene **4h** (245 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5h** (105 mg, 0.38 mmol, 54% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be >40:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 2979 (w), 2933 (w), 1706 (s), 1508 (m), 1454 (m), 1393 (m), 1367 (m), 1243 (s), 1162 (s), 1090 (w), 1045 (m), 959 (w), 913 (w), 857 (w), 735 (s), 699 (s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (br s, 1H), 7.32 – 7.25 (m, 2H), 7.24 – 7.16 (m, 3H), 6.53 (br s, 0.5H), 5.00 (br s, 0.5H), 3.59 – 2.52 (m, 5H), 1.41 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.1, 177.9, 157.7, 155.9, 138.1, 128.8, 128.5, 126.6, 81.2, 79.7, 47.4, 47.2, 42.0, 41.3, 35.6, 28.3, 28.3. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{15}H_{20}NO_4$, 278.1398; found, 278.1422.

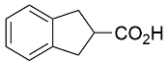


2-methyl-3-phenylpropanoic acid (**5i**)

The general procedure C was followed using *cis*-β-methylstyrene **4i** (124 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in

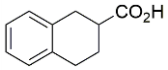
hexanes) to afford an acid **5i** (75 mg, 0.46 mmol, 66% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be >40:1 by ^{1}H NMR analysis.

The ^{1}H and ^{13}C NMR spectra are in agreement with **5f.**



2,3-dihydro-1*H*-indene-2-carboxylic acid (**5j**)

The general procedure C was followed using styrene **4j** (122 mg, 1.05 mmol) and the the crude mixture was collected for 55 min (0.5 mmol scale). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5j** (46 mg, 0.28 mmol, 57% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 14:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3069 (w), 2921 (w), 2855 (w), 2756 (w), 1695 (s), 1485 (w), 1430 (m), 1350 (w), 1325 (w), 1269 (m), 1237 (m), 1187 (w), 1100 (w), 1025 (w), 1010 (w), 923 (m), 746 (s), 693 (m). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.30 (br s, 1H), 7.25 – 7.13 (m, 4H), 3.44 – 3.18 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.0, 141.4, 126.6, 124.3, 43.4, 36.1. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{10}H_9O_2$, 161.0608; found, 161.0614.



1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (**5k**)

The general procedure C was followed using styrene **4k** (137 mg, 1.05 mmol). The residue was purified by column chromatography (Biotage 10 g KP-sil, 2–70% ethyl acetate in hexanes) to afford an acid **5k** (66 mg, 0.38 mmol, 54% yield) as a white solid. The selectivity of mono/di carboxylation was determined to be 17:1 by ^{1}H NMR analysis. IR (neat, cm^{-1}) 3019 (w), 2927 (w), 1699 (s), 1494 (m), 1452 (m), 1418 (m), 1292 (m), 1262 (m), 1229 (m), 1199 (m), 1111 (w), 1060 (w), 1038 (w), 947 (m), 839 (w), 816 (w), 741 (s), 699 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (br s, 1H), 7.16 – 7.06 (m, 4H), 3.14 – 2.97 (m, 2H), 2.97 – 2.74 (m, 3H), 2.31 – 2.20 (m, 1H), 1.96 – 1.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 135.6, 134.6, 129.1, 128.9, 126.0, 125.9, 39.7, 31.3, 28.4, 25.6. HRMS (*m*/*z*) $[M - H]^-$ calcd for $C_{11}H_{11}O_2$, 175.0765; found, 175.0771.

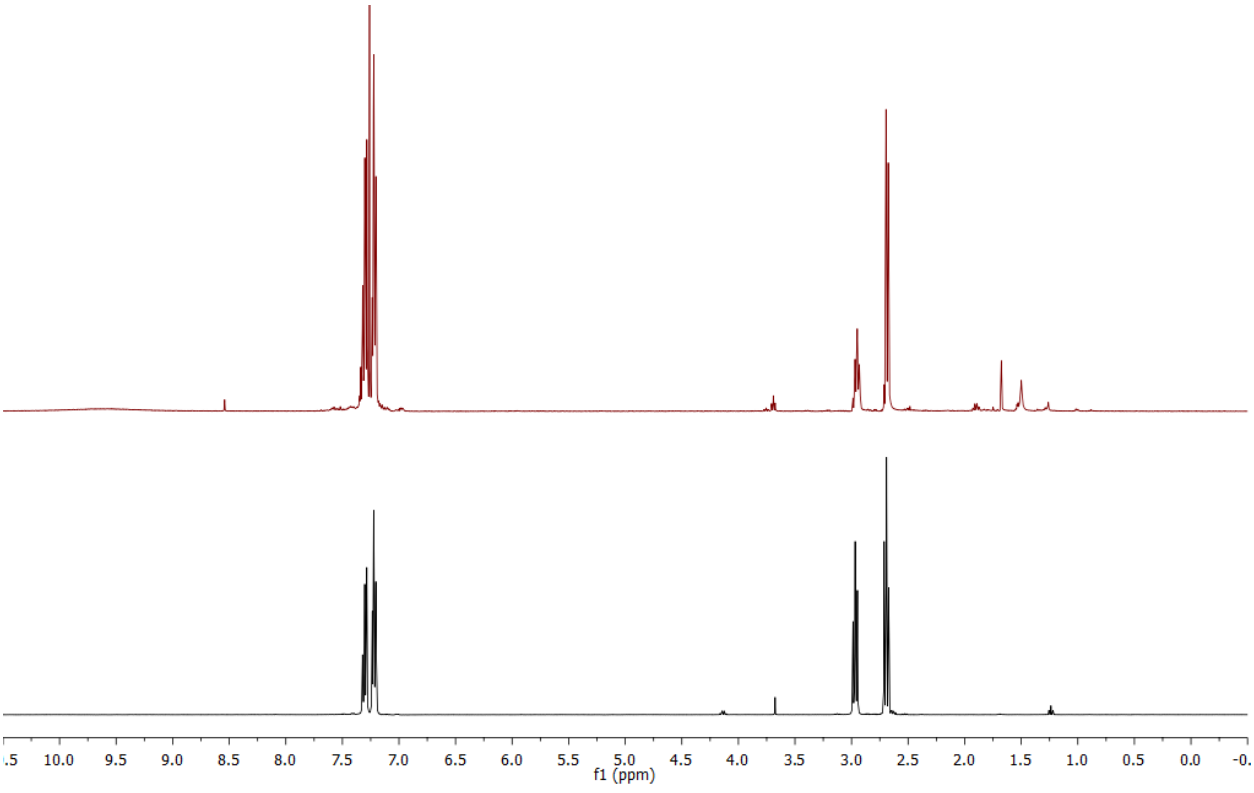
7. Deuterium labeling experiments

Hydrocarboxylation of styrene (**1a**) using D_2O:

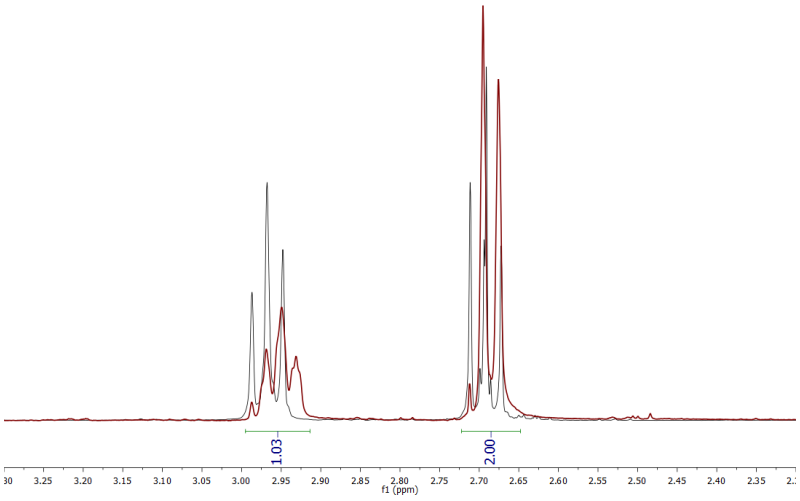
General procedure C was followed using styrene (109 mg, 1.05 mmol, 1.0 equiv), *p*-terphenyl (69 mg, 0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine (326 mg, 2.1 mmol, 2.0 equiv), D_2O (0.4 mL, 20 mmol, 19 equiv), DMF (7 mL), and hexanes (2.3 mL). The isolated product **2aa-*d*$_1$** was obtained 67%, with >95% deuterium incorporation at the α-position of the hydrocarboxylated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.23 (m, 3H), 2.96 (t, *J* = 7.6 Hz, 1H), 2.69 (d, *J* = 8.0 Hz, 2H).

Figure S6. (a) Stacked NMR plots of 2a (black) and 2aa-*d*$_1$ (red). (b) superimposed spectra (δ 3.30 – 2.30 ppm)

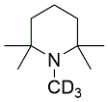
(a)



(b)



Synthesis of **S4**



2,2,6,6-tetramethyl-1-(methyl-*d*3)piperidine (**S4**)[17]

To a solution of tetramethylpiperidine (2.53 mL, 15 mmol, 1.0 equiv) in THF (10 mL) was added dropwise *n*-butyllithium (2.5 M in hexanes, 7.2 mL, 15 mmol, 1.0 equiv) at –78 °C. After the addition was completed, the reaction mixture was allowed to warm to room temperature and stir for 20 min. The reaction mixture was cooled to –78 °C and iodomethane-*d*3 (1.24 mL, 20 mmol, 1.3 equiv) was added dropwise. After the addition was completed, the reaction mixture was allowed to warm to room temperature and stir for 2 h. The reaction mixture was quenched with water, and the aqueous portion was extracted with ethyl acetate. 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 25 g Ultra-sil, 10–40% ethyl acetate in hexanes) to afford **S4** (1.01 g, 6.38 mmol, 43% yield) as a colorless oil. ^{1}H NMR (400 MHz, Benzene-d_6) δ 1.43 (s, 6H), 1.02 (s, 12H). HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{10}H_{19}D_3N$, 159.1935; found, 159.1925.

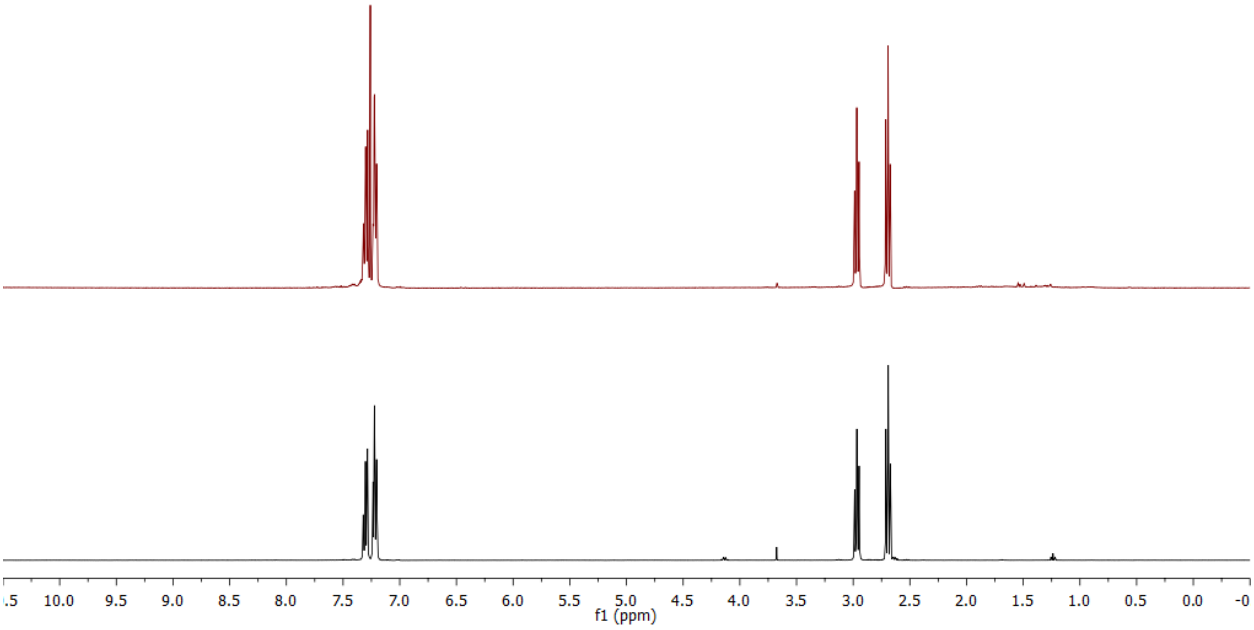
The ^{1}H NMR spectra are in agreement with those reported in the literature**.**[17]

Hydrocarboxylation of styrene (**1a**) using PMP-d_3 (**S4**) and H_2O:

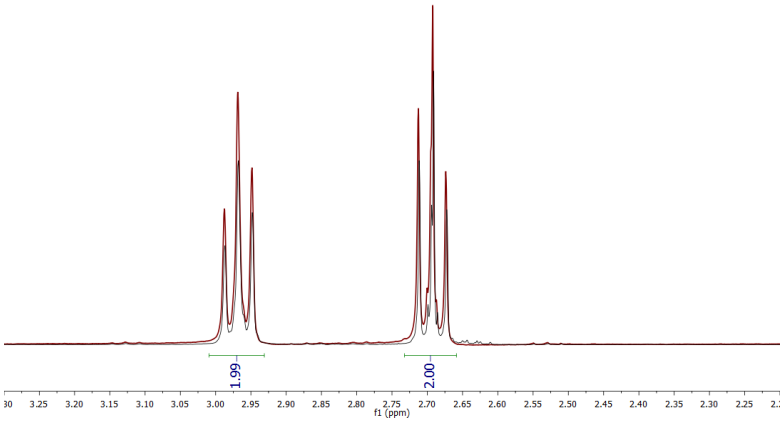
General procedure C was followed using styrene (109 mg, 1.05 mmol, 1.0 equiv), *p*-terphenyl (69 mg, 0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine-d_3 **S4** (332 mg, 2.1 mmol, 2.0 equiv), H_2O (0.4 mL, 20 mmol, 19 equiv), DMF (7 mL), and hexanes (2.3 mL). The isolated product **2ab-*d*$_1$** was obtained 87%, with <1% deuterium incorporation at the α-position of the hydrocarboxylated product.

Figure S7. (a) Stacked NMR plots of 2a (black) and 2ab-*d*$_1$ (red). (b) superimposed spectra (δ 3.30 – 2.30 ppm)

(a)



(b)

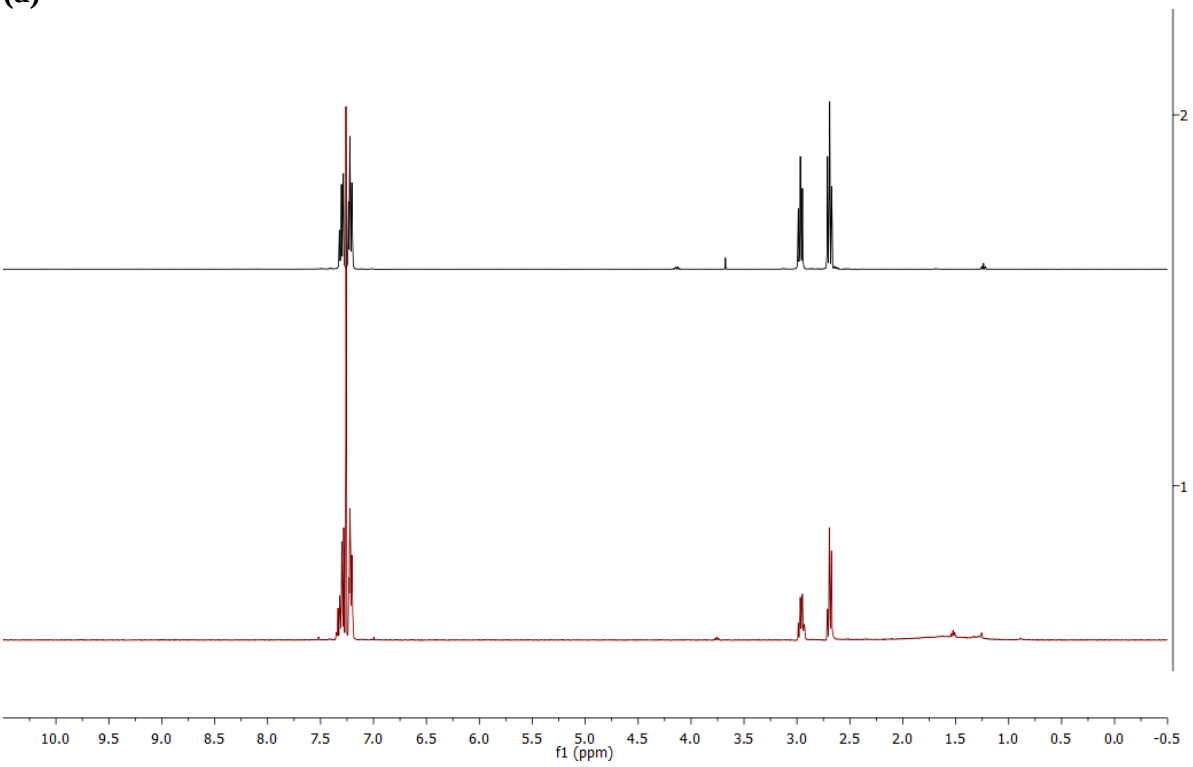


Hydrocarboxylation of styrene (**1a**) using PMP-d_3 (**S4**) in dry DMF:

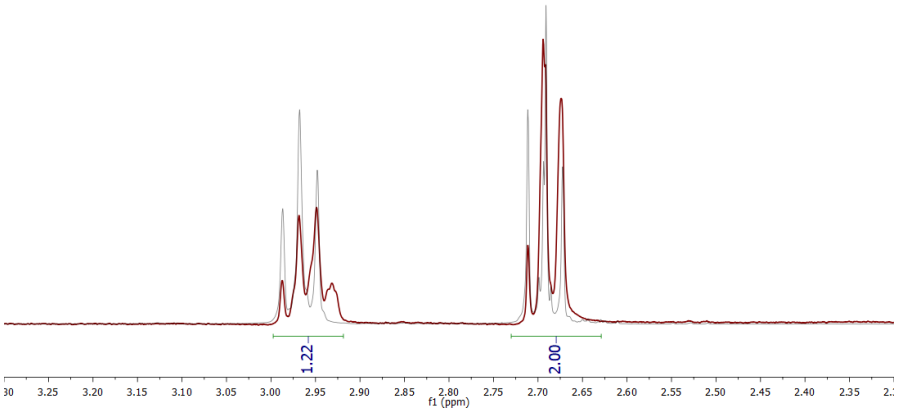
General procedure C was followed using styrene (109 mg, 1.05 mmol, 1.0 equiv), *p*-terphenyl (69 mg, 0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine-d_3 **S4** (332 mg, 2.1 mmol, 2.0 equiv), DMF (7 mL, dried by five cycles of freeze-pump-thaw over molecular sieve 4A, water content: 144 ppm, determined by Karl-Fischer titration), and hexanes (2.3 mL). The isolated product **2ac-*d*$_1$** was obtained 26%, with 78% deuterium incorporation at the α-position of the hydrocarboxylated product.

Figure S8. (a) Stacked NMR plots of 2a (black) and 2ac-*d*$_1$ (red). (b) superimposed spectra (δ 3.30 – 2.30 ppm)

(a)



(b)

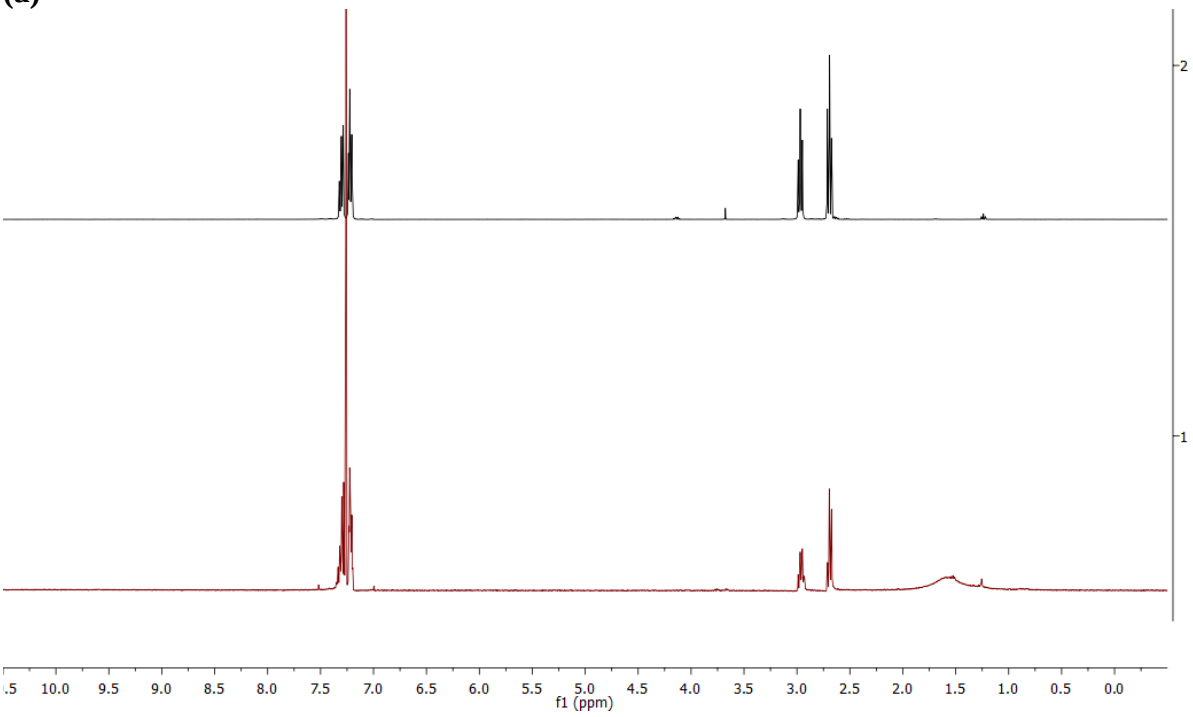


Hydrocarboxylation of styrene (**1a**) using PMP-d_3 (**S4**) in dry DMF-d_7:

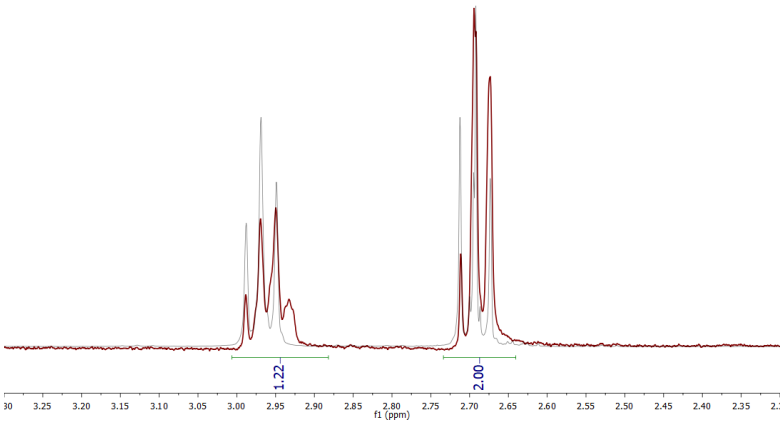
General procedure C was followed using styrene (109 mg, 1.05 mmol, 1.0 equiv), *p*-terphenyl (69 mg, 0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine-d_3 **S4** (332 mg, 2.1 mmol, 2.0 equiv), DMF-d_7 (7 mL, dried by five cycles of freeze-pump-thaw over molecular sieve 4A, water content: 107 ppm, determined by Karl-Fischer titration), and hexanes (2.3 mL). The isolated product **2ad-d_1** was obtained 25%, with 78% deuterium incorporation at the α-position of the hydrocarboxylated product.

Figure S9. (a) Stacked NMR plots of 2a (black) and 2ad-d_1 (red). (b) superimposed spectra (δ 3.30 – 2.30 ppm)

(a)



(b)

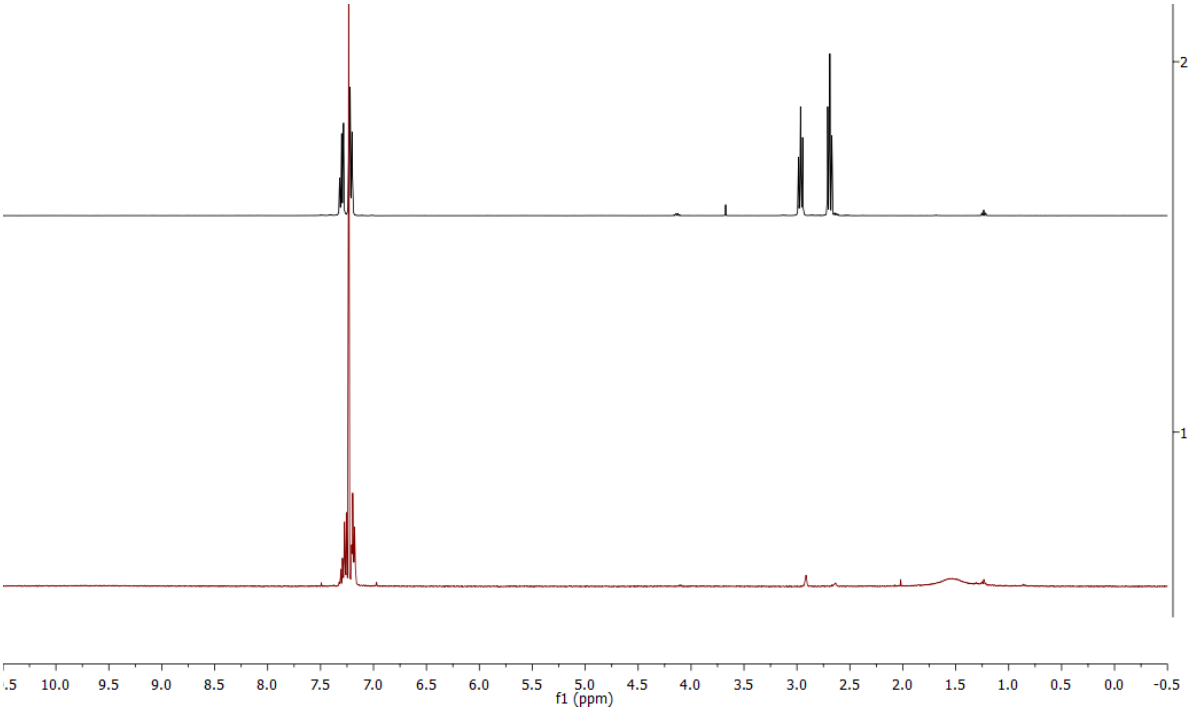


Hydrocarboxylation of styrene-α,β,β-d_3 using PMP-d_3 (**S4**) in dry DMF:

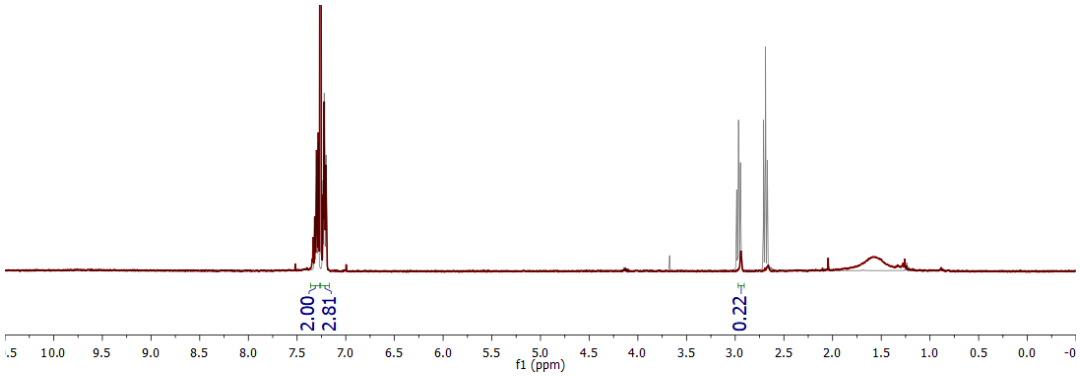
General procedure C was followed using styrene-α,β,β-d_3 (≥98 atom % D, 109 mg, 1.05 mmol, 1.0 equiv), *p*-terphenyl (69 mg, 0.21 mmol, 20 mol%), 1,2,2,6,6-pentamethylpiperidine-d_3 **S4** (332 mg, 2.1 mmol, 2.0 equiv), DMF (7 mL, dried by five cycles of freeze-pump-thaw over molecular sieve 4A, water content: 170 ppm, determined by Karl-Fischer titration), and hexanes (2.3 mL). The isolated product **2ae-*d*$_4$** was obtained 25%, with 78% deuterium incorporation at the α-position of the hydrocarboxylated product.

Figure S10. (a) Stacked NMR plots of 2a (black) and 2ae-*d*$_4$ (red). (b) superimposed spectra (δ 10.5 – –0.5 ppm)

(a)



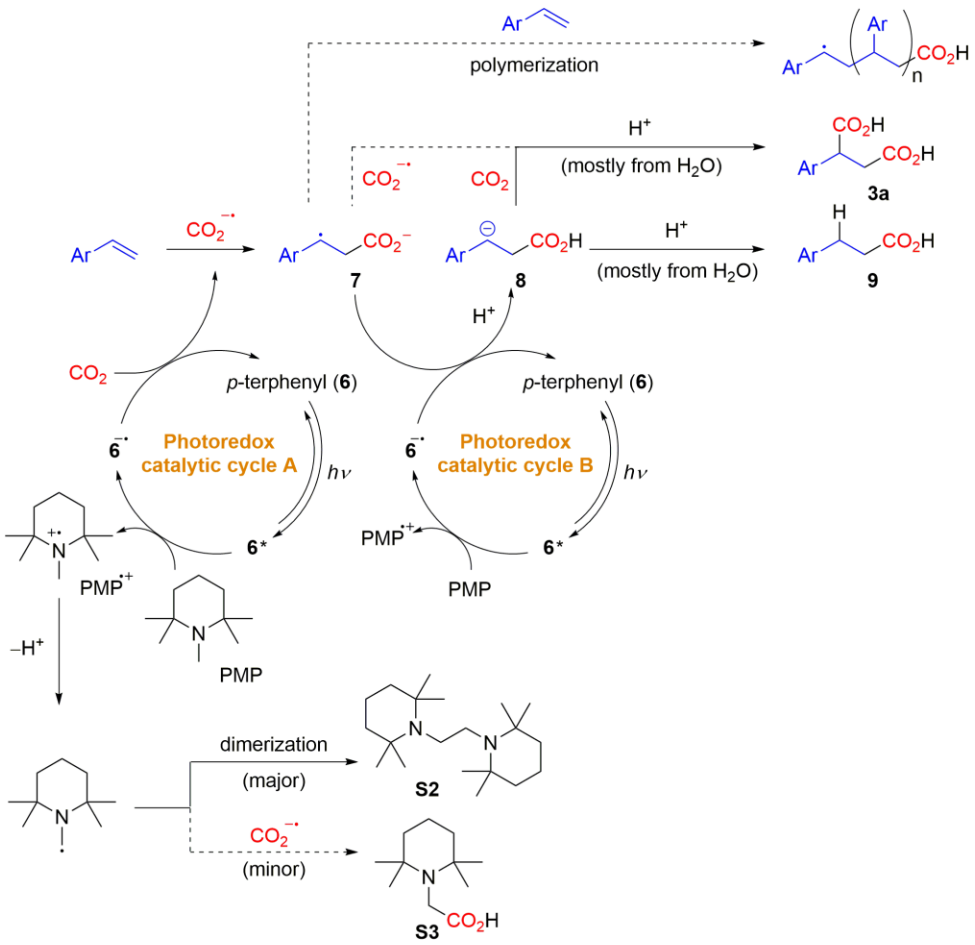
(b)



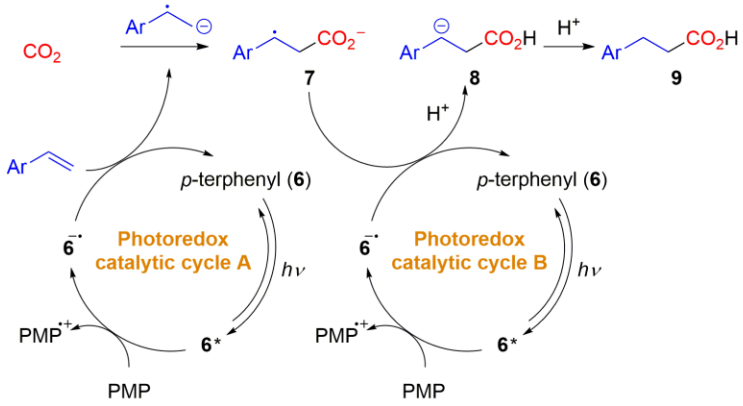
8. Proposed mechanisms.

Figure S11. (a) Proposed mechanism with details, (b) alternative mechanism for substrates 1g and 4c.

(a) Proposed mechanism with details



(b) Alternative mechanism of substrates **1g** and **4c**.



9. References

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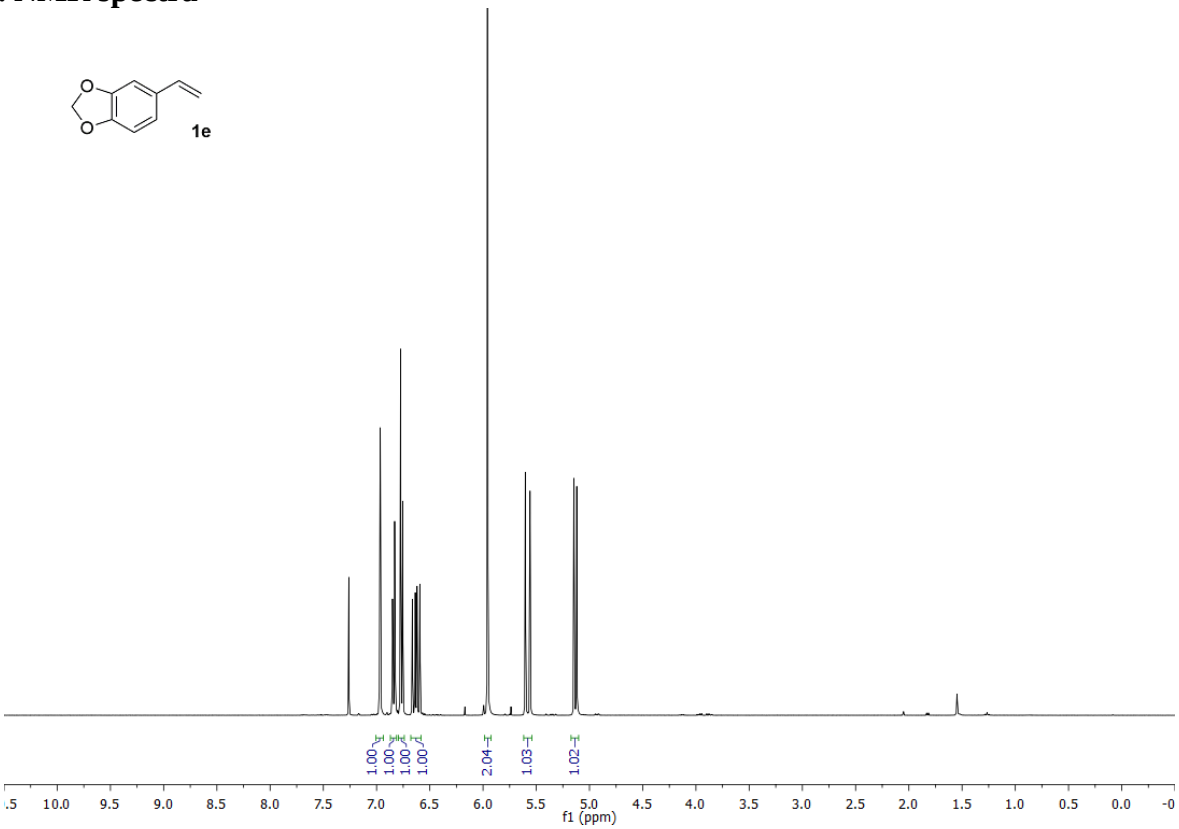
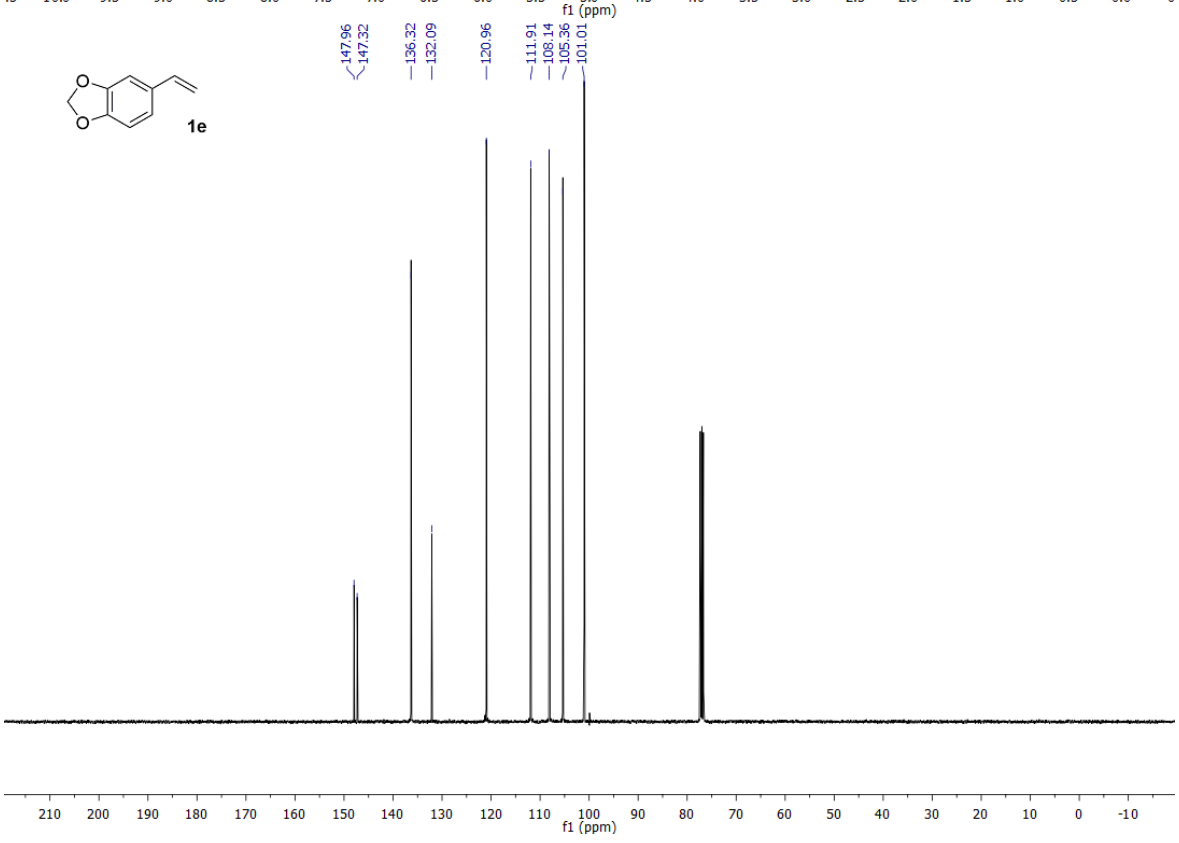
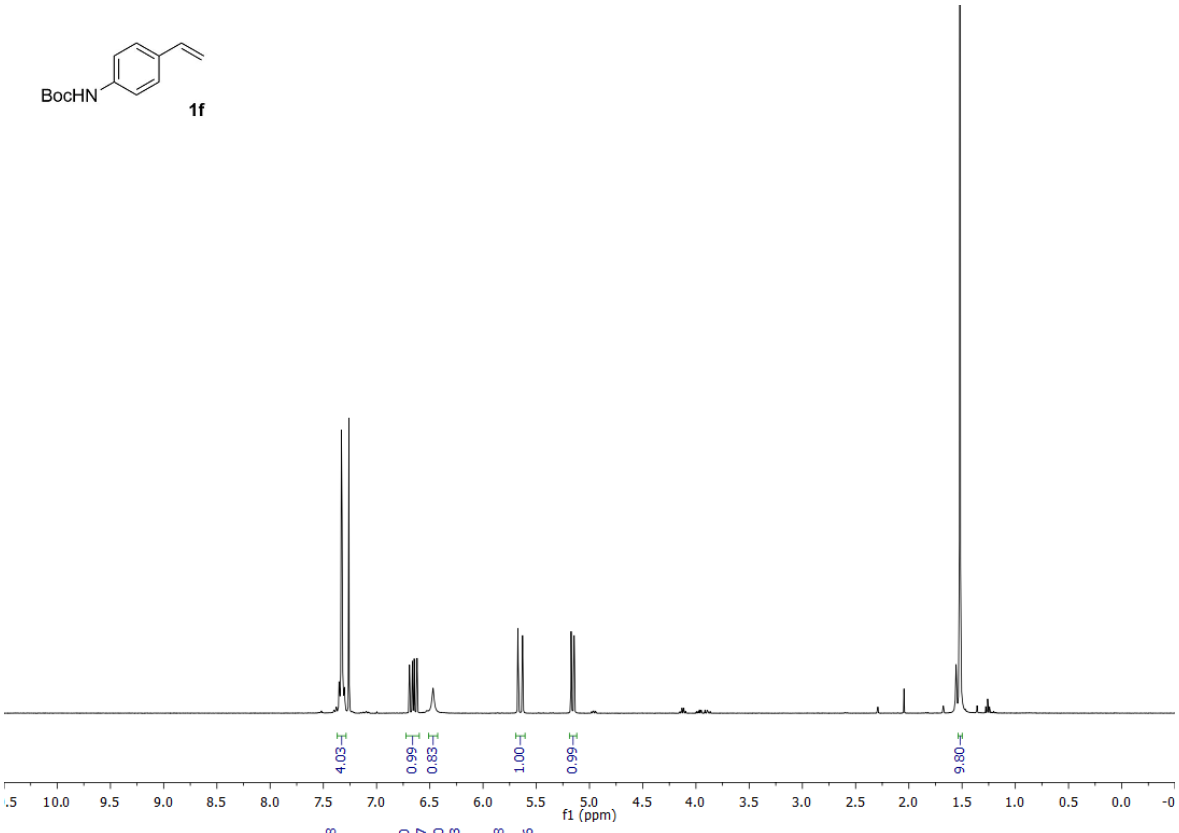
(17) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253.

10. NMR spectra



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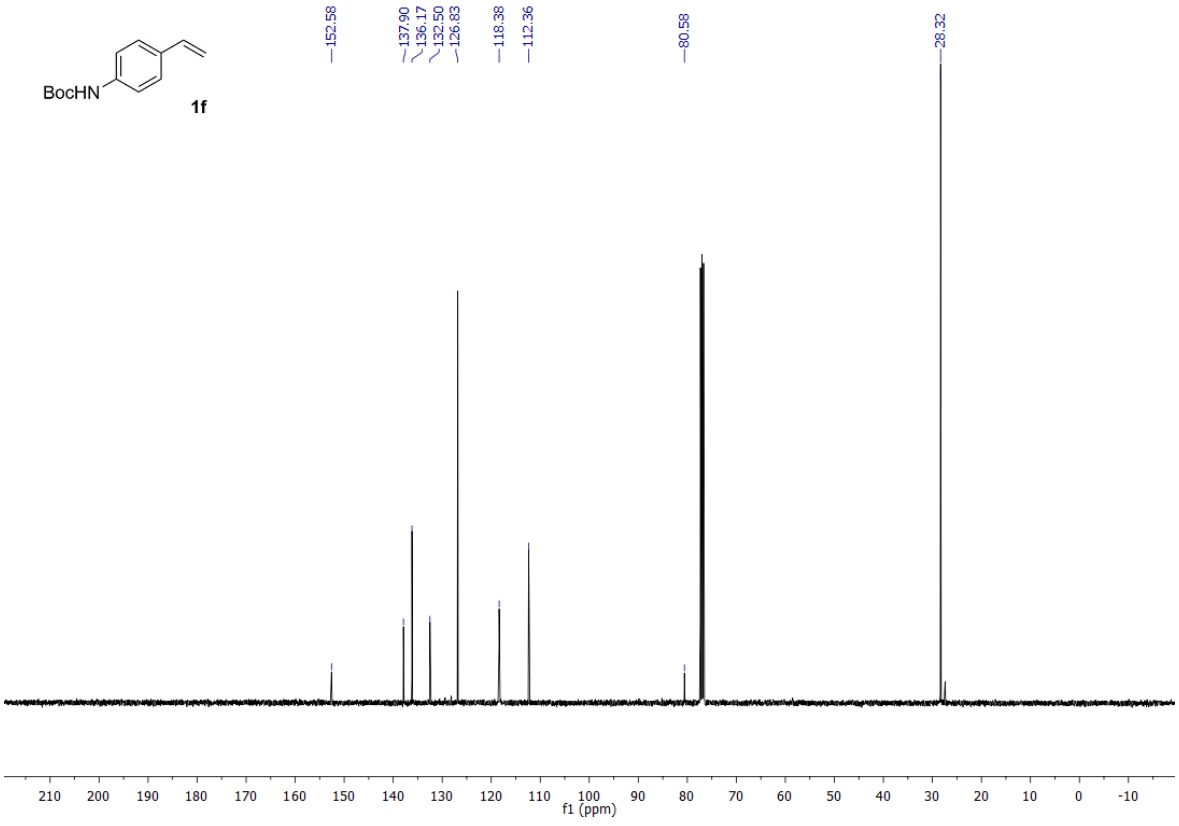
0.99
0.83
1.00
0.99
9.80
f1 (ppm)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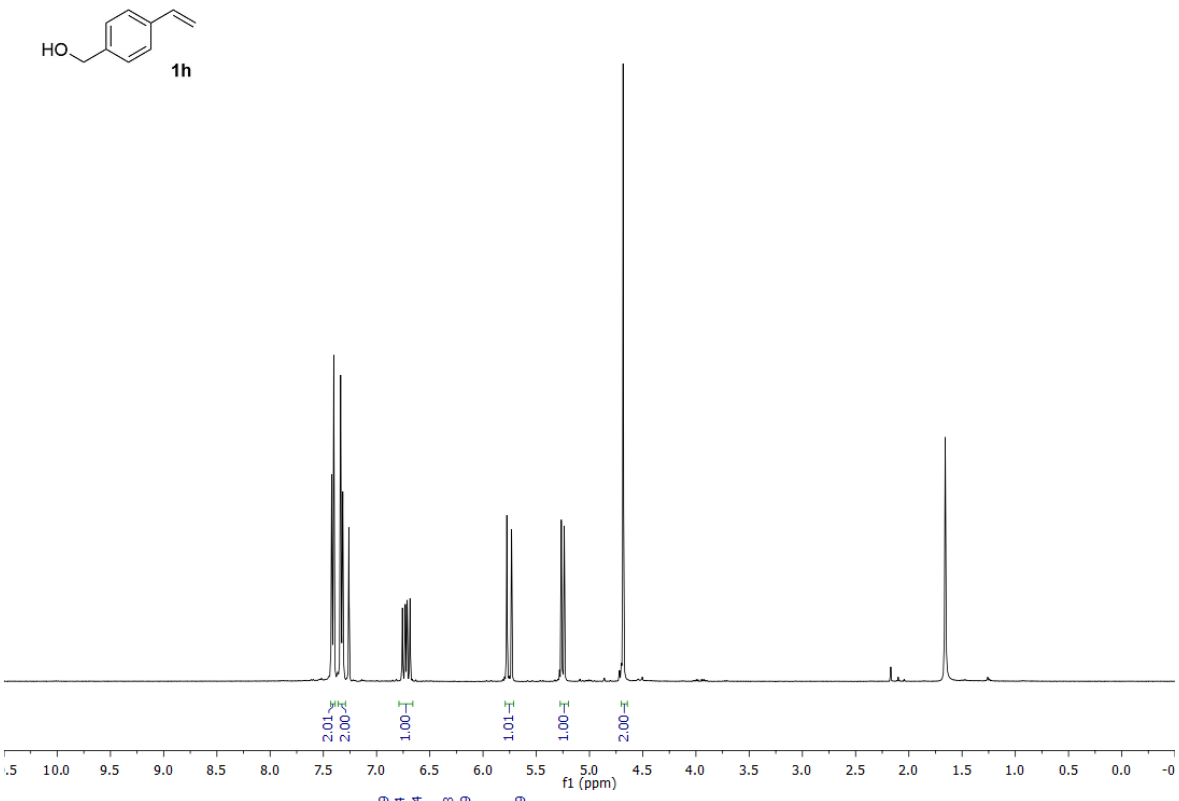
80.58
28.32
f1 (ppm)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1h
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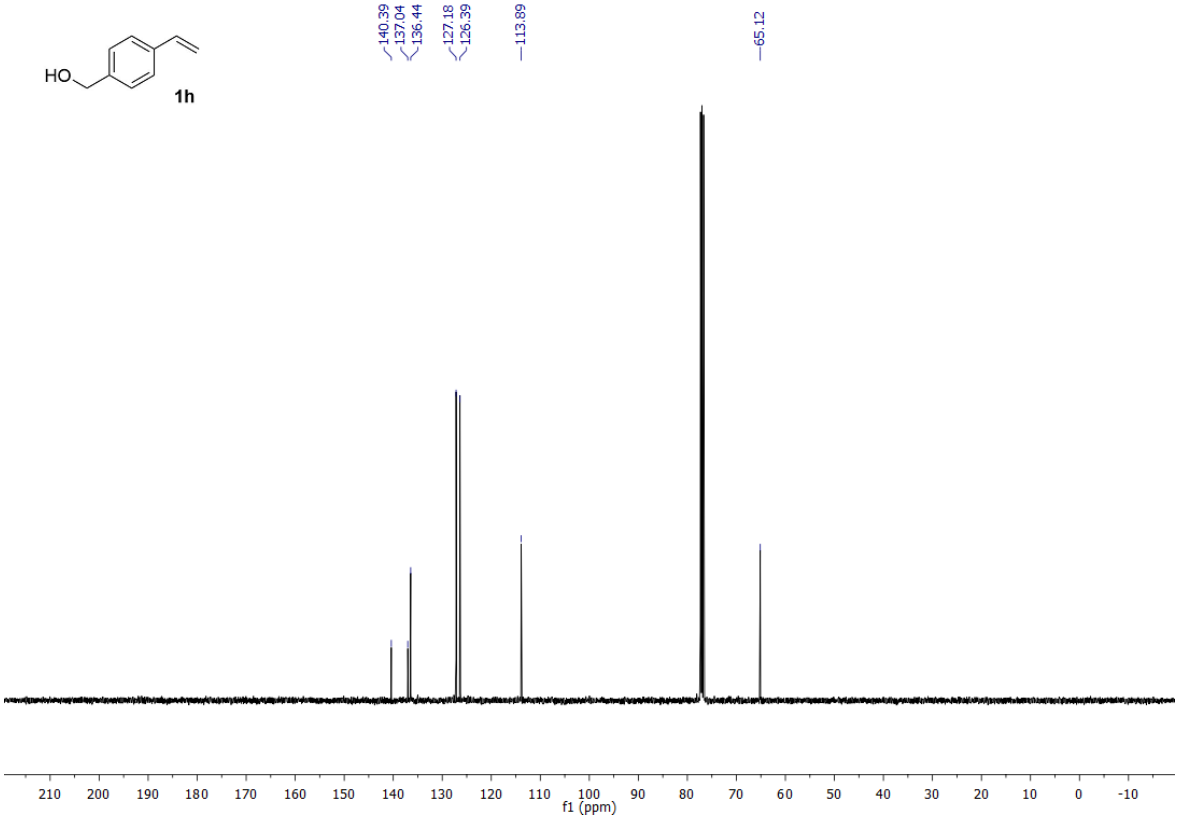
2.00
1.00
1.01
1.00
2.00
f1 (ppm)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1h
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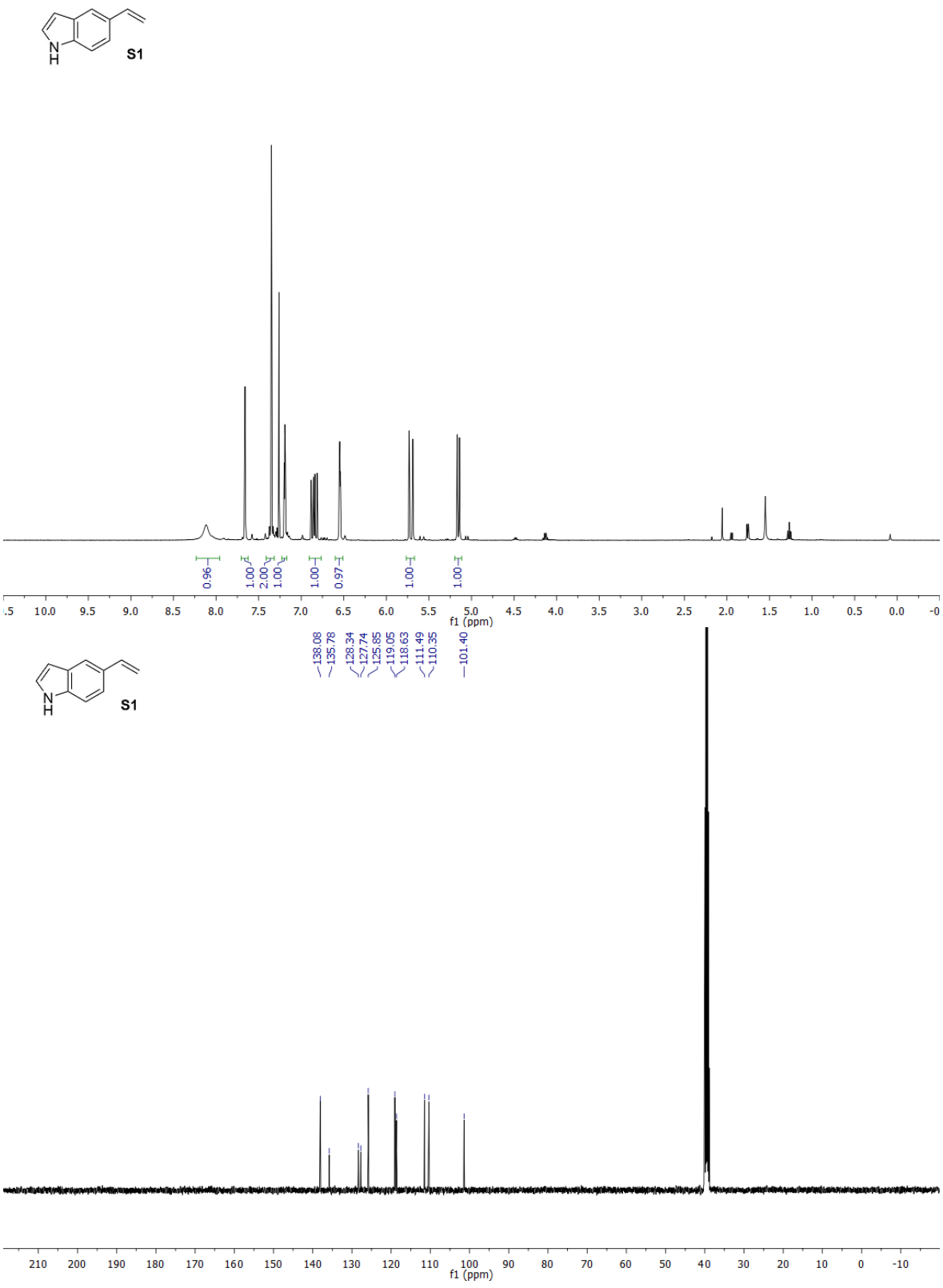
65.12
f1 (ppm)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1.00
1.00
f1 (ppm)
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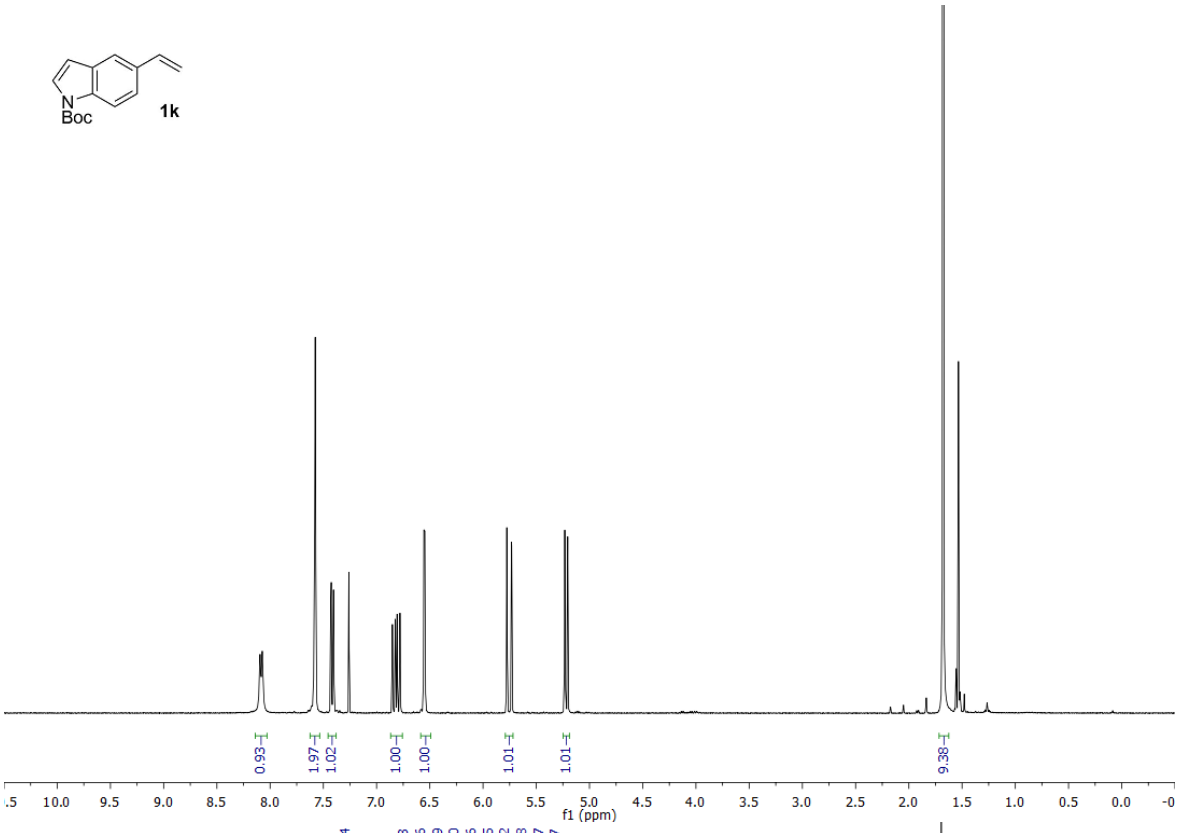
118.63
111.49
110.35
101.40
S1
f1 (ppm)


N
Boc
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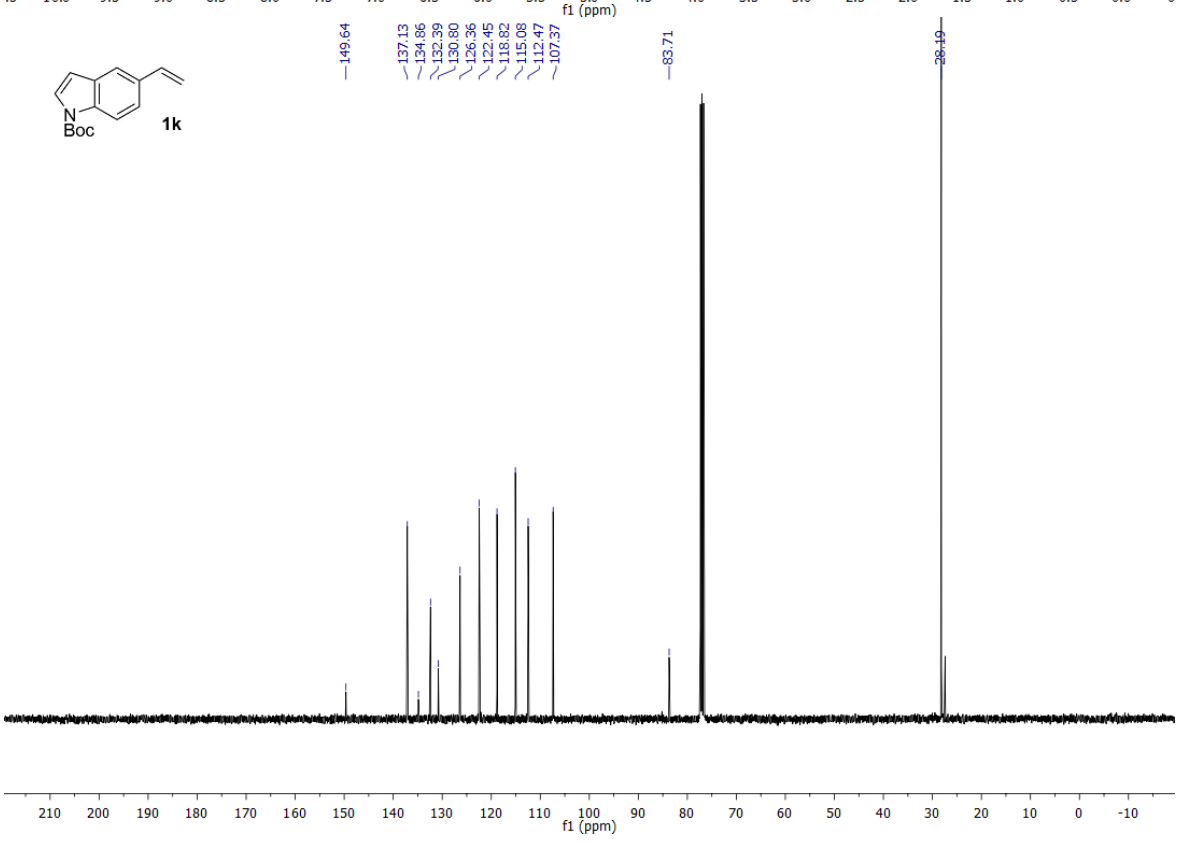
1.02
1.00
1.00
1.01
1.01
9.38
f1 (ppm)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Boc
1k
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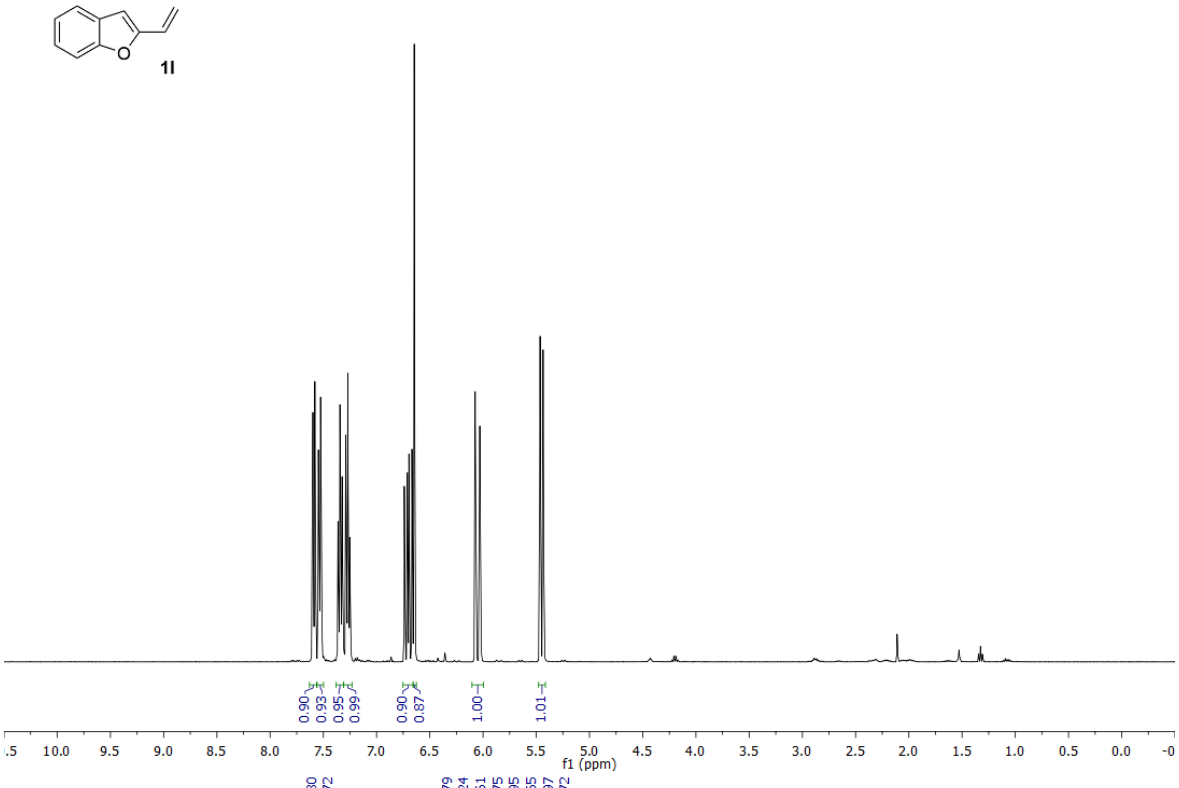
107.37
83.71
28.19
f1 (ppm)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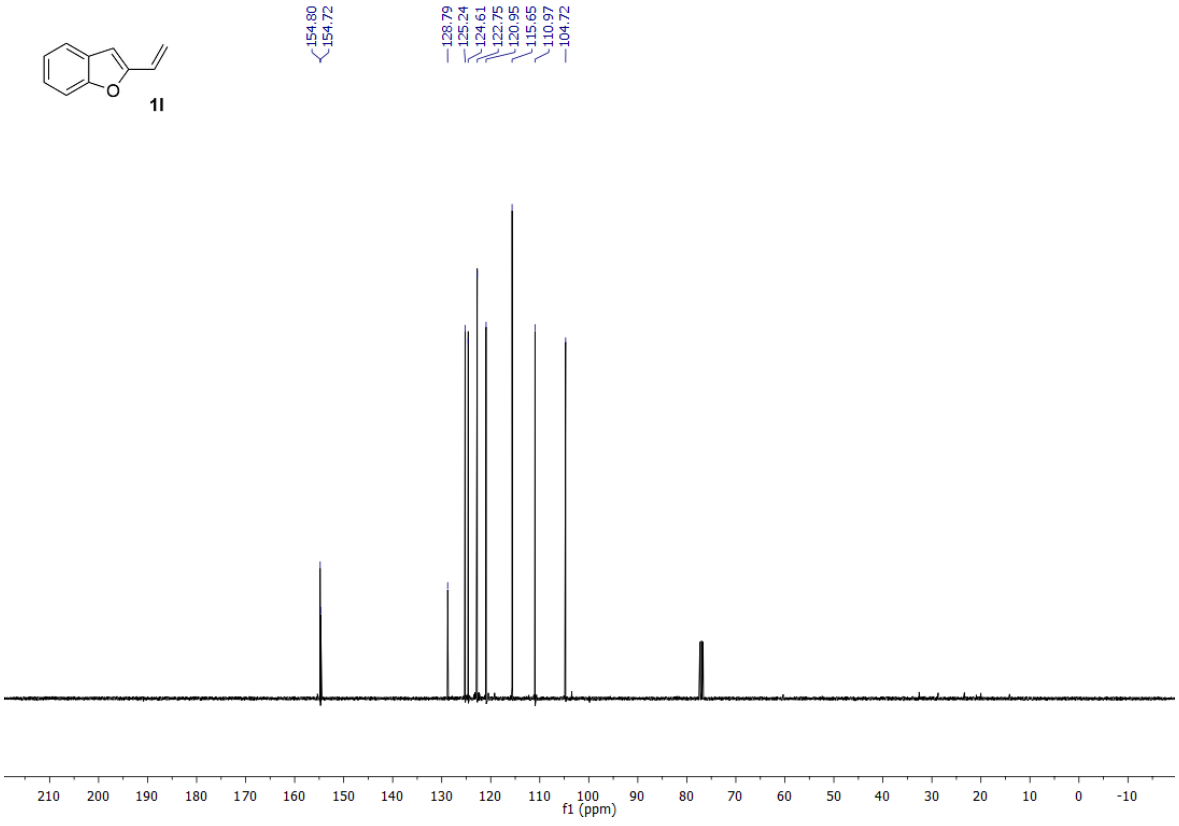
0.99
0.90
0.87
1.00
1.01
f1 (ppm)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120.95
115.65
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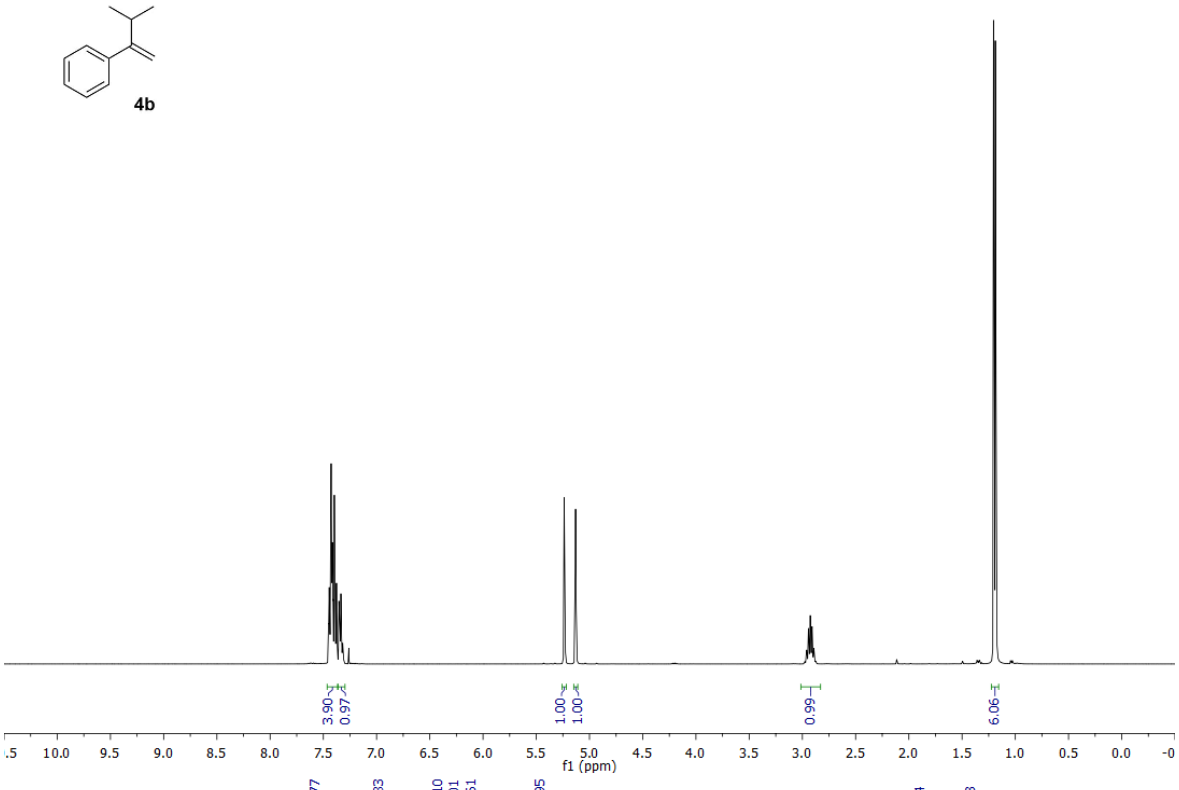
f1 (ppm)


4b
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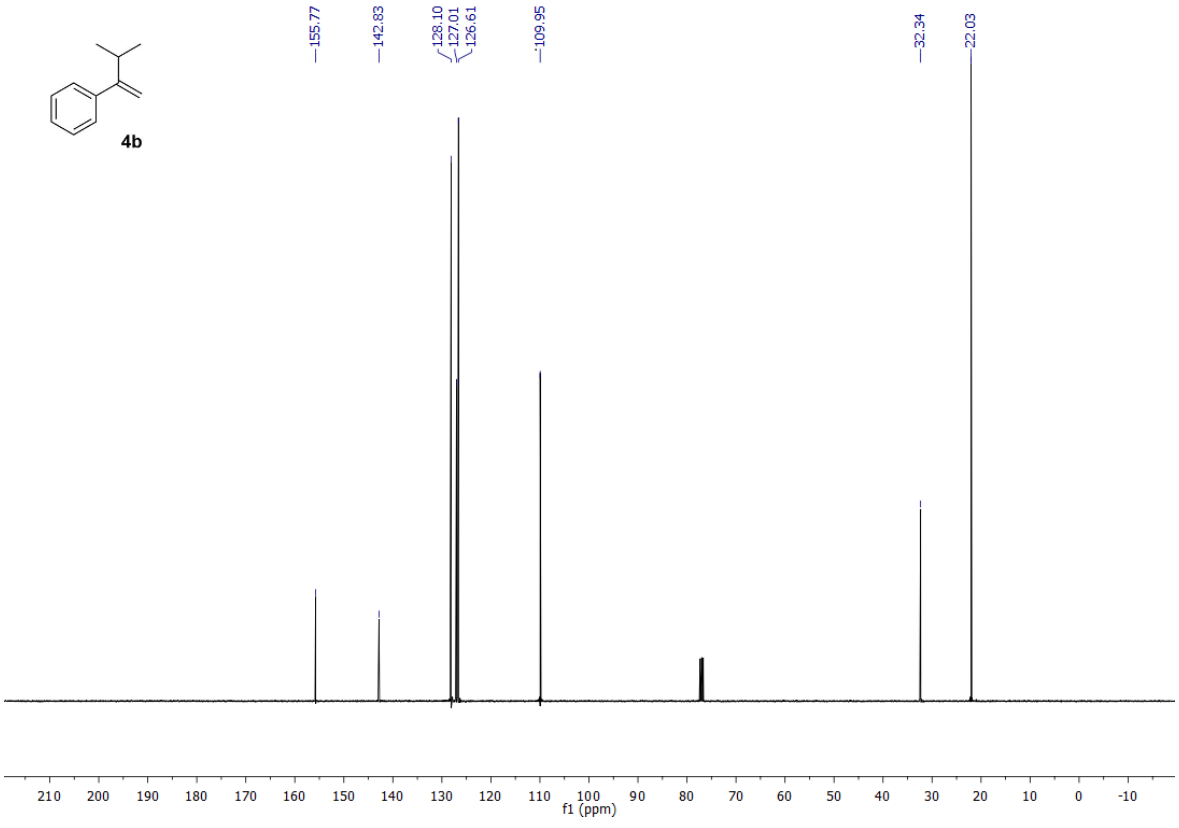
1.00
1.00
0.99
6.06
f1 (ppm)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126.61
109.95
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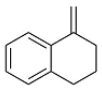
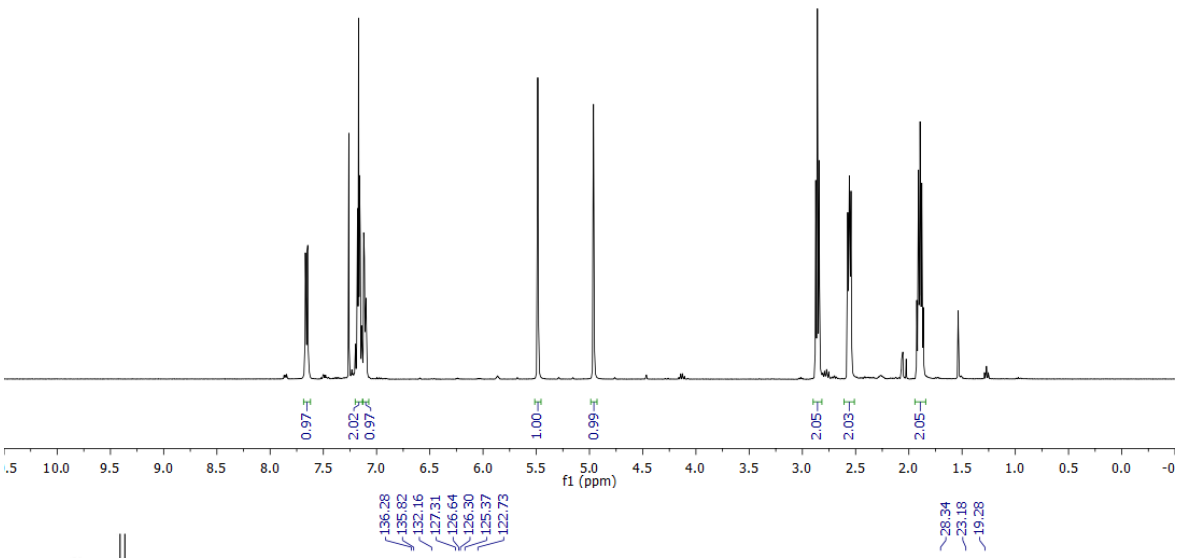
22.03
f1 (ppm)



4d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0.99
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2.03
2.05
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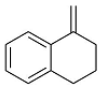
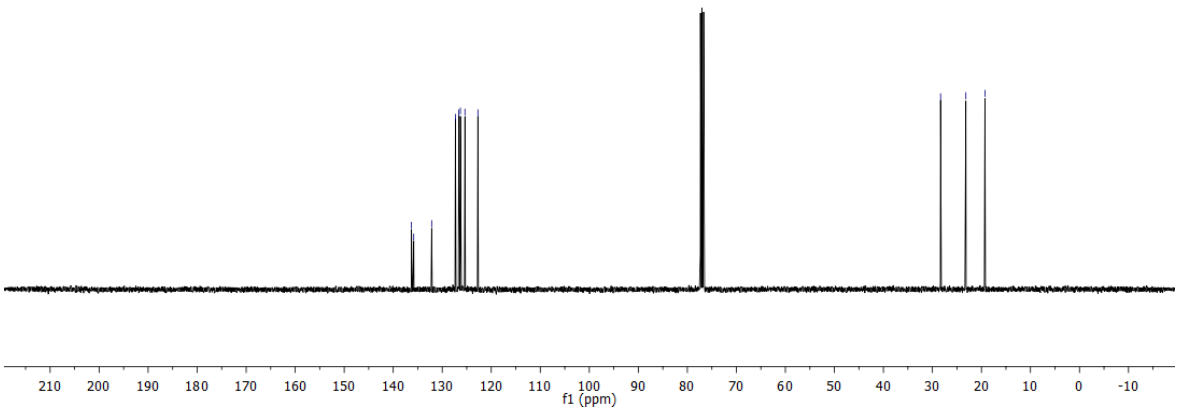
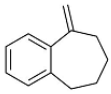
19.28

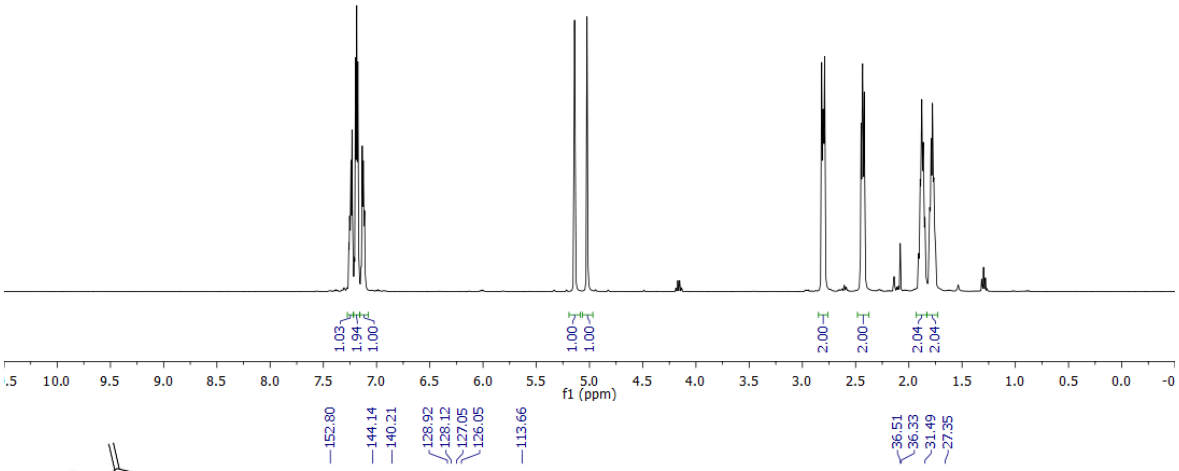


4d

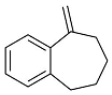

f1 (ppm)



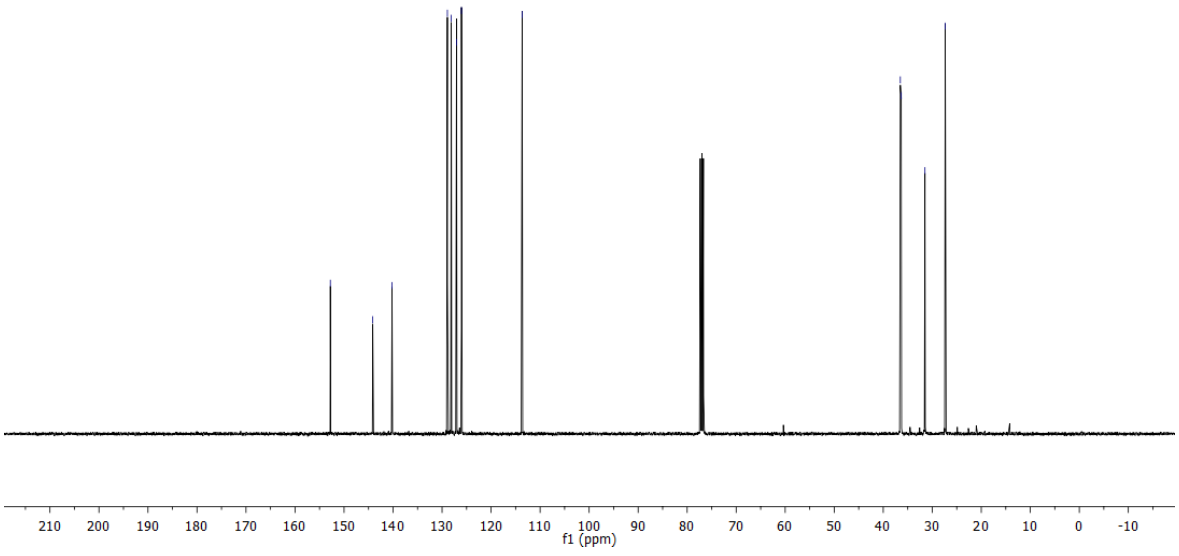
4e

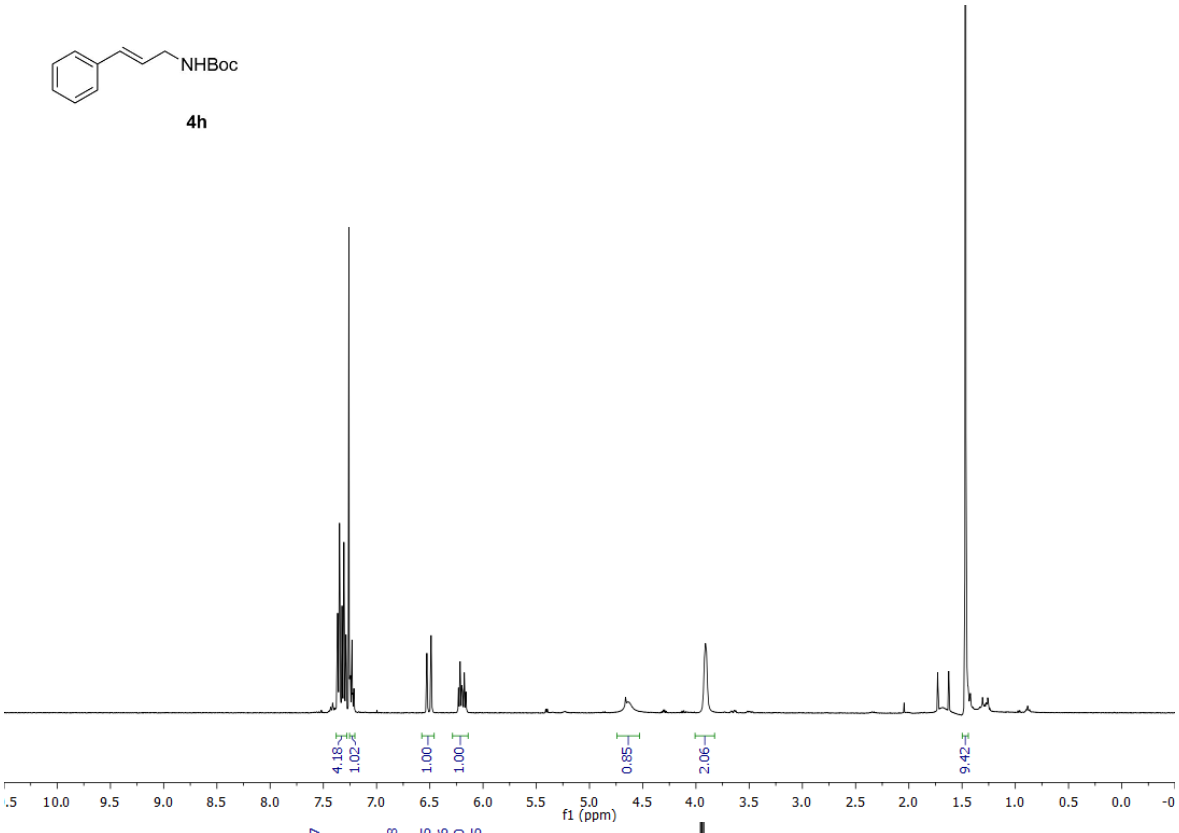

1.03
1.94
1.00
1.00
1.00
2.00
2.00
2.04
2.04
f1 (ppm)

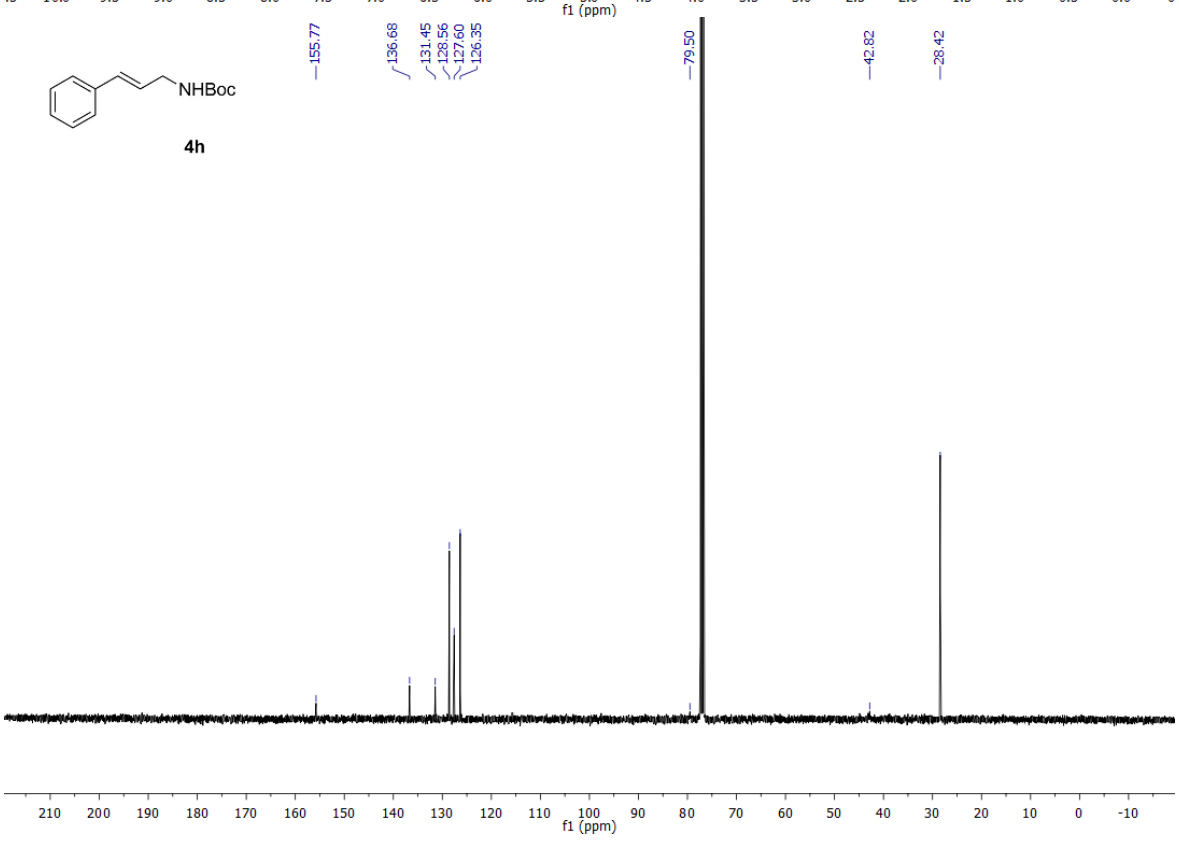
152.80
144.14
140.21
128.92
128.12
127.05
126.05
113.66
36.51
36.33
31.49
27.35

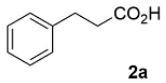


4e

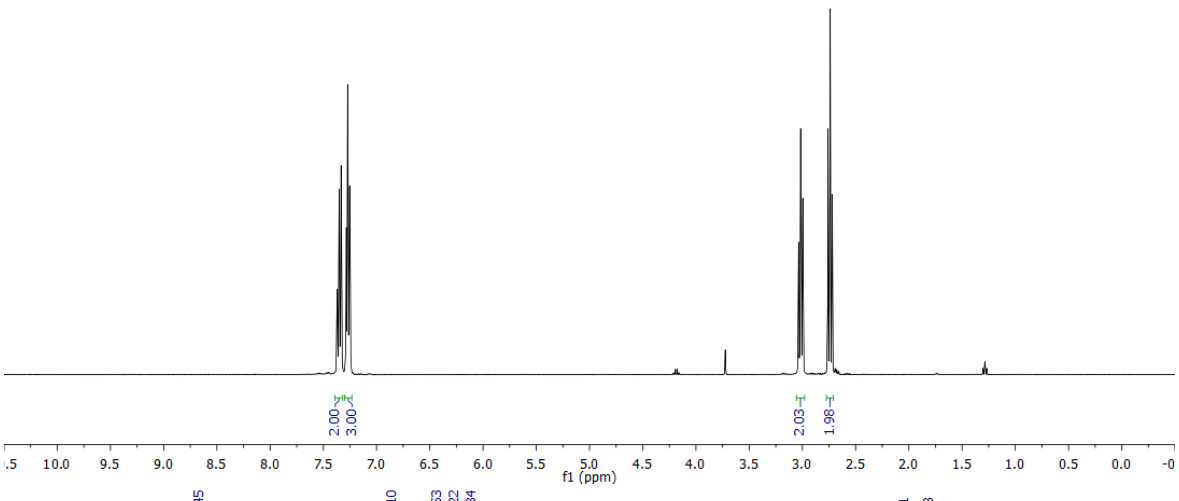

f1 (ppm)

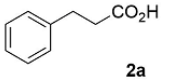

NHBoc
4h
4.18
1.02
1.00
1.00
0.85
2.06
9.42
f1 (ppm)


NHBoc
4h
155.77
136.68
131.45
128.56
127.60
126.35
79.50
42.82
28.42
f1 (ppm)


CO2H

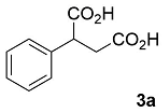
2a


2.00
3.00
2.03
1.98
f1 (ppm)

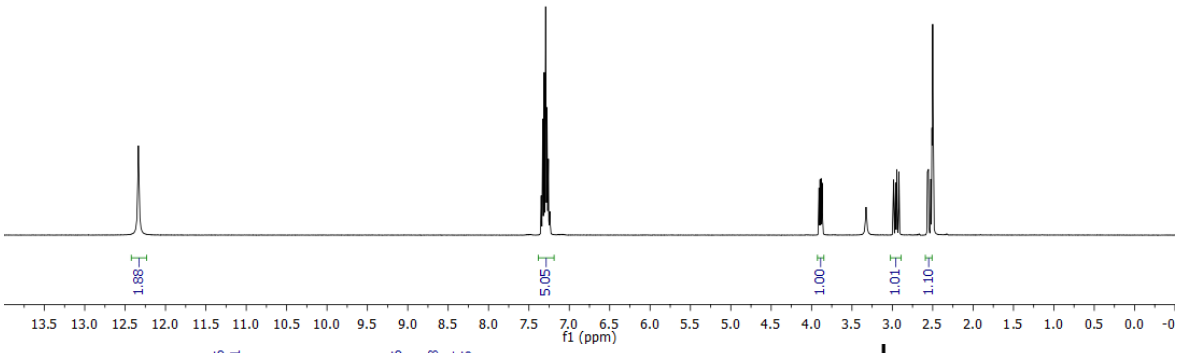

CO2H

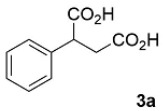
2a

179.45
140.10
128.53
128.22
126.34
35.61
30.53
f1 (ppm)


CO2H
CO2H

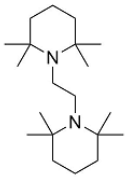
3a


1.88
5.05
1.00
1.01
1.10
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


CO2H
CO2H

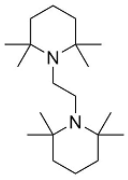
3a

173.96
172.61
138.66
128.58
127.71
127.15
46.83
37.42
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)

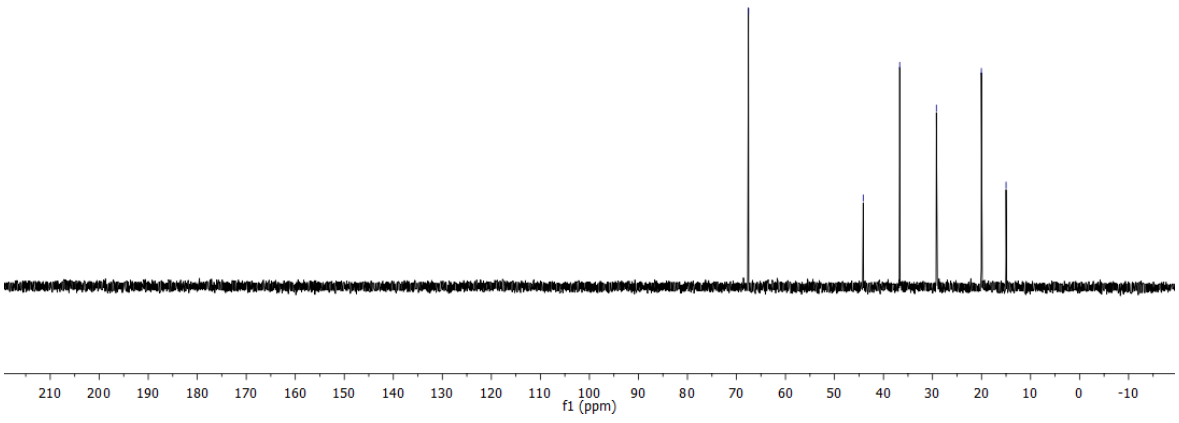


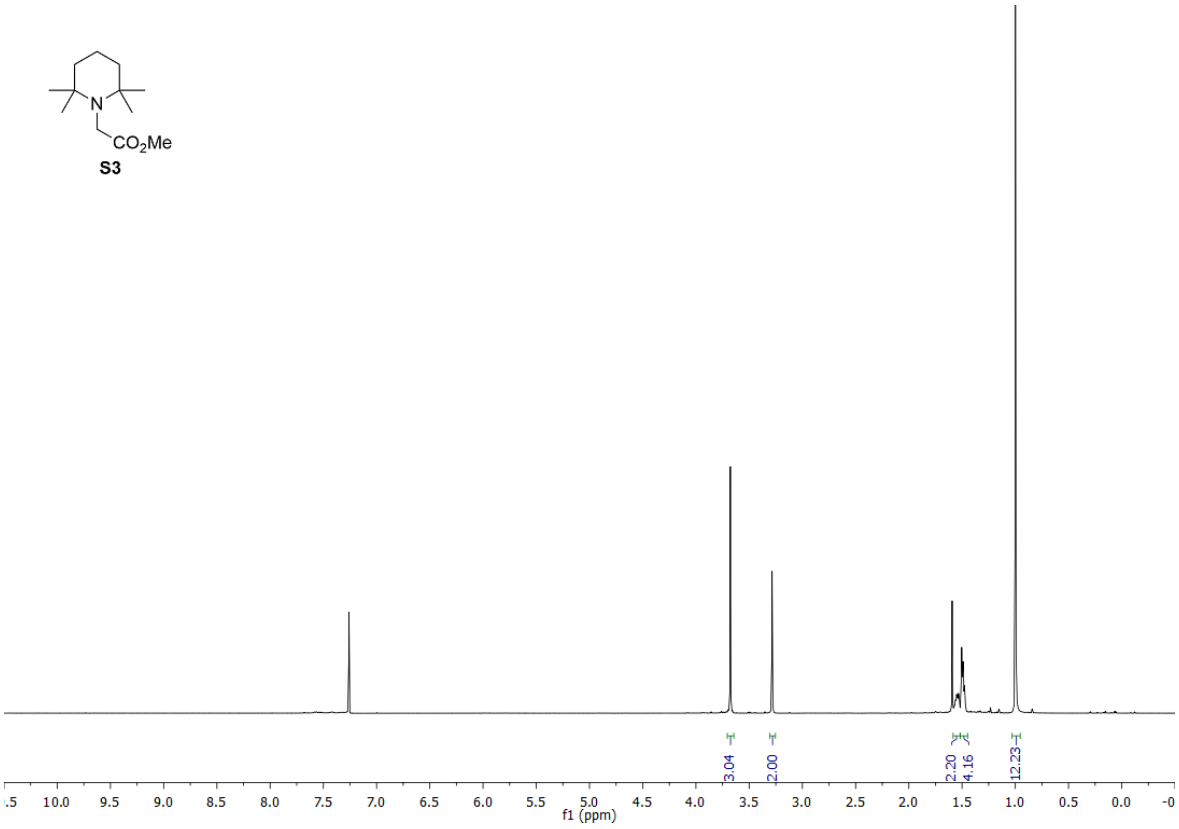
S2

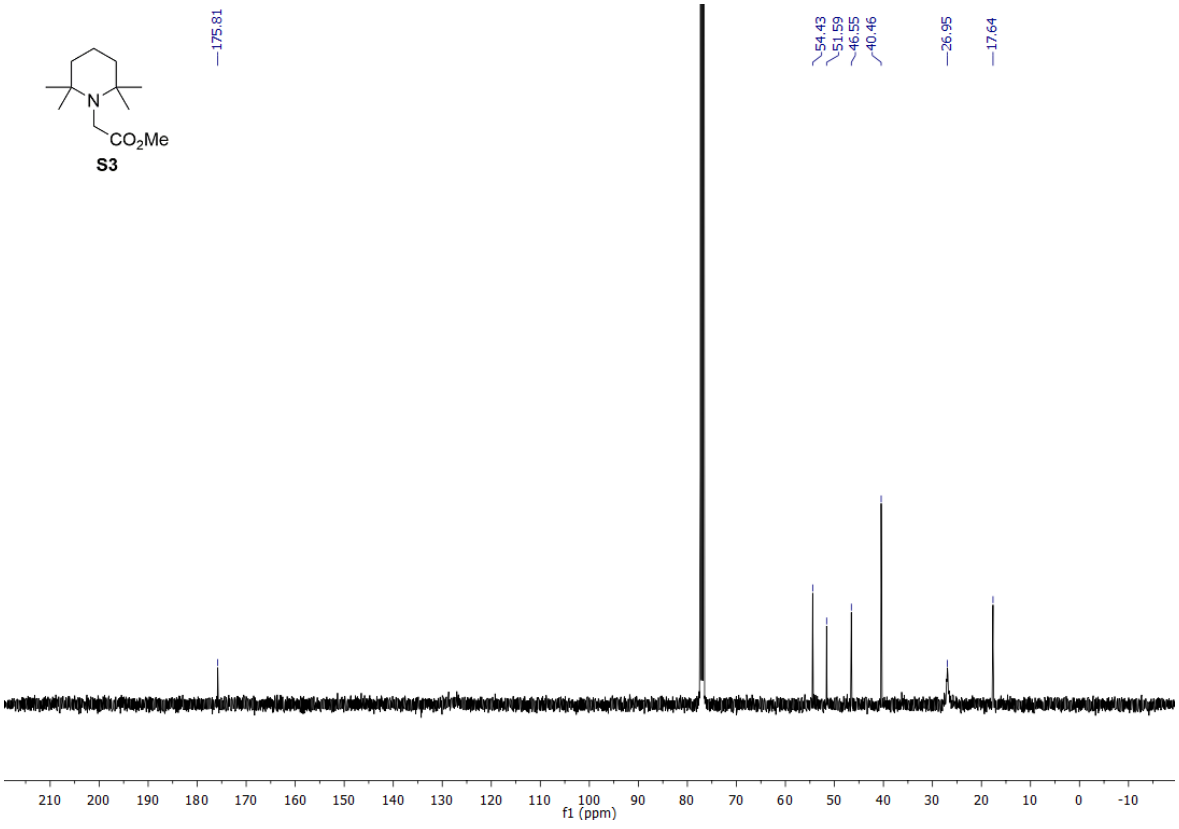
4.00
10.06
2.08
11.82
12.25
f1 (ppm)

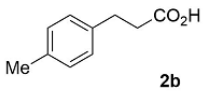


S2

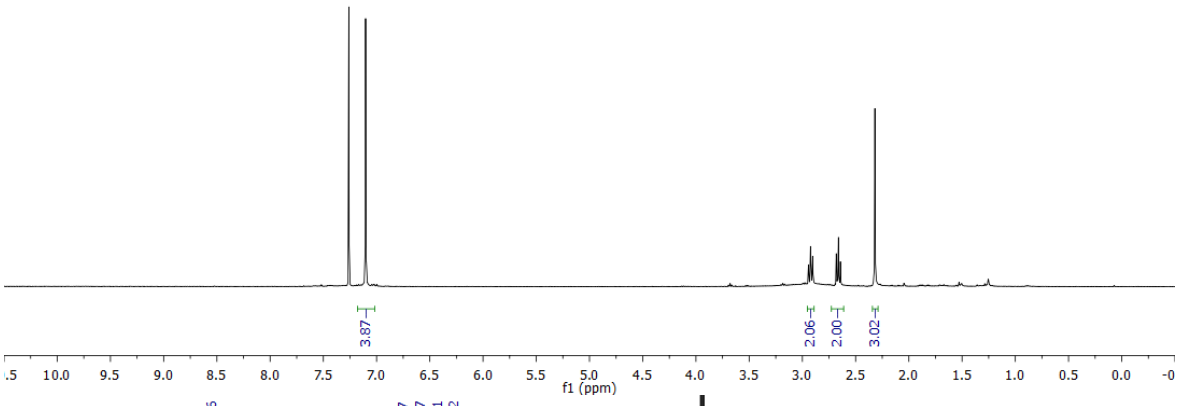

67.56
44.14
36.70
29.22
20.04
15.00
f1 (ppm)

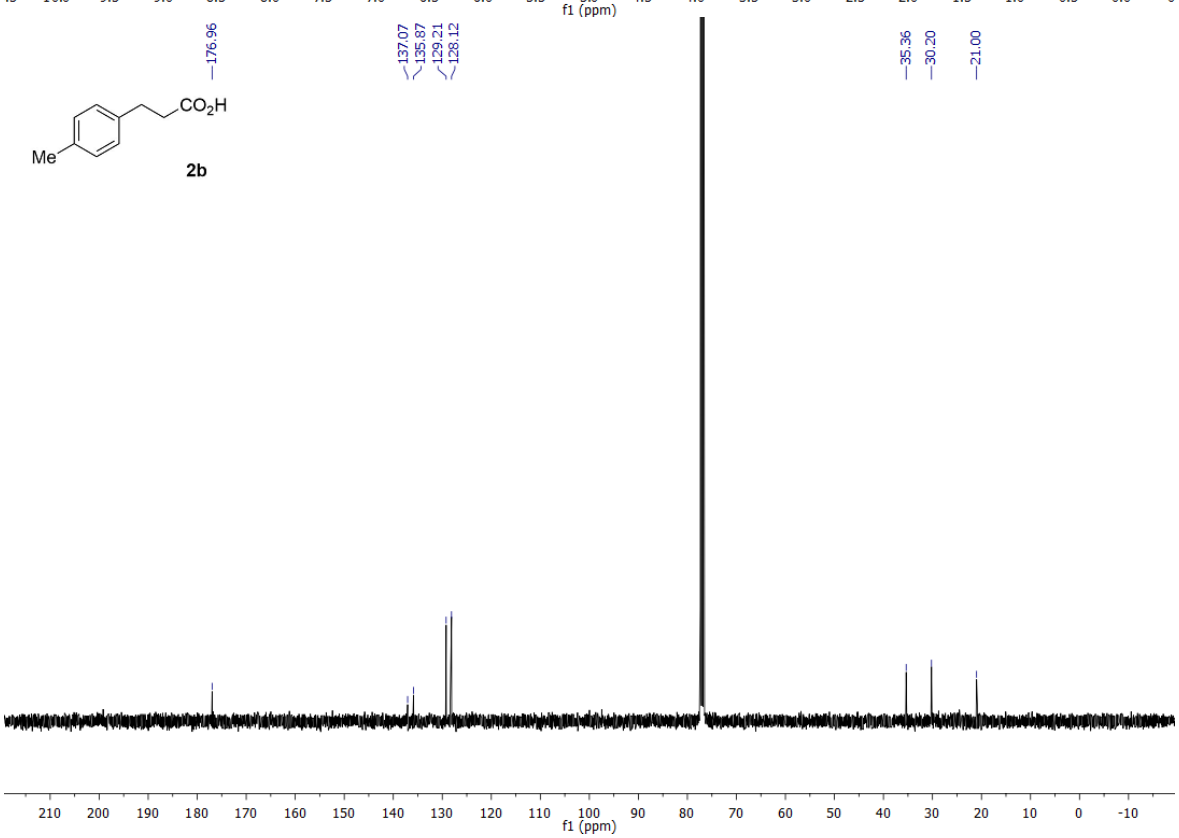

N
CO2Me
S3
3.04
2.00
2.20
4.16
12.23
f1 (ppm)

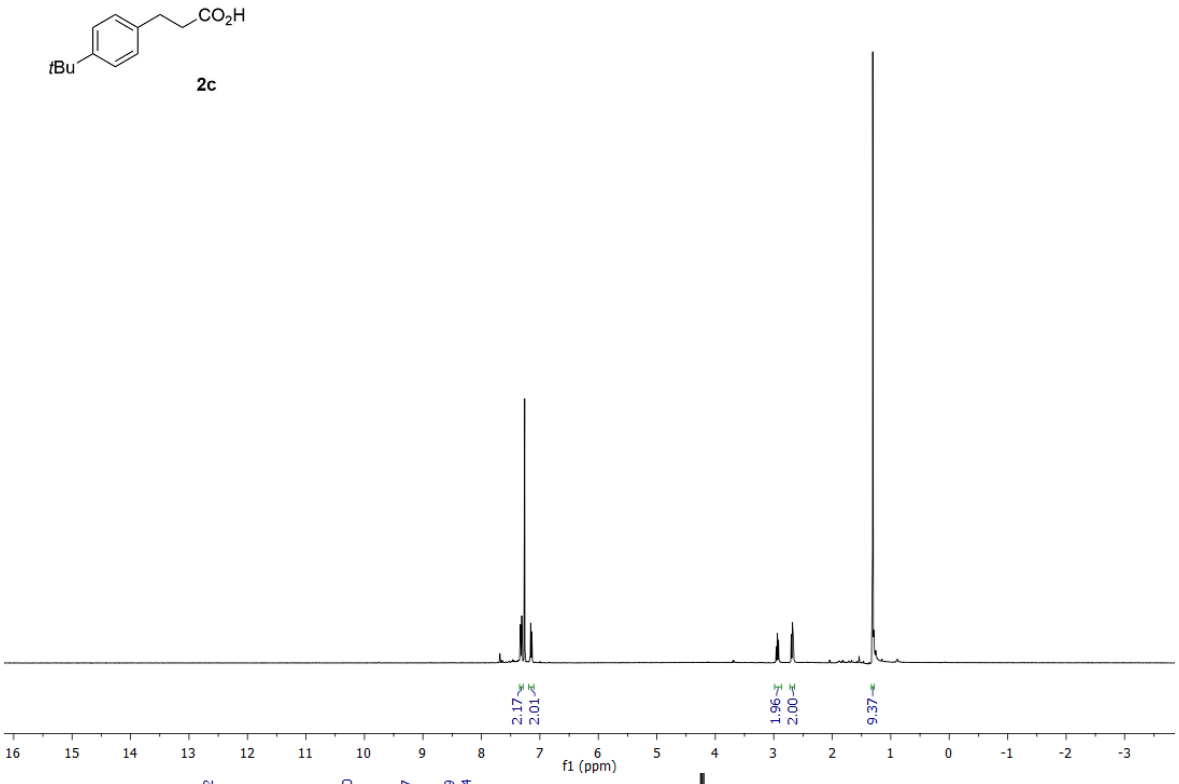

N
CO2Me
S3
175.81
54.43
51.59
46.55
40.46
26.95
17.64
f1 (ppm)

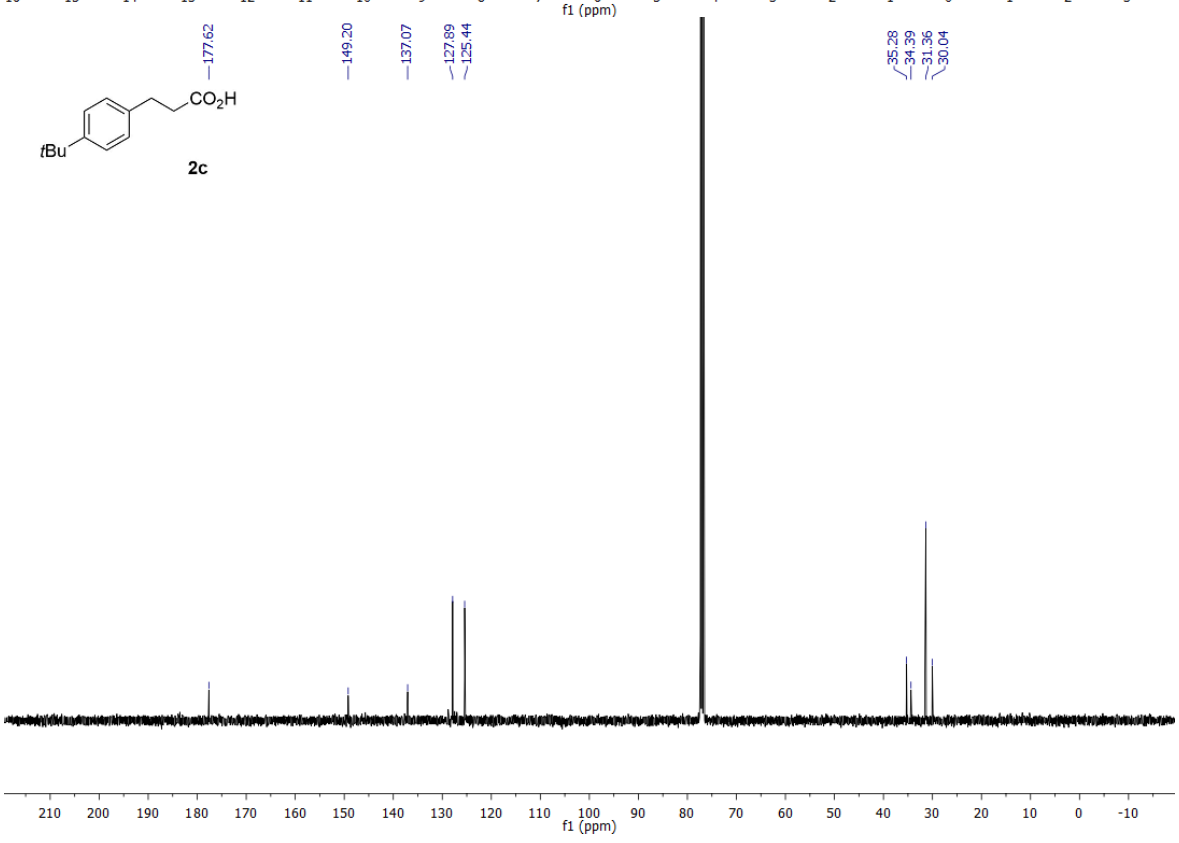

CO2H
Me

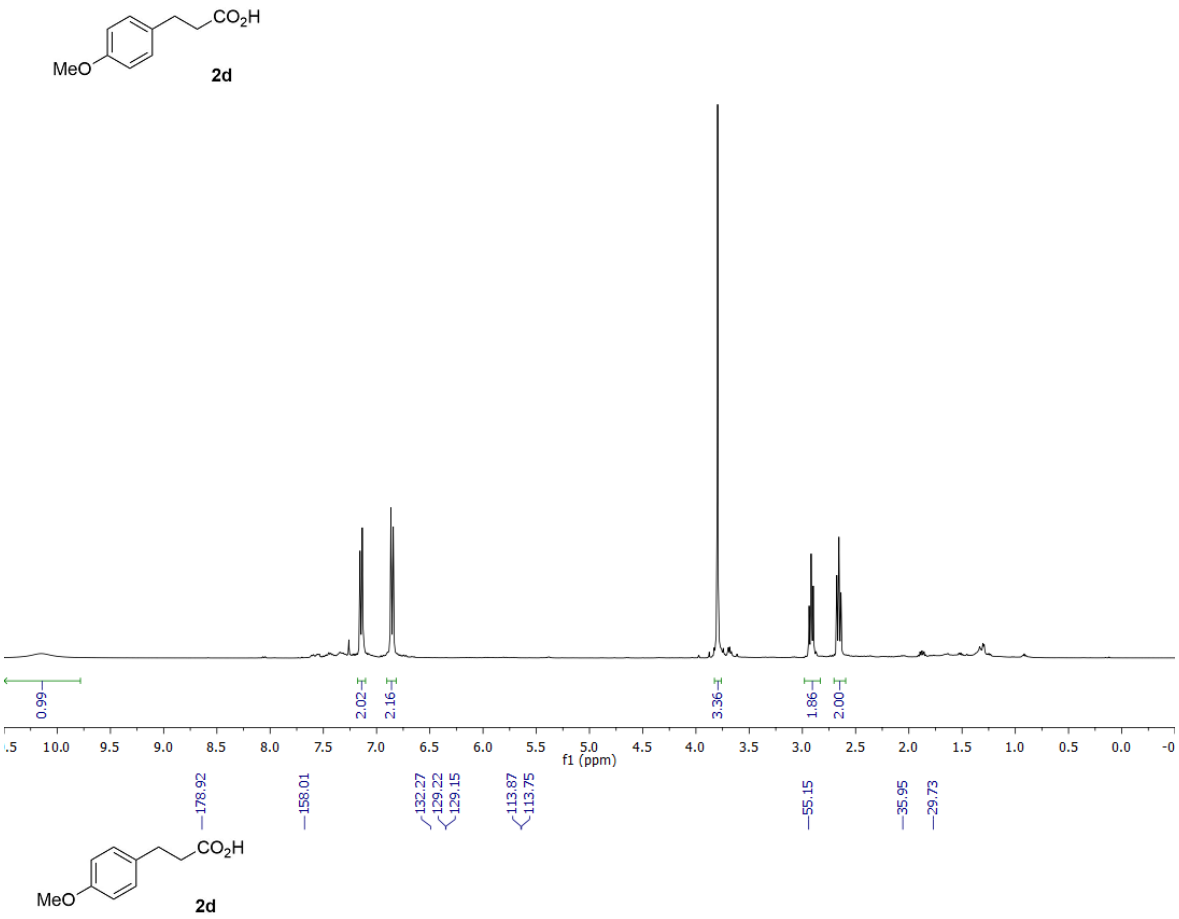
2b

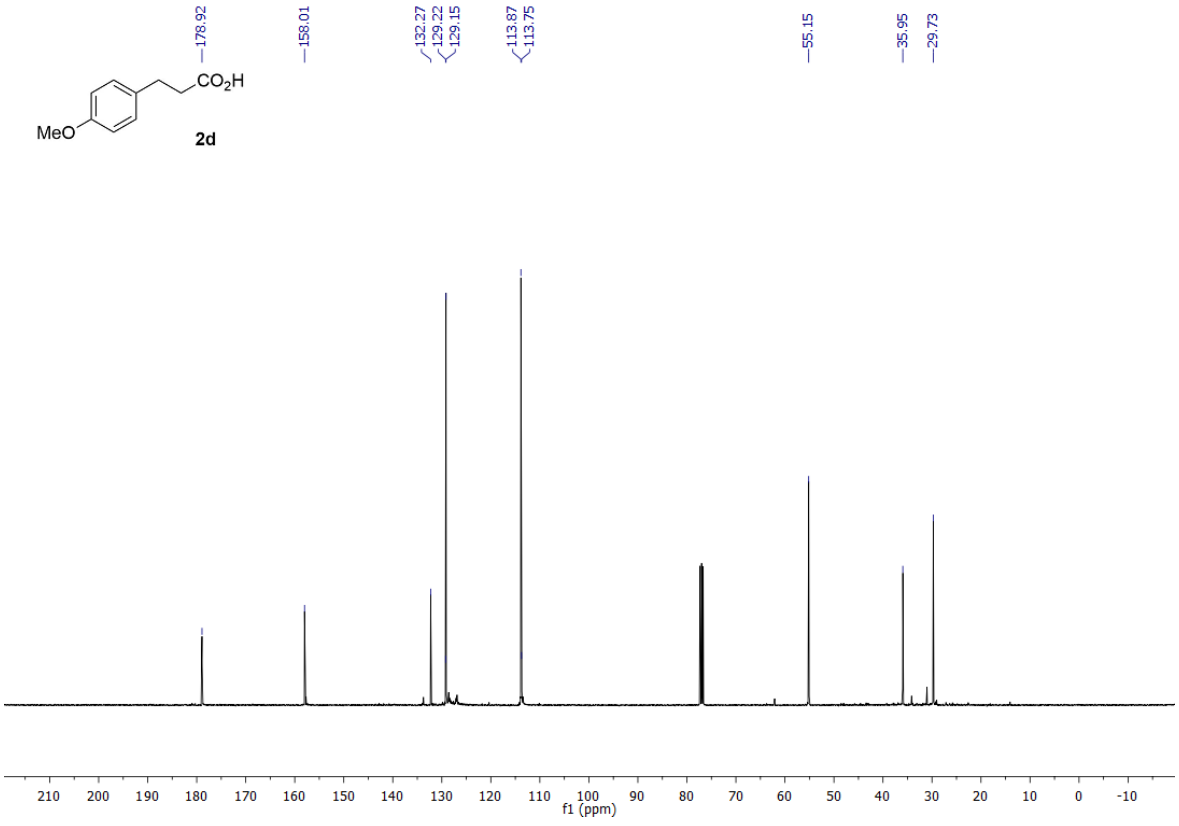

3.87
2.06
2.00
3.02
f1 (ppm)

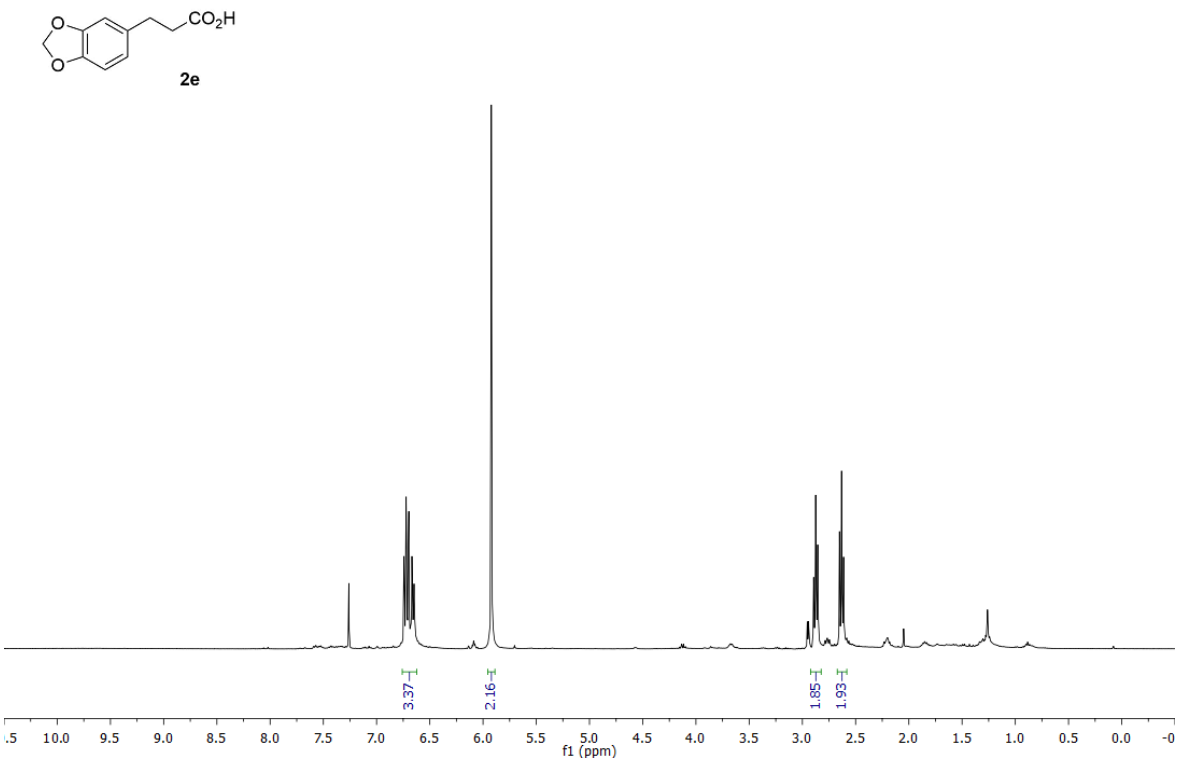

176.96
137.07
135.87
129.21
128.12
35.36
30.20
21.00
CO2H
Me
2b
f1 (ppm)

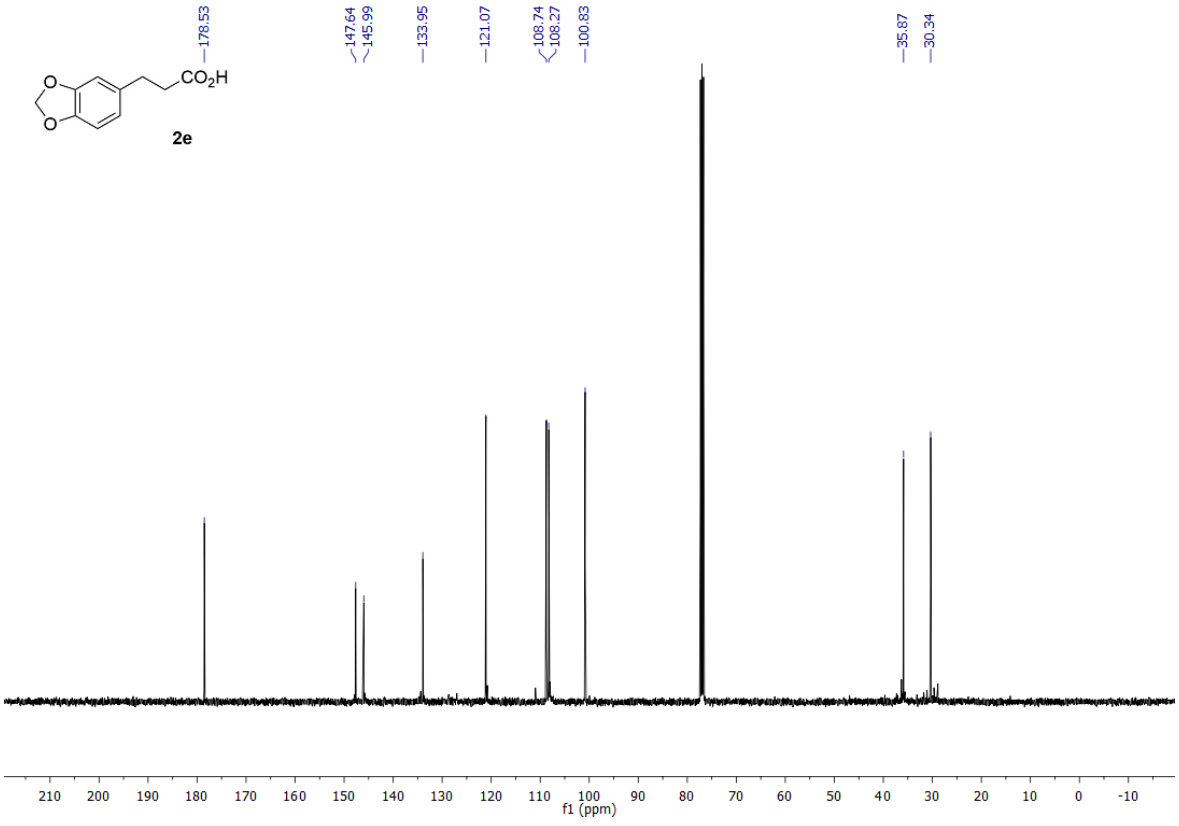

CO2H
tBu
2c
2.17
2.01
1.96
2.00
9.37
f1 (ppm)

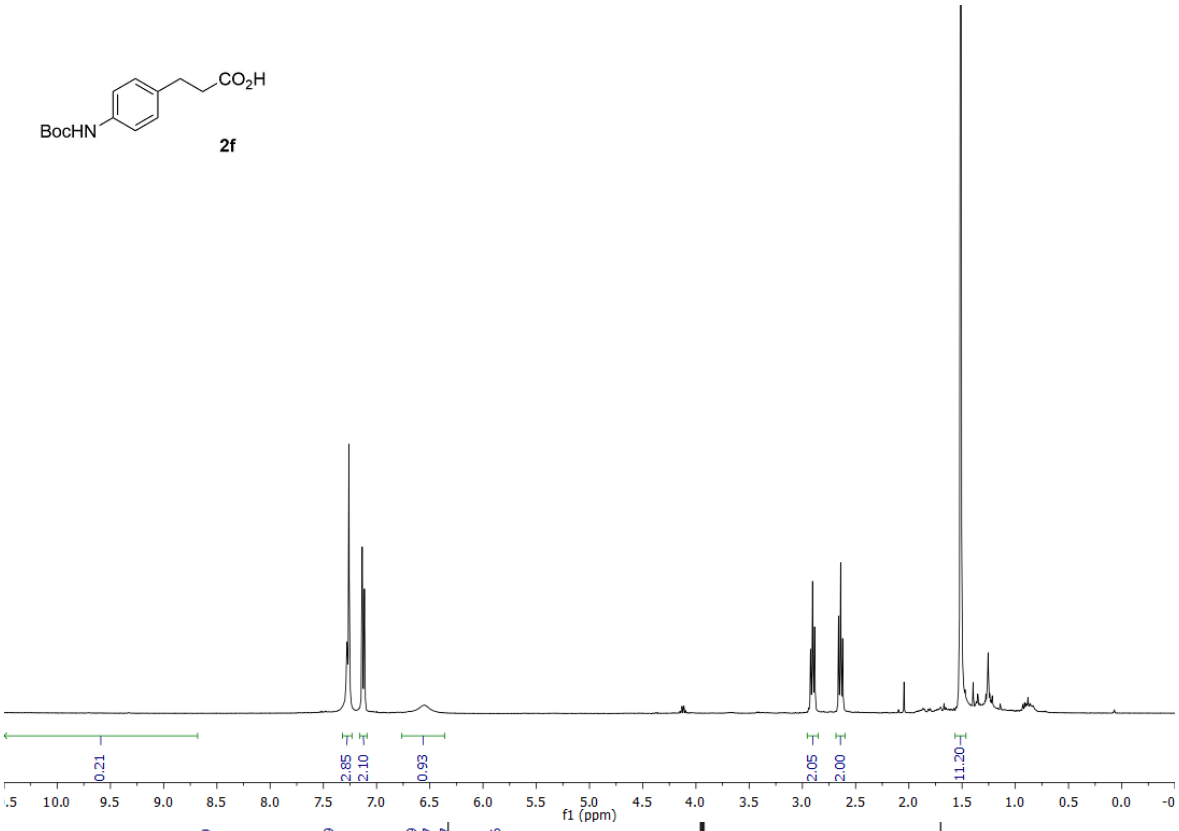

177.62
149.20
137.07
127.89
125.44
35.28
34.39
31.36
30.04
CO2H
tBu
2c
f1 (ppm)

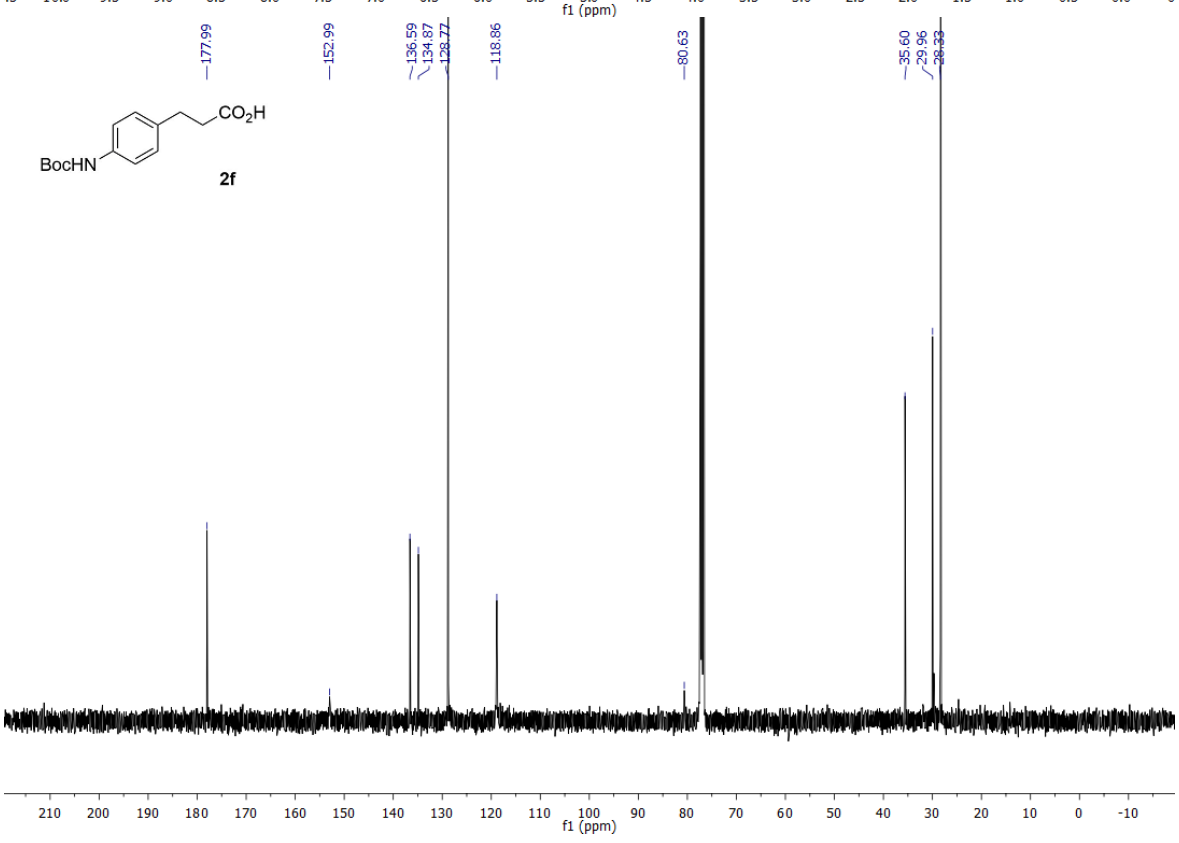

CO2H
MeO
2d
0.99
2.02
2.16
3.36
1.86
2.00
f1 (ppm)

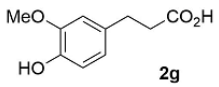

178.92
158.01
132.27
129.22
129.15
113.87
113.75
55.15
35.95
29.73
CO2H
MeO
2d
f1 (ppm)


CO2H
2e
3.37
2.16
1.85
1.93
f1 (ppm)

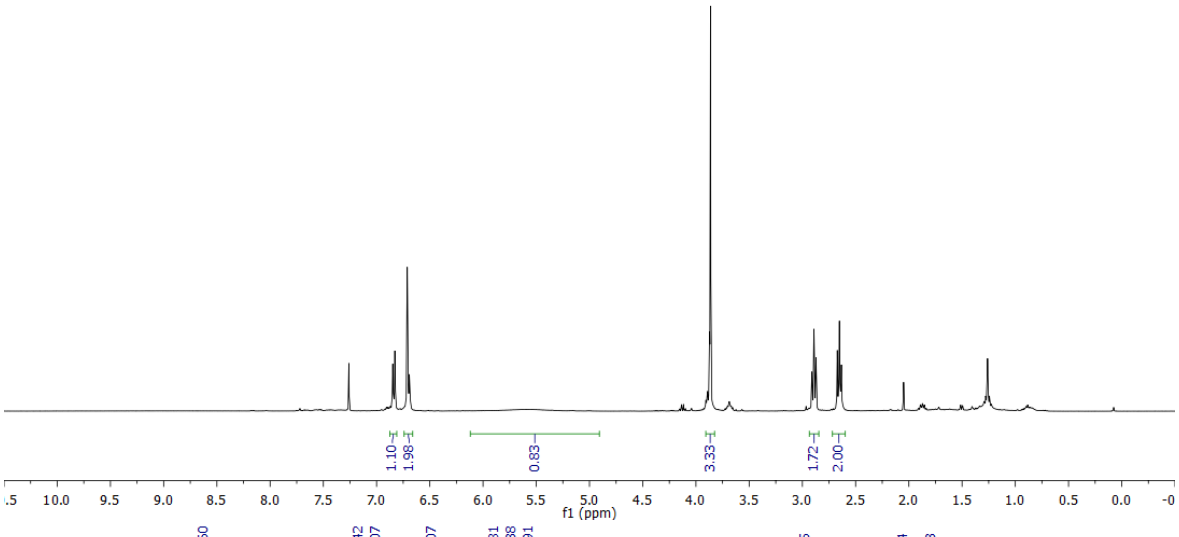

178.53
147.64
145.99
133.95
121.07
108.74
108.27
100.83
35.87
30.34
CO2H
2e
f1 (ppm)


CO2H
BocHN
2f
0.21
2.85
2.10
0.93
2.05
2.00
11.20
f1 (ppm)

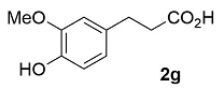

177.99
152.99
136.59
134.87
128.77
118.86
80.63
35.60
29.96
28.33
CO2H
BocHN
2f
f1 (ppm)


MeO
CO2H
HO

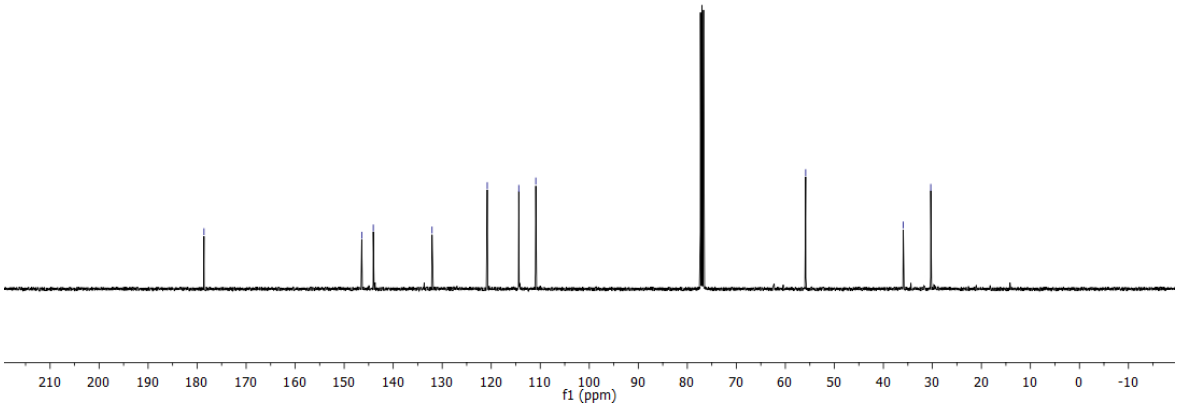
2g

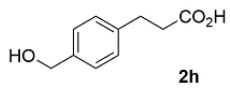

1.10
1.98
0.83
3.33
1.72
2.00
f1 (ppm)


178.60
146.42
144.07
132.07
120.81
114.38
110.91
55.85
35.94
30.33

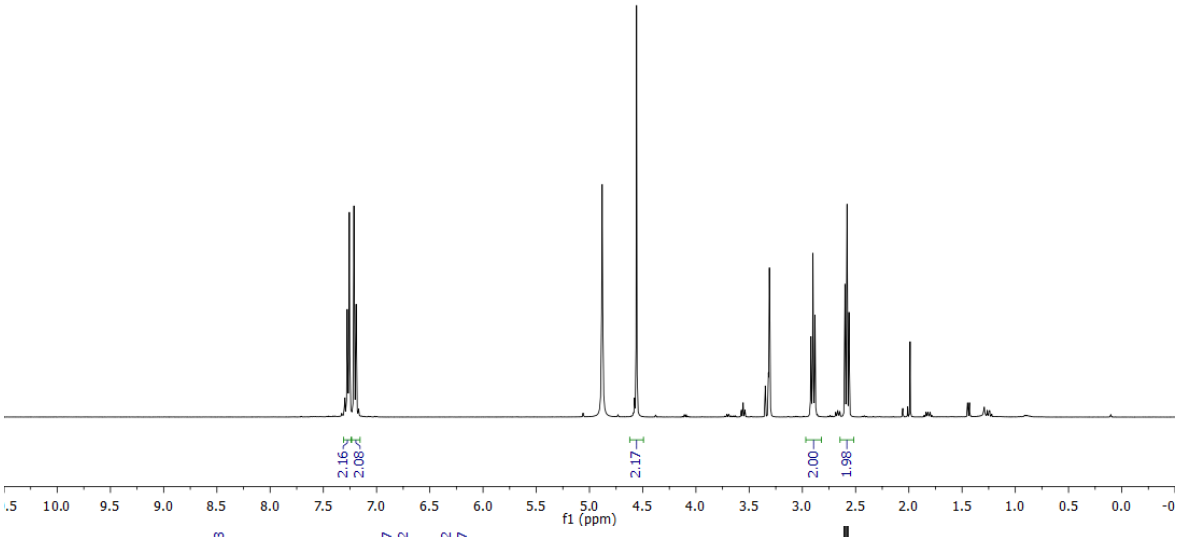

MeO
CO2H
HO

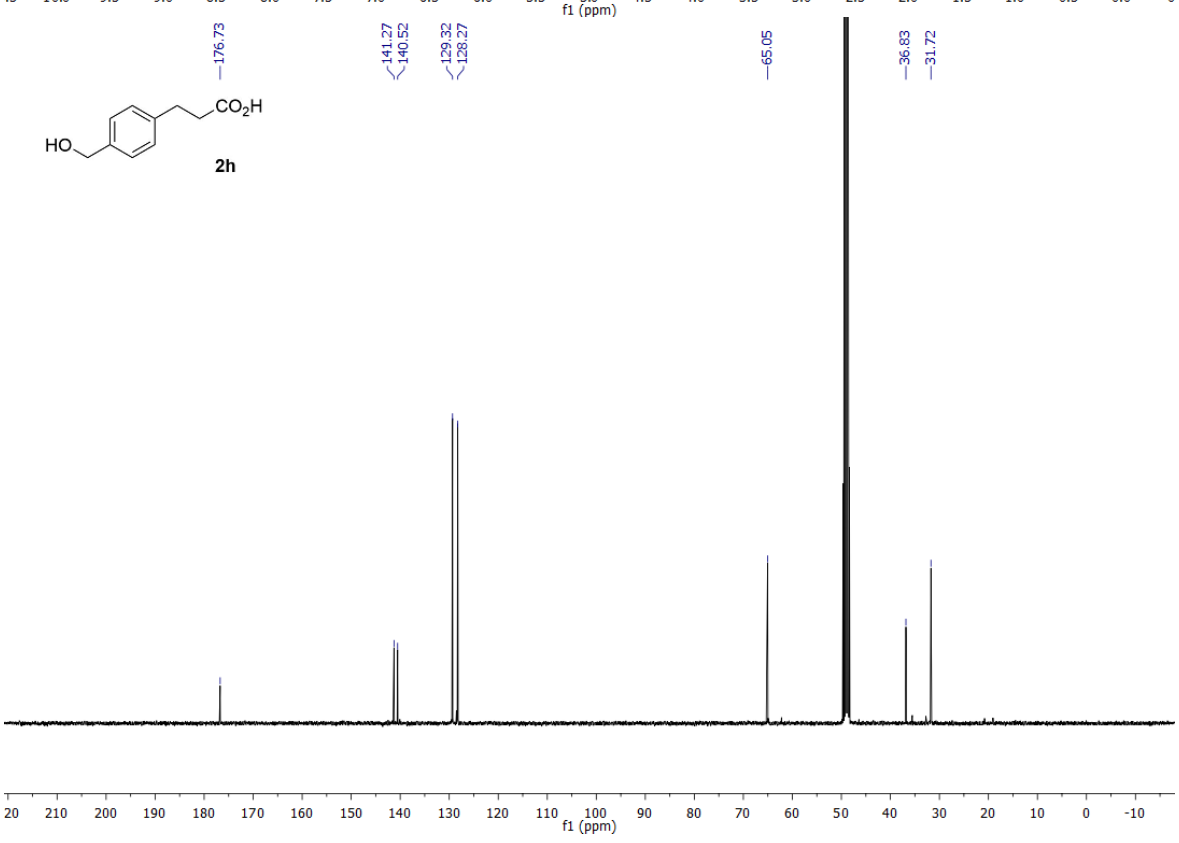
2g


f1 (ppm)


HO
CO2H

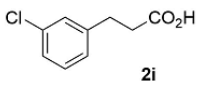
2h


2.16
2.08
2.17
2.00
1.98
f1 (ppm)

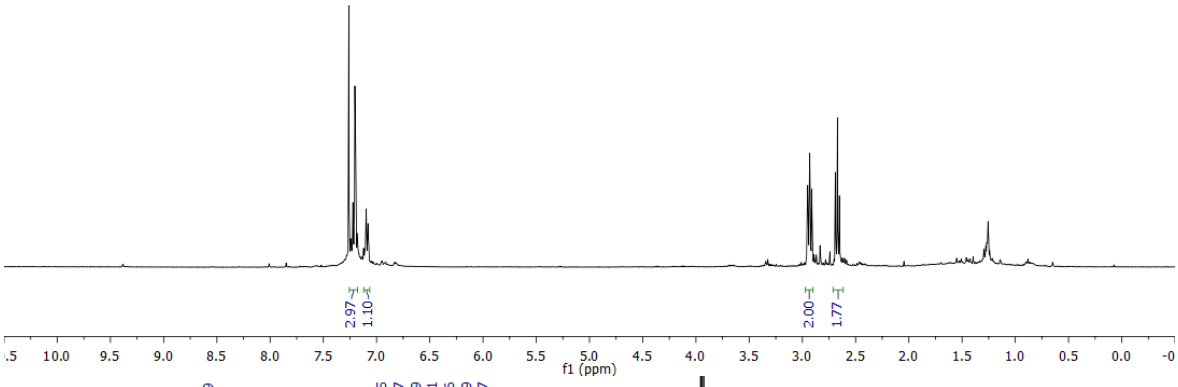

176.73
141.27
140.52
129.32
128.27
65.05
36.83
31.72
f1 (ppm)

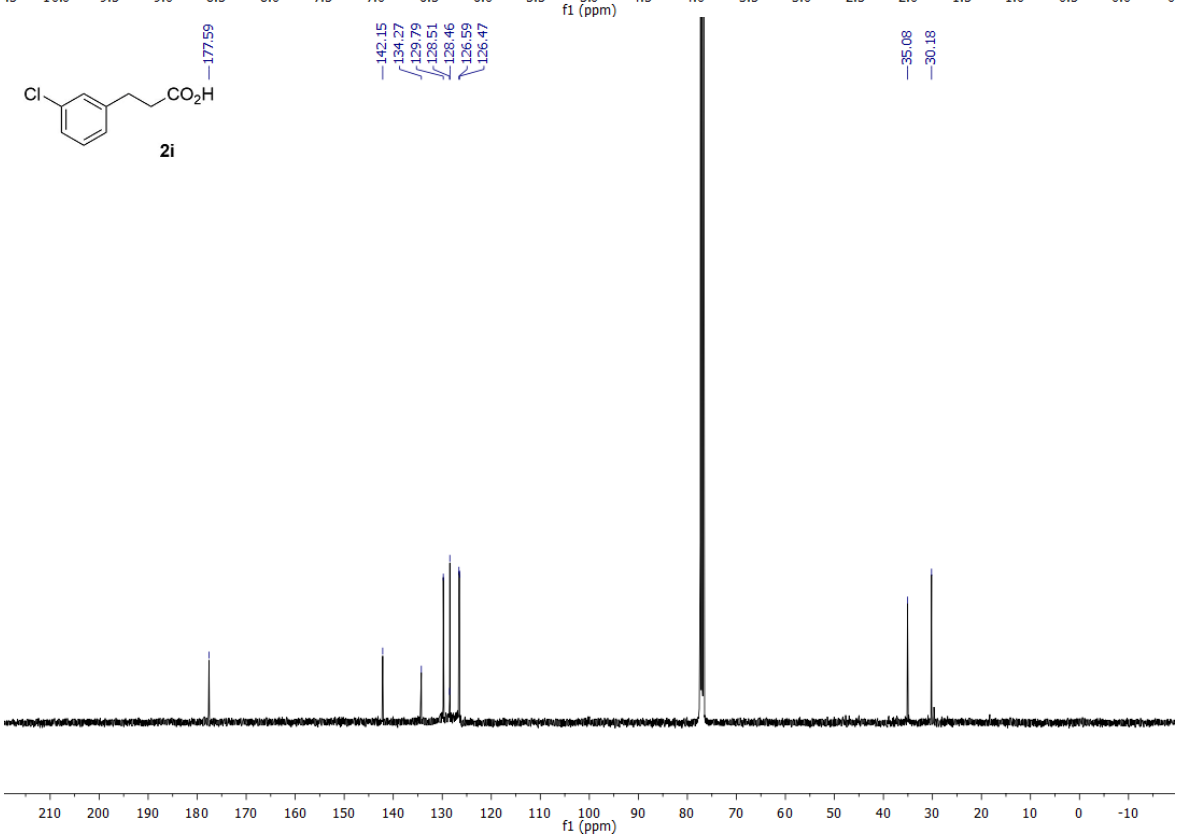
HO
CO2H

2h


Cl
CO2H

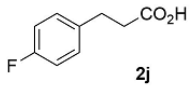
2i


2.97
1.10
2.00
1.77
f1 (ppm)

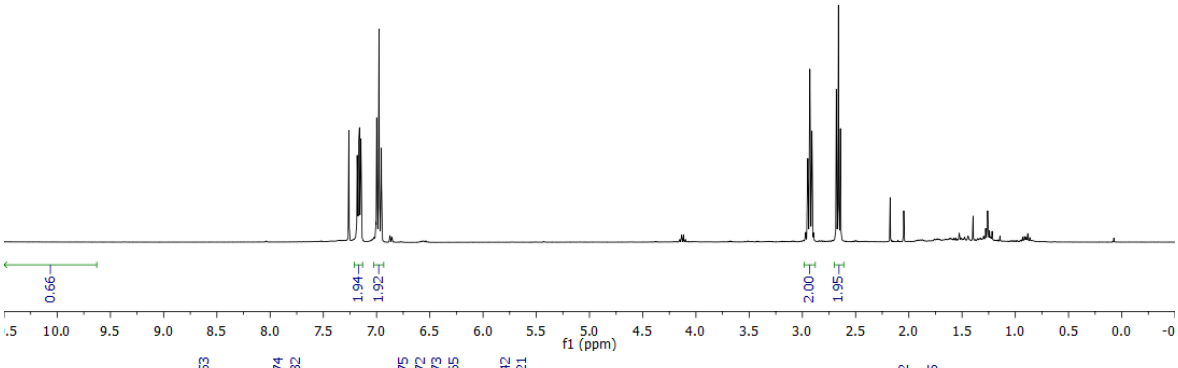

177.59
142.15
134.27
129.79
128.51
128.46
126.59
126.47
35.08
30.18
f1 (ppm)

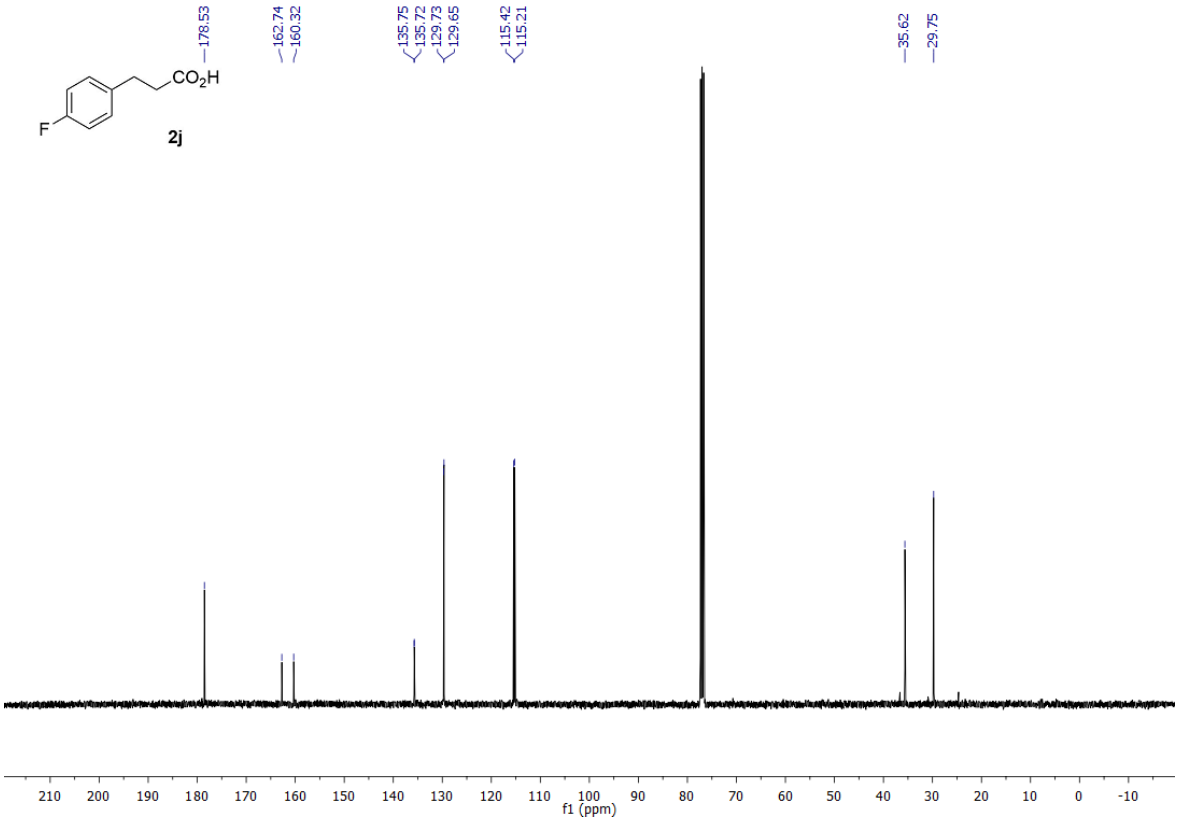
Cl
CO2H

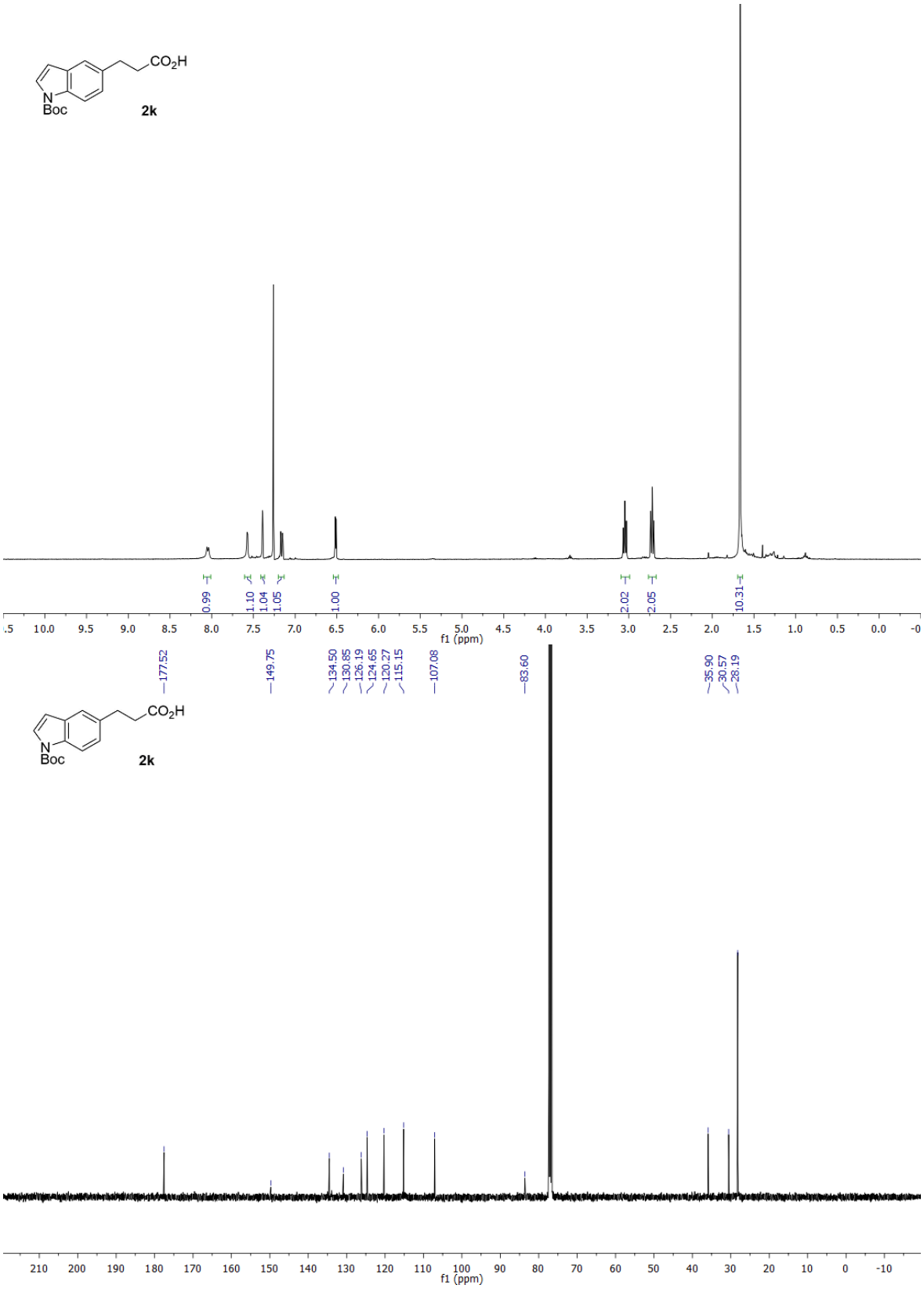
2i

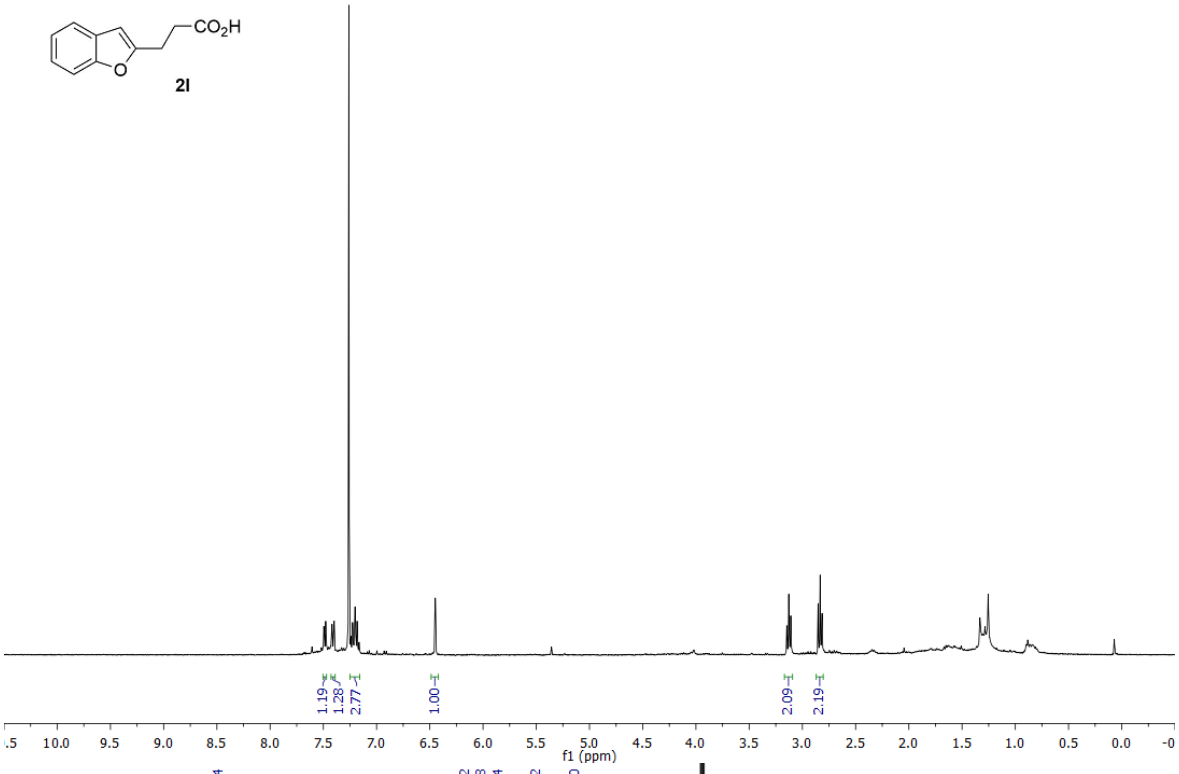

CO2H
F

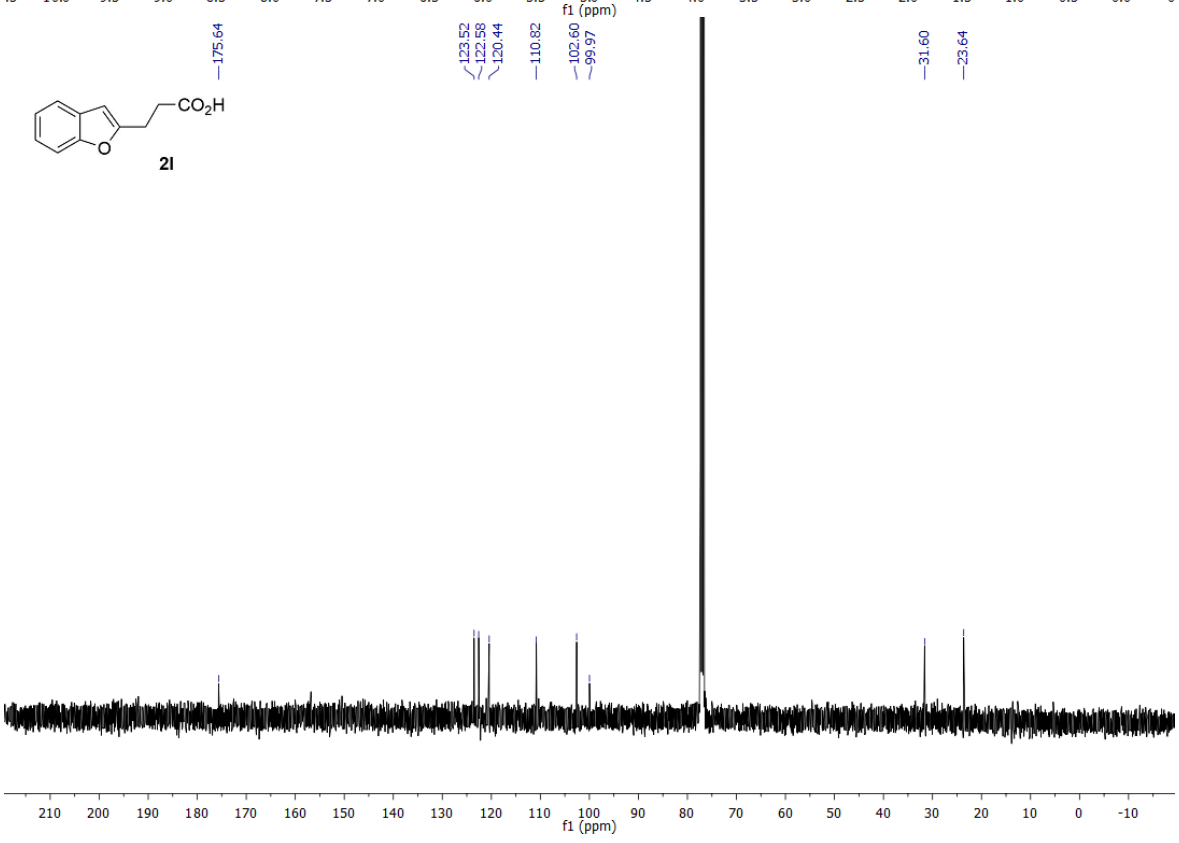
2j

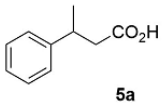

0.66
1.94
1.92
2.00
1.95
f1 (ppm)


178.53
162.74
160.32
135.75
135.72
129.73
129.65
115.42
115.21
35.62
29.75
CO2H
F
2j
f1 (ppm)

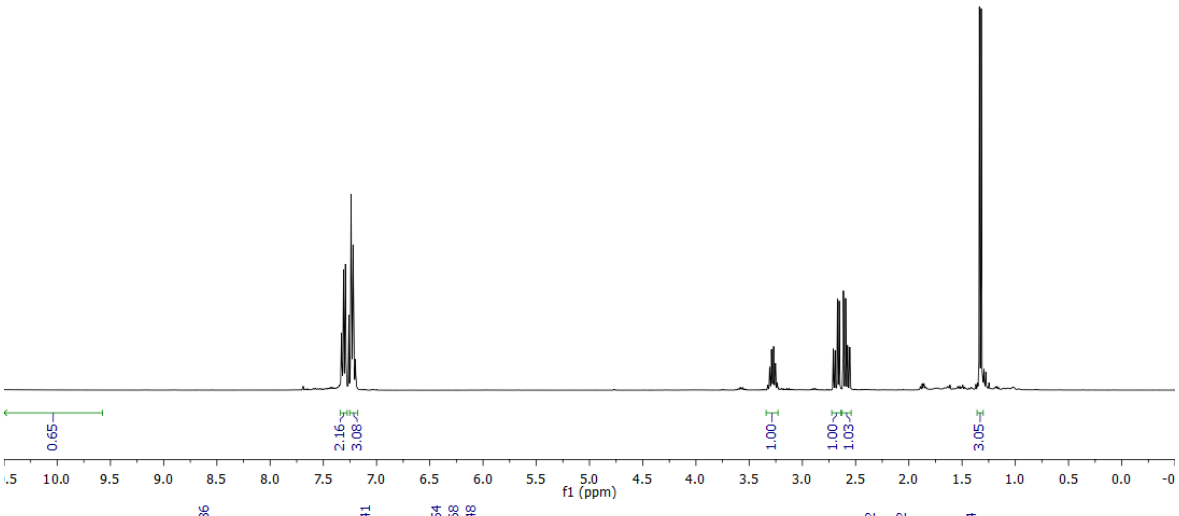

CO2H
N
Boc
2k
0.99
1.10
1.04
1.05
1.00
2.02
2.05
10.31
f1 (ppm)
177.52
149.75
134.50
130.85
126.19
124.65
120.27
115.15
107.08
83.60
35.90
30.57
28.19
CO2H
N
Boc
2k
f1 (ppm)


CO2H
O
2l
1.19
1.28
2.77
1.00
2.09
2.19
f1 (ppm)

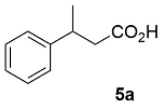

175.64
123.52
122.58
120.44
110.82
102.60
99.97
31.60
23.64
CO2H
O
2l
f1 (ppm)


CO2H

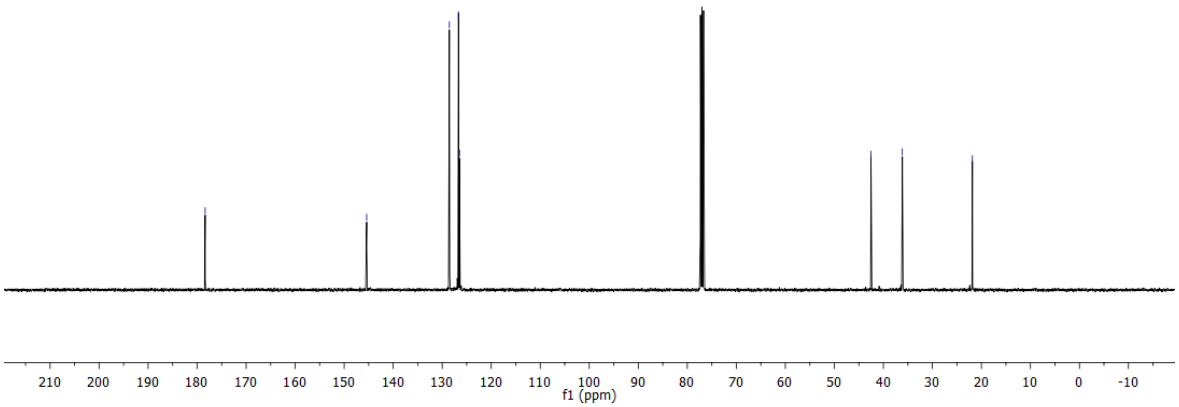
5a

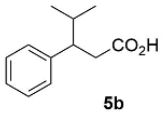

0.65
2.16
3.08
1.00
1.00
1.03
3.05
f1 (ppm)


178.36
145.41
128.54
126.68
126.48
42.52
36.12
21.84

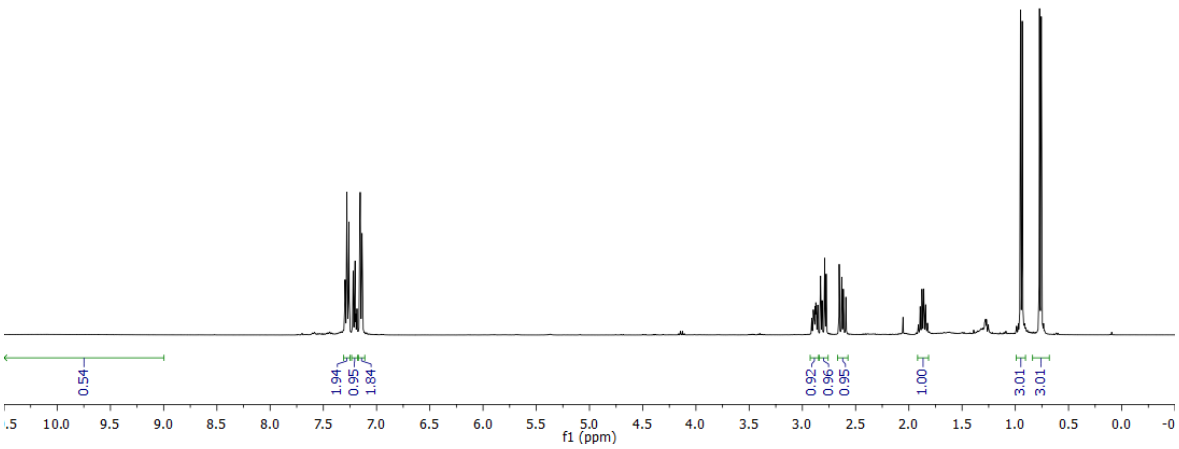

CO2H

5a


f1 (ppm)


CO2H

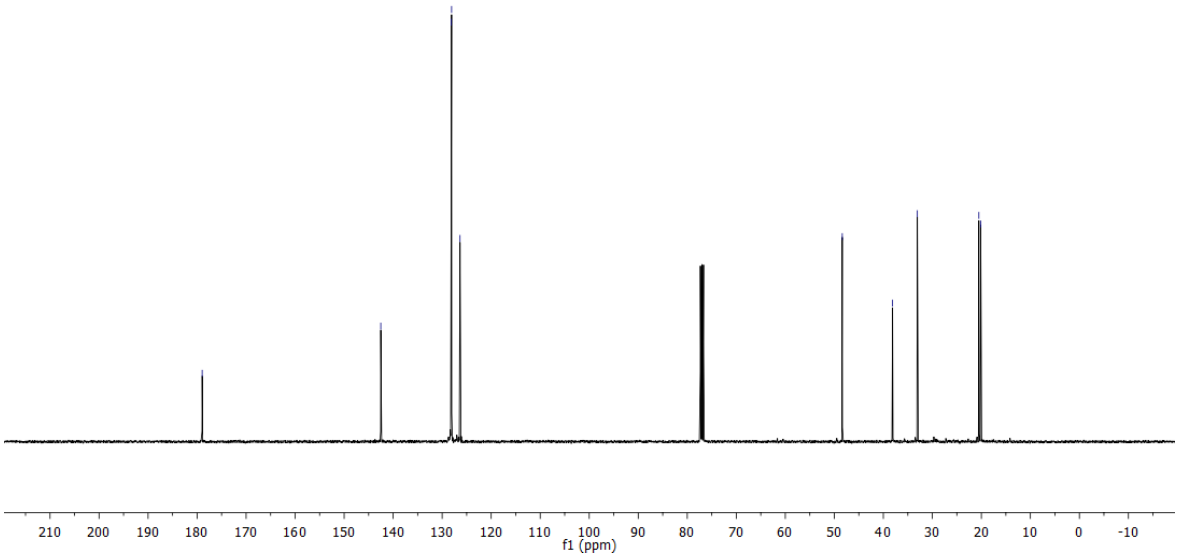
5b

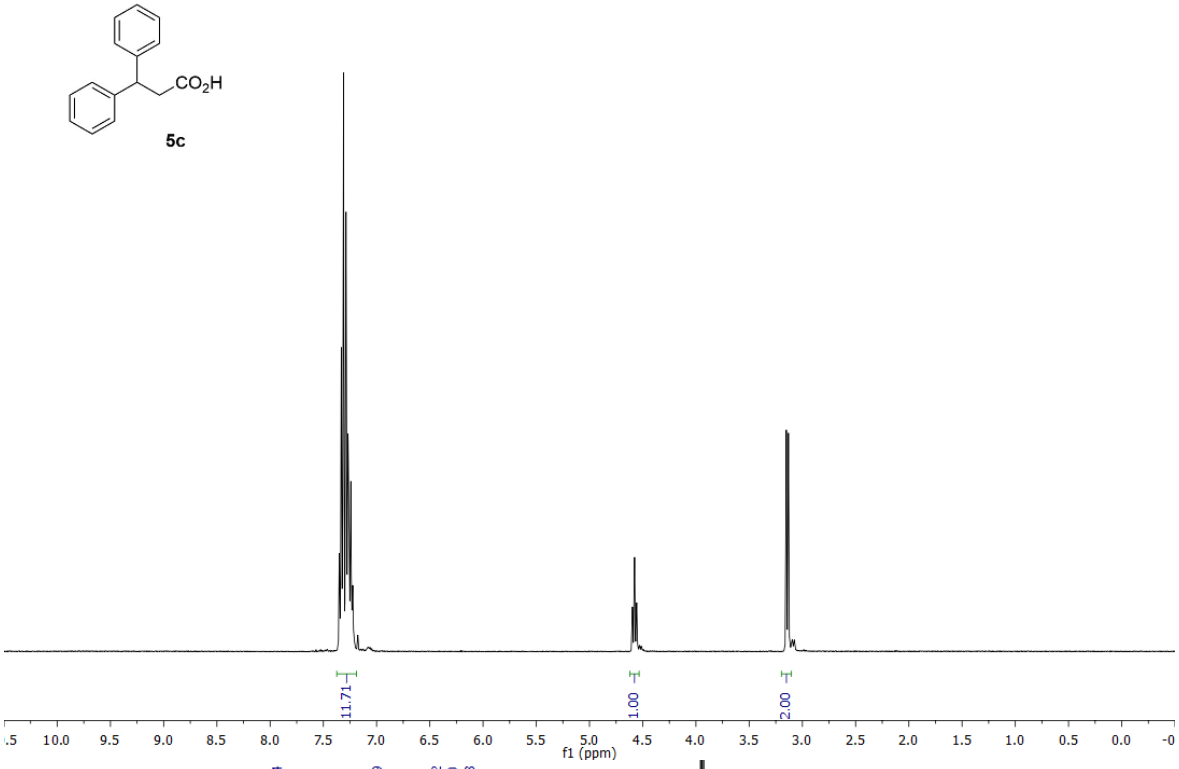

0.54
1.94
0.95
1.84
0.92
0.96
0.95
1.00
3.01
3.01
f1 (ppm)

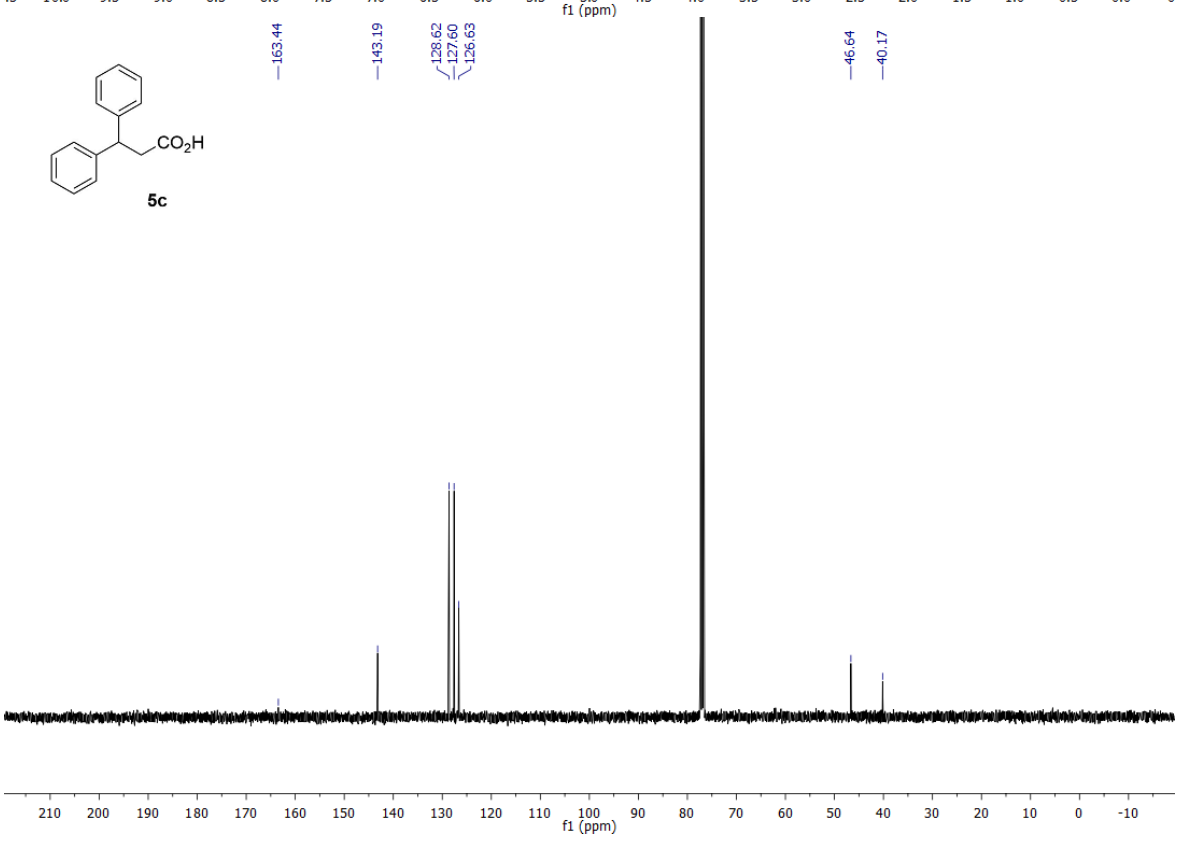

178.96
142.52
128.16
128.08
126.36
48.38
38.11
33.06
20.51
20.14

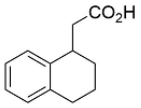
CO2H

5b

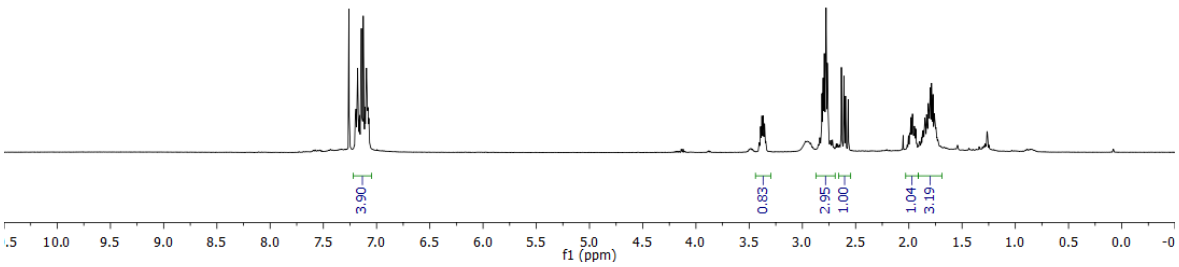

f1 (ppm)

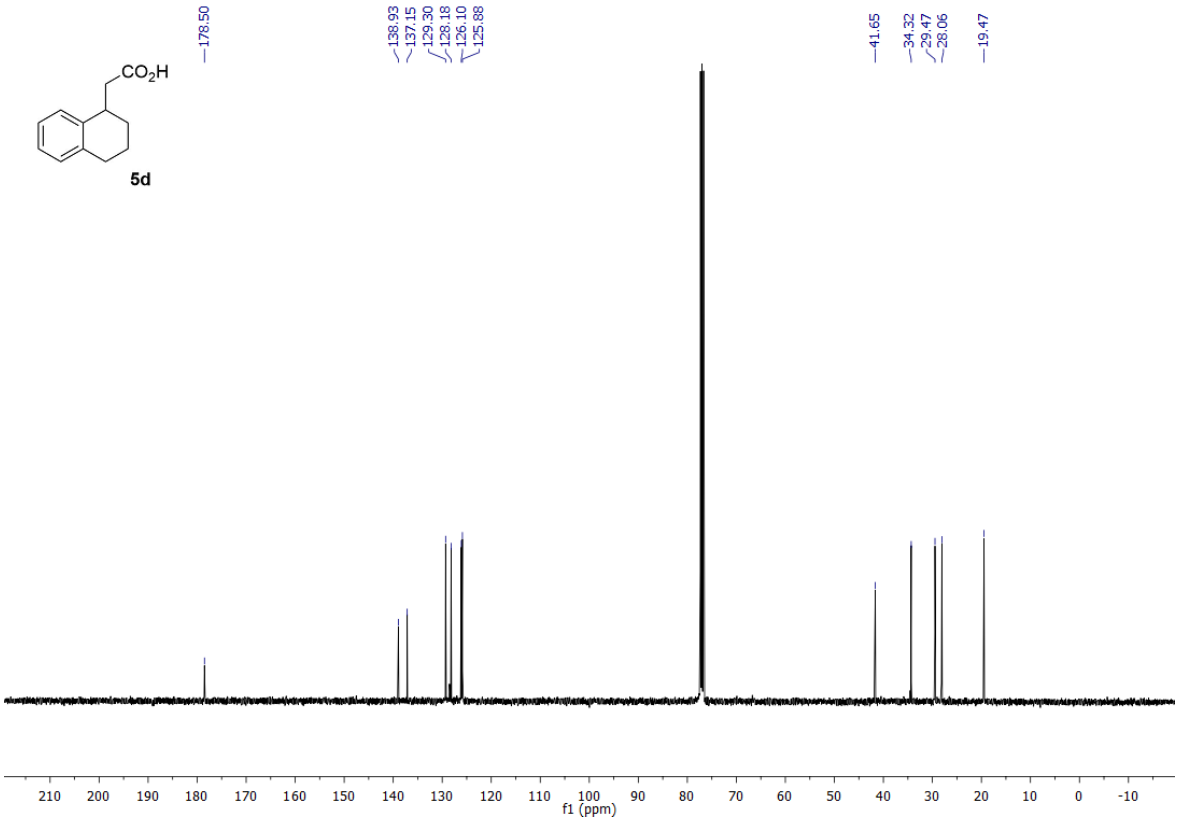

CO2H
5c
11.71
1.00
2.00
f1 (ppm)


163.44
143.19
128.62
127.60
126.63
46.64
40.17
CO2H
5c
f1 (ppm)


CO2H

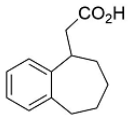
5d


3.90
0.83
2.95
1.00
1.04
3.19
f1 (ppm)

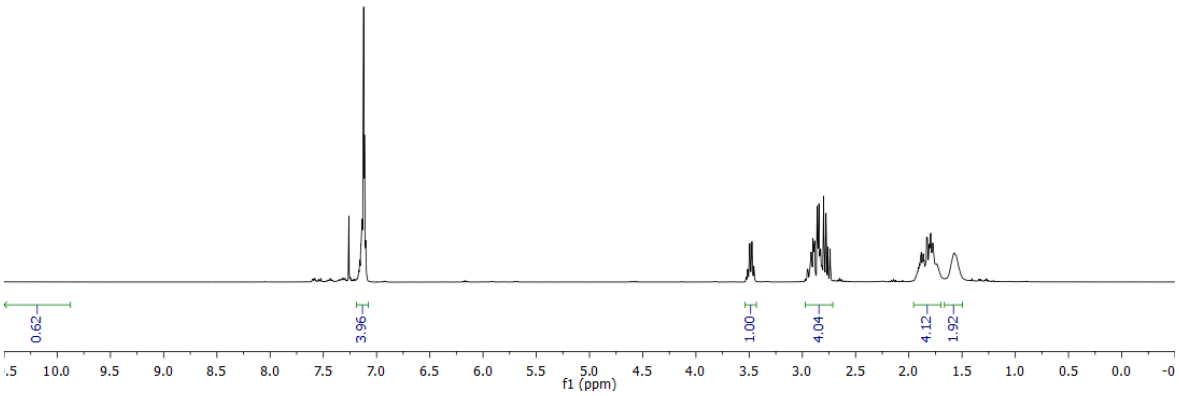

178.50
138.93
137.15
129.30
128.18
126.10
125.88
41.65
34.32
29.47
28.06
19.47
f1 (ppm)

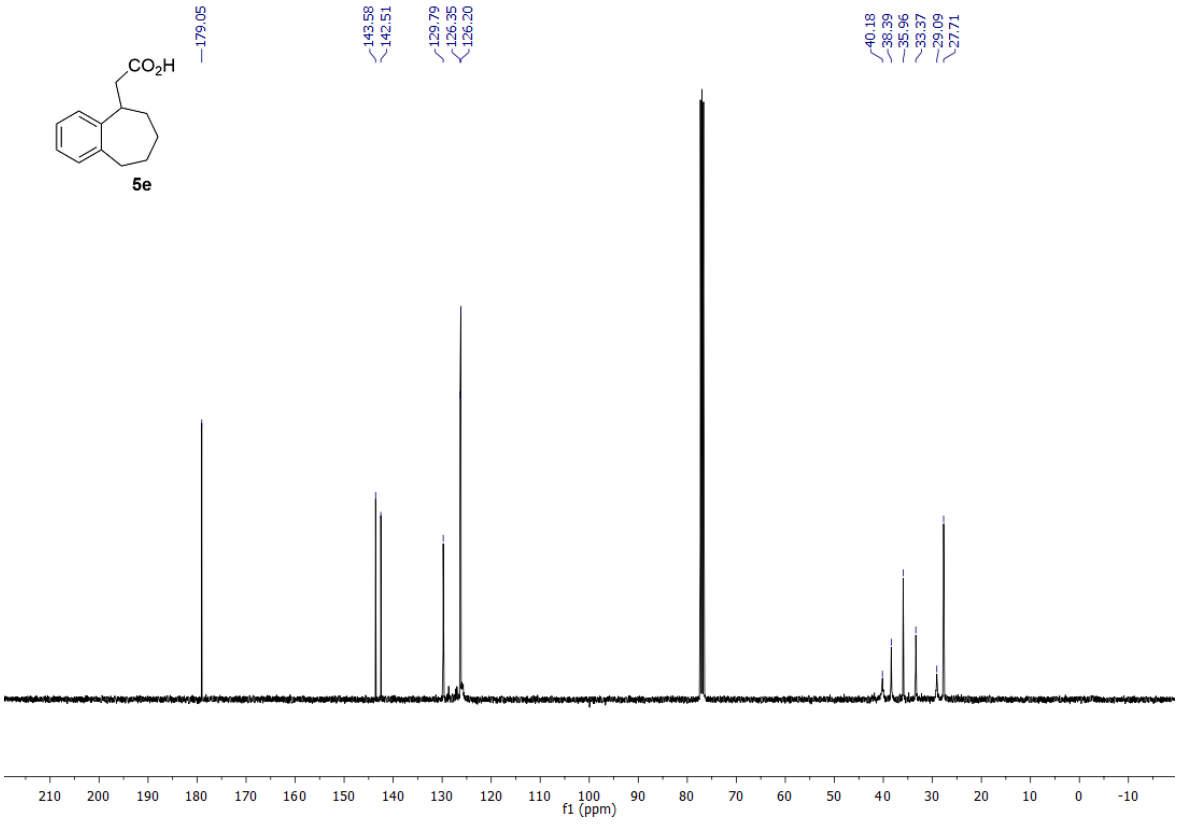
CO2H

5d


CO2H

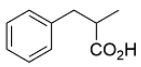
5e


0.62
3.96
1.00
4.04
4.12
1.92
f1 (ppm)

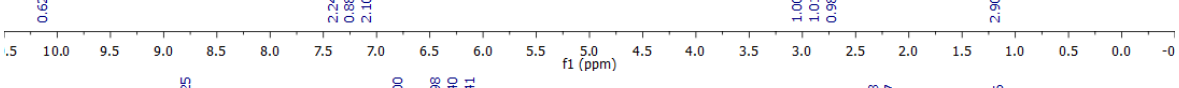

179.05
143.58
142.51
129.79
126.35
126.20
40.18
38.39
35.96
33.37
29.09
27.71
f1 (ppm)

CO2H

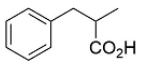
5e


CO2H

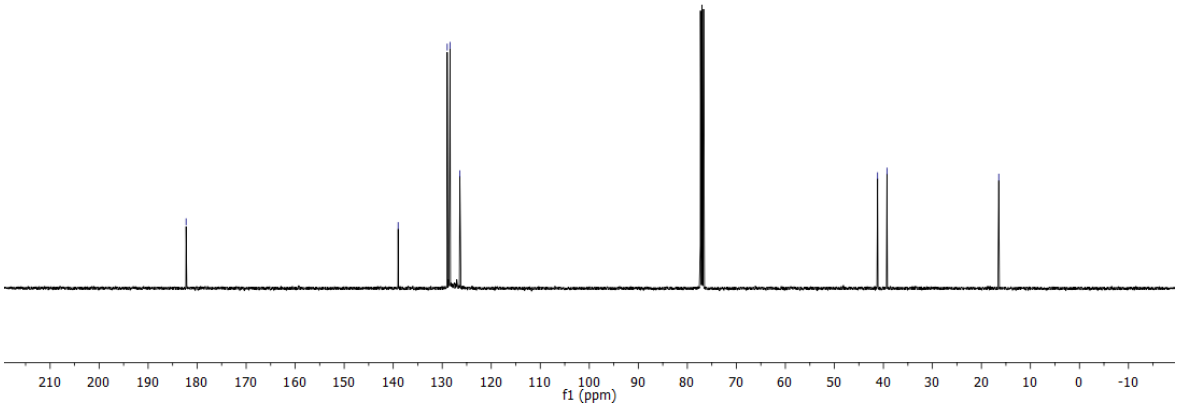
5f

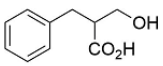

0.62
2.24
0.88
2.10
1.00
1.01
0.98
2.90
f1 (ppm)


182.25
139.00
128.98
128.40
126.41
41.18
39.27
16.46

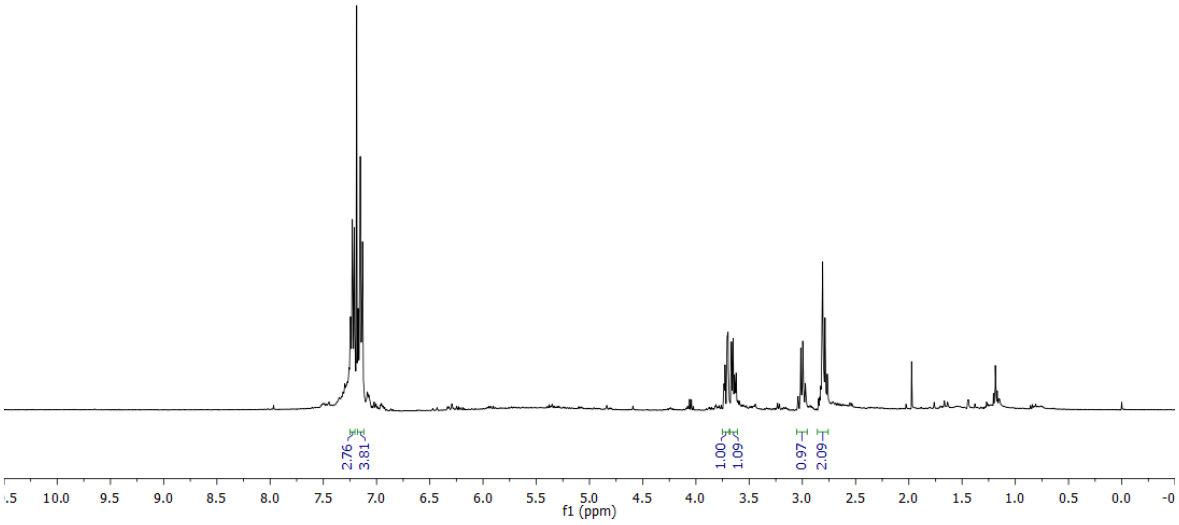

CO2H

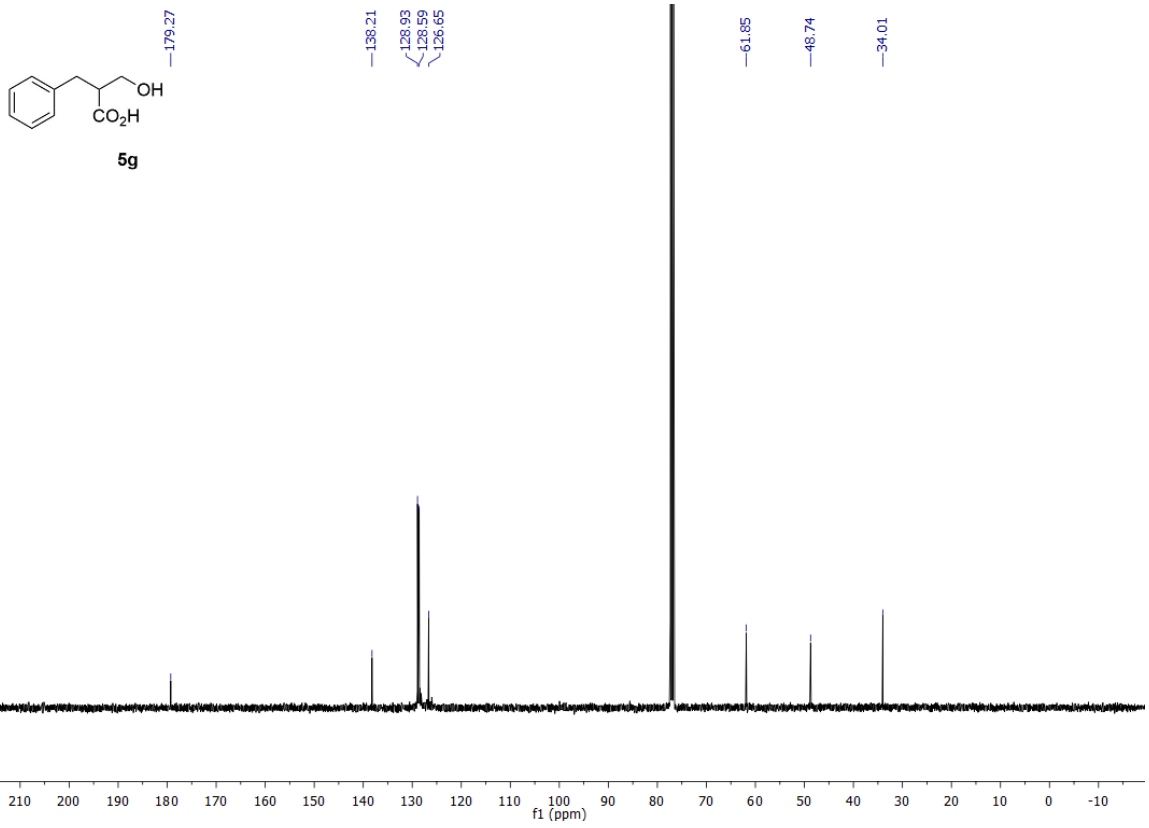
5f


f1 (ppm)

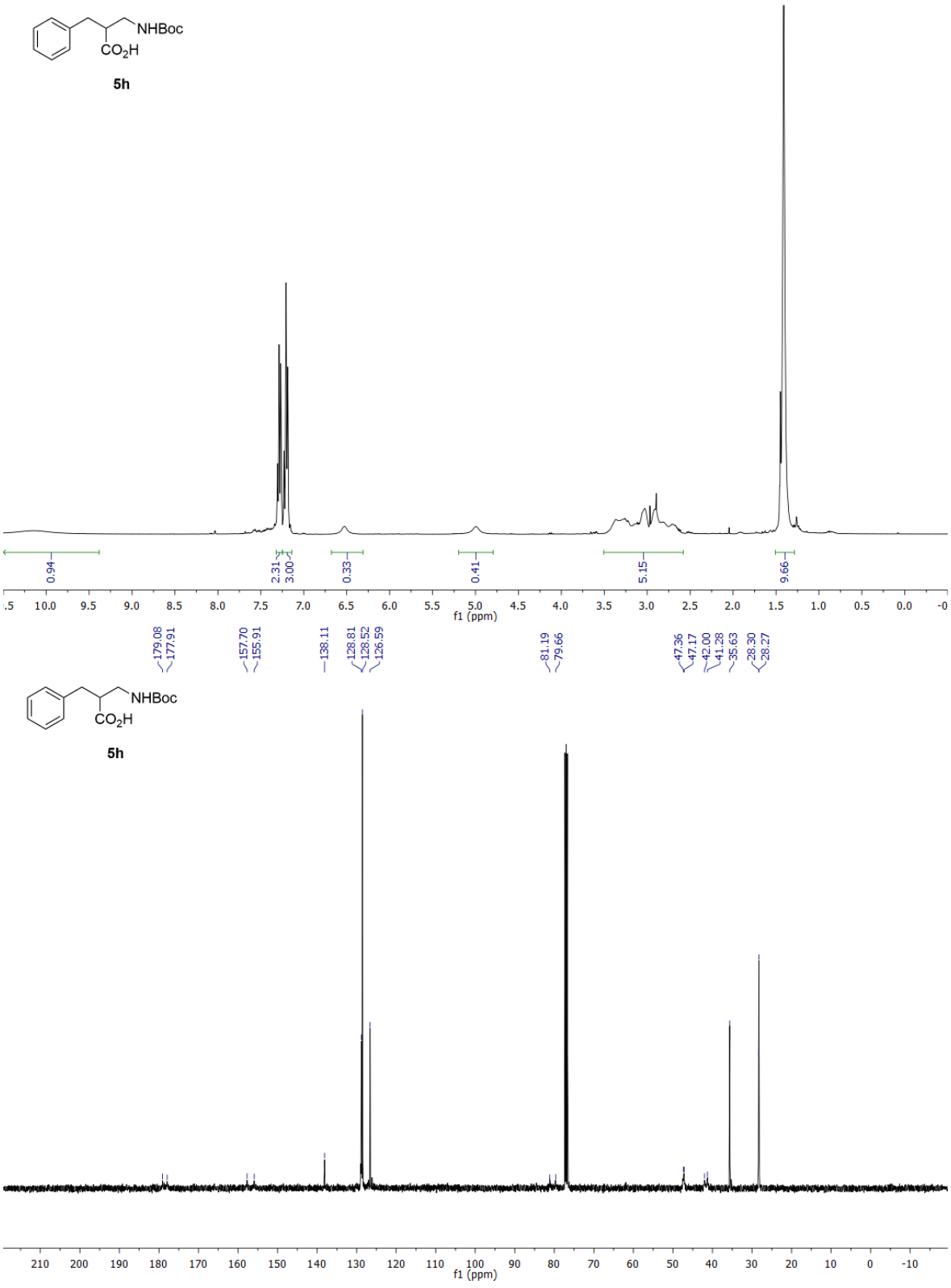

OH
CO2H

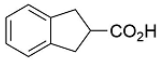
5g


2.76
3.81
1.00
1.09
0.97
2.09
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)

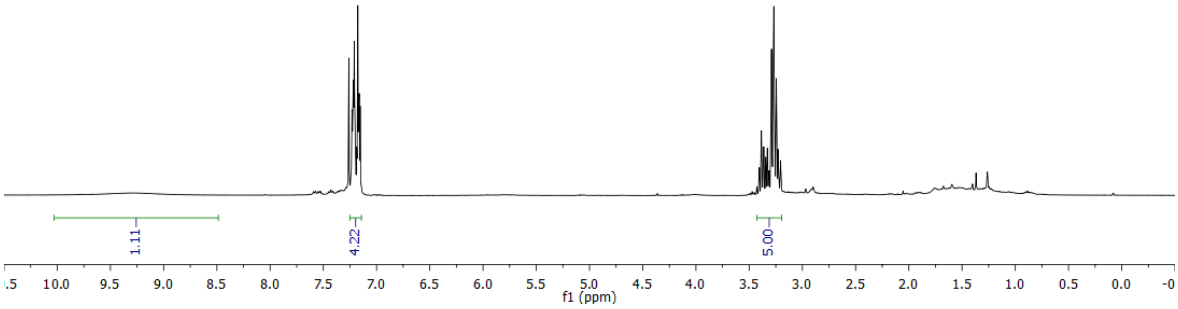

179.27
138.21
128.93
128.59
126.65
61.85
48.74
34.01
OH
CO2H
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

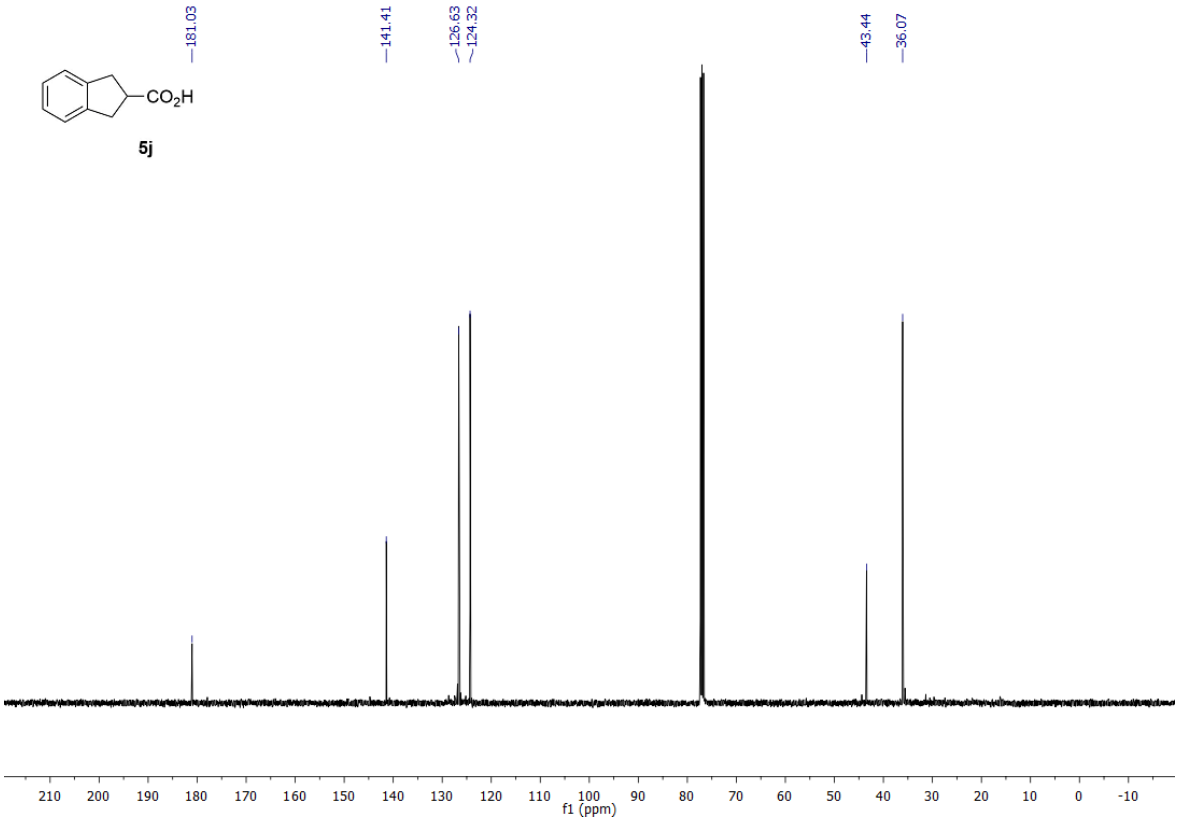
5g


NHBoc
CO2H
5h
0.94
2.31
3.00
0.33
0.41
5.15
9.66
f1 (ppm)
179.08
177.91
157.70
155.91
138.11
128.81
128.52
126.59
81.19
79.66
47.36
47.17
42.00
41.28
35.63
28.30
28.27
NHBoc
CO2H
5h
f1 (ppm)

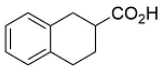

CO2H

5j

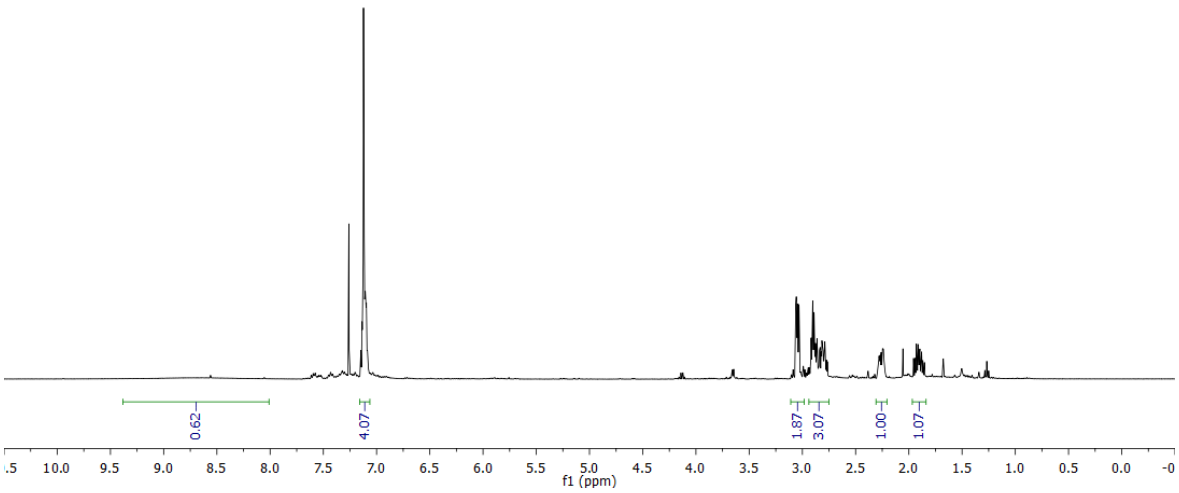

1.11
4.22
5.00
f1 (ppm)

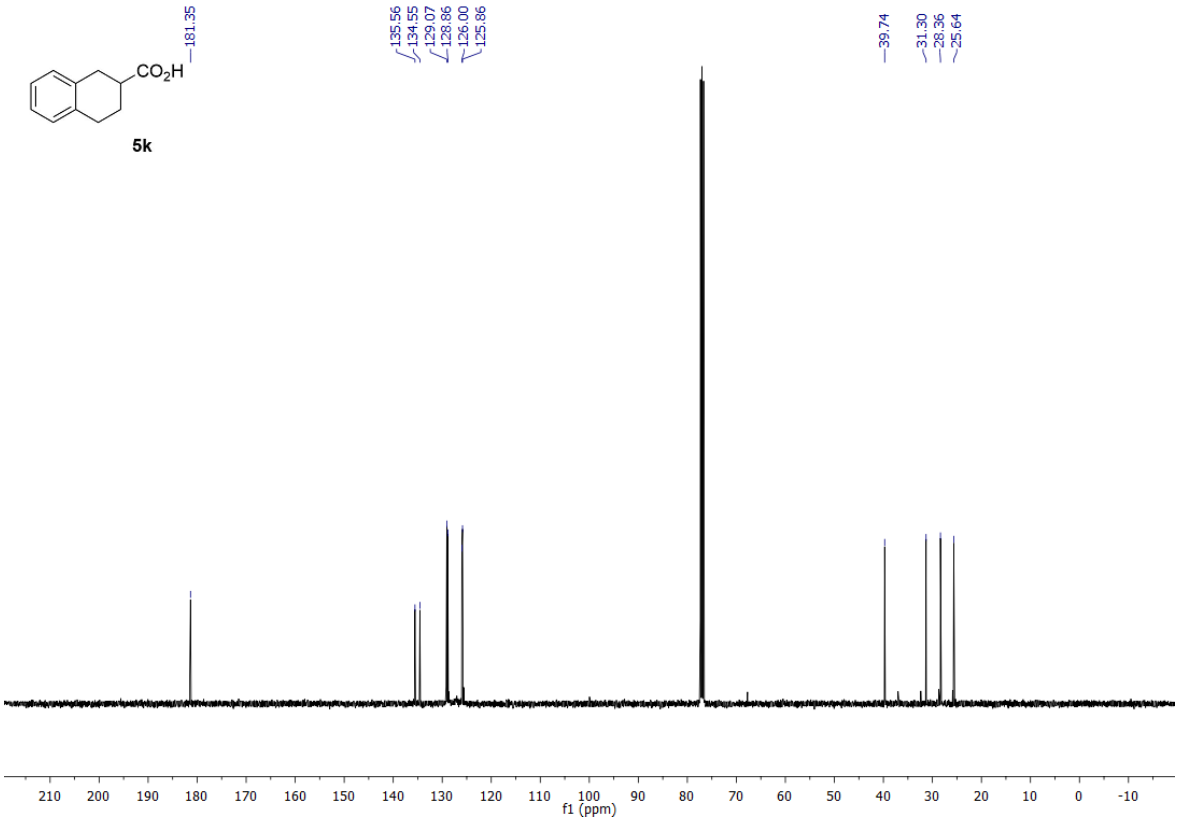

181.03
141.41
126.63
124.32
43.44
36.07
CO2H
f1 (ppm)

5j


CO2H

5k


0.62
4.07
1.87
3.07
1.00
1.07
f1 (ppm)


181.35
135.56
134.55
129.07
128.86
126.00
125.86
39.74
31.30
28.36
25.64
CO2H
f1 (ppm)

5k