Ligand-Accelerated Cross-Coupling of C(sp^2)–H Bonds with Organoboron Reagents

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SUPPORTING INFORMATION

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***General Information**:* Unless otherwise noted, all materials were used as received from commercial sources without further purification. Phenylacetic acid substrates were purchased from Acros, Sigma-Aldrich, TCI, Alfa-Aesar, and MP Biomedical and were used as received. 2-(Trifluoromethyl)phenylacetic acid (**1a**) was purchased from TCI; samples of **1a** from other commercial sources were found to give inconsistent results. Organoboron coupling partners were procured from Frontier Scientific, Sigma Aldrich, and Combi-Blocks and used as received. 1,4-Benzoquninone (BQ) was sublimed prior to use. *t*-AmylOH was purchased from Sigma-Aldrich. Newly opened and/or freshly distilled samples of *t*-Amyl-OH gave the most consistent results. Commercially available amino acid ligands were purchased from Bachem, EMD, or Novabiochem. To examine whether racemic Ac-Ile-OH would give better yields with chiral (racemic) substrates, Ac-D-Ile-OH was prepared.[1] All other ligands were prepared following literature precedent.[2] Palladium acetate and potassium hydrogen carbonate were purchased from Sigma-Aldrich and Fisher, respectively, and were used without further purification. All reactions were run on hot plates with oil baths calibrated to an external thermometer. Prior to beginning an experiment, the hot plate was turned on, and the oil bath was allowed to equilibrate to the desired temperature for 30 minutes. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova (400 MHz and 100 MHz, respectively) and Bruker DRX equipped with a 5mm DCH cryoprobe (600 MHz and 150 MHz, respectively) instruments internally referenced to tetramethylsilane or chloroform signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and a = apparent. The enantiomeric ratio of **Me-(*S*)-3n** was determined by integration of the HPLC trace, acquired using an Agilent Technologies 1200 series HPLC system with an integrate diode array detector (*vide infra*). High resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

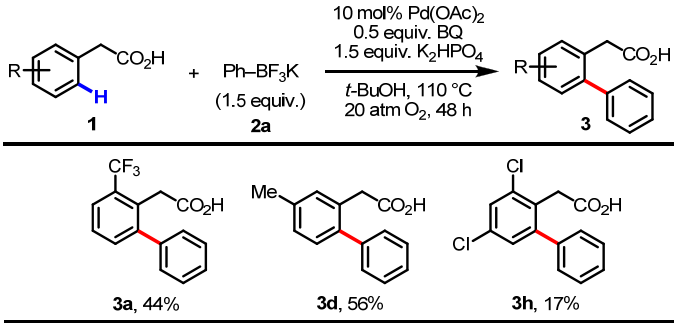
Experimental Procedures:

Previous Conditions: Representative Problematic Substrates

Previously reported procedure[3] for Pd(II)-catalyzed C–H/organoboron cross-coupling with phenylacetic acids (1): A 45 mL high pressure vessel equipped with a magnetic stir bar was charged with the phenylacetic acid substrate (**1**) (0.50 mmol), potassium phenyltrifluoroborate (**2a**) (184.0 mg, 0.75 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), BQ (27.0 mg, 0.25 mmol), K_2HPO_4 (130.7 mg, 0.75 mmol), and *t*-BuOH (2.5 mL). The vessel was pressurized to 20 atm with O_2, and transferred to an oil bath at 110 °C. *A note of caution: when working with high-pressure O_2, proper safety measures (including the use of a blast shield) should be taken.* After being allowed to stir vigorously for 48 h, the reaction vessel was removed from the oil bath and cooled to room temperature. The pressure was released, and a 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a**,

3.79 ppm for **3a**, 3.61 for **1d** 3.60 for **3d** 3.79 for **1h**, and 3.71 for **3h**). The results are shown in Table S1; these data were not included in the original publication.[3]

Table S1: Representative problematic substrates using previously reported conditions.[a]



[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

Ligand Acceleration: Optimization with Ag_2CO_3 as the Oxidant

Ligand optimization for Pd(II)-catalyzed C–H/organoboron cross-coupling with 2-(trifluoromethyl)phenylacetic acid (1a): A 25 mL sealed tube equipped with a magnetic stir bar was charged with 2-(trifluoromethyl)phenylacetic acid (**1a**) (102.1 mg, 0.50 mmol), potassium phenyltrifluoroborate (**2a**) (184.0 mg, 0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), ligand (0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ag_2CO_3 (137.2 mg, 0.5 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for 2 h, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a** and 3.79 ppm for **3a**). The results are shown in Table 1 and Table S2.

Table S2: Results from the ligand screening experiments.[a]

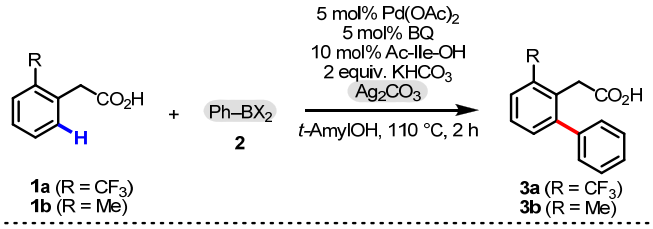
Entry	Ligand[b]	% Conv.	Entry	Ligand[b]	% Conv.
1	—	13	10	H-Ile-OH	0
2	Boc-Gly-OH	61	11	Me-Ile-OH	0
3	Boc-Ala-OH	77	12	Cbz-Ile-OH	76
4	Boc-Phe-OH	83	13	FormyI-Ile-OH	62
5	Boc-Val-OH	82	14	Fmoc-Ile-OH	79
6	Boc-allo-Ile-OH	83	15	Ac-Ile-OH	89
7	Boc-*t*-Leu-OH	79	16	Ac-Val-OH	79
8	Boc-Leu-OH	81	17	Ac-Leu-OH	87
9	Boc-Ile-OH	81	18	Ac-Ala-OH	86

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Boc = *tert*-butyloxycarbonyl , Cbz = carbobenzyloxy, Fmoc = fluorenylmethyloxycarbonyl, Ac = acetyl.

Coupling partner optimization for Pd(II)-catalyzed C–H/organoboron cross-coupling with 2-(trifluoromethyl)phenylacetic acid (1a): A 25 mL sealed tube equipped with a magnetic stir bar was charged with 2-(trifluoromethyl)phenylacetic acid **1a** (102.1 mg, 0.50 mmol), the phenylboron reagent (**2**) (0.75 mmol),[4] $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), Ac-Ile-OH (8.7 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ag_2CO_3 (137.2 mg, 0.5 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for 2 h, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a** and 3.79 ppm for **3a**). The results are shown in Tables 3.

Optimization of $PhBF_3K$ / Ag_2CO_3 loading with 2-(trifluoromethyl)phenylacetic acid (1a) and *o*-tolylacetic acid (1b): A 25 mL sealed tube equipped with a magnetic stir bar was charged with the phenylacetic acid substrate (**1a** or **1b**) (0.50 mmol), phenyltrifluoroborate (**2a**), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), Ac-Ile-OH (8.7 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ag_2CO_3, and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for 2 h, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a**, 3.79 ppm for **3a**, 3.67 ppm for **1b**, and 3.63 ppm for **3b**). To isolate the pure product **3a** or **3b**, the biphasic mixture was basified with concentrated aqueous NaOH until the pH > 12 (as monitored by pH paper), and the resulting solution was extracted with DCM (2 × 10 mL) to remove BQ and biphenyl (the undesired homocoupling byproduct), and the organic layers were back-extracted once with 2.0 M NaOH (10 mL). The combined aqueous layers were acidified *via* dropwise addition of concentrated HCl until the pH < 2, and the solution was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography using 2:1 hexanes:EtOAc (with 3% HOAc) as the eluent. The results are shown in Tables 2 and S3.

Table S3: Optimization of $PhBF_3K$ / Ag_2CO_3 loading with substrates **1a** and **1d**.[a]



% Conv. (**3a**)

$PhBF_3$ (equiv.)

Ag_2CO_3 (equiv.)	1.5	2.0	3.0
1.0	89	87	86
1.5	88	>99	>99
2.0	87	>99	>99 (98)[b]

% Conv. (**3b**)

$PhBF_3$ (equiv.)

Ag_2CO_3 (equiv.)	1.5	2.0	3.0
1.0	68	68	70
1.5	75	90	92
2.0	90	88	>99 (97)

PhBPin (equiv.)

Ag_2CO_3 (equiv.)	1.5	2.0	3.0
2.0	>99	>99	>99 (92)

PhBPin (equiv.)

Ag_2CO_3 (equiv.)	1.5	2.0	3.0
2.0	80	93	>99 (96)

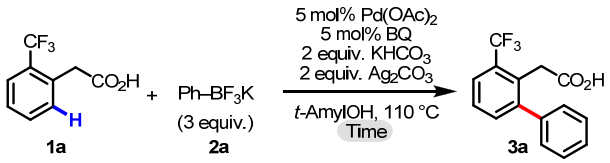
[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parenthesis. [b] Under otherwise identical conditions, 74% conversion was observed using 2 mol% $Pd(OAc)_2$, 2 mol% BQ, and 4 mol% Ac-Ile-OH.

Pd(II)-catalyzed C–H/organoboron cross-coupling with 2-(trifluoromethyl)phenylacetic acid (1a) at 70 °C: A 25 mL sealed tube equipped with a magnetic stir bar was charged with 2-(trifluoromethyl)phenylacetic acid (**1a**) (102.1 mg, 0.50 mmol), potassium phenyltrifluoroborate (**2a**) (184.0 mg, 0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), ligand (0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ag_2CO_3 (137.2 mg, 0.5 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 70 °C. After being allowed to stir vigorously for 36 h, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a** and 3.79 ppm for **3a**). The results are shown in Table 4.

Rate Profile Measurements

Rate profile measurements with 2-(trifluoromethyl)phenylacetic acid (1a) and *o*-tolylacetic acid (1b): For each substrate, two different reaction conditions were examined: (1) without Ac-Ile-OH and (2) with Ac-Ile-OH. A 100 mL Schlenk tube containing a magnetic stir bar was charged with **1a** (or **1b**) (1.00 mmol), phenyltrifluoroborate (**2a**) (552.0 mg, 3.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol), BQ (5.4 mg, 0.050 mmol), Ac-Ile-OH (8.7 mg, 0.05 mmol) (when used), $KHCO_3$ (200.2 mg, 2.0 mmol), Ag_2CO_3 (551.5 mg, 2.0 mmol), and *t*-AmylOH (5.0 mL). The reaction tube was capped with a rubber septum, then stirred at 110 °C. At the indicated time points, a small aliquot (< 0.1 mL) was removed from the vial. The aliquots were added to independent 10 mL scintillation vials containing a biphasic mixture of 2.0 N HCl solution (1.0 mL) and diethyl ether (2.0 mL). An aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a**, 3.79 ppm for **3a**, 3.67 ppm for **1b**, and 3.63 ppm for **3b**). The procedure was repeated thee times. The resulting data were plotted, and linear regression of the time points in the 5–20 min period established the initial rate. The results are shown in Tables S4–S7 and Figures S1–S4.

Table S4: Rate profile measurements for **1a** in the absence of Ac-Ile-OH.[a]



% Conv.

Entry	Time (min)	Trial 1	Trial 2	Trial 3	Average	Std. Dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	5	0.0	0.6	0.9	0.5	0.5
3	7.5	1.2	0.9	1.2	1.1	0.2
4	10	1.3	1.2	2.4	1.6	0.7
5	15	3.2	1.6	3.7	2.8	1.1
6	20	4.3	3.2	5.1	4.2	1.0
7	30	6.7	3.4	6.5	5.5	1.9
8	60	11.2	6.2	12.9	10.1	3.5
9	90	13.0	9.6	17.7	13.4	4.1
10	120	16.4	12.8	22.0	17.1	4.6

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

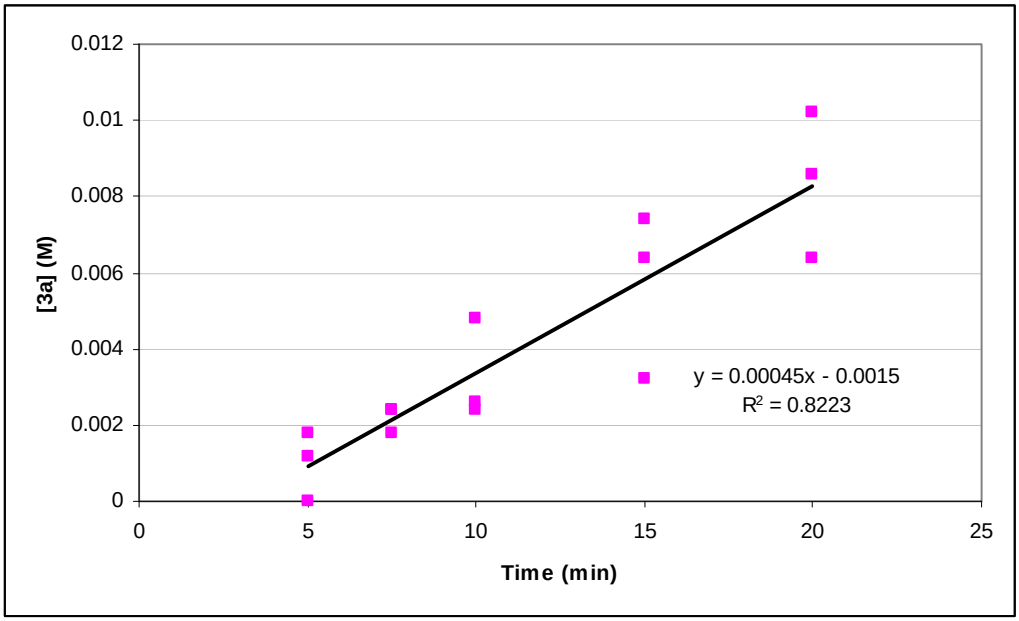
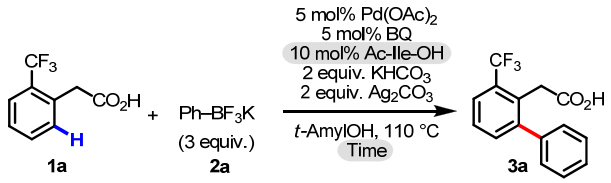


Figure S1: Initial rate data for the formation of **3a** in the absence of Ac-Ile-OH.

Table S5: Rate profile measurements for **1a** with Ac-Ile-OH.[a]



% Conv.

Entry	Time (min)	Trial 1	Trial 2	Trial 3	Average	Std. Dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	5	5.2	5.3	0.1	3.5	3.0
3	7.5	13.6	5.9	3.6	7.7	5.2
4	10	22.2	8.3	5.5	12.0	8.9
5	15	36.6	12.3	12.1	20.2	13.9
6	20	62.0	14.1	19.9	32.0	26.1
7	30	96.3	28.3	40.8	55.1	36.2
8	60	97.0	62.7	98.9	86.2	20.4
9	90	100	100	100	100	0.0
10	120	100	100	100	100	0.0

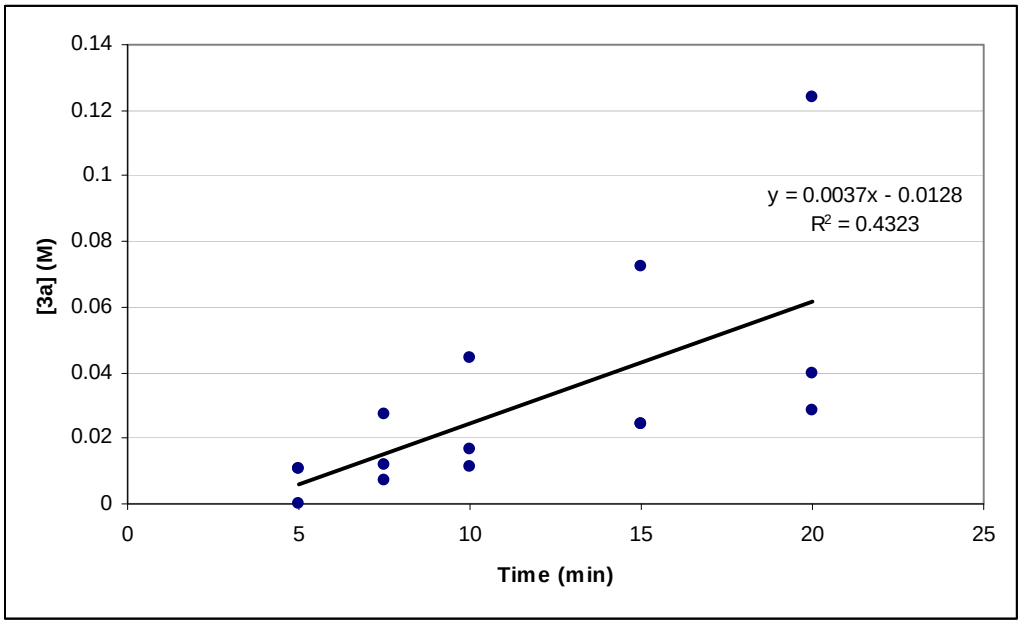
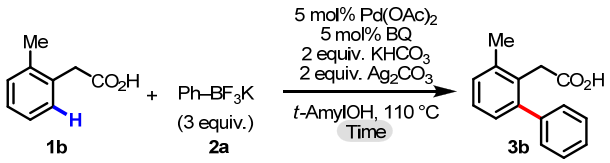


Figure S2: Initial rate data for the formation of **3a** in the absence of Ac-Ile-OH.

Table S6: Rate profile measurements for **1b** in the absence of Ac-Ile-OH.[a]



% Conv.

Entry	Time (min)	Trial 1	Trial 2	Trial 3	Average	Std. Dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	5	0.0	1.4	0.0	0.5	0.8
3	7.5	2.8	2.2	0.0	1.7	1.5
4	10	3.1	4.1	1.1	2.8	1.5
5	15	4,5	6.3	2.2	4.3	2.1
6	20	5.1	8.2	4.4	5.9	2.0
7	30	6.5	12.4	6.7	8.5	3.4
8	60	13.0	20.9	10.8	14.9	5.3
9	90	18.2	21.7	13.7	17.9	4.0
10	120	25.6	33.7	19.5	26.3	7.1

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

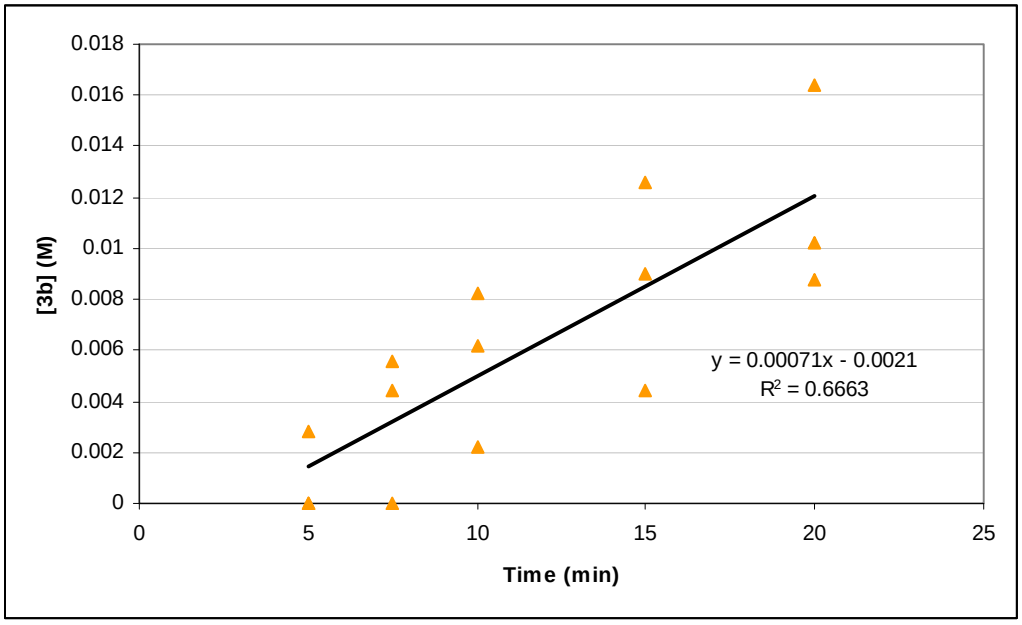
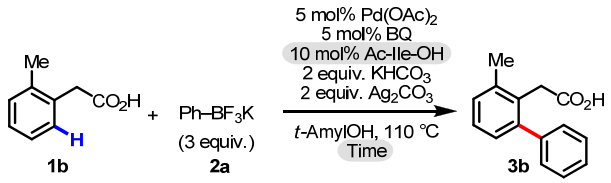


Figure S3: Initial rate data for the formation of **3a** in the absence of Ac-Ile-OH.

Table S7: Rate profile measurements for **1b** with Ac-Ile-OH.[a]



		% Conv.				
Entry	Time (min)	Trial 1	Trial 2	Trial 3	Average	Std. Dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	5	1.8	2.0	0.0	1.3	1.1
3	7.5	2.6	2.4	2.0	2.3	0.3
4	10	3.4	3.9	3.4	3.6	0.3
5	15	4.8	11.4	7.2	7.8	3.3
6	20	10.0	15.0	11.5	12.2	2.6
7	30	21.0	20.0	16.6	19.2	2.3
8	60	61.9	59.8	54.4	58.7	3.9
9	90	91.5	93.6	94.6	93.2	1.6
10	120	97.2	94.9	100.0	97.4	2.6

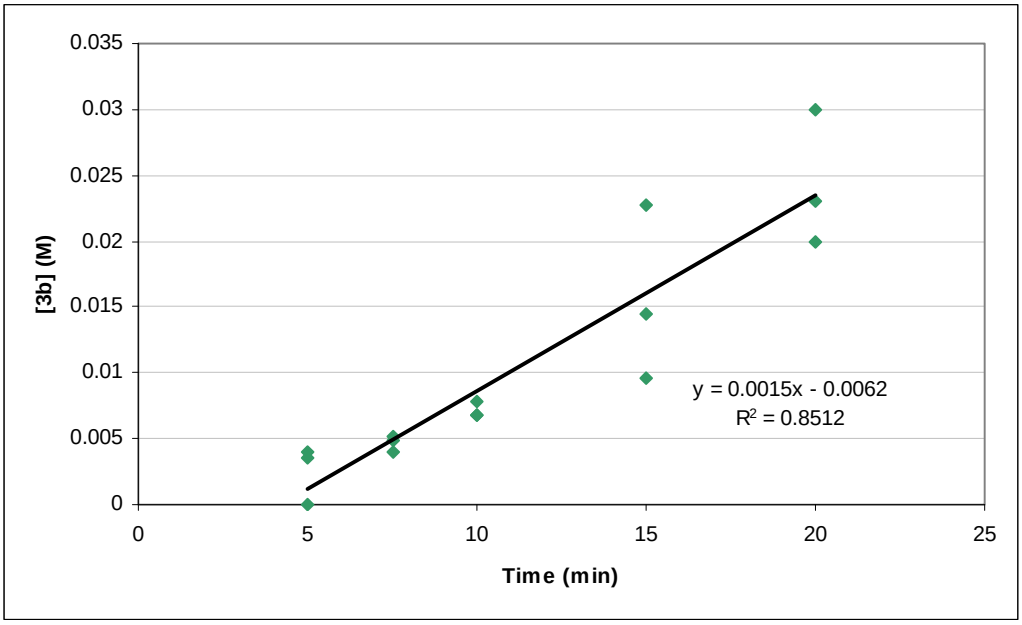
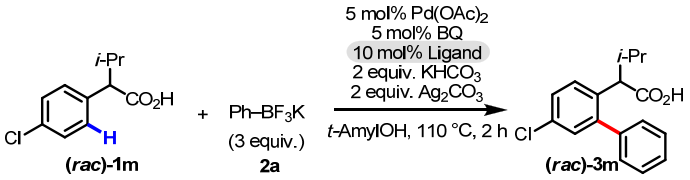


Figure S4: Initial rate data for the formation of **3a** in the absence of Ac-Ile-OH.

Potential Match/Mismatch Effect with Chiral Substrates

It was observed that some α-substituted phenylacetic acids gave lower conversions than their unsubstituted counterparts (*e.g.*, **(*rac*)-3m**). This finding prompted us to question whether we were observing a match/mismatch effect between the racemic, chiral starting material and the non-racemic, chiral catalyst. Based on this thinking, we hypothesized that one of the two enantiomers of the racemic starting material was reacting preferentially (*i.e.*, a partial kinetic resolution) and that that was leading to the low overall conversions. To test this hypothesis, we exposed 2-(4-chlorophenyl)-3-methylbutyric acid (**(*rac*)-1m**) to our reaction conditions using enantiopure and racemic versions of Ac-Ile-OH and Boc-Ile-OH. In both cases the racemic versions of the ligands, were prepared by mixing the L- and D-amino acids in a 1:1 ratio. Because Ac-D-Ile-OH was not commercially available, we synthesized it *via* routine *N*-acylation.[1] The data, which is shown in Table S8, seems to refute this hypothesis, since both the (*rac*)- and the L-amino acids gave similar conversions after 2 h.

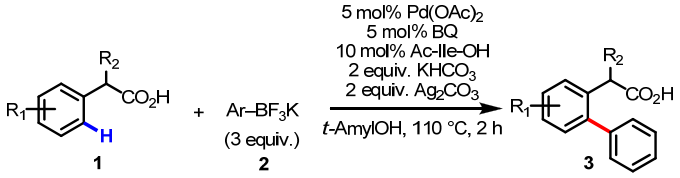
Table S8: The effect of ligand stereochemistry on the conversion with a representative chiral starting material, **(*rac*)-1m**.[a]



Entry	Ligand	% Conv.
1	Ac-L-Ile-OH	77
2	Ac-(*rac*)-Ile-OH	77
3	Boc-L-Ile-OH	60
4	Boc-(*rac*)-Ile-OH	59

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

General Procedure with Ag_2CO_3 as the Oxidant



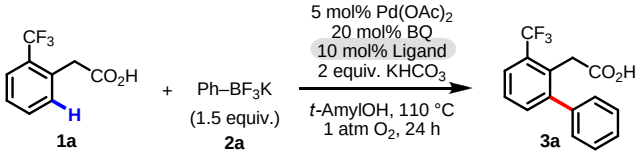
Scheme S1: General procedure for C–H/organoboron cross-coupling using Ag_2CO_3 as the oxidant.

General procedure for Pd(II)-catalyzed C–H/organoboron cross-coupling with phenylacetic acids (1) and potassium trifluoroborates (2) using Ag_2CO_3 as the oxidant: A 25 mL sealed tube equipped with a magnetic stir bar was charged with the phenylacetic acid substrate (**1**) (0.50 mmol), the aryltrifluoroborate (**2**) (1.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), Ac-Ile-OH (8.7 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ag_2CO_3 (275.8 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for 2 h, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic proton signals—**3** generally appears upfield from **1**. To isolate the pure product **3**, the biphasic mixture was basified with concentrated aqueous NaOH until the pH > 12 (as monitored by pH paper), and the resulting solution was extracted with DCM (2 × 10 mL) to remove BQ and the biaryl homocoupling byproduct, and the organic layers were back-extracted once with 2.0 N NaOH (10 mL). The combined aqueous layers were acidified *via* dropwise addition of concentrated HCl until the pH < 2, and the solution was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography using 2:1 hexanes:EtOAc (with 3% HOAc) as the eluent. Products **3i**, **(*rac*)-3o**, **3s**, and **3w** were prepared on a 0.2 mmol scale, using the same relative amounts of reagents. For each substrate, a control experiment in the absence of Ac-Ile-OH was run, and the conversion was determined in a similar manner; however the product (which was generally observed in scant quantities) was not isolated. The results in the presence and absence of ligand are shown in Tables 5 and 6.

Ligand Acceleration: Optimization of Aerobic Conditions

Ligand optimization for Pd(II)-catalyzed C–H/organoboron cross-coupling with 2-(trifluoromethyl)phenylacetic acid (1a): A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with 2-(trifluoromethyl)phenylacetic acid (**1a**) (102.1 mg, 0.50 mmol), potassium phenyltrifluoroborate (**2a**) (184.0 mg, 0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (10.8 mg, 0.1 mmol), ligand (0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). It was then immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for 24 h, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a** and 3.79 ppm for **3a**). The results are shown in Tables 7 and S9.

Table S9: Results from the ligand screening experiments under aerobic conditions.[a]



Entry	Ligand[b]	% Conv.	Entry	Ligand[b]	% Conv.
1	---	9	13	H-Val-OH	6
2	Boc-Ala-OH	39	14	Formyl-Val-OH	52
3	Boc-Phe-OH	48	15	Piv-Val-OH	9
4	Boc-Ser-OH	26	16	Ada-Val-OH	24
5	Boc-Thr(*t*-Bu)-OH	40	17	Me(O_2C)-Val-OH	50
6	Boc-Aib-OH	44	18	Et(O_2C)-Val-OH	46
7	Boc-Leu-OH	57	19	Cbz-Val-OH	52
8	Boc-*t*-Leu-OH	57	20	Fmoc-Val-OH	20
9	Boc-Ile-OH	49	21	*i*-Bu(O_2C)-Val-OH	49
10	Boc-Abu-OH	60	22	Ac-Val-OH	52
11	Boc-Nle-OH	48	23	Ac-Leu-OH	56
12	Boc-Val-OH	65	24	Ac-Ile-OH	56

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Aib = *α*-aminoisobutyric acid, Abu = L-2-aminobutyric acid, Nle = L-Norleucine, Ada = 1-adamantyl(CO), Piv = pivaloyl.

Optimization of BQ loading / reaction time 2-(trifluoromethyl)phenylacetic acid (1): A 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar was charged with 2-(trifluoromethyl)phenylacetic acid (**1a**) (102.1 mg, 0.50 mmol), potassium phenyltrifluoroborate (**2a**) (184.0 mg, 0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ, Boc-Val-OH (10.9 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). It was then immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for the appropriate amount of time, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a** and 3.79 ppm for **3a**). The results are shown in Table S10.

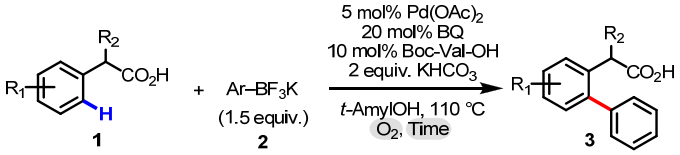
Table S10: Optimization of BQ loading / reaction time.[a]

% Conv. (**3a**)

BQ (mol %)	Time: 2 h	24 h	48 h
—	5	5	5
5	27	50	54
10	13	56	56
20	13	65	65
50	13	33	34

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

General Procedure with Aerobic Conditions



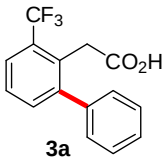
Scheme S2: General procedure for C–H/organoboron cross-coupling under aerobic conditions.

General procedure for Pd(II)-catalyzed C–H/organoboron cross-coupling of phenylacetic acids (1) with potassium trifluoroborates (2) using O_2 (or air) as the oxidant : For experiments using >1 atm of pressure, a 45 mL high pressure vessel was used. For experiments using 1 atm of pressure, a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) was used. The reaction flask was equipped with a magnetic stir bar and was charged with the phenylacetic acid substrate (**1**) (0.50 mmol), the aryltrifluoroborate (**2**) (0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (10.8 mg, 0.1 mmol), Boc-Val-OH (10.9 mg, 0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction vessel was capped and adjusted to the appropriate pressure of O_2 (or air). *A note of caution: when working with high pressure O_2, proper safety measures (including the use of a blast shield) should be taken.* After being allowed to stir vigorously for the appropriate time, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. The pressure was released, and a 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets—**3** generally appears upfield from **1**. To isolate the pure product (**3**), the biphasic mixture was basified with

concentrated aqueous NaOH until the pH > 12 (as monitored by pH paper), the resulting solution was extracted with DCM (2 × 10 mL) to remove BQ and biphenyl (the undesired homocoupling byproduct), and the organic layers were back-extracted once with 2.0 M NaOH (10 mL). The combined aqueous layers were acidified *via* dropwise addition of concentrated HCl until the pH < 2, and the solution was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash column chromatography using 2:1 hexanes:EtOAc (with 3% HOAc) as the eluent. For each substrate under each of the conditions reported, a control experiment in the absence of Ac-Ile-OH was run, and the conversion was determined in a similar manner; however the product (which was generally observed in scant quantities) was not isolated. The results are shown in Table 8.

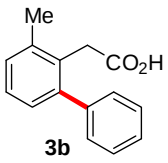
Characterization of New Compounds

Our group has previously reported a procedure for Pd(II)-catalyzed C–H/arylboron cross-coupling using benzoic and phenylacetic acid substrates under high pressure O_2 (20 atm).[3] In that publication, **3i**, **(*rac*)-3m**, and **3l** were also synthesized but were isolated as their methyl esters following treatment of the crude product mixture with CH_2N_2. This was done to simplify the separation of the product from residual unreacted starting material, which is problematic using the free acids. Because the reactions reported here generally gave quantitative yields, the pure products could consistently be isolated as free acids. We have included the analytical data for free acids **3i**, **(*rac*)-3m**, and **3l**. To determine whether racemization took place during the reaction with enantiopure (*S*)-naproxen (**(*S*)-1n**) as the starting material, chiral HPLC was used. Compound **(*S*)-3n** was prepared using the standard reaction conditions from commercially available (*S*)-naproxen (**(*S*)-1n**) (MP Biomedical). Compound **(*rac*)-3n** was prepared using the standard reaction conditions from a 1:1 mixture of commercially available (*S*)-naproxen (**(*S*)-1n**) (MP Biomedical) and (*R*)-naproxen (**(*R*)-1n**) (Aldrich). These products were converted to the corresponding methyl esters, **Me-(*S*)-3n** and **Me-(*rac*)-3n**, in order to improve separation with chiral HPLC. Because the analytical data for the enantiopure and racemic forms of **3n** and **Me-3n** are identical, only the data for **(*S*)-1n** and **Me-(*S*)-3n** are reported below. The chiral HPLC method was optimized using **Me-(*rac*)-3n** as the standard, and the er of **Me-(*S*)-3n** was subsequently determined



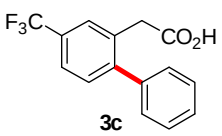
3a

2-(2-(trifluoromethyl)phenyl)acetic acid (3a): The title compound was prepared on a 0.5 mmol scale and obtained as a yellow oil (137 mg, 98% yield). $\mathbf{R_f}$ = 0.82 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (t, J = 5.6 Hz, 1 H), 7.46–7.38 (m, 5 H), 7.28–7.24 (m, 2 H), 3.80 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.38, 145.41, 139.95, 133.78, 129.64, 129.55 (q, J_{C-F} = 29.5 Hz), 128.88, 128.46, 127.87, 127.33, 125.45 (q, J_{C-F} = 5.7 Hz), 124.38 (q, J_{C-F} = 272.5 Hz), 35.18; **IR** (neat) ν 3026, 2930, 1713, 1325, 1232, 1164, 1118, 1047, 942 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{12}F_3O_2$ $[M+H]^+$ 281.0789, found 281.0788.



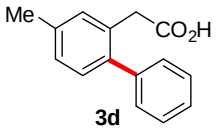
3b

2-(3-methylbiphenyl-2-yl)acetic acid (3b): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (129 mg, 97% yield). $\mathbf{R_f}$ = 0.74 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.35 (m, 3 H), 7.31–7.21 (m, 4 H), 7.14–7.12 (m, 1 H), 3.65 (s, 2 H), 2.36 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.48, 143.30, 141.65, 137.64, 129.96, 129.50, 129.09, 128.22, 127.92, 127.16, 127.13, 36.03, 20.19; **IR** (neat) ν 3.025, 2924, 1704, 1466, 1410, 1232, 762, 703 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 227.1067, found 227.1059.



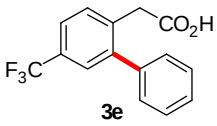
3c

2-(4-(trifluoromethyl)biphenyl-2-yl)acetic acid (3c) The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (136 mg, 97% yield). $\mathbf{R_f}$ = 0.66 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64–7.59 (m, 2 H), 7.45–7.40 (m, 4 H), 7.30–7.26 (m, 2 H), 3.69 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.16, 146.14, 139.51, 131.91, 130.72, 129.82 (q, J_{C-F} = 32.6 Hz), 128.88, 128.51, 127.94, 127.35 (q, J_{C-F} = 3.7 Hz), 124.22 (q, J_{C-F} = 3.4 Hz), 123.99 (q, J_{C-F} = 270.9 Hz), 38.36; **IR** (neat) ν 3029, 2928, 1695, 1420, 1332, 1234, 1171, 1119, 1084, 912, 838 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{12}F_3O_2$ $[M+H]^+$ 281.0784, found 281.0783.



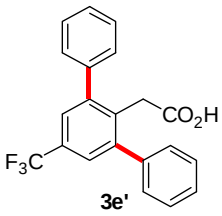
3d

2-(4-methylbiphenyl-2-yl)acetic acid (3d: The title compound was prepared on a 0.5 mmol scale and obtained as a yellow oil (126 mg, 95% yield). $\mathbf{R_f}$ = 0.71 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$) δ 7.41–7.34 (m, 3 H), 7.30–7.28 (m, 2 H), 7.19–7.16 (m, 3 H), 3.60 (s, 2 H), 2.39 (s, 3 H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ173.12, 142.22, 140.48, 137.65, 133.07, 132.13, 130.65, 130.06, 129.01, 128.48, 127.78, 38.84, 21.05; **IR** (neat) ν 3024, 2922, 1705, 1484, 1412, 1291, 916, 824, 764 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 227.1067, found 227.1062.



3e

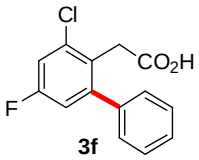
2-(5-(trifluoromethyl)biphenyl-2-yl)acetic acid (3e: The title compound was prepared on a 0.5 mmol scale and obtained as a white solid (73 mg, 52% yield). $\mathbf{R_f}$ = 0.63 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 1 H), 7.55 (s, 1 H), 7.50 (d, J = 8.0 Hz, 1 H), 7.45–7.41 (m, 3 H), 7.30 (d, J = 6.8 Hz, 2 H), 3.69 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.61, 143.20, 139.42, 134.95, 130.95, 129.72 (q, J_{C-F} = 32.4 Hz), 129.02, 128.54, 127.93, 127.08 (q, J_{C-F} = 3.8 Hz), 124.28 (q, J_{C-F} = 3.8 Hz), 123.95 (q, J = 270.8 Hz), 38.10; **IR** (neat) ν 3033, 2926, 1712, 1413, 1337, 1259, 1168, 1125, 1078, 904, 771 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{12}F_3O_2$ $[M+H]^+$ 281.0784, found 281.0783.



3e'

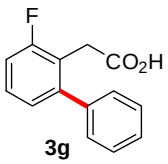
2,6-diphenyl-4-(trifluoromethyl)phenylacetic acid (3e'): The title compound was generated during the synthesis of **3e** and isolated as a white solid (50 mg, 28% yield). $\mathbf{R_f}$ = 0.71 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 (s, 2 H), 7.45–7.40 (m, 6 H), 7.35–7.30 (m, 4 H), 3.59 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.83, 144.21, 140.06, 133.24,

129.26 (q, J_{C-F} = 32.4 Hz), 128.89, 128.52, 127.94, 125.95 (q, J_{C-F} = 3.7 Hz), 123.92 (J_{C-F} = 270.9 Hz), 36.44; **IR** (neat) ν 2926, 2855, 1709, 1421, 1363, 1266, 1170, 1128, 897, 772 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{21}H_{16}F_3O_2$ $[M+H]^+$ 357.1097, found 357.1108.



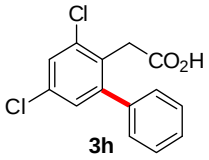
3f

2-(3-chloro-5-fluorobiphenyl-2-yl)acetic acid (3f): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (130 mg, 98% yield). $\mathbf{R_f}$ = 0.56 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.39 (m, 3 H), 7.28–7.26 (m, 2 H), 7.19 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 1 H), 6.95 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 1 H), 3.71 (s, 2 H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 171.77, 161.66 (d, J_{C-F} = 246.3 Hz), 147.19 (d, J_{C-F} = 8.5 Hz), 140.68, 129.51, 129.42, 129.00, 128.63 (d, J_{C-F} = 3.6 Hz), 116.35 (d, J = 22.7 Hz), 116.34 (d, J = 23.2 Hz), 36.66; **IR** (neat) ν 3027, 2926, 1709, 1598, 1585, 1575, 1459, 1411, 1302, 1236, 11.78, 1140, 943, 870 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{11}ClFO_2$ $[M+H]^+$ 265.0432, $[(M+2)+H]^+$ 267.0402, found 265.0425, 267.0413 $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.



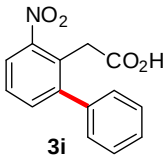
3g

2-(3-fluorobiphenyl-2-yl)acetic acid (3g): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (110 mg, 96% yield). $\mathbf{R_f}$ = 0.59 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 3 H), 7.36–7.30 (m, 3 H), 7.11–7.07 (m, 2 H), 3.66 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.04, 161.56 (d, J_{C-F} = 245.2 Hz), 144.68 (d, J_{C-F} = 3.7 Hz), 139.62 (d, J_{C-F} = 2.6 Hz), 128.99, 128.56 (d, J_{C-F} = 9.2 Hz), 128.44, 127.68, 125.62 (d, J_{C-F} = 3.1 Hz), 119.31 (d, J_{C-F} = 15.9 Hz), 114.08 (d, J_{C-F} = 22.1 Hz), 32.20; **IR** (neat) ν 3025, 2927, 1707, 1573, 1462, 1410, 1289, 1238, 947, 795, 761, 703 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}FO_2$ $[M+H]^+$ 231.0816, found 231.0812.



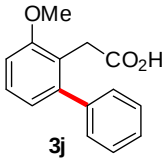
3h

2-(3,5-dichlorobiphenyl-2-yl)acetic acid (3h): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (138 mg, 98% yield). $\mathbf{R_f}$ = 0.56 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44–7.41 (m, 4 H), 7.27–7.25 (m, 2 H), 7.21 (s, 1 H), 3.71 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.53, 145.85, 139.27, 136.29, 133.36, 128.72, 128.67, 128.66, 128.61, 128.26, 128.17, 36.35; **IR** (neat) ν 3027, 2928, 1706, 1584, 1556, 1411, 1392, 1234, 1158, 937, 863, 768, 701 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{11}Cl_2O_2$ $[M+H]^+$ 281.0136, $[(M+2)+H]^+$ 283.0107, $[(M+4)+H]^+$ 282.0170, found 281.0124, 283.0106, 285.0078 $[M+H]^+$: $[(M+2)+H]^+$: $[(M+4)+H]^+$= 9:6:1.



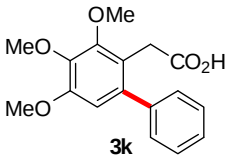
3i

2-(3-nitrobiphenyl-2-yl)acetic acid (3i): The title compound was prepared on a 0.2 mmol scale and obtained as a white solid (35 mg, 69% yield). $\mathbf{R_f}$ = 0.40 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (dd, J_1 = 10.1 Hz, J_1 = 3.0, 1 H), 7.58–7.43 (m, 5 H), 7.29–7.26 (m, 2 H), 3.93 (2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.44, 149.57, 145.84, 139.05, 135.23, 128.98, 128.74, 128.27, 127.90, 126.73, 124.40, 36.03; **IR** (neat) ν 2928, 2856, 1710, 1528, 1347, 1228, 704 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{12}NO_4$ $[M+H]^+$ 258.0761, found 258.0770.



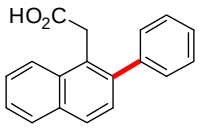
3j

2-(3-methoxybiphenyl-2-yl)acetic acid (3j): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (114 mg, 94% yield). $\mathbf{R_f}$ = 0.47 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 6 H), 6.87 (ad, *J* = 8.0 Hz, 2 H), 3.83 (s, 3 H), 3.57 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.10, 157.83, 143.92, 140.84, 129.11, 128.23, 128.01, 127.23, 122.35, 120.65, 109. 26, 55.72, 33.33; **IR** (neat) ν 3021, 2938, 1704, 1584, 1466, 1434, 1258, 1203, 1117, 1020, 761, 703 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{15}O_2$ $[M+H]^+$ 243.1016, found 243.1022.



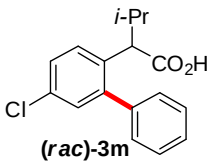
3k

2-(3,4,5-trimethoxybiphenyl-2-yl)acetic acid (3k): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (128 mg, 85% yield). $\mathbf{R_f}$ = 0.50 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.34 (m, 3 H), 7.31–7.28 (m, 2 H), 6.60 (s, 1 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.85 (s, 3 H), 3.54 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.02, 152.44, 152.00, 140.97, 140.82, 138.19, 129.09, 128.31, 127.31, 118.19, 108.78, 60.75, 60.58, 55.94, 33.32; **IR** (neat) ν 2939, 2838, 1707, 1484, 1403, 1250, 1247, 1199, 1110, 1048, 914, 842, 772 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{17}H_{19}O_5$ $[M+H]^+$ 303.1227, found 303.1224.



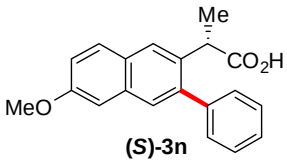
3l

2-(2-phenylnaphthalen-1-yl)acetic acid (3l): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (105 mg, 80% yield). $\mathbf{R_f}$ = 0.71 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.59 (t, *J* = 8.0 Hz, 1 H), 7.53 (t, *J* = 8.0 Hz, 1 H), 7.47–7.38 (m, 6 H), 4.07 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.67, 141.72, 140.80, 132.90, 132.38, 129.38, 128.75, 128.32, 128.17, 127.79, 127.33, 127.03, 126.69, 125.75, 123.94, 35.65; **IR** (neat) ν 3054, 2930, 1707, 1471, 1411, 1216, 1112, 1074, 1003, 820, 766, 743 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{18}H_{15}O_2$ $[M+H]^+$ 263.1067, found 263.1059.



(*rac*)-3m

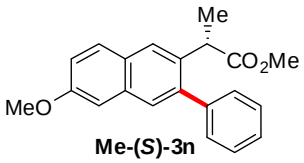
2-(5-chlorobiphenyl-2-yl)-3-methylbutanoic acid ((*rac*)-3m): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (113 mg, 78% yield). $\mathbf{R_f}$ = 0.81 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 1 H), 7.45–7.37 (m, 3 H), 7.35–7.32 (m, 3 H), 7.25 (d, *J* = 2.0 Hz, 1 H), 3.39 (d, *J* = 10.8 Hz, 1 H), 2.28–2.20 (m, 1 H), 0.92 (d, *J* = 6.8 Hz, 3 H), 0.52 (d, *J* = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.23, 144.81, 139.71, 134.25, 132.54, 129.99, 129.64, 128.77, 128.24, 127.89, 127.55, 53.62, 32.67, 21.35, 19.65; **IR** (neat) ν 2963. 2929, 1704, 1468, 1616, 1389, 1293, 1220, 1097, 771, 702 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{17}H_{18}ClO_2$ $[M+H]^+$ 289.0995, $[(M+2)+H]^+$ 291.0966, found 289.1004, 291.0976 $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.



(*S*)-3n

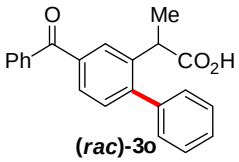
(*S*)-2-(6-methoxy-3-phenylnaphthalen-2-yl)propanoic acid ((*S*)-3n): The title compound was prepared on a 0.5 mmol scale and obtained as

an off-white solid (149 mg, 97% yield). **R_f** = 0.80 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.74 (d, J = 9.0 Hz, 1 H), 7.62 (s, 1 H), 7.47–7.40 (m, 5 H), 7.15 (dd, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1 H), 7.09 (d, J_1 = 2.4 Hz, 1 H), 4.00 (q, J = 6.8 Hz, 1 H), 3.91 (s, 3 H), 1.44 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.45, 157.99, 141.05, 140.69, 134.26, 133.29, 129.58, 129.13, 128.37, 128.18, 127.93, 127.23, 125.72, 119.18, 105.26, 55.32, 40.81, 19.23; **IR** (neat) ν 2950, 2935, 1702, 1633, 1605, 1491, 1464, 1397, 1233, 1210, 1032, 897 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{20}H_{19}O_3$ $[M+H]^+$ 307.1329, found 307.1331.



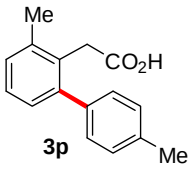
Me-(*S*)-3n

(*S*)-methyl 2-(6-methoxy-3-phenylnaphthalen-2-yl)propanoate (Me-(*S*)-3n): The title compound was synthesized from **(*S*)-3n**, which was prepared on a 0.5 mmol scale using the standard procedure and a modified work-up that avoids strongly basic conditions (to reduce the risk of racemization). After the reaction was stopped and cooled to 0 °C in an ice bath, a 2.0 N HCl solution (5 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was dissolved in a 1:1 mixture of CH_2Cl_2:MeOH (5 mL). Excess CH_2N_2[5,6] was added dropwise until bubbling was no longer observed. The solution was allowed to stir for 20 min, at which point several drops of HOAc were added to quench the residual CH_2N_2. *A note of caution: CH_2N_2 is explosive and toxic and should be handled in a well-maintained fume hood. The operator should have appropriate protection at all times.* Following removal of the solvent *in vacuo*, the purification was carried out using silica gel flash column chromatography with a 20:1 hexanes:EtOAc solvent system. The title compound was obtained as a colorless oil (152 mg, 95% yield over two steps). **R_f** = 0.73 (hexanes:EtOAc 4:1); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.74 (d, J = 8.9 Hz, 1 H), 7.61 (s, 1 H), 7.48–7.44 (m, 2 H), 7.41–7.39 (m, 3 H), 7.15 (d, J = 8.9 Hz, 1 H), 7.09 (s, 1 H), 3.97 (q, J = 7.0 Hz, 1 H), 3.91 (s, 3 H), 3.62 (s, 3 H), 1.43 (d, J = 7.0 Hz, 3 H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ 175.64, 157.93, 141.22, 140.67, 134.90, 133.18, 129.55, 129.14, 128.42, 128.14, 127.89, 127.18, 125.52, 119.11, 105.26, 55.32, 51.98, 41.01, 19.54; **IR** (neat) ν 2933, 2850, 1735, 1633, 1605, 1491, 1463, 1397, 1232, 1218, 1198, 1167, 1032, 897 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485, found 321.1481. **HPLC** >99:1 er (Chiralcel OD-H, 0.5 mL/min, 10% *i*-PrOH/hexanes) t_R = 12.23 min (major), t_R = 16.80 min (minor).



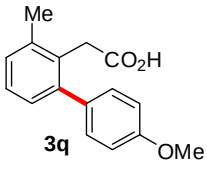
(*rac*)-3o

2-(4-benzoylbiphenyl-2-yl)propanoic acid ((*rac*)-3o): The title compound was prepared on a 0.2 mmol scale and obtained as a yellow oil (58 mg, 88% yield). **R_f** = 0.64 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.83 (d, J = 7.6 Hz, 2 H), 7.73 (d, J = 7.6 Hz, 1 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.50–7.42 (m, 5 H), 7.40–7.36 (m, 3 H), 4.00 (q, J = 7.2 Hz, 1 H), 1.42 (d, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.07, 179.85, 145.97, 139.99, 138.22, 137.41, 136.90, 132.53, 130.26, 130.11, 129.12, 129.07, 128.65, 128.45, 128.29, 127.79, 40.94, 18.95; **IR** (neat) ν 3060, 2980, 1738, 1705, 1659, 1598, 1446, 1286, 1249, 957, 912, 700 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{22}H_{19}O_3$ $[M+H]^+$ 331.1329, found 331.1324.



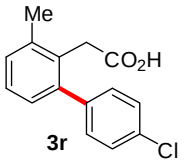
3p

2-(3,4'-dimethylbiphenyl-2-yl)acetic acid (3p): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (119 mg, 99% yield). $\mathbf{R_f}$ = 0.68 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23–7.14 (m, 6 H), 7.12 (d, *J* = 7.2 Hz, 1 H), 3.65 (s, 2 H), 2.40 (s, 3 H), 2.35 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.28, 143.28, 138.72, 137.61, 136.78, 130.06, 129.33, 128.96, 128.92, 128.00, 127.13, 36.02, 21.17, 20.20; **IR** (neat) ν 3023, 2975, 1706, 1467, 1412, 1231, 939, 822, 782 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{17}O_2$ $[M+H]^+$ 241.1223, found 241.1218.



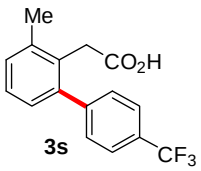
3q

2-(4'-methoxy-3-methylbiphenyl-2-yl)acetic acid (3q): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (118 mg, 92% yield). $\mathbf{R_f}$ = 0.55 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23–7.19 (m, 4 H), 7.11 (d, *J* = 6.8 Hz, 1 H), 6.93 (d, *J* = 8.4 Hz, 2 H), 3.85 (s, 3 H), 3.66 (s, 2 H), 2.35 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.44, 158.75, 142.96, 137.61, 134.03, 130.23, 130.18, 129.27, 128.13, 127.12, 113.63, 55.27, 36.06, 20.22; **IR** (neat) ν 3005, 2930, 1705, 1610, 1513, 1465, 1289, 1247, 1177, 1033, 837, 789 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{17}O_3$ $[M+H]^+$ 257.1172, found 257.1172.



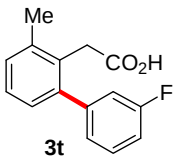
3r

2-(4'-chloro-3-methylbiphenyl-2-yl)acetic acid (3r): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (124 mg, 95% yield). $\mathbf{R_f}$ = 0.58 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2 H), 7.27–7.22 (m, 4 H), 7.10–7.07 (m, 1 H), 3.61 (s, 2 H), 2.35 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.52, 142.07, 140.06, 137.80, 133.30, 130.46, 129.89, 129.83, 128.43, 127.84, 127.29, 35.98, 20.19; **IR** (neat) ν 3027, 2923, 1704, 1493, 1464, 1412, 1233, 1090, 1016, 837, 785 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{14}ClO_2$ $[M+H]^+$ 261.0682, $[(M+2)+H]^+$ 263.0653, found 261.0677, 263.0646 $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.



3s

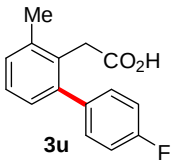
2-(3-methyl-4'-(trifluoromethyl)biphenyl-2-yl)acetic acid (3s): The title compound was prepared on a 0.2 mmol scale and obtained as a white solid (51 mg, 87% yield). $\mathbf{R_f}$ = 0.61 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.28–7.25 (m, 2 H), 7.10–7.08 (m, 1 H), 3.60 (s, 2 H), 2.36 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.42, 145.33, 141.89, 137.93, 130.14, 129.93, 129.50, 129.44 (q, J_{C-F} = 32.3 Hz), 127.71, 127.37, 125.20 (q, J_{C-F} = 3.7 Hz), 124.19 (q, J_{C-F} = 270.7 Hz); **IR** (neat) ν 3024, 2927, 1706, 1618, 1403, 1323, 1235, 1163, 1123, 1063, 849, 787 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{14}F_3O_2$ $[M+H]^+$ 295.0940, found 295.0941.



3t

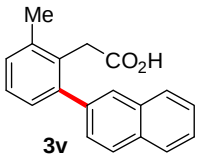
2-(3'-fluoro-3-methylbiphenyl-2-yl)acetic acid (3t): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (115 mg, 94% yield). $\mathbf{R_f}$ = 0.67 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.33

(m, 1 H), 7.25–7.22 (m, 2 H), 7.11–7.03 (m, 4 H), 3.63 (s, 2 H), 2.35 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.98, 162.45 (d, J_{C-F} = 245.4 Hz), 143.81 (d, J_{C-F} = 7.6 Hz), 141.99 (d, J_{C-F} = 1.8 Hz), 137.80, 129.93, 129.86, 129.72 (d, J_{C-F} = 8.4 Hz), 127.67, 127.20, 124.89 (d, J_{C-F} = 2.8 Hz), 116.17 (d, J_{C-F} = 21.3 Hz), 114.08 (d, J_{C-F} = 20.9 Hz), 36.12, 20.13; **IR** (neat) ν 3064, 2925, 1703, 1612, 1579, 1466, 1425, 1411, 1233, 1203, 889, 780 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{14}FO_2$ $[M+H]^+$ 245.0972, found 245.0980.



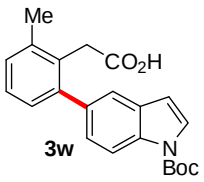
3u

2-(4'-fluoro-3-methylbiphenyl-2-yl)acetic acid (3u): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (120 mg, 98% yield). **R_f** = 0.60 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27–7.21 (m, 4 H), 7.10–7.06 (m, 3 H), 3.61 (s, 2 H), 2.35 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.05, 162.11 (d, J_{C-F} = 244.8 Hz), 142.26, 137.71, 137.55 (d, J_{C-F} = 3.3 Hz), 130.69 (d, J_{C-F} = 7.9 Hz), 130.06, 129.67, 128.00, 127.21, 115.12 (J_{C-F} = 21.2 Hz), 36.06, 20.20; **IR** (neat) ν 3023, 2920, 1702, 1604, 1509, 1465, 1413, 1221, 1158, 939, 909, 840, 785 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{14}FO_2$ $[M+H]^+$ 245.0972, found 245.0975.



3v

2-(2-methyl-6-(naphthalen-2-yl)phenyl)acetic acid (3v): The title compound was prepared on a 0.5 mmol scale and obtained as an off-white solid (120 mg, 87% yield). **R_f** = 0.68 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 3 H), 7.76 (s, 1 H), 7.53–7.49 (m, 2 H), 7.74 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz), 7.31–7.21 (m, 4 H), 3.68 (s, 2 H), 2.39 (s, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.80, 143.22, 139.17, 137.74, 133.15, 132.36, 130.16, 129.61, 128.02, 127.86, 127.81, 127.68, 127.43, 127.21, 126.32, 126.02, 26.15, 2 0.21; **IR** (neat) ν 3055, 2956, 1704, 1410, 1233, 935, 907, 860, 823, 785, 744 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{19}H_{17}O_2$ $[M+H]^+$ 277.1223, found 277.1231.



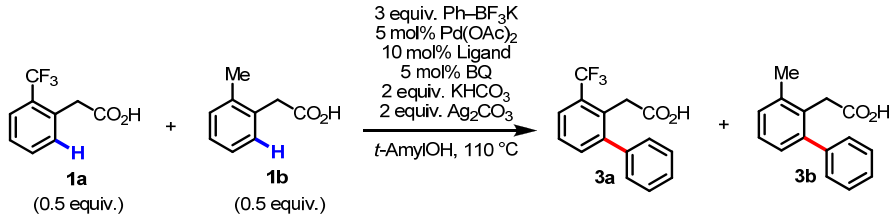
3w

2-(2-(1-(*tert*-butoxycarbonyl)-1*H*-indol-5-yl)-6-methylphenyl)acetic acid (3w): The title compound was prepared on a 0.2 mmol scale and obtained as a yellow oil (27 mg, 37% yield). **R_f** = 0.69 (hexanes:EtOAc 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (d, J = 7.2 Hz, 1 H), 7.64 (d, J = 3.6 Hz, 1 H), 7.47 (s, 1 H), 7.27–7.16 (m, 4 H), 6.57 (d, J = 3.6 Hz, 1 H), 3.67 (s, 2 H), 2.34 (s, 3 H), 1.69 (s, 9 H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 173.03, 150.39, 144.36, 138.73, 137.64, 135.19, 132.59, 131.58, 130.00, 128.81, 127.52, 127.47, 126.28, 122.22, 115.48, 108.22, 84.60, 36.62, 28.30, 20.32; **IR** (neat) ν 2977, 2927, 1734, 1707, 1457, 1369, 1341, 1239, 1159, 1135, 1084, 1023 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{22}H_{24}NO_4$ $[M+H]^+$ 366.1700, found 366.1704.

Competition Experiments:

Procedure for intermolecular competition experiments between compounds 1a and 1b: A 25 mL sealed tube equipped with a magnetic stir bar was charged with **1a** (51.1 mg, 0.25 mmol), **1b** (37.6 mg, 0.25 mmol), $PhBF_3K$ (**2a**) (276.0mg, 1.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), BQ (2.7 mg, 0.025 mmol), ligand (0.05 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ag_2CO_3 (275.8 mg, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tube was capped and immediately transferred to an oil bath at 110 °C. After being allowed to stir vigorously for the appropriate time, the reaction vessel was removed from the oil bath and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were added. A small aliquot of the organic phase was taken, concentrated *in vacuo*, and analyzed by ^{1}H NMR. The conversion was determined by integration of the benzylic methylene proton signals, which appear as singlets (approximately 3.87 ppm for **1a**, 3.79 ppm for **3a**, 3.67 ppm for **1b**, and 3.63 ppm for **3b**). The results are shown in Tables 8 and S11.

Table S11: Competition experiments between **1a** and **1b**.[a]



Entry[a]	Ligand	Time (min)	% Conv. **3a**	% Conv. **3b**	k_{3a} ([M]/min)	k_{3b} ([M]/min)	k_{3a} / k_{3b}
1	—	60	8.6	17.8	2.9×10^{-4}	5.9×10^{-4}	0.48
2	Ac-Ile-OH	20	35.6	16.4	7.1×10^{-3}	3.2×10^{-3}	2.17

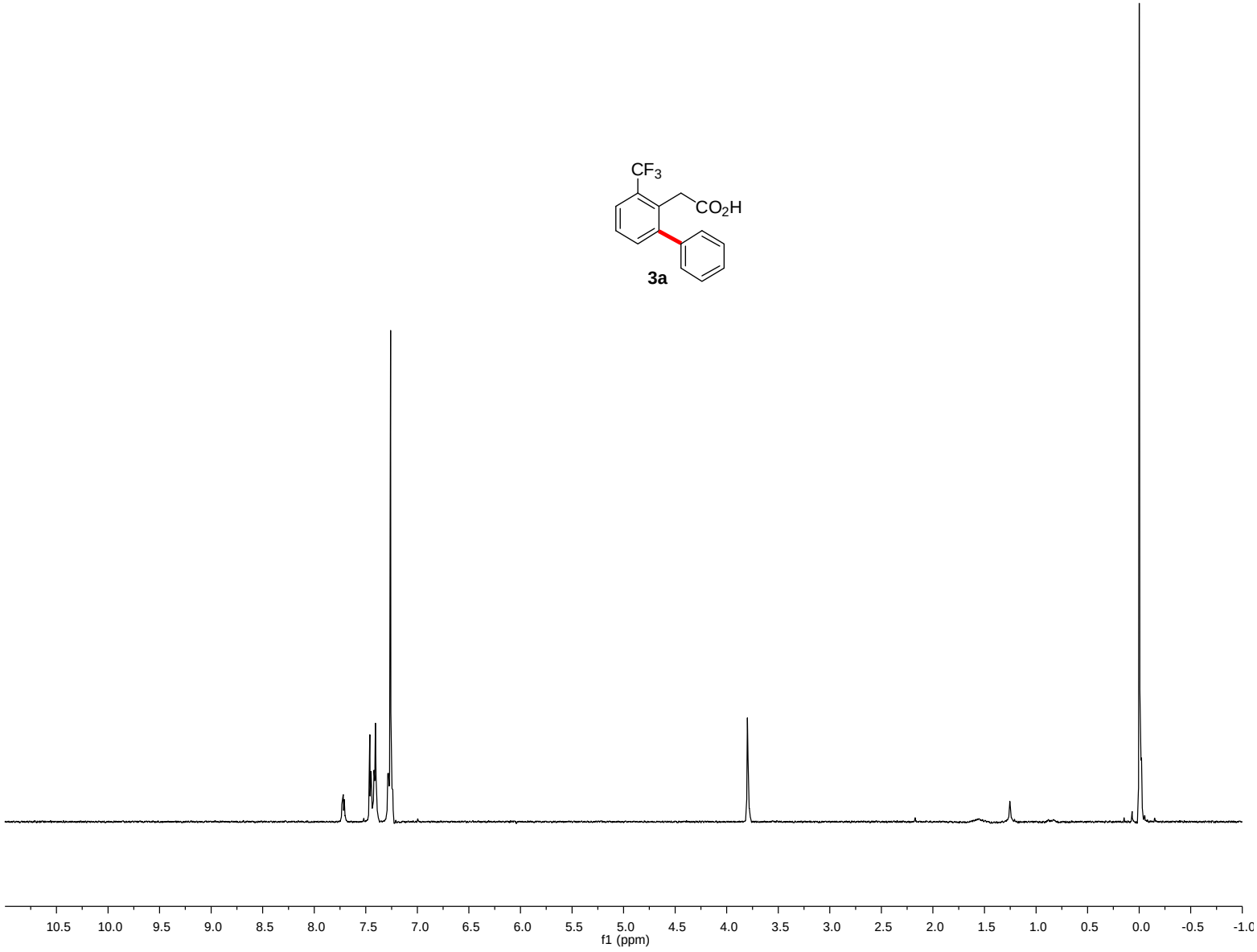
[a] The conversion was determined by ^{1}H NMR of the crude reaction mixture.

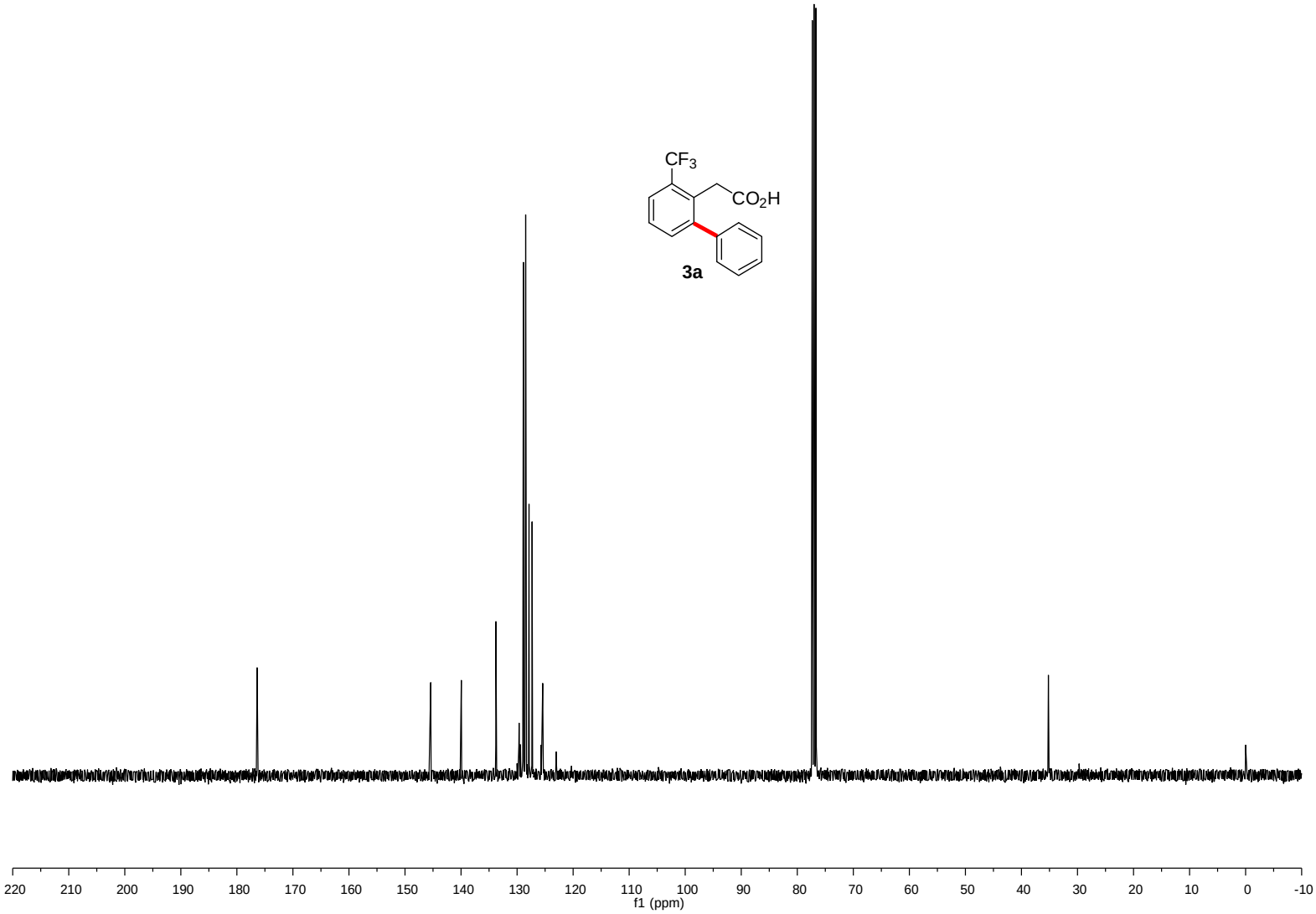
Procedure for initial rate studies for single-component reactions of 1a and 1b: The procedure for reactions run with and without Ac-Ile-OH is described on page S-7. The reactions were repeated three times, and determination of the initial rate was performed using linear regression. The overall results are shown in Table 9.

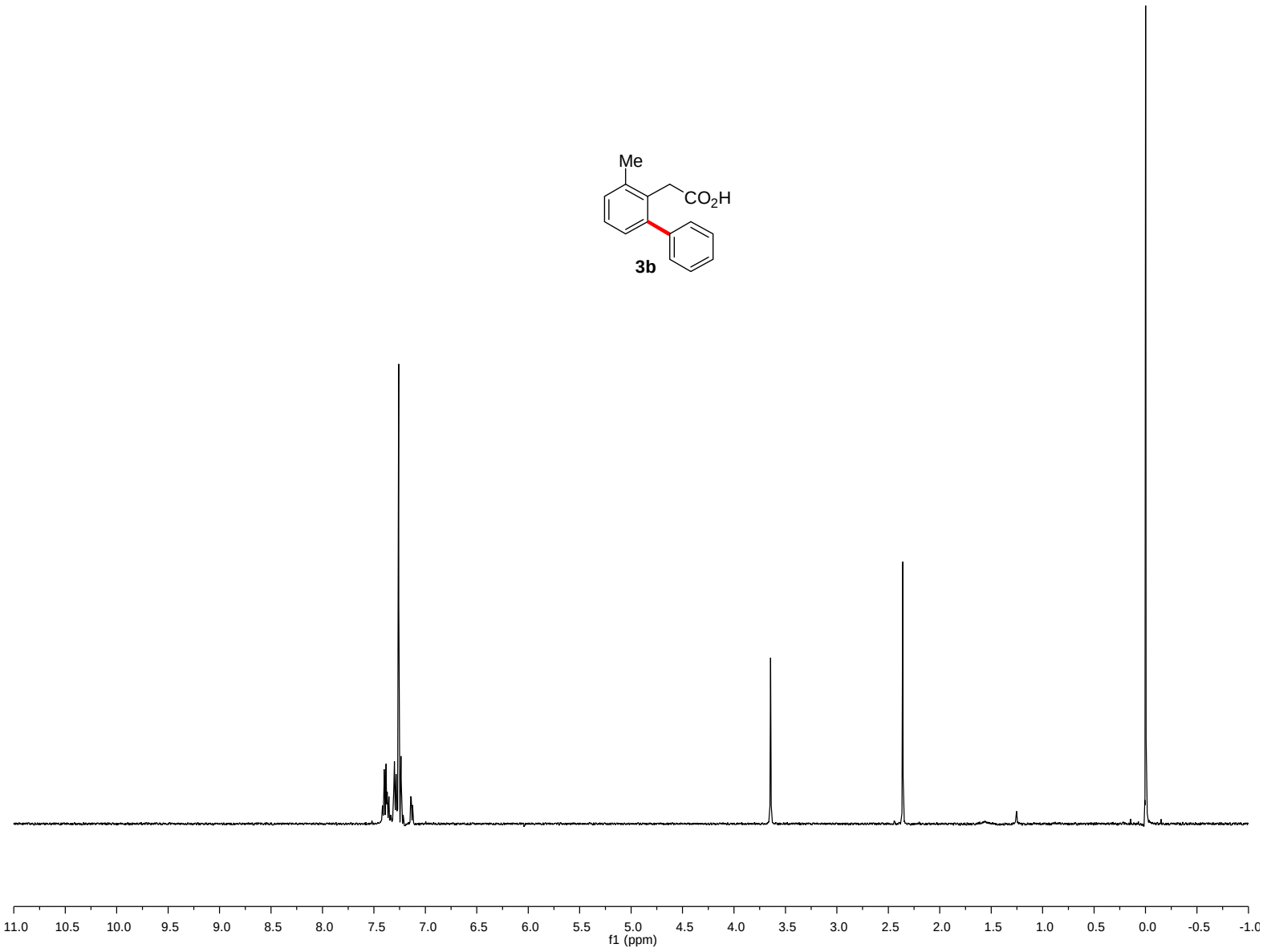
References:

(1) J. W. Sims, E. W. Schmidt, *J. Am. Chem. Soc.* **2008**, *130*, 11149–11155.
(2) K. M. Engle, D.-H. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 14137–14151.
(3) D.-H. Wang, T.-S. Mei, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 17676–17677.
(4) E. P. Gillis, M. D. Burke, *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.
(5) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377–5378.
(6) Please see the *Aldrich Technical Bulletin* AL-180, "Diazald® and Diazomethane Generators," for a detailed experimental procedure.

NMR Spectra:


CF3
CO2H
3a
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


CF3
CO2H
3a
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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CO2H
3b
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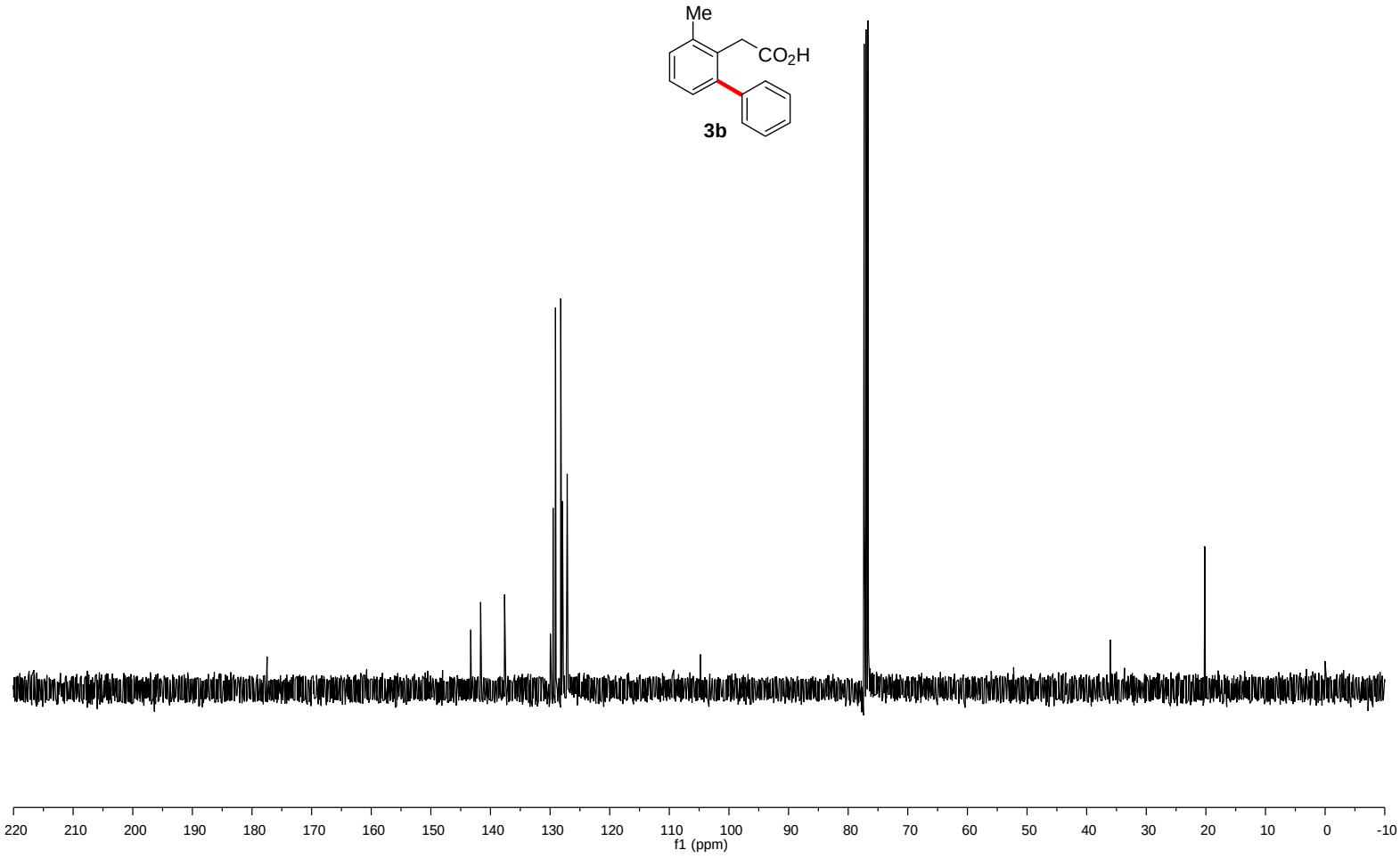
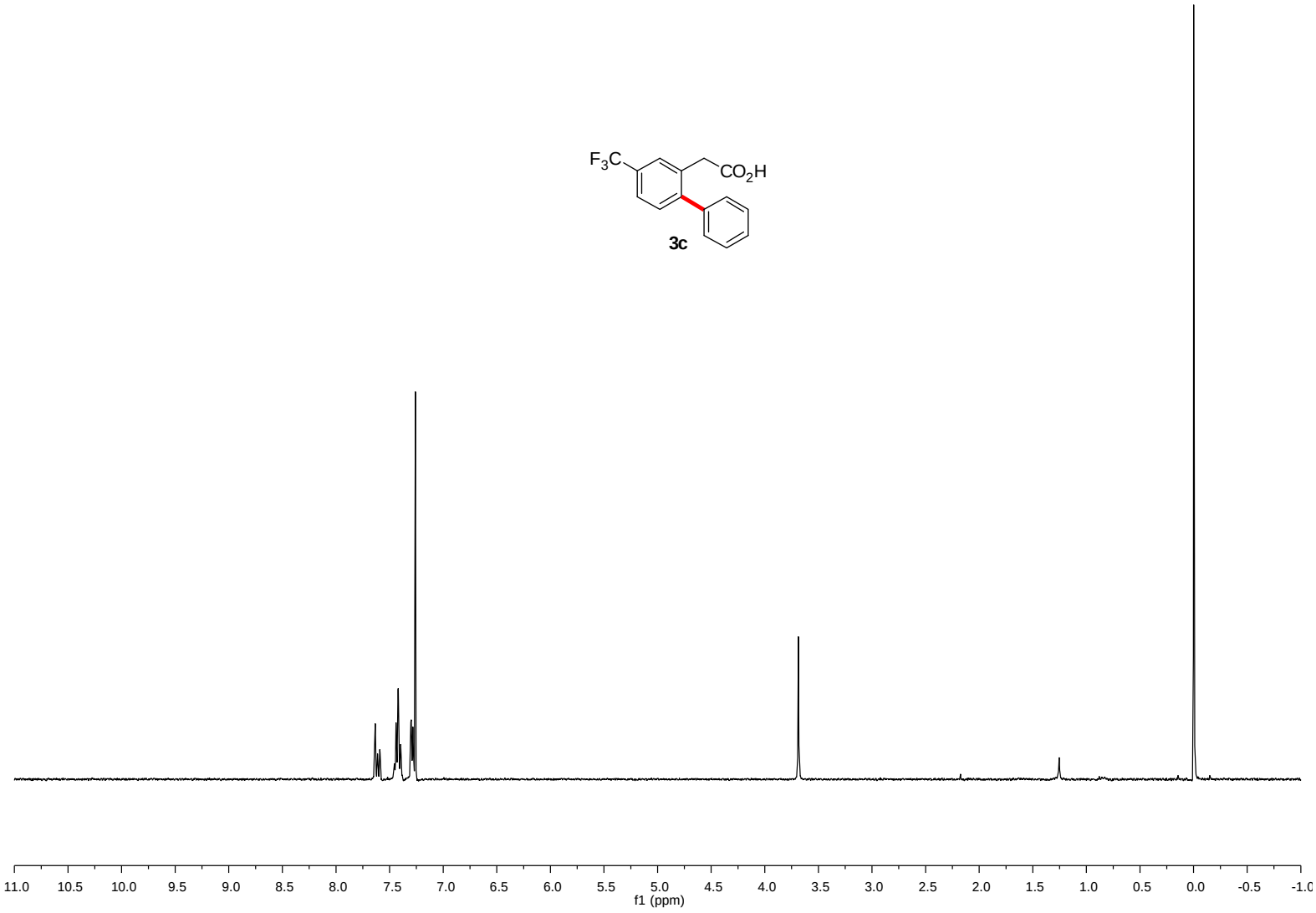
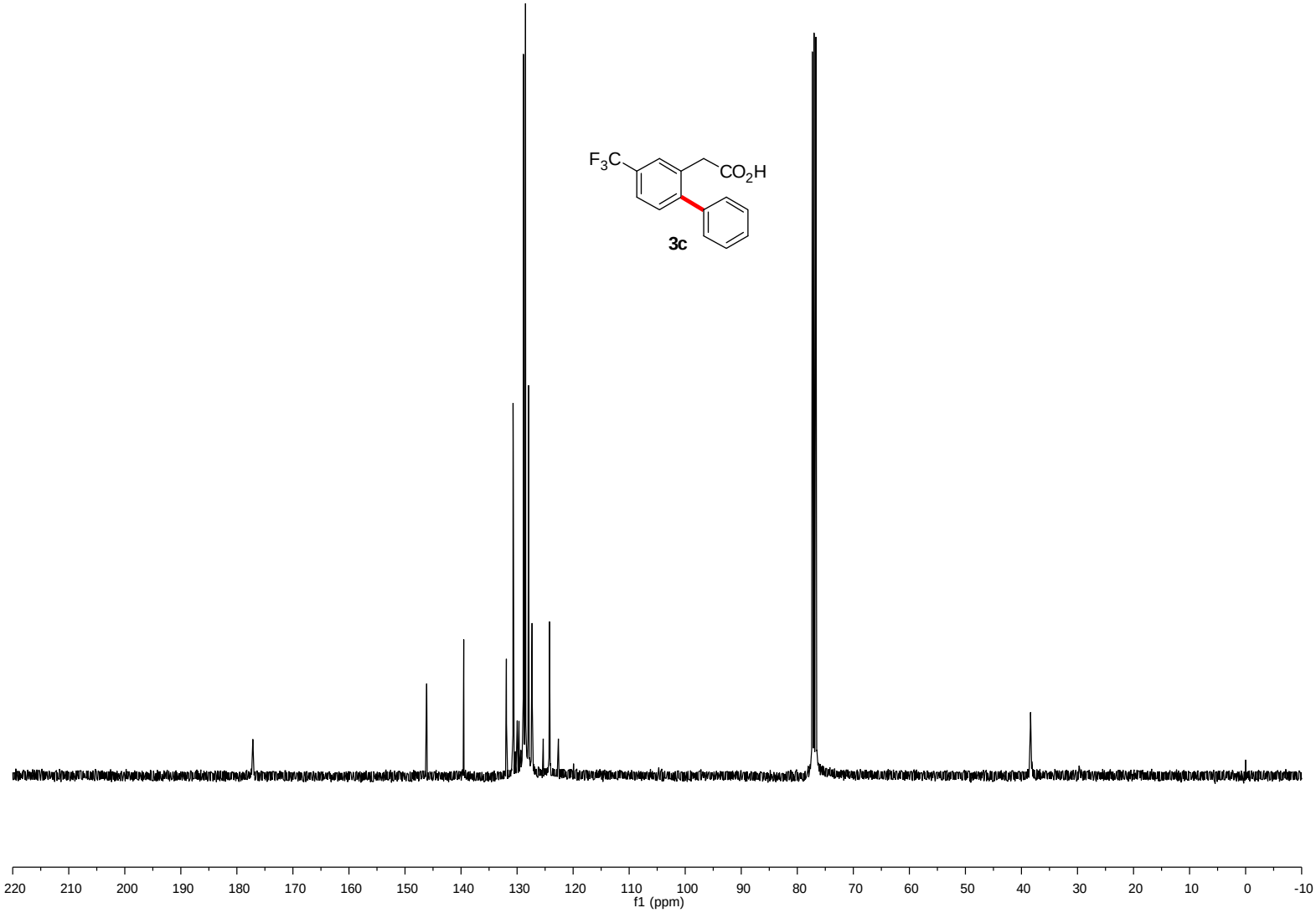
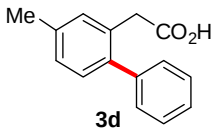
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

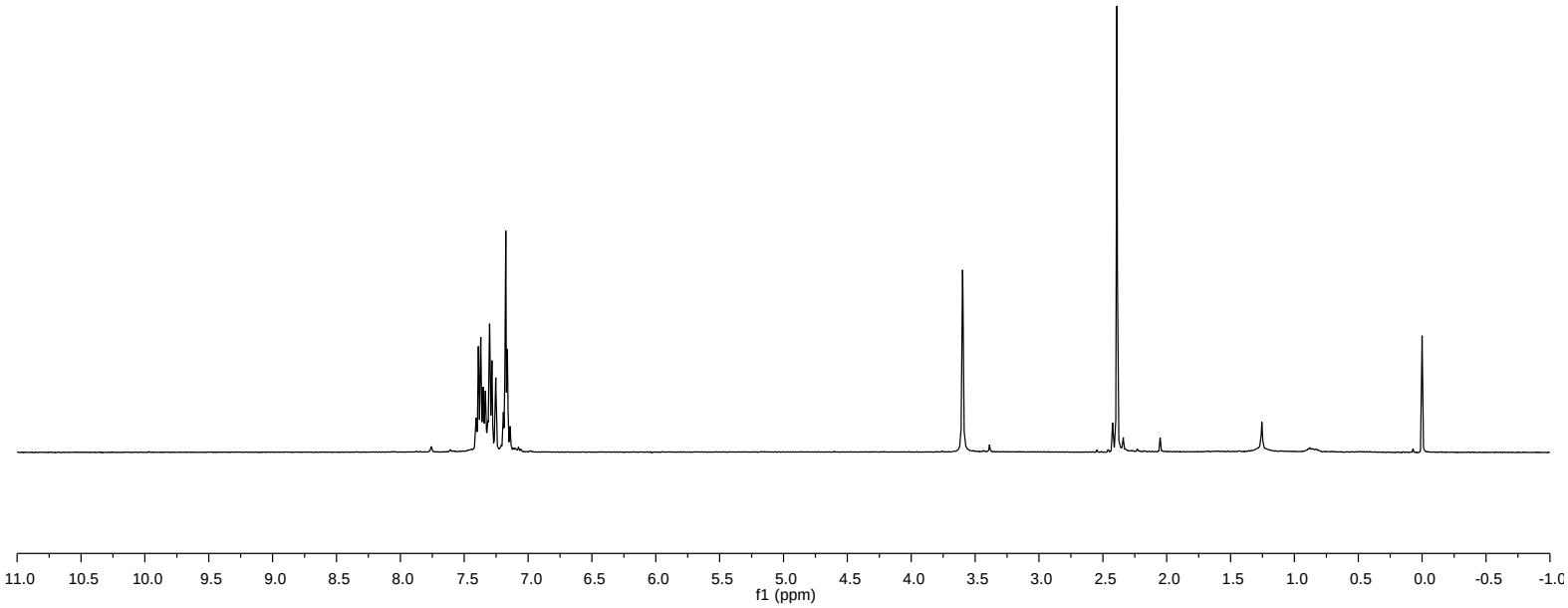

Me
CO2H
3b
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


F3C
CO2H
3c
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
-0.5
f1 (ppm)


F3C
CO2H
3c
220
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)


Me
CO2H

3d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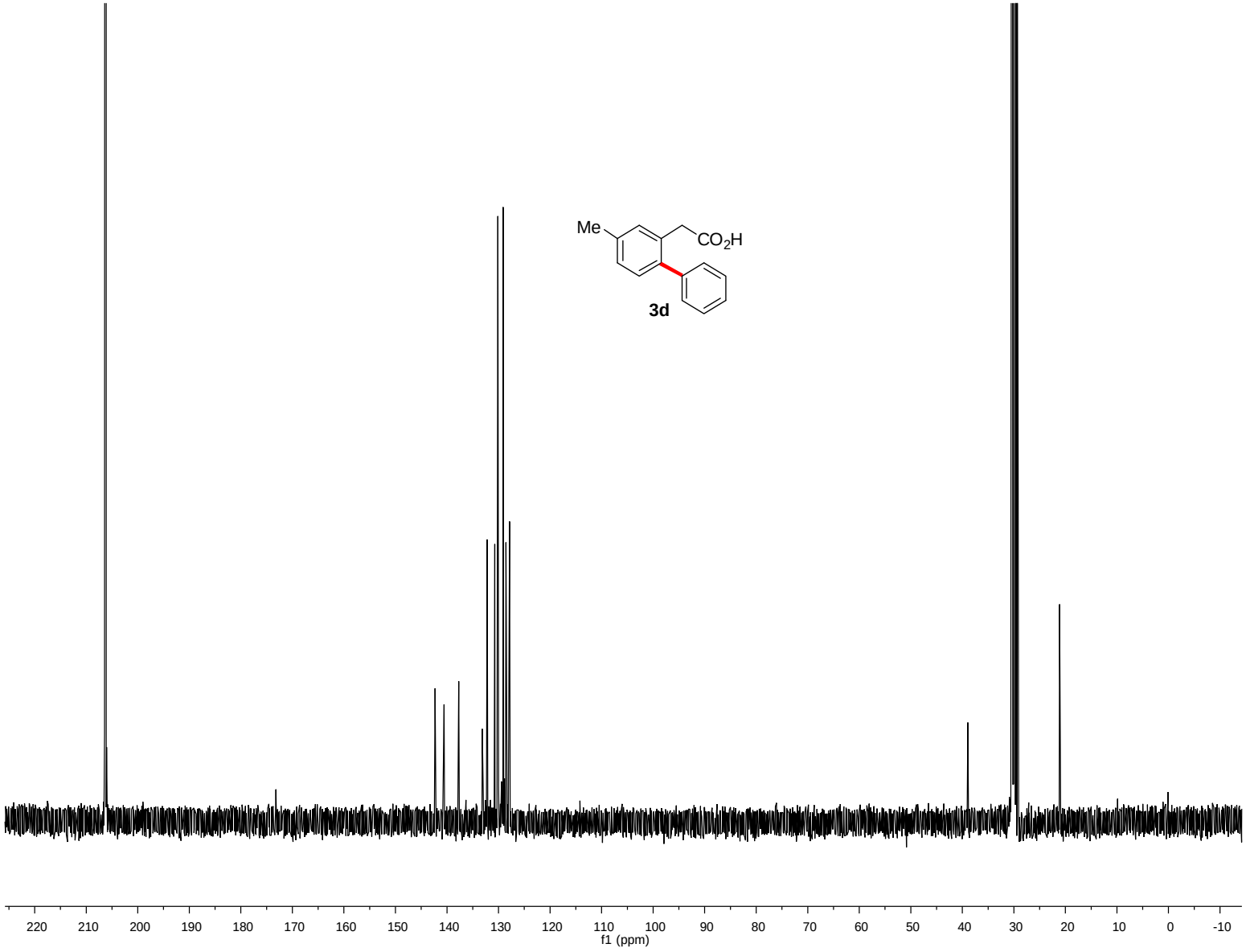
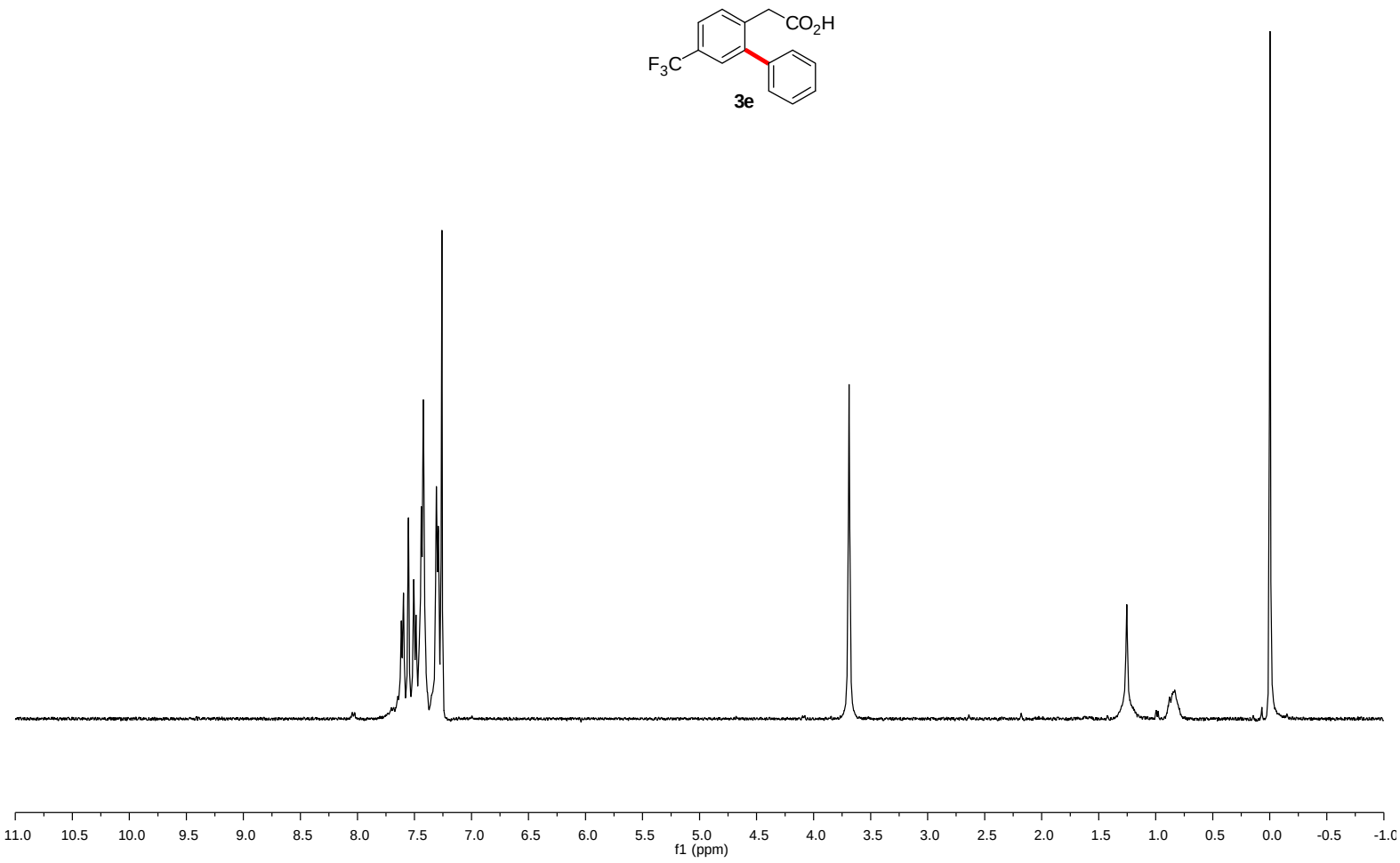
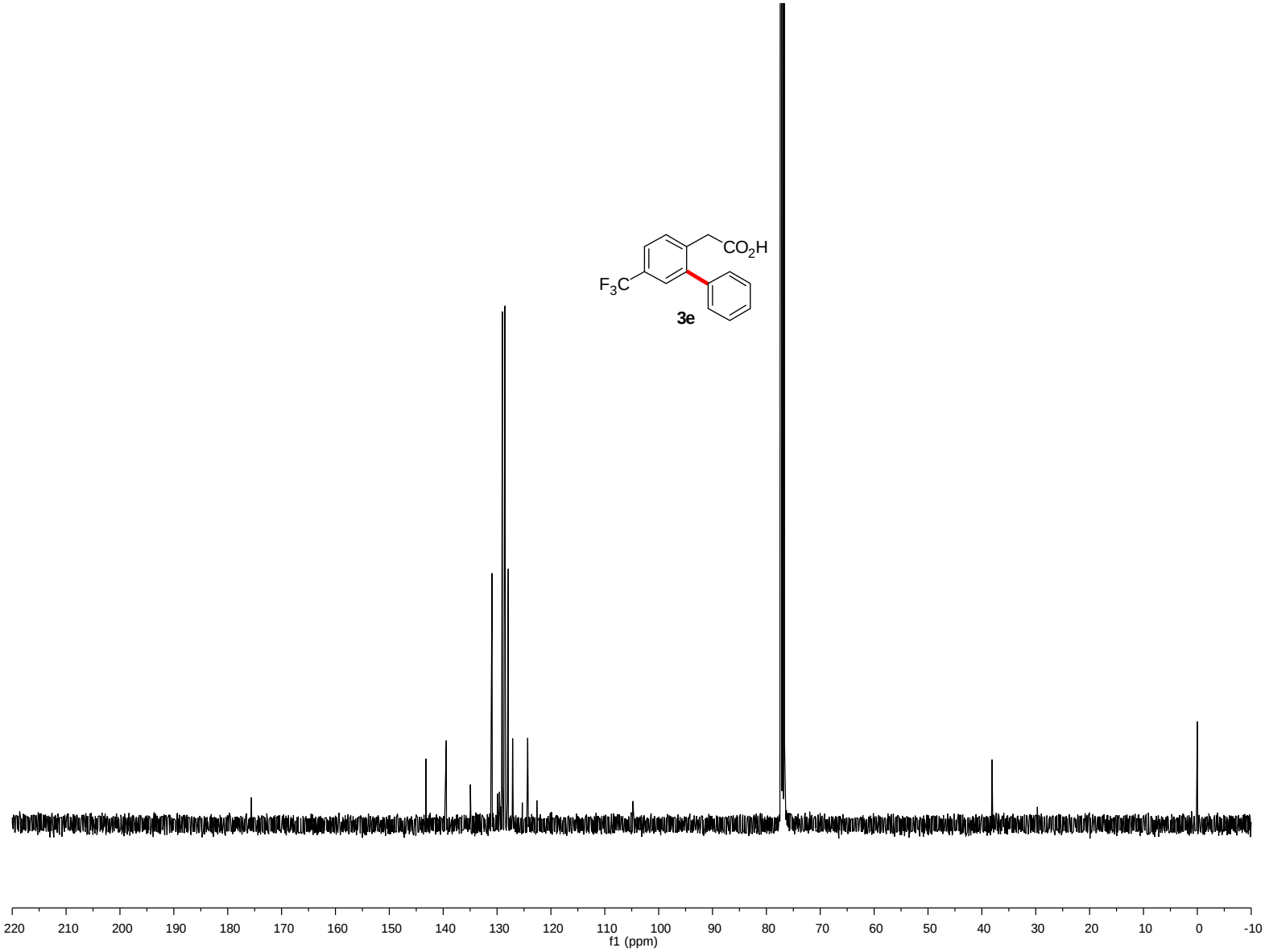
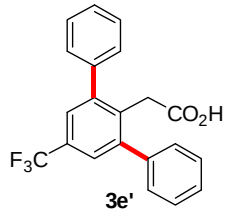
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

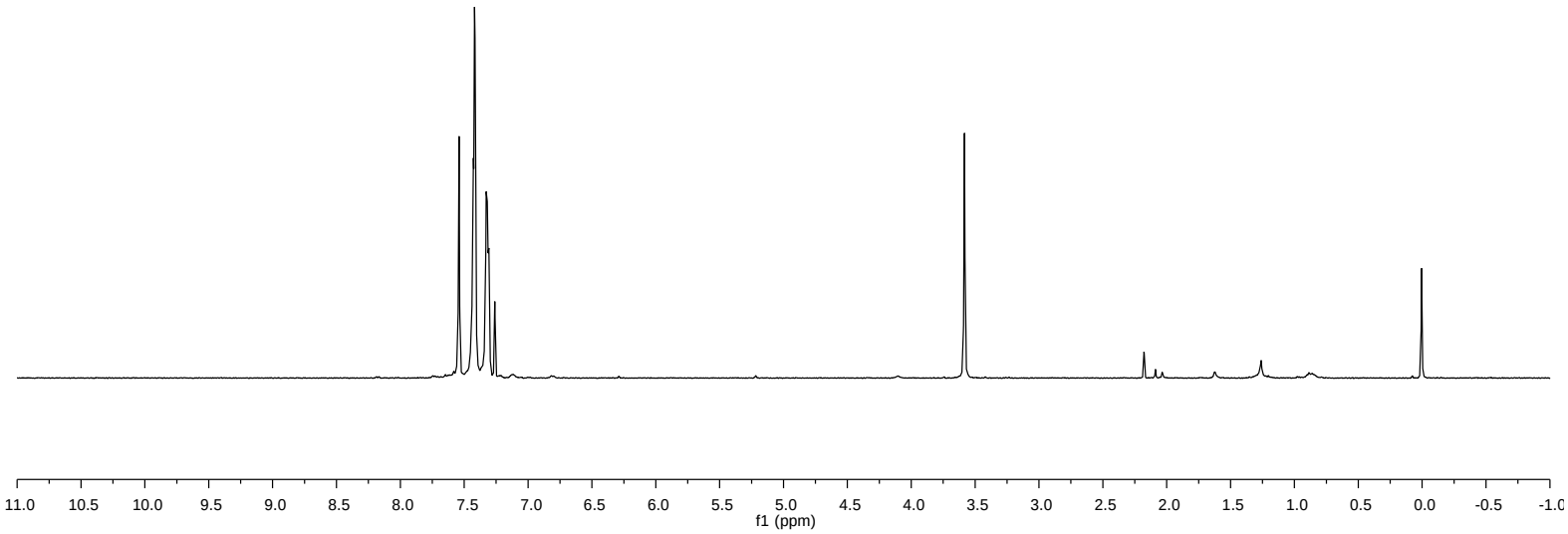

Me
CO2H
3d
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


CO2H
F3C
3e
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
-0.5
f1 (ppm)


CO2H
F3C
3e
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CO_2H
F_3C

3e'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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
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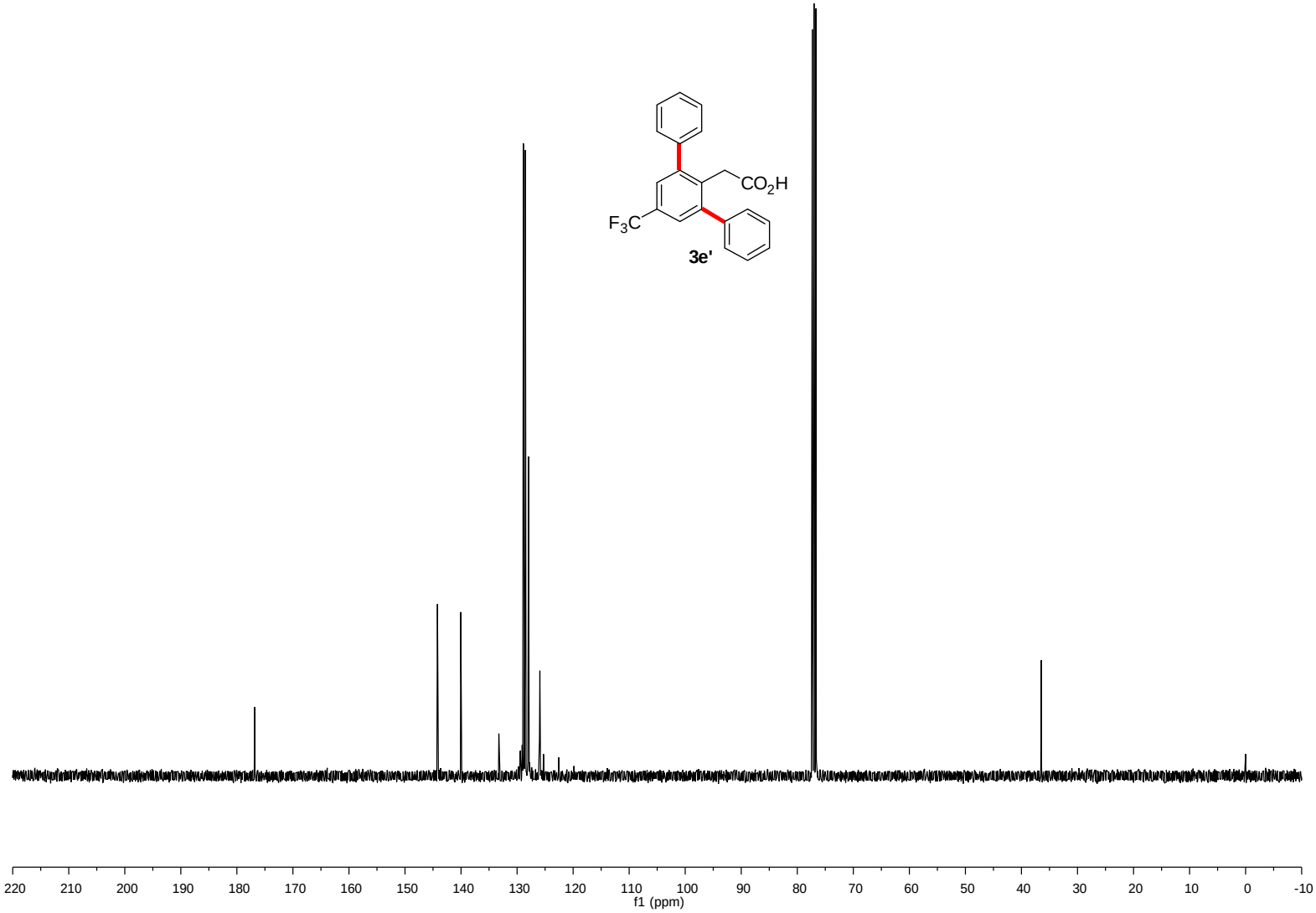
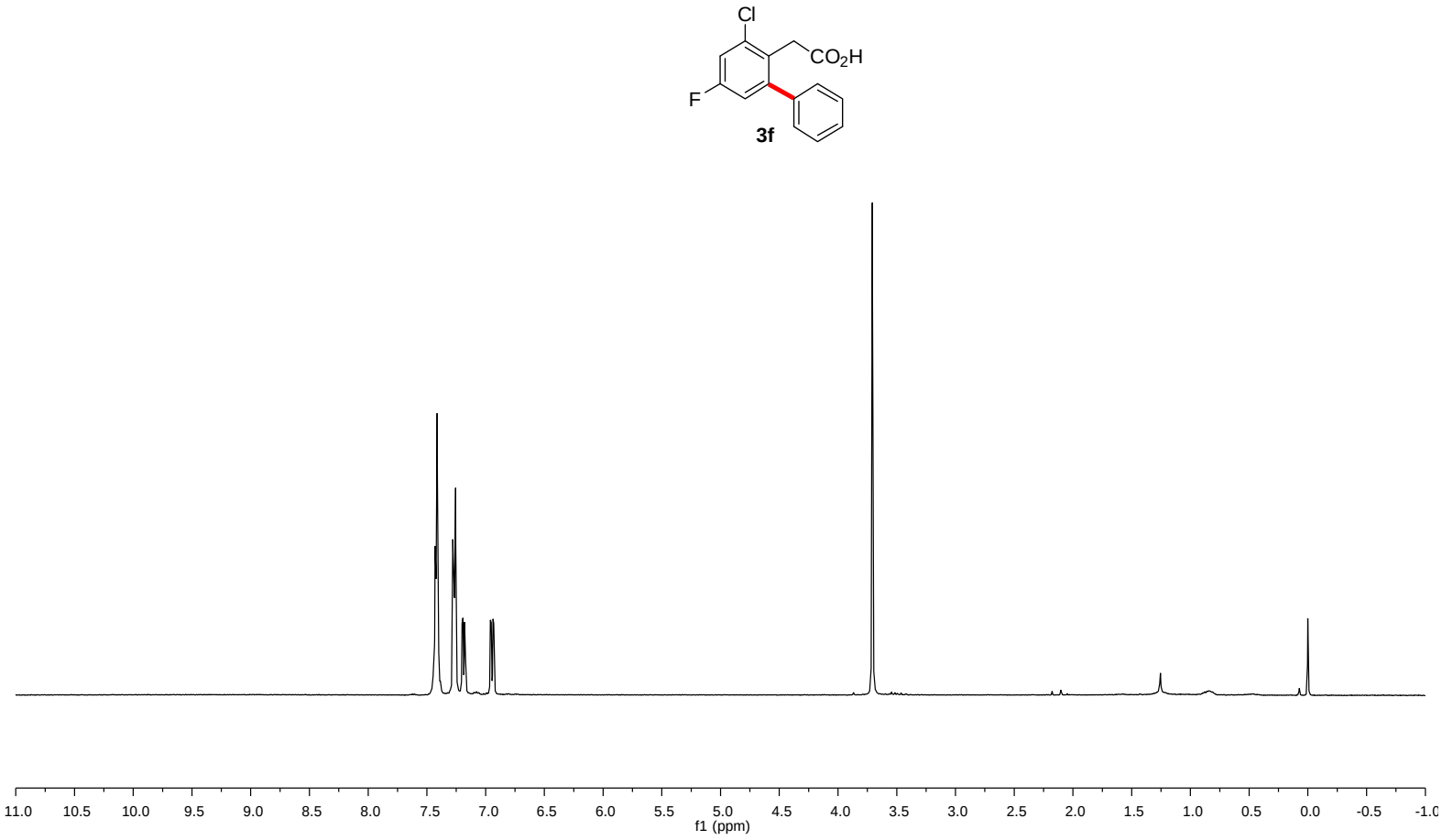
0.0
-0.5
f1 (ppm)


CO2H
F3C
3e'
220
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)


Cl
CO2H
F
3f
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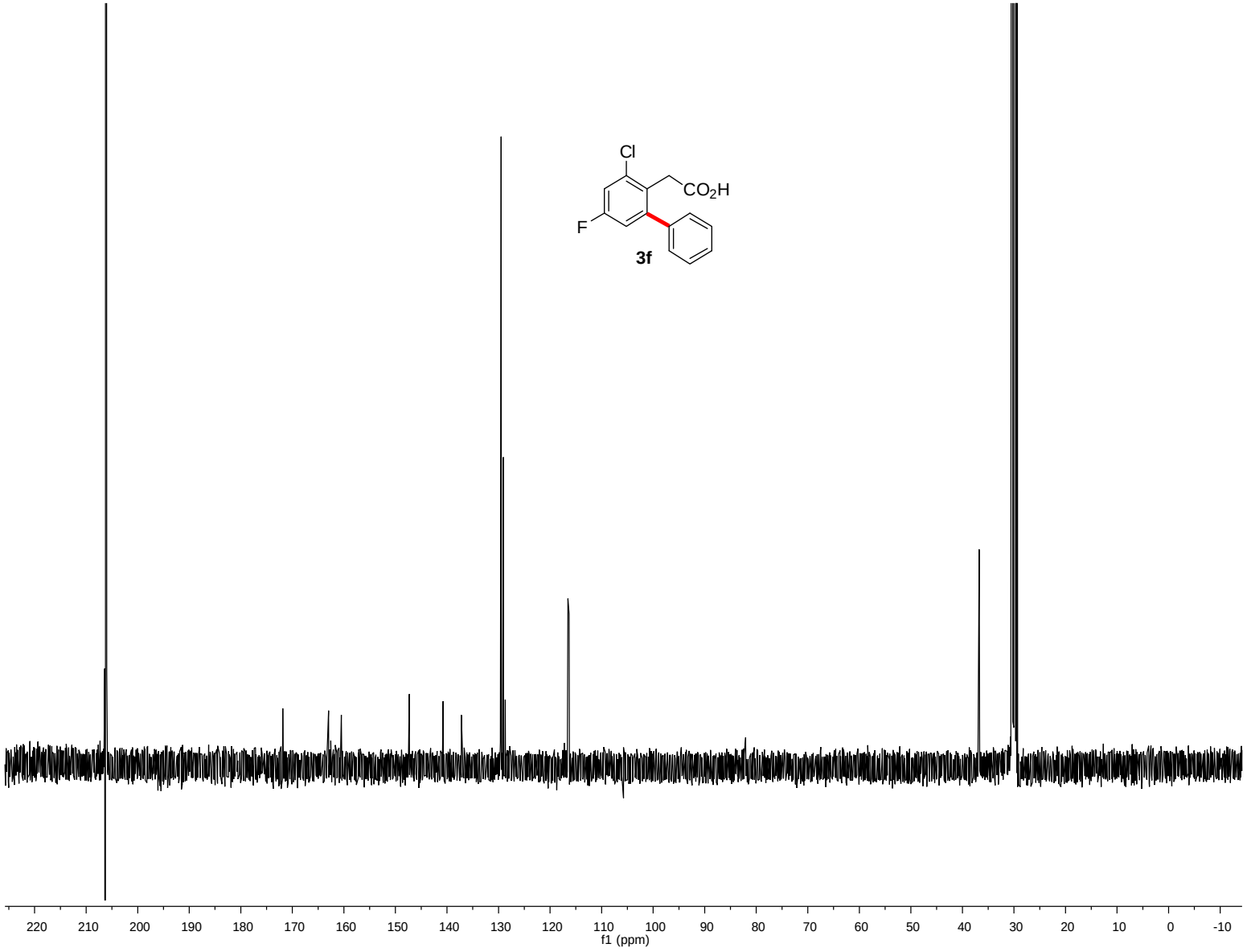
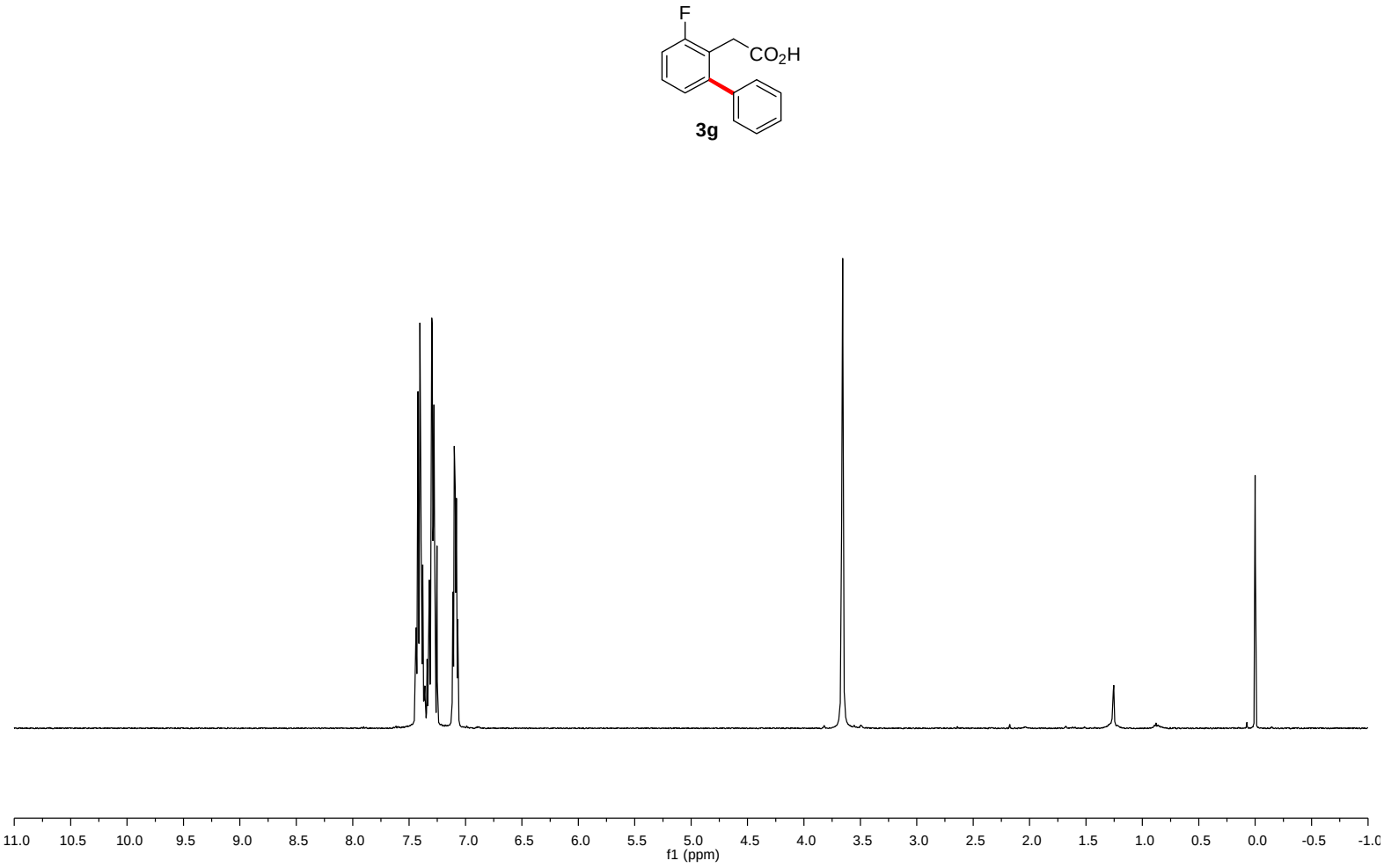
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Cl
CO2H
F
3f
220
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)


F
CO2H
3g
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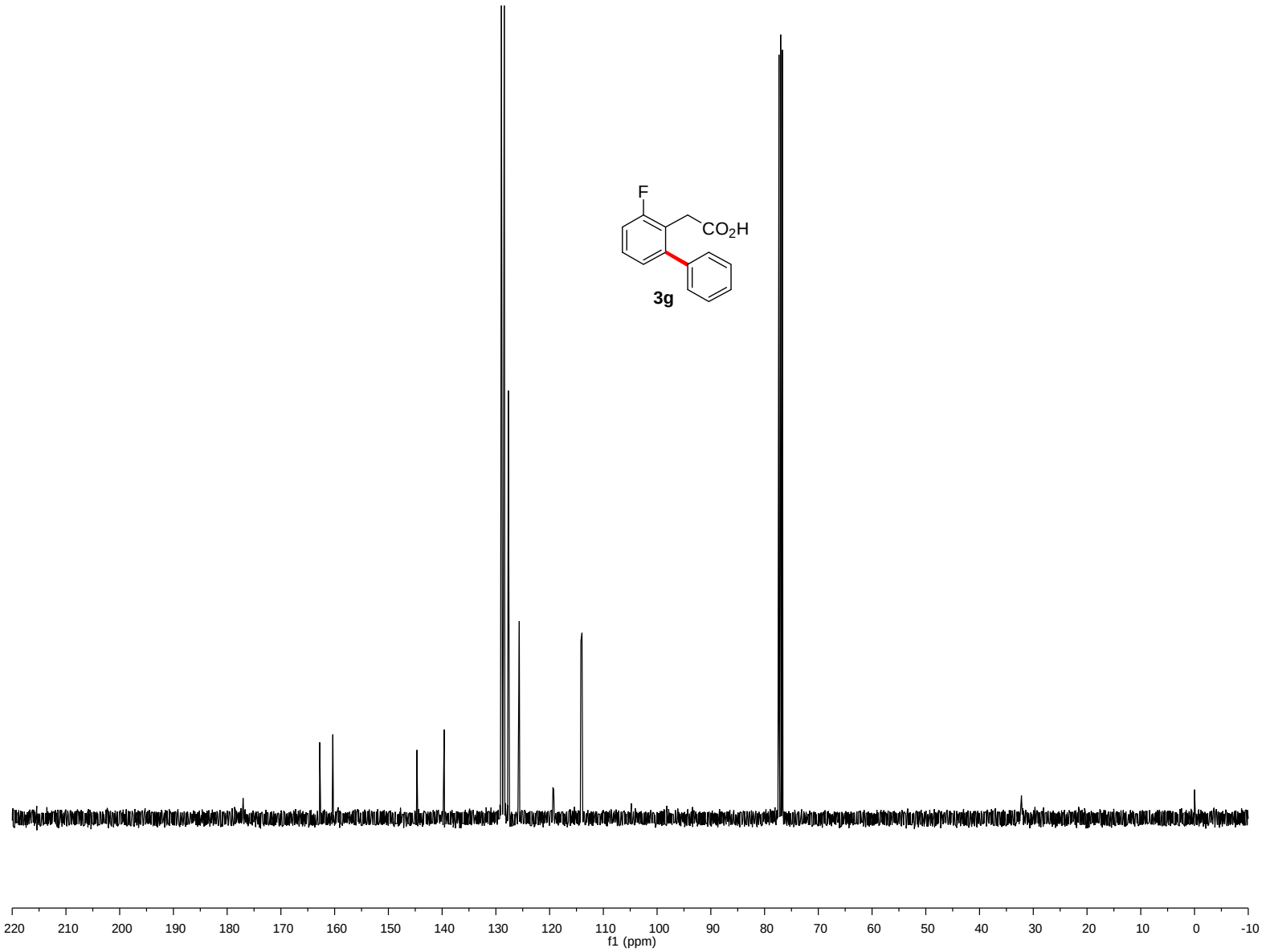
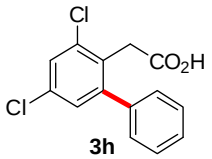
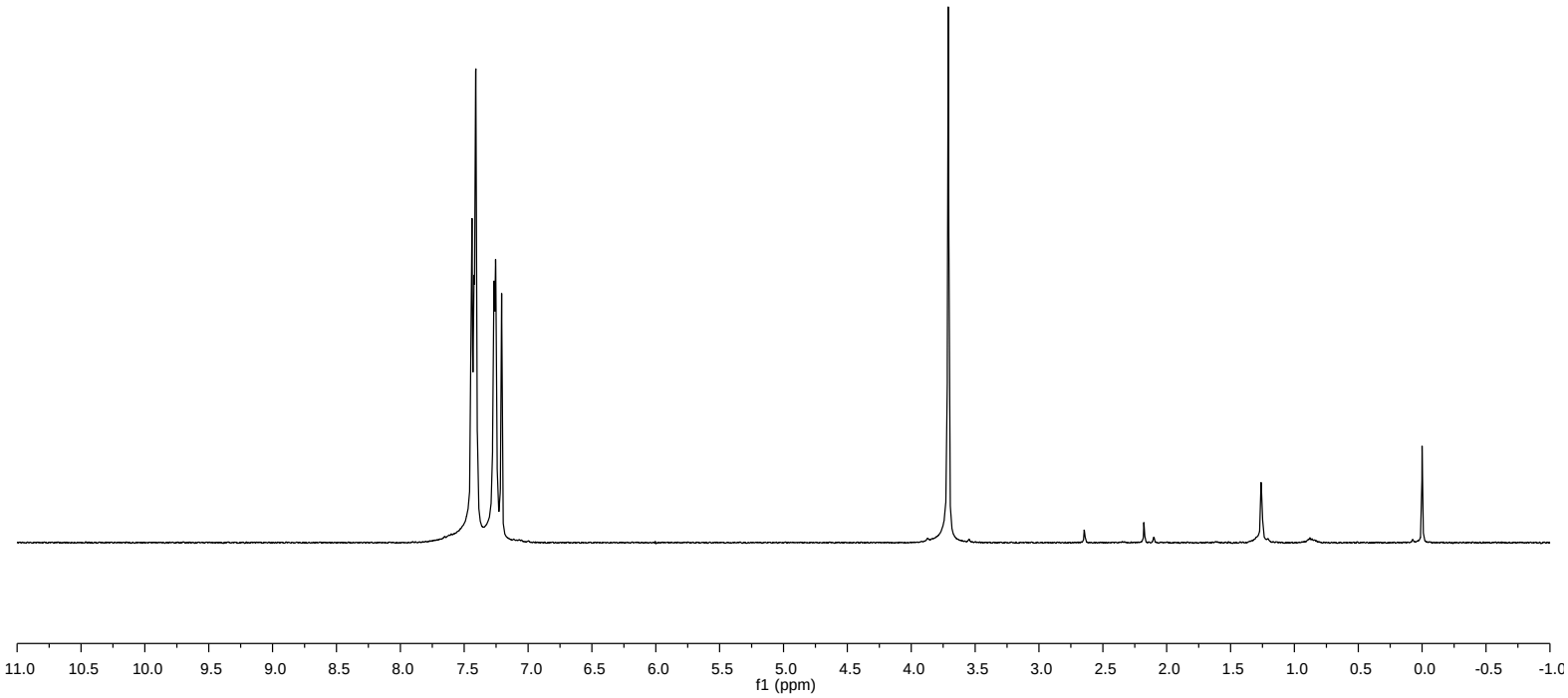
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


F
CO2H
3g
220
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)


Cl
CO2H
Cl

3h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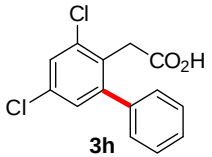
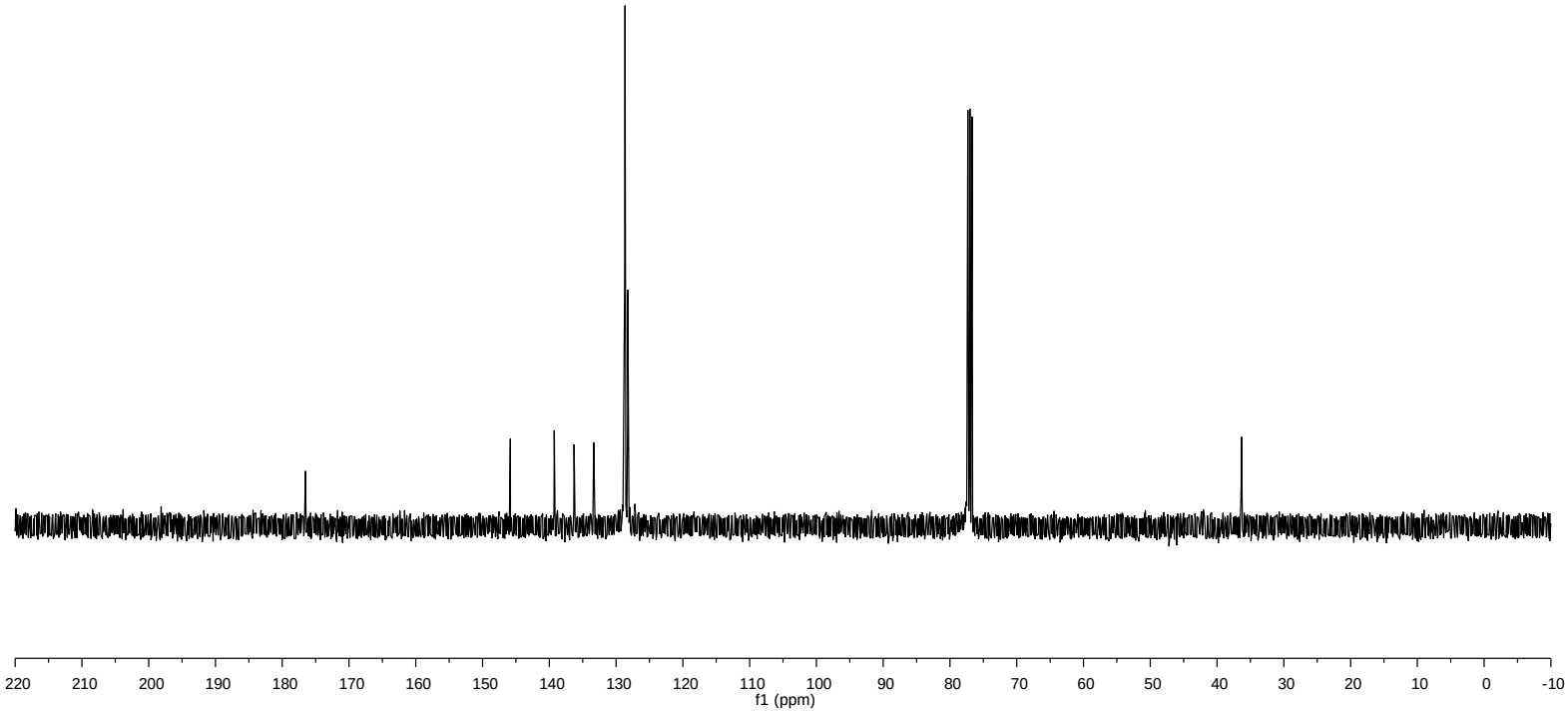
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Cl
CO2H
Cl

3h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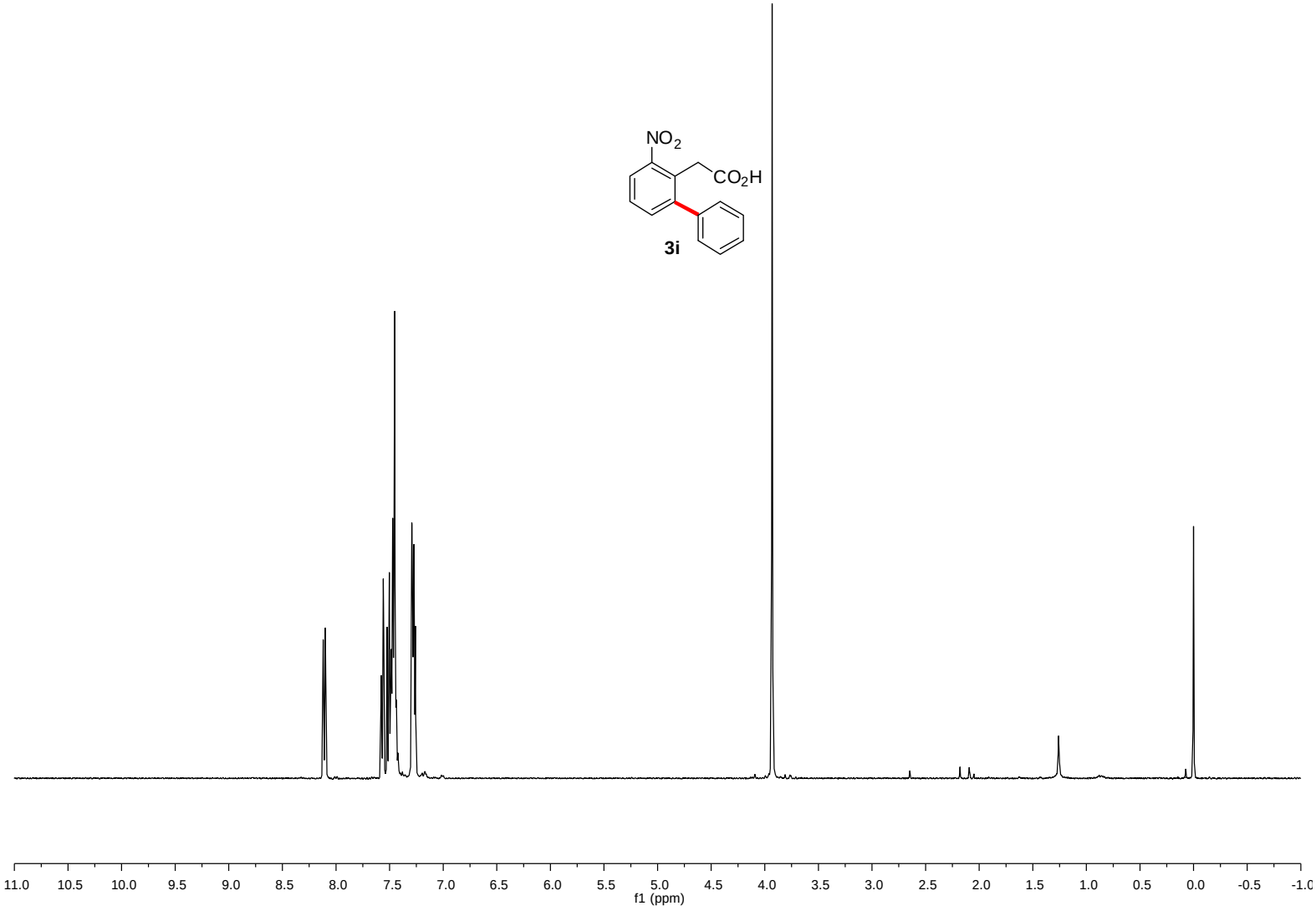
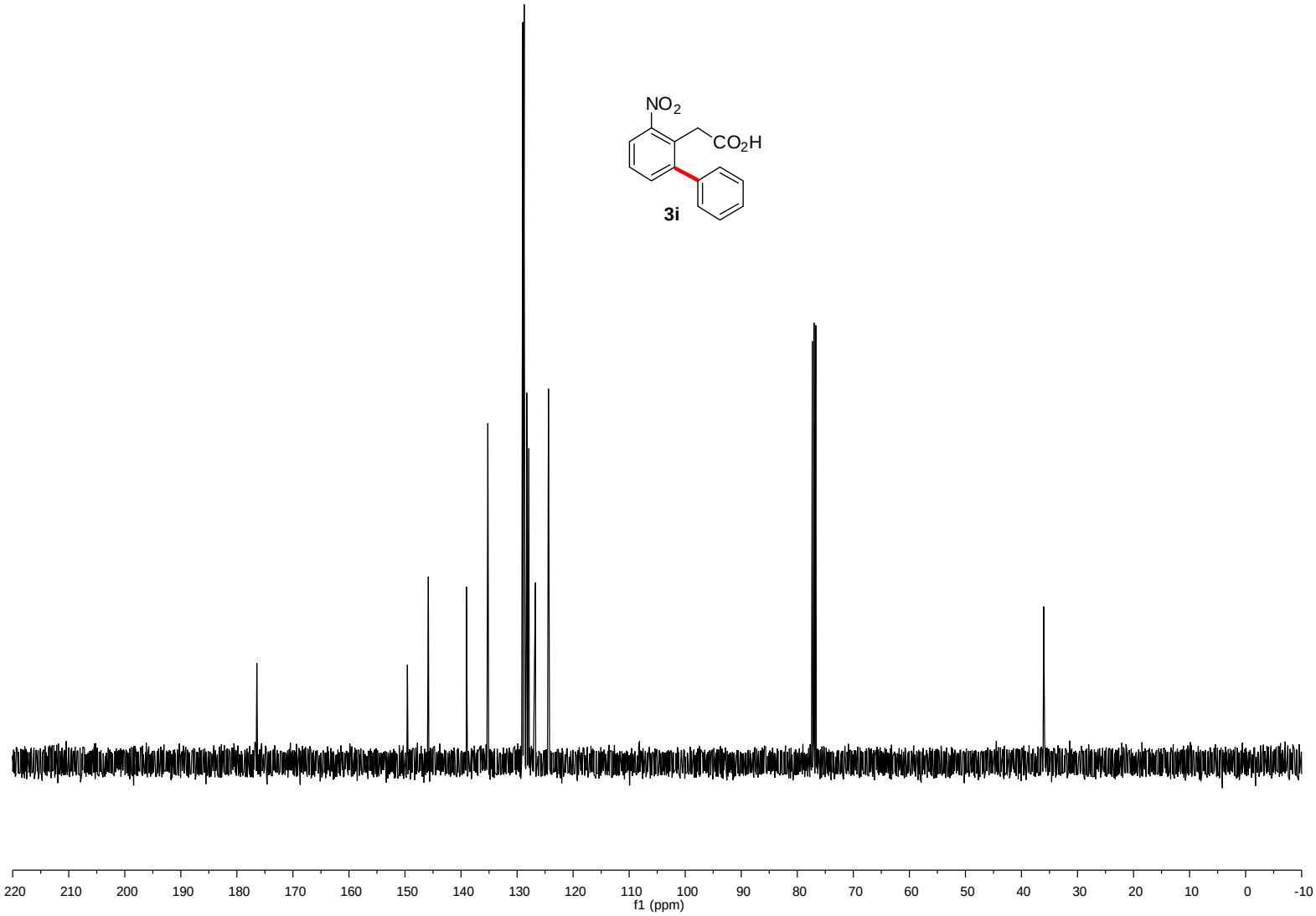
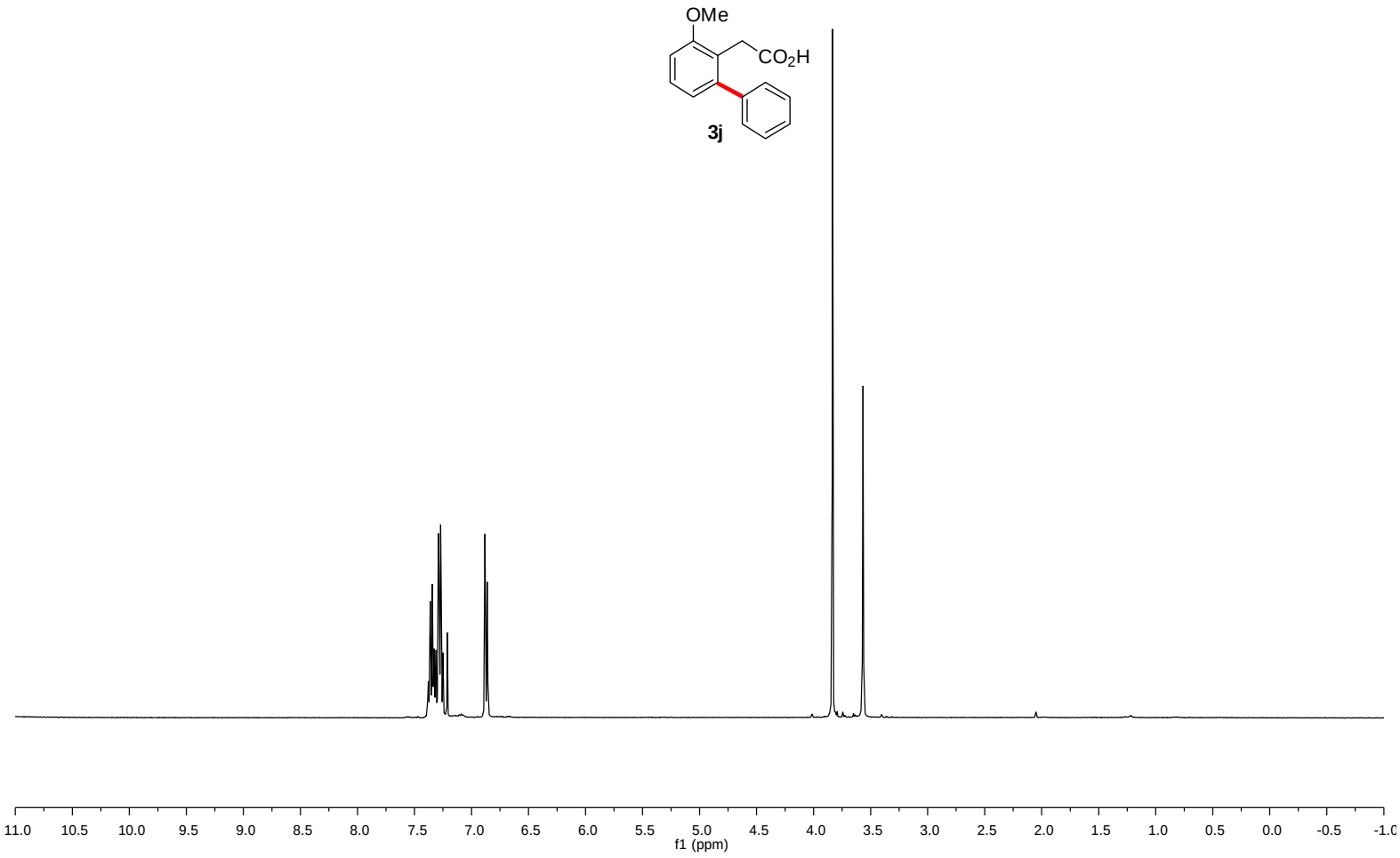
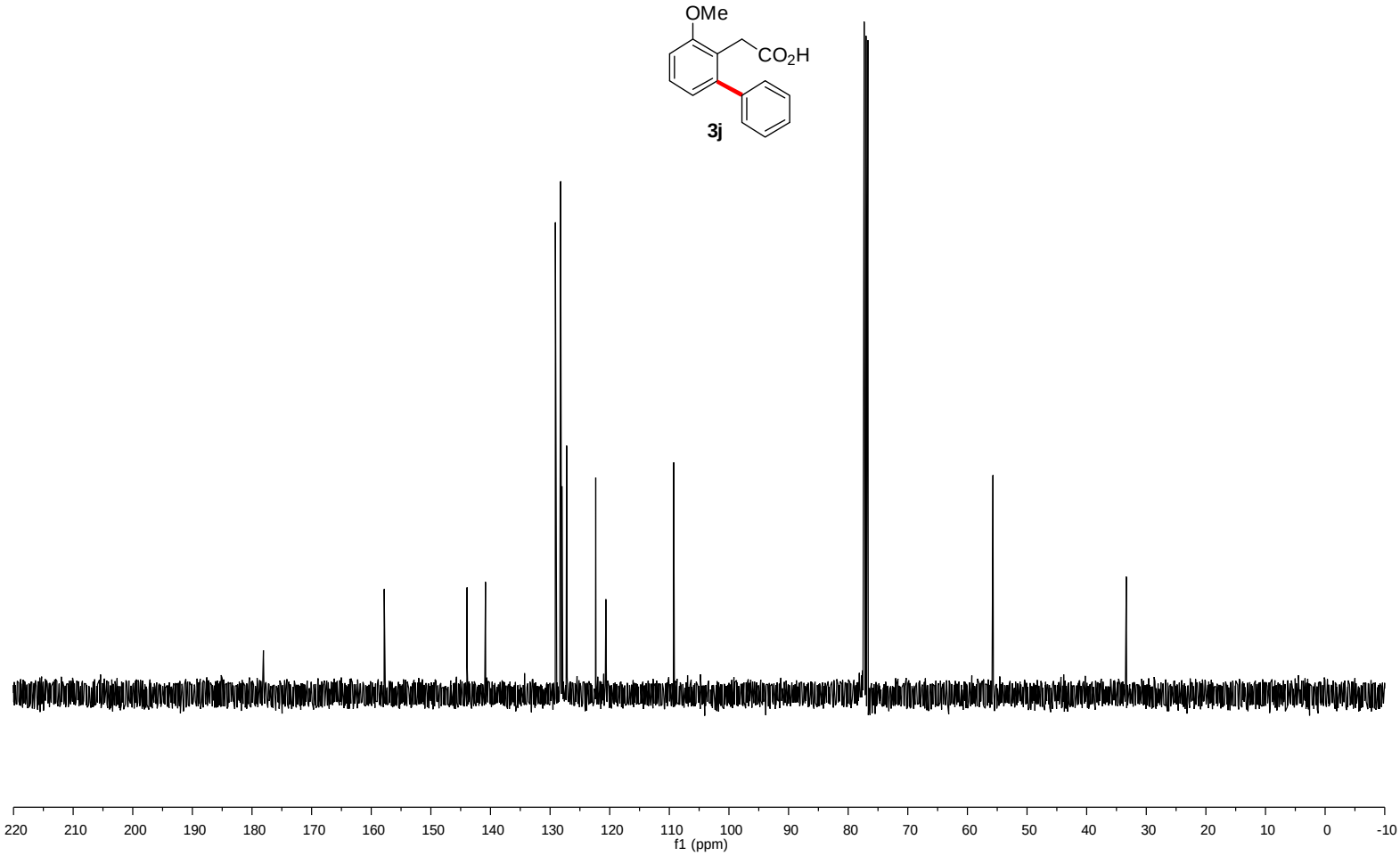
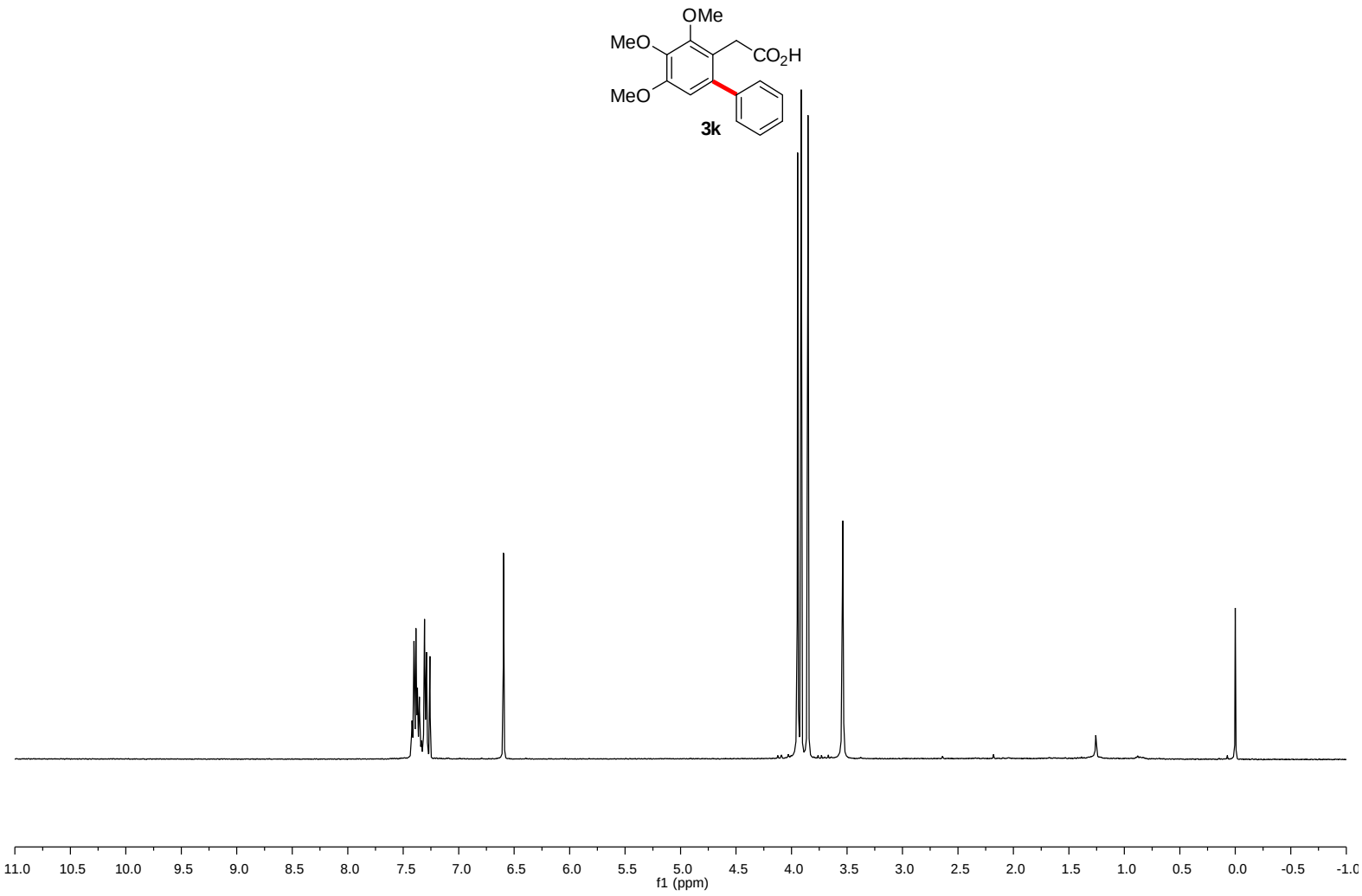
f1 (ppm)

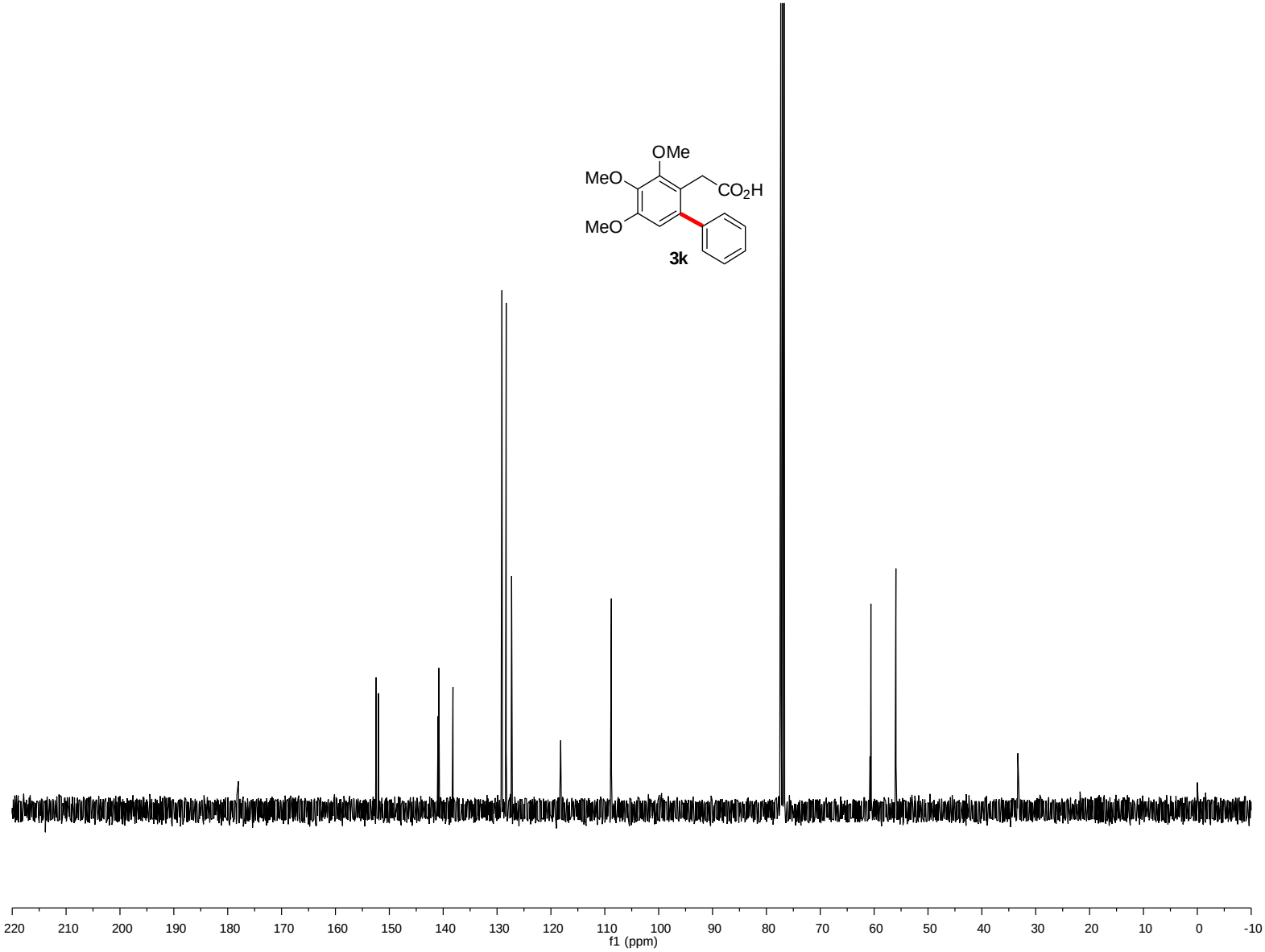

NO2
CO2H
3i
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

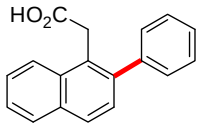

NO2
CO2H
3i
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OMe
CO2H
3j
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
-0.5
f1 (ppm)

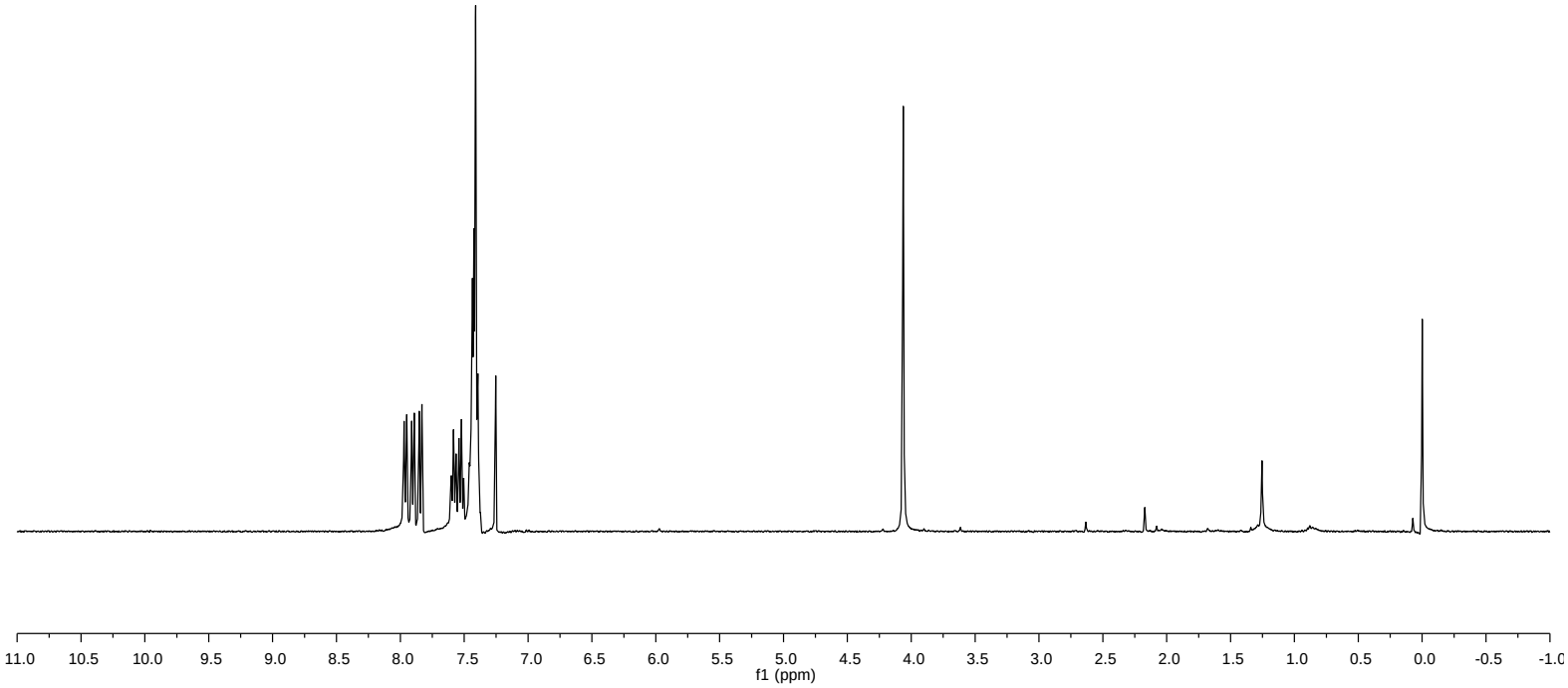

OMe
CO2H
3j
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

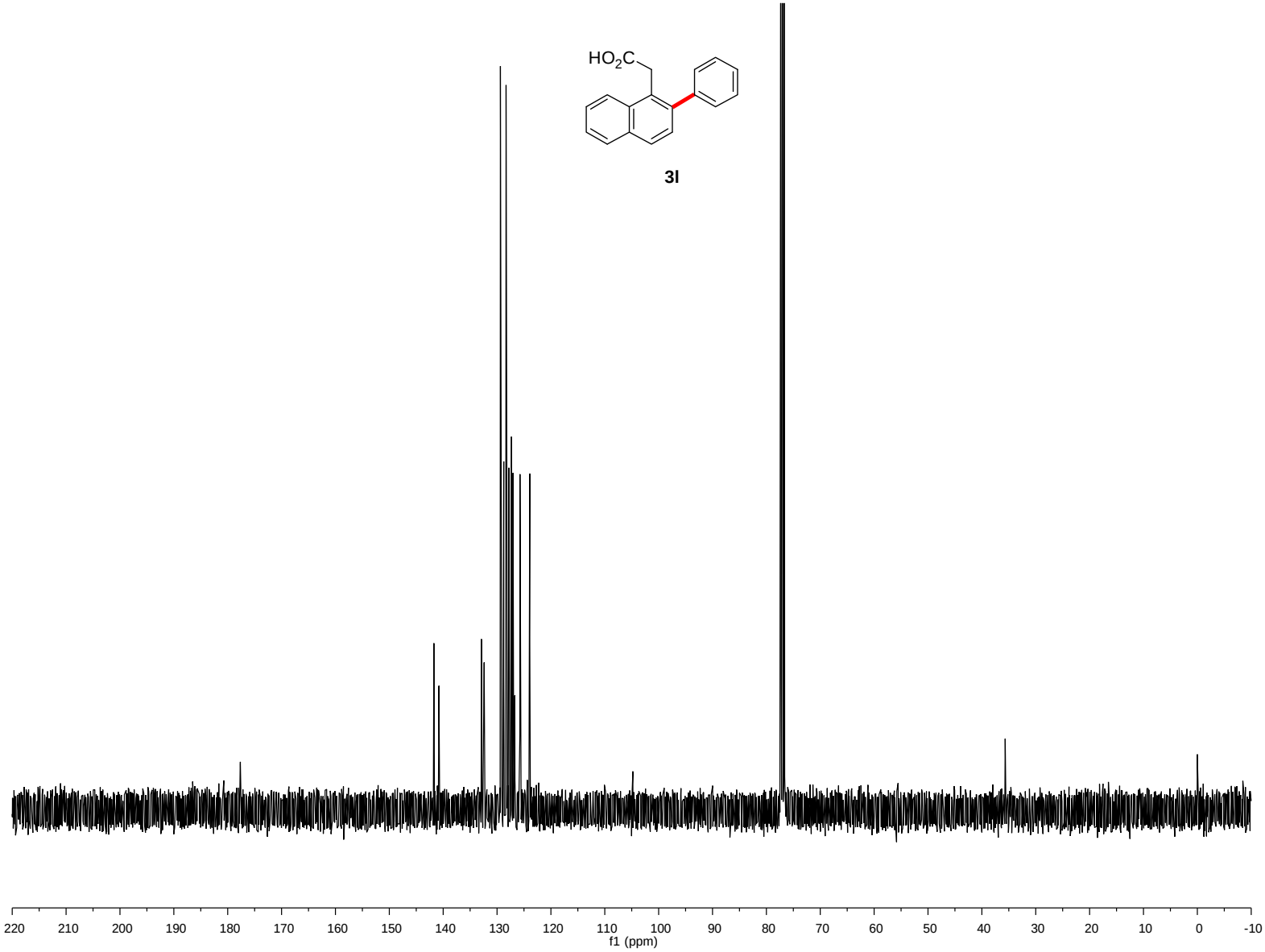

OMe
MeO
CO2H
MeO
3k
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

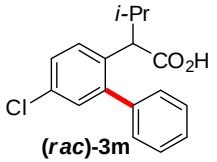

OMe
MeO
CO2H
MeO
3k
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


HO2C

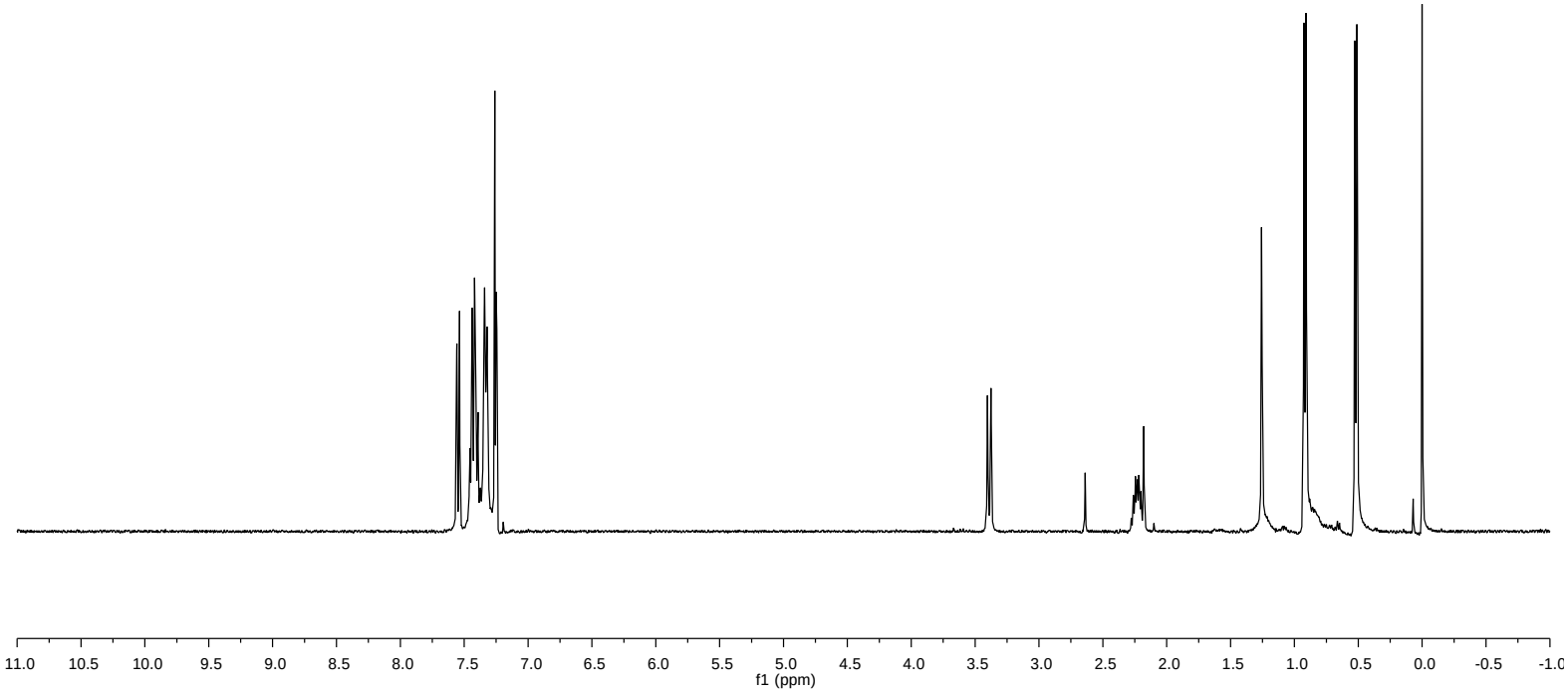
3l

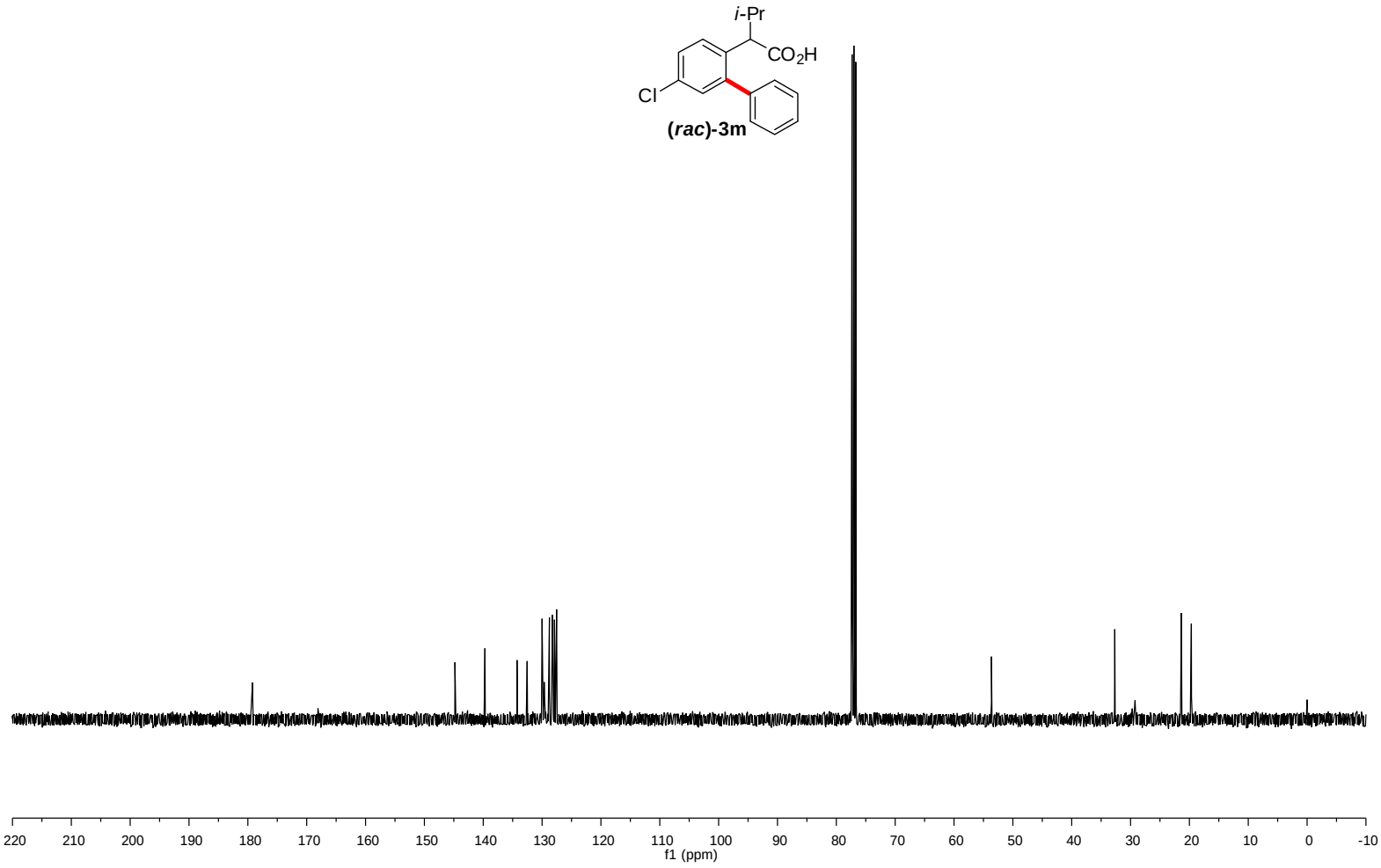

11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

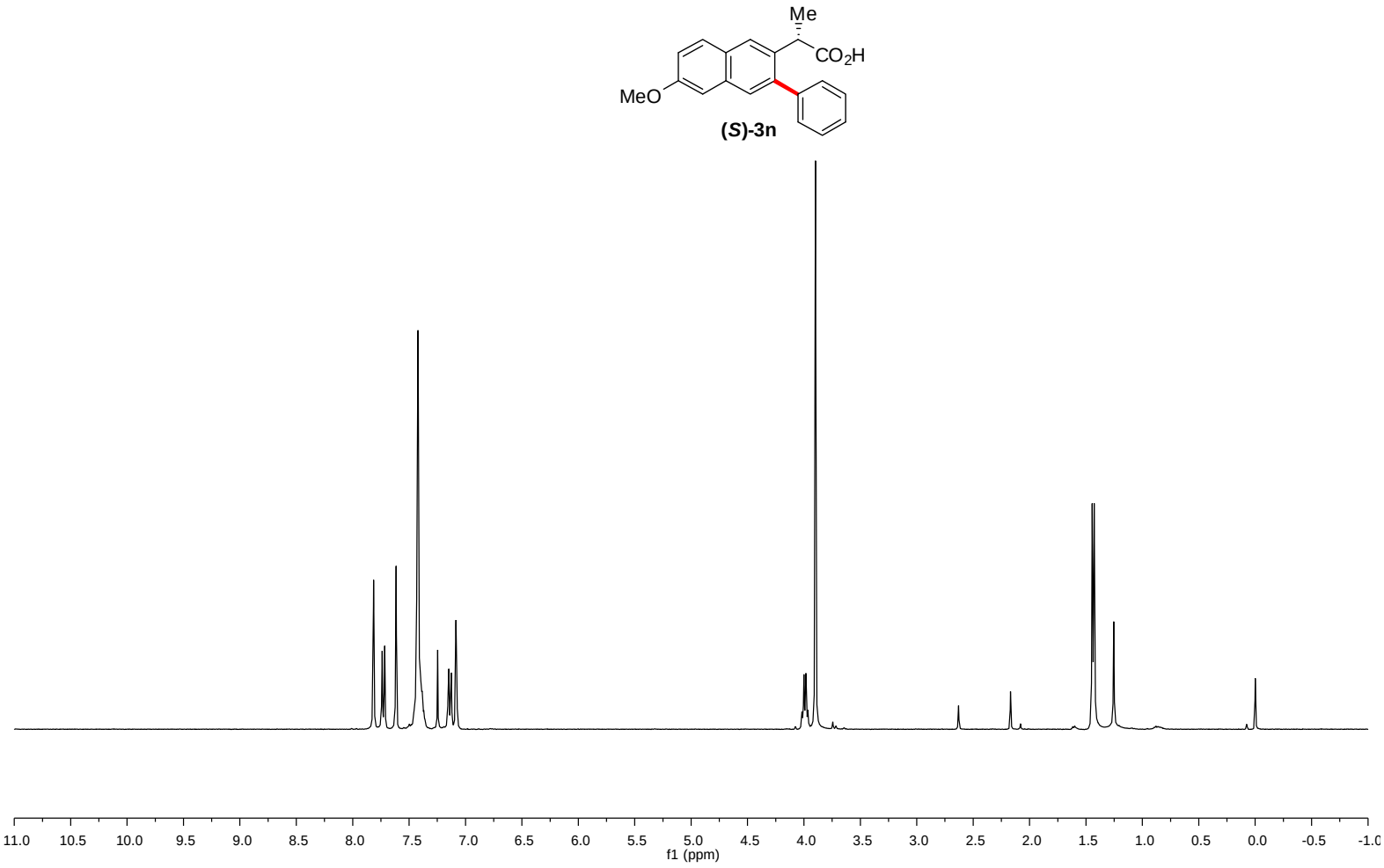

HO2C
3l
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

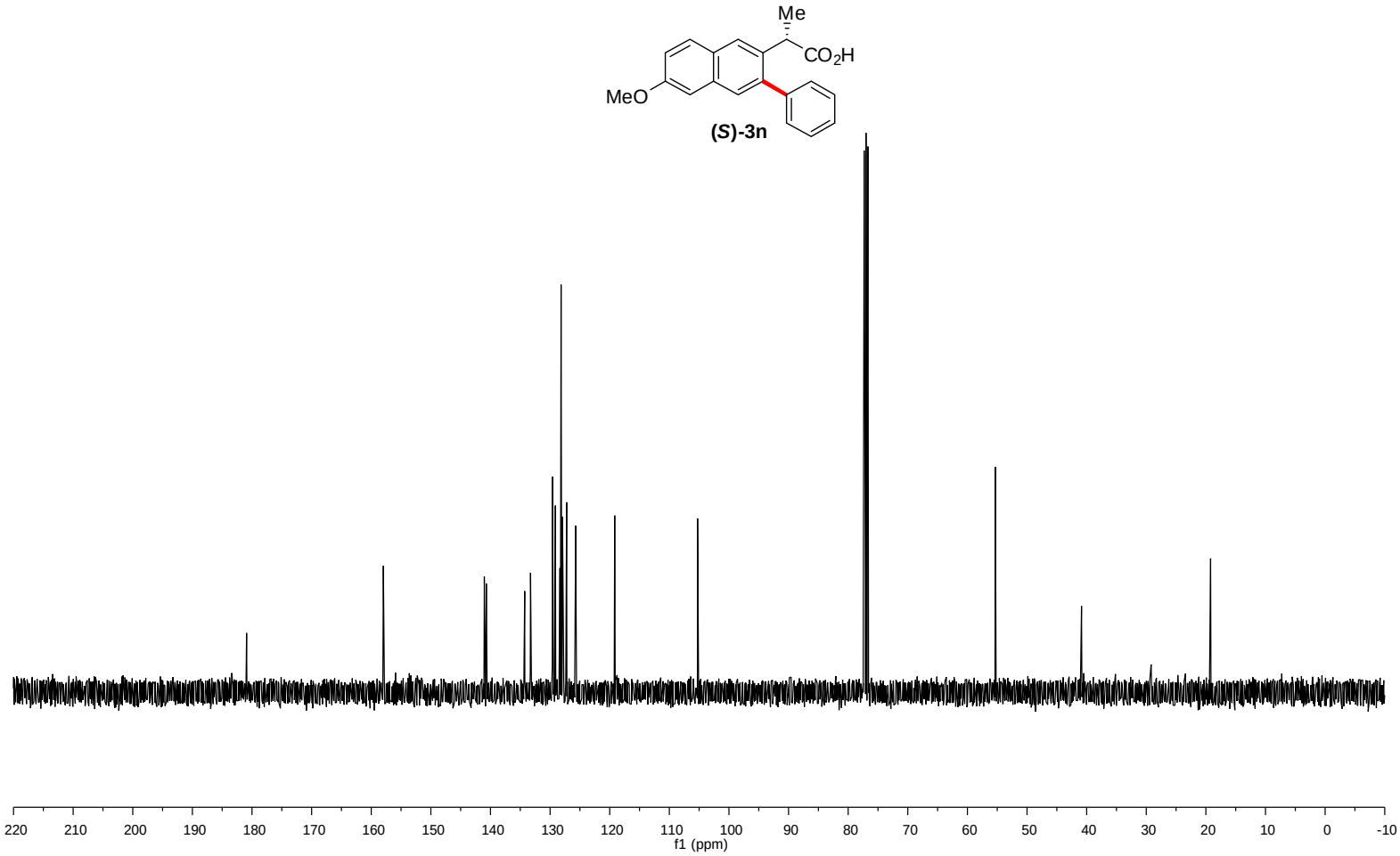

i-Pr
CO2H
Cl

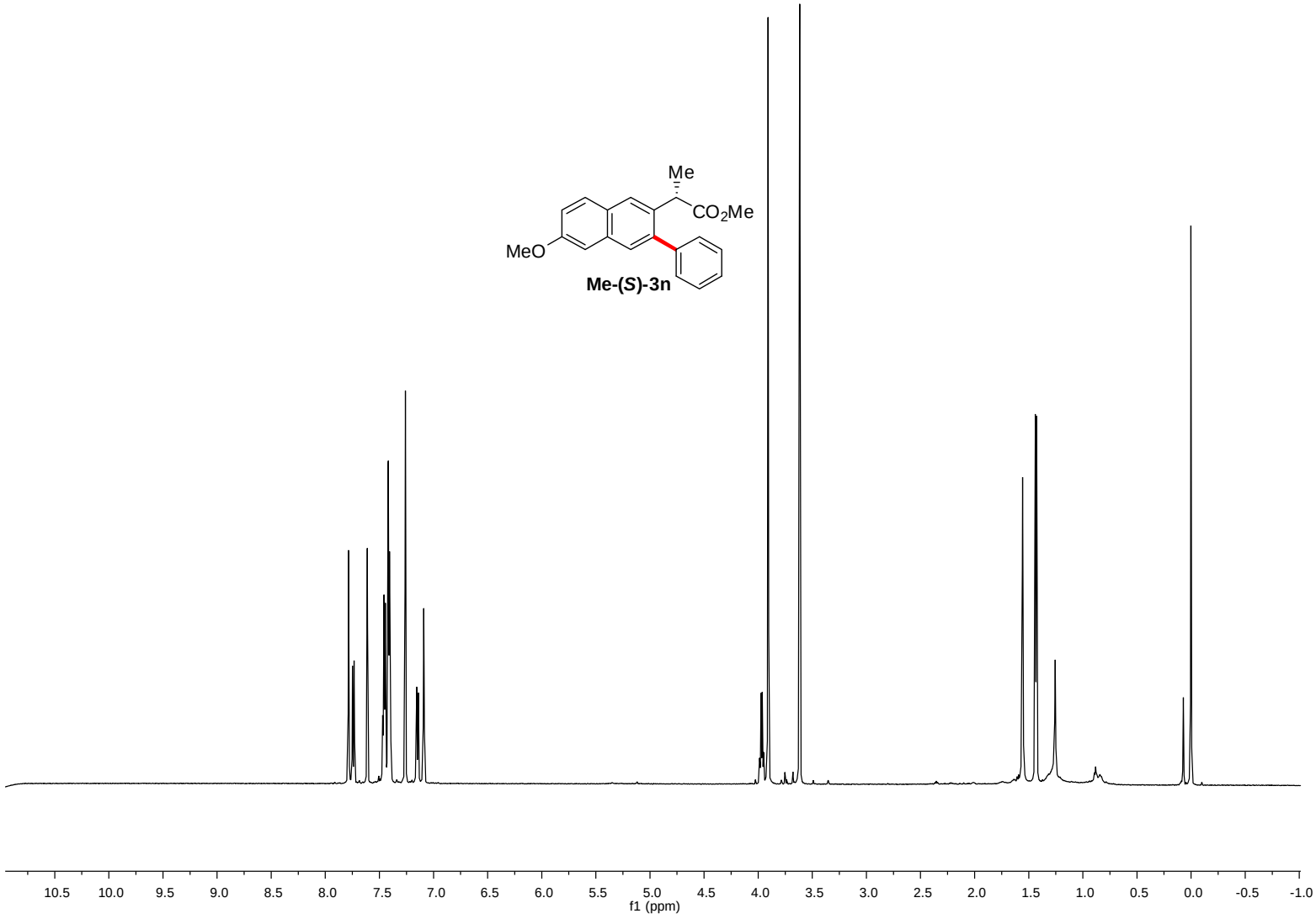
(*rac*)-3m

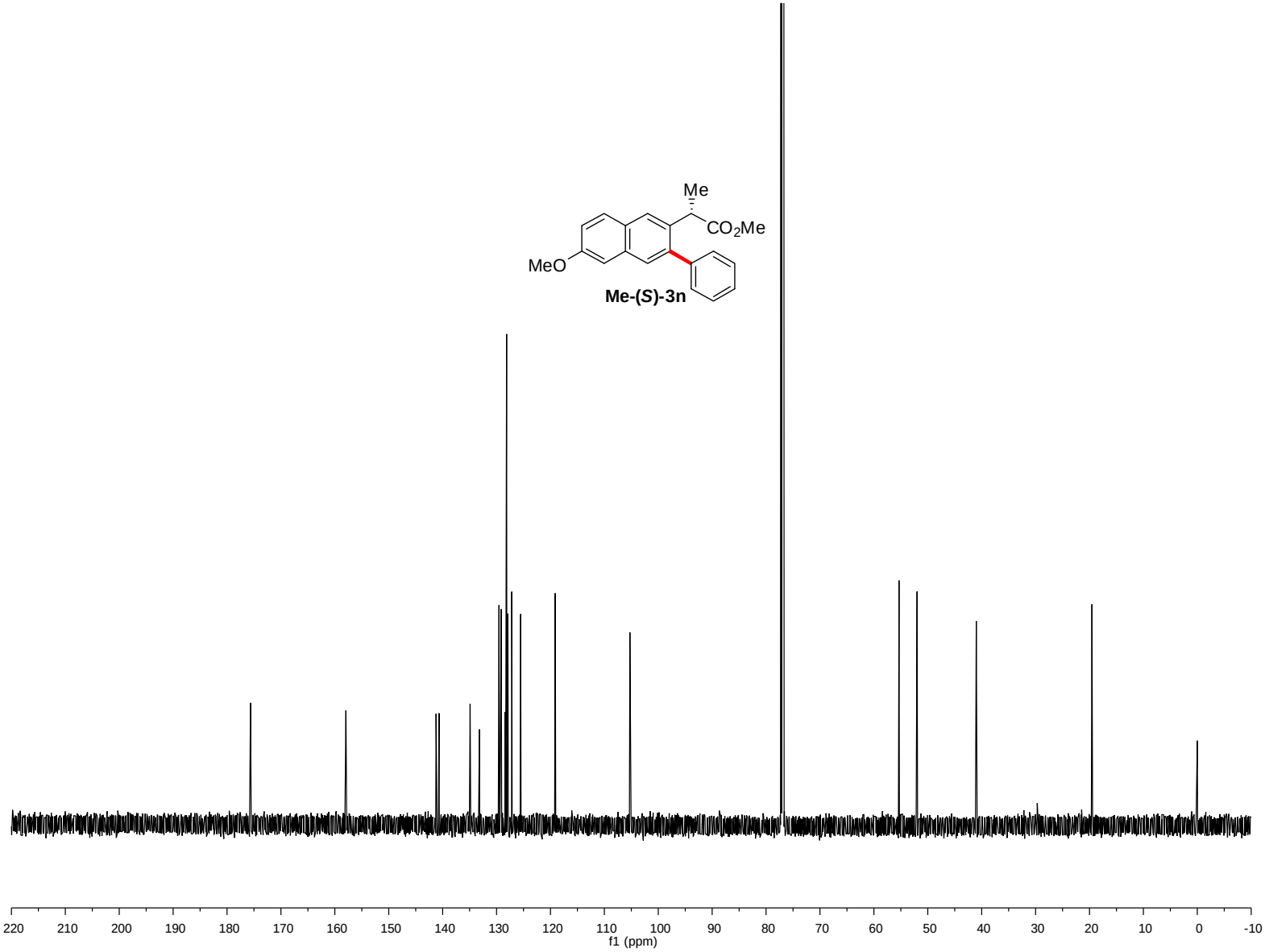

11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

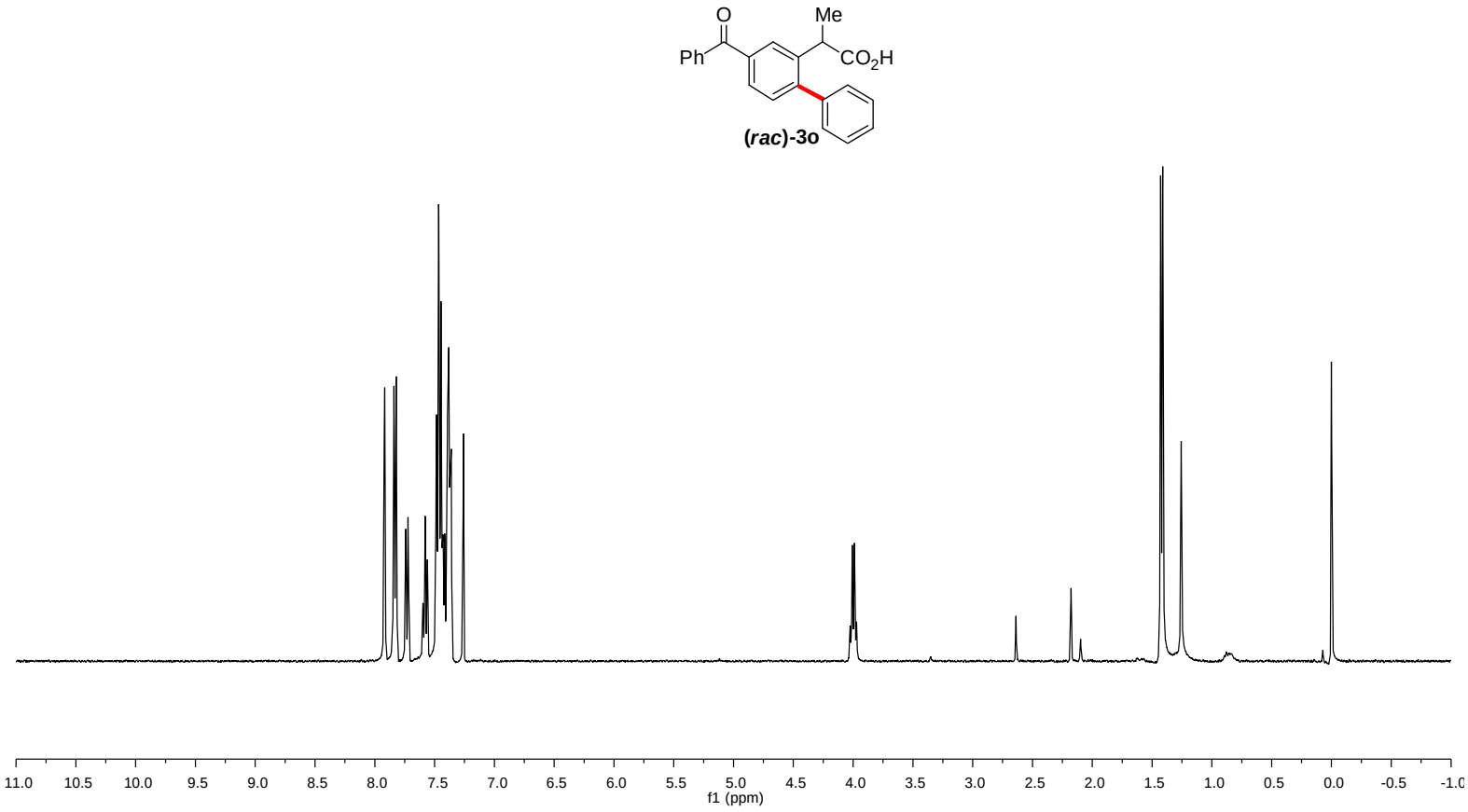

i-Pr
CO2H
Cl
(rac)-3m
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

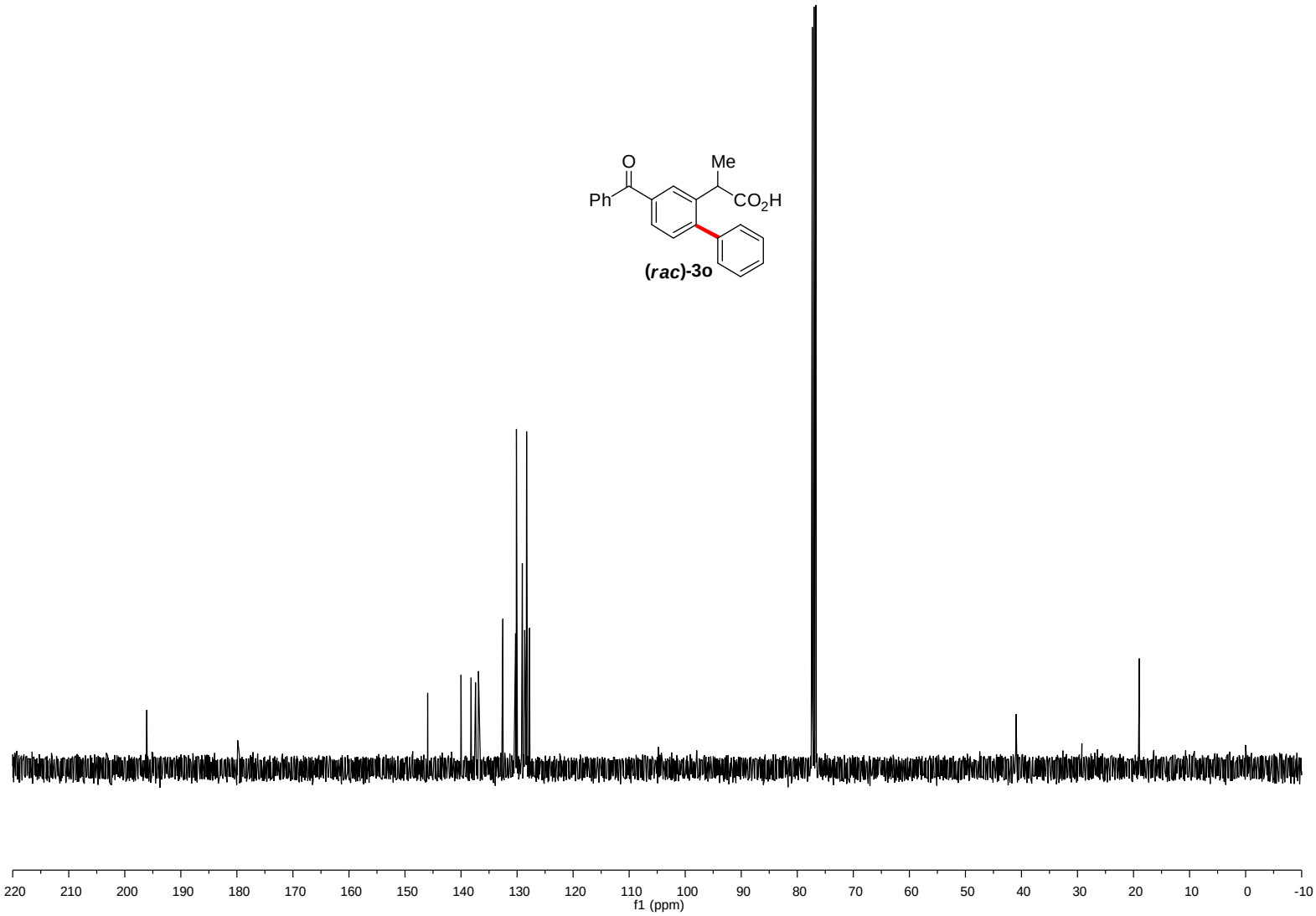

Me
CO2H
MeO
(S)-3n
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

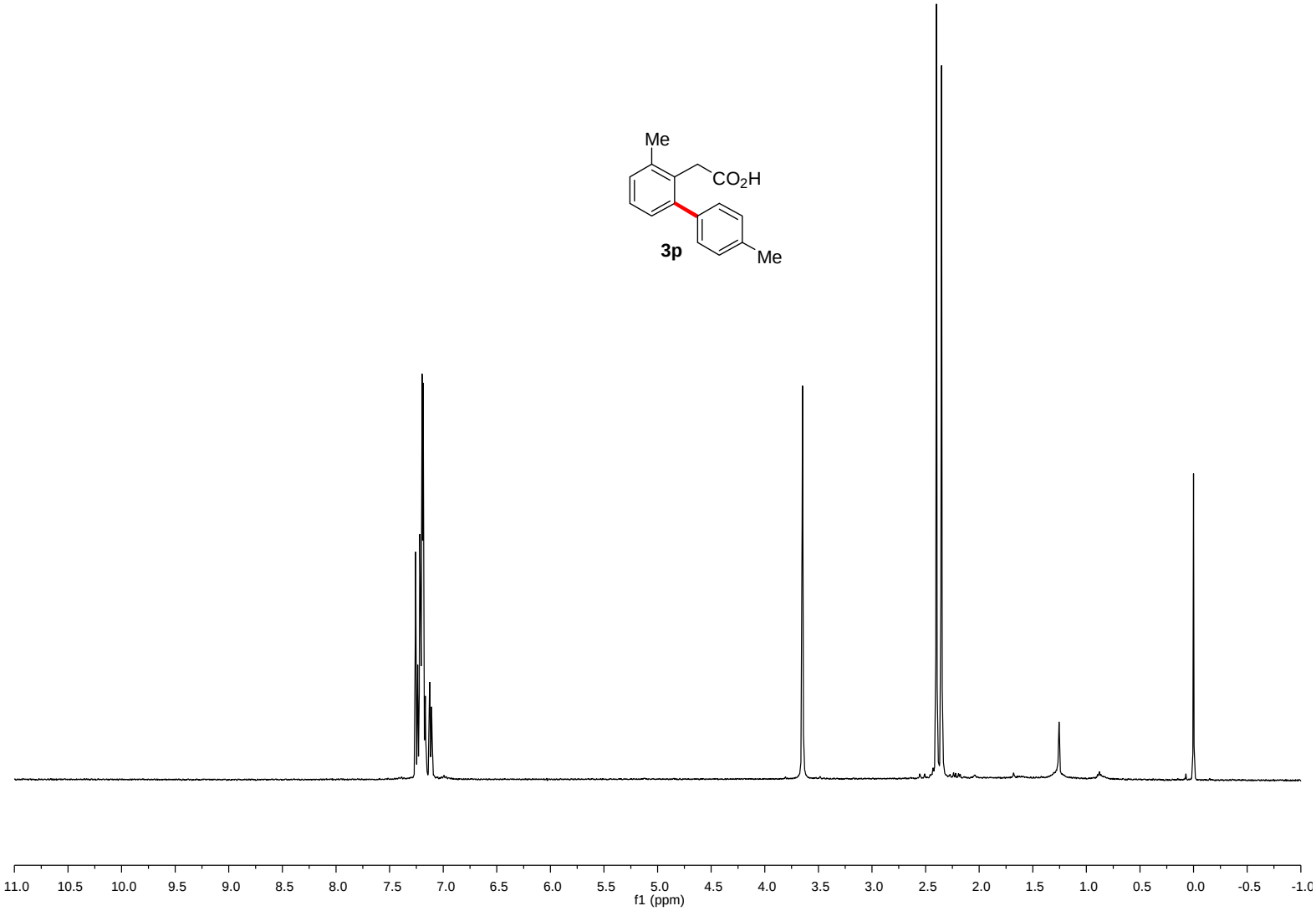

Me
CO2H
MeO
(S)-3n
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

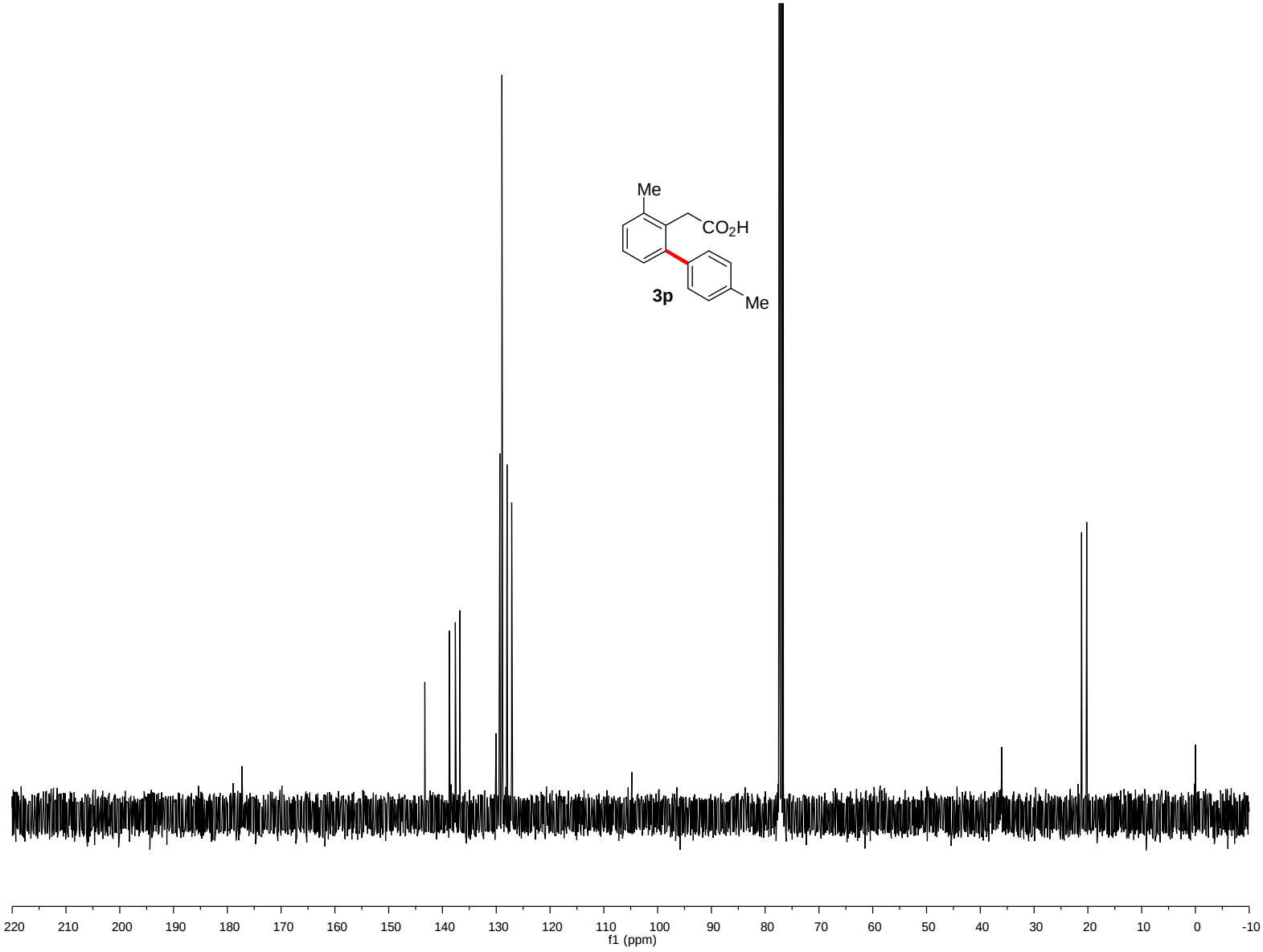

Me
CO2Me
MeO
Me-(S)-3n
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

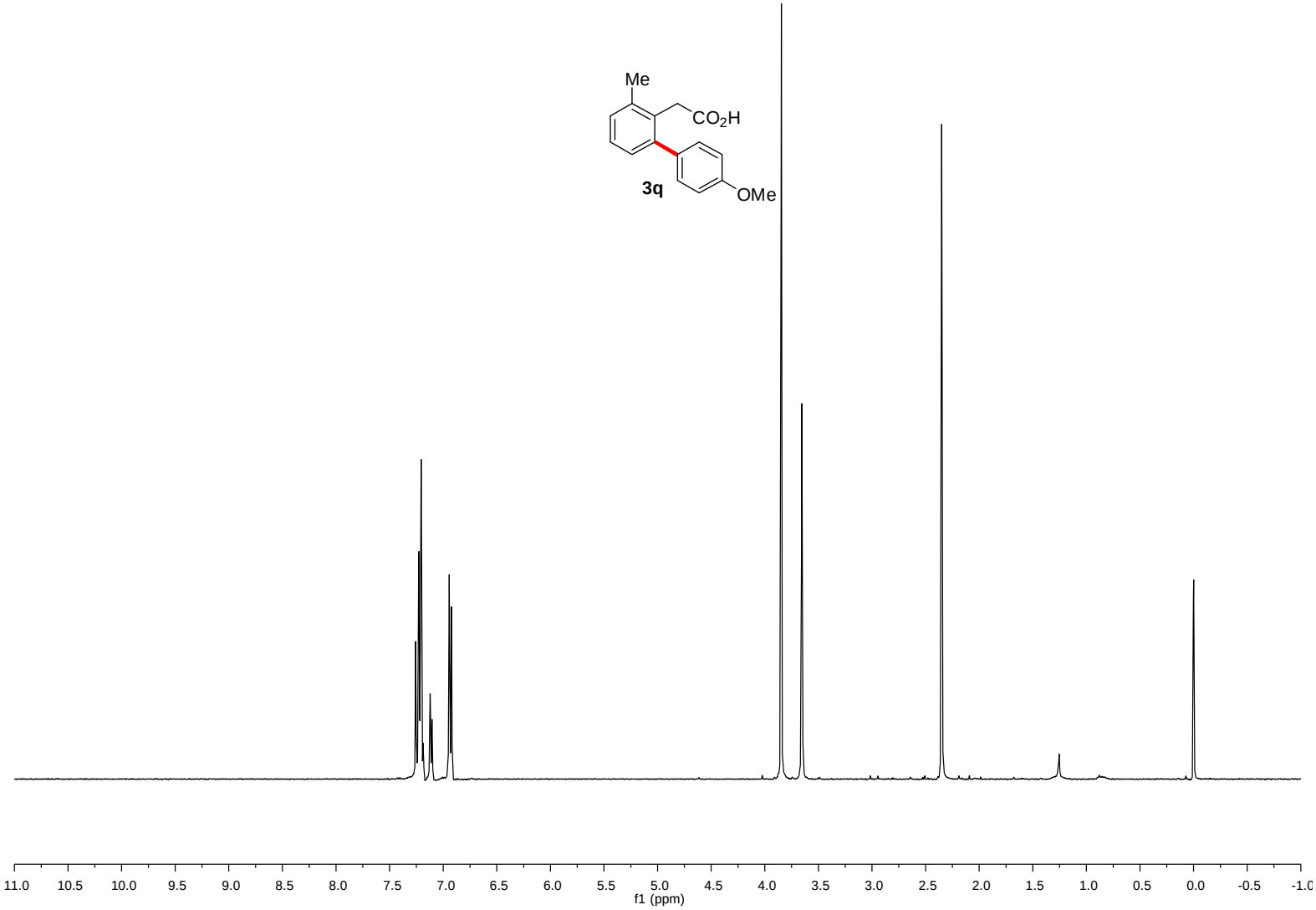

Me
CO2Me
MeO
Me-(S)-3n
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

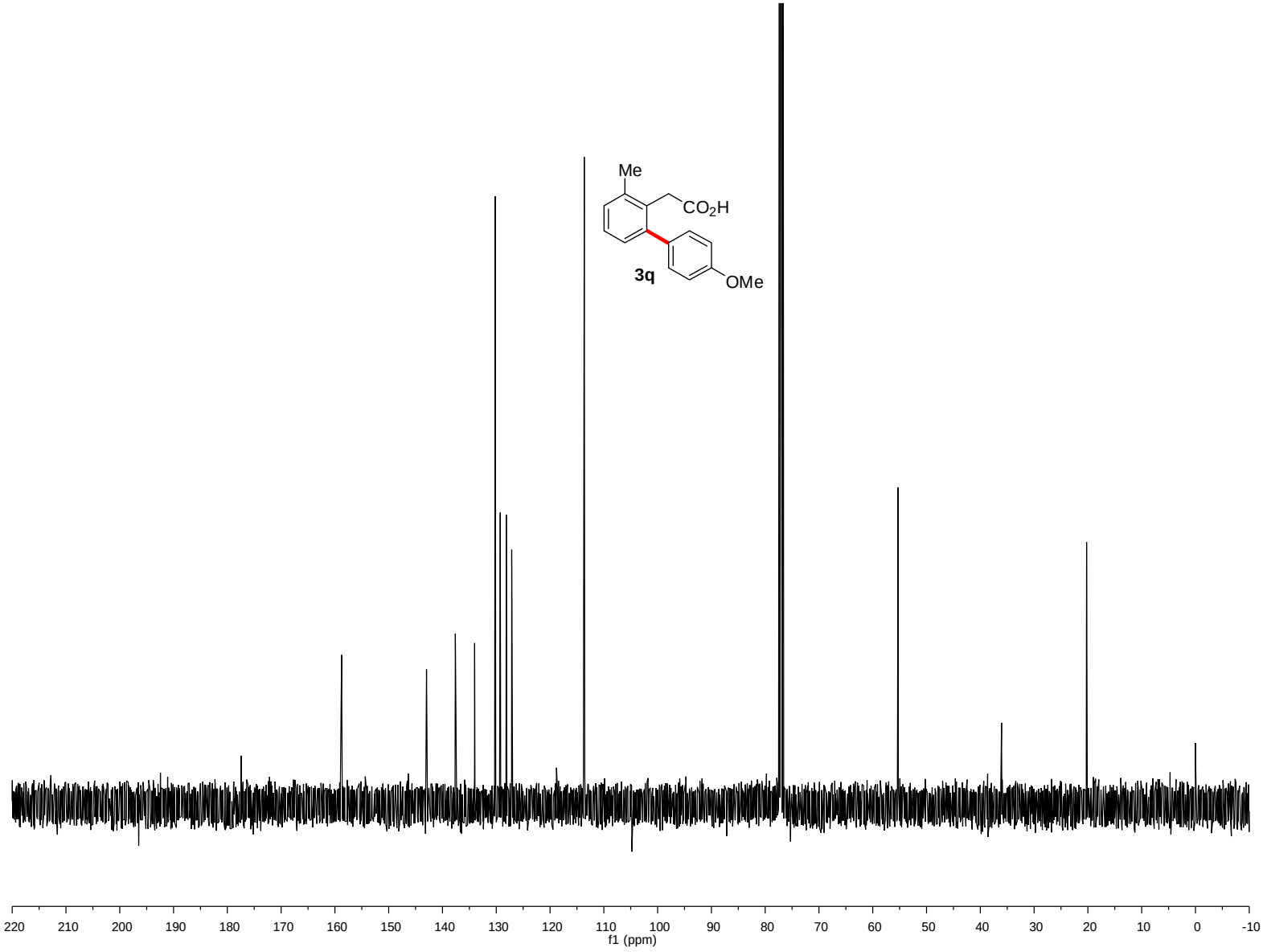

O
Me
Ph
CO2H
(rac)-3o
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

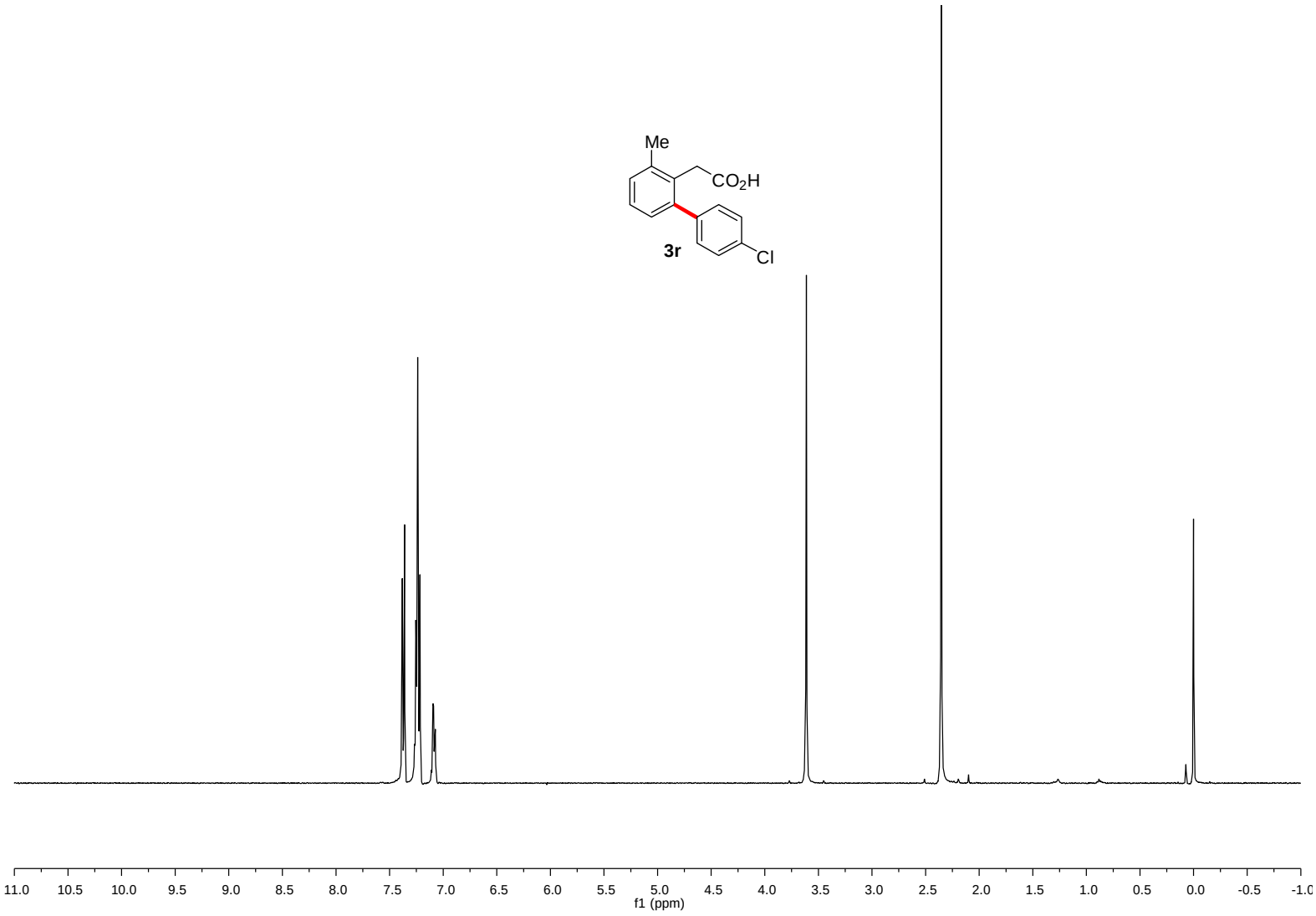

O
Me
Ph
CO2H
(rac)-3o
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

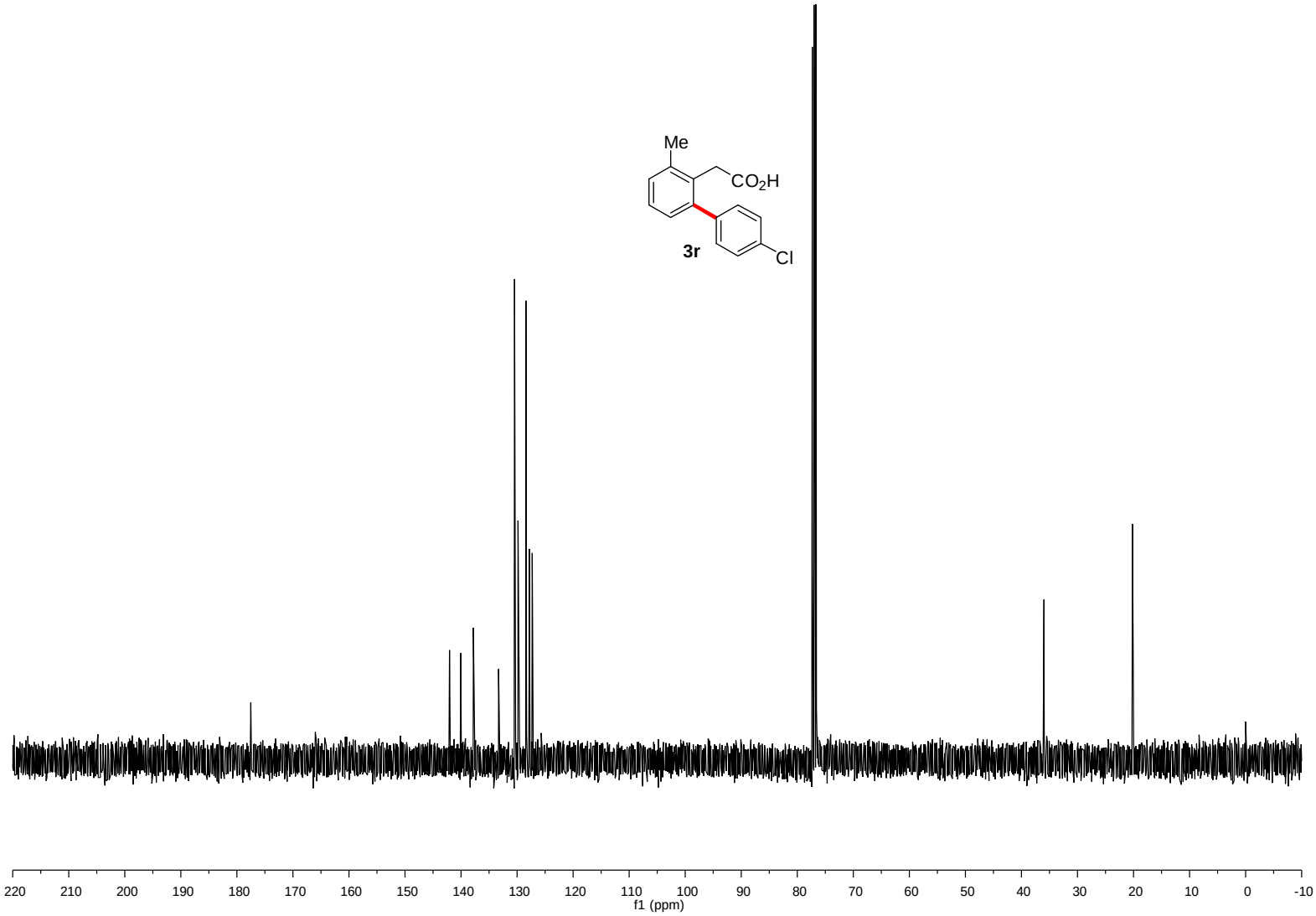

Me
CO2H
Me
3p
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

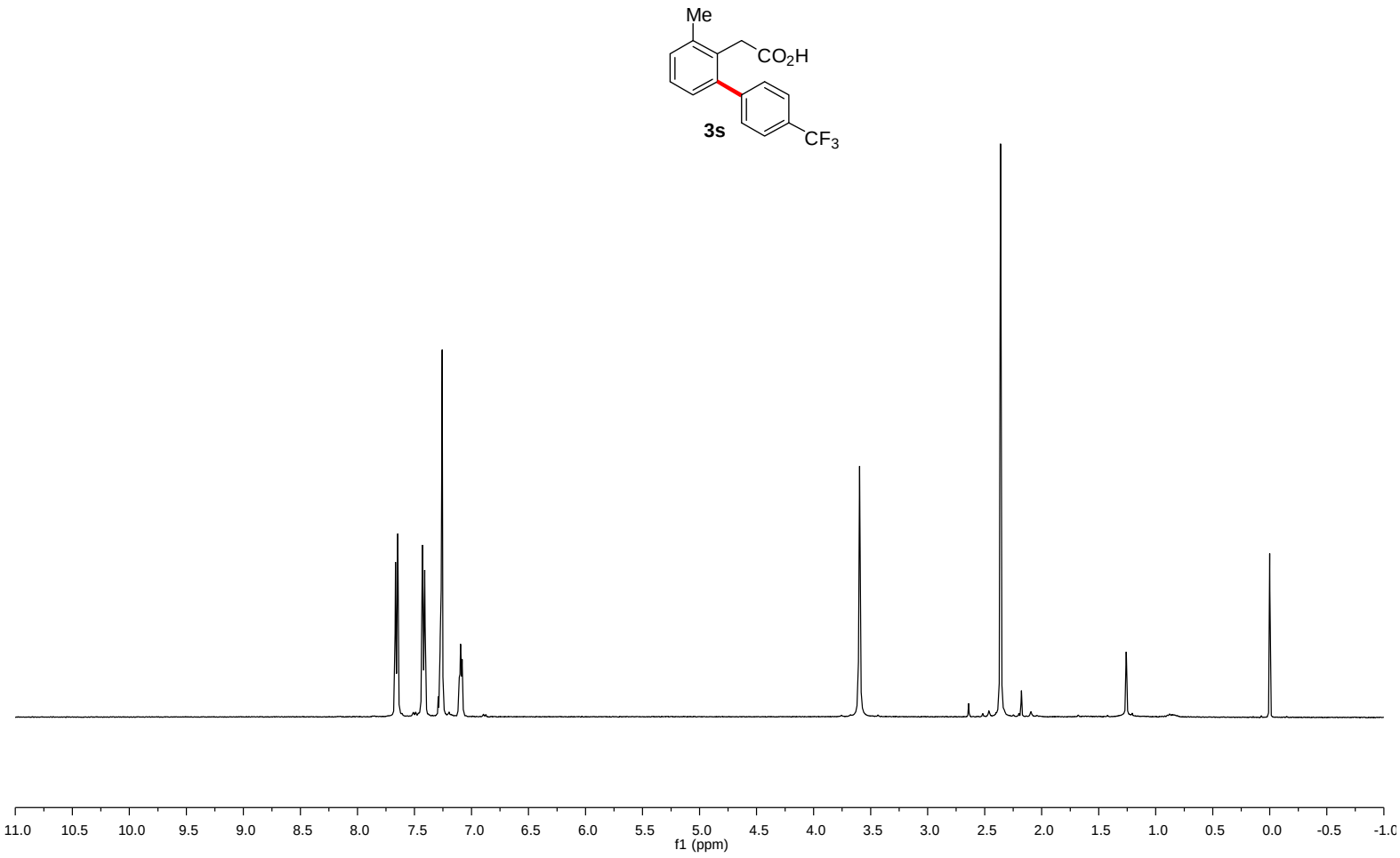

Me
CO2H
3p
Me
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

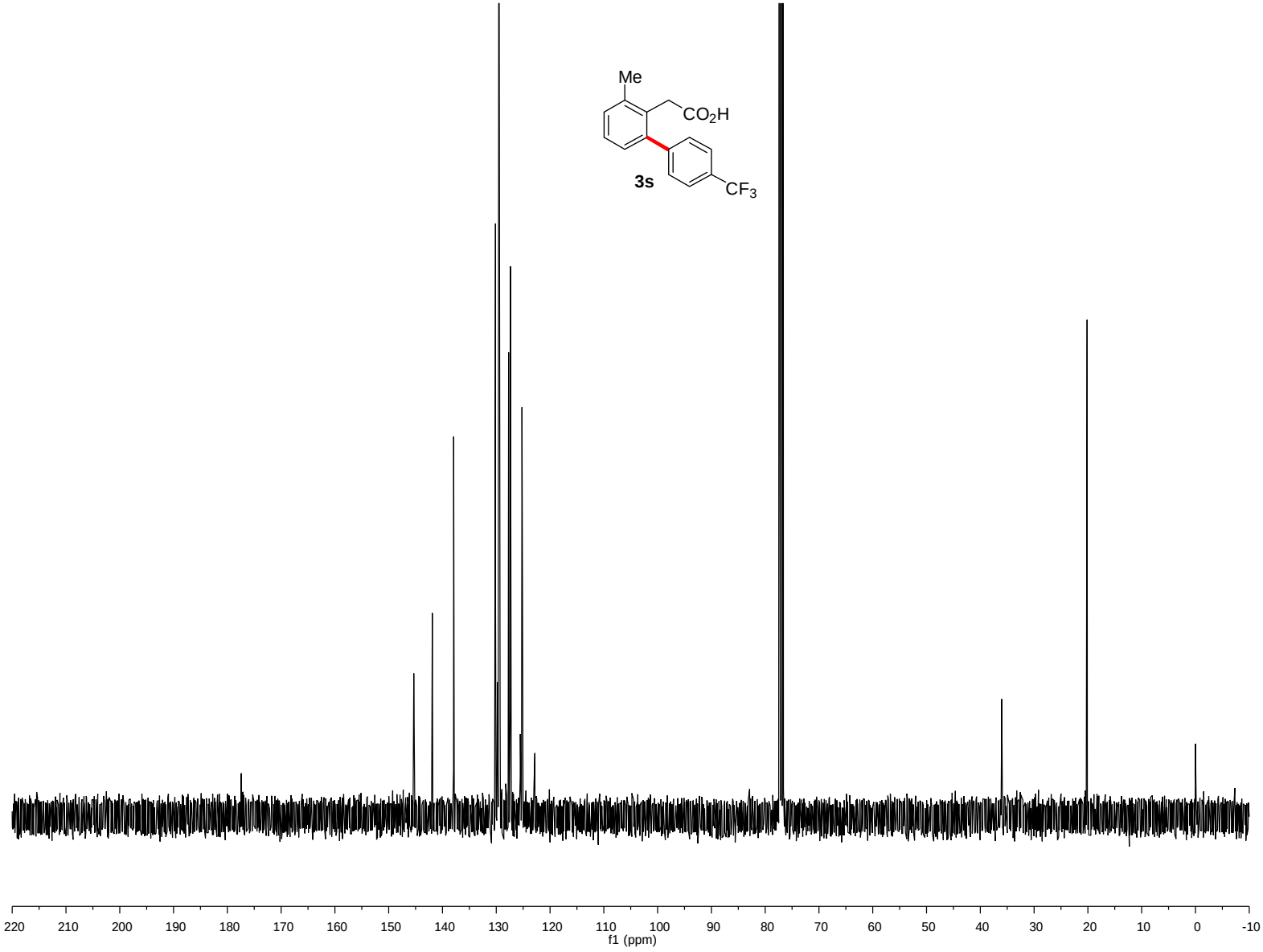

Me
CO2H
OMe
3q
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

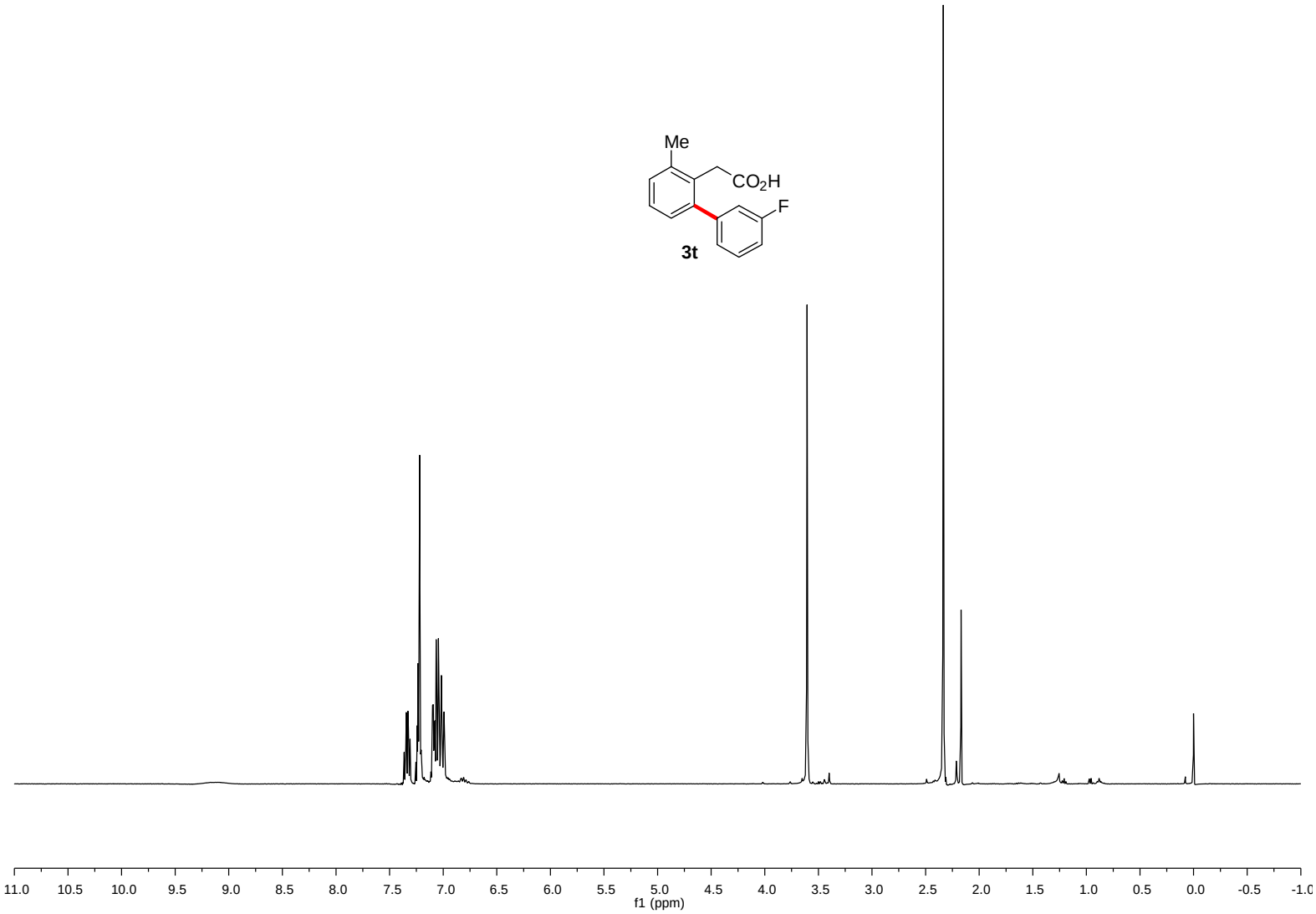

Me
CO2H
3q
OMe
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

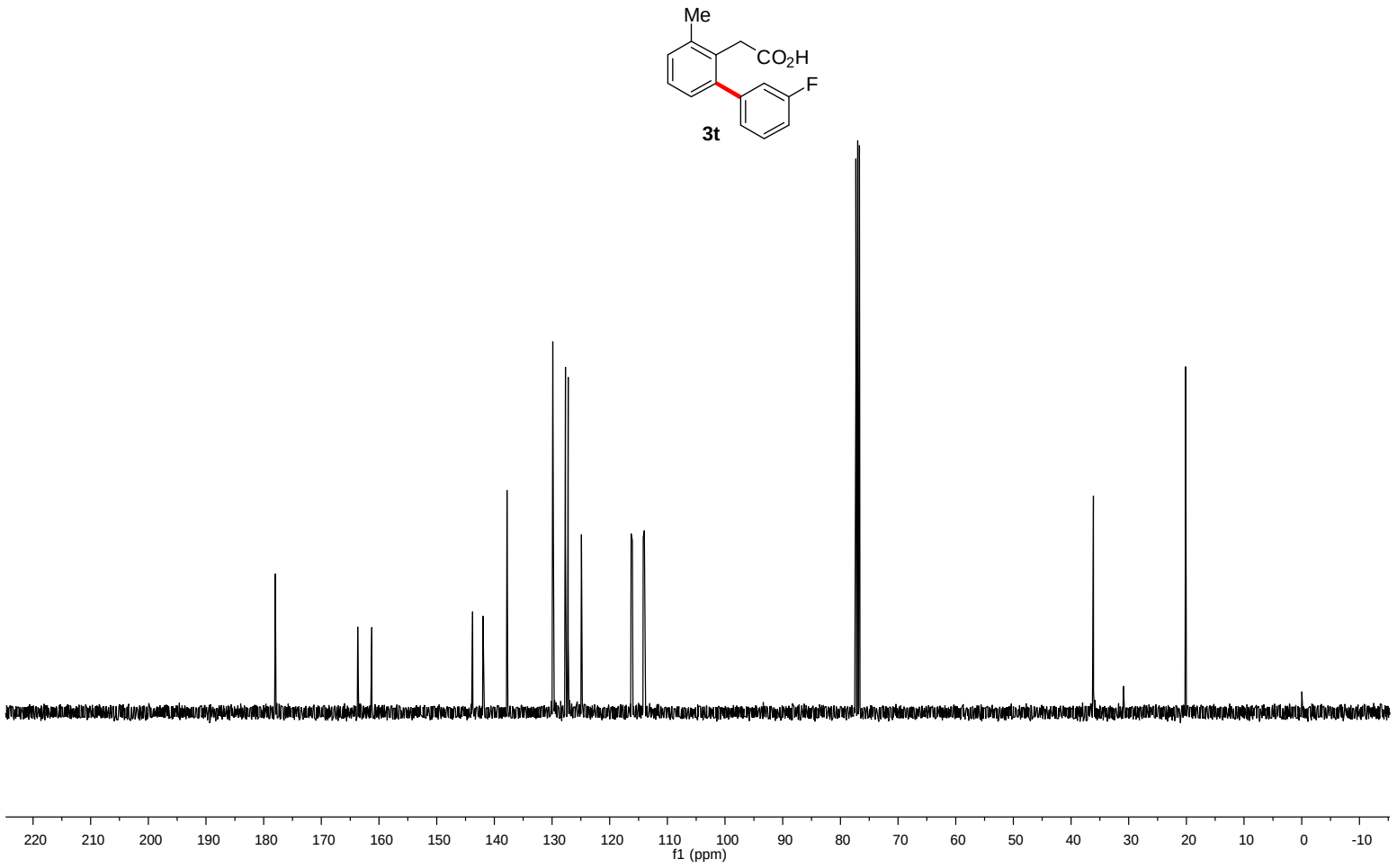

Me
CO2H
Cl
3r
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

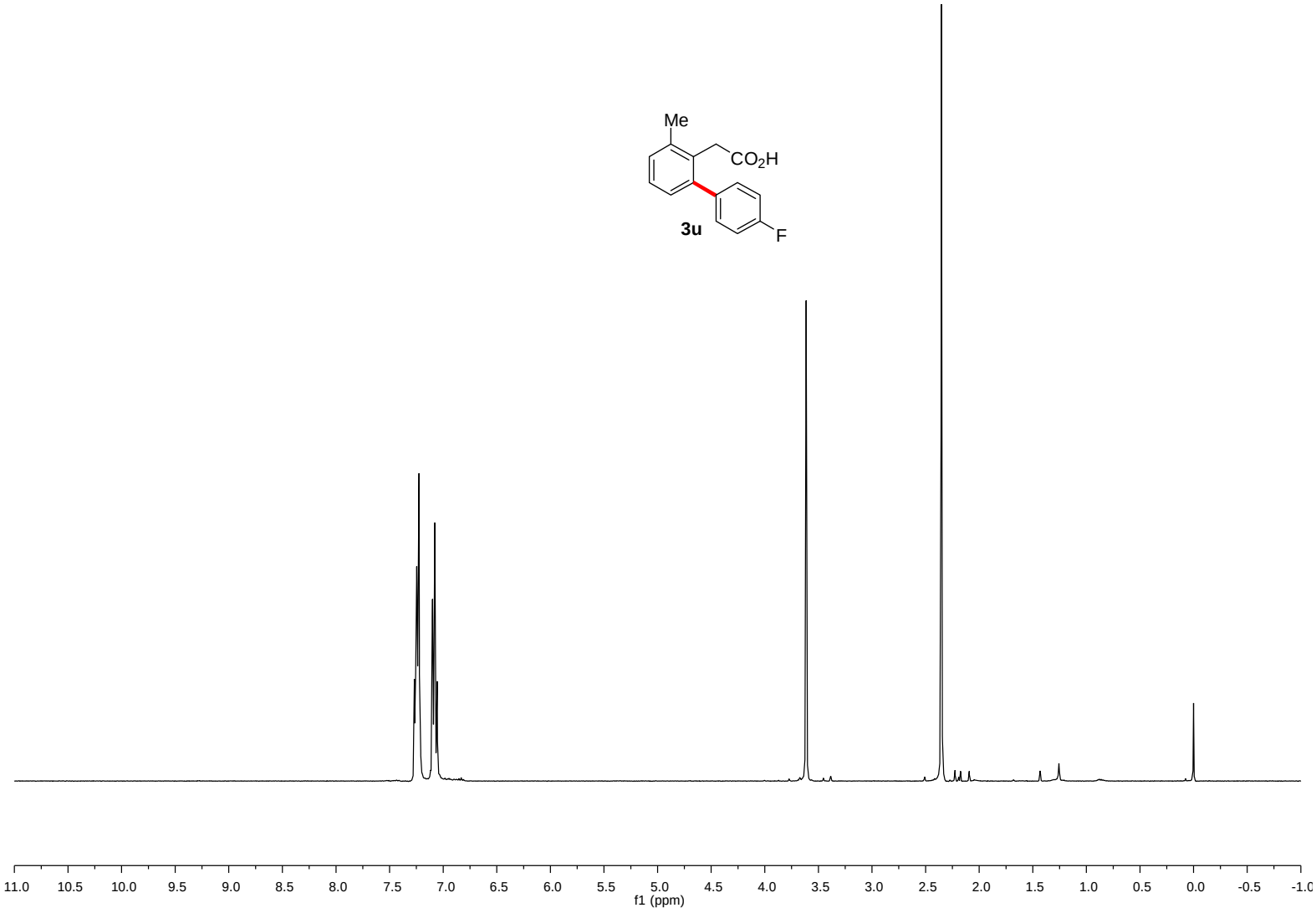

Me
CO2H
Cl
3r
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

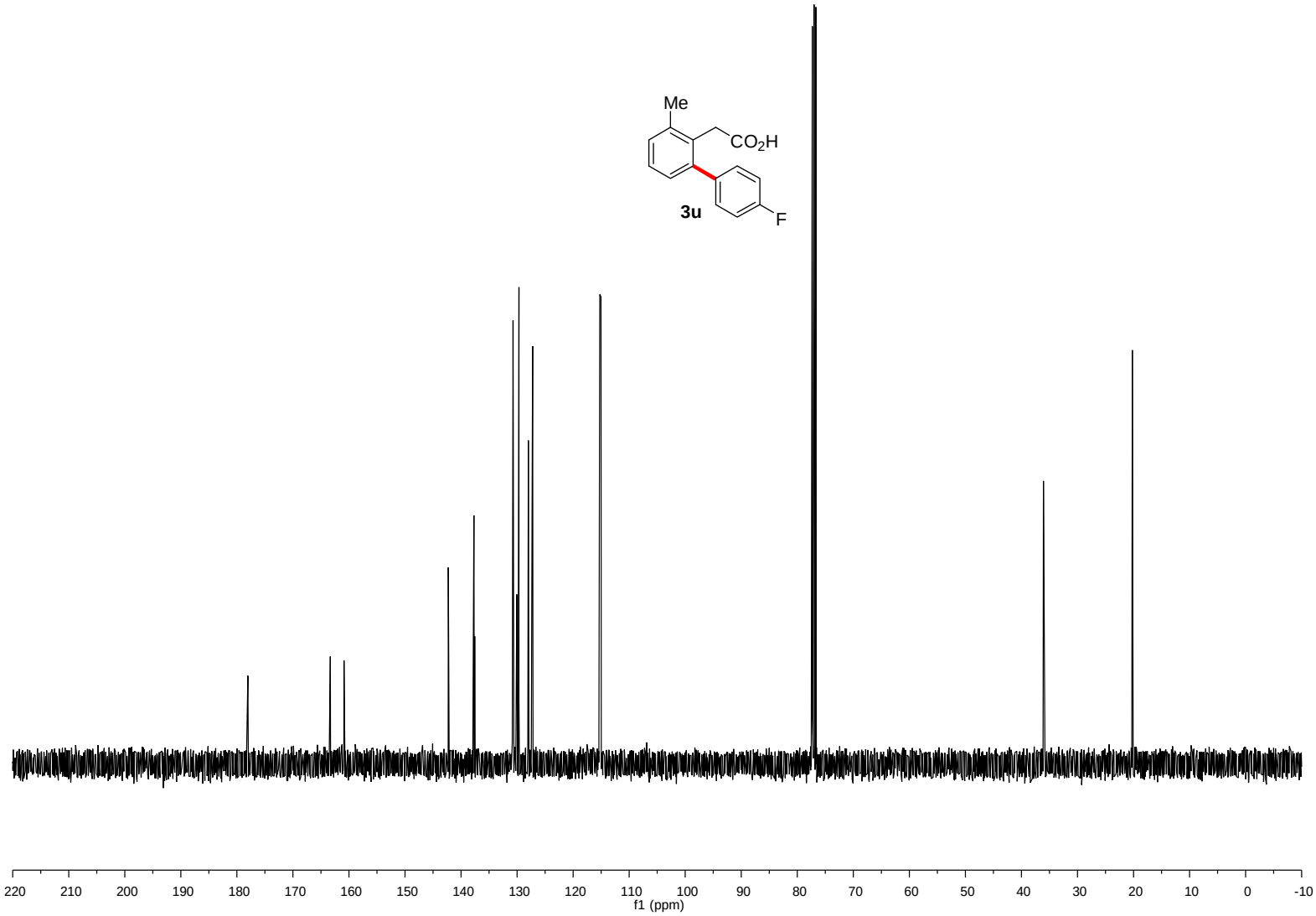

Me
CO2H
3s
CF3
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

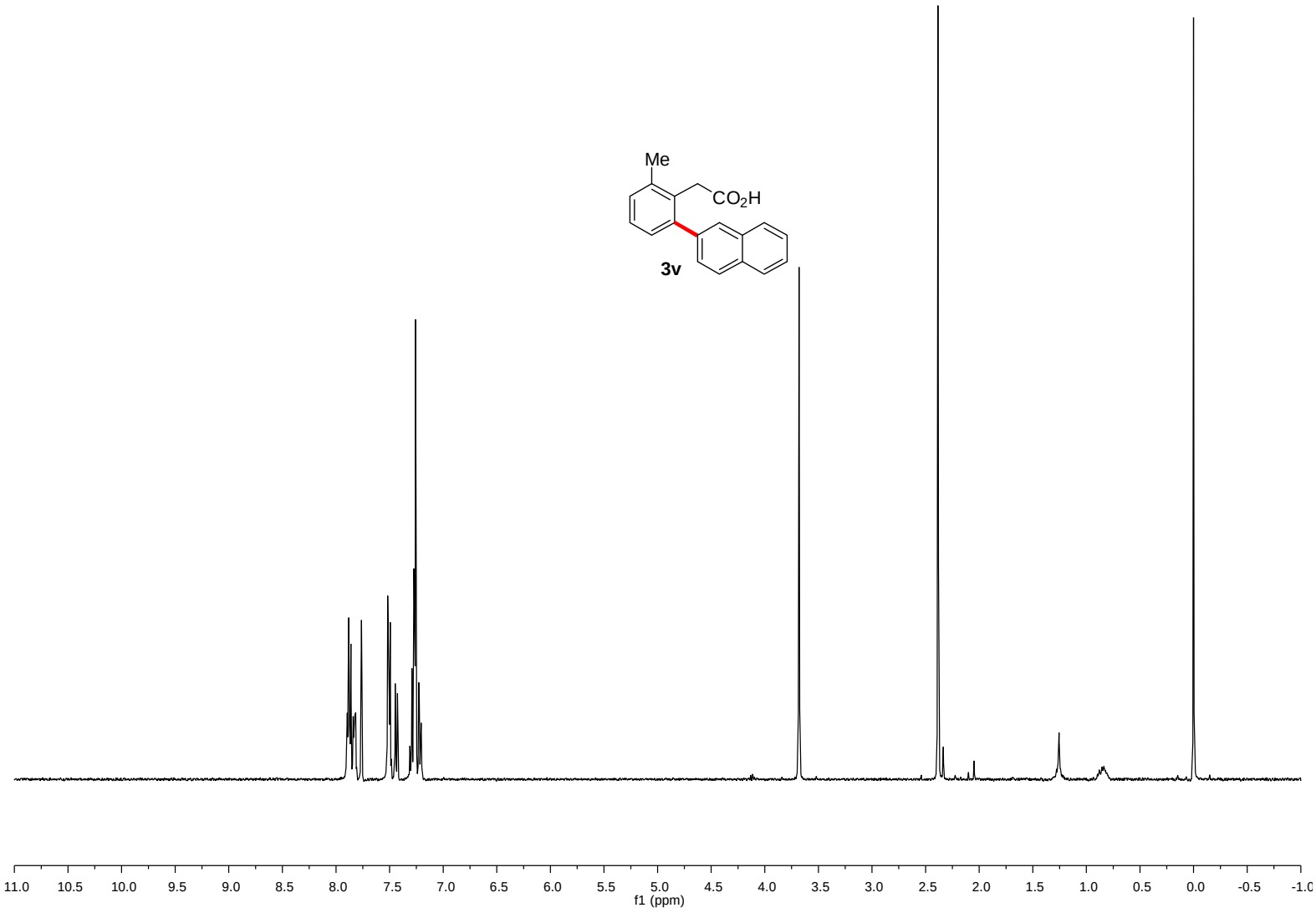

Me
CO2H
3s
CF3
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

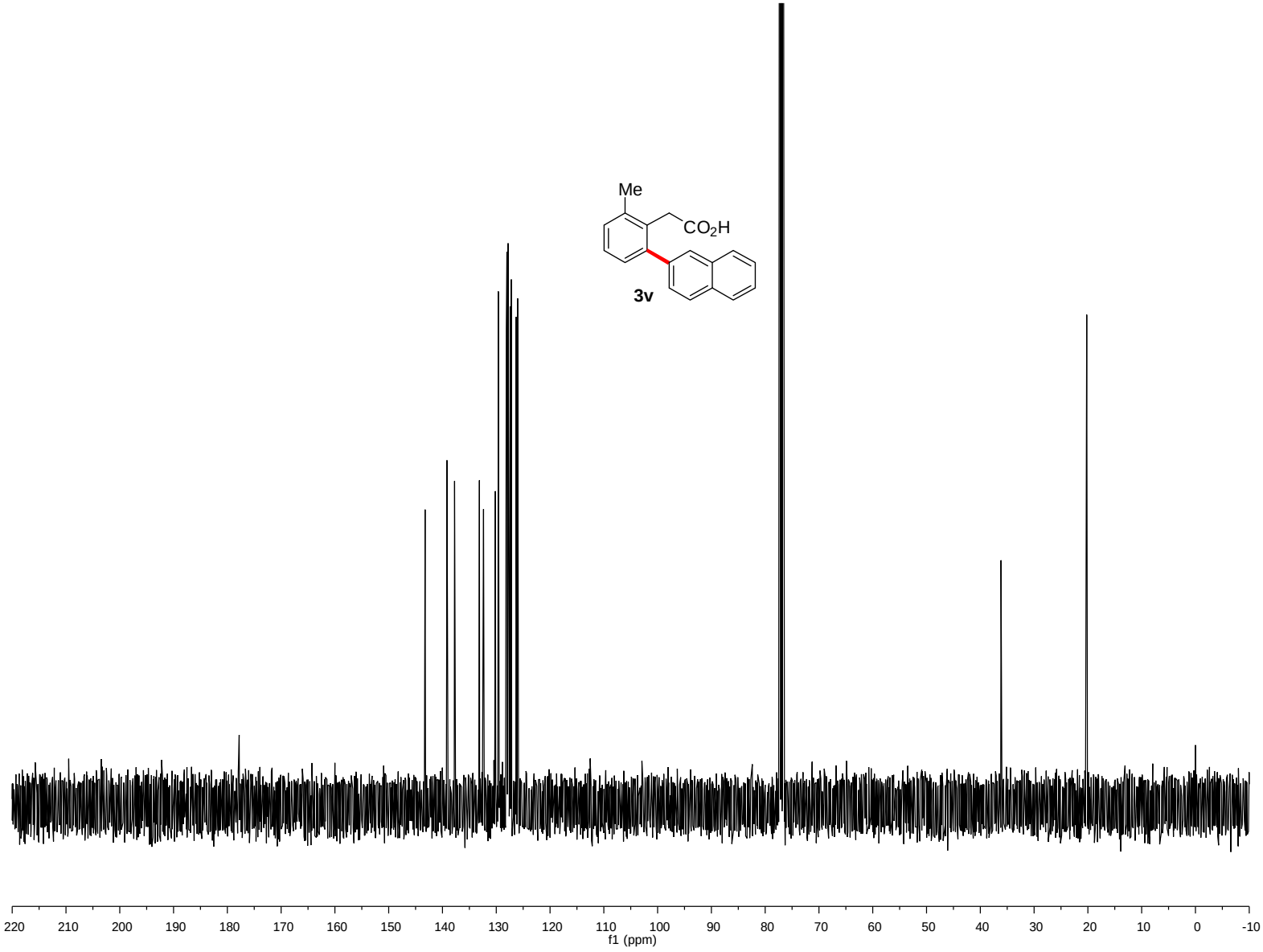

Me
CO2H
F
3t
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

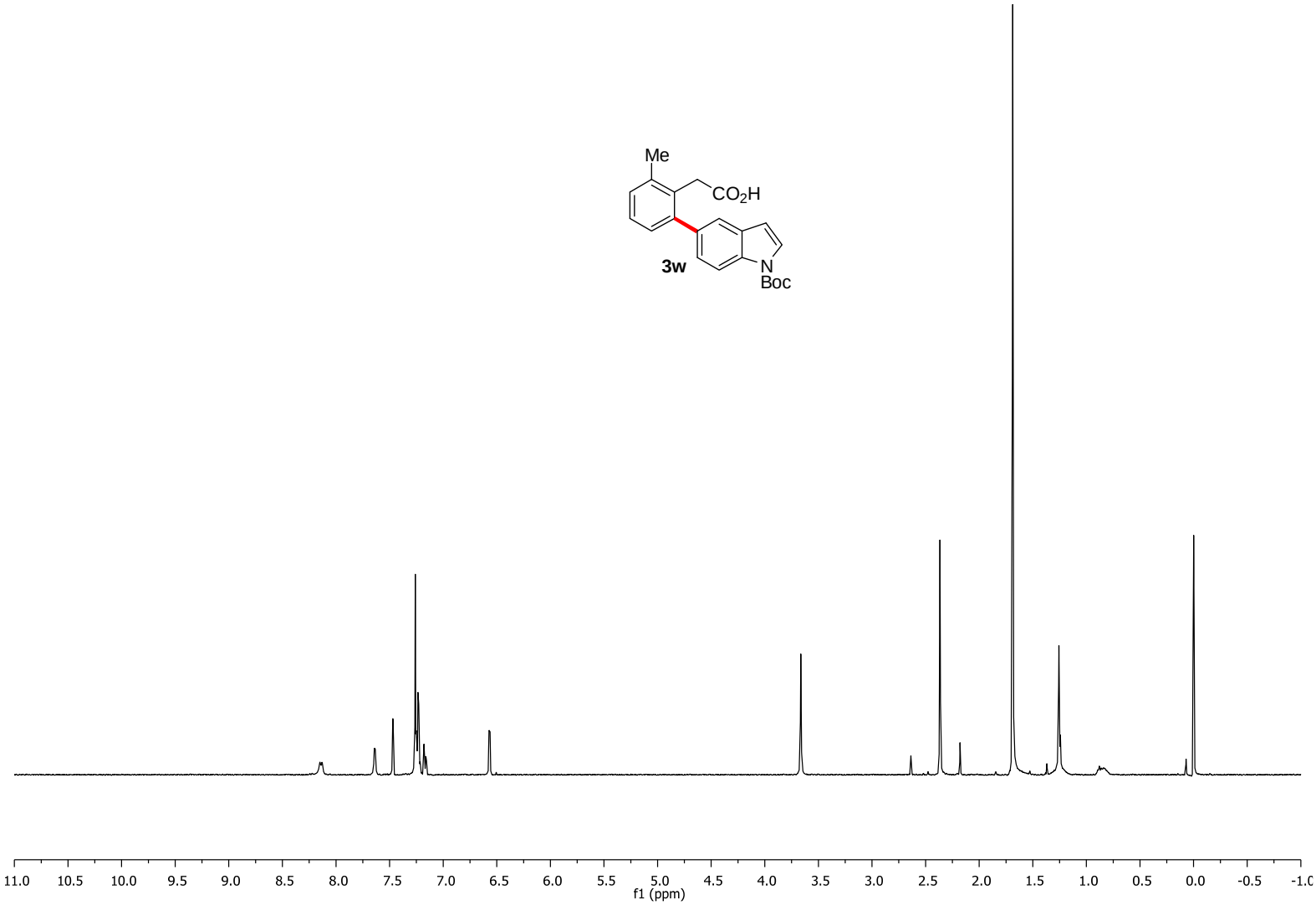

Me
CO2H
F
3t
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

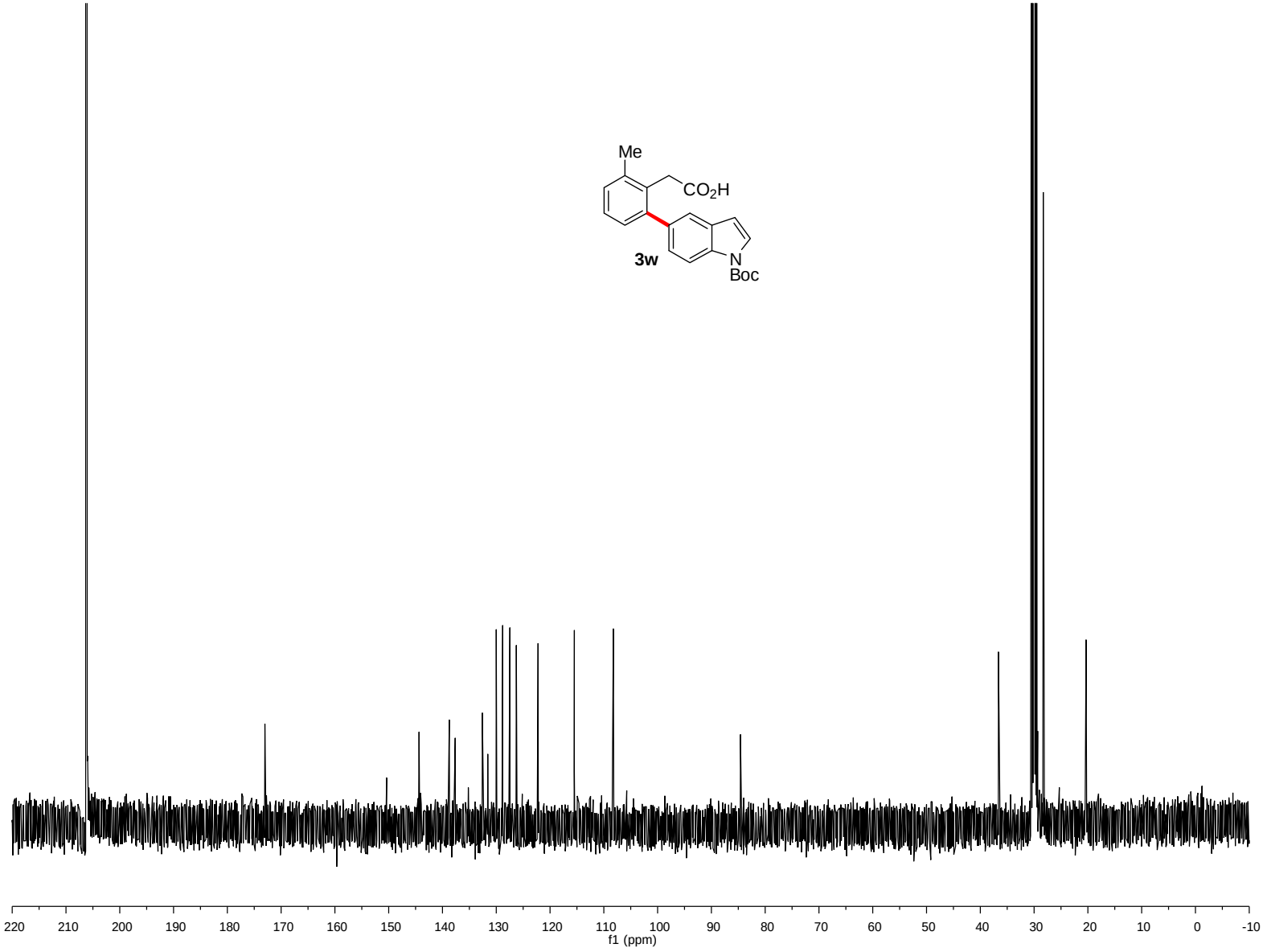

Me
CO2H
F
3u
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


Me
CO2H
F
3u
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
CO2H
3v
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
-0.5
f1 (ppm)


Me
CO2H
3v
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
CO2H
3w
N
Boc
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
-0.5
f1 (ppm)


Me
CO2H
3w
N
Boc
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)