Ligand-Accelerated C–H Activation Reactions: Evidence for a Switch of Mechanism

Keary M. Engle, Dong-Hui Wang, and Jin-Quan Yu*

Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA.

SUPPORTING INFORMATION

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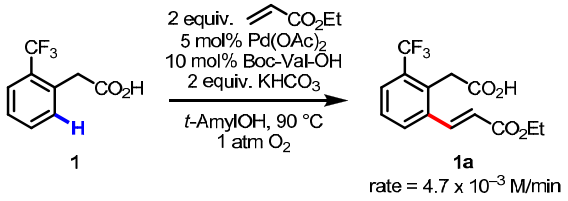
General Information: Unless otherwise noted, all materials were used as received from commercial sources without further purification. The phenylacetic acid substrates and olefin coupling partners were purchased from Acros, Sigma-Aldrich, TCI and Alfa-Aesar and were used as received. 2-(Trifluoromethyl)phenylacetic acid (**1**) was purchased from TCI; samples of **1** from other commercial sources were found to give irreproducible results. 1,4-Benzoquinone (BQ) was sublimed prior to used. Freshly distilled methyl vinyl ketone was used in the synthesis of **1g**. Commercially available organic acid ligands were purchased from Acros, Sigma Aldrich, and Alfa Aesar. In the optimization studies **5a** was used as a ligand; its synthesis is described herein. Commercially available amino acid ligands were purchased from Bachem, EMD, or Novabiochem. **L4** was prepared according to a method developed by Burgess.[1] **L6** was prepared according to a literature procedure.[2] All others were prepared following literature precedent.[3,4] 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 Mercury (300 MHz and 75 MHz, respectively), Varian Inova (400 MHz and 100 MHz, respectively) and Bruker DRX (500 MHz and 125 MHz, respectively) instruments internally referenced to $SiMe_4$ 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. High resolution mass spectra were recorded at the Center for Mass Spectrometry, The Scripps Research Institute.

Experimental:

Initial Rate Measurements:

General procedure for determining the initial reaction rate for C–H olefination of 1 (or 2) under different conditions: Four different reaction conditions were examined: (1) without Boc-Val-OH, without BQ, (2) without Boc-Val-OH, with BQ, (3) with Boc-Val-OH, without BQ, (4) with Boc-Val-OH, with BQ. To establish the initial rate under each of the conditions, four parallel reactions were set up simultaneously. Four 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) were obtained, each equipped with a magnetic stir bar. Each tube was charged with **1** (or **2**) (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), BQ (2.7 mg, 0.025 mmol) (when used), Boc-Val-OH (10.9 mg, 0.05 mmol) (when used), ethyl acrylate (106 μL, 1.0 mmol), and *t*-AmylOH (2.5 mL). The reaction tubes were capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixtures were stirred at room temperature for 5 min, then at 90 °C for the appropriate time. At regular intervals (every 5 minutes, or every 30 minutes), one of the reactions would be removed from the hot plate and cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) and diethyl ether (10 mL) were then 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 **1**, 4.01 ppm for **1a**¸ 3.67 ppm for **2**, and 3.84 ppm for **2a**). For each condition, this process was repeated three times. The resulting data was plotted, and linear regression

established the initial rate. Representative data for the determination of one initial rate are shown in Figure S1.



Entry[a]	Time (min)	% Conv. (T1)	% Conv. (T2)	% Conv. (T3)	Average	Std. Dev.
1	0	0.0	0.0	0.0	0.0	0.0
2	5	8.7	7.3	6.7	7.6	1.0
3	10	13.3	17.5	27.9	19.6	7.5
4	15	33.3	26.2	42.4	34.0	8.1
5	20	50.8	43.1	43.7	45.9	4.3

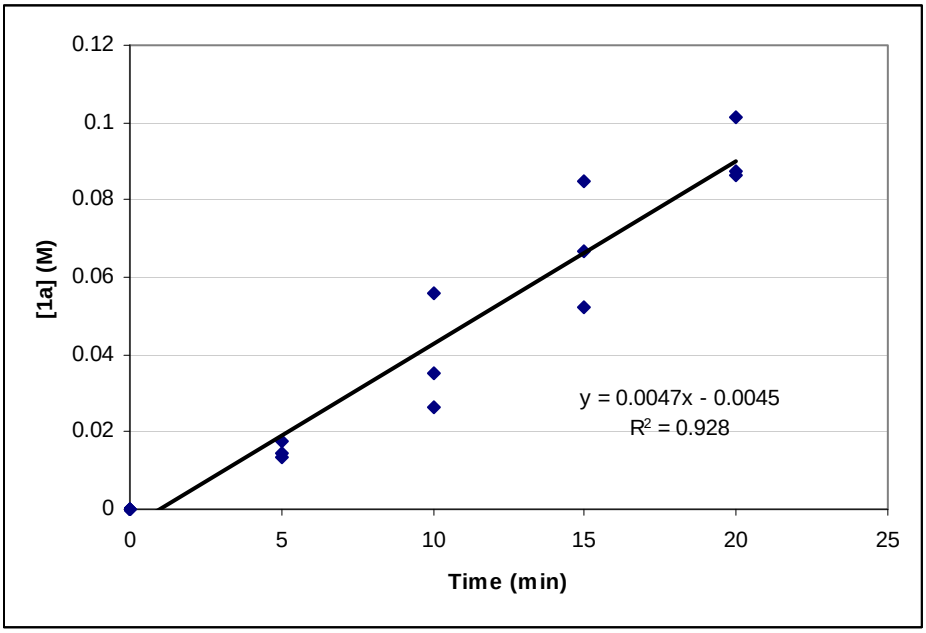
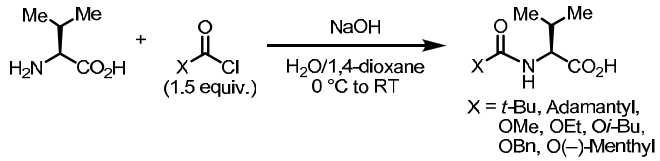


Figure S1: Representative initial rate data for C–H olefination of **1** with Boc-Val-OH and without BQ.

Synthesis of New Ligands:

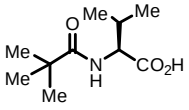


Scheme S1: General procedure for *N*-protection for L-valine.

General procedure for the synthesis of mono-*N*-protected L-valine ligands:[3,4] A 500 mL round bottom flask equipped with a magnetic stir bar was charged with distilled H_2O (100 mL) and NaOH (100 mmol, 4.0 g). The resulting solution was cooled to 0 °C in an ice bath. L-valine (35 mmol, 4.1 g) was added, and the solution was stirred until it was homogeneous. The flask was equipped with an addition funnel. The corresponding carbonyl chloride (45.5 mmol) in 1,4-dioxane (40 mL) was added dropwise. The reaction mixture was then allowed to stir at room temperature overnight. The following morning, the solution was extracted with Et_2O (3 × 50 mL), and the organic layers were discarded. The aqueous layer was again cooled to 0 °C in an ice bath, and concentrated HCl was added dropwise until the pH had reached 2 (as observed by pH paper). The aqueous solution was extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to give the crude product. The pure product was obtained following recrystallization from Et_2O/hexanes or column chromatography using 15:1 DCM:MeOH as the solvent system. For a general depiction of this procedure, see Scheme S1.

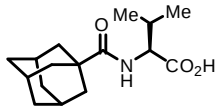
Characterization of New Ligands:

N-Carbamoyl-protected amino acids are known to exist as *syn*- and *anti*-rotamers,[5] with the latter being more thermodynamically stable than the former. In the ^1H and ^{13}C NMR spectra of MeO_2C-Val-OH, EtO_2C-Val-OH, *i*-BuO_2C-Val-OH, Cbz-Val-OH, and Men-Val-OH, we detected both rotamers, generally observing <10% of the *syn*-rotamers in solution at room temperature. For simplicity, the ^1H and ^{13}C NMR spectral data described below correspond exclusively to the *anti*-rotamers.



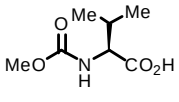
Piv-Val-OH

(*S*)-3-methyl-2-pivalamidobutanoic acid (Piv-Val-OH): The title compound was obtained as a white solid (4.1 g, 58% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.18 (br, 1 H), 4.56 (dd, J_1 = 8.0 Hz, J_2 = 4.8 Hz, 1 H), 2.29–2.21 (m, 1 H), 1.23 (s, 9 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.09, 175.94, 56.93, 38.91, 30.98, 27.42, 19.00, 17.67; **IR** (neat) ν 3376, 2964, 2875, 1725, 1625, 1518, 1486, 1403, 1370, 1198, 1141, 917, 840 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{10}H_{19}NO_3$ $[M+H]^+$ 202.1438, found 202.1447.



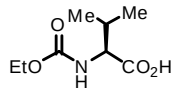
Ada-Val-OH

(*S*)-3-methyl-2-adamantanecarbonylamidobutanoic acid (Ada-Val-OH): The title compound was obtained as a white solid (3.7 g, 75% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.11 (br, 1 H), 4.51 (dd, J_1 = 8.0 Hz, J_2 = 5.2 Hz, 1 H), 2.30–2.22 (m, 1 H), 2.06 (s, 3 H), 1.90–1.86 (m, 6 H), 1.77–1.69 (m, 6 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.96 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.96, 56.96, 40.83, 39.12, 36.41, 30.71, 28.02, 19.07, 17.77; **IR** (neat) ν 3375, 2962, 2906, 2852, 1728, 1624, 1520, 1301, 1207, 1147, 1110, 984 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{25}NO_3$ $[M+H]^+$ 280.1907, found 280.1915.



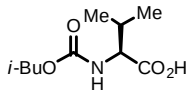
MeO_2C-Val-OH

(*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (MeO_2C-Val-OH): The title compound was obtained as a white solid (4.1 g, 67% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.17 (br, 1 H), 4.33 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1 H), 3.70 (s, 3 H), 2.28–2.20 (m, 1 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.97, 157.08, 58.78, 52.50, 30.96, 18.98, 17.29; **IR** (neat) ν 3324, 2966, 1695, 1526, 1466, 1373, 1304, 1214, 1098, 1041, 1021, 840, 778 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_7H_{13}NO_4$ $[M+H]^+$ 176.0917, found 176.0918.



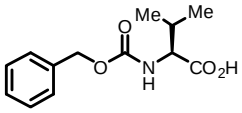
EtO_2C-Val-OH

(*S*)-2-(ethoxycarbonylamino)-3-methylbutanoic acid (EtO_2C-Val-OH): The title compound was obtained as a colorless oil (3.9 g, 59% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.13 (br, 1 H), 4.33 (dd, J_1 = 8.8 Hz, J_2 = 4.8 Hz, 1 H), 4.15 (q, J = 6.8 Hz, 2 H), 2.28–2.20 (m, 1 H), 1.26 (t, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.81, 156.69, 61.36, 58.68, 30.98, 18.99, 17.31, 14.45; **IR** (neat) ν 3323, 2967, 2936, 1693, 1523, 1419, 1382, 1343, 1303, 1216, 1098, 1030, 871, 778 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_8H_{15}NO_4$ $[M+H]^+$ 190.1074, found 190.1073.



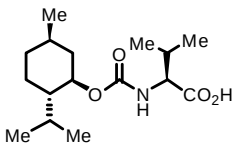
***i*-BuO_2C-Val-OH**

(*S*)-2-(isobutoxycarbonylamino)-3-methylbutanoic acid (*i*-BuO_2C-Val-OH): The title compound was obtained as a colorless oil (7.4 g, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.16 (br, 1 H), 4.33 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1 H), 3.86 (d, J = 6.8 Hz, 2 H), 2.26–2.18 (m, 1 H), 1.97–1.87 (m, 1 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.81, 156.83, 71.47, 58.71, 31.03, 27.93, 18.96, 17.34; **IR** (neat) ν 3323, 2964, 2876, 1705, 1516, 1468, 1421, 1217, 1095, 1036, 777 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{10}H_{19}NO_4$ $[M+H]^+$ 218.1387, found 218.1380.



Cbz-Val-OH

(*S*)-2-(benzyloxycarbonylamino)-3-methylbutanoic acid (Cbz-Val-OH): The title compound was obtained as a colorless oil (8.4 mg, 96% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5 H), 5.25 (br, 1 H), 5.12 (s, 2 H), 4.36 (dd, J_1 = 9.2 Hz, J_2 = 4.8 Hz, 1 H), 2.28–2.20 (m, 1 H), 1.01 (d, 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.99, 156.35, 136.05, 128.52, 128.23, 128.14, 67.20, 58.81, 31.02, 18.98, 17.32; **IR** (neat) ν 3321, 2966, 2936, 1705, 1514, 1454, 1413, 1346, 1302, 1214, 1094, 1026, 909, 731 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{13}H_{17}NO_4$ $[M+H]^+$ 252.1230, found 252.1233.



Men-Val-OH

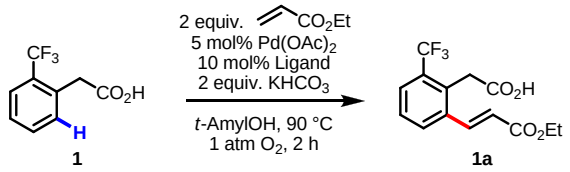
(*S*)-2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)carbonylamino)-3-methylbutanoic acid (Men-Val-OH): The title compound was obtained as a white solid (6.0 g, 57% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.10 (br, 1 H), 4.58–4.54 (m, 1 H), 4.33 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1 H), 2.26–2.18 (m, 1 H), 2.02 (ad, J = 12.0 Hz, 1 H), 1.98–1.86 (m, 1 H), 1.66 (ad, J = 12.0 Hz, 2 H), 1.53–1.41 (m, 1 H), 1.31 (at, J = 12.0 Hz, 1 H), 1.09–0.99 (m, 2 H), 1.01 (d, J = 6.8 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.90–0.83 (m, 7 H), 0.76 (d, J = 6.8 Hz, 3

H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.22, 156.41, 75.16, 58.71, 47.33, 41.27, 34.25, 31.35, 31.07, 26.11, 23.45, 22.02, 20.77, 19.04, 17.37, 16.34; **IR** (neat) ν 3319, 2958, 2929, 2871, 1713, 1665, 1513, 1456, 1414, 1305, 1224, 1094, 1027, 983, 909 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{29}NO_4$ $[M+H]^+$ 300.2169, found 300.2167.

Optimization Studies:

Ligand optimization for Pd(II)-catalyzed olefination with 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 **1** (102.1 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), ligand (0.05 mmol), ethyl acrylate (106 µL, 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). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for the appropriate time. The reaction vessel was removed from the oil bath and immediately 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 **1** and 4.01 ppm for **1a**). When indicated, the reactions were performed in triplicates, and the values shown represent the average result from the three experiments. In our initial efforts, we measured the conversion after 2 h (Table S1), but we observed quantitative conversion for many ligands. We then adjusted our assay and examined the conversion after 20 min (Tables S2 and S3).

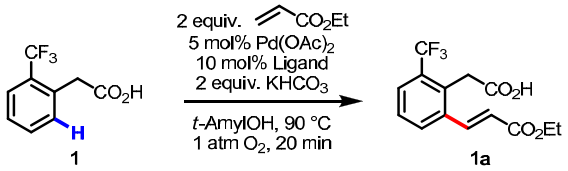
Table S1: Initial results from the amino acid ligand optimization experiments.[a]



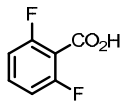
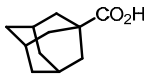
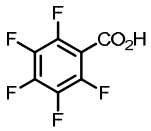
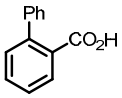
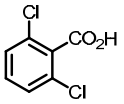
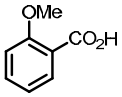
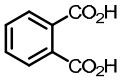
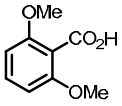
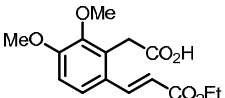
Entry	Ligand	% Conv.	Entry	Ligand	% Conv.
1	---	7[b]	8	Boc-Ser-OH	16
2	Boc-Val-OH	98 (96)	9	Ac-Val-OH	>99
3	Boc-Ile-OH	98	10	Ac-Ile-OH	>99 (96)
4	Boc-Leu-OH	92	11	Ac-Leu-OH	>99
5	Boc-*t*-Leu-OH	98	12	Formyl-Ile-OH	36
6	Boc-Ala-OH	88	13	Formyl-Leu-OH	37
7	Boc-Phe-OH	96	14	Men-Leu-OH[c]	71

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parentheses. [b] Average of three trials. [c] Men = (–)-Menthyl(O_2C).

Table S2: Results from the organic acid ligand optimization experiments.[a]



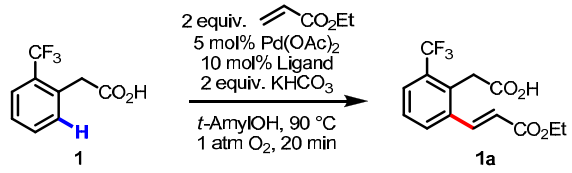
1 **1a**

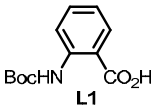
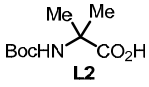
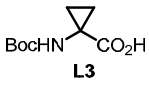
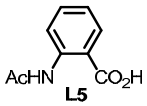
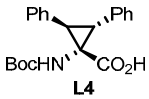
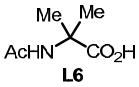
Entry	Ligand	% Conv.	Entry	Ligand	% Conv.
1	—	<5			
2	*p*-TsOH•H_2O	0	8		<5
3	PivOH	<5			
4		<5	9		<5
5		<5	10		0
6		<5	11		<5
7		<5	12		<5

5a

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

Table S3: Results from the amino acid ligand optimization experiments.[a]



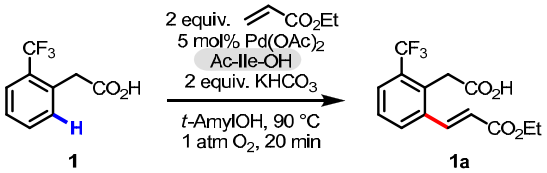
Entry	Ligand	% Conv.	Entry	Ligand	% Conv.
1	—	<5	17	H-Val-OH	0
2	BQ	<5	18	Ac-Val-OH	57
3	Boc-Val-OH	46[b]	19	Ada-Val-OH[c]	4
4	Boc-Ile-OH	37	20	Piv-Val-OH	2
5	Boc-Leu-OH	37	21	Formyl-Val-OH	31
6	Boc-*t*-Leu-OH	38	22	Fmoc-Val-OH	19
7	Boc-Nva-OH	30	23	MeO_2C-Val-OH	21
8	Boc-Ala-OH	28	24	EtO_2C-Val-OH	26
9	Boc-Gly-OH	17	25	*i*-BuO_2C-Val-OH	27
10	Boc-Phe-OH	33	26	Cbz-Val-OH	18
11	Boc-Ser-OH	8	27	Bz-Val-OH	3
12	Boc-β-Ala-OH	8	28	Men-Val-OH[d]	39
13	 **L1**	6	29	Ac-Leu-OH	55
			30	Ac-Ala-OH	71
			31	Ac-Gly-OH	51
14	 **L2**	21	32	Ac-Ile-OH	72[b]
			33	Ac-Phe-OH	60
15	 **L3**	5	34	 **L5**	5
16	 **L4**	16	35	 **L6**	31

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Average of three trials. [c] Ada = Adamantyl(OC). [d] Men = (–)-Menthyl(O_2C).

Additional optimization for Pd(II)-catalyzed olefination with 2-(Trifluoromethyl)phenylacetic acid (1): The effects of ligand loading (Table S4), olefin loading (Table S5), and reaction temperature (Tables S6–S10) were explored using Ac-Ile-OH as the ligand. 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 **1** (102.1 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), Ac-Ile-OH, ethyl acrylate, 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). The reaction mixture was stirred at room temperature for 5 min, then at the appropriate temperature for the indicated time. The reaction vessel was then 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 **1** and 4.01 ppm for **1a**). When indicated, the reactions were performed in triplicates, and the values shown represent the average result from the three experiments.

Table S4: Optimization of ligand loading.[a]

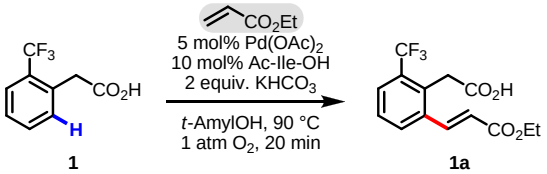


1 **1a**

Entry	Ac-Ile-OH	% Conv.
1	---	<5[b]
2	2.5 mol%	56
3	5 mol%	73
4	10 mol%	72[b]
5	15 mol%	74

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parenthesis. [b] Average of three trials.

Table S5: Optimization of olefin loading.[a]

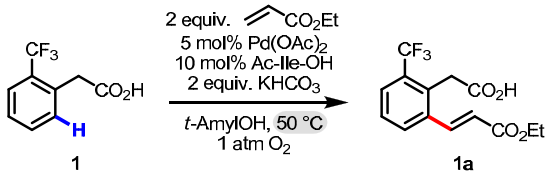


1 **1a**

Entry	CO$_2$Et	% Conv.
1	1 equiv.	48[b]
2	2 equiv.	46[b]
3	3 equiv.	21[b]

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parenthesis. [b] Average of three trials.

Table S6: Conversion versus time at 50 °C.[a]

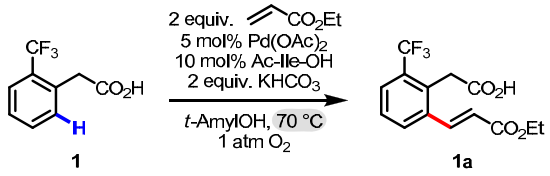


1 **1a**

Entry	Time (h)	% Conv.
1	0	0
2	1	6
3	8	37
4	24	85
5	48	96

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

Table S7: Conversion versus time at 70 °C.[a]

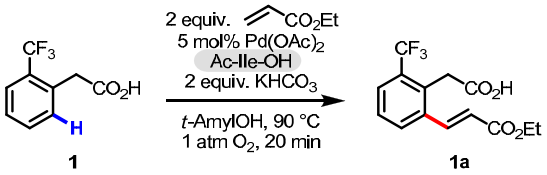


1 **1a**

Entry	Time (h)	% Conv.
1	0	0
2	1	54
3	2	84
4	3	94
5	4	96

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

Table S8: Conversion versus time at 90 °C.[a]

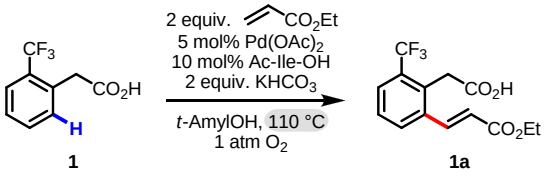


1 **1a**

Entry	Ac-Ile-OH	% Conv.
1	---	<5[b]
2	2.5 mol%	56
3	5 mol%	73
4	10 mol%	72[b]
5	15 mol%	74

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture. Isolated yield is given in parenthesis. [b] Average of three trials.

Table S9: Conversion versus time at 110 °C.[a]

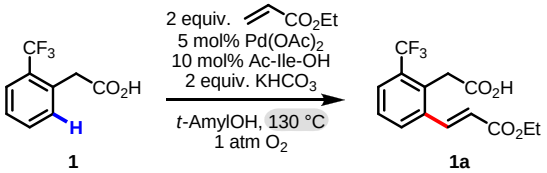


1 **1a**

Entry	Time (min)	% Conv.
1	0	0
2	5	27
3	10	66
4	15	88
5	20	93

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

Table S10: Conversion versus time at 130 °C.[a]

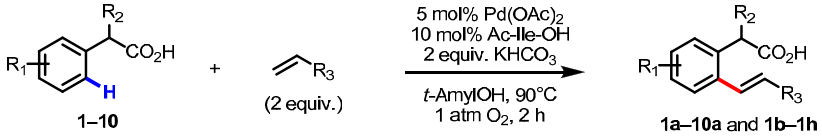


1 **1a**

Entry	Time (min)	% Conv.
1	0	0
2	10	11
3	20	36

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

General Procedure:

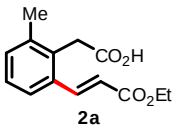


Scheme S2: General procedure for C–H olefination of phenylacetic acids.

General procedure for Pd(II)-catalyzed *ortho*-C–H olefination of phenylacetic acids 1–10: 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 the phenylacetic acid starting material (**1–10**) (0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), ligand (0.05 mmol), the olefin coupling partner (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). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for 2 h (longer, when noted). The reaction vessel was then cooled to 0 °C in an ice bath. A 2.0 N HCl solution (5 mL) was then added, and the mixture was extracted with EtOAc (3 × 20 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 3:1 hexanes:EtOAc (with 3% HOAc) as the eluent. For a general depiction of this procedure, see Scheme S2.

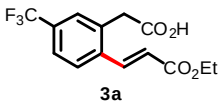
Characterization of New C–H Olefinated Products:

Our group has previously reported analytical data for **1a**, **5a**, **6a**, and **8a'**.[6] In this same publication, **7a**, **9a**, and **10a** 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. 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 **7a**, **9a**, and **10a**.



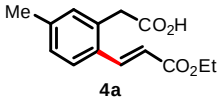
2a

(*E*)-2-(2-(3-ethoxy-3-oxoprop-1-enyl)-6-methylphenyl)acetic acid (2a): The title compound was obtained as a white solid (122 mg, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (d, J = 15.6 Hz, 1 H), 7.42, (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1 H), 7.24–7.18 (m, 2 H), 6.33 (d, J = 15.6 Hz, 1 H), 4.26 (q, J = 7.2 Hz, 2 H), 3.84 (s, 2 H), 2.34 (s, 3 H), 1.33 (t, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.45, 166.83, 142.47, 138.03, 134.75, 131.96, 131.50, 127.69, 124.92, 121.10, 60.61, 34.67, 20.21, 14.26; **IR** (neat) ν 2981, 2935, 1704 (br), 1631, 1446, 1368, 1313, 1269, 1237, 1179, 1162 (br), 1093, 1035, 979, 788 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1121, found 249.1124.



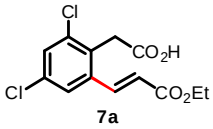
3a

(*E*)-2-(2-(3-ethoxy-3-oxoprop-1-enyl)-5-(trifluoromethyl)phenyl)acetic acid (3a): The title compound was obtained as a white solid (147 mg, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.91 (d, J = 15.6 Hz, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.55 (s, 1 H), 6.43 (d, J = 15.6 Hz, 1 H), 4.28 (q, J = 7.2 Hz, 2 H), 3.87 (s, 2 H), 1.34 (t, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.95, 166.29, 140.01, 137.74, 133.40, 131.69 (q, J_{C-F} = 32.7 Hz), 128.02 (q, J_{C-F} = 3.7 Hz), 127.47, 124.90 (q, J_{C-F} = 3.7 Hz), 123.60 (q, J_{C-F} = 270.7 Hz), 122.24, 60.98, 38.23, 14.22; **IR** (neat) ν 2987, 2932, 1715 (br), 1638, 1422, 1335, 1283, 1222, 1167 (br), 1127, 1080, 1035, 979 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{14}F_3O_4$ $[M+H]^+$ 303.0839, found 303.0844.



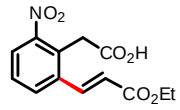
4a

(*E*)-2-(2-(3-ethoxy-3-oxoprop-1-enyl)-5-methylphenyl)acetic acid (4a): The title compound was obtained as a colorless oil (103 mg, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J = 15.6 Hz, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.12 (d, J = 8.0 Hz, 1 H), 7.09 (s, 1 H), 6.34 (d, J = 15.6 Hz, 1 H), 4.25 (q, J = 7.2 Hz, 2 H), 3.77 (s, 2 H), 2.35 (s, 3 H), 1.32 (t, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.44, 167.01, 141.31, 140.54, 132.79, 131.87, 131.14, 128.92, 126.83, 119.53, 60.56, 38.31, 21.26, 14.27; **IR** (neat) ν 2982, 2927, 1708 (br), 1632, 1610, 1368, 1315, 1283, 1179 (br), 1159, 1095, 1035, 979, 816 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{17}O_4$ $[M+H]^+$ 249.1121, found 249.1118.



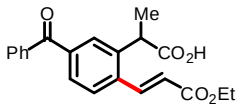
7a

(*E*)-2-(2,4-dichloro-6-(3-ethoxy-3-oxoprop-1-enyl)phenyl)acetic acid (7a): The title compound was obtained as a white solid (150 mg, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, J = 15.6 Hz, 1 H), 7.45 (s, 2 H), 6.35 (d, J = 15.6 Hz, 1 H), 4.27 (q, J = 7.2 Hz, 2 H), 3.69 (s, 2 H), 1.33 (t, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.83, 166.03, 139.96, 137.75, 136.67, 134.17, 130.21, 129.49, 125.72, 123.73, 61.05, 34.83, 14.21; **IR** (neat) ν 2982, 2930, 1708 (br), 1637, 1584, 1553, 1446, 1398, 1368, 1310, 1274, 1237, 1178 (br), 1153, 1031, 972, 911, 859 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{13}H_{13}Cl_2O_4$ $[M+H]^+$ 303.0190, $[(M+2)+H]^+$ 305.0161, $[(M+4)+H]^+$ 307.0132, found 303.0188, 305.0160, 307.0140 $[M+H]^+$: $[(M+2)+H]^+$: $[(M+4)+H]^+$= 9:6:1.



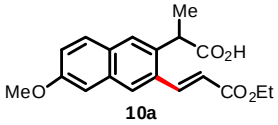
8a

(*E*)-2-(2-(3-ethoxy-3-oxoprop-1-enyl)-6-nitrophenyl)acetic acid (8a): The title compound was obtained as a white solid (98 mg, 70% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.6 Hz, 1 H), 7.92 (d, *J* = 15.6 Hz, 1 H), 7.78 (d, *J* = 7.6 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 6.38 (d, *J* = 15.6 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.08 (s, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.40, 165.93, 150.32, 140.10, 137.86, 132.00, 128.61, 127.26, 125.83, 124.68, 61.15 34.36, 14.22; **IR** (neat) ν 3089, 2985, 1710 (br), 1638, 1607, 1529, 1351, 1317, 1185 (br), 1032, 975, 894, 808, 744 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{13}H_{14}NO_6$ $[M+H]^+$ 280.0816, found 280.0822.



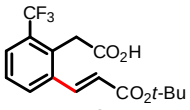
9a

(*E*)-2-(5-benzoyl-2-(3-ethoxy-3-oxoprop-1-enyl)phenyl)propanoic acid (9a): The title compound was obtained as a viscous yellow oil (188 mg, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 15.6 Hz, 1 H), 7.83–7.45 (m, 8 H), 6.44 (d, *J* = 15.6 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.20 (q, *J* = 7.2 Hz, 1 H), 1.55 (d, *J* = 7.2 Hz, 3 H), 1.35 (t, *J* = 6.8 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.66, 178.57, 166.28, 140.56, 139.19, 138.64, 137.38, 137.06, 132.74, 130.05, 129.33, 129.18, 128.37, 127.23, 123.40, 60.91, 40.92, 18.02, 14.27; **IR** (neat) ν 2982, 2938, 1708 (br), 1657, 1635, 1598, 1447, 1410, 1368, 1314, 1272, 1217, 1178 (br), 1031, 960, 843, 754, 721 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{21}H_{21}O_5$ $[M+H]^+$ 353.1383, found 353.1388.



10a

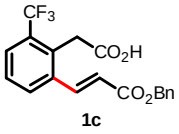
(*E*)-2-(3-(3-ethoxy-3-oxoprop-1-enyl)-6-methoxynaphthalen-2-yl)propanoic acid (10a): The title compound was obtained as a viscous yellow oil (153 mg, 93% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 15.6 Hz, 1 H), 7.92 (s, 1 H), 7.72 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 7.14 (d, *J* = 9.2 Hz, 1 H), 7.09 (s, 1 H), 6.46 (d, *J* = 15.6 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 4.21 (q, *J* = 6.8 Hz, 1 H), 3.92 (s, 3 H), 1.59 (d, *J* = 6.8 Hz, 3 H), 1.35 (t, *J* = 7.2, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.98, 166.70, 158.08, 142.39, 133.98, 133.42, 132.44, 129.53, 129.14, 126.11, 125.92, 121.53, 120.18, 105.56, 60.66, 55.30, 41.03, 18.31, 14.28; **IR** (neat) ν 2980, 2934, 1704 (br), 1634, 1600, 1499, 1465, 1397, 1368, 1301, 1266, 1207, 1166 (br), 1029, 975, 896, 866, 811 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{19}H_{21}O_5$ $[M+H]^+$ 329.1383, found 329.1378.



1b

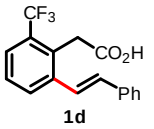
(*E*)-2-(2-(3-tert-butoxy-3-oxoprop-1-enyl)-6-(trifluoromethyl)phenyl)acetic acid (1b): The title compound was obtained as a white solid (163 mg, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 15.6 Hz, 1 H), 7.73 (d, *J* = 7.6 Hz, 1 H), 7.70 (d, *J* = 7.6 Hz, 1 H), 7.43 (t, *J* = 7.6 Hz, 1 H), 6.31 (d, *J* = 15.6 Hz, 1 H), 4.01 (s, 2 H), 1.53 (s, 9 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.21, 165.63, 139.64, 137.37, 130.88, 130.61, 130.16 (q, J_{C-F} = 29.5 Hz), 127.88, 127.06 (q, J_{C-F} = 5.6 Hz), 124.66, 124.02 (q, J_{C-F} = 272.6 Hz), 81.28, 34.21, 28.07; **IR** (neat) ν 2981, 2935, 1710 (br), 1637, 1454,

1324 (br), 1149, 1119, 1099, 981, 961, 842, 806, 752 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{16}H_{17}F_3O_4Na$ $[M+Na]^+$ 353.0971, found 353.0977.



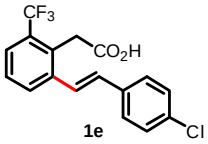
1c

(*E*)-2-(2-(3-(benzyloxy)-3-oxoprop-1-enyl)-6-(trifluoromethyl)phenyl)acetic acid (1c): The title compound was obtained as a white solid (165 mg, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 16.0 Hz, 1 H), 7.74 (d, *J* = 7.6, 1 H), 7.72 (d, *J* = 8.0, 1 H), 7.46–7.34 (m, 6 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 5.25 (s, 2 H), 4.01 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.29, 166.06, 141.15, 137.06, 135.65, 131.00, 130.63, 130.25 (q, *J* = 29.6 Hz), 128.58, 128.44, 128.32, 128.27, 127.38 (q, *J* = 5.7 Hz), 123.96 (q, *J* = 272.3 Hz), 122.77, 66.71, 34.18; **IR** (neat) ν 3034, 2962, 1702 (br), 1455, 1422, 1372, 1315, 1275, 1239, 1163 (br), 1110, 1004, 975, 963, 804, 748 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{19}H_{16}F_3O_4$ $[M+H]^+$ 365.0995, found 365.0997.



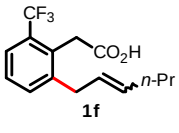
1d

(*E*)-2-(2-styryl-6-(trifluoromethyl)phenyl)acetic acid (1d): The title compound was obtained as a white solid (153 mg, 99% yield). **^{1}H NM**R (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.6, 1 H), 7.56 (d, *J* = 7.6, 1 H), 7.44–7.17 (m, 7 H) 6.92 (d, *J* = 16.0 Hz, 1 H), 3.95 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.53, 140.21, 136.61, 134.05, 130.29, 129.79 (q, J_{C-F} = 29.3 Hz), 129.40, 128.78, 128.35, 127.81, 126.82, 125.18 (q, J_{C-F} = 5.7 Hz), 124.71, 124.27 (q, J_{C-F} = 272.8 Hz), 34.58; **IR** (neat) ν 3026, 1708 (br), 1495, 1455, 1412, 1315 (br), 1155, 1114, 1098, 957, 798, 749 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}F_3O_2$ $[M+H]^+$ 307.0940, found 307.0941.



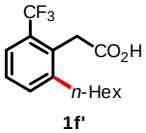
1e

(*E*)-2-(2-(4-chlorostyryl)-6-(trifluoromethyl)phenyl)acetic acid (1e): The title compound was obtained as a white solid (111 mg, 65% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.45–7.32 (m, 5 H), 7.22 (d, *J* = 16.0 Hz, 1 H), 6.93 (d, *J* = 16.0 Hz, 1 H), 4.00 (s, 2 H); **^{13}C NM**R (100 MHz, $(CD_3)_2CO$) δ 171.51, 140.93, 136.90, 134.07, 134.07, 1332.07, 132.59, 132.19, 131.02, 130.15 (q, J_{C-F} = 28.9 Hz), 129.62, 129.27, 128.49, 126.70, 125.88 (q, J_{C-F} = 5.9 Hz), 125.61 (q, J_{C-F} = 272.0 Hz), 34.94; **IR** (neat) ν 3034, 2962, 1702 (br), 1634, 1455, 1422, 1372, 1315, 1275, 1239, 1163 (br), 1099, 1004, 975, 963, 804, 748 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{17}H_{13}ClF_3O_2$ $[M+H]^+$ 341.0551, $[(M+2)+H]^+$ 343.0527, found 341.0556, 343.0527 $[M+H]^+$: $[(M+2)+H]^+$ = 3:1.



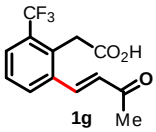
1f

2-(2-(hex-2-enyl)-6-(trifluoromethyl)phenyl)acetic acid (1f): The title compound was obtained as an inseparable mixture of the *E*- and *Z*-stereoisomers (89 mg, 62% yield). By ^{1}H NMR, the *E*:*Z* ratio was determined to be approximately 4:1. The ^{1}H NMR data reported here represent only the major isomer. Following hydrogenation, **1f** was converted to **1f'**, and a complete set of analytical data were collected (included below). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 5.53–5.39 (m, 2 H), 3.93 (s, 2 H), 3.36 (d, *J* = 6.0 Hz, 2 H), 1.98 (aq, *J* = 7.2 Hz, 2 H), 1.44–1.32 (m, 2 H), 0.88 (t, *J* = 7.2 Hz, 3 H).



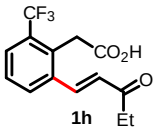
1f'

2-(2-hexyl-6-(trifluoromethyl)phenyl)acetic acid (1f'): To a 25 mL round bottom flask equipped with a stir bar were added **1f** (72.5 mg, 0.25 mmol), MeOH (10 mL), and Pd/C (10 wt%) (2.7 mg, 0.0025 mmol). The flask was evacuated under vacuum, then capped under H_2 (1 atm, balloon). After 6 h, the solution was filtered through a pad of Celite. The title compound was obtained as a colorless oil (71 mg, 99% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 3.89 (s, 2 H), 2.60 (t, J = 7.8 Hz, 2 H), 1.62–1.51 (m, 2 H), 1.40–1.24 (m, 6 H), 0.89 (t, J = 6.6 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.09, 144.06, 132.96, 129.87, 129.54 (q, $J_{C–F}$ = 28.9 Hz), 127.36, 124.48 (q, $J_{C–F}$ = 272.5 hz), 123.76 (q, $J_{C–F}$ = 5.7 Hz), 34.10, 32.89, 31.64, 30.55, 29.25, 22.55, 14.02; **IR** (neat) ν 2929, 2856, 1713 (br), 1462, 1412, 1316, 1157, 1116 (br), 1094, 954, 803 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{15}H_{20}F_3O_2$ $[M+H]^+$ 289.1410, found 289.1409.



1g

(*E*)-2-(2-(3-oxobut-1-enyl)-6-(trifluoromethyl)phenyl)acetic acid (1g): The title compound was obtained as an amorphous off-white solid (123 mg, 90% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 3 H), 7.46 (t, J = 8.0 Hz, 1 H), 6.64 (d, J = 16.0 Hz, 1 H), 4.01 (s, 2 H), 2.38 (s, 3 H); **^{13}C NMR** (100 MHz, $(CD_3)_2CO$) δ 197.90, 171.27, 139.72, 138.66, 133.64, 132.04, 131.75, 130.40 (q, $J_{C–F}$ = 29.2 Hz), 128.80, 127.88 (q, $J_{C–F}$ = 5.9 Hz), 125.39 (q, $J_{C–F}$ = 272.0 Hz), 34.84, 27.72; **IR** (neat) ν 2923, 1746 (br), 1719 (br), 1604, 1467, 1321, 1245, 1155, 1115 (br), 1050, 986, 800 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{13}H_{12}F_3O_3$ $[M+H]^+$ 273.0733, found 273.0740.



1h

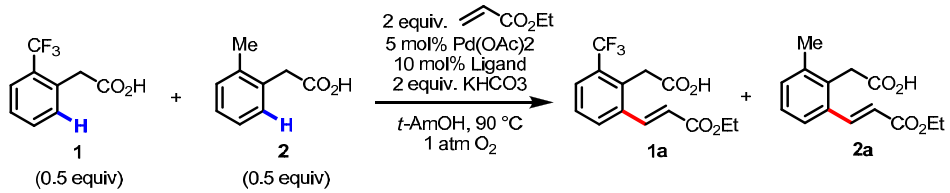
(*E*)-2-(2-(3-oxopent-1-enyl)-6-(trifluoromethyl)phenyl)acetic acid (1h): The title compound was obtained as an amorphous off-white solid (138 mg, 97% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 16.0 Hz, 1 H), 7.76–7.71 (m, 2 H), 7.45 (t, J = 8.0 Hz, 1 H), 6.66 (d, J = 16.0 Hz, 1 H), 4.01 (s, 2 H), 2.69 (q, J = 7.2 Hz, 2 H), 1.16 (t, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, ($CDCl_3$) δ 200.59, 175.18, 138.03, 137.40, 131.16, 130.59, 130.33, 130.27 (q, $J_{C–F}$ = 29.5 Hz), 128.01, 127.34 (q, $J_{C–F}$ = 5.7 Hz), 123.97 (q, $J_{C–F}$ = 273.0 Hz), 34.53, 34.25, 7.93; **IR** (neat) ν 2982, 2943, 1716, 1671, 1614, 1454, 1319, 1188, 1159, 1119, 1100, 1042, 973, 808 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_{14}H_{14}F_3O_3$ $[M+H]^+$ 287.0890, found 287.0902.

Competition Experiments:

Procedure for intermolecular competition experiments between compounds 1 and 2: 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 **1** (51.1 mg, 0.25 mmol), **2** (37.6 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $KHCO_3$ (100.1 mg, 1.0 mmol), ligand (0.05 mmol), ethyl acrylate (106 µL, 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). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for the appropriate time. The reaction vessel was then 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 **1**, 4.01 ppm for **1a**, 3.67 ppm for **2**, and 3.84 ppm for **2a**). The results are shown in Table S11.

Table S11: Competition experiments between **1** and **2**.[a]

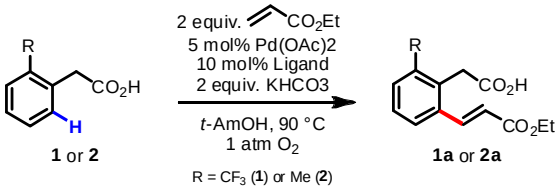


Entry[a]	Ligand	Time (min)	% Conv. **1a**	% Conv. **2a**	k_1 ([M]/min)	k_2 ([M]/min)	k_1 / k_2
1	—	120	3.0	13.9	2.5×10^{-5}	1.2×10^{-4}	0.22
2	Boc-Val-OH	10	17.6	30.5	1.8×10^{-3}	3.1×10^{-3}	0.58
3	Ac-Ile-OH	10	40.0	21.4	4.0×10^{-3}	2.1×10^{-3}	1.87

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

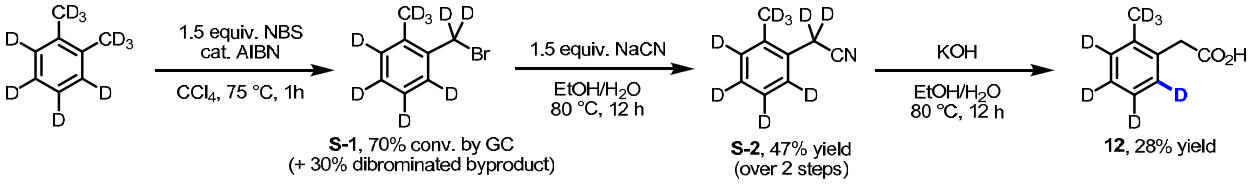
Procedure for initial rate studies for single-component reactions of 1 and 2: The procedure for reactions run with and without Boc-Val-OH is described on page S-2. An identical protocol was followed to determine the initial rate in the presence of Ac-Ile-OH (8.7 mg, 0.05 mmol), with reactions stopped at 5 min, 7.5 min, 10 min, and 15 min. The reactions were repeated three times, and determination of the initial rate was performed using linear regression. The overall results are shown in Table S12.

Table S12: Results from the single-component initial rate studies for reactions with **1** and **2**. For an example data set, see Table S1.

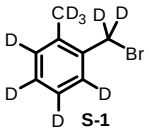


Entry[a]	Ligand	k_1 ([M]/min)	k_2 ([M]/min)	k_1 / k_2
1	---	1.3×10^{-4}	3.5×10^{-4}	0.37
2	Boc-Val-OH	4.7×10^{-3}	5.2×10^{-3}	0.90
3	Ac-Ile-OH	7.6×10^{-3}	5.5×10^{-3}	1.38

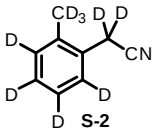
Kinetic Isotope Effect Experiments:



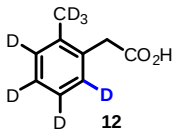
Scheme S3: Synthetic route to **12**.


S-1

***ortho*-tolyl-d_7 bromide (S-1):** To a 250 mL round bottom flask equipped with a magnetic stir bar, were added *ortho*-xylene-d_{10} (2.4 mL, 20 mmol, 99+% atom D), NBS (5.3 g, 30 mmol), and CCl_4 (125 mL). The flask was fitted with a reflux condenser, and the solution was heated to refluxing conditions. Catalytic AIBN (75 mg) was added. The reaction was monitored every 20 minutes by GC-MS. After 1 h, it was observed that the reaction had progressed to completion (70% desired mono-brominated product, 30% undesired di-brominated byproduct). The solution was allowed to cool to room temperature, at which point it was filtered to remove the succinimide precipitate. The filtrate was concentrated *in vacuo*, and the crude product mixture was obtained as a colorless oil. This mixture was taken on to the next step without further purification.


S-2

***ortho*-tolyl-d_9 cyanide (S-2):** To a 100 mL round bottom flask equipped with a magnetic stir bar, were added crude **S-1** (20 mmol), NaCN (1.5 g, 30 mmol), EtOH (50 mL), and distilled H_2O (10 mL). *(CAUTION: NaCN is an extremely toxic chemical and should be handled in a well maintained fume hood. The operator should have appropriate protection at all times.)* The solution was stirred under refluxing conditions for 12 h. Following careful removal of EtOH by distillation, the reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water (3 × 100 mL) and brine (100 mL). The solution was concentrated *in vacuo*, and the crude product. Purification by column chromatography (15:1 hexanes:EtOAc) gave pure **S-2** as a colorless oil (1.48 g, 47% yield over two steps).


12

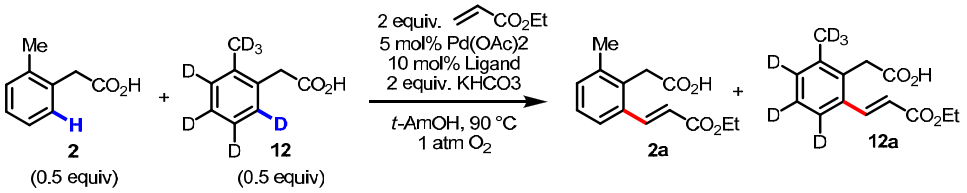
***ortho*-tolyl-d_7 acetic acid (12):** To a 250 mL round bottom flask equipped with a magnetic stir bar, were added **S-2**, KOH (1.7 g, 30 mmol), EtOH (100 mL), and distilled H_2O (25 mL). The solution was heated to reflux for 12 h, at which point EtOH was removed *via* distillation. The resulting aqueous solution was extracted with EtOAc (3 × 50 mL), and the organic layers were discarded. Concentrated HCl was added to the aqueous layer until the pH had reached 2 (as monitored by pH paper). The solution was extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification via column chromatography (3:1 hexanes:EtOAc, 3% HOAc) gave **12** as a white solid (448 mg, 28% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.69 (s, 2 H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.37, 136.95, 130.20 (t, J_{C-D} = 23.2 Hz), 130.07 (t, J_{C-D} = 23.9 Hz), 25.8 Hz, 127.38 (t, J_{C-D} = 25.8 Hz), 125.91 (t, J_{C-D} = 24.5 Hz), 39.07 (Note: the CD_3 signal could not be seen in the ^{13}C NMR spectrum due to its complex splitting.); **IR** (neat) ν 2918, 1690 (br), 1416, 1327, 1230, 908 cm^{-1}; **HRMS** (ESI-TOF) *m/z* Calcd for $C_9H_4D_7O_2$ $[M+H]^+$ 158.1186, found 158.1190.

Procedure for intermolecular kinetic isotope experiments between compounds 2 and 12: To a 20 mL scintillation vial were added, **2** (15.0 mg, 0.1 mmol), **12** (15.7 mg, 0.1 mmol), and $CDCl_3$ (0.5 mL). The solution was stirred until homogenous, and a small aliquot was taken for ^1H NMR analysis to ensure that the weighed quantities corresponded to a mixture with 50% ± 2% of each component. The solvent was removed *in vacuo*, and the mixture of **2** and **12** was transferred in *t*-AmylOH (1 mL) to a 50 mL Schlenk-type sealed tube (with a Teflon high pressure valve and side arm) equipped with a magnetic stir bar. $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), $KHCO_3$ (40.0 mg, 0.4 mmol), ligand (0.02 mmol), and ethyl acrylate (43 μL, 0.4 mmol) were then added. The reaction tube was capped, then evacuated briefly under high vacuum and charged with O_2 (1 atm, balloon) (×3). The reaction mixture was stirred at room temperature for 5 min, then at 90 °C for the appropriate time. The reaction vessel was then 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 ^1H NMR. The conversion of **2a**, X_{2a}, was determined by integration of the methyl proton signals, which appear as singlets (approximately 2.32 ppm for **2** and 2.36 ppm for **2a**). The total conversion X_{total} was determined by integration of the benzylic methylene group signals, which also appear as singlets (3.67 ppm for **2**/**12** and 3.84 ppm for **2a**/**12a**). The conversion of **12a**, X_{12a}, could then be determined from the following formula:

$$X_{12a} = 2 \cdot X_{total} - X_{2a}$$

The experiments were repeated three times without ligand, three times with Boc-Val-OH, and five times with Ac-Ile-OH. The results are shown in Table S13.

Table S13: Results from the kinetic isotope experiments with **2** and **12**.[a]



Entry[a]	Ligand	Time (min)	% Conv. **2a**	% Conv. **12a**	k_H ([M]/min)	k_D ([M]/min)	k_H / k_D
1	—	120	42.5	7.9	3.5×10^{-4}	6.6×10^{-5}	5.38
2	—	120	26.1	5.1	2.2×10^{-4}	4.3×10^{-5}	5.12
3	—	120	29.1	3.8	2.4×10^{-4}	3.2×10^{-5}	7.67
4	Boc-Val-OH	10	23.7	3.7	2.4×10^{-3}	3.7×10^{-4}	6.41
5	Boc-Val-OH	10	18.3	3.7	1.8×10^{-3}	3.7×10^{-4}	4.90
6	Boc-Val-OH	10	18.0	3.4	1.8×10^{-3}	3.4×10^{-4}	5.29
7	Ac-Ile-OH	10	26.0	22.0	2.6×10^{-3}	2.2×10^{-3}	1.18
8	Ac-Ile-OH	10	26.4	11.0	2.6×10^{-3}	1.1×10^{-3}	2.40
9	Ac-Ile-OH	10	26.1	19.5	2.6×10^{-3}	2.0×10^{-3}	1.34
10	Ac-Ile-OH	10	23.5	11.1	2.4×10^{-3}	1.1×10^{-3}	2.11
11	Ac-Ile-OH	10	21.4	18.2	2.1×10^{-3}	1.8×10^{-3}	1.43

[a] The conversion was determined by ^{1}H NMR analysis of the crude reaction mixture, as discussed in the preceding section.

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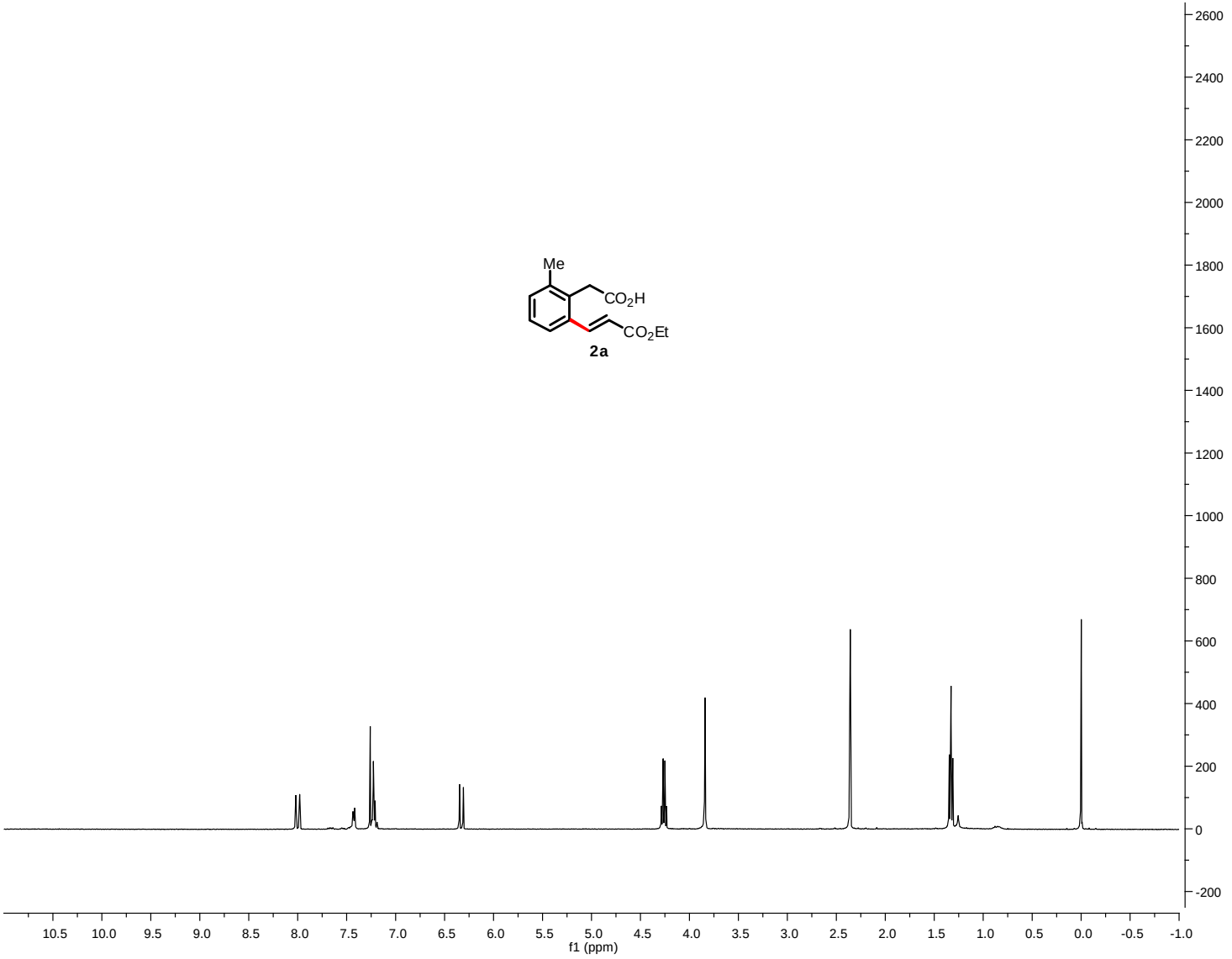
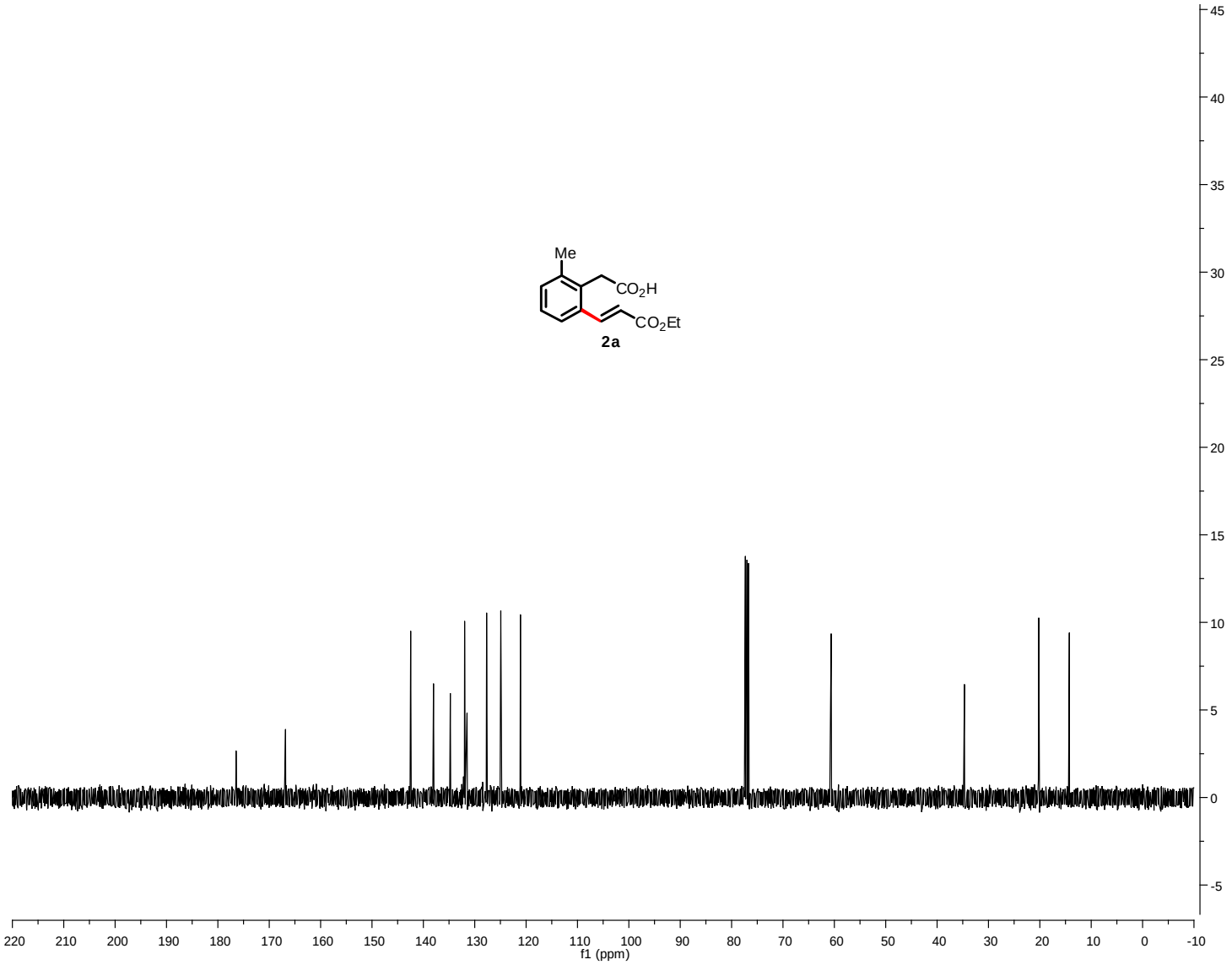
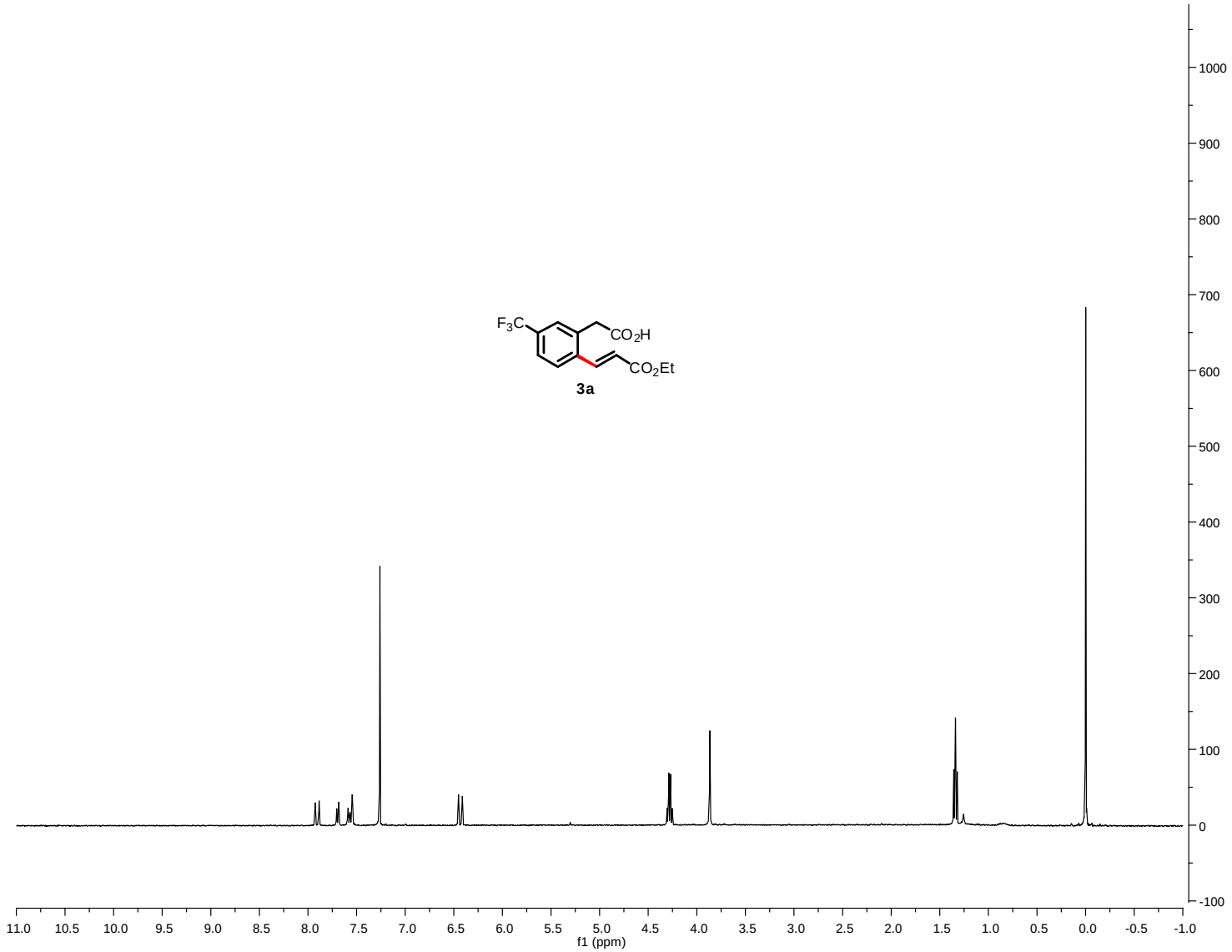
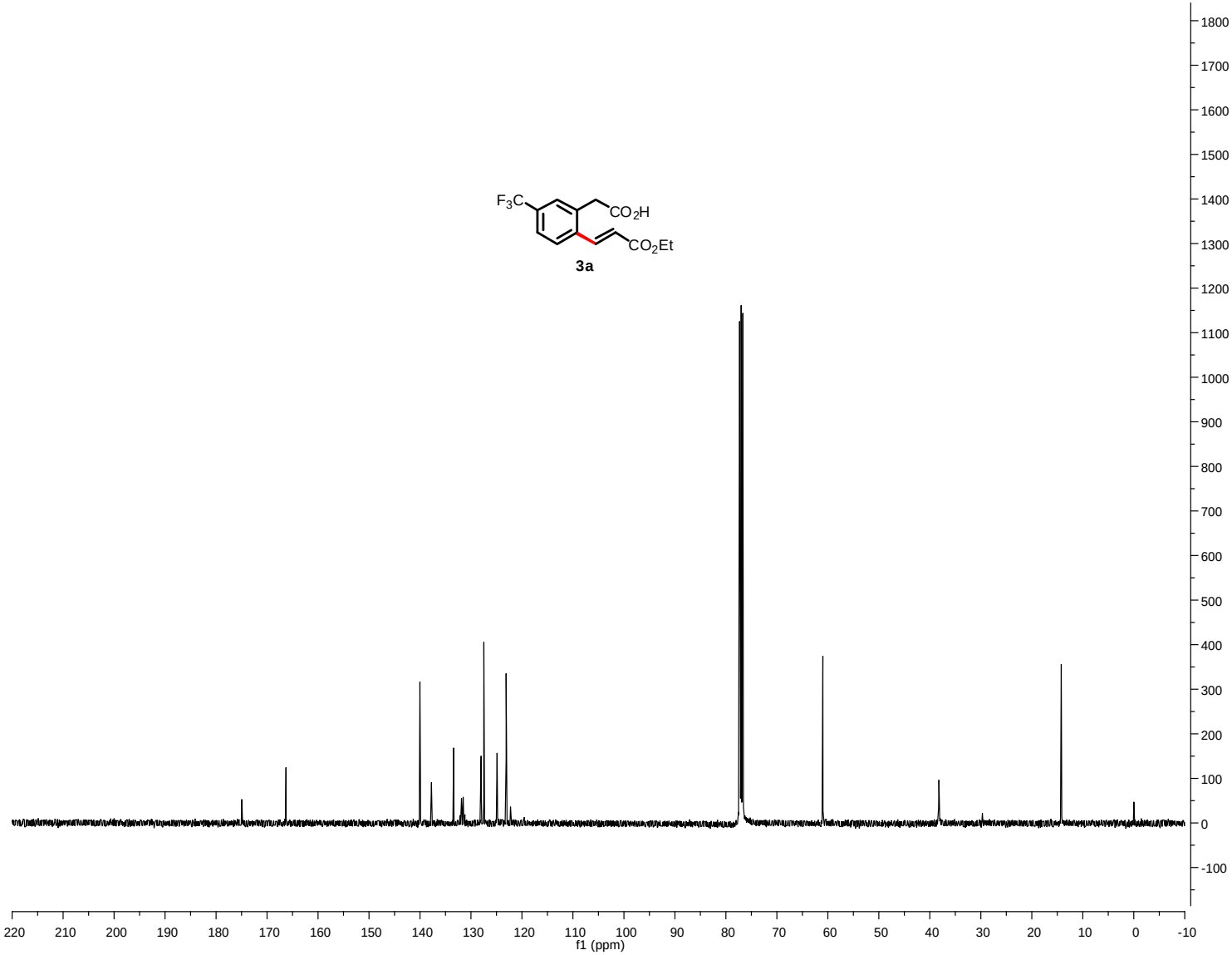
(6) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315.

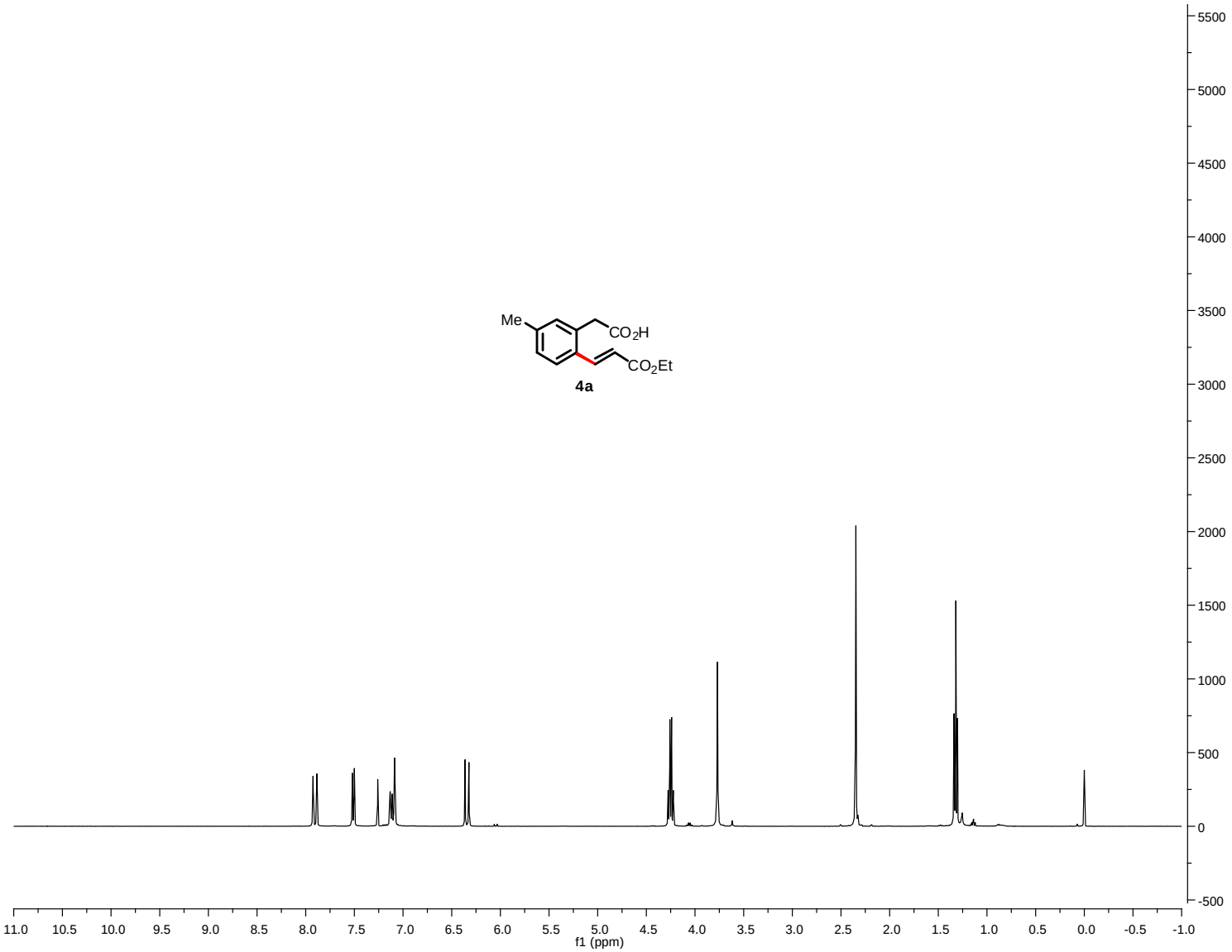
NMR Spectra

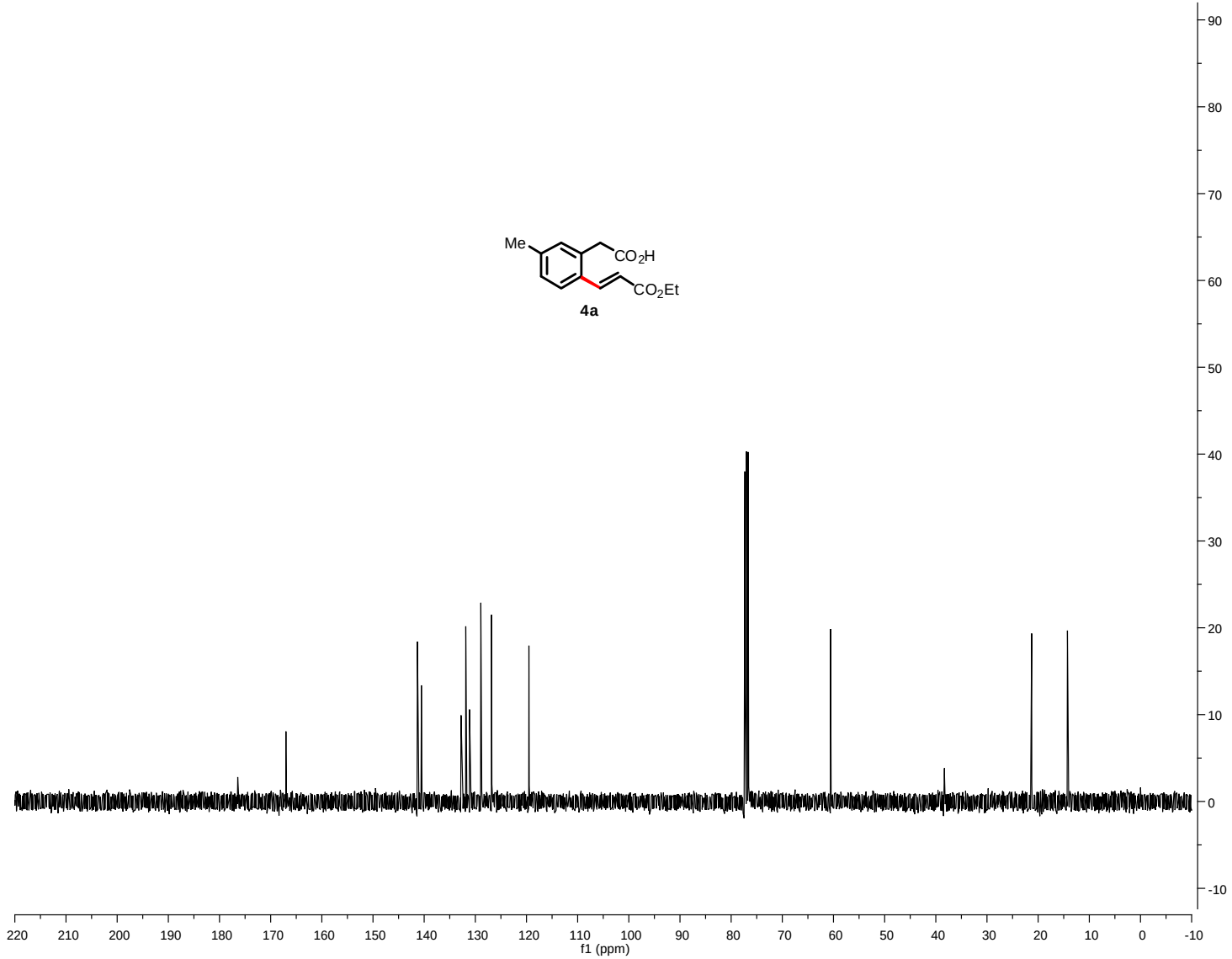

Me
CO2H
CO2Et
2a
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

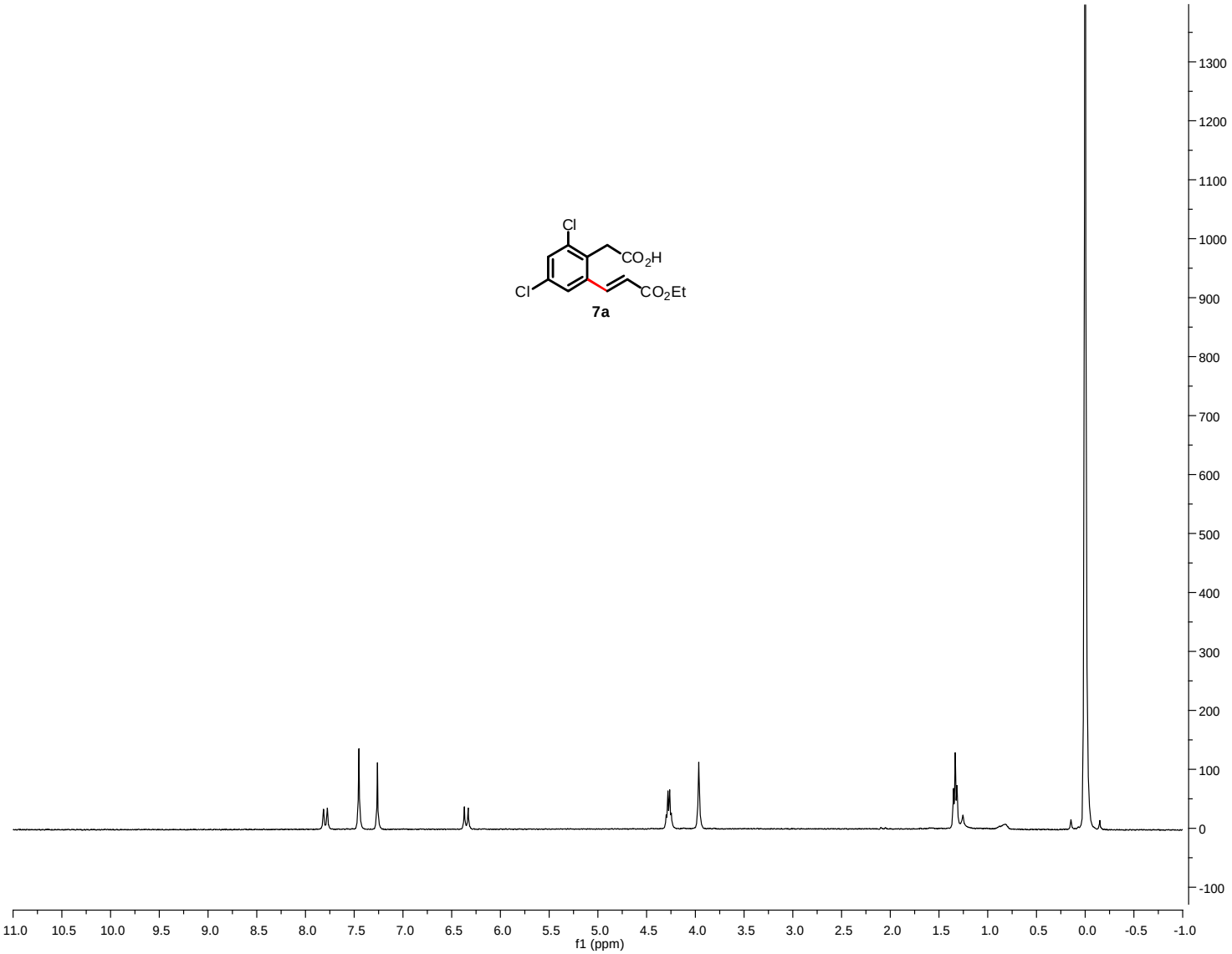

Me
CO2H
CO2Et
2a
f1 (ppm)

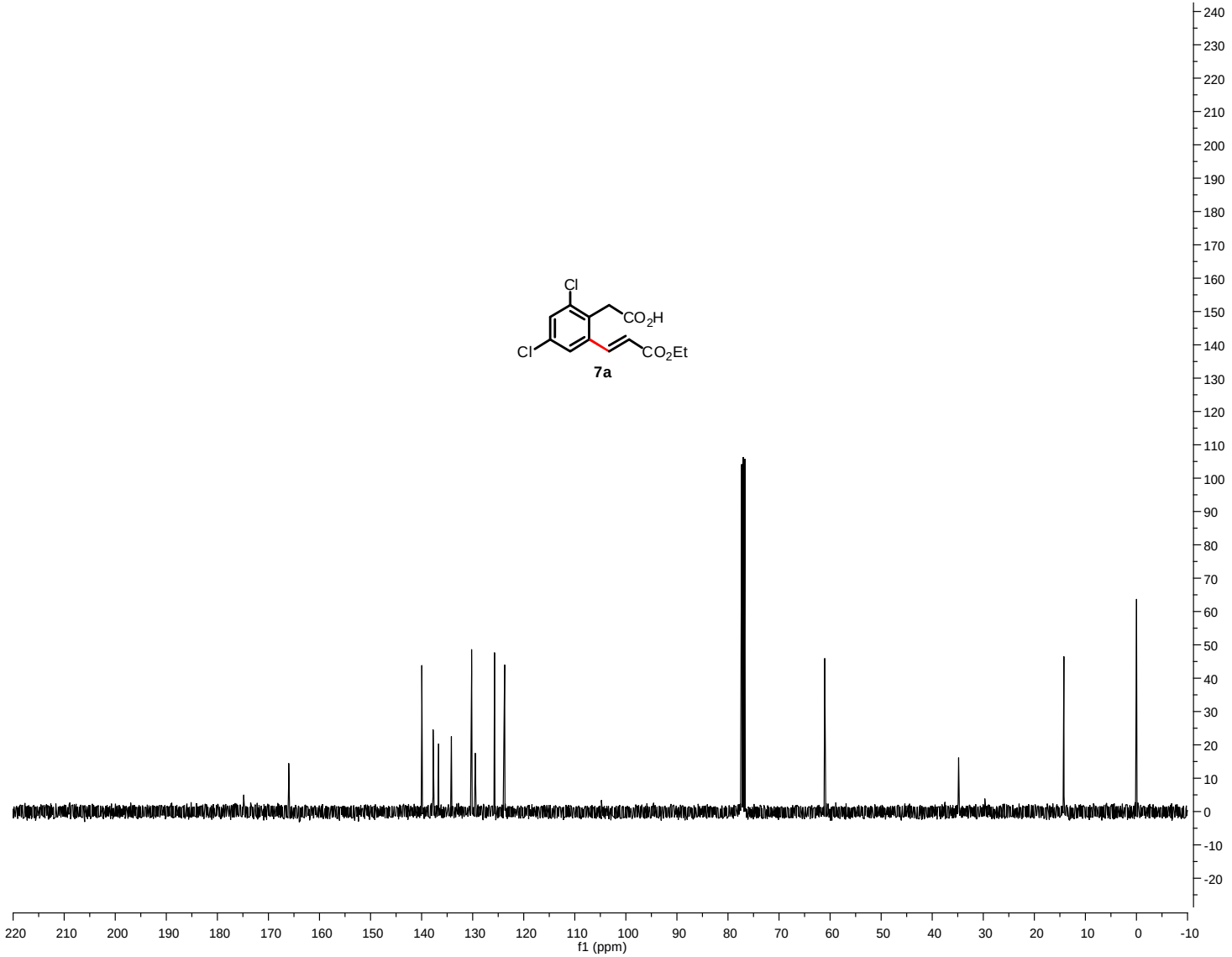

F3C
CO2H
CO2Et
3a
1000
900
800
700
600
500
400
300
200
100
0
-100
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

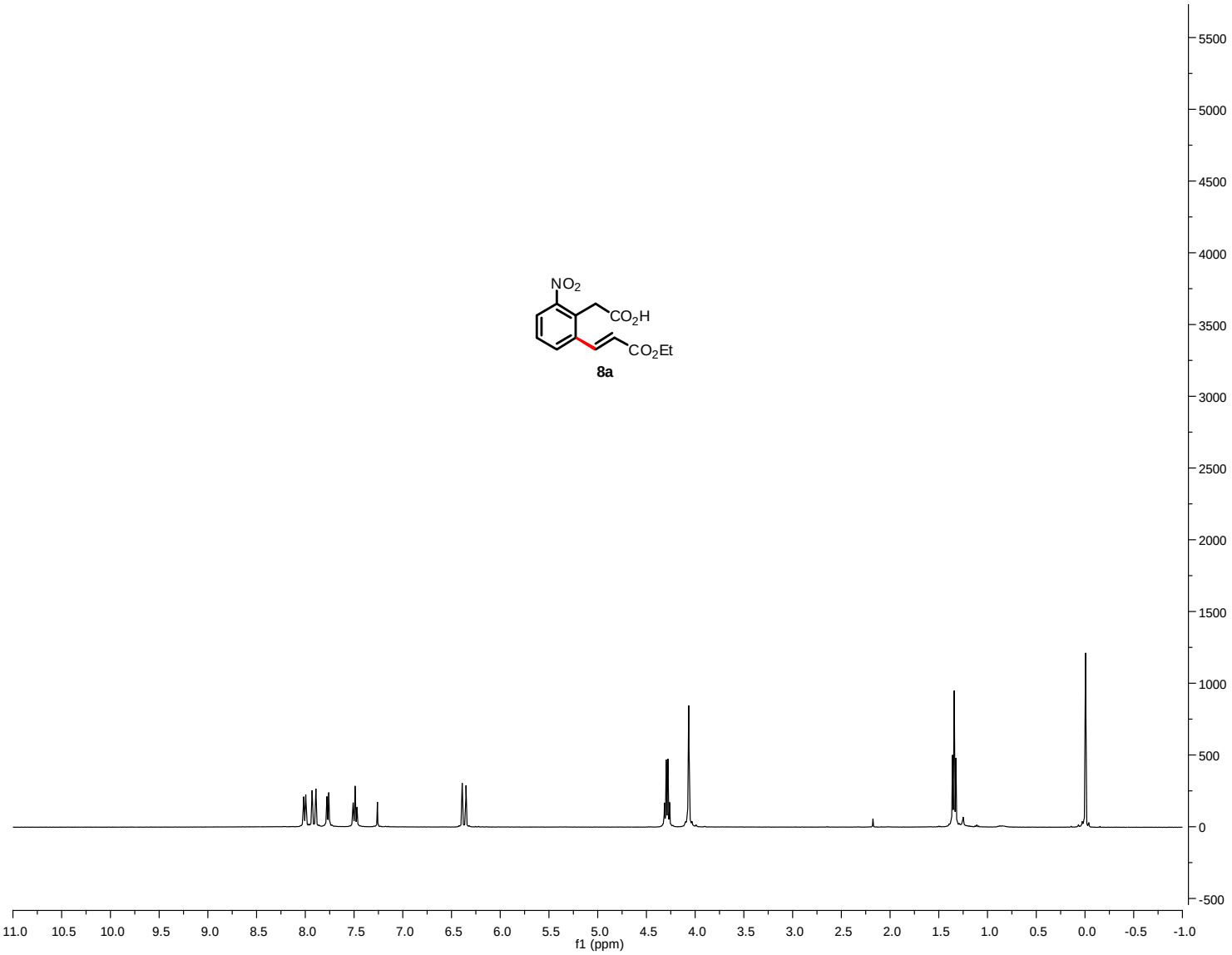

F3C
CO2H
CO2Et
3a
f1 (ppm)

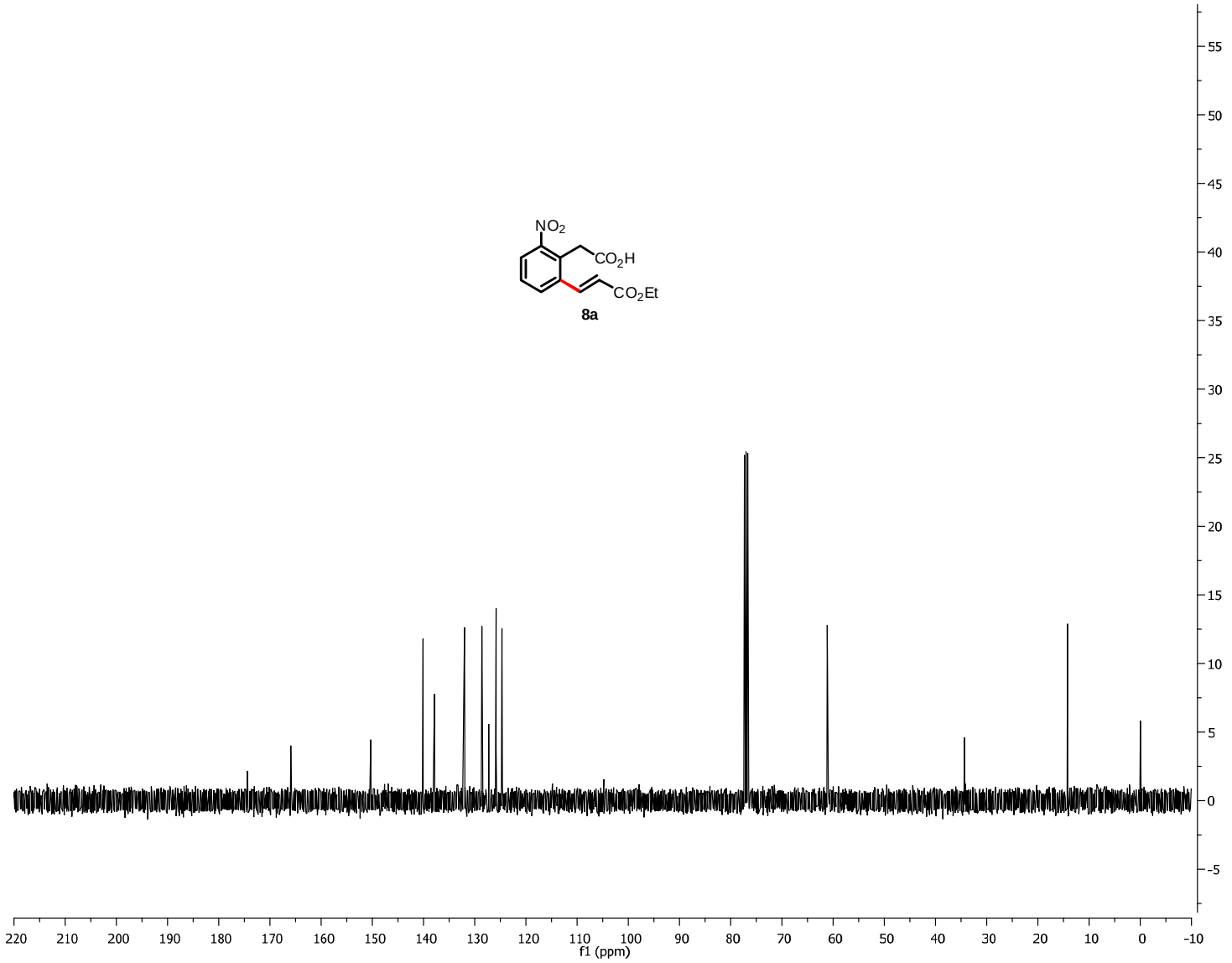

Me
CO2H
CO2Et
4a
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

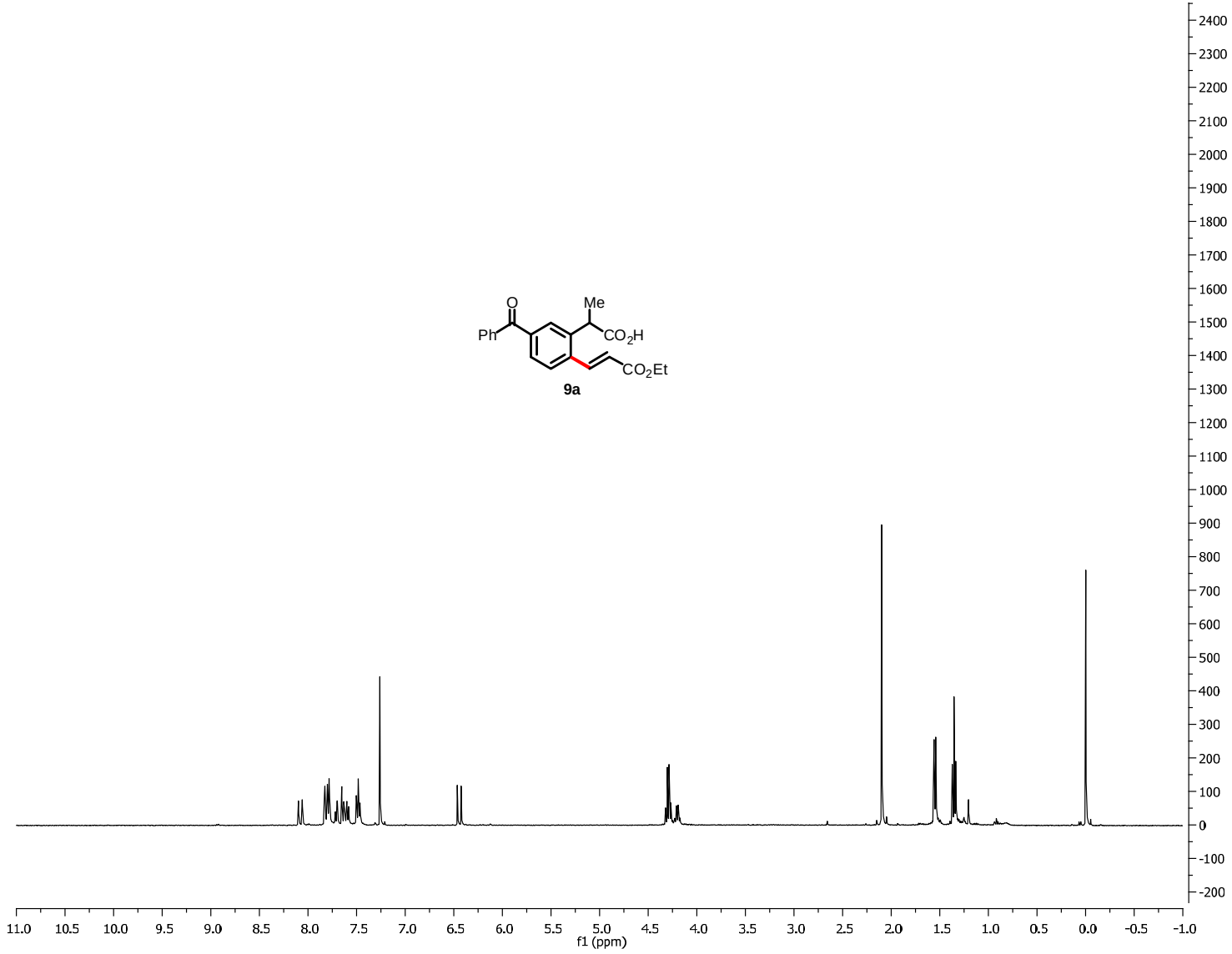

Me
CO2H
CO2Et
4a
f1 (ppm)

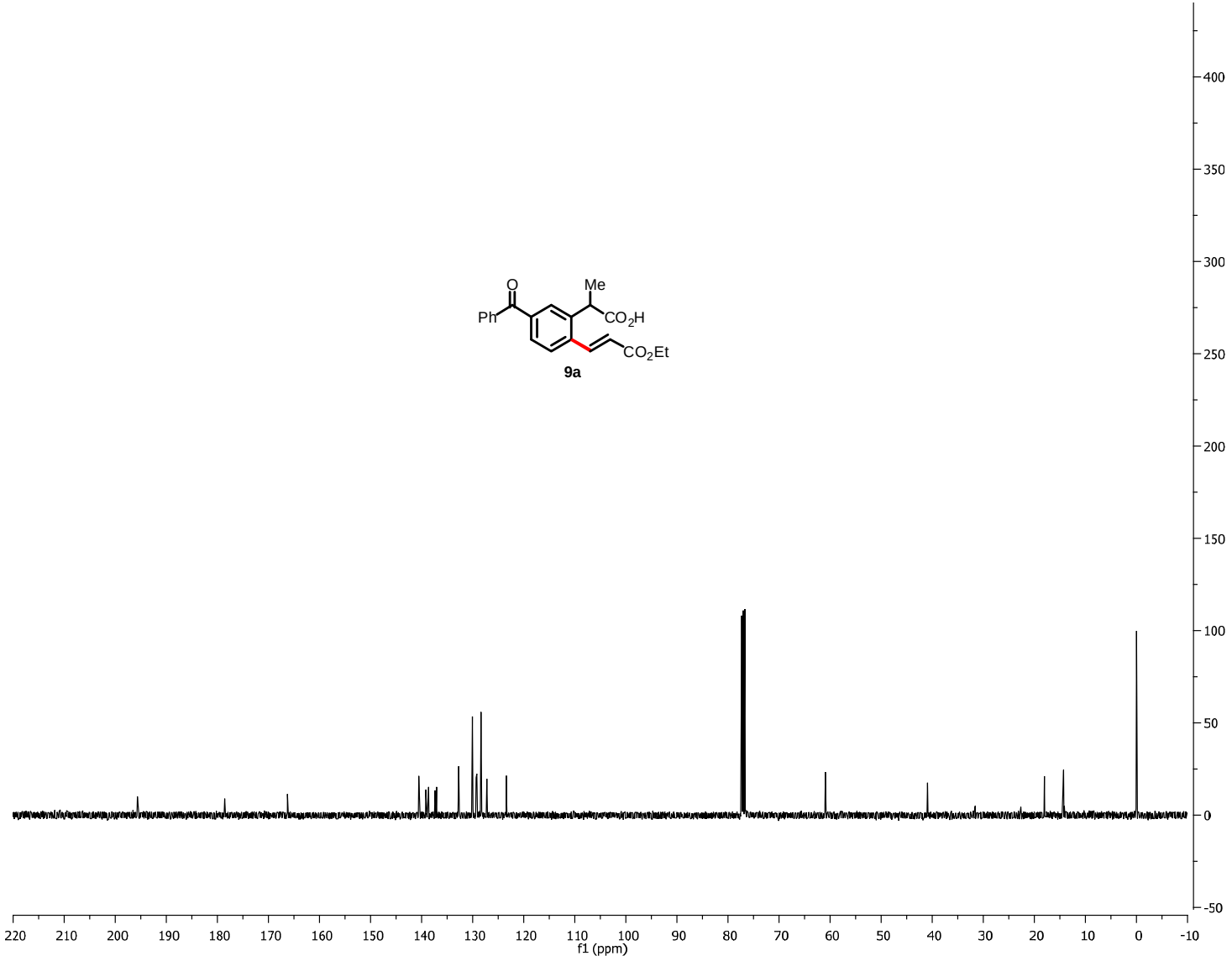

Cl
CO2H
Cl
CO2Et
7a
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

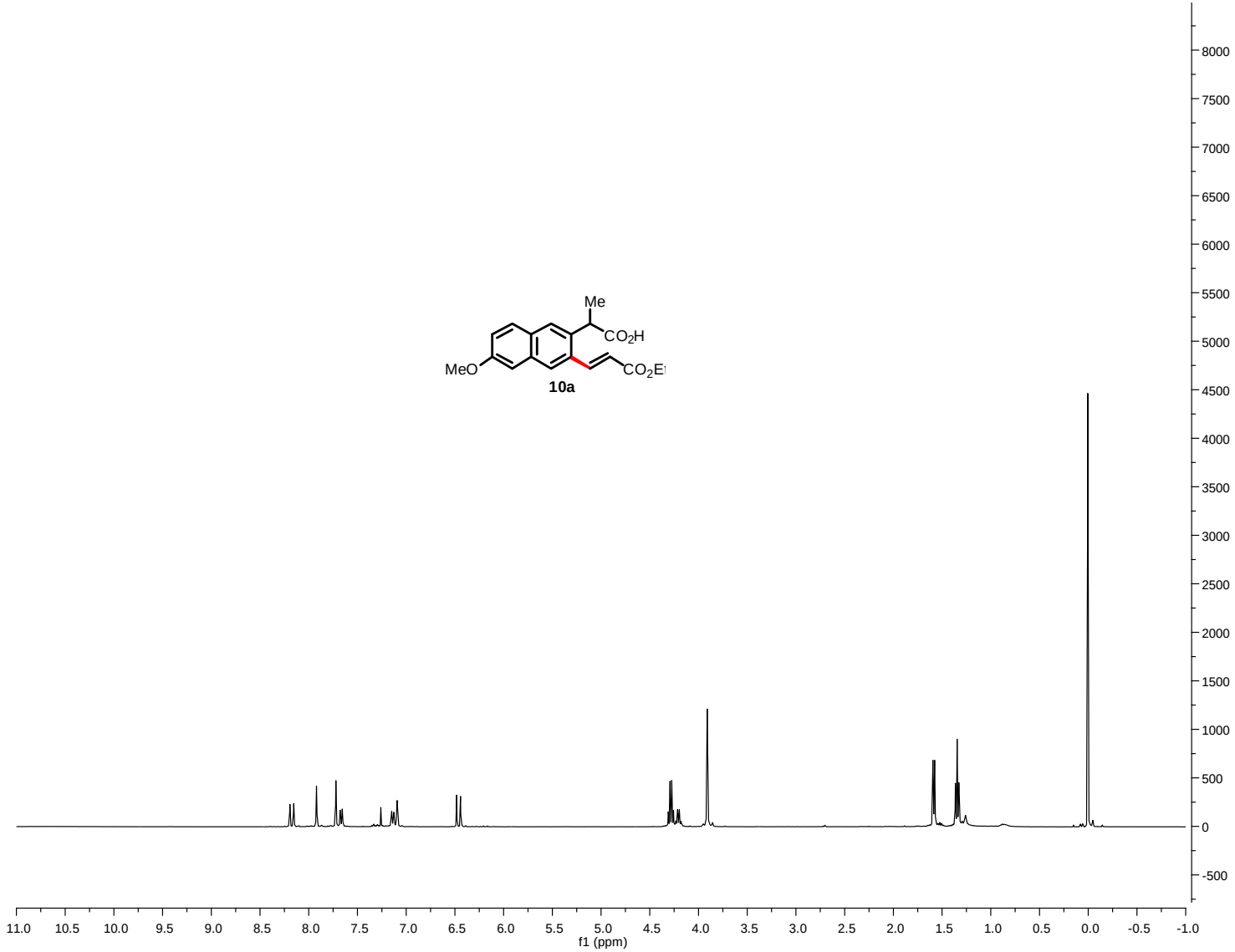

Cl
CO2H
Cl
CO2Et
7a
f1 (ppm)

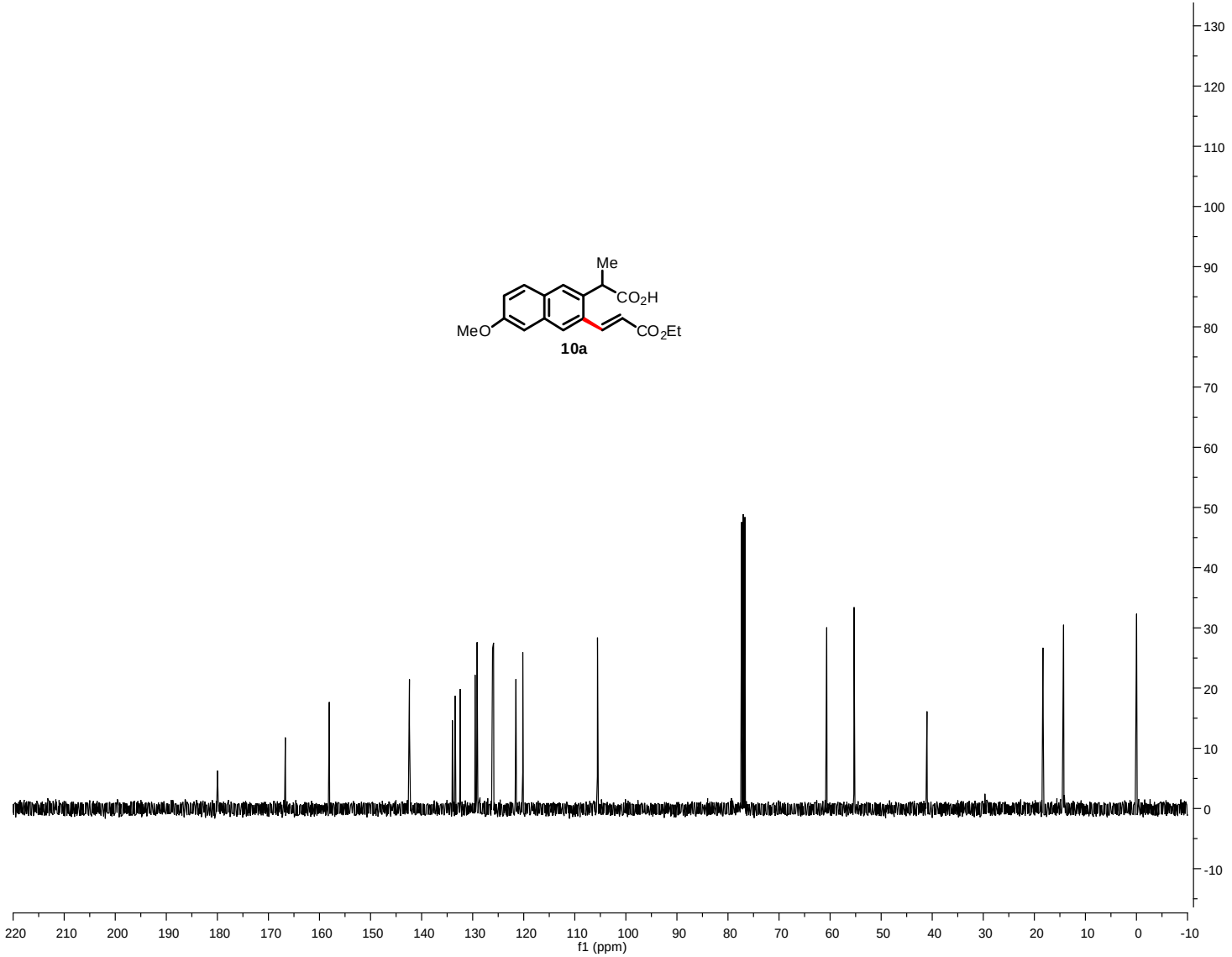

NO2
CO2H
CO2Et
8a
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

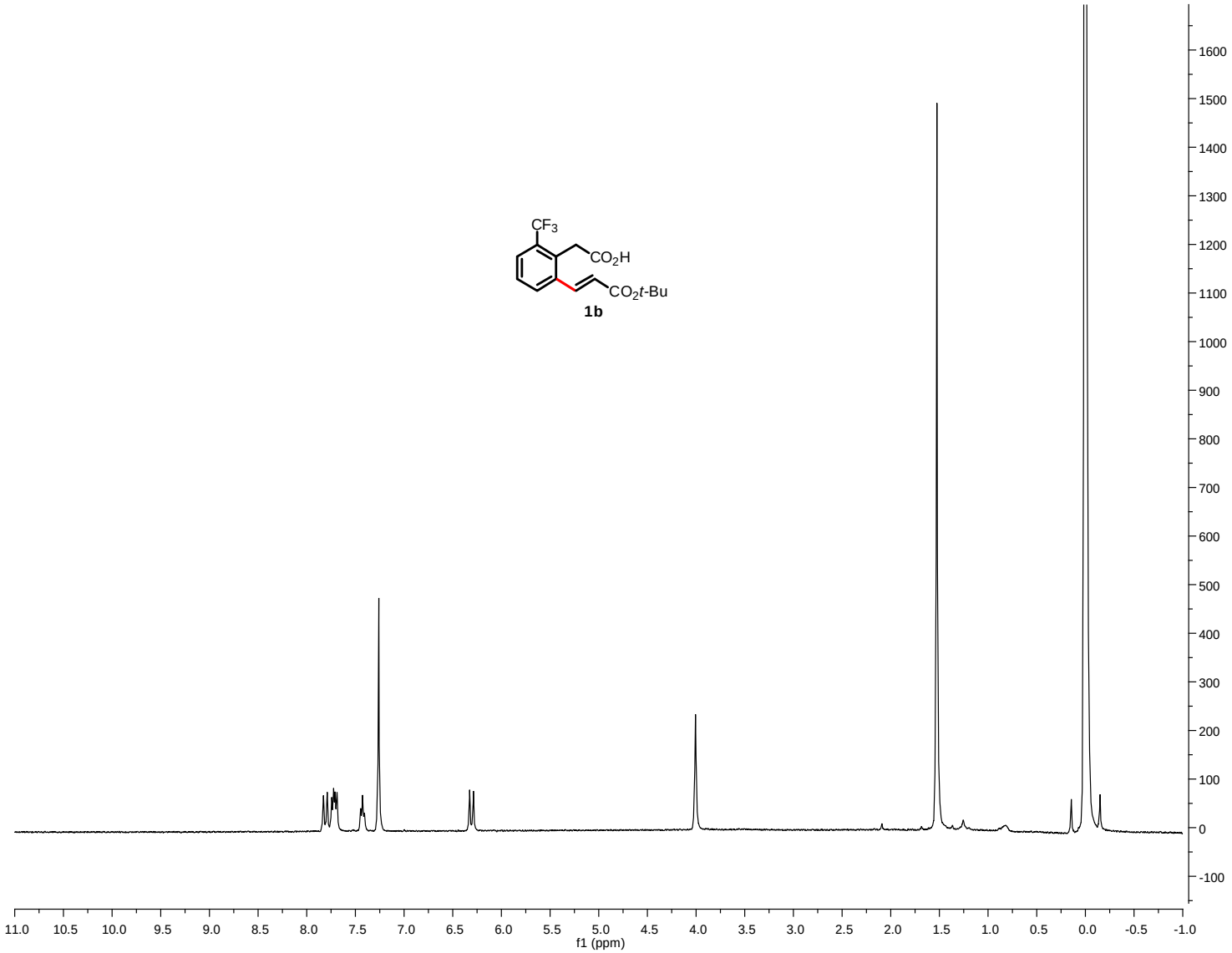

NO2
CO2H
CO2Et
8a
55
50
45
40
35
30
25
20
15
10
5
0
-5
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

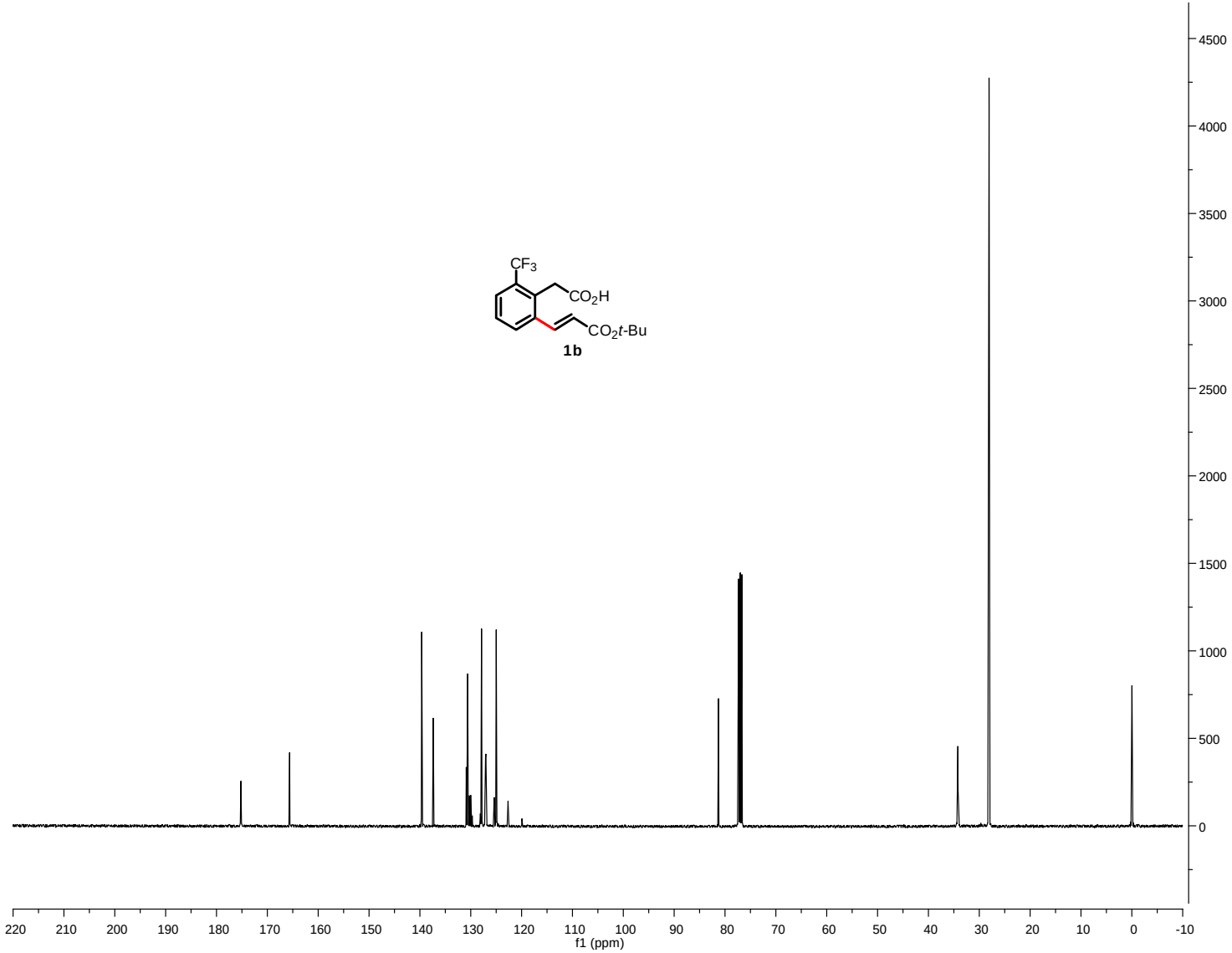

O
Me
Ph
CO2H
CO2Et
9a
f1 (ppm)

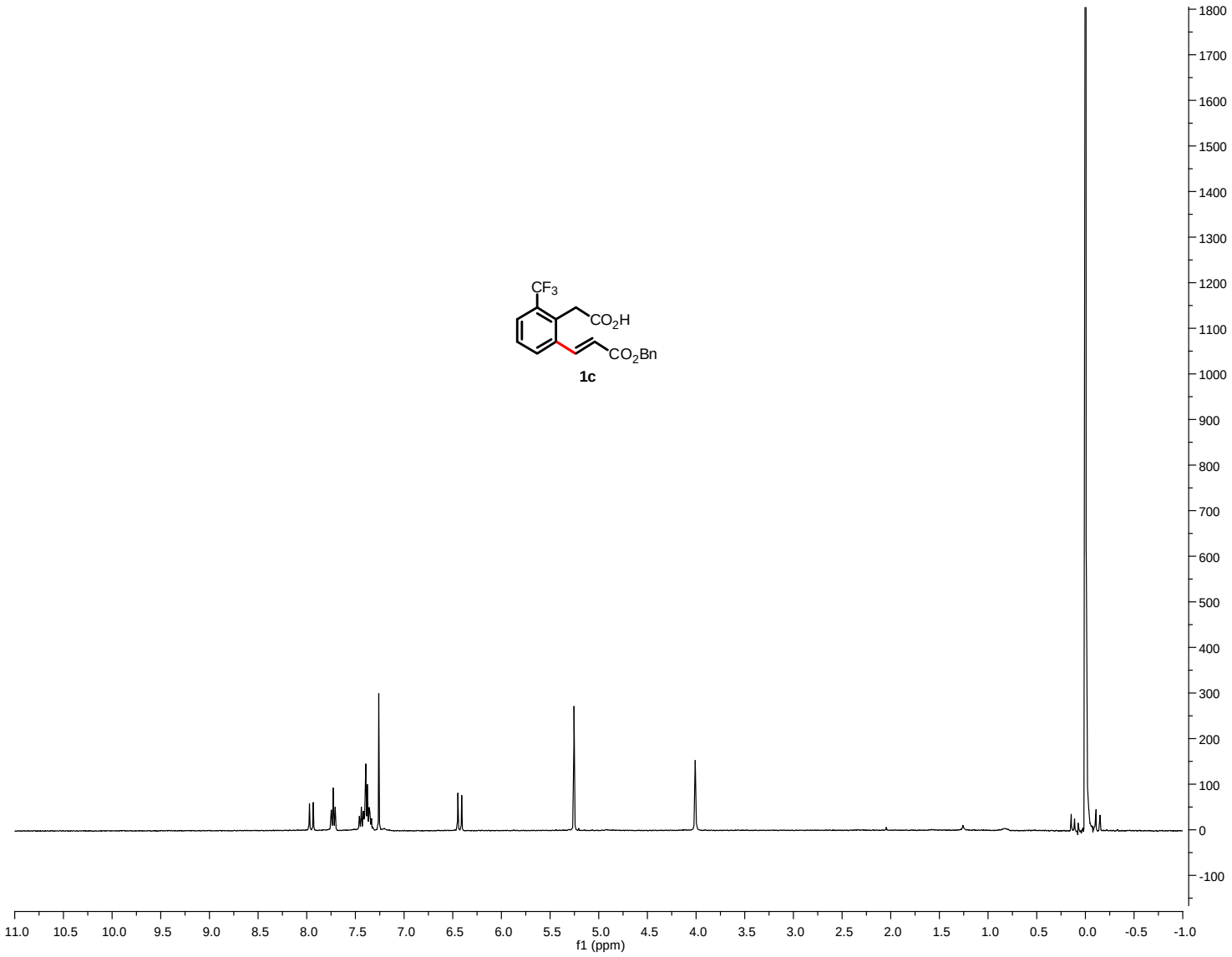

O
Me
Ph
CO2H
CO2Et
9a
400
350
300
250
200
150
100
50
0
-50
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

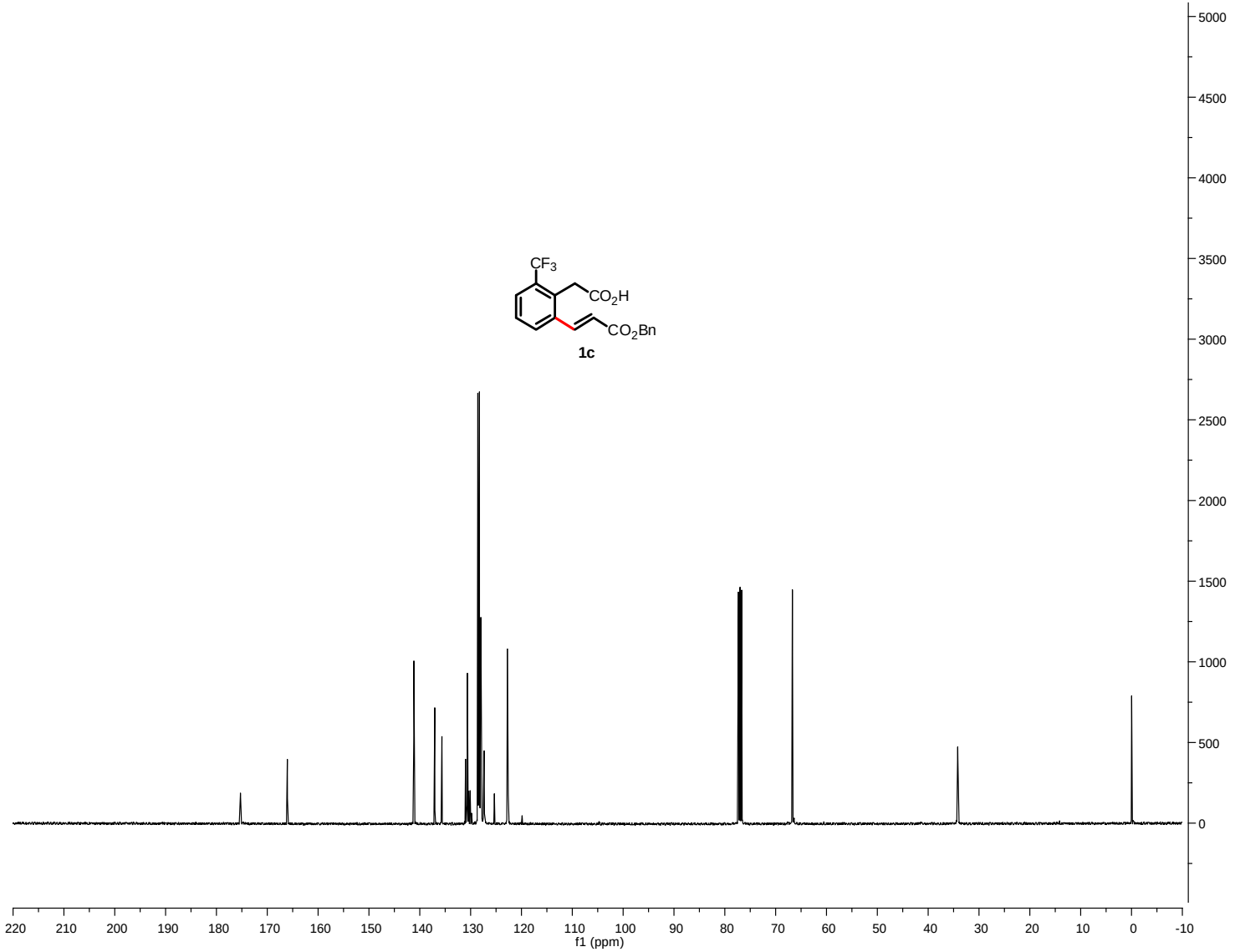

Me
CO2H
MeO
CO2Et
10a
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

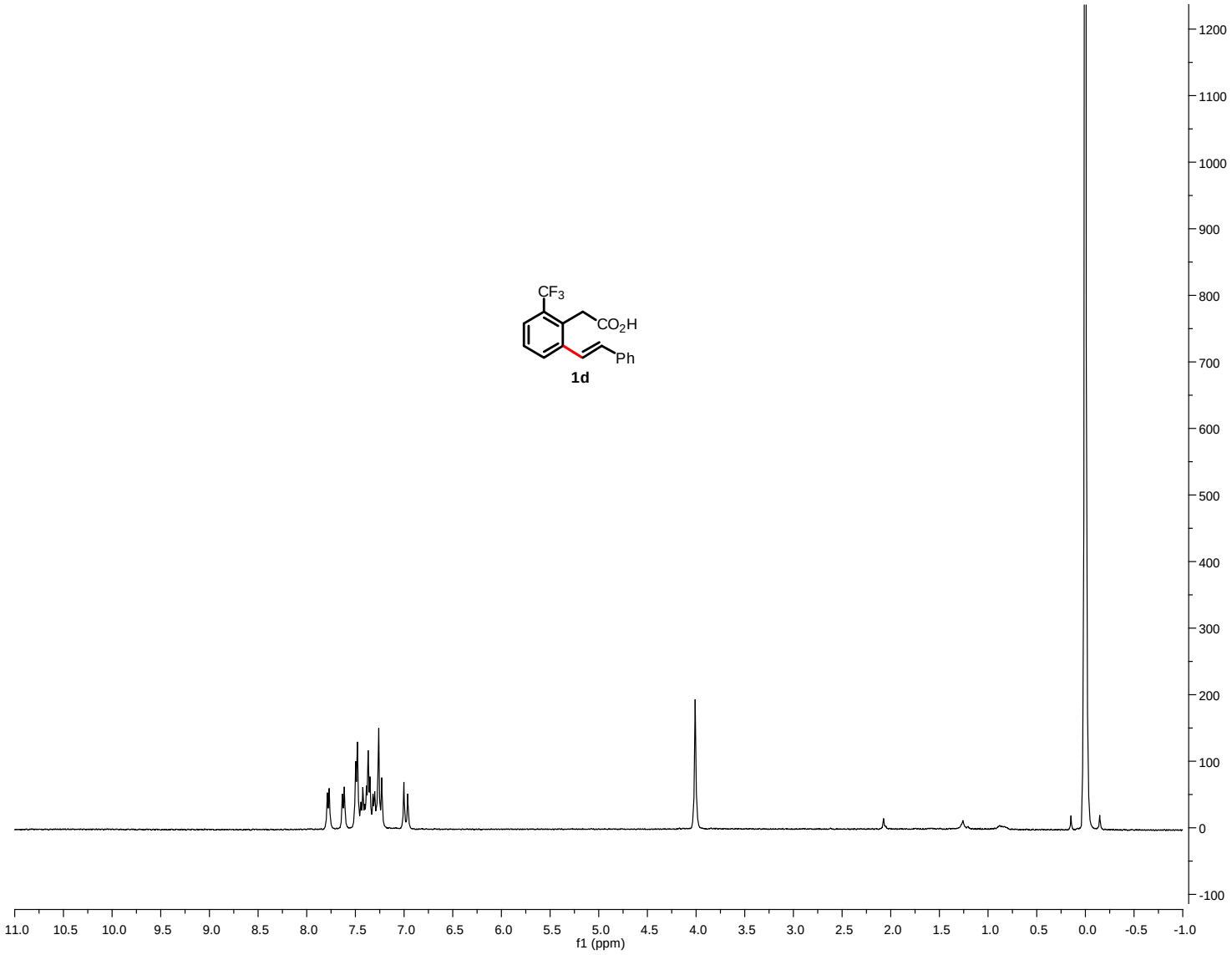

Me
CO2H
MeO
CO2Et
10a
f1 (ppm)

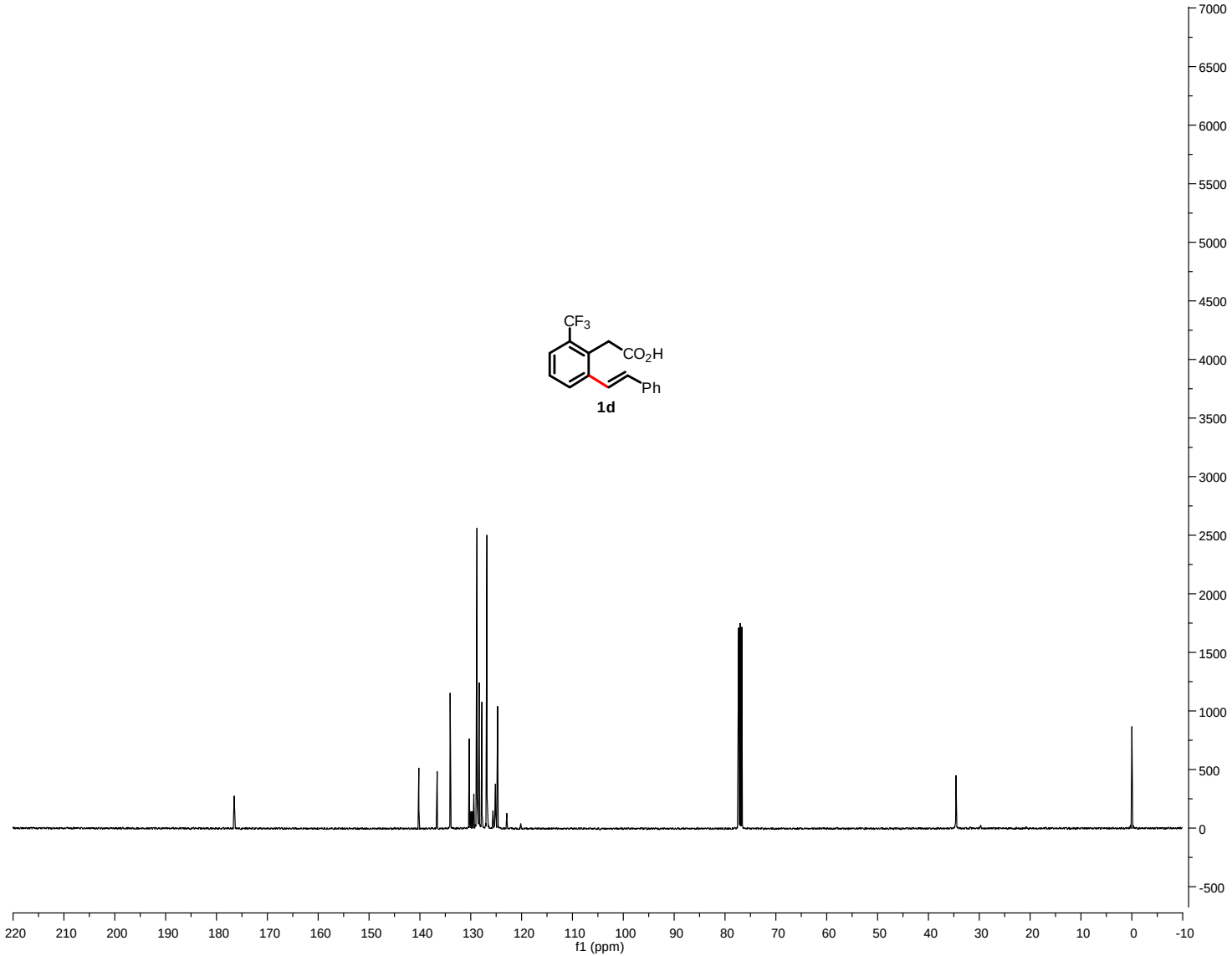

CF3
CO2H
CO2t-Bu
1b
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

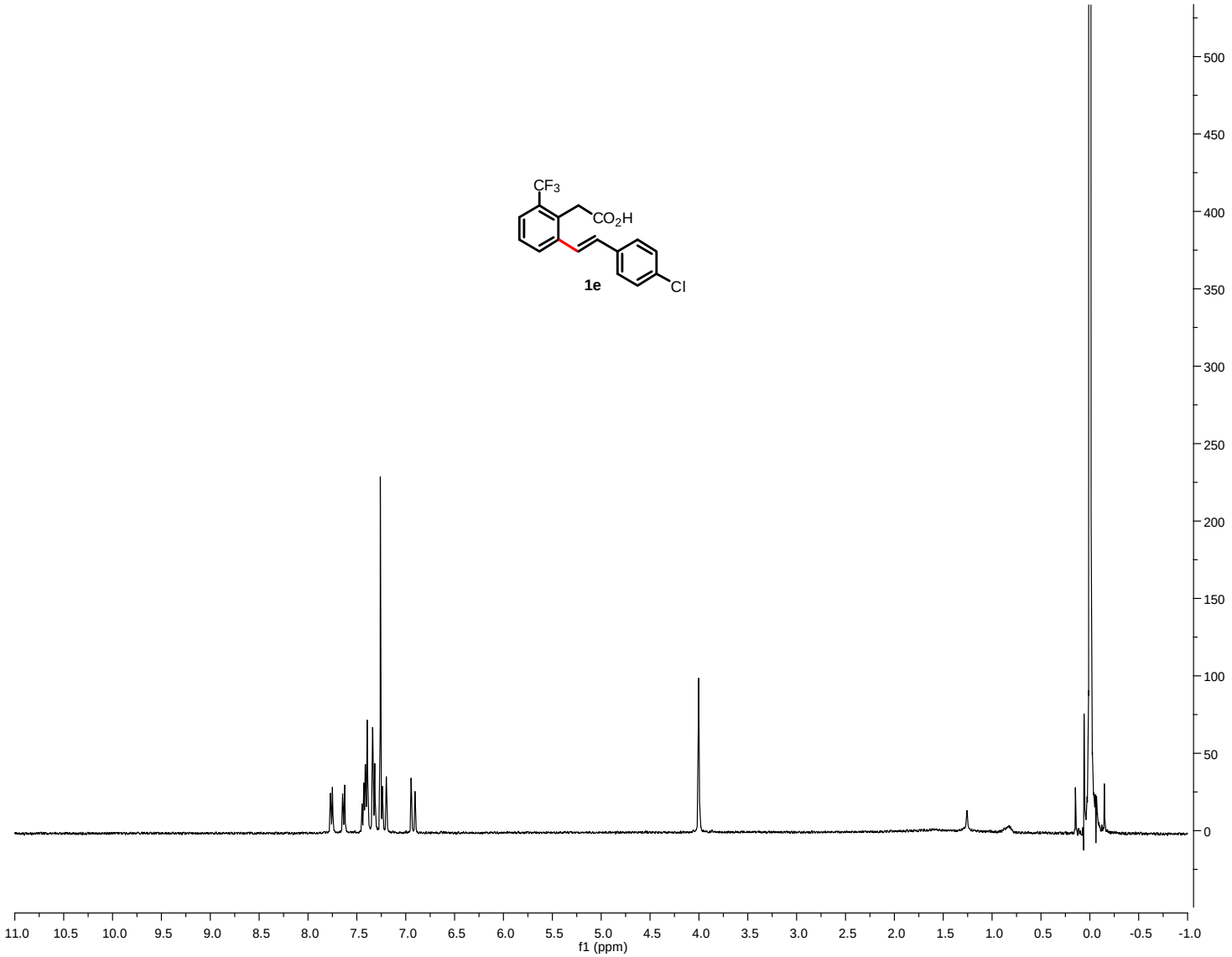

CF3
CO2H
CO2t-Bu
1b
4500
4000
3500
3000
2500
2000
1500
1000
500
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

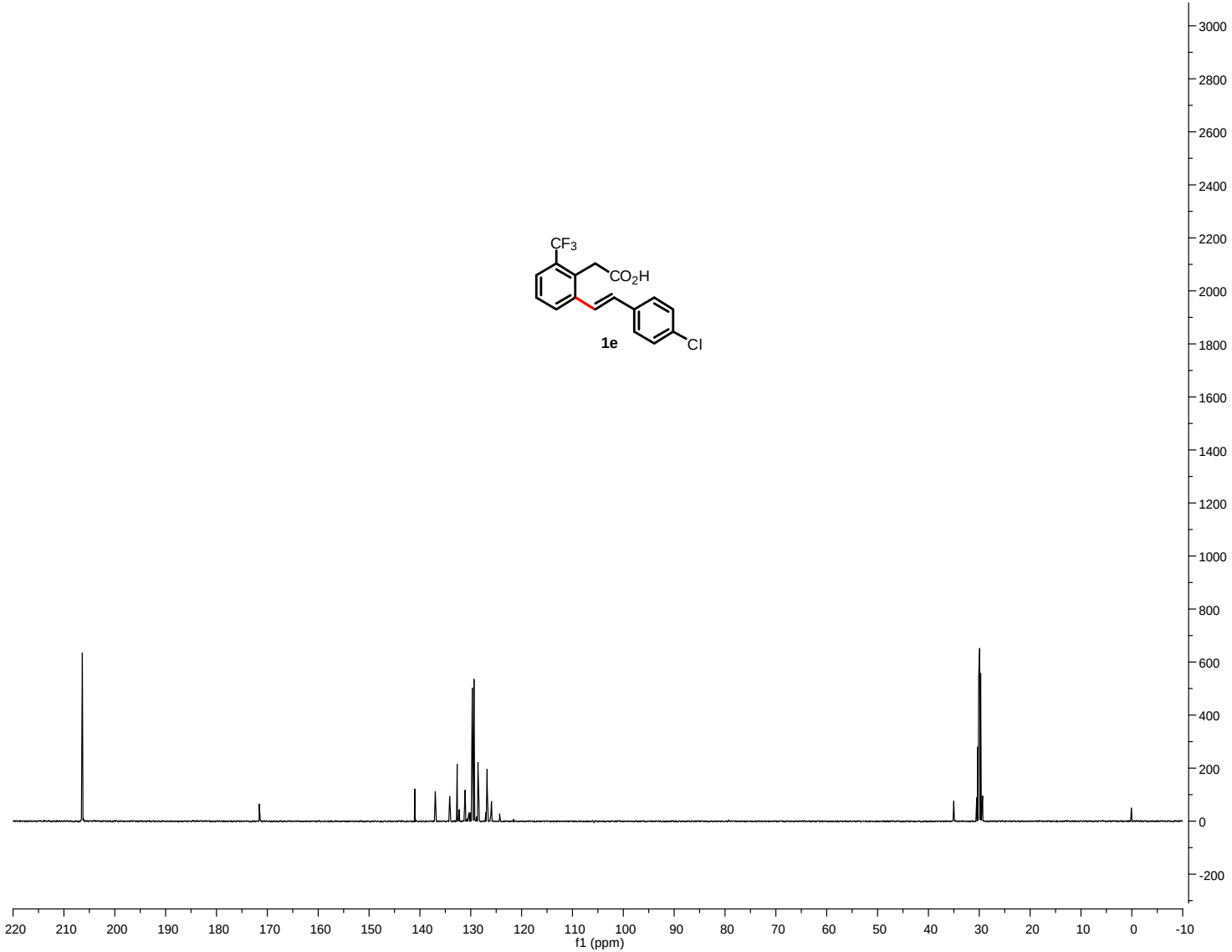

CF3
CO2H
CO2Bn
1c
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

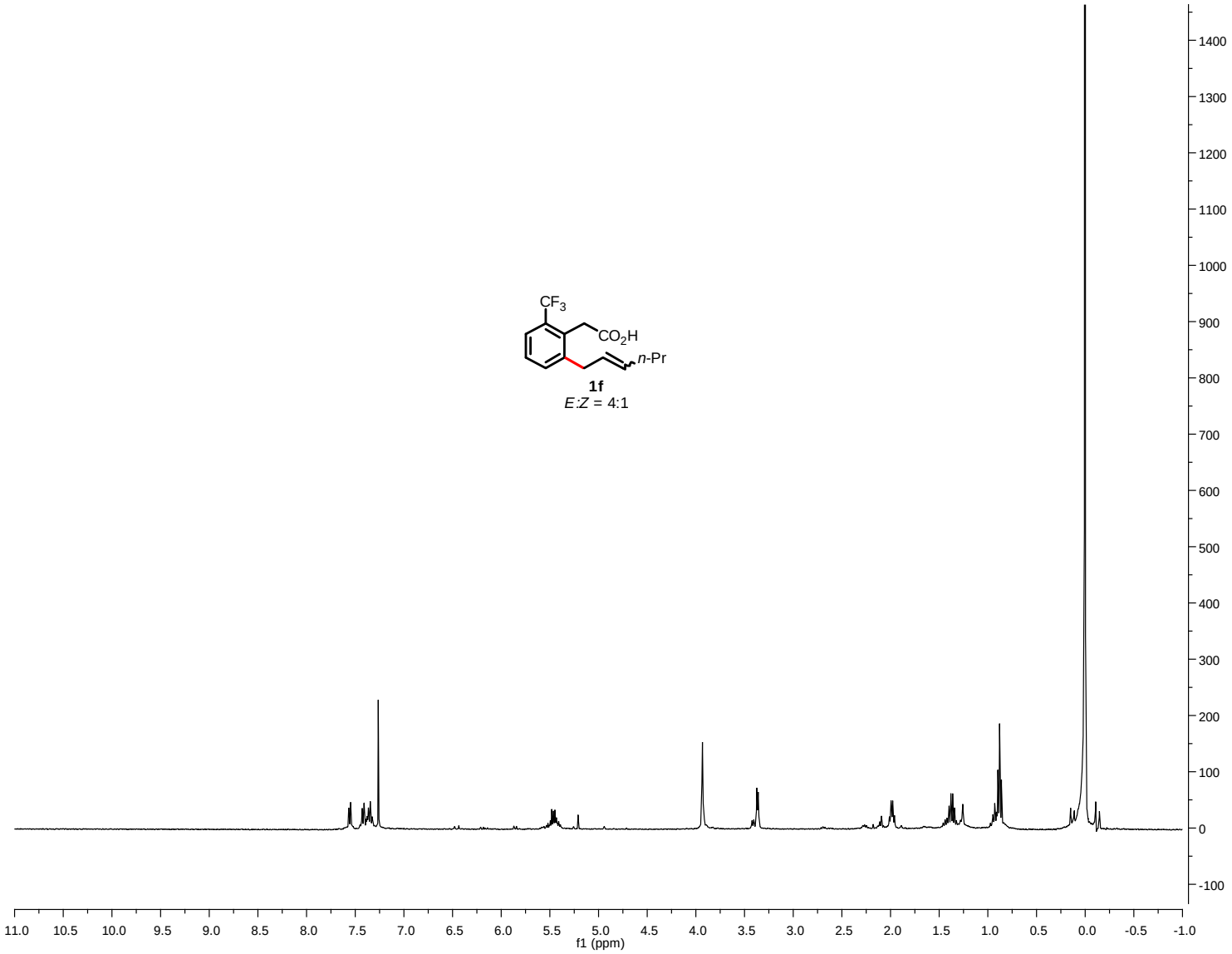

CF3
CO2H
CO2Bn
1c
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

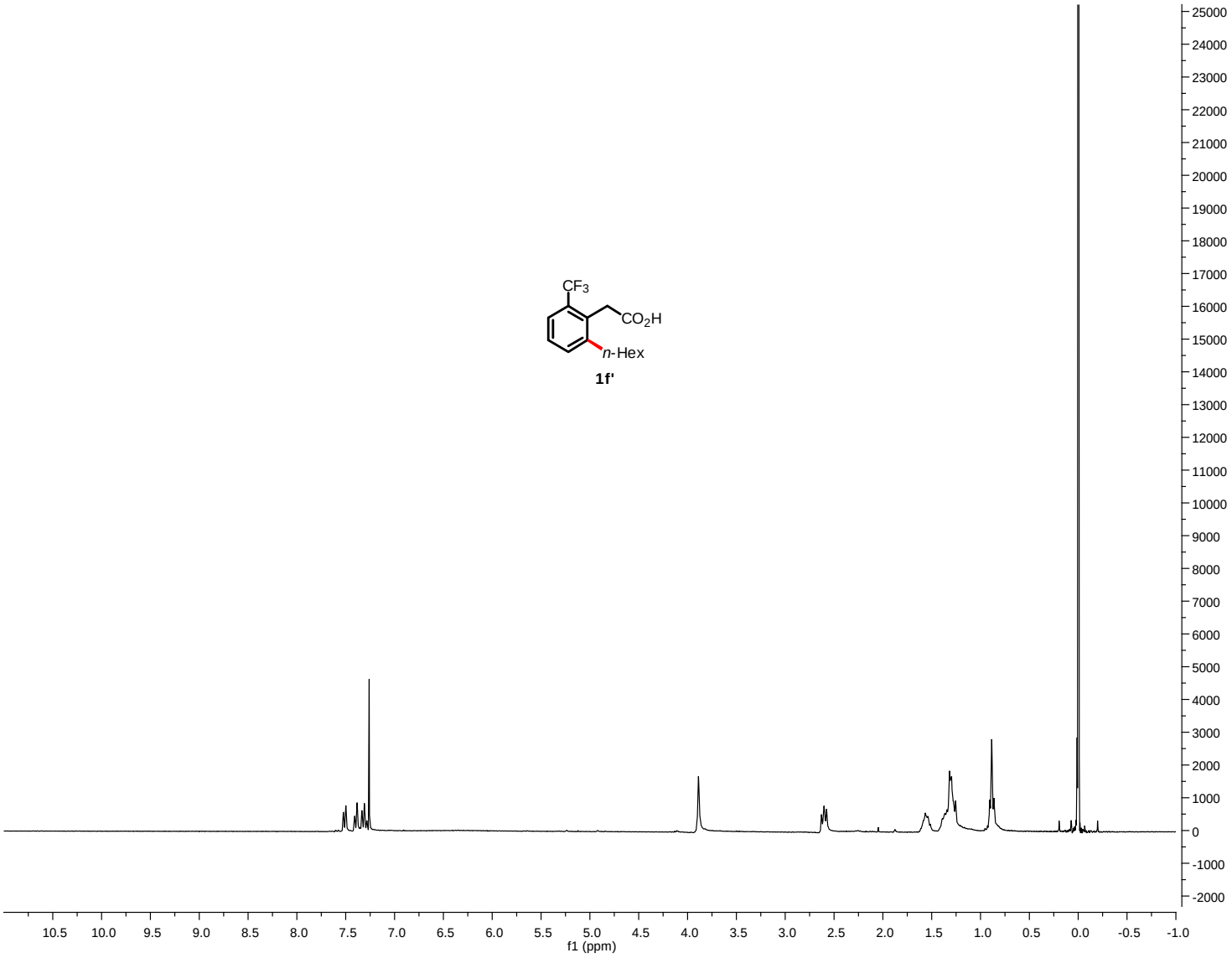

CF3
CO2H
Ph
1d
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
-1.0
f1 (ppm)

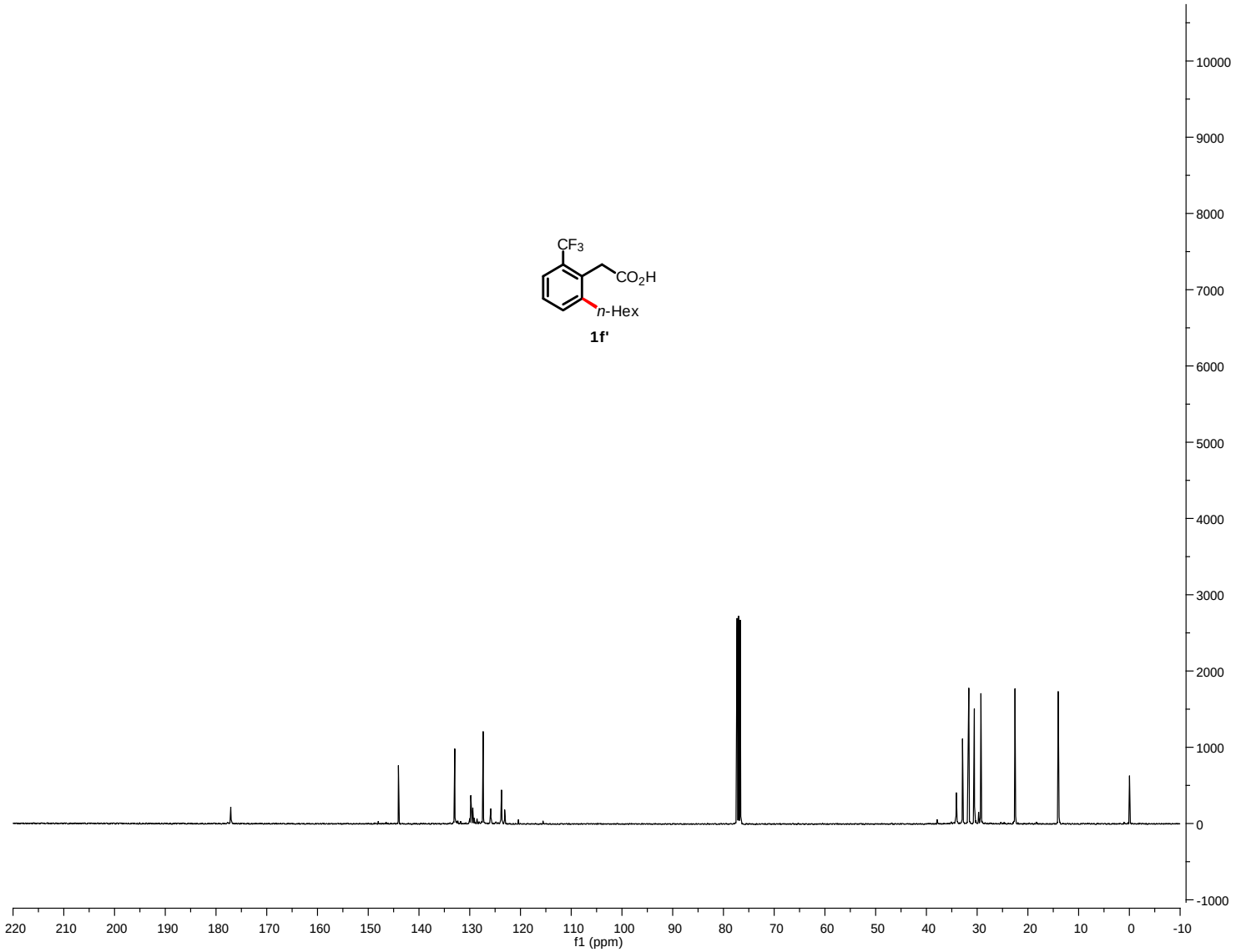

CF3
CO2H
Ph
1d
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

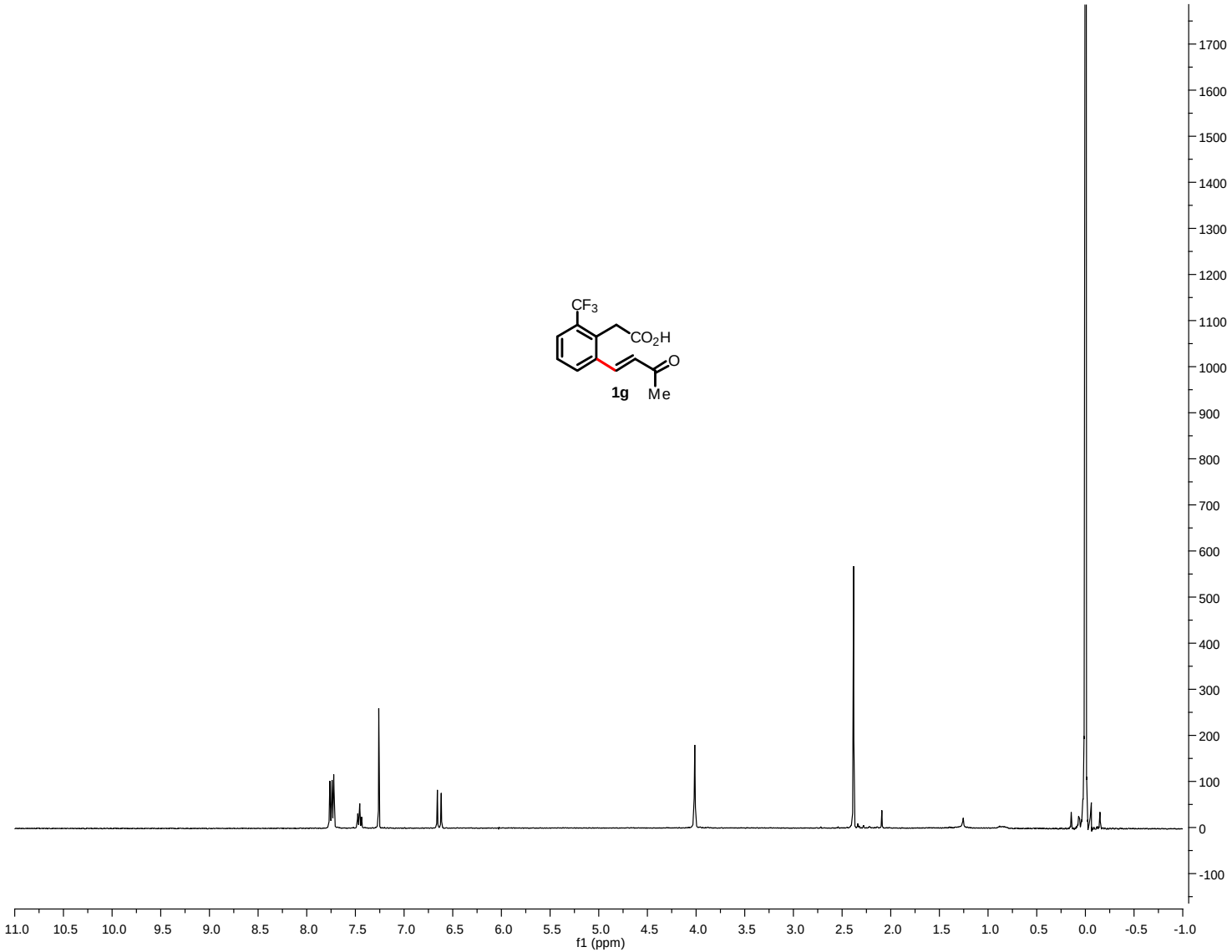

CF3
CO2H
Cl
1e
500
450
400
350
300
250
200
150
100
50
0
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

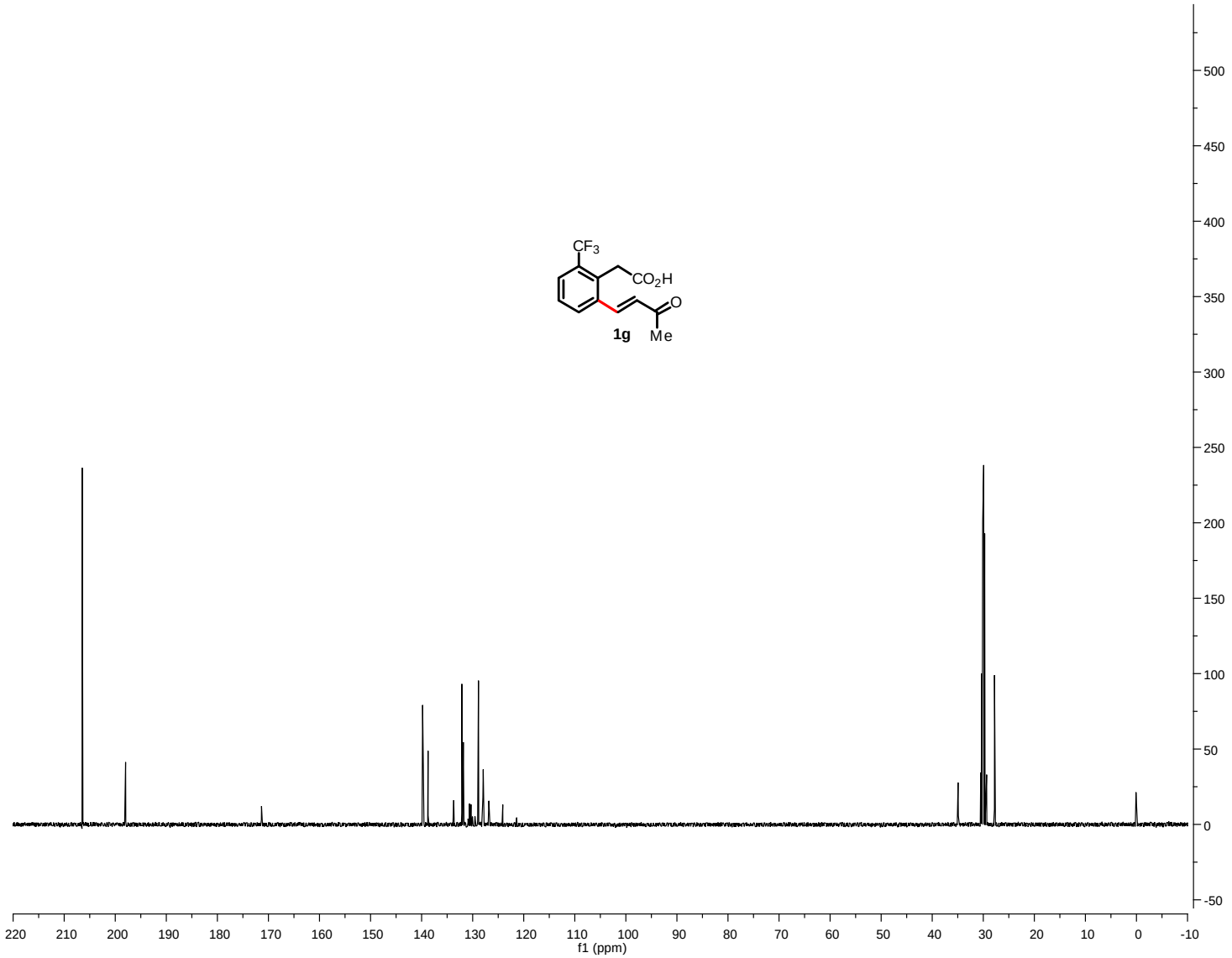

CF3
CO2H
Cl
1e
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

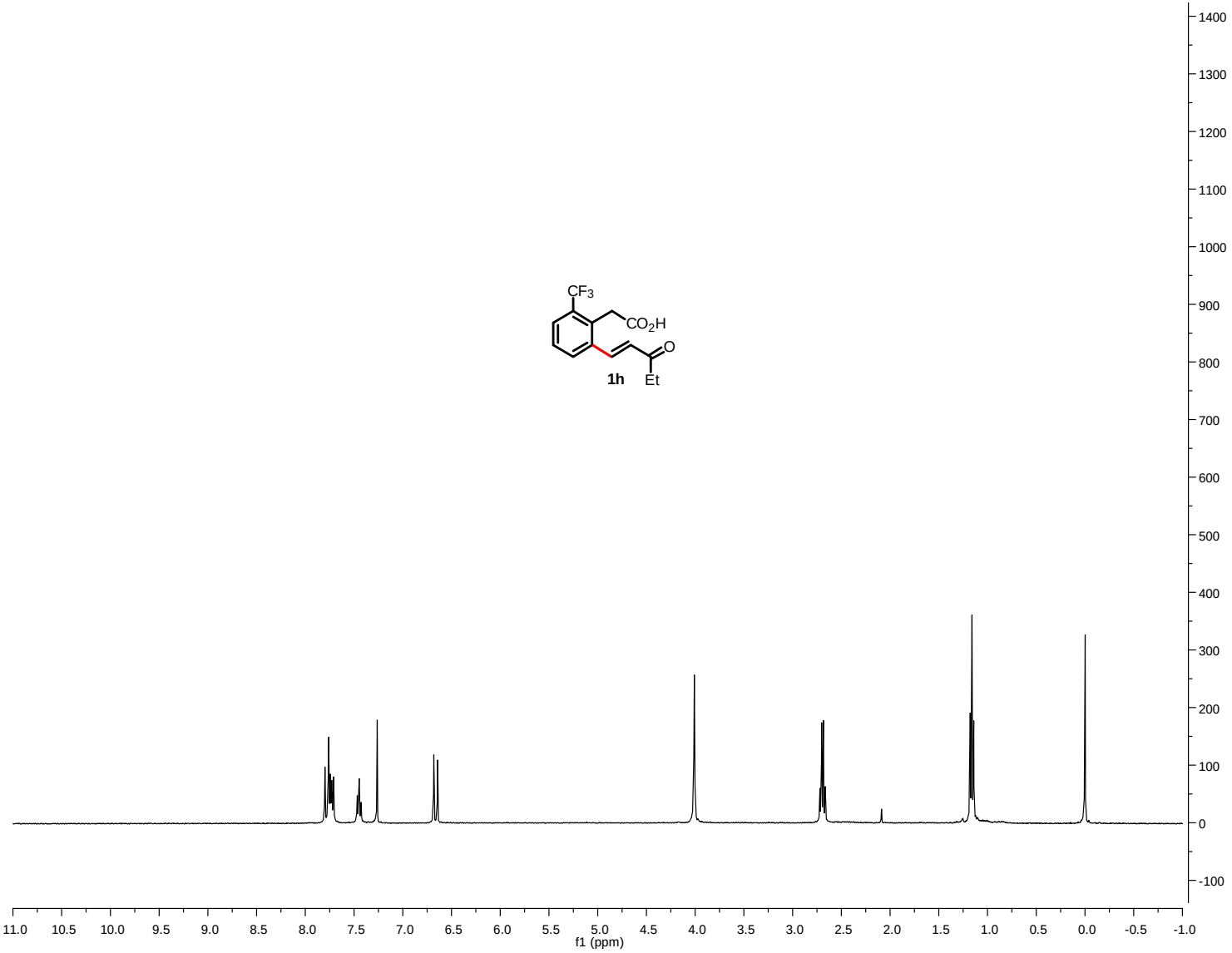

CF3
CO2H
n-Pr
1f
E:Z = 4:1
f1 (ppm)

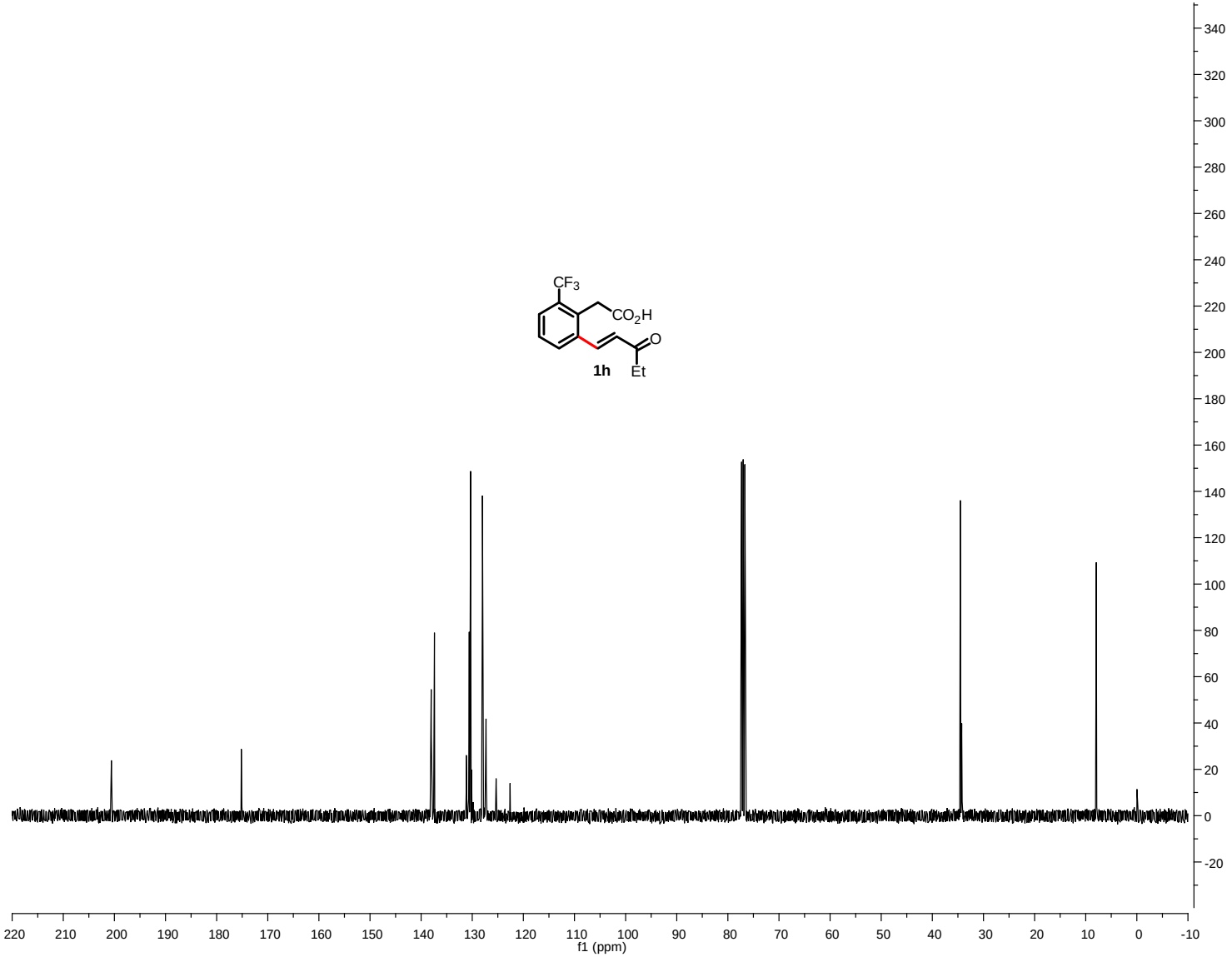

CF3
CO2H
n-Hex
1f'
25000
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


CF3
CO2H
n-Hex
1f'
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
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)


CF3
CO2H
O
Me
1g
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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 -1.0
f1 (ppm)


CF3
CO2H
O
Me
1g
500
450
400
350
300
250
200
150
100
50
0
-50
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)


CF3
CO2H
O
Et
1h
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
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
-1.0
f1 (ppm)


CF3
CO2H
O
1h
Et
340
320
300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
-20
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)