Catalyst and Additive-free Electrochemical CO_2 Fixation into Morita-Baylis-Hillman Acetates

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Table of contents

1. General Methods

^{1}H-NMR spectra were recorded on Varian 400 (400 MHz) . Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CHCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd= double doublet, t = triplet, td = triple doublet, dt = double triplet, q = quartet, b = broad, m = multiplet), coupling constants (Hz).

^{13}C-NMR spectra were recorded on a Varian 400 (400 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard ($CHCl_3$: 77.0 ppm).

HRMS spectra were obtained with a G2XS QTof mass spectrometer using either ESI or APCI ionization techniques, as specified case by case.

Chromatographic purification was done with 240-400 mesh silica gel.

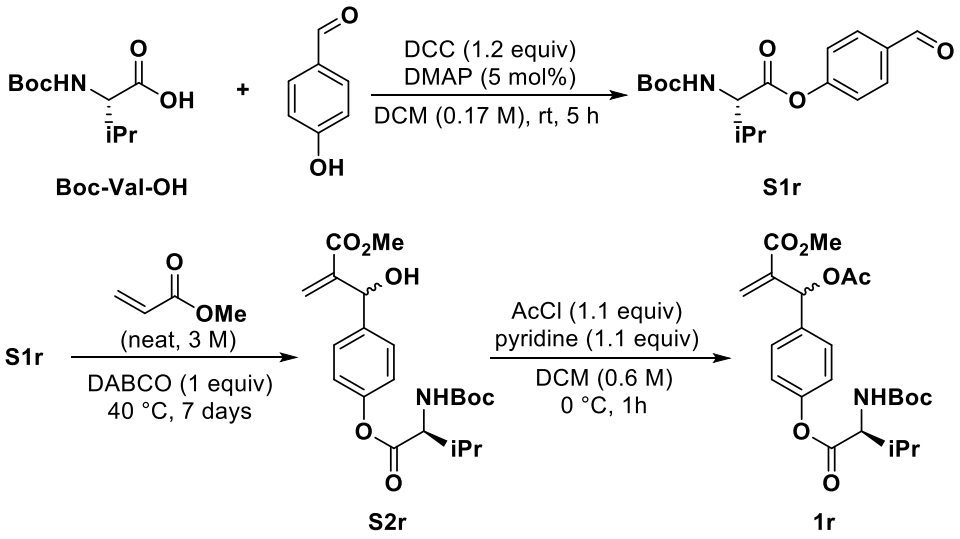
Anhydrous solvents, including DMF for the electrochemical processes, were supplied by Merck in Sureseal® bottles and used without any further purification.

All other commercially available starting materials and (non-anhydrous) solvents were purchased from Merck, TCI chemicals, Fluorochem or Alfa Aesar and were used as such without further purification.

Cyclic voltammetry experiments were carried out at room temperature in argon-purged dried CH_3CN by using an EcoChemie Autolab 30 potentiostat in a three-electrode setup. The working electrode consisted of a glassy carbon electrode (3 mm diameter), the counter electrode was a Pt spiral and a Ag wire was used as quasi-reference electrode (AgQRE). Working electrode and quasi-reference electrodes were polished on a felt pad with 0.05 or 0.3 μm alumina suspension and sonicated in deionized water for 1 minute before each experiment; the Pt wire was flame-cleaned. Tetrabutylammonium hexafluorophosphate ($TBAPF_6$, 0.1 M) is added to the solution as a supporting electrode. Ferrocene (purified by sublimation at reduced pressure) is used as an internal reference ($E_{Fc+/0}$ = 0.40 V vs. SCE).[1]

2. Synthesis of Starting Materials

MBH acetate **1r** was prepared from **S1r** following modified literature procedures.[2] **S1r** was prepared from Boc-Val-OH and 4-hydroxybenzaldehyde.

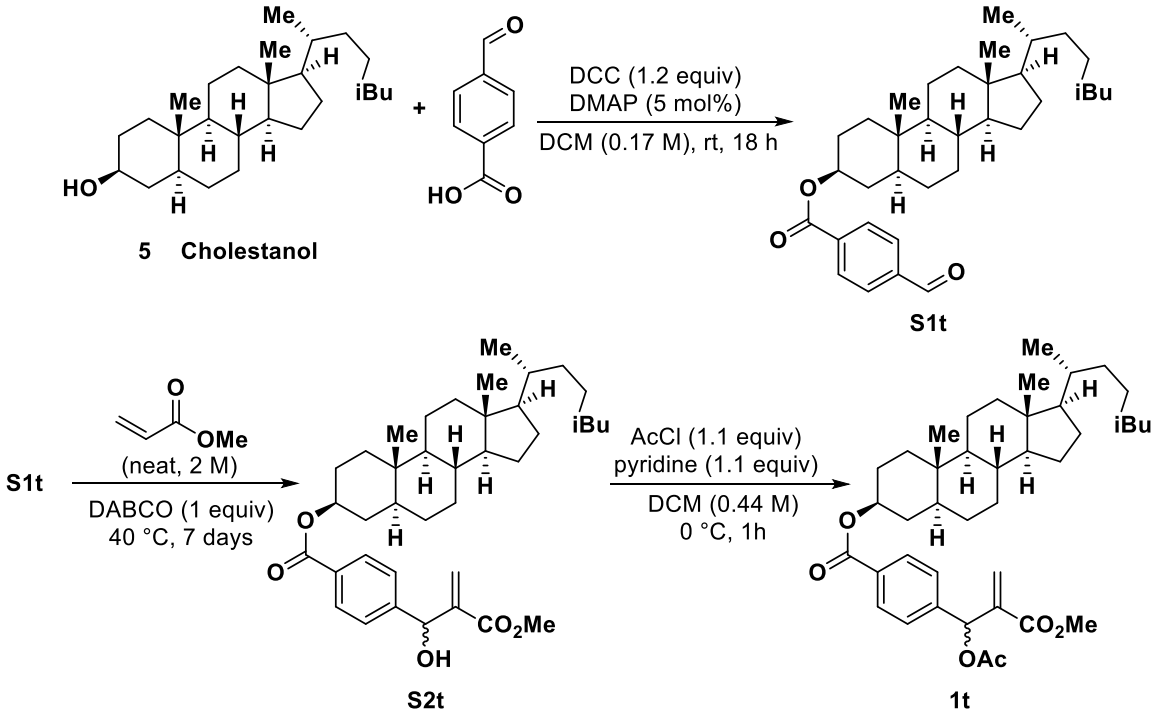


In a Schlenk tube under N_2 atmosphere, were added 4-hydroxybenzaldehyde (5.0 mmol, 560 mg), DCM (20 mL), Boc-Val-OH (5.0 mmol, 1.09 g) and DMAP (0.25 mmol, 31 mg). The suspension was cooled to 0 °C and a solution of *N,N'*-dicyclohexylcarbodiimide (DCC, 5.5 mmol, 1.13 g) in DCM (10 mL) was added dropwise. The mixture was then stirred at room temperature until TLC indicated full consumption of the starting materials (ca. 5 h). The mixture was then concentrated under reduced pressure to about 10 mL and the thick white suspension was filtered over Celite, washing with two small aliquots (2 mL ca.) of DCM. The filtrate was then diluted with DCM (20 mL) and transferred to a separatory funnel. The organic phase was washed with std. $NH_4Cl_{(aq)}$ (3 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude **S1r** that was used in the next step without further purification.

In a screw-capped 20-mL vial, crude **S1r** (3.0 mmol, 963 mg) and 1,4-diazabicyclo[2.2.2]octane (DABCO, 3.0 mmol, 522 mg) were stirred in methyl acrylate (10 mmol, 861 mg, 910 µL) for 7 days at 40 °C. The mixture was then evaporated under reduced pressure, dissolved in EtOAc and transferred to a separatory funnel. The organic phase was washed with 2M HCl (3 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude **S2r** that was used in the next step without further purification.

In a heat gun-dried Schlenk tube under N_2 atmosphere, were added **S2r** (3.0 mmol, from previous step), dry DCM (5 mL) and pyridine (3.3 mmol, 261 mg, 267 µL). The solution was cooled to 0 °C and acetyl chloride (3.3 mmol, 259 mg, 236 µL) was added dropwise. The resulting white suspension was stirred at 0 °C until TLC indicated full consumption of the starting materials (ca. 1 h). The reaction was quenched with H_2O (5 mL) and std. NH_4Cl_{aq} (5 mL), transferred to a separatory funnel, the aqueous phase extracted with DCM (2 x 10 mL), and the organic phase dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by FC on silica gel (*c*Hex/EtOAc: 2:1) to afford **1r** (*dr* = 1:1) as a very thick, sticky colorless oil (738 mg, 1.56 mmol, 52% yield over 2 steps). **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 7.41 – 7.33 (m, 2H), 7.08 – 7.01 (m, 2H), 6.65 (s, 1H), 6.37 (s, 1H), 5.86 (s, 1H), 5.05 (d, *J* = 9.0 Hz, 1H), 4.41 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.68 (s, 3H), 2.33 – 2.22 (m, 1H), 2.07 (s, 3H), 1.44 (s, 9H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), the signals of the two diastereoisomers overlap completely, appearing as a single compound; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 170.9, 169.3, 165.2, 155.7, 150.3, 139.4, 135.6, 128.9 (2C), 125.7, 121.4 (2C), 80.0, 72.4, 58.7, 52.0, 31.3, 28.3 (3C), 21.0, 19.0, 17.7, the signals of the two diastereoisomers overlap completely, appearing as a single compound. **HRMS (APCI)** m/z: $[M+H]^+$ calcd. for $C_{23}H_{32}NO_8$ 450.2122; found 450.2114.

MBH acetate **1t** was prepared from **S1t** following modified literature procedures.[2] **S1t** was prepared from 5α-Cholestanol and 4-formylbenzoic acid.



In a Schlenk tube under N_2 atmosphere, were added 4-formylbenzoic acid (4.0 mmol, 600 mg), DCM (15 mL), 5α-Cholestanol (4.0 mmol, 1.55 g) and DMAP (0.20 mmol, 25 mg). The suspension was cooled to 0 °C and a solution of DCC (4.4 mmol, 906 mg) in DCM (8 mL) was added dropwise. The mixture was then stirred at room temperature until TLC indicated full consumption of the starting materials (ca. 18 h). The mixture was then concentrated under reduced pressure to about 8 mL and the thick white suspension was filtered over Celite, washing with two small aliquots (2 mL ca.) of DCM. The filtrate was then diluted with DCM (20 mL) and transferred to a separatory funnel. The organic phase was washed with std. $NH_4Cl_{(aq)}$ (3 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude **S1t** that was used in the next step without further purification.

In a screw-capped 20-mL vial, crude **S1t** (2.0 mmol, 1.04 mg) and DABCO (2.0 mmol, 348 mg) were stirred in methyl acrylate (10 mmol, 861 mg, 910 µL) for 7 days at 40 °C, until a clear solution was obtained. The mixture was then evaporated under reduced pressure, dissolved in EtOAc and transferred to a separatory funnel. The organic phase was washed with 2M HCl (3 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford crude **S2t** that was used in the next step without further purification.

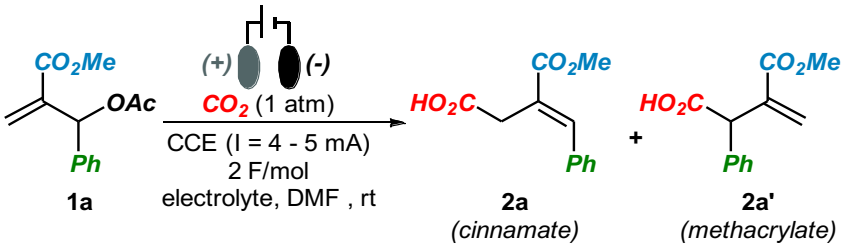
In a heat gun-dried Schlenk tube under N_2 atmosphere, were added **S2t** (2.0 mmol, from previous step), dry DCM (5 mL) and pyridine (2.2 mmol, 174 mg, 178 µL). The solution was cooled to 0 °C and acetyl chloride (2.2 mmol, 173 mg, 157 µL) was added dropwise. The resulting white suspension was stirred at 0 °C until TLC indicated full consumption of the starting materials (ca. 1 h). The reaction was quenched with H_2O (5 mL) and std. NH_4Cl_{aq} (5 mL), transferred to a separatory funnel, the aqueous phase extracted with DCM (2 x 10 mL), and the organic phase dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by FC on silica gel (100% DCM) to afford **1t** (*d.r.* = 1.0:1) as a white solid (1.02 g, 1.54 mmol, 77% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 – 7.95 (m, 2H), 7.45 – 7.38 (m, 2H), 6.68 (s, 1H), 6.39 (s, 1H), 5.86 (s, 1H), 4.91 (tt, *J* = 11.3, 4.9 Hz, 1H), 3.68 (s, 3H), 2.09 (s, 3H), 1.99 – 1.86 (m, 2H), 1.84 – 1.72 (m, 2H), 1.72 – 1.60 (m, 3H), 1.60 – 1.41 (m, 4H), 1.40 – 1.16 (m, 10H), 1.15 – 0.92 (m, 9H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H) overlapped with 0.84 (s, 3H) overlapped with 0.83 (d, *J* = 6.5 Hz, 3H), 0.71 – 0.63 (m, 1H) overlapped with 0.64 (s, 3H), the signals of the two diastereoisomers overlap completely, appearing as a single compound; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 169.2, 165.6, 165.1, 142.5, 139.2, 130.9, 129.7 (2C), 127.4 (2C), 126.3, 74.4, 72.6, 56.4, 56.3, 54.2, 52.0, 44.7, 42.6, 40.0, 39.5, 36.8, 36.1, 35.8, 35.5, 34.1, 32.0, 31.6, 28.6, 28.2, 28.0, 27.5, 24.2, 23.8, 22.8, 22.5, 21.2, 21.0, 18.6,

12.3, 12.1, the signals of the two diastereoisomers overlap completely, appearing as a single compound; **HRMS (APCI)** m/z: $[M+H]^+$ calcd. for $C_{41}H_{61}O_6$ 649.4463; found 649.4471.

3. Additional Optimization Tables

3.1. **Table S1**: Additional optimization entries



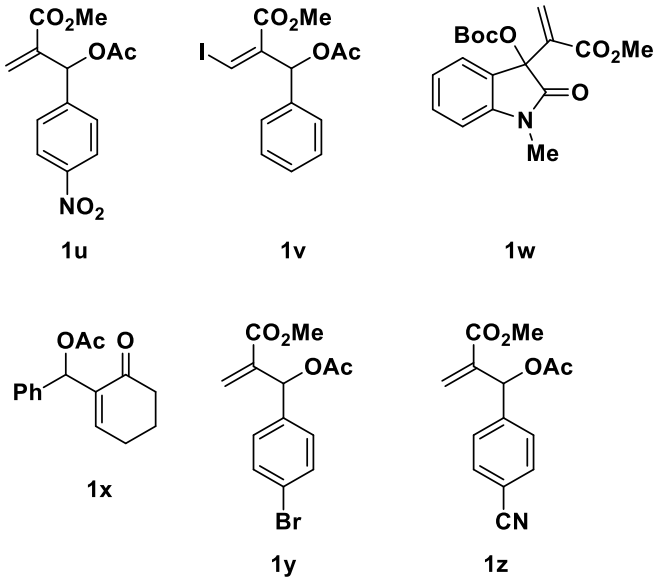
Entry[a]	Electrolyte (0.1 M)	Additive (10 mol%)	Anode	Cathode	CCE, I [mA]	Yield [%][b] (**2a**:**2a'**)
1	$TEABF_4$	-	Zn	Ni_{foam}	5	48
2	$TEABF_4$	-	Zn	Ag	5	61
3	$TEABF_4$	$Zn(OAc)_2$	Zn	Ni	5	NR
4	$TEABF_4$	$Zn(OTf)_2$	Zn	Ni	5	NR
5	$TEABF_4$	Ni(**L1**)Cl_2[c]	Zn	$C_{(graphite)}$	4	24 (1.5:1)
6	$TEABF_4$	Ni(**L2**)Cl_2[d]	Zn	$C_{(graphite)}$	4	11 (1.5:1)
7	$TEABF_4$	PPh_3	Zn	$C_{(graphite)}$	4	dec.
8	$LiBF_4$	-	Zn	$C_{(graphite)}$	6	NR
9	$TBAClO_4$	-	Zn	$C_{(graphite)}$	6	70 (1.4:1)
10	$TBAPF_6$	-	Zn	$C_{(graphite)}$	6	7 (2.1:1)

[a] All reactions were carried in the Electrasyn 2.0 apparatus (undivided cell) under constant stirring and a net CO_2 atmosphere, [**1a**] = 0.05 M. [b] Isolated yields after flash chromatography. Regioisomeric ratios were determined via ^{1}H-NMR analysis on the reaction. [c] **L1** = 1,10-phenanthroline. [d] **L2** = neocuproine. NR: no reaction. dec.: decomposition.

Other metal cathodes (entries 1 and 2) promoted the reaction with less efficiency with respect to optimal Ni. Lewis acid additives or electrolytes (entries 3, 4 and 8) suppressed the reactivity completely. A Lewis basic additive (entry 7) led to decomposition of **1a**. Attempts to modify the reactivity and the selectivity of the present reaction by means of Ni catalysis (entries 5 and 6) proved unsuccessful. While a low chemical yield (and unmodified regiochemical outcomes) where recorded, substantial decomposition of **1a** was observed (complete consumption, as judged form

the ^{1}H NMR recorded on the crude mixture). Inert electrolytes different from $TEABF_4$ were screened: while $TBAClO_4$ led to almost the same result, $TBAPF_6$ decreased the reaction efficiency.

3.2. Unsuccessful substrates



Complex mixtures were obtained in the case of substrates **1u** and **1z**, probably due to the concomitant reduction of electron-deficient nitro- and cyano-groups. Dehalogenation was observed in the case of **1v** (without carboxylation) and **1y** (with small amounts of carboxylated material). Substantial decomposition was observed for **1w** and **1x** showed no reactivity.

4. Cyclovoltammetry Experiments

Cyclic voltammetry experiments were carried out in ACN with $TBAPF_6$ as the supporting electrolyte. MBH Acetate **1a** shows a chemically irreversible reduction process with E_{pc} = -2.08 V *vs* SCE at a scan rate of 3 V/s. No significant oxidation processes were identified in the available potential window.

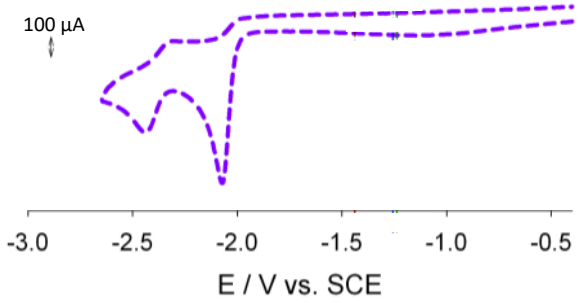
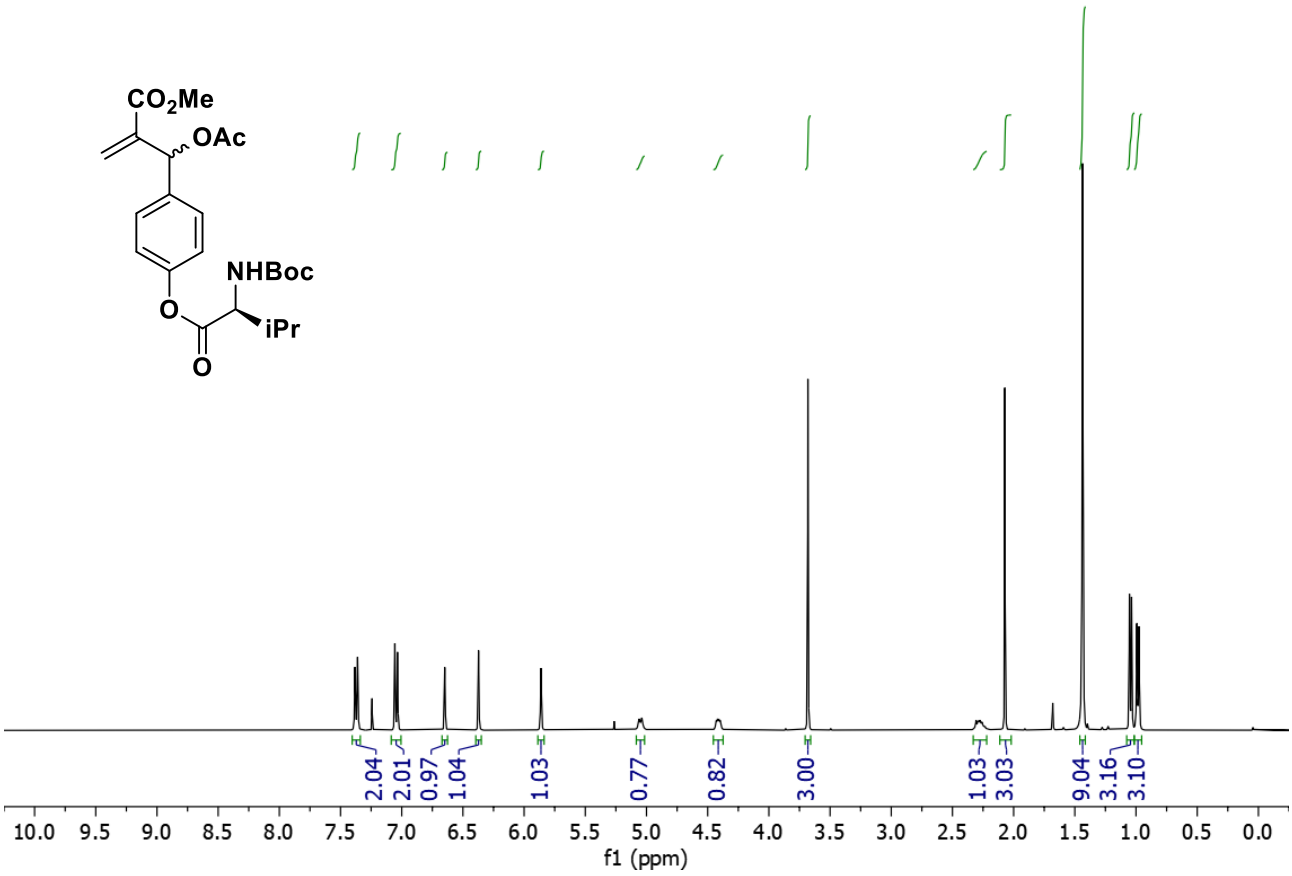


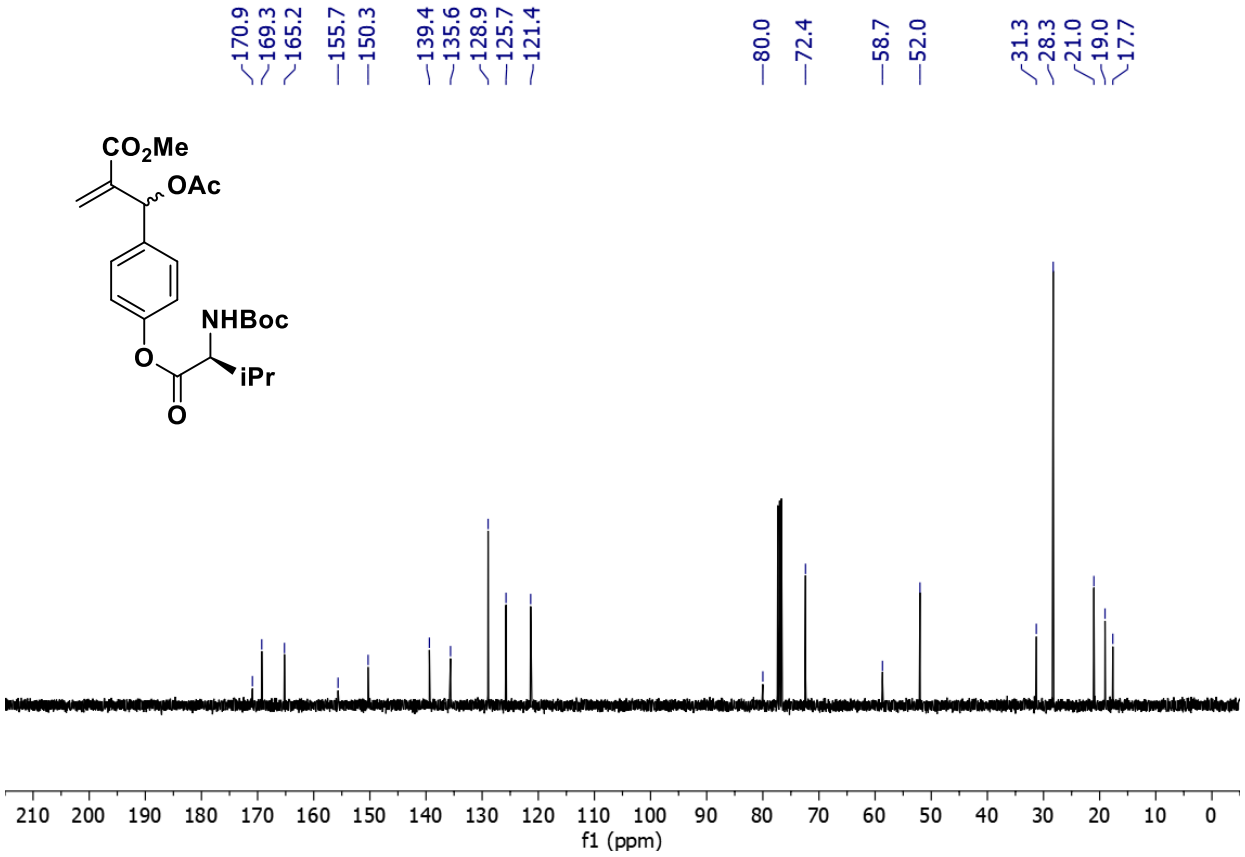
Figure S2. Reduction wave in CH_3CN for **1a** (1.0 mM, scan rate 3 V/s) The vertical arrow indicates a 100 µA current.

5. ^{1}H-, ^{19}F-, ^{13}C-NMR Spectra of New Compounds

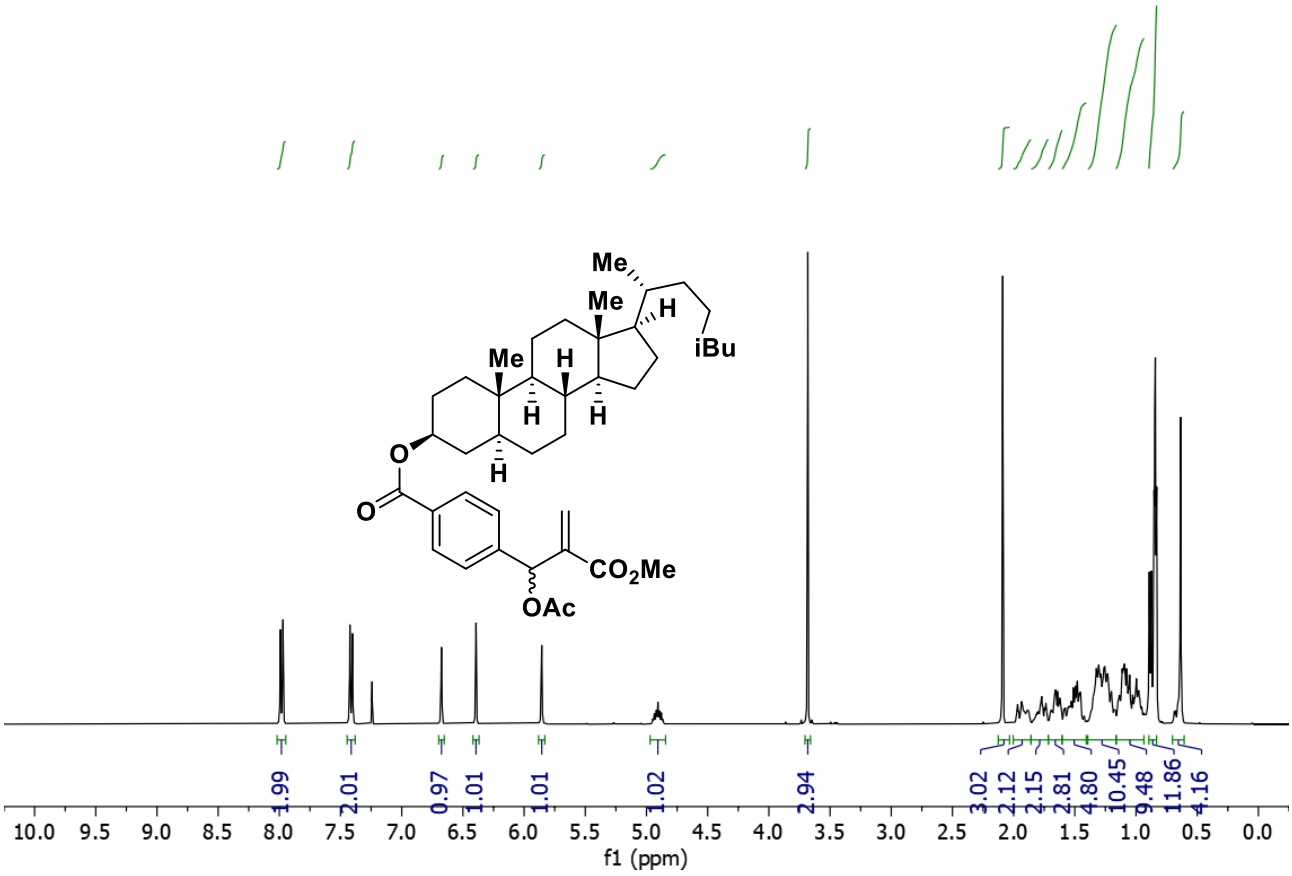
1r ^{1}H NMR (400 MHz, $CDCl_3$)



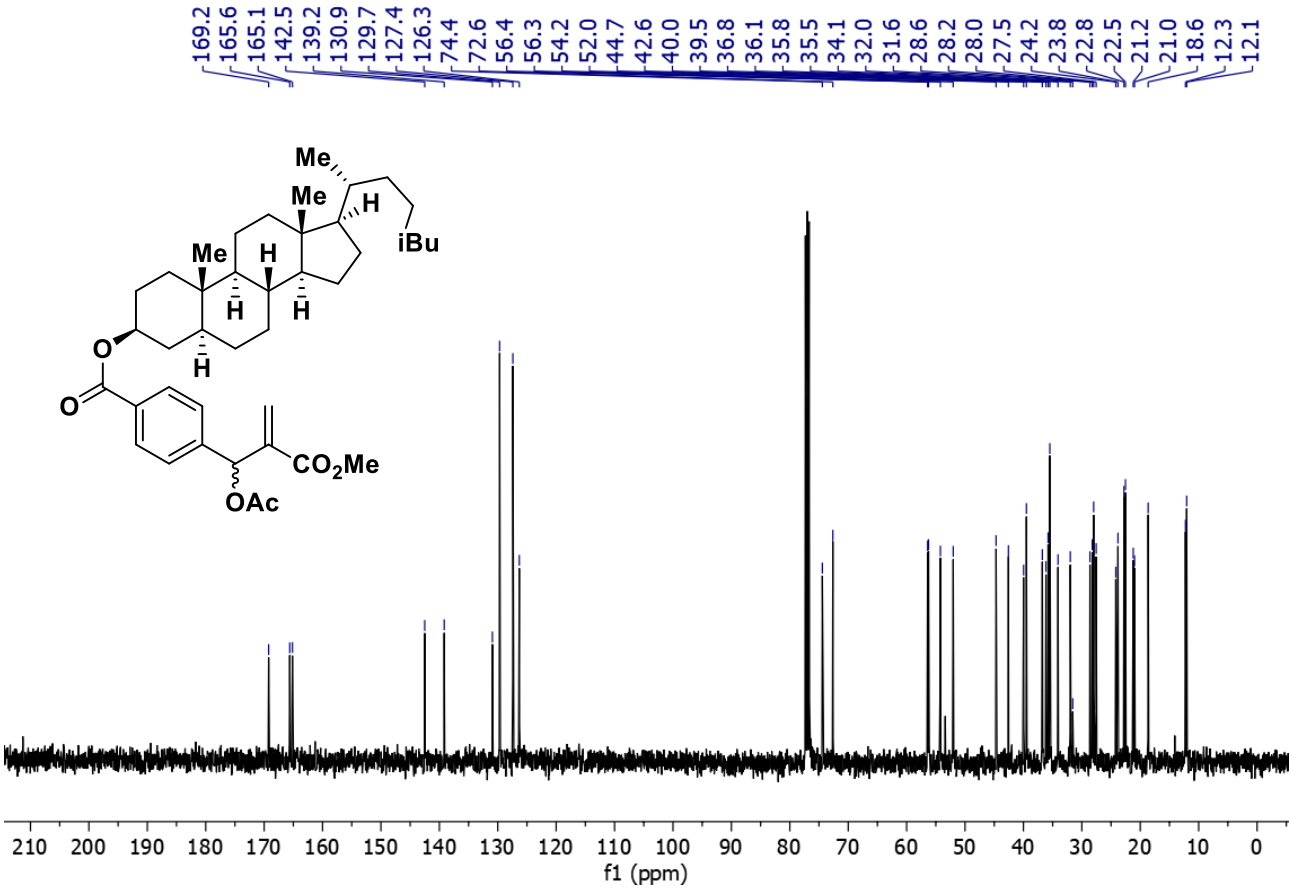
1r ^{13}C NMR (100 MHz, $CDCl_3$)


170.9
169.3
165.2
155.7
150.3
139.4
135.6
128.9
125.7
121.4
80.0
72.4
58.7
52.0
31.3
28.3
21.0
19.0
17.7
CO2Me
OAc
NHBoc
O
iPr
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

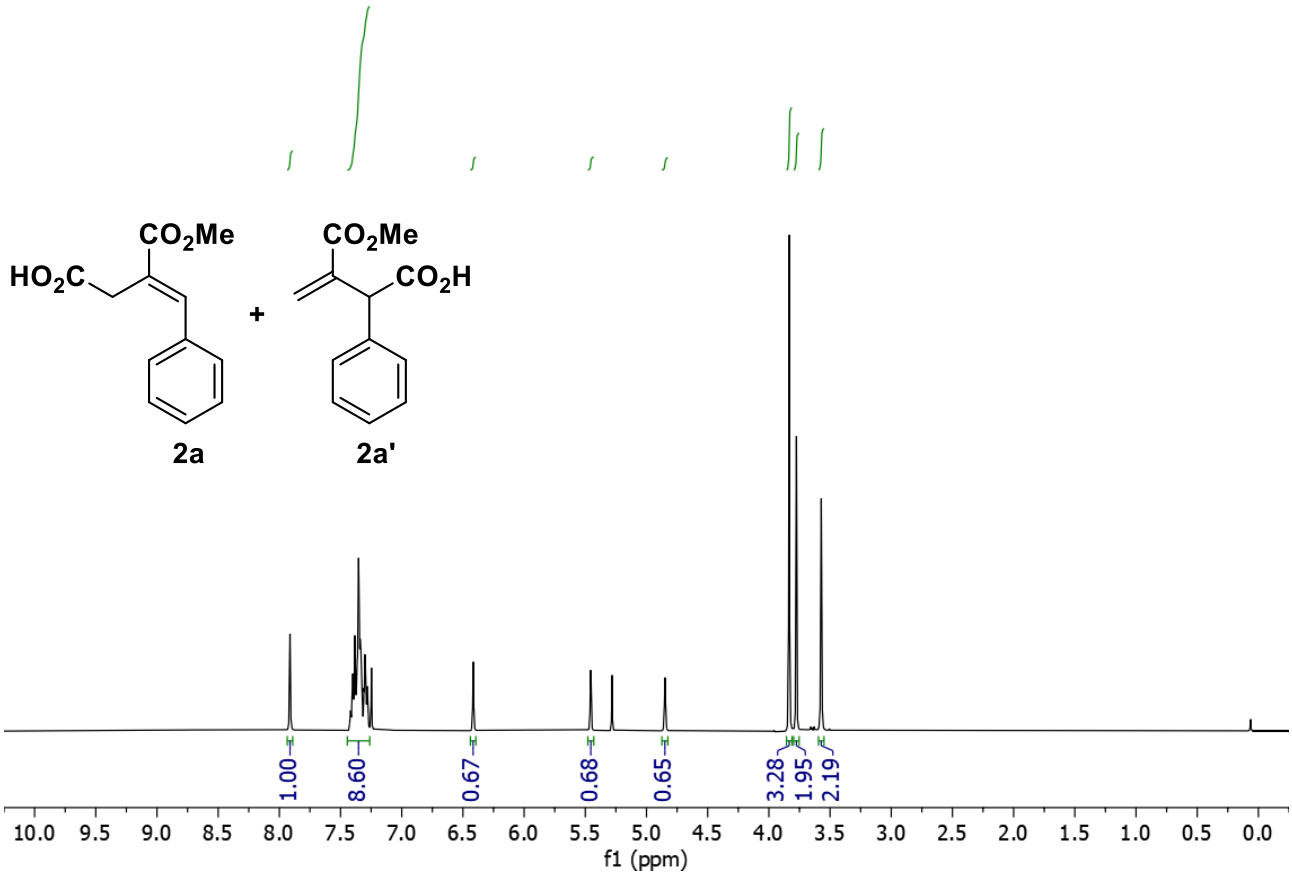
1t ^{1}H NMR (400 MHz, $CDCl_3$)



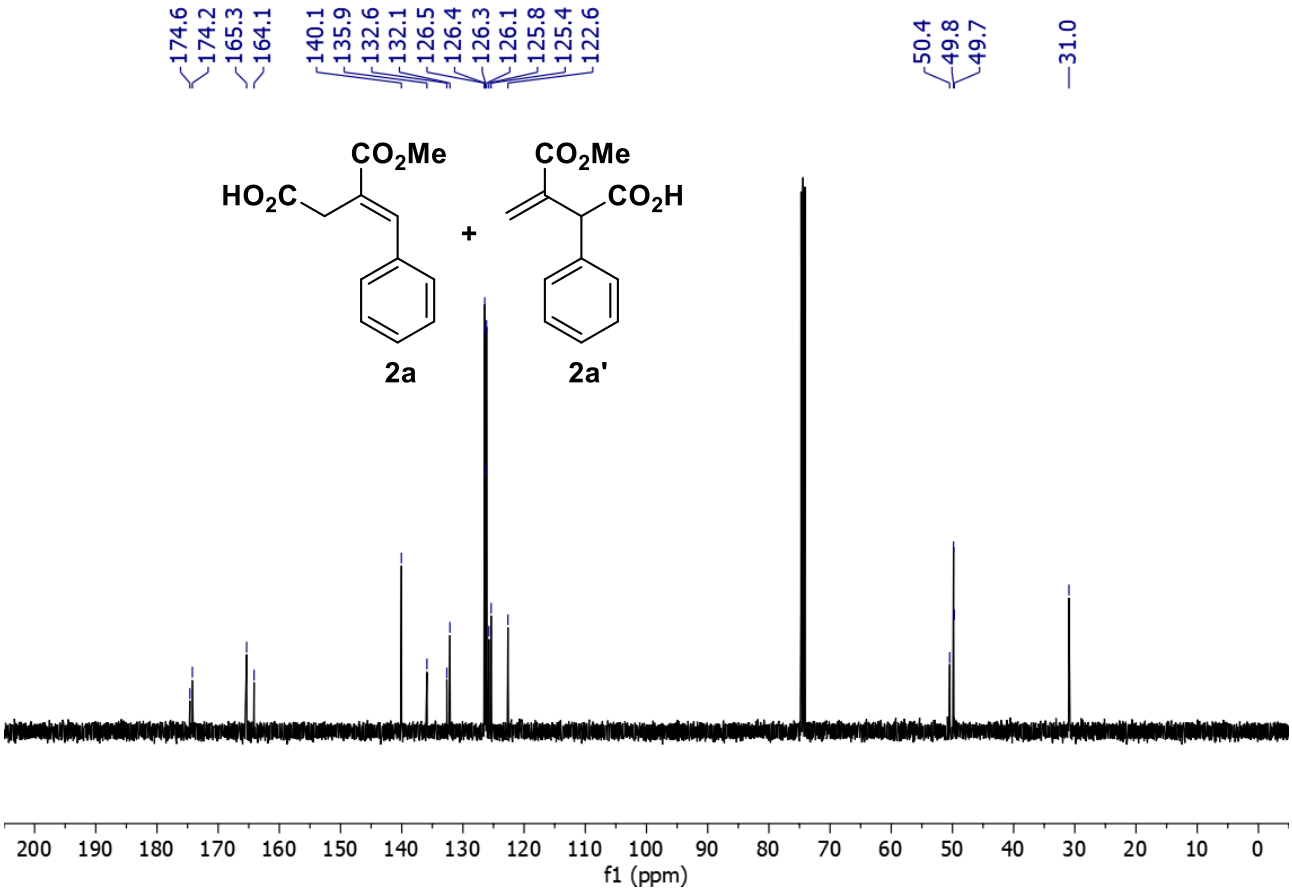
1t ^{13}C NMR (100 MHz, $CDCl_3$)



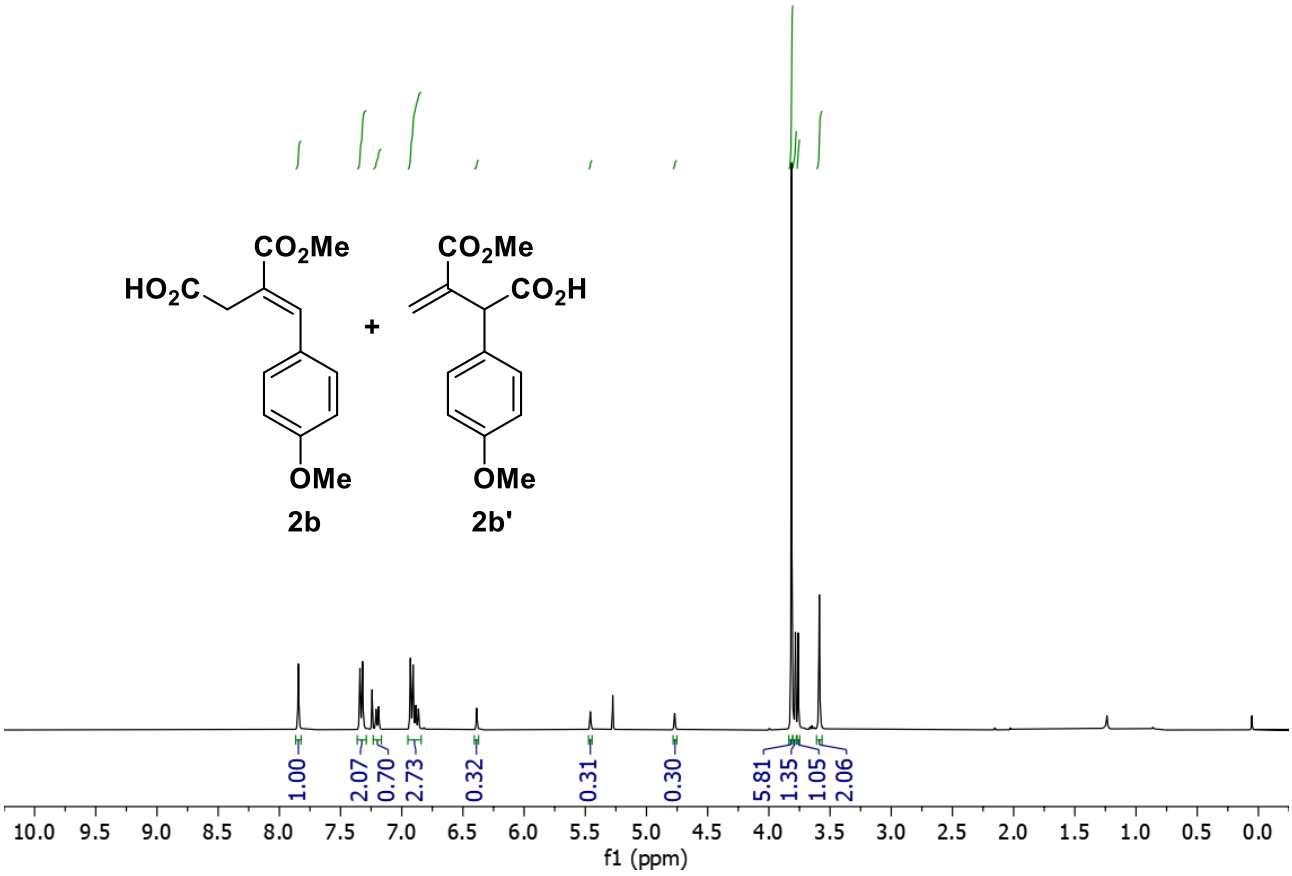
2a and 2a' ^{1}H NMR (400 MHz, $CDCl_3$)



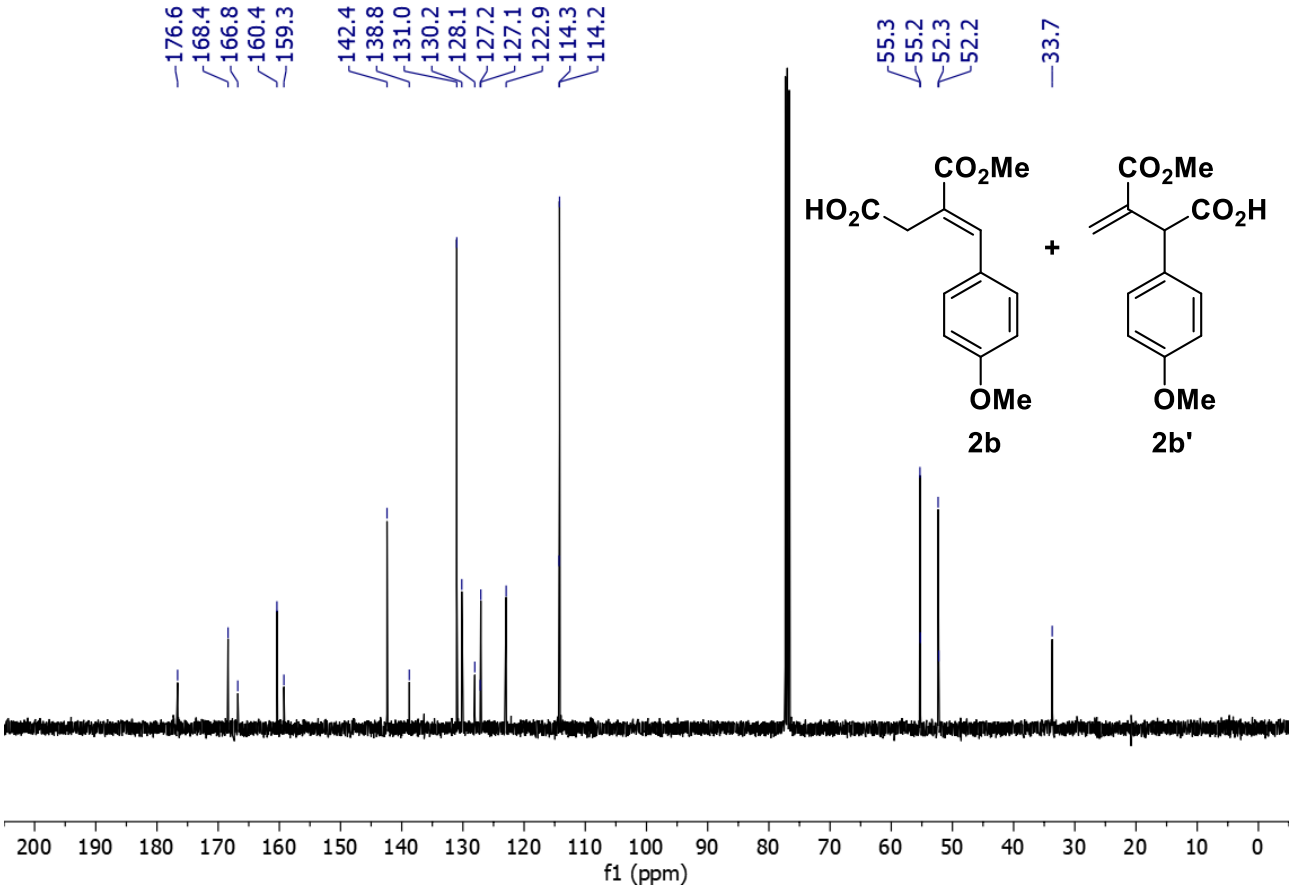
2a and 2a' ^{13}C NMR (100 MHz, $CDCl_3$)


174.6
174.2
165.3
164.1
140.1
135.9
132.6
132.1
126.5
126.4
126.3
126.1
125.8
125.4
122.6
50.4
49.8
49.7
31.0
CO2Me
HO2C
+
CO2Me
CO2H
2a
2a'
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

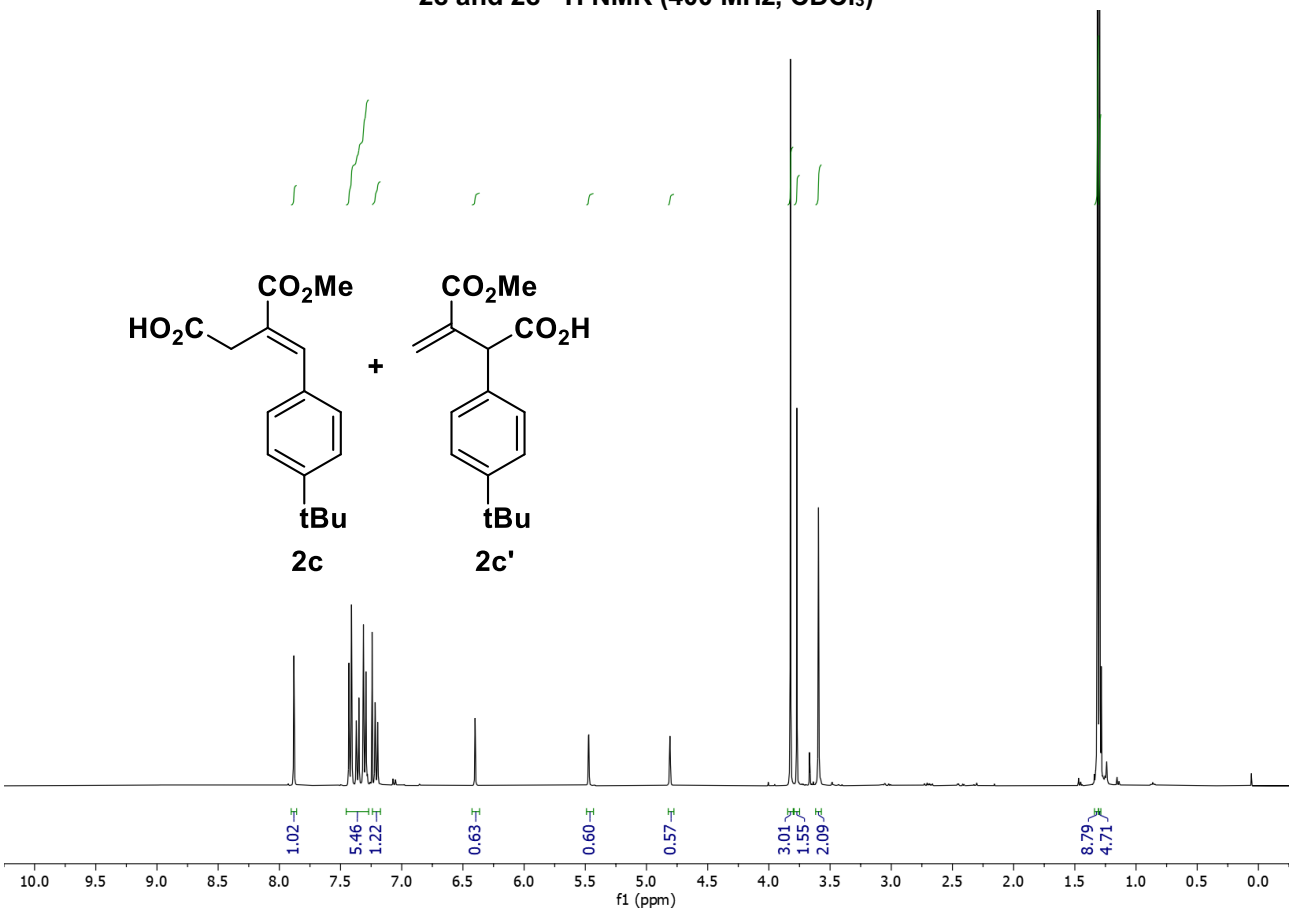
2b and 2b' ^{1}H NMR (400 MHz, $CDCl_3$)



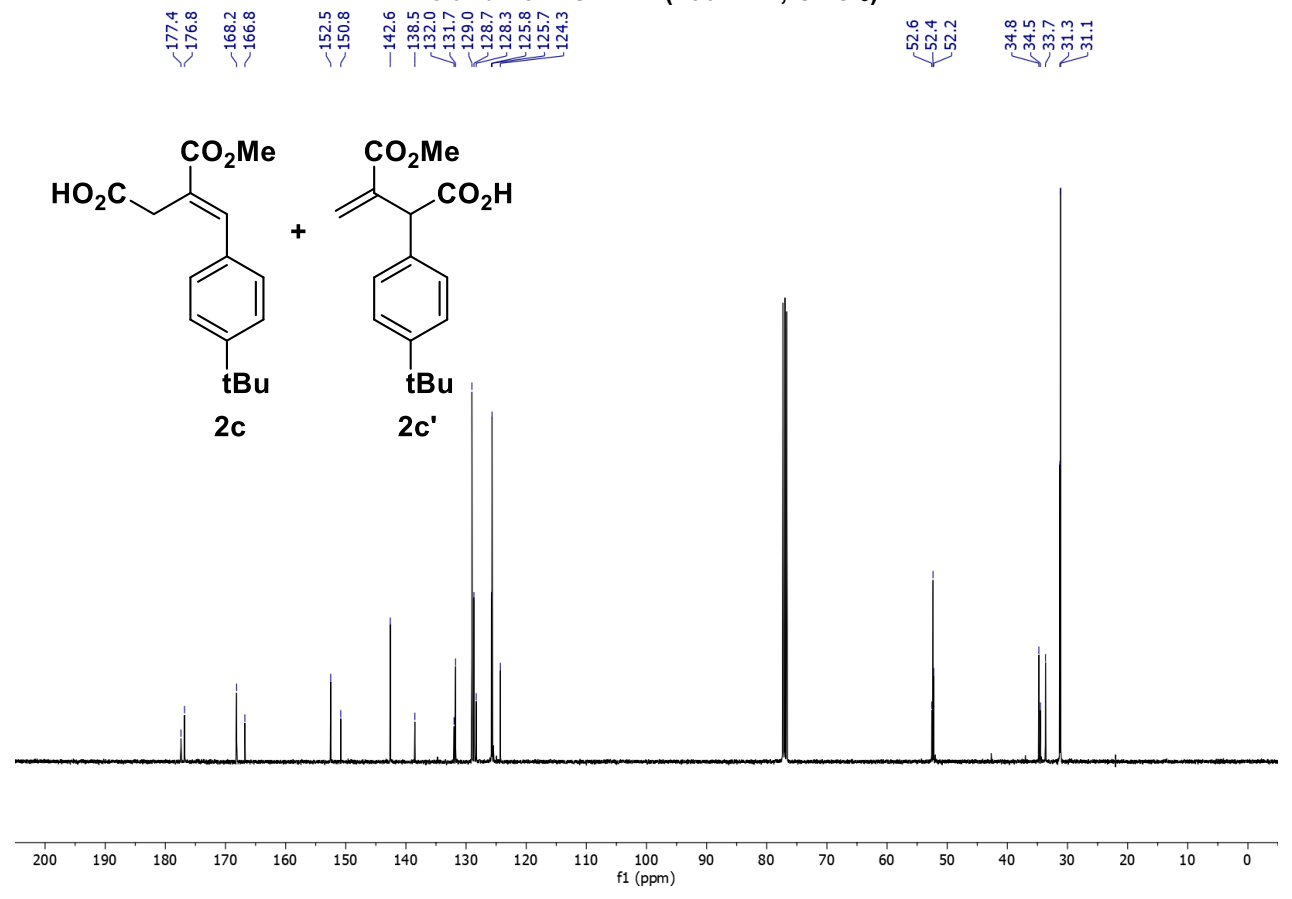
2b and 2b' ^{13}C NMR (100 MHz, $CDCl_3$)



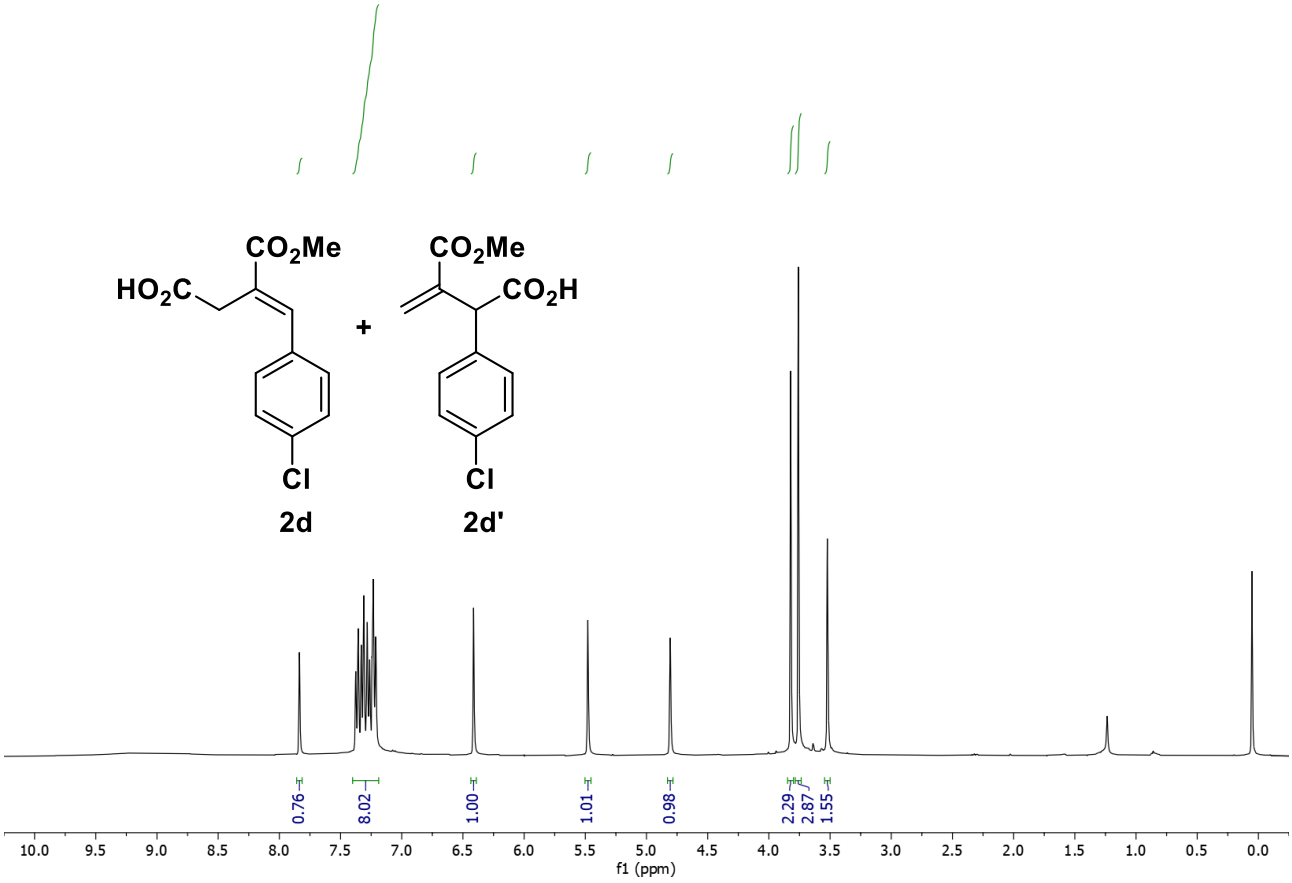
2c and 2c' ^{1}H NMR (400 MHz, $CDCl_3$)



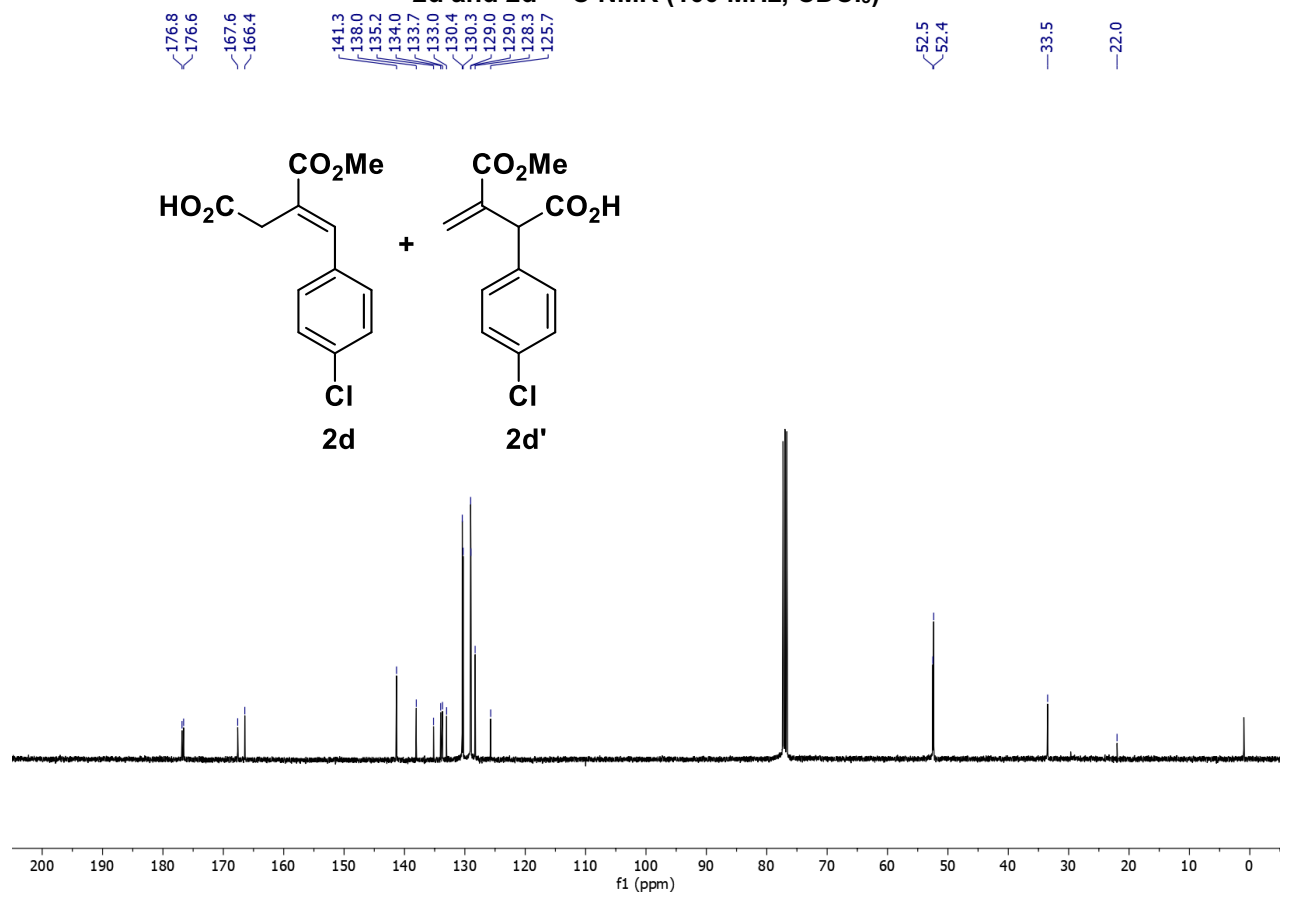
2c and 2c' ^{13}C NMR (100 MHz, $CDCl_3$)



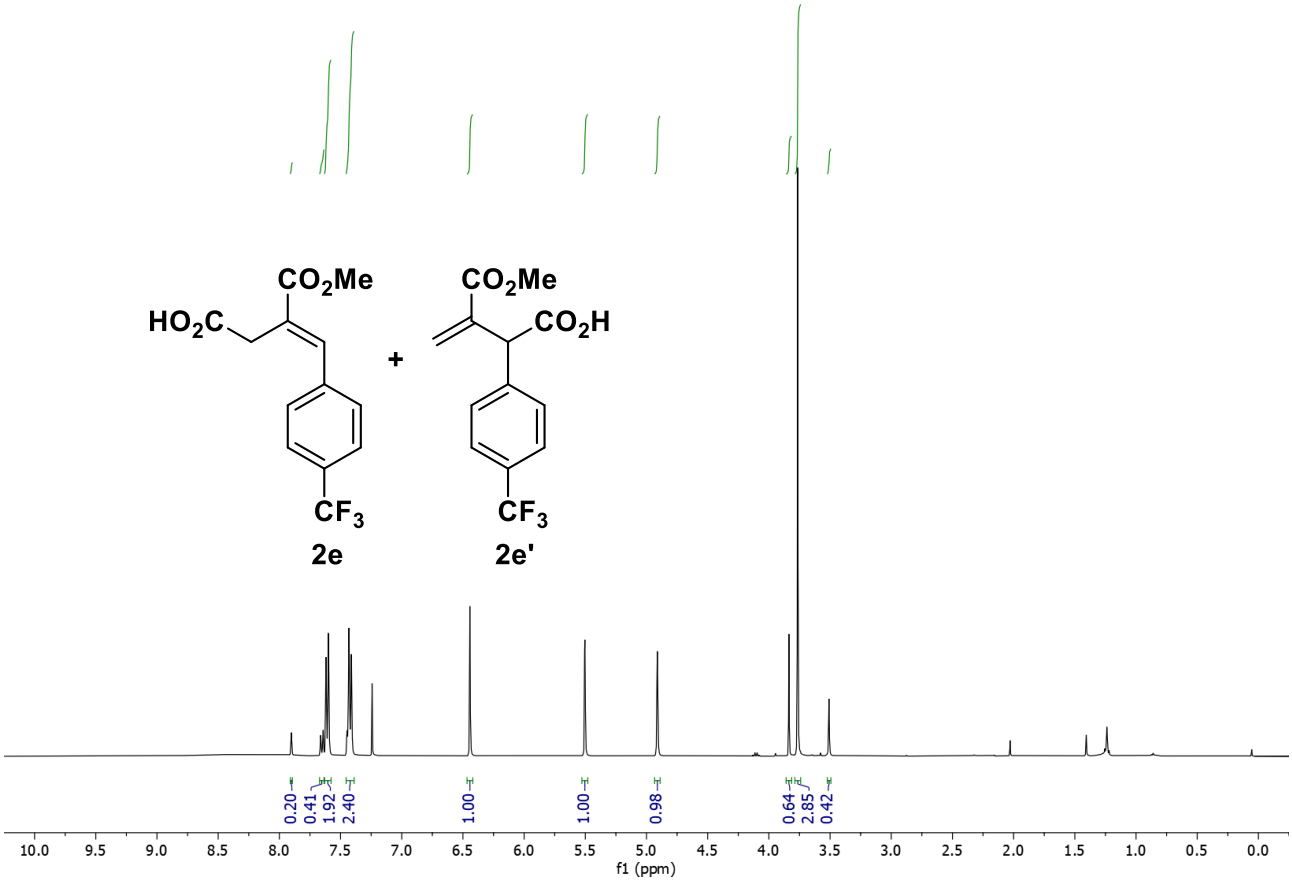
2d and 2d' ^{1}H NMR (400 MHz, $CDCl_3$)



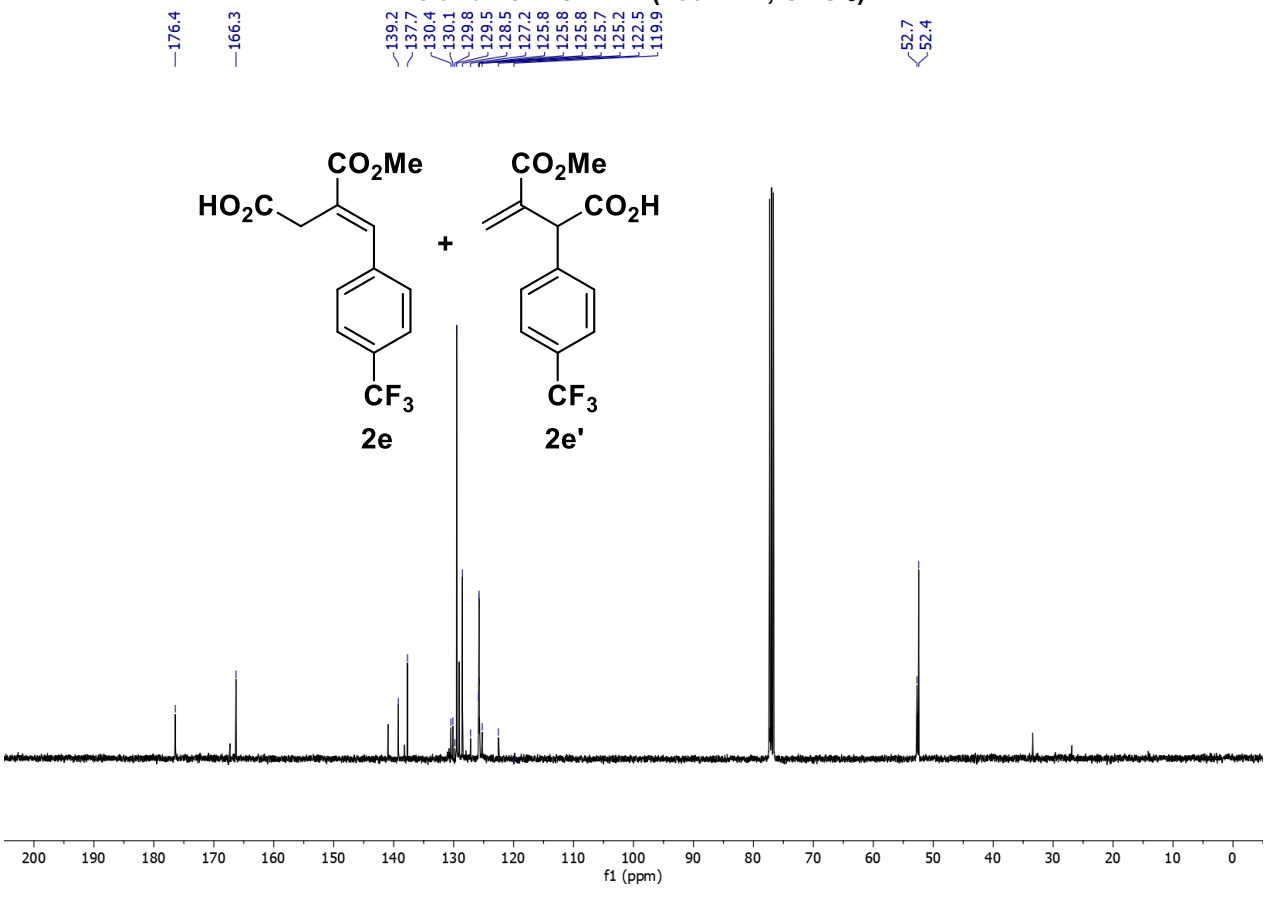
2d and 2d' ^{13}C NMR (100 MHz, $CDCl_3$)



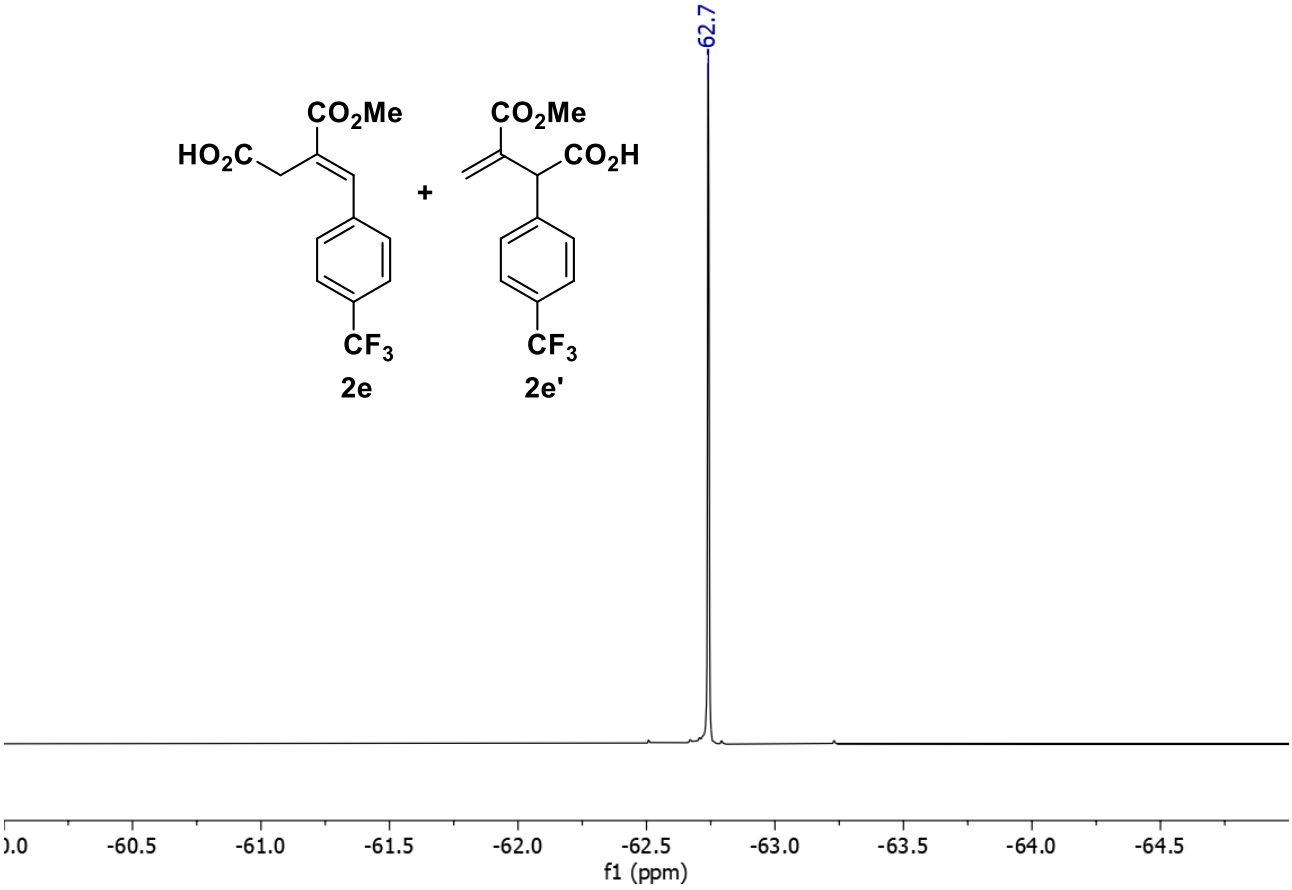
2e and 2e' ^{1}H NMR (400 MHz, $CDCl_3$)



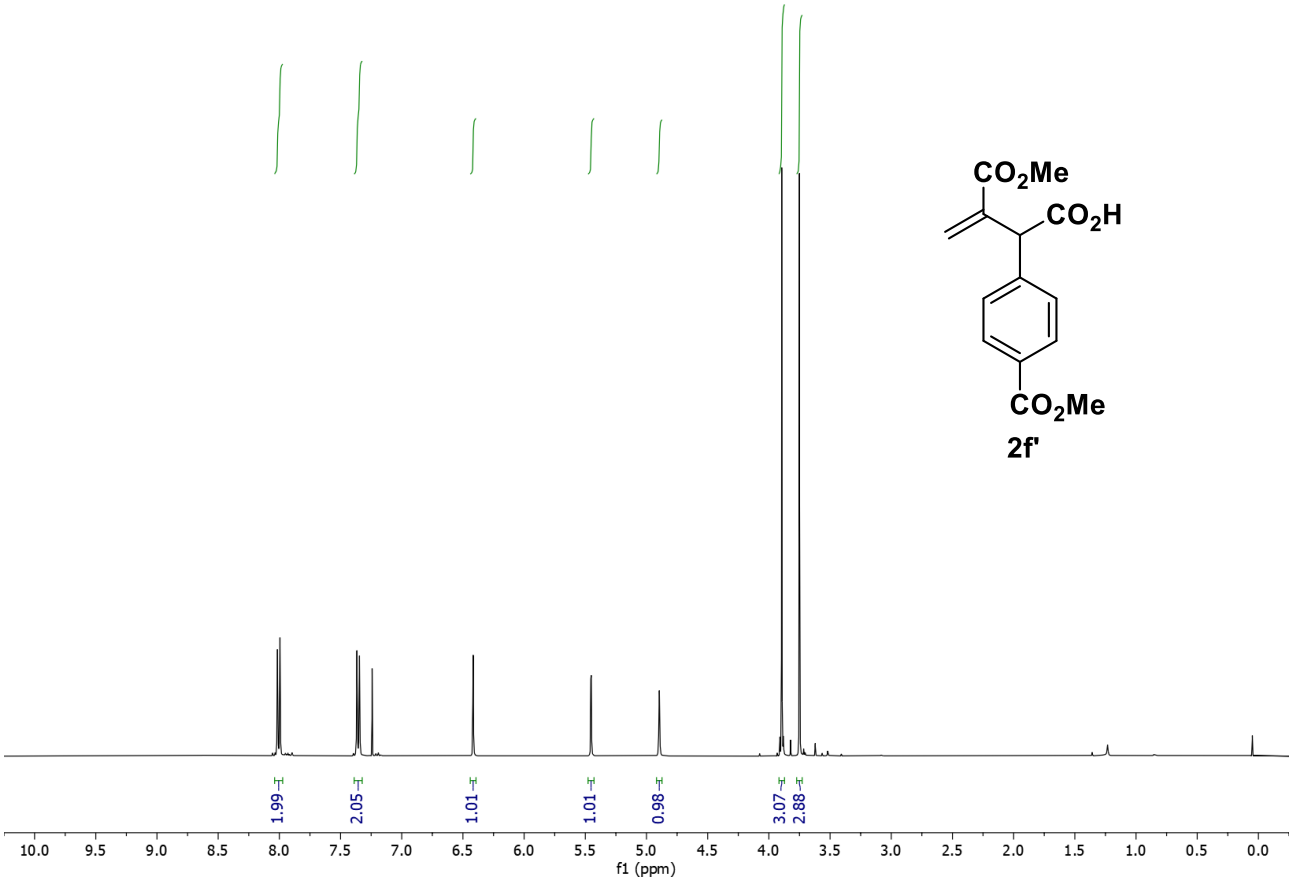
2e and 2e' ^{13}C NMR (100 MHz, $CDCl_3$)



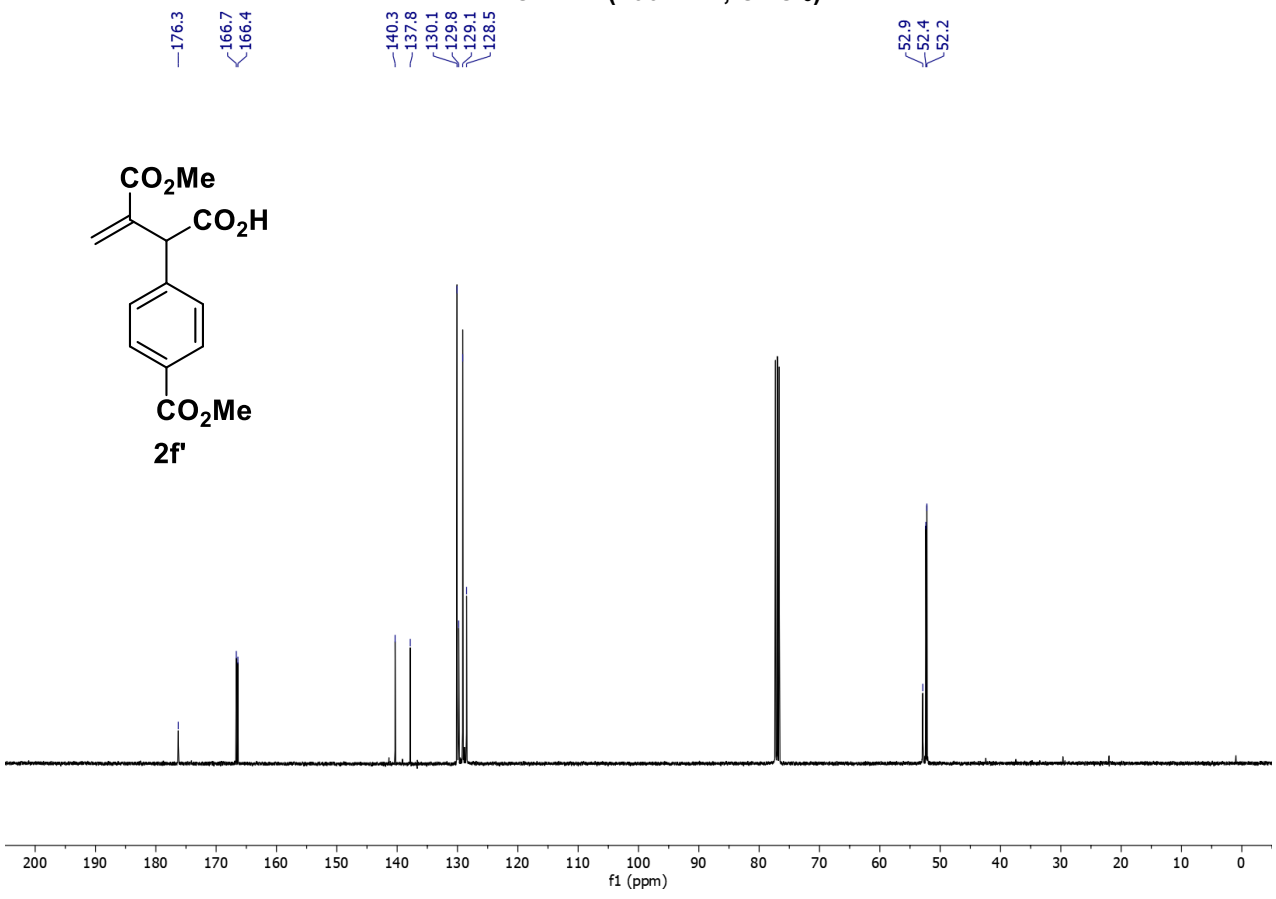
2e and 2e' ^{13}C NMR (376 MHz, $CDCl_3$)



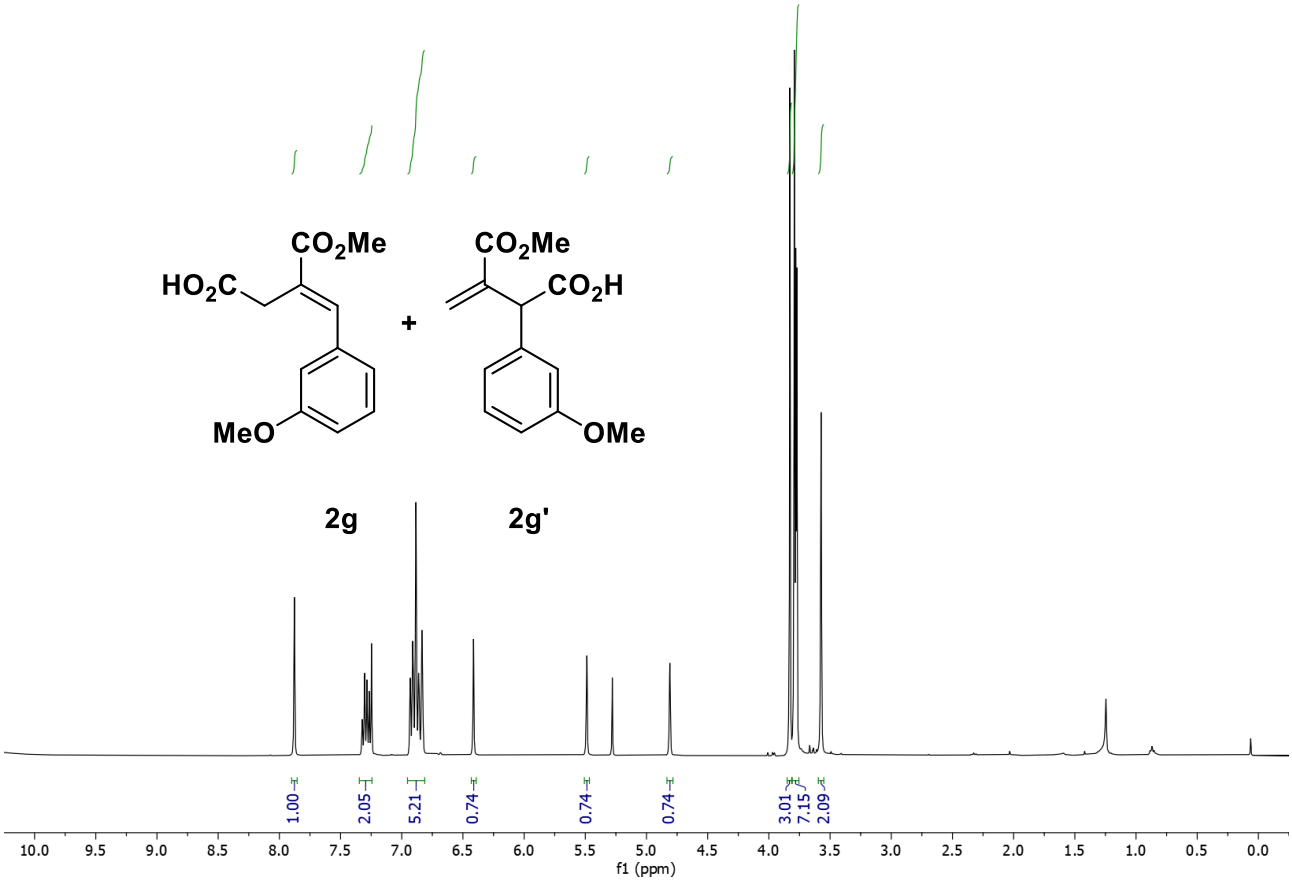
2f' ^{1}H NMR (400 MHz, $CDCl_3$)



2f' ^{13}C NMR (100 MHz, $CDCl_3$)

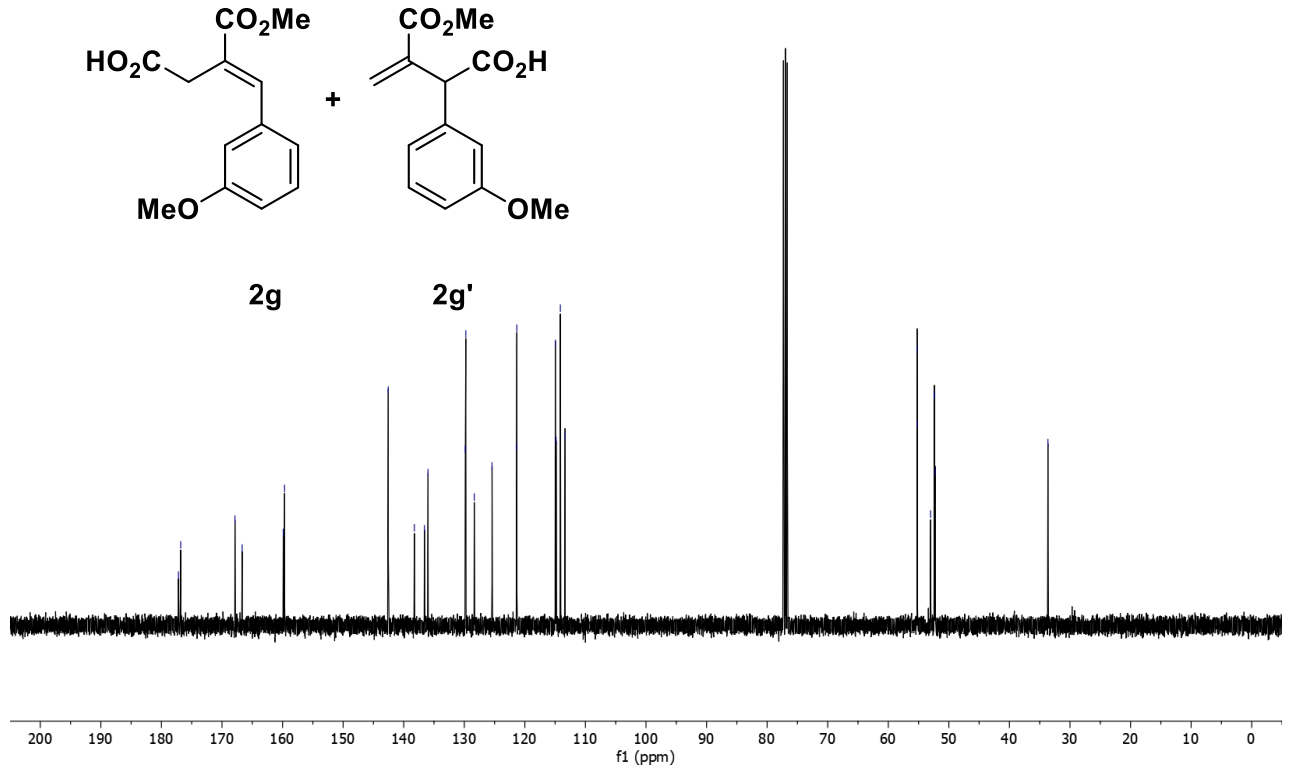


2g and 2g' ^{1}H NMR (400 MHz, $CDCl_3$)

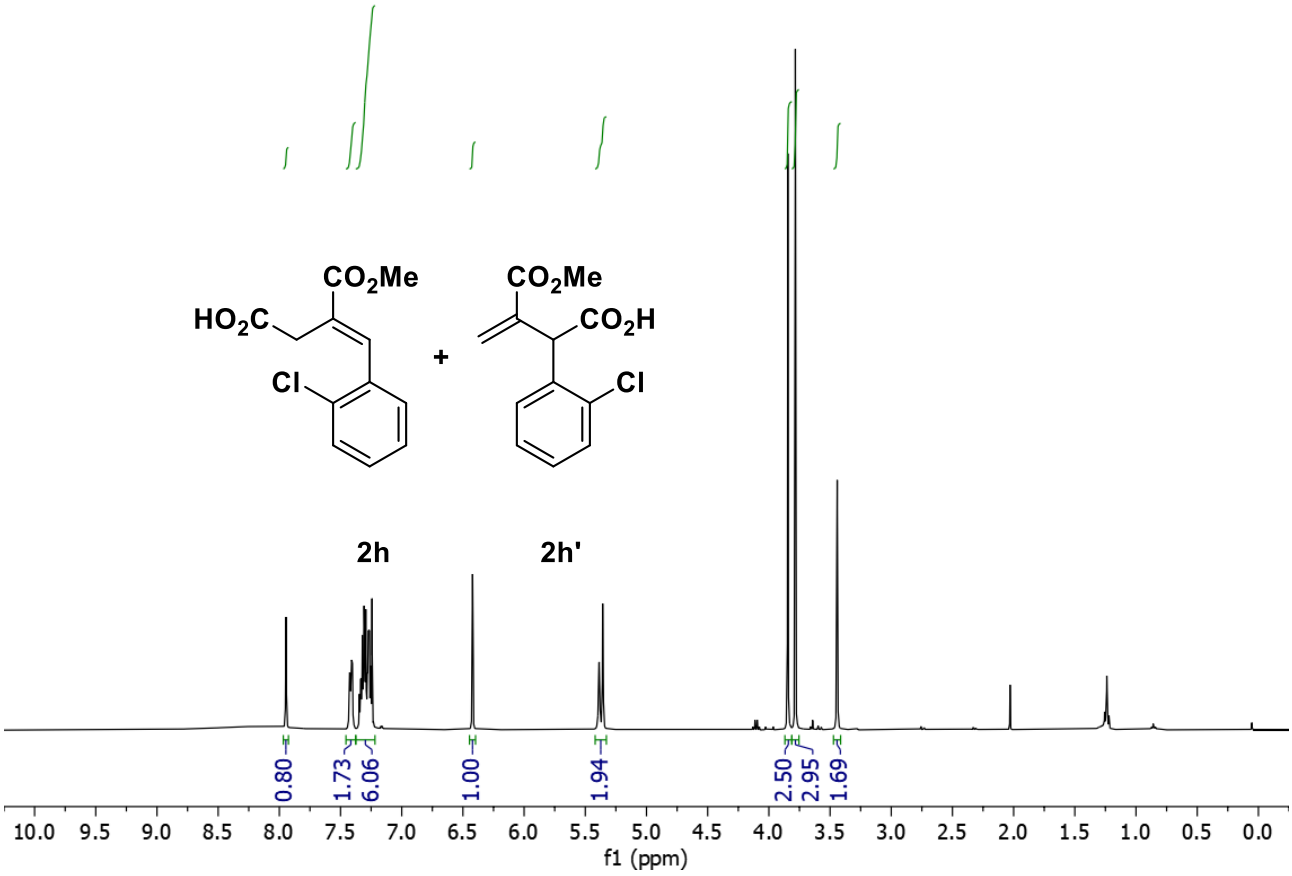


2g and 2g' ^{13}C NMR (100 MHz, $CDCl_3$)

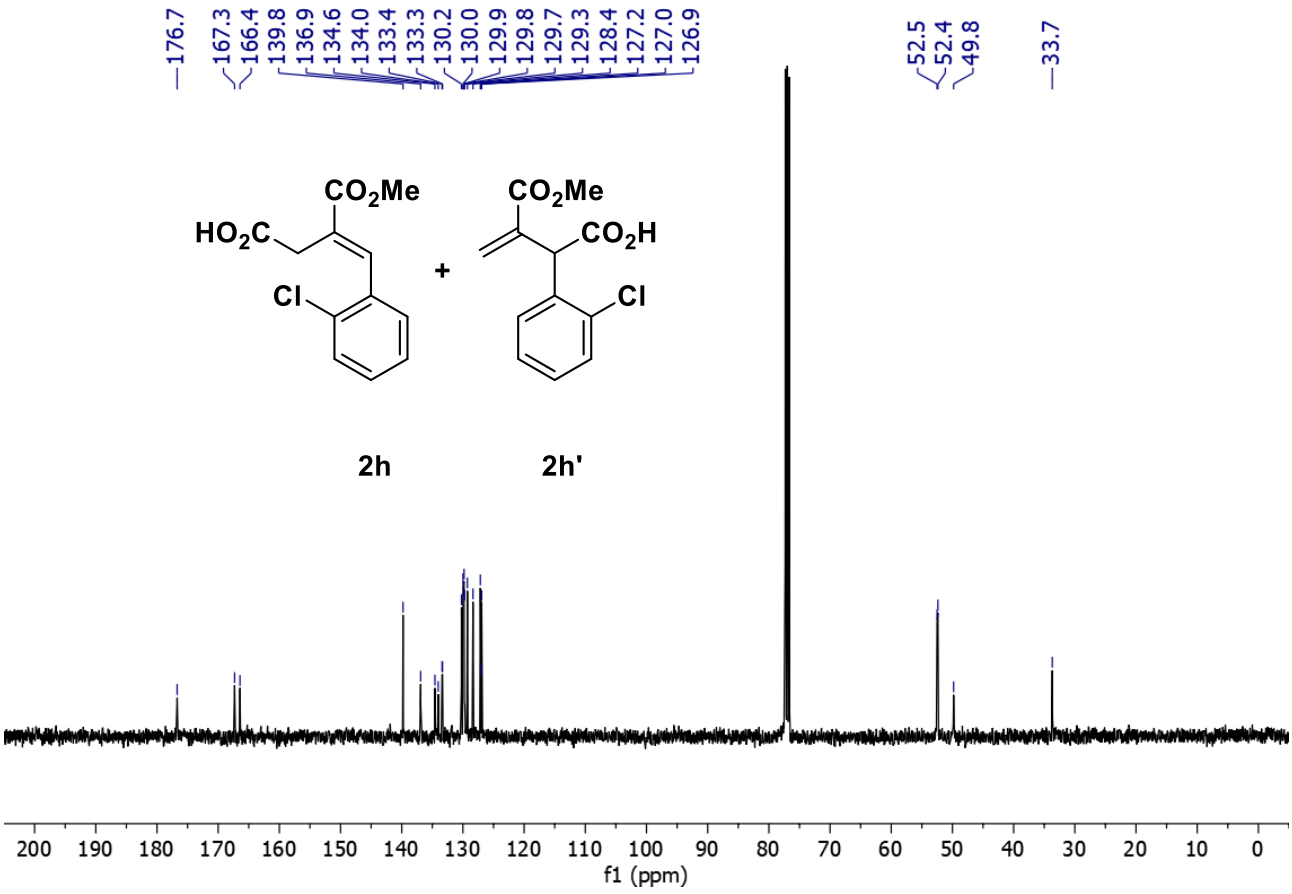
177.2 176.8 167.9 166.7 159.9 159.7 142.6 138.2 136.6 136.0 129.8 129.7 128.4 125.4 121.4 121.3 115.0 114.8 114.1 113.4 55.2 55.2 53.0 52.4 52.3 33.6



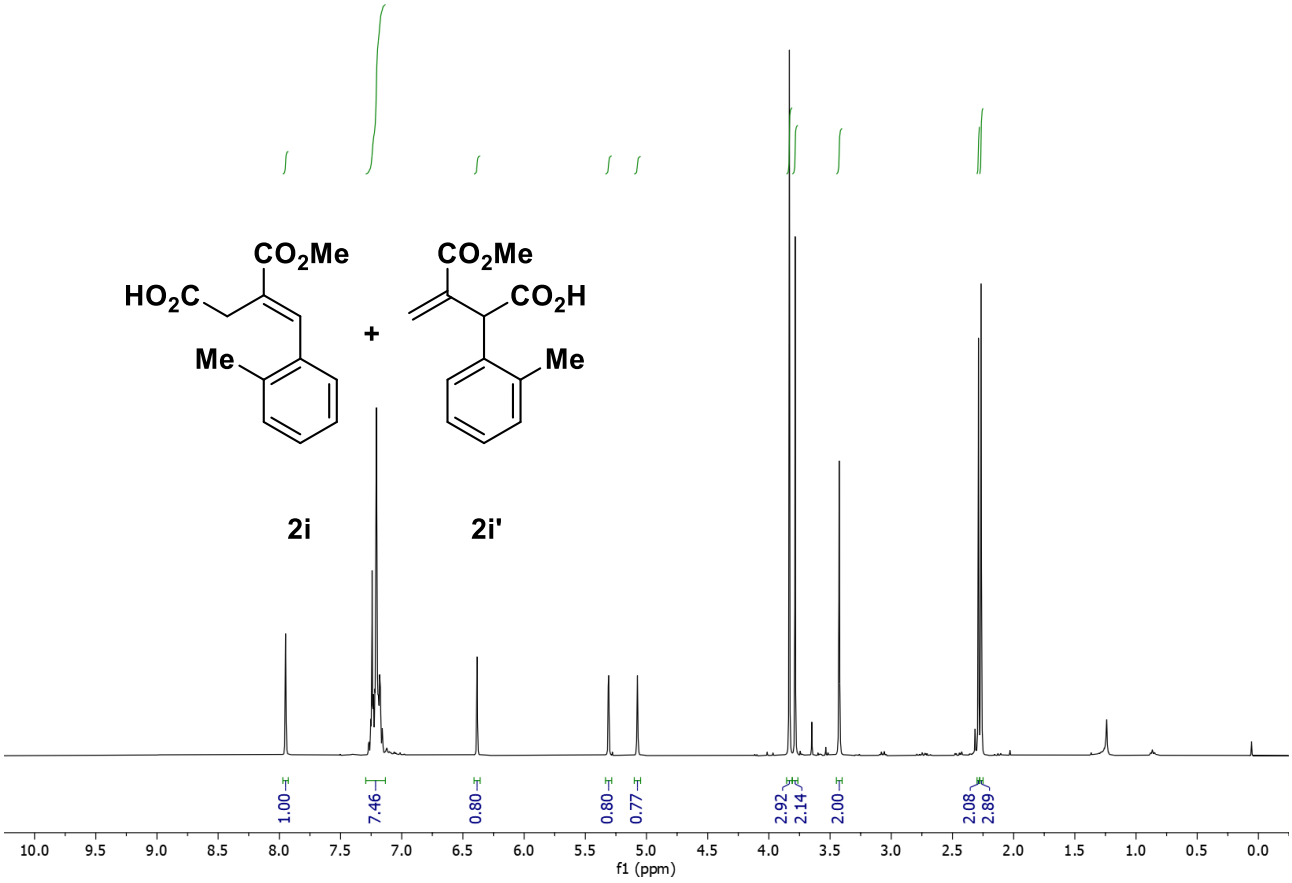
2h and 2h' ^{1}H NMR (400 MHz, $CDCl_3$)



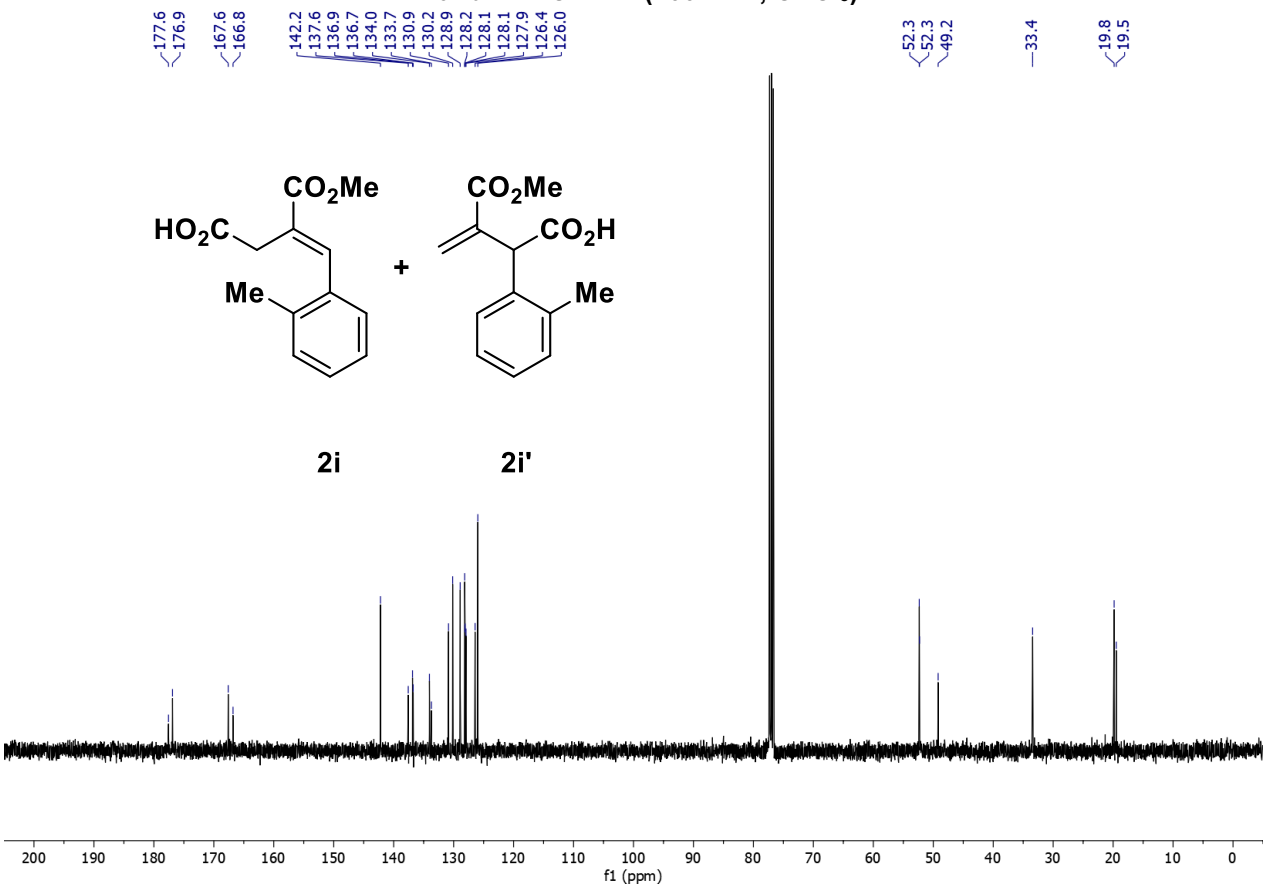
2h and 2h' ^{13}C NMR (100 MHz, $CDCl_3$)



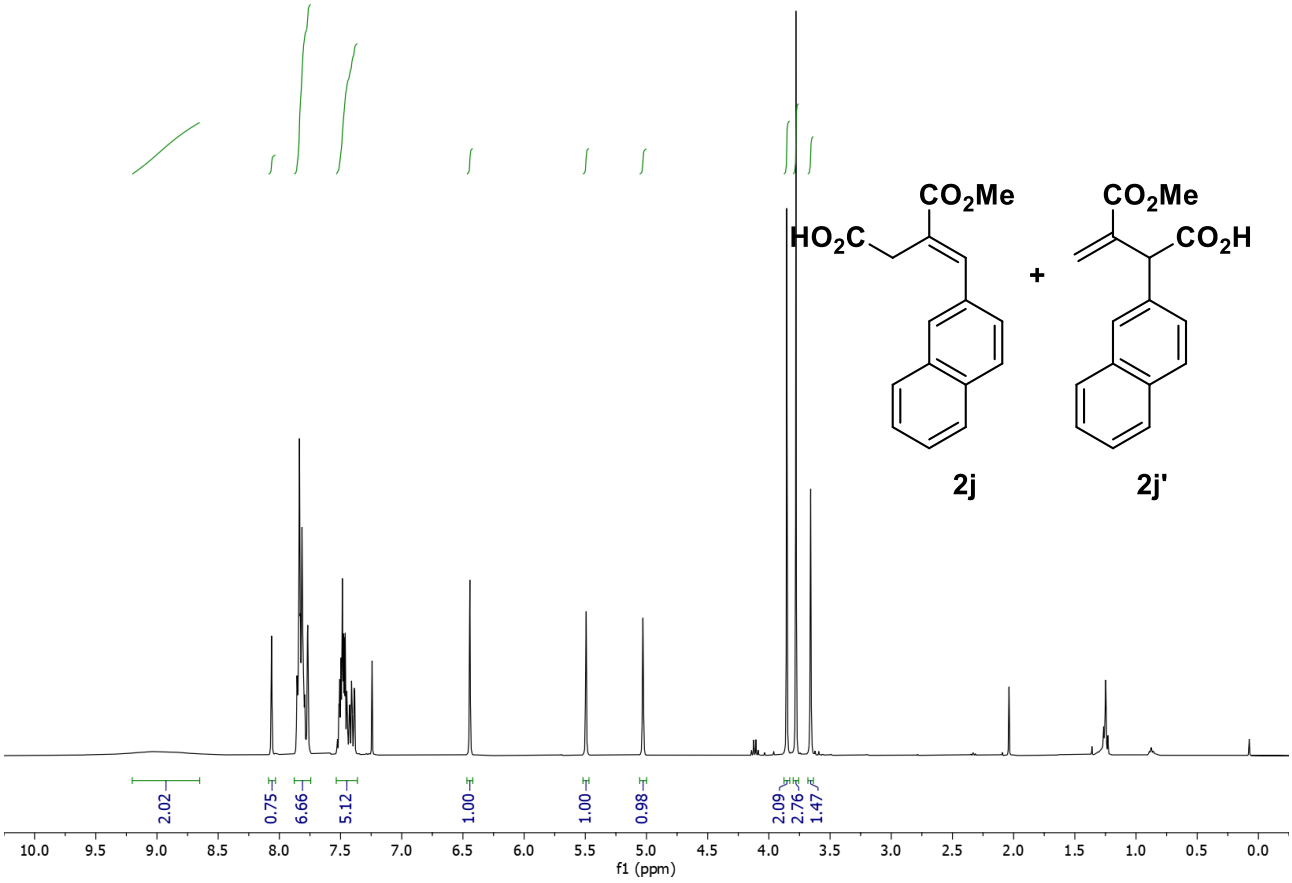
2i and 2i' ^{1}H NMR (400 MHz, $CDCl_3$)



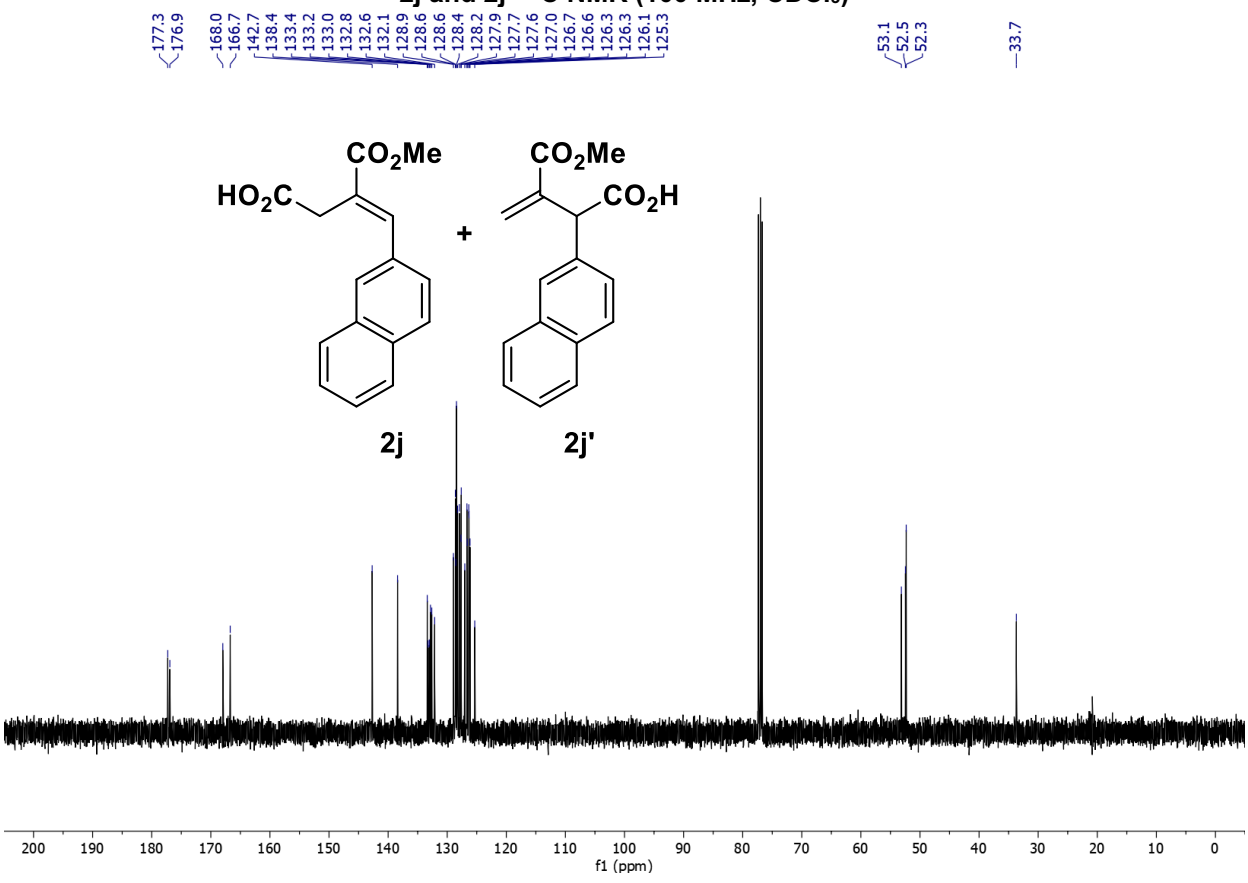
2i and 2i' ^{13}C NMR (100 MHz, $CDCl_3$)



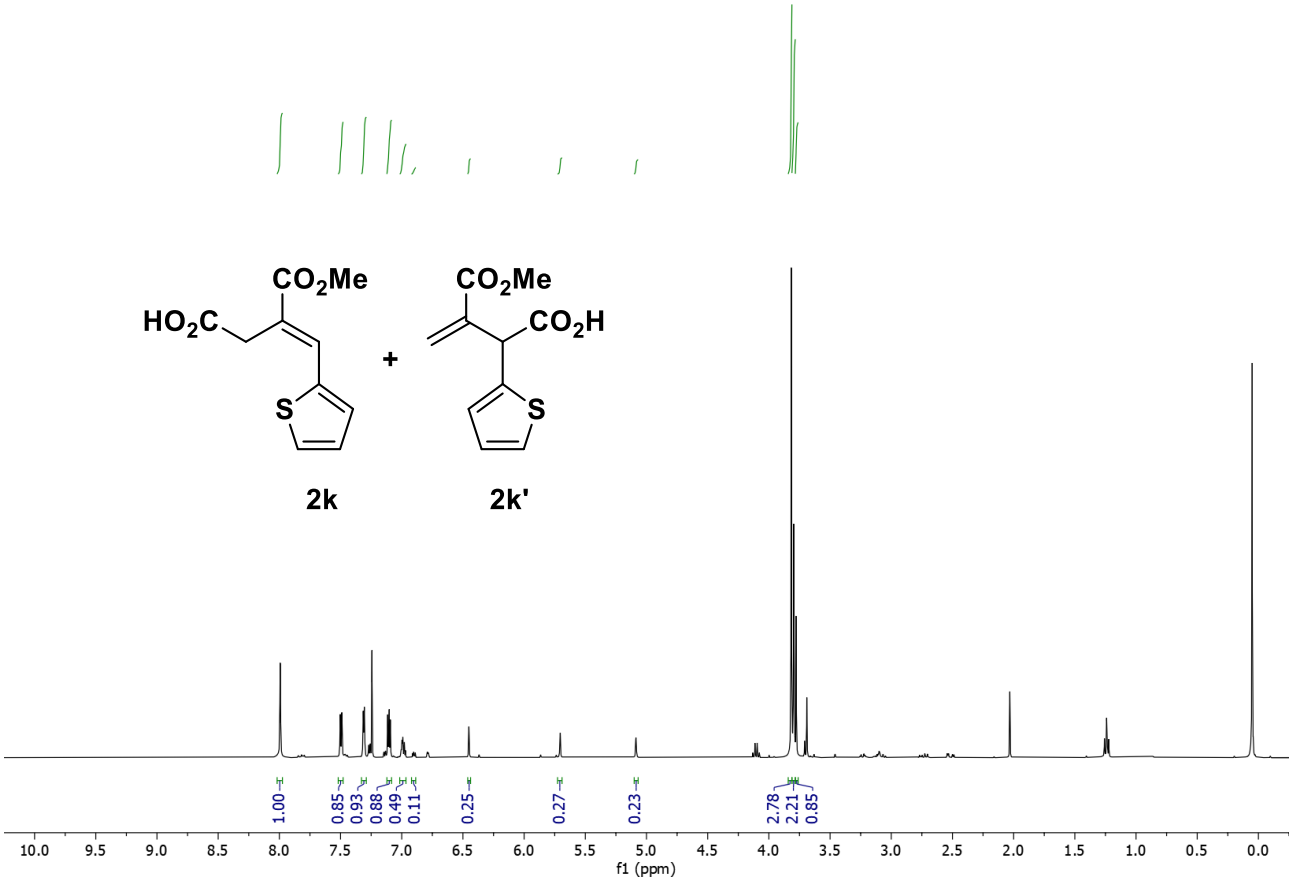
2j and 2j' ^{1}H NMR (400 MHz, $CDCl_3$)



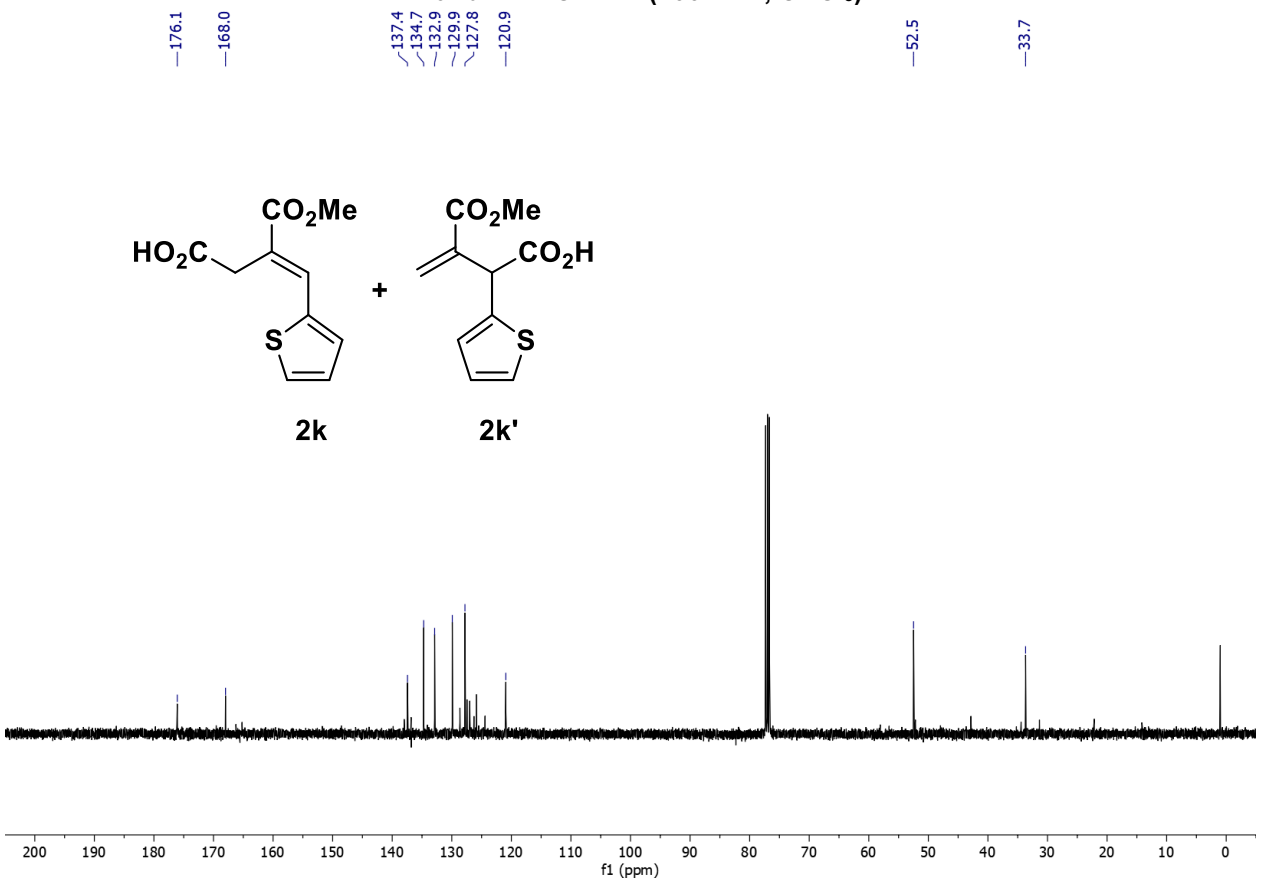
2j and 2j' ^{13}C NMR (100 MHz, $CDCl_3$)



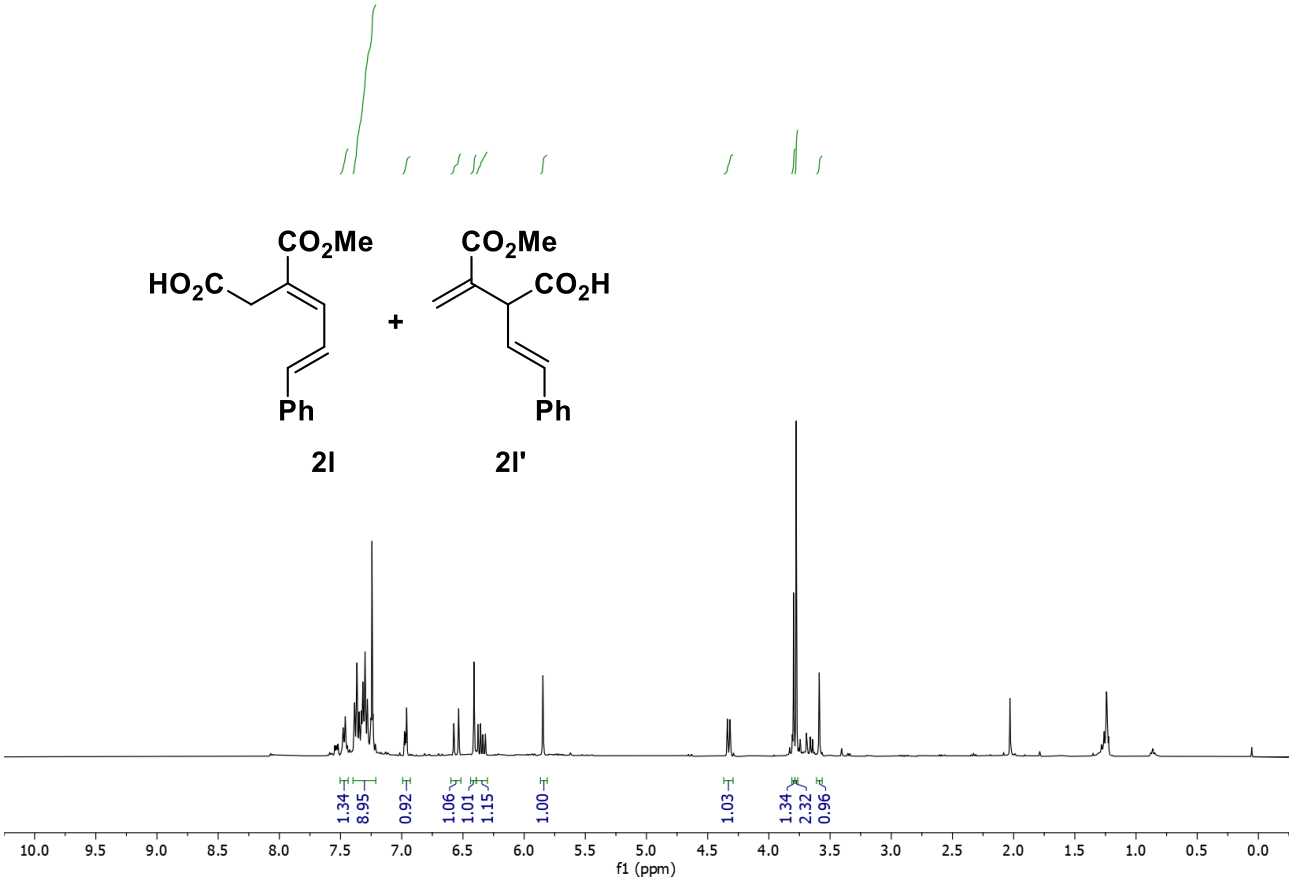
2k and 2k' ^{1}H NMR (400 MHz, $CDCl_3$)



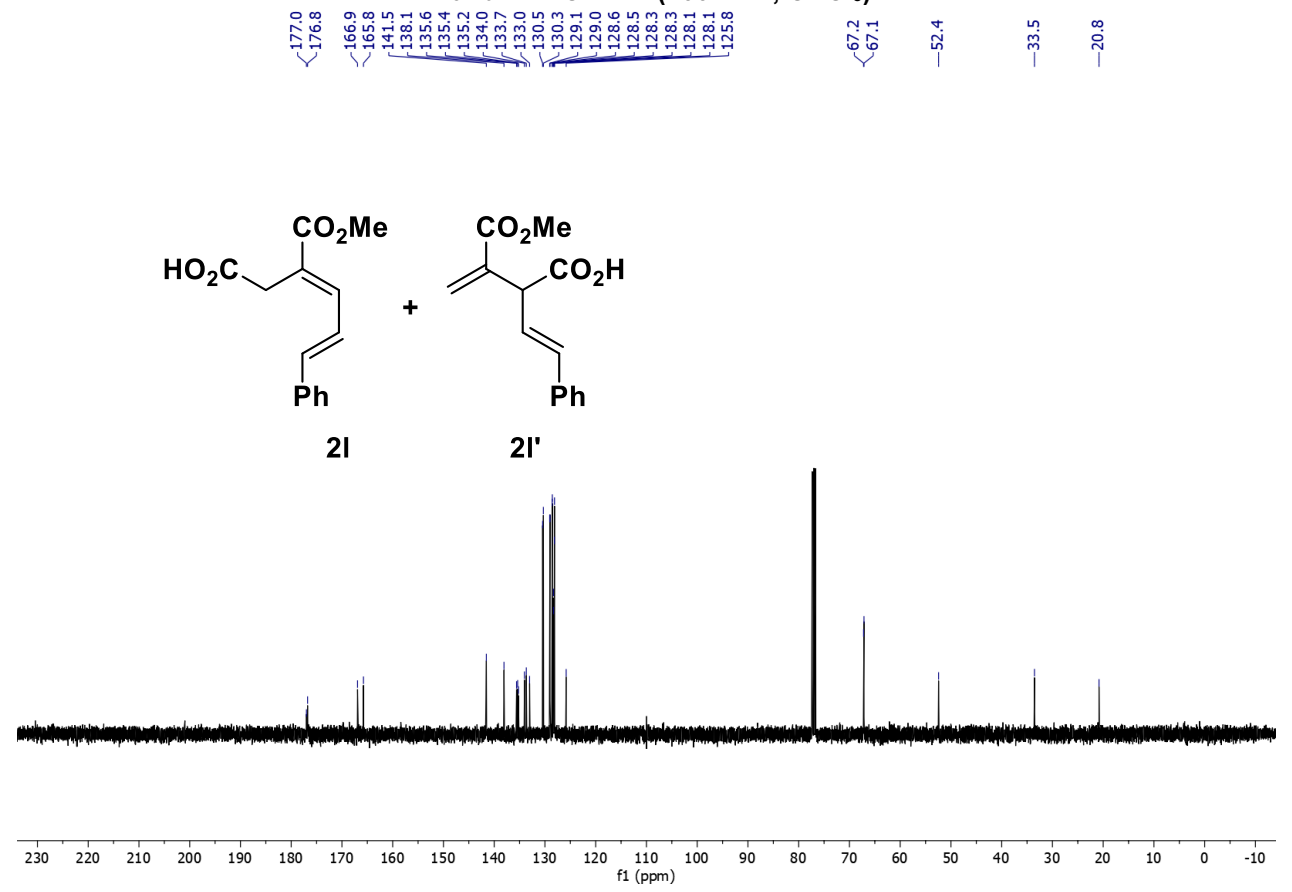
2k and 2k' ^{13}C NMR (100 MHz, $CDCl_3$)



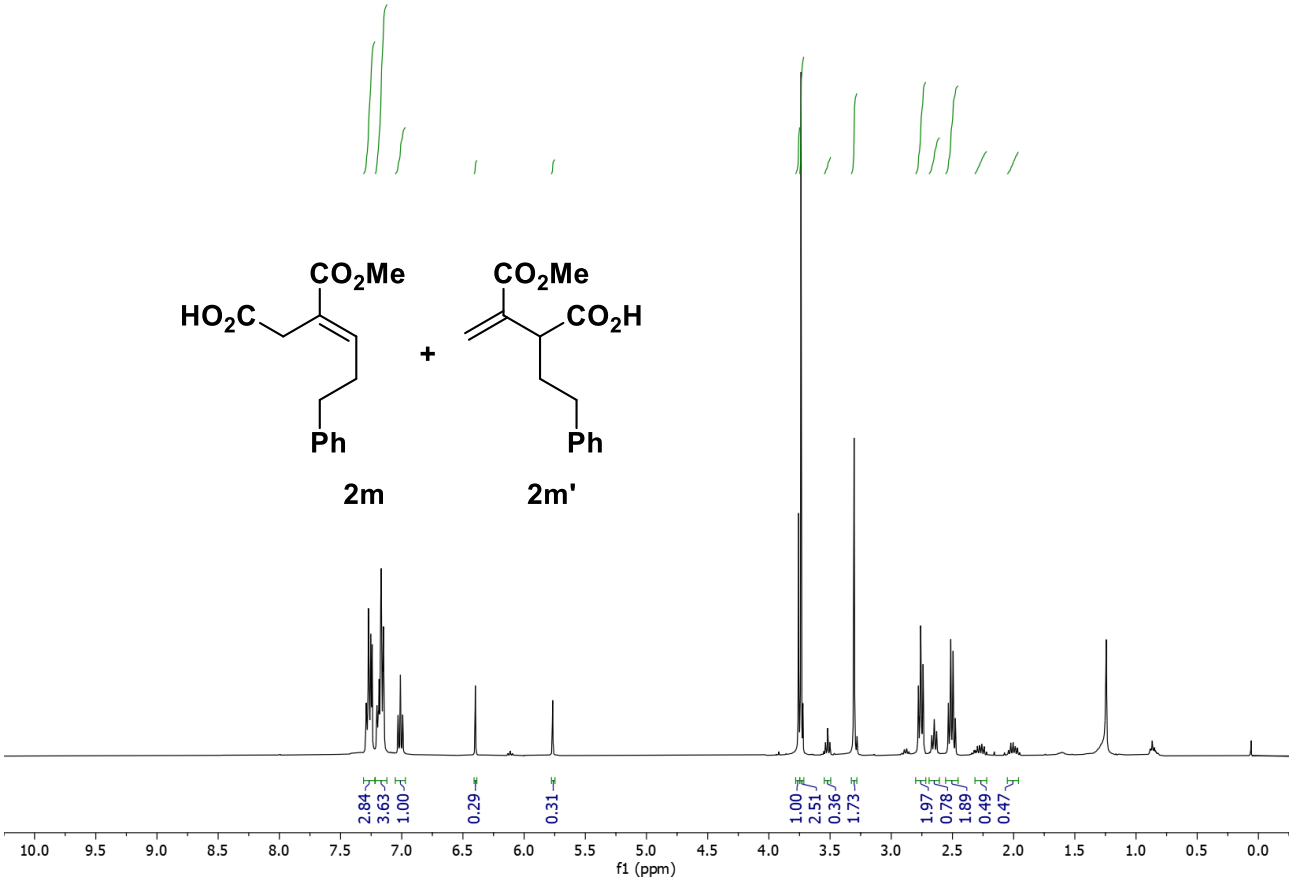
2l and 2l' ^{1}H NMR (400 MHz, $CDCl_3$)



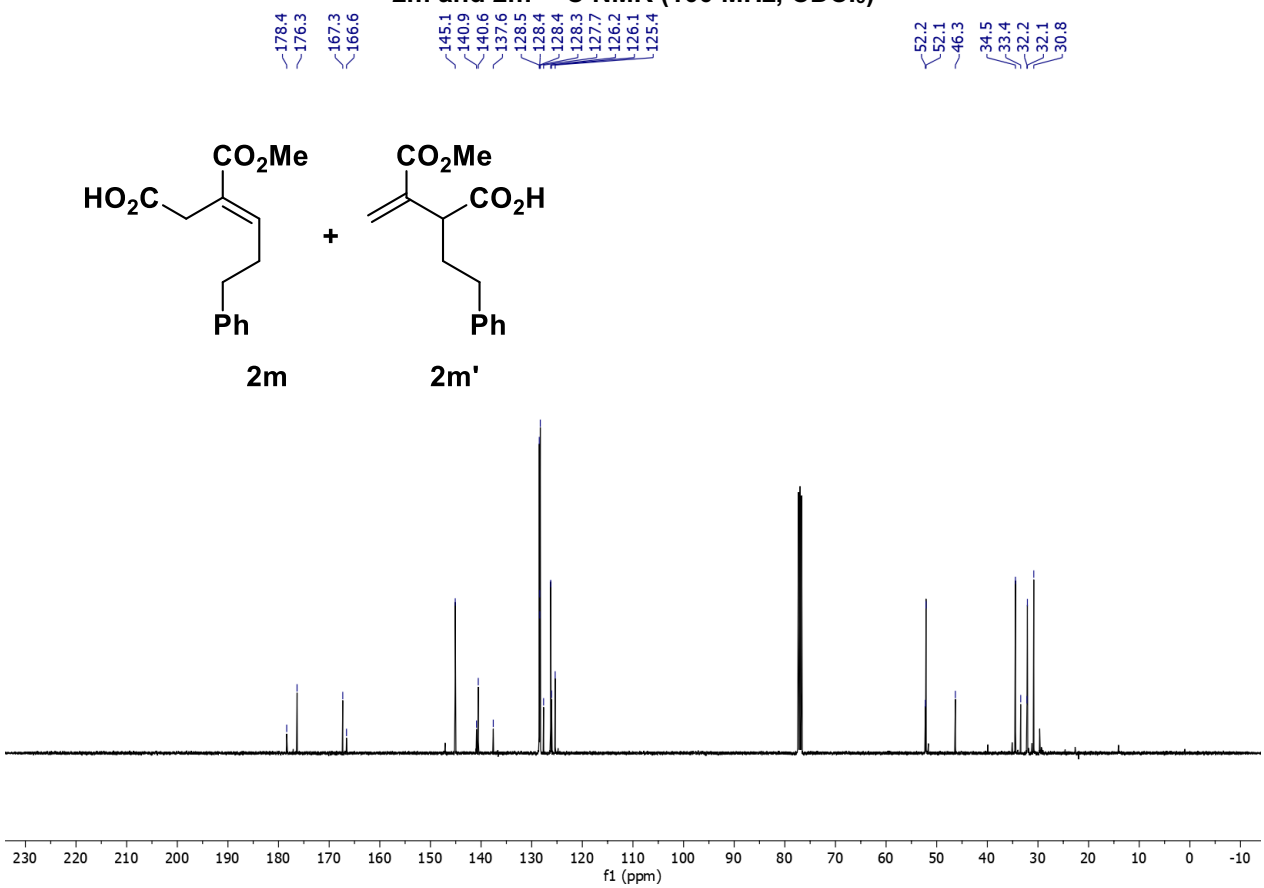
2l and 2l' ^{13}C NMR (100 MHz, $CDCl_3$)



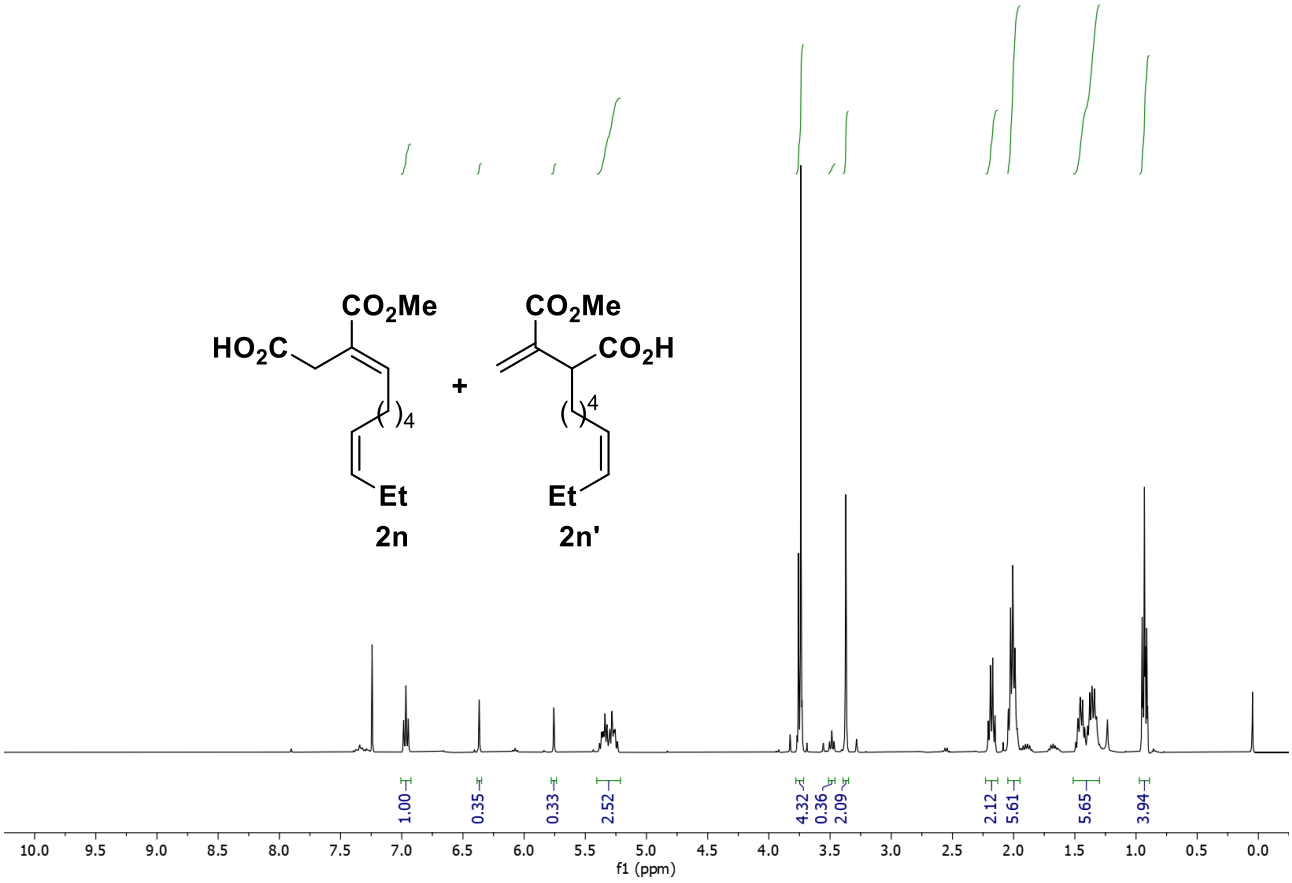
2m and 2m' ^{1}H NMR (400 MHz, $CDCl_3$)



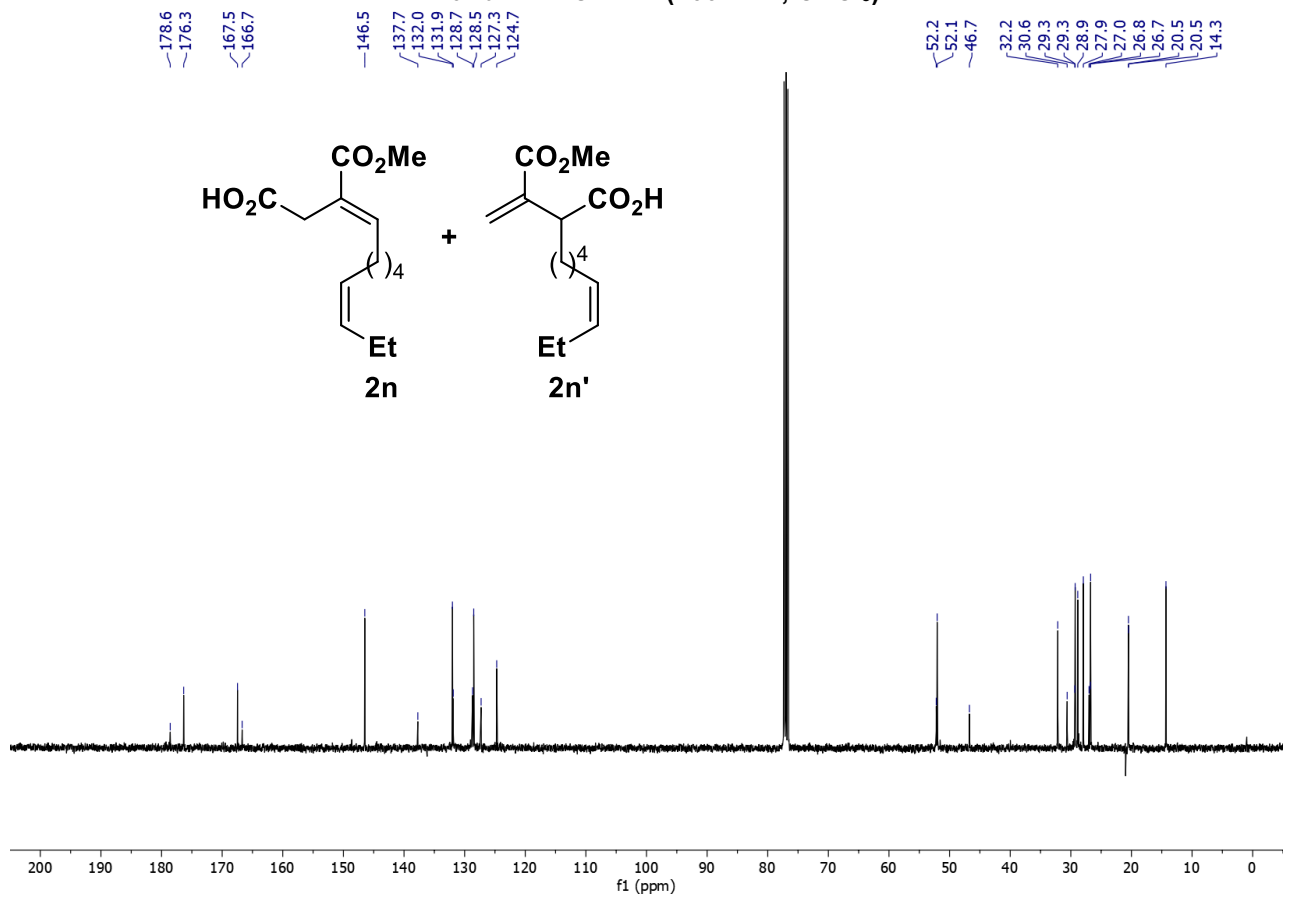
2m and 2m' ^{13}C NMR (100 MHz, $CDCl_3$)



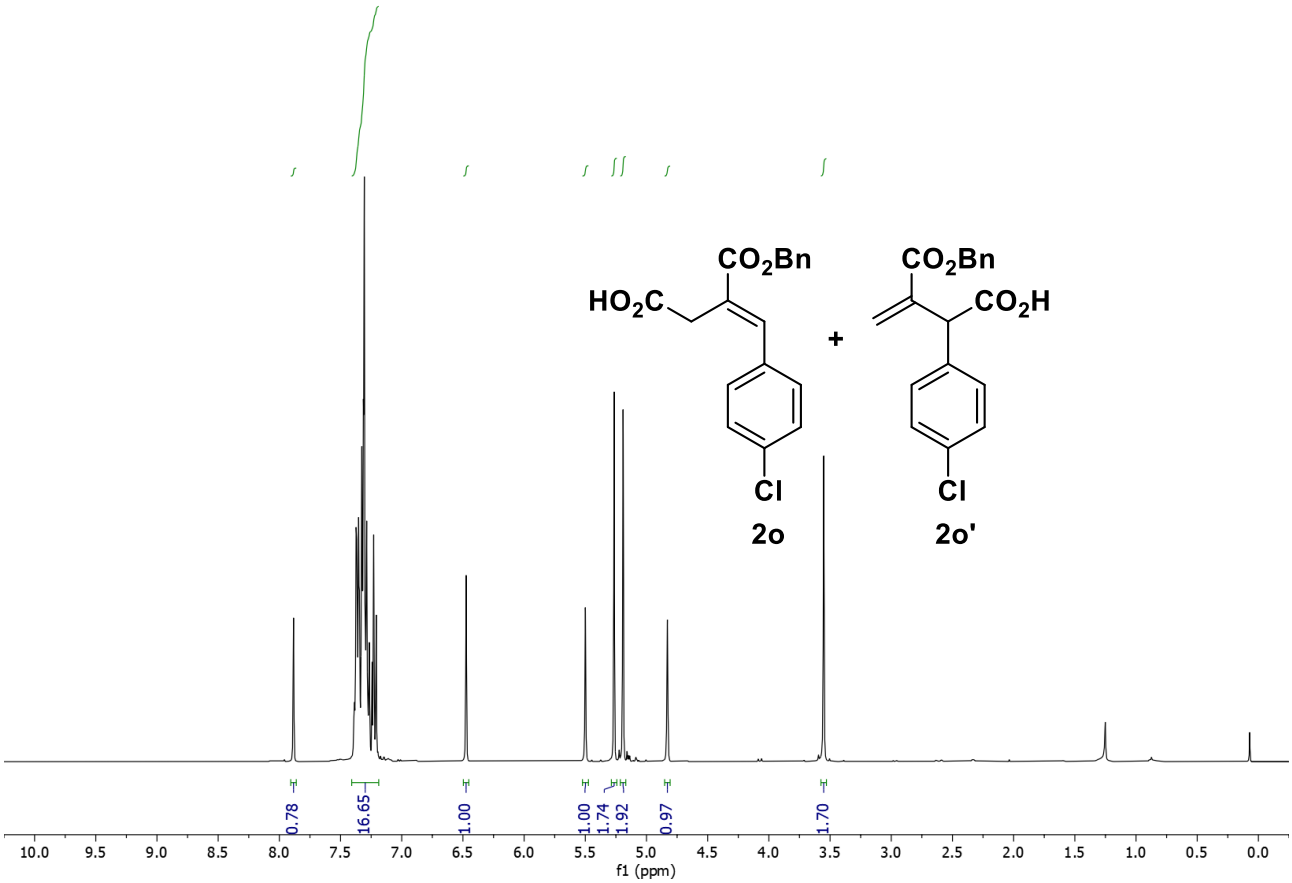
2n and 2n' ^{1}H NMR (400 MHz, $CDCl_3$)



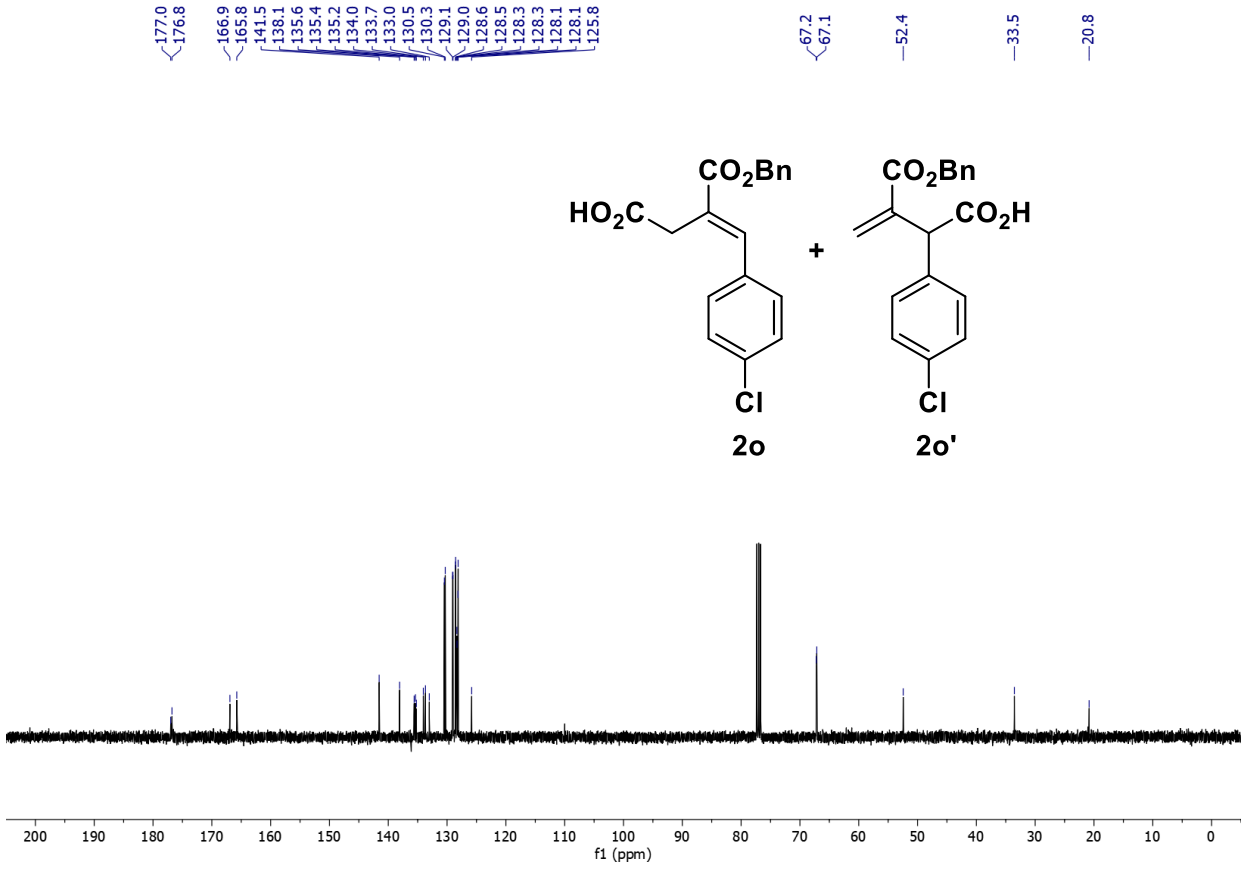
2n and 2n' ^{13}C NMR (100 MHz, $CDCl_3$)



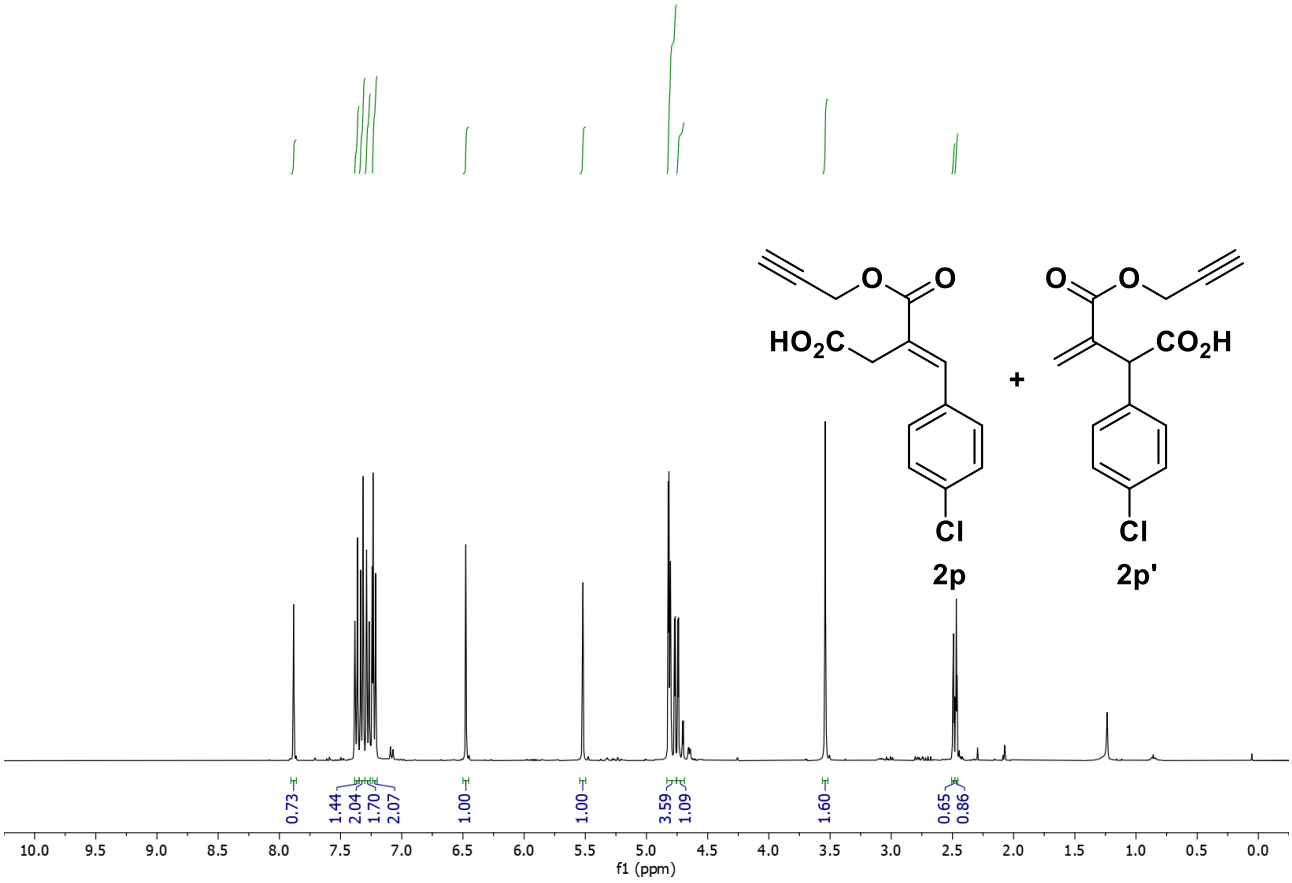
2o and 2o' ^{1}H NMR (400 MHz, $CDCl_3$)



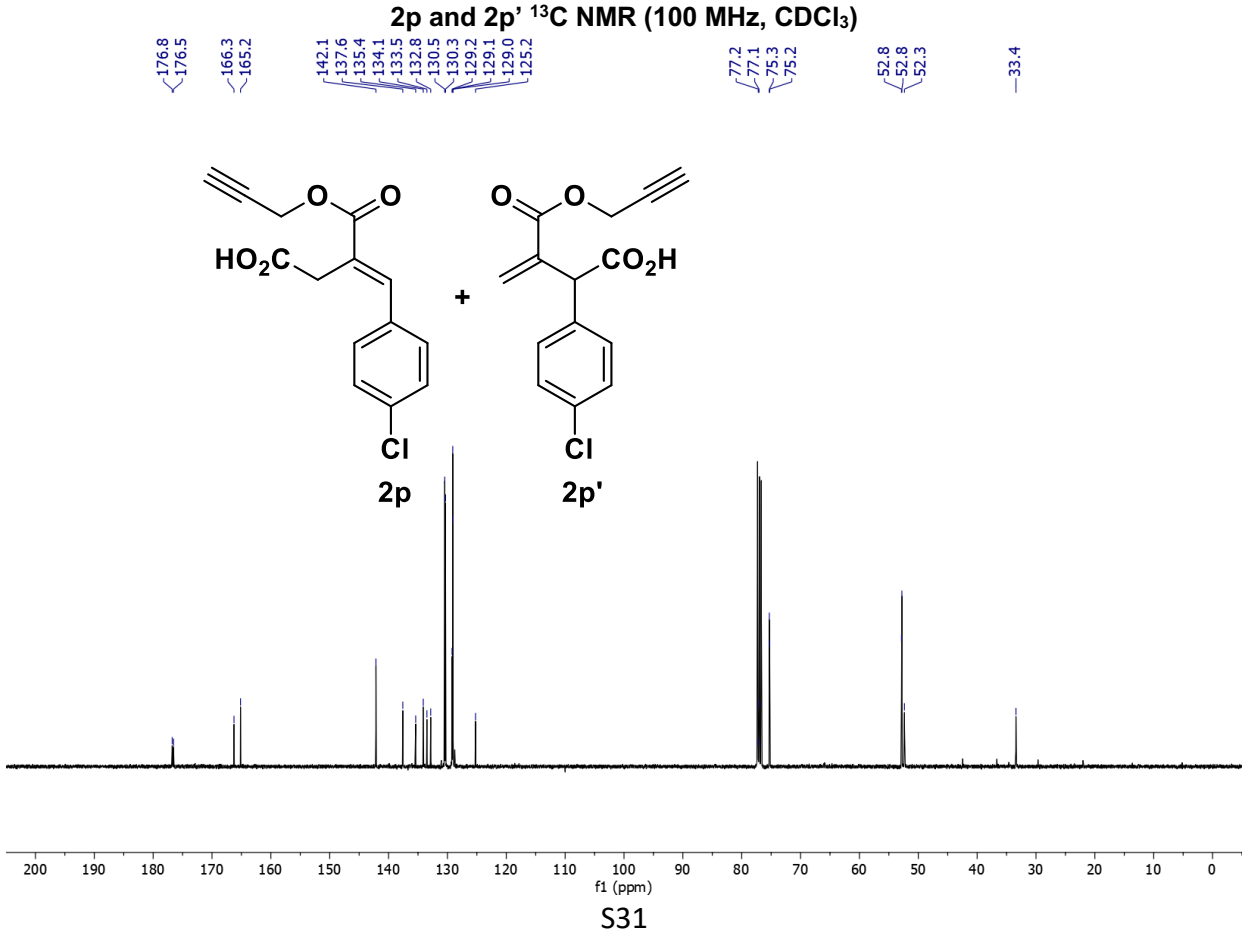
2o and 2o' ^{13}C NMR (100 MHz, $CDCl_3$)



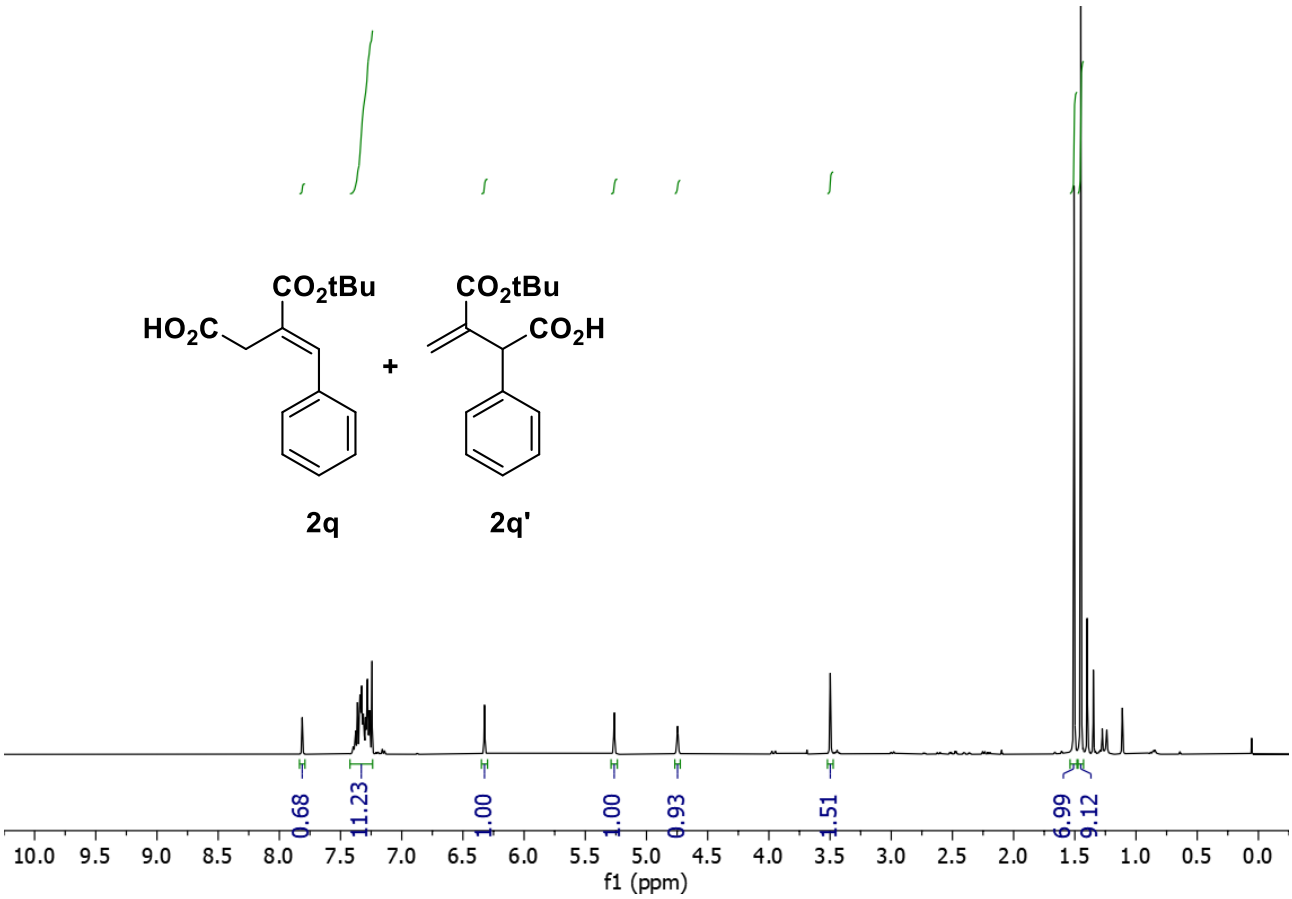
2p and 2p' ^{1}H NMR (400 MHz, $CDCl_3$)



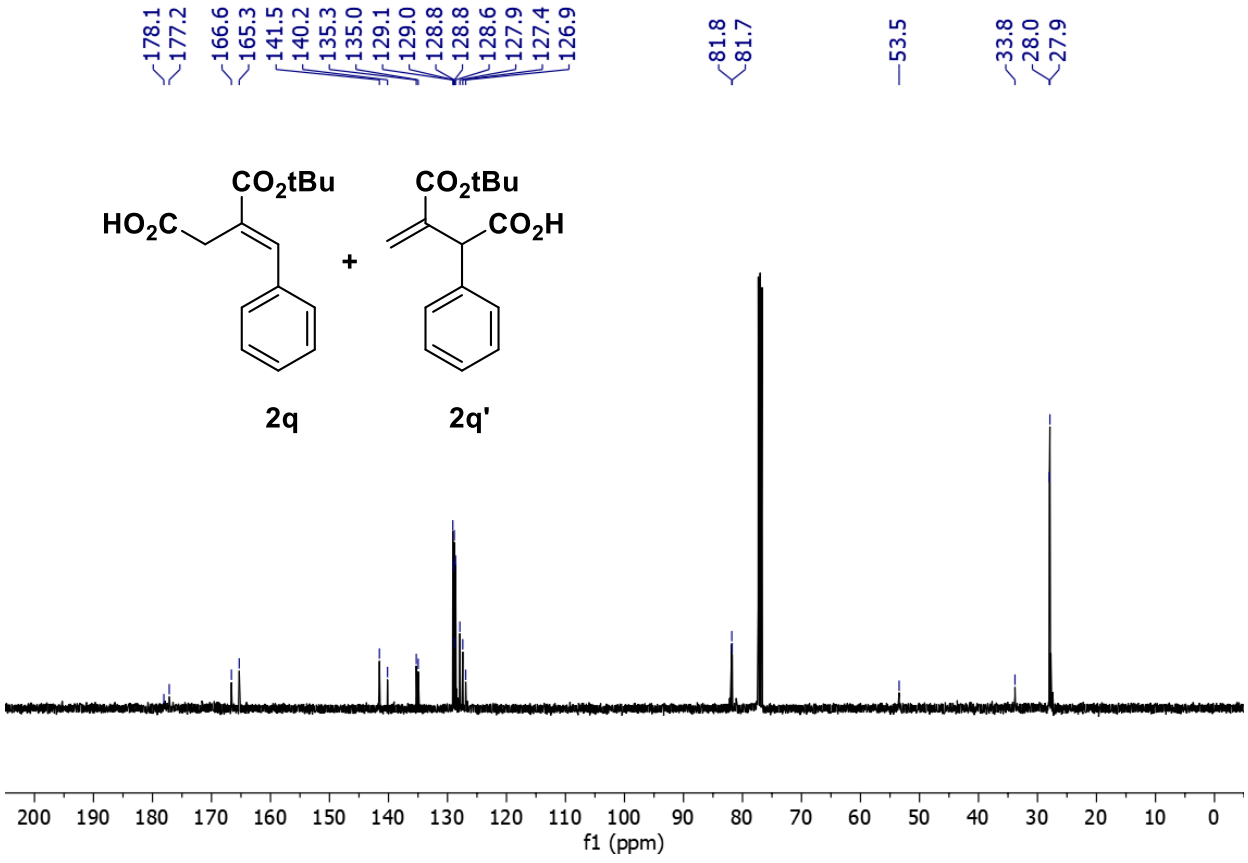
2p and 2p' ^{13}C NMR (100 MHz, $CDCl_3$)



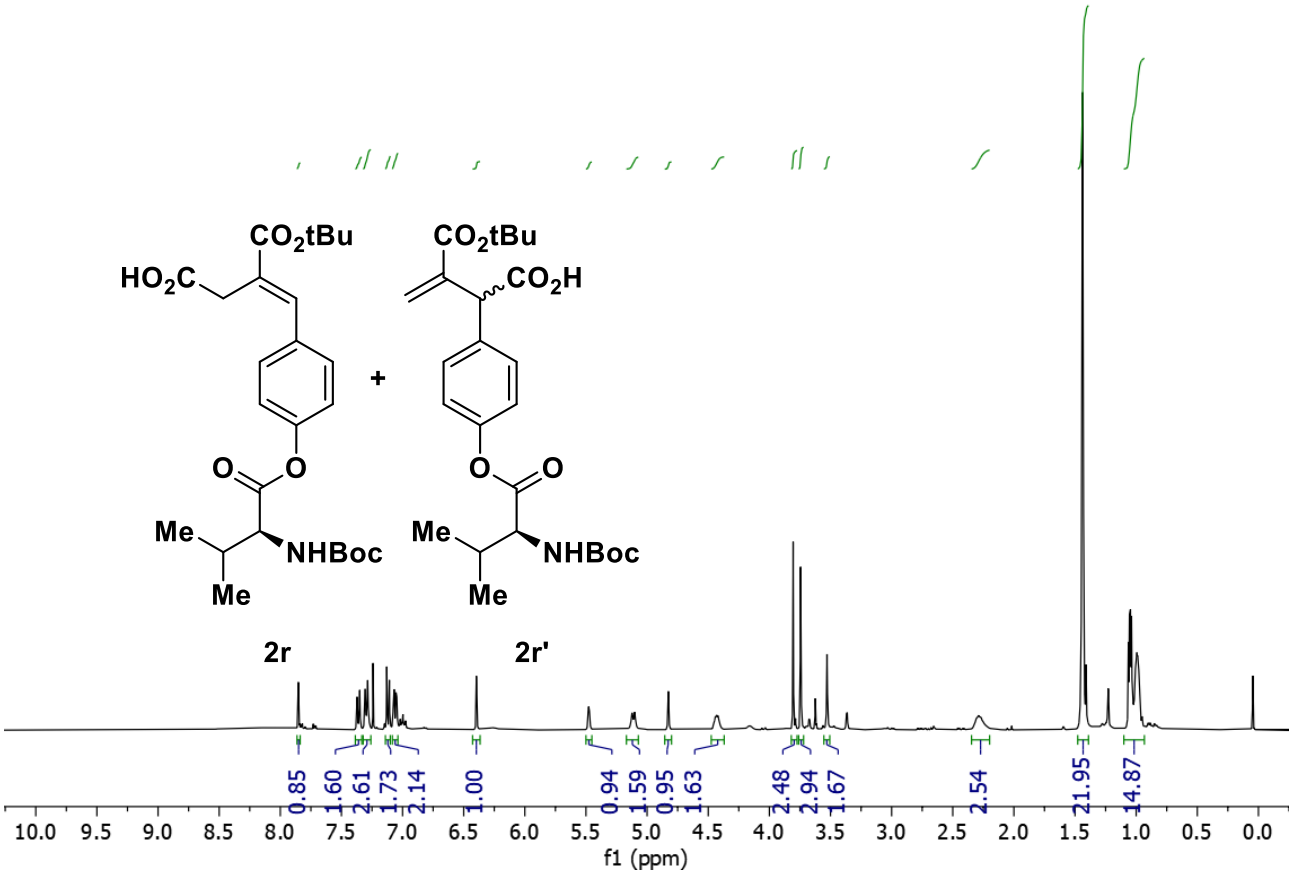
2q and 2q' ^{1}H NMR (400 MHz, $CDCl_3$)



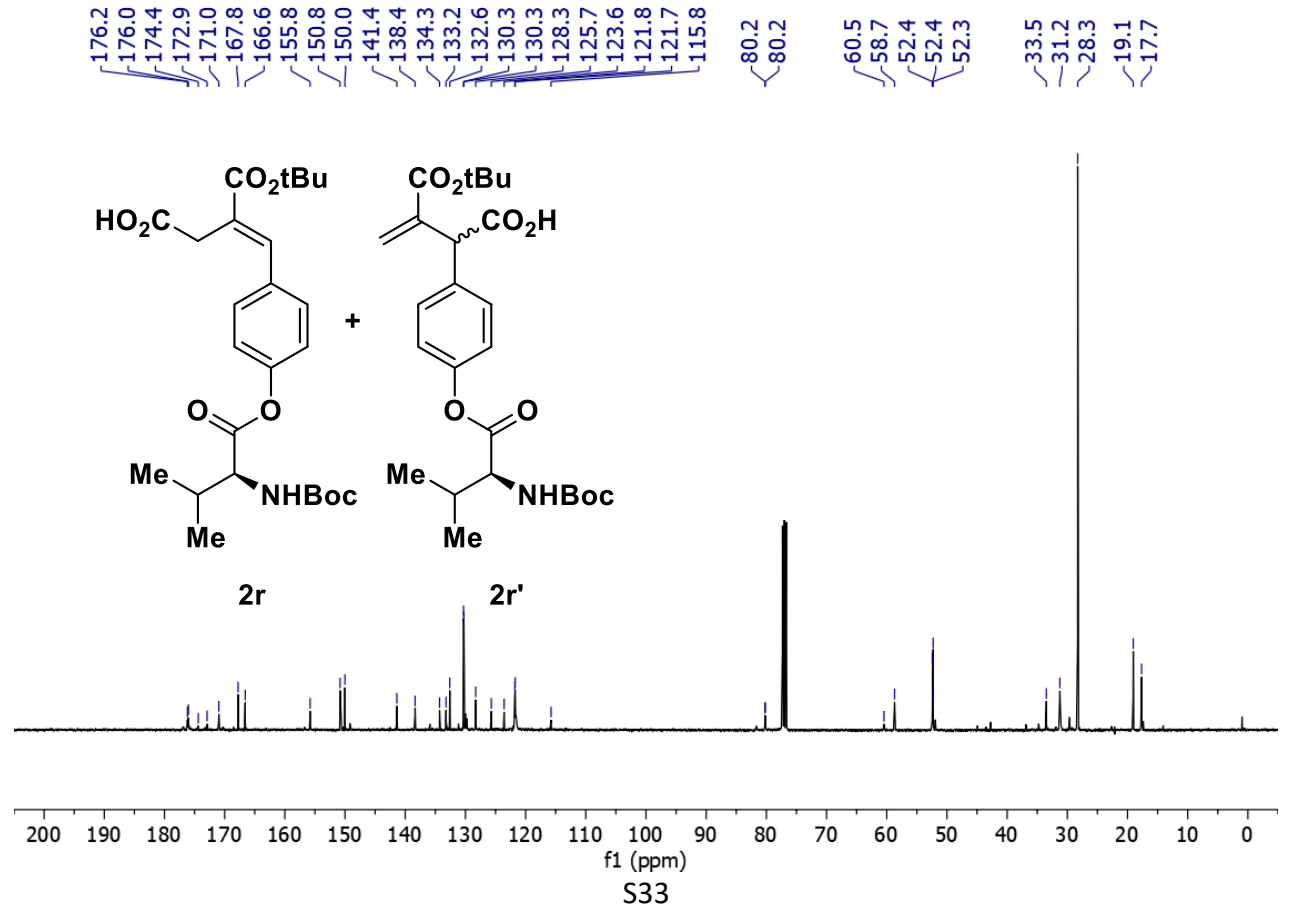
2q and 2q' ^{13}C NMR (100 MHz, $CDCl_3$)



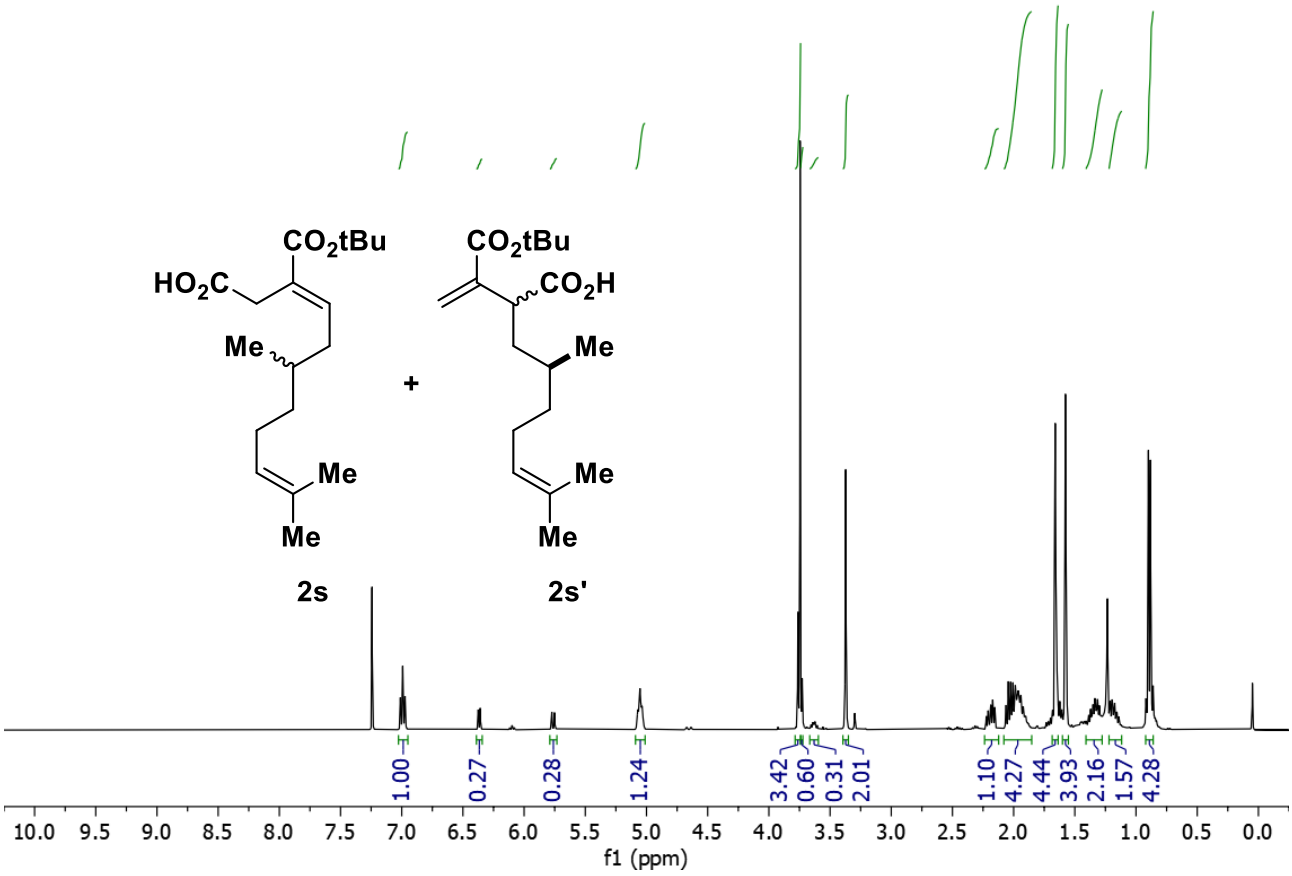
2r and 2r' ^{1}H NMR (400 MHz, $CDCl_3$)



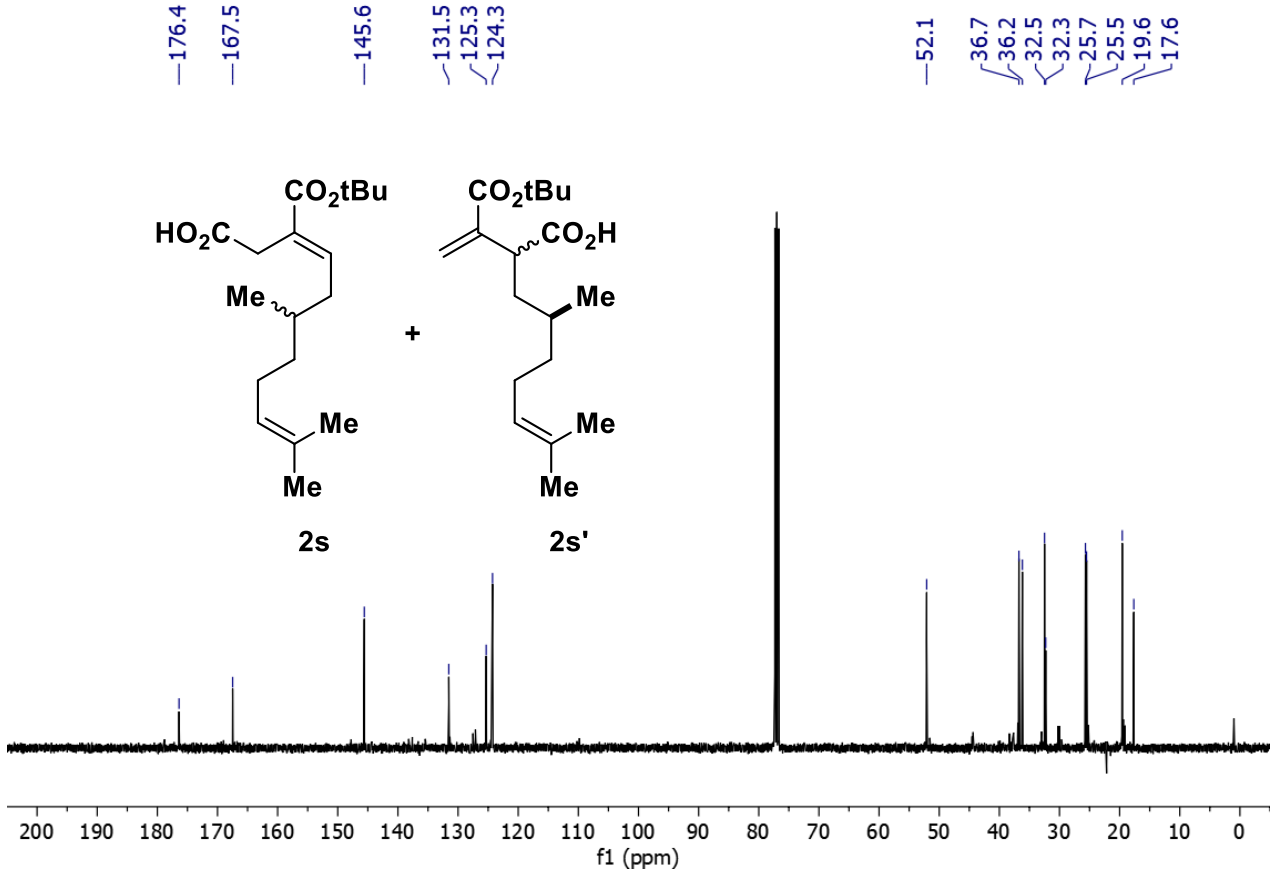
2r and 2r' ^{13}C NMR (100 MHz, $CDCl_3$)



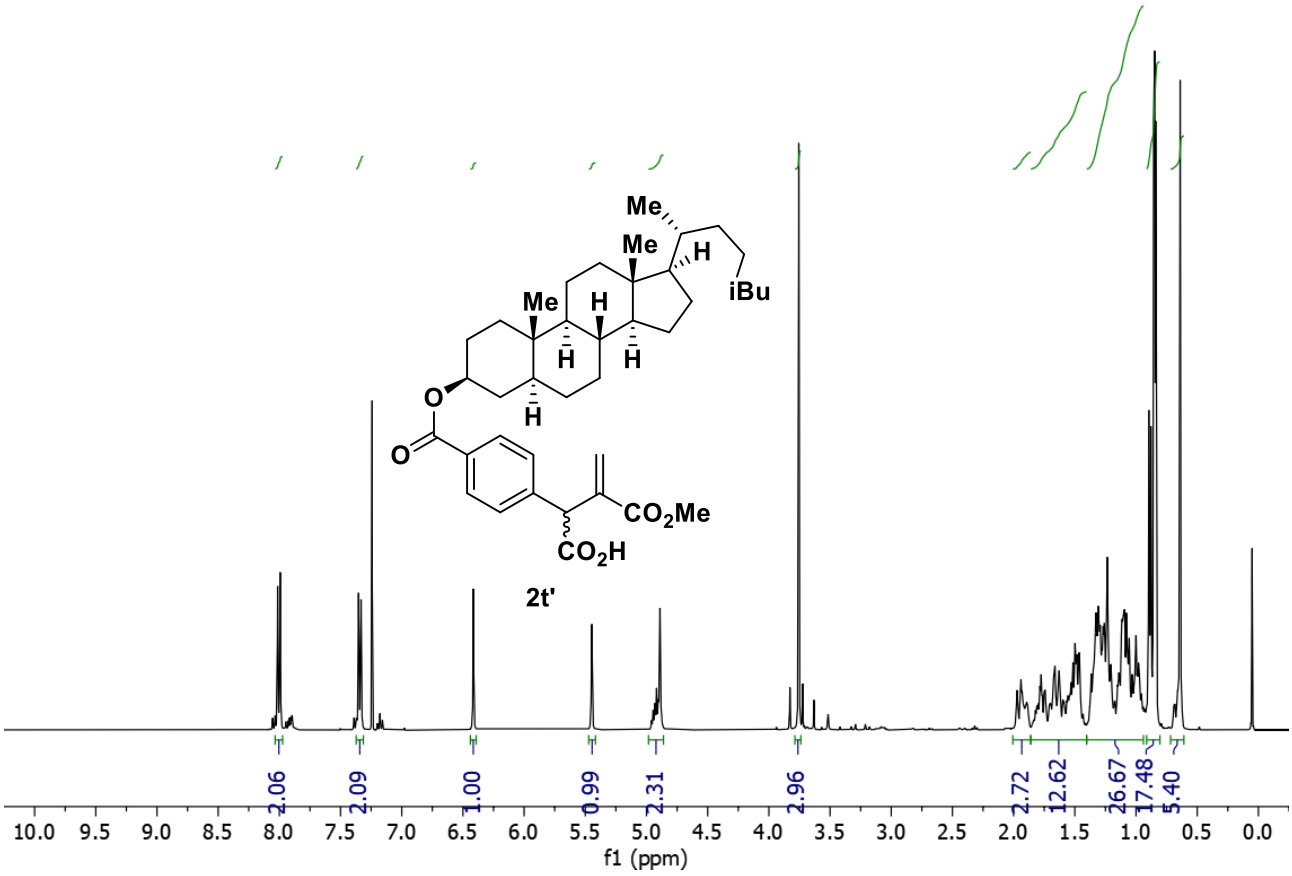
2s and 2s' ^{1}H NMR (400 MHz, $CDCl_3$)



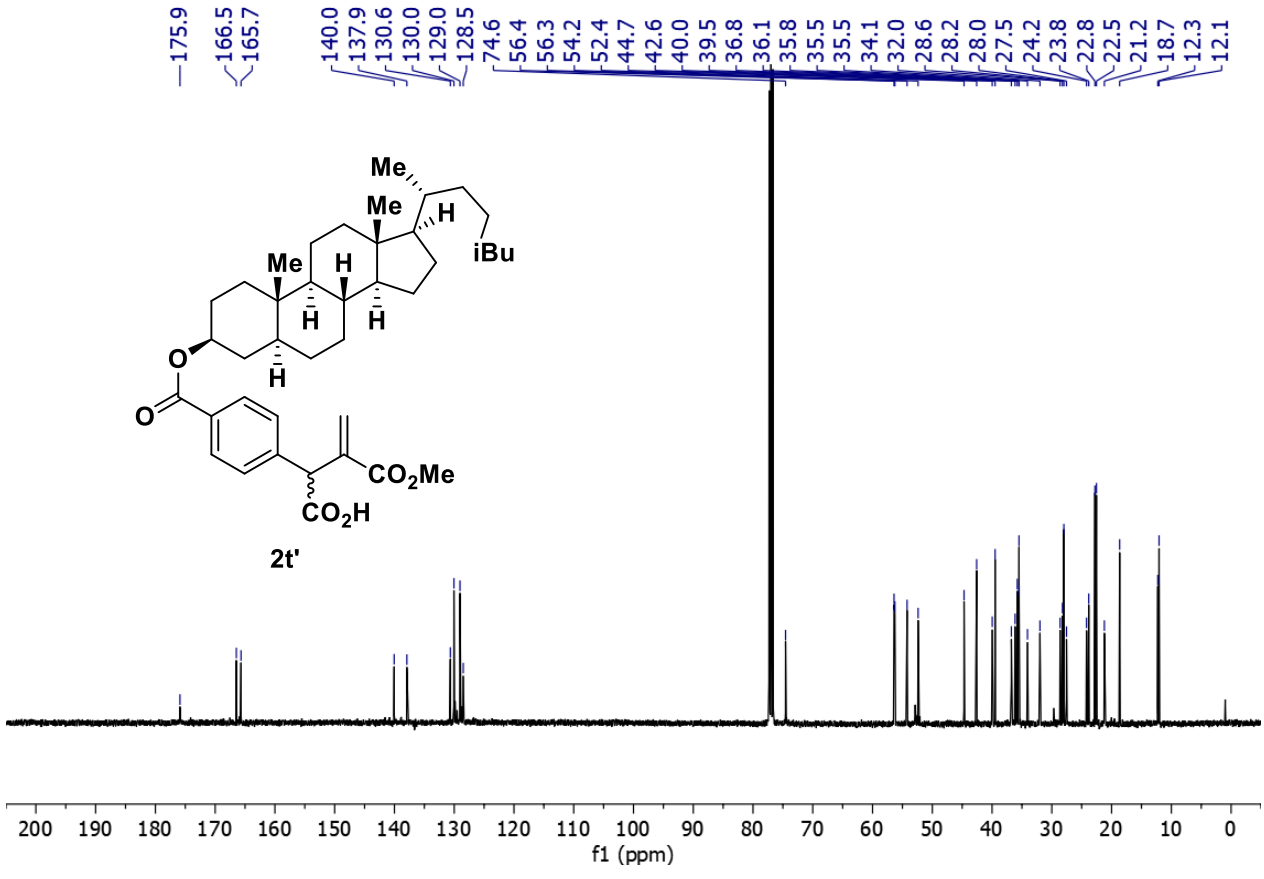
2s and 2s' ^{13}C NMR (100 MHz, $CDCl_3$)



2t' ^{1}H NMR (400 MHz, $CDCl_3$)



2t' ^{13}C NMR (100 MHz, $CDCl_3$)



6. References

[1] N.G. Connelly and W.E. Geiger, *Chem. Rev.* **1996**, *96*, 877.
[2] For the MBH reaction of aldehydes and acrylates see the supporting information of: (a) Batchu, H.; Bhattacharyya, S.; Batra, S. *Org. Lett.* **2012**, *14*, 6330and references therein. The acetylation of the MBH adducts was carried out following the methodology reported in: (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *J. Org. Chem.* **1995**, *60*, 4697.