A Sustainable Route for the Synthesis of Alkyl Arylacetates *via* Halogen and Base Free Carbonylation of Benzyl Acetates

by

Roberto Sole, Sofia Toldo, Marco Bortoluzzi, Valentina Beghetto

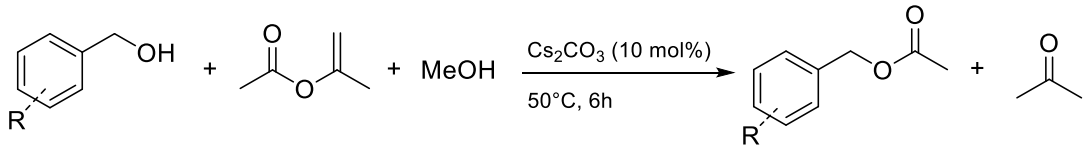
Summary

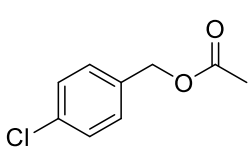
1. Synthesis of benzyl acetates

1.1. General procedure for the synthesis of benzyl acetates

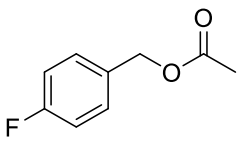
In a 50 mL round bottom flask the aryl alcohol (5 mmol) and $CsCO_3$ (2.5 mmol) were added in 10 mL of isopropenyl acetate. The heterogenous mixture obtained was allowed to stir overnight at 50 °C. Afterwards, the reaction mixture was cooled down to room temperature and solids were removed by filtration. Residues were concentrated under vacuum to yield the corresponding acetate pure without further purification.

1.2. Synthesised products





(93%)[a]



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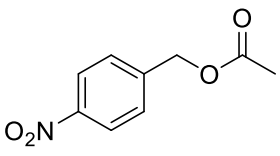

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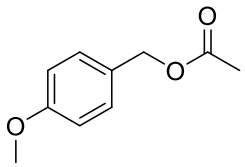

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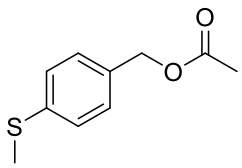

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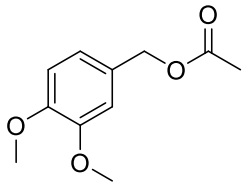

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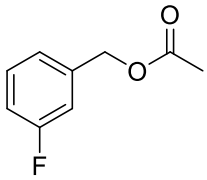
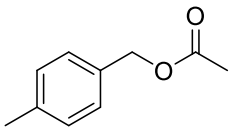
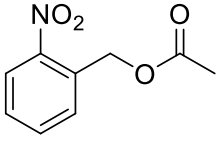


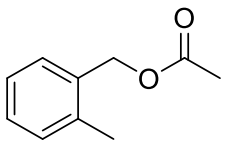
(89%)[a]



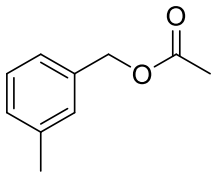
(89%)[a]



(92%)[a]



(79%)[a]



(78%)[a]

Reaction conditions: Alcohol (5 mmol), Cs_2CO_3 (2.5 mmol), IPAc (10 mL) T = 50°C; t = 6h.
[a] Isolated yields

2. Carbonylation Experiments

2.1. General procedure

The carbonylation experiments were carried out in a magnetically stirred stainless steel autoclave (total volume 150 ml) connected to a thermostatic bath in order to maintain the reaction temperature constant within ±1°C. Palladium precursor, the ligand and solid substrates were weighed under air in a 4 mL vial, which was then closed with a PTFE/rubber septum pierced with a needle and purged with nitrogen. Afterwards, the solvent, mesitylene and the liquid reagent were added in this order. The vials were then placed in the pre-purged autoclave along with a PTFE support to prevent the vial from moving (See below Figure S1).

Figure S1. Typical set-up (Left) and 4 mL vial with a PTFE/rubber septum pieced with a needle (right) for a carbonylation reaction.

2.2. GC method and Calibration Curve

Gas–liquid chromatography (GLC) analyses were performed on an Agilent 6850 gas chromatograph mounting an Agilent HP-5 GC column. The GC methods employed is the following:

Starting Temperature = 50°C X 4 min

Rate = 20°C/min

Final temperature = 230°C X 20 min

Total time = 33 min.

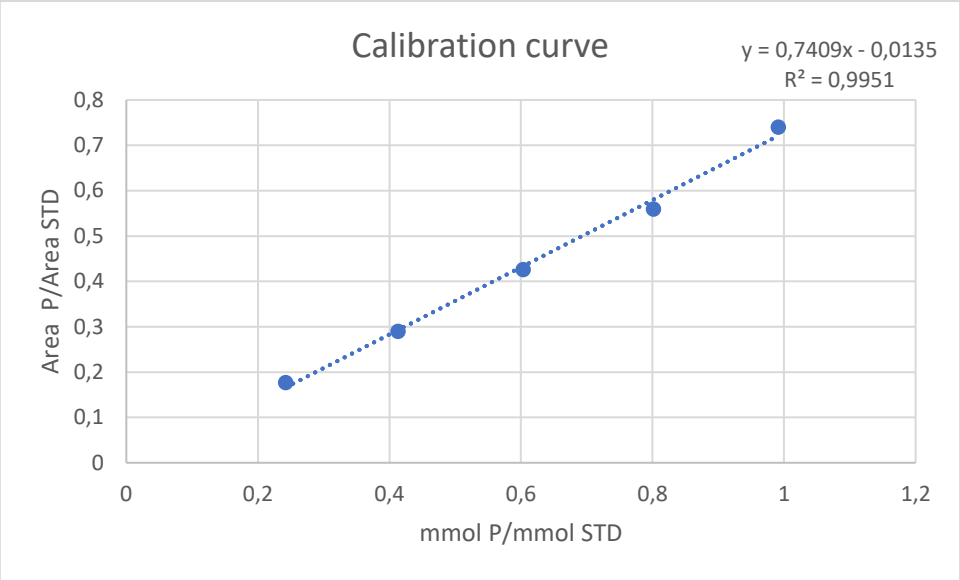


Figure S2. Calibration curve for the carbonylation of BzAc to $MeAc^{Ph}$.

2.3. Effect of Pd/P ratio (Table S1)

Entry[a]	P/Pd ratio	Conversion BzAc (%)[b]
1	0	n.d.
2	0.5	n.d.
3	1	12
4	2	92
5	4	89

Reaction conditions: [a] BzAc = 1mmol, Pd = $PdAc_2$, P = DPPP, MeOH = 1 mL, Time = 18 h, T = 135°C, P = 20 bar; [b] Conversion of BzAc and selectivity of was calculated by GLC analysis using mesitylene as internal standard.

2.4. Effect of CO pressure (Table S2)

Entry[a]	P_{CO} (bar)	Conversion BzAc (%)[b]	Selectivity of $MeAc^{Ph}$ (%)[b]
1	1	99	99
2	5	99	99
3	10	98	99
4	20	97	99
5	30	65	97
6	40	50	91

Reaction conditions: [a] BzAc = 1mmol, $PdAc_2$= 2 mol%, DPPF = 4 mol%, MeOH = 1 mL, Time = 18 h, T = 135°C; [b] Conversion of BzAc and selectivity of (1) were calculated by GLC analysis using mesitylene as internal standard.

2.5. One-pot methoxycarbonylation of benzyl alcohols

Under inert atmosphere, in a 4 mL vial equipped with a small magnetic bar were introduced MeOH (1 mL), $Pd(OAc)_2$ (5 mol%, 0.05 mmol), DPPF (10 mol%, 0.1 mmol) and acetic acid (1 mmol). Then, under nitrogen was added benzyl acetate (1 mmol), obtaining a reddish solution. Afterwards, the ice bath was removed and the vial was placed in a pre-purged 150 mL autoclave and CO was added (5 bar). The autoclave was then heated at 130°C and kept under constant magnetic stirring. After 18 h, the autoclave was cooled to room temperature, and the residual gas was carefully vented off. The raw reaction mixture was analysed by GLC to determine substrate conversion and product composition.

3. Mechanistic studies

3.1. Synthesis of [Pd(DPPF)$_2$]

The complex was synthesized following a procedure reported by Hor and co-workers.[1]
A suspension of [$PdCl_2(\eta^2$-DPPF)] (0.365 g) and DPPF (0.277 g, 0.5 mmol) in THF (20 ml) was stirred at 50 °C for 1 h under argon, after which an aqueous solution (10 ml) of $NaBH_4$, (0.070 g, 1.83 mmol) was added dropwise. The solution was allowed to stir overnight (18 h). The solvent was removed under reduced pressure and the orange residue thus obtained was extracted with benzene. Precipitation with hexane, followed by filtration and washing with hexane gave the desired product. The freshly prepared product is yellowish orange but turns orange-brown upon prolonged storage. Yield: 82%. NMR characterization of [$Pd(DPPF)_2$] is in accordance with data present in literature.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.75-7.70 (m), 7.01-6.95 (m), 4.74-4.73 (m), 4.29-4.27 (m). ^{31}P NMR (300 MHz, $CDCl_3$) δ (ppm) = 24.1.

3.2. Synthesis of [PdAc$_2$(DPPF)]

The complex was synthesised following a procedure reported by Gusev and co-workers.[2]
To a solution of DPPF (0.277 g, 0.5 mmol) in benzene (10 mL) a solution of $PdAc_2$ (0.112 g, 0.5 mmol) in benzene (10 mL) was added under argon. The orange solution thus obtained was stirred overnight at room temperature. Afterwards, a yellow precipitate was formed, the solvent was reduced by half under vacuum. The precipitate was filtered off and washed with benzene (3 X 10 mL). Finally, the yellowish solid obtained was dried under vacuum to afford the desired product. NMR characterization of [$PdAc_2$(DPPF)] is in accordance with data present in literature.
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.75-7.70 (m), 7.01-6.95 (m), 4.74-4.73 (m), 4.29-4.27 (m). ^{31}P NMR (300 MHz, $CDCl_3$) δ (ppm) = 24.1.

3.3. Synthesis of [Pd(η^3-C_3H_5)(DPPF)]ClO_4

The complex was synthesized following a procedure reported by Gusev and co-workers.[3]
To a solution of [Pd(Me-PyCH_2SPh)(η^3-allyl)]ClO_4 (0.1 g, 0.2 mmol) in 10 ml of anhydrous dichloromethane, a solution of DPPF (0.116 g, 0.2 mmol) in 5 ml of CH_2Cl_2 was added. The mixture was stirred at room temperature for 15 min, and the solvent was then reduced under vacuum. The final product (orange microcrystalline powder) was precipitated by addition of diethylether and filtered off on a gooch filter. NMR characterization of [Pd(η^3-C_3H_5)(DPPF)]ClO_4 is in accordance with data present in literature.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.63–7.44 (m), 5.95–5.85 (m), 4.49–4.45 (m), 4.40–4.39 (m), 4.20–4.18 (m), 4.04–4.01 (m), 3.55–3.50 (m).
^{31}P NMR (300 MHz, $CDCl_3$) δ (ppm) = 23.2.

3.4. Computational studies

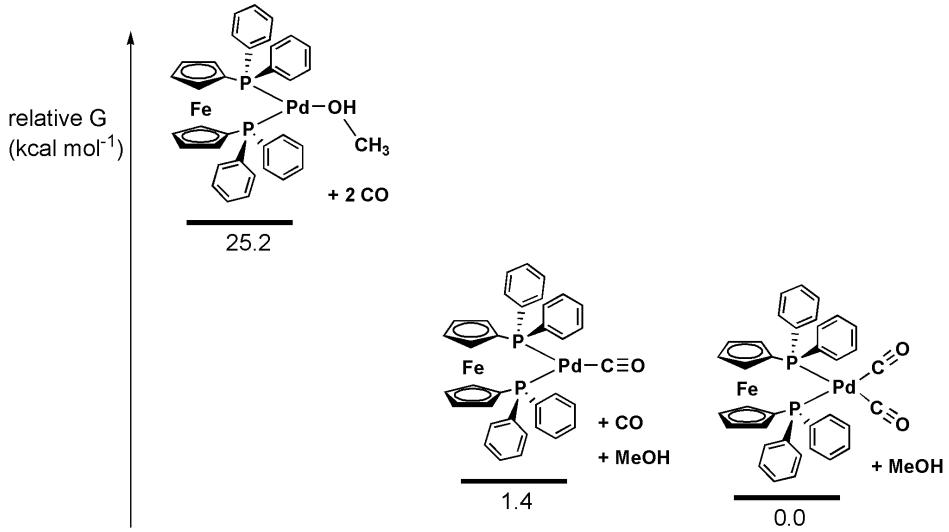


Figure S3. Gibbs energy differences between [Pd(MeOH)(DPPF)] + 2 CO, [Pd(CO)(DPPF)] + CO + MeOH and [$Pd(CO)_2$(DPPF)] + MeOH. C-PCM/PBE1PBE/def2-SVP, methanol as continuous medium. Thermodynamic data computed at 403 K and 7.8 atm.

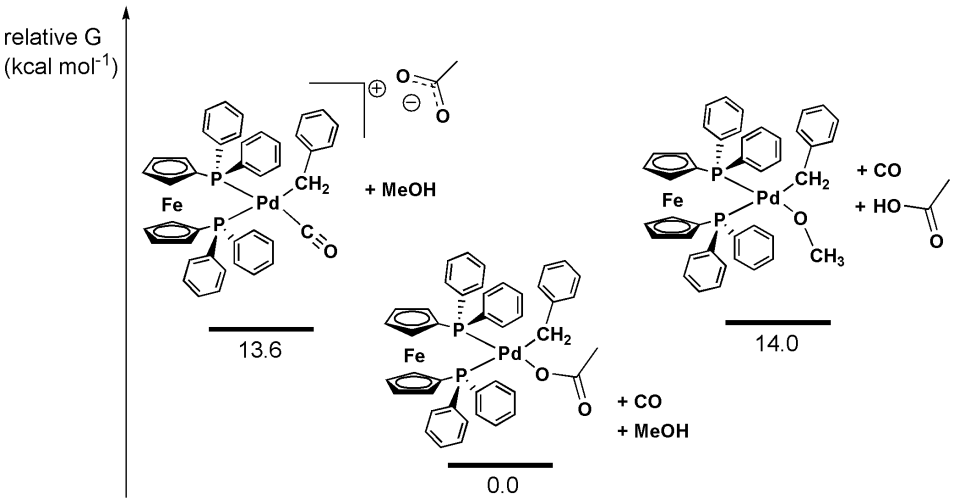


Figure S4. Gibbs energy differences between [$Pd(CH_2Ph)(CO)(DPPF)$][Ac] + MeOH, [$Pd(CH_2Ph)(Ac)(DPPF)$] + CO + MeOH and [$Pd(CH_2Ph)(OMe)(DPPF)$] + CO + HAc. C-PCM/PBE1PBE/def2-SVP, methanol as continuous medium. Thermodynamic data computed at 403 K and 7.8 atm.

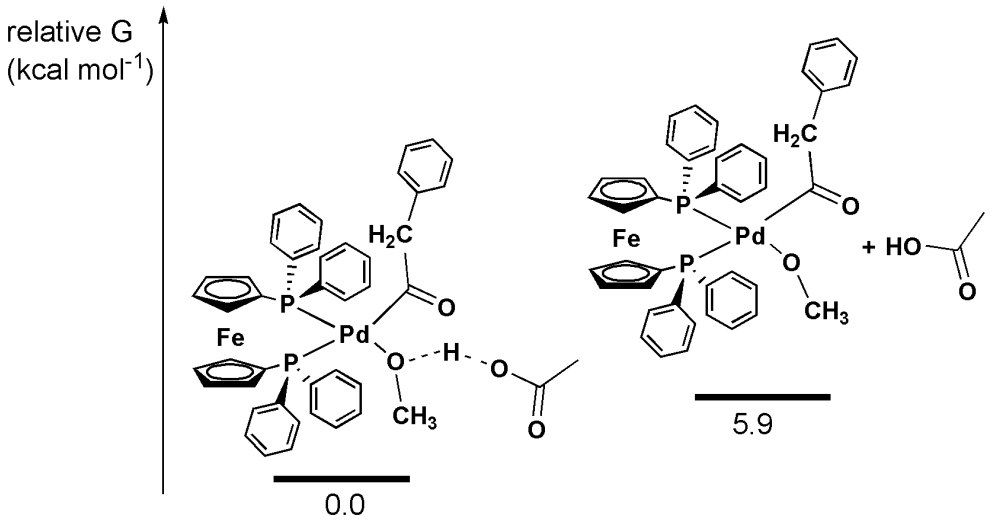


Figure S5. Gibbs energy differences between [Pd(COCH$_2$Ph)(MeOH---Ac)(DPPF)] and [Pd(COCH$_2$Ph)(OMe)(DPPF)] + HAc. C-PCM/PBE1PBE/def2-SVP, methanol as continuous medium. Thermodynamic data computed at 403 K and 7.8 atm.

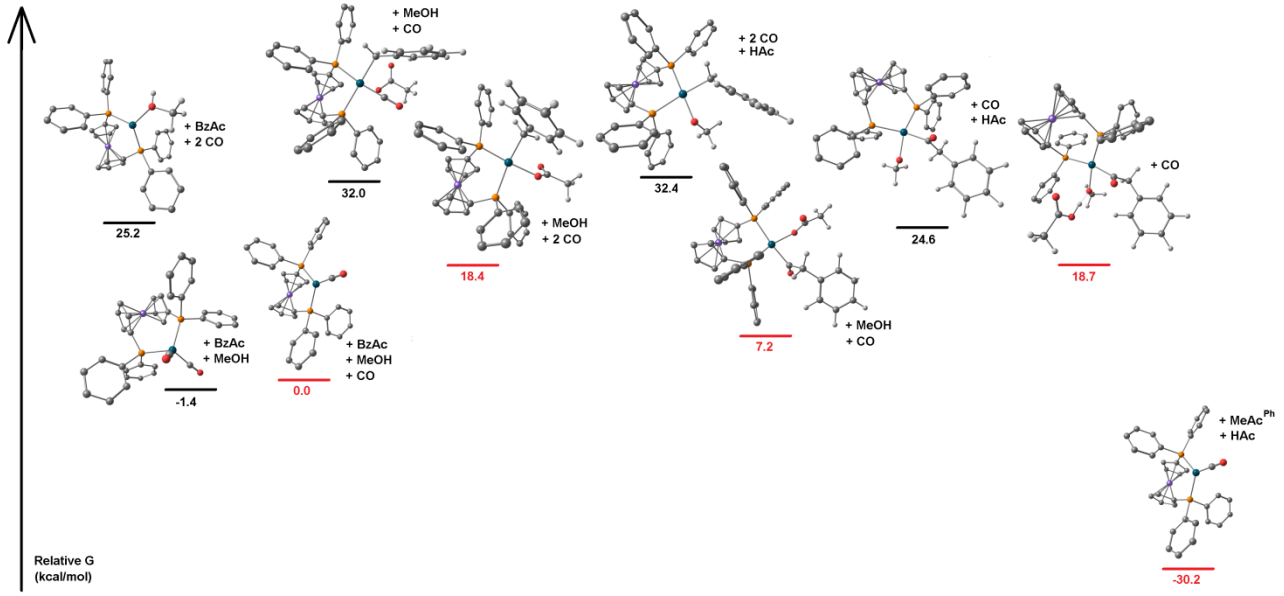


Figure S6. DFT-optimized structures and relative Gibbs free energy values (kcal mol^{-1}). Intermediate species possibly involved in the Pd-catalysed methoxycarbonilation of BzAc are highlighted in red. C-PCM/PBE1PBE/def2-SVP, methanol as continuous medium. Thermodynamic data computed at 403 K and 7.8 atm. Colour map: Pd, green; Fe, violet; P, orange; O, red; C, grey; H, white. Hydrogen atoms of DPPF are omitted for clarity.

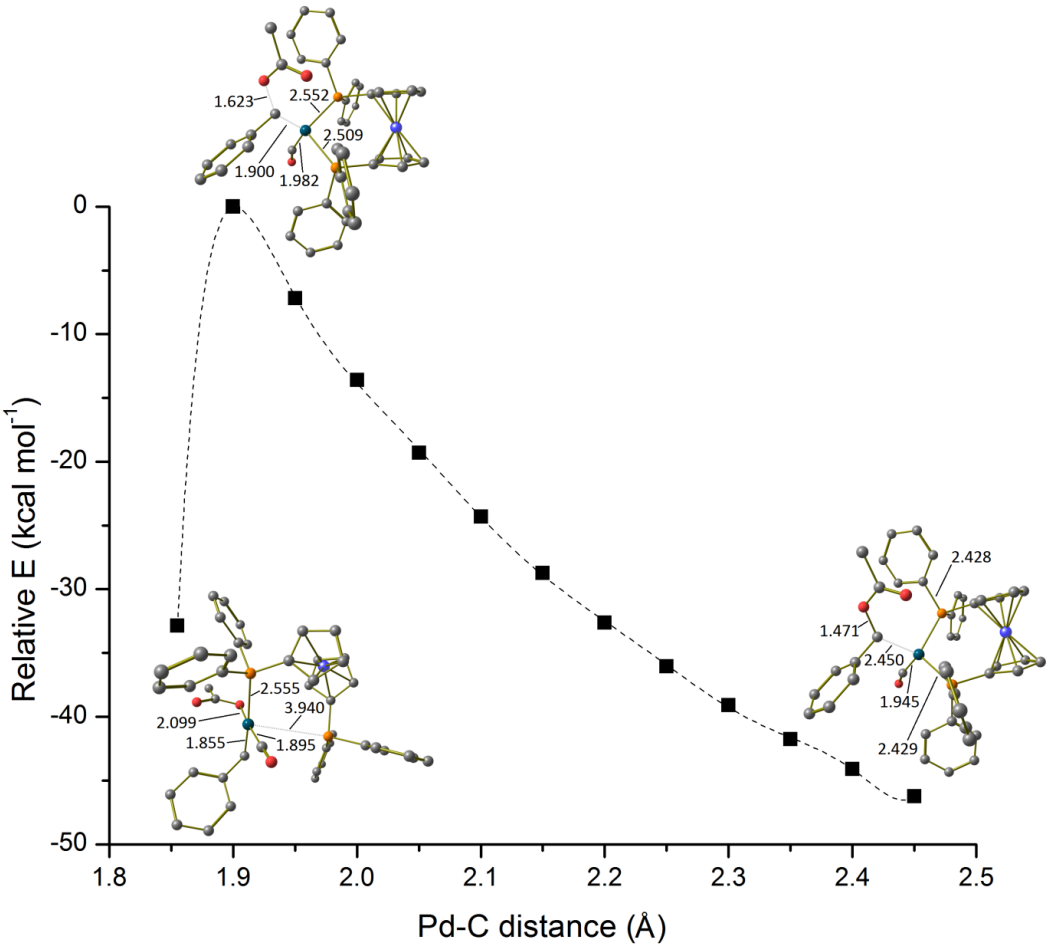


Figure S7. Energy profile of the constrained geometry optimization of [Pd(CO)(DPPF)] + BzAc, following the Pd---PhCH$_2$OC(O)CH$_3$ distance. EDF2/6-31G*/LANL2DZ. Colour map: Pd, green; Fe, violet; P, orange; O, red; C, grey. Hydrogen atoms are omitted for clarity. Selected computed bond lengths in Å.

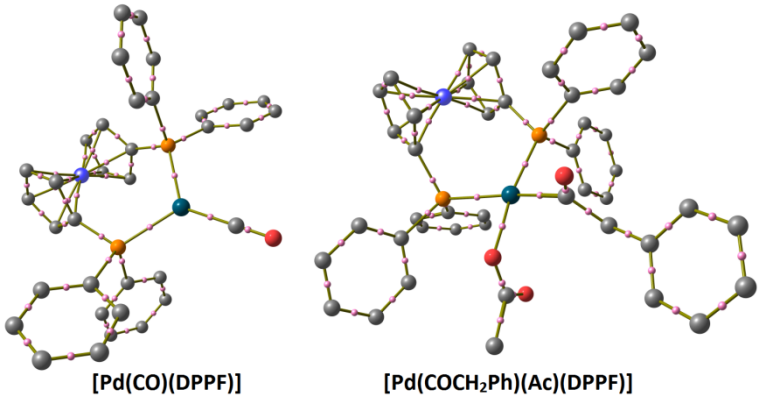
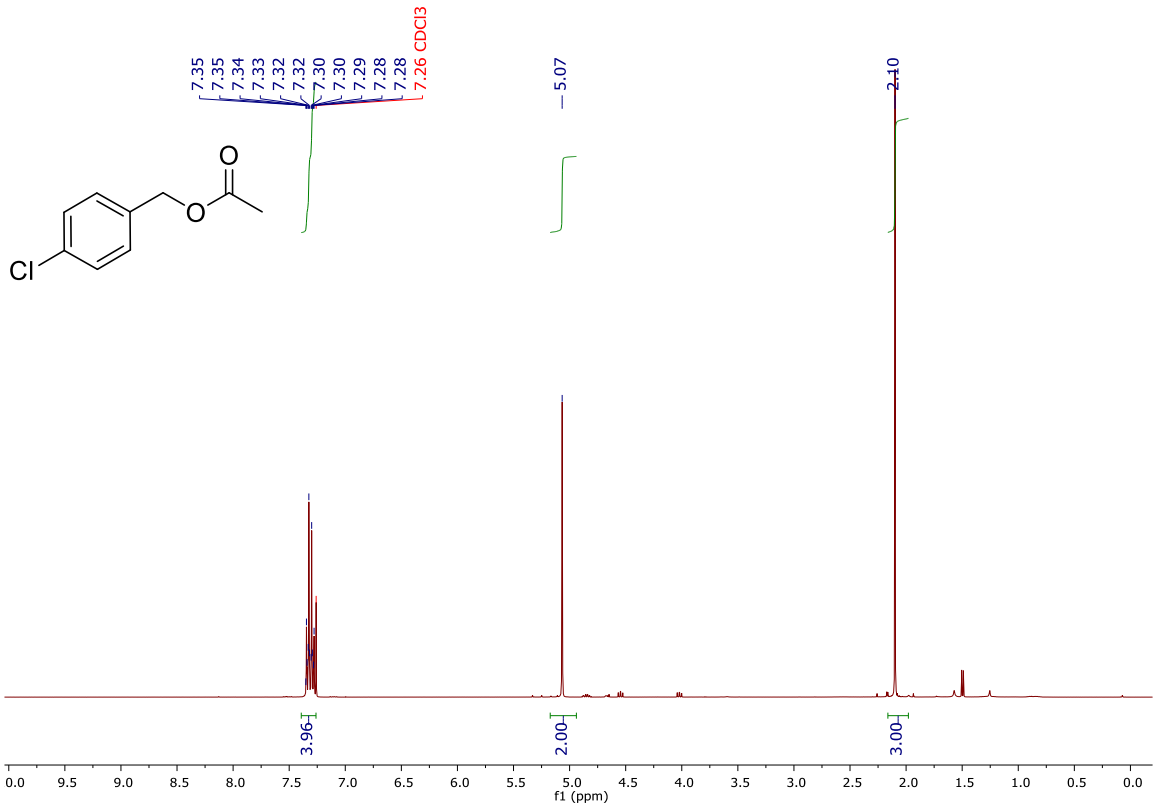
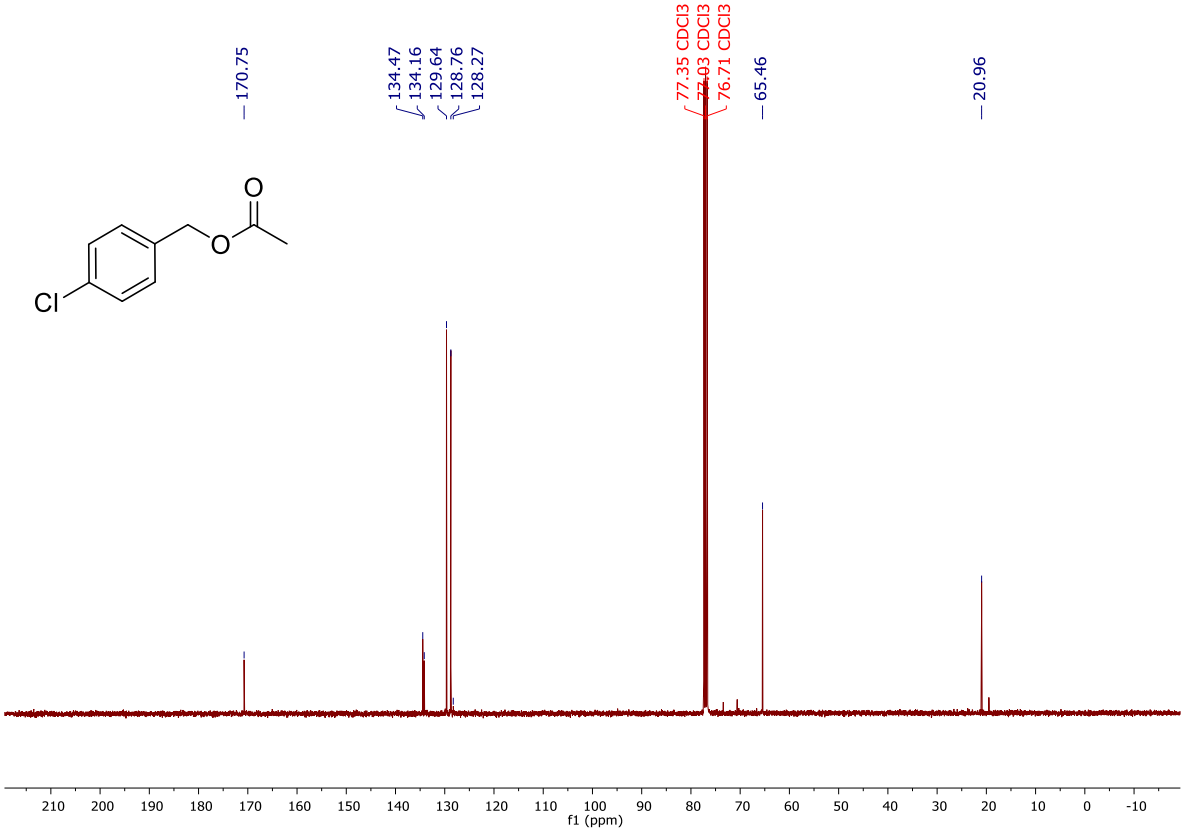


Figure S8. DFT-optimized structures of [Pd(CO)(DPPF)] and [Pd(COCH$_2$Ph)(Ac)(DPPF)] with (3,-1) b.c.p. highlighted (pink spheres). C-PCM/PBE1PBE/def2-SVP, methanol as continuous medium. Colour map: Pd, green; Fe, violet; P, orange; O, red; C, grey. Hydrogen atoms and relative (3,-1) b.c.p are omitted for clarity.

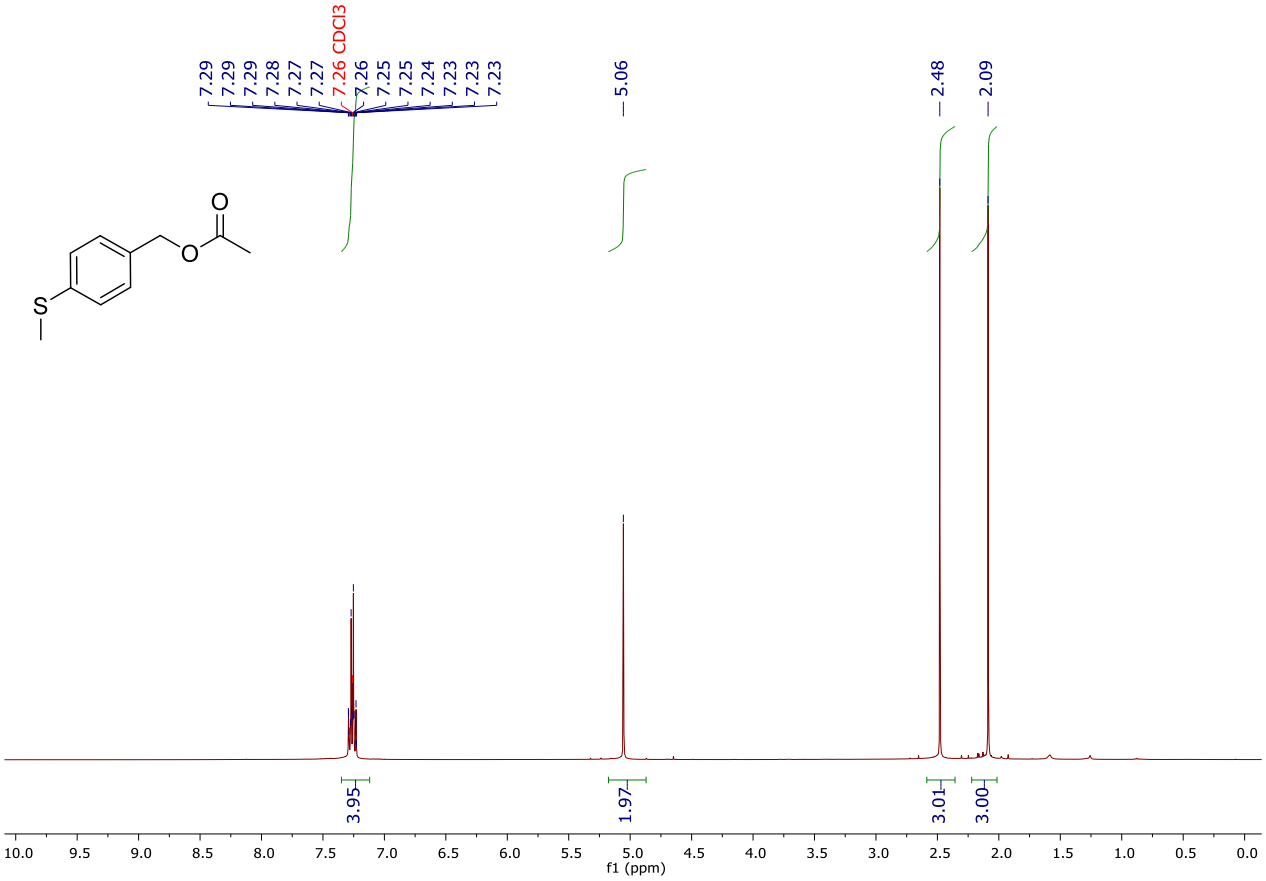
^{1}H and $^{13}C\{^{1}H\}$ NMR of synthesized acetates

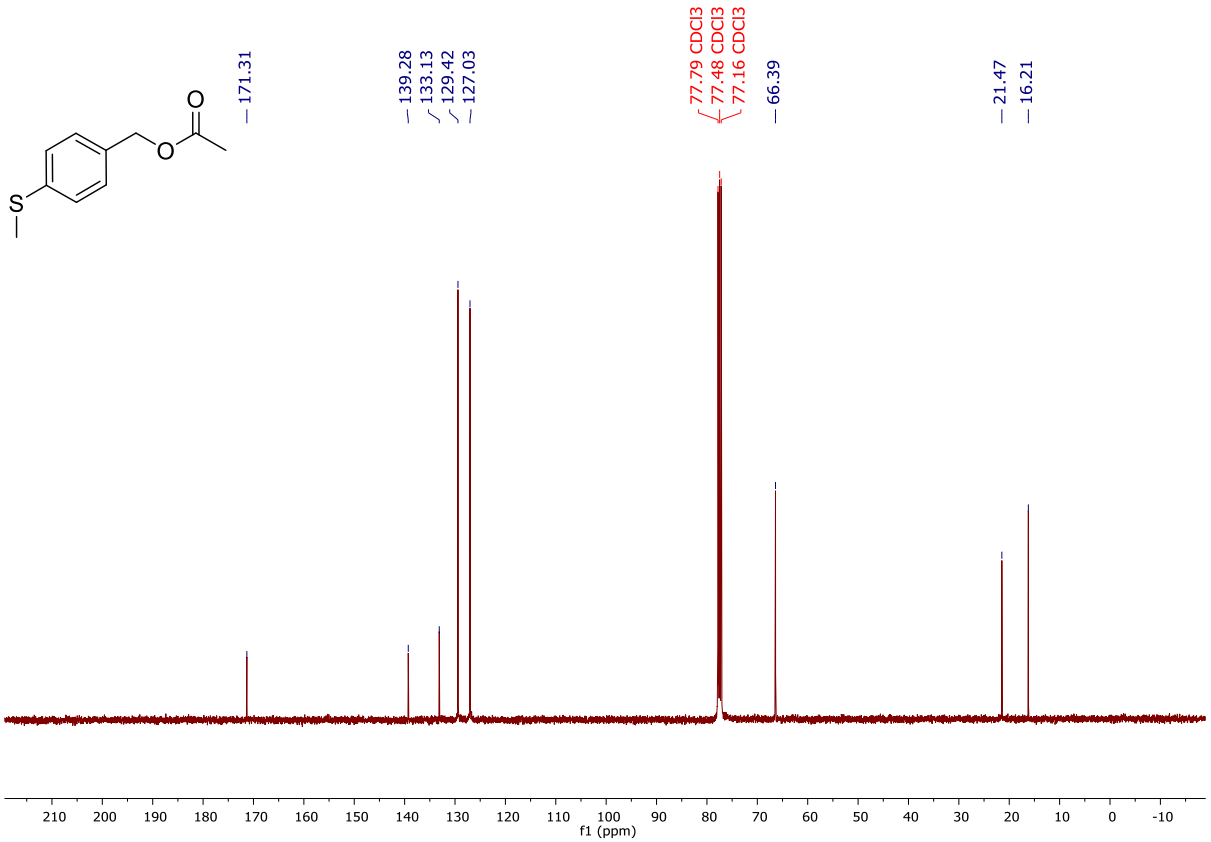
4-chlorobenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.39-7.24 (m, 4H), 5.07 (s, 2H), 2.10 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 170.7, 134.4, 134.2, 129.6, 128.7, 128.3, 77.3, 77.2, 77.0, 76.7, 65.4, 20.9



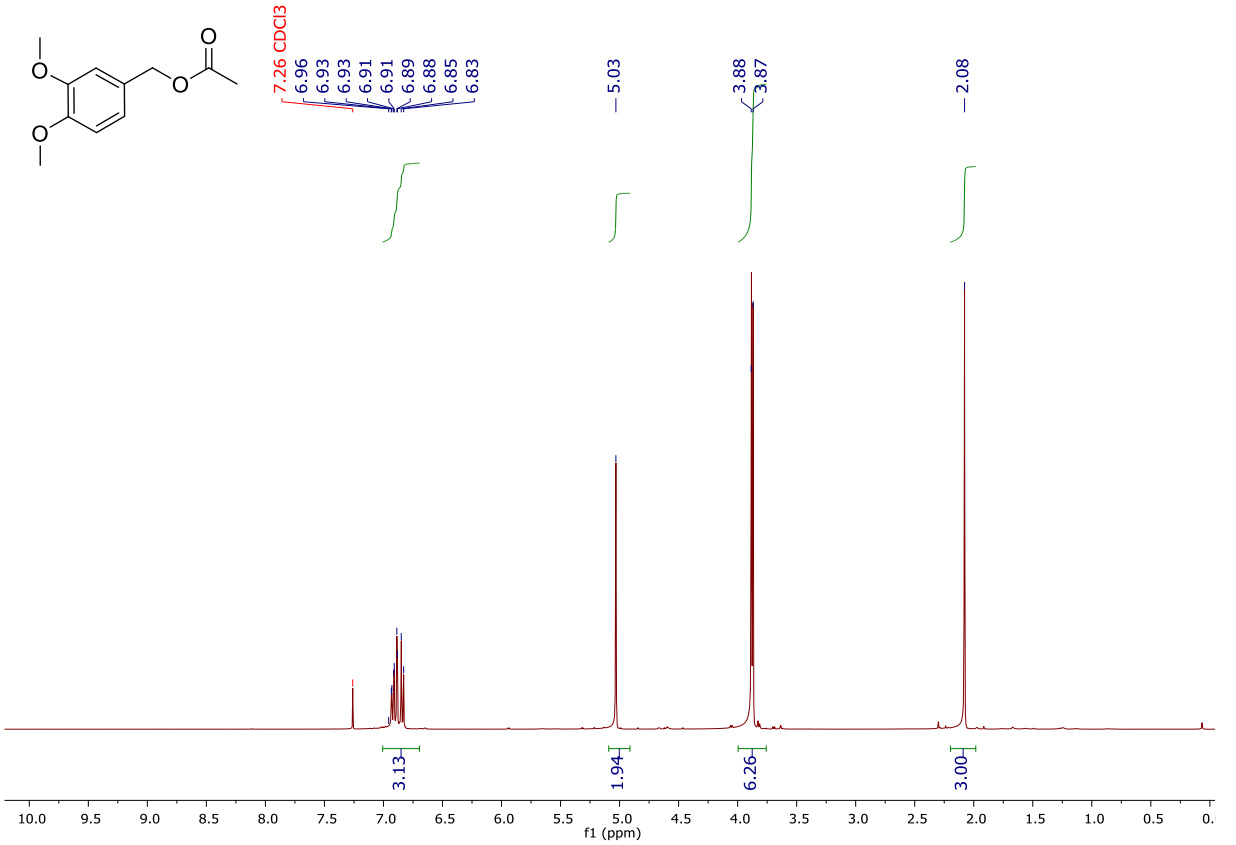


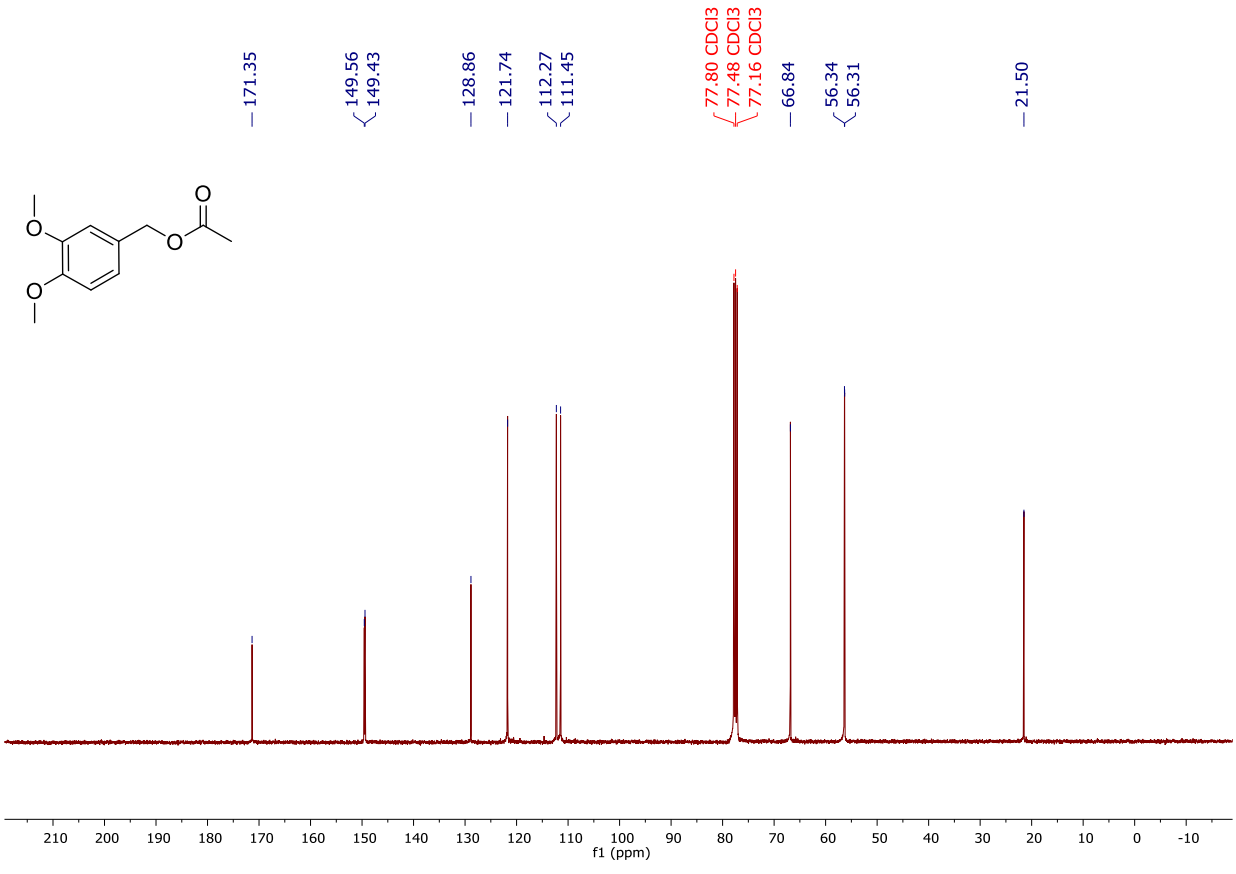
4-(methylthio)benzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.36-7.11 (m, 4H), 5.06 (s, 2H), 2.49 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 171.3, 139.3, 133.1, 129.4, 127.0, 77.8, 77.7, 77.5, 66.3, 21.4, 16.1



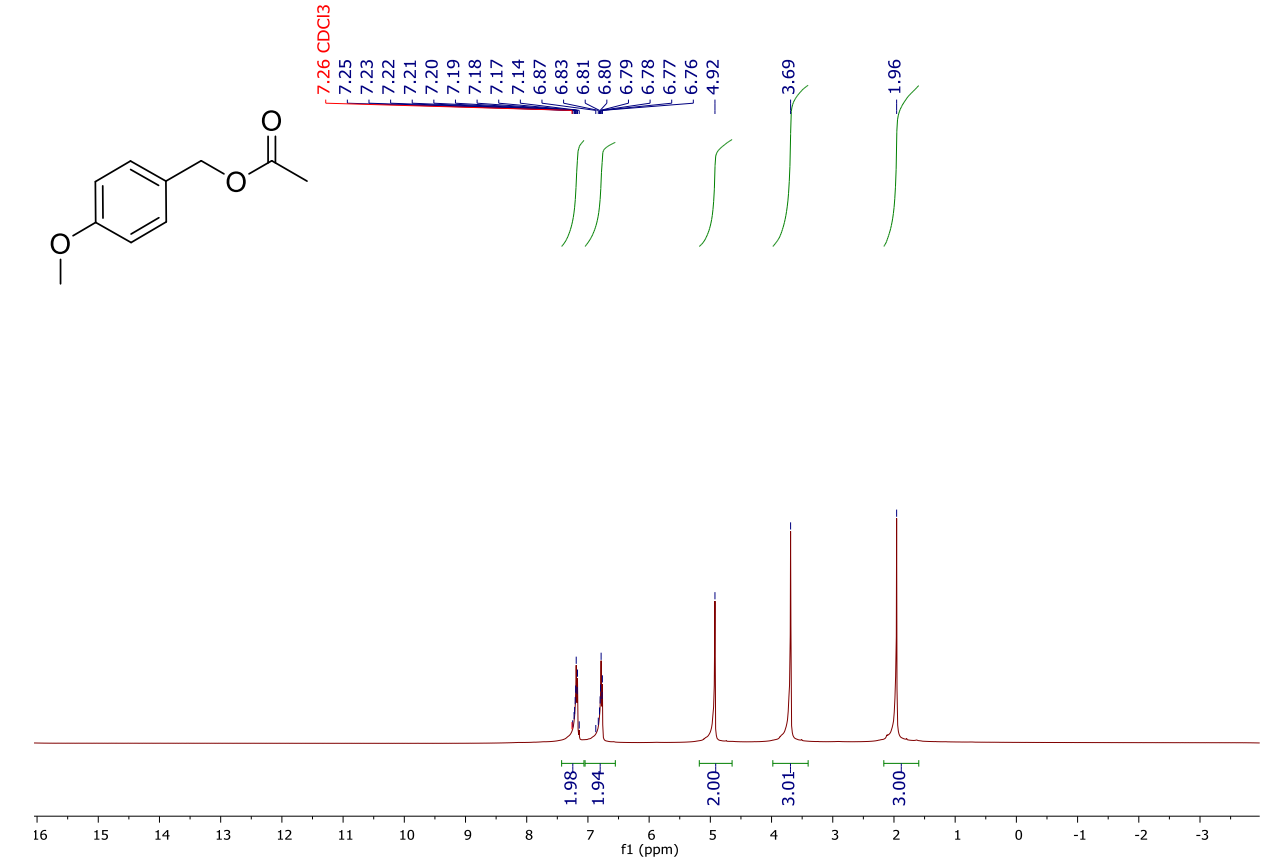


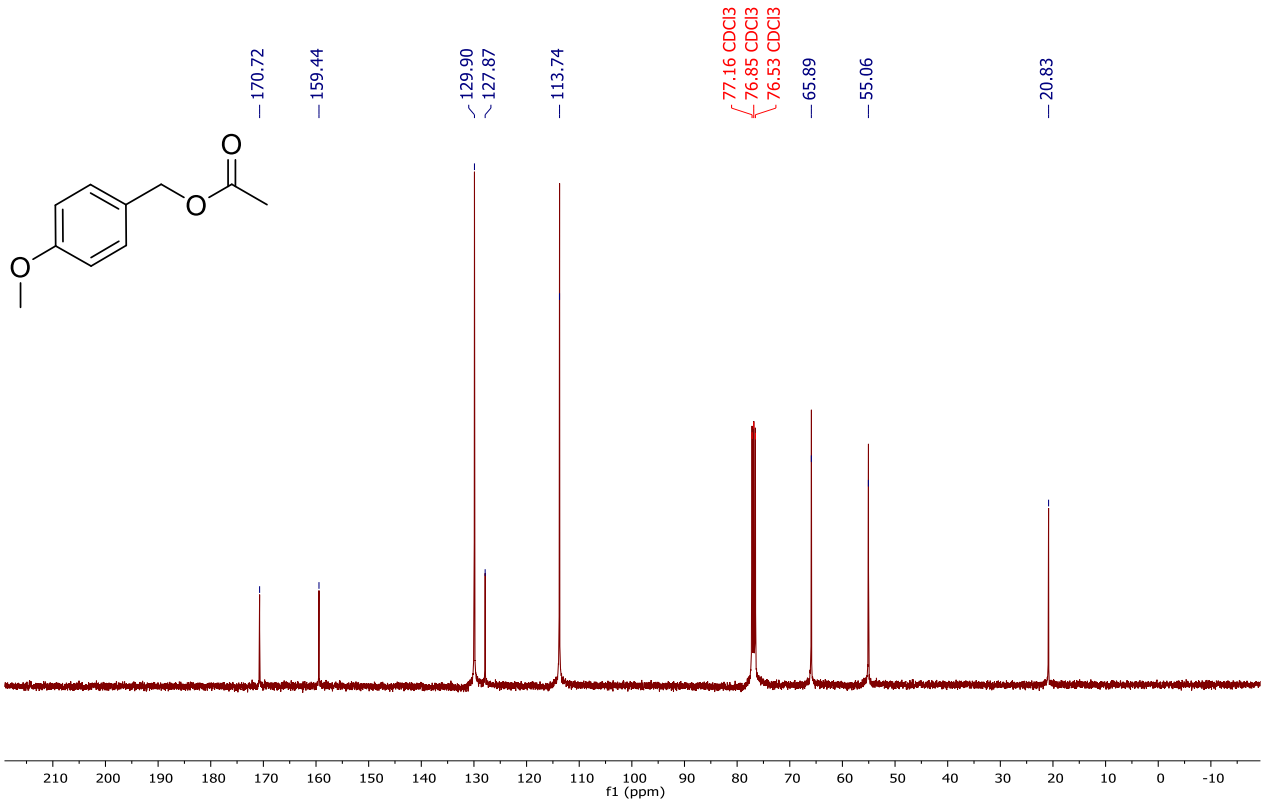
3,4-dimethoxybeznyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, CDCl3) δ (ppm) = 7.02-6.68 (m, 4H), 5.03 (s, 2H), 3.88 (d, 6H), 2.09 (s, 3H). ^{13}C NMR (300 MHz, CDCl3) δ (ppm) = 171.3, 149.5, 149.4, 149.4, 128,9, 121.7, 120.6, 114.7, 112.2, 111.7, 111.4, 110.3, 77.8, 77.7, 77.4, 77.1, 66.9, 56.3, 56.3, 21.5.



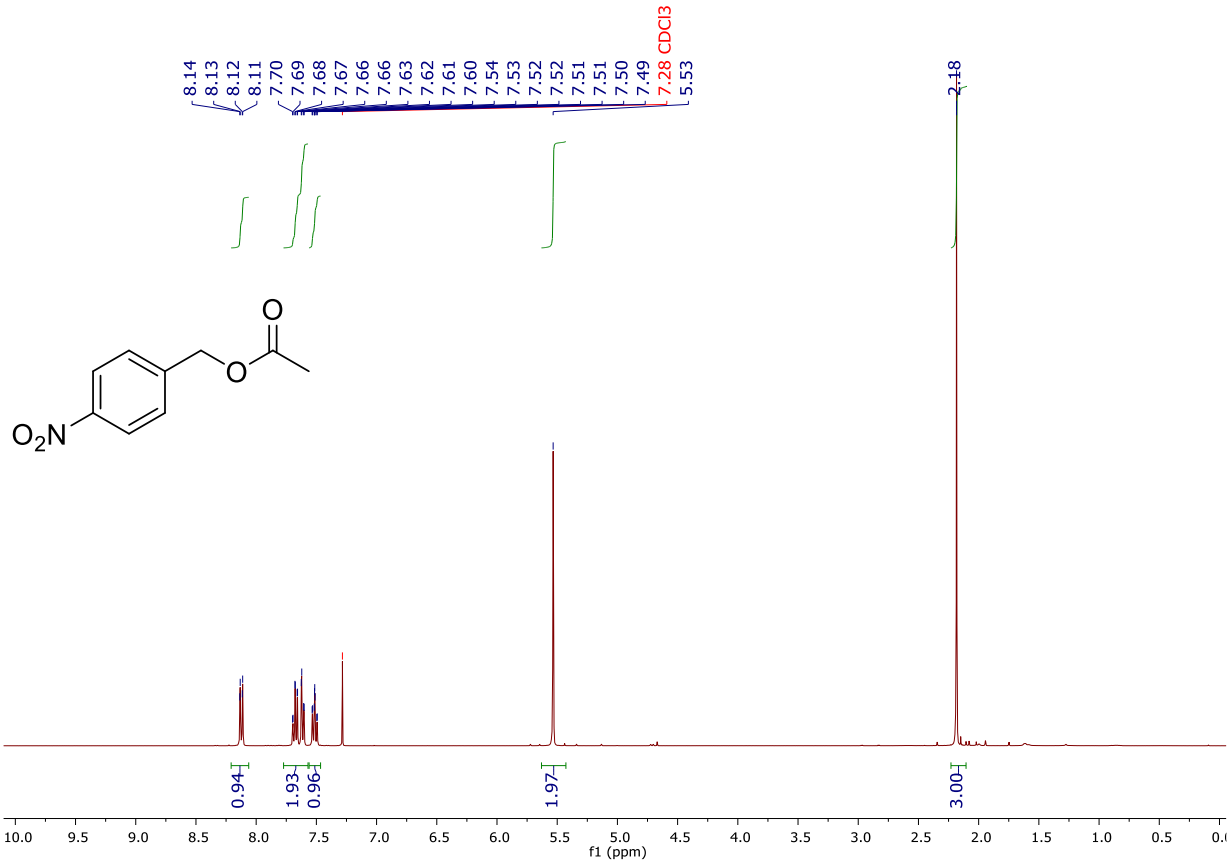


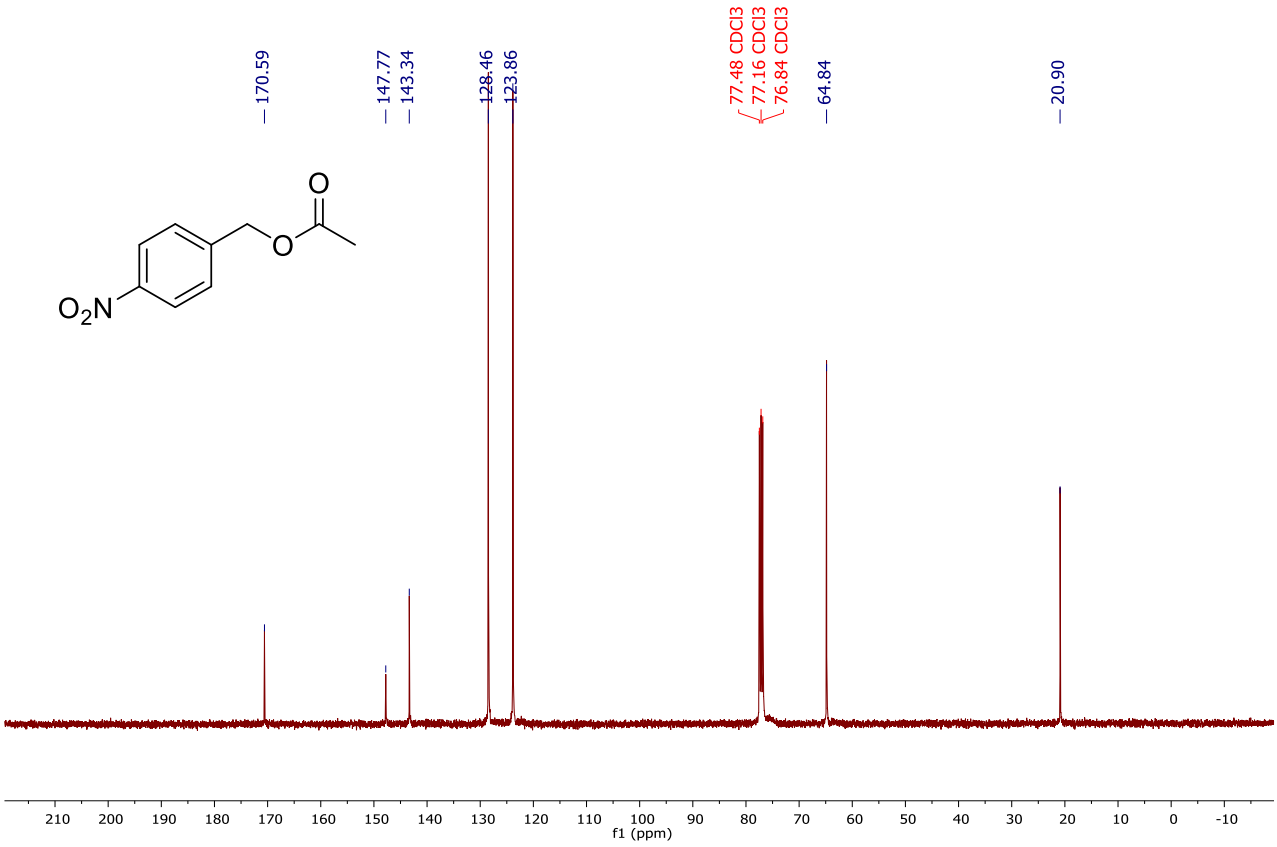
4-methoxybenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.42-7.06 (d, 2H), 7.05-6.55 (d, 2H), 4.92 (s, 2H), 3.69 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 170.7, 159.4, 129.9, 127.9, 113.8, 113.7, 77.1, 77.0, 76.8, 76.5, 65.9, 55.0, 20.8.



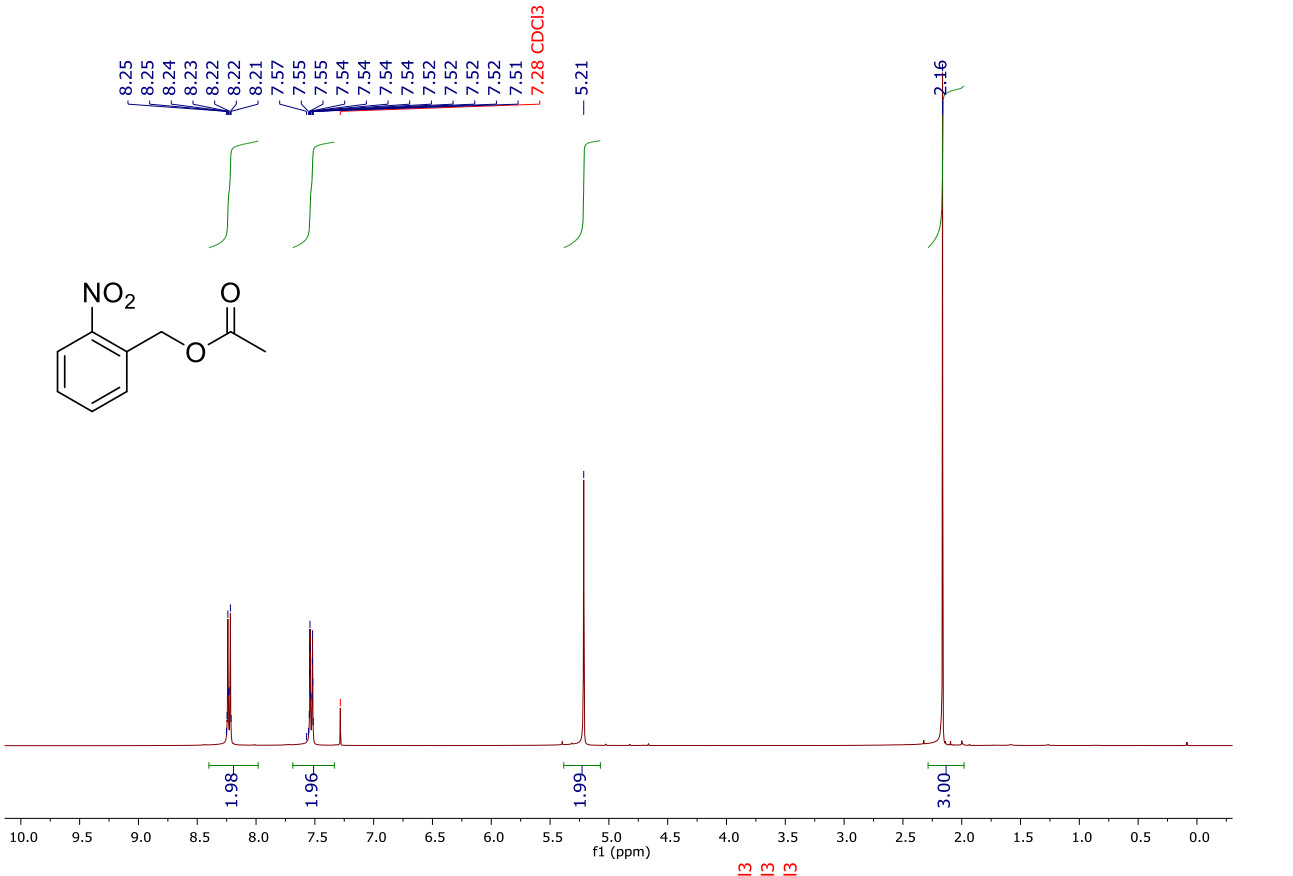


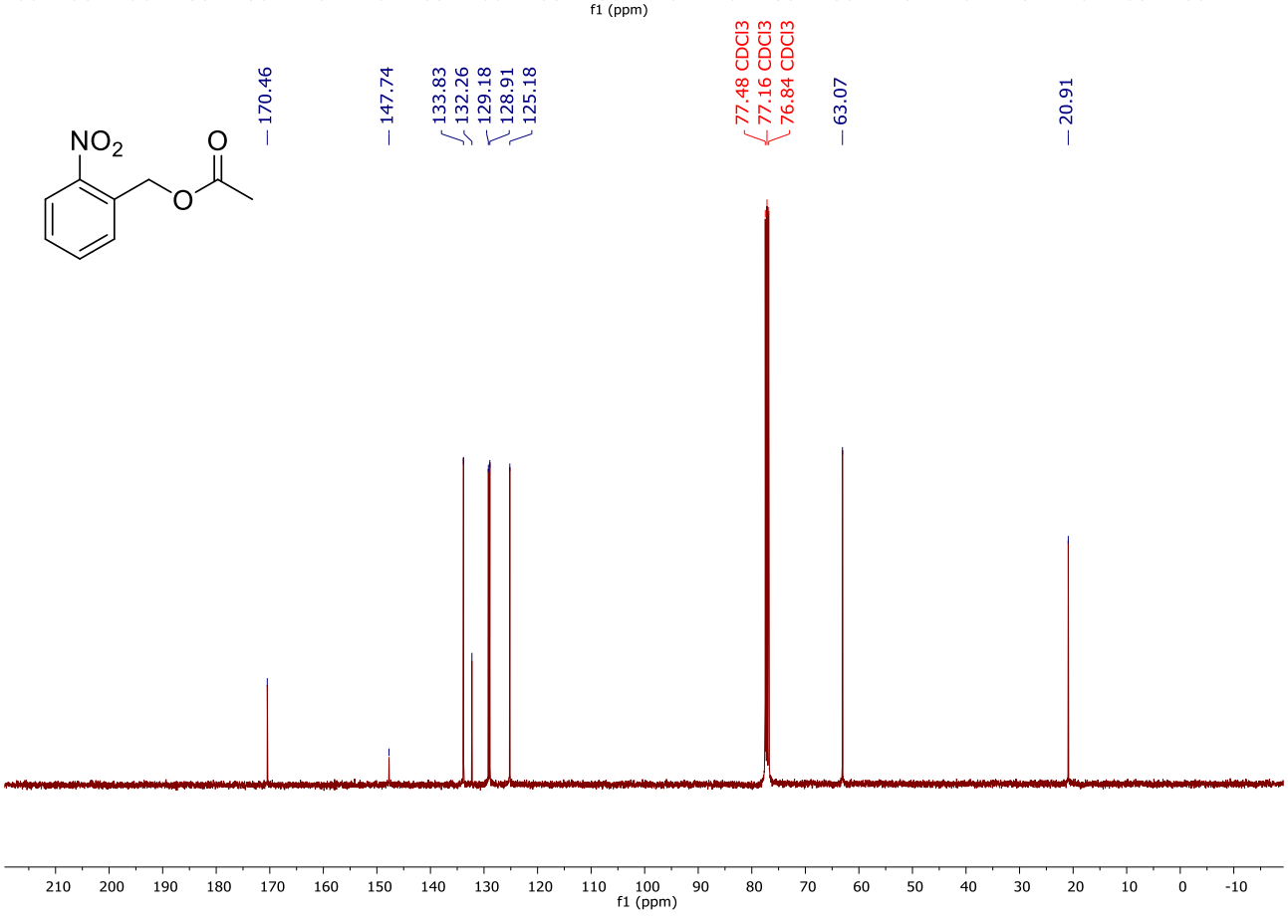
4-nitrobenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.21-8.06 (d, 2H), 7.77-7.47 (m, 2H), 5.53 (s, 2H), 2.18 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 170.59, 147.77, 143.34, 128.46, 123.86, 77.48, 77.16, 76.84, 64.84.



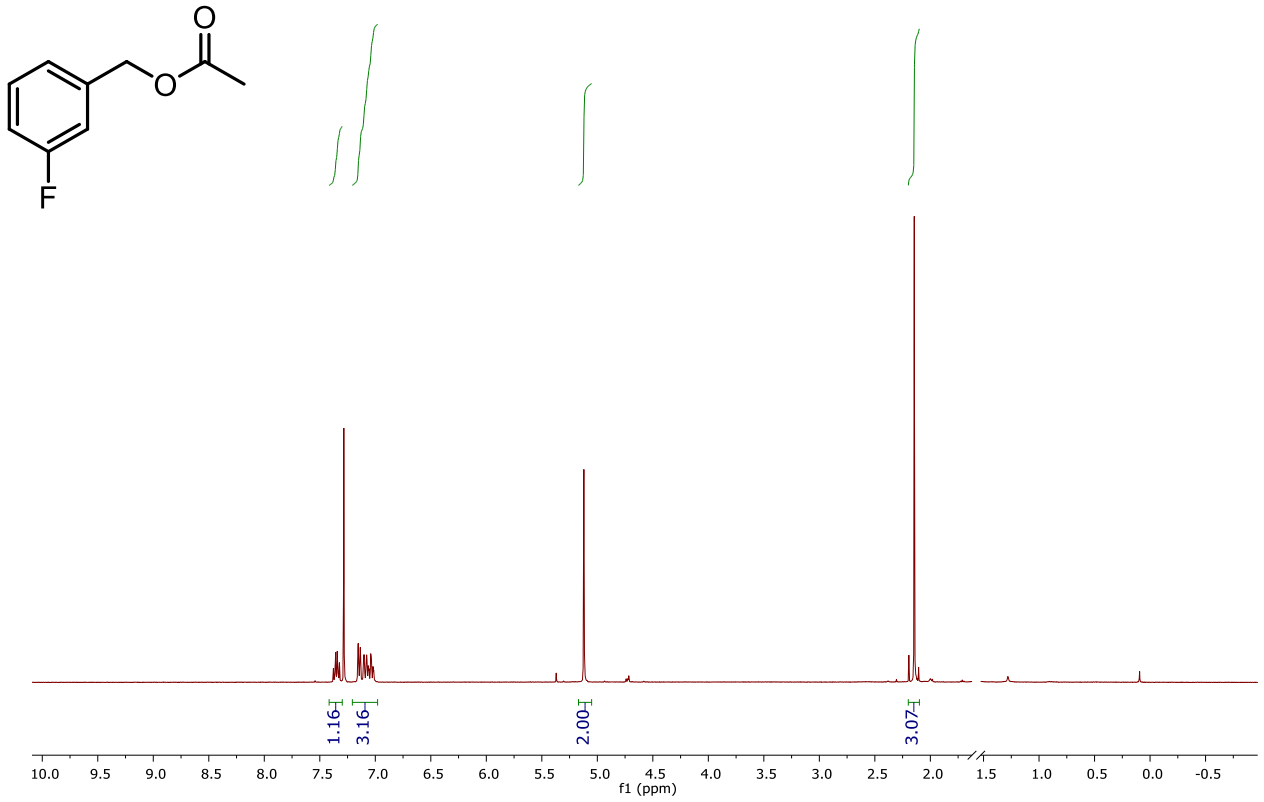


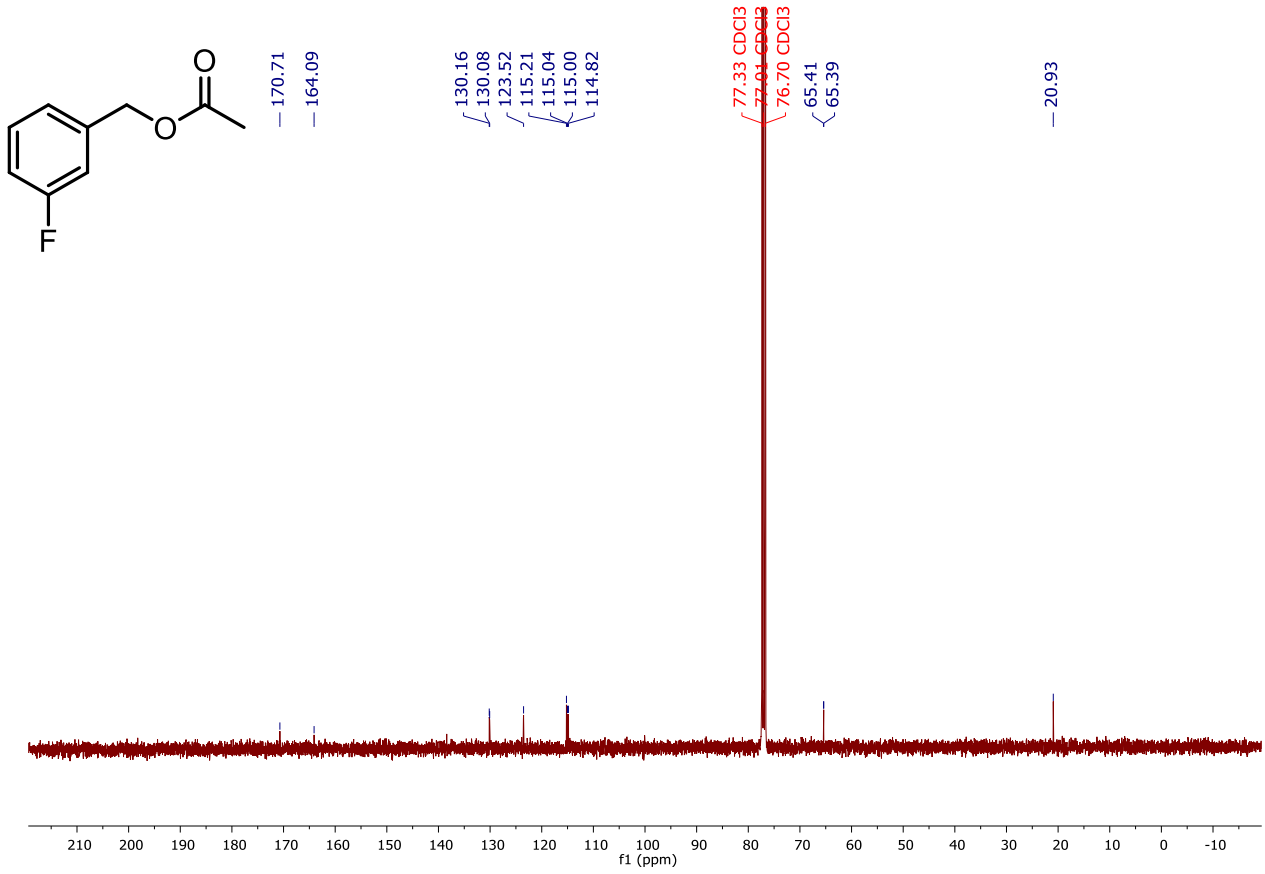
2-nitrobenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 8.23 (d, 2H), 7.53 (d, 2H), 5.21 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 170.7, 147.7, 133.8, 132.3, 129.2, 128.9, 125.2, 77.4, 77.3, 77.2, 76.8, 63.1, 20.9.



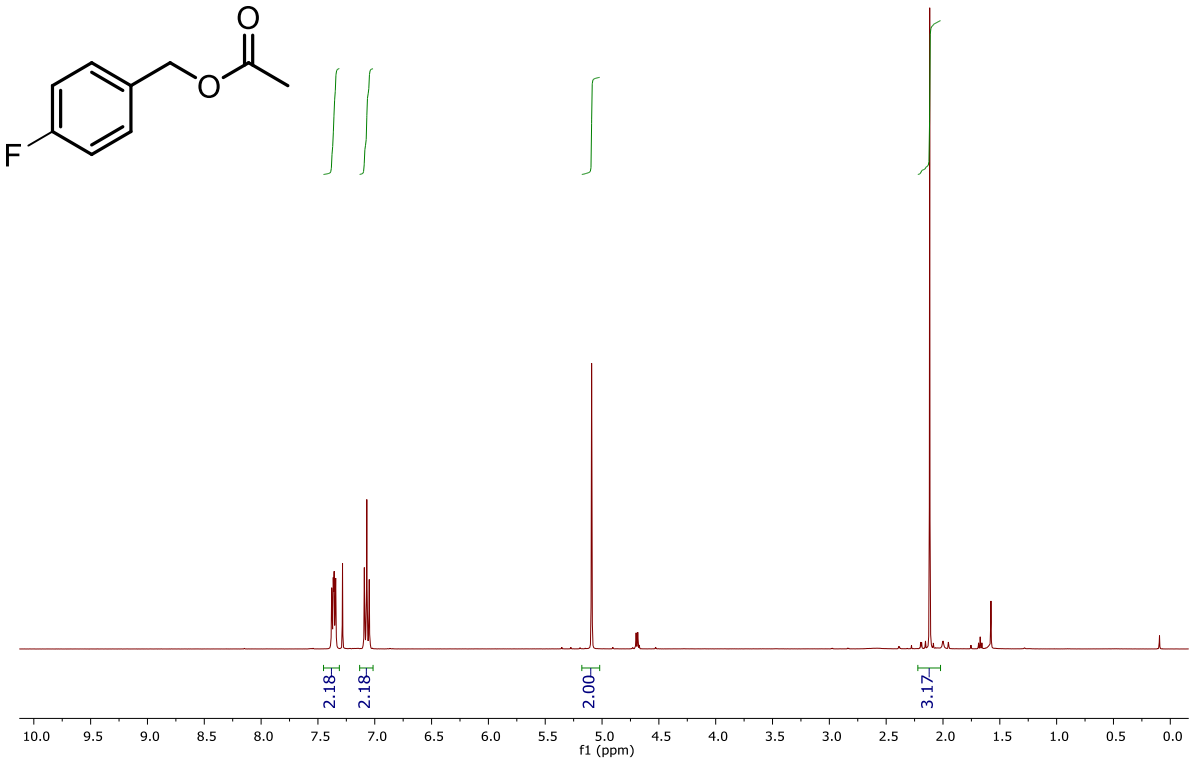


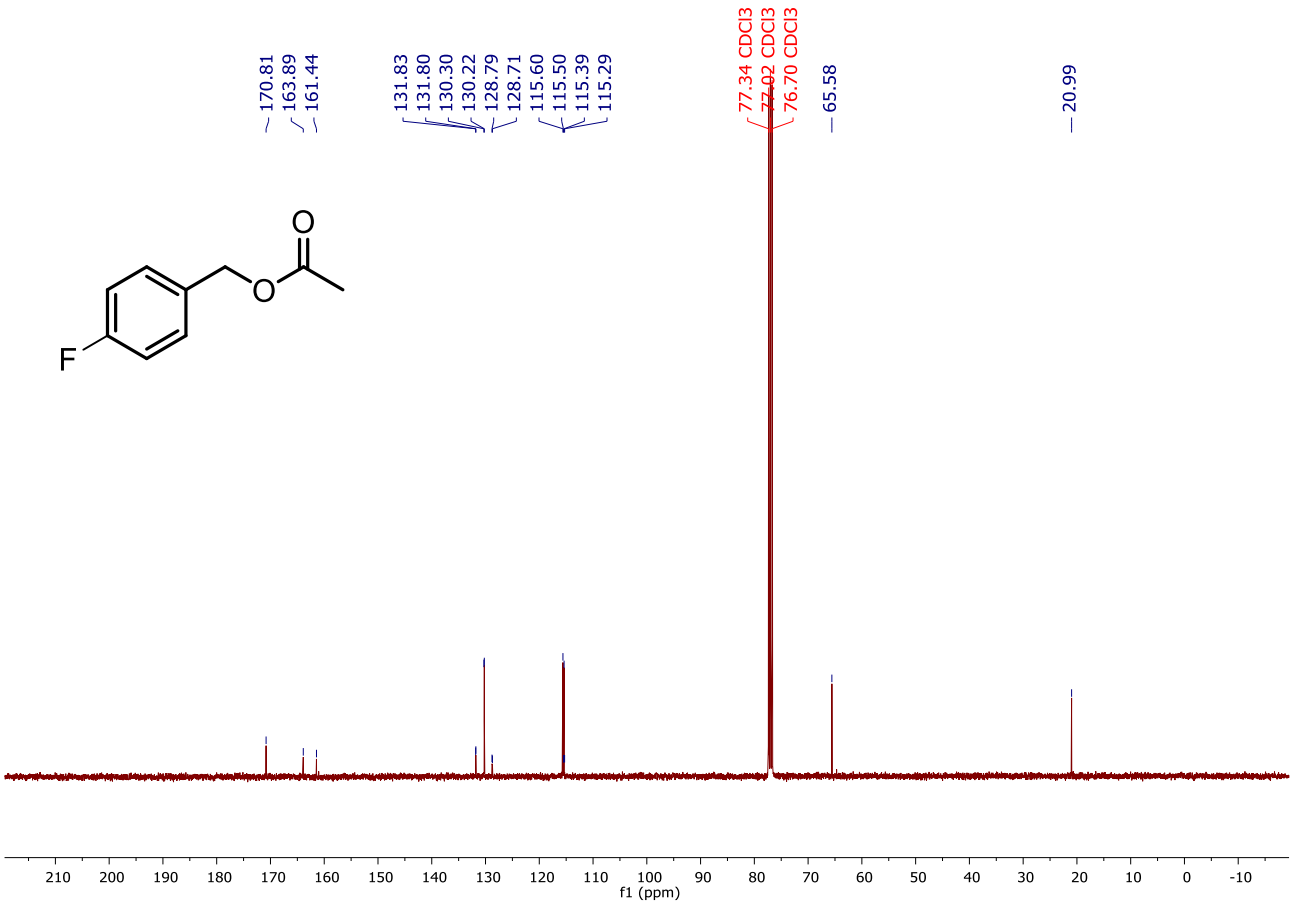
3-fluorobenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.45-7.31 (m, 2H), 7.07 (t, 2H), 5.09 (s, 2H), 2.12 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 170.8, 163.9, 161.4, 131.8, 131.8, 130.3, 130.2, 128.8, 128.7, 115.6, 115.5, 115.4, 115.3, 77.3, 77.2, 77.0, 76.7, 65.6, 20.9.



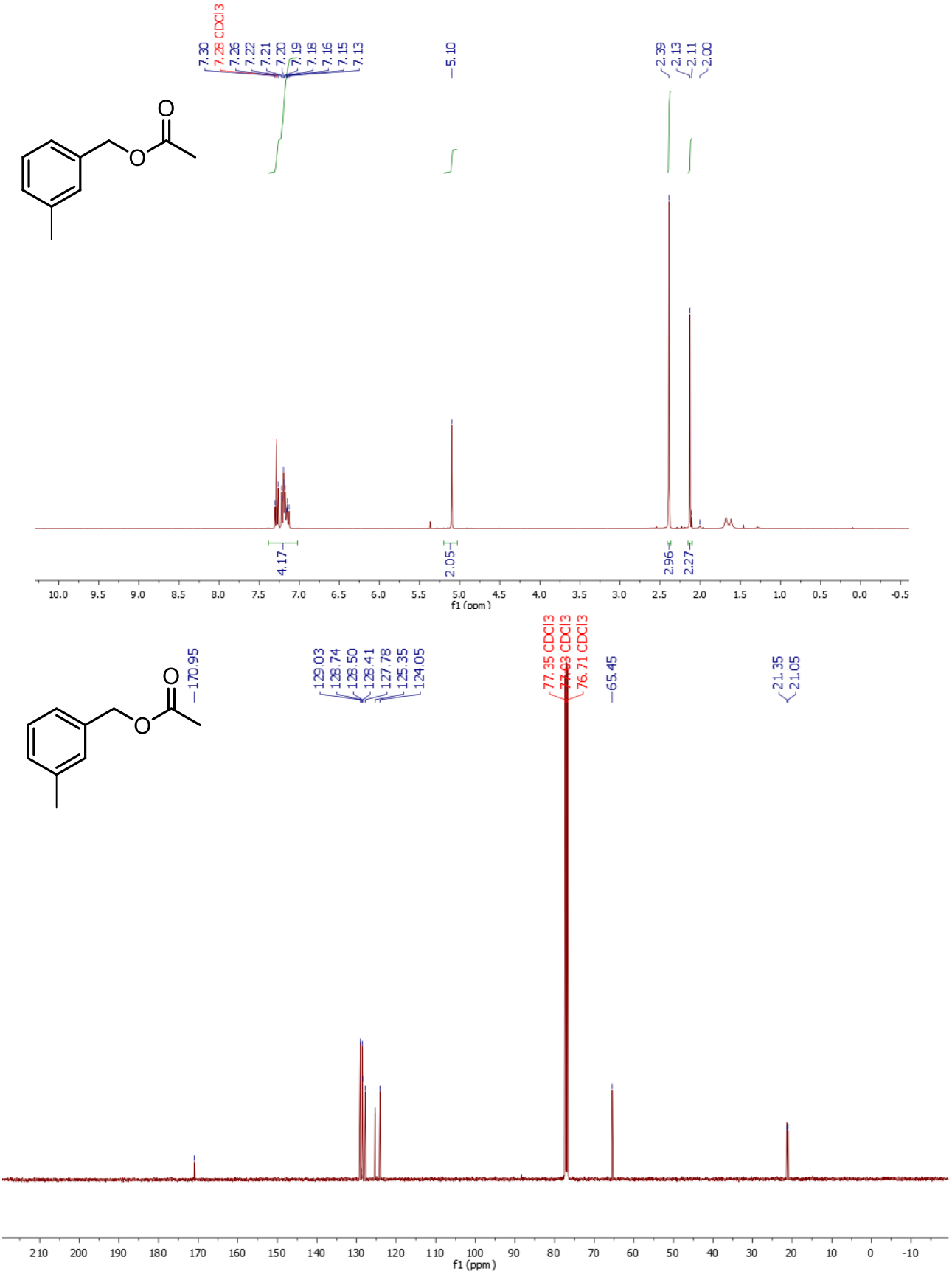


4-fluorobenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.43-7.28 (m, 2H), 7.21-6.97 (m, 2H), 5.13 (s, 2H), 2.15 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 170.71,164.1, 130.1, 130.1, 123.5, 115.2, 115.0, 115.0, 114.8, 77.3, 77.2, 77.0, 76.7, 65.4, 65.4, 20.9.

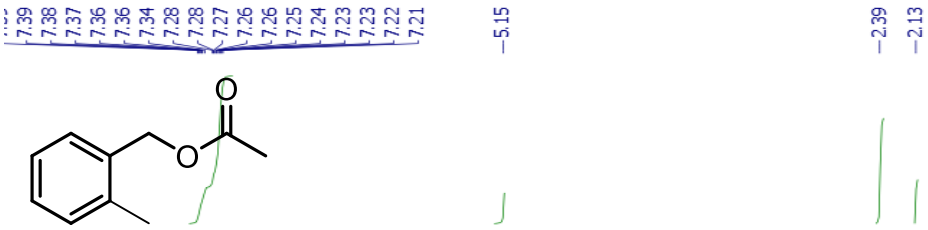


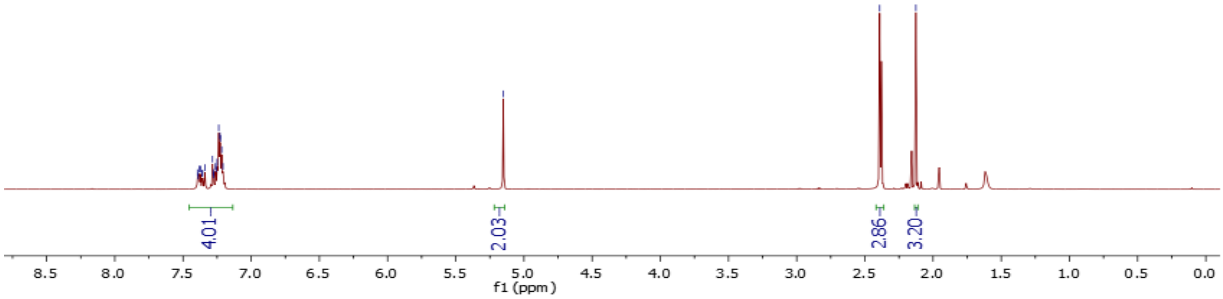


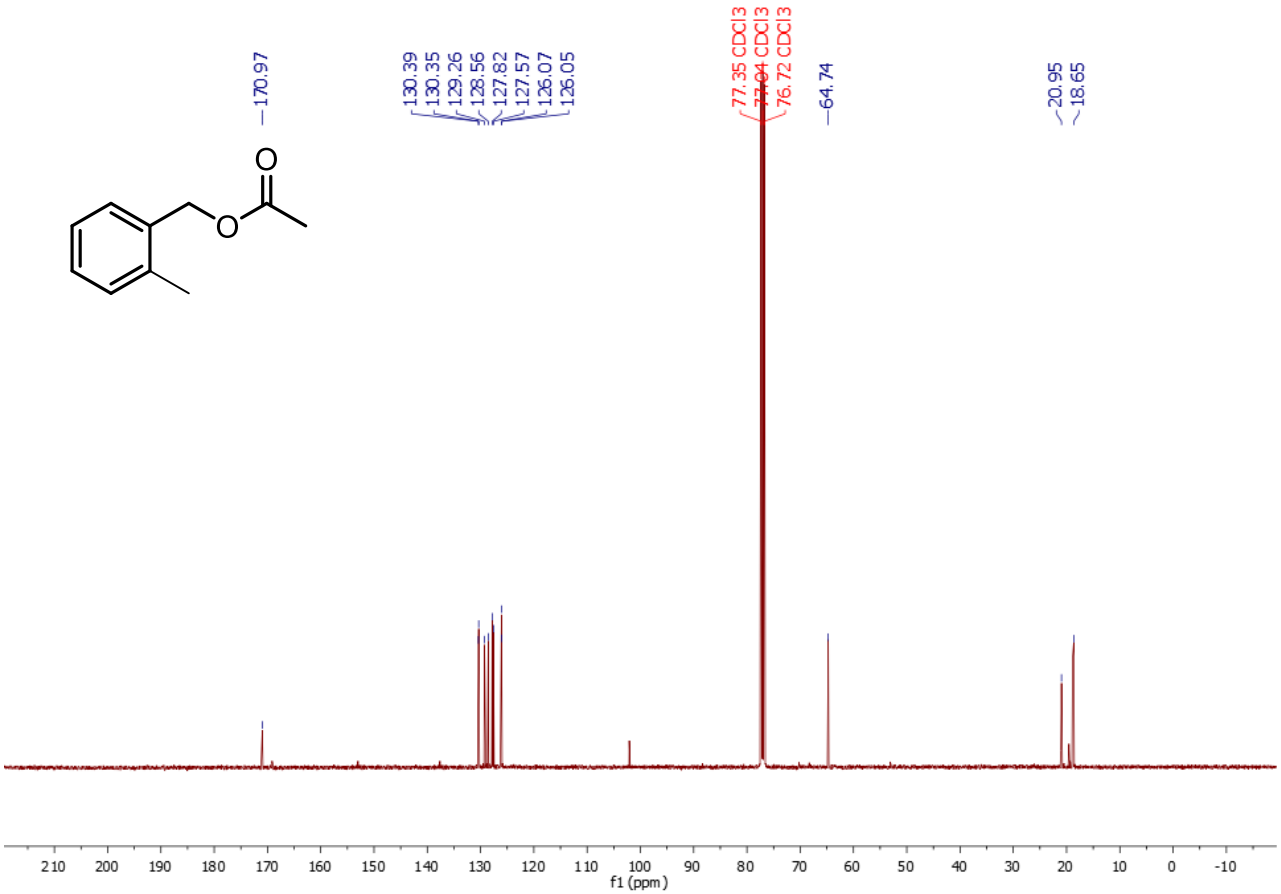
3-methylbenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.30-7.13 (m, 4H), 7.21-6.97 (m, 2H), 5.10 (s, 2H), 2,39 (s, 3H), 2.13-2.11 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 129.03, 128.74, 128.50, 128.41, 127.78, 125.35, 124.05, 65.45, 21.35, 21.05.



2-methylbenzyl acetate: Yellow Oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.39-7.21 (m, 4H), 5.15 (s, 2H), 2,39 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm) = 130.39, 130.35, 129.26, 128.56, 127.82, 127.57, 126.07, 126.05, 64.74, 20.95, 18.65.

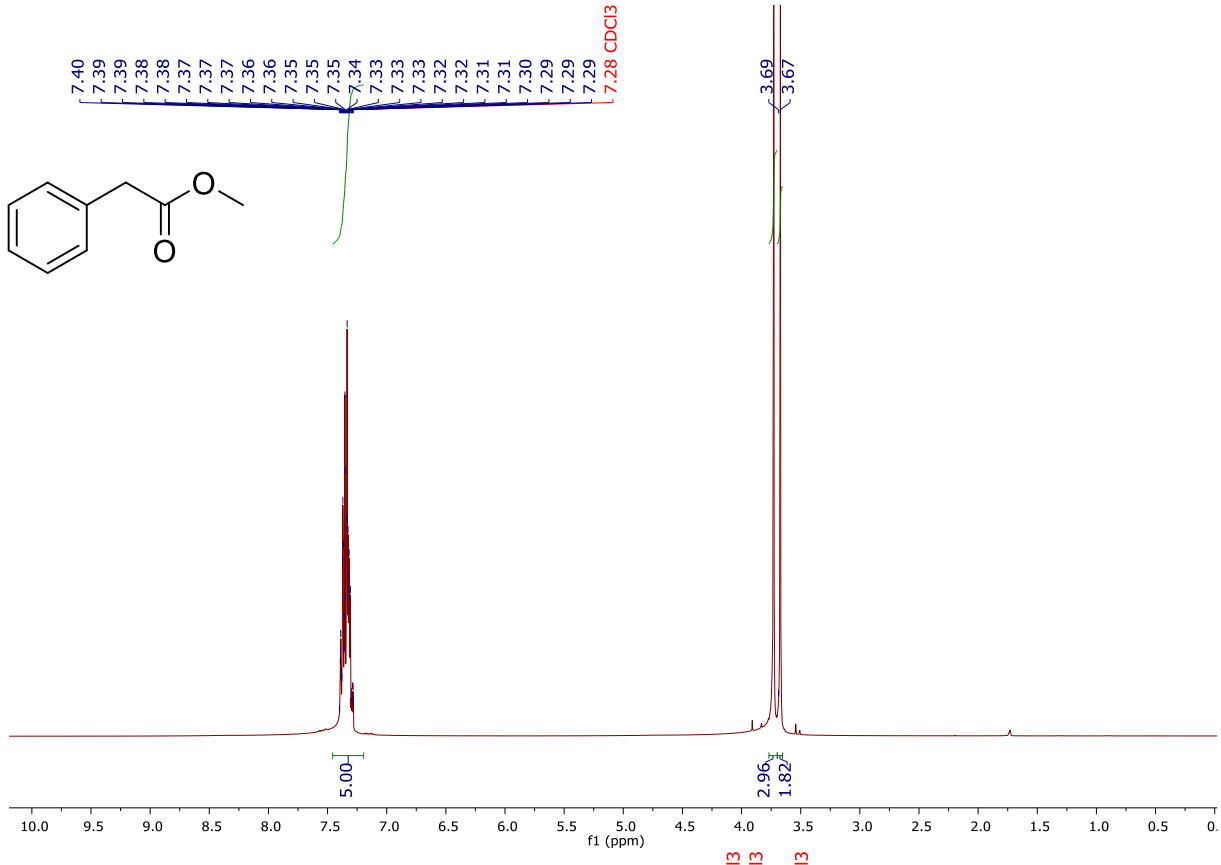


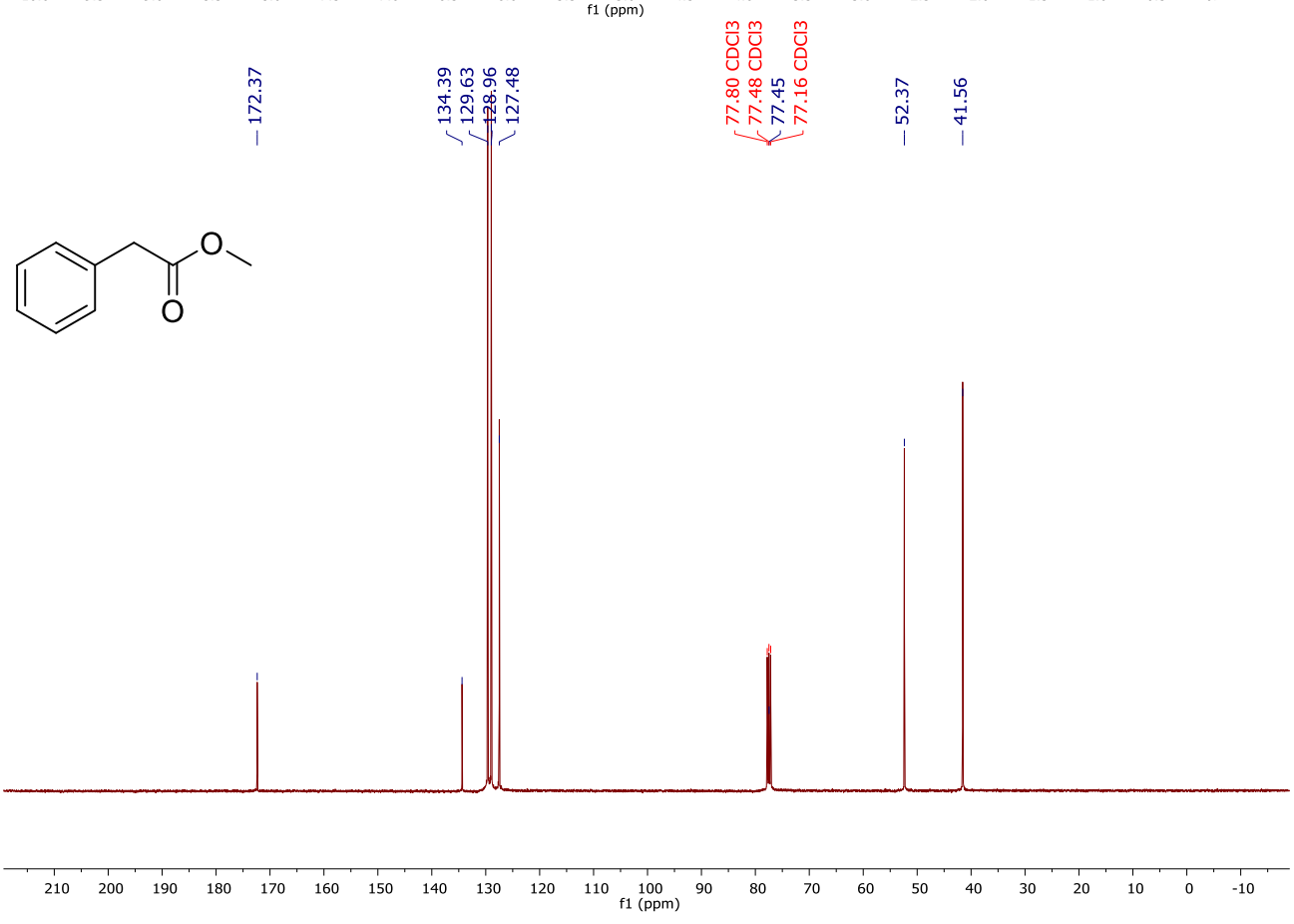




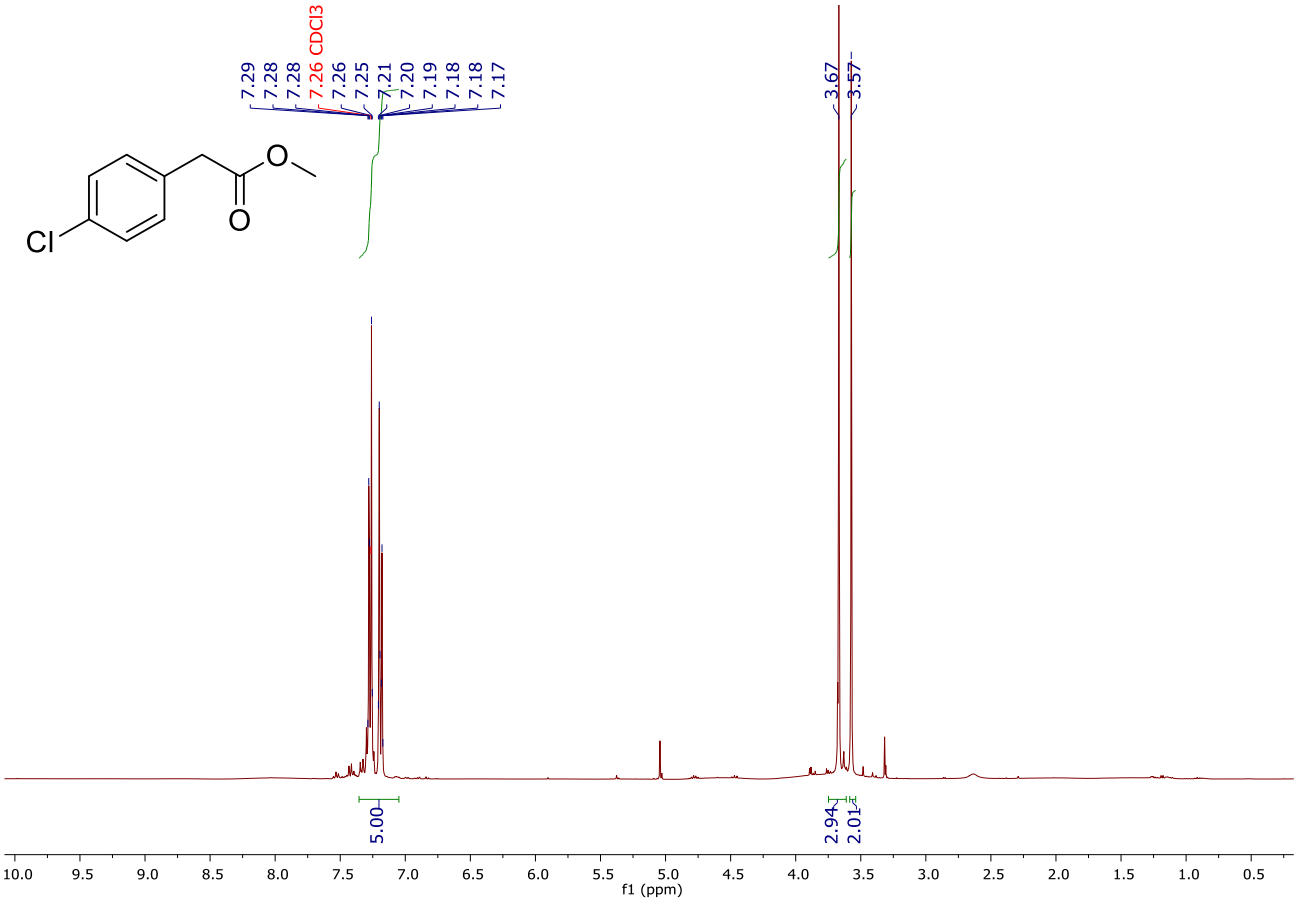
^{1}H and $^{13}C\{^{1}H\}$ NMR of products

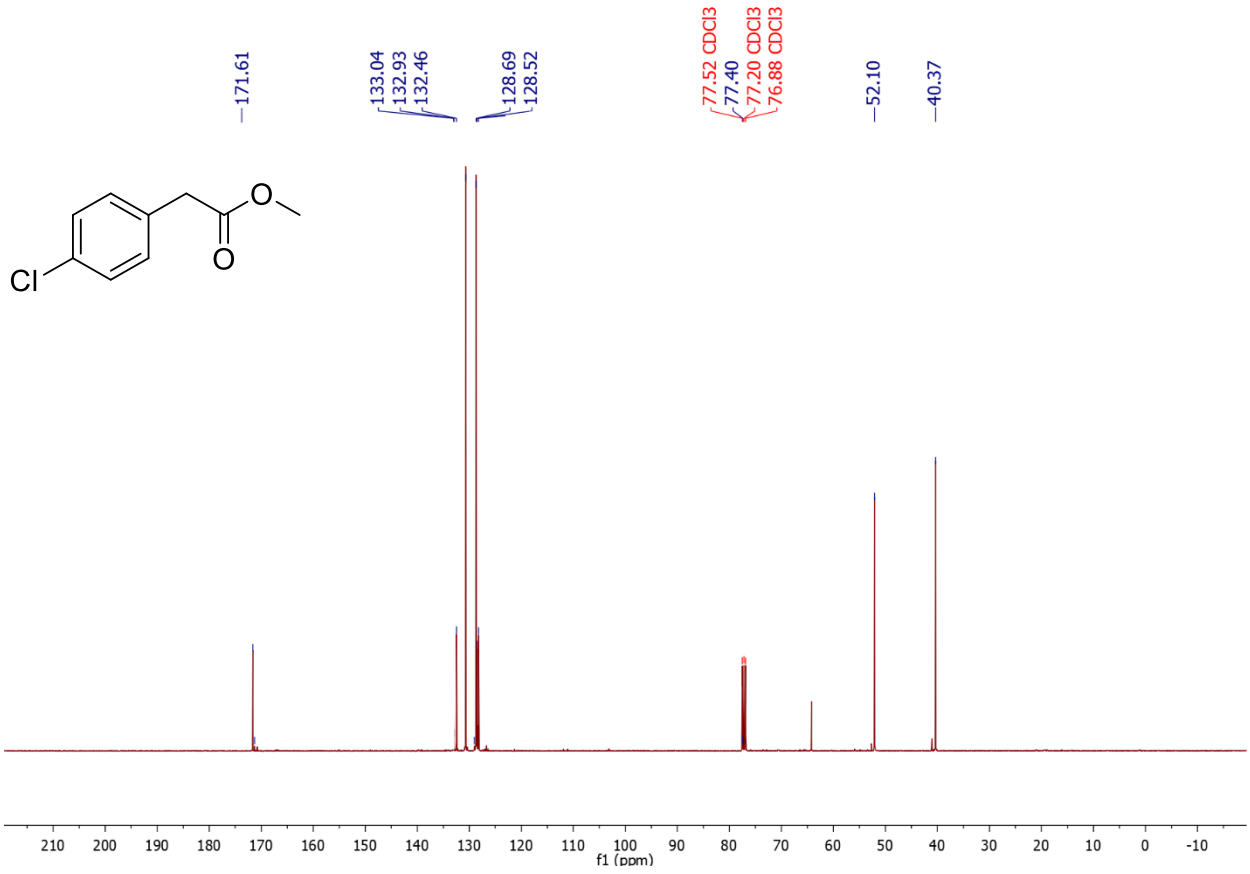
Methyl phenylacetate (Table 2, Entry 1)



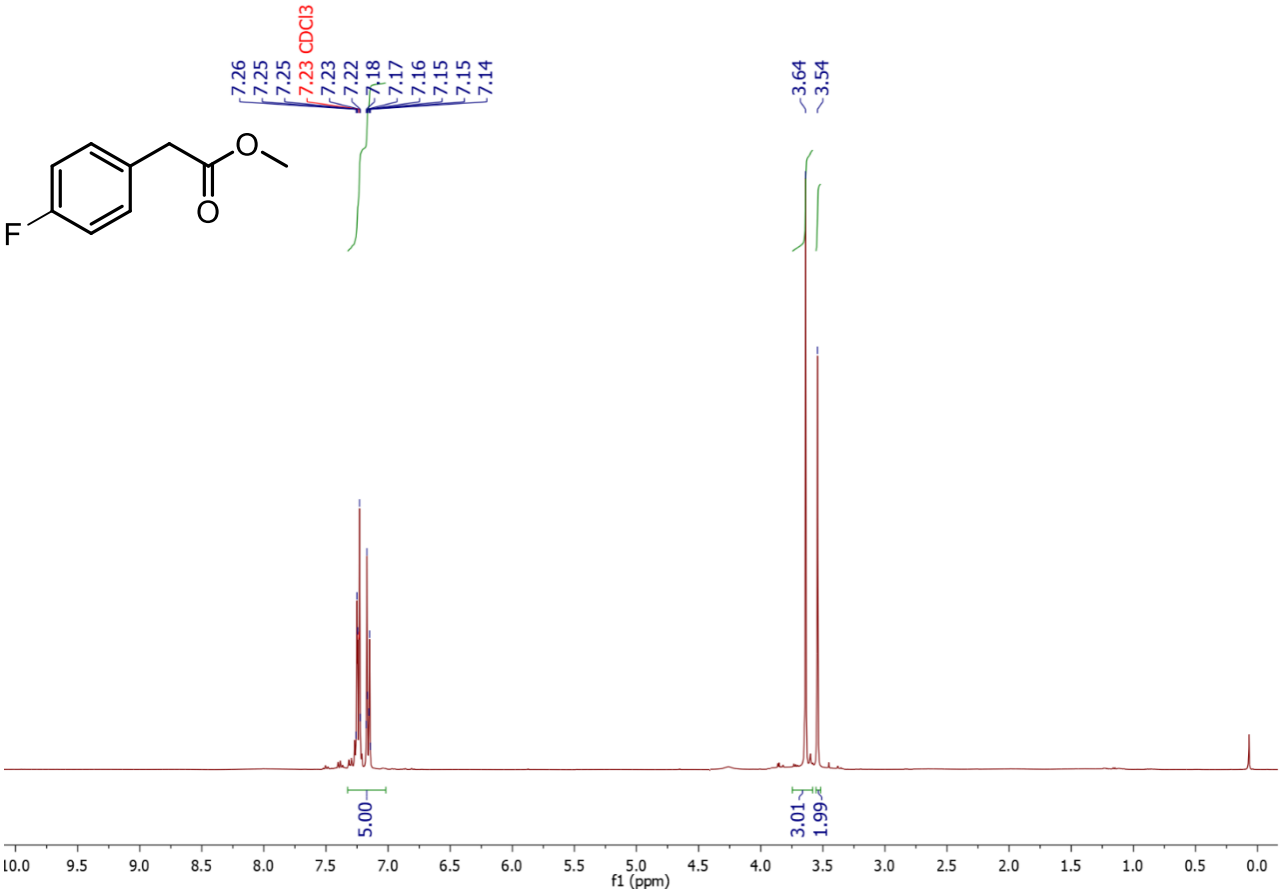


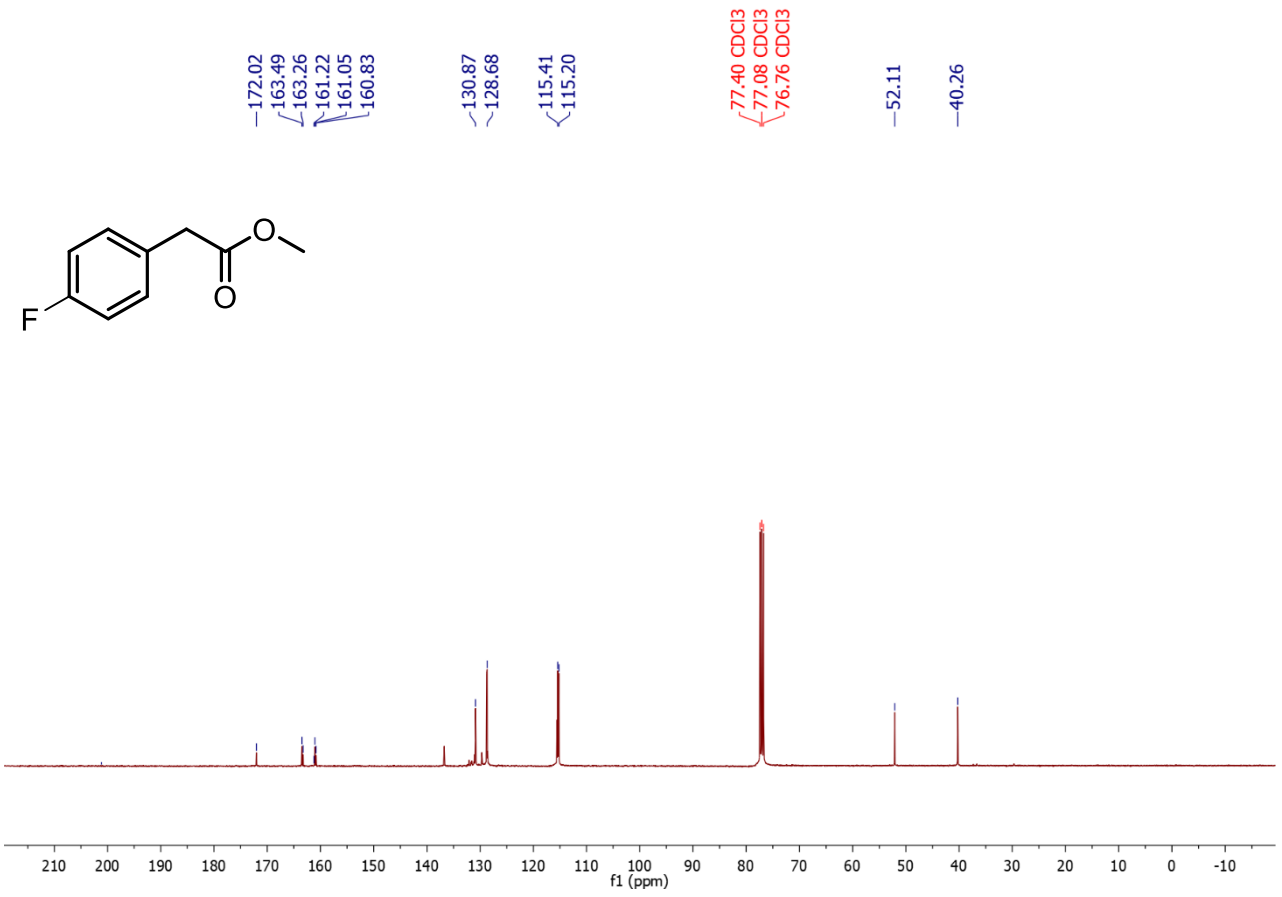
Methyl (4-chlorophenyl)acetate (Table 2, Entry 2)



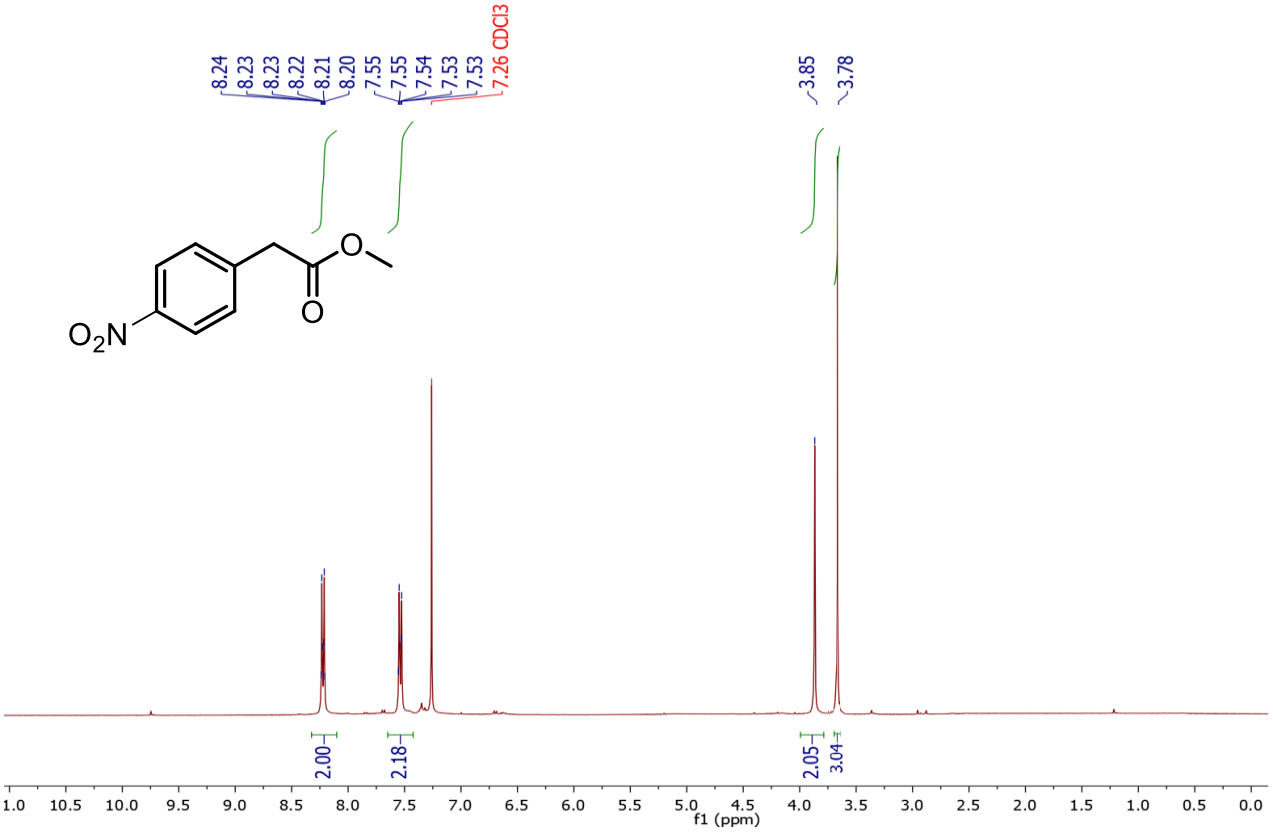


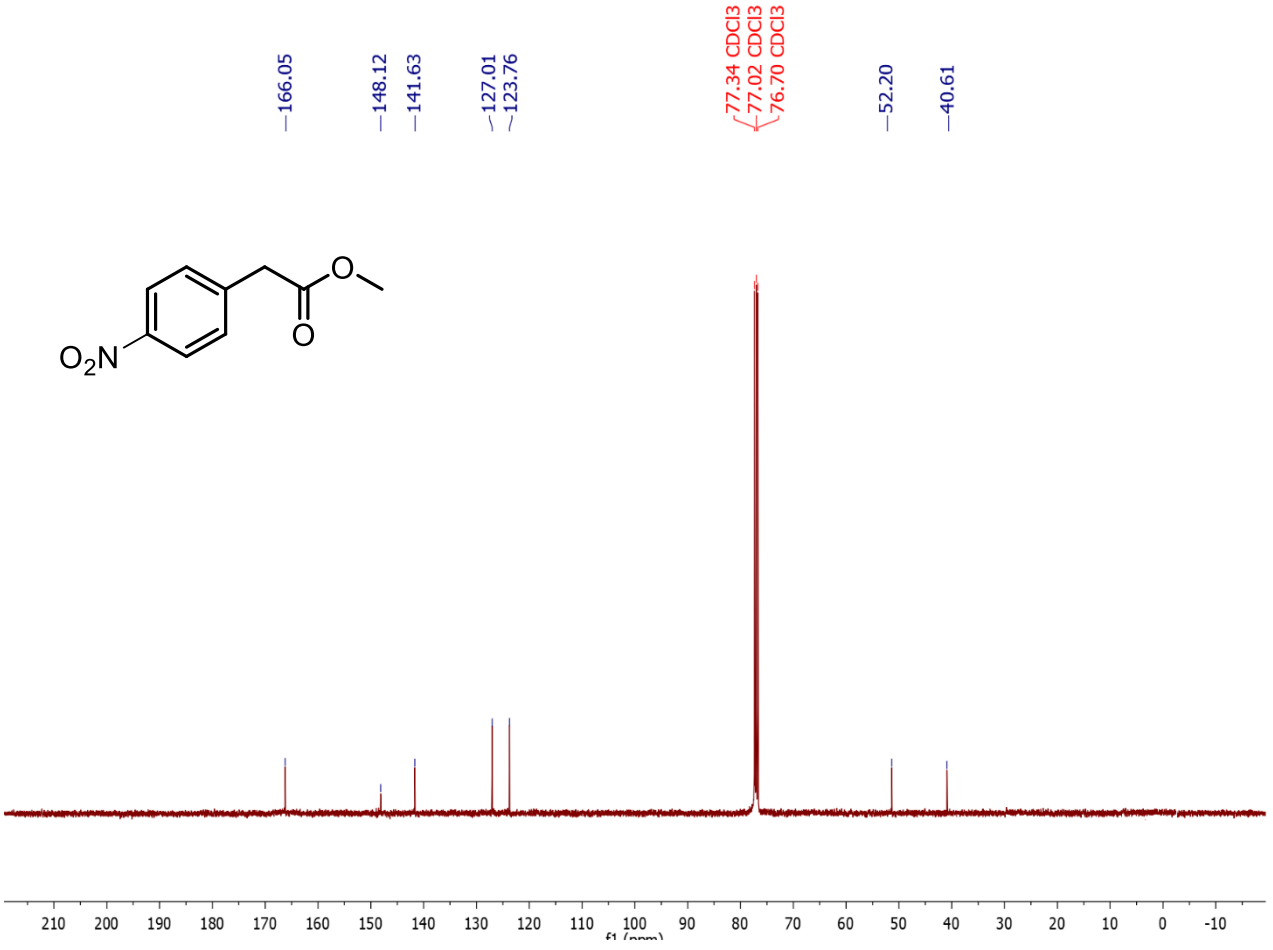
Methyl (4-fluorophenyl)acetate (Table 2, Entry 3)



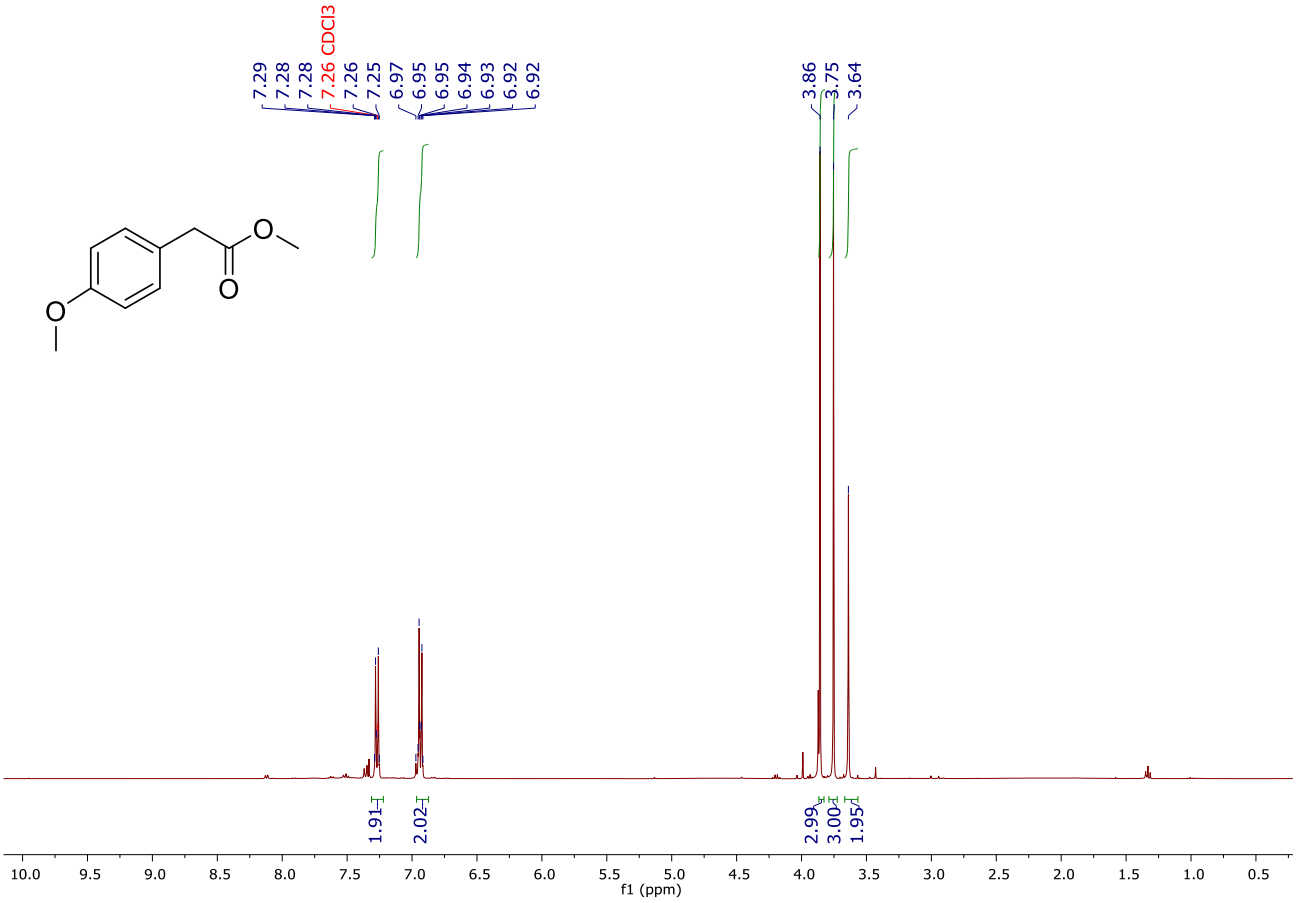


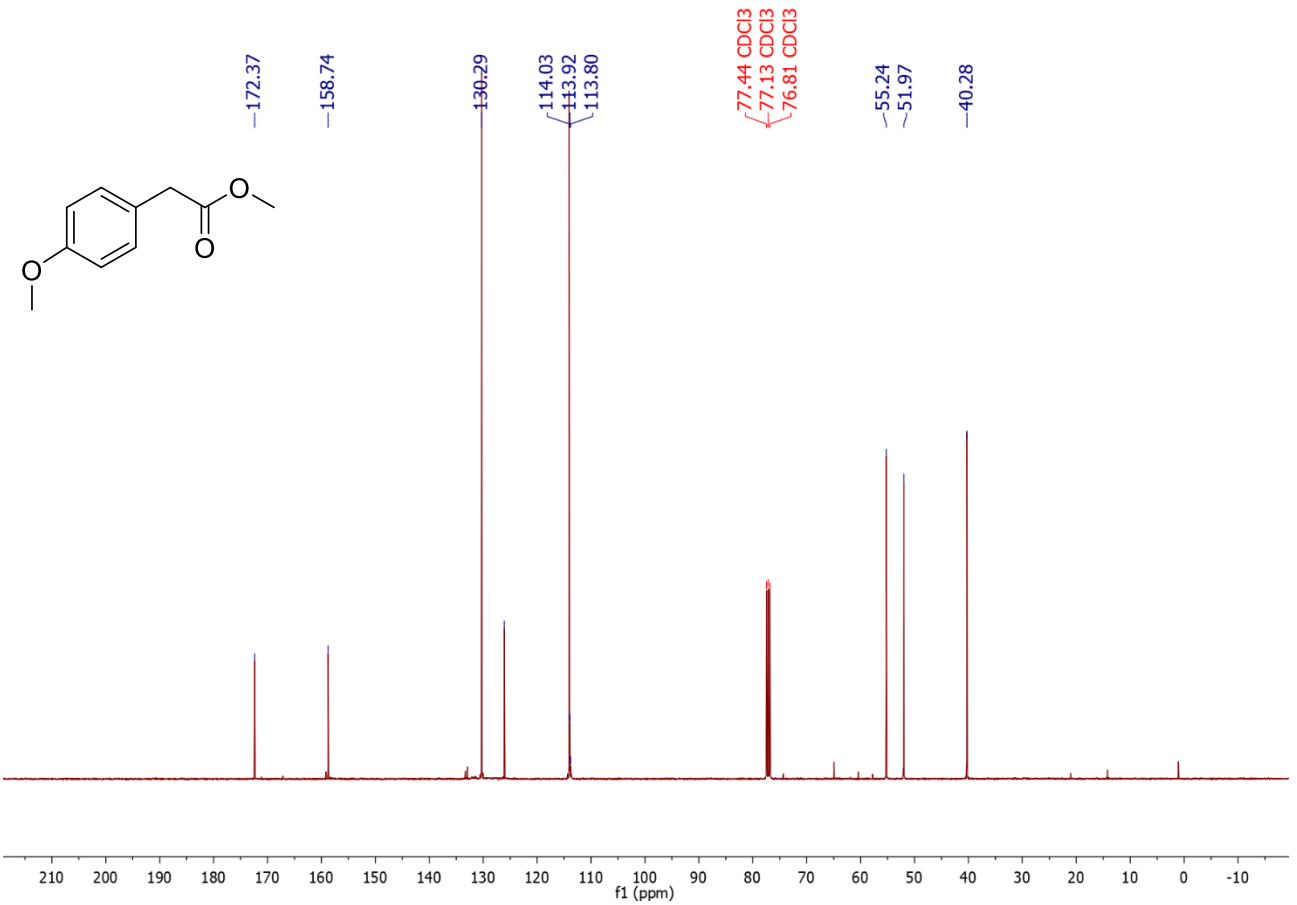
Methyl (4-nitrophenyl)acetate (Table 2, Entry 4)



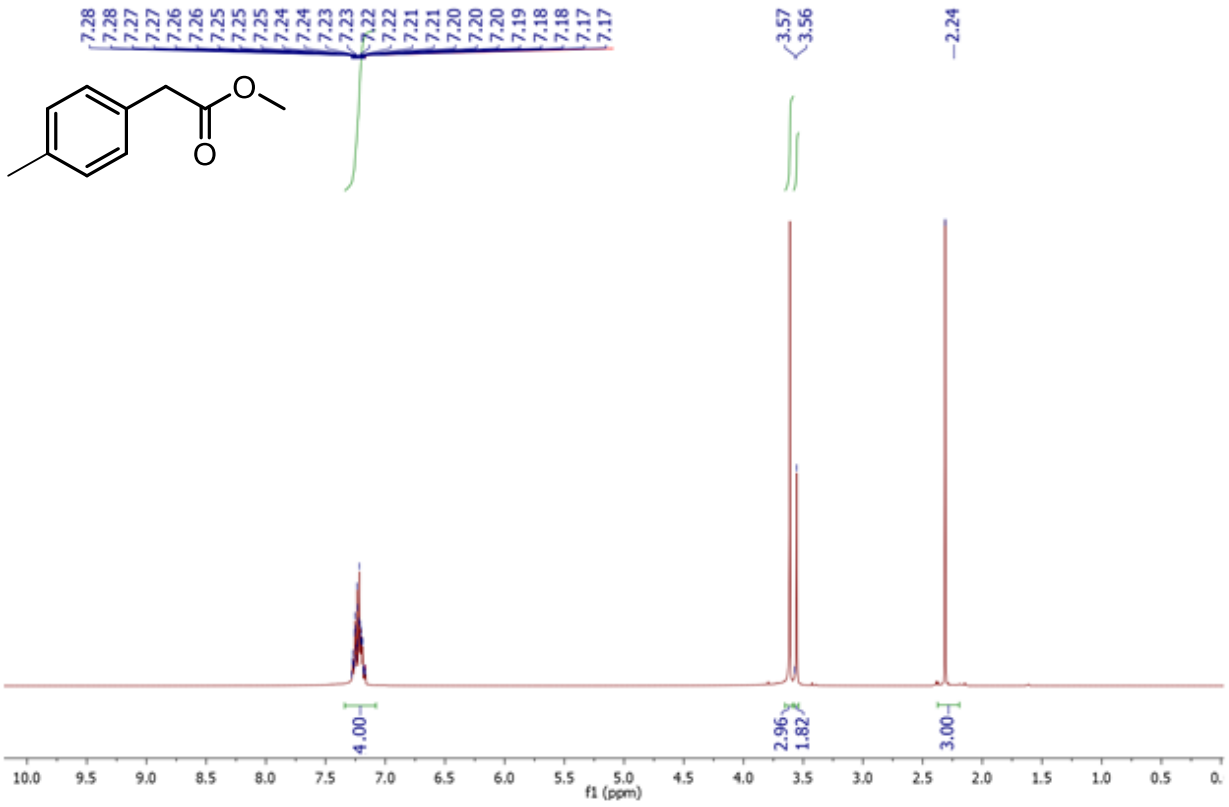


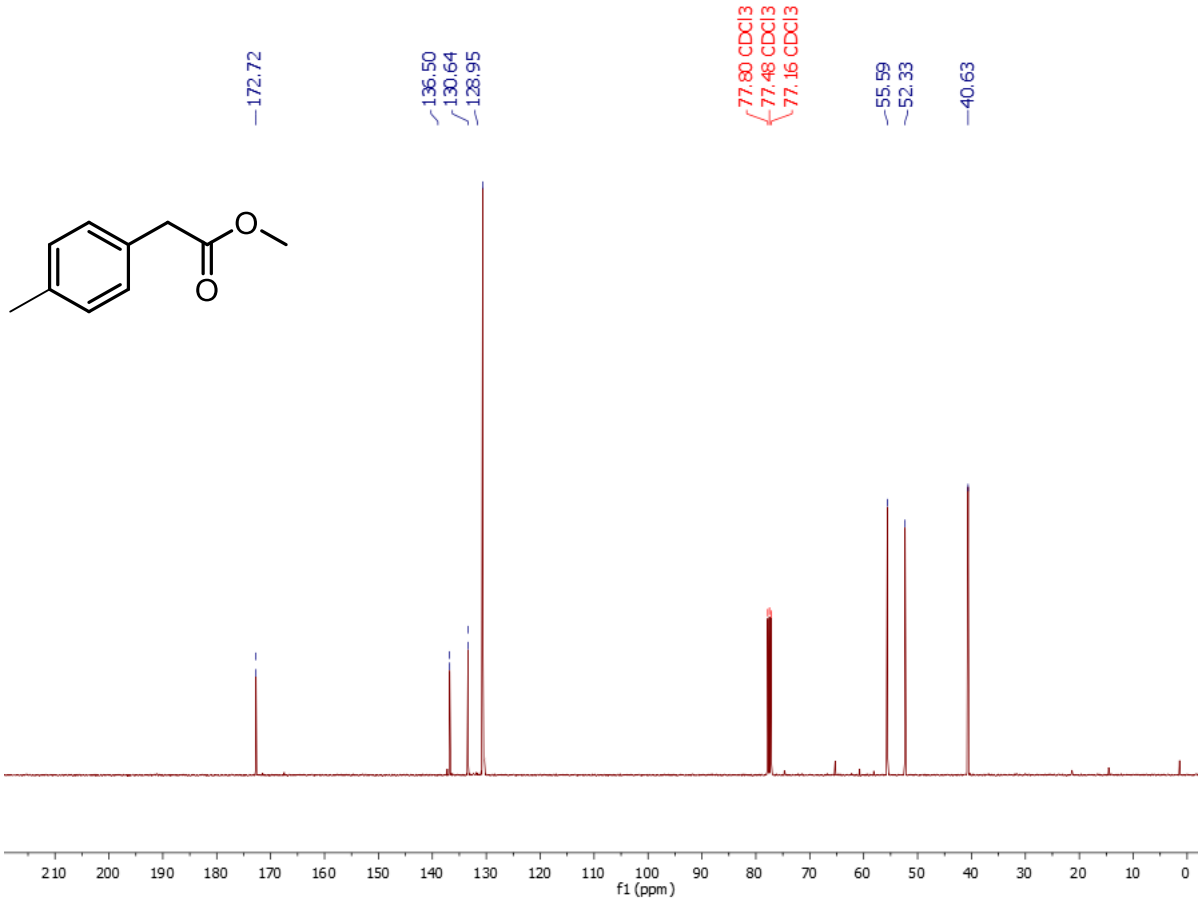
Methyl (4-methoxyphenyl)acetate (Table 2, Entry 5)



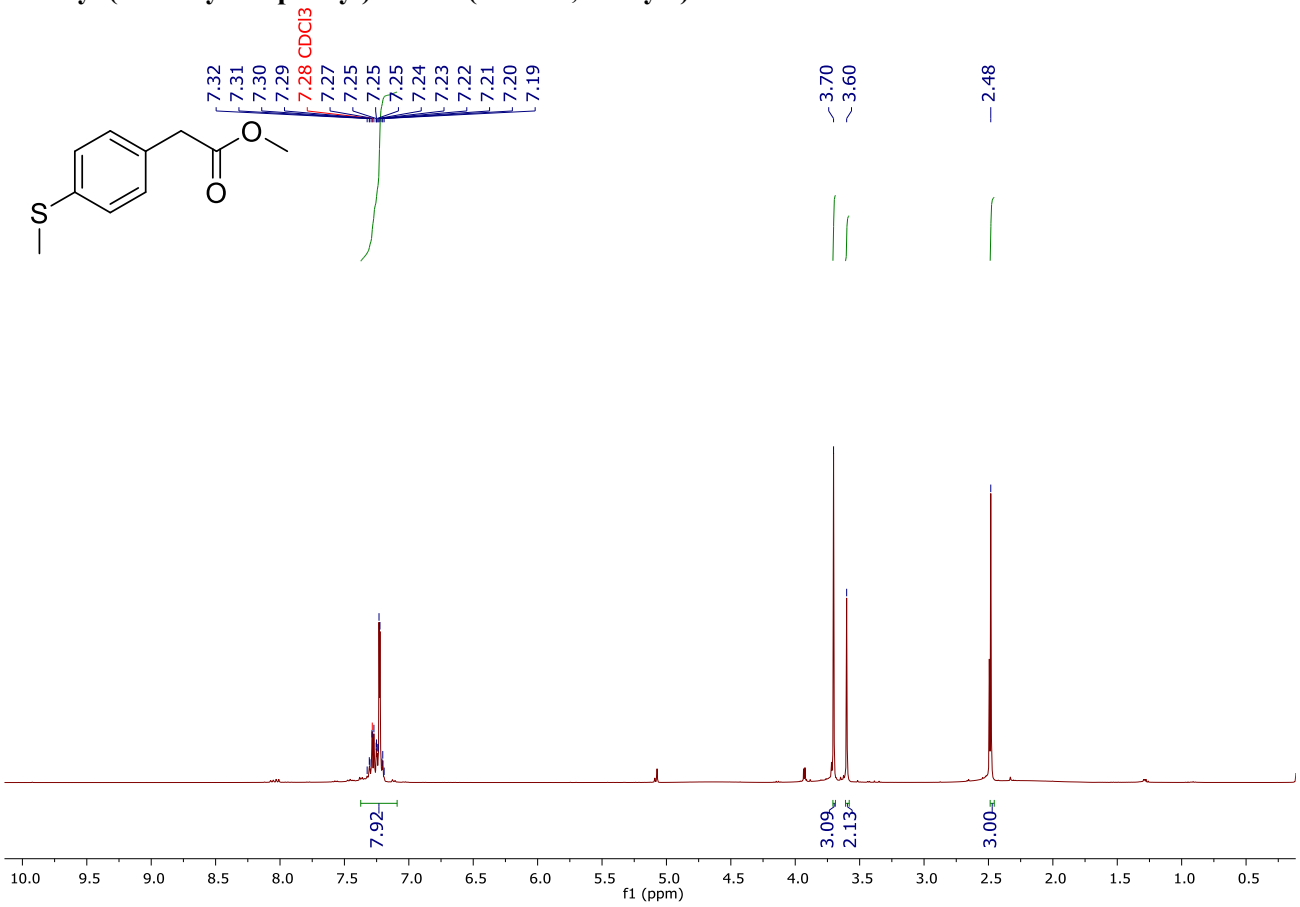


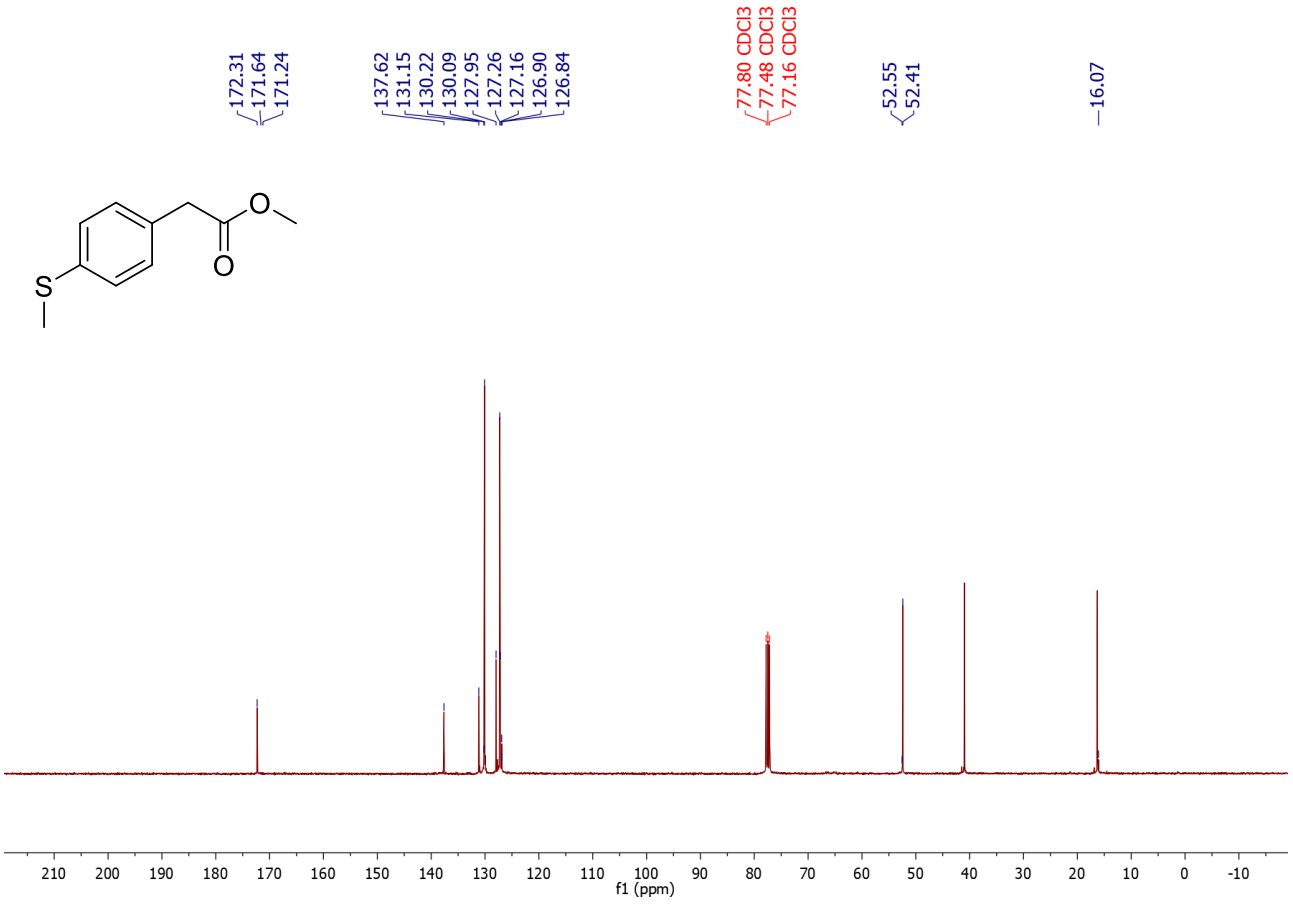
Methyl (4-tolyl)acetate (Table 2, Entry 6)



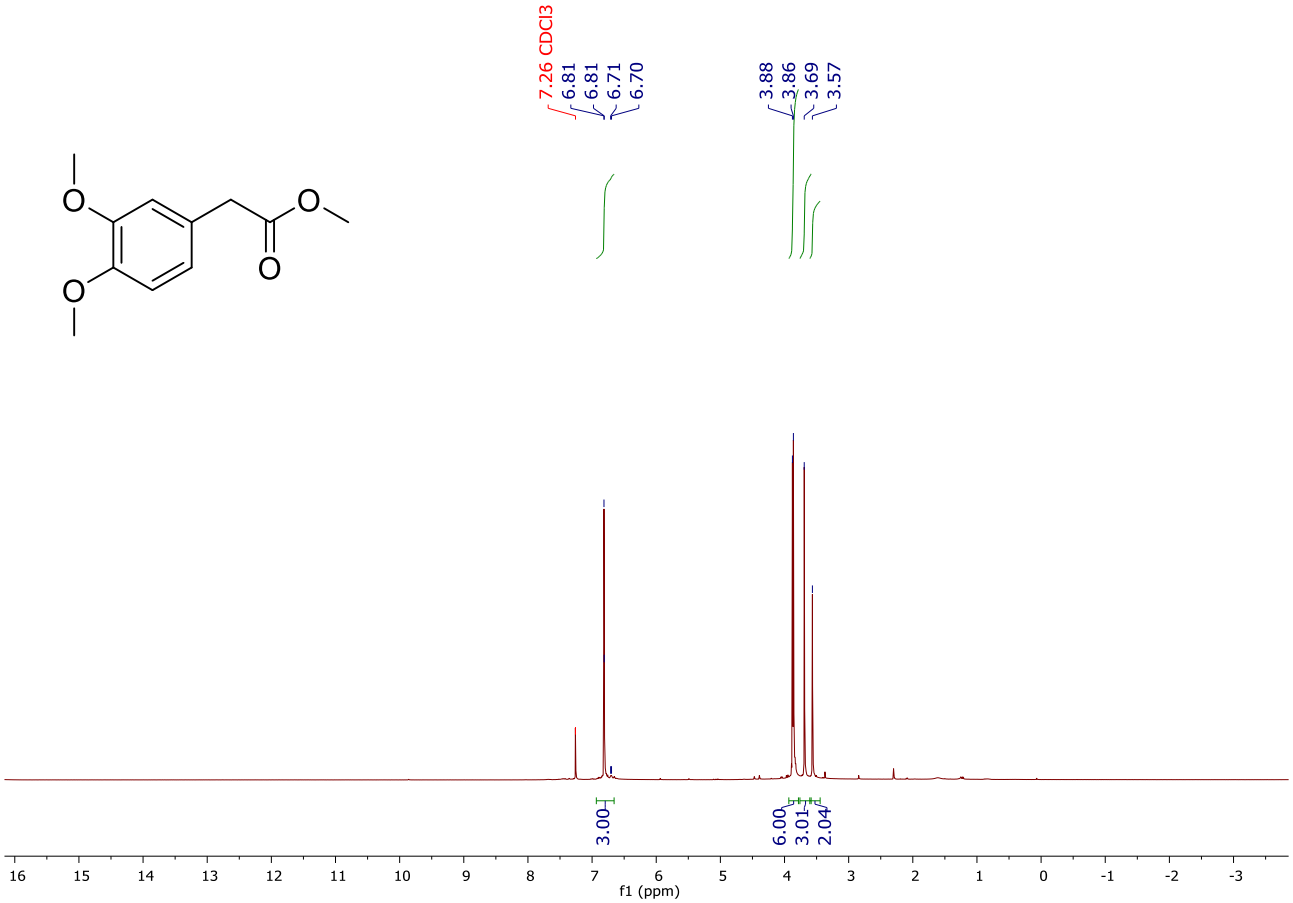


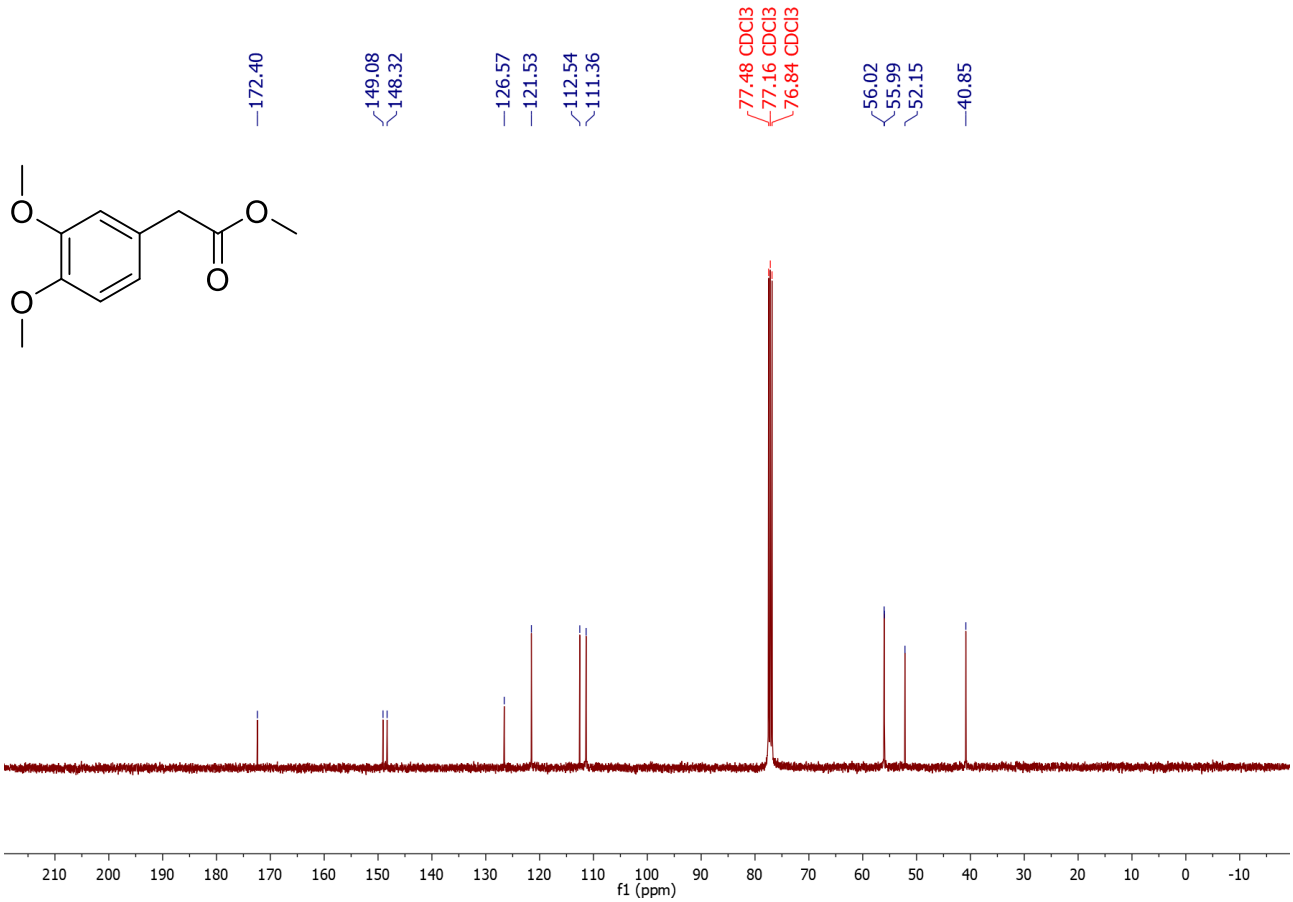
Methyl (4-methylthiophenyl)acetate (Table 2, Entry 7):



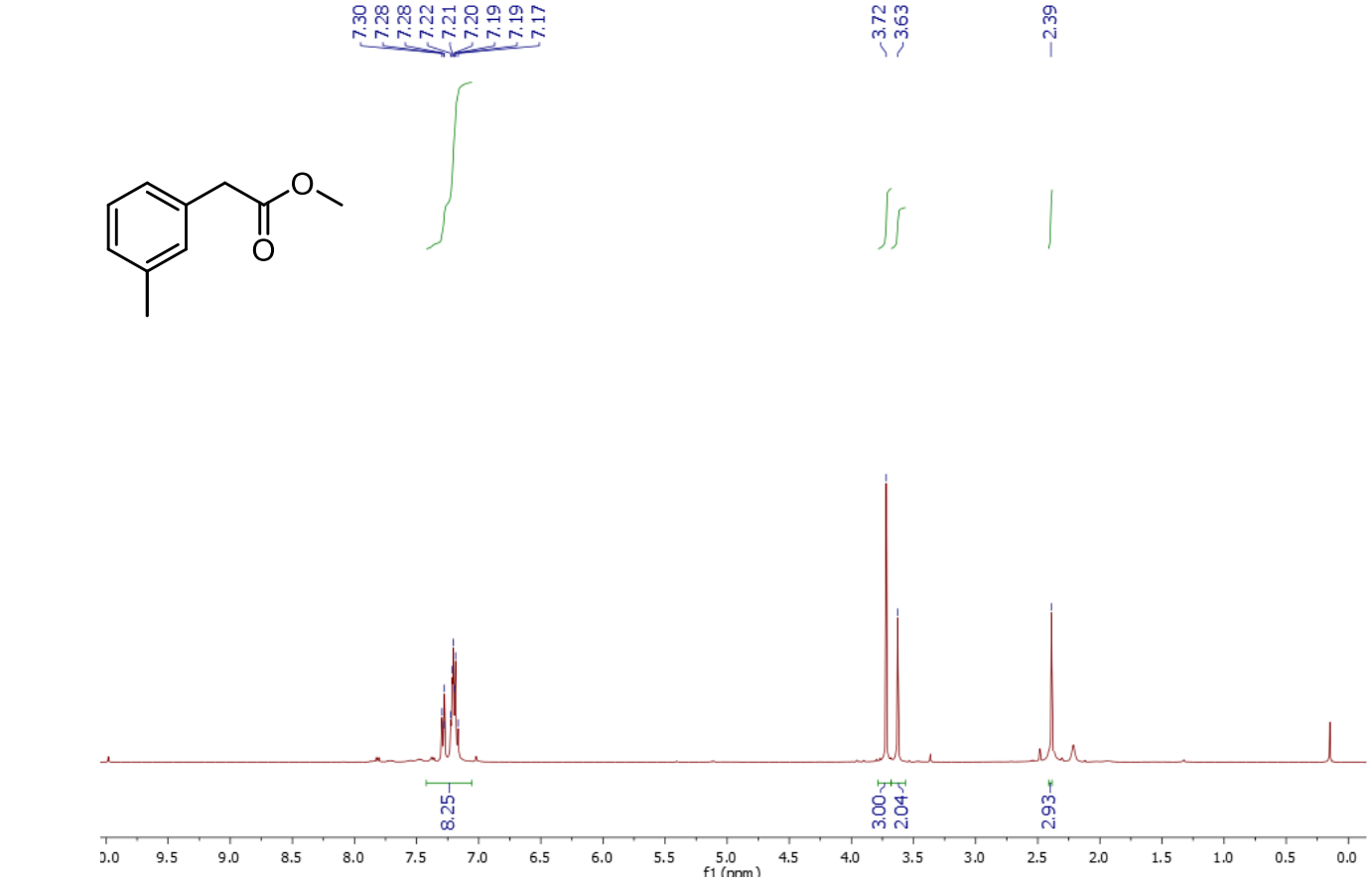


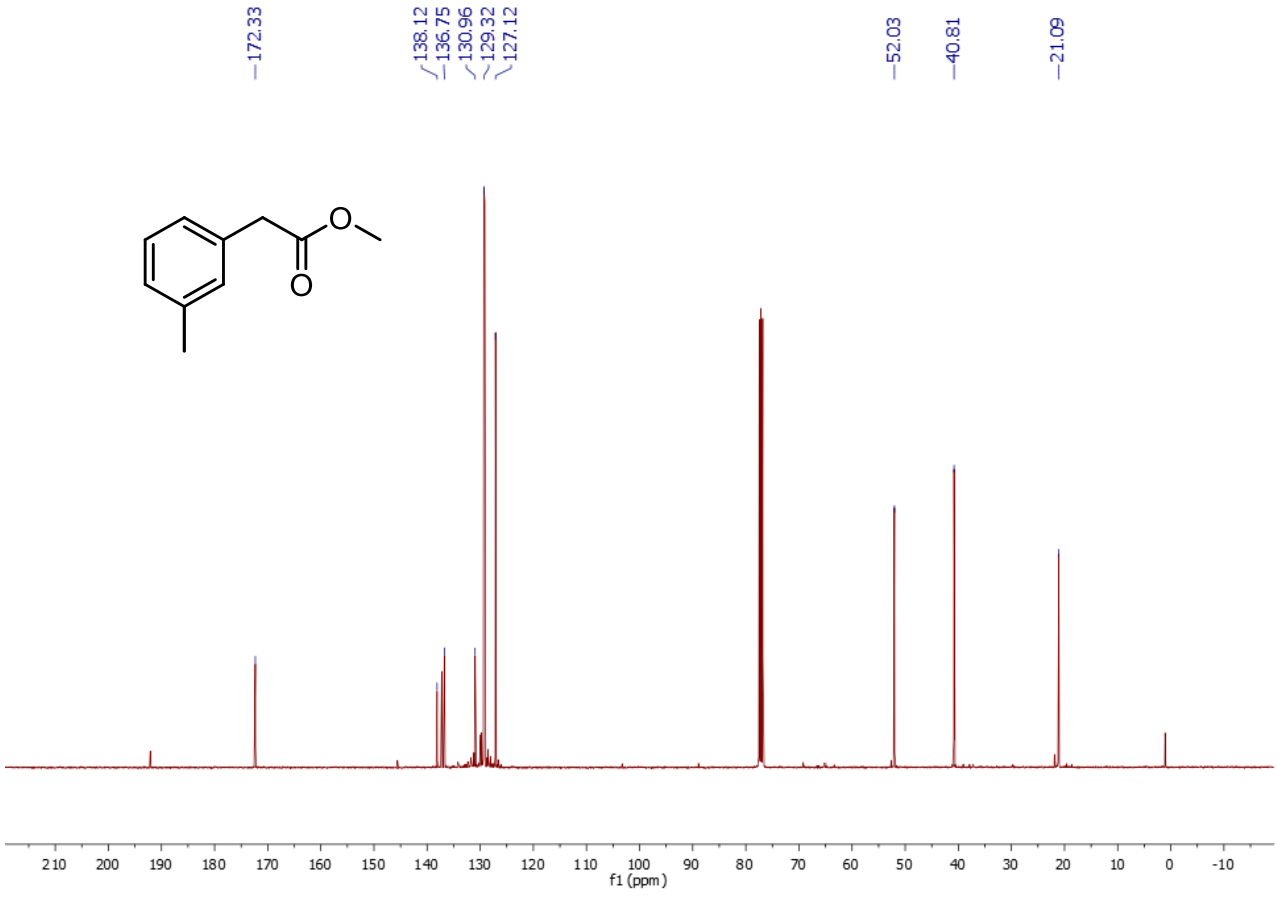
Methyl (3,4-dimethoxyphenyl)acetate (Table 2, Entry 8)



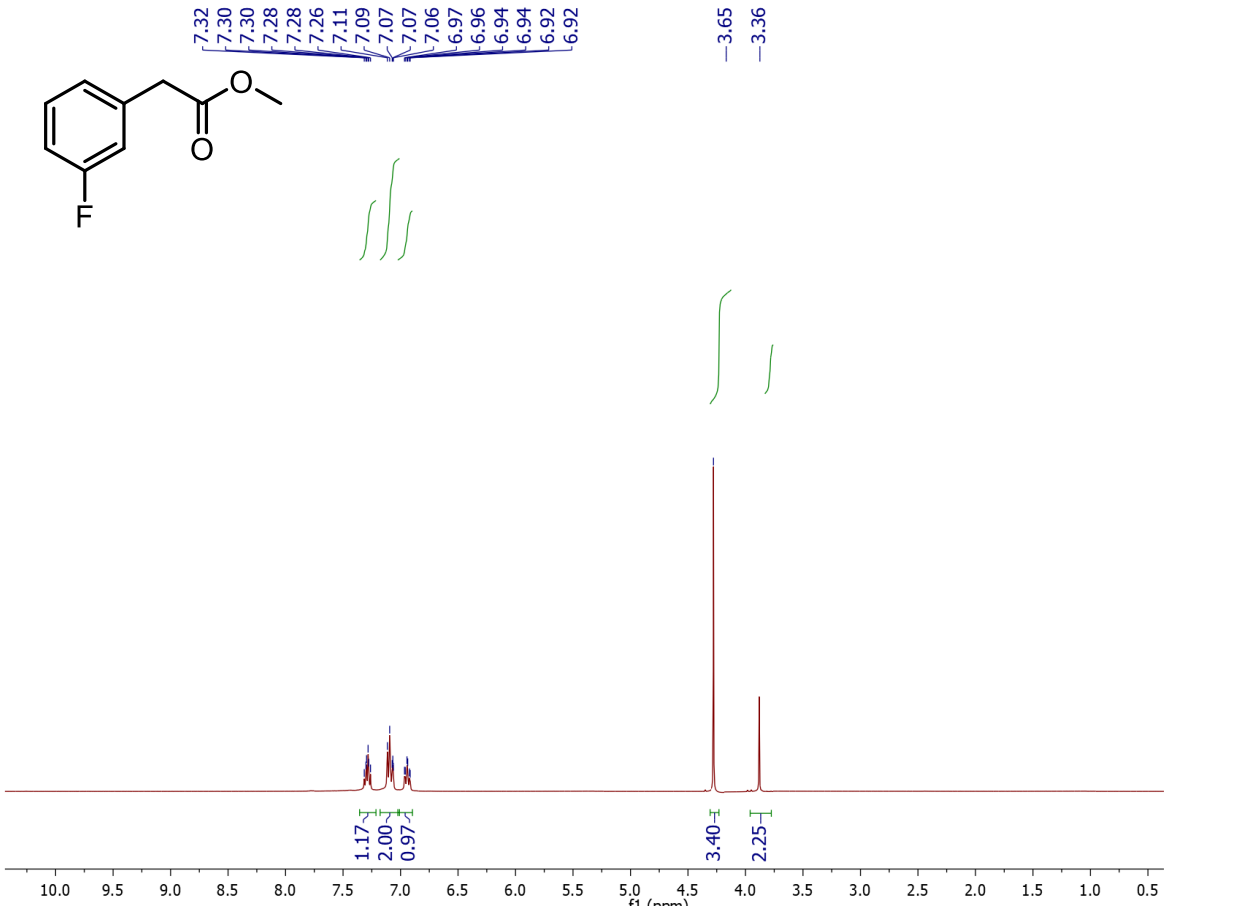


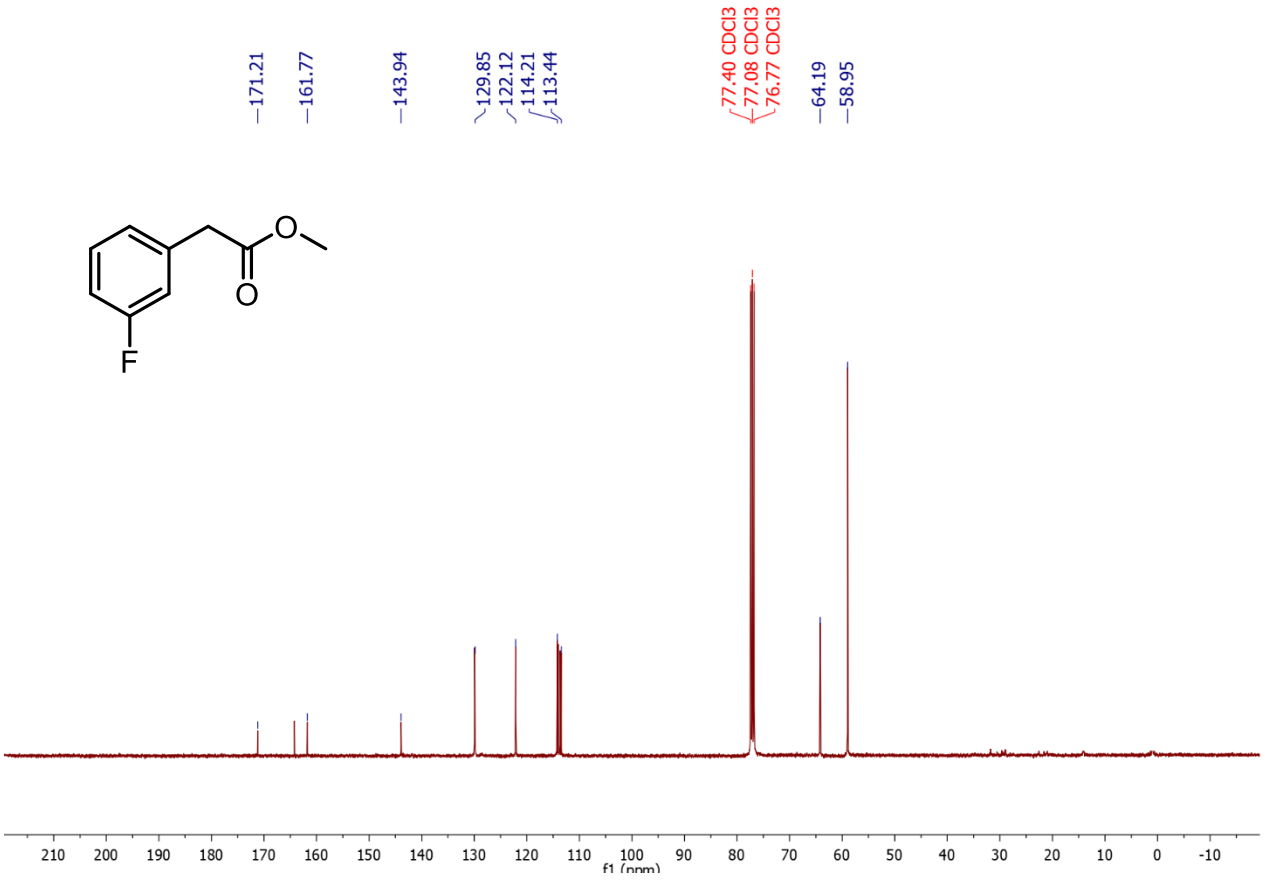
Methyl (3-tolyl)acetate (Table 2, Entry 9)



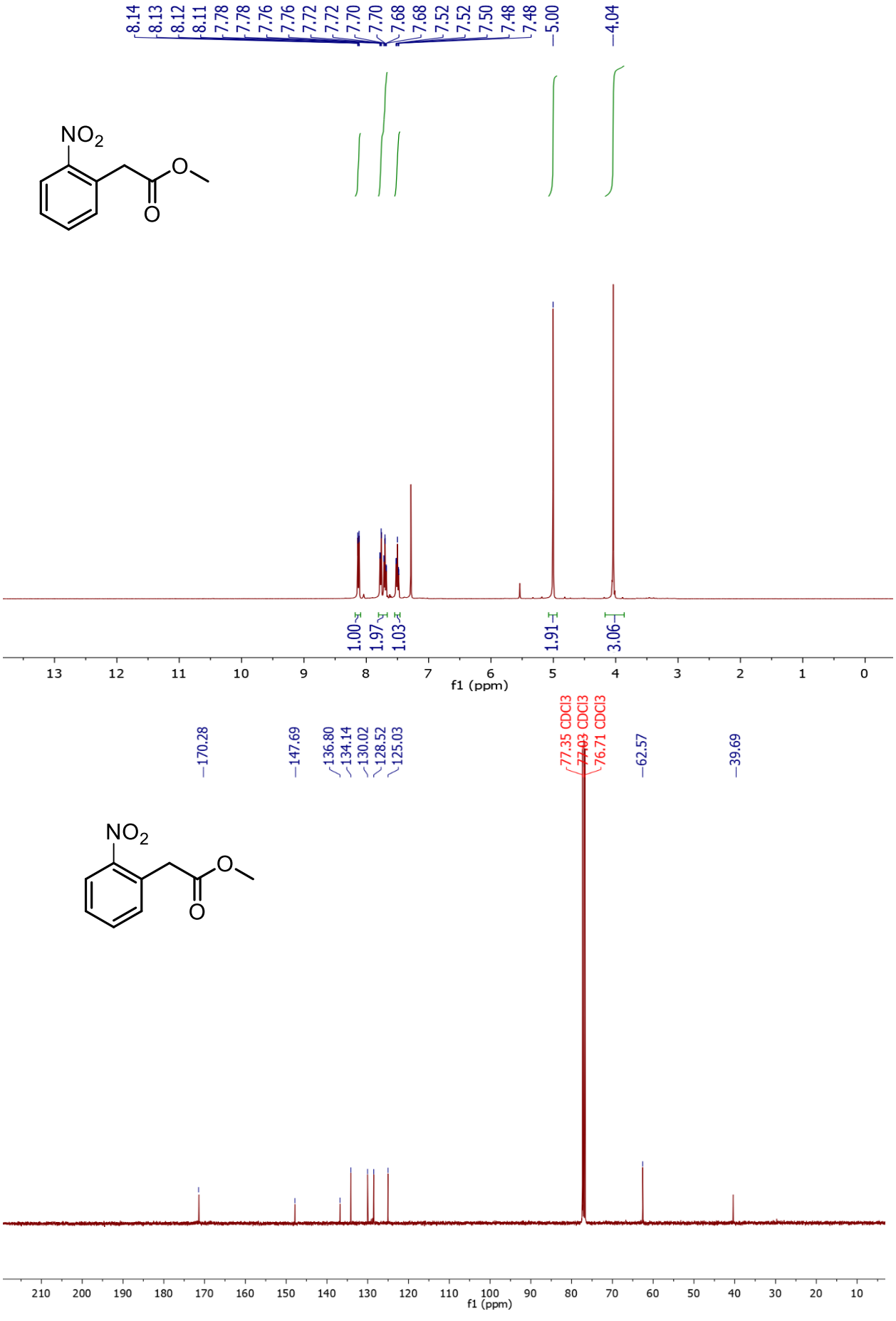


Methyl (3-fluorophenyl)acetate (Table 2, Entry 10):

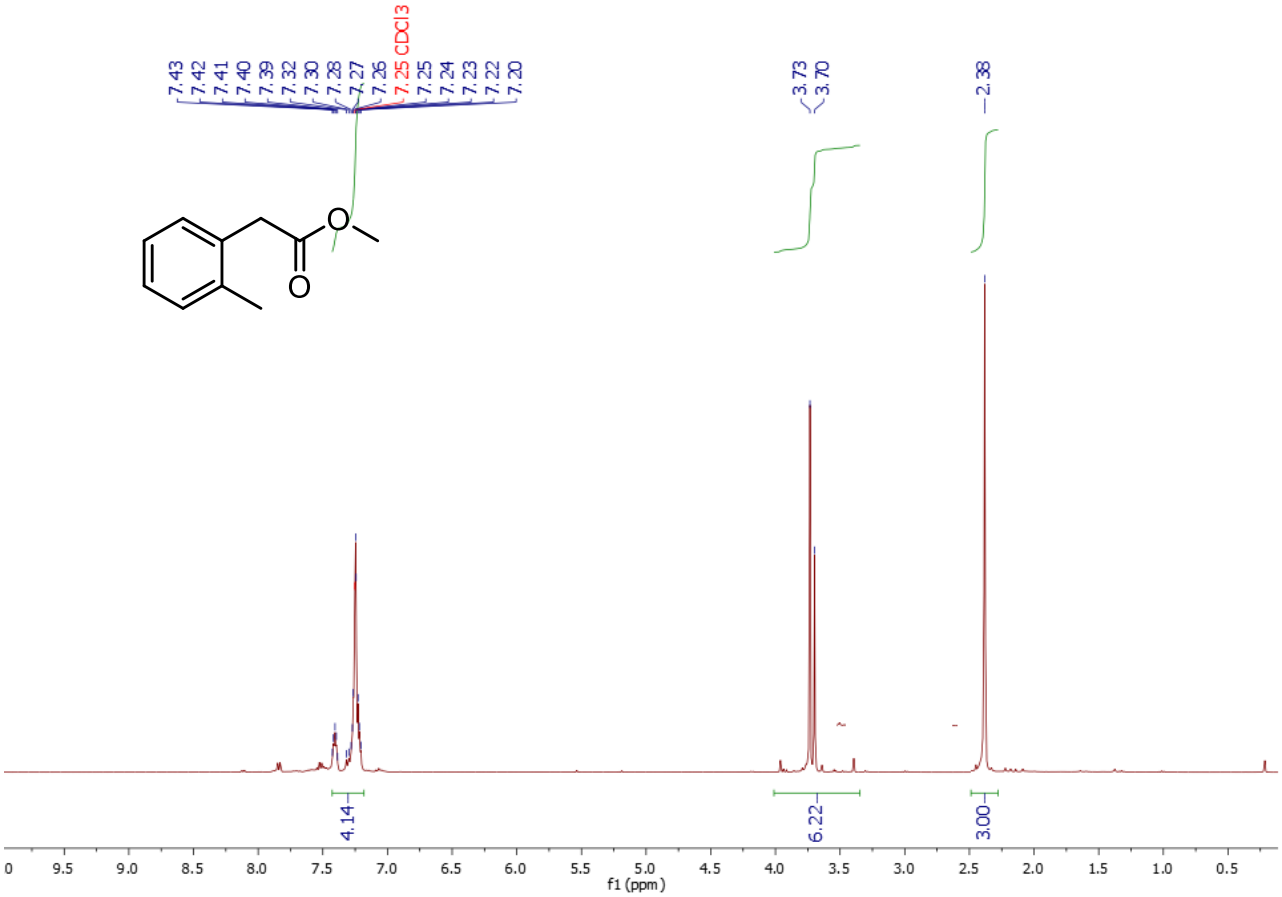


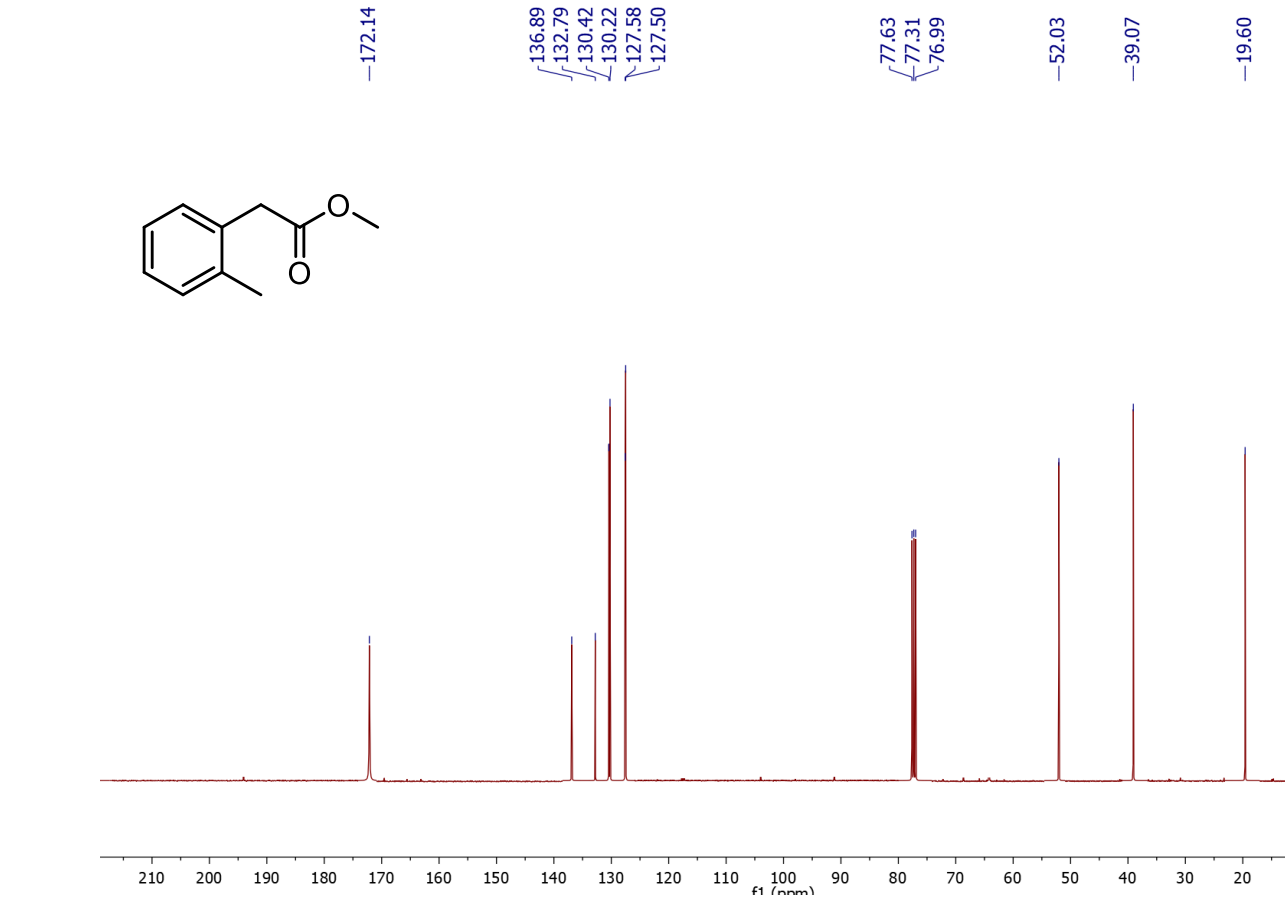


Methyl (2-nitrophenyl)acetate (Table 2, Entry 11)

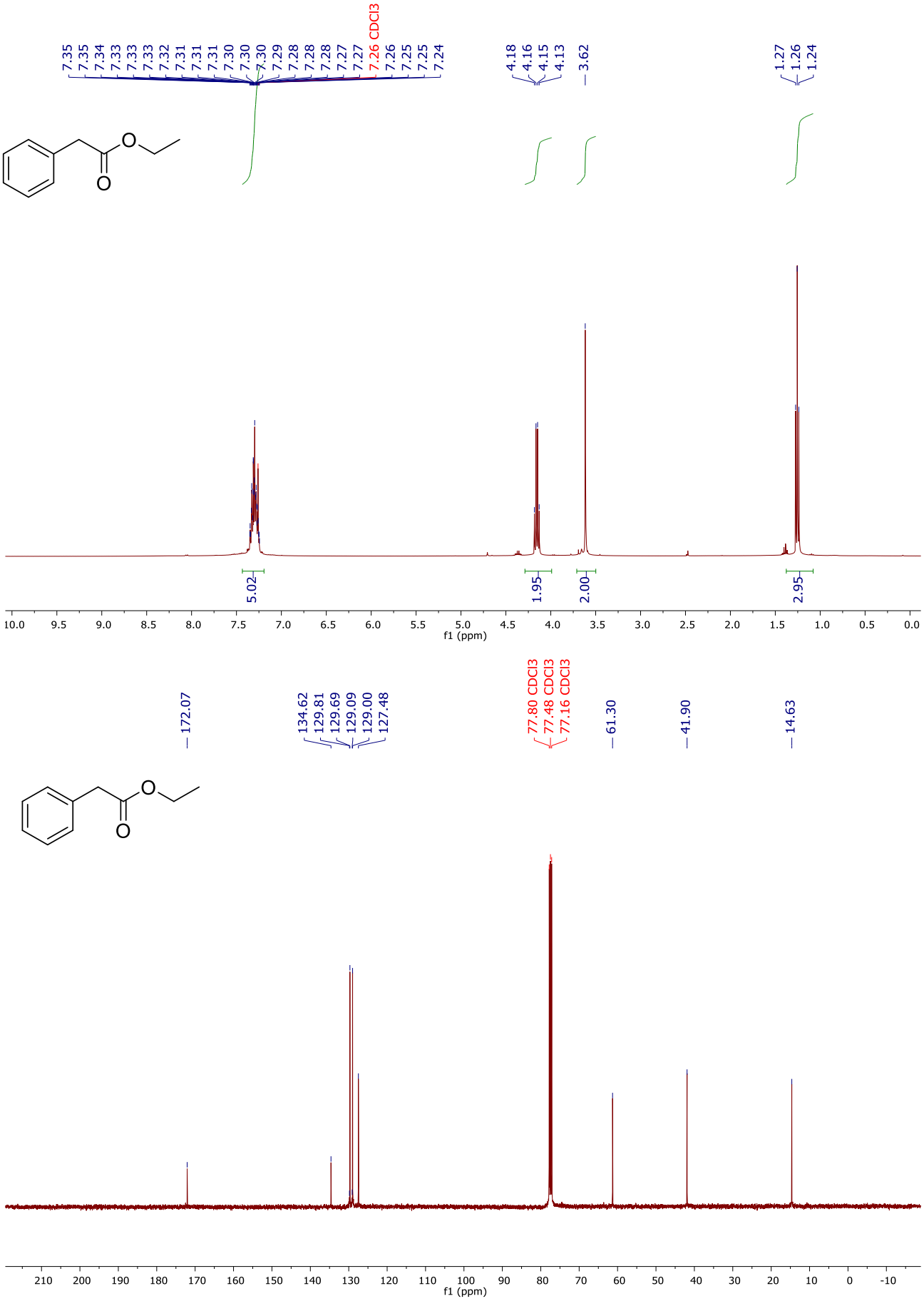


Methyl (2-tolyl)acetate (Table 2, Entry 12)

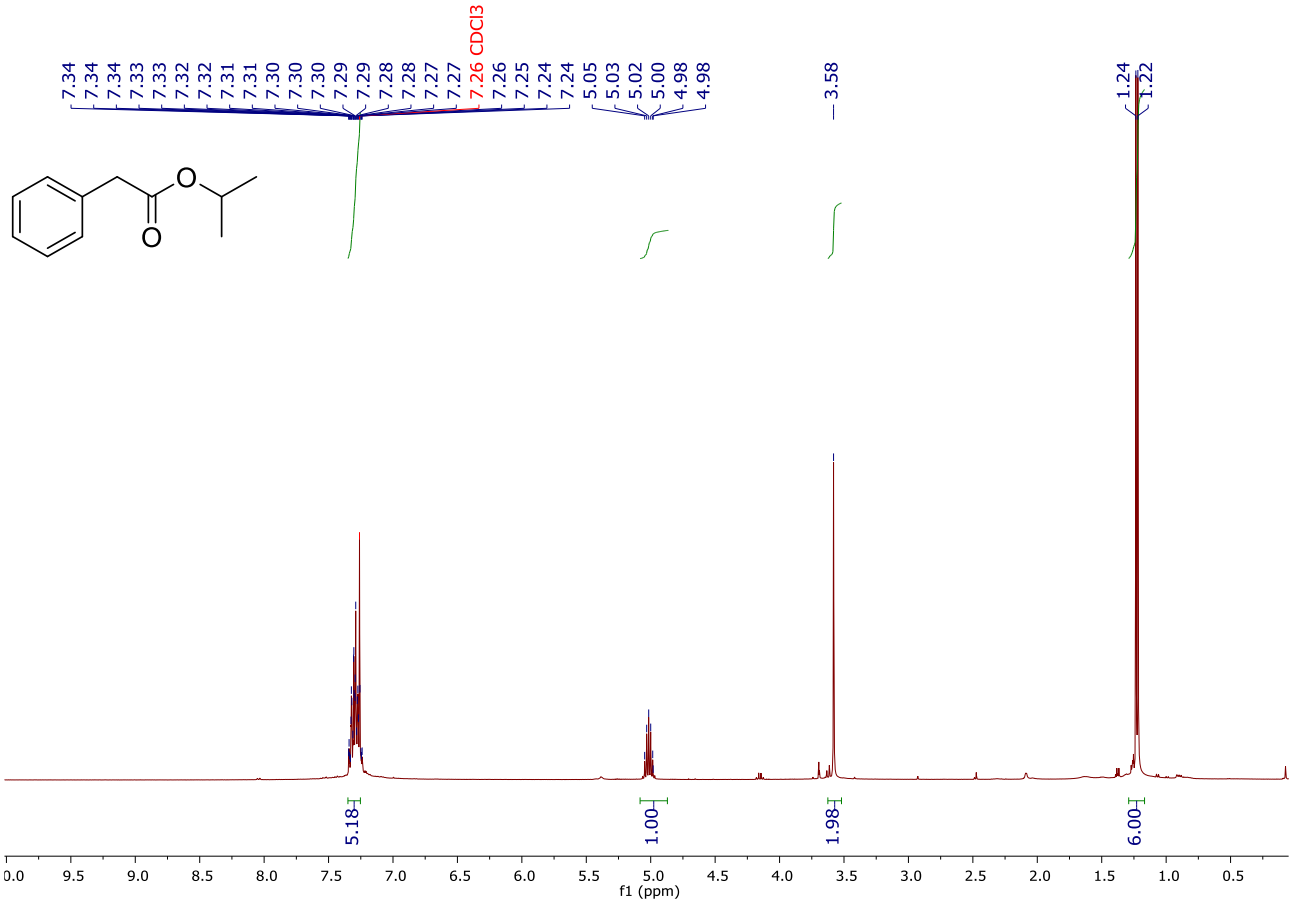


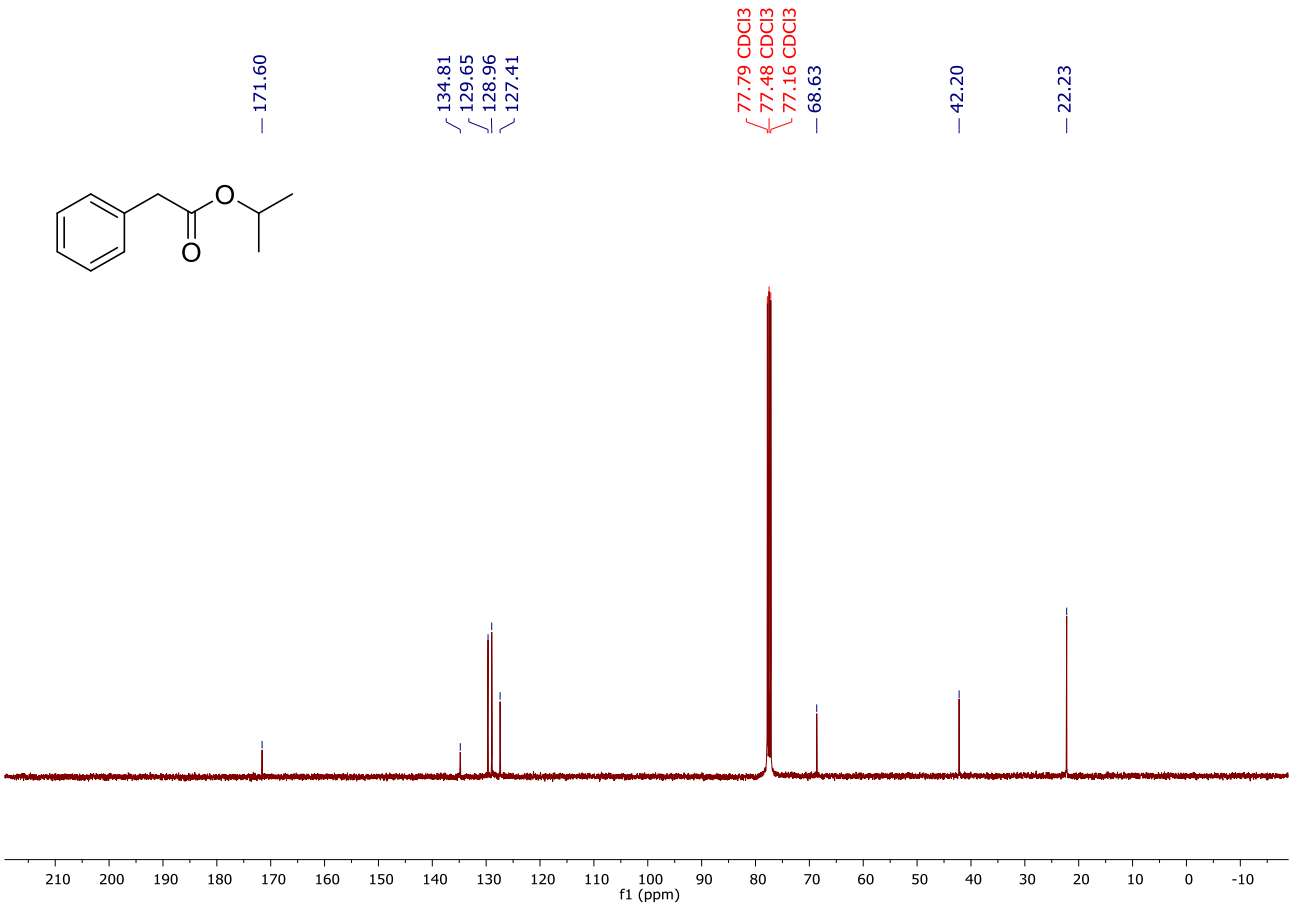


Ethyl phenylacetate (Table 3, Entry 2)

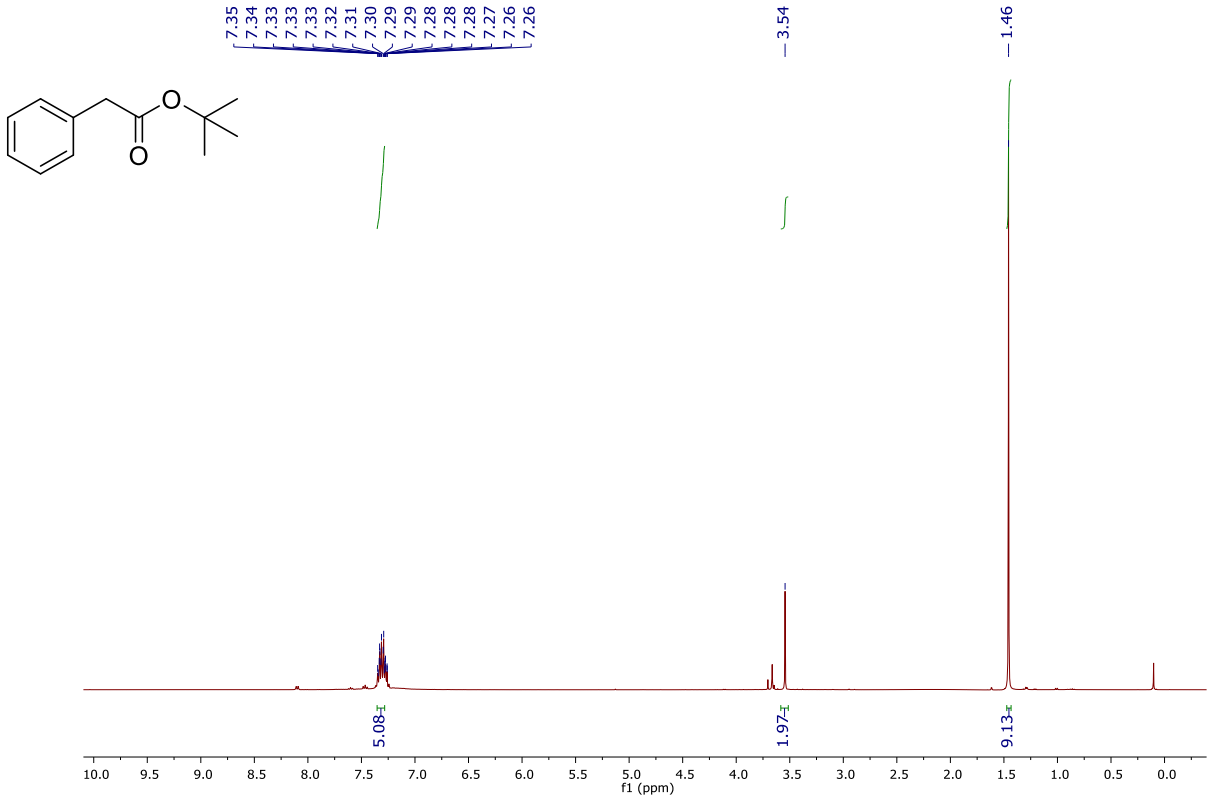


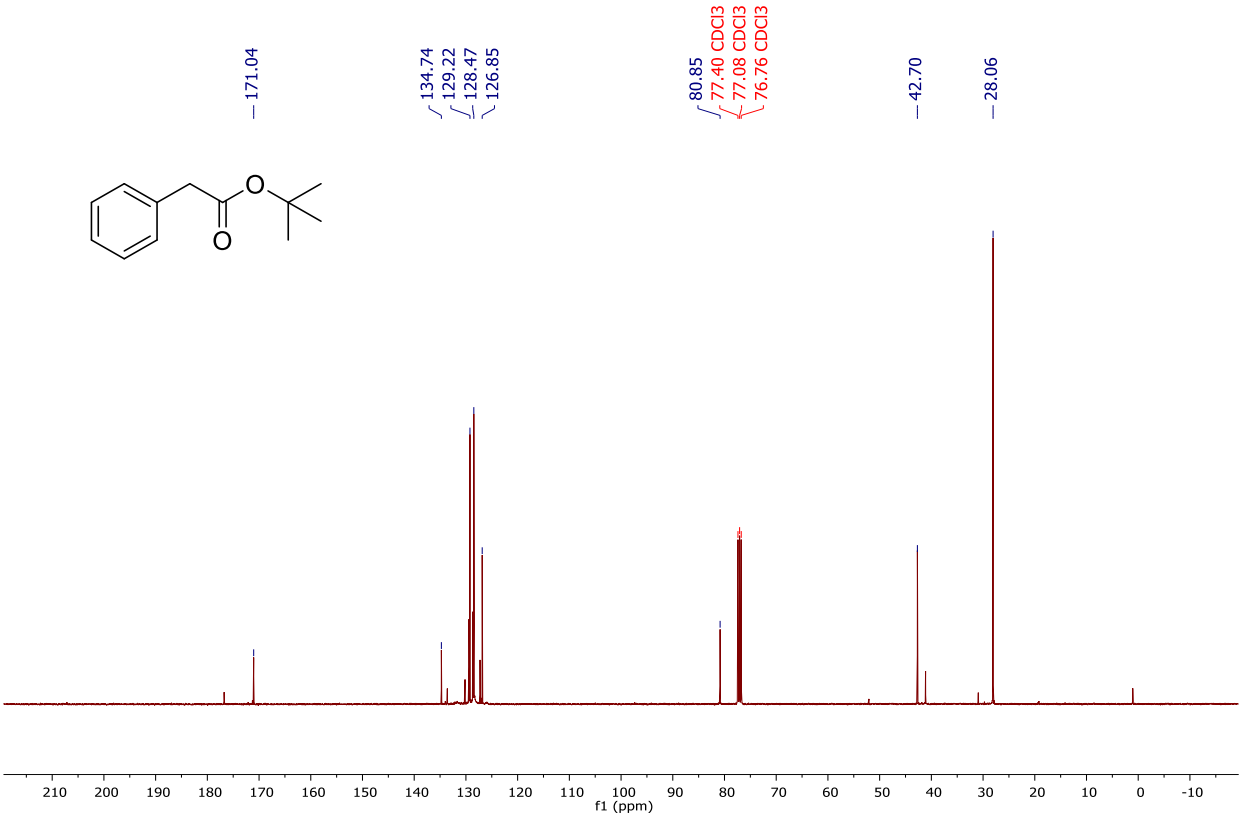
Isopropyl phenylacetate (Table 3, Entry 3)



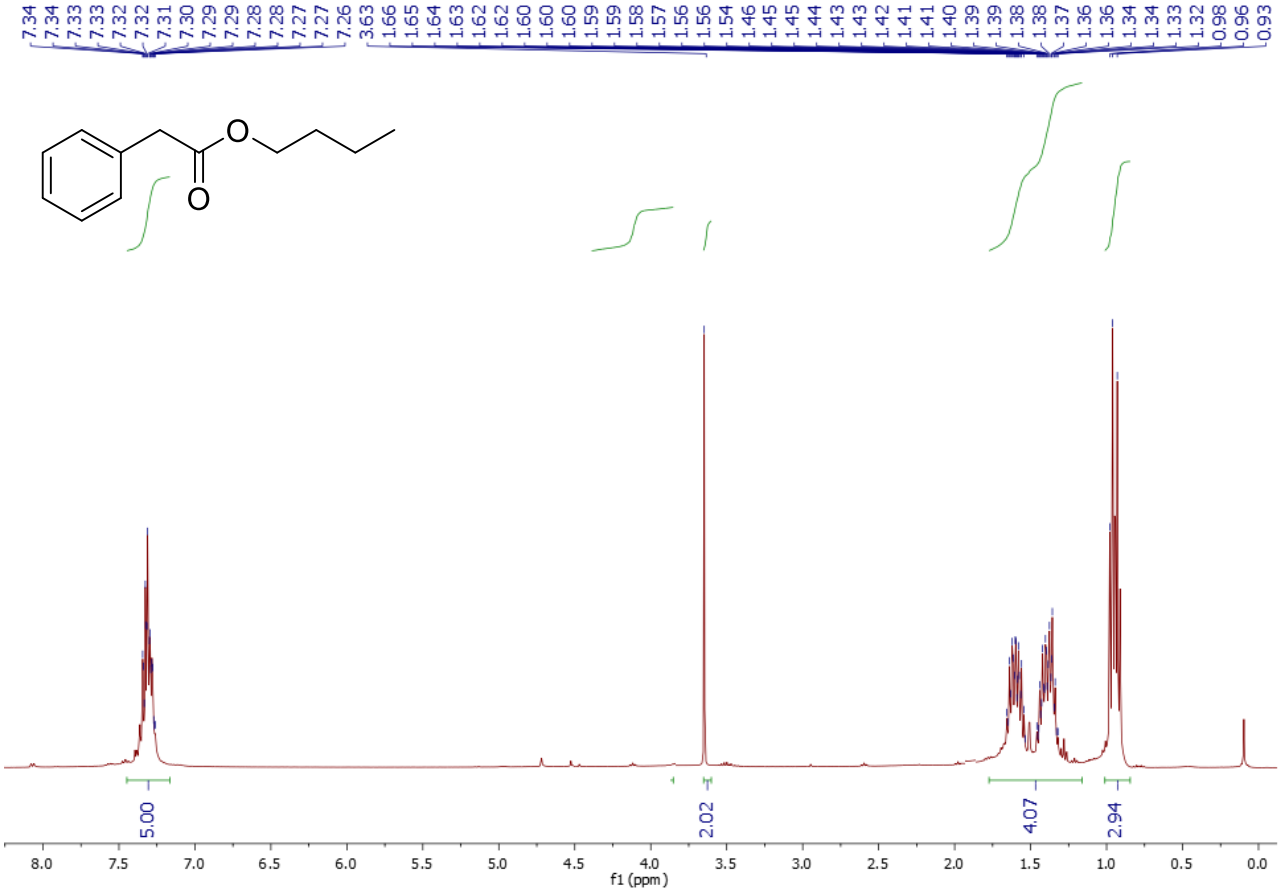


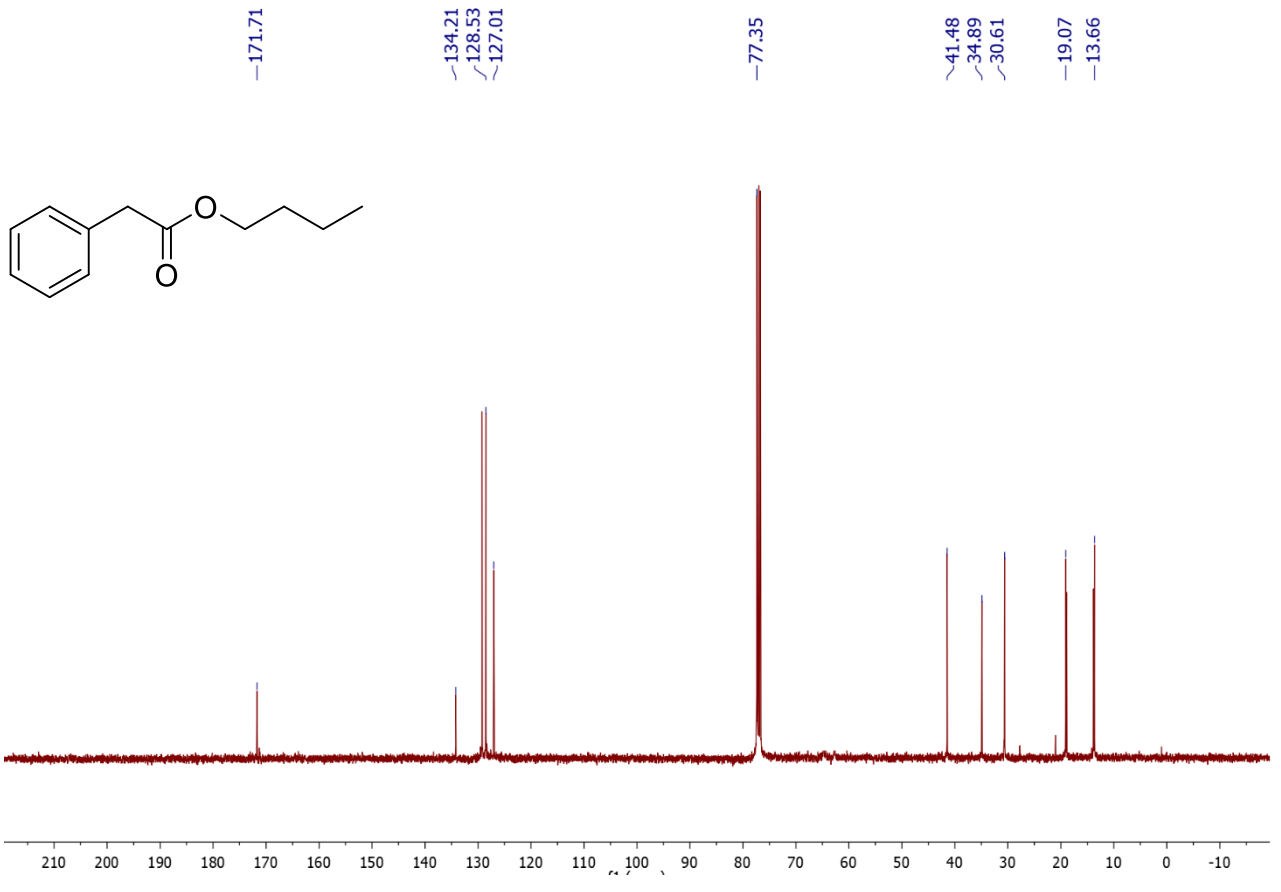
***tert*-butyl phenylacetate (Table 3, Entry 4):**



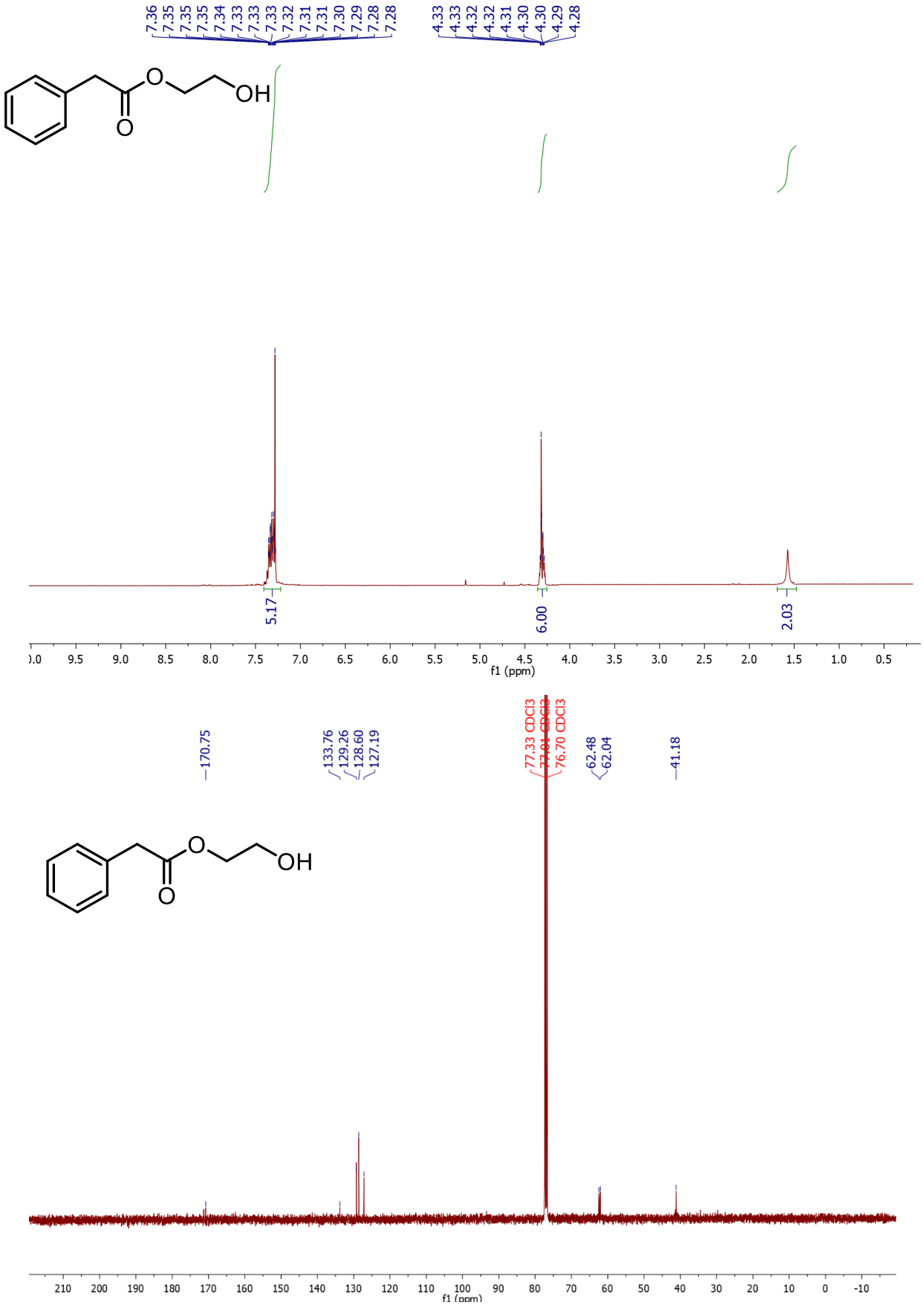


Butyl phenylacetate (Table 3, Entry 5):

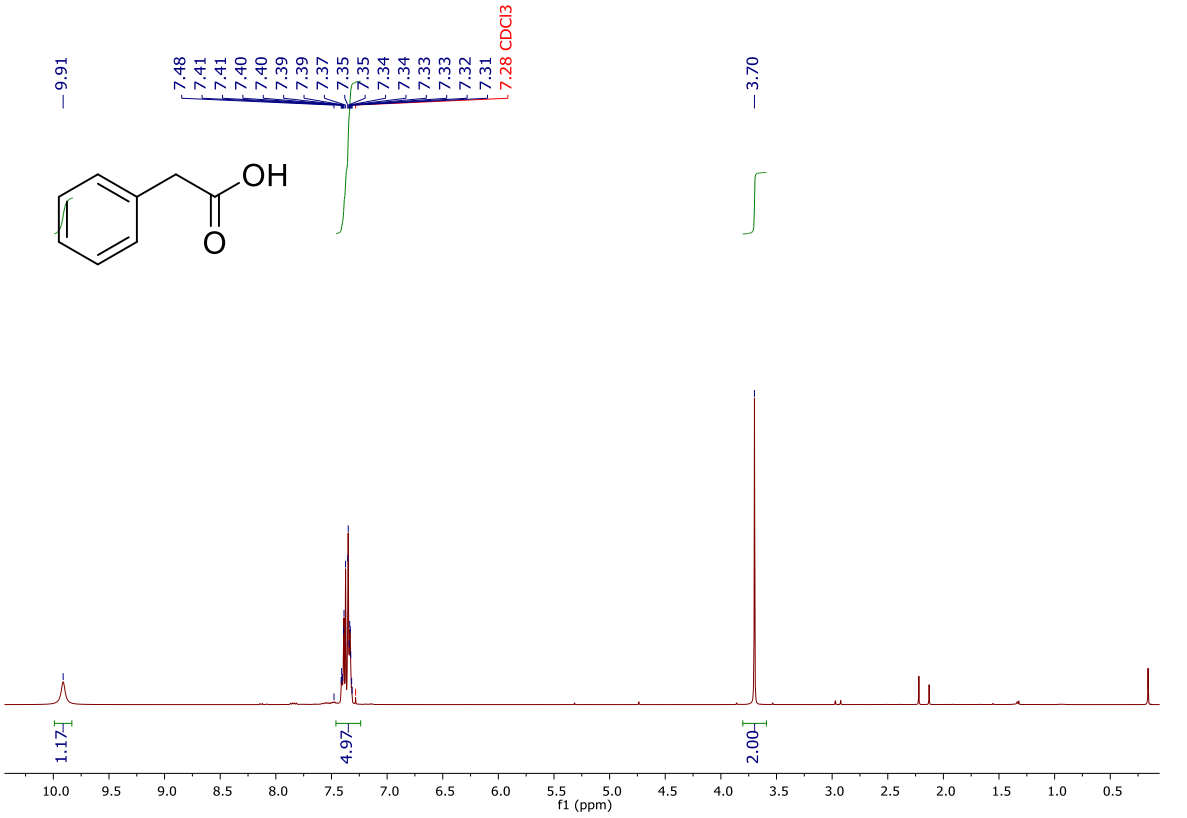


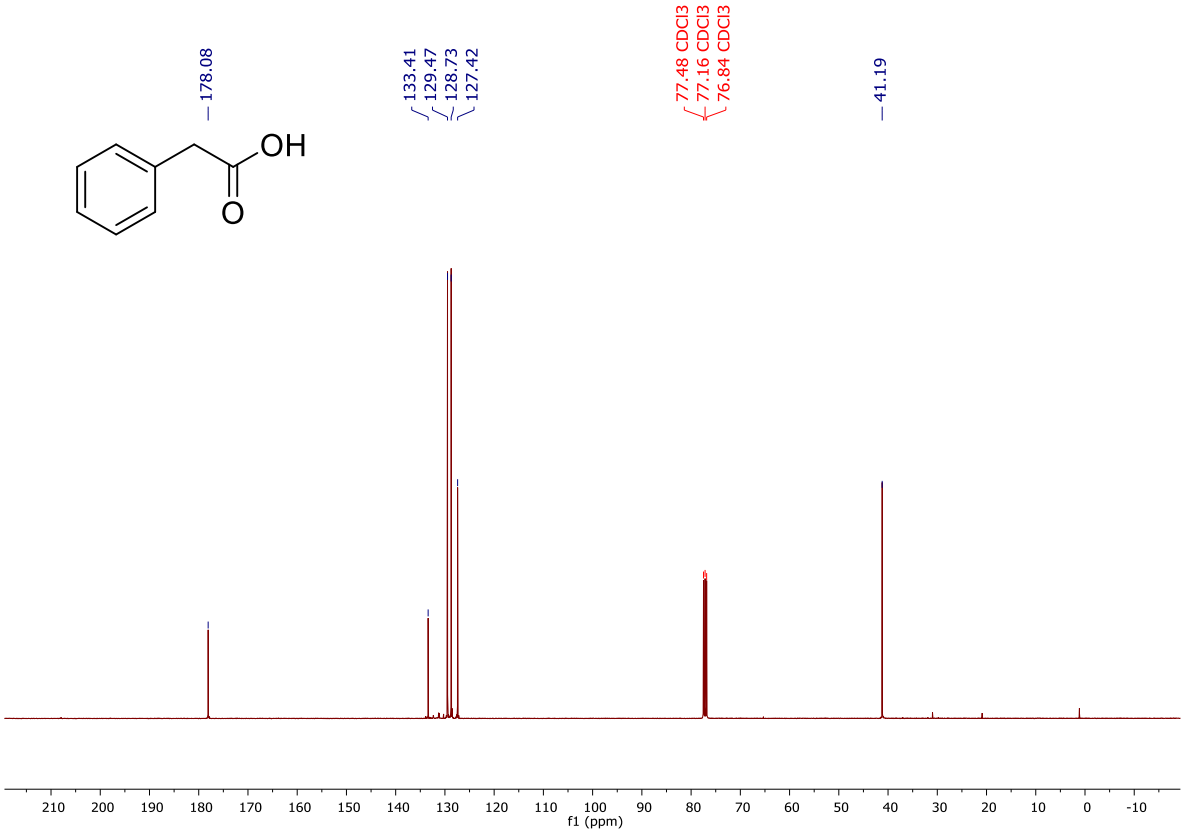


hydroxyethyl phenylacetate (Table 3, Entry 6):



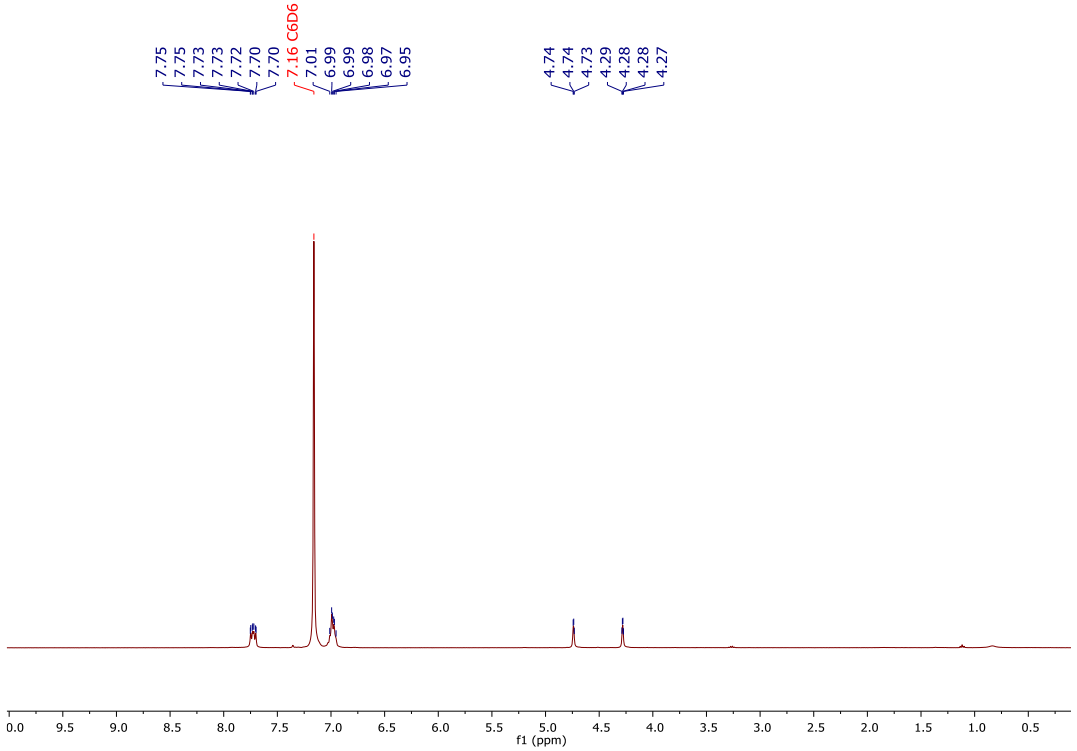
phenylacetic acid (Table 3, Entry 7)

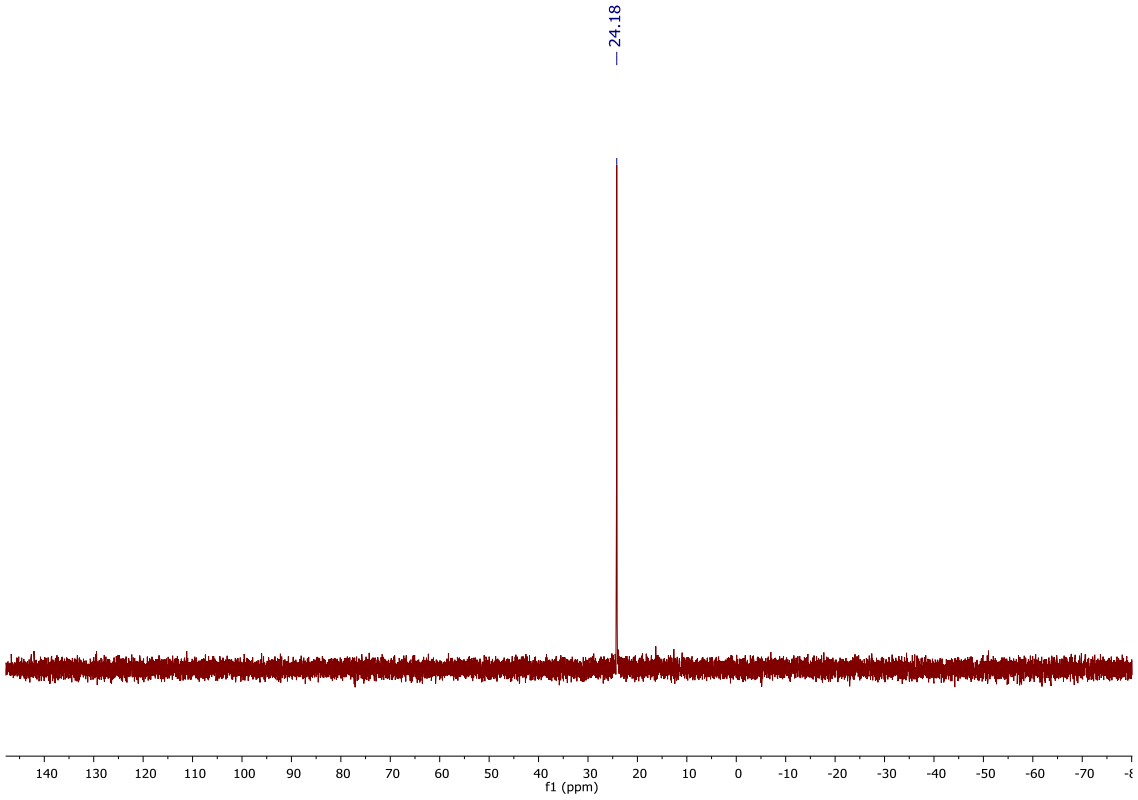




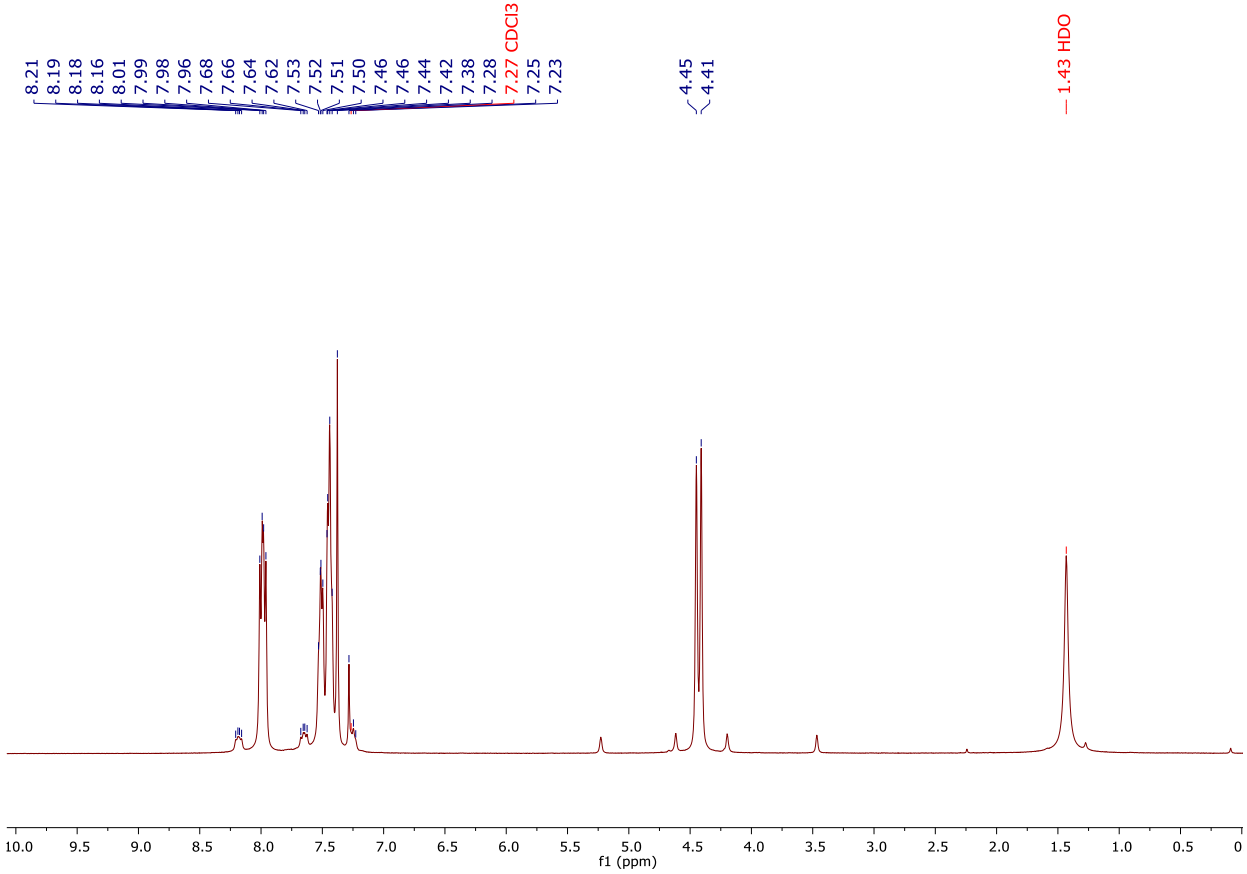
4.3. NMR characterization of synthetized complexes

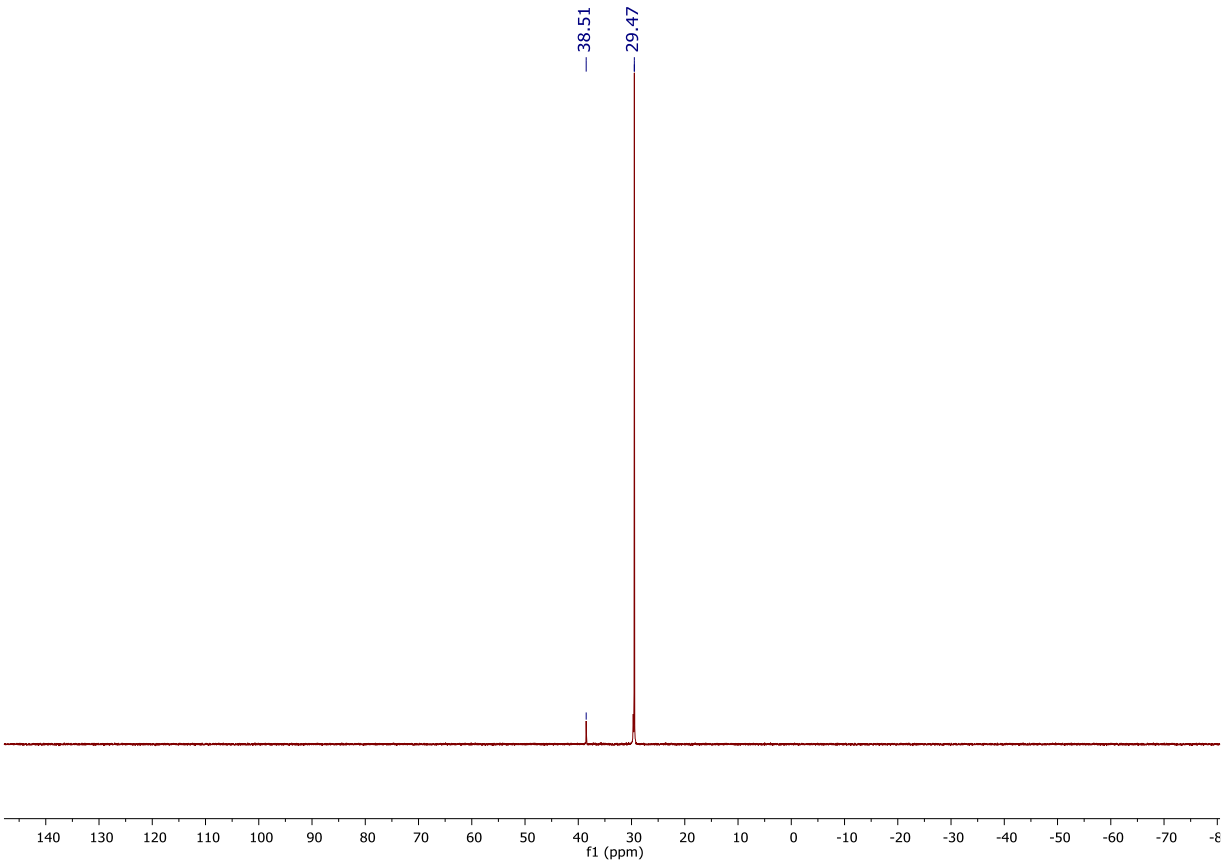
4.3.1. ^{1}H NMR and ^{31}P NMR of $Pd(DPPF)_2$



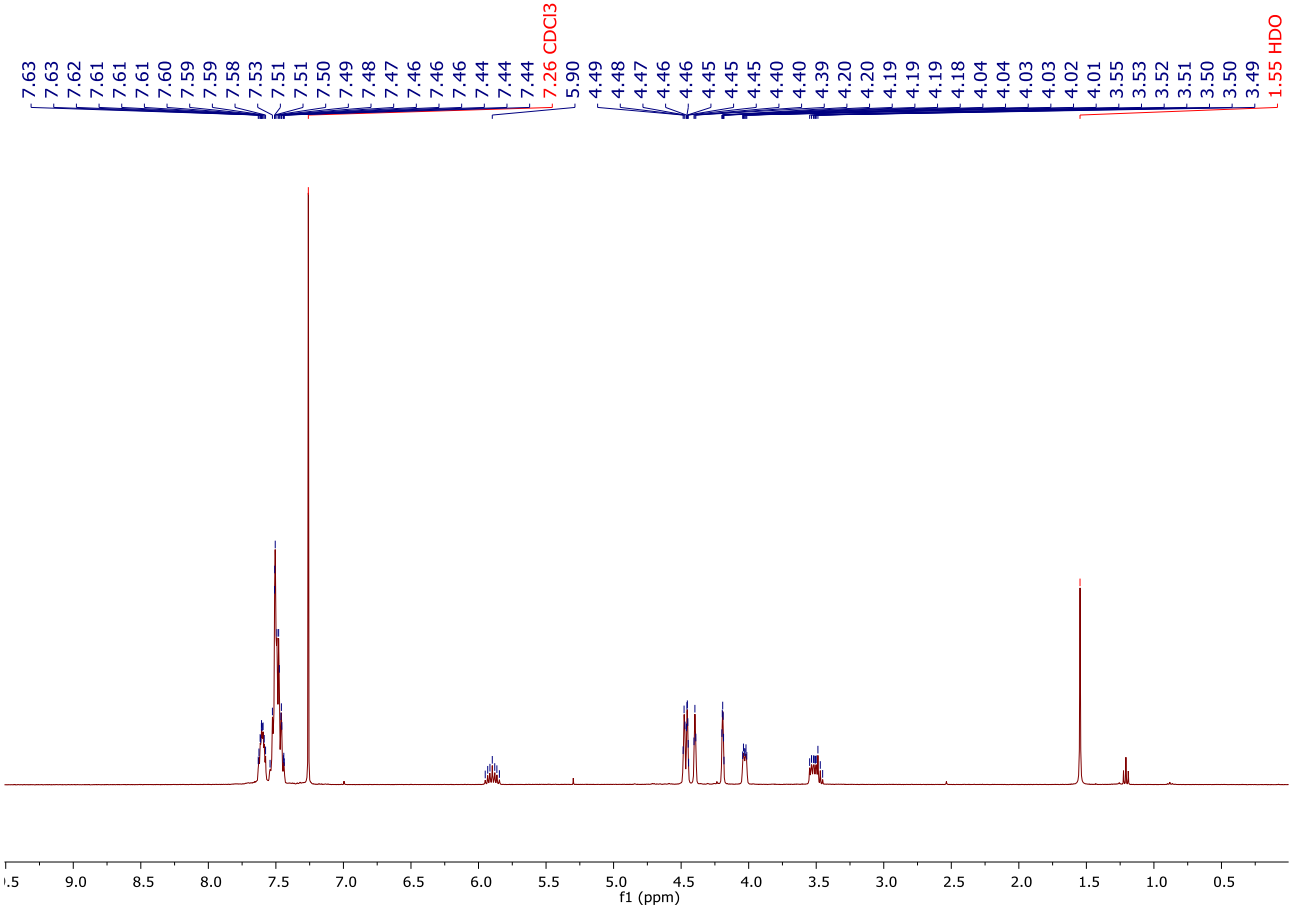


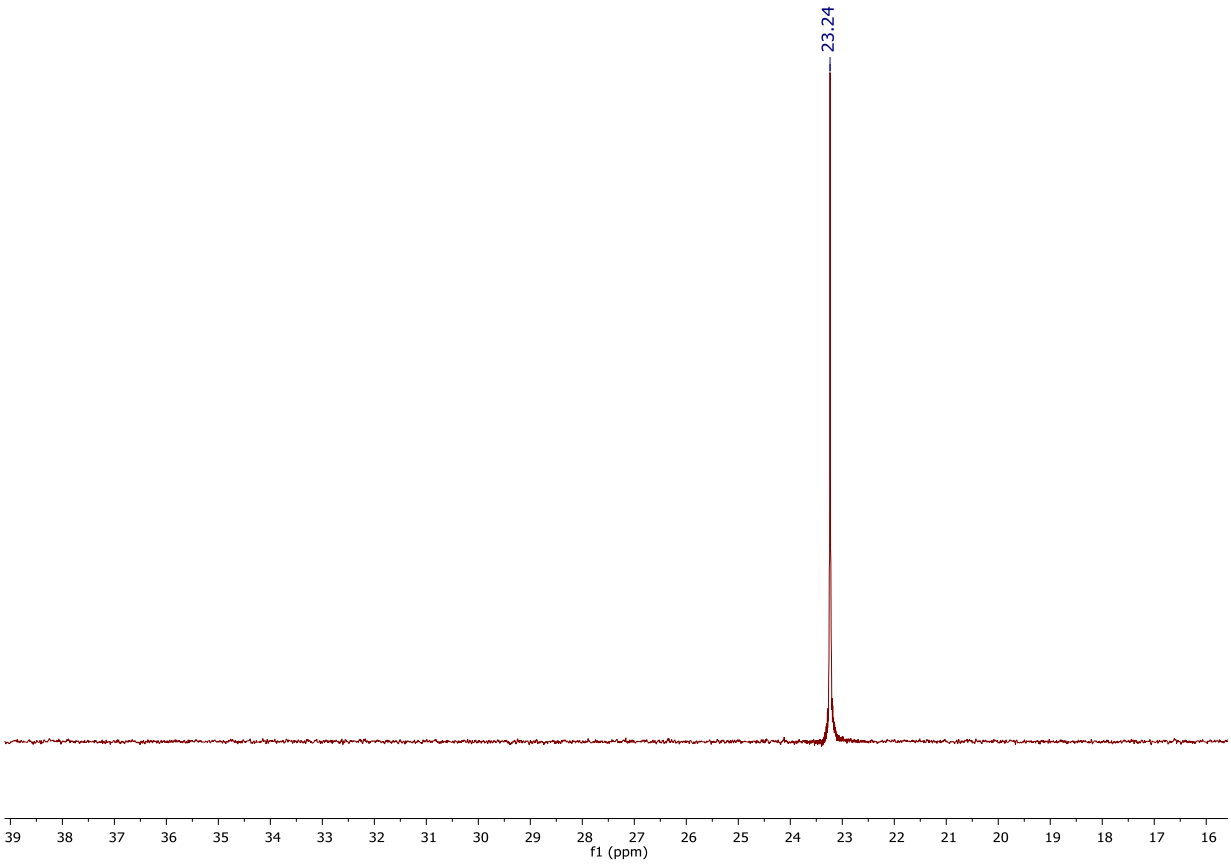
4.3.2. ^{1}H NMR and ^{31}P NMR of $PdAc_2(DPPF)$





4.3.3. ^{1}H NMR and ^{31}P NMR of Pd(η^3-C_3H_5)(DPPF)]ClO_4





5. References

[1] Z.-G. Fang, P. M.N. Low, S.C. Ng and T.S and A. Hor, *J. Organomet. Chem.*, 1994, **483**, 17-20.

[2] O. V. Gusev, A. M. Kalsin, M. G. Peterleitner, P. V. Petrovskii and K. A. Lyssenko, *Organometallics,* 2002, **21**, 3637-3649.

[3] T. Scattolin, G. Moro, A. Serena, A. Guadagnin Pattaro, F. Rizzolio, V. Canzonieri, N. Demitri, E. Bortolamiol, L. M. Moretto and Fabiano Visentin, *Appl. Organomet. Chem.* 2022, e6629.