One Pot Electrochemical Nickel Catalyzed Decarboxylative Sp^2-Sp^3 Cross-Coupling

Takaoki Koyanagi, Ananda Herath, Ashley Chong, Maxim Ratnikov, Andrew Valiere, Jim Chang, Valentina Molteni, Jon Loren*

Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego California 92121, United States of America

Table of Contents

1. General Information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Flash column chromatography was performed with Teledyne ISCO CombiFlash® Systems. ^{1}H NMR spectra were recorded using a Bruker 400 UltraShield® spectrometer (400 MHz) in deuterated solvent and chemical shifts were reported in ppm (δ) relative to residual deuterated solvent peak ($CDCl_3$, δ 7.26 ppm). ^{13}C NMR spectra were recorded using a Bruker 400 UltraShield® spectrometer (101 MHz) in deuterated solvent and chemical shifts were reported in ppm (δ) relative to residual deuterated solvent peak ($CDCl_3$, δ 77.0 ppm). ^{19}F NMR spectra were recorded using a Bruker 400 UltraShield® spectrometer (377 MHz) in deuterated solvent and chemical shifts were unreferenced. The FID file was analyzed using MestReNova version 12.0.2-20910. UPLC spectra were recorded using Waters Acquity I-Class LC/MS system with QDa, photodiode array and ELSD detectors. The sample was injected onto a Waters Acquity HSS T3 C18 column, 2.1 x 30 mm, 1.8 µm with the flow rate of 1mL/min at 50 °C 5-100% B in 1.90 mins (Mobile phase A = H_2O + 0.1 % formic acid, Mobile phase B = ACN + 0.1 % formic acid). HRMS spectra were recorded using Thermo Q-Exactive Mass Spec with Thermo Vanquish UHPLC and diode array detector. The sample was injected onto an XSelect HSS T3 C18 column, 2.1 x 30 mm, 2.5 µm with the flow rate of 0.50 mL/min; hold 5% for 0.40 min; 5-100% B in 4.00 min, hold 100% B for 0.50 min at 50 °C; 5.00 min runtime (Mobile phase A = H_2O + 0.1 % formic acid, Mobile phase B = ACN + 0.1 % formic acid).

Olympus BX41 phase contrast microscope was used to determine whether solids were crystalline or amorphous. Melting point of the crystalline solids were obtained using an Electrothermal Mel-Temp 30 melting point apparatus with a ramp rate of 2 °C/min and calibrated with trimethylamine (lit mp: 102-104)[1].

Electrochemical cells, electrodes, and programmable DC power supply (Keysight, E36104A) were purchased from IKA. The electrochemical cells were soldered to copper wires and connected in series to run up to 8 constant current reactions (as shown in **Figure S1.**)

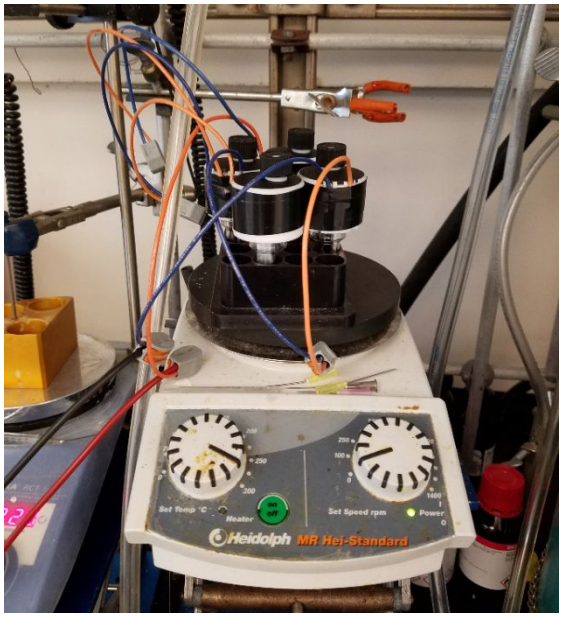


Figure S1. Picture of 4 electrochemical cells connected in series.

2. *In situ* Phthalimide Ester Formation Using Sodium Acetate

To a glass vial, **PITU** (229 mg, 0.563 mmol), cyclohexane carboxylic acid (72.2 mg, 0.563 mmol), and sodium acetate (46.2 mg, 0.563 mmol) were dissolved in 2 mL of DMA and mixed at RT for 15 minutes. The reaction was monitored using UPLC (shown in Figure S2) that reveals the formation of both phthalimide ester derivatives (one from cyclohexane carboxylic acid and the other from sodium acetate; along with unreacted starting carboxylic acids).

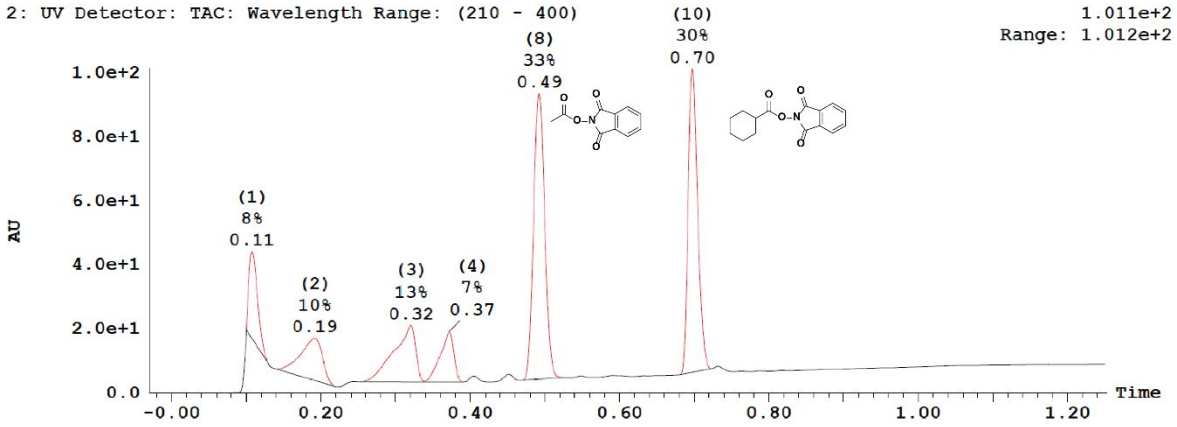


Figure S2. UPLC spectra of crude phthalimide ester reaction mixture.

3. Cyclic Voltammetry

Cyclic voltammetry experiments were conducted using an IKA Electrasyn 2.0 equipped with a carbon disk working electrode, platinum coated counter electrode and AgCl reference electrode. Redox potentials are reported against Ag/AgCl reference electrode at a sweep rate of 50 mV/s. Standard procedure for cyclic voltammetry experiment protocol: To a 5 mL IKA Electrasyn vial, 0.0375/0.375 mmol of compound of interest and 0.75 mmol of NaI was dissolved in DMA and degassed with Ar for 2 minutes before cyclic voltammetry measurements were taken (Figure S3).

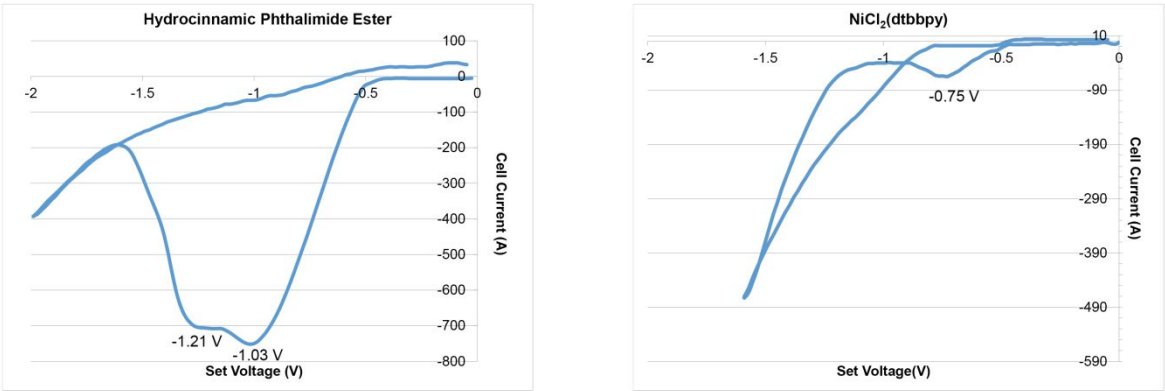


Figure S3. Cyclic voltammetry spectra.

4. General Procedures for Cross-Coupling Reactions

4.1. Detailed synthetic method for a 1.0 mmol scale reaction of 3a

Hydrocinnamic acid (225.3 mg, 1.5 mmol) was dissolved in 0.500 mL of MeOH, then 1.5 mL of 1.0 M NaOH (aq) was added. The solution was dried under vacuum overnight. Next, to a glass vial, $NiCl_2$dme (23 mg, 0.1 mmol) and dtbbpy (27.5 mg, 0.1 mmol) were dissolved in 1.0 mL of DMA and mixed at 60 °C for 15 minutes. In parallel, PITU (618.8 mg, 1.5 mmol) and 1.0 mL of DMA were added to the dried sodium hydrocinnamate and stirred at room temperature for 10 minutes. The two solutions, along with NaI (180 mg, 0.3 M), *p*-iodoacetophenone (246 mg, 1.0 mmol), and 2.0 mL of DMA were added to a 10 mL IKA Electrasyn vial and degassed with argon for 10 minutes. Subsequently, the reaction was stirred at room temperature and 3 mA of current was passed through for 2 F (17 hours and 52 minutes).

After the reaction, the crude reaction mixture was transferred to a separatory funnel while ensuring to rinse the electrodes thoroughly using ethyl acetate then diluted with more EtOAc (30 mL). To the mixture, 10 mL of sat. aq. NH_4Cl and 30 mL of water were added then extracted with 20 mL EtOAc three times. The organic layer was combined and back extracted with 30 mL of water, 30 mL of brine, dried over $MgSO_4$, and dried under vacuum. A dry load of the crude reaction mixture was made and purified using flash chromatography with a gradient of (Heptane: EtOAc 95/5) over 30 minutes to obtain 173 mg of **3a** as a white crystalline solid (77% yield, mp: 68.8-69.1 °C).

4.2. Preparation of Nickel Catalyst

To a glass vial, $NiCl_2$dme (8.5 mg, 0.0375 mmol) and dtbbpy (10 mg, 0.0375 mmol) were dissolved in 1 mL of DMA and mixed at 60 °C for 15 minutes.

4.3. General Procedures for Cross-Coupling Reactions (Procedure A)

Reaction conditions for parameter optimization

To a 5 mL IKA Electrasyn vial, 1,3-dioxoisoindolin-2-yl 3-phenylpropanoate (166 mg, 0.563 mmol), p-iodoacetophenone (92 mg, 0.375 mmol), 1 mL of nickel catalyst, and sodium iodide (135 mg, 0.900 mmol) were dissolved in 2 mL of DMA were added then degassed with argon for 1 minute. The reaction mixture was stirred at RT and 3 mA of constant current was administered for 2.0 F (6 hours 46 mins). The yield was determined either by UPLC using methyl 4-phenethylbenzoate as an internal standard or isolation of product.

Isolation of cross-couple product began by first transferring the reaction mixture to a separatory funnel while ensuring to rinse the electrodes thoroughly using ethyl acetate then diluted with more EtOAc (20 mL). To the mixture, 5 mL of sat. aq. NH_4Cl and 20 mL of water were added then extracted with 15 mL EtOAc three times. The organic layer was combined and back extracted with 20 mL of water, 20 mL of brine, dried over $MgSO_4$, and dried under vacuum. A dry load of the crude reaction mixture was made and purified using flash chromatography with a gradient of (Heptane: EtOAc 95/5) over 30 minutes.

4.4. General Procedures for Cross-Coupling Reactions (Procedure B)

Reaction conditions used to examine the effect of bases on cross-couplings

To a 5 mL IKA Electrasyn vial, hydrocinnamic acid (84.5 mg, 0.563 mmol), PITU (229 mg, 0.563 mmol), and base (0.563 mmol) were added and dissolved in 1 mL of DMA then stirred at RT for

10 minutes. To the reaction mixture, *p*-iodoacetophenone (92 mg, 0.375 mmol), 1 mL of nickel catalyst, sodium iodide (135 mg, 0.900 mmol) and 1 mL of DMA were added then degassed with argon for 1 minute. The reaction mixture was stirred at RT and 3 mA of constant current was administered for 2.0 F (6 hours 46 mins). The yield was determined by UPLC using methyl 4-phenethylbenzoate as an internal standard.

4.5. General Procedures for Cross-Coupling Reactions (Procedure C)

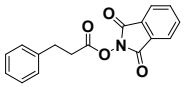
Reaction procedure for determination of substrate scope

To a 5 mL IKA Electrasyn vial, desired carboxylate (formed with 1 M NaOH (aq.) was added and dried overnight) (84.5 mg, 0.563 mmol). Next, to the reaction mixture, PITU (229 mg, 0.563 mmol) was added and dissolved in 1 mL of DMA and stirred at RT for 10 minutes (note: slight heating helps to dissolve certain carboxylate derivatives). Then, to the reaction mixture, desired aryl iodide (0.375 mmol), 1 mL of nickel catalyst, sodium iodide (135 mg, 0.900 mmol) and 1 mL of DMA were added then degassed with argon for 1 minute. The reaction mixture was stirred at RT and 3 mA of constant current was administered for 2.0 F (6 hours 46 mins).

Isolation of cross-couple product began by first transferring the reaction mixture to a separatory funnel while ensuring to rinse the electrodes thoroughly using ethyl acetate and diluted with more EtOAc (20 mL). To the mixture, 5 mL of sat. aq. NH_4Cl, and 20 mL of water were added then extracted with 15 mL EtOAc three times. The organic fractions were combined and back extracted with 20 mL of water, 20 mL of brine, dried over $MgSO_4$, and dried under vacuum. A dry load of the crude reaction mixture was made and purified using flash chromatography.

5. Synthetic Procedures and Characterization Data

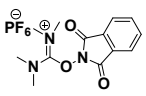
1,3-dioxoisoindolin-2-yl 3-phenylpropanoate (**1**)



To a solution of hydrocinnamic acid (3 g, 20.0 mmol) in anhydrous DCM (100 mL), *N*-hydroxy phthalimide (3.3 g, 20.0 mmol), DMAP (0.24 g, 2.0 mmol), and DIC (3.1 mL, 20.0 mmol) were added at 0 °C. The reaction mixture was then warmed to RT and stirred for 3.5 hours. The reaction mixture was dried under vacuum and purified using flash chromatography (Heptane: EtOAc 6/4) to recover 5.1 g of **1** as a white amorphous solid (86% yield).

Spectroscopic data agreed with previously reported data.[2]

N-hydroxyphthalimide tetramethyluronium hexafluorphosphate (**PITU**)



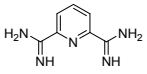
In a round bottom flask, *N*-hydroxy phthalimide (3.0 g, 18.39 mmol), tetramethylchloroformamidinium hexafluorophosphate (5.2 g, 18.39 mmol), and trimethylamine (2.6 mL, 18.65 mmol) were dissolved in DCM (100 mL) and stirred at RT for 2 hours. The product was precipitated and collected by filtration, then washed with DCM and dried under vacuum to isolate 6.1 g of **PITU** as a white crystalline solid (81% yield, mp: 183.9-190.9 °C).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (m, 4H), 3.21 (s, 12H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 162.93, 162.21, 136.29, 129.23, 124.83.

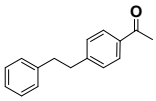
ESI-MS: 262.0 $[M]^+$; HRMS calcd for $[C_{13}H_{17}N_3O_3]^+$ 262.1186, found 262.1179 .

pyridine-2,6-bis(carboximidamide)•2HCl (**L2**)



Ligand **L2** was synthesized following a previously reported method.[3] Spectroscopic data matched published results.

1-(4-phenethylphenyl)ethan-1-one (**3a**)



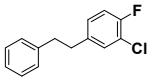
Compound **3a** was synthesized using procedure C with *p*-iodoacetophenone (92 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 68 mg of white crystalline solid (81 % yield, mp: 68.8-69.1 °C). NMR spectra agreed with previously published data.[4]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.95 – 7.88 (m, 2H), 7.36 – 7.16 (m, 7H), 3.06 – 2.94 (m, 4H), 2.61 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 197.83, 147.47, 141.10, 135.20, 128.73, 128.53, 128.46, 128.43, 126.13, 37.85, 37.43, 26.58.

ESI-MS: 225.1 $[M + H]^+$

2-chloro-1-fluoro-4-phenethylbenzene (**3b**)



Compound **3b** was synthesized using procedure C with 2-chloro-1-fluoro-4-iodobenzene (96 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/(Heptane/DCM 4:1) 0 to 100% gradient over 30 minutes) to give 80 mg of clear oil (91 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.37 – 7.31 (m, 2H), 7.29 – 7.17 (m, 4H), 7.10 – 7.00 (m, 2H), 2.97 – 2.89 (m, 4H).

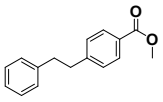
^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 156.59 (d, J = 246.4 Hz), 140.96, 138.64 (d, J = 4.0 Hz), 130.44, 128.47 (d, J = 0.5 Hz), 128.10 (d, J = 6.9 Hz), 126.19, 120.52 (d, J = 17.7 Hz), 120.43, 116.28 (d, J = 20.8 Hz), 37.72 (d, J = 1.1 Hz), 36.87.

^{19}F NMR (377 MHz, $CDCl_3$-d_1) δ -119.80

ESI-MS: 257.7 $[M + Na]^+$

Elemental Analysis: (calcd) C, 71.65; H, 5.15; Cl, 15.10; F, 8.09 (found) C, 71.41; H, 5.30; Cl, 15.25; F, 8.15

methyl 4-phenethylbenzoate (**3c**)



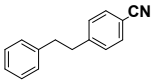
Compound **3c** was synthesized using procedure C with methyl 4-iodobenzoate (98 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 78 mg of clear oil (87 % yield). NMR spectra agreed with previously published data.[5]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 8.16 – 8.11 (m, 2H), 7.50 – 7.29 (m, 7H), 4.07 (s, 3H), 3.18 – 3.07 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 167.14, 147.19, 141.17, 129.72, 128.58, 128.48, 128.43, 127.99, 126.12, 51.99, 37.91, 37.48.

ESI-MS: 241.1 $[M + H]^+$

4-phenethylbenzonitrile (**3d**)



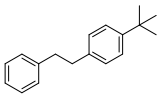
Compound **3d** was synthesized using procedure C with 4-iodobenzonitrile (86 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 66 mg of clear oil (85 % yield). NMR spectra agreed with previously published data.[6]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.69 – 7.48 (m, 2H), 7.37 – 7.22 (m, 5H), 7.21 – 7.09 (m, 2H), 3.07 – 2.93 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 147.26, 140.64, 132.16, 129.37, 128.50, 128.46, 126.29, 119.12, 109.87, 37.93, 37.24.

ESI-MS: 230.9 $[M + Na]^+$

1-(tert-butyl)-4-phenethylbenzene (**3e**)



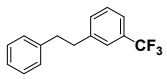
Compound **3e** was synthesized using procedure C with 1-(*tert*-butyl)-4-iodobenzene (97 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/(Heptane/DCM 4:1) 0 to 100% gradient over 30 minutes) to give 68 mg of clear oil (76 % yield). NMR spectra agreed with previously published data.[7]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.45 – 7.36 (m, 4H), 7.34 – 7.22 (m, 5H), 3.09 – 2.93 (m, 4H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 148.77, 142.07, 138.83, 128.43, 128.37, 128.06, 125.91, 125.27, 37.95, 37.44, 34.41, 31.46.

ESI-MS: 239.2 $[M + H]^+$

1-phenethyl-3-(trifluoromethyl)benzene (**3f**)



Compound **3f** was synthesized using procedure C with 1-iodo-3-(trifluoromethyl)benzene (102 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/(Heptane/DCM 4:1) 0 to 100% gradient over 30 minutes) to give 56 mg of white amorphous solid (72 % yield). NMR spectra agreed with previously published data.[7]

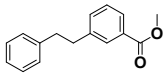
^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.46 – 7.05 (m, 9H), 3.10 – 2.96 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 144.00, 141.08, 129.56, 128.45, 128.42, 126.93, 126.13, 121.03, 118.41, 37.59, 37.57.

^{19}F NMR (377 MHz, $CDCl_3$-d_1) δ -57.69.

ESI-MS: 251.4 $[M + H]^+$

methyl 3-phenethylbenzoate (**3g**)



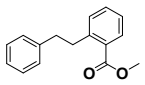
Compound **3g** was synthesized using procedure C with methyl 3-iodobenzoate (98 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 54 mg of clear oil (60 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 8.01 – 7.85 (m, 2H), 7.42 – 7.18 (m, 7H), 3.96 (s, 3H), 3.05 – 2.95 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 167.25, 142.06, 141.32, 133.19, 130.25, 129.58, 128.47, 128.42, 128.37, 127.29, 126.07, 52.08, 37.78, 37.72.

ESI-MS: 241.1 $[M + H]^+$; HRMS calcd for $[C_{16}H_{17}O_2]^+$ 241.1223, found 241.1214.

methyl 2-phenethylbenzoate (**3h**)



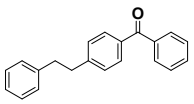
Compound **3h** was synthesized using procedure C with methyl 2-iodobenzoate (98 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 30 mg of clear oil (33 % yield). NMR spectra agreed with previously published data.[8]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.78 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.22 – 7.02 (m, 7H), 3.77 (s, 3H), 3.20 – 3.09 (m, 2H), 2.87 – 2.73 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 167.99, 143.63, 141.97, 131.98, 131.21, 130.77, 129.49, 128.57, 128.32, 126.06, 125.89, 51.96, 38.17, 36.84.

ESI-MS: 241.2 $[M + H]^+$

(4-phenethylphenyl)(phenyl)methanone (**3i**)



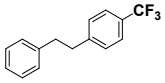
Compound **3i** was synthesized using procedure C with (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 82 mg of white amorphous solid (76 % yield). NMR spectra agreed with previously published data.[9]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.82 – 7.70 (m, 4H), 7.59 – 7.52 (m, 1H), 7.49 – 7.42 (m, 2H), 7.30 – 7.14 (m, 7H), 3.03 – 2.92 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.46, 146.88, 141.20, 137.95, 135.42, 132.25, 130.41, 130.00, 128.50, 128.48, 128.47, 128.27, 126.17, 37.92, 37.51.

ESI-MS: 287.1 $[M + H]^+$

1-phenethyl-4-(trifluoromethyl)benzene (**3j**)



Compound **3j** was synthesized using procedure C with 1-iodo-4-(trifluoromethyl)benzene (108 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/(Heptane/DCM 4:1) 0 to 100% gradient over 30 minutes) to give 56 mg of white amorphous solid (60 % yield). NMR spectra agreed with previously published data.[7]

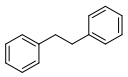
^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.61 (d, J = 8.0 Hz, 2H), 7.46 – 7.15 (m, 7H), 3.14 – 2.96 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 145.76, 141.05, 128.81, 128.45, 126.17, 125.27 (q, J = 4.1 Hz), 37.67, 37.52.

^{19}F NMR (377 MHz, $CDCl_3$-d_1) δ -62.27

ESI-MS: 251.1 $[M + H]^+$

1,2-diphenylethane (**3k**)



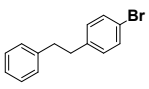
Compound **3k** was synthesized using procedure C with iodobenzene (76 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/(Heptane/DCM 4:1) 0 to 100% gradient over 30 minutes) to give 46 mg of white amorphous solid (67 % yield). NMR spectra agreed with previously published data.[7]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.39 – 7.33 (m, 4H), 7.31 – 7.24 (m, 6H), 3.01 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 141.84, 128.51, 128.39, 125.98, 125.71, 38.01.

ESI-MS: 183.6 $[M + H]^+$

1-bromo-4-phenethylbenzene (**3l**)



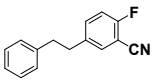
Compound **3l** was synthesized using procedure C with 1-bromo-4-iodobenzene (106 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/(Heptane/DCM 4:1) 0 to 100% gradient over 30 minutes) to give 52 mg of clear oil (53 % yield). NMR spectra agreed with previously published data.[6]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.49 – 7.43 (m, 2H), 7.37 – 7.31 (m, 2H), 7.29 – 7.20 (m, 3H), 7.12 – 7.07 (m, 2H), 2.99 – 2.92 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 141.25, 140.64, 131.37, 130.27, 128.47, 128.40, 126.06, 119.68, 37.70, 37.27.

ESI-MS: 283.2 $[M + Na]^+$

2-fluoro-5-phenethylbenzonitrile (**3m**)



Compound **3m** was synthesized using procedure C with 2-fluoro-5-iodobenzonitrile (96 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 41 mg of clear oil (49 % yield).

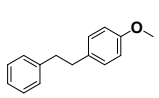
^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.31 – 7.17 (m, 4H), 7.17 – 7.10 (m, 1H), 7.06 – 6.96 (m, 3H), 2.91 – 2.76 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 161.65 (d, *J* = 257.2 Hz), 160.37, 140.25, 138.52 (d, *J* = 3.8 Hz), 135.20 (d, *J* = 8.0 Hz), 133.06, 128.49 (d, *J* = 8.7 Hz), 126.38, 116.21 (d, *J* = 19.4 Hz), 114.11, 101.12 (d, *J* = 15.4 Hz), 37.44 (d, *J* = 1.0 Hz), 36.57.

^{19}F NMR (377 MHz, $CDCl_3$-d_1) δ -110.75.

ESI-MS: 226.3 $[M + H]^+$; HRMS calcd for $[C_{15}H_{13}FN]^+$ 226.1027, found 226.1019.

1-methoxy-4-phenethylbenzene (**3n**)



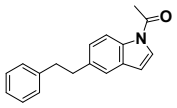
Compound **3n** was synthesized using procedure C with 1-iodo-4-methoxybenzene (88 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 17 mg of white amorphous solid (21 % yield). NMR spectra agreed with previously published data.[10]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 7.14 – 7.08 (m, 2H), 6.87 – 6.81 (m, 2H), 3.81 (s, 3H), 2.97 – 2.83 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 157.85, 141.87, 133.91, 129.35, 128.49, 128.31, 125.87, 113.76, 55.27, 38.22, 37.04.

ESI-MS: 213.3 $[M + H]^+$

1-(5-phenethyl-1H-indol-1-yl)ethan-1-one (**3o**)



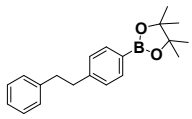
Compound **3o** was synthesized using procedure C with 1-(5-iodo-1*H*-indol-1-yl)ethan-1-one (107 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 90:10 gradient over 30 minutes) to give 19 mg of white amorphous solid (20 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 8.35 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 3.8 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.18 (m, 4H), 6.64 – 6.57 (m, 1H), 3.08 – 2.96 (m, 4H), 2.66 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 168.48, 141.82, 137.28, 128.49, 128.33, 125.91, 125.88, 125.33, 120.31, 109.08, 38.39, 37.88.

ESI-MS: 264.1 $[M + H]^+$; HRMS calcd for $[C_{18}H_{18}NO]^+$ 264.1383, found 264.1375.

4,4,5,5-tetramethyl-2-(4-phenethylphenyl)-1,3,2-dioxaborolane (**3p**)



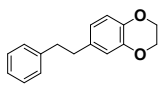
Compound **3p** was synthesized using procedure C with 2-(4-iodophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (124 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 18 mg of white crystalline solid (15 % yield, mp: 84.6-85.0 °C). NMR spectra agreed with previously published data.[11]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.68 – 7.62 (m, 2H), 7.24 – 7.16 (m, 2H), 7.14 – 7.07 (m, 5H), 2.88 – 2.82 (m, 4H), 1.27 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 145.17, 141.67, 134.90, 128.45, 128.34, 127.93, 125.92, 83.67, 38.15, 37.75, 24.89.

ESI-MS: 331.4 $[M + Na]^+$

6-phenethyl-2,3-dihydrobenzo[1,4]dioxine (**3q**)



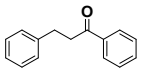
Compound **3q** was synthesized using procedure C with 6-iodo-2,3-dihydrobenzo[1,4]dioxine (98 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 over 30 minutes) to give 10 mg of clear oil (11 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.24 – 7.16 (m, 2H), 7.16 – 7.08 (m, 3H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 2.1 Hz, 1H), 6.58 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.16 (s, 4H), 2.83 – 2.71 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 143.28, 141.82, 141.71, 135.19, 128.42, 128.33, 125.89, 121.35, 117.00, 116.99, 64.43, 64.34, 38.02, 37.17.

ESI-MS: 241.3 $[M + H]^+$; HRMS calcd for $[C_{16}H_{17}O_2]^+$ 241.1223, found 241.1215.

1,3-diphenylpropan-1-one (**3t**)



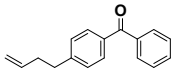
Compound **3t** was synthesized using procedure C with benzoyl chloride (53 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 56 mg of white crystalline solid (71 % yield, mp: 69.1-70.3 °C). NMR spectra agreed with previously published data.[12]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.95 – 7.79 (m, 2H), 7.52 – 7.39 (m, 1H), 7.39 – 7.29 (m, 2H), 7.26 – 7.05 (m, 5H), 3.25 – 3.16 (m, 2H), 3.02 – 2.93 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 199.21, 141.33, 136.90, 133.08, 128.63, 128.56, 128.46, 128.07, 126.17, 40.47, 30.17.

ESI-MS: 211.1 $[M + H]^+$

(4-(but-3-en-1-yl)phenyl)(phenyl)methanone (**5a**)



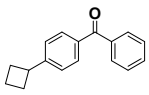
Compound **5a** was synthesized using procedure C with sodium cyclopropane acetate (56 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 84 mg of clear liquid (95 % yield). NMR spectra agreed with previously published data.[13]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.83 – 7.72 (m, 4H), 7.61 – 7.54 (m, 1H), 7.50 – 7.45 (m, 2H), 7.33 – 7.27 (m, 2H), 5.86 (ddt, *J* = 16.9, 10.3, 6.6 Hz, 1H), 5.12 – 4.98 (m, 2H), 2.84 – 2.76 (m, 2H), 2.47 – 2.38 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.44, 147.03, 137.95, 137.51, 135.33, 132.21, 130.37, 129.96, 128.42, 128.24, 115.43, 35.40, 35.09.

ESI-MS: 237.1 $[M + H]^+$

(4-cyclobutylphenyl)(phenyl)methanone (**5b**)



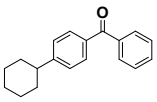
Compound **5b** was synthesized using procedure C with sodium cyclobutanecarboxylate (69 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 79 mg of clear liquid (89 % yield). NMR spectra agreed with previously published data.[14]

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.84 – 7.77 (m, 4H), 7.63 – 7.57 (m, 1H), 7.52 – 7.47 (m, 2H), 7.38 – 7.31 (m, 2H), 3.73 – 3.57 (m, 1H), 2.51 – 2.36 (m, 2H), 2.30 – 2.14 (m, 2H), 2.14 – 2.02 (m, 1H), 1.99 – 1.85 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.46, 151.34, 138.01, 135.10, 132.17, 130.32, 130.07, 129.96, 128.30, 128.23, 126.21, 40.29, 29.60, 18.35.

ESI-MS: 237.1 $[M + H]^+$

(4-cyclohexylphenyl)(phenyl)methanone (**5c**)



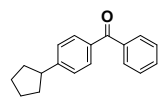
Compound **5c** was synthesized using procedure C with sodium cyclohexanecarboxylate (84 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 87 mg of clear liquid (87 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.86 – 7.77 (m, 4H), 7.61 – 7.57 (m, 1H), 7.52 – 7.47 (m, 2H), 7.40 – 7.30 (m, 2H), 2.71 – 2.53 (m, 1H), 2.08 – 1.86 (m, 4H), 1.84 – 1.73 (m, 1H), 1.60 – 1.37 (m, 4H), 1.34 – 1.20 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.44, 153.14, 138.03, 135.26, 132.14, 130.42, 130.07, 129.96, 128.30, 128.22, 126.80, 44.73, 34.19, 26.79, 26.08.

ESI-MS: 265.1 $[M + H]^+$; HRMS calcd for $[C_{19}H_{21}O]^+$ 265.1587, found 265.1575.

(4-cyclopentylphenyl)(phenyl)methanone (**5d**)



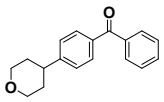
Compound **5d** was synthesized using procedure C with sodium cyclopentanecarboxylate (77 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 62 mg of clear liquid (66 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.86 – 7.81 (m, 2H), 7.81 – 7.73 (m, 2H), 7.62 – 7.57 (m, 1H), 7.53 – 7.48 (m, 2H), 7.45 – 7.30 (m, 2H), 3.22 – 2.98 (m, 1H), 2.25 – 2.03 (m, 2H), 1.93 – 1.60 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.47, 151.91, 138.03, 135.15, 132.14, 130.34, 130.07, 129.96, 128.29, 128.21, 127.04, 46.03, 34.56, 25.62.

ESI-MS: 251.1 $[M + H]^+$; HRMS calcd for $[C_{18}H_{19}O]^+$ 251.1430, found 251.1420.

phenyl(4-(tetrahydro-2H-pyran-4-yl)phenyl)methanone (**5e**)



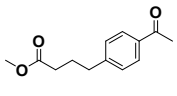
Compound **5e** was synthesized using procedure C with sodium tetrahydropyran-4-carboxylate (86 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 43 mg of white solid (44 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.87 – 7.77 (m, 4H), 7.64 – 7.57 (m, 1H), 7.53 – 7.46 (m, 2H), 7.39 – 7.33 (m, 2H), 4.18 – 4.08 (m, 2H), 3.65 – 3.51 (m, 2H), 2.94 – 2.82 (m, 1H), 1.94 – 1.79 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.34, 150.71, 137.82, 135.78, 132.28, 130.55, 129.97, 128.26, 126.73, 68.23, 41.69, 33.63.

ESI-MS: 267.1 $[M + H]^+$; HRMS calcd for $[C_{18}H_{19}O_2]^+$ 267.1380, found 267.1369.

methyl 4-(4-acetylphenyl)butanoate (**5f**)



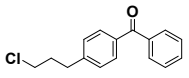
Compound **5f** was synthesized using procedure C with sodium monomethyl glutaric carboxylate (82 mg, 0.563 mmol) and *p*-iodoacetophenone (92 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 90:10 gradient over 30 minutes) to give 34 mg of clear liquid (41 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.94 – 7.84 (m, 2H), 7.32 – 7.26 (m, 2H), 3.68 (s, 3H), 2.72 (m, 2H), 2.59 (s, 3H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.05 – 1.93 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 197.77, 173.64, 147.17, 135.27, 128.68, 128.58, 51.56, 35.07, 33.24, 26.54, 26.08.

ESI-MS: 221.5 $[M + H]^+$; HRMS calcd for $[C_{13}H_{17}O_3]^+$ 221.1172, found 221.1165.

(4-cyclobutylphenyl)(phenyl)methanone (**5g**)



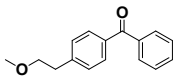
Compound **5g** was synthesized using procedure C with sodium 4-chlorobutanecarboxylate (103 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 42 mg of clear liquid (43 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.77 – 7.60 (m, 4H), 7.55 – 7.46 (m, 1H), 7.44 – 7.34 (m, 2H), 7.29 – 7.20 (m, 2H), 3.47 (t, *J* = 6.4 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.12 – 1.99 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.37, 145.83, 137.80, 135.67, 132.30, 130.50, 129.97, 128.51, 128.27, 44.03, 33.65, 32.80.

ESI-MS: 259.0 $[M + H]^+$; HRMS calcd for $[C_{16}H_{16}ClO]^+$ 259.0884, found 259.0874.

(4-(2-methoxyethyl)phenyl)(phenyl)methanone (**5h**)



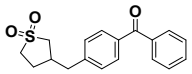
Compound **5h** was synthesized using procedure C with sodium 3-methoxypropanecarboxylate (59 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 90:10 gradient over 30 minutes) to give 36 mg of clear liquid (40 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.79 – 7.59 (m, 4H), 7.55 – 7.42 (m, 1H), 7.43 – 7.32 (m, 2H), 7.31 – 7.21 (m, 2H), 3.57 (t, *J* = 6.8 Hz, 2H), 3.28 (s, 3H), 2.88 (t, *J* = 6.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.43, 144.30, 137.87, 135.64, 132.24, 130.35, 129.97, 128.80, 128.24, 77.40, 58.74, 36.24.

ESI-MS: 241.1 $[M + H]^+$; HRMS calcd for $[C_{16}H_{17}O_2]^+$ 241.1223, found 241.1212.

(4-((1,1-dioxidotetrahydrothiophen-3-yl)methyl)phenyl)(phenyl)methanone (**5i**)



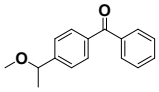
Compound **5i** was synthesized using procedure C with sodium 2-(1,1-dioxidotetrahydrothiophen-3-yl)acetate (105 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 32 mg of clear liquid (27 % yield).

^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.81 – 7.63 (m, 4H), 7.58 – 7.49 (m, 1H), 7.47 – 7.38 (m, 2H), 7.25 – 7.19 (m, 2H), 3.26 – 3.05 (m, 2H), 3.05 – 2.93 (m, 1H), 2.83 (d, *J* = 6.6 Hz, 2H), 2.76 – 2.62 (m, 2H), 2.33 – 2.19 (m, 1H), 1.98 – 1.78 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.13, 142.90, 137.52, 136.42, 132.51, 130.68, 129.98, 128.69, 128.35, 56.51, 52.20, 40.36, 38.18, 28.83.

ESI-MS: 315.0 $[M + H]^+$; HRMS calcd for $[C_{18}H_{19}O_3S]^+$ 315.1049, found 315.1035.

(4-(2-methoxyethyl)phenyl)(phenyl)methanone (**5j**)



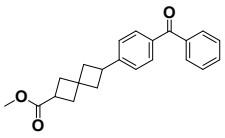
Compound **5j** was synthesized using procedure C with sodium 2-methoxypropanecarboxylate (59 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 18 mg of clear liquid (20 % yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.77 (m, 4H), 7.63 – 7.55 (m, 1H), 7.53 – 7.39 (m, 4H), 4.38 (q, *J* = 6.5 Hz, 1H), 3.27 (s, 3H), 1.46 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.41, 148.52, 137.72, 136.83, 132.37, 130.43, 130.02, 128.28, 126.01, 79.30, 56.72, 23.77.

ESI-MS: 241.1 $[M + H]^+$; HRMS calcd for $[C_{16}H_{17}O_2]^+$ 241.1229, found 241.1223.

methyl 6-(4-benzoylphenyl)spiro[3.3]heptane-2-carboxylate (**5m**)



Compound **5m** was synthesized using procedure C with sodium 6-(methoxycarbonyl)spiro[3.3]heptane-2-carboxylate (124 mg, 0.563 mmol) and (4-iodophenyl)(phenyl)methanone (115 mg, 0.375 mmol). Purification was performed using flash chromatography (Heptane/EtOAc 95:5 gradient over 30 minutes) to give 46 mg of clear liquid (37 % yield).

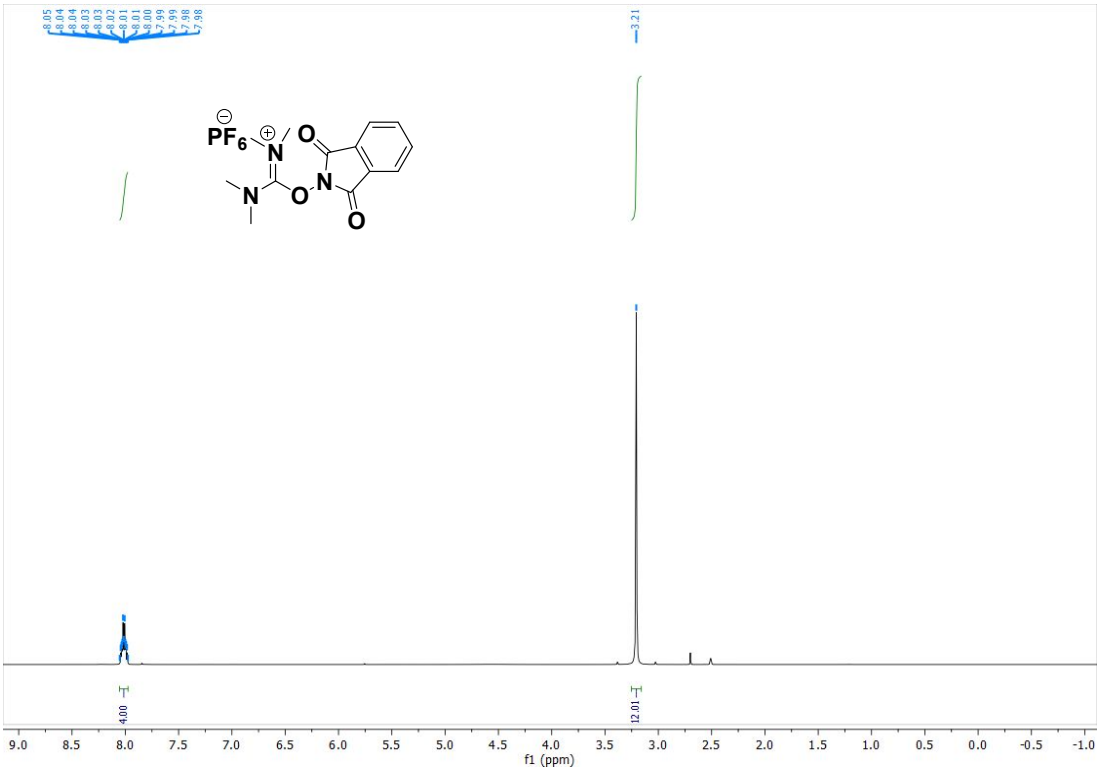
^{1}H NMR (400 MHz, $CDCl_3$-d_1) δ 7.77 – 7.62 (m, 4H), 7.55 – 7.44 (m, 1H), 7.44 – 7.35 (m, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 3.61 (s, 3H), 3.47 – 3.32 (m, 1H), 2.99 (p, *J* = 8.5 Hz, 1H), 2.53 – 2.41 (m, 1H), 2.40 – 2.30 (m, 3H), 2.25 – 2.04 (m, 4H).

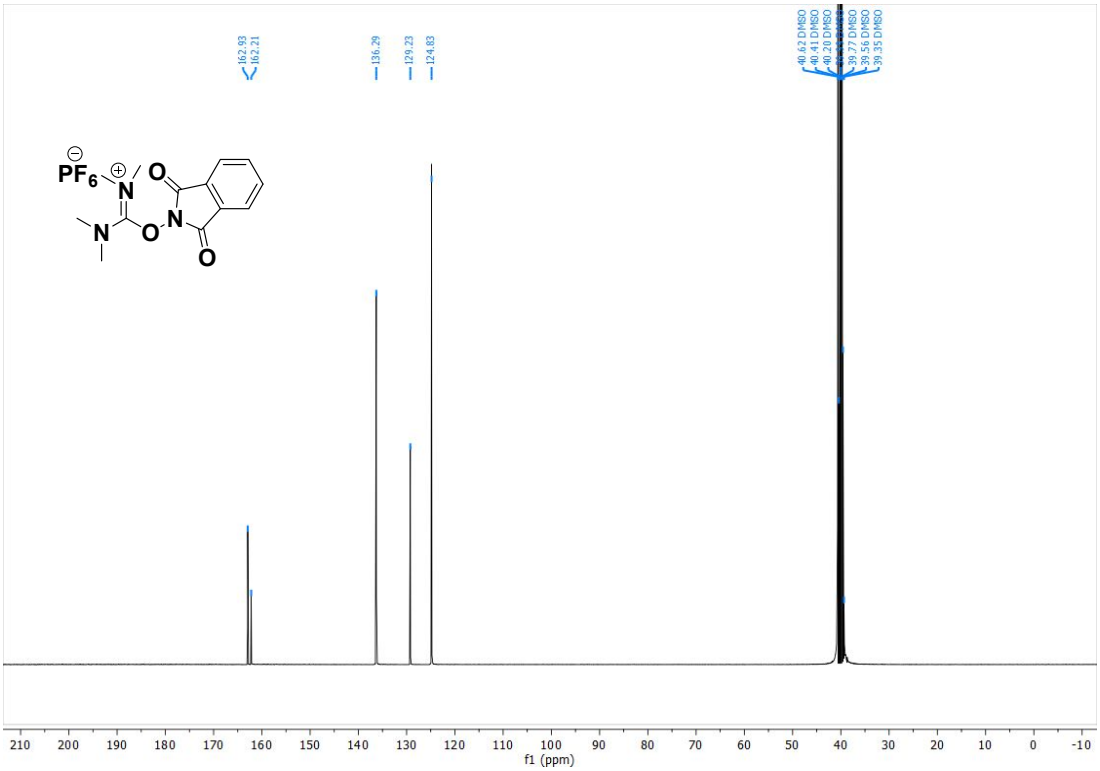
^{13}C NMR (101 MHz, $CDCl_3$-d_1) δ 196.41, 175.87, 150.58, 137.94, 135.20, 132.19, 130.32, 129.95, 128.22, 126.26, 51.70, 42.15, 41.47, 38.15, 37.03, 36.32, 34.37, 33.01.

ESI-MS: 335.1 $[M + H]^+$; HRMS calcd for $[C_{22}H_{23}O_3]^+$ 335.1642, found 335.1626.

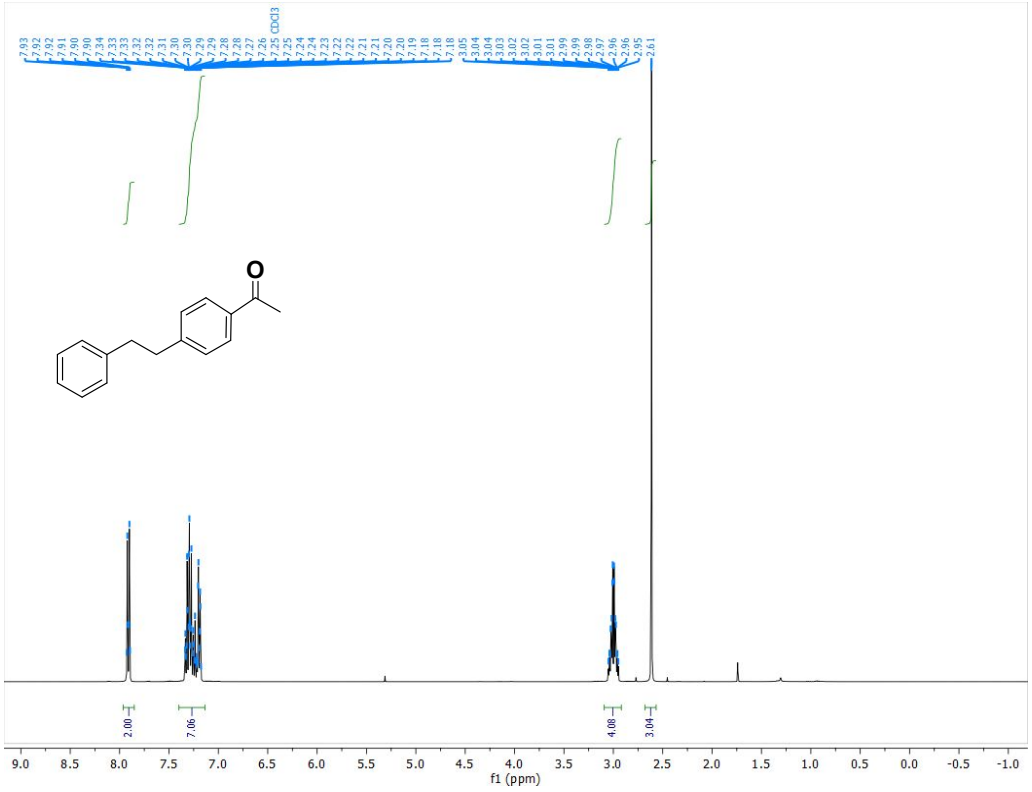
6. NMR Spectra

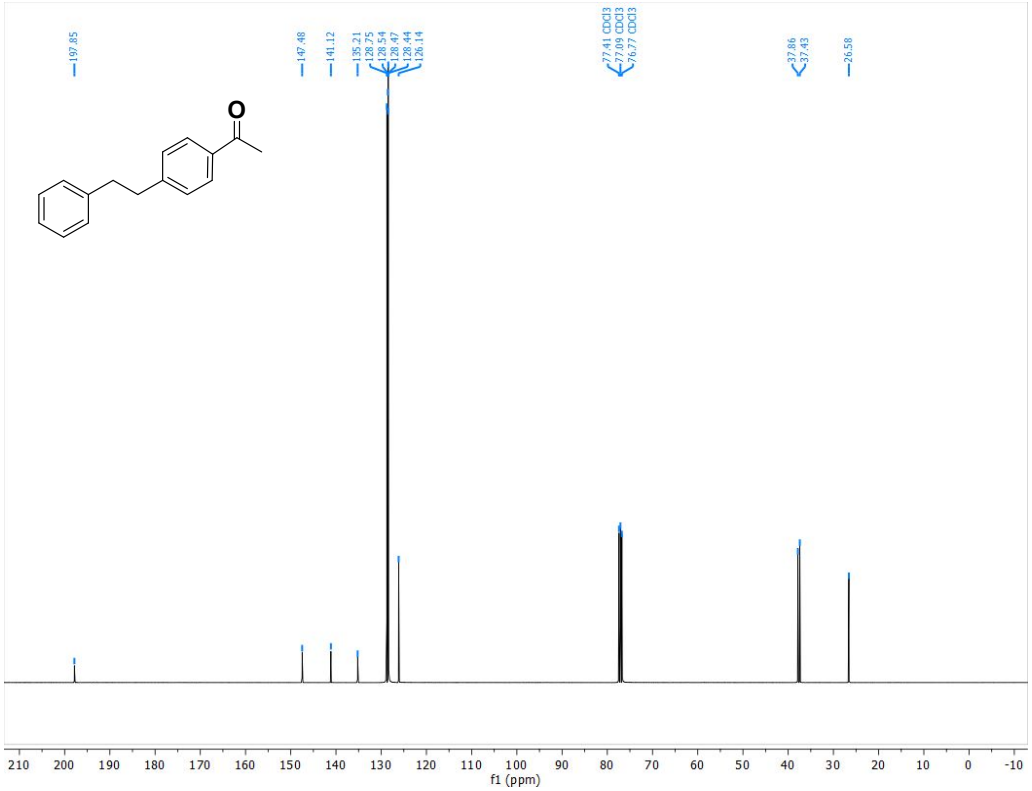
Compound **PITU**



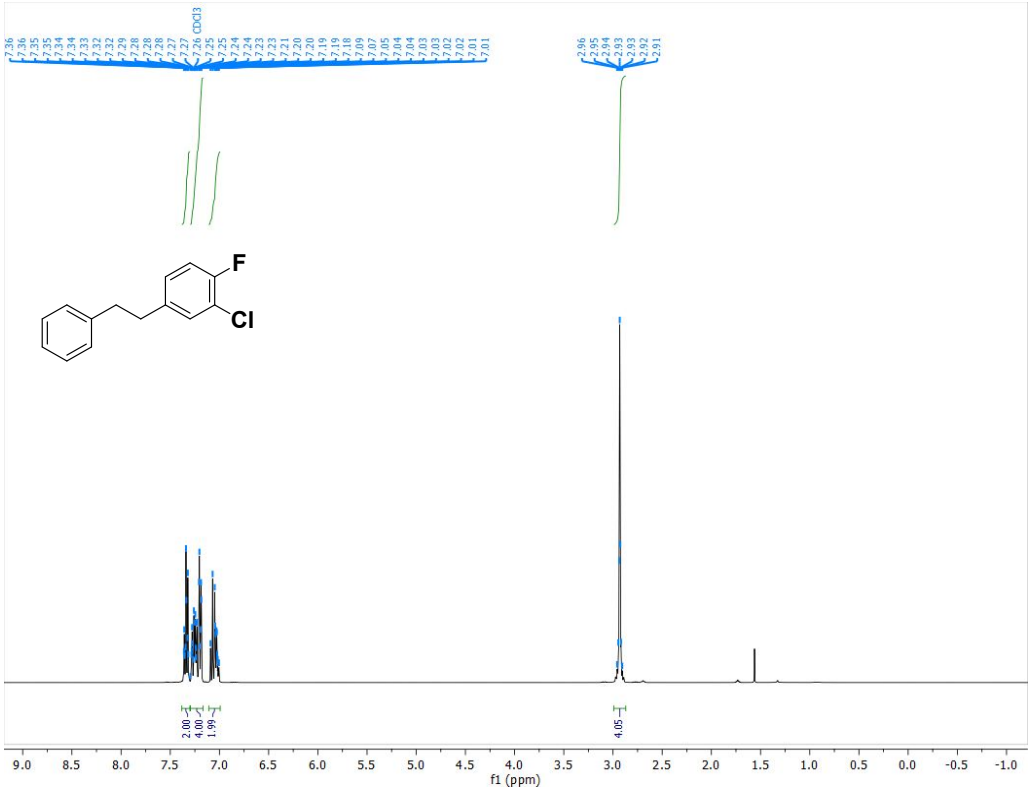


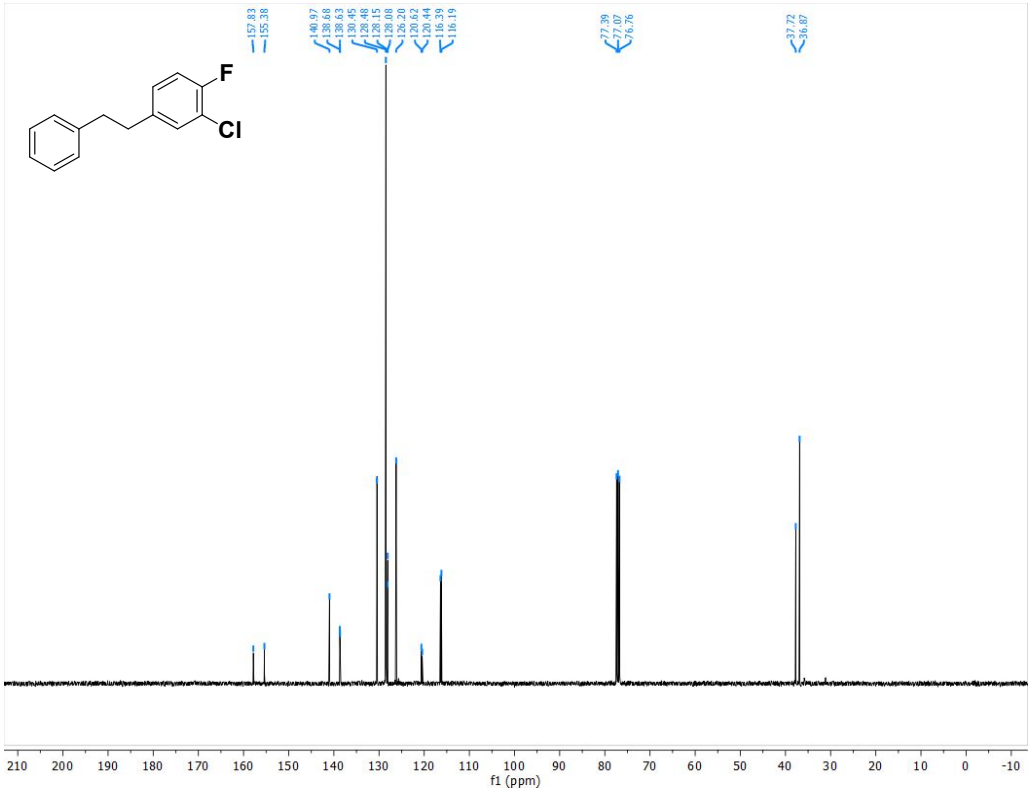
Compound **3a**

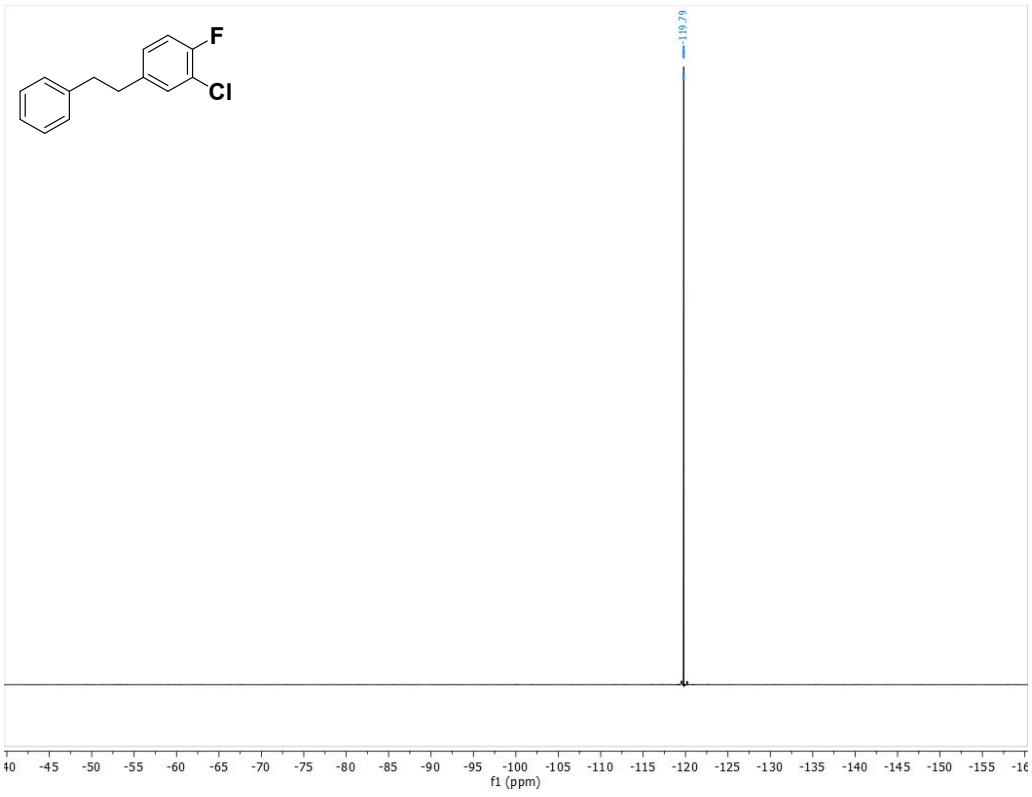

7.93
7.92
7.92
7.91
7.90
7.90
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.26
7.25 CDCl3
7.25
7.24
7.24
7.23
7.22
7.22
7.21
7.21
7.20
7.20
7.19
7.19
7.18
7.18
7.18
3.05
3.04
3.04
3.03
3.03
3.02
3.02
3.01
3.01
2.99
2.99
2.98
2.97
2.96
2.96
2.95
2.61
O
2.00
7.06
4.08
3.04
9.0 8.5 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)


197.85
147.48
141.12
135.21
128.75
128.54
128.47
128.44
126.14
77.41 CDCl3
77.09 CDCl3
76.77 CDCl3
37.86
37.43
26.58
O
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)

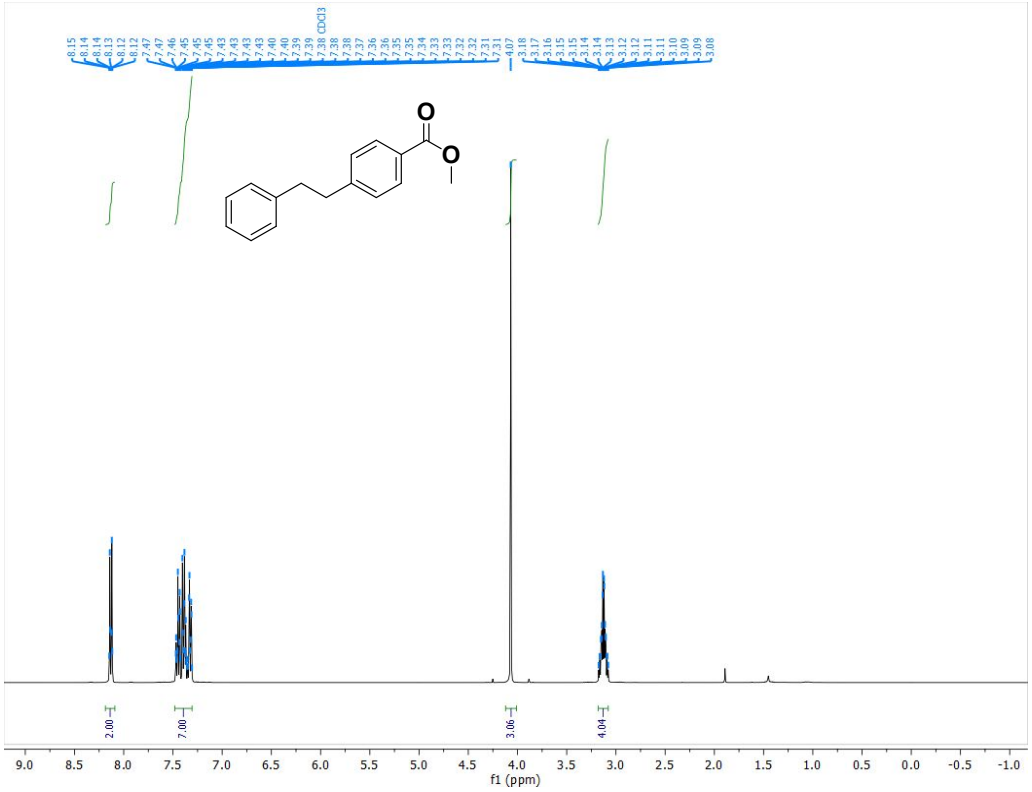
Compound **3b**

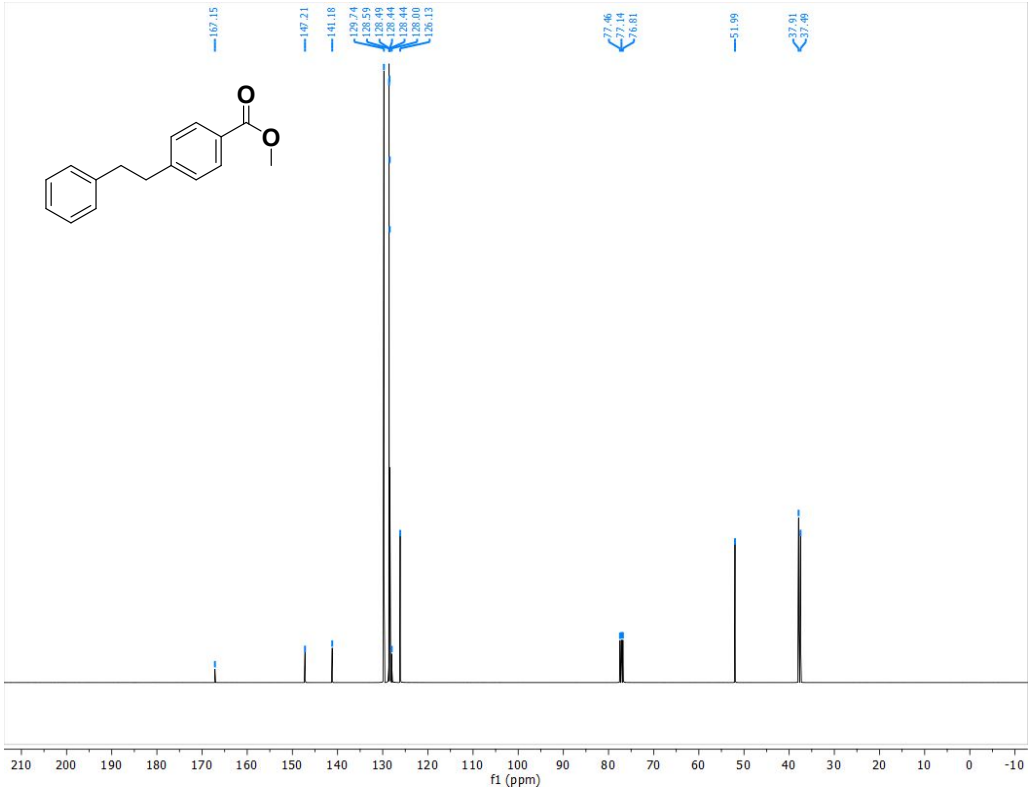




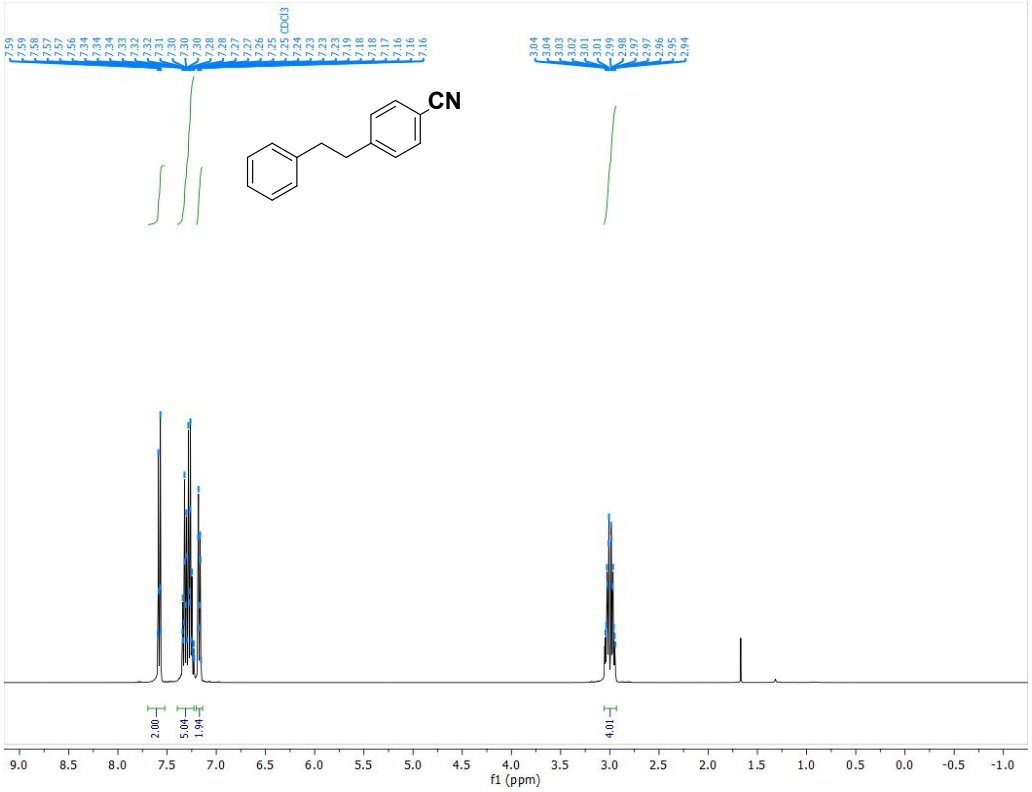

F
Cl
-119.79
-40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160
f1 (ppm)

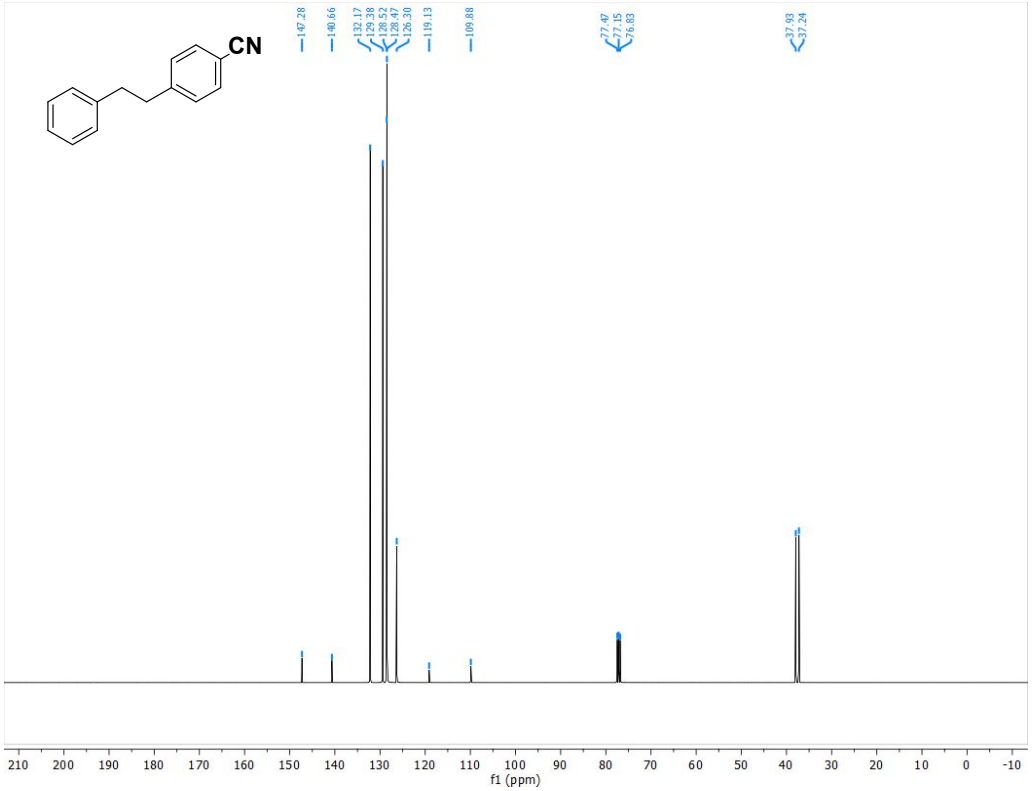
Compound **3c**


8.15
8.14
8.14
8.13
8.12
7.47
7.47
7.46
7.45
7.45
7.45
7.43
7.43
7.43
7.43
7.40
7.40
7.39
7.39
7.38 CDCl3
7.38
7.38
7.37
7.36
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.31
4.07
3.18
3.17
3.16
3.15
3.15
3.14
3.14
3.13
3.12
3.12
3.11
3.11
3.10
3.09
3.09
3.08
O
O
2.00
7.00
3.06
4.04
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)

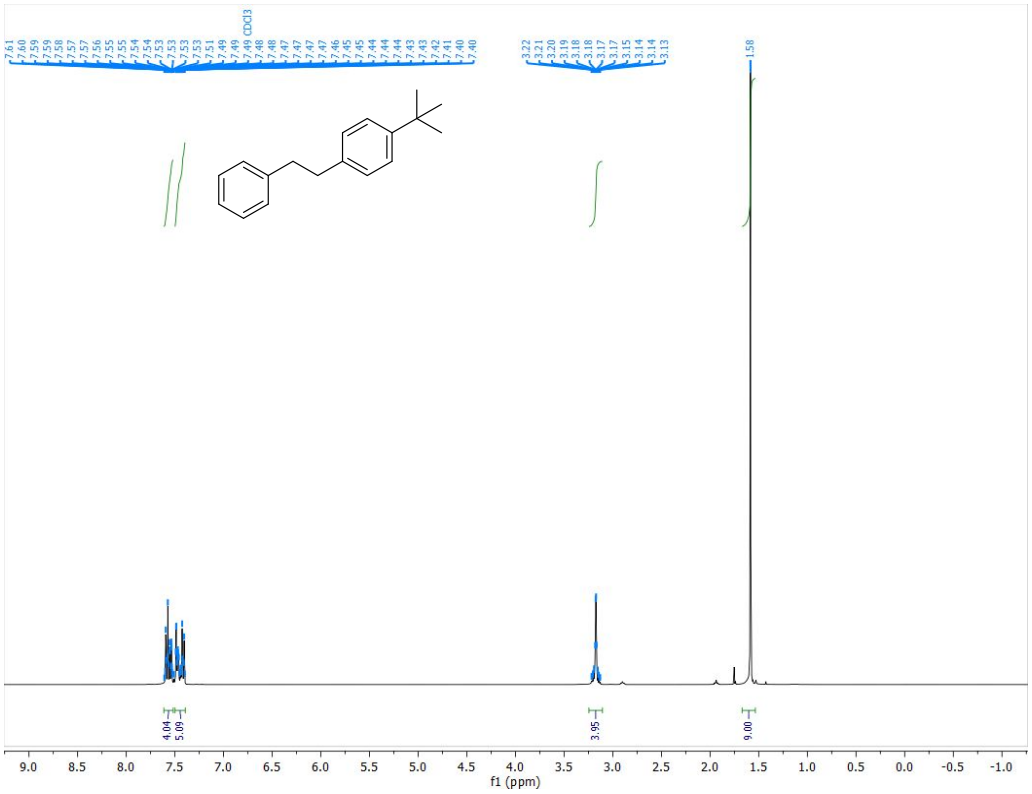

167.15
147.21
141.18
129.74
128.59
128.49
128.44
128.44
128.00
126.13
77.46
77.14
76.81
51.99
37.91
37.40
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

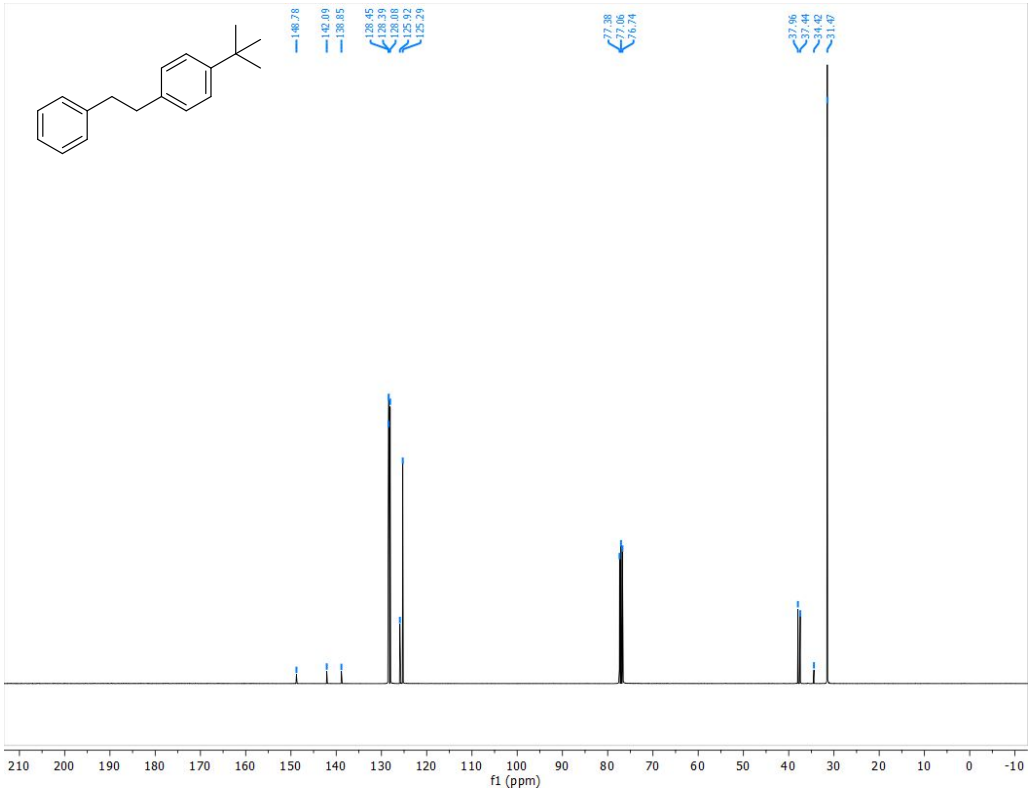
Compound **3d**


CN
2.00
5.04
1.94
4.01
f1 (ppm)

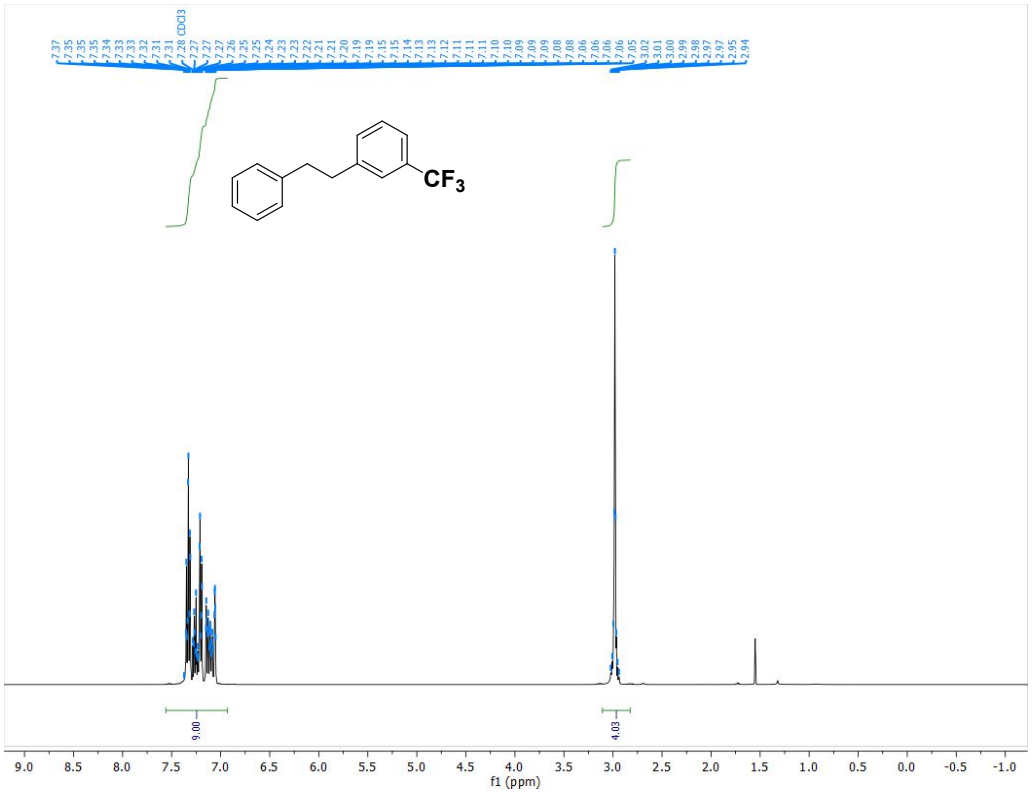

CN
147.28
140.66
132.17
129.38
128.52
128.47
126.30
119.13
109.88
77.47
77.15
76.83
37.93
37.24
f1 (ppm)

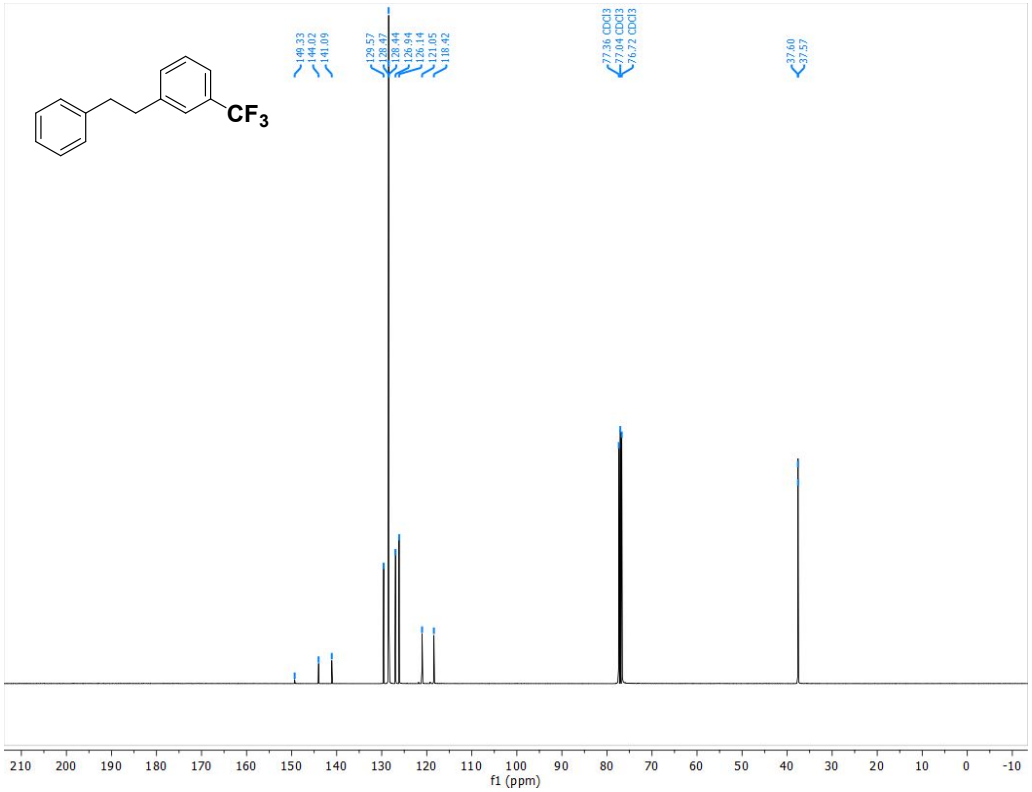
Compound **3e**

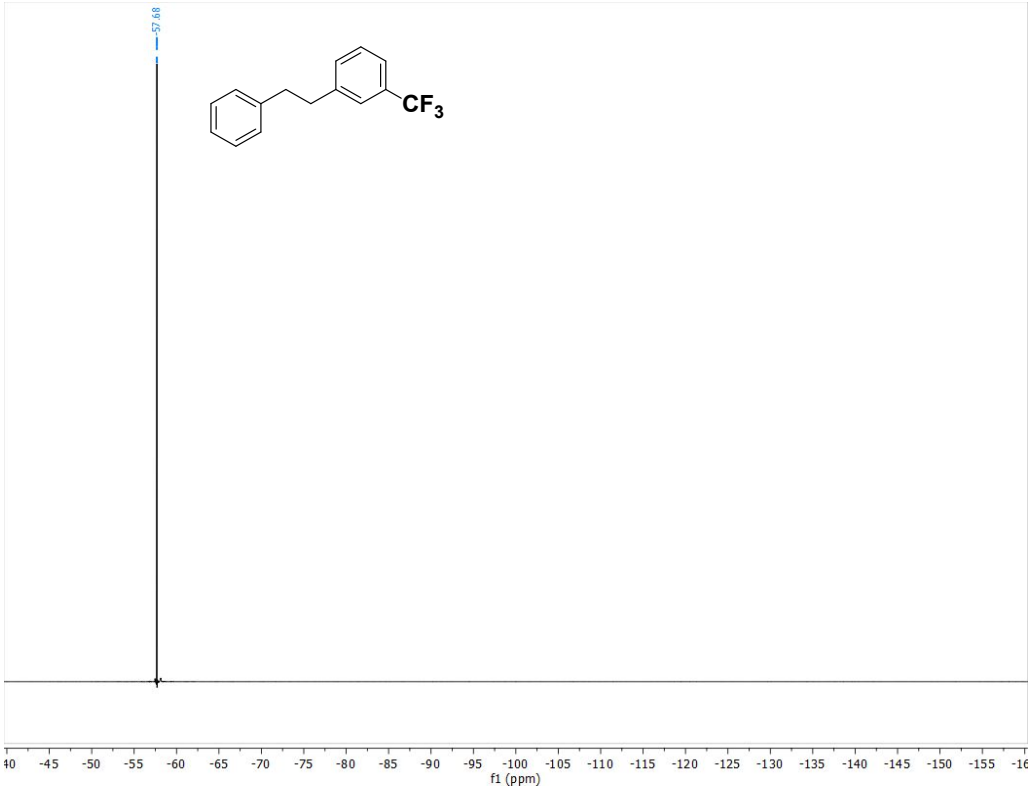

7.61
7.60
7.59
7.59
7.58
7.57
7.57
7.56
7.55
7.55
7.54
7.54
7.53
7.53
7.53
7.53
7.51
7.49
7.49
7.49
CDCl3
7.48
7.47
7.47
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.42
7.41
7.40
7.40
3.22
3.21
3.20
3.19
3.18
3.18
3.17
3.17
3.15
3.14
3.14
3.13
1.58
4.04
5.09
3.95
9.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 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)


148.78
142.09
138.85
128.45
128.39
128.08
125.92
125.29
77.38
77.06
76.74
37.96
37.44
34.42
31.47
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)

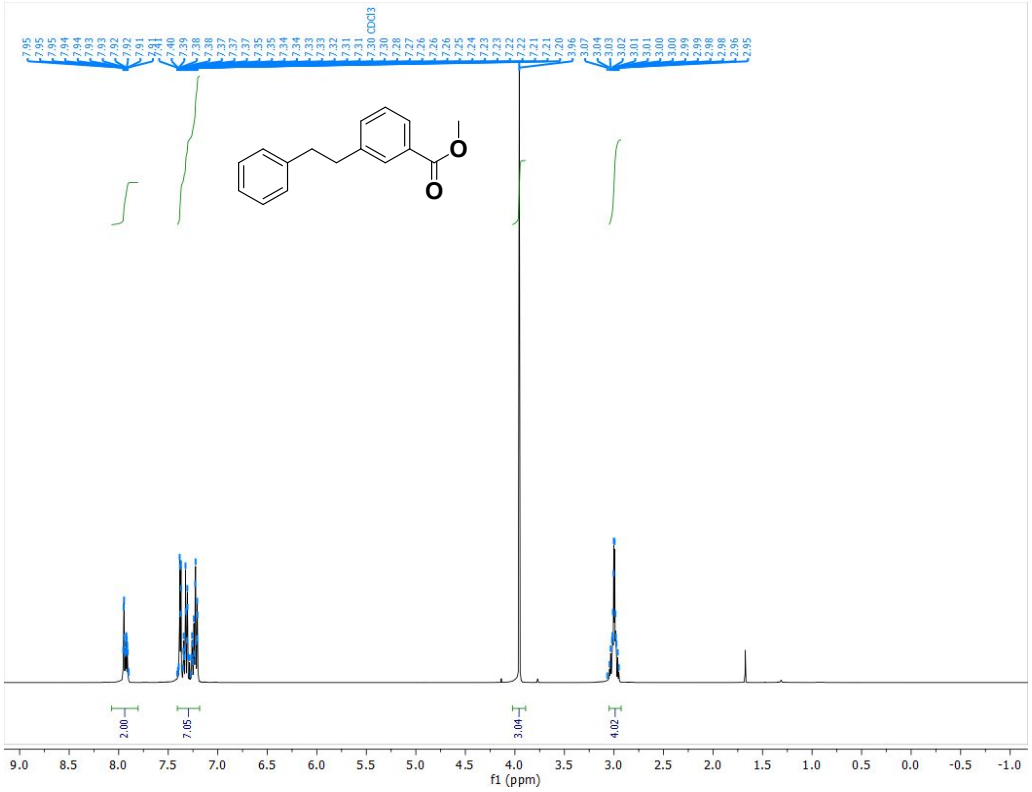
Compound **3f**

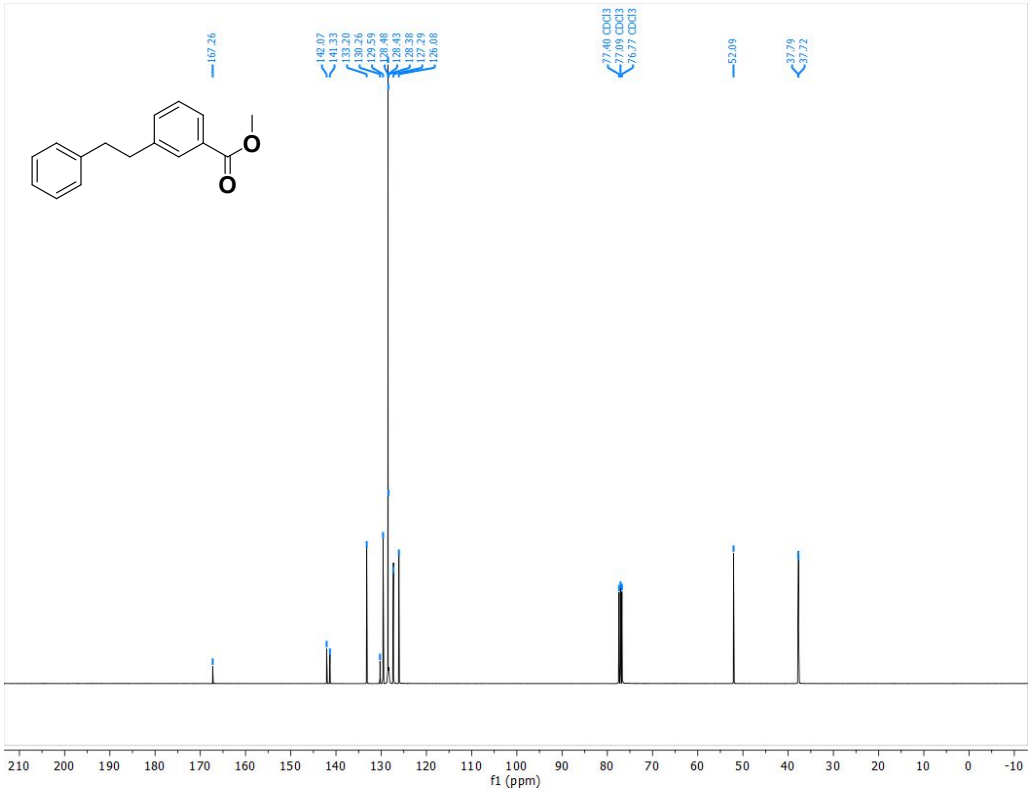




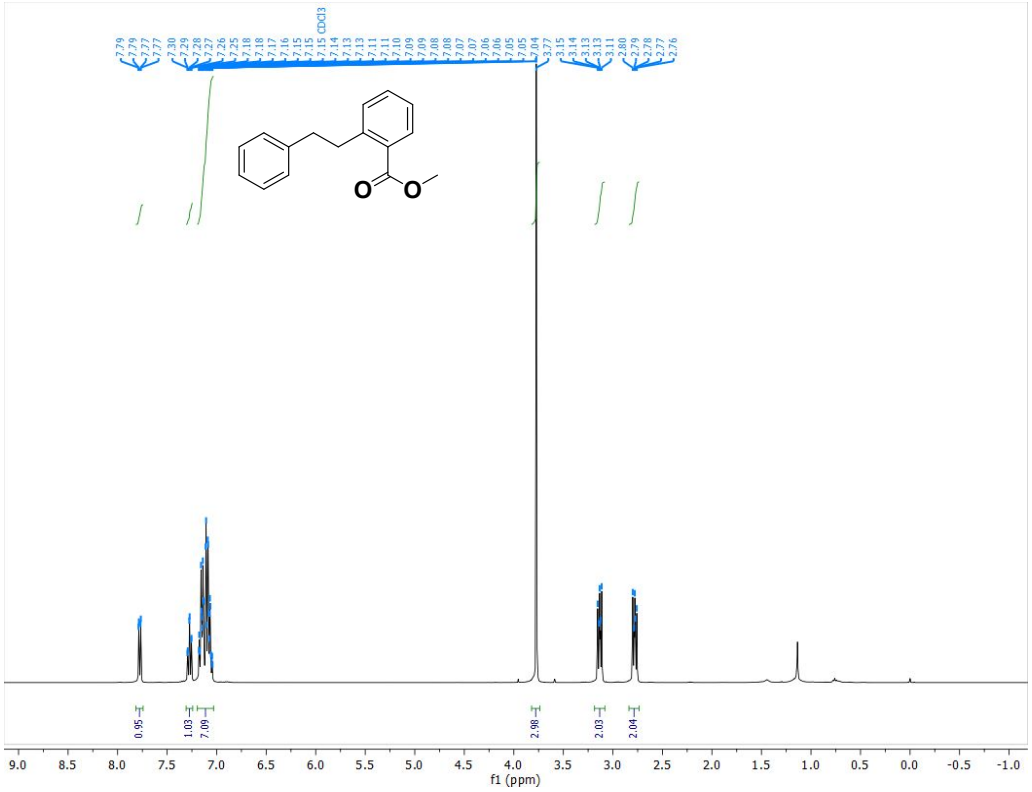

-57.68
CF3
40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -16
f1 (ppm)

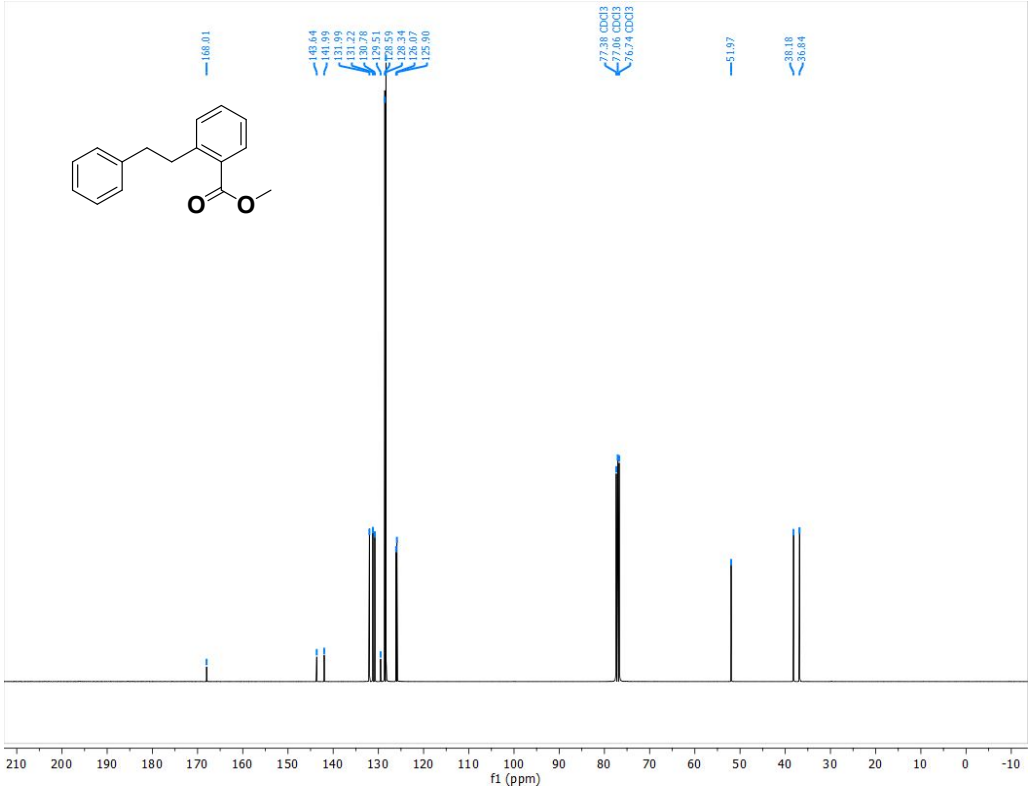
Compound **3g**


O
O
2.00
7.05
3.04
4.02
f1 (ppm)

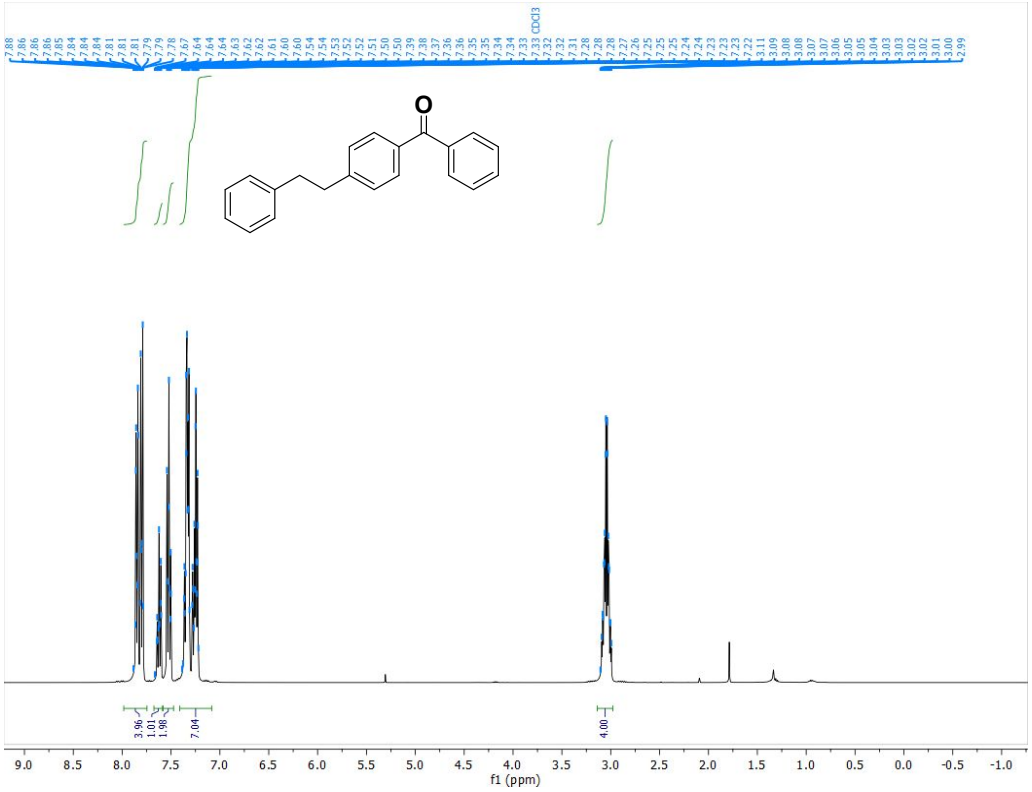

O
O
167.26
142.07
141.33
133.20
130.26
128.55
128.48
128.43
128.38
127.29
126.08
77.40 CDCl3
77.09 CDCl3
76.77 CDCl3
52.09
37.79
37.72
f1 (ppm)

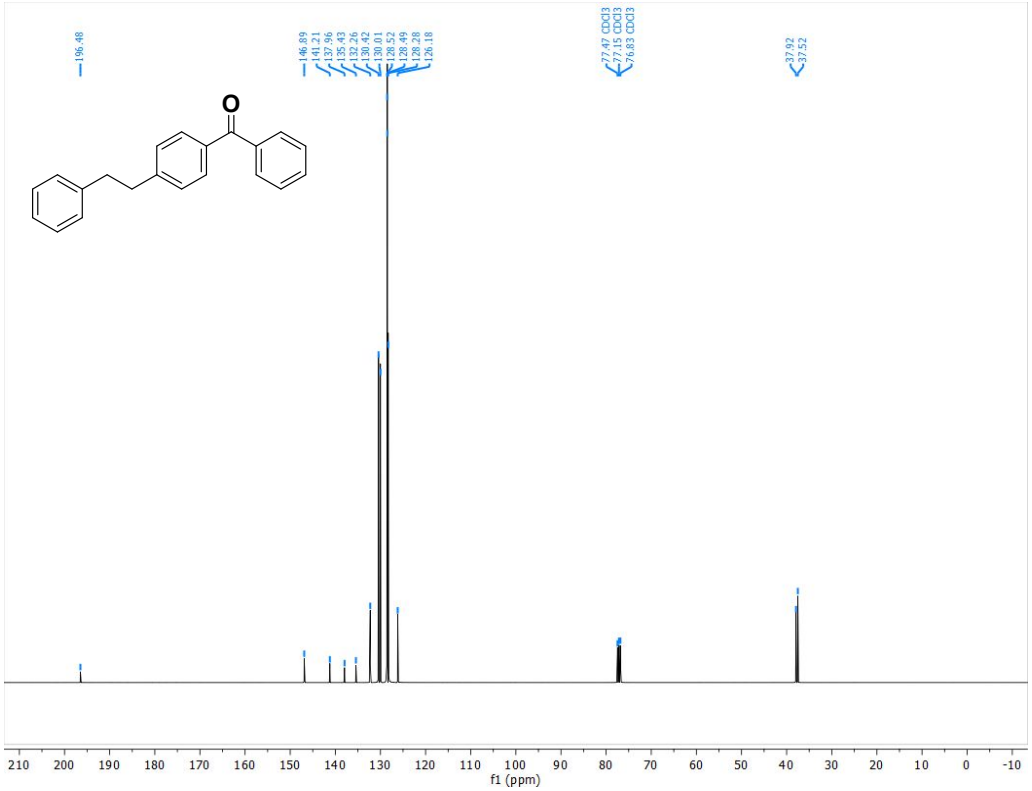
Compound **3h**


7.79
7.79
7.77
7.77
7.30
7.29
7.28
7.27
7.26
7.25
7.18
7.18
7.17
7.16
7.15
7.15
7.15 CDCl3
7.14
7.13
7.13
7.11
7.11
7.10
7.09
7.09
7.08
7.08
7.07
7.07
7.06
7.06
7.05
7.05
7.04
3.77
3.15
3.14
3.13
3.13
3.11
3.00
2.79
2.78
2.77
2.76
O
O
0.95
1.03
7.09
2.98
2.03
2.04
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)

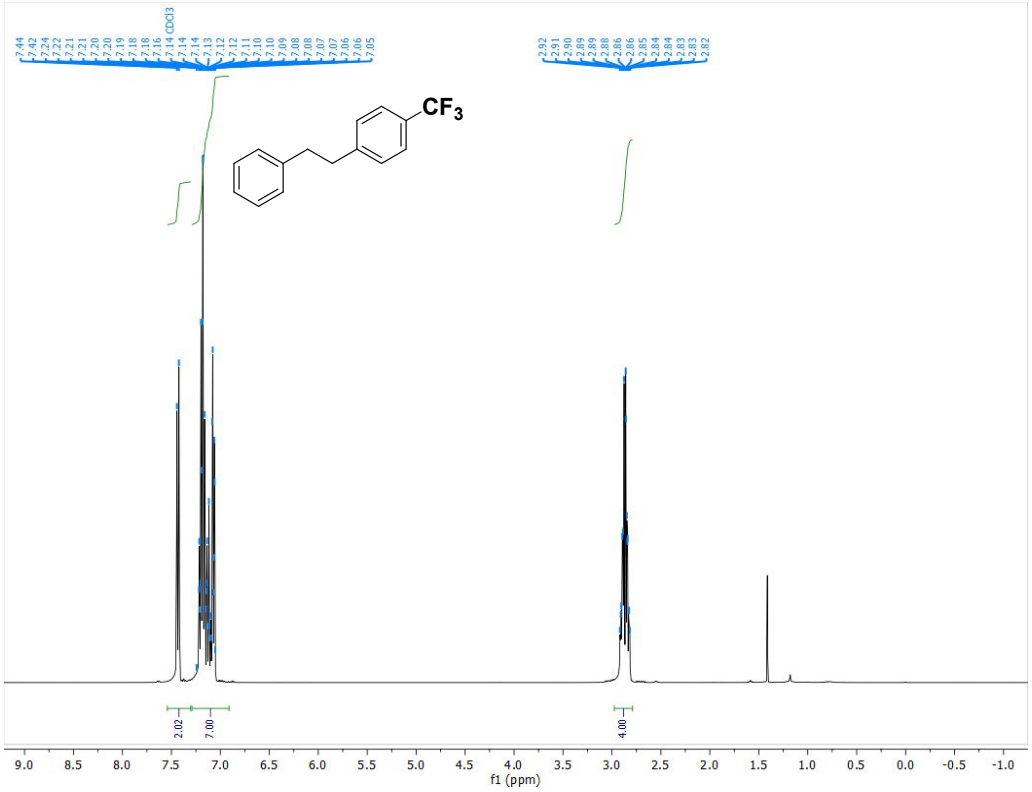

168.01
143.64
141.99
131.99
131.22
130.78
129.51
128.59
128.34
126.87
125.90
77.38 CDCl3
77.06 CDCl3
76.74 CDCl3
51.97
38.18
36.84
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

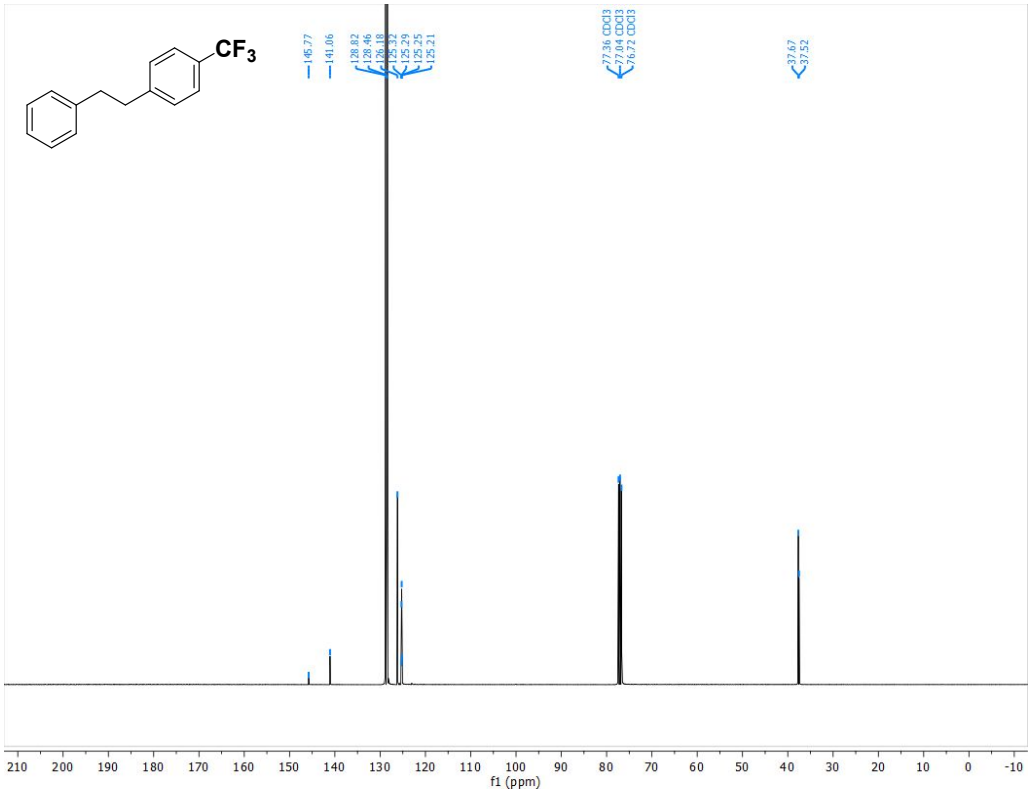
Compound **3i**

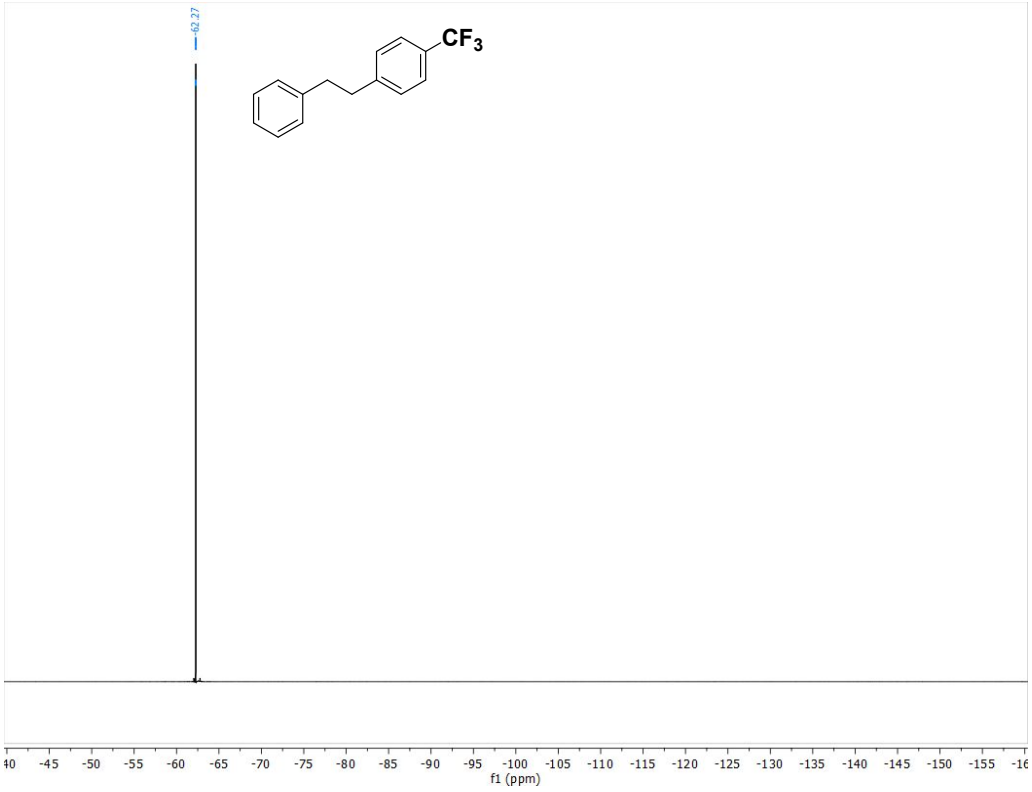

O
3.96
1.01
1.98
7.04
4.00
f1 (ppm)


O
196.48
146.89
137.96
135.43
132.26
130.42
130.01
128.52
128.49
128.28
126.18
77.47 CDCl3
77.15 CDCl3
76.83 CDCl3
37.92
37.52
f1 (ppm)

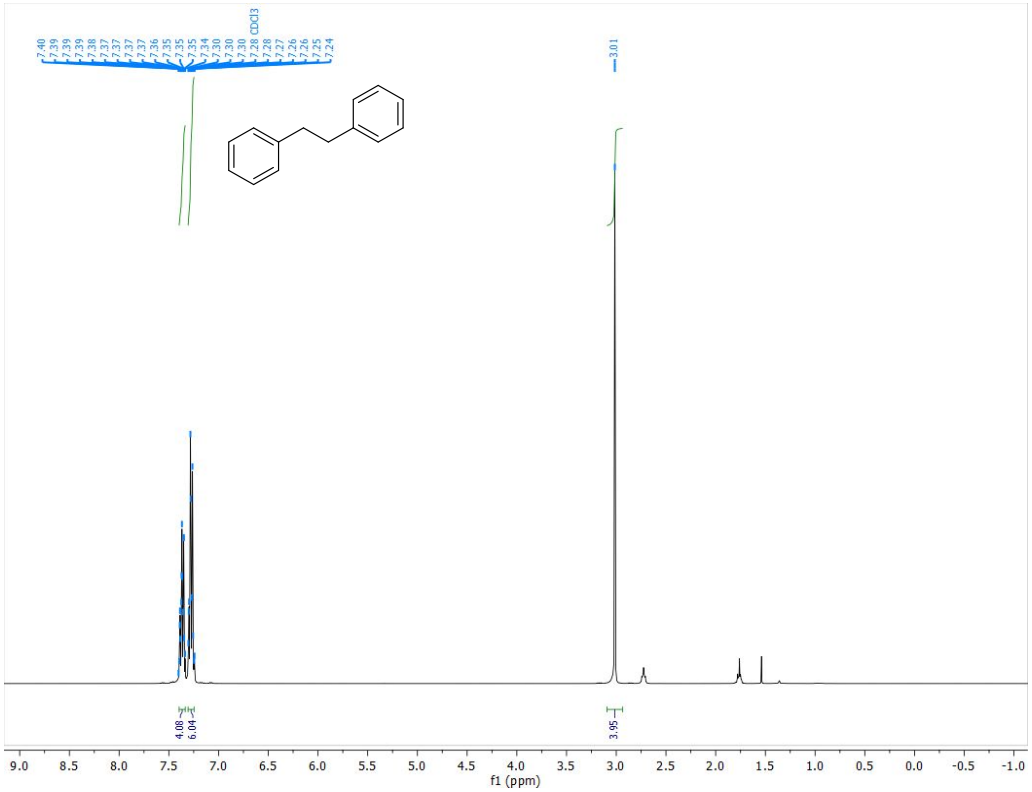
Compound **3j**

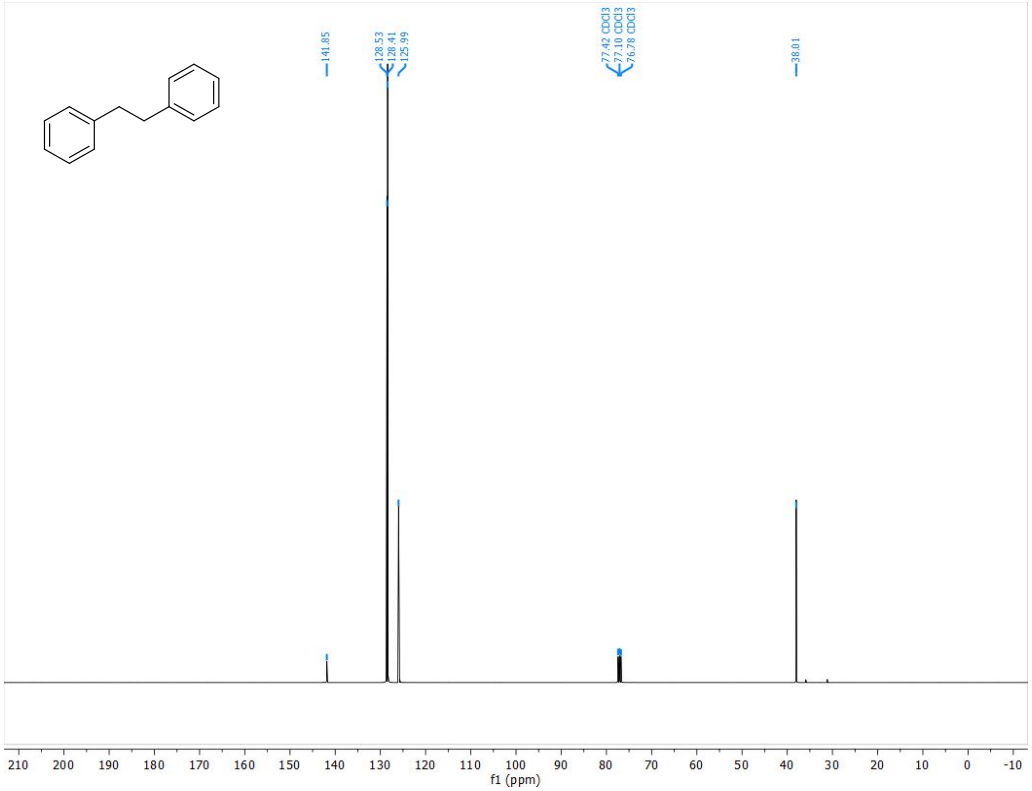




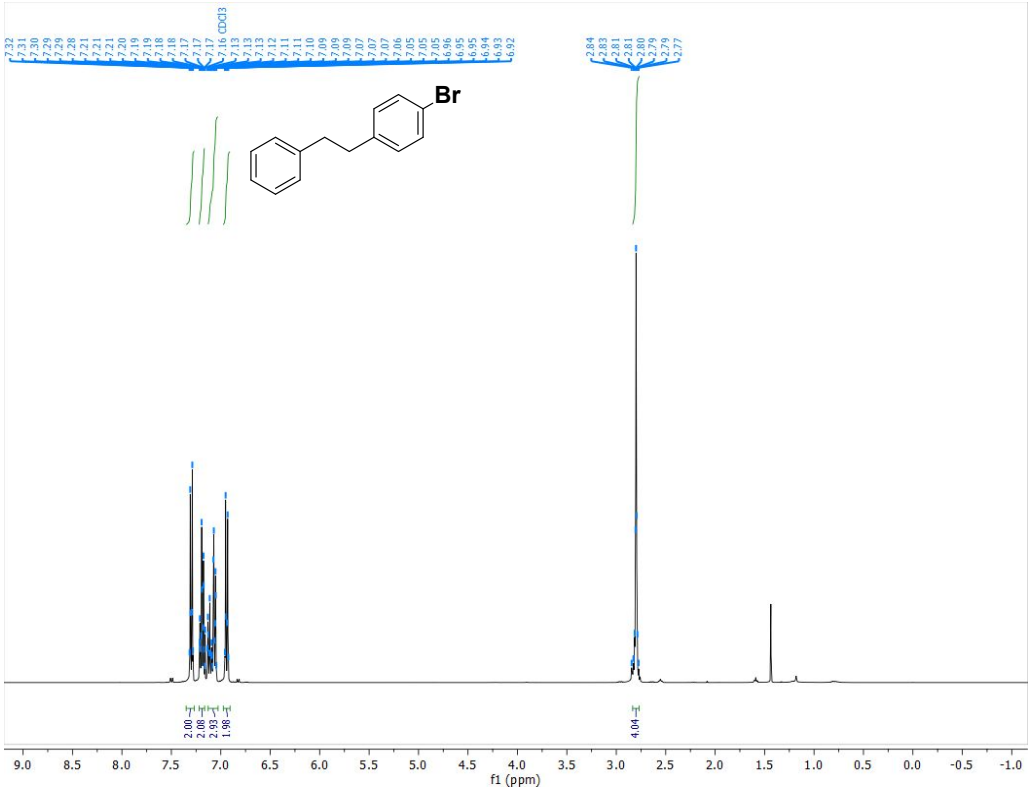

62.27
CF3
40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -16
f1 (ppm)

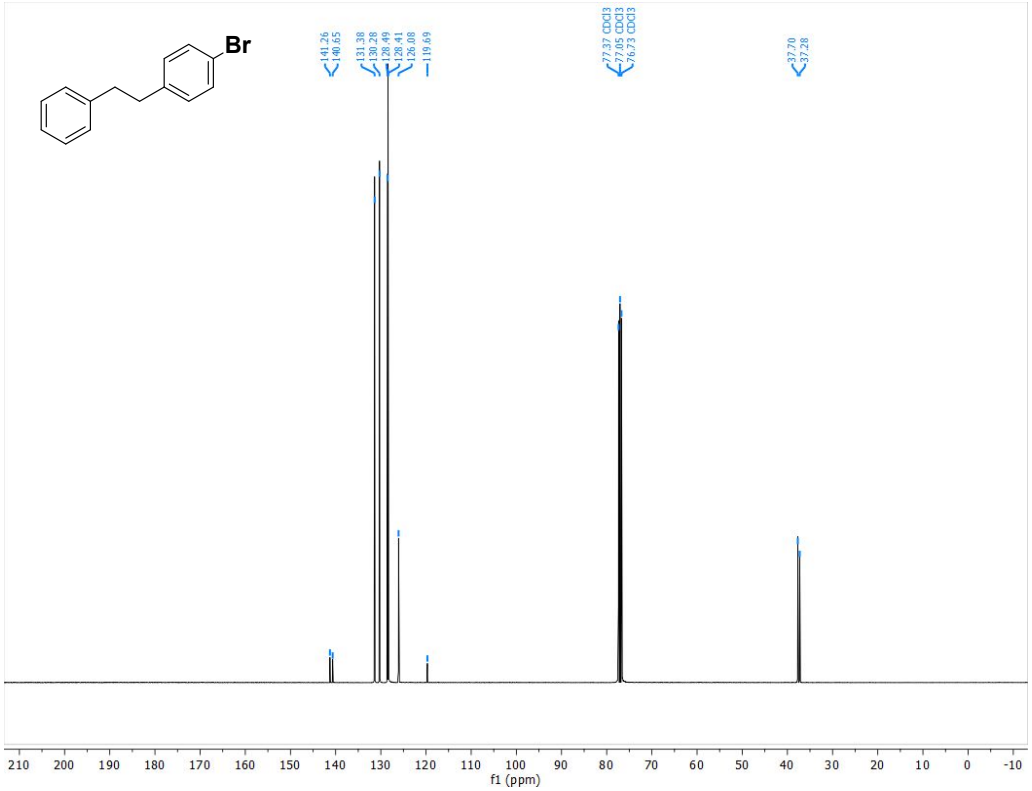
Compound **3k**


7.40
7.39
7.39
7.39
7.38
7.37
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.34
7.30
7.30
7.28 CDCl3
7.28
7.27
7.26
7.26
7.25
7.24
3.01
4.08
6.04
3.95
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)

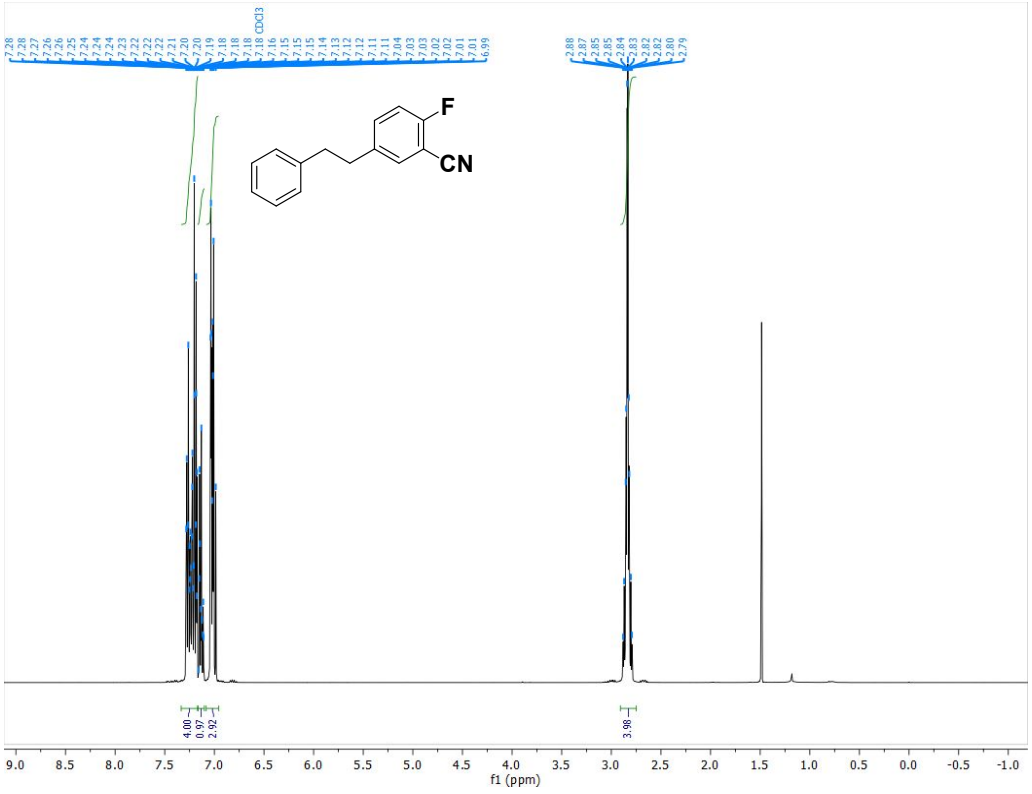

141.85
128.53
128.41
125.99
77.42 CDCl3
77.10 CDCl3
76.78 CDCl3
38.01
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

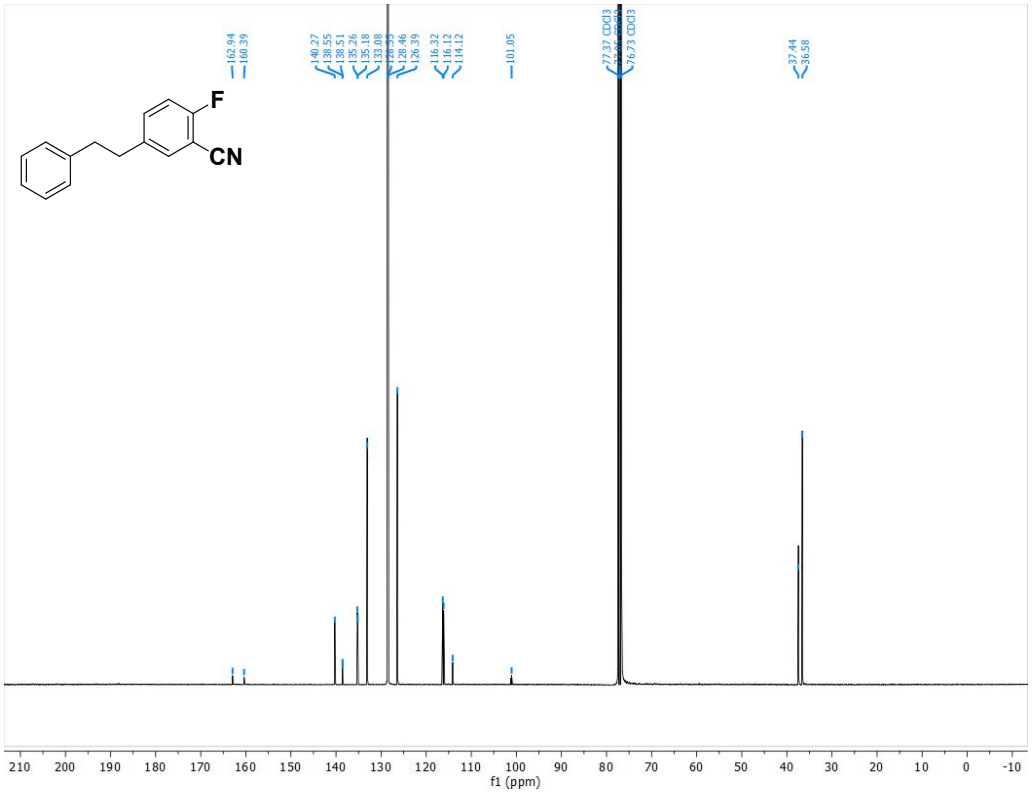
Compound **3l**

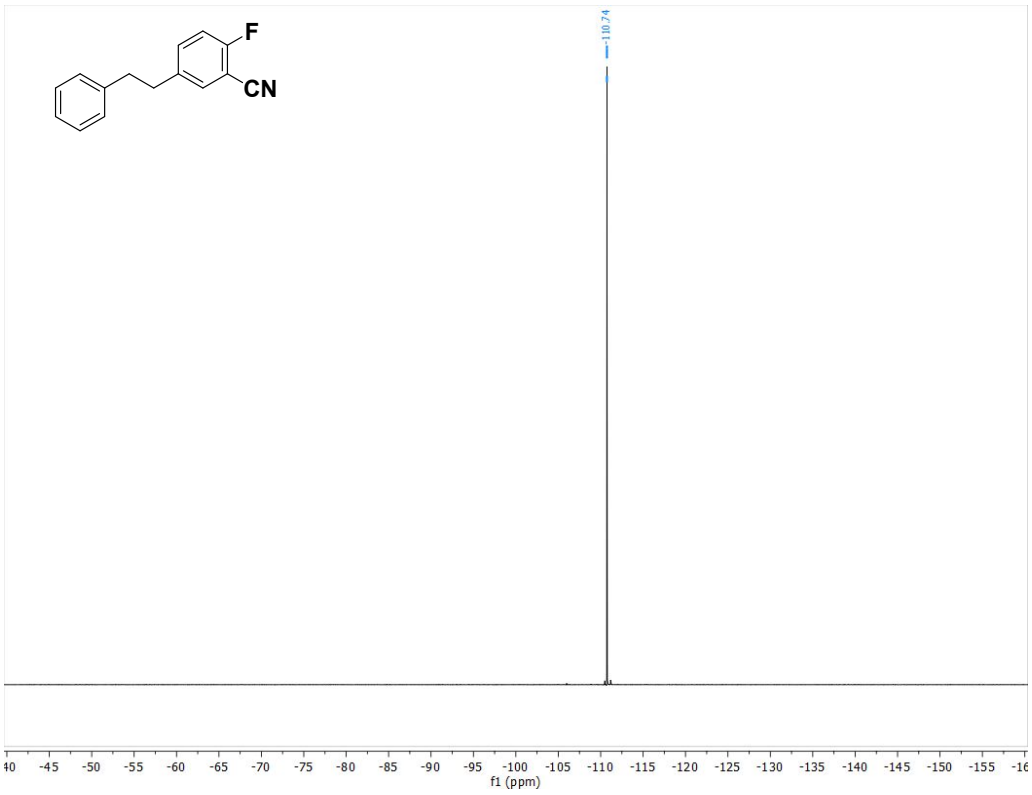




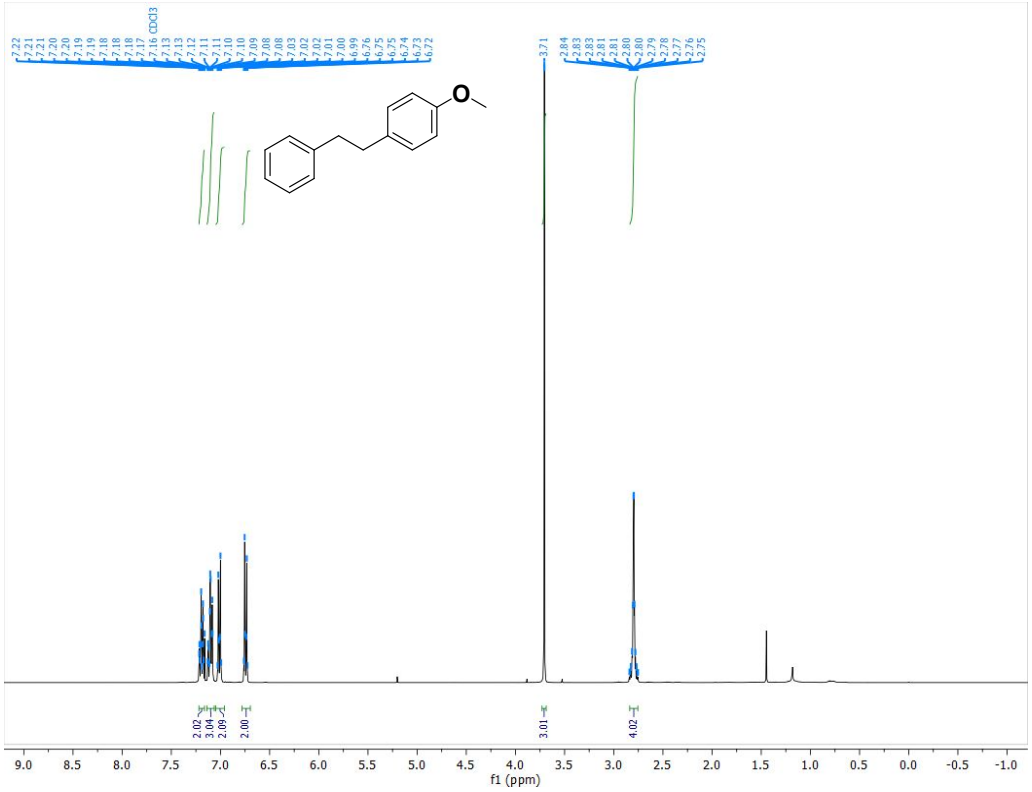
Compound **3m**

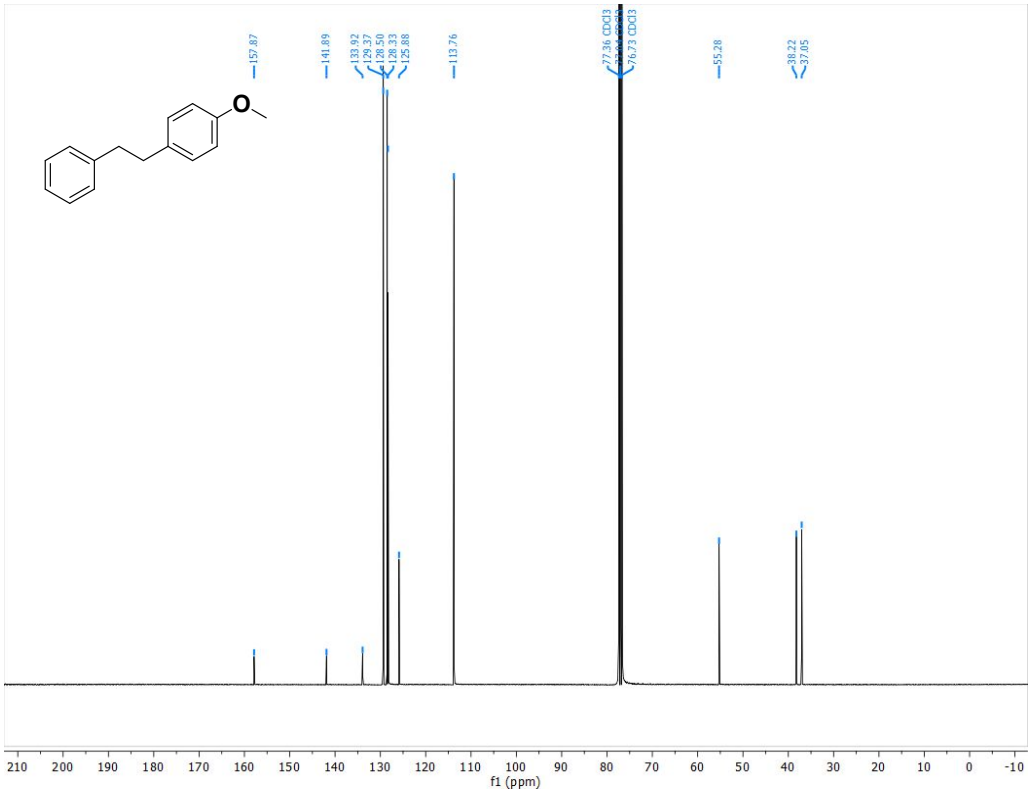




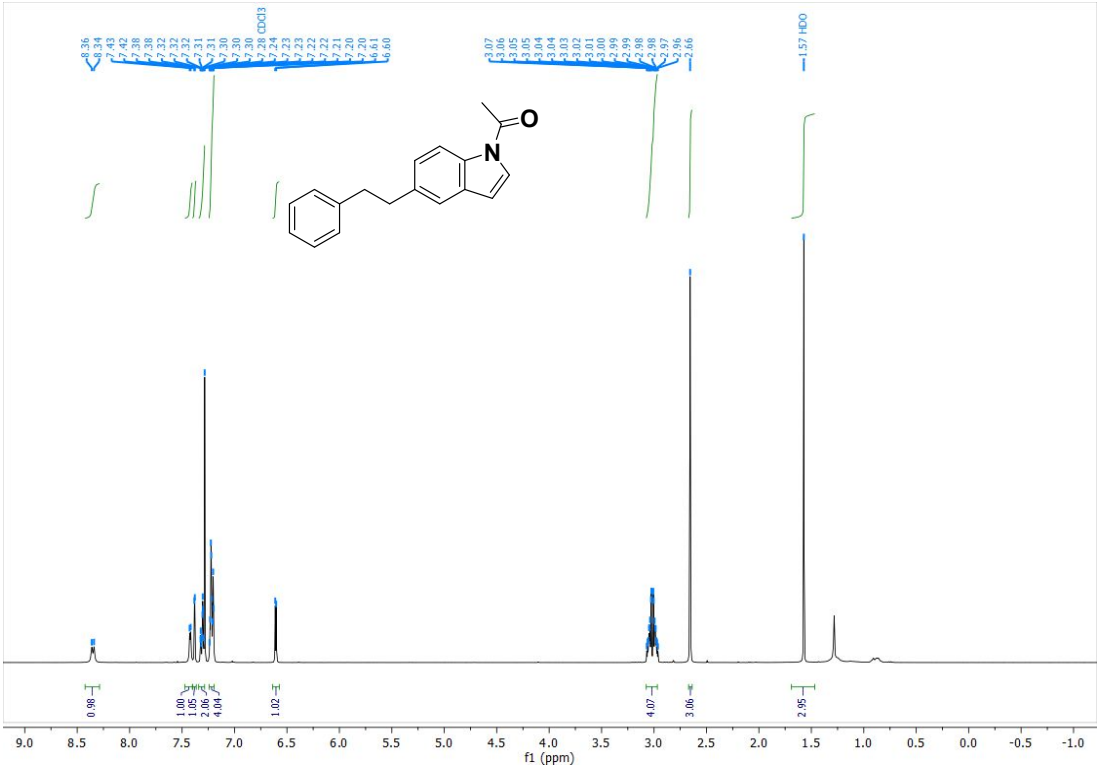

F
CN
-110.74
40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -16
f1 (ppm)

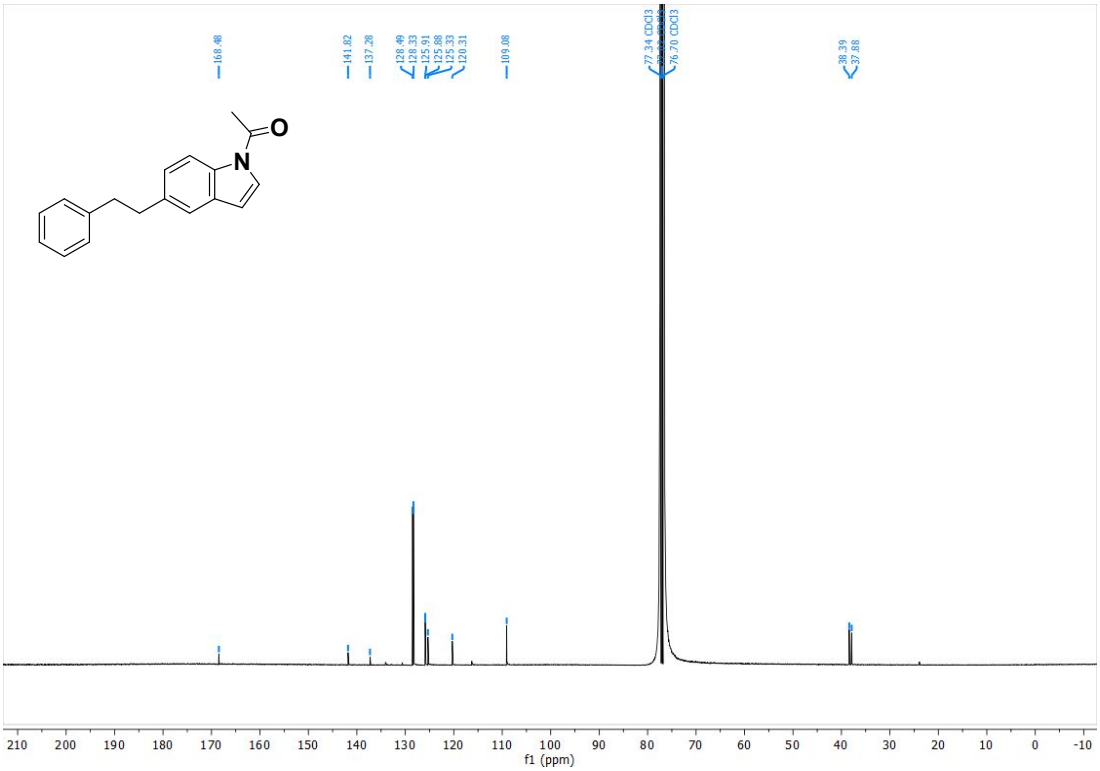
Compound **3n**


7.22
7.21
7.21
7.20
7.20
7.19
7.19
7.18
7.18
7.18
7.17
7.16 CDCl3
7.13
7.12
7.11
7.11
7.10
7.10
7.09
7.08
7.08
7.03
7.02
7.02
7.01
7.00
6.99
6.76
6.75
6.75
6.74
6.73
6.72
3.71
2.84
2.83
2.83
2.81
2.81
2.80
2.80
2.79
2.78
2.77
2.76
2.75
O
2.02
3.04
2.09
2.00
3.01
4.02
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)

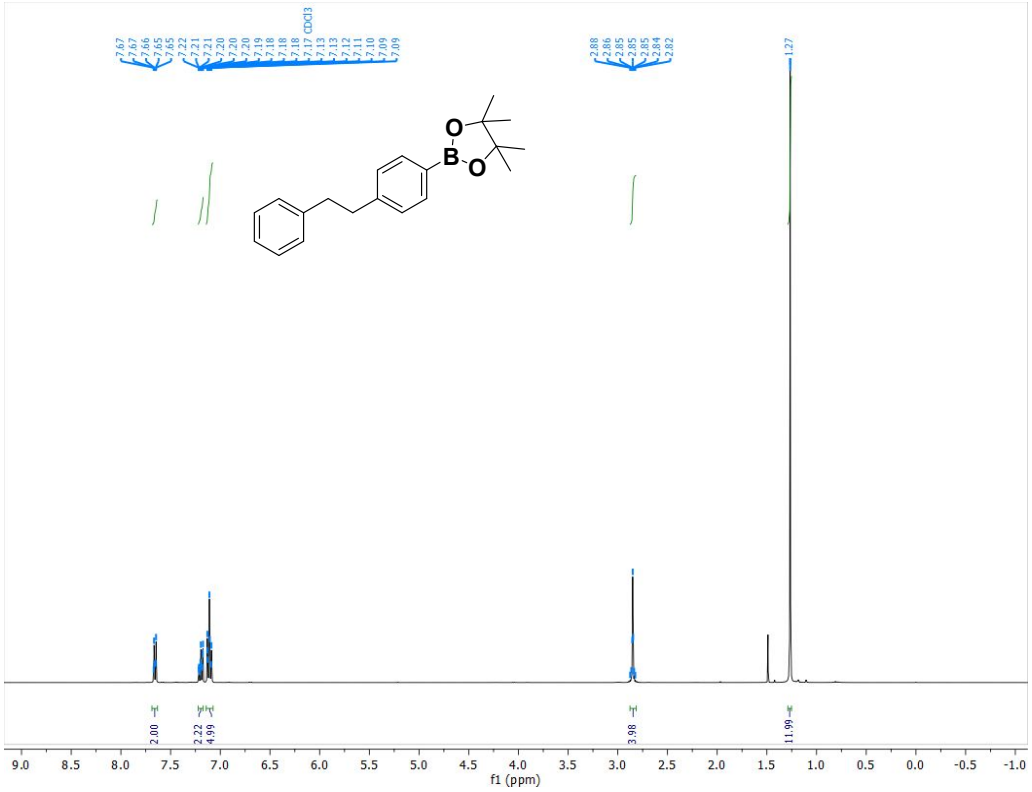

157.87
141.89
133.92
129.37
128.50
128.33
125.88
113.76
77.36 CDCl3
77.04 CDCl3
76.73 CDCl3
55.28
39.22
37.65
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

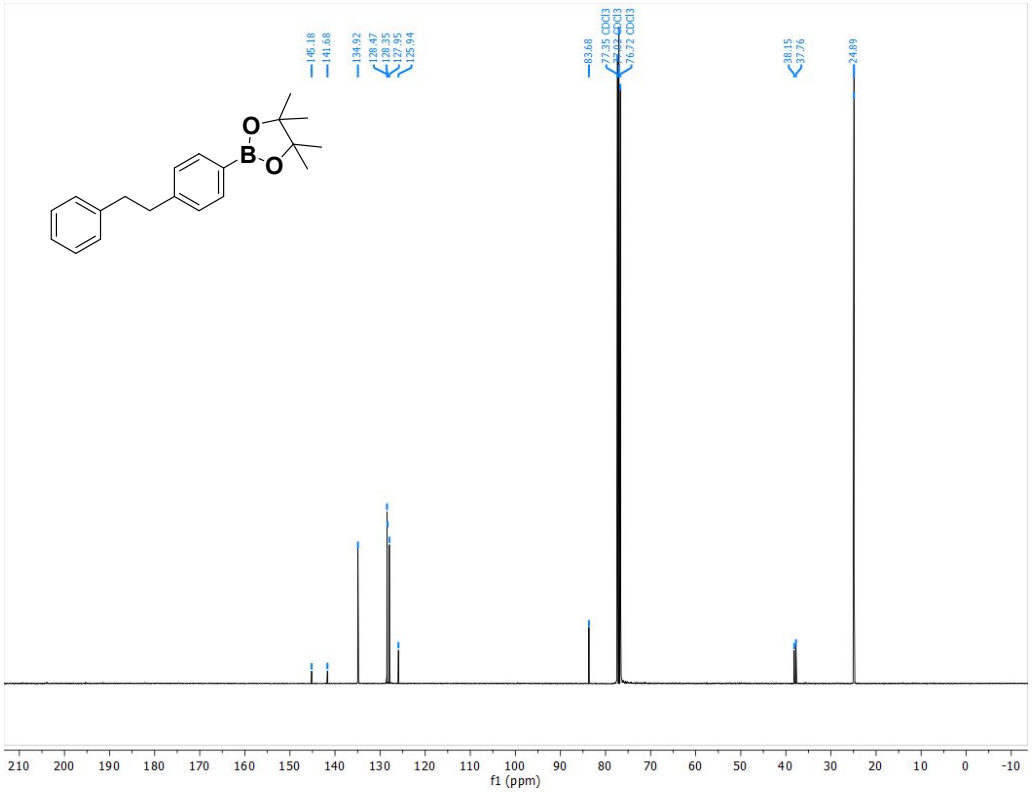
Compound **3o**


8.36
8.34
8.18
7.42
7.38
7.32
7.32
7.32
7.31
7.31
7.30
7.30
7.28 CDCl3
7.24
7.23
7.22
7.22
7.21
7.20
7.20
6.61
6.60
3.07
3.06
3.05
3.05
3.04
3.04
3.03
3.02
3.01
3.00
2.99
2.99
2.98
2.98
2.97
2.96
2.66
1.57 HDO
O
N
0.98
1.00
1.05
2.06
4.04
1.02
4.07
3.06
2.95
f1 (ppm)

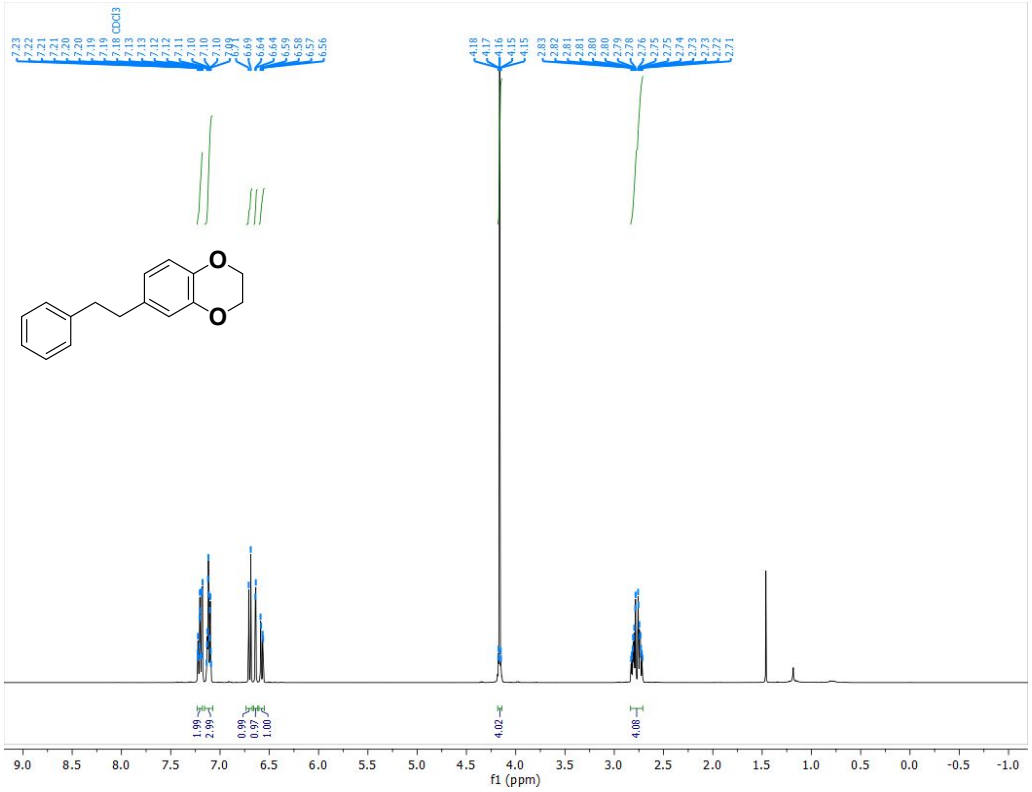

168.48
141.82
137.28
128.49
128.33
125.91
125.88
125.33
120.31
109.08
77.34 CDCl3
76.70 CDCl3
38.39
37.88
O
N
f1 (ppm)

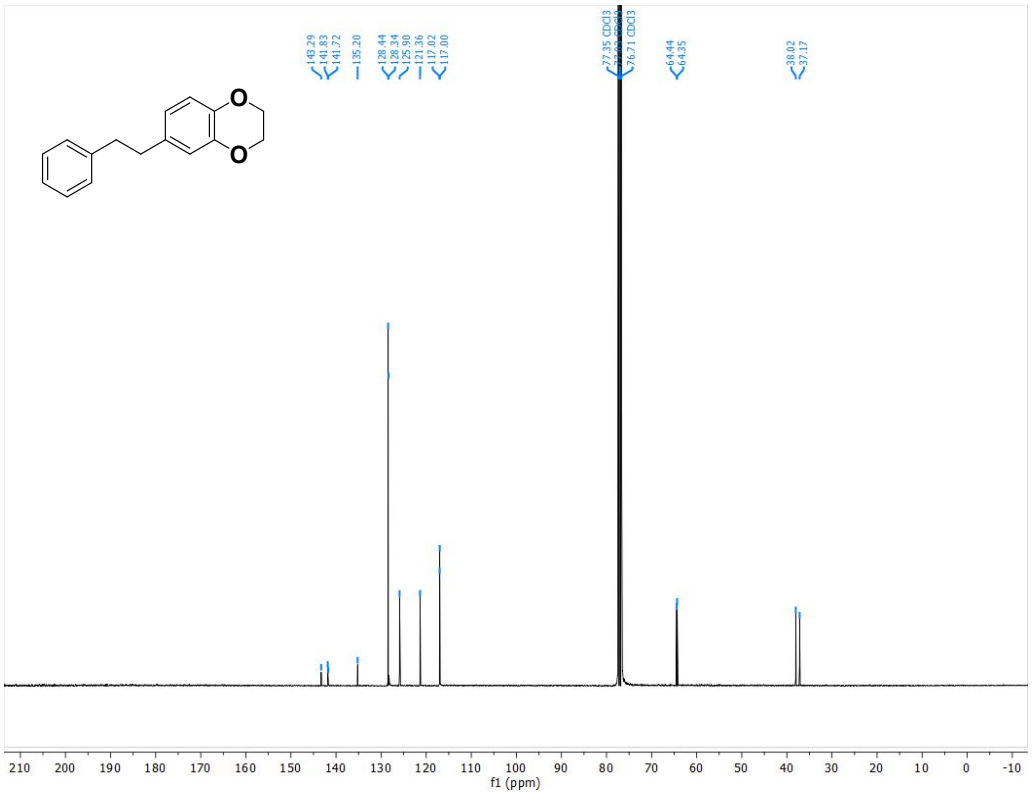
Compound **3p**


7.67
7.67
7.66
7.65
7.65
7.22
7.21
7.21
7.20
7.20
7.20
7.19
7.18
7.18
7.18
7.17 CDCl3
7.13
7.13
7.12
7.11
7.10
7.09
7.09
2.88
2.86
2.85
2.85
2.85
2.84
2.82
1.27
2.00
2.22
4.99
3.98
11.99
f1 (ppm)

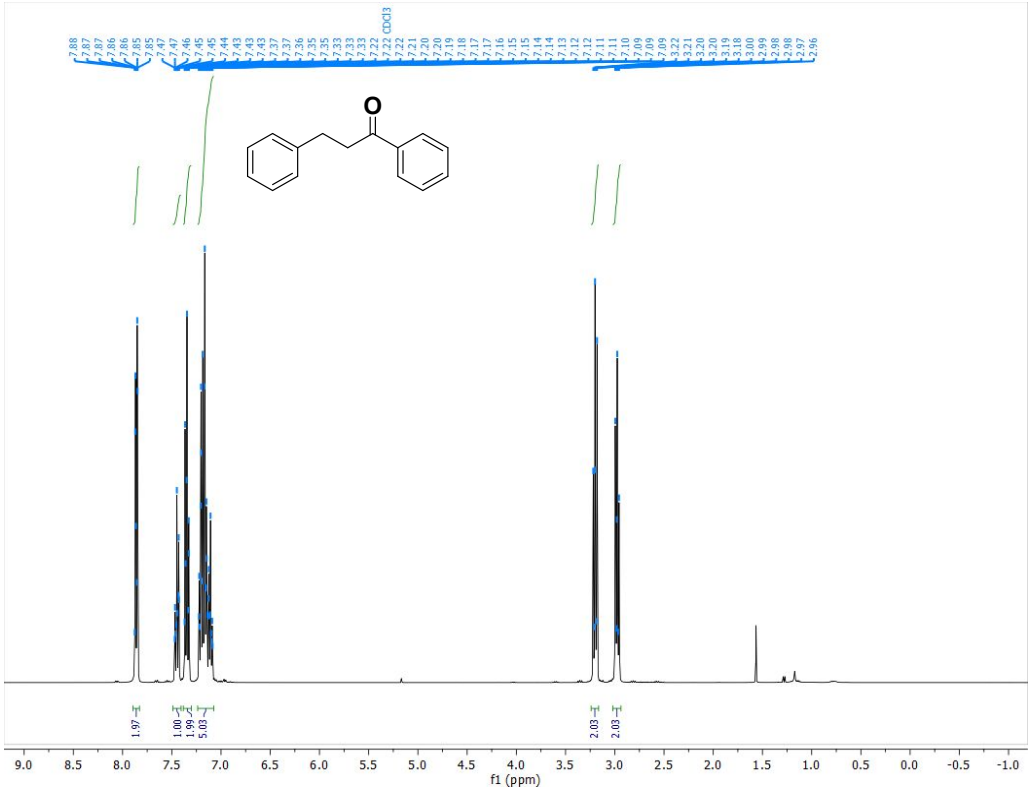

145.18
141.68
134.92
128.47
128.35
127.95
125.94
83.68
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
38.15
37.76
24.89
f1 (ppm)

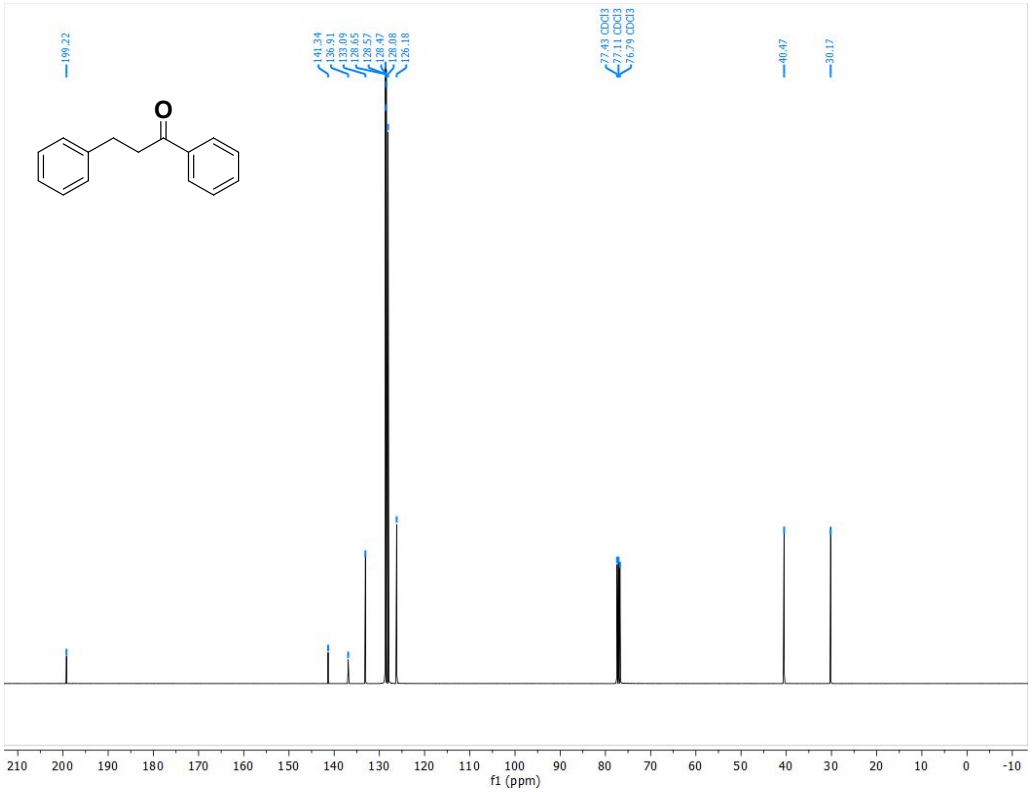
Compound **3q**


7.23
7.22
7.21
7.21
7.20
7.20
7.19
7.19
7.18 CDCl3
7.13
7.13
7.12
7.12
7.11
7.10
7.10
7.10
7.09
6.91
6.69
6.64
6.64
6.59
6.58
6.57
6.56
4.18
4.17
4.16
4.15
4.15
2.83
2.82
2.81
2.81
2.80
2.80
2.79
2.78
2.76
2.75
2.75
2.74
2.73
2.73
2.72
2.71
O
O
1.99
2.99
0.99
0.97
1.00
4.02
4.08
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)

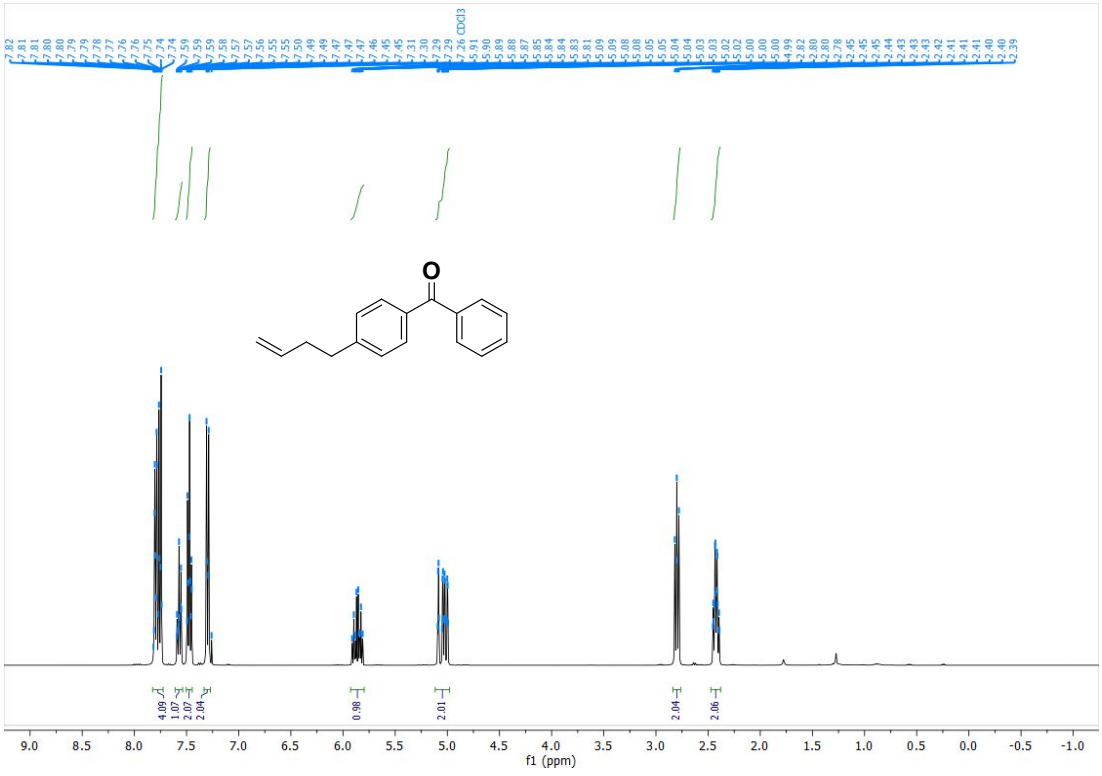

143.29
141.83
141.72
135.20
128.44
128.34
125.90
121.36
117.02
117.00
77.35 CDCl3
77.03
76.71 CDCl3
64.44
64.35
38.02
37.17
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

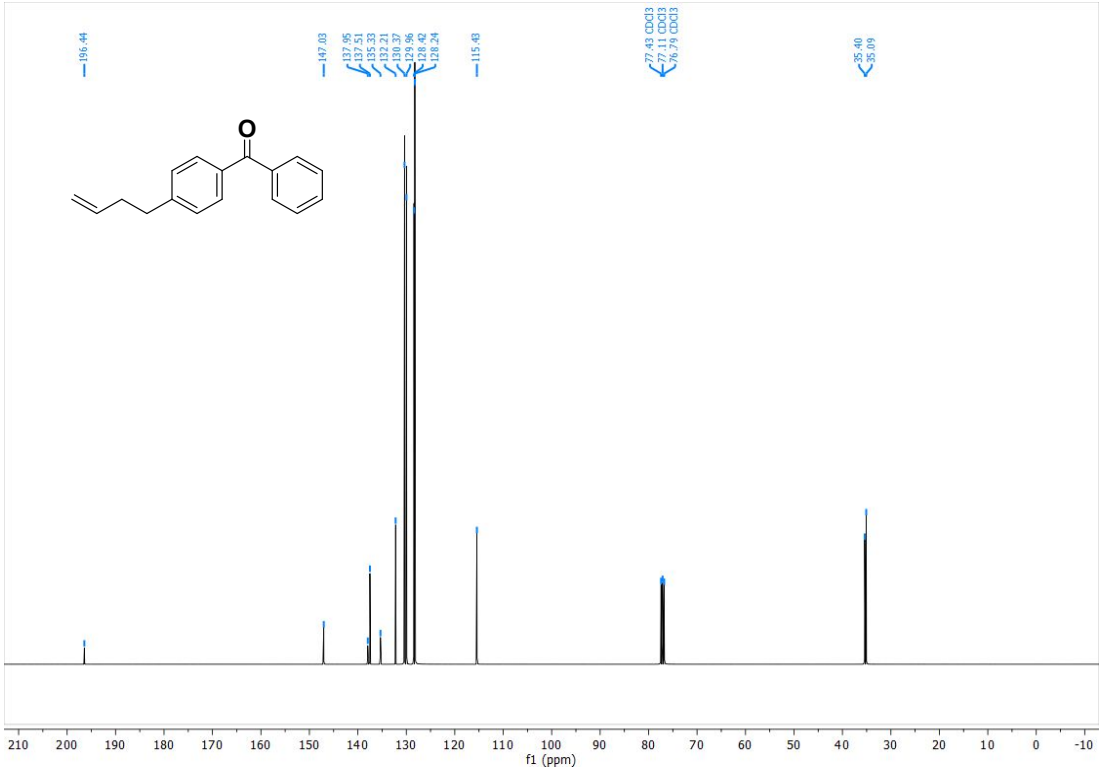
Compound **3t**


CDCl3
O
1.97
1.00
1.99
5.03
2.03
2.03
f1 (ppm)

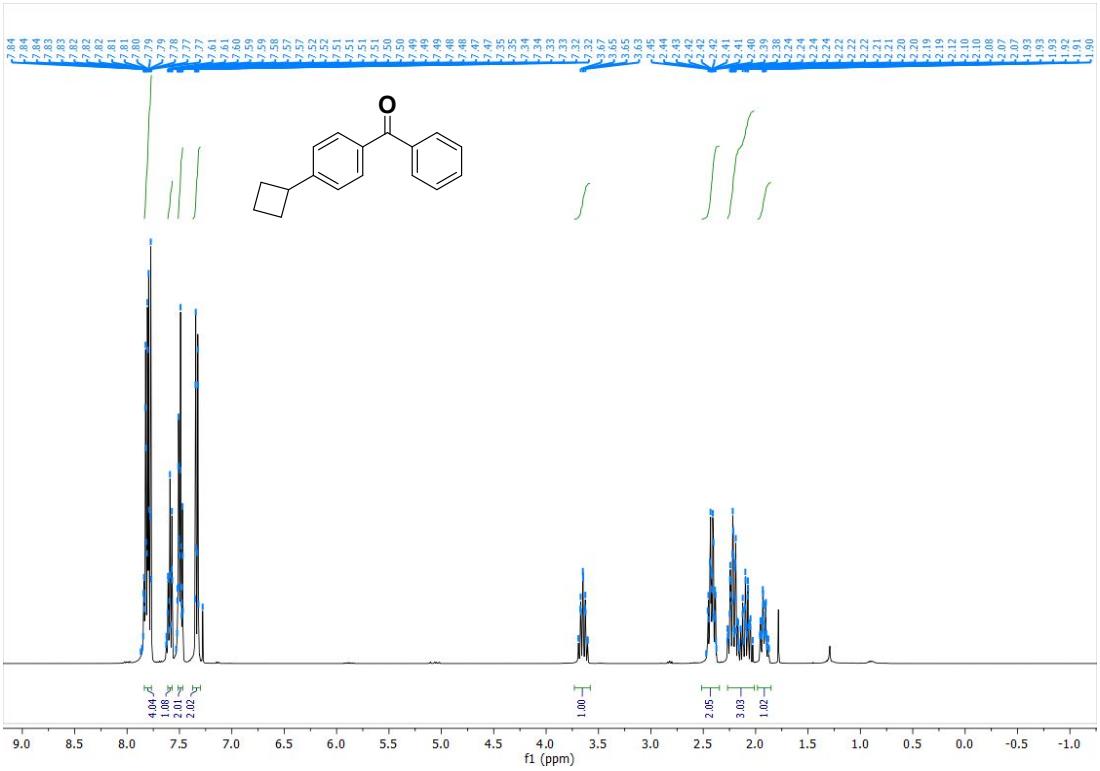

199.22
141.34
136.91
133.00
128.65
128.57
128.47
128.08
126.18
77.43 CDCl3
77.11 CDCl3
76.79 CDCl3
40.47
30.17
O
f1 (ppm)

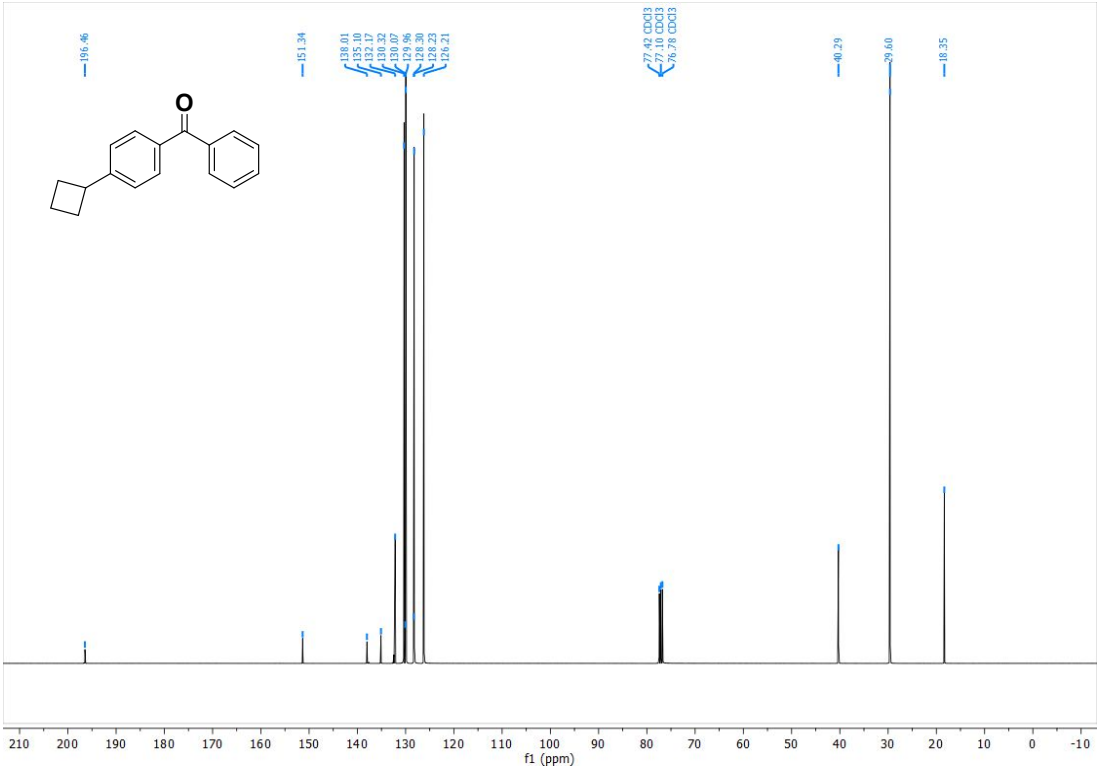
Compound **5a**


O
4.09
1.07
2.07
2.04
0.98
2.01
2.04
2.06
f1 (ppm)

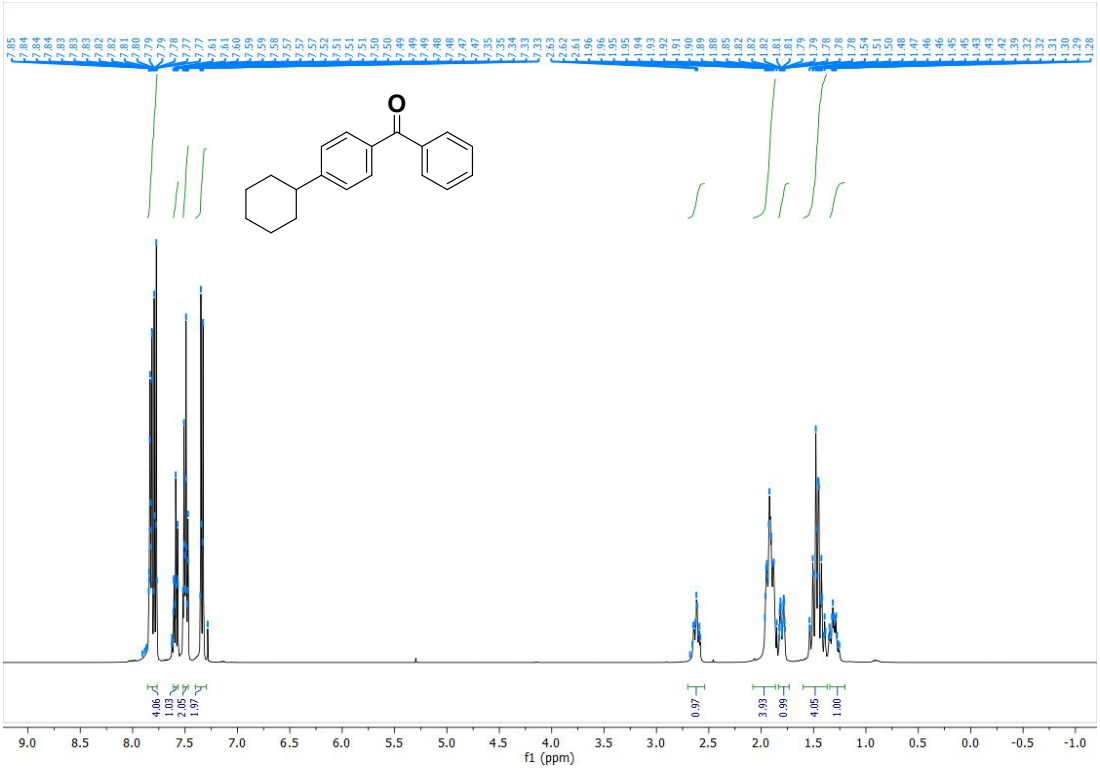

196.44
147.03
137.95
137.51
135.33
132.21
130.37
129.96
128.43
128.24
115.43
77.43 CDCl3
77.11 CDCl3
76.79 CDCl3
35.40
35.09
O
f1 (ppm)

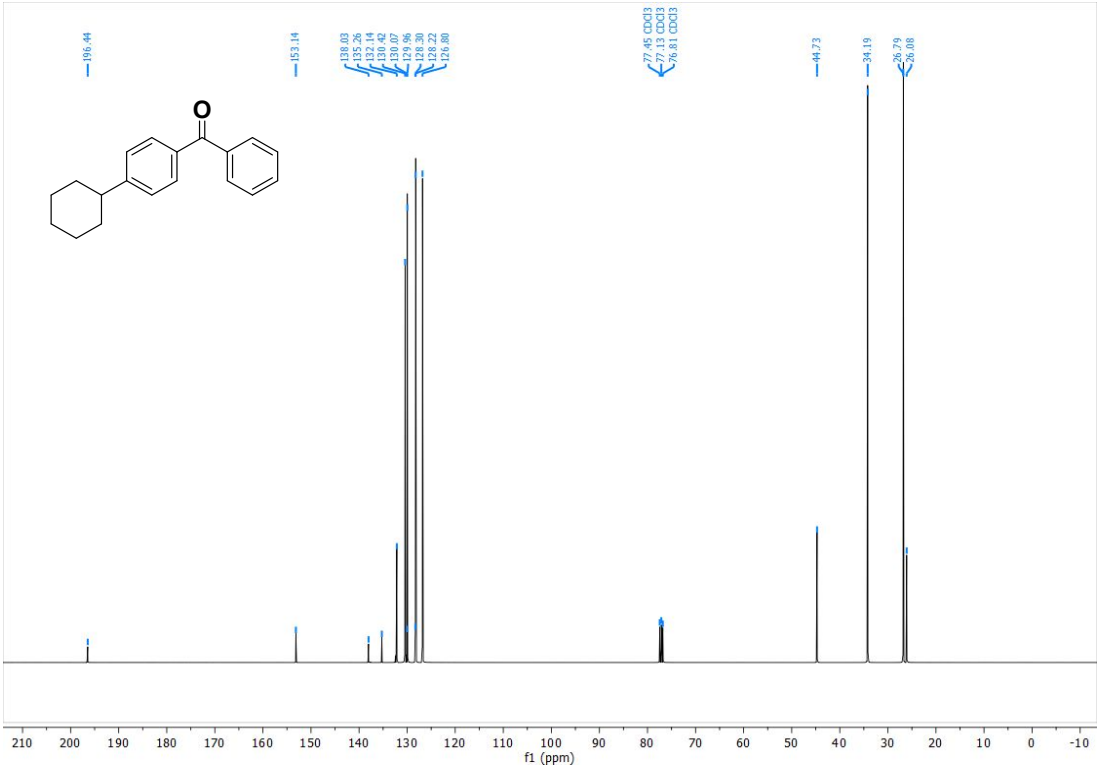
Compound **5b**


O
4.04
1.08
2.01
2.02
1.00
2.05
3.03
1.02
f1 (ppm)

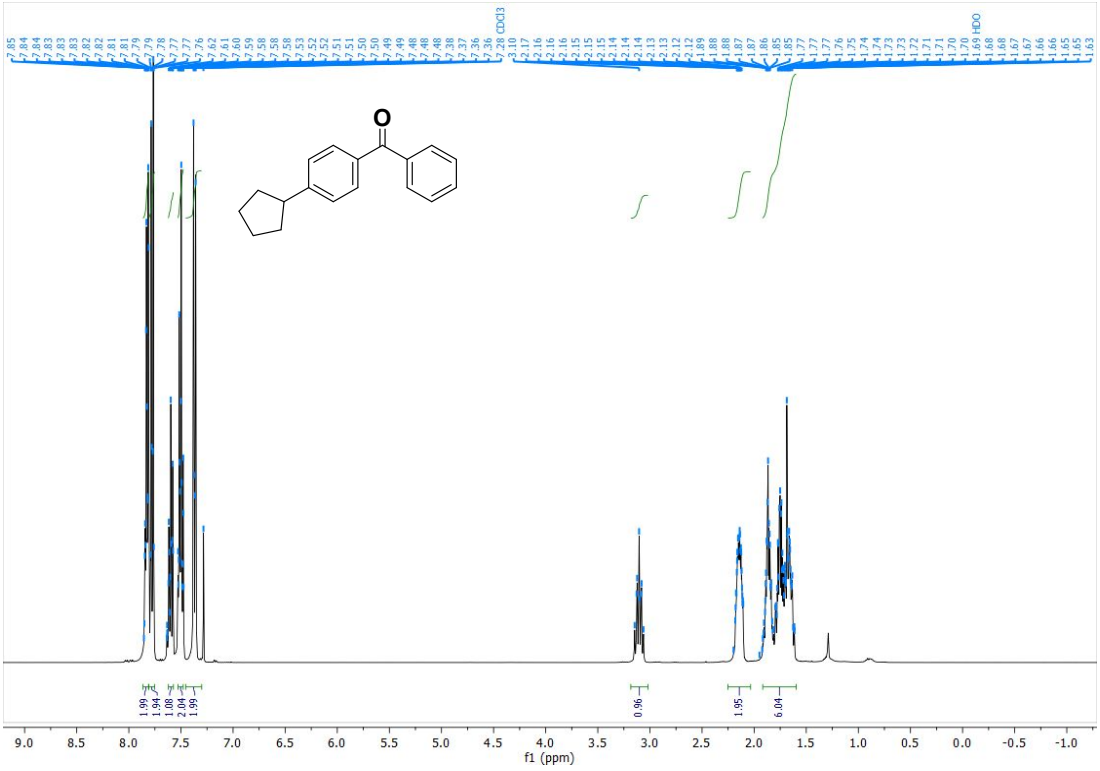

O
196.46
151.34
138.01
135.10
132.17
130.32
130.07
129.96
128.80
128.23
126.21
77.42 CDCl3
77.10 CDCl3
76.78 CDCl3
40.29
29.60
18.35
f1 (ppm)

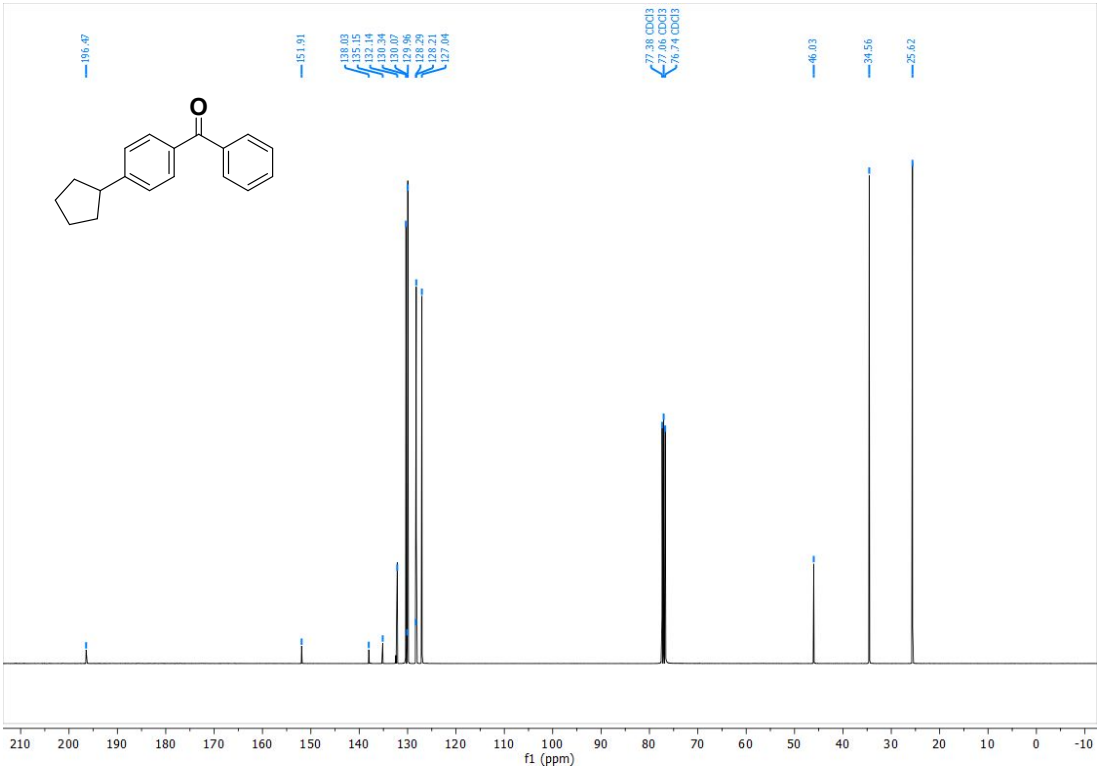
Compound **5c**


O
4.06
1.03
1.05
1.97
0.97
3.93
0.99
4.05
1.00
f1 (ppm)

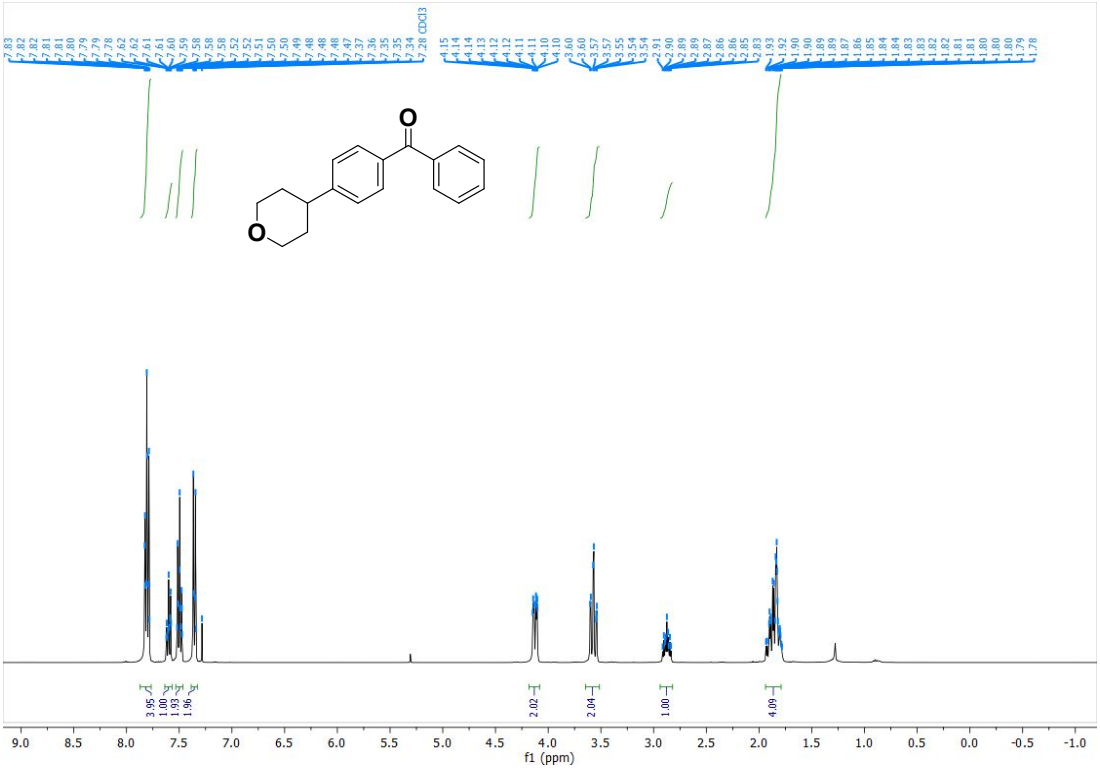

196.44
153.14
138.03
135.26
132.14
130.42
130.07
129.96
128.30
128.22
126.80
77.45 CDCl3
77.13 CDCl3
76.81 CDCl3
44.73
34.19
26.79
26.08
O
f1 (ppm)

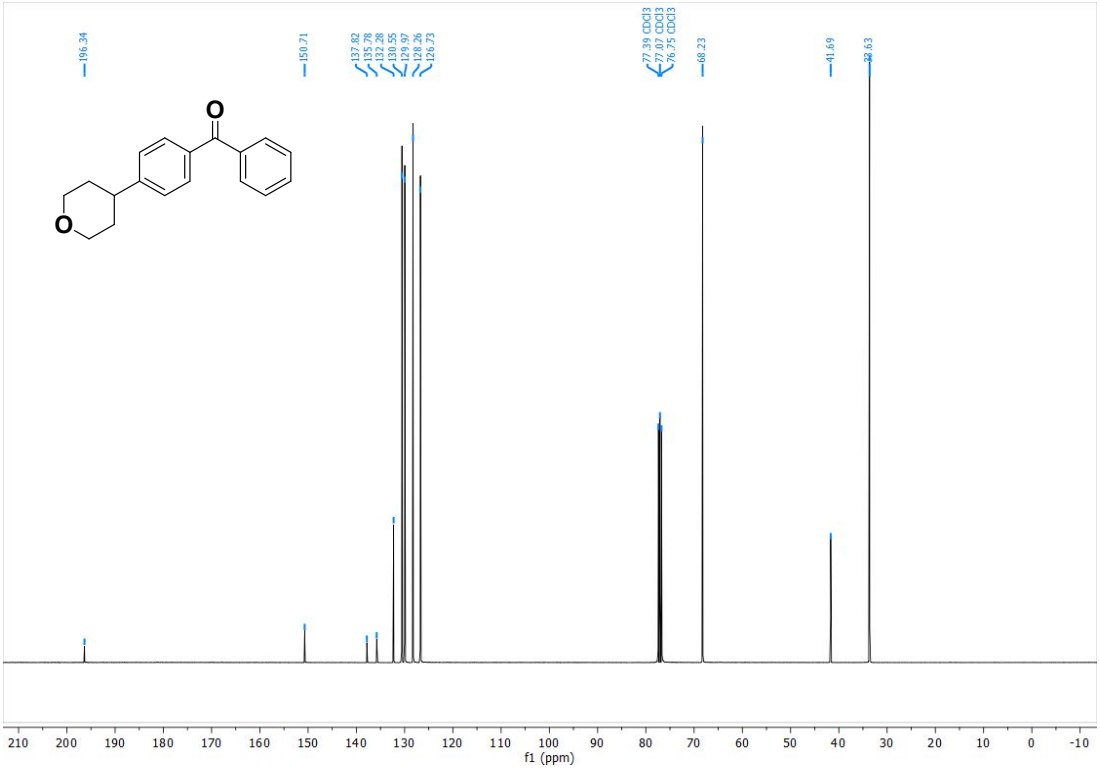
Compound **5d**



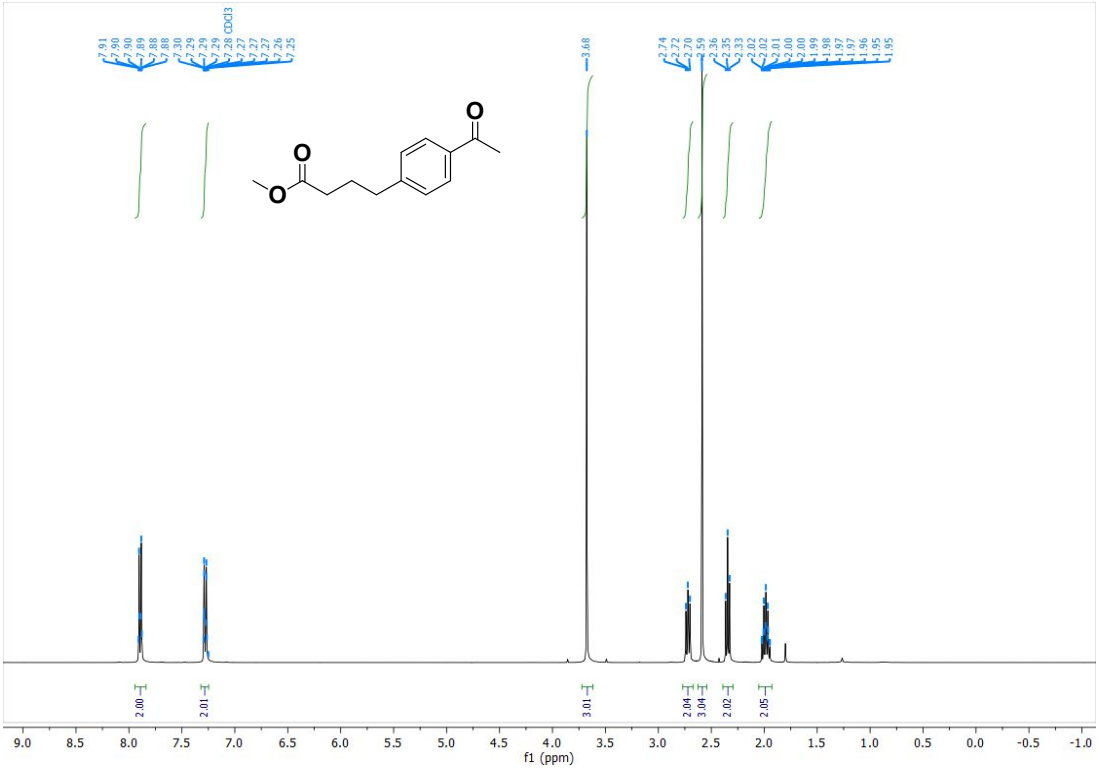


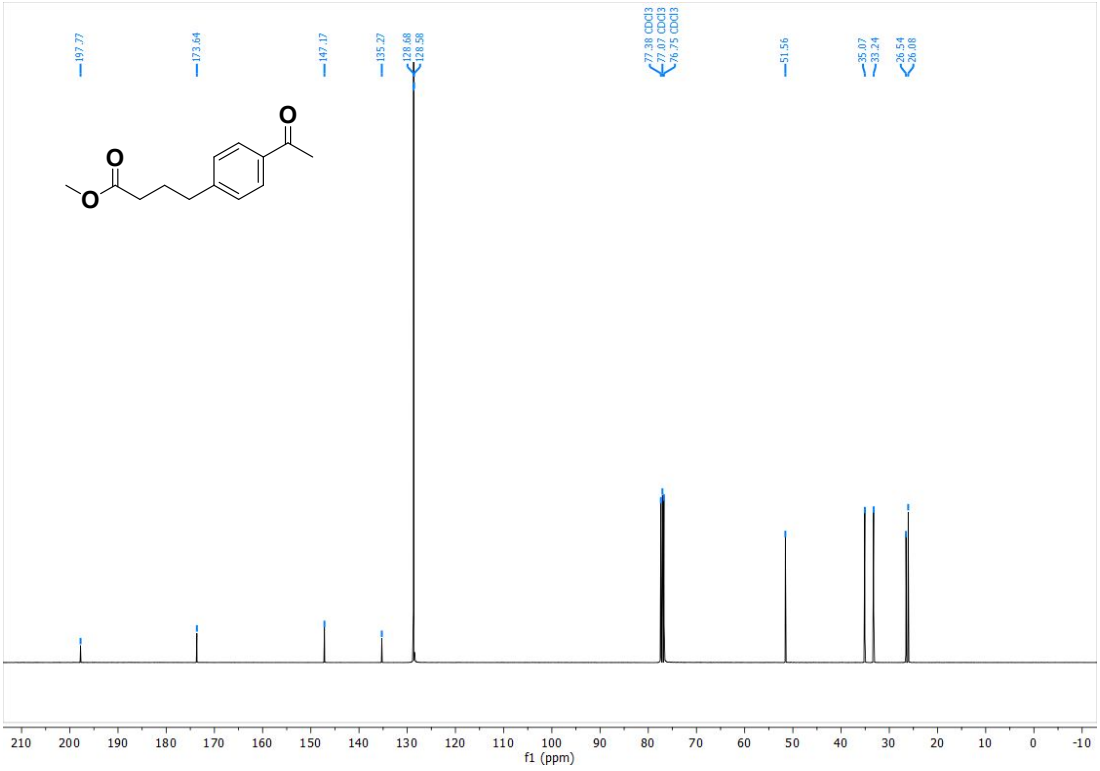
Compound **5e**


O
O
3.95
1.00
1.93
1.96
2.02
2.04
1.00
4.09
f1 (ppm)

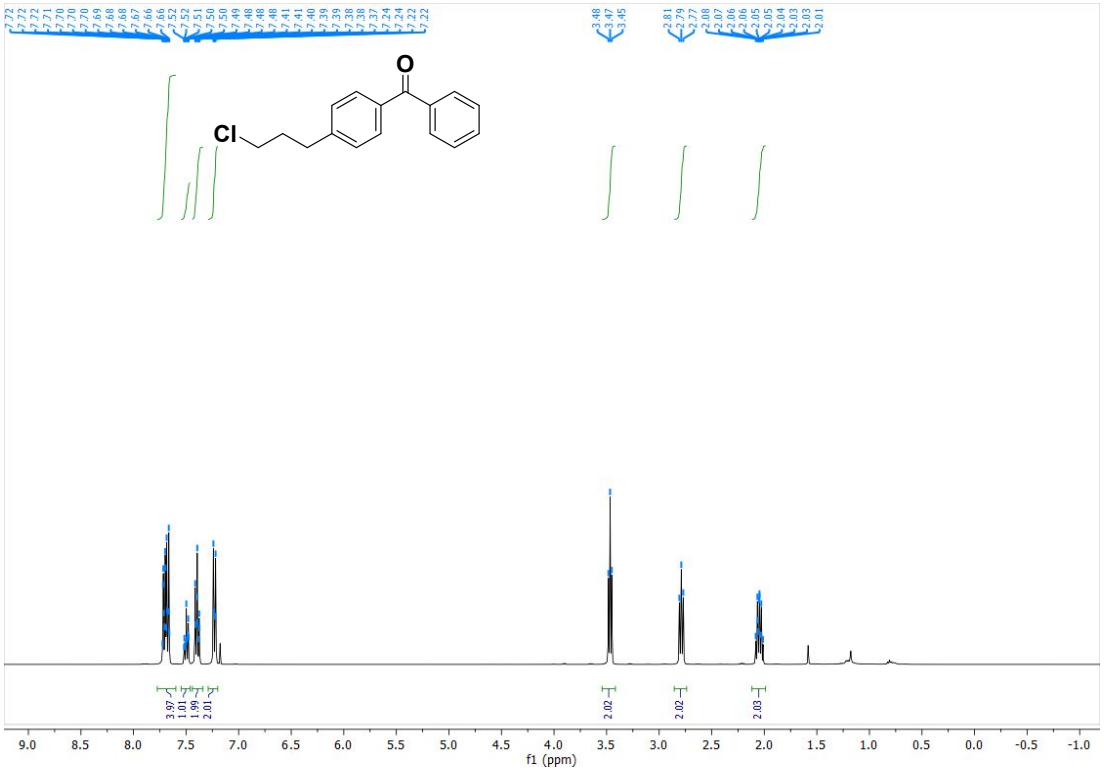

196.34
150.71
137.82
135.78
132.28
130.55
128.97
128.26
126.73
77.39 CDCl3
77.07 CDCl3
76.75 CDCl3
68.23
41.69
32.63
O
O
f1 (ppm)

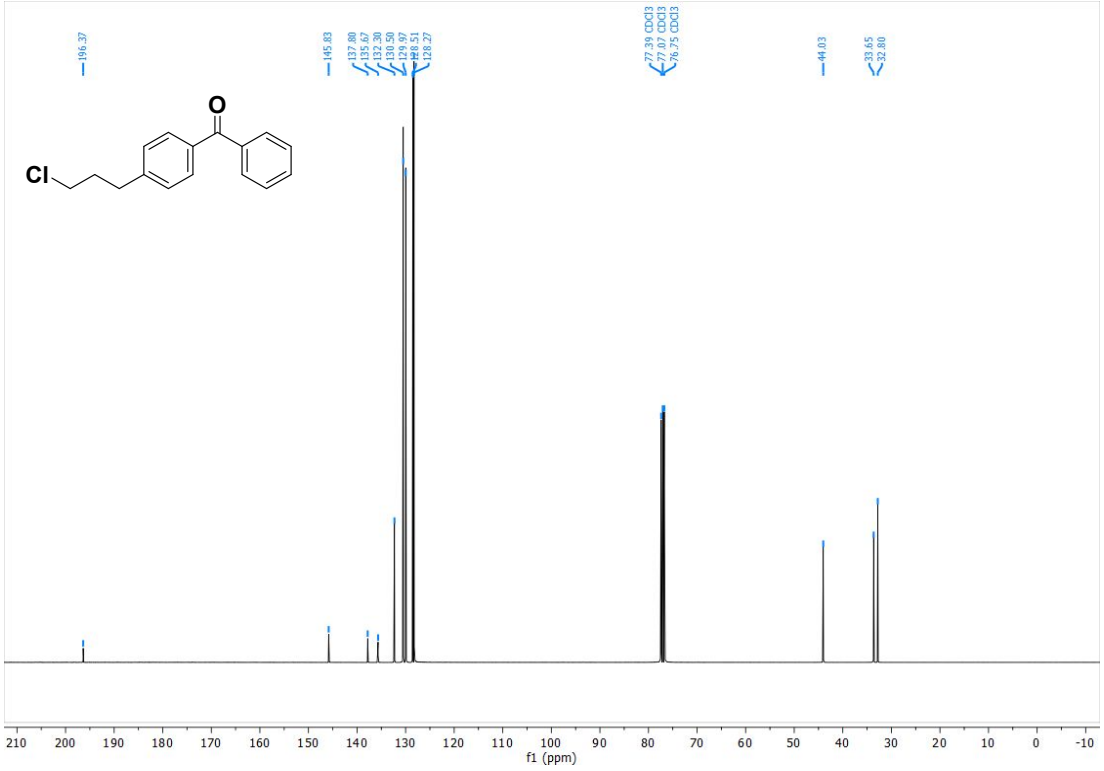
Compound **5f**


7.91
7.90
7.90
7.89
7.88
7.88
7.30
7.29
7.29
7.29
7.28 CDCl3
7.27
7.27
7.27
7.27
7.26
7.25
3.68
2.74
2.72
2.70
2.59
2.36
2.35
2.33
2.02
2.02
2.01
2.00
2.00
1.99
1.98
1.97
1.97
1.96
1.95
1.95
O
O
O
2.00
2.01
3.01
2.04
3.04
2.02
2.05
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)

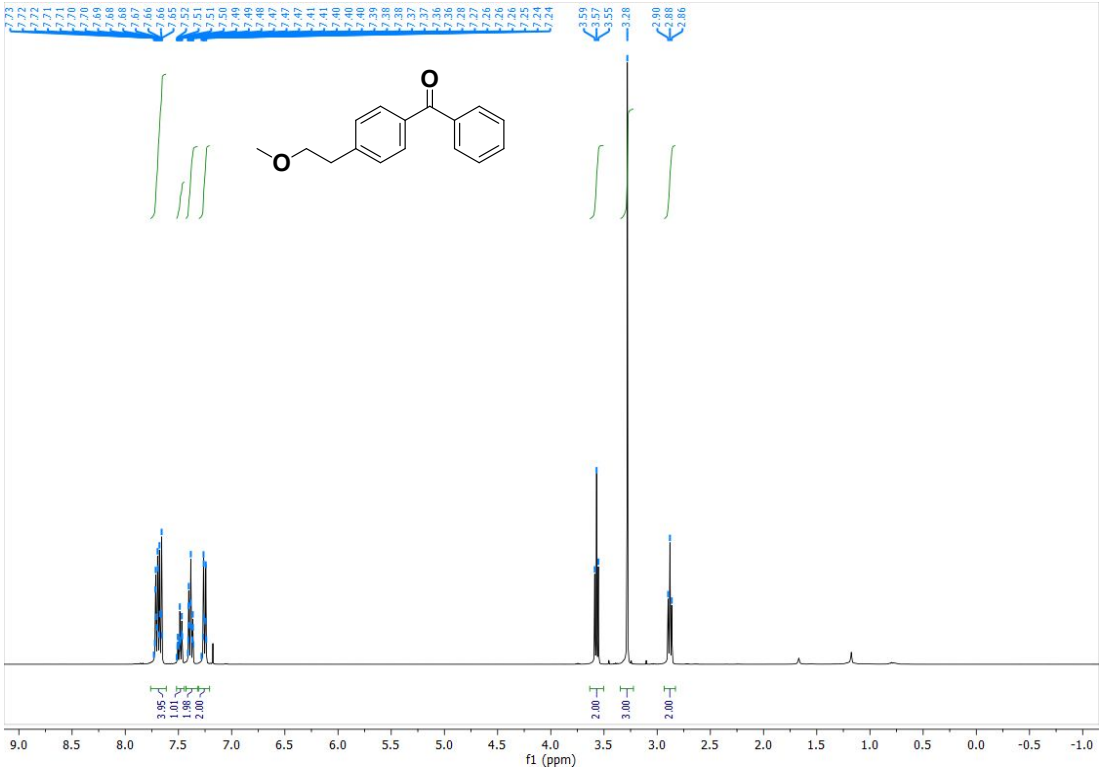

197.77
173.64
147.17
135.27
128.68
128.50
77.38 CDCl3
77.07 CDCl3
76.75 CDCl3
51.56
35.07
33.24
26.54
26.08
O
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

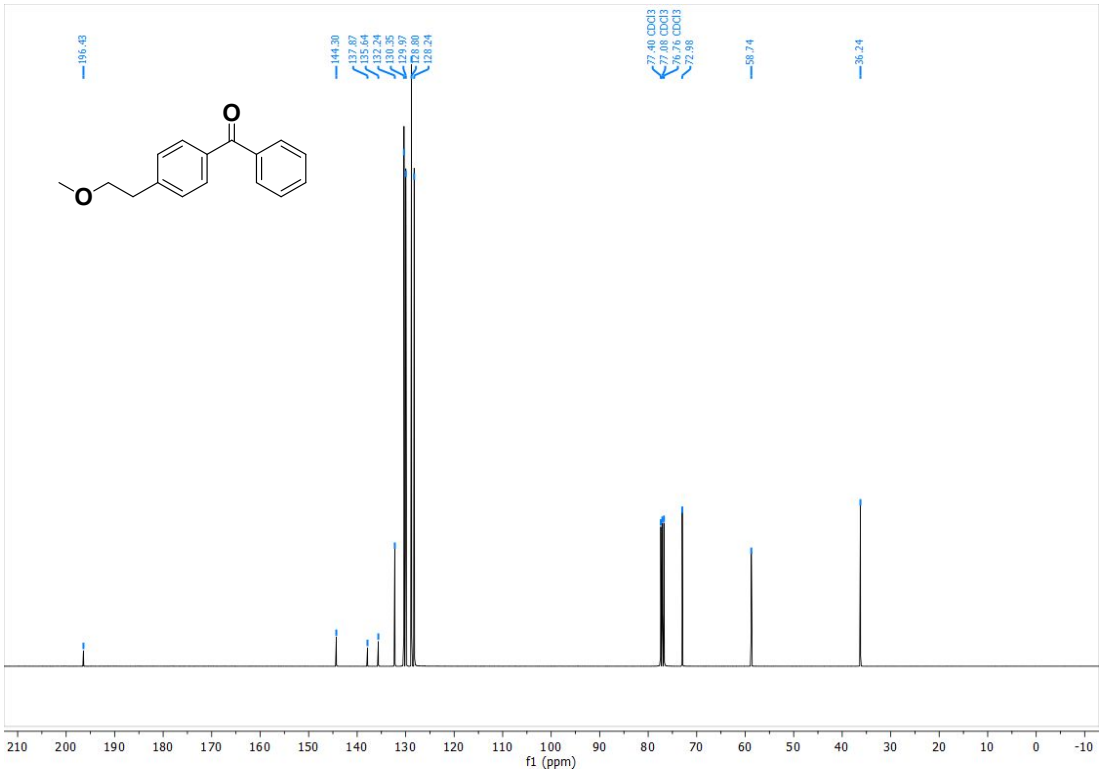
Compound **5g**



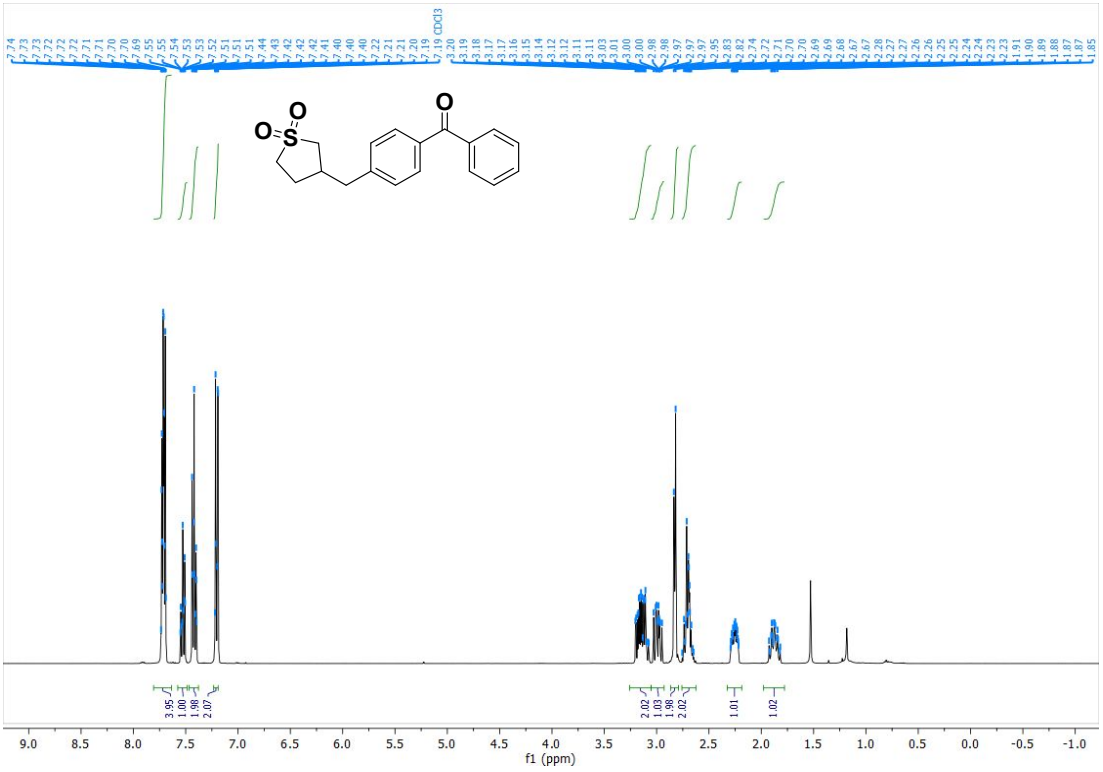


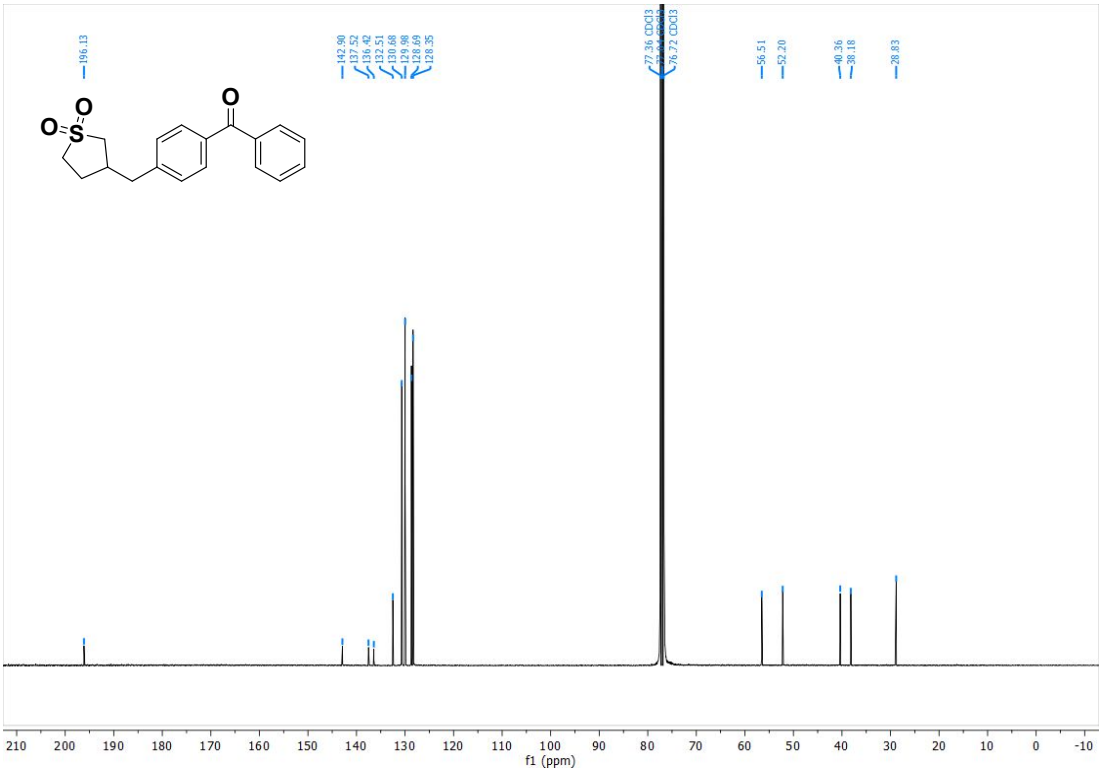
Compound **5h**


O
O
f1 (ppm)

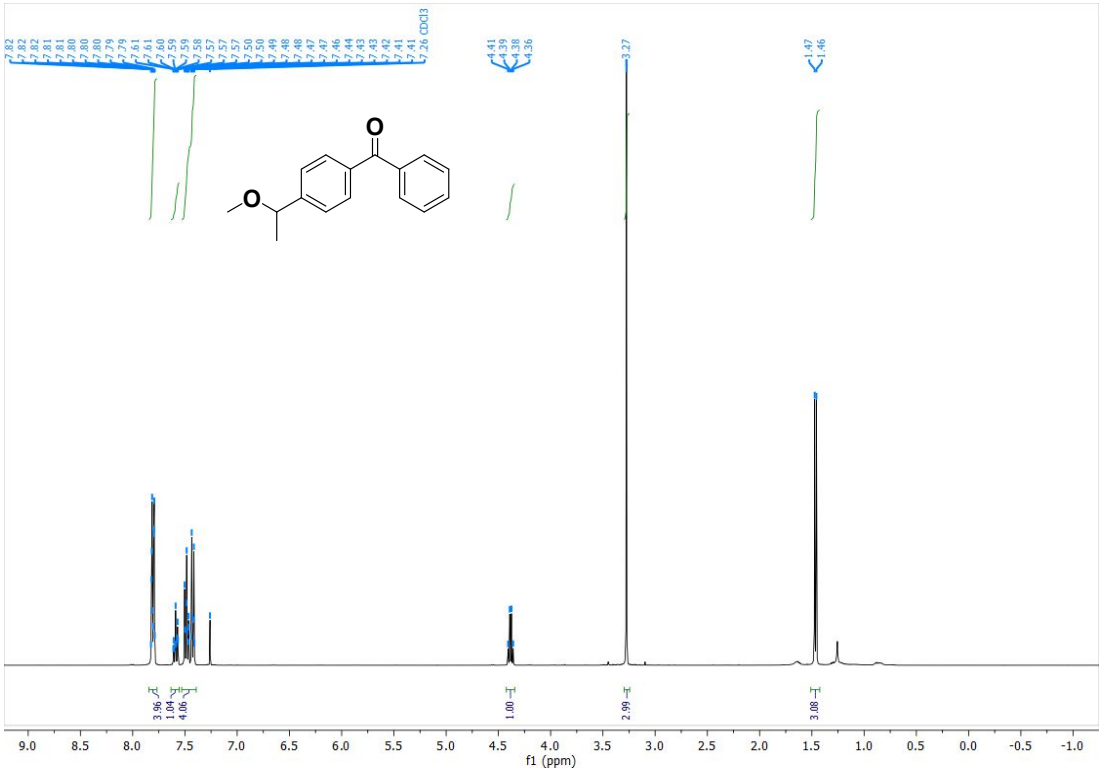

196.48
144.30
137.87
135.64
132.24
130.35
129.97
128.80
128.24
77.40 CDCl3
77.08 CDCl3
76.76 CDCl3
72.98
58.74
36.24
O
O
f1 (ppm)

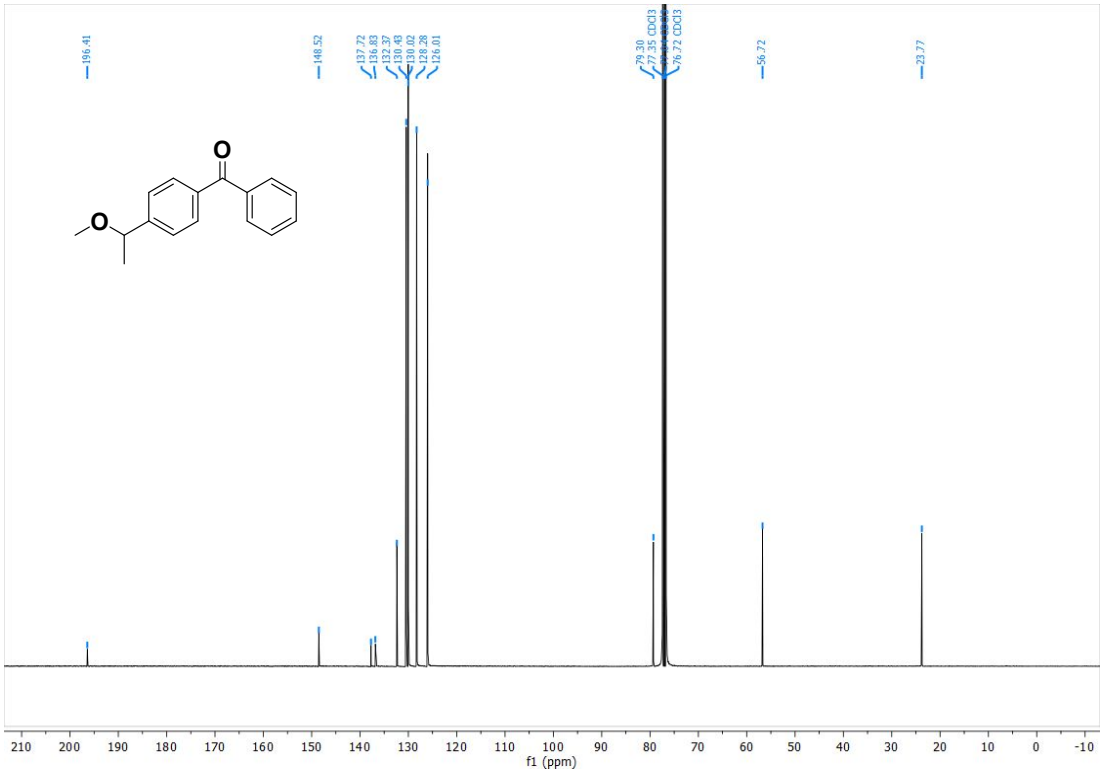
Compound **5i**



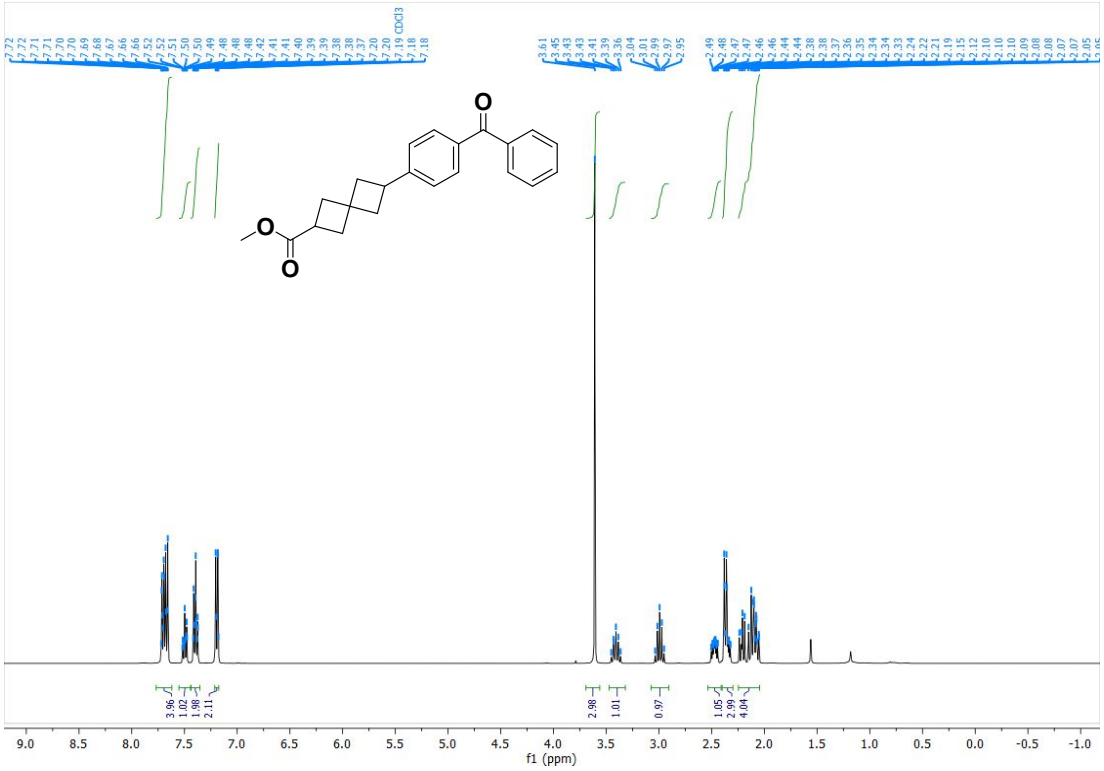


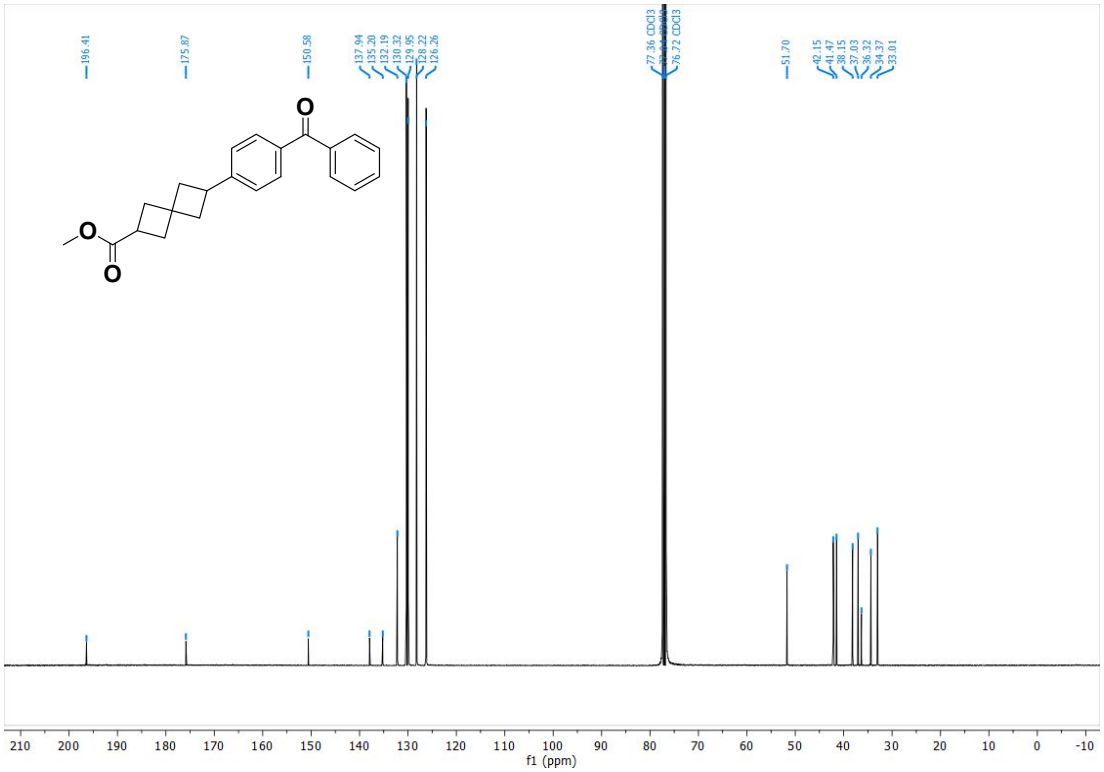
Compound **5j**


7.82
7.82
7.82
7.81
7.81
7.80
7.80
7.80
7.79
7.79
7.61
7.61
7.61
7.60
7.59
7.59
7.59
7.58
7.57
7.57
7.57
7.50
7.50
7.49
7.48
7.48
7.47
7.47
7.46
7.44
7.43
7.43
7.42
7.41
7.41
7.26 CDCl3
4.41
4.39
4.38
4.36
3.27
1.47
1.46
O
O
3.96
1.04
4.06
1.00
2.99
3.08
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)


196.41
148.52
137.72
136.83
132.37
130.43
128.02
128.38
126.01
79.30
77.35 CDCl3
76.72 CDCl3
56.72
23.77
O
O
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)

Compound **5m**





7. References

(1) Branchaud, B. P. Studies on the Preparation and Reactions of Tritylsuffenimines. *J. Org. Chem.* **1983**, *48* (20), 3531–3538.

(2) Sheikh, M. C.; Takagi, S.; Sakai, M.; Mori, T.; Hayashi, N.; Fujie, T.; Ono, S.; Yoshimura, T.; Morita, H. Syntheses and Reactivities of Non-Symmetrical “active Ester” bi-Dentate Cross-Linking Reagents Having a Phthalimidoyl and Acid Chloride, 2-Benzothiazole, or 1-Benzotriazole Group. *Org. Biomol. Chem.* **2011**, *9* (4), 1244–1254.

(3) Hansen, E. C.; Pedro, D. J.; Wotal, A. C.; Gower, N. J.; Nelson, J. D.; Caron, S.; Weix, D. J. New Ligands for Nickel Catalysis from Diverse Pharmaceutical Heterocycle Libraries. *Nat. Chem.* **2016**, *8* (12), 1126–1130.

(4) Chen, B.-Z.; Zhi, M.-L.; Wang, C.-X.; Chu, X.-Q.; Shen, Z.-L.; Loh, T.-P. Synthesis of Alkyl Indium Reagents by Using Unactivated Alkyl Chlorides and Their Applications in Palladium-Catalyzed Cross-Coupling Reactions with Aryl Halides. *Org. Lett.* **2018**, *20* (7), 1902–1905.

(5) Rushworth, P. J.; Hulcoop, D. G.; Fox, D. J. Iron/Tetramethylethylenediamine-Catalyzed Ambient-Temperature Coupling of Alkyl Grignard Reagents and Aryl Chlorides. *J. Org. Chem.* **2013**, *78* (18), 9517–9521.

(6) Tran, U. P. N.; Hock, K. J.; Gordon, C. P.; Koenigs, R. M.; Nguyen, T. V. Efficient Phosphine-Mediated Formal C(sp 3)–C(sp 3) Coupling Reactions of Alkyl Halides in Batch and Flow. *Chem. Commun.* **2017**, *53* (36), 4950–4953.

(7) Zhou, F.; Hu, X.; Zhang, W.; Li, C. J. Copper-Catalyzed Radical Reductive Arylation of Styrenes with Aryl Iodides Mediated by Zinc in Water. *J. Org. Chem.* **2018**, *83* (14), 7416–7422.

(8) Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K. Novel Rh Catalysis in Cross-Coupling between Alkyl Halides and Arylzinc Compounds Possessing Ortho -COX (X = OR, NMe 2 , or Ph) Groups. *Org. Lett.* **2006**, *8* (14), 3037–3040.

(9) Molander, G. A.; Yun, C.-S. Cross-Coupling Reactions of Primary Alkylboronic Acids with Aryl Triflates and Aryl Halides. *Tetrahedron* **2002**, *58* (8), 1465–1470.

(10) Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D.; Qiao, W.; Sun, L.; Collins, M. R.; et al. Modular Radical Cross-Coupling with Sulfones Enables Access to Sp 3 -Rich (Fluoro)alkylated Scaffolds. *Science (80-.).* **2018**, *360* (6384), 75–80.

(11) Yan, C. S.; Peng, Y.; Xu, X. B.; Wang, Y. W. Nickel-Mediated Inter- and Intramolecular Reductive Cross-Coupling of Unactivated Alkyl Bromides and Aryl Iodides at Room Temperature. *Chem. - A Eur. J.* **2012**, *18* (19), 6039–6048.

(12) Gevorgyan, A.; Mkrtchyan, S.; Grigoryan, T.; Iaroshenko, V. O. Application of Silicon-Initiated Water Splitting for the Reduction of Organic Substrates. *Chempluschem* **2018**, *83* (5), 375–382.

(13) Ruberu, S. R.; Dukes, K. E.; Forbes, M. D. E. Dynamics of Spin-Polarized Radical Pairs at the Solid/Solution Interface. *J. Am. Chem. Soc.* **1994**, *116* (16), 7299–7307.

(14) Creary, X.; Hinckley, J.; Kraft, C.; Genereux, M. Photochemical Behavior of Cyclopropyl-Substituted Benzophenones and Valerophenones. *J. Org. Chem.* **2011**, *76* (7), 2062–2071.