Supporting Information

i-Pr_2NMgCl·LiCl enables the synthesis of ketones by direct addition of Grignard reagents to carboxylate anions

Kilian Colas, A. Catarina V. D. dos Santos and Abraham Mendoza*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University,

106 91 Stockholm, Sweden

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Contents

General information

Materials. All reactions were carried out using oven dried glassware under an atmosphere of argon unless otherwise specified. Unless otherwise specified, carboxylic acids were purchased from Sigma-Aldrich, Fluorochem, TCI Chemicals, Acros Organics or Alfa-Aesar. Dry solvents were obtained by passing them through activated alumina columns. The solvents used in column chromatography, petroleum ether, pentane, toluene, dichloromethane, methanol and ethyl acetate, were obtained from commercial suppliers and used without further purification. Isopropylmagnesium chloride lithium chloride complex (1.3 M in THF) may be obtained from Sigma-Aldrich (745038-86-2) or may be prepared through the reported procedure by Knochel.[1] As we have experienced inconstent performances from commercial batches, we advise the fresh preparation of this reagent. Grignard reagents were either purchased from commercial suppliers or prepared by the specified reported procedure, with the exception of new reagent 8**w** which was prepared by Mg insertion from the corresponding chloride (see section I). All Grignard reagents were titrated before use by Knochel's iodine titration method.[2] Magnesium turnings were purchased from Sigma-Aldrich (Reagent grade, 7439-95-4) and used without further treatment. Diisopropylamine **S1** (Sigma-Aldrich, 108-18-9) was distilled before use and stored under Ar.

Chromatography. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light (λ = 254 nm) as visualizing agent and a vanillin solution and heat as developing agents, as specified. Flash silica gel chromatography was performed using E. Merck silica gel (60 Å, particle size 0.043-0.063mm).

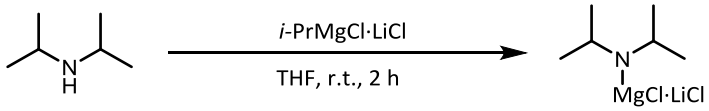
Characterization. NMR spectra for the characterization of compounds were recorded at room temperature on a Bruker instrument 400 MHz (^{1}H) and at 100 MHz (^{13}C) and 377 MHz (^{19}F), or 500 MHz (^{1}H) and at 125 MHz (^{13}C). Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (δ_H = 7.26 and δ_C = 77.2 ppm) or DMSO (δ_H = 2.50 and δ_C = 39.5 ppm) as internal reference or the trifluorotoluene signal as external reference (δ_F = –62.73 ppm), coupling constants (^{n}J) are given in hertz (Hz). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, t: triplet, q: quartet, br: broad, m: multiplet), coupling constants and integration.

High-resolution mass spectra (HRMS) were determined at Stockholm University with a Bruker Daltonics microTOF Mass Spectrometer using an ESI ion source.

Experimental details. Reactions were performed in common Pyrex® round bottom or Schlenk flasks, microwave vials 0.5 – 2 mL (VWR), or 5 – 20 mL flat bottom vials (Cronus, SMI-LabHut Ltd.) crimped on top with 20 mm Sil/PTFE Septa (Cronus, SMI-LabHut Ltd.).

I - Synthesis of starting materials

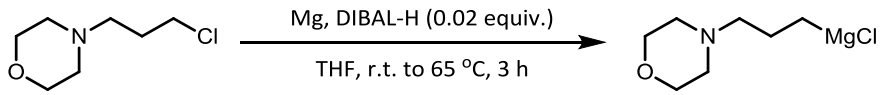
Preparation of *i*-$Pr_2NMgCl{\cdot}LiCl$ (9a)



S1 **9a**

The preparation was adapted from the procedure reported by Knochel and co-workers,[3] as follows: To a solution of diisopropylamine **S1** (0.31 mL, 2.2 mmol, 1.1 equiv.) in THF (1.6 mL) stirred at r.t. under Ar, ^{i}PrMgCl·LiCl[1] (1.54 mL of 1.3 M solution in THF; 2.0 mmol, 1.0 equiv.) was added dropwise. The resulting clear solution was stirred for 2 h at room temperature. The concentration of *i*-$Pr_2NMgCl{\cdot}LiCl$ (**9a**) in the solution was determined using Knochel's procedure,[4] reproducibly yielding a concentration of 0.58-0.62 M.

Preparation of (3-morpholinopropyl)magnesium chloride (8w)

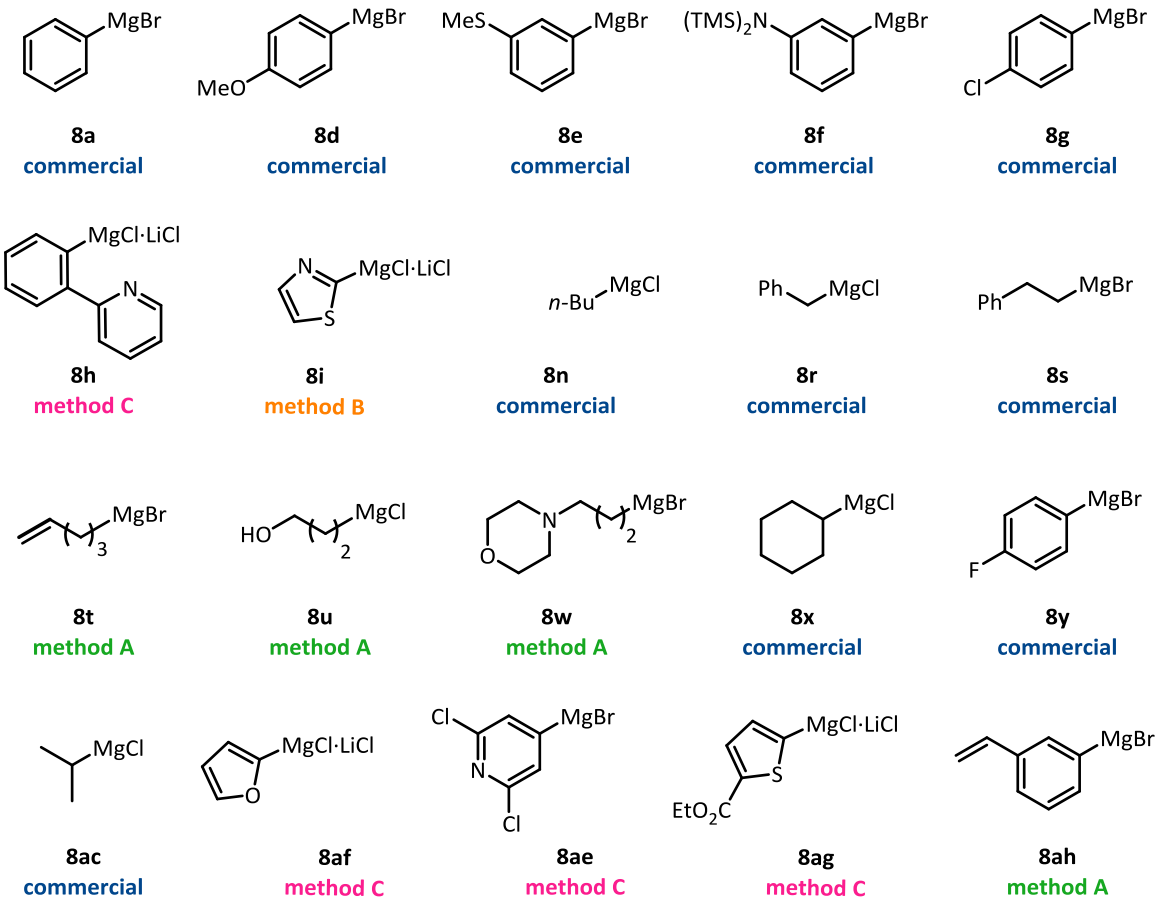


S2 **8w**

To a suspension of magnesium turnings (367 mg, 15.1 mmol, 1.3 equiv.) in THF (12 mL), DIBAL-H (0.24 ml of 1 M solution in hexanes, 0.24 mmol, 0.02 equiv.) was added dropwise. The resulting suspension was stirred at r.t. for 10 min, then a solution of 4-(3-chloropropyl)morpholine[5] (1.90 g, 11.6 mmol, 1.0 equiv.) in THF (12 mL) was added dropwise over *ca.* 15 min. After completion of the addition, the yellow mixture was refluxed for 3 h, then filtered under Ar to remove remaining magnesium particles, affording (3-morpholinopropyl)magnesium chloride **8w** as a clear yellow solution, which was titrated as 0.28 M.

II – Synthesis of Ketones 1

Figure S1. List of Grignard reagents (**8**) used in this study.



8a commercial | **8d** commercial | **8e** commercial | **8f** commercial | **8g** commercial

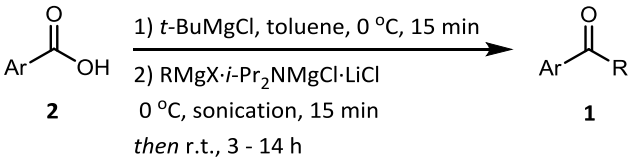
8h method C | **8i** method B | **8n** commercial | **8r** commercial | **8s** commercial

8t method A | **8u** method A | **8w** method A | **8x** commercial | **8y** commercial

8ac commercial | **8af** method C | **8ae** method C | **8ag** method C | **8ah** method A

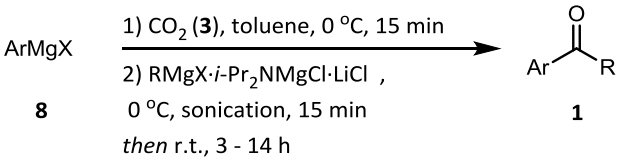
Preparation of the Grignard reagent: **method A**: Mg insertion; **method B** : halogen-magnesium exchange; **method C** : C–H magnesiation

General procedure A: synthesis of ketones from carboxylic acids.



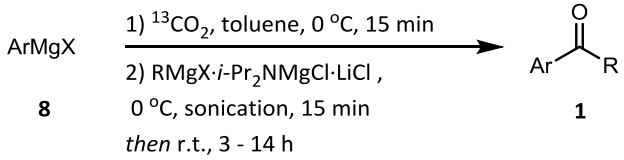
To a solution of carboxylic acid **2** (0.5 mmol, 1.0 equiv) in anhydrous toluene (7.5 mL) stirred at 0 °C under Ar, ^{t}BuMgCl (0.5 mL of 1 M solution in THF, 0.5 mmol, 1.0 equiv.) was added dropwise. The resulting solution was stirred at 0 °C for 15 min. In a separate flask, the appropriate Grignard reagent **8** (0.6 – 1.0 mmol, 1.2 - 2.0 equiv., as specified) was added dropwise to a solution of *i*-Pr_2NMgCl·LiCl **9a** (0.6 – 1.0 mmol, 1.2 - 2.0 equiv., as specified) stirred at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min, then was added dropwise over *ca.* 2 min to the carboxylate solution. The resulting mixture was sonicated at 0 °C for 15 min, then stirred at r.t. for 3 to 24 h, as specified, monitoring by TLC of quenched aliquots. The reaction was quenched at 0 °C with 1M aq. HCl (5 mL). The crude mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude ketone **1** which was purified by flash column chromatography (SiO_2).

General procedure B: synthesis of ketones from CO_2.



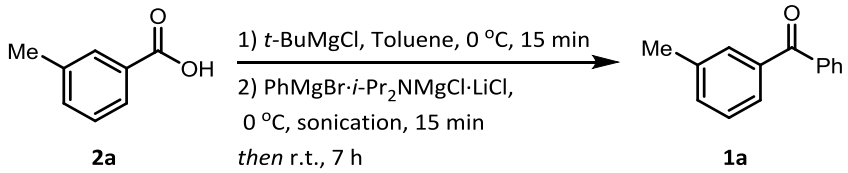
A microwave vial was charged with dry ice, crimped and allowed to release CO_2 (**3**) *via* cannula, bubbling for 15 min through a solution of Grignard reagent **8** (0.5 mmol, 1.0 equiv) in anhydrous toluene (7.5 mL) stirred at r.t. under Ar. Afterwards, Ar was bubbled through the solution for 15 min in order to purge unreacted CO_2. In a separate flask, the appropriate Grignard reagent **8'** (0.6 – 1.0 mmol, 1.2 - 2.0 equiv., as specified) was added dropwise to a solution of *i*-PrN_2MgCl·LiCl **9a** (0.6 – 1.0 mmol, 1.2 - 2.0 equiv., as specified) stirred at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min, then was added dropwise to the carboxylate solution stirred at 0 °C. The resulting mixture was sonicated at 0 °C for 15 min, then stirred at r.t. for 3 to 14 h, as specified, monitoring by TLC of quenched aliquots. The reaction was quenched at 0 °C with 1M aq. HCl (5 mL). The crude mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude ketone **1** which was purified by flash column chromatography (SiO_2).

General procedure C: synthesis of ketones from ^{13}C-CO_2



$^{13}CO_2$ (**[^{13}C]-3**)was bubbled for 5 min through a solution of Grignard reagent **8** (0.5 mmol, 1.0 equiv) in anhydrous toluene (7.5 mL) stirred at r.t. under Ar. Afterwards, Ar was bubbled through the solution for 15 min in order to purge unreacted CO_2. In a separate flask, the appropriate Grignard reagent **8'** (0.6 – 1.0 mmol, 1.2 - 2.0 equiv., as specified) was added dropwise to a solution of *i*-PrN$_2$MgCl·LiCl **9a** (0.6 – 1.0 mmol, 1.2 - 2.0 equiv., as specified) stirred at 0 °C under Ar. The resulting colorless solution was stirred at 0 °C for 15 min, then was added dropwise to the carboxylate solution stirred at 0 °C. The resulting mixture was sonicated at 0 °C for 15 min, then stirred at r.t. for 3 to 14 h, as specified, monitoring by TLC of quenched aliquots. The reaction was quenched at 0 °C with 1M aq. HCl (5 mL). The crude mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide the crude ketone **1** which was purified by flash column chromatography (SiO_2).

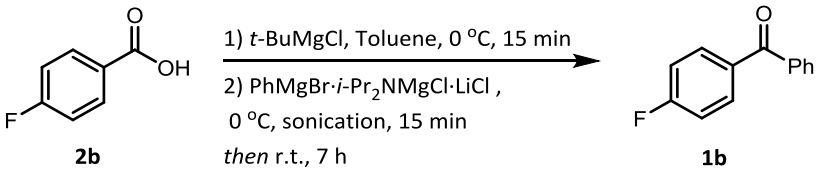
Synthesis of phenyl(*m*-tolyl)methanone (1a):



General Procedure A was applied using 3-methylbenzoic acid **2a** (68 mg, 0.5 mmol, 1.0 equiv.) and phenylmagnesium bromide **8a** (0.30 mL of 2 M solution in Et_2O, 0.6 mmol, 1.2 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1a** as a colorless oil (90 mg; 92 % yield) whose characterization data were in accordance with reported literature.[6]

Appearance: colorless oil.
TLC: R_f = 0.30 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.83 – 7.78 (m, 2H), 7.63 (br s, 1H), 7.61 – 7.56 (m, 2H), 7.51 – 7.45 (m, 2H), 7.41 – 7.33 (m, 2H), 2.42 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 196.9, 138.2, 137.8, 137.7, 133.2, 132.3, 130.5, 130.0, 128.2, 128.1, 127.4, 21.4.
HRMS: (ESI-TOF) calc'd for $[C_{14}H_{12}O + Na]^+$ 219.0780; found 219.0779.

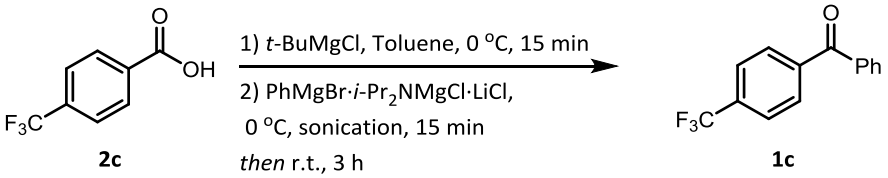
Synthesis of (4-fluorophenyl)(phenyl)methanone (1b):



General Procedure A was applied using 4-fluorobenzoic acid **2b** (70 mg, 0.5 mmol, 1.0 equiv.) and phenylmagnesium bromide **8a** (0.30 mL of 2 M solution in Et_2O, 0.6 mmol, 1.2 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1b** as a yellow solid (78 mg; 78 % yield) whose characterization data were in accordance with reported literature.[6]

Appearance: yellow solid.
TLC: R_f = 0.30 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.88 – 7.82 (m, 2H), 7.79 – 7.75 (m, 2H), 7.62 – 7.57 (m, 1H), 7.52 – 7.46 (m, 2H), 7.19 – 7.13 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.4, 165.5 (d, J_{CF} = 254.1 Hz), 137.6, 133.9 (d, J_{CF} = 3.1 Hz), 132.8 (d, J_{CF} = 9.2 Hz), 132.6, 130.0, 128.5, 115.6 (d, J_{CF} = 21.8 Hz).
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 106.00.
HRMS: (ESI-TOF) calc'd for $[C_{13}H_9FO + Na]^+$ 223.0530; found 223.0535.

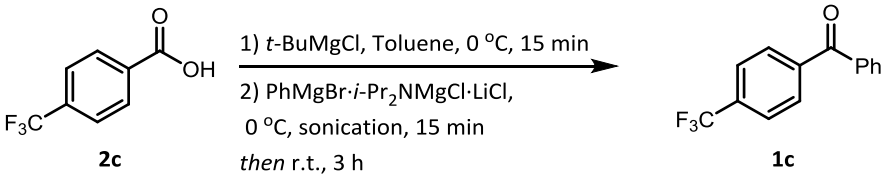
Synthesis of phenyl(4-(trifluoromethyl)phenyl)methanone (1c):



General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and phenylmagnesium bromide **8a** (0.30 mL of 2 M solution in Et_2O, 0.6 mmol, 1.2 equiv.) over 3 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1c** as a yellow solid (102 mg; 82 % yield) whose characterization data were in accordance with reported literature.[6]

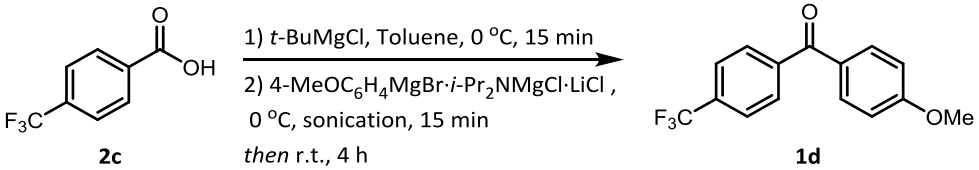
Appearance: yellow solid.
TLC: R_f = 0.32 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.92 – 7.87 (m, 2H), 7.83 – 7.79 (m, 2H), 7.78 – 7.73 (m, 2H), 7.65 – 7.60(m, 1H), 7.54 – 7.48 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.5, 140.7, 136.7, 133.7 (q, J_{CF} = 32.5 Hz), 133.1, 130.1, 130.0, 128.5, 125.3 (q, J_{CF} = 3.7 Hz), 123.7 (q, J_{CF} = 272.7 Hz).
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 63.01.
HRMS (ESI-TOF) calc'd for $[C_{14}H_9F_3O + Na]^+$ 273.0498; found 273.0498.

Gram-scale synthesis of phenyl(4-(trifluoromethyl)phenyl)methanone (1c):



To a solution of 4-(trifluoromethyl)benzoic acid **2c** (1.5 g, 7.9 mmol, 1.0 equiv) in anhydrous toluene (200 mL) stirred at 0 °C under Ar, ^{t}BuMgCl (7.9 mL of 1.0 M solution in THF, 7.9 mmol, 1.0 equiv.) was added dropwise. The resulting solution was stirred at 0 °C for 15 min. In a separate flask, phenylmagnesium bromide **8a** (4.93 mL of a 1.93 M solution in THF, 9.5 mmol, 1.2 equiv.) was added dropwise to a solution of DIPAMgCl·LiCl **9a** (15.8 mL of a 0.6 M solution in THF, 9.5 mmol, 1.2 equiv.) stirred at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min, then was added dropwise to the carboxylate solution. The resulting mixture was allowed to warm up to r.t. and stirred for 3 h. The reaction was quenched at 0 °C with 1M aq. HCl. The crude mixture was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1c** as a yellow solid (1.93 g; 98 % yield) whose characterization data matched those previously reported (see page S-11).

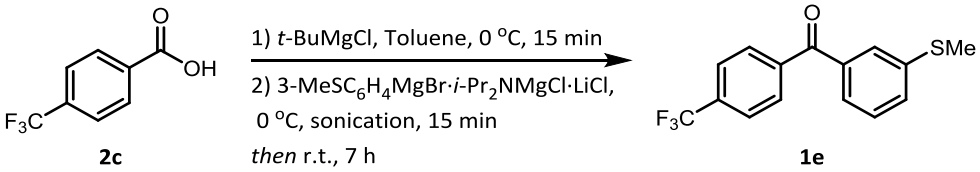
Synthesis of (4-methoxyphenyl)(4-(trifluoromethyl)phenyl)methanone (1d):



General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide **8d** (1.2 mL of 0.5 M solution in THF, 0.6 mmol, 1.2 equiv.) over 4 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 25:1) to obtain pure **1d** as a yellow solid (119 mg; 85 % yield) whose characterization data were in accordance with reported literature.[7]

Appearance: yellow solid.
TLC: R_f = 0.22 (Pentane/EtOAc, 25:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.86 – 7.79 (m, 4H), 7.76 – 7.71 (m, 2H), 7.00 – 6.94 (m, 2H), 3.89 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.2, 163.7, 141.5, 133.2 (q, J_{CF} = 32.6 Hz), 132.6, 129.8, 129.4, 125.2 (q, J_{CF} = 3.7 Hz), 123.7 (q, J_{CF} = 272.6 Hz), 113.8, 55.5.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 62.94.
HRMS: (ESI-TOF) calc'd for $[C_{15}H_{11}F_3O_2 + Na]^+$ 303.0603; found 303.0605.

Synthesis of (3-(methylthio)phenyl)(4-(trifluoromethyl)phenyl)methanone (1e):

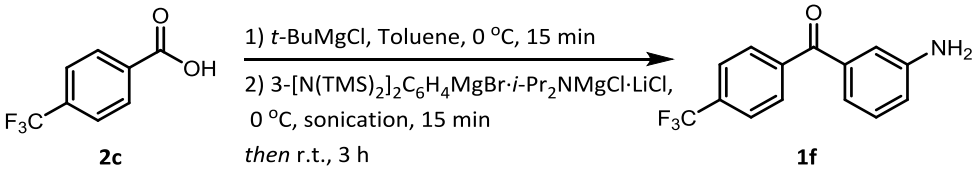


2c **1e**

General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and 3-(methylthio)phenylmagnesium bromide **8e** (1.2 mL of 0.5 M solution in THF, 0.6 mmol, 1.2 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 20:1) to obtain pure **1e** as a white solid (101 mg; 68 % yield).

Appearance: white solid.
TLC: R_f = 0.30 (Pentane/EtOAc, 20:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.91 – 7.86 (m, 2H), 7.78 – 7.73 (m, 2H), 7.69 – 7.66 (m, 1H), 7.52 – 7.47 (m, 2H), 7.43 – 7.37 (m, 1H),2.52 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.1, 140.5, 139.9, 137.3, 133.8 (q, J_{CF} = 32.7 Hz), 130.7, 130.1, 128.7, 127.2, 126.7, 125.4 (q, J_{CF} = 3.7 Hz), 123.6 (q, J_{CF} = 272.7 Hz), 15.6.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 63.02.
HRMS: (ESI-TOF) calc'd for $[C_{15}H_{11}F_3OS + Na]^+$ 319.0375; found 319.0378.

Synthesis of (3-aminophenyl)(4-(trifluoromethyl)phenyl)methanone (1f):

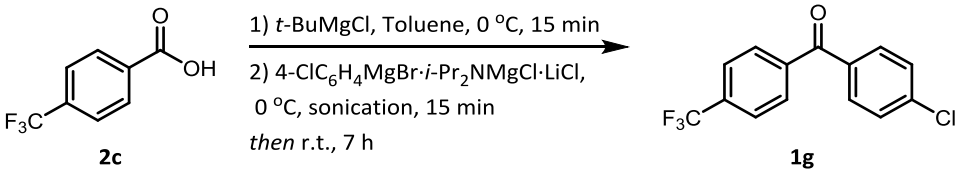


2c **1f**

General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and 3-(bis(trimethylsilyl)amino)phenylmagnesium bromide **8f** (0.6 mL of 1 M solution in THF, 0.6 mmol, 1.2 equiv.) over 3 h. The crude mixture was purified by column chromatography (DCM) to obtain pure **1f** as a yellow solid (110 mg; 83 % yield). *NB*: The TMS protecting groups were cleaved on silica upon purification.

Appearance: yellow solid.
TLC: R_f = 0.33 (DCM, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.90 – 7.86 (m, 2H), 7.75 – 7.71 (m, 2H), 7.28 – 7.23 (m, 1H), 7.13 – 7.07 (m, 2H), 6.93 – 6.89 (m, 1H), 3.78 (br s, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 195.7, 146.8, 141.0, 137.8, 133.6 (q, J_{CF} = 32.6 Hz), 130.1, 129.3, 125.2 (q, J_{CF} = 3.8 Hz), 123.7 (q, J_{CF} = 272.6 Hz), 120.6, 119.6, 115.7.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 62.98.
HRMS: (ESI-TOF) calc'd for $[C_{14}H_{10}F_3NO + H]^+$ 266.0787; found 266.0783.

Synthesis of (4-chlorophenyl)(4-(trifluoromethyl)phenyl)methanone (1g):

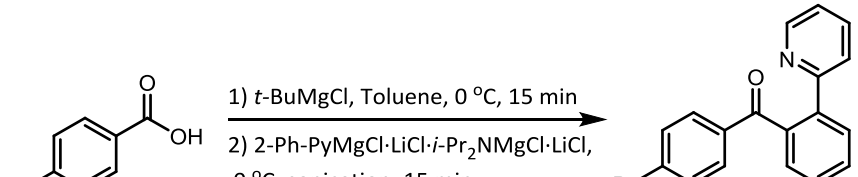


2c **1g**

General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and 4-chlorophenylmagnesium bromide **8g** (0.30 mL of 2 M solution in THF, 0.6 mmol, 1.2 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1g** as a yellow solid (129 mg; 91 % yield) whose characterization data were in accordance with reported literature.[8]

Appearance: yellow solid.
TLC: R_f = 0.38 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.88 – 7.83 (m, 2H), 7.78 – 7.72 (m, 4H), 7.51 – 7.45 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.2, 140.4, 139.7, 135.0, 133.9 (q, J_{CF} = 32.8 Hz), 131.4, 130.0, 128.9, 125.5 (q, J_{CF} = 3.7 Hz), 123.6 (q, J_{CF} = 272.7 Hz).
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 63.06.
HRMS: (ESI-TOF) calc'd for $[C_{14}H_8ClF_3O + Na]^+$ 307.0108; found 307.0103.

Synthesis of (4-bromophenyl)(2-(pyridin-2-yl)phenyl)methanone (1h):

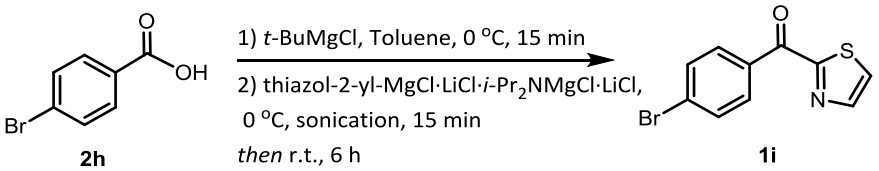


2h **1h**

General procedure A was applied using 4-bromobenzoic acid **2h** (101 mg, 0.5 mmol, 1.0 equiv (2-(pyridin-2-yl)phenyl)magnesium chloride lithium chloride complex[3] **8h** (1.6 mL of 0.37 M solution in THF , 0.6 mmol, 1.2 equiv.) over 6 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 5:1) and subsequent recrystalization from EtO_2/MeOH to obtain pure **1h** as a colorless solid (123 mg; 73 % yield) whose characterization data were in accordance with reported literature.[9]

Appearance: colorless solid.
TLC: R_f = 0.47 (pentane/EtOAc, 5:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.38 – 8.35 (m, 1H), 7.79 – 7.76 (m, 1H), 7.64 – 7.58 (m, 2H), 7.56 – 7.50 (m, 5H), 7.42 – 7.38 (m, 2H), 7.07 – 7.03 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 197.1, 156.4, 149.0, 139.4, 139.0, 136.9, 136.5, 131.3, 130.8, 130.4, 129.0, 128.7, 128.6, 127.3, 122.4, 122.1.
HRMS: (ESI-TOF) calc'd for $[C_{18}H_{12}BrNO + H]^+$ 338.0175; found 338.0166.

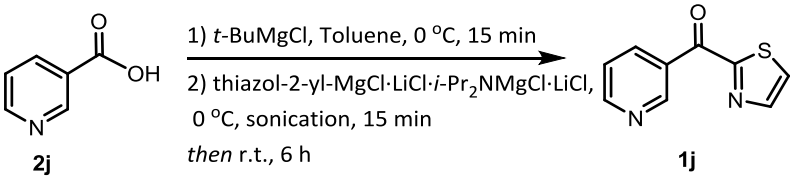
Synthesis of (4-bromophenyl)(thiazol-2-yl)methanone (1i):



General procedure A was applied using 4-bromobenzoic acid **2h** (101 mg, 0.5 mmol, 1.0 equiv.) and thiazol-2-ylmagnesium chloride lithium chloride complex[1] **8i** (1.1 mL of 0.54 M solution in THF , 0.6 mmol, 1.2 equiv.) over 6 h. The crude mixture was purified by column chromatography (EtO_2) to obtain pure **1i** as a brown solid (114 mg; 84 % yield) whose characterization data were in accordance with reported literature.[10]

Appearance: brown solid.
TLC: R_f = 0.95 (EtO_2, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.44 – 8.40 (m, 2H), 8.11 (d, *J* = 3.1 Hz, 1H), 7.76 (d, *J* = 3.1 Hz, 1H), 7.71 – 7.67 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 183.0, 167.5, 144.2, 133.9, 132.6, 131.7, 129.1, 126.6
HRMS: (ESI-TOF) calc'd for $[C_{10}H_6BrNOS + Na]^+$ 289.9246; found 289.9248.

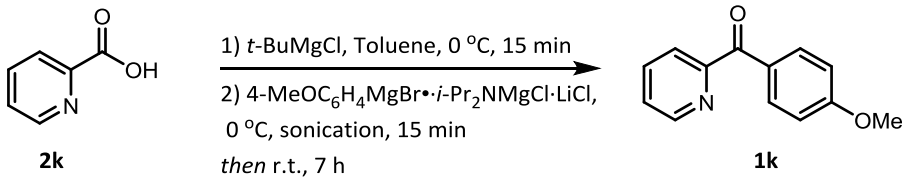
Synthesis of pyridin-3-yl(thiazol-2-yl)methanone (1j):



General procedure A was applied using nicotinic acid **2j** (62 mg, 0.5 mmol, 1.0 equiv) and thiazol-2-ylmagnesium chloride lithium chloride complex[1] **8i** (1.1 mL of 0.54 M solution in THF , 0.6 mmol, 1.2 equiv.) over 6 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 4:6) to obtain pure **1j** as a white solid (92 mg; 97 % yield).

Appearance: white solid.
TLC: R_f = 0.40 (Pentane/EtOAc, 4:6, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.69 – 9.66 (m, 1H), 8.87 – 8.84 (m, 1H), 8.82 – 8.78 (m, 1H), 8.15 (d, *J* = 3.1 Hz, 1H), 7.81 (d, *J* = 3.1 Hz, 1H), 7.51 – 7.47 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 183.0, 167.0, 153.6, 152.2, 145.2, 138.3, 130.9, 126.9, 123.2
HRMS: (ESI-TOF) calc'd for $[C_9H_6N_2OS + H]^+$ 191.0274; found 191.0263.

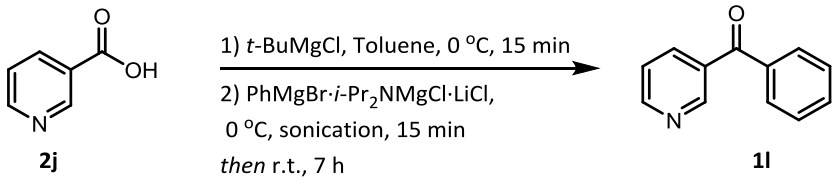
Synthesis of (4-methoxyphenyl)(pyridin-2-yl)methanone (1k):



General Procedure A was applied using picolinic acid **2k** (62 mg, 0.5 mmol, 1.0 equiv.) and 4-methoxyphenylmagnesium bromide **8d** (1.2 mL of 0.5 M solution in THF, 0.6 mmol, 1.2equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 7:3) to obtain **1k** as a white solid (91 mg; 85 % yield) whose characterization data were in accordance with reported literature.[11]

Appearance: white solid.
TLC: R_f = 0.44 (Pentane/EtOAc, 7:3).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.73 – 8.70 (m, 1H), 8.15 – 8.11 (m, 2H), 8.00 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.89 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (ddd, *J* = 7.7, 4.8, 1.2 Hz, 1H), 6.98 – 6.93 (m, 2H), 3.86 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 192.3, 163.6, 155.8, 148.4, 137.0, 133.5, 129.0, 125.8, 124.5, 113.5, 55.5.
HRMS: (ESI-TOF) calc'd for $[C_{13}H_{11}NO_2 + H]^+$ 214.0863; found 214.0873.

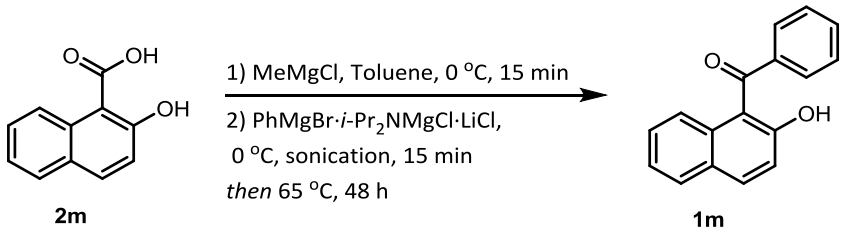
Synthesis of phenyl(pyridin-3-yl)methanone (1l):



General Procedure A was applied using nicotinic acid **2j** (62 mg, 0.5 mmol, 1.0 equiv.) and phenylmagnesium bromide **8a** (0.30 mL of 2 M solution in Et_2O, 0.6 mmol, 1.2 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 6:4) to obtain **1l** as a yellow oil (82 mg; 90 % yield) whose characterization data were in accordance with reported literature.[12]

Appearance: yellow oil.
TLC: R_f = 0.52(Pentane/EtOAc, 6:4).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.99 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.80 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.11 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.83 – 7.78 (m, 2H), 7.66 – 7.60 (m, 1H), 7.54 – 7.48 (m, 2H), 7.44 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 194.9, 152.8, 151.0, 137.2, 136.7, 133.2, 130.0, 128.6, 123.4. As noted in the reported literature,[12] one carbon resonance is not observed.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_9NO + H]^+$ 184.0757; found 184.0762.

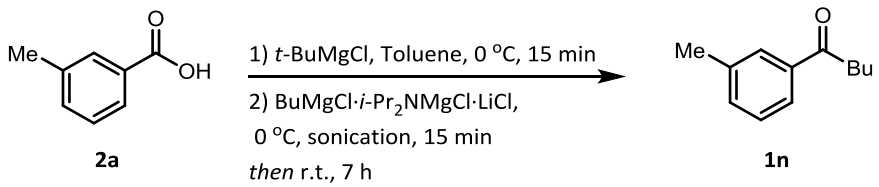
Synthesis of (2-hydroxynaphthalen-1-yl)(phenyl)methanone (1m):



General procedure A was applied using 2-hydroxy-1-naphthoic acid **2m** (94 mg, 0.5 mmol, 1.0 equiv.) and phenylmagnesium bromide **8a** (0.31 mL of 1.92 M solution in Et_2O, 0.6 mmol, 1.2 equiv.) over 48 h at 65 °C. The crude mixture was purified by preparative TLC (Petroleum ether/EtOAc, 5:1) to obtain pure **1m** as a yellow solid (97 mg; 78 % yield) whose characterization data were in accordance with reported literature.[13] *NB*: MeMgCl (2.0 equiv.) was used in step one instead of *t*-BuMgCl.

Appearance: yellow solid.
TLC: R_f = 0.65 (Petroleum ether/EtOAc, 5:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 11.20 (s, 1H), 7.94 (d, *J* = 6.5 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.66 – 7.61 (m, 2H), 7.59 – 7.52 (m, 1H), 7.45 – 7.37 (m, 2H), 7.33 – 7.23 (m, 3H), 7.19 – 7.12 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 200.4, 161.4, 140.3, 136.3, 132.7, 132.4, 129.4, 128.6, 128.5, 128.4, 126.7, 126.3, 123.7, 119.2, 114.4.
HRMS: (ESI-TOF) calc'd for $[C_{17}H_{12}O_2 + Na]^+$ 271.0730; found 271.0728.

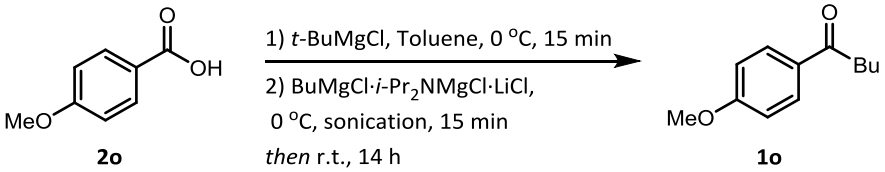
Synthesis of 1-(*m*-tolyl)pentan-1-one (1n):



General Procedure A was applied using 3-methylbenzoic acid **2a** (68 mg, 0.5 mmol, 1.0 equiv.) and butylmagnesium chloride **8n** (0.5 mL of 2 M solution in Et_2O, 1 mmol, 2.0 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1n** as a colorless oil (81 mg; 97 % yield) whose characterization data were in accordance with reported literature.[14]

Appearance: colorless oil.
TLC: R_f = 0.35 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.78 – 7.73 (m, 2H), 7.38 – 7.30 (m, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.71 (p, *J* = 7.4 Hz, 2H), 1.41 (s, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 200.8, 138.3, 137.2, 133.6, 128.6, 128.4, 125.3, 38.4, 26.5, 22.5, 21.4, 14.0.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_{16}O + Na]^+$ 199.1093; found 199.1097.

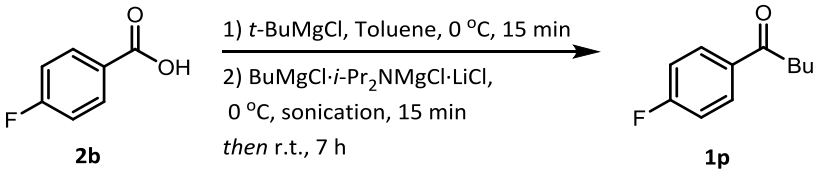
Synthesis of 1-(4-methoxyphenyl)pentan-1-one (1o):



General Procedure A was applied using 4-methoxybenzoic acid **2o** (76 mg, 0.5 mmol, 1.0 equiv.) and butylmagnesium chloride **8n** (0.5 mL of 2 M solution in Et_2O, 1 mmol, 2.0 equiv.) over 14 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1o** as a yellow solid (91 mg; 95 % yield) whose characterization data were in accordance with reported literature.[15]

Appearance: yellow solid.
TLC: R_f = 0.12 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.95 – 7.91 (m, 2H), 6.94 – 6.89 (m, 2H), 3.85 (s, 3H), 2.90 (t, *J* = 7.4 Hz, 2H), 1.69 (p, *J* = 7.4 Hz, 2H), 1.39 (s, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 199.2, 163.3, 130.3, 130.2, 113.6. 55.4, 38.0, 26.7, 22.5, 14.0.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_{16}O_2 + Na]^+$ 215.1043; found 215.1038.

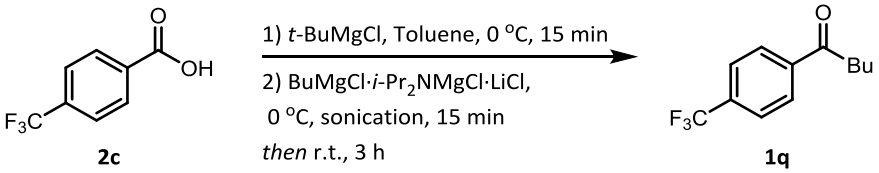
Synthesis of 1-(4-fluorophenyl)pentan-1-one (1p):



General Procedure A was applied using 4-fluorobenzoic acid **2b** (70 mg, 0.5 mmol, 1.0 equiv.) and butylmagnesium chloride **8n** (0.5 mL of 2 M solution in Et_2O, 1 mmol, 2.0 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1p** as a colorless oil (87 mg; 97 % yield) whose characterization data were in accordance with reported literature.[15]

Appearance: colorless oil.
TLC: R_f = 0.32 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.00 – 7.94 (m, 2H), 7.14 – 7.07 (m, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.70 (p, *J* = 7.4 Hz, 2H), 1.47 – 1.33 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 199.0, 165.73 (d, J_{CF} = 254.2 Hz), 133.64 (d, J_{CF} = 3.0 Hz), 130.76 (d, J_{CF} = 9.2 Hz), 115.71 (d, J_{CF} = 21.8 Hz), 38.4, 26.6, 22.6, 14.0.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 105.8.
HRMS: (ESI-TOF) calc'd for $[C_{11}H_{13}FO + Na]^+$ 203.0843; found 203.0842.

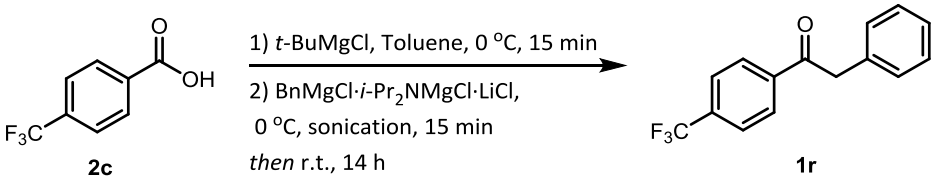
Synthesis of 1-(4-(trifluoromethyl)phenyl)pentan-1-one (1q):



General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and butylmagnesium chloride **8n** (0.50 mL of 2 M solution in Et_2O, 1.0 mmol, 2.0 equiv.) over 3 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1q** as a yellow solid (106 mg; 93 % yield) whose characterization data were in accordance with reported literature.[15]

Appearance: yellow solid.
TLC: R_f = 0.38 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.07 – 8.03 (m, 2H), 7.74 – 7.70 (m, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 1.78 – 1.68 (m, 2H), 1.48 – 1.36 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 199.4, 139.8, 134.2 (q, J_{CF} = 32.7 Hz), 128.3, 125.6 (q, J_{CF} = 3.7 Hz), 123.6 (q, J_{CF} = 272.6 Hz), 38.6, 26.2, 22.4, 13.8.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 63.12.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_{13}F_3O + Na]^+$ 253.0811; found 253.0803.

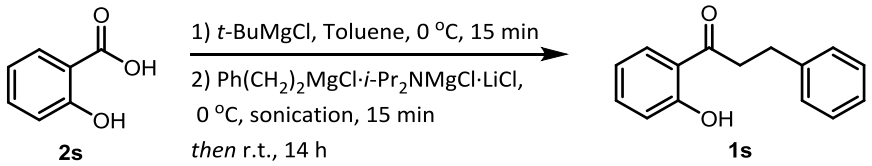
Synthesis of 2-phenyl-1-(4-(trifluoromethyl)phenyl)ethan-1-one (1r):



General procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and benzylmagnesium chloride **8r** (0.77 mL of 0.24 M solution in THF , 1.0 mmol, 2 equiv.) over 14 h. The crude mixture was purified by column chromatography (Petroleum ether/EtOAc, 10:1) to obtain pure **1r** as a yellow solid (111 mg; 84 % yield) whose characterization data were in accordance with reported literature.[16]

Appearance: yellow solid.
TLC: R_f = 0.67 (Petroleum ether/EtOAc, 10:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.13 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.32 – 7.27 (m, 3H), 4.33 (s, 2H)
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 196.6, 139.2, 134.4 (q, *J* = 32.7 Hz), 133.8, 129.4, 129.0, 128.9, 127.2, 125.8 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 272.7 Hz), 45.8.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 63.17.
HRMS: (ESI-TOF) calc'd for $[C_{15}H_{11}F_3O - H]^-$ 263.0689; found 263.0694.

Synthesis of 1-(2-hydroxyphenyl)-3-phenylpropan-1-one (1s):

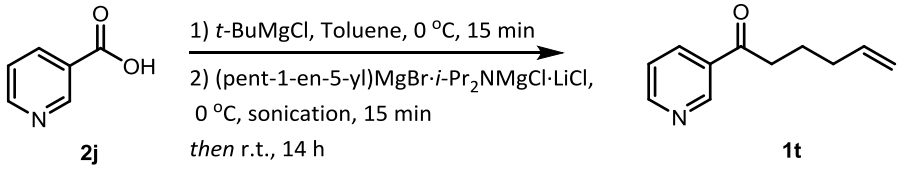


2s **1s**

General procedure A was applied using salicylic acid **2s** (95 mg, 0.5 mmol, 1.0 equiv.) and phenethylmagnesium chloride **8s** (1.96 mL of 0.51 M solution in THF , 1.0 mmol, 2 equiv.) over 14 h. The crude mixture was purified by column chromatography (Petroleum ether/EtOAc, 5:1) to obtain pure **1s** as a yellow oil (111 mg; 98 % yield) whose characterization data were in accordance with reported literature.[17]

Appearance: yellow oil.
TLC: R_f = 0.24 (Petroleum ether/EtOAc, 5:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 12.30 (s, 1H), 7.75 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.20 (m, 3H), 6.99 (dd, *J* = 8.5, 1.2 Hz, 1H), 6.91 – 6.86 (m, 1H), 3.34 (dd, *J* = 8.5, 6.9 Hz, 2H), 3.08 (dd, *J* = 8.5, 6.9 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 205.4, 162.5, 140.7, 136.4, 129.8, 128.6, 128.4, 126.3, 119.3, 118.9, 118.6, 40.1, 30.0.
HRMS: (ESI-TOF) calc'd for $[C_{15}H_{14}O_2 + Na]^+$ 249.0886; found 249.0877.

Synthesis of 1-(pyridin-3-yl)hex-5-en-1-one (1t):

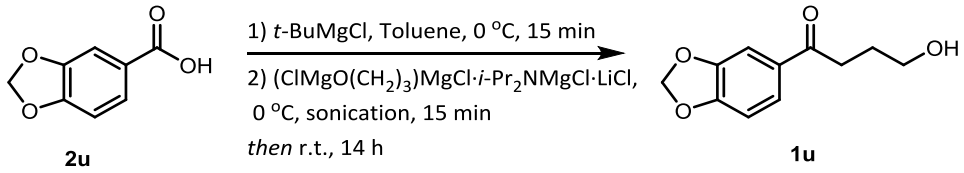


2j **1t**

General procedure A was applied using nicotinic acid **2j** (61 mg, 0.5 mmol, 1.0 equiv.) and (pent-1-en-5-yl)magnesium bromide[18] **8t** (3.0 mL of 0.33 M solution in THF, 1.0 mmol, 2.0 equiv.) over 14 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 4:6) to obtain pure **1t** as a brown solid (70 mg; 80 % yield). *NB*: the compound displays poor solubility in organic solvents.

Appearance: brown solid.
TLC: R_f = 0.46 (Pentane/EtOAc, 4:6, UV active).
^{1}H NMR (400 MHz, DMSO) δ (ppm) = 9.12 (s, 1H), 8.81 – 8.78 (m, 1H), 8.29 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.59 – 7.55 (m, 1H), 5.89 – 5.80 (m, 1H), 5.09 – 4.96 (m, 2H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.14 – 2.06 (m, 2H), 1.73 (p, *J* = 7.2 Hz, 2H).
^{13}C NMR (100 MHz, DMSO) δ (ppm) = 199.9, 153.8, 149.6, 138.7, 135.8, 124.4, 115.7, 100.0, 38.0, 33.0, 23.1.
HRMS: (ESI-TOF) calc'd for $[C_{11}H_{13}NO + H]^+$ 176.1070; found 176.1073.

Synthesis of 1-(benzo[d][1,3]dioxol-5-yl)-4-hydroxybutan-1-one (1u):

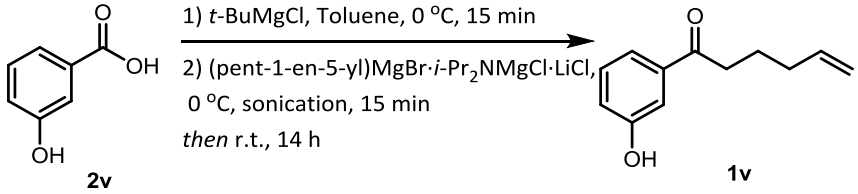


2u **1u**

General procedure A was applied using piperonylic acid **2u** (83 mg, 0.5 mmol, 1.0 equiv.) and propan-1-ol-3-magnesium chloride[19] **8u** (4.2 mL of 0.24 M solution in THF , 1.0 mmol, 2 equiv.) over 14 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 1:5) to obtain pure **1u** as a white solid (71 mg; 68 % yield).

Appearance: white solid.
TLC: R_f = 0.57 (Pentane/EtOAc, 1:5, UV active and stains red with vanilin).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 12.67 – 11.95 (br s, 1H), 7.61 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.48 (d, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.04 (s, 2H), 3.76 (t, *J* = 6.0 Hz, 2H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.07 – 1.99 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 198.5, 151.8, 148.2, 131.8, 124.4, 107.9, 107.8, 101.8, 62.4, 35.1, 27.1
HRMS: (ESI-TOF) calc'd for $[C_{11}H_{12}O_4 + Na]^+$ 231.0628; found 231.0634.

Synthesis of 1-(3-hydroxyphenyl)hex-5-en-1-one (1v):

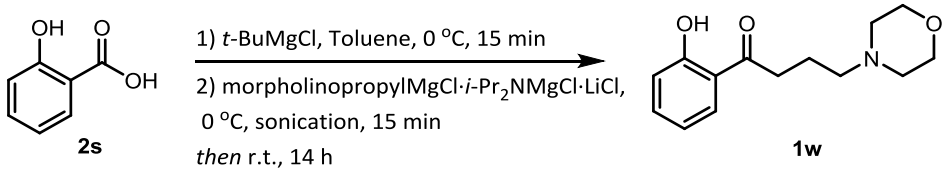


2v **1v**

General procedure A was applied using 3-hydroxybenzoic acid **2v** (69 mg, 0.5 mmol, 1.0 equiv.) and (pent-1-en-5-yl)magnesium bromide **8t** (3.0 mL of 0.33 M solution in THF, 1.0 mmol, 2.0 equiv.) over 14 h. The crude mixture was purified by column chromatography (Petroleum ether/EtOAc, 5:1) to obtain pure **1v** as a white solid (88 mg; 93 % yield). *NB*: 1.0 additional equivalent of ^{t}BuMgCl was used in step 1.

Appearance: white solid.
TLC: R_f = 0.63 (Petroleum ether/EtOAc, 5:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.57 – 7.49 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.11 – 7.06 (m, 1H), 5.84 (m, 1H), 5.52 (br s, 1H), 5.11 – 4.99 (m, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 2.18 (q, *J* = 7.1 Hz, 2H), 2.01 (p, *J* = 7.4 Hz, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 200.4, 156.0, 138.5, 138.0, 129.9, 120.7, 120.2, 115.4, 114.5, 37.9, 33.2, 23.3.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_{14}O_2 + Na]^+$ 213.0886; found 213.0877.

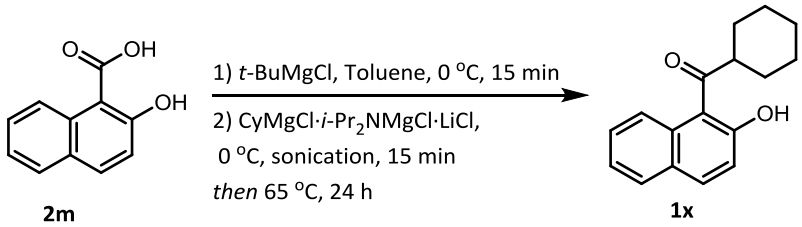
Synthesis of 1-(2-hydroxyphenyl)-4-morpholinobutan-1-one (1w):



General procedure A was applied using salicylic acid **2s** (69 mg, 0.5 mmol, 1.0 equiv.) and morpholinopropylmagnesium chloride **8w** (3.6 mL of 0.28 M solution in THF, 1.0 mmol, 2.0 equiv.) over 14 h. The crude mixture was purified by column chromatography (Toluene/MeOH, 95:5) to obtain pure **1w** as a yellow solid (117 mg; 94 % yield). *NB*: 1.0 additional equivalent of *t*-BuMgCl was used in step 1.

Appearance: yellow solid.
TLC: R_f = 0.23 (Toluene/MeOH, 95:5, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.82 (m, 1H), 7.49 (m, 1H), 7.01 (m, 1H), 6.92 (m, 1H), 3.66 – 3.62 (m, 4H), 3.06 (t, *J* = 7.1 Hz, 2H), 2.46 – 2.41 (m, 6H), 1.98 (p, *J* = 7.1 Hz, 2H). *OH resonance not observed.*
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 206.4, 162.4, 136.1, 129.9, 119.7, 118.8, 118.6, 66.8, 58.0, 53.5, 35.9, 21.5.
HRMS: (ESI-TOF) calc'd for $[C_{14}H_{19}NO_3 + H]^+$ 250.1438; found 250.1427.

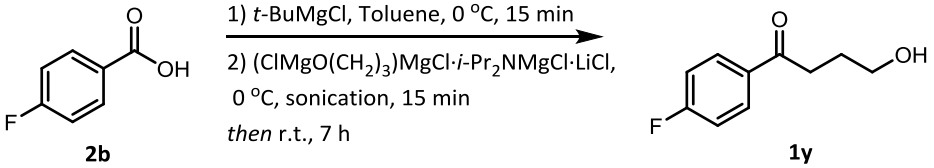
Synthesis of cyclohexyl(2-hydroxynaphthalen-1-yl)methanone (1x):



General procedure A was applied using 2-hydroxy-1-naphthoic acid **2m** (94 mg, 0.5 mmol, 1.0 equiv.) and cyclohexylmagnesium bromide **8x** (0.55 mL of 1.81 M solution in Et_2O, 1.0 mmol, 2.0 equiv.) at 65 °C over 24 h. The crude mixture was purified by column chromatography (Petroleum ether/EtOAc, 10:1) to obtain pure **1x** as a brown solid (98 mg; 77 % yield) whose characterization data were in accordance with reported literature.[13] *NB*: 1.0 additional equivalent of ^{t}BuMgCl was used in step 1.

Appearance: brown solid.
TLC: R_f = 0.38 (Petroleum ether/EtOAc, 10:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 12.0 (s, 1H), 7.94 – 7.90 (m, 1H), 7.88 (d, *J* = 9.0 Hz, 1H) 7.81 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.45 – 7.38 (m, 1H), 7.16 (d, *J* = 9.0 Hz, 1H), 3.52 (tt, *J* = 11.5, 3.2 Hz, 1H), 2.01 – 1.93 (m, 2H), 1.90 – 1.82 (m, 2H), 1.80 – 1.63 (m, 3H), 1.41 – 1.26 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 212.0, 161.2, 136.1, 131.7, 129.3, 128.7, 127.8, 124.3, 123.8, 119.4, 115.6, 50.3, 29.9, 25.8, 25.6.
HRMS: (ESI-TOF) calc'd for $[C_{17}H_{18}O_2 + Na]^+$ 277.1199; found 277.1211.

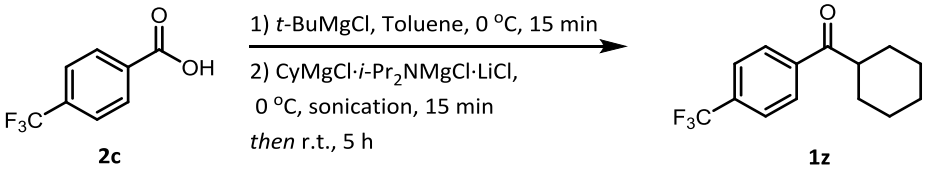
Synthesis of 1-(4-fluorophenyl)-4-hydroxybutan-1-one (1y):



General procedure A was applied using 4-fluorobenzoic acid **2b** (70 mg, 0.5 mmol, 1.0 equiv.) and propan-1-ol-3-magnesium chloride[19] **8u** (4.2 mL of 0.24 M solution in THF, 1.0 mmol, 2.0 equiv.) over 24 h. The crude mixture was purified by preparative TLC (Petroleum ether/EtOAc, 1:4) to obtain pure **1y** as a colorless oil (90 mg; 99 % yield) whose characterization data were in accordance with reported literature.[20]

Appearance: colorless oil.
TLC: R_f = 0.50 (Petroleum ether/EtOAc, 1:4, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.04 – 7.98 (m, 2H), 7.16 – 7.09 (m, 2H), 3.75 (t, *J* = 6.0 Hz, 2H), 3.11 (t, *J* = 6.9 Hz, 2H), 2.02 (d, *J* = 6.0 Hz, 2H). *OH resonance not observed.*
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 105.25.
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 198.8, 165.8 (d, J_{CF} = 253.9 Hz), 133.3, 130.7 (d, J_{CF} = 9.3 Hz), 115.7 (d, J_{CF} = 21.9 Hz), 62.3, 35.2, 26.7.
HRMS: (ESI-TOF) calc'd for $[C_{10}H_{11}FO_2 + Na]^+$ 205.0635; found 205.0642.

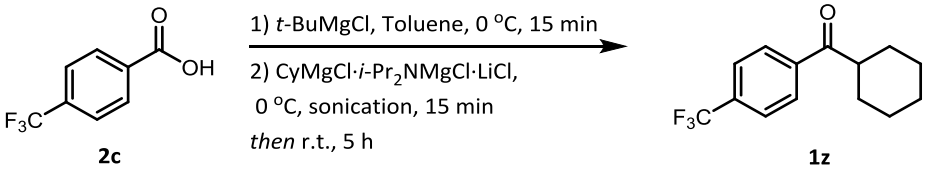
Synthesis of cyclohexyl(4-(trifluoromethyl)phenyl)methanone (1z):



General Procedure A was applied using 4-(trifluoromethyl)benzoic acid **2c** (95 mg, 0.5 mmol, 1.0 equiv.) and cyclohexylmagnesium chloride **8x** (0.50 mL of 2 M solution in THF, 1.0 mmol, 2.0 equiv.) over 5 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1z** as a yellow oil (109 mg; 96 % yield) whose characterization data were in accordance with reported literature.[21]

Appearance: yellow oil.
TLC: R_f = 0.42 (Pentane/EtOAc, 30:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.03 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 3.29 – 3.20 (m, 1H), 1.93 – 1.82 (m, 4H), 1.79 – 1.71 (m, 1H), 1.55 – 1.35 (m, 4H), 1.33 – 1.23 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 202.8, 139.2, 134.0 (q, J_{CF} = 32.7 Hz), 128.6, 125.7 (q, J_{CF} = 3.7 Hz), 123.7 (q, J_{CF} = 272.6 Hz), 46.0, 29.2, 25.9, 25.7.
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 63.09.
HRMS: (ESI-TOF) calc'd for $[C_{14}H_{15}F_3O + Na]^+$ 279.0967; found 279.0956.

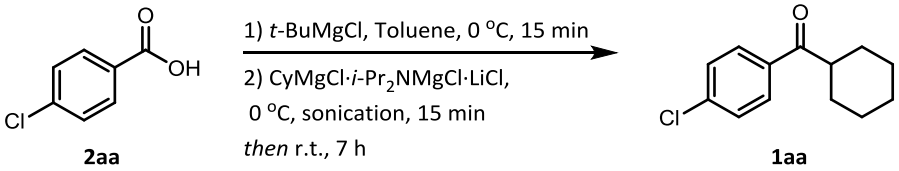
Gram-scale synthesis of cyclohexyl(4-(trifluoromethyl)phenyl)methanone (1z):



2c **1z**

To a solution of 4-(trifluoromethyl)benzoic acid **2c** (1.5 g, 7.9 mmol, 1.0 equiv) in anhydrous toluene (200 mL) stirred at 0 °C under Ar, ^{t}BuMgCl (9.7 mL of 0.81 M solution in THF, 7.9 mmol, 1.0 equiv.) was added dropwise. The resulting solution was stirred at 0 °C for 15 min. In a separate flask, cyclohexylmagnesium chloride **8x** (8.8 mL of a 1.8 M solution in THF, 15.8 mmol, 2.0 equiv.) was added dropwise to a solution of DIPAMgCl·LiCl (**9a**, 26.3 mL of a 0.6 M solution in THF, 15.8 mmol, 2.0 equiv.) stirred at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min, then was added dropwise to the carboxylate solution. The resulting mixture was allowed to warm up to r.t. and stirred for 5 h. The reaction was quenched at 0 °C with 1M aq. HCl. The crude mixture was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The crude mixture was purified by column chromatography (Pentane/EtOAc, 30:1) to obtain pure **1z** as a yellow oil (1.86 g; 92 % yield) whose characterization data match those previously reported (see page S-23).

Synthesis of (4-chlorophenyl)(cyclohexyl)methanone (1aa):

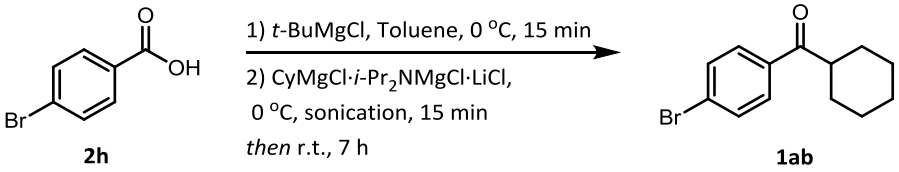


2aa **1aa**

General Procedure A was applied using 4-chlorobenzoic acid **2aa** (78 mg, 0.5 mmol, 1.0 equiv.) and cyclohexylmagnesium chloride **8x** (0.50 mL of 2 M solution in THF, 1.0 mmol, 2.0 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 15:1) to obtain pure **1aa** as a yellow oil (99 mg; 89 % yield) whose characterization data were in accordance with reported literature.[21]

Appearance: yellow oil.
TLC: R_f = 0.50 (Pentane/EtOAc, 15:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.90 – 7.85 (m, 2H), 7.45 – 7.40 (m, 2H), 3.20 (tt, *J* = 11.3, 3.2 Hz, 1H), 1.91 – 1.81 (m, 4H), 1.77 – 1.70 (m, 1H), 1.55 – 1.24 (m, 5H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 202.6, 139.1, 134.6, 129.7, 128.8, 45.6, 29.4, 25.9, 25.8.
HRMS: (ESI-TOF) calc'd for $[C_{13}H_{15}ClO + Na]^+$ 245.0704; found 245.0714.

Synthesis of (4-bromophenyl)(cyclohexyl)methanone (1ab):

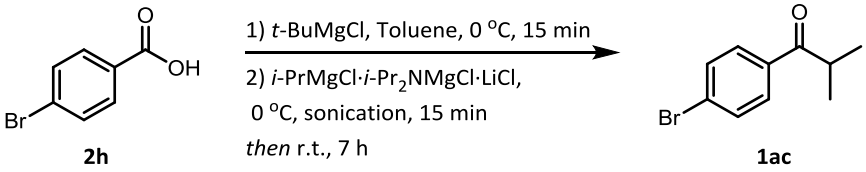


2h **1ab**

General Procedure A was applied using 4-bromobenzoic acid **2h** (101 mg, 0.5 mmol, 1.0 equiv.) and cyclohexylmagnesium chloride **8x** (0.50 mL of 2 M solution in THF, 1.0 mmol, 2.0 equiv.) over 7 h. The crude mixture was purified by preparative TLC (Pentane/EtOAc, 20:1) to obtain **1ab** as a yellow oil (114 mg; 85 % yield) whose characterization data were in accordance with reported literature.[21]

Appearance: yellow oil.
TLC: R_f = 0.50 (Pentane/EtOAc, 20:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.80 (d, *J* = 8.5 Hz, 2H), 7.59 (d, J = 8.5 Hz, 2H), 3.19 (tt, *J* = 11.3, 3.2 Hz, 1H), 1.90 – 1.81 (m, 4H), 1.76 – 1.70 (m, 1H), 1.53 – 1.43 (m, 2H), 1.42 – 1.34 (m, 2H), 1.33 – 1.23 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 202.8, 135.0, 131.9, 129.8, 127.8, 45.6, 29.4, 25.9, 25.8.
HRMS: (ESI-TOF) calc'd for $[C_{13}H_{15}BrO + Na]^+$ 289.0198; found 289.0190.

Synthesis of 1-(4-bromophenyl)-2-methylpropan-1-one (1ac):

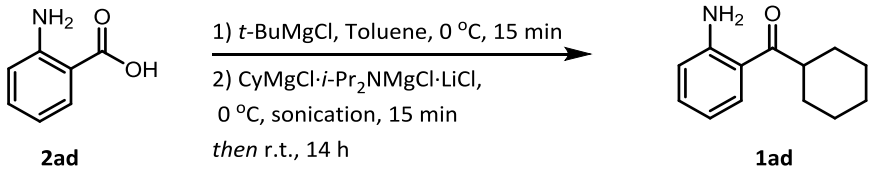


2h **1ac**

General Procedure A was applied using 4-bromobenzoic acid **2h** (101 mg, 0.5 mmol, 1.0 equiv.) and isopropylmagnesium chloride **8ac** (0.76 mL of 1.3 M solution in Et_2O, 1.0 mmol, 2.0 equiv.) over 7 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 20:1) to obtain **1ac** as a yellow oil (107 mg; 94 % yield) whose characterization data were in accordance with reported literature.[22]

Appearance: yellow oil.
TLC: R_f = 0.42 (Pentane/EtOAc, 20:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.84 – 7.79 (m, 2H), 7.62 – 7.58 (m, 2H), 3.49 (hept, *J* = 7.0 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 203.4, 134.9, 131.9, 129.9, 127.9, 35.4, 19.1.
HRMS: (ESI-TOF) calc'd for $[C_{10}H_{11}BrO + Na]^+$ 248.9885; found 248.9877.

Synthesis of (2-aminophenyl)(cyclohexyl)methanone (1ad):

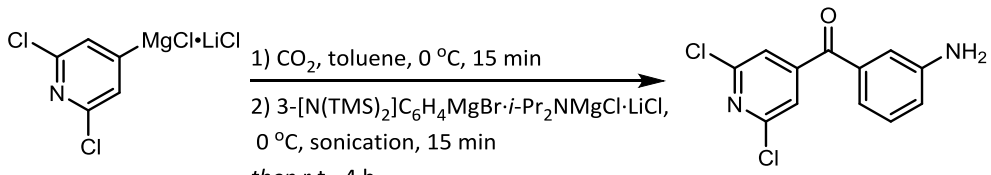


2ad **1ad**

General Procedure A was applied using anthranilic acid **2ad** (69 mg, 0.5 mmol, 1.0 equiv.) and cyclohexylmagnesium chloride **8x** (0.5 mL of 2 M solution in Et_2O, 1 mmol, 2.0 equiv.) over 14 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 20:1) to obtain pure **1ad** as a yellow solid (92 mg; 91 % yield)) whose characterization data were in accordance with reported literature.[23] NB: 2.0 additional equivalent of ^{t}BuMgCl were used in step 1.

Appearance: yellow solid.
TLC: R_f = 0.39 (Pentane/EtOAc, 20:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.80 – 7.76 (m, 1H), 7.30 – 7.22 (m, 1H), 6.70 – 6.64 (m, 2H), 6.32 (br s, 2H), 3.29 (tt, *J* = 11.5, 3.2 Hz, 1H), 1.93 – 1.83 (m, 4H), 1.79 – 1.73 (m, 1H), 1.60 – 1.48 (m, 2H), 1.47 – 1.36 (m, 2H), 1.35 – 1.24 (m, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 206.4, 150.9, 134.0, 130.9, 117.6, 117.0, 115.7, 45.9, 29.9, 26.1, 26.0.
HRMS: (ESI-TOF) calc'd for $[C_{13}H_{17}NO + Na]^+$ 226.1202; found 226.1190.

Synthesis of (3-aminophenyl)(2,6-dichloropyridin-4-yl)methanone (1ae):

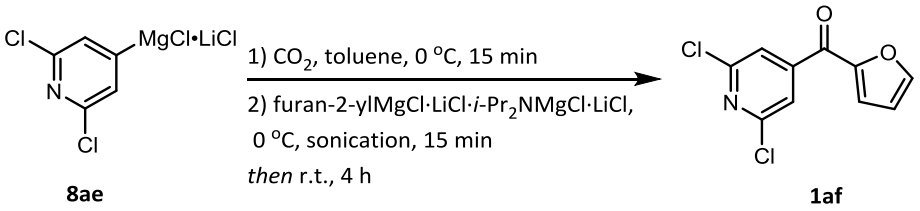


8ae **1ae**

General procedure B was applied using 2,6-dichloropyridin-4-ylmagnesiumchloride lithium chloride complex[3] **8ae** (1.45 mL of a 0.35 M solution in THF, 0.5 mmol, 1.0 equiv.) and 3-(bis(trimethylsilyl)amino)phenylmagnesium bromide **8f** (0.6 mL of 1 M solution in THF, 0.6 mmol, 1.2 equiv.) over 4 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 1:1) to obtain pure **1ae** as a yellow oil (99 mg; 74 % yield). *NB*: The TMS protecting groups were cleaved on silica upon purification.

Appearance: yellow oil.
TLC: R_f = 0.33 (Pentane/EtOAc, 1:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.28 (s, 2H), 7.11 (t, *J* = 7.9 Hz, 1H), 6.65 – 6.61 (m, 1H), 6.57 – 6.52 (m, 1H), 6.52 – 6.50 (m, 1H), 3.58 (br s, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 207.4, 161.5, 150.2, 146.3, 145.7, 129.5, 122.0, 118.1, 114.9, 114.4.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_8Cl_2N_2O + Na]^+$ 288.9906; found 288.9905.

Synthesis of (2,6-dichloropyridin-4-yl)(furan-2-yl)methanone (1af):

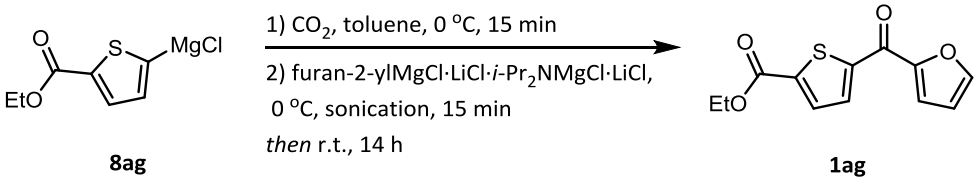


8ae **1af**

General procedure B was applied using 2,6-dichloropyridin-4-ylmagnesiumchloride lithium chloride complex[3] **8ae** (1.45 mL of a 0.35 M solution in THF, 0.5 mmol, 1.0 equiv.) and furan-2-ylmagnesium chloride lithium chloride complex[3] **8af** (0.75 mL of 0.8 M solution in THF, 0.6 mmol, 1.2 equiv.) over 4 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 8:1) to obtain pure **1af** as a colorless oil (116 mg; 96 % yield).

Appearance: colorless oil.
TLC: R_f = 0.28 (Pentane/EtOAc, 8:1, UV active, stains pink with vanillin).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.78 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.76 (s, 2H), 7.40 (dd, *J* = 3.7, 0.8 Hz, 1H), 6.68 (dd, *J* = 3.7, 1.7 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 177.6, 151.4, 151.2, 148.5, 148.4, 122.2, 122.1, 113.2.
HRMS: (ESI-TOF) calc'd for $[C_{10}H_5Cl_2NO_2 + H]^+$ 241.9770; found 241.9759.

Synthesis of ethyl 5-(furan-2-carbonyl)thiophene-2-carboxylate (1ag):

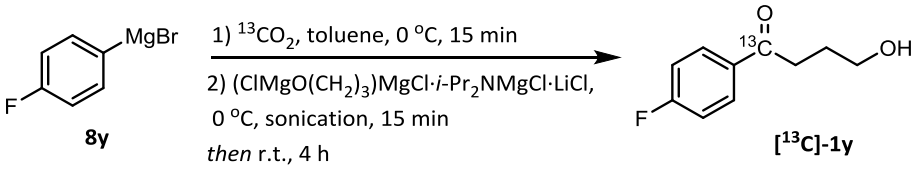


8ag **1ag**

General procedure B was applied using (5-(ethoxycarbonyl)thiophen-2-yl)magnesium chloride[24] **8ag** (0.8 mL of a 0.63 M solution in THF, 0.5 mmol, 1.0 equiv.) and furan-2-ylmagnesium chloride lithium chloride complex[3] **8af** (0.75 mL of 0.8 M solution in THF, 0.6 mmol, 1.2 equiv.) over 14 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 4:1) to obtain pure **1ag** as a yellow oil (76 mg; 61 % yield).

Appearance: yellow oil.
TLC: R_f = 0.50 (Pentane/EtOAc, 4:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.10 (d, *J* = 4.0 Hz, 1H), 7.82 (d, *J* = 4.0 Hz, 1H), 7.72 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.46 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.64 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 173.1, 161.7, 152.2, 146.9, 146.2, 140.2, 133.2, 133.1, 119.7, 112.8, 61.8, 14.3.
HRMS: (ESI-TOF) calc'd for $[C_{12}H_{10}O_4S + Na]^+$ 273.0192; found 273.0202.

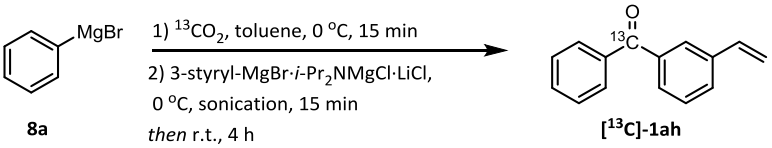
Synthesis of 1-(4-fluorophenyl)-4-hydroxybutan-1-one-1-^{13}C ([^{13}C]-1y):



General procedure C was applied using 4-fluorophenylmagnesium bromide **8y** (0.96 mL of a 0.52 M solution in THF, 0.5 mmol, 1.0 equiv.) and propan-1-ol-3-magnesium chloride[19] **8u** (4.2 mL of 0.24 M solution in THF, 1.0 mmol, 2.0 equiv.) over 4 h. The crude mixture was purified by preparative TLC (Pentane/EtOAc, 1:4) to obtain pure **[^{13}C]-1y** as a colorless oil (88 mg; 97 % yield) whose characterization data were consistent with those of compound **1y**[20] (see page S-23).

Appearance: colorless oil.
TLC: R_f = 0.50 (Pentane/EtOAc, 1:4, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.05 – 7.96 (m, 2H), 7.17 – 7.09 (m, 2H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.14 – 3.07 (m, 2H), 2.06 – 1.97 (m, 2H). *OH resonance not observed.*
^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) = – 105.25.
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 198.8, 165.8 (d, J_{CF} = 255.8 Hz), 130.7 (dd, J_{CF} = 9.3, J_{CC} =3.1 Hz), 115.7 (dd, J_{CF} = 21.8, J_{CC} = 4.2 Hz), 108.5, 62.2 (d, J_{CC} = 2.6 Hz), 35.2 (d, J_{CC} = 41.7 Hz), 26.9 (d, J_{CC} = 1.8 Hz).
HRMS: (ESI-TOF) calc'd for [$^{13}C_1{}^{12}C_9H_{11}FO_2$ + Na]$^+$ 206.0674; found 206.0606.

Synthesis of phenyl(3-vinylphenyl)methanone-^{13}C ([^{13}C]-1ah):

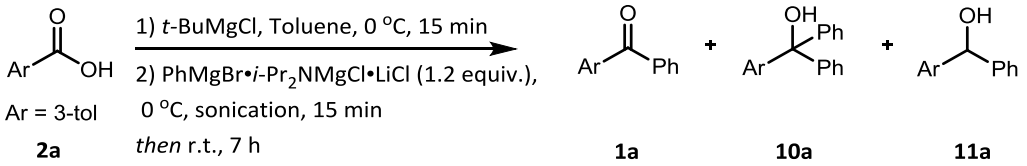


General procedure C was applied using phenylmagnesium bromide **8a** (0.52 mL of a 0.96 M solution in THF, 0.5 mmol, 1.0 equiv.) and 3-styrylmagnesium bromide **8ah** (0.65 mL of 0.96 M solution in THF, 0.6 mmol, 1.2 equiv.) over 4 h. The crude mixture was purified by column chromatography (Pentane/EtOAc, 9:1) to obtain pure **[^{13}C]-1ah** as a colorless oil (100 mg; 96 % yield).

Appearance: colorless oil.
TLC: R_f = 0.62 (Pentane/EtOAc, 9:1, UV active).
^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.87 – 7.78 (m, 3H), 7.70 – 7.56 (m, 3H), 7.53 – 7.41 (m, 3H), 6.77 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 10.9 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 196.7, 138.0 (d, J_{CC} = 43.3 Hz), 137.8 (d, J_{CC} = 1.8 Hz), 137.5 (d, J_{CC} = 41.3 Hz), 136.0, 132.5, 130.1 (d, J_{CC} = 2.8 Hz), 129.9, 129.4 (d, J_{CC} = 2.9 Hz), 128.4 (d, J_{CC} = 4.2 Hz), 128.3 (d, J_{CC} = 4.0 Hz), 127.7 (d, J_{CC}= 2.7 Hz), 115.3.
HRMS: (ESI-TOF) calc'd for [$^{13}C_1{}^{12}C_{14}H_{12}O$ + Na]$^+$ 232.0819; found 232.0754.

III – Optimization Tables

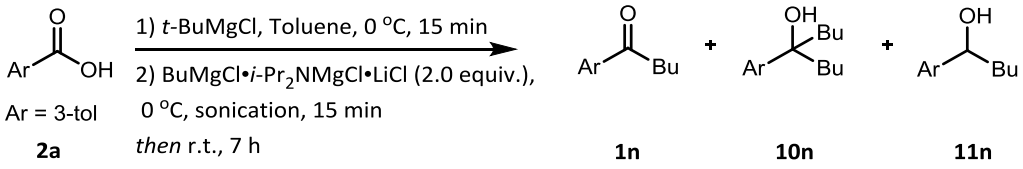
Table S1: optimization of the reaction conditions with aryl-Grignard reagents.



Entry	Deviation from standard conditions	2a[b] (%)	1a[b] (%)	10a[b] (%)	11a[b] (%)
1	**none**	**0**	**92**	**0**	**5**
2	LDA instead of *i*-Pr_2NMgCl·LiCl	70	22	4	8
3	TMPLi instead of *i*-Pr_2NMgCl·LiCl	61	25	3	8
4	DIPAMgCl instead of *i*-Pr_2NMgCl·LiCl	55	36	4	4
5	*n*-PrNHLi instead of *i*-Pr_2NMgCl·LiCl	65	21	14	0
6	*t*-BuOMe instead of Toluene	17	81	0	0
7	Et_2O instead of Toluene	5	91	0	0
8	TMPMgCl·LiCl instead of *i*-Pr_2NMgCl·LiCl [c]	7	72	2	8
9	*i*-PrMgCl·LiCl instead of *t*-BuMgCl	44	45	0	3
10	*i*-Pr_2NMgCl·LiCl instead of *t*-BuMgCl	40	45	0	8
11	NaH instead of *t*-BuMgCl	9	77	14	0
12	1 extra equiv. *i*-Pr_2NMgCl·LiCl	12	60	3	17
13	1.5 equiv *i*-Pr_2NMgCl·LiCl /PhMgBr	0	90	0	6
14	2.0 equiv. *i*-Pr_2NMgCl·LiCl /PhMgBr	0	90	0	9
15	No sonication	26	49	3	25
16	1h sonication	0	81	0	16

[a] Standard conditions: **2a** (0.1 mmol), toluene (2 mL), *t*-BuMgCl (0.1 mmol) at 0 °C for 15 min. In separate vial, PhMgBr (**8a**, 0.12 mmol) and *i*-Pr_2NMgCl·LiCl (**9a**, 0.12 mmol) at 0 °C for 15 min, *then* added to the carboxylate solution, *then* sonication, 0 °C, 15 min, *then* r.t., 7 h. [b] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [c] Et_2O was used instead due to observed deprotonation of Toluene by TMPMgCl·LiCl.

Table S2: optimization of the reaction conditions with alkyl-Grignard reagents.

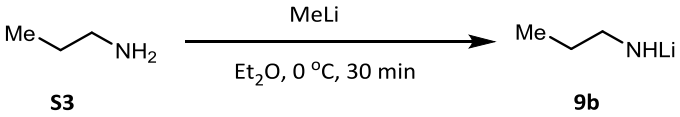


Entry	Deviation from standard conditions	2a[b] (%)	1n[b] (%)	10n[b] (%)	11n[b] (%)
1	**none**	**0**	**97**	**0**	**0**
2	LDA instead of *i*-Pr_2NMgCl·LiCl	58	49	0	3
3	TMPLi instead of *i*-Pr_2NMgCl·LiCl	54	51	0	0
4	DIPAMgCl instead of *i*-Pr_2NMgCl·LiCl	73	8	0	15
5	TMPMgCl·LiCl instead of *i*-Pr_2NMgCl·LiCl[c]	4	84	5	0
6	1 extra equiv. *i*-Pr_2NMgCl·LiCl	6	62	0	21
7	1.5 equiv. *i*-Pr_2NMgCl·LiCl /BuMgCl	18	78	0	4
8	1.2 equiv. *i*-Pr_2NMgCl·LiCl /BuMgCl	62	36	0	5
9	No sonication	57	36	0	6
10	1h sonication	0	79	0	17
11	65 °C instead of r.t.	0	85	0	15

[a] Standard conditions **2a** (0.1 mmol), toluene (2 mL), *t*-BuMgCl (0.1 mmol) at 0 °C for 15 min. In separate vial, BuMgCl (**8n**, 0.2 mmol) and *i*-Pr_2NMgCl·LiCl (**9a**, 0.2 mmol) at 0 °C for 15 min, *then* added to the carboxylate solution, *then* sonication, 0 °C, 15 min, *then* r.t., 7 h. [b] Determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [c] Et_2O was used instead due to observed deprotonation of Toluene by TMPMgCl·LiCl.

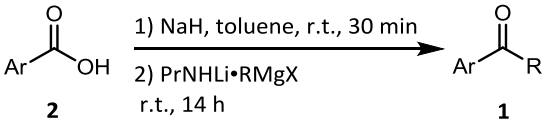
IV – Miscellaneous experimental information

Preparation of *n*-PrNHLi (9b)



The reagent was prepared following the procedure reported by Asaoka.[25] To a solution of *n*-propylamine (**S3**, 59 mg, 1.0 mmol, 1.0 equiv.) in Et_2O (1 mL) stirred at 0 °C under Ar, a solution of methyllithium (0.63 mL of a 1.6 M solution in Et_2O, 1.0 mmol, 1.0 equiv.) was added dropwise. The resulting colorless solution was stirred for 30 min at 0 °C and used directly in the next step.

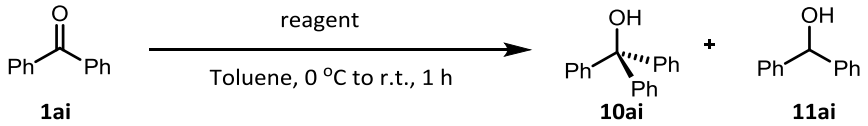
Comparative synthesis of ketones 1 with *n*-PrNHLi (9b)



The control experiments were run following the procedure reported by Asaoka.[25] To a suspension of carboxylic acid **2** (0.1 mmol, 1.0 equiv.) in toluene (1 mL) stirred at 0 °C under Ar, sodium hydride (0.15 mmol, 1.5 equiv.) was added portionwise. The resulting suspension was stirred at 0 °C for 30. In a separate flask, to a solution of freshly prepared *n*-PrNHLi (**9b**, 0.2 mmol, 2.0 equiv.) stirred at 0 °C under Ar, the appropriate Grignard reagent (**8**, 2.0 mmol, 2.0 equiv.) was added dropwise. The

resulting heterogeneous mixture was stirred at 0 °C for 30 min, *then* was added dropwise to the sodium carboxylate suspension. The resulting solution was allowed to warm up to r.t. and stirred for 14 h, monitoring by GC-MS of quenched aliquots. The reaction was quenched with acetone (2 mL) and 2M aq. HCl (2 mL). The crude mixture was extracted with EtOAc (3 x 2 mL), washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo.* The results were determined by ^{1}H NMR using trimethoxybenzene as internal standard.

Table S3: Reduction of benzophenone

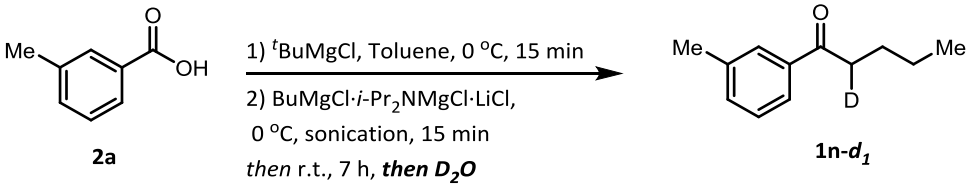


1ai **10ai** **11ai**

Entry	Reagent	Recovered 1ai (%)	10ai (%)	11ai (%)
1	BuMgCl·*i*-Pr_2NMgCl·LiCl	0	17	83
2	PhMgBr·*i*-Pr_2NMgCl·LiCl	0	73	27
3	*i*-Pr_2NMgCl·LiCl	15	0	85
4	*i*-Pr_2NMgCl	93	0	0

Procedure: to a solution of benzophenone **1ai** (0.1 mmol, 1.0 equiv.) in toluene (1.5 mL) stirred at 0 °C under Ar, a solution of the appropriate reagent (0.12 mmol, 1.2 equiv.) was added dropwise. The resulting solution was allowed to warm up to r.t. and stirred for 1h. The reaction was quenched with 1M aq. HCl. The crude mixture was extracted with ethyl acetate (3 x 10 mL), and the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The results were determined by ^{1}H NMR using trimethoxybenzene as internal standard. *NB*: For entries 1-3, the solution was bright pink upon addition of the reagent. For entry 4, the solution was colorless.

Deuteration experiment



2a **1n-d_1**

To a solution of 3-toluic acid **2a** (14 mg, 0.1 mmol, 1.0 equiv.) in anhydrous toluene (1.5 mL) stirred at 0 °C under Ar, ^{t}BuMgCl (0.1 mL of 1 M solution in THF, 0.1 mmol, 1.0 equiv.) was added dropwise. The resulting solution was stirred at 0 °C for 15 min. In a separate flask, butylmagnesium chloride **8n** (0.1 mL of a 1.0 M solution in THF, 0.2 mmol, 2.0 equiv.) was added dropwise to a solution of *i*-Pr_2NMgCl·LiCl (**9a**, 0.33 of a 0.6 M solution in THF, 0.2 mmol, 2.0 equiv.) stirred at 0 °C under Ar. The resulting solution was stirred at 0 °C for 15 min, then was added dropwise to the carboxylate solution. The resulting mixture was sonicated at 0 °C for 15 min, then stirred at r.t. for 7h. The reaction was quenched with deuterated water. The crude mixture was extracted with EtOAc (3 x 2mL) and concentrated *in vacuo*. The yield and the amount of deuterium incorporation were determined by ^{1}H NMR using trimethoxybenzene as internal standard.

V - References

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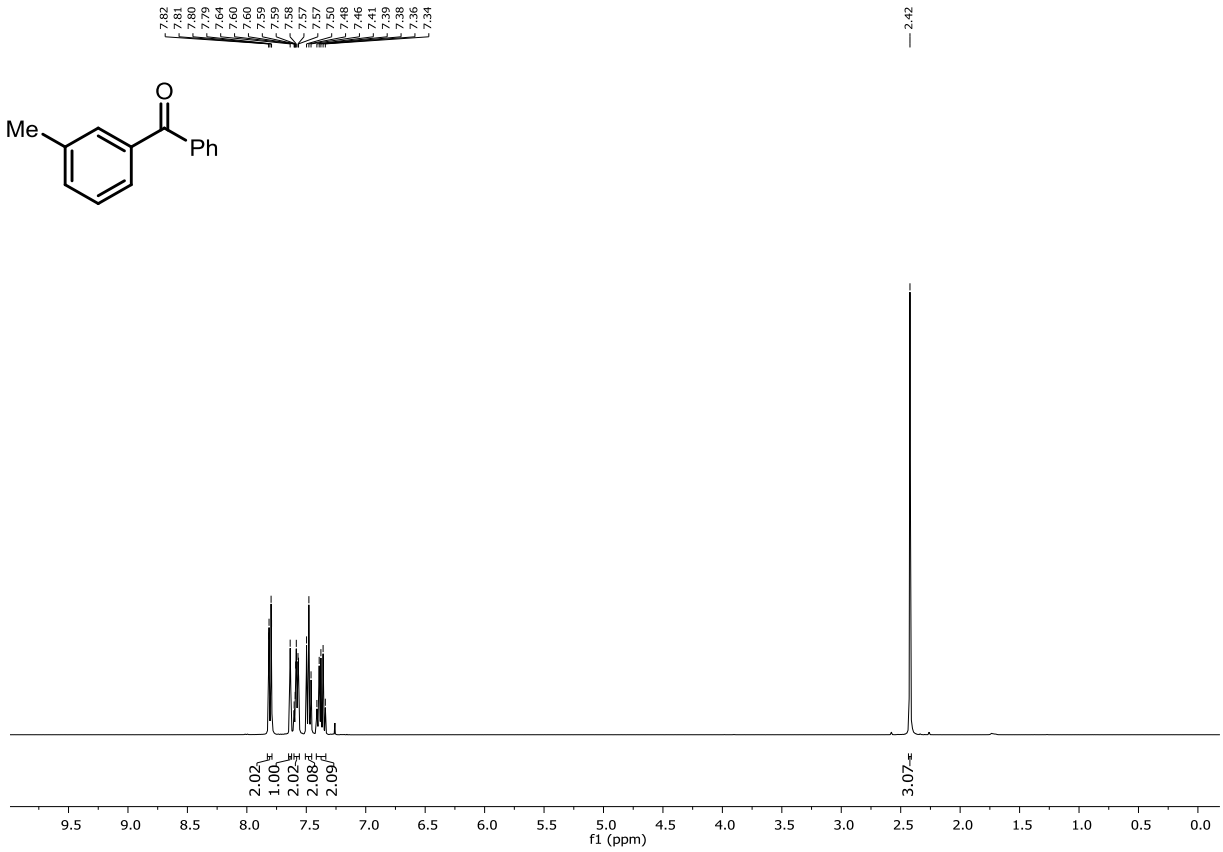
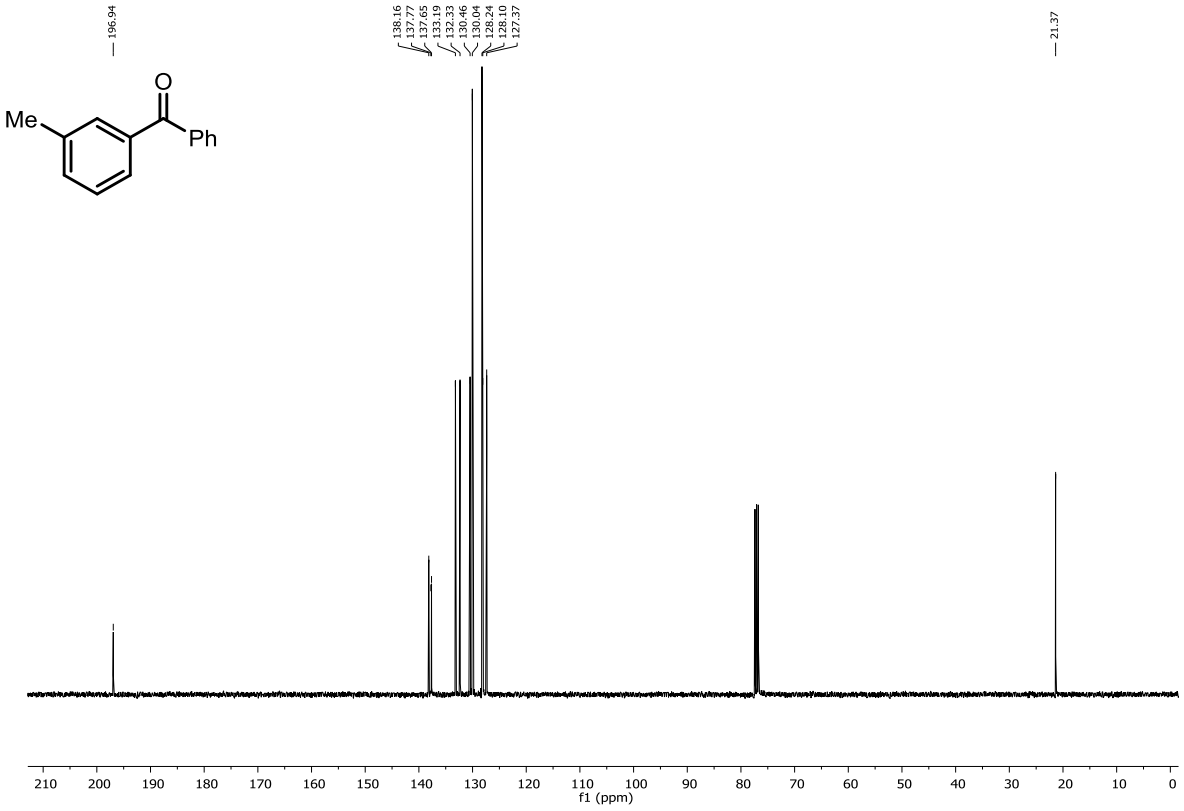
VI – NMR spectra of synthesized compounds

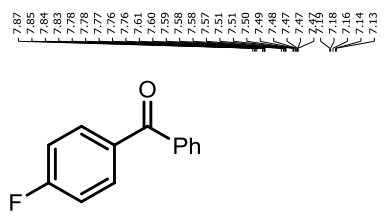
^{1}H NMR (400 MHz, $CDCl_3$) ***1a***

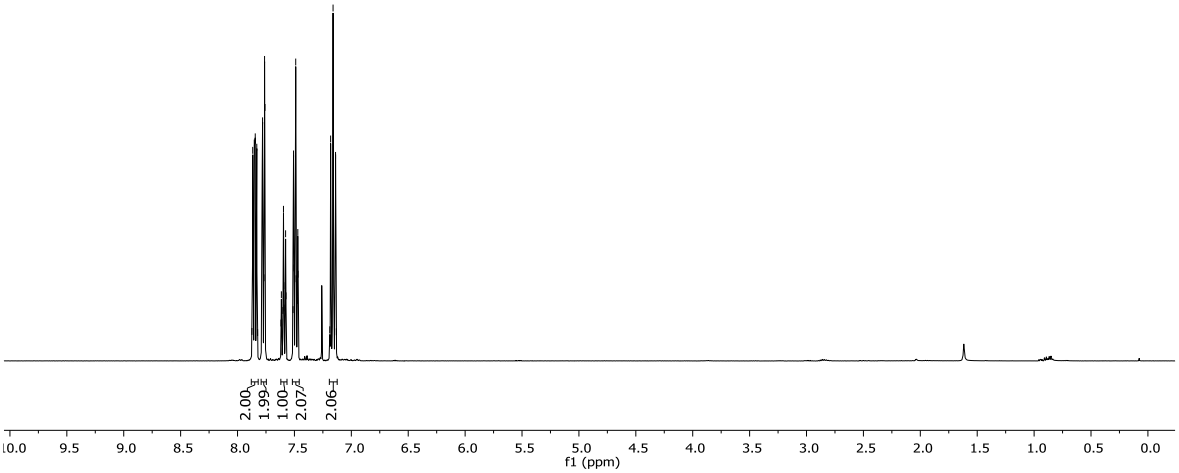


^{13}C NMR (100 MHz, $CDCl_3$) ***1a***

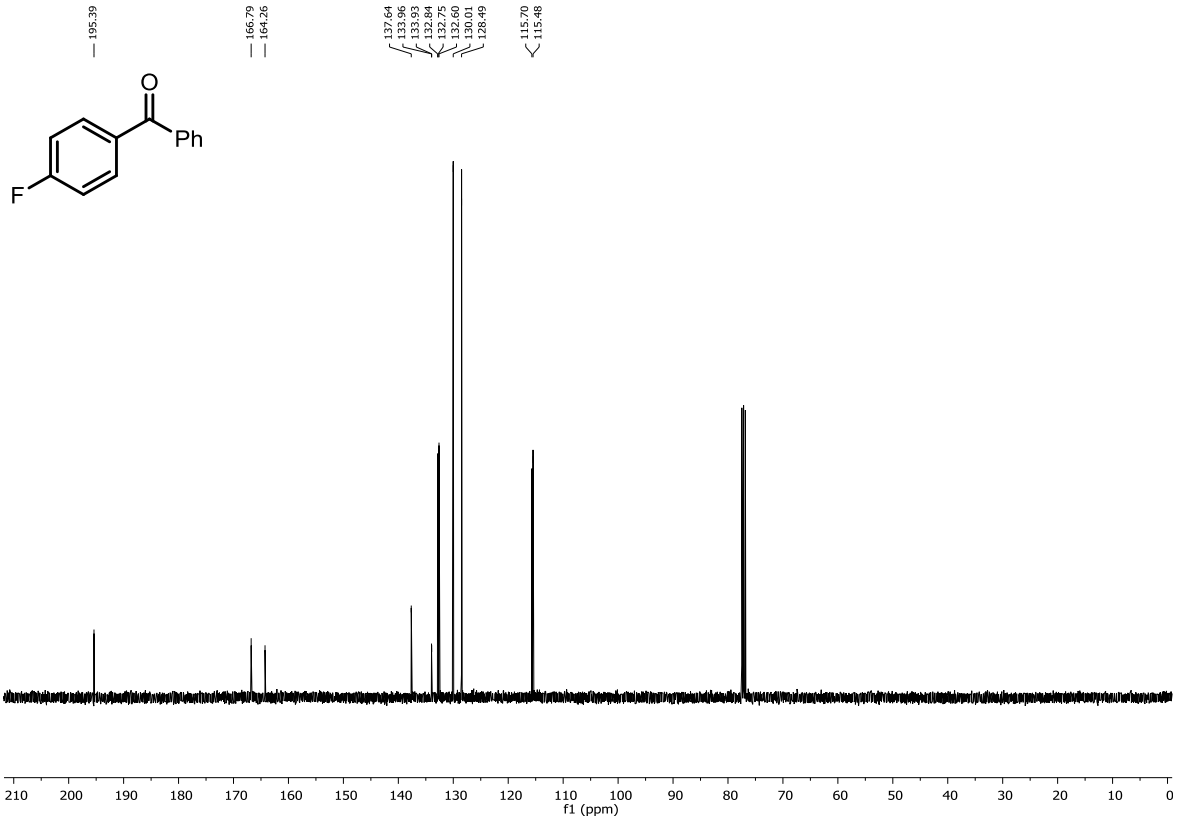


^{1H} NMR (400 MHz, $CDCl_3$) ***1b***

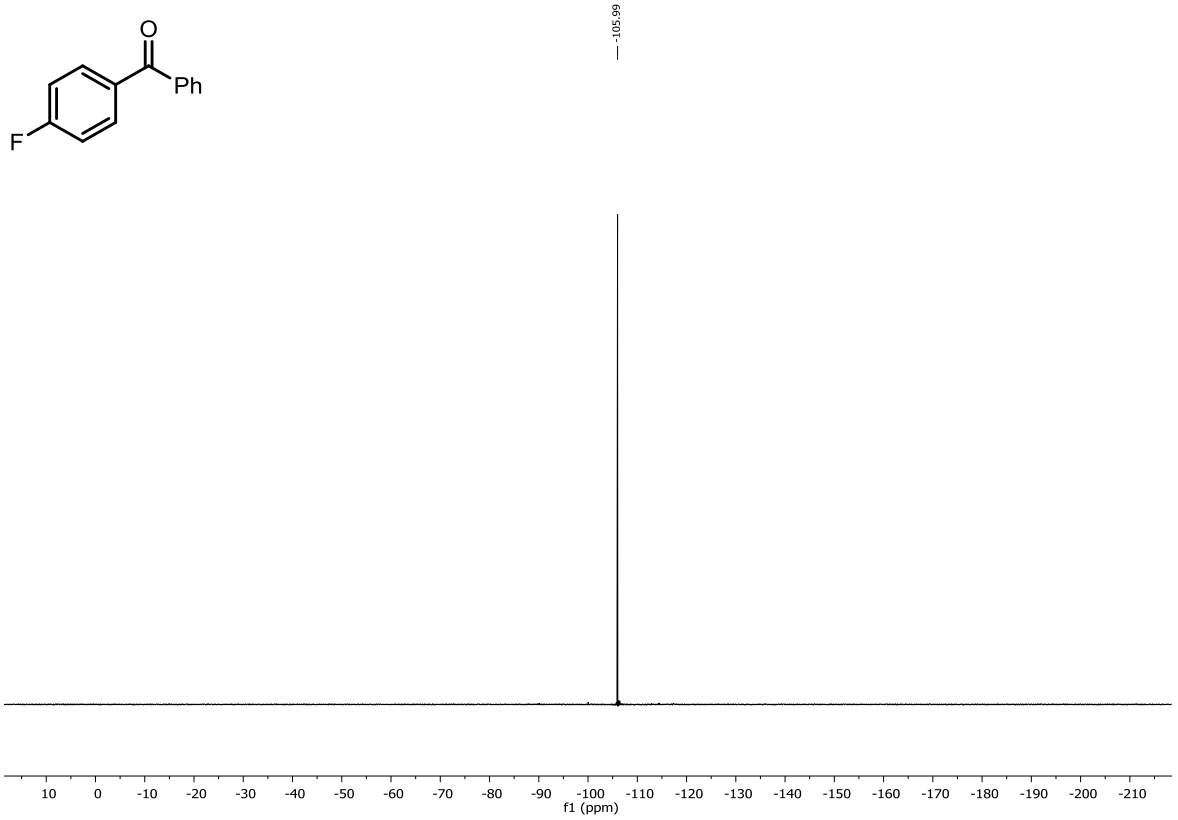




^{13}C NMR (100 MHz, $CDCl_3$) ***1b***



^{19}F NMR (377 MHz, $CDCl_3$) ***1b***



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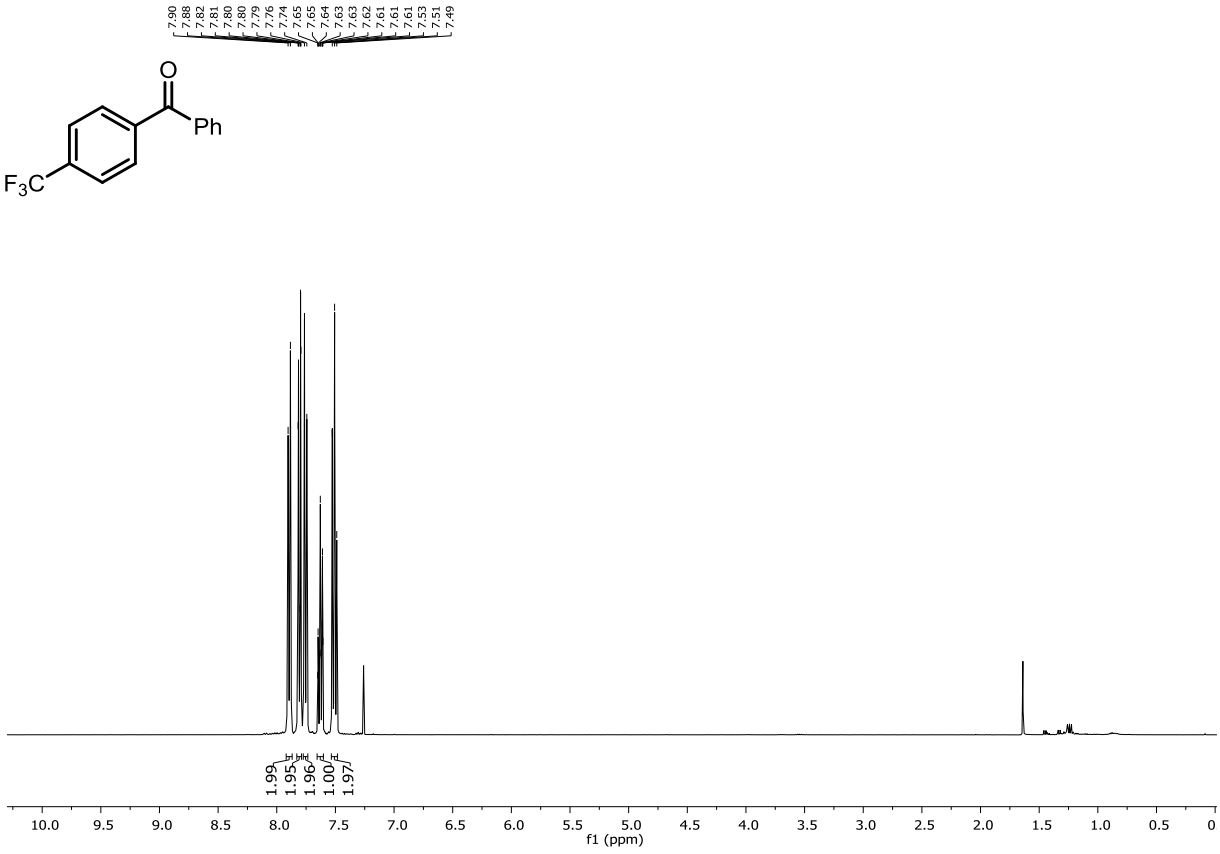
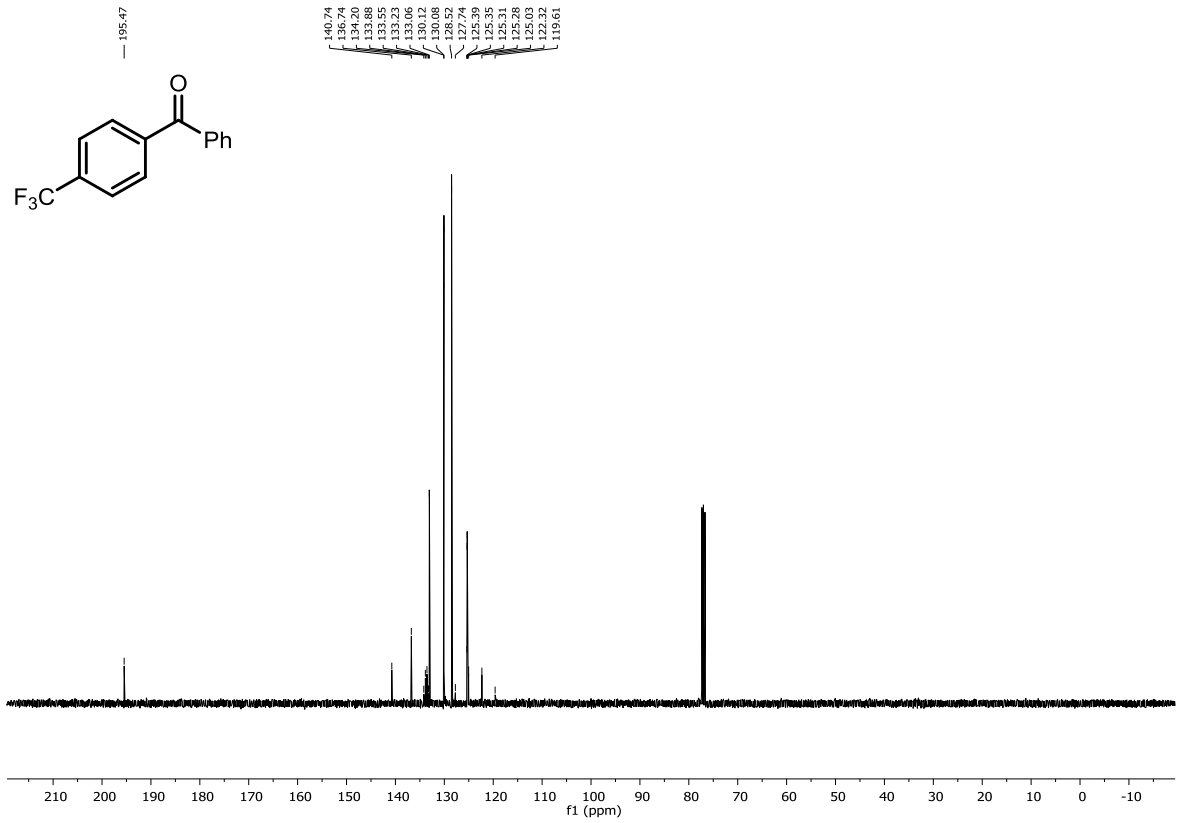
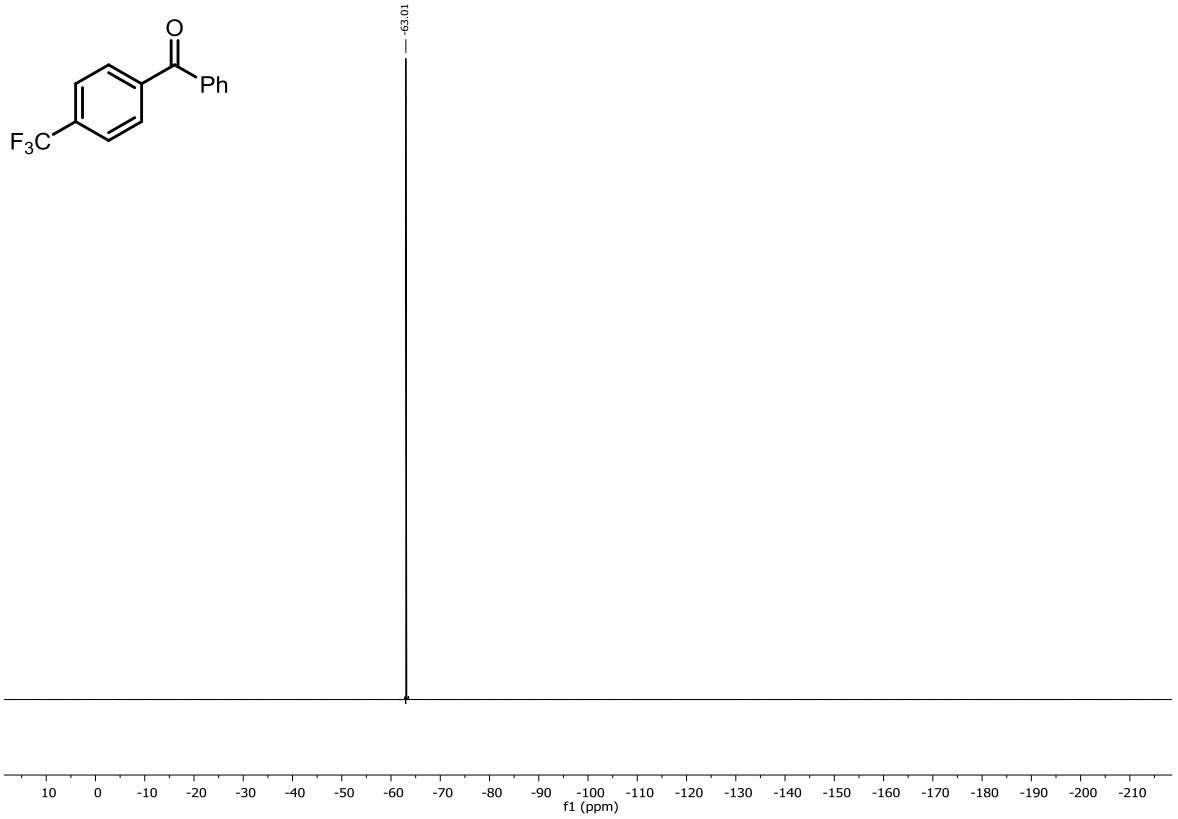


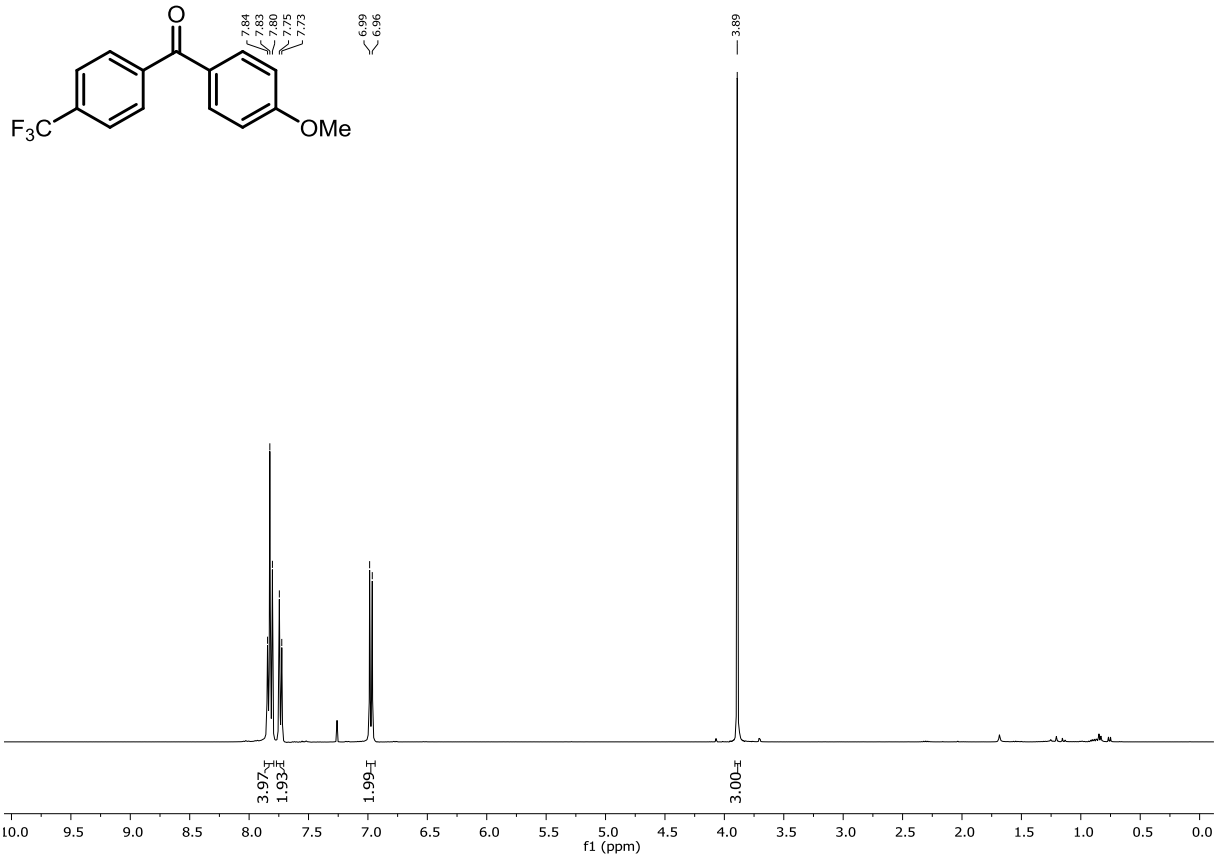
^{13}C NMR (100 MHz, $CDCl_3$) ***1c***



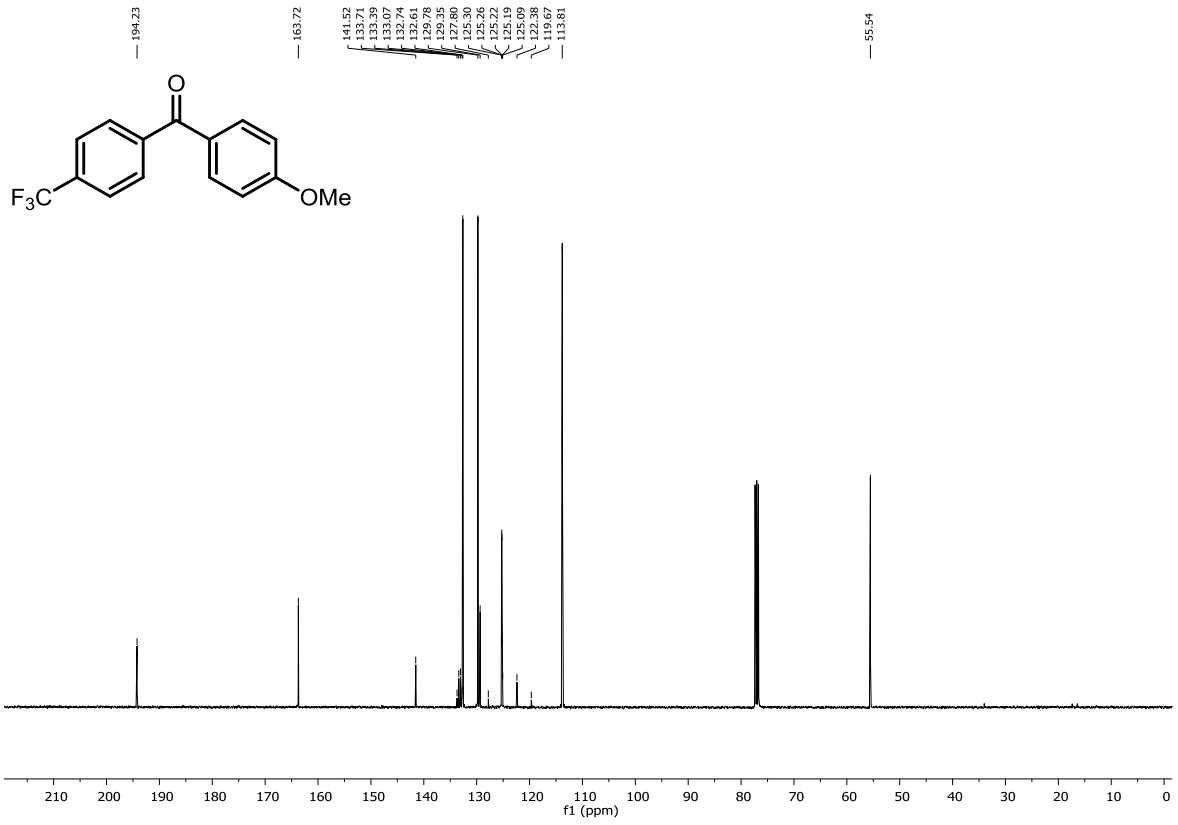
^{19}F NMR (377 MHz, $CDCl_3$) ***1c***



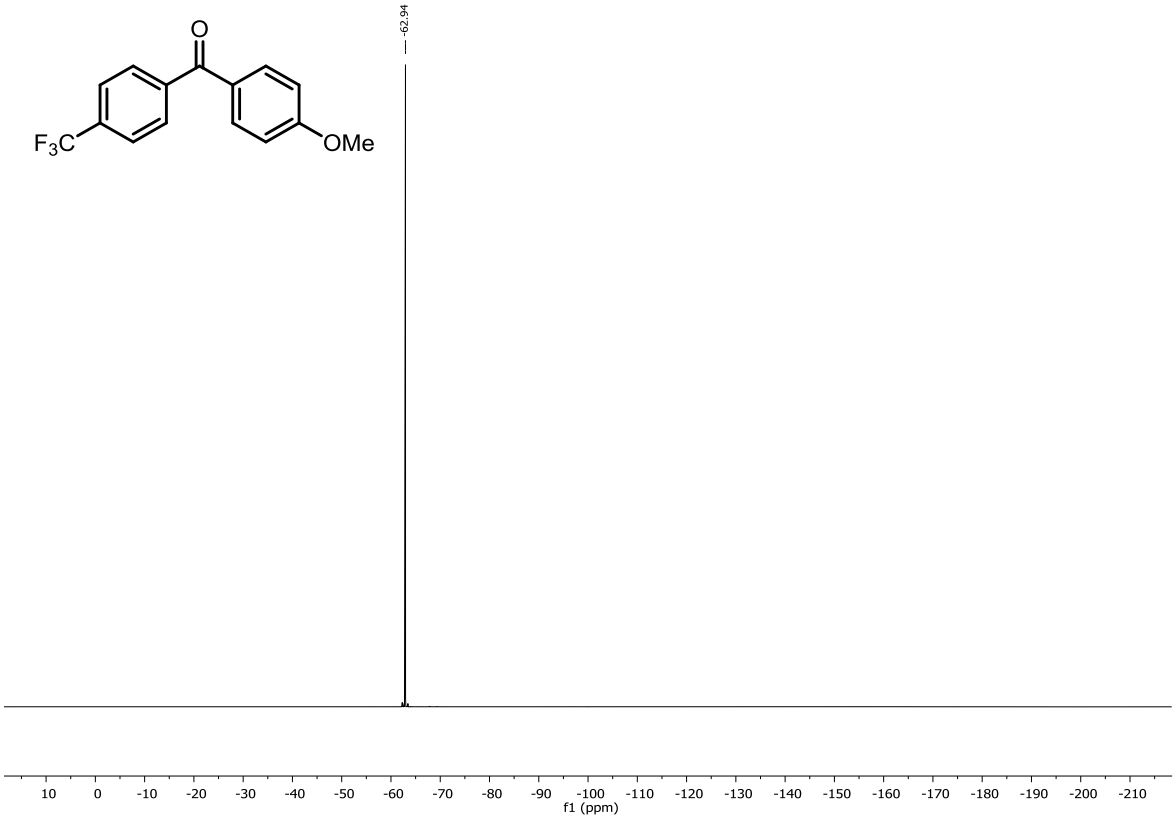
^{1H} NMR (400 MHz, $CDCl_3$) ***1d***



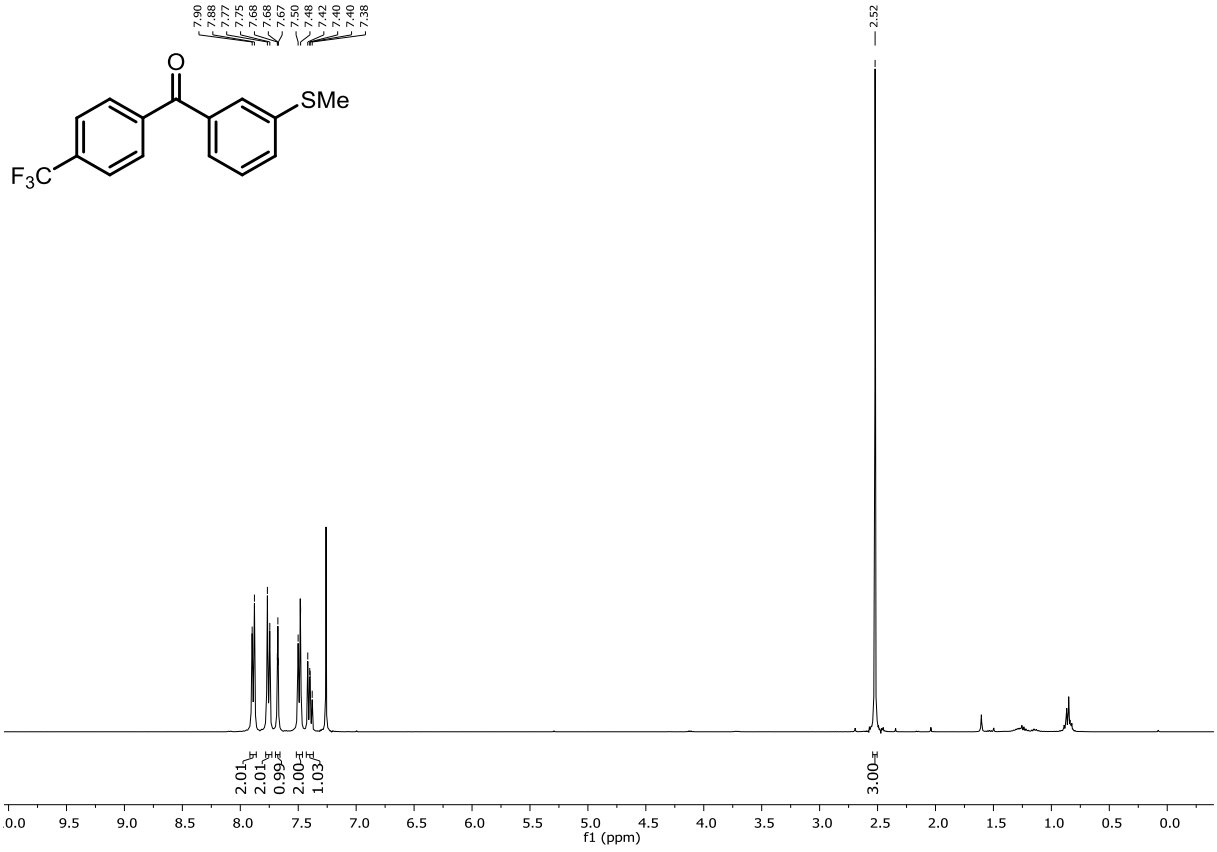
^{13}C NMR (100 MHz, $CDCl_3$) ***1d***



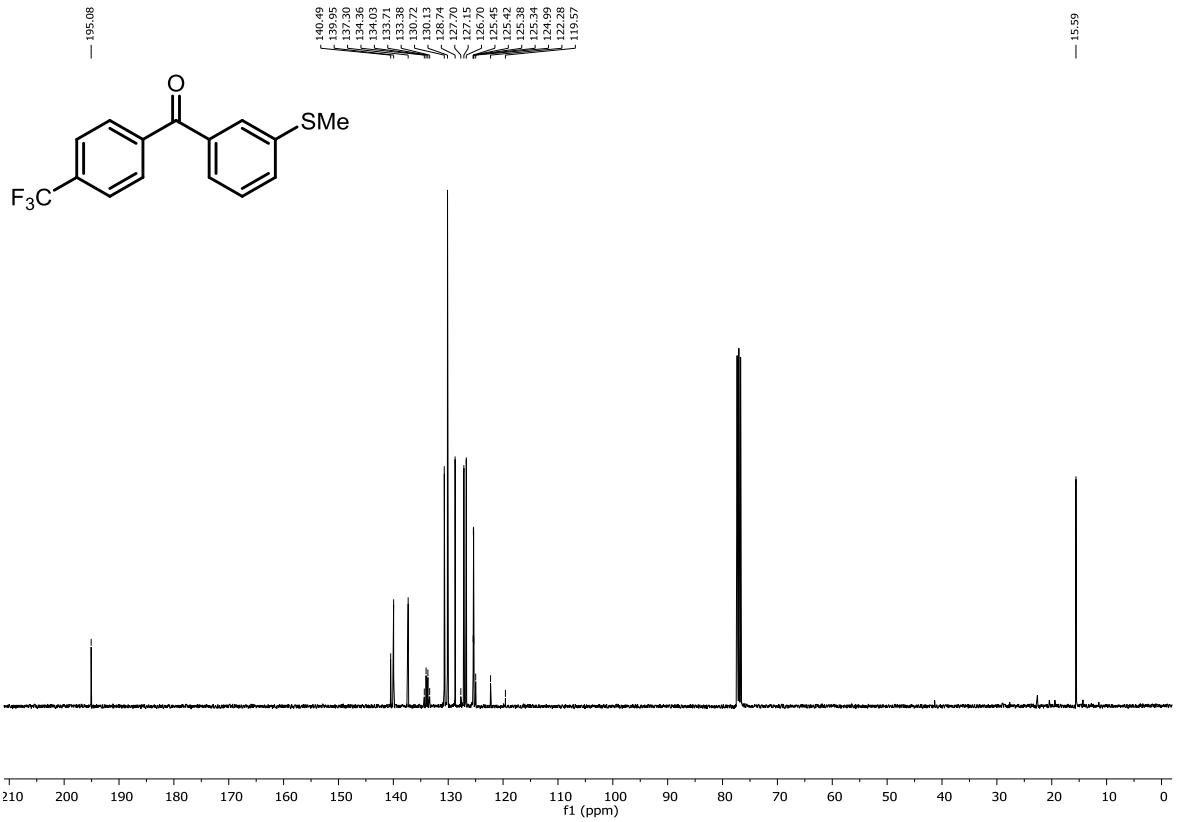
^{19}F NMR (377 MHz, $CDCl_3$) ***1d***



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

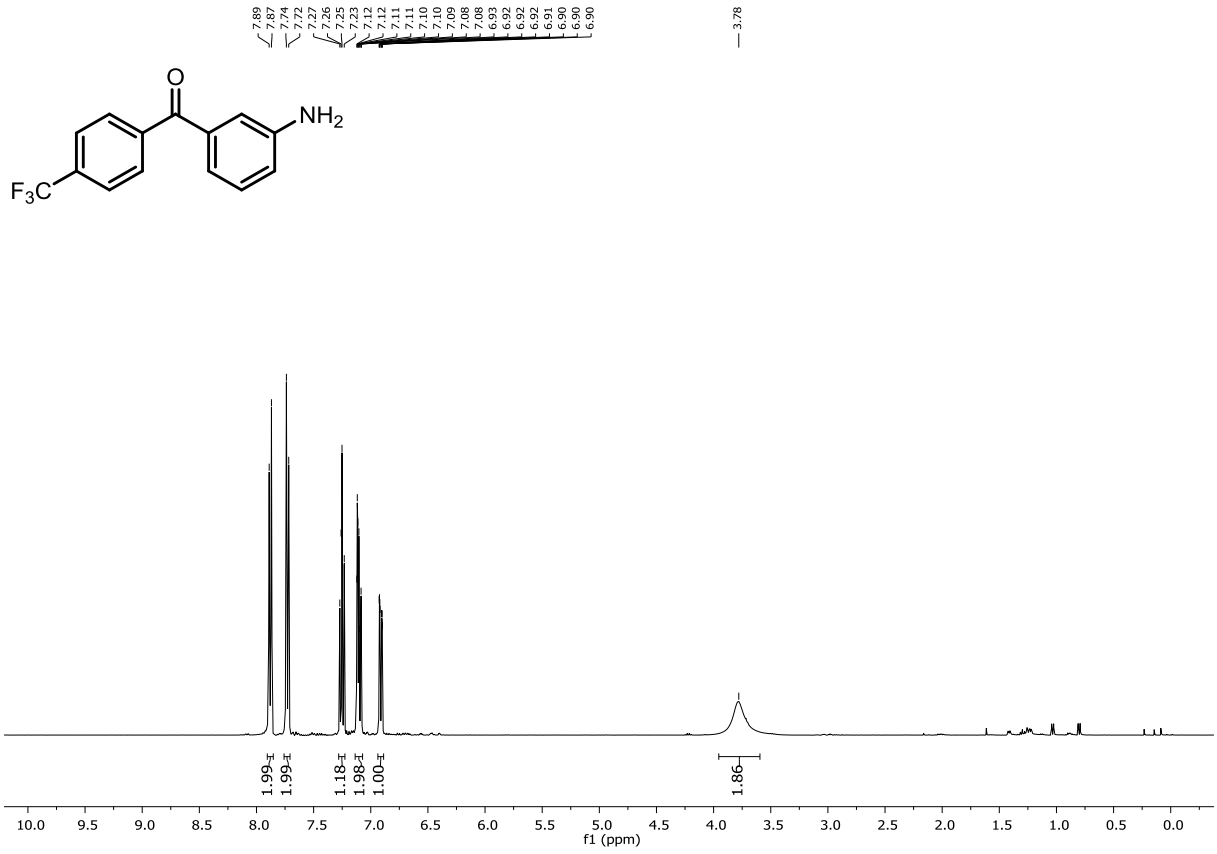


^{13}C NMR (100 MHz, $CDCl_3$) ***1e***



^{19}F NMR (377 MHz, $CDCl_3$) ***1e***

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



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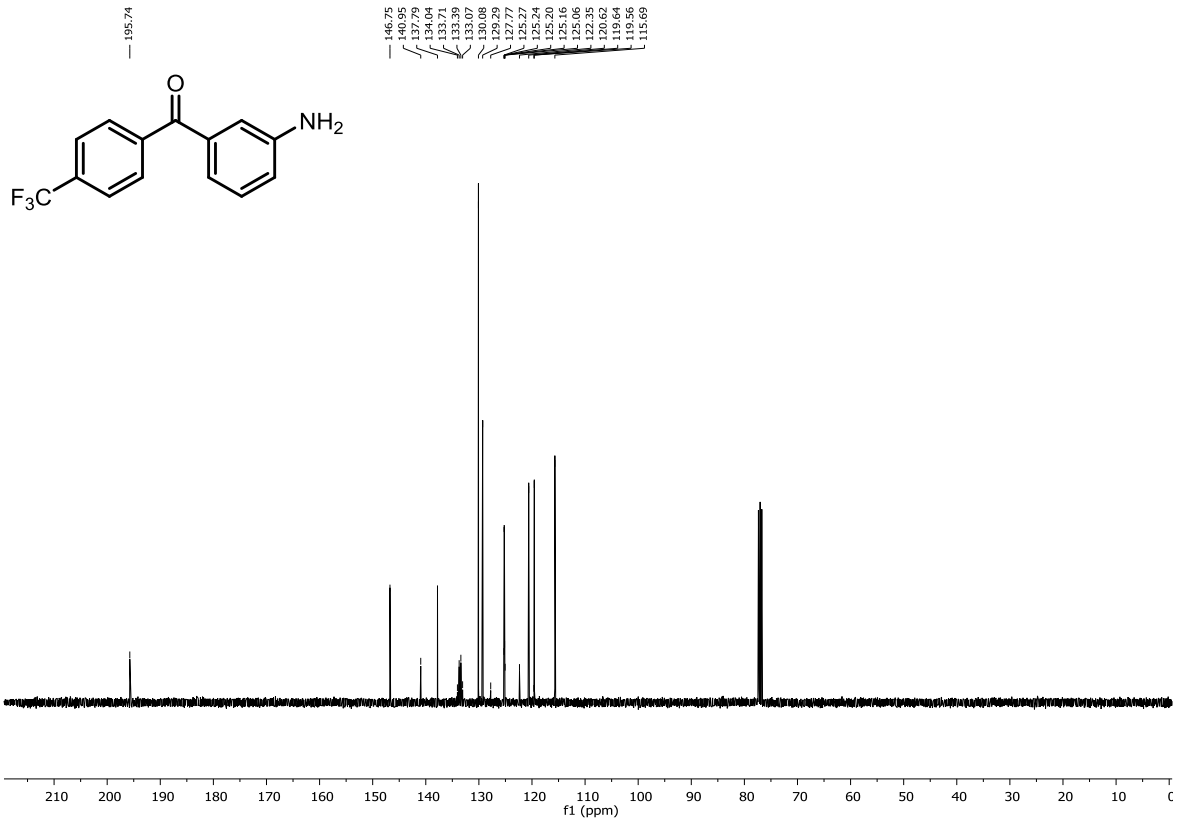

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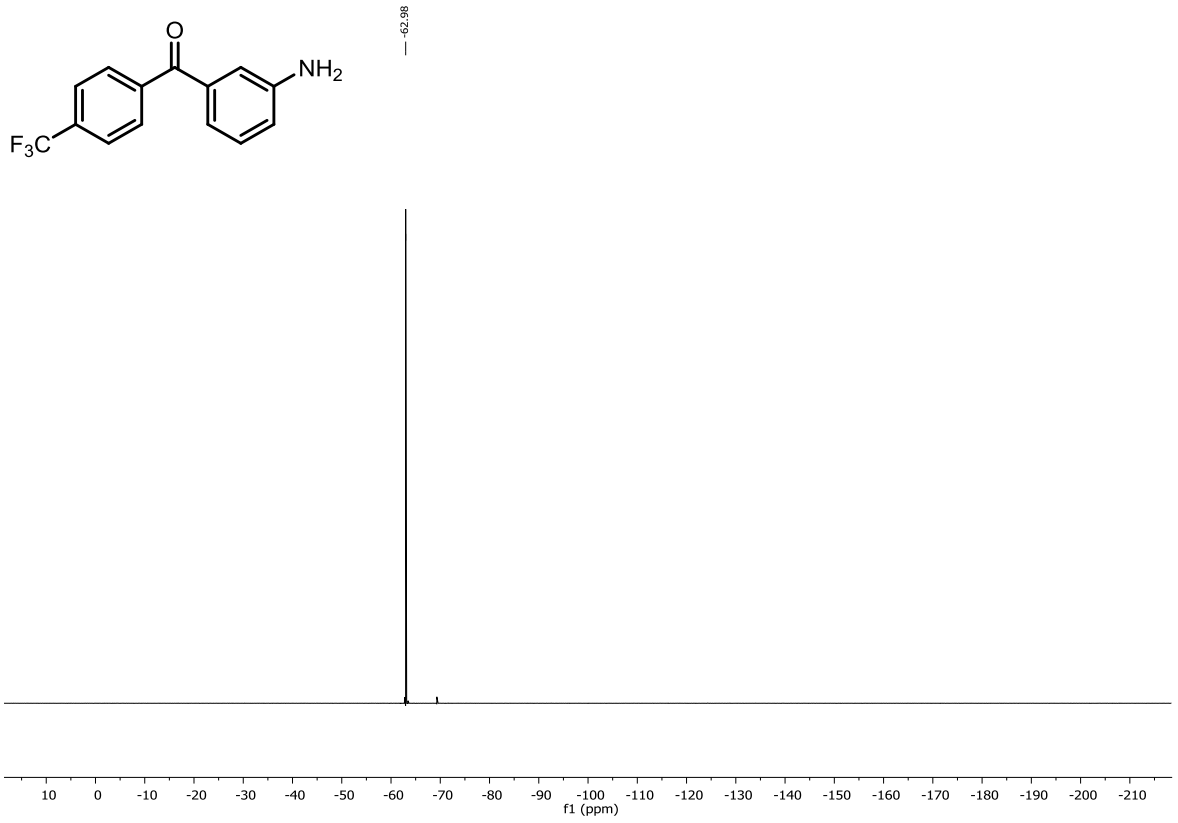
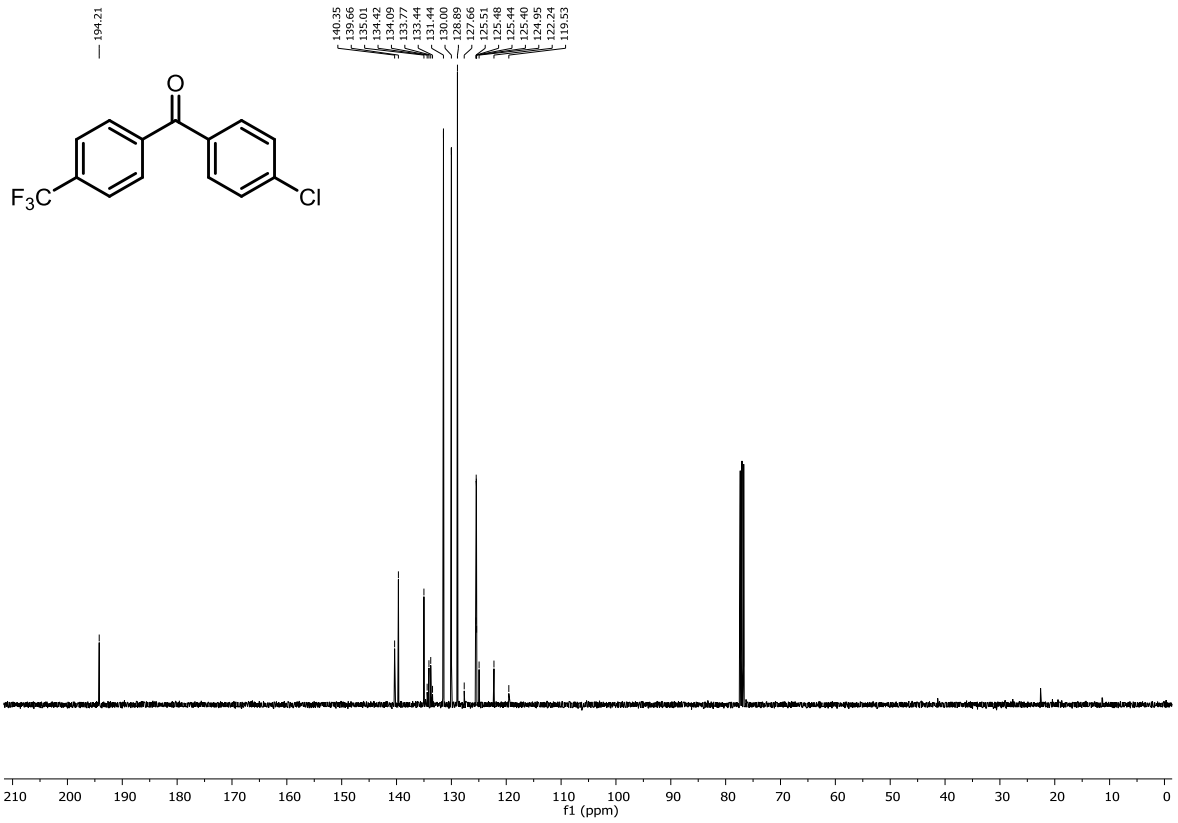


^{1H} NMR (400 MHz, $CDCl_3$) ***1g***

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



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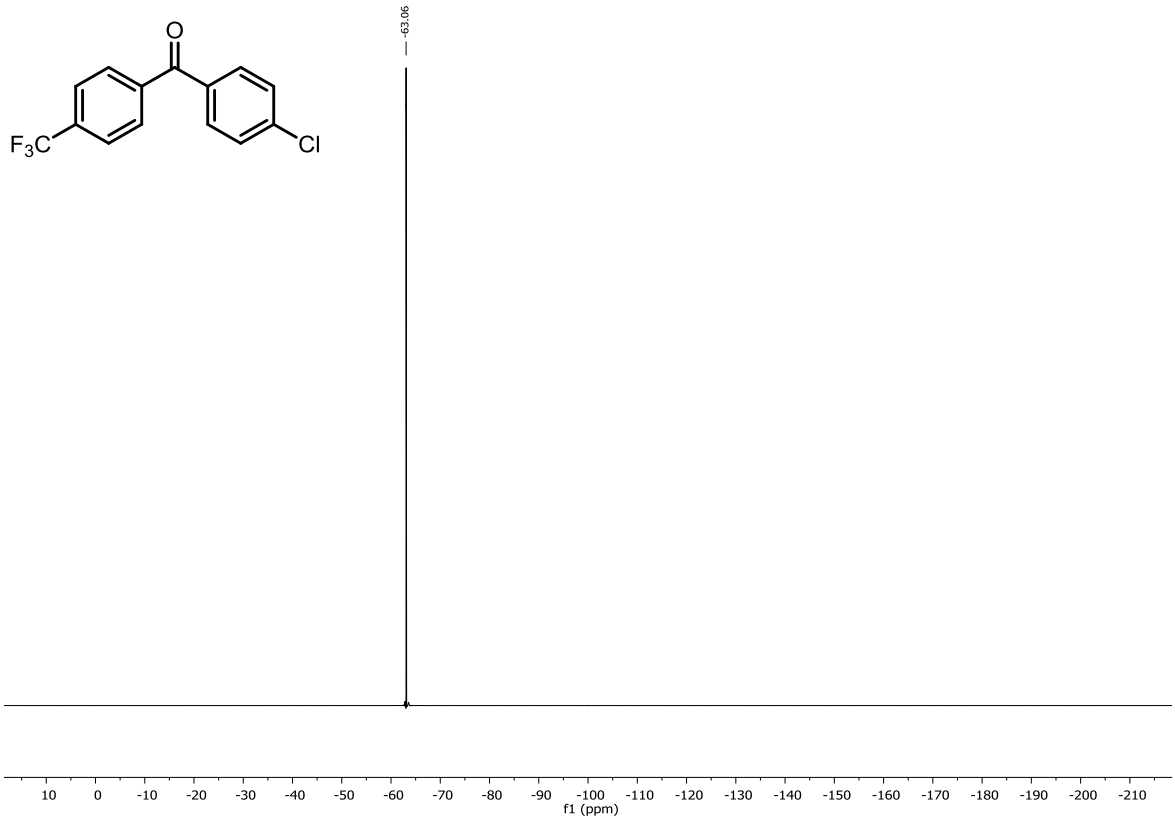
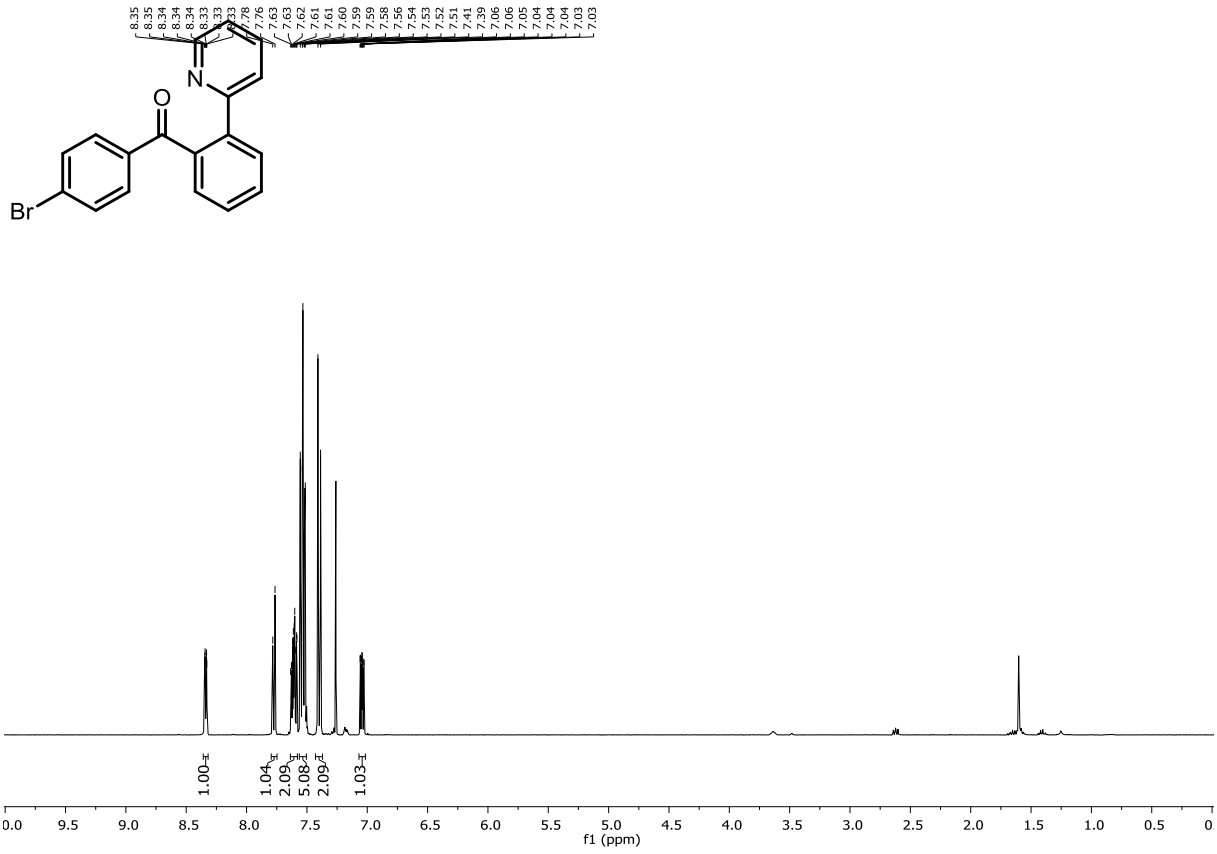
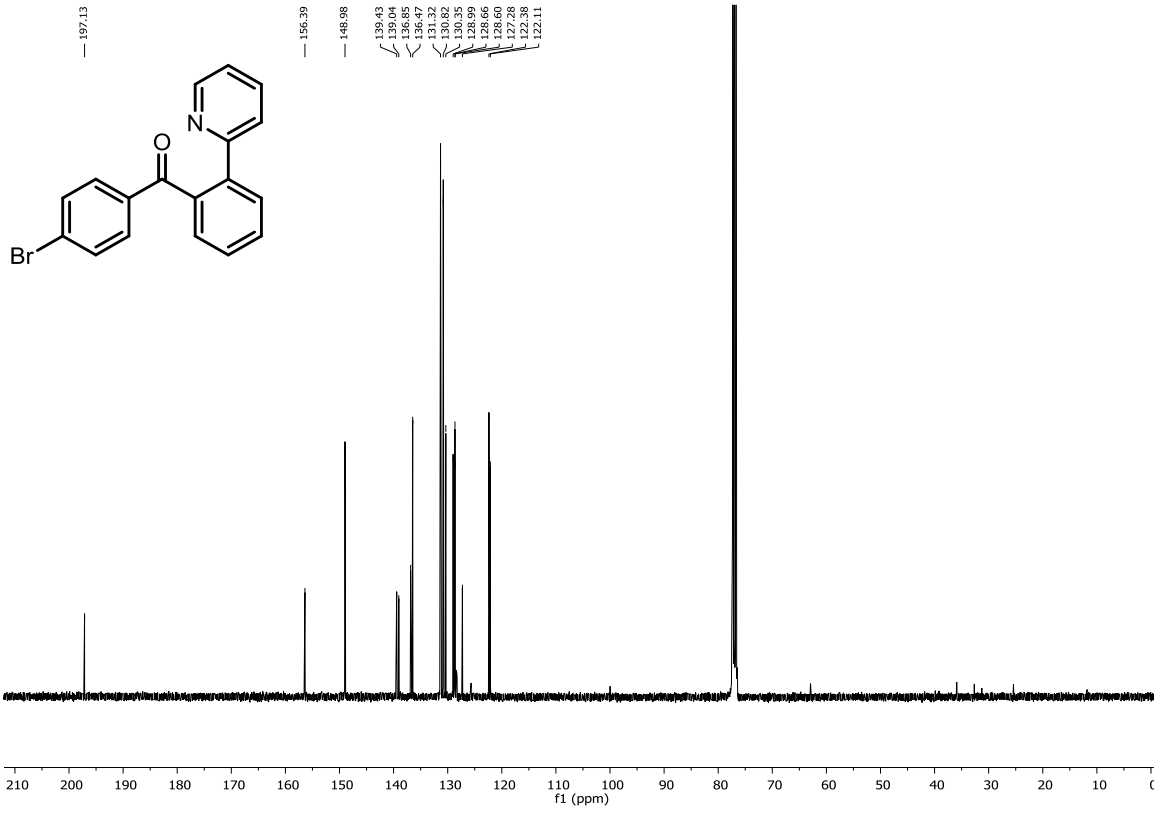


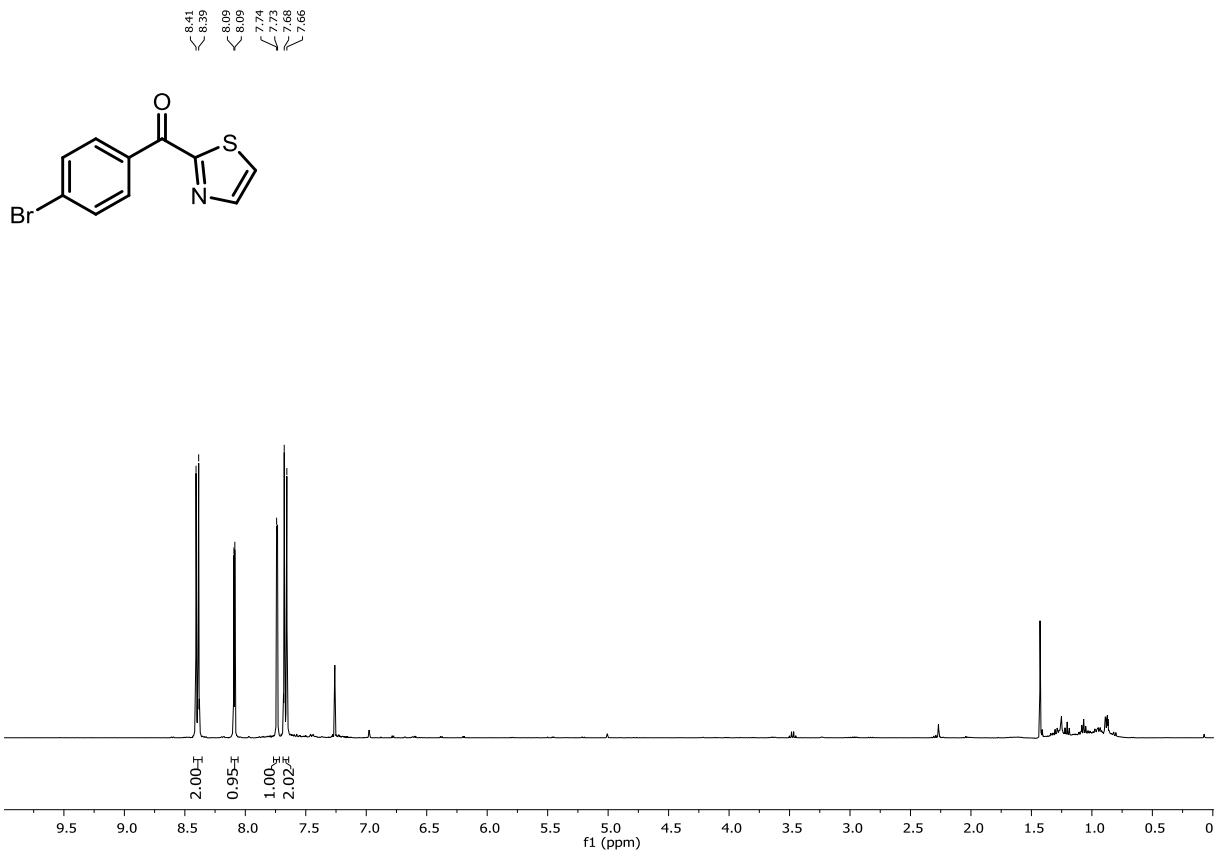
^{1H} NMR (400 MHz, $CDCl_3$) ***1h***



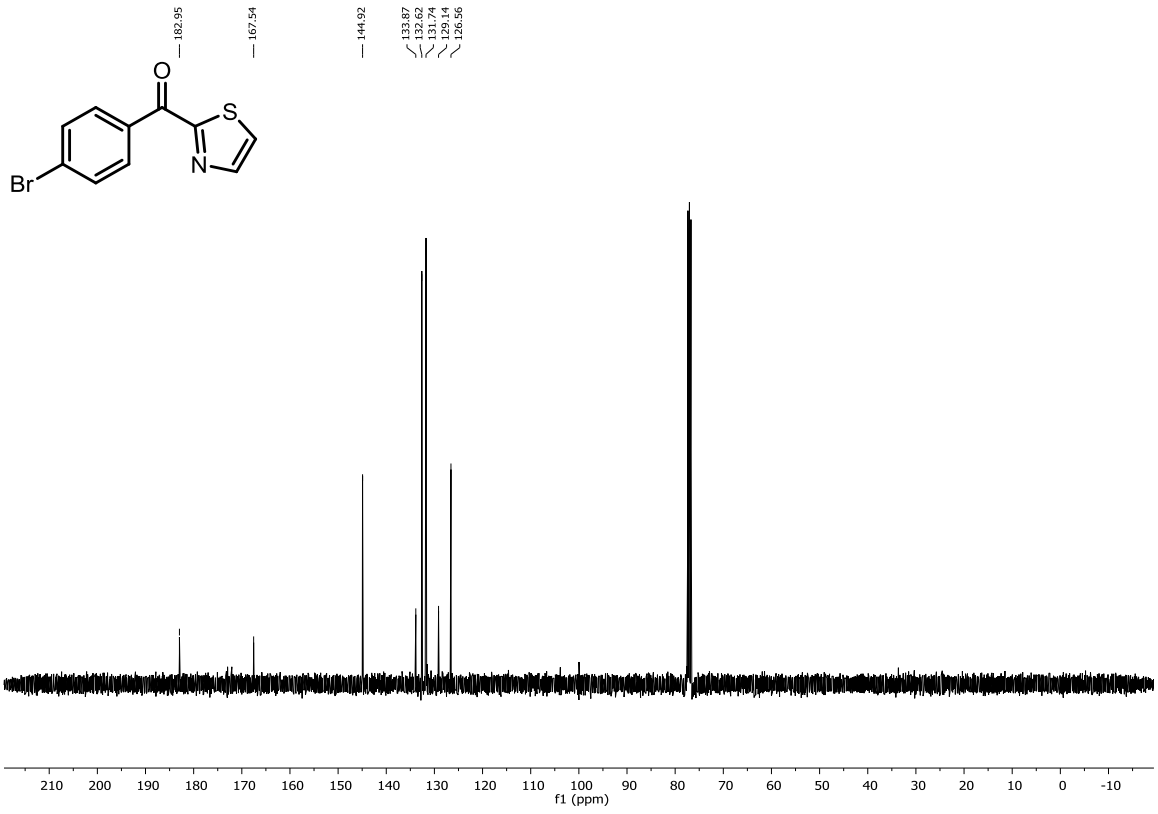
^{13}C NMR (100 MHz, $CDCl_3$) ***1h***



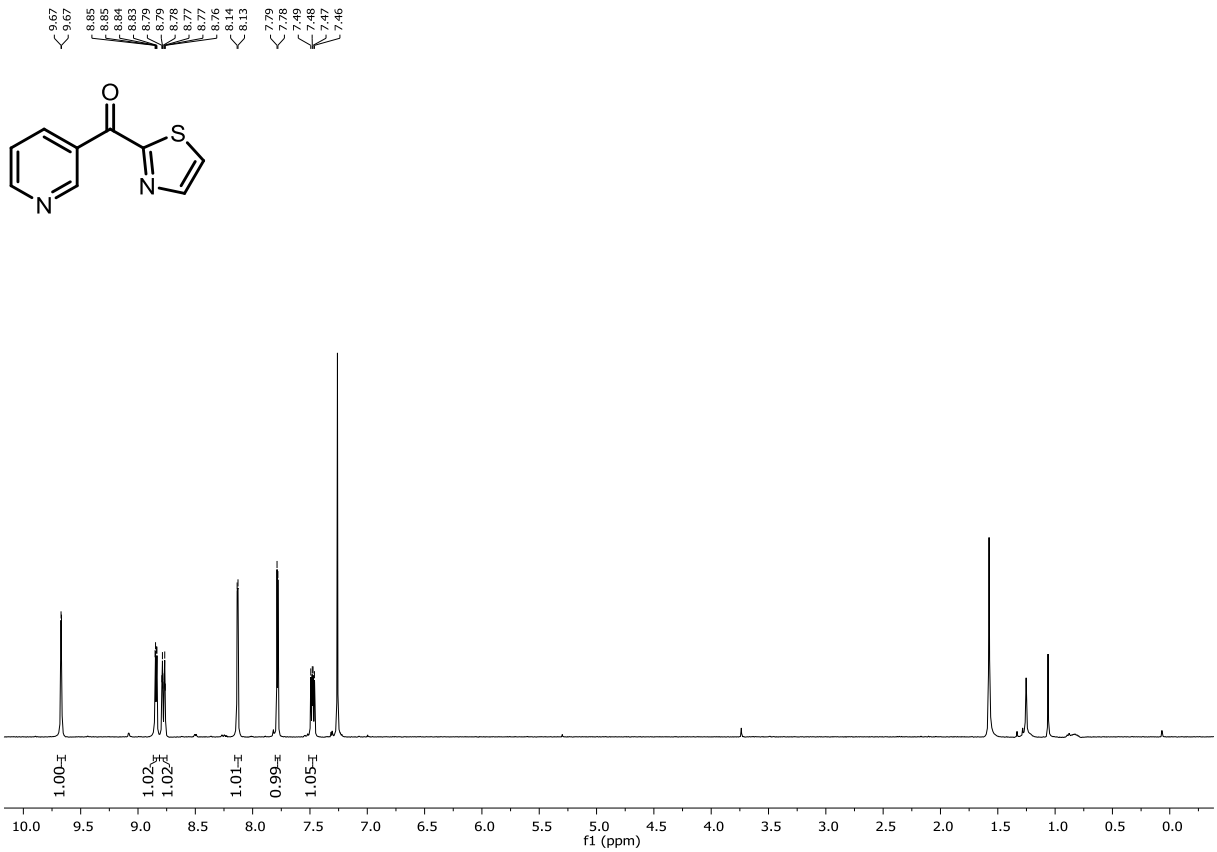
^{1H} NMR (400 MHz, $CDCl_3$) ***1i***



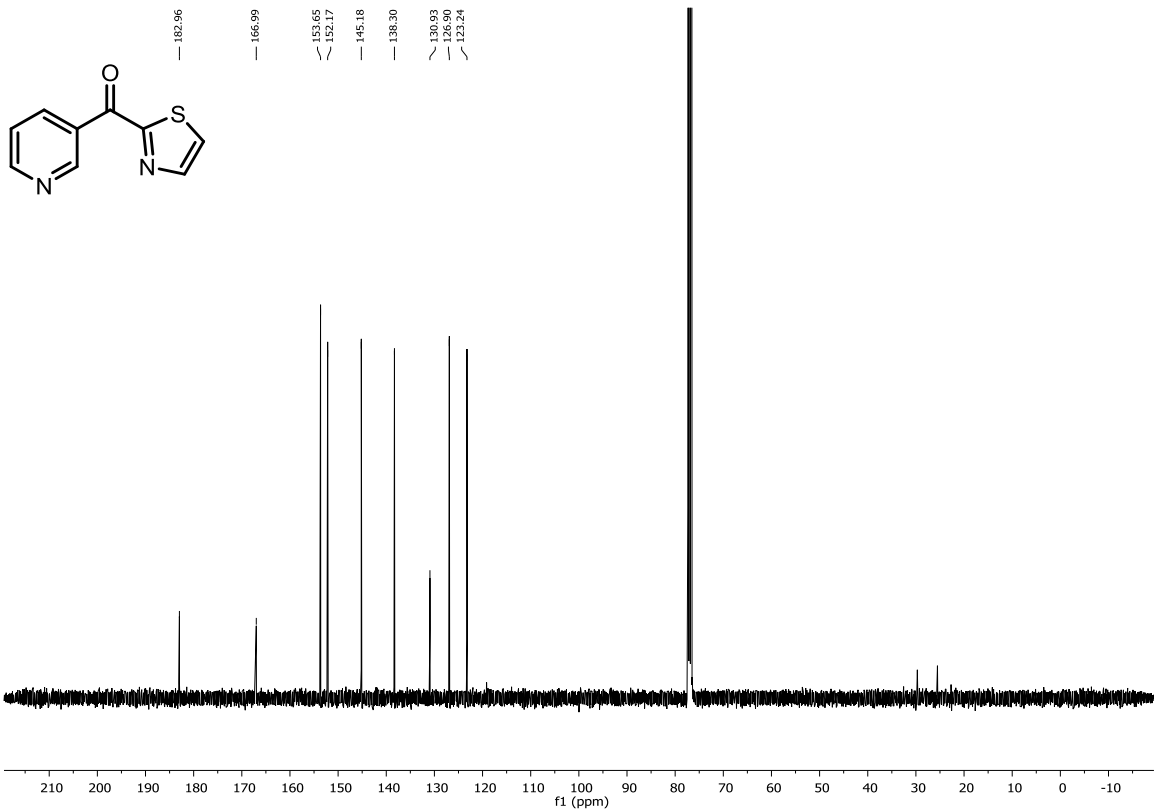
^{13}C NMR (100 MHz, $CDCl_3$) ***1i***



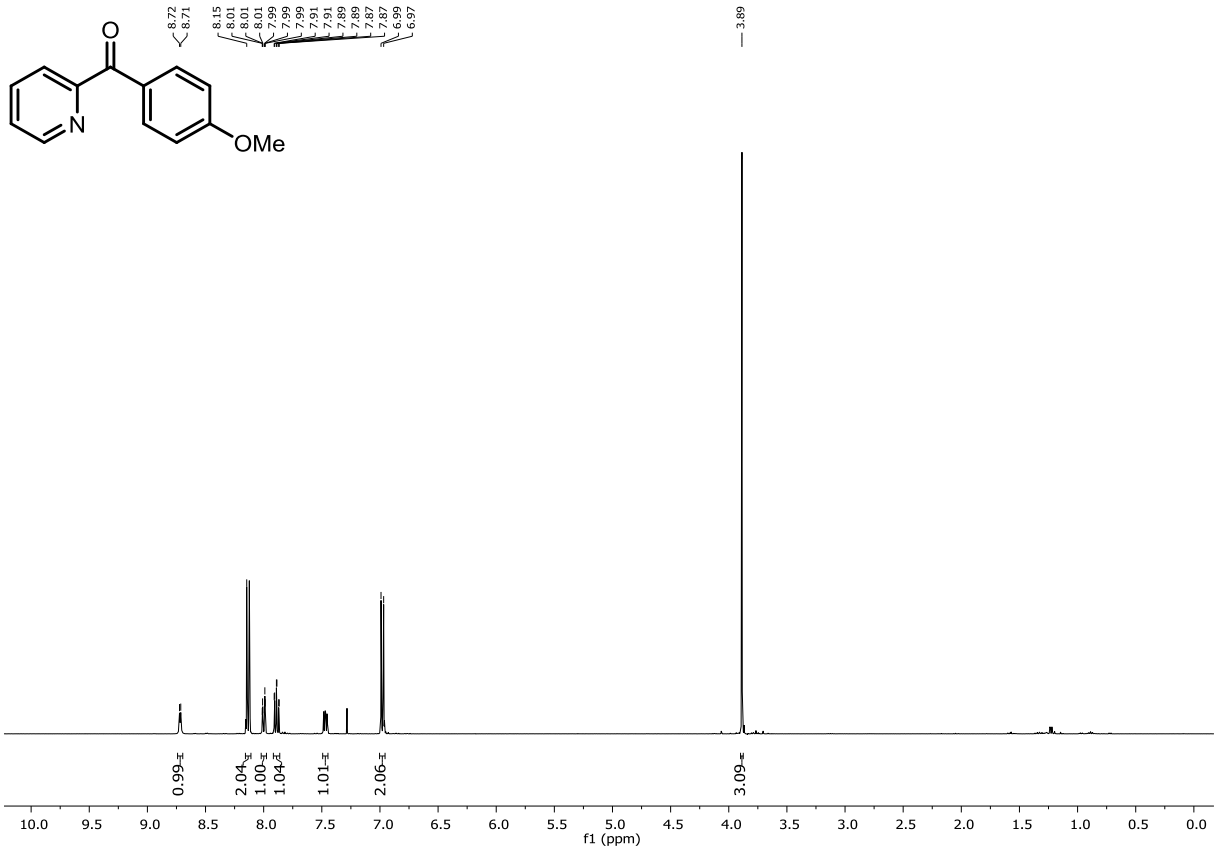
^{1H} NMR (400 MHz, $CDCl_3$) ***1j***



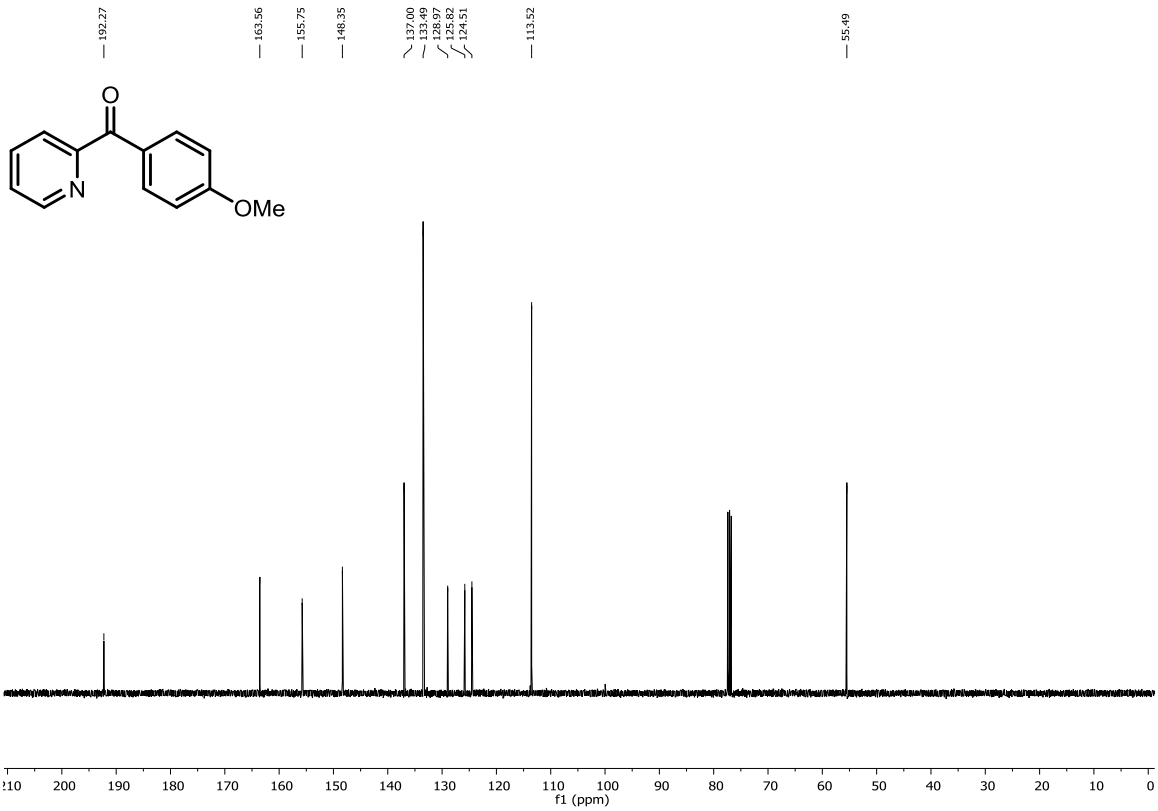
^{13}C NMR (100 MHz, $CDCl_3$) ***1j***



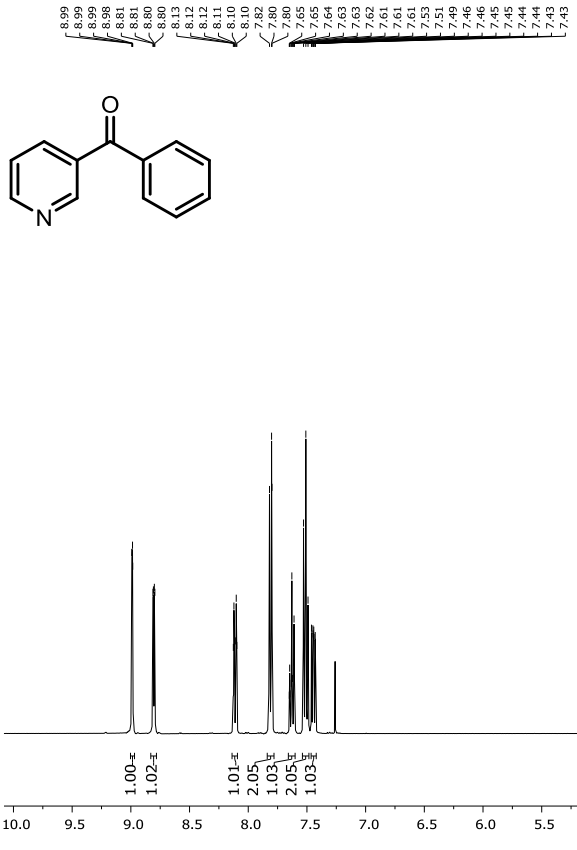
^{1H} NMR (400 MHz, $CDCl_3$) ***1k***



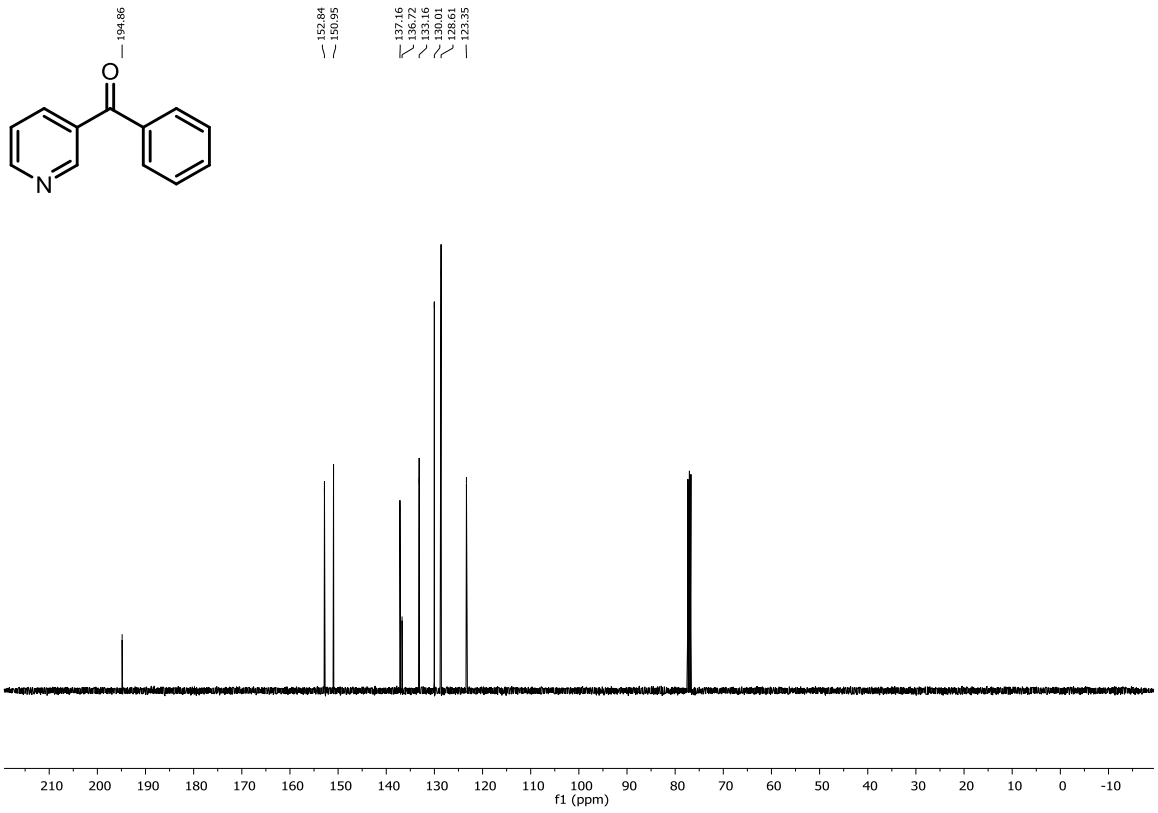
^{13}C NMR (100 MHz, $CDCl_3$) ***1k***



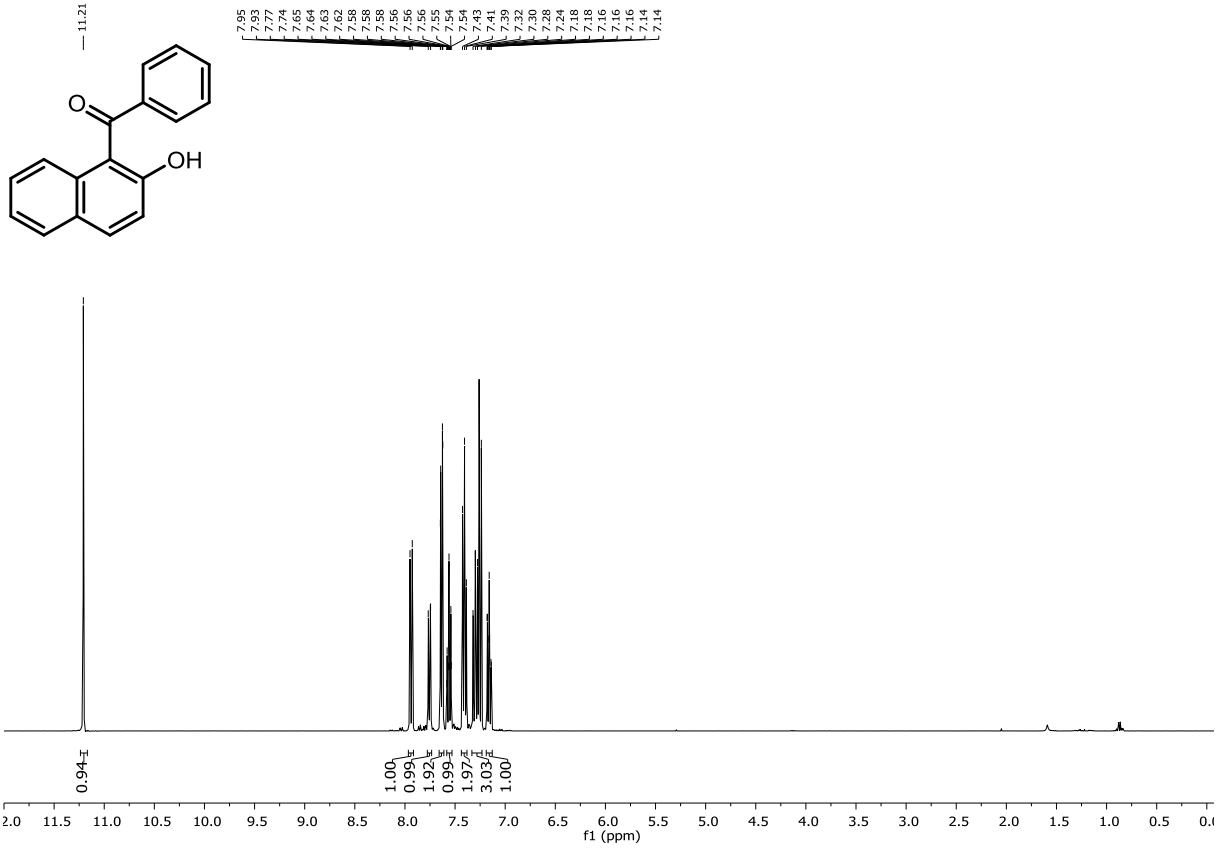
^{1H} NMR (400 MHz, $CDCl_3$) ***1l***



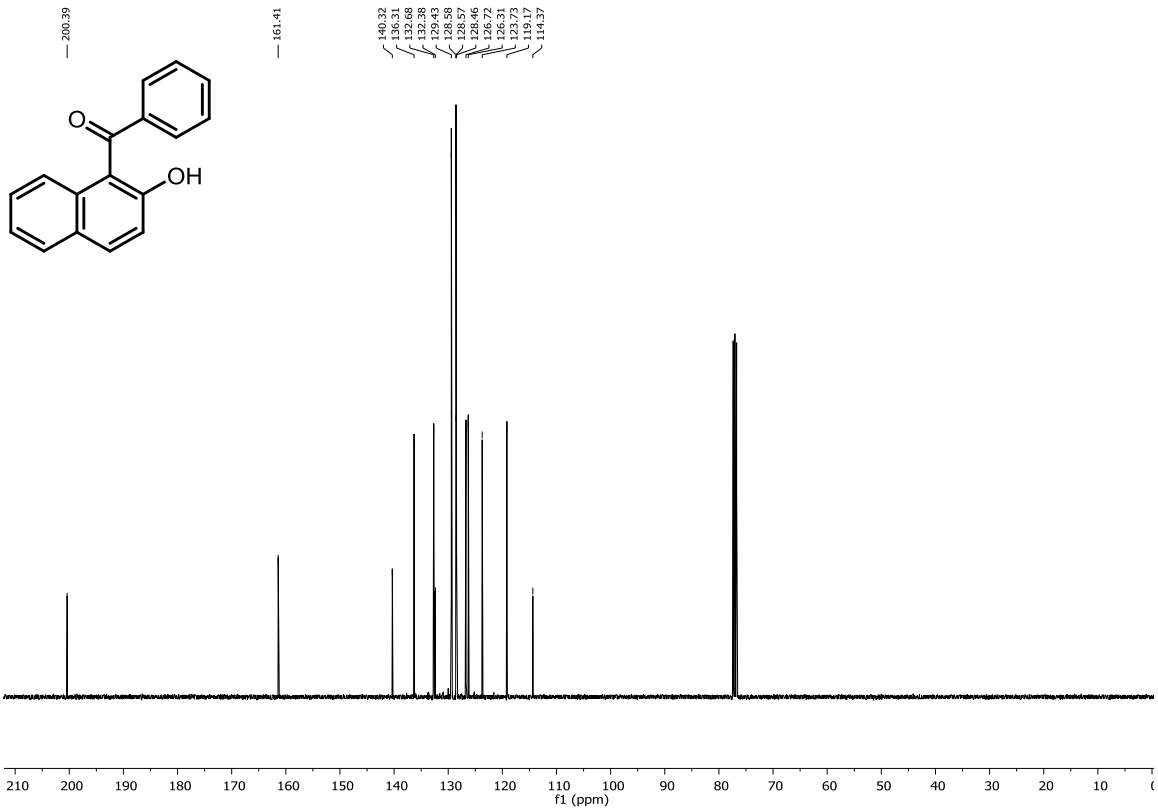
^{13}C NMR (100 MHz, $CDCl_3$) ***1l***



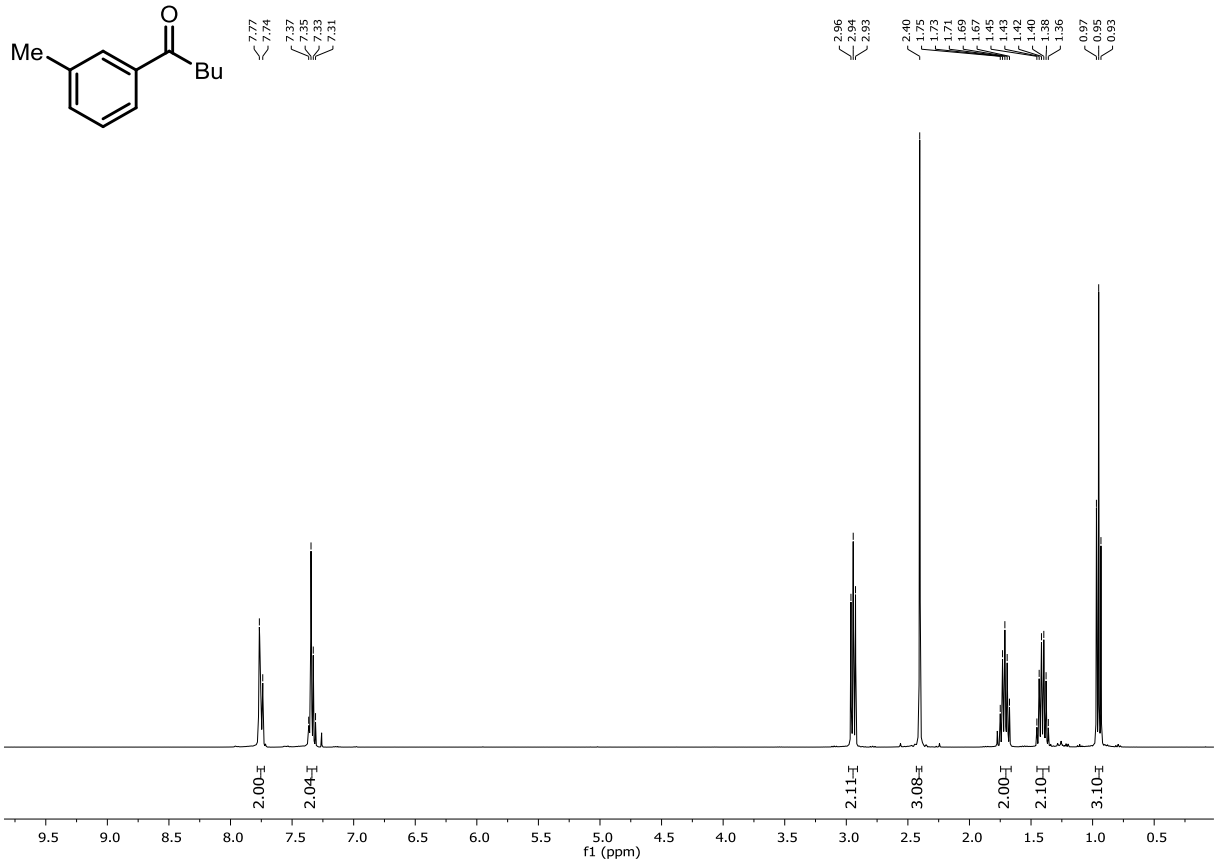
^{1H} NMR (400 MHz, $CDCl_3$) ***1m***



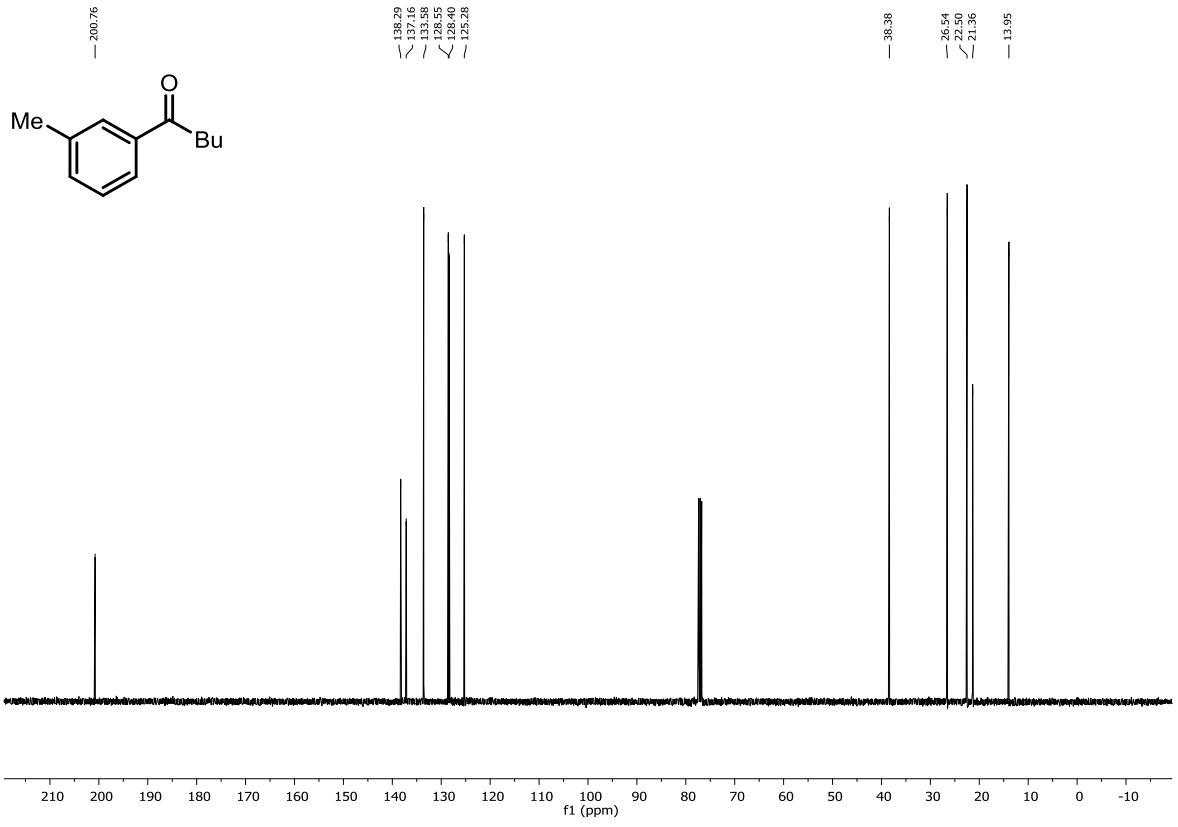
^{13}C NMR (100 MHz, $CDCl_3$) ***1m***



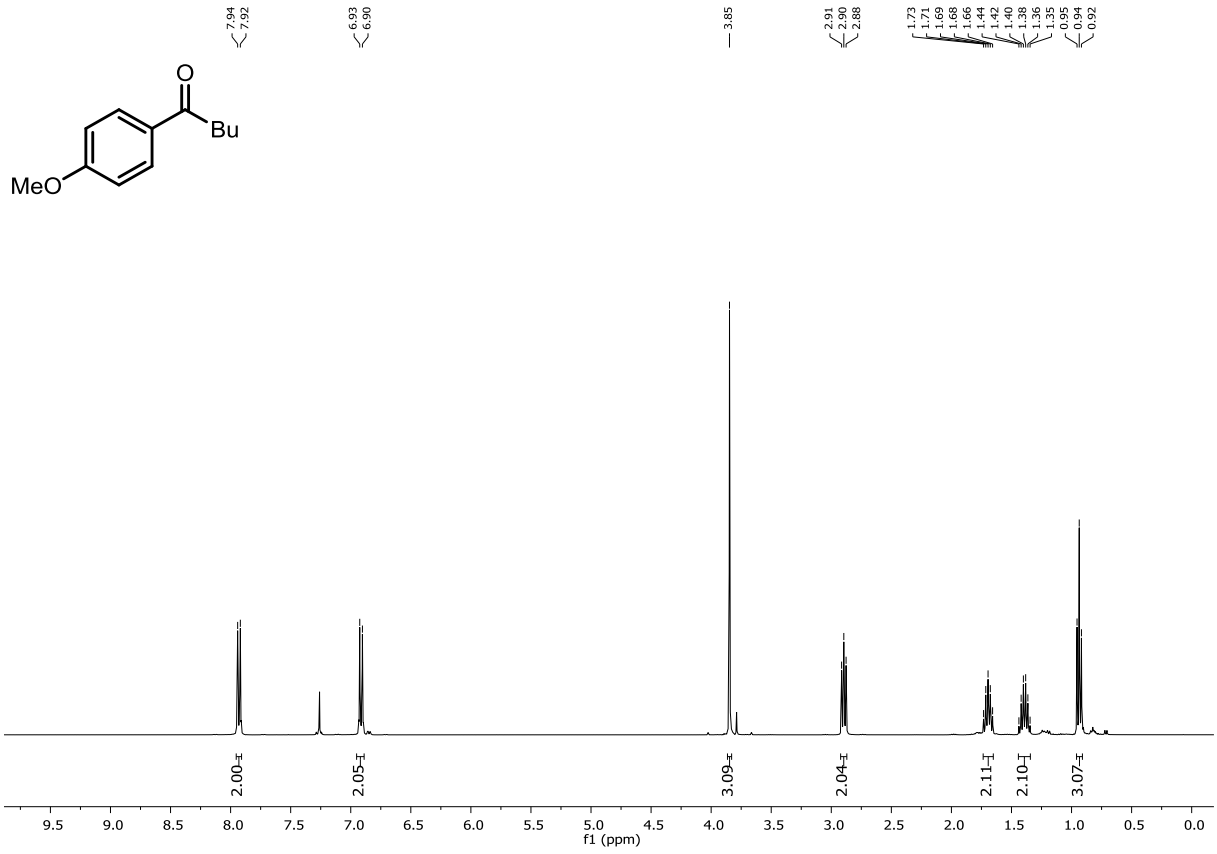
^{1H} NMR (400 MHz, $CDCl_3$) ***1n***



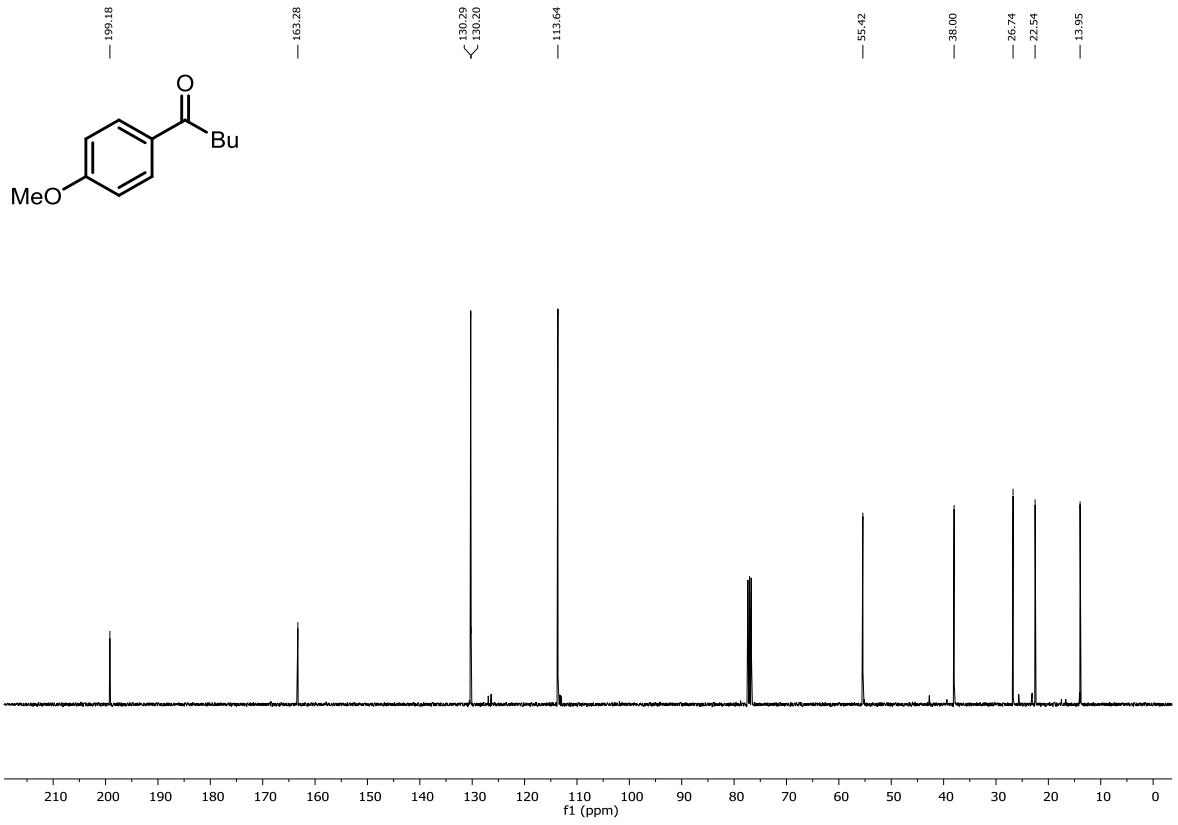
^{13}C NMR (100 MHz, $CDCl_3$) ***1n***



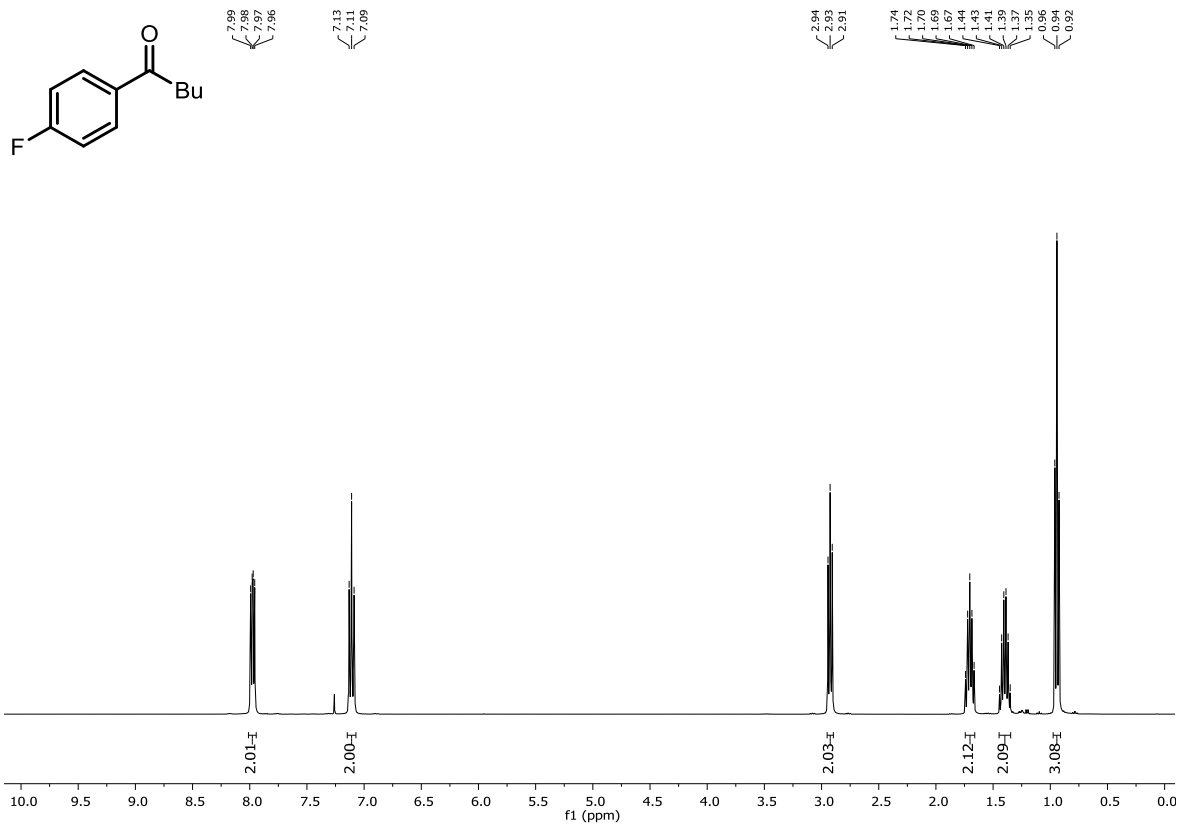
^{1H} NMR (400 MHz, $CDCl_3$) ***1o***



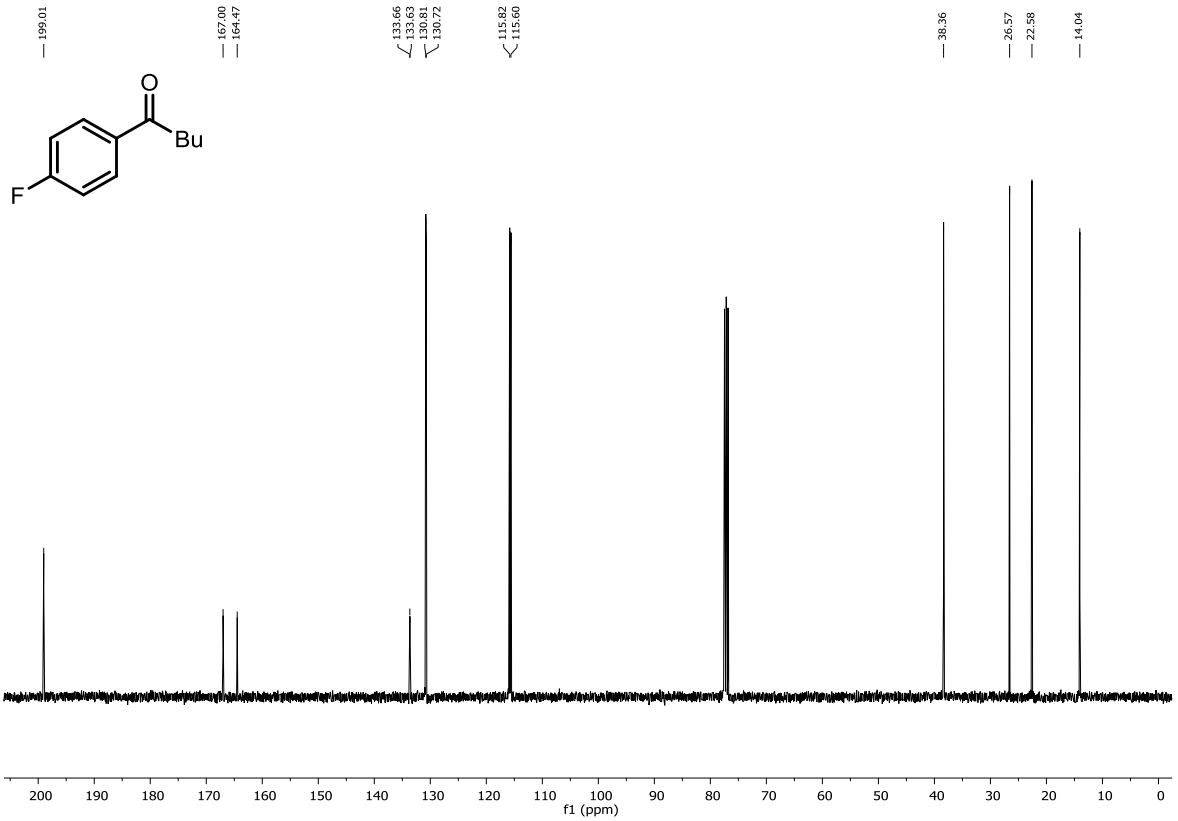
^{13}C NMR (100 MHz, $CDCl_3$) ***1o***



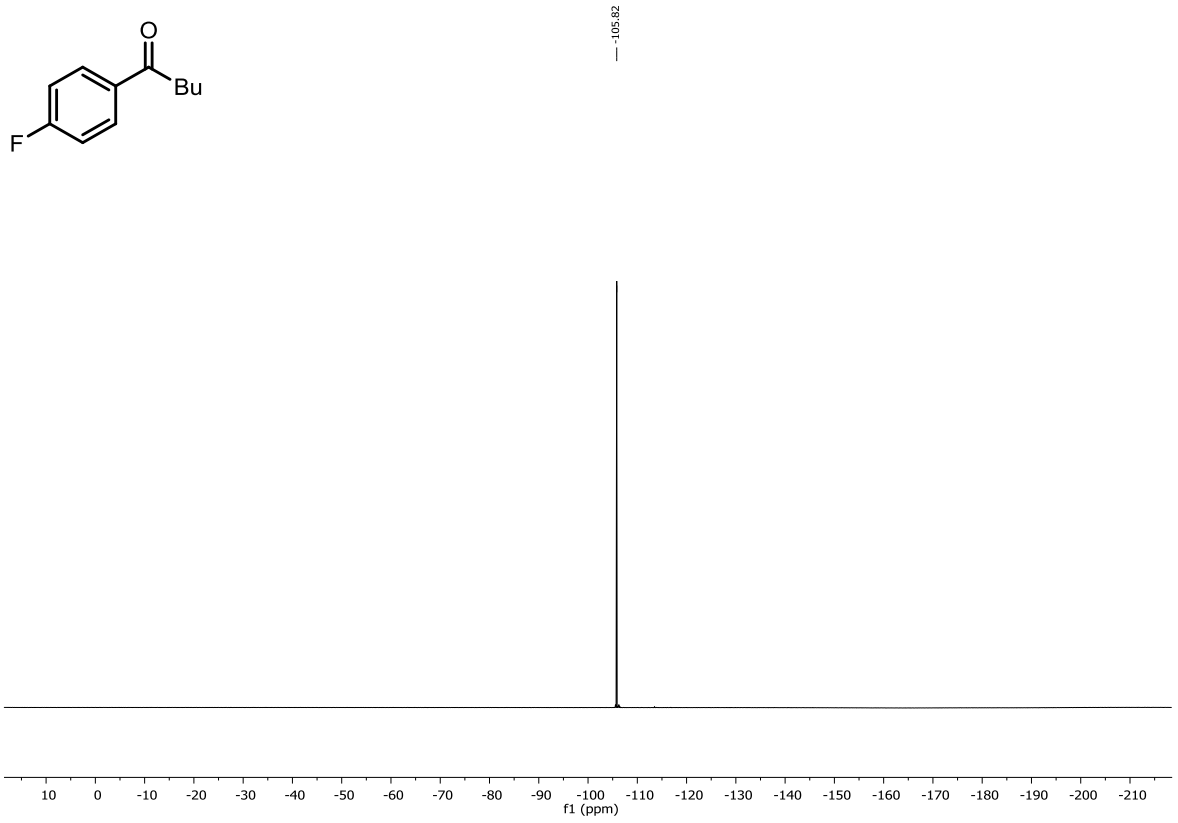
^{1H} NMR (400 MHz, $CDCl_3$) ***1p***



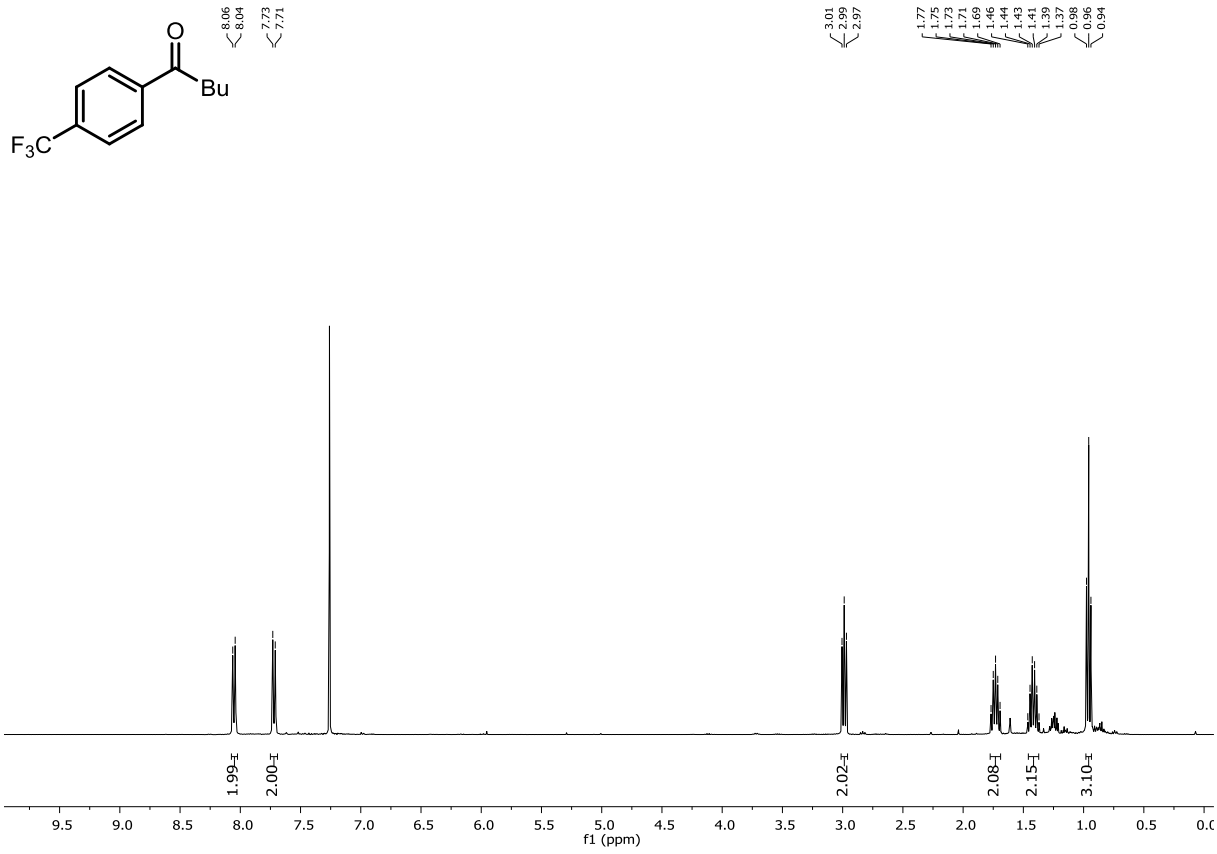
^{13}C NMR (100 MHz, $CDCl_3$) ***1p***



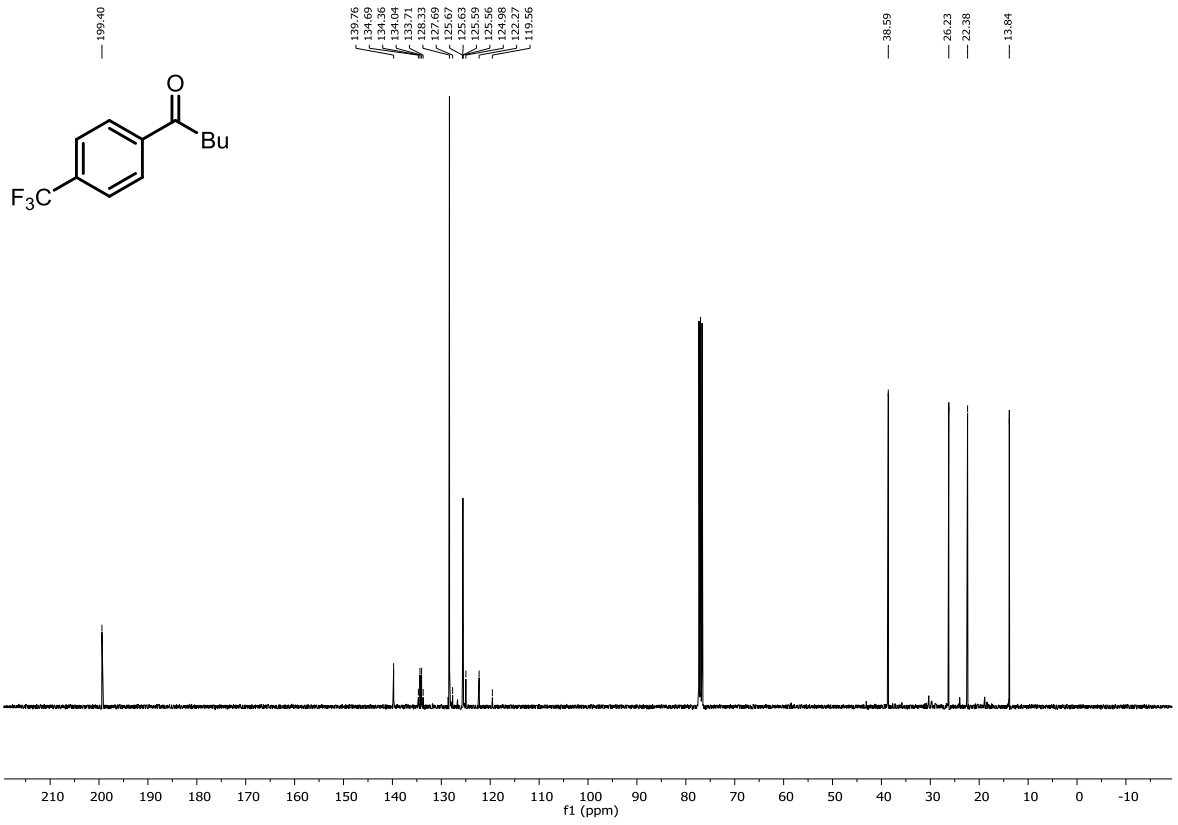
^{19}F NMR (377 MHz, $CDCl_3$) ***1p***



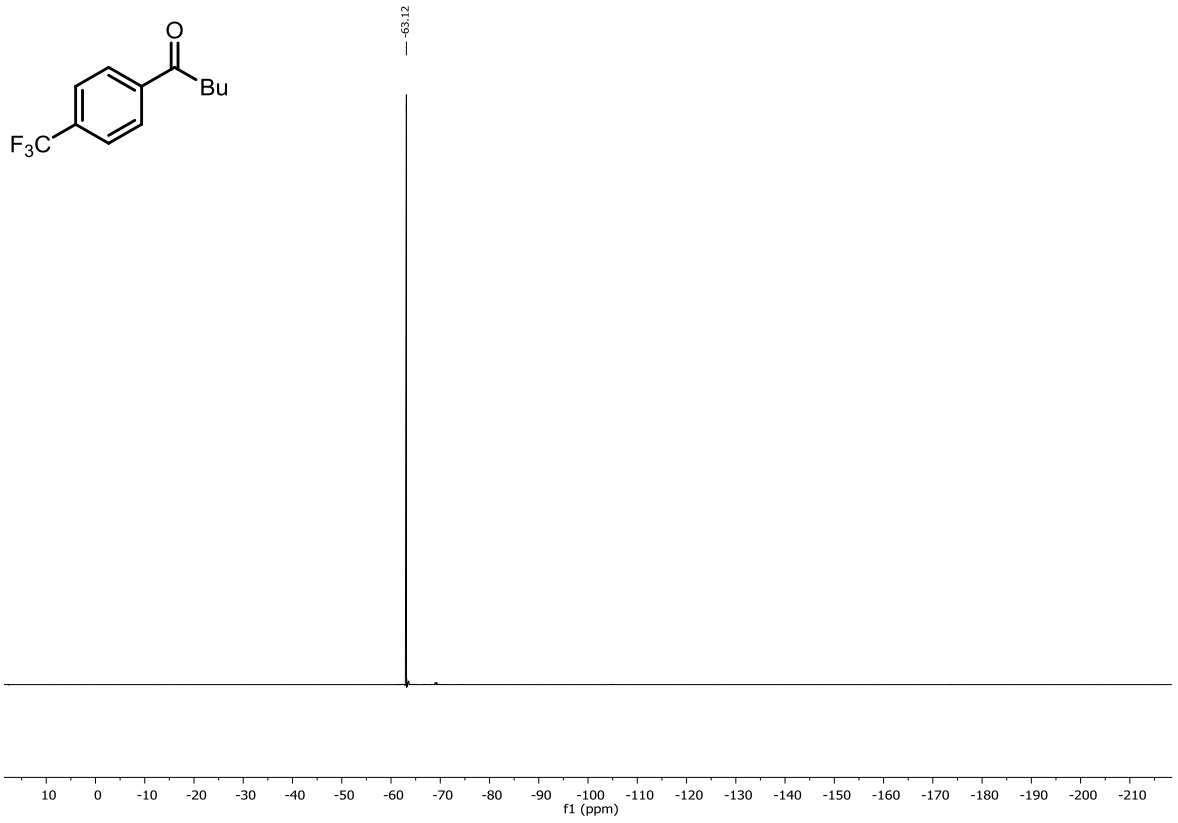
^{1H} NMR (400 MHz, $CDCl_3$) ***1q***



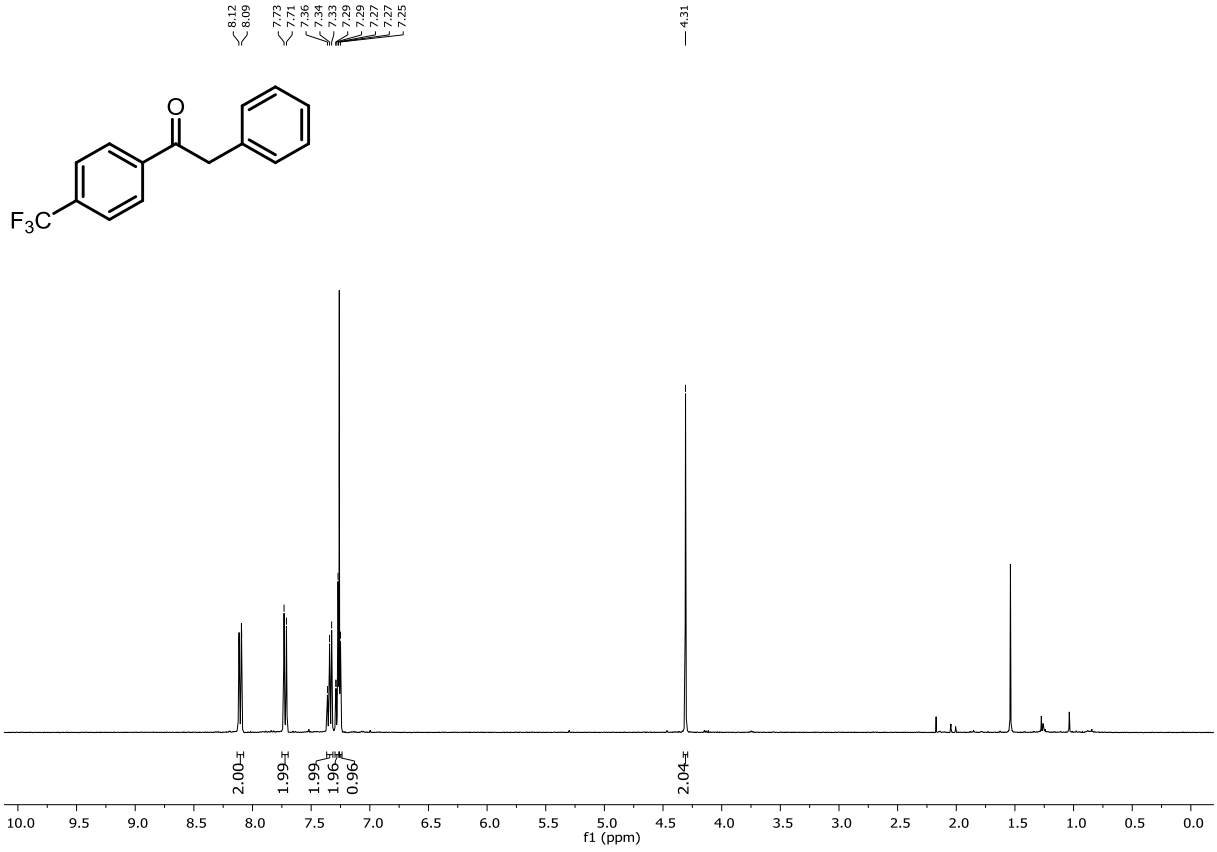
^{13}C NMR (100 MHz, $CDCl_3$) ***1q***



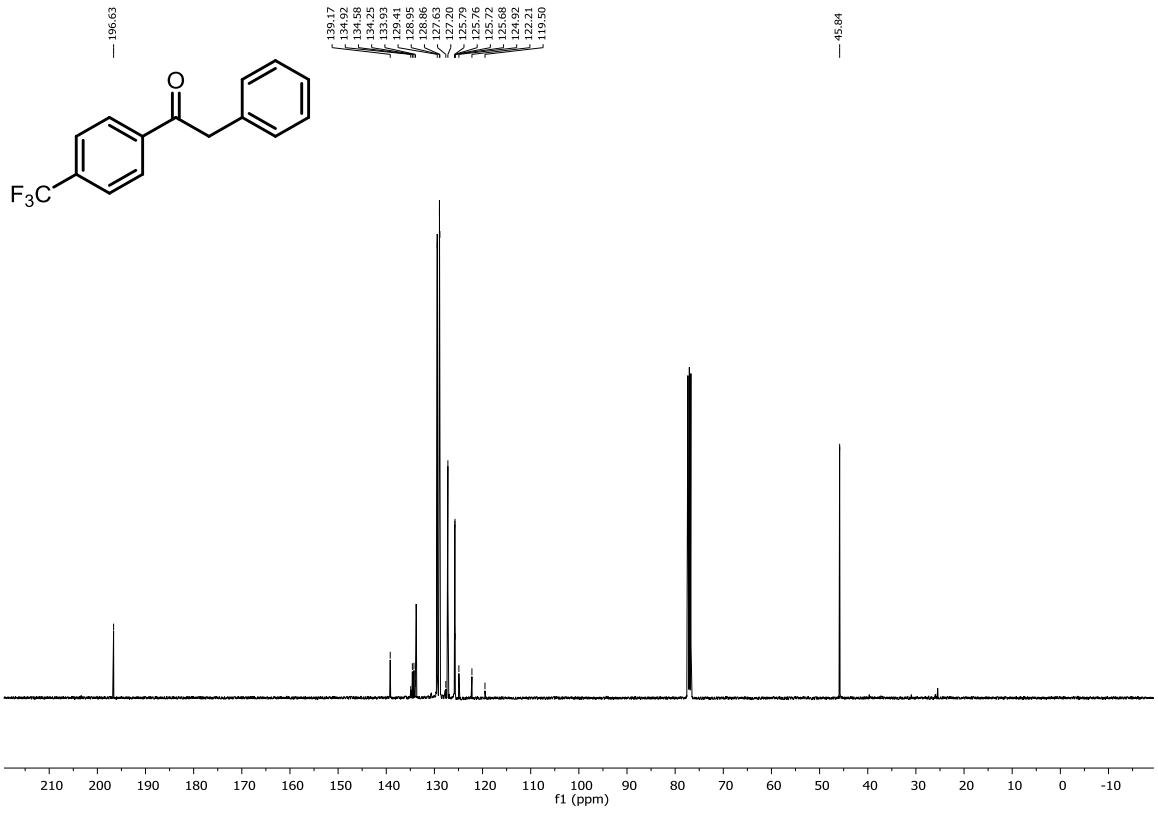
^{19}F NMR (377 MHz, $CDCl_3$) ***1q***



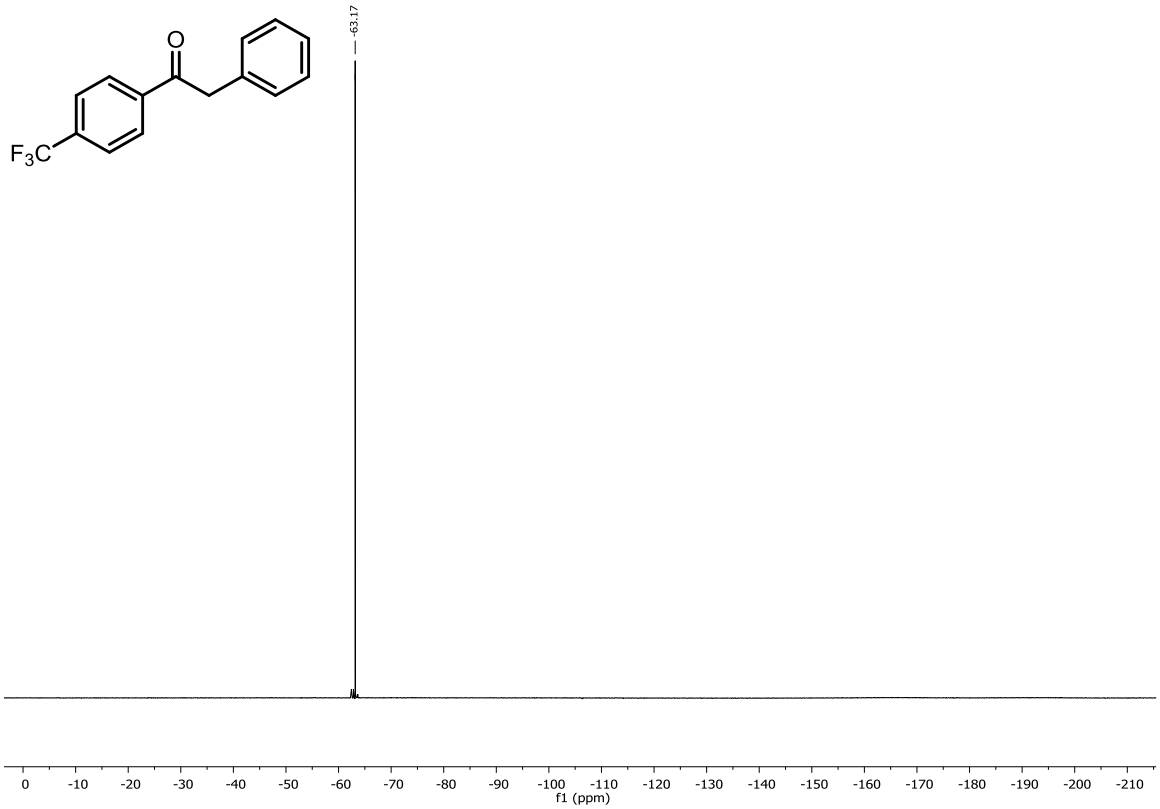
[1H] NMR (400 MHz, $CDCl_3$) ***1r***



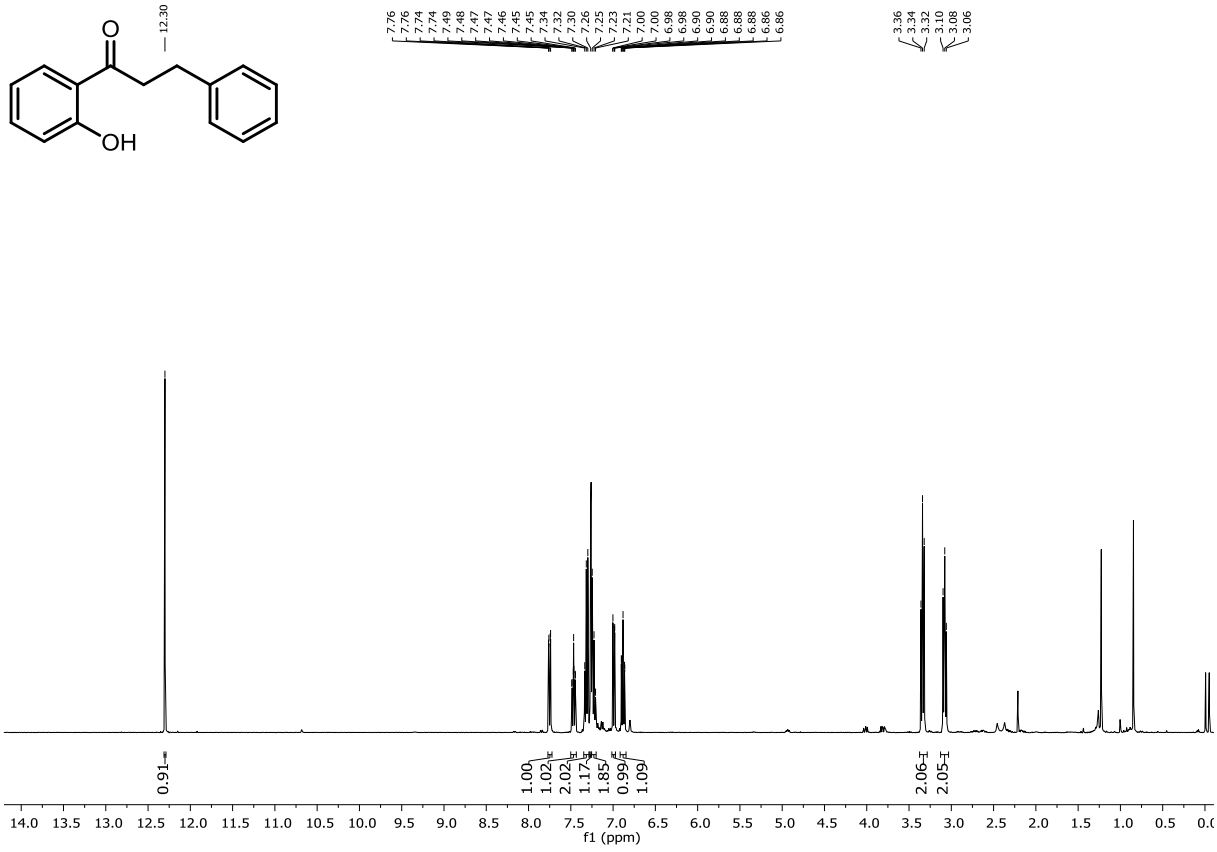
[13]C NMR (100 MHz, $CDCl_3$) ***1r***



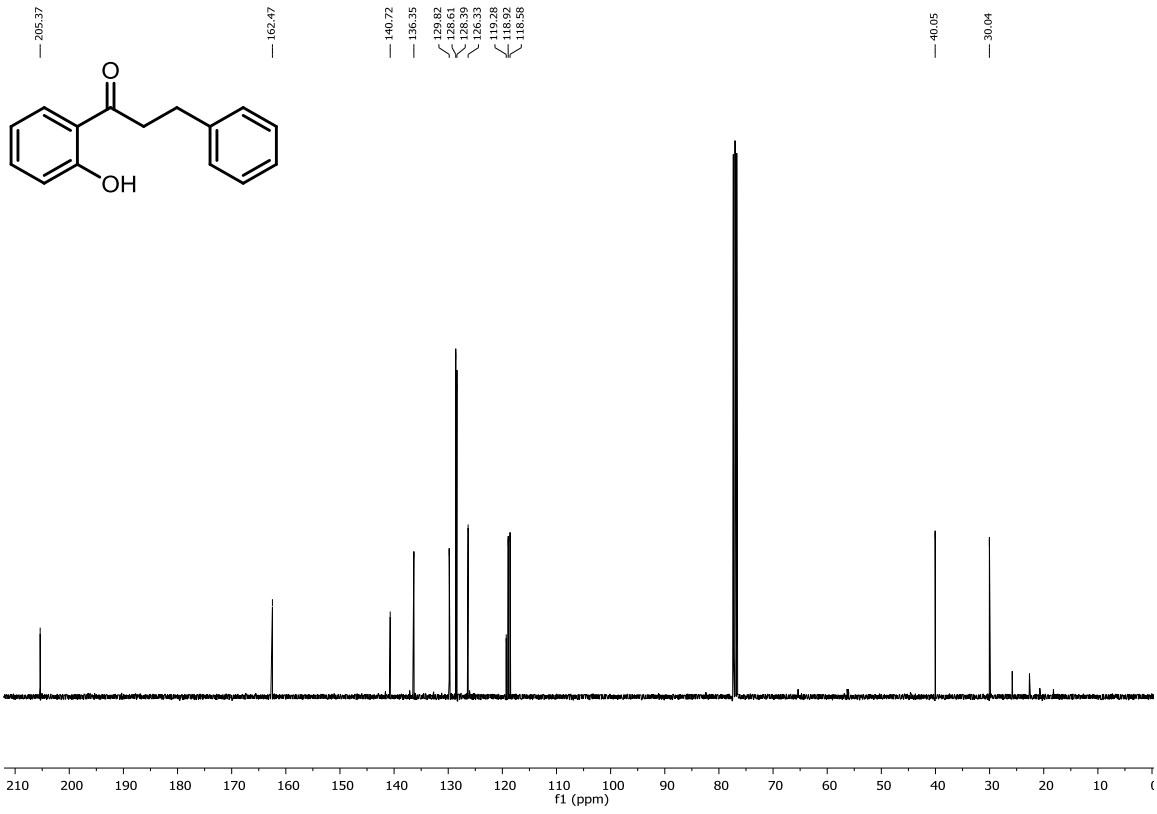
^{19}F NMR (377 MHz, $CDCl_3$) ***1r***



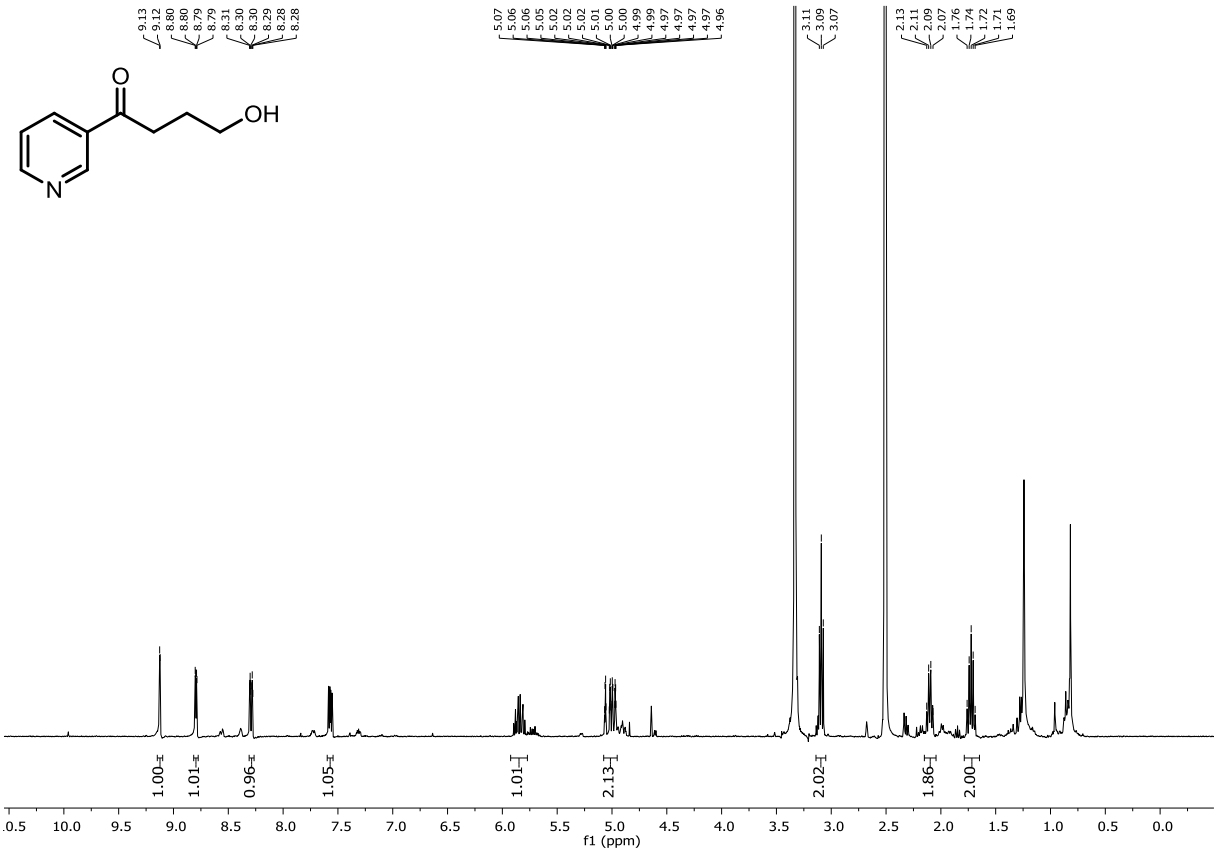
^{1H} NMR (400 MHz, $CDCl_3$) ***1s***



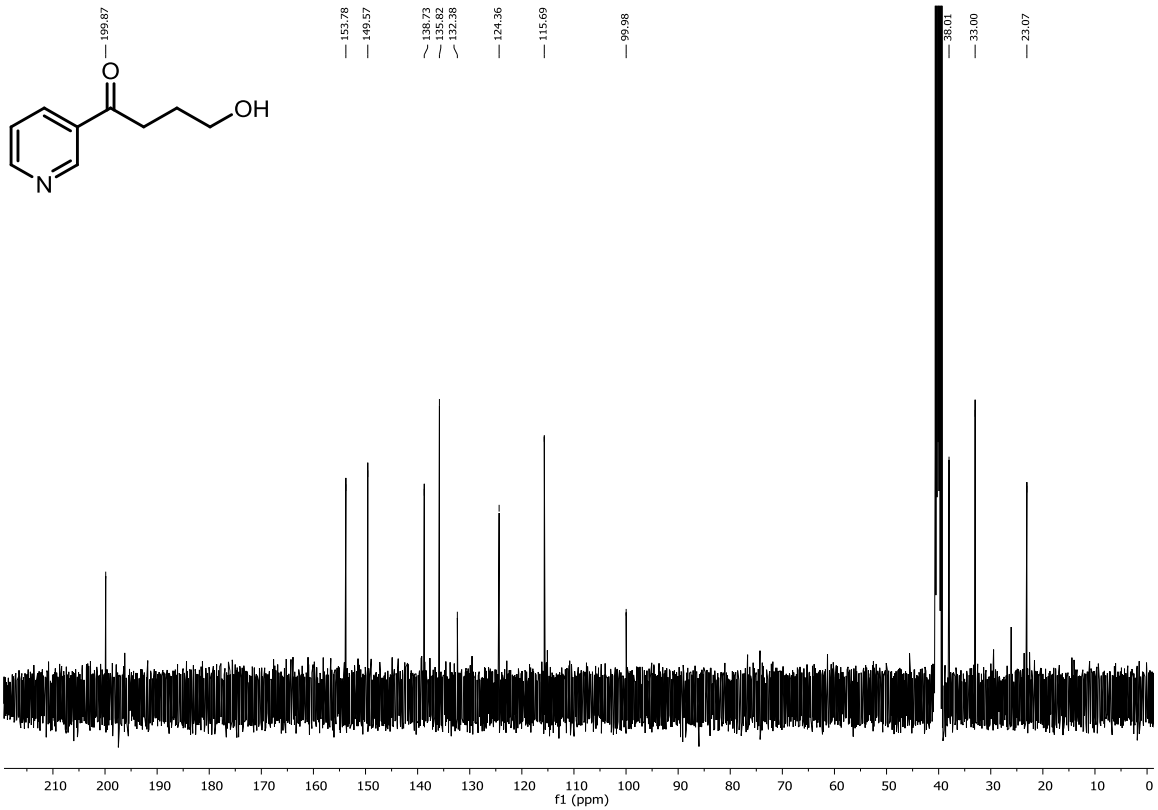
^{13}C NMR (100 MHz, $CDCl_3$) ***1s***



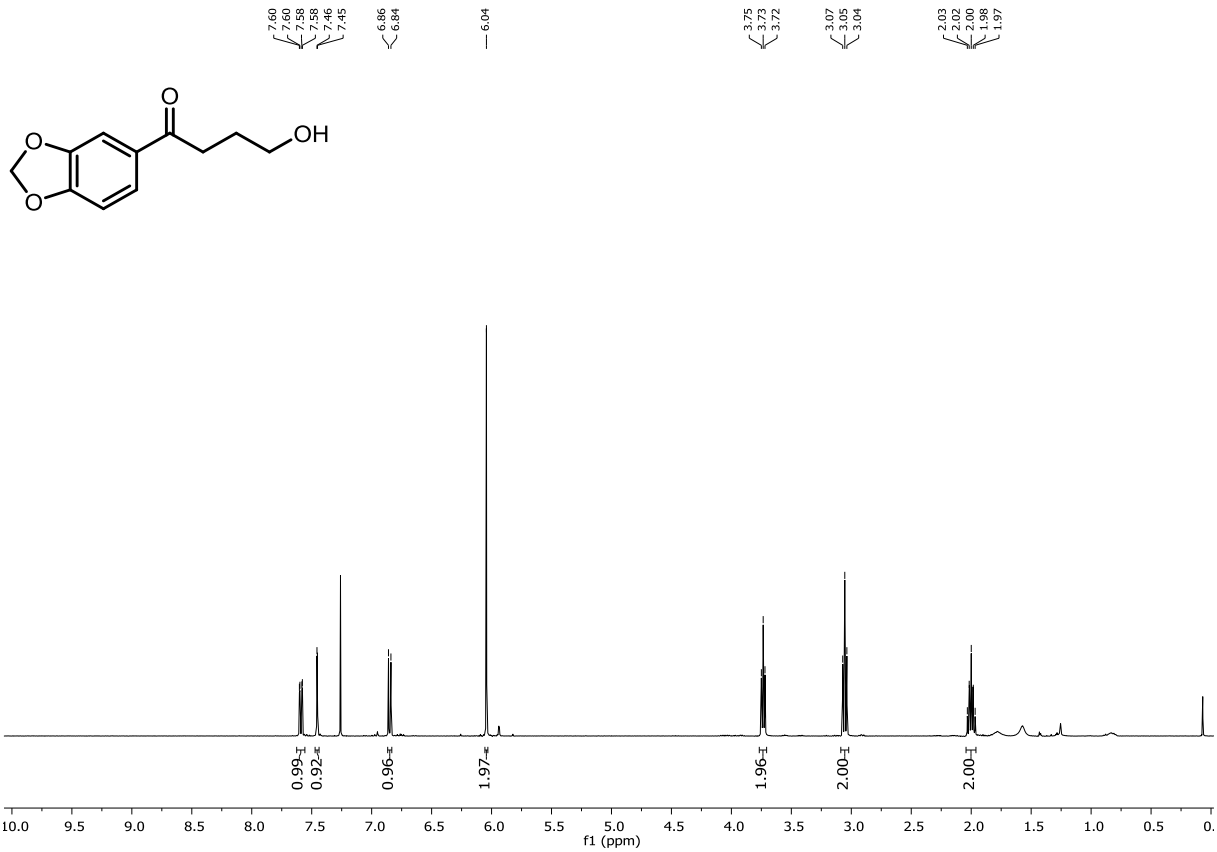
^{1H} NMR (400 MHz, DMSO-d_6) ***1t***



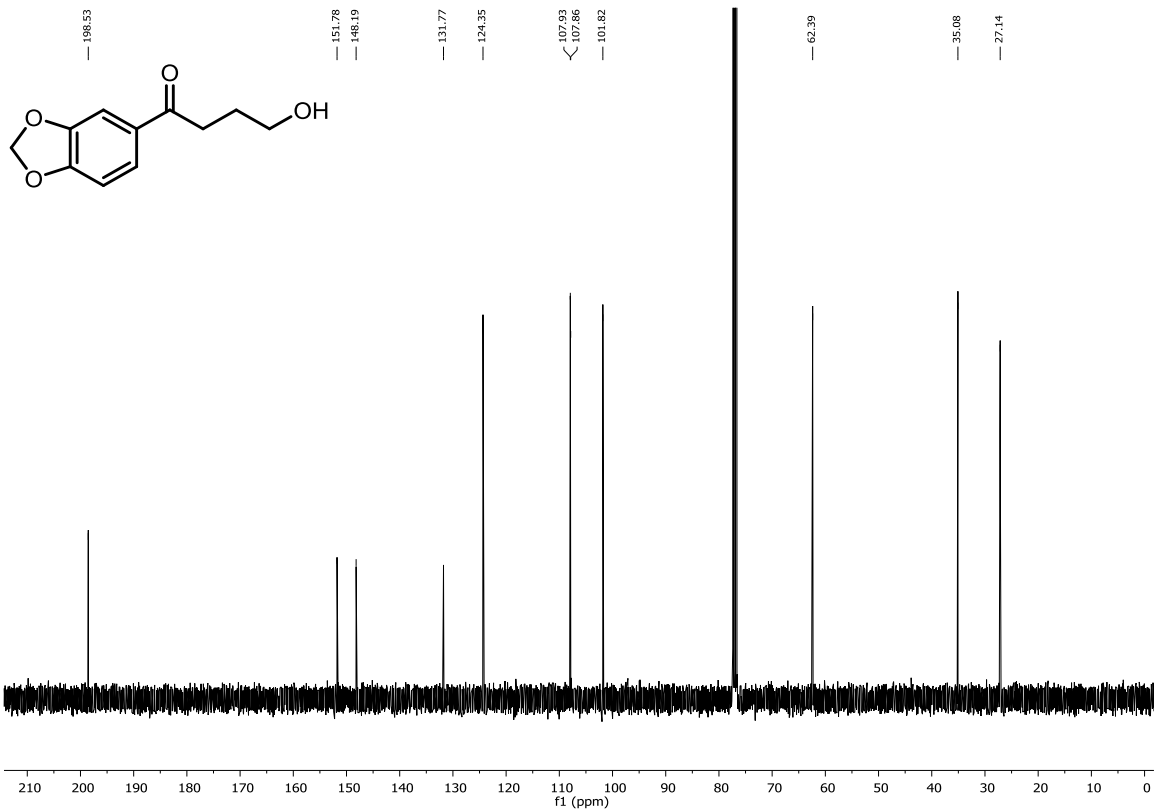
^{13}C NMR (100 MHz, DMSO-d_6) ***1t***



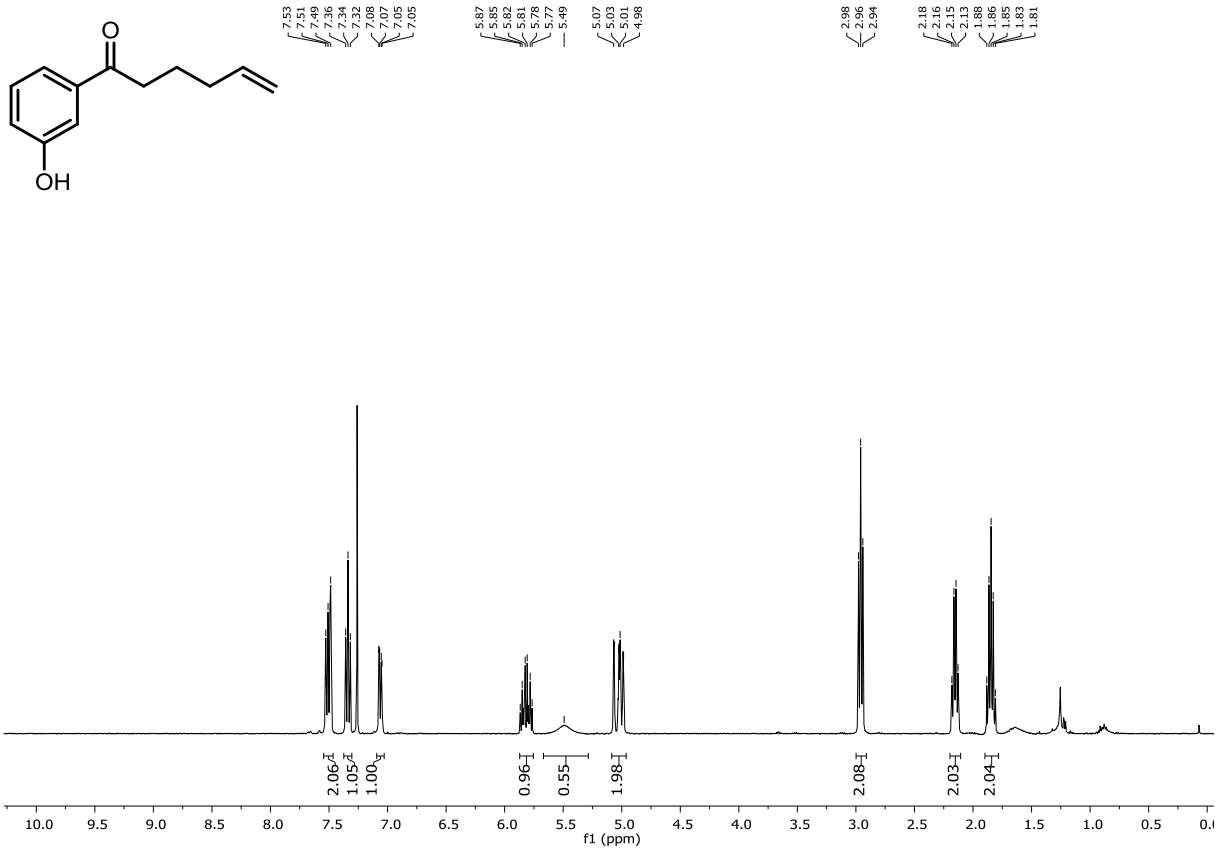
^{1H} NMR (400 MHz, $CDCl_3$) ***1u***



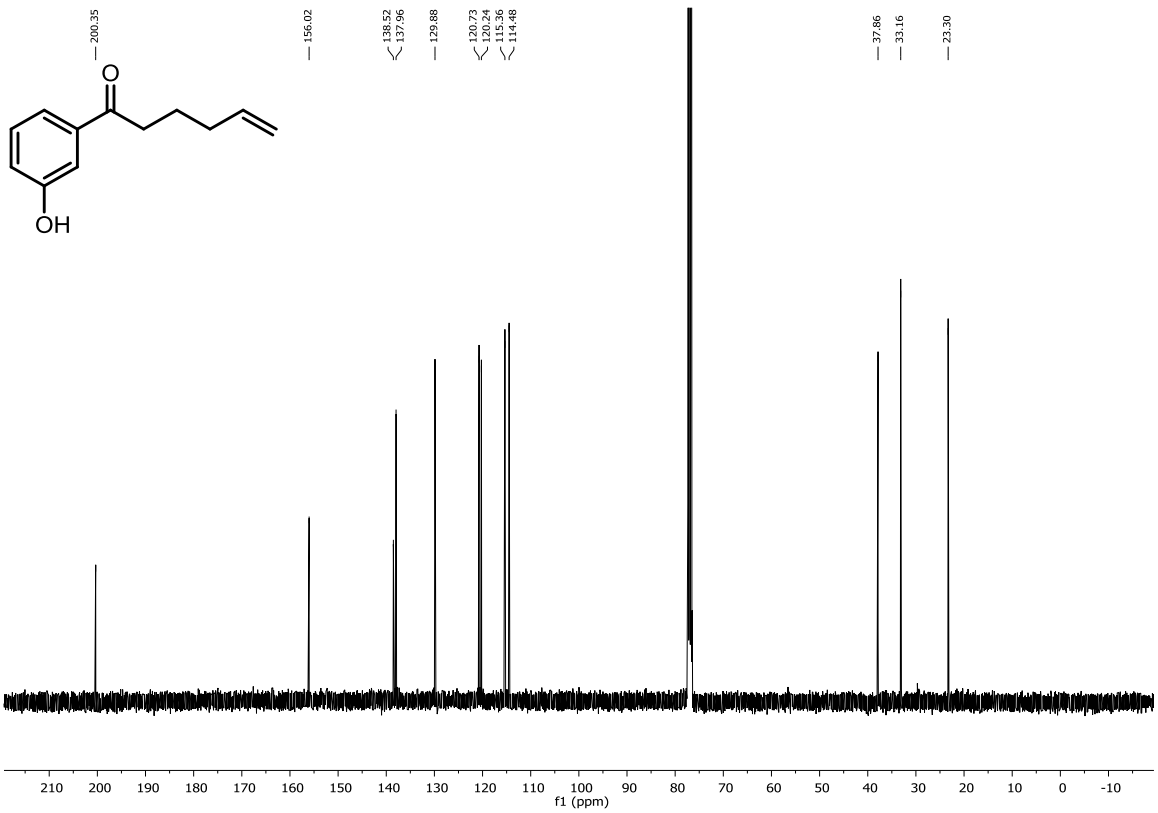
^{13}C NMR (100 MHz, $CDCl_3$) ***1u***



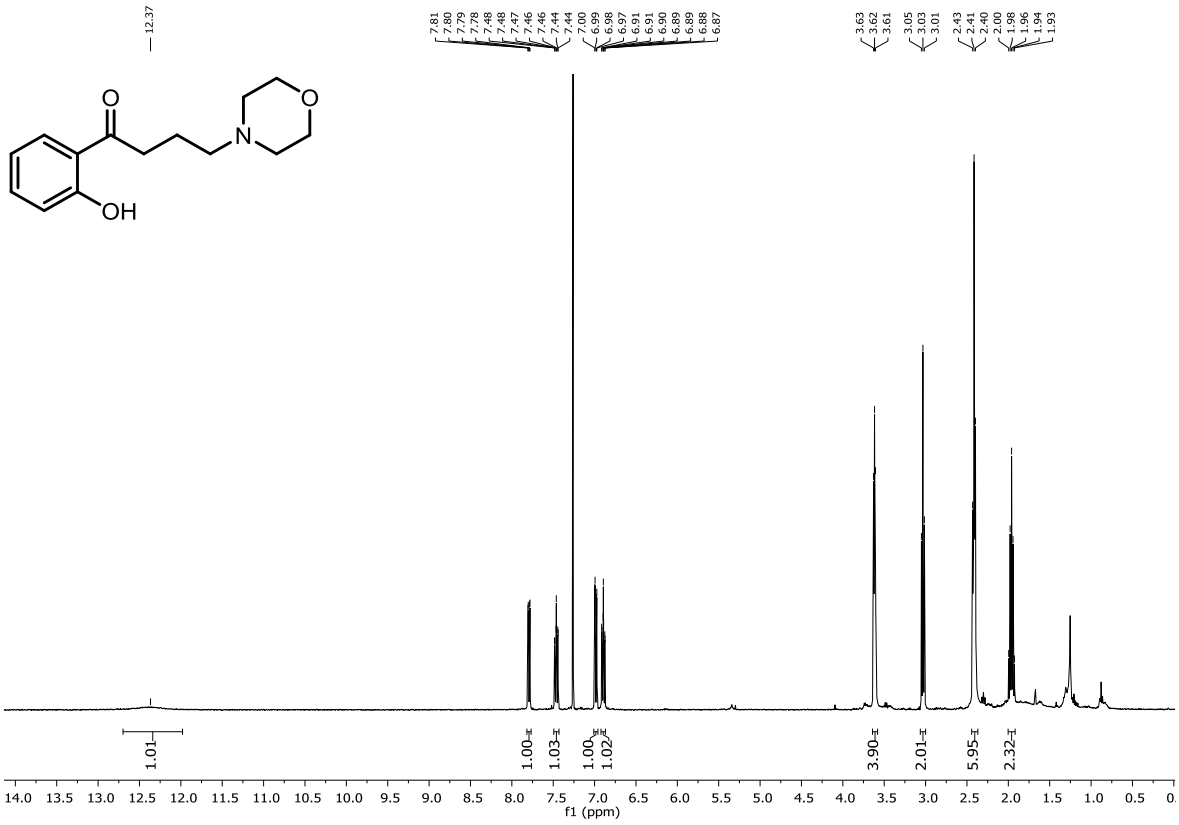
^{1H} NMR (400 MHz, $CDCl_3$) ***1v***



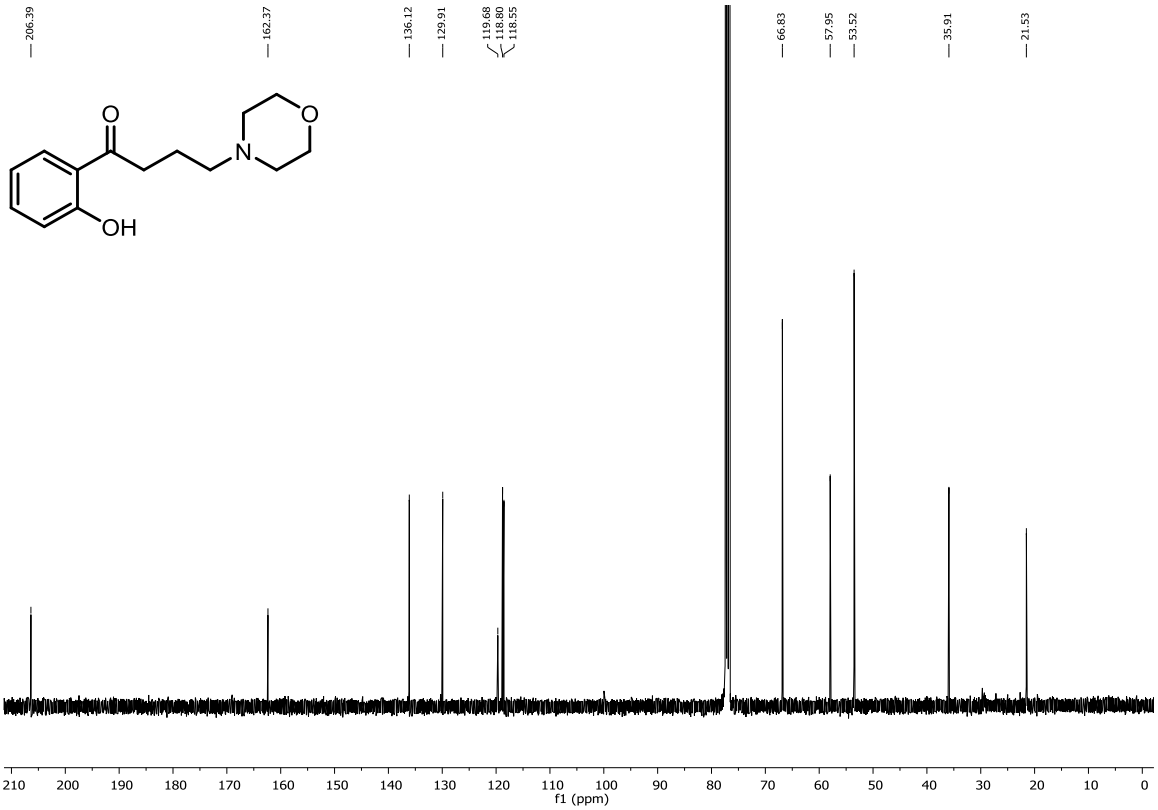
^{13}C NMR (100 MHz, $CDCl_3$) ***1v***



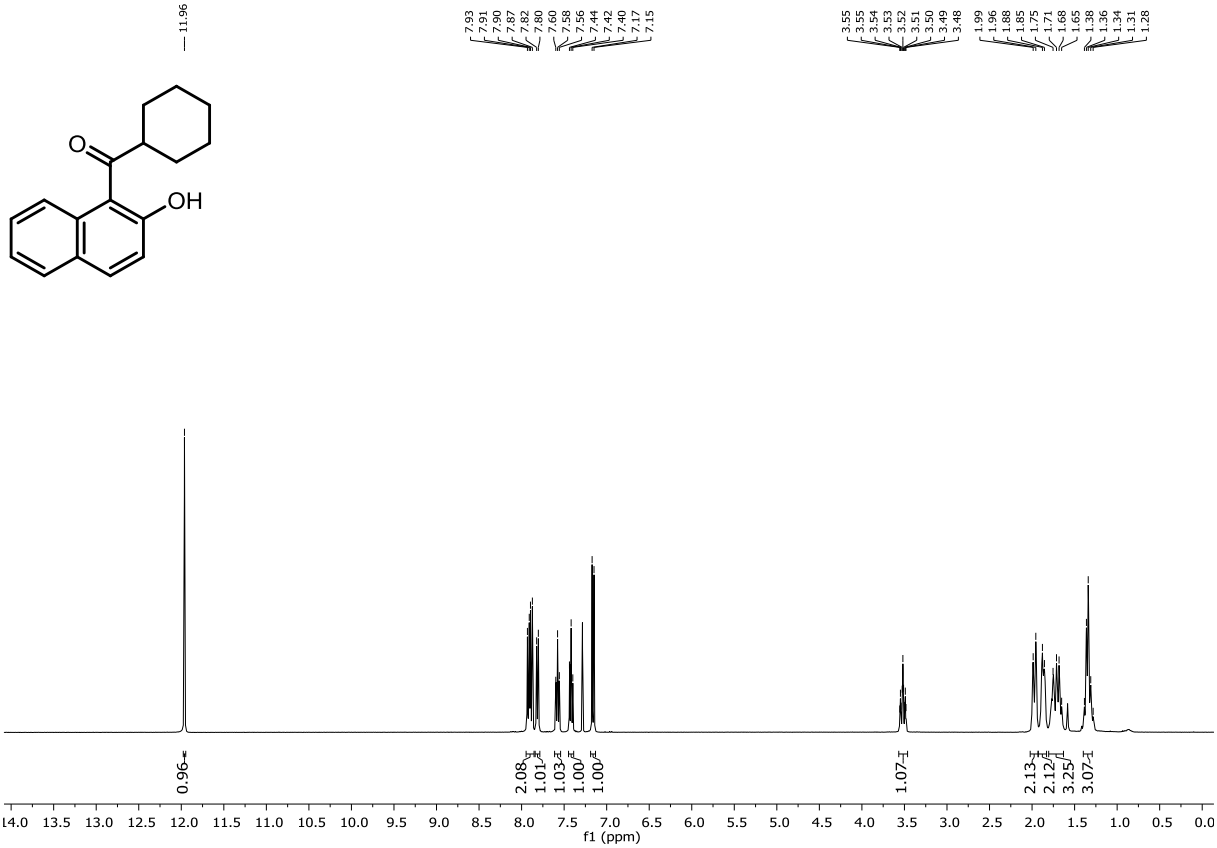
^{1H} NMR (400 MHz, $CDCl_3$) ***1w***



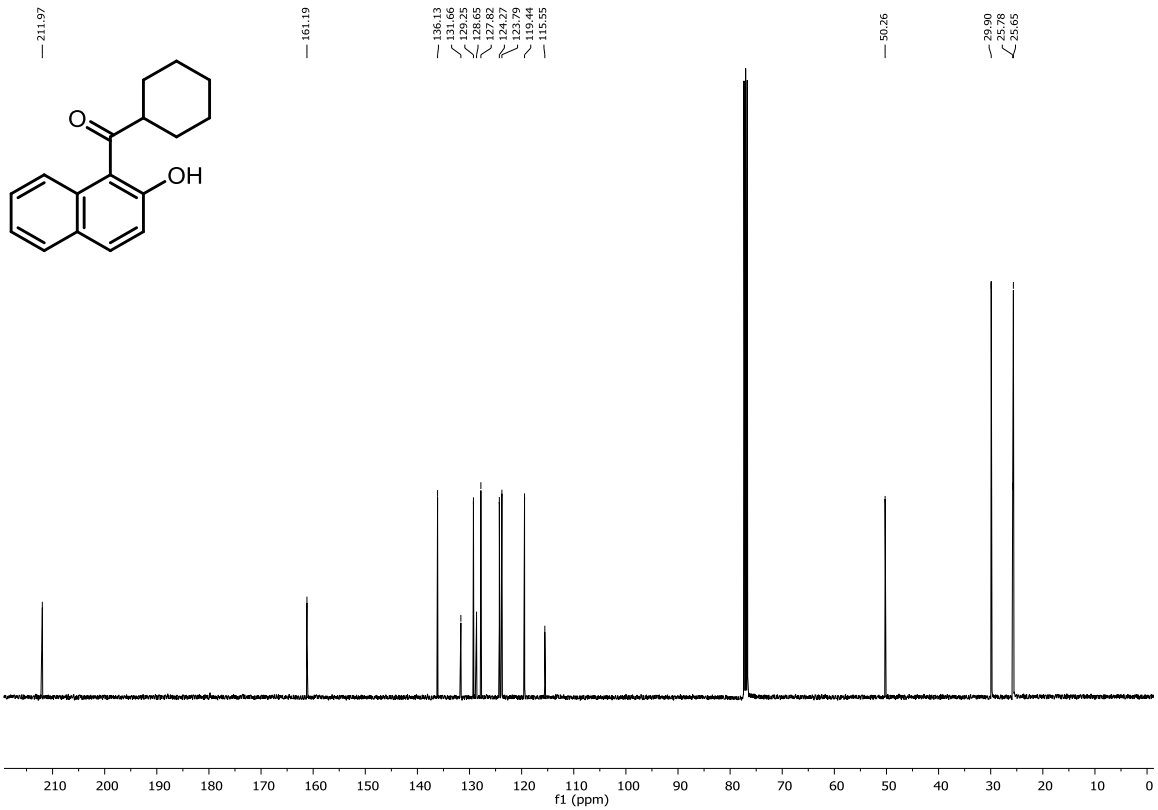
^{13}C NMR (100 MHz, $CDCl_3$) ***1w***



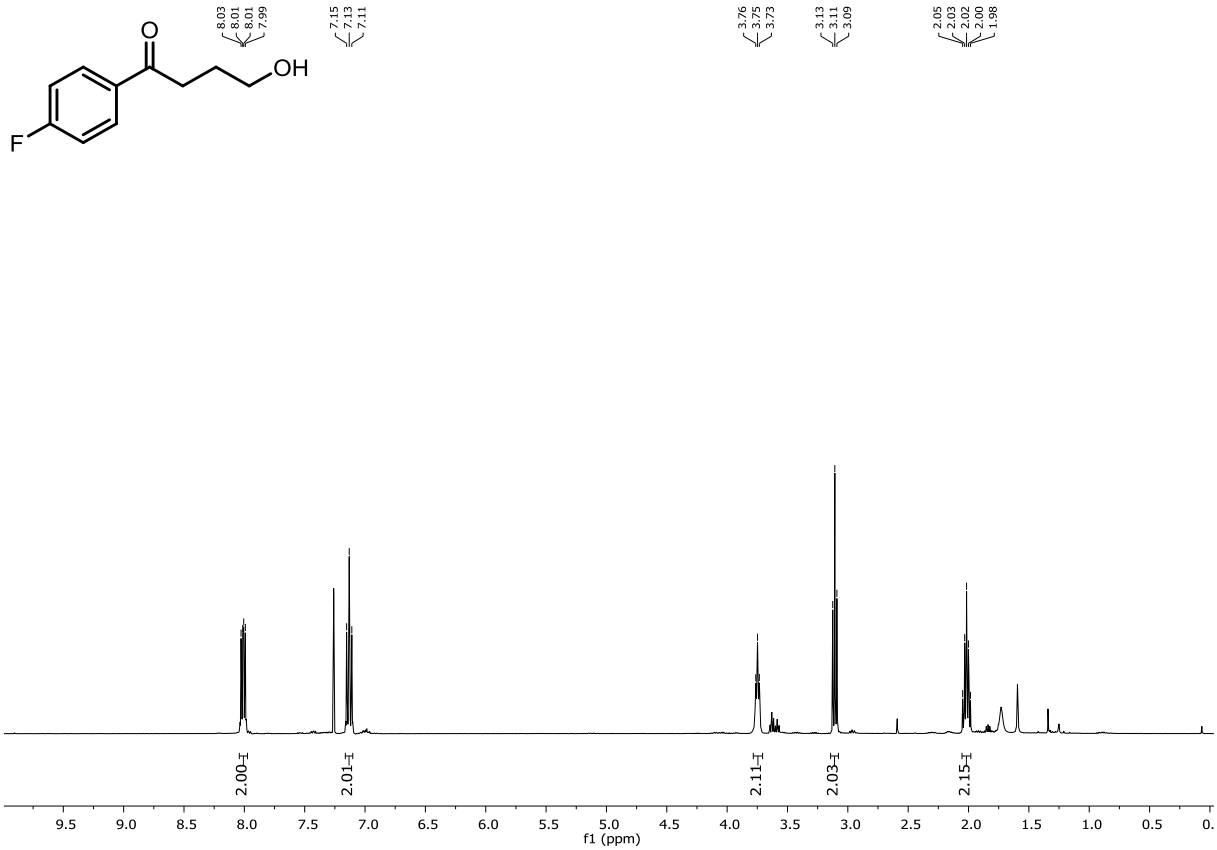
^{1H} NMR (400 MHz, $CDCl_3$) ***1x***



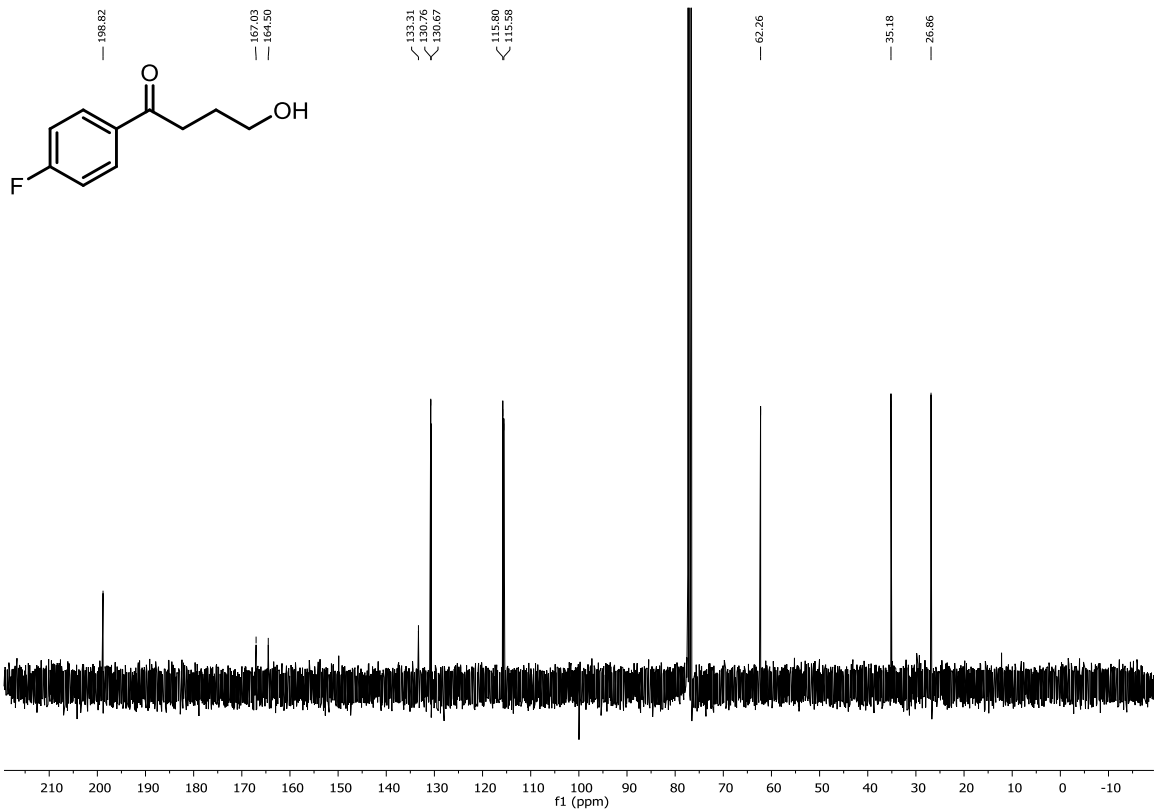
^{13}C NMR (100 MHz, $CDCl_3$) ***1x***



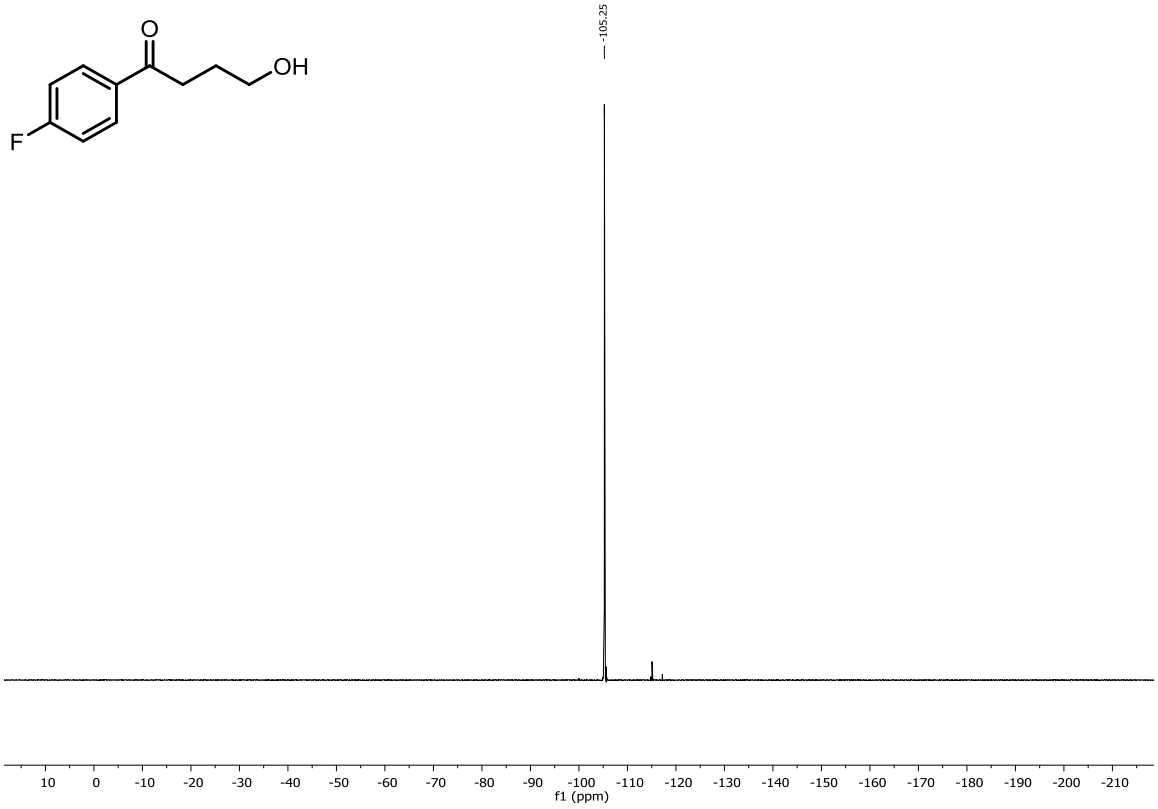
^{1H} NMR (400 MHz, $CDCl_3$) ***1y***



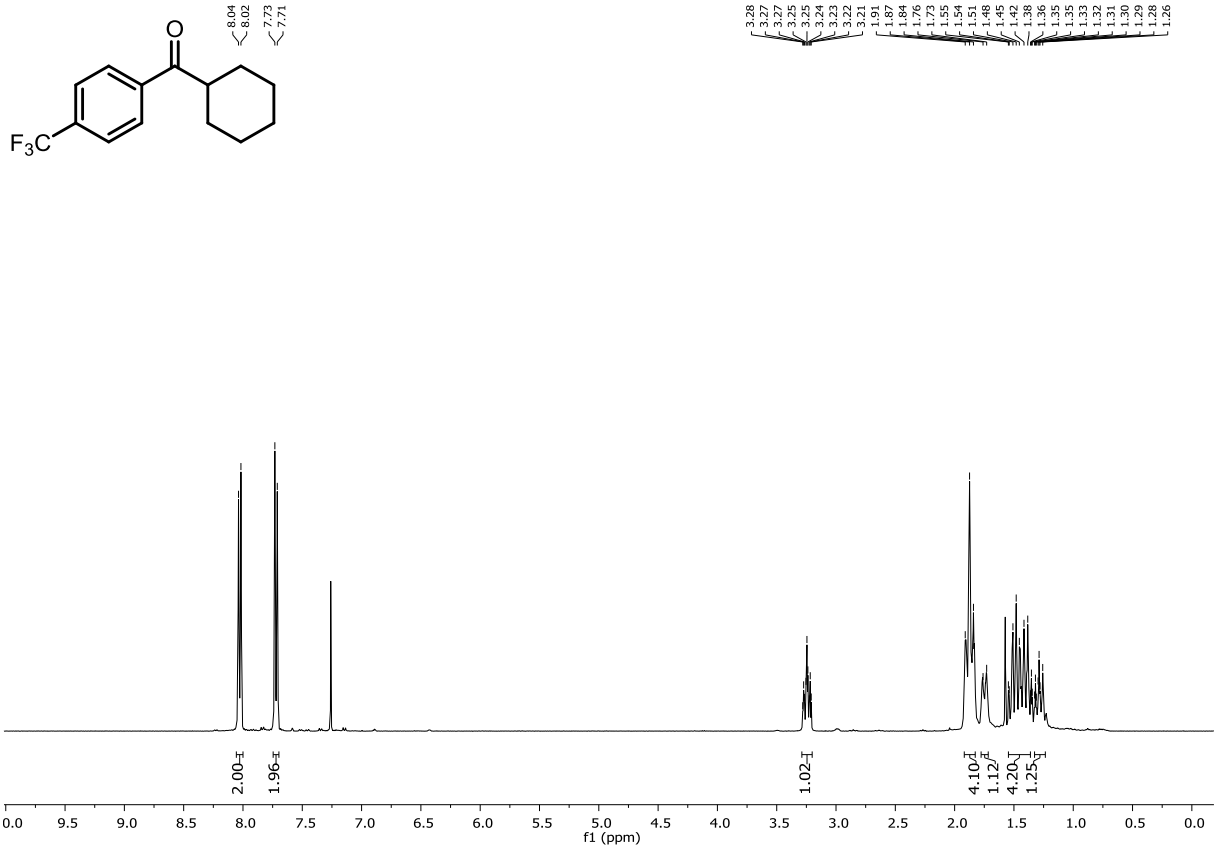
^{13}C NMR (100 MHz, $CDCl_3$) ***1y***



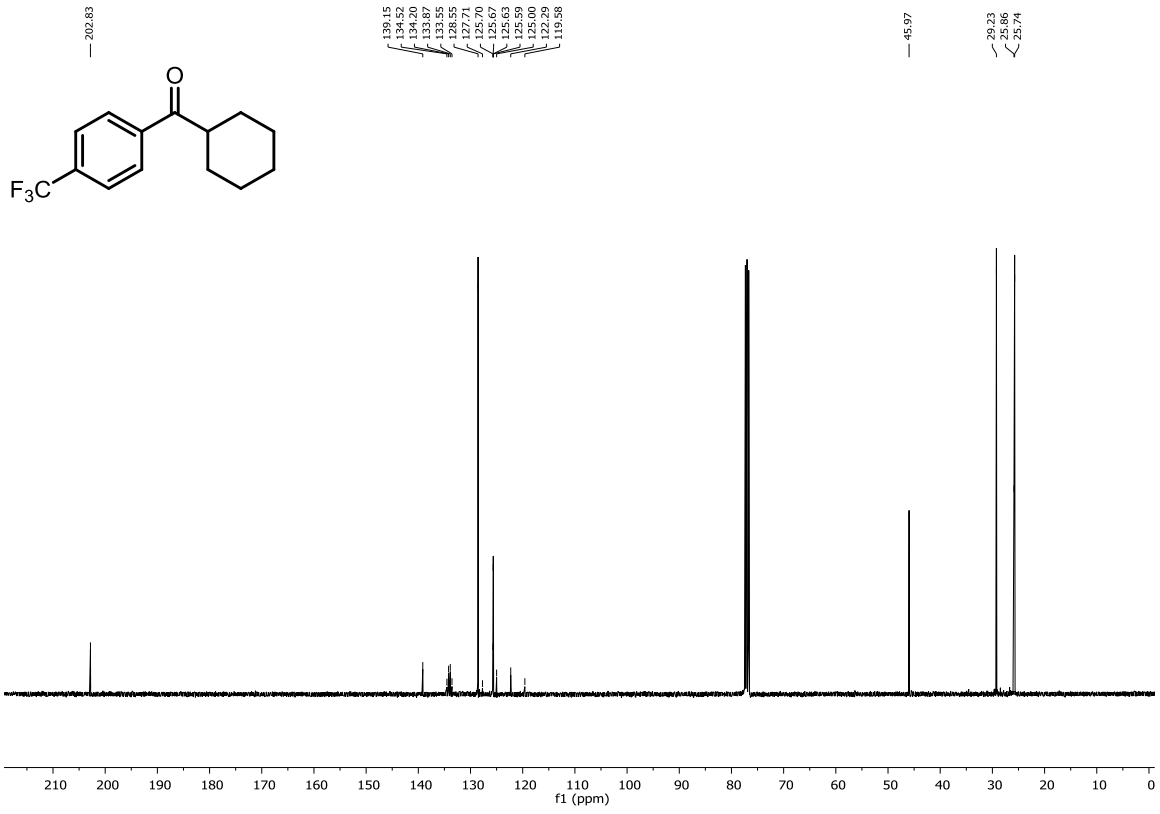
^{19}F NMR (377 MHz, $CDCl_3$) ***1y***



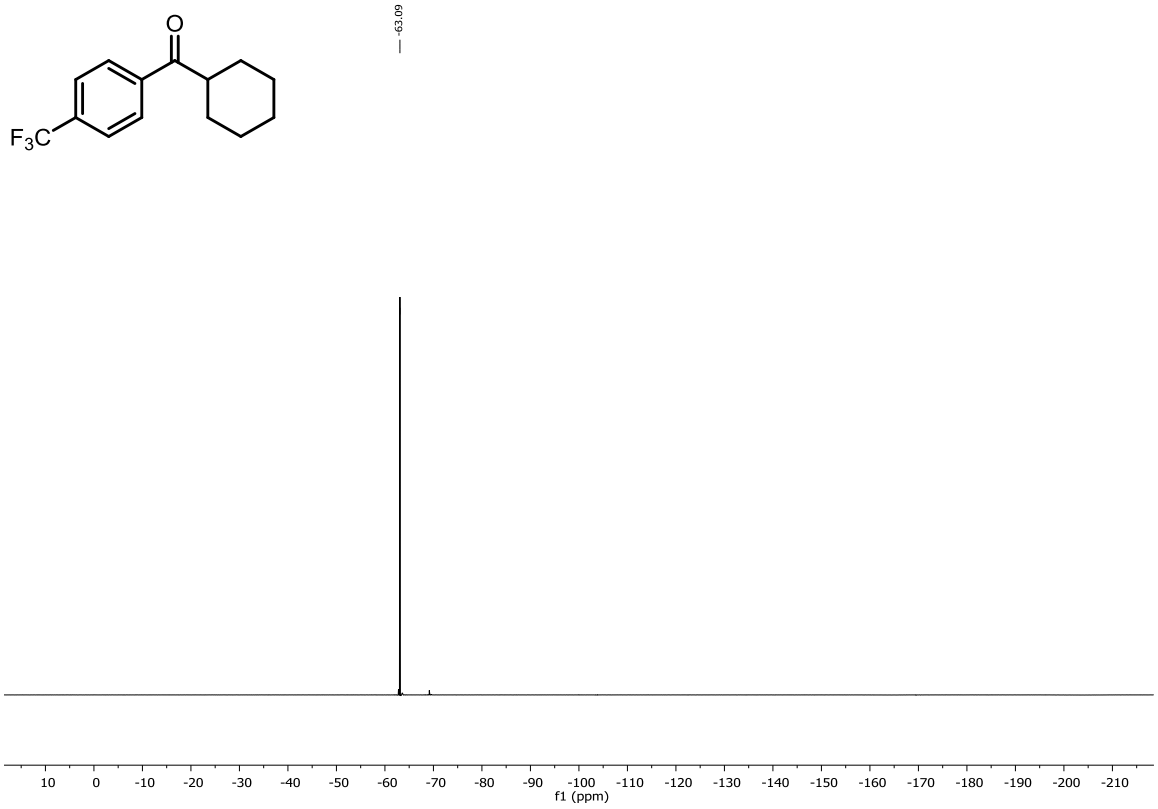
^{1H} NMR (400 MHz, $CDCl_3$) ***1z***



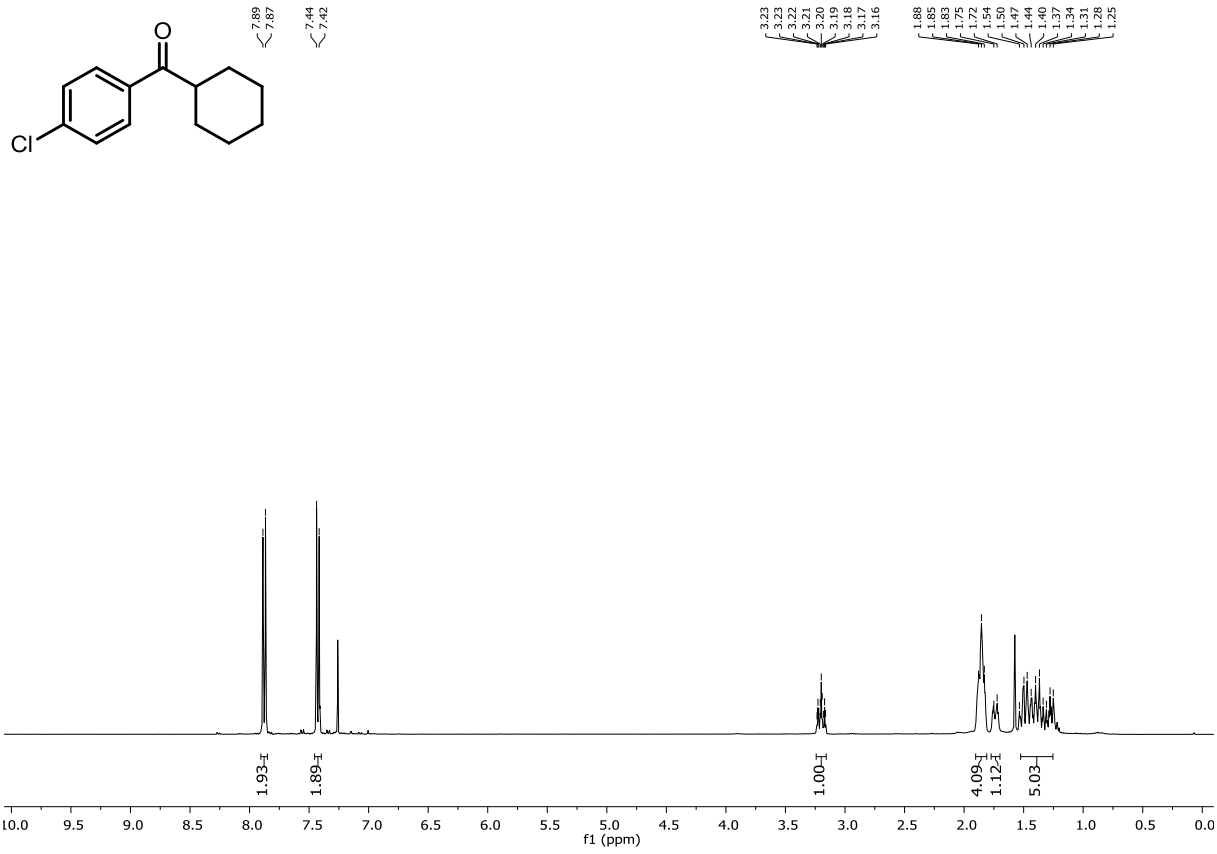
^{13}C NMR (100 MHz, $CDCl_3$) ***1z***



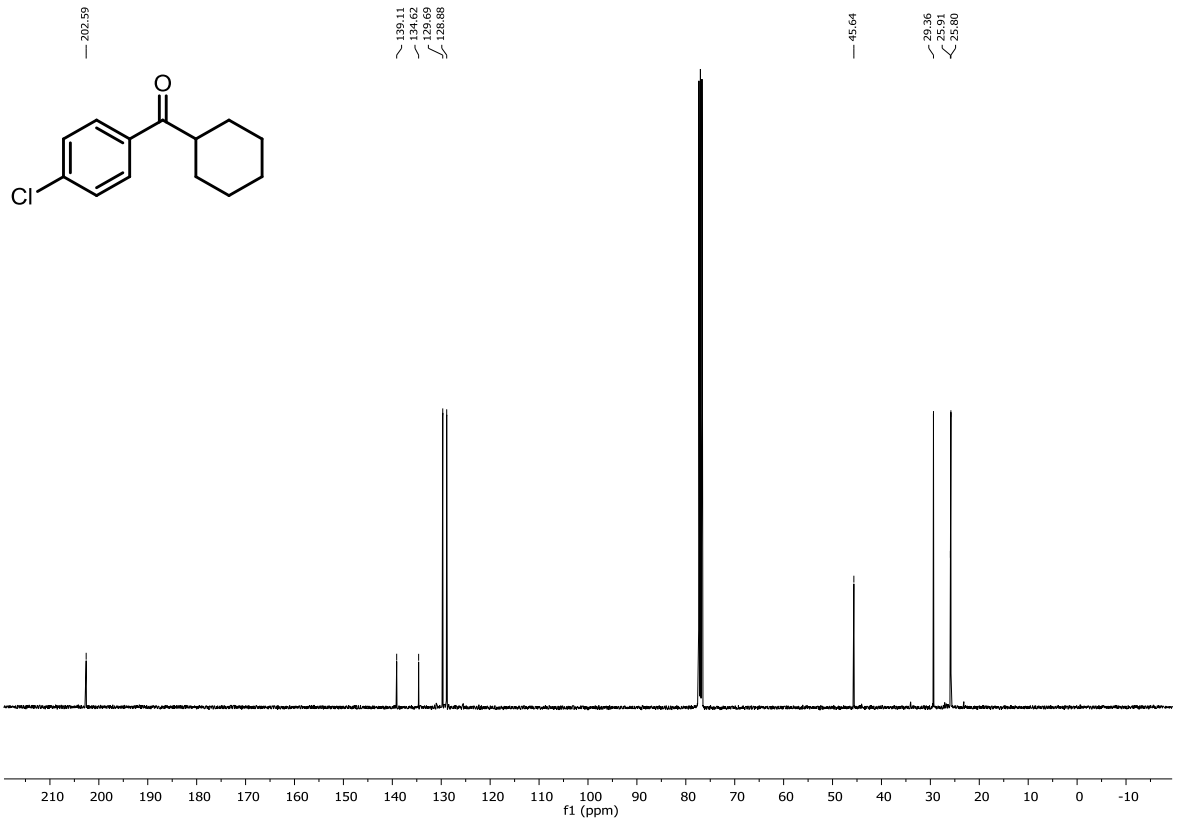
^{19}F NMR (377 MHz, $CDCl_3$) ***1z***



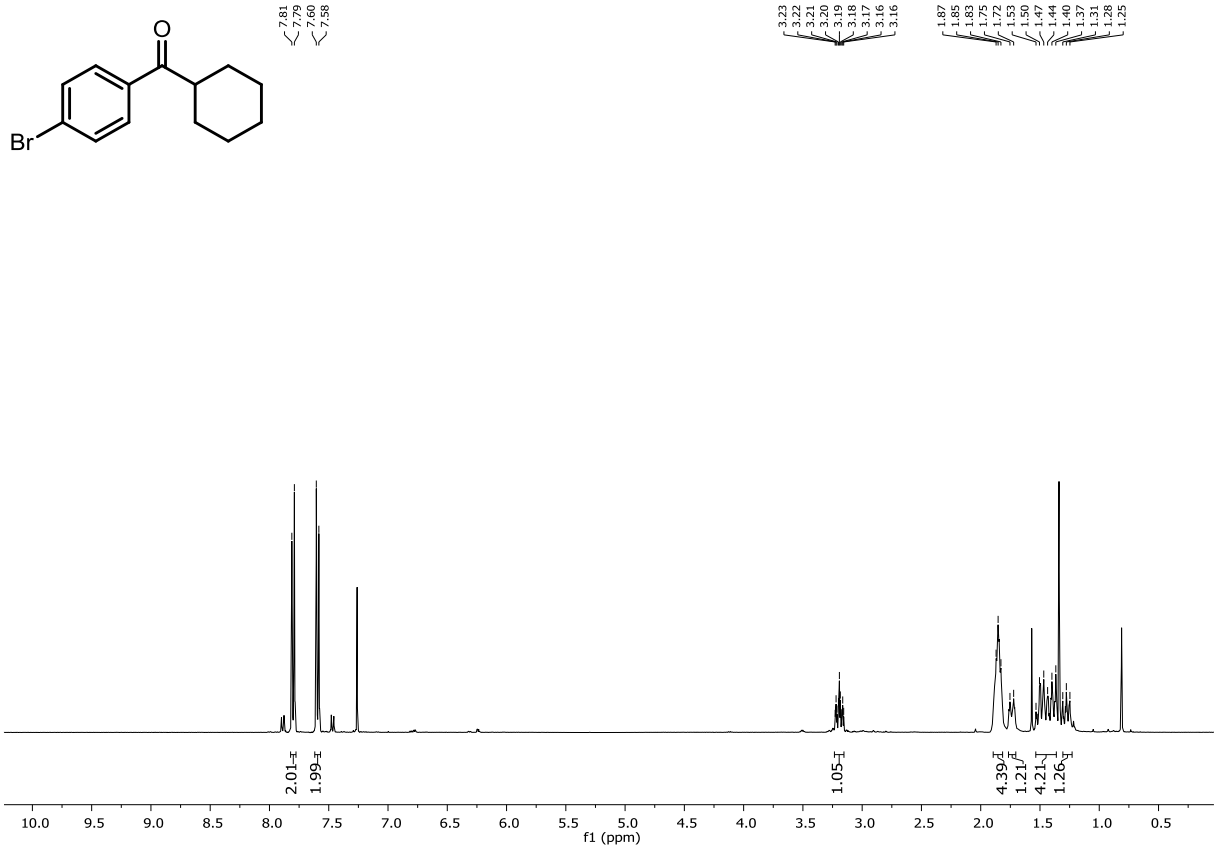
^{1H} NMR (400 MHz, $CDCl_3$) ***1aa***



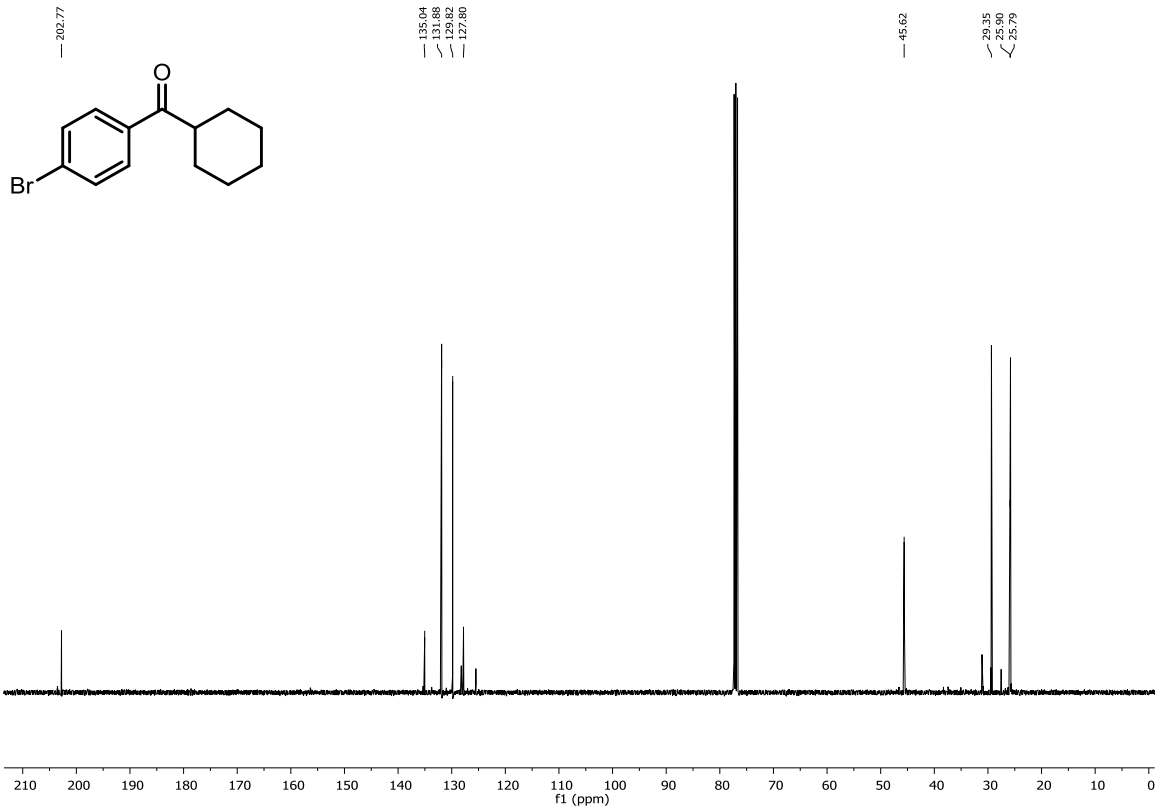
^{13}C NMR (100 MHz, $CDCl_3$) ***1aa***



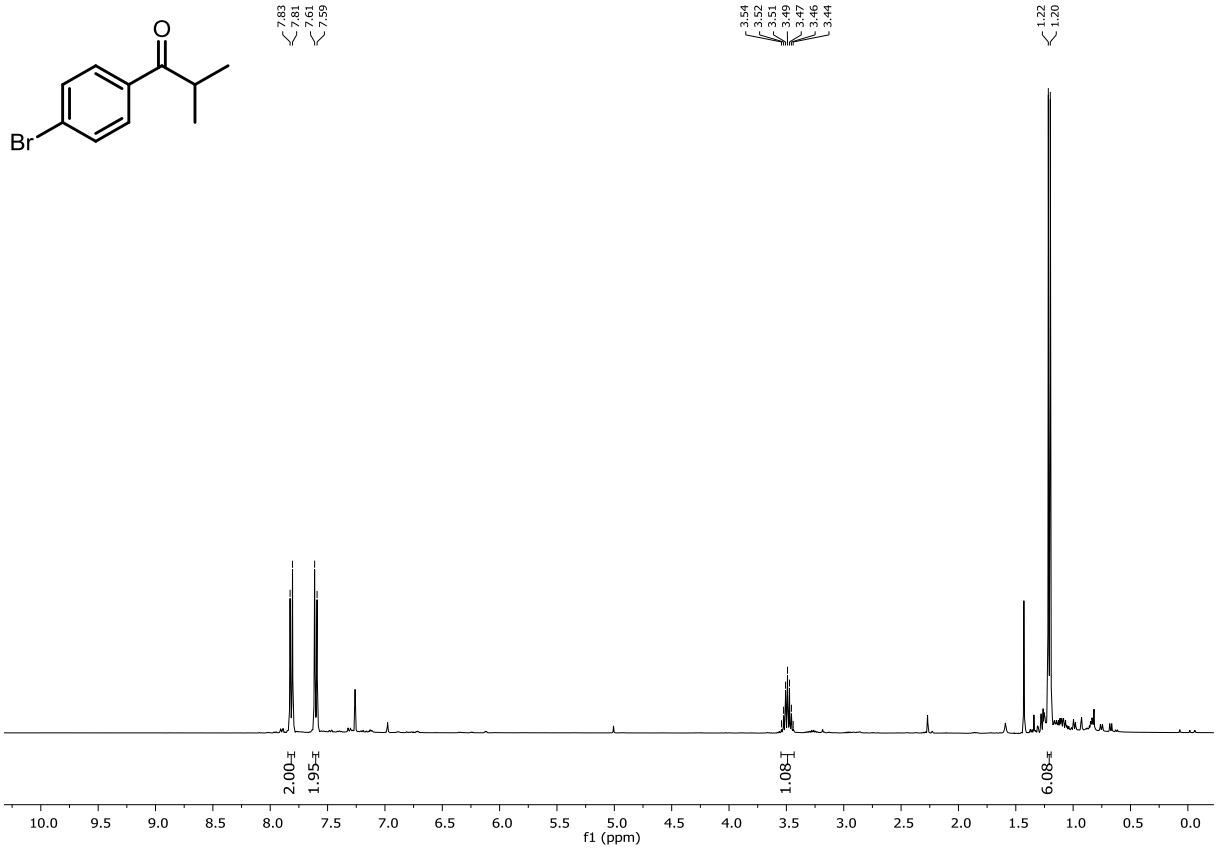
^{1H} NMR (400 MHz, $CDCl_3$) ***1ab***



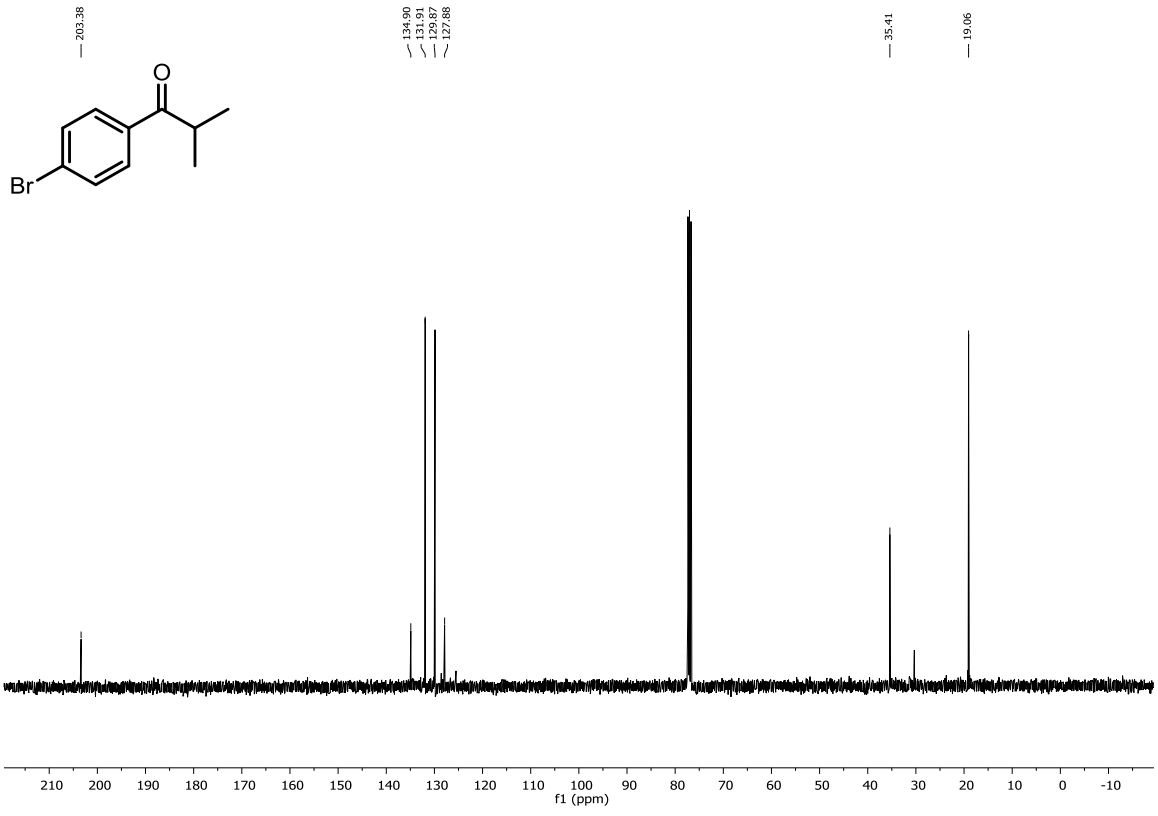
^{13}C NMR (100 MHz, $CDCl_3$) ***1ab***



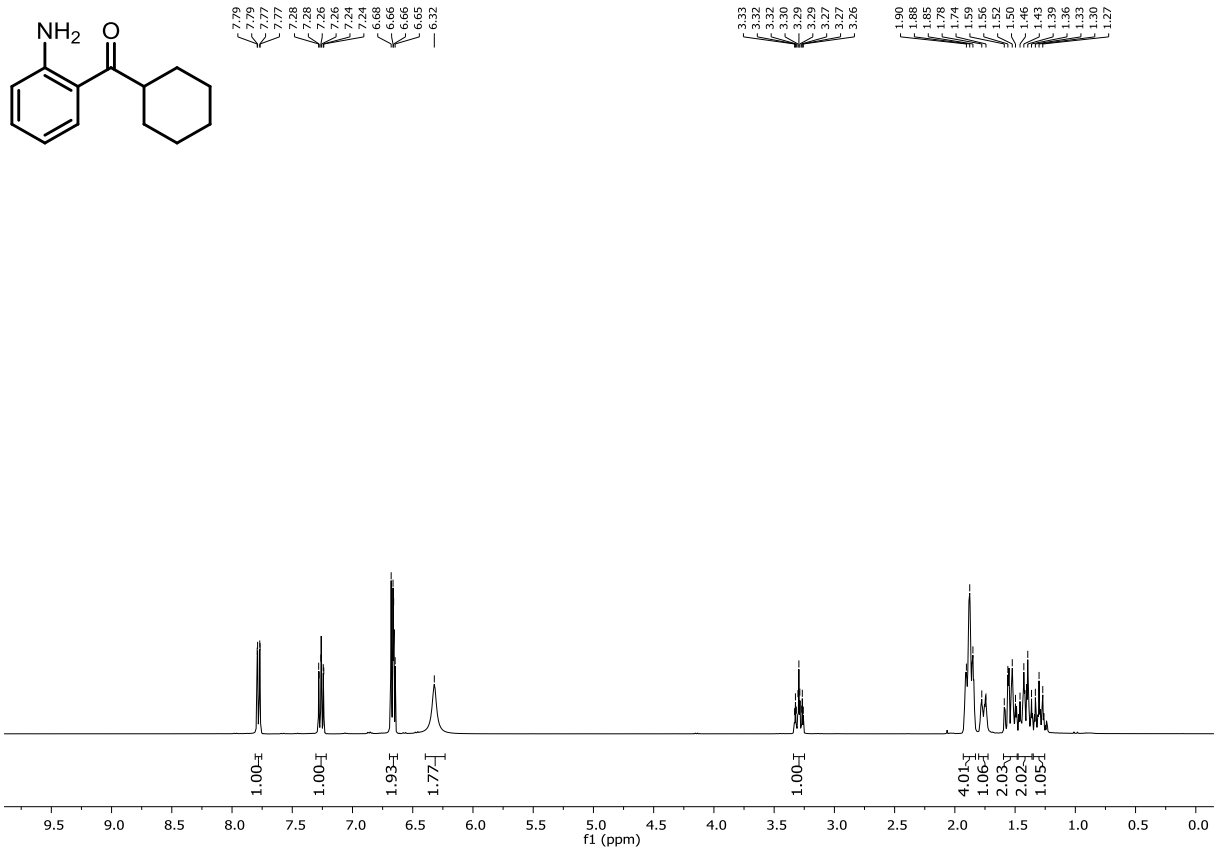
^{1H} NMR (400 MHz, $CDCl_3$) ***1ac***



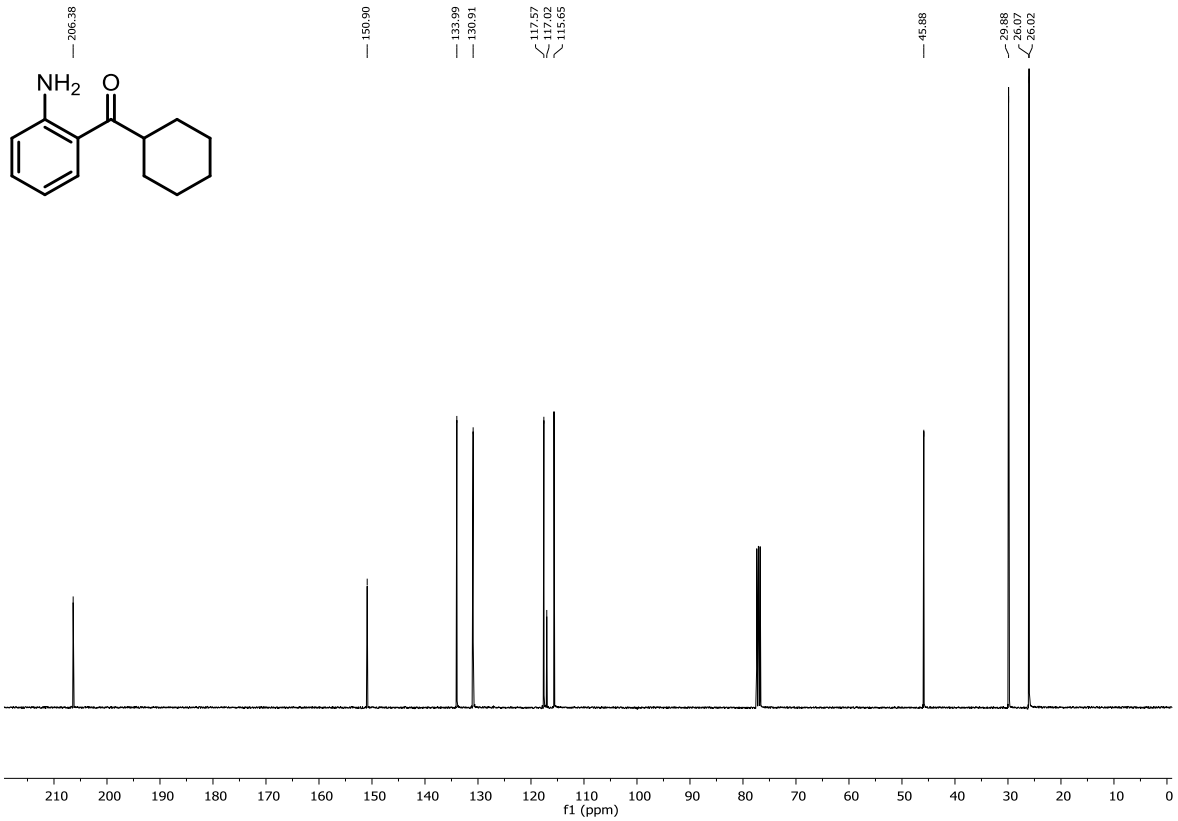
^{13}C NMR (100 MHz, $CDCl_3$) ***1ac***



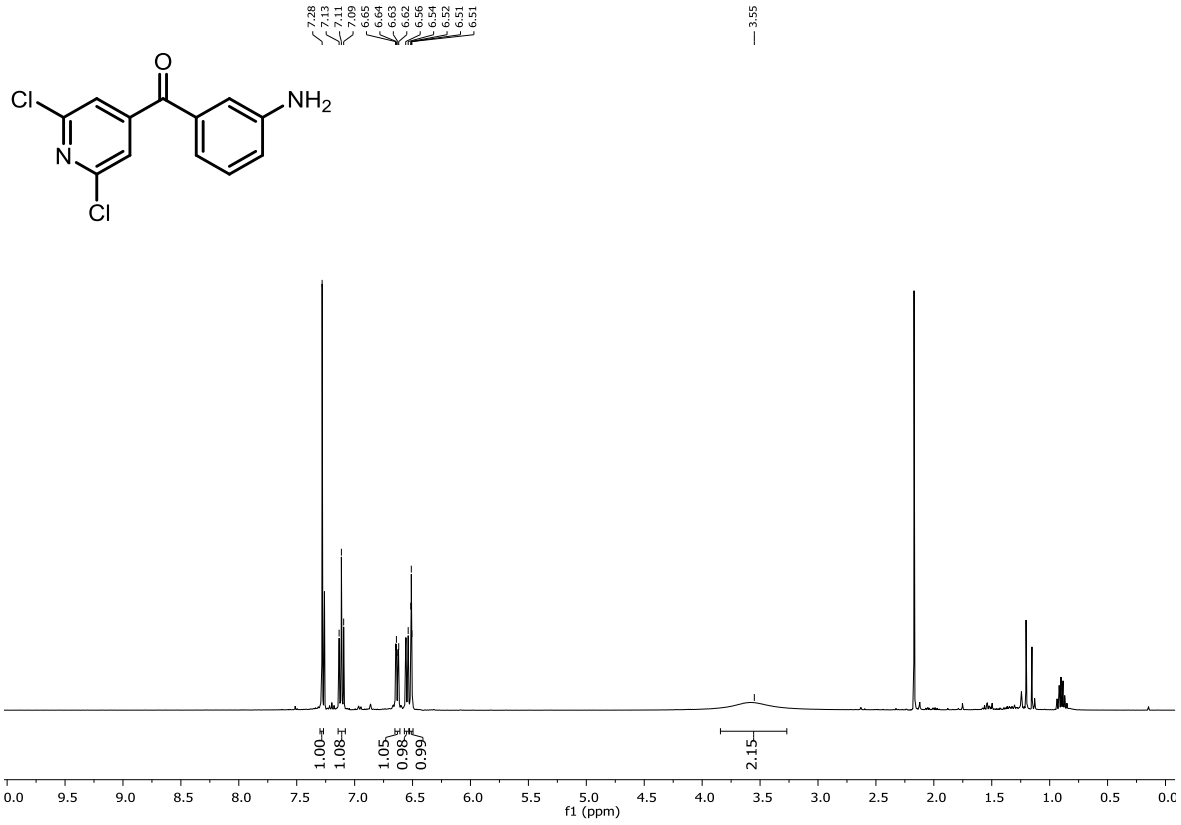
^{1H} NMR (400 MHz, $CDCl_3$) ***1ad***



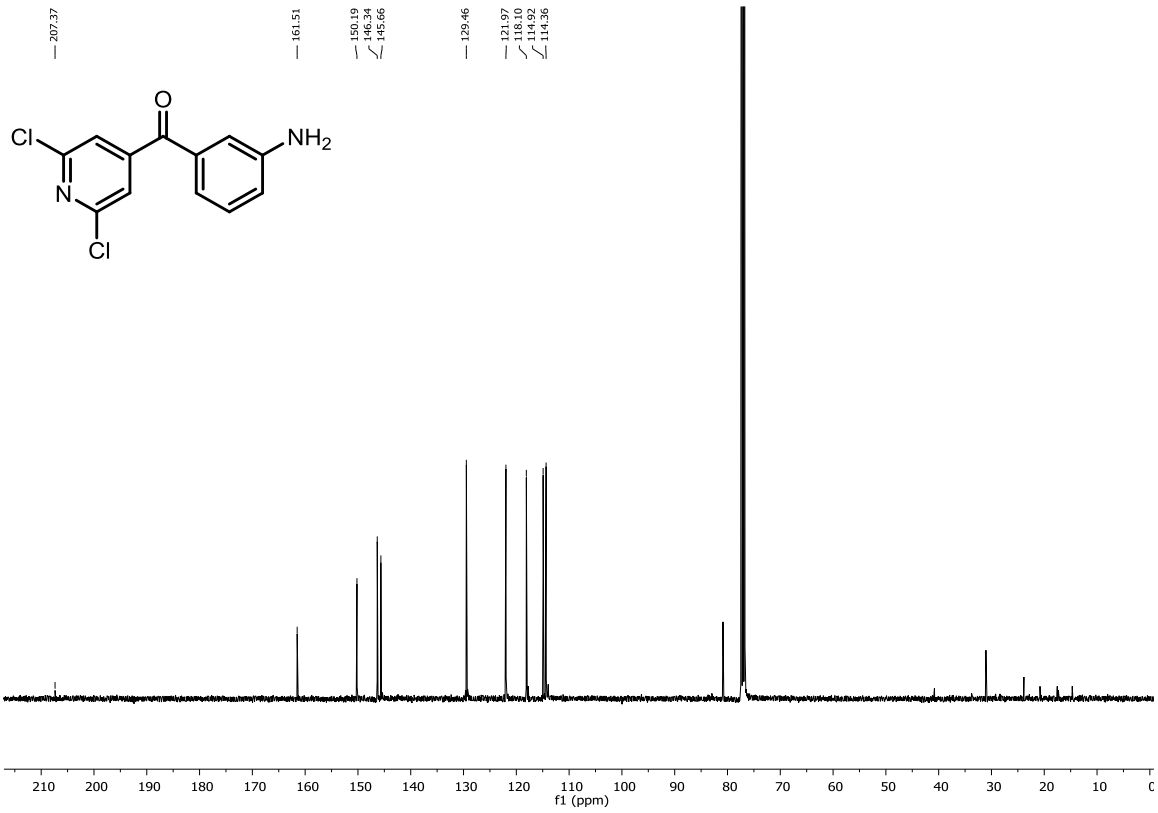
^{13}C NMR (100 MHz, $CDCl_3$) ***1ad***



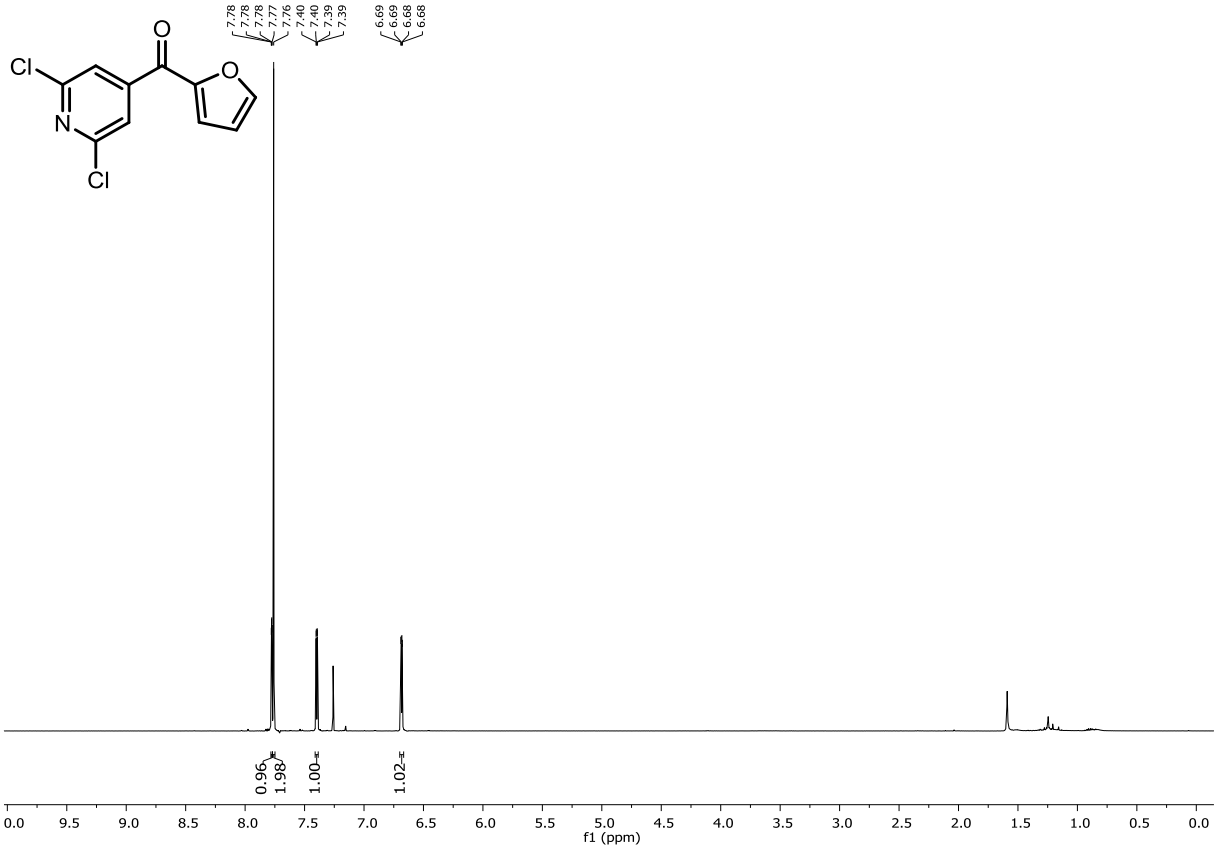
^{1H} NMR (400 MHz, $CDCl_3$) ***1ae***



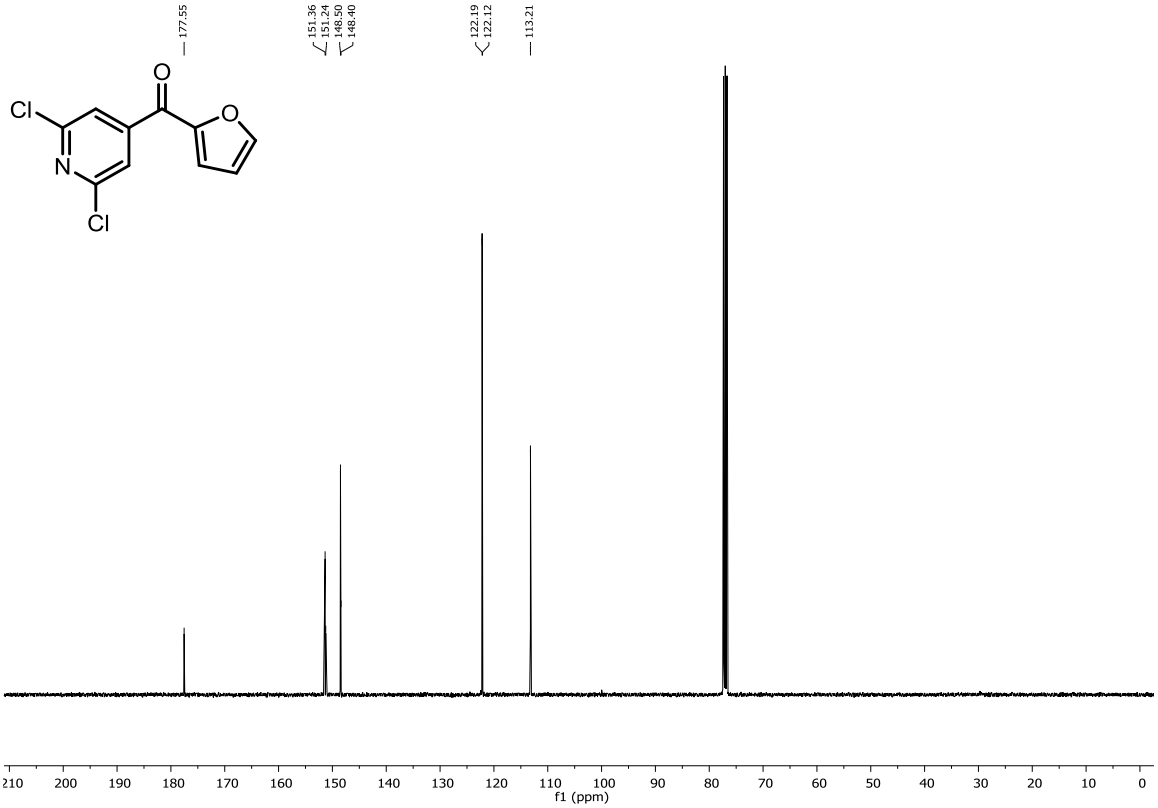
^{13}C NMR (100 MHz, $CDCl_3$) ***1ae***



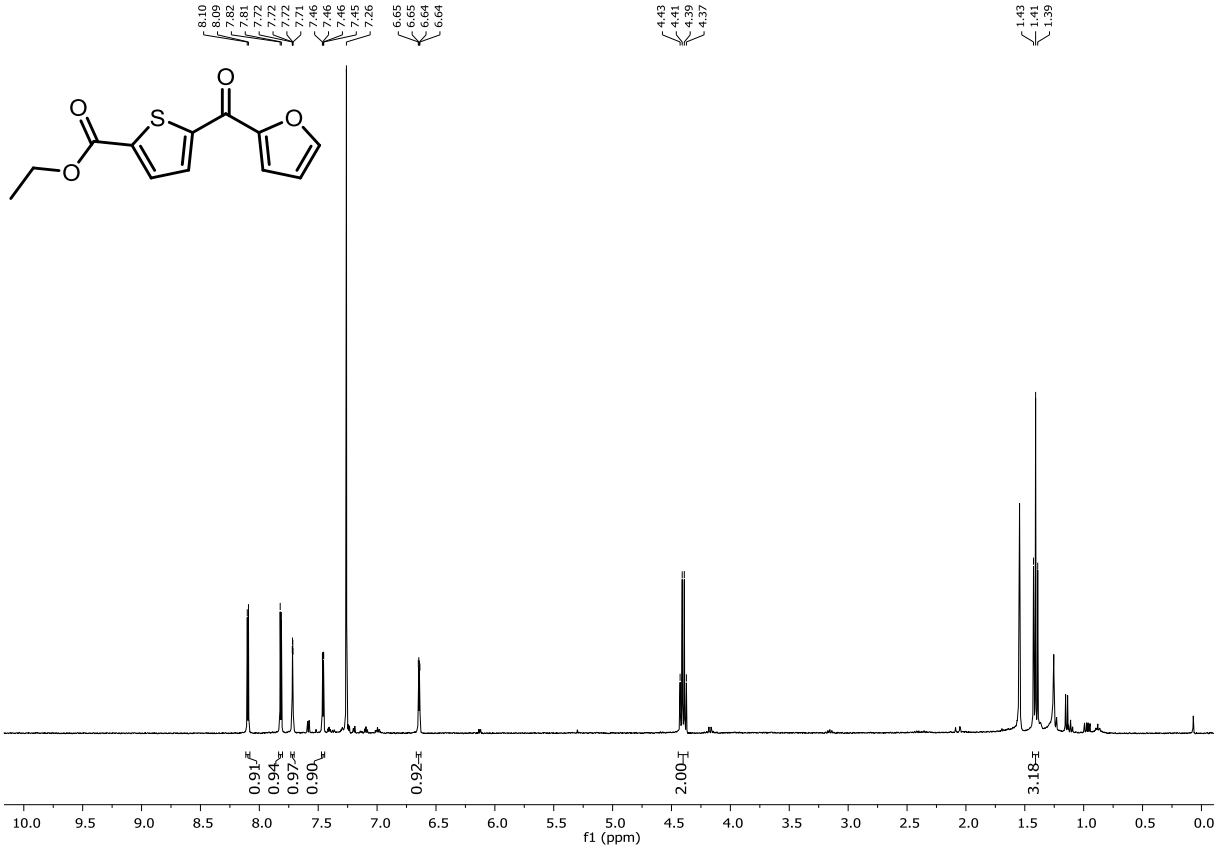
^{1H} NMR (400 MHz, $CDCl_3$) ***1af***



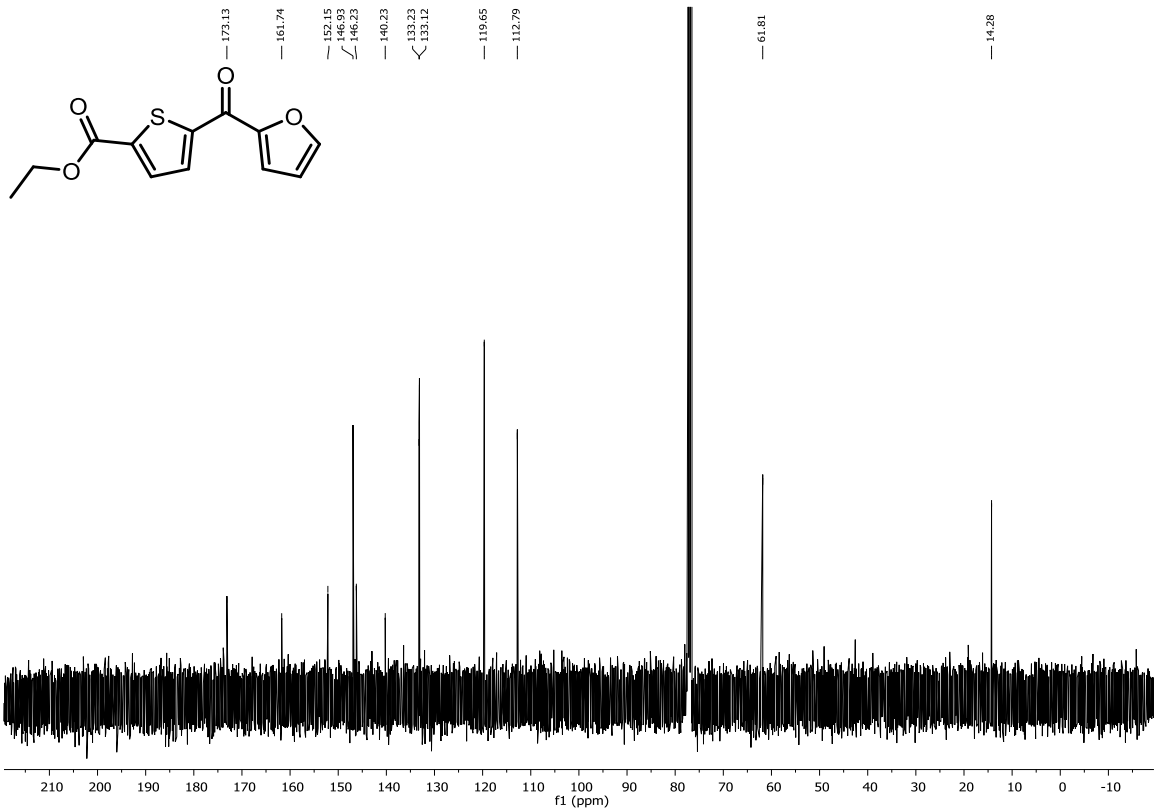
^{13}C NMR (100 MHz, $CDCl_3$) ***1af***



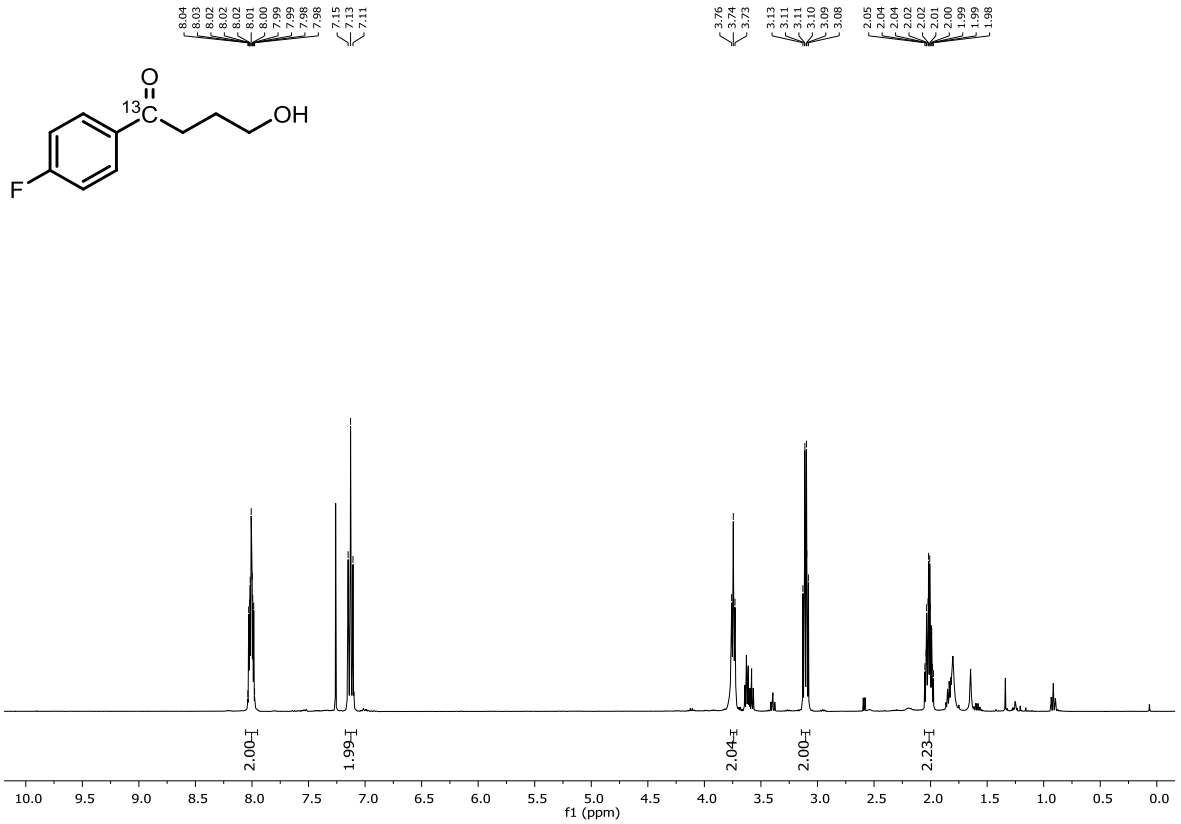
^{1H} NMR (400 MHz, $CDCl_3$) ***1ag***



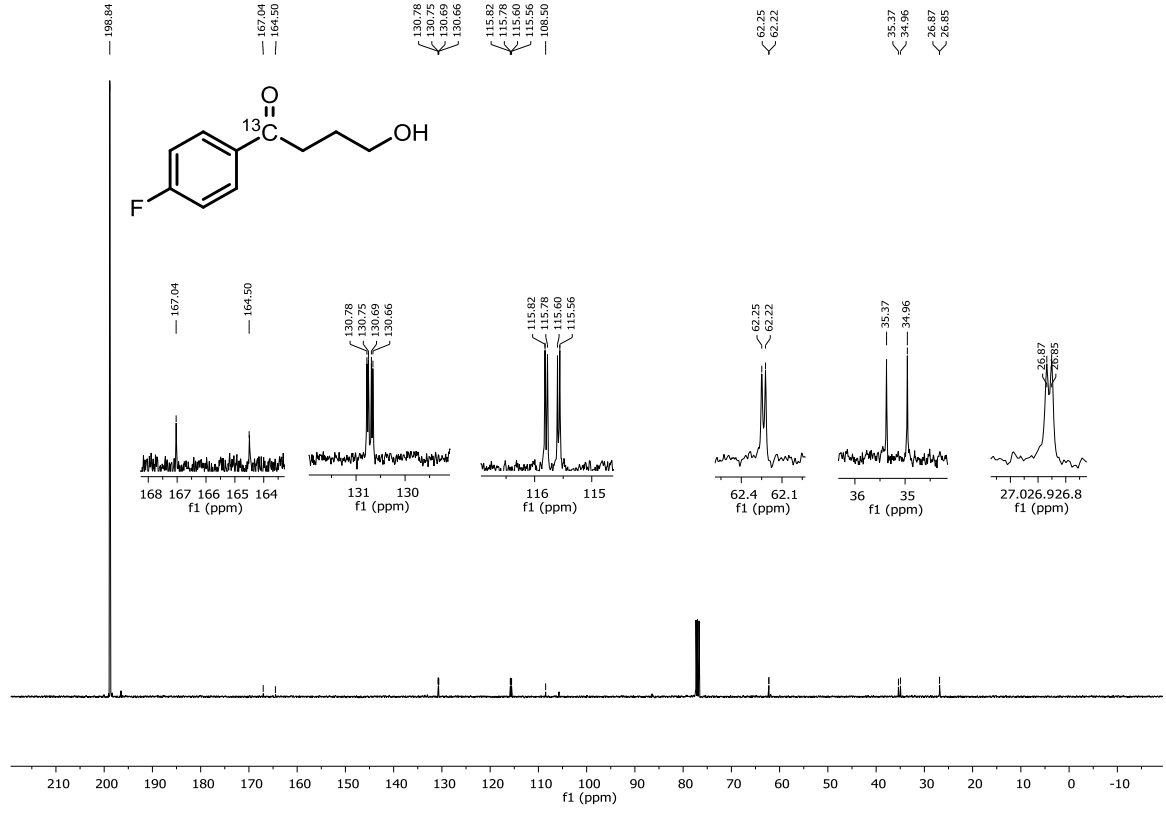
^{13}C NMR (100 MHz, $CDCl_3$) ***1ag***



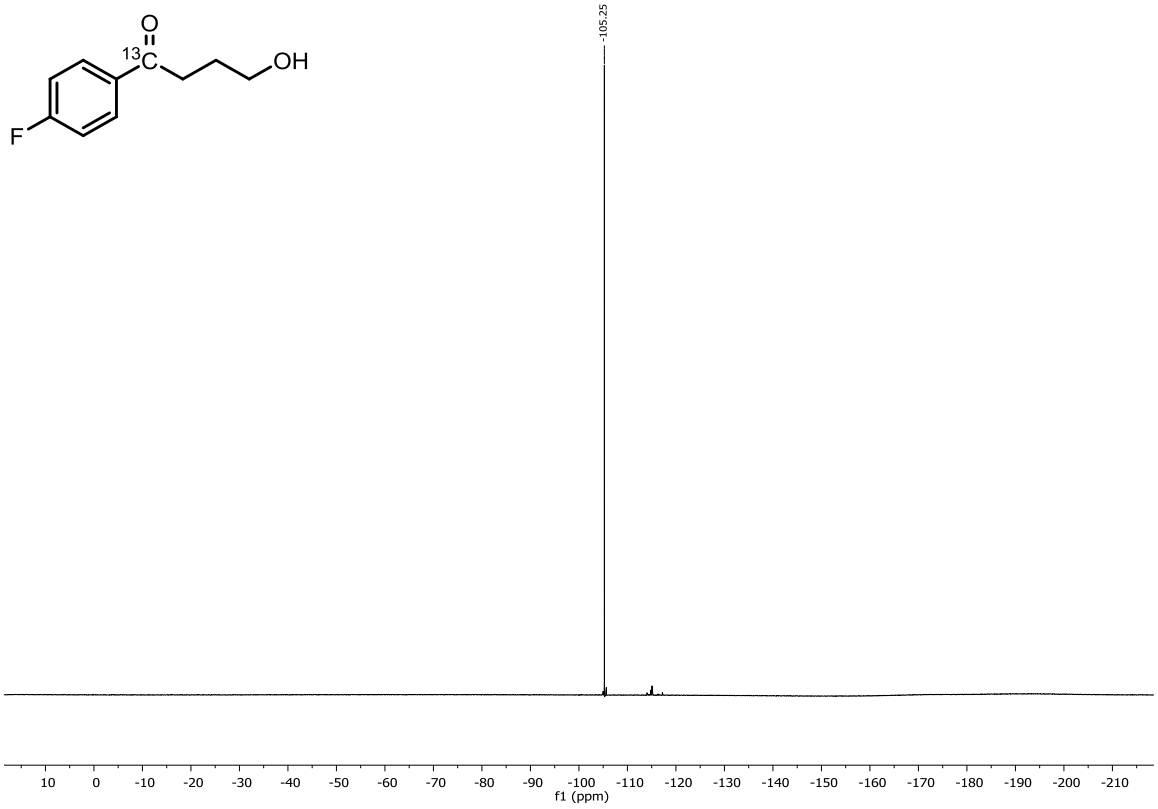
^{1H} NMR (400 MHz, $CDCl_3$) ***[^{13}C]-1y***



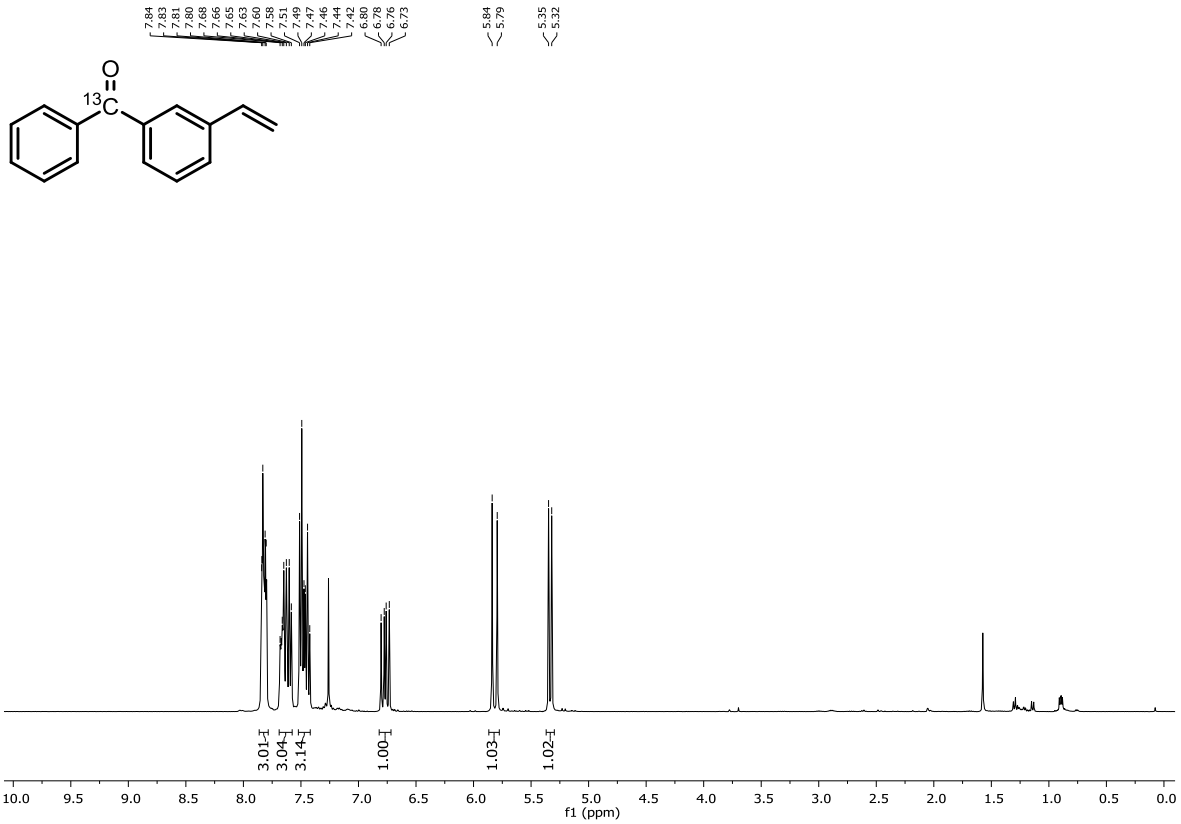
^{13}C NMR (100 MHz, $CDCl_3$) ***[^{13}C]-1y***



^{19}F NMR (377 MHz, $CDCl_3$) ***[^{13}C]-1y***



^{1H} NMR (400 MHz, $CDCl_3$) ***[^{13}C]-1ah***



^{13}C NMR (100 MHz, $CDCl_3$) ***[^{13}C]-1ah***