

Exploring tandem ruthenium-catalyzed hydrogen transfer and S_NAr chemistry

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SUPPORTING INFORMATION

Table of Contents

1. General information	2
2. Experimental and characterization data (hydrogen transfer-S_NAr)	3
2.1. Synthesis of secondary benzylic alcohols.....	3
2.1.1. General procedure 1	3
2.1.2. General procedure 2	3
2.2. Optimization of hydrogen transfer- S_NAr protocol	28
2.2.1. Optimization of hydrogen transfer- S_NAr protocol (dehydrogenative).....	30
2.2.2. General procedure 3	31
2.2.3. Optimization of hydrogen transfer- S_NAr protocol (redox neutral).....	32
2.2.4. General procedure 4	33
2.3. Scope of dehydrogenative S_NAr protocol.....	35
2.3.1. General procedure 5	64
2.4. Scope of redox neutral S_NAr protocol	80
3. Experimental and characterization data (isomerisation protocol)	89
3.1. Synthesis of 2-aryloxy-1-ethanols	89
3.1.1. Synthesis of 43	89
3.2. General procedure 6	93
3.3. Optimisation of isomerisation protocol	114
3.4. General procedure 7	114
3.5. Scope of isomerisation protocol	116
4. Experimental and characterisation data (telescoped diaryl ether synthesis)	123
4.1. Preparation of 2-(4-fluorophenyl)oxirane.....	123
4.2. Telescoped one pot diaryl ether synthesis from epoxide: 1-(4-phenoxyphenyl)-ethan-1-one	124
5. References.....	125

1. General information

Unless stated otherwise, all reactions were performed using oven-dried 10 mL microwave vials sealed with an aluminium crimp caps, and were stirred with Teflon-coated magnetic stirrer bars. Dry tetrahydrofuran (THF), toluene, hexanes and diethyl ether were obtained after passing these previously degassed solvents through activated alumina columns (Mbraun, SPS-800). All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Ice/water and CO₂(s)/acetone baths were used to obtain temperatures of 0 °C and -78 °C respectively. All reactions involving heating were carried out using DrySyn blocks and a contact thermometer. *In vacuo* refers to reduced pressure through the use of a rotary evaporator

Analytical thin layer chromatography was carried out using aluminium plates coated with silica (Kieselgel 60 F₂₅₄ silica) and visualization was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO₄ solution. Flash chromatography used Kieselgel 60 silica in the solvent system stated.

Melting points were recorded on an Electrothermal 100 apparatus and are uncorrected.

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier Transform ATIR spectrometer as thin films using a Pike MIRacle ATR accessory. Characteristic peaks are quoted (ν_{\max} / cm⁻¹).

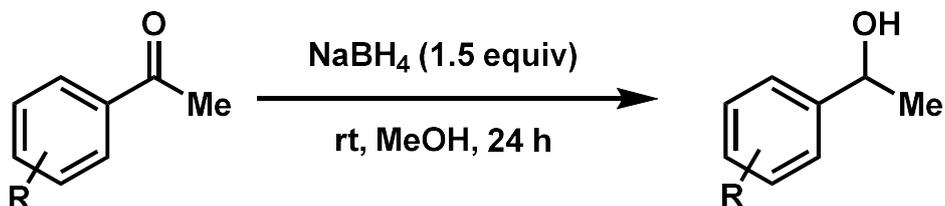
¹H, ¹³C, ¹⁹F NMR spectra were obtained on either a Bruker Avance 400 (400 MHz ¹H, 101 MHz ¹³C, 376 MHz ¹⁹F) or a Bruker Avance 500 (500 MHz ¹H, 126 MHz ¹³C, 471 MHz ¹⁹F) spectrometer at rt in the solvent stated. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent signal. All coupling constants, *J*, are quoted in Hz. Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and multiples thereof. The abbreviation Ph to denote phenyl, br to denote broad.

High resolution mass spectrometry (HRMS, *m/z*) data was acquired either at Cardiff University on a Micromass LCT spectrometer or at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

2. Experimental and characterization data (hydrogen transfer-S_NAr)

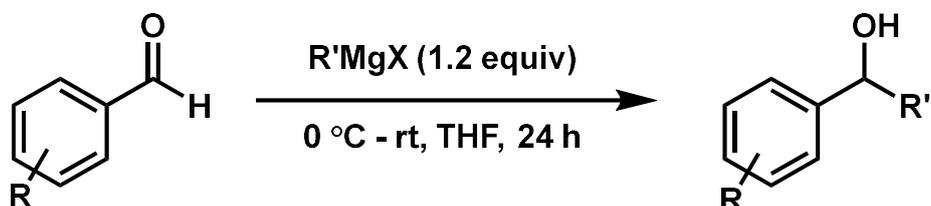
2.1. Synthesis of secondary benzylic alcohols

2.1.1. General procedure 1



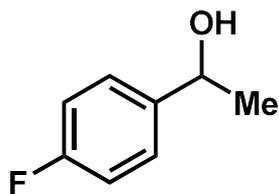
A round-bottomed flask containing a magnetic stirrer bar was charged with the requisite acetophenone (1 equiv), methanol (0.4 M) and NaBH₄ (1.5 equiv). The reaction mixture was stirred at rt for 24 h. The reaction mixture cooled to 0 °C and quenched with sat. aq. NH₄Cl and H₂O. It was transferred to separatory funnel followed by the addition of EtOAc and H₂O. The organic layer was collected and the aqueous phase washed with EtOAc (x 2). The organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

2.1.2. General procedure 2



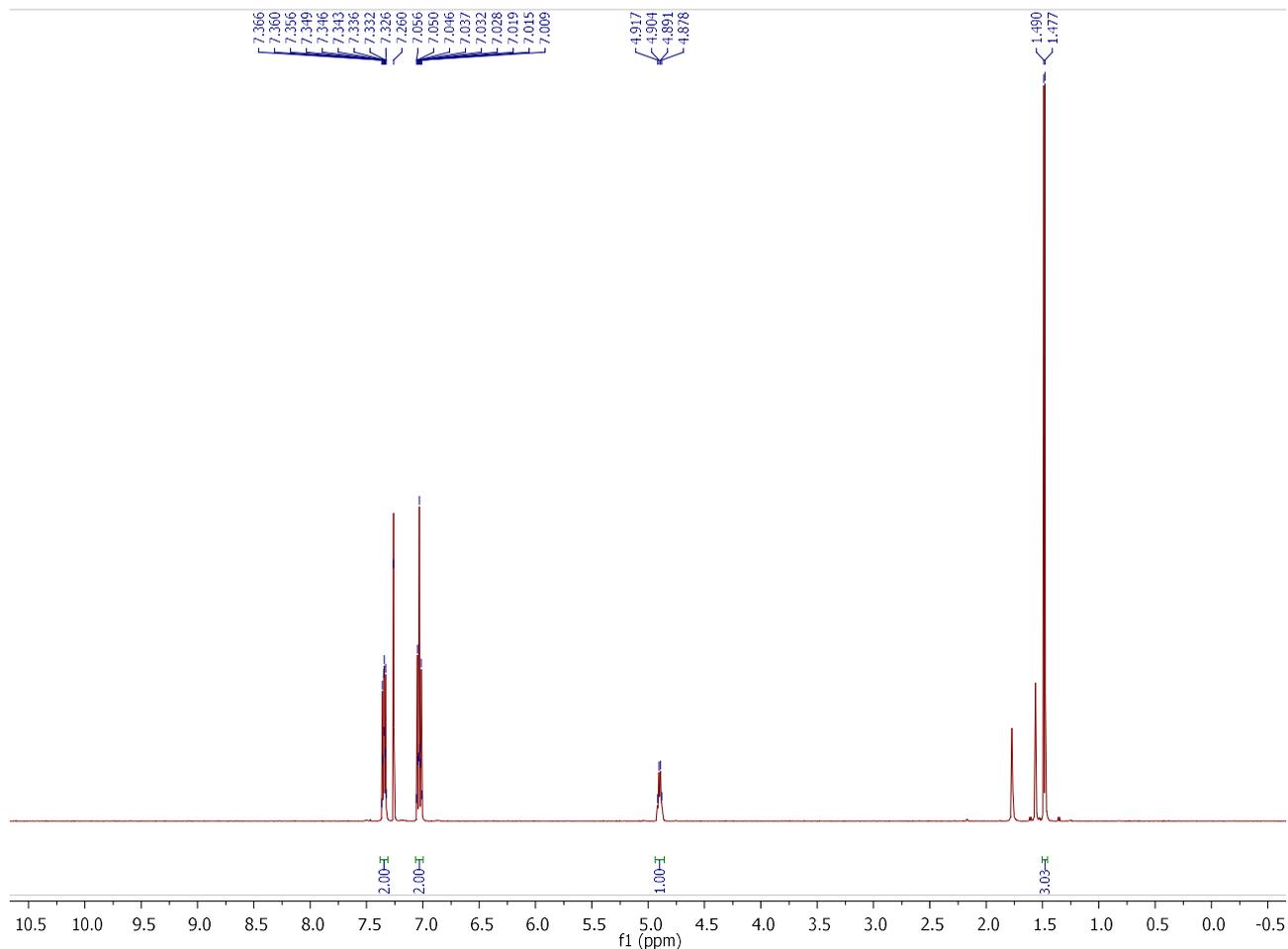
A flame dried round-bottomed flask containing a magnetic stirrer bar was charged with the requisite aldehyde (1 equiv) and dry THF. The mixture was cooled to 0 °C and to this solution was added dropwise the appropriate Grignard reagent (1.2 equiv). The reaction mixture was stirred at rt for 24 h. The reaction mixture cooled to 0 °C and quenched with sat. aq. NH₄Cl and H₂O. It was transferred to separatory funnel followed by the addition of EtOAc and H₂O. The organic layer was collected and the aqueous phase washed with EtOAc (x 2). The organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

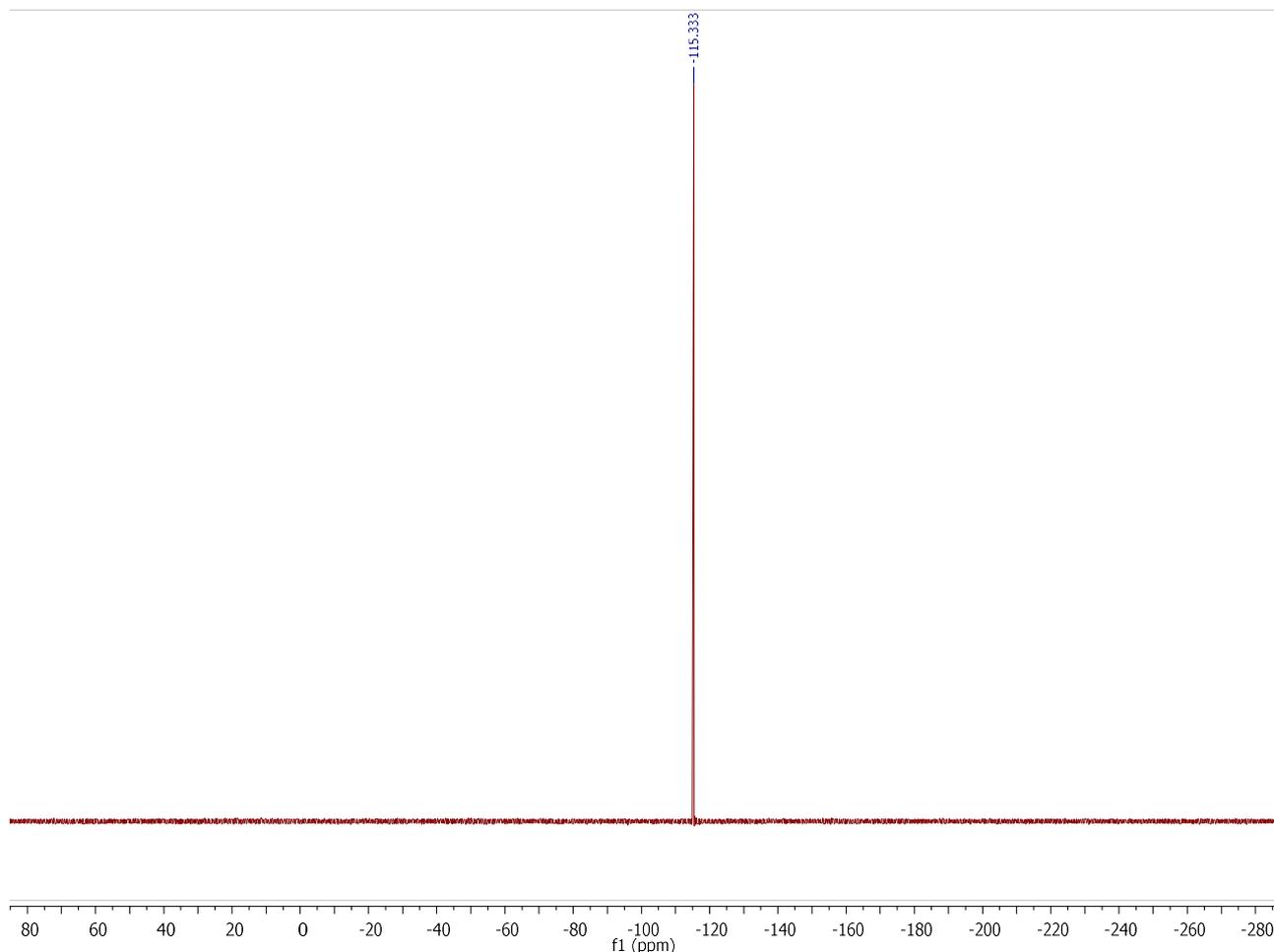
1-(4-fluorophenyl)ethan-1-ol



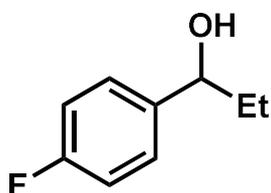
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The title compound 1-(4-fluorophenyl)ethan-1-ol was prepared according to general procedure 1 from 4'-fluoroacetophenone (11.0 mL, 12.5 g, 90.6 mmol) with NaBH₄ (5.14 g, 136 mmol) in methanol (250 mL). Purification by flash silica column chromatography (eluent = 10% EtOAc in hexanes, 50 x 150 mm silica) gave a colourless oil (10.6 g, 83%). R_f = 0.30 (eluent = 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H: 1.48 (3H, d, *J* 6.5), 1.77 (1H, br s), 4.90 (1H, q, *J* 6.5), 6.98-7.08 (2H, m), 7.30-7.39 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δ_F: -115.3. Spectroscopic data in accordance with that stated in the literature.¹

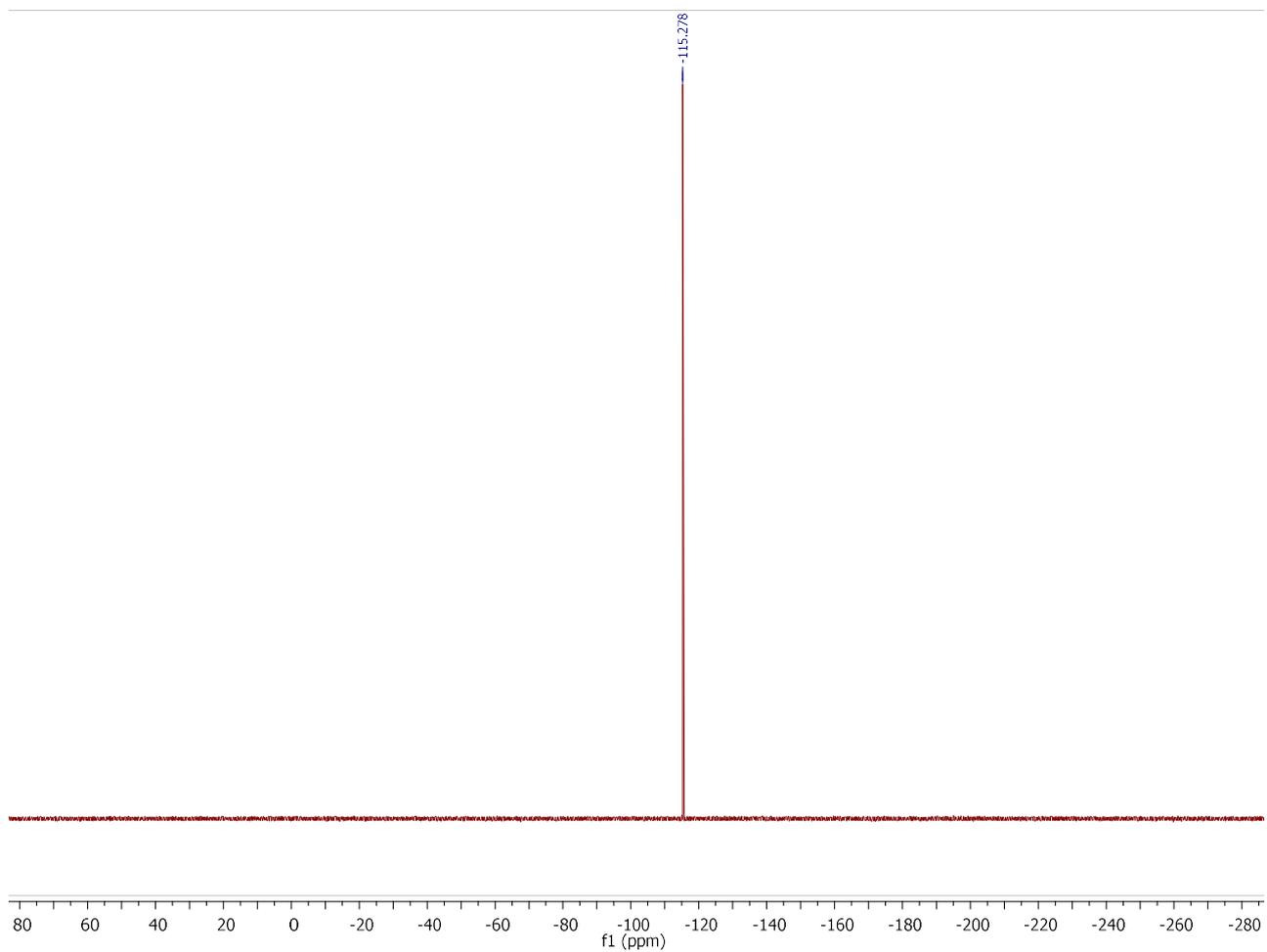
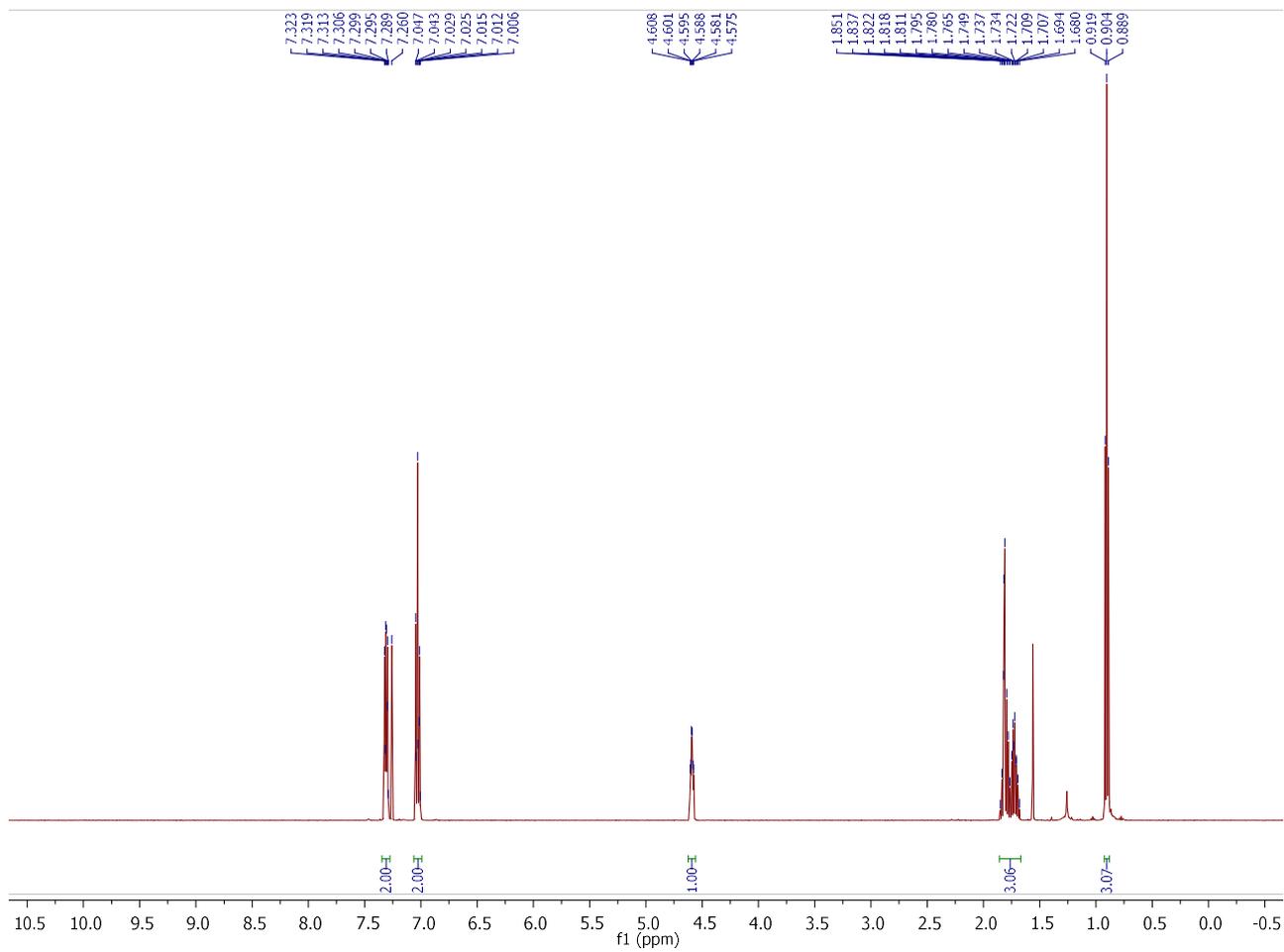


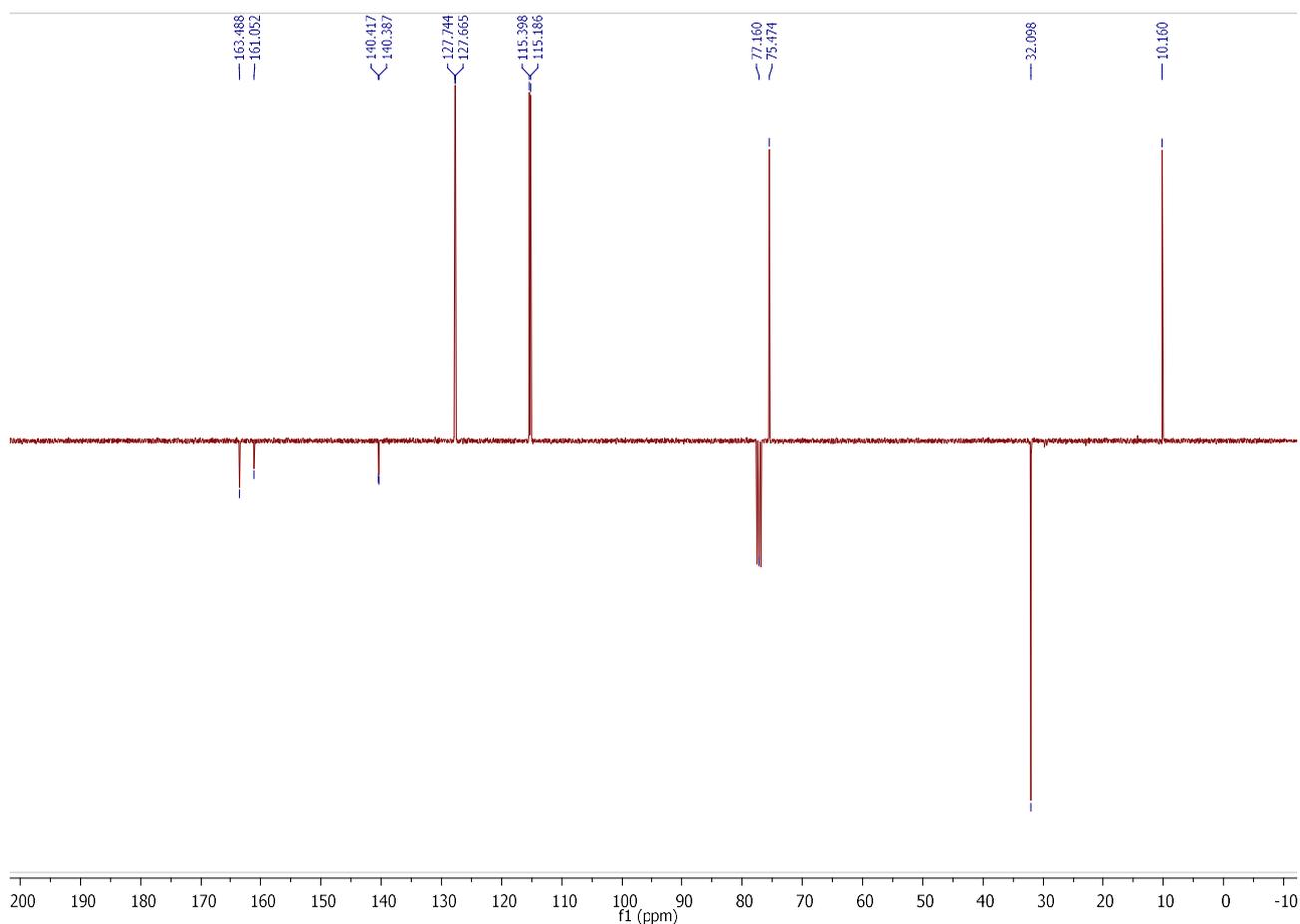


1-(4-fluorophenyl)propan-1-ol

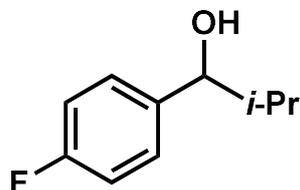


The title compound 1-(4-fluorophenyl)propan-1-ol was prepared according to general procedure 2 from 4-fluorobenzaldehyde (1.00 mL, 1.16 g, 9.32 mmol) using a 3.0 M ethylmagnesium bromide in Et_2O solution (3.70 mL, 11.2 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 50 x 130 mm silica) gave a pale yellow oil (1.41 g, 98%). $R_f = 0.38$ (eluent = 20 % EtOAc in hexanes); $\nu_{\text{max}} / \text{cm}^{-1}$ (film) 3343, 2970, 1604, 1508, 1221, 1155, 1011, 972, 827, 528, 538; **^1H NMR (500 MHz, CDCl_3)** δ_{H} : 0.90 (3H, t, J 7.5), 1.66-1.88 (3H, m), 4.59 (1H, dt, J 6.6, 3.4), 6.99-7.07 (2H, m), 7.28-7.34 (2H, m); **^{19}F NMR (377 MHz, CDCl_3)** δ_{F} : -115.3; **^{13}C NMR (101 MHz, CDCl_3)** δ_{C} : 10.2, 32.1, 75.5, 115.3 (d, J 21.4), 127.7 (d, J 8.0), 140.4 (d, J 3.0), 162.3 (d, J 246.0); HRMS (CI^+) calculated for $[\text{C}_9\text{H}_{10}\text{OF}]^+$ (M-H) $^+$ m/z 153.0721, found 153.0720, (-0.8 ppm).

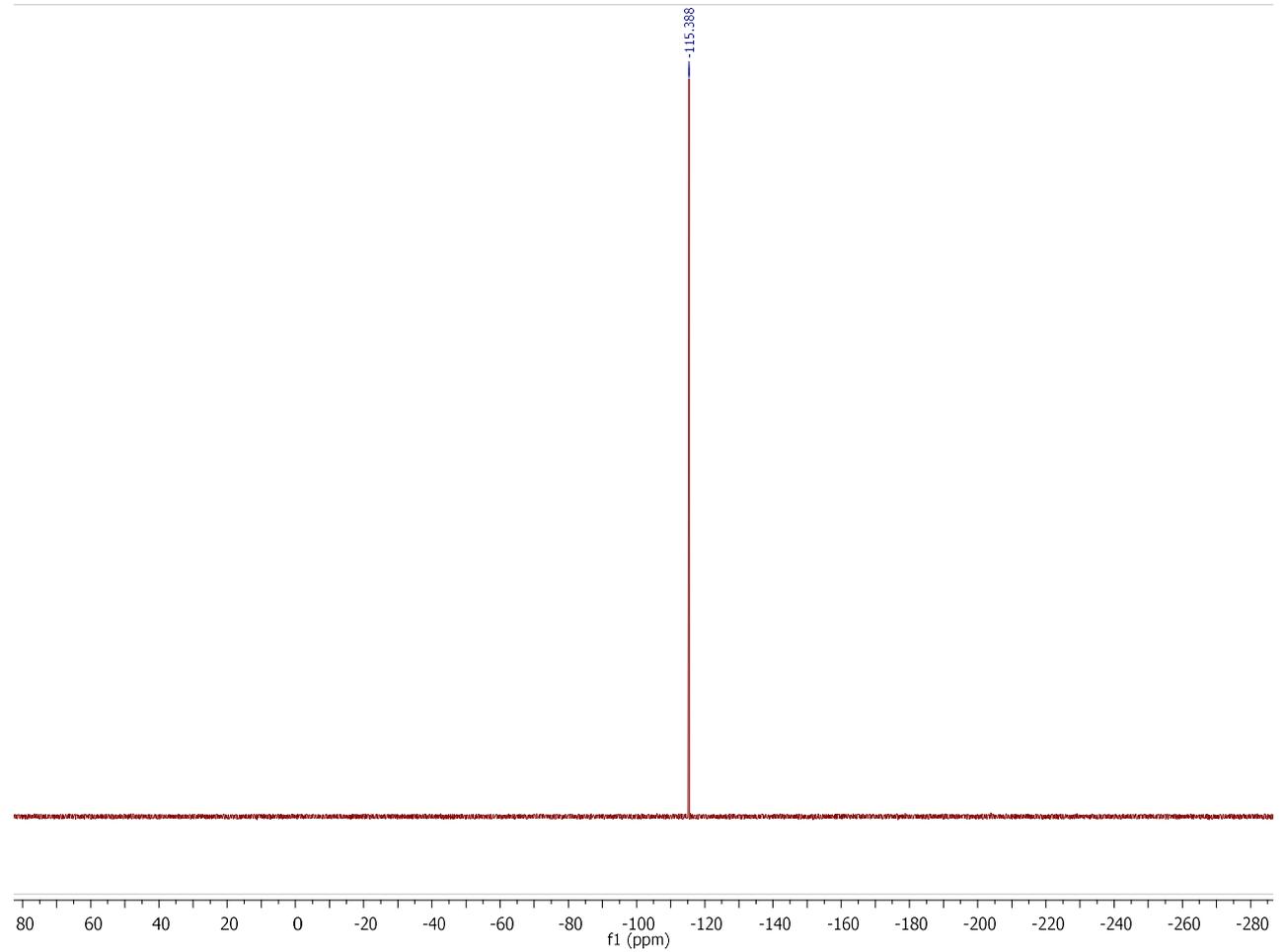
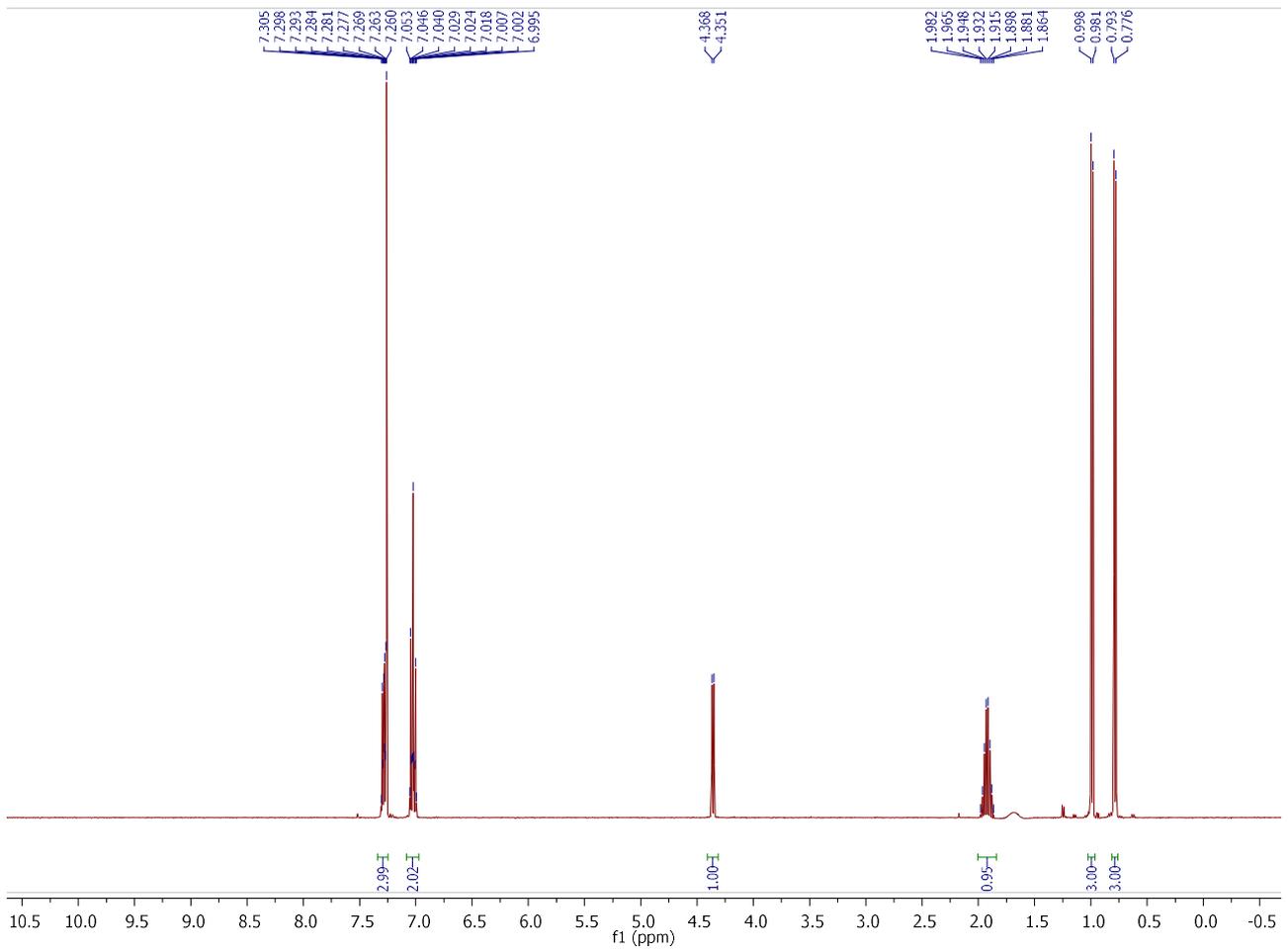


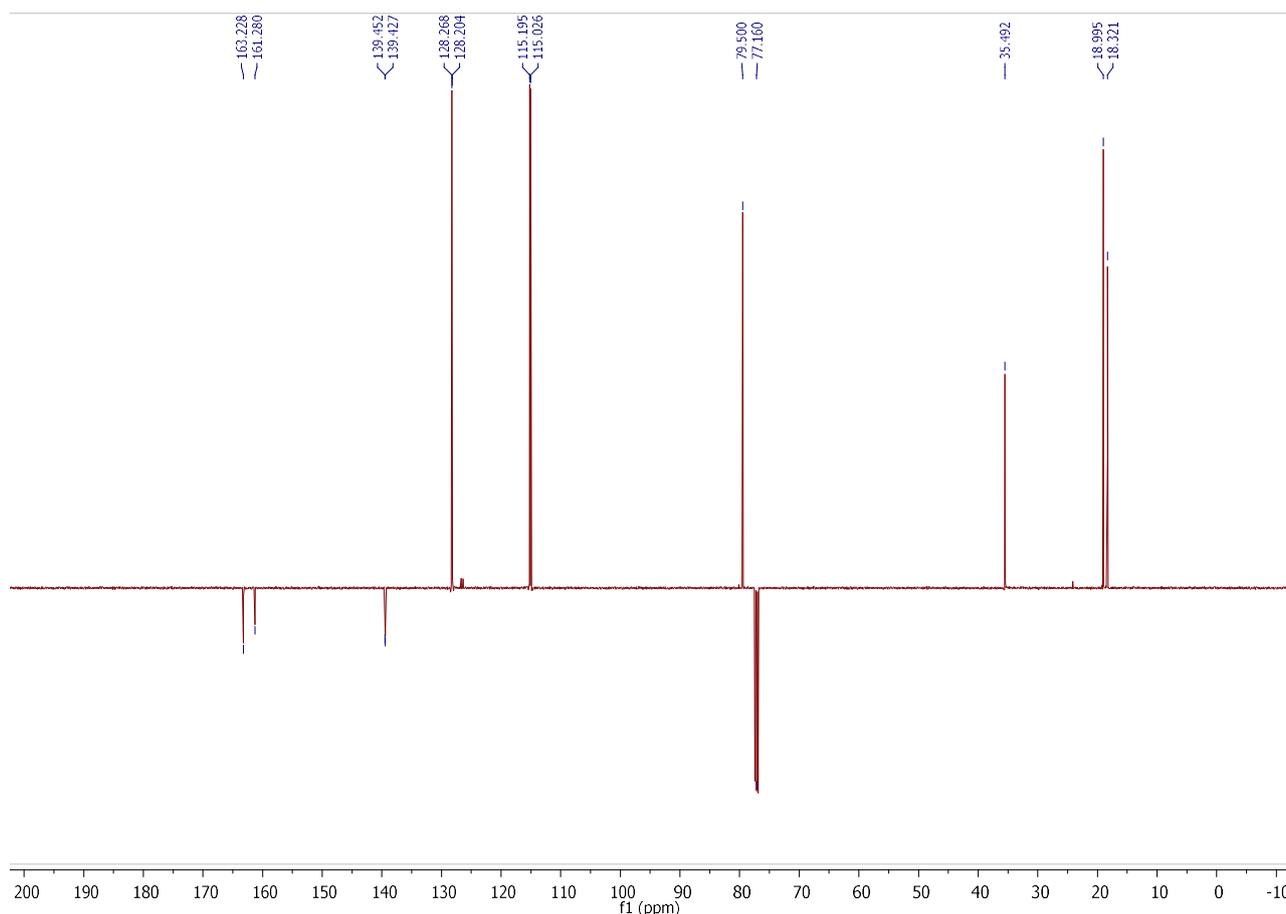


1-(4-fluorophenyl)-2-methylpropan-1-ol

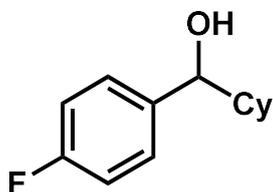


The title compound 1-(4-fluorophenyl)-2-methylpropan-1-ol was prepared according to general procedure 2 from 4-fluorobenzaldehyde (1.00 mL, 1.16 g, 9.32 mmol) using a 2.0 M isopropylmagnesium chloride in Et₂O (5.60 mL, 11.2 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 40 x 150 mm silica) gave the title compound (639 mg, 41%) as a yellow oil. $R_f = 0.46$ (eluent = 20% EtOAc in hexanes); $\nu_{\max} / \text{cm}^{-1}$ (film) 3375, 2965, 2876, 1601, 1506, 1219, 1155, 1028, 1009, 841, 818, 773, 579, 542; **¹H NMR (400 MHz, CDCl₃)** δ_H : 0.79 (3H, d, J 6.8), 0.99 (3H, d, J 6.8), 1.92 (1H, oct, J 6.8), 4.36 (1H, d, J 6.8), 6.97-7.07 (2H, m), 7.25-7.32 (2H, m); **¹⁹F NMR (377 MHz, CDCl₃)** δ_F : -115.4; **¹³C NMR (126 MHz, CDCl₃)** δ_C : 18.3, 19.0, 35.5, 79.5, 115.1 (d, J 21.3), 128.2 (d, J 8.1), 139.4 (d, J 3.2), 162.3 (d, J 245.4); HRMS (NSI⁺) calculated for [C₁₀H₁₂OF]⁺ (M-H)⁺ : m/z 167.0878, found 167.0882, (+2.6 ppm).

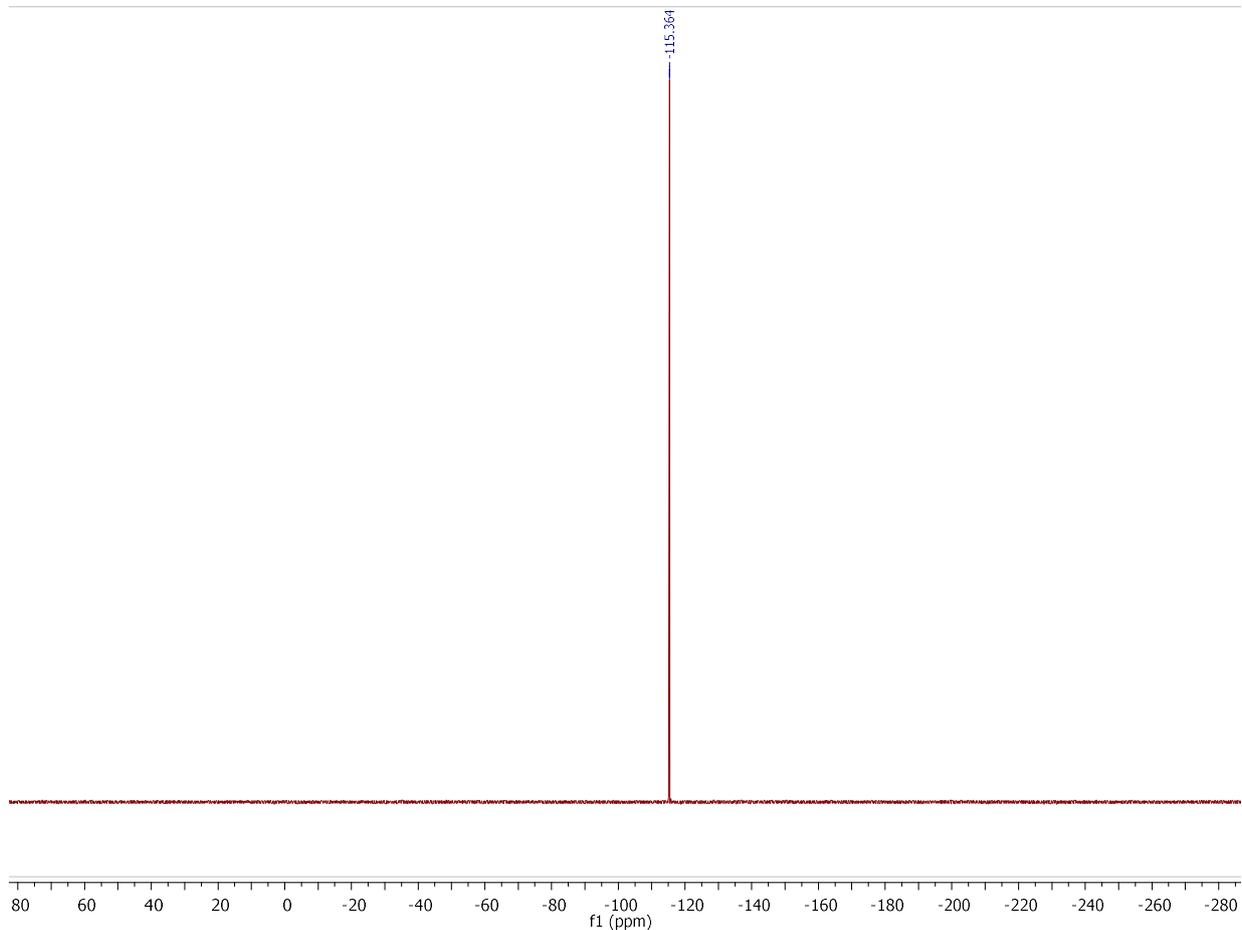
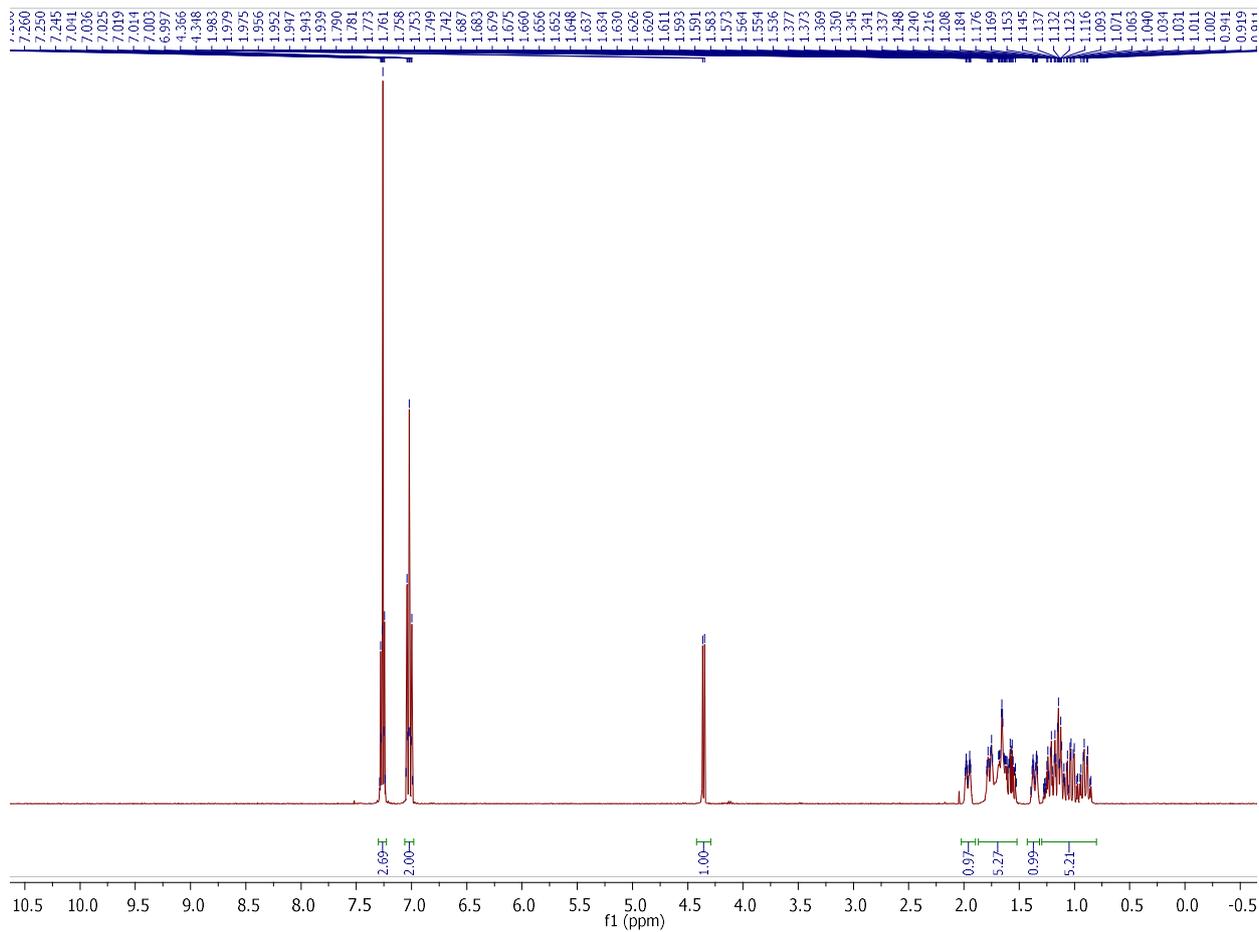


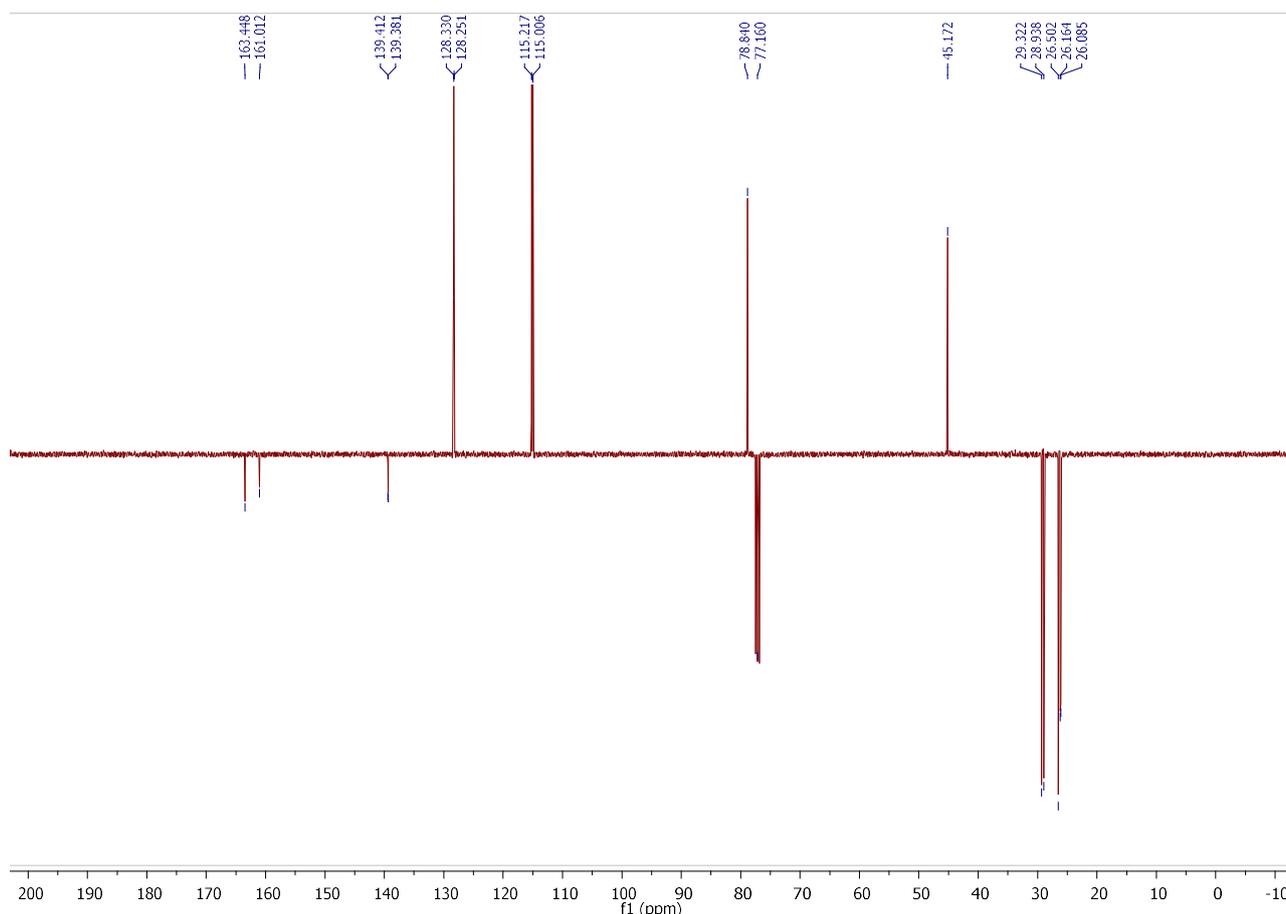


Cyclohexyl(4-fluorophenyl)methanol

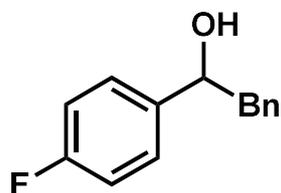


The title compound cyclohexyl(4-fluorophenyl)methanol was prepared according to general procedure 2 from 4-fluorobenzaldehyde (1.00 mL, 1.16 g, 9.32 mmol) using a 1.3 M cyclohexylmagnesium chloride in THF/toluene solution (8.60 mL, 11.2 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 50 x 150 mm silica) gave the title compound (1.48 g, 76%) as a yellow oil. $R_f = 0.54$ (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3362, 2920, 2851, 1605, 1512, 1450, 1219, 1152, 1078, 1013, 835, 565, 529; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 0.82-1.30 (5H, m), 1.30-1.42 (1H, m), 1.51-1.84 (5H, m), 1.91-2.01 (1H, m), 4.36 (1H, d, J 7.2), 6.97-7.06 (2H, m), 7.22-7.30 (2H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -115.4; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.1, 26.2, 26.5, 28.9, 29.3, 45.2, 78.8, 115.1 (d, J 21.3), 128.3 (d, J 8.0), 139.4 (d, J 3.1), 162.2 (d, J 246.0); HRMS (CI^+) calculated for $[\text{C}_{13}\text{H}_{16}\text{OF}]^+$ (M-H) $^+$: m/z 207.1191, found 207.1193, (+1.1 ppm).

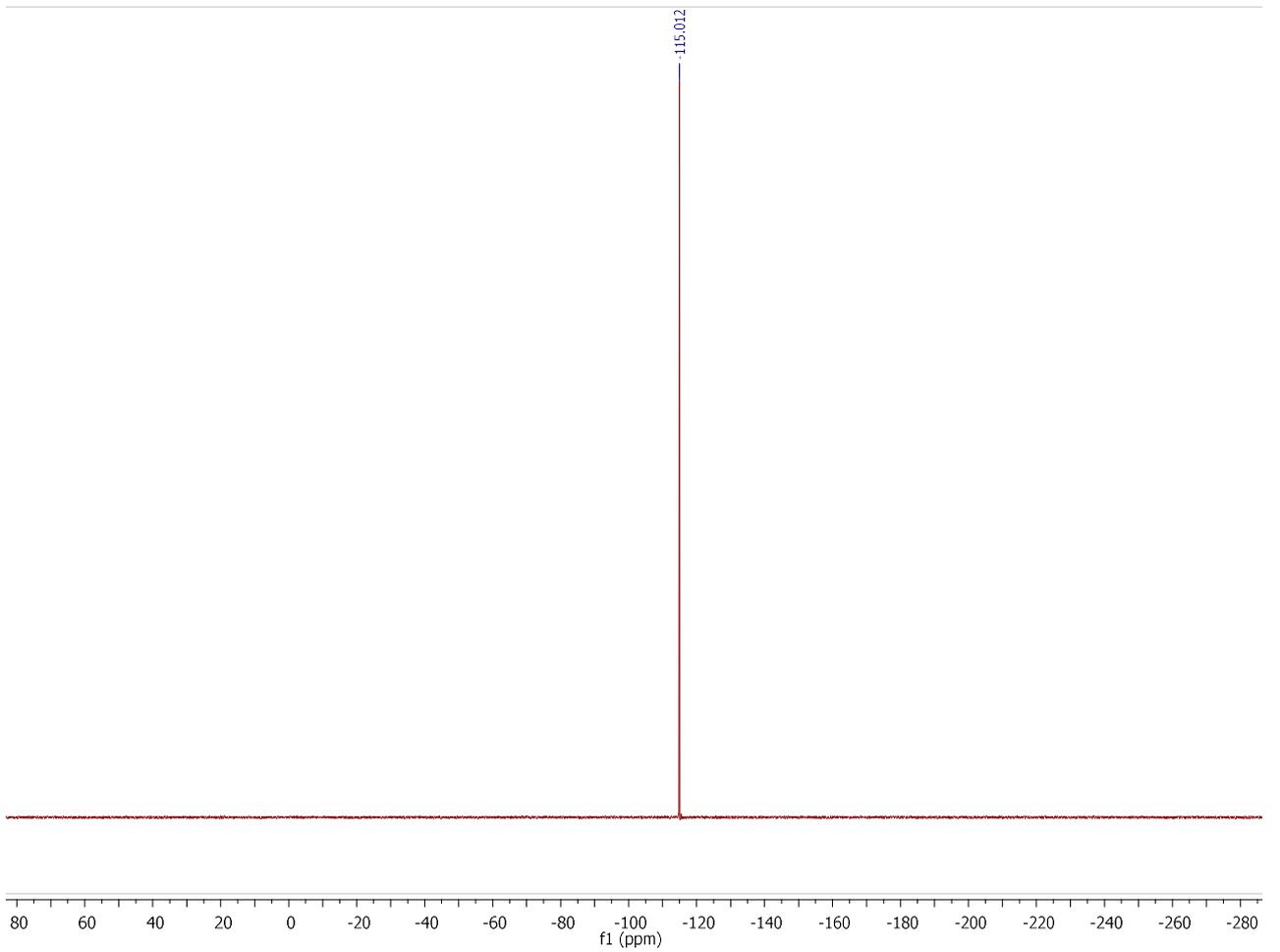
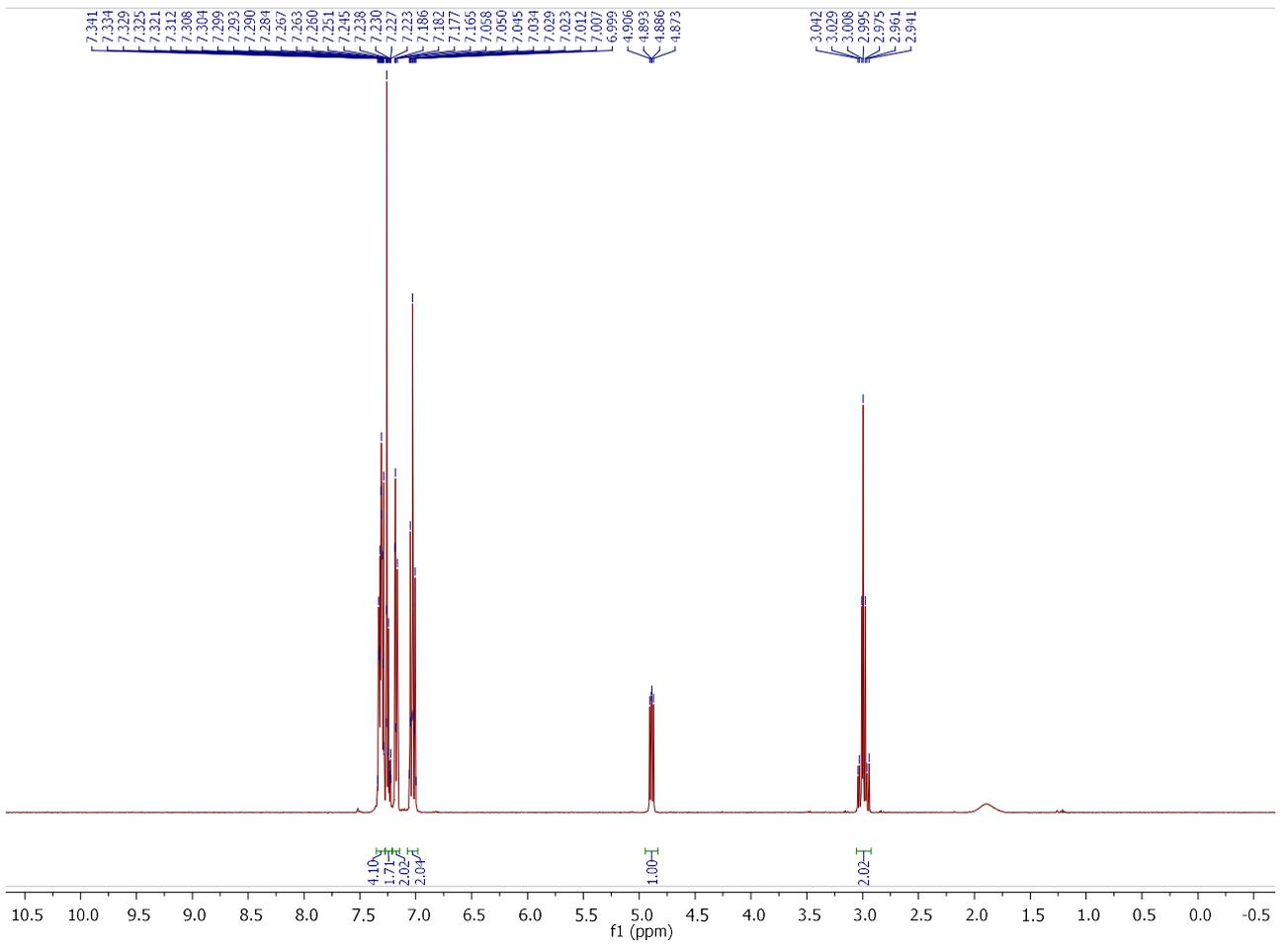


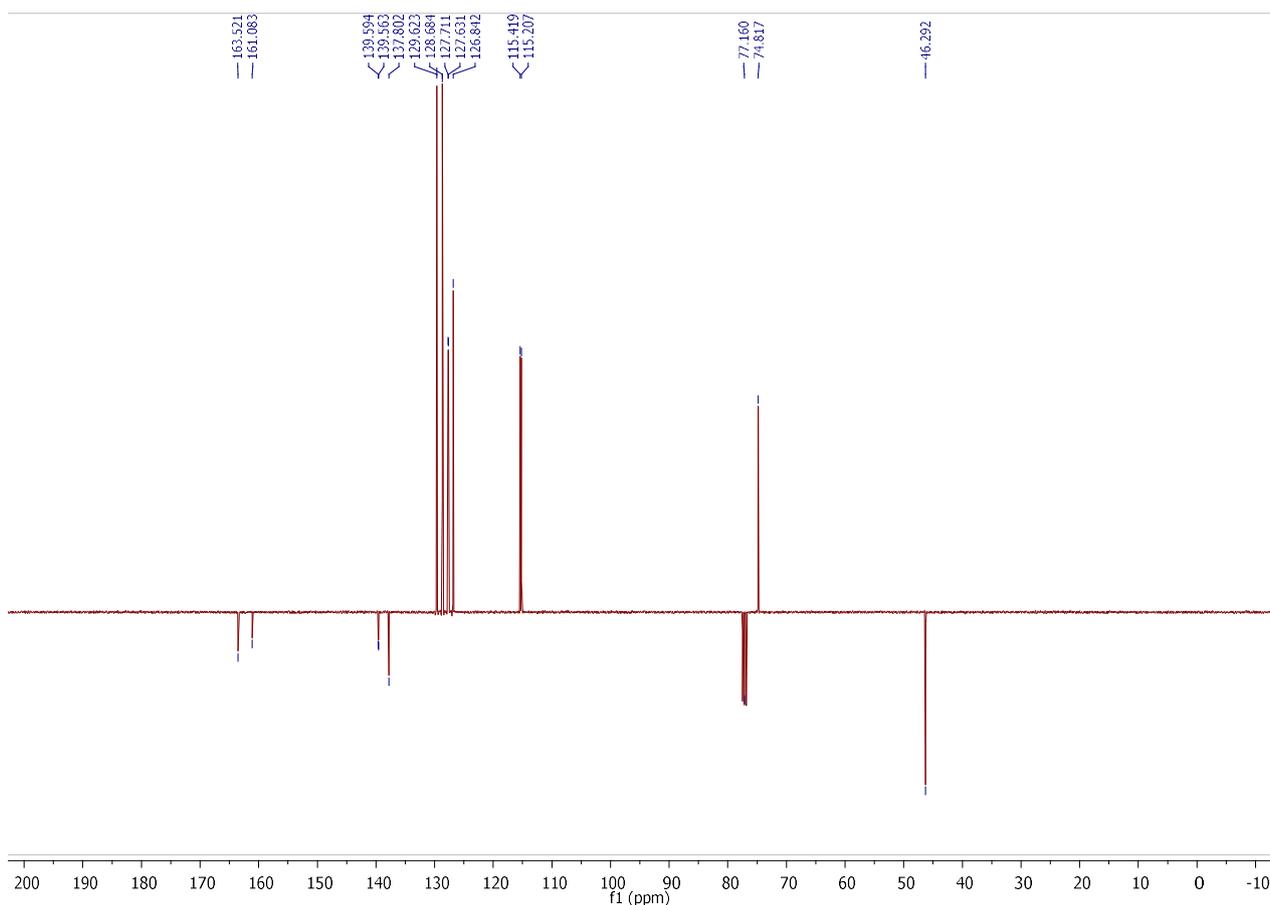


1-(4-fluorophenyl)-2-phenylethan-1-ol

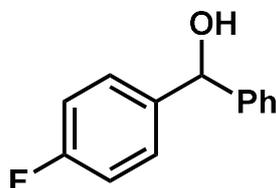


The title compound 1-(4-fluorophenyl)-2-phenylethan-1-ol was prepared according to general procedure 2 from 4-fluorobenzaldehyde (1.00 mL, 1.16 g, 9.32 mmol) using a 1.4 M benzylmagnesium chloride in THF (8.00 mL, 11.2 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 40 x 150 mm silica) gave the title compound (1.23 g, 61%) as a yellow solid. mp 34-37 °C (Lit. 43-44 °C)²; R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3343, 2909, 1599, 1512, 1452, 1223, 1161, 1051, 995, 820, 731, 691, 544; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.92-3.06 (2H, m), 4.89 (1H, dd, J 8.0, 5.2), 6.98-7.07 (2H, m), 7.14-7.20 (2H, m), 7.21-7.27 (1H, m), 7.27-7.35 (4H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -115.0; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 46.3, 74.8, 115.3 (d, J 21.4), 126.8, 127.7 (d, J 8.1), 128.7, 129.6, 137.8, 139.6 (d, J 3.1), 162.3 (d, J 246.2); HRMS (NSI⁺) calculated for $[\text{C}_{14}\text{H}_{12}\text{OF}]^+$ (M-H)⁺ : m/z 215.0878, found 215.0880, (+1.1 ppm).

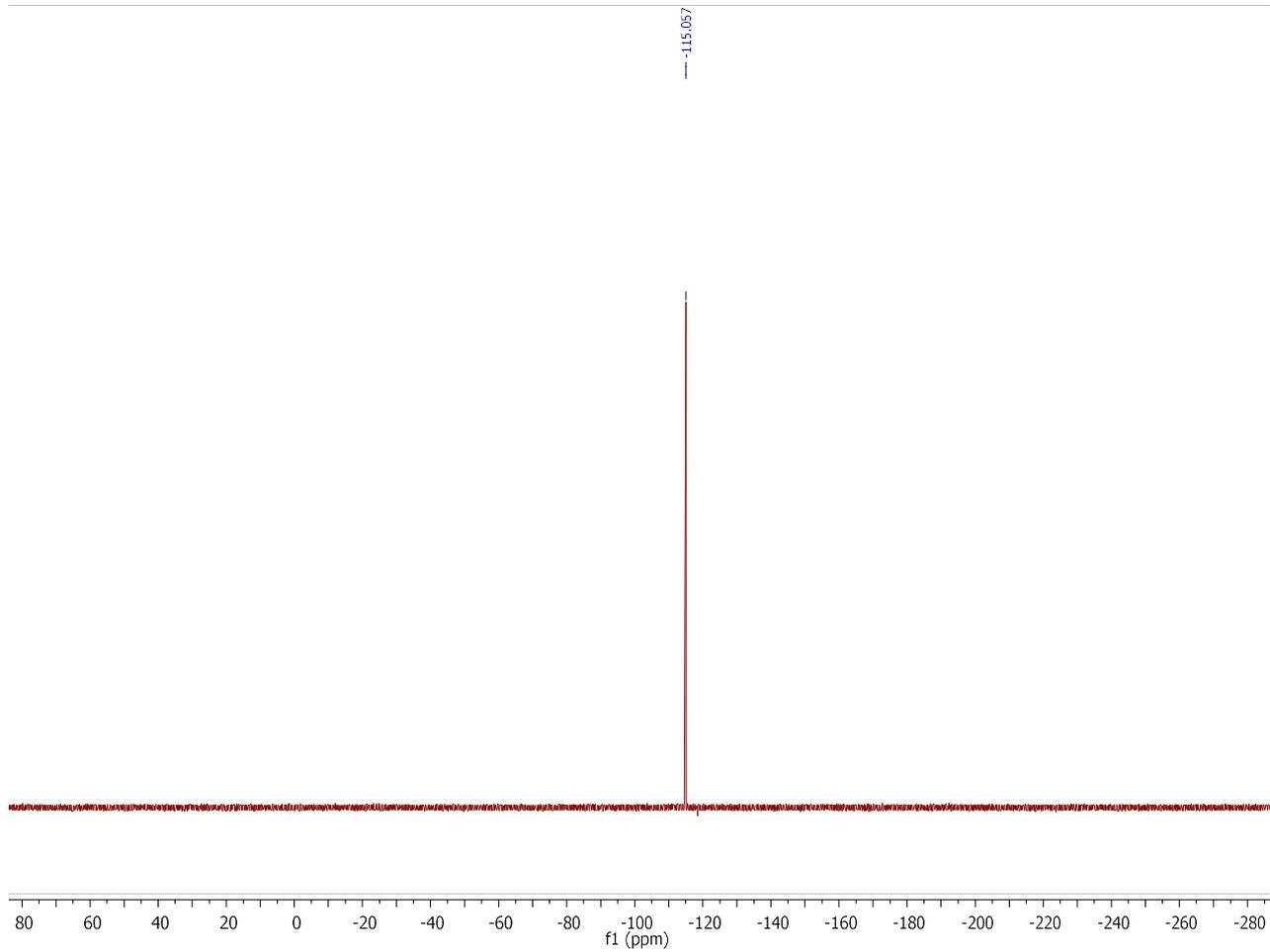
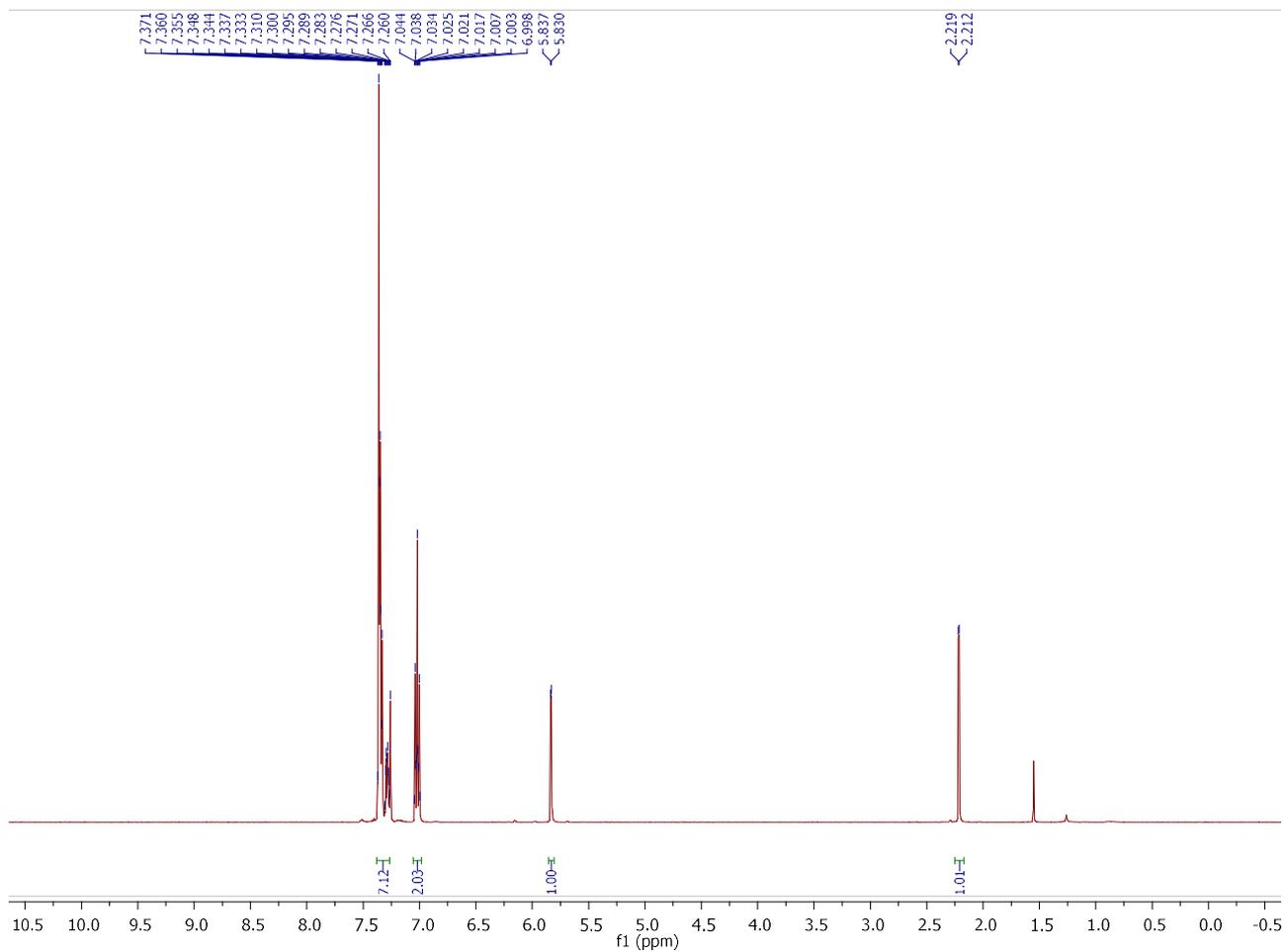


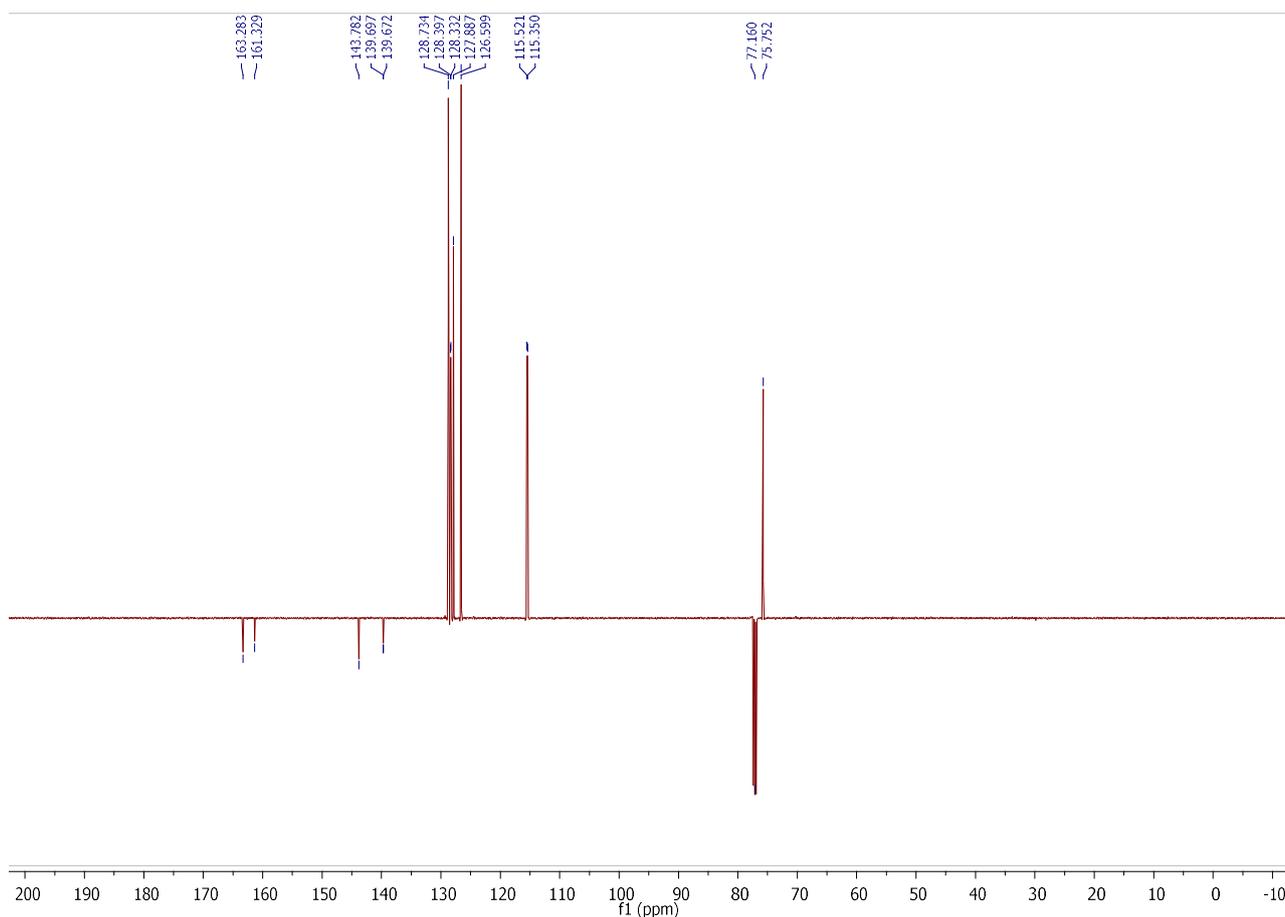


(4-Fluorophenyl)(phenyl)methanol

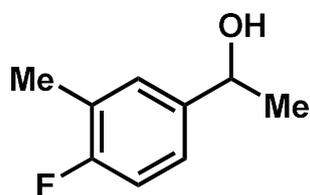


The title compound (4-fluorophenyl)(phenyl)methanol was prepared according to general procedure 1 from 4-fluorobenzophenone (1.00 g, 5.00 mmol) with NaBH₄ (284 mg, 7.50 mmol) in methanol (12 mL). Purification by flash silica column chromatography (eluent = 10-30% EtOAc in hexanes) gave a white solid (918 mg, 91%). mp 34-37 °C (Lit. 42-43 °C)³; R_f = 0.40 (eluent = 20% EtOAc in hexanes, 50 x 130 mm silica); ν_{max} / cm⁻¹ (film) 3383, 3300, 3022, 1601, 1508, 1491, 1449, 1227, 1159, 1036, 1013, 851, 814, 723, 694, 646, 563; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.22 (1H, d, *J* 3.5), 5.83 (1H, d, *J* 3.5), 6.98-7.06 (2H, m), 7.26-7.39 (7H, m); ¹⁹F NMR (377 MHz, CDCl₃) δ_F: -115.1; ¹³C NMR (126 MHz, CDCl₃) δ_C: 75.8, 115.4 (d, *J* 21.5), 126.6, 127.9, 128.4 (d, *J* 8.2), 128.7, 139.7 (d, *J* 3.2), 143.8, 162.3 (d, *J* 246.0); HRMS (CI⁺) calculated for [C₁₃H₁₀OF]⁺ (M-H)⁺ : m/z 201.0721, found 201.0720, (-0.6 ppm).

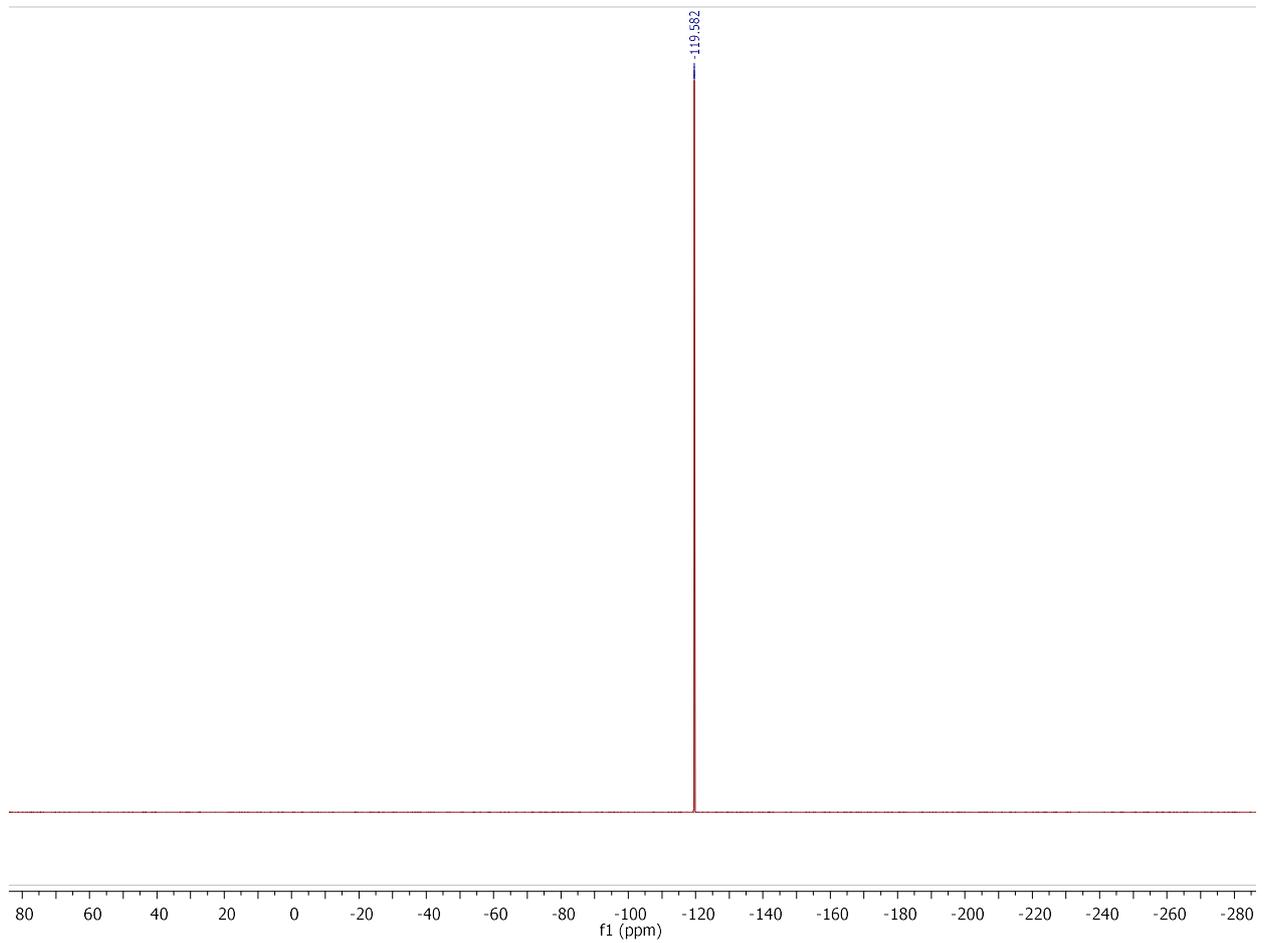
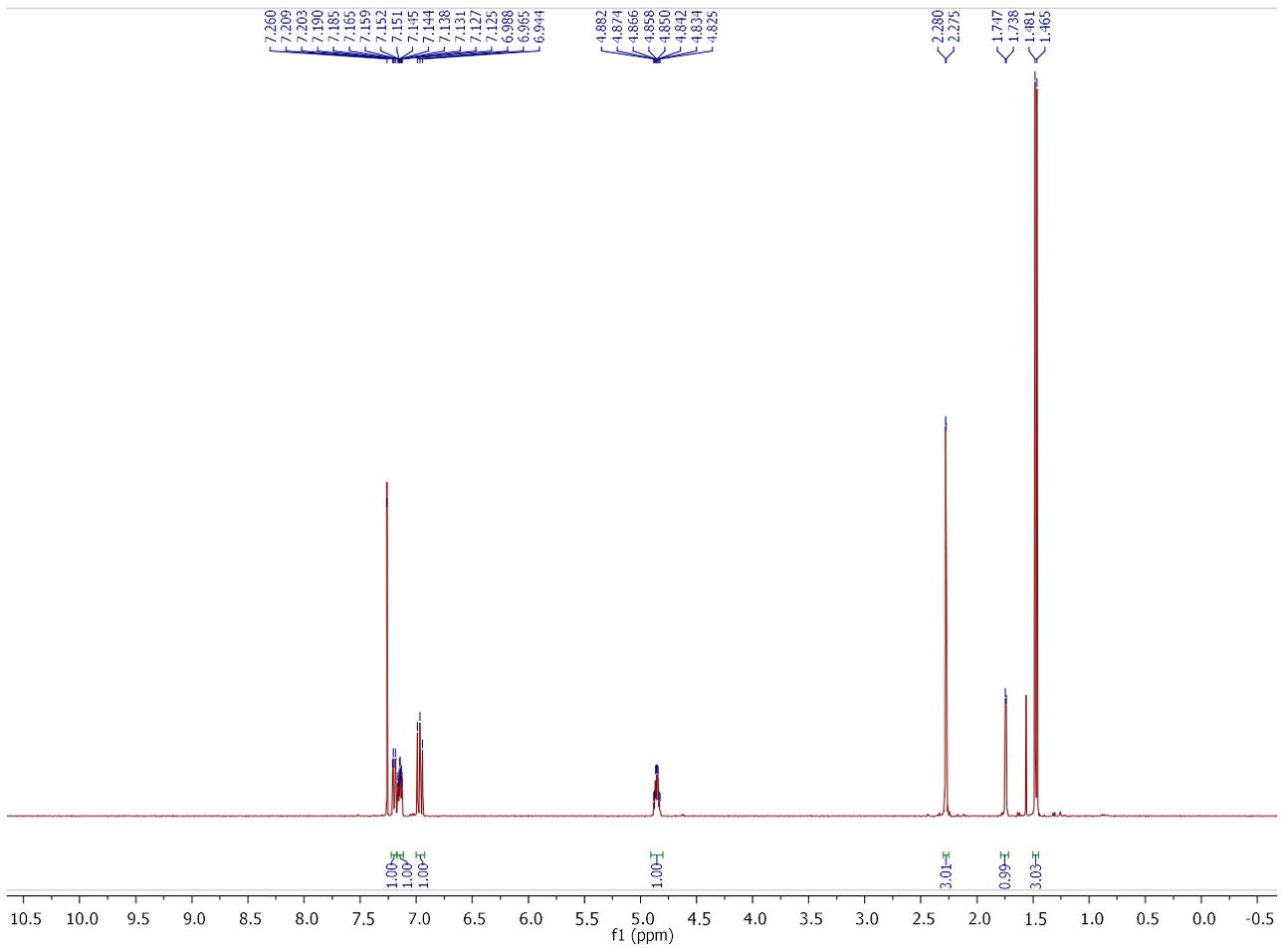


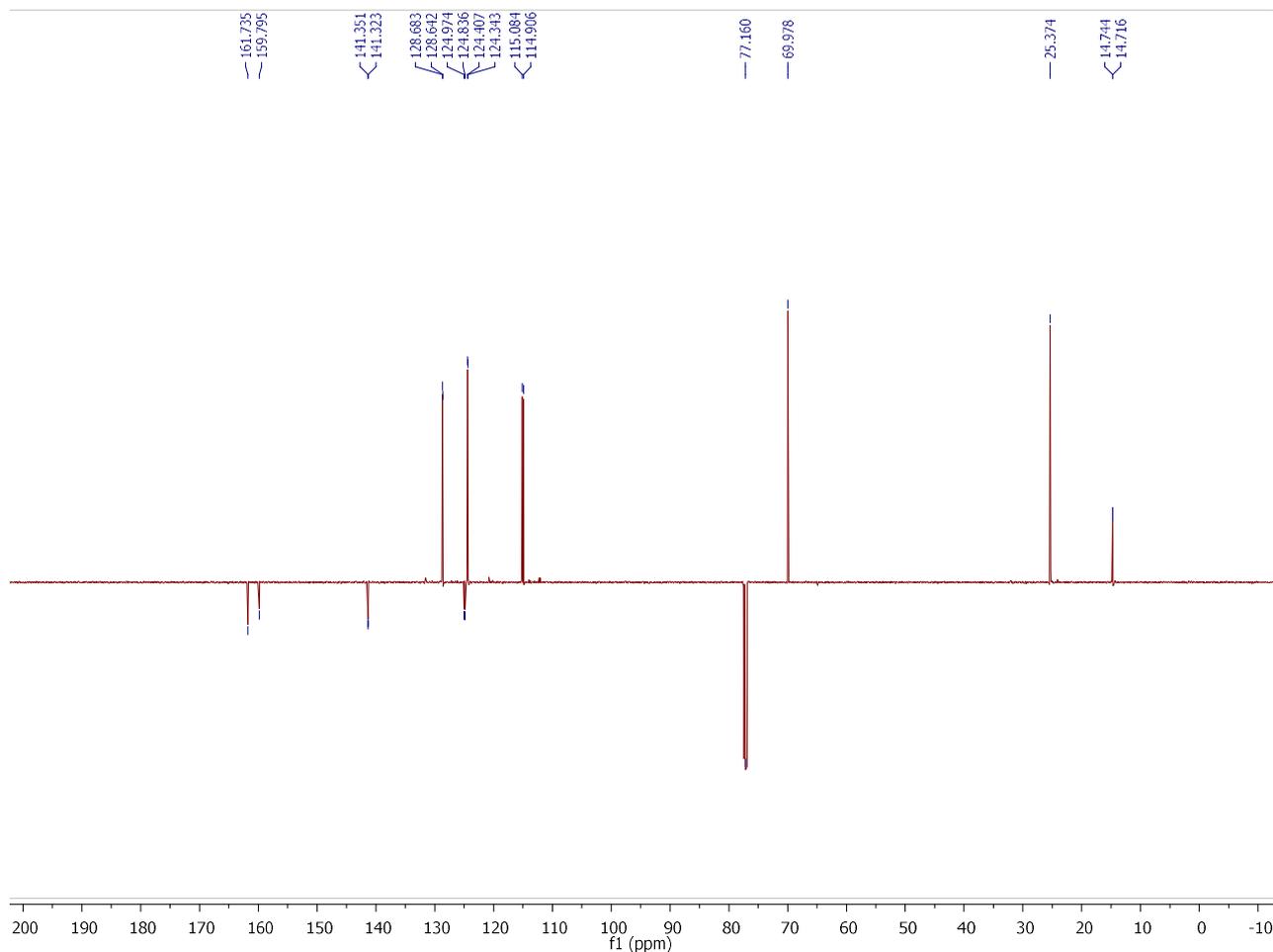


1-(4-fluoro-3-methylphenyl)ethan-1-ol

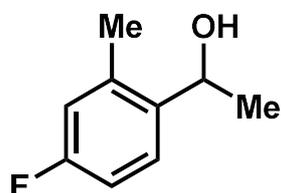


The title compound 1-(4-fluoro-3-methylphenyl)ethan-1-ol was prepared according to general procedure 2 from 4-fluoro-3-methylbenzaldehyde (967 mg, 7.00 mmol) using a 3.0 M methylmagnesium bromide in Et₂O solution (2.80 mL, 8.40 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 10-25% EtOAc in hexanes, 40 x 140 mm silica) gave a pale yellow oil (1.01 g, 94%). *R_f* = 0.34 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 3337, 2970, 1503, 1371, 1248, 1209, 1146, 1115, 928, 876, 818, 756, 604, 440; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.47 (3H, d, *J* 6.4), 1.74 (1H, d, *J* 3.6), 2.28 (3H, d, *J* 2.0), 4.85 (1H, dq, *J* 6.4, 3.2), 6.92-7.01 (1H, m), 7.11-7.17 (1H, m), 7.20 (1H, dd, *J* 7.5, 2.4); ¹⁹F NMR (377 MHz, CDCl₃) δ_{F} : -119.6; ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 14.7 (d, *J* 3.5), 25.4, 70.0, 115.0 (d, *J* 22.4), 124.4 (d, *J* 8.1), 124.9 (d, *J* 17.4), 128.7 (d, *J* 5.2), 141.3 (d, *J* 3.5), 160.8 (d, *J* 244.3); HRMS (NSI⁺) calculated for [C₉H₁₀OF]⁺ (M-H)⁺: *m/z* 153.0721, found 153.0725, (+2.5 ppm).

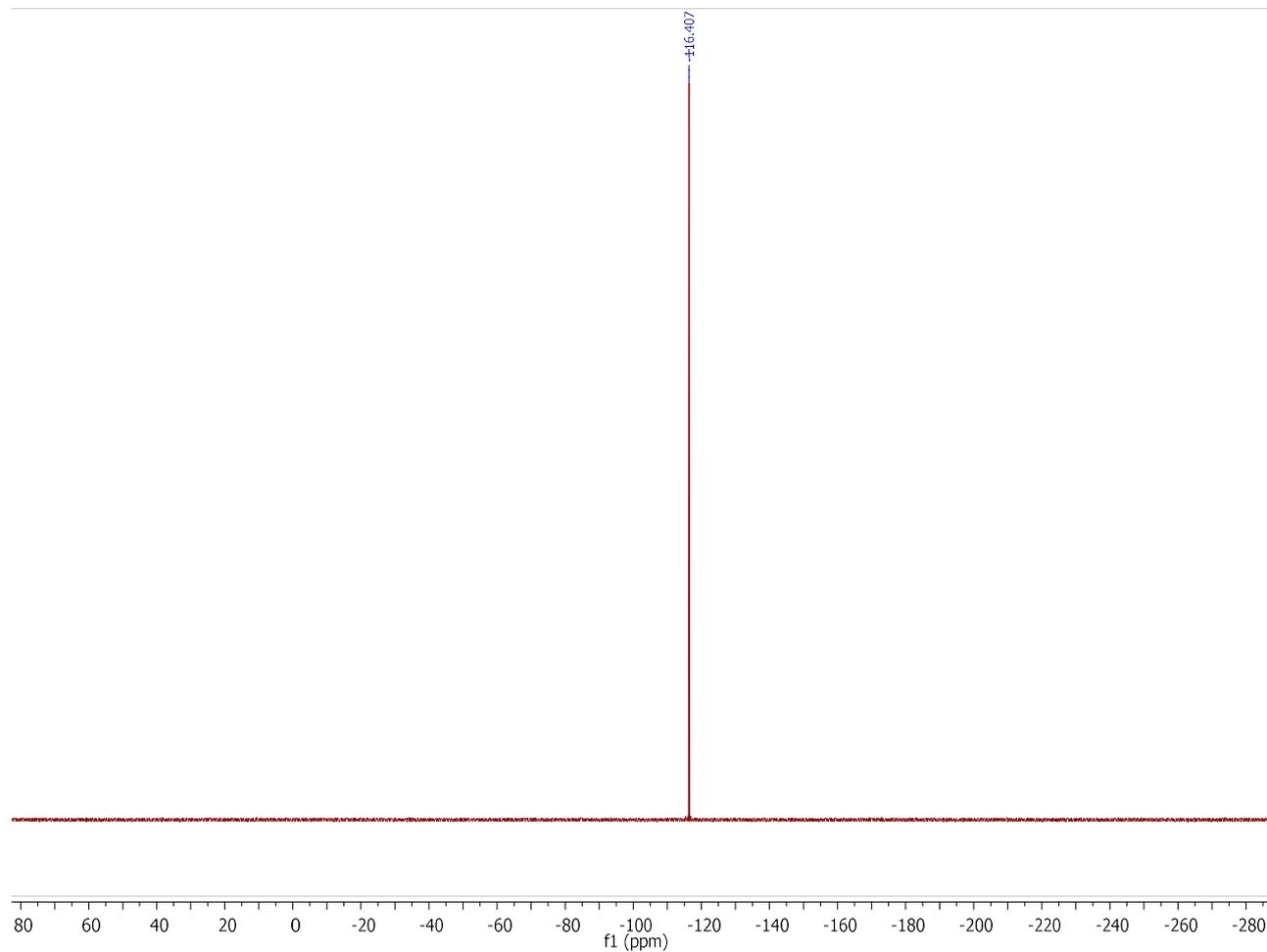
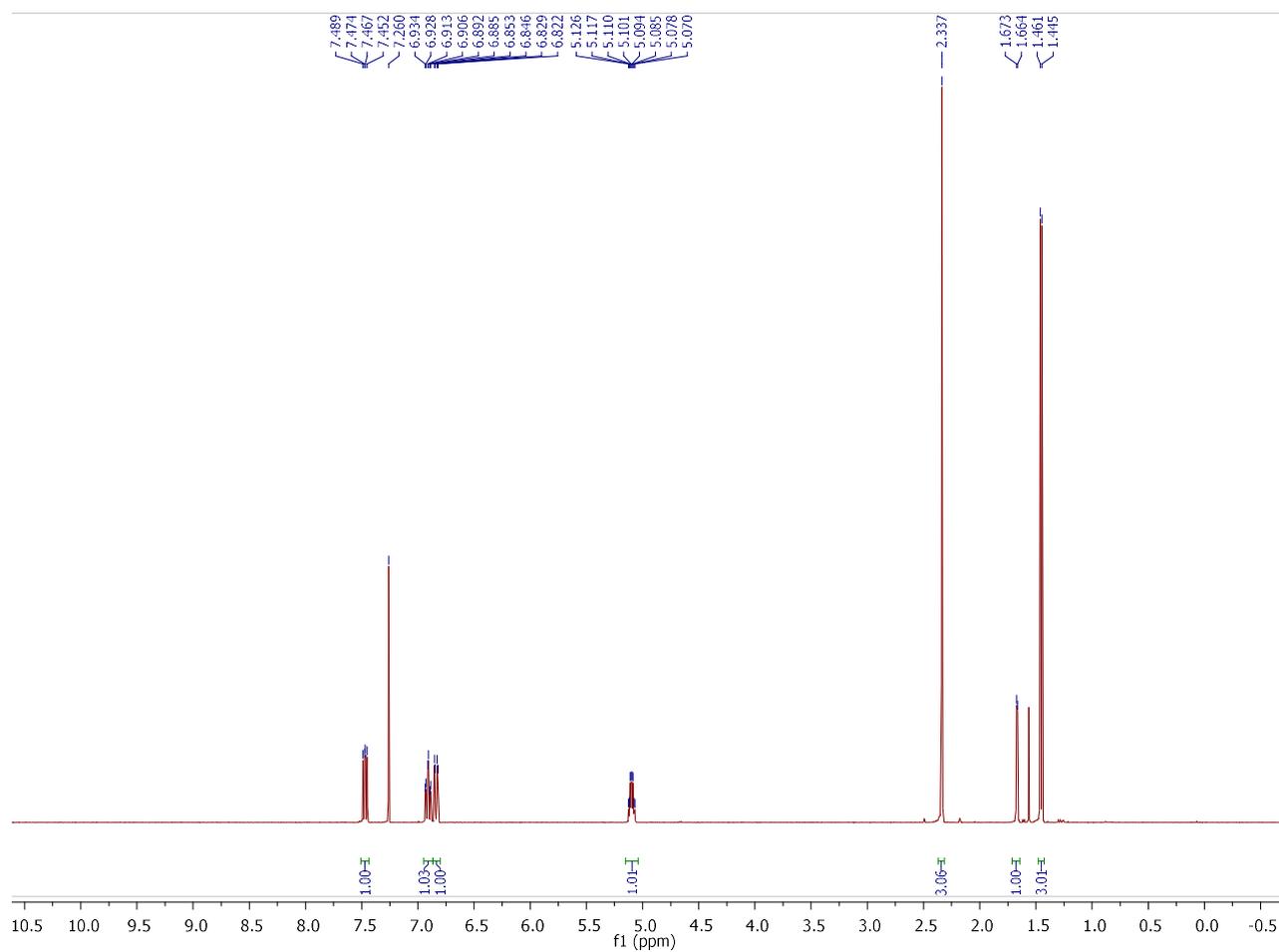


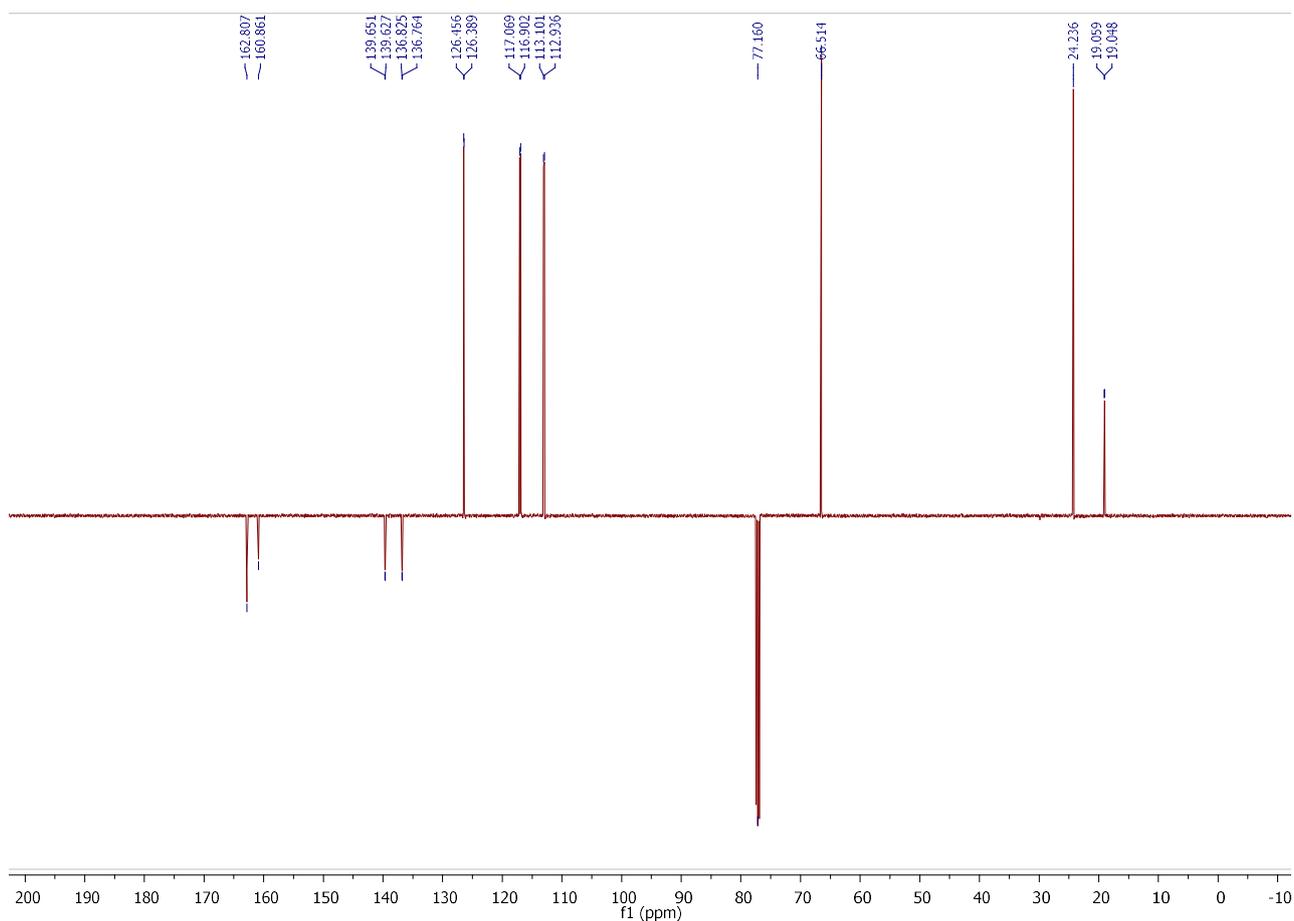


1-(4-fluoro-2-methylphenyl)ethan-1-ol

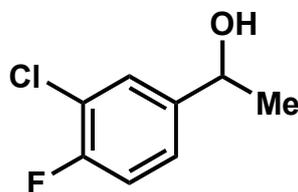


The title compound 1-(4-fluoro-2-methylphenyl)ethan-1-ol was prepared according to general procedure 2 from 4-fluoro-2-methylbenzaldehyde (967 mg, 7 mmol) using a 3.0 M methylmagnesium bromide in Et₂O solution (2.80 mL, 8.40 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 10-25% EtOAc in hexanes, 40 x 140 mm silica) gave a pale yellow oil (1.00 g, 93%). *R_f* = 0.34 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 3325, 2982, 1614, 1589, 1495, 1447, 1269, 1244, 1150, 1113, 1074, 1003, 953, 889, 860, 816, 584, 480; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.45 (3H, d, *J* 6.4), 1.67 (1H, d, *J* 3.6), 2.34 (3H, s), 5.10 (1H, dq, *J* 6.4, 3.6), 6.84 (1H, dd, *J* 9.6, 2.8), 6.91 (1H, dt, *J* 8.4, 2.8), 7.47 (1H, dd, *J* 8.8, 6.0); ¹⁹F NMR (377 MHz, CDCl₃) δ_{F} : -116.4; ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 19.1 (d, *J* 1.4), 24.2, 66.5, 113.0 (d, *J* 20.8), 117.0 (d, *J* 21.0), 126.4 (d, *J* 8.4), 136.8 (d, *J* 7.7), 139.6 (d, *J* 3.0), 161.8 (d, *J* 245.2); HRMS (NSI⁺) calculated for [C₉H₁₀OF]⁺ (M-H)⁺: *m/z* 153.0721, found 153.0725, (+2.5 ppm).

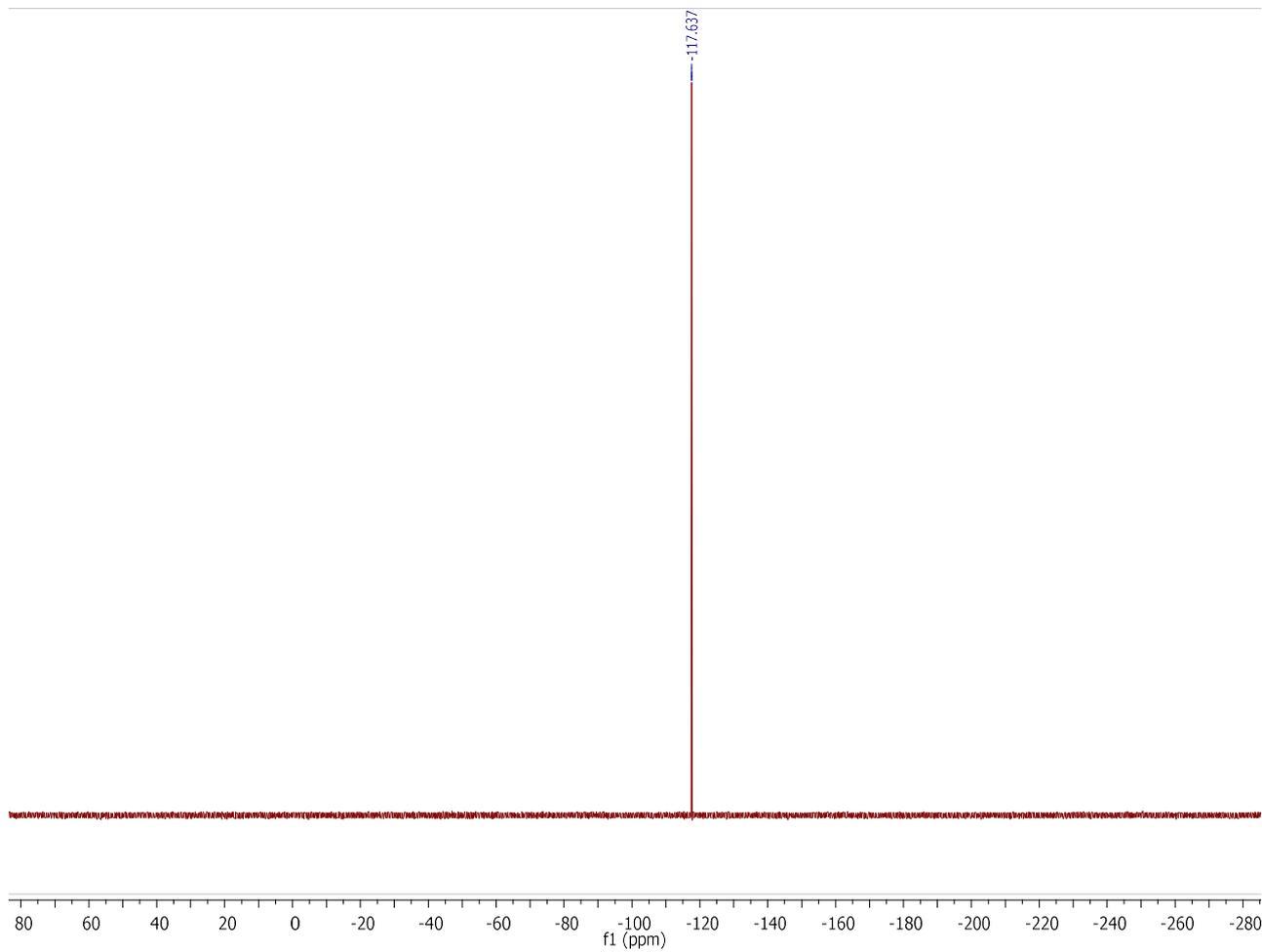
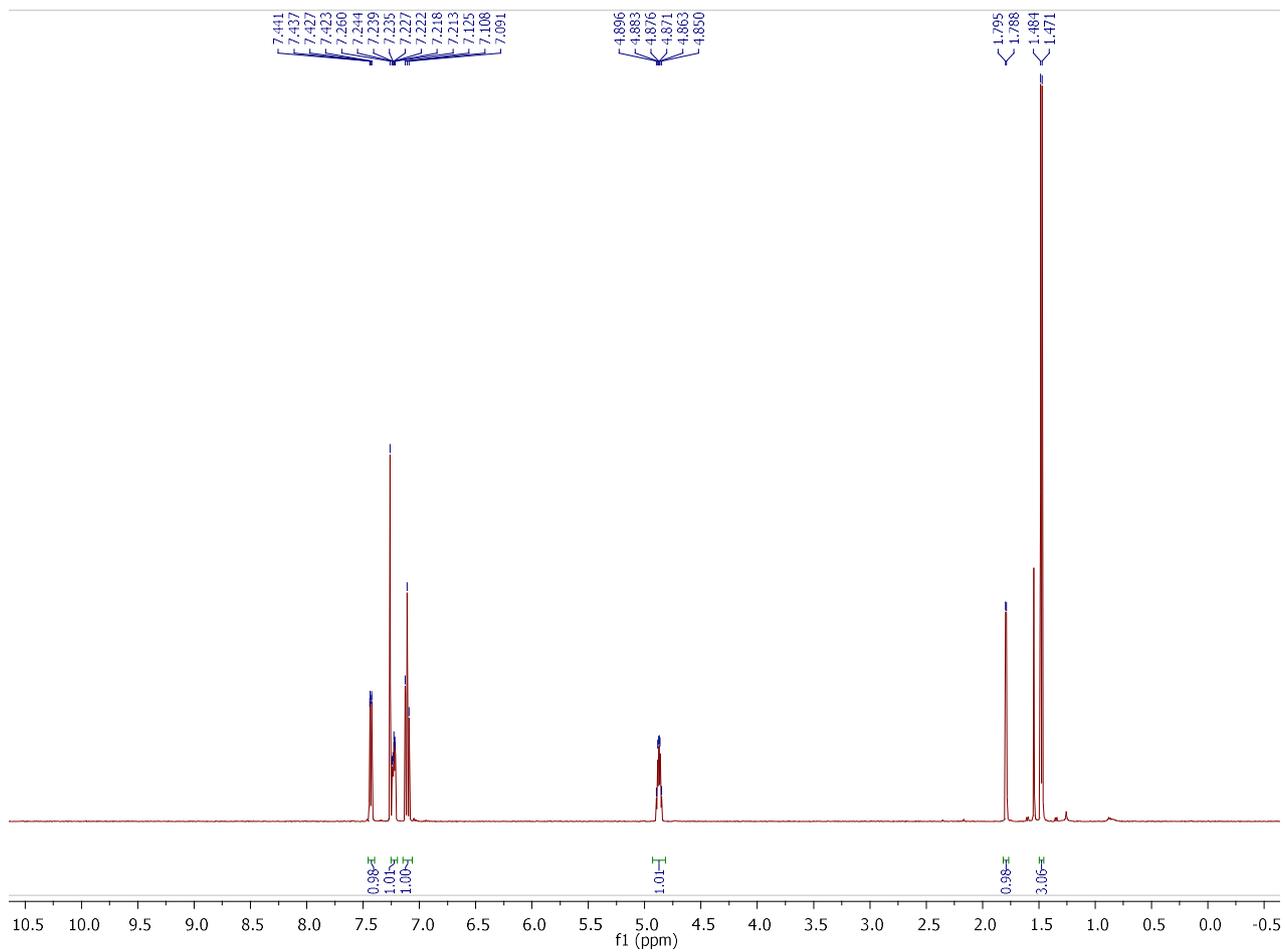


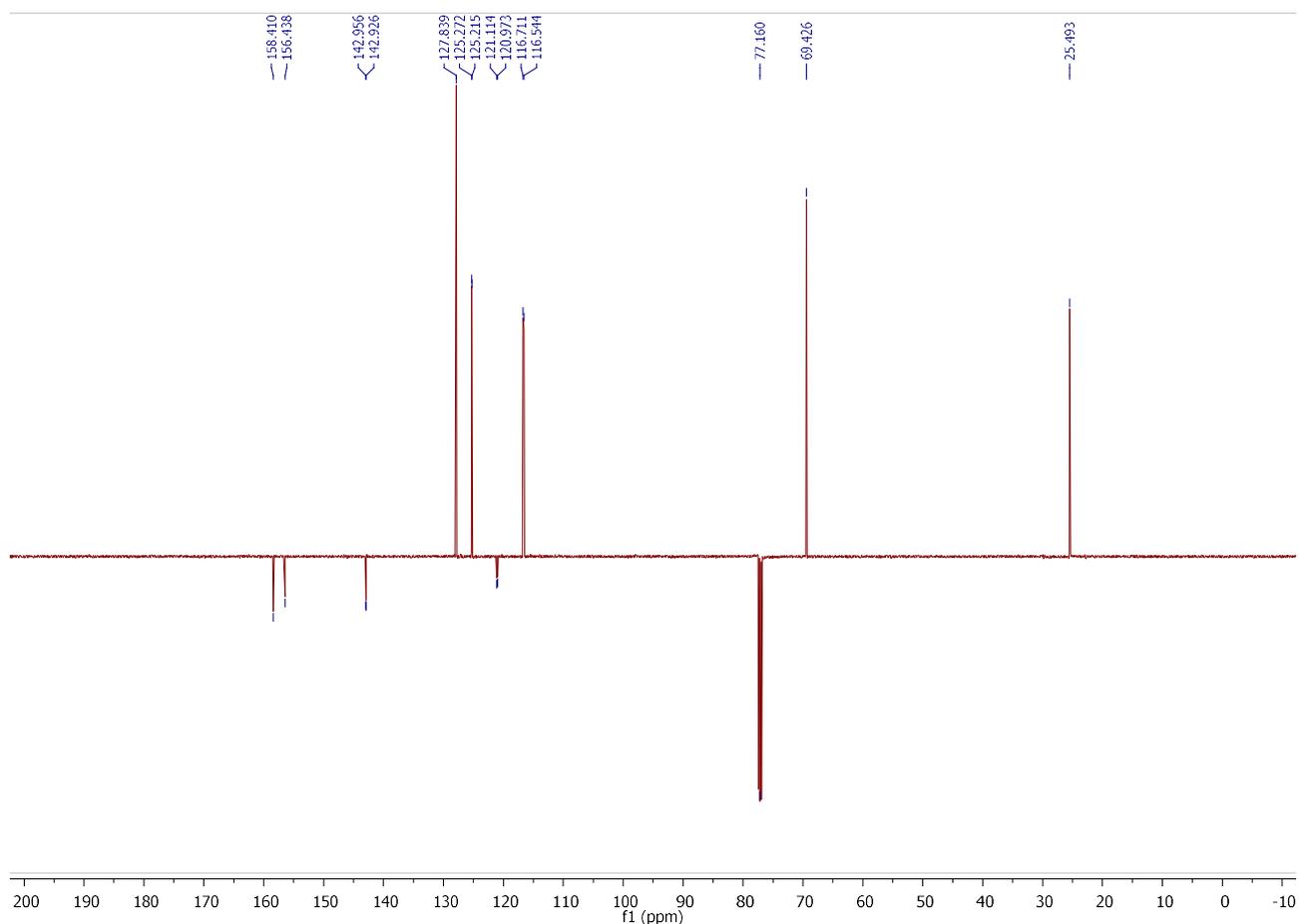


1-(3-chloro-4-fluorophenyl)ethan-1-ol

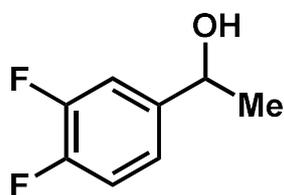


The title compound 1-(3-chloro-4-fluorophenyl)ethan-1-ol was prepared according to general procedure 1 from 3'-chloro-4'-fluoroacetophenone (690 mg, 4.00 mmol) with NaBH₄ (227 mg, 6.00 mmol) and methanol (10 mL). Purification by flash silica column chromatography (eluent = 15% EtOAc in hexanes, 30 x 110 mm silica) gave a pale yellow oil (669 mg, 96%). R_f = 0.34 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3321, 2982, 1499, 1248, 1090, 1074, 916, 818, 708, 677, 513, 466; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.48 (3H, d, *J* 6.5), 1.79 (1H, d, *J* 3.5), 4.83-4.92 (1H, m), 7.11 (1H, t, *J* 8.5), 7.20-7.25 (1H, m), 7.43 (1H, dd, *J* 7.0, 2.0); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -117.6; ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 25.5, 69.4, 116.6 (d, *J* 21.0), 121.0 (d, *J* 17.8), 125.2 (d, *J* 7.2), 127.8, 142.9 (d, *J* 3.8), 157.4 (d, *J* 248.5); HRMS (CI⁺) calculated for [C₈H₁₀NCIF]⁺ [M+NH₄-H₂O]⁺ : m/z 174.0480, found 174.0481, (+0.4 ppm).

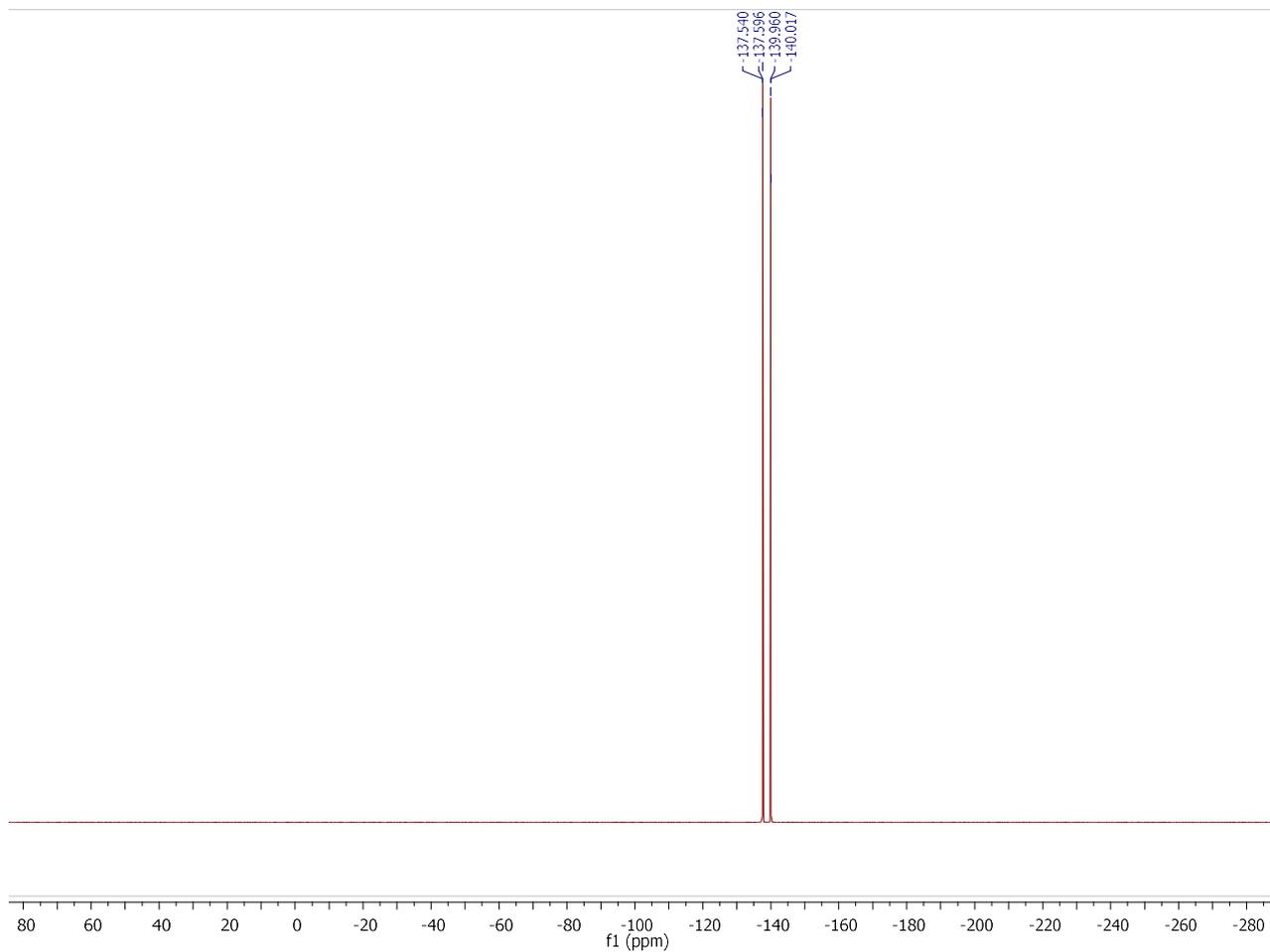
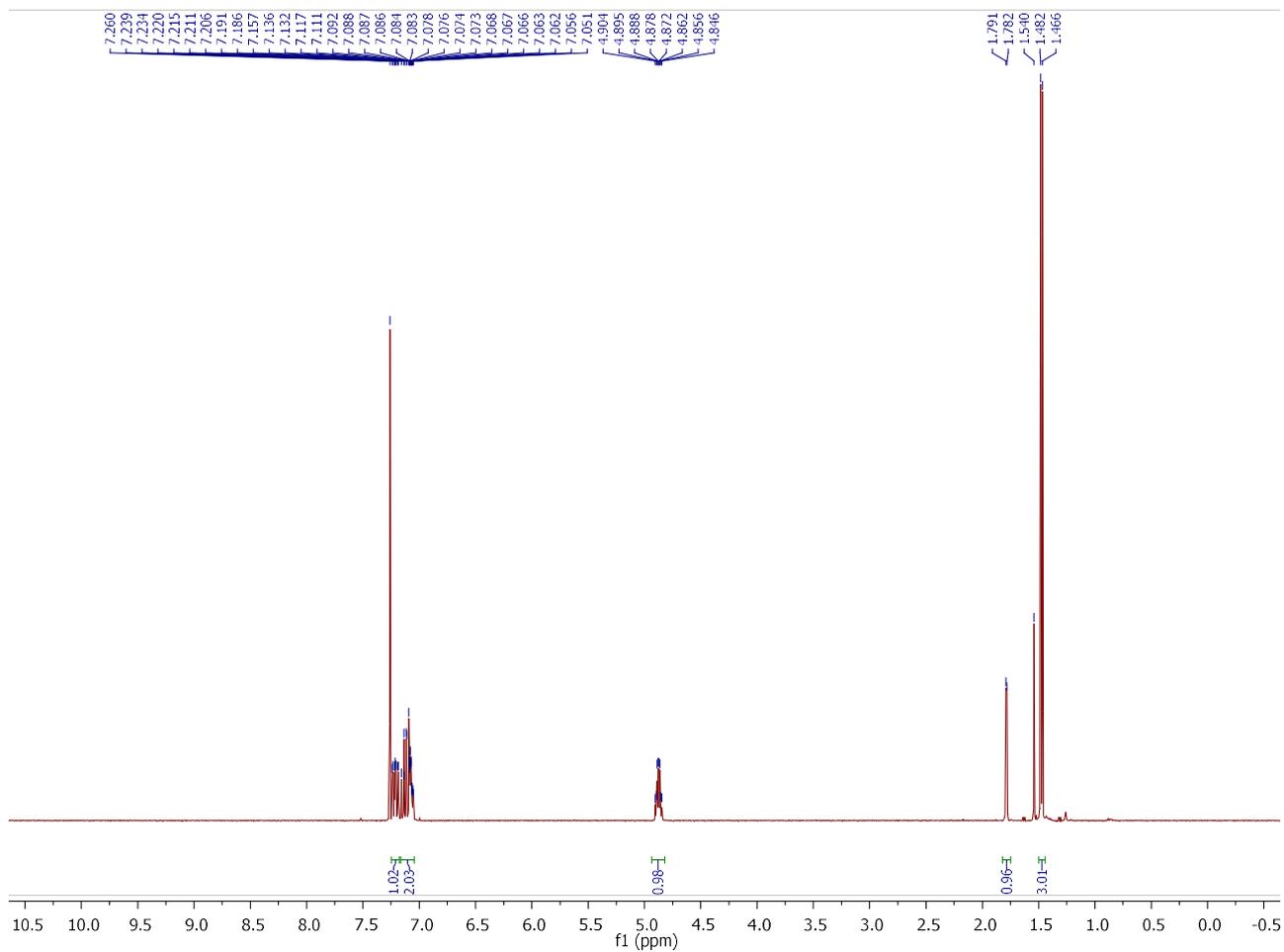


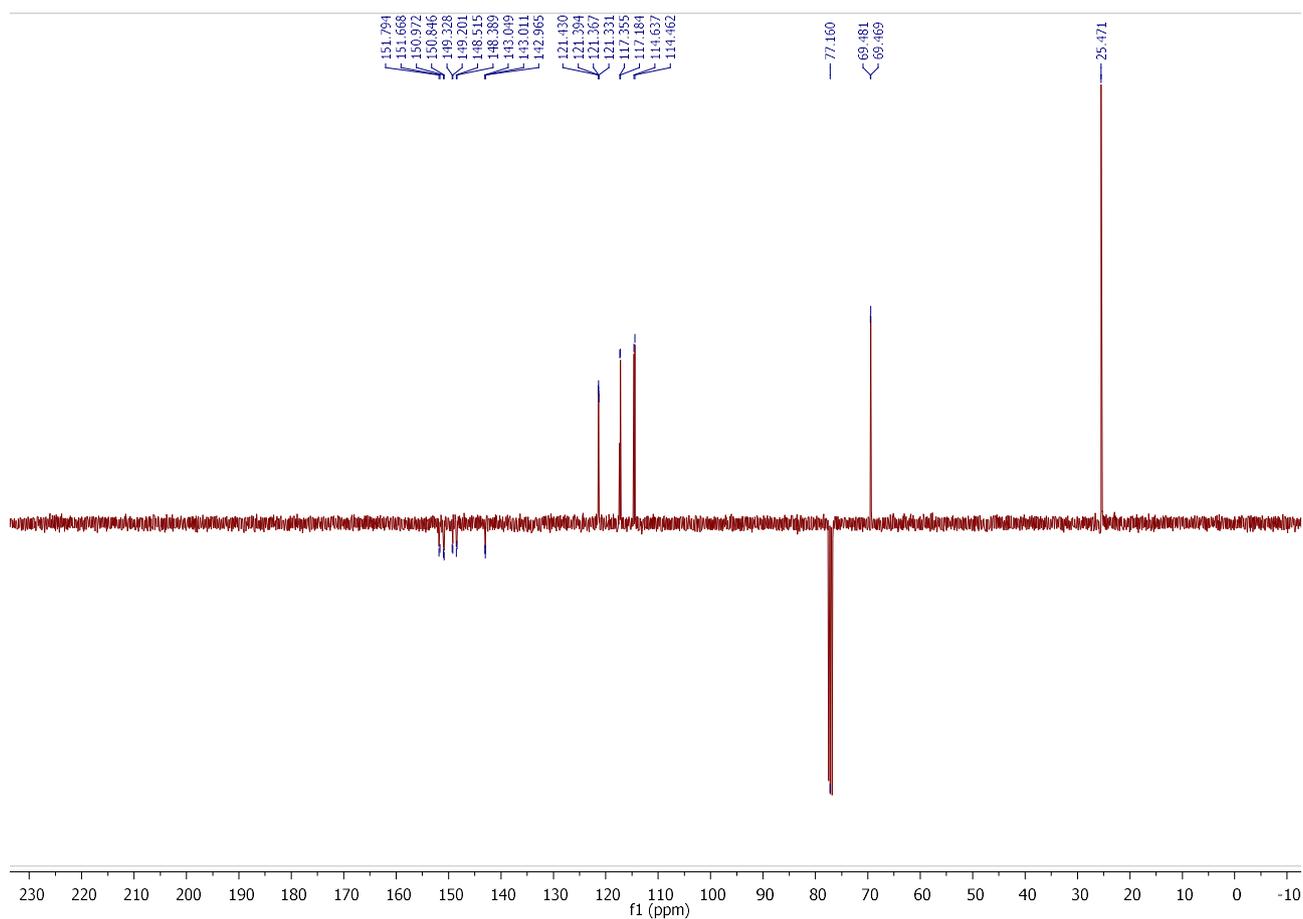


1-(3,4-difluorophenyl)ethan-1-ol

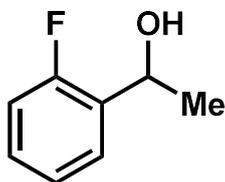


The title compound 1-(3,4-difluorophenyl)ethan-1-ol was prepared according to general procedure 1 from 3',4'-difluoroacetophenone (401 μ L, 500 mg, 3.20 mmol) with NaBH_4 (182 mg, 4.80 mmol) in methanol (8 mL). Purification by flash silica column chromatography (eluent = 15% EtOAc in hexanes, 30 x 100 mm silica) gave a colourless oil (478 mg, 94%). $R_f = 0.28$ (eluent = 20% EtOAc in hexanes); $\nu_{\text{max}} / \text{cm}^{-1}$ (film) 3325, 2982, 1610, 1517, 1433, 1371, 1277, 1150, 1117, 876, 818, 778, 629; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.47 (3H, d, J 6.4), 1.79 (1H, d, J 3.6), 4.88 (1H, dq, J 3.6, 6.4), 7.03-7.17 (2H, m), 7.17-7.25 (1H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -140.0 (d, J_{FF} 21.1), -137.6 (d, J_{FF} 21.1); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 25.5, 69.5 (d, J 1.2), 114.5 (d, J 17.7), 117.3 (d, J 17.3), 121.4 (dd, J 6.4, 3.6), 143.0 (m), 148.9 (dd, J 82.1, 12.8), 151.3 (dd, J 83.0, 12.7); HRMS (CI^+) calculated for $[\text{C}_8\text{H}_7\text{OF}_2]^+$ (M-H) $^+$: m/z 157.0470, found 157.0470, (-0.3 ppm).

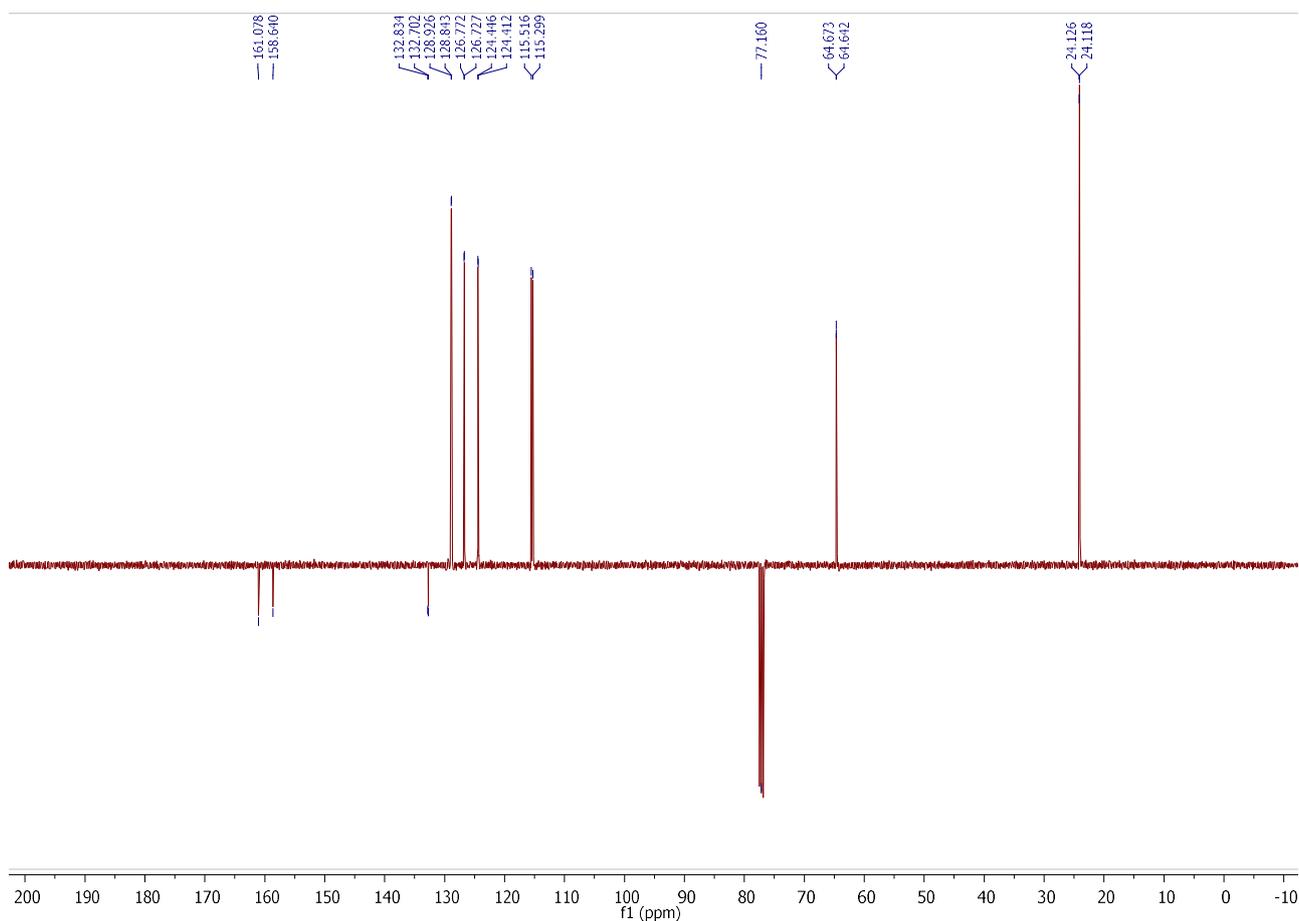




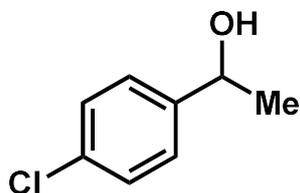
1-(2-fluorophenyl)ethan-1-ol



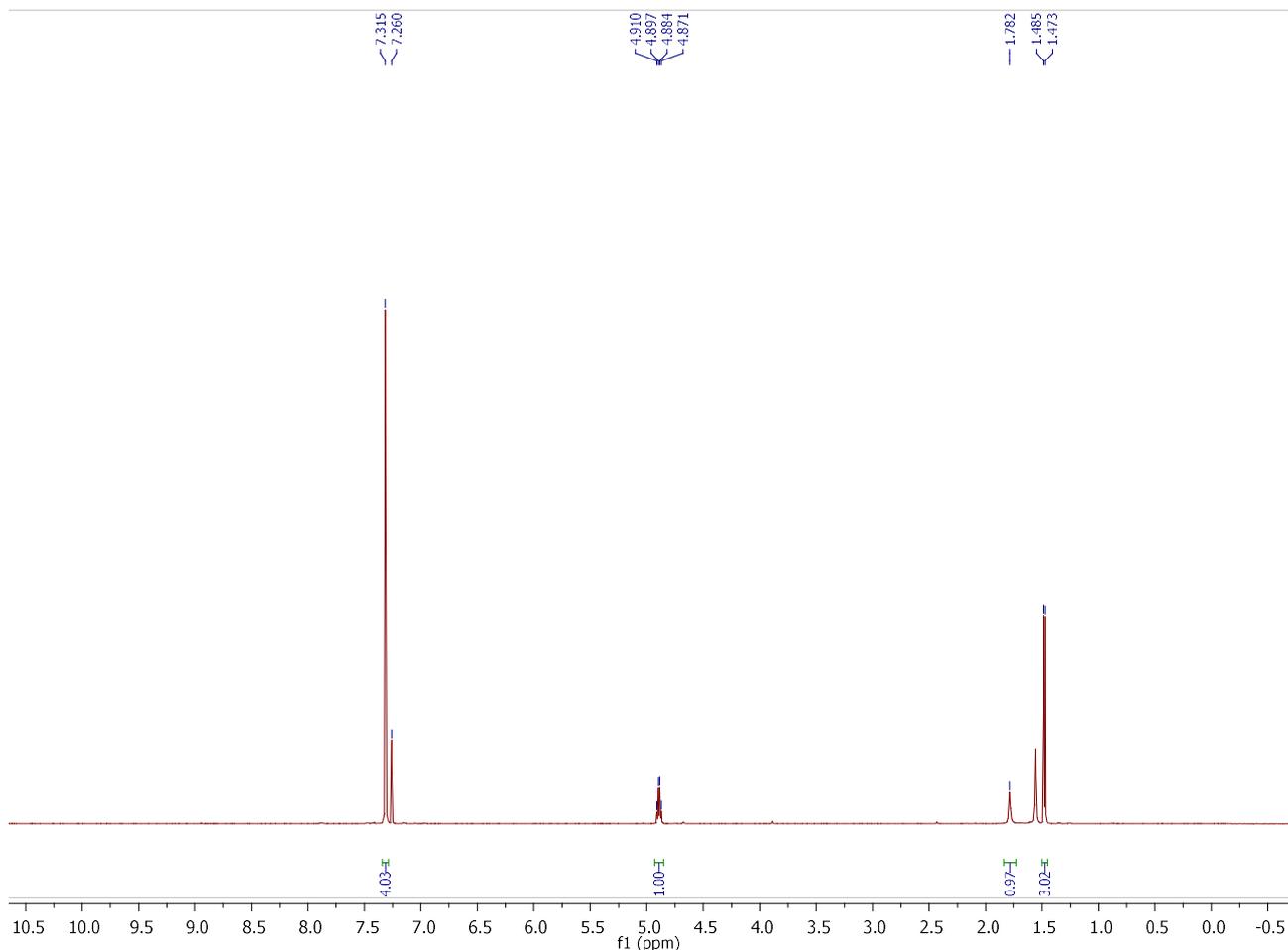
The title compound 1-(2-fluorophenyl)ethan-1-ol was prepared according to general procedure 2 from 2-fluorobenzaldehyde (1.00 mL, 1.18 g, 9.49 mmol) using a 3.0 M methylmagnesium bromide in Et₂O solution (3.80 mL, 11.4 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 40 x 130 mm silica) gave a pale yellow oil (1.11 g, 84%). *R_f* = 0.42 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3321, 2978, 1616, 1585, 1487, 1452, 1222, 1179, 1074, 1009, 901, 824, 750. 484; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.53 (3H, d, *J* 6.5), 1.87 (1H, d, *J* 4.5), 5.17-5.25 (1H, m), 7.02 (1H, ddd, *J* 10.6, 8.2, 1.2), 7.15 (1H, dt, *J* 7.5, 1.5), 7.21-7.28 (1H, m), 7.49 (1H, dt, *J* 7.5, 1.5); ¹⁹F (377 MHz, CDCl₃) δ_{F} : -120.1; ¹³C NMR (101 MHz, CDCl₃) δ_{C} : 24.1 (d, *J* 0.8), 64.7 (d, *J* 3.1), 115.4 (d, *J* 21.9), 124.4 (d, *J* 3.4), 126.8 (d, *J* 4.5), 128.9 (d, *J* 8.4), 132.8 (d, *J* 13.3), 159.9 (d, *J* 246.0); HRMS (CI⁺) calculated for [C₈H₁₃ONF]⁺ (M+NH₄)⁺ : *m/z* 158.0976, found 158.0979, (+2.1 ppm).



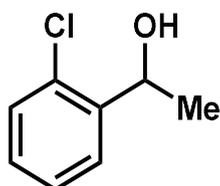
1-(4-chlorophenyl)ethan-1-ol



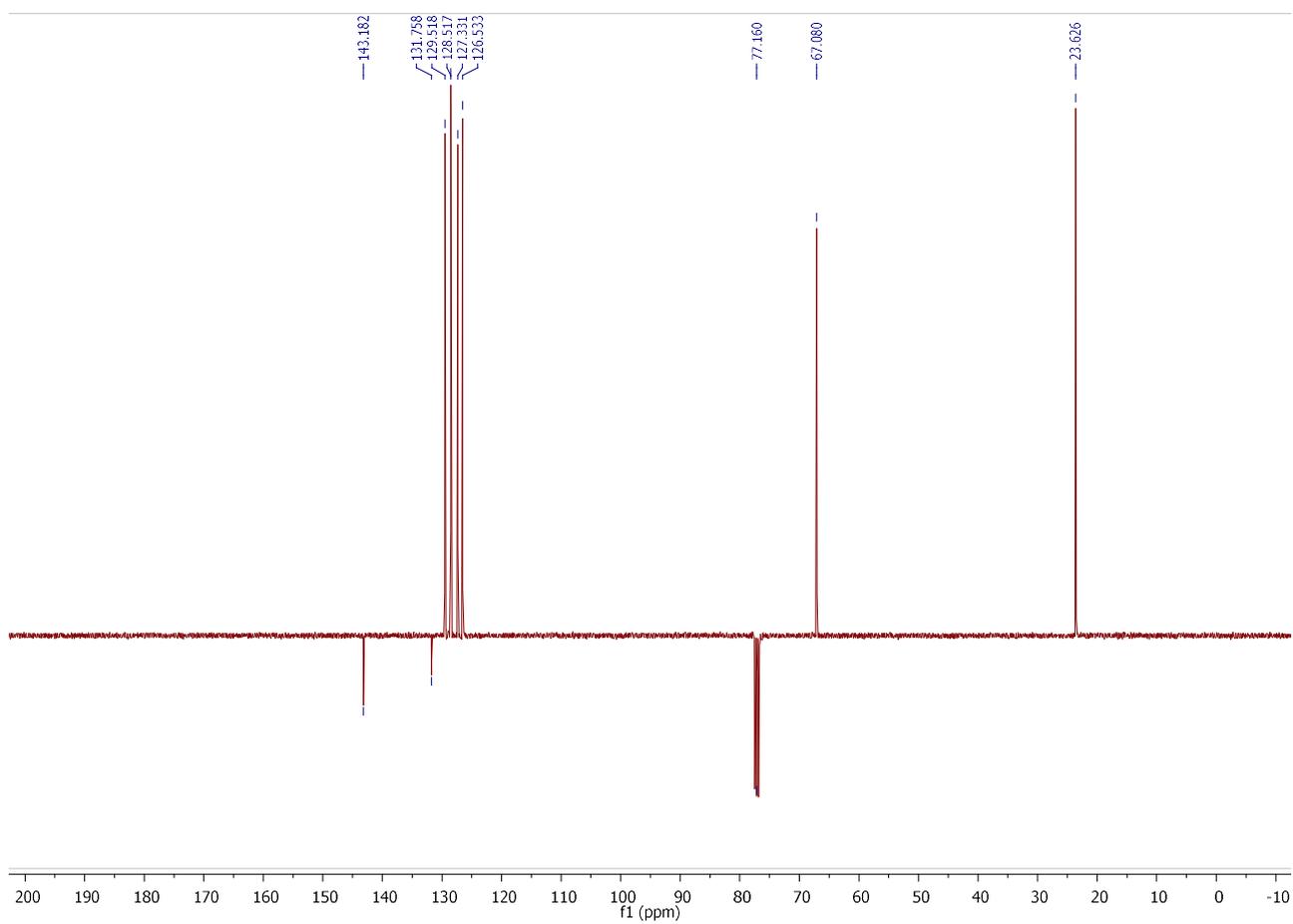
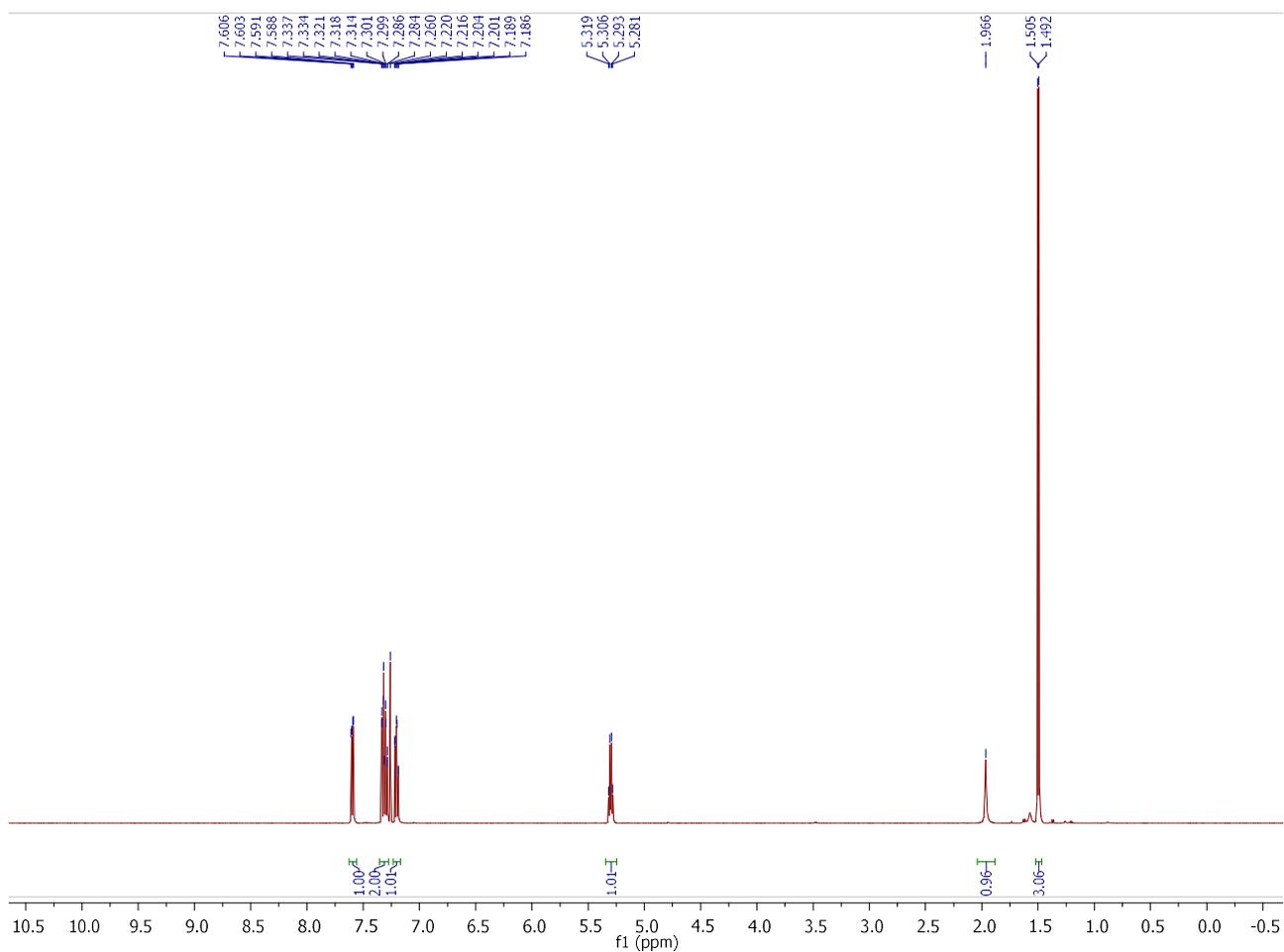
The title compound 1-(4-chlorophenyl)ethan-1-ol was prepared according to general procedure 2 from 4-chlorobenzaldehyde (1.97 g, 14.0 mmol) using a 3.0 M methylmagnesium bromide in Et₂O solution (7.00 mL, 21.0 mmol) in dry THF (60 mL). Purification by flash silica chromatography (eluent = 10-30% EtOAc in hexanes, 50 x 150 mm silica) gave a pale yellow oil (1.86 g, 85%). R_f = 0.30 (eluent = 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H: 1.48 (3H, d, *J* 6.0), 1.78 (1H, br), 4.89 (1H, q, *J* 6.5), 7.32 (4H, s). Spectroscopic data in accordance with that stated in the literature.⁴



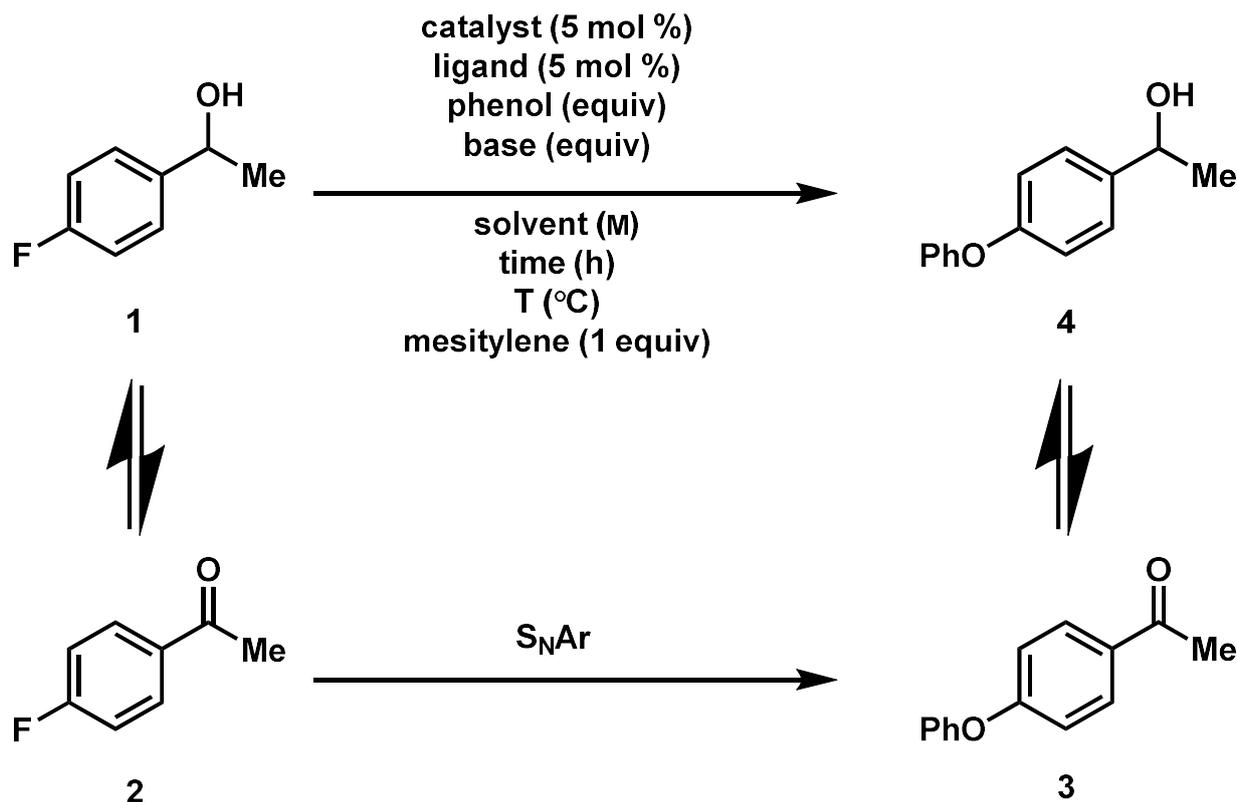
1-(2-chlorophenyl)ethan-1-ol



The title compound 1-(2-chlorophenyl)ethan-1-ol) was prepared according to general procedure 2 from 2-chlorobenzaldehyde (1.00 mL, 1.25 g, 8.87 mmol) using a 3.0 M methylmagnesium bromide in Et₂O solution (3.60 mL, 10.7 mmol) in dry THF (20 mL). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 50 x 140 mm silica) gave a pale yellow oil (1.28 g, 92%). *R*_f = 0.46 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 3318, 2978, 1477, 1435, 1200, 1132, 1094, 1047, 1032, 1007, 899, 748, 691, 606, 461; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 1.50 (3H, d, *J* 6.5), 1.97 (1H, br), 5.30 (1H, q, *J* 6.5), 7.20 (1H, dt, *J* 7.5, 1.5), 7.27-7.35 (2H, m), 7.60 (1H, dd, *J* 7.5, 1.5); ¹³C NMR (101 MHz, CDCl₃) δ_{C} : 23.6, 67.1, 126.5, 127.3, 128.5, 129.5, 131.8, 143.2; HRMS (CI⁺) calculated for [C₈H₁₃ClON]⁺ (M+NH₄)⁺ : *m/z* 174.0680, found 174.0680, (-0.1 ppm).



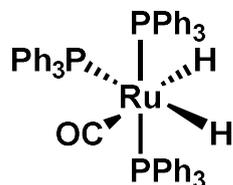
2.2. Optimization of hydrogen transfer-S_NAr protocol



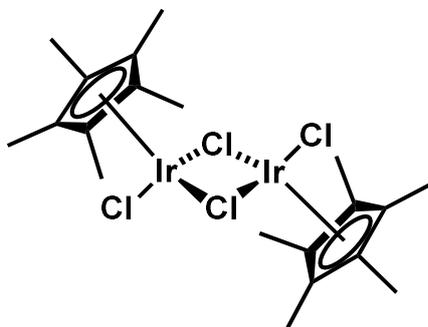
A 10 mL microwave vial was charged with phenol (41.4 mg, 0.440 mmol, 1.1 equiv), K₂CO₃ (60.8 mg, 0.440 mmol, 1.1 equiv), ligand (5.00 mol %) and catalyst (5.00 mol %). The vial was then charged with solvent (0.4 mL) and 1-(4-fluorophenyl)ethan-1-ol (50.6 μL, 56.1 mg, 0.400 mmol, 1 equiv), it was sealed with a cap and left to react at 130 °C for 24 hours. After cooling to room temperature, mesitylene (55.6 μL, 48.1 mg, 0.400 mmol) was added to the mixture followed by H₂O (1 mL) and Et₂O (1 mL). The vial was stirred for 30 seconds and the top layer was sampled and analysed using ¹H NMR.

Entry	Catalyst (5 mol %)	Ligand / Additive	Phenol (equiv)	Base (equiv)	Solvent (M)	Temp (°C)	Time (h)	1 (%)	2 (%)	3 (%)	4 (%)
1	-	-	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	98	0	0	0
2	Ru(PPh ₃) ₃ (CO)(H) ₂	-	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	23	2	38	25
3	[Cp*IrCl ₂] ₂	-	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	29	1	37	3
4	[Knolker]	Me ₃ NO.2H ₂ O (10 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	95	-	-	-
5	Ru(PPh ₃) ₃ (CO)(H) ₂	Xantphos (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	7	1	35	33
6	Ru(PPh ₃) ₃ (CO)(H) ₂	DPEphos (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	7	2	37	40
7	Ru(PPh ₃) ₃ (CO)(H) ₂	DCPB (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	4	1	48	30

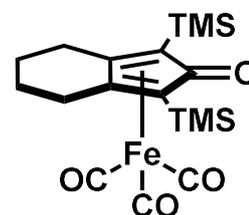
8	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	0	1	62	28
9	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPP (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	1	1	56	36
10	Ru(PPh ₃) ₃ (CO)(H) ₂	DCPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	2	1	49	36
11	Ru(PPh ₃) ₃ (CO)(H) ₂ (2.5 mol %)	DPPE (2.5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	24	63	1	25	7
12	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.5	K ₂ CO ₃ (1.5)	DMSO (1)	130	24	4	2	46	38
13	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	Cs ₂ CO ₃ (1.1)	DMSO (1)	130	24	2	2	44	34
14	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	Et ₃ N (1.1)	DMSO (1)	130	24	43	26	10	3
15	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMAC (1)	130	24	6	3	46	44
16	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMF (1)	130	24	38	0	30	23
17	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (0.5)	130	24	2	2	45	37
18	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (2)	130	24	8	0	58	34
19	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	115	24	10	3	47	39
20	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	150	24	14	-	52	26
21	Ru(PPh ₃) ₃ (CO)(H) ₂	DPPE (5 mol %)	1.1	K ₂ CO ₃ (1.1)	DMSO (1)	130	16	<1	<1	52	34



Ru(PPh₃)(CO)(H)₂

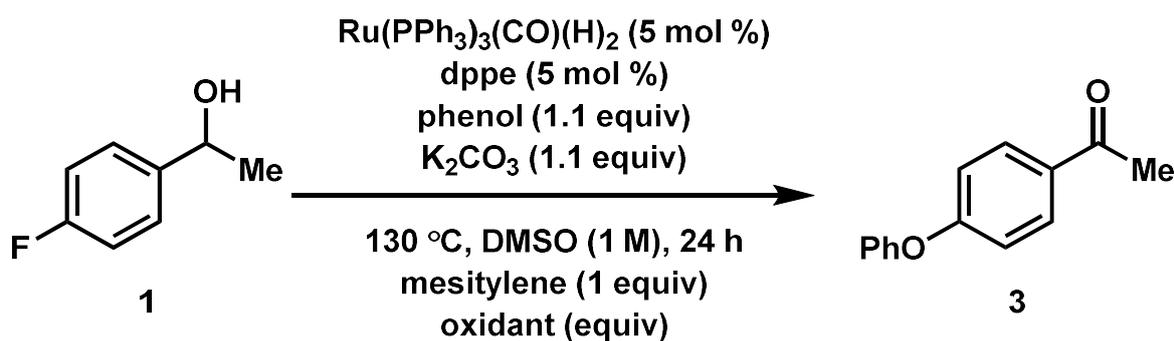


[Cp*IrCl₂]₂



Knölker

2.2.1. Optimization of hydrogen transfer-S_NAr protocol (dehydrogenative)



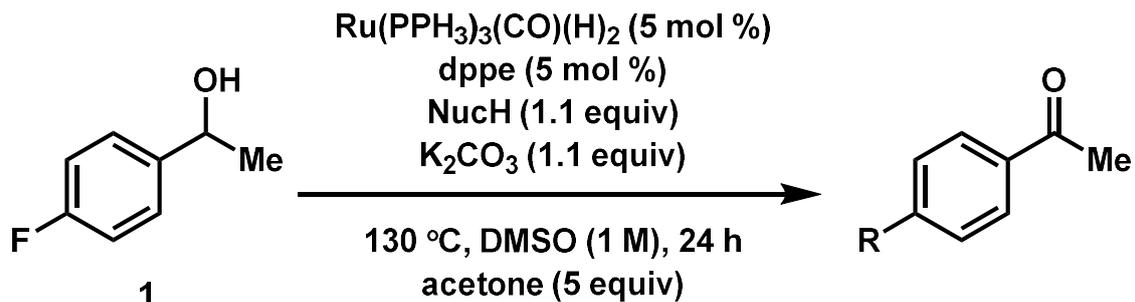
A 10 mL microwave vial was charged with phenol (41.4 mg, 0.440 mmol, 1.1 equiv), K_2CO_3 (60.8 mg, 0.4400 mmol, 1.1 equiv), DPPE (8.00 mg, 5.00 mol %) and $\text{Ru(PPh}_3\text{)}_3\text{(CO)(H)}_2$ (18.3 mg, 5.00 mol %). The vial was then charged with DMSO (0.4 mL), oxidant (equiv) and 1-(4-fluorophenyl)ethan-1-ol (50.6 μL , 56.1 mg, 0.400 mmol), it was sealed with a cap and left to react at 130 °C for 24 hours. After cooling to room temperature, mesitylene (55.6 μL , 48.1 mg, 0.400 mmol) was added to the mixture followed by H_2O (1 mL) and Et_2O (1 mL). The vial was stirred for 30 seconds and the top layer was sampled and analysed using ^1H NMR.

Entry	Oxidant	Oxidant (equiv)	3 (%) ^a
1	Acetone	2	75
2	Acetophenone	2	81
3	2-Butanone	2	76
4	Cyclohexanone	2	56
5	3,3-Dimethylbutanone	2	67
6	3,3-Dimethylbut-1-ene	2	46
7	1-hexene	2	53
8	3-Methyl-2-butanone	2	72
9	4-Methyl-2-pentanone	2	72
10	Styrene	2	42
11	Crotonitrile	2	54
12	Acetone	5	81 (79) ^b
13	Acetophenone	5	86
14	2-Butanone	5	85
15	3-Methyl-2-butanone	5	89
16	4-Methyl-2-pentanone	5	85

^aNMR yield with respect to mesitylene as internal standard.

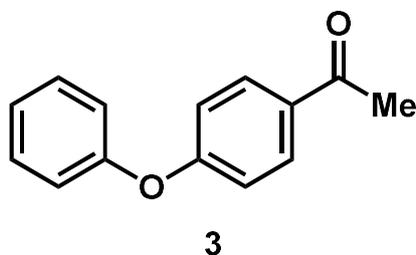
^bIsolated yield.

2.2.2. General procedure 3

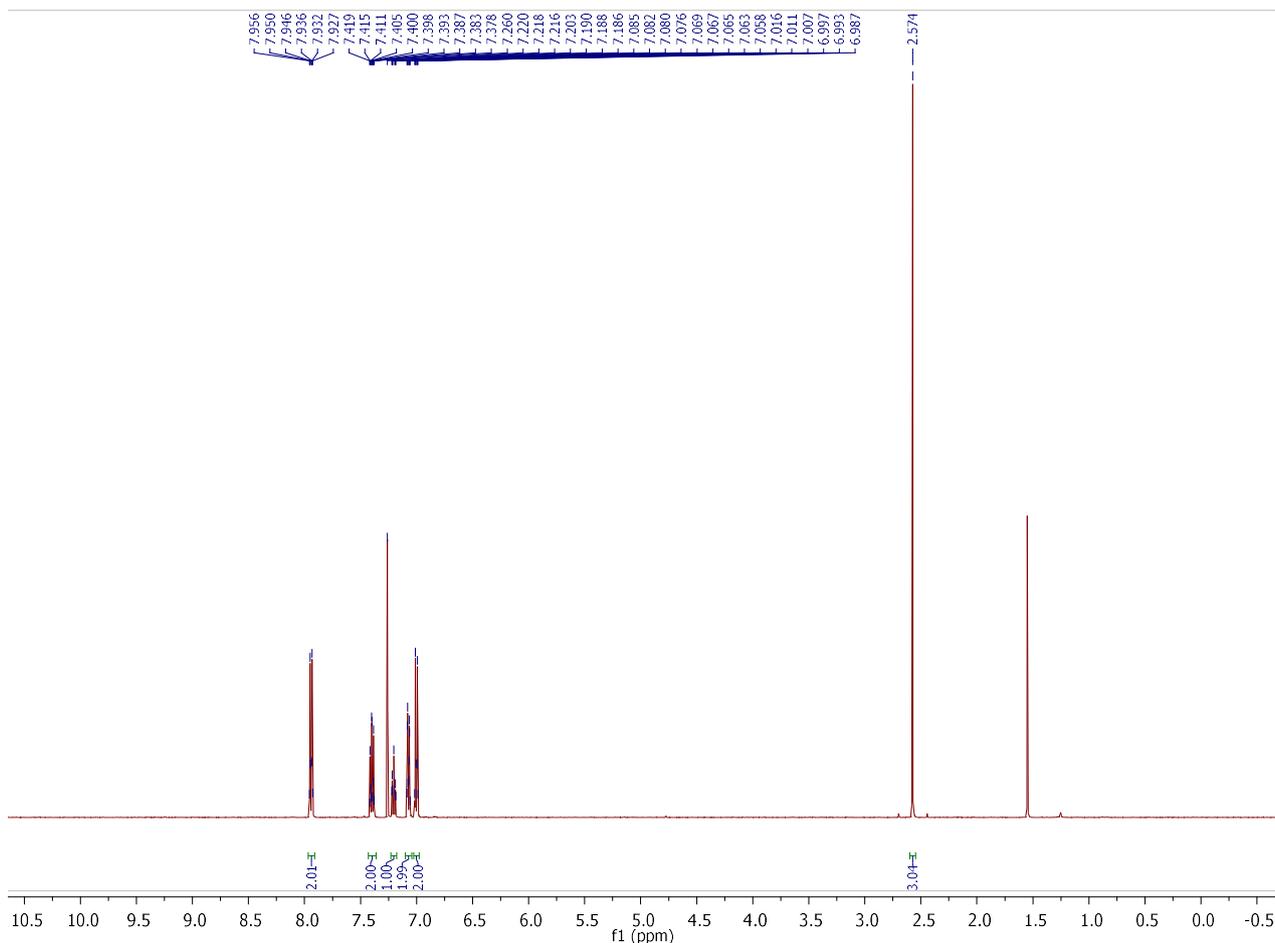


A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with Ru(PPh₃)₃(CO)(H)₂ (18.3 mg, 5.00 mol %), DPPE (8.0 mg, 5.00 mol %), nucleophile (0.4400 mmol, 1.1 equiv) and K₂CO₃ (60.8 mg, 0.4400 mmol). To this mixture was added DMSO (0.4 mL), acetone (147 μL, 116.2 mg, 2 mmol) and 1-(4-fluorophenyl)ethan-1-ol (50.6 μL, 56.1 mg, 0.400 mmol). (**Entry 12 conditions**). The vial was sealed with a cap and left to react at 130 °C for 24 hours. After cooling, the reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H₂O (25 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

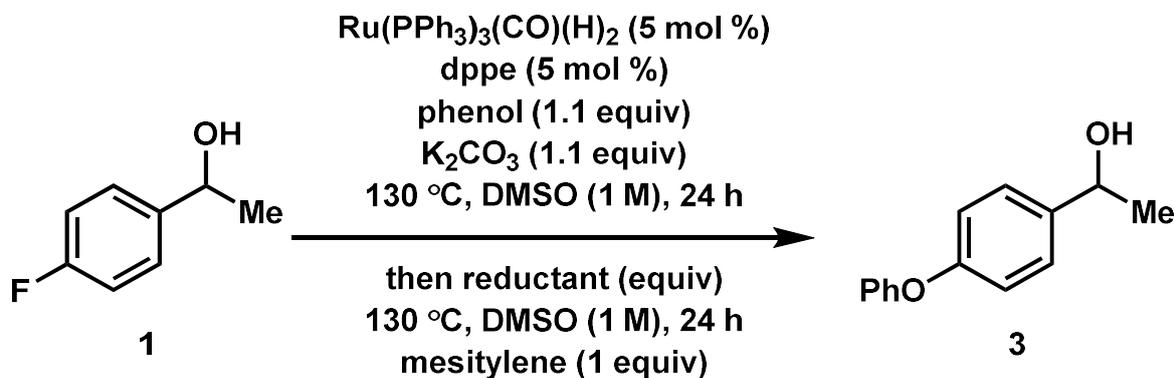
1-(4-phenoxyphenyl)ethan-1-one



The title compound 1-(4-phenoxyphenyl)ethan-1-one (**3**) was prepared according to general procedure 3 using phenol (41.4 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 160 mm silica) gave an off-white solid (67 mg, 79%). mp 40–43 °C (Lit. 45-47 °C)⁵; R_f = 0.43 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 3059, 2994, 1672, 1572, 1414, 1360, 1244, 1161, 1111, 957, 847, 799, 768, 696, 575, 501; ¹H NMR (500 MHz, CDCl₃) δ_H: 2.57 (3H, s), 6.97-7.03 (2H, m), 7.04-7.10 (2H, m), 7.17-7.23 (1H, m), 7.36-7.44 (2H, m), 7.91-7.97 (2H, m). Spectroscopic data in accordance with that stated in the literature.⁵



2.2.3. Optimization of hydrogen transfer-S_NAr protocol (redox neutral)



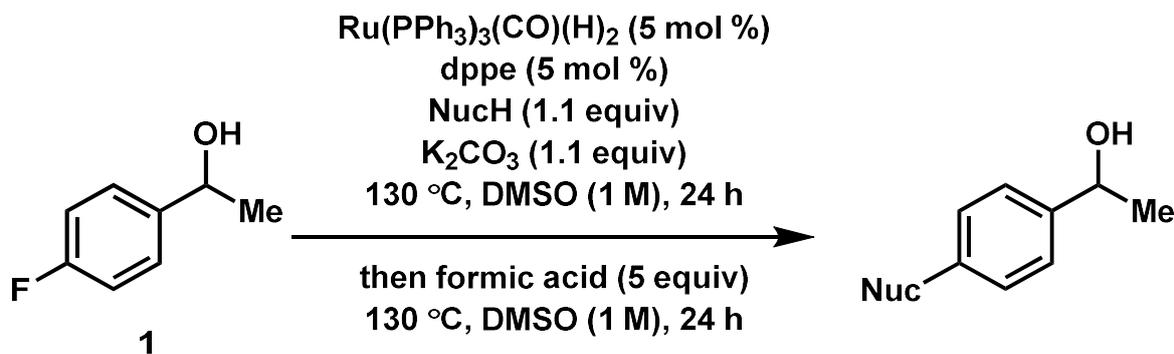
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with Ru(PPh₃)₃(CO)(H)₂ (18.3 mg, 5.00 mol %), DPPE (8.0 mg, 5.00 mol %), phenol (41.4 mg, 0.440 mmol) and K₂CO₃ (60.8 mg, 0.440 mmol). To this mixture was added DMSO (0.4 mL) and 1-(4-fluorophenyl)ethan-1-ol (50.6 μL, 56.1 mg, 0.400 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 hours. After cooling, reductant (2.00 mmol) was then added to the reaction mixture and was then heated for a further 24 h at 130 °C. After cooling to room temperature, mesitylene (55.6 μL, 48.1 mg, 0.400 mmol) was added to the mixture followed by H₂O (1 mL) and Et₂O (1 mL). The vial was stirred for 30 seconds and the top layer was sampled and analysed using ¹H NMR.

Entry	Reductant	Reductant (equiv)	Time (h)	4 (%) ^a
1	1,4-Butanediol	2	24	52
2	Formic Acid	2	24	74
3	<i>Cis</i> -2-butene-1,4-diol	2	24	30
4	Isopropanol	2	24	44
5	Sodium Formate	2	24	74
6	Formic Acid	5	24	82 (80) ^b
7	Isopropanol	5	24	73
8	Sodium Formate	5	24	73

^aNMR yield with respect to mesitylene as internal standard.

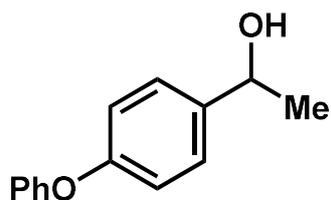
^bIsolated yield.

2.2.4. General procedure 4



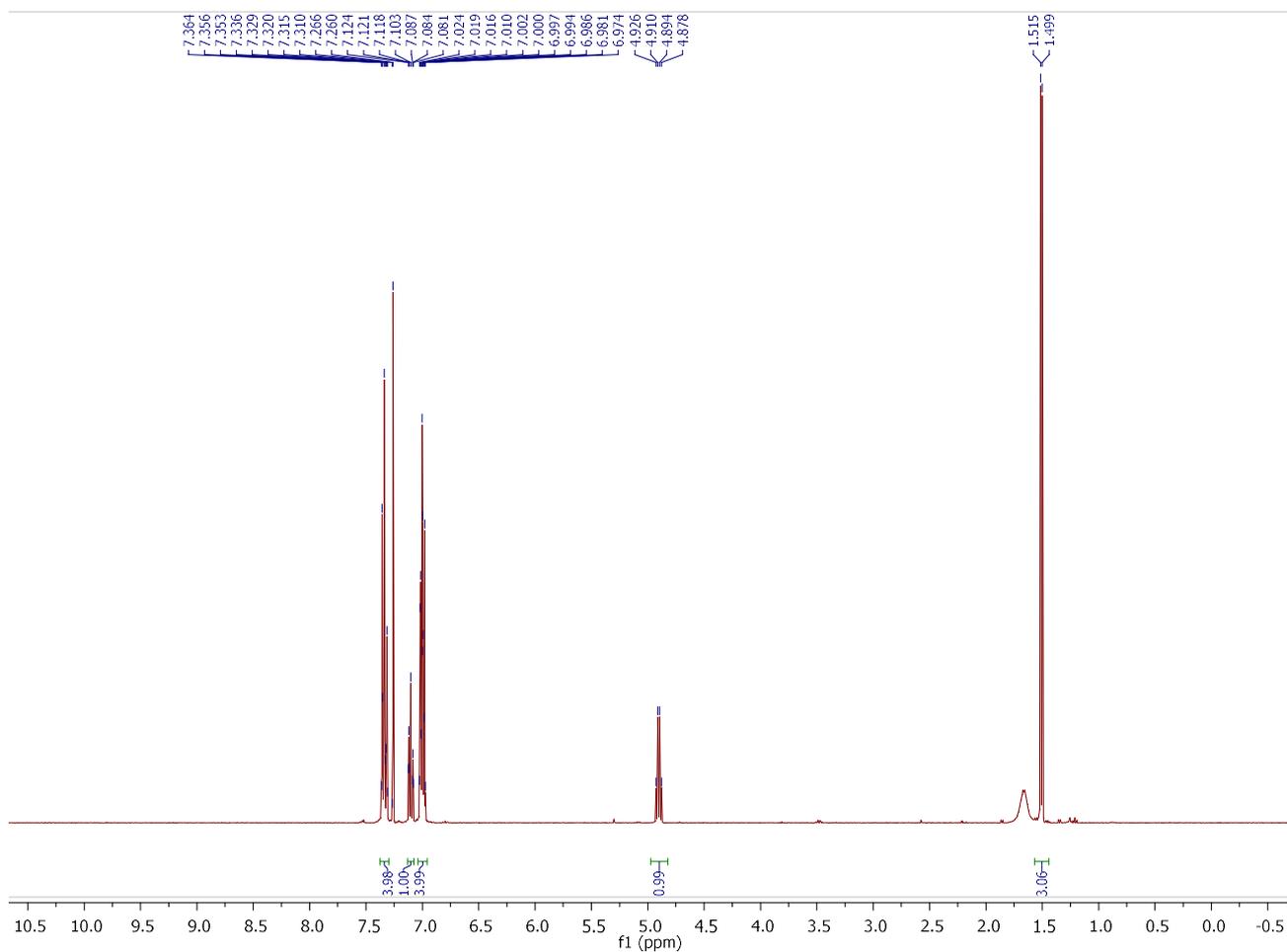
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with $\text{Ru(PPh}_3)_3\text{(CO)(H)}_2$ (18.3 mg, 5.00 mol %), DPPE (8.0 mg, 5.00 mol %), requisite nucleophile (0.440 mmol) and K_2CO_3 (60.8 mg, 0.440 mmol). To this mixture was added DMSO (0.4 mL) and 1-(4-fluorophenyl)ethan-1-ol (50.6 μL , 56.1 mg, 0.400 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 hours. After cooling, formic acid (75.4 μL , 92.0 mg, 2.00 mmol) was then added to the reaction mixture (**Entry 6 conditions**). The reaction was then heated for a further 24 h at 130 °C. The reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*.

1-(4-phenoxyphenyl)ethan-1-ol



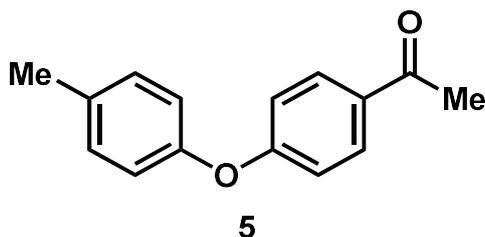
4

The title compound 1-(4-phenoxyphenyl)ethan-1-ol (**4**) was prepared according to general procedure 4 using phenol (41.4 mg, 0.440 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-20% EtOAc in hexanes, 30 x 150 mm silica) gave a pale yellow oil (68 mg, 80%). $R_f = 0.28$ (eluent = 20% EtOAc in hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.51 (3H, d, J 6.4), 4.90 (1H, q, J 6.4), 6.96-7.04 (4H, m), 7.06-7.14 (1H, m), 7.29-7.38 (4H, m). Spectroscopic data in accordance with that stated in the literature.⁶

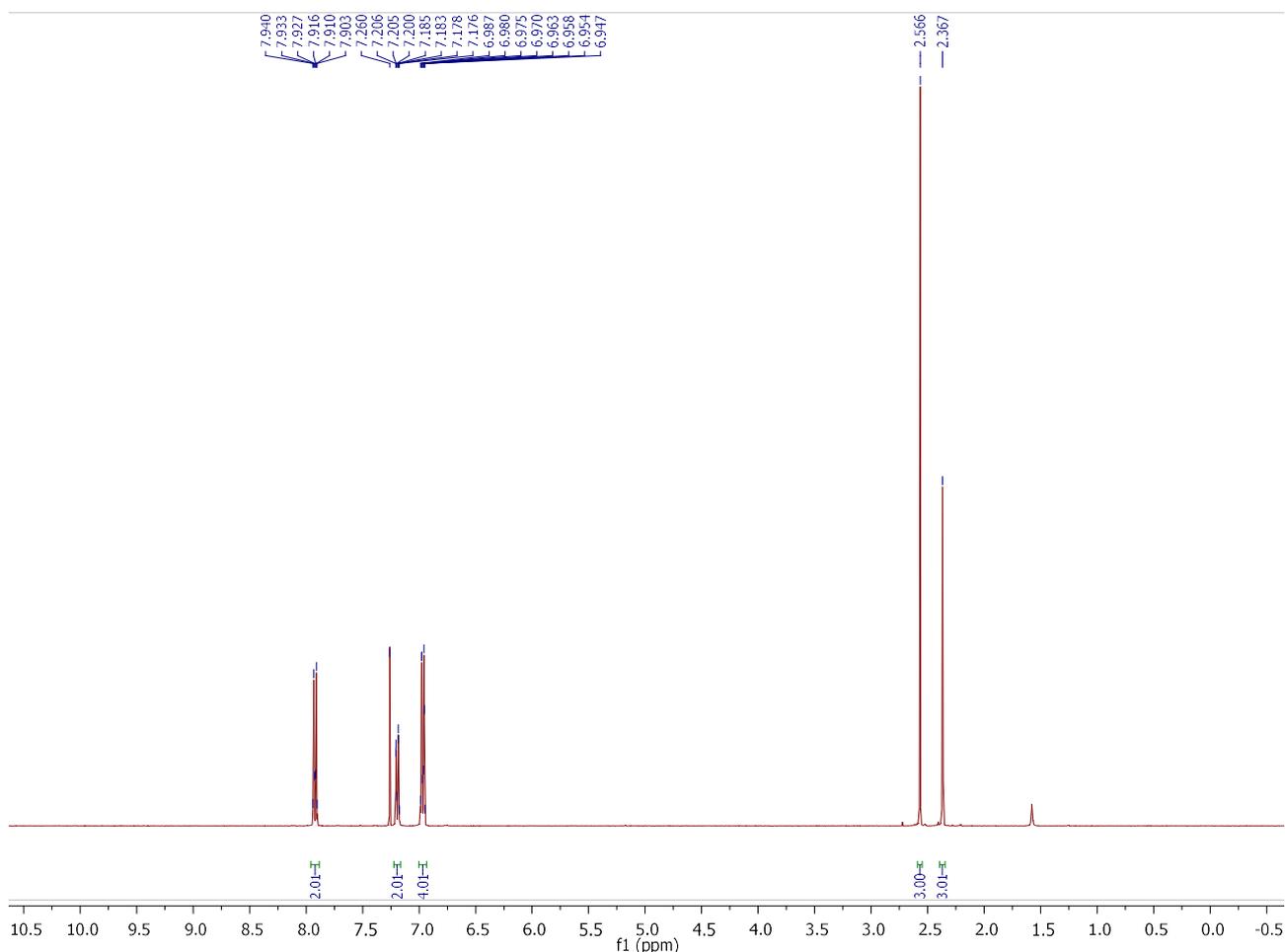


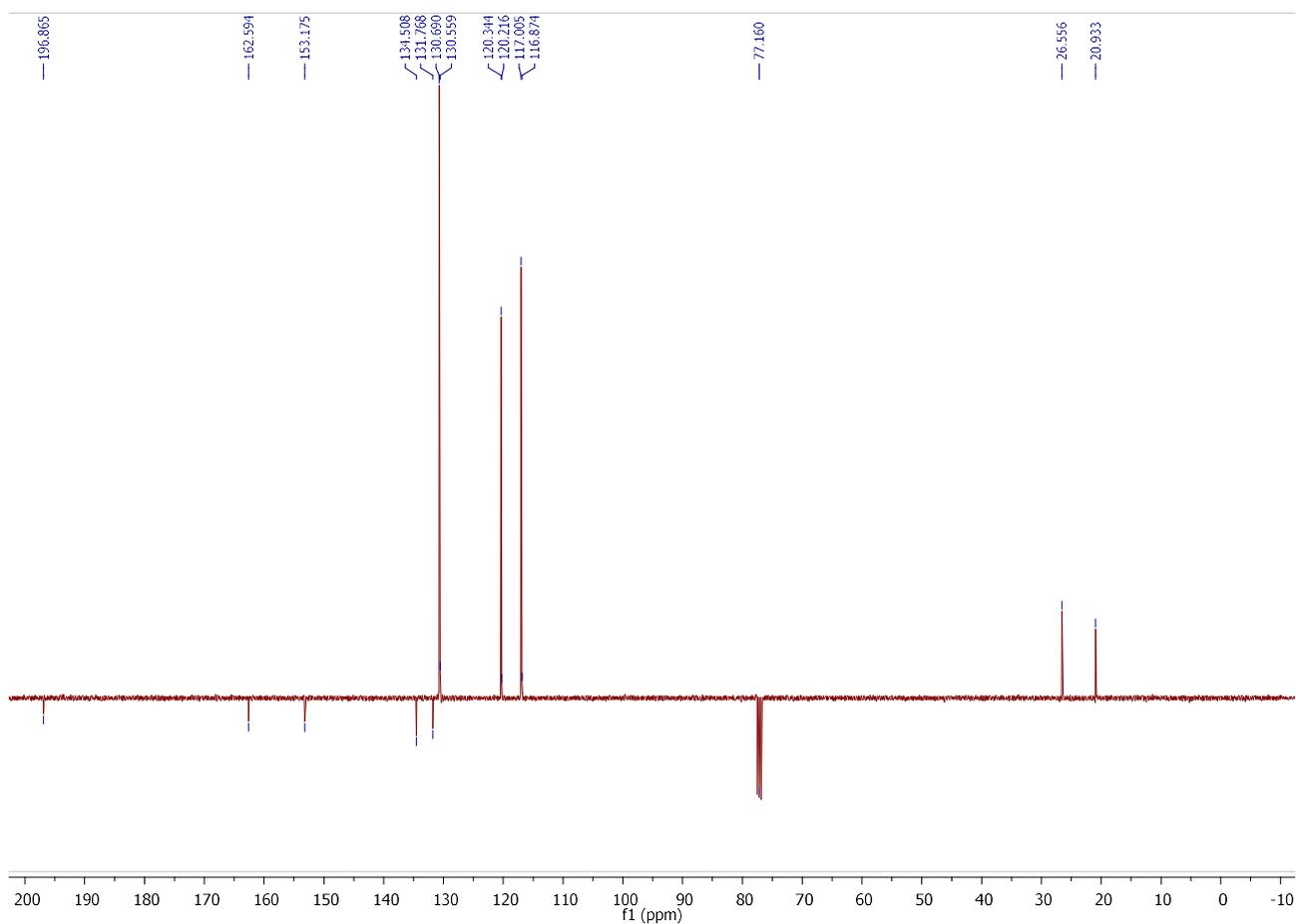
2.3. Scope of dehydrogenative S_NAr protocol

1-(4-(*p*-toloxy)phenyl)ethan-1-one

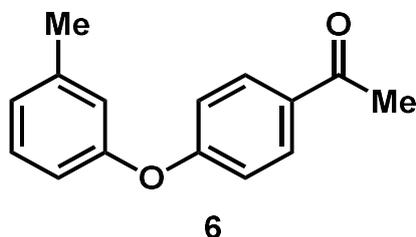


The title compound 1-(4-(*p*-toloxy)phenyl)ethan-1-one (**5**) was prepared according to general procedure 3 using *p*-cresol (47.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave a white solid (78 mg, 86%). mp 40-43 °C (Lit. 46-47 °C)⁷; R_f = 0.48 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 1676, 1587, 1576, 1497, 1416, 1242, 1163, 961, 833, 820, 586, 544; ¹H NMR (400 MHz, CDCl₃) δ_H: 2.37 (3H, s), 2.57 (3H, s), 6.93-7.01 (4H, m), 7.16-7.23 (2H, m), 7.88-7.96 (2H, m); ¹³C NMR (101 MHz, CDCl₃) δ_C: 20.9, 26.6, 117.0, 120.3, 130.6, 130.7, 131.8, 134.5, 153.2, 162.6, 196.9; HRMS (NSI⁺) calculated for [C₁₅H₁₅O₂]⁺ (M+H)⁺ : m/z 227.1067, found 227.1068, (+0.6 ppm).

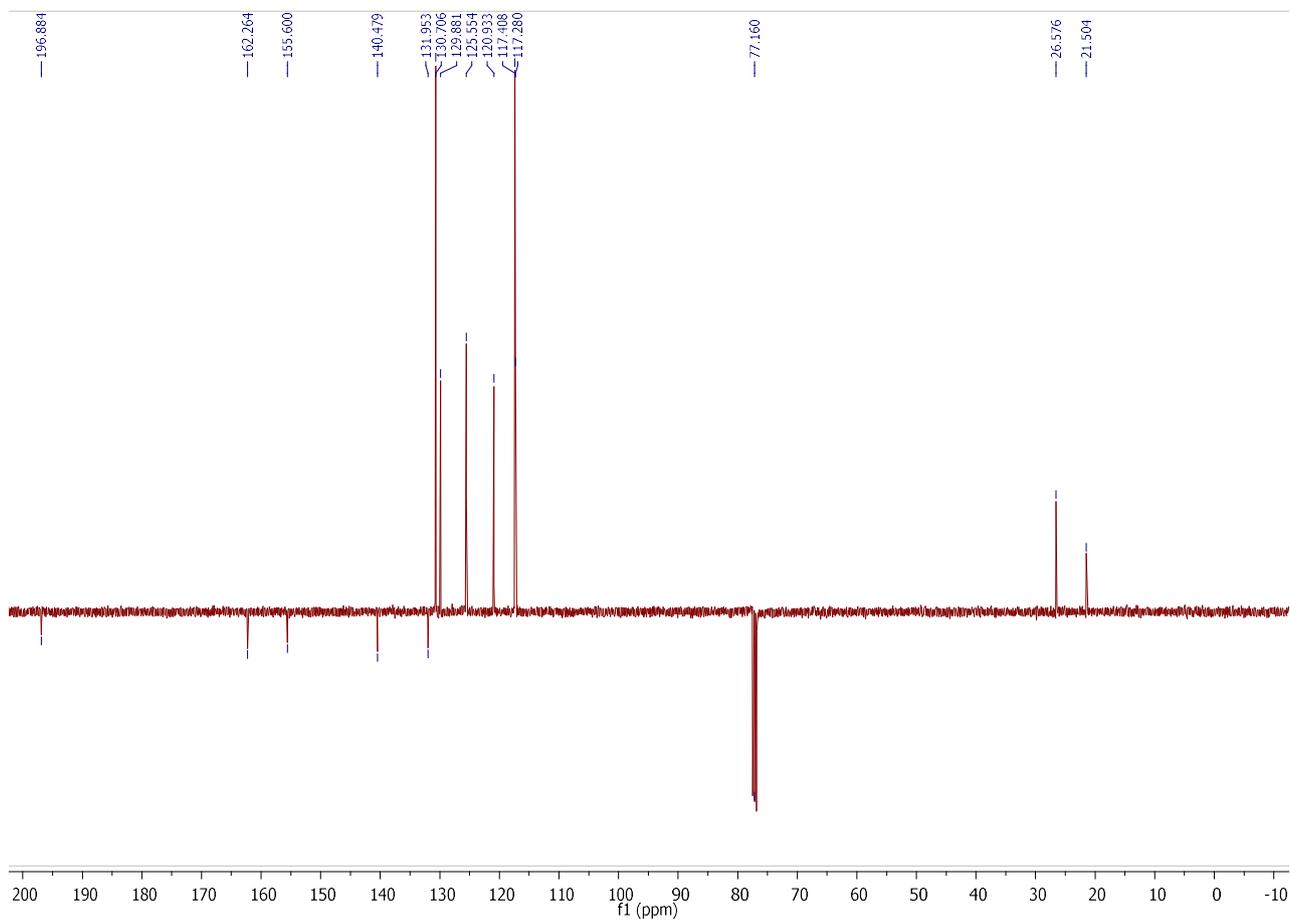
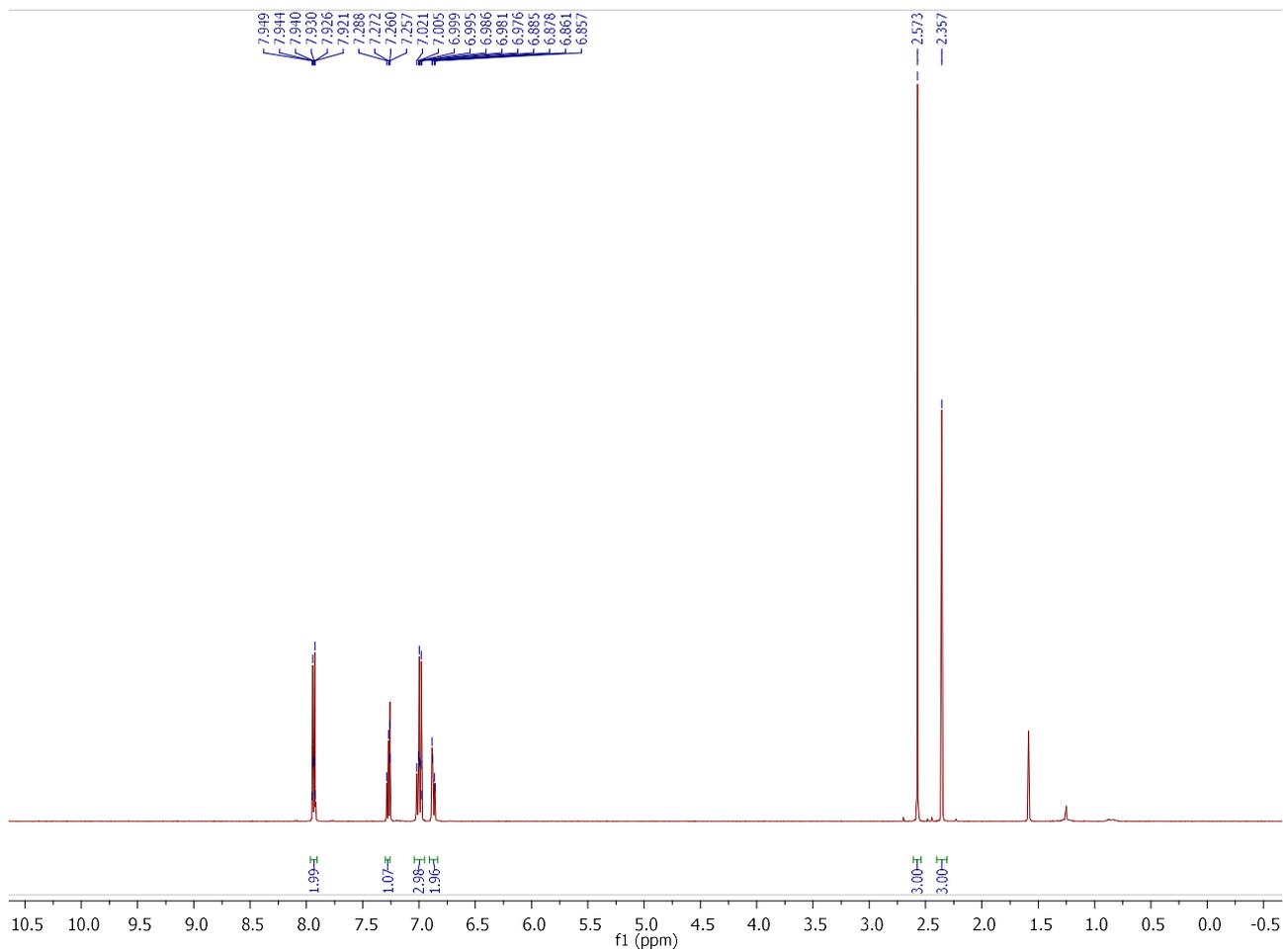




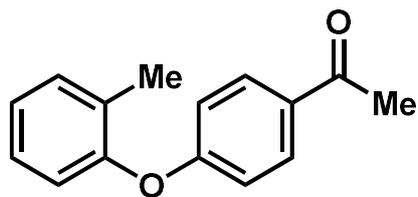
1-(4-(*m*-tolyl)oxy)phenyl)ethan-1-one



The title compound 1-(4-(*m*-tolyl)oxy)phenyl)ethan-1-one (**6**) was prepared according to general procedure 3 using *m*-cresol (46.0 μ L, 47.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave a white solid (64 mg, 71%). mp 39-42 $^{\circ}$ C; R_f = 0.50 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 2924, 2855, 1670, 1599, 1572, 1503, 1483, 1416, 1354, 1273, 1252, 1240, 1167, 934, 820, 791, 588, 575; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.36 (3H, s), 2.57 (3H, s), 6.84-6.91 (2H, m), 6.95-7.05 (3H, m), 7.23-7.31 (1H, m), 7.90-7.96 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 21.5, 26.6, 117.3, 117.4, 120.9, 125.4, 129.9, 130.7, 131.9, 140.5, 155.6, 162.3, 196.9; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{15}\text{O}_2]^+$ ($\text{M}+\text{H}^+$): m/z 227.1067, found 227.1068, (+0.6 ppm).

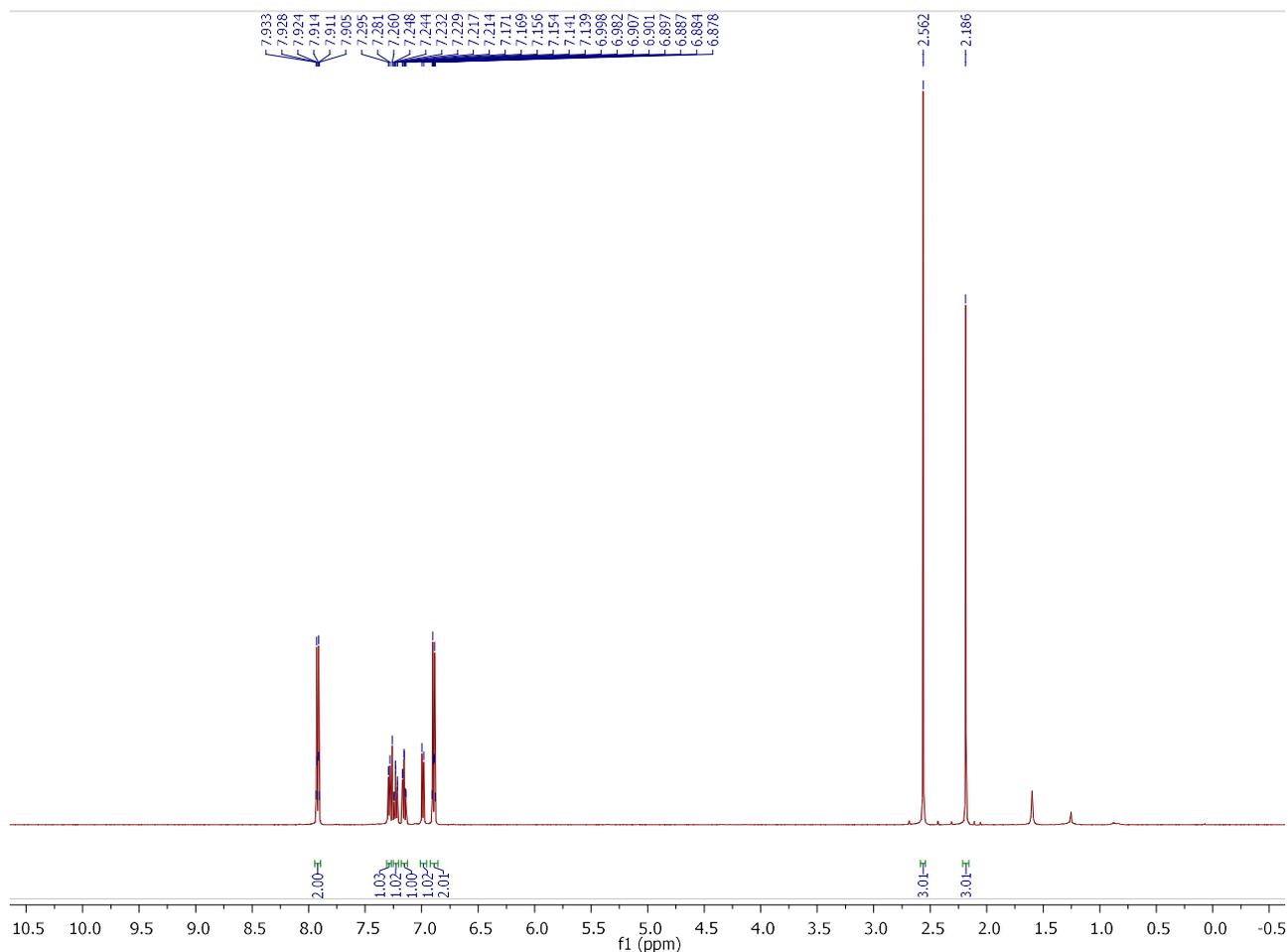


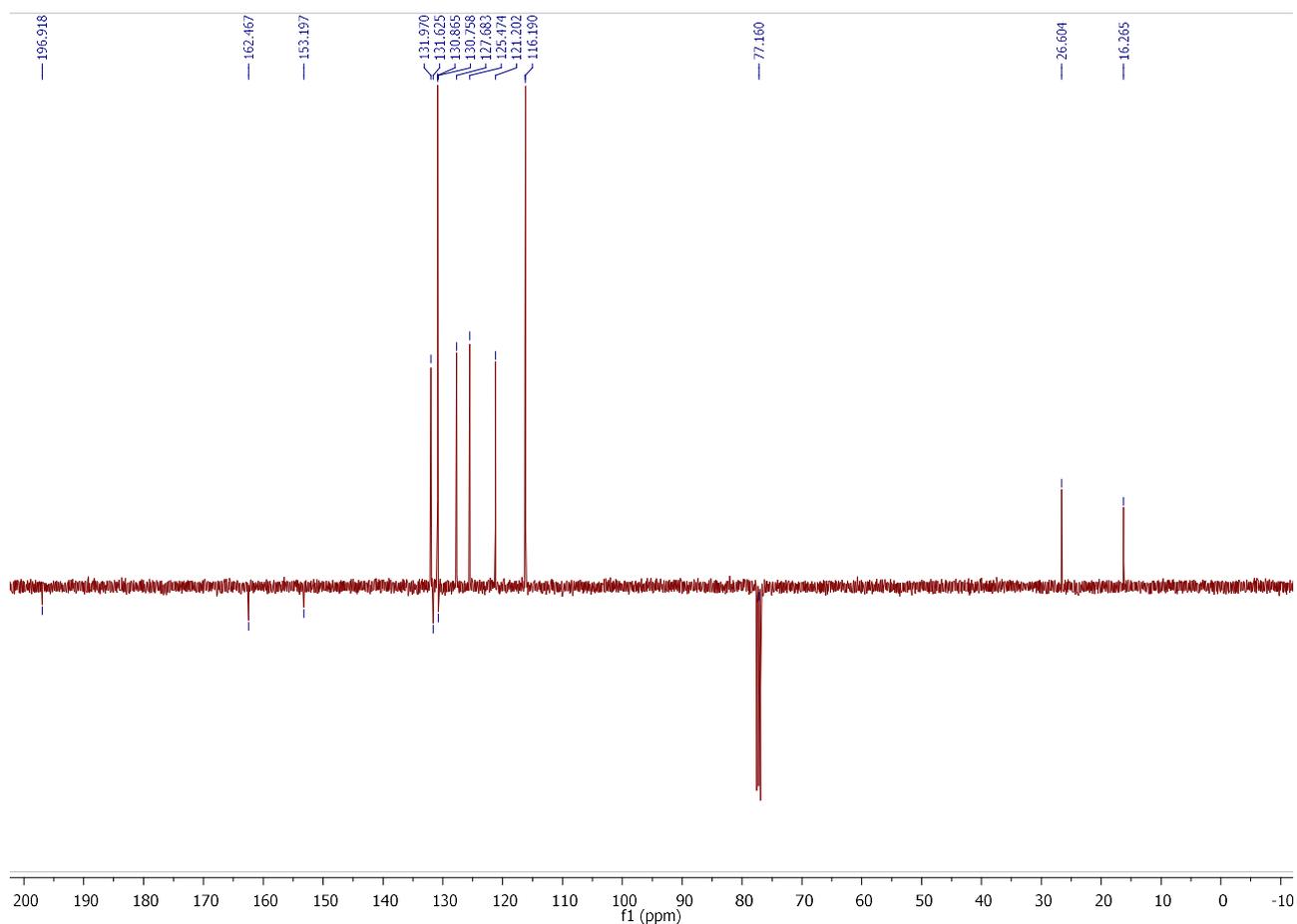
1-(4-(*o*-tolylloxy)phenyl)ethan-1-one



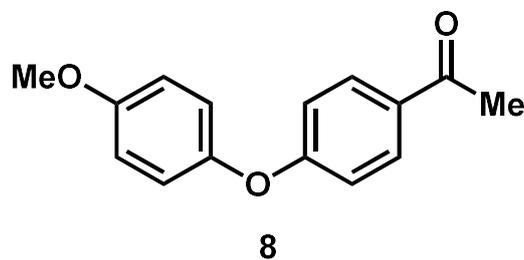
7

The title compound 1-(4-(*o*-tolylloxy)phenyl)ethan-1-one (**7**) was prepared according to general procedure 3 using *o*-cresol (45 μ L, 47.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave a colourless oil (64 mg, 71%). R_f = 0.33 (eluent = 10% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 1676, 1603, 1576, 1501, 1485, 1358, 1233, 1159, 1109, 1040, 957, 874, 839, 777, 752, 581; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.19 (3H, s), 2.56 (3H, s), 6.86-6.93 (2H, m), 6.99 (1H, d, J 8.0), 7.16 (1H, dt, J 7.5, 1.0), 7.20-7.26 (1H, m), 7.29 (1H, d, J 7.0), 7.88-7.96 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 16.3, 26.6, 116.2, 121.2, 125.5, 127.7, 130.6, 130.9, 131.6, 132.0, 153.2, 162.5, 196.9; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{15}\text{O}_2]^+$ ($\text{M}+\text{H}$) $^+$: m/z 227.1067, found 227.1067, (+0.2 ppm).

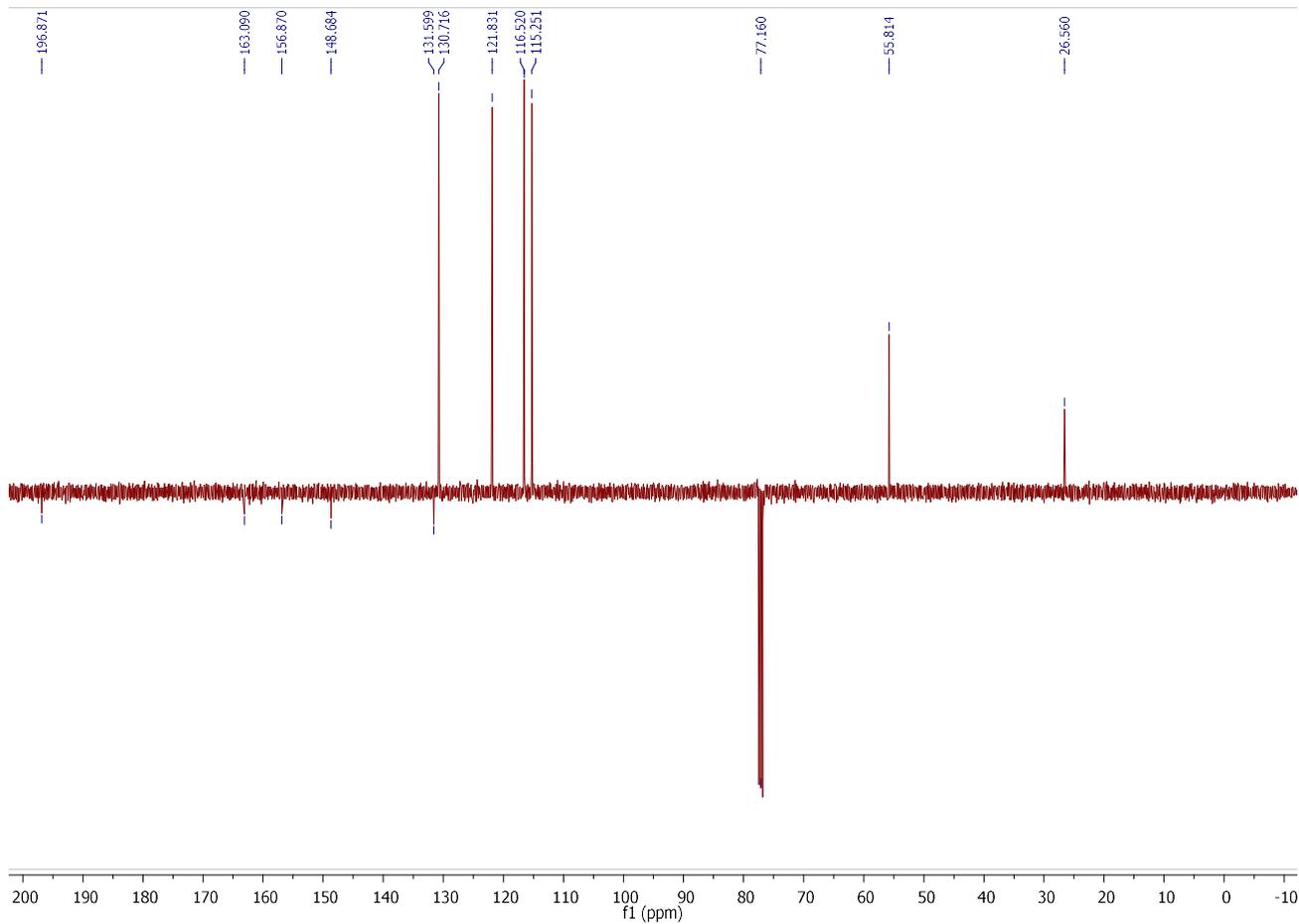
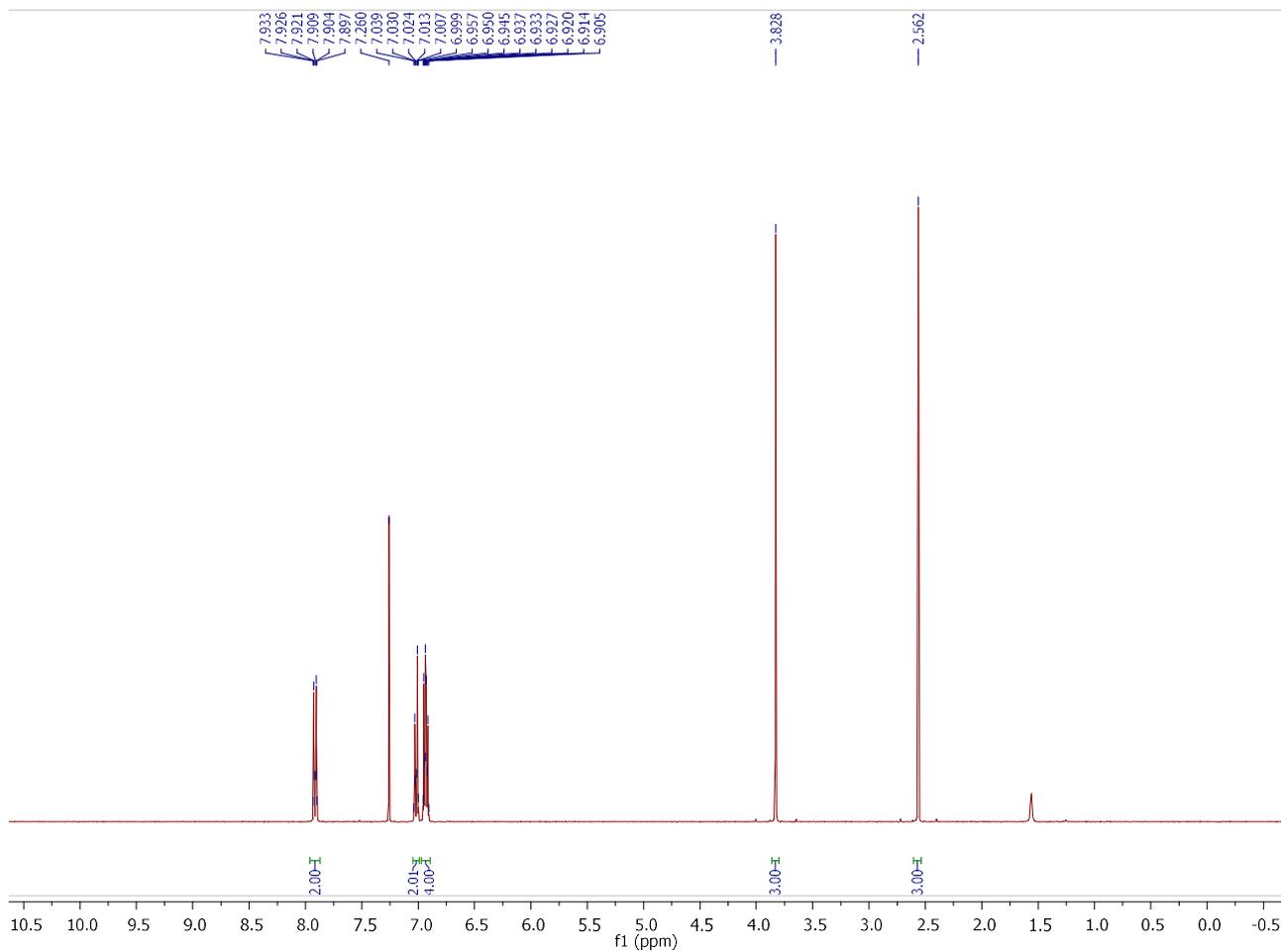




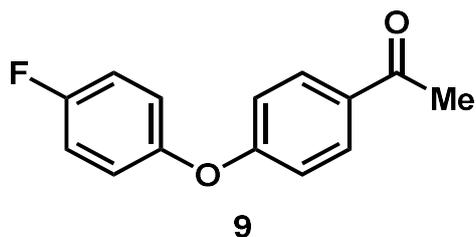
1-(4-(4-methoxyphenoxy)phenyl)ethan-1-one



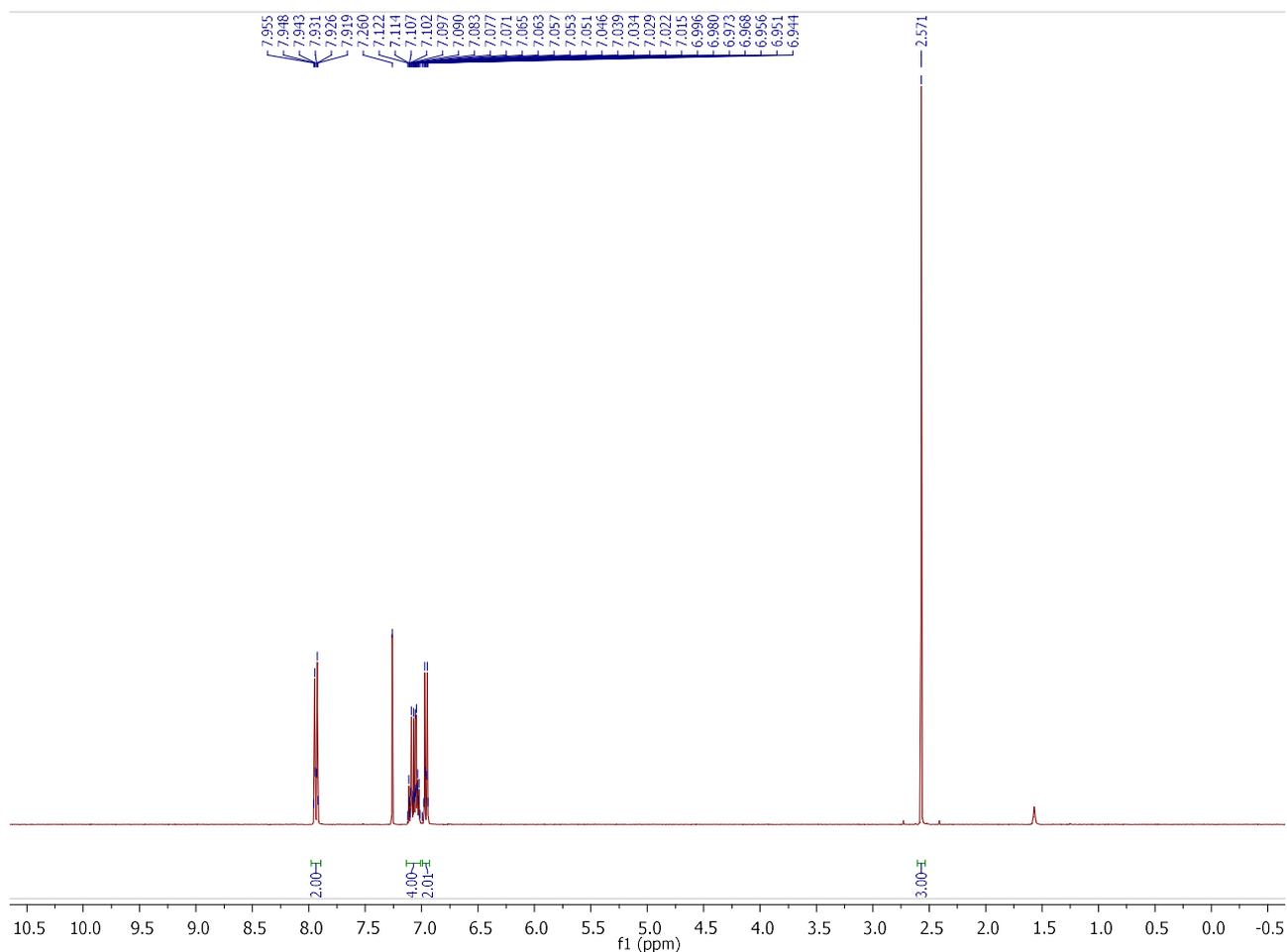
The title compound 1-(4-(4-methoxyphenoxy)phenyl)ethan-1-one (**8**) was prepared according to general procedure 3 using 4-methoxyphenol (54.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave an off-white solid (81 mg, 84%). mp 48-51 °C (Lit. 58-59 °C)⁷; R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3003, 2957, 1670, 1597, 1503, 1350, 1194, 1161, 1103, 1030, 841, 827, 818, 594, 581, 511; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.56 (3H, s), 3.83 (3H, s), 6.89-6.97 (4H, s), 6.98-7.06 (2H, m), 7.88-7.95 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.6, 55.8, 115.3, 116.5, 121.8, 130.7, 131.6, 148.7, 156.9, 163.1, 196.9; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{15}\text{O}_3]^+$ ($\text{M}+\text{H}$)⁺ : m/z 243.1016, found 243.1018, (+0.9 ppm).

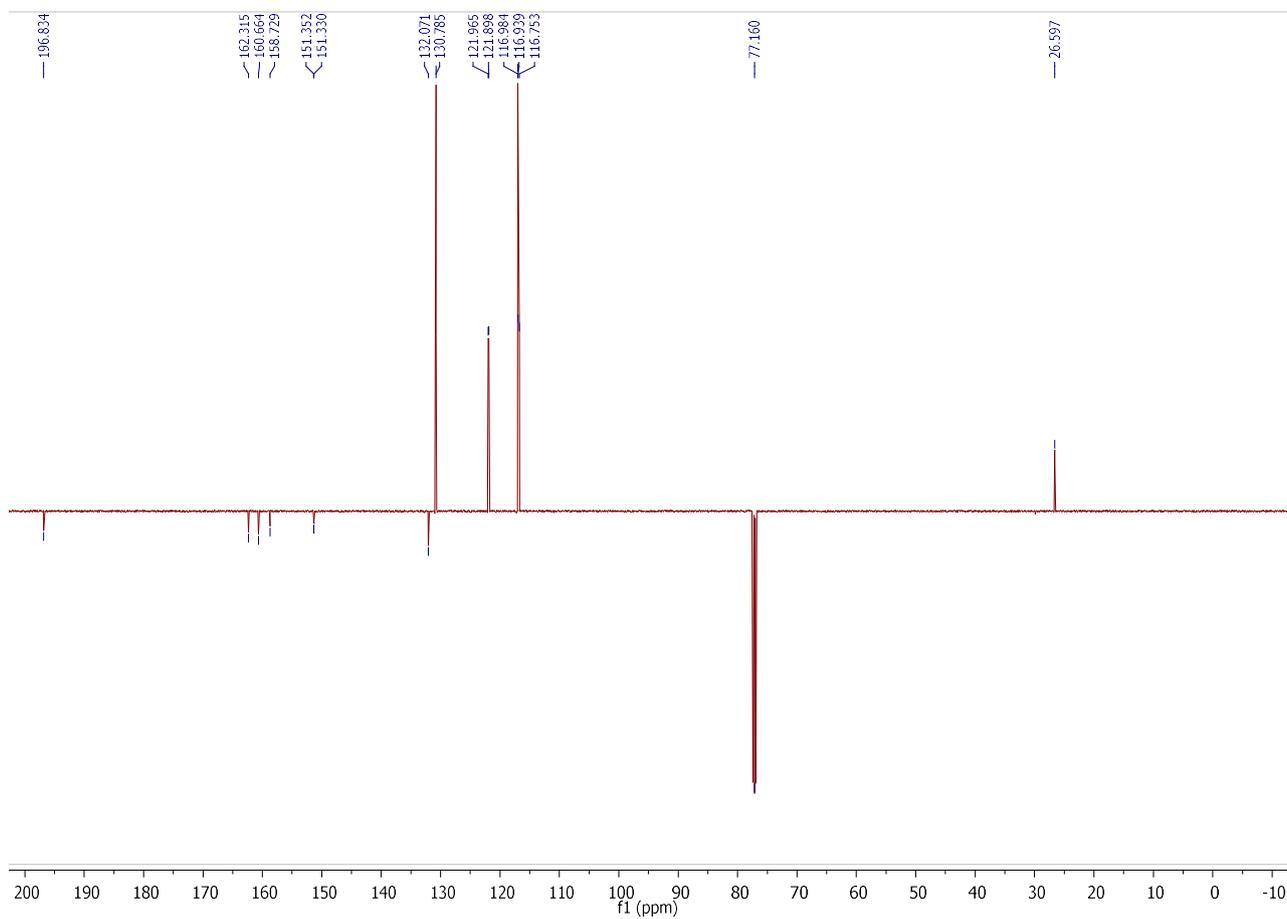
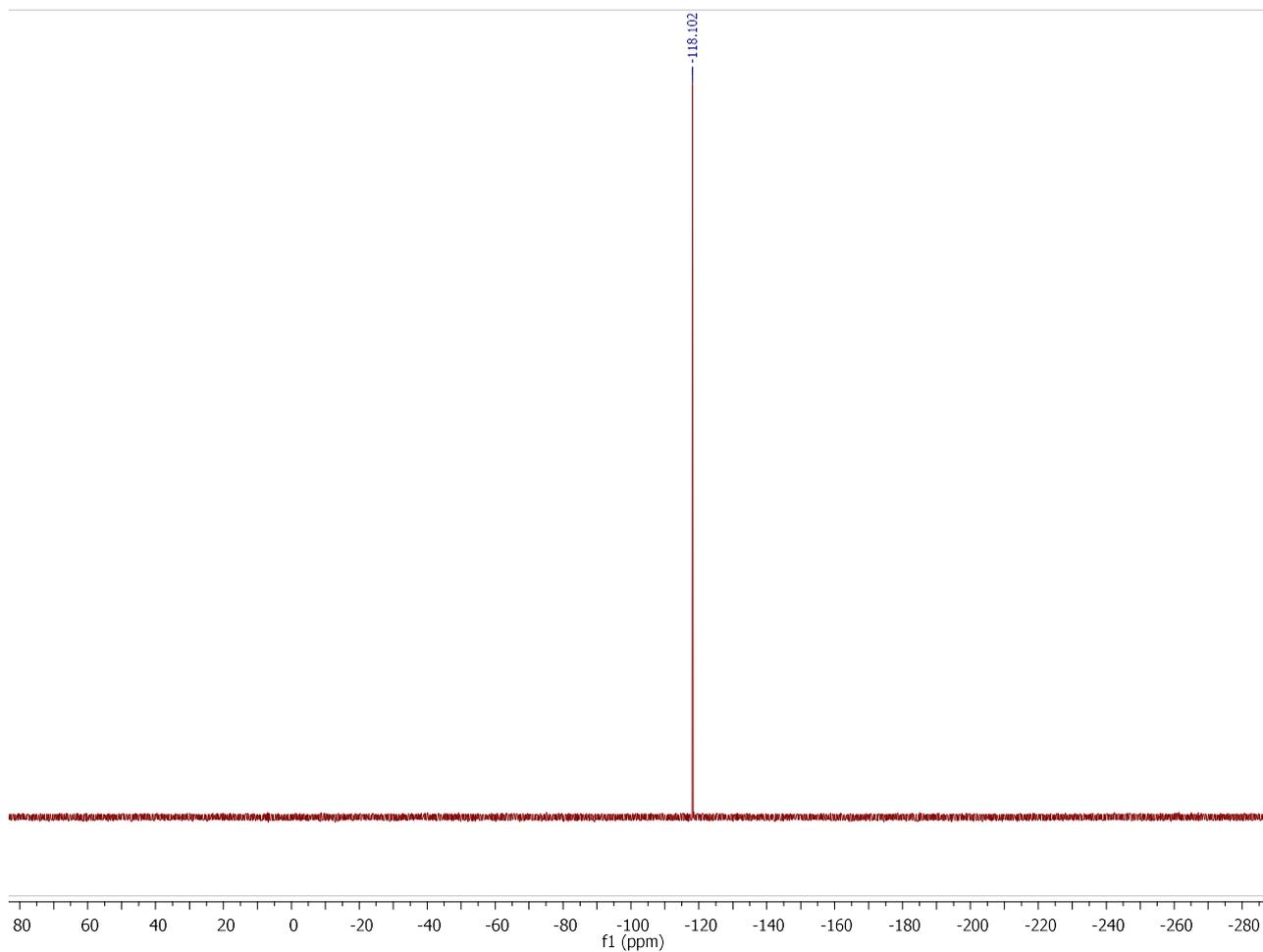


1-(4-(fluorophenoxy)phenyl)ethan-1-one

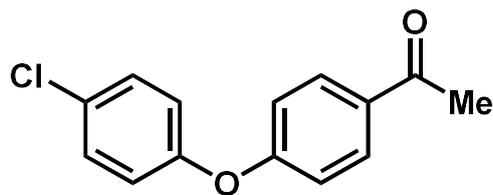


The title compound 1-(4-(fluorophenoxy)phenyl)ethan-1-one (**9**) was prepared according to general procedure 3 using 4-fluorophenol (49.3 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave a white solid (71 mg, 78%). mp 56-59 °C (Lit. 67-69 °C)⁷, R_f = 0.43 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 1664, 1603, 1591, 1576, 1495, 1416, 1354, 1248, 1215, 1188, 1163, 954, 880, 843, 812, 586, 546, 496; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.57 (3H, s), 6.93-7.00 (2H, m), 7.00-7.13 (4H, m), 7.90-7.97 (2H, m); $^{19}\text{F NMR}$ (376 MHz, CDCl_3) δ_{F} : -118.1; $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 26.6, 116.9 (d, J 23.4), 117.0, 121.9 (d, J 8.4), 130.8, 132.1, 151.3 (d, J 2.8), 159.8 (d, J 244.0), 162.3, 196.8; HRMS (NSI^+) calculated for $[\text{C}_{14}\text{H}_{12}\text{O}_2\text{F}]^+$ ($\text{M}+\text{H}$)⁺ : m/z 231.0816, found 231.0817, (+0.5 ppm).



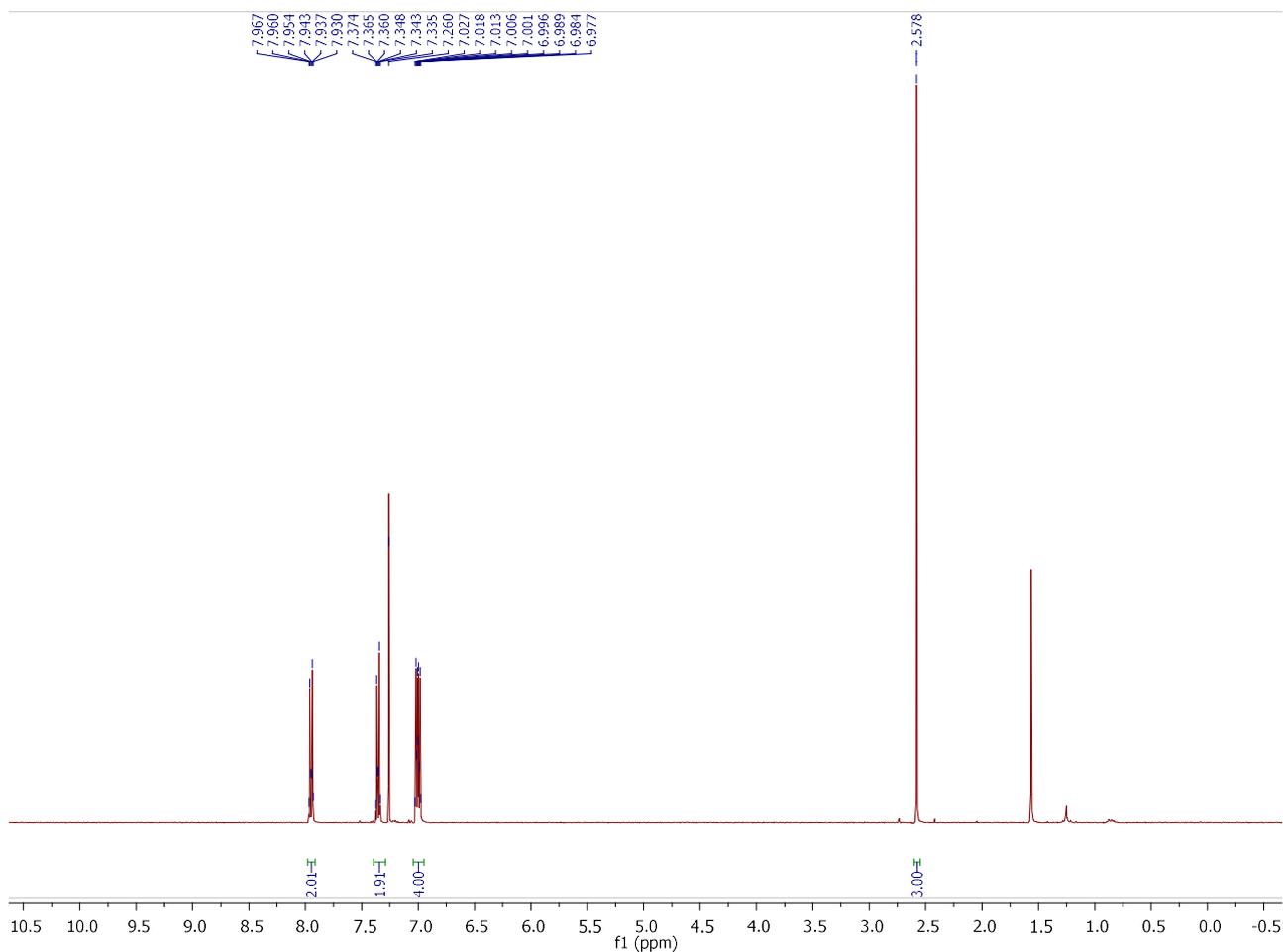


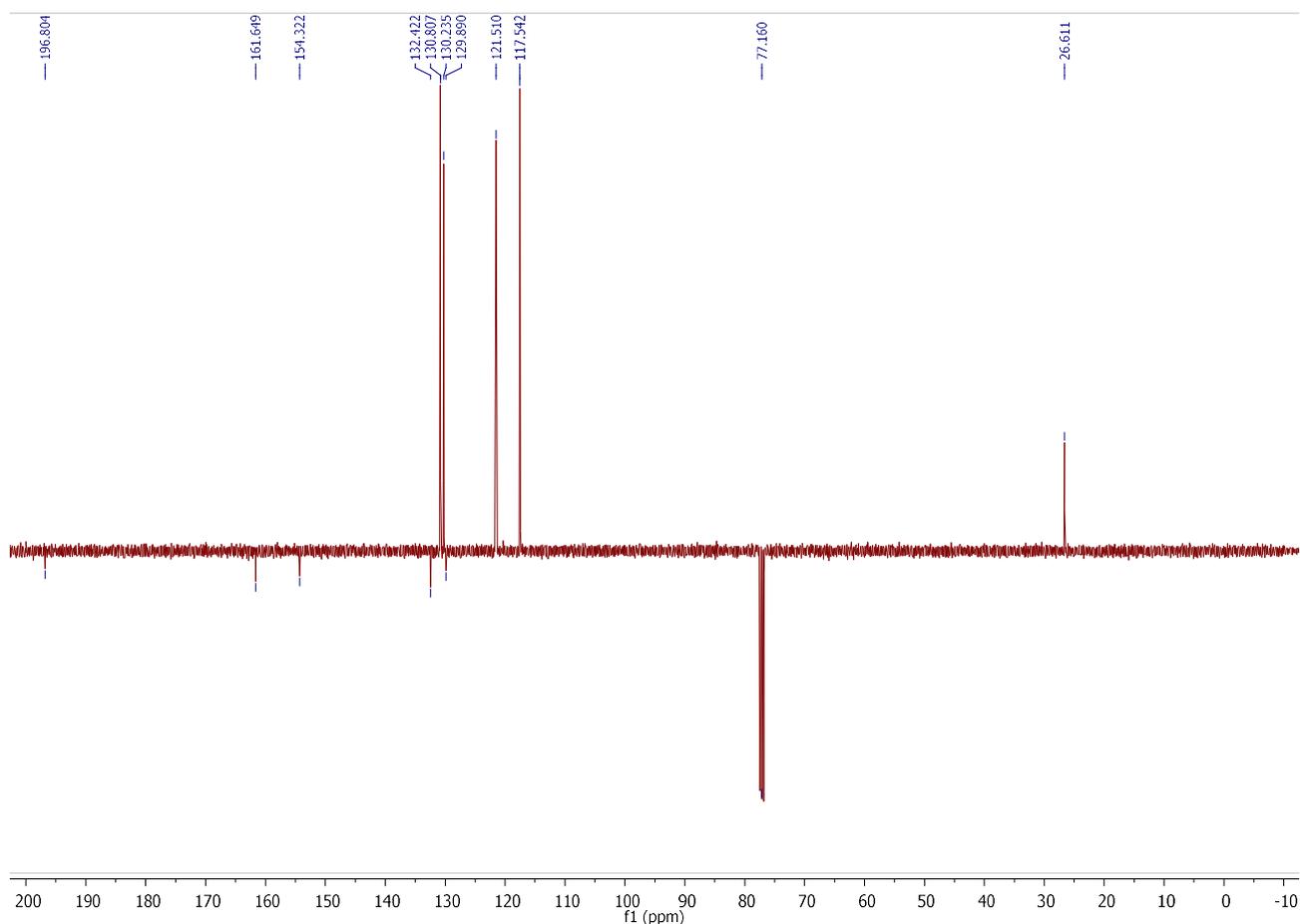
1-(4-(chlorophenoxy)phenyl)ethan-1-one



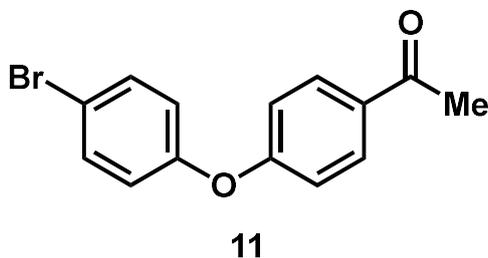
10

The title compound 1-(4-(chlorophenoxy)phenyl)ethan-1-one (**10**) was prepared according to general procedure 3 using 4-chlorophenol (56.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave an off-white solid (69 mg, 70%). mp 58-61 °C (Lit. 63-64 °C)⁷; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 2957, 2924, 2851, 1672, 1601, 1584, 1481, 1356, 1246, 1167, 1082, 1009, 961, 843, 820, 588, 577, 515, 486; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.58 (3H, s), 6.96-7.04 (4H, m), 7.32-7.39 (2H, m), 7.91-7.98 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.6, 117.5, 121.5, 129.9, 130.2, 130.8, 132.4, 154.3, 161.4, 196.8; HRMS (NSI⁺) calculated for $[\text{C}_{14}\text{H}_{12}\text{O}_2\text{Cl}]^+$ (M+H)⁺ : m/z 247.0520, found 247.0522, (+0.7 ppm).

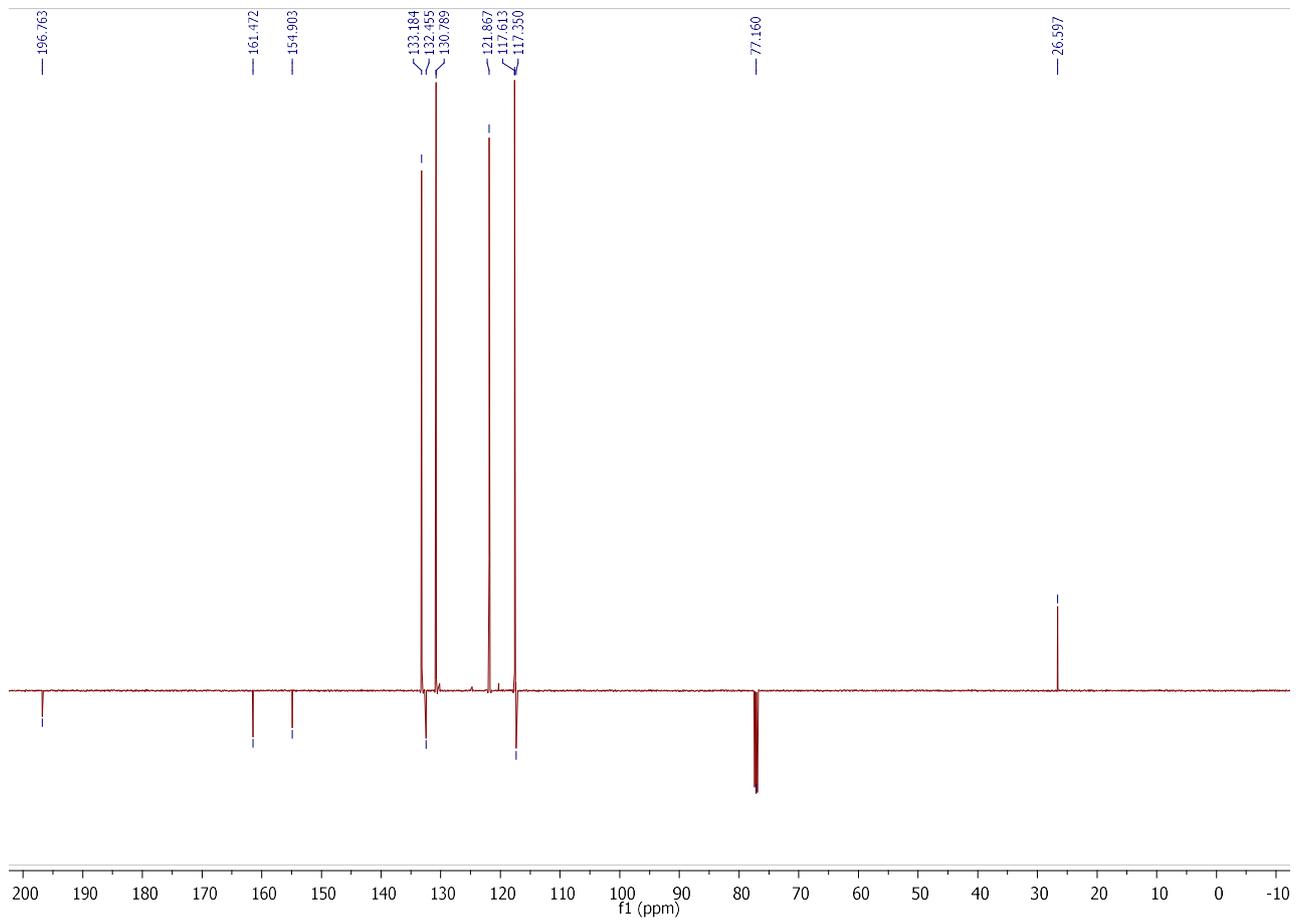
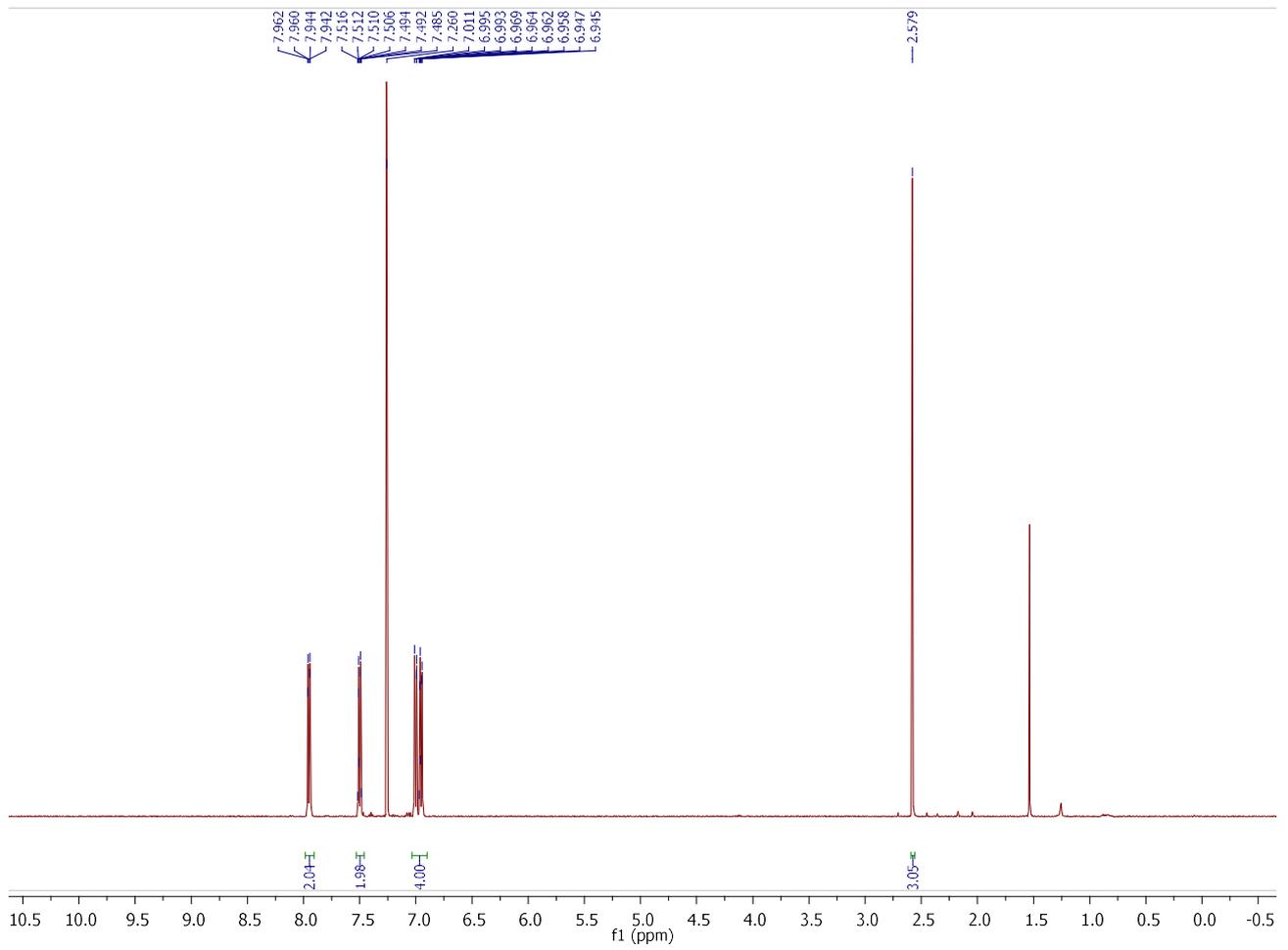




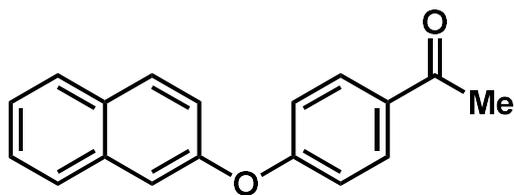
1-(4-(4-bromophenoxy)phenyl)ethan-1-one



The title compound 1-(4-(4-bromophenoxy)phenyl)ethan-1-one (**11**) was prepared according to general procedure 3 using 4-bromophenol (76.1 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave a white solid (84 mg, 72%). mp 66-69 °C (Lit. 74-75 °C)⁷; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 1670, 1597, 1580, 1479, 1354, 1163, 1069, 1007, 843, 826, 816, 594, 578, 501, 486; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.58 (3H, s), 6.92-7.03 (4H, m), 7.47-7.53 (2H, m), 7.92-7.98 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 26.6, 117.4, 117.6, 121.9, 130.8, 132.5, 133.2, 154.9, 161.5, 196.8; HRMS (ASAP⁺) calculated for $[\text{C}_{14}\text{H}_{12}\text{O}_2\text{Br}]^+$ (M+H)⁺ m/z : 291.0021, found 291.0025, (+1.4 ppm).

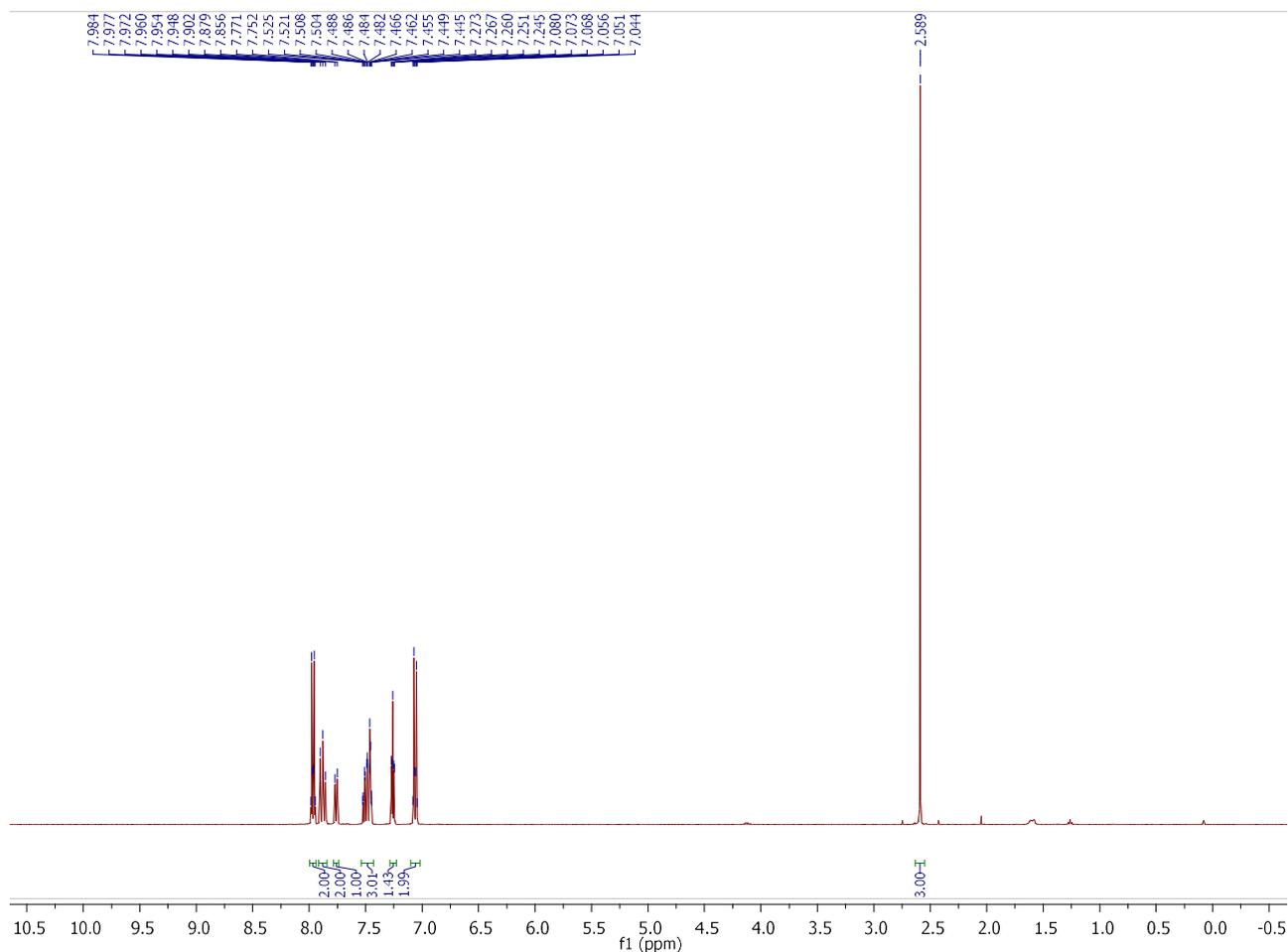


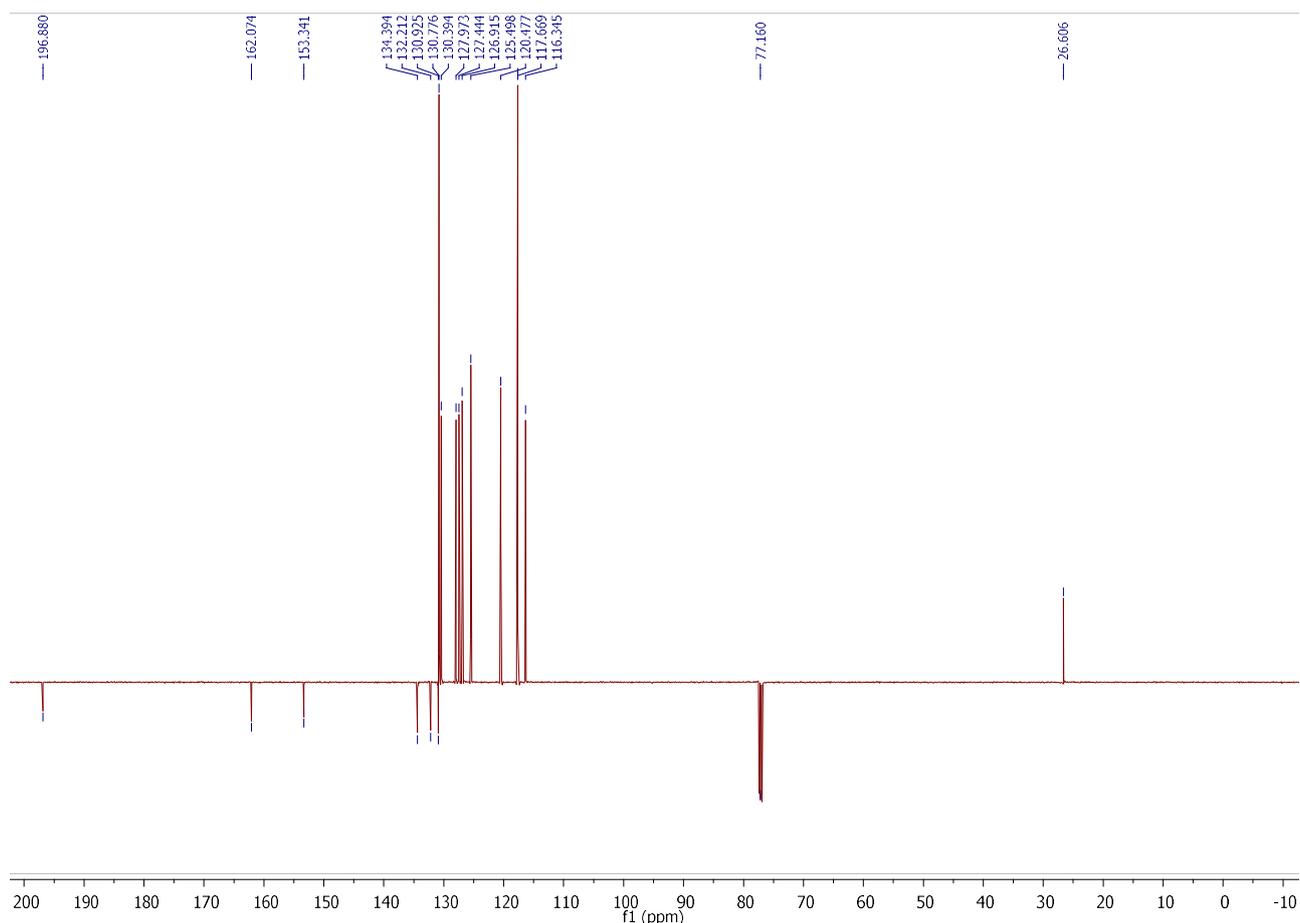
1-(4-(naphthalen-2-yloxy)phenyl)ethan-1-one



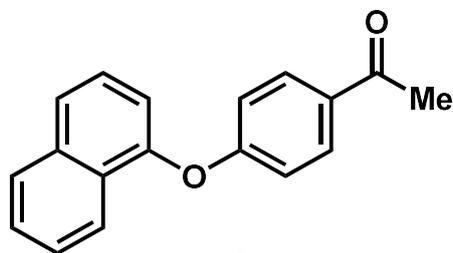
12

The title compound 1-(4-(naphthalen-2-yloxy)phenyl)ethan-1-one (**12**) was prepared according to general procedure 3 using 2-naphthol (63.4 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave an off-white solid (76 mg, 72%). mp 62-65 °C (Lit. 68-72 °C)⁸; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3055, 1676, 1593, 1570, 1501, 1354, 1261, 1229, 1163, 1013, 959, 833, 797, 772, 583; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.59 (3H, s), 7.03-7.09 (2H, m), 7.23-7.28 (1H, m), 7.43-7.54 (3H, m), 7.73-7.79 (1H, m), 7.83-7.92 (2H, m), 7.93-8.00 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 26.6, 116.3, 117.7, 120.5, 125.5, 126.9, 127.4, 128.0, 130.4, 130.8, 130.9, 132.2, 134.4, 153.3, 162.1, 196.9; HRMS (NSI⁺) calculated for $[\text{C}_{18}\text{H}_{15}\text{O}_2]^+$ (M+H)⁺: m/z 263.1067, found 263.1069, (+0.9 ppm).



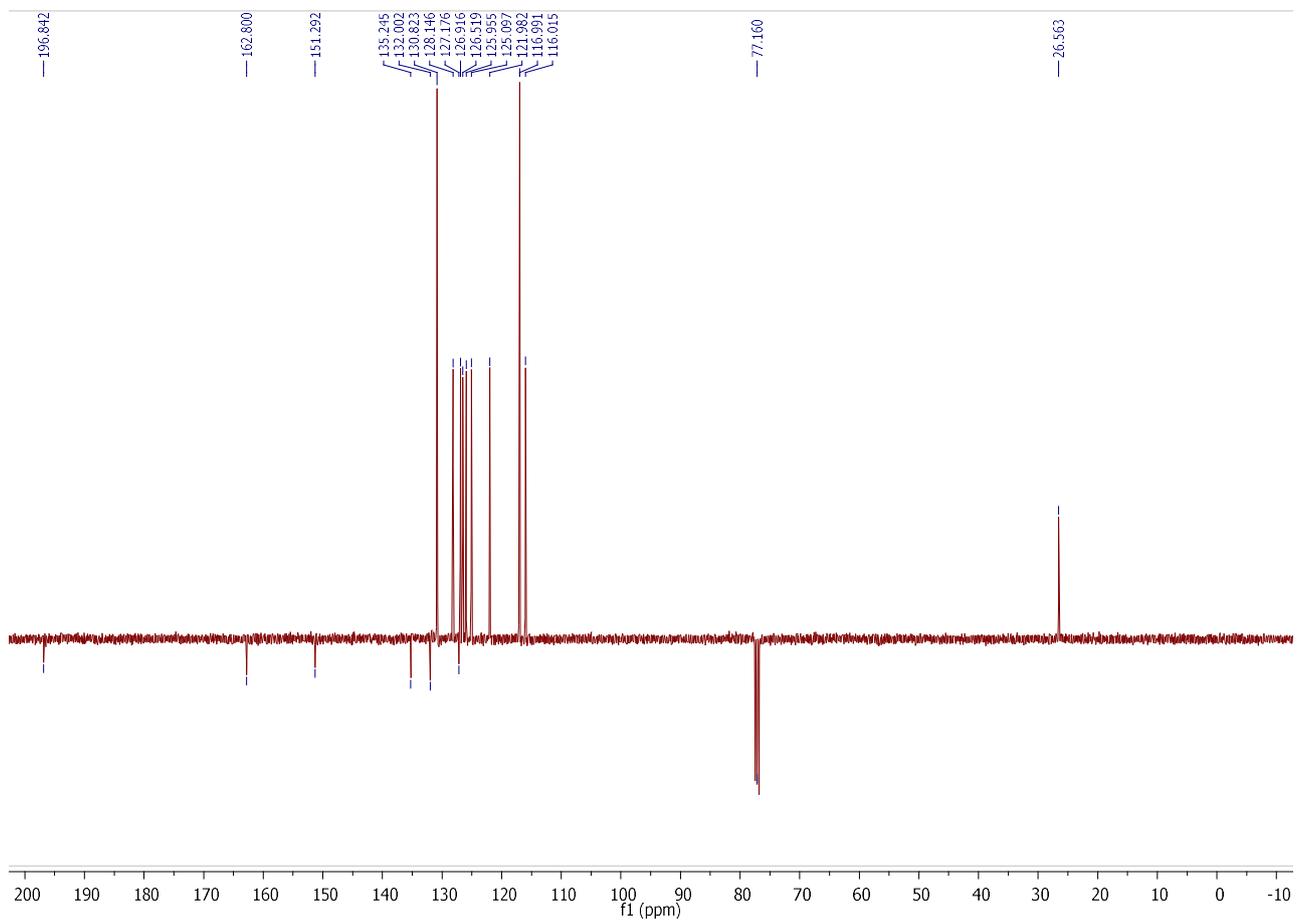
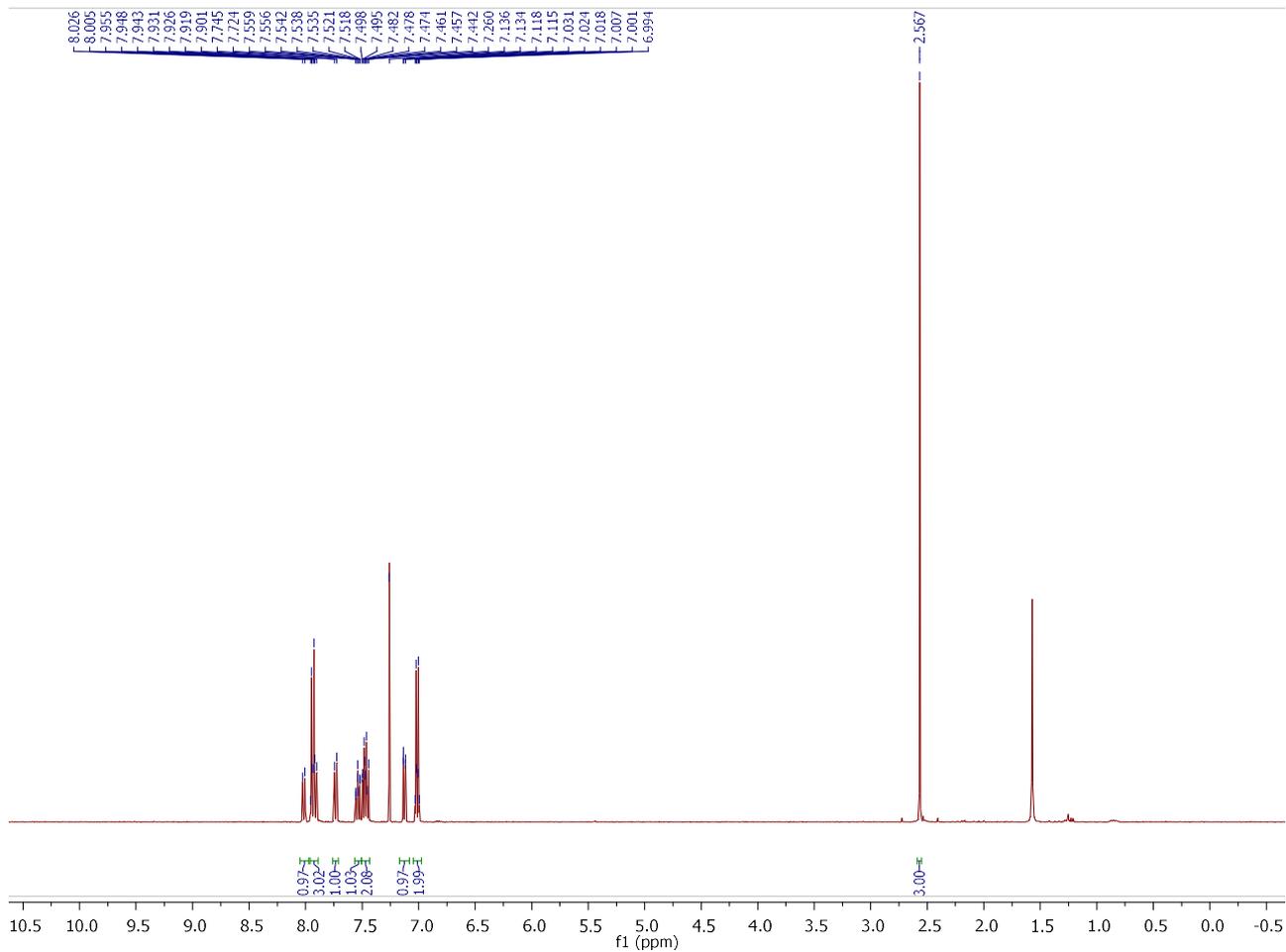


1-(4-(naphthalen-1-yloxy)phenyl)ethan-1-one

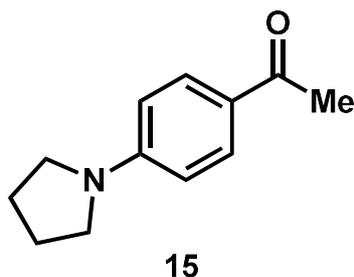


13

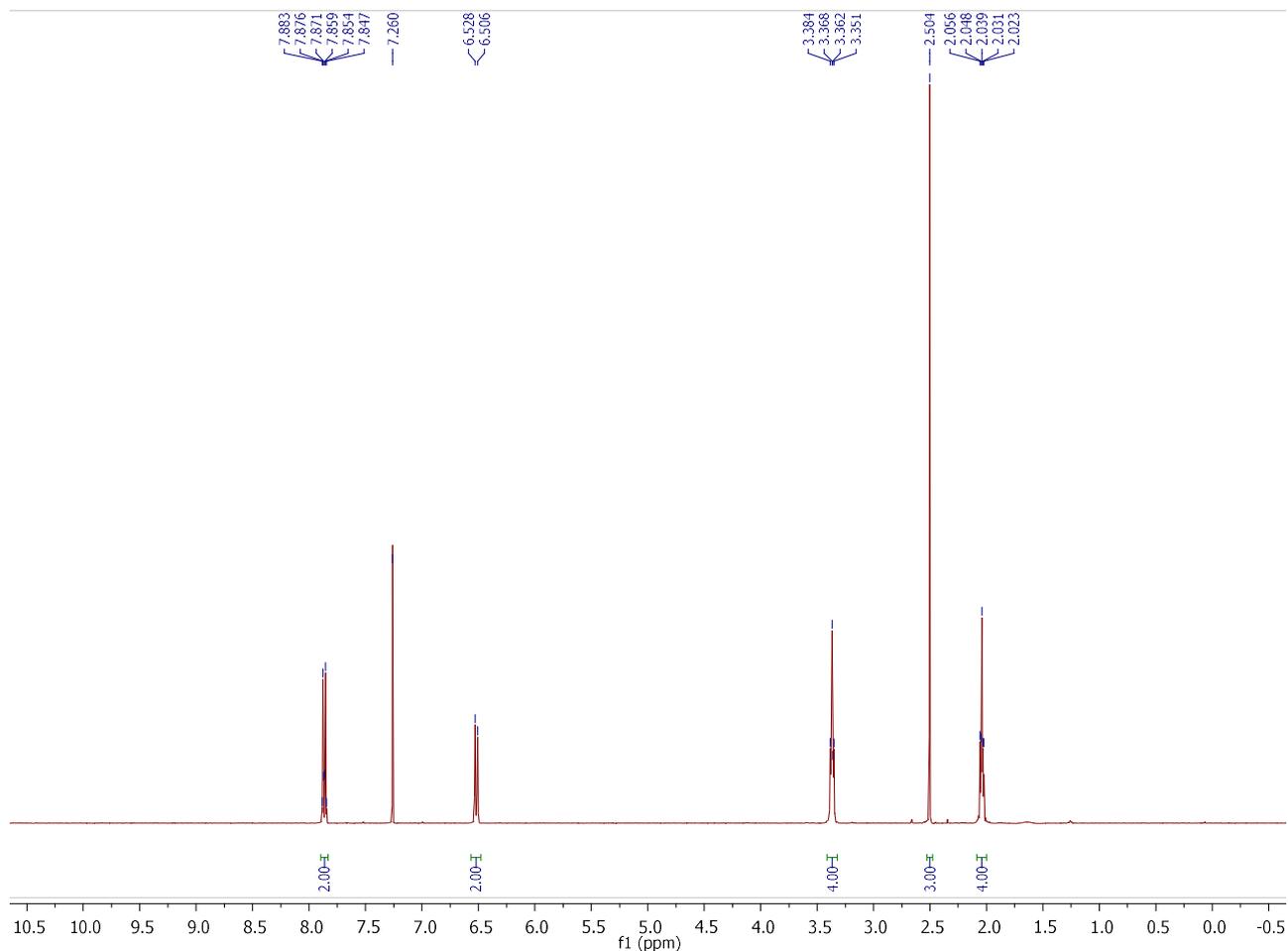
The title compound 1-(4-(naphthalen-1-yloxy)phenyl)ethan-1-one (**13**) was prepared according to general procedure 3 using 1-naphthol (63.4 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 50% CH₂Cl₂ in hexanes, 30 x 150 mm silica) gave a brown oil (29.0 mg, 27%). *R_f* = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 2990, 1676, 1589, 1503, 1416, 1248, 953, 866, 831, 762, 583, 478; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.57 (3H, s), 6.97-7.05 (2H, m), 7.10-7.15 (1H, m), 7.43-7.51 (2H, m), 7.51-7.57 (1H, m), 7.74 (1H, d, *J* 8.4), 7.88-7.97 (3H, m), 8.01 (1H, d, *J* 8.4); ¹³C NMR (101 MHz, CDCl₃) δ_{C} : 26.6, 116.0, 117.0, 122.0, 125.1, 126.0, 126.5, 127.0, 127.2, 128.1, 130.8, 132.0, 135.2, 151.3, 162.8, 196.8; HRMS (NSI⁺) calculated for [C₁₈H₁₅O₂]⁺ (M+H)⁺: *m/z* 263.1067, found 263.1068, (+0.9 ppm).

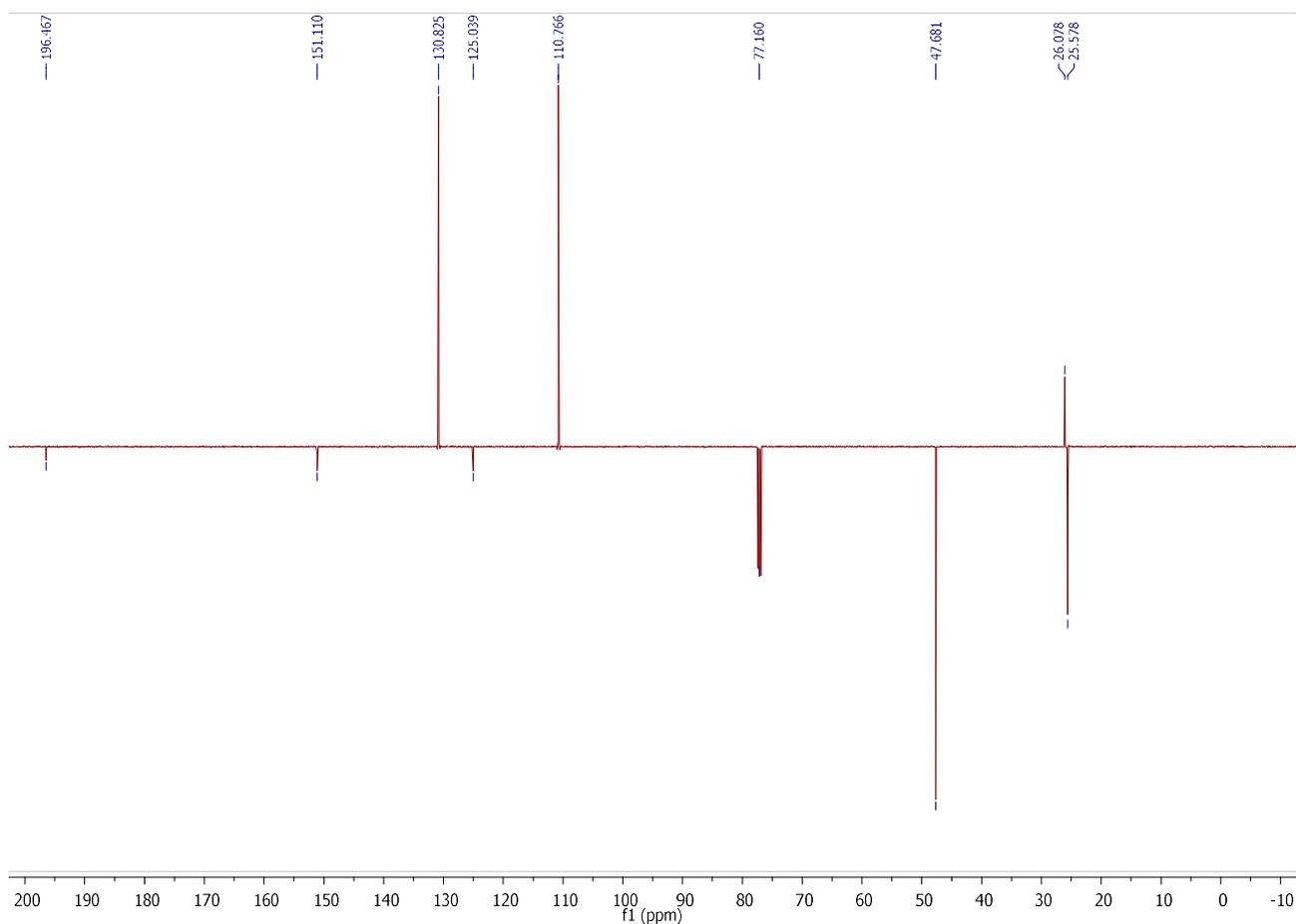


1-(4-(pyrrolidin-1-yl)phenyl)ethan-1-one

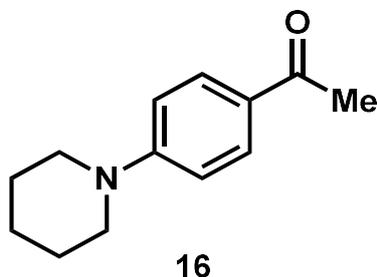


The title compound 1-(4-(pyrrolidin-1-yl)phenyl)ethan-1-one (**15**) was prepared according to general procedure 3 using pyrrolidine (37.0 μ L, 31.3 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 110 mm silica) gave a yellow solid (53 mg, 70%). mp 114-118 $^{\circ}$ C (Lit. 126-127 $^{\circ}$ C)⁹; R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 2970, 2912, 2851, 1651, 1587, 1526, 1393, 1348, 1277, 1184, 1157, 955, 820, 594; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 1.98-2.09 (4H, m), 2.51 (3H, m), 3.32-3.42 (4H, m), 6.48-6.56 (2H, m), 7.83-7.90 (2H, m); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} : 25.5, 26.0, 47.7, 110.8, 125.0, 130.8, 151.1, 196.5; HRMS (NSI⁺) calculated for $[\text{C}_{12}\text{H}_{16}\text{ON}]^+$ (M+H)⁺ : m/z 190.1226, found 190.1225, (-0.7 ppm).

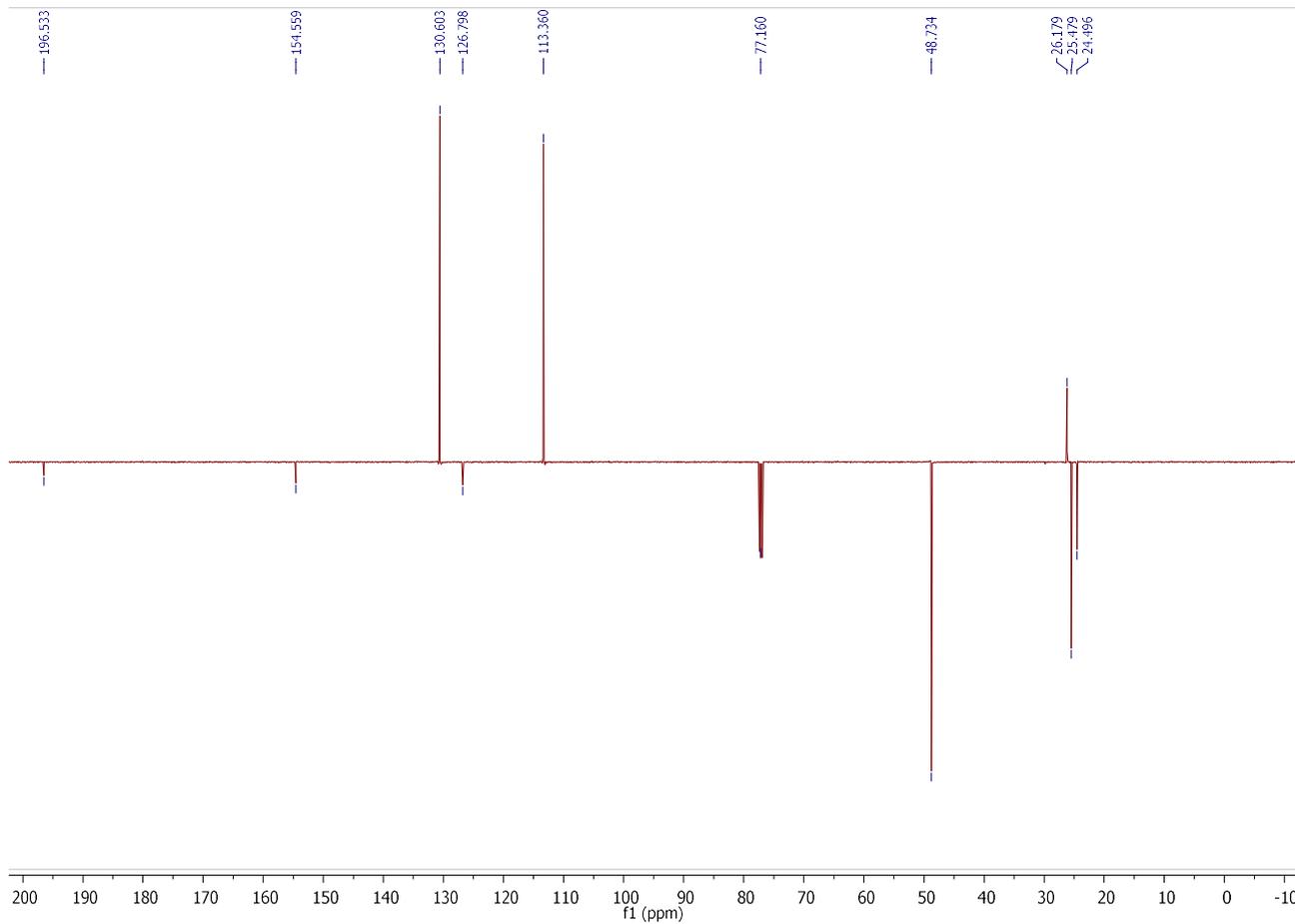
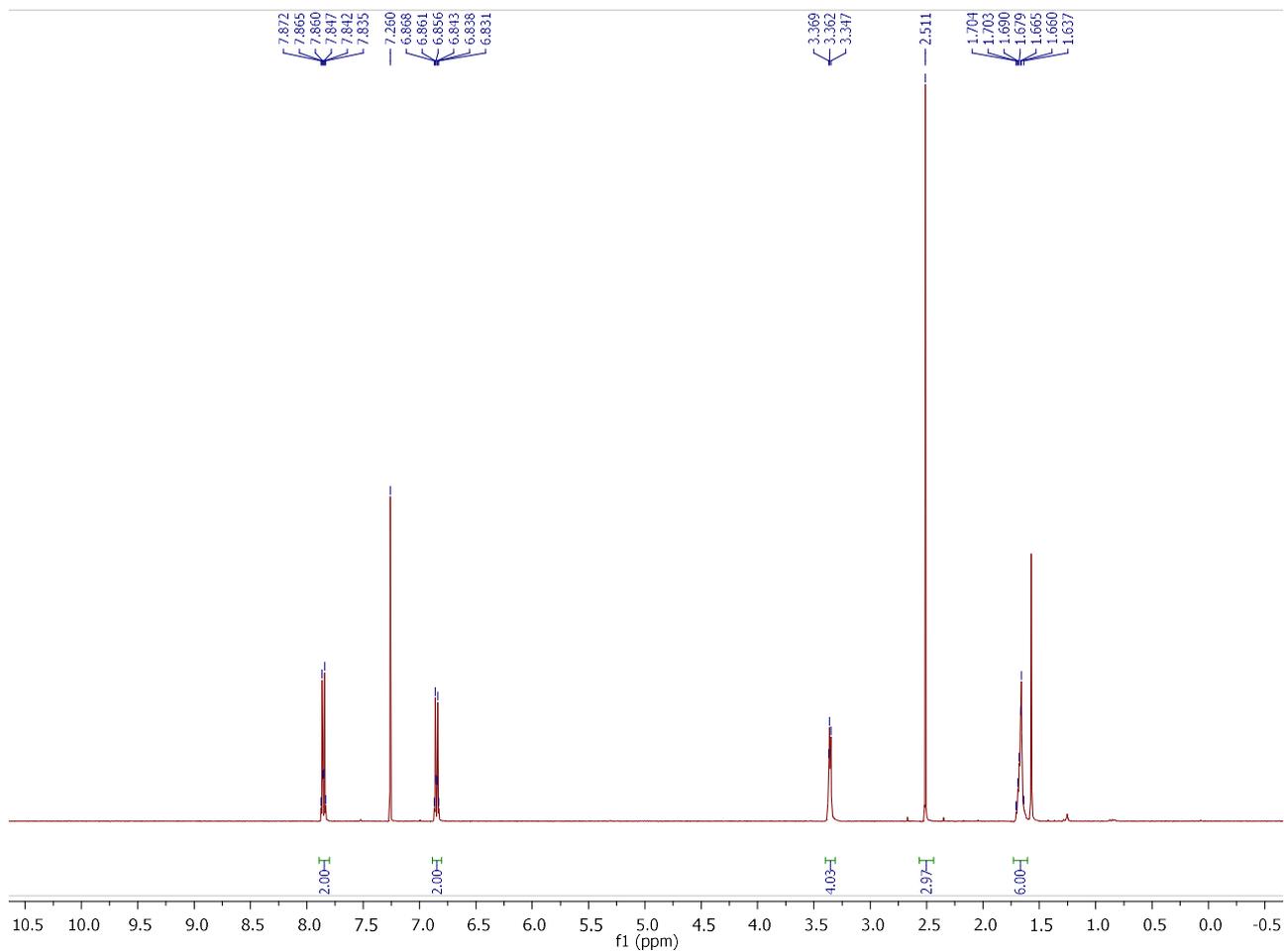




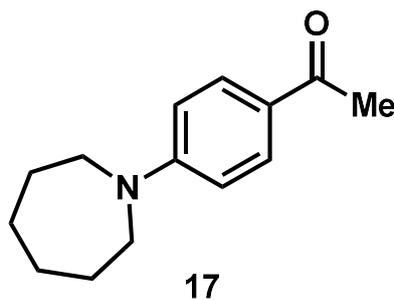
1-(4-(piperidin-1-yl)phenyl)ethan-1-one



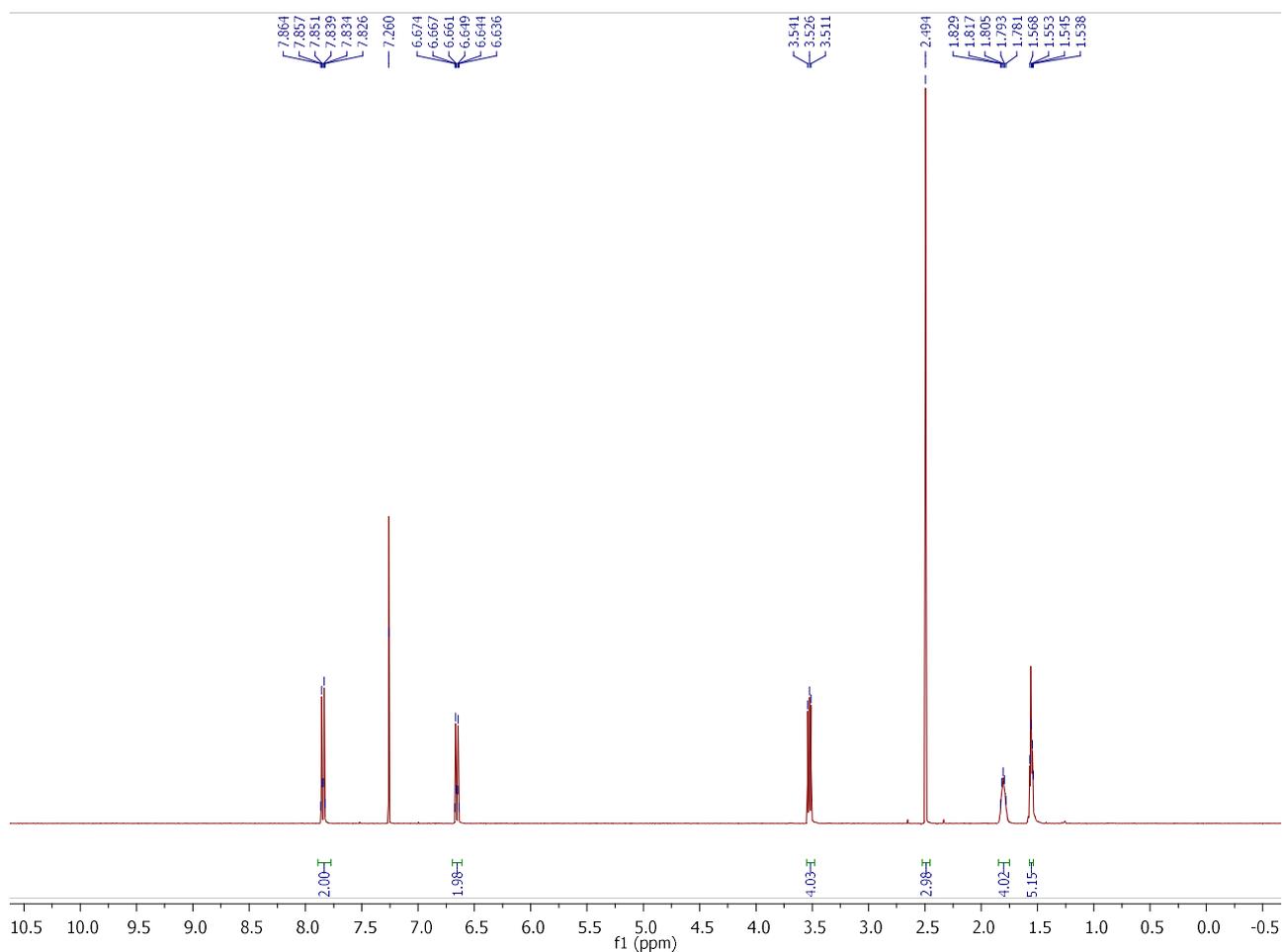
The title compound 1-(4-(piperidin-1-yl)phenyl)ethan-1-one (**16**) was prepared according to general procedure 3 using piperidine (43.0 μ L, 37.5 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 110 mm silica) gave an off-white solid (68 mg, 83%). mp 74-78 $^{\circ}$ C (Lit. 86 $^{\circ}$ C)¹⁰; R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 2999, 2938, 2922, 2847, 1653, 1587, 1545, 1427, 1385, 1356, 1223, 1123, 912, 820, 582; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.60-1.73 (6H, m), 2.51 (3H, s), 3.31-3.40 (4H, m), 6.81-6.89 (2H, m), 7.81-7.89 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 24.5, 25.5, 26.2, 48.7, 113.4, 130.6, 126.8, 154.6, 196.5; HRMS (NSI^+) calculated for $[\text{C}_{13}\text{H}_{18}\text{ON}]^+$ ($\text{M}+\text{H}$) $^+$: m/z 204.1383, found 204.1383, (+0.0 ppm).



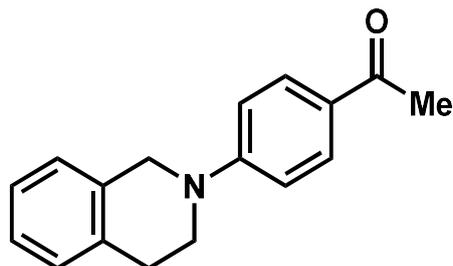
1-(4-(azepan-1-yl)phenyl)ethan-1-one



The title compound 1-(4-(azepan-1-yl)phenyl)ethan-1-one (**17**) was prepared according to general procedure 3 using hexamethyleneimine (50.0 μ L, 43.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 30 x 100 mm silica) gave a yellow solid (58 mg, 66%). mp 33-36 $^{\circ}$ C (Lit. 40-42 $^{\circ}$ C)¹¹; R_f = 0.38 (eluent = 20% EtOAc in hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.51-1.59 (4H, m), 1.74-1.86 (4H, m), 2.49 (3H, s), 3.53 (4H, t, J 6.0), 6.62-6.69 (2H, m), 7.81-7.88 (2H, m). Spectroscopic data in accordance with that stated in the literature.¹¹

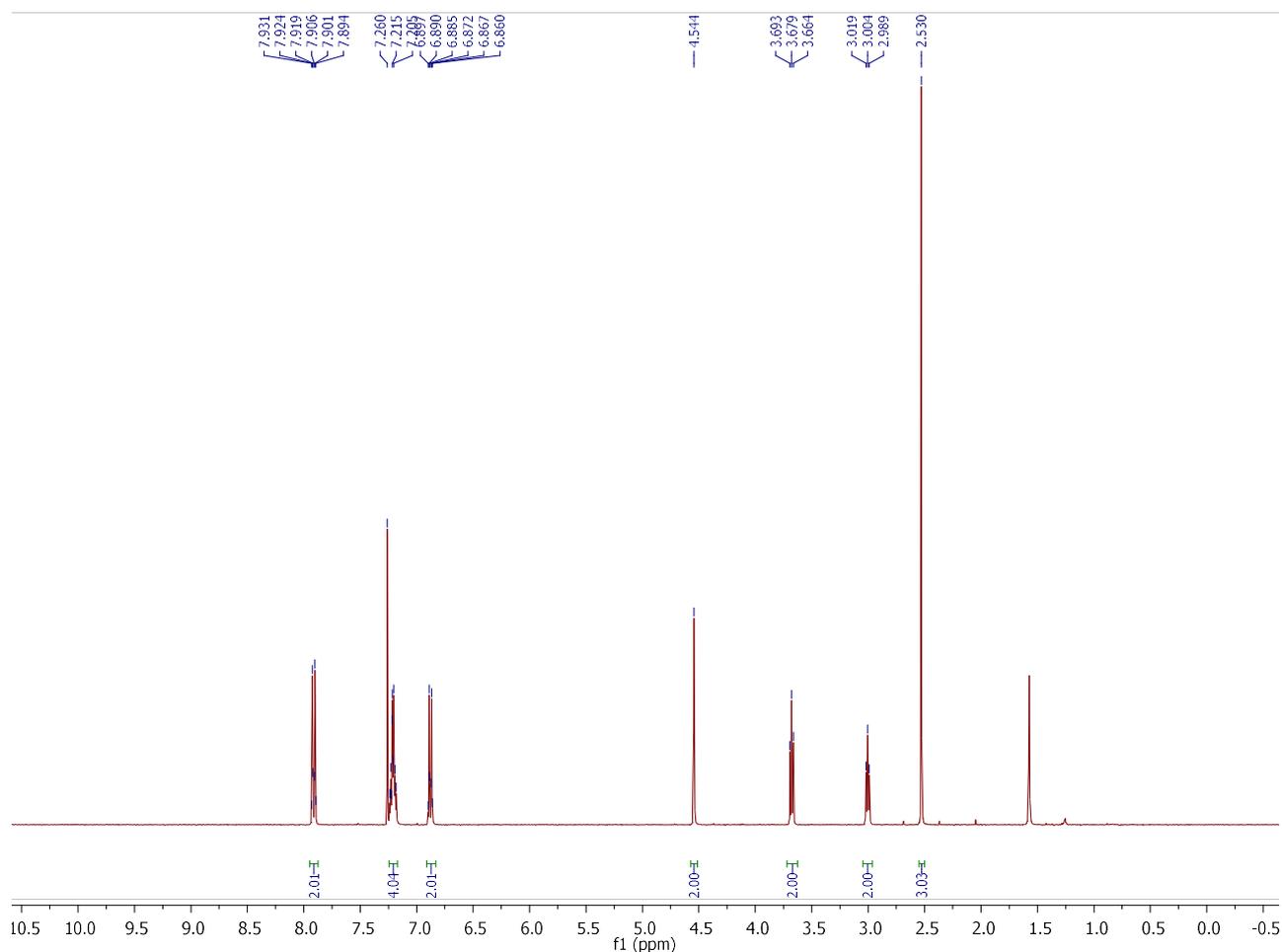


1-(4-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)ethan-1-one

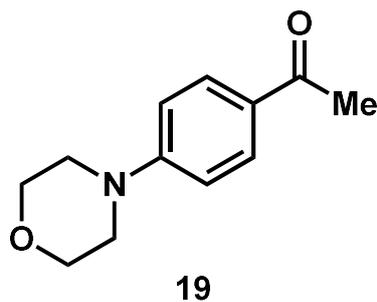


18

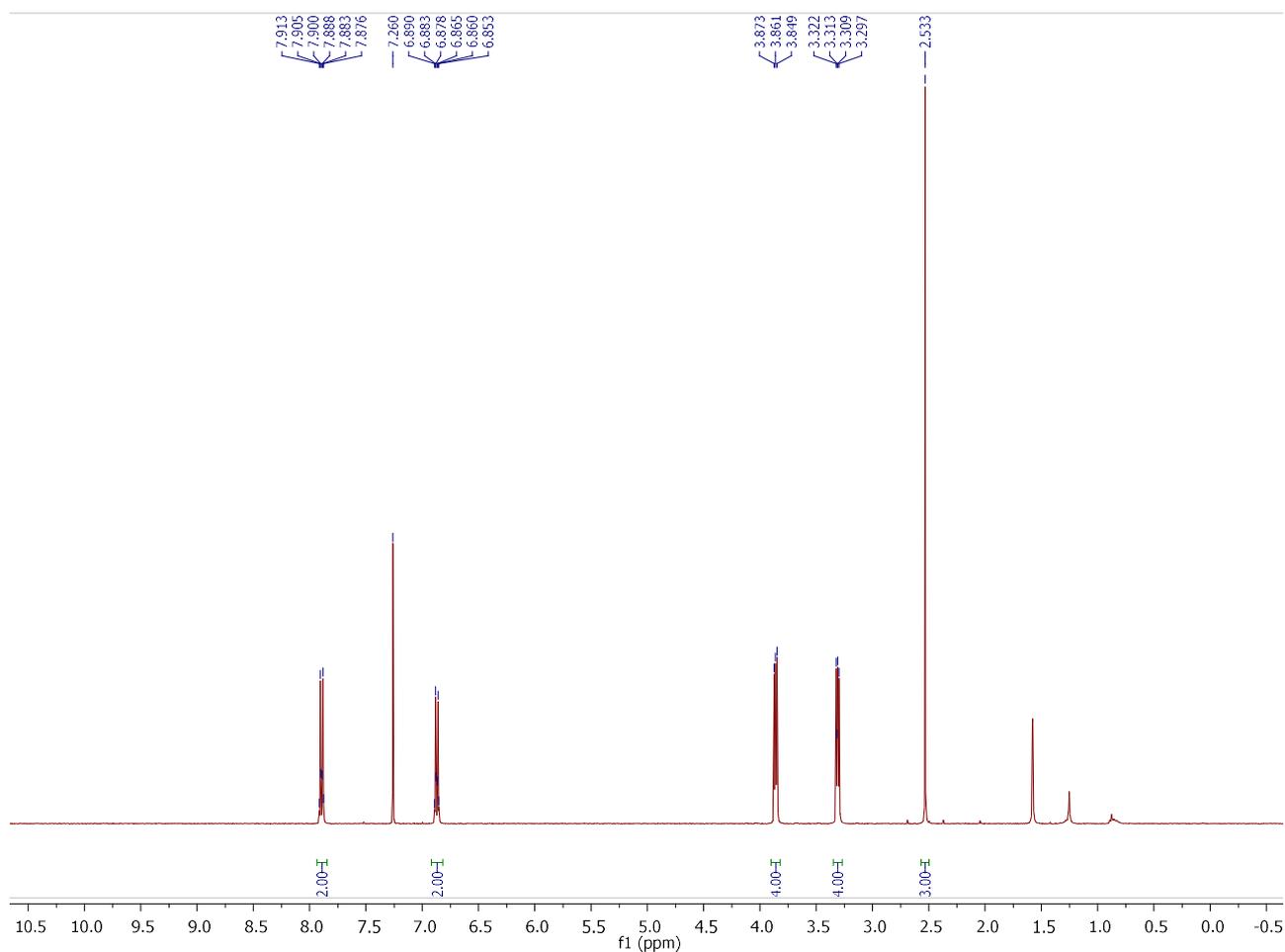
The title compound 1-(4-(3,4-dihydroisoquinolin-2(1H)-yl)phenyl)ethan-1-one (**18**) was prepared according to general procedure 3 using 1,2,3,4-tetrahydroisoquinoline (55.0 μ L, 58.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 120 mm silica) gave an off-white solid (69 mg, 68%). mp 89-92 $^{\circ}$ C (Lit. 105 $^{\circ}$ C)¹²; R_f = 0.33 (eluent = 20% EtOAc in hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.53 (3H, s), 3.00 (2H, t, J 6.0), 3.68 (2H, t, J 6.0), 4.54 (2H, s), 6.84-6.92 (2H, m), 7.16-7.25 (4H, m), 7.88-7.95 (2H, m). Spectroscopic data in accordance with that stated in the literature.¹²

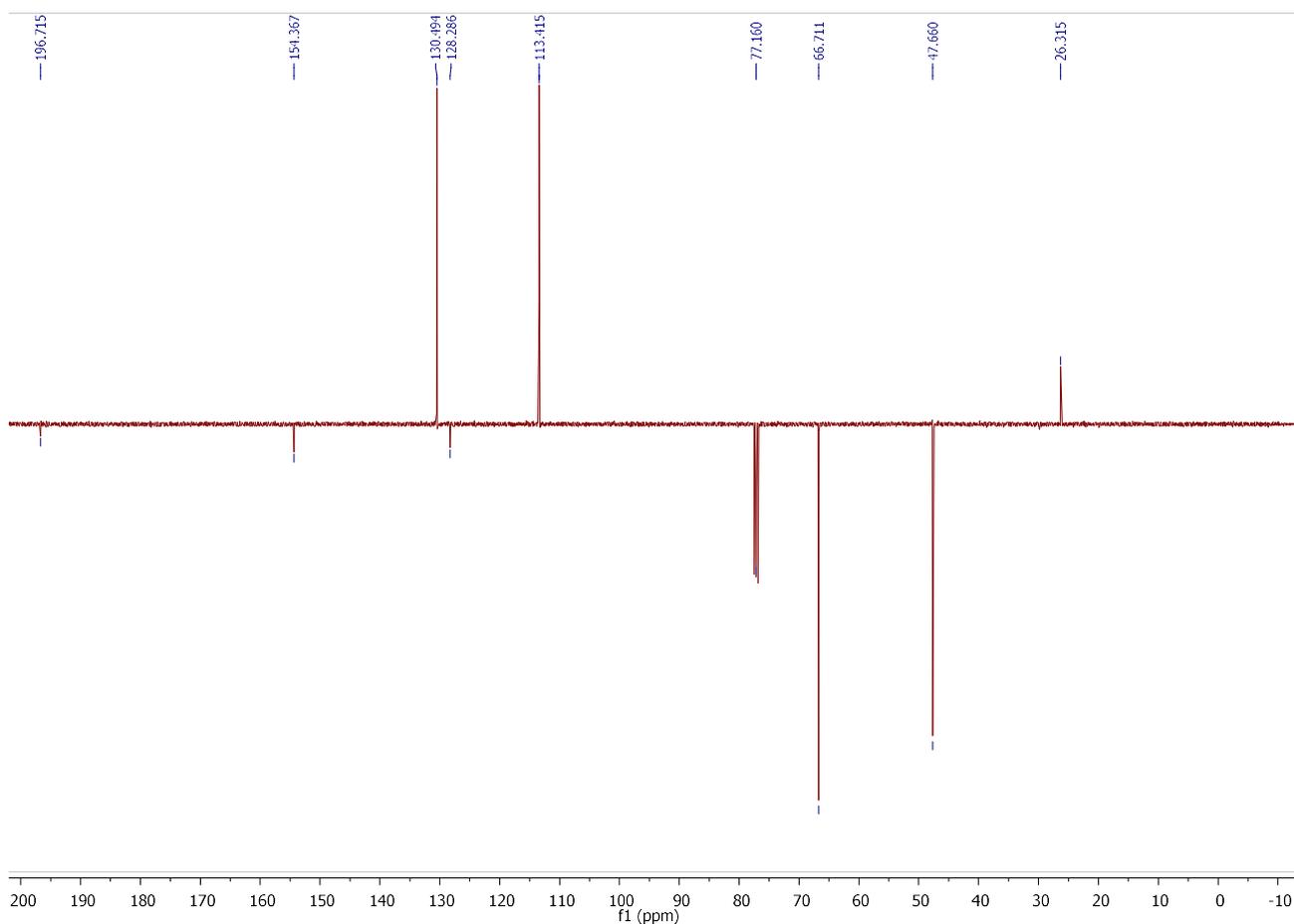


1-(4-morpholinophenyl)ethan-1-one

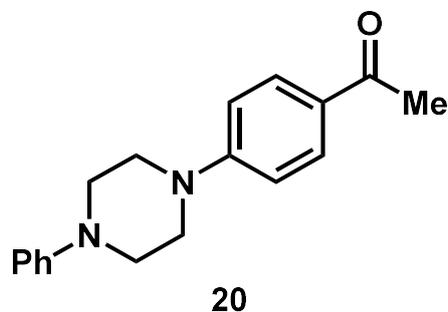


The title compound 1-(4-morpholinophenyl)ethan-1-one (**19**) was prepared according to general procedure 3 using morpholine (38.0 μ L, 38.3 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-20% EtOAc in hexanes, 30 x 120 mm silica) gave an off-white solid (67 mg, 82%). mp 83-86 $^{\circ}$ C (Lit. 97 $^{\circ}$ C)¹⁰; R_f = 0.13 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 2961, 2913, 2851, 1655, 1591, 1549, 1514, 1385, 1362, 1238, 1115, 930, 816, 602, 584; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.53 (3H, s), 3.26-3.35 (4H, m), 3.82-3.90 (4H, m), 6.83-6.91 (2H, m), 7.85-7.93 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.3, 47.7, 66.7, 113.4, 128.3, 130.5, 154.4, 196.7; HRMS (NSI^+) calculated for $[\text{C}_{12}\text{H}_{16}\text{O}_2\text{N}]^+$ ($\text{M}+\text{H}$) $^+$: m/z 206.1176, found 206.1176, (+0.2 ppm).

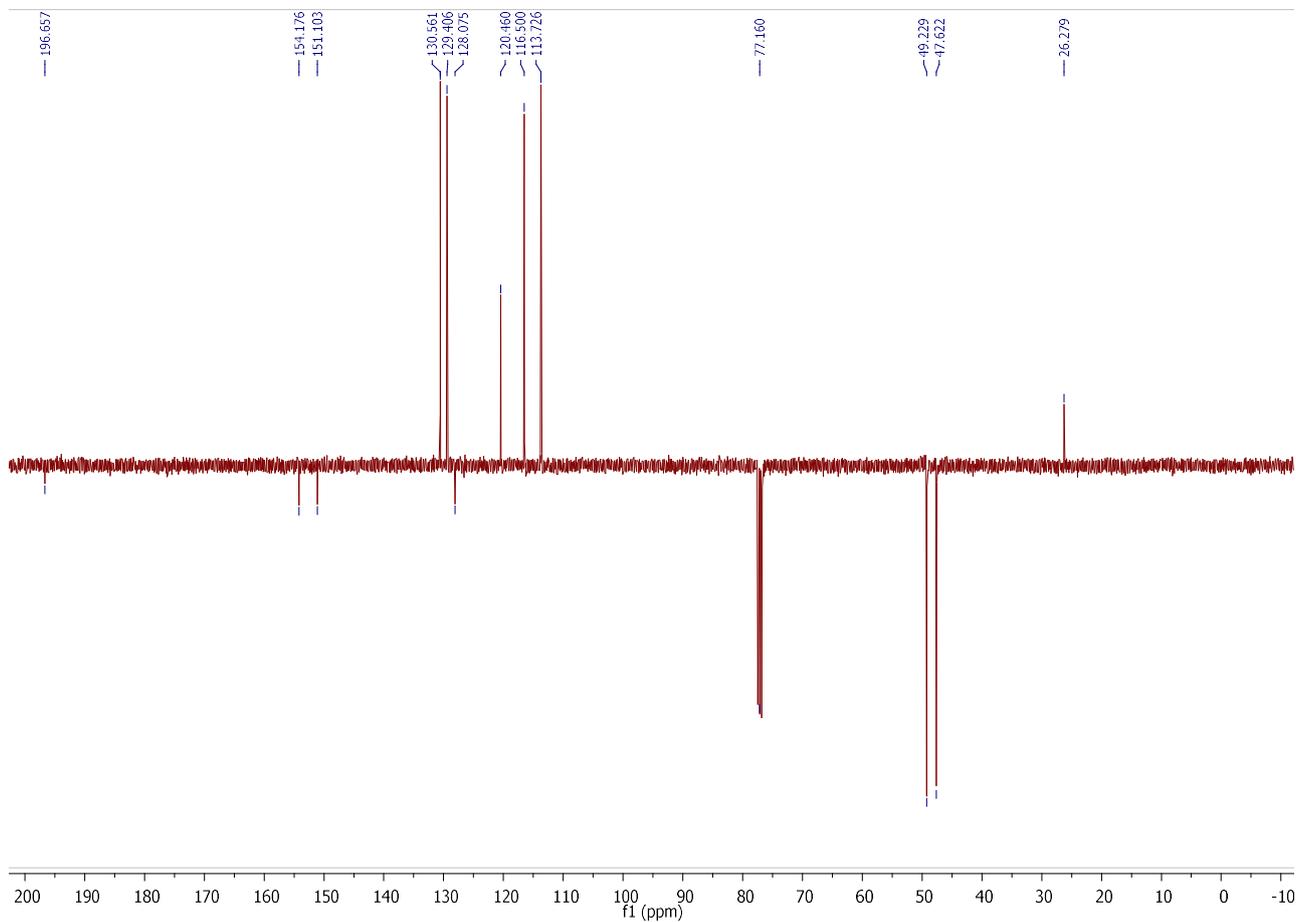
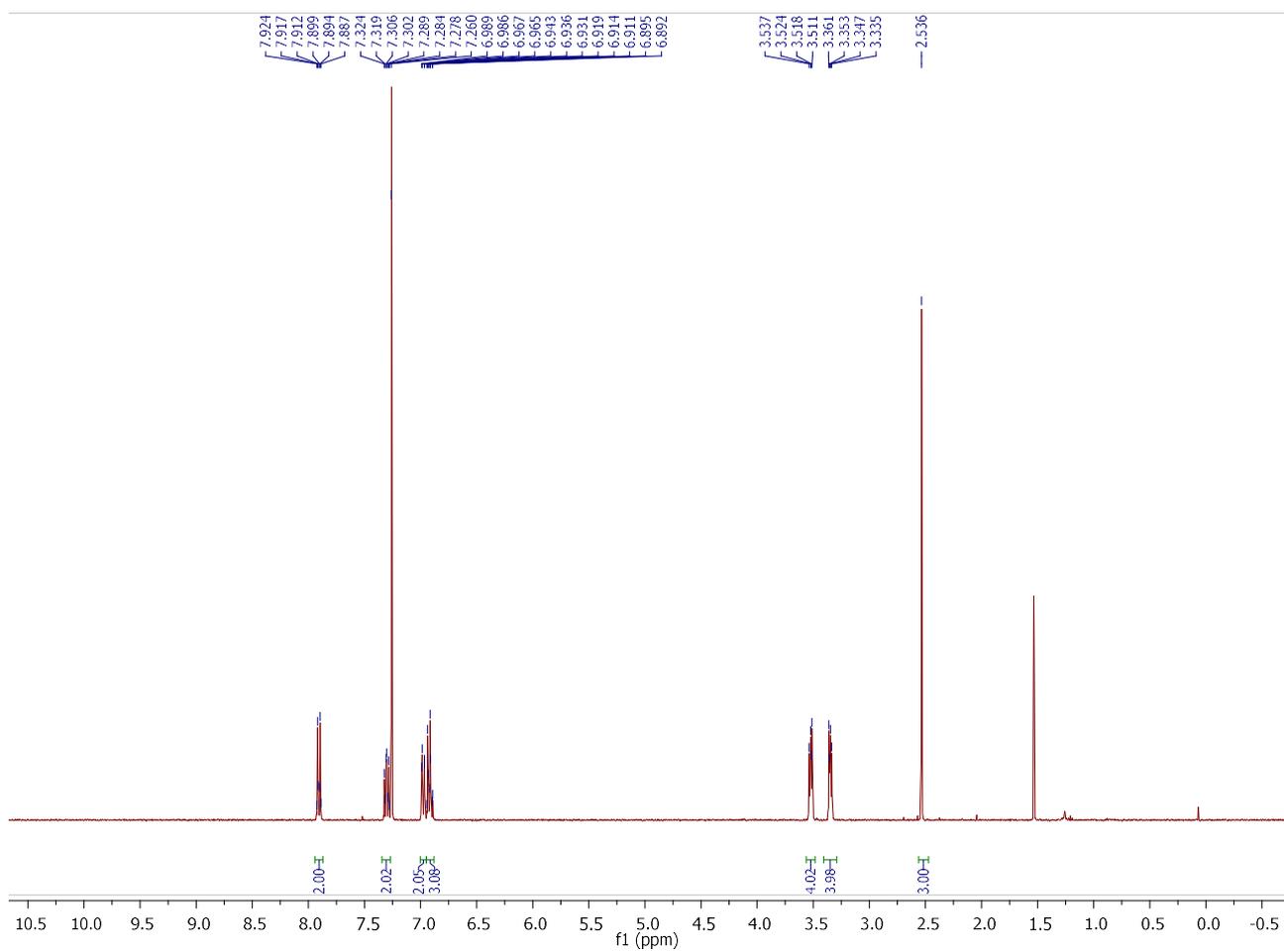




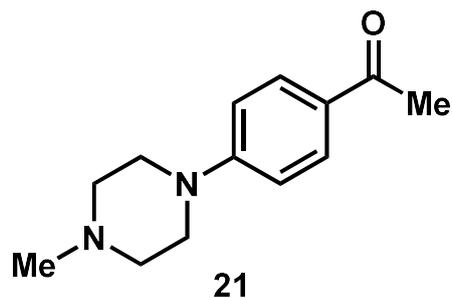
1-(4-(4-phenylpiperazin-1-yl)phenyl)ethan-1-one



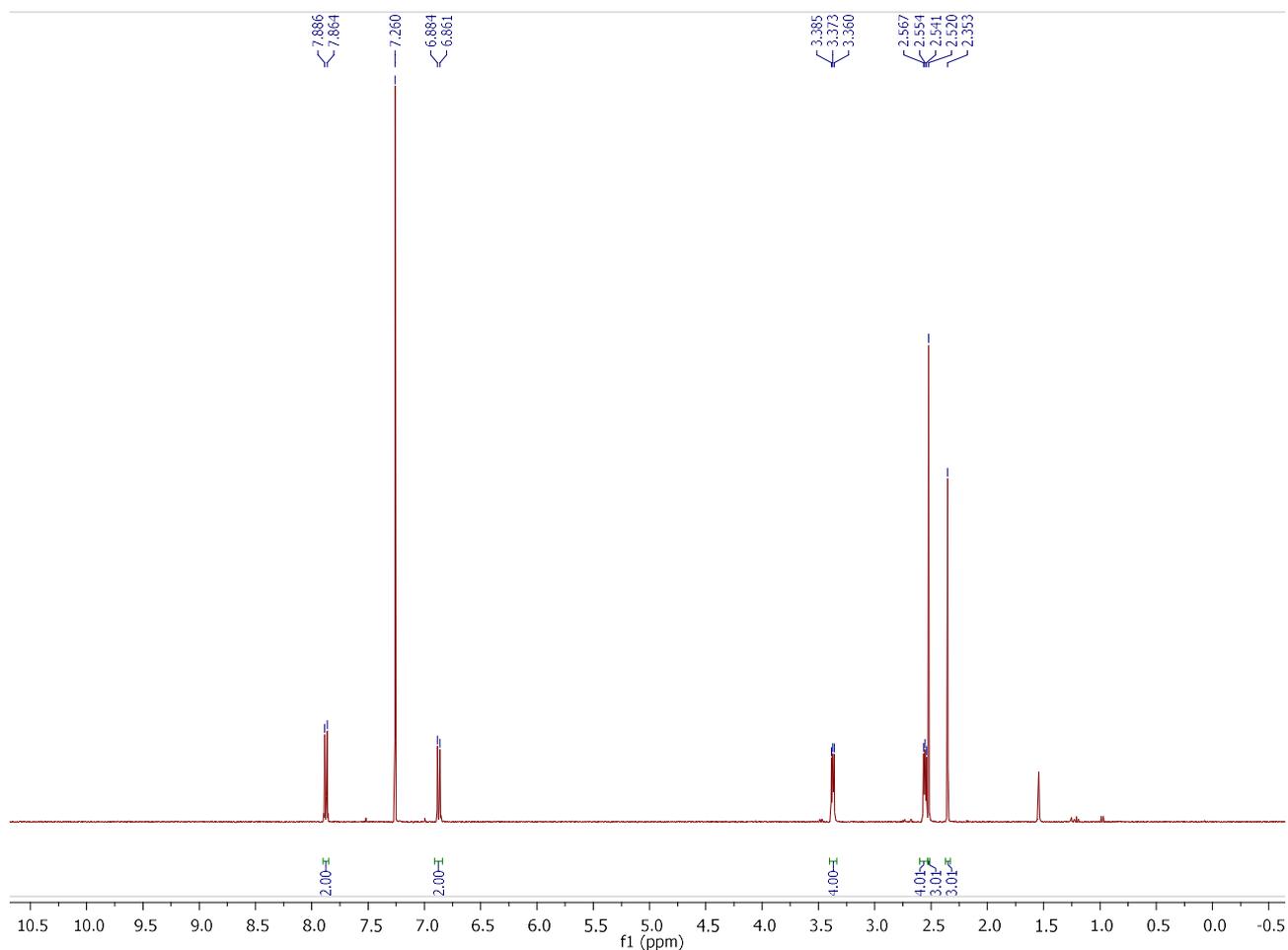
The title compound 1-(4-(4-phenylpiperazin-1-yl)phenyl)ethan-1-one (**20**) was prepared according to general procedure 3 using *N*-phenylpiperazine (67.0 μ L, 71.4 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 x 120 mm silica) gave an off-white solid (85 mg, 76%). mp 167-170 $^{\circ}$ C; R_f = 0.25 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2839, 1663, 1593, 1576, 1358, 1227, 1158, 943, 808, 756; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.54 (3H, s), 3.31-3.39 (4H, m), 3.49-3.56 (4H, m), 6.88-6.95 (3H, m), 6.95-7.01 (2H, m), 7.27-7.35 (2H, m), 7.87-7.94 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.3, 47.6, 49.2, 113.7, 116.5, 120.5, 128.1, 129.4, 130.6, 151.1, 154.2, 196.7. HRMS (NSI^+) calculated for $[\text{C}_{18}\text{H}_{21}\text{ON}_2]^+$ ($\text{M}+\text{H}$) $^+$: m/z 281.1650, found 281.1648, (+0.6 ppm).

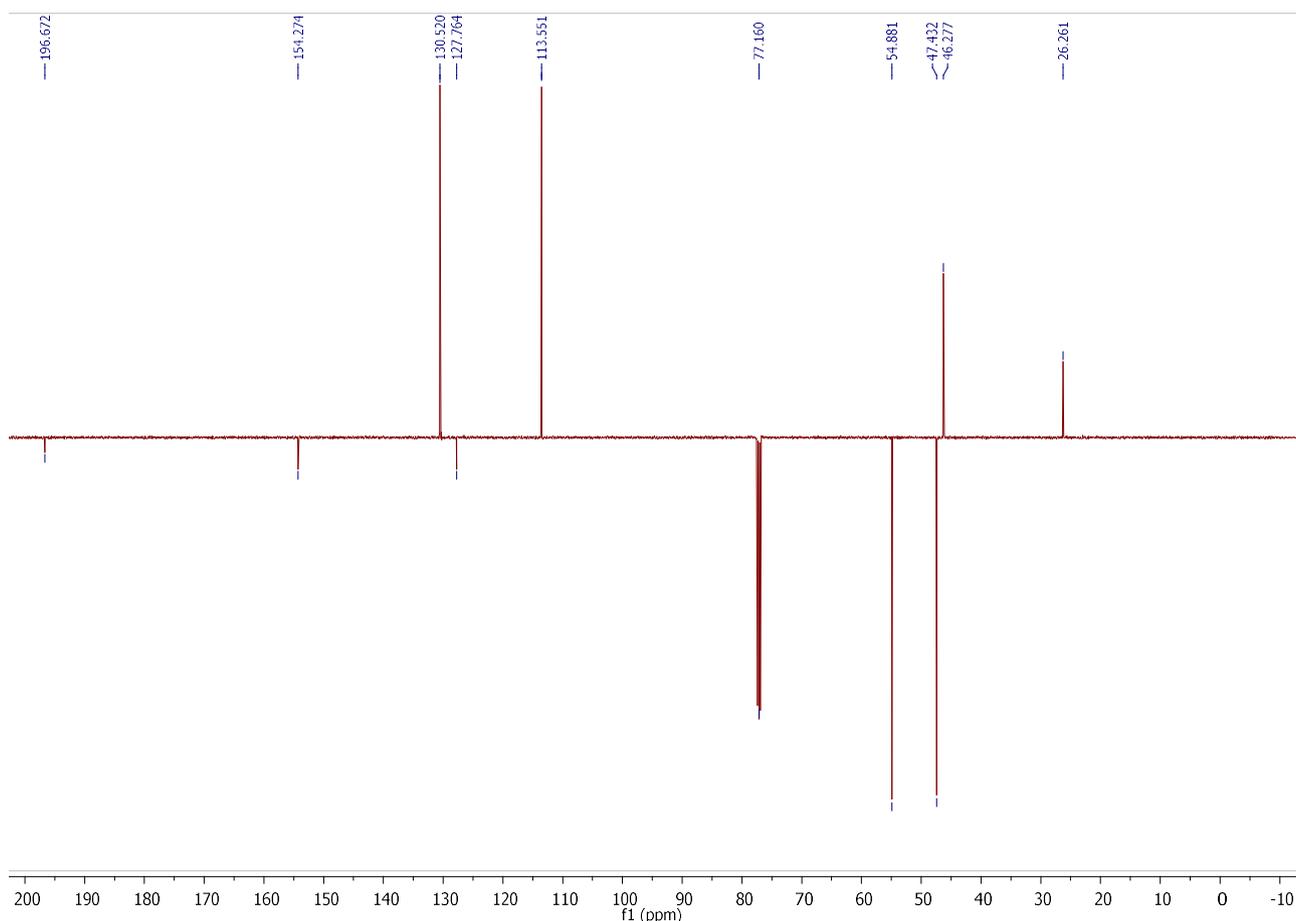


1-(4-(4-methylpiperazin-1-yl)phenyl)ethan-1-one

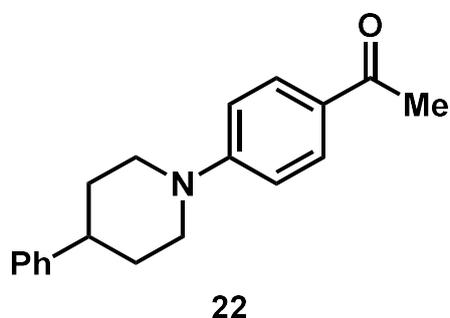


The title compound 1-(4-(4-methylpiperazin-1-yl)phenyl)ethan-1-one (**21**) was prepared according to general procedure 3 using *N*-methylpiperazine (49.0 μ L, 44.1 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5% Et₃N in EtOAc, 30 x 100 mm silica) gave an orange-yellow solid (63 mg, 72%). mp 81-84 °C; R_f = 0.34 (eluent = 20% Et₃N in EtOAc); ν_{max} / cm⁻¹ (film) 2990, 2932, 2839, 2778, 2745, 1653, 1591, 1508, 1454, 1371, 1358, 1283, 1233, 1157, 1007, 920, 822, 592; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.35 (3H, s), 2.52 (3H, s), 2.53-2.58 (4H, m), 3.33-3.41 (4H, m), 6.84-6.91 (2H, m), 7.84-7.91 (2H, m); ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 26.3, 46.3, 47.4, 54.9, 113.6, 127.8, 130.5, 154.3, 196.7; HRMS (NSI⁺) calculated for [C₁₃H₁₉ON₂]⁺ (M+H)⁺ : m/z 219.1492, found 219.1493, (+0.5 ppm).

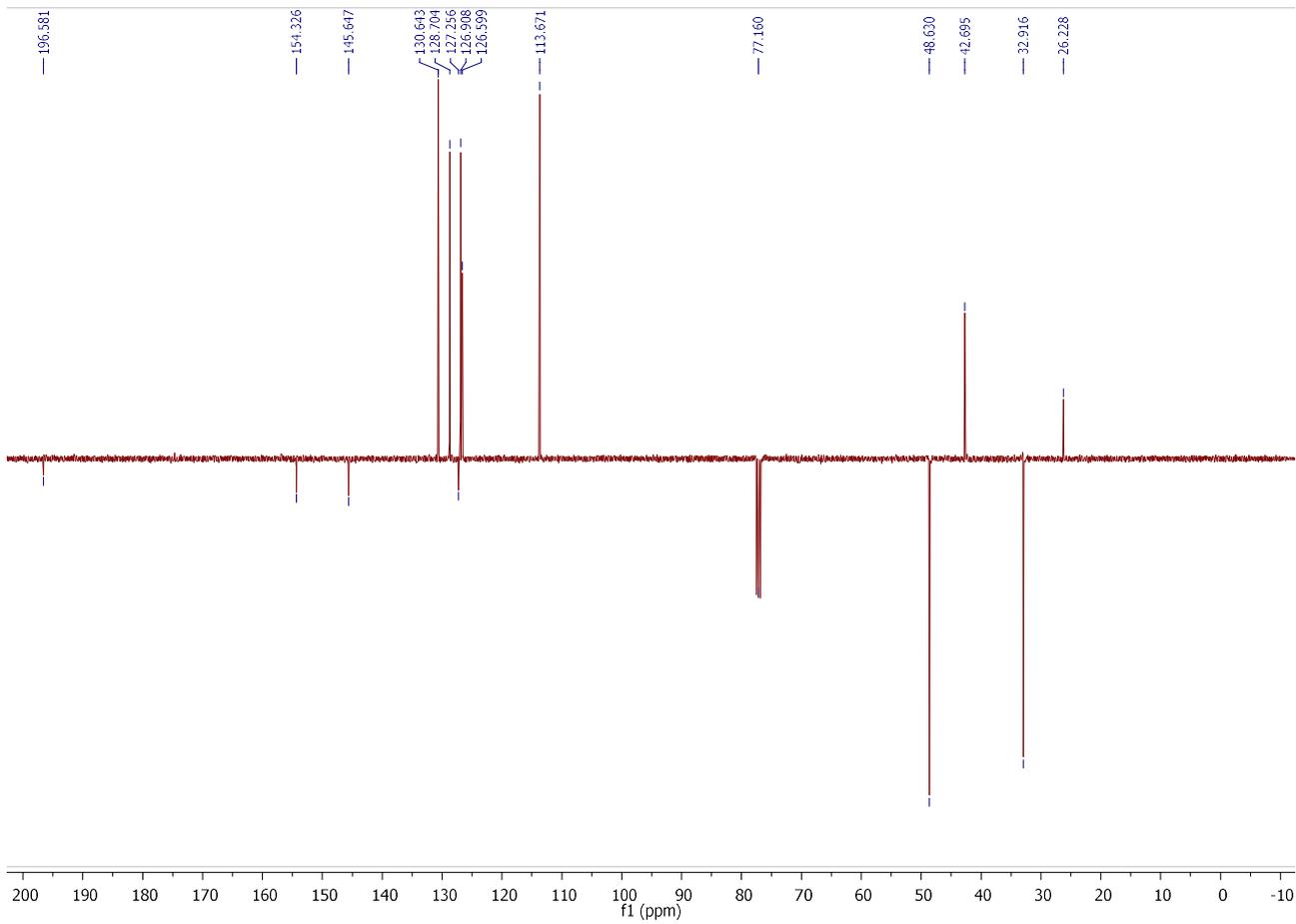
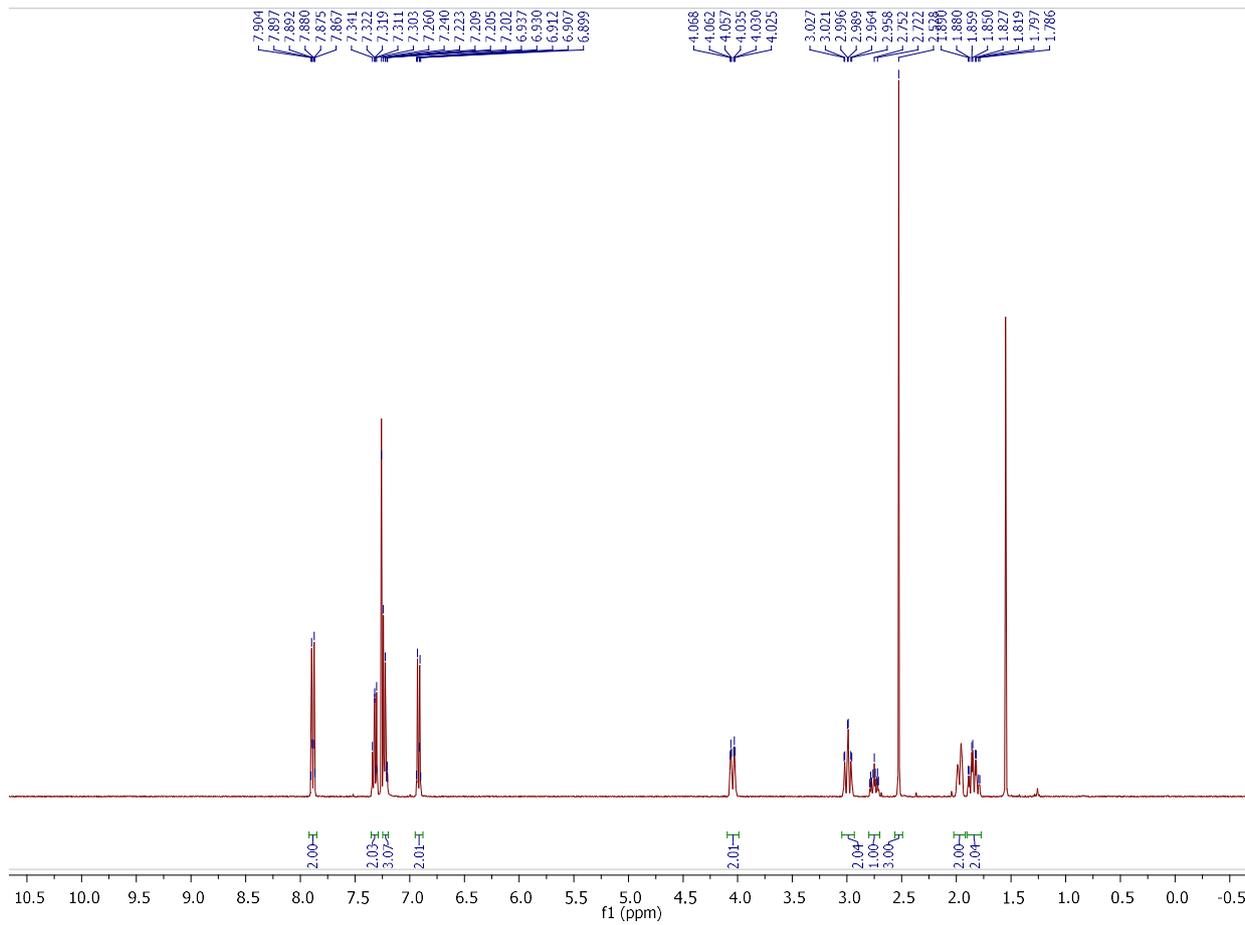




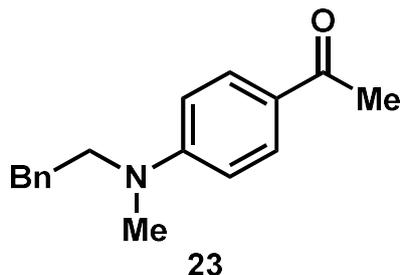
1-(4-(4-phenylpiperidin-1-yl)phenyl)ethan-1-one



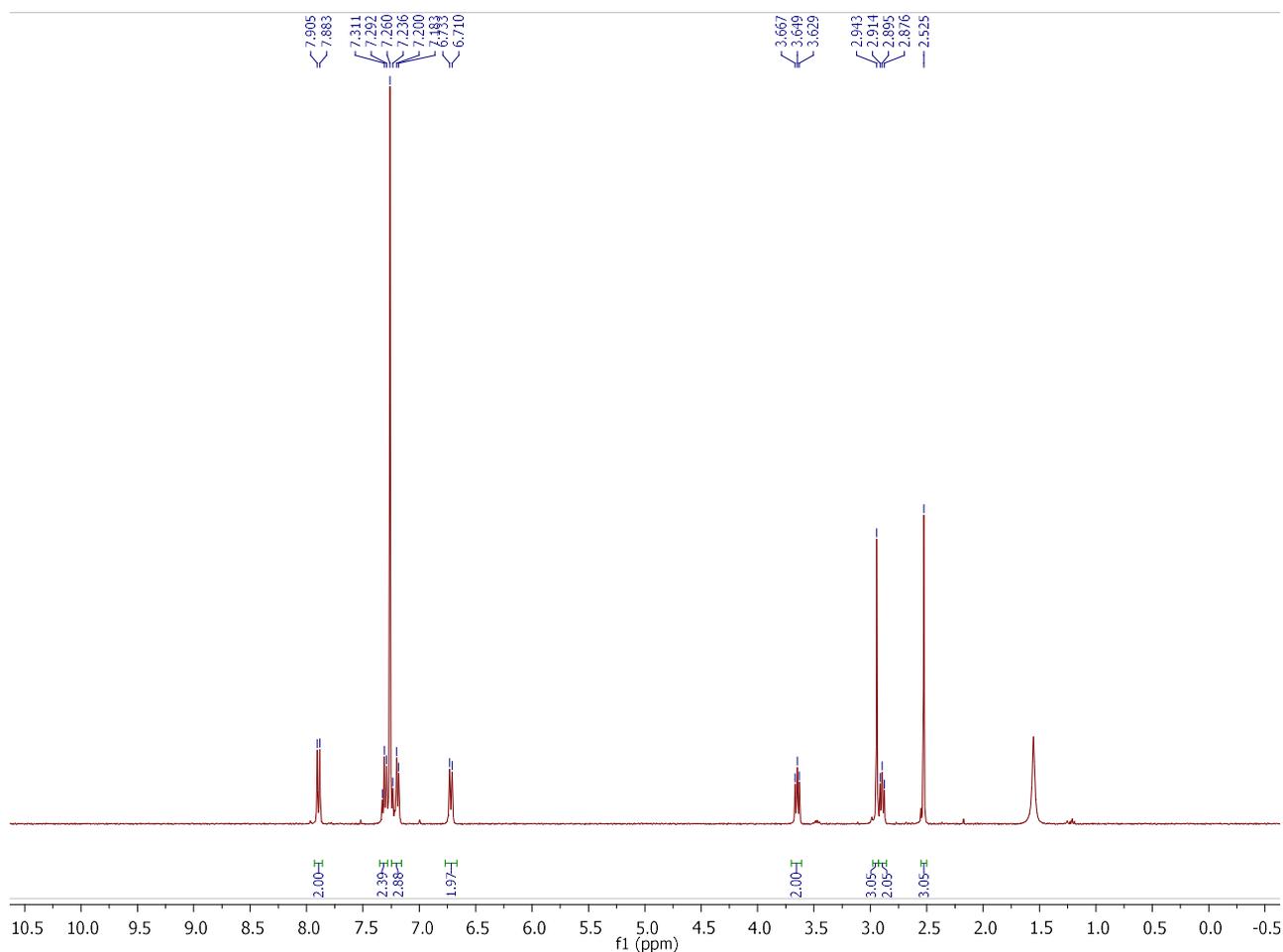
The title compound 1-(4-(4-phenylpiperidin-1-yl)phenyl)ethan-1-one (**22**) was prepared according to general procedure 3 using 4-phenylpiperidine (70.9 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 120 mm silica) gave a white solid (98 mg, 83%). mp 137-140 °C; R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 1655, 1593, 1514, 1385, 1362, 1273, 1213, 1190, 1007, 924, 820, 756, 702, 584; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.84 (2H, dq, J 12.4, 4.1 Hz), 1.92-2.02 (2H, m), 2.53 (3H, s), 2.75 (1H, tt, J 12.4, 3.6), 2.99 (2H, dt, J 12.4, 2.4), 3.99-4.10 (2H, m), 6.88-6.96 (2H, m), 7.19-7.25 (3H, m), 7.28-7.36 (2H, m), 7.85-7.92 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.2, 32.9, 42.7, 48.6, 113.7, 126.6, 126.9, 127.3, 128.7, 130.6, 145.6, 154.3, 196.9; HRMS (NSI^+) calculated for $[\text{C}_{19}\text{H}_{22}\text{ON}]^+$ ($\text{M}+\text{H}^+$) : m/z 280.1696, found 280.1695, (-0.3 ppm).

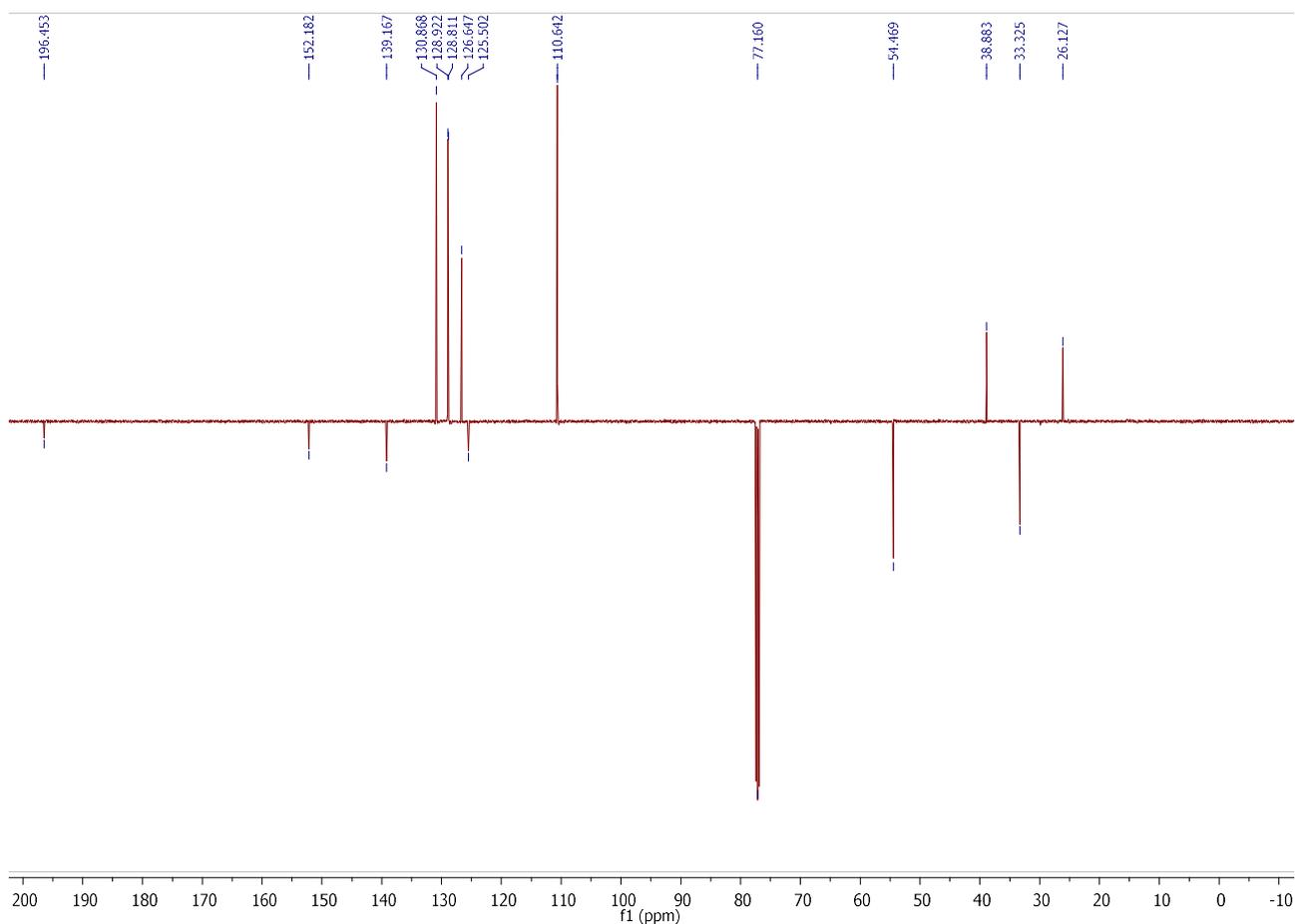


1-(4-(methyl(phenethyl)amino)phenyl)ethan-1-one

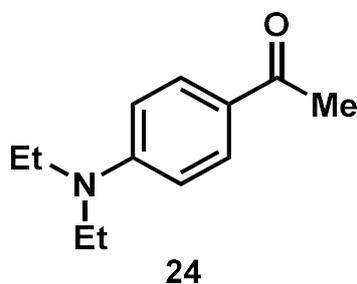


The title compound 1-(4-(methyl(phenethyl)amino)phenyl)ethan-1-one (**23**) was prepared according to general procedure 3 using *N*-methylphenethylamine (64.0 μ L, 59.5 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 140 mm silica) gave an off-white solid (67 mg, 67%). mp 99-102 $^{\circ}$ C; R_f = 0.34 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 2993, 2913, 1655, 1589, 1548, 1391, 1356, 1290, 1194, 951, 820, 750, 608, 592, 494; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.52 (3H, s), 2.85-2.92 (2H, m), 2.93 (3H, s), 3.61-3.69 (2H, m), 6.63-6.70 (2H, m), 7.16-7.26 (3H, m), 7.27-7.35 (2H, m), 7.84-7.92 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 26.1, 33.3, 38.9, 54.5, 110.6, 125.5, 126.6, 128.8, 128.9, 130.9, 139.2, 152.2, 196.5; HRMS (NSI^+) calculated for $[\text{C}_{16}\text{H}_{20}\text{ON}]^+$ ($\text{M}+\text{H}$) $^+$: m/z 254.1539, found 254.1543, (+0.5 ppm).

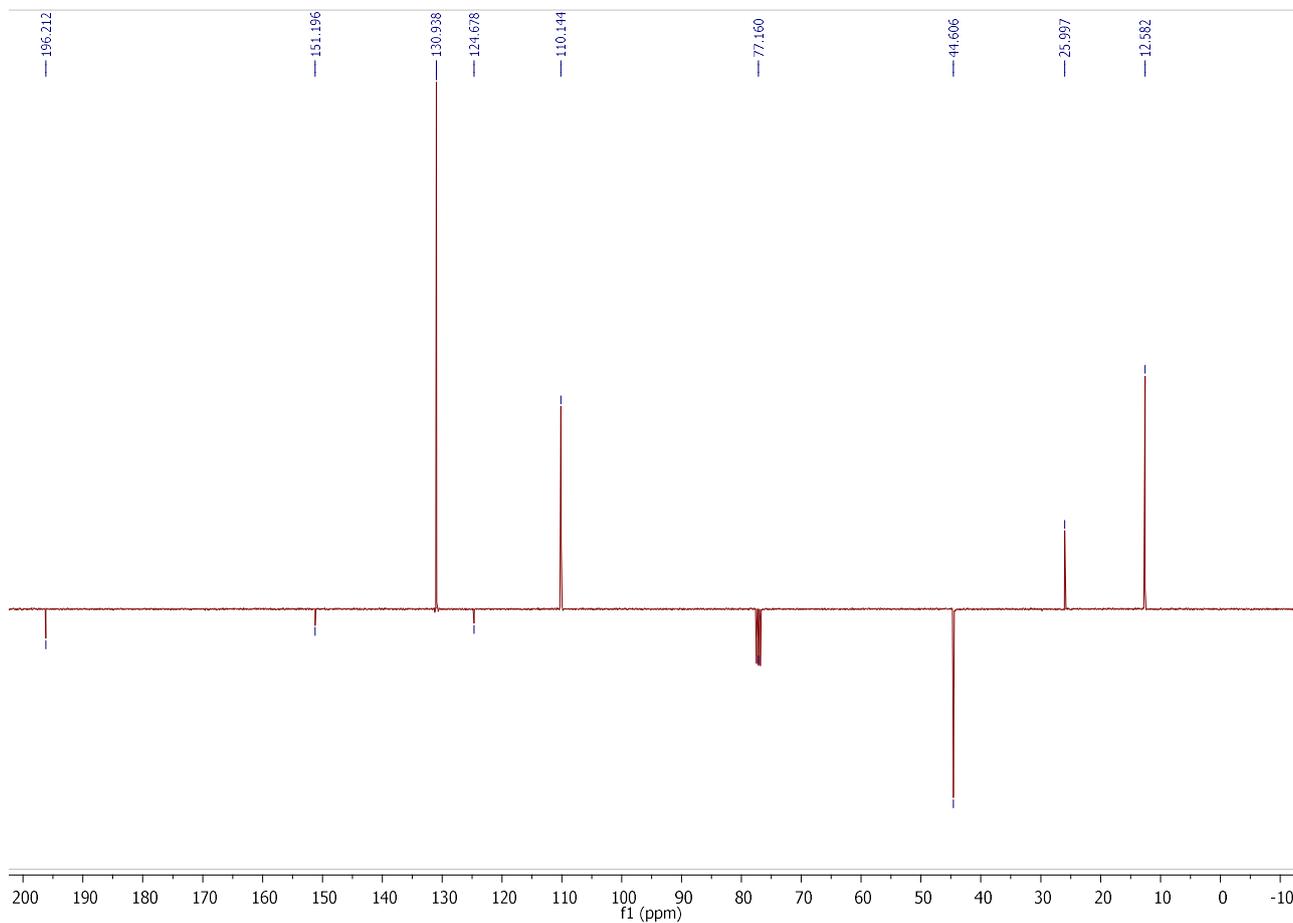
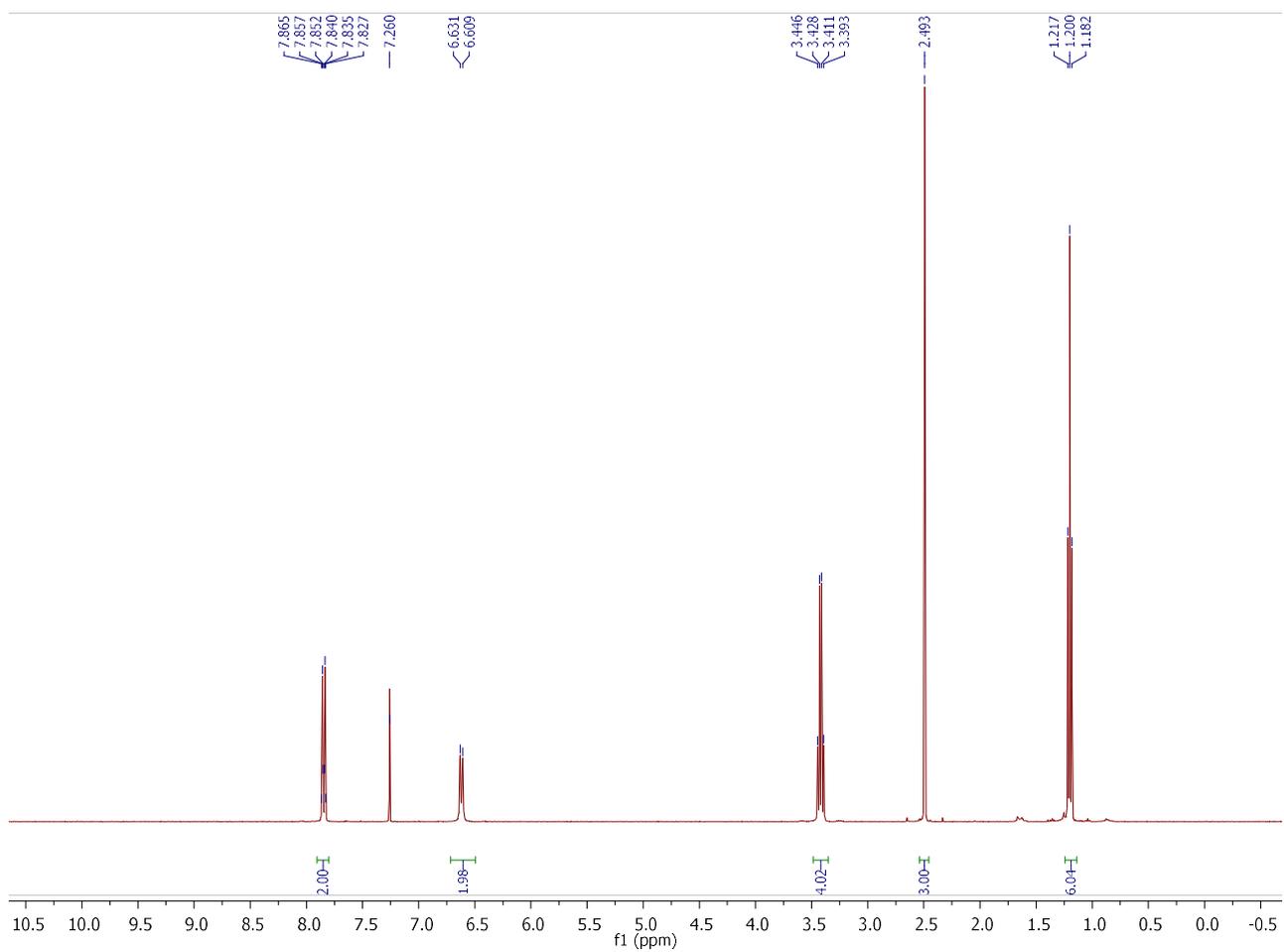




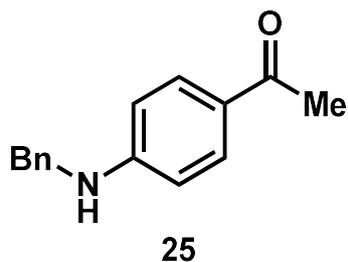
1-(4-(diethylamino)phenyl)ethan-1-one



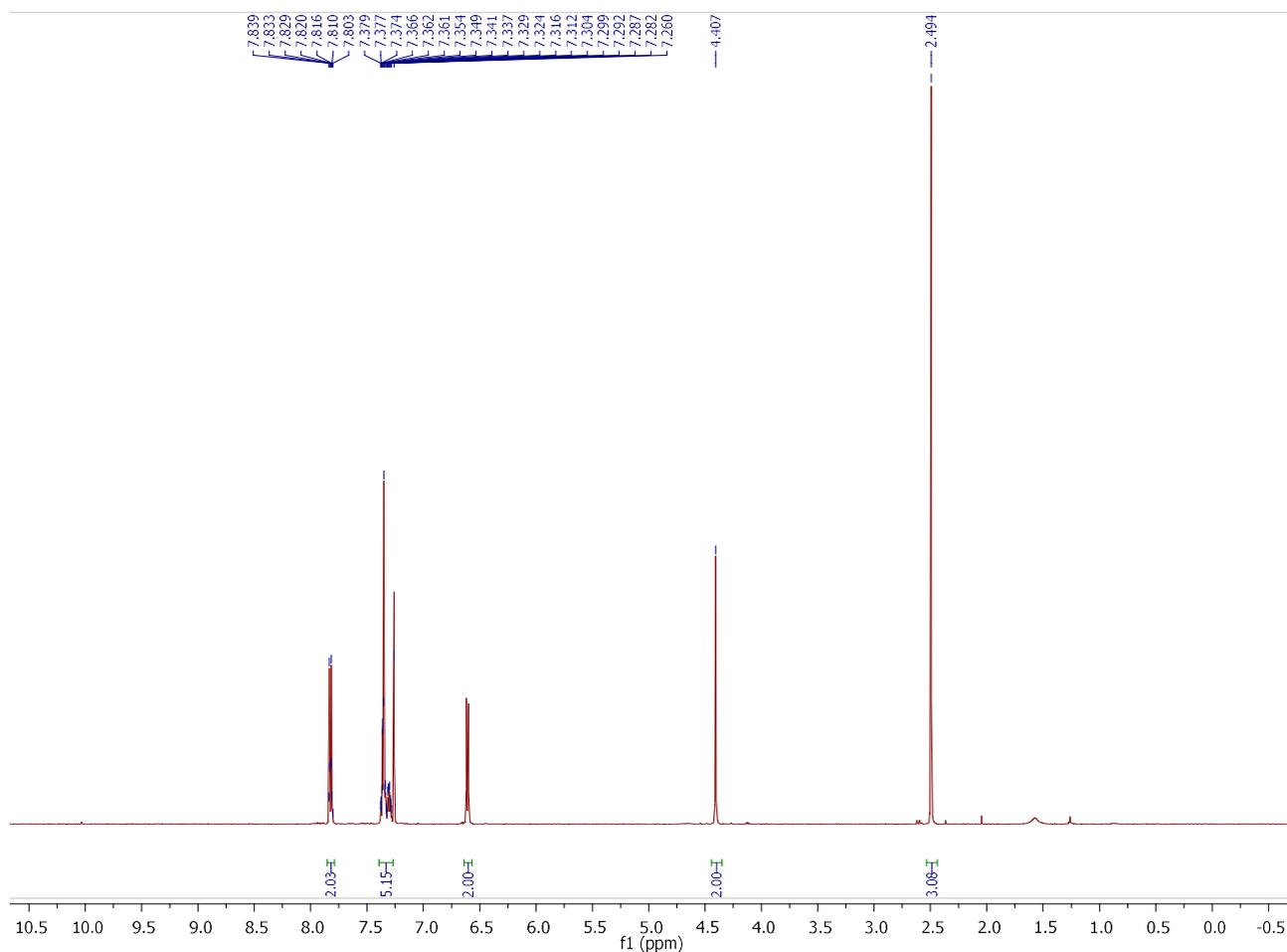
The title compound 1-(4-(diethylamino)phenyl)ethan-1-one (**24**) was prepared according to general procedure 3 using diethylamine (46.0 μL , 32.2 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 30 x 120 mm silica) gave an off-white solid (34 mg, 45%). mp 34-37 $^{\circ}\text{C}$ (Lit. 41.5-44.5 $^{\circ}\text{C}$)¹³; R_f = 0.36 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2972, 2922, 2868, 1651, 1585, 1524, 1404, 1356, 1267, 1190, 1157, 1070, 951, 818, 791, 592, 565; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.20 (6H, t, J 7.1), 2.49 (3H, s), 3.42 (4H, q, J 7.1), 6.62 (2H, d, J 8.8), 7.81-7.88 (2H, m); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 12.6, 26.0, 44.6, 110.1, 124.7, 130.9, 151.2, 196.2; HRMS (ESI⁺) calculated for $[\text{C}_{12}\text{H}_{18}\text{NO}]^+$ ($\text{M}+\text{H}$)⁺: m/z 192.1388, found 192.1385, (-1.6 ppm).

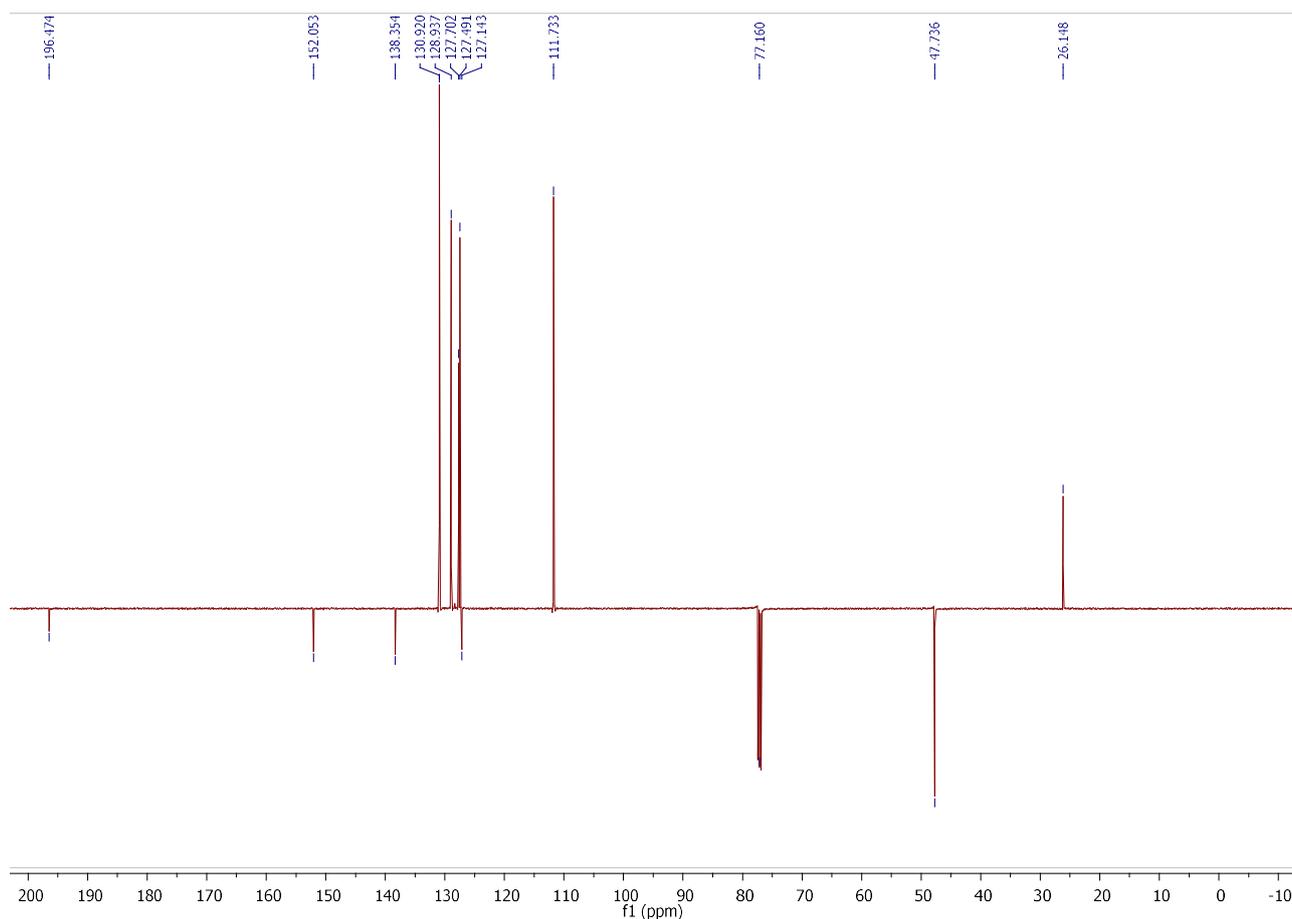


1-(4-(benzylamino)phenyl)ethan-1-one

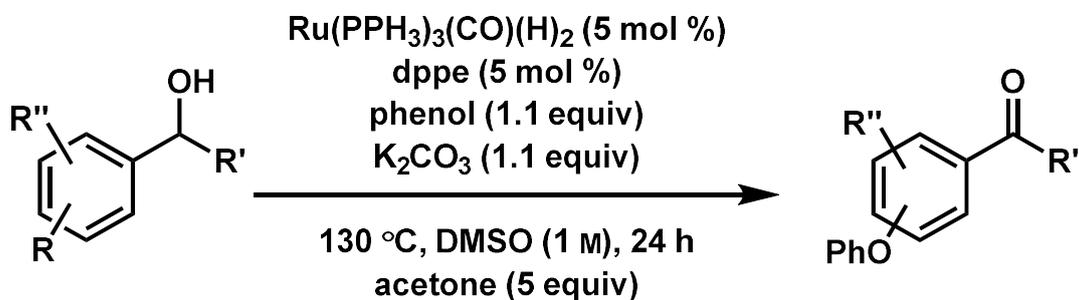


The title compound 1-(4-(benzylamino)phenyl)ethan-1-one (**25**) was prepared according to general procedure 3 using benzylamine (48.0 μ L, 47.1 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 150 mm silica) gave a yellow solid (24 mg, 25%). mp 80-83 $^{\circ}$ C (Lit. 84-86 $^{\circ}$ C)¹⁴; R_f = 0.30 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3350, 3063, 3024, 1645, 1585, 1564, 1530, 1356, 1279, 1263, 1179, 947, 837, 741, 694; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 2.49 (3H, s), 4.41 (2H, s), 6.57-6.63 (2H, m), 7.27-7.40 (5H, m), 7.78-7.86 (2H, m); ^{13}C NMR (126 MHz, CDCl_3) δ_{C} : 26.1, 47.7, 111.7, 127.1, 127.5, 127.7, 128.9, 130.9, 138.4, 152.1, 196.5; HRMS (AP^+) calculated for $[\text{C}_{15}\text{H}_{16}\text{NO}]^+$ ($\text{M}+\text{H}$) $^+$: m/z 226.1232, found 226.1232, (+0.0 ppm).



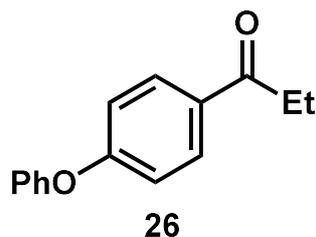


2.3.1. General procedure 5

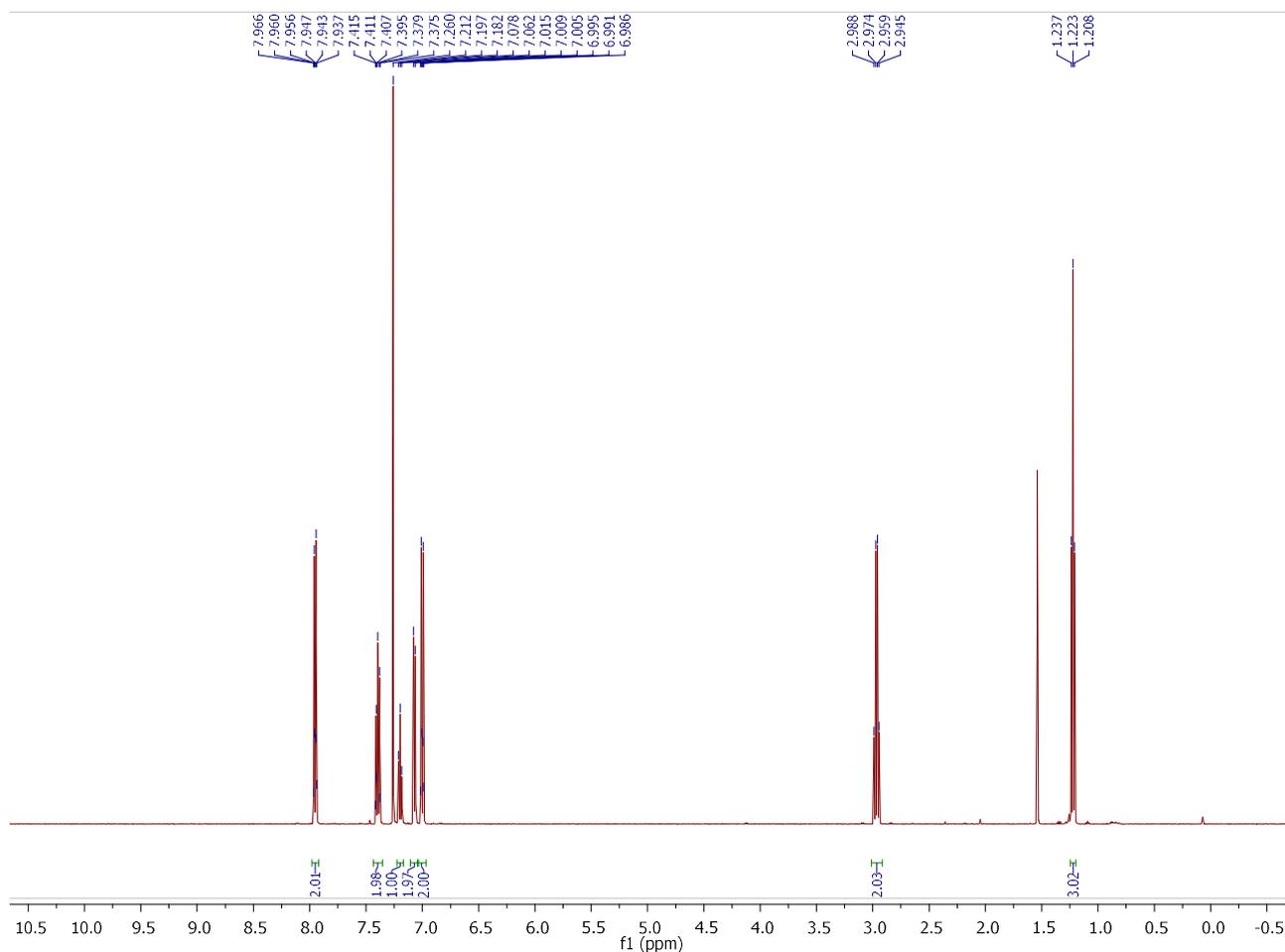


A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$ (18.3 mg, 5.00 mol %), DPPE (8.0 mg, 5.00 mol %), phenol (41.4 mg, 0.440 mmol, 1.1 equiv) and K_2CO_3 (60.8 mg, 0.440 mmol, 1.1 equiv). To this mixture was added DMSO (0.4 mL), acetone (147 μL , 116.2 mg, 2 mmol) and fluoroarene (0.400 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 hours. After cooling, the reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified by flash silica column chromatography.

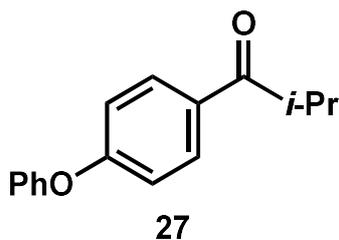
1-(4-phenoxyphenyl)propan-1-one



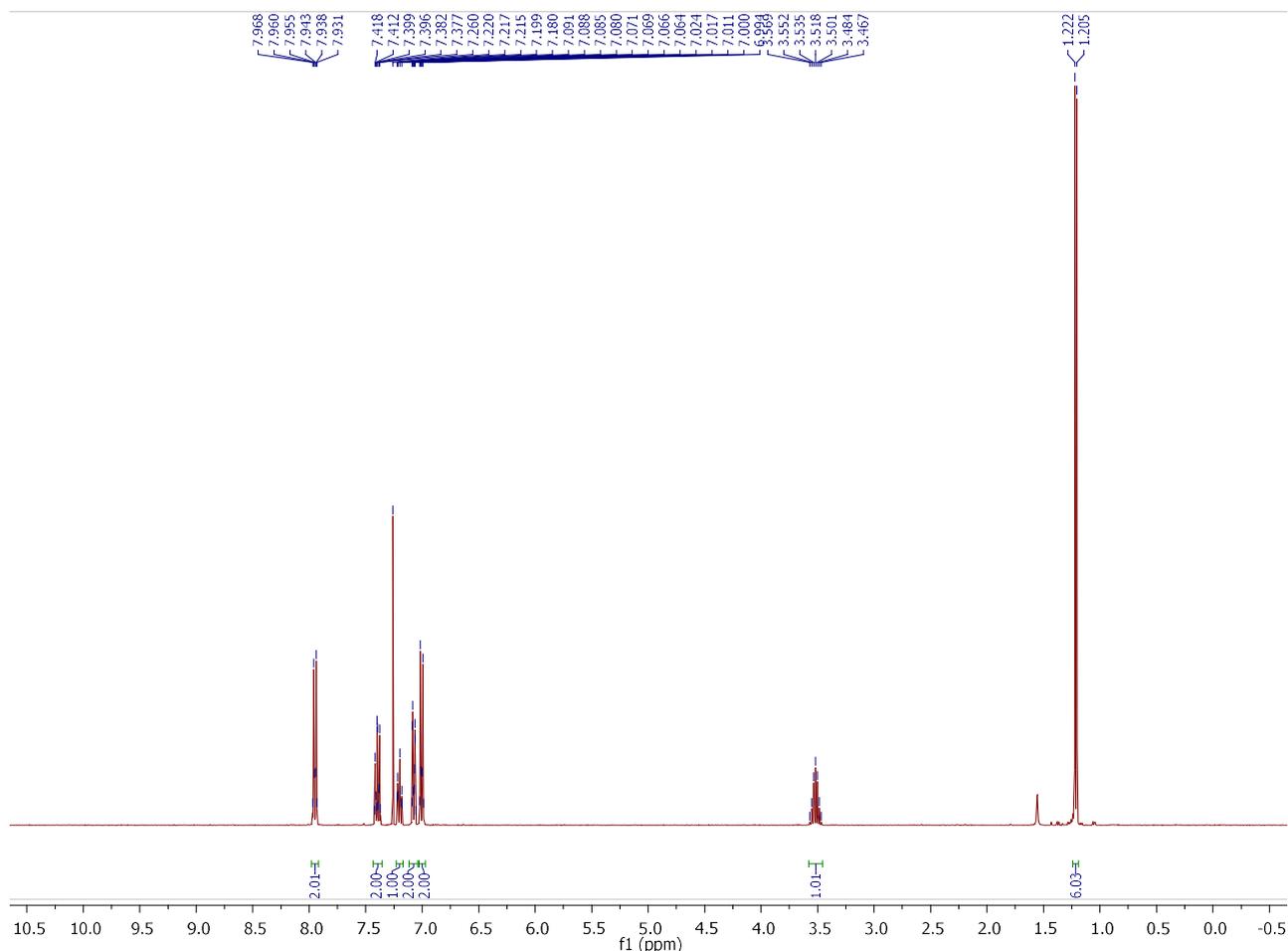
The title compound 1-(4-phenoxyphenyl)propan-1-one (**26**) was prepared according to general procedure 5 using 1-(4-fluorophenyl)propan-1-ol (61.7 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave an off-white solid (73 mg, 81%). mp 30-33 °C (Lit. 39-40 °C)¹⁵; R_f = 0.68 (eluent = 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H : 1.22 (3H, t, J 7.3), 2.97 (2H, q, J 7.3), 6.97-7.03 (2H, m), 7.04-7.10 (2H, m), 7.20 (1H, t, J 7.3), 7.36-7.42 (2H, m), 7.92-7.98 (2H, m); Spectroscopic data in accordance with that stated in the literature.¹⁵

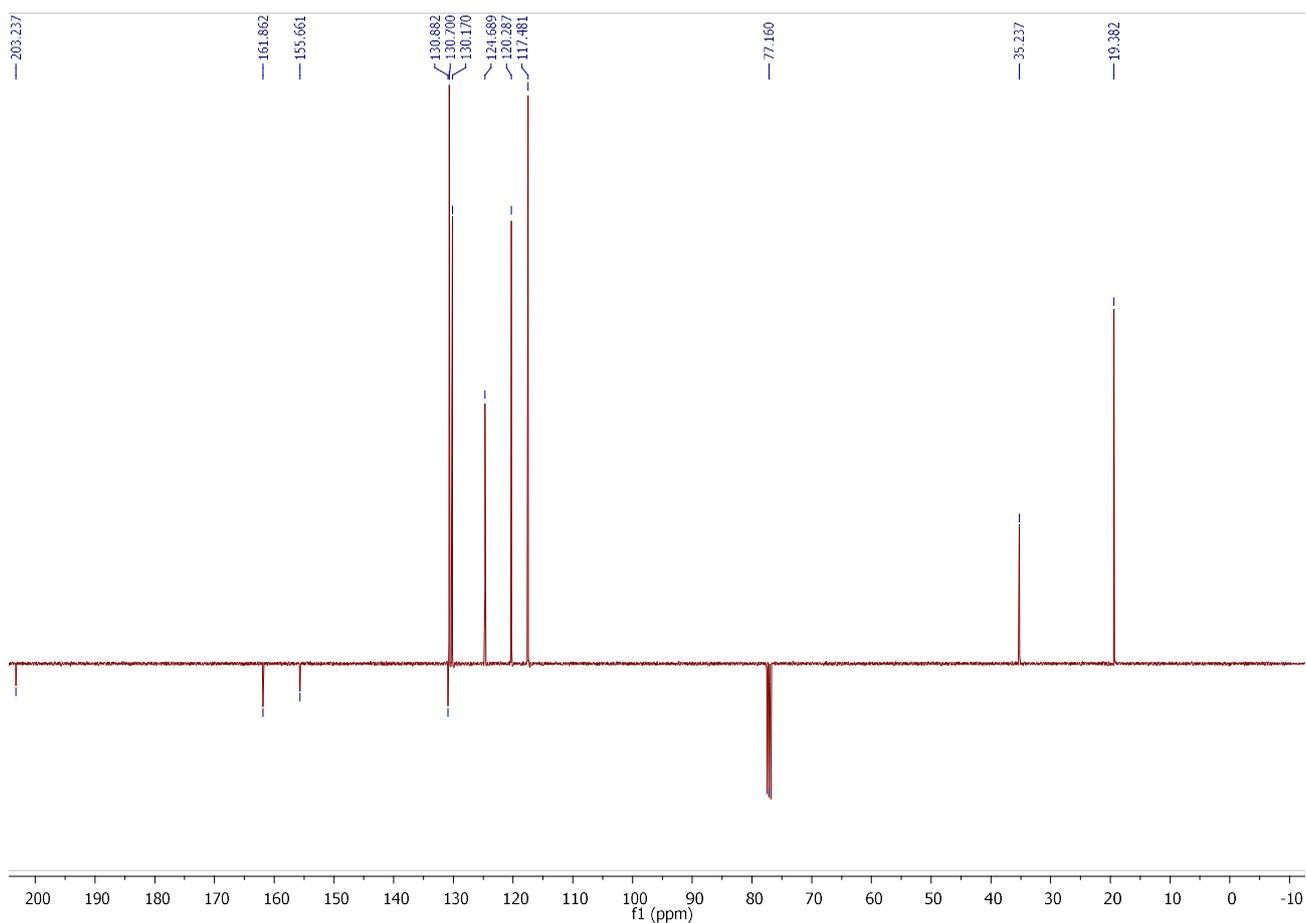


2-methyl-1-(4-phenoxyphenyl)propan-1-one

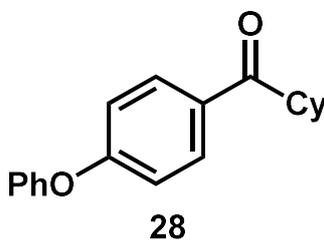


The title compound 2-methyl-1-(4-phenoxyphenyl)propan-1-one (**27**) was prepared according to general procedure 5 using 1-(4-fluorophenyl)-2-methylpropan-1-ol (67.3 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1-5 % Et₂O in hexanes, 30 x 160 mm silica) gave a colourless oil (67 mg, 70%). *R*_f = 0.72 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3063, 2974, 2928, 1678, 1584, 1487, 1381, 1217, 1155, 976, 874, 843, 752, 689, 490; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.21 (6H, d, *J* 6.8), 3.52 (1H, sept, *J* 6.8), 6.97-7.04 (2H, m), 7.04-7.11 (2H, m), 7.16-7.24 (1H, m), 7.35-7.44 (2H, m), 7.91-7.99 (2H, m); ¹³C NMR (101 MHz, CDCl₃) δ_{C} : 19.4, 35.2, 117.5, 120.3, 124.7, 130.2, 130.7, 130.9, 155.7, 161.9, 203.2; HRMS (NSI⁺) calculated for [C₁₆H₁₇O₂]⁺ (M+H)⁺ : *m/z* 241.1223, found 241.1223, (+0.0 ppm).

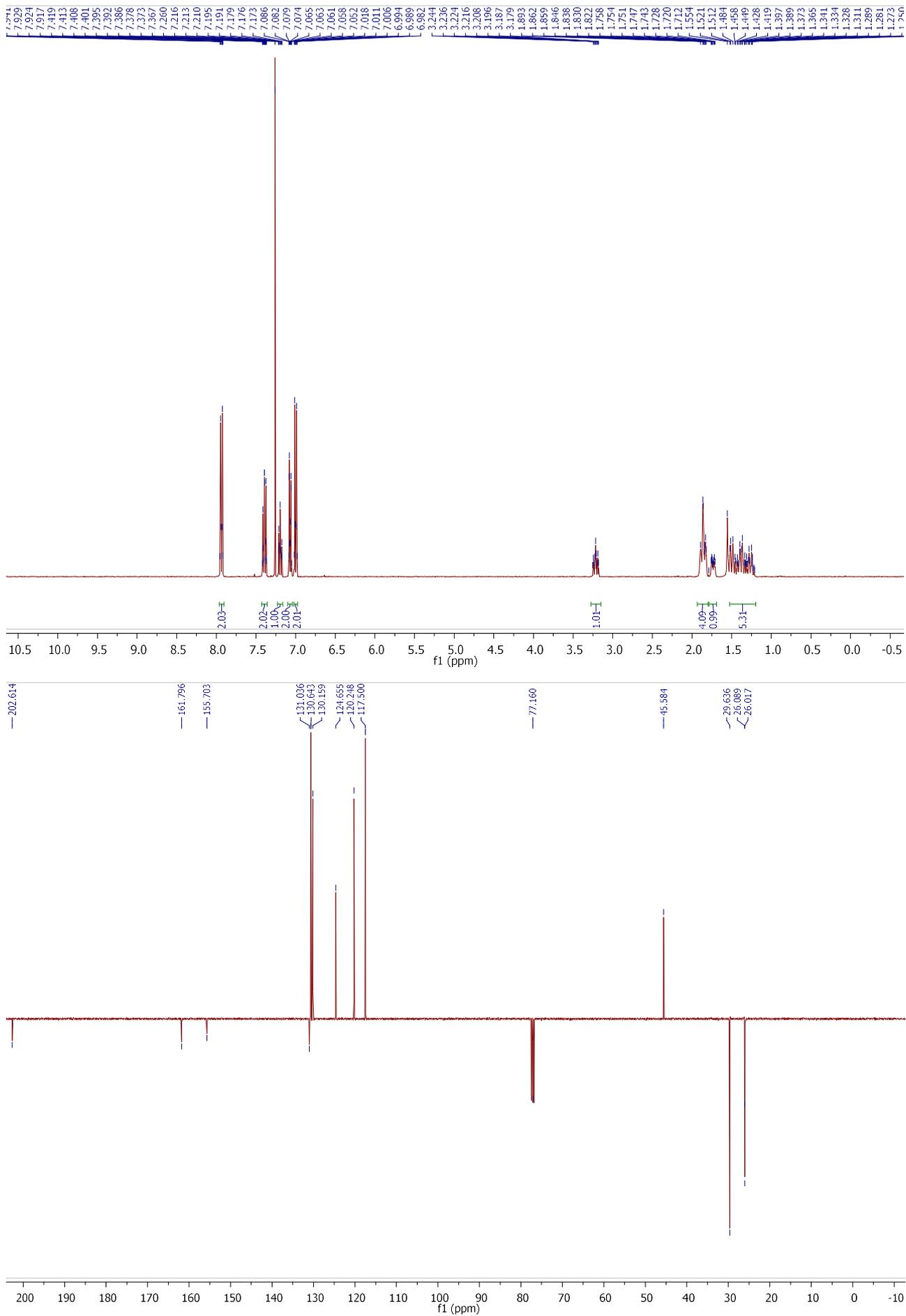


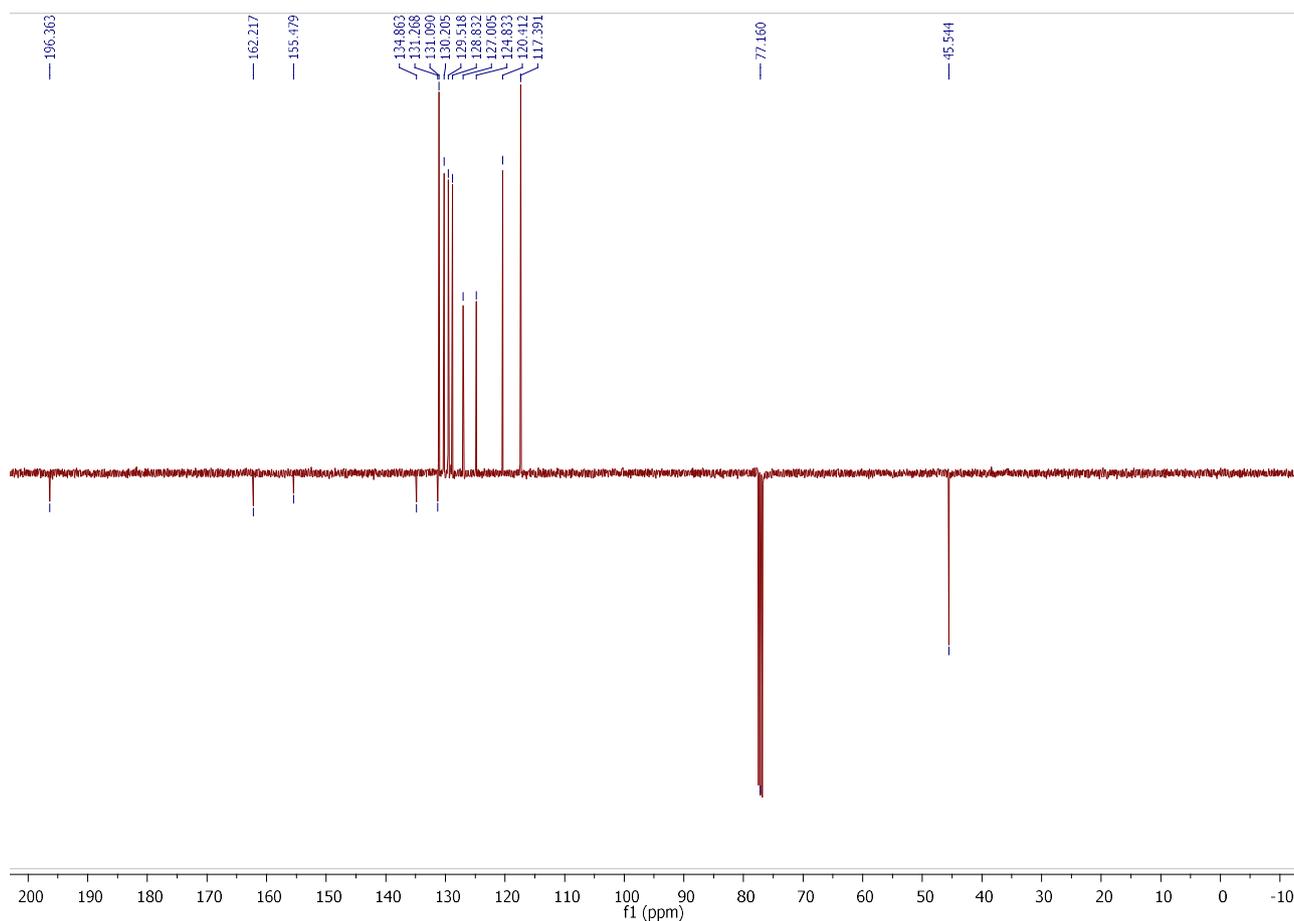


Cyclohexyl(4-phenoxyphenyl)methanone

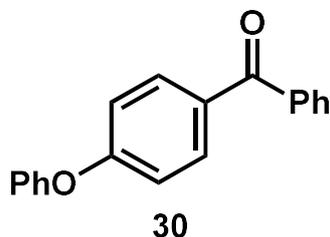


The title compound cyclohexyl(4-phenoxyphenyl)methanone (**28**) was prepared according to general procedure 5 using cyclohexyl(4-fluorophenyl)methanol (83.2 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1-5% Et₂O in hexanes, 30 x 160 mm silica) gave an off-white solid (74 mg, 66%). mp 45-48 °C; R_f = 0.72 (eluent: 20% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3059, 2924, 2855, 1670, 1584, 1485, 1234, 1206, 1157, 974, 872, 746, 690, 500; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 1.18-1.54 (5H, m), 1.67-1.79 (1H, m), 1.80-1.93 (4H, m), 3.22 (1H, tt, *J* 11.2, 3.2), 6.97-7.03 (2H, m), 7.04-7.10 (2H, m), 7.16-7.23 (1H, m), 7.35-7.43 (2H, m), 7.90-7.97 (2H, m); ¹³C NMR (101 MHz, CDCl₃) δ_{C} : 26.0, 26.1, 29.6, 45.6, 117.5, 120.2, 124.7, 130.2, 130.6, 131.0, 155.7, 161.8, 202.6; HRMS (ESI⁺) calculated for [C₁₉H₂₁O₂]⁺ (M+H)⁺: *m/z* 281.1542, found 281.1545, (+1.1 ppm).

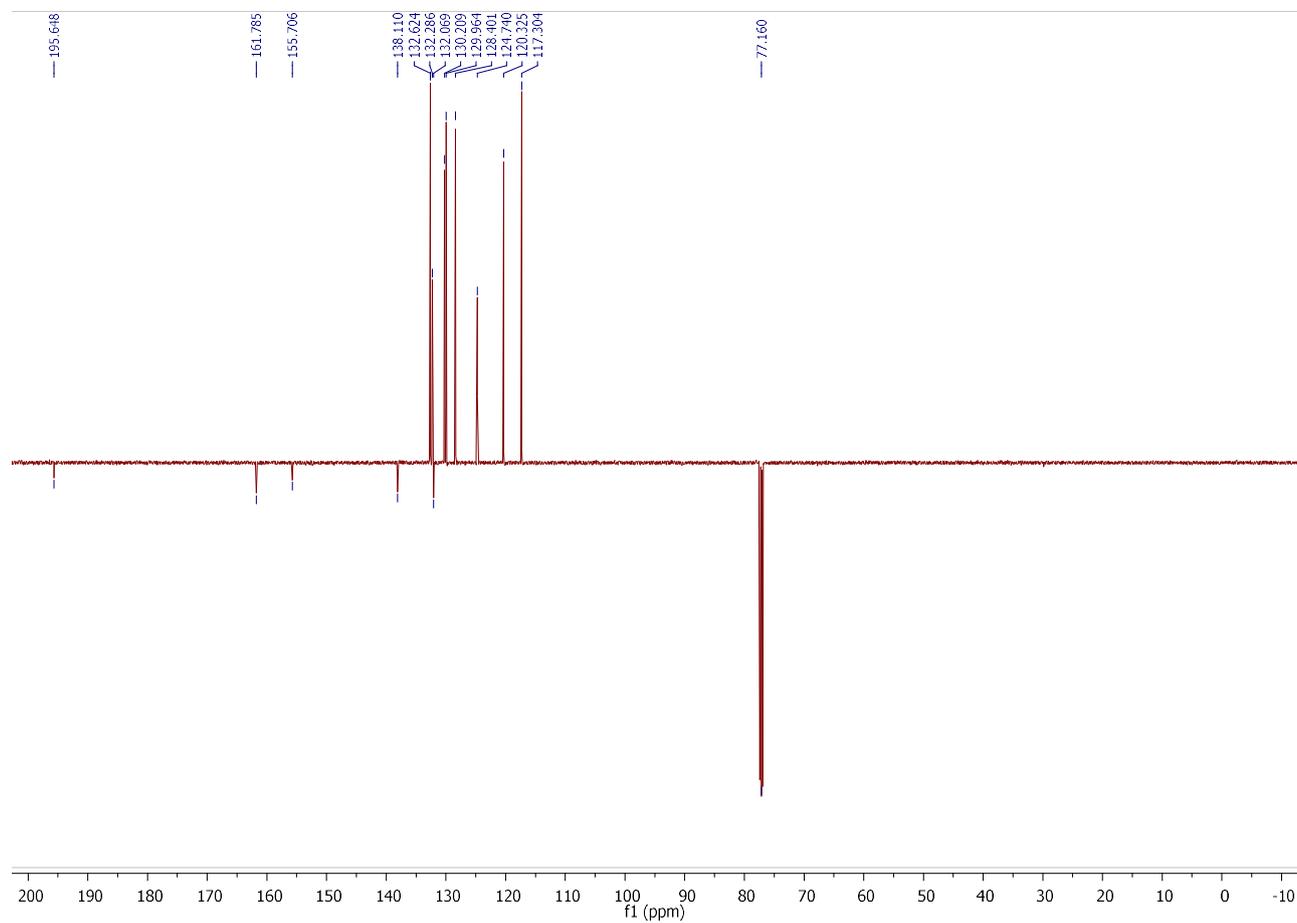
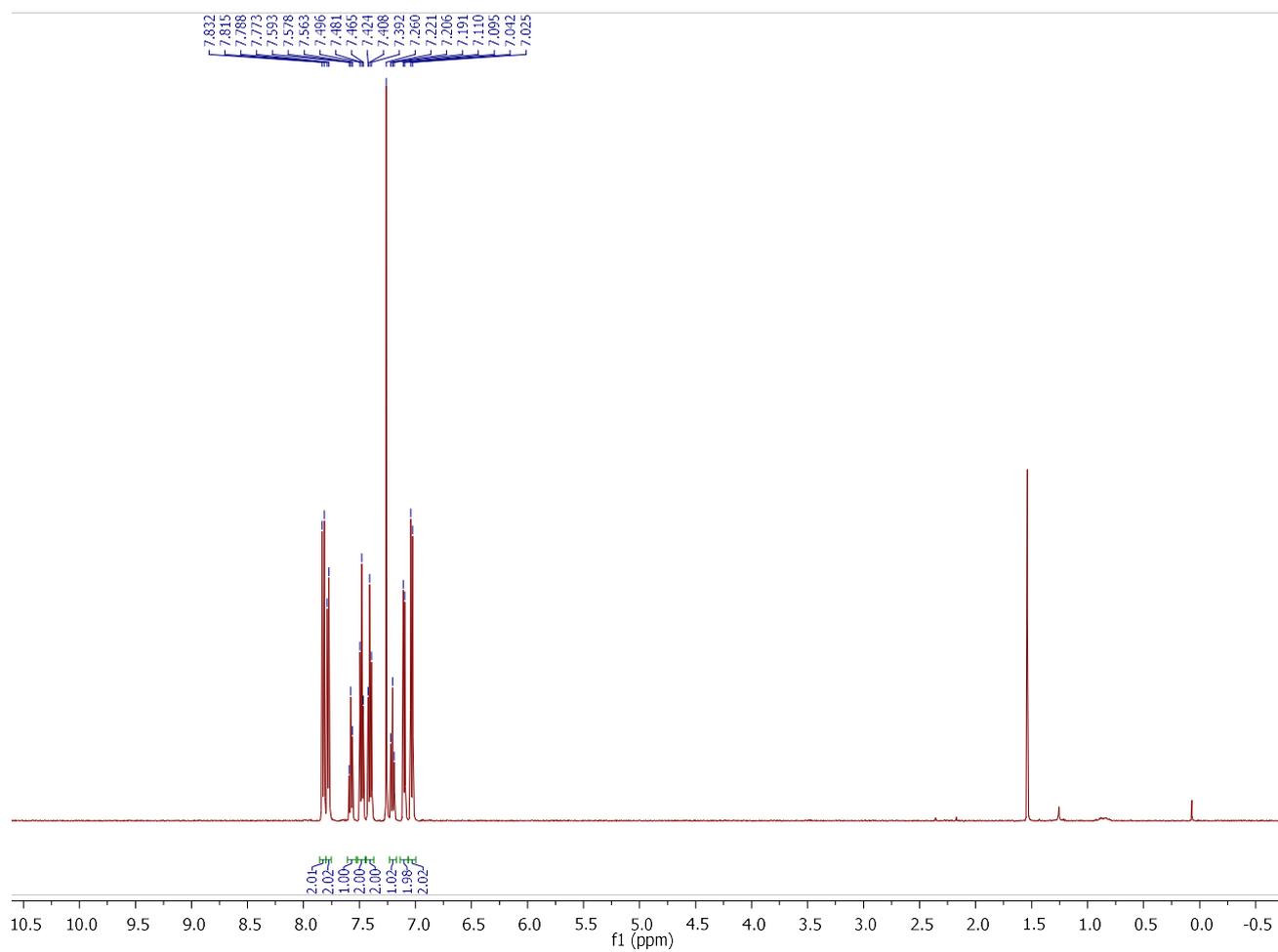




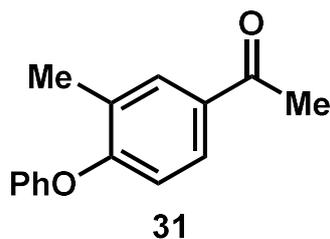
(4-phenoxyphenyl)(phenyl)methanone



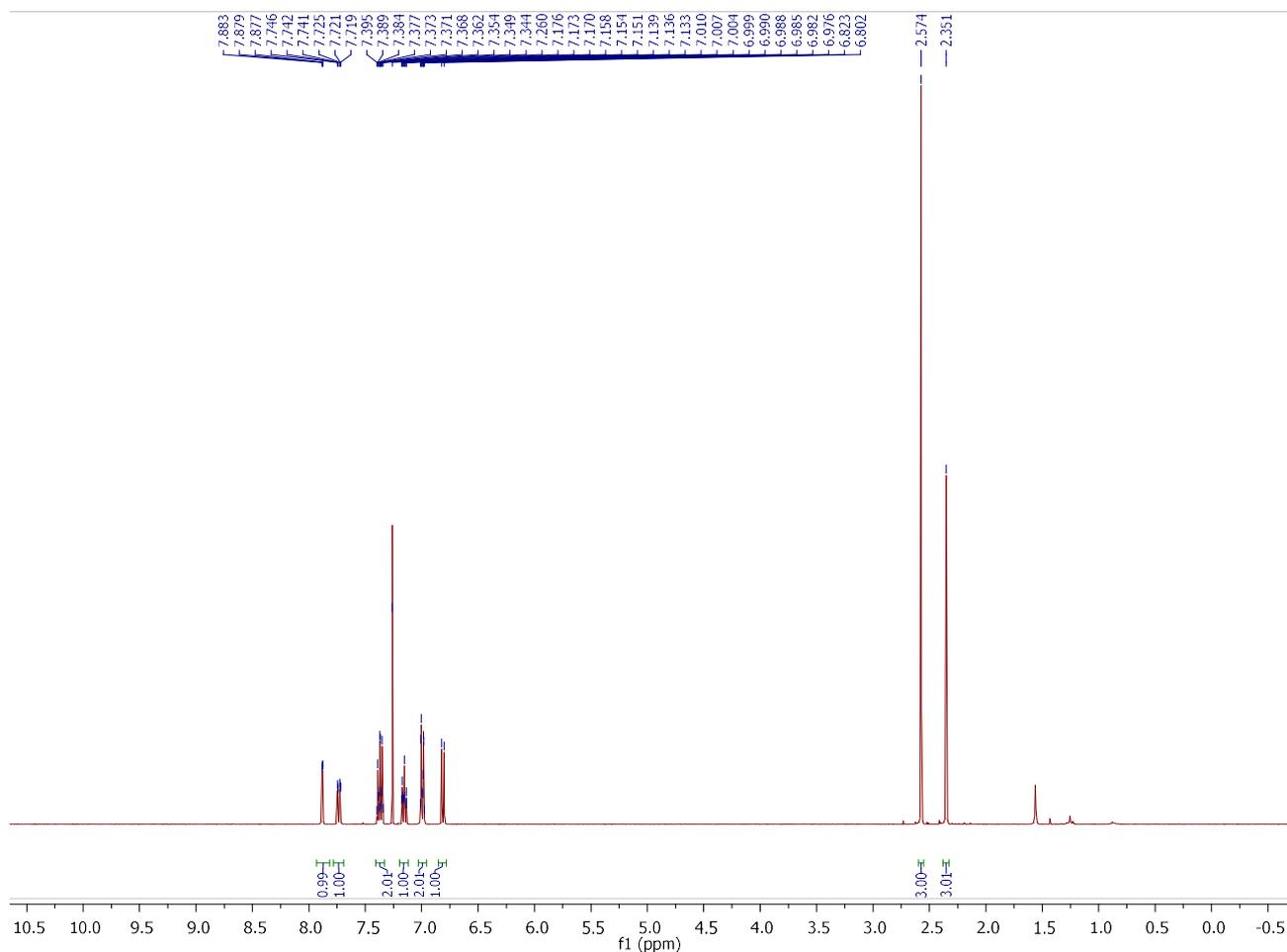
The title compound (4-phenoxyphenyl)(phenyl)methanone (**30**) was prepared according to general procedure 5 using (4-fluorophenyl)(phenyl)methanol (80.9 mg, 0.400 mmol) as the starting alcohol. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave a white solid (87 mg, 80%). mp 68-71 °C (Lit. 74-75 °C)⁷; R_f = 0.66 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3034, 1649, 1584, 1489, 1310, 1285, 1246, 1074, 939, 847, 799, 733, 691, 677, 627, 501; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 7.03 (2H, d, J 8.5), 7.10 (2H, d, J 7.5), 7.21 (1H, t, J 7.5), 7.41 (2H, t, J 8.0), 7.48 (2H, t, J 7.5), 7.58 (1H, t, J 7.5), 7.75-7.80 (2H, m), 7.82 (2H, d, J 8.5); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 117.3, 120.3, 124.7, 128.4, 130.0, 130.2, 132.1, 132.3, 132.6, 138.1, 155.7, 161.8, 195.6; HRMS (NSI⁺) calculated for $[\text{C}_{19}\text{H}_{15}\text{O}_2]$ (M+H)⁺ : m/z 275.1067, found 275.1068, (+0.5 ppm).

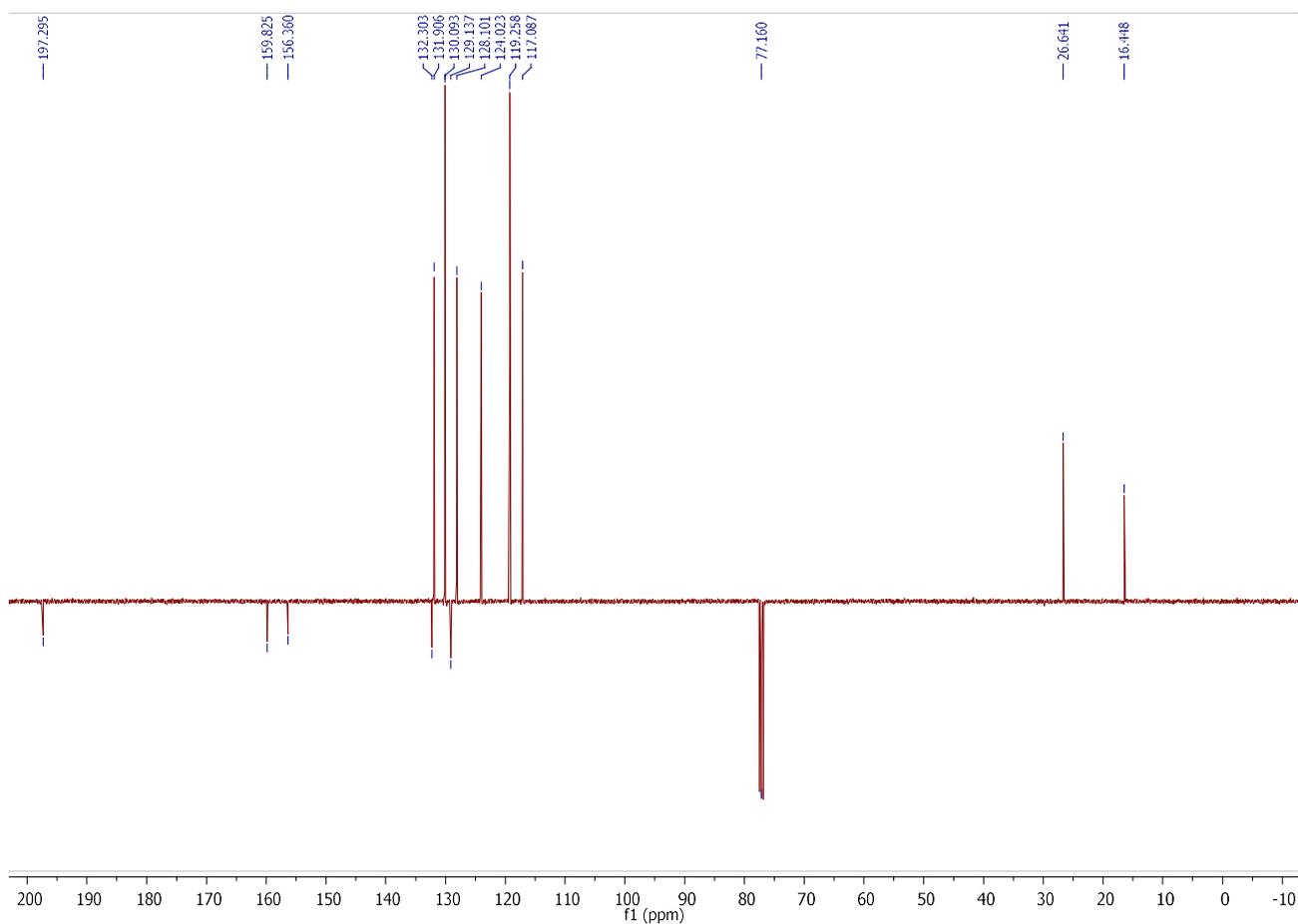


1-(3-methyl-4-phenoxyphenyl)ethan-1-one

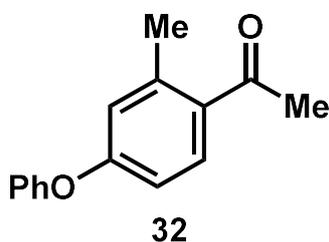


The title compound 1-(3-methyl-4-phenoxyphenyl)ethan-1-one (**31**) was prepared according to general procedure 5 using 1-(4-fluoro-3-methylphenyl)ethan-1-ol (61.7 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1-5% Et₂O in hexanes, 30 x 160 mm silica) gave a pale yellow oil (57 mg, 63%). *R_f* = 0.54 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3059, 2918, 1678, 1582, 1485, 1356, 1287, 1252, 1236, 1198, 1128, 961, 847, 741, 691, 592, 575; ¹H NMR (400 MHz, CDCl₃) δ_{H} : 2.35 (3H, s), 2.57 (3H, s), 6.81 (1H, d, *J* 8.4), 6.95-7.04 (2H, m), 7.11-7.19 (1H, m), 7.33-7.41 (2H, m), 7.70-7.77 (1H, m), 7.86-7.90 (1H, m); ¹³C NMR (101 MHz, CDCl₃) δ_{C} : 16.4, 26.6, 117.0, 119.3, 124.0, 128.1, 129.1, 130.1, 131.9, 132.3, 156.4, 159.8, 197.3; HRMS (NSI⁺) calculated [C₁₅H₁₅O₂]⁺ (M+H)⁺ : *m/z* : 227.1067, found 227.1066, (-0.2 ppm).

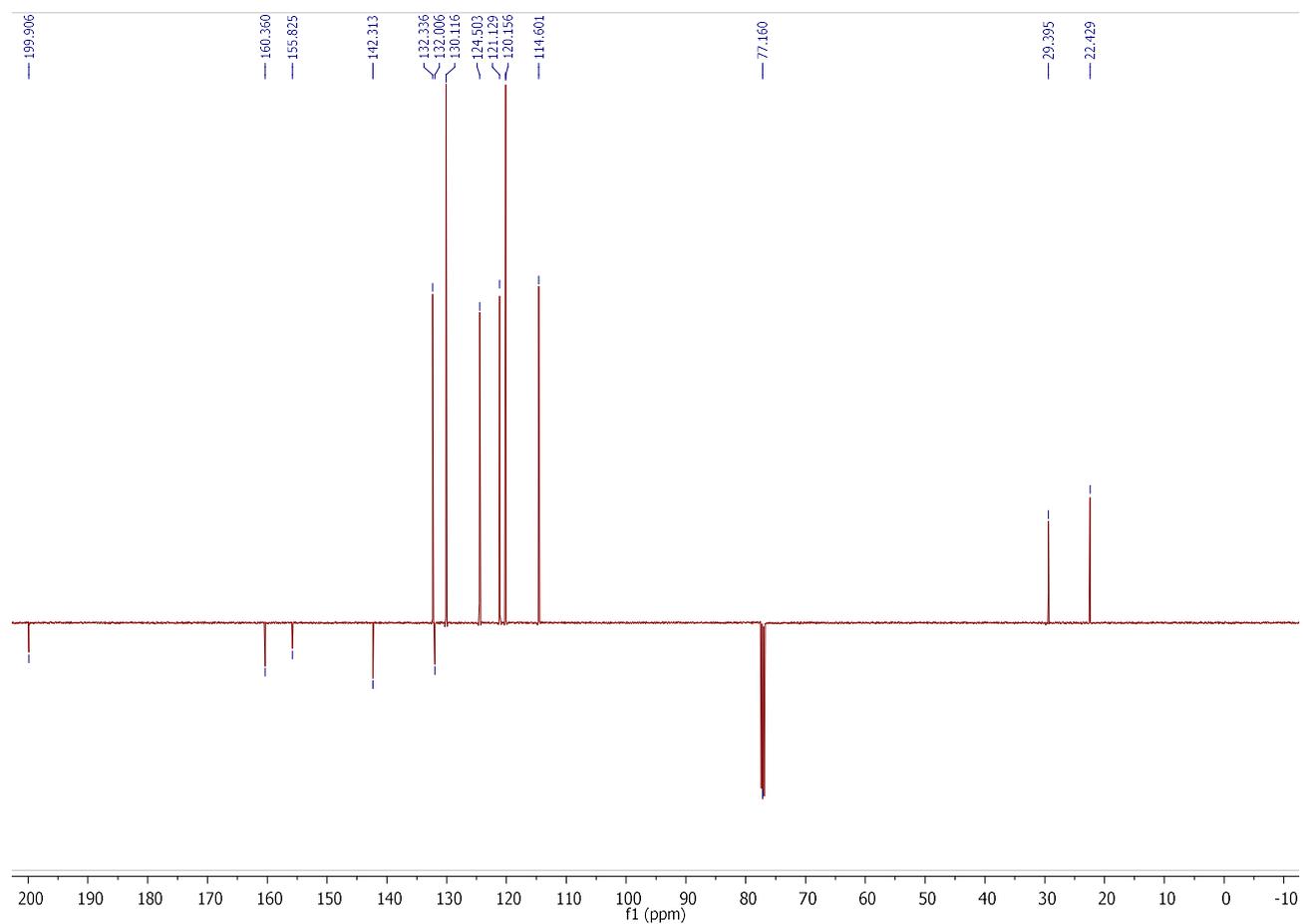
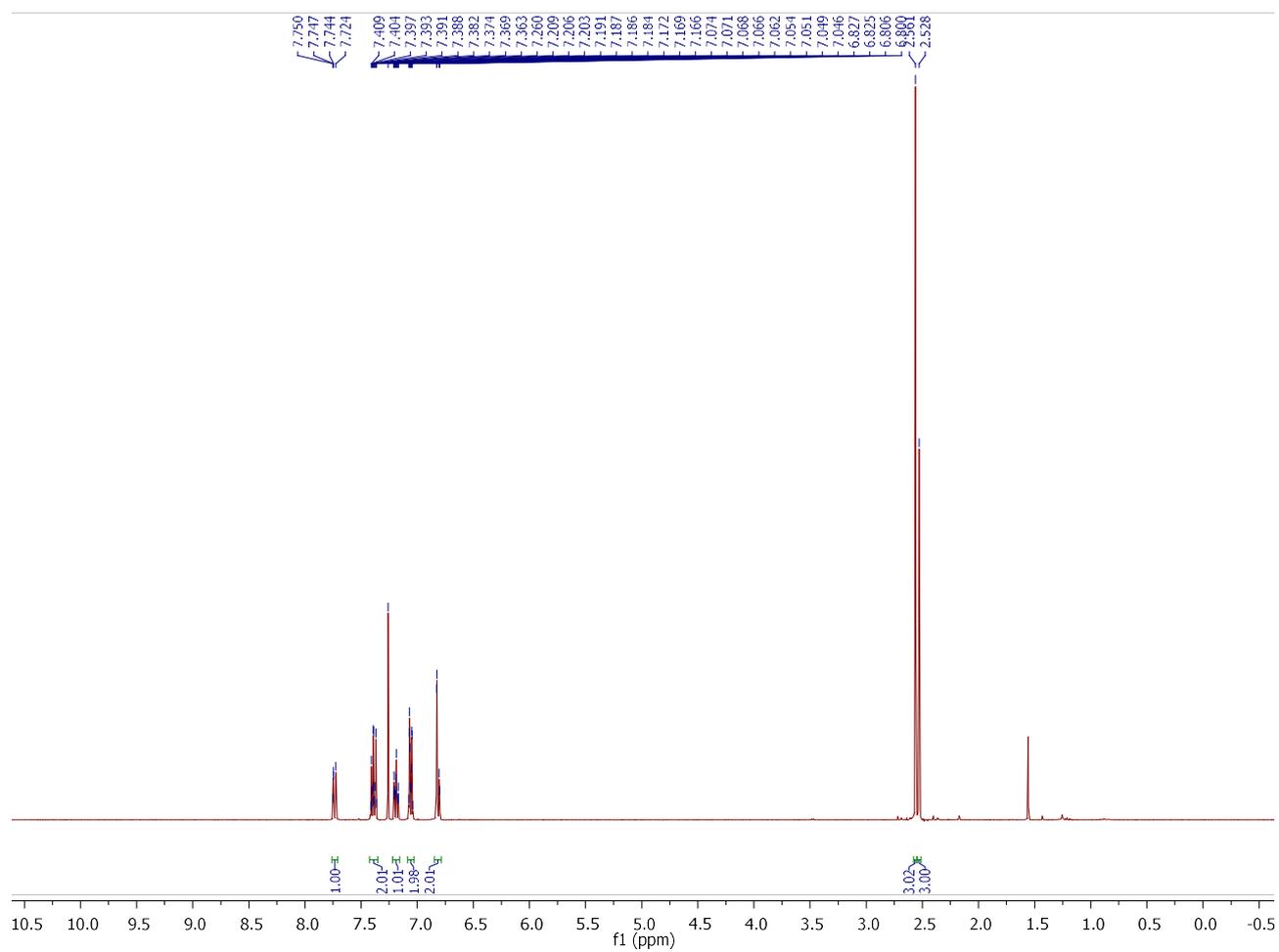




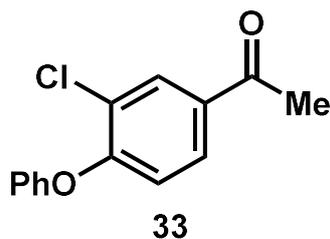
1-(2-methyl-4-phenoxyphenyl)ethan-1-one



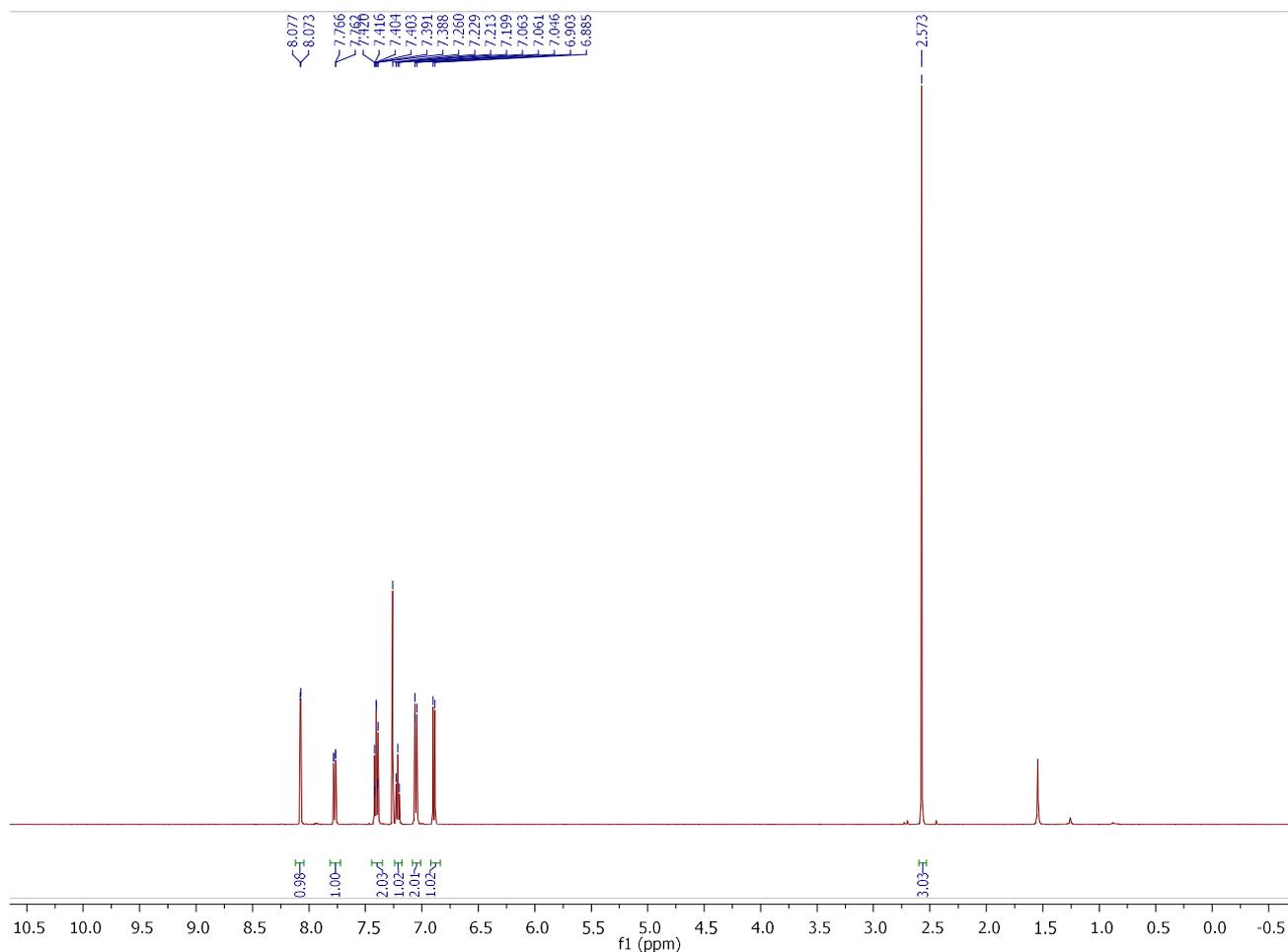
The title compound 1-(2-methyl-4-phenoxyphenyl)ethan-1-one (**32**) was prepared according to general procedure 5 using 1-(4-fluoro-2-methylphenyl)ethan-1-ol (61.7 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 160 mm silica) gave a colourless oil (47 mg, 52%). $R_f = 0.60$ (eluent = 20% EtOAc in hexanes); $\nu_{\max} / \text{cm}^{-1}$ (film) 2974, 2916, 1674, 1589, 1562, 1489, 1449, 1354, 1234, 1202, 1165, 1124, 974, 773, 694, 579, 490; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.53 (3H, s), 2.56 (3H, s), 6.78-6.85 (2H, m), 7.02-7.09 (2H, m), 7.15-7.22 (1H, m), 7.35-7.43 (2H, m), 7.70-7.76 (1H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 22.4, 29.4, 114.6, 120.2, 121.1, 124.5, 130.1, 132.0, 132.3, 142.3, 155.8, 160.4, 199.9; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{15}\text{O}_2]^+$ ($\text{M}+\text{H}$) $^+$: m/z 227.1067, found 227.1066, (-0.2 ppm).

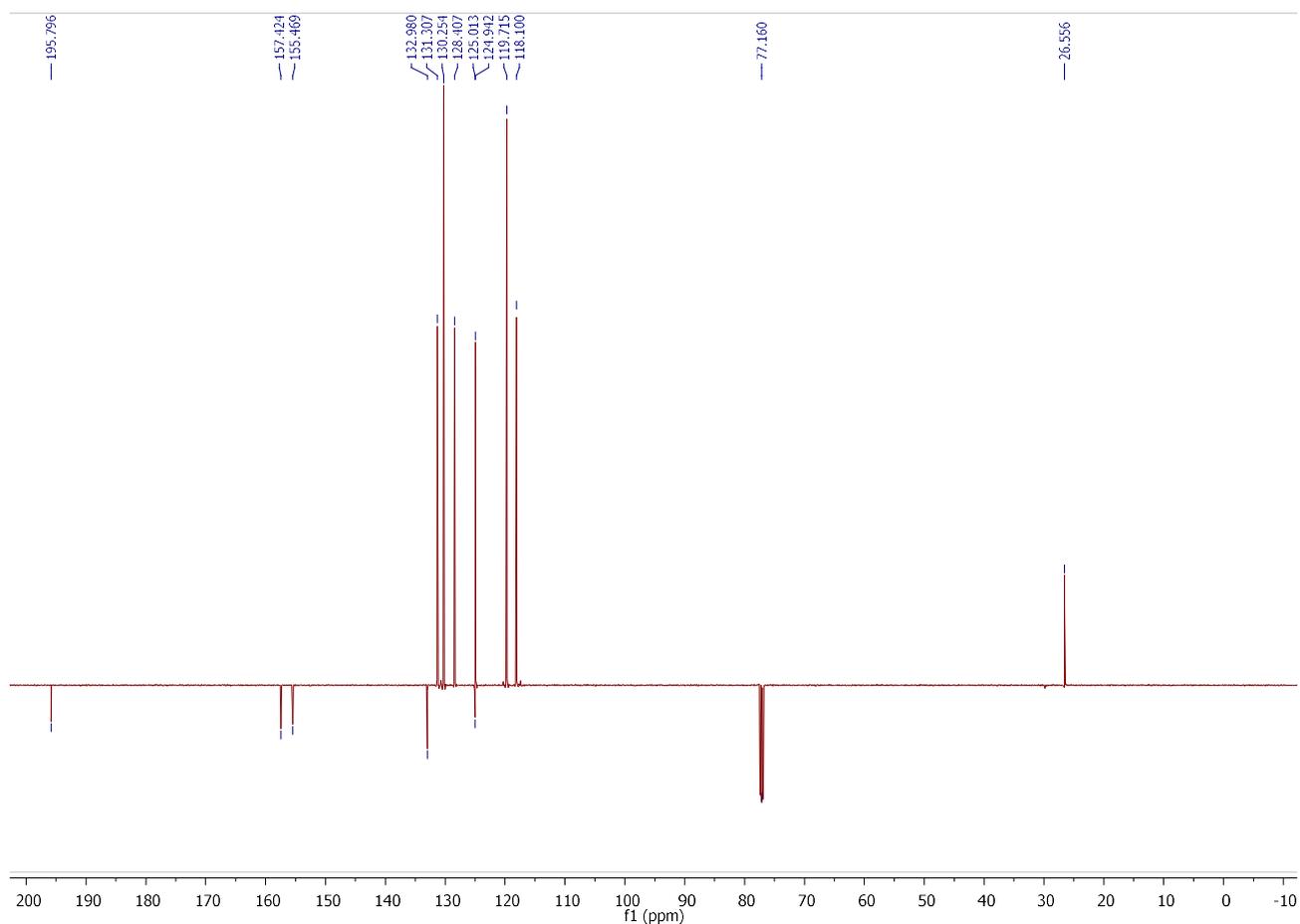


1-(3-chloro-4-phenoxyphenyl)ethan-1-one

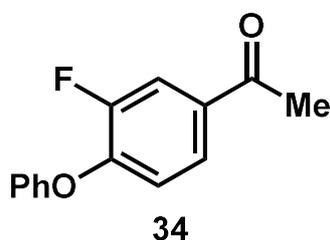


The title compound 1-(3-chloro-4-phenoxyphenyl)ethan-1-one (**33**) was prepared according to general procedure 5 using 1-(3-chloro-4-fluorophenyl)ethan-1-ol (69.8 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 160 mm silica) gave a pale yellow oil (58 mg, 58%). $R_f = 0.52$ (eluent = 20% EtOAc in hexanes); $\nu_{\max} / \text{cm}^{-1}$ (film) 1682, 1582, 1481, 1356, 1250, 1192, 1161, 881, 781, 687, 573, 502; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.57 (3H, s), 6.89 (1H, d, J 9.0), 7.02-7.09 (2H, m), 7.18-7.24 (1H, m), 7.37-7.44 (2H, m), 7.77 (1H, dd, J 8.5, 2.0), 8.08 (1H, d, J 2.0); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 26.6, 118.1, 119.7, 124.9, 125.0, 128.4, 130.3, 131.3, 133.0, 155.5, 157.4, 195.8; HRMS (NSI^+) calculated for $[\text{C}_{14}\text{H}_{12}\text{O}_2\text{Cl}]^+$ ($\text{M}+\text{H}$) $^+$: m/z 247.0520, found 247.0522, (+0.7 ppm).

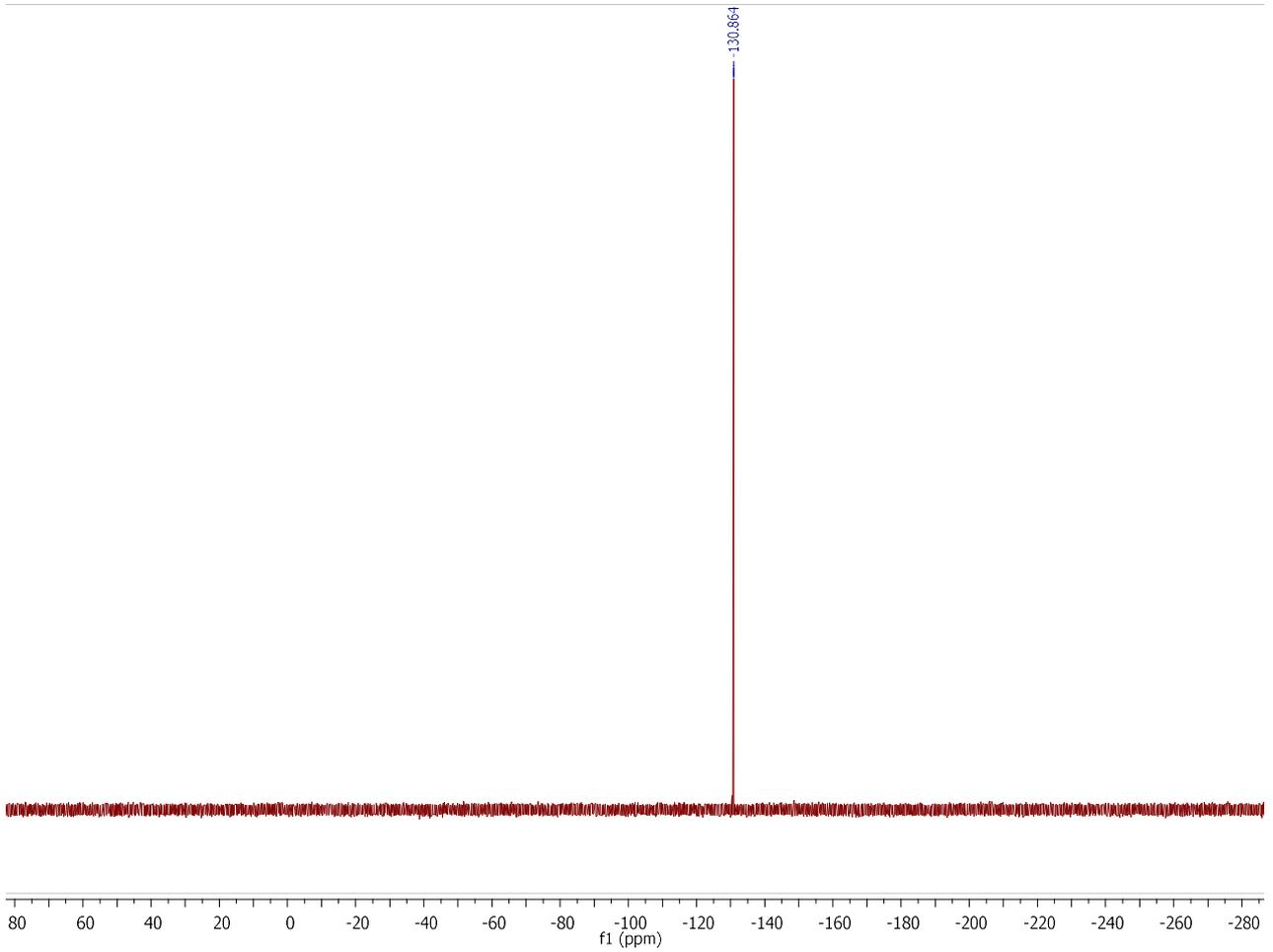
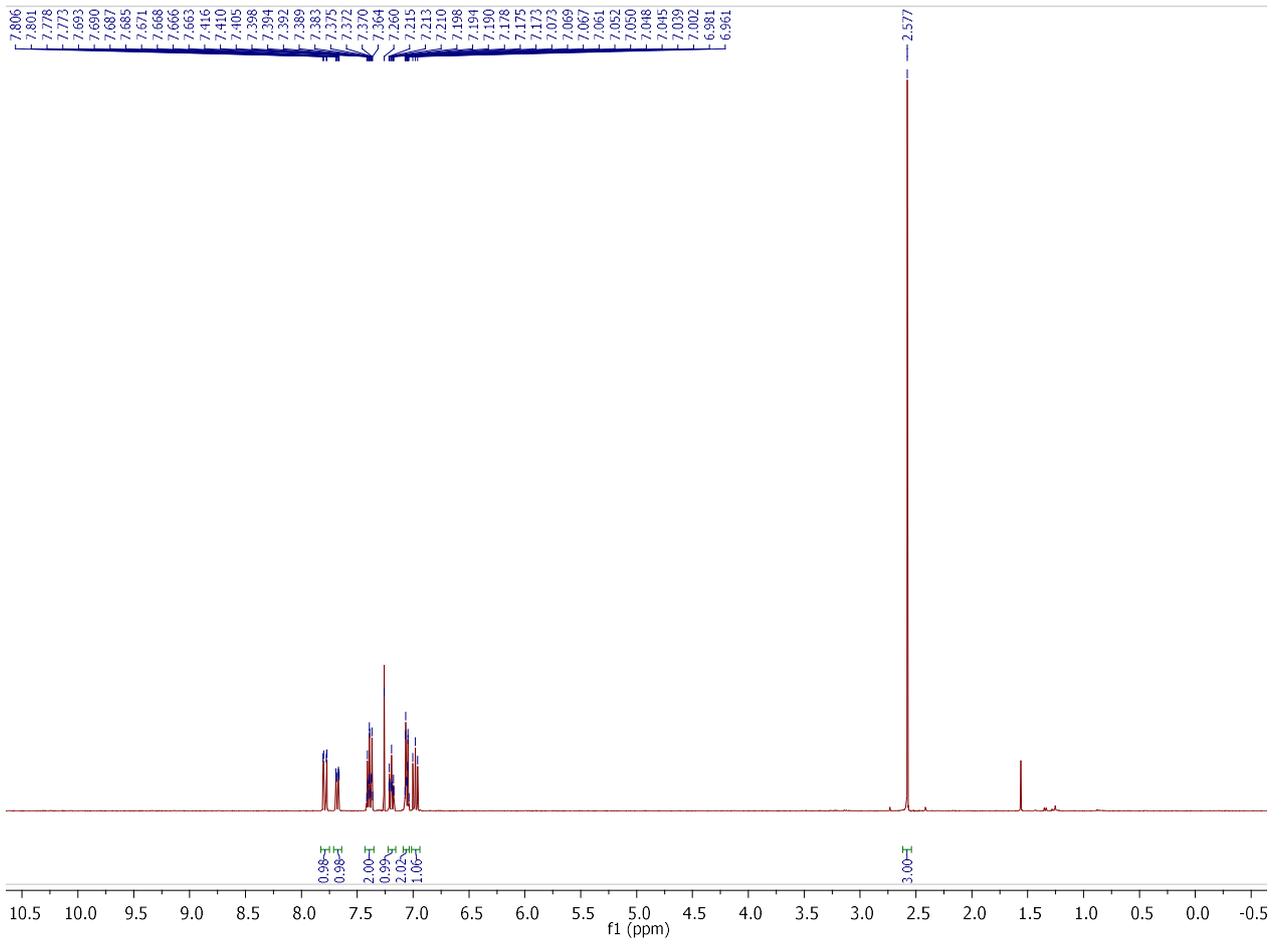


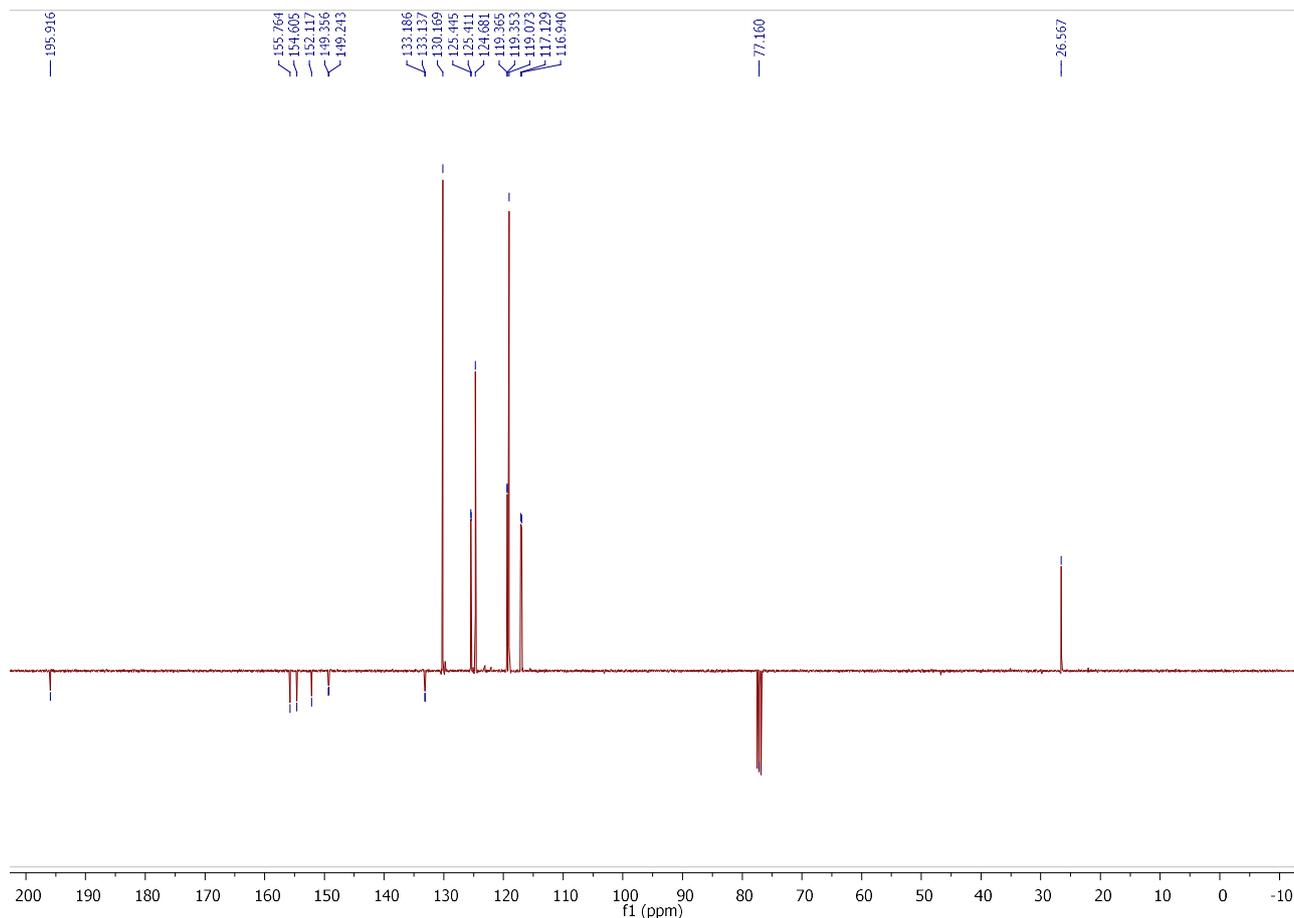


1-(3-fluoro-4-phenoxyphenyl)ethan-1-one

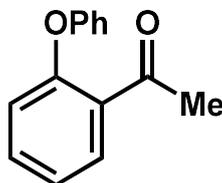


The title compound 1-(3-fluoro-4-phenoxyphenyl)ethan-1-one (**34**) was prepared according to general procedure 5 using 1(3,4-difluorophenyl)ethan-1-ol (63.3 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 170 mm silica) gave a pale yellow oil (48 mg, 52%). R_f = 0.50 (eluent = 20 % EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3073, 1684, 1587, 1506, 1485, 1425, 1273, 1194, 903, 849, 745, 687, 592, 542; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.58 (3H, s), 6.94-7.02 (1H, m), 7.02-7.09 (2H, m), 7.15-7.23 (1H, m), 7.34-7.43 (2H, m), 7.65-7.71 (1H, m), 7.75-7.83 (1H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -130.9; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 26.6, 117.0 (d, J 19.1), 119.1, 119.4 (d, J 1.2), 124.7, 125.4 (d, J 3.4), 130.2, 133.2 (d, J 4.9), 149.3 (d, J 11.4), 153.3 (d, J 251.2), 155.8, 195.9; HRMS (NSI^+) calculated for $[\text{C}_{14}\text{H}_{12}\text{O}_2\text{F}]^+$ ($\text{M}+\text{H}$) $^+$: m/z 231.0816, found 231.0817, (+0.5 ppm).



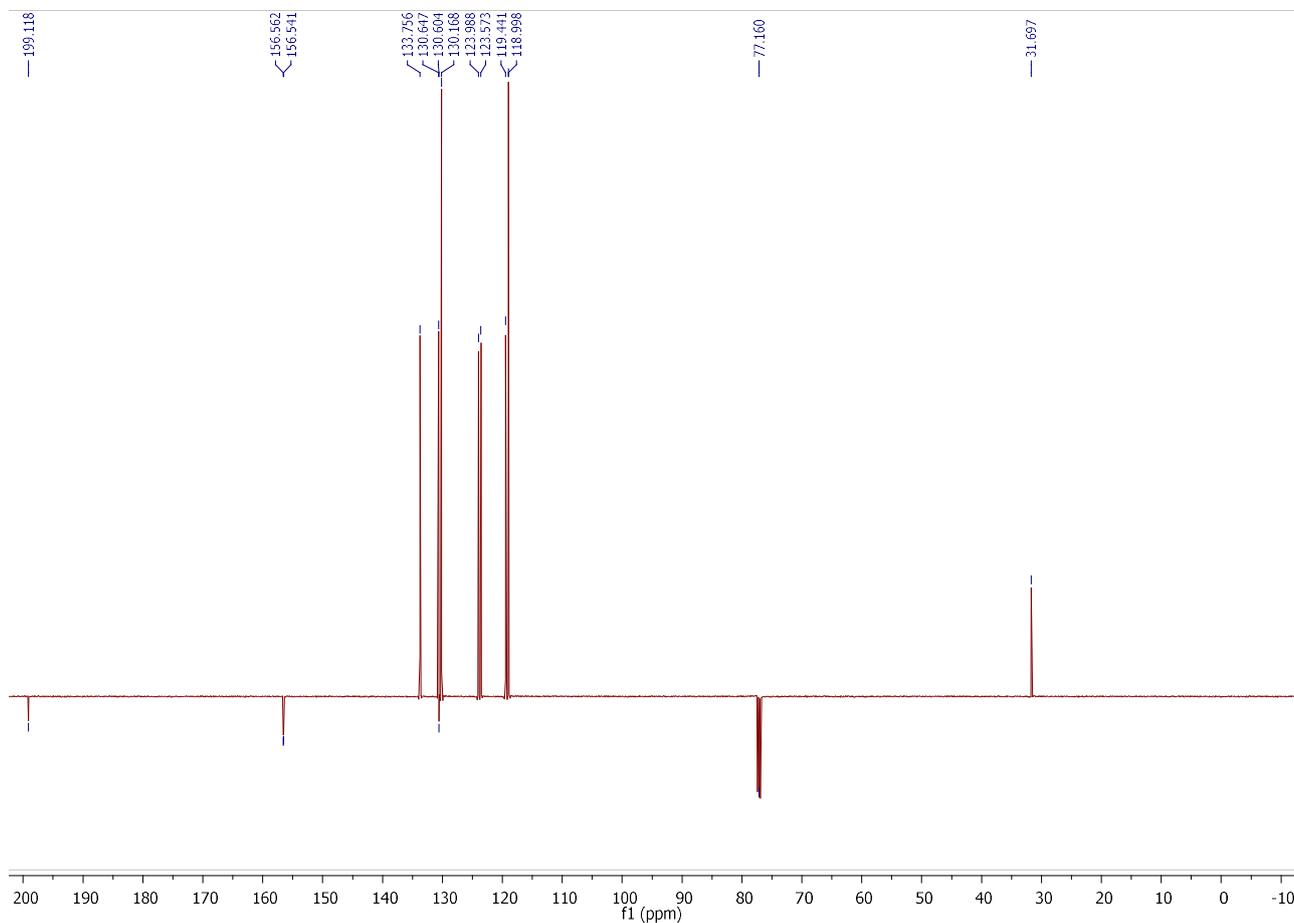
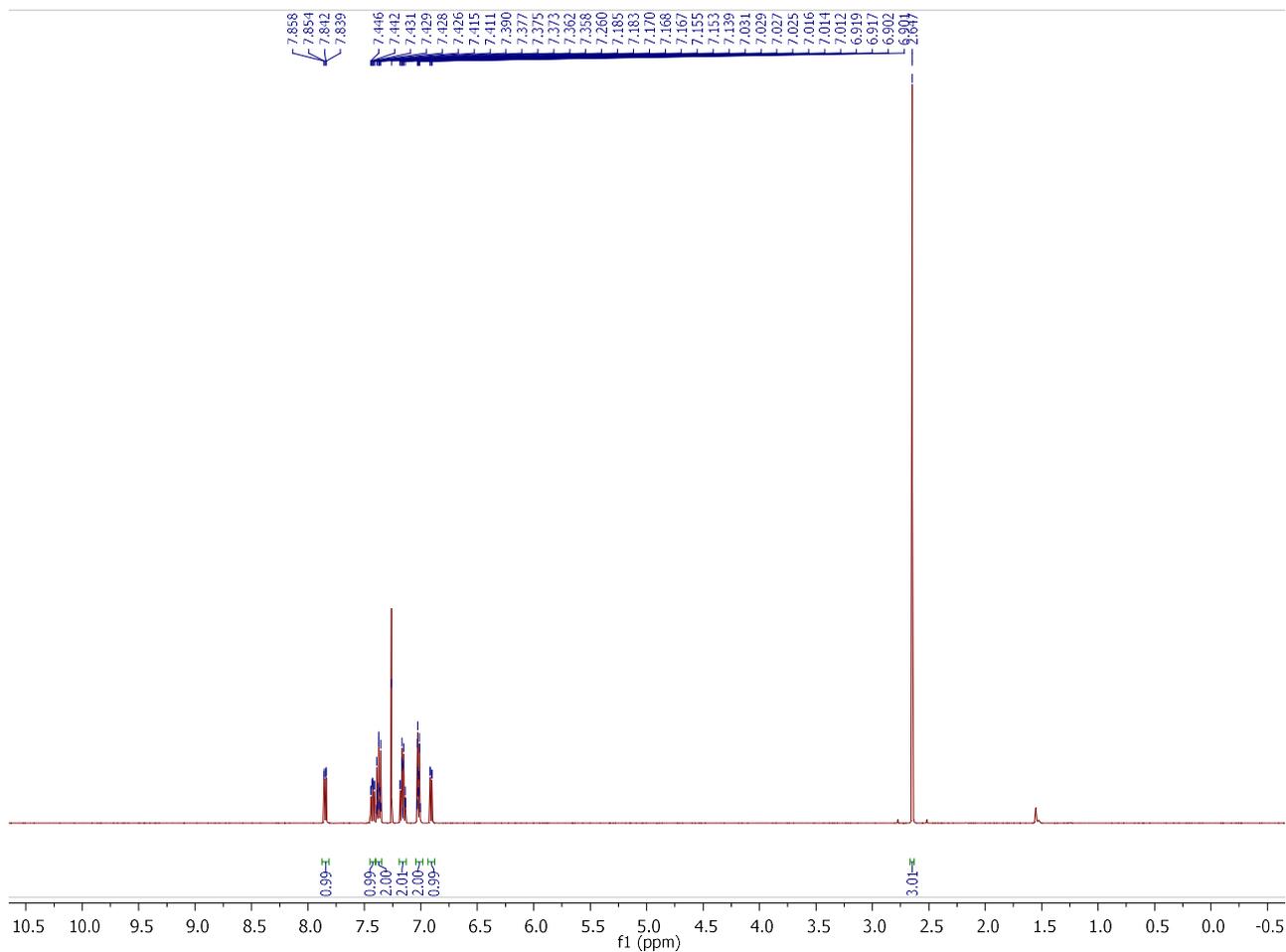


1-(2-phenoxyphenyl)ethan-1-one



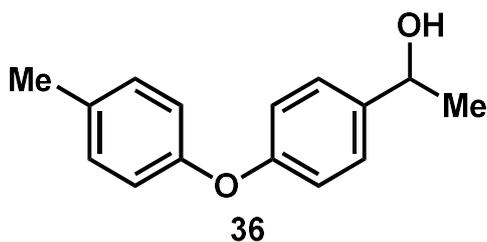
35

The title compound 1-(2-phenoxyphenyl)ethan-1-one (**35**) was prepared according to general procedure 5 using 1-(2-fluorophenyl)ethan-1-ol (56.1 mg, 0.400 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 170 mm silica) gave a colourless oil (45 mg, 53%). $R_f = 0.66$ (eluent = 20% EtOAc in hexanes); $\nu_{\max} / \text{cm}^{-1}$ (film) 3073, 1676, 1597, 1570, 1474, 1445, 1287, 1219, 1153, 872, 754, 691, 596, 496; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.65 (3H, s), 6.91 (1H, dd, J 8.0, 1.0), 6.99-7.04 (2H, m), 7.12-7.20 (2H, m), 7.34-7.40 (2H, m), 7.40-7.46 (1H, m), 7.85 (1H, dd J 8.0, 2.0); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 31.7, 119.0, 119.4, 123.6, 124.0, 130.2, 130.6, 130.6, 133.9, 156.5, 156.6, 199.1; HRMS (NSI^+) calculated for $[\text{C}_{14}\text{H}_{13}\text{O}_2]^+$ ($\text{M}+\text{H}^+$) : m/z 213.0910, found 213.0909, (-0.5 ppm).

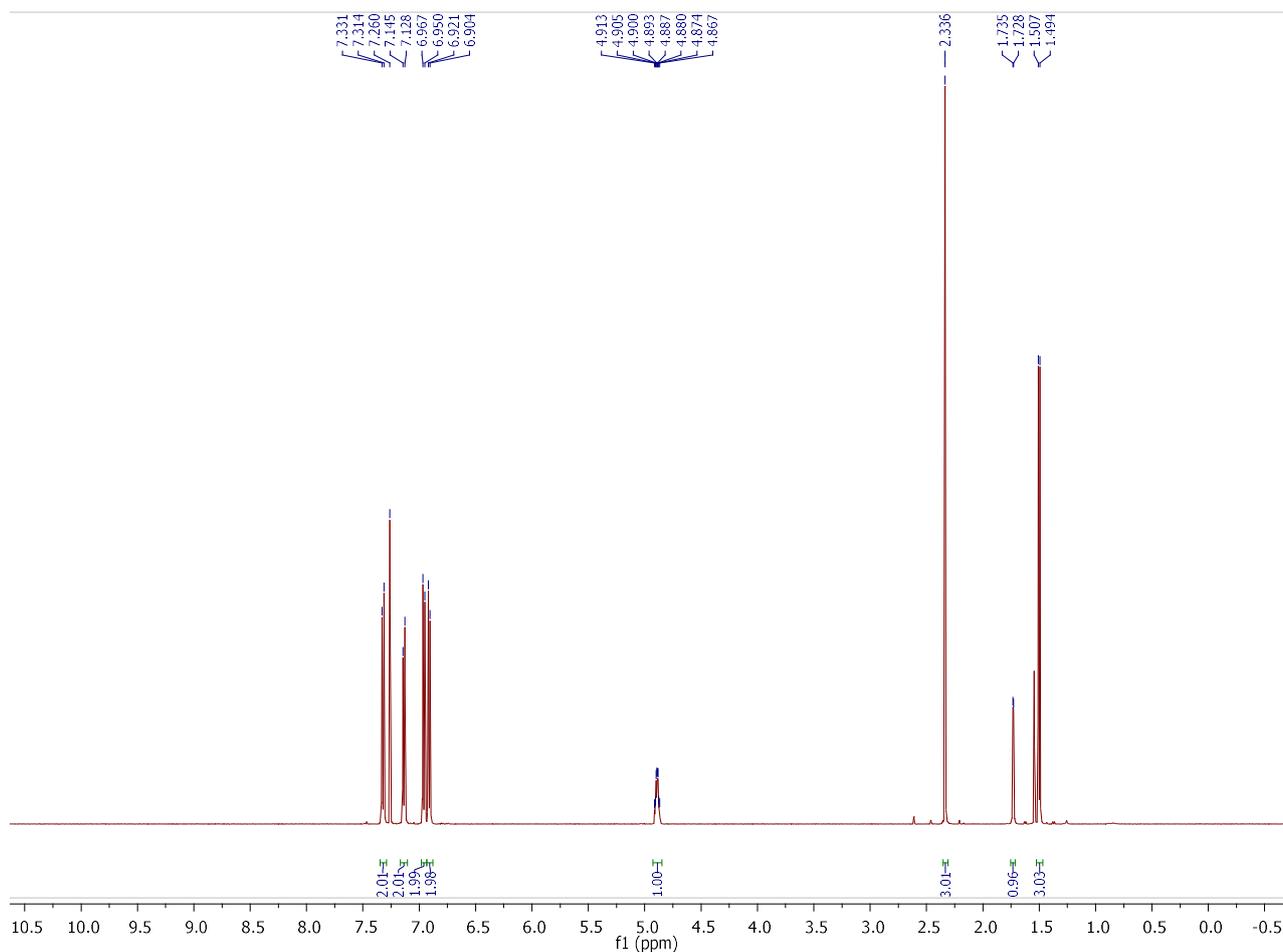


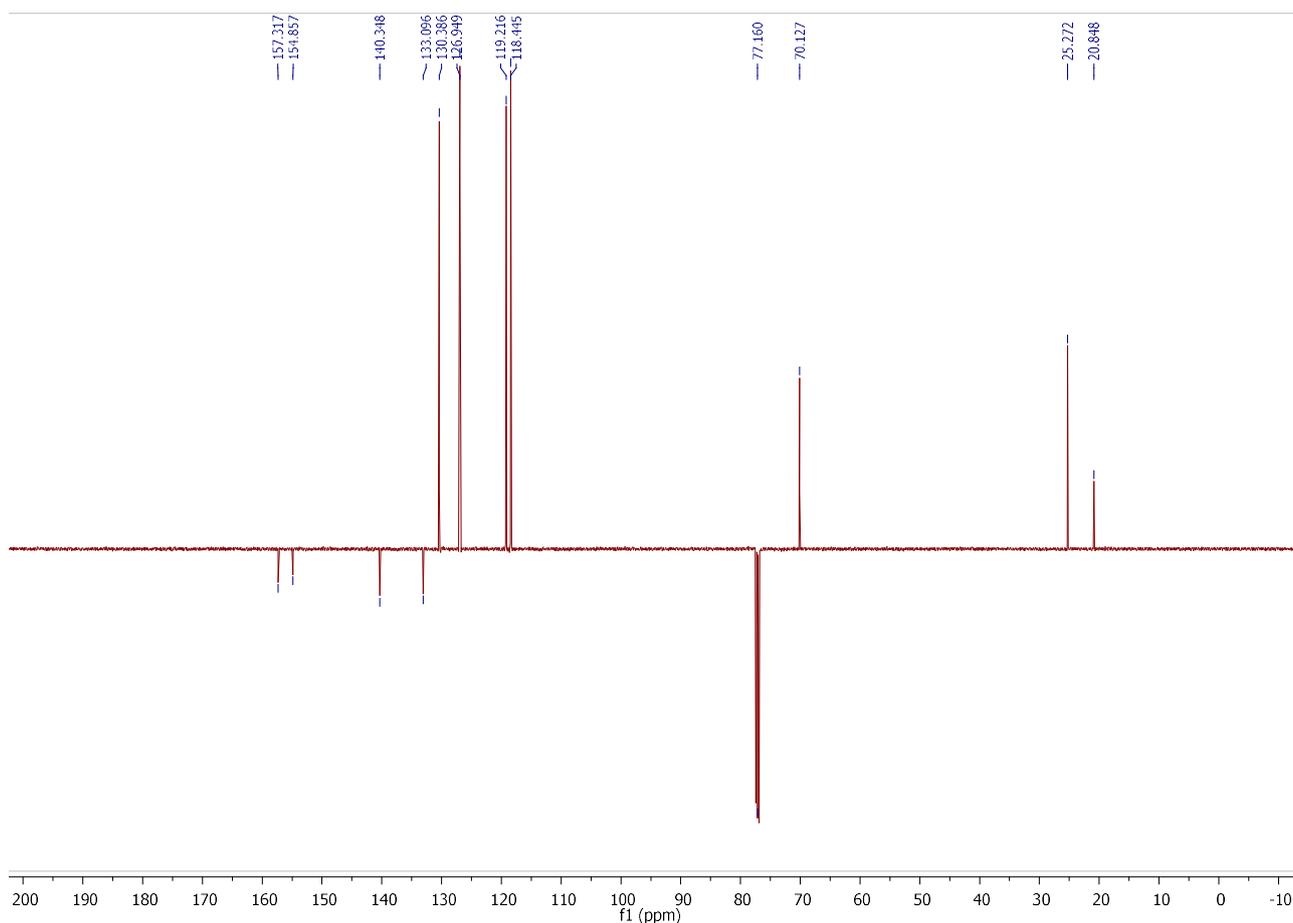
2.4. Scope of redox neutral S_NAr protocol

1-(4-(*p*-toloxy)phenyl)ethan-1-ol

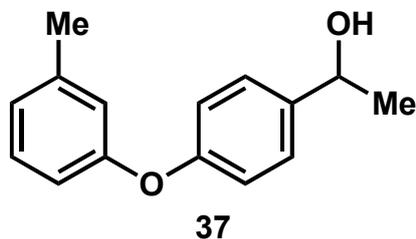


The title compound 1-(4-(*p*-toloxy)phenyl)ethan-1-ol (**36**) was prepared according to general procedure 4 using *p*-cresol (47.6 mg, 0.440 mmol) as a nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 100 mm silica) gave a pale yellow oil (76 mg, 83%). $R_f = 0.28$ (eluent = 20% EtOAc in hexanes); $\nu_{\max} / \text{cm}^{-1}$ (film) 3343, 3034, 2970, 1599, 1499, 1233, 1206, 1084, 1011, 870, 814, 492; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 1.50 (3H, d, J 6.5), 1.74 (1H, d, J 3.5), 2.34 (3H, s), 4.89 (1H, dq, J 6.5, 3.5), 6.91 (2H, d, J 8.5), 6.96 (2H, d, J 8.5), 7.14 (2H, d, J 8.5), 7.32 (2H, d, J 8.5); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 20.8, 25.3, 70.1, 118.4, 119.2, 126.9, 130.4, 133.1, 140.3, 154.9, 157.3; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{16}\text{O}_2\text{Na}]^+$ ($\text{M}+\text{Na}$) $^+$: m/z 251.1043, found 251.1045, (+1.0 ppm).

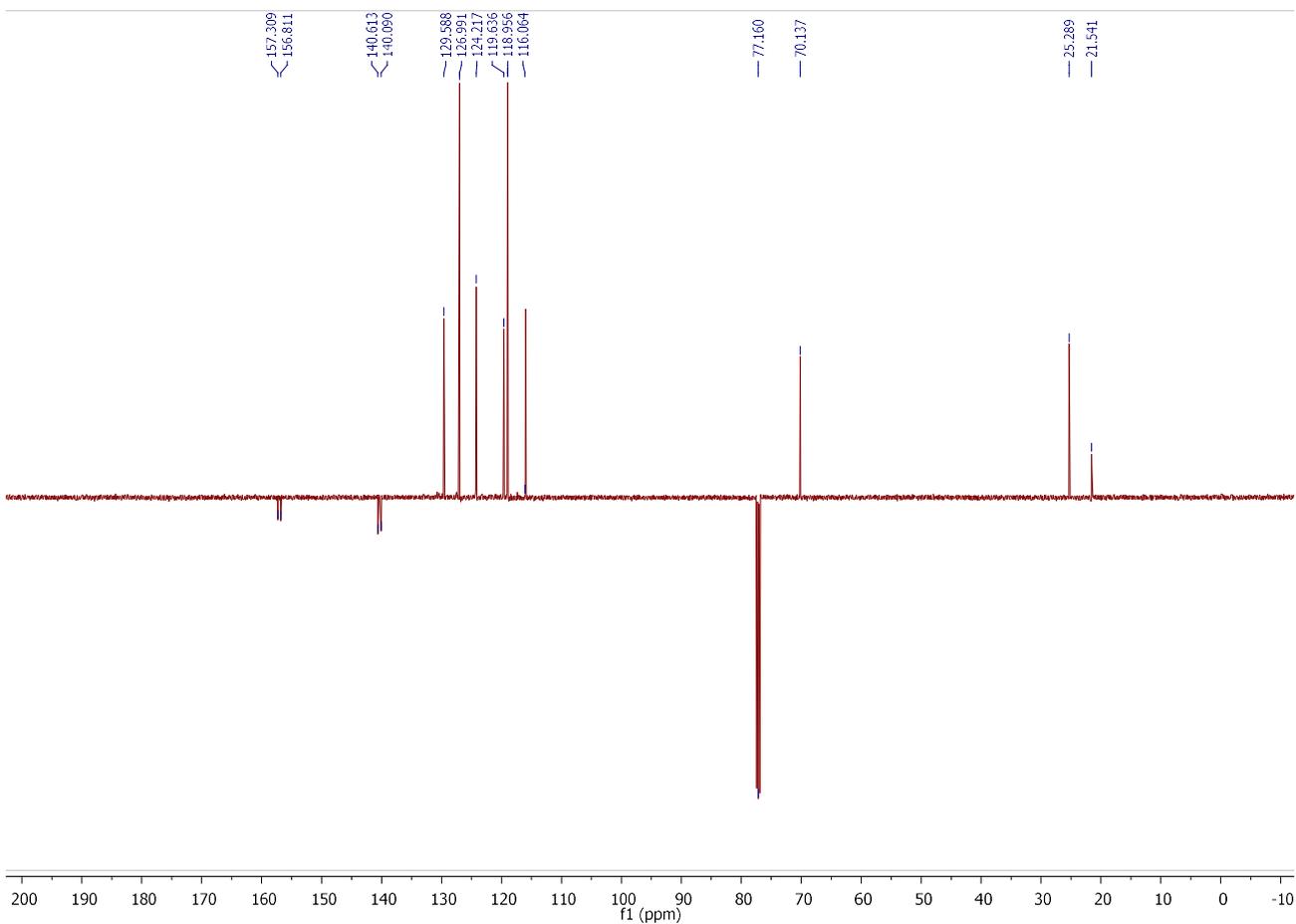
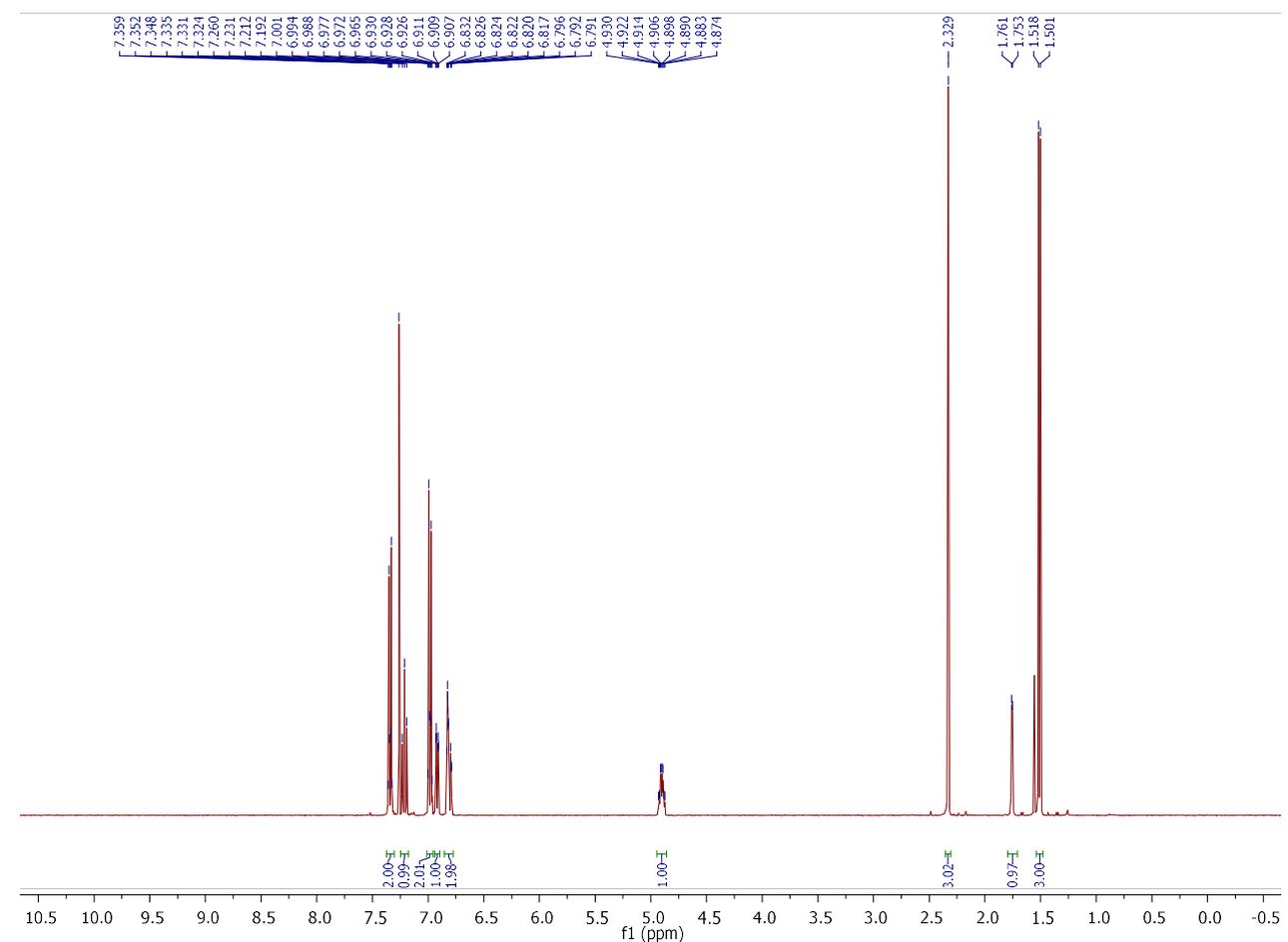




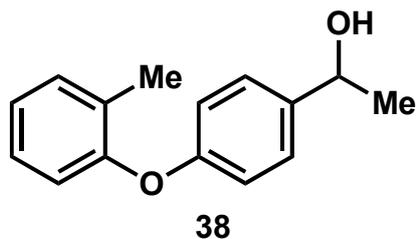
1-(4-(*m*-tolyloxy)phenyl)ethan-1-ol



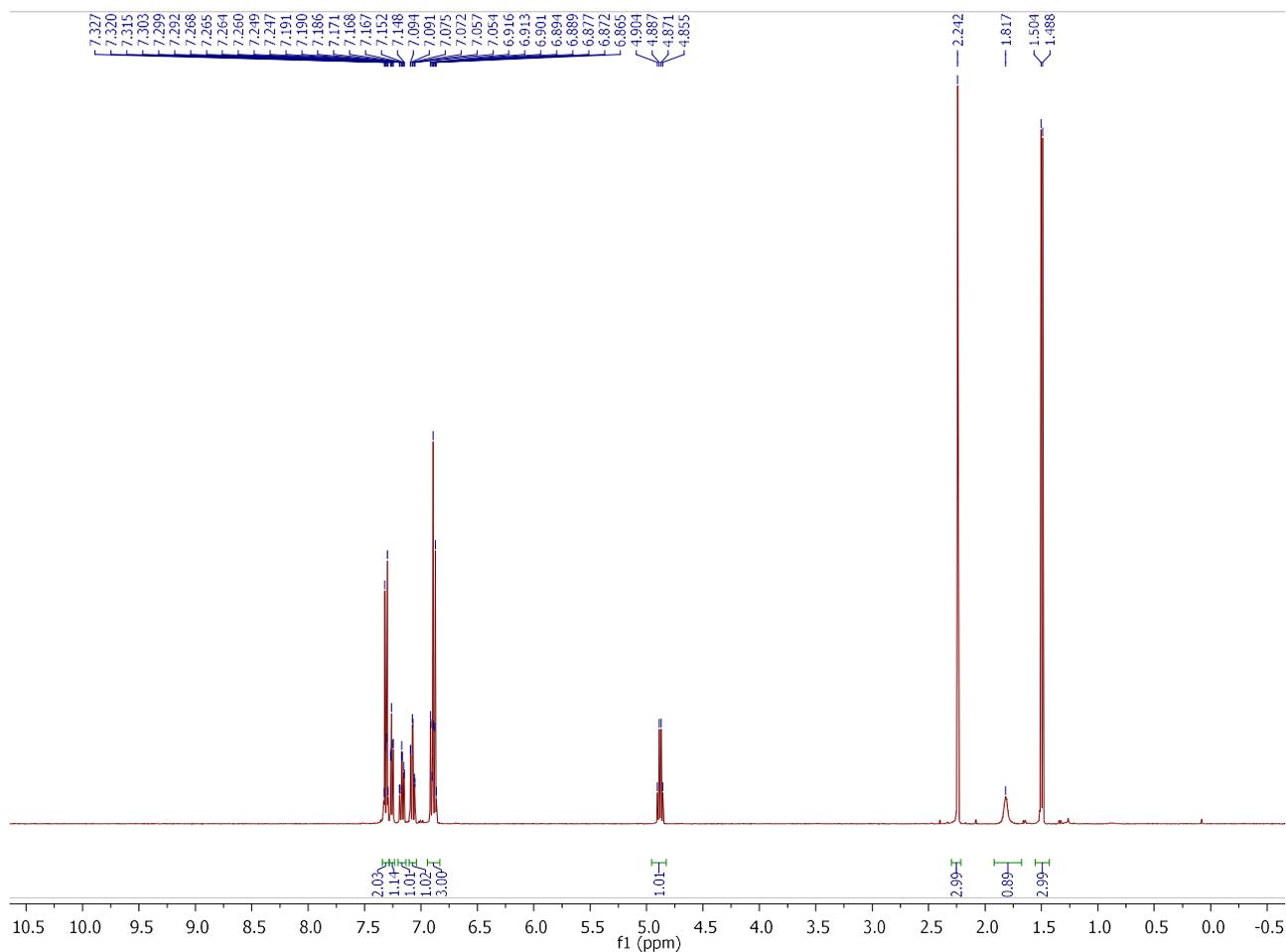
The title compound 1-(4-(*m*-tolyloxy)phenyl)ethan-1-ol (**37**) was prepared according to general procedure 4 using *m*-cresol (46.0 μ L, 47.6 mg, 0.440 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 100 mm silica) gave a pale yellow oil (73 mg, 80%). R_f = 0.28 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3337, 2974, 1607, 1584, 1504, 1483, 1086, 1070, 1007, 935, 779, 687, 542, 442; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.51 (3H, d, J 6.4), 1.76 (1H, d, J 3.2), 2.33 (3H, s), 4.90 (1H, dq, J 6.4, 3.2), 6.77-6.85 (2H, m), 6.89-6.95 (1H, m), 6.95-7.02 (2H, m), 7.21 (1H, t, J 8.0), 7.31-7.38 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 21.5, 25.3, 70.1, 116.1, 119.0, 119.6, 124.2, 127.0, 129.6, 140.0, 140.6, 156.8, 157.3; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{15}\text{O}_2]^+$ (M-H^+) : m/z 227.1078, found 227.1082, (+2.0 ppm).

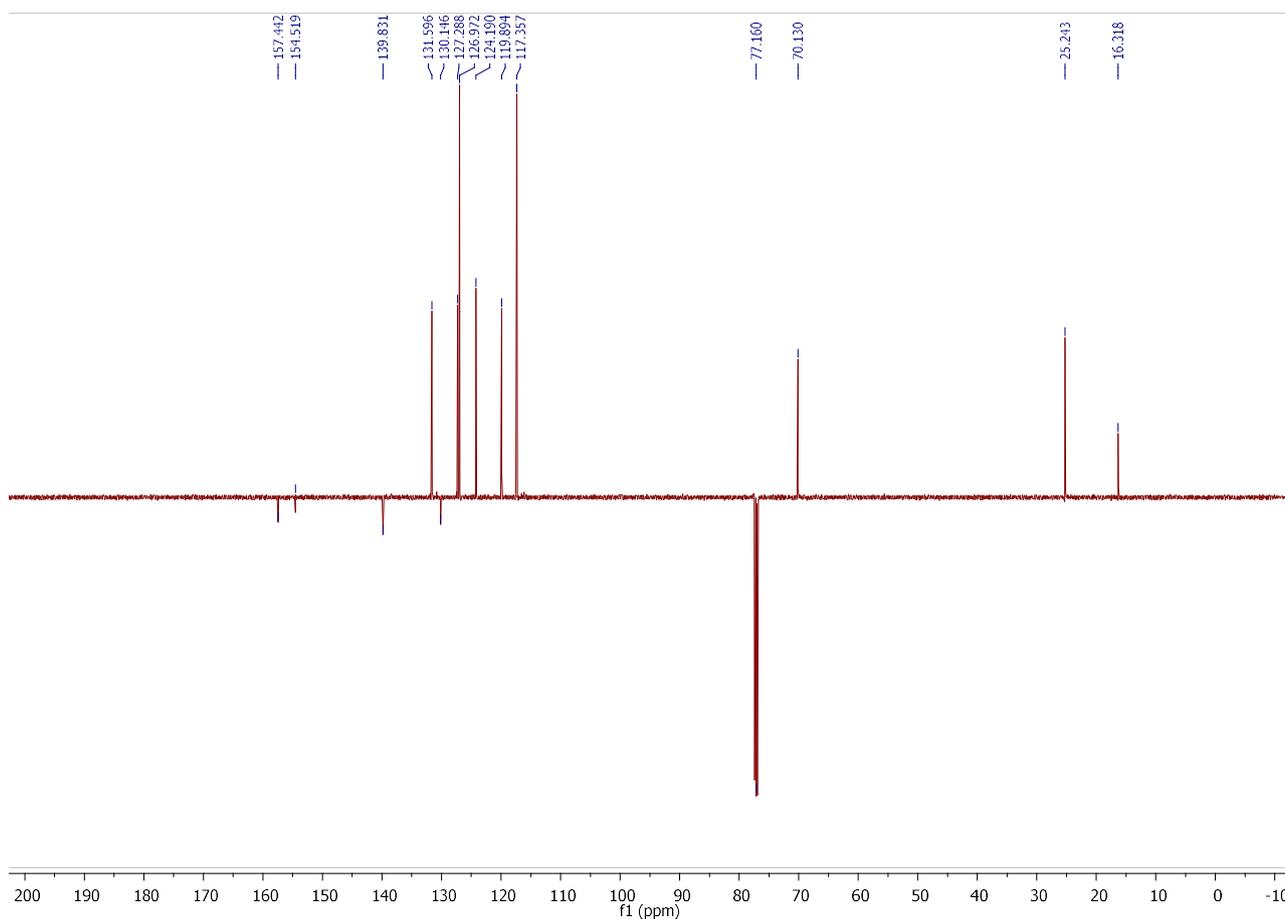


1-(4-(*o*-tolylloxy)phenyl)ethan-1-ol

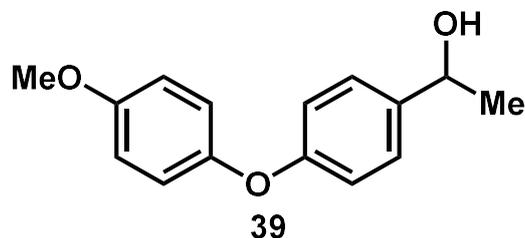


The title compound 1-(4-(*o*-tolylloxy)phenyl)ethan-1-ol (**38**) was prepared according to general procedure 4 using *o*-cresol (45.0 μ L, 47.6 mg, 0.440 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 100 mm silica) gave a pale yellow oil (71 mg, 78%). R_f = 0.28 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3325, 2970, 1605, 1582, 1504, 1483, 1233, 1180, 878, 835, 756, 540, 442; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.50 (3H, d, J 6.4), 1.82 (1H, br), 2.24 (3H, s), 4.88 (1H, q, J 6.4), 6.84-6.93 (3H, m), 7.07 (1H, dt, J 7.8, 1.2), 7.13-7.21 (1H, m), 7.23-7.28 (1H, m), 7.28-7.34 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 16.3, 25.2, 70.1, 117.4, 119.9, 124.2, 127.0, 127.3, 130.1, 131.6, 139.8, 154.5, 157.4; HRMS (NSI^+) calculated for $[\text{C}_{15}\text{H}_{16}\text{O}_2\text{Na}]^+$ ($\text{M}+\text{Na}$) $^+$: m/z 251.1043, found 251.1045, (+1.0 ppm).

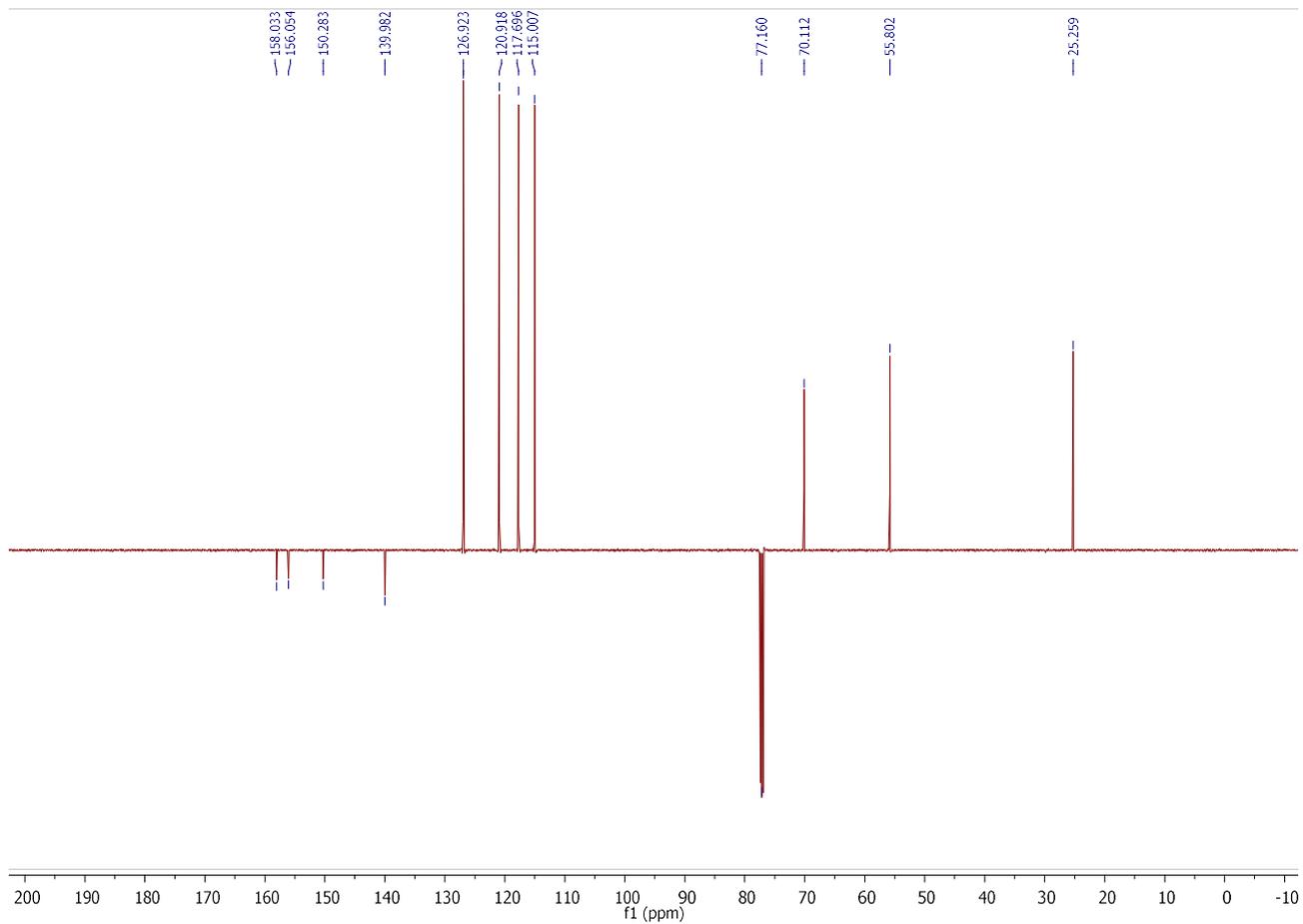
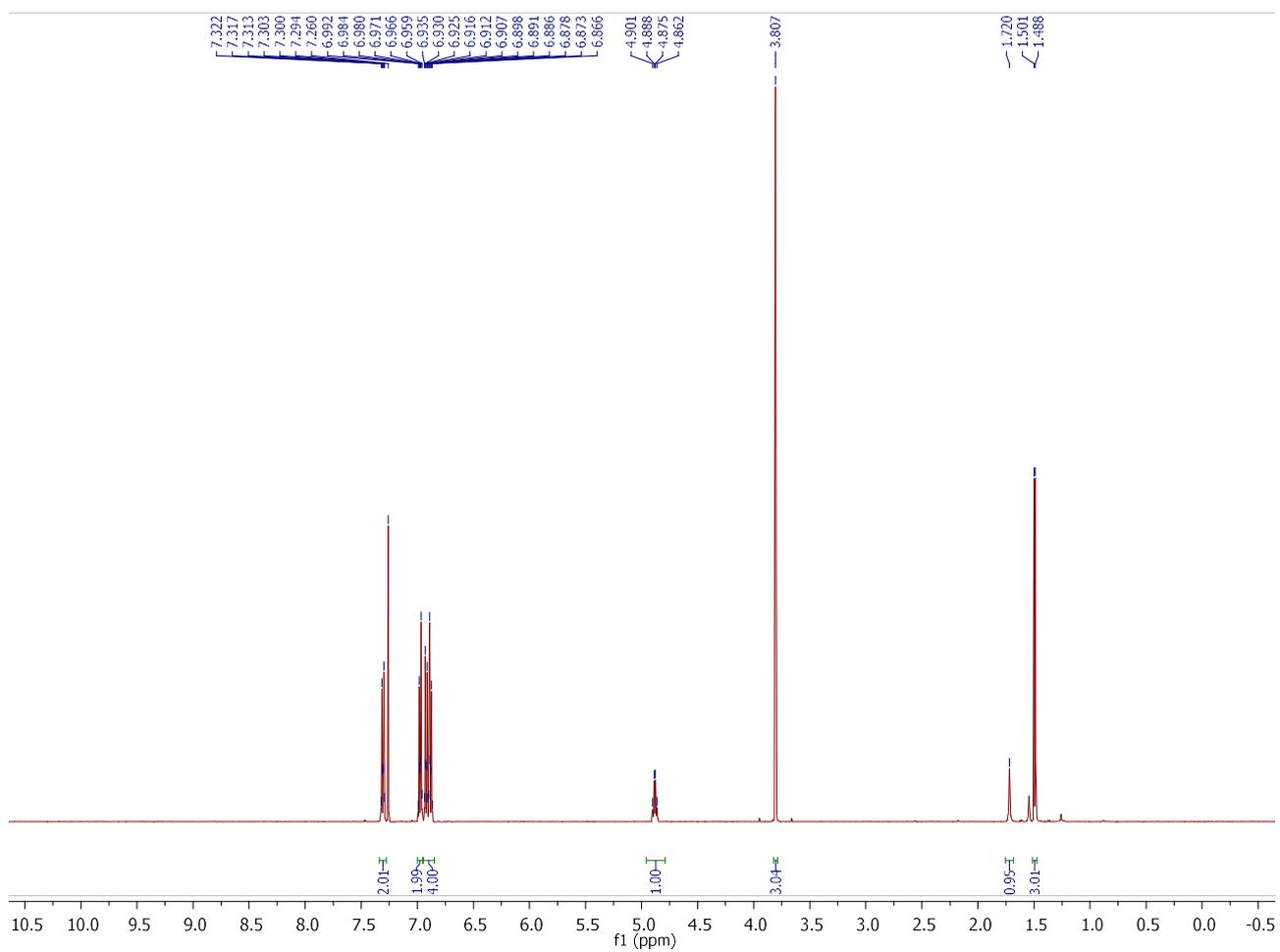




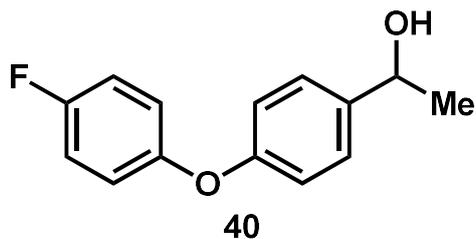
1-(4-(4-methoxyphenoxy)phenyl)ethan-1-ol



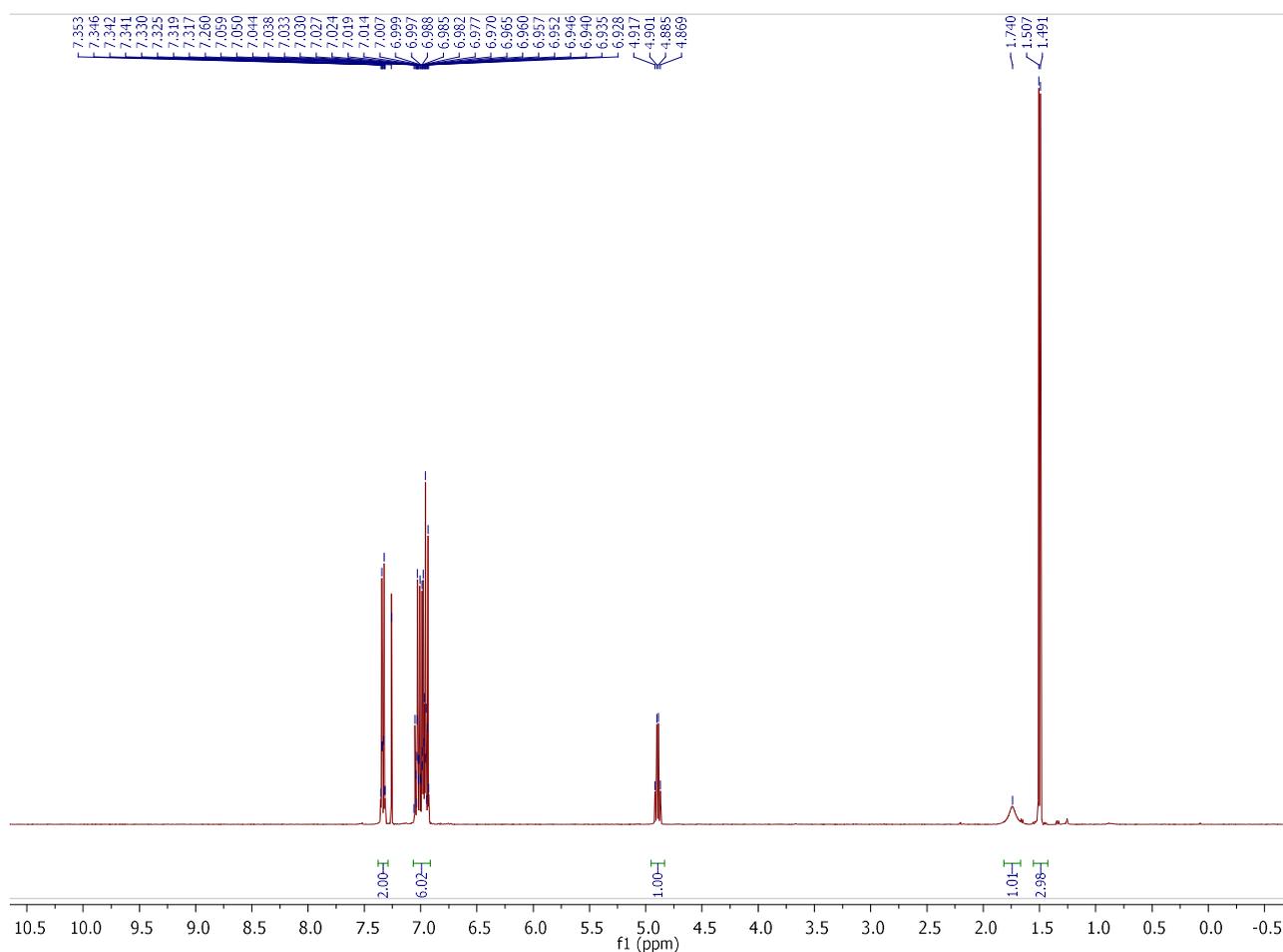
The title compound 1-(4-(4-methoxyphenoxy)phenyl)ethan-1-ol (**39**) was prepared according to general procedure 4 using 4-methoxyphenol (54.6 mg, 0.440 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-20 % EtOAc in hexanes, 30 x 100 mm silica) gave an off-white solid (87 mg, 89%). mp 40-43 °C; R_f = 0.17 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3271, 2970, 2839, 1605, 1501, 1229, 1072, 1007, 899, 880, 847, 831; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 1.49 (3H, d, J 6.5), 1.72 (1H, br s), 3.81 (3H, s), 4.88 (1H, q, J 6.5), 6.85-6.95 (4H, m), 6.95-7.01 (2H, m), 7.28-7.34 (2H, m); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 25.3, 55.8, 70.1, 115.0, 117.7, 120.9, 126.9, 140.0, 150.3, 156.1, 158.0; HRMS (ASAP⁺) $[\text{C}_{15}\text{H}_{15}\text{O}_3]^+$ (M-H)⁺ : m/z 243.1016, found 243.1012, (-1.5 ppm).

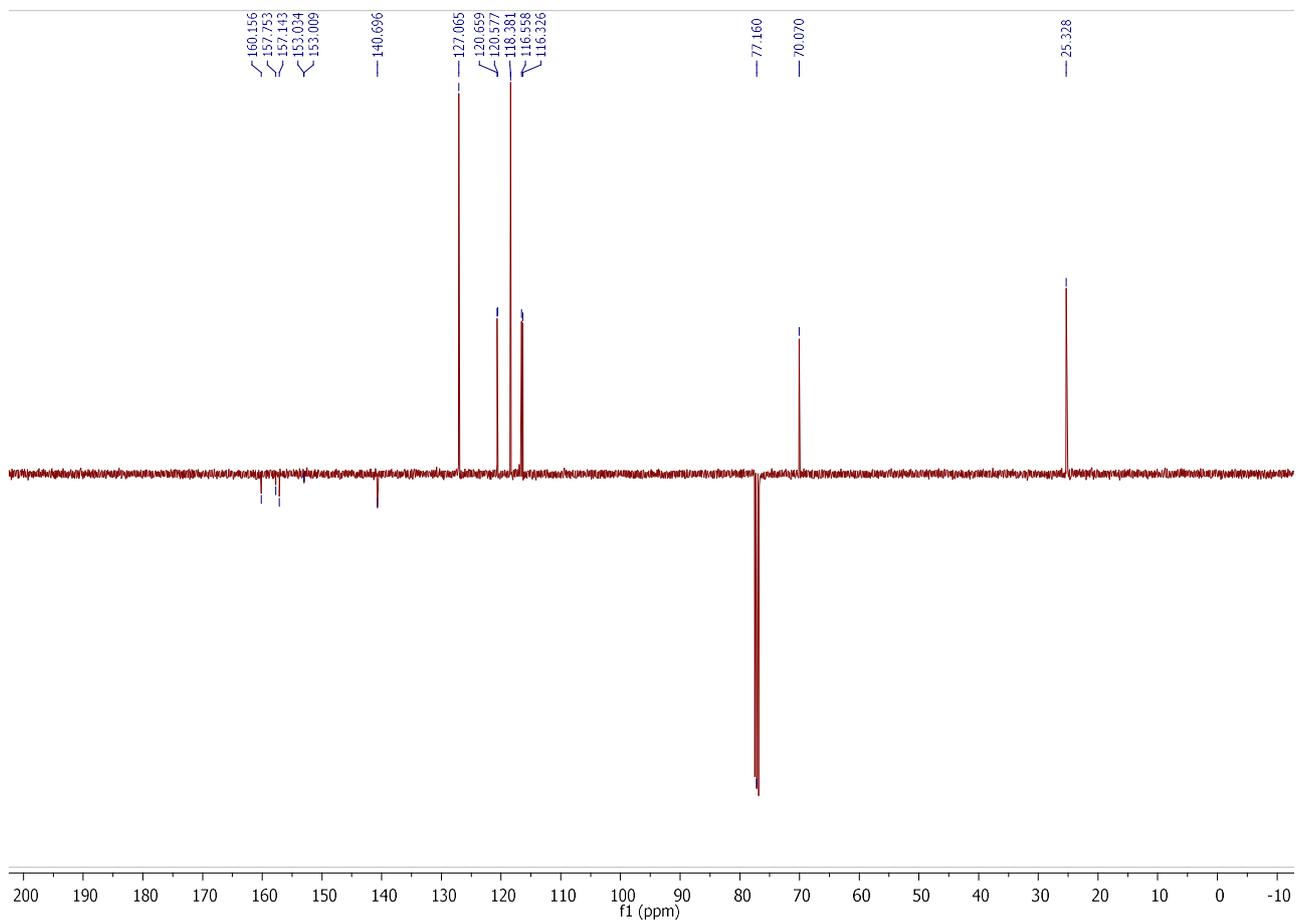
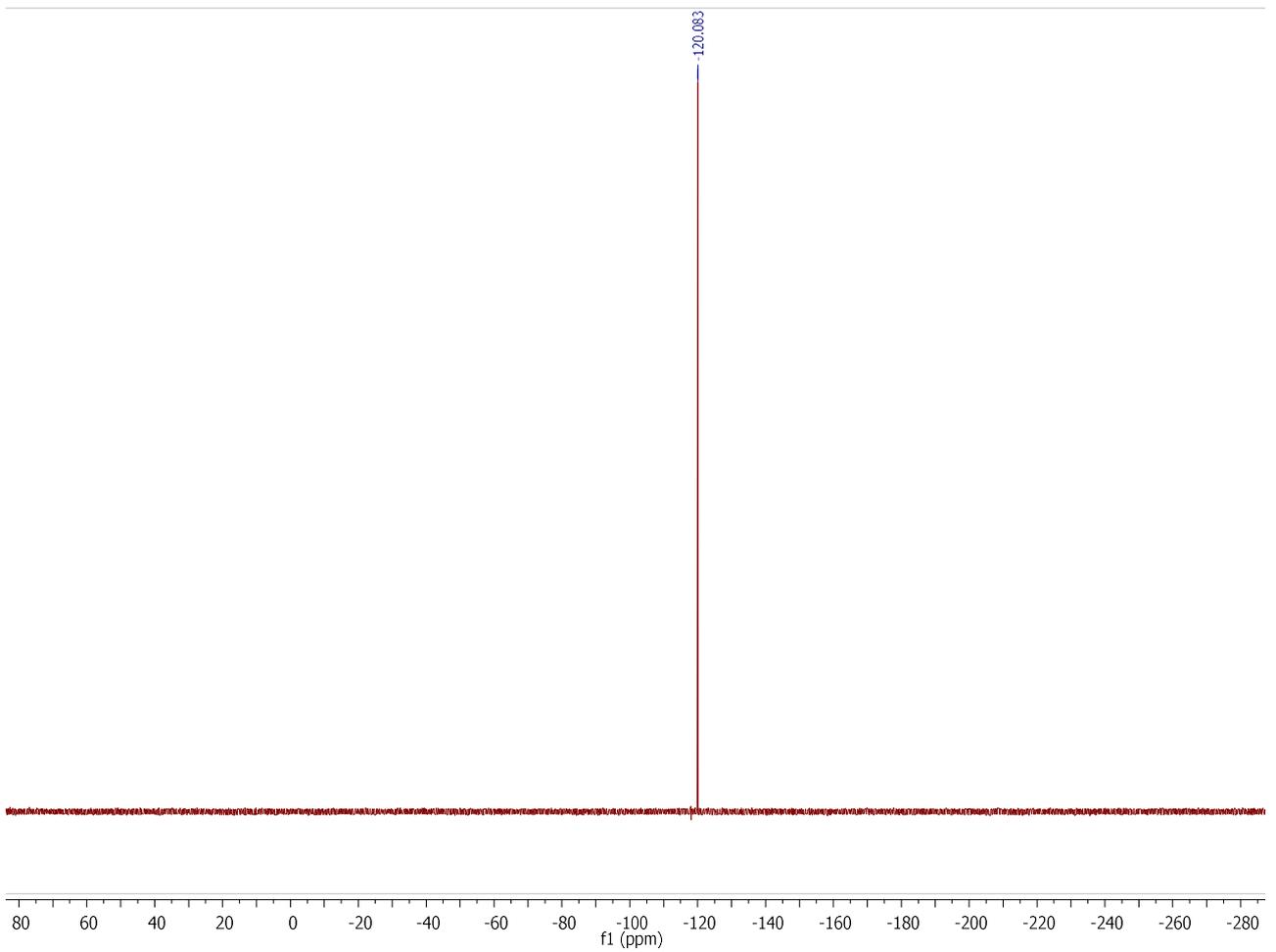


1-(4-(4-fluorophenoxy)phenyl)ethan-1-ol

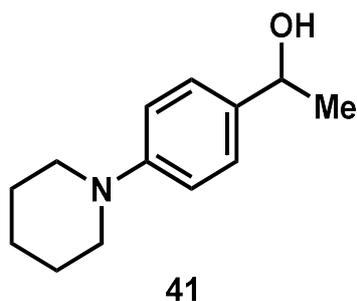


The title compound 1-(4-(4-fluorophenoxy)phenyl)ethan-1-ol (**40**) was prepared according to general procedure 4 using 4-fluorophenol (49.3 mg, 0.440 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-15 % EtOAc in hexanes, 30 x 120 mm silica) gave an off-white solid (83 mg, 89%). mp 32-35 °C; R_f = 0.22 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3402, 3310, 2974, 2961, 1611, 1497, 1364, 1254, 1211, 1188, 1084, 1063, 1005, 899, 847, 824, 768, 552, 540, 494; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 1.50 (3H, d, J 6.4), 1.74 (1H, br), 4.90 (1H, q, J 6.4), 6.91-7.07 (6H, m), 7.30-7.37 (2H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -120.1; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 25.3, 70.1, 116.4 (d, J 23.4), 118.4, 120.6 (d, J 8.2), 127.1, 140.7, 153.0 (d, J 2.5), 157.1, 158.9 (d, J 242.7). HRMS (CI^+) calculated for $[\text{C}_{14}\text{H}_{17}\text{O}_2\text{NF}]^+$ ($\text{M}+\text{NH}_4$) $^+$: m/z 250.1238, found 250.1239, (+0.5 ppm).

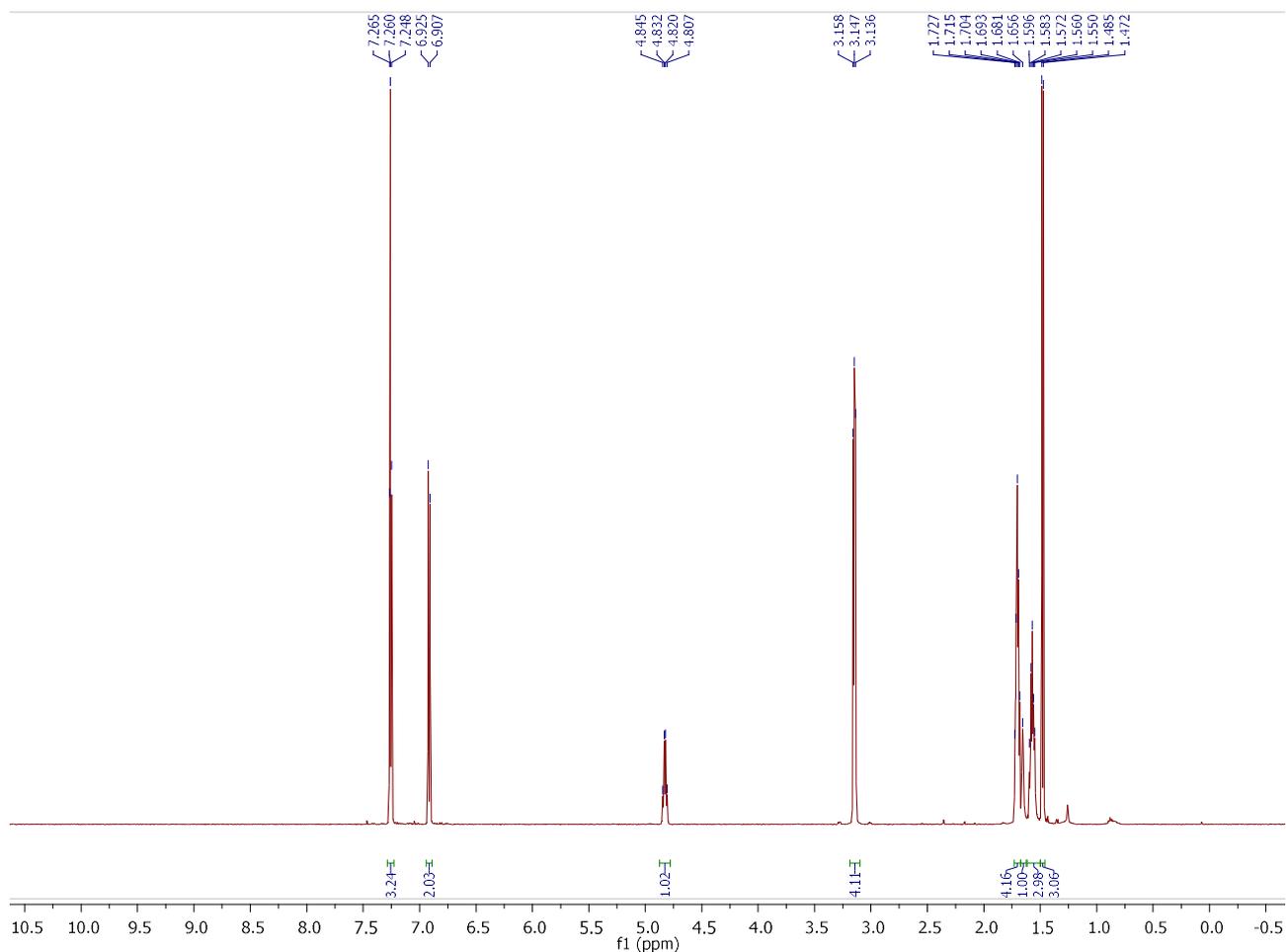


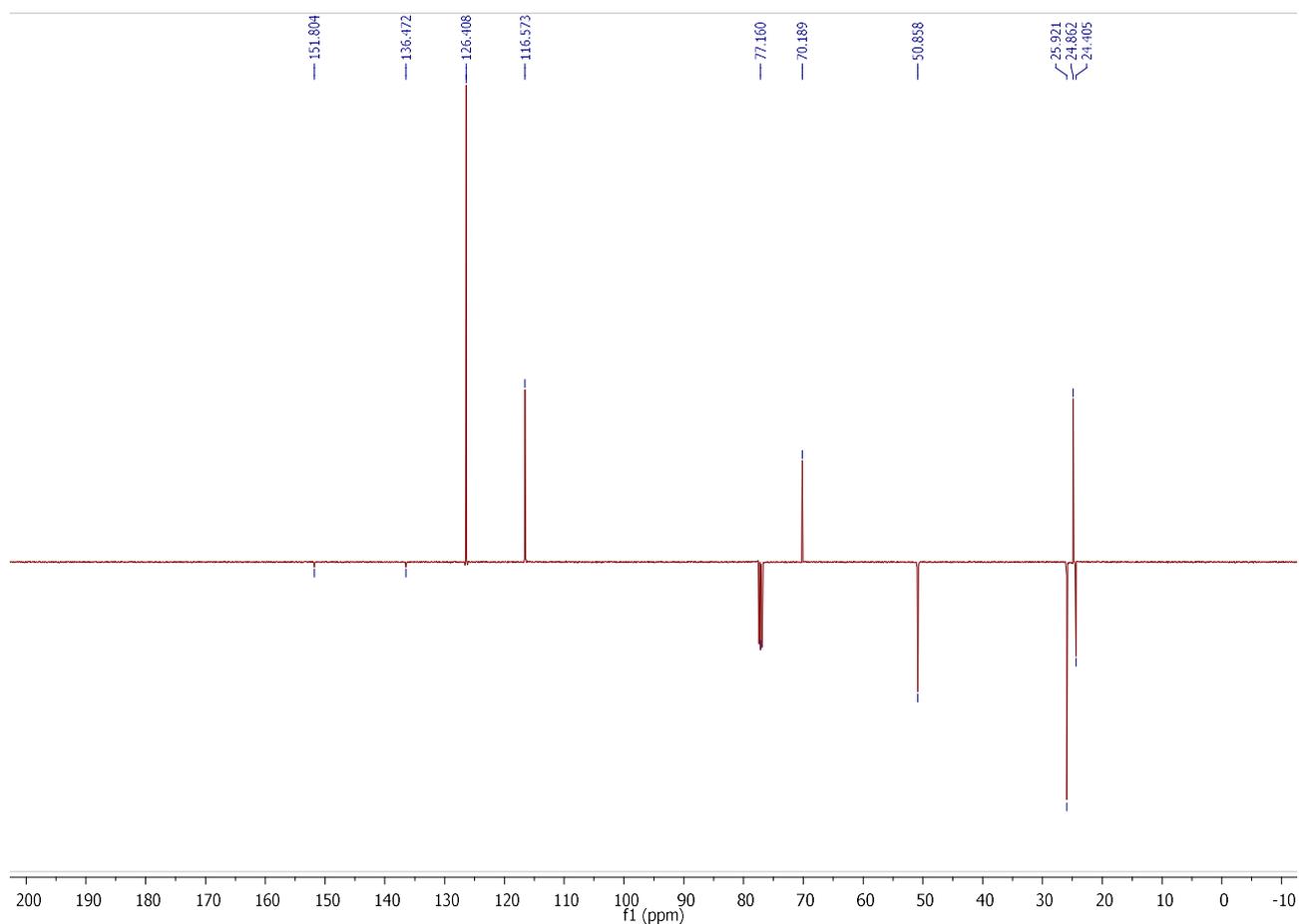


1-(4-(piperidin-1-yl)phenyl)ethan-1-ol



The title compound 1-(4-(piperidin-1-yl)phenyl)ethan-1-ol (**41**) was prepared according to general procedure 4 using piperidine (43.0 μ L, 37.5 mg, 0.440 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 120 mm silica) gave an off-white solid (46 mg, 57%). mp 49-52 $^{\circ}$ C; R_f = 0.21 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3246, 2972, 2932, 2851, 2828, 1609, 1508, 1454, 1233, 1132, 1094, 1067, 1013, 1005, 907, 866, 827, 814, 554; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 1.48 (3H, d, J 6.5), 1.52-1.62 (2H, m), 1.66 (1H, br), 1.67-1.74 (4H, m), 3.15 (4H, t, J 5.5), 4.83 (1H, q, J 6.5), 6.92 (2H, d, J 9.0), 7.26 (2H, d, J 8.5); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 24.4, 24.9, 25.9, 50.9, 116.7, 126.4, 136.5, 151.8; HRMS (EI^+) calculated for $[\text{C}_{13}\text{H}_{19}\text{NO}]^+$ (M) $^+$: m/z 205.1467, found 205.1465, (-1.0 ppm).



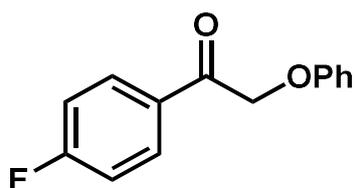


3. Experimental and characterization data (isomerisation protocol)

3.1. Synthesis of 2-aryloxy-1-ethanols

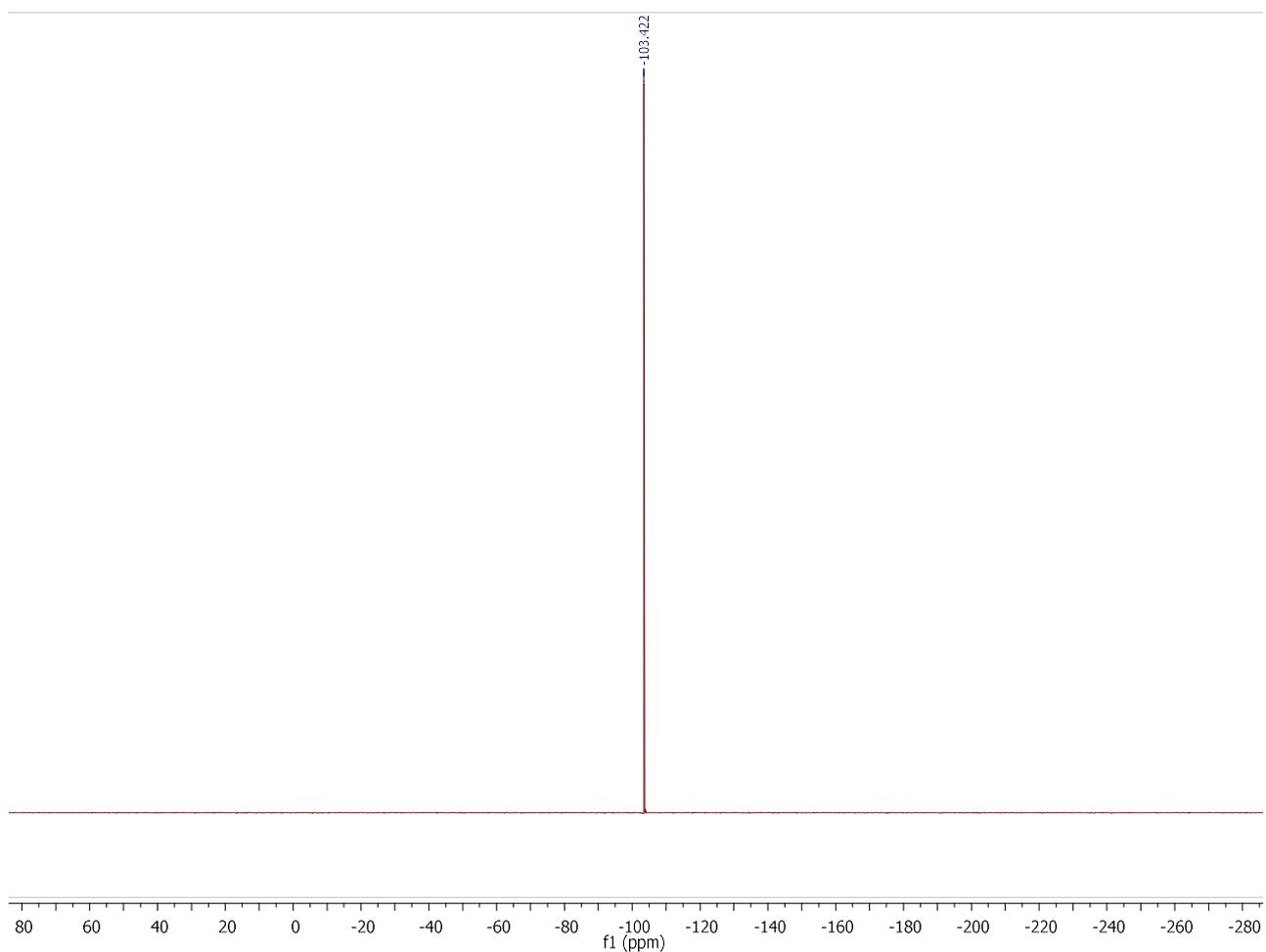
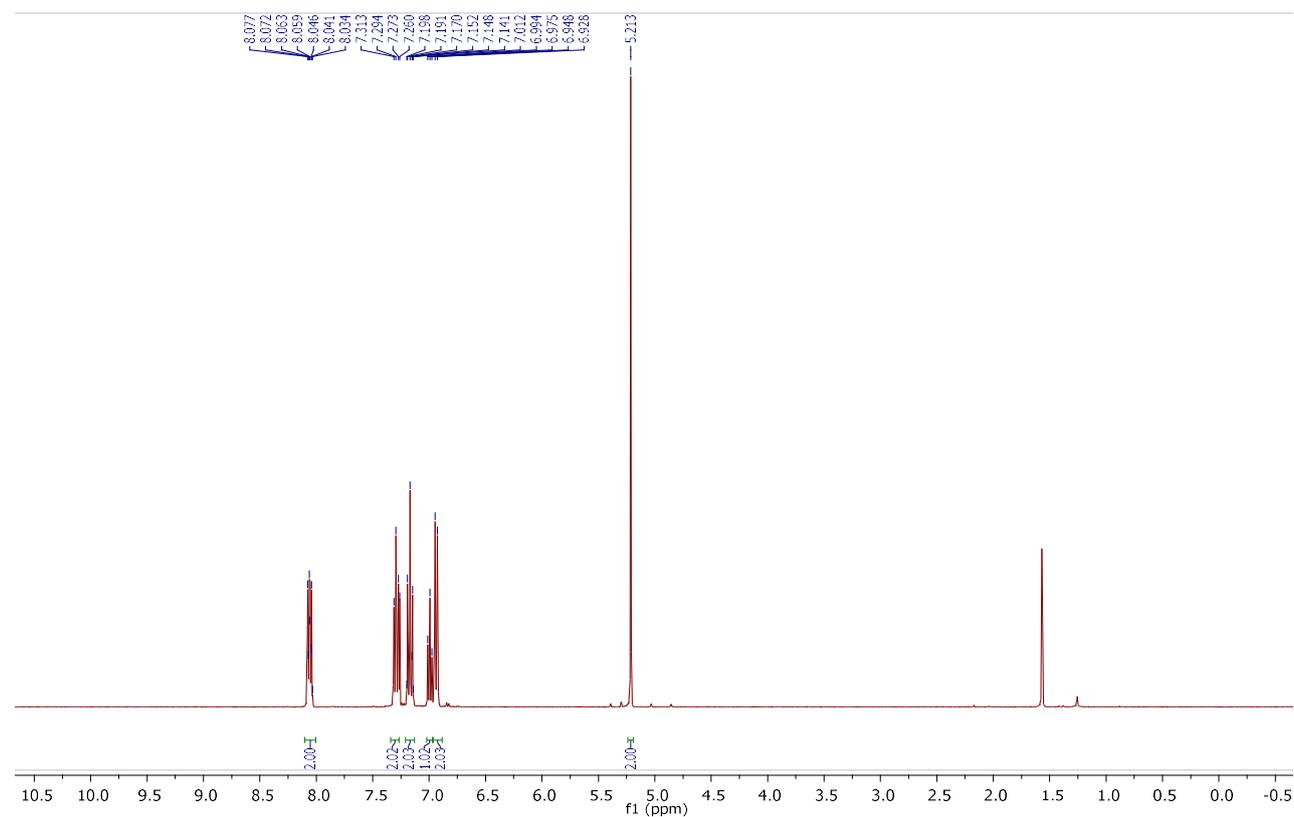
3.1.1. Synthesis of 43

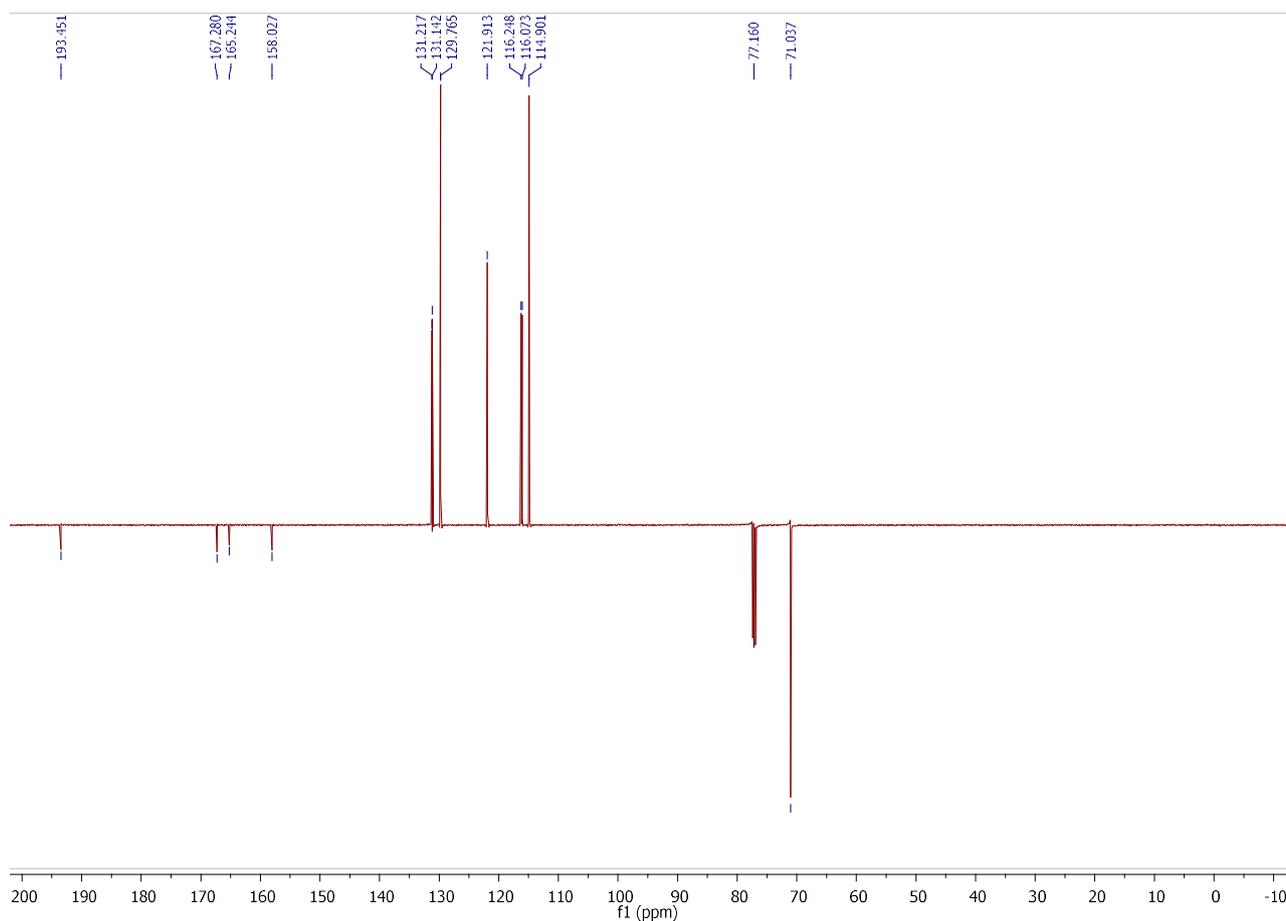
1-(4-fluorophenyl)-2-phenoxyethan-1-one



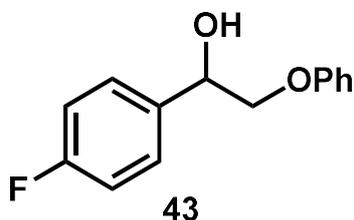
A 500 mL round bottomed flask containing a magnetic stirrer bar was charged with K_2CO_3 (9.54 g, 69.0 mmol), Phenol (4.30 g, 46.0 mmol) and acetone (200 mL) To this mixture was added dropwise a solution of 2-bromo-4'-fluoroacetophenone (10.0 g, 46.0 mmol) in acetone (50 mL) over 30 min at rt. The resulting suspension was heated under reflux for 4 h. It was then cooled, filtered and concentrated *in vacuo*. Purification by recrystallization yielded a white solid (7.21 g, 68 %). mp 77-80 °C (pet. ether); $R_f = 0.53$ (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3059, 2899, 1699, 1587, 1497, 1431, 1248, 1221, 1159, 1094, 980, 837, 750, 685, 550, 511; 1H NMR (400 MHz, $CDCl_3$) δ_H : 5.21 (2H, s), 6.94 (2H, d, J 8.0), 6.99 (1H, t, J 7.6), 7.17 (2H, m), 7.29 (2H, m), 8.06 (2H, m); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F : -103.4; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C : 71.0, 114.9, 116.2 (d, J 22.1), 121.9,

129.8, 131.1, 131.2 (d, *J* 9.5), 158.0, 166.3 (d, *J* 256.5), 193.5; HRMS (**NSI**⁺) calculated for [C₁₄H₁₂O₂F]⁺ (M+H)⁺ : *m/z* 231.0816, found 231.0816, (+0.2 ppm).



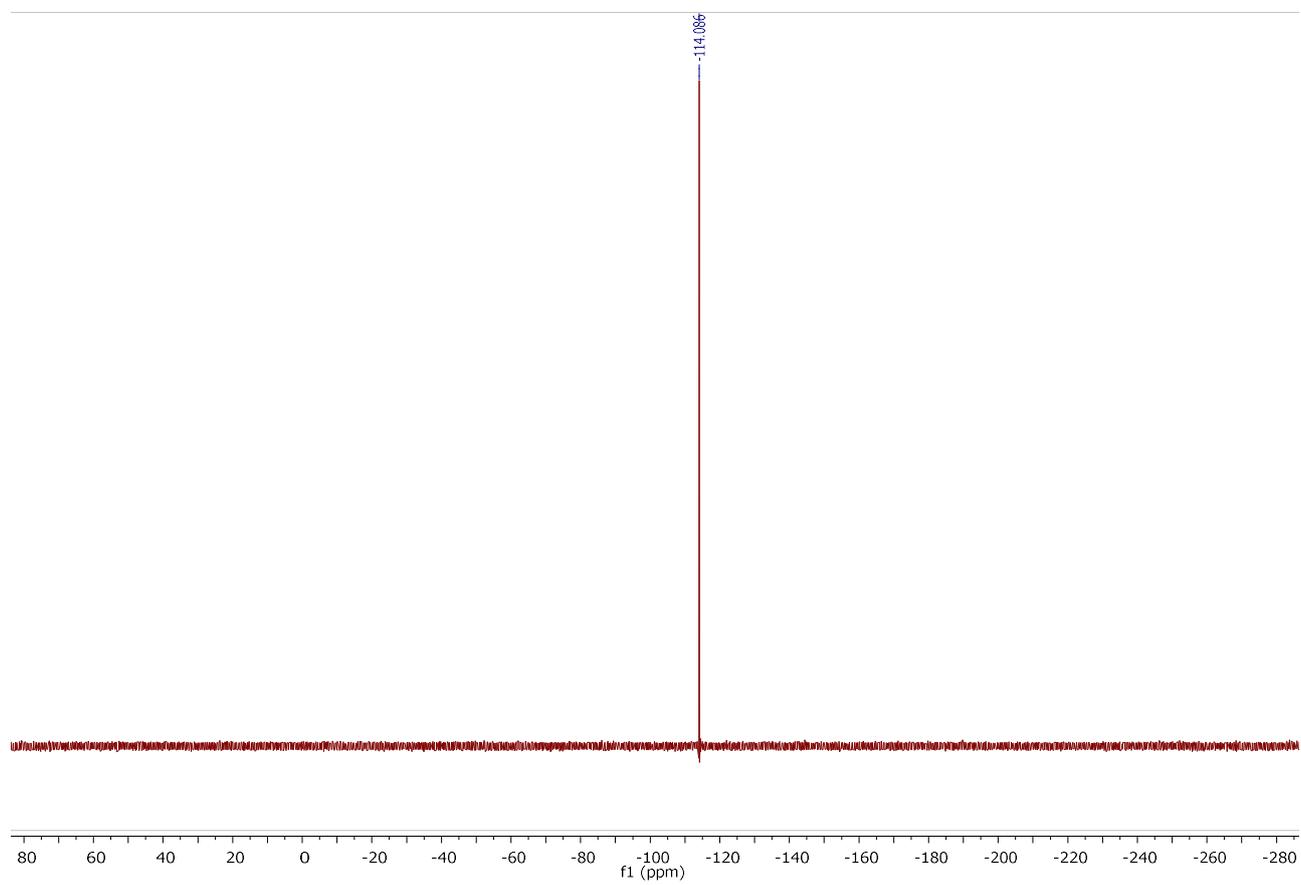
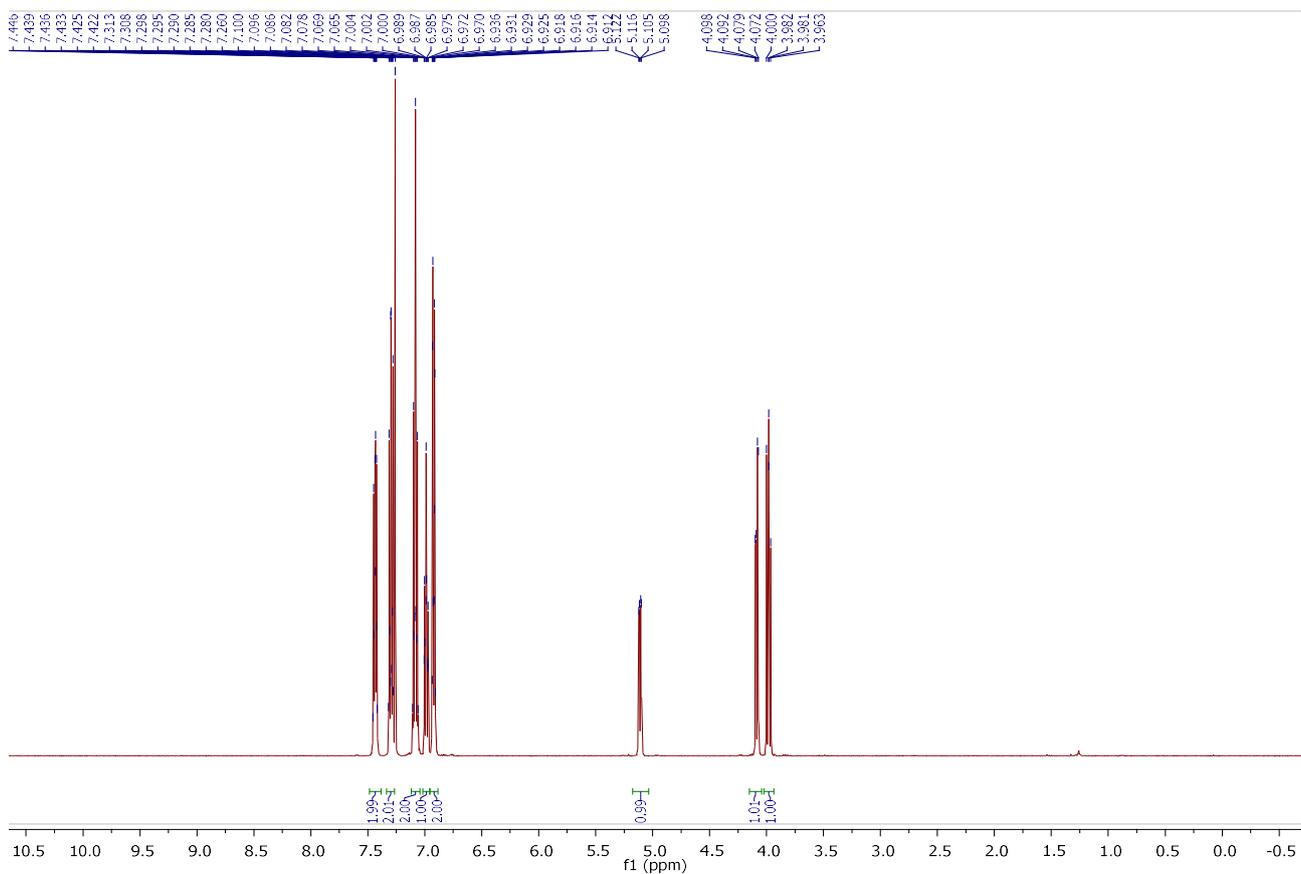


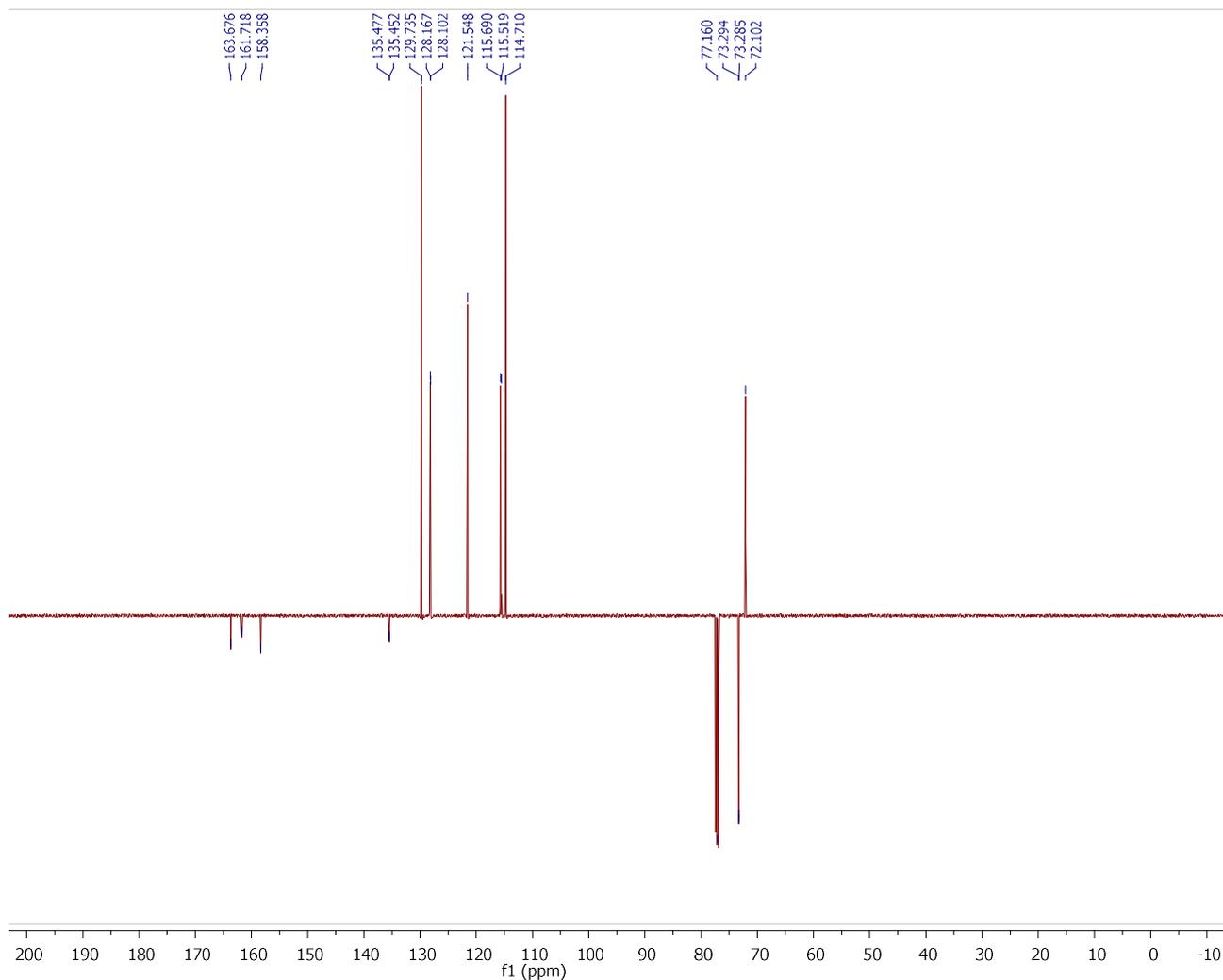
1-(4-fluorophenyl)-2-phenoxyethan-1-ol



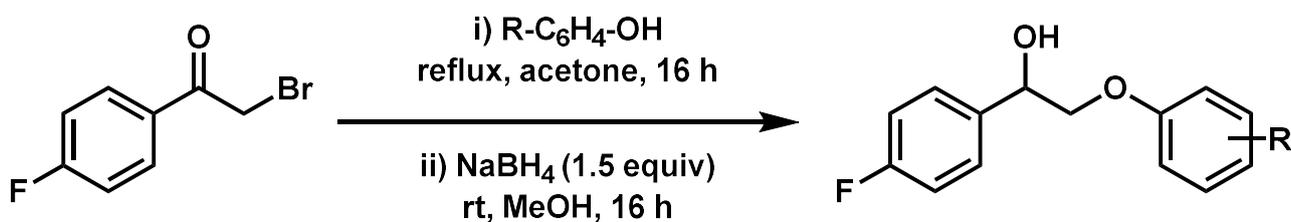
A 500 mL round bottomed flask was charged with 1-(4-fluorophenyl)-2-phenoxyethan-1-one (6.50 g, 28.2 mmol) and methanol (300 mL). Sodium borohydride (1.17 g, 30.9 mmol) was then added portion wise at 0 °C. The mixture was left to react at RT for 4 h. Sat. aq. NH₄Cl (200 mL) was then added to the mixture. The reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (100 mL) and H₂O (100 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 100 mL). The organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by recrystallization yielded a white solid (5.05 g, 77%). mp 42-45 °C (*n*-hexane); R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 3237, 3067, 2938, 2878, 1599, 1585, 1510, 1497, 1456, 1225, 1152, 1078, 1042, 870, 752, 691, 592; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 3.98 (1H, dd, 9.5, 9.0), 4.09 (1H, dd, *J* 10.0, 3.0), 5.11 (1H, dd, *J* 9.0, 3.0), 6.89-6.95 (2H, m), 6.95-7.02 (1H, m), 7.04-7.10 (2H, m), 7.27-7.33 (2H, m), 7.40-7.47 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -114.1; ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 72.1, 73.3, 114.7, 115.6 (d, *J*

21.5), 121.6, 128.1 (d, *J* 8.2), 129.7, 135.5, 158.4, 162.7 (d, *J* 247.0); HRMS (EI⁺) calculated for [C₁₄H₁₃FO₂]⁺ (M)⁺ : m/z 232.0901, found 232.0900, (+0.4 ppm).





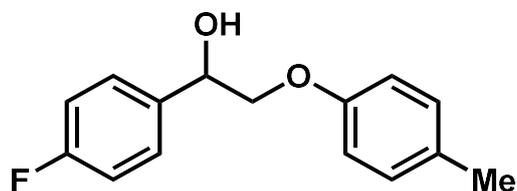
3.2. General procedure 6



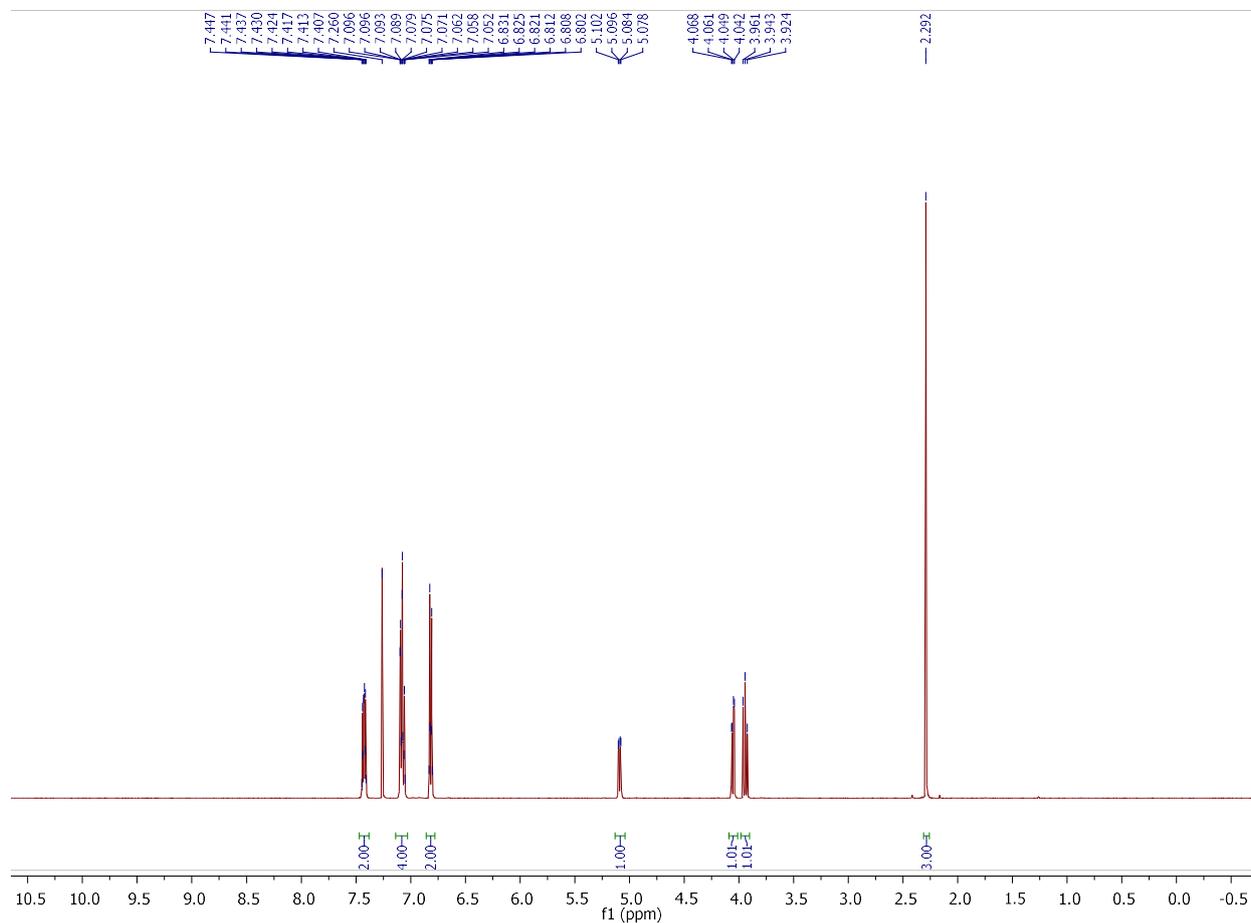
A 250 mL flask equipped with a magnetic stirrer bar was charged with 2-bromo-4'-fluoroacetophenone (2.17 g, 10.0 mmol), a substituted phenol (10.0 mmol), and potassium carbonate (2.07 g, 15.0 mmol). Acetone (100 mL) was then added to the mixture and the reaction was stirred and heated to reflux for 16 hours. The reaction was then filtered, and the filtrate concentrated *in vacuo*. The crude 2-aryloxyacetophenone was used for the next step without further purification. The resulting mixture was dissolved in methanol (80.0 mL), and a magnetic stirrer was added to the flask. The reaction was then cooled to 0 °C, and sodium borohydride (416 mg, 11.0 mmol) added portionwise under vigorous stirring. Sat. aq. NH₄Cl (20 mL) was then added to the mixture. The reaction mixture was transferred to a separatory funnel and the flask washed with EtOAc (30 mL) and H₂O (20 mL). The organic layer was collected and the aqueous phase washed

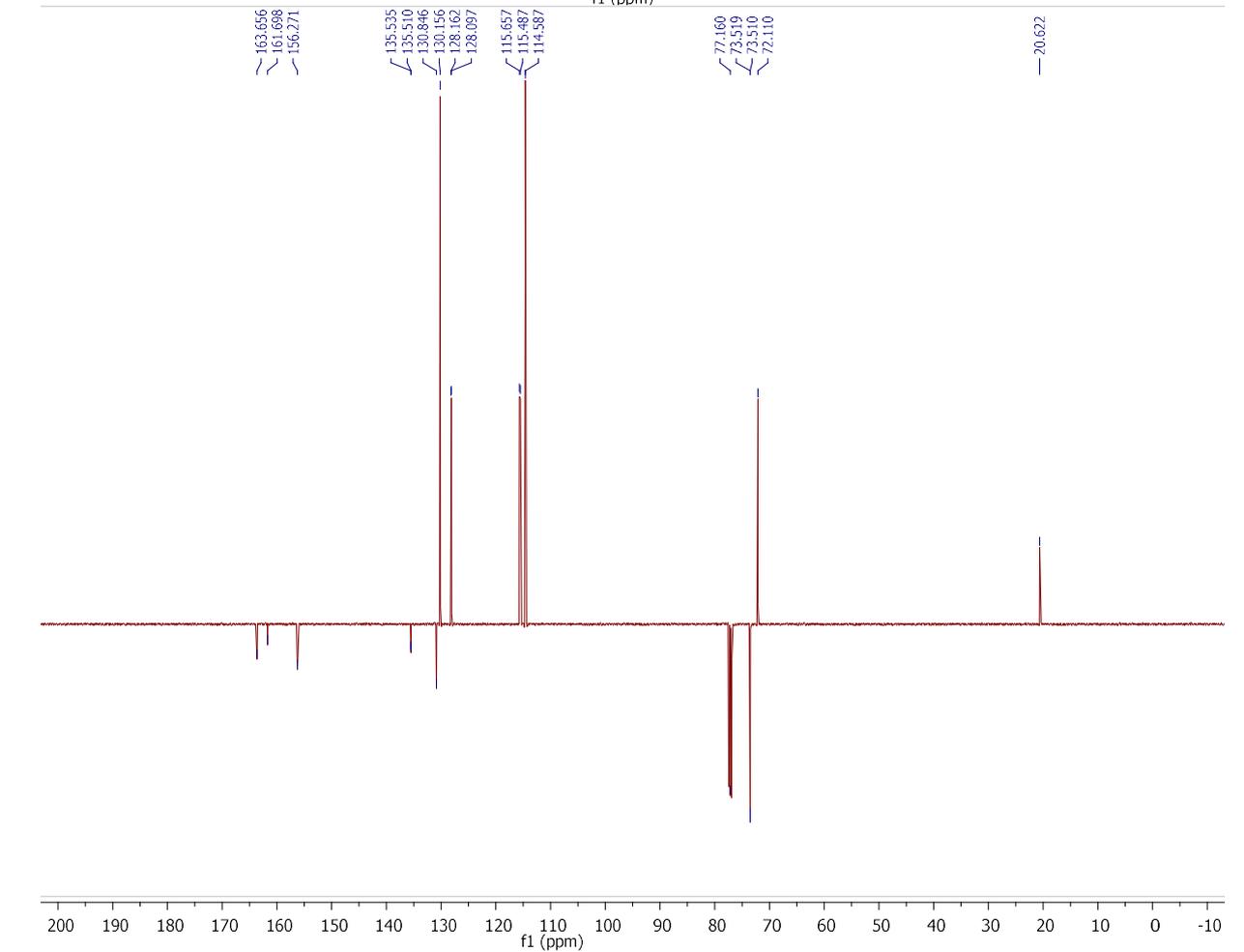
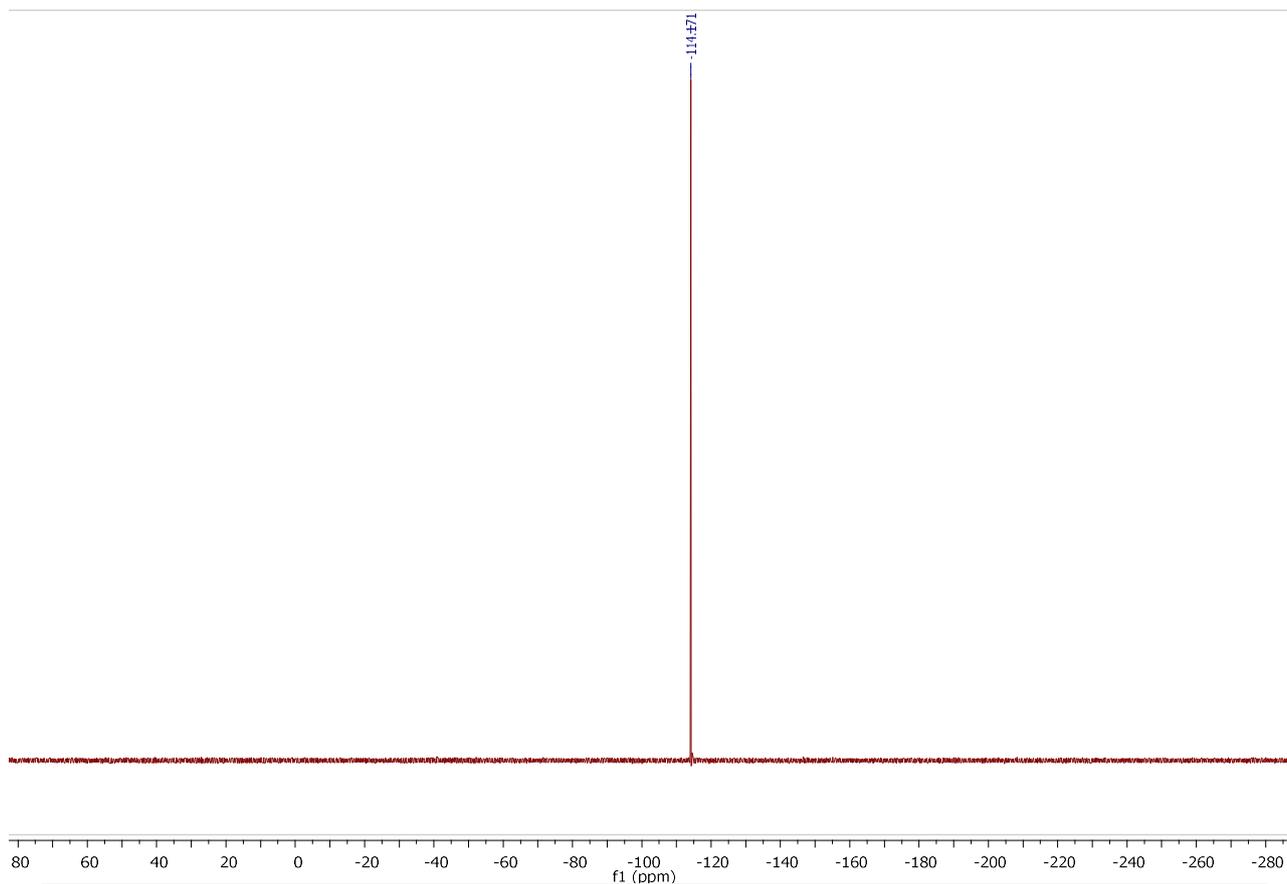
with EtOAc (2 x 30 mL). The organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by silica flash chromatography.

1-(4-fluorophenyl)-2-(*p*-tolylloxy)ethan-1-ol

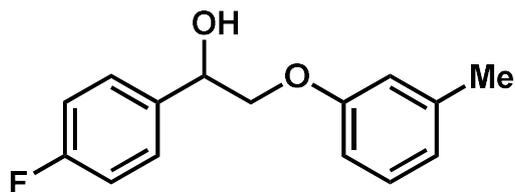


The title compound 1-(4-fluorophenyl)-2-(*p*-tolylloxy)ethan-1-ol was prepared according to general procedure 6 using *p*-cresol (1.08 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 60 x 150 mm silica) gave the title compound as an off-white solid (1.75 g, 71%). mp 54-57 °C; R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{max} / cm⁻¹ (film) 3422, 2922, 2832, 1602, 1504, 1217, 1155, 1105, 1036, 1013, 870, 821, 729; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 2.29 (3H, s), 3.90-3.98 (1H, m), 4.06 (1H, dd, *J* 9.5, 3.5), 5.09 (1H, dd, *J* 9.0, 3.0), 6.78-6.85 (2H, m), 7.03-7.12 (4H, m), 7.39-7.46 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -114.2; ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 20.6, 72.1, 73.5 (d, *J* 1.0), 114.6, 115.6 (d, *J* 21.4), 128.1 (d, *J* 8.2), 130.2, 130.8, 135.5 (d, *J* 3.2), 156.3, 162.7 (d, *J* 247.0); HRMS (EI⁺) calculated for [C₁₅H₁₅FO₂]⁺ (M)⁺ : m/z 246.1056, found 246.1068, (+4.9 ppm).

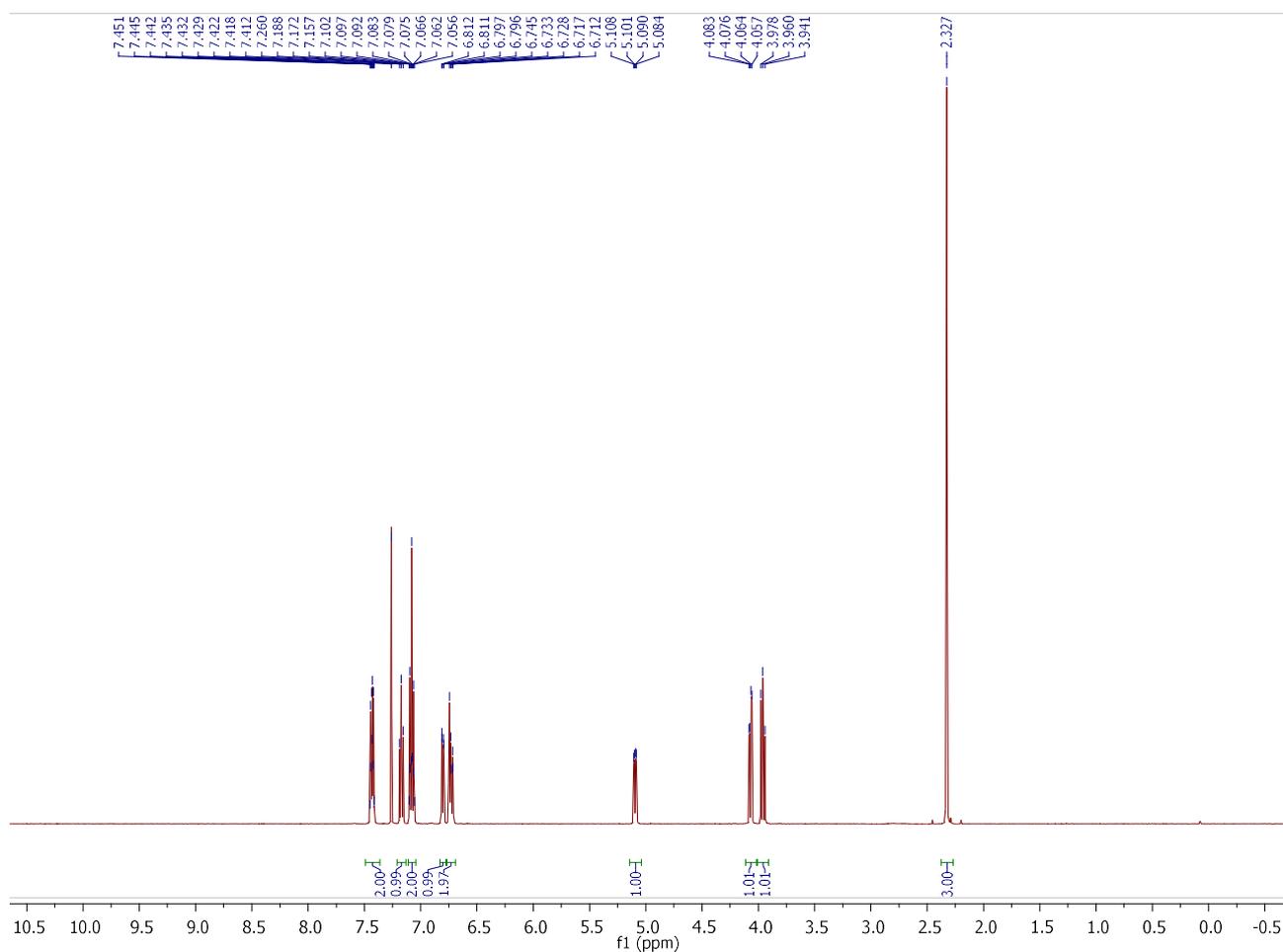


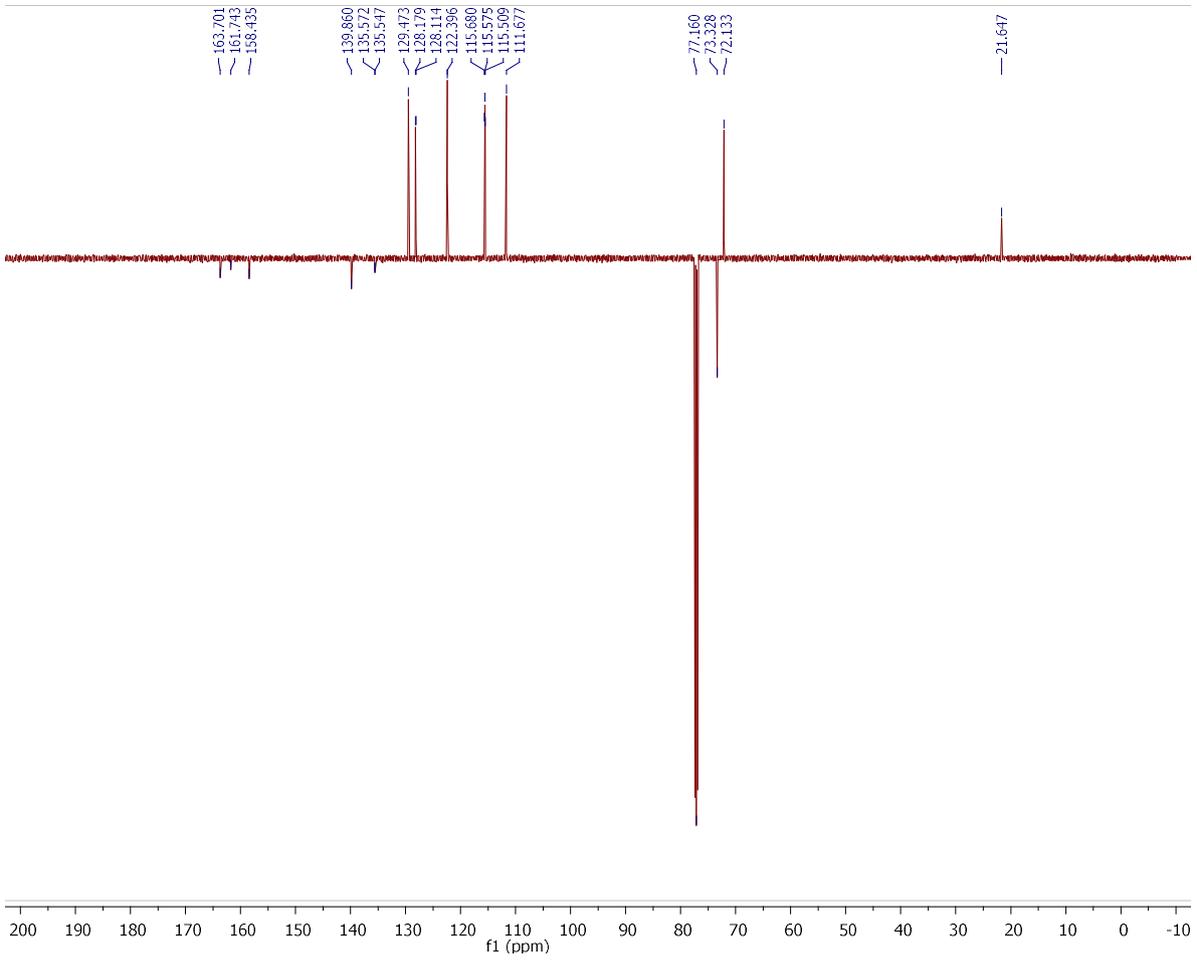
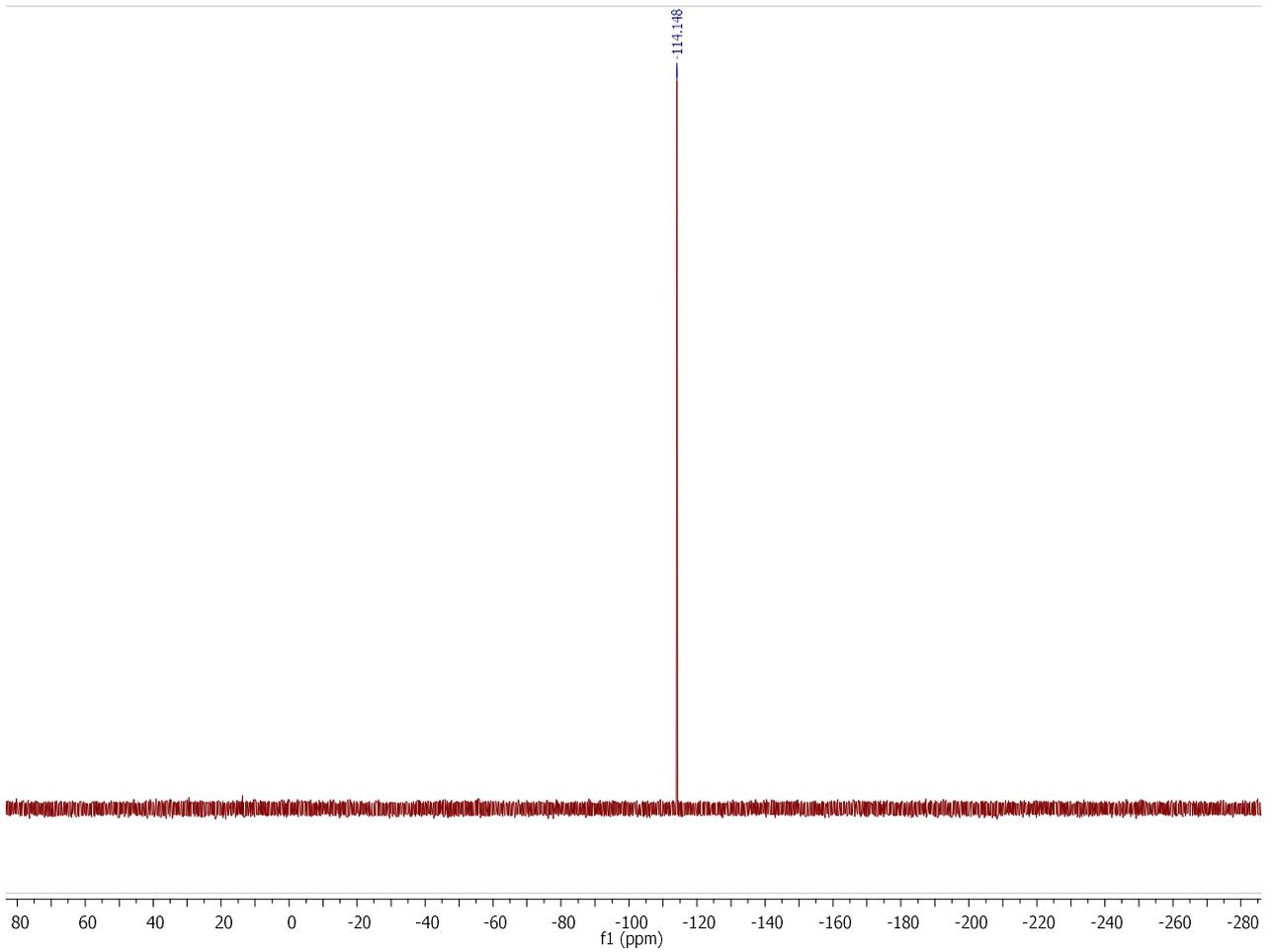


1-(4-fluorophenyl)-2-(*m*-tolylloxy)ethan-1-ol

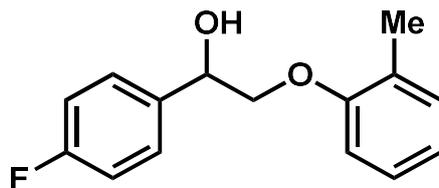


The title compound 1-(4-fluorophenyl)-2-(*m*-tolylloxy)ethan-1-ol was prepared according to general procedure 6 using *m*-cresol (1.05 mL, 1.08 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 50 x 170 mm silica) gave a white solid (1.51 g, 61%). mp 72-75 °C, R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3285, 3206, 2922, 2868, 1601, 1582, 1508, 1485, 1454, 1288, 1260, 1234, 1221, 1155, 1107, 1084, 1053, 920. 878, 853, 831, 772, 731, 691, 606, 575, 542, 525; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.33 (3H, s), 3.92-4.00 (1H, m), 4.07 (1H, dd, J 9.5, 3.5), 5.10 (1H, dd, J 9.0, 3.5), 6.69-6.77 (2H, m), 6.78-6.83 (1H, m), 7.03-7.12 (2H, m), 7.17 (1H, t, J 7.8), 7.39-7.47 (2H, m); $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ_{F} : -114.1; $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 21.6, 72.1, 73.3, 111.7, 115.6, 115.6 (d, J 21.5), 122.4, 128.1 (d, J 8.2), 129.5, 135.6 (d, J 3.2), 139.9, 158.4, 162.7 (d, J 247.0); HRMS (EI^+) calculated for $[\text{C}_{15}\text{H}_{15}\text{FO}_2]^+$ (M) $^+$: m/z 246.1056, found 246.1051, (-2.0 ppm).

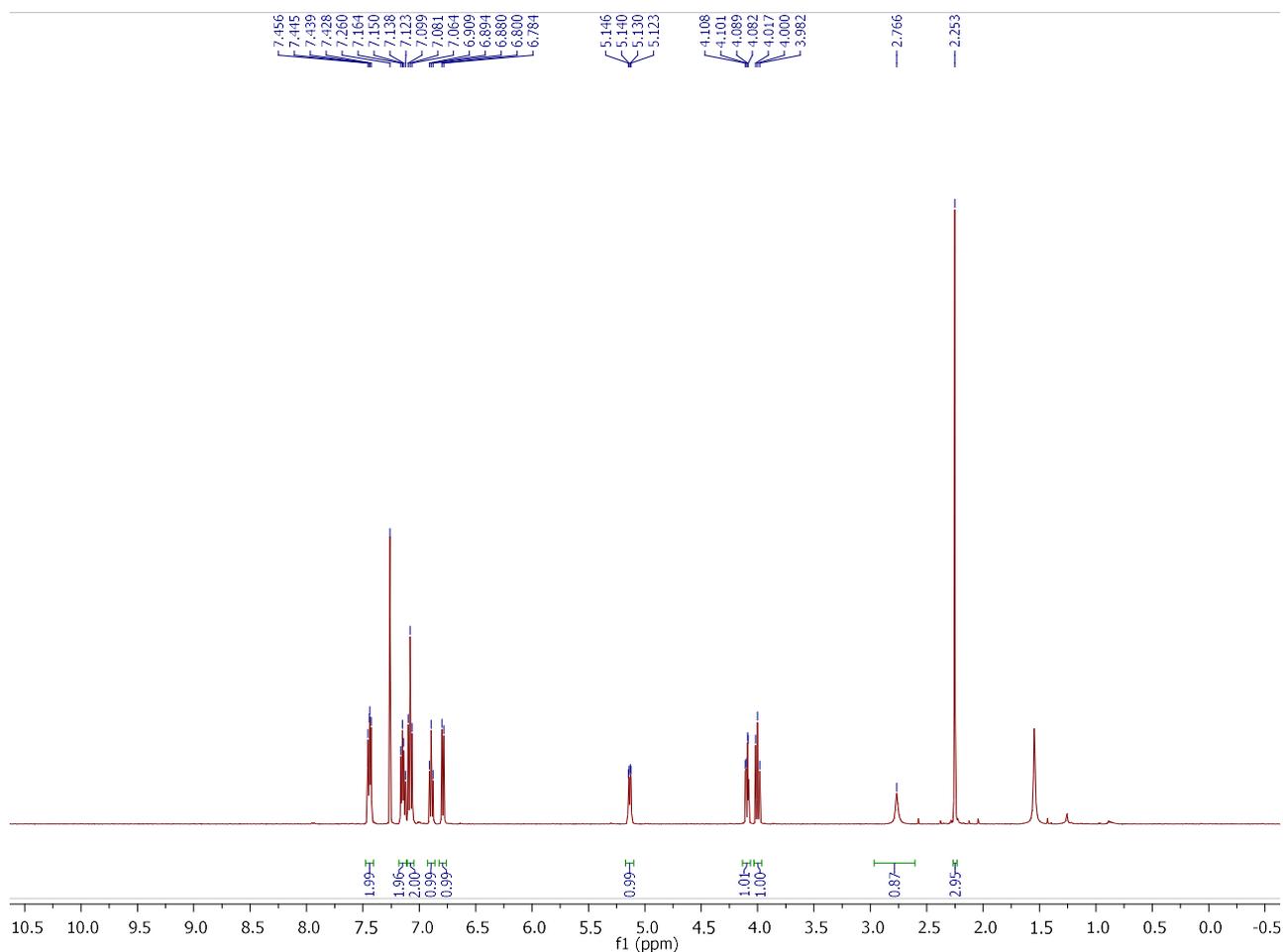


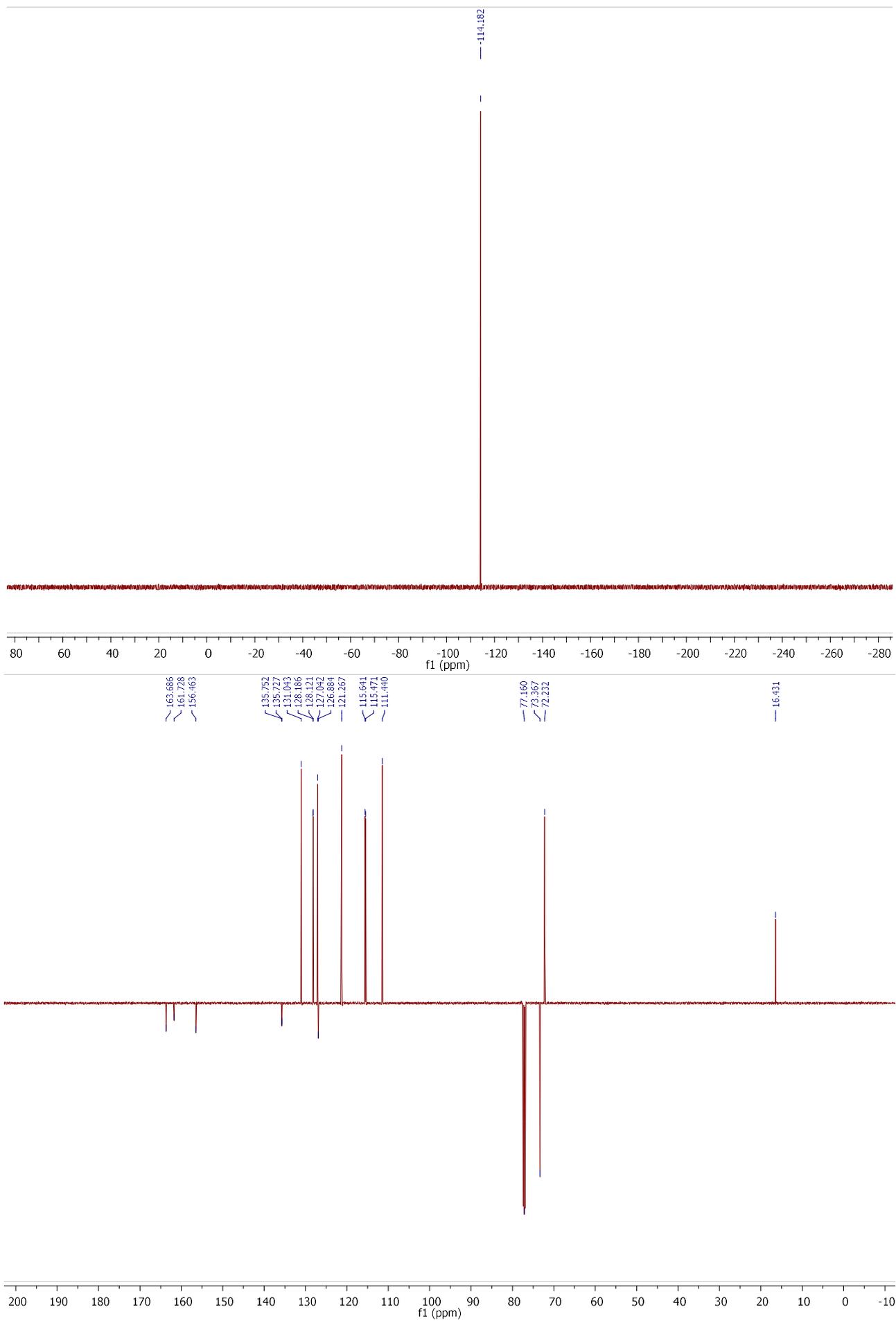


1-(4-fluorophenyl)-2-(*o*-tolyl)oxyethan-1-ol

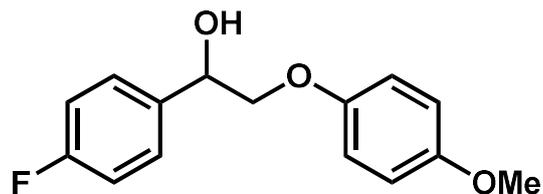


The title compound 1-(4-fluorophenyl)-2-(*o*-tolyl)oxyethan-1-ol was prepared according to general procedure 6 using *o*-cresol (1.03 mL, 1.08 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 5-7% EtOAc in hexanes, 50 x 170 mm silica) gave a pale yellow oil (1.47 g, 60%). $R_f = 0.33$ (eluent = 20% EtOAc in hexanes); $\nu_{\max} / \text{cm}^{-1}$ (film) 3385, 3028, 2928, 2860, 1603, 1589, 1510, 1491, 1462, 1437, 1184, 1157, 1121, 1036, 835, 750, 714, 608, 579; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.25 (3H, s), 2.77 (1H, br), 4.00 (1H, t, J 8.5), 4.10 (1H, dd, J 9.5, 3.5), 5.14 (1H, dd, J 8.5, 3.5), 6.79 (1H, d, J 8.0), 6.90 (1H, t, J 7.5), 7.08 (2H, t, J 9.0), 7.11-7.18 (2H, m), 7.43-7.46 (2H, m); $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ_{F} : -114.2; $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 16.4, 72.2, 73.4, 111.4, 115.6 (d, J 21.4), 121.3, 126.9, 127.0, 128.2 (d, J 8.2), 131.0, 135.7 (d, J 3.2), 156.5, 162.7 (d, J 246.7); HRMS (EI^+) [$\text{C}_{15}\text{H}_{15}\text{FO}_2$] $^+$ (M) $^+$: m/z 246.1056, found 246.1057, (+0.4 ppm).

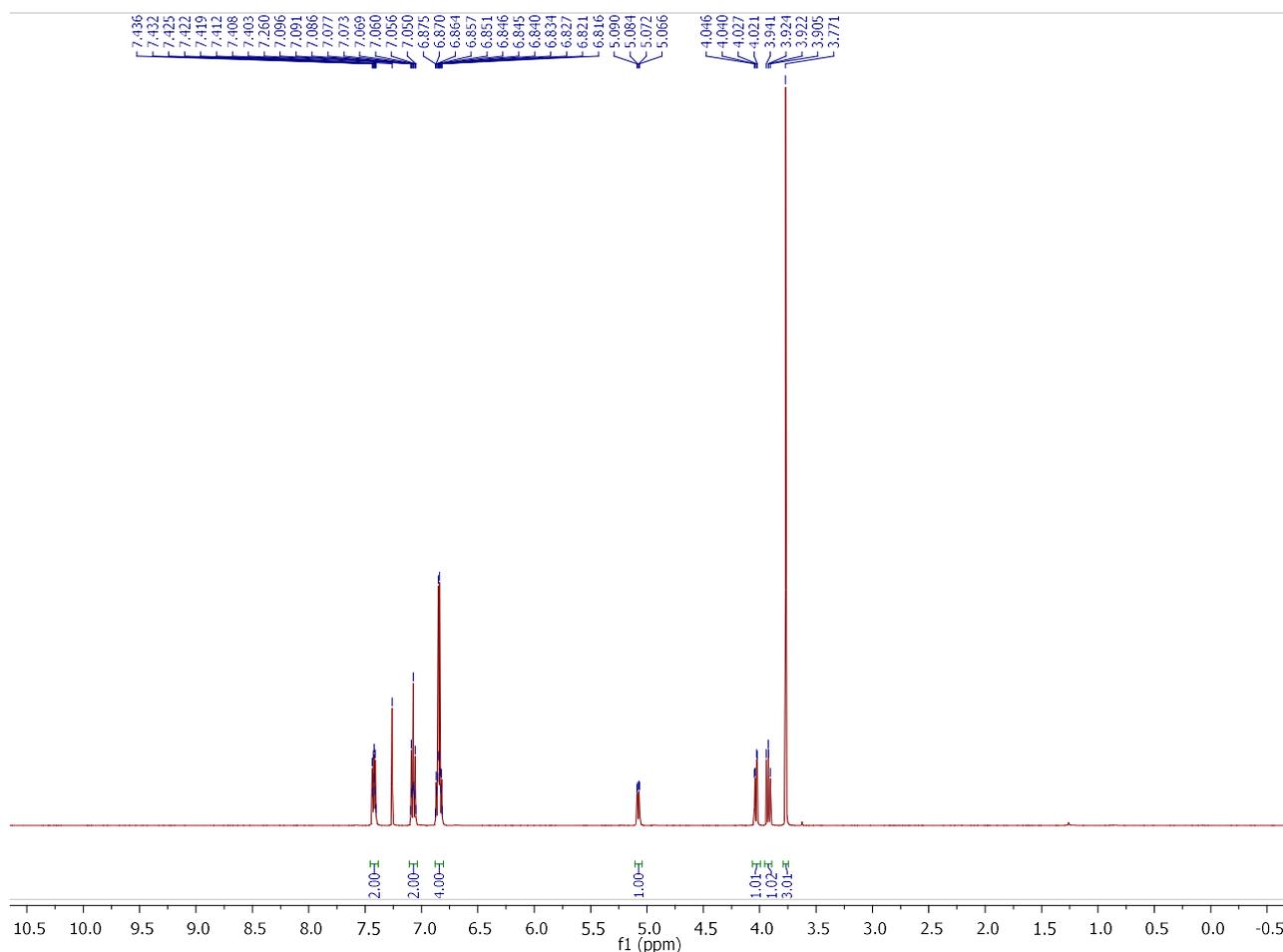


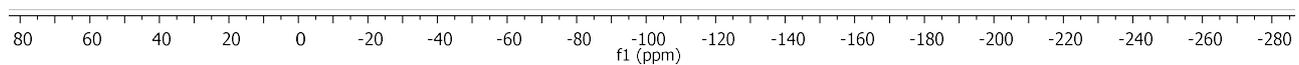
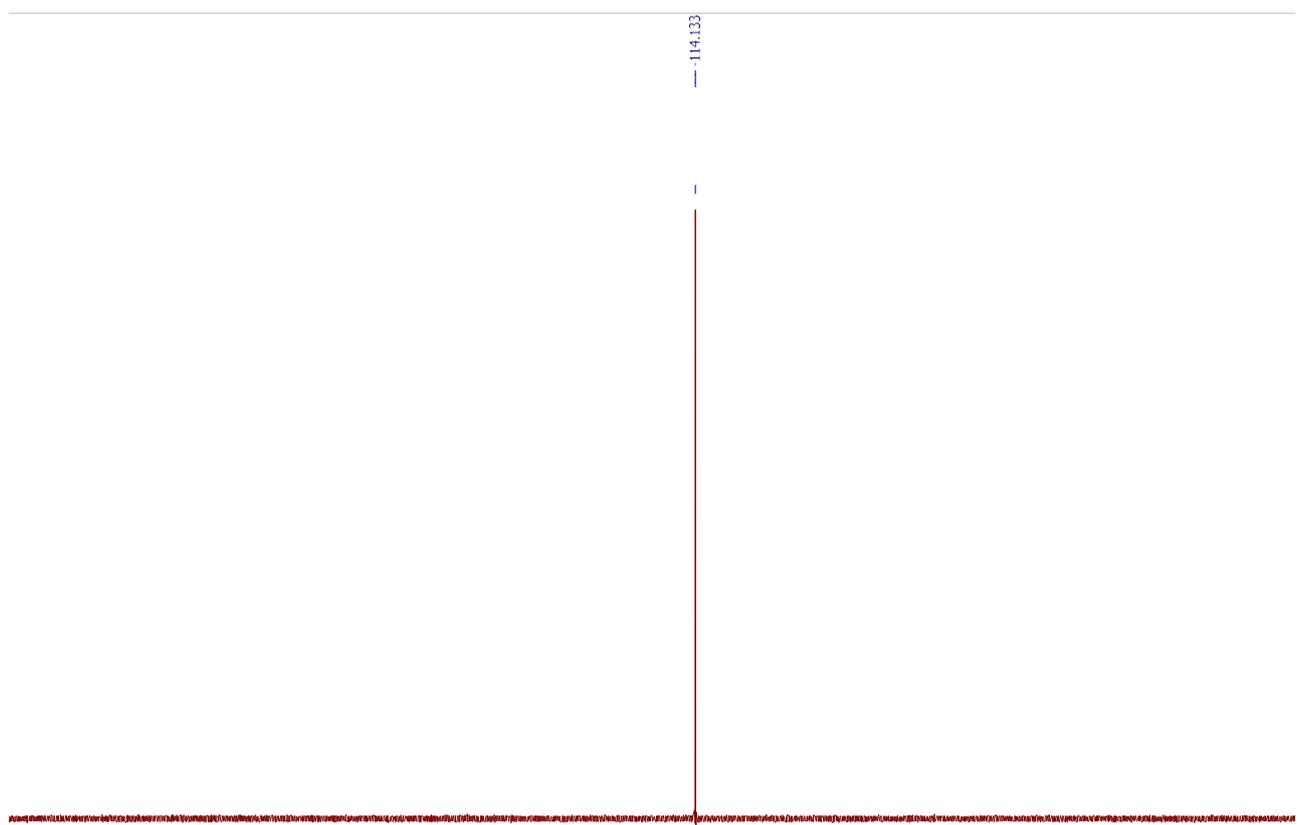


1-(4-fluorophenyl)-2-(4-methoxyphenoxy)ethan-1-ol

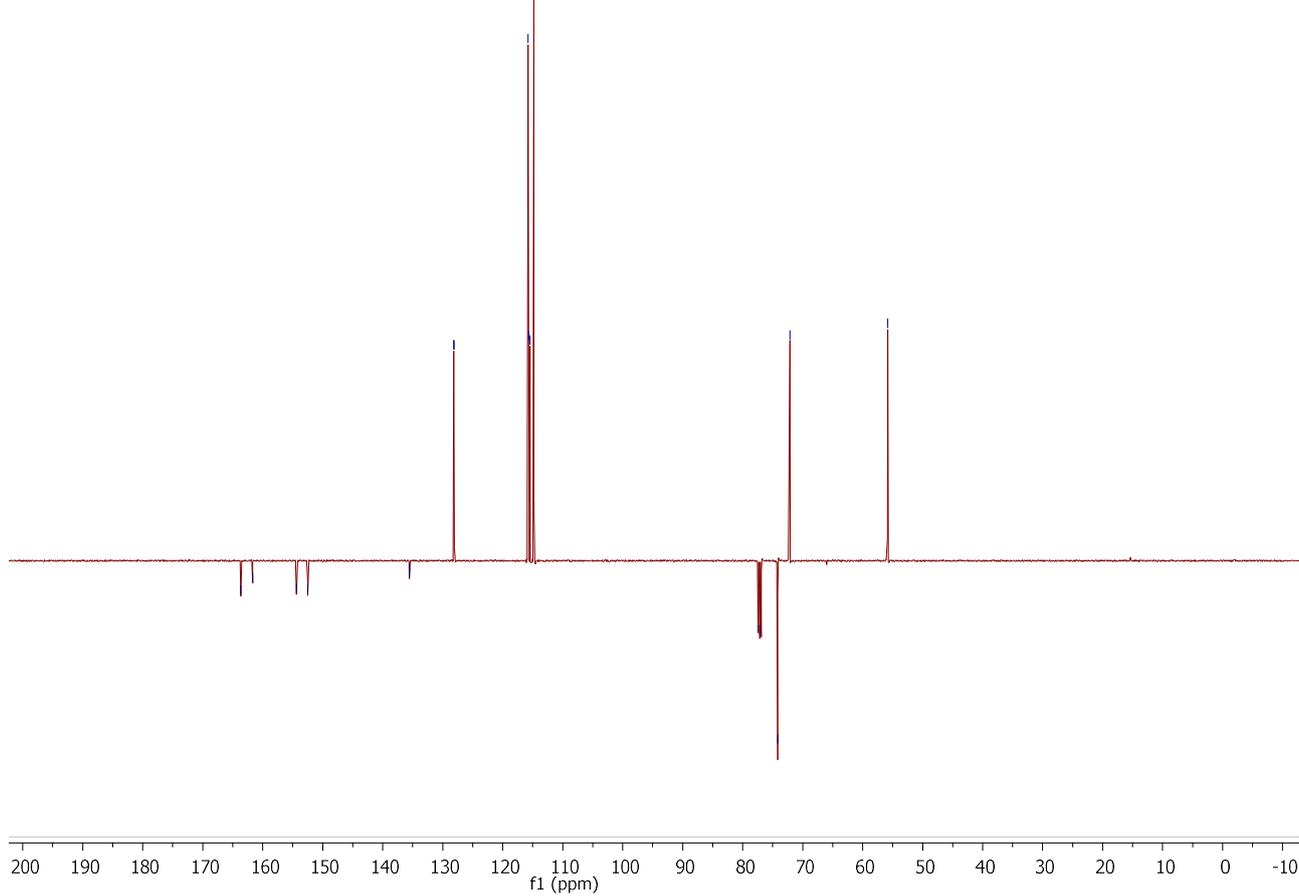


The title compound 1-(4-fluorophenyl)-2-(4-methoxyphenoxy)ethan-1-ol was prepared according to general procedure 6 using 4-methoxyphenol (1.24 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 2% MeOH in CH₂Cl₂, 60 x 200 mm silica) gave a pale yellow oil (1.28 g, 49%). R_f = 0.17 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3422, 2922, 2832, 1603, 1504, 1456, 2127, 1155, 1105, 1036, 1012, 870, 822, 729; ¹H NMR (500 MHz, CDCl₃) δ_{H} : 3.77 (3H, s), 3.88-3.95 (1H, m), 4.03 (1H, dd, *J* 9.5, 3.0), 5.08 (1H, dd, 9.0, 3.0), 6.79-6.89 (4H, m), 7.02-7.12 (2H, m), 7.37-7.46 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δ_{F} : -114.1; ¹³C NMR (126 MHz, CDCl₃) δ_{C} : 55.8, 72.1, 74.1, 114.8, 115.5 (d, *J* 21.4), 115.8, 128.1 (d, *J* 8.2), 135.6 (d, *J* 3.0), 152.5, 154.4, 162.7 (d, *J* 247.0); HRMS (EI⁺) calculated for [C₁₅H₁₅FO₃]⁺ (M)⁺: *m/z* 262.1005, found 262.1010, (+1.9 ppm).

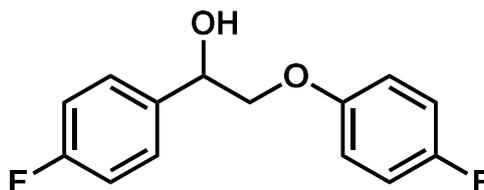




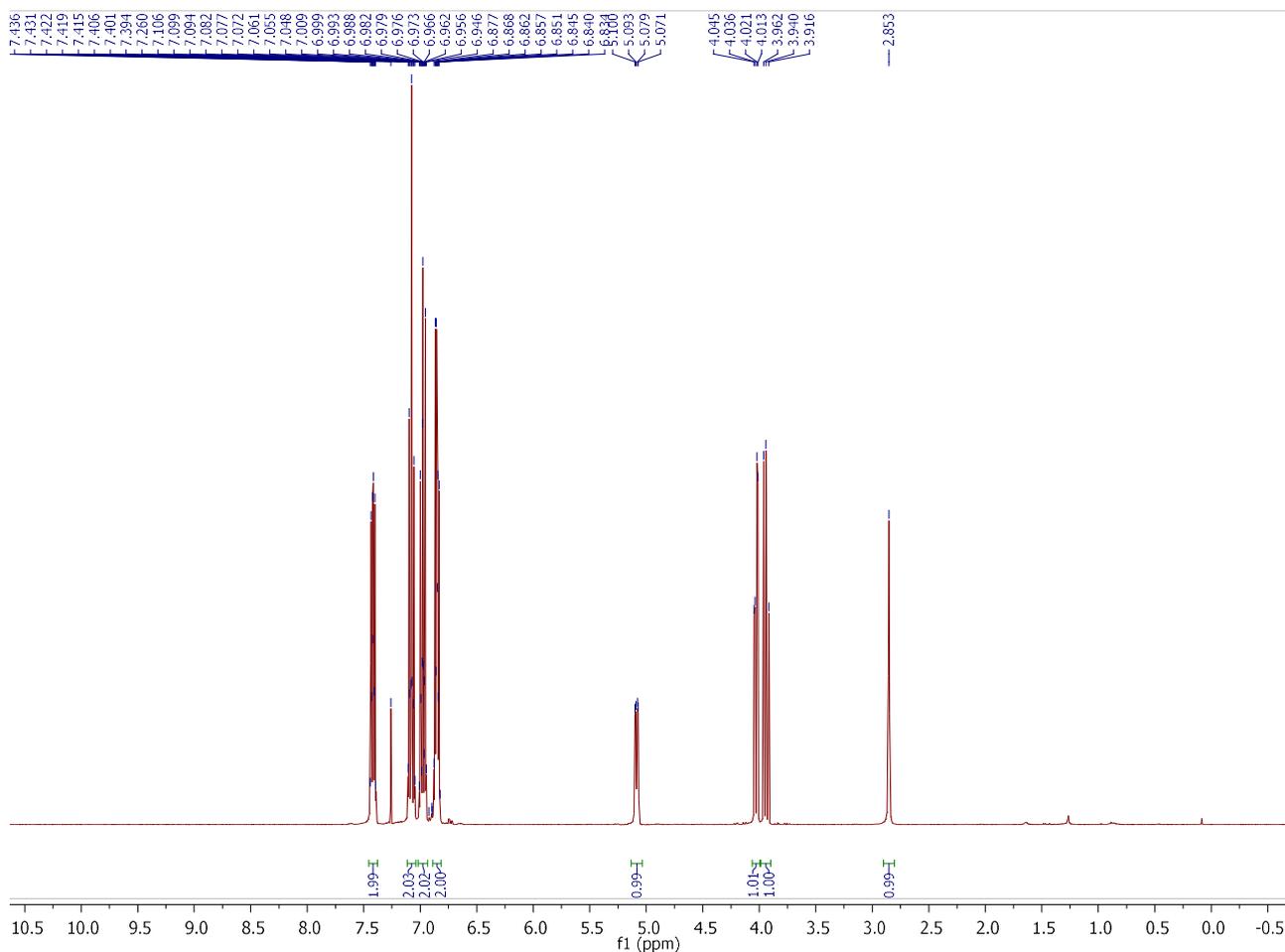
163.633
161.676
154.382
152.508
135.571
135.547
128.146
128.081
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115.468
114.820
114.133
77.160
74.144
72.119
55.829

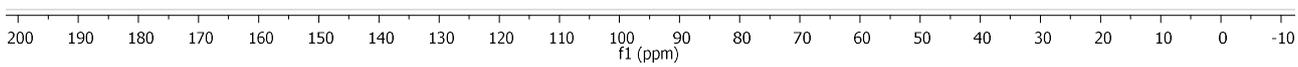
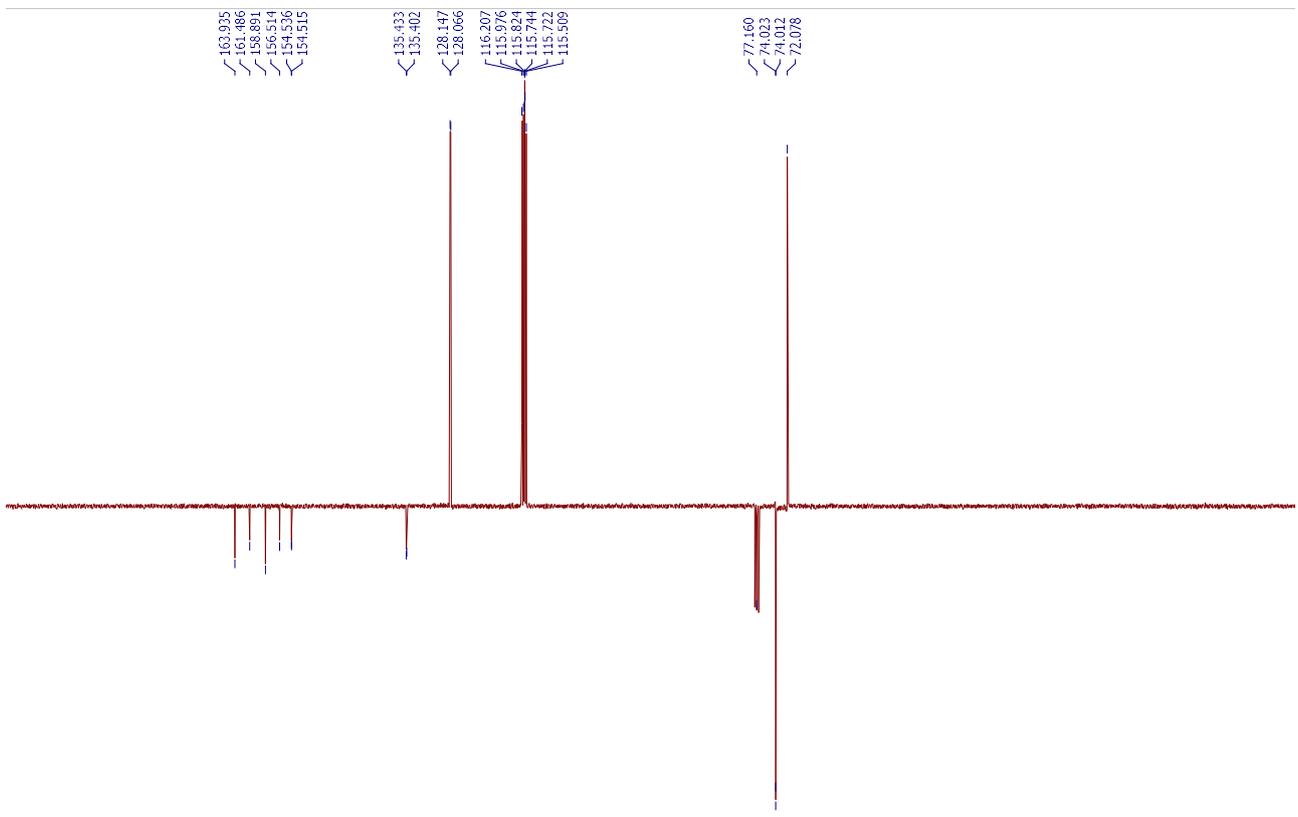
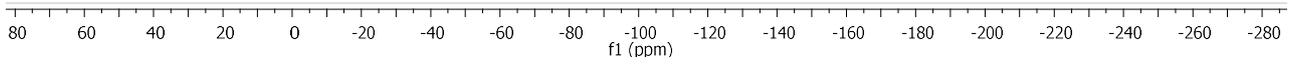
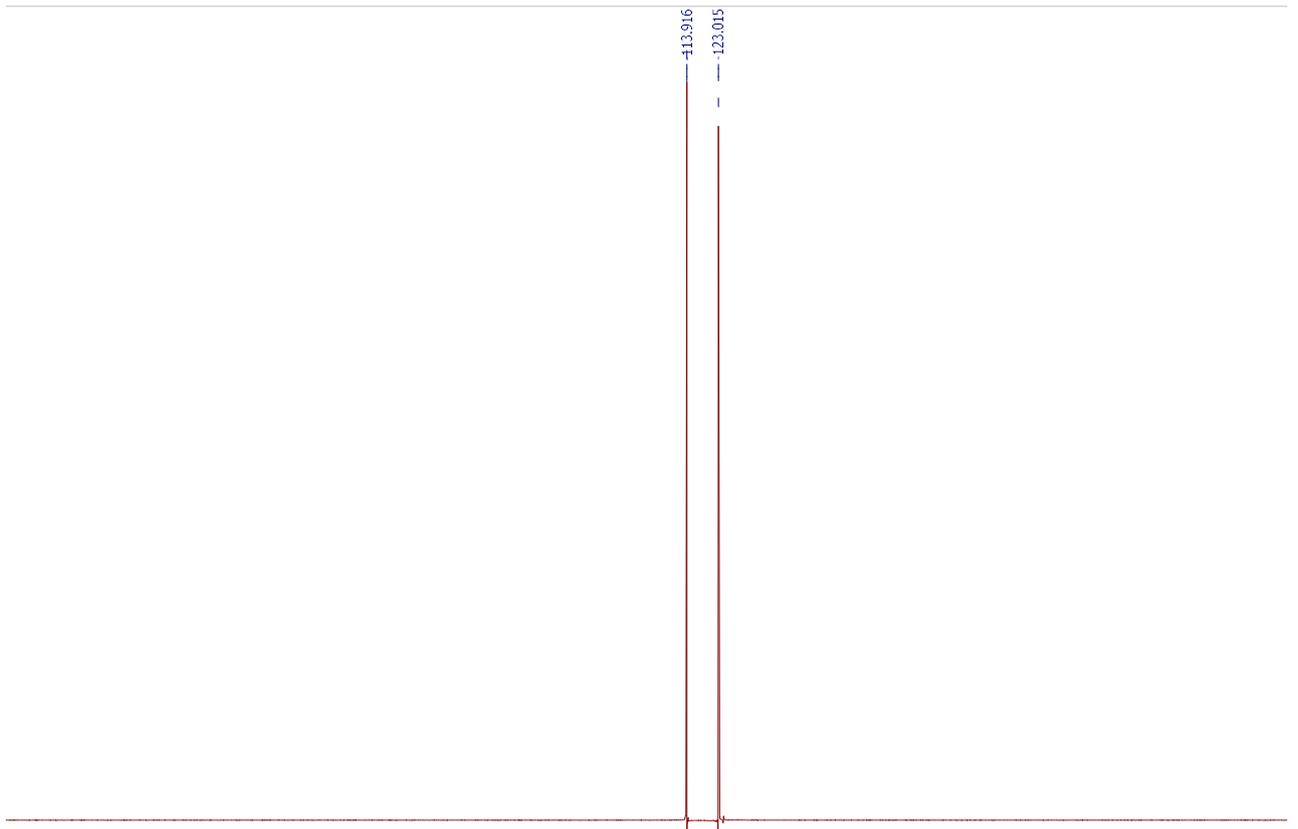


2-(4-fluorophenoxy)-1-(4-fluorophenyl)ethan-1-ol

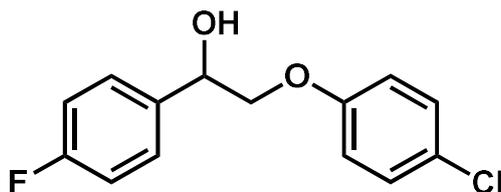


The title compound 2-(4-fluorophenoxy)-1-(4-fluorophenyl)ethan-1-ol was prepared according to general procedure 6 using 4-fluorophenol (1.12 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 40% EtOAc in hexanes, 45 × 75 mm silica) gave a pale orange solid (1.42 g, 95%). mp 47-50 °C; R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3289, 2938, 2872, 1601, 1504, 1458, 1296, 1253, 1219, 1192, 1155, 1105, 912, 876, 827, 800, 727, 577, 561, 513, 490; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 2.85 (1H, s), 3.92-3.96 (1H, m), 4.03 (1H, dd, J 9.5, 3.3), 5.09 (1H, dd, J 8.6, 3.0), 6.82-6.88 (2H, m), 6.95-7.01 (2H, m), 7.05-7.11 (2H, m), 7.39-7.44 (2H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -113.9, -123.0; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ_{C} : 72.1, 74.0 (d, J 1.1), 115.6 (d, J 23.7), 115.8 (d, J 10.3), 116.1 (d, J 23.3), 128.1 (d, J 8.2), 135.4 (d, J 3.1), 154.5 (d, J 3.1), 157.7 (d, J 240.0), 162.7 (d, J 247.3); HRMS (NSI^+) calculated for $[\text{C}_{14}\text{H}_{11}\text{F}_2\text{O}_2]^+$ ($\text{M}-\text{H}$) $^+$: m/z 249.0733, found 249.0733, (+0.2 ppm).

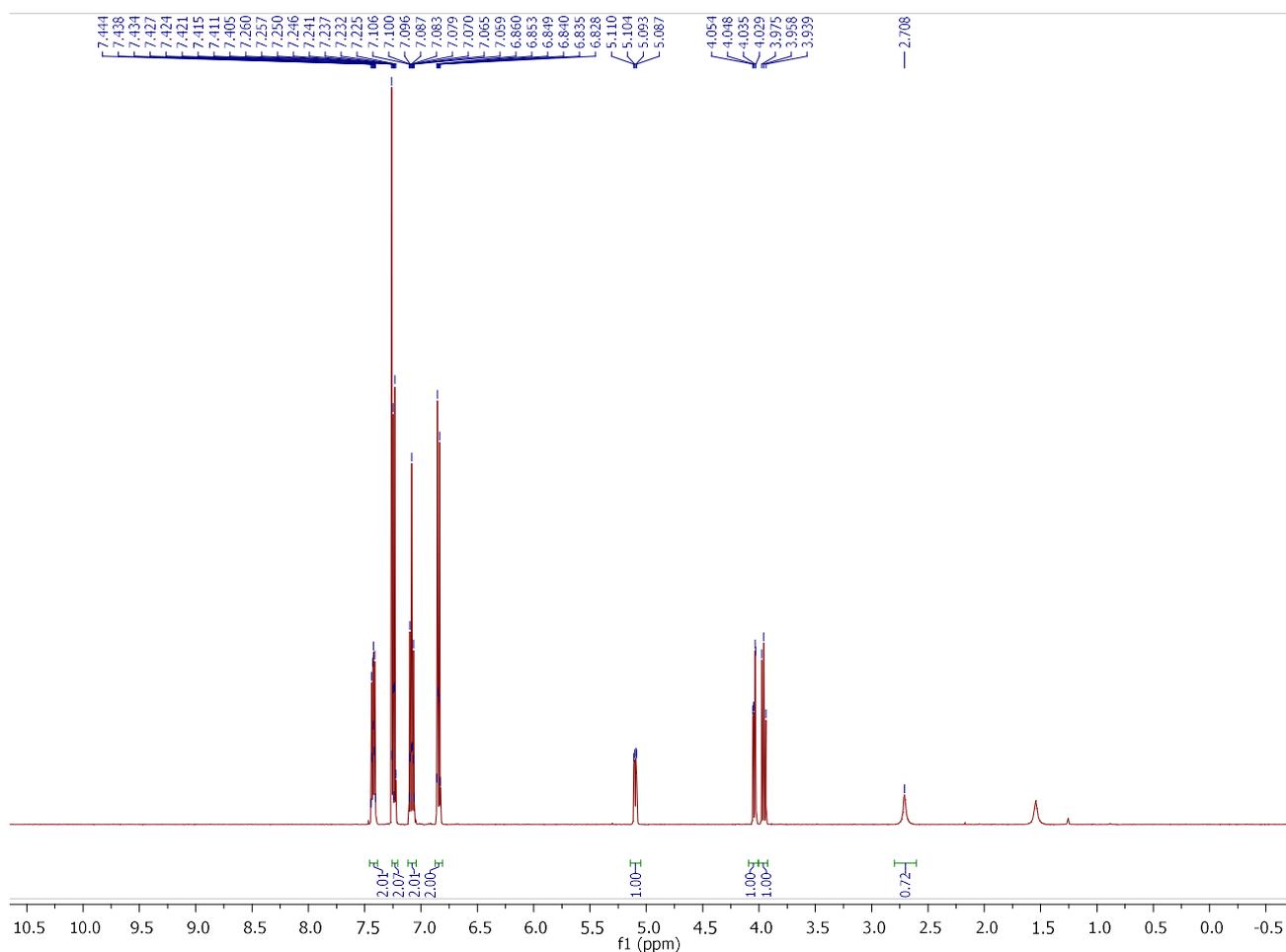


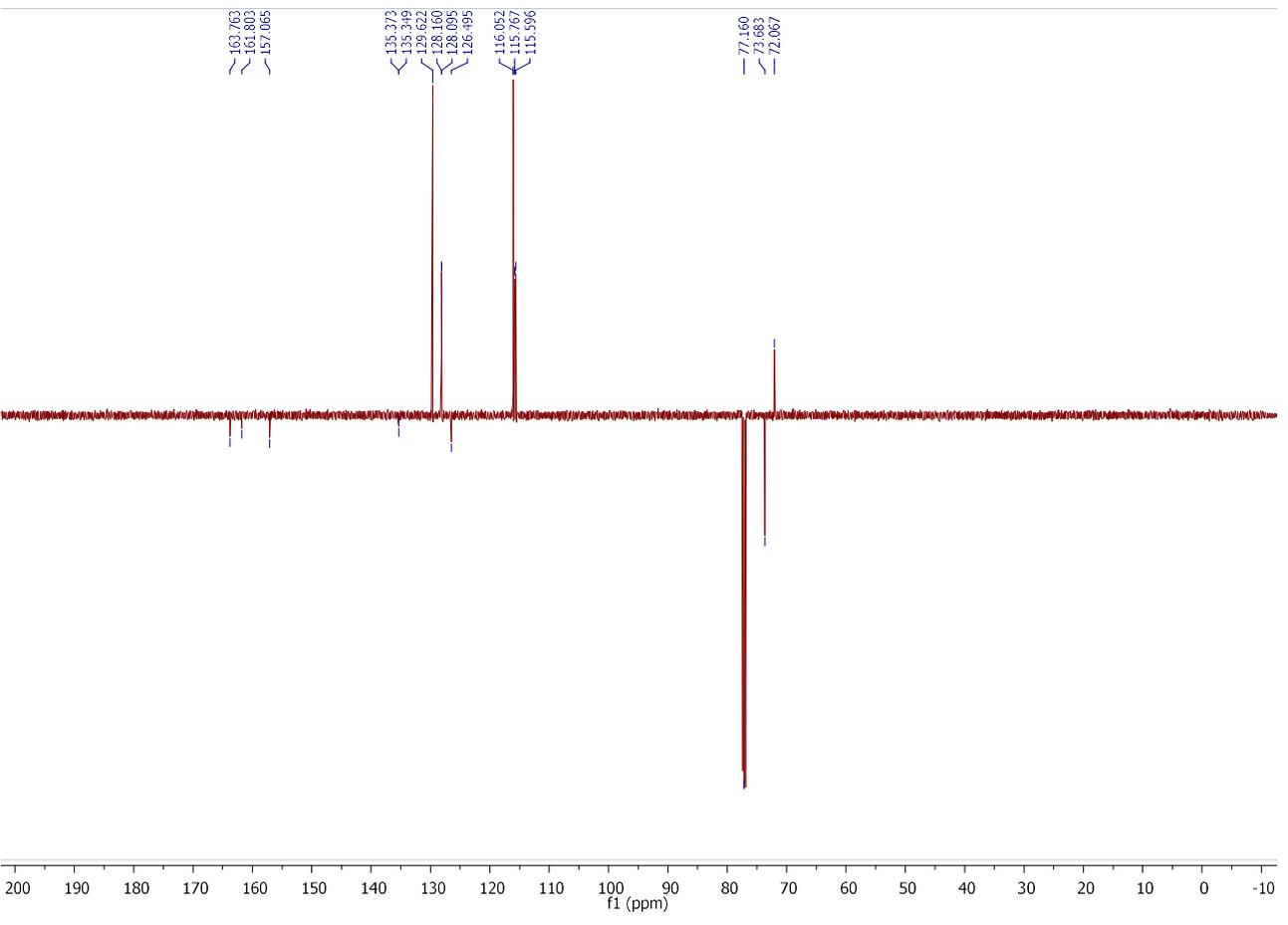
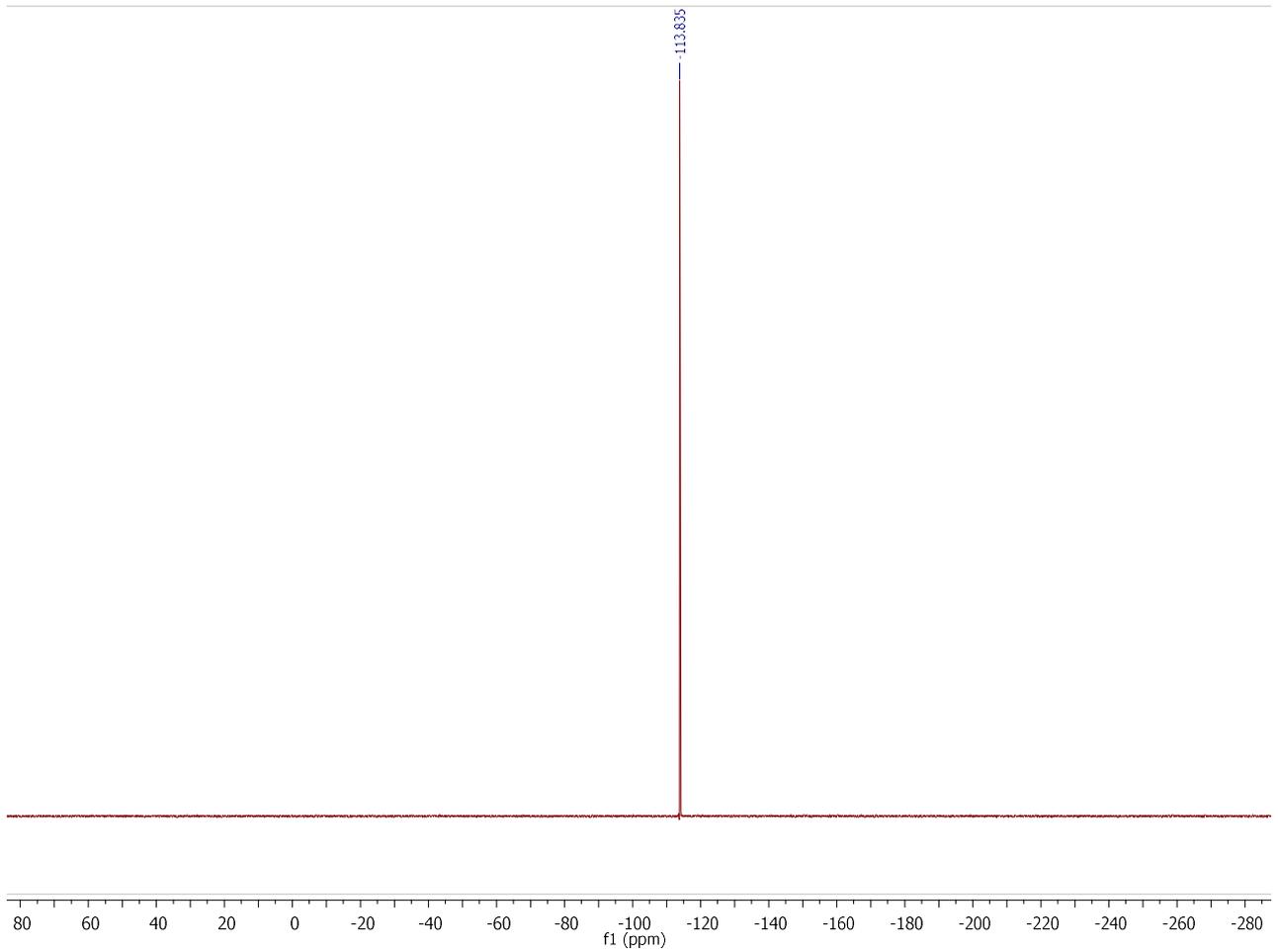


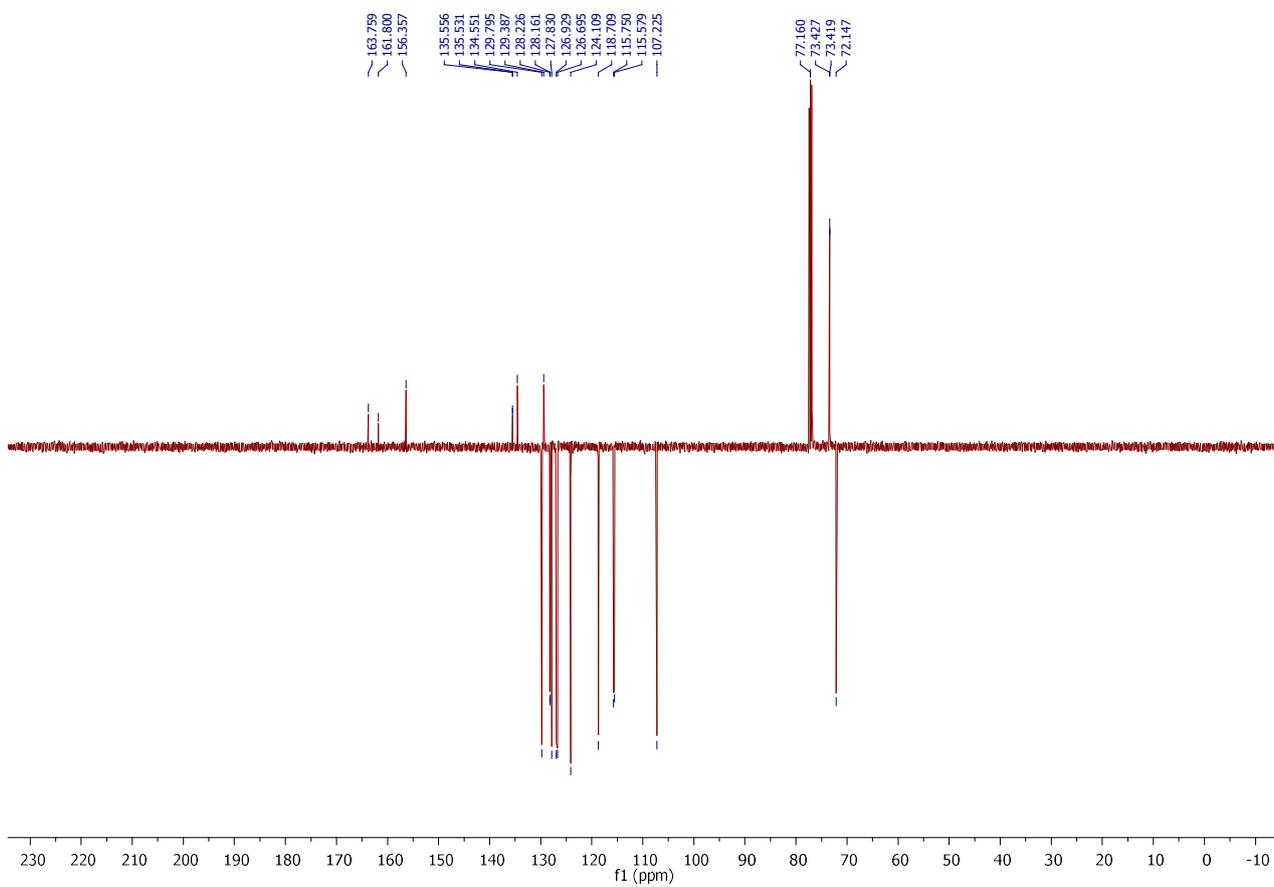
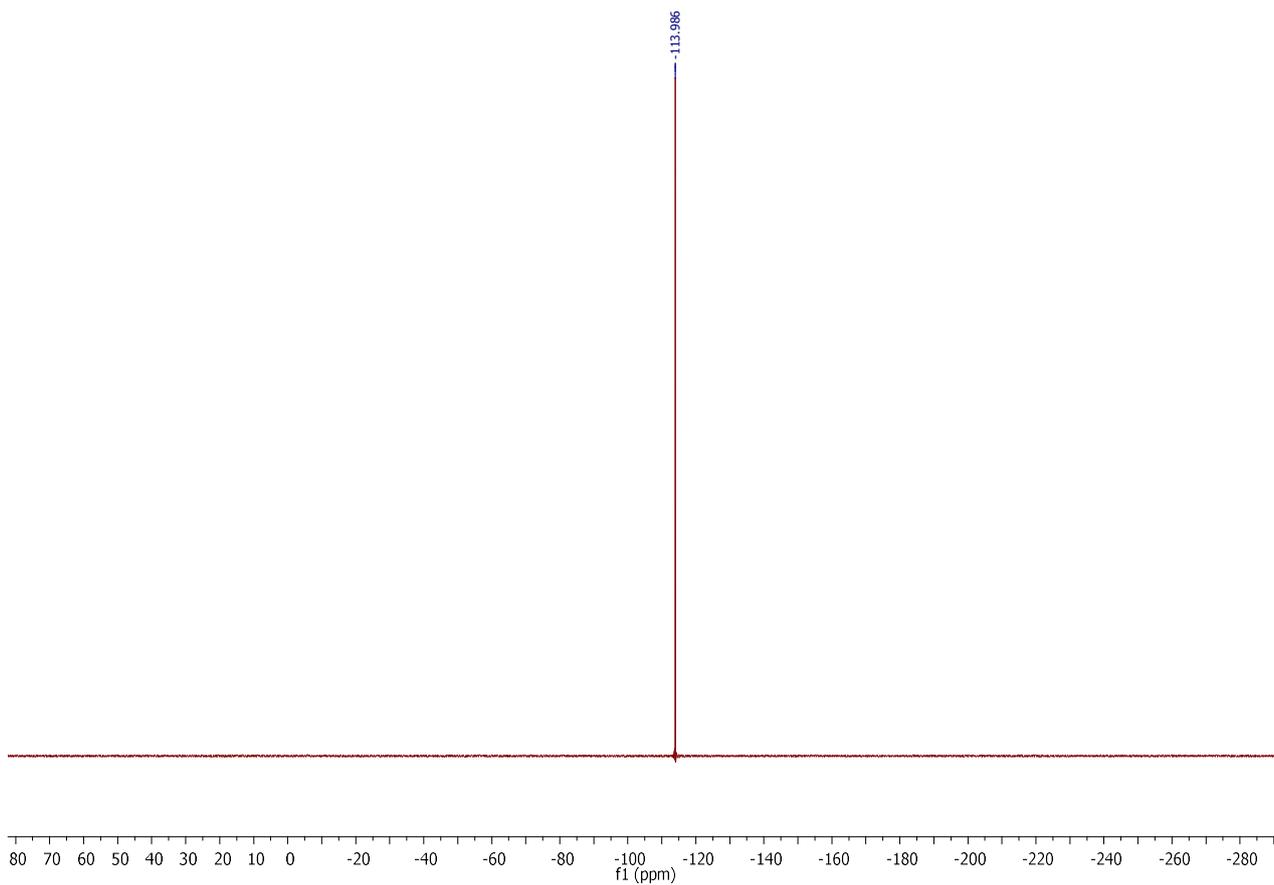
2-(4-chlorophenoxy)-1-(4-fluorophenyl)ethan-1-ol



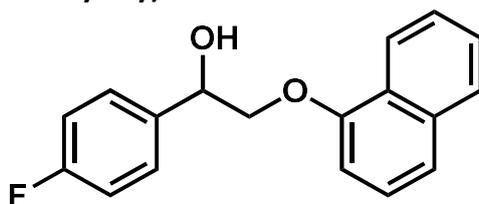
The title compound 2-(4-chlorophenoxy)-1-(4-fluorophenyl)ethan-1-ol was prepared according to general procedure 6 using 4-chlorophenol (1.29 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes) gave an off-white solid (1.85 g, 69%). mp 52-54 °C; R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3537, 2928, 2868, 1603, 1578, 1510, 1487, 1454, 1281, 1217, 1157, 1094, 1080, 1018, 1005, 924, 910, 870, 826, 808, 658, 571, 550, 507; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.71 (1H, br), 3.94-3.98 (1H, m), 4.04 (1H, dd, J 9.5, 3.0), 5.10 (1H, dd, J 8.7, 3.2), 6.81-6.88 (2H, m), 7.04-7.12 (2H, m), 7.21-7.27 (2H, m), 7.38-7.49 (2H, m); $^{19}\text{F NMR}$ (377 MHz, CDCl_3) δ_{F} : -113.8; $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 72.1, 73.7, 115.7 (d, J 21.5), 116.1, 126.5, 128.1 (d, J 8.2), 129.6, 135.4 (d, J 3.0), 157.1, 162.8 (d, J 247.0). HRMS (NSI^+) calculated for $[\text{C}_{14}\text{H}_{11}\text{ClFO}_2]^+$ (M-H) $^+$: m/z 265.4037, found 265.0437 (-0.0 ppm).



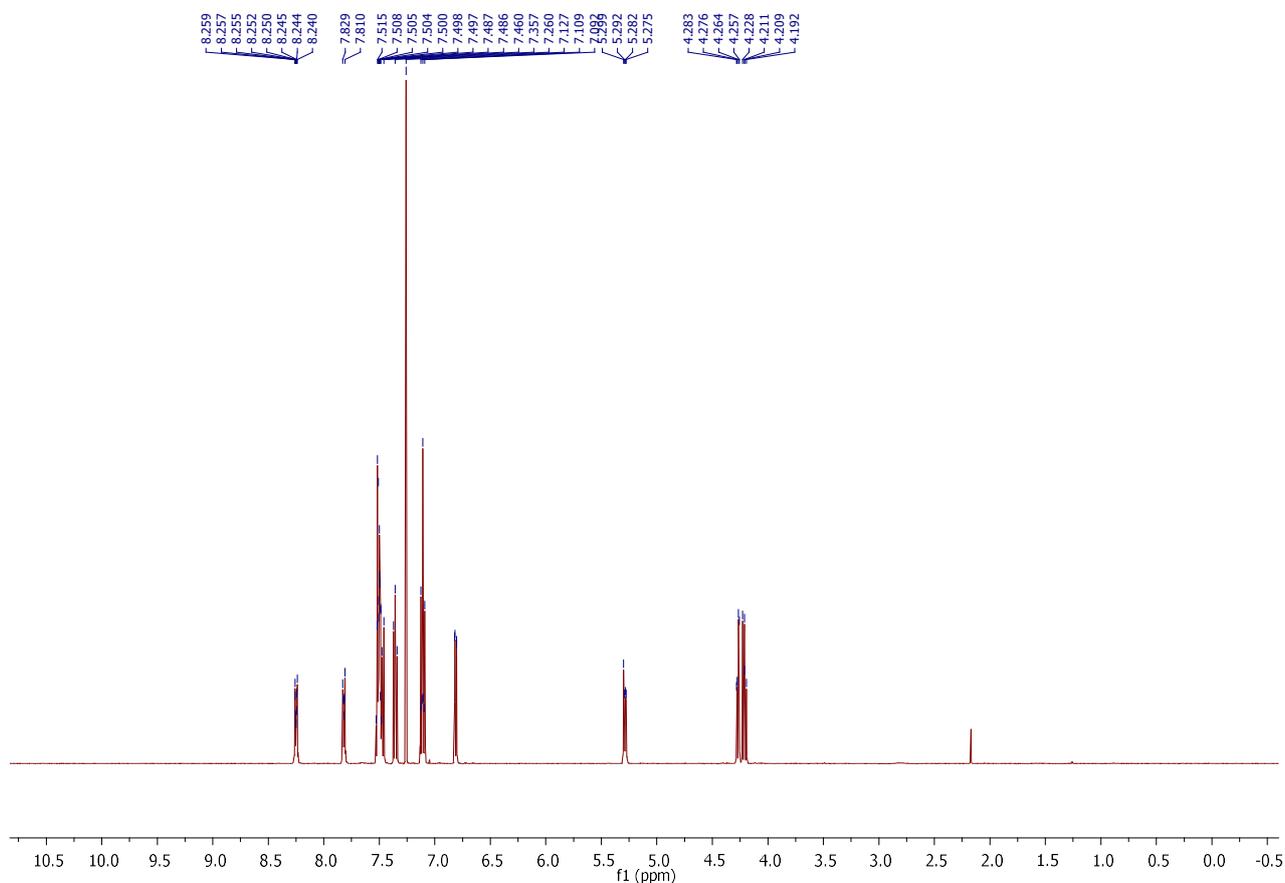


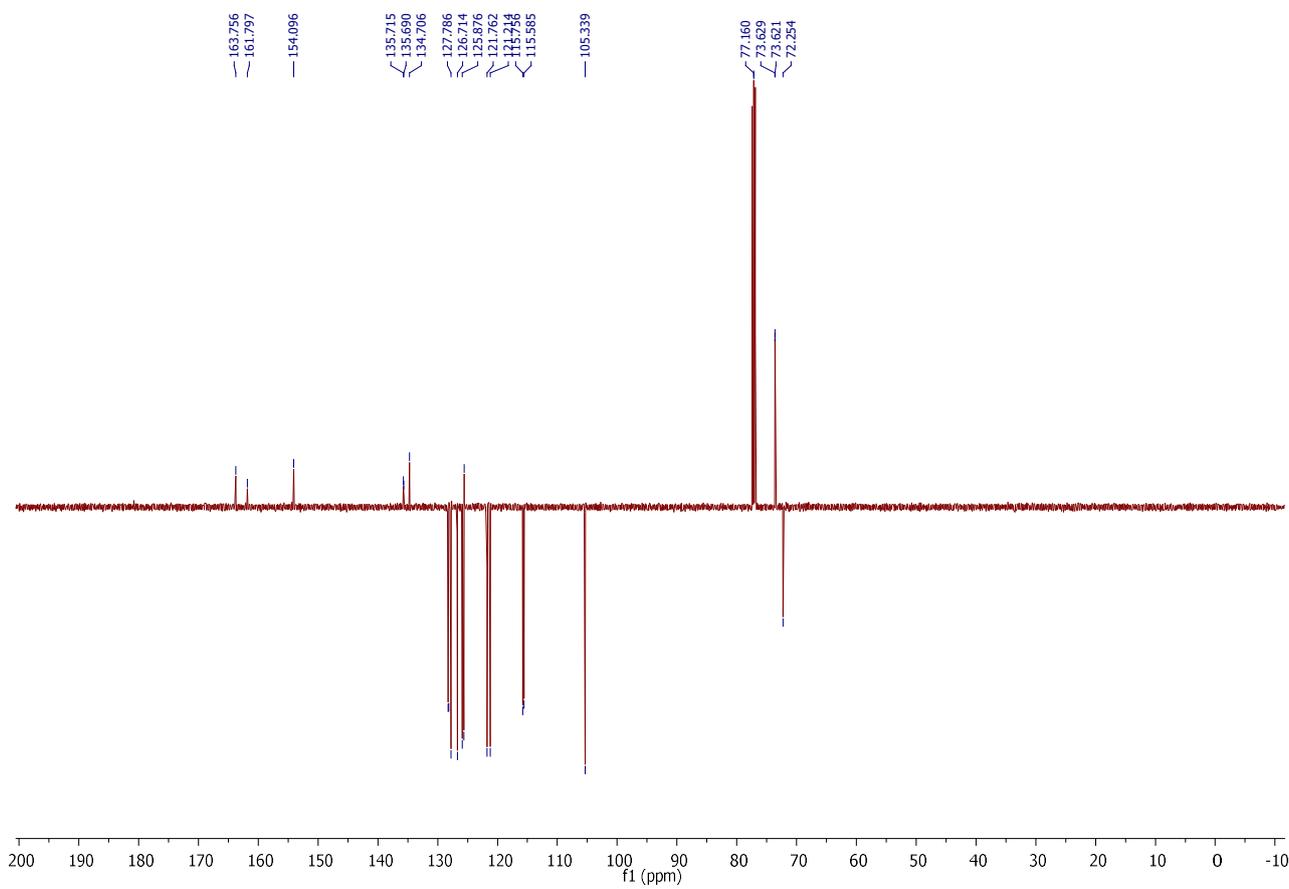
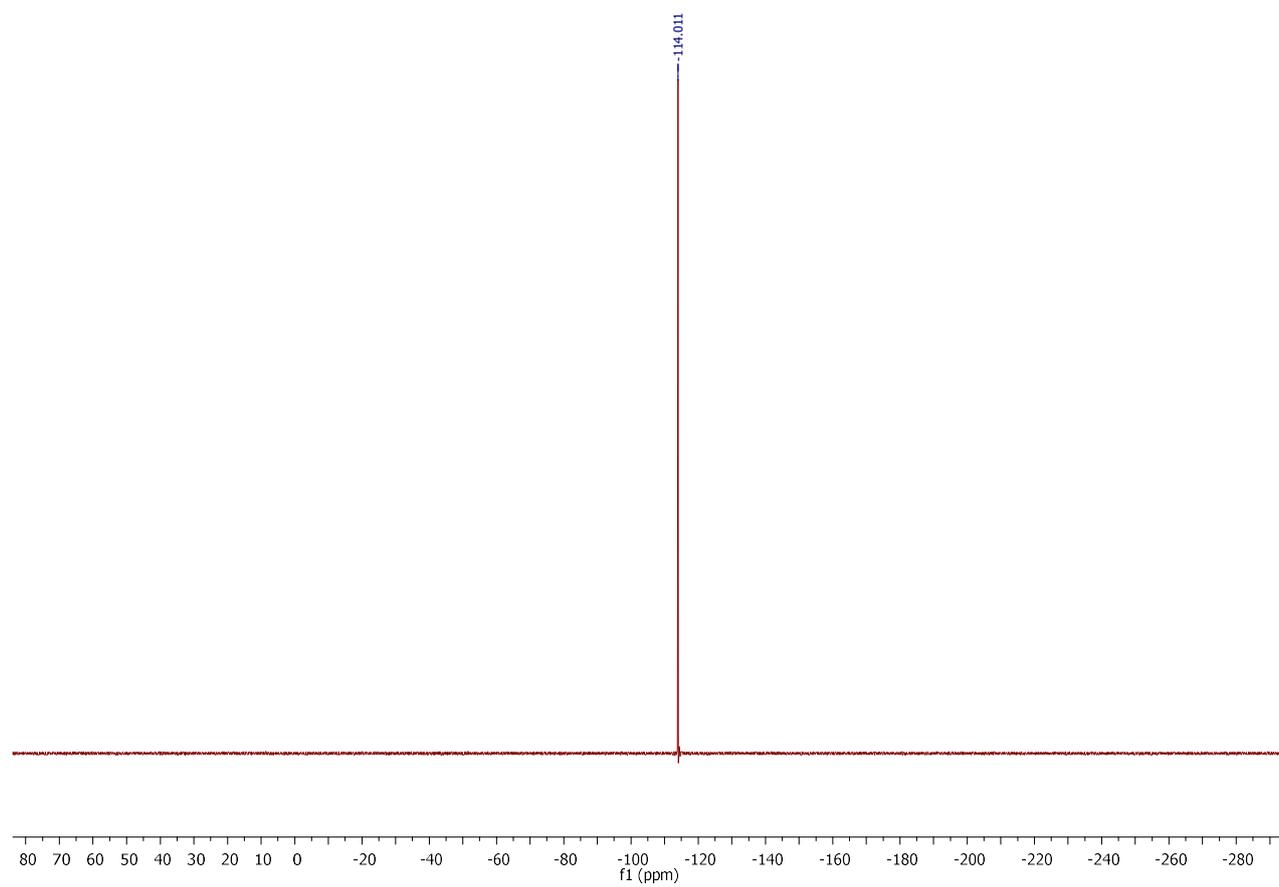


1-(4-fluorophenyl)-2-(naphthalen-1-yloxy)ethan-1-ol

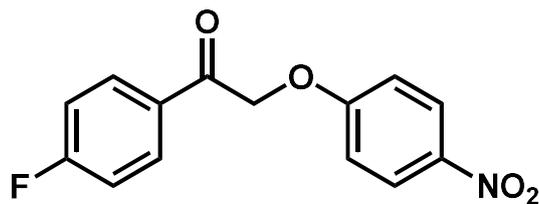


The title compound 1-(4-fluorophenyl)-2-(naphthalen-1-yloxy)ethan-1-ol was prepared according to general procedure 6 using 1-naphthol (1.44 g, 10.0 mmol). Purification by flash silica chromatography (eluent = 10-20% ethyl acetate in hexanes, 55 x 160 mm silica) gave an off-white solid (2.32 g, 82%). mp 92-96 °C' R_f = 0.27 (eluent = 20% EtOAc in hexanes); ν_{\max} / cm^{-1} (film) 3291, 3053, 2922, 2862, 1607, 1593, 1578, 1506, 1456, 1389, 1267, 1221, 1163, 1109, 1086, 1024, 1013, 918, 883, 835, 787, 768, 723. 611, 581, 567, 534, 515; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 4.21 (1H, dd, J 8.4, 9.5), 4.27 (1H, dd, J 3.6, 9.6), 5.29 (1H, dd, J 3.7, 8.4), 6.81 (1H, dd, J 0.6, 7.6), 7.07-7.16 (2H, m), 7.33-7.39 (1H, m), 7.43-7.57 (5H, m), 7.77-7.86 (1H, m), 8.21-8.27 (1H, m); $^{19}\text{F NMR}$ (471 MHz, CDCl_3) δ_{F} : -114.0. $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ_{C} : 72.3, 73.6 (d, J 1.0), 105.3, 115.7 (d, J 22.0), 121.2, 121.8, 125.6, 125.6, 125.9, 126.7, 127.8, 128.2 (d, J 8.2), 134.7, 135.7 (d, J 3.2), 154.1, 162.8 (d, J 246.8). HRMS (ASAP⁺) calculated for $[\text{C}_{18}\text{H}_{15}\text{FO}_2]^+$ (M)⁺ : m/z 282.0156, found 282.0157, (+0.4 ppm).

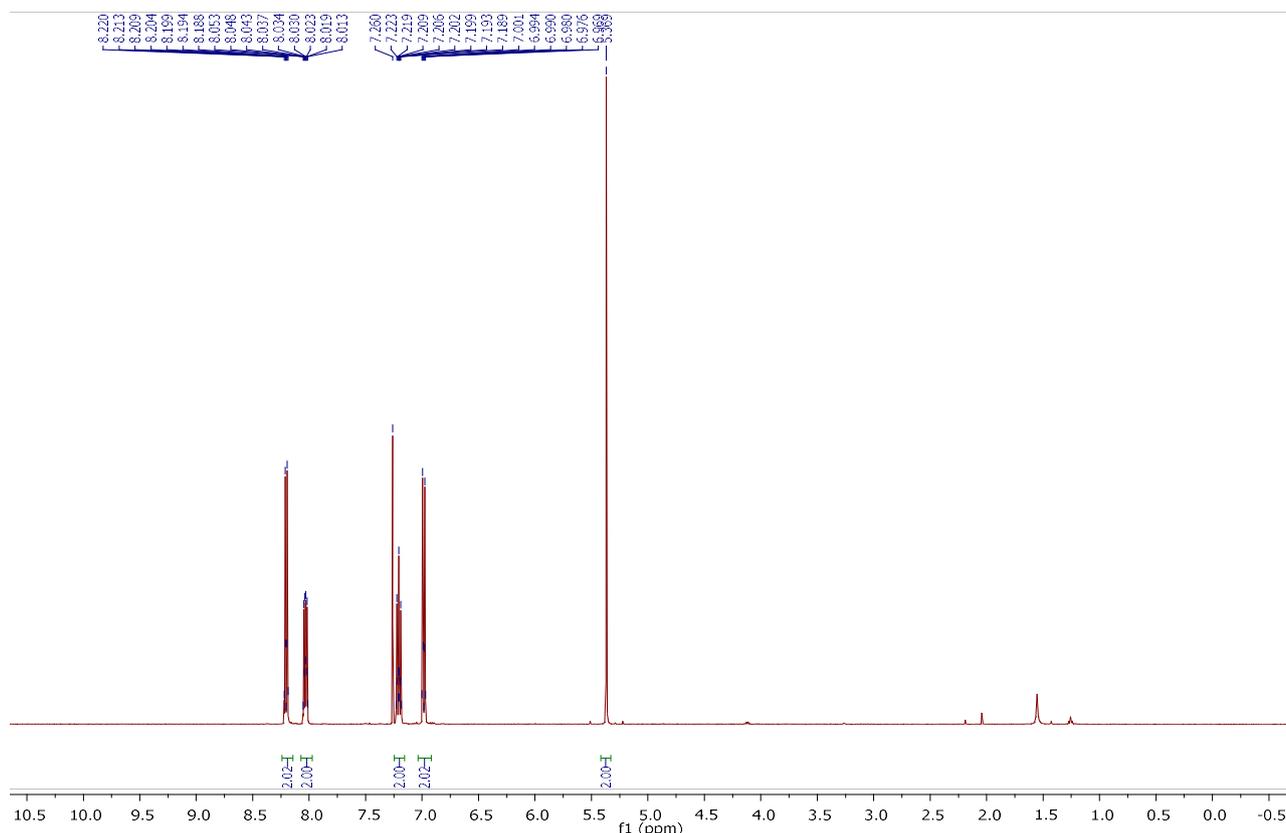


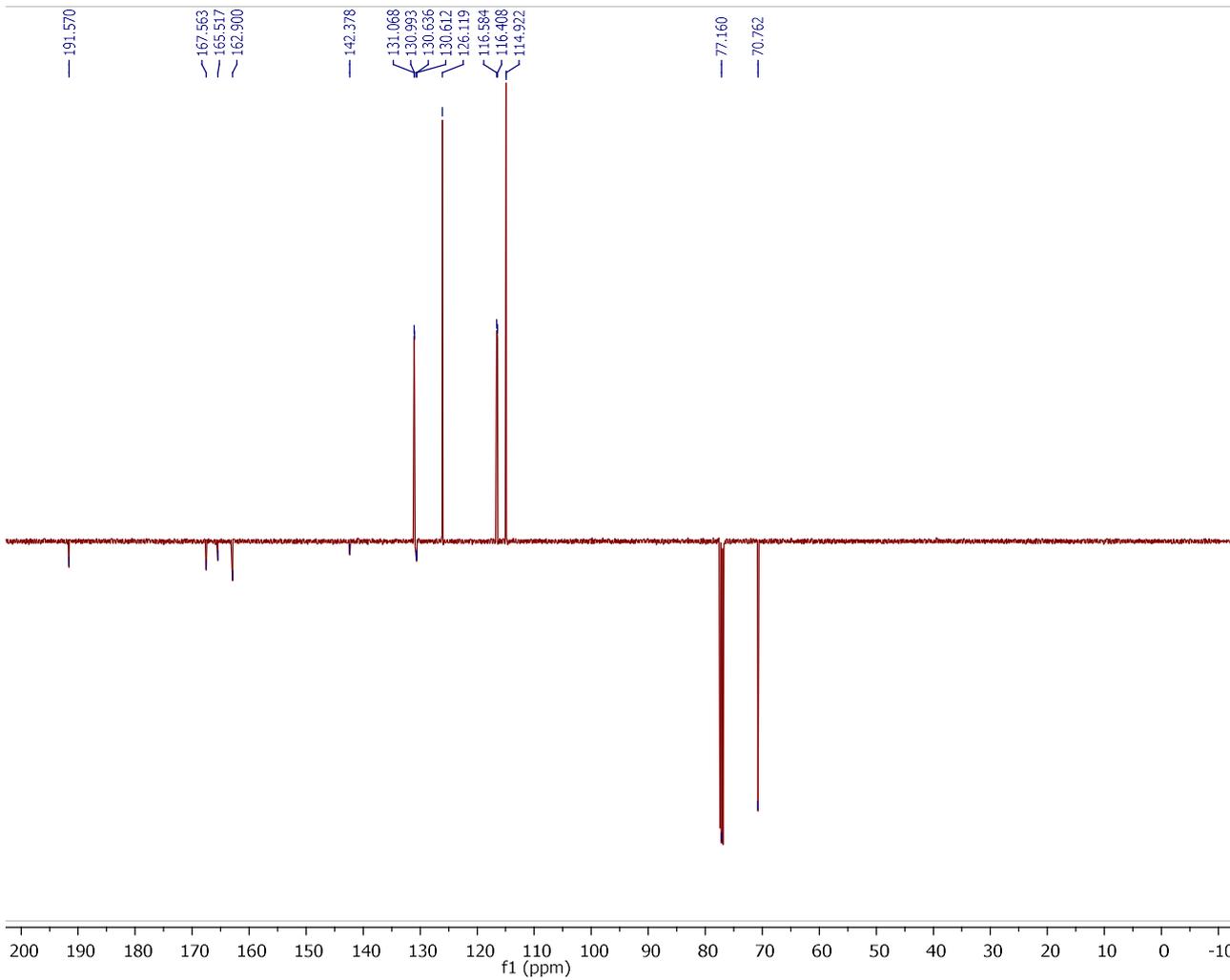
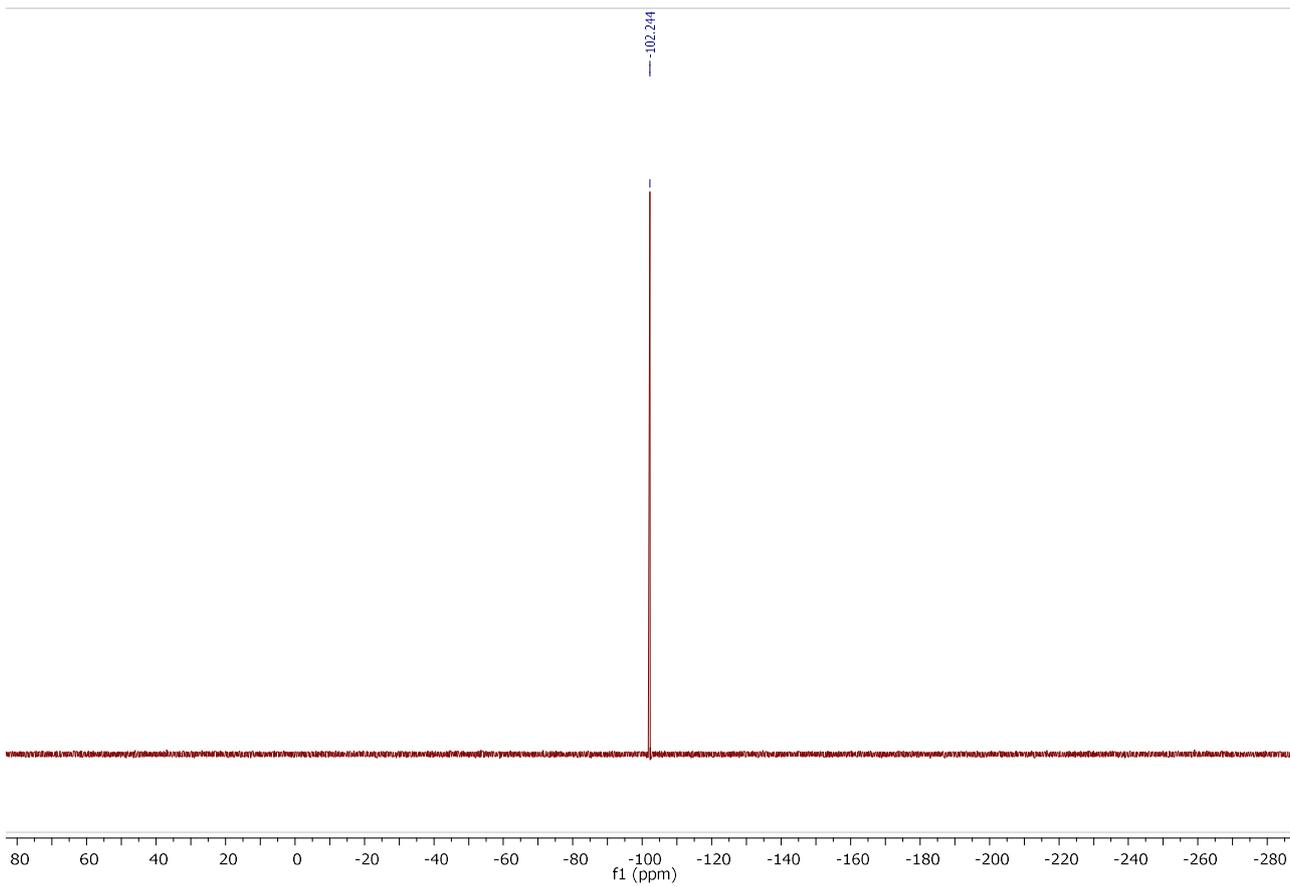


1-(4-fluorophenyl)-2-(4-nitrophenoxy)ethan-1-one

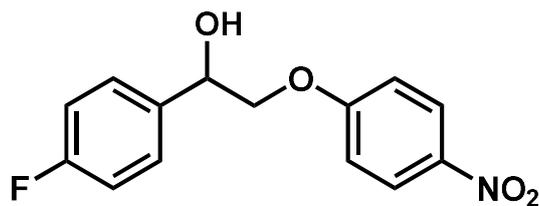


A 250 mL round-bottomed flask containing a magnetic stirrer bar was charged with K_2CO_3 (2.07 g, 15 mmol), 4-nitrophenol (1.39 g, 10.0 mmol) and acetone (50.0 mL). To this mixture was added dropwise a solution of 2-bromo-4'-fluoroacetophenone (2.17 g, 10.0 mmol) in acetone (50.0 mL) over 30 min at rt. The suspension was heated under reflux for 4 h and left to react at room temperature for 20 h. The mixture was filtered, washed with brine and the organic layer was collected in CH_2Cl_2 (50 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 25 mL), the organics combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallization from ethyl acetate gave a yellow solid (1.69 g, 61%). mp 150-154 °C (EtOAc); $R_f = 0.28$ (eluent: 20 % EtOAc in Hexanes); ν_{max} / cm^{-1} (film) 3128, 3082, 2968, 2903, 1701, 1593, 1503, 1327, 1265, 1221, 1159, 1009, 982, 841, 324, 750, 691, 642, 590; 1H NMR (500 MHz, $CDCl_3$) δ_H : 5.37 (s, 2H), 6.96-7.01 (m, 2H), 7.18-7.23 (m, 2H), 8.01-8.06 (m, 2H), 8.18-8.23 (m, 2H); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F : -102.2; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C : 70.8, 114.9, 116.5 (d, J 22.2), 126.1, 130.6 (d, J 3.0), 131.0 (d, J 9.5), 142.4, 162.9, 166.5 (d, J 257.8), 191.6. HRMS (EI⁺) calculated for $[C_{14}H_{10}NO_4F]^+$ (M)⁺ : m/z 275.0594, found 275.0592, (-0.4 ppm).

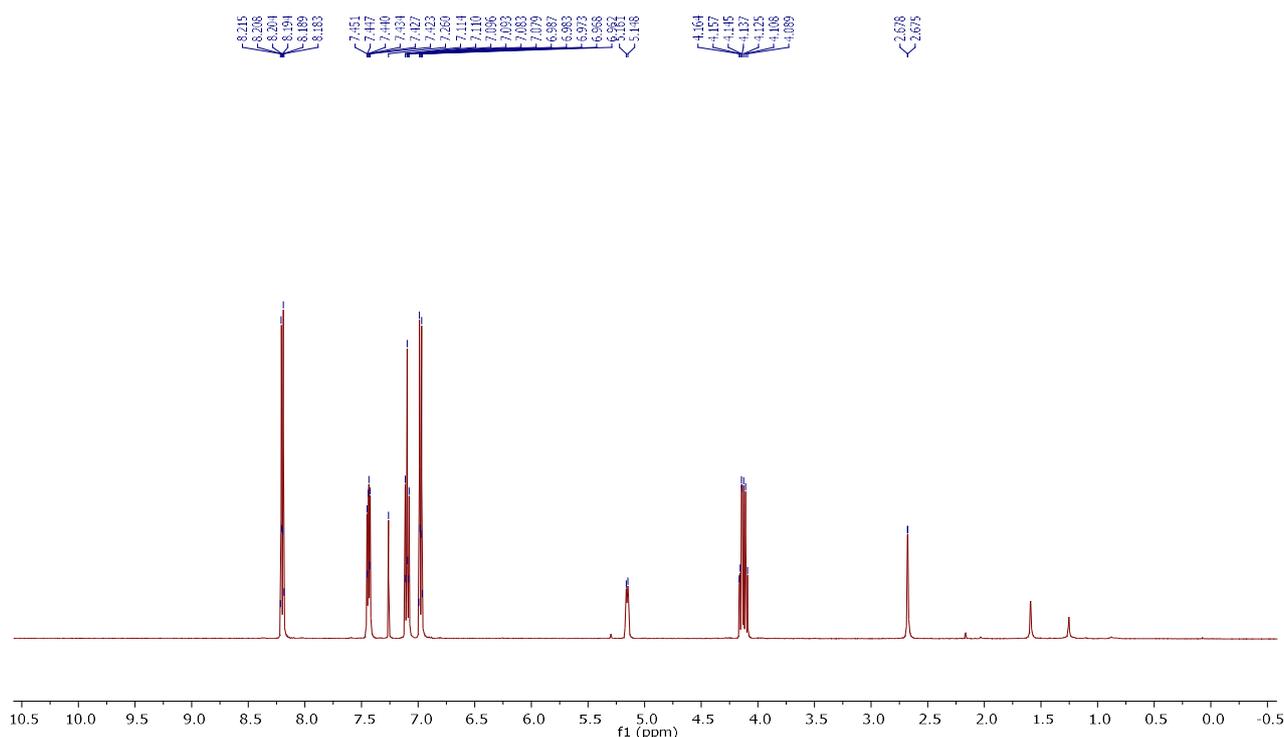


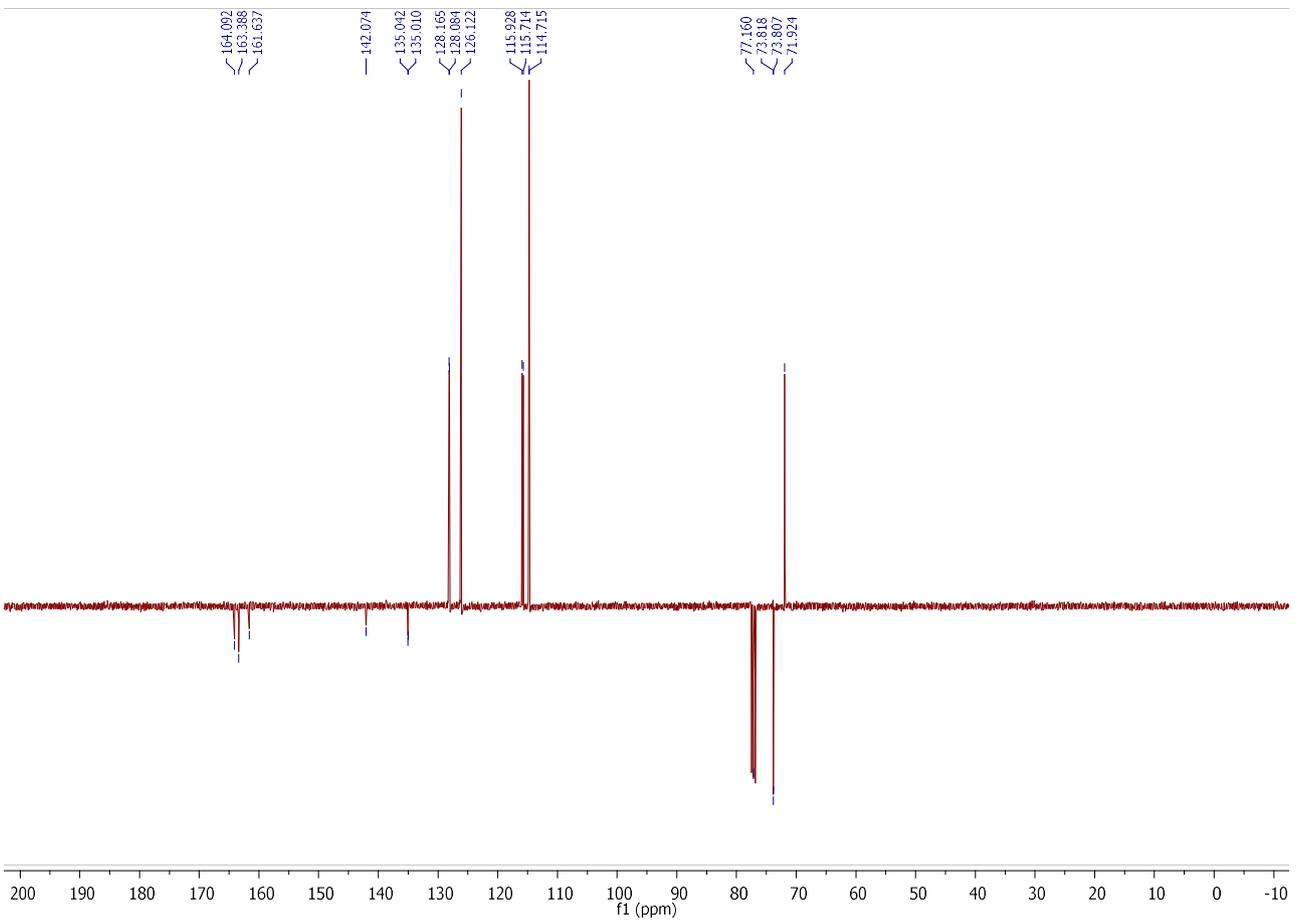
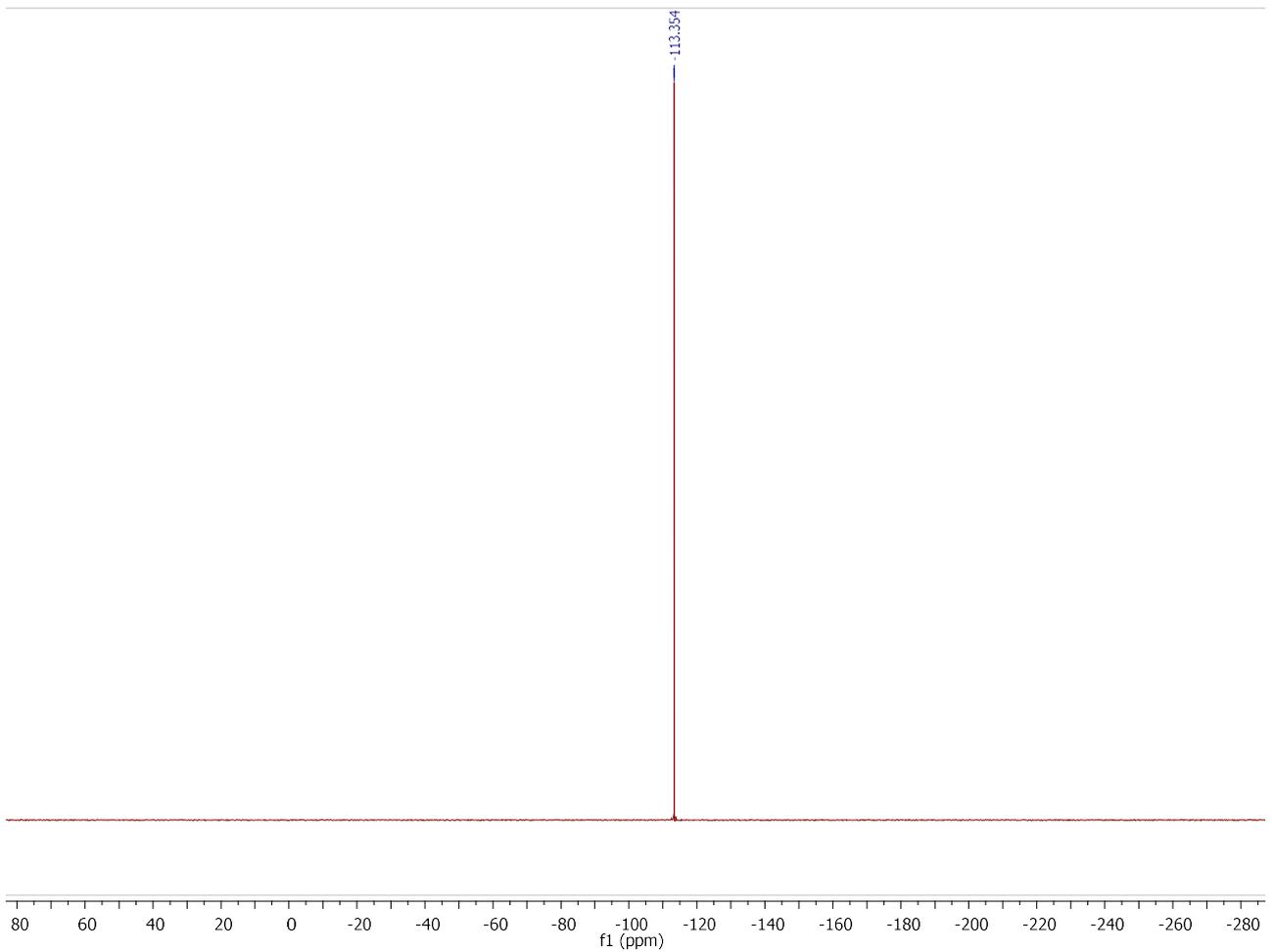


1-(4-fluorophenyl)-2-(4-nitrophenoxy)ethan-1-ol

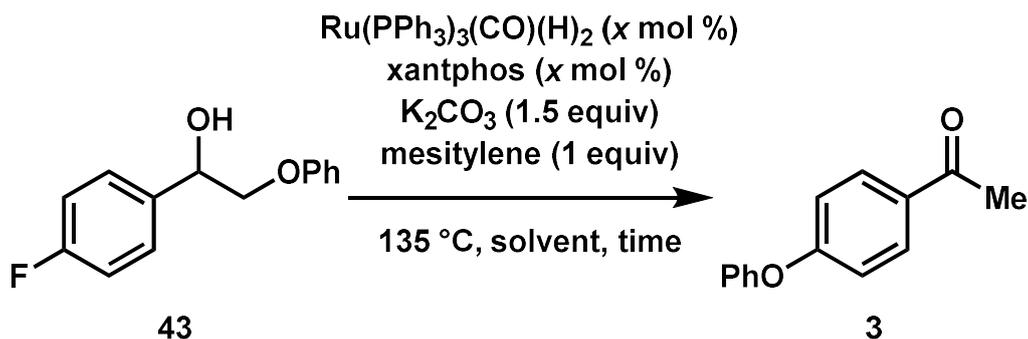


A 500 mL round bottomed flask was charged with 1-(4-fluorophenyl)-2-(4-nitrophenoxy)ethan-1-ol (1.38 g, 5.00 mmol) and methanol (40.0 mL). Sodium borohydride (208 mg, 5.5 mmol) was then added portion wise at 0 °C. The mixture was left to react at rt for 16 h. Sat. aq. NH₄Cl (20 mL) was then added to the mixture. The reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (30 mL) and H₂O (20 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 30 mL). The organics were combined, washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 40% EtOAc in hexanes, 40 x 75 mm silica) gave a white solid (1.33 g, 96%). mp 102-104 °C; R_f = 0.46 (eluent = 40% EtOAc in hexanes); ν_{\max} / cm⁻¹ (film) 3244, 2916, 2862, 1605, 1586, 1503, 1454, 1339, 1331, 1298, 1252, 1221, 1194, 1173, 1084, 1076, 1026, 908, 874, 849, 829, 750, 691, 648, 575, 545, 530, 500; ¹H NMR (400 MHz, CDCl₃) δ _H: 2.67 (1H, d, *J* 2.8), 4.13 (2H, dq, *J* 9.6, 6.0), 5.16 (1H, dt, 8.0, 3.1), 6.96-7.00 (2H, m), 7.07-7.13 (2H, m), 7.41-7.46 (2H, m), 8.18-8.22 (2H, m); ¹⁹F NMR (376 MHz, CDCl₃) δ _F: -113.35; ¹³C NMR (101 MHz, CDCl₃) δ _C: 71.9, 73.8 (d, *J* 1.1), 114.7, 115.8 (d, *J* 21.6), 126.1, 128.1 (d, *J* 8.2), 135.0 (d, *J* 3.2), 142.1, 162.9, (d, *J* 248.0), 164.1; HRMS (ASAP⁺) calculated for [C₁₄H₁₃FNO₄] (M+H)⁺ : m/z 278.0829, found 278.0832 (+1.1 ppm).





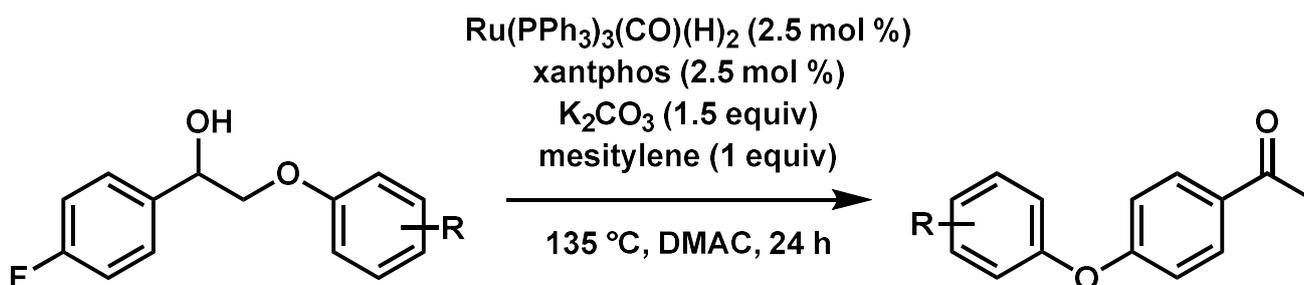
3.3. Optimisation of isomerisation protocol



A 10 mL microwave vial was charged with dihydridocarbonyltris(triphenylphosphine)ruthenium (23.0 mg, 2.50 mol %), xantphos (14.5 mg, 2.50 mol %), 1-(4-fluorophenyl)-2-phenoxyethan-1-ol (232 mg, 1.00 mmol), a polar aprotic solvent (varied amounts), potassium carbonate (207 mg, 1.50 mmol), a magnetic stirrer, and mesitylene (139 μL , 1.00 mmol) as internal standard. The reaction vial was then crimped shut, and heated to $135\text{ }^\circ\text{C}$ for varied times. After the allotted time, the reaction was sampled and analysed using ^1H NMR.

Entry	[Ru] and ligand (mol %)	Time (h)	Solvent (Conc)	NMR yield (Isolated)
1	5	24	DMF (0.4 M)	91%
2	5	24	DMSO (0.4 M)	76%
3	5	24	DMAC (0.4 M)	100%
4	2.5	24	DMAC (0.4 M)	95%
5	1	24	DMAC (0.4 M)	26%
6	2.5	24	DMAC (1 M)	100% (79%)
7	2.5	16	DMAC (1 M)	100%

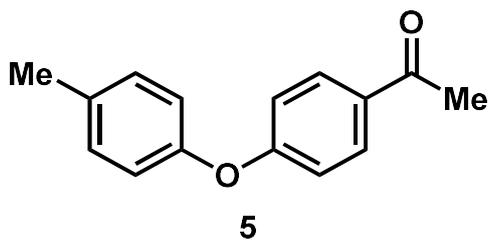
3.4. General procedure 7



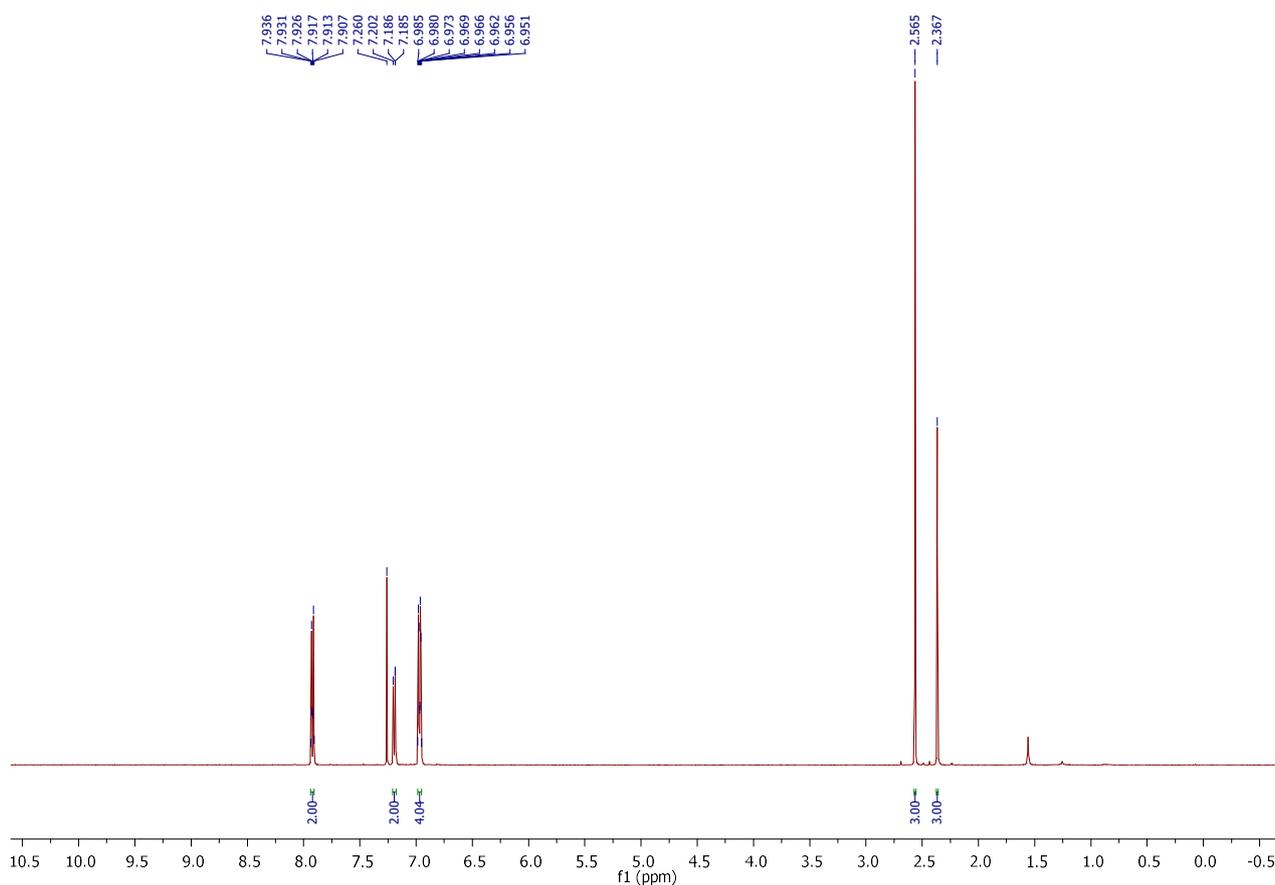
A 10 mL microwave vial was charged with $\text{Ru}(\text{PPh}_3)_3(\text{CO})(\text{H})_2$ (23.0 mg, 2.50 mol %), xantphos (14.5 mg, 2.50 mol %), a 1-(4-fluorophenyl)-phenoxyethanol (1.00 mmol), dimethylacetamide (1.00 mL), potassium carbonate (207 mg, 1.50 mmol) and a magnetic stirrer. The reaction vial was then crimped shut, and heated to $135\text{ }^\circ\text{C}$ for 24 hours. The reaction was then cooled, and the contents of the vial poured over H_2O (50 mL). The layers are separated, and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic extracts are then washed with brine, dried over magnesium sulfate, filtered, and dried under reduced pressure. The resulting crude diaryl ether was then purified by flash silica column chromatography.

3.5. Scope of isomerisation protocol

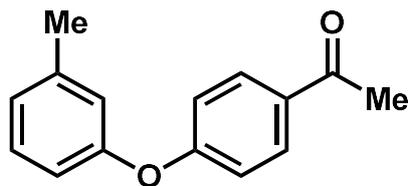
1-(4-(*p*-toloxy)phenyl)ethan-1-one



The title compound was prepared according to general procedure 7, using 1-(4-fluorophenyl)-2-(*p*-toloxy)-ethan-1-ol (246 mg, 1.00 mmol. Purification by flash silica column chromatography (eluent = 5% ethyl acetate in hexanes, 150 x 30 mm silica) gives the title compound (177mg, 78%) as a white solid. mp 40-43 °C (Lit. 46-47 °C)⁷; R_f = 0.48 (eluent = 20% EtOAc in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.38 (3H, s), 2.57 (3H, s), 6.95-6.99 (4H, m), 7.19-7.20 (2H, m), 7.91-7.94 (2H, m). Spectroscopic data is in accordance with that reported previously.

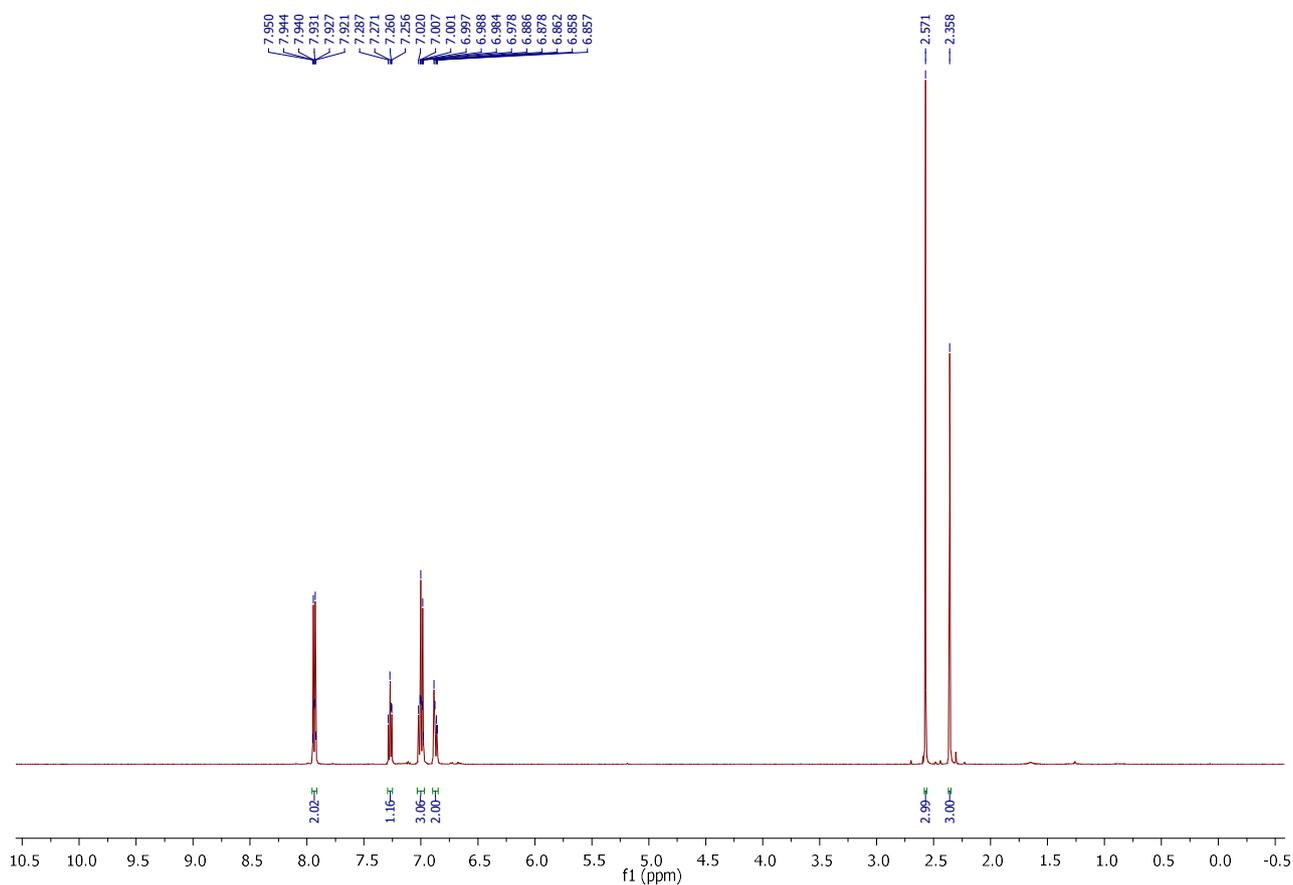


1-(4-(*m*-tolylloxy)phenyl)ethan-1-one

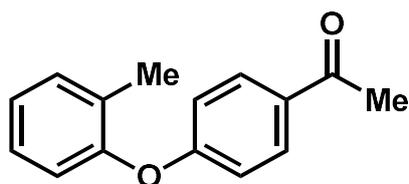


6

The title compound was prepared according to general procedure 7, using 1-(4-fluorophenyl)-2-(*m*-tolylloxy)-ethan-1-ol (246 mg, 1.00 mmol). Purification by flash silica column chromatography (eluent = CH₂Cl₂, 130 x 30 mm silica) gives the title compound (186 mg, 82 %) as a white solid. mp 39-42 °C; R_f = 0.50 (eluent = 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.36 (3H, s), 2.57 (3H, s), 6.86-6.89 (2H, m), 6.98-7.02 (3H, m), 7.27 (1H, t, *J* 7.7), 7.92-7.95 (2H, m). Spectroscopic data is in accordance with that reported previously.

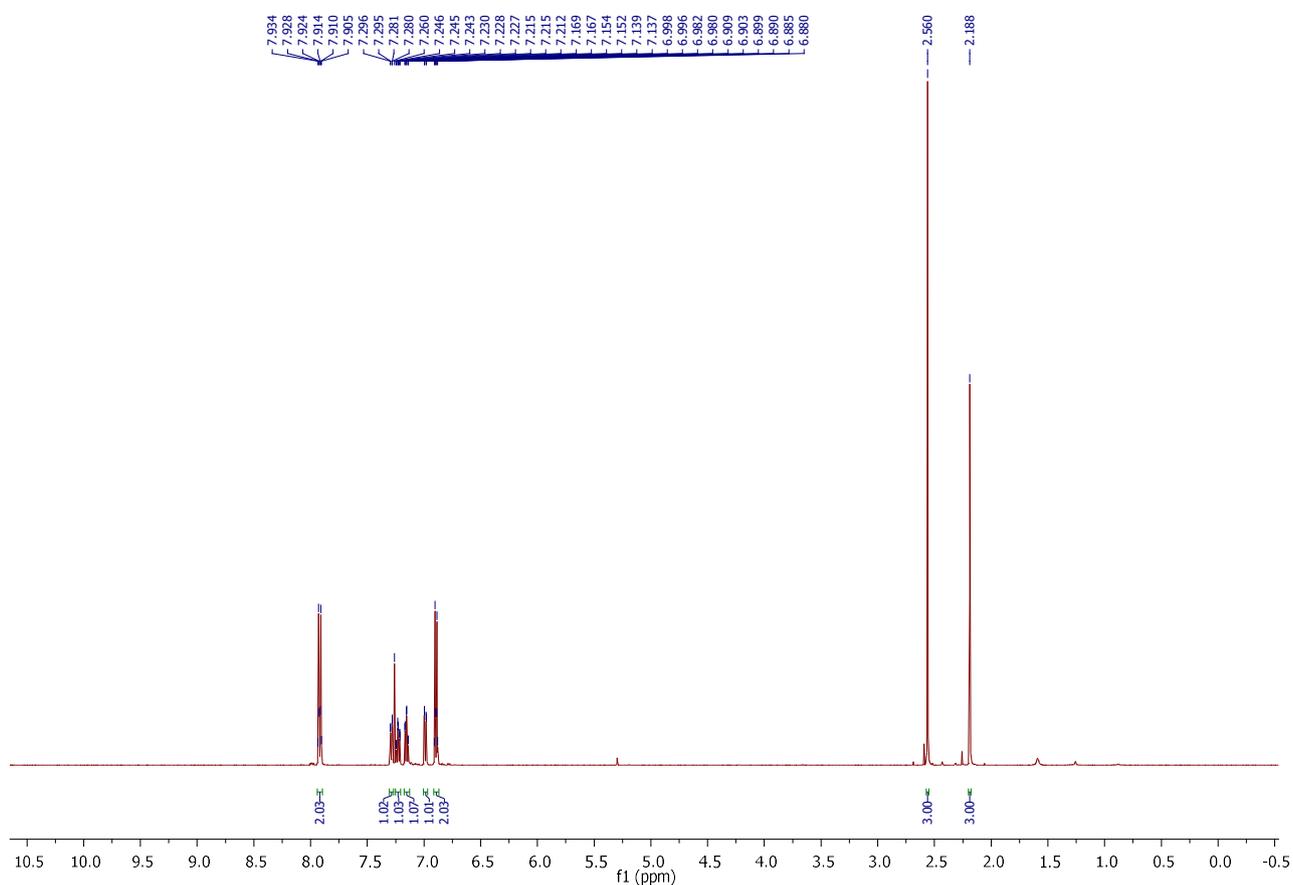


1-(4-(*o*-tolylloxy)phenyl)ethan-1-one

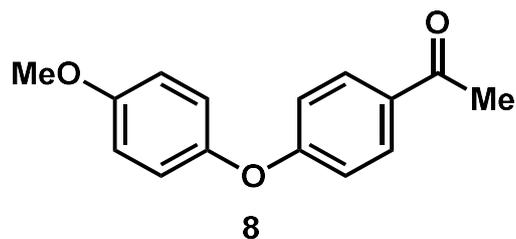


7

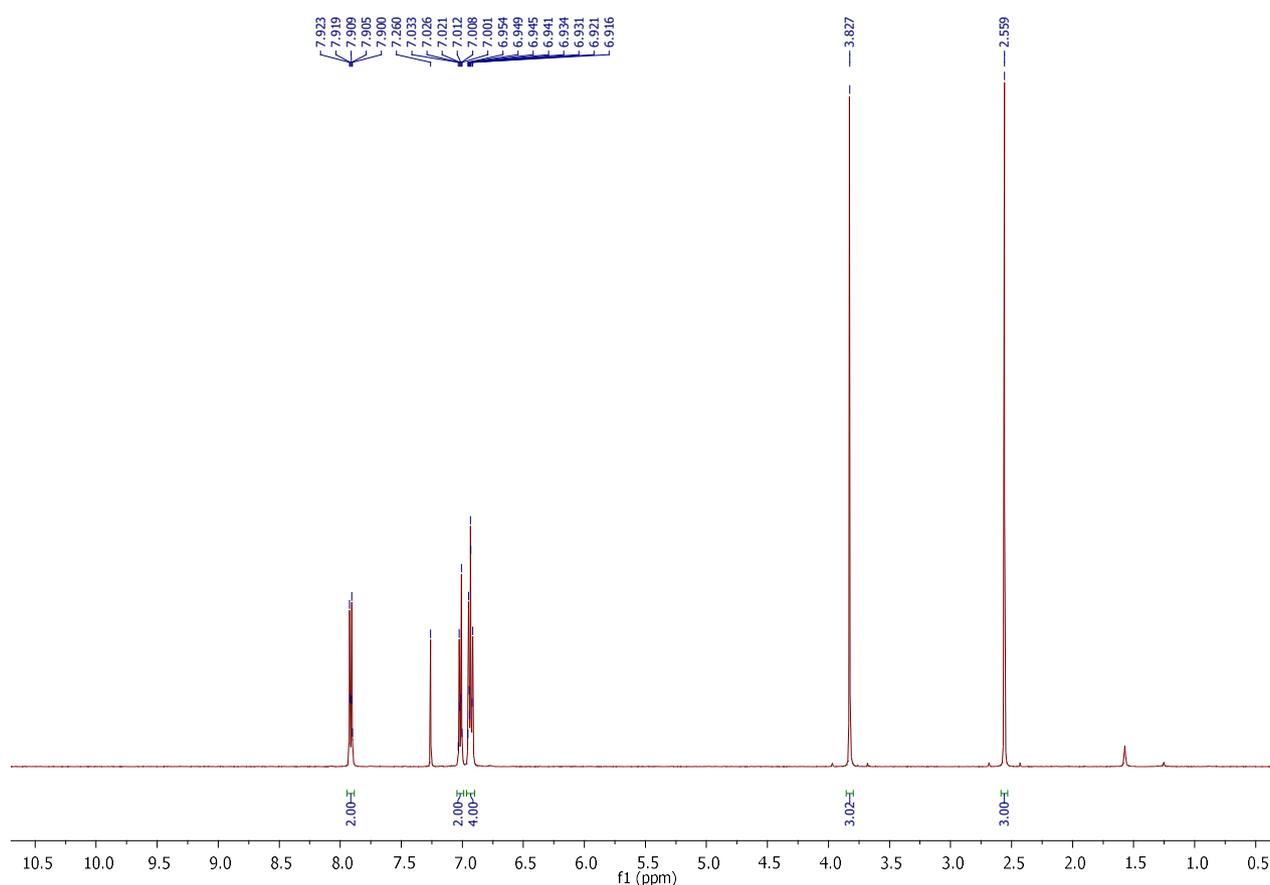
The title compound was prepared according to general procedure 7, using 1-(4-fluorophenyl)-2-(*o*-tolylloxy)-ethan-1-ol (246 mg, 1.00 mmol). Purification by flash silica column chromatography (eluent = CH₂Cl₂ 30 x 140 mm silica) gives the title compound (174 mg, 77%) as a colourless oil. R_f = 0.33 (eluent = 10% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.19 (3H, s), 2.56 (3H, s), 6.88-6.91 (2H, m), 6.99 (1H, dd, *J* 8.0, 1.0), 7.15 (1H, td, 7.4, 1.2), *J* 7.21-7.25 (1H, m), 7.29 (1H, dd, *J* 7.5, 1.0), 7.91-7.93 (2H, m). Spectroscopic data is in accordance with that reported previously.



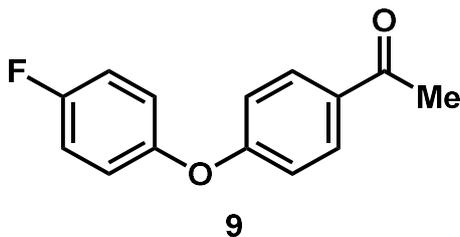
1-(4-(4-methoxyphenoxy)phenyl)ethan-1-one



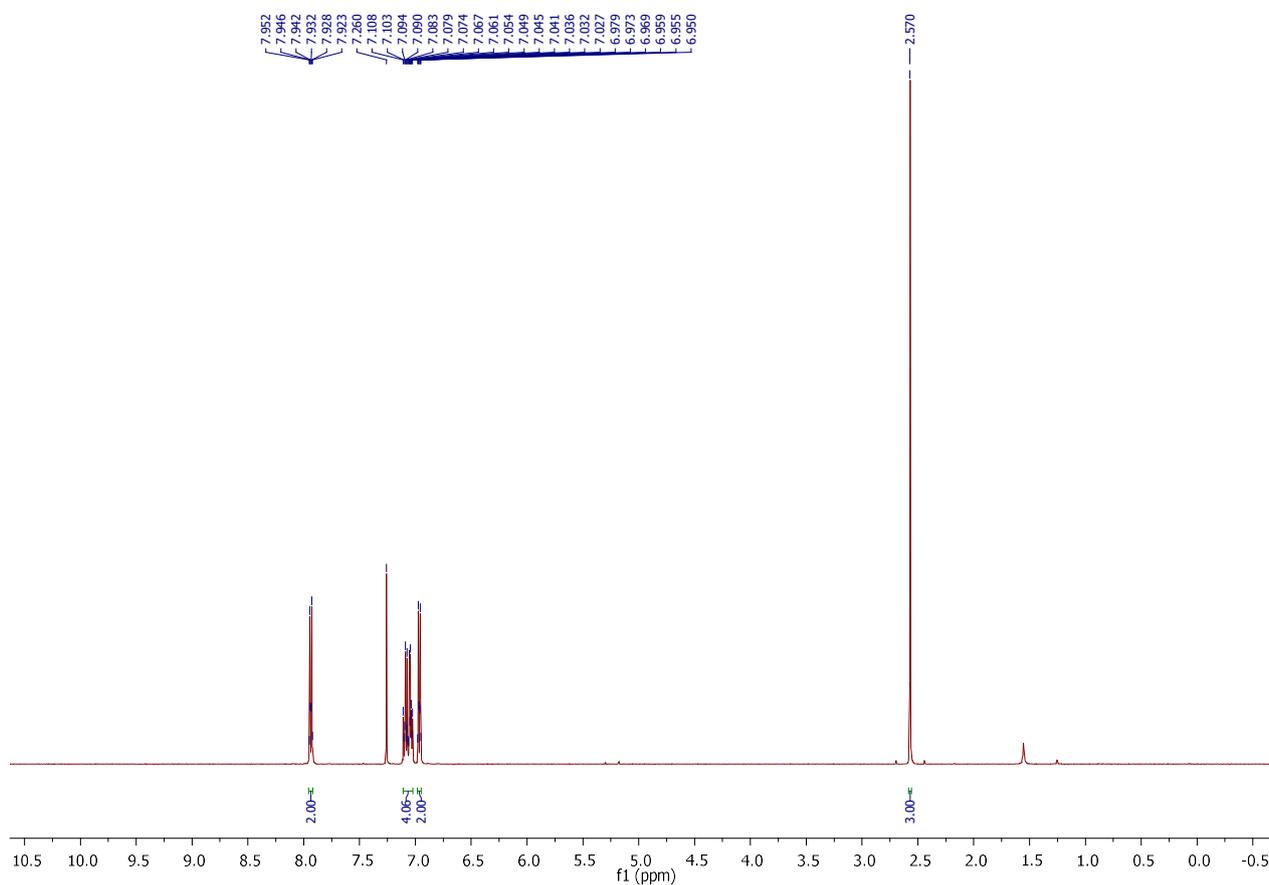
The title compound was prepared according to general procedure 7 using 1-(4-fluorophenyl)-2-(4-methoxyphenoxy)ethan-1-ol (262 mg, 1.00 mmol). Purification by flash silica column chromatography (eluent = 10% ethyl acetate in hexanes, 150 x 30 mm silica) gives the title compound (206 mg, 85%) as a white solid. mp 48-51 °C (Lit. 58-59 °C)⁷; R_f = 0.35 (eluent = 20% ethyl acetate in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.56 (3H, s), 3.83 (3H, s), 6.94 (4H, ddd, J 9.1, 6.1, 2.5), 7.00-7.03 (2H, m), 7.90-7.92 (2H, m). Spectroscopic data is in accordance with that reported previously.



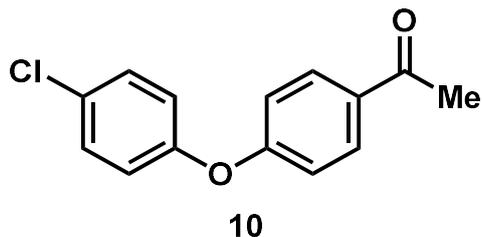
1-(4-(4-fluorophenoxy)phenyl)ethan-1-one



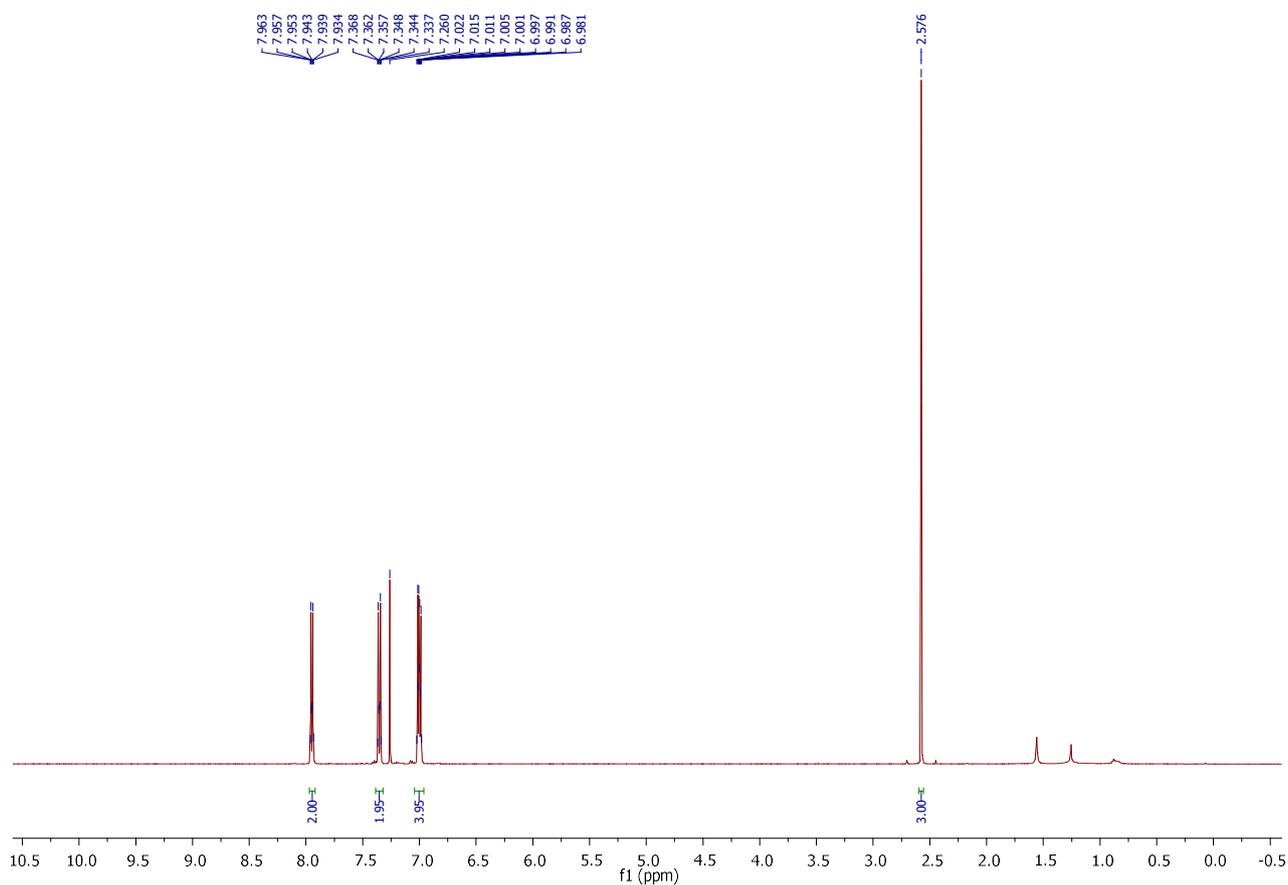
The title compound was prepared according to general procedure 7, using 2-(4-fluorophenoxy)-1-(4-fluorophenyl)ethan-1-ol (250 mg, 1.00 mmol). Purification by flash silica column chromatography (eluent = 10% ethyl acetate in hexanes, 145 x 30 mm silica) gives the title compound (184 mg, 80%) as a white solid. mp 56-59 °C (Lit. 67-69 °C)⁷; R_f = 0.43 (eluent = 20% EtOAc in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.57 (3H, s), 6.95-6.98 (2H, m), 7.03-7.12 (4H, m), 7.93-7.95 (2H, m). Spectroscopic data is in accordance with that reported previously.



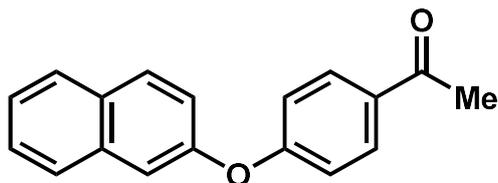
1-(4-(4-chlorophenoxy)phenyl)ethan-1-one



The title compound was prepared according to general procedure 7, using 2-(4-chlorophenoxy)-1-(4-fluorophenyl)ethan-1-ol (267 mg, 1.00 mmol). Purification by flash silica column chromatography (eluent = 10% ethyl acetate in hexanes) to give the title compound (193 mg, 78%) as a white solid. mp 58-61 °C (Lit. 63-64 °C)⁷; R_f = 0.45 (eluent = 20% EtOAc in hexanes); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 2.58 (3H, s), 6.98-7.02 (4H, m), 7.34-7.37 (2H, m), 7.93-7.96 (2H, m). Spectroscopic data is in accordance with that reported previously.

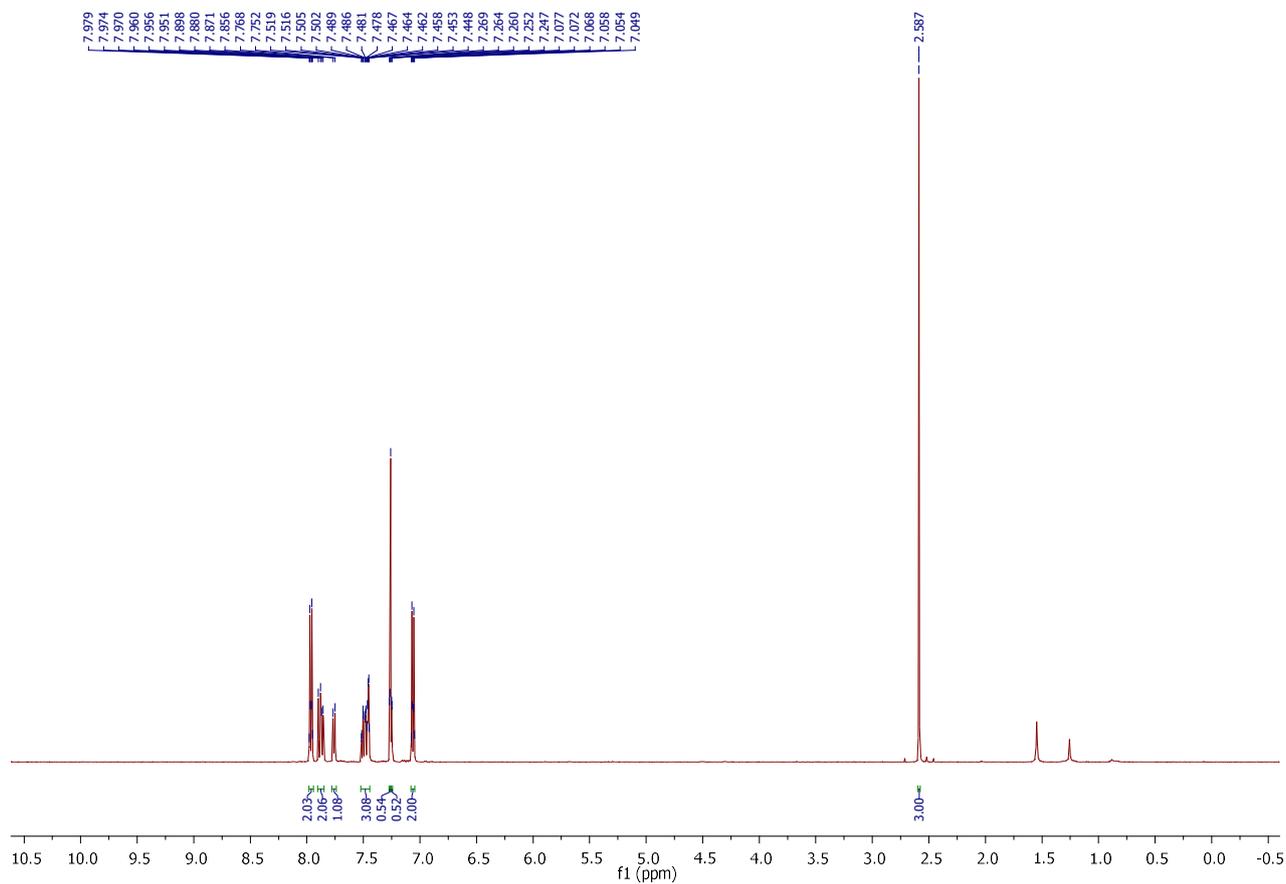


1-(4-(naphthalen-2-yloxy)phenyl)ethan-1-one



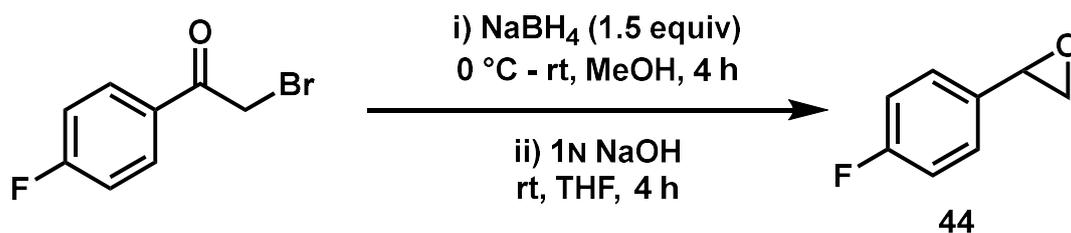
12

The title compound was prepared according to general procedure 7, using 1-(4-fluorophenyl)-2-(naphthalen-2-yloxy)ethan-1-ol (282 mg, 1.00 mmol). Purification by flash silica column chromatography (eluent = CH₂Cl₂, 100 x 45 mm silica) gives the title compound (226 mg, 86%) as a white solid. mp 62-65 °C (Lit. 68-72 °C)⁸; R_f = 0.45 (eluent = 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.59 (3H, s), 7.05-7.08 (2H, m), 7.26 (1H, dd, *J* 8.8, 2.4), 7.48 (3H, m), 7.76 (1H, d, *J*, 8.0), 7.88 (2H, dd, *J* 12.9, 8.4), 7.95-7.98 (2H, m). Spectroscopic data is in accordance with that reported previously.



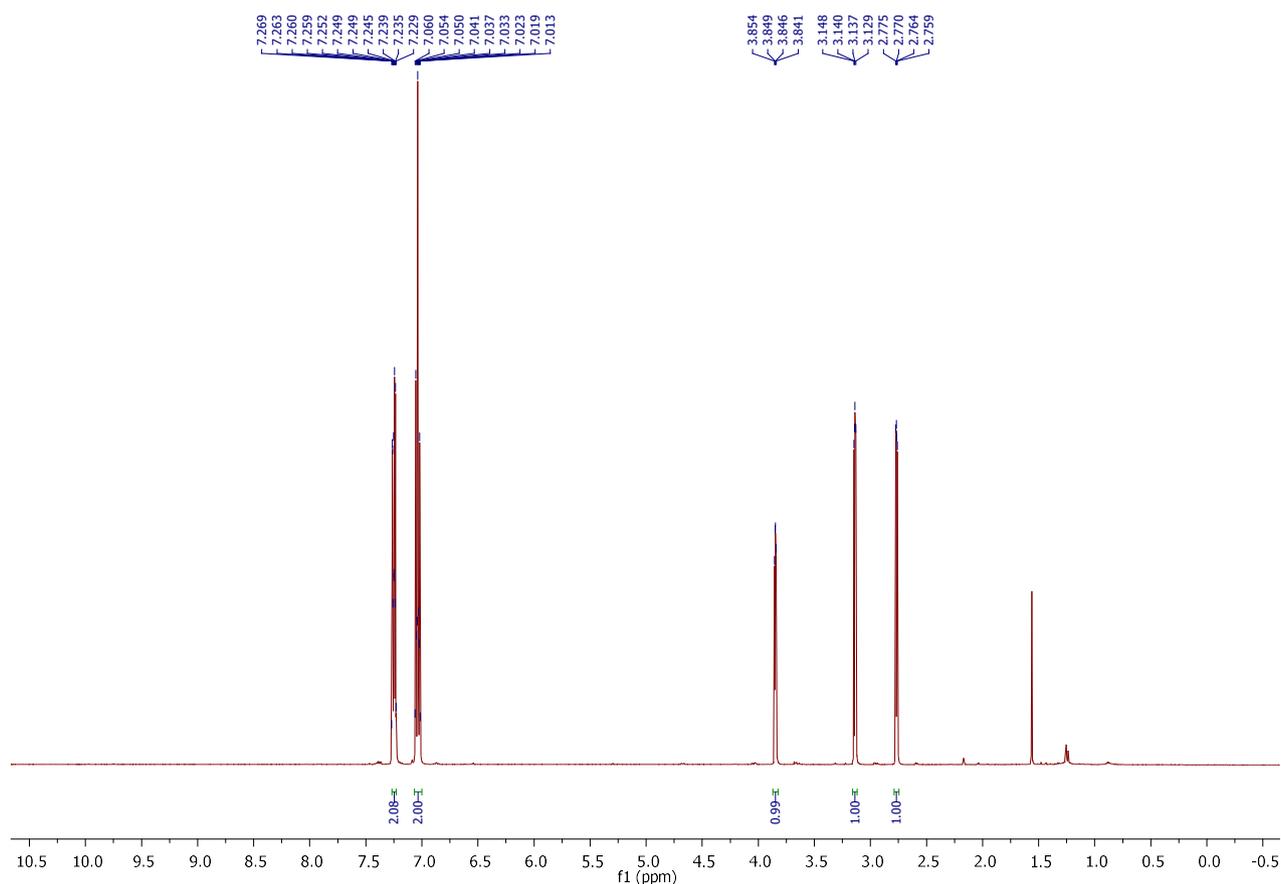
4. Experimental and characterisation data (telescoped diaryl ether synthesis)

4.1. Preparation of 2-(4-fluorophenyl)oxirane

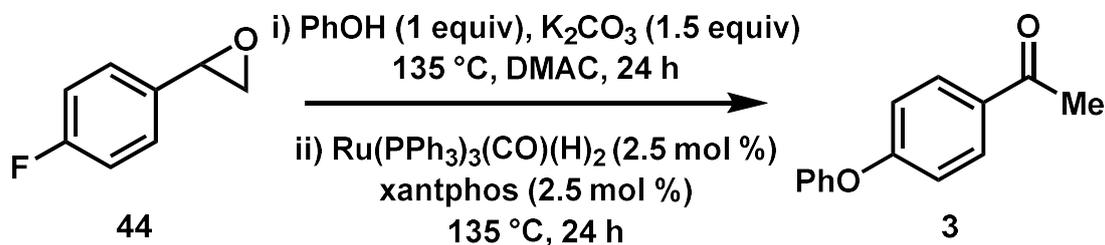


Following a modified literature procedure,¹⁶ a 100 mL round bottomed flask was charged with 2-bromo-1-(4-fluorophenyl)-ethan-1-one (2.17 g, 10.0 mmol) and methanol (20 mL). The reaction was then cooled to 0 °C, and NaBH₄ (267 mg, 15.0 mmol) added portionwise. The reaction was then warmed to room temperature, and stirred until reaction completion (ca. 4 hours, confirmed by TLC), then concentrated *in vacuo*, and partitioned with water (20 mL). The layers were separated, and the aqueous layer extracted in Et₂O (3 x 30 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

The resulting crude material was dissolved in THF (30 mL). The reaction was stirred at room temperature, and aq. NaOH (1 N, 20 mL, 40 mmol) was added. The reaction was then stirred at this temperature until completion (ca. 4 hours, confirmed by TLC), at which point water (50 mL) was added. The reaction was then separated, and the aqueous layer extracted in Et₂O (3 x 40 mL). The combined organic extracts were washed in brine, dried over magnesium sulfate, filtered, and dried carefully *in vacuo*. Purification by flash chromatography (eluent = 10% ethyl acetate in hexanes, 30 x 40 mm silica) gave the title compound (980 mg, 80%) as a colourless oil. $R_f = 0.36$ (eluent = 10% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H : 2.77 (1H, dd, *J* 2.6, 5.4), 3.14 (1H, dd, *J* 4.0, 5.4), 3.85 (1H, dd, *J* 2.6, 4.0), 7.00-7.07 (2H, m), 7.21-7.28 (2H, m). Spectroscopic data is in accordance with the literature.¹⁷

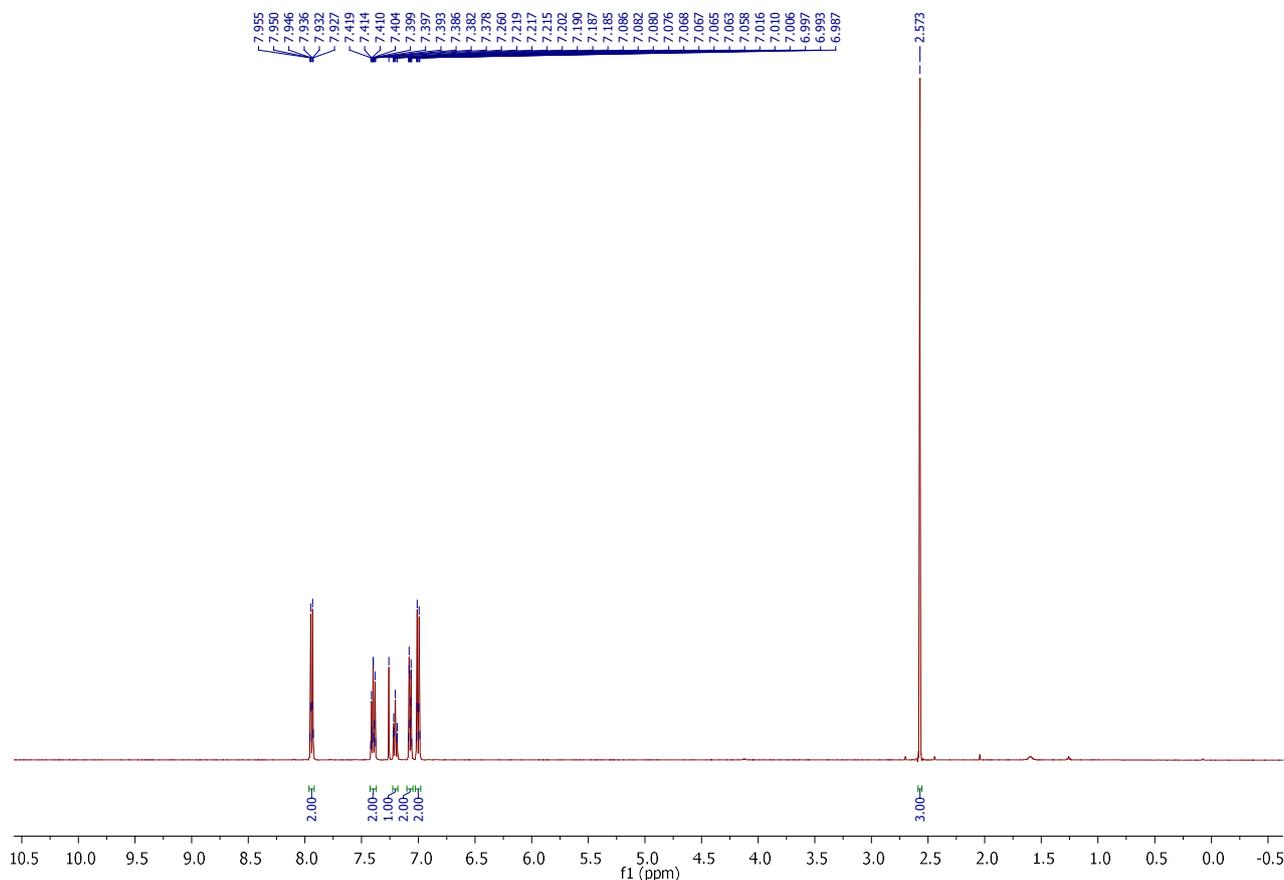


4.2. Telescoped one pot diaryl ether synthesis from epoxide: 1-(4-phenoxyphenyl)ethan-1-one



A 10 mL microwave vial was charged with 2-(4-fluorophenyl)oxirane (138 mg, 1.00 mmol), phenol (94.1 mg, 1.00 mmol), potassium carbonate (207 mg, 1.50 mmol), dimethylacetamide (1.00 mL) and a magnetic follower. The reaction vessel was crimped shut, and the reaction heated to 135 °C, and stirred at this temperature for 24 hours. The reaction vessel was then cooled to room temperature, and opened. Ru(PPh₃)(CO)(H)₂ (23.0 mg, 2.50 mol%) and xantphos (14.5 mg, 2.50 mol%) were then added, the reaction vessel crimped shut once more, and heated to 135 °C. The reaction was stirred at this temperature for 24 hours, cooled to room temperature, and the contents of the vial poured over H₂O (50 mL). The layers are separated, and the aqueous layer extracted with EtOAc (3 x 10 mL). The combined organic extracts are then washed with brine, dried over magnesium sulfate, filtered, and dried under reduced pressure. The resulting crude diaryl ether was then purified by flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 x 150 mm silica) to give the title

compound (124 mg, 59%) as a white solid. mp 40-43 (lit. 45-47)⁵; R_f = 0.43 (eluent = 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) δ_H: 2.57 (3H, s), 6.99-7.02 (2H, m), 7.06-7.09 (2H, m), 7.19-7.22 (1H, m), 7.38-7.42 (2H, m), 7.93-7.96 (2H, m). Spectroscopic data is in accordance with that in the literature.⁵



5. References

1. Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Org. Lett.* **2013**, *15*, 2278–2281
2. Das, M.; Shea, D. F. O. *Tetrahedron* **2013**, *69*, 6448–6460.
3. Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Onomura, O. *Tetrahedron* **2010**, *66*, 6814–6819.
4. García-Muñoz, Á.; Ortega-Arizmendi, A. I.; García-Carrillo, M. A.; Díaz, E.; Gonzalez-Rivas, N.; Cuevas-Yañez, E. *Synthesis*, **2012**, *44*, 2237–2242.
5. Zhai, Y.; Chen, X.; Zhou, W.; Fan, M.; Lai, Y.; Ma, D. *J. Org. Chem.* **2017**, *82*, 4964–4969.
6. Inagaki, T.; Phong, L. T.; Furuta, A.; Ito, J. I.; Nishiyama, H. *Chem. Eur. J.* **2010**, *16*, 3090-3096.
7. Chen, J.; Wang, X.; Zheng, X.; Ding, J.; Liu, M.; Wu, H. *Tetrahedron* **2012**, *68*, 8905–8907.
8. Han, Y. T.; Choi, G.-I.; Son, D.; Kim, N.-J.; Yun, H.; Lee, S.; Chang, D. J.; Hong, H.-S.; Kim, H.; Ha, H.-J.; Kim, Y.-H.; Park, H.-J.; Lee, J.; Suh, Y.-G. *J. Med. Chem.* **2012**, *55*, 9120–9135.
9. Wang, Y.; Ling, J.; Zhang, Y.; Zhang, A.; Yao, Q. *Eur. J. Org. Chem.* **2015**, *19*, 4153–4161.

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10. Soni, R.; Hall, T. H.; Mitchell, B. P.; Owen, M. R.; Wills, M. J. *Org. Chem.* **2015**, *80*, 6784–6793.
 11. Watson, A. J. A.; Fairbanks, A. J. *Eur. J. Org. Chem.* **2013**, *30*, 6784–6788.
 12. Rusch, F.; Unkel, L. N.; Alpers, D.; Hoffmann, F.; Brasholz, M. *Chem. Eur. J.* **2015**, *21*, 8336–8340.
 13. Kauffman, J. M.; Moyna, G. J. *Org. Chem.* **2003**, *2*, 839–853.
 14. Zhou, Y.; Zhou, H.; Liu, S.; Pi, D.; Shen, G. *Tetrahedron* **2017**, *73*, 3898–3904.
 15. Watson, A. J. A.; Atkinson, B. N.; Maxwell, A. C.; Williams, J. M. J. *Adv. Synth. Catal.* **2013**, *355*, 734–740.
 16. Huang K.; Wang H.; Stepanenko V.; De Jesús M.; Torruellas C.; Correa W.; Ortiz-Marciales M. J. *Org. Chem.* **2011**, *76*, 1883–1886.
 17. Man, K.T.; Klawonn, M.; Bhor, S.; Doeblner, C.; Maegerlein, W.; Beller, M., *Org. Lett.* **2005**, *7*, 987-990.