Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information for

Directed *ortho*-Metalation–Nucleophilic Acyl Substitution Strategies in Deep Eutectic Solvents: The Organolithium Base Dictates the Chemoselectivity

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Experimental Details

Materials and methods. Unless specified, all reagents were used as received without further purifications. *N*,*N*-dimethylformamide was distilled under vacuum from CaH_2 prior to use. Ethyl benzoate and benzaldehyde were distilled under vacuum prior to use. Reactions were monitored by GC-MS analysis or by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. Chromatographic separations were carried out under pressure on silica gel (40-63 μm, 230-400 mesh) using flash-column techniques. The following solutions of organolithium reagents were furnished by both Albemarle (Germany) and Aldrich and were used with the following concentration: *n*-BuLi 2.0 M in cyclohexane, *s*-BuLi 1.4 M in cyclohexane, *t*-BuLi 1.7 M in pentane, *n*-HexLi 2.3 M in hexane, MeLi 1.6 M in Et_2O, and PhLi 1.9 M in dibutyl ether. The exact concentration of the organolithium solutions was determined by titration with diphenylacetic acid in anhydrous THF prior to use.[1] *N*,*N*-diisopropylbenzamides **1a-d** were synthesized according to the procedures reported in the literature.[2] *Deep Eutectic Solvents* [choline chloride (ChCl)/L-lactic acid (LA) (1:2 mol/mol); ChCl/urea (1:2 mol/mol); ChCl/glycerol (Gly) (1:2 mol/mol), ChCl/H_2O (1:2 mol/mol)] were prepared by heating under stirring at 60–80 °C for 10–30 min the corresponding individual components until a clear solution was obtained.[3] Full characterisation data, including copies of ^1H and ^{13}C NMR spectra, have been reported for both the newly synthesized compounds and the known compounds.

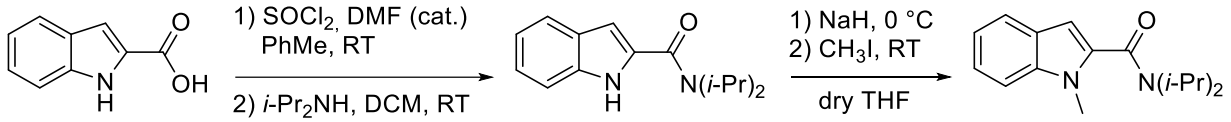
Instrumentation. ^1H NMR (600 MHz) and $^{13}C\{1H\}$ (150 MHz) NMR spectra were recorded on a Jeol ECZR600 spectrometer at room temperature using residual solvent peak as an internal reference. ^2H NMR (92.07 MHz) spectra were obtained in CH_2Cl_2 using residual CD_2Cl_2 as an internal standard. Chemical shifts (δ) are given in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). Multiplicities are reported as follows: s (singlet), d (doublet), t (triplet), quint (quintet), sext (sextet), sept (septet), m (multiplet), br (broad). Low-resolution MS spectra were recorded at an ionizing voltage of 70 eV on a HP 5989B mass selective detector connected to an HP 5890 GC with a methyl silicone capillary column (EI) or on a Micromass Quattro microTM API instrument (ESI, Waters Corporation, Milford, MA, USA). GC analyses were performed on a PerkinElmer Autosistem XL chromatographic system equipped with a methyl silicone capillary columns. The MS flow-injection analyses were run on a high resolving power hybrid mass spectrometer (HRMS) Orbitrap Fusion (Thermo Scientific, Rodano, Italy), equipped with an a ESI ion source. The samples were analyzed in acetonitrile solution using a syringe pump at a flow rate of 5 μL/min. The tuning parameters adopted for the ESI source were: source voltage 4.0 kV. The heated capillary temperature was maintained at 275 °C. The mass accuracy of the recorded ions (vs. the calculated ones) was ± 2.5 mmu (milli-mass units). Analyses were run using both full MS (150-2000 m/z range) and MS/MS acquisition, at 500000 resolutions (200 m/z). Nitromethane was used as internal standard for quantitative NMR analyses on crude reaction mixtures. For each ^1H NMR the amount of product was determined by applying the following equation (Eq. 1):

$$yield\ (\%) = \frac{x\ (product) \cdot n\ (CH_3NO_2)}{n(starting\ material)} \cdot f \cdot 100$$

where:

- *x* is the value of integral/number of protons;
- *n* is the amount of starting material or CH_3NO_2 in mmol;
- *f* the diluting factor used for the preparation of the sample.

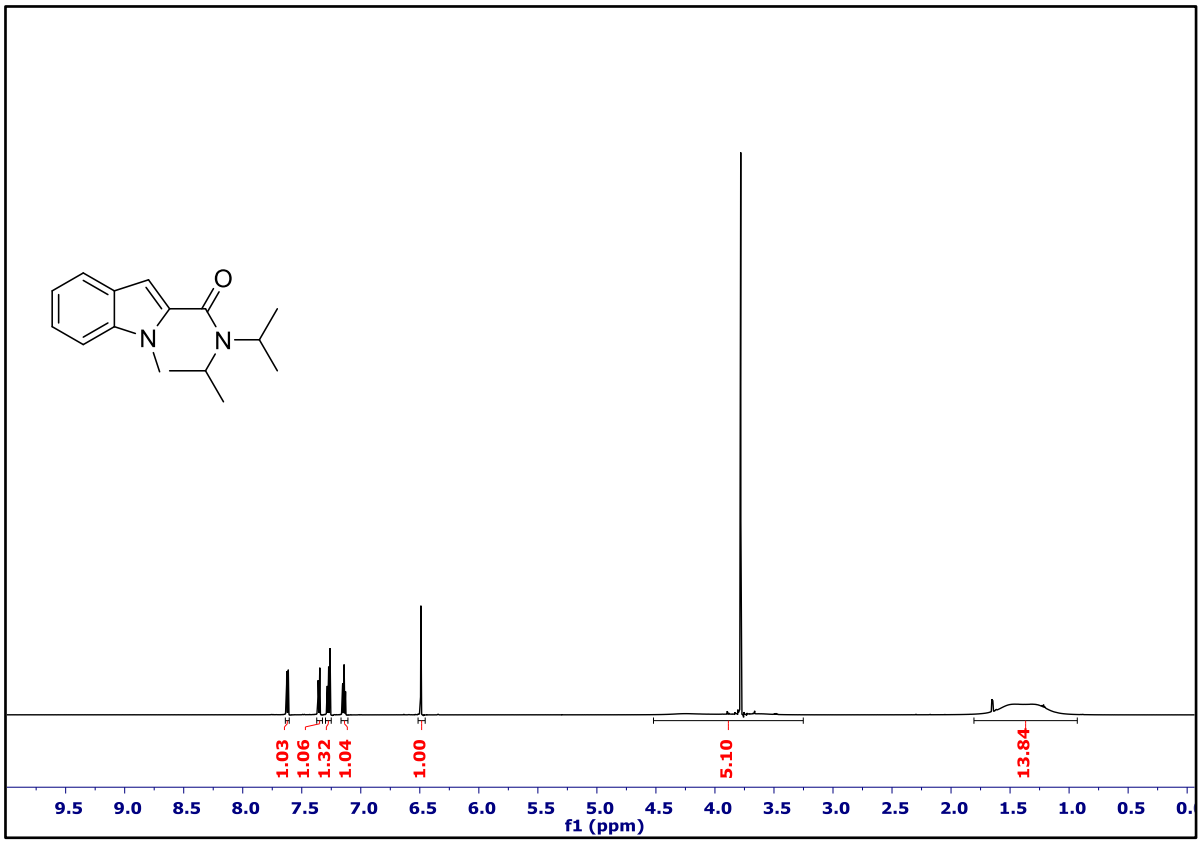
Synthesis and analysis of compound **1e**.



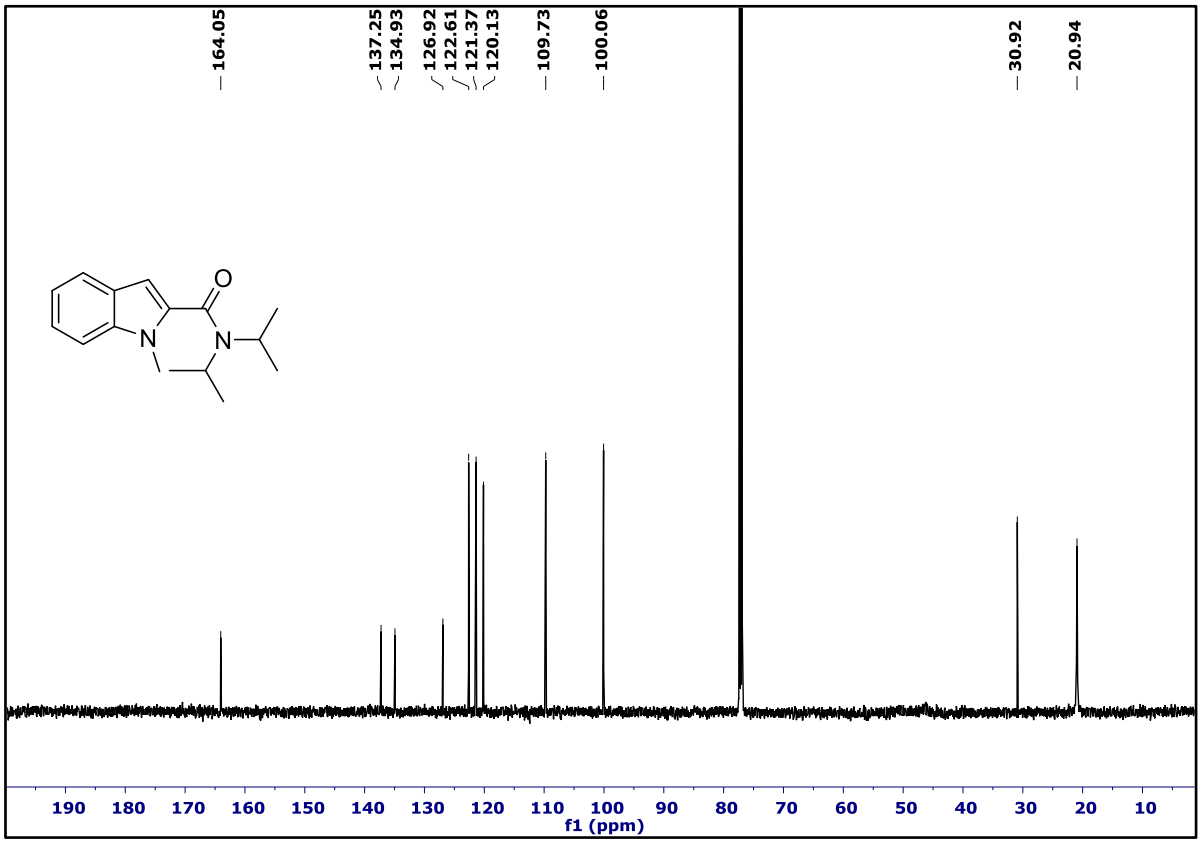
***N,N*-Diisopropyl-1-methyl-1*H*-indole-2-carboxamide (1e).** To a stirred suspension of 1*H*-indole-2-carboxylic acid (1.61 g, 10 mmol, 1.0 eq.) in toluene (10 mL, 1 M) at room temperature was slowly added thionyl chloride (1.45 mL, 20 mmol, 2.0 eq.), followed by DMF (39 µL, 0.5 mmol, 0.05 eq.). The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane and cooled to 0 °C. *N*,*N*-Diisopropylamine (4.23 mL, 30 mmol, 3.0 eq.) was added at 0 °C and the resulting mixture was warmed to room temperature and stirred for additional 30 min. Then, the reaction mixture was quenched with water (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude *N*,*N*-diisopropyl-1*H*-indole-2-carboxamide was dissolved in dry THF (30 mL, 0.3 M) under nitrogen, then NaH (0.29 g, 12 mmol, 1.2 eq.) was added in a single portion at 0 °C. The resulting suspension was stirred at 0 °C for 1 h, iodomethane (0.75 mL, 12 mmol, 1.2 eq.) was added and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched with water (10 mL) at 0 °C and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **1e** as a white solid (1.37 g, 53%, R_f = 0.28 PE/EtOAc 9/1 v/v), mp 89.1-90.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.29-7.26 (m, 1H), 7.16-7.12 (m, 1H), 6.49 (s, 1H), 4.47-3.38 (br m, 2H) superimposed to 3.78 (s, 3H), 1.85-0.96 (br m, 12H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 164.1, 137.3, 134.9, 126.9, 122.6, 121.4, 120.1, 109.7, 100.1, 30.9, 20.9. (Note: *i*-Pr tertiary C not observed). EI-MS *m/z* (%): 258 (M^+, 38), 159 (37), 158 (100), 131 (75), 89 (36).

N,*N*-Diisopropyl-1-methyl-1*H*-indole-2-carboxamide (1e)

^{1}H NMR (600 MHz, $CDCl_3$)



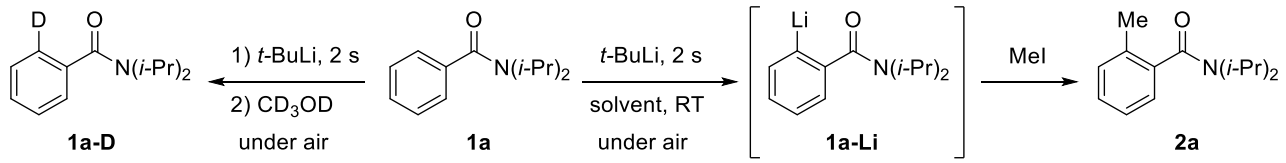
^{13}C NMR (150 MHz, $CDCl_3$)



Directed *ortho* metalation of *N*,*N*-diisopropylbenzamide **1a** under different reaction conditions

All reactions were performed under air. In an open screw cap vial, *N*,*N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1 eq.) was dissolved in the selected unconventional solvent and the resulting mixture was vigorously stirred for 5 min. A selected amount of *t*-BuLi (1.7 M in pentane) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched by addition of iodomethane or deuterated methanol after 2 seconds (experimental details are reported in each Figure caption). The mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Yields of **2a** were determined by quantitative ^{1}H NMR analysis of the crude reaction mixtures using nitromethane (0.093 mmol, 5 µL) as internal standard and a diluting factor 2 for the preparation of the sample (see Eq. 1). A sample of **2a** was synthesized according to the procedure reported in the literature[4] and used as reference for qNMR analyses (^{1}H NMR reported in Figure S1).

Table S1: Metalation reaction of *N*,*N*-diisopropylbenzamide **1a** using *t*-BuLi under different conditions.[a]



Entry	Solvent	*t*-BuLi (eq.)	E^+ (eq.)	Prod. (%)[b]
1	ChCl/Gly 1:2	2	MeI (5)	-
2	CPME[c], ChCl/Gly 1:2	2	MeI (5)	**2a** (70)
3	CPME[c], ChCl/Gly 1:2	2	CD_3OD (5)	**1a-D** (83)[d]
4	CPME[c], ChCl/Gly 1:2[e]	2	MeI (5)	**2a** (67)
5	CPME[c], ChCl/Gly 1:2	1.5	MeI (5)	**2a** (60)
6	CPME[c], ChCl/Gly 1:2	2	MeI (3)	**2a** (63)
7	CPME[c], ChCl/urea 1:2	2	MeI (5)	**2a** (67)
8	CPME[c], ChCl/H_2O 1:2	2	MeI (5)	-
9	H_2O	2	MeI (5)	-
10	Gly	2	MeI (5)	-
11	CPME	2	MeI (5)	**2a** (41)
12	CPME[f], ChCl/Gly 1:2	2	MeI (5)	**2a** (34)
13	CPME[g], ChCl/Gly 1:2	2	MeI (5)	**2a** (60)
14[h]	CPME, ChCl/Gly 1:2	2	MeI (5)	**2a** (60)

[a] Reaction conditions: 1.0 g DES per 0.2 mmol of **1a**. [b] Determined by ^{1}H NMR using CH_3NO_2 as the internal standard. [c] CPME: 0.2 mL. [d] 66% isolated yield, 86% D incorporation. [e] T = 0 °C. [f] CPME: 0.1 mL. [g] CPME: 0.15 mL. [h] 'normal stirring'.

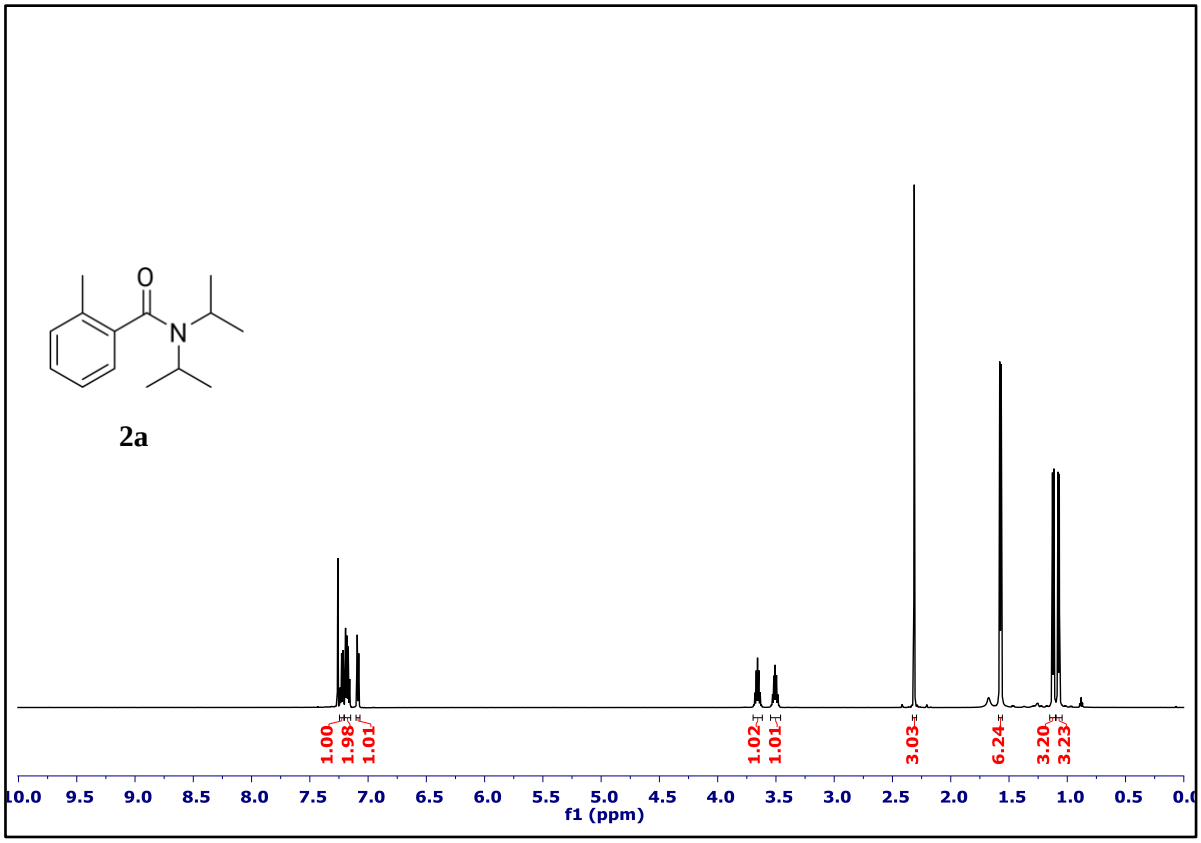


Figure S1: ^{1}H NMR spectrum of *N*,*N*-diisopropyl-2-methylbenzamide **2a**

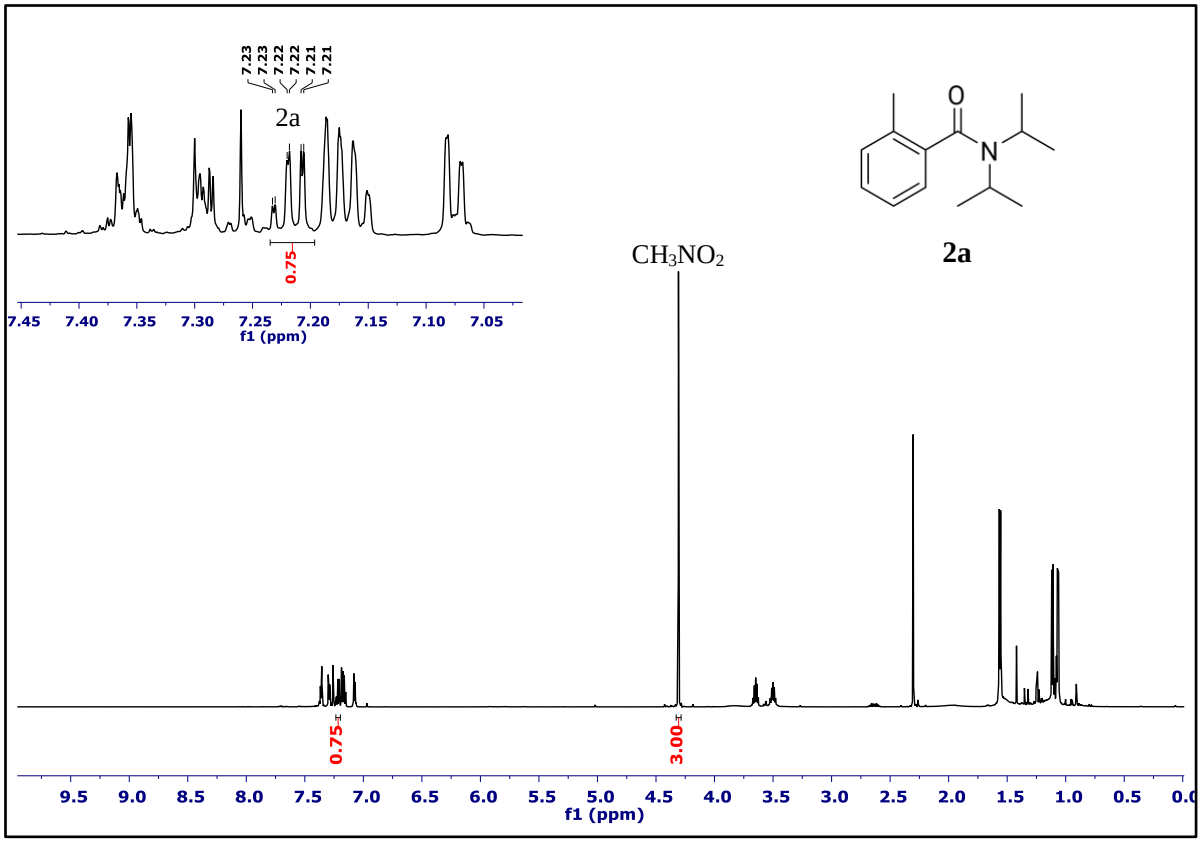


Figure S2 - Table S1 entry 2: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g), 2 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature. Yield of **2a**: 70%

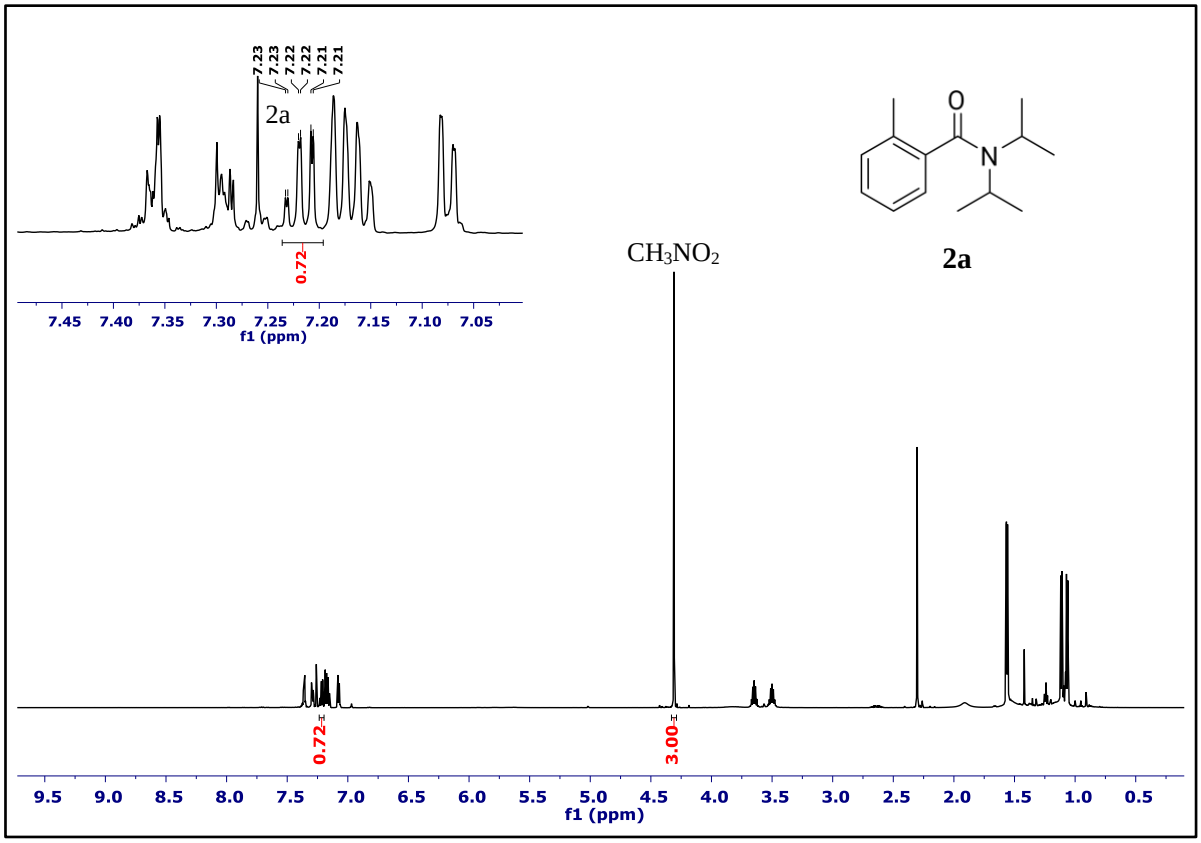


Figure S3 - Table S1 entry 4: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g), 2 eq. of *t*-BuLi, 5 eq. of CH_3I. 0 °C. Yield of **2a**: 67%

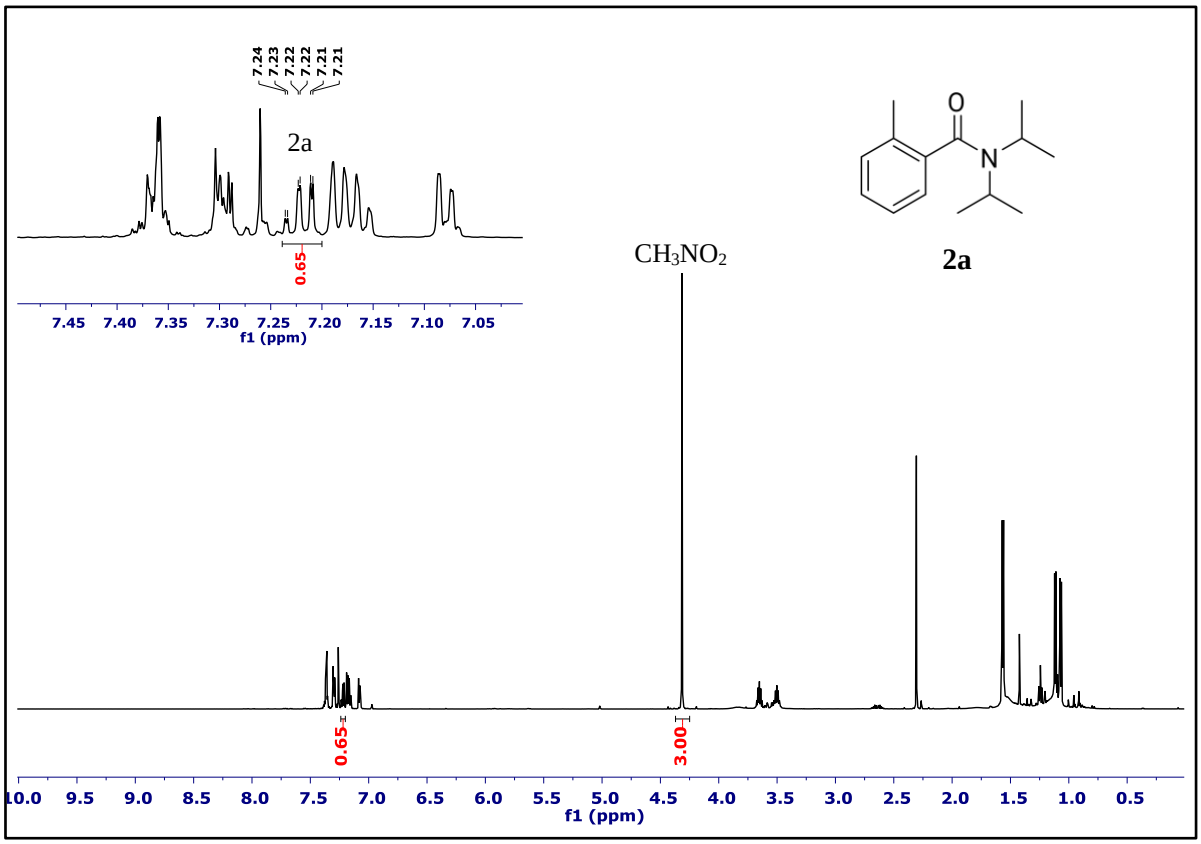


Figure S4 – Table S1 entry 5: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g), 1.5 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature. Yield of **2a**: 60%

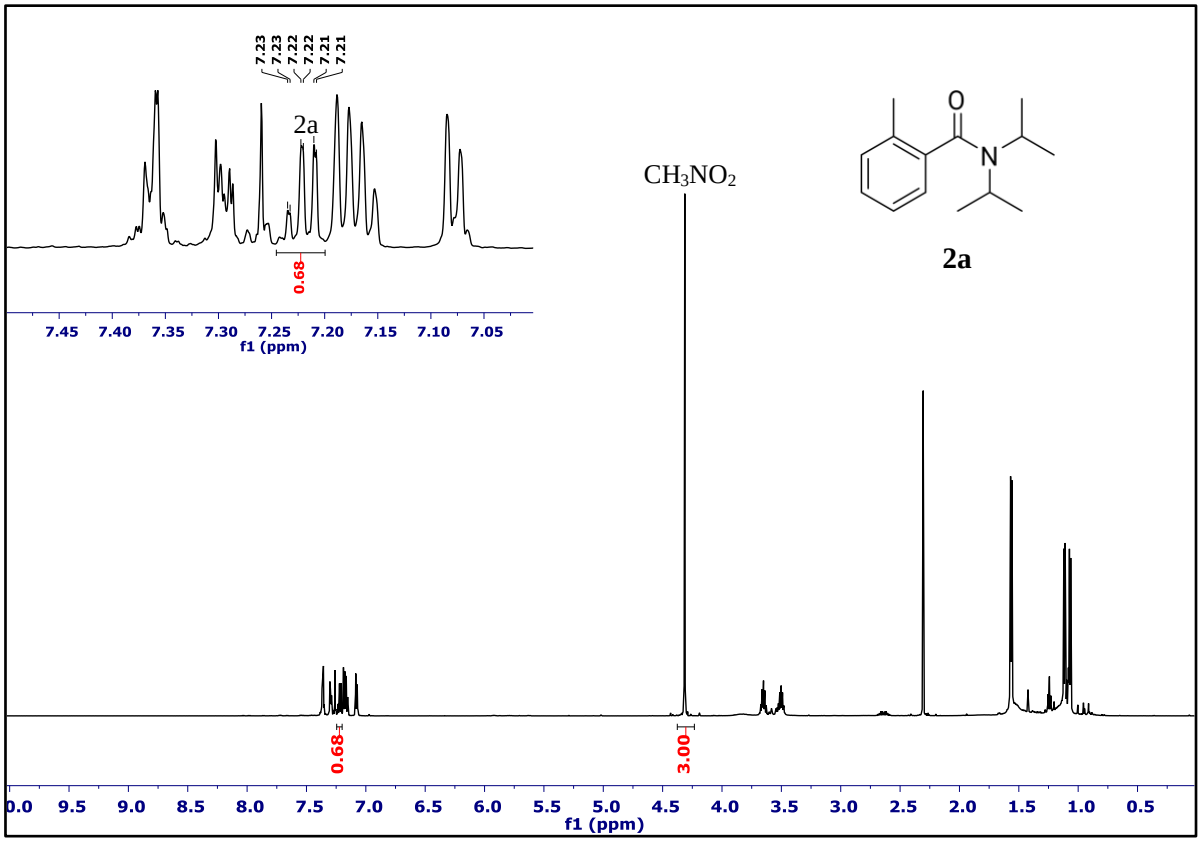


Figure S5 - Table S1 entry 6: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g), 2 eq. of *t*-BuLi, 3 eq. of CH_3I. Room temperature. Yield of **2a**: 63%

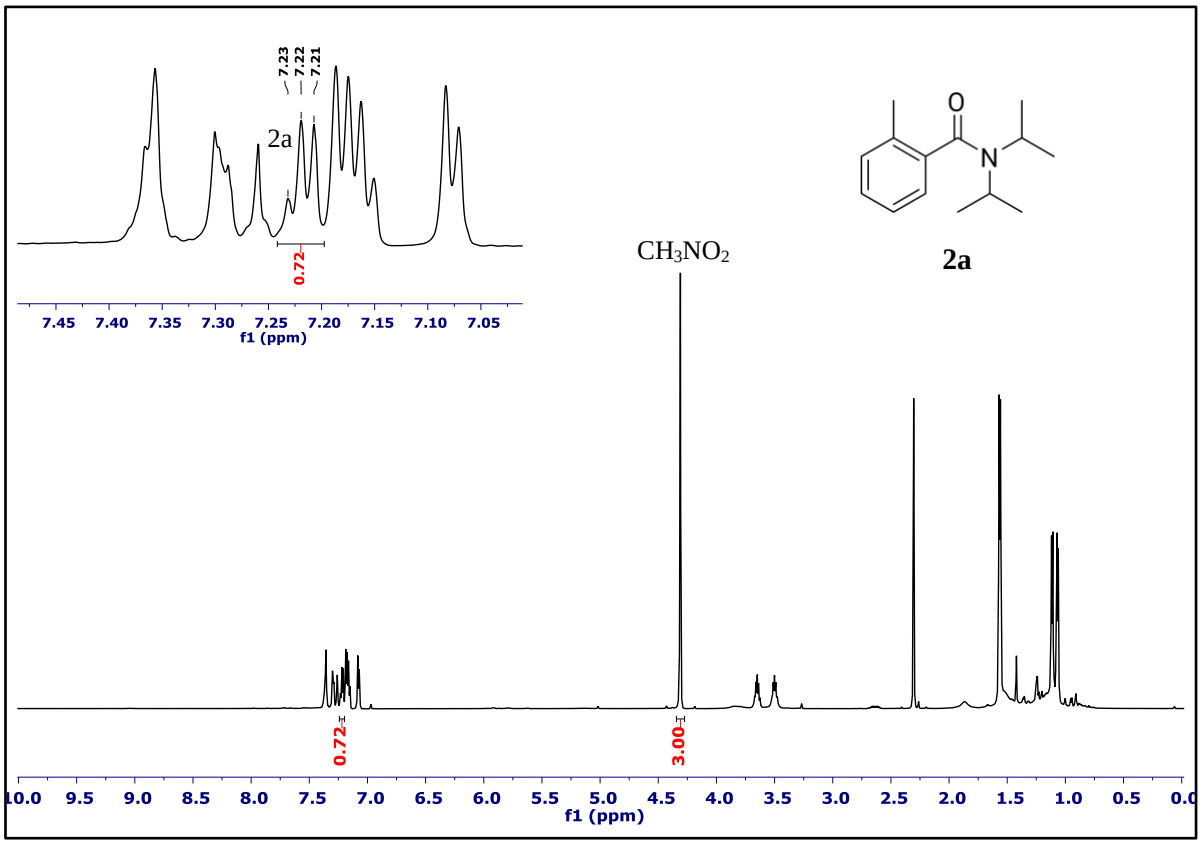


Figure S6 – Table S1 entry 7: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/urea 1:2* (1 g) as solvent, 2 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature. Yield of **2a**: 67%

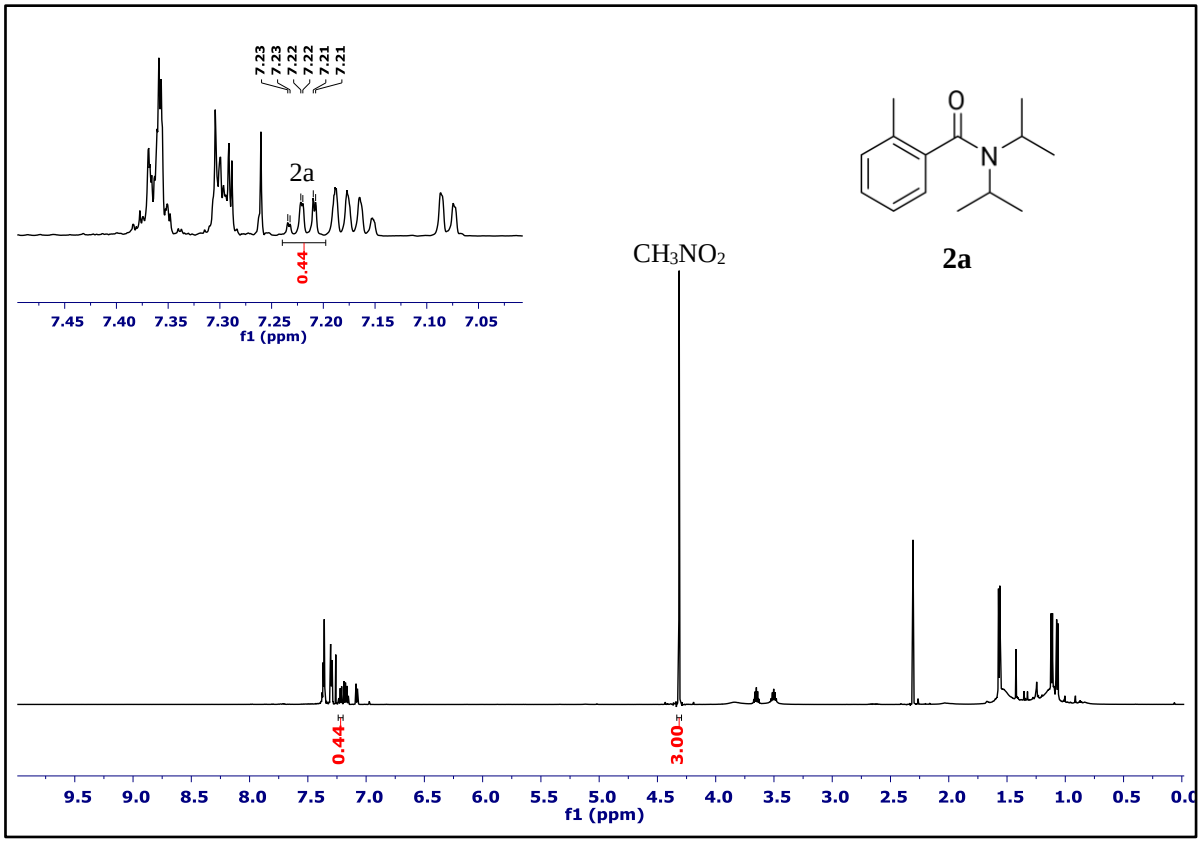


Figure S7 – Table S1 entry 11: crude ^{1}H NMR spectrum of the reaction performed in CPME (1.16 mL), 2 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature. Yield of **2a**: 41%

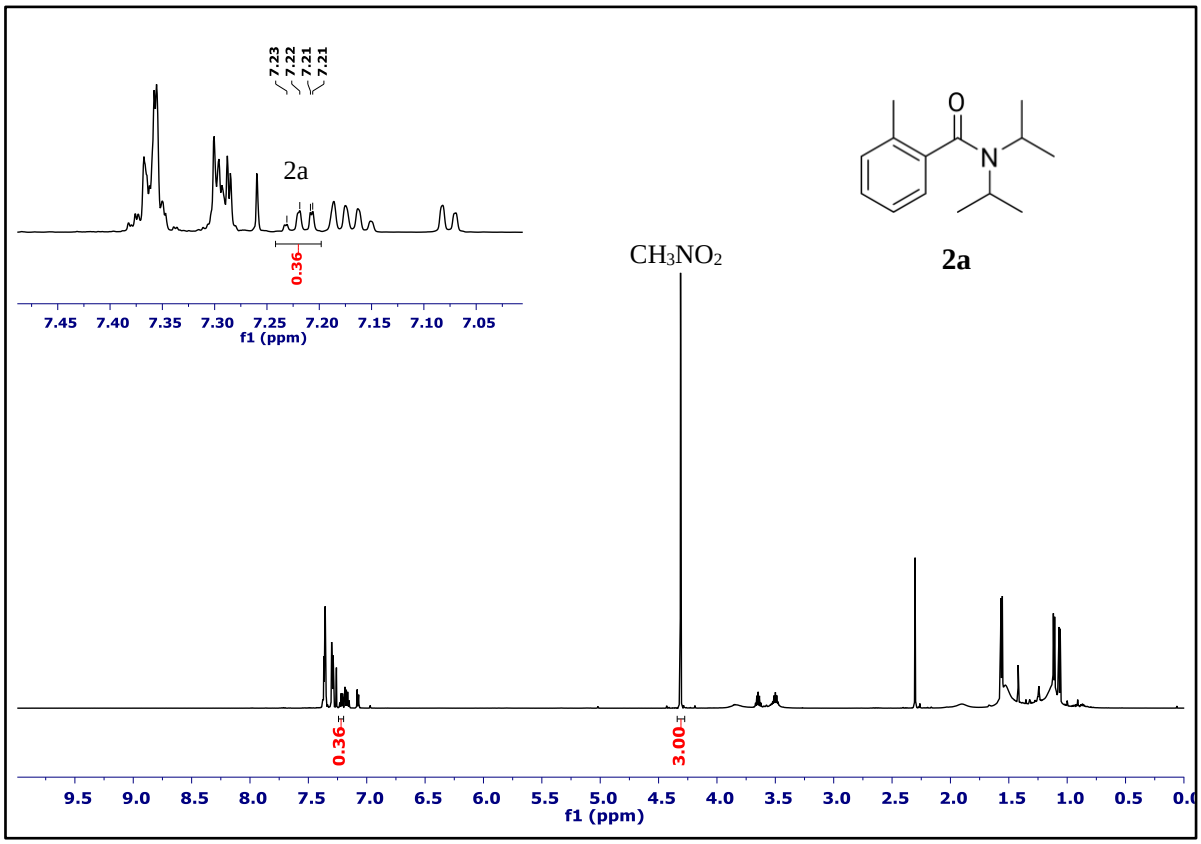


Figure S8 - Table S1 entry 12: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.1 mL) - *ChCl/Gly 1:2* (1 g), 2 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature. Yield of **2a**: 34%

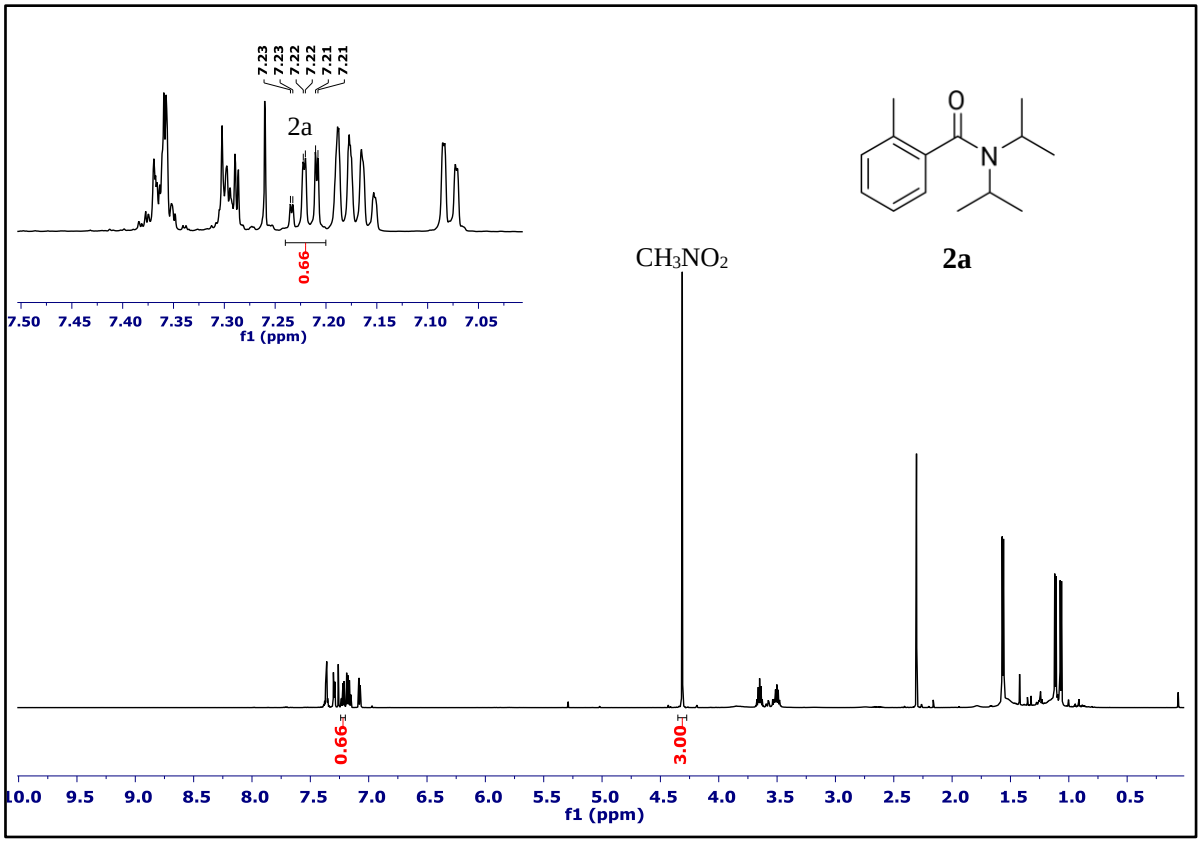


Figure S9 – Table S1 entry 13: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.15 mL) - *ChCl/Gly 1:2* (1 g), 2 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature. Yield of **2a**: 60%

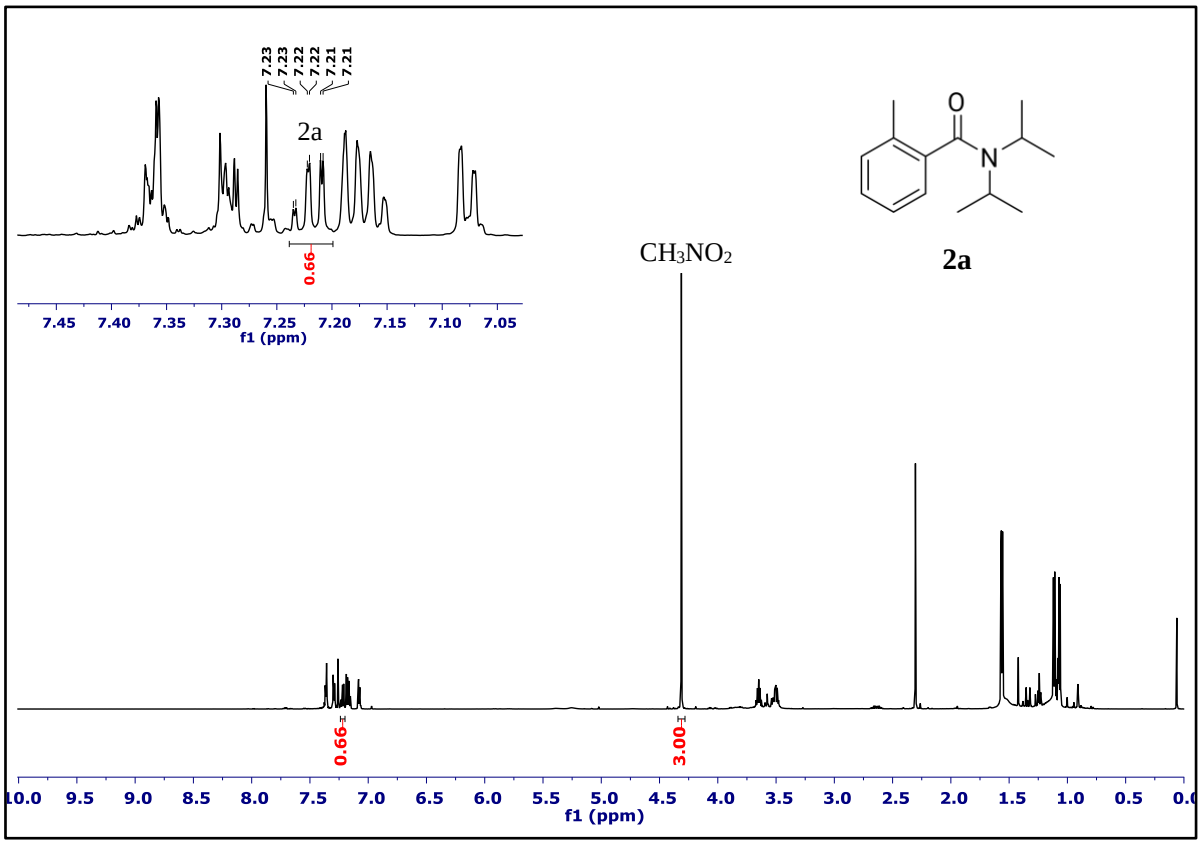
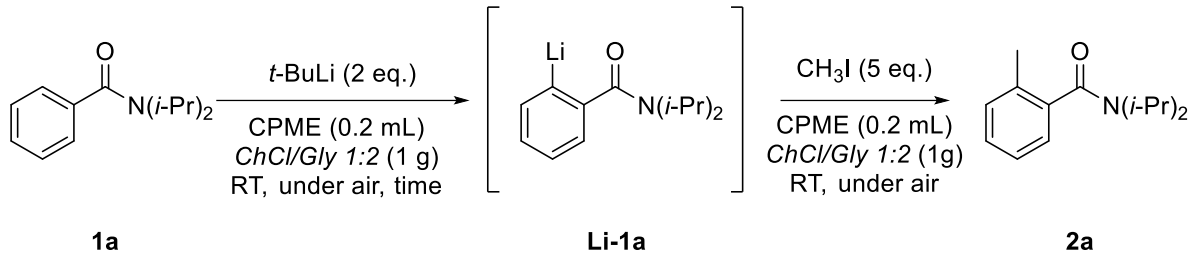


Figure S10 – Table S1 entry 14: crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g), 2 eq. of *t*-BuLi, 5 eq. of CH_3I. Room temperature, 'normal stirring'. Yield of **2a**: 60%

Kinetic analysis of **Li-1a** in CPME-*ChCl/Gly (1:2 mol mol^{-1})*

All reactions were performed under air at room temperature. In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1 eq.) was dissolved in CPME (0.2 mL, 1 M), then *ChCl/Gly (1:2 mol mol^{-1})* (1 g) was added and the resulting mixture was vigorously stirred for 5 min. *t*-BuLi (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring then quenched by addition of iodomethane (62 µL, 1 mmol, 5 eq.) after different times. The mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Yields were determined by quantitative ^1H NMR analysis of the crude reaction mixtures using nitromethane (0.093 mmol, 5 µL) as internal standard and a diluting factor 2 for the preparation of the sample (see Eq. 1).

Table S2. Study of half-life of organolithium species **Li-1a**



1a **Li-1a** **2a**

Entry	CH_3I addition time [s]	Yield %
1	2	70
2	4	56
3	6	46
4	8	42
5	10	32
6	15	1
7	20	0

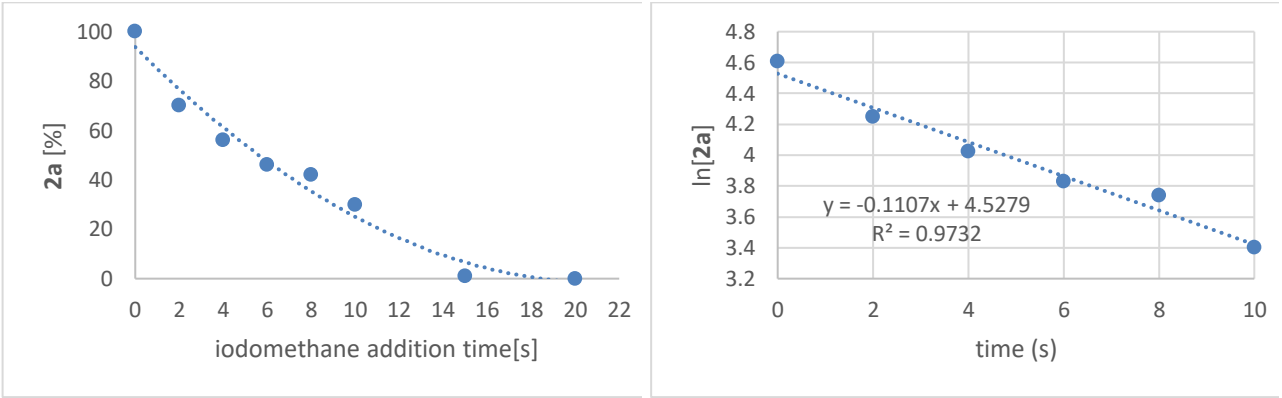


Figure S11: Kinetic analysis of directed *ortho*-metalation of **1a**

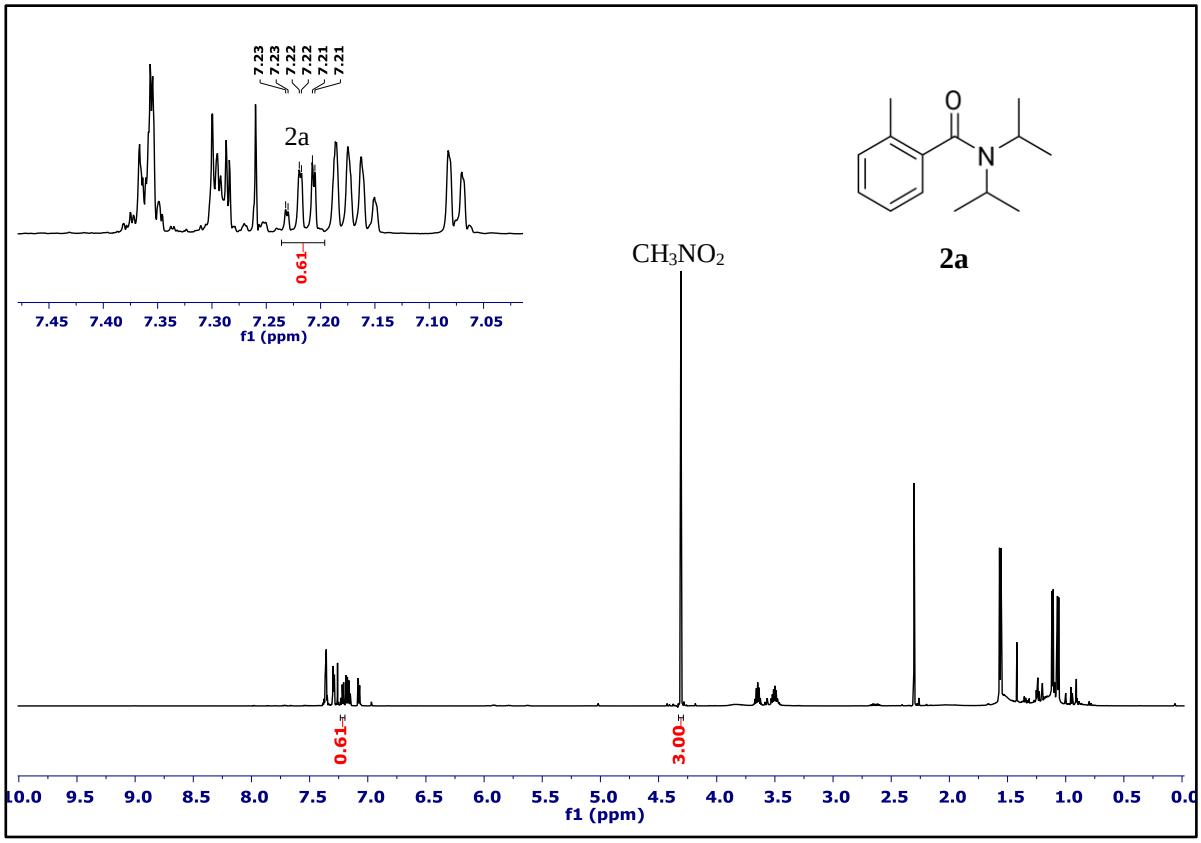


Figure S12 – Table S2 entry 2: crude ^{1}H NMR spectrum of the reaction, quench after 4 s. Yield of **2a**: 56%

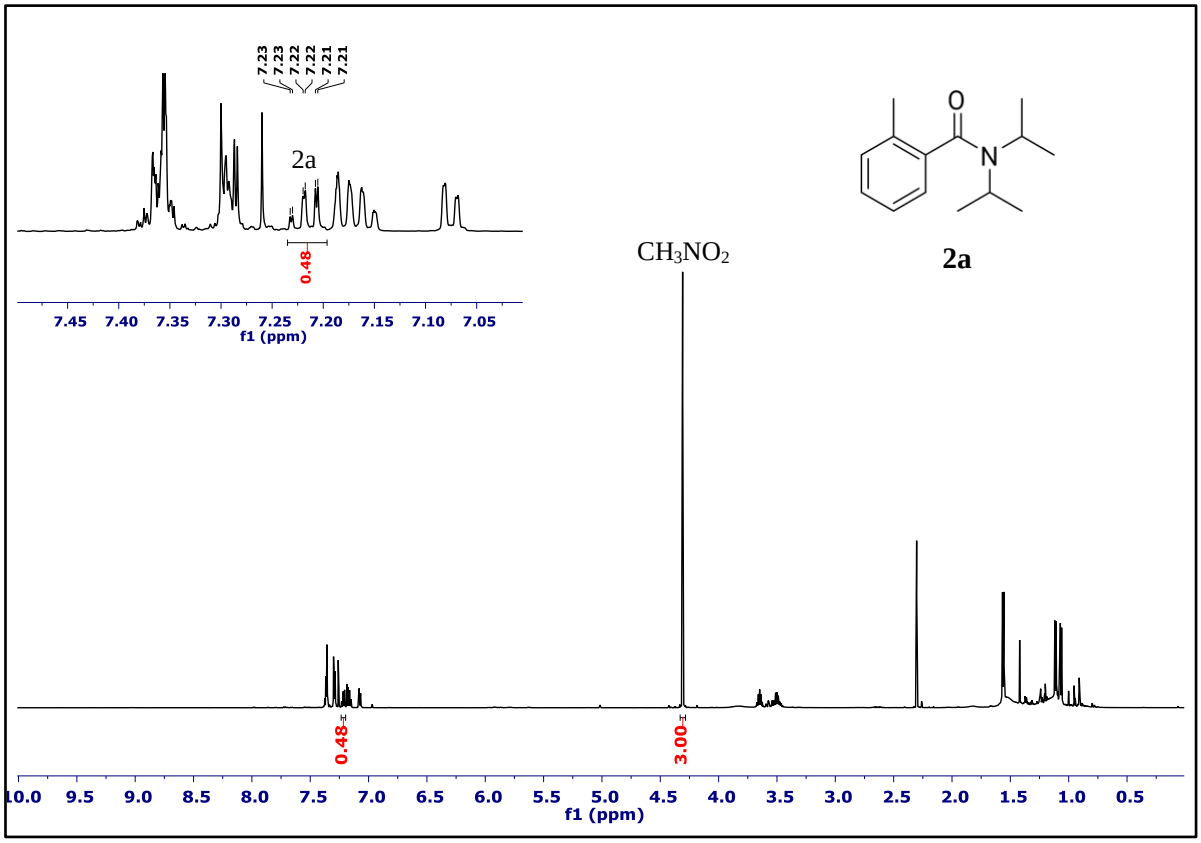


Figure S13 – Table S2 entry 3: crude ^{1}H NMR spectrum of the reaction, quench after 6 s. Yield of **2a**: 46%

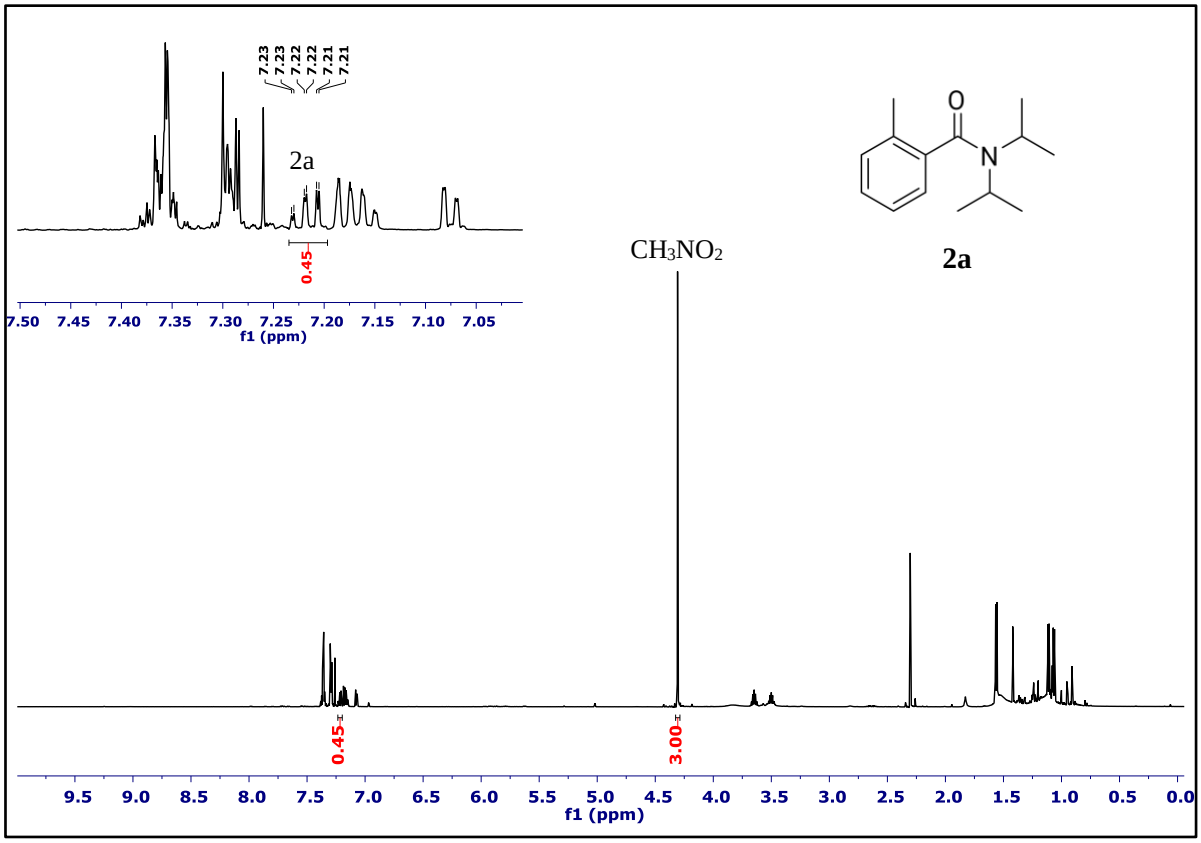


Figure S14 – Table S2 entry 4: crude ^{1}H NMR spectrum of the reaction, quench after 8 s. Yield of **2a**: 42%

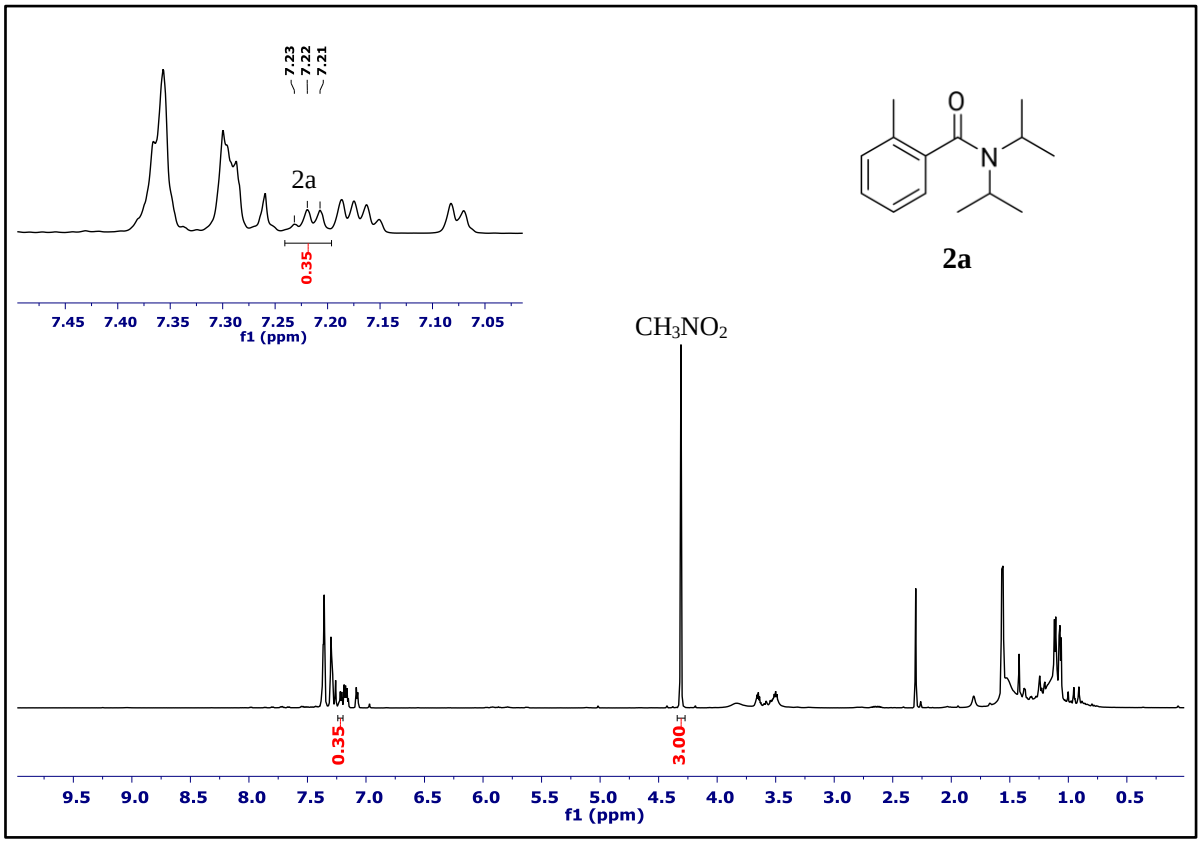


Figure S15 – Table S2 entry 5: crude ^{1}H NMR spectrum of the reaction, quench after 10 s. Yield of **2a**: 32%

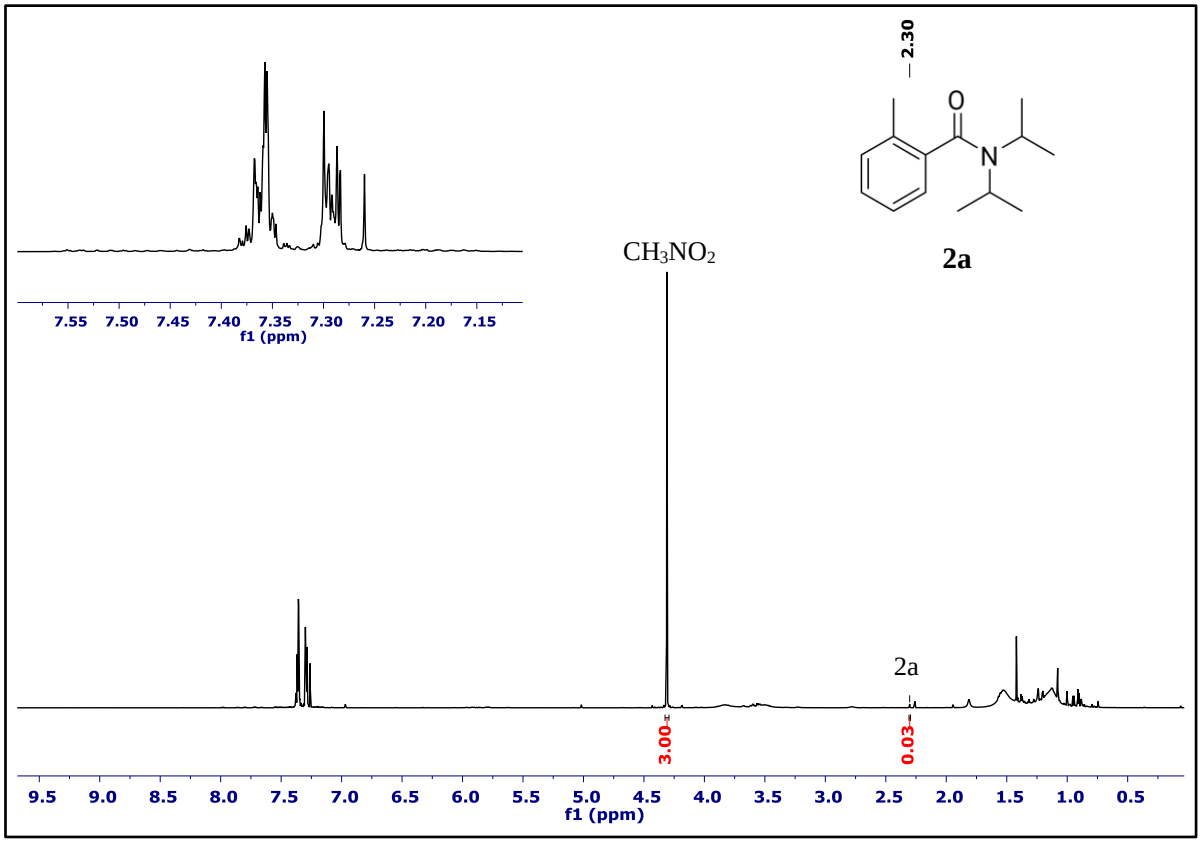
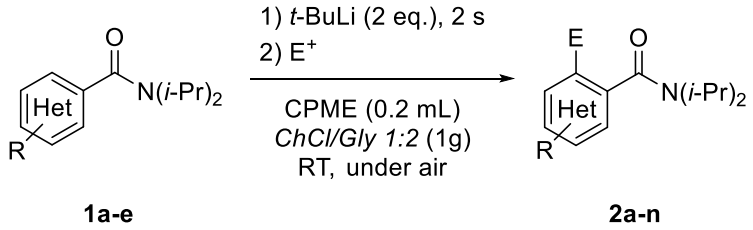


Figure S16 – Table S2 entry 6: crude ^{1}H NMR spectrum of the reaction, quench after 15 s. Yield of **2a**: 1%

Synthesis and analysis of compounds **2a-n**

General procedure. Reactions were performed under air at room temperature. In an open screw cap vial, *N,N*-diisopropylcarboxamides **1a-e** (0.2 mmol, 1 eq.) were dissolved in CPME (0.2 mL, 1 M), then *ChCl/Gly (1:2 mol mol^{-1})* (1 g) was added and the resulting mixture was vigorously stirred for 5 min. *t*-BuLi (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring and quenched by addition of a selected electrophile after 2 seconds. The mixture was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude products were purified by flash column chromatography on silica gel.



1a-e **2a-n**

***N,N*-Diisopropyl-2-methylbenzamide (2a):** general procedure starting from **1a** and CH_3I (5 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2a** as a white solid (31 mg, 70%, R_f = 0.33 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24-7.21 (m, 1H), 7.19-7.16 (m, 2H), 7.09 (d, *J* = 7.4 Hz, 1H), 3.65 (sept, *J* = 6.7 Hz, 1H), 3.50 (sept, *J* = 6.7 Hz, 1H), 2.31 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 3H) superimposed to 1.57 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.8, 138.8, 133.7, 130.5, 128.2, 125.9, 124.8, 50.9, 45.9, 21.1, 20.9, 20.8, 20.7, 18.9. EI-MS *m/z* (%): 219 (M^+, 19), 218 (11), 176 (19), 119 (100), 91 (25).[4]

2-Deuterio-*N,N*-diisopropylbenzamide (1a-D): general procedure starting from **1a** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **1a-D** (86% D incorporation) as a white solid (27 mg, 66%, R_f = 0.32 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38-7.35 (m, 3H), 7.31-7.29 (m, 1H), 3.99-3.29 (br m, 2H), 1.68-0.99 (br m, 12H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 171.2, 139.0 (t, *J* = 15.1 Hz, 1C), 128.7, 128.6, 128.5, 125.4 (t, *J* = 24.3 Hz, 1C), 51.0, 46.0, 20.9. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.31 (s). EI-MS *m/z* (%): 206 (M^+, 10), 163 (21), 107 (48), 106 (100), 105 (39).[4]

2-(Hydroxy(phenyl)methyl)-*N,N*-diisopropylbenzamide (2b): general procedure starting from **1a** and PhCHO (5 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2b** as a yellow semisolid (37 mg, 60%, R_f = 0.13 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers): δ 7.53 (dd, *J* = 7.7, 1.3 Hz, 2H minor), 7,41 (td, *J* = 7.6, 1.5 Hz, 2H minor), 7.37-7.33 (m, 4H major), 7.31-7.28 (m, 2H minor), 7.29-7.25 (m, 4H major), 7.19-7.16 (m, 1H major), 7.17-7.15 (m, 2H minor), 7.13-7.09 (m, 1H minor), 5,97 (s, 1H minor), 5.74 (s, 2H major), 4.09 (br s, 1H minor), 3.86 (sept, *J* = 6.7 Hz, 1H minor), 3.56-3.49 (m, 1H minor), 3.50-3.43 (m, 1H major), 3.25 (sept, *J* = 6.8 Hz, 1H major), 1.58 (d, *J* = 6.8 Hz, 3H minor) superimposed to 1.56 (d, *J* = 6.8 Hz, 3H minor), 1.41 (d, *J* = 6.9 Hz, 3H major), 1.28 (d, *J* = 6.8 Hz, 3H major),

1.19 (d, *J* = 6.6 Hz, 3H minor), 1.07 (d, *J* = 6.7 Hz, 3H major), 0.97 (d, *J* = 6.7 Hz, 3H minor), 0.39 (d, *J* = 6.7 Hz, 3H major). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$, mixture of rotamers): δ 172.1, 171.5, 144.3, 143.0, 141.9, 141.6, 137.8, 136.6, 131.4, 129.6, 129.2, 128.5, 128.4, 128.2, 127.5, 127.5, 127.3, 127.3, 127.2, 126.7, 126.2, 124.9, 77.1 (major), 72.9 (minor), 51.5 (minor), 51.2 (major), 46.3 (minor), 46.3 (major), 20.8 (minor), 20.6 (minor), 20.6 (major), 20.5 (minor), 20.2 (major), 20.2 (major). EI – MS *m/z* (%): 311 (M^+, 3), 210 (83), 209 (100), 194 (23), 181 (18), 165 (24), 133 (32). ESI-HRMS $[M+Na]^+$: *m/z* 334.1780, $C_{20}H_{25}NO_2Na^+$ requires 334.1778.

2-Formyl-*N,N*-diisopropylbenzamide (2c): general procedure starting from **1a** and DMF (5 eq.). Purification by flash column chromatography (PE/EtOAc 6/4 v/v) gave **2c** as a white solid (32 mg, 68%, R_f = 0.34 PE/EtOAc 6/4 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 10.09 (s, 1H), 7.92 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H) 7.50 (td, *J* = 7.6, 0.6 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 3.60-3.54 (m, 2H), 1.60 (d, *J* = 6.6 Hz, 6H), 1.09 (d, *J* = 6.7 Hz, 6H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 190.8, 168.4, 141.30, 134.4, 132.7, 129.8 128.8, 126.1, 51.3, 46.3, 20.6. EI-MS *m/z* (%): 233 (M^+, 1), 190 (42), 148 (33), 133 (100), 105 (37), 100 (17).[5]

2-Bromo-*N,N*-diisopropylbenzamide (2d): general procedure starting from **1a** and 1,2-dibromoethane (1.2 eq.). Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2d** as a white solid (37 mg, 65%, R_f = 0.40 DCM/EtOAc 96/4 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.32 (td, *J* = 7.5, 1.0 Hz, 1H), 7.21-7.17 (m, 2H) 3.60 (sept, *J* = 6.7 Hz, 1H), 3.52 (sept, *J* = 6.7 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H) superimposed to 1.56 (d, *J* = 6.9 Hz, 3H), 1.24 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 168.3, 140.3, 133.0, 129.6, 127.7, 126.7, 119.1, 51.3, 46.1, 20.9, 20.8, 20.8, 20.2. EI-MS *m/z* (%): 285 (M^+, 13), 283 (M^+, 13), 242 (29), 240 (29), 185 (95) 183 (100).[2a]

2-Iodo-*N,N*-diisopropylbenzamide (2e): general procedure starting from **1a** and I_2 (5 eq.) in 2-MeTHF (2 M) solution. Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2e** as a white solid (41 mg, 62%, R_f = 0.46 DCM/EtOAc 96/4 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.35 (td, *J* = 7.5, 1.0 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.03 (td, *J* = 7.6, 1.6, 1H), 3.58 (sept, *J* = 6.6 Hz, 1H), 3.51 (sept, *J* = 6.6 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.56 (d, *J* = 6.8 Hz, 3H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 170.0, 144.4, 139.5, 129.6, 128.3, 126.0, 92.4, 51.4, 46.1, 20.9, 20.8, 20.2. EI-MS *m/z* (%): 331 (M^+, 18), 330 (16), 288 (31), 231 (100); 203 (17).[4]

***N,N*-Diisopropyl-2-(methylthio)benzamide (2f):** general procedure starting from **1a** and $(SMe)_2$ (1.2 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2f** as a white solid (32 mg, 63%, R_f = 0.10 PE/EtOAc 9/1 v/v), mp 132.1-133.0 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.29 (d, *J* = 7.3 Hz, 2H), 7.18-7.15 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 3.60 (sept, *J* = 6.8 Hz, 1H), 3.51 (sept, *J* = 6.8 Hz, 1H), 2.47 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H) superimposed to 1.56 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.4 Hz, 3H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 169.1, 139.2, 134.7, 128.7, 127.6, 125.7, 125.5, 51.2, 46.0, 20.9, 20.4, 16.7. EI – MS *m/z* (%): 253 (M^+, 1), 251 (M^+, 17), 250 (14), 153 (6), 151 (100). ESI-HRMS $[M+Na]^+$: *m/z* 274.1237, $C_{14}H_{21}NOSNa^+$ requires 274.1236.

***N,N*-Diisopropyl-2-(trimethylsilyl)benzamide (2g)** general procedure starting from **1a** and TMSI (5 eq.). Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2g** as a white solid (39 mg, 70%, R_f = 0.23 DCM/EtOAc 96/4 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61-7.59 (m, 1H), 7.34-7.29 (m, 2H), 7.17-7.14 (m, 1H), 3.80 (sept, *J* = 6.6 Hz, 1H), 3.49 (sept, *J* = 6.6 Hz, 1H), 1.56 (br s, 6H), 1.15 (br s, 6H), 0.31 (s, 9H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 172.4, 144.2, 138.3, 135.4, 128.3, 127.8, 125.3, 51.0, 45.9, 20.8, 0.3. EI-MS *m/z* (%): 277 (M^+, 14), 262 (42), 218 (60), 204 (29); 178 (46), 177 (100), 160 (25).[4]

2-Benzoyl-*N,N*-diisopropylbenzamide (2h): general procedure starting from **1a** and PhCOOEt (5 eq.). Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **2h** as a white solid (14 mg, 23%, R_f = 0.20 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.56 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.51 (td, *J* = 7.5, 1.2 Hz, 1H), 7.48-7.42 (m, 3H), 7.39 (td, *J* = 7.6, 1.1 Hz, 1H) 7.33 (d, *J* = 7.6 Hz, 1H), 3.84 (sept, *J* = 6.7 Hz, 1H), 3.45 (sept, *J* = 6.7 Hz, 1H), 1.43 (br s, 6H), 1.20 (br s, 6H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 196.9, 169.7, 140.0, 137.5, 136.9, 133.0, 130.9, 130.5, 130.1, 128.4, 127.6, 126.2, 51.5, 45.9, 20.3. EI-MS *m/z* (%): 309 (M^+, 2), 210 (41), 209 (100), 152 (23), 100 (30).[6]

2-(Diisopropylcarbamoyl)benzoic acid (2i): general procedure starting from **1a** and CO_2 (bubbled for 15 seconds). Purification by flash column chromatography (PE/EtOAc 1/1 v/v + HCOOH 0.5%) gave **2i** as a white solid (17 mg, 34%, R_f = 0.32 PE/EtOAc 1/1 v/v + HCOOH 0.5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.80 (br s, 1H), 8.07 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.43 (td, *J* = 7.4, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.5, 0.9 Hz, 1H), 3.58 (sept, *J* = 6.6 Hz, 1H) superimposed to 3.52 (sept, *J* = 6.6 Hz, 1H), 1.58-1.56 (br m, 6H), 1.14-1.07 (br m, 6H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.3, 170.2, 140.7, 133.4, 131.6, 128.4, 126.4, 126.2, 51.4, 46.0, 20.8, 20.6, 20.1, 19.9. ESI-MS *m/z*: 248.17 $[M-H]^-$.[7]

2-Deuterio-*N,N*-diisopropyl-3-methylbenzamide (1b-D) and **6-Deuterio-*N,N*-diisopropyl-3-methylbenzamide (1b'-D)**: general procedure starting from **1b** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave an inseparable mixture of **1b-D** (30% D incorporation) and **1b'-D** (34% D incorporation) as a white solid (41 mg, 93%, R_f = 0.20 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.26-7.23 (m, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H, 30%D), 7.08 (d, *J* = 7.6 Hz, 1H, 34%D), 3.95-3.38 (br m, 2H), 2.35 (s, 3H), 1.77-0.94 (br m, 12H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 171.3, 139.1, 139.0, 138.4, 138.3, 129.4, 128.4, 128.3, 126.4, 122.3 (t, *J* = 23.8 Hz, 1C), 50.9, 45.9, 21.5, 21.5, 20.8. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.11 (s). EI-MS *m/z* (%): 220 (M^+, 17), 176 (24), 177 (22), 120 (86), 119 (100), 91 (27). ESI-HRMS $[M+Na]^+$: *m/z* 243.1571, $C_{14}H_{20}DNONa^+$ requires 243.1578.

2-Deuterio-*N,N*-diisopropyl-4-methoxybenzamide (1c-D): general procedure starting from **1c** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 8/2 v/v) gave **1c-D** (78% D incorporation) as a yellow oil (47 mg, 99%, R_f = 0.25 PE/EtOAc 8/2 v/v). ^{1}H NMR (600 MHz, acetone-d_6): δ 7.27-7.25 (m, 1H), 6.95-6.94 (m, 2H), 3.86-3.62 (br m, 2H) superimposed to 3.82 (s, 3H), 1.32 (br s, 12H). ^{13}C{1H} NMR (150 MHz, acetone-d_6): δ 171.0, 160.9, 132.9 (t, *J* = 13.9 Hz, 1C), 128.0 (t, *J* = 21.1 Hz, 1C), 114.5, 114.4, 55.7,

49.2, 21.1. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.27 (s). EI-MS *m/z* (%): 236 (M^+, 10), 193 (20), 137 (36), 136 (100). ESI-HRMS $[M+Na]^+$: *m/z* 259.1527, $C_{14}H_{20}DNO_2Na^+$ requires 259.1527.

4-Chloro-2-deuterio-*N,N*-diisopropylbenzamide (1d-D): general procedure starting from **1d** and CD_3OD. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **1d-D** (95% D incorporation) as a white solid (39 mg, 82%, R_f = 0.22 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35-7.34 (m, 2H), 7.25-7.24 (m, 1H), 3.76-3.46 (br m, 2H), 1.49-1.15 (br m, 12H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.0, 137.3 (t, *J* = 13.3 Hz, 1C), 134.7, 128.9, 128.8, 127.0 (t, *J* = 24.6 Hz, 1C), 51.1, 46.1, 20.8. ^{2}H NMR (92.07 MHz, CH_2Cl_2): δ 7.27 (s). EI-MS *m/z* (%): 242 (M^+, 4), 240 (M^+, 10), 199 (9), 197 (22), 143 (14), 142 (36), 141 (58), 140 (100). ESI-HRMS $[M+Na]^+$: *m/z* 263.1033, $C_{13}H_{17}DClNONa^+$ requires 263.1032.

2-Formyl-*N,N*-diisopropyl-3-methylbenzamide (2j) and **2-formyl-*N,N*-diisopropyl-5-methylbenzamide (2k)**: general procedure starting from **1b** and DMF (5 eq.). Purification by flash column chromatography (PE/EtOAc 75/25 v/v) gave an inseparable mixture of regioisomers **2j** and **2k** in 1:1 ratio as a white solid (36 mg, 73%, R_f = 0.25 PE/EtOAc 75/25 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.33 (s, 1H), 10.02 (s, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.9, 1H), 7.23 (d, *J* = 7.6, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 3.60-3.52 (m, 4H), 2.66 (s, 3H), 2.42 (s, 3H), 1.65-1.52 (br m, 12H), 1.13-1.04 (br m, 12H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 191.7, 190.4, 169.3, 168.6, 145.7, 142.8, 141.5, 141.4, 133.5, 131.9, 130.3, 130.1, 129.9, 129.6, 126.6, 123.9, 51.3, 51.3, 46.2, 46.1, 22.0, 20.8, 20.7, 20.6, 20.5. EI-MS *m/z* (%): **2j**: 247 (M^+, 1), 204 (65), 162 (58), 147 (100), 119 (36); **2k**: 247 (M^+, 1), 204 (53), 162 (41), 147 (100), 119 (39).[8]

2-Bromo-*N,N*-diisopropyl-4-methoxybenzamide (2l): general procedure starting from **1c** and 1,2-dibromoethane (1.2 eq.). Purification by flash column chromatography (DCM/EtOAc 96/4 v/v) gave **2l** as a white solid (52 mg, 83%, R_f = 0.30 DCM/EtOAc 96/4 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.09-7.08 (m, 2H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.62 (sept, *J* = 6.7 Hz, 1H), 3.49 (sept, *J* = 6.7 Hz, 1H), 1.56 (d, *J* = 6.8 Hz, 3H) superimposed to 1.54 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 1.05 (d, *J* = 6,7 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 168.4, 159.8, 132.9, 127.4, 119.6, 118.0, 113.8, 55.7, 51.3, 46.0, 21.0, 20.8, 20.8, 20.2. EI-MS *m/z* (%): 315 (M^+, 9), 313 (M^+, 10), 272 (27), 270 (28), 258 (4), 256 (4), 215 (97), 213 (100).[9]

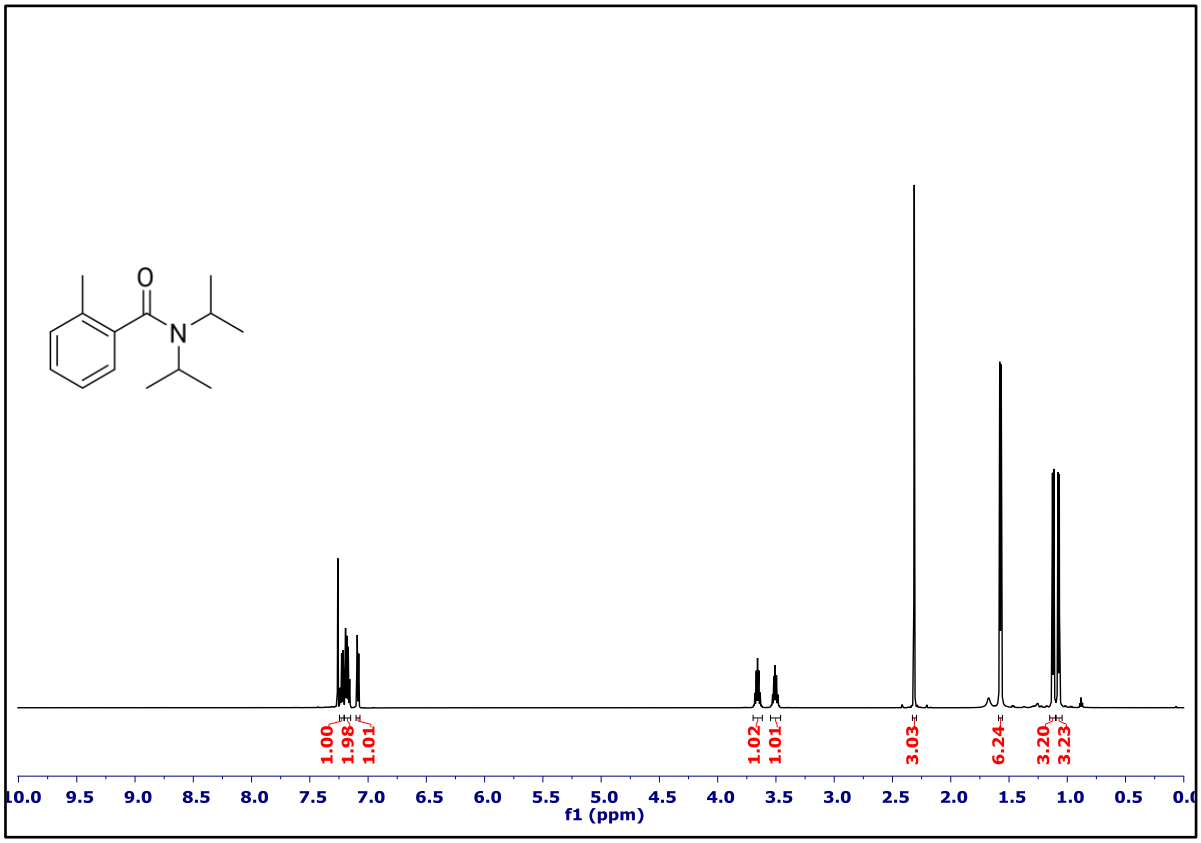
4-Chloro-2-formyl-*N,N*-diisopropylbenzamide (2m): general procedure starting from **1d** and DMF (5 eq.). Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **2m** as a white solid (32 mg, 61%, R_f = 0.30 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.03 (s, 1H), 7.90 (d, *J* = 2.1 Hz, 1H), 7.58 (dd, *J* = 8.1, 2.2 Hz, 1H) 7.24 (d, *J* = 8.0 Hz, 1H), 3.56 (sept, *J* = 6.6 Hz, 2H), 1.58 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.7 Hz, 6H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 189.3, 167.3, 139.6, 135.2, 134.2, 133.8, 129.3, 127.6, 51.4, 46.4, 20.6, 20.5. EI-MS *m/z* (%): 267 (M^+, 1), 226 (13), 224 (41), 184 (10), 182 (31), 169 (33), 167 (100), 141 (11), 139 (36).[10]

3-Deuterio-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (1e-D): general procedure starting from **1e** and CD_3OD. Purification by flash column chromatography (PE/DEE 8/2 v/v) gave **1e-D** (83% D incorporation) as a white solid (47 mg, 90%, R_f = 0.20 PE/DEE 8/2 v/v). ^1H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.29-7.26 (m, 1H), 7.16-7.12 (m, 1H), 4.47-3.38 (br m, 2H) superimposed to 3.78 (s, 3H), 1.85-0.96 (br m, 12H). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$): δ 164.1, 137.3, 134.9, 126.9, 122.6, 121.4, 120.2, 109.8, 99.9 (t, *J* = 26.2 Hz, 1C), 51.0, 45.9, 30.9, 21.0. ^2H NMR (92.07 MHz, CH_2Cl_2): δ 6.49 (s), 3.73 (t, *J* = 2.0 Hz). EI-MS *m/z* (%): 259 (M^+, 22), 159 (100), 132 (73), 90 (38). ESI-HRMS $[M + Na]^+$: *m/z* 282.1684, $C_{16}H_{21}DN_2ONa^+$ requires 282.1687.

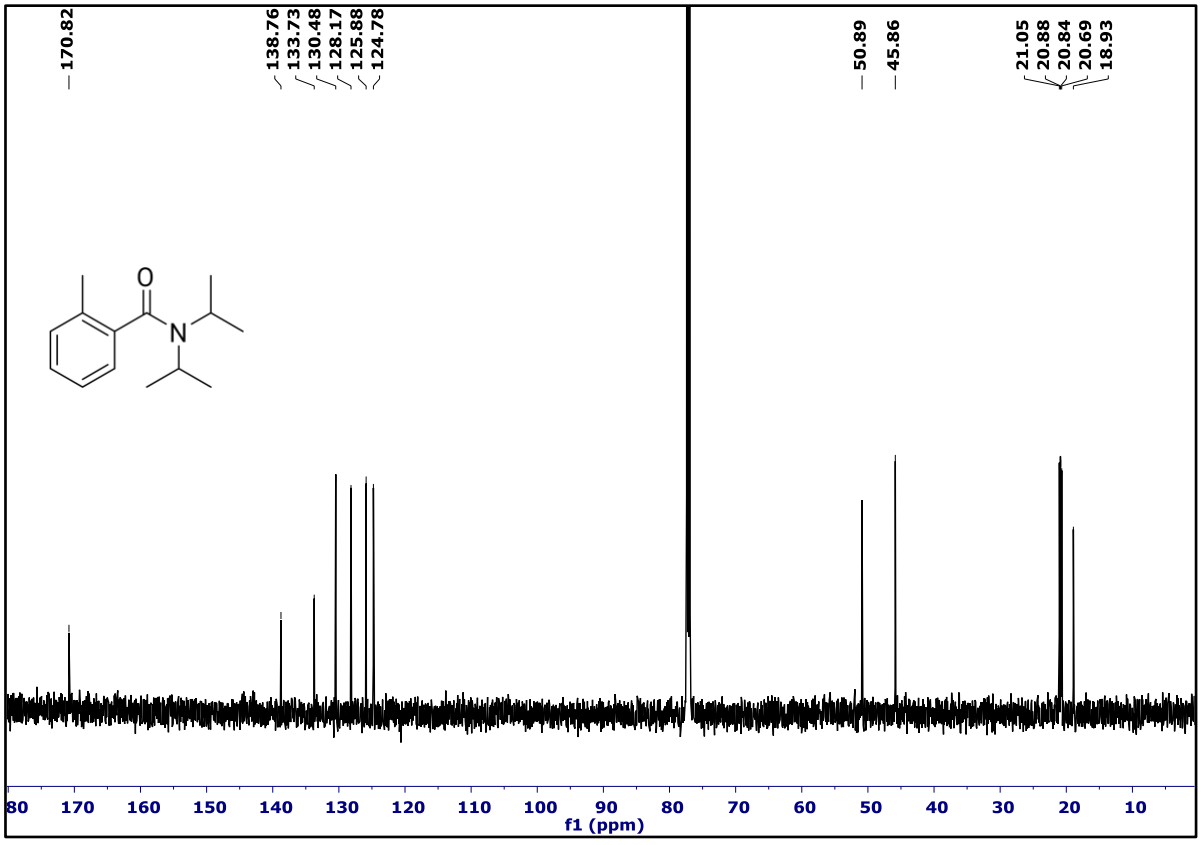
3-(Hydroxy(phenyl)methyl)-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (2n): general procedure starting from **1e** and PhCHO (5 eq.). Purification by flash column chromatography (PE/EtOAc 75/25 v/v) gave **2n** as a white solid (50 mg, 68%, R_f = 0.25 PE/EtOAc 75/25 v/v), mp 59.0-60.2 °C. ^1H NMR (600 MHz, $CDCl_3$, mixture of rotamers): δ 7.61-6.91 (m, 18H major + minor), 6.12 (d, *J* = 6.0 Hz, 1H major), 6.07 (d, *J* = 4.2 Hz, 1H minor), 3.88-3.75 (m, 2H minor), 3.71 (s, 3H minor), 3.70 (s, 3H major), 3.60-3.43 (m, 3H major), 2.76 (br s, 1H minor), 1.62 (d, *J* = 6.8 Hz, 3H minor) superimposed 1.59 (d, *J* = 6.8 Hz, 3H major) superimposed to 1.57 (d, *J* = 6.8 Hz, 3H minor) superimposed to 1.55 (d, *J* = 6.8 Hz, 3H major), 1.18 (d, *J* = 6.8 Hz, 3H minor) superimposed to 1.16 (d, *J* = 6.6 Hz, 3H major), 1.03 (d, *J* = 6.6 Hz, 3H minor), 0.79 (d, *J* = 6.6 Hz, 3H major). $^{13}C\{1H\}$ NMR (150 MHz, $CDCl_3$, mixture of rotamers): δ 164.5, 144.4, 143.2, 137.0, 136.8, 134.3, 133.6, 128.5, 128.2, 127.6, 127.2, 126.8, 126.0, 125.8, 125.5, 122.9, 122.6, 121.1, 120.4, 120.1, 116.9, 114.7, 109.8, 109.6, 70.3 (minor), 69.0 (major), 51.5 (minor), 51.4 (minor), 46.5 (major), 46.4 (major), 31.1 (major), 30.8 (minor), 21.0 (major), 20.7 (minor), 20.5 (major + minor), 20.5 (major + minor), 20.3 (minor). EI-MS *m/z* (%): 364 (M^+, 22), 263 (89), 262 (100), 247 (27), 218 (20), 158 (38). ESI-HRMS $[M+Na]^+$: *m/z* 387.2043, $C_{23}H_{28}N_2O_2Na^+$ requires 387.2043.

_N,N_-Diisopropyl-2-methylbenzamide (2a)

^{1}H NMR (600 MHz, $CDCl_3$)

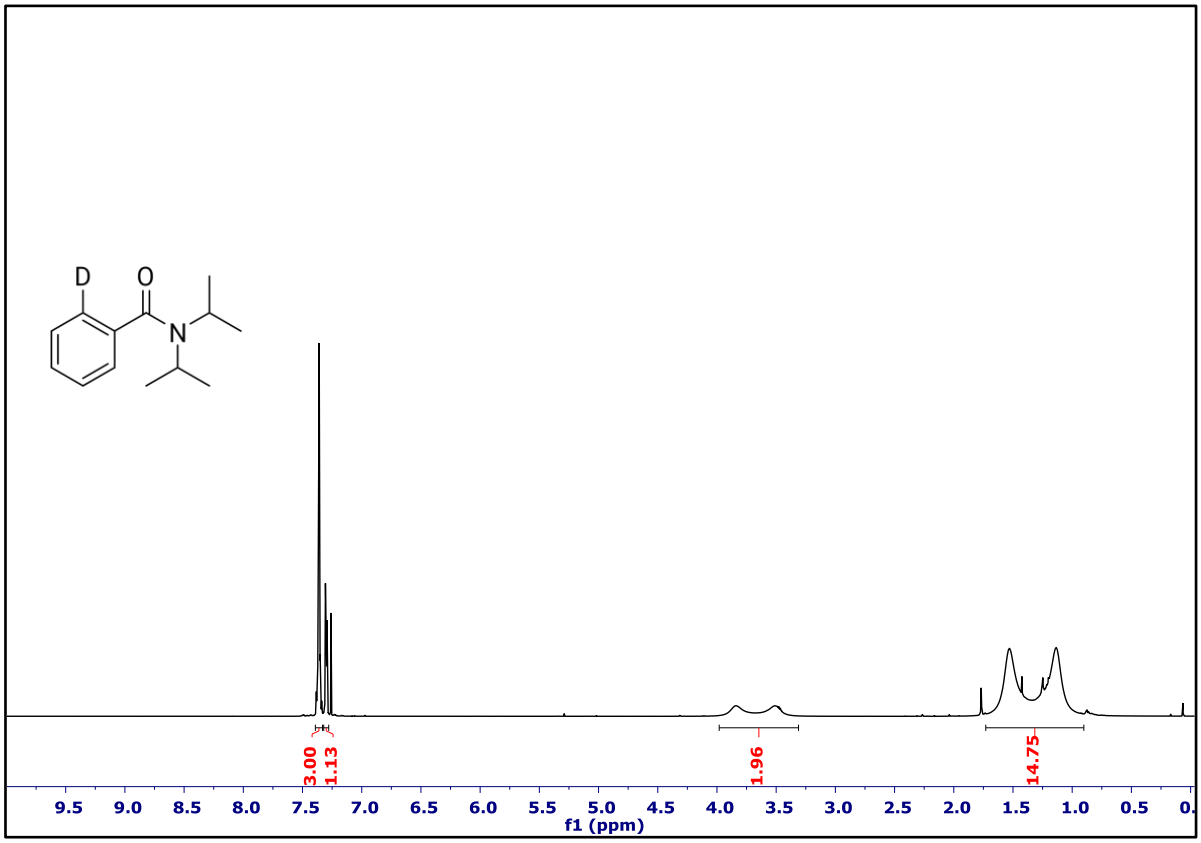


^{13}C NMR (150 MHz, $CDCl_3$)

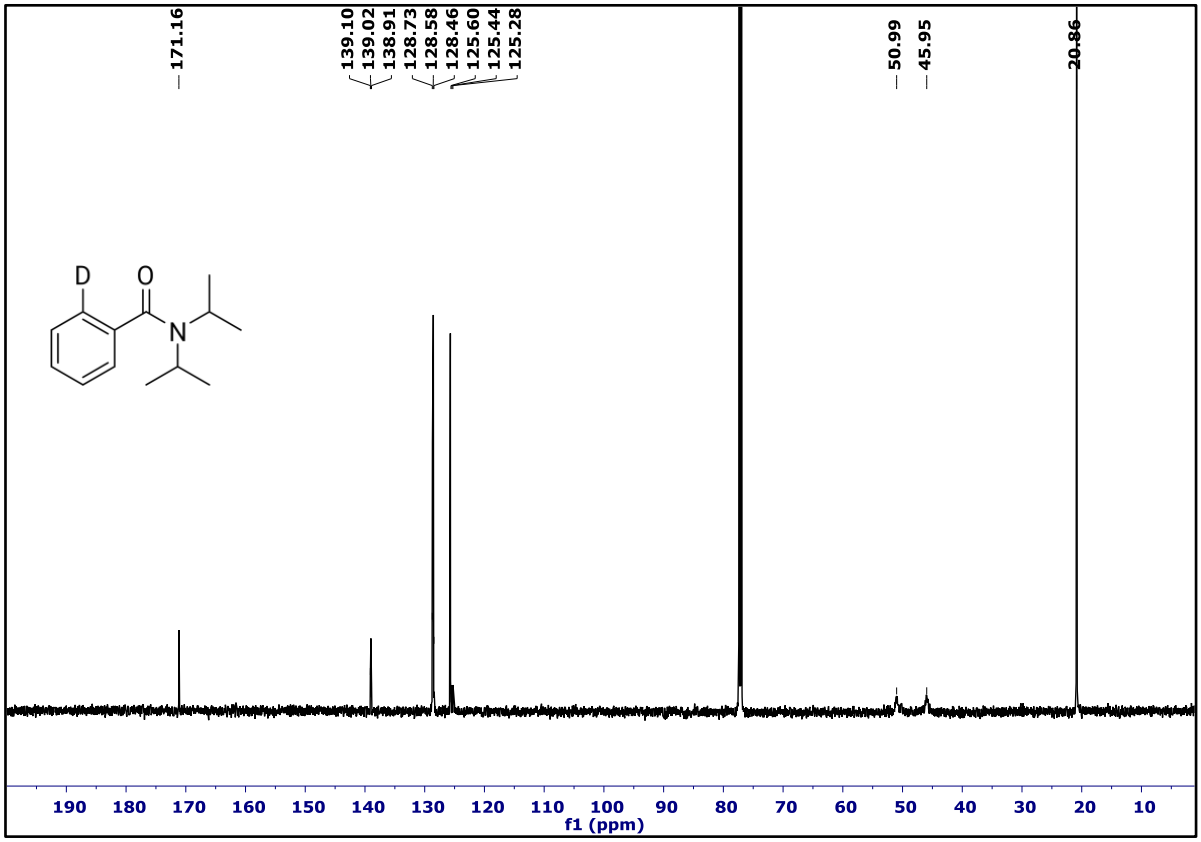


2-Deuterio-*N*,*N*-diisopropylbenzamide (1a-D)

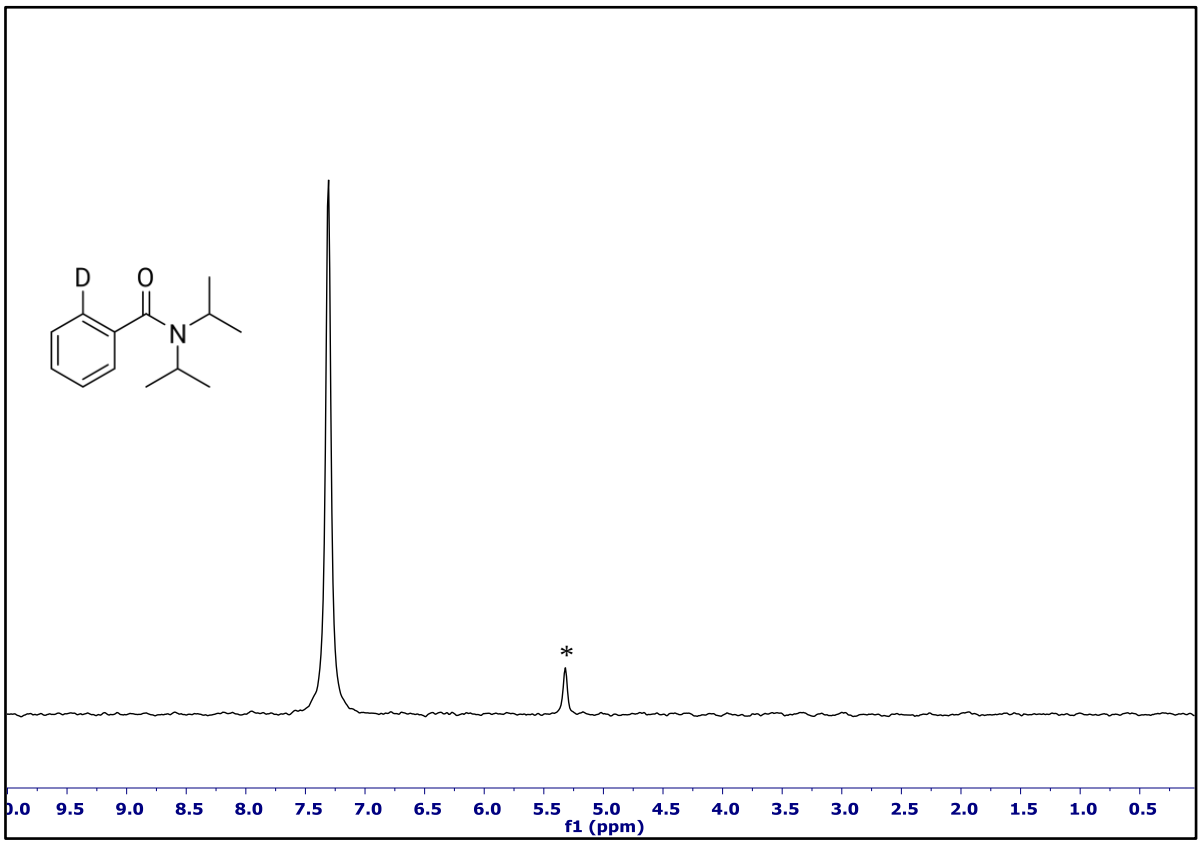
^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (150 MHz, $CDCl_3$)



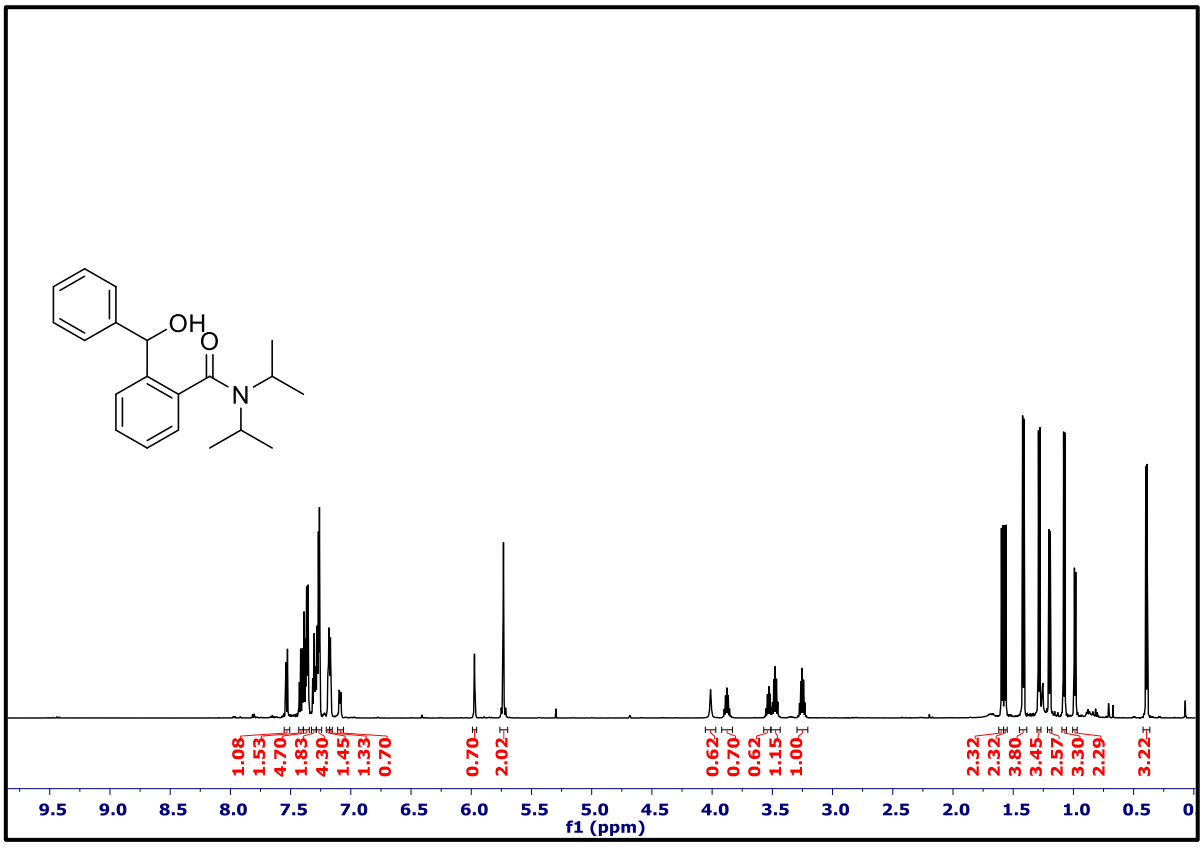
^{2}H NMR (92.07 MHz, CH_2Cl_2)



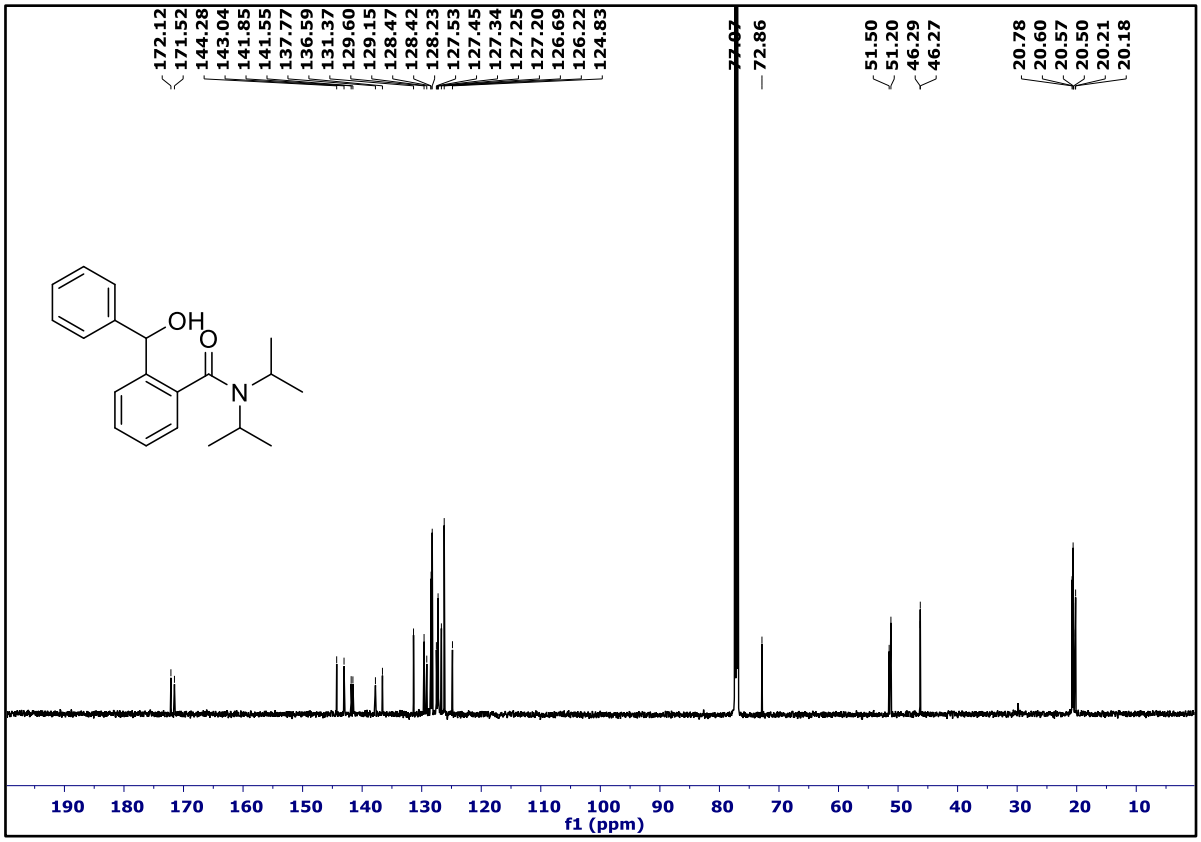
***** residual solvent peak

2-(Hydroxy(phenyl)methyl)-*N*,*N*-diisopropylbenzamide (2b)

^{1}H NMR (600 MHz, $CDCl_3$)

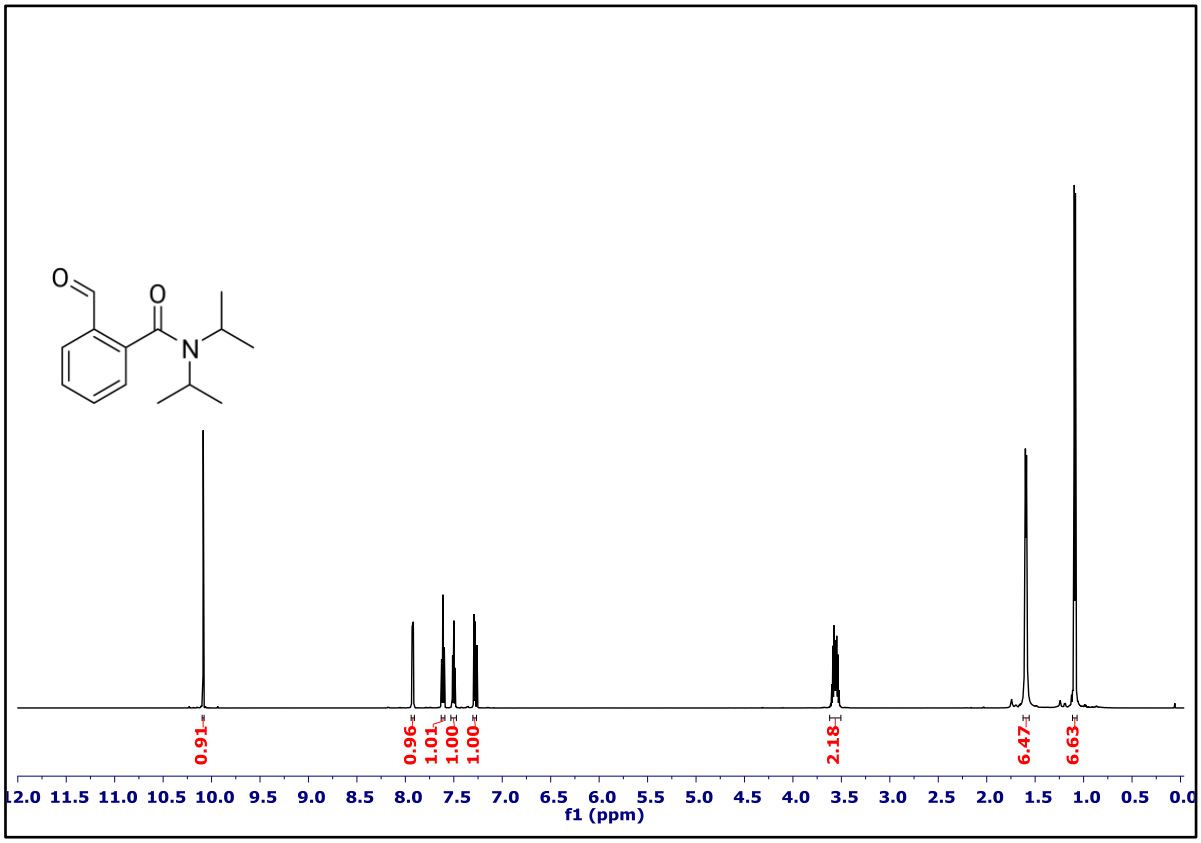


^{13}C NMR (150 MHz, $CDCl_3$)

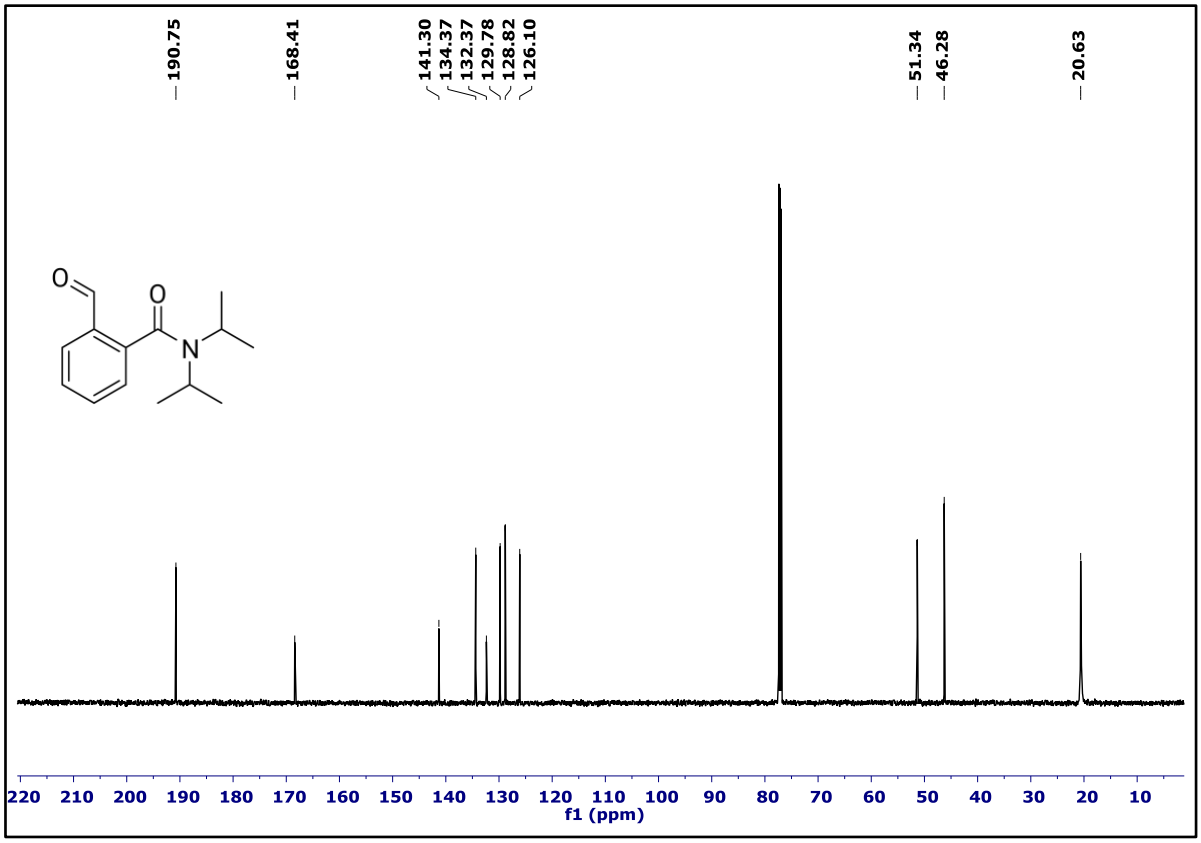


2-Formyl-*N*,*N*-diisopropylbenzamide (2c)

^{1}H NMR (600 MHz, $CDCl_3$)

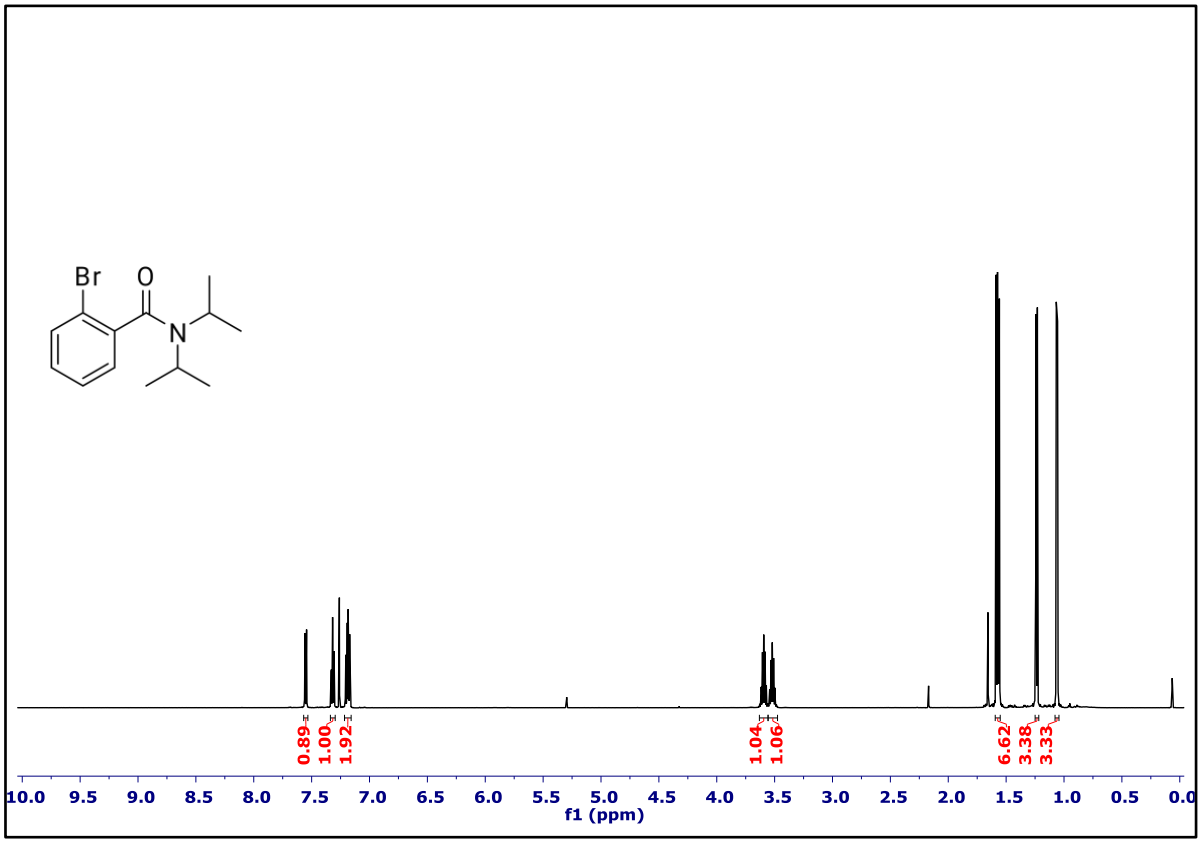


^{13}C NMR (150 MHz, $CDCl_3$)

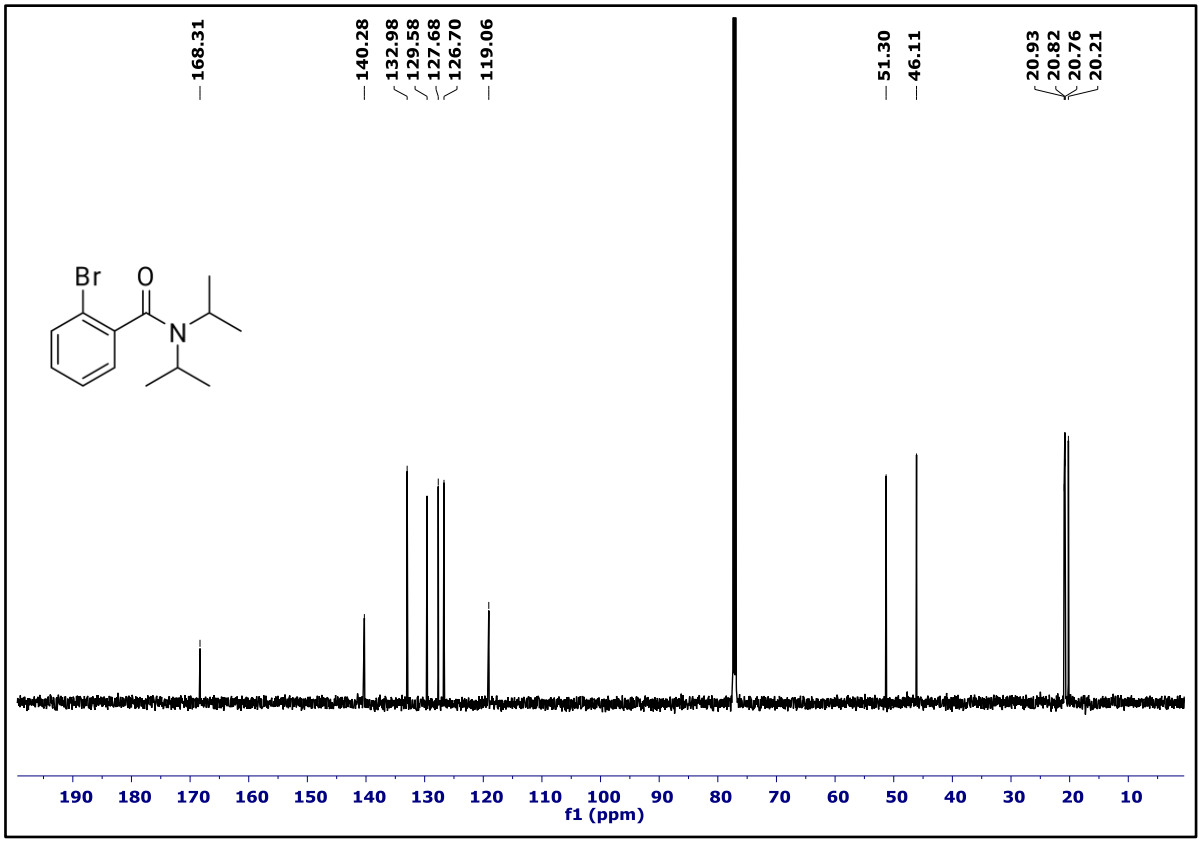


2-Bromo-*N*,*N*-diisopropylbenzamide (2d)

^{1}H NMR (600 MHz, $CDCl_3$)

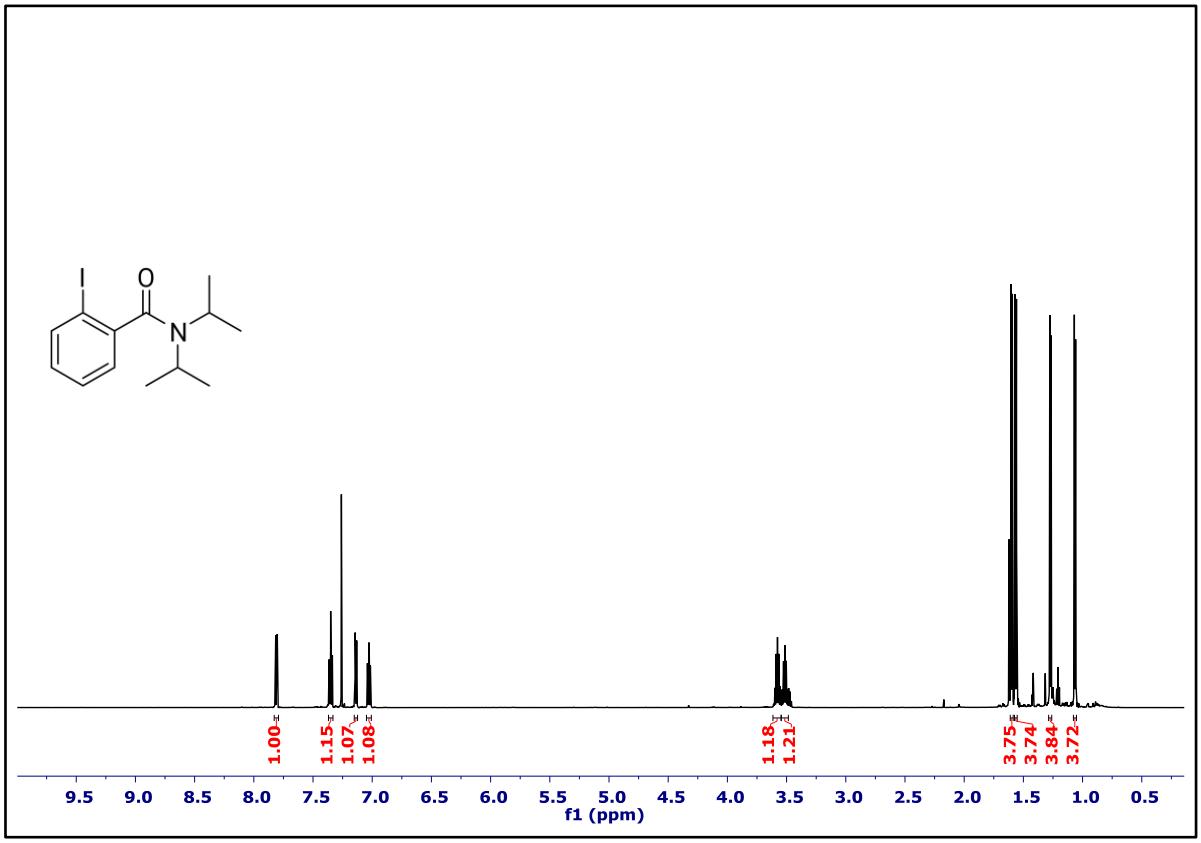


^{13}C NMR (150 MHz, $CDCl_3$)

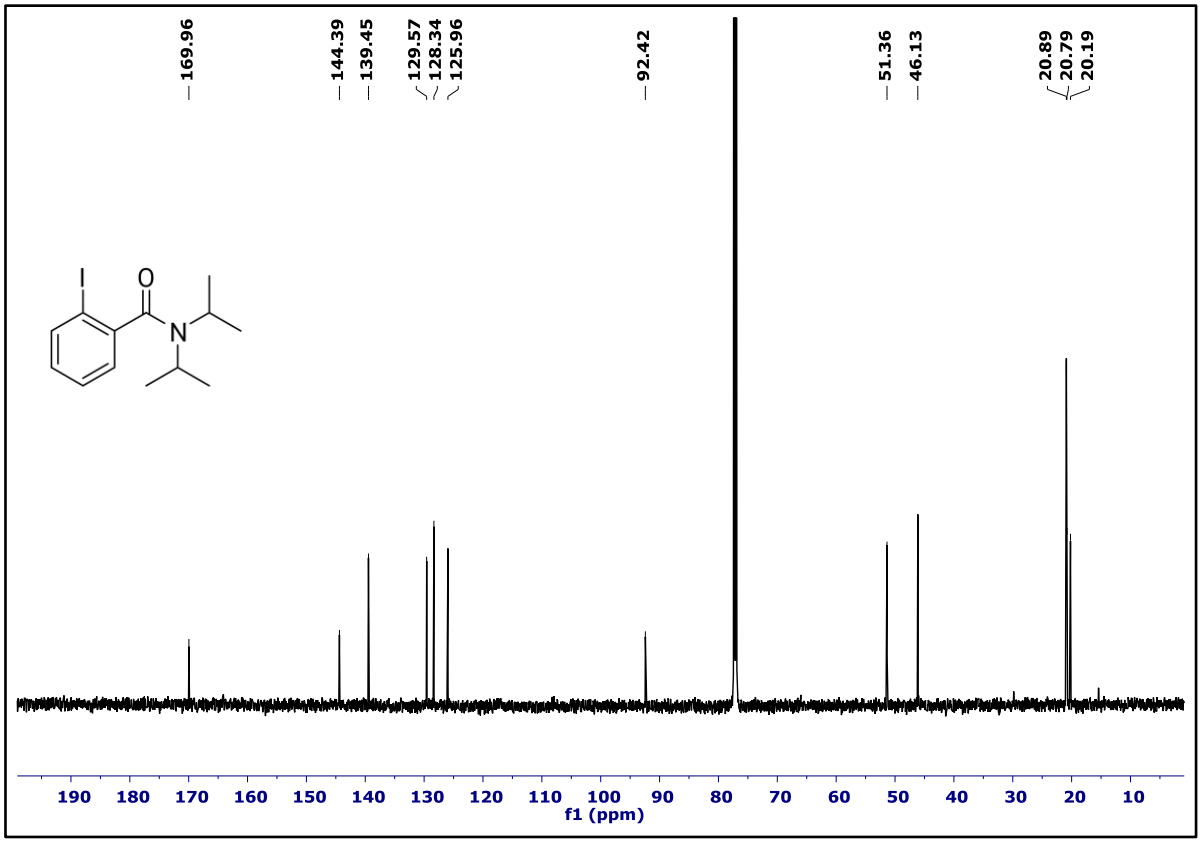


2-Iodo-*N*,*N*-diisopropylbenzamide (2e)

^{1}H NMR (600 MHz, $CDCl_3$)

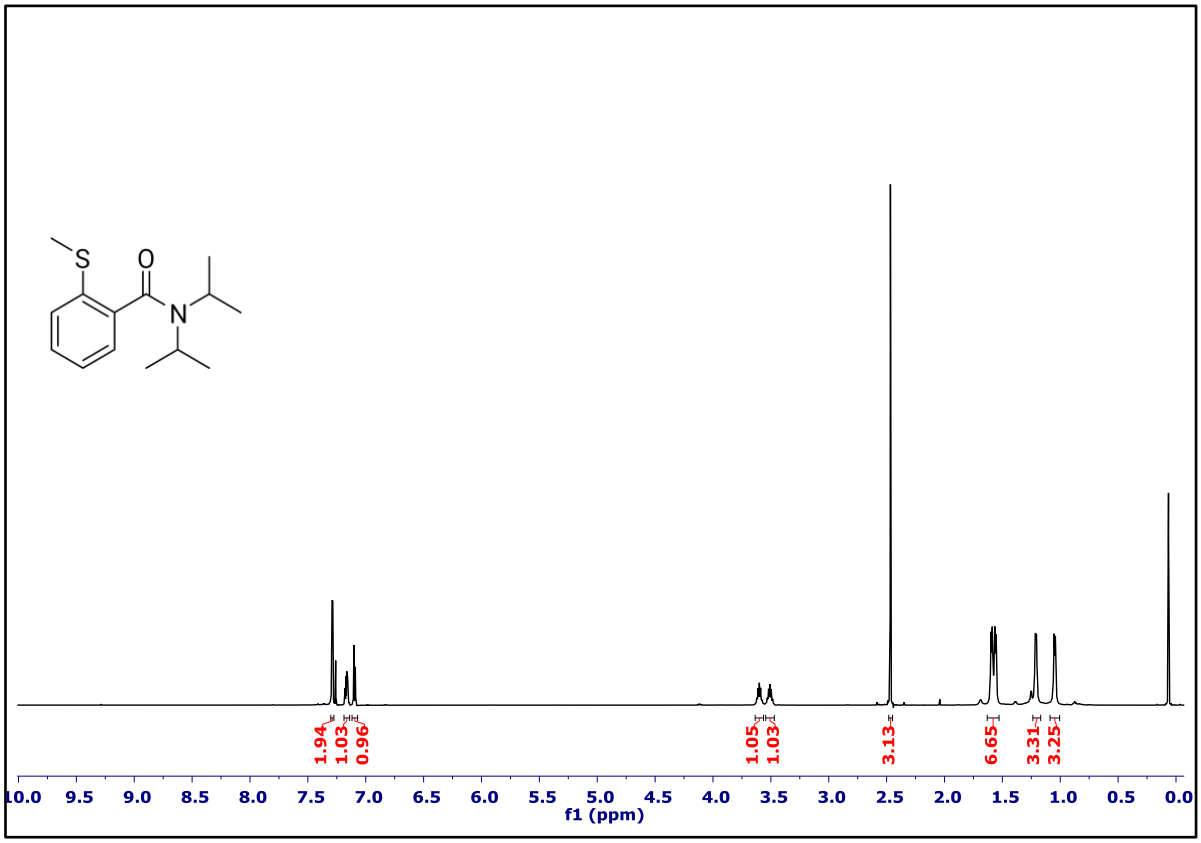


^{13}C NMR (150 MHz, $CDCl_3$)

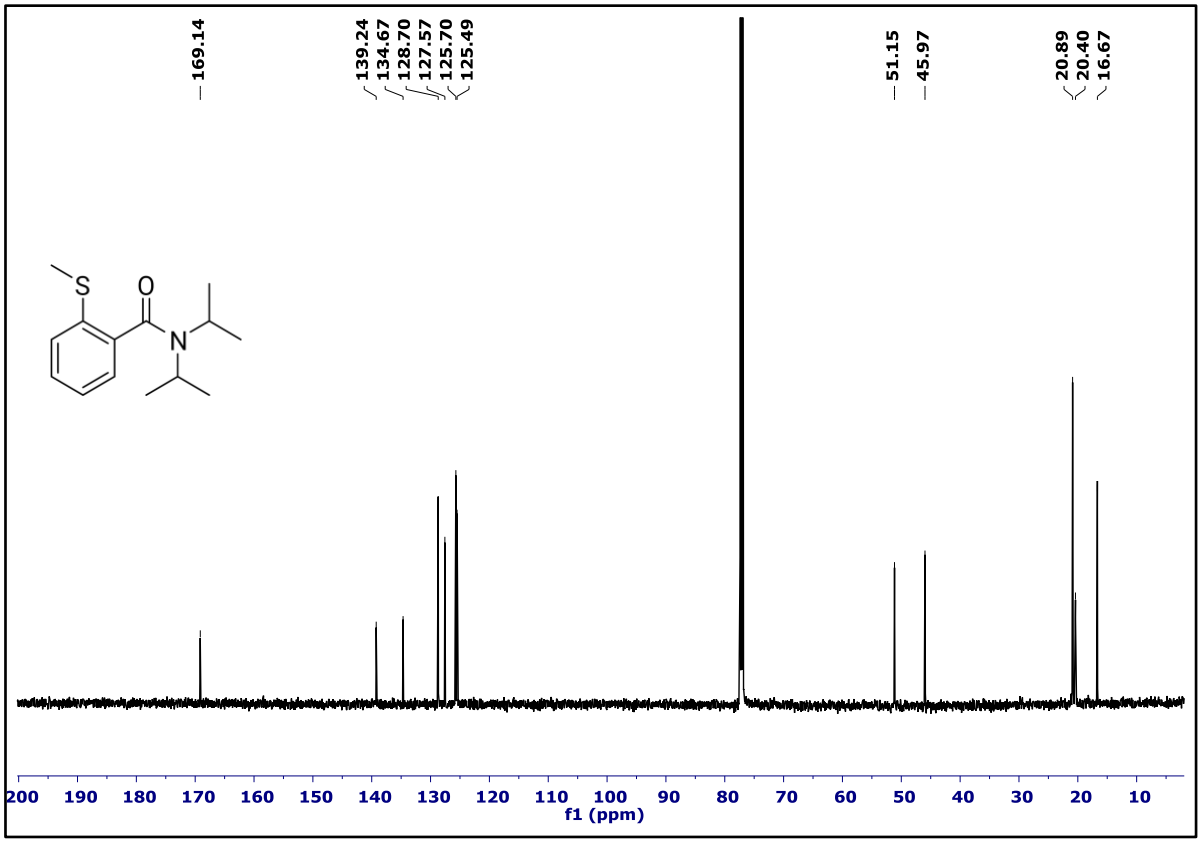


***N*,*N*-Diisopropyl-2-(methylthio)benzamide (2f)**

^{1}H NMR (600 MHz, $CDCl_3$)

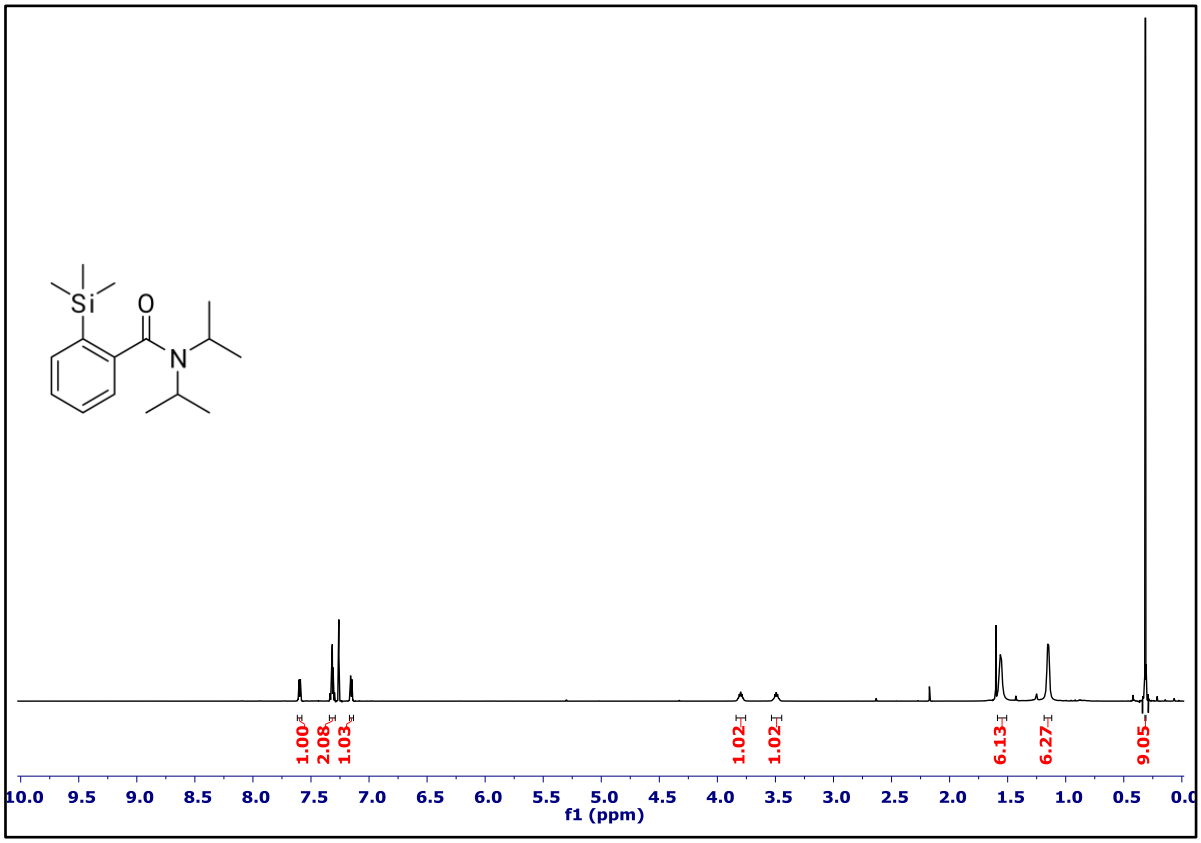


^{13}C NMR (150 MHz, $CDCl_3$)

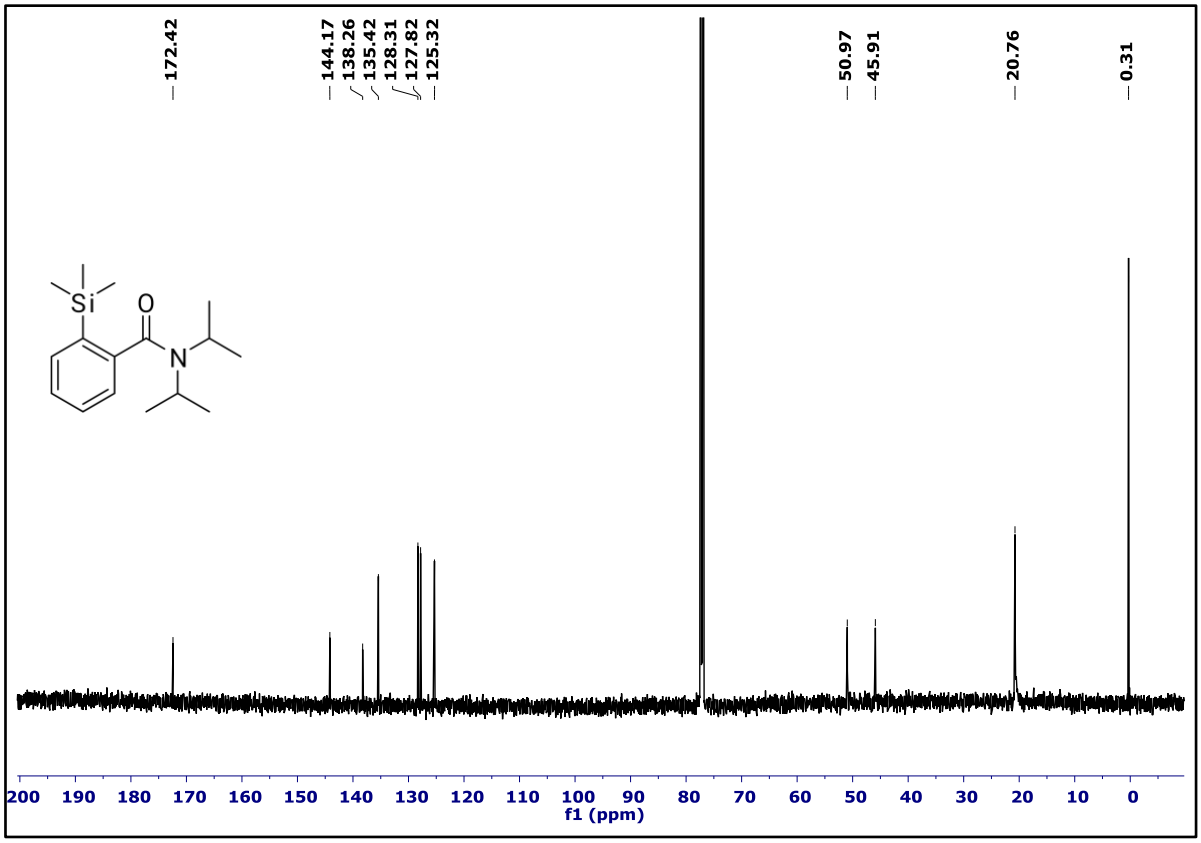


***N*,*N*-Diisopropyl-2-(trimethylsilyl)benzamide (2g)**

^{1}H NMR (600 MHz, $CDCl_3$)

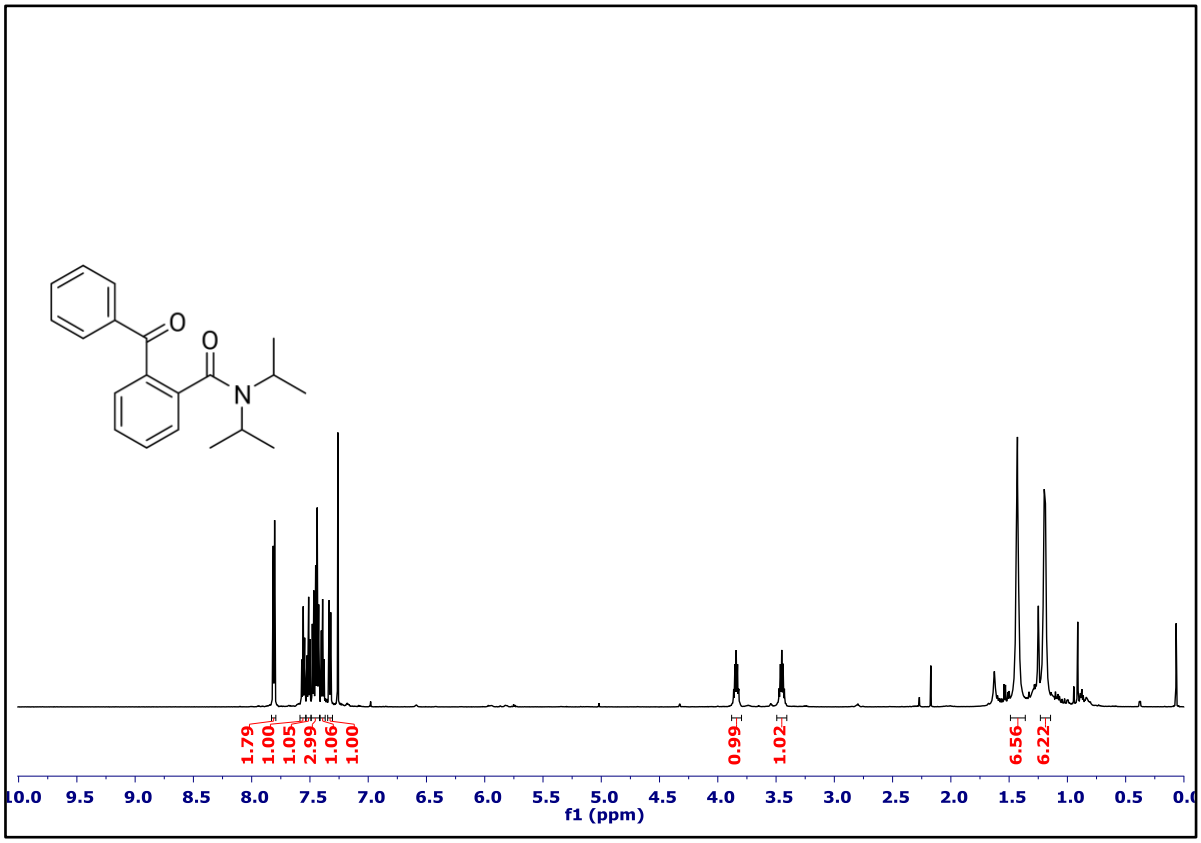


^{13}C NMR (150 MHz, $CDCl_3$)

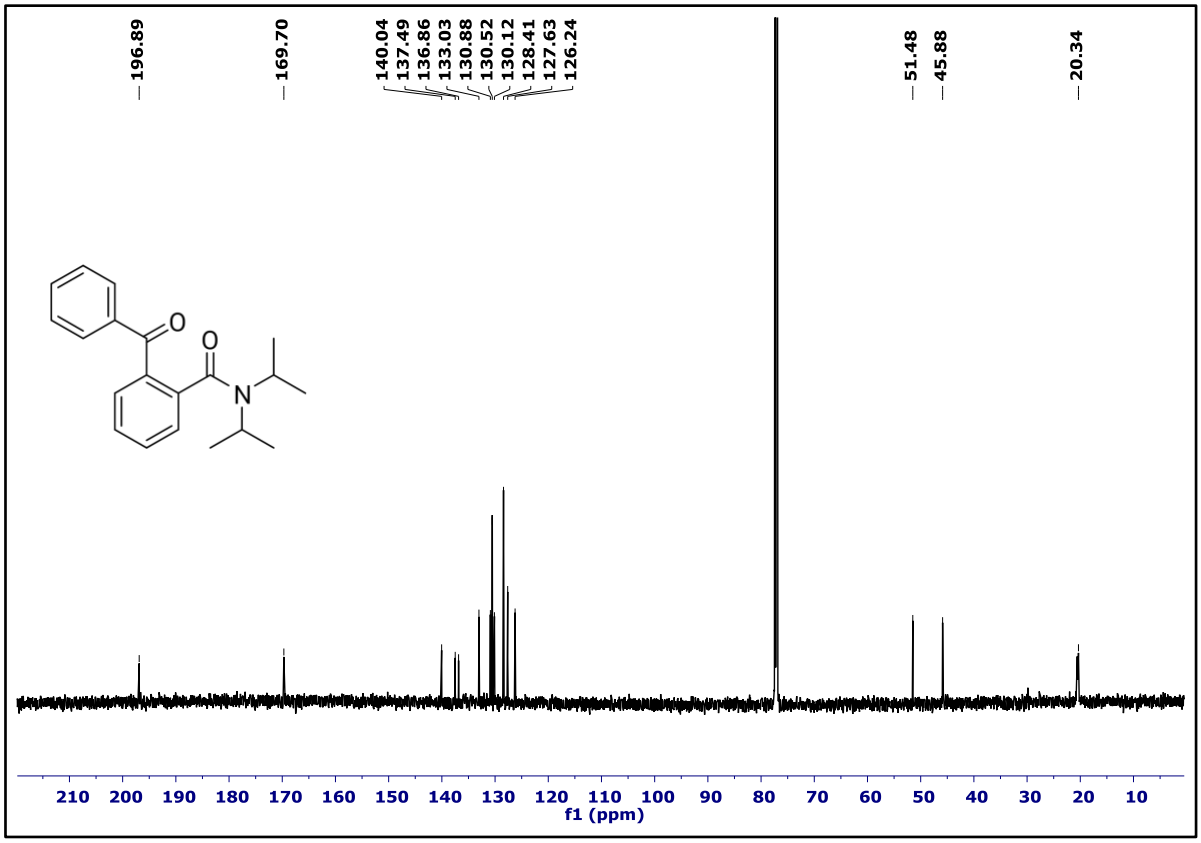


2-Benzoyl-*N*,*N*-diisopropylbenzamide (2h)

^{1}H NMR (600 MHz, $CDCl_3$)

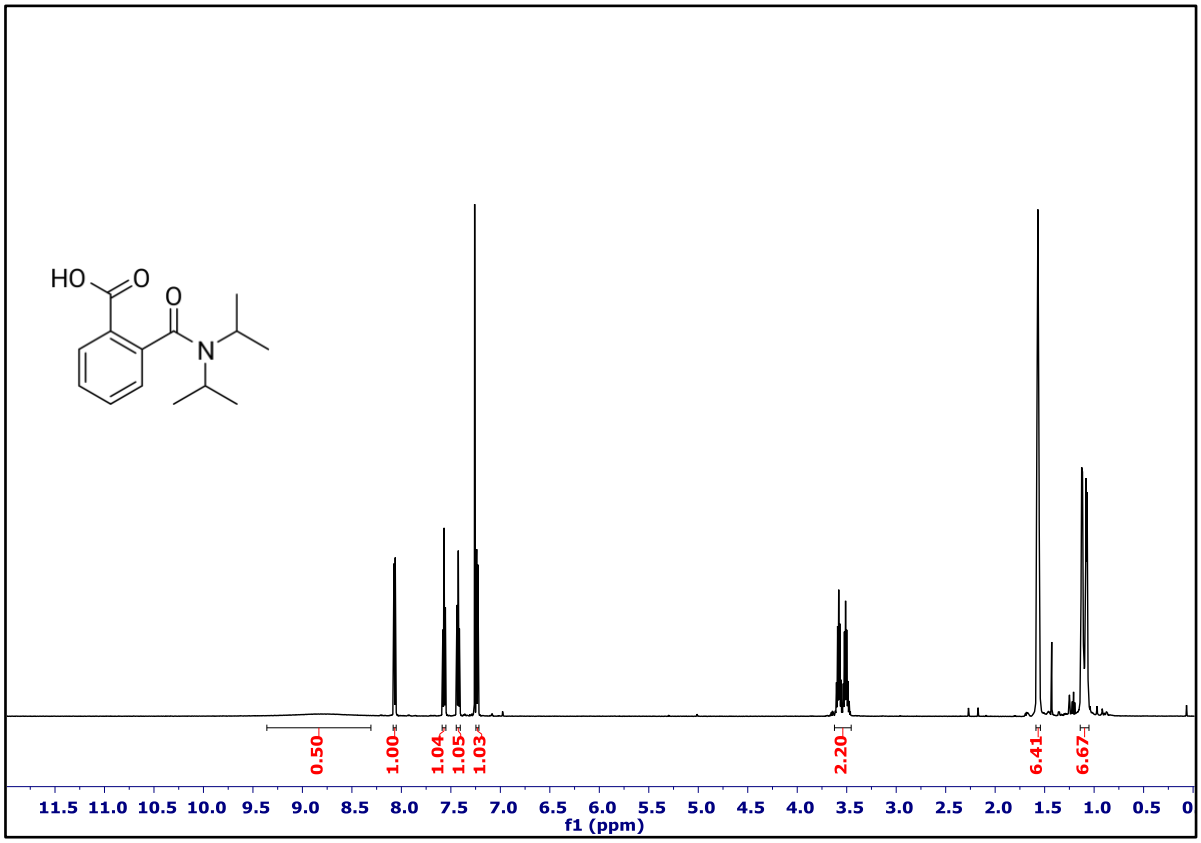


^{13}C NMR (150 MHz, $CDCl_3$)

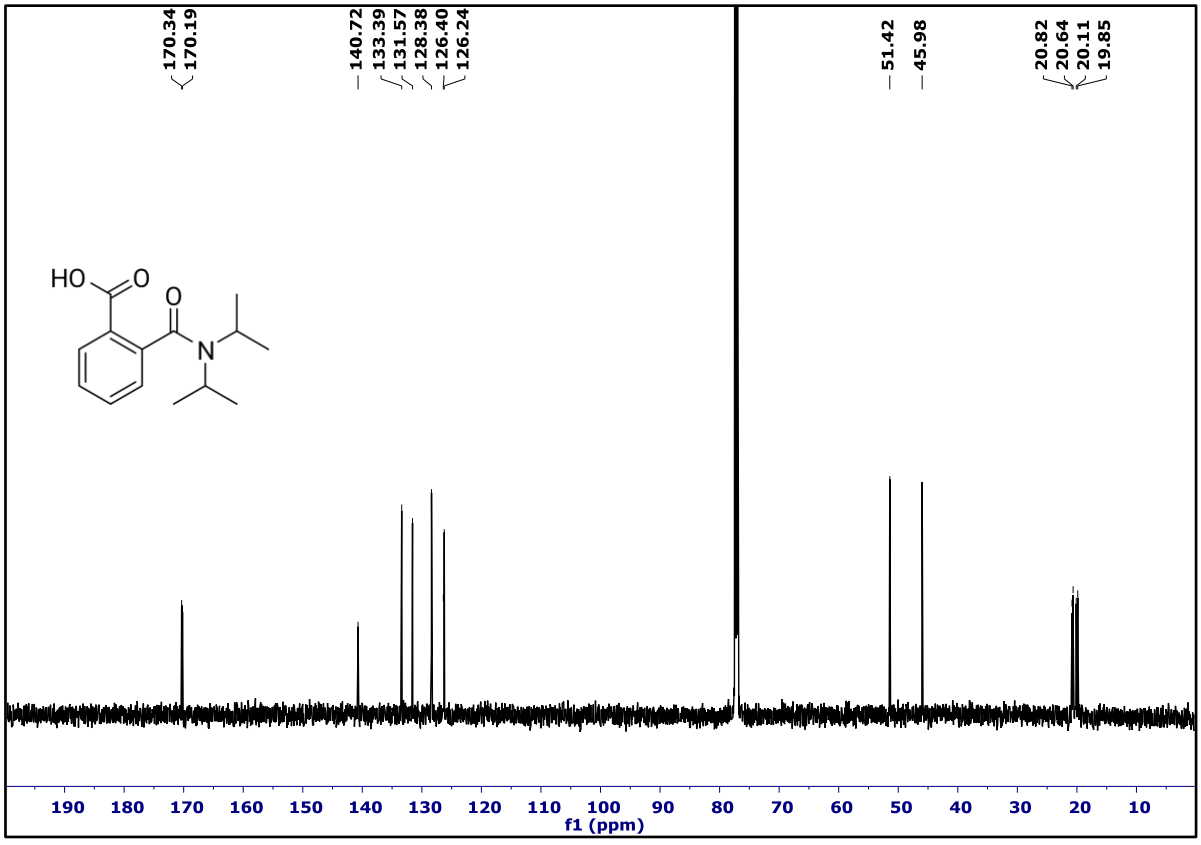


2-(Diisopropylcarbamoyl)benzoic acid (2k)

^{1}H NMR (600 MHz, $CDCl_3$)

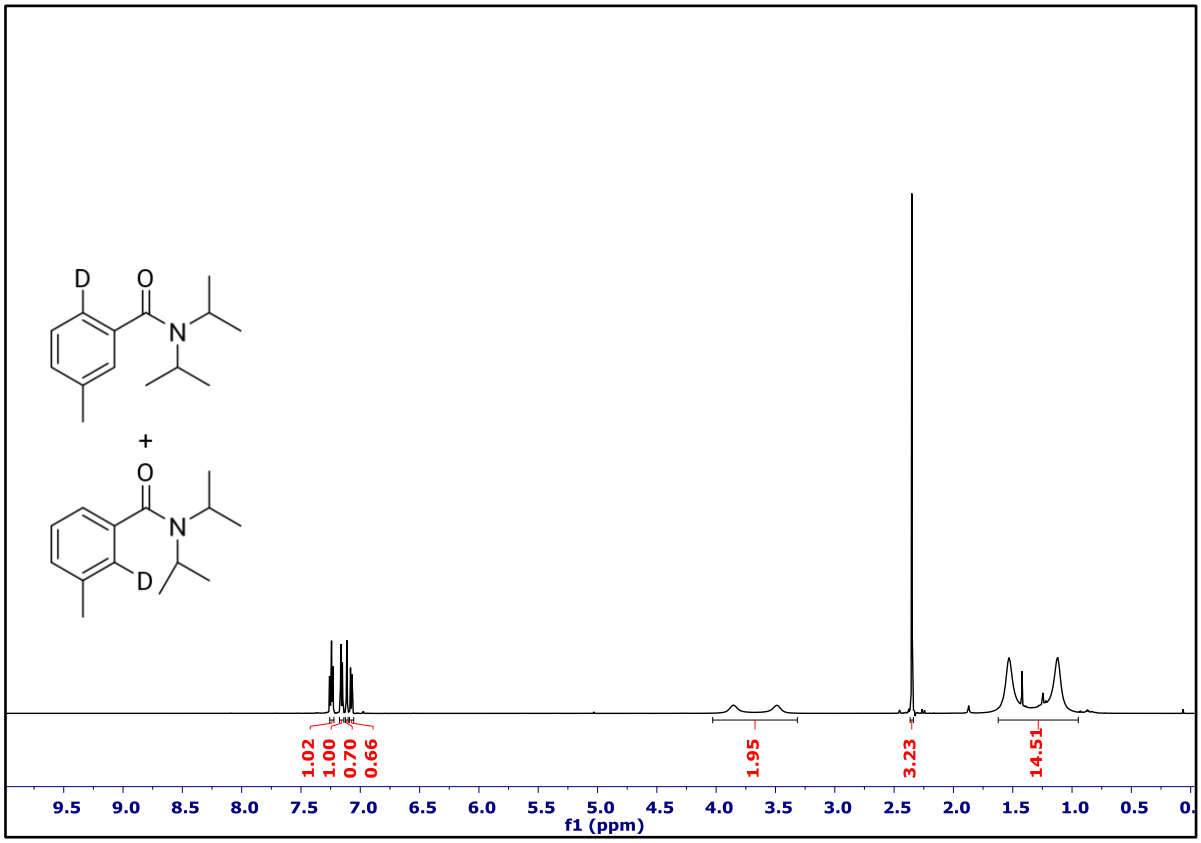


^{13}C NMR (150 MHz, $CDCl_3$)

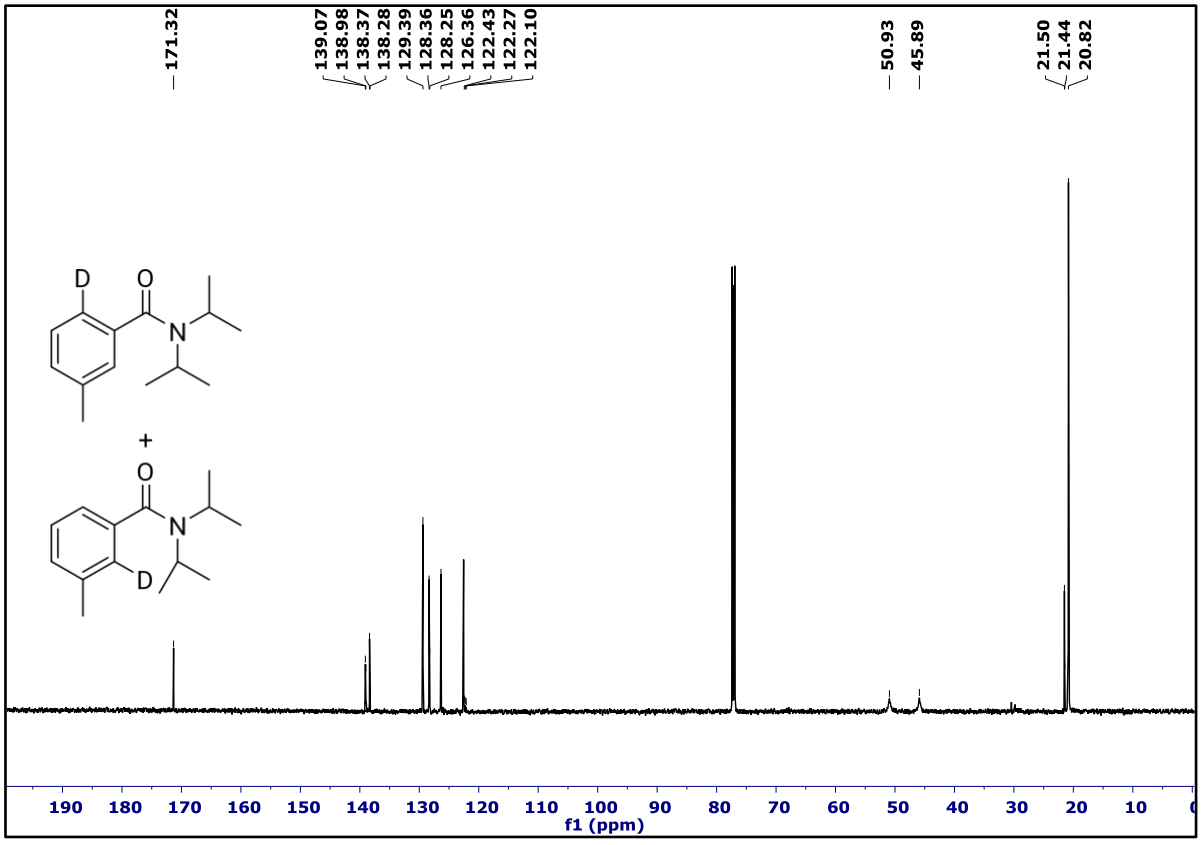


2-Deuterio- and 6-Deuterio-*N*,*N*-diisopropyl-3-methylbenzamide (1b-D and 1b'-D)

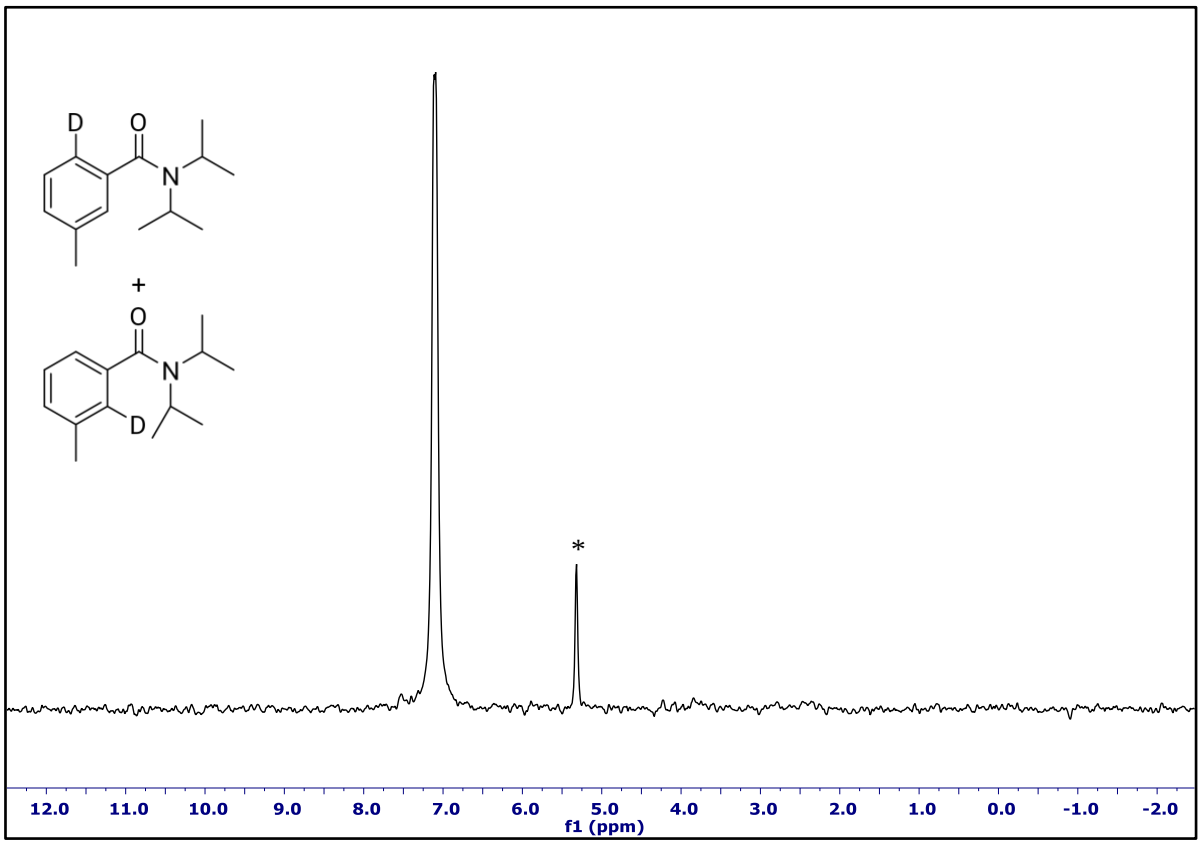
^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (150 MHz, $CDCl_3$)



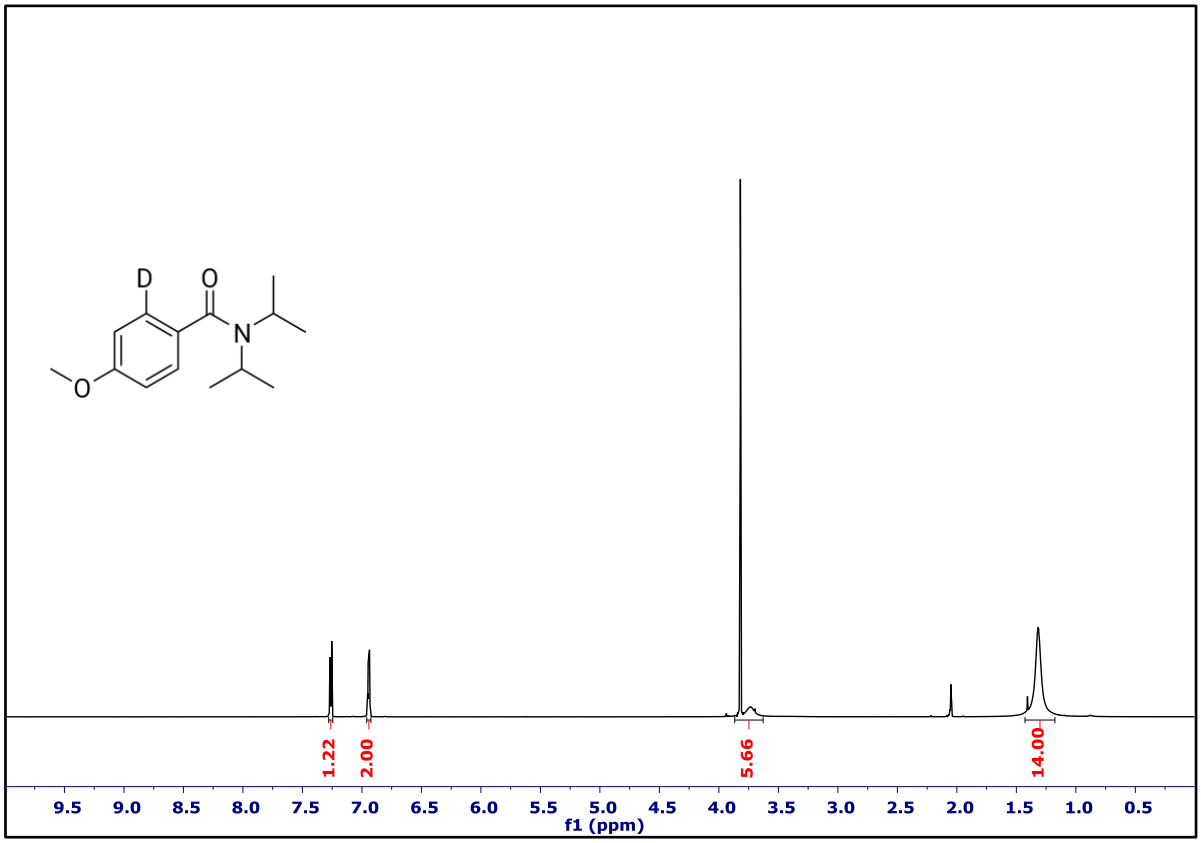
^{2}H NMR (92.07 MHz, CH_2Cl_2)



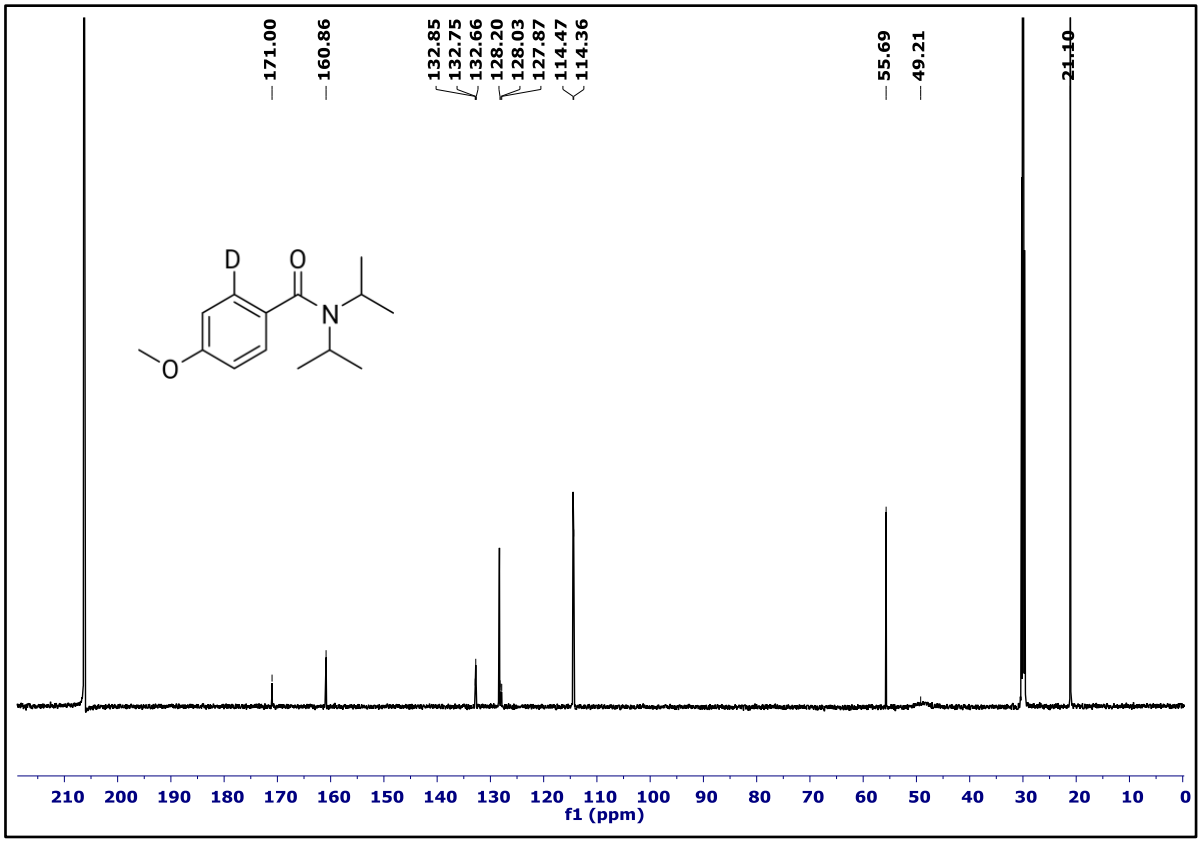
* residual solvent peak

2-Deuterio-*N*,*N*-diisopropyl-4-methoxybenzamide (1c-D)

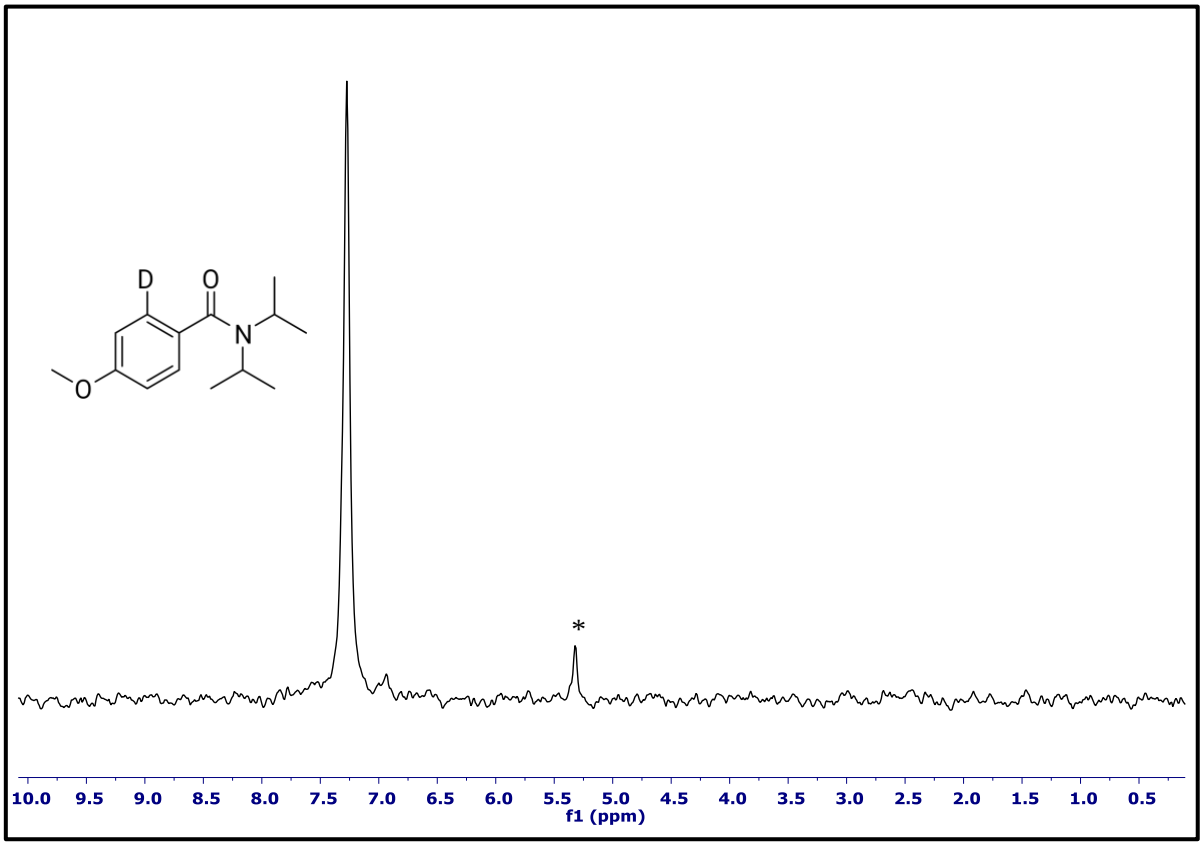
^{1}H NMR (600 MHz, acetone-d_6)



^{13}C NMR (150 MHz, acetone-d_6)



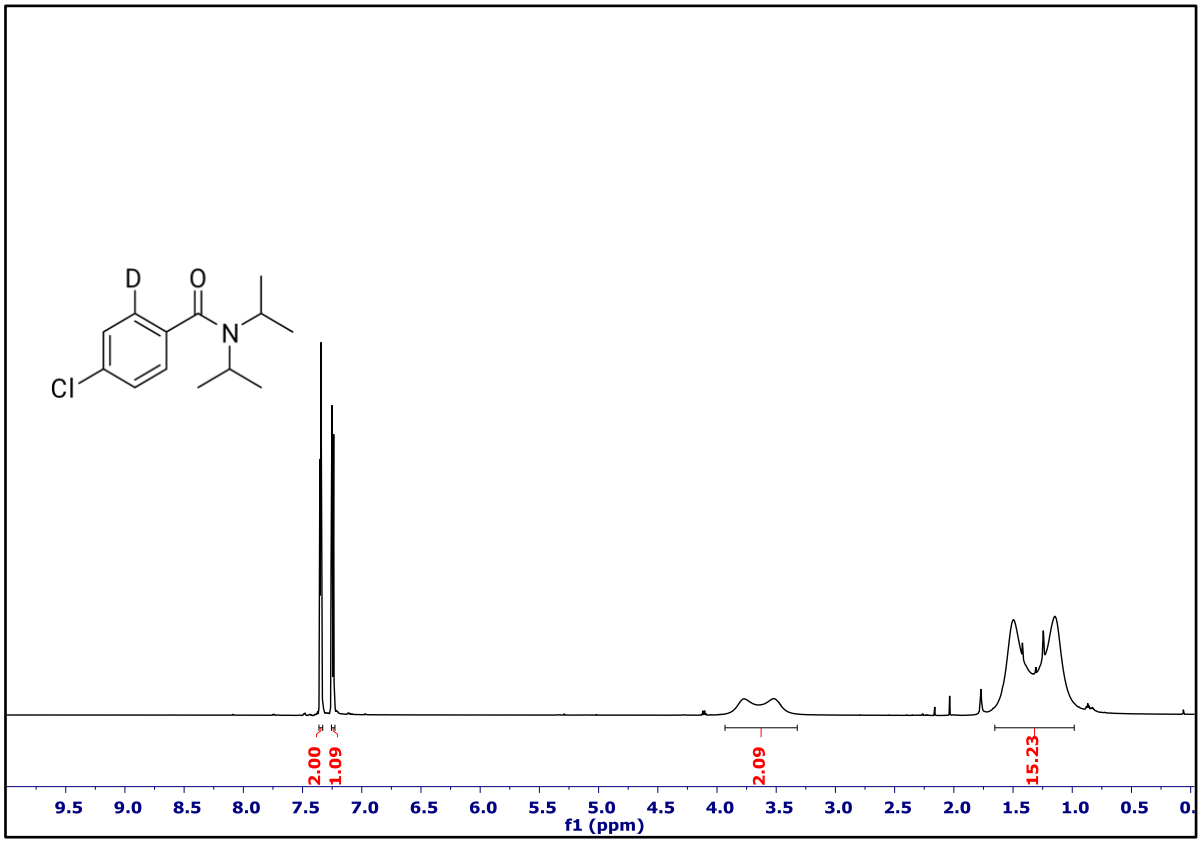
^{2}H NMR (92.07 MHz, CH_2Cl_2)



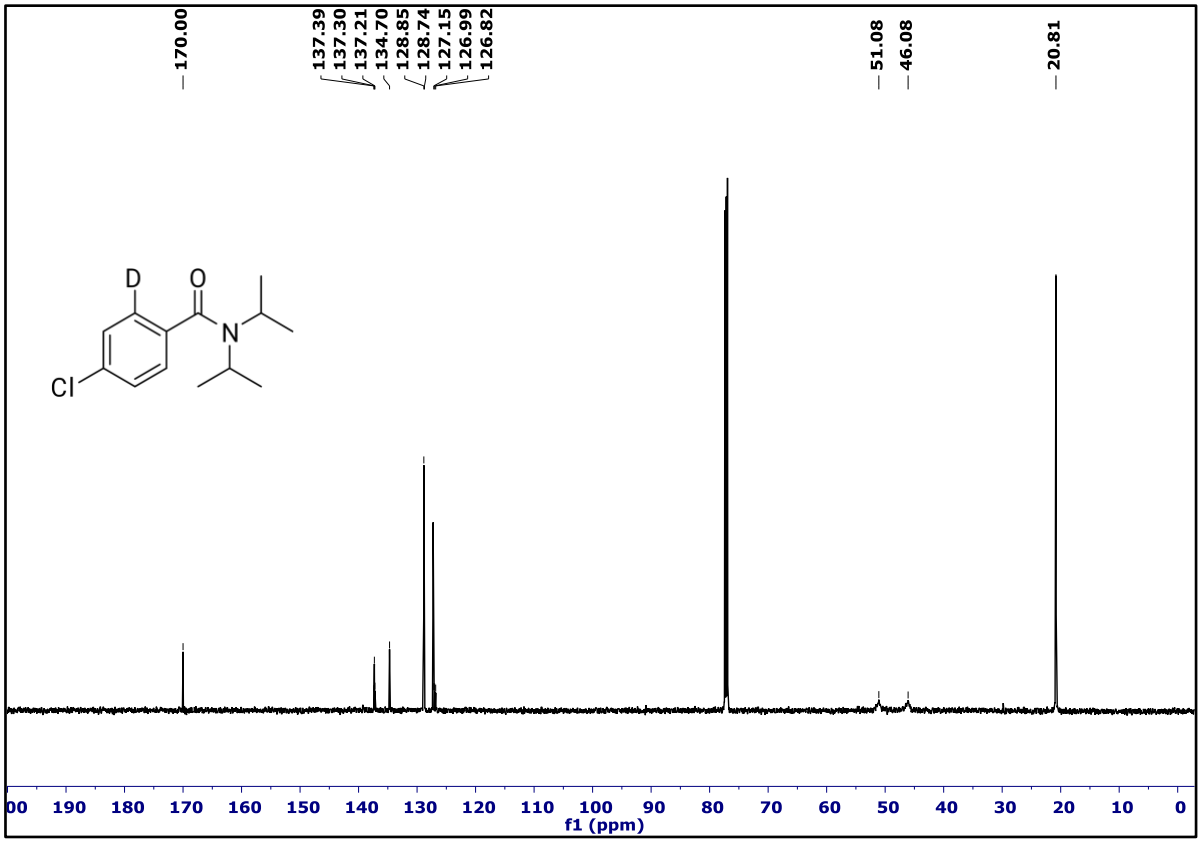
* residual solvent peak

4-Chloro-2-deuterio-*N*,*N*-diisopropylbenzamide (1d-D)

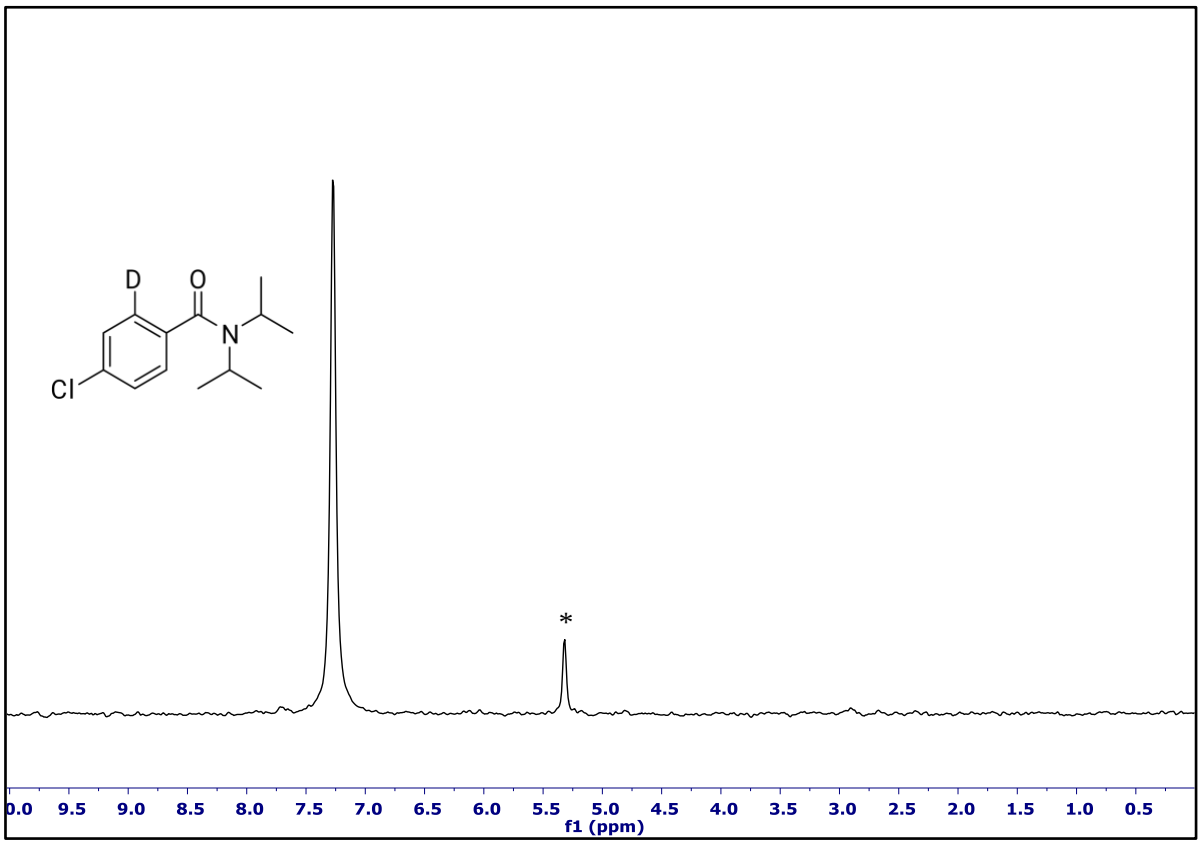
^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (150 MHz, $CDCl_3$)



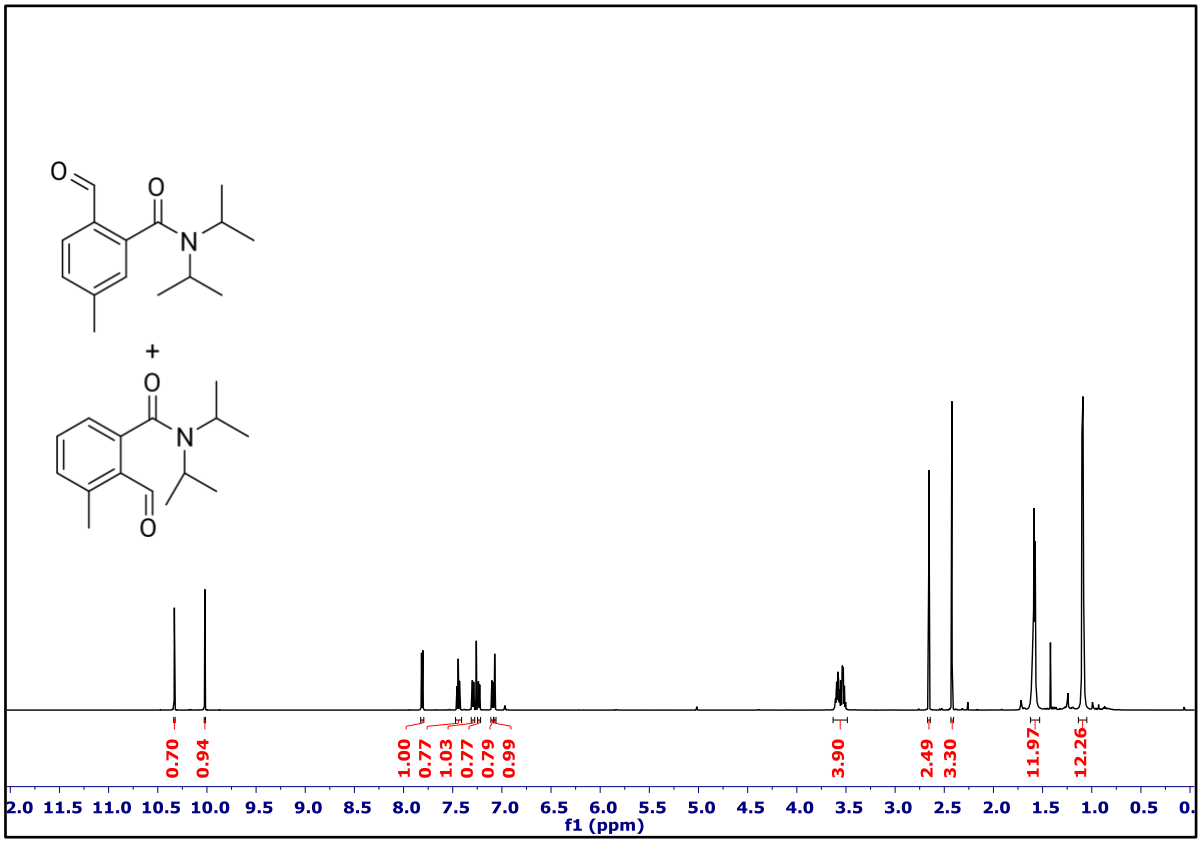
^{2}H NMR (92.07 MHz, CH_2Cl_2)



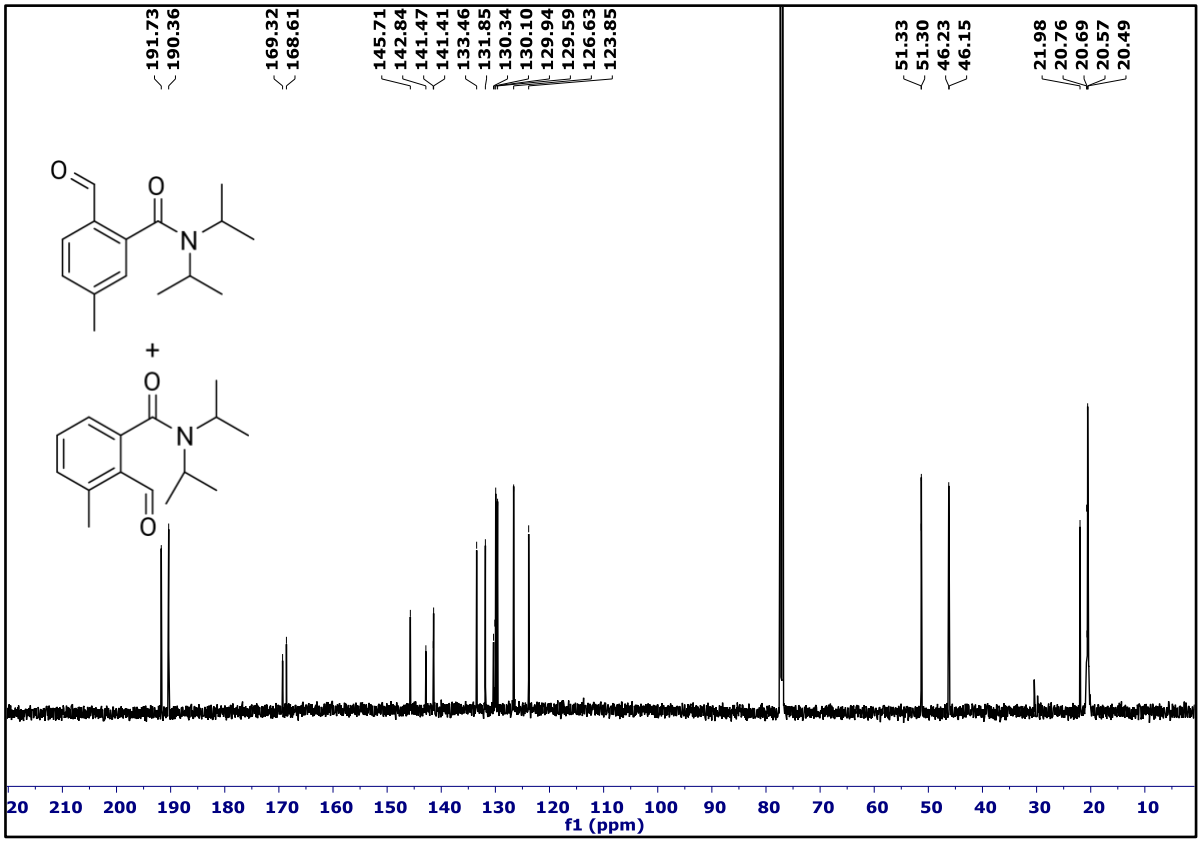
* residual solvent peak

2-Formyl-*N*,*N*-diisopropyl-3-methylbenzamide (2j) and **2-formyl-*N*,*N*-diisopropyl-5-methylbenzamide (2k)**

^{1}H NMR (600 MHz, $CDCl_3$)

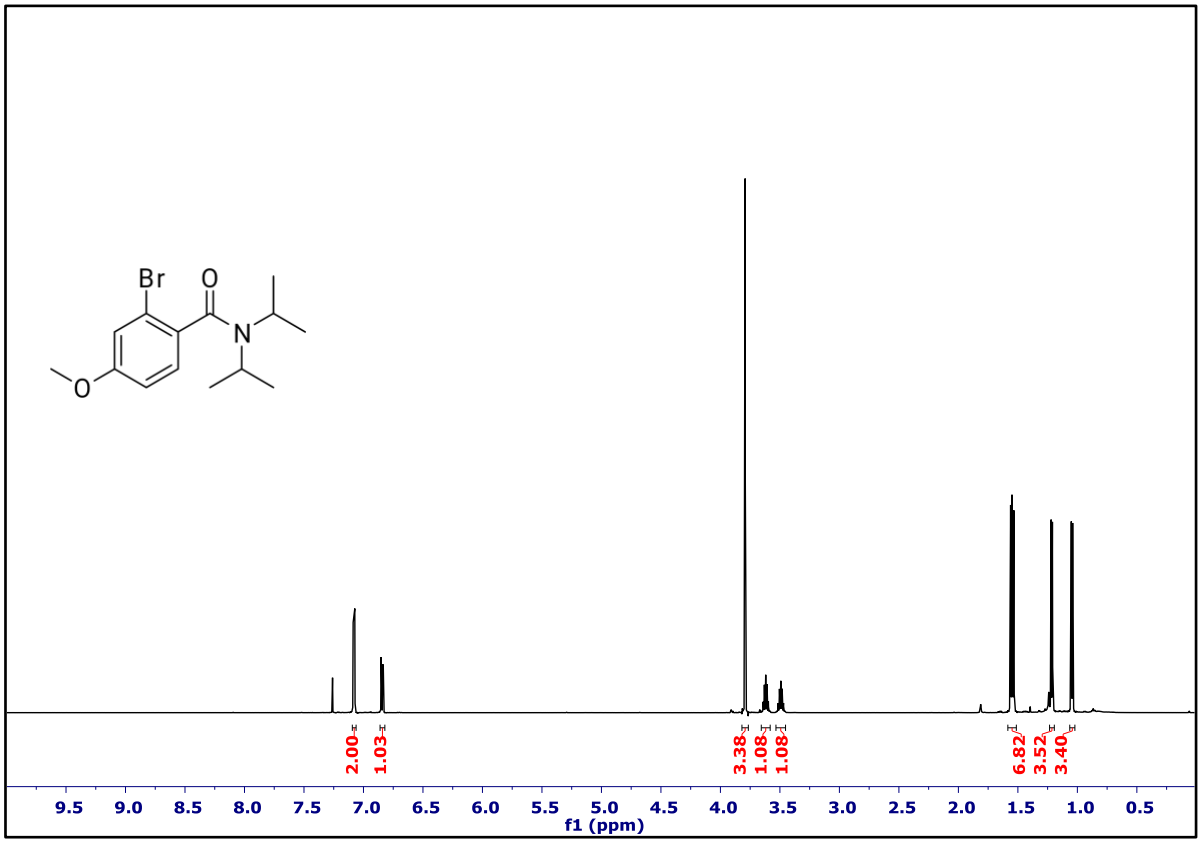


^{13}C NMR (150 MHz, $CDCl_3$)

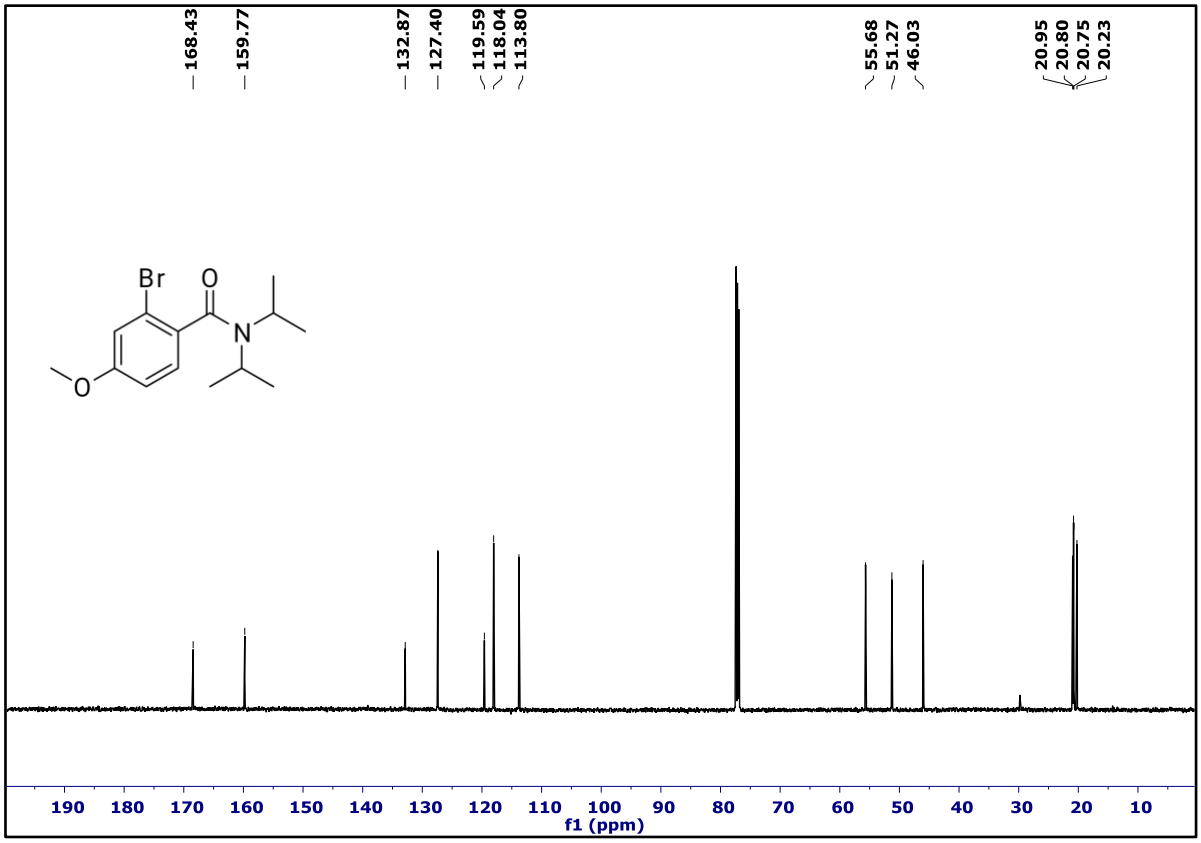


2-Bromo-*N*,*N*-diisopropyl-4-methoxybenzamide (2l)

^{1}H NMR (600 MHz, $CDCl_3$)

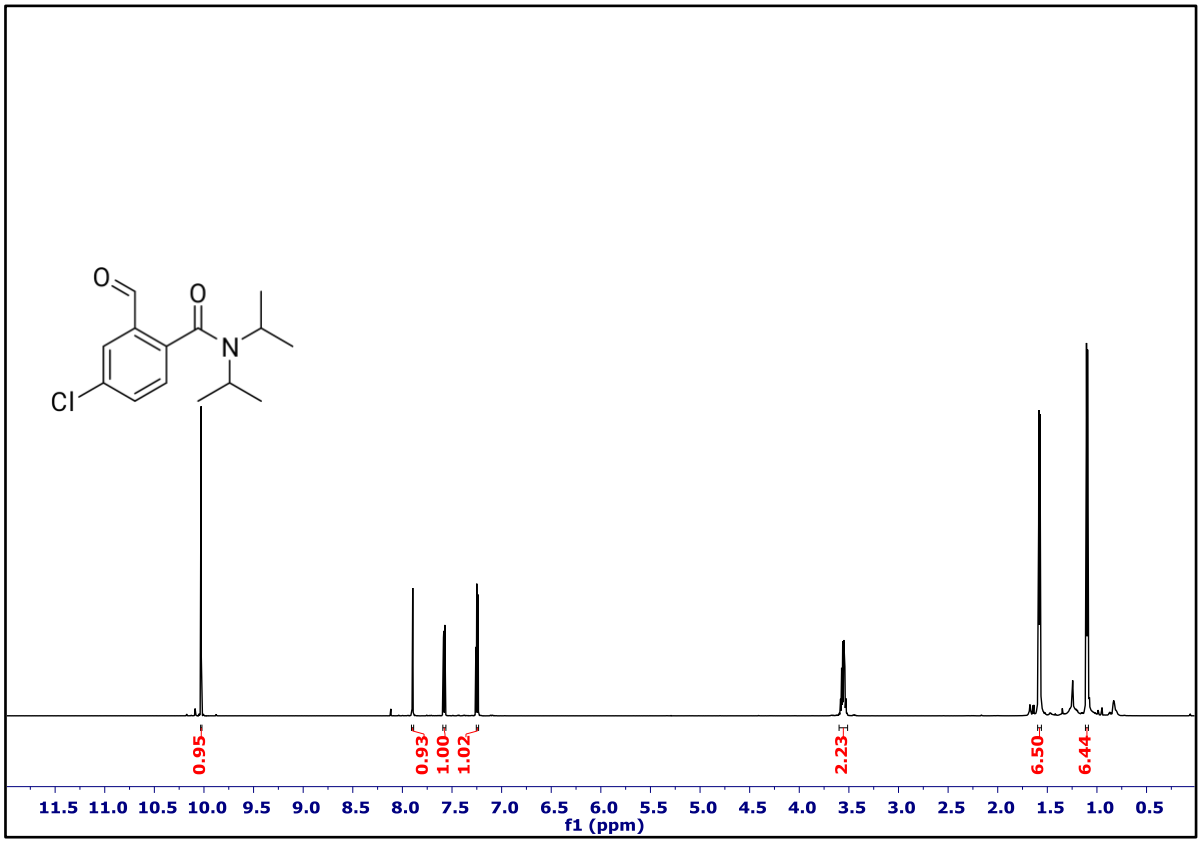


^{13}C NMR (150 MHz, $CDCl_3$)

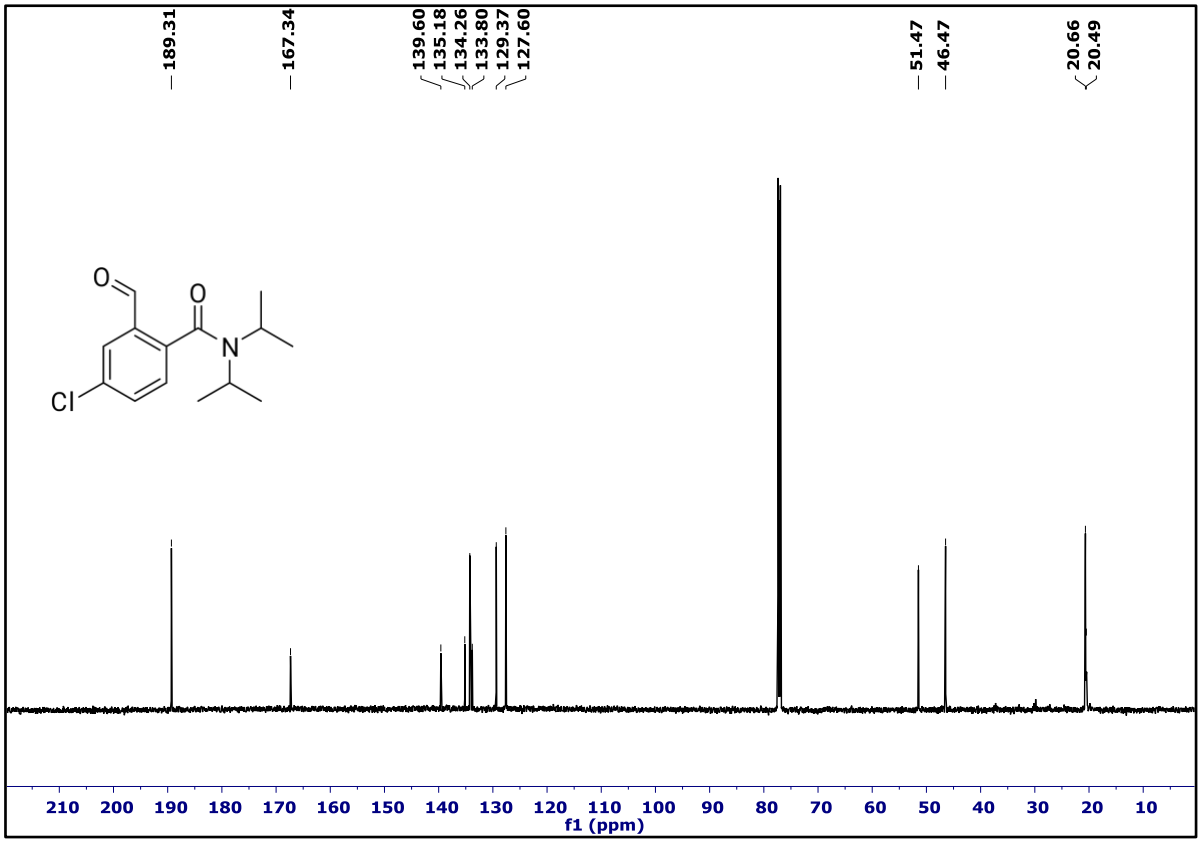


4-Chloro-2-formyl-*N*,*N*-diisopropylbenzamide (2m)

^{1}H NMR (600 MHz, $CDCl_3$)

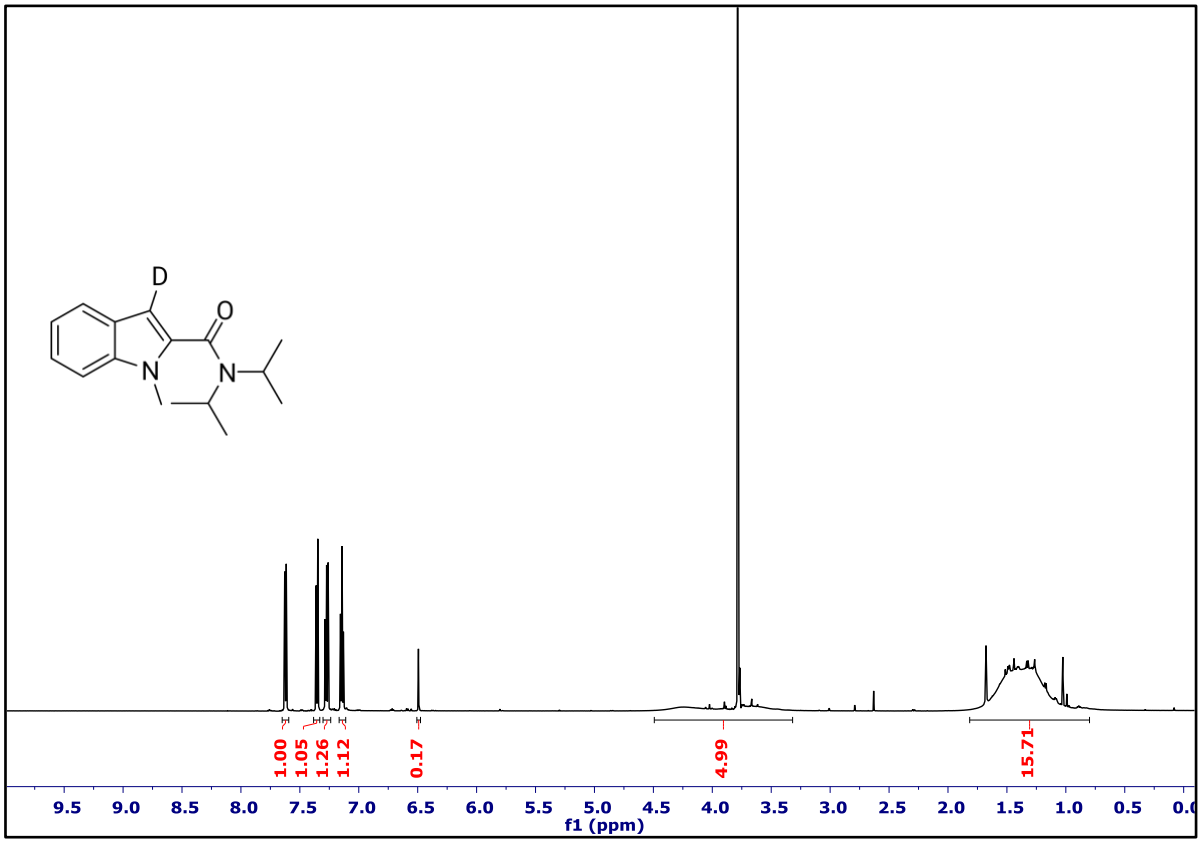


^{13}C NMR (150 MHz, $CDCl_3$)

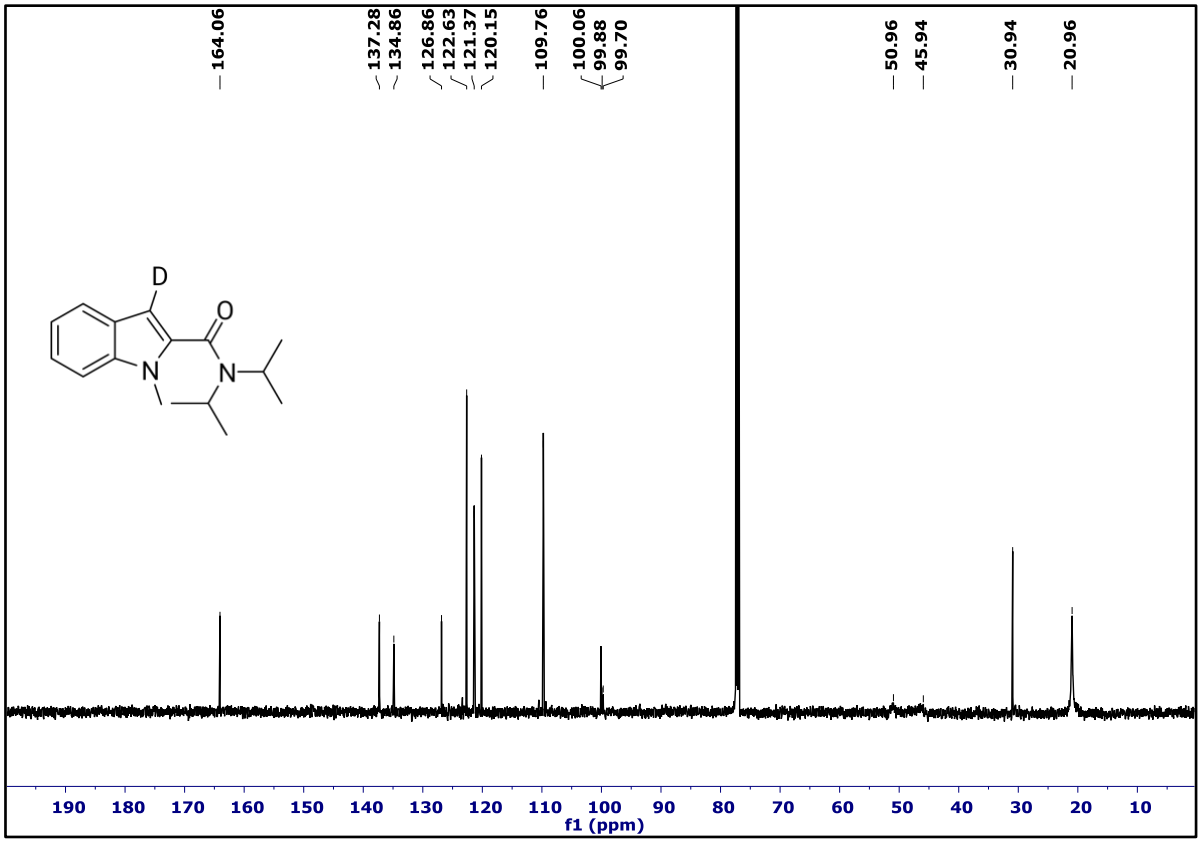


3-Deuterio-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (1e-D)

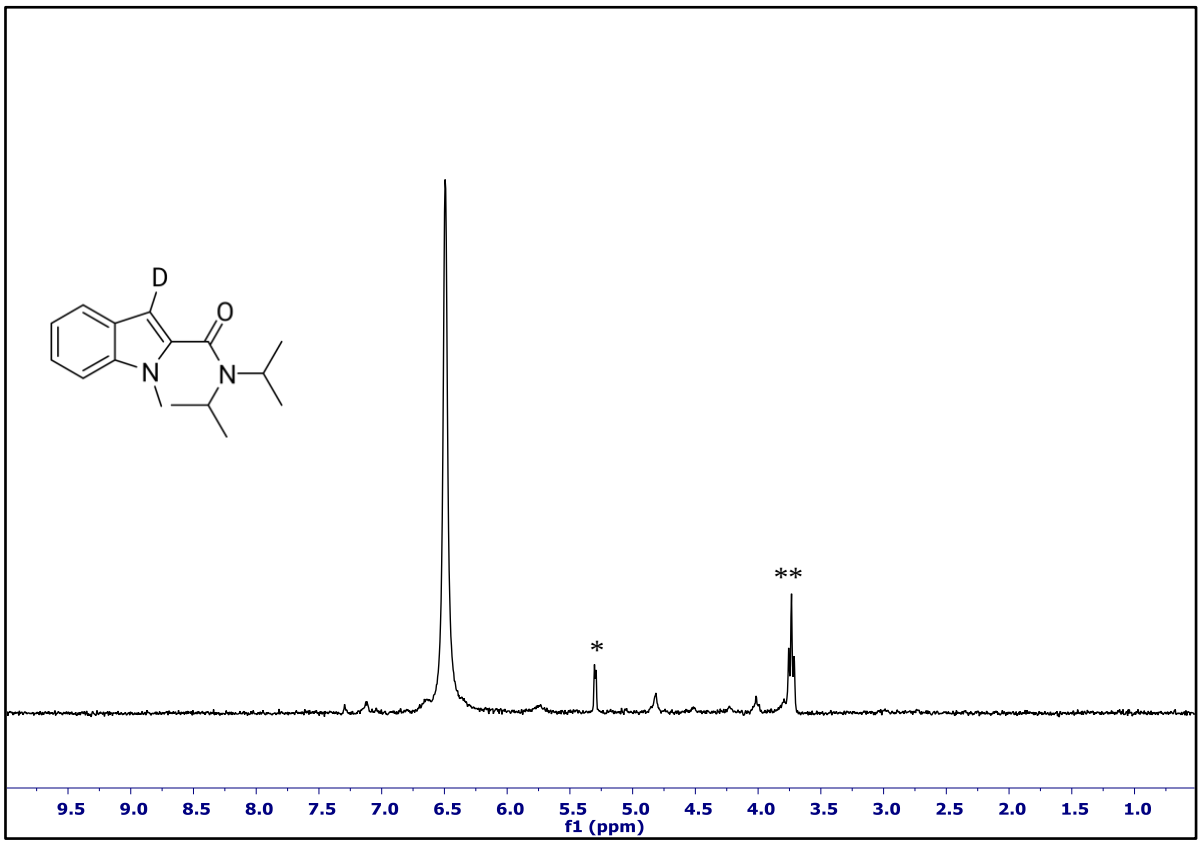
^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (150 MHz, $CDCl_3$)



^{2}H NMR (92.07 MHz, CH_2Cl_2)

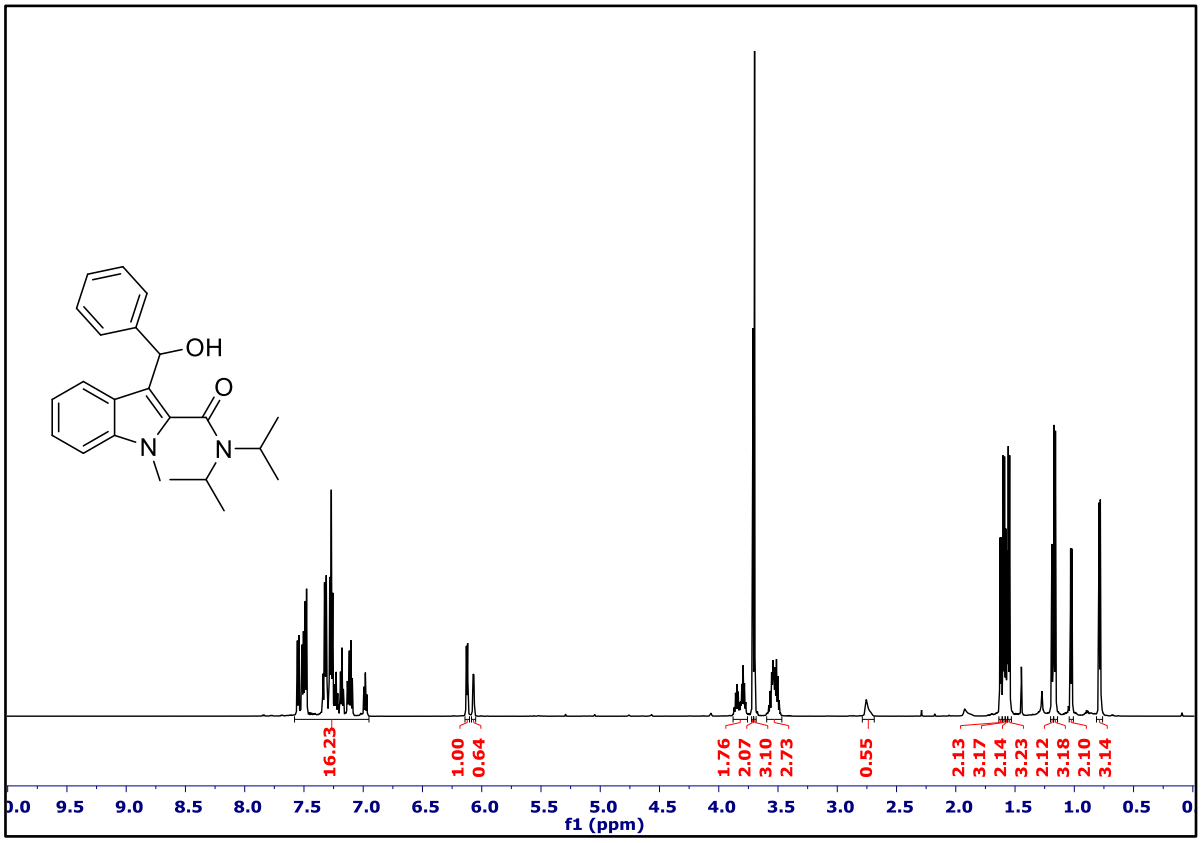


* residual solvent peak

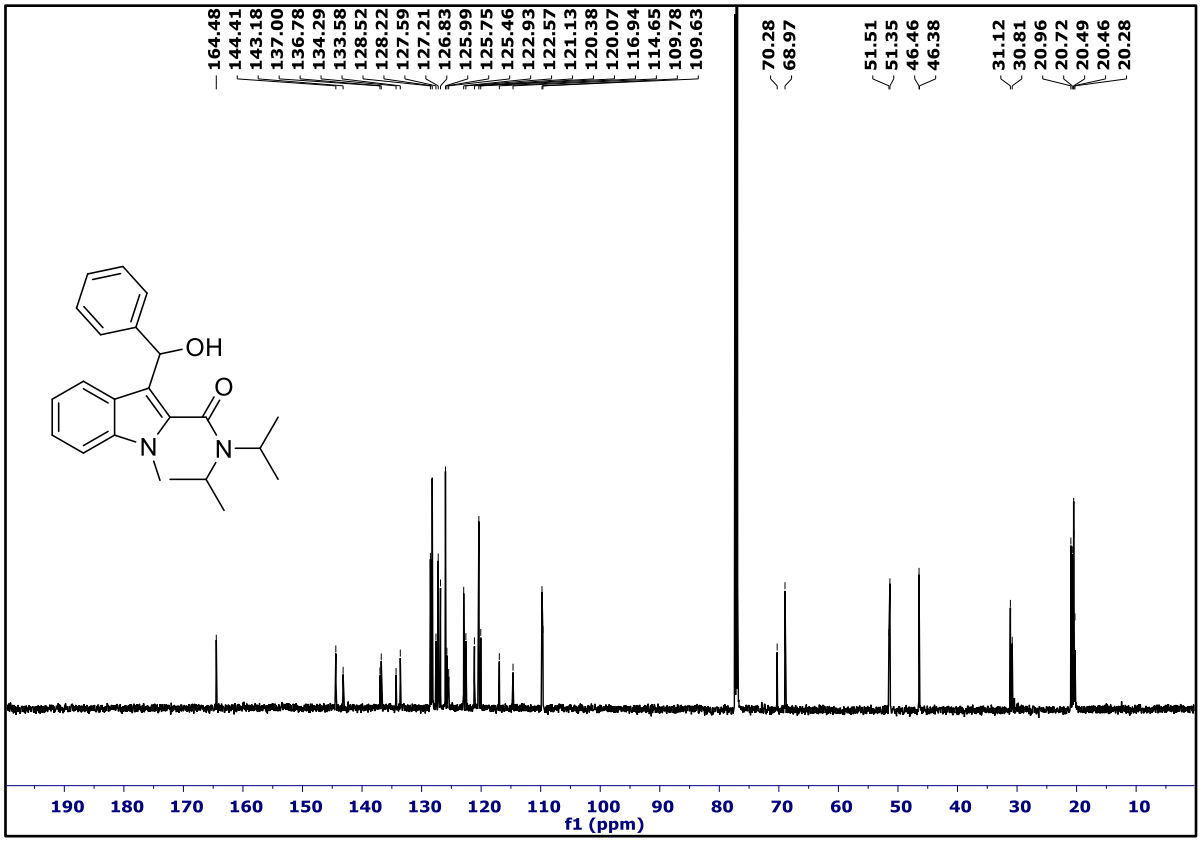
** *N*-CH_2D peak

3-(Hydroxy(phenyl)methyl)-*N*,*N*-diisopropyl-1-methyl-1*H*-indole-2-carboxamide (2n)

^{1}H NMR (600 MHz, $CDCl_3$)



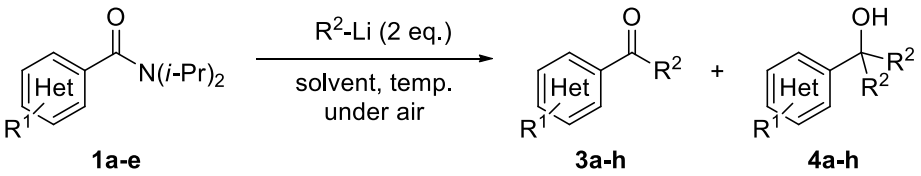
^{13}C NMR (150 MHz, $CDCl_3$)



Addition of organolithium reagents to **1a** in different unconventional solvents

Reactions were performed under air at room temperature or at 0 °C (Table S3). In an open screw cap vial, *N*,*N*-diisopropylcarboxamides **1a-e** (0.2 mmol, 1 eq.) were dissolved in the selected unconventional solvent under air and the resulting mixture was vigorously stirred for 5 min. The organolithium reagent (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was vigorously stirred for 20 s (30 s for PhLi, 60 s for MeLi) and then diluted with water. The mixture was washed twice with 1 M HCl (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent removed under reduced pressure. Conversion and **3**:**4** ratios were determined by ^1H NMR analysis of the crude reaction mixture. Ratio for **3d**:**4d** products was determined by GC(FID) analysis of reaction crude (see Table S5).

Table S3. Study of the reaction of organolithiums with *N*,*N*-diisopropylcarboxamides **1a-e** in different unconventional solvents.



1a-e **3a-h** **4a-h**

Entry	Solvent[a]	**1**	R^2	T (° C)	% conv.[b,c]	Product	**3:4** ratio[b]
1	CPME, ChCl/Gly 1:2	**1a**	*n*-Bu	25	85	**3a**	5:1
2	CPME, ChCl/urea 1:2	**1a**	*n*-Bu	25	80	**3a**	5:1
3	CPME, ChCl/H_2O 1:2	**1a**	*n*-Bu	25	50	**3a**	2:1
4	CPME, ChCl/LA 1:2	**1a**	*n*-Bu	25	-	**3a**	-
5	CPME, ChCl/Gly 1:2	**1a**	*n*-Bu	0	90 (65)	**3a**	6:1
6	CPME, ChCl/Gly 1:2	**1a**	Me[d]	0	70 (60)	**3b**	5:1
7	CPME, ChCl/Gly 1:2	**1a**	*n*-Hex	0	87 (69)	**3c**	5:1
8	CPME, ChCl/Gly 1:2	**1a**	Ph[e]	0	89 (70)	**3d**	6:1
9	CPME, ChCl/Gly 1:2	**1b**	*n*-Bu	0	70 (50)	**3e**	6:1
10	CPME, ChCl/Gly 1:2	**1c**	*n*-Bu	0	78 (56)	**3f**	4:1
11	CPME, ChCl/Gly 1:2	**1d**	*n*-Bu	0	74 (50)	**3g**	5:1
12	CPME, ChCl/Gly 1:2	**1e**	*n*-Bu	0	90 (60)	**3h**	7:1
13	CPME, ChCl/Gly 1:2	**1a**	*t*-Bu	0	0	-	-
14	CPME, ChCl/Gly 1:2	**1a**	*sec*-Bu	0	0	-	-
15	ChCl/Gly 1:2	**1a**	*n*-Bu	25	20	**3a**	1:1
16	ChCl/urea 1:2	**1a**	*n*-Bu	25	12	**3a**	1:1
17	ChCl/H_2O 1:2	**1a**	*n*-Bu	25	18	**3a**	1:1
18	ChCl/LA 1:2	**1a**	*n*-Bu	25	-	**3a**	-
19	CPME, ChCl/urea 1:2	**1a**	*n*-Bu	0	85	**3a**	5:1
20	CPME	**1a**	*n*-Bu	0	100	**3a**	3:1
21	Gly	**1a**	*n*-Bu	25	24	**3a**	1:1
22	CPME, ChCl/Gly 1:2[f]	**1a**	*n*-Bu	0	60	**3a**	3:1

[a] Conditions: **1a-e** (0.2 mmol), CPME (0.2 mL), DES or solvent (1 g). Reaction time of 20 s unless otherwise stated. Commercially available solutions of *n*-BuLi (2.5 M in hexane), PhLi (1.8 M in dibutyl ether), *n*-HexLi (2.3 M in hexane), MeLi (1.6 M in diethyl ether), *sec*-BuLi (1.4 M in cyclohexane), *t*-BuLi (1.7 M in pentane) were used (2 eq.). [b] Conversion and ratios were determined by GC analysis and/or ^{1}H NMR spectroscopy. [c] In brackets, isolated yield of ketone **3** after flash column chromatography. [d] Reaction time of 60 s. [e] Reaction time of 30 s. [f] 'normal stirring'

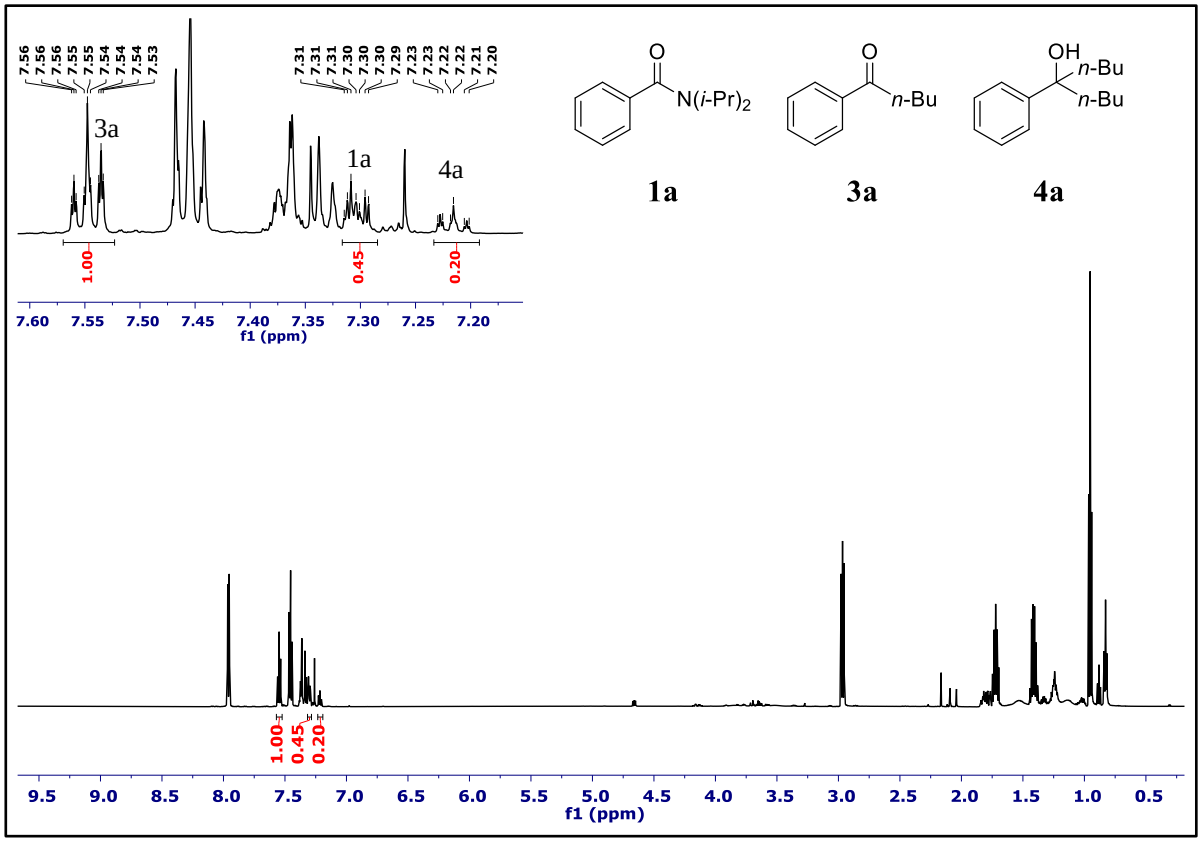


Figure S17 – Table S3 entry 1**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) – *ChCl/Gly 1:2* (1 g). Room temperature. Conversion 85%; **3a**/**4a** ratio 5/1

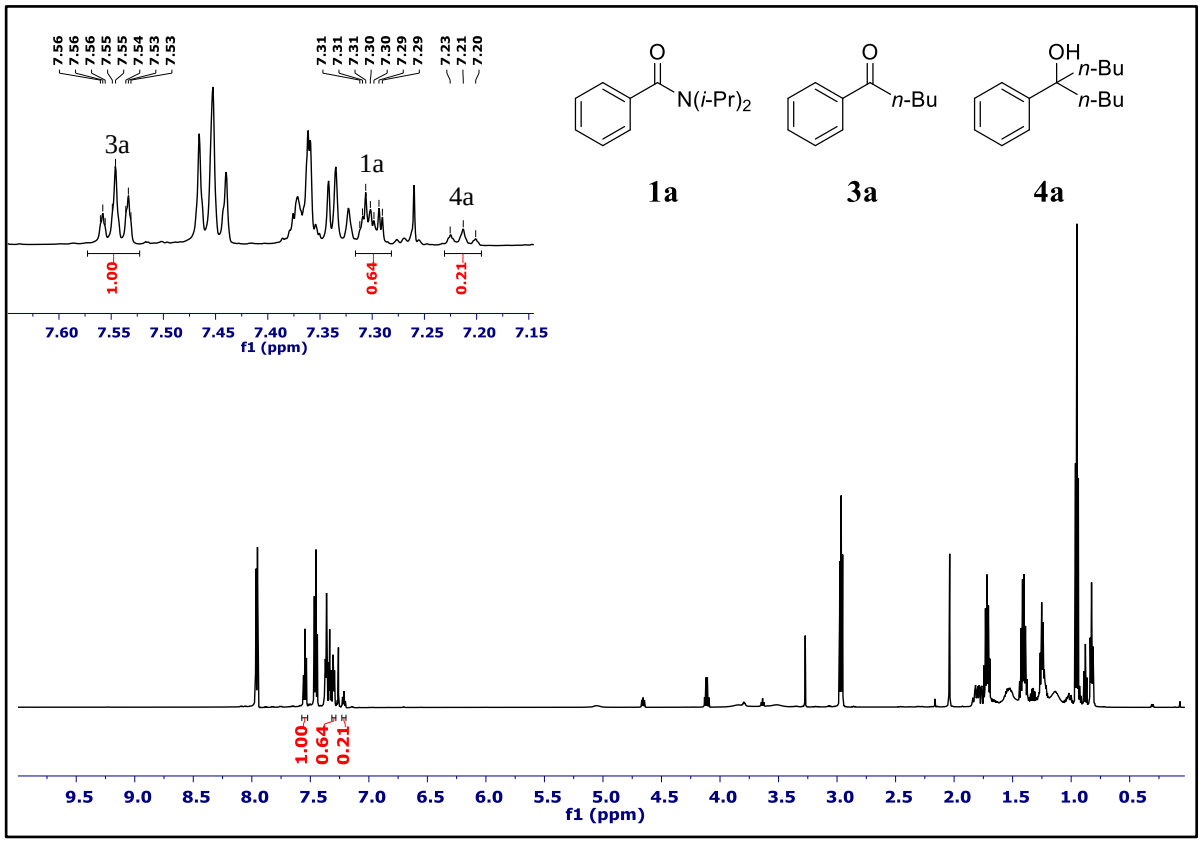


Figure S18 – Table S3 entry 2**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) – *ChCl/urea 1:2* (1 g). Room temperature. Conversion 80%; **3a**/**4a** ratio 5/1

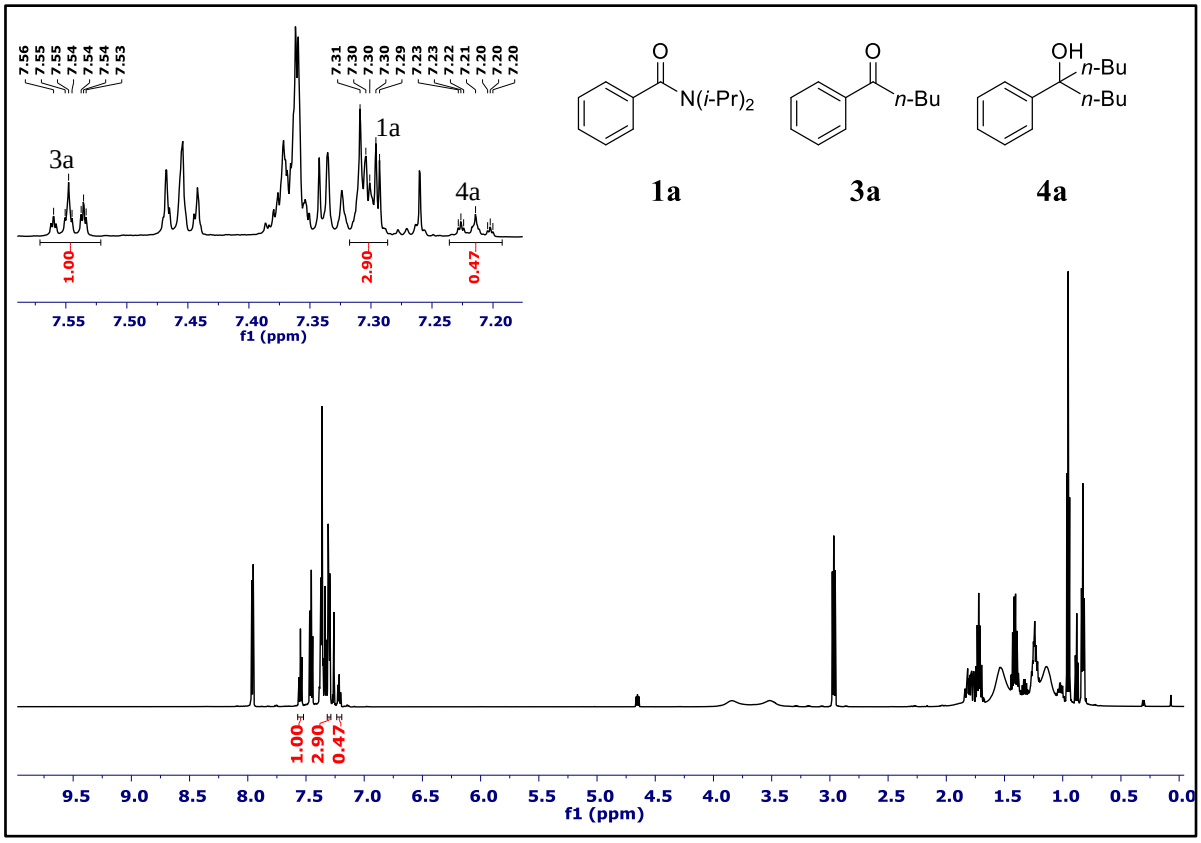


Figure S19 – Table S3 entry 3**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) – *ChCl/H$_2$O 1:2* (1 g). Room temperature. Conversion 50%; **3a**/**4a** ratio 2/1

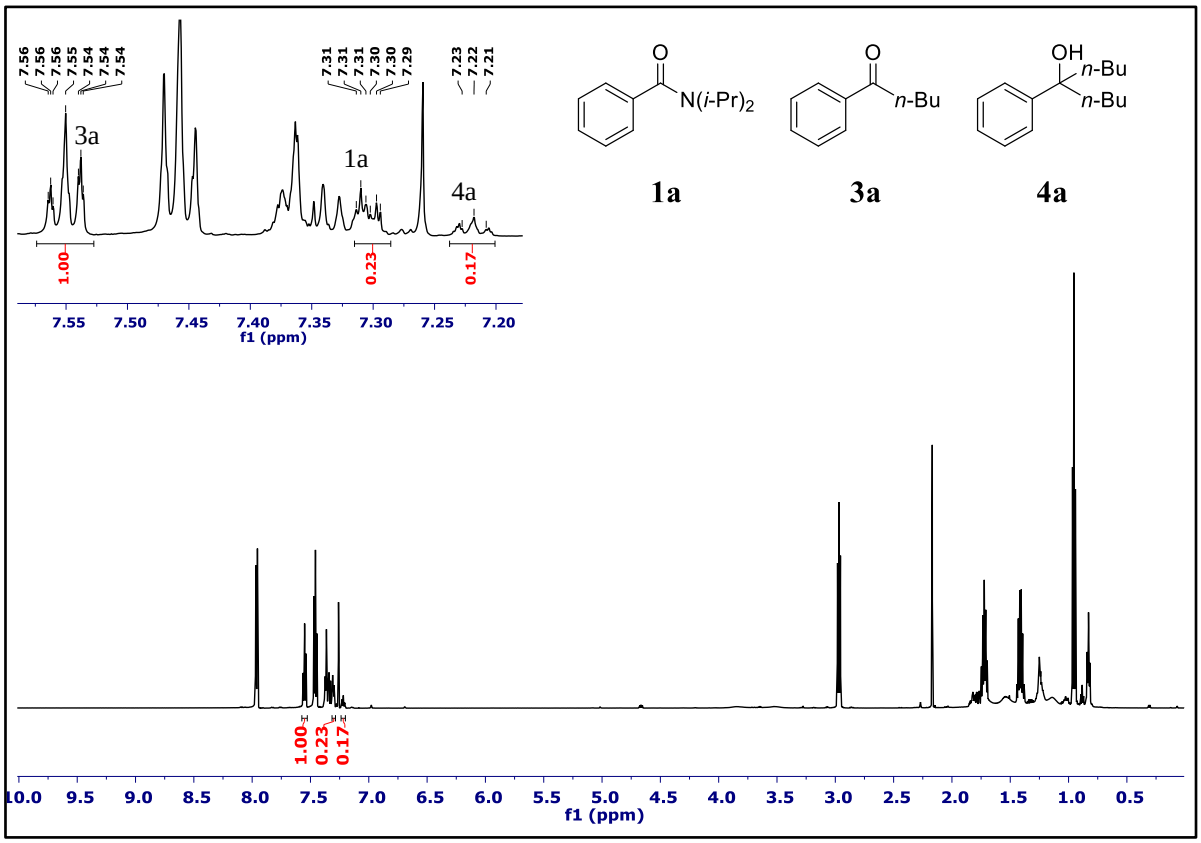


Figure S20 – Table S3 entry 5**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 90%; **3a**/**4a** ratio 6/1

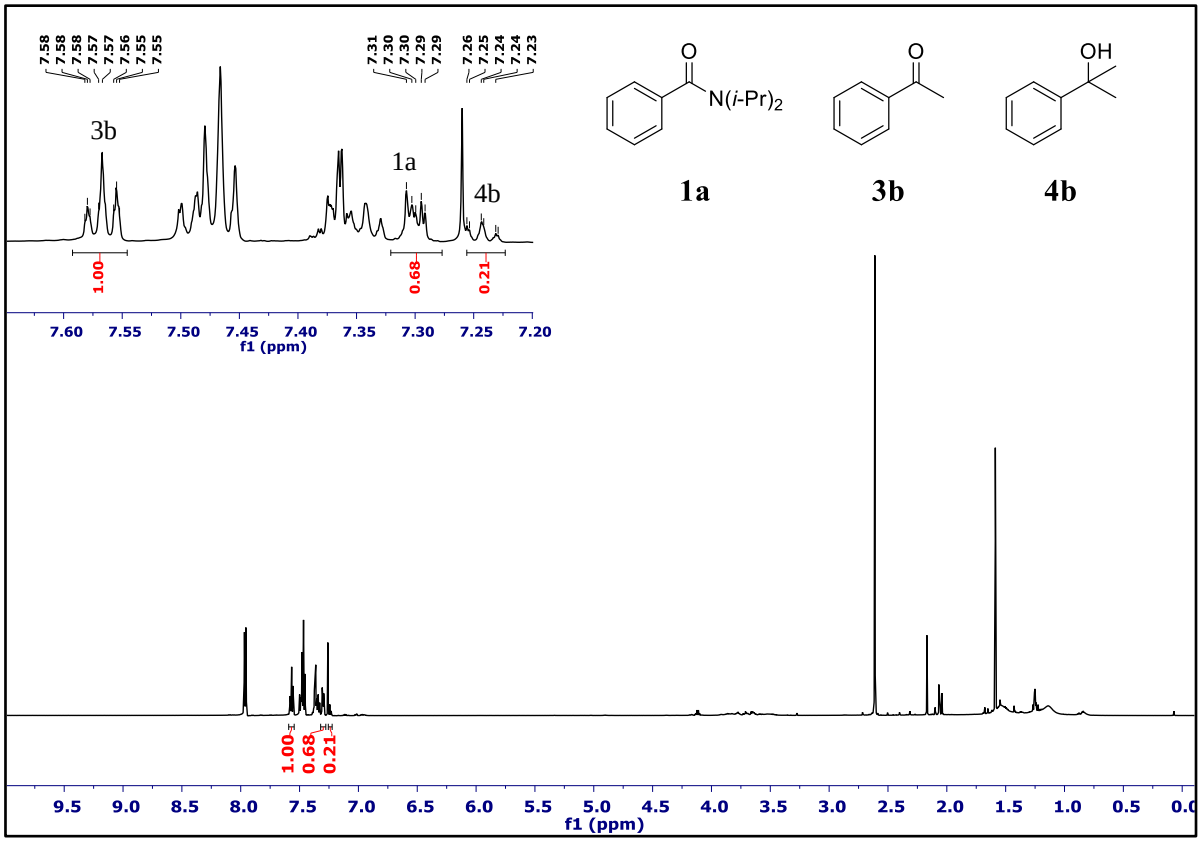


Figure S21 – Table S3 entry 6**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 70%; **3b**/**4b** ratio 5/1

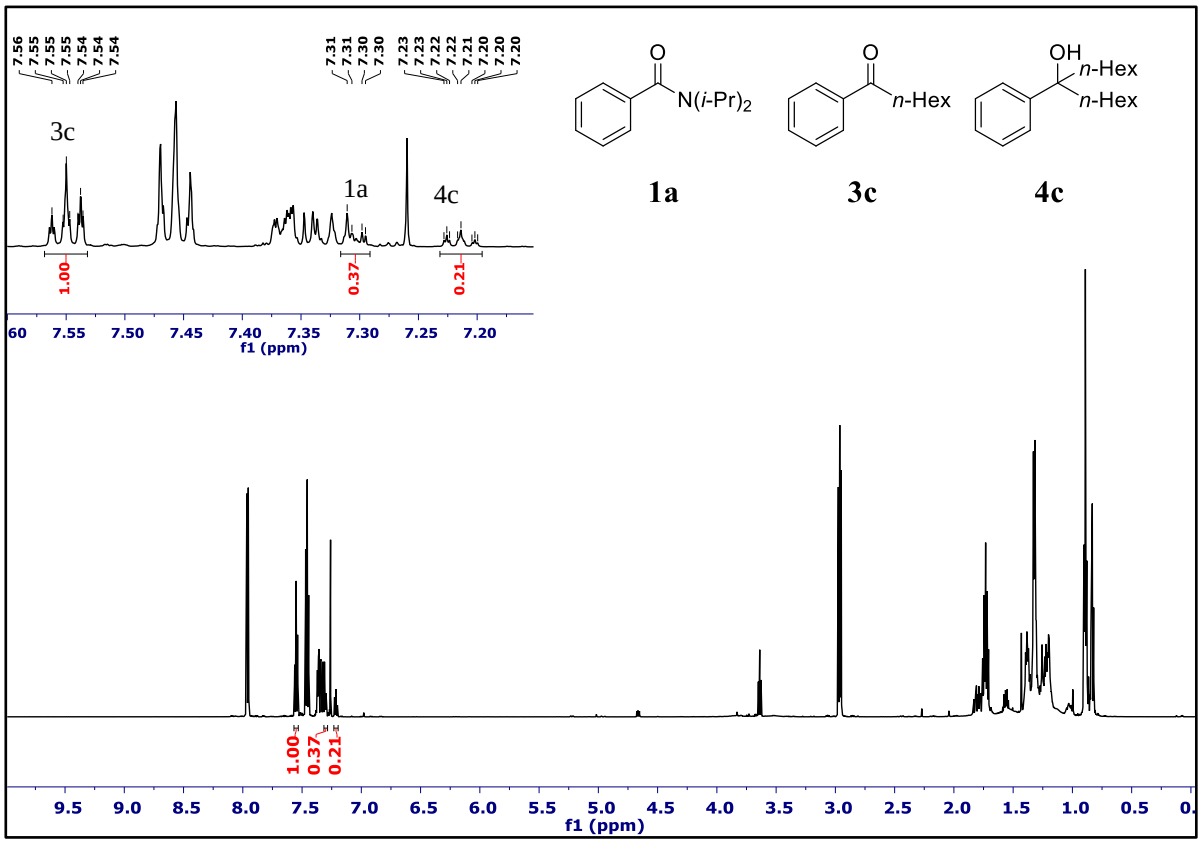


Figure S22 – Table S3 entry 7**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 87%; **3c**/**4c** ratio 5/1

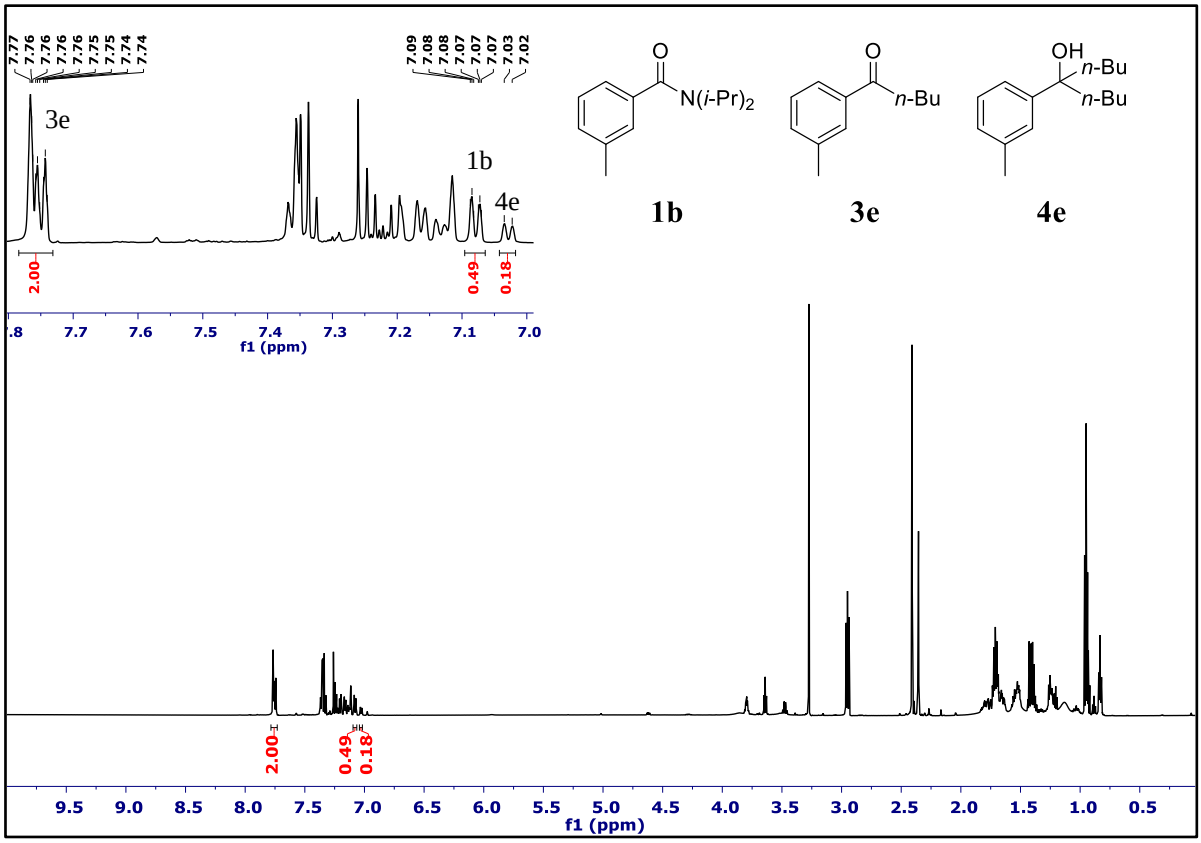


Figure S23 – Table S3 entry 9**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 70%; **3e**/**4e** ratio 6/1

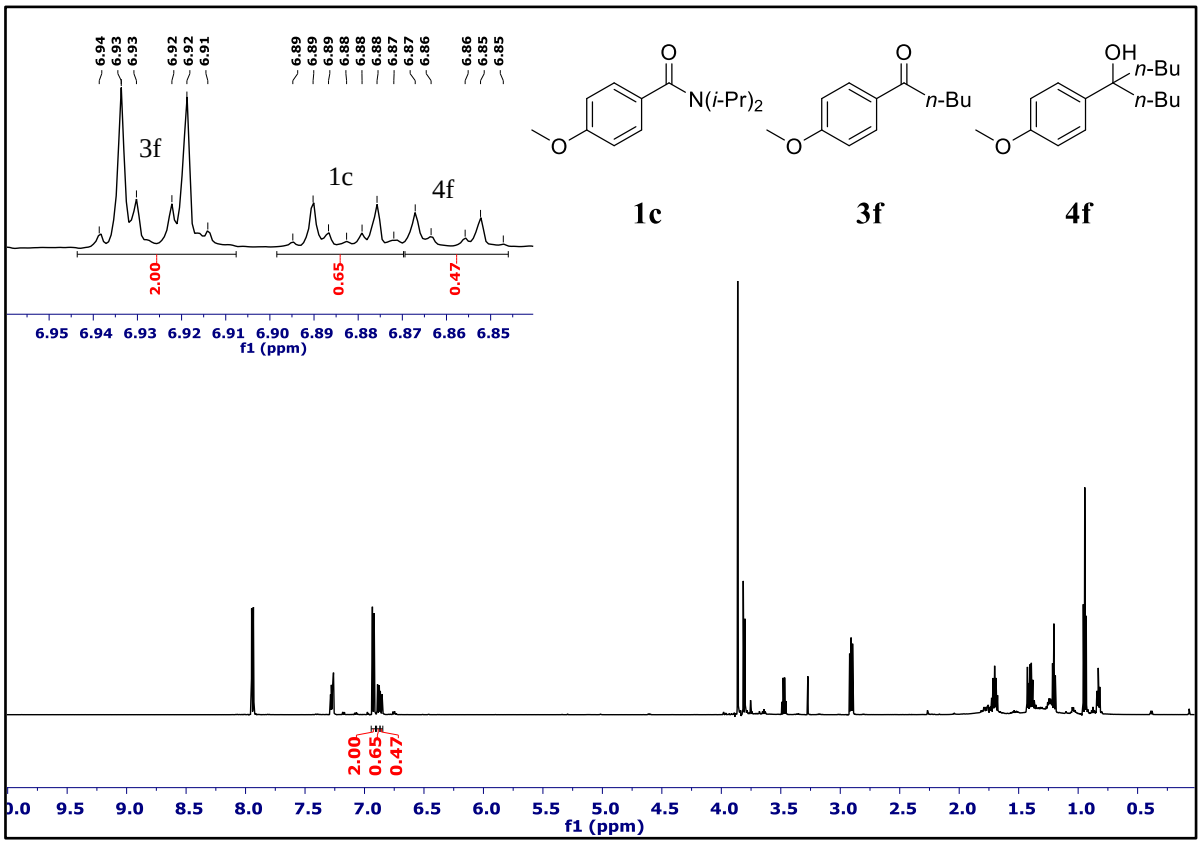


Figure S24 – Table S3 entry 10**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 78%; **3f**/**4f** ratio 4/1

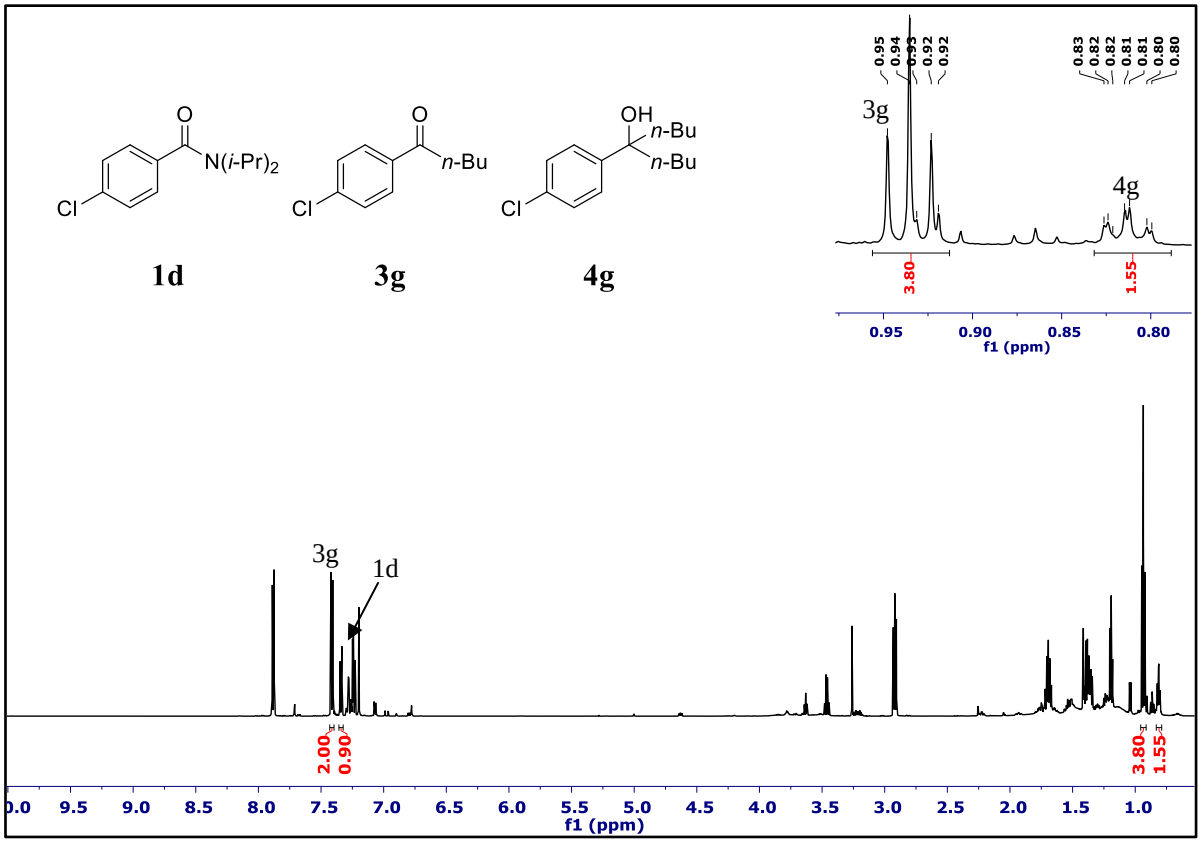


Figure S25 – Table S3 entry 11**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 74%; **3g**/**4g** ratio 5/1

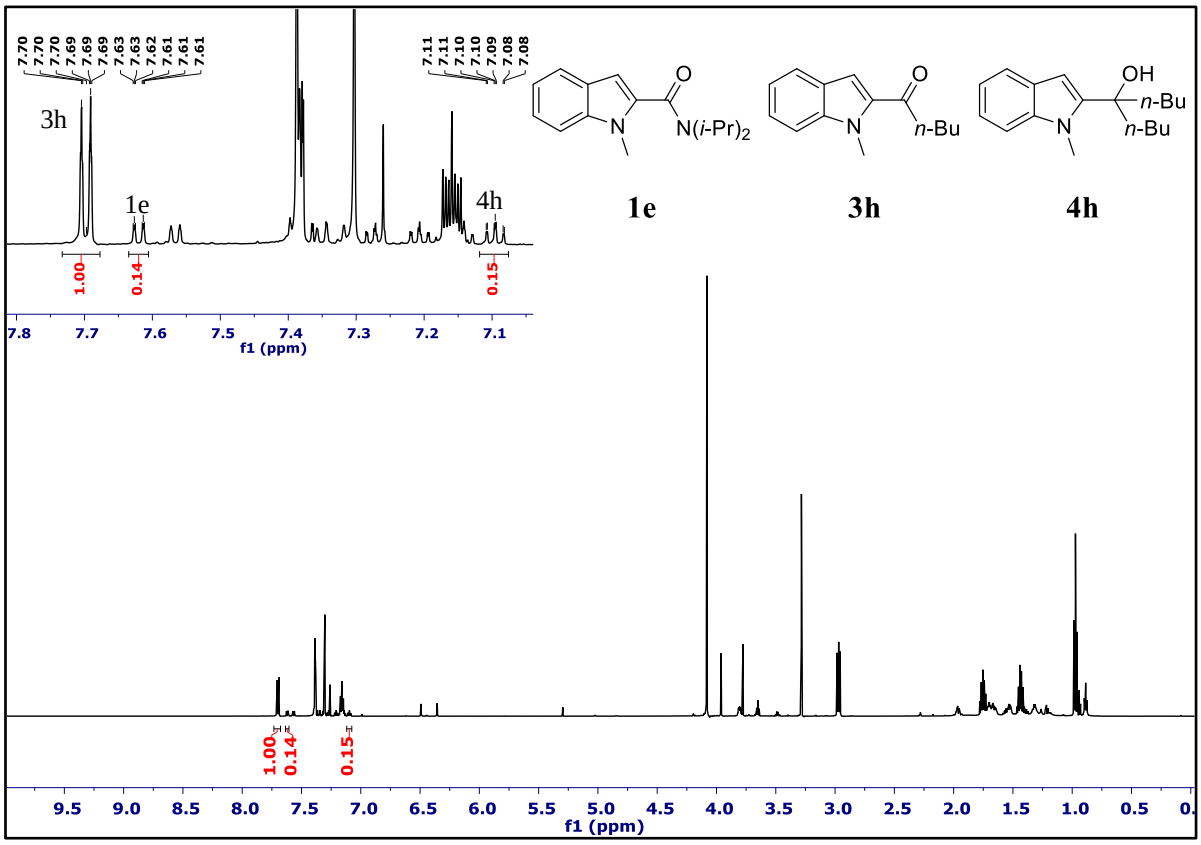


Figure S26 – Table S3 entry 12**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) - *ChCl/Gly 1:2* (1 g). 0 °C. Conversion 90%; **3h**/**4h** ratio 7/1

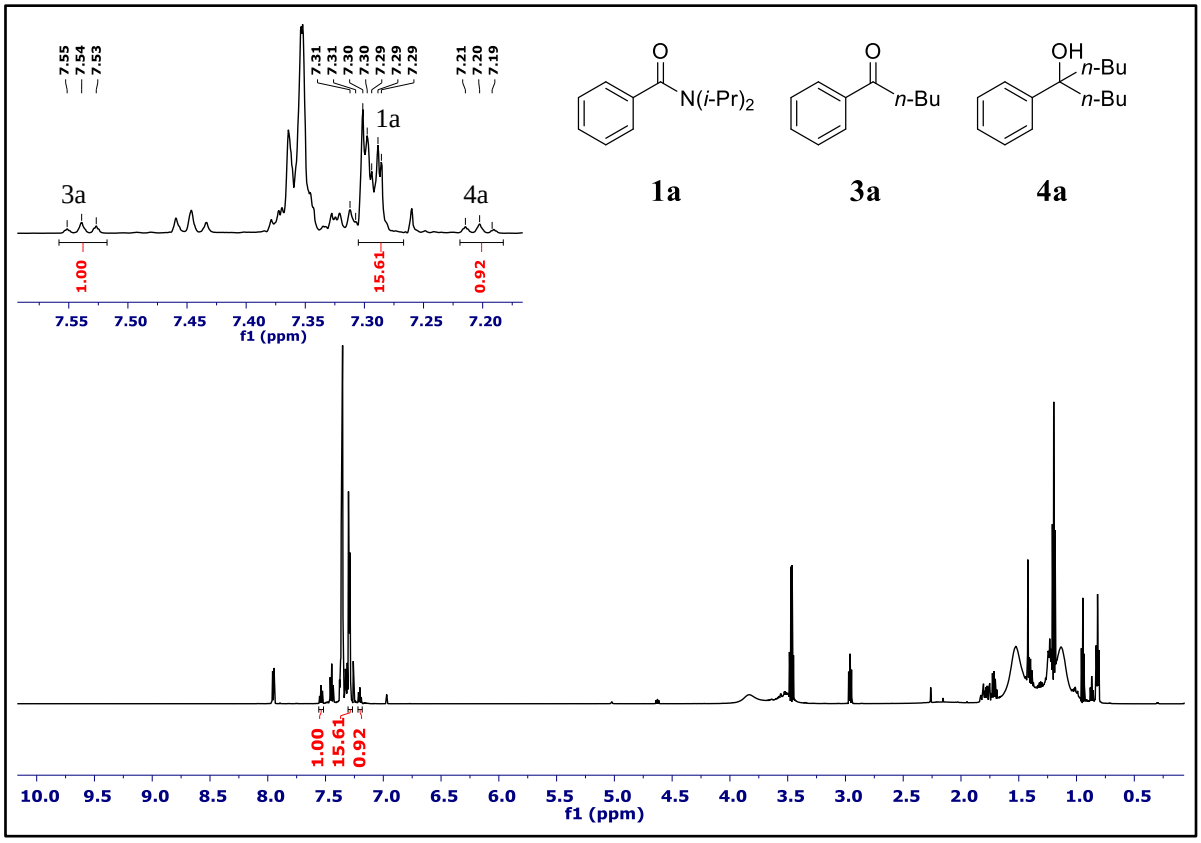


Figure S27 – Table S3 entry 15**:** crude ^{1}H NMR spectrum of the reaction performed in *ChCl/Gly 1:2* (1 g). Room temperature. Conversion 20%; **3a**/**4a** ratio 1/1

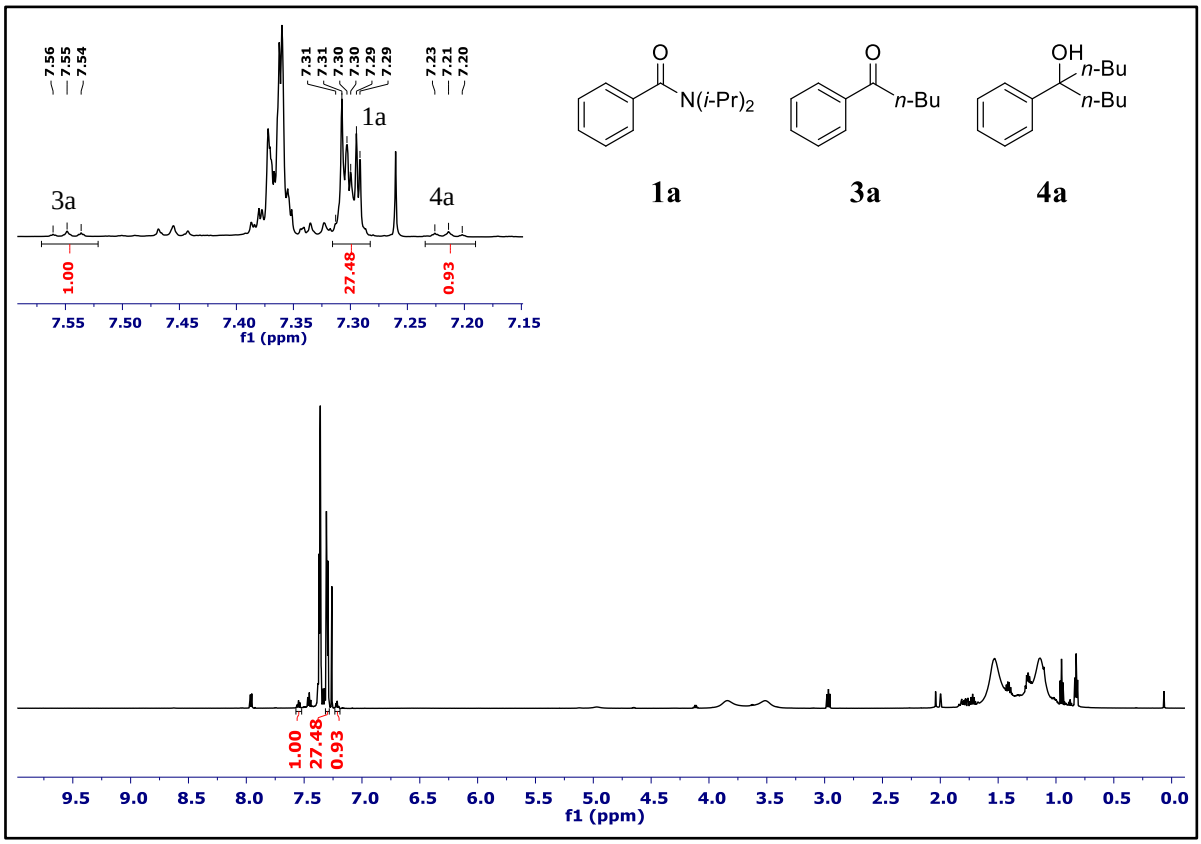


Figure S28 – Table S3 entry 16**:** crude ^{1}H NMR spectrum of the reaction performed in *ChCl/urea 1:2* (1 g). Room temperature. Conversion 12%; **3a**/**4a** ratio 1/1

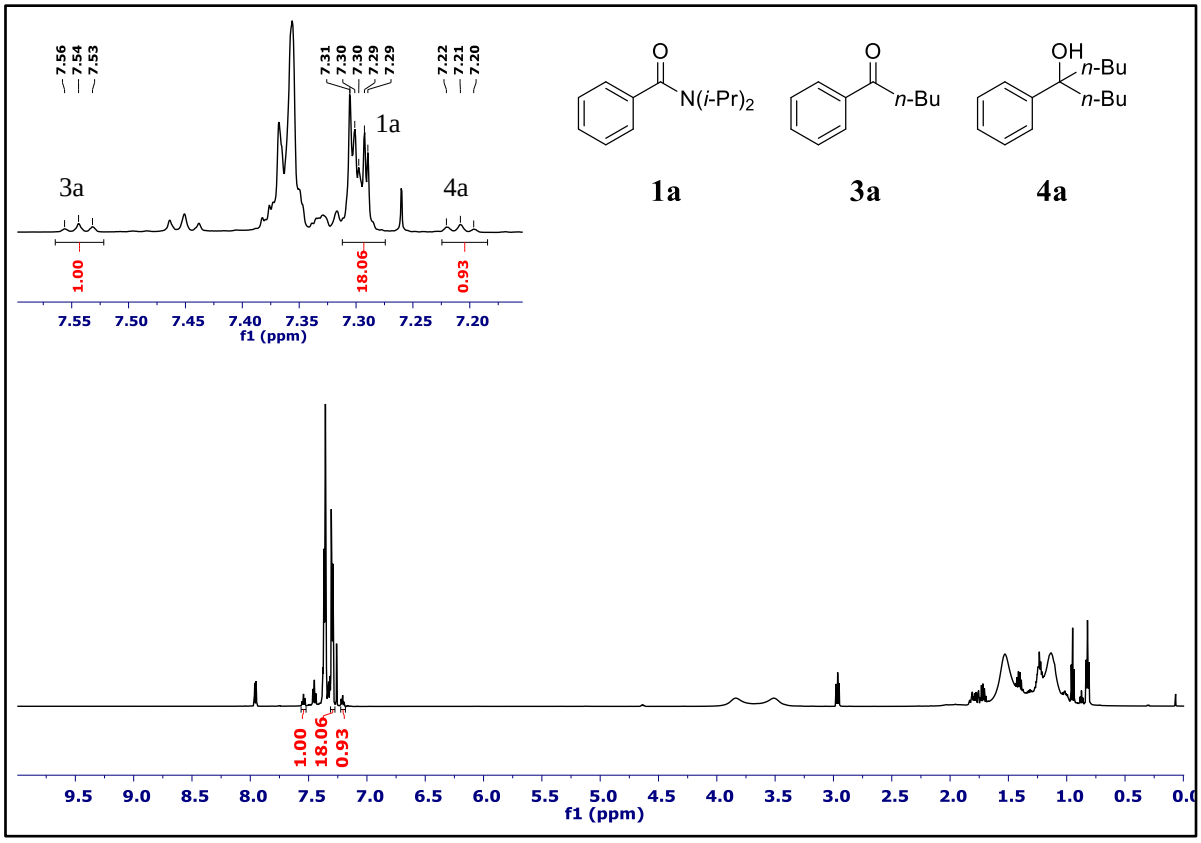


Figure S29 – Table S3 entry 17**:** crude ^{1}H NMR spectrum of the reaction performed in *ChCl/H₂O 1:2* (1 g). Room temperature. Conversion 18%; **3a**/**4a** ratio 1/1

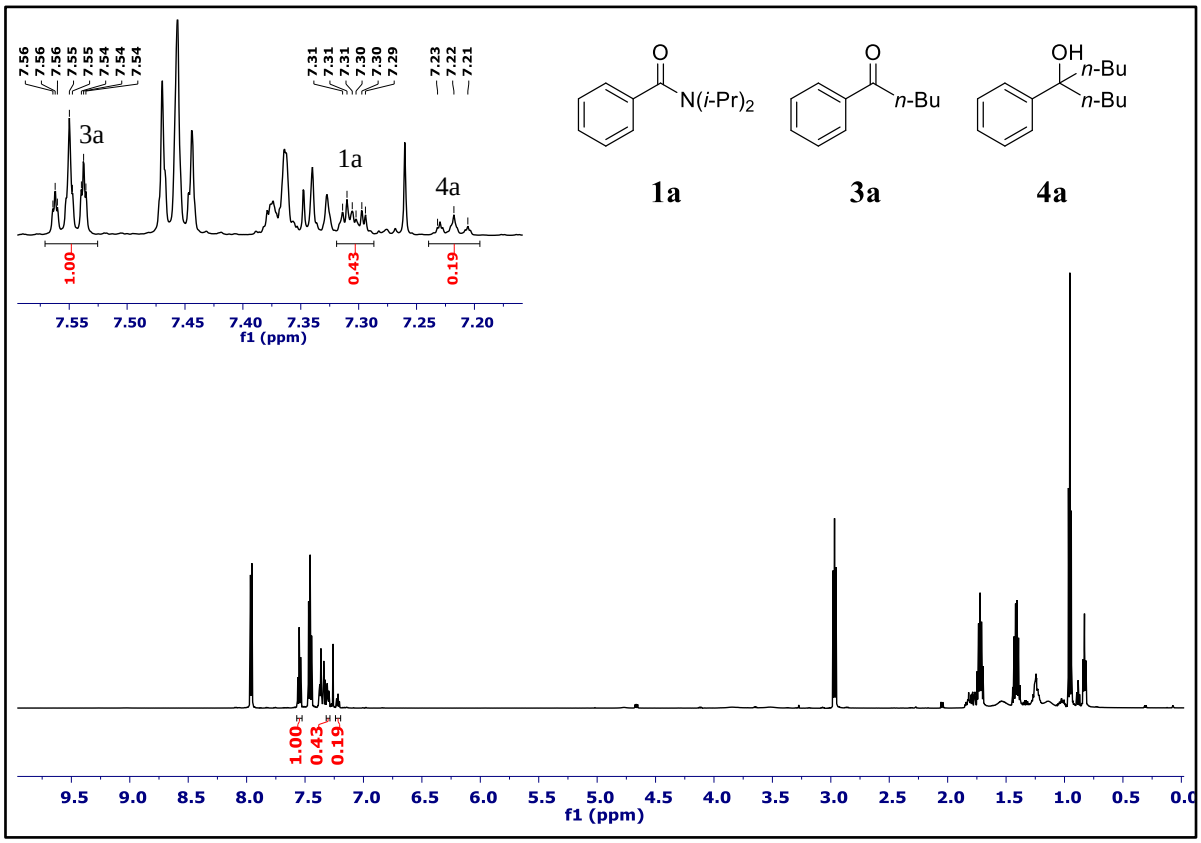


Figure S30 – Table S3 entry 19**:** crude ^{1}H NMR spectrum of the reaction performed in CMPE (0.2 mL) - *ChCl/urea 1:2* (1 g). 0 °C. Conversion 85%; **3a**/**4a** ratio 5/1

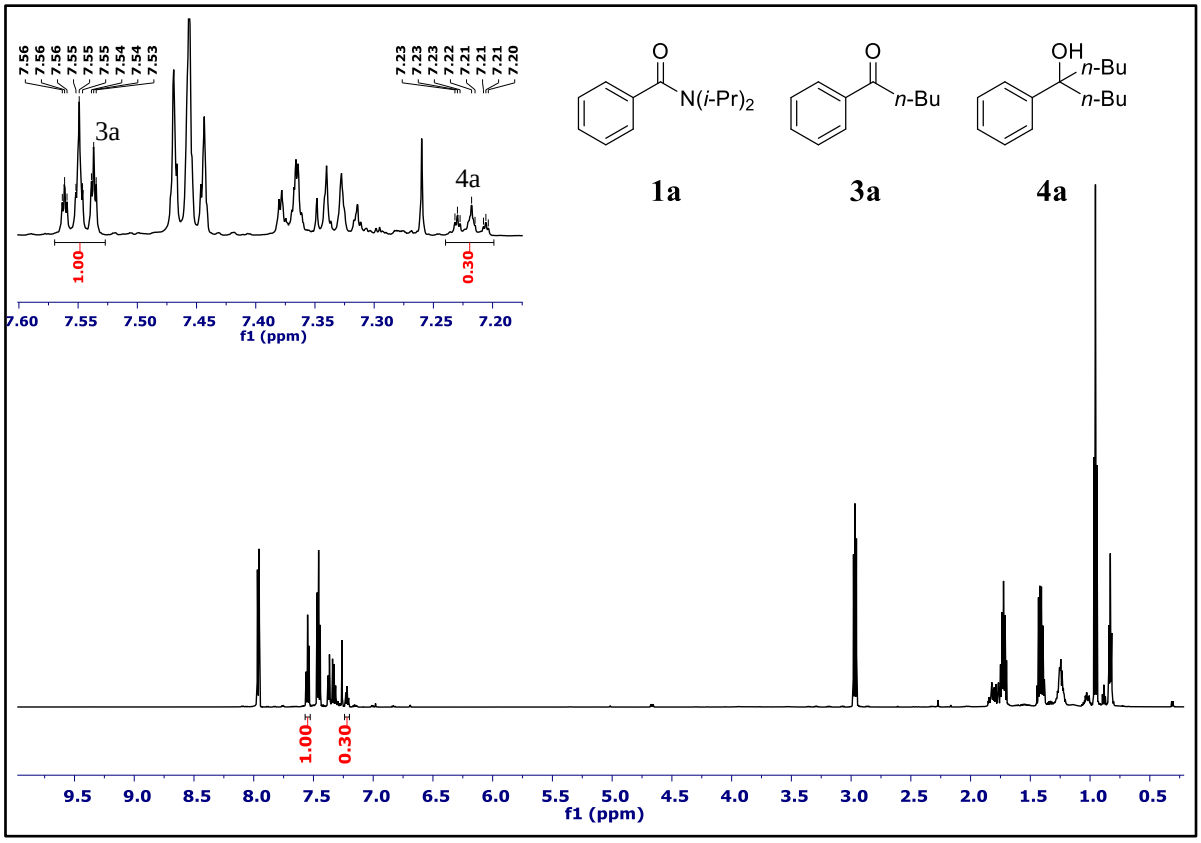


Figure S31 – Table S3 entry 20**:** crude ^{1}H NMR spectrum of the reaction performed in CMPE (1.16 mL). 0 °C. Conversion 100%; **3a**/**4a** ratio 3/1

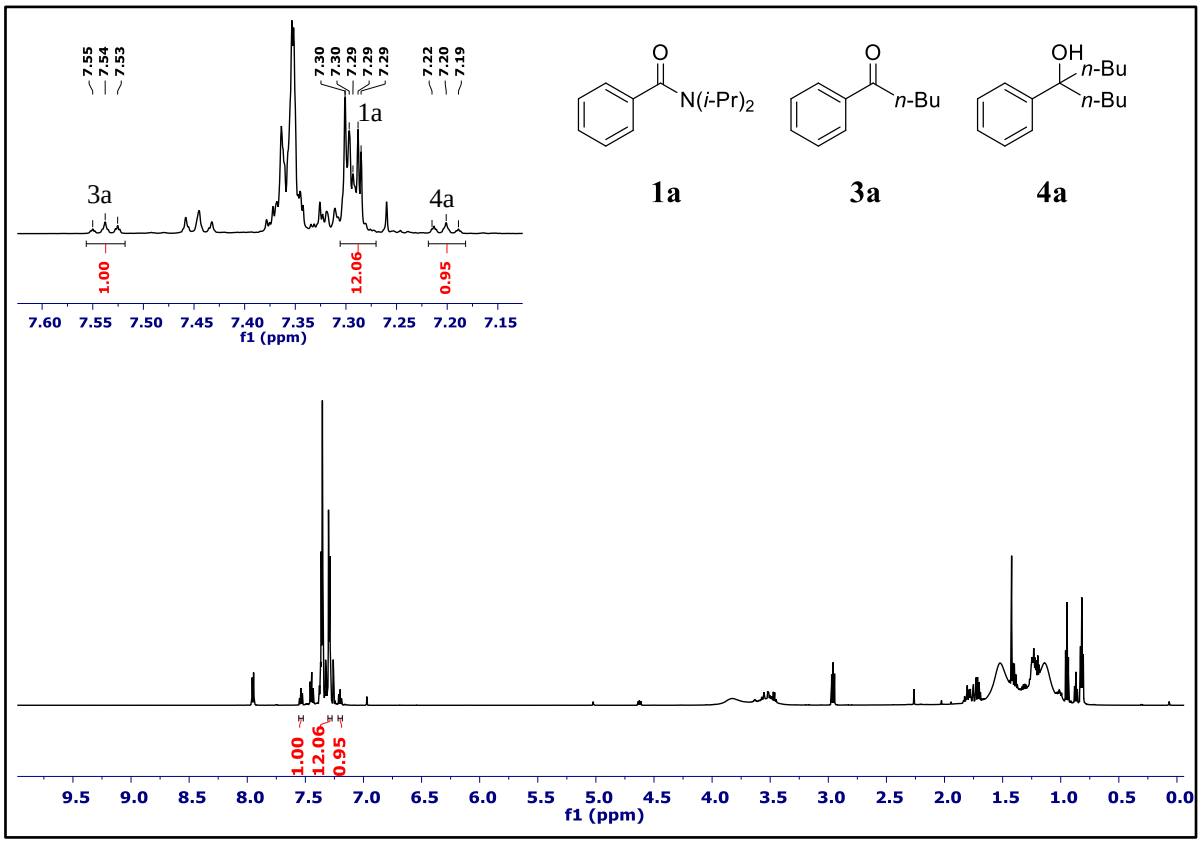


Figure S32 – Table S3 entry 21**:** crude ^{1}H NMR spectrum of the reaction performed in Gly (1 g). Room temperature. Conversion 24%; **3a**/**4a** ratio 1/1

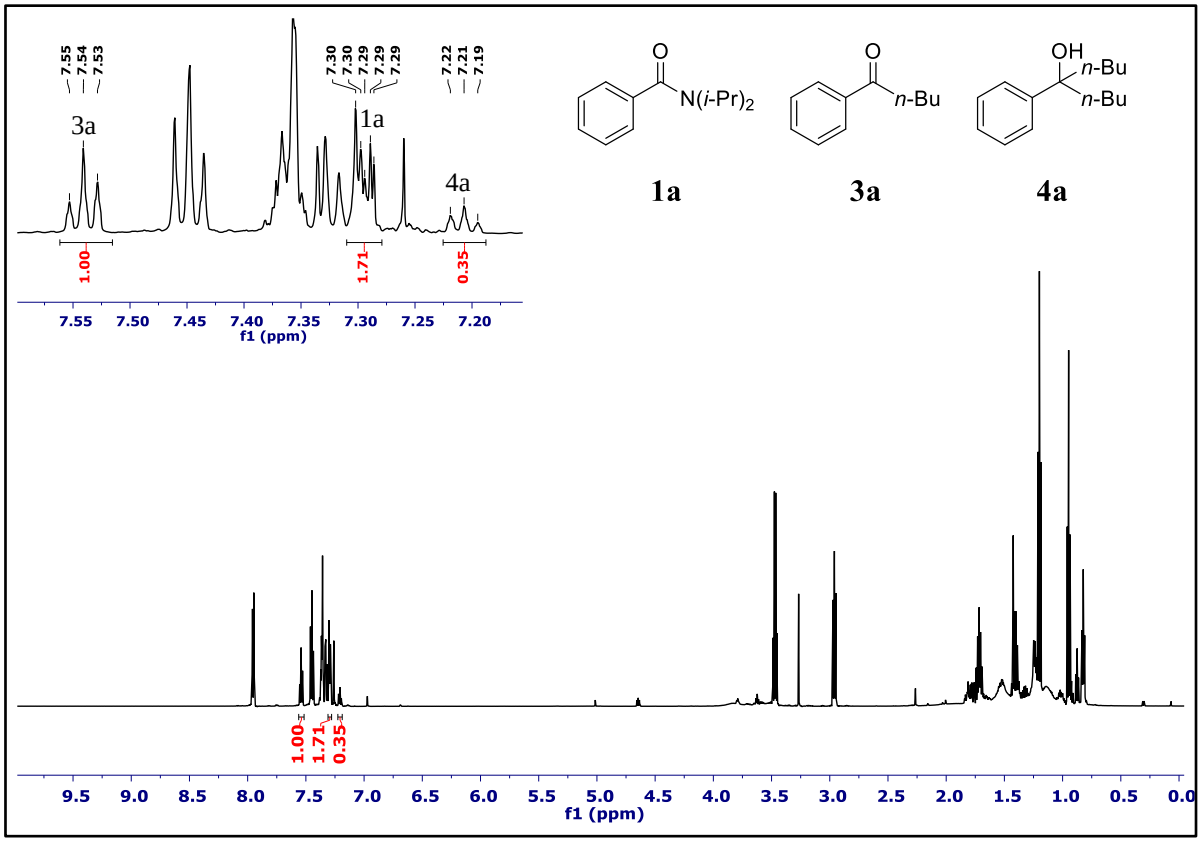


Figure S33 – Table S3 entry 22**:** crude ^{1}H NMR spectrum of the reaction performed in CPME (0.2 mL) – *ChCl/Gly 1:2* (1g). 0 °C; 'normal stirring'. Conversion 60%; **3a**/**4a** ratio 3/1

Benzophenone **3d** – triphenylmethanol **4d** ratio quantification by GC-FID

Table S4: GC-FID calibration data for benzophenone **3d** and triphenylmethanol **4d**

[**3d**] (M)	Peak area	[**4d**] (M)	Peak area
0.02	458081.35	0.005	235578.44
0.04	1099568.84	0.008	359426.36
0.05	1400833.50	0.010	467288.60
0.08	2090934.94	0.020	1162051.46
0.10	2620326.38	0.050	2588836.12

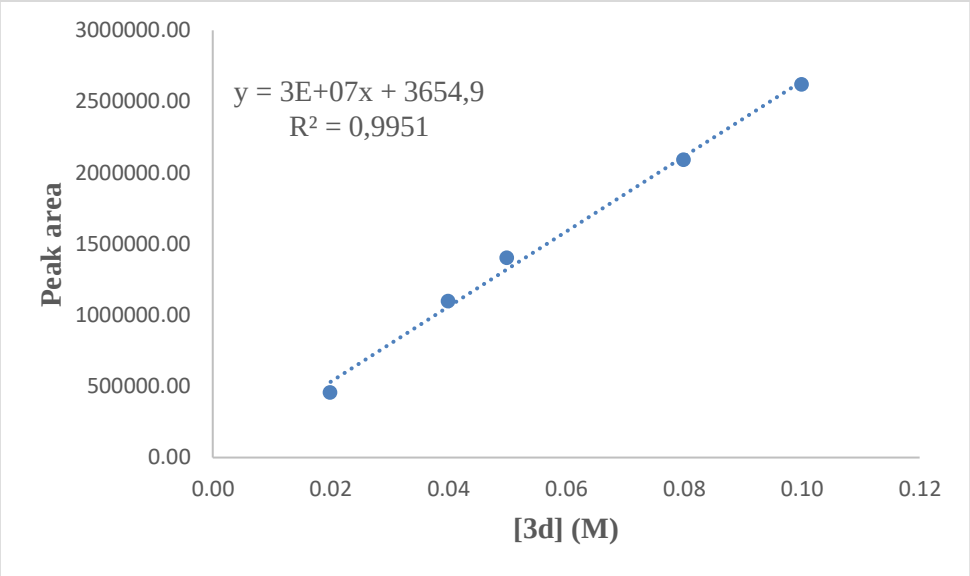


Figure S34: GC-FID calibration curve for **3d**

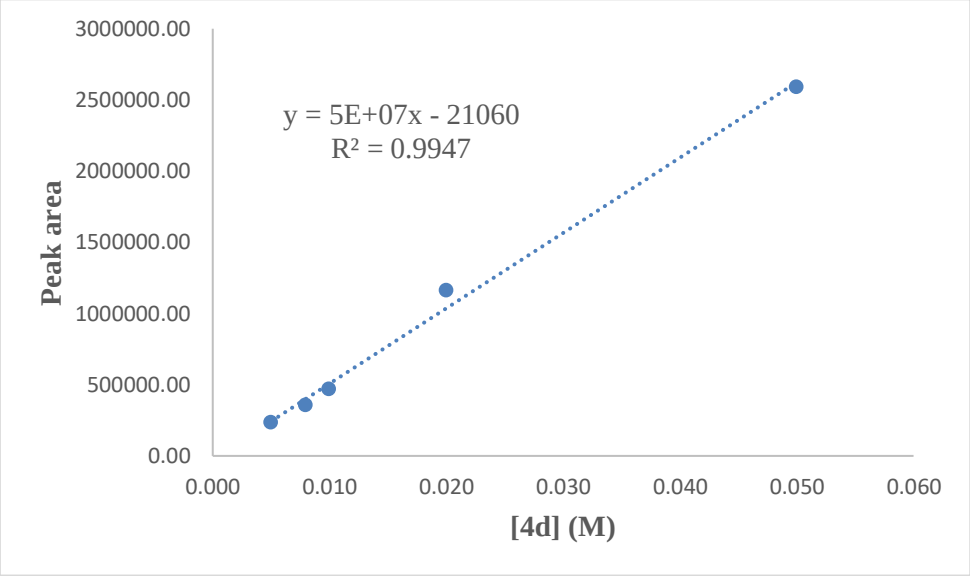


Figure S35: GC-FID calibration curve for **4d**

Table S5. **3d**/**4d** ratio of the reaction crude using **1a** (0.2 mmol, 1 eq.), PhLi (0.4 mmol, 2 eq.), CPME (0.2 mL) and *ChCl/Gly 1:2* (1g) as solvent at 0°C.

Peak area 3d	Peak area 4d	[3d] (M)	[4d] (M)	3d/4d ratio
752464.84	226369.25	0.028381	0.004678	6.066276

Synthesis and analysis of compounds **3a-h**

1-Phenylpentan-1-one (3a): general procedure starting from **1a** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3a** as colorless liquid (21 mg, 65%, R_f = 0.54 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.73 (quint, *J* = 7.3 Hz, 2H), 1.42 (sext, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 200.8, 137.2, 133.0, 128.7, 128.2, 38.5, 26.6, 22.6, 14.1. EI-MS *m/z* (%): 162 (M^+, 80), 120 (49), 105 (100), 77 (46).[11]

Acetophenone (3b): general procedure starting from **1a** and MeLi. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **3b** as colorless liquid (15 mg, 60%, R_f = 0.46 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.45 (m, 2H), 2.61 (s, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 198.4, 137.2, 133.3, 128.7, 128.5, 26.8. EI-MS *m/z* (%): 120 (M^+, 34), 105 (100), 77 (75), 51 (24).[12]

1-Phenylheptan-1-one (3c): general procedure starting from **1a** and *n*-HexLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3c** as colorless liquid (26 mg, 69%, R_f = 0.57 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97-7.95 (m, 2H), 7.56-7.54 (m, 1H), 7.47-7.44 (m, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.41-1.30 (m, 6H), 0.91-0.88 (m, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): 200.8, 137.2, 133.0, 128.7, 128.2, 38.8, 31.8, 29.2, 24.5, 22.7, 14.2. δ. EI-MS *m/z* (%): 190 (M^+, 10), 120 (77), 105 (100), 77 (40).[13]

Benzophenone (3d): general procedure starting from **1a** and PhLi. Purification by flash column chromatography (PE/EtOAc 9/1 v/v) gave **3d** as white solid (25 mg, 70%, R_f = 0.50 PE/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.83-7.78 (m, 4H), 7.61-7.58 (m, 2H), 7.50-7.47 (m, 4H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 196.9, 137.7, 132.6, 130.2, 128.4. EI-MS *m/z* (%): 182 (M^+, 74), 105 (100), 77 (56), 51 (18).[12]

1-(*m*-Tolyl)pentan-1-one (3e): general procedure starting from **1b** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3e** as colorless liquid (18 mg, 50%, R_f = 0.60 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.37-7.33 (m, 2H), 2.95 (t, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.71 (quint, *J* = 7.6 Hz, 2H), 1.40 (sext, *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 201.0, 138.5, 137.3, 133.7, 128.7, 128.5, 125.4, 38.5, 26.7, 22.6, 21.5, 14.1. EI-MS *m/z* (%): 176 (M^+, 13), 134 (42), 119 (100), 91 (44).[14]

1-(3-Methoxyphenyl)pentan-1-one (3f): general procedure starting from **1c** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 9/1 v/v) gave **3f** as colorless liquid (21 mg, 56%, R_f = 0.37 PE/DEE 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 6.94-6.91 (m, 2H), 3.86 (s, 3H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.70 (quint, *J* = 7.5 Hz, 2H), 1.40 (sext, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). ^{13}C{1H} NMR (150

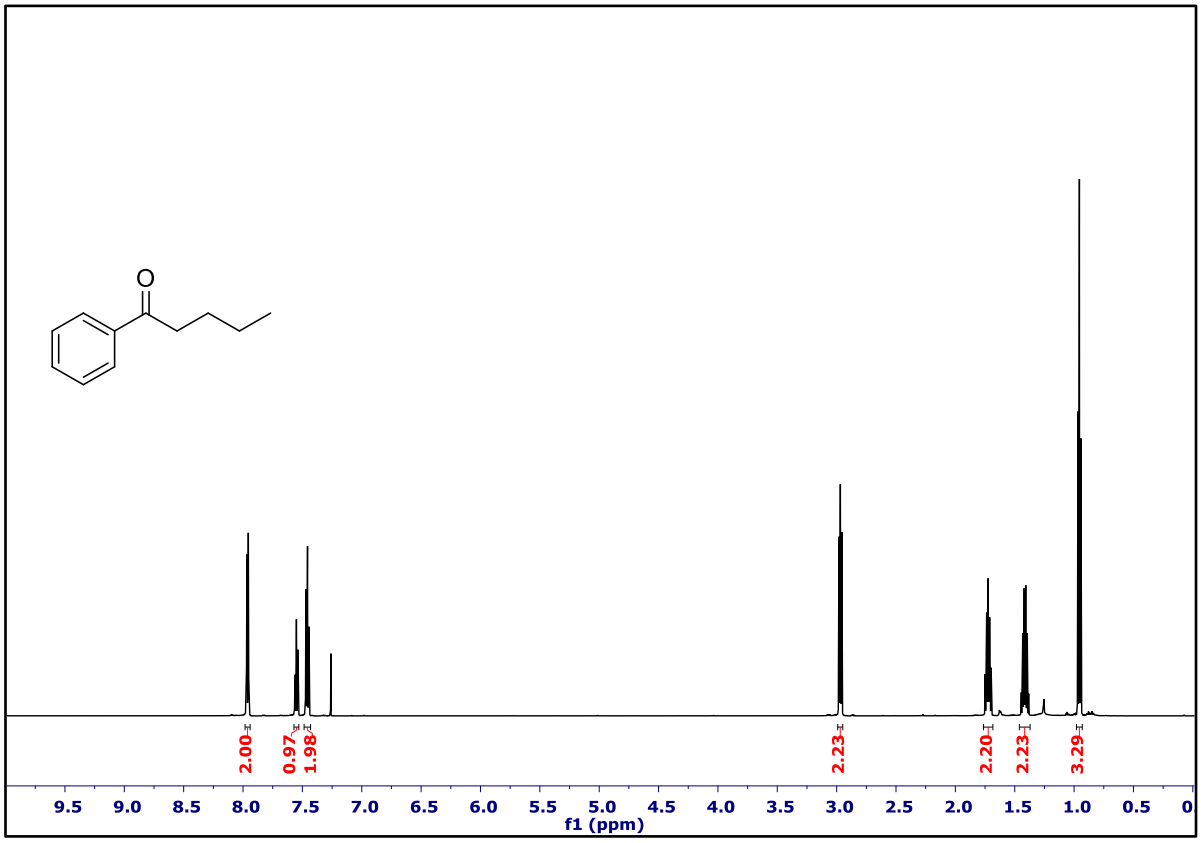
MHz, $CDCl_3$): δ 199.4, 163.4, 130.5, 130.3, 113.8, 55.6, 38.2, 26.9, 22.7, 14.1. EI-MS *m/z* (%): 192 (M^+, 4), 150 (46), 135 (100), 107 (8).[14]

1-(3-Chlorophenyl)pentan-1-one (3g): general procedure starting from **1d** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 95/5 v/v) gave **3g** as colorless liquid (20 mg, 50%, R_f = 0.57 PE/DEE 95/5 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91-7.88 (m, 2H), 7.44-7.42 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.71 (quint, *J* = 7.3 Hz, 2H), 1.40 (sext, *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 199.5, 139.4, 135.5, 129.6, 129.0, 38.5, 26.5, 22.6, 14.1. EI-MS *m/z* (%): 196 (M^+, 1), 156 (19), 154 (56), 141 (34), 139 (100), 113 (10), 111 (31).[14]

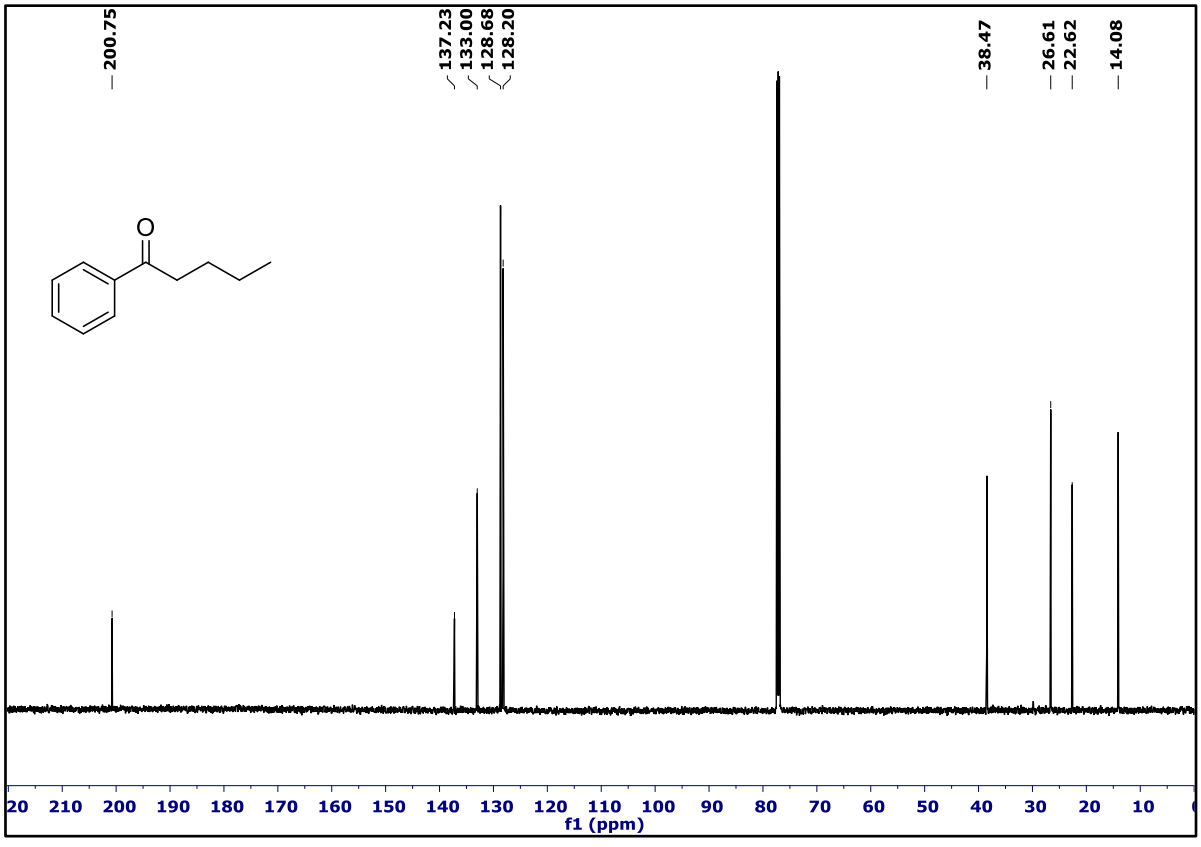
1-(1-Methyl-*1H*-indol-2-yl)pentan-1-one (3h): general procedure starting from **1e** and *n*-BuLi. Purification by flash column chromatography (PE/DEE 9/1 v/v) gave **3h** as white solid (26 mg, 60%, R_f = 0.43 PE/DEE 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.1 Hz, 1H), 7.40-7.37 (m, 2H), 7.30 (s, 1H), 7.18-7.14 (m, 1H), 4.08 (s, 3H), 2.97 (t, *J* = 7.4 Hz, 2H), 1.76 (quint, *J* = 7.7 Hz, 2H), 1.44 (sext, *J* = 7.7 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 194.6, 140.1, 135.1, 125.9, 125.9, 123.0, 120.8, 111.3, 110.5, 39.9, 32.3, 27.5, 22.7, 14.1. EI-MS *m/z* (%): 215 (M^+, 59), 173 (39), 159 (41), 158 (100), 144 (16), 131 (27), 89 (50).[15]

1-Phenylpentan-1-one (3a)

^{1}H NMR (600 MHz, $CDCl_3$)

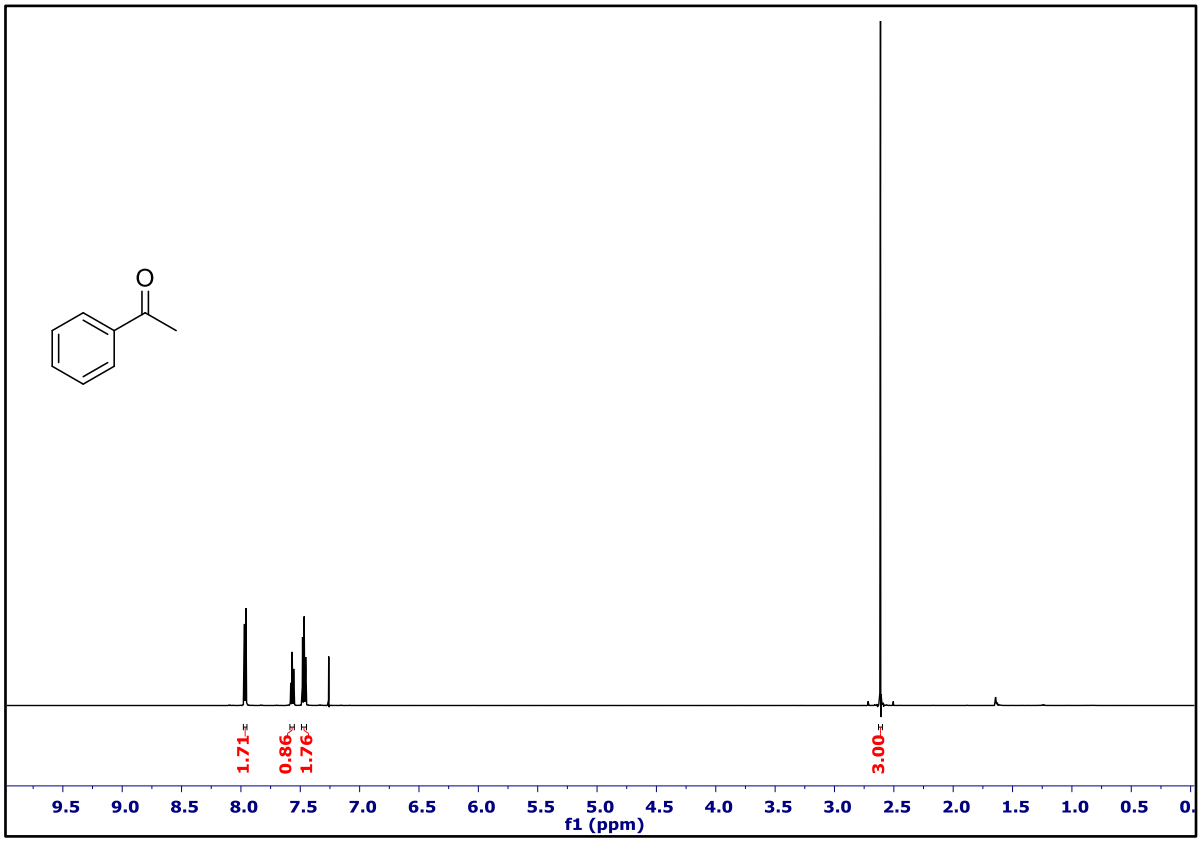


^{13}C NMR (150 MHz, $CDCl_3$)

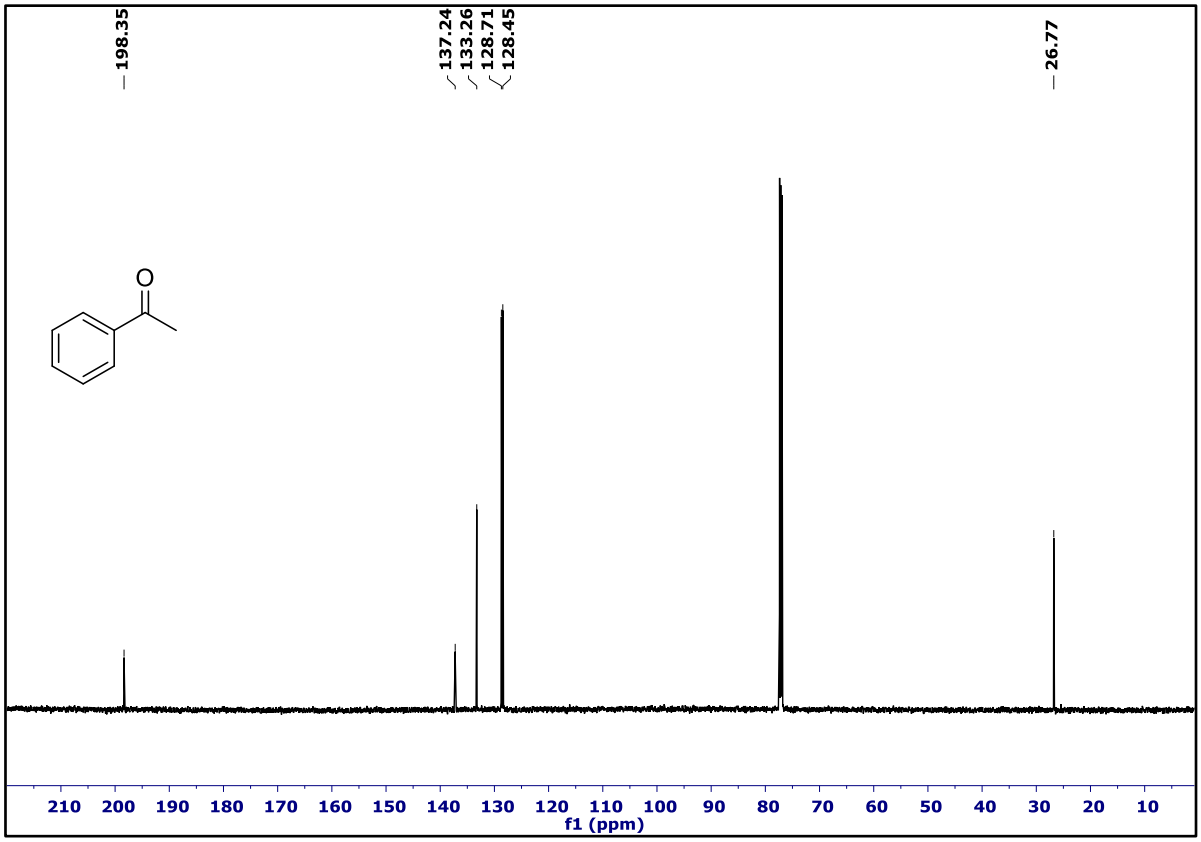


Acetophenone (3b)

^{1}H NMR (600 MHz, $CDCl_3$)

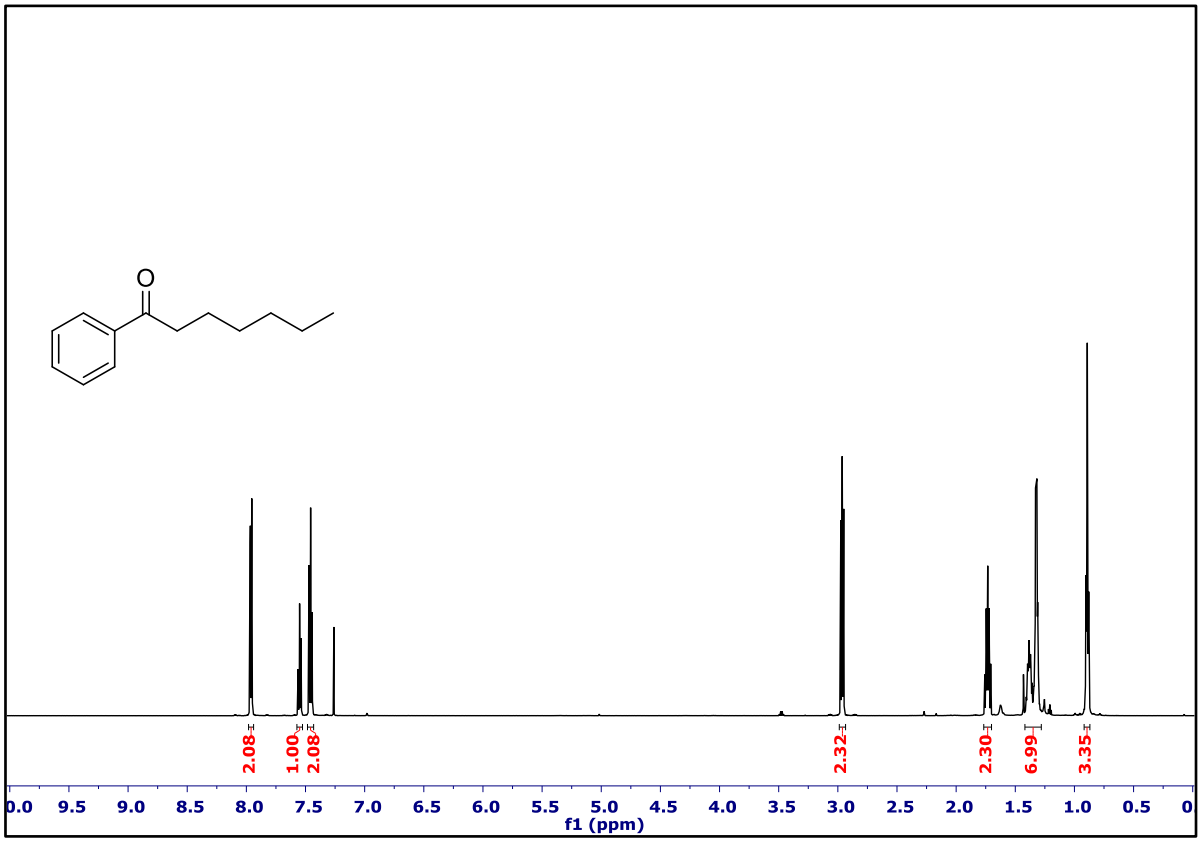


^{13}C NMR (150 MHz, $CDCl_3$)

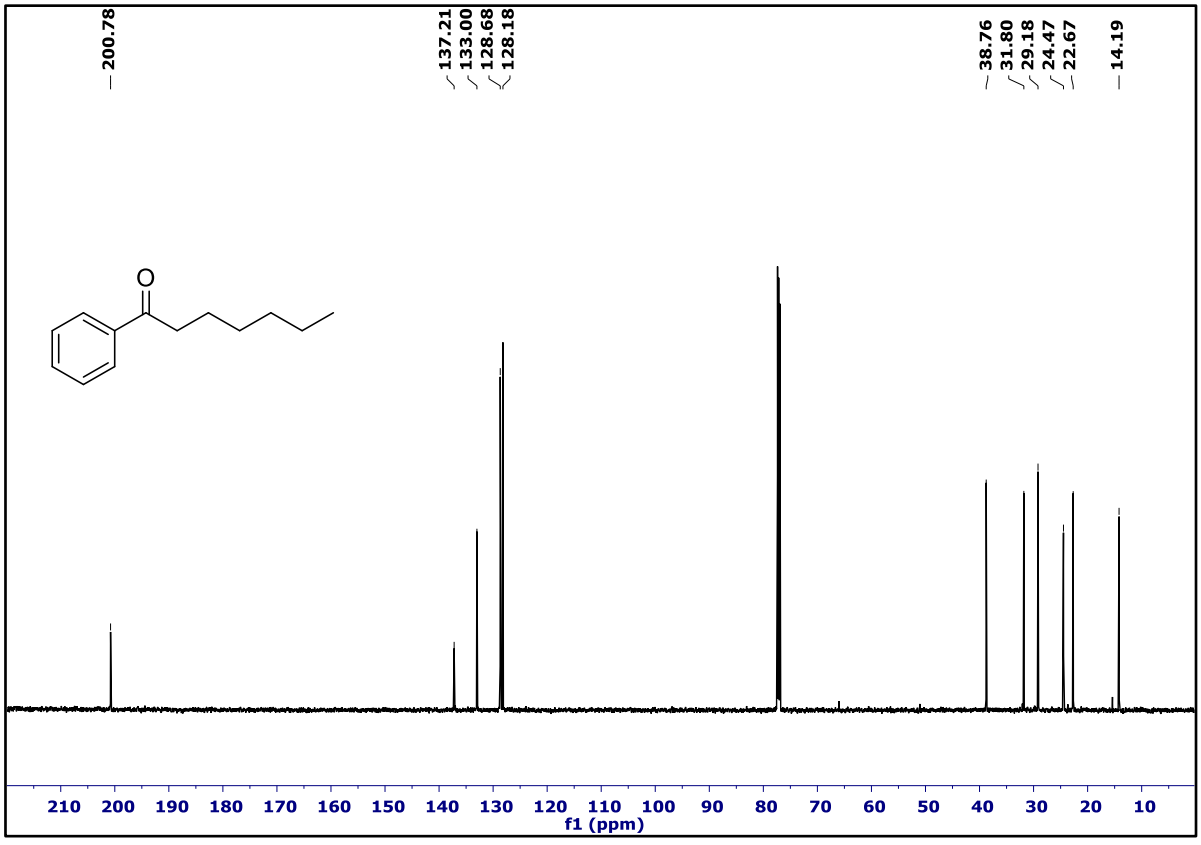


1-Phenylheptan-1-one (3c)

^{1}H NMR (600 MHz, $CDCl_3$)

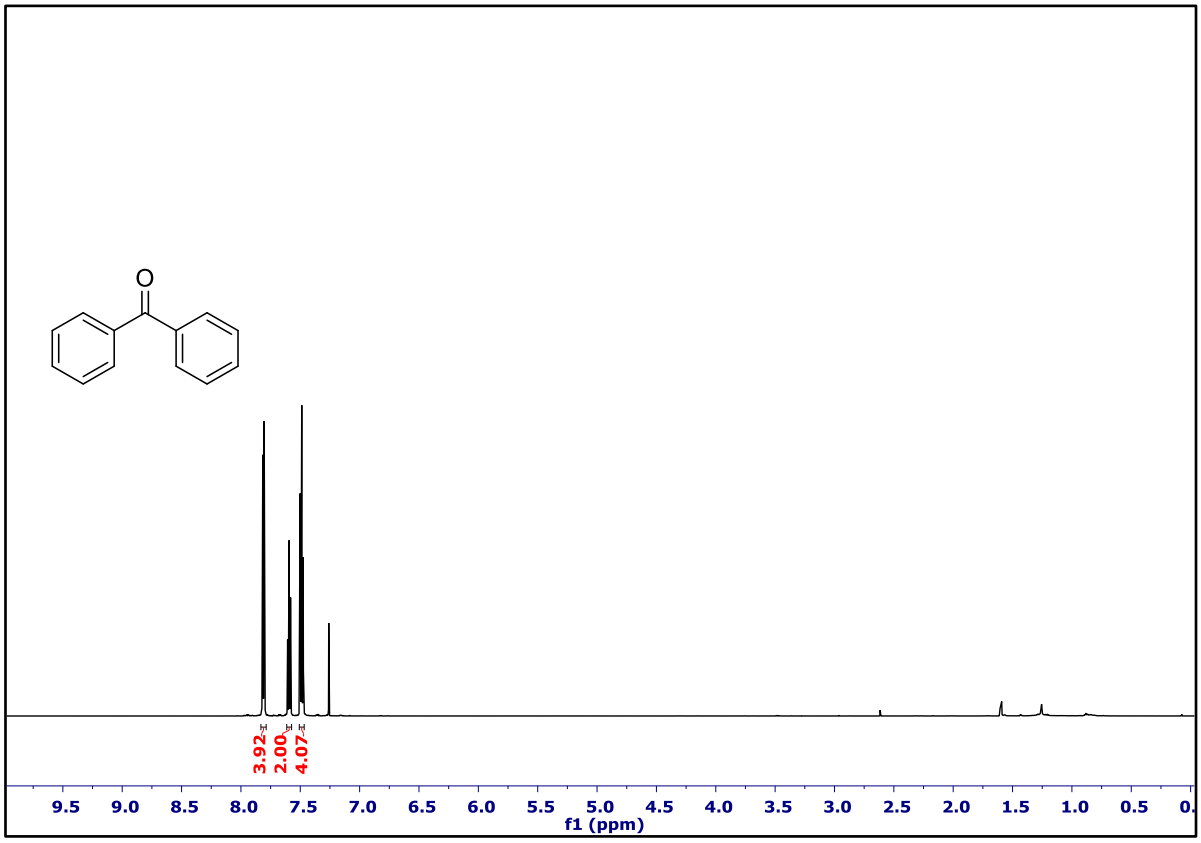


^{13}C NMR (150 MHz, $CDCl_3$)

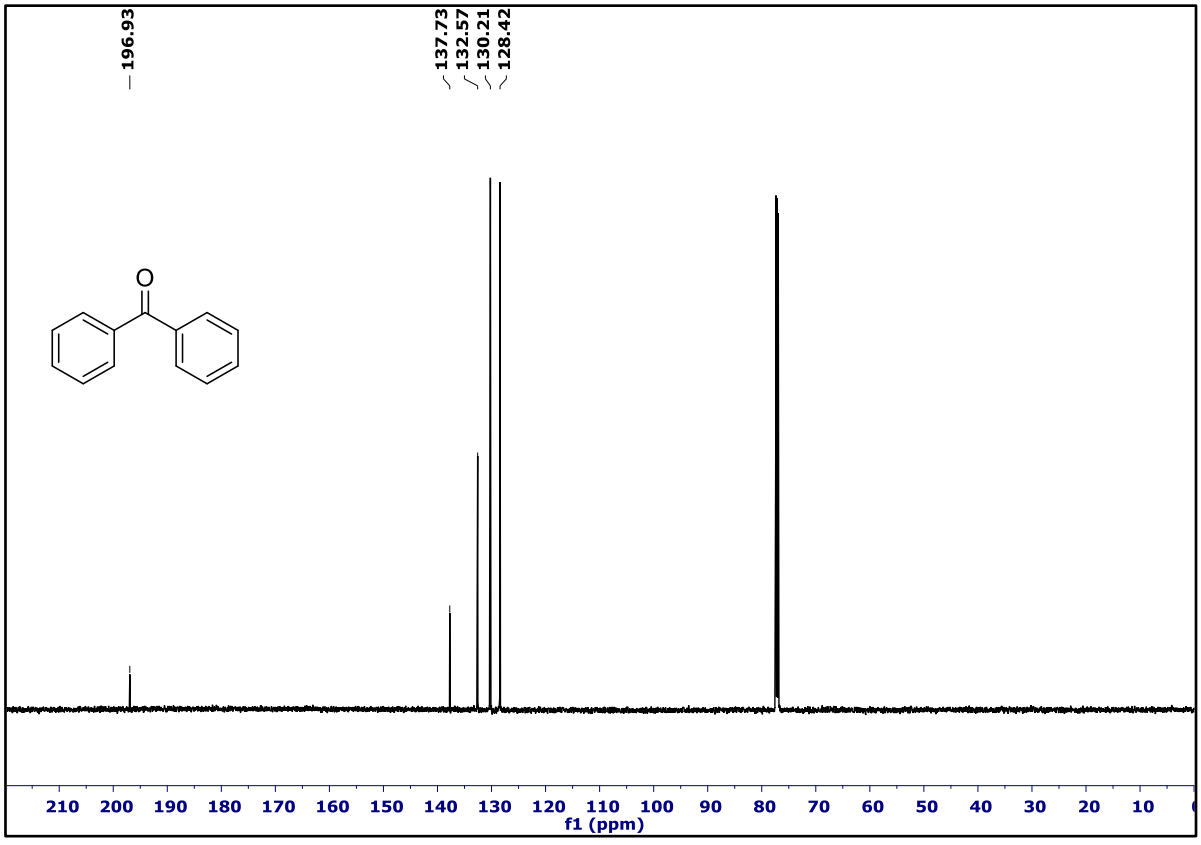


Benzophenone (3d)

^{1}H NMR (600 MHz, $CDCl_3$)

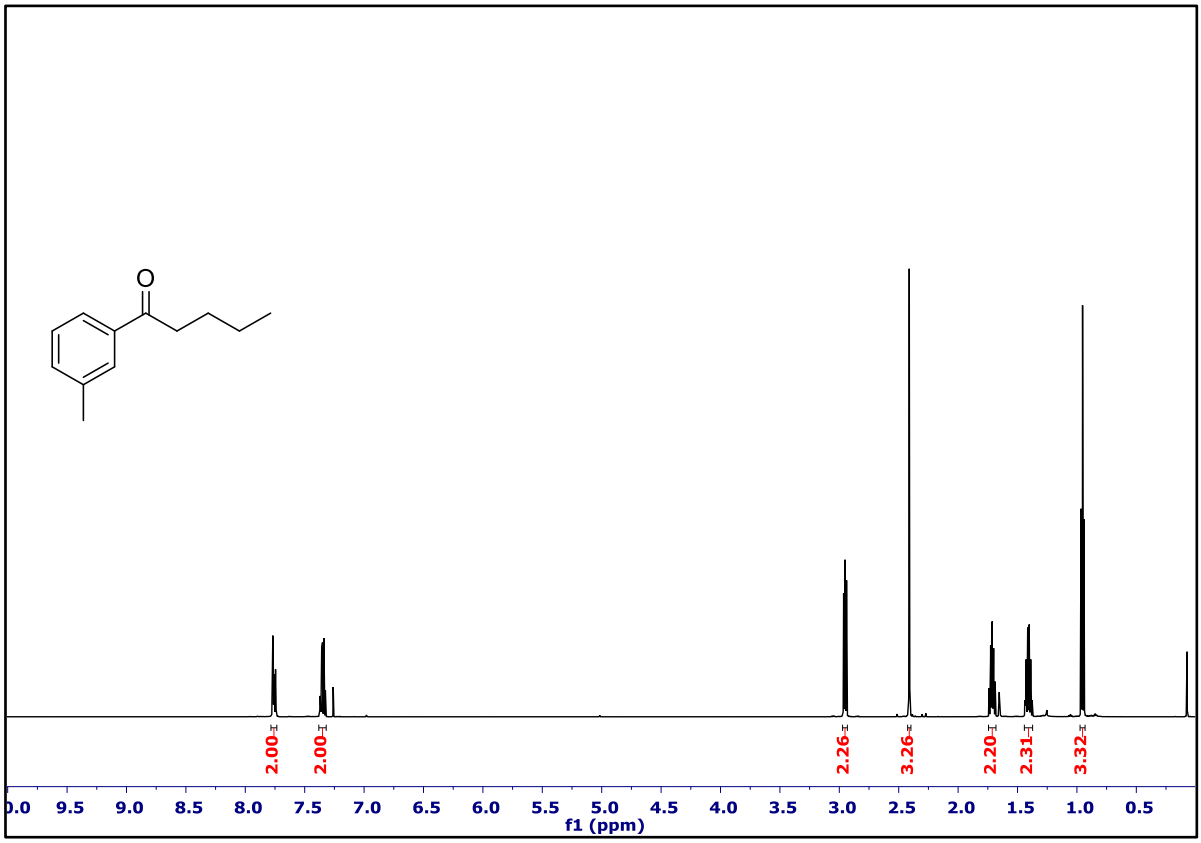


^{13}C NMR (150 MHz, $CDCl_3$)

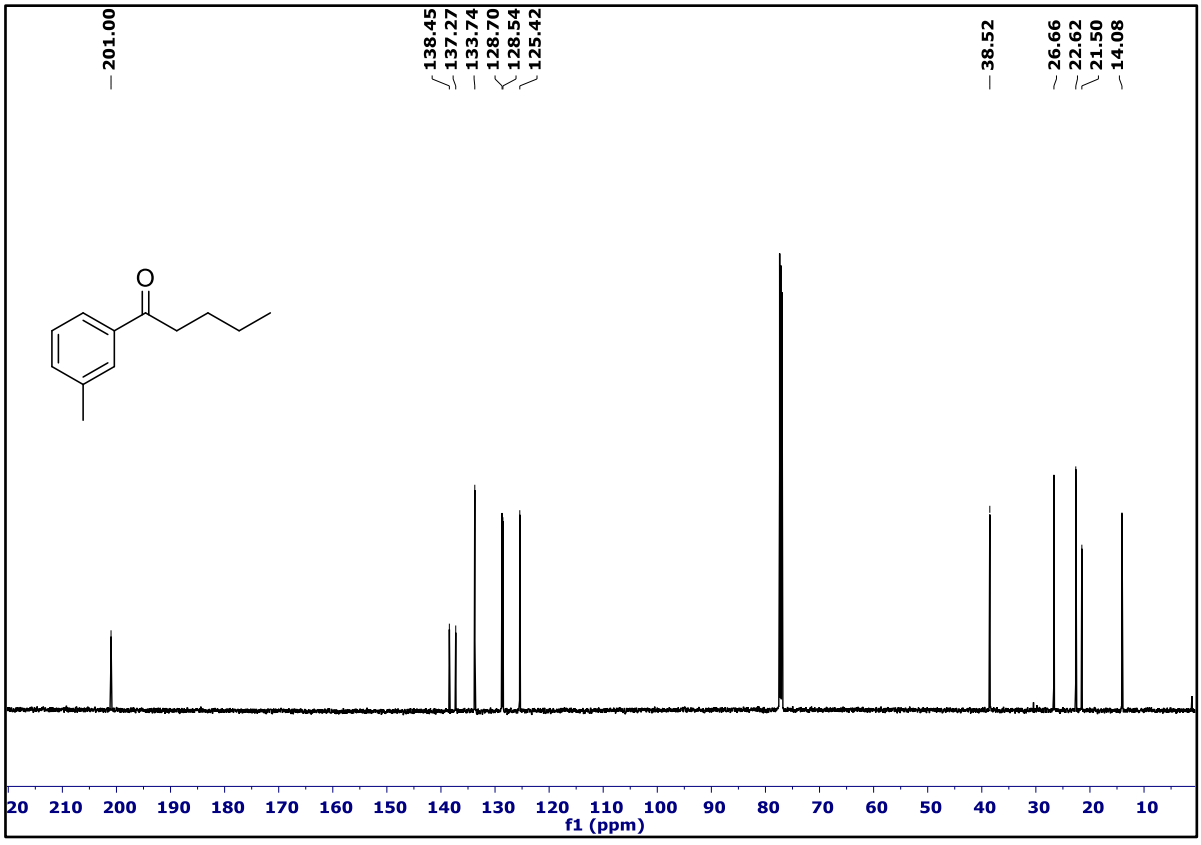


1-(*m*-Tolyl)pentan-1-one (3e)

^{1}H NMR (600 MHz, $CDCl_3$)

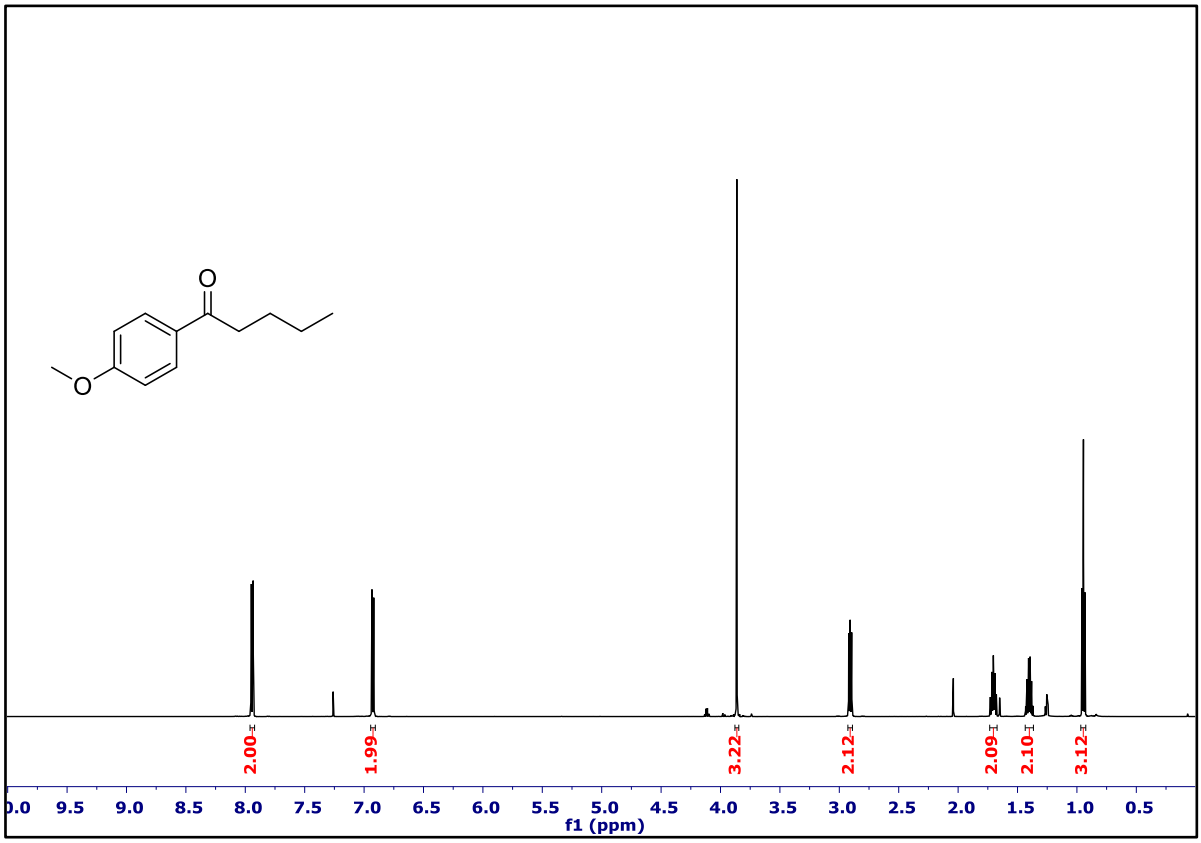


^{13}C NMR (150 MHz, $CDCl_3$)

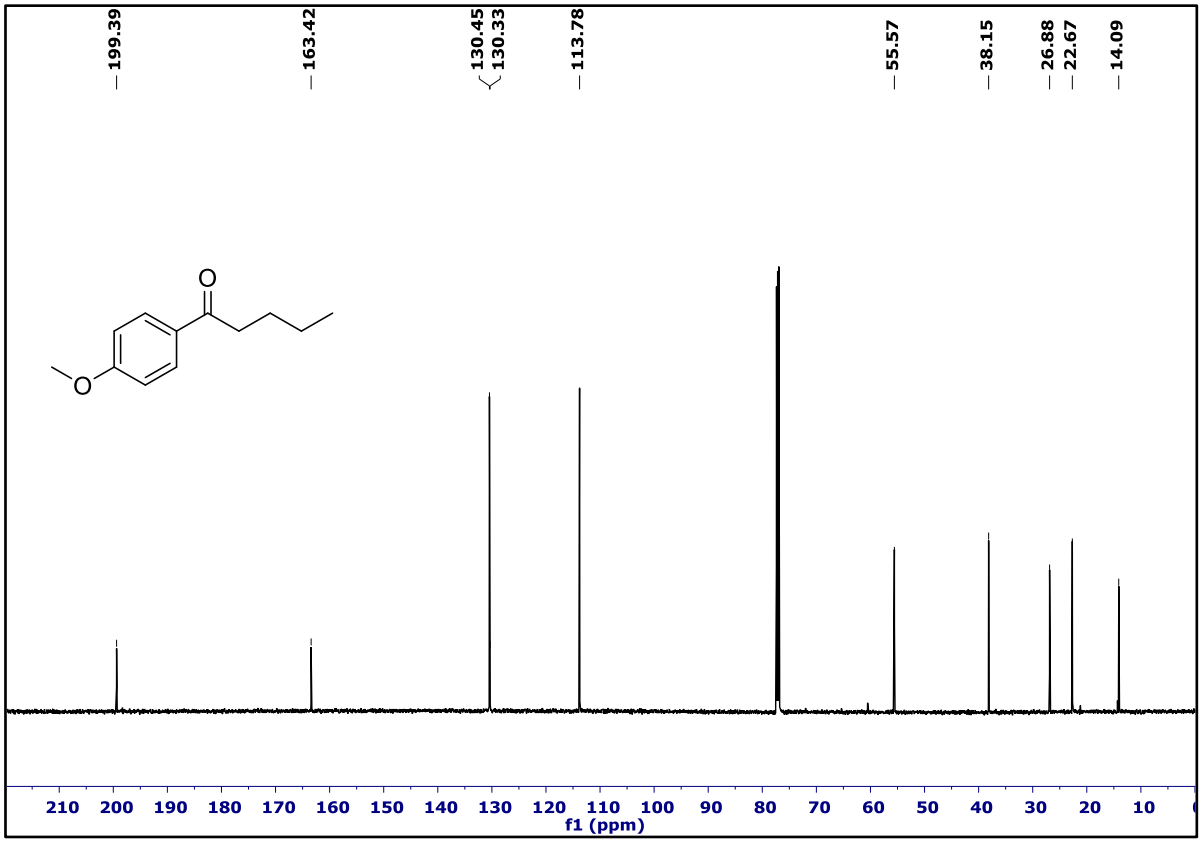


1-(3-Methoxyphenyl)pentan-1-one (3f)

^{1}H NMR (600 MHz, $CDCl_3$)

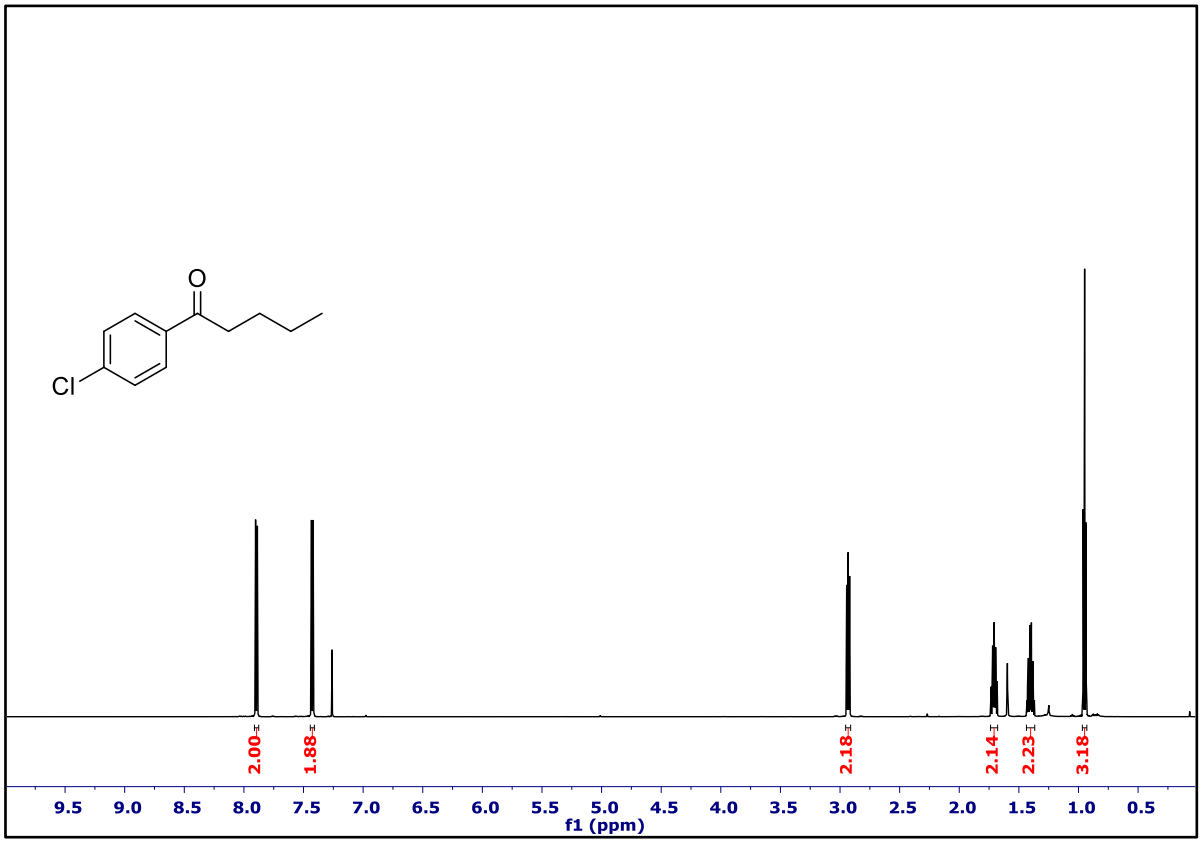


^{13}C NMR (150 MHz, $CDCl_3$)

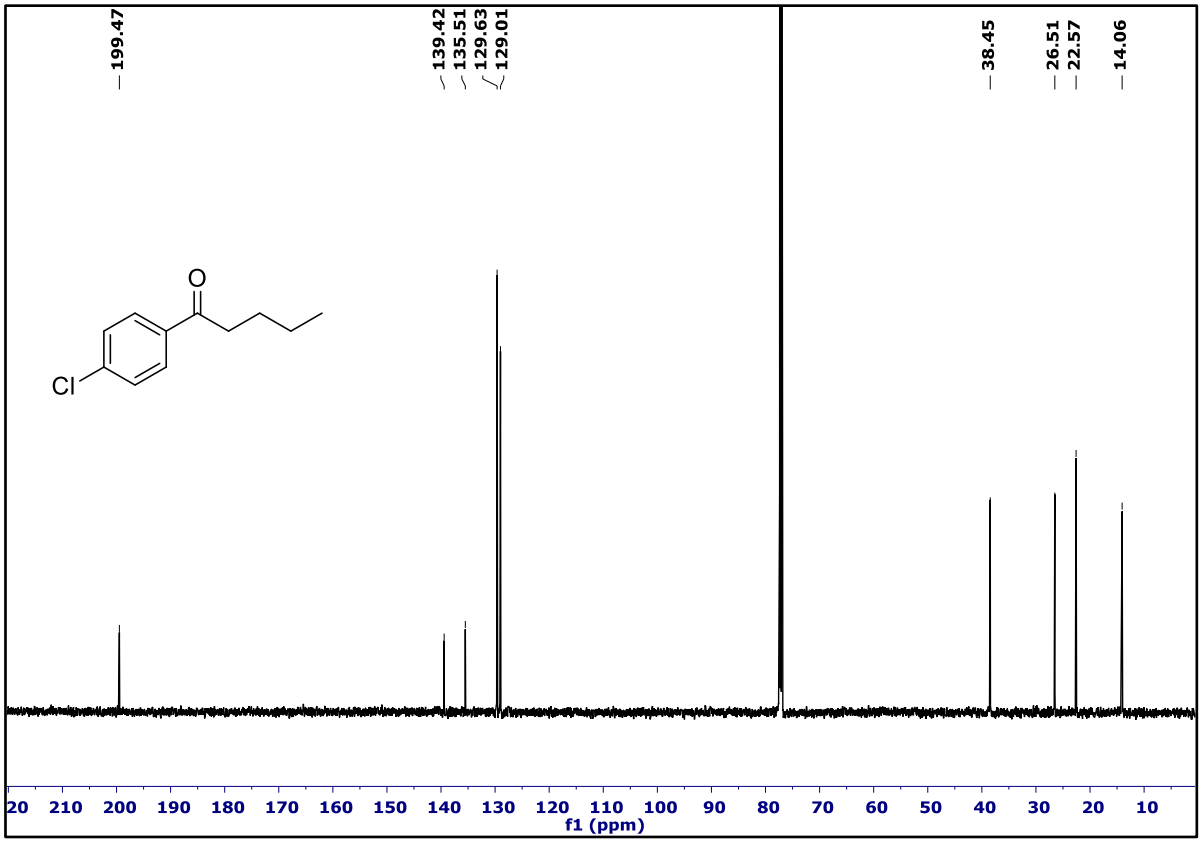


1-(3-Chlorophenyl)pentan-1-one (3g)

^{1}H NMR (600 MHz, $CDCl_3$)

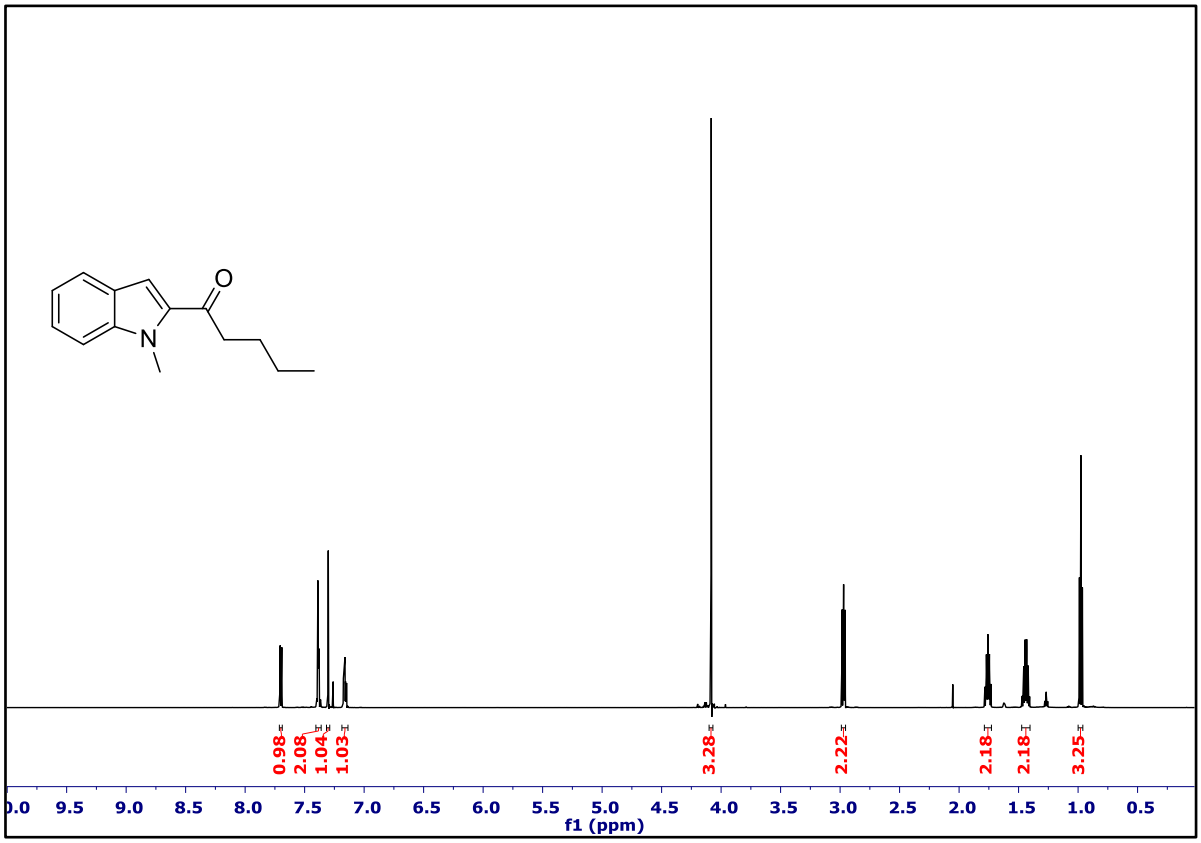


^{13}C NMR (150 MHz, $CDCl_3$)

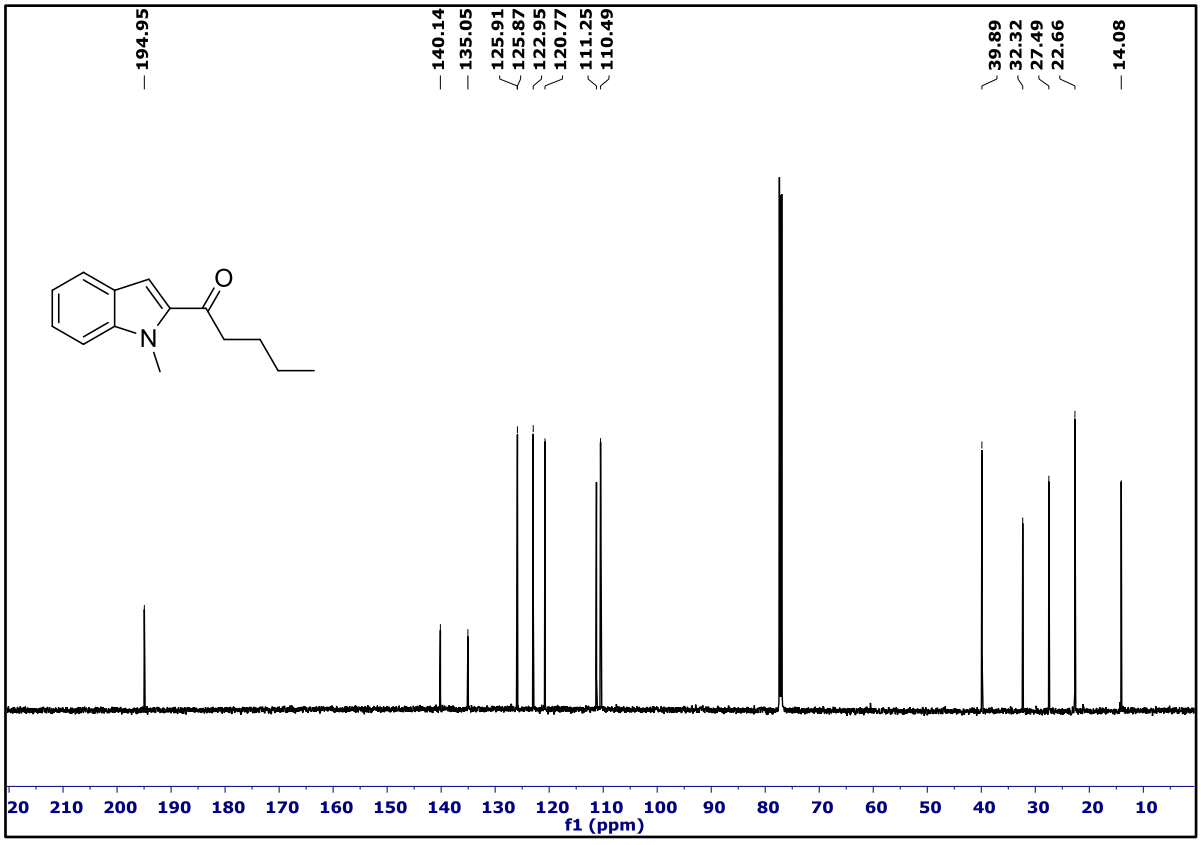


1-(1-Methyl-*1H*-indol-2-yl)pentan-1-one (3h)

^{1}H NMR (600 MHz, $CDCl_3$)



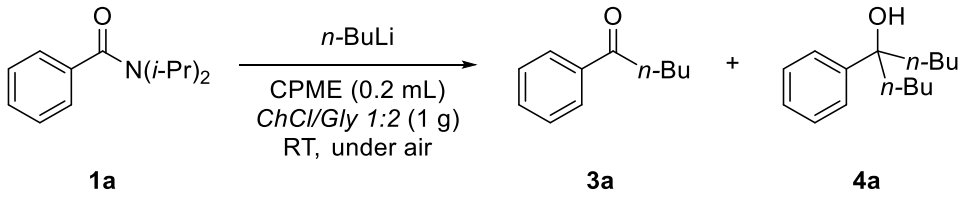
^{13}C NMR (150 MHz, $CDCl_3$)



Addition of *n*-BuLi to *N,N*-diisopropylbenzamide **1a** in CPME-*ChCl/Gly (1:2 mol mol^{-1})*: optimization of *n*-BuLi equivalents

Reactions were performed under air at room temperature. In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1 eq.) was dissolved in CPME (0.2 mL, 1 M) under air, then *ChCl/Gly 1:2* (DES, 1 g) was added and the resulting mixture was vigorously stirred for 5 min. A selected amount of *n*-BuLi was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring for further 20 s and finally diluted with water. The mixture was washed twice with 1 M HCl (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Conversion and **3a**:**4a** ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

Table S6. Optimization of *n*-BuLi equivalents



Entry	Eq. *n*-BuLi	% conv.	**3a**:**4a** ratio
1	1	54	4.5:1
2	2	85	5:1
3	3	80	2:1

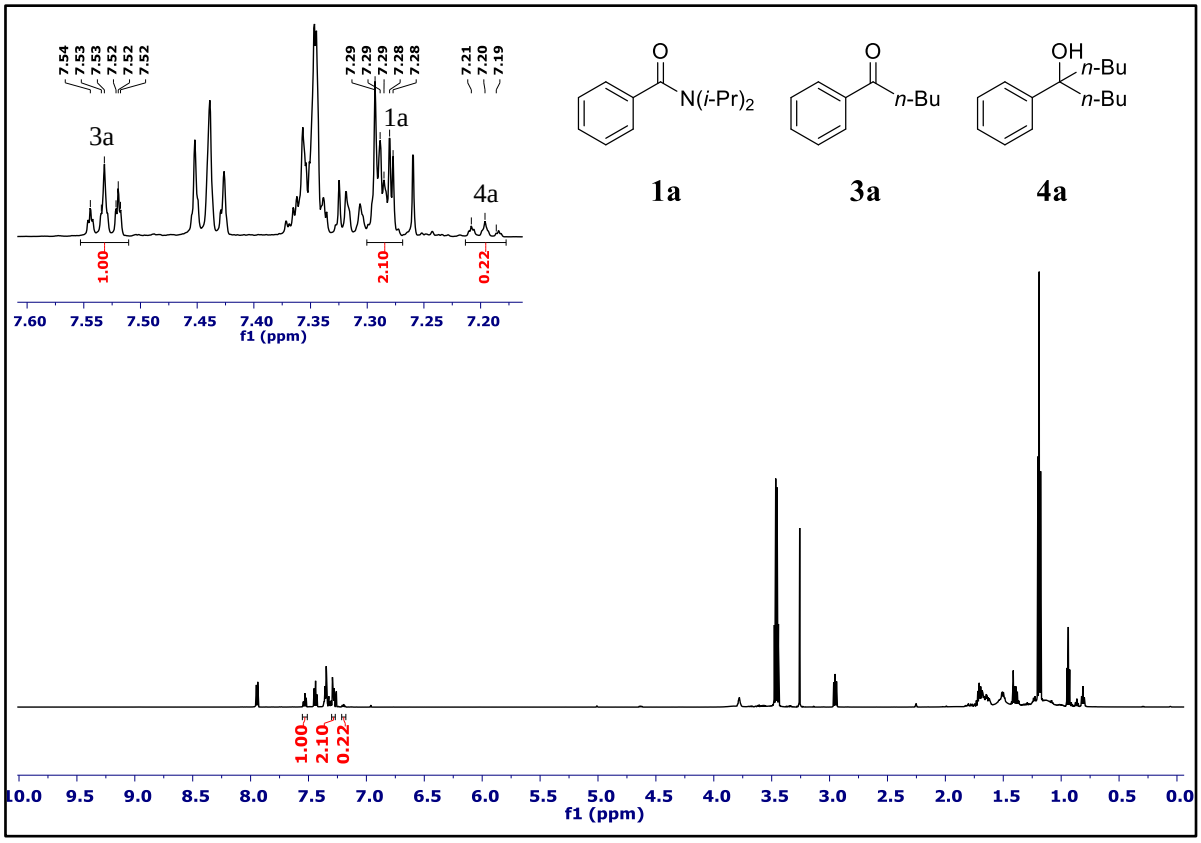


Figure S36 – Table S6 entry 1: crude ^{1}H NMR spectrum of the reaction using 1 eq. of *n*-BuLi. Conversion 54%; **3a**/**4a** ratio 4.5/1

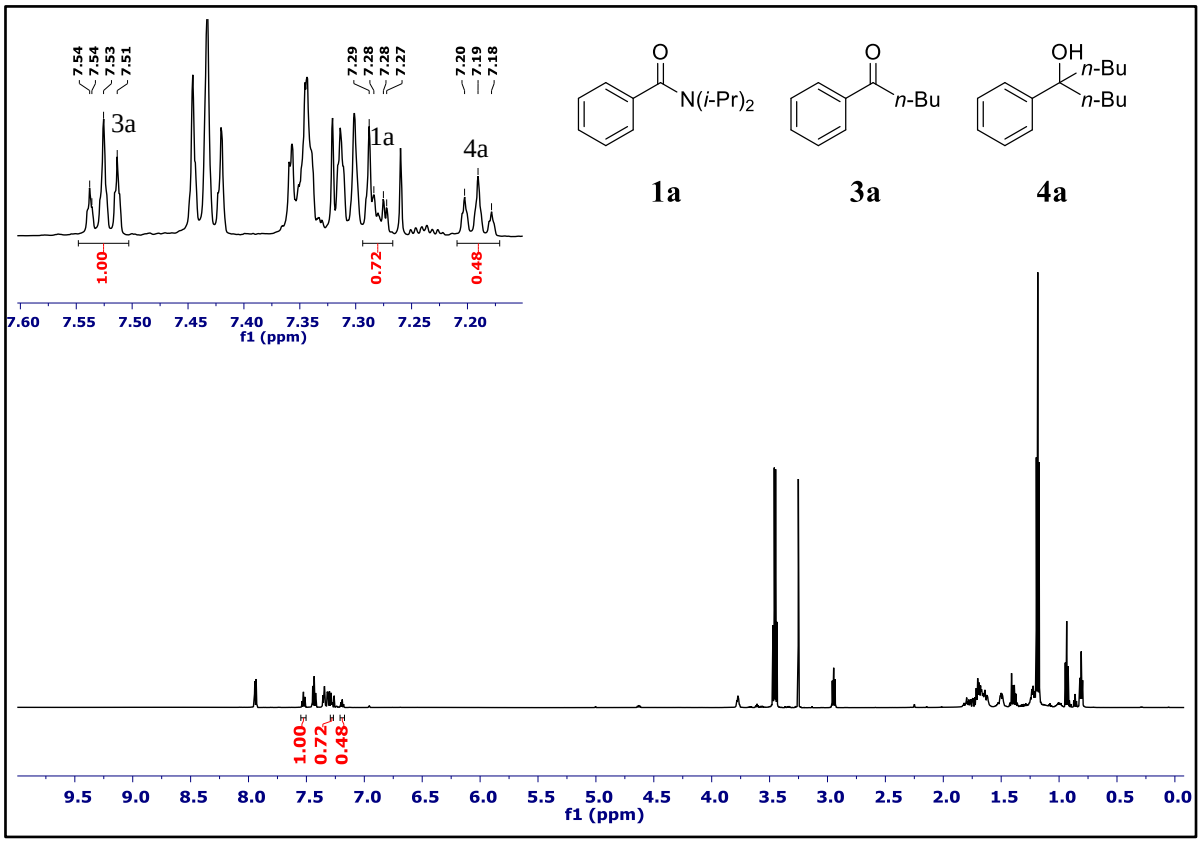
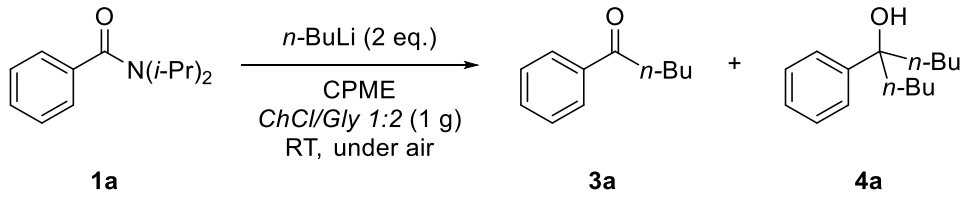


Figure S37 – Table S6 entry 3: crude ^{1}H NMR spectrum of the reaction using 3 eq. of *n*-BuLi. Conversion 80%; **3a**/**4a** ratio 2/1

Addition of *n*-BuLi to *N,N*-diisopropylbenzamide **1a** in *ChCl/Gly (1:2 mol mol^{-1}):* optimization of additive (CPME) concentration

Reactions were performed under air and at room temperature. In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1 eq.) was dissolved in different amounts of CPME under air, then *ChCl/Gly 1:2* (DES, 1 g) was added and the resulting mixture was vigorously stirred for 5 min. *n*-BuLi (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring for further 20 s and finally diluted with water. The mixture was washed twice with 1 M HCl (5 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed under reduced pressure. Conversion and **3a**:**4a** ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.

Table S7. Optimization of additive (CPME) concentration



1a **3a** **4a**

Entry	CPME (mL)	% conv.	**3a**:**4a** ratio
1	0.100	23	1:1
2	0.150	70	3:1
3	0.200	85	5:1

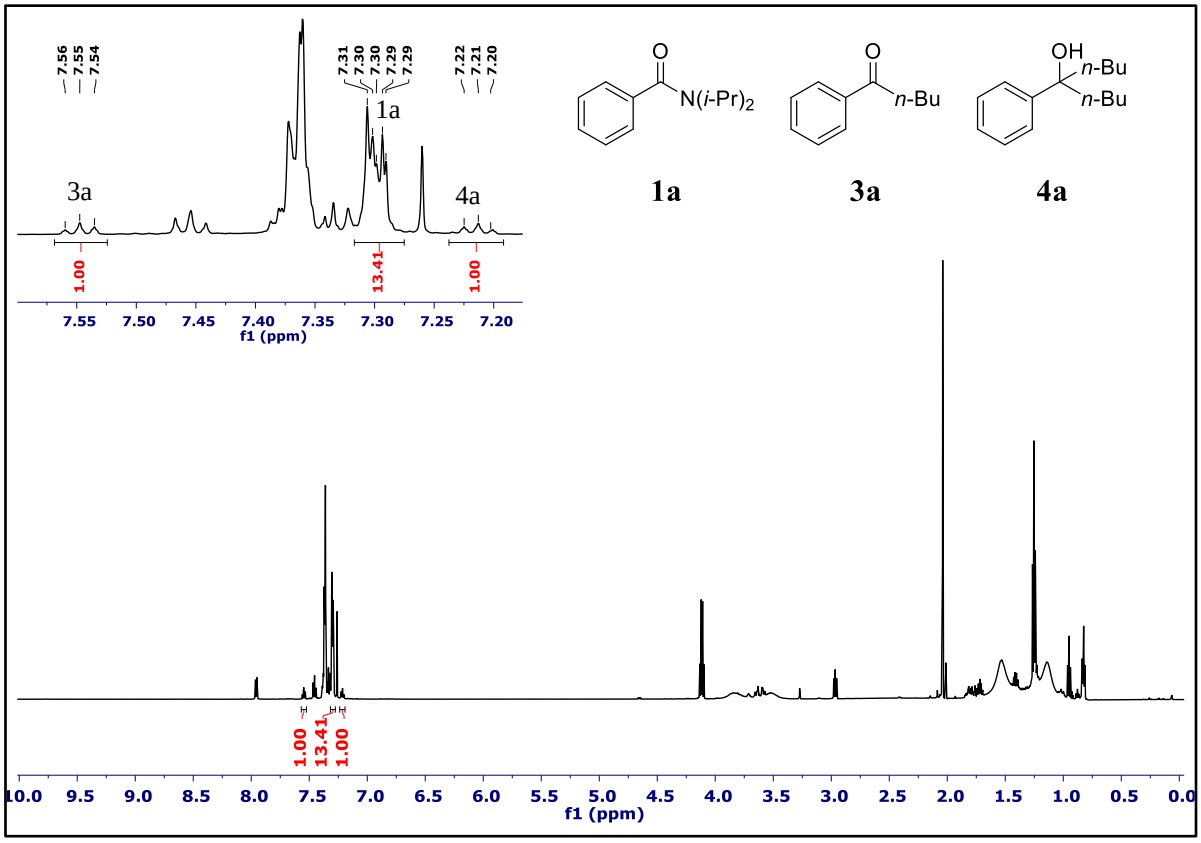


Figure S38 – Table S7 entry 1: crude ^{1}H NMR spectrum of the reaction using 0.100 mL of CPME. Conversion 23%; **3a**/**4a** ratio 1/1

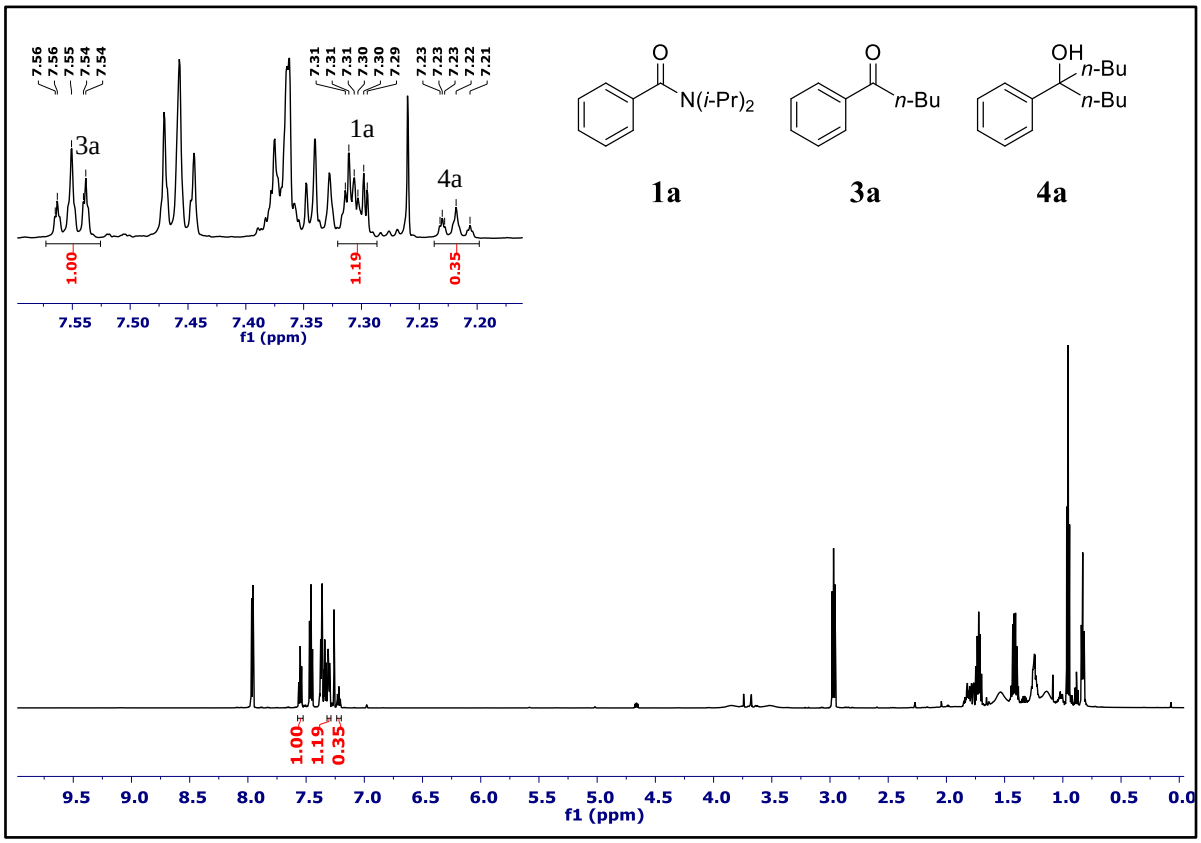


Figure S39 – Table S7 entry 2: crude ^{1}H NMR spectrum of the reaction using 0.150 mL of CPME. Conversion 70%; **3a**/**4a** ratio 3/1

Telescoped directed *ortho* metalation/Suzuki–Miyaura coupling reaction

Synthesis and analysis of compounds **6a-c**

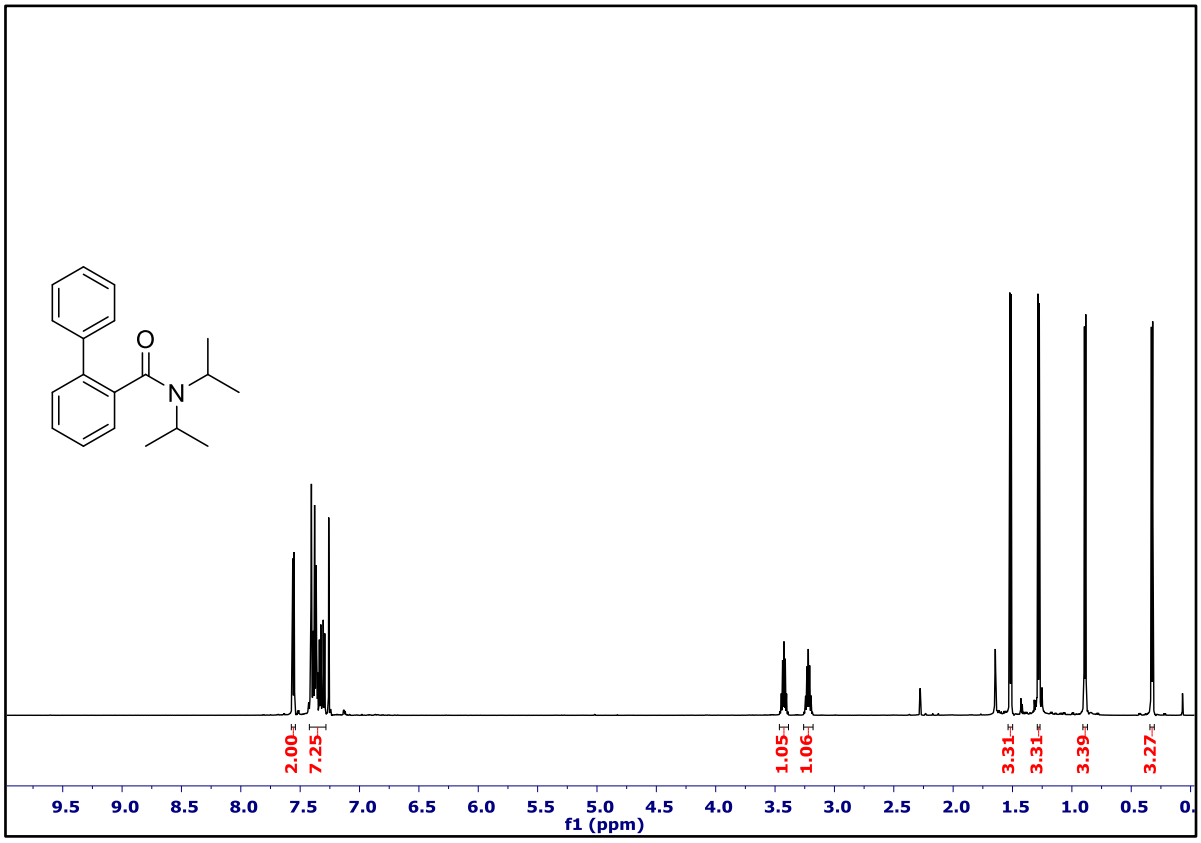
***N,N*-Diisopropyl-[1,1'-biphenyl]-2-carboxamide (6a):** In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1.0 eq.) was dissolved in CPME (0.2 mL, 1 M), then *ChCl/Gly 1:2* (1 g) was added and the resulting mixture was vigorously stirred for 5 min. *t*-BuLi (0.4 mmol, 2.0 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring then quenched by addition of a solution of iodine (61 mg, 0.24 mmol, 1.2 eq.) in 2-MeTHF (0.12 mL, 2 M) after 2 seconds. Then phenylboronic acid (61 mg, 0.5 mmol, 2.5 eq.), Na_2CO_3 (53 mg, 0.5 mmol, 2.5 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 eq.) were sequentially added and the reaction mixture was stirred overnight at 100 °C under air. The mixture was cooled to room temperature, filtered through a Celite pad, then extracted with 1 mL of CPME and concentrated under reduced pressure. Purification by flash column chromatography (toluene/EtOAc 9/1 v/v) gave **6a** as a white solid (25 mg, 45%, R_f = 0.38 toluene/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57-7.55 (m, 2H), 7.42-7.26 (m, 7H), 3.43 (sept, *J* = 6.8 Hz, 1H), 3.22 (sept, *J* = 6.7 Hz, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.32 (d, *J* = 6.7 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.4, 140.0, 138.1, 137.8, 129.5, 129.4, 128.6, 128.4, 127.7, 127.7, 126.7, 50.7, 45.7, 21.0, 20.9, 19.6, 19.6. EI-MS *m/z* (%): 281 (M^+, 23), 280 (25), 238 (31), 181 (100), 152 (36).[4]

***(E)*-*N,N*-Diisopropyl-2-styrylbenzamide (6b):** In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1.0 eq.) was dissolved in CPME (0.2 mL, 1 M), then *ChCl/Gly 1:2* (1 g) was added and the resulting mixture was vigorously stirred for 5 min. *t*-BuLi (0.4 mmol, 2.0 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring then quenched by addition of a solution of iodine (61 mg, 0.24 mmol, 1.2 eq.) in 2-MeTHF (0.12 mL, 2 M) after 2 seconds. Then potassium styryltrifluoroborate (105 mg, 0.5 mmol, 2.5 eq.), Na_2CO_3 (53 mg, 0.5 mmol, 2.5 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 eq.) were sequentially added and the reaction mixture was stirred overnight at 100 °C under air. The mixture was cooled to room temperature, filtered through a Celite pad then extracted with 1 mL of CPME and concentrated under reduced pressure. Purification by flash column chromatography (toluene/EtOAc 9/1 v/v) give **6b** as a white solid (22 mg, 35%, R_f = 0.40 toluene/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.46-7.44 (m, 2H), 7.35-7.31 (m, 3H), 7.28-7.23 (m, 2H), 7.19 (d, *J* = 16.3 Hz, 1H) superimposed to 7.18-7.16 (m, 1H), 7.08 (d, *J* = 16.3 Hz, 1H), 3.62 (sept, *J* = 6.8 Hz, 1H), 3.51 (sept, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.8 Hz, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H) superimposed to 1.02 (d, *J* = 6.7 Hz, 3H).^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.4, 138.1, 137.3, 133.5, 130.7, 128.9, 128.5, 128.0, 127.8, 126.7, 125.5, 125.5, 51.1, 46.0, 20.9, 20.8, 20.7, 20.6. EI-MS *m/z* (%): 307 (M^+, 43), 264 (9), 207 (100), 178 (57).[16]

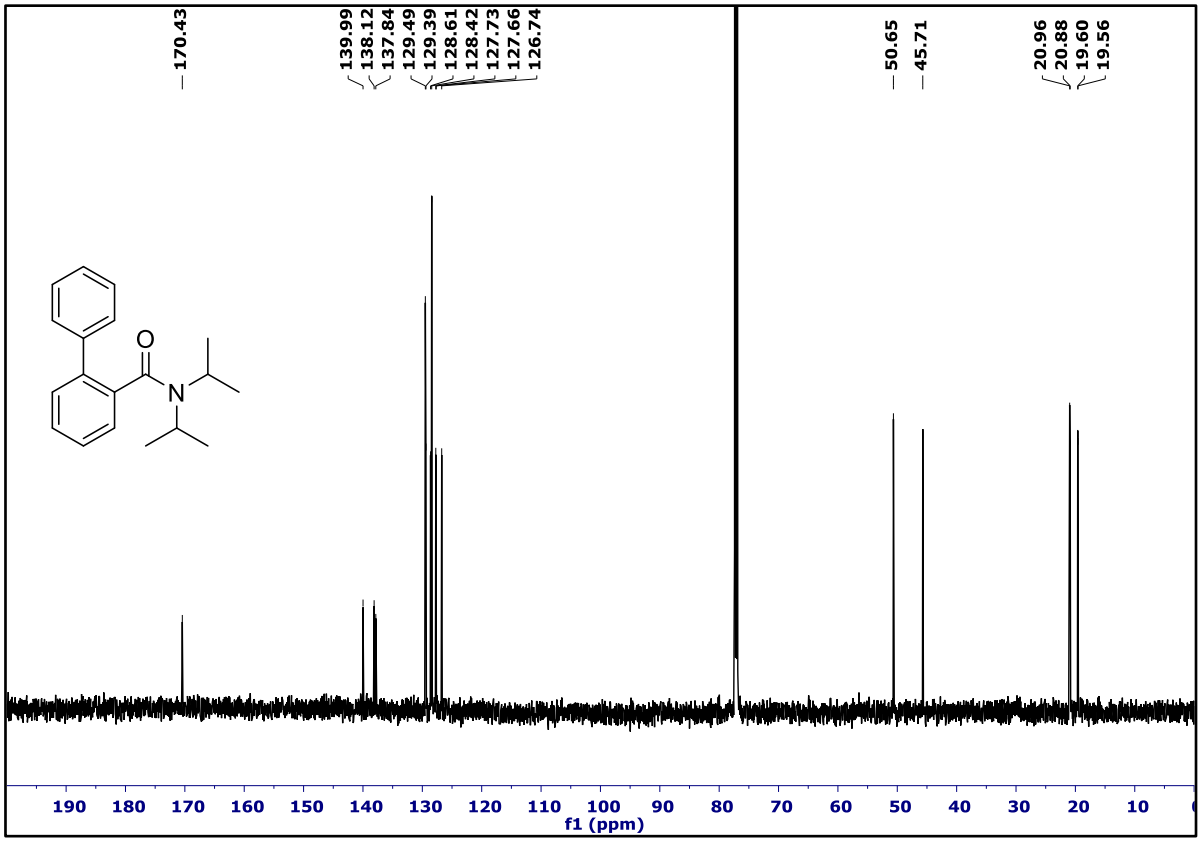
***N,N*-Diisopropyl-2-(thiophen-2-yl)benzamide (6c):** In an open screw cap vial, *N,N*-diisopropylbenzamide **1a** (41 mg, 0.2 mmol, 1.0 eq.) was dissolved in CPME (0.2 mL, 1 M), then *ChCl/Gly 1:2* (1 g) was added and the resulting mixture was vigorously stirred for 5 min. *t*-BuLi (0.4 mmol, 2 eq.) was rapidly spread over the heterogeneous mixture, which was kept under vigorous stirring then quenched by addition of a solution of iodine (61 mg, 0.24 mmol, 1.2 eq.) in 2-MeTHF (0.12 mL, 2 M) after 2 seconds. Then thienylboronic acid pinacol ester (105 mg, 0.5 mmol, 2.5 eq.), Na_2CO_3 (53 mg, 0.5 mmol, 2.5 eq.) and $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 eq.) were sequentially added and the reaction mixture was stirred overnight at 100 °C under air. The mixture was cooled to room temperature, filtered through a Celite pad, then extracted with 1 mL of CPME and concentrated under reduced pressure. Purification by flash column chromatography (toluene/EtOAc 9/1 v/v) give **6c** as a white solid (17 mg, 30%, R_f = 0.38 toluene/EtOAc 9/1 v/v). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.48 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.37-7.29 (m, 4H), 7.26-7.22 (m, 1H), 7.03 (dd, *J* = 5.1, 3.7 Hz, 1H), 3.46 (sept, *J* = 6.6 Hz, 1H), 3.32 (sept, *J* = 6.6 Hz, 1H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.41 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.53 (d, *J* = 6.5 Hz, 3H). ^{13}C{1H} NMR (150 MHz, $CDCl_3$): δ 170.2, 141.3, 137.8, 130.6, 129.4, 128.6, 128.0, 127.9, 127.4, 126.6, 126.0, 50.9, 45.8, 20.9, 20.7, 19.8. EI-MS *m/z* (%): 287 (M^+, 22), 244 (9), 187 (100), 115 (25).[17]

***N*,*N*-Diisopropyl-[1,1'-biphenyl]-2-carboxamide (6a)**

^{1}H NMR (600 MHz, $CDCl_3$)

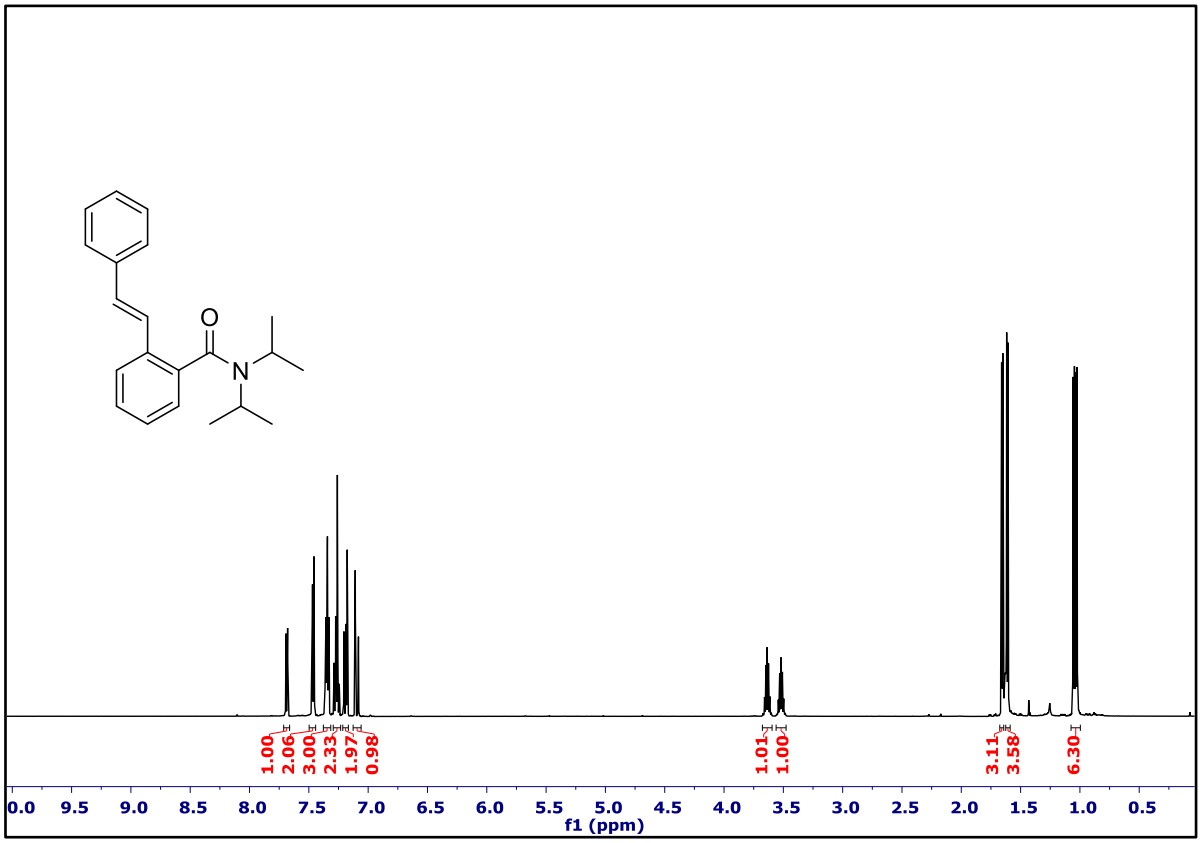


^{13}C NMR (150 MHz, $CDCl_3$)

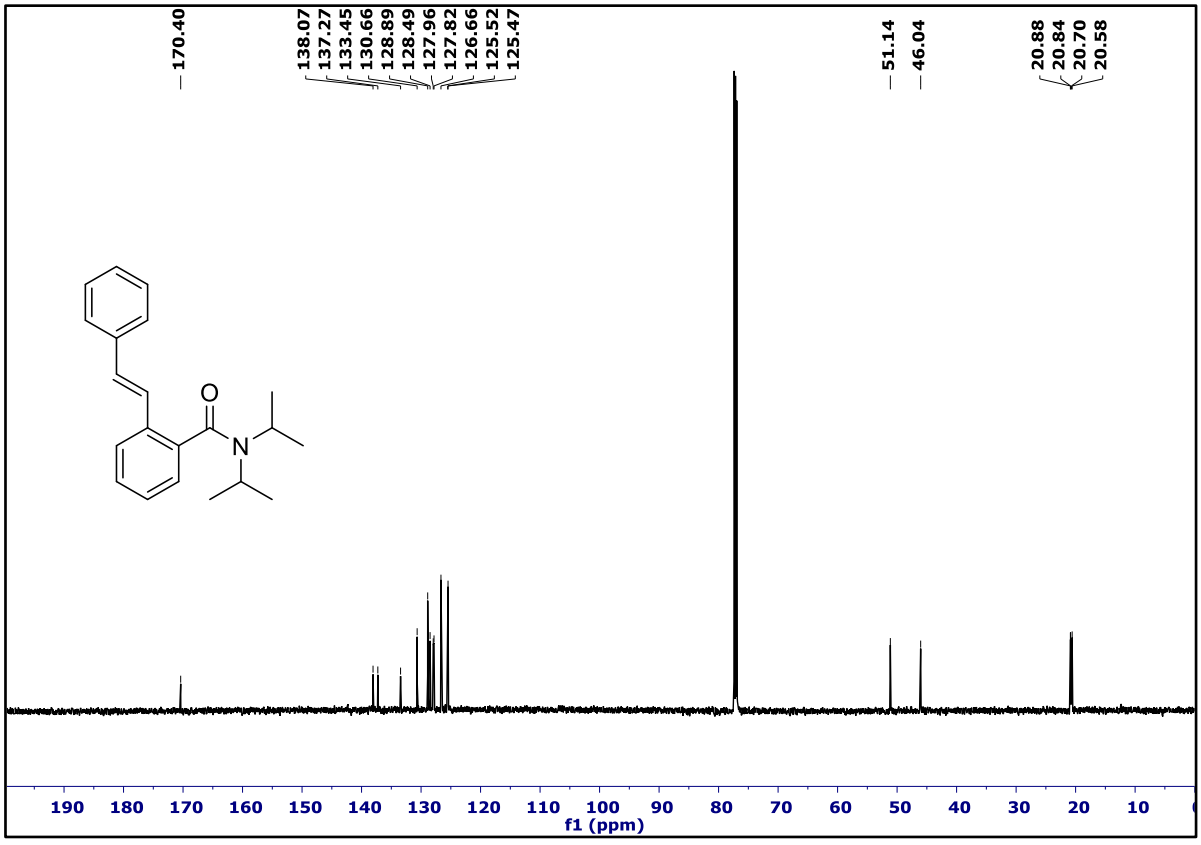


***(E)*-*N*,*N*-Diisopropyl-2-styrylbenzamide (6b)**

^{1}H NMR (600 MHz, $CDCl_3$)

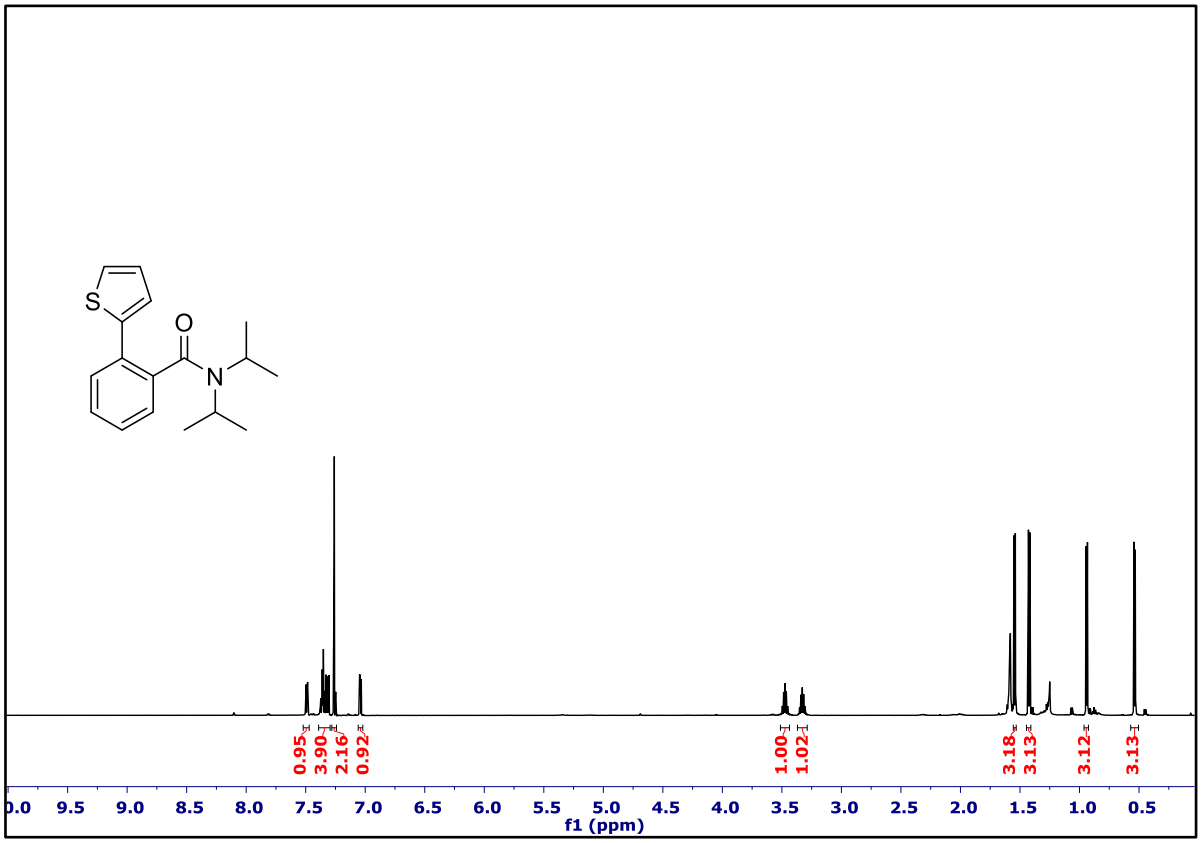


^{13}C NMR (150 MHz, $CDCl_3$)

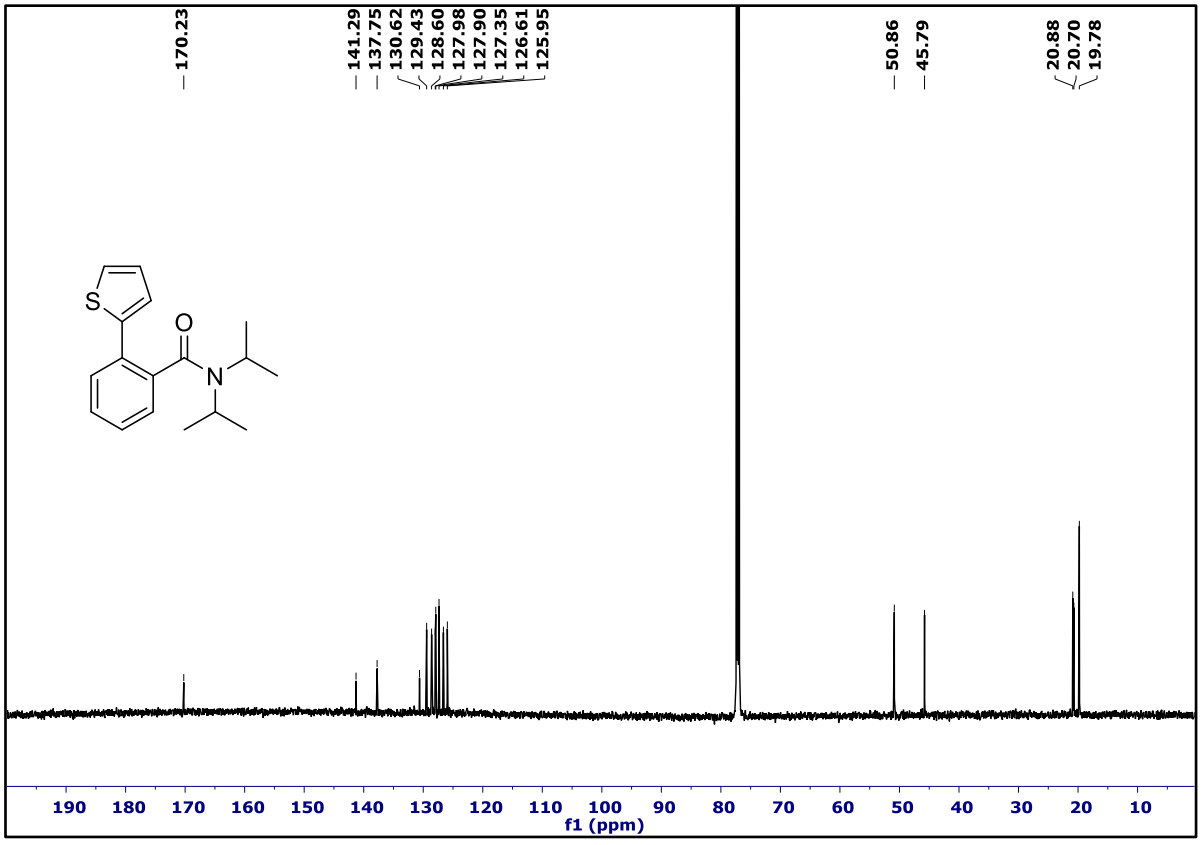


_N,N_-Diisopropyl-2-(thiophen-2-yl)benzamide (6c)

^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (150 MHz, $CDCl_3$)



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