Supporting Information

Towards a Sustainable Synthesis of Amides: Chemoselective Palladium-catalysed Aminocarbonylation of Aryl Iodides in Deep Eutectic Solvents

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1. General Information

Deep Eutectic Solvents [choline chloride (ChCl)−glycerol (Gly) (1:2 mol/mol), ChCl−urea (1:2 mol/mol), lactic Acid−D-glucose (1:2 mol/mol)], were prepared by heating under stirring at 75 °C for 10–30 min the corresponding individual components until a clear solution was obtained. All other reagents, catalysts and solvents were high-grade commercial products, used without further purification. ^{1}H-NMR spectra were obtained using a Bruker spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.62 MHz), $CDCl_3$ was used as the solvent. Dimethyl sulfone has been used as the internal standard for yield determination by ^{1}H NMR analysis on the crude reaction mixtures. IR spectra were recorded with a Jasco FT-IR spectrophotometer. Gas chromatography (GC) was conducted on an Rtx-5 30 m fused silica capillary column (split ratio 100:1). The following program was used: method A = initial temperature of 100 °C for 0.0 min, ramp 10 °C/min to 280 °C, and held for 15 min; the standard operating conditions were 300 °C injector temperature and 290 °C detector temperature. GC-MS analyses, conducted using method A, were performed with a gas chromatograph equipped with a 5% phenylpolymethylsiloxane capillary column, 30 m, 0.25 mm i.d., and a mass-selective detector operating at 70 eV. High-resolution mass spectrometry (HRMS) analyses were performed using a Bruker microTOF QII mass spectrometer equipped with an electrospray ion source (ESI). Analytical thin layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F254; visualisation was accomplished by UV light (254 nm). Chromatographic separations were performed on silica gel (63−200 mesh) using petroleum ether/ethyl acetate (AcOEt) mixture as the eluent.

Compounds **3aa** [1], **3ba**[2], **3cb**[3], **3db**[4], **3ea**[5], **5ab**[6], **5ca**[7], **5ea**[8], **5eb**[9], **5ec**[10], **5ed**[11], **5fa**[12], **5ia**[13], **5id**[14] are known, and their characterisation data are in agreement with those reported in the literature (see Refs. 1–14).

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2. Experimental Protocols

2.1 Preparation of amides (5) in Deep Eutectic Solvents. Typical procedure.

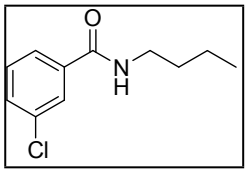
Aromatic iodide **1** (1.0 mmol), amine **4** (6.0 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), K_2CO_3 (414 mg, 3.0 mmol) and DES (2.0 g) were placed in a 25 mL autoclave reactor. The autoclave was purged three times with CO, pressurized to 27 atm CO, and then placed in an oil bath pre-heated at 60 °C. The reaction mixture was vigorously stirred at 60 °C for 12 h. After this time, the autoclave was depressurized, allowed to cool to room temperature, and the reaction mixture extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, and the solvent was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel [petroleum ether/AcOEt (90:10–30:70)] to give the corresponding amide **5**.

2.2 General procedure for the catalyst/DES recycling.

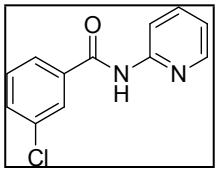
The recyclability of Pd/DES system was investigated with reference to the carbonylative coupling between 1-cloro-3-iodobenzene **1a** and *n*-$BuNH_2$ **4a** as a model reaction. 1-Chloro-3-iodobenzene **1a** (476 mg, 2.0 mmol), *n*-$BuNH_2$ **4a** (878 mg, 12.0 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol, 5 mol%) [or Pd/C (21.2 mg, 0.02 mmol, 1 mol%)], K_2CO_3 (828 mg, 6.0 mmol) and 4.0 g of the eutectic mixture ChCl/urea (1:2 mol/mol), [or ChCl/Gly (1:2) when Pd/C was used as the catalyst)] were placed in a 25 mL autoclave reactor. The autoclave was purged three times with CO, pressurized to 27 atm CO, and then placed in an oil bath pre-heated at 60 °C. The reaction mixture was vigorously stirred at 60 °C for 12 h. After this time, the autoclave was depressurized, allowed to cool to room temperature, and the eutectic mixture extracted with AcOEt (3 x 5 mL). The combined organic phases were separated, and the crude product **5aa** recovered. The DES phase was dried under vacuum until constant weight. Then, upon simply adding to the eutectic phase new, fresh reagents [**1a** (2.0 mmol), **4a** (12.0 mmol) and K_2CO_3 (2.0 mmol)], carbonylative coupling could be successfully run over four times (for details, see main text, Figure 1).

3. Spectroscopic Characterisation of New Compounds

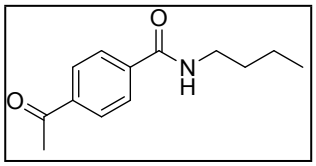
3.1 Characterisation data



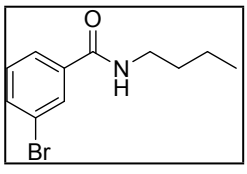
***N*-Butyl-3-chlorobenzamide (5aa)**: ^{1}H NMR (400.12 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.3 Hz, 3 H), 1.25–1.32 (m, 2 H), 1.45–1.53 (m, 2 H), 3.31–3.36 (m, 2 H), 6.69 (br s, 1 H), 7.22–7.26 (m, 1 H), 7.35 (d, J = 8.9 Hz, 1 H), 7.56 (d, J = 7.7 Hz, 1 H), 7.68 (s, 1 H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.2, 20.5, 32.0, 40.4, 125.5, 127.7, 130.1, 131.6, 134.9, 137.0, 166.7; FT-IR ($CHCl_3$): ν = 3451, 3069, 3008, 2961, 2932, 2874, 1657, 1521, 1470, 1287, 1079 cm^{-1}; GC-MS (70 eV): *m/z (%)* = 211 (M^+, 12), 168 (23), 139 (100), 111 (34), 75 (16), 50 (4). HRMS (ESI): *m/z* calcd for $C_{11}H_{15}ClNO$ $[M + H]^+$ 212.0842, found 212.0851.



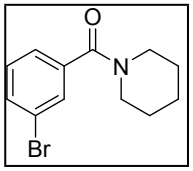
3-Chloro-*N*-(pyridin-2-yl)benzamide (5ac): ^{1}H NMR (400.12 MHz, $CDCl_3$): δ = 7.02–7.04 (m, 1 H), 7.37 (t, J = 7.9 Hz, 1 H), 7.48–7.50 (m, 1 H), 7.73–7.78 (m, 2 H), 7.91−7.92 (m, 1 H), 8.10–8.12 (m, 1 H), 8.36 (d, J = 8.4 Hz, 1 H), 9.38 (br s, 1 H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 114.5, 120.1, 125.4, 127.9, 130.0, 132.1, 135.0, 136.2, 138.3, 147.6, 151.4, 164.7; FT-IR ($CHCl_3$): ν = 3417, 3072, 3027, 3011, 2959, 2927, 2855, 1681, 1577, 1520, 1434, 1308, 1254; GC-MS (70 eV): *m/z (%)* = 232 (M^+, 17), 203 (100), 139 (84), 111 (65), 75 (26), 50 (8). HRMS (ESI): *m/z* calcd for $C_{12}H_{10}ClN_2O$ $[M + H]^+$ 233.0482, found 233.0470.



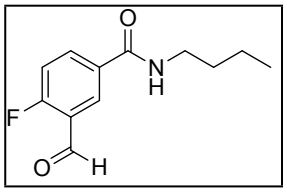
4-Acetyl-*N*-butylbenzamide (5ba): ^{1}H NMR (400.12 MHz, $CDCl_3$): δ= 0.96 (t, J = 7.3 Hz, 3 H), 1.37–1.45 (m, 2 H), 1.58–1.64 (m, 2 H), 2.63 (s, 3 H), 3.44–3.49 (m, 2 H), 6.44 (br s, 1H), 7.85 (d, J = 8.2 Hz, 2 H), 7.97 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 13.7, 20.1, 26.7, 31.6, 40.0, 127.2, 128.4, 138.8, 139.0, 166.6, 197.5; FT-IR ($CHCl_3$): ν = 3026, 3010, 2961, 2930, 2874, 2862, 1686, 1660, 1526, 1466, 1359, 1267 cm^{-1}; GC-MS (70 eV): *m/z (%)* = 219 (M^+, 18), 204 (5), 190 (4), 147 (100), 119 (9), 104 (14), 91 (14), 76 (11), 65 (3), 50 (4). HRMS (ESI): *m/z* calcd for $C_{13}H_{18}NO_2$ $[M + H]^+$ 220.1338, found 220.1342.



3-Bromo-*N*-butylbenzamide (5ga): ^{1}H NMR (400.12 MHz, $CDCl_3$): δ = 0.97 (t, J = 7.3 Hz, 3 H), 1.37–1.45 (m, 2 H), 1.57–1.64 (m, 2 H), 3.43–3.48 (m, 2 H), 6.07 (br s, 1 H), 7.30 (t, J = 7.9 Hz, 1 H), 7.61−7.63 (m, 1H), 7.67−7.69 (m, 1 H), 7.89−7.90 (m, 1 H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 13.7, 20.1, 31.6, 39.9, 122.7, 125.3, 130.0, 130.1, 134.2, 136.8, 166.0 ppm; FT-IR ($CHCl_3$): ν = 3451, 3009, 2961, 2932, 2874, 1658, 1566, 1521, 1469, 1285 cm^{-1}; GC-MS (70 eV): *m/z (%)* = 255 (M^+, 13), 213 (28), 183 (100), 157 (33), 76 (23), 50 (9). HRMS (ESI): *m/z* calcd for $C_{11}H_{15}BrNO$ $[M + H]^+$ 256.0337, found 256.0347.

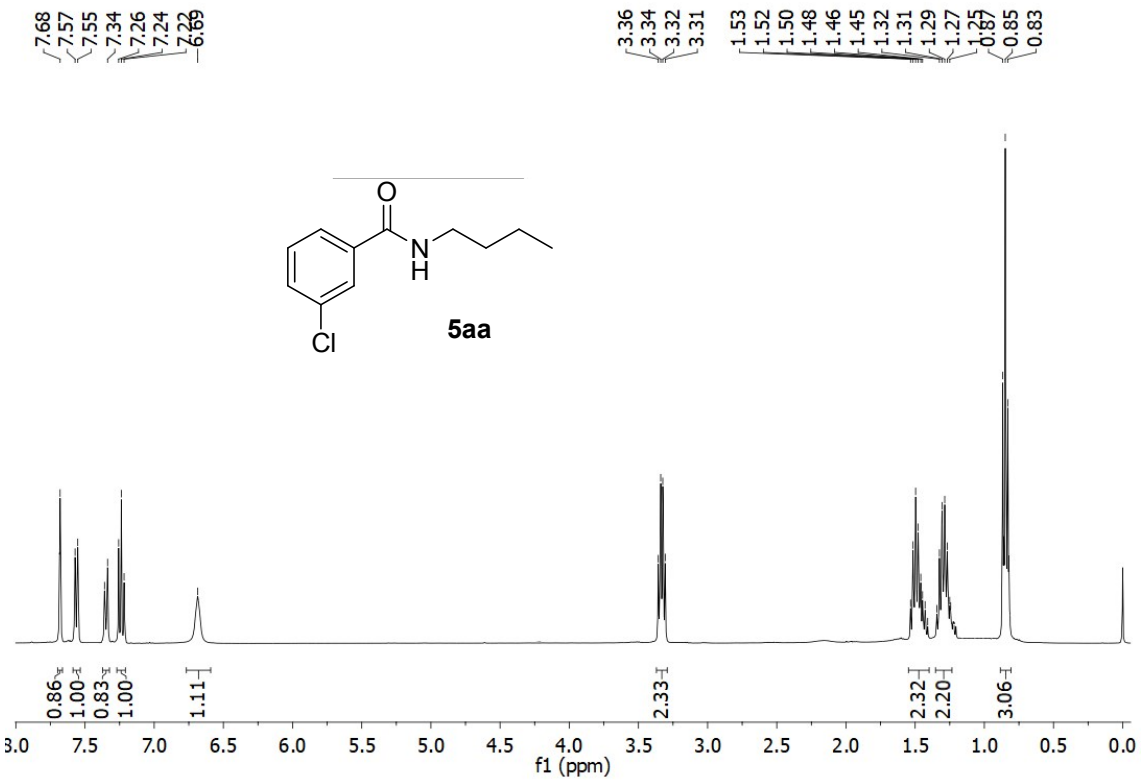


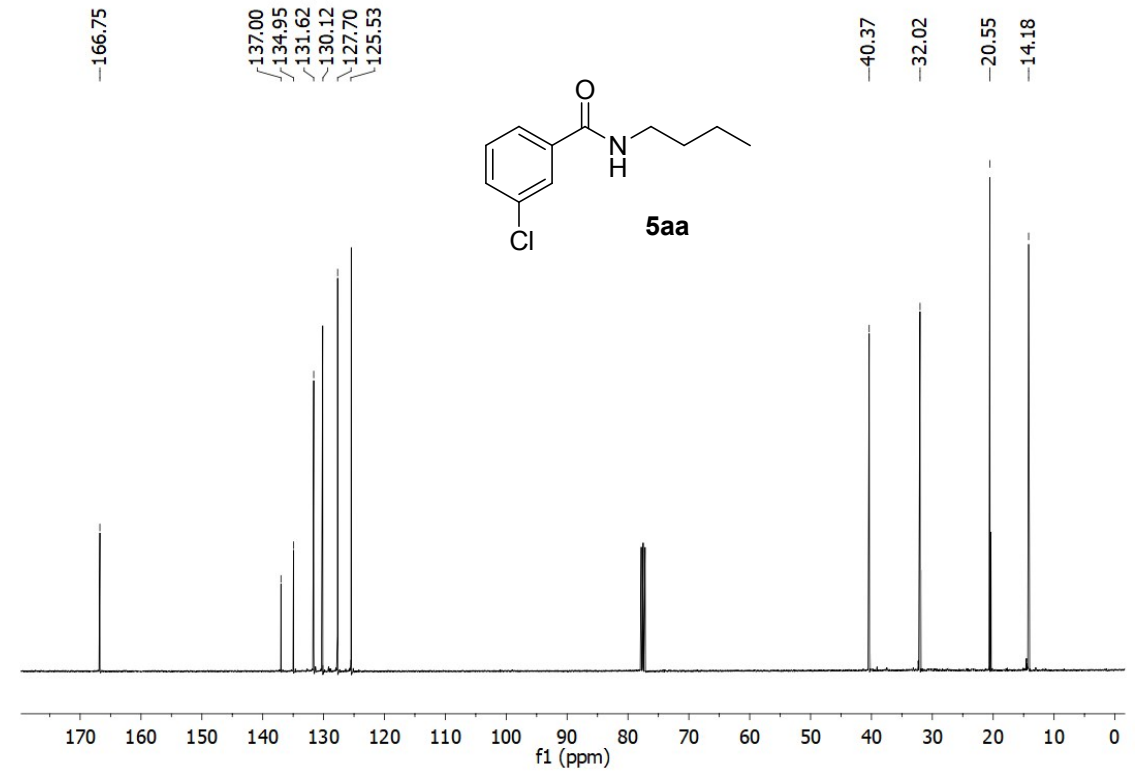
3-Bromophenyl(piperidin-1-yl)methanone (5gb): ^{1}H NMR (400.12 MHz, $CDCl_3$): δ = 1.24–1.28 (m, 2 H), 1.52–1.68 (m, 4 H), 3.33 (br s, 2 H), 3.70 (br s, 2 H), 7.25–7.32 (m, 3 H), 7.52–7.54 (m, 1 H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 25.5, 26.5, 29.6, 43.2, 48.7, 122.5, 125.3, 129.8, 130.0, 132.4, 138.4, 168.5; FT-IR ($CHCl_3$): ν = 2955, 2923, 2853, 2360, 2341, 1731, 1463, 1377, 1286, 1272 cm^{-1}; GC-MS (70 eV): *m/z (%)* = 267 (M^+, 100), 183 (66), 155 (32), 76 (20), 50 (7). HRMS (ESI): *m/z* calcd for $C_{12}H_{15}BrNO$ $[M + H]^+$ 268.0337, found 268.0329.

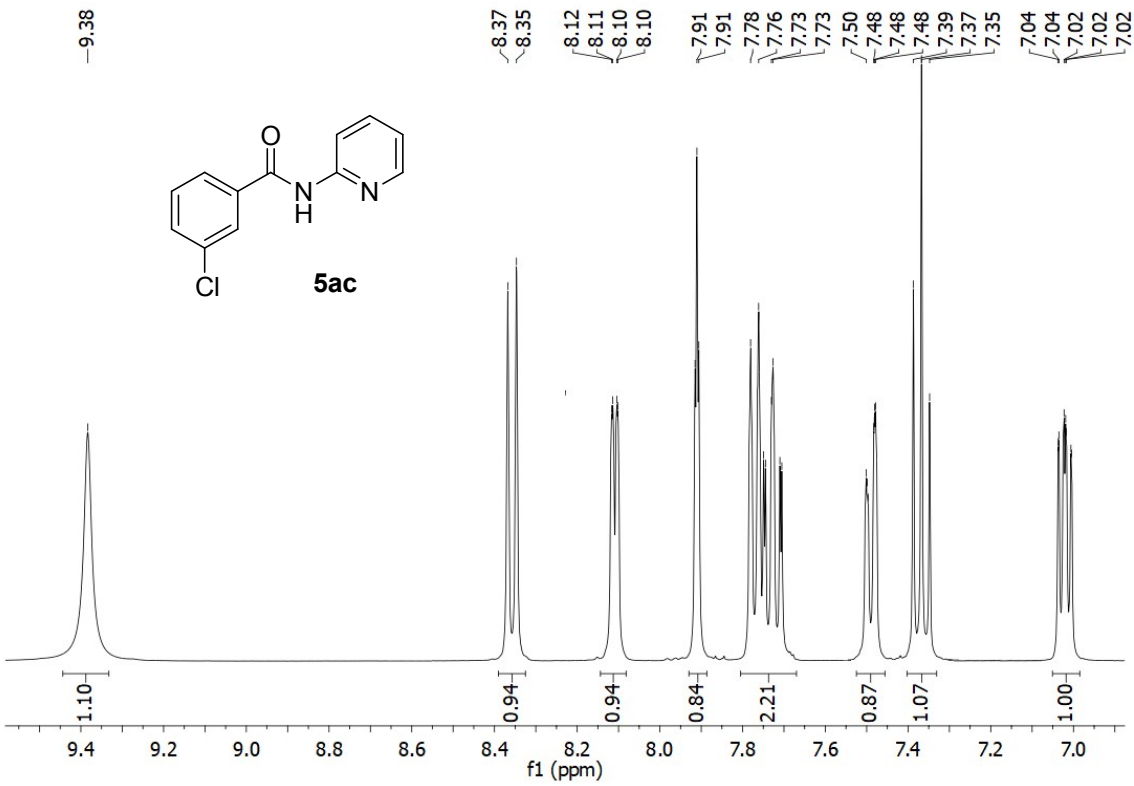


N*-Butyl-4-fluoro-3-formylbenzamide (5ha):* ^{1}H NMR (400.12 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H), 1.39–1.45 (m, 2 H), 1.58–1.65(m, 2 H), 3.44–3.49 (m, 2 H), 6.39 (br s, 1 H), 7.27 (t, *J* = 9.5 Hz, 1 H), 8.18–8.21 (m, 2 H), 10.38 (s, 1 H); ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 13.7, 20.1, 31.6, 40.0, 117.2 (d, *J* = 21.1 Hz), 123.5 (d, *J* = 8.7 Hz), 126.3 (d, *J* = 2.2 Hz), 131.6 (d, *J* = 3.2 Hz), 136.1 (d, *J* = 9.9 Hz), 165.1, 166.1 (d, *J* = 263.7), 186.4 (d, *J* = 6.2 Hz); FT-IR ($CHCl_3$): ν = 3009, 2961, 2931, 2873, 1695, 1660, 1608, 1527, 1488 cm^{-1}; GC-MS (70 eV): *m/z (%)* = 223 (M^+, 8), 181 (28), 151 (100), 123 (17), 95 (12), 75 (12). HRMS (ESI): *m/z* calcd for $C_{12}H_{15}FNO_2$ $[M + H]^+$ 224.1087, found 224.1095.

3.2 Copies of ^{1}H- and ^{13}C-NMR spectra



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H
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Cl
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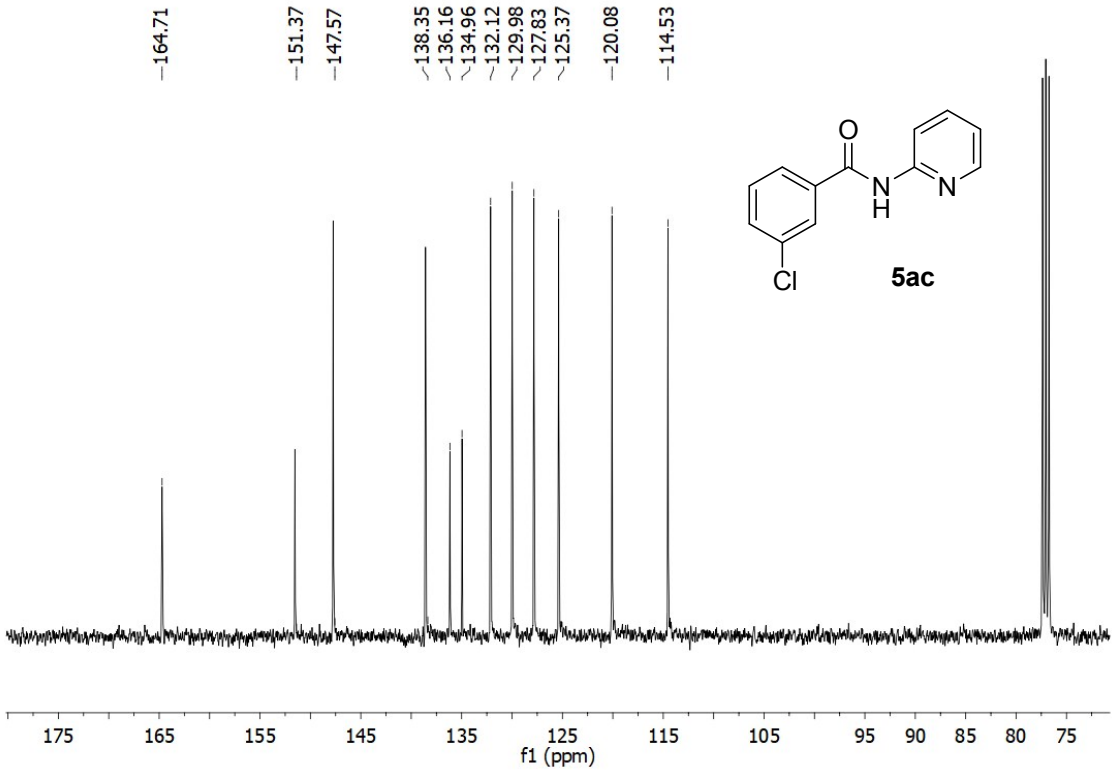
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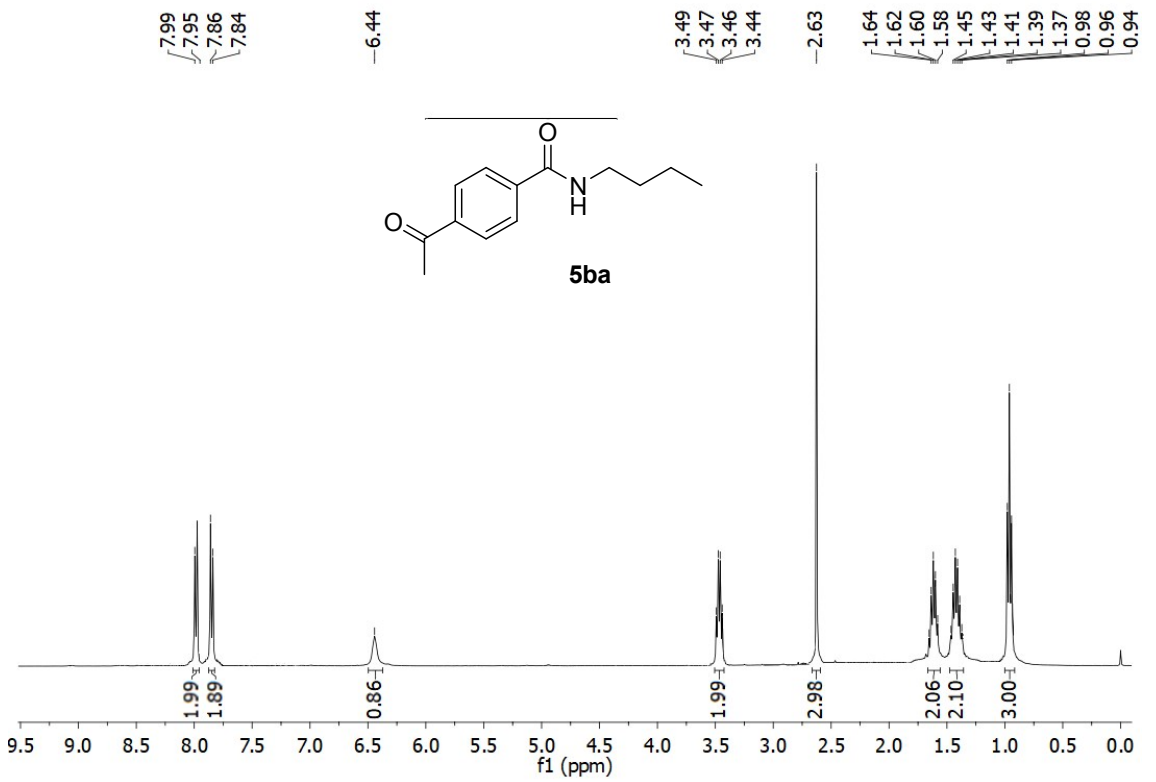
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H
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2.98
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3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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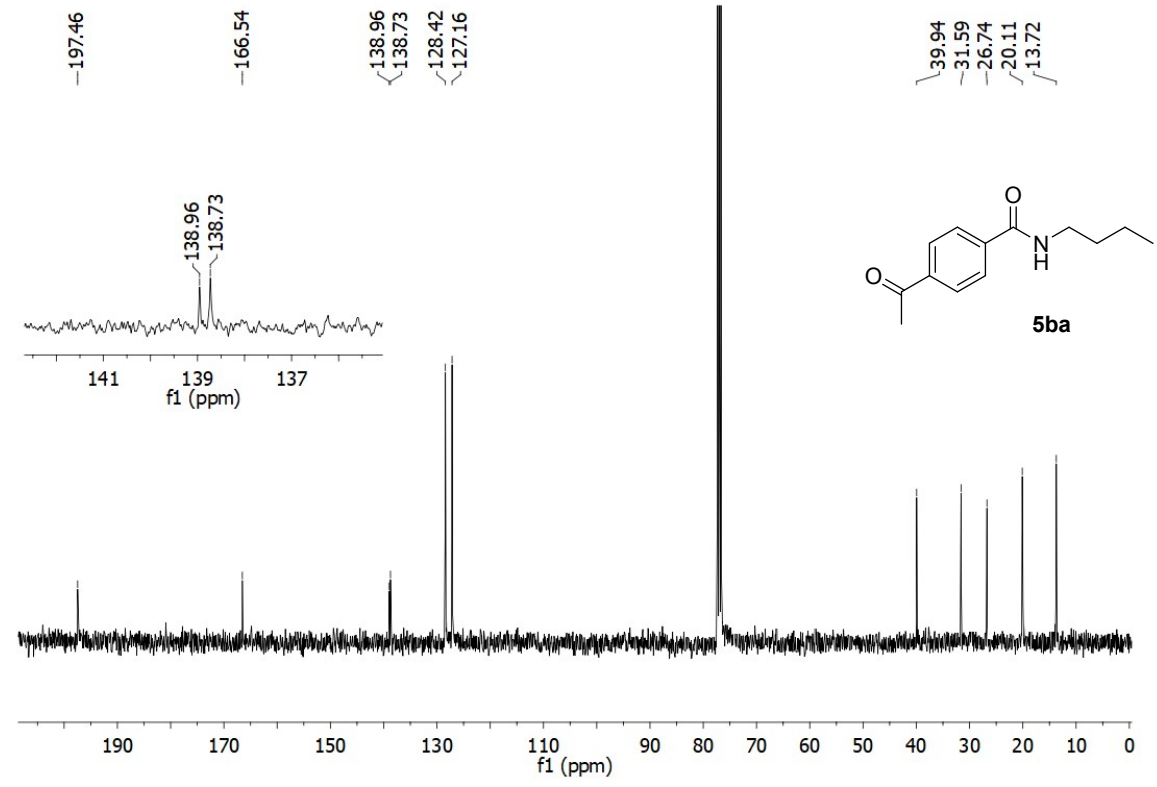
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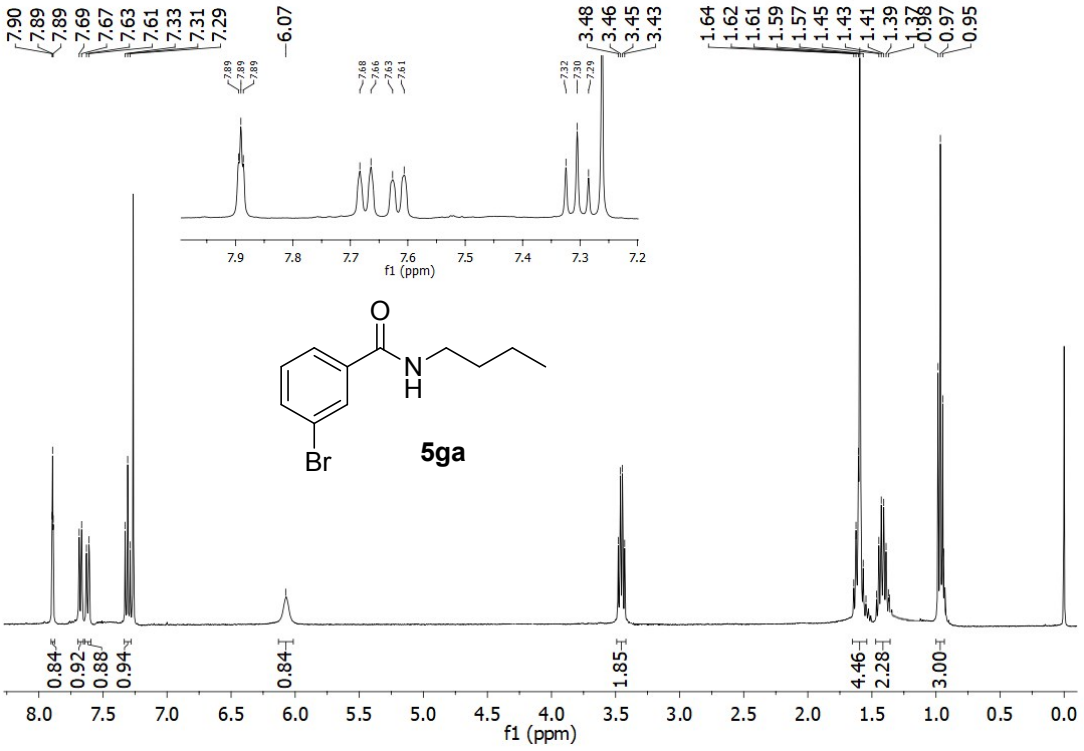
f1 (ppm)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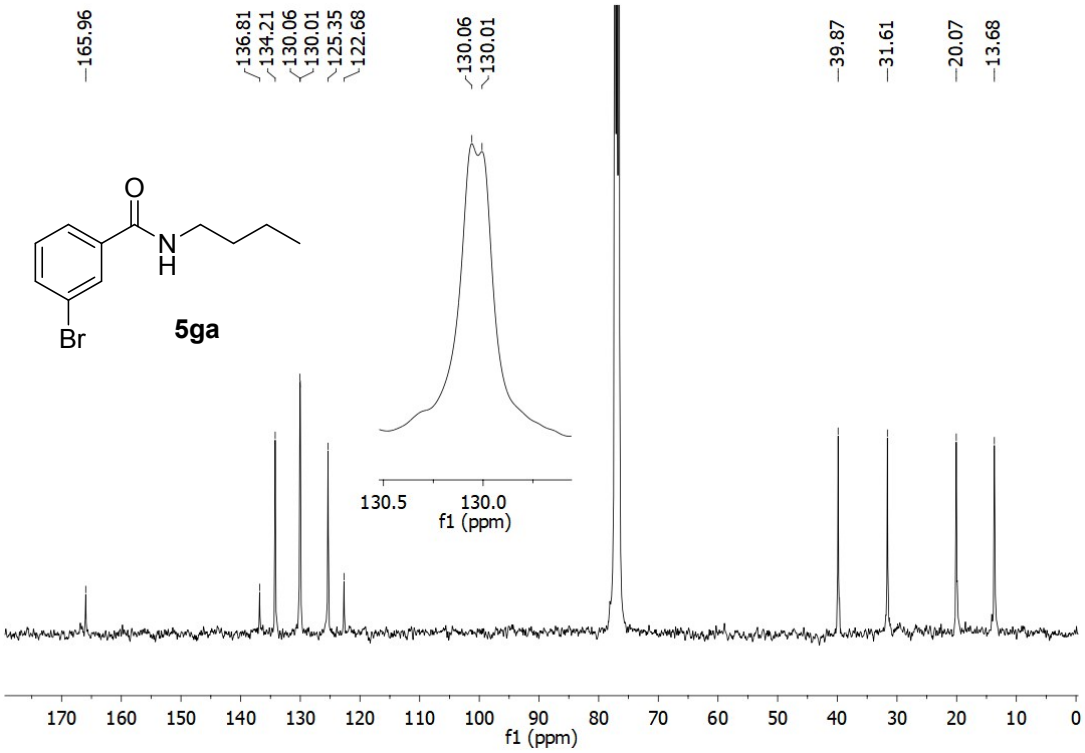
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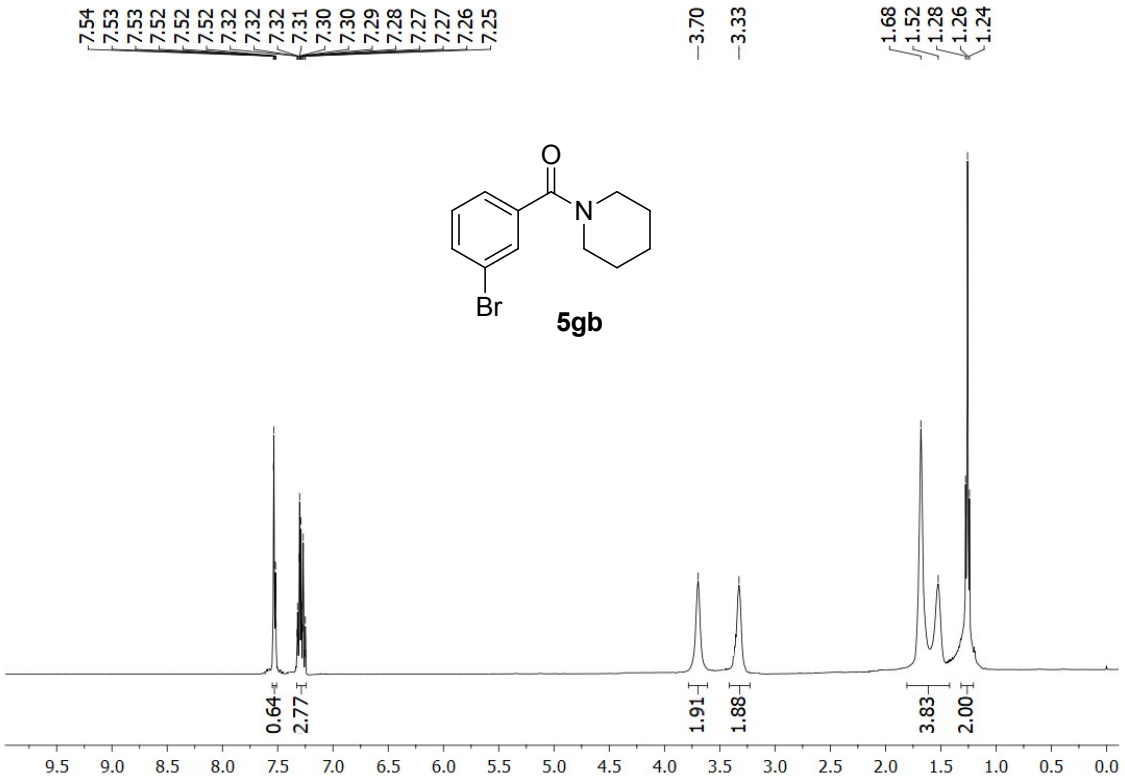
f1 (ppm)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7.25
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1.26
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N
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3.83
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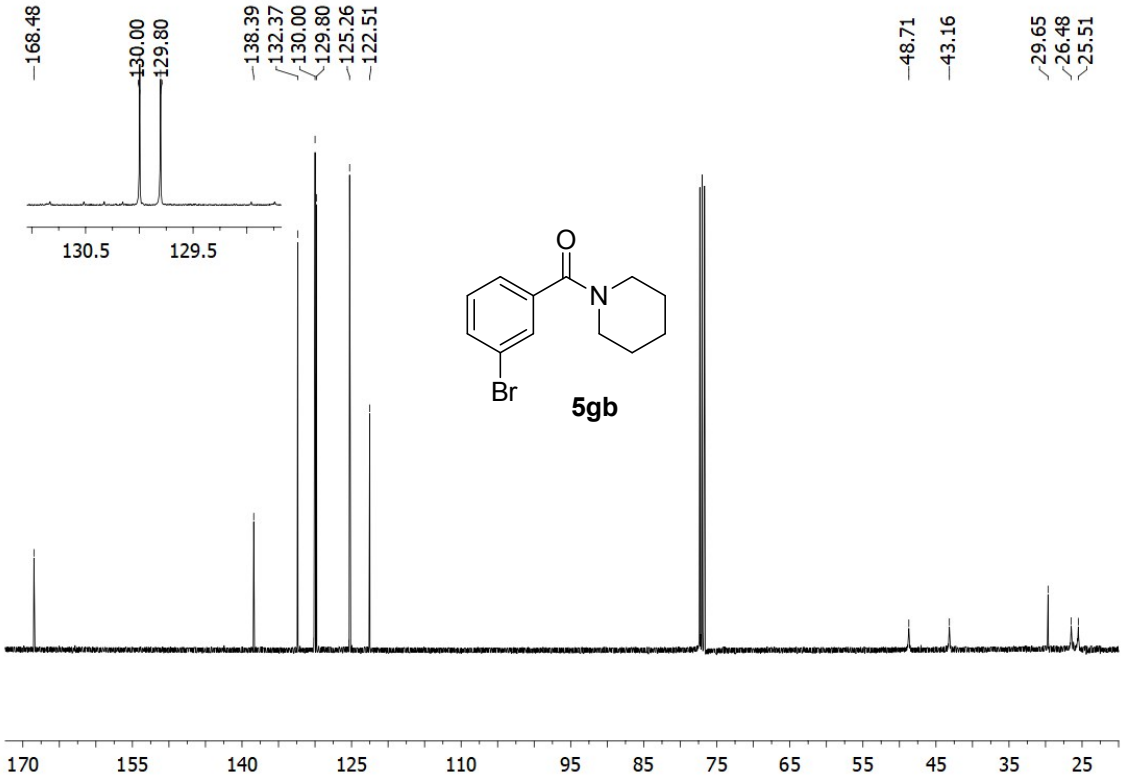
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Br
5gb
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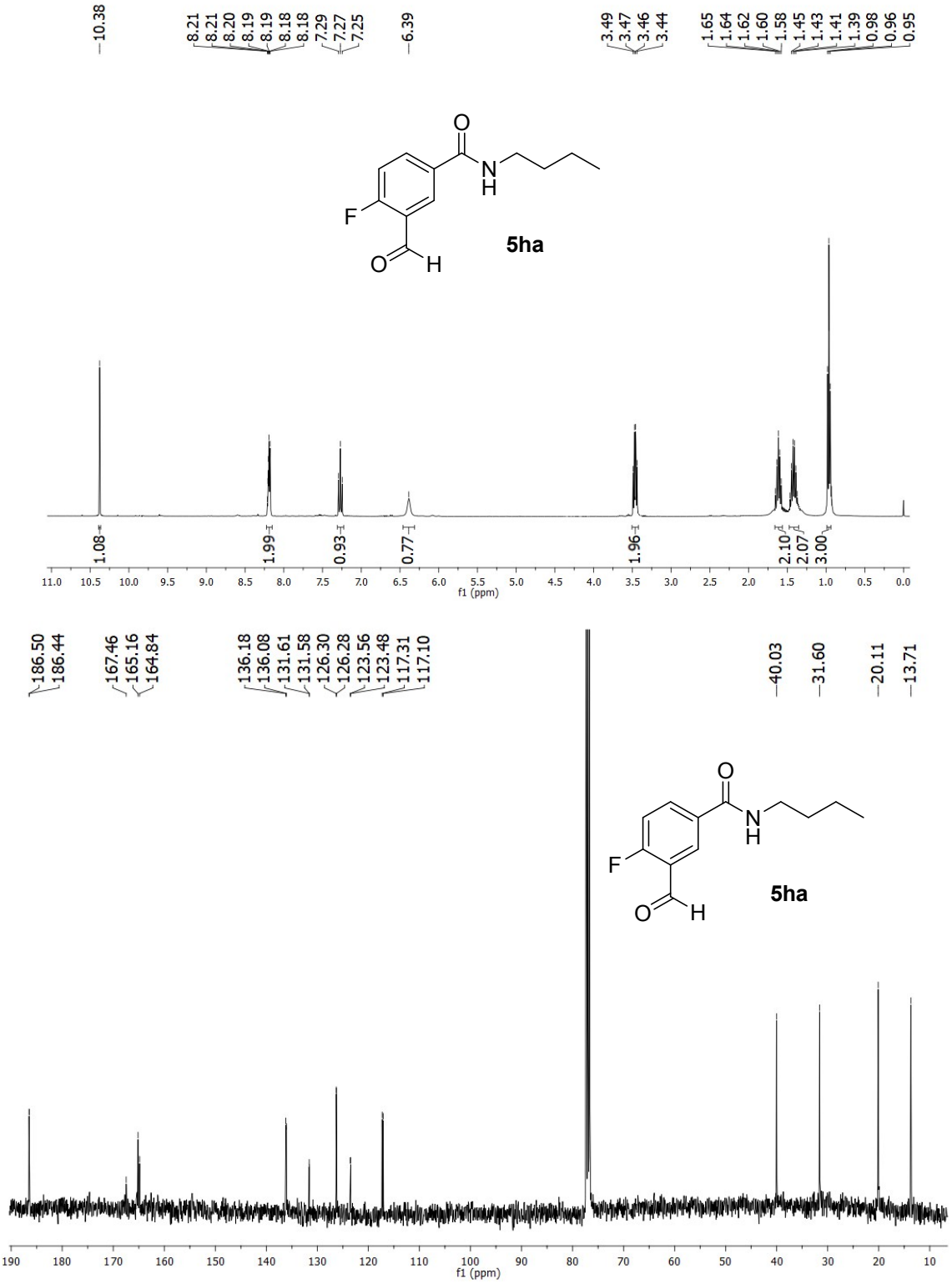
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3.47
3.46
3.44
1.65
1.64
1.62
1.60
1.58
1.45
1.43
1.41
1.39
0.98
0.96
0.95
O
N
H
F
O
H
5ha
1.08
1.99
0.93
0.77
1.96
2.10
2.07
3.00
f1 (ppm)
186.50
186.44
167.46
165.16
164.84
136.18
136.08
131.61
131.58
126.30
126.28
123.56
123.48
117.31
117.10
40.03
31.60
20.11
13.71
f1 (ppm)