Tandem Copper-Catalysed Aryl and Alkenyl Amination Reactions: The Synthesis of *N*-Functionalised Indoles

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Electronic Supporting Information

General Information: All reactions were performed under an inert atmosphere of nitrogen or argon, in oven or flame dried glassware unless otherwise stated. All chemicals were purchased from Acros or Aldrich chemical companies and used without further purification, unless otherwise stated. Copper(I) iodide and copper(I) acetate was purchased from Strem Chemicals Inc. Copper(I) thiophene-2-carboxylate was purchased from Frontier Scientific. Potassium carbonate and potassium phosphate were ground and dried in a Kugelrohr oven for 24 hours at 70 ^{o}C before use. Petroleum ether refers to the fraction obtained between 30-40 ^{o}C. Anhydrous toluene was purchased from Acros Organic as the extra dry over molecular sieves.

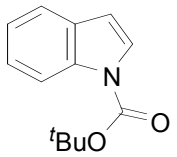
Analytical thin layer chromatography was carried out using pre-coated aluminium backed silica plates (Merck Kieselgel 60F254) and pre-coated plastic backed silica plates (Polygram® Sil G/UV254). Plates were visualised under ultraviolet light (254 nm) or by staining with $KMnO_4$ or vanillin. Flash column chromatography was carried out using Merck Kieselgel 60H silica. Pressure was applied at the column head *via* hand bellows.

Melting points were determined using a Büchi 535 melting point apparatus and a Leica Galen III and are reported uncorrected. Infrared measurements were carried out as liquid films on NaCl discs or as a KBr disc using a Perkin-Elmer 1600 series FTIR spectrometer and Bruker Tensor 27 FT-IR with internal calibration in the range 4000-500 cm-1. Mass spectrometry was carried out either on a Bruker microTOF or a Bruker FT-ICR-MS Apex III at the University of Oxford, or using a Micromass Quattro II and a Finnegan MAT 95XP at the EPSRC mass spectrometry service at the University of Wales, Swansea.

^{1}H, and ^{13}C nuclear magnetic resonance experiments were carried out using a Bruker ACAC-300 MHz or AC-400 MHz NMR spectrometers. Chemical shifts were reported in parts per million from tetramethylsilane for ^{1}H and ^{13}C experiments. The residual solvent peak was used as an internal standard. The multiplicities of the spectra are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Coupling constants (*J*) are given in Hz.

Compounds Table 2 entry 1,[1] Table 2 entry 2,[2] Table 2 entry 3,[3] Table 2 entry 4,[4] Table 2 entry 5,[5] Table 2 entry 6,[6] Table 2 entry 7,[7] Table 3 entry 1,[8] Table 3 entry 2,[9] Table 3 entry 4,[10] were isolated and all data was in accordance with that reported in the literature.

Method 1: the synthesis of indoles using copper(I) iodide; *N*-(*tert*-butoxycarbonyl) indole (2)

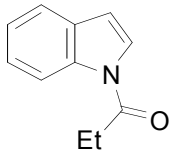


Potassium carbonate (316 mg, 2.29 mmol) and *tert*-butylcarbamate (179 mg, 1.52 mmol) were added to an oven dried flask charged with CuI (14 mg, 0.08 mmol) and *N,N'*-methylethyldiamine (13 mg, 16 μL, 0.15 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.38 mL) and treated with (*Z*)-1-bromo-2-(2-bromovinyl)benzene[11] (200 mg, 0.76 mmol). The reaction mixture was stirred for 24 hour at 110 ^{o}C. The reaction was diluted with ethyl acetate, filtered through celite, and reduced *in vacuo*. The product was purified by flash chromatography (10% EtOAc: Hexane) to yield the *indole* (142 mg, 85%) as a yellow oil. All data in accordance with that was reported in the literature.[4]

Method 2: the synthesis of indoles using copper(I) acetate; *N*-(*tert*-butoxycarbonyl) indole (2)

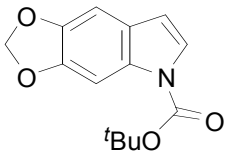
Potassium phosphate (485 mg, 2.29 mmol) and *tert*-butylcarbamate (179 mg, 1.52 mmol) were added to an oven dried flask charged with CuOAc (9 mg, 0.08 mmol) and *N,N'*-dimethylethylenediamine (13 mg, 16 μL, 0.15 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.38 mL) and treated with (*Z*)-1-bromo-2-(2-bromovinyl)benzene[11] (200 mg, 0.76 mmol). The reaction mixture was stirred for 24 hour at 110 ^{o}C. The reaction was cooled to rt diluted with ethyl acetate (10 mL), filtered through celite, and filtrate reduced *in vacuo*. The product was purified by flash chromatography (10% EtOAc: Hexane) to yield the *indole* (146 mg, 88%).

Method 3: the synthesis of indoles using copper(I) thiophene-2-carboxylate; 1-Propionyl-indole (Table 3, entry 6)



Potassium carbonate (157 mg, 1.14 mmol) and propionamide (56 mg, 0.76 mmol) were added to an oven dried flask charged with CuTC (8 mg, 0.04 mmol) and *N,N'*-dimethylethylenediamine (7 mg, 9 μL, 0.08 mmol) under nitrogen. The reagents were suspended in anhydrous toluene (0.19 mL) and treated with (*Z)*-1-bromo-2-(2-bromovinyl) benzene (100 mg, 0.38 mmol). The reaction mixture was stirred for 24 h at 110 ^{o}C. The reaction was cooled to rt and quenched with ethyl acetate, filtered through celite, and reduced under *in vacuo*. The product was purified by flash chromatography (10% EtOAc: Hexane) to yield the *indole* (58 mg, 89%). All data in accordance with literature.[5]

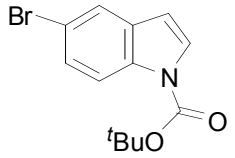
[1,3] Dioxolo[4,5-*f*]indole-5-carboxylic acid *tert*-butyl ester (Table 3, entry 3)



Prepared following method 2, using (*Z*)-5-bromo-6-(2-bromovinyl)benzo (1,3)dioxole[11] (100 mg, 0.35 mmol), *tert*-butyl carbamate (247 mg, 2.10 mmol) and cesium carbonate (519 mg, 0.98 mmol). The product was purified by flash chromatography (10% EtOAc: Hexane) to yield the *indole* (55 mg, 62%) as a white solid. m.p: 150^{o}C (dec.) ν_{max}/cm^{-1} (thin film) 2978, 2901, 1732, 1463, 1294, 1392, 1158, 1095; δ_{1H} (400 MHz, Acetone) 1.67 (9H, s, Me), 6.01 (2H, s, CH_2O_2), 6.53 (1H, d, *J* 3.7, H3), 7.01 (1H, s, ArH), 7.51 (1H, d, *J* 3.7, H2), 7.51 (1H, s ArH); δ_{13C} (100

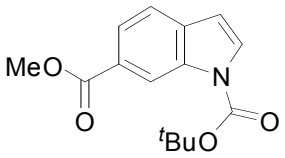
MHz, Acetone) 28.7 (3C), 84.9, 97.7, 101.0, 102.5, 108.7, 125.9 (2C), 131.3, 145.9, 147.5, 150.8; HRMS (ES^+) 284.0894 ($[M+Na]^+$. $C_{14}H_{15}NNaO_2$ requires: 284.0893).

5-Bromo-indole-1-carboxylic acid *tert*-butyl ester (Table 3, entry 5)



Prepared following method 2, using (*Z*)-1,3-dibromo-2-(2-bromovinyl)benzene (100 mg, 0.29 mmol), *tert*-butyl carbamate (60 mg, 0.81 mmol) and copper(I) acetate (3 mg, 0.02 mmol). The product was purified by flash chromatography (10% EtOAc: Hexane) to yield the *indole* (43 mg, 53%) as a yellow oil. ν_{max}/cm^{-1} (thin film) 2979, 2933, 1737, 1449, 1396, 1344, 1158, 1132, 1084; δ_{1H} (500 MHz, $CDCl_3$) 1.68 (9H, s, Me), 6.51 (1H, d, *J* 3.6, H3), 7.40 (1H, dd, *J* 8.8, 1.9, ArH), 7.60 (1H, d, *J* 3.6, H2), 7.69 (1H, d, *J* 1.9, ArH), 8.03 (1H, d, *J* 7.9, ArH); δ_{13C} (125 MHz, $CDCl_3$) 28.2(3C), 84.1, 111.5 115.9, 116.5, 118.4, 120.7, 121.6 123.5, 132.2, 149.4; HRMS (EI^+): 318.0100 ($[M+Na]^+$. $C_{13}H_{14}{}^{79}BrNNaO_2$ requires: 318.0100).

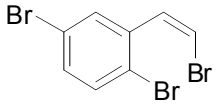
Indole-1,6-dicarboxylic acid 1-*tert*-butyl ester 6-methyl ester (Table 3, entry 6)



Prepared following method 2, using (*E*)-methyl-3-bromo-4-(2-bromovinyl)benzoate (100 mg, 0.31 mmol), *tert*-butyl carbamate (145 mg, 1.24 mmol) and copper(I) acetate (2 mg, 0.02 mmol). The product was purified by flash chromatography (10% EtOAc: Hex) to yield the *indole* (79 mg, 70%) as a yellow oil. ν_{max}/cm^{-1} (thin film) 2951, 1719, 1614, 1524, 1437, 1370, 1300, 1239, 1122, 1025, 908, 780; δ_{1H} (500

MHz, $CDCl_3$) 1.71 (9H, s, Me), 3.95 (3H, s, OMe), 6.62 (1H, d, *J* 4, H3), 7.60 (1H, d, *J* 8.1, ArH), 7.75 (1H, d, *J* 4, H2), 7.94 (1H, dd, *J* 8.1, 1.6, ArH), 8.88 (1H, s, ArH); δ_{13C} (125 MHz, $CDCl_3$) 28.1(3C), 52.1, 84.3, 107.1, 117.1, 120.6, 123.8, 125.9, 128.0, 128.6, 133.5, 149.4, 167.7; HRMS (ES^+): 298.1048 ($[M+Na]^+$ $C_{15}H_{17}NNaO_4$; requires: 298.1050).

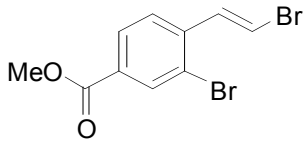
(*Z*)-1,4-Dibromo-2-(2-bromovinyl)benzene



(Bromomethyl) triphenylphosphonium bromide (1.98 g, 4.6 mmol) was added portion-wise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 109 mg, 4.6 mmol) in anhydrous THF (200 mL) under nitrogen at 0 ^oC. The reaction was allowed to stir at 0^oC for 90 min, before 2,5-dibromobenzaldehyde (1 g, 3.8 mmol) was added slowly to the resultant pale orange suspension. The reaction was allowed to warm to room temperature and stirred for 3 h under nitrogen. The resulting mixture was quenched with petroleum ether (50 mL) and cast into petroleum ether (200 mL). The white suspension was filtered though a celite pad, washing with petroleum ether (150 mL). The filtrate was partially reduced in *vacuo.* The suspension was filtered though a second celite pad, washing with petroleum ether (200 mL). The filtrate was reduced in *vacuo*. The product was separated by flash chromatography (petroleum ether) to yield the *vinyl bromide* (864 mg, *E/Z* 1:5, 67 %). ν_{max}/cm^{-1} (thin film) 2923, 2852, 1617, 1544, 1452, 1385, 1318, 1083, 1027, 808; δ_{1H} ($CDCl_3$) 6.65 (1H, d, *J* 7.9, CH=C*H*Br), 6.80 (1H, d, *J* 14, CH=C*H*Br), 7.13 (1H, d, *J* 7.9, C*H*=CHBr) 7.29-7.73 (6H, m, ArH and (*E)* C*H*=CHBr), 7.90 (1H, d, *J* 2.05, ArH);

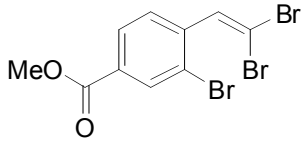
δ_{13C} ($CDCl_3$) 110.7, 118.0, 122.3, 131.2, 132.7, 133.2, 133.9, 136.9; HRMS (FI^+): 337.7951 ($[M]^+$ $C_8H_5{}^{79}Br_3$ requires: 337.7941).

(*E*)-3-Bromo-4-(2-bromovinyl)-methylbenzoate



In an oven dried flask 3-bromo-4-(2,2-dibromovinyl)-methylbenzoate (1.5 g, 3.76 mmol) and dimethyl phosphate (1.66g, 1.38 mL, 15.04 mmol) in DMF (30 mL). Then triethylamine (1.71 g, 2.36 mL, 16.92 mmol) was added and heated at 70 ^oC for 16 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (3 x 30 mL) and concentrated *in vacuo*. The product was separated by flash chromatography (petroleum ether) to yield the *vinyl bromide* as a single isomer (869 g, 72%). mp: 96-98. ν_{max}/cm^{-1} (thin film) 1711, 1387, 1293, 939, 753; δ_{1H} (500 MHz, $CDCl_3$) 3.93 (3H, s, OMe), 6.92 (1H, d, *J* 14.0, CH=C*H*Br), 7.47 (1H, d, *J* 14.0, C*H*=CHBr), 7.47 (1H, d, *J* 8.4, ArH), 7.92-7.94 (1H, m, ArH), 8.23 (1H, d, *J* 1.2, ArH); δ_{13C} (125 MHZ, $CDCl_3$) 52.5, 111.8, 122.5, 126.8, 128.6, 131.0, 134.4, 135.5, 139.9, 165.4; HRMS (ES^+): 340.8783 ($[M+Na]^+$ $C_{10}H_8{}^{79}Br_2O_2Na$ requires: 340.8783).

Procedure for the preparation of 3-bromo-4-(2,2-dibromovinyl)-methylbenzoate.



A solution of carbon tetrabromide (4.09 g, 12.34 mmol) in DCM (50 ml) was added dropwise to a stirred solution of triphenyl phosphine (6.47 g, 24.67 mmol) in DCM

(100 ml) at 0 ^{o}C under nitrogen and stirred for 30 mins at 0 ^{o}C, which was then treated portion-wise with 3-bromo-4-formyl-methylbenzoate[12] (1.5 g, 6.17 mmol). The resulting reaction mixture was stirred for 2 h and allowed to warm to rt and stirred for 16 h. The reaction mixture was poured into hexane (100 mL), filtered through celite and concentrated *in vacuo* to give a yellow oil. The crude product was purified *via* flash chromatography (hexane) to yield the *dibromide* (1.85 g, 75%) as pale yellow crystals.; m.p. 101-103^{o}C; ν_{max}/cm^{-1} (thin film) 1720, 1379, 1301, 1263, 1113, 785, 755; δ_{1H} (500 MHz, $CDCl_3$) 3.94 (3H, s, OMe), 7.54 (1H, s, $CH=CBr_2$), 7.69 (1H, d, *J* 8, ArH), 7.99 (1H, dd, *J* 8, 1.4, ArH), 8.26 (1H, d, *J* 8, ArH); δ_{13C} (125 MHZ, $CDCl_3$) 52.4, 94.4, 123.0, 128.2, 130.3, 131.4, 133.8, 135.9, 140.3, 165.3; HRMS (FI^+): 395.7996($[M]^+$ $C_{10}H_7$ ^{81}Br $^{79}Br_2O_2$; requires: 395.7979).

Reference

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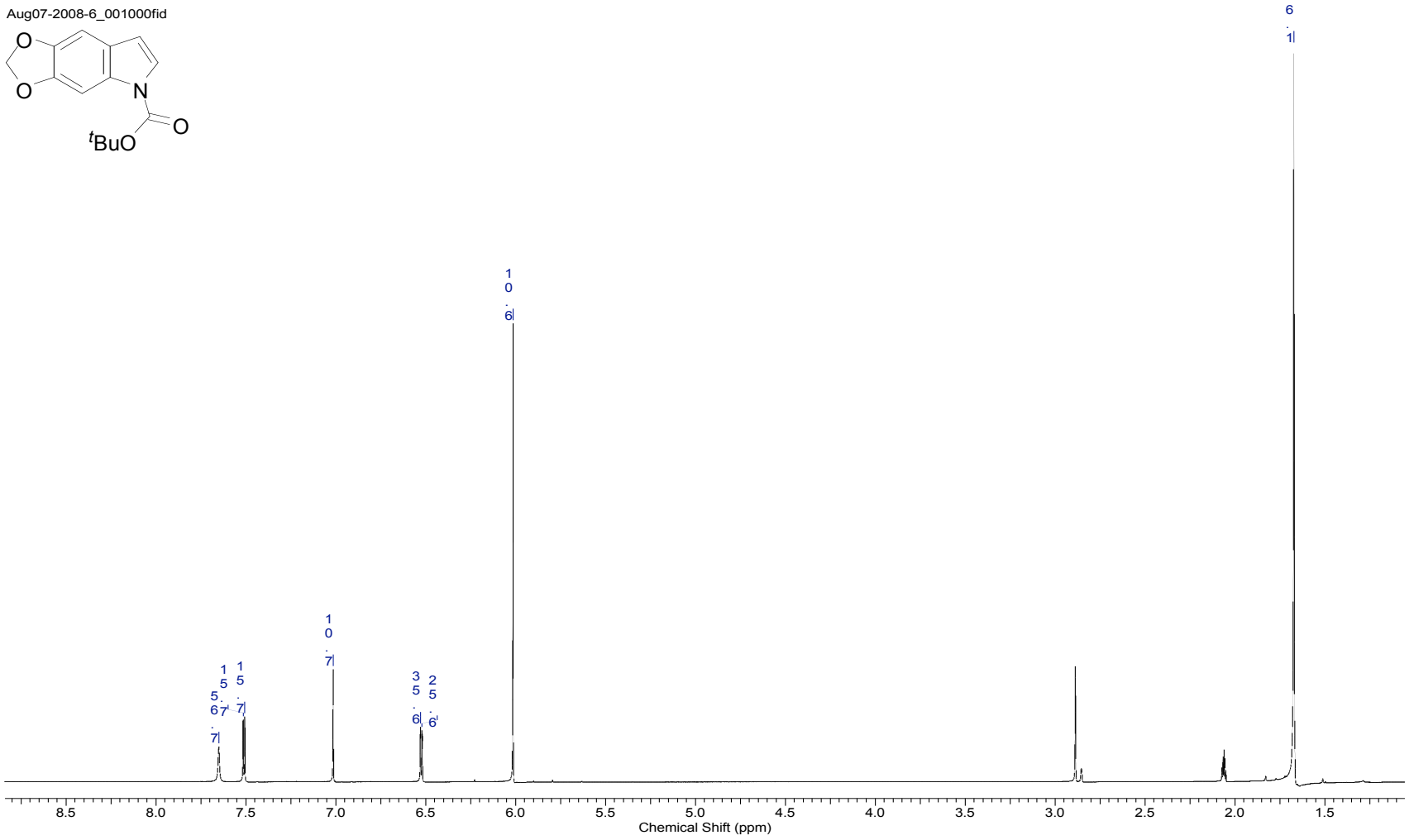
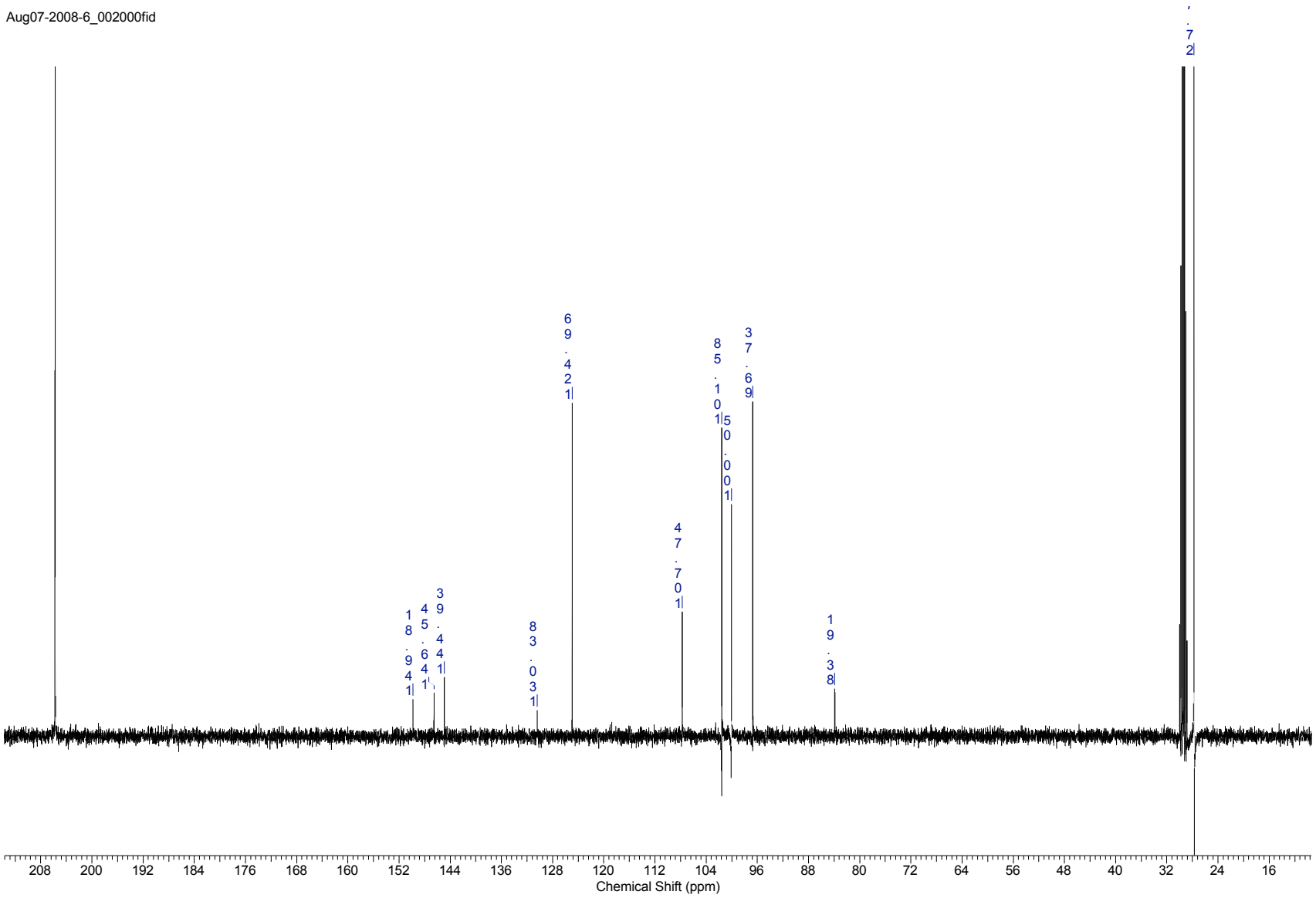
Table 3 Entry 3

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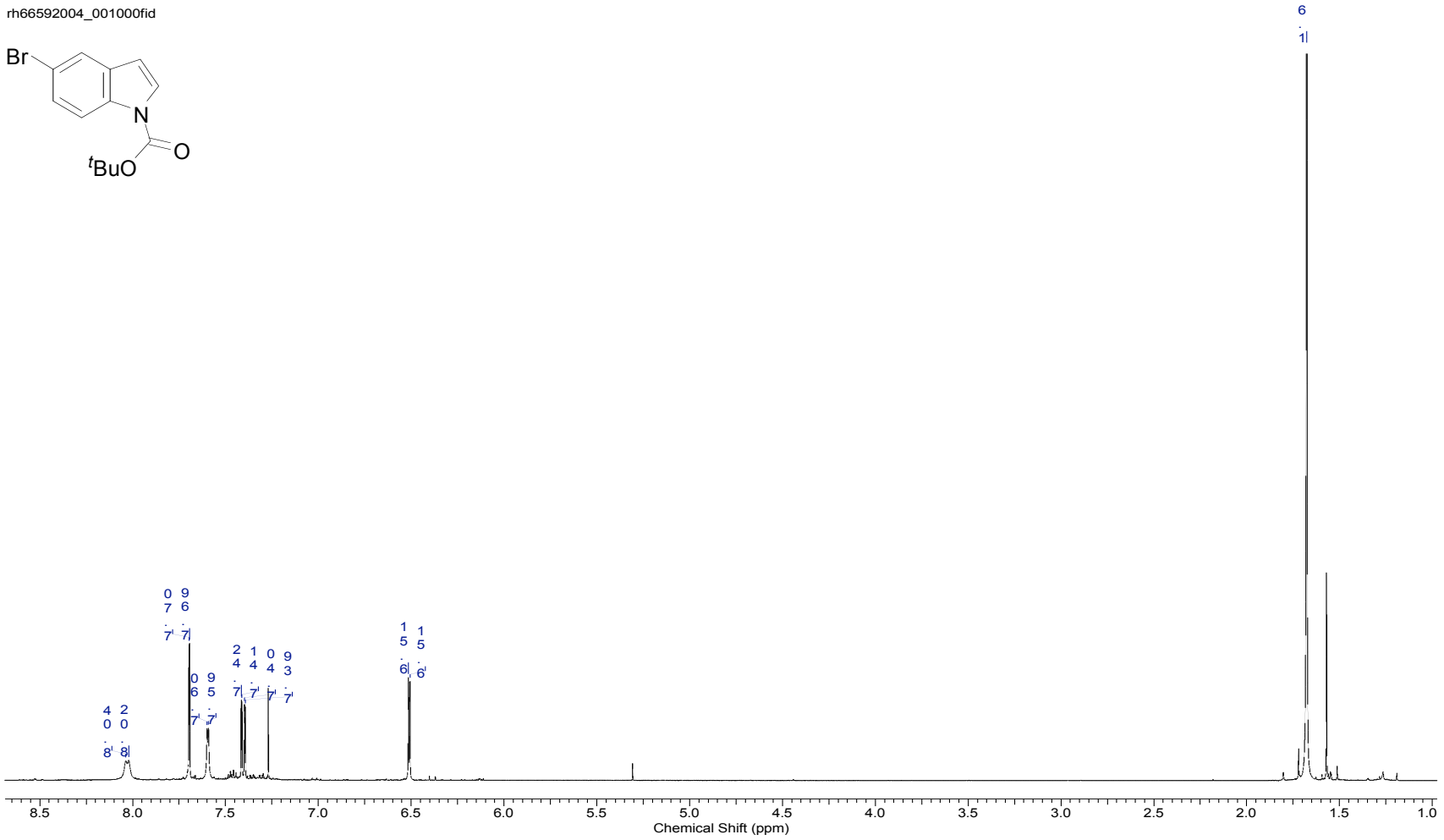
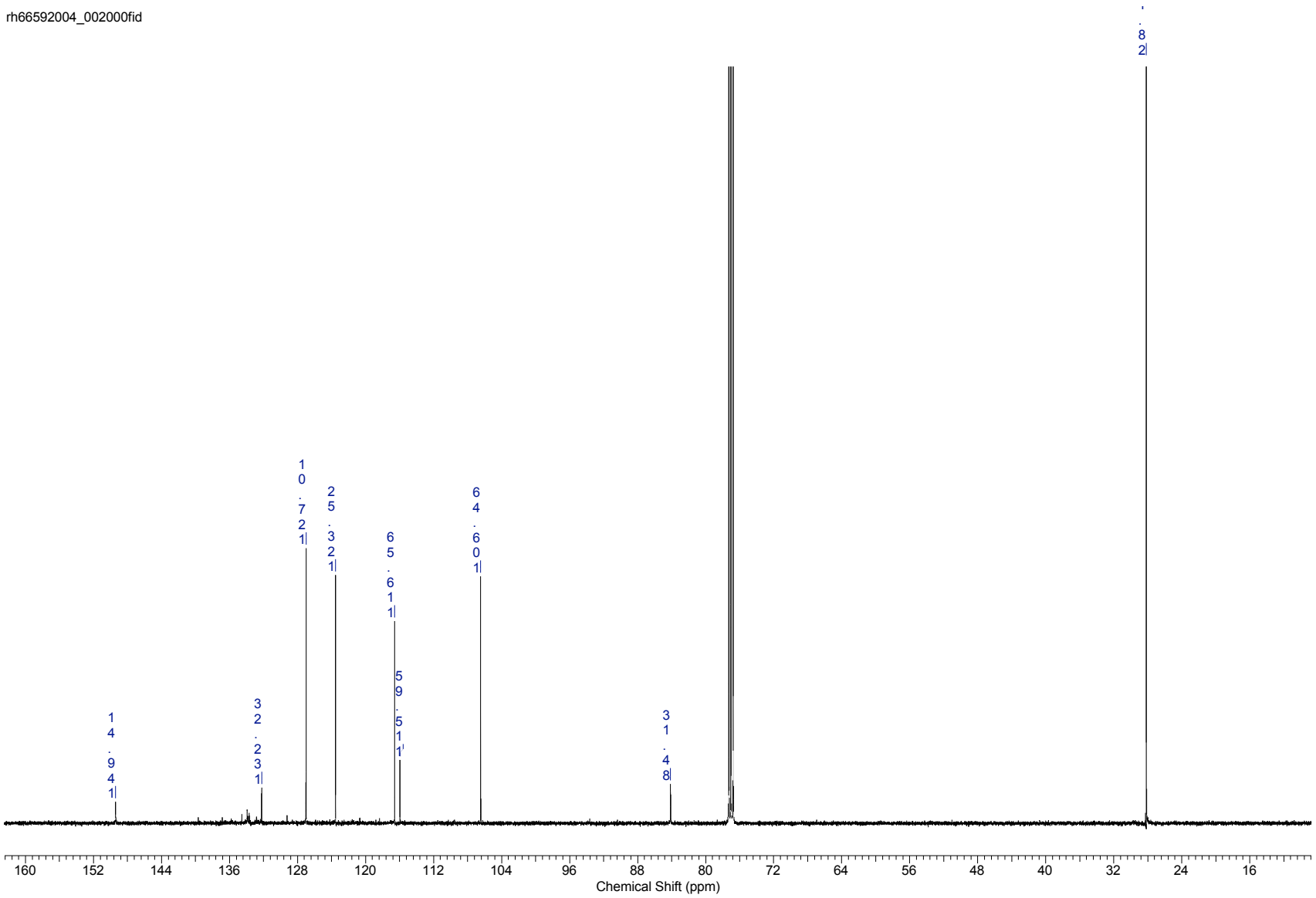
Chemical Shift (ppm)

Table 3 Entry 5

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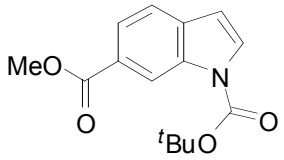

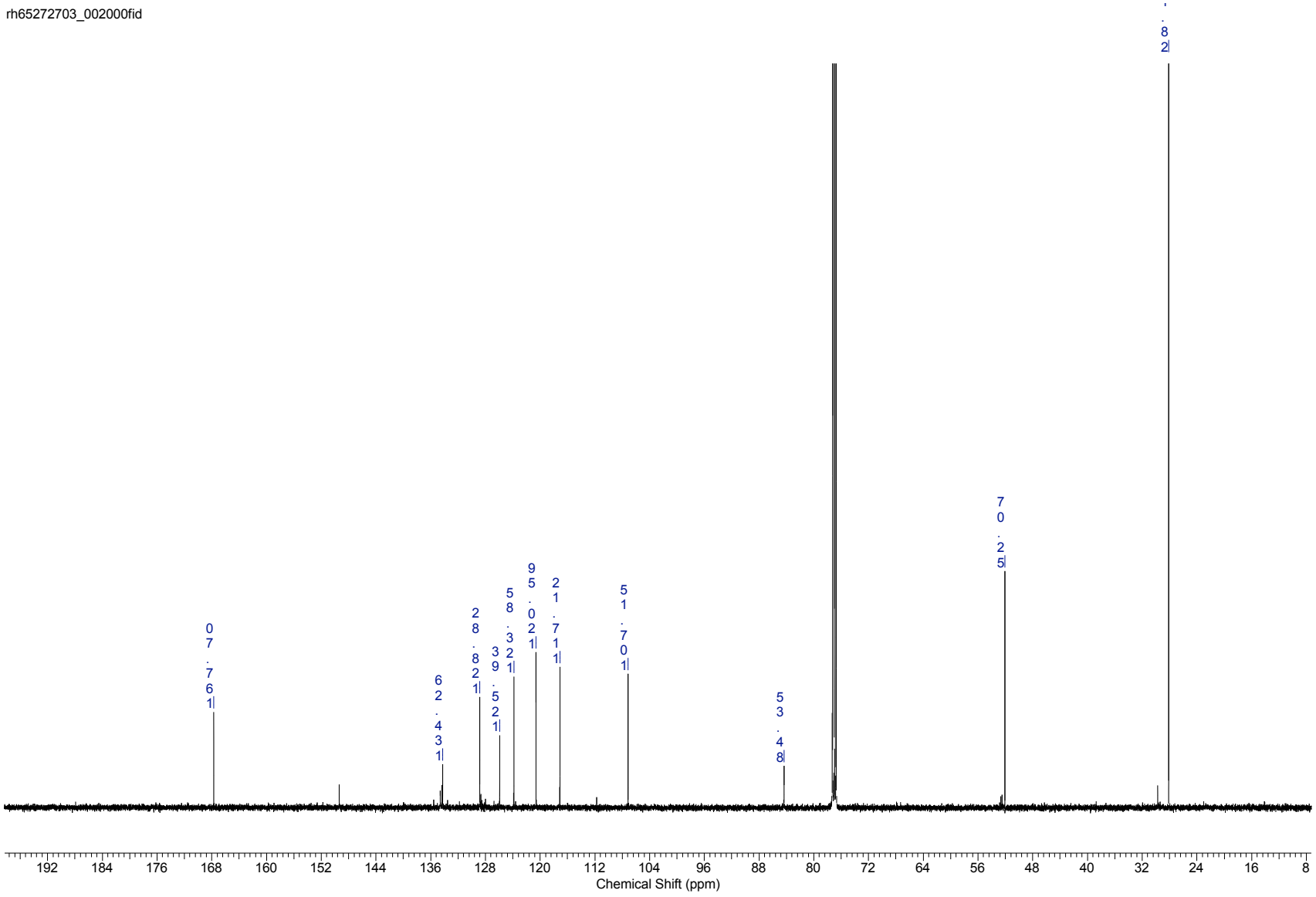
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Chemical Shift (ppm)