Supporting Information

Ortho-Metalation of Unprotected 3-Bromo and 3-Chlorobenzoic Acids with Hindered Lithium Dialkylamides

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General. For standard working practice, see recent publications (e.g. refs[1,2]). NMR spectra were recorded on a 200- or 400-MHz spectrometer. ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, chemical shifts are recorded relative to the internal TMS (tetramethylsilane) reference signal. For DMSO-d_6 and CD_3COCD_3 used as solvents, chemical shifts are given relative to the solvent signals. Elemental analyses were obtained from the Service de microanalyse, CNRS ICSN, Gif-sur-Yvette. All melting points are uncorrected.

Synthesis of 2-substituted 3-chlorobenzoic acids (9).

General procedure. To a stirred solution of *n*-butyllithium 1.6 M in hexanes (17.5 mL, 28.1 mmol) was added at –20 °C under argon 2,2,6,6-tetramethylpiperidine (4.7 mL, 28.1 mmol) in anhydrous THF (40 mL). After cooling (–50 °C), 3-chlorobenzoic acid **1** (12.8 mmol) in anhydrous THF (10 mL) was added dropwise and the mixture was stirred for 4 h. The mixture was then treated with an excess of the appropriate electrophile (50.4 mmol, 4 equiv). The resulting solution was allowed to warm up to ambient temperature, after which water was added. The aqueous layer was washed with diethyl ether, and shaken, and then acidified with 4*M* HCl. The mixture was diluted with diethyl ether and the organic layer was separated and dried with $MgSO_4$. Filtration and concentration in *vacuo* gave the crude benzoic acids, which were purified by recrystallization for characterization in each case.

3-Chloro-2-methylbenzoic acid (9a). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **9a** (1.33 g, 61%) as a white solid: mp 154-155 °C (lit[1a] mp 153-155 °C). ^1H NMR (400 MHz, DMSO-d_6) δ TMS: 7.69 (dd, J = 7.9, 1.2 Hz, 1H), 7.60 (dd, J = 7.9, 1.2 Hz, 1H), 7.30 (t, J = 7.9 Hz, 1H), 2.51 (s, 3H).

3-Chloro-2-ethylbenzoic acid (9b). The general procedure gave 41% of crude **9b**. ^1H NMR (400 MHz, $CDCl_3$) δ TMS: 7.91 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.23 (t, J = 7.9 Hz, 1H), 3.20 (q, J = 7.3 Hz, 2H), 1.29 (t, J = 7.3 Hz, 3H).

4-Chloro-3-phenyl-2-benzofuran-1(*3H*)-one (13c). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **13c** (1.99 g, 63%) as a white solid: mp 132-134 °C. ^1H NMR (400 MHz, $CDCl_3$) δ TMS: 7.90 (dd, J = 7.9, 1.1 Hz, 1H), 7.61 (dd, J = 7.9, 1.1 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.34-7.39 (m, 3H), 7.20-7.24 (m, 2H), 6.40 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:

169.1, 146.2, 134.7, 134.0, 131.2, 129.7, 129.6, 128.7, 128.4, 128.1, 124.0, 82.4. IR (KBr): 2979, 1764, 1464, 1290, 729, 622 cm^{-1}. Anal. Calcd for $C_{13}H_9ClO_2$: C, 68.73; H, 3.71. Found: C, 68.39; H, 3.69.

4-Chloro-3-hydroxy-2-benzofuran-1(*3H*)-one (13d). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **13d** (1.49 g, 63%) as a white solid: mp 128-130 °C (lit[1a] mp 128-130 °C). ^{1}H NMR (400 MHz, $CDCl_3$)• δ TMS: 7.79 (d, J = 7.9 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 6.70 (s, 1H), 4.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.7, 143.1, 135.1, 132.6, 130.4, 129.1, 123.9, 95.5.

2-Bromo-3-chlorobenzoic acid (9f). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **9f** (2.08 g, 68%) as a white solid: mp 146-147 °C (lit[1a] mp 146-147 °C). ^{1}H NMR (400 MHz, $CDCl_3$)• δ TMS: 7.79 (dd, J = 7.8, 1.7 Hz, 1H), 7.65 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H).

3-Chloro-2-iodobenzoic acid (9g). According to the general procedure, recrystallization (chloroform) afforded **9g** (2.01 g, 55%) as a white solid: mp 142-143 °C. ^{1}H NMR (400 MHz, $CDCl_3$)• δ TMS: 7.71 (dd, J = 8.0, 1.2 Hz, 1H), 7.64 (dd, J = 8.0, 1.2 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 141.0, 137.5, 132.1, 128.7, 128.6, 98.6. Anal Calcd for $C_7H_4ClIO_2$: C, 29.77; H, 1.43. Found: C, 29.85; H, 1.38.

3-Chloro-2-(methylsulfanyl)benzoic acid (9i). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **9i** (1.79 g, 69%) as a white solid: mp 123-124 °C (lit[1a] mp 126-128 °C). ^{1}H NMR (400 MHz, $CDCl_3$)• δ TMS: 7.74 (dd, J = 7.9, 1.2 Hz, 1H), 7.62 (dd, J = 7.9, 1.2 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 2.50 (s, 3H).

3-Chloro-2-(trimethylsilyl)benzoic acid (9h). To a stirred solution of LDA (28.4 mmol) in anhydrous THF (21 mL) at –78 °C was added dropwise under argon the recrystallized 3-chlorobenzoic acid (**1**) (12.8 mmol) dissolved in dry THF (10 mL). After 1 h at –78 °C, the mixture was treated with chlorotrimethylsilane (51.6 mmol) in dry THF (8 mL). After usual workup, recrystallization (ethyl acetate/heptane) gave **9h** (2.19 g, 75%) as a white solid: mp 72-74 °C (lit[1a] mp 72-73 °C). ^{1}H NMR (400 MHz, $CDCl_3$)• δ TMS: 7.60 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 0.46 (s, 9H).

3-Chloro-4-fluoro-2-methylbenzoic acid (11a). According to the general procedure (from 3-chloro-4-fluorobenzoic acid **7**, 5.7 mmol), recrystallization (ethyl acetate/heptane) afforded **11a** (0.77 g, 71%) as a white solid: mp 180-182 °C (lit[3] mp 186 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.68 (dd, J = 8.5, 5.8 Hz, 1H), 7.22 (t, J = 8.5 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6)• δ: 167.7, 159.0 (d, J = 249 Hz), 139.5, 130.5 (d, J = 9 Hz), 129.3 (d, J = 3 Hz), 121.7 (d, J = 16 Hz), 114.0 (d, J = 21 Hz), 17.3. Anal. Calcd for $C_8H_7ClFO_2$: C, 50.95; H, 3.21. Found: C, 51.01; H, 3.23.

3-Chloro-4-fluoro-2-(trimethylsilyl)benzoic acid (11h). According to the general procedure (from 3-chloro-4-fluorobenzoic acid **7**, 5.7 mmol), recrystallization (ethyl acetate/heptane) afforded **11h** (0.97 g, 69%) as a white solid: mp 118-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$)•δ TMS: 7.66 (dd, J = 8.4, 5.0 Hz, 1H), 7.17 (t, J = 8.4 Hz, 1H), 0.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.3, 159.0 (d, J = 256 Hz), 142.8 (d, J = 3 Hz), 135.1, 135.0, 129.1 (d, J = 10 Hz), 116.3 (d, J = 23 Hz), 1.1. IR (KBr): 3500 (br), 2995, 1692, 1262, 775, 654 cm^{-1}.

Synthesis of 2-substituted 3-bromobenzoic acids 10.

General procedure. To a stirred solution LTMP (21.8 mmol) in anhydrous THF (35 mL) was added dropwise at –50 °C under argon 3-bromobenzoic acid **2** (9.9 mmol) in THF (10 mL). The mixture was stirred for 1 h and then treated with an excess of the appropriate electrophile (39.6 mmol) in THF (8 mL). Workup in the usual manner followed by recrystallization provided the benzoic acids **10a-i**.

3-Bromo-2-methylbenzoic acid (10a). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **10a** (0.92 g, 44%) as a white solid: mp 151-153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 7.92 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 2.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.2, 140.3, 137.5, 131.6, 130.7, 127.9, 127.3, 21.3. IR (KBr): 2975, 1688, 1258, 753, 692 cm^{-1}. Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 44.51; H, 3.23.

3-(2,2,6,6-Tetramethylpiperidino)benzoic acid (**5**) and 4-(2,2,6,6-tetramethylpiperidino)benzoic acid (**6**) were isolated from the aqueous layer by column chromatography on silica gel of the residue (dichloromethane/diethyl ether 95:5).

3-(2,2,6,6-Tetramethylpiperidino)benzoic acid (5). White solid: mp 168-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 7.99 (s, 1H), 7.95 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.36 (t, J = 8 Hz, 1H),

1.74 (m, 2H), 1.58 (m, 4H), 1.03 (m, 12H). ^{13}C NMR (100MHz, $CDCl_3$) δ: 172.1, 146.5, 139.3, 134.9, 128.9, 127.3, 127.1, 54.1, 41.6, 29.2, 17.8. IR (KBr): 3454, 2970, 1680, 1601, 1420, 1271, 759, 559 cm^{-1}.

4-(2,2,6,6-Tetramethylpiperidino)benzoic acid (6). White solid: mp 164-166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 8.0 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 1.72 (m, 2H), 1.57 (m, 4H), 1.03 (m, 12H). ^{13}C NMR (100MHz, $CDCl_3$) δ: 171.8, 152.9, 134.1, 129.7, 126.6, 54.3, 42.1, 29.7, 18.3. IR (KBr): 3440, 2969, 1691, 4576, 1246, 756, 677 cm^{-1}.

3-Bromo-2-ethylbenzoic acid (10b). From the general procedure, **10b** was obtained in 15% yield. Alternatively, to a stirred solution of LDA (13.8 mmol) in anhydrous THF (10 mL) at –50 °C, was added dropwise under argon 3-bromo-2-methylbenzoic acid (**10a**) (1 g, 4.6 mmol) dissolved in dry THF (5 mL). After 1 h at –50 °C, the mixture was treated with an excess of iodomethane (1.5 mL, 23.0 mmol) in dry THF (5 mL). After usual workup, recrystallization (ethyl acetate/heptane) afforded **10b** (0.80 g, 76%) as a white solid: mp 94.5-96.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 7.93 (dd, J = 7.9, 1.3 Hz, 1H), 7.76 (dd, J = 7.9, 1.3 Hz, 1H), 7.14 (t, J = 7.9 Hz, 1H), 3.18 (q, J = 7.4 Hz, 2H) , 1.26 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.8, 145.3, 137.4, 130.6, 130.5, 127.0, 126.6, 27.3, 14.1. IR (KBr): 2974, 1688, 1278, 752, 688 cm^{-1}.

4-Bromo-3-phenyl-2-benzofuran-1(*3H*)-one (14c). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **14c** (1.32 g, 46%) as a white solid: mp 139-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 7.95 (dd, J = 7.9, 0.7 Hz, 1H), 7.78 (dd, J = 7.9, 0.7 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.34-7.39 (m, 3H), 7.20-7.22 (m, 2H), 6.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.6, 148.8, 138.5, 134.6, 131.9, 130.2, 129.4, 129.2, 129.1, 125.2, 118.5, 84.1. IR (KBr): 3510 (br), 1769, 1456, 753, 618 cm^{-1}.

4-Bromo-3-hydroxy-2-benzofuran-1(*3H*)-one (14d). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **14d** (1.22 g, 45%) as a white solid: mp 138-140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ TMS: 7.97 (d, J = 7.9 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 6.61 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 67.4, 146.1, 137.9, 132.8, 129.0, 124.0, 117.5, 98.3. IR (KBr): 3380 (br), 1756, 1349, 767, 598 cm^{-1}. Anal. Calcd for $C_7H_5BrO_3$: C, 41.95, H 2.20. Found: C, 41.94, H, 2.21.

3-Bromo-2-chlorobenzoic acid (10e). According to the general procedure, recrystallization (chloroform) afforded **10e** (1.00 g, 43%) as a white solid: mp 167-168 °C (lit[4] mp 163-165 °C). ^{1}H NMR (400 MHz, DMSO-d_6)• δ TMS: 7.91 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 166.7, 136.1, 134.9, 131.0, 129.5, 128.9, 123.9. IR (KBr): 3495 (br), 1692, 1419, 1260, 765, 695 cm^{-1}.

2,3-Dibromobenzoic acid (10f). According to the general procedure, recrystallization (chloroform) afforded **10f** (1.19 g, 43%) as an orange solid: mp 144-146 °C (lit[5] mp 149-150 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 7.81 (m, 2H), 7.26 (t, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 137.6, 134.6, 130.7, 128.7, 128.5, 124.7.

3-Bromo-2-iodobenzoic acid (10g). According to the general procedure, recrystallization (chloroform) afforded **10g** (1.47 g, 50%) as a pale yellow solid: mp 141.5-142 °C. ^{1}H NMR (400 MHz, DMSO-d_6)• δ TMS: 7.92 (dd, J = 7.8, 1.2 Hz, 1H), 7.59 (dd, J = 7.8, 1.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 1H). ^{13}C RMN (100 MHz, DMSO-d_6) δ: 168.9, 143.0, 133.9, 131.4, 129.9, 127.1, 100.7. IR (KBr): 3446 (br), 1678, 1414, 1285, 750, 685 cm^{-1}. Anal. Calcd for $C_7H_4BrIO_2$: C, 25.72; H, 1.23. Found: C, 25.77; H, 1.21.

3-Bromo-2-(methylsulfanyl)benzoic acid (10i). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **10i** (1.03 g, 42%) as a white solid: mp 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$)•δ TMS: 7.81 (d, J = 7.8 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 138.2, 136.3, 135.3, 132.4, 129.7, 129.0, 19.9. IR (KBr): 2998, 1682, 1412, 1250, 757, 684 cm^{-1}. Anal. Calcd for $C_8H_7BrO_2S$: C, 38.88; H, 2.86. Found: C, 38.93; H, 2.85.

3-Bromo-2-(trimethylsilyl)benzoic acid (10h). According to the general procedure, recrystallization (ethyl acetate/heptane) afforded **10h** (1.03 g, 38%) as a white solid: mp 86-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ TMS: 7.68 (dd, J = 7.8, 0.9 Hz, 1H), 7.62 (dd, J = 7.8, 0.9 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 0.5 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.5, 140.7, 140.1, 135.8, 131.4, 129.4, 126.8, 1.3. IR (KBr): 2987, 1693, 1441, 1287, 705 cm^{-1}. Anal. Calcd for $C_{10}H_{13}BrO_2Si$: C, 43.96; H, 4.80. Found: C, 44.31; H, 4.89.

Synthesis of 3-bromo-4-fluoro-2-methylbenzoic acid (12a). According to the general procedure (from 3-bromo-4-fluorobenzoic acid **8**, 4.6 mmol), recrystallization (ethyl acetate/heptane) afforded **12a** (0.56 g, 53%) as a white solid: mp 179-181 °C. ^{1}H NMR (400 MHz, DMSO-d_6)• δ TMS: 7.91 (dd, J = 8.5, 5.9 Hz, 1H), 7.37 (t, J = 8.5 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 167.8, 160.0 (d, J = 247 Hz), 141.0, 131.2 (d, J = 9 Hz), 129.6, 113.8 (d, J = 23 Hz), 113.1 (d, J = 19 Hz), 20.5. IR (KBr): 3452 (br), 1686, 1572, 1254, 775, 633 cm^{-1}. Anal. Calcd for $C_8H_7BrFO_2$: C, 41.23; H, 2.60. Found: C, 41.34; H, 2.63.

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