Supplementary Material (ESI) for Chemical Communications

High Temperature Metalation of Functionalized Aromatics and Heteroaromatics using TMPZnCl·LiCl and Microwave Irradiation**

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General All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by 1H-NMR (25 °C) and capillary GC. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.25 ppm for 1H NMR and δ 77.0 ppm for 13C NMR). Abbreviations for signal coupling are as followed: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. Column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated. TMPH and liquid acid chlorides were distilled prior to use. The given Watt numbers refer to the maximum magnetron power output.

Typical Procedure for the Preparation of the Reagent TMPZnCl·LiCl (1) (TP1):

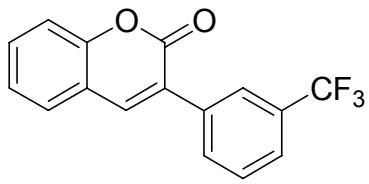
A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with freshly 2,2,6,6-tetramethylpiperidine (10.2 mL, 60 mmol) dissolved in THF (60 mL). This solution was cooled to -40 °C and *n*-BuLi (2.4 M in hexane, 25 mL, 60 mmol) was dropwise added. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. $ZnCl_2$ (1.0 M in THF, 66 mL, 66 mmol) was dropwise added and the resulting solution was stirred for 30 min at -10 °C and then for 30 min at 25 °C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The freshly prepared TMPZnCl·LiCl (**1**) solution was titrated prior to use at 25 °C

with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 1.3 M in THF was obtained.

Typical Procedure for the Zincation of Polyfunctionalized Aromatics and Heterocycles with TMPZnCl·LiCl (1) using Microwave Irradation (TP2):

A dry and argon flushed 10-mL pressurized vial, equipped with a magnetic stirring bar was charged with a solution of the corresponding arene or heteroarene (1.0 mmol) in dry THF (1-2 mL). The zinc base (1.1 mmol) was added and the reaction mixture was heated in a 10-mL pressurized vial, by using a Discover BenchMate Microwave system under the indicated conditions. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a solution of I_2 in dry THF. The subsequent reactions with electrophiles were carried out with the indicated conditions.

Synthesis of 3-(3-(trifluoromethyl)phenyl)-2H-chromen-2-one (8a):



To a solution of coumarin (**2**) (168 mg, 1.0 mmol) in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 80 °C (100 W) for 1 h according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **8a** (182 mg, 85%) as a colourless solid.

m.p.: 124.0 – 125.0 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.91 – 7.94 (m, 2 H), 7.86 (s, 1 H), 7.63 – 7.66 (m, 1 H), 7.52 – 7.58 (m, 3 H), 7.28 – 7.37 (m, 2 H).

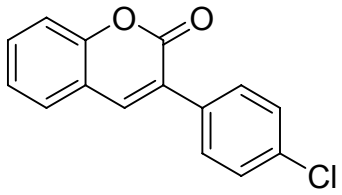
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.1, 153.6, 140.7, 135.4, 132.0, 130.9 (q, *J* = 32.4 Hz), 128.9, 128.1, 126.8, 125.4 (q, *J* = 3.9 Hz), 125.2 (q, *J* = 3.9 Hz), 124.7, 123.9 (d, *J* = 272.5 Hz), 119.3, 116.5.

MS (EI, 70 eV) m/z (%): 290 (85) [M^+], 262 (100), 233 (15), 183 (12), 165 (72).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2925, 2853, 1711, 1608, 1562, 1491, 1458, 1429, 1339, 1331, 1290, 1259, 1166, 1148, 1109, 1076, 967, 956, 920, 904, 859, 808, 773, 759, 734, 692, 654, 644, 626.

HRMS (EI) for $C_{16}H_9F_3O_2$ (290.0555): 290.0550.

Synthesis of 3-(4-chlorophenyl)-2H-chromen-2-one (8b):



To a solution of coumarin (**2**) (168 mg, 1.0 mmol) in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 80 °C (100 W) for 1 h according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (308 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **8b** (182 mg, 71%) as a colourless solid.

m.p.: 189.2 – 191.3 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.79 (s, 1 H), 7.65 (d, *J* = 8.9 Hz, 2 H), 7.50 – 7.56 (m, 2 H), 7.40 (d, *J* = 8.9 Hz, 2 H), 7.26 – 7.36 (m, 2 H).

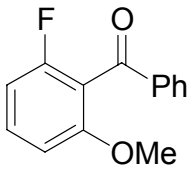
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.3, 153.5, 139.9, 134.9, 133.0, 131.6, 129.8, 128.6, 128.0, 127.1, 124.6, 119.4, 116.5.

MS (EI, 70 eV) m/z (%): 256 (100) [^{35}Cl-M^+], 228 (72), 165 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 1708, 1685, 1608, 1566, 1489, 1452, 1401, 1352, 1297, 1259, 1228, 1153, 1123, 1091, 1013, 952, 923, 838, 815, 776, 748, 742, 706, 633, 622.

HRMS (EI) for $C_{15}H_9ClO_2$ (256.0291): 256.0288.

Synthesis of (2-fluoro-6-methoxy-phenyl)-phenyl-methanone (9a):



To a solution of 3-fluoroanisole (**4**) (126 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (250 W) for 2 h according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoyl chloride (155 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether 7:3) furnished the compound **9a** (165 mg, 72%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.86 – 7.84 (m, 2 H), 7.59 – 7.56 (m, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 7.39 – 7.35 (m, 1 H), 6.76 – 6.78 (m, 2 H), 3.74 (s, 3 H).

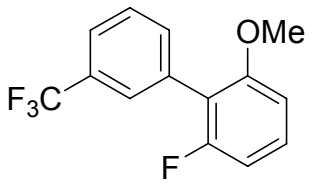
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 192.0, 159.8 (d, *J* (C – F) = 247.4 Hz), 158.1 (d, *J* (C – F) = 8.0 Hz), 137.2, 133.7, 131.3 (d, *J* (C – F) = 10.0 Hz, 129.5, 128.5, 117.3 (d, *J* (C – F) = 21.1 Hz), 108.3 (d, *J* (C – F) = 21.9 Hz, 106.9 (d, *J* (C – F) = 3.1 Hz, 56.14.

MS (EI, 70 eV) m/z (%): 230 (47) [M^+], 213 (13), 154 (11), 153 (100), 139 (38), 138 (11), 110 (11), 105 (58), 83 (10), 77 (43), 69 (11), 57 (13), 55 (11), 43 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3331, 3085, 3063, 3009, 2974, 2940, 2890, 2842, 2743, 2582, 2547, 2409, 2341, 2216, 2161, 1974, 1924, 1825, 1734, 1672, 1613, 1596, 1580, 1468, 1449, 1438, 1378, 1316, 1308, 1278, 1267, 1239, 1179, 1168, 1124, 1144, 1079, 1026, 1001, 976, 947, 923, 847, 782, 755, 731, 702, 689,

HRMS (EI) for $C_{14}H_{11}FO_2$ (230.0743): 230.0730.

Synthesis of 2-fluoro-6-methoxy-3-trifluoromethyl-biphenyl (9b):



To a solution of 3-fluoroanisole (**4**) (126 mg, 1.0 mmol) in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (250 W) for 2 h according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 3-iodobenzotrifluoride (354 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:8) furnished the compound **9b** (194 mg, 72%) as a colourless oil.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.73 (s, 1 H), 7.54 – 7.66 (m, 3 H), 7.28 – 7.38 (m, 1 H), 6.81 – 6.88 (m, 2 H), 3.82 (s, 3 H).

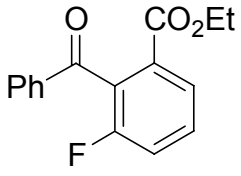
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 160.3 (d, J = 245.7 Hz), 157.7 (d, J = 6.7 Hz), 134.1 (quint., J = 1.6 Hz), 132.4 (d, J = 0.8 Hz), 130.3 (q, J = 32.3 Hz), 129.6 (d, J = 10.8 Hz), 128.3, 127.6 (dddd, J = 1.5 Hz), 124.3 (q, J = 3.7 Hz), 124.2 (q, J = 272.4 Hz), 117.2 (d, J = 17.6 Hz), 108.4 (d, J = 23.2 Hz), 106.8 (d, J = 2.8 Hz), 56.1.

MS (EI, 70 eV) m/z (%): 270 (100) [M^+], 255 (14), 235 (36), 201 (13), 186 (37), 157 (11), 136 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2941, 2848, 1616, 1580, 1499, 1471, 1431, 1331, 1285, 1271, 1251, 1238, 1163, 1120, 1098, 1072, 1027, 942, 904, 825, 803, 780, 752, 728, 700, 655.

HRMS (EI) for $C_{14}H_{10}F_4O$ (270.0668): 270.0657.

Synthesis of ethyl 2-benzoyl-3-fluorobenzoate (10a):



To a solution of ethyl 3-fluorobenzoate (**5**) (168 mg, 1.0 mmol) in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (200 W) for 1.5 h according to **TP2**. CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was slowly added at –30 °C and the reaction mixture was stirred at the same temperature for 30 min. Then, benzoyl chloride (281 mg, 2.0 mmol) was added dropwise at –30 °C and the resulting mixture was allowed to warm up slowly to 25 °C overnight. The reaction mixture was then quenched with a sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished compound **10a** (196 mg, 72%) as a colourless solid.

m.p.: 101.6 – 103.1 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.90 – 7.93 (m, 1 H), 7.79 – 7.82 (m, 2 H), 7.31 – 7.59 (m, 5 H), 4.13 (q, J = 7.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H).

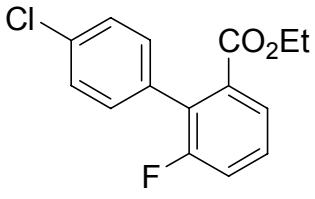
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 192.5, 164.6 (d, J (C-F) = 3.1 Hz), 159.1 (d, J (C-F) = 248.0 Hz), 137.0, 133.5, 130.9 (d, J (C-F) = 3.8 Hz), 130.5 (d, J (C-F) = 8.0 Hz), 129.5 (d, J (C-F) = 20.1 Hz), 129.0, 128.6, 126.2 (d, J (C-F) = 3.1 Hz), 120.2 (d, J (C-F) = 21.9 Hz), 61.8, 13.6.

MS (70 eV, EI) *m/z* (%): 272 (39) [M^+], 227 (35), 195 (46), 170 (15), 167 (100), 151 (13), 105 (71), 77 (44).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2983, 1716, 1597, 1577, 1498, 1454, 1397, 1367, 1284, 1242, 1177, 1140, 1090, 1073, 1020, 1006, 954, 938, 865, 824, 751, 685.

HRMS (EI) for **$C_{16}H_{13}FO_3$** (272.0849): 272.1014.

Synthesis of ethyl 4'-chloro-6-fluorobiphenyl-2-carboxylate (10b):



To a solution of ethyl 3-fluorobenzoate (**5**) (168 mg, 1.0 mmol) in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (200 W) for 1.5 h according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with 1-chloro-4-iodobenzene (308 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The

resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:2) furnished the compound **10b** (209 mg, 76%) as a colourless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.65 – 7.68 (m, 1 H), 7.36 – 7.43 (m, 3 H), 7.21 – 7.30 (m, 3 H), 4.07 (q, J = 7.2 Hz, 2 H), 1.02 (t, J = 7.2 Hz, 3 H).

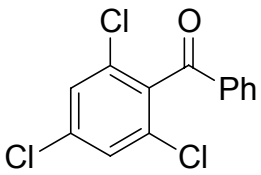
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 167.0 (d, J (C-F) = 3.3 Hz), 159.6 (d, J (C-F) = 246.4 Hz), 133.8, 133.5 (d, J (C-F) = 2.5 Hz), 132.6, 130.6 (d, J (C-F) = 1.3 Hz), 129.0 (d, J (C-F) = 8.5 Hz), 128.7 (d, J (C-F) = 17.5 Hz), 128.2, 125.5 (d, J (C-F) = 3.7 Hz), 118.8 (d, J (C-F) = 23.4 Hz), 61.2, 13.6.

MS (70 eV, EI) *m/z* (%): 278 (52) [M^+], 270 (37), 250 (20), 233 (100), 199 (19), 186 (22), 170 (72), 149 (14), 85 (14), 44 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3070, 2987, 1716, 1675, 1607, 1594, 1579, 1476, 1449, 1366, 1292, 1273, 1194, 1152, 1114, 1027, 963, 928, 811, 762, 709, 660.

HRMS (EI) for **$C_{15}H_{12}ClFO_2$** (278.0510): 278.0506.

Synthesis of 2-benzoyl-1,3,5-trichlorobenzene (12a):



To a solution of 1,3,5-trichlorobenzene (**11**) (181 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (200 W) for 1 h according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was added. After 30 min of stirring at the same temperature, benzoyl chloride (155 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether 9:1) furnished the compound **12a** (244 mg, 85%) as a pale yellow solid.

m.p.: 106.0 – 107.8 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.82 – 7.79 (m, 2 H), 7.66 – 7.61 (m, 1 H), 7.51 – 7.46 (m, 2 H), 7.41 (s, 2 H).

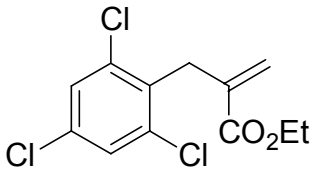
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 191.7, 136.2, 135.9, 135.2, 134.5, 132.6, 129.6, 129.0, 128.2.

MS (70 eV, EI) m/z (%): 284 (23) [^{35}Cl-M^+], 209 (20), 207 (21), 105 (100), 77 (25).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3080, 2956, 2926, 2869, 1962, 1756, 1735, 1720, 1677, 1596, 1569, 1544, 1492, 1448, 1430, 1379, 1365, 1315, 1269, 1263, 1230, 1187, 1178, 1163, 1158, 1134, 1068, 1045, 1020, 1002, 928, 869, 853, 816, 804, 758, 735, 704, 691, 683.

HRMS (EI) for $C_{13}H_7Cl_3O$: (283.9562): 283.9552.

Synthesis of 2-(2,4,6-trichloro-benzyl)-acrylic acid ethyl ester (12b):



To a solution of 1,3,5-trichlorobenzene (**11**) (181 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 160 °C (200 W) for 1 h according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1.0 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 30 min of stirring at the same temperature, 2-bromomethyl-acrylic acid ethyl ester (212 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether 9:1) furnished the compound **12b** (220 mg, 75%) as a colorless oil.

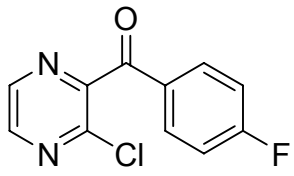
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 7.35 (s, 2 H), 6.18 (t, J = 1.7 Hz, 1 H), 4.96 (t, J = 1.9 Hz, 1 H), 4.26 (q, J = 7.1 Hz, 2 H), 3.90 (t, J = 1.9 Hz, 2 H), 1.34 (t, J = 7.3 Hz, 3 H).

^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 166.5, 136.6, 136.1, 133.6, 133.2, 128.2, 124.4, 61.1, 32.5, 14.20.

MS (70 eV, EI) m/z (%): 292 (5) [^{35}Cl-M^+], 259 (58), 257 (66), 249 (20), 247 (23), 231 (59), 229 (86), 185 (24), 184 (25), 149 (45), 97 (26), 83 (29), 81 (26), 71 (33), 69 (75), 57 (52), 55 (46), 44 (100), 43 (37), 41 (50).

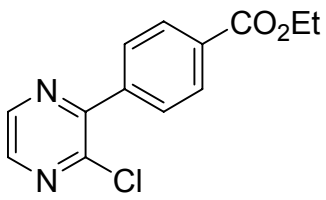
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3317, 3080, 2982, 2933, 1714, 1635, 1582, 1549, 1442, 1428, 1395, 1374, 1344, 1276, 1253, 1208, 1164, 1131, 1095, 1072, 1046, 1024, 946, 856, 813, 785, 700.
HRMS (EI) for $C_{12}H_{11}Cl_3O_2$: (291.9825): 291.9809.

Synthesis of (3-chloropyrazin-2-yl)(4-fluorophenyl)methanone (14a):



To a solution of 2-chloropyrazine (**13**) (115 mg, 1.0 mmol) in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 70 °C (100 W) for 45 min according to **TP2**. $Pd(PPh_3)_4$ (100 mg) dissolved in THF (1 mL) was then simultaneous added to the reaction mixture with 4-fluorobenzoyl chloride (317 mg, 2.0 mmol) at the same temperature. The resulting mixture was then stirred at 65 °C and quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **14a** (158 mg, 67%) as a yellowish oil.
^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 8.57 (d, *J* = 2.5 Hz, 1 H), 8.53 (d, *J* = 2.5 Hz, 1 H), 7.84 – 7.88 (m, 2 H), 7.12 – 7.18 (m, 2 H).
^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 189.2, 166.5 (d, *J* = 257.8 Hz), 150.4, 146.6, 144.9, 141.6, 133.0 (d, *J* = 9.8 Hz), 131.0 (d, *J* = 2.9 Hz), 116.1 (d, *J* = 22.2 Hz).
MS (EI, 70 eV) m/z (%): 236 (8) [^{35}Cl-M$^+$], 123 (100), 95 (28).
IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3076, 2924, 1675, 1595, 1548, 1505, 1438, 1411, 1372, 1297, 1280, 1234, 1212, 1182, 1147, 1082, 1056, 1012, 936, 849, 820, 799, 769, 753, 723, 687, 652, 633, 622, 606.
HRMS (EI) for $C_{11}H_6ClFN_2O$ (236.0153): 236.0141.

Synthesis of ethyl 4-(3-chloropyrazin-2-yl)benzoate (14b):



To a solution of 2-chloropyrazine (**13**) (115 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.3 M in THF, 0.85 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 70 °C (100 W) for 45 min according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with ethyl 4-iodobenzoate (359 mg, 1.3 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1.5 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) furnished the compound **14b** (216 mg, 82%) as a brown solid.

m.p.: 90.1 – 91.7 °C.

^{1}H-NMR ($CDCl_3$, 400 MHz) δ: 8.56 (d, *J* = 2.4 Hz, 1 H), 8.33 (d, *J* = 2.4 Hz, 1 H), 8.12 (d, *J* = 8.8 Hz, 2 H), 7.83 (d, *J* = 8.8 Hz, 2 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 4.37 (t, *J* = 7.1 Hz, 3 H).

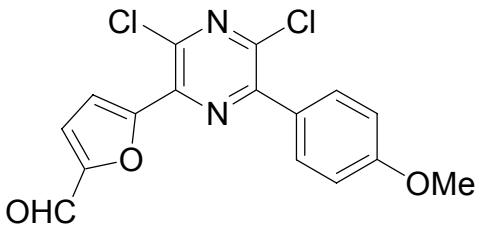
^{13}C-NMR ($CDCl_3$, 100 MHz) δ: 165.8, 152.2, 147.3, 142.5, 142.3, 140.1, 131.2, 129.3, 129.2, 61.1, 14,2.

MS (EI, 70 eV) m/z (%): 262 (97) [^{35}Cl-M$^+$], 234 (35), 217 (100), 199 (13), 189 (27).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3053, 2983, 2918, 1704, 1611, 1573, 1510, 1486, 1464, 1436, 1364, 1312, 1284, 1267, 1187, 1157, 1129, 1108, 1053, 1023, 1010, 963, 872, 856, 841, 813, 789, 760, 699, 652, 642, 625, 604.

HRMS (EI) for $C_{13}H_{11}ClN_2O_2$ (262.0509): 262.0498.

Synthesis of 5-[3,5-dichloro-6-(4-methoxy-phenyl)-pyrazine-2-yl]-furan-2-carbaldehyde (16a):



To a solution of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**15**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 100 °C (200 W) for 1 h according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (13 mg, 6 mol%) dissolved in THF (2 mL) and mixed with 5-iodo-2-furancarboxaldehyde (290 mg, 1.3 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **16a** (226 mg, 65%) as a colourless solid.

m.p.: 110.9 – 112.0 °C.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 9.80 (s, 1 H), 7.88 (d, *J* = 9.1 Hz, 2 H), 7.52 (d, *J* = 3.8 Hz, 1 H), 7.36 (d, *J* = 3.8 Hz, 1 H), 7.0 (d, *J* = 8.6 Hz, 2 H), 3.86 (s, 3 H).

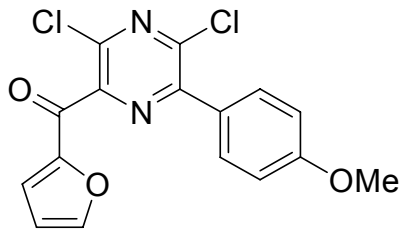
^{13}C-NMR (150 MHz, $CDCl_3$) δ: 178.3, 161.2, 153.4, 150.3, 140.0 , 139.0, 131.2, 126.6, 116.5, 113.8, 55.4.

MS (70 eV, EI) m/z (%): 348 (100) [^{35}Cl-M$^+$], 180 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3127, 2838, 2156, 2040, 1690, 1611, 1570, 1530, 1514, 1464, 1408, 1379, 1338, 1312, 1300, 1257, 1245, 1225, 1180, 1143, 1116, 1048, 1027, 1015, 969, 947, 869, 841, 818, 794, 770, 735, 665, 638.

HRMS (EI) for $C_{16}H_{10}Cl_2N_2O_3$ (348.0068): 348.0067.

Synthesis of (3,5-dichloro-6-(4-methoxyphenyl)pyrazine-2-yl)(furan-2-yl)methanone (16b):



To a solution of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**15**) (254 mg, 1.0 mmol) dissolved in THF (1 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 100 °C (200 W) for 1 h according to **TP2**. The reaction mixture was then cooled to –20 °C and CuCN·2LiCl (1.0 M solution in THF, 1.1 mL,

1.1 mmol) was added. After 30 min of stirring at the same temperature, 2-furyl-chloride (170 mg, 1.3 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C for 2 h. The resulting mixture was then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/pentane 1:1) furnished the compound **16b** (244 mg, 70 %) as a colourless solid.

m.p.: 137.9 – 139.5 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 9.0 Hz, 2 H), 7.73 (m, 1 H), 7.31 (m, 1 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 6.60 (m, 1 H), 3.86 (s, 3 H).

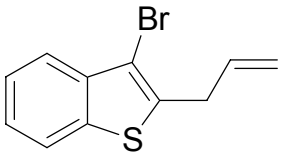
^{13}C-NMR (75 MHz, $CDCl_3$) δ: 176.8, 161.3, 150.9, 149.6, 148.7, 145.7, 145.6, 142.0, 131.2, 126.3, 123.0, 113.9, 112.9, 55.4.

MS (70 eV, EI) m/z (%): 348 (36) [^{35}Cl-M^+], 320 (20), 95 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3141, 3113, 3000, 2918, 2848, 1647, 1604, 1558, 1511, 1486, 1459, 1421, 1396, 1367, 1349, 1304, 1255, 1183, 1157, 1125, 1115, 1093, 1019, 964, 918, 883, 838, 826, 797, 790, 773, 759, 717, 696, 663, 649, 635, 619, 614, 608.

HRMS (EI) for $C_{16}H_{10}Cl_2N_2O_3$ (348.0068): 348.0067.

Synthesis of 2-allyl-3-bromobenzothiophene (18a):



To a solution of 3-bromobenzothiophene (**17**) (213 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 50 °C (120 W) for 30 min according to **TP2**. The reaction mixture was cooled to -20 °C and CuCN·2LiCl (1 M solution in THF, 0.1 mL, 0.1 mmol) was added. After 30 min of stirring at the same temperature, allyl bromide (133 mg, 1.1 mmol) was added and the resulting mixture was allowed to warm up slowly to 25 °C within 2 h. The reaction mixture was quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether 95:5) furnished the compound **18a** (196 mg, 77%) as a yellow oil.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 7.76 – 7.73 (m, 1 H), 7.44 – 7.41 (m, 1H), 7.39 – 7.31 (m, 2 H), 6.05 – 5.92 (m, 1 H), 5.19 – 5.12 (m, 2 H), 3.70 (d,t, *J* = 6.6 Hz, 2 H).

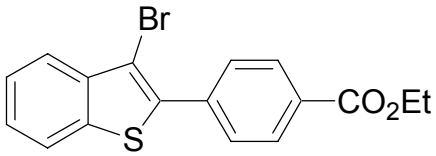
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 138.4, 138.1, 137.4, 134.1, 124.9, 124.9, 122.7, 122.3, 117.5, 106.2, 34.2.

MS (70 eV, EI) m/z (%): 252 (54) [^{79}Br, ^{32}S-M^+], 251 (23), 243 (20), 241 (25), 227 (29), 225 (28), 212 (15), 187 (44), 173 (89), 172 (100), 171 (51), 158 (17), 147 (29), 146 (16), 145 (20), 134 (29), 129 (48), 128 (17), 115 (28), 89 (15), 86 (21), 83 (17), 71 (17), 69 (17), 57 (27), 55 (18), 45 (24), 44 (35), 43 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3974, 3778, 3350, 3060, 3028, 3006, 2979, 2898, 2750, 2627, 2558, 2310, 2270, 1941, 1905, 1821, 1783, 1689, 1640, 1605, 1561, 1531, 1504, 1494, 1456, 1432, 1376, 1320, 1306, 1278, 1252, 1224, 1160, 1125, 1099, 1077, 1067, 1049, 1018, 989, 945, 915, 864, 851, 820, 748, 724, 700, 654.

HRMS (EI) for $C_{11}H_9BrS$: (251.9608): 251.9601

Synthesis of 4-(3-bromo-benzothiophen-2-yl)-benzoic acid ethyl ester (18b):



To a solution of 3-bromobenzothiophene (**17**) (213 mg, 1.0 mmol) dissolved in THF (2 mL) was added TMPZnCl·LiCl (**1**) (1.4 M in THF, 0.8 mL, 1.1 mmol) at 25 °C and the resulting mixture was heated at 50 °C (120 W) for 30 min according to **TP2**. $Pd(dba)_2$ (17 mg, 3 mol%) and P(o-furyl)$_3$ (14 mg, 6 mol%) dissolved in THF (2 mL), and mixed with ethyl 4-iodobenzoate (303 mg, 1.1 mmol, 1.1 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 25 °C for 2 h and then quenched with a sat. aq. NH_4Cl solution (30 mL), extracted with diethyl ether (3 x 50 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (pentane/ether 9:1) furnished the compound **18b** (336 mg, 93 %) as colorless solid.

^{1}H-NMR ($CDCl_3$, 600 MHz) δ: 8.15 – 8.14 (m, 2 H), 7.88 (d, *J* = 8.1, 1 H), 7.85 – 7.82 (m, 3 H), 7.50 – 7.41 (m, 2 H), 4.41 (q, *J* = 7.15, 2 H), 1.42 (t, *J* = 7.15, 3 H).

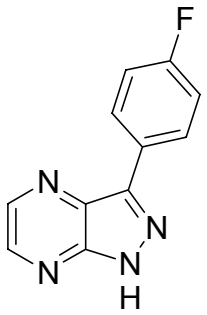
^{13}C-NMR ($CDCl_3$, 150 MHz) δ: 166.1, 139.1, 137.8, 137.4, 136.9, 130.5, 129.8, 129.5, 125.9, 125.4, 123.9, 122.2, 106.0, 61.2, 14.3.

MS (70 eV, EI) m/z (%): 360 (95) [^{79}Br, ^{32}S-M^+], 334 (29), 332 (23), 318 (11), 317 (47), 315 (54), 209 (13), 208 (86), 163 (14), 157 (11), 104 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3054, 2992, 2915, 2873, 2253, 1934, 1814, 1717, 1607, 1568, 1539, 1483, 1466, 1454, 1446, 1433, 1404, 1360, 1307, 1292, 1280, 1250, 1181, 1127, 1110, 1100, 1072, 1030, 1020, 976, 933, 890, 858, 793, 762, 743, 718, 690, 697.

HRMS (EI) for $C_{17}H_{13}BrO_2S$: (359.9820): 359.9815

Synthesis of 3-(4-fluoro-phenyl)-1H-pyrazolo[3,4-b]pyrazine (JNK kinase inhibitor (19)):



Hydrazine (64% in water; 0.17 mL, 3.4 mmol) was added to a solution of **14a** (236 mg, 1.0 mmol) dissolved in 2 mL THF at 70 °C. The resulting mixture was stirred at the same temperature for 30 min, then quenched with a sat. aq. Na_2CO_3 solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated *in vacuo*. Purification by flash chromatography (CH_2Cl_2/Et_2O 19:1) furnished **19** as a colourless solid (150 mg, 70%).

m.p.: 249.1 – 251.5 °C.

^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 8.68 (s, 1 H), 8.61 (s, 1 H), 8.42 – 8.45 (m, 2 H), 7.31 – 7.36 (m, 2 H).

^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 162.2 (d, J = 245.8 Hz), 145.3, 143.1, 140.9, 140.6, 130.6, 128.4 (d, J = 3.1 Hz), 128.1 (d, J = 8.4 Hz), 115.7 (d, J = 21.8 Hz).

MS (EI, 70 eV) m/z (%): 214 (100) [M^+], 187 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3202, 3157, 3035, 2911, 1598, 1552, 1530, 1494, 1460, 1411, 1379, 1332, 1258, 1215, 1193, 1162, 1098, 1042, 992, 931, 849, 814, 801, 770, 738, 690.

HRMS (EI) for $C_{11}H_7FN_4$ (214.0655): 214.0648.

NMR Spectra: