Electronic Supplementary Material (ESI) for Chemical Communications

Metalated N-Heterocyclic Reagents Prepared by the Frustrated Lewis Pair TMPMgCl·BF_3 and their Addition to Aromatic Aldehydes and Activated Ketones

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Supporting Information

Experimental Details

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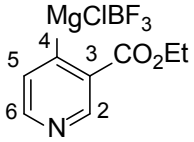
General All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. TMPH, liquid aldehydes and $BF_3 \cdot OEt_2$ were distilled under argon prior to use. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by ^{1}H-NMR (25 °C) and capillary-GC analysis. NMR spectra were recorded on a JEOL 400E instrument operating at 400 MHz (^{1}H), 100 MHz (^{13}C), 128 MHz (^{11}B) and 376 MHz (^{19}F). The spectra were obtained from solutions in deuterated chloroform ($CDCl_3$) or THF-d_8. Chemical shifts are referred to TMS (^{1}H, ^{13}C), $BF_3 \cdot OEt_2$ (^{11}B) and $CFCl_3$ (^{19}F) as external standards. Assignment of the signals in the ^{1}H and ^{13}C-NMR spectra is based on ^{1}H,^{1}H-COSY45, ^{1}H,^{13}C-HMQC and ^{1}H,^{13}C-HMBC two dimensional NMR experiments. Column chromatographical purifications were performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck if not indicated otherwise.

Typical Procedure for the metalation with "TMPMgCl·BF_3·LiCl"(1) (TP1)

A dry and argon flushed 20 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with TMPMgCl·LiCl[1] (1.95 mL, 2.2 mmol, 1.13 M in THF) and cooled to the indicated temperature. $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) was added dropwise and the resulting mixture was stirred for 10 min before the corresponding *N*-heteroarene (2.0 mmol) dissolved in dry THF (10 mL) was added. The reaction mixture was stirred at the given temperature for the indicated time. Complete metalation was monitored by GC-analysis of reaction aliquots, quenched with iodine in dry THF using decane as internal standard.

[1] A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 2958.

Low temperature NMR-studies of the metalated intermediate 9a



In order to provide structural information on the 4-metalated pyridines of type **9** we investigated the metalation of ethyl nicotinate (**8a**) with TMPMgCl·BF_3 (**1**) at -40 °C (the metalation of the other 3-substituted pyridines **8b-d** could not be examined due to the low stability of the metalated intermediates). Therefore 0.55 mmol (0.49 mL, 1.13 M in THF) of TMPMgCl·LiCl were put in a dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar. The solvent was removed *in vacuo* to give TMPMgCl·LiCl as a light brown slurry. The base was redissolved in THF-d_8 (ca. 0.5 mL) and reacted with BF_3·OEt_2 (0.55 mmol, 78 mg, see **TP1**). Ethyl nicotinate (**8a**, 0.5 mmol, 75.6 mg), dissolved in 1.5 mL THF-d_8, was slowly added at -40 °C and the reaction was stirred for 30 min. Then the Schlenk-tube was cooled down to -50 °C and ca. 0.7 mL of the reaction mixture were cannulated in a dry, argon flushed NMR-tube, which was cooled at -78 °C. Then several NMR studies were performed at -50 °C, including ^{1}H-, ^{13}C- ^{11}B and ^{19}F-NMR. The spectra showed in addition to the characteristic signals of the BF_3-complex **9a** also the signals of free TMPH and BF_3·OEt_2 in addition the BF_3 complex **11**.

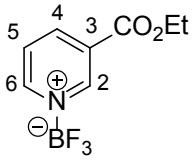
^{1}H-NMR (400 MHz, THF-d_8): δ / (ppm): 8.68 (1H, s, 2-H), 8.42 (1H, d, J_{56} 4.0 Hz, 6-H), 8.18 (1H, d, J_{56} 4.0 Hz, 5-H), 4.43 (2H, q, J_{CH2CH3} 6.8 Hz, CH_2), 1.46 (3H, J_{CH2CH3} 6.8 Hz, CH_3, 3H).

^{13}C-NMR (100 MHz, THF-d_8): δ / (ppm): 223.0 (4-C), 173.6 (C=O), 137.2 (6-C), 137.0 (2-C), 136.6 (5-C), 135.9 (3-C), 63.8 (CH_2), 13.7 (CH_3).

^{11}B-NMR (128 MHz, THF-d_8): δ / (ppm): -0.5.

^{19}F-NMR (376 MHz, THF-d_8): δ / (ppm): -151.64 (^{10}B isotopomer), -151.71 (^{11}B isotopomer).

Synthesis and NMR-studies of (3-(ethoxycarbonyl)pyridin-1-ium-1-yl)trifluoroborate (11)



A dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with 45 mg ethyl nicotinate (0.3 mmol) in 0.6 mL THF-d_8 and cooled to 0 °C. $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. The complex **11** was then transferred in a dry, argon flushed NMR-tube which was cooled at -50 °C, and characterized with ^{1}H-, ^{13}C- ^{11}B and ^{19}F-NMR. The spectra showed in addition to the characteristic signals of the BF_3-complex **11** also the signals of $BF_3 \cdot OEt_2$.

^{1}H-NMR (400 MHz, THF-d_8): δ / (ppm): 9.14 (1H, s, 2-H), 9.00 (1H, d, J_{56} 5.6 Hz, 6-H), 8.94 (1H, dt, J_{45} 8.0 Hz, J_{46} 1.6 Hz, 4-H), 8.12 (1H, dd, J_{45} 8.0 Hz, J_{56} 5.6 Hz, 5-H), 4.44 (2H, q, J_{CH2CH3} 7.2 Hz, CH_2), 1.43 (3H, t, J_{CH2CH3} 7.2 Hz, CH_3).

^{13}C-NMR (100 MHz, THF-d_8): δ / (ppm): 162.4 (C=O), 146.8 (q, J_{CF} 2.0 Hz, 6-C), 144.0 (4-C), 143.9 (q, J_{CF} 2.2 Hz, 2-C), 129.5 (3-C), 127.1 (5-C), 62.4 (CH_2), 13.6 (CH_3).

^{11}B-NMR (128 MHz, THF-d_8): δ / (ppm): -0.4.

^{19}F-NMR (376 MHz, THF-d_8): δ / (ppm): -151.15 (^{10}B isotopomer), -151.22 (^{11}B isotopomer).

When complex **11** was treated with another equivalent of $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) at 0 °C in THF-d_8, no shift change for the carbonyl group could be observed in the ^{13}C-NMR indicating that the ester group coordinates to the excess Lewis acid. However, what can be observed is a coordination of the BF_3 to the THF-d_8 resulting in a low field shift in the ^{13}C-NMR from 66.7 to 69.4 ppm and 24.4 to 25.5 ppm, respectively (see Figure 1 and 2).

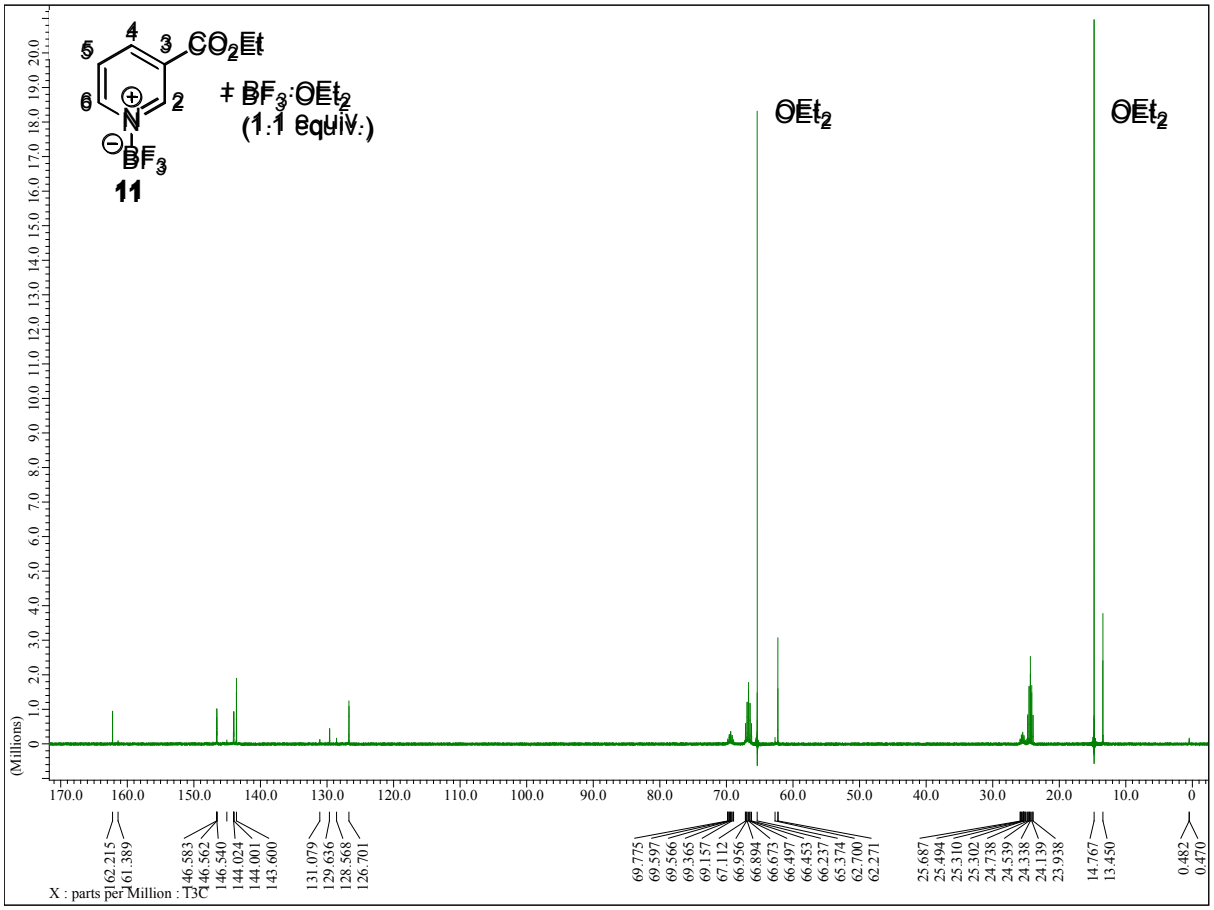


Figure 1: ^{13}C-NMR spectrum of complex **11** with another 1.1 equivalents of $BF_3 \cdot OEt_2$ in THF-d_8 at -50 °C.

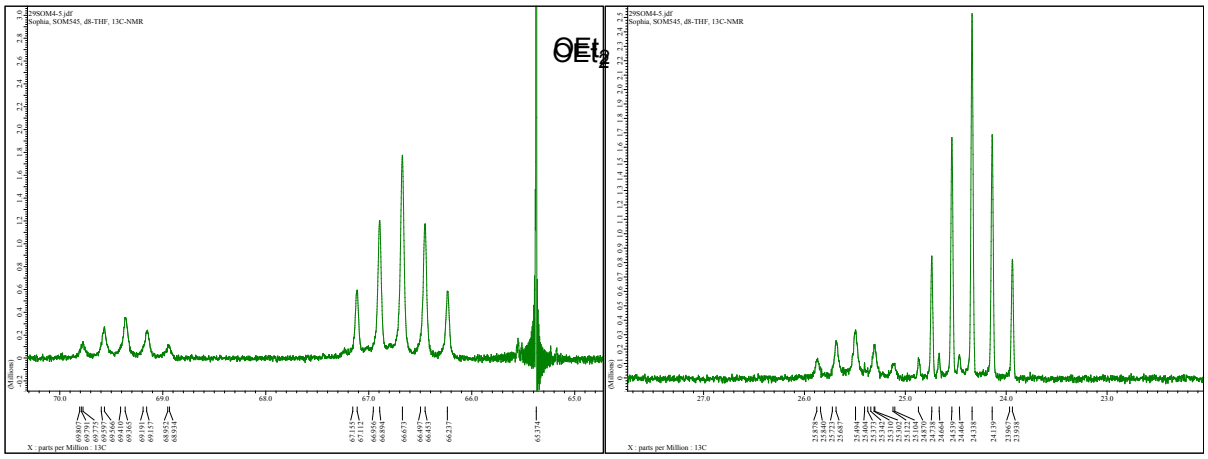


Figure 2: Expansion of the THF-d_8 signals of figure 1.

The same effect can be observed, when ethyl benzoate (45 mg, 0.3 mmol) is treated with 1.1 equivalents of $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) in THF-d_8 (0.6 mL) under the same conditions (Figure 3 and 4).

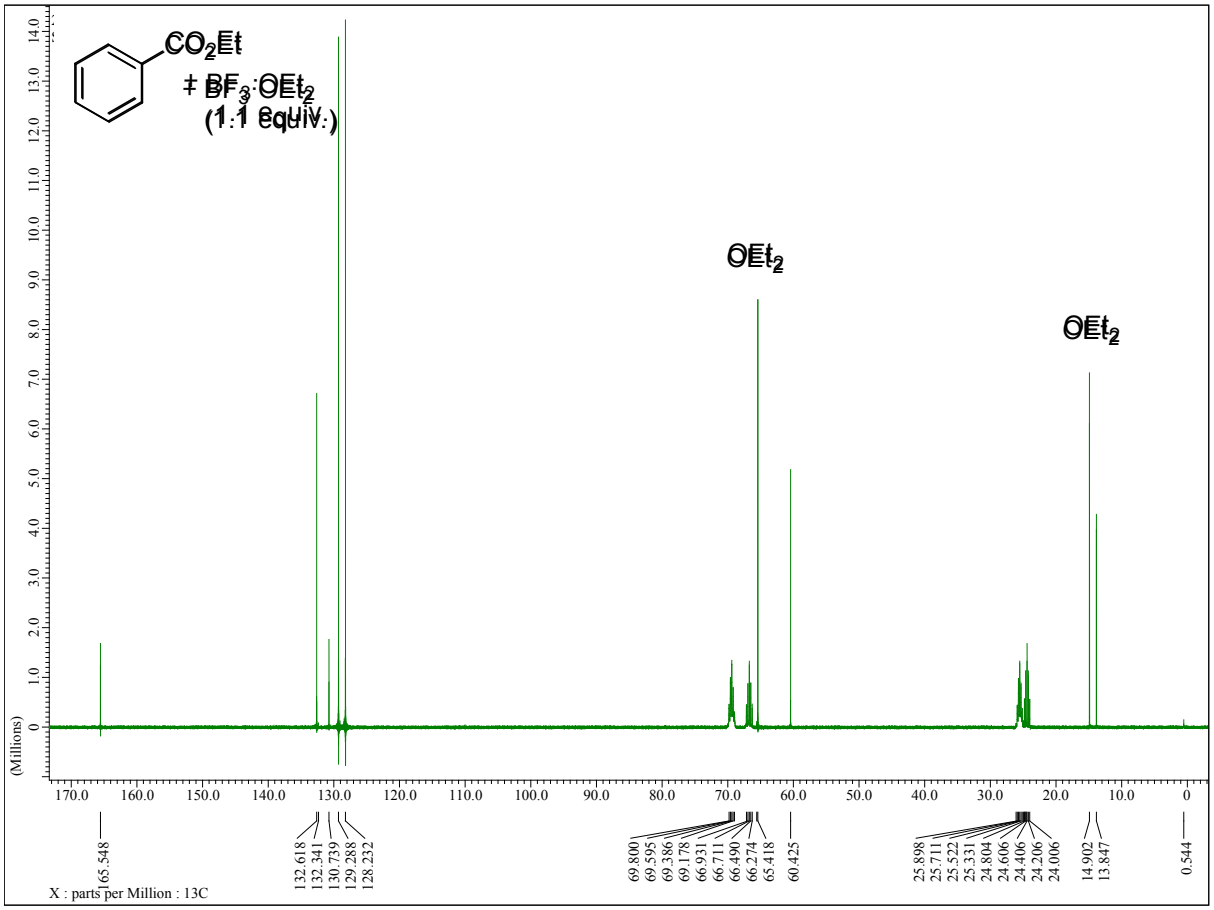


Figure 3: ^{13}C-NMR spectrum of ethyl benzoate with 1.1 equivalents of $BF_3 \cdot OEt_2$ in THF-d_8 at -50 °C.

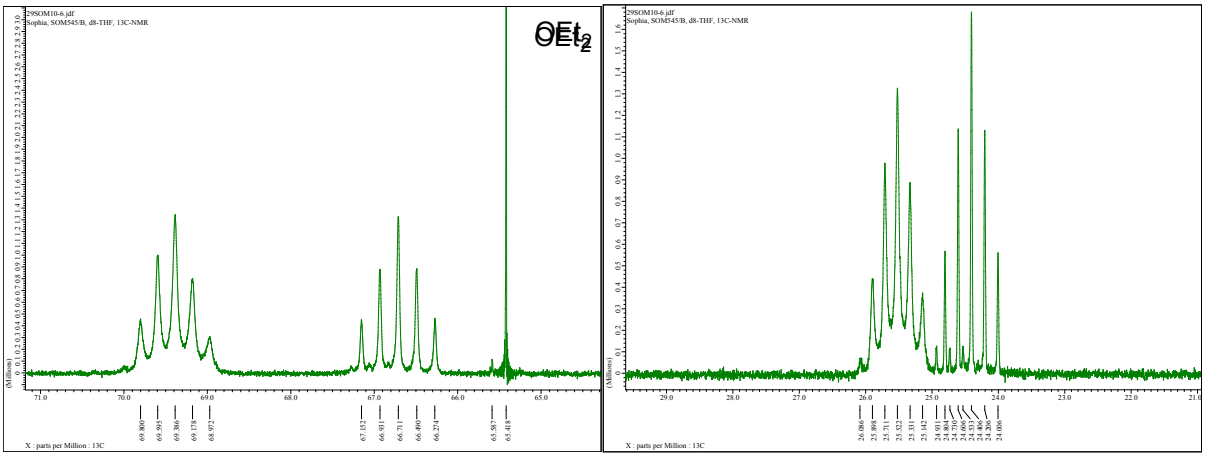
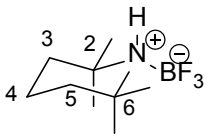


Figure 4: Expansion of the THF-d_8 signals of figure 3.

Synthesis and NMR-studies of trifluoro(2,2,6,6-tetramethylpiperidin-1-ium-1-yl)borate (12)



A dry and argon flushed 10 mL Schlenk-tube, equipped with a magnetic stirring bar, was charged with 42 mg 2,2,6,6-tetramethylpiperidine (0.3 mmol) in 0.6 mL THF-d_8 and cooled to 0 °C. $BF_3 \cdot OEt_2$ (47 mg, 0.33 mmol) was added and the reaction mixture was stirred for 15 min at the same temperature. The solution of complex **12** was then transferred in a dry, argon flushed NMR-tube which was cooled at -50 °C, and characterized. The spectra showed in addition to the characteristic signals of the BF_3-complex **12** also the signals of free TMPH and $BF_3 \cdot OEt_2$. Due to superposition of those signals in the ^{1}H-NMR spectrum no clear assignment for the ^{1}H-NMR signals was possible.

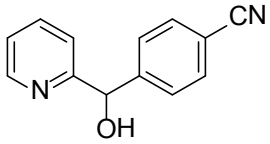
^{13}C-NMR (100 MHz, THF-d_8): δ / (ppm): 58.1 (2-C, 6-C), 40.6 (3-C, 5-C), 31.5 (q, J_{CF} 4.4 Hz, CH_3), 22.2 (q, J_{CF} 3.2 Hz, CH_3), 16.5 (4-C).

^{11}B-NMR (128 MHz, THF-d_8): δ / (ppm): -0.5 (q, J_{BF} 20.8 Hz).

^{19}F-NMR (376 MHz, THF-d_8): δ / (ppm): -132.35 (d, J_{BF} 20.3 Hz, ^{10}B isotopomer), -132.46 (d, J_{BF} 20.3 Hz, ^{11}B isotopomer).

The experiments described above show clearly, that in the case of **9a** the BF_3 is bonded neither to TMPH nor to THF. It is also reasonable to conclude, that the BF_3 does not coordinate to the ester group of the metalated ethyl nicotinate (**9a**). Unfortunately the ^{13}C-NMR signals of the metalated species **9a** are broad ($\Delta_{1/2}$ ca. 5 Hz) and do not show any evidence for a splitting due to coupling with fluorine. Thus we have no evidence for the coordination of BF_3 to the pyridine nitrogen atom.

Synthesis of 4-[hydroxy(pyridin-2-yl)methyl]benzonitrile (4a):



According to **TP1**, pyridine (**2a**, 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 4-Cyanobenzaldehyde (1.6 mmol, 288 mg) was added and the mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:2) furnished **4a** as pale yellow oil (246 mg, 73%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / (ppm): 8.58 (1H, d, J_{65} 6.0 Hz, 6-H), 7.62-7.70 (3H, m, 4-H, 11-H, 13-H), 7.52 (2H, d, J_{1011} 8.0 Hz, 10-H, 14-H), 7.20-7.26 (1H, m, 3-H), 7.18 (1H, J_{65} 6.0 Hz, 5-H) 5.81 (1H, s, 7-H).

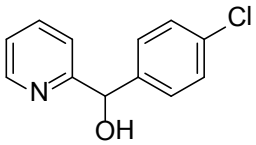
^{13}C-NMR (100 MHz, $CDCl_3$): δ / (ppm): 159.4, 148.3, 148.0, 137.0, 132.2, 127.4, 122.8, 121.0, 118.5, 111.4, 74.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3192, 3062, 2872, 2228, 1738, 1724, 1668, 1608, 1592, 1572, 1502, 1472, 1436, 1406, 1312, 1196, 1114, 1056, 870, 810, 780, 750, 616.

MS (70 eV, EI) *m/z* (%) = 210 [M^+] (100), 192 (15), 130 (17), 108 (42), 102 (18), 80 (18), 79 (91), 51 (20).

HRMS (EI) for **$C_{13}H_{10}N_2O$** (210.0793): 210.0791 (M^+).

Synthesis of (4-chlorophenyl)(pyridin-2-yl)methanol (4b):



According to **TP1**, pyridine (**2a**, 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 4-Chlorobenzaldehyde (1.6 mmol, 225 mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers

were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 2:1) furnished **4b** as pale yellow solid (239 mg, 68%).

M. p. (°C): 96.3-97.5.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / (ppm): 8.59 (1H, d, J_{65} 4.5 Hz, 6-H), 7.73 (1H, t, $J_{45,43}$ 7.7, 4-H), 7.15-7.44 (6H, m, 3-H, 5-H, 10-H, 13-H, 14-H), , 5.95 (1H, br, OH), 5.84 (1H, s, 7-H).

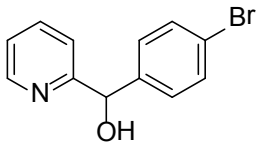
^{13}C-NMR (100 MHz, $CDCl_3$): δ / (ppm): 160.2, 146.8, 141.2, 138.2, 133.8, 128.8, 128.4, 122.9, 121.8, 73.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3142, 2848, 1592, 1572, 1492, 1468, 1438, 1410, 1334, 1192, 1114, 1090, 1056, 1018, 1002, 856, 812, 770, 748, 624.

MS (70 eV, EI) *m/z* (%) =219 [M^+] (100), 217 (41), 201 (47), 188 (46), 139 (40), 111 (25), 108 (40), 79 (94).

HRMS (EI) for **$C_{12}H_{10}ClNO$** (219.0451): 219.0444.

Synthesis of (4-bromophenyl)(pyridin-2-yl)methanol (4c):



According to **TP1**, pyridine (**2a,** 158 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 4-Bromobenzaldehyde (1.6 mmol, 296 mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 2:1) furnished **4c** as pale white solid (282 mg, 67%).

M.p. (°C): 97.5-99.1.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56 (1H, dt, J_{56} 5.0, J_{46} 1.6 Hz Hz, 6-H), 7.66 (1H, td, $J_{45,43}$ 7.6, J_{46} 1.6 Hz, 4-H), 7.42-7.50 (2H, m, 11-H, 13-H), 7.19-7.31 (3H, m, 5-H, 10-H, 14-H), 7.13-7.18 (1H, m, 3-H), 5.74 (1H, s, 7-H), 5.12 (1H, br s, OH).

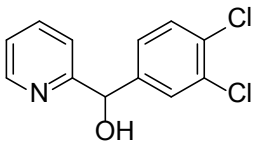
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 160.3, 147.6, 142.1, 137.2, 131.6, 128.7, 122.7, 121.8, 121.3, 74.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = cm-1, 3136, 2919, 2896, 2848, 1738, 1591, 1570, 1489, 1469, 1438, 1404, 1333, 1232, 1215, 1190, 1154, 1112, 1072, 1056, 1014, 1001, 946, 855, 846, 831, 808, 769, 745, 714, 682.

MS (EI, 70 eV): m/z (%) = 264 [$M+H^+$] (16), 166 (6), 108 (31), 79 (100), 52 (10).

HRMS (EI) for **$C_{12}H_{11}BrNO^+$** (264.0019): 263.9923.

Synthesis of (3,4-dichlorophenyl)(pyridin-2-yl)methanol (4d):



According to **TP1**, pyridine (**2a,** 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 3,4-Dichlorobenzaldehyde (1.6 mmol, 280 mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:1) furnished **4d** as pale yellow oil (268 mg, 68%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.56 (1H, dt, J_{56} 4.7, J_{46} 1.7 Hz, 6-H), 7.66 (1H, td, $J_{45,34}$ 7.7, J_{46} 1.7 Hz, 4-H), 7.49 (1H, d, J_{1014} 1.9 Hz, 10-H), 7.40 (1H, d, J_{1314} 8.3 Hz, 13-H), 7.14-7.26 (3H, m, 3-H, 5-H, 14-H), 5.70 (1H, s, 7-H).

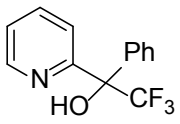
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.7, 148.0, 143.4, 137.1, 132.6, 131.7, 130.5, 128.9, 126.3, 122.8, 121.2, 73.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3178, 1738, 1593, 1571, 1466, 1435, 1416, 1385, 1312, 1257, 1230, 1216, 1190, 1148, 1129, 1099, 1045, 1029, 1002, 908, 895, 847, 811, 787, 748, 720, 706, 678.

MS (EI, 70 eV): m/z (%) = 253 [M^+] (33), 111 (12), 108 (38), 79 (100), 52 (11).

HRMS (EI) for **$C_{12}H_9Cl_2NO$** (253.0061): 253.0052.

Synthesis of 2,2,2-trifluoro-1-phenyl-1-(pyridin-2-yl)ethanol (4e):



According to **TP1**, pyridine (**2a,** 158 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40 °C for 15 min. 2,2,2-Trifluoro-1-phenylethanone (1.6 mmol, 279mg) was added and the solution was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:1) furnished **4e** as yellow oil (292 mg, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.60-8.63 (1H, m, 6-H), 7.73-7.79 (1H, m, 4-H), 7.64-7.69 (2H, m, 12-H, 16-H), 7.50 (1H, dq, J_{34} 8.0 Hz, J_{3F} 1.0 Hz 3-H), 7.30-7.40 (4H, m, 5-H, 13-H, 14-H, 15-H), 6.02 (1H, s, br, OH).

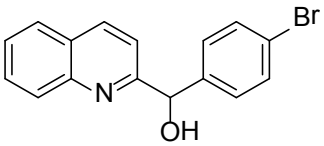
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 155.0, 147.2, 138.3, 137.4, 128.6, 128.4, 127.8 (q, J_{CF} 10.0 Hz) 127.0 (q, J_{CF} 2.0 Hz), 125.0 (q, J_{CF} 286.0 Hz), 124.0, 122.9 (q, J_{CF} 2:0 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ (cm^{-1}): 3286, 2928, 2856, 2362, 1734, 1718, 1594, 1576, 1498, 1468, 1450, 1436, 1406, 1262, 1196, 1150, 1120, 1096, 1072, 1050, 1036, 1002, 966, 948, 932, 912, 780, 760, 750, 736, 698, 684, 656, 628.

MS (EI, 70 eV): m/z (%) = 253 [M^+] (2), 111 (14), 97 (32), 85 (52), 83 (31), 71 (68), 69 (35), 57 (100), 41 (25).

HRMS (EI) for **$C_{13}H_{10}F_3NO$** (253.0714): 253.0722.

Synthesis of (4-bromophenyl)(quinolin-2-yl)methanol (4f)



According to **TP1**, quinoline (**2b,** 302 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 40 min. 4-Bromobenzaldehyde (1.6 mmol, 296 mg) was added and the reaction mixture was slowly warmed to -20 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **4f** as white solid (325 mg, 65%).

M.p. (°C): 118.9-120.0.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.14 (1H, d, J_{89} 9.6 Hz, 9-H), 8.08 (1H, d, J_{34} 8.5 Hz, 4-H), 7.74-7.84 (2H, m, 8-H, 3-H), 7.55-7.60 (1H, m, 7-H), 7.45-7.50 (2H, m, 15-H, 17-H), 7.27-7.33 (2H, m, 14-H, 18-H), 7.16 (1H, d, J_{34} 8.5 Hz, 3-H), 5.84 (1H, s, 11-H).

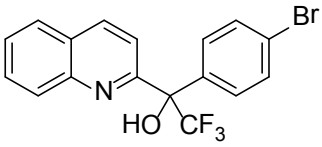
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.8, 145.9, 141.8, 137.2, 131.7, 130.1, 129.1, 128.7, 127.6, 127.5, 126.8, 122.0, 119.0, 74.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2360, 2334, 1738, 1729, 1665, 1585, 1565, 1502, 1480, 1459, 1427, 1392, 1316, 1293, 1274, 1248, 1230, 1209, 1179, 1165, 1109, 1067, 1045, 1008, 967, 958, 923, 858, 846, 830, 794, 770, 741, 720, 693.

MS (EI, 70 eV): m/z (%) = 313 [M^+] (100), 298 (11), 217 (14), 158 (48), 129 (93), 77 (11).

HRMS (EI) for **$C_{16}H_{12}BrNO$** (313.0102): 313.0089.

Synthesis of 1-(4-bromophenyl)-2,2,2-trifluoro-1-(quinolin-2-yl)ethanol (4g)



According to **TP1**, quinoline (**2b**, 302 mg, 2.0 mmol) reacted with $BF_3{\cdot}OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 40 min. 1-(4-bromophenyl)-2,2,2-trifluoroethanone (1.6 mmol, 405 mg) was added and the reaction mixture was slowly warmed to 0 °C and stirred for 19 h at this temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 10:1) furnished **4g** as colorless viscous oil (325 mg, 65%).

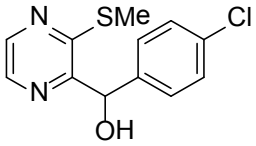
^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.23 (1H, d, J_{34} 8.9 Hz, 4-H), 8.17 (1H, d, J_{89} 8.6 Hz, 9-H), 7.88 (1H, d, J_{67} 8.3 Hz, 6-H), 7.79-7.86 (1H, m, 8-H), 7.48-7.68 (6H, m, 3-H, 7-H, 16-H, 17-H, 19H, 20-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 154.0 (q, J_{CF} 0.8 Hz), 145.2, 138.0, 137.1, 131.6, 130.6, 128.8 (q, J_{CF} 2.0 Hz), 128.8, 127.9, 127.8, 127.5, 124.8 (q, J_{CF} 286 Hz), 123.0, 119.4 (q, J_{CF} 2.6 Hz), 77.7 (q, J_{CF} 29 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3264, 3065, 2353, 2323, 2155, 1738, 1620, 1596, 1573, 1504, 1489, 1470, 1454, 1398, 1380, 1306, 1278, 1259, 1218, 1191, 1158, 1153, 1124, 1084, 1010, 989, 941, 932, 870, 823, 809, 787, 776, 754, 736, 712, 665.

MS (EI, 70 eV): m/z (%) = 381 [M^+] (16), 314 (35), 256 (10), 226 (21), 204 (12), 128 (100).
HRMS (EI) for **$C_{17}H_{11}BrF_3NO$** (380.9976): 380.9973.

Synthesis of (4-chlorophenyl)(3-(methylthio)pyrazin-2-yl)methanol (7a):



According to **TP1**, 2-(methylthio)pyrazine (**6**, 252 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40°C for 10 min. 4-Chlorobenzaldehyde (1.6 mmol, 225 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **7a** as yellow solid (268 mg, 63%).

M.p. (°C): 123.6-124.7.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.36 (2H, m, 5-H, 6-H), 7.33 (4H, s, 12-H, 13-H, 15-H, 16-H), 5.78 (1H, s, 9-H), 2.55 (3H, s, SCH_3).

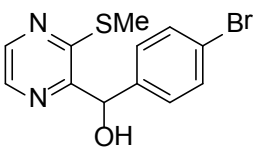
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.4, 150.8, 141.9, 141.4, 140.6, 133.9, 128.9, 128.1, 73.1, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3292, 2357, 2333, 1738, 1730, 1591, 1502, 1488, 1466, 1454, 1411, 1378, 1371, 1366, 1334, 1324, 1284, 1276, 1268, 1233, 1217, 1195, 1112, 1092, 1070, 1029, 1016, 960, 928, 901, 872, 842, 823, 771, 732, 702, 690.

MS (EI, 70 eV): m/z (%) = 266 [M^+] (100), 250 (32), 139 (37), 127 (73), 111 (23), 77 (27), 43 (36).

HRMS (EI) for **$C_{12}H_{11}ClN_2OS$** (266.0281): 266.0276.

Synthesis of (4-bromophenyl)(3-(methylthio)pyrazin-2-yl)methanol (7b):



According to **TP1**, 2-(methylthio)pyrazine (**6**, 252 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40°C for 10 min. 4-Bromobenzaldehyde (1.6 mmol, 296 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **7b** as yellow solid (329 mg, 66%).

M.p. (°C): 129.8-131.4.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.37 (1H, d, J_{56} 1.7 Hz, 6-H), 8.34 (1H, d, J_{56} 1.7 Hz, 5-H), 7.45-7.50 (2H, m, 13-H, 15-H), 7.24-7.29 (2H, m, 12-H, 14-H), 5.77 (1H, s, 9-H), 2.55 (3H, s, SCH_3).

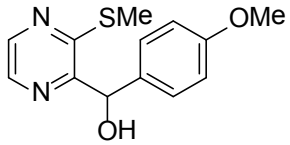
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 156.5, 150.7, 141.9, 141.4, 141.1, 131.8, 128.4, 122.1, 73.2, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3288, 2931, 2872, 2360, 1738, 1589, 1574, 1503, 1483, 1464, 1406, 1333, 1293, 1282, 1265, 1234, 1192, 1112, 1072, 1065, 1028, 1011, 961, 928, 900, 871, 840, 818, 769, 731, 725, 699, 668.

MS (EI, 70 eV): m/z (%) = 228 [M+H$^+$] (3), 127 (20), 77 (9), 61 (16), 45 (13), 43 (100).

HRMS (EI) for **$C_{12}H_{12}BrN_2OS^+$** (310.9848): 310.9771.

Synthesis of (4-methoxyphenyl)(3-(methylthio)pyrazin-2-yl)methanol (7c):



According to **TP1**, 2-(methylthio)pyrazine (**6**, 252 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –40°C for 10 min. 4-Methoxybenzaldehyde (1.6 mmol, 218 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 5:1) furnished **7c** as yellow solid (282 mg, 67%).

M.p. (°C): 65.7-67.8.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.34 (2H, s, 5-H, 6-H), 7.22-7.31 (2H, m, 13-H, 15-H), 6.82-6.29 (2H, m, 12-H, 16-H), 5.74 (1H, s, 9-H), 3.76 (3H, s, OCH_3), 3.66 (1H, br, s, OH), 2.53 (3H, s, SCH_3).

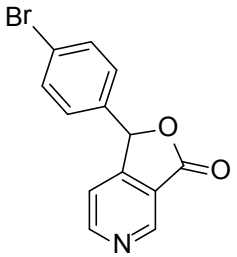
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 159.4, 155.8, 151.6, 142.0, 141.2, 134.3, 128.1, 114.1, 73.4, 55.2, 12.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3266, 3017, 2928, 1738, 1607, 1586, 1508, 1461, 1440, 1428, 1366, 1352, 1337, 1305, 1286, 1242, 1228, 1205, 1181, 1133, 1116, 1057, 1025, 970, 960, 932, 895, 871, 838, 828, 787, 755, 738, 709, 666.

MS (EI, 70 eV): m/z (%) = 262 [M^+] (68), 154 (17), 137 (100), 135 (72), 121 (29), 77 (26).

HRMS (EI) for **$C_{13}H_{14}N_2O_2S$** (262.0776): 262.0770.

Synthesis of 1-(4-bromophenyl)furo[3,4-c]pyridin-3(1H)-one (10a)



According to **TP1**, ethyl nicotinate (**8a,** 302 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at -40°C for 30 min. 4-Bromobenzaldehyde (1.6 mmol, 296 mg) was added and the reaction mixture was slowly warmed to 25 °C. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:1) furnished **10a** as white solid (416 mg, 72%).

M.p. (°C): 155.5-157.3.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.24 (1H, s, 9-H), 8.86 (1H, d, J_{67} 5.3 Hz, 7-H), 7.50-7.58 (2H, m, 11-H, 15-H), 7.34 (1H, d, J_{67} 5.3 Hz, 6-H), 7.11-7.19 (2H, m, 14-H, 12-H), 6.39 (1H, s, 2-H).

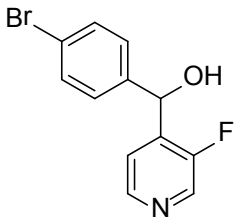
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.1, 157.3, 153.6, 148.1, 133.7, 132.5, 128.4, 124.1, 121.8, 117.8, 81.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1758, 1606, 1590, 1487, 1421, 1410, 1334, 1301, 1241, 1212, 1201, 1149, 1110, 1068, 1028, 1014, 984, 957, 944, 904, 862, 833, 824, 794, 762, 728, 695, 664.

MS (EI, 70 eV): m/z (%) = 289 [M^+] (90), 210 (43), 183 (34), 166 (100), 139 (26), 133 (21), 105 (51).

HRMS (EI) for **$C_{13}H_8BrNO_2$** (288.9738): 288.9732.

Synthesis of (4-bromophenyl)(3-fluoropyridin-4-yl)methanol (10b)



According to **TP1**, 3-fluoropyridine (**8b**, 194 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –78 °C for 10 min. 4-Bromobenzaldehyde (1.6 mmol, 296 mg) was added and the reaction mixture was stirred for 45 min at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:2) furnished **10b** as white solid (360 mg, 80%).

M.p. (°C): 161.6-163.2.

^{1}H-NMR (400 MHz,THF-d_8): δ / ppm = 8.36 (1H, d, J_{56} 4.9 Hz, 6-H), 8.32 (1H, s, 2-H), 7.59 (1H, t, J_{56} 4.9 Hz, 5-H), 7.48-7.82 (2H, m, 12-H, 14-H), 7.30-7.36 (2H, m, 11-H, 15-H), 6.00 (1H, d, $J_{8\text{-HF}}$ 2.6 Hz, 8-H), 5.50 (1H, d, J_{OHF} 3.5 Hz, OH).

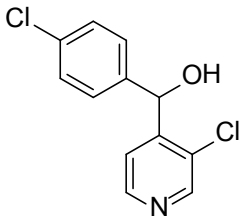
^{13}C-NMR (100 MHz, THF-d_8): δ / ppm = 157.7 (d, *J* 254 Hz), 147.2 (d, *J* 5.0 Hz), 143.6 (d, *J* 0.8 Hz), 141.2 (d, *J* 11.1 Hz), 138.5 (d, *J* 23.4 Hz), 132.4, 129.4 122.4, 122.3, 68.6 (d, *J* 2.3 Hz).

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3124, 2854, 2682, 2351, 2199, 1973, 1754, 1738, 1729, 1715, 1612, 1588, 1494, 1482, 1470, 1462, 1453, 1446, 1434, 1413, 1401, 1378, 1372, 1332, 1313, 1275, 1240, 1227, 1194, 1184, 1166, 1151, 1103, 1069, 1052, 1010, 960, 909, 875, 840, 825, 795, 754, 738, 714, 676.

MS (EI, 70 eV): m/z 281 (M^+, 68%), 202 (100), 187 (25), 157 (18), 124 (71), 97 (20), 77 (22).

HRMS (EI) for **$C_{12}H_9BrFNO$** (280.9852): 280.9842.

Synthesis of (4-chlorophenyl)(3-chloropyridin-4-yl)methanol (10c)



According to **TP1**, 3-chloropyridine (**8c,** 227 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at −78 °C for 15 min. 4-Chlorobenzaldehyde (1.6 mmol, 225 mg) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL) and NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 3:2) furnished **10c** as white solid (293 mg, 72%).

M.p. (°C): 139.9-140.7.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.46 (1H, d, J_{56} 5.0 Hz, 6-H), 8.43 (1H, s, 2-H), 7.66 (1H, d, J_{56} 5.0 Hz, 5-H), 7.31 (4H, s, 11-H, 12-H, 14-H, 15-H), 6.09 (1H, s, 8-H).

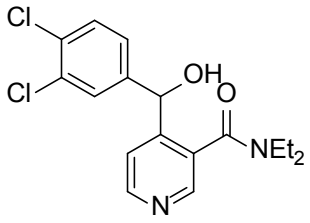
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 149.5, 149.2, 148.0, 139.2, 134.3, 130.0, 128.9, 128.5, 121.9, 71.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3116, 2846, 2359, 1908, 1590, 1488, 1475, 1434, 1403, 1331, 1314, 1288, 1269, 1216, 1180, 1165, 1104, 1092, 1064, 1041, 1013, 982, 960, 868, 856, 836, 825, 808, 750, 732, 714, 692.

MS (EI, 70 eV): m/z (%) = 253 [M^+] (100), 218 (85), 139 (84), 111 (37), 77 (47).

HRMS (EI) for **$C_{12}H_9Cl_2NO$** (253.0061): 253.0060.

Synthesis of 4-((3,4-dichlorophenyl)(hydroxy)methyl)-*N*,*N*-diethylnicotinamide (10d)



According to **TP1**, *N,N*-diethylnicotinamide (**8d**, 366 mg, 2.0 mmol) reacted with $BF_3 \cdot OEt_2$ (312 mg, 2.2 mmol) and TMPMgCl·LiCl (1.95 mL, 2.2 mmol, 1.13 M in THF) at –78 °C for 10 min. 3,4-Dichlorobenzaldehyde (280 mg, 1.6 mmol) was added and the reaction mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution (9 mL), NH_3 (conc.) (1 mL) followed by extraction with EtOAc (3x30 mL). The combined organic layers were dried over Na_2SO_4 and after filtration the solvents were evaporated *in vacuo*. Purification by flash column chromatography (silica gel, pentane / EtOAc = 1:5) furnished **10d** as white solid (360 mg, 80%).

M.p. (°C): 108.8-110.0.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.64 (1H, d, J_{56} 5.0 Hz, 6-H), 8.44 (1H, s, 2-H), 7.35-7.48 (3H, m, 5-H, 18-H, 19-H), 7.09-7.16 (1H, m, 15-H), 5.75 (1H, s, 9-H), 3.24-3.53 (2H, m, CH_2), 2.68-3.01 (2H, m, CH_2), 0.37-0.84 (6H, m, 2xCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 168.8, 151.2, 150.1, 147.0, 142.0, 132.5, 131.7, 130.6, 130.2, 128.7, 128.5, 126.0, 77.2, 43.3, 39.4, 13.7, 12.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3075, 3063, 2996, 2975, 2877, 2838, 1628, 1597, 1566, 1504, 1462, 1437, 1408, 1396, 1375, 1364, 1348, 1339, 1318, 1308, 1295, 1274, 1244, 1227, 1215, 1200, 1183, 1151, 1126, 1103, 1082, 1066, 1057, 1029, 998, 981, 957, 944, 902, 882, 869, 849, 834, 808, 792, 776, 748, 734, 701, 678.

HRMS (ESI) for $\mathbf{C_{17}H_{19}C_{l2}N_2O_2^+}$ (353.0818): 353.0815.