Halogen-Magnesium Exchange on Unprotected Aromatic and Heteroaromatic Carboxylic Acids

Supporting Information

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General: All reactions involving the use of Grignard reagents were carried out under an argon atmosphere in dried glassware using Schlenk techniques. As not otherwise stated, the starting materials were purchased from commercial sources and used without further purification. Ethyl 2-(bromomethyl) acrylate,[1] 3,5-diiodobenzoioc acid,[2] *S*-phenyl benzenesulfonothioate[3] and CuCN·2LiCl in THF[4] were prepared according to literature known procedures. Benzaldehyde, cyclohexane carbaldehyde benzoyl chloride, triisopropyl borate and ethyl chloridocarbonate were distilled under reduced pressure prior to use. THF was continously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen.

The reactions of all acid derivatives were monitored by TLC of reaction aliquots after a microextraction (2 M HCl / EtOAc; silica plates; CH_2Cl_2:MeOH-mixtures, in almost all cases 19:1) versus the staring material and/or the equivalent for the quenched Grignard reagent, as far as commercially available. Analogously, the extractions in course of workups were always monitored by TLC to ensure completeness of the extractions. Yields refer to isolated yields of compounds estimated to be >95 % pure by NMR.

Preparation of LiCl in THF (0.50 M)

LiCl (5.25 g, 125 mmol) was placed in a 500 mL Schenk flask equipped with a magnetic stirring bar and a glas stopper. For all purposes, teflon grease should be employed. The salt is heated at 150 °C in an oil bath for 4 h. Then, after cooling to rt, the stopper was changed to a rubber septum and absolute THF (250 mL) was added. Afterwards, the septum was replaced again by a glas

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[1] Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.
[2] Endres, A; Maas, G. *Tetrahedron* **2002**, *58*, 3999.
[3] Fujili, K.; Tanifuji, N; Sasaki, Y.; Yokoyama, T. *Synthesis* **2002**, 343.
[4] Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

stopper and the suspension was left stirring over night at rt. After at least 12 h, the LiCl had completely dissolved, the stirring wass stopped and the solution was left for some more time to become completely clear (little particles and insoluble impurities are allowed settle down by that way). The solution was stored under Ar upon use.

1. Preparation of the functionalized benzoic acid derivatives of type 3

1.1 Typical procedure for the double metallation of *ortho*-, *metha*-, and *para*-iodobenzoic acid (1a-c) (TP1):

The iodobenzoic acid (**1**; 2.00 mmol) was placed in a dry and argon-flushed Schlenk tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for 5 min at rt., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. The exchange reaction was monitored by TLC and was usually complete after 45 min. The resulting slurry was cooled to – 20 °C and the respective electrophile was added at this temperature, then the mixture was allowed to warm up to rt. The reaction was again monitored using TLC. After the completion of the reaction, the mixture was subjected to workup and purification (see below).

Synthesis of 4-[hydroxy(phenyl)methyl]benzoic acid (3a):

The double magnesiated reagent **2a** was prepared according to **TP1** from 4-iodobenzoic acid (**1a**; 496 mg, 2.00 mmol) and reacted with benzaldehyde (254 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*, to give pure 4-[hydroxy(phenyl)methyl]benzoic acid (**3a**) as a colourless solid (433 mg, 1.90 mmol, 95 %)

mp.: 166.8-168.1 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 5.77 (s, 1 H); 6.03 (brs, 1 H); 7.17-7.39 (m, 5 H); 7.50 (d, *J* = 8.2 Hz); 7.89 (d, *J* = 8.2 Hz); 12.25 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 73.9; 126.2; 126.3; 126.9; 128.2; 129.2; 129.2; 145.1; 150.6; 167.2.

IR (KBr): ν [cm^{-1}] = 3285 (m); 3032 (w); 2898 (m); 2643 (m); 1702 (vs); 1611 (m); 1578 (w); 1509 (w); 1496 (w); 1554 (m); 1416 (m); 1316 (m); 1276 (vs); 1193 (m); 1178 (m); 1172 (w); 1110 (w), 1080 (w); 1034 (s); 1024 (m); 1014 (s); 923 (w); 876 (m); 826 (w); 790 (m); 779 (w); 758 (s); 742 (s); 700 (s); 634 (w); 620 (w); 556 (w); 530 (w); 490 (w).

MS (EI): (m/z) (%) = 228 (M^+; 24); 183 (16); 165 (20); 149 (42); 123 (100);105 (55); 79 (46); 77 (48); 65 (10); 51 (14).

HR-MS ($C_{14}H_{12}O_3$): calculated: 228.0786 found: 228.0790.

Synthesis of 4-benzoylbenzoic acid (3b):

The double magnesiated reagent **2a** was prepared according to TP1 from 4-iodobenzoic acid (**1a**; 496 mg, 2.00 mmol) and reacted with benzoyl chloride (366 mg, 2.40 mmol 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M; 0.40 mL, 0.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After recrystallization from MeOH, 4-benzoylbenzoic acid (**3b**) was obtained as a colourless solid (375 mg, 1.42 mmol, 71 %).

mp.: 197.0-198.0 °C

^{1}H-NMR (dmso-d_6, 300 MHz): δ [ppm] = 7.55-8.11 (m, 9 H); 13.31 (s, 1 H).

^{13}C-NMR (dmso-d_6, 75 MHz): δ [ppm] = 129.0; 129.7; 130.0; 130.1; 133.4; 134.3; 136.8; 140.9; 167.0; 195.7.

IR (KBr): ν [cm^{-1}] = 3423 (br); 3058 (br); 2678 (w); 2553 (w); 1962 (w); 1704 (s); 1682 (m); 1681 (vs); 1599 (m); 1579 (w); 1501 (m); 1446 (w); 1430 (m); 1407 (m); 1385 (w); 1320 (m); 1279 (vs); 1226 (m); 1180 (w); 1150 (w); 1110 (m); 1077 (w); 1016 (w); 1000 (w); 978 (w); 942 (m); 928 (m); 872 (m); 809 (w); 792 (w); 766 (m); 710 (s); 692 (m); 656 (w); 578 (w); 524 (w).

MS (EI): (m/z) (%) = 226 (M^+; 52); 181 (11); 149 (40); 121 (10); 105 (100); 77 (33); 65 (11); 51 (9).

HR-MS ($C_{14}H_{10}O_3$): calculated: 226.0630 found: 226.0621.

Synthesis of 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoic acid (3c):

The double magnesiated reagent **2a** was prepared according to **TP1** from 4-iodobenzoic acid (**1a**; 496 mg, 2.00 mmol) and reacted with B(O*i*-Pr)$_3$ (451 mg, 2.40 mmol 1.20 equiv) at –20 °C, then the reaction mixture was warmed up to rt and stirred for 1 h. Then, 2,2-dimethyl-1,3-propanediol (270 mg, 2.60 mmol, 1.30 equiv) was added neat at rt, the mixture was stirred for another 2 h. The reaction mixture was poured on water, the aqueous layer carefully acidified by addition of sat. aq. citric acid to reach a pH of 5-6 (indicator paper). The resulting mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo*. After recrystallization from MeOH, 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoic acid (**3c**) was obtained as a highly crystalline, colorless solid (234 mg, 1.00 mmol, 50 %).

mp.: 236.9-238.1 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 0.94 (s, 6 H); 3.76 (s, 4 H); 7.77-7.92 (m, 4 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 21.2; 31.4; 39.5; 71.4; 112.1; 128.3; 132.6; 133.6; 167.3.

IR (KBr): ν [cm^{-1}] = 3434 (w); 2963 (m); 2874 (m); 2674 (w); 2551 (w); 1693 (vs); 1561 (w); 1508 (m); 1479 (m); 1427 (s); 1377 (m); 1342 (m); 1307 (s); 1253 (s); 1180 (w); 1135 (s); 1121 (m); 1020 (w); 932 (w); 860 (w); 813 (w); 719 (m); 707 (m); 657 (w); 641 (m); 545 (w); 500 (w).

MS (EI): (m/z) (%) = 234 (M$^+$; 74); 191 (23); 163 (6); 149 (11); 135 (5); 103 (5); 56 (100); 41 (15).

HR-MS ($C_{12}H_{15}BO_4$): calculated: 234.1063 found: 234.1040.

Synthesis of 3-[2-(ethoxycarbonyl)-2-propenyl]benzoic acid (3d):

The double magnesiated reagent **2b** was prepared according to **TP1** from 3-iodobenzoic acid (**1b**; 496 mg, 2.00 mmol) and treated at –20 °C with CuCN·2LiCl in THF (1.00 M; 2.30 mL, 1.15 equiv) and stirred for 40 min at the same temperature. Afterwards, ethyl 2-(bromomethyl)-acrylate (461 mg, 2.40 mmol, 1.20 equiv) is added and the mixture is allowed to warm up to room temperature. After TLC indicated completion of the reaction, MeOH (2.0 mL) was added and the mixture was transferred to a separation funnel containing sat. aq. NH_4Cl (10 mL). By careful addition of 2.0 M HCl, the pH was adjusted to 5-6. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo*. After flash column chromatography (silica; CH_2Cl_2:MeOH; 19:1), 3-[2-(ethoxycarbonyl)-2-propenyl]benzoic acid (**3d**) was obtained as a colorless solid (366 mg, 1.56 mmol, 78 %).

mp.: 93.3-95.8 °C (decomposition)

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 1.16 (t, *J* = 6.9 Hz, 3 H); 3.66 (s, 2 H); 4.10 (q, *J* = 6.9 Hz, 2 H); 5.71 (d, *J* = 1,5 Hz, 1 H); 6.16 (d, *J* = 1,5 Hz, 1 H); 7.41-7.80 (m, 4 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 14.3; 37.5; 60.8; 127.1; 127.6; 128.9; 129.6; 131.1; 133.2; 133.6; 139.6; 166.2; 167.2.

IR (KBr): ν [cm^{-1}] = 3427 (w); 3060 (w); 2995 (m); 2677 (w); 2564 (w); 1709 (vs); 1695 (vs); 1634 (m); 1607 (m); 1591 (m); 1490 (w); 1476 (m); 1450 (m); 1425 (m); 1392 (w); 1372 (w); 1350 (w); 1318 (m); 1294 (s); 1239 (w); 1214 (m); 1194 (m); 1140 (s); 1083 (w); 1029 (s); 948 (br); 932 (m); 870 (w); 820 (w); 785 (m); 748 (s); 708 (s); 674 (w); 662 (m); 650 (m); 537 (w); 482 (w).

MS (EI): (m/z) (%) = 234 (M$^+$; 8); 216 (100); 188 (51); 187 (11); 171 (14); 170 (10); 161 (18); 160 (91); 117 (32); 116 (34); 115 (81); 91 (13); 89 (7); 77 (8).

HR-MS ($C_{13}H_{14}O_4$): calculated: 234.0892 found: 234.0892.

Synthesis of 3-cyclohexyl-2-benzofuran-1(3*H*)-one (3e):

The double magnesiated reagent **2c** was prepared according to **TP1** from 2-iodobenzoic acid (**1c**; 496 mg, 2.00 mmol) and reacted with cyclohexane carboxaldehyde (269 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 ML) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After recrystallization from MeOH, 3-cyclohexyl-2-benzofuran-1(3*H*)-one (**3e**) was obtained as a colorless solid (375 mg, 1.74 mmol, 87 %).

mp.: 95.0-97.0 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 0.98-2.14 (m, 11 H); 5.57 (d, *J* = 3.3 Hz, 1 H); 7.62-7.72 (m, 2 H); 7.80-7.89 (m, 2 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 25.2; 25.6; 25.7; 28.9; 30.6; 40.9; 84.6; 122.8; 124.8; 125.7; 129.1; 134.2; 148.7; 169.9.

IR (KBr): ν [cm^{-1}] = 3483 (w); 2932 (s); 2850 (m); 1750 (vs); 1614 (w); 1594 (w); 1466 (w); 1455 (m); 1380 (w); 1350 (m); 1314 (w); 1291 (m); 1272 (w); 1214 (m); 1198 (w); 1098 (m); 1076 (m); 1058 (s); 956 (w); 986 (s); 896 (w); 848 (w); 784 (w); 750 (s); 712 (w); 697 (s); 654 (m); 608 (w); 562 (w); 526 (w); 496 (w).

MS (EI): (m/z) (%) = 216 (M$^+$; 5); 135 (74); 134 (90); 133 (100); 105 (78); 83 (25); 77 (41); 55 (56); 51 (11); 41 (29).

HR-MS ($C_{14}H_{16}O_2$): calculated: 216.1150 found: 216.1157.

1.2. Typical procedure for the double metallation of functionalized iodobenzoic acids (1d; 1f-h) (TP2):

The iodobenzoic acid of type **1** (2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for 5 min at rt, the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF, 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting solution was stirred at the same temperature. After TLC indicated full conversion, the respective electrophile was added at -20 °C and the mixture was allowed to warm up to rt. The reaction was again monitored using TLC. After the completion of the reaction, the mixture was subjected to workup and purification (see examples).

Synthesis of 3-bromo-5-[cyclohexyl(hydroxy)methyl]benzoic acid (3f):

The double magnesiated reagent **2d** was prepared according to **TP2** from 3-bromo-5-iodobenzoic acid (**1d**; 654 mg, 2.00 mmol) and reacted with cyclohexane carboxaldehyde (269 mg, 2.40 mmol 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After recrystallization from MeOH, 3-bromo-5-[cyclohexyl(hydroxy)methyl]benzoic acid (**3f**) was obtained as a colorless solid (570 mg, 1.82 mmol, 91 %).

mp.: 179.2-180.3 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 0.83-1.72 (m, 11 H); 4.34 (d, *J* = 5.58 Hz, 1 H); 5.31 (brs, 1 H); 7.67 (s, 1 H); 7.83 (s, 1 H); 7.88 (s, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 25.5; 25.6; 25.0; 27.6; 28.9; 44.6; 75.7; 121.1; 126.4; 129.9; 132.5; 133.4; 148.4; 166.1.

IR (KBr): ν [cm^{-1}] = 3386 (s); 3057 (m); 2922 (vs); 2852 (s); 2646 (w); 1685 (vs); 1601 (w); 1575 (m); 1451 (m); 1386 (m); 1365 (w); 1314 (m); 1278 (s); 1265 (s); 1252(s); 1199 (m); 1083 (w); 1028 (m); 972 (w); 909 (w); 893 (m); 843 (w); 772 (m); 686 (m); 658 (w); 572 (w).

MS (EI): (m/z) (%) = 314 (M^+; ^{81}Br; 3); 312 (M^+; ^{79}Br; 3); 232 (10); 230 (11); 185 (12); 151 (41); 105 (18); 83 (40); 77 (35); 55 (56); 41 (24).

HR-MS ($C_{14}H_{17}BrO_3$): calculated: 312.0361 found: 312.0367.

Synthesis of 3-bromo-5-[(4-bromophenyl)(hydroxy)methyl]benzoic acid (3g):

The double magnesiated reagent **2d** was prepared according to **TP2** from 3-bromo-5-iodobenzoic acid (**1d**; 654 mg, 2.00 mmol) and reacted with 4-bromo-benzaldehyde (444 mg, 2.40 mmol 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After recrystallization from MeOH, 3-bromo-5-[(4-bromophenyl)(hydroxy)methyl]benzoic acid (**3g**) was obtained as a colorless solid (533 mg, 1.38 mmol, 69 %).

mp.: 226.9-228.0 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 5.80 (s, 1 H); 6.24 (brs, 1 H); 7.35 (d, *J* = 8.0; 7.51(d, *J* = 8.0; 7.81 (s, 1 H); 7.88 (s, 1 H); 7.90 (s, 1 H); 12.72 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 72.3; 120.2; 121.5; 126.0; 128.5; 130.2; 131.2; 133.0; 133.0; 144.0; 148.4; 165.8.

IR (KBr): ν [cm^{-1}] = 3436 (br); 3028 (w); 2956 (m); 2835 (m); 2169 (m); 1603 (w); 1495 (s); 1454 (s); 1373 (m); 1361 (m); 1300 (w); 1248 (vs); 1230 (s); 11048 (s); 1077 (m); 1029 (m); 987 (s); 956 (m); 853 (vs); 794 (m); 752 (vs); 699 (vs); 644 (m); 610 (m); 532 (w); 503 (w); 486 (w).

MS (EI): (m/z) (%) = 388 (M$^+$; 2 × ^{81}Br; 18); 386 (M$^+$; ^{79}Br + ^{81}Br; 37); 384 (M$^+$; 2 × ^{79}Br; 23); 307 (30); 305 (30); 247 (20); 229 (100); 227 (95); 203 (37); 201 (42); 199 (19); 187 (26); 185 (61); 183 (38); 157 (35); 105 (16); 77 (64).

HR-MS ($C_{14}H_{10}Br_2O_3$): calculated: 383.8997 found: 383.8974.

Synthesis of 3-(ethoxycarbonyl)-5-(1-hydroxy-2,2-dimethylpropyl)benzoic acid (3j):
The double magnesiated reagent **2f** was prepared according to **TP2** from 3-(ethoxycarbonyl)-5-iodobenzoic acid (**1d**; 654 mg, 2.00 mmol) and reacted with pivaldehyde (206 mg, 2.40 mmol 1.20 equiv). The reaction mixture was poured on water (40 mL), the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After column chromatography (silica; CH_2Cl_2:MeOH; 19:1) 3-(ethoxycarbonyl)-5-(1-hydroxy-2,2-dimethylpropyl)benzoic acid (**3j**) was obtained as colorless, crystalline solid (389 mg, 1.39 mmol, 70 %).

mp.: 167.4-168.7 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 0.82 (s, 9 H); 1.33 (t, *J* = 7.1 Hz, 3 H); 4.34 (q, *J* = 7.1 Hz, 2 H); 4.39 (s, 1 H); 5.43 (s, 1 H); 8.08 (m, 2 H); 8.35 (s, 1 H); 13.25 (s, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 14.1; 25.7; 35.2; 61.0; 79.0; 128.1; 129.3; 130.3; 132.2; 132.8; 145.0; 165.2; 166.7.

IR (KBr): ν [cm^{-1}] = 3394 (w); 2966 (m); 2938 (m); 2904 (m); 2874 (m); 1720 (s); 1688 (vs); 1650 (w); 1642 (w); 1602 (m); 1480 (w); 1462 (w); 1446 (w); 1398 (m); 1390 (m); 1366; 1342 (w); 1318 (m); 1262 (s); 1234 (vs); 1200 (s); 1182 (m); 1124 (m); 1106 (m); 1070 (w); 1052 (m); 1012 (s);

976 (w); 954 (w); 946 (w); 934 (m); 916 (m); 876 (w); 862 (w); 772 (m); 748 (s); 692 (m); 684 (m); 670 (s).

MS (ESI): (m/z) (%) = 281 ($[M+H]^+$; 3); 273 (8); 265 (13); 235 (9); 224 (100); 195 (57); 150 (15); 121 (4); 105 (6); 79 (11); 57 (23); 41 (11).

HR-MS ($C_{15}H_{21}O_5$; $[M+H^+]$): calculated: 281.1389 found: 281.1391.

Synthesis of 5-[9-anthryl(hydroxy)methyl]-2-[(2,2-dimethylpropanoyl)oxy]benzoic acid (3k):
The double magnesiated reagent **2g** was prepared according to **TP2** from 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (**1g**; 696 mg, 2.00 mmol) and a slight excess of *i*-PrMgCl·LiCl (1.30 M; 1.60 mL; 1.05 equiv) and reacted with anthraldehyde (453 mg, 2.20 mmol 1.10 equiv) in THF (4.0 mL). The reaction mixture was poured on water (20 mL) and sat. aq. NH_4Cl (20 mL), the aqueous layer was carefully adjusted to pH 5-6 (indicator paper) by dropwise addition of HCl (2.0 M) accompanied by vigorous shaking and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and reduced in *vacuo*. Then, heptane was added, followed by some drops of diethyl ether. The resulting slurry was sonicated (30 min) and subsequently filtered. The residue was washed with heptane. After drying the crude product in high vacuum (30 min), 5-[9-anthryl(hydroxy)methyl]-2-[(2,2-dimethylpropanoyl)oxy]benzoic acid (**3k**) was obtained as a grey-yellow solid (574 mg, 1.34 mmol, 67 %).

mp.: 183.5-185.6 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 1.24 (s, 9 H); 6.63 (brs, 1 H); 7.03 (d, *J* = 8.4, Hz, 1 H); 7.31 (s, 1 H); 7.42-7.52 (m, 5 H); 7.83 (s, 1 H); 8.10 (d, *J* = 8.4 Hz, 2 H); 8.51 (d, *J* = 8.35 Hz, 2 H); 8.62 (s, 1 H); 13.01 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 26.8; 38.3; 67.5; 123.3; 123.8; 125.0; 125.6-125.7 (broad, 2 signals); 127.9; 128.1; 129.0; 129.3; 130.4; 131.3; 135.4; 143.5; 148.5; 165.8; 176.0.

IR (KBr): ν [cm^{-1}] = 3054 (w); 2976 (w); 2934 (w); 2872 (w); 1748 (m); 1684 (s); 1610 (w); 1586 (w); 1492 (w); 1482 (m); 1446 (m); 1426 (w); 1398 (w); 1366 (w); 1280 (m); 1232 (w); 1210 (s); 1124 (vs); 1062 (m); 1022 (m); 1000 (m); 958 (w); 942 (m); 922 (w); 896 (m); 870 (w); 854 (w); 842 (m); 788 (w); 734 (s); 724 (s); 692 (w); 674 (w); 654 (w); 636 (w); 610 (w).

MS (ESI): (m/z) (%) = 428 (M^+; 44); 344 (10); 324 (13); 252 (11); 207 (18); 205 (24); 194 (9); 179 (74); 165 (17); 152 (18); 147 (11); 120 (16); 85 (10); 57 (100); 41 (30).

HR-MS ($C_{27}H_{24}O_5$): calculated: 428.1624 found: 428.1646.

Synthesis of 3-(4-bromobenzoyl)-4-methylbenzoic acid (3l):

The double magnesiated reagent **2h** was prepared according to **TP2** from 3-iodo-4-methylbenzoic acid (**1h**; 524 mg, 2.00 mmol) and reacted with 4-bromobenzoyl chloride (526 mg, 2.40 mmol 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M; 0.40 mL, 0.20 equiv) . The reaction mixture was poured on water (40 mL), the aqueous layer was adjusted to pH 5-6 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The collected organic layers were washed with a saturated aqueous solution of sodium-potassium-tartrate to remove remaining copper. The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After column chromatography (silica; CH_2Cl_2:MeOH, 19:1), the resulting white solid was subjected to sonication (30 min) in little heptane. After filtration and drying in high vacuum (30 min), 3-(4-bromobenzoyl)-4-methylbenzoic acid (**3l**) was obtained as a white solid (517 mg, 1.62 mmol, 81 %).

mp.: 189.5-190.8 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 2.30 (s, 3 H); 7.50 (d, *J* = 7.9 Hz, 1 H); 7.62 (d, *J* = 8.1 Hz, 2 H); 7.77 (d, *J* = 8.1 Hz, 2 H); 7.82 (s, 1 H), 8.00 (d, *J* = 7.9 Hz, 1 H); 12.99 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 20.0; 128.3; 129; 129.3; 131.6; 131.9; 132.0; 132.4; 136.2; 138.1; 141.6; 167.0; 196.4.

IR (neat): ν [cm^{-1}] = 2968 (w); 2840 (w); 2556 (w); 2546 (w); 1686 (s); 1662 (vs); 1606 (m); 1584 (s), 1566 (m); 1480 (w); 1430 (m); 1396 (m); 1378 (w); 1310 (s); 1294 (s); 1280 (s); 1254 (s); 1176 (m); 1162 (m); 1138 (m); 1110 (w); 1100 (m); 1068 (m); 1034 (w); 1010 (m); 952 (s); 936 (m); 926 (m); 850 (s); 840 (s); 772 (s); 754 (s); 740 (m); 712 (w); 696 (w); 658 (m); 632 (m); 624 (m).

MS (EI): (m/z) (%) = 319 ($[M-H]^+$; ^{81}Br; 9); 317 ($[M-H]^+$; ^{79}Br; 8); 239 (100); 195 (24); 194 (24); 185 (15); 183 (15); 177 (11); 165 (11); 163 (16); 156 (11); 155 (12); 135 (8); 107 (4); 89 (5); 77 (6).

HR-MS ($C_{15}H_{10}BrO_3$; $[M-H]^+$): calculated: 316.9813 found: 316.9812 .

1.3. Typical procedure for the double metallation of 3,5-diiodobenzoic acid (1e) (TP3):

3,5-Diiodobenzoic acid (**1e**; 748 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for 5 min at rt., the resulting red solution was cooled to -50 °C. After stirring 15 min at -50 °C, MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -50 °C for further 30 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added very slowly, the solution turned dark brown immediately. The mixture was stirred at -50 °C. After TLC indicated full conversion (60 min), the respective electrophile was added at -50 °C, the mixture was stirred 20 min at this temperature and was subsequently allowed to warm up to rt. After the completion of the reaction, the reaction was quenched (MeOH, 2.0 mL), subjected to workup and purification (see examples).

Synthesis of 3-allyl-5-iodobenzoic acid (3g):

The double magnesiated reagent **2e** was prepared according to **TP3** from 3,5-diiodobenzoic acid (**1e**; 748 mg, 2.00 mmol) and reacted with allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). The reaction mixture was poured on water (40 ML). The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After gel filtration (silica; CH_2Cl_2:MeOH; 19:1) (**3f**) was obtained as an off white solid (403 mg, 1.40 mmol, 70 %).

mp.: 115.4-117.8 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 3.40 (d, *J* = 6.7 Hz, 2 H); 5.05-5.15 (m, 2 H); 5.88-5.98 (m, 1 H); 7.75 (s, 1 H); 7.81 (s, 1 H); 8.05 (s, 1 H); 13.22 (s, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 38.5; 94.8; 116.8; 128.7; 132.8; 135.4; 136.7; 141.2; 142.9; 165.9.

IR (neat): ν [cm^{-1}] = 2980 (w); 2808 (w); 2662 (w); 2538 (w); 1692 (vs); 1642 (m); 1594 (m); 1560 (s); 1452 (s); 1412 (s); 1310 (m); 1292 (s); 1276 (vs); 1248 (m); 1196 (m); 1122 (m); 1102 (w); 994 (m); 928 (vs); 890 (s); 862 (s); 798 (m); 766 (vs); 746 (m); 694 (vs); 662 (s).

MS (EI): (m/z) (%) = 288 (M^+; 100); 242(10); 161(8), 117 (56); 115 (82); 105 (5); 91 (15); 89 (12); 77 (10); 63 (14); 51 (7).

HR-MS ($C_{10}H_9IO_2$): calculated: 287.9647 found: 287.9665.

Synthesis of 3-cyano-5-iodobenzoic acid (3h):

The double magnesiated reagent **2e** was prepared according to **TP3** from 3,5-diiodobenzoic acid (**1e**; 748 mg, 2.00 mmol) and tosyl cyanide (95 %, technical quality; 434 mg, 2.40 mmol, 1.20 equiv) in in THF (3.0 mL) was added at -50 °C. The mixture was slowly warmed up to room temperature. The reaction mixture was quenched with MeOH (4.0 mL) and poored on water. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After filter column chromatography (Silica; CH_2Cl_2:MeOH; 19:1) 3-cyano-5-iodobenzoic acid (**3h**) was obtained as an pale yellow solid (300 mg, 1.10 mmol, 55 %).

mp.: 169.3-171.2 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 8.26 (s, 1 H); 8.45 (s, 1 H); 8.49 (s, 1 H); 13.75 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 95.3; 113.6; 116.6; 132.0; 133.5; 142.0; 143.8; 164.5.

IR (KBr): ν [cm^{-1}] = 3065 (w); 2956 (w); 2926 (w); 2855 (w); 2667 (w); 2550 (w); 2236 (m); 1831 (w); 1691 (vs); 1593 (w); 1560 (m); 1444 (m); 1427 (m); 1400 (m); 1284 (vs); 1256 (m); 1202 (m); 1122 (w); 997 (w); 930 (m); 900 (s); 823 (w); 796 (m); 768 (s); 756 (m); 700 (s); 668 (vs).

MS (EI): (m/z) (%) = 273 (100); 256 (23); 228 (9); 146 (11); 130 (7); 127 (8); 101 (16); 90 (16); 75 (14); 63 (8); 50 (15).

HR-MS ($C_8H_4O_2NI$): calculated: 272.9287 found: 272.9293.

2. Preparation of functionalized furane and thiophene carboxylic acids of type 5-9

2.1 Typical procedure for the double metallation of 5-bromo-2-furoic acid (4) and 5-bromothiophene-2-carboxylic acid (5) (TP4):

The carboxylic acid of type **4** or **5** (2.00 mmol) was placed in a dry and argon-flushed Schlenk tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added slowly and the resulting mixture was allowed to warm up to room temperature. A first check after 30 min did indicate complete conversion. The Grignard reagent did precipitate as a thick, greyish slurry, which was cooled to 20 °C. Subsequently, the respective electrophile was added at this temperature, the mixture was allowed to warm up to rt. The reaction was again monitored using TLC. After the completion of the reaction, the mixture was subjected to workup and purification (see examples).

Synthesis of 5-allyl-2-furoic acid (7a):

The double magnesiated reagent was prepared according to **TP4** from 5-bromo-2-furoic acid (**4**; 382 mg, 2.00 mmol) and reacted with allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). The reaction mixture was poured on water (40 mL). The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. Pure 5-allyl-2-furoic acid (**7a**) was obtained as a colourless solid (280 mg, 1.84 mmol, 92 %).

mp.: 195.0-196.0 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 3.45 (d, *J* = 6.5 Hz, 2 H); 5.10-5.19 (m, 2 H); 5.84-5.98 (m, 1 H); 6.30 (d, *J* = 3.2 Hz, 1 H); 7.12 (d, *J* = 3.2 Hz, 1 H); 12.86 (s, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 32.0; 108.4; 117.7; 118.8; 133.2; 143.7; 158.0; 159.2.

IR (KBr): ν [cm^{-1}] = 3424 (w); 3121 (m); 3014 (m); 2924 (m); 2681 (m); 2582 (m); 2058 (w); 1861 (w); 1690 (vs); 1645 (m); 1594 (m); 1522 (vs); 1428 (s); 1384 (w); 1292 (s); 1232 (m); 1212 (m);

1161 (s); 1022 (s), 1003 (m); 975 (w); 966 (w); 929 (s); 901 (w); 880 (w); 802 (m); 761 (m); 748 (w); 726 (w); 589 (w); 561 (m).

MS (EI): (m/z) (%) = 152 (M^+; 100); 125 (10); 107 (32); 79 (41); 77 (35); 53 (6); 51 (13).

HR-MS ($C_8H_8O_3$): calculated: 152.0456 found: 152.0445.

Synthesis of 5-{hydroxy[4-(trifluoromethyl)phenyl]methyl}-2-furoic acid (7b):

The double magnesiated reagent was prepared according to **TP4** from 5-bromo-2-furoic acid (**4**; 382 mg, 2.00 mmol) and reacted with 4-(trifluoromethyl)benzaldehyde (415 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (1.0 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. The crude product is suspended in little heptane and subjected to sonication (30 min). After filtration and washing with pentane, 5-{hydroxy[4-(trifluoromethyl)phenyl]methyl}-2-furoic acid (**7b**) was obtained as a colourless solid (501 mg, 1.75 mmol, 88 %).

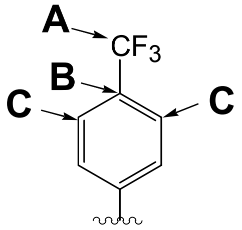
mp.: 137.5-139.0 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 5.87 (s, 1 H); 6.40 (d, J = 3.4 Hz, 1 H); 7.12 (d, J = 3.4 Hz, 1 H); 7.62 (d, J = 8.1 Hz, 2 H); 7.73 (d, J = 8.1 Hz, 2 H). Both acidic OH groups can not be detected.

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 108.9; 118.2; 118.8; 122.4; 125.1-125.2 (q); 126.0; 127.2; 127.5; 127.9; 128.3; 128.8; 129.6; 144.5; 146.4; 159.3; 160.4.

Thereby, the following assignments can be done:

A: 129.6; 126.0; 122.4; 118.8: q, ^1J = 271 Hz;
B: 127.5; 127.9; 128.3; 128.8: q, ^2J = 31 Hz;
C: 125.1-125.2; q, ^3J = 4 Hz.



IR (KBr): ν [cm^{-1}] = 3402 (m); 2704 (w); 2579 (w); 1689 (vs); 1621 (m); 1594 (m); 1526 (s); 1415 (s); 1329 (vs); 1275 (w); 1211 (w); 1198 (m); 1164 (w); 1124 (m); 1113 (w); 1069 (vs); 1018 (vs);

970 (w); 959 (m); 930 (w); 858 (m); 813 (m); 785 (m); 767 (m); 725 (m); 641 (w); 601 (m); 551 (w); 425 (w).

MS (EI): (m/z) (%) = 286 (M^+; 24); 284 (6); 269 (14); 267 (11); 242 (14); 241 (100); 225 (6); 223 (7); 217 (7); 213 (17); 195 (10);173 (22); 165 (13);146 (21); 141 (8); 139 (22); 128 (19); 123 (15); 113 (38); 95 (13);

HR-MS ($C_{13}H_9F_3O_4$): calculated: 286.0453 found: 286.0447.

Synthesis of 5-(methylthio)thiophene-2-carboxylic acid (8a):

The double magnesiated reagent was prepared according to **TP4** from 5-bromothiophene-2-carboxylic acid (**5**; 414 mg, 2.00 mmol) and reacted with *S*-methyl methanesulfonothioate (610 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on diluted aq. NaOH (ca 1.00 M; 40 mL) and extracted with diethyl ether (40 mL), the ether layer was discarded. The aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After gel filtration (silica; CH_2Cl_2:MeOH; 19:1), 5-(methylthio)thiophene-2-carboxylic acid (**8a**) was obtained as a pale pink solid (324 mg, 1.86 mmol, 93%).

mp.: 104.4-105.6 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 2.59 (s, 3 H); 7.06 (d, J = 3.7 Hz, 1 H); 7.59 (d, J = 3.7 Hz, 1 H); 13.06 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 18.9; 127.5; 133.3; 133.7; 146.3; 162.1.

IR (KBr): ν [cm^{-1}] = 3437 (m); 2926 (w); 2853 (w); 2573 (w); 1658 (vs); 1525 (vs); 1427 (vs); 1405 (vs); 1304 (vs); 1278 (m); 1224 (m); 1106 (vs); 1066 (m); 1009 (m); 966 (m); 915 (br); 800 (s); 764 (m); 748 (s); 670 (w); 533 (m); 490 (m); 469 (m).

MS (EI): (m/z) (%) = 174 (M^+; 100); 159 (28); 157 (12); 131 (16); 114 (9); 103 (7); 71 (6); 69 (8); 57 (4); 44 (6).

HR-MS ($C_6H_6O_2S_2$): calculated: 173.9809 found: 173.9803.

Synthesis of 5-[4-(dimethylamino)phenyl]thiophene-2-carboxylic acid (8b):

The double magnesiated reagent was prepared according to **TP4** from 5-bromothiophene-2-carboxylic acid (**5**; 414 mg, 2.00 mmol). Then, $ZnCl_2$ (1.00 M in THF; 2.20 mL, 2.20 mmol, 1.10 equiv) was added at -20 °C, the resulting solution was warmed up to room temperature and stirred for 30 min at this temperature.

Concurrently, $Pd(dba)_2$ (57.5 mg, 5.00 mol%) and tri-2-furylphosphine (46.4 mg, 10.0 mol%) were placed in a second, dry and argon-flushed Schlenk flask and dissolved in THF (4.0 mL). After stirring this mixture for 5 min at rt, the colour changed from orange to green. Then, a solution of 4 iodo-*N*,*N*-dimethylaniline in THF [due to the low stability of the iodoarene, it was prepared in situ by quenching 4-(dimethylamino)phenylmagnesium bromide/LiCl (1.10 M; 2.18 mL, 2.40 mmol, 1.20 equiv; prepared by insertion in the presence of LiCl) with I_2 (610 mg, 2.40 mmol 1.20 equiv)] was added *via* a cannula and the resulting mixture was stirred for 10 min at rt. Afterwards, it was cannulated to the zinc reagent prepared above, the mixture was heated at 50 °C for 3 h. Then, MeOH (2.0 mL) was added and the reaction mixture was poured on water (40 mL). The aqueous layer was carefully adjusted to pH 5-6 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo*. The residue was suspended in CH_2Cl_2 (20 mL) and subjected to sonication (30 min). After filtration and thorough washing with CH_2Cl_2, the desired product **7b** was obtained as a solid of intensive green colour (470 mg, 1.90 mmol, 95 %).

mp.: 100.4-202.3 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 2.94 (s, 6 H); 6.74 (d, J = 8.2 Hz, 2 H); 7.30 (d, J = 4.0 Hz, 1 H); 7.53 (d, J = 8.2 Hz, 2 H); 7.60 (d, J = 4.0 Hz, 1 H). The acid proton can not be detected.

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 40.5; 112.9; 121.3; 122.1; 127.4; 132.0; 134.7; 151.2; 151.6; 163.8.

IR (KBr): ν [cm^{-1}] = 3430 (m); 3044 (m), 2679 (w); 2560 (m); 1660 (s); 1607 (vs); 1540 (m); 1481 (w); 1451 (vs); 1440 (vs); 1366 (s); 1302 (m); 1254 (w); 1230 (w); 1198 (m); 1106 (m); 1044 (w); 960 (w), 945 (w); 809 (m); 758 (s); 671 (w); 580 (w); 524 (w).

UV/Vis: λ_{max} = 363, 251, 202.

MS (EI): (m/z) (%) = 247 (M$^+$; 100); 231 (13); 203 (5); 158 (4); 115 (6); 79 (4).

HR-MS ($C_{13}H_{13}NO_2S$): calculated: 247.0667 found: 247.0652.

2.2 Typical procedure for the bromine/magnesium-exchange on 4,5-dibromo-2-thiophenecarboxylic acid (6) (TP5):

4,5-dibromo-2-thiophenecarboxylic acid (572 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 4.00 mL, 2.00 mmol, 1.00 equiv) was added and after stirring for some minutes at rt., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 0.67 mL, 2.00 mmol, 1.00 equiv) was added dropwise. Strong bubbling of methane out of the solution did indicate the proceeding deprotonation. After completion of the addition, the mixture was stirred at -20 °C for further 20 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was and the resulting mixture was stirred at the same temperature. After 60 min, TLC indicated complete conversion. Subsequently the respective electrophile was added at this temperature and the mixture was allowed to warm up to rt. After the completion of the reaction, the mixture was subjected to workup and purification (see examples).

The selectivity of the reaction was proven by quenching a 2 mmol batch of the Grignard reagent with MeOH, affording, after standard workup, pure 4-bromo-2 thiophenecarboxylic acid. The ^{1}H-NMR data in $CDCl_3$ were compared with the literature data of 4-bromo-2 thiophenecarboxylic acid (*J. Med. Chem.* **1992**, *35*, 1109) as well as the data for 5-bromo-2 thiophenecarboxylic acid (*J. Mat. Chem.* **2000**, *10*, 1777). Furthermore, the data for 5-allyl-4-bromo-2-thiophenecarboxylic acid (**9a**) are known (*J. Org. Chem.* **2000**, *65*, 4681). Thus, the exchange was clearly assigned to proceed in 5-position.

Synthesis of 5-allyl-4-bromo-2-thiophenecarboxylic acid (9a):

The double magnesiated reagent was prepared according to **TP5** from 4,5-dibromo-2-thiophenecarboxylic acid (**6**; 572 mg, 2.00 mmol) and reacted with allyl bromide (290 mg, 2.40 mmol, 1.20 equiv) in the presence of CuCN·2LiCl (1.00 M in THF; 0.02 mL, 1.00 mol%). The reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with CH_2Cl_2 (3 × 40 mL). The combined CH_2Cl_2-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After drying in high vacuum, 5-allyl-

4-bromo-2-thiophenecarboxylic acid (**9a**) was obtained as a colourless, crystalline solid (477 mg, 1.93 mmol, 97 %).

mp.: 107.3-108.6 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 3.53 (d, *J* = 6.4 Hz, 2 H); 5.12-5.23 (m, 2 H); 5.86-5.99 (m, 1 H); 7.62 (s, 1 H); 13.36 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 33.2; 109.1; 117.9; 132.6; 134.0; 134.9; 144.5; 161.8.

IR (KBr): ν [cm^{-1}] = 3001 (m); 2671 (m); 1665 (vs); 1528 (s); 1451 (s); 1411 (m); 1390 (m); 1312 (s); 1275 (s); 1151 (m); 1145 (m); 1096 (w); 1046 (w); 996 (m); 922 (s); 868 (m); 801 (w); 771 (m); 751 (m); 688 (w); 589 (w); 512 (m).

MS (EI): (m/z) (%) = 248 (M$^+$; ^{81}Br; 100); 246 (M$^+$; ^{79}Br; 95); 231 (6); 229 (5); 221 (20); 219 (19); 167 (25); 149 (5); 123 (82); 95 (7); 79 (18); 77 (12); 69 (7); 51 (7); 45 (21).

HR-MS ($C_8H_7BrO_2S$): calculated: 245.9350 found: 245.9318.

Synthesis of 5-bromo-4-(ethoxycarbonyl)-2-thiophenecarboxylic acid (9b):

The double magnesiated reagent was prepared according to **TP5** from 4,5-dibromo-2-thiophenecarboxylic acid (**6**; 572 mg, 2.00 mmol) and reacted with ethyl chloridocarbonate (259 mg, 2.40 mmol, 1.20 equiv). The reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined EtOAc-layers were dried (Na_2SO_4) and evaporated in *vacuo*. After recrystallization from heptane/EtOAc (4:1), 5-bromo-4-(ethoxycarbonyl)-2-thiophenecarboxylic acid (**9a**) was obtained as a pale orange, crystalline solid (477 mg, 1.12 mmol, 56 %).

mp.: 188.2-190.1 °C

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 1.30 (t, *J* = 7.1 Hz, 3 H); 4.31 (q, *J* = 7.1 Hz, 2 H); 7.75 (s, 1 H); 13.81 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 13.9; 39.5; 61.8; 88.2; 115.9; 131.6; 136.7; 139.0; 159.5; 161.3.

IR (KBr): ν [cm^{-1}] = 3086 (m); 2996 (w); 2984 (w); 2942 (w); 2870 (w); 2566 (w); 1724 (m); 1686 (s); 1658 (s); 1518 (s); 1460 (m); 1412 (s); 1330 (m); 1296 (s); 1276 (m); 1226 (vs); 1160 (m); 1120 (w); 1090 (s); 1080 (m); 1010 (s); 888 (s); 840 (m); 814 (w); 774 (m); 760 (s); 692.

MS (EI): (m/z) (%) = 280 (M$^+$; ^{81}Br; 47); 278 (M$^+$; ^{79}Br; 44); 252 (48); 250 (46); 235 (100); 233 (96); 208 (9); 206 (9); 191 (11); 189 (11); 109 (10); 82 (21); 45 (5).

HR-MS ($C_8H_7BrO_4S$): calculated: 277.9248 found: 277.9242.

3. Synthesis of 5-cyano-2-hydroxy-3-(phenylthio)benzoic acid via a triple anionic intermediate

5-Cyano-2-hydroxy-3-iodobenzoic acid (578 mg, 2.00 mmol) was placed in a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. Then, a solution of LiCl in THF (0.50 M; 8.00 mL, 4.00 mmol, 2.00 equiv) was added and after stirring for some minutes at rt., the resulting solution was cooled to -20 °C and MeMgCl (3.00 M in THF; 1.33 mL, 4.00 mmol, 2.00 equiv) was added dropwise. After completion of the addition, the mixture was stirred at -20 °C for further 40 min. Afterwards, *i*-PrMgCl·LiCl (1.32 M in THF; 1.67 mL, 2.20 mmol, 1.10 equiv) was added and the resulting mixture was stirred at the same temperature. After 120 min, TLC indicated complete conversion. Subsequently, $PhSSO_2Ph$ (600 mg, 2.40 mmol, 1.20 equiv) in THF (4.0 mL) was added at this temperature, then the mixture was allowed to warm up to rt. After completion of the reaction (TLC), the reaction mixture was poured on water (40 mL) and the aqueous layer was adjusted to pH 3-4 (indicator paper) by addition of HCl (2.0 M) and extracted with EtOAc (3 × 40 mL). The combined EtOAc-layers were dried (Na_2SO_4) and evaporated in *vacuo*. The crude product was purified by flash column chromatography (silica; CH_2Cl_2: MeOH, 19:1) and subsequent recrystallization from MeOH to yield 5-cyano-2-hydroxy-3-(phenylthio)benzoic acid (**12**) as crystalline, beige solid (298 mg, 1.10 mmol, 55 %).

mp.: 227.4-229.2 °C (decomposition, starting at 200 °C)

^{1}H-NMR (dmso-d$_6$, 300 MHz): δ [ppm] = 7.23 (d, *J* = 1.9 Hz, 1 H); 7.31-7.43 (m, 5 H); 7.95 (d, *J* = 1.9 Hz, 1 H); the acidic protons were not detected.

^{13}C-NMR (dmso-d$_6$, 75 MHz): δ [ppm] = 97.1; 116.6; 119.1; 125.9; 127.7; 129.6; 131.4; 133.0; 133.4; 135.9; 167.2; 169.5.

IR (KBr): ν [cm^{-1}] = 3070 (m); 2230. (s); 1652 (m); 1626 (m); 1580 (m); 1456 (s); 1440 (s); 1421 (s); 1382 (m); 1354 (m); 1292 (w); 1250 (m); 1183 (s); 1108 (w); 1082 (w); 1068 (w); 1024 (m); 926 (w); 910 (w); 888 (w); 870 (w); 808 (m); 776 (m); 744 (s); 706 (m); 688 (s).

MS (EI): (m/z) (%) = 271 (M^+; 52); 253 (100); 227 (55); 225 (13); 196 (31); 121 (13); 78 (17); 77 (14); 51 (15).

HR-MS ($C_{14}H_9NO_3S$): calculated: 271.0303 found: 271.0304.

4. Starting material Synthesis

Synthesis of ethyl 3,5-diiodobenzoate:

3,5-Diiodobenzoic acid (**1e**; 1.87 g, 5.00 mmol) was placed under N_2 in a 50 mL Schlenk flask equipped with a magnetic stirring bar and a reflux condendser. $SOCl_2$ (5.0 mL, 67 mmol, 14 equiv) was carefully added and the resulting mixture was heated at reflux for one hour. Then, toluene (30 mL) was added and the excess thionyl chloride was removed by azeotropic destillation. The residue was cooled in an ice bath and dry ethanol (20 mL; excess) was added. Afterwards, the mixture was refluxed for another 15 min. Chilling (ice bath) of the resulting solution resulted in the crystallization of the product. Filtration afforded the product as a pale orange, crystalline solid (1.43 g, 3.56 mmol, 71 %).

mp.: 90.2-91.6 °C

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 1.38 (t, *J* = 7.2 Hz, 3 H); 4.37 (q, *J* = 7.2 Hz, 2 H); 8.21 (s, 1 H); 8.31 (s, 2 H).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ [ppm] = 14.3; 61.8; 94.3; 133.7; 137.7; 149.1; 163.7.

IR (neat): ν [cm^{-1}] = 3050 (w); 2978 (w); 2935 (w); 2110 (w); 1720 (s); 1674 (w); 1543 (m); 1466 (w); 1448 (w); 1414 (m); 1407 (m); 1391 (m); 1364 (m); 1257 (vs); 1130 (m); 1112 (m); 1104 (m); 1020 (s); 911 (w); 885 (m); 872 (m); 862 (m); 761 (s); 705 (s); 659 (m).

MS (EI): (m/z) (%) = 401 (M^+; 100); 374 (37); 357 (62); 329 (18); 247 (7); 201 (9); 191 (4); 75 (9).

HR-MS ($C_9H_8I_2O_2$): calculated: 401.8614 found: 401.8601.

Synthesis of 3-(ethoxycarbonyl)-5-iodobenzoic acid (1f):

Ethyl 3,5-diiodobenzoate (1.21 g, 3.00 mmol) was placed in a dry and argon flushed Schlenk-tube equipped with a magnetic stirring bar and a septum. THF (6.0 mL) was added and the resulting solution was cooled to –50 °C. *i*-PrMgCl (1.00 M in THF; 3.06 mL, 1.03 equiv) was added dropwise and after 15 min at –50 °C, the GC analysis of reaction aliquots indicated complete conversion to the desired Grignard reagent. Then, predried ($CaCl_2$) CO_2 was bubbled through the solution and the reaction mixture was at the same time slowly warmed up to room temperature. The conversion was checked by TLC (silica; CH_2Cl_2:MeOH, 19:1). When the reaction was complete, the mixture was poored on water (50 mL) and the pH of the aqueous layer was adjusted to 3-4 (indicator paper) by addition of 2.0 M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), the completeness of the reaction was checked by TLC of the fractions. The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo*. The resulting solid was suspended in little heptane and subjected to sonication. After filtration the desired product was obtained as pale orange solid (604 mg, 1.89 mmol, 63 %).

mp.: 167.5-169.5 °C

^{1}H-NMR (dmso-d$_6$, 400 MHz): δ [ppm] = 1.33 (t, *J* = 7.0 Hz, 3 H); 4.33 (q, *J* = 7.0 Hz, 2 H); 8.38-8.43 (m, 3 H); 13.56 (brs, 1 H).

^{13}C-NMR (dmso-d$_6$, 100 MHz): δ [ppm] = 14.0; 61.5; 94.9; 128.8; 132.1; 133.2; 141.1; 141.7; 163.7; 165.1.

IR (neat): ν [cm^{-1}] = 3072 (w); 2982 (w); 2872 (w); 2636 (w); 2524 (w); 1724 (s); 1686 (vs); 1598 (w); 1566 (m); 1468 (w); 1446 (m); 1434 (w); 1404 (m); 1394 (m); 1366 (m); 1304 (m); 1246 (vs); 1150 (m); 1116 (m); 1102 (m); 1024 (s); 998 (w); 932 (m); 922 (m); 898 (m); 864 (m); 824 (w); 750 (vs); 730 (w); 718 (m); 696 (s); 658 (m).

MS (EI): (m/z) (%) = 320 (M$^+$; 89); 292 (58); 275 (100); 247 (16); 191 (8); 165 (6); 149 (7); 120 (10); 92 (11); 75 (21); 64 (6); 50 (6).

HR-MS ($C_{10}H_8IO_4$): calculated: 319.9546 found: 319.9549.

Synthesis of 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (1g):

In a round bottom flask, equipped with a reflux condenser and a magnetic stirring bar, 5-iodosalicylic acid (3.96 g, 15.0 mmol) was dissolved in pivalic anhydride (6.10 mL, 30.1 mmol, 2.01 equiv). Concentrated sulfuric acid (5 drops) was added as a catalyst and the resulting mixture was refluxed (110 °C) for 2 h. After cooling to rt, upon careful treatment with water (5.0 mL), the product precipitated as white solid, which was filtered. After drying in high vacuum, 2-[(2,2-dimethylpropanoyl)oxy]-5-iodobenzoic acid (**1g**) was obtained as colorless, crystalline solid (3.96 g, 11.4 mmol, 76 %).

mp.: 174.3-176.2 °C

^{1}H-NMR (dmso-d$_6$, 400 MHz): δ [ppm] = 1.27 (s, 9 H); 6.99 (d, *J* = 8.5 Hz, 1 H); 7.95 (dd, *J* = 8.5 Hz, *J'* = 2.3 Hz, 1 H); 8.14 (d, *J* = 2.3 Hz, 1 H); 13.37 (s, 1 H).

^{13}C-NMR (dmso-d$_6$, 100 MHz): δ [ppm] = 26.8; 38.4; 90.5; 126.1; 126.7; 139.3; 142.1; 150.0; 164.4; 175.8.

IR (neat): ν [cm^{-1}] = 2972 (m); 2930 (w); 2904 (w); 2868 (w); 2822 (w); 2704 (w); 2656 (w); 2592 (w); 2554 (w); 2518 (w); 1748 (s); 1696 (vs); 1592 (m); 1562 (m); 1472 (m); 1458 (m); 1422 (m); 1394 (w); 1382 (w); 1366 (w); 1300 (s); 1264 (s); 1234 (m); 1202 (s); 1102 (vs); 1090 (vs); 1076 (s); 1028 (m); 968 (m); 932 (m); 892 (s); 864 (m); 838 (m); 808 (m); 776 (m); 748 (m); 682 (s); 640 (m).

MS (EI): (m/z) (%) = 348 (M$^+$; 16); 265 (98); 246 (>99); 218 (10); 85 (15); 63 (20); 57 (100); 41 (26).

HR-MS ($C_{12}H_{13}IO_4$): calculated: 347.9859 found: 347.9840.

Synthesis of 5-cyano-2-hydroxy-3-iodobenzoic acid (10):

In a dry and argon-flushed Schlenk tube equipped with a septum and a magnetic stirring bar, 4-hydroxy-3,5-diiodobenzonitrile (1.86 g, 5.00 mmol) was dissolved in a solution of LiCl in THF (0.50 M; 10.0 mL, 5.00 mmol, 1.00 equiv) and cooled to -30 °C. Then, MeMgCl (3.00 M in THF; 1.67 mL, 5.00 mmol, 1.00 equiv) was added dropwise. The reaction mixture was kept stirring at -30 °C for 40 min, then *i*-PrMgCl (1.00 M in THF; 5.50 mL, 5.50 mmol, 1.10 equiv) was slowly added and the mixture was stirred for 30 min at –30 °C. After the exchange reaction was complete (TLC), predried ($CaCl_2$) CO_2 was bubbled through the solution and the reaction mixture was at the same time slowly warmed up to room temperature. The conversion was checked by TLC (silica; CH_2Cl_2:MeOH, 19:1). When the reaction was complete, the mixture was poored on water (50 mL) and the pH of the aqueous layer was adjusted to 3-4 (indicator paper) by addition of 2.0 M HCl. The aqueous layer was extracted with EtOAc (3 × 50 mL), the completeness of the extraction was checked by TLC of the fractions. The combined organic layers were dried (Na_2SO_4) and evaporated in *vacuo*. The resulting solid was covered CH_2Cl_2 (ca 5 mL) and the slurry was subjected to sonication (30 min). After filtration and washing with small amounts of CH_2Cl_2 and pentane, the desired product was obtained as off white solid (1.14 g, 3.94 mmol, 79 %).

mp.: 174.3-176.2 °C

^{1}H-NMR (dmso-d$_6$, 400 MHz): δ [ppm] = 7.99 (d, *J* = 2.0 Hz, 2 H); 8.12 (d, *J* = 2.0 Hz, 2 H). The acidic protons could not be detected.

^{13}C-NMR (dmso-d$_6$, 100 MHz): δ [ppm] = 89.8; 98.1; 116.4; 118.4; 134.7; 144.3; 168.6; 168.9.

IR (neat): ν [cm^{-1}] = 3057 (w); 2868 (w); 2233 (m); 1811 (w); 1675 (s); 1579 (m); 1554 (m); 1437 (vs); 1391 (m), 1328 (m); 1300 (w); 1269 (w); 1243 (vs); 1202 (m); 1155 (vs); 1097 (w); 930 (w); 917 (w); 898 (m); 868 (s); 818 (m); 795 (m); 756 (m); 727 (m); 703 (vs); 622 (w).

MS (EI): (m/z) (%) = 289 (M$^+$; 62); 271 (100); 245 (94); 144 (24); 128 (50); 127 (43); 117 (9); 90 15); 88 (21); 63 (13); 44 (42).

HR-MS ($C_8H_4INO_3$): calculated: 288.9236 found: 288.9220.