

Generation of Functionalized Aryl and Heteroaryl Aluminum Reagents by Halogen/Lithium Exchange

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Supporting Information

Experimental Details

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General

All reactions were carried out under an argon atmosphere in dried glassware. Syringes and needles were flushed with argon three times before use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen and kept over 4 Å molecular sieves. Yields refer to isolated yields of compounds estimated to be of >95 % purity as determined by ¹H-NMR and capillary-GC analysis. NMR spectra were recorded in solutions in deuterated chloroform (CDCl₃) with residual chloroform (δ 7.26 ppm for ¹H NMR and δ 77.16 ppm for ¹³C NMR) or deuterated benzene (C₆D₆) with residual benzene (7.16 ppm for ¹H NMR and δ 128.06 ppm for ¹³C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Column chromatography was performed using SiO₂ (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck if not indicated otherwise.

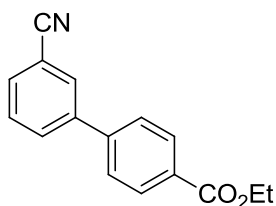
General procedures for the preparation of CuCN·2LiCl (1 M solution in THF)

A Schlenk-flask was charged with LiCl (16.96 g, 0.40 mol) and CuCN (17.95 g, 0.20 mol) and dried for 6 h at 150 °C under high vacuum ($5 \cdot 10^{-2}$ mbar; dry stirring). Careful addition of THF (200 mL) and stirring overnight furnishes a slightly yellowish to greenish solution which is kept over molecular sieves (4 Å).

Typical Procedure for the preparation of aryl aluminum reagents (TP1)

A dry and argon-flushed 20 mL Schlenk-tube equipped with a magnetic stirring bar was charged with the aryl halide (1.5 mmol), THF (2.5 mL) and the internal standard (undecane) and cooled to -78 °C. A solution of *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) was added, and the resulting mixture was stirred for 10 min before a solution of *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 5 min and then allowed to warm to room temperature. The reaction was monitored by GC-analysis of reaction aliquots, quenched with iodine in dry THF.

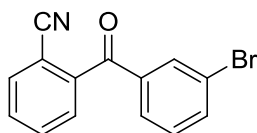
Synthesis of Ethyl 3'-cyano-[1,1'-biphenyl]-4-carboxylate (**5a**)



The aluminum reagent **3a** was prepared according to **TP1** from 3-bromobenzonitrile (**1a**, 273 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 81 % organometallic reagent (**3a**, 1.21 mmol). A solution of ethyl 4-iodobenzoate (**4a**, 414 mg, 1.5 mmol), Pd₂dba₃ (34 mg, 0.0375 mmol), P(*t*-Bu)₃ (1 M in toluene, 0.15 mL, 0.15 mmol) in THF (1 mL) was added. The resulting mixture was stirred at 50 °C for 12 h. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5a** as colorless oil (198 mg, 65 %).

The analytical data matches the reported one in the literature.¹

Synthesis of 2-(3-Bromobenzoyl)benzonitrile (**5b**)



The aluminum reagent **3b** was prepared according to **TP1** from 2-bromobenzonitrile (**1b**, 273 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 64 % organometallic reagent (**3b**, 0.96 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and 3-bromobenzoyl chloride (**4b**, 362 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5b** as yellowish oil (198 mg, 72 %).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.94 (t, J = 1.8 Hz, 1 H), 7.88 - 7.83 (m, 1 H), 7.79 - 7.74 (m, 1 H), 7.73 - 7.67 (m, 3 H), 7.65 - 7.61 (m, 1 H), 7.38 (t, J = 7.9 Hz, 1 H).

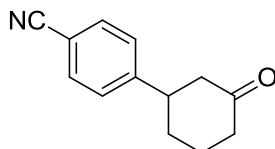
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 192.4, 140.8, 137.9, 136.8, 134.5, 133.1, 132.4, 131.9, 130.4, 130.1, 129.0, 123.1, 117.0, 112.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3084, 3067, 2959, 2922, 2853, 2225, 1914, 1850, 1657, 1588, 1558, 1482, 1465, 1450, 1412, 1301, 1261, 1158, 1068, 996, 953, 897, 886, 812, 785, 759, 726, 699, 664.

MS (EI, 70 eV): m/z (%) = 287 (47), 285 (42), 207 (11), 206 (75), 185 (95), 183 (100), 157 (32), 155 (34), 130 (73), 102 (52), 76 (43), 75 (36), 74 (10), 50 (25), 41 (10).

HRMS (EI) for C₁₄H₈BrNO (284.9789): 284.9780 (M⁺).

Synthesis of 4-(3-Oxocyclohexyl)benzonitrile (**5c**)



The aluminum reagent **3c** was prepared according to **TP1** from 4-bromobenzonitrile (**1c**, 273 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 80 % organometallic reagent (**3c**, 1.2 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) was added, followed by a solution of cyclohexenone (**4c**, 216 mg, 2.25 mmol) and chlorotrimethylsilane (611 mg, 5.63 mmol) and the resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5c** as a yellowish oil (122 mg, 51 %).

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.00 (m, 2 H), 6.44 (m, 2 H), 2.30 - 2.16 (m, 3 H), 1.83 - 1.73 (m, 2 H), 1.49 - 1.43 (m, 1 H), 1.30 - 1.26 (m, 1 H), 1.20 - 1.11 (m, 1 H), 1.05 - 0.97 (m, 1 H).

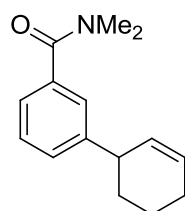
¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 207.1, 149.3, 132.3, 127.4, 118.8, 111.1, 47.9, 44.2, 40.8, 32.0, 25.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3045, 2940, 2866, 2225, 1707, 1606, 1505, 1447, 1416, 1345, 1314, 1249, 1224, 1177, 1100, 1071, 1056, 1025, 997, 972, 902, 832.

MS (EI, 70 eV): m/z (%) = 200 (15), 199 (62), 157 (12), 156 (100), 143 (43), 142 (30), 130 (16), 129 (48), 128 (19), 116 (23), 115 (11), 102 (13), 84 (30), 74 (16), 59 (27), 55 (10), 45 (16), 44 (20), 43 (10), 42 (13), 41 (18).

HRMS (EI) for $\text{C}_{13}\text{H}_{13}\text{NO}$ (199.0997): 199.0991 (M^+).

Synthesis of *N,N*-Dimethyl-1',2',3',4'-tetrahydro-[1,1'-biphenyl]-3-carboxamide (**5d**)



The aluminum reagent **3d** was prepared according to **TP1** from 3-bromo-*N,N*-dimethylbenzamide (**1d**, 342 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 75 % organometallic reagent (**3d**, 1.13 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) and 3-bromocyclohexene (**4d**, 290 mg, 1.8 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5d** as a yellowish oil (188 mg, 73 %).

¹H-NMR (300 MHz, CDCl₃): δ / ppm = 7.35 - 7.21 (m, 4 H), 5.94 - 5.86 (m, 1 H), 5.69 (dq, J = 10.2, 2.2 Hz, 1 H), 3.46 - 3.38 (m, 1 H), 3.10 (s, 9 H), 2.97 (s, 3 H), 2.11 - 1.97 (m, 3 H), 1.78 - 1.69 (m, 1 H), 1.67 - 1.50 (m, 2 H).

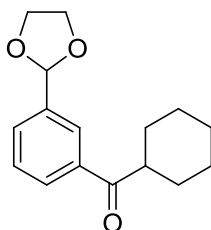
¹³C-NMR (75 MHz, CDCl₃): δ / ppm = 172.1, 147.0, 136.4, 129.7, 129.1, 128.9, 128.3, 126.5, 124.8, 41.8, 39.7, 35.4, 32.6, 25.1, 21.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031, 2934, 2860, 2837, 2244, 1624, 1603, 1582, 1503, 1447, 1408, 1398, 1270, 1261, 1174, 1081, 1059, 921, 900, 802, 741, 712, 671.

MS (EI, 70 eV): m/z (%) = 229 (45), 228 (24), 186 (14), 185 (100), 129 (14), 128 (16), 115 (15).

HRMS (EI) for $C_{15}H_{19}NO$ (229.1467): 229.1451 (M^+).

Synthesis of (3-(1,3-Dioxolan-2-yl)phenyl)(cyclohexyl)methanone (5e)



The aluminum reagent **3e** was prepared according to **TP1** from 2-(3-bromophenyl)-1,3-dioxolane (**1e**, 344 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 71 % organometallic reagent (**3e**, 1.07 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and cyclohexanecarbonyl chloride (**4e**, 242 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5e** as a yellowish oil (216 mg, 78 %).

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 8.32 (t, *J* = 1.8 Hz, 1 H), 7.84 (ddd, *J* = 7.9, 1.5, 1.4 Hz, 1 H), 7.60 (ddd, *J* = 7.6, 1.4, 1.2 Hz, 1 H), 7.13 (t, *J* = 7.7 Hz, 1 H), 3.63 - 3.55 (m, 2 H), 5.69 (s, 1 H), 3.50 - 3.42 (m, 2 H), 3.03 - 2.96 (m, 1 H), 1.79 - 1.74 (m, 2 H), 1.63 - 1.57 (m, 2 H), 1.54 - 1.46 (m, 3 H), 1.15 - 1.05 (m, 3 H).

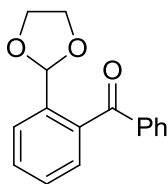
¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 202.3, 139.7, 137.1, 130.9, 129.1, 128.8, 126.9, 103.5, 65.2, 45.6, 29.7, 26.3, 26.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2928, 2853, 1721, 1677, 1604, 1588, 1448, 1373, 1289, 1254, 1241, 1189, 1162, 1132, 1075, 1027, 974, 942, 911, 805, 779, 715, 694, 666.

MS (EI, 70 eV): *m/z* (%) = 260 (3), 259 (4), 193 (10), 187 (15), 178 (13), 177 (100), 73 (34).

HRMS (EI) for $C_{16}H_{20}O_3$ (260.1412): 260.1377 (M^+).

Synthesis of (2-(1,3-Dioxolan-2-yl)phenyl)(phenyl)methanone (**5f**)



The aluminum reagent **3f** was prepared according to **TP1** from 2-(2-bromophenyl)-1,3-dioxolane (**1f**, 344 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 83 % organometallic reagent (**3f**, 1.25 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and benzoyl chloride (**4f**, 232 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5f** as a yellowish oil (231 mg, 73 %).

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.91 - 7.87 (m, 2 H), 7.76 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.15 - 7.06 (m, 3 H), 7.04 - 6.96 (m, 3 H), 6.25 (s, 1 H), 3.41 - 3.36 (m, 2 H), 3.23 - 3.23 (m, 1 H), 3.25 - 3.21 (m, 2 H).

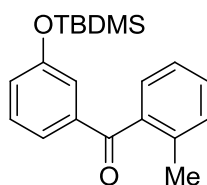
¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 196.8, 139.5, 138.5, 137.9, 132.8, 130.4, 129.7, 128.5, 128.3, 128.2, 127.1, 101.6, 65.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3058, 3026, 2960, 2888, 2766, 1663, 1596, 1579, 1473, 1448, 1394, 1313, 1267, 1209, 1151, 1112, 1071, 1025, 970, 926, 848, 804, 764, 758, 700, 687.

MS (EI, 70 eV): *m/z* (%) = 253 (12), 210 (23), 209 (83), 194 (19), 182 (19), 182 (57), 181 (52), 165 (33), 153 (16), 152 (26), 149 (52), 148 (16), 133 (15), 105 (100), 104 (12), 78 (13), 77 (54), 76 (12), 73 (17), 45 (10).

HRMS (EI) for C₁₆H₁₄O₃ (254.0943): 254.0924 (M⁺).

Synthesis of (3-((*tert*-Butyldimethylsilyloxy)phenyl)(*o*-tolyl)methanone (**5g**)



The aluminum reagent **3g** was prepared according to **TP1** from (3-bromophenoxy)(*tert*-butyl)dimethylsilane (**1g**, 431 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 81 % organometallic reagent (**3g**, 1.22 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and 2-methylbenzoyl chloride (**4g**, 255 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5g** as a colorless oil (298 mg, 75 %).

¹H-NMR (300 MHz, C₆D₆): δ / ppm = 7.65 - 7.63 (m, 1 H), 7.38 (dt, *J* = 7.2, 1.5 Hz, 1 H), 7.18 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.10 - 7.04 (m, 1 H), 6.99 - 6.89 (m, 4 H), 2.25 (s, 3 H), 0.92 (s, 9 H), 0.07 (s, 6 H).

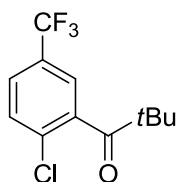
¹³C-NMR (75 MHz, C₆D₆): δ / ppm = 197.2, 156.4, 140.1, 139.4, 137.1, 131.2, 130.2, 129.9, 128.8, 125.3, 125.1, 123.9, 121.2, 25.8, 20.0, 18.4, -4.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3064, 3023, 2955, 2929, 2891, 2857, 2388, 2279, 2269, 1664, 1595, 1578, 1479, 1472, 1433, 1362, 1330, 1292, 1276, 1253, 1227, 1139, 1106, 1003, 980, 904, 892, 837, 827, 779, 740, 684.

MS (EI, 70 eV): *m/z* (%) = 326 (37), 270 (31), 269 (100), 119 (56), 91 (23).

HRMS (EI) for C₂₀H₂₆O₂Si (326.1702): 326.1687 (M⁺).

Synthesis of 1-(2-Chloro-5-(trifluoromethyl)phenyl)-2,2-dimethylpropan-1-one (**5h**)



The aluminum reagent **3h** was prepared according to **TP1** from 2-bromo-1-chloro-4-(trifluoromethyl)benzene (**1h**, 389 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65

mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 64 % organometallic reagent (**3h**, 0.96 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and pivaloyl chloride (**4h**, 199 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5h** as a colorless oil (170 mg, 67 %).

¹H-NMR (300 MHz, C₆D₆): δ / ppm = 7.24 (d, *J* = 2.2 Hz, 1 H), 6.95 - 6.90 (m, 1 H), 6.83 - 6.78 (m, 1 H), 1.02 - 0.99 (m, 9 H).

¹³C-NMR (75 MHz, C₆D₆): δ / ppm = 208.0, 141.6, 134.0 (q, *J* = 1 Hz), 130.7, 128.8 (q, *J* = 32 Hz), 126.6 (q, *J* = 4 Hz), 124.1 (q, *J* = 273 Hz), 123.4 (q, *J* = 4 Hz), 45.1, 26.6.

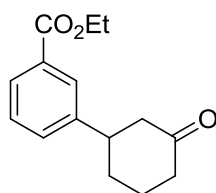
¹⁹F-NMR (211 MHz, C₆D₆): δ / ppm = -62.49.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 2971, 2907, 2871, 2365, 2330, 2278, 2269, 1704, 1609, 1581, 1479, 1401, 1330, 1286, 1266, 1184, 1173, 1134, 1084, 978, 901, 832, 810, 714.

MS (EI, 70 eV): *m/z* (%) = 264 (1), 209 (22), 207 (43), 57 (100), 41 (32).

HRMS (EI) for C₁₂H₁₂ClF₃O (264.0529): 264.0532 (M⁺).

Synthesis of Ethyl 3-(3-oxocyclohexyl)benzoate (**5i**)

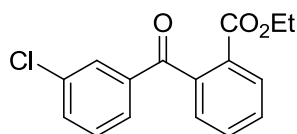


The aluminum reagent **3i** was prepared according to **TP1** from ethyl 3-iodobenzoate (**1i**, 414 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 65 % organometallic reagent (**3i**, 0.98 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) was added, followed by a solution of cyclohexenone (**4c**, 216 mg, 2.25 mmol) and chlorotrimethylsilane (611 mg, 5.63 mmol) and the resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction

mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 x 15 mL) and dried over MgSO_4 . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5i** as a yellowish oil (175 mg, 73 %).

The analytical data matches the reported one in the literature.²

Synthesis of Ethyl 2-(3-chlorobenzoyl)benzoate (**5j**)



The aluminum reagent **3j** was prepared according to **TP1** from ethyl 2-iodobenzoate (**1j**, 414 mg, 1.5 mmol), *i*- Bu_2AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*- BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at $-78\text{ }^\circ\text{C}$ for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 72 % organometallic reagent (**3j**, 1.08 mmol). The reaction mixture was cooled to $-40\text{ }^\circ\text{C}$, then $\text{CuCN}\cdot 2\text{LiCl}$ (1 M in THF, 0.3 mL, 0.3 mmol) and 3-chlorobenzoyl chloride (**4j**, 289 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to $25\text{ }^\circ\text{C}$ and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH_4Cl solution (5 mL), extracted with Et_2O (3 x 15 mL) and dried over MgSO_4 . After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5j** as a colorless oil (253 mg, 81 %).

$^1\text{H-NMR}$ (300 MHz, C_6D_6): δ / ppm = 7.98 (t, $J = 1.8$ Hz, 1 H), 7.94 - 7.89 (m, 1 H), 7.49 (dt, $J = 7.7, 1.4$ Hz, 1 H), 7.09 (ddd, $J = 8.0, 2.2, 1.1$ Hz, 1 H), 7.05 - 7.00 (m, 3 H), 6.75 (t, $J = 7.9$ Hz, 1 H), 3.78 (q, $J = 7.1$ Hz, 2 H), 0.72 (t, $J = 7.2$ Hz, 3 H).

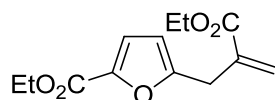
$^{13}\text{C-NMR}$ (75 MHz, C_6D_6): δ / ppm = 194.7, 165.6, 141.6, 139.8, 135.1, 132.7, 132.3, 130.3, 130.1, 130.1, 129.7, 129.3, 127.9, 127.7, 61.5, 13.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3068, 2982, 2936, 2903, 2872, 1713, 1675, 1596, 1571, 1466, 1445, 1424, 1366, 1275, 1253, 1153, 1126, 1079, 1041, 1014, 957, 944, 896, 854, 771, 763, 735, 709, 685, 673.

MS (EI, 70 eV): m/z (%) = 288 (15), 245 (11), 243 (34), 177 (53), 152 (19), 149 (100), 139 (22), 111 (14).

HRMS (EI) for $\text{C}_{16}\text{H}_{13}\text{ClO}_3$ (288.0553): 288.0552 (M^+).

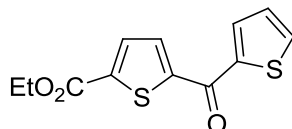
Synthesis of Ethyl 5-(2-(ethoxycarbonyl)allyl)furan-2-carboxylate (**9a**)



The aluminum reagent **7a** was prepared according to **TP1** from ethyl 5-bromofuran-2-carboxylate (**6a**, 329 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 82 % organometallic reagent (**7a**, 1.23 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 1.5 mL, 1.5 mmol) and ethyl 2-(bromomethyl)acrylate (**8a**, 347 mg, 1.8 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **9a** as a yellowish oil (258 mg, 83 %).

The analytical data matches the reported one in the literature.³

Synthesis of Ethyl 5-(thiophene-2-carbonyl)thiophene-2-carboxylate (**9b**)



The aluminum reagent **7b** was prepared according to **TP1** from ethyl 5-bromothiophene-2-carboxylate (**6b**, 353 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 72 % organometallic reagent (**7b**, 1.08 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and thiophene-2-carbonyl chloride (**8b**, 242 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **9b** as a yellow solid (196 mg, 68 %).

m.p. (°C): 73-75.

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.54 (d, J = 3.9 Hz, 1 H), 7.39 (dd, J = 3.8, 1.1 Hz, 1 H), 7.26 (d, J = 4.3 Hz, 1 H), 6.91 - 6.86 (m, 1 H), 6.54 - 6.51 (m, 1 H), 4.03 - 3.97 (m, 2 H), 0.94 (t, J = 7.1 Hz, 3 H).

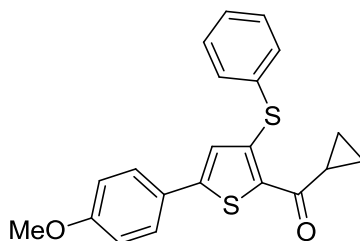
¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 178.1, 161.4, 147.5, 143.1, 139.9, 134.0, 133.5, 133.1, 132.4, 128.0, 61.6, 14.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3078, 2979, 2945, 1712, 1603, 1584, 1524, 1520, 1412, 1346, 1288, 1247, 1230, 1212, 1172, 1101, 1092, 1084, 1052, 1039, 1003, 865, 834, 790, 751, 743, 726, 703.

MS (EI, 70 eV): m/z (%) = 266 (41), 238 (13), 221 (49), 111 (100), 97 (11), 85 (18), 83 (11), 83 (10), 71 (28), 69 (14), 57 (46), 56 (10), 55 (18), 43 (40), 42 (10), 41 (18).

HRMS (EI) for C₁₂H₁₀O₃S₂ (266.0071): 266.0079 (M⁺).

Synthesis of Cyclopropyl(5-(4-methoxyphenyl)-3-(phenylthio)thiophen-2-yl)methanone (9c)



The aluminum reagent **7c** was prepared according to **TP1** from 2-bromo-5-(4-methoxyphenyl)-3-(phenylthio)thiophene (**6c**, 566 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 93 % organometallic reagent (**7c**, 1.40 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 0.3 mL, 0.3 mmol) and cyclopropanecarbonyl chloride (**8c**, 172 mg, 1.65 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **9c** as a yellow solid (435 mg, 85 %).

m.p. (°C): 174-181.

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.50 - 7.47 (m, 2 H), 7.18 - 7.14 (m, 3 H), 7.03 - 6.95 (m, 3 H), 6.69 - 6.62 (m, 2 H), 3.26 (s, 3 H), 2.28 - 2.22 (m, 1 H), 1.36 - 1.30 (m, 2 H), 0.65 - 0.60 (m, 2 H).

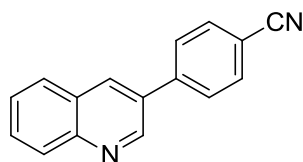
¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 194.3, 160.0, 147.2, 142.3, 138.4, 135.0, 133.9, 129.9, 129.3, 127.1, 126.6, 123.2, 114.7, 54.9, 19.2, 11.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3087, 3070, 3017, 3005, 2969, 2935, 2841, 1627, 1606, 1538, 1501, 1438, 1427, 1411, 1293, 1254, 1217, 1176, 1121, 1111, 1084, 1031, 1019, 998, 993, 951, 897, 833, 821, 808, 751, 708, 704, 695, 673.

MS (EI, 70 eV): m/z (%) = 368 (13), 367 (25), 366 (100), 325 (23), 309 (14), 221 (11), 151 (10), 69 (14), 41 (13).

HRMS (EI) for C₂₁H₁₈O₂S₂ (366.0748): 366.0747 (M⁺).

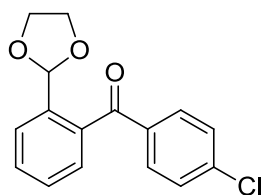
Synthesis of 4-(Quinolin-3-yl)benzonitrile (**9d**)



The aluminum reagent **7d** was prepared according to **TP1** from 3-bromoquinoline (**1a**, 312 mg, 1.5 mmol), *i*-Bu₂AlCl (1 M in THF, 1.65 mL, 1.65 mmol) and *n*-BuLi (2.5 M in hexane, 0.66 mL, 1.65 mmol). The reaction was carried out in THF (2.5 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 63 % organometallic reagent (**7d**, 0.95 mmol). A solution of 4-iodobenzonitrile (**8d**, 344 mg, 1.5 mmol), Pd₂dba₃ (34 mg, 0.0375 mmol), P(*t*-Bu)₃ (1 M in toluene, 0.15 mL, 0.15 mmol) in NMP (2 mL) was added. The resulting mixture was stirred at 50 °C for 12 h. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (5 mL), extracted with Et₂O (3 x 15 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **5a** as a yellow solid (159 mg, 73 %).

The analytical data matches the reported one in the literature.⁴

Synthesis of (2-(1,3-dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**10**)



The aluminum reagent **3f** was prepared according to an upscaled **TP1** from 2-(2-bromophenyl)-1,3-dioxolane (**1f**, 2.29 g, 10 mmol), *i*-Bu₂AlCl (1 M in THF, 11 mL, 11 mmol) and *n*-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol). The reaction was carried out in THF (10 mL) at -78 °C for 10 min and was then allowed to warm to room temperature. Iodolysis indicated a yield of 84 % organometallic reagent (**3f**, 8.4 mmol). The reaction mixture was cooled to -40 °C, then CuCN·2LiCl (1 M in THF, 2 mL, 2 mmol) and 4-chlorobenzoyl chloride (**4f**, 1.93 g, 11 mmol) were added. The resulting mixture was allowed to warm to 25 °C and stirred overnight. Then, the reaction mixture was quenched with sat. aq. NH₄Cl solution (35 mL), extracted with Et₂O (3 x 100 mL) and dried over MgSO₄. After filtration, the solvents were evaporated *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **10** as a yellowish solid (1.82 g, 75 %).

m.p. (°C): 86.

¹H-NMR (400 MHz, C₆D₆): δ / ppm = 7.71 (d, *J* = 8.4 Hz, 1 H), 7.62 - 7.58 (m, 2 H), 7.16 - 7.12 (m, 1 H), 7.02 - 6.96 (m, 4 H), 6.15 (s, 1 H), 3.39 - 3.33 (m, 2 H), 3.30 - 3.23 (m, 2 H).

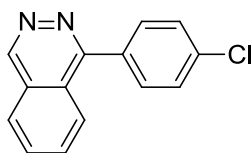
¹³C-NMR (100 MHz, C₆D₆): δ / ppm = 195.5, 139.2, 138.9, 137.8, 136.7, 131.7, 129.9, 128.8, 128.4, 128.1, 127.2, 101.6, 65.0.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3085, 3062, 3036, 2989, 2961, 2895, 2859, 2758, 1671, 1662, 1584, 1569, 1482, 1470, 1446, 1396, 1305, 1287, 1267, 1211, 1177, 1150, 1112, 1087, 1075, 1064, 1011, 972, 954, 940, 927, 852, 781, 773, 758, 744, 671.

MS (EI, 70 eV): *m/z* (%) = 289 (22), 288 (14), 287 (61), 246 (14), 245 (39), 244 (38), 243 (100), 209 (20), 181 (50), 165 (11), 153 (11), 152 (42), 149 (40), 148 (13), 139 (60), 111 (27), 105 (16), 104 (11), 77 (12), 76 (15), 75 (12), 73 (10).

HRMS (EI) for C₁₆H₁₃ClO₃ (288.0553): 288.0522 (M⁺).

Synthesis of 1-(4-chlorophenyl)phthalazine (11)



(2-(1,3-Dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**10**, 577 mg, 2 mmol) was dissolved in MeOH (20 mL). Hydrazine hydrate (801 mg, 16 mmol) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) were added and the resulting mixture was stirred under reflux. After stirring for 14 h, the reaction mixture was concentrated *in vacuo*. The crude product obtained was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **11** greenish solid (361 mg, 75 %).

m.p. (°C): 156-157.

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 9.54 (s, 1 H), 8.06 - 8.01 (m, 2 H), 7.95 - 7.86 (m, 2 H), 7.71 - 7.67 (m, 2 H), 7.56 - 7.50 (m, 2 H).

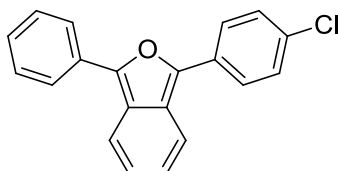
¹³C-NMR (100 MHz, CDCl₃): δ / ppm = 159.0, 150.7, 135.9, 134.5, 133.1, 132.6, 131.4, 128.9, 127.1, 127.0, 125.9, 125.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm⁻¹ = 3074, 3059, 3032, 2976, 1615, 1591, 1540, 1485, 1408, 1379, 1352, 1292, 1267, 1225, 1180, 1132, 1105, 1085, 1015, 993, 952, 945, 880, 834, 812, 797, 762, 733, 716, 667, 662.

MS (EI, 70 eV): m/z (%) = 242 (18), 241 (39), 240 (51), 239 (100), 206 (12), 205 (74), 177 (16), 176 (21), 88 (13), 75 (13).

HRMS (EI) for C₁₄H₉ClN₂ (240.0454): 240.0418 (M⁺).

Synthesis of 1-(4-chlorophenyl)-3-phenylisobenzofuran (13)

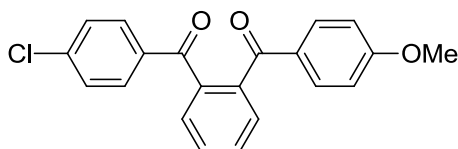


(2-(1,3-Dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**10**, 577 mg, 2 mmol) was dissolved in acetone (10 mL) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added at room temperature. After stirring for 1 h, the reaction mixture was quenched with sat. aq. NH₄Cl solution (15 mL), extracted with Et₂O (3 x 50 mL) and dried over MgSO₄. After filtration, the solvents were removed *in vacuo* and the crude aldehyde **12** was obtained as a colorless oil (465 mg, 1.9 mmol). A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer, was charged with **12** (465 mg, 1.9 mmol) in anhydrous THF (15 mL). A

solution of anisyl Grignard (1.1 M in THF, 1.73 mL, 1.9 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Then, an aqueous solution of HCl (4 M, 10 mL) was slowly added at 0 °C. The mixture (still under argon) was warmed to room temperature and stirred for 1 h, then extracted with ether (3 x 50 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃, brine and dried over Na₂SO₄. After filtration, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (dichloromethane:ethyl acetate = 1:1) to give **13** as a yellow solid (527 mg, 91 %).

The analytical data matches the reported one in the literature.⁵

Synthesis of (2-(4-chlorobenzoyl)phenyl)(4-methoxyphenyl)methanone (**14**)



(2-(1,3-Dioxolan-2-yl)phenyl)(4-chlorophenyl)methanone (**10**, 577 mg, 2 mmol) was dissolved in acetone (10 mL) and *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol) was added at room temperature. After stirring for 1 h, the reaction mixture was quenched with sat. aq. NH₄Cl solution (15 mL), extracted with Et₂O (3 x 50 mL) and dried over MgSO₄. After filtration, the solvents were removed *in vacuo* and the crude aldehyde **12** was obtained as a colorless oil (465 mg, 1.9 mmol). A dry and argon-flushed *Schlenk*-flask, equipped with a magnetic stirrer, was charged with **12** (465 mg, 1.9 mmol) in anhydrous THF (15 mL). A solution of PhMgCl (1.7 M in THF, 1.1 mL, 1.9 mmol) was added dropwise at 0 °C and the resulting mixture was stirred at 0 °C for 30 min. Then, an aqueous solution of HCl (4 M, 10 mL) was slowly added at 0 °C. The mixture (still under argon) was warmed to room temperature and stirred for 1 h, then extracted with ether (3 x 50 mL). The combined organic extracts were washed with a saturated solution of NaHCO₃, brine and dried over Na₂SO₄. After filtration, the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (pentane:diethyl ether = 9:1) to give **14** as a yellowish solid (447 mg, 67 %).

m.p. (°C): 138-140.

¹H-NMR (400 MHz, CDCl₃): δ / ppm = 7.66 (m, 4 H), 7.61 - 7.55 (m, 4 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 3.82 (s, 3 H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): δ / ppm = 195.6, 195.1, 163.7, 140.2, 139.6, 139.5, 135.7, 132.4, 131.2, 130.5, 130.3, 130.0, 129.6, 129.4, 128.7, 113.7, 55.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059, 2961, 2926, 2836, 1770, 1742, 1665, 1655, 1596, 1584, 1567, 1509, 1459, 1438, 1397, 1313, 1282, 1254, 1173, 1150, 1088, 1033, 1013, 936, 923, 839, 831, 787, 782, 748, 734, 684, 679.

MS (EI, 70 eV): m/z (%) = 352 (28), 351 (18), 350 (71), 243 (21), 240 (11), 239 (64), 211 (10), 152 (14), 139 (13), 136 (10), 135 (100), 111 (12), 92 (10), 77 (17).

HRMS (EI) for $\text{C}_{21}\text{H}_{15}\text{ClO}_3$ (350.0710): 350.0707 (M^+).

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