Supplementary Material (ESI) for Chemical Communications

Direct Preparation of Copper Organometallics Bearing an Aldehyde Function *via* an Iodine-Copper Exchange Reaction

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Supporting Information

General: Unless otherwise indicated, all reactions were carried out with a magnetic stirring in flame-dried glassware under argon. Syringes used to transfer reagents and solvents were purged with argon prior to use. The reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC). Solvents (diethyl ether and THF) were dried according to the standard methods by distillation over Na/benzophenone and were stored under argon. Preparative flash-chromatography was performed on silica gel 60 (0.063-0.200 mm) from Merck. The yields referred to isolated yields of compounds estimated to be > 95% pure by ^{1}H-NMR, capillary GC-analysis and combustion analysis (in the case of new compounds).

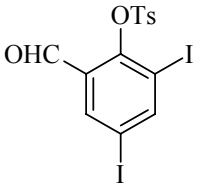
5-Iodo-thiophene-2-carbaldehyde (**1c**),[1] 1-benzenesulfonyl-3-iodo-1H-indole-2-carbaldehyde (**1f**),[2] 2-iodo-1-methoxymethyl-1H-indole-3-carbaldehyde (**1g**),[3] and (2*Z*)-3-iodo-2-heptenal (**6**)[4] were prepared according to literature procedures.

Synthesis of lithium dineophylcuprate ((Nphyl)$_2$CuLi: 2)

A 500 mL round-bottomed flask, flame dried and flushed with argon, was charged with lithium metal (3.0 g, 432 mmol) and neophyl chloride (14.0 mL, 86.9 mmol) in hexane (75 mL). The reaction mixture was heated under reflux overnight. After cooling to rt, hexane was removed *in vacuo* and diethyl ether was added to the resulting mixture. It was stirred at rt for few minutes and was allowed to stand for another few minutes. The solution was cannulated into a flame dried Schlenk tube and was centrifuged (2000 rpm, 30 min). The clear solution of neophyllithium thus obtained was titrated before use with menthol, using *o*-phenantroline as indicator.[5] It can be stored at -30 °C for several days.[6]

A 25 mL round-bottomed flask, flame dried and flushed with argon was charged with CuCN (110 mg, 1.2 mmol). THF (3 mL) was added and the suspension cooled to -78 °C. The freshly titrated solution of neophyllithium (2.4 mmol) was added and the mixture quickly warmed to rt and stirred for 10 min, until a clear yellow solution of the desired cuprate **2** was obtained.

3,5-Diiodo-2-tosyloxybenzaldehyde (1b)



To a solution of 2-hydroxy-3,5-diiodobenzaldehyde (5.6 g, 15.0 mmol) and TsCl (3.0 g, 15.7 mmol) in CH_2Cl_2 (50 mL) at rt, Et_3N (5 mL) was added and the resulting mixture was stirred at rt for 12 h. The solid was filtered off and the resulting clear solution was concentrated in vacuum. The residue was purified by flash-chromatography (SiO_2, *n*-pentane/diethyl ether = 10/1) to yield **1b** as a white solid (7.1 g, 90%); mp 137 ^oC.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.93 (s, 1 H), 8.36-8.35 (d, *J* = 2.21 Hz, 1 H), 8.22-8.21 (d, *J* = 2.21 Hz, 1 H), 7.85-7.82 (d, *J* = 8.40 Hz, 2 H), 7.43-7.40 (d, *J* = 8.40 Hz, 2 H), 2.52 (s, 3 H).

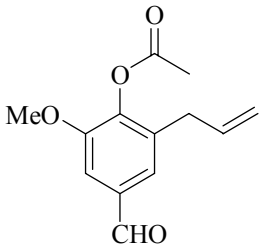
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 186.1, 153.1, 151.8, 147.3, 138.2, 133.0, 132.4, 130.7, 129.5, 94.3, 93.4, 22.3.

IR (film, cm^{-1}): $\tilde{\nu}$ = 3045 (w), 1681 (vs), 1558 (w), 1386 (vs), 1223 (m), 1174 (vs), 1126 (s), 1085 (s), 833 (m).

MS (EI, 70 eV): 528 (M^+, 32), 372 (32), 218 (15), 155 (100), 91 (80), 65 (17).

HRMS (EI): calcd. for $C_{14}H_{10}I_2O_4S$ [M^+]: 527.8389, found 527.8393.

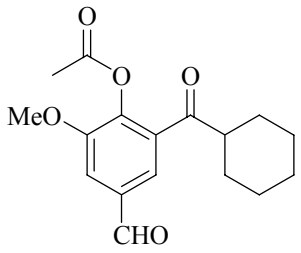
4-Acetoxy-3-allyl-5-methoxybenzaldehyde (4a)



Typical Procedure: A freshly prepared $(Nphyl)_2CuLi$ (**2**, 1.2 mmol) solution was cannulated into a solution of 4-acetoxy-3-iodo-5-methoxybenzaldehyde (**1a**; 320 mg, 1.0 mmol) in dry THF (5 mL) at –78°C. The resulting mixture was stirred at -78 °C for 2 h. Allyl bromide (360 mg, 3.0 mmol) was added and the solution was stirred at rt for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and poured into water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic fractions were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash-chromatography (SiO_2, *n*-pentane/diethyl ether = 3/1) to give the aldehyde **4a** as a colorless oil (197 mg, 84% yield).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.98 (s, 1 H), 7.44 (s, 1 H), 6.03-5.90 (m, 1 H), 5.22-5.15 (m, 2 H), 3.96 (s, 3 H), 3.45-3.42 (dt, J = 6.63 Hz, J = 1.44 Hz, 2 H), 2.41 (s, 3 H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 191.6, 168.4, 152.5, 143.8, 135.3, 135.0, 134.7, 126.1, 117.5, 109.2, 56.6, 34.8, 20.8.
IR (film, cm^{-1}): $\tilde{\nu}$ 2977 (w), 1767 (vs), 1697 (vs), 1591 (m), 1464 (m), 1301 (m), 1188 (vs), 1135 (vs), 899 (w), 730 (w).
MS (EI, 70 eV): 234 (M^+, 5), 192 (100), 177 (4), 163 (6), 149 (5), 131 (20), 121 (7), 103 (18), 91 (15), 77 (12), 51 (3).
HRMS (EI): calcd. for $C_{13}H_{14}O_4$ [M^+]: 234.0892, found 234.0883.

4-Acetoxy-3-(cyclohexylcarbonyl)-5-methoxybenzaldehyde (4b)



Prepared according to the typical procedure from 4-acetoxy-3-iodo-5-methoxybenzaldehyde (**1a**; 320 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol) and cyclohexylcarbonyl chloride (438 mg, 3.0 mmol). Reaction time: 2 h at –78 °C. Purification by flash-chromatography (SiO_2, *n*-pentane/diethyl ether = 3/2) yielded the aldehyde **4b** as a white solid (222 mg, 73%); mp 94 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.99 (s, 1 H), 7.71-7.70 (d, *J* = 1.77 Hz, 1 H), 7.60-7.59 (d, *J* = 1.77 Hz, 1 H), 3.94 (s, 3 H), 3.07-2.97 (m, 1 H), 2.36 (s, 3 H), 1.91-1.21 (m, 10 H).

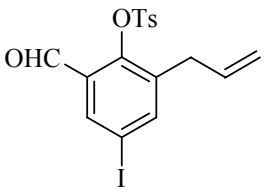
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 203.6, 190.8, 168.3, 153.2, 143.5, 134.8, 133.9, 124.1, 113.2, 56.9, 49.6, 29.1, 26.2, 26.1, 20.9.

IR (KBr, cm^{-1}): $\tilde{\nu}$ 3436 (vs), 2932 (s), 1761 (vs), 1706 (vs), 1690 (vs), 1589 (m), 1469 (w), 1386 (m), 1289 (s), 1187 (vs), 1136 (vs), 1004 (m), 893 (w), 674 (w).

MS (EI, 70 eV): 304 (M^+, 3), 262 (32), 233 (11), 215 (4), 194 (5), 179 (100), 164 (2), 136 (3), 55 (3).

HRMS (EI): calcd. for $C_{17}H_{20}O_5$ [M^+]: 304.1311, found 304.1286.

3-Allyl-5-iodo-2-tosyloxybenzaldehyde (4c)



Prepared according to the typical procedure from 3,5-diiodo-2-tosyloxybenzaldehyde (**1b**; 527 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol) and allyl bromide (360 mg, 3.0 mmol). Reaction time: 20 min at –78 °C. Purification by flash-chromatography (SiO_2, *n*-pentane/diethyl ether = 3/1) yielded the aldehyde **4c** as a light yellow oil (415 mg, 94%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.78 (s, 1 H), 8.08-8.07 (dt, *J* = 2.32 Hz, *J* = 0.44 Hz, 2 H), 7.82-7.81 (dt, *J* = 2.32 Hz, *J* = 0.55 Hz, 1 H), 7.80-7.77 (d, *J* = 8.40 Hz, 2 H), 7.43-7.40 (d, *J* = 8.40 Hz, 2 H), 5.85-5.72 (m, 1 H), 5.18-5.08 (m, 2 H), 3.32-3.30 (d, *J* = 6.75 Hz, 2 H), 2.51 (s, 3 H).

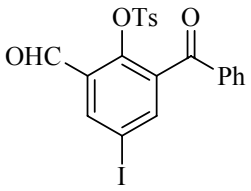
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 186.4, 149.1, 147.1, 145.3, 138.6, 136.2, 134.6, 132.1, 131.8, 130.8, 128.9, 118.6, 92.9, 33.9, 22.2.

IR (film, cm^{-1}): $\tilde{\nu}$ = 2874 (w), 1694 (s), 1494 (m), 1385 (vs), 1234 (m), 1195 (s), 1180 (s), 1153 (s), 1088 (s), 866 (m), 816 (s), 721 (vs), 579 (m).

MS (EI, 70 eV): 442 (M^+, 1), 287 (80), 155 (78), 131 (20), 115 (5), 103 (15), 91 (100), 77 (12), 65 (13).

HRMS (EI): calcd. for $C_{17}H_{15}IO_4S$ [M^+]: 441.9736, found 441.9719.

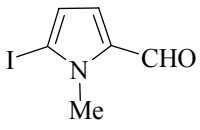
3-Benzoyl-5-iodo-2-tosyloxybenzaldehyde (4d)



Prepared according to the typical procedure from 3,5-diiodo-2-tosyloxybenzaldehyde (**1b**; 527 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol) and benzoyl chloride (420 mg, 3.0 mmol). Reaction time: 20 min at –78 °C. Purification by flash-chromatography (SiO_2, *n*-pentane/diethyl ether = 2/1) yielded the aldehyde **4d** as a light yellow solid (404 mg, 80%); mp 106 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 10.07 (s, 1 H), 8.43-8.42 (d, *J* = 2.32 Hz, 1 H), 8.05-8.04 (d, *J* = 2.32 Hz, 1 H), 7.73-7.70 (d, *J* = 7.62 Hz, 2 H), 7.67-7.62 (m, 1 H), 7.51-7.46 (m, 4H), 7.25-7.22 (d, *J* = 7.62 Hz, 2 H), 2.42 (s, 3 H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 191.0, 147.9, 147.1, 144.7, 140.3, 137.1, 136.2, 134.2, 132.8, 130.9, 130.6, 130.5, 129.4, 129.0, 128.9, 92.4, 22.2.
IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3436 (vs), 1696 (vs), 1670 (vs), 1596 (m), 1448 (w), 1386 (vs), 1286 (m), 1178 (s), 1157 (s), 1087 (s), 841 (w), 707 (vs), 563 (m).
MS (EI, 70 eV): 506 (M^+, 1), 351 (88), 273 (9), 223 (6), 155 (75), 139 (18), 105 (20), 91 (100), 77 (43), 51 (6).
HRMS (EI): calcd. for $C_{21}H_{15}IO_5S$ [M^+]: 505.9685, found 505.9689.

5-Iodo-1-methyl-1H-pyrrole-2-carbaldehyde (1e)

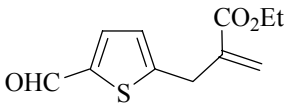


A dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of *N*-methylpiperazine (2.7 mL, 24.2 mmol) in dry benzene (70 mL) at 0 °C. *n*-BuLi (1.68 M in hexane, 13.1 mL, 22 mmol) was added. After 15 min, 1-methyl-2-pyrrolecarboxaldehyde (2.2 g, 20 mmol) was added and the resulting mixture was stirred at 0 °C for 15 min. Then TMEDA (9.1 mL, 60 mmol) and *n*-BuLi (1.68 M in hexane, 36 mL,

60 mmol) were added. The resulting mixture was first stirred at rt for 12 h. Then the reaction mixture was cooled to 0 °C and dry THF (70 mL) was added. The resulting mixture was further cooled to –42 °C and a solution of iodine (32 g, 126 mmol) in dry THF (50 mL) was added. The reaction mixture was stirred at rt for 1 h and then poured into a solution of $Na_2S_2O_3$ (10%, 300 mL). The mixture was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash-chromatography (pentane/Et_2O = 10/1) yielded **1e** as a light yellow solid (0.5 g, 11%); mp 100 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.26 (s, 1H), 7.03-7.02 (d, *J* = 4.20 Hz, 1H), 6.56-6.55 (dd, *J* = 4.20 Hz, 1H), 3.87 (s, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 193.5, 135.0, 125.6, 119.8, 92.0, 37.2.
IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3096 (w), 1650 (vs), 1500 (m), 1450 (s), 1355 (m), 1074 (w), 846 (w), 798 (s), 763 (m), 630 (m).
MS (EI, 70 eV): 235 (M^+, 100), 206 (4), 165 (7), 108 (8), 80 (6).
HRMS (EI): calcd. for C_6H_6INO [M^+]: 234.9494, found 234.9481.

α-((5-Formyl-thiophen-2-yl)methyl)-acrylic acid ethyl ester (4e)



Prepared according to the typical procedure from 5-iodo-thiophene-2-carbaldehyde (**1c**; 238 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and ethyl (2-bromomethyl)acrylate (580 mg, 3.0 mmol). Reaction time: 15 min at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 3/1) yielded the aldehyde **4e** as a light yellow oil (190 mg, 85%).

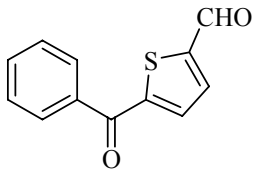
^{1}H-NMR (DMSO, 300 MHz): δ = 9.81 (s, 1H), 7.86-7.85 (d, *J* = 3.66 Hz, 1H), 7.08-7.07 (d, *J* = 3.66 Hz, 1H), 6.20 (s, 1H), 5.84 (s, 1H), 4.15-4.10 (q, *J* = 7.02 Hz, 2H), 3.88 (s, 2H), 1.20-1.16 (t, *J* = 7.02 Hz, 3H).
^{13}C-NMR (DMSO, 75 MHz): δ = 184.3, 165.9, 153.4, 142.4, 138.8, 138.7, 128.1, 128.1, 61.1, 33.0, 14.4.

IR (film, cm^{-1}): $\tilde{\nu}$ = 2982 (w), 1714 (vs), 1667 (vs), 1633 (m), 1456 (vs), 1226 (s), 1198 (vs), 1155 (s), 1026 (m), 815 (m).

MS (EI, 70 eV): 224 (M^+, 100), 195 (19), 178 (35), 167 (26), 150 (73), 139 (10), 121 (38), 97 (13), 77 (10).

HRMS (EI): calcd. for $C_{11}H_{12}O_3S$ [M^+]: 224.0507, found 224.0483.

5-Benzoyl-thiophene-2-carbaldehyde (4f)



Prepared according to the typical procedure from 5-iodo-thiophene-2-carbaldehyde (**1c**; 238 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and benzoyl chloride (420 mg, 3.0 mmol). Reaction time: 15 min at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 1/1) yielded the aldehyde **4f** as a white solid (173 mg, 80%); mp 108 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 10.05 (s, 1H), 8.10-8.09 (d, *J* = 3.97 Hz, 1H), 7.88-7.85 (m, 2H), 7.84-7.83 (d, *J* = 3.97 Hz, 1H), 7.73-7.70 (m, 1H), 7.61-7.57 (m, 2H).

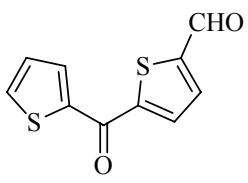
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 188.2, 186.0, 148.8, 148.5, 137.7, 137.0, 135.8, 133.7, 129.6, 129.3.

IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3436 (vs), 1675 (vs), 1633 (vs), 1577 (m), 1320 (w), 1283 (vs), 1212 (vs), 1125 (w), 705 (m).

MS (EI, 70 eV): 216 (M^+, 100), 187 (25), 273 (10), 139 (58), 105 (75), 177 (40), 51 (8).

HRMS (EI): calcd. for $C_{12}H_8O_2S$ [M^+]: 216.0245, found 216.0232.

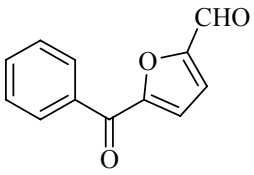
5-(Thiophene-2-carbonyl)-thiophene-2-carbaldehyde (4g)



Prepared according to the typical procedure from 5-iodo-thiophene-2-carbaldehyde (**1c**; 238 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and 2-thiophenecarbonyl chloride (440 mg, 3.0 mmol). Reaction time: 15 min at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 1/1) yielded the aldehyde **4g** as a yellow solid (160 mg, 72%); mp 79 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 10.07 (s, 1H), 8.20-8.11 (m, 4H), 7.37-7.34 (dd, *J* = 4.87 Hz, *J* = 3.87 Hz, 1H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 185.8, 178.7, 148.2, 147.8, 141.7, 137.7, 136.9, 135.5, 134.2, 129.6.
IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3101 (w), 1760 (vs), 1713 (s), 1678 (s), 1590 (m), 1515 (w), 1410 (s), 1353 (m), 1202(vs), 1048 (m), 1004 (vs), 859 (w), 727 (s).
MS (EI, 70 eV): 222 (M^+, 59), 139 (16), 273 (10), 111 (100), 183 (12), 57 (13).
HRMS (EI): calcd. for $C_{10}H_6O_2S_2$ [M^+]: 221.9809, found 221.9806.

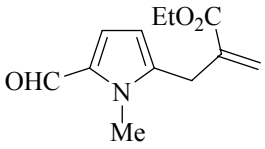
5-Benzoyl-furan-2-carbaldehyde (4h)



Prepared according to the typical procedure from 5-iodo-furan-2-carbaldehyde (**1d**; 221 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and benzoyl chloride (420 mg, 3.0 mmol). Reaction time: 15 min at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 1/1) yielded the aldehyde **4h** as a yellow solid (122 mg, 61%); mp 78 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.81 (s, 1H), 7.97-7.95 (m, 2H), 7.73-7.69 (m, 1H), 7.67-7.66 (d, *J* = 3.66 Hz, 1H), 7.61-7.57 (m, 2H), 7.53-7.52 (d, *J* = 3.66 Hz, 1H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 182.8, 180.8, 154.0, 136.5, 133.9, 133.3, 129.7, 129.7, 129.3, 121.5.
IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3436 (s), 1684 (vs), 1646 (vs), 1580 (m), 1294 (s), 1260 (s), 1212 (w), 965 (w), 707 (m).
MS (EI, 70 eV): 200 (M^+, 70), 171 (34), 123 (12), 139 (58), 105 (100), 77 (46), 51 (12).
HRMS (EI): calcd. for $C_{12}H_8O_3$ [M^+]: 200.0473, found 200.0456.

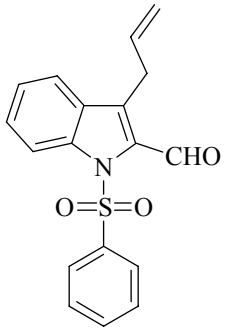
α-((5-Formyl-1-methyl-1H-pyrrol-2-yl)methyl)-acrylic acid ethyl ester (4i)



Prepared according to the typical procedure from 5-iodo-1-methyl-1H-pyrrole-2-carbaldehyde (**1e**; 235 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and ethyl (2-bromomethyl)acrylate (580 mg, 3.0 mmol). Reaction time: 1 h at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 4/1) yielded **4i** as a colourless oil (175 mg, 79%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.43 (s, 1H), 6.96-6.94 (d, *J* = 4.09 Hz, 1H), 6.19 (d, *J* = 0.88 Hz, 1H), 6.03-6.02 (d, *J* = 3.98 Hz, 1H), 5.53-5.52 (d, *J* = 1.11 Hz, 1H), 4.19-4.12 (q, *J* = 7.19 Hz, 2H), 3.81 (s, 3H), 3.66 (s, 2H), 1.23-1.19 (t, *J* = 7.19 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 179.2, 166.0, 141.4, 137.4, 132.1, 127.1, 124.2, 110.0, 61.0, 32.3, 28.4, 14.3.
IR (film, cm^{-1}): $\tilde{\nu}$ = 3421 (w), 2982 (s), 1714 (vs), 1658 (vs), 1486 (vs), 1430 (m), 1368 (s), 1146 (s), 1036 (m), 958 (m), 778 (s), 629 (w).
MS (EI, 70 eV): 221 (M^+, 100), 204 (3), 192 (8), 176 (6), 164 (11), 146 (20), 118 (14) 94 (7), 77 (6).
HRMS (EI): calcd. for $C_{12}H_{15}NO_3$ [M^+]: 221.1052, found 221.1030.

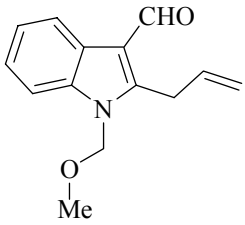
3-Allyl-1-benzenesulfonyl-1H-indole-2-carbaldehyde (4j)



Prepared according to the typical procedure from 1-benzenesulfonyl-3-iodo-1H-indole-2-carbaldehyde (**1g**; 206 mg, 0.5 mmol), lithium dineophylcuprate **2** (0.6 mmol), and allyl bromide (180 mg, 1.5 mmol). Reaction time: 30 min at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 5/1) yielded the aldehyde **4k** as a colorless solid (135 mg, 83%); mp 117 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 10.65 (s, 1H), 8.30-8.26 (dd, *J* = 8.51 Hz, *J* = 0.89 Hz, 1H), 7.75-7.72 (m, 2H), 7.65-7.53 (m, 2H), 7.44-7.35 (m, 4H), 6.00-5.87 (m, 1H), 5.04-4.88 (m, 2H), 3.83-3.80 (dt, *J* = 5.97 Hz, *J* = 1.66 Hz, 1H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 185.1, 138.1, 137.3, 134.8, 134.5, 133.9, 133.4, 130.4, 129.5, 127.0, 125.2, 122.3, 116.6, 116.4, 29.2.
IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2962 (w), 1666 (s), 1540 (s), 1445 (m), 1358 (s), 1223 (m), 1171 (vs), 1145 (vs), 1085 (m), 912 (s), 721 (vs) 697 (vs).
MS (EI, 70 eV): 325 (M^+, 75), 184 (35), 156 (100), 154 (25), 128 (20), 77 (20).
HRMS (ESI): calcd. for $C_{18}H_{16}NO_3S$ $[M + H]^+$: 326.0851, found 326.0851.

2-Allyl-1-methoxymethyl-1H-indole-3-carbaldehyde (4k)



Prepared according to the typical procedure from 2-iodo-1-methoxymethyl-1H-indole-3-carbaldehyde (**1h**) (315 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and allyl bromide (360 mg, 3.0 mmol). Reaction time: 30 min at -78 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 1/1) yielded the aldehyde **4l** as a light yellow solid (213 mg, 93%); mp 96 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.99 (s, 1H), 8.20-8.18 (d, *J* = 6.75 Hz, 1H), 7.70-7.68 (d, *J* = 7.63 Hz, 1H), 7.35-7.24 (m, 3H), 6.88-6.81 (dq, *J* = 15.81 Hz, *J* = 3.43 Hz, *J* = 1.66 Hz, 1 H), 6.52-6.40 (m. 1H), 5.59 (s, 2H), 3.25 (s, 3H), 2.05-2.02 (dd, *J* = 6.63 Hz, *J* = 1.66 Hz, 2H).

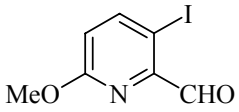
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 186.1, 149.2, 140.8, 137.0, 125.3, 124.3, 123.2, 121.2, 117.6, 114.9, 111.2, 74.2, 56.1, 19.6.

IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2941 (w), 1637 (vs), 1607 (w), 1521 (m), 1462 (m), 1378 (s), 1191 (w), 1114 (m), 1040 (s), 1048 (m), 968 (w), 756 (m), 633 (w).

MS (EI, 70 eV): 229 (M^+, 38), 214 (100), 198 (10), 184 (12), 170 (13), 154 (15), 128 (10), 77 (5).

HRMS (EI): calcd. for $C_{14}H_{15}NO_2$ [M^+]: 229.1103, found 229.1116.

3-Iodo-6-methoxy-pyridine-2-carbaldehyde (1h)



A dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septum, was charged with a solution of *N,N,N'*-trimethylethylenediamine (12 mmol) in dry THF (50 mL) at –78 °C. *n*-BuLi (1.68 M in *n*-hexane, 6.5 mL, 11 mmol) was added. After 15 min, 6-methoxypyridinecarboxaldehyde (1.37 g, 10 mmol) was added and the resulting mixture was stirred at –78 °C for 15 min. Then *n*-BuLi (1.68 M in hexane, 12 mL, 20 mmol) was added. The resulting mixture was first stirred at –78 °C for 5 h and then at – 42 °C for 5 h. The reaction mixture was cooled to – 78 °C and a solution of iodine (7.6 g, 30 mmol) in dry THF (20 mL) was added. The reaction mixture was stirred at rt for 30 min and poured into a solution of $Na_2S_2O_3$ (10%, 100 mL). The mixture extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash-chromatography (*n*-pentane/Et_2O = 10/1) yielded **1i** as a light yellow solid (0.9 g, 35%); mp 61 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.89-9.88 (d, *J* = 0.55 Hz, 1H), 8.29-8.26 (dd, *J* = 8.63 Hz, *J* = 0.55 Hz, 1H), 6.89-6.86 (d, *J* = 8.63 Hz, 1H), 4.00 (s. 3H).

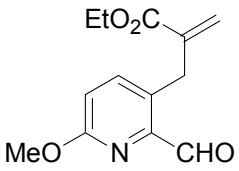
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 192.8, 165.3, 152.7, 148.7, 118.4, 82.3, 54.6.

IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3006 (w), 1697 (vs), 1579 (vs), 1467 (vs), 1414 (m), 1322 (s), 1269 (m), 1170 (m), 1032 (s), 1003 (m), 830 (m), 741 (m), 612 (m).

MS (EI, 70 eV): 263 (M^+, 100), 234 (16), 219 (10), 205 (5), 108 (12), 106 (11), 64 (7).

HRMS (EI): calcd. for $C_7H_6INO_2$ [M^+]: 262.9443, found 262.9452.

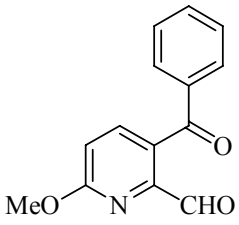
2-(2-Formyl-6-methoxy-pyridin-3-ylmethyl)-acrylic acid ethyl ester (4l)



Prepared according to the typical procedure from 3-iodo-6-methoxy-pyridine-2-carbaldehyde (**1i**; 263 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol), and ethyl (2-bromomethyl)acrylate (580 mg, 3.0 mmol). Reaction time: 3 h from –78 °C to –60 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 10/1) yielded the aldehyde **4m** as a colorless oil (204 mg, 82%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 10.03-10.03 (d, *J* = 0.66 Hz, 1H), 7.74-7.71 (dd, *J* = 8.51 Hz, *J* = 0.55 Hz, 1H), 7.03-7.00 (d, *J* = 8.51 Hz, 1H), 6.18-6.17 (q, *J* = 1.11 Hz, 1H), 5.41-5.40 (q, *J* = 1.55 Hz, 1H), 4.21-4.14 (q, *J* = 7.08 Hz, 1H), 4.05 (s. 2H), 1.27-1.23 (t, *J* = 7.08 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 195.1, 167.3, 164.0, 148.0, 144.2, 141.0, 130.5, 126.5, 116.5, 61.7, 54.2, 33.0, 14.8.
IR (film, cm^{-1}): $\tilde{\nu}$ = 3407 (w), 2981 (m), 1713 (vs), 1601 (vs), 1573 (w), 1481 (vs), 1426 (s), 1368 (m), 1337 (s), 1234 (s), 1029 (s), 944 (m), 820 (w), 651 (w).
MS (EI, 70 eV): 249 (M^+, 18), 220 (100), 204 (18), 192 (26), 176 (96), 148 (30), 133 (14), 77 (11).
HRMS (EI): calcd. for $C_{13}H_{15}NO_4$ [M^+]: 249.1001, found 249.1006.

3-Benzoyl-6-methoxy-pyridine-2-carbaldehyde (4m)

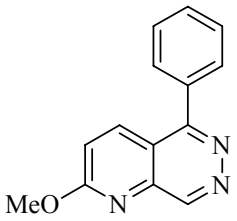


Prepared according to the typical procedure from 3-iodo-6-methoxy-pyridine-2-carbaldehyde (**1i**; 145 mg, 0.55 mmol), lithium dineophylcuprate **2** (0.7 mmol), and benzoyl chloride (168 mg, 1.2 mmol). Reaction time: 3 h at from –78 °C to –60 °C. Purification by flash-

chromatography (*n*-pentane/diethyl ether = 8/1) yielded the aldehyde **4n** as a light yellow solid (84 mg, 63%); mp 69 °C.

^{1}H-NMR (Acetone-d_6, 300 MHz): δ = 10.09-10.08 (d, *J* = 0.55 Hz, 1H), 8.08-8.05 (dd, *J* = 8.40 Hz, *J* = 0.55 Hz, 1H), 7,97-7.93 (m, 2H), 7.85-7.80 (m, 1H), 7.73-7.66 (m, 2H), 7.84-7.38 (d, *J* = 8.51 Hz, 1H), 4.49 (s. 3H).
^{13}C-NMR (Acetone-d_6, 75 MHz): δ = 192.9, 165.8, 149.8, 140.6, 138.5, 134.5, 131.3, 130.4, 130.0, 129.9, 116.6, 54.8.
IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3437 (br), 2857 (w), 1705 (s), 1667 (s), 1591 (vs), 1481 (s), 1332 (s), 1268 (vs), 1022 (m), 919 (w), 838 (m), 705 (m).
MS (EI, 70 eV): 241 (M^+, 75), 226 (36), 212 (100), 198 (17), 184 (19), 136 (35), 105 (19), 77 (23).
HRMS (EI): calcd. for $C_{14}H_{11}NO_3$ [M^+]: 241.0739, found 241.0711.

2-Methoxy-5-phenyl-pyrido[2,3-d]pyridazine (5)

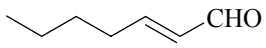


A 10 mL flask, equipped with a magnetic stirrer, a reflux condenser and a septum, was charged with a solution of 3-benzoyl-6-methoxy-pyridine-2-carbaldehyde (**4n**, 80 mg, 0.33 mmol) in ethanol (5 mL). The solution was refluxed and a solution of hydrazine monohydrate in ethanol (0.5 M/ethanol, 0.8 mL, 0.4 mmol) was added. The resulting mixture was refluxed for 15 min to complete the cyclization. The reaction mixture was directly concentrated *in vacuo*. The residue was purified by flash-chromatography (*n*-pentane/diethyl ether = 1/2) yielded the pyridopyridazine **5** as a light yellow solid (74 mg, 95%); mp 158 °C.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.51-9.50 (d, *J* = 0.66 Hz, 1H), 8.15-8.11 (dd, *J* = 9.07 Hz, *J* = 0.77 Hz, 1H), 7.66-7.62 (m, 2 H), 7.52-7.49 (m, 3H), 7.15-7.12 (d, *J* = 9.18 Hz, 1H), 4.10 (s. 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 167.0, 159.5, 151.4, 142.9, 136.9, 135.7, 130.4, 130.1, 129.1, 119.7, 118.8, 54.9.

IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3435 (br), 3076 (w), 1606 (vs), 1556 (m), 1473 (s), 1395 (vs), 1372 (s), 1303 (vs), 1253 (w), 1126 (w), 1033 (m), 866 (w) 691 (m).
MS (EI, 70 eV): 237 (M^+, 36), 236 (100), 222 (47), 166 (5), 139 (12), 126 (2), 77 (4).
HRMS (EI): calcd. for $C_{14}H_{11}N_3O$ [M^+]: 237.0902, found 237.0893.

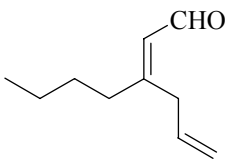
(2*E*)-2-Heptenal[7]



A dry and argon flushed 25 mL flask, equipped with a magnetic stirrer and a septumwas charged with CuCN (108 mg, 1.2 mmol) and dry THF (5 mL). A solution of neophyllithium (1.3 M/Et_2O, 1.9 mL, 2.4 mmol) was added at -78 °C. The resulting solution was stirred at rt for 10 min and then the Et_2O was removed carefully under vacuum. The remaining solution was cooled to -100 °C and cannulated into a solution of (2*Z*)-3-iodo-2-heptenal (**6**; 238 mg, 1.0 mmol) in dry THF (4 mL) at – 100 °C. After 5 min, water (0.5 ml) was added and the mixture stirred at rt for 30 min. The reaction was quenched with sat. aqueous NH_4Cl solution (5 mL) and poured into water (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic fractions were washed with brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash-chromatography yielded (2*E*)-2-heptenal (95 mg, 85%) as a light yellow oil.

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 9.52-9.50 (d, *J* = 7.85 Hz, 1H), 6.91-6.81 (dt, *J* = 15.59 Hz, *J* = 6.85 Hz, 1H), 6.17-6.08 (ddt, *J* = 15.59 Hz, *J* = 7.85 Hz, *J* = 1.55 Hz, 1H), 2.39-2.31 (m, 2H), 1.56-1.31 (m, 4H), 0.96-0.91 (t, *J* = 7.29 Hz, 3H).
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 194.5, 159.3, 133.4, 32.8, 30.3, 22.6, 14.1.
MS (EI, 70 ev), *m/z* (%): 112 (6) [M^+], 97 (10), 83 (100), 70 (52), 55 (92).

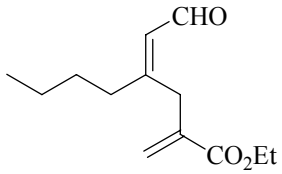
(2*Z*)-3-Butyl-2,5-hexadienal (8a)



Prepared according to the procedure for synthesis of (2*E*)-2-heptenal from (2*Z*)-3-iodo-2-heptenal (**6**; 238 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol) and allyl bromide (360 mg, 3.0 mmol). Reaction time: 5 min at –100 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 30/1) yielded the dienic aldehyde **8a** as a colorless oil (123 mg, 81%).

^{1}H-NMR (DMSO, 300 MHz): δ = 9.94-9.92 (d, *J* = 7.94, 1H), 5.90-5.79 (m, 2H), 5.16-5.06 (m, 2H), 3.34-3.33 (d, *J* = 6.41, 2H), 2.21-2.17 (dt, *J* = 7.63 Hz, *J* = 0.92 Hz, 2H), 1.46-1.38 (m, 2H), 1.32-1.24 (m, 2H), 0.88-0.85 (t, *J* = 7.32 Hz, 3H).
^{13}C-NMR (DMSO, 75 MHz): δ = 192.1, 165.6, 135.8, 127.6, 117.5, 37.4, 35.4, 29.3, 22.3, 14.1.
IR (film, cm^{-1}): $\tilde{\nu}$ = 3400 (w), 2958 (s), 2931 (s), 2872 (m), 1673 (vs), 1638 (m), 1466 (w), 1173 (w), 917 (w).
MS (EI, 70 ev), *m/z* (%): 152 (9) [M$^+$], 137 (100), 123 (4), 110 (10), 95 (40), 81 (25), 67 (30).
HRMS (EI): calcd. for $C_{10}H_{16}O$ [M$^+$]: 152.1201, found 152.1194.

Ethyl (4*Z*)-4-butyl-2-methylene-6-oxo-4-hexenoate (8b)



Prepared according to the procedure for synthesis of (2*E*)-2-heptenal from (2*Z*)-3-iodo-2-heptenal (**6**; 238 mg, 1.0 mmol), lithium dineophylcuprate **2** (1.2 mmol) and ethyl (bromomethyl)acrylate (580 mg, 3.0 mmol). Reaction time: 5 min at –100 °C. Purification by flash-chromatography (*n*-pentane/diethyl ether = 30/1) yielded the aldehyde **8b** as a colorless oil (164 mg, 73%).

^{1}H-NMR (DMSO, 300 MHz): δ = 10.00-9.99 (d, *J* = 8.11, 1H), 6.23-5.75 (d, *J* = 287.29, 2H), 5.89-5.99 (d, *J* = 8.11, 1H), 4.16-4.13 (q, *J* = 6.91, 2H), 3.63 (s, 2H), 2.17-2.14 (d, *J* = 7.63, 1H), 1.45-1.26 (m, 4H), 1.22-1.20 (t, *J* = 7.15 Hz, 3H), 0.89-0.86 (t, *J* = 7.39 Hz, 3H).
^{13}C-NMR (DMSO, 75 MHz): δ = 190.8, 164.7, 161.9, 136.2, 127.1, 126.3, 50.6, 35.0, 31.7, 27.9, 20.7, 12.9, 12.6.

IR (film, cm^{-1}): $\tilde{\nu}$ = 3422 (w), 2959 (s), 2933 (s), 2872 (m), 1717 (vs), 1675 (vs), 1628 (m), 1466 (w), 1177 (m), 1143 (m), 1027 (m), 915 (w).

MS (EI, 70 ev), *m/z* (%): 224 (5) [M^+], 195 (16), 167 (17), 151 (100), 135 (7), 121 (12), 108 (27), 95 (10), 79 (15).

HRMS (EI): calcd. for $C_{13}H_{20}O_3$ [M^+]: 224.1412, found 224.1382.

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