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Scaleable Preparation of Functionalized Organometallics *via* Directed Ortho Metalation Using Mg- and Zn-Amide Bases

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Abstract:

A range of aryl and heteroaryl organometallics are efficiently prepared in THF *via* directed ortho metalation by using the previously reported amide bases tmpMgCl·LiCl (tmp = 2,2,6,6-tetramethylpiperidyl), $tmp_2Mg·2LiCl$ and $tmp_2Zn·2MgCl_2·2LiCl$. These metalation reactions are carried out at 80−100 mmol scale. The unsaturated organometallic compounds undergo smooth reactions with various electrophiles, e.g. additions to carbonyl groups, Pd-catalyzed cross-coupling reactions or Cu-catalyzed acylations. In all cases, the metalation rates have been compared with corresponding small-scale reactions (1−2 mmol). Moreover, a procedure for the recovery of the valuable tmp-H from the aqueous layer is reported.

Introduction

Over the last few decades, the directed ortho metalation for the functionalization of unsaturated substrates has become more and more important.[1] The use of lithium reagents for performing such transformations has been thoroughly investigated, but the tolerance towards functional groups (especially esters) was unsatisfactory.[2] In addition to this pioneering work of Snieckus and Beak, several ate-bases for the selective metalation of arenes and heteroarenes under mild conditions have been reported by Kondo, Mongin, Mulvey and Uchiyama.[3] Recently, we found that the LiCl-complexed and solubilized amide base tmpMgCl·LiCl (**1**) allows the smooth magnesiation of various activated aromatics and heteroaromatics.[4] The presence of LiCl is essential since it leads to monomeric metallic amides reacting in a stoechimometric manner (e.g., no excess of magnesium amide is required in contrast to previously reported magnesium bases[5]). Also, the high kinetic basicity of tmpMgCl·LiCl results due to the presence of LiCl.[6] This commercially available reagent can be stored under inert gas atmosphere at 25 °C for at least 6 months without significant loss of activity. For the metalation of less activated aromatic substrates, the highly reactive $tmp_2Mg·2LiCl$ (**2**) proved to be a powerful metalation agent.[7] The only drawback is the stability of $tmp_2Mg·2LiCl$ (**2**) since it is only stable for a maximum of 24 h at 25 °C which is a drawback for its larger scale application. Compared to earlier reported neutral Mg-amides,[8] the corresponding $tmp_2Mg·2LiCl$ (**2**) also reacts in a stoichiometric manner resulting in products of the type ArMgtmp·2LiCl. Additionally, the metalation of more sensitive substrates can be accomplished by using the zinc base $tmp_2Zn·2MgCl_2·2LiCl$ (**3**).[9] Both $MgCl_2$ and LiCl are essential for the high kinetic basicity and good solubility of this

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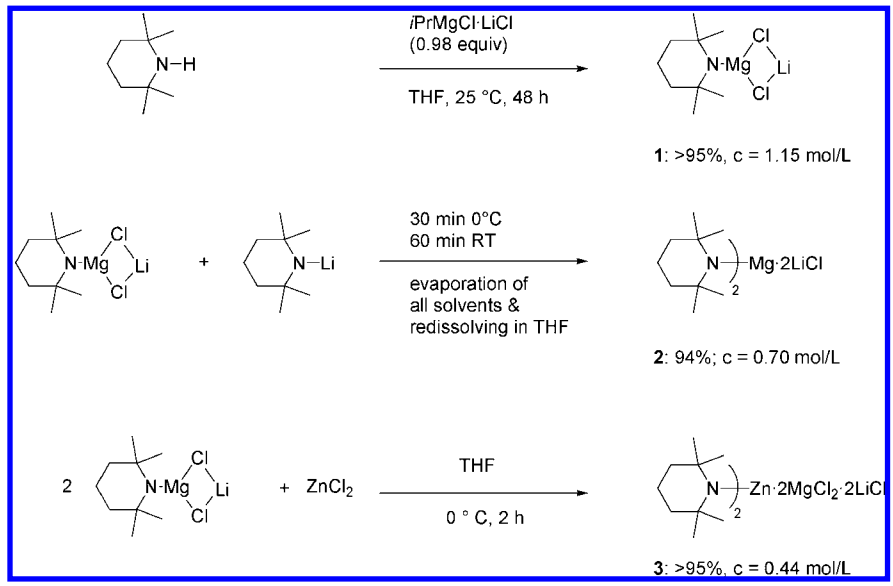
Scheme 1. **Preparation of the amide bases 1−3**



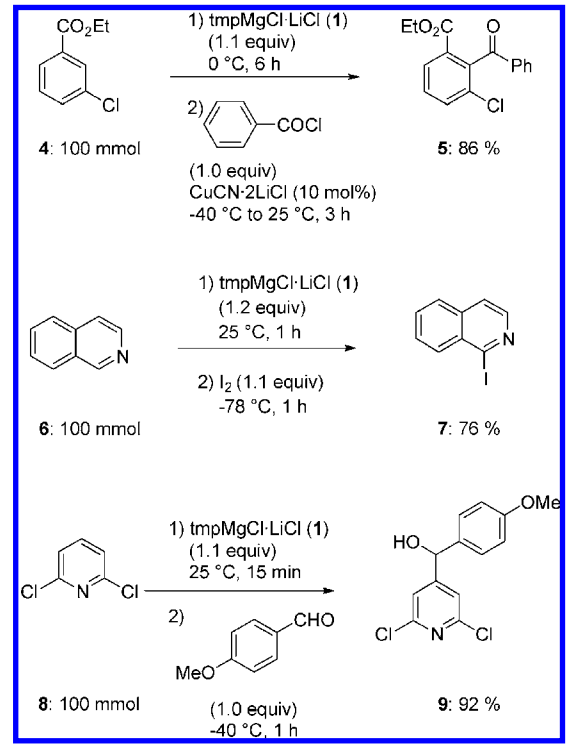
long-term stable reagent (6 months). This zincation method tolerates sensitive functionalities such as aldehydes or nitro groups as well as heterocycles which are prone to undergo ring opening. The zincations usually occur at close to room temperature, but elevated temperature (up to 120 °C) can be used for unreactive substrates. The tolerance towards functional groups still remains excellent at these temperatures. Usually, the optimization of these metalation procedures was carried out in 1−2 mmol scale. Herein, we report the extension of these metalation reagents to larger-scale experiments (80−100 mmol).

Results and Discussion

For the experiments described in this paper, the amide bases were prepared on a larger scale than previously described in the literature. Therefore, tmpMgCl·LiCl (**1**) is obtained by the reaction of *i*PrMgCl·LiCl (1.31 M in THF, 850 mL) with tmp-H (161 g, 194 mL, 1.02 equiv) under inert gas atmosphere (N_2) at 25 °C for 48 h with purging to remove the formed propane.[10] A concentration of 1.15 M in THF (>95% yield) is obtained. Due to the high reactivity of tmp_2Mg·2LiCl (**2**), this base is prepared separately for each reaction by reacting tmpMgCl·LiCl (**1**; 1.15 M in THF; 87 mL,) with freshly prepared tmpLi (100 mL, 1 M in hexane/THF).[11] After evaporation of all solvents and redissolution of the residue in THF, the concentration of tmp_2Mg·2LiCl (**2**) was found to be 0.7 M in THF (94% yield). For the preparation of tmp_2Zn·$2MgCl_2$·2LiCl (**3**), tmpMgCl·LiCl (*1*; 1.15 M in THF; 348 mL) is cooled to 0 °C and $ZnCl_2$ (1.0 M in THF, 200 mL, 0.5 equiv) is added over a period of 15 min. After stirring this mixture for 2 h at 0 °C, the solution of tmp_2Zn·$2MgCl_2$·2LiCl (**3**) is concentrated *in vacuo*. A concentration of 0.44 M in THF (>95% yield) is obtained (Scheme 1).

We have carried out several larger-scale metalations using tmpMgCl·LiCl (**1**; Scheme 2) and subsequent

Scheme 2. **Metalation of ethyl 3-chlorobenzoate (4), isoquinoline (6) and 2,6-dichloropyridine (8) using tmpMgCl·LiCl (1) and subsequent reactions with electrophiles**



reactions with electrophiles. Ethyl 3-chlorobenzoate (**4**; 18.5 g. 100 mmol) was added to a solution of tmpMgCl·LiCl (**1**; 1.15 M in THF, 96 mL, 1.1 equiv), and metalation is performed at 0 °C for 6 h (same metalation rate as for reactions performed at a 2 mmol scale; metalation progress checked by iodolysis of reaction aliquots and gas chromatographical analysis).[4b] The resulting mixture is cooled to −40 °C, and reacted with PhCOCl (14.2 g, 1.0 equiv) in the presence of CuCN·2LiCl (1 M in THF, 10 mL).[12] After a slow warming of the reaction mixture to 25 °C within 3 h, the benzophenone **5** is obtained in 86% yield

(10) Tmp-H can be added at once to *i*PrMgCl·LiCl at 25 °C; a slight exothermic reaction was observed. For the preparation in 1.1 mol scale, no external cooling was necessary.

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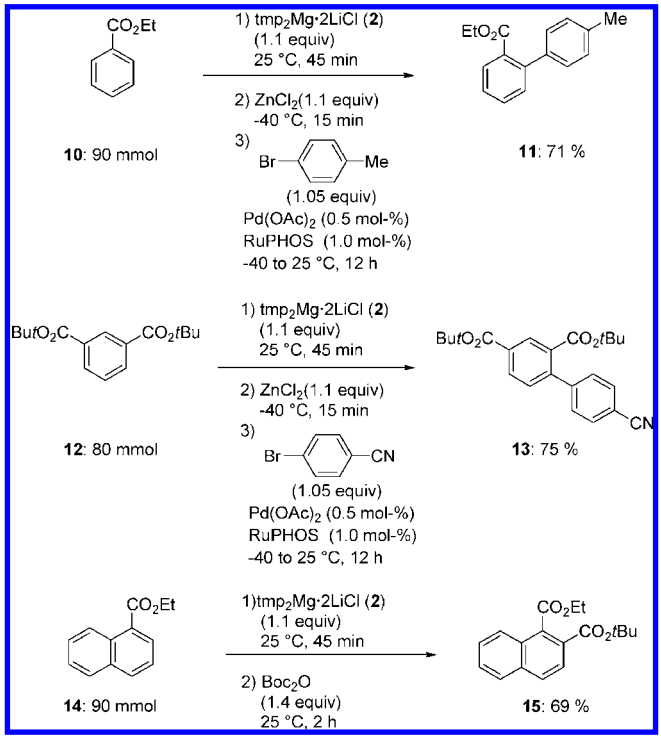
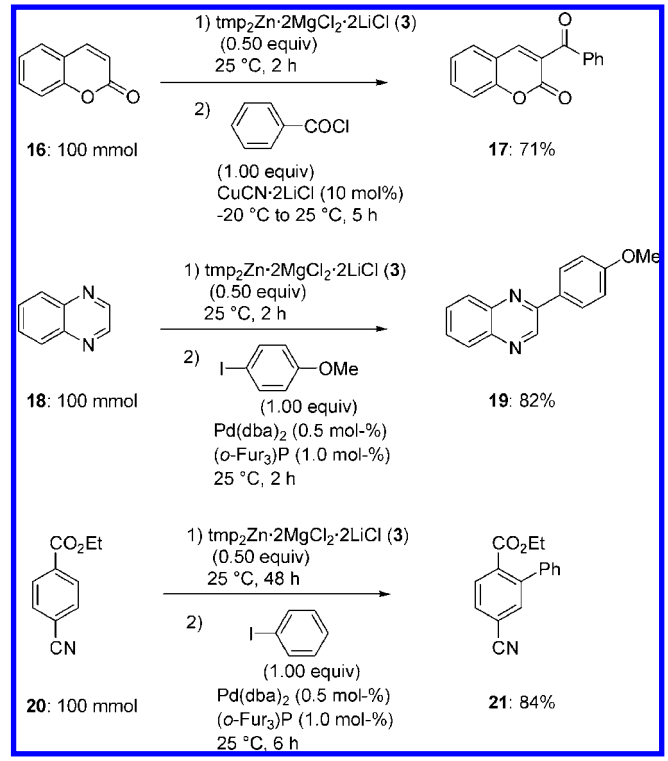
Scheme 3. **Metalation of ethyl benzoate (10), di-*tert*-butylisophthalate (12) and ethyl 1-naphthoate (14) using $tmp_2Mg \cdot 2LiCl$ (2) and subsequent reactions with electrophiles**



Scheme 4. **Metalation of coumarin (16), quinoxaline (18) and ethyl 4-cyanobenzoate (20) using $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (3) and subsequent reactions with electrophiles**



(81% in 2 mmol scale[4b]). Isoquinoline (**6**; 12.9 g,) is regioselectively metalated in position 2 using tmpMgCl·LiCl (**1**; 1.15 M in THF, 104 mL, 1.2 equiv) within 1 h (compared to 2 h for 2 mmol scale) and the addition *of the metalated species to a solution of* I_2 in THF (1 M in THF, 110 mL, 1.1 equiv) at −78 °C furnishes the expected heterocyclic iodide **7** after 1 h in 76% yield.[13] Similarly, 2,6-dichloropyridine (**8**; 14.8 g) is converted into the fully magnesiated species within 15 min at 25 °C (same metalation rate compared that of to 2 mmol scale reactions) using tmpMgCl·LiCl (**1**; 1.15 M in THF, 96 mL, 1.1 equiv). The alcohol **9** is obtained in 92% yield after the reaction with 4-methoxybenzaldehyde (1.0 equiv).

Furthermore, the larger-scale magnesiation of unactivated aromatics was performed by using the more reactive $tmp_2Mg \cdot 2LiCl$ (**2**) under the optimized conditions as shown in Scheme 3. Thus, a 500 mL Schlenk-flask is charged with freshly prepared $tmp_2Mg \cdot 2LiCl$ (**2**; 143 mL). Ethyl benzoate (**10**; 13.5 g) is added at 25 °C to the magnesium base **2** in one portion. After 45 min of metalation time (compared to 1 h for 2 mmol scale; metalation progress checked by iodolysis of reaction aliquots and gas chromatographical analysis) and subsequent cooling to −40 °C, $ZnCl_2$ (100 mL, 1.1 equiv) is added, and the resulting mixture is stirred for 15 min. Then, a Pd-catalyzed cross-coupling[14] reaction with 4-bromotoluene (1.0 equiv) using $Pd(OAc)_2$ (0.5 mol %) and RuPhos (1 mol %) as catalytic system[15] leads to the biaryl ester **11** in 71% yield. The magnesiation of di-*tert*-butylisophthalate (**12**; 22.2 g) using $tmp_2Mg \cdot 2LiCl$ (**2**; 128 mL, 1.1 equiv) is complete within 45 min at 25 °C (compared to 1 h for 2 mmol scale). Subsequently, after transmetalation with $ZnCl_2$ (90 mL, 1.1 equiv) a Pd-catalyzed cross-coupling[14] reaction with 4-bromobenzonitrile (1.0 equiv) using $Pd(OAc)_2$ (0.5 mol %) and RuPhos (1 mol %) as catalytic system[15] provides the functionalized biaryl **13** in 75% yield. Additionally, the full metalation of ethyl 1-naphthoate (**14**; 18.0 g) is obtained within 45 min at 25 °C using $tmp_2Mg \cdot 2LiCl$ (**2**; 143 mL, compared to 1 h for 2 mmol scale reactions)[7a] by applying this large-scale protocol. After quenching with Boc_2O (1.4 equiv), the desired mixed diester **15** is isolated in 69% yield.[16]

Finally, we report larger-scale zincations (Scheme 4). Thus, a 250 mL Schlenk-flask is charged with $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**; 0.44 M in THF, 114 mL), and coumarin (**16**; 14.6 g) is added to the zinc base **3** in one portion at 25 °C. After 2 h (compared to 4 h for the 2 mmol scale reaction[9a]), the metalation of coumarin is complete (indicated by iodolysis of reaction aliquots and gas chromatographical analysis), and the resulting mixture is cooled to −20 °C. Then, CuCN·2LiCl (10 mL, 10 mol %) is added, followed by benzoyl chloride (14.2 g, 1.0 equiv).[12] The acylation reaction proceeds while the reaction

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(13) In a 1 mmol scale, a yield of 92% was observed (ref 4a). The order and the rate of addition of iodine are important for larger scales. Different conditions than the ones reported in the Experimental Section lead even to lower yields.

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mixture is slowly warmed to reach 25 °C over 5 h. The desired benzoylated coumarin **17** is obtained in 69% yield (compared to 75% in 2 mmol scale). Accordingly, the zincation of quinoxaline (**18**; 13.5 g) is achieved within 3 h (compared to 6 h for the 2 mmol scale reaction[9d]) using $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**; 0.44 M in THF, 114 mL). Subsequently, a Pd-catalyzed cross-coupling reaction with 4-iodoanisole (1.0 equiv) using $Pd(dba)_2$ (0.5 mol %) and $(o\text{-fur})_3$-P (1 mol %) as catalytic system furnishes the arylated quinoxaline **19** in 82% yield (compared to 85% for 2 mmol scale reaction). Interestingly, the metalation of coumarin (**16**) and quinoxaline (**18**) proceeds twice as fast when carried out in 100 mmol scale. In contrast, the metalation of ethyl 4-cyanobenzoate (**20**; 17.5 g, 100 mmol) using $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**; 0.44 M in THF, 114 mL) takes 48 h at 25 °C (compared to 24 h for the 2 mmol scale reaction). A subsequent Pd-catalyzed cross-coupling[14] with iodobenzene (1.0 equiv) using $Pd(dba)_2$ (0.5 mol %) and $(o\text{-fur})_3$-P (1 mol %) as catalytic system leads to the biaryl **21** in 84% yield (compared to 85% for the 2 mmol scale reaction).

To regenerate 2,2,6,6-tetramethylpiperidine (tmp-H), the aqueous layers of the above-described reaction mixtures are collected and treated with NaOH (pH = 12−13) until tmp-H separates as its own layer above the aqueous phase. Then, tmp-H can easily be separated and is recovered after distillation from CaH_2 in up to 75% yield.

Summary and Outlook

In conclusion, we have shown that metalation processes using tmpMgCl·LiCl (**1**), $tmp_2Mg \cdot 2LiCl$ (**2**) and $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**) can readily and safely be carried out at multigram scale with comparable yields as obtained for small scales. Interestingly, the metalation steps occur usually with an enhanced rate. Remarkably, acylation reactions can be carried out with only 10 mol % CuCN·2LiCl (in general 20−100% CuCN·2LiCl for small scales), and the catalyst loading of cross-coupling reactions can be decreased to 0.5% of Pd.

Experimental Section

General Considerations. All reactions were carried out under air and moisture exclusion. All glassware was oven-dried (80 °C) overnight (min 12 h), evacuated in high vacuum ($1 \cdot 10^{-3}$mbar) and backfilled with nitrogen (this procedure was repeated three times). Syringes which were used to transfer anhydrous solvents or reagents were purged with nitrogen prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H NMR (25 °C) and capillary GC analysis. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$) with residual chloroform (δ 7.25 ppm for ^{1}H NMR and δ 77.0 ppm for ^{13}C NMR) or d_6-DMSO (δ 2.49 ppm for ^{1}H NMR and δ 39.5 ppm for ^{13}C NMR). Column chromatographical purifications were performed using SiO_2 (0.040−0.063 mm, 230−400 mesh ASTM) from Merck if not indicated otherwise. tmpH, liquid aldehydes and acid chlorides were distilled prior to use. The completion of the metalation reaction was checked by GC analysis of reaction aliquots (reaction aliquots were quenched with 0.2 mL of a 0.5 M I_2 solution in dry THF, then shaken with NH_4Cl (1 mL) and sat. aq $Na_2S_2O_3$ solution (1 mL) and extracted with 1 mL diethyl ether (1 mL)).

Preparation of tmpMgCl·LiCl (1). A dried and nitrogen-flushed 2 L Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with *i*PrMgCl·LiCl (1.31 M in THF, 850 mL, 1.11 mol). Then 2,2,6,6-tetramethylpiperidine (161 g, 194 mL, 1.14 mol, 1.02 equiv) is added at once, and the mixture is stirred until gas evolution ceases (48 h). Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use shows a concentration of 1.15 M.

Preparation of $tmp_2Mg \cdot 2LiCl$ (2). A flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with 100 mL of dry THF cooled in a −40 °C cooling bath and stirred for 15 min at this temperature. Then *n*-BuLi (45.5 mL, 2.22 M in hexanes, 100 mmol, 1.1 equiv) is added at once via syringe. After stirring for 15 min at −40 °C, 2,2,6,6-tetramethylpiperidine (14.1 g, 100 mmol, 1.1 equiv) is added at once via syringe. The resulting mixture is stirred at −40 °C for 5 min and stirred at 0 °C for further 30 min. Then, tmpMgCl·LiCl (87 mL, 1.15 M in THF, 100 mmol, 1.1 equiv.) is added via syringe in one portion (addition time <1 min.). The mixture is stirred at 0 °C for 30 min and at 25 °C for another 1 h. The solvents are removed *in vacuo*. The resulting pale-brown solid is redissolved in dry THF (100−120 mL) and stirred for 10 min at 25 °C. Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use shows a concentration of 0.70 M.

Preparation of $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (3). A flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of tmpMgCl·LiCl (**1**; 348 mL, 400 mmol) and cooled to 0 °C. Then, $ZnCl_2$ (1.0 M in THF, 200 mL, 200 mmol, 0.5 equiv) is added over a period of 15 min. After stirring this mixture for 2 h at 0 °C, the solution of $tmp_2Zn \cdot 2MgCl_2 \cdot 2LiCl$ (**3**) is concentrated *in vacuo*. Titration with benzoic acid using 4-(phenylazo)diphenylamine as indicator prior to use shows a concentration of 0.44 M.

Preparation of ethyl 2-benzoyl-3-chlorobenzoate (5). A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of tmpMgCl·LiCl (**1**; 96 mL, 110 mmol) and cooled to 0 °C. Then, ethyl 3-chlorobenzoate (**4**; 18.5 g, 100 mmol) is added and the mixture is stirred for 6 h at 0 °C. The resulting mixture is cooled to −40 °C and PhCOCl (14.2 g, 100 mmol, 1.0 equiv) and CuCN·2LiCl (1 M in THF, 10 mL, 10 mmol) were added. After slow warming to 25 °C within 3 h, the reaction mixture is quenched with a mixture of a sat. aqueous NH_4Cl solution (300 mL) and conc. aqueous NH_3-solution (50 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*-heptane/ethyl acetate) to give **5** as a colourless solid (24.8 g, 86%).

mp: 108.6−109.6 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (m, 1 H), 7.81 (m, 2 H), 7.44−7.68 (m, 5 H), 4.17 (q, ^3J = 7.1 Hz, 2 H), 1.10 (t, ^3J = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.52, 164.82, 140.65, 136.91, 134.15, 133.63, 131.97, 130.89, 130.11, 129.24, 128.93, 62.09, 13.84.

MS (70 eV, EI) m/z (%): 290 (19), 288 (43) [M^+], 242 (32), 211 (73), 211 (26), 185 (32), 183 (100), 152 (10), 151 (13), 105 (87), 77 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 1706, 1672, 1584, 1564, 1430, 1366, 1284, 1202, 1152, 1074, 1028, 928, 866, 764, 744, 734, 702, 652, 618.

HRMS (EI): for $C_{16}H_{13}ClO_3$ (288.0553) 288.0569.

Preparation of 2-Iodoisoquinoline (7). A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of tmpMgCl·LiCl (**1**; 104 mL, 120 mmol). Isoquinoline (**6**; 12.9 g, 100 mmol) is added, and the mixture is stirred for 1 h at 25 °C. Then, the reaction mixture is cannulated slowly to a solution of I_2 in THF (1 M in THF, 110 mL, 110 mmol, 1.1 equiv) at −78 °C. The resulting mixture is stirred for 1 h at −78 °C and then quenched with a sat. aq $Na_2S_2O_3$ solution (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by column chromatography (pentane/diethyl ether = 9:1) to give **7** (19.4 g, 76%) as a yellowish solid.

mp: 73.9−75.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 5.6 Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.72−7.62 (m, 3 H), 7.54 (d, J = 5.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.96, 136.14, 132.82, 131.91, 131.06, 128.98, 127.44, 127.22, 121.29.

MS (70 eV, EI) m/z: 255 (39) [M^+], 129 (10), 128 (100), 127 (5), 101 (17), 77 (7), 75 (8), 51 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3047, 1992, 1904, 1834, 1774, 1619, 1576, 1539, 1490, 1443, 1363, 1316, 1302, 1251, 1219, 1173, 1136, 1038, 954, 871, 822, 808, 787, 776, 751, 654, 637.

HRMS (EI): for C_9H_6IN (254.9545) 254.9535.

Preparation of (2,6-Dichloropyridin-4-yl)(4-methoxyphenyl)methanol (9). A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of tmpMgCl·LiCl (**1**; 96 mL, 110 mmol). 2,6-Dichloropyridine (**8**; 14.8 g, 100 mmol) is added, and the mixture is stirred for 15 min at 25 °C. The resulting mixture is cooled to −40 °C, and 4-methoxybenzaldehyde (13.6 g, 100 mmol, 1.0 equiv) is added. The resulting mixture is stirred for 1 h at −78 °C and then quenched with brine (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*-heptane/ethyl acetate) to give **9** as a colourless solid (26.1 g, 92%).

mp: 90.6−93.8 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ. 7.26 (d, J = 0.75 Hz, 2 H), 7.21−7.18 (m, 2 H), 6.88−6.86 (m, 2 H), 5.67 (s, 1 H), 3.78 (s, 3 H), 2.67 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ. 159.88, 158.75, 150.48, 133.62, 128.22, 120.33, 114.45, 73.88, 55.32.

MS (70 eV, EI) m/z. 285 (55), 283 (35) [M^+], 176 (13), 174 (20), 137 (100), 135 (12), 109 (69), 94 (17), 77 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}). 3340, 3100, 3000, 2835, 1739, 1584, 1554, 1544, 1508, 1464, 1426, 1378, 1362, 1303, 1240, 1167, 1150, 1113, 1098, 1069, 1030, 993, 920, 834, 828, 813, 774, 768, 736, 680, 666, 630, 610.

HRMS (EI): for $C_{13}H_{11}Cl_2NO_2$ (283.0167) 283.0164.

Preparation of Ethyl 4′-methylbiphenyl-2-carboxylate (11). In a flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of tmp_2Mg·2LiCl (**2**; 110 mL, 100 mmol) is provided; ethyl benzoate (**10**; 13.5 g, 90 mmol) is added, and the reaction mixture is stirred for 45 min at 25 °C. The resulting solution is cooled to −40 °C, and $ZnCl_2$ (100 mL, 100 mmol, 1.1 equiv) is added, and the resulting mixture is stirred for 15 min. Then, $Pd(OAc)_2$ (0.5 mol %), RuPhos (1 mol %) and 4-bromotoluene (16.2 g, 95 mmol, 1.05 equiv) are added. After warming to 25 °C and stirring for 12 h at 25 °C, the reaction is quenched with a sat. aq NH_4Cl solution (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by column chromatography (pentane/diethyl ether = 9:1) to give **11** as pale-yellow oil (15.4 g, 71%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (m, 1 H), 7.53 (m, 1 H), 7.44 (m, 2 H), 7.29 (m, 4 H), 4.21 (q, J = 7.0 Hz, 2 H), 2.47 (s, 3 H), 1.12 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.89, 142.48, 138.63, 136.84, 131.45, 131.10, 130.69, 129.69, 128.79, 128.37, 126.98, 60.91, 21.23, 13.82.

MS (70 eV, EI) m/z: 240 (51) [M^+], 213 (10), 212 (10), 196 (18), 195 (100),167 (23), 166 (18), 165 (51), 153 (10), 152 (48), 82 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3060, 3024, 2981, 2924, 2870, 1713, 1600, 1518, 1445, 1365, 1286, 1276, 1241, 1172, 1125, 1112, 1085, 1047, 1016, 1006, 854, 819, 758, 730, 709, 656.

HRMS (EI): for $C_{16}H_{16}O_2$ (240.1150)240.1142.

Preparation of Di-*tert*-butyl 4′-cyanobiphenyl-2,4-dicarboxylate (13). In a flame-dried and nitrogen-flushed 500 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of tmp_2Mg·2LiCl (**2**; 100 mL, 90 mmol) is provided; di-*tert*-butylisophthalate (**12**; 22.2 g, 80 mmol) is added, and the reaction mixture is stirred for 45 min at 25 °C. The resulting solution is cooled to −40 °C, and $ZnCl_2$ (90 mL, 90 mmol, 1.1 equiv) is added; the resulting mixture is stirred for 15 min. Then, $Pd(OAc)_2$ (0.5 mol %), RuPhos (1 mol %) and 4-bromobenzonitrile (15.3 g, 84 mmol, 1.05 equiv) are added. After warming to 25 °C and stirring for 12 h at 25 °C, the reaction mixture is quenched with a sat. aq NH_4Cl solution (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the

solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*-heptane/ethyl acetate) to give **13** as a yellow solid (22.8 g, 75%).

mp: 158.5−158.8 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (d, J = 1.5 Hz, 1 H), 8.13 (dd, J = 8.0, 1.9 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 2 H), 7.43 (d, J = 8.5 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 1 H), 1.61 (s, 9 H), 1.37 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.31, 164.51, 145.98, 143.92, 132.60, 132.01, 131.83, 131.73, 131.13, 130.33, 129.23, 118.67, 111.40, 82.21, 81.84, 28.16, 27.64.

MS (70 eV, EI) m/z: 323 (19) [M^+ − *t*Bu], 306 (17), 268 (53), 267 (100), 266 (11), 250 (50), 177 (22), 166 (10), 57 (76), 56 (17).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972, 2933, 2228, 1722, 1711, 1604, 1477, 1368, 1324, 1302, 1276, 1254, 1250, 1158, 1146, 1121, 1089, 838, 775, 754, 740.

HRMS (EI): for $C_{23}H_{25}NO_4$ (379.1784) 379.1785.

Preparation of 2-*tert*-Butyl 1-Ethyl naphthalene-1,2-dicarboxylate (15). In a flame-dried and nitrogen-flushed 500-mL Schlenk flask, equipped with a magnetic stirring bar and rubber septum, the freshly prepared solution of $tmp_2Mg\cdot 2LiCl$ (**2**; 110 mL, 100 mmol) is added followed by ethyl 1-naphthoate (**14**; 18.0 g, 90 mmol), and the reaction mixture is stirred for 45 min at 25 °C. Boc_2O (28.0 g, 130 mmol, 1.44 equiv) is added in one portion at 25 °C, and the reaction mixture was stirred for 2 h. A sat. aq NH_4Cl solution (250 mL) is added, and the mixture is extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*-heptane/ethyl acetate) to give **15** as a colourless solid (12.4 g, 69%).

mp: 70.5−70.9 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ; 7.92 (m, 4 H), 7.59 (m, 2 H), 4.58 (q, J = 7.3 Hz, 2 H), 1.64 (s, 9 H), 1.46 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.03, 165.07, 134.85, 134.30, 129.38, 129.25, 128.07, 127.52, 127.03, 125.93, 125.24, 82.23, 61.73, 28.13, 14.14.

MS (70 eV, EI) m/z: 300 (16) [M^+], 244 (41), 227 (10), 216 (11), 200 (20), 199 (100), 198 (10), 172 (21), 155 (29), 154 (14), 127 (25), 126 (30), 57 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3058, 2982, 2939, 1720, 1708, 1365, 1294, 1269, 1238, 1168, 1139, 1116, 1036, 1014, 860, 848, 833, 798, 790, 764, 733.

HRMS (EI): for $C_{13}H_{11}O_2$ (300.1362) 300.1358.

Preparation of 3-Benzoyl-2H-chromen-2-one (17). A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $tmp_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**3**; 114 mL, 100 mmol). Coumarin (**16**; 14.6 g, 100 mmol) is added neatly, and the mixture is stirred for 2 h at 25 °C. The resulting mixture is cooled to −20 °C, then PhCOCl (14.2 g, 100 mmol, 1.0 equiv) and $CuCN\cdot 2LiCl$ (1 M in THF, 10 mL, 10 mmol) were added. After slow warming to 25 °C within 5 h, the reaction mixture is quenched with a mixture of a sat. aq NH_4Cl solution (300 mL) and conc. aq NH_3-solution (50 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*-heptane/ethyl acetate) to give **17** as a yellowish solid (17.8 g, 71%).

mp: 136.0−137.1 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.1 (s, 1 H), 7.90 (d, J = 8.4 Hz, 2 H), 7.67−7.57 (m, 3 H), 7.51−7.44 (m, 2 H), 7.40 (d, J = 8.5 Hz, 1 H), 7.34 (d, J = 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.6, 158.4, 154.8, 145.3, 136.2, 133.8, 133.6, 129.5, 129.2, 128.6, 127.0, 125.0, 118.2, 116.9.

MS (70 eV, EI) m/z: 251 (13), (250) (100) [M^+], 222 (24), 221 (59), 173 (21), 105 (98), 77 (61), 51 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061, 1712, 1656, 1607, 1595, 1580, 1563, 1487, 1453, 1449, 1445, 1363, 1318, 1305, 1297, 1264, 1237, 1214, 1182, 1164, 1144, 1120, 1073, 1041, 1026, 1000, 962, 952, 946, 937, 920, 865, 857, 816, 793, 769, 759, 754, 736, 696, 681.

HRMS (EI): for $C_{16}H_{10}O_3$ (250.0630) 250.0605.

Preparation of 2-(4-Methoxyphenyl)quinoxaline (19). A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $tmp_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**3**; 114 mL, 100 mmol). Quinoxaline (**18**; 13.0 g, 100 mmol) is added and the mixture is stirred for 3 h at 25 °C. Then, $Pd(dba)_2$ (280 mg; 0.5 mol %), (o-fur)$_3$-P (230 mg; 1 mol %) and 4-iodoanisole (23.4 g, 100 mmol, 1.00 equiv) are added and the reaction mixture is stirred for 2 h at 25 °C. The reaction mixture is quenched with a sat. aqueous NH_4Cl solution (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by recrystallization (*n*-heptane/ethyl acetate) to give **19** as a colourless solid (19.4 g, 82%).

mp: 100.2−101.9 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 9.28 (s, 1 H), 8.16 (d, J = 8.8 Hz, 2 H), 8.12 (t, J = 8.1.Hz, 2 H), 7.77−7.67 (m, 2 H), 7.11 (d, J = 8.8 Hz, 2 H), 3.88 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 161.52, 151.41, 143.00, 142.26, 141.11, 130.27, 129.36, 129.20, 129.13, 129.02, 114.62, 55.47.

MS (70 eV, EI) m/z: 236 (100) [M+], 233 (14), 221 (17), 209 (12), 166 (8), 118 (8), 57 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3057, 3005, 2930, 2833, 1602, 1576, 1536, 1488, 1427, 1291, 1270, 1246, 1226, 1181, 1130, 1030, 957, 847, 810, 795, 758, 728, 670, 655, 630, 609.

HRMS (EI): for $C_{15}H_{12}N_2O$ (236.0950) 236.0945.

Preparation of Ethyl 5-cyanobiphenyl-2-carboxylate (21). A flame-dried and nitrogen-flushed 250 mL Schlenk-flask, equipped with a magnetic stirring bar and rubber septum, is charged with a solution of $tmp_2Zn\cdot 2MgCl_2\cdot 2LiCl$ (**3**; 114 mL, 100 mmol). Ethyl 4-cyanobenzoate (**20**; 17.5 g, 100 mmol) is added, and the mixture is stirred for 48 h at 25 °C. Then, $Pd(dba)_2$ (280 mg; 0.5 mol %), (o-fur)$_3$-P (230 mg; 1 mol %) and iodobenzene (20.4 g, 100 mmol, 1.00 equiv) are added, and the reaction mixture is stirred for 5 h at 25 °C. The reaction mixture is quenched with a sat. aq NH_4Cl solution (250 mL)

and extracted with Et_2O (3 × 250 mL). The combined organic layers are washed with brine (250 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent is removed *in vacuo*. The crude product is purified by column chromatography (pentane/ether 7:1) to give **21** as a yellowish oil (21.1 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13−8.17 (m, 1 H), 7.89−7.91 (m, 1 H), 7.70−7.77 (m, 2 H), 7.40−7.47 (m, 2 H), 7.29−7.34 (m, 2 H), 4.10 (q, J = 7.3 Hz, 2 H), 0.98 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.4, 143.2, 139.1, 135.5, 134.0, 132.2, 130.2, 130.1, 128.4, 128.2, 116.3, 114.8, 61.6, 13.6.

MS (70 eV, EI) m/z; 251 (35) [M^+], 223 (11), 207 (16), 206 (100), 178 (16), 177 (16), 151 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3098, 3052, 2990, 2980, 2938, 2904, 2232, 1712, 1674, 1602, 1578, 1568, 1558, 1504, 1480, 1472, 1444, 1398, 1366, 1350, 1318, 1280, 1250, 1186, 1158, 1138, 1124, 1106, 1076, 1048, 1020, 968, 920, 902, 872, 854, 842, 788, 764, 710, 696, 668, 642, 630, 614, 604, 580, 566.

HRMS (EI): for $C_{16}H_{13}NO_2$ (251.0946) 251.0941.

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Supporting Information Available

Copies of ^{1}H- and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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