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An efficient and mild *ortho*-zincation of aromatics and heterocycles by using $TMP_2Mg{\cdot}2LiCl$ in the presence of $ZnCl_2$

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ABSTRACT

A variety range of functionalized aryl and heteroaryl zinc reagents were efficiently generated by using $TMP_2Mg{\cdot}2LiCl$ (TMP = 2,2,6,6-tetramethylpiperamidyl) in the presence of $ZnCl_2$. The subsequently functionalization gave after reaction with electrophiles the expected polyfunctionalized products in good yields. A detailed study concerned on the point how we found the protocol and how we optimized it was depicted.

1. Introduction

The directed *ortho*-metalation of aromatics and heterocycles is an efficient method for the functionalization of these compounds [1–10]. However, deprotonation of some heterocyclic aromatic rings gave unsatisfactory results due to the high reactivity of the generated organometallic intermediates [11,12], and it is already known that the metalation of diazines is challenging since very facile competitive nucleophilic addition reactions occur [13–16]. To resolve this problem, recently, we (Knochel and Dong et al.) have reported a simple method for the zincation of some sensitive aromatic and heteroaromatic substrates by using $TMP_2Mg{\cdot}2LiCl$ (TMP = 2,2,6,6-tetramethylpiperamidyl) [17,18] in the presence of $ZnCl_2$ [19]. Thus, with addition of $ZnCl_2$ to the substrates, prior to the addition of the magnesium base $TMP_2Mg{\cdot}2LiCl$, the relatively active aromatics and heterocycles can be smoothly metalated at 25 °C, after reaction with electrophiles, the expected functionalized products can be obtained in good yields. Herein, we wish to report a detailed study of the reaction and an expanded application to further illustrate this efficient and mild method.

2. Results and discussion

During the course of the metalation and the subsequent functionalization of quinoxaline (**1a**) by using the magnesium base $TMP_2Mg{\cdot}2LiCl$, the desired quinoxalyl iodide (**2**) was obtained only traces, while the major product, the dimeric heterocycle (**3**) was isolated in 34% yield (Scheme 1).

This is probably due to the relatively high reactivity of the organomagnesium intermediate, and we speculate that the less reactive organozinc intermediate might not lead to this result. Then, we first investigated the metalation of **1a** by an *in situ* procedure via which the less reactive zinc intermediate might be generated. Thus, 0.5 equivalent of $TMP_2Mg{\cdot}2LiCl$ was added to the substrate, subsequently 0.5 equivalent of $ZnCl_2$ was added to the reaction solution under the setting temperature, the metalation was checked by iodination and was analyzed by GC machine. To our disappointment, no matter how the reaction temperature changes, the metalation always gave a mixture without any favoured selectivity (Scheme 2).

However, when the addition of $ZnCl_2$ to the substrate, prior to the addition of the magnesium base $TMP_2Mg{\cdot}2LiCl$, an exciting result was obtained: only traces of dimer was observed and quinoxalyl iodide was isolated in 94% yield (Scheme 3).

The optimal ratio of $ZnCl_2$ to $TMP_2Mg{\cdot}2LiCl$ (0.5:0.55) was obtained by studying the metalation of pyrazine which is also a reactive heterocycle (Scheme 4). The order of addition of all the reaction partners (first $ZnCl_2$, then base $TMP_2Mg{\cdot}2LiCl$) is essential for achieving the reported metalation time in this paper, which indicates a probable precomplexation of the aromatic or heteroaromatic substrate facilitates the deprotonation with $TMP_2Mg{\cdot}2LiCl$ [19]. Alternatively, base $TMP_2Mg{\cdot}2LiCl$ reacts first with quinoxaline affording the organomagnesium intermediate, after a fast transmetalation with $ZnCl_2$ (0.5 equiv.), the quinoxalylzinc intermediate could be formed [19].

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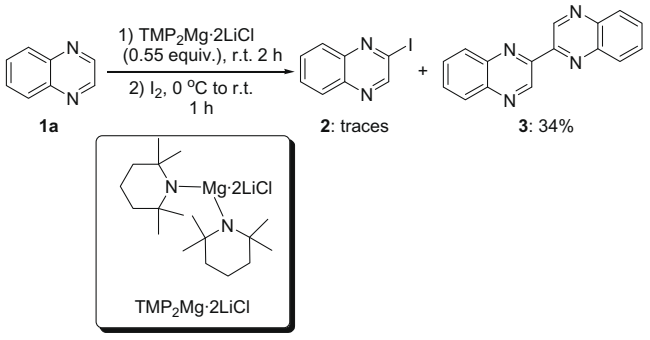
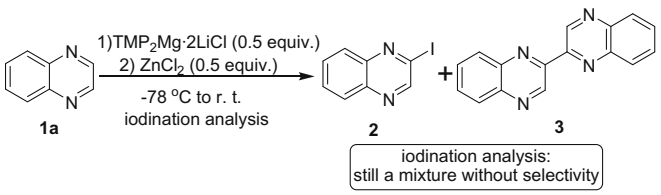
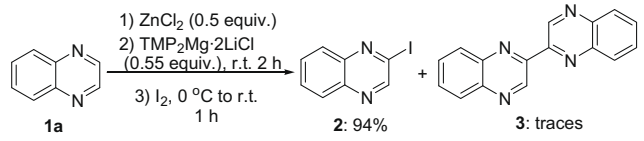


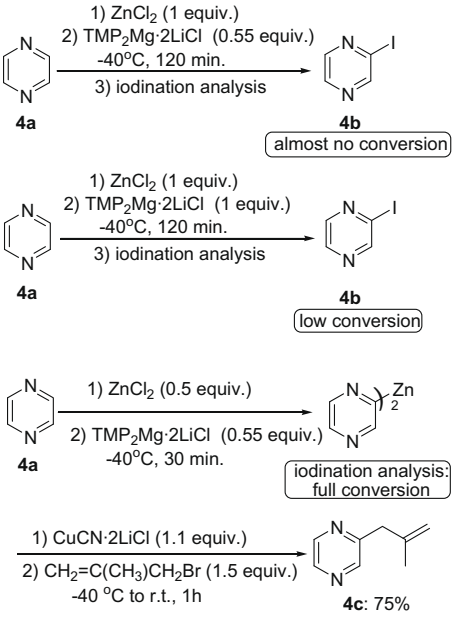
Scheme 1. Functionalization of quinoxaline by using $TMP_2Mg{\cdot}2LiCl$ without $ZnCl_2$.



Scheme 2. Metalation of quinoxaline by using $TMP_2Mg{\cdot}2LiCl$ prior to the addition of $ZnCl_2$.

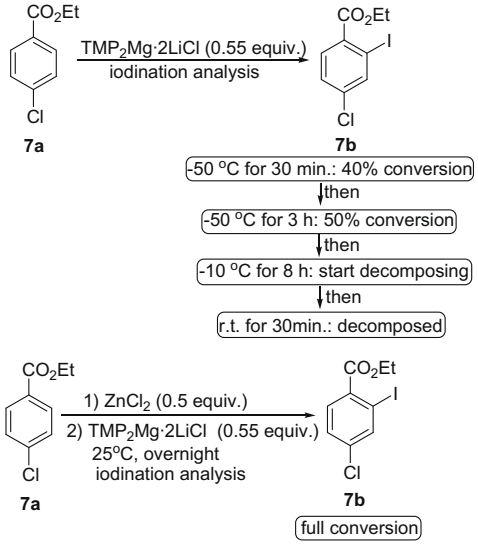


Scheme 3. Functionalization of quinoxaline by using the new protocol.



Scheme 4. Ratio optimization of $ZnCl_2$ to $TMP_2Mg{\cdot}2LiCl$.

We also studied the metalation of the aromatic substrate **7a** (ethyl 4-chlorobenzoate) to make a further illustration of this method. As we can see from Scheme 5, the metalation of **7a** by using the powerful base $TMP_2Mg{\cdot}2LiCl$ under low temperature is relatively slow while the organomagnesium intermediate started



Scheme 5. Metalation of ethyl 4-chlorobenzoate by using $TMP_2Mg{\cdot}2LiCl$ and the new protocol.

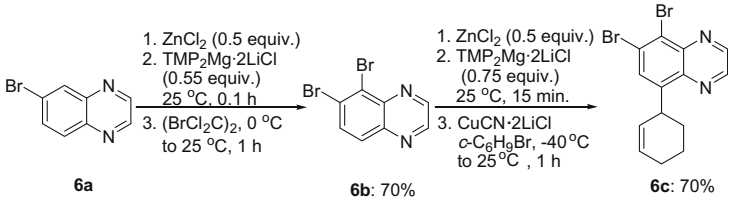
to decompose when the reaction was performed under a higher temperature to accelerate the reaction, this made the metalation of this substrate in a dilemma (Scheme 5). However, by using the new protocol, we can resolve this problem in a smooth way. Thus, by using the optimal reaction condition, the metalation of ethyl 4-chlorobenzoate was accomplished with a full conversion at 25 °C overnight (Scheme 5).

Further, a variety range of functionalized substrates were cleanly *ortho*-deprotonated by using this protocol (Table 1). The zincated quinoxaline **1a** was transmetalated to copper intermediate which further underwent an allylation [20] to give the functionalized product **1b** in 75% yield (entry 1). The metalation of pyrazine **4a** was achieved within 30 min, similarly, a further copper-mediated allylations gave the corresponding functionalized pyrazines in 70–75% yield (entries 3–4, see **4c** in Scheme 4 also). The zincation of 3-bromoquinoline **5a** occurred at position 2 providing, after the reaction with 3-chloroprop-1-enyl-benzene, the corresponding product **5b** in 78% yield (entry 5). In addition, the *ortho*-metalations of the esters **7a**, **8a** and **9a** were accomplished with a full conversion at r.t., and the functionalized ethyl benzoates **7c–d**, **8b** and **9b** were obtained in 70–86% yields after quenching with various electrophiles (entries 6–9).

By using this methodology, a multiple functionalization of heterocycles was also performed under mild condition (Scheme 6). For example, due to the inductive effect of the extra bromine atom in position 6, the metalation of 6-bromoquinoxaline **6a** (up to 8 mmol) was first occurred at position 5, and the dibromide **6b** was obtained in 70% yield by bromination with $(BrCl_2C)_2$. The second metalation occurred at position 8, giving after a copper-mediated allylation the multifunctionalized product **6c** in 70% yield. We also performed the metalation and the subsequent functionalization of **1a** scaled-up to 12 mmol, thus, the zincated quinoxaline underwent a Negishi [21–24] cross-coupling to give the expected product **1c** in 80% yield (Table 1, entry 2). The scaled-up metalation of **1a** and **6a** illustrates this method in a typical practical procedure.

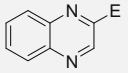
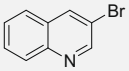
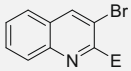
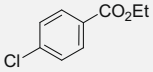
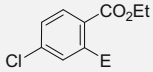
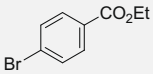
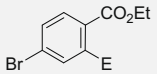
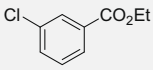
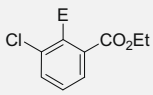
3. Conclusion

In summary, an efficient *ortho*-deprotonation and subsequent functionalization of various sensitive aromatics and heterocycles by using $TMP_2Mg{\cdot}2LiCl$ in the presence of $ZnCl_2$ was demonstrated.



Scheme 6. Multiple functionalization of heterocycles by using the new protocol.

Table 1
Products obtained by direct *ortho*-metalation of the substrates with $TMP_2Mg{\cdot}2LiCl$ at 25 °C in the presence of $ZnCl_2$ (0.5 equiv) followed by the reaction with electrophiles.

Entry	Substrate	*t*(h)	E–X	Products	Yield (%)[a]
					
1	**1a**	2	$CH_2{=}C(CH_3)CH_2Br$	**1b**: E = $CH_2(CH_3)C{=}CH_2$	75[b]
2	**1a**	2	*p*-$IC_6H_4CO_2Et$	**1c**: E = *p*-$C_6H_4CO_2Et$	80[c]
					
3	**4a**	0.5	I_2	**4b**: E = I	71
4	**4a**	0.5	*c*-C_6H_9Br	**4d**: E = *c*-C_6H_9	70[b]
					
5	**5a**	2.5	$PhCH{=}CHCH_2Cl$	**5b**: E = $CH_2CH{=}CHPh$	78[b]
					
6	**7a**	12	PhCOCl	**7c**: E = COPh	86[b]
7	**7a**	12	$(BrCl_2C)_2$	**7d**: E = Br	74
					
8	**8a**	12	$CH_2{=}C(CH_3)CH_2Br$	**8b**: E = $CH_2(CH_3)C{=}CH_2$	70[b]
					
9	**9a**	2.5	I_2	**9b**: E = I	79

[a] Isolated yield of analytically pure product.
[b] A transmetalation CuCN·2LiCl (1.1 equiv) was performed.
[c] Obtained by a palladium-catalyzed cross-coupling.

All the reactions were carried out under mild conditions with good yields. A detailed study concerned on the point how we found the protocol and how we optimized it was depicted. It is noteworthy that this methodology also allows multiple functionalizations of heterocyclic substrates.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. All starting materials were purchased from commercial suppliers and used without further purification unless otherwise stated. THF was continuously refluxed and freshly distilled from Na benzophenone ketyl under N_2. Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^1H NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated.

4.1.1. Bis(2,2,6,6-tetramethylpiperidin-1-yl)magnesium–Bis(lithium chloride): $TMP_2Mg{\cdot}2LiCl$

In an argon-flushed Schlenk flask, 2,2,6,6-tetramethylpiperidine (TMPH) (5.07 mL, 30 mmol) was dissolved in THF (30 mL). This solution was cooled to −40 °C and *n*-BuLi (2.4 M in Hexane, 12.5 mL, 30 mmol) was added dropwise. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated TMPMgCl·LiCl [25,26] (1.0 M in THF, 30 mL, 30 mmol) was then added dropwise to the LiTMP solution and the reaction mixture was stirred at 0 °C for 30 min, warmed to 25 °C and stirred for 1 h. The solvents were then removed *in vacuo* affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring, until the complete dissolution of the salts. The freshly prepared $(TMP)_2Mg{\cdot}2LiCl$ solution was titrated prior to use at 0 °C with benzoic acid using 4-(phenylazo)-diphenylamine as indicator [27]. A concentration of 0.6 M in THF was obtained.

4.1.2. 1 M $ZnCl_2$ solution in THF

A dry and argon-flushed 500-mL Schlenk flask, equipped with a magnetic stirrer and a glass stopper, was charged with $ZnCl_2$

(20.45 g, 150 mmol) and heated to 150 °C under high vacuum for 5 h. After cooling to 25 °C under argon, freshly distilled THF (150 mmol) was added and the mixture was stirred continuously until the salts got dissolved. The reagent $ZnCl_2$ (1 M in THF) appears as a colorless solution.

4.1.3. 1 M CuCN·2LiCl solution in THF

A dry and argon-flushed 50-mL Schlenk flask, equipped with a magnetic stirrer and a glass stopper, was charged with LiCl (848 mg, 20 mmol) and heated to 130 °C under high vacuum for 1 h. After cooling to 25 °C under argon, CuCN (869 mg, 10 mmol) was added under an inert atmosphere inside a glove box. The Schlenk flask was further heated to 140 °C for 5 h under high vacuum and cooled to 25 °C. It was then charged with freshly distilled THF (20 mL) under an argon flush and wrapped with aluminum foil to protect it from light. The mixture was stirred vigorously until all the solid went into solution to furnish 1.0 M CuCN·2LiCl in THF.

4.1.4. Typical procedure for the zincation of polyfunctionalized aromatics and heterocycles with TMP_2Mg·2LiCl (**TP**)

A dry and argon-flushed 25-mL Schlenk flask, equipped with a magnetic stirrer and a septum, the given starting material (1 mmol) was dissolved in THF (2 mL), and $ZnCl_2$ (1 M solution in THF, 0.5 mL, 0.5 mmol) was added. TMP_2Mg·2LiCl (0.6 m in THF, 0.92 mL, 0.55 mmol) was added dropwise and the reaction mixture was stirred at 25 °C for the indicated time. Complete metalation was detected by GC-analysis of reaction aliquots which were quenched with I_2 in dry THF.

4.1.5. 2-(2-Methylallyl)quinoxaline (**1b**) [28]

According to **TP**, the metalation of quinoxaline (**1a**, 260 mg, 2 mmol) was completed within 2 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C overnight. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (pentane:diethyl ether = 5:1) to give **1b** (276 mg, 75%) as a colorless oil. IR (ATR): 3020, 2962, 2922, 1404, 1260, 1085, 1058, 1017, 882, 787, 758, 723, 701, 685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.79 (s, 1H), 8.11–8.03 (m, 2H), 7.79–7.68 (m, 2H), 4.96–4.94 (m, 1H), 4.81–4.80 (m, 1H), 3.76 (s, 2H), 1.81 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.0, 145.9, 142.5, 142.1, 141.2, 130.0, 129.2, 129.2, 129.0, 113.9, 45.2, 22.5. MS (EI, 70 eV): *m/z* (%) = 184 (27) [M^+], 183 (64), 170 (13), 169(100), 168 (17), 144 (32), 102 (11), 76 (11). HRMS (EI): *m/z* calcd for $C_{12}H_{12}N_2$: 184.1000; found: 184.0973.

4.1.6. 4-Quinoxalin-2-yl-benzoic acid ethyl ester (**1c**) [19]

According to **TP**, the metalation of quinoxaline (**1a**, 1560 mg, 12 mmol) was completed within 2 h at 25 °C. A solution of $Pd(dba)_2$ (180 mg) and P(2-fur)$_3$ (150 mg) in THF (12 mL) was added, followed by ethyl 4-iodobenzoate (4968 mg, 18 mmol). The reaction mixture was stirred at 25 °C for 6 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (20 mL), extracted with diethyl ether (3 × 30 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (pentane:diethyl ether = 3:1) to give **1c** (2668 mg, 80%) as a colorless solid. Mp: 88.8–90.9 °C. IR (ATR): 2923, 1713, 1607, 1363, 1271, 1183, 1126, 1099, 1048, 1017, 958, 861, 772, 758, 752, 698, 668, 615 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.39 (s, 1H), 8.33–8.16 (m, 6H), 7.85–7.80 (m, 2H), 4.46 (q, *J* = 7.2 Hz, 2H), 1.47 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 150.7, 143.1, 142.3, 141.8, 131.8, 130.6, 130.3, 130.1, 129.8, 129.2, 127.4, 61.3, 14.4. MS (EI, 70 eV): *m/z* (%) = 279 (15), 278 (74) [M^+], 250 (32), 233 (100), 206 (12), 205 (32), 102 (12), 76 (14). HRMS (EI): *m/z* calcd for $C_{17}H_{14}O_2N_2$: 278.1055; found: 278.1030.

4.1.7. 2-Iodopyrazine (**4b**) [12]

According to **TP**, the metalation of pyrazine (**4a**, 160 mg, 2.0 mmol) was completed within 30 min at 25 °C. Iodine (760 mg, 3 mmol) dissolved in THF (3 mL) was added to the reaction and the reaction mixture was stirred at 25 °C for 1 h and was quenched with aq. sat. NH_4Cl solution (10 mL). After extraction with diethyl ether (3 × 20 mL), the combined organic layers were washed with sat $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (pentane:diethyl ether = 10:1) to give **4b** (293 mg, 71%) as a pale yellow solid. Mp: 90–91 °C, decomposition. IR (ATR): 3433, 2925, 2867, 1503, 1447 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.87 (d, *J* = 1.3 Hz, 1H), 8.51 (d, *J* = 2.8 Hz, 1H), 8.39 (dd, *J* = 1.3, 2.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 118.3, 143.1, 146.1, 153.5. MS (EI, 70 eV): *m/z* (%) = 206 (100) [M^+], 127 (37), 79 (67), 52 (57). HRMS (EI): *m/z* calcd for $C_4H_3N_2I$: 205.9341; found: 205.9350.

4.1.8. 2-(2-Methylallyl)pyrazine (**4c**)

According to **TP**, the metalation of pyrazine (**4a**, 160 mg, 2.0 mmol) was completed within 30 min at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C overnight. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated the solvent (*Caution!* The evaporation should be done carefully since the product is volatile.) The residue was purified by flash chromatography on silica gel (pentane:diethyl ether = 2:1) to give **4c** (200 mg, 75%) as a pale yellow oil. IR (ATR): 2961, 2923, 1401, 1257, 1084, 1056, 1015, 787, 701, 685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.50 (s, 2H), 8.42 (s, 1H), 4.91 (t, *J* = 1.5 Hz, 1H), 4.78 (d, *J* = 0.6 Hz, 1H), 3.54 (s, 2H), 1.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.5, 144.9, 144.1, 142.5, 142.3, 113.68, 44.2, 22.3. MS (EI, 70 eV): *m/z* (%) = 134 (13) [M^+], 133 (87), 119 (100), 94 (45). HRMS (EI): *m/z* calcd for $C_8H_{10}N_2$: 134.0844; found: 134.0831.

4.1.9. 2-(Cyclohex-2-enyl)pyrazine (**4d**)

According to **TP**, the metalation of pyrazine (**4a**, 160 mg, 2.0 mmol) was completed within 30 min at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 2.2 mL, 2.2 mmol) and 3-bromocyclohex-1-ene (483 mg, 3.0 mmol) were added. The mixture was allowed to warm to 25 °C overnight. The reaction mixture was quenched with sat. NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated the solvent (*Caution!* The evaporation should be done carefully since the product is volatile.) The residue was purified by flash chromatography on silica gel (pentane:diethyl ether = 4:1) to give **4d** (224 mg, 70%) as a colorless oil. IR (ATR): 2971, 2934, 1696, 1589, 1567, 1476, 1364, 1210, 1155, 1115, 1082, 1023, 946, 890, 871, 836, 806, 787, 739, 688, 592 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 1.8 Hz, 2 H), 8.35 (d, *J* = 1.8 Hz, 1H), 5.95–5.89 (m, 1H), 5.76–5.70 (m, 1H), 3.60–3.54 (m, 1H), 2.08–2.00 (m, 3H), 1.73–1.64 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6, 144.0, 142.2, 129.7, 127.2, 41.7, 30.2, 24.7, 20.9. MS (EI, 70 eV): *m/z* (%) = 160 (49) [M^+], 159 (48), 145 (32), 132 (30), 131 (100), 119 (16), 118 (14), 94 (44), 79 (15), 77 (11), 67

(10), 53 (10), 52 (12). HRMS (EI): *m/z* calcd for $C_{10}H_{12}N_2$: 160.1000; found: 160.0996.

*4.1.10. 3-Bromo-2-cinnamylquinoline (**5b**)*

According to **TP**, the metalation of 3-bromoquinoline (**5a**, 416 mg, 2 mmol) was completed within 2.5 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 2.2 mL, 2.2 mmol) and 3-chloroprop-1-enyl-benzene (456 mg, 3 mmol) were added. The mixture was allowed to warm to 25 °C and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (pentane:diethyl ether = 80:1) to give **5b** (505 mg, 78%) as a white solid, Mp: 97.6–99.9 °C. IR (ATR): 3022, 2860, 1586, 1486, 1448, 1394, 1298, 1196, 1169, 1141, 1122, 980, 970, 956, 930, 905, 857, 798, 778, 746, 714, 693 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.38 (s, 1H), 8.13 (s, 1H), 7.73 (t, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.38 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 2H), 7.21–7.18 (m, 1H), 6.63–6.54 (m, 2H), 4.13 (d, *J* = 4.8 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.1, 137.3, 128.4, 128.1, 127.2, 126.5, 126.3, 118.4, 41.7. MS (EI, 70 eV): *m/z* (%) = 326 (11), 325 (59), 324 (50), 323 (63) [M^+], 322 (41), 248 (34), 246 (36), 245 (18), 244 (65), 243 (26), 242 (24), 241 (32), 224 (12), 223 (100), 222 (12), 221 (100), 167 (23), 166 (14), 140 (16), 127 (18), 121 (12), 116 (10), 115 (40), 91 (11), 77 (10). HRMS (EI): *m/z* calcd for $C_{18}H_{14}N_1Br_1$: 323.0310; found: 323.0293.

*4.1.11. 5,6-Dibromo-quinoxaline (**6b**) [19]*

According to **TP**, the metalation of 6-bromoquinoxaline (**6a**; 1672 mg, 8 mmol) was completed within 5 min at 25 °C. $BrCl_2CCCl_2Br$ (3900 mg, 12 mmol) was added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 25 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by fast chromatography on silica gel (pentane:diethyl ether = 5:1) to give **6b** (1613 mg, 70%) as a colorless solid. Mp: 182.0–184.3 °C, decomposition. IR (ATR): 3076, 3044, 1591, 1548, 1469, 1430, 1352, 1338, 1188, 1112, 1030, 965, 880, 865, 830, 776, 640, 616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.99 (d, *J* = 1.8 Hz, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.03 (d, *J* = 9 Hz, 1H), 8.00 (d, *J* = 9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 145.4, 142.6, 142.0, 134.5, 129.7, 128.1, 127.1. MS (EI, 70 eV): *m/z* (%) = 290 (50), 289 (10), 288 (100) [M^+], 286 (53), 261 (18), 236 (12), 234 (24), 232 (12). HRMS (EI): *m/z* calcd for $C_8H_6N_2Br_2$: 287.8721; found: 287.8677.

*4.1.12. 5,6-Dibromo-8-(cyclohex-2-enyl)quinoxaline (**6c**)*

According to **TP**, the metalation of 5, 6-dibromoquinoxaline (**6b**, 144 mg, 0.5 mmol) was completed (treated with 0.5 equiv. of $ZnCl_2$ and 0.75 equiv. of TMP_2Mg·2LiCl) within 15 min at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 0.55 mL, 0.55 mmol) and 3-bromocyclohex-1-ene (121 mg, 0.75 mmol) were added. The mixture was allowed to warm to 25 °C and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 10 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (pentane:diethyl ether = 10:1) to give **6c** (128 mg, 70%) as a pale yellow solid. Mp: 140 °C, decomposition. IR (ATR): 2914, 2854, 1580, 1473, 1453, 1444, 1430, 1356, 1294, 1268, 1214, 1130, 1056, 1032, 1021, 981, 947, 880, 862, 728, 705, 681, 659 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 8.94 (d, *J* = 1.8 Hz, 1H), 8.88 (d, *J* = 1.8 Hz, 1H), 7.84 (s, 1H), 6.08–6.05 (m, 1H), 5.73(dd, *J* = 10.2, 2.4 Hz, 1H), 4.72–4.68 (m, 1H), 2.17–2.14 (m, 3H), 1.73–1.66 (m, 2H), 1.58–1.53 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 146.3, 145.5, 144.0, 142.0, 140.7, 132.9, 130.3, 128.5, 128.1, 124.3, 34.7, 31.1, 25.1, 20.7. MS (EI, 70 eV): *m/z* (%) = 370 (50), 369 (32), 368 (100) [M^+], 367 (48), 366 (53), 365 (22), 342 (14), 341 (34), 340 (31), 339 (63), 338 (16), 337 (31), 329 (37), 328 (20), 327 (75), 326 (27), 325 (40), 324 (12), 315 (12), 313 (22), 311 (11), 303 (10), 302 (18), 301 (17), 290 (11), 289 (66), 288 (15), 287 (70), 261 (19), 260 (11), 259 (21), 235 (14), 233 (17), 208 (18), 207 (22), 206 (11), 205 (10), 193 (11), 192 (12), 180 (24), 179 (29), 167 (35), 166 (26), 154 (15), 153 (46), 152 (19), 151 (10), 140 (12), 127 (15), 126 (19), 77 (13), 76 (11), 75 (12), 67 (20). HRMS (EI): *m/z* calcd for $C_{14}H_{14}N_2Br_2$: 367.9347; found: 367.9356.

*4.1.13. Ethyl 2-benzoyl-4-chlorobenzoate (**7c**)*

According to **TP**, the metalation of ethyl 4-chlorobenzoate (**7a**; 369 mg, 2.0 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 2.2 mL, 2.2 mmol) and benzoyl chloride (0.35 mL, 3 mmol) were added. The mixture was allowed to warm to 25 °C and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography silica gel (pentane:diethyl ether = 6:1) to give **7c** (500 mg, 86%) as a yellow solid. Mp: 78.9–80.9 °C. IR (ATR): 2983, 2909, 1712, 1677, 1619, 1590, 1583, 1560, 1490, 1473, 1450, 1445, 1385, 1363, 1319, 1311, 1283, 1267, 1243, 1177, 1153, 1134, 1105, 1089, 1074, 1021, 1001, 979, 966, 954, 942, 899, 875, 860, 843, 815, 808, 780, 770, 712, 698, 690, 643, 619, 609, 591, 585 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1H), 7.77–7.73 (m, 2H), 7.57–7.52 (m, 2H), 7.46–7.41 (m, 2H), 7.36 (d, *J* = 8.4 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.04 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5, 165.2, 143.3, 139.2, 136.7, 133.7, 131.9, 129.9, 129.6, 128.9, 128.0, 127.8, 62.0, 13.8. MS (EI, 70 eV): *m/z* (%) = 288 (24) [M^+], 245 (16), 244 (15), 243 (35), 213 (11), 211 (36), 183 (56), 152 (21), 105 (100), 77 (45), 57 (13). HRMS (EI): *m/z* calcd for $C_{16}H_{13}ClO_3$:288.0553; found: 288.0550.

*4.1.14. Ethyl 2-bromo-4-chlorobenzoate (**7d**)*

According to **TP**, the metalation of ethyl 4-chlorobenzoate (**7a**; 369 mg, 2.0 mmol) was completed within 12 h at 25 °C. $BrCl_2CCCl_2Br$ (974 mg, 3 mmol) was added at 25 °C and the resulting mixture was stirred for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (pentane:diethyl ether = 160:1) to give **7d** (390 mg, 74%) as a semi-solid. IR (ATR): 3089, 2981, 1727, 1582, 1554, 1468, 1366, 1281, 1241, 1100, 1037, 1015, 869, 855, 831, 794, 767, 680, 661 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 8.4, 0.6 Hz, 1 H), 7.65–7.64 (m, 1H), 7.32–7.30 (m, 1H), 4.37 (qd, *J* = 7.2, 0.6 Hz, 2 H), 1.38 (td, *J* = 7.2, 0.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 165.2, 138.0, 134.0, 132.2, 130.6, 127.4, 122.4, 61.8, 14.2. MS (EI, 70 eV): *m/z* (%) = 264 (19), 262 (15) [M^+], 236 (33), 234 (25), 221 (25), 220 (10), 219 (100), 217 (77), 191 (18), 189 (14), 110 (13), 75 (14), 74 (11). HRMS (EI): *m/z* calcd for $C_9H_8O_2Br_1Cl_1$: 261.9396; found: 261.9389.

*4.1.15. Ethyl 4-bromo-2-(2-methylallyl)benzoate (**8b**)*

According to **TP**, the metalation of ethyl 4-bromobenzoate (**8a**; 458 mg, 2.0 mmol) was completed within 12 h at 25 °C. The reaction mixture was cooled to −40 °C, then CuCN·2LiCl (1 m in THF, 2.2 mL, 2.2 mmol) and 3-bromo-2-methylpropene (406 mg,

3.0 mmol) were added. The mixture was allowed to warm to 25 °C and stirred overnight. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL), extracted with diethyl ether (3 × 20 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (pentane:diethyl ether = 160:1) to give **8b** (396 mg, 70%) as a colorless oil. IR (ATR): 3079, 2980, 2937, 1717, 1587, 1561, 1476, 1445, 1390, 1366, 1251, 1131, 1092, 1073, 1019, 888, 864, 835, 770, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (dd, J = 8.7, 0.9 Hz, 1H), 7.43–7.40 (m, 2H), 4.83 (s, 1H), 4.50 (s, 1H), 4.34 (qd, J = 7.2, 0.6 Hz, 2H), 3.70 (s, 2H), 1.75 (s, 3H), 1.38 (td, J = 7.2, 0.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 144.5, 143.1, 134.1, 132.0, 129.5, 129.4, 126.4, 112.1, 61.0, 41.4, 22.8, 14.2. MS (EI, 70 eV): *m/z* (%) = 284 (27), 282 (28) [M^+], 269 (46), 267 (48), 241 (47), 240 (11), 239 (86), 238 (31), 237 (44), 236 (26), 223 (10), 158 (44), 157 (45), 131 (12), 130 (67), 129 (100), 128 (63), 127 (21), 116 (11), 115 (39), 89 (15). HRMS (EI): *m/z* calcd for $C_{13}H_{15}O_2Br_1$: 282.0255; found: 282.0258.

4.1.16. Ethyl 3-chloro-2-(2-methylallyl)benzoate (**9b**) [29]

According to **TP**, the metalation of ethyl 3-chlorobenzoate (**9a**; 369 mg, 2.0 mmol) was completed within 2.5 h at 25 °C. Iodine (760 mg, 3 mmol) dissolved in THF (3 mL) was added to the reaction and the reaction mixture was stirred at 25 °C for 1 h and was quenched with aq. sat. NH_4Cl solution (10 mL). After extraction with diethyl ether (3 × 20 mL), the combined organic layers were washed with sat $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (pentane, and then diethyl ether) to give **9b** as a pale yellow oil (491 mg, 79%). IR (ATR): 2963, 2936, 1725, 1576, 1443, 1400, 1366, 1281, 1254, 1191, 1149, 1129, 1088, 1014, 791, 757, 731 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.56–7.53 (m, 1H), 7.44–7.41 (m, 1H), 7.34–7.31 (m, 1H), 4.40 (qd, J = 7.2, 0.6 Hz, 2H), 1.40 (td, J = 7.2, 0.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 167.4, 140.8, 140.7, 131.2, 129.1, 127.5, 98.0, 62.2, 14.1. MS (EI, 70 eV): *m/z* (%) = 312 (17), 310 (52) [M^+], 282 (27), 265 (100), 110 (32), 75 (35). HRMS (EI): *m/z* calcd for $C_9H_8ClIO_2$: 309.9258; found: 309.9235.

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