Article

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Base-controlled regioselective functionalization of chloro-substituted quinolines

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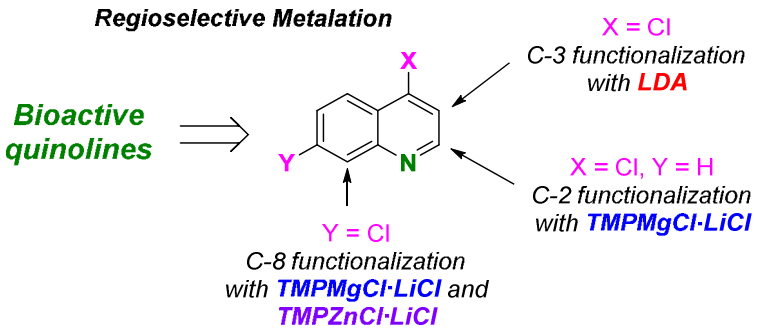


ABSTRACT: We have prepared a number of di- and tri-functionalized quinolines by selective metalation of chloro-substituted quinolines with metal amides followed by reaction with different electrophiles. Metalation of the C-3 position of the quinolinic ring with LDA at -70 ºC is easy to achieve, whereas reaction with lithium-magnesium and lithium-zinc amides affords C-2 or C-8 functionalized derivatives in a regioselective fashion. These complementary methods could be rationalized by DFT calculations and are convenient strategies toward the synthesis of bioactive quinoline derivatives such as chloroquine analogs.

INTRODUCTION

According to recent analyses of the US FDA databases, 59% of approved drugs contain a nitrogen heterocycle.[1] This finding has raised the interest of organic synthesis researchers in obtaining nitrogen heterocycle-bearing molecules with potential biological activity.[1] In this context, quinoline has been one of the most investigated azanaphthalene scaffolds with a view

to preparing bioactive compounds.[2] Due to the importance of quinine, quinolines have historically been highlighted as antimalarial compounds since the 17th century.[3] The quinolinic framework has been related to many other biological activities such as antifungal,[4] anti-tubercular,[5] anticancer,[6] and anti-leishmaniasis actions,[7] and it has been implicated in neurodegenerative diseases[8] as well as other disorders.[9]

In general, substituted quinolines are synthesized by classic cyclization reactions such as Skraup,[10] Friedländer,[11] Doebner-von Miller, Pfitzinger, Conrad-Limpach, and Combes syntheses, among others.[12] Another important strategy to obtain quinolones involves the use of organometallic intermediates[13] generated from metal-halogen exchange[14] or directed metalation reactions.[15] In this scenario, lithium,[16] magnesium,[17] zinc,[18] copper,[19] and aluminum[20] bases have been used to deprotonate quinolines.

Chloro-substituted quinolines are common intermediates in medicinal chemistry,[21] and 4,7-dichloroquinoline is an important substrate to prepare the antimalarial chloroquine[22] as well as other bioactive derivatives.[23] Notably, Knochel and coworkers achieved zincation of the C-8 position of 4,7-dichloroquinoline by using TMPMgCl·LiCl in the presence of $ZnCl_2$.[24] Similarly, Mongin reported C-8 metalation of 1 by using the ate base $(TMP)_2CuLi$, however further benzoylation of the organocopper intermediate gave the product in low yield.[19a]

Over the last years, computational chemistry has been an important tool to rationalize experimental results and to guide experimental planning.[25] Interestingly, DFT calculations performed by Mongin[19a] and us (Figure 1)[26] in THF have indicated that the hydrogen at the C-3 position of 4,7-dichloroquinoline is 100 times more acidic than the hydrogen at the C-8 position of 4,7-dichloroquinoline. Therefore, on the basis of our last results on the selective metalation of aromatic and heteroaromatic substrates with lithium and mixed magnesium-lithium amides,[27] we envisaged that selective metalation of the C-3 position of 4,7-dichloroquinoline could be achieved if we used reactive lithium bases. Despite the absence of the competitive deprotonation site at the C-8 position of 4,7-dichloroquinoline, previous results on direct lithiation of 4-chloroquinoline reported by Quéguiner[16a] corroborated with this proposal.

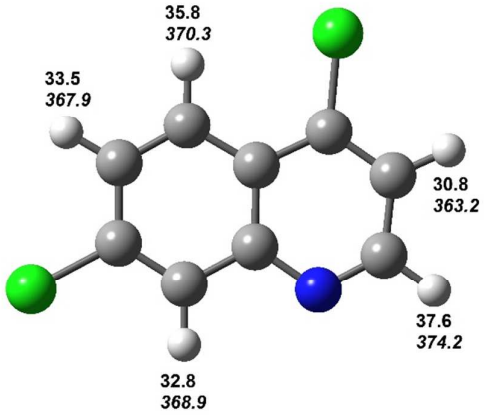
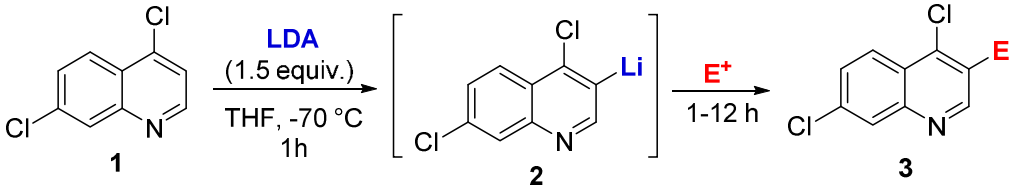


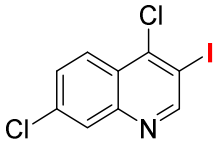
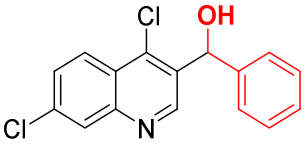
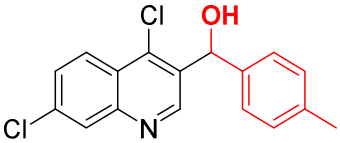
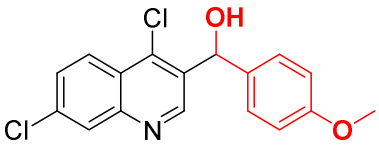
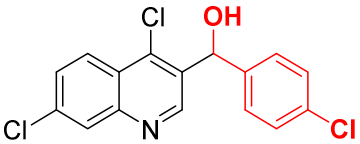
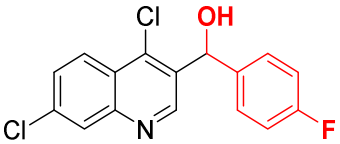
FIGURE 1. 4,7-dichloroquinoline pK_a values (in units of pK_a). Values in italics correspond to the Gibbs energy ($\Delta_{acid}G$) of H atoms in the gas phase.

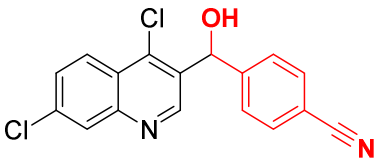
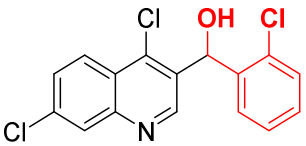
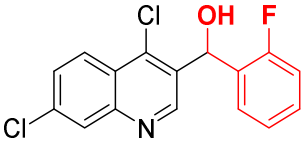
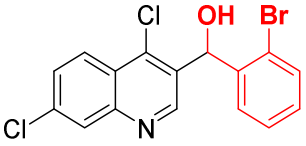
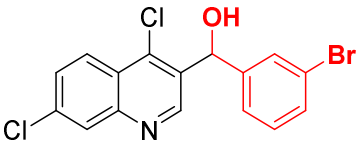
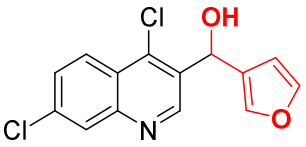
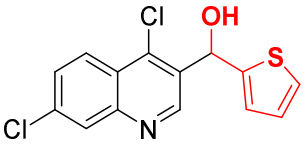
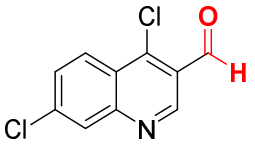
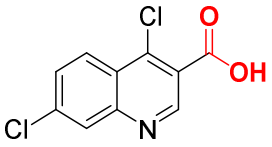
RESULTS AND DISCUSSION

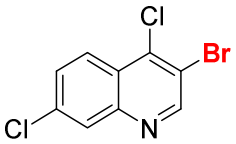
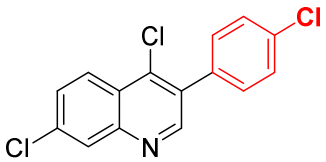
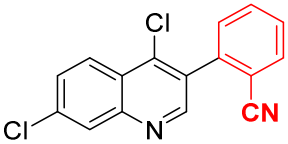
We initiated this work by performing a methodological study with different lithium bases and reaction conditions. Not surprisingly, attempts to lithiate 4,7-dichloroquinoline with *n*-butyllithium (-70 ºC, 1 h) afforded the C-2 butyl-addition derivative as the major product. Moreover, metalation of 4,7-dichloroquinoline with the hindered lithium amide TMPLi (1.1 equiv.) at -70 ºC gave a 1:1 mixture of C-3- and C-8-substituted products after we quenched the reaction with iodine. At -40 ºC, the same reaction provided a complex mixture of products as revealed by GC-MS analysis. To our delight, when we used LDA (1.1 equiv.) as a base at -70 ºC for 1 h, the desired C-3-substituted compound was the exclusive product, obtained in 42% conversion. Further optimization of the reaction conditions allowed full conversion of the starting material into organolithium **2** in the presence of 1.5 equiv. of the base.

TABLE 1. Selective directed lithiation of 4,7-dichloroquinoline (1) followed by reactions with different electrophiles



Entry	Electrophile	Product	Yield (%)
1	I_2	 **3a**	70
2	C_6H_5CHO	 **3b**	73
3	$4\text{-}MeC_6H_4CHO$	 **3c**	75
4	$4\text{-}MeOC_6H_4CHO$	 **3d**	86
5	$4\text{-}ClC_6H_4CHO$	 **3e**	81
6	$4\text{-}FC_6H_4CHO$	 **3f**	72

7	4-CNC_6H_4CHO	 **3g**	87
8	2-ClC_6H_4CHO	 **3h**	67
9	2-FC_6H_4CHO	 **3i**	68
10	2-BrC_6H_4CHO	 **3j**	93
11	3-BrC_6H_4CHO	 **3k**	84
12	3-C_4H_4OCHO	 **3l**	57
13	2-C_4H_4SCHO	 **3m**	93
14	$HCONMe_2$	 **3n**	74
15	CO_2		50

		3o	
16	$C_2Br_2Cl_4$	 **3p**	72
17	4-IC_6H_4Cl	 **3q**[a]	50
18	2-IC_6H_4CN	 **3r**[a]	75

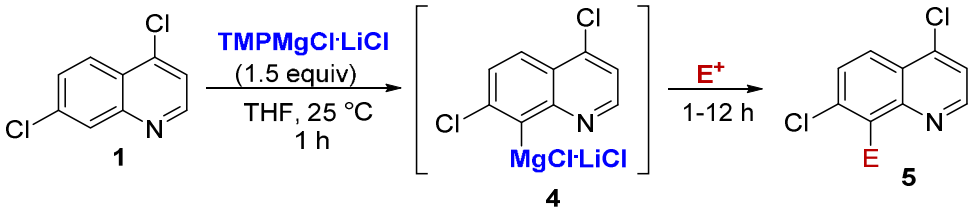
[a] 5 mol% $[Pd(PPh_3)_4]$ after transmetalation with a 1 mol.L^{-1} $ZnCl_2$ solution was used

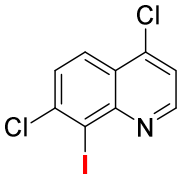
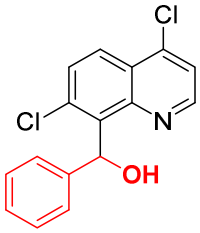
Quenching of organolithium **2** with different electrophiles produced a number of novel C-3-functionalized derivatives of the **3** type in reasonable to excellent yields (Table 1). For example, reaction of organolithium **2** with iodine led to isolation of iodide **3a** in 70% yield (entry 1). Reaction of organolithium **2** with benzaldehyde and its derivatives bearing electron-donating or electron-withdrawing groups at the *ortho*, *meta*, or *para* positions of the aromatic ring afforded diaryl alcohols **3b-k** in yields varying from 67 to 93% (entries 2-11). In turn, reaction of organolithium **2** with furfural or thiophene-2-carbaldehyde generated alcohols **3l** or **3m** in 57 and 93% yields, respectively (entries 12 and 13). Quenching of organolithium **2** with dimethylformamide and carbonic gas gave aldehyde **3n** or carboxylic acid **3o**, respectively (entries 14 and 15). Remarkably, trihalogenated quinoline **3p** was originated in 72% yield after organolithium **2** reacted with 1,2-dibromotetrachloroethane (entry 16).

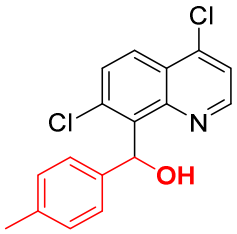
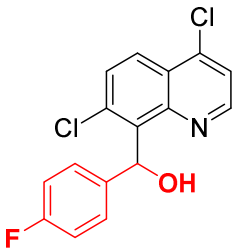
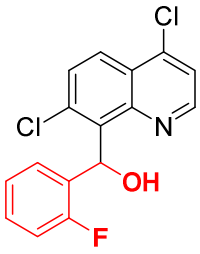
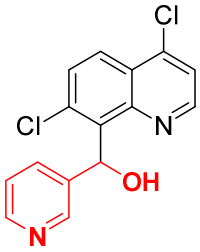
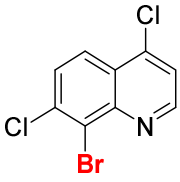
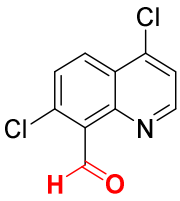
Palladium-catalyzed coupling reactions are among the most important tools to functionalize aromatics and heterocyclic substrates.[28] After transmetalation of organolithium **2** with $ZnCl_2$, Negishi cross-coupling reactions with 1-chloro-4-iodobenzene or 2-iodobenzonitrile in the presence of $[Pd(PPh_3)_4]$ (5 mol%) produced the expected arylated derivatives **3q** or **3r** in 50 and 75% yield, respectively (entries 17 and 18).

Considering our interest in preparing a library of functionalized 4,7-dichloroquinoline derivatives, we also revisited the C-8 metalation of 4,7-dichloroquinoline with mixed metal amides. To investigate the reactivity of the corresponding organomagnesium intermediate against electrophiles and the influence of $ZnCl_2$ on the regioselectivity of 4,7-dichloroquinoline metalation with TMPMgCl·LiCl,[24,29] we first studied the metalation step in the absence of $ZnCl_2$. Albeit slower, reactions with TMPMgCl·LiCl (1.5 equiv, 1 h) were very selective and gave the C-8 substituted products with modest to good yields after we quenched intermediate **4** with different electrophiles (Table 2).

TABLE 2. Selective directed magnesiation of 4,7-dichloroquinoline (1) followed by reactions with different electrophiles

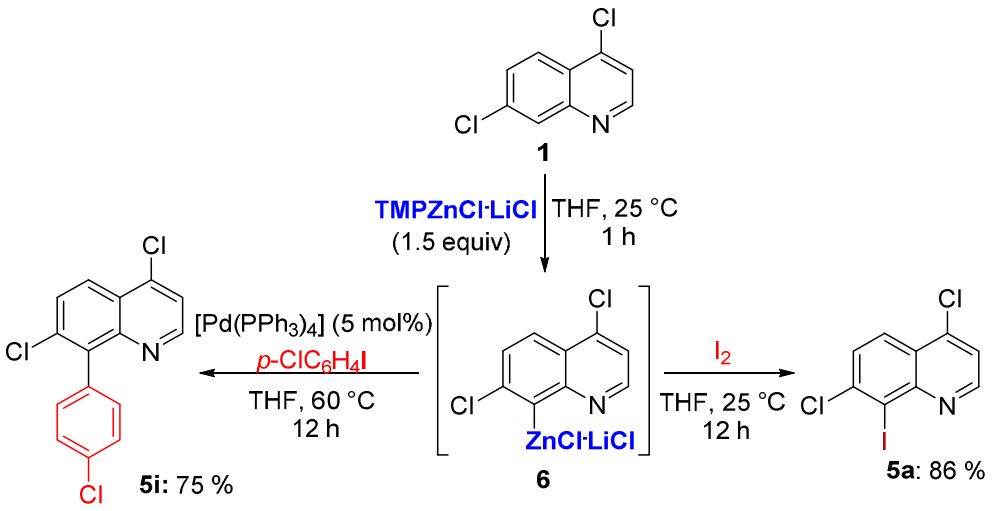


Entry	Reagent	Product	Yield (%)
1	I_2	 **5a**	81
2	C_6H_5CHO	 **5b**	66

3	4-MeC_6H_4CHO	 **5c**	51
4	4-FC_6H_4CHO	 **5d**	57
5	2-FC_6H_4CHO	 **5e**	48
6	3-C_5H_5NCHO	 **5f**	51
7	$C_2Br_2Cl_4$	 **5g**	42
8	$HCONMe_2$	 **5h**	44

Interestingly, we achieved the same selectivity when we used the mixed lithium-zinc base TMPZnCl·LiCl (1.5 equiv, 1 h) at room temperature. Hence, by quenching the reaction with iodine, we isolated 4,7-dichloro-8-iodoquinoline **5a** in 86% yield. Furthermore, palladium-catalyzed coupling of intermediate **6** with 1-chloro-4-iodobenzene afforded the biaryl derivative **5i** in 75% yield (Scheme 1).

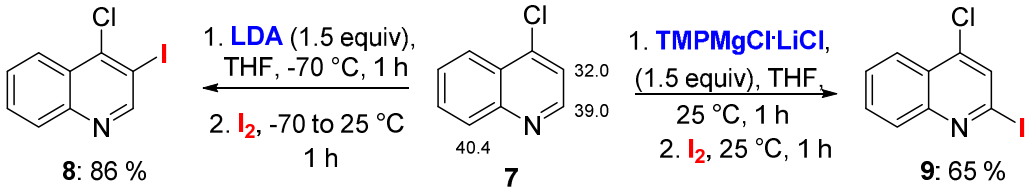
SCHEME 1. C-8 selective functionalization of 4,7-dichloroquinoline (1) with TMPZnCl·LiCl



At this point, preference of the mixed lithium-magnesium and lithium-zinc amides for the C-8 position clearly resulted from pre-coordination of the bases with the nitrogen atom of the 4,7-dichloroquinoline ring. Also, the chloro substituent at the C-7 position acted as directing group, to play a crucial role in reaction selectivity. In fact, DFT calculations showed that the H-8 atom of 4-chloroquinoline (**7**) has pK_a 40.4, so it is less acidic than H-2 (pK_a 39). Bearing this information in mind, we examined metalation of 4-chloroquinoline by using our standard metalation protocols and iodine as electrophile. Whereas lithiation of 4-chloroquinoline with LDA took place at the expected C-3 position (pK_a 32), magnesiation with TMPMgCl·LiCl

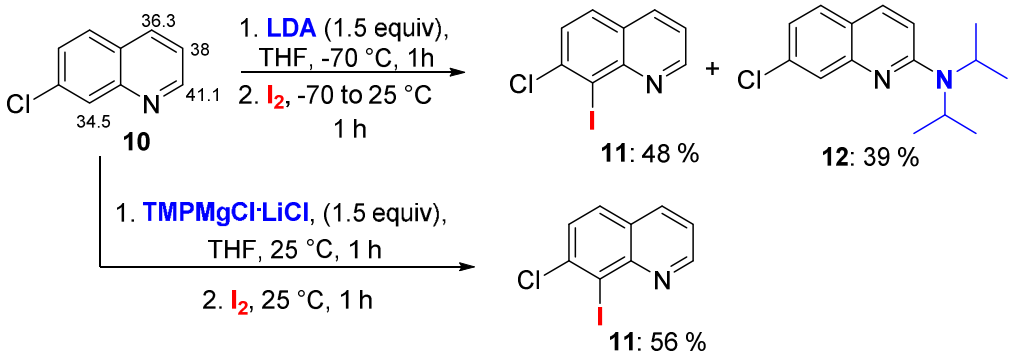
exclusively occurred at the C-2 position, to give iodides **8** and **9** in 86 and 65% yields, respectively (Scheme 2).

SCHEME 2. Regioselective metalations of 4-chloroquinoline (7) with LDA and TMPMgCl·LiCl followed by reaction with iodine



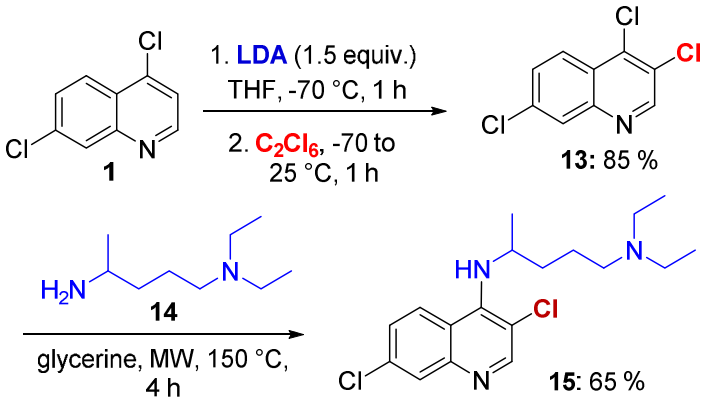
For complete rationalization of the base-controlled functionalization of 4,7-dichloroquinoline, we also investigated metalation of 7-chloroquinoline (**10**) with LDA and TMPMgCl·LiCl. As expected, both reagents deprotonated the most acidic H-8 hydrogen (pK_a 34.5). However, lithiation was accompanied by competitive C-2 nucleophilic addition of the diisopropylamide anion. On the other hand, magnesiation of 7-chloroquinoline was very regioselective, affording the expected iodide **11** in 56% yield (Scheme 3).

SCHEME 3. Regioselective metalations of 7-chloroquinoline (10) with LDA and TMPMgCl·LiCl followed by reaction with iodine



To illustrate the synthetic relevance of the selective functionalization of chloro-substituted quinolines, we evaluated the synthesis of a chloroquine analog. After selective metalation of 4,7-dichloroquinoline with LDA, we quenched the reaction with hexachloroethane, to obtain 3,4,7-trichloroquinoline (**13**) in 85% yield (Scheme 3). According to the literature, chloroquine can be prepared by refluxing 4,7-dichloroquinoline and *N*,*N*-diethylpentane-1,4-diamine (**14**) in phenol under acidic conditions.[30] However, direct adaptation of these conditions to aminate 3,4,7-trichloroquinoline led to a pyrrolidine derivative[31] as the major product. Over the last years, microwave (MW) irradiation has been used as a valuable tool to improve processes.[32] We achieved 3-chloro chloroquine (**15**) in 65% yield when we performed the reaction in a MW reactor using glycerin as green polar solvent (Scheme 4).

SCHEME 4. Synthesis of 3-chloro chloroquine analog.



3-chloro chloroquine analog

CONCLUSION

In summary, we have described the base-controlled regioselective functionalization of chloro-substituted quinolines with metal amides. Selective metalation of 4,7-dichloroquinoline is easily achieved by using LDA at -70 ºC, which affords different C-3 functionalized derivatives after quenching of the reaction with distinct electrophiles. Selective magnesiation or zincation of 4,7-dichloroquinoline with TMPMgCl·LiCl or TMPZnCl·LiCl, respectively, occurs smoothly at room temperature. Further reaction with several electrophiles allows isolation of a number of C-

8-functionalized products. DFT calculations and metalation studies with quinolines **7** and **10** helped to investigate how the chloro substituents influence the acidity of the aromatic hydrogens. Whereas LDA attacks the more acidic hydrogen, metalation with mixed lithium-magnesium and lithium-zinc amides results from pre-coordination with the nitrogen atom of the quinoline ring. Finally, application of the strategy developed herein to synthesize a chloroquine analog illustrates that this approach has potential application in medicinal chemistry. The scope of these methodologies is currently being investigated in our laboratories.

EXPERIMENTAL SECTION

General experimental methods: All solvents were purified according to standard procedures.[33] The starting material, electrophiles, *n*-butyllithium, diisopropylamine and 2,2,6,6-tetramethylpiperidine were purchased from Sigma-Aldrich Corp. All water-sensitive reactions were carried out with dry solvents under anhydrous conditions and nitrogen atmosphere. The transference of the dry solvent and air-sensitive reagents was carried out by means of standard syringe techniques. Reactions were monitored by TLC on Fluka Analytical silica gel (silica gel matrix, with fluorescent indicator 254 nm) by using UV light and gas chromatography on Shimadzu GC-2014 with capillary column (Restek, RTX-1, 30 m × 0,25 mm), nitrogen gas as mobile phase and flame ionization detector. Silica gel (particle size 0.040 – 0.063 mm) from Sigma Aldrich was used as stationary phase for flash column chromatography. NMR analysis were recorded with Bruker DRX 400 and 500 (at 400 and 500 MHz for protons and 100 and 125 MHz for carbon-13, respectively) using chloroform, dimethyl sulfoxide or methanol deuterated solvents. The chemical shifts are reported as δ units in parts per million (ppm) relative to the solvent residual peak as internal reference. IR spectra of the compounds were analyzed using either the IR 400 (PerkinElmer®) spectrophotometer with the attenuated total reflectance device (zinc selenide crystal), from 600 to 4000 cm^{-1} with 4 cm^{-1} resolution or the Perkin-Elmer-mod.1420 in KBr pellets, the frequencies are given in cm^{-1}. High Resolution Mass Spectra were obtained with a Bruker Daltonics micrOTOF QII/ESI-TOF. HPLC preparative purifications were performed in a Shimadzu LC-20AP constituted of two gradient pumps

equipped with a DAD detector. HPLC analysis were carried out on a self-packed column ODS (250 × 50 mm, 5um) (Shimadzu, Japan). Samples elutions were monitored at 254 and 343 nm at gradient 870 mL formic acid 1%, 120 mL acetonitrile and 10 mL isopropyl alcohol. Injected volumes were made via syringes of 0.5 mL with a flow rate of 100–150 mL min^{-1} and room temperature (25 °C). Control of fraction collection and processing chromatographic data were performed on a computer running with a Lab Solution software (Shimadzu, Japan). Microwave irradiation reactions were carried out using a dedicated single-mode microwave reactor (Monowave 300, Anton Paar, Graz Austria) able to provide 850 W maximum continuous microwave power in combination with an efficient magnetic stirring system. The reaction temperature was monitored by an internal fiber-optic temperature probe (ruby thermometer).

Typical Procedure 1 (TP1): Selective lithiation of chloroquinolines followed by reaction with electrophiles: In a dry nitrogen-flushed round-bottom flask under magnetic stirring, LDA was prepared by the slowly addition of *n*-butyllithium (2.35 M in hexanes, 0.75 mmol, 0.32 mL, 1.5 equiv.) to a solution of diisopropylamine (0.82 mmol, 0.11 mL, 1.65 equiv.) in THF (1 mL) at -70°C. After 10 minutes, the reaction mixture was allowed to warm to 0 °C and stirred for 20 minutes at the same temperature. Thus, the reaction flask was cooled to -70 °C and a solution of 4,7-dichloroquinoline (99.0 mg, 0.50 mmol, 1.0 equiv.) or other chloroquinoline (**7** or **10**, 1.0 equiv.) in THF (2.0 mL) was added dropwise to the reaction mixture. After stirring for 60 minutes, a solution of an appropriate electrophile (1.2 equiv.) in THF (1.0 mL) was added and the reaction mixtures was kept under stirring for 1 h (for iodine) and 12 h (other electrophiles). The reaction was quenched with saturated aqueous NH_4Cl, the products were extracted with ethyl acetate (3 × 15 mL), the organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate). Results are presented in table 1.

4,7-dichloro-3-iodoquinoline (3a): Following TP1, 4,7-dichloroquinoline (**1**, 98.0 mg, 0.49 mmol) and iodine (150.8 mg, 0.59 mmol) afforded **3a** (112.8 mg, 70 %) as a white solid after

chromatographic purification with ethyl acetate/hexanes (1:19) as eluent; m.p. 110-112°C; IR (ATR, cm^{-1}): 1545, 1333, 812; ^1H NMR (400MHz, $CDCl_3$) δ 9.10 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 2.0 Hz, 1H), 7.58 (dd, J^3 = 9.0 Hz, J^4 = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 148.1, 146.3, 137.0, 129.7, 129.0, 126.5, 126.2, 95.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_5Cl_2IN$ 323.8838; Found 323.8833.

(4,7-dichloroquinolin-3-yl)(phenyl)metanol (3b): Following TP1, 4,7-dichloroquinoline (**1**, 160.0 mg, 0.81 mmol) and benzaldehyde (0.09 mL, 0.97 mmol) afforded **3b** (179.9 mg, 73 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 165-167 °C; IR (ATR, cm^{-1}): 3077, 1477, 761; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 9.13 (s, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.77 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.35 – 7.32 (m, 2H), 7.27 – 7.23 (m, 1H), 6.53 (d, J = 4.0 Hz, 1H), 6.28 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 151.3, 147.7, 142.8, 138.0, 135.5, 135.0, 128.9, 128.4 (2C), 128.0, 127.5, 126.5 (2C), 126.0, 123.8, 70.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Cl_2NO$ 304.0290; Found 304.0271.

(4,7-dichloroquinolin-3-yl)(4-methylphenyl)methanol (3c): Following TP1, 4,7-dichloroquinoline (**1**, 118.2 mg, 0.60 mmol) and 4-methylbenzaldehyde (0.08 mL, 0.72 mmol) afforded **3c** (142.1 mg, 75 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 157-159 °C; IR (ATR, cm^{-1}): 3121, 1475, 783; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 9.12 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.76 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 6.45 (d, J = 4.3 Hz, 1H), 6.23 (d, J = 4.3 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 151.3, 147.7, 139.8, 137.9, 136.6, 135.7, 134.9, 129.0 (2C), 128.8, 128.0, 126.4 (2C), 126.0, 123.8, 69.9, 20.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}Cl_2NO$: 318.0447; Found 318.0429.

(4,7-dichloroquinolin-3-yl)(4-methoxyphenyl)methanol (3d): Following TP1, 4,7-dichloroquinoline (**1**, 170.0 mg, 0.86 mmol) and 4-methoxybenzaldehyde (0.08 mL, 0.72 mmol) afforded **3d** (246.7 mg, 86 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 125-127 °C; IR (ATR, cm^{-1}): 3131, 1508, 785; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ 9.14 (s, 1H), 8.20 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.76 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.40 (d, J = 4.2 Hz, 1H), 6.21 (d, J = 4.2 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 158.5, 151.2, 147.6, 137.8, 135.7, 134.9, 134.8, 128.8, 128.0, 127.8 (2C), 125.9, 123.8, 113.8 (2C), 69.7, 55.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}Cl_2NO_2$ 334.0396; Found 334.0378.

(4-chlorophenyl)(4,7-dichloroquinolin-3-yl)methanol (3e): Following TP1, 4,7-dichloroquinoline (**1**, 229.1 mg, 1.16 mmol) and 4-chlorobenzaldehyde (195.1 mg, 1.39 mmol) afforded **3e** (317.5 mg, 81 %) as a white solid after cromatoghrafic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 177-178 °C; IR (ATR, cm^{-1}): 3098, 1475, 769; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ 9.09 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.79 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 4.2 Hz, 1H), 6.27 (d, J = 4.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 151.2, 147.8, 141.7, 138.2, 135.1, 135.0, 132.1, 129.0, 128.4 (2C), 128.4 (2C), 128.0, 126.0, 123.6, 69.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}Cl_3NO$ 337.9901; Found 337.9892.

(4,7-dichloroquinolin-8-yl)(4-fluorophenyl)metanol (3f): Following TP1, 4,7-dichloroquinoline (**1**, 129.0 mg, 0.65 mmol) and 4-fluororobenzaldehyde (0.08 mL, 0.79 mmol) afforded **3f** (150.3 mg, 72 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 196-198 °C; IR (ATR, cm^{-1}): 3077, 1504, 795; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ 9.12 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.78 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.79 – 7.77 (m, 2H), 7.18 – 7.14 (m, 2 H), 6.57 (d, J = 4.2 Hz, 1H), 6.27 (d, J = 4.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 161.4 (d, J = 243.3 Hz,

1C), 151.2, 147.8, 139.0 (d, J = 2.1 Hz, 1C), 138.1, 135.3, 135.0, 128.9, 128.6 (d, J = 8.2 Hz, 2C), 128.0, 126.0, 123.8, 115.2 (d, J = 21.3 Hz, 2C), 69.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}Cl_2FNO$ 322.0196; Found 322.0177.

4-((4,7-dichloroquinolin-3-yl)(hydroxy)methyl)benzonitrile (3g): Following TP1, 4,7-dichloroquinoline (**1**, 125.8 mg, 0.63 mmol) and 4-formylbenzonitrile (99.9 mg, 0.76 mmol) afforded **3g** (182.0 mg, 87 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 182-184 °C; IR (ATR, cm^{-1}): 3061, 2228, 785; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 9.06 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 2.0 Hz, 1H); 7.82 – 7.78 (m, 3H), 7.65 (d, J = 8.3 Hz, 2H), 6.78 (d, J = 4.3 Hz, 1H), 6.35 (d, J = 4.3 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 151.2, 148.1, 147.8, 138.5, 135.2, 134.5, 132.5 (2C), 129.0, 128.0, 127.4 (2C), 126.1, 123.8, 118.7, 110.3, 69.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{11}Cl_2N_2O$ 329.0243; Found 329.0239.

(2-chlorophenyl)(4,7-dichloroquinolin-3-yl)methanol (3h): Following TP1, 4,7-dichloroquinoline (**1**, 114.0 mg, 0.57 mmol) and 2-chlorobenzaldehyde (0.08 mL, 0.69 mmol) afforded **3h** (130.5 mg, 67 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 175-176 °C; IR (ATR, cm^{-1}): 3139, 1474, 820; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 8.81 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.80 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.65 (dd, J^3 = 7.6 Hz, J^4 = 1.5 Hz 1H), 7.43 (ddd, J^3 = 8.1 Hz, J^3 = 7.7 Hz, J^4 = 3.0 Hz, 2H), 7.35 (td, J^3 = 7.5 Hz, J^4 = 1.7 Hz, 1H), 6.62 (d, J = 4.9 Hz, 1H), 6.47 (d, J = 4.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 151.3, 147.8, 139.7, 139.6, 135.3, 133.5, 131.9, 129.5 (2C), 129.0, 128.8, 128.0, 127.4, 126.1, 124.0, 67.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}Cl_3NO$ 337.9901; Found 337.9890.

(4,7-dichloroquinolin-3-yl)(2-fluorophenyl)methanol (3i): Following TP1, 4,7-dichloroquinoline (**1**, 228.0 mg, 1.15 mmol) and 2-fluorobenzaldehyde (0.12 mL, 1.38 mmol) afforded **3i** (252.0 mg, 68 %) as a white solid after chromatographic purification with ethyl

acetate/hexanes (1:4) as eluent; m.p. 197-199 °C; IR (ATR, cm^{-1}): 3114, 1487, 755; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 9.09 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.78 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.55 (td, J^3 = 7.7 Hz, J^4 = 1.6 Hz, 1H), 7.36 – 7.33 (m, 1H), 7.22 (td, J^3 = 7.5 Hz, J^4 = 1.0 Hz, 1H), 7.18 – 7.13 (m, 1H), 6.62 (d, J = 4.6 Hz, 1H), 6.45 (d, J = 4.6 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 159.5 (d, J = 245.8 Hz, 1C), 151.3, 147.8, 138.4, 135.1, 134.1, 129.8 (d, J = 8.2 Hz, 1C), 129.4 (d, J = 13.4 Hz, 1C), 128.9, 128.8 (d, J = 4.0 Hz, 1C), 128.0, 126.0, 124.6 (d, J = 3.2 Hz, 1C), 123.9, 115.4 (d, J = 21.3 Hz, 1C), 64.9 (d, J = 2.8 Hz, 1C). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}Cl_2FNO$ 322.0196; Found 322.0183.

(2-bromophenyl)(4,7-dichloroquinolin-3-yl)methanol (3j): Following TP1, 4,7-dichloroquinoline (**1**, 153.9 mg, 0.78 mmol) and 2-bromobenzaldehyde (0.11 mL, 0.93 mmol) afforded **3j** (276.5 mg, 93 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 176-178 °C; IR (ATR, cm^{-1}): 3105, 1470, 752; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 8.76 (s, 1H), 8.26 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.80 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.64-7.61 (m, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.28 (td, J^3 = 7.6 Hz, J^4 = 1.5 Hz, 1H), 6.62 (d, J = 5.1 Hz, 1H), 6.40 (d, J = 5.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 151.2, 147.9, 141.1, 140.1, 135.3, 133.4, 132.8, 129.8, 129.1, 129.0, 128.0, 127.9, 126.1, 124.0, 122.4, 69.8. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}BrCl_2NO$ 381.9396; Found 381.9381.

(3-bromophenyl)(4,7-dichloroquinolin-3-yl)methanol (3k): Following TP1, 4,7-dichloroquinoline (**1**, 107.0 mg, 0.54 mmol) and 3-bromobenzaldehyde (0.08 mL, 0.65 mmol) afforded **3k** (172.5 mg, 84 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; yield; m.p. 153-155 °C; IR (ATR, cm^{-1}): 3134, 1557, 763; ^1H NMR (400 MHz, DMSO-$_{d6}$) δ 9.10 (s, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.77 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.66 (aps, 1H), 7.47 – 7.45 (m, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 4.3 Hz, 1H), 6.27 (d, J = 4.3 Hz, 1H). ^{13}C NMR (100

MHz, DMSO-$_{d6}$) δ 151.2, 147.8, 145.5, 138.3, 135.1, 134.8, 130.7, 130.4, 129.1, 128.9, 128.0, 126.0, 125.6, 123.8, 121.8, 69.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}BrCl_2NO$ 381.9396; Found 381.9382.

(4,7-dichloroquinolin-3-yl)(furan-3-yl)methanol (3l): Following TP1, 4,7-dichloroquinoline (**1**, 557.0 mg, 2.81 mmol) and furan-3-carbaldehyde (0.30 mL, 3.37 mmol) afforded **3l** (471.1 mg, 57 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 149-151 °C; IR (ATR, cm^{-1}): 3141, 1557,784; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ 9.14 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.78 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.59 (apd, J = 1.4 Hz, 2H), 6.49 (apt, J = 1.4 Hz, 1H), 6.36 (s, 1H), 6.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ151.1, 147.8, 143.7 (2C), 139.7, 137.7, 134.9, 128.8, 128.0, 127.6, 126.0, 123.8, 109.2, 63.6. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{10}Cl_2NO_2$ 294.0083; Found 294.0087.

(4,7-dichloroquinolin-3-yl)(thiophen-2-yl)methanol (3m): Following TP1, 4,7-dichloroquinoline (**1**, 143.0 mg, 0.72 mmol) and thiophene-2-carbaldehyde (0.10 mL, 1.07 mmol) afforded **3m** (208.3 mg, 93 %) as a pale yellow solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 155-157 °C; IR (ATR, cm^{-1}): 3123, 1591, 778; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ 9.14 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.79 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.48 – 7.46 (m, 1H), 6.95 (d, J = 3.5 Hz, 2H), 6.85 (d, J = 4.5 Hz, 1H), 6.49 (d, J = 4.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 150.8, 147.8, 146.9, 138.0, 135.2, 135.0, 129.0, 128.0, 126.8, 126.1, 125.8, 124.6, 123.8, 66.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{10}Cl_2NOS$ 309.9855; Found 309.9846.

4,7-dichloroquinoline-3-carbaldehyde (3n): Following TP1, 4,7-dichloroquinoline (**1**, 166.0 mg, 0.84 mmol) and *N*,*N*-dimethylformamide (0.08 mL, 1.00 mmol) afforded **3n** (140.6 mg, 74 %) as a pale yellow solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 118-120 °C; IR (ATR, cm^{-1}): 2879, 1694, 1551, 770; ^{1}H NMR (400 MHz, $CDCl_3$) δ

10.68 (s, 1H), 9.26 (s, 1H), 8.33 (d, J = 9.0 Hz, 1H), 8.16 (d, J = 2.1 Hz, 1H), 7.69 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 151.3, 150.0, 148.1, 139.8, 129.9, 129.4, 126.6, 124.6, 124.3. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_6Cl_2NO$ 225.9821; Found 225.9809.

4,7-dichloroquinoline-3-carboxylic acid (3o): Following TP1, 4,7-dichloroquinoline (**1**, 118.0 mg, 0.60 mmol) and carbono dioxide (excess) afforded **3o** (73.0 mg, 50 %) as a pale yellow solid after an acid-base extraction as purification method; m.p. 271-273 °C; IR (ATR, cm^{-1}): 3071, 1611, 1457, 794; ^{1}H NMR (400 MHz, DMSO-$_{d6}$) δ 13.80 (s, 1H), 8.88 (s, 1H), 8.26 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.61 (dd, J^3 = 8.7 Hz, J^4 = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-$_{d6}$) δ 177.9, 166.1, 145.8, 140.3, 138.4, 127.3, 126.6, 123.2, 118.9, 108.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_6Cl_2NO_2$ 241.9770; Found 241.9783.

3-bromo-4,7-dichloroquinoline (3p): Following TP1, 4,7-dichloroquinoline (**1**, 155.3 mg, 0.78 mmol) and 1,2-dibromotetrachloroethane (306.4 mg, 0.94 mmol) afforded **3p** (155.7 mg, 72 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:49) as eluent; m.p. 105-107 °C; IR (ATR, cm^{-1}): 1550, 1332, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.16 (d, J = 9.0 Hz, 1H), 8.08 (d, J = 2.1 Hz, 1H), 7.60 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 147.7, 141.7, 136.7, 129.7, 129.0, 126.0, 126.0, 118.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ calcd for $C_9H_5BrCl_2N$ 275.8977; Found 275.8970.

4-chloro-3-iodoquinoline (8): Following TP1, 4-chloroquinoline (**7**, 81.8 mg, 0.50 mmol) and iodine (149.2 mg, 0.59 mmol) afforded **8** (140.0 mg, 86 %) as a white solid after chromatorgraphic purification with ethyl acetate/hexanes (1:49) as eluent; m.p. 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 8.26 (dd, J^3 = 8.5 Hz, J^4 = 1.2 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.76 (ddd, J^3 = 8.4 Hz, J^3 = 7.7 Hz J^4 = 1.2 Hz, 1H), 7.65 (ddd, J^3 = 8.4 Hz, J^3 = 7.7 Hz J^4 = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 147.8, 146.2, 130.7, 130.0, 128.6,

127.7, 125.0, 95.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for C_9H_6ClIN 289.9228; Found 289.9230.

7-chloro-8-iodoquinoline (11): Following TP1, 7-chloroquinoline (**10**, 174.1 mg, 1.06 mmol) and iodine (324.3 mg, 1.28 mmol) afforded **11** (148.8 mg, 48 %) as a pale yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 73-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (dd, J^3 = 4.3 Hz, J^4 = 1.7 Hz, 1H), 8.10 (dd, J^3 = 8.2 Hz, J^4 = 1.7 Hz, 1H), 7.73 (d, J^3 = 8.7 Hz, 1H), 7.59 (d, J^3 = 8.7 Hz, 1H), 7.44 (dd, J^3 = 8.2 Hz, J^3 = 4.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 148.9, 141.5, 136.7, 129.2, 127.9, 126.7, 121.9, 107.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for C_9H_6ClIN 289.9228; Found 289.9218.

7-chloro-*N*,*N*-diisopropylquinolin-2-amine (12): Following TP1, 7-chloroquinoline (**10**, 174.1 mg, 1.06 mmol) and iodine (324.3 mg, 1.28 mmol) afforded **12** (109.0 mg, 39 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 51-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 9.3 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.08 (dd, J^3 = 8.5 Hz, J^4 = 2.1 Hz, 1H), 6.87 (d, J = 9.3 Hz, 1H), 4.39 (hept, J = 6.6 Hz, 2H), 1.39 (d, J = 6.6 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 149.0, 135.8, 134.8, 128.3, 125.6, 122.0, 120.8, 112.0, 46.2, 21.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}ClN_2$ 263.1310; Found 263.1302.

3,4,7-trichloroquinoline (13): Following TP1, 4,7-dichloroquinoline (**1**, 355.0 mg, 1.79 mmol) and hexachloroethane (480.0mg, 2.02 mmol) afforded **13** (352.9 mg, 85 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:49) as eluent; m.p. 115-116 °C; IR (ATR, cm^{-1}): 1548, 1331, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.53 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 147.3, 139.4, 136.5, 129.7, 129.0, 127.7, 125.7, 125.5. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_5Cl_3N$ 231.9482; Found 231.9474.

Typical Procedure 2 (TP2): Selective lithiation of chloroquinolines followed by Negishi cross coupling reaction: After the lithiation step (according to TP1), the temperature was warmed at -40 °C and $ZnCl_2$ (1.0 M in THF, 1.65 equiv.) was added dropwise to the reaction mixture which was kept first at -40°C for 20 min. Thus, 1 mL of a THF solution of $[Pd(PPh_3)_4]$ (5 mol%) and 1 mL of a THF solution of appropriate electrophile (1.2 equiv.) were added and the reaction mixture was kept under stirring for 12 hours at 60°C. The reaction was quenched with saturated aqueous NH_4Cl, the products were extracted with ethyl acetate (3 x 15 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed under reduction pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate). Results are presented in table 1.

4,7-dichloro-3-(4-chlorophenyl)quinoline (3q): Following TP2, 4,7-dichloroquinoline (**1**, 207.0 mg, 1.04 mmol) and 1-chloro-4-iodobenzene (299.1 mg, 1.25 mmol) afforded **3q** (160.4 mg, 50 %) as a needle crystalline solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 167-169 °C; IR (ATR, cm^{-1}): 1496, 1340, 817; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.64 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.52 – 7.46 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 148.6, 140.1, 136.6, 135.0, 134.4, 132.4, 131.3 (2C), 129.3, 129.0 (2C), 128.8, 126.3, 125.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_9Cl_3N$ 307.9795; Found 307.9781.

2-(4,7-dichloroquinolin-3-yl)benzonitrile (3r): Following TP2, 4,7-dichloroquinoline (**1**, 523.0 mg, 2.64 mmol) and 2-iodobenzonitrile (725.7 mg, 3.17 mmol) afforded **3r** (597.0 mg, 75 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:4) as eluent; m.p. 133-135 °C; IR (ATR, cm^{-1}): 2234, 1545, 1338, 766; ^1H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 8.29 (d, J = 9.1 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 7.86 (dd, J^3 = 7.8 Hz, J^4 = 0.9 Hz, 1H), 7.76 (td, J^3 = 7.7 Hz, J^4 = 1.3Hz, 1H), 7.67 (dd, J^3 = 9.1 Hz, J^4 = 2.1 Hz, 1H), 7.61 (td, J^3 = 7.7 Hz, J^4 = 1.3 Hz, 1H), 7.54 (dd, J^3 = 7.8 Hz, J^4 = 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 149.2, 141.5, 139.7, 137.3, 133.4, 133.0, 131.2, 130.5, 129.5, 129.3, 129.0,

126.4, 124.7, 117.4, 113.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_9Cl_2N_2$ 299.0137; Found 299.0123.

Typical Procedure 3 (TP3): Preparation of TMPMgCl·LiCl in THF: A dry and nitrogen-flushed Schlenk flask equipped with a magnetic stirring bar and rubber septum was charged with *i*-PrMgCl·LiCl (1.0 M in THF, 20 mL 20 mmol). Then, 2,2,6,6-tetramethylpiperidine (3.52 mL, 21 mmol) was added dropwise through a syringe within 5 min. The mixture was stirred until the gas evolution ceased (24-48 h). Titration against benzoic acid in THF (0 °C) in the presence of 4-(phenylazo)diphenylamine as the indicator showed that the base concentration ranged from 0.90 to 0.98 M.

Typical Procedure 4 (TP4): Selective magnesiation of chloroquinolines followed by reaction with electrophiles: In a dry nitrogen-flushed round-bottom flask under magnetic stirring containing 2 mL of THF and 4,7-dichloroquinoline (**1**, 99.0 mg, 0.50 mmol) or other chloroquinoline (**7** or **10**, 1.0 equiv.), it was added dropwise a THF solution of TMPMgCl·LiCl (1.0 M, 0.75 mmol, 0.75 mL) to the reaction mixture. After stirring at 60 minutes, a solution of an appropriate electrophile (1.2 equiv.) in THF (1.0 mL) was added and the reaction mixtures was kept under stirring for 1 h (for iodine) to 12 h (other electrophiles). The reaction was quenched with saturated aqueous NH_4Cl, the products were extracted with ethyl acetate (3 × 15 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed under reduction pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate). Results are presented in table 2.

4,7-dichloro-8-iodoquinoline (5a): Following TP4, 4,7-dichloroquinoline (**1**, 65.0 mg, 0.33 mmol) and iodine (99.9 mg 0.39 mmol) afforded **5a** (80.7 mg, 81 %) as a white solid after purification with ethyl acetate/hexanes (1:19) as eluent; m.p. 139-141 °C; IR (ATR, cm^{-1}): 1475, 1388, 724; ^1H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 4.7 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 149.6,

143.0, 142.9, 128.7, 125.6, 124.9, 121.9, 108.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_5Cl_2IN$ 323.8838; Found 323.8847.

(4,7-dichloroquinolin-8-yl)(phenyl)methanol (5b): Following TP4, 4,7-dichloroquinoline (**1**) (200.0 mg, 1.0098 mmol) and benzaldehyde (0.12 mL, 1.21 mmol) afforded **5b** (201.9 mg, 66 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 116-118 °C; IR (ATR, cm^{-1}): 3334, 1481, 810; ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 1H), 8.06 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 7.50 (d, J = 11.2 Hz, 1H), 7.42 (d, J = 4.8 Hz, 1H), 7.38 – 7.36 (m, 2H), 7.21 – 7.16 (m, 2H), 7.13 – 7.10 (m, 1H), 6.60 (d, J = 11.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 148.1, 144.1, 144.0, 137.1, 135.6, 129.8, 128.3 (2C), 127.2, 126.4, 126.3 (2C), 124.7, 121.6, 74.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{12}Cl_2NO$ 304.0290; Found 304.0282.

(4,7-dichloroquinolin-8-yl)(4-methylphenyl)methanol (5c): Following TP4, 4,7-dichloroquinoline (**1**, 159.0 mg, 0.80 mmol) and 4-methylbenzaldehyde (0.11 mL, 0.96 mmol) afforded **5c** (129.2 mg, 51 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 132-134 °C; IR (ATR, cm^{-1}): 3246, 1485, 829; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.8 Hz, 1H), 8.10 (d, J = 9.1 Hz, 1H), 7.64 (d, J = 9.1 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 7.06 (d, J = 8.1 Hz, 2H), 6.63 (s, 1H), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.1, 144.0, 137.2, 136.8, 135.5, 129.7, 129.0 (2C), 126.3, 126.3 (2C), 124.5, 121.5, 74.3, 21.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{14}Cl_2NO$ 318.0447; Found 318.0431.

(4,7-dichloroquinolin-8-yl)(4-fluorophenyl)methanol (5d): Following TP4, 4,7-dichloroquinoline (**1**, 152.0 mg, 0.77 mmol) and 4-fluorobenzaldehyde (0.10 mL, 0.92 mmol) afforded **5d** (141.0 mg, 57 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 103-105 °C; IR (ATR, cm^{-1}): 3266, 1595845; ^1H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 4.8 Hz, 1H), 8.14 (d, J = 9.1 Hz, 1H), 7.67 (d, J = 9.1 Hz, 1H),

7.60 (d, J = 10.4 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.42 – 7.39 (m, 2H), 6.96 – 6.91 (m, 2H), 6.62 (d, J = 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 245.1 Hz, 1C), 148.8, 148.0, 144.2, 139.7, 136.8, 135.6, 129.8, 128.0 (d, J = 8.0 Hz, 1C), 126.4, 124.8, 121.7, 115.1 (d, J = 21.3 Hz, 1C), 73.9. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}Cl_2FNO$ 322.0196; Found 322.0166.

(4,7-dichloroquinolin-8-yl)(2-fluorophenyl)methanol (5e): Following TP4, 4,7-dichloroquinoline (**1**, 130.0 mg, 0.66 mmol) and 2-fluorobenzaldehyde (0.08 mL, 0.79 mmol) afforded **5e** (100.6 mg, 48 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 119-121 °C; IR (ATR, cm^{-1}): 3246, 1485, 808; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 4.8 Hz, 1H), 8.16 (d, J = 9.1 Hz, 1H), 7.93 – 7.91 (m, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.55 (d, J = 4.8 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.06 – 7.01 (m, 1H), 6.98 – 6.94 (m, 1H), 6.92 – 6.90 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (d, J = 248.6 Hz, 1C), 148.6, 144.2, 136.0, 135.5, 130.5, 130.4, 130.0, 129.3 (d, J = 8.4 Hz, 1C), 129.0, 126.2, 124.8, 123.8, 121.6, 115.8 (d, J = 21.7 Hz, 1C), 69.7. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{11}Cl_2FNO$ 322.0196; Found 322.0192.

(4,7-dichloroquinolin-8-yl)(pyridin-3-yl)methanol (5f): Following TP4, 4,7-dichloroquinoline (**1**, 114.0 mg, 0.57 mmol) and 3-pyridinecarboxaldehyde (0.06 mL, 0.69 mmol) afforded **5f** (89.3 mg, 51 %) as a brown solid after cromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 123-125 °C; IR (ATR, cm^{-1}): 2924, 1576, 815; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 – 8.65 (m, 2H), 8.44 (dd, J^3 = 4.7 Hz, J^4 = 1.2 Hz, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.69 (d, J = 9.1 Hz, 1H), 7.61 (d, J = 11.1 Hz, 1H), 7.53 (J = 4.8 Hz, 1H), 7.22 – 7.18 (m, 1H), 6.70 (d, J = 11.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 148.4, 147.9, 147.7, 144,2, 139.3, 135.8, 135.5, 133.9, 129.6, 126.3, 125.1, 123.1, 121.7, 72.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{11}Cl_2N_2O$ 305.0243; Found 305.0233.

8-bromo-4,7-dichloroquinoline (5g): Following TP4, 4,7-dichloroquinoline (**1**,171.0 mg, 0.86 mmol) and 1,2-dibromotetrachloroethane (337.3 mg, 1.04 mmol) afforded **5g** (101.0 mg, 42 %) as a yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 125-127 °C; IR (KBr): 1528, 1322, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 4.7 Hz, 1H), 8.16 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 147.5, 143.3, 138.1, 129.3, 126.0, 125.4, 124.4, 122.1. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_9H_5BrCl_2N$ 275.8977; Found 275.8962.

4,7-dichloroquinoline-8-carbaldehyde (5h): Following TP4, 4,7-dichloroquinoline (**1**, 166.0 mg, 0.84 mmol) and *N*,*N*-dimethylformamide (0.08 mL, 1.00 mmol) afforded **5h** (83.0 mg, 44 %) as yellow solid after chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 158-160 °C; IR (ATR, cm^{-1}): 3061, 1688, 1552, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.27 (s, 1H), 8.89 (d, J = 4.7 Hz, 1H), 8.35 (d, J = 9.1 Hz, 1H), 7.70 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 4.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 148.6, 142.9, 138.4, 135.9, 135.0, 134.2, 132.1 (2C), 129.3, 128.5 (2C), 125.6, 125.0, 121.4. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_6Cl_2NO$ 225.9821; Found 225.9811.

4-chloro-2-iodoquinoline (9): Following TP4, 4-chloroquinoline (**10**, 355.0 mg, 1.79 mmol) and hexachloroethane (480.0mg, 2.02 mmol) afforded **9** (352.9 mg, 85 %) as a white solid after chromatographic purification with ethyl acetate/hexanes (1:12) as eluent; m.p. 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.76 (s, 1H), 7.69 (ddd, J^3 = 7.6 Hz, J^3 = 7.6 Hz J^4 = 1.3 Hz, 1H), 7.58 (ddd, J^3 = 7.6 Hz, J^3 = 7.6 Hz J^4 = 1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 142.6, 131.4, 131.3, 129.3, 128.1, 125.7, 124.5, 117.0. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for C_9H_6ClIN 289.9228; Found 289.9229.

7-chloro-8-iodoquinoline (11): Following TP4, 7-chloroquinoline (**10**, 128.0 mg, 0.78 mmol) and iodine (237.7 mg, 0.94 mmol) afforded **11** (127.0 mg, 56 %) as a pale yellow solid after

chromatographic purification with ethyl acetate/hexanes (1:9) as eluent; m.p. 73-74 °C; spectroscopic data were reported previously.

Typical Procedure 5 (TP5): Selective zincation of 4,7-dichloroquinoline using TMPZnCl·LiCl: In a dry nitrogen-flushed round-bottom flask under magnetic stirring containing 1 mL of THF and 2,2,6,6-tetramethylpiperidine (0.82 mmol, 0.14 mL) at -70 °C, it was added dropwise *n*-butyllithium (2.35 M in hexanes, 0.75 mmol, 0.32 mL). After 10 minutes, the reaction mixture was allowed to warm to 0 °C and stirred for 20 minutes at the same temperature. Thus, the system was cooled to -40 °C and $ZnCl_2$ (1.0 M in THF, 0.75 mmol, 0.75 mL) was added dropwise to the reaction mixture which was kept first at -40 °C for 10 min, after at 0 °C for 10 min and, finally, the reaction was allowed to warm to 25 °C and stirring for 20 min. Then, a solution of 4,7-dichloroquinoline (**1**) (99.0 mg, 0.50 mmol) in THF (2.0 mL) was added dropwise to the reaction mixture. After stirring for 60 min, a solution of iodine (152.4 mg, 0.60 mmol, 1.2 equiv.) in THF (1.0 mL) was added and the reaction mixtures was kept under stirring for 1 hour. The reaction was quenched with saturated aqueous $Na_2S_2O_3$, the product was extracted with ethyl acetate (3 × 15 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed under reduction pressure. The residue was purified by flash column chromatography (silica gel, hexanes/ethyl acetate).

4,7-dichloro-8-iodoquinoline (5a): Following TP5, 4,7-dichloroquinoline (**1**, 111.0 mg, 0.56 mmol) and iodine (156.6 mg, 0.61 mmol) afforded **5a** (156.4 mg, 86 %) as a white solid after purification with ethyl acetate/hexanes (1:19) as eluent; m.p. 139-141 °C; spectroscopic data were reported previously.

Synthesis of 4,7-dichloro-8(4-chlorophenyl)quinoline (5i): After zincation step of 4,7-dichloroquinoline (**1**, 207.0 mg, 1.04 mmol) (according to TP5), 1 mL of a THF solution of $[Pd(PPh_3)_4]$ (61.2 mg, 5 mol%) and 1 mL of a THF solution of 1-chloro-4-iodobenzene (299.1 mg, 1.25 mmol) were added and the reaction mixture was kept under stirring for 12 hours at

60°C. The reaction was quenched with saturated aqueous NH_4Cl, the products were extracted with ethyl acetate (3 x 15 mL), the organic layer was dried over $MgSO_4$ and the solvent was removed under reduction pressure. The residue was purified by flash column chromatography using hexane/ethyl acetate (1:9) as eluent to afford compound **5i** (188.9 mg, 75 %) as a white solid; m.p. 164-166 °C; IR (ATR, cm^{-1}): 1479, 1275814; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.7 Hz, 1H), 8.24 (d, J = 9.1 Hz, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.50 – 7.28 (m, 3H), 7.32 (d, J = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 151.3, 149.4, 143.2, 137.0, 130.7, 129.8, 129.2, 125.3, 122.2. HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_9Cl_3N$ 307.9795; Found 307.9797.

Synthesis of N^4-(3,7-dichloroquinolin-4-yl)-N^1,N^1-diethylpentane-1,4-diamine (15): N^1,N^1-diethylpentane-1,4-diamine (0.15 mL, 0.81 mmol) was added to a vial containing 3,4,7-trichloroquinoline (**33**) (117.0 mg, 0.50 mmol) and glycerin (4,40 g). The microwave was programmed to work at 150 °C for 4 hours. After completed reaction, the reactional mixture was extracted with chloroform (3 x 20 mL) and organic layer was washed with NaOH 10 % (3 x 20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/triethylamine (100:1) to afford compound **15** (116.0 mg, 65 %) as a yellow oil; IR (KBr): 2972, 1573, 1418, 890; ^{1}H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 8.20 (d, J = 9.1 Hz, 1H), 7.86 (d, J = 1.8 Hz, 1H), 7.53 (dd, J^3 = 9.1 Hz, J^4 = 1.8 Hz, 1H), 4.42 – 4.36 (m, 1H), 2.96 – 2.88 (m, 6H), 1.81 – 1.66 (m, 4H), 1.37 (d, J = 6.44 Hz, 3H), 1.15 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, MeOD) δ 152.5, 149.8, 149.1, 136.7, 128.5, 127.5, 125.8, 121.5, 114.0, 53.9, 48.2 (2C), 36.4, 22.7, 22.3, 9.7 (2C). HRMS (ESI/Q-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{26}Cl_2N_3$ 354.1498; Found 354.1495.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra and details of computational study. This material is available free of charge on the ACS Publications website at http://pubs.acs.org.

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AUTHOR CONTRIBUTIONS

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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