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Chelation-assisted de-aryloxylative amination of 2-aryloxy quinolines: a new synthetic route to a key fragment of a bioactive PRMT5 inhibitor†

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A highly regioselective de-aryloxylative amination of *O*- or *N*-chelating group-functionalized 2-aryloxy quinolines has been accomplished by means of a copper catalyst. The chelating functional groups of the substrate play a crucial role in directing the C-2-selective amination process, which proceeds through a novel aromatic nucleophilic substitution of the aryloxy group. The methodology provides expedient access to an important class of functionalized 2-aminoquinolines (up to 88% isolated yield) and was successfully applied for the synthesis of a key fragment of an important bioactive PRMT5 inhibitor.

C-2-aminated quinolines, particularly embracing 8-hydroxy- or 8-amino-substituents, are ubiquitous in a broad range of pharmaceutically active compounds and functional materials (Fig. 1).[1] In addition, these molecules have been used both as efficient ligands in metal-catalyzed transformations and organocatalysts.[2] Thus, the development of catalytic methods leading to these molecules are of fundamental importance. Traditionally, these molecules are synthesised *via* metal-catalyzed cross-coupling reactions or nucleophilic substitution reactions between 2-haloquinolines and an amine.[1,3,4] These rather employ harsh reaction conditions and activated quinoline substrates, making them unsuitable for the late-stage functionalization of complex molecules. Modern amination techniques involving inert C–H or C–O bond activation are also restricted to a limited number of N-heteroarene substrates.[5,6] Thus, a powerful, efficient and convenient C-2 amination technique allowing for the straightforward synthesis of 2-amino-8-hydroxyquinoline- and 2,8-diaminoquinoline-derivatives has appeared as a longstanding problem for synthetic organic chemists and needs an urgent solution.

In recent years, the use of aryl ethers has emerged as an attractive replacement to the frequently used aryl halides as the electrophilic coupling partner primarily due to the environmentally benign character, natural abundance, and easy accessibility of phenols and their derivatives.[7] Typically, the C(aryl)–O bonds of unactivated aryl ethers are regioselectively functionalized by various Ni catalysts,[7a–h] and a few Rh, Pd or Cu catalysts,[8] with noteworthy exceptions of using harsh acidic[9] or basic[10] conditions and recently developed Nicewicz's mild and efficient organic photoredox catalysis.[11] However, none of these approaches address the underlying challenges to functionalize the C(aryl)–O bond of 2-alkoxy/aryloxyquinolines.[6b] In this paper, we describe a new approach for the de-aryloxylative amination of unactivated 2-aryloxy quinolines that proceeds *via* a unique chelation-assisted nucleophilic substitution reaction.

We postulated that if the hydroxy- or amine-function of a quinoline nucleus exists in an appropriate arrangement with the N-heteroatom and the 2-alkoxy/aryloxy substituent, it would immediately bind to a metal catalyst forming a metalla-

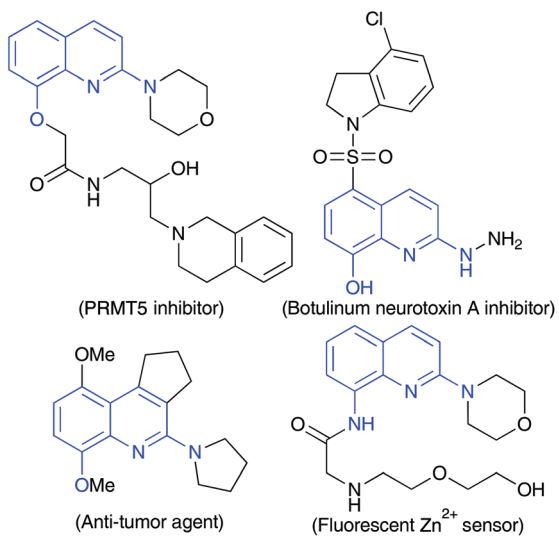

Fig. 1 Selected examples illustrating the significance of 2-amino-8-hydroxyquinolines and 2,8-diaminoquinolines.

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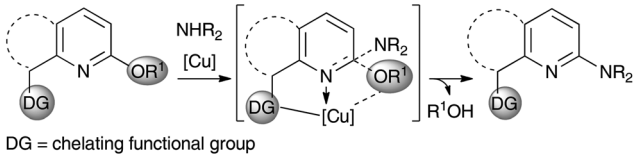


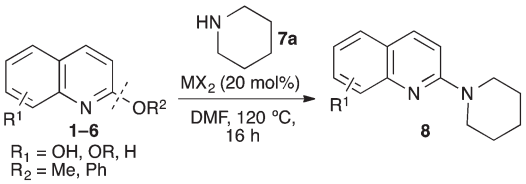
Scheme 1 Chelation-assisted C-2-selective *ipso*-amination of N-heteroaryl ethers.

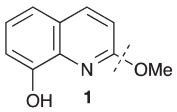
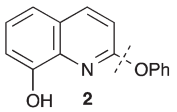
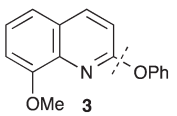
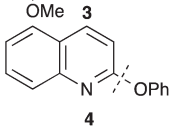
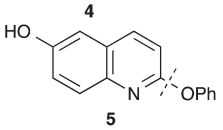
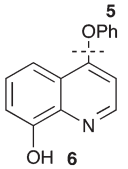
cycle intermediate, which concurrently facilitates C(aryl)–O bond cleavage and the nucleophilic attack by an amine at the relatively electrophilic C-2-position (Scheme 1). This C-2 amination strategy would also avoid the stoichiometric use of waste-intensive halide precursors.[7e] Herein, we report the chelation-assisted C-2-selective *ipso*-amination of hydroxy or amine-functionalized 2-aryloxy quinoline derivatives by means of a copper catalyst.

To probe the viability of this approach, we started investigating the regiospecific C-2-amination of various 8-hydroxyquinoline derived ethers using $Cu(OTf)_2$ as a Lewis acid catalyst (Table 1 and Table S1, ESI†).[12] Thus, the amination of 2-methoxy-8-hydroxyquinoline with piperidine was conducted in the presence of 20 mol% $Cu(OTf)_2$ in DMF at 120 °C. However, this reaction did not proceed to give the desired aminated product (Table 1, entry 1). Gratifyingly, when 2-phenoxy-8-hydroxyquinoline **2** was subjected to the amination with piperidine under identical reaction conditions, the desired C-2 aminated product was formed in high yield (85%) (entry 2). Soon it turned out that the amination could also be operational at a lower catalyst loading (10 mol%) and at a temperature as low as 70 °C. Further alteration of the reaction parameters, such as temperature, solvent *etc*. did not lead to the complete conversion of the substrate even after a prolonged period. Other metal catalysts including $PdCl_2$, $NiBr_2$, $Mg(OTf)_2$ and other copper salts remained ineffective for this transformation (entry 2 and Table S1, ESI†). As expected, the C-2 selective amination was not functional for 2-phenoxy-8-methoxyquinoline (**3**), 2-phenoxyquinoline (**4**), and 2-phenoxy-6-hydroxyquinoline (**5**) indicating the anchoring effect of the free hydroxy function of the substrate (entries 3–5). An attempted C-4-selective dearyloxylative amination of 4-phenoxy 8-hydroxyquinoline (**6**) also failed to proceed, demonstrating the obligatory requirement of the 2-aryloxy substituent for this reaction (entry 6).

With an effective reaction system in hand, we subsequently studied the scope of the amination of 2-phenoxy-8-hydroxyquinoline with regard to the amine nucleophiles. As can be seen in Scheme 2, a diverse range of secondary amines was successfully introduced at the C-2 position of the hydroxyquinoline nucleus *via* the new amination method (**8a–8i**). Both cyclic amines with varied ring size and different substitution patterns (**8a–8e**), as well as acyclic *N*,*N*-dialkyl amines (**8f–8i**) were successfully coupled with 2-phenoxy-8-hydroxyquinoline furnishing the corresponding C-2 aminated products in a practically useful yield. However, the C-2-selective amination failed

Table 1 Identification of the appropriate aryl ether for the C-2-selective amination[a]

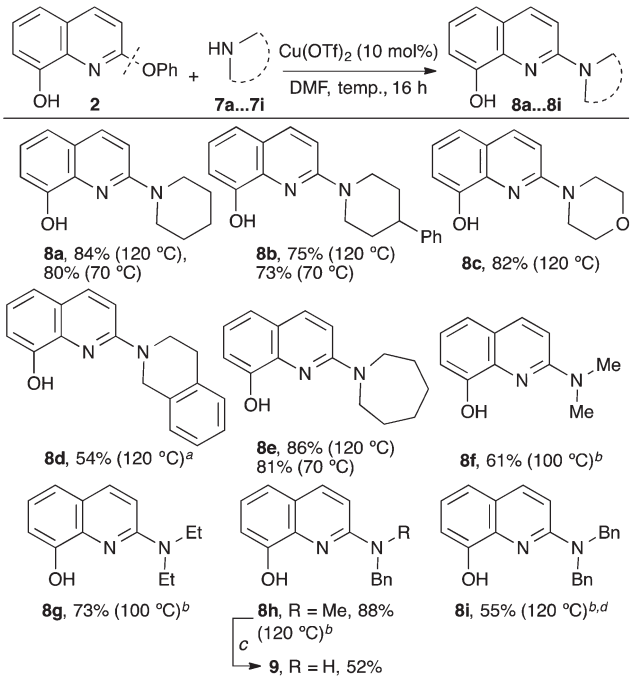


Entry	Substrate	MX_2	**8** (%)
1		$Cu(OTf)_2$	**8a** (0)
2		$Cu(OTf)_2$	**8a** (85)
		$PdCl_2$	**8a** (21)
		$NiBr_2$	**8a** (0)
		$Mg(OTf)_2$	**8a** (0)
		$CuBr_2$	**8a** (25)
		$Cu(OAc)_2$	**8a** (68)
		$Cu(OTf)_2$	**8a** (84)[b]
		$Cu(OTf)_2$	**8a** (80)[c]
		$Cu(OTf)_2$	**8a** (41)[d]
3		$Cu(OTf)_2$	**8a-1** (0)
4		$Cu(OTf)_2$	**8a-2** (0)
5		$Cu(OTf)_2$	**8a-3** (0)
6		$Cu(OTf)_2$	**8a-4** (0)

[a] Reaction conditions: **1–6** (0.15 mmol), piperidine (0.75 mmol), MX_2 (20 mol%), DMF (2.5 mL), 120 °C, 16 h; isolated yields of pure products. [b] 10 mol% $Cu(OTf)_2$. [c] 70 °C. [d] r.t., 36 h.

to proceed with primary amines, imidazole and aniline-derivatives under the optimized reaction conditions. Although primary amines remained ineffective to afford the corresponding secondary amines, we were delighted to find that an intended secondary amine **9** can be simply accessed *via* hydrogenolysis of the benzylated tertiary amine product **8h**.

We further examined the scope of the amination with respect to various 2-aryloxy-8-hydroxyquinolines (Scheme 3). It appeared that 20 mol% $Cu(OTf)_2$ was necessary to improve the yield of the aminated products under otherwise identical reaction conditions (Table S2, ESI†). 8-Hydroxyquinolines bearing either an electron-withdrawing or -donating aryloxy leaving group were found to be consistently functional under the optimized reaction conditions (**10–12**). An additional *N*-chelating group in the aryloxy leaving group can be used (**13–15**).

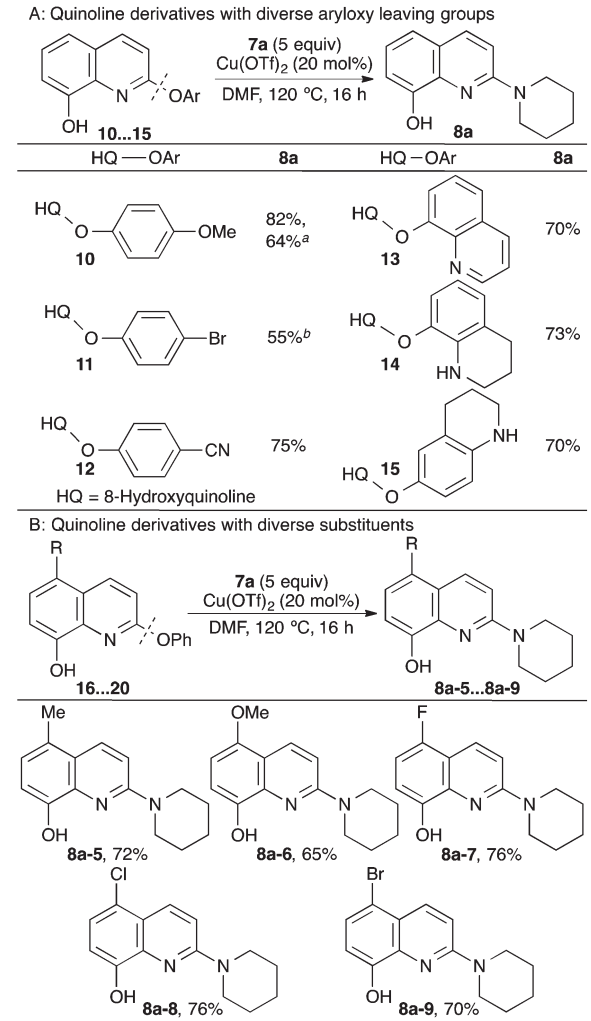


Scheme 2 Scope of the C-2-selective amination with regard to amines. Reaction conditions: **2** (0.15 mmol), amine (**7a–7i**) (0.75 mmol), $Cu(OTf)_2$ (10 mol%), DMF (2.5 mL), 16 h; isolated yields of pure products. [a] 1.5 equiv. of Cs_2CO_3 were used as an additive. [b] 20 mol% $Cu(OTf)_2$. [c] H_2-balloon. 10 wt% Pd–C (180 mg $mmol^{-1}$), MeOH, r.t., 24 h. [d] 72 h.

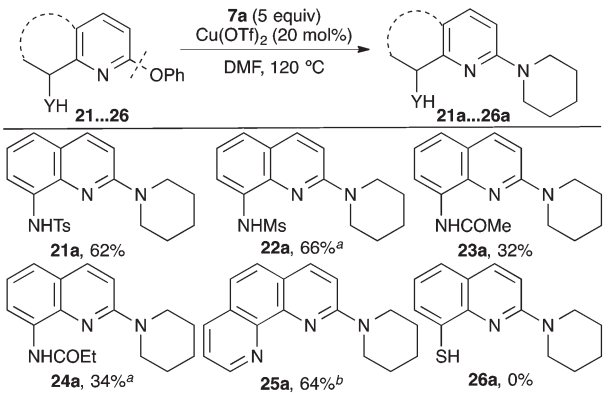
Various functional groups in the quinoline nucleus were also tolerant to the reaction conditions of the amination process to furnish the corresponding C-2-aminated 8-quinolinol derivatives regioselectively (Scheme 3B). Notably, competitive C–N cross-couplings at the C–Br and C–Cl bonds were completely suppressed (**11**, **8a-8** and **8a-9**). These C–Br and C–Cl bonds are expected to be replaced by a nucleophile under otherwise developed metal-catalyzed cross-coupling and/or nucleophilic substitution reaction conditions of the corresponding 2-haloquinoline. The C-2 amination was regiospecific in all cases; no other nucleophilic addition/substitution product at the quinoline ring was detected and the corresponding phenol was obtained as the single by-product.[13] Importantly, the reaction system is robust and does not employ any anhydrous conditions or an inert atmosphere.

In order to establish the general synthetic applicability of this new approach, we further expanded the substrate scope of our de-aryloxylative amination to 8-aminoquinoline and 1,10-phenanthroline derived ethers (Scheme 4). In all cases, the desired C-2 aminated products (**21a–25a**) were formed in moderate to good yields. However, when 2-phenoxy 8-mercaptoquinoline was subjected to amination with piperidine, it led to a complicated reaction mixture and could not produce the desired aminated compound **26a** under the optimized reaction conditions.

To shed light on the reaction mechanism, a series of experiments were conducted (see the ESI†). The presence of a radical



Scheme 3 Scope of the C-2-selective amination with regard to 2-aryloxy 8-hydroxyquinolines. Reaction conditions: Substrate (**10–20**) (0.15 mmol), piperidine (0.75 mmol), $Cu(OTf)_2$ (20 mol%), DMF (2.5 mL), 120 °C, 16 h; isolated yields. [a] 10 mol% $Cu(OTf)_2$. [b] 36 h.

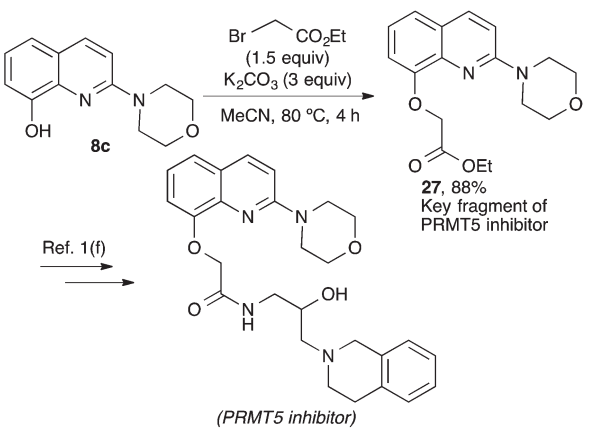


Scheme 4 C-2-selective amination of 2-phenoxy 8-amino/8-mercaptoquinolines. Reaction conditions: Substrate (**21–26**) (0.15 mmol), piperidine (0.75 mmol), $Cu(OTf)_2$ (20 mol%), DMF (2.5 mL), 120 °C, 24 h; isolated yields. [a] 36 h. [b] THF, 70 °C, 16 h. Ts = *p*-toluenesulfonyl; Ms = Methanesulfonyl.

scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) (1.5 equiv.) could not alter the rate of the reaction, thus precluding the involvement of the radical steps. A reaction pathway consisting of dephenoxylation of **2** and a subsequent C–H amination of the resulting compound was excluded as 8-hydroxyquinoline could not be converted into **8a** under the optimized conditions.[14,15]

When 1 equiv. of **2** was heated with 1 equiv. of $Cu(OTf)_2$ in DMF at 120 °C for 5 h prior to the addition of 5 equiv. of piperidine, **8a** was produced in the expected yield; however, when **2** was added to a preheated equimolar mixture of $Cu(OTf)_2$ and piperidine in DMF at 120 °C, **8a** was not formed (see the ESI†). Furthermore, substrates **3**, **4**, and **5** that cannot form a cupracycle intermediate *via* chelation assistance do not undergo the title reaction. These findings indicate that the copper complex, which is formed by the reaction between the substrate and the Cu catalyst, facilitates the amine to attack at the relatively electrophilic C-2 position of the quinoline nucleus, and rule out the involvement of a copper-mediated amine-transfer process.[15] Furthermore, the initially formed substrate–copper complex may favourably be stabilized *via* an *ortho*-cupration of the phenoxy leaving group.[16] The *ortho*-cupration event is also supported by the fact that 2-methoxy 8-hydroxyquinoline **1** and 4-phenoxy 8-hydroxyquinoline **6** could not be aminated at the C-2 and C-4 positions, respectively, under the optimized conditions. All these findings are in accord with the feasibility of an S_NAr pathway. An excess of piperidine possibly acts as a bifunctional mediator to accelerate the rate of the title reaction (see Table S1, ESI†).[6a]

Finally, to demonstrate the synthetic utility of this dearyloxylative amination approach in the synthesis of complex structures, the synthesis of a key fragment of a bioactive PRMT5 inhibitor **27** has been exemplified using one of our C-2 aminated products **8c** as the precursor. This PRMT5 inhibitor is capable of preventing the activity of PRMT5 and thereby helps to prevent the associated diseases, such as proliferative disorders, metabolic disorders, and blood disorders. We were delighted to find that **8c** was readily converted into **27** in high yield *via* a base-mediated *O*-alkylation process within a single reaction step (Scheme 5). Compound **27**, thus obtained, can be successively converted into the desired PRMT5 inhibitor by means of a known literature procedure.[1f]



Scheme 5 Synthesis of the key fragment of the PRMT5 inhibitor starting from **8c**.

Conclusions

In conclusion, we have developed a regiospecific C-2 selective amination of 2-aryloxy quinolines *via* chelation assistance. This dearyloxylative transformation represents a rare example of an aromatic nucleophilic substitution reaction giving expedient access to 2-aminoquinolines starting from the corresponding aryl ethers. The synthetic utility of the amination process has been demonstrated by achieving the key fragment of a bioactive PRMT5 inhibitor. To the best of our knowledge, this is the first instance, in which the chelating interaction between the substrate and the catalyst in promoting a C(aryl)–O bond functionalization has been accomplished. Thus, this method opens up new avenues in the field of "substrate directed organic synthesis".[17]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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