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Copper-Catalyzed Direct Amination of Quinoline *N*-Oxides via C−H Bond Activation under Mild Conditions

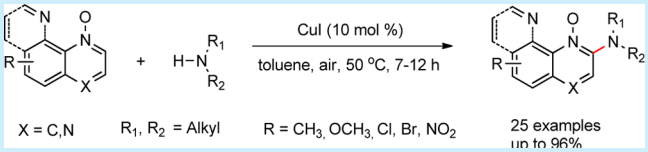
Chongwei Zhu,[†] Meiling Yi,[†] Donghui Wei,[†] Xuan Chen,[†] Yangjie Wu,*[,†] and Xiuling Cui*[,†,‡]

[†]Department of Chemistry, Henan Key Laboratory of Chemical Biology and Organic Chemistry, Key Laboratory of Applied Chemistry of Henan Universities, Zhengzhou University, Zhengzhou 450052, P. R. China

[‡]School of Biomedical Sciences, Engineering Research Centre of Molecular Medicine of Chinese Education Ministry, Xiamen Key Laboratory of Ocean and Gene Drugs, Institute of Molecular Medicine of Huaqiao University, Fujian, Xiamen 361021, P. R. China

Supporting Information

ABSTRACT: A highly efficient and concise one-pot strategy for the direct amination of quinoline *N*-oxides via copper-catalyzed dehydrogenative C−N coupling has been developed. The desired products were obtained in good to excellent yields for 22 examples starting from the parent aliphatic amines. This methodology provides a practical pathway to 2-aminoquinolines and features a simple system, high efficiency, environmental friendliness, low reaction temperature, and ligand, additives, base, and external oxidant free conditions.



2-Aminoquinolines exist widely in pharmaceuticals and biological activity antagonists. Some representative examples are shown in Figure 1. Compound **A** is a novel potent antagonist

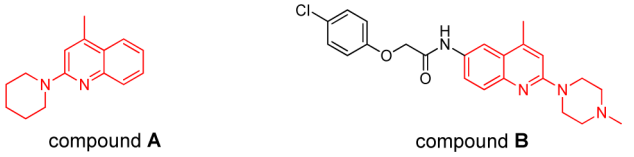
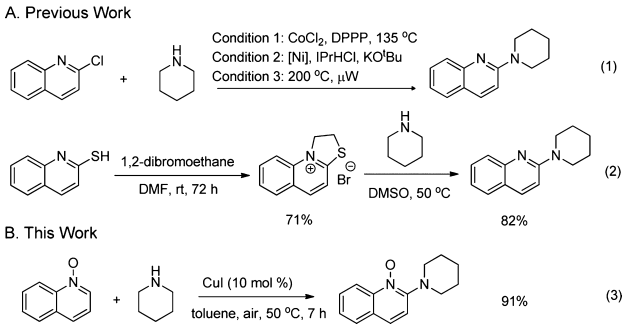


Figure 1. Two examples illustrating the importance of the compounds with 2-aminoquinoline moiety.

that selectively modulates native TRPC4/C5 ion channels and has a wide use in physiological and pathophysiological studies;[1] **B** is an antagonist of the MCH-1R for the treatment of obesity.[2] Their high incidence of pharmacological activity has stimulated many research efforts to prepare such a core. The condensation of 2-chloroquinoline with amines catalyzed by Co/DPPP[3] or Ni(II)-(α-Aryl)/IPr[4] or promoted by microwave[1,5] could provide 2-aminoquinolines (eq 1, Scheme 1). The 2-mercaptoquinoline could also be served as a substrate to build 2-aminoquinoline through two steps (eq 2, Scheme 1).[6] There are some disadvantages with these procedures, such as requirement of the expensive starting materials (2-choloroquinoline, 2-mercaptoquinoline), harsh reaction conditions, and low efficiency. Hence, development of a simple, highly efficient, and atomic-economic method to synthesize 2-aminoquinolines is highly desired.

Transition-metal-catalyzed C−N bond formation via C−H bond activation has become a powerful and efficient method due to its atom economy.[7] Palladium, copper, rhodium, or ruthenium was usually reported as a catalyst in the literatures.[8] Since the pioneering work on the direct amination of C_{arene}−H

Scheme 1. Synthesis of 2-Aminoquinolines



bond from Yu and co-workers,[9] copper-catalyzed dehydrogenative C−N coupling has been increasingly attractive due to its cheapness and abundance on the earth.[10] However, the protected or activated amines were usually employed as substrates since the high electron density of nitrogen atom in the parent amines could strongly coordinate with the catalyst and reduce the electrophilicity of metal, which hindered the C−H bond cleavage.[11] Therefore, the parent amines were employed rarely as substrates for C−H amination. Cu-catalyzed direct amination of azoles at 140 °C under 1 atm O_2 were reported by Mori.[12] The Chang, Daugulis, and Warren groups also reported their elegant work on copper-catalyzed direct dehydrogenative C−N coupling from parent amines. However, a stoichiometric amount of oxidant, such as silver salt or TBHP, was required.[13] In our previous work, we successfully realized the olefination, sulfonylation, alkylation, and acetoxylation of quinoline *N*-oxides via metal-catalyzed C−H bond activation.[14]

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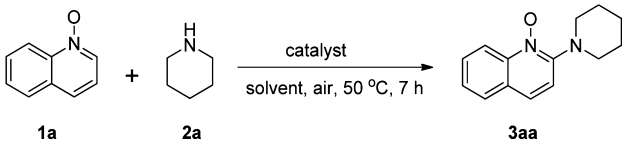
In our continuing effort to develop versatile C–X (X = C, O, S, N) bond formation of quinoline *N*-oxides, we embarked on the development of C–N bond formation. Herein, we present an extremely simple and highly efficient copper-catalyzed synthesis of 2-aminoquinoline via a direct C–H amination of quinoline *N*-oxides using the parent amines as substrates at 50 °C and under ligand, additives, base, and external oxidant free conditions (eq 3, Scheme 1).

The condensation of quinoline *N*-oxide **1a** with piperidine **2a** was initially chosen as a model reaction to screen the various reaction parameters (Table 1). To our delight, the desired product **3aa** was obtained in 85% isolated yield in the presence of $Cu(OAc)_2$ (20 mol %) in toluene at 50 °C under air (entry 1, Table 1). The product **3aa** was identified by MS, NMR spectra, and X-ray diffraction. Inspired by this result, some catalysts were screened (entries 2–9, Table 1). Copper salts, such as $Cu(OAc)_2$, $Cu(OTf)_2$, $CuBr_2$, CuBr, CuCl, and CuI, could provide 80–94% isolated yields (entries 1–6). CuI was slightly superior to the others and proved to be the best catalyst (entry 6, Table 1). No desired product was observed when $NiCl_2{\cdot}6H_2O$, $Pd(OAc)_2$, or $CoCl_2$ was used as a catalyst (entries 7–9). The solvent also played a crucial role. Among the solvents tested (toluene, THF, CH_3CN, DMSO, DCE, and DMF), toluene was proved to be the best for this transformation (entries 6, 10–14, Table 1). The loading of catalyst and amine was also screened. The reaction could proceed smoothly in the presence of 10 mol % of CuI and 8 equiv of amine (entries 15–20, Table 1). A yield of 91% could also be obtained in the presence of 10 mol % of CuI in toluene at 50 °C with 4 equiv of amines by prolonging the reaction time to 15 h. However, 8 equiv of amines was employed to shorten the reaction time. The yield decreased to 86% and 70% when the temperature was reduced to 40 and 30 °C, respectively (entries 21–22, Table 1). After surveying the reaction parameters, the optimal reaction conditions were determined: CuI (10 mol %), amine (8.0 equiv), toluene, 50 °C, under air.

With the optimized reaction conditions in hand (entry 18, Table 1), the scope of substrates for this transformation was investigated (Schemes 2 and 3). A series of representative amines were tested with quinoline *N*-oxide **1a** in Scheme 2. Cyclic amines readily underwent conversion to the desired products. Piperidine and pyrrolidine could provide the products **3aa** and **3ab** in 91% and 86% yields, respectively. 2-Methylpiperidine, 2-arylpyrrolidine, and benzopiperidine were also suitable substrates for this transformation and provided the corresponding products in 45%, 86%, and 88% yields, respectively (**3ac–ae**, Scheme 2). Morpholine and 1-methylpiperazine, with two heteroatoms, were smoothly coupled with quinoline *N*-oxide, affording the desired products **3af** and **3ag** in 93% and 44% yields, respectively. Moreover, acyclic secondary aliphatic amines could also be employed for this conversion to smoothly provide the corresponding products **3ah**, **3ai**, and **3aj** (Scheme 2). Diallylamine and dibenzylamine gave **3ak** and **3al** in 27% and 25% yields, which might be caused by the lower nucleophilicity of diallylamine and dibenzylamine.[15] No desired products were obtained when primary amines, aromatic amines, or amides were employed under the standard reaction conditions.

Table 1. Optimizing Reaction Parameters for the Condensation of Quinoline *N*-Oxide 1a with Piperidine 2a[a]

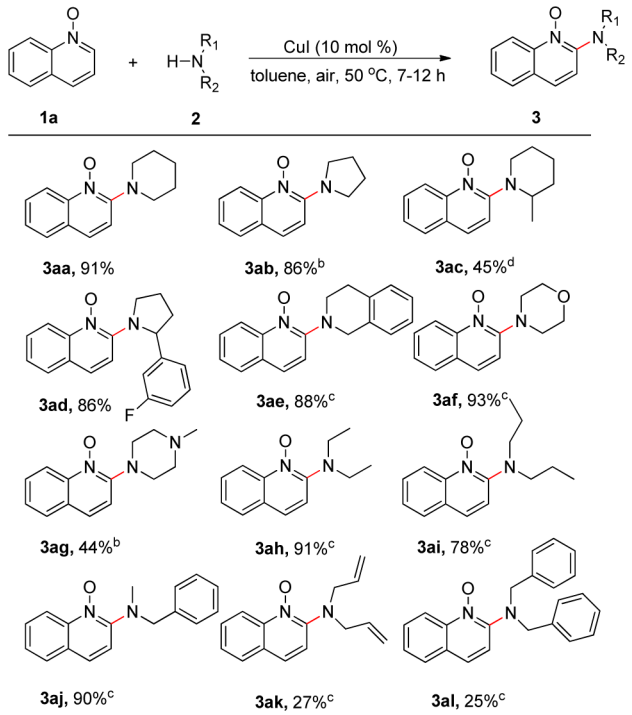


1a 2a 3aa

entry	catalyst (equiv)	solvent	amine (equiv)	yield[b] (%)
1	$Cu(OAc)_2$ (0.2)	toluene	8.0	85
2	$Cu(OTf)_2$ (0.2)	toluene	8.0	84
3	$CuBr_2$ (0.2)	toluene	8.0	83
4	CuBr (0.2)	toluene	8.0	80
5	CuCl (0.2)	toluene	8.0	89
6	CuI (0.2)	toluene	8.0	94
7	$NiCl_2{\cdot}6H_2O$ (0.2)	toluene	8.0	NR
8	$Pd(OAc)_2$ (0.2)	toluene	8.0	NR
9	$CoCl_2$ (0.2)	toluene	8.0	NR
10	CuI (0.2)	THF	8.0	80
11	CuI (0.2)	CH_3CN	8.0	78
12	CuI (0.2)	DMSO	8.0	NR
13	CuI (0.2)	DCE	8.0	NR
14	CuI (0.2)	DMF	8.0	trace
15	CuI (0.2)	toluene	7.0	85
16	CuI (0.2)	toluene	6.0	82
17	CuI (0.2)	toluene	4.0	75
18	**CuI (0.1)**	**toluene**	**8.0**	**91**
19	CuI (0.08)	toluene	8.0	86
20	CuI (0.05)	toluene	8.0	78
21	CuI (0.1)	toluene	8.0	86[c]
22	CuI (0.1)	toluene	8.0	70[d]

[a]Reaction conditions: **1a** (0.2 mmol), solvent (1.5 mL), 50 °C, 7 h. [b]Isolated yield based on **1a**. [c]40 °C. [d]30 °C. NR = no reaction.

Scheme 2. Copper-Catalyzed Amination of Quinoline *N*-Oxide with Various Amines[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (1.6 mmol), CuI (10 mol %), toluene (1.5 mL), 50 °C, 7 h. [b]12 h. [c]9 h. [d]20 h. Isolated yields based on **1a**.

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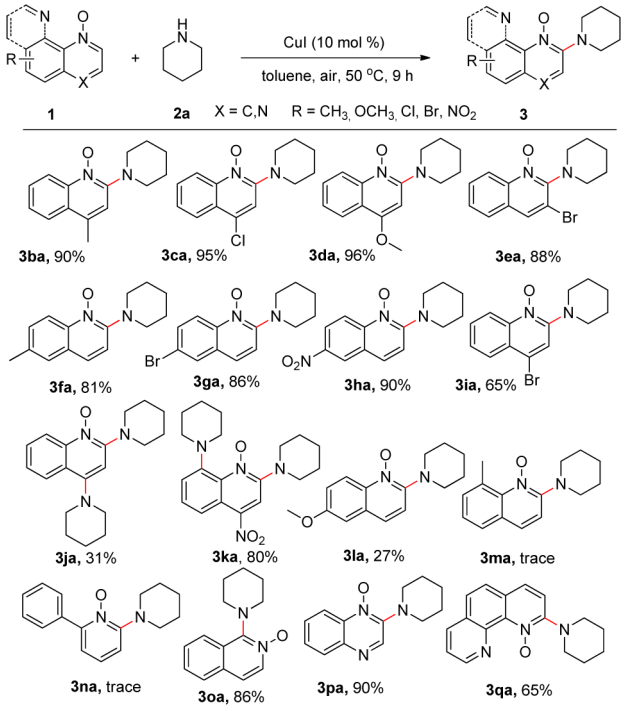
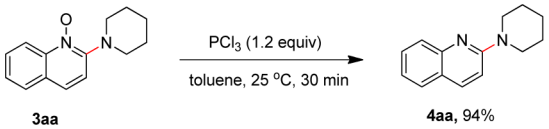
Scheme 3. Copper-Catalyzed Amination of Quinoline *N*-Oxides with Piperidine[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (1.6 mmol), CuI (10 mol %), toluene (1.5 mL), 50 °C, 9 h. Isolated yields based on **1**.

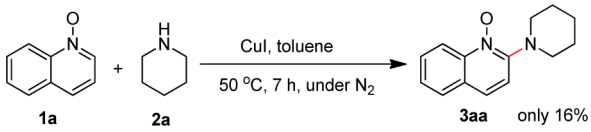
We next investigated a range of *N*-oxide derivatives with piperidine under the optimized conditions (Scheme 3). Excitingly, quinoline *N*-oxide substituted with 4-methyl, 4-methoxy, 4-chloro, 3-bromo, 6-methyl, 6-bromo, and 6-nitro reacted smoothly with piperidine and provided the desired product in excellent yields (**3ba**–**ha**, Scheme 3). Electron-donating and electron-withdrawing groups in quinoline *N*-oxides did not significantly influence on this transformation. 4-Bromoquinoline *N*-oxide gave monoaminated product **3ia** and diaminated product **3ja** in 65% and 31% yields, respectively. 2,8-Diaminated quinoline *N*-oxide **3ka** was obtained as a main product (80% yield) for 4-nitroquinoline *N*-oxide. However, 6-methoxyquinoline *N*-oxide only delivered the desired product in 27% yield (**3la**), probably because the electron-donating group ($-OCH_3$) reduced the activity of C_2-H bond of the quinoline *N*-oxide. 8-Methylquinoline *N*-oxide with steric hindrance and pyridine *N*-oxide were limited to this catalytic system. Only a trace amount of product was detected (**3ma**, **3na**). Notably, isoquinoline *N*-oxide, quinoxaline *N*-oxide, and 1,10-phenanthroline *N*-oxide could proceed efficiently and afford the corresponding products in 86%, 90%, and 65% yields, respectively (**3oa**, **3pa**, **3qa**, Scheme 3).

The 2-aminoquinoline *N*-oxides were easily reduced by PCl_3[16] and delivered the corresponding 2-aminoquinolines in excellent yields (eq 4), showing that this protocol through dehydrogenative C–N coupling is practical for the construction of 2-aminoquinoline skeleton.



(4)

To investigate the reaction mechanism, the following controlled experiment was performed (eq 5). The copper-

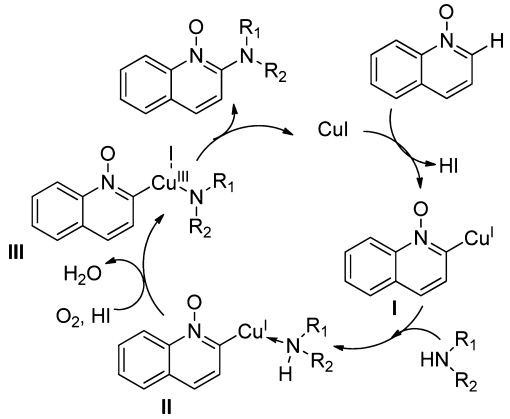


(5)

catalyzed coupling of **1a** with **2a** was conducted under nitrogen atmosphere and obtained the product **3aa** only in 16% yield. This result suggested that O_2 might act as an oxidant in this catalytic system.

Based on the results obtained and literature reports,[17] a plausible pathway was proposed as shown in Scheme 4.

Scheme 4. Plausible Reaction Mechanism



First, the 2-carbon of the quinoline *N*-oxide was attacked by copper and afforded intermediate **I**.[14b,18] Then, the high electron density of nitrogen atom of the aliphatic amines could smoothly coordinate with copper atom and give intermediate **II** easily. Being surrounded by high electron density of the donor atom could make Cu(I) be oxidized into Cu(III) complex **III** by O_2 from air. Finally, Cu(III) complex expedited C–N bond formation and delivered directly the target product by reductive elimination. CuI was regenerated to continue the catalytic cycle. The feasibility of the mechanism was also verified by density functional theory (DFT) (see the Supporting Information).

In summary, we have developed an extremely simple and highly efficient protocol for the direct amination of quinoline N-oxide and its analogues with secondary aliphatic amines based on copper-catalyzed C–H bond activation. This method features with a simple system, high efficiency, atomic economy, environmental friendliness, low reaction temperature, and ligand, additives, base, and external oxidant free conditions. Further investigations on the applications of products are in process in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: wyj@zzu.edu.cn.
*E-mail: cuixl@zzu.edu.cn.

Notes

The authors declare no competing financial interest.

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