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Copper-Catalyzed Intermolecular Dehydrogenative Amidation/Amination of Quinoline *N*-Oxides with Lactams/Cyclamines

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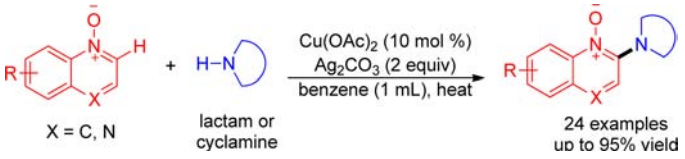
ABSTRACT



C–H, N–H dehydrogenative coupling of quinoline *N*-oxides with lactams/cyclamines has been achieved in the presence of the $Cu(OAc)_2$ catalyst to give good to excellent yields. This study provides a new strategy for the construction of a 2-aminoquinoline skeleton via direct functionalization of aryl C–H bonds.

Over the past several years, transition-metal-catalyzed selective C–H bond functionalization has attracted considerable attention for its outstanding advantages in atom efficiency and synthesis step efficiency compared to the traditional cross-coupling of organic halides with organometallic compounds.[1] Aryl C–N is an important structural unit, which widely exists in pharmaceuticals and natural compounds with diverse biological activities.[2] Compared to the Buchwald–Hartwig amination,[3] Ullman coupling,[4] and Chan–Lam oxidative coupling[5] to construct aryl C–N bonds using aryl halides/tosylates or organometallic reagents as reactants, undoubtedly, dehydrogenative coupling of aryl C–H and N–H is an intriguing method to prepare arylamines. Recently, significant progress has been achieved for aryl C–N bond construction via dehydrogenative coupling of C–H and N–H.[6] Cross Dehydrogenative Coupling (CDC) of quinoline *N*-oxide catalyzed by transition metals has been developed and reported in the literature. Wu (eqs 1, 4),[7] Chang (eq 2),[8] and Li (eq 3)[9] reported respectively the reactions of

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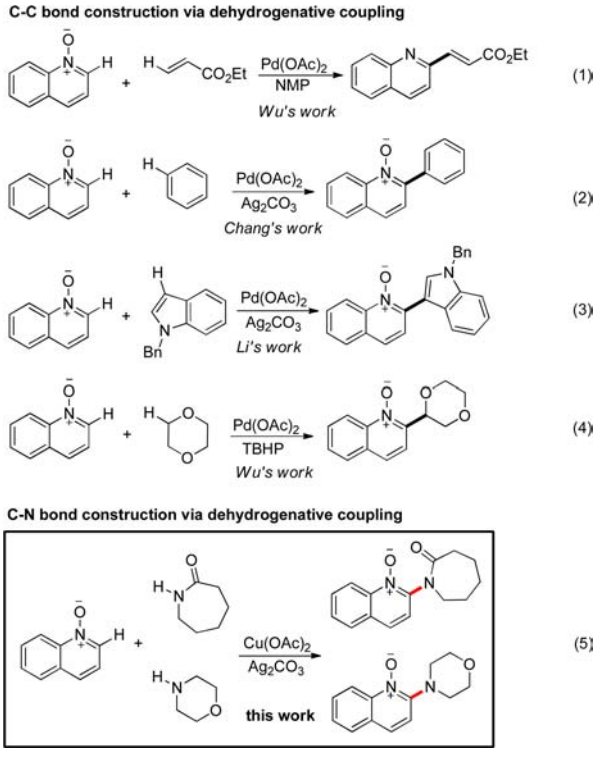
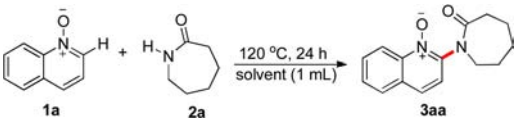
quinoline *N*-oxide with acrylates, ethers, arenes, and indoles to construct various C−C bonds. However, C−N bond construction catalyzed by transition metals via dehydrogenative coupling of quinoline *N*-oxide is still a challenge. Herein, we present a dehydrogenative amination/amidation of quinoline *N*-oxides with lactams/cyclamines to construct 2-aminoquinoline in the presence of the $Cu(OAc)_2$ catalyst.



Initially, we selected the low-cost and readily available quinoline *N*-oxide (**1a**) and hexanolactam (**2a**) as typical substrates to screen the conditions of dehydrogenative coupling. The reaction was performed at 120 °C for 24 h in a sealed tube. As shown in Table 1, with solely 2 equiv of $Cu(OAc)_2$ or Ag_2CO_3 in the system (entries 1, 2), no dehydrogenative coupling could proceed. To our delight,

Table 1. Dehydrogenative Amidation of Quinoline *N*-Oxide



entry	catalyst	oxidant	solvent (1 mL)	yield (%)
1	$Cu(OAc)_2$ (2 equiv)		benzene	trace
2	Ag_2CO_3 (2 equiv)		benzene	trace
3	$Cu(OAc)_2$ (10 mol %)	oxone (2 equiv)	benzene	10
4	$Cu(OAc)_2$ (10 mol %)	$K_2S_2O_8$ (2 equiv)	benzene	18
5	$Cu(OAc)_2$ (10 mol %)	$^tBuOO^tBu$ (2 equiv)	benzene	trace
6	$Cu(OAc)_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	benzene	93
7	$CuCl_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	benzene	72
8	$CuCO_3$ (10 mol %)	Ag_2CO_3 (2 equiv)	benzene	no
9	$Pd(OAc)_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	benzene	no
10	$Pd(OAc)_2$ (10 mol %)	$Cu(OAc)_2$ (2 equiv)	benzene	trace
11	$Cu(OAc)_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	toluene	66
12	$Cu(OAc)_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	xylene	80
13	$Cu(OAc)_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	acetonitrile	49
14	$Cu(OAc)_2$ (10 mol %)	Ag_2CO_3 (2 equiv)	1,4-dioxane	75
15	Ag_2CO_3 (10 mol %)	$Cu(OAc)_2$ (2 equiv)	benzene	81

when oxone, $K_2S_2O_8$, $^tBuOO^tBu$, and Ag_2CO_3 respectively were employed as oxidants in the presence of $Cu(OAc)_2$ (entries 3, 4, 5, 6), Ag_2CO_3 was effective in providing the desired product in 93% isolated yield, which was obviously superior to the others. $CuCl_2$ was found to promote the reaction (entry 7), although the yield was inferior to that using $Cu(OAc)_2$, while $CuCO_3$ was thoroughly invalid (entry 8). $Pd(OAc)_2$ also displayed hardly any catalytic performance (entries 9, 10). Among benzene, toluene, xylene, acetonitrile, and 1,4-dioxane (entries 6, 11, 12, 13, 14), benzene was the optimal solvent. The reaction proceeded in other solvents but gave a lower yield due to the appearance of byproduct. When adding Ag_2CO_3 (10 mol %) and $Cu(OAc)_2$ (2 equiv) into the system (entry 15), the product was obtained in 81% isolated yield.

With the optimized conditions in hand, we set out to explore the scope and generality of the dehydrogenative amidation/amination of quinoline *N*-oxides with amides/amines. Several quinoline *N*-oxide derivatives were employed as a coupling partner with hexanolactam as summarized in Scheme 1. Quinoline *N*-oxide bearing an alkyl (**3ba**, **3ca**, **3da**) and aryl (**3ea**) group in different positions reacted smoothly to give the products in excellent yields. Meanwhile, the good reactivity of 8-methyl-quinoline *N*-oxide demonstrated that the reaction site is the

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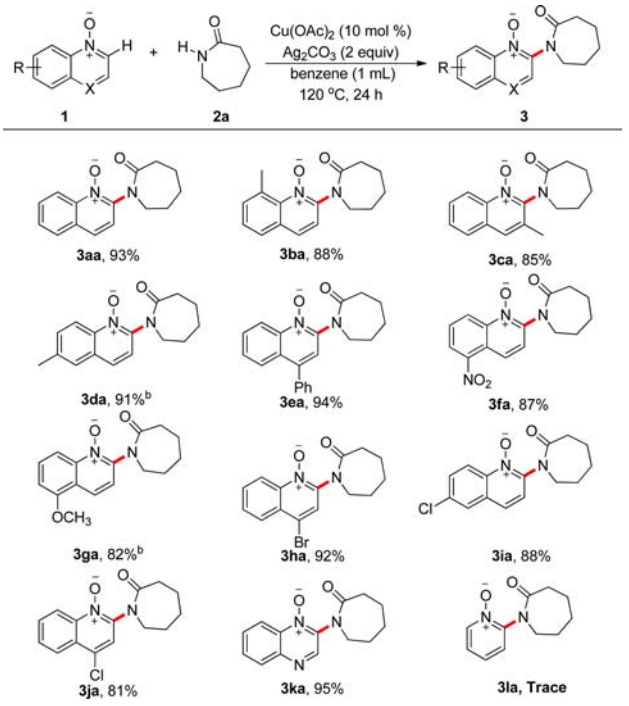
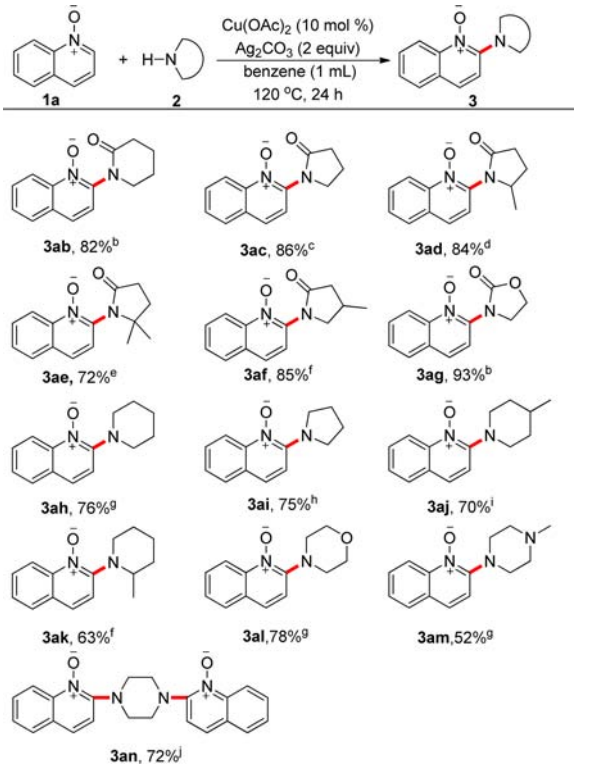
Scheme 1. Dehydrogenative Amidation of Quinoline *N*-Oxide Derivatives with Hexanolactam[a]



[a] Reaction conditions: quinoline *N*-oxide (0.2 mmol), hexanolactam (0.6 mmol, 3 equiv), $Cu(OAc)_2$ (10 mol %), Ag_2CO_3 (0.4 mmol, 2 equiv), benzene (1 mL), 120 °C, 24 h. [b] 130 °C.

Scheme 2. Dehydrogenative Amidation/Amination of Quinoline *N*-Oxide with Various Lactams/Cyclamines[a]

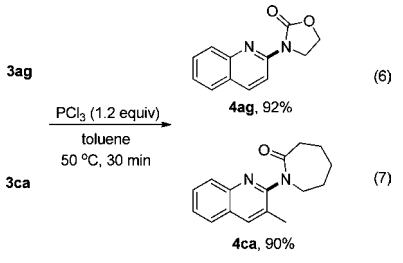


[a] Reaction conditions: quinoline *N*-oxide (0.2 mmol), lactam/cyclamine (0.6 mmol, 3 equiv), $Cu(OAc)_2$ (10 mol %), Ag_2CO_3 (0.4 mmol, 2 equiv), benzene (1 mL), 120 °C, 24 h. [b] 80 °C. [c] 100 °C, 8 h. [d] 110 °C. [e] 140 °C. [f] 90 °C. [g] 50 °C. [h] 40 °C. [i] 55 °C. [j] Quinoline *N*-oxide (0.6 mmol), piperazine (0.2 mmol), $Cu(OAc)_2$ (0.04 mmol), Ag_2CO_3 (1.2 mmol), 100 °C, 24 h.

2-position of the substrate. The methyl at the 3-position of quinoline *N*-oxide did not display an obvious steric hindrance effect in this course. Both strong electron-withdrawing ($-NO_2$, **3fa**) and electron-donating ($-OCH_3$, **3ga**) functional groups were well tolerated on quinoline *N*-oxide. Excellent yields could be obtained for halogen-bearing substrates (**3ha**, **3ia**, **3ja**). The survival of a halogen substituent offered a great opportunity to further functionalize the products. Quinoxaline *N*-oxide exhibited an outstanding reactivity to give the desired product (**3ka**) in 95% isolated yield. Regrettably, pyridine *N*-oxide could not progress well under the same conditions, and only a trace amount of product was obtained (**3la**).

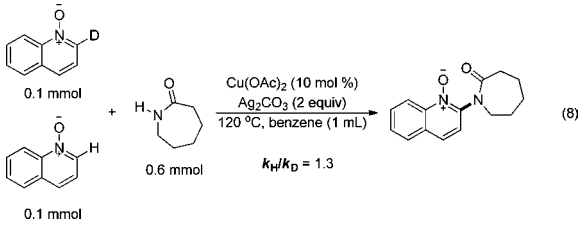
Moreover, various lactams were further surveyed under the same conditions as shown in Scheme 2. Different size ring lactams gave the corresponding products in excellent yields (**3ab, 3ac**). 2-Pyrrolidone with methyl substituents in different positions were also suitable substrates for this transformation although with obvious steric hindrance in 5,5-dimethyl-2-pyrrolidone (**3ad, 3ae, 3af**). 2-Oxazolinone was an excellent coupling partner in the reaction, and the desired product was obtained in 93% isolated yield. Further trials found that the condition was also effective for the dehydrogenative amination of quinoline *N*-oxide with cyclamines. Not only piperidine (**3ah**), pyrrolidine (**3ai**), and methylpiperidine (**3aj, 3ak**) exhibited excellent reactivities, but also morpholine (**3al**) and piperazine (**3am**) with a heteroatom (O, N) gave the desired products in good yields under a lower temperature. In addition, the amination of bimolecular quinoline *N*-oxides with dual N−H bonds of piperazine proceeded smoothly in one pot to give a good yield by simply controlling the stoichiometry of the reactants (**3an**).

The dehydrogenative coupling products were readily reduced by PCl_3 to give corresponding 2-aminoquinoline derivatives in excellent yields (eqs 6, 7).[8] It showed that the combination of the present dehydrogenative coupling of C−H, N−H and subsequent reduction was a useful method to construct the 2-aminoquinoline skeleton.



Next, the deuterium kinetic isotope effect (KIE) of the amidation was measured in an intermolecular competitive coupling of an equimolar mixture of quinoline *N*-oxide and 2-d_1-quinoline *N*-oxide with hexanolactam (eq 8). The

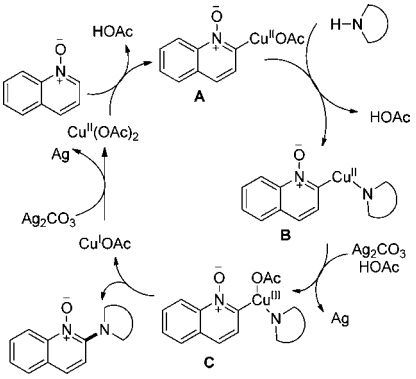
observed KIE was $k_H/k_D = 1.3$ via ^1H NMR analysis of the residual material mixture. The data showed the C−H bond cleavage in quinoline *N*-oxide was not likely involved in the rate-limiting step.



According to the mechanism studies in related literature[6l−p] and our experimental observation, a plausible catalytic cycle is proposed to rationalize the $Cu(OAc)_2$ catalyzed dehydrogenative amidation/amination course. As shown in Scheme 3, metallization of quinoline *N*-oxide with $Cu(OAc)_2$ generated intermediate **A**, which reacted with amide/amine to form species **B**. Ag_2CO_3 oxidized intermediate **B** to obtain complex **C**, which underwent a reductive elimination to release Cu^IOAc and final product 2-amidated quinoline *N*-oxide. Then, Cu^IOAc was oxidized by Ag_2CO_3 to give the active catalyst to restart the catalytic cycle.

In conclusion, we have developed the dehydrogenative coupling of quinoline *N*-oxides with lactams/cyclamines in the presence of the $Cu(OAc)_2$ catalyst. The development provides a new strategy to synthesize the 2-aminoquinoline compounds via direct functionalization of aryl C−H bonds. Further investigations to expand the substrate scope and apply such chemistry in synthesis are underway.

Scheme 3. Proposed Pathway of the Dehydrogenative Coupling



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Supporting Information Available. Experimental details, ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.