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Direct Carbamoylation of Quinoline *N*-oxides with Hydrazinecarboxamides via C-H Bond Activation Catalyzed by Copper Catalyst

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Abstract. An efficient method for the carbamoylation of quinoline N-oxides catalyzed by copper was developed. A variety of quinoline N-oxides and hydrazinecarboxamides with different groups was well tolerated in this system.

Keywords: quinolone N-oxides; hydrazinecarboxamides; C-H activation; copper

Quinoline derivatives are one of the most valuable compounds and have been found widespread application in diverse areas, such as bioactive natural products,[1] pharmaceuticals,[2] and functional materials.[3] Although the direct functionalization of pyridine ring still remains a significant challenge because of its low reactivity and poor selectivity, there has been much effort devoted to the functionalization of quinolone skeleton in the past few decades.[4] For example, series of quinoline derivatives have been efficiently synthesized from quinolone N-oxides in recent years.[5] Without using any base and organic solvent, various functionalized quinolin-2(1H)-ones were synthesized from the reaction of quinolone N-oxides with water by He's group.[6] This group also realized the reaction between quinolone N-oxides and nitriles, obtaining various *N*-acylated 2-aminoquinolines.[7] Zhao's group developed an efficient one-pot methodology for C2-selective amination and alkylation of quinoline N-oxides. A large variety of primary and secondary amines, as well as active methylene compounds were well tolerated in this system.[8] In 2013, an efficient and direct 2-acetoxylation of quinoline N-oxides via copper(I) catalyzed C–H bond activation was presented by Wu and coworkers. However, this reaction was limited to the electron-withdrawing aldehydes and heterocyclic aldehydes (Scheme 1a).[9] Direct C-2 alkylation of quinoline N-oxides with ethers via Palladium-catalyzed dehydrogenative cross-coupling reaction was also realized by the same group, providing quinoline-containing heterocyclic molecules in moderate to excellent yields (Scheme 1b).[10] In 2011, a Pd(II)-catalyzed oxidative coupling between quinoline N-oxides and N-substituted indoles via 2-fold C-H bond activation was presented by Li group (Scheme 1c).[11] In 2013, Wu *et al.* found that aryl sulfonyl chlorides was good reagent for the synthesis of sulfonylated quinoline N-oxides. (Scheme 1d).[12] Additionally, lactams/cyclamines were also good pater to react with quinolone N-oxides. The $Cu(OAc)_2$-catalyzed dehydrogenative coupling of quinoline N-oxides with lactams/cyclamines was achieved by Li's group for the construction of 2-aminoquinoline skeleton (Scheme 1e).[13] Although various reactions for the synthesis of quinoline derivatives have been realized, trying to develop new versatile and practical methods are still desirable. Recently, Tian's group realized carbamoylation of *N*-arylacrylamides[16a] and nitrogen heteroarenes using hydrazinecarboxamides as substrates.[16b] Encouraged by Tian's work and on the basis of our continued pursuit of C-H bond activation,[14] herein we disclose a new strategy to access carbamoylated quinolone *N*-oxides via CuBr-catalyzed carbamoylation of quinolone N-oxides with hydrazinecarboxamides.

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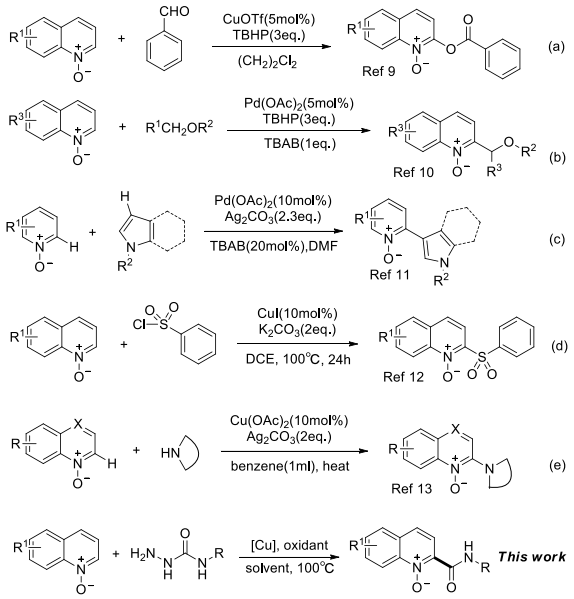
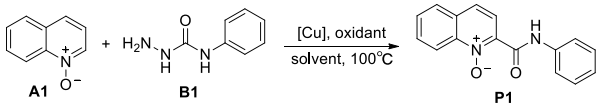


Scheme 1. Functionalization of quinoline N-oxides.

At the start of our investigation, the reaction between quinoline 1-oxide (**A1**) and N-phenylhydrazinecarboxamide (**B1**) was selected as a model reaction. As show in Table 1, when the reaction of **A1** and **B1** was carried out in the presence of $CuSO_4$, product **P1** was obtained in 21% yield (table 1, entry 1). When other copper catalysts such as CuOTf, CuI, $Cu(OAc)_2$, CuO, $Cu(OTf)_2$ and CuBr were subjected to the reaction, CuBr was found to be the best catalyst (table 1, entries 2-7). Palladium catalyst $Pd(OAc)_2$ and $PdCl_2$ were also tested in this reaction, but the result was disappointing (table 1, entries 8-9). The effect of solvents on the model reaction was also examined. Among these solvents examined in the model reaction, DMSO was optimal. Only 16-57% yields of the product was isolated when other solvents (CH_3CN, DMF, PhCl, Toluene) were used (table 1, entries 10-13). Encouraged by this result, various oxidants were further investigated and performed with lower yields in this reaction (table 1, entries 14-16). Finally, the best yield of P1(92%) was obtained by employing CuBr as catalyst and TBHP as oxidant in DMSO under air. To put the structure beyond any ambiguity, a single crystal of **P1**[15] cultivated by slow evaporation of solvent from its solution in a mixture of ethyl acetate and chloroform and its X-ray molecular structure was determined (Fig 1).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield(%)
1	$CuSO_4$	DMSO	21
2	CuOTf	DMSO	54
3	CuI	DMSO	34
4	$Cu(OAc)_2$	DMSO	10
5	CuO	DMSO	5
6	$Cu(OTf)_2$	DMSO	17
7	CuBr	DMSO	92
8	$Pd(OAc)_2$	DMSO	Trace
9	$PdCl_2$	DMSO	Trace
10	CuBr	CH_3CN	16
11	CuBr	DMF	38
12	CuBr	PhCI	57
13	CuBr	Toluene	36
14[b]	CuBr	DMSO	19
15[c]	CuBr	DMSO	43
16[d]	CuBr	DMSO	23

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), TBHP (5−6 M in decane, 3.0 equiv), DMSO(2 mL), under air, 100 °C, 12 h. [b]3.0 equiv of H_2O_2 was used. [c]3.0 equiv of TBPB was used. [d]3.0 equiv DTBP was used.

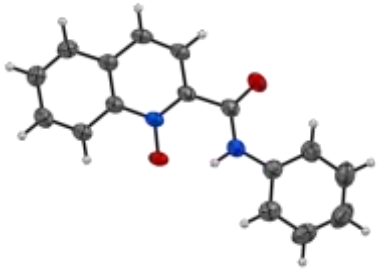


Fig 1. X-Ray molecular structure of **P1**.

Using the developed optimized reaction conditions, the substrates scope of this reaction was examined with respect to both hydrazinecarboxamides and quinoline N-oxides and the results were summarized in Table 2. Under the optimal reaction conditions, the reaction of hydrazinecarboxamides containing both electron-withdrawing and electron-donating groups, such as CH_3, Br, Cl and F, on the benzene ring with quinoline 1-oxide took place smoothly and generated the corresponding products in moderate to high yields (table 2, P1-P6). Different quinolone N-oxides were tested for this transformation. 6-chloroquinoline 1-oxide afforded the desired products in 82-90% yields (table 2, P7-P10). 65-85% yields of the products were obtained when 6-fluoroquinoline 1-oxide was tested as substrates (table 2, P11-P14). To our delight, *N*-cyclohexylhydrazinecarboxamide and *N*-(naphthalen-1-yl)hydrazinecarboxamide were also well tolerated in this system. They were all reacted smoothly with quinolone N-oxides and give the corresponding products with moderate to high yields (table 2, P15-P20). To our disappointment, no reaction occurred when 6-methoxyquinoline *N*-oxide, 6-

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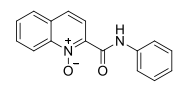
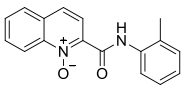
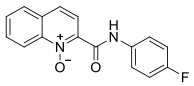
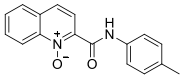
methylquinoline *N*-oxide, 3-bromoquinoline *N*-oxide and 6-(methoxycarbonyl)quinoline *N*-oxide were subjected to this reaction (Table 2).

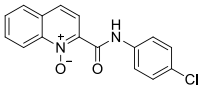
Table 2. Reaction scope[a]

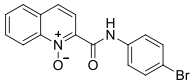

P1 (92%)

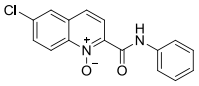

P2 (80%)

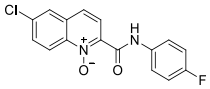

P3 (75%)

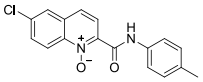

P4 (70%)

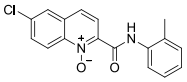

P5 (78%)


P6 (81%)


P7 (84%)


P8 (90%)


P9 (82%)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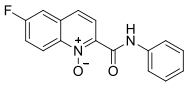
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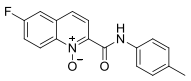
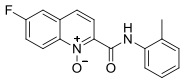
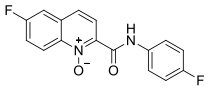
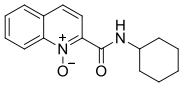
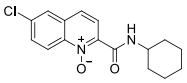
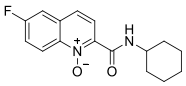

P12 (80%)

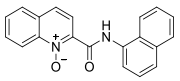

P13 (85%)

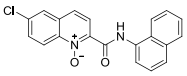

P14 (84%)

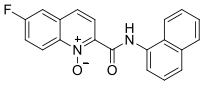

P15 (65%)

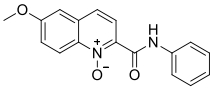

P16 (63%)

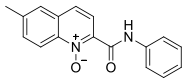

P17 (66%)

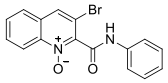

P18 (82%)

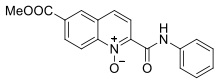

P19(90%)


P20 (70%)


P21 NR

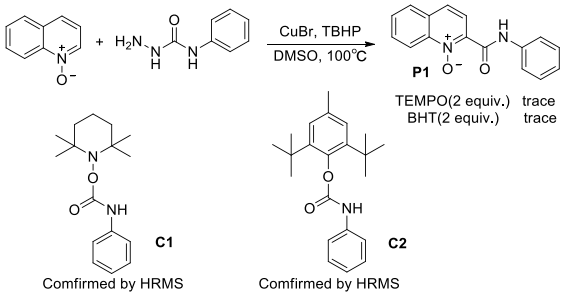

P22 NR


P23 NR

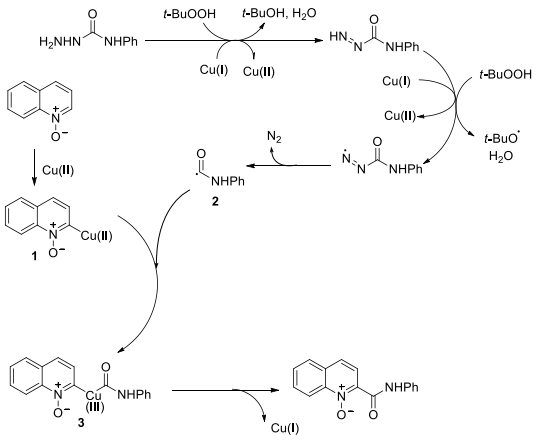

P24 NR

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), CuBr (5 mol%), TBHP (5−6 M in decane, 3.0 equiv), DMSO(2 mL), under air, 100 °C, 12 h.

To gain insight into the reaction mechanism, some control experiments were conducted (Scheme 3). When the reaction was conducted in the presence of di-tert-butylhydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) as a radical trapping reagent, the oxidation was seriously suppressed and only a trace amount of **P1** was observed. The radical adducts between the active intermediate and BHT or TEMPO have been identified by HRMS (Scheme 2). These results indicated that a free radical intermediate was involved in this oxidation.



Scheme 2. Mechanism Research.



Scheme 3. Possible reaction pathway.

Based on the above experimental results and previous reports,[16] a possible reaction pathway was proposed as shown in Scheme 3. Firstly，carbamoyl radical **2** generated from the reaction of hydrazinecarboxamide with TBHP.[17] Subsequently, the reaction of carbamoyl radical **2** and intermediate**1**, which was generated from the reaction of quinolone N-oxides

and CuBr, give the corresponding intermediate **3**. Finally, the desired product was produced with the concomitant formation of copper catalyst.

In summary, a facile and highly efficient method has been successfully developed for the synthesis of carbamoylated quinoline *N*-oxides. A series of structurally diverse products could be effectively obtained using TBHP as oxidant in the presence of CuBr. Further studies on the scope, mechanism, and synthetic application of this reaction are under investigation

Experimental Section

A sealable reaction tube equipped with a magnetic stirrer bar was charged with quinoline N-oxide (0.2 mmol), N-phenylhydrazinecarboxamide (2.0 equiv.), CuBr (5mol%), TBHP(5.0-6.0 mol/L in decane, 3.0 equiv.), DMSO (2.0 ml). The reaction vessel was carried out 100℃. After completion, it was diluted with ethyl acetate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel to afford the corresponding product.

Acknowledgements

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[15] CCDC-1851712 contains the supplementary crystallographic data for this paper (P1). These data can

be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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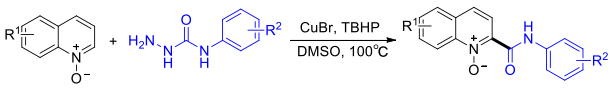
Adv. Synth. Catal. **Year**, *Volume*, Page – Page



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