ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c6cc00946h

Received 2nd February 2016,
Accepted 29th February 2016

DOI: 10.1039/c6cc00946h

www.rsc.org/chemcomm

Copper-catalyzed oxidative coupling between quinazoline 3-oxides and unactivated aldehydes: an efficient approach to functionalized quinazolines†

Liwen Fan,[a] Tao Wang,*[ab] Ying Tian,[a] Fei Xiong,[a] Simei Wu,[a] Qingjin Liang[a] and Junfeng Zhao*[ab]

A copper-catalyzed oxidative coupling between quinazoline 3-oxides and unactivated aldehydes was described. The reaction worked well for both aliphatic and aromatic aldehydes and produced not only the direct oxidative coupling ketones but also cyclic hydroxamic esters derived from quinazolines.

Oxidative coupling of two C–H bonds for the construction of C–C bond has emerged as an attractive and ideal tool for organic chemists because prior functionalization is avoided thus making this strategy environmentally friendly, atom- and step-economic, and sustainable.[1] Among these transformations, the oxidative acylation of arenes involving cross-dehydrogenative coupling between Csp^2–H of arenes and Csp^2–H of aldehydes has attracted a great deal of attention because it offered a straightforward approach to aryl ketones, which have found widespread applications in pharmaceuticals, agrochemicals and materials science. In the past decade, extensive efforts have been made on transition metal such as Pd,[2] Rh[3] and Fe[4] catalyzed oxidative acylation of arenes. However, most of these studies are limited to electron-rich arenes while few methods are available for oxidative acylation of heteroarenes and electron-deficient arenes with aldehydes because both coupling partners are electron-deficient. Very recently, transition metal-free oxidative acylation of arenes has been reported and showed promising solution for oxidative acylation of heteroarenes including isoquinolines, quinolines and quinoxalines.[5] These efforts addressed the challenge of oxidative acylation of heteroarenes with aldehydes to some extent, however, more robust strategies are still in great demand regarding the versatility and potential applications of aryl ketones.

Quinazoline represents one of the privileged scaffolds of pharmaceutical agents and natural products with interesting biological activities.[6] As a consequence, considerable efforts have been made for the synthesis and direct functionalization of quinazoline derivatives.[7] However, it is still far from being developed due to the low efficiency and poor regioselectivity of the current available methods. In the past decade, the *N*-oxide functional group has been recognized as a powerful and removable directing group for *ortho* C–H bond activation of N-containing heterocycles.[8] We believed that the oxidative coupling between Csp^2–H of quinazoline 3-oxides and Csp^2–H of aldehydes would be an efficient method for site selective acylation of quinazoline 3-oxides and furnish quinazoline ketone derivatives. It is noted that some copper reagents have been proved to be effective catalysts for oxidative acylation of Csp^2–H with aldehydes. Li and co-workers demonstrated that the synthesis of isatin derivatives could be accomplished by employing a copper-catalyzed intramolecular C–H oxidative acylation of formyl-*N*-arylformamides (Fig. 1, eqn (1)).[9] Later, the Fu group developed a copper-catalyzed intermolecular version by employing secondary anilines and reactive ethyl glyoxalate (Fig. 1, eqn (2)).[10] Very recently, Lei and co-workers reported an elegant direct oxidative coupling between aldehydes

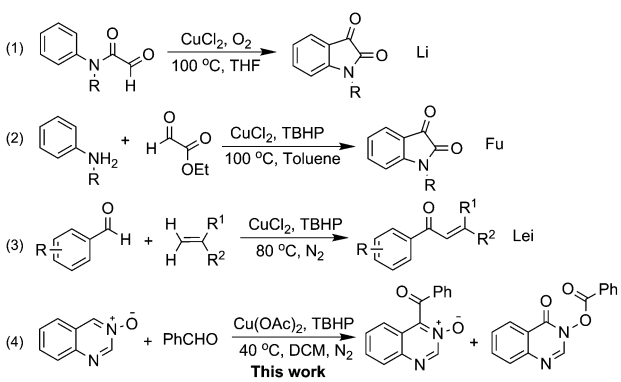


Fig. 1 Copper-catalyzed oxidative coupling of Csp^2–H with aldehydes.

[a] College of Chemistry & Chemical Engineering, Jiangxi Normal University, 99, Ziyang Road, Nanchang, Jiangxi, 330022, P. R. China. E-mail: wangtao@jxnu.edu.cn, zhaojf@jxnu.edu.cn

[b] National Research Center for Carbohydrate Synthesis, Key Laboratory of Chemical Biology, Jiangxi Province, China

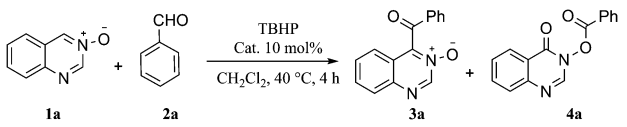
† Electronic supplementary information (ESI) available. CCDC 1450112 and 1450113. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc00946h

and alkenes (Fig. 1, eqn (3)).[11] Significantly different from Li and Fu's work, in which the activated aldehyde glyoxalates were employed, unactivated aldehydes were used as valid coupling partners in Lei's work. Inspired by these accomplishments and considering the low toxicity and cost of copper catalysts, we conceived that copper would be a useful catalyst for the oxidative coupling of N-containing heterocycles with unactivated aldehydes. Herein, we report a copper-catalyzed oxidative coupling of quinazoline 3-oxides with unactivated aldehydes to furnish quinazoline ketones, which could be further transformed into quinazolinone esters in a one-pot manner (Fig. 1, eqn (4)). To the best of our knowledge, the copper catalyzed oxidative acylation of heteroarenes with unactivated aldehydes remains unexplored.

To test the validity of our hypothesis, various copper salts were evaluated with quinazoline 3-oxide as the model substrate. As shown in Table 1, however, no matter what kinds of reaction conditions are employed, only a trace amount of **3a** was isolated. On the other hand, quinazolinone benzoate **4a** (**3a** and **4a** were confirmed by X-ray crystallography, see the ESI†) was isolated in a significant amount. This unexpected result provided a straightforward approach to synthesize cyclic hydroxamic esters derived from quinazoline,[12] which are a series of important heterocyclic compounds in drug discovery. For example, **4a** analogues had been identified as novel inhibitors of *Mycobacterium tuberculosis* acetohydroxyacid synthase (MTB-AHAS).[13] Their synthesis generally required several steps and efficient synthetic strategies are highly demanded.[14] In this regard, we believed that the reaction disclosed here would be an efficient approach to these compounds. As shown in Table 1, copper catalysts influenced the reaction remarkably and cyclic hydroxamic esters **4a** could be obtained directly from quinazoline 3-oxides up to 84% yield in the presence of 10 mol% of $Cu(OAc)_2$, (Table 1, entry **9**).

Next, the substrate scope of this reaction was evaluated. It is observed that a variety of aldehydes are valid substrates for this

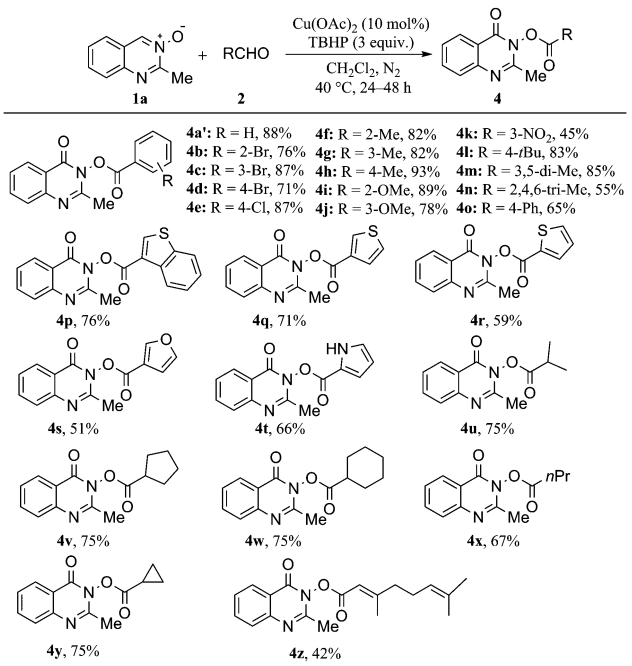
Table 1 Optimization of reaction conditions[a]



1a 2a 3a 4a

Entry	Catalyst	Ratio of **3** : **4**	Yield of **4**[b] (%)
1	CuBr	<1 : 99	65
2	CuCl	7 : 8	32
3	CuI	<1 : 99	41
4	Cu_2O	<1 : 99	80
5	$CuBr_2$	<1 : 99	49
6	$CuCl_2$	<1 : 99	11
7	CuF_2	<1 : 99	84
8	$Cu(OTf)_2$	1 : 2	39
9	**$Cu(OAc)_2$**	**<1 : 99**	**88 (84)**
10	$Cu(BF)_2$	1 : 7	44
11	$Cu(OH)_2$	<1 : 99	68
12	$CuCO_3$	3 : 1	5
13	—	—	—

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), TBHP (5.5 M in decane, 0.6 mmol), 4 h, catalyst (10 mol%), CH_2Cl_2 (2 mL), N_2. [b] GC yield, isolated yield is indicated in parentheses.

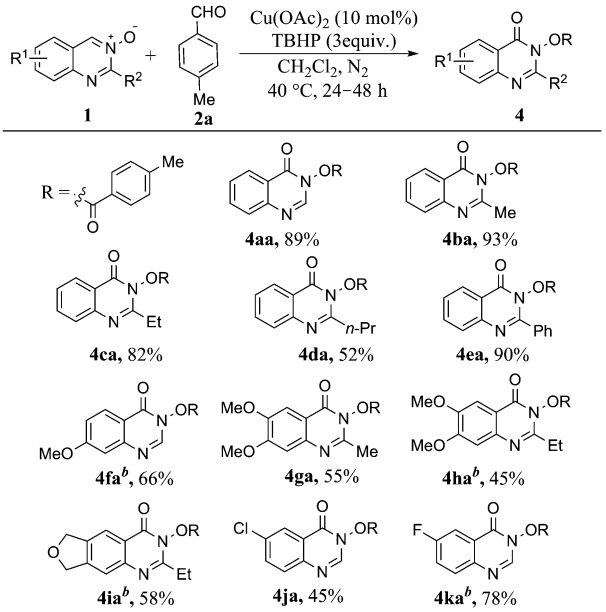


Scheme 1 Copper(II)-catalyzed reaction of quinazoline-3-oxide with various aldehydes. Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), TBHP (5.5 M in decane, 0.6 mmol), CH_2Cl_2 (2 mL), $Cu(OAc)_2$ (10 mol%), N_2. Isolated yields based on **1a**.

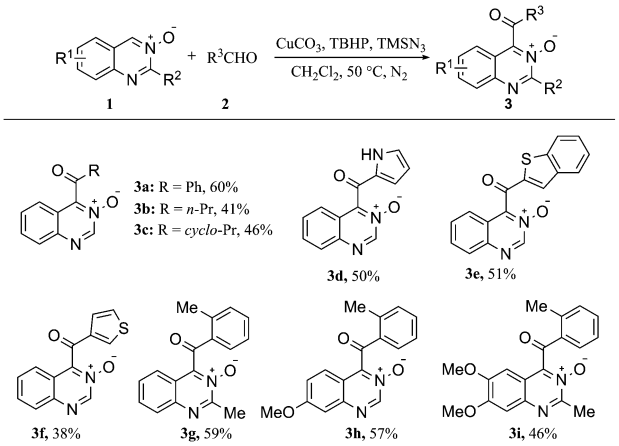
reaction. In terms of benzylaldehyde derivatives, both electron-donating and -withdrawing groups on the phenyl ring are compatible albeit the strong electron-withdrawing group such as $-NO_2$ (Scheme 1, entry **4k**) caused a drop in yield. The reaction is less susceptible to steric hindrance (Scheme 1, entries **4f** and **4i**) and even sterically demanding *ortho* substituents are tolerated (Scheme 1, entry **4n**). α,β-Unsaturated aldehydes are also valid substrates for this transformation (Scheme 1, entry **4z**). Heteroaryl aldehydes and aliphatic aldehydes can also be used as acyl donors to give cyclic hydroxamic esters in good to excellent yields (Scheme 1, entries **4p**–**4y**).

The versatility regarding the quinazoline 3-oxide moiety had also been examined. The substituent at the 2-position of quinazoline 3-oxide has a minor effect on the reaction efficiency (Scheme 2, entries **4aa**–**4ea**). For example, both aliphatic and aromatic substituents are tolerated at this position. It is observed that the yields decreased with the increase of the chain length from the methyl to the propyl group (Scheme 2, entries **4ba**–**4da**). In contrast, substituents on the phenyl ring moiety of quinazoline 3-oxide influenced the reaction remarkably. Both the electron-withdrawing and -donating groups have a significant negative effect on the reaction efficiency (Scheme 2, entries **4fa**–**4ka**).

During the extensive study of the synthesis of cyclic hydroxamic esters **4** derived from quinazoline, careful monitoring of the reaction disclosed that the direct cross coupling product **3** was indeed formed but disappeared slowly along the reaction course. In some cases, compound **3** could be isolated in a small amount if the reactions were quenched prematurely. One oxygen atom component difference between compounds **3** and **4** stimulated us to envision a cascade reaction involving the



Scheme 2 Copper(II)-catalyzed reaction of quinazoline-*N*-oxides with *p*-tolualdehyde. [a] Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), TBHP (5.5 M in decane, 0.6 mmol), CH_2Cl_2 (2 mL), $Cu(OAc)_2$ (10 mol%), N_2. Isolated yields based on **1**. [b] **2a** (1.0 mmol), TBHP (5.5 M in decane, 1.0 mmol).



Scheme 3 Copper(II)-catalyzed direct oxidative coupling reaction of quinazoline-3-oxides with various aldehydes. Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), CH_2Cl_2 (2 mL), TBHP (70% aqueous solution, 0.6 mmol), $TMSN_3$ (0.6 mmol), $CuCO_3$ (5 mol%), N_2. Isolated yields based on **1**.

Baeyer–Villiger oxidation of **3** and a subsequent intramolecular acyl transfer to realize the transformation from **3** to **4**. This proposal was confirmed by a control experiment and we observed that **4a** was formed smoothly with 51% isolated yield when **3a** was treated with 3 equiv. of *m*-chloroperbenzoic acid (*m*-CPBA) and 1 equiv. of CF_3CO_2H, under the classic Baeyer–Villiger oxidation reaction conditions (Fig. 2, eqn (1)). Similarly, **4a** could be isolated in 60% yield in the presence of 3 equiv. of aldehyde under the standard reaction conditions after 12 hours (Fig. 2, eqn (2)). This result clearly illustrated that **3a** would be an intermediate for the formation of **4a**. Encouraged by these experimental results, we hypothesized that aryl ketone **3** would be obtained as the major product if the subsequent Baeyer–Villiger oxidation could be suppressed. To this end, we examined the factors which governed the reaction efficiency (for details of reaction condition optimization, see the ESI†). Decreasing the loading of the oxidant and aldehyde only led to a sluggish reaction while it did not change the ratio between **3** and **4**. Screening of copper catalysts disclosed that $CuCO_3$, a poor catalyst for the formation of compound **4**, is beneficial for stopping the reaction at ketone **3**. To our delight, $TMSN_3$, which played an important role in the metal-free cross-dehydrogenative coupling of heterocycles with aldehydes,[5c] could suppress the subsequent reaction efficiently. Finally, we found that **3** could be obtained as the major product in good yield in the presence of $TMSN_3$ with $CuCO_3$ as the catalyst. As shown in Scheme 3, all of the tested aryl aldehydes including heteroaryl aldehydes proceeded smoothly to afford the target diaryl ketone in moderate to good yields. Aliphatic aldehydes also worked well albeit slightly lower yields were obtained. A substituent on the phenyl ring moiety of quinazoline 3-oxide could be tolerated.

Based on our experimental results, a tentative reaction mechanism was proposed (Scheme 4). The treatment of aldehyde with TBHP gave rise to acyl radical **I**, which could be trapped by quinazoline 3-oxide **1** to release a new radical **II**. Further oxidation of radical **II** furnished aryl ketone **3**. Followed by a Baeyer–Villiger oxidation, in which aryl ketone **3** was transformed into an ester intermediate **III**, which offered cyclic hydroxamic ester **4** upon a subsequent intramolecular acyl transfer (path I). Path II is also operative because it is well established that nitroxides are effective radical trapping reagents.[15] The *tert*-butylperoxy radical, formed *in situ* from TBHP, was trapped by quinazoline 3-oxide to form a

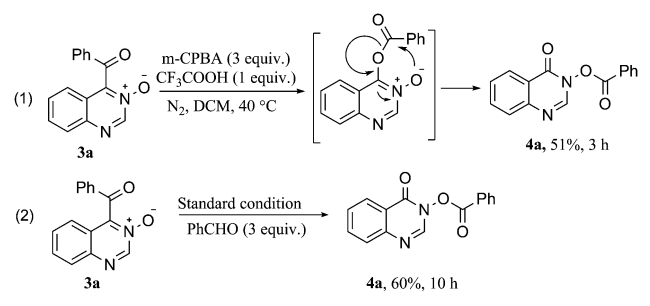
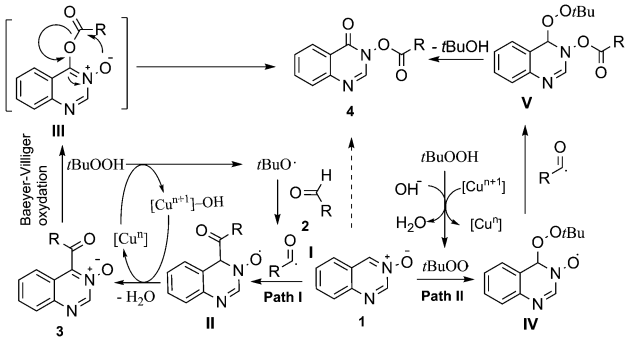


Fig. 2 Control experiments.



Scheme 4 Proposed reaction mechanism.

new O-centered radical **IV**, which coupled with the acyl radical to afford the ester **V**. Both **IV** and **V** were detected by ESI-MS (for details, see the ESI†). Further fragmentation[16] of the ester **V** produced the cyclic hydroxamic ester **4**. $TMSN_3$ might inhibit both the Baeyer–Villiger oxidation of path I and path II directly, thus making **3** as the major product.

We have developed the first copper-catalyzed oxidative coupling of heteroarenes with unactivated aldehydes as acyl donors. This method not only offered a straightforward approach to synthesize quinazoline based diaryl ketones but also provided an unexpected synthetic strategy for the cyclic hydroxamic esters derived from quinazolines. Owing to the mild reaction conditions, easy handling and versatility of the substrate, this method should find broad application in the context of building a quinazoline library for drug discovery and materials science.

This work was supported by the National Natural Science Foundation of China (21462023, 21262018) and the Natural Science Foundation of Jiangxi Province (20143ACB20007, 20133ACB20008).

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