SCIENCE CHINA
Chemistry

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https://doi.org/10.1007/s11426-017-9175-2

Cu(II)-catalyzed aerobic oxidative amidation of azoarenes with amides

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Received September 21, 2017; accepted November 13, 2017; published online December 29, 2017

A method for Cu(II)-catalyzed dehydrogenative amidation of azoarene using air as the terminal oxidant was developed. Various amides, such as arylamides, alkylamides, lactams, and imides, are all effective amidation reagents and provide the desired products in moderate to excellent yields. Notably, good yields can also be obtained on a gram-scale with this amidation reaction. In this protocol of azoarene amidation, the catalyst ($Cu(OAc)_2$) and oxidant (air) are inexpensive and readily available, and the process is highly efficient and atom economical.

copper, C−H activation, amination, aerobic oxidative, azo compounds

Citation: Li G, Chen X, Lv X, Jia C, Gao P, Wang Y, Yang S. Cu(II)-catalyzed aerobic oxidative amidation of azoarenes with amides. *Sci China Chem*, 2018, 61, https://doi.org/10.1007/s11426-017-9175-2

Owing to their characteristic structural skeletons, azoarenes and their derivatives are widely applied not only as traditional dyes and pigments but also as many newly developed functional materials, such as indicators, light-responsive materials, food additives and therapeutic agents [1]. Therefore, the streamlined synthesis of azoarene derivatives in recent years has attracted an enormous amount of attention. Usually, symmetrical azoarene compounds can be readily prepared via reduction of nitroarenes and oxidation of arylamines [2]. In addition, asymmetric compounds can be obtained by cross coupling of arylamines with nitroarenes, nitroso arenes, or diazonium salts with an electron-rich aromatic ring [3]. However, these synthetic methodologies usually suffer from harsh reaction conditions or narrow substrate scopes. The modification and functionalization of easily available symmetrical azoarenes are steps in an up-and-coming method for the synthesis of unsymmetrical azoarenes. In recent years, with the rapid development of transition-metal catalyzed C–H bond activation, various unsymmetrical azoarenes can now be obtained via selective aryl C–H bond functionalization (e.g., acylation, alkoxylation, nitration, halogenation, olefination, alkylation, arylation, phosphorylation, cyanation, aminocarbonylation, and tandem cyclization) of azoarenes using azo-metal chelation [4].

Selective-C–H bond amidations of azoarenes have also been used to synthesize 2-amino azoarenes in the presence of transition metals. Lee, Xu and Jia *et al.* [5] reported rhodium-catalyzed amidation of azobenzenes using azides as the amidation reagents respectively (Scheme 1(a)). Most recently, Lee, Patel and Kim *et al.* [6] independently synthesized 2-amino azobenzene via rhodium-catalyzed C–H bond functionalization employing dioxazolones as the amidation reagent (Scheme 1(b)). In these amidation processes, not only the price of the catalyst and the amidation reagent (azide and dioxazolone) are high, but also the atom and step economy is poor.

Undoubtedly, C–H amidation via cross-dehydrogenative coupling (CDC) reaction is an intriguing method for the

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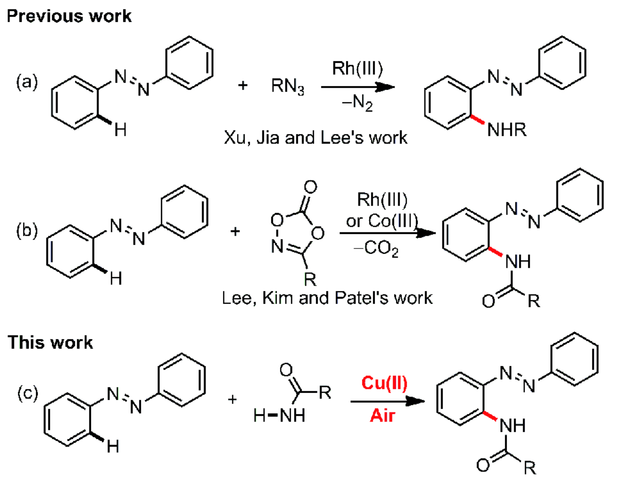
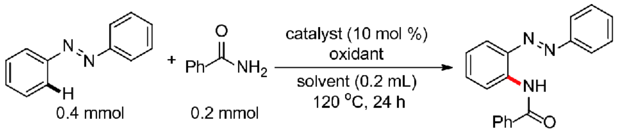


Scheme 1 C–H amidation of azoarene (color online).

Table 1 Optimization of the aerobic oxidative amidation of azoarenes



Entry	catalyst	oxidant	solvent	yield
1	Cu(OAc)$_2$	Air	Xylene	62%
2	Cu(OAc)$_2$	Air	Toluene	43%
3	Cu(OAc)$_2$	Air	Benzene	56%
4	Cu(OAc)$_2$	Air	1,4-Dioxane	18%
5	Cu(OAc)$_2$	Air	Acetonitrile	32%
6	Cu(OAc)$_2$	Air	—	21%
7	**Cu(OAc)$_2$**	**Air**	**Xylene (0.1 mL), Benzene (0.1 mL)**	**81%**
8	Cu(OAc)$_2$	O_2	Xylene (0.1 mL), Benzene (0.1 mL)	83%
9	Cu(OAc)$_2$	Air	Xylene (0.5 mL), Benzene (0.5 mL)	trace
10	Cu(OAc)$_2$	N_2	Xylene (0.1 mL), Benzene (0.1 mL)	0
11	CuBr	Air	Xylene (0.1 mL), Benzene (0.1 mL)	38%
12	CuBr$_2$	Air	Xylene (0.1 mL), Benzene (0.1 mL)	trace
13	CuCl$_2$	Air	Xylene (0.1 mL), Benzene (0.1 mL)	trace
14	—	Air	Xylene (0.1 mL), Benzene (0.1 mL)	0
15	Pd(OAc)$_2$	Air	Xylene (0.1 mL), Benzene (0.1 mL)	0

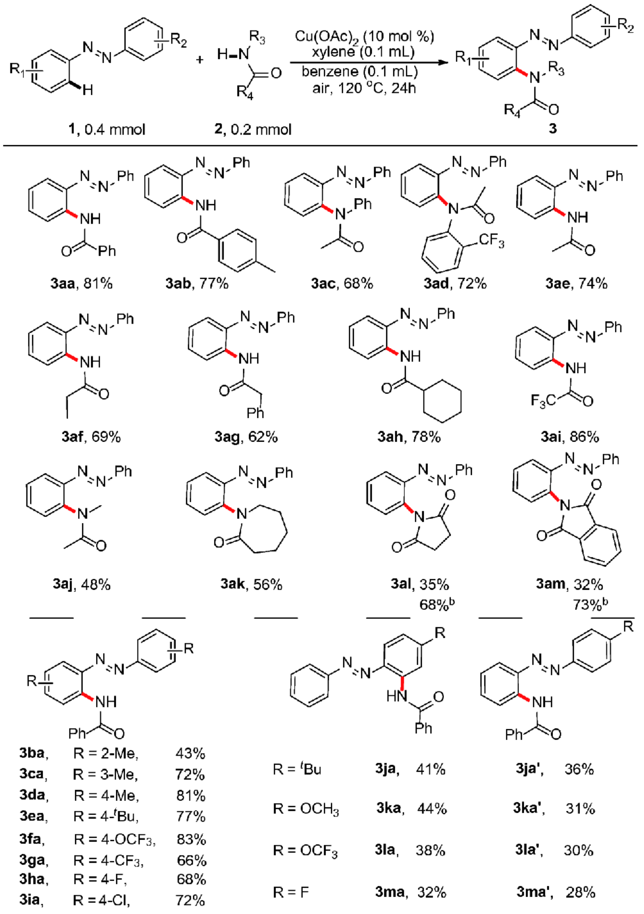
construction of C–N bond because it does not require preactivation of either substrate, reducing the reaction waste and number of steps [7]. Generally, oxidants are a key part in the amidation process. Although oxidants such as peroxides [8], PhI(OAc)$_2$ [9], Cu(II) salts [10], and Ag(I) salts [11] have been demonstrated to be excellent and practical oxidants, pure oxygen, particularly air, is an ideal oxidant due to its environmental benignity and ready availability [12]. Here, we achieved inexpensive copper-catalyzed dehydrogenative amidation of azobenzenes with amides using air as the terminal oxidant (Scheme 1(c)).

First, the low-cost azobenzene **1a** and benzamide **2a** were employed as typical substrates to screen the conditions of the dehydrogenative amidation. The reaction was performed under an air atmosphere at 120 °C for 24 h, as shown in Table 1. To our delight, when Cu(OAc)$_2$ was employed as the catalyst with aromatic solvents such as benzene, toluene, and xylene, the desired product (**3aa**) was obtained in moderate yields (entries 1–3). In acetonitrile, 1,4-dioxane, or even a solvent-free system, the dehydrogenative coupling could still proceed, although the yields were lower (entries 4–6). Further research showed that a mixture of 0.1 mL xylene and 0.1 mL benzene was the most efficient solvent system, affording the desired product in 81% isolated yield (entry 7). Pure oxygen and air were both effective oxidants in the reaction (entry 8). The volume of solvent was also critical for this transformation. Both increasing and decreasing the volume of solvent remarkably depressed the yields of the product (entry 9). The desired product was not obtained under a nitrogen atmosphere (entry 10). CuBr was also an efficient catalyst and gave product in a low yield (entry 11); however, other Cu salts, such as CuBr$_2$ and CuCl$_2$, are inefficient in this transformation (entries 12, 13). When using Pd(OAc)$_2$ as the catalyst or without a catalyst, no desired product was found in the reaction mixture (entries 14, 15).

With the optimized conditions in hand, the scope and generality of the copper-catalyzed aerobic oxidative amidation were explored using various azoarenes and amides, as shown in Scheme 2. Initially, various amide derivatives were employed as coupling partners with azobenzene. The experimental results indicated that many types of amides, such as arylamides (**3aa**, **3ab**), alkylamides (**3ac**–**3aj**), lactams (**3ak**) and imides (**3al**, **3am**) were all good amidation reagents in this dehydrogenative amidation process, affording the desired products in moderate to excellent yields. Although yields are low for imides using air as the oxidant, the yield can be improved using pure oxygen as the oxidant (**3al**, **3am**). Unfortunately, the desired product could not be obtained in the amidation process when sulfonamides and amines were used as coupling partners.

However, many azoarene derivatives were good substrates in the dehydrogenative amidation. Phenyl rings with various substitution patterns (*ortho*, *meta* and *para*) were compatible with the transformation, although *ortho*-substituted substrates displayed certain steric hindrance effects (**3ba**–**3da**). Regardless of whether the substrates were electron rich or electron deficient, all the substrates exhibited good to excellent reactivities (**3ea**–**3ga**). Halogen substituents survived the transformation (**3ha**, **3ia**), providing a significant opportunity for further functionalization from the C–X bond. Unsymmetrical azobenzenes were also suitable substrates for this transformation and gave the products in good to excellent yields. However, the regioselectivity was poor. Two isolable isomers were obtained (**3ja**–**3ma**).

In a gram-scale experiment, the copper-catalyzed aerobic oxidative amidation of azobenzene with amides also proceeded smoothly and provided the desired product in a good yield with a prolonged reaction time (Scheme 3). The present



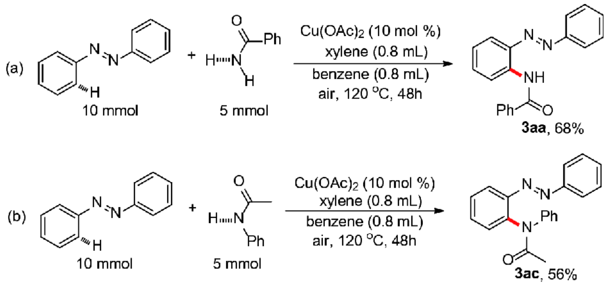
[a] Reaction Conditions: **1** (0.4 mmol), **2** (0.2 mmol), Cu(OAc)$_2$ (10 mol %), air, xylene (0.1 mL), benzene (0.1 mL), 120 °C, 24 h. Isolated yield, [b] O_2 (balloon)

Scheme 2 Scope of Cu(II)-catalyzed aerobic oxidative amidation of azobenzenes with amides (color online).

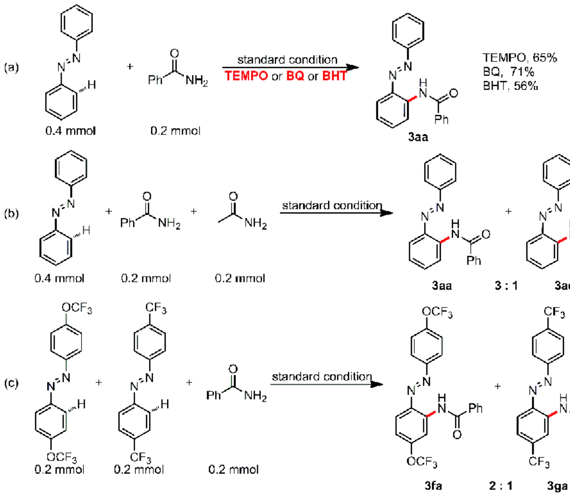
amidation provides a practical and cost-effective approach to synthesizing 2-amino azoarene derivatives.

To gain insight into the mechanism of copper-catalyzed aerobic oxidative amidation of azobenzene with amides, several experiments were designed and conducted, as shown in Scheme 4. First, the desired product could be obtained when either the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or radical inhibitors, such as BHT and BQ, were added to the standard reaction (Scheme 4(a)). This result indicates that amidation is not a radical process. Second, in an intermolecular competitive reaction of azobenzene with arylamide (benzamide) and alkylamides (acetamide) under the optimized conditions, product **3aa** was evidently favored over **3ae**, indicating that the arylamide was more reactivity than the alkylamide in the amidation of azoarene (Scheme 4(b)). Third, to study impact of the electronics of the azoarene on the amidation, a scrambling test of (*E*)-1,2-bis(4-(trifluoromethoxy)phenyl)diazene, which bears an electron-donating group, and (*E*)-1,2-bis(4-(trifluoromethyl)phenyl)diazene, which bears an electron-withdrawing group, with benzamide under the optimized conditions provided predominantly **3fa**. This result strongly suggested that the amidation of azoarene was an electrophilic reaction (Scheme 4(c)).

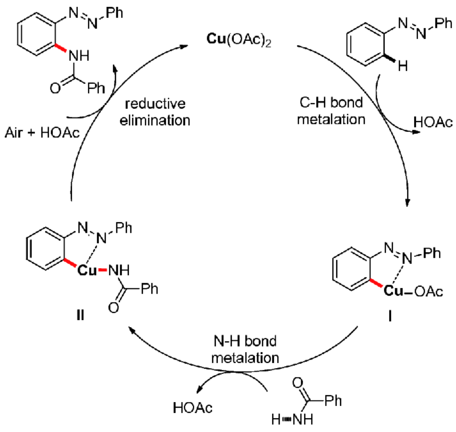
According to the experimental observations and mechanistic studies of other Cu(II)-catalyzed dehydrogenative couplings in related literatures [7g–7j], a possible catalytic cycle for the Cu(II)-catalyzed aerobic oxidative amidation of azoarenes was proposed, as shown in Scheme 5. Initially, under the chelation assistance of the azo group, *ortho*-C–H



Scheme 3 A gram-scale experiment (color online).



Scheme 4 Designed experiments (color online).



Scheme 5 The proposed catalytic cycle (color online).

bond electrophilic metalation of the arene with $Cu(OAc)_2$ provides active cyclometalated complex **I**. Cu(II) complex **I** further coupled with the amide to give active species **II**, which delivers the dehydrogenative amidation product by reductive elimination, followed by aerobic reoxidation of the catalyst.

In conclusion, we developed a copper-catalyzed intermolecular dehydrogenative coupling of azoarenes with several amides using air as the terminal oxidant. Good yields can be obtained at the gram scale. This discovery provides an efficient and practical method for the synthesis of 2-amino azoarene derivatives, which are widely used as various functional materials.

Acknowledgements This work was supported by the National Natural Science Foundation of China (21102005) and Program for Innovative Research Team of Science and Technology in the University of Henan Province (18IRTSTHN004).

Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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