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# Copper-Catalyzed N−H Insertion and Oxidative Aromatization Cascade: Facile Synthesis of 2-Arylaminophenols

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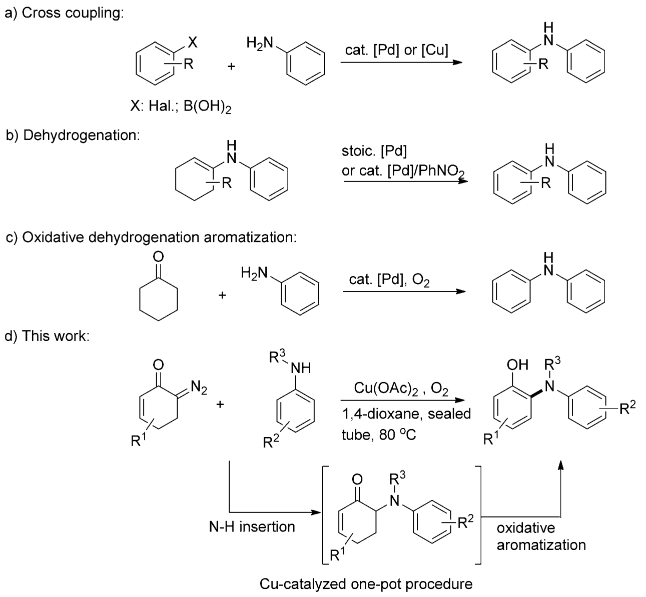
**Abstract:** A copper-catalyzed cascade reaction of N-H insertion and oxidative aromatization has been developed. 2-Arylaminophenols have been prepared in moderate to high yields from the diazo substrates. Moreover, this newly established methodology allows efficient access to natural 1-oxygenated carbazole alkaloids, such as glycozolicine and murrayafoline A.

Carbon–nitrogen bonds are ubiquitous in organic molecules, and thus the construction of C−N bonds is of considerable importance for the field of synthetic organic chemistry.[1] The insertion of metal carbene into N−H bonds of amine derivatives represents one of the most efficient approaches to prepare α-amino acids, α-amino ketones, and nitrogen-containing heterocycles.[2] Even though Yates reported the first copper-catalyzed N−H insertion (NHI) of diazo acetates over 60 years,[3] the introduction of dirhodium(II) catalysts made this reaction practical in organic synthesis.[4] Recently, the groups of Zhou,[5] Fu,[6] and Feng[7] reported the copper-catalyzed enantioselective NHI, in which privileged ligands were required to achieve high enantioselectivity as well as good reactivity. Recent reports highlighted the combination of copper-catalyzed NHI with other transformations in one-pot,[8] which further broadened the application of copper carbenoid chemistry. Copper complexes are relatively cheap and readily available, so it is still highly desirable to develop a novel organic transformation based on copper-catalyzed NHI, instead of precious rhodium catalyst.

Palladium-catalyzed oxidative dehydrogenative aromatization is a fundamental methodology to prepare aromatic compounds from nonaromatic precursors (Scheme 1 b,c).[9] Although copper complexes have been widely utilized in various aerobic oxidative reactions,[10] copper-catalyzed dehydrogenative aromatization reactions remain scare. In 2012, Li and co-workers reported an elegant copper-mediated intermolecular condensation/aromatization cascade procedure for synthesizing aromatic ethers.[11] However, this procedure required one equivalent of copper complex, or the addition of *N*-hydoxyphthalimide (NHPI) was essential if a catalytic amount of copper complex was used. Just recently, Zhai and co-workers described a Pd-catalyzed cross-coupling reaction of aryl iodides and 6-diazo-2-cyclohexenones to produce the 2-aryl-phenols,[12] which featured migratory insertion of Pd-carbene species followed by β-H elimination to afford a newly formed C=C bond as the key step.



Scheme 1. Our synthetic plan towards 2-arylaminophenols.

Herein, we report a copper-catalyzed NHI and oxidative dehydrogenative aromatization cascade process for the synthesis of 2-arylaminophenols (Scheme 1 d). This type of phenol is a common motif in a variety of natural products and pharmaceuticals with significantly biological activities.[13] In our strategy, the remaining challenge is to realize these two different transformations in one-pot catalyzed by only one copper complex, but without the commonly used metals rhodium and palladium. This protocol, which started from the reaction of diazo substrates, represents an alternative approach to the traditional Buchwald–Hartwig reaction,[14] Ullmann-type amination[15] (Scheme 1 a), and other methodologies to access the diarylamine scaffold.[16]

We initially tested the reaction of **1a** and **2a** in the presence of 10 mol % CuI in 1,4-dioxane at room temperature in

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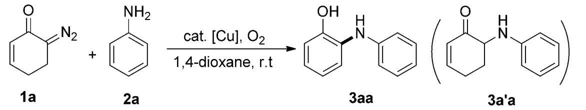
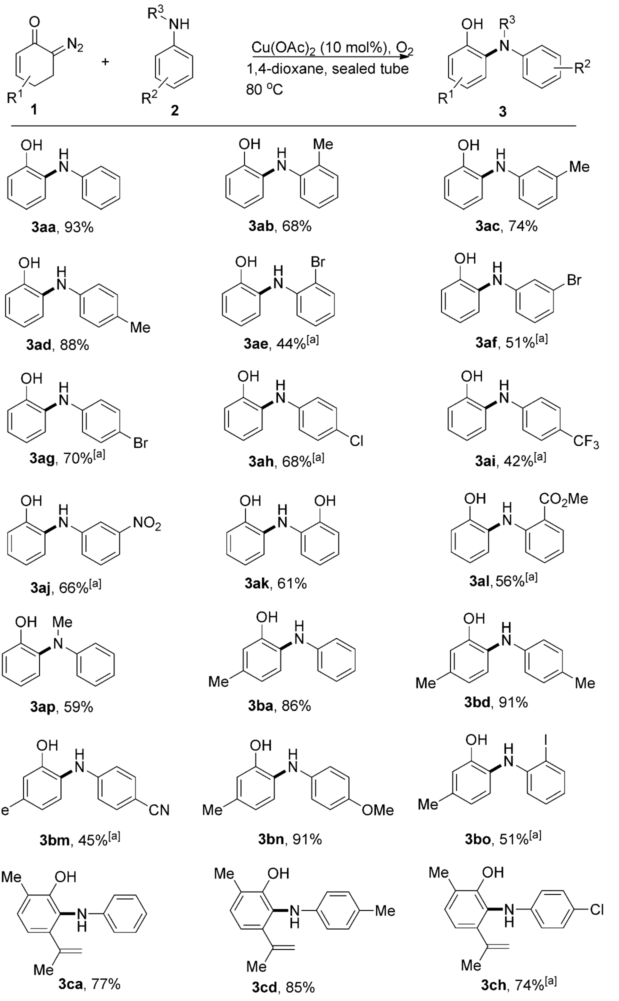
Table 1. Optimization of the reaction conditions.[a]



| Entry | Cu complex (equiv) | Solvent | $T$ [°C] | $t$ [h] | **3aa** (**3a'a**) [%][b] |
|---|---|---|---|---|---|
| 1 | CuI (0.1) | 1,4-dioxane | 25 | 12 | 32 (48) |
| 2 | CuBr (0.1) | 1,4-dioxane | 25 | 12 | 12 (53) |
| 3 | CuCl (0.1) | 1,4-dioxane | 25 | 12 | 14 (35) |
| 4 | CuO (0.1) | 1,4-dioxane | 25 | 12 | 26 (45) |
| 5 | $CuBr_2$ (0.1) | 1,4-dioxane | 25 | 12 | 25 (48) |
| 6 | $[Cu(acac)_2]$ (0.1) | 1,4-dioxane | 25 | 12 | 12 (31) |
| 7 | $Cu(OTf)_2$ (0.1) | 1,4-dioxane | 25 | 12 | 26 (22) |
| 8 | $Cu(OAc)_2$ (0.1) | 1,4-dioxane | 25 | 12 | 46 (45) |
| 9[c] | $Cu(OAc)_2$ (0.1) | 1,4-dioxane | 40 | 8 | 74 (12) |
| **10**[d] | **$Cu(OAc)_2$** (0.1) | 1,4-dioxane | **80** | **3** | **93 (0)** |
| 11[c] | $Cu(OAc)_2$ (0.1) | $CH_2Cl_2$ | 40 | 3 | $<5$ (57) |
| 12[d] | $Cu(OAc)_2$ (0.1) | DCE | 80 | 3 | $<5$ (63) |
| 13[d] | $Cu(OAc)_2$ (0.1) | DMF | 80 | 3 | 48 ($<5$) |
| 14[d] | $Cu(OAc)_2$ (0.1) | DMSO | 80 | 3 | 42 ($<5$) |
| 15[d] | $Cu(OAc)_2$ (0.1) | toluene | 80 | 3 | 62 (0) |
| 16[d] | $Cu(OAc)_2$ (0.1) | $CH_3CN$ | 80 | 3 | 66 (0) |
| 17[d] | $Cu(OAc)_2$ (0.1) | THF | 66 | 3 | 60 ($<5$) |
| 18[d] | $Cu(OAc)_2$ (0.05) | 1,4-dioxane | 80 | 3 | 82 (0) |
| 19[d] | $Cu(OAc)_2$ (1.0) | 1,4-dioxane | 80 | 3 | 11 (0) |

[a] Reaction conditions: **1a** (1 mmol), **2a** (0.5 mmol), copper catalyst (0.05 mmol), solvent (3 mL) under air at 25 °C unless otherwise noted. [b] Isolated yields of **3aa**. The yields in parenthesis refer to the yield of **3a'a**. [c] The reaction was performed at 40 °C under $O_2$ in a sealed tube for 8 h. [d] The reactions were performed at 80 °C under $O_2$ in a sealed tube. acac = pentane-2,4-dione, OTf = $CF_3SO_3$.

an air atmosphere. After 12 h, **3aa** was isolated in 32 % yield along with 48 % **3a'a** (Table 1, entry 1). Next, catalyst screening showed $Cu(OAc)_2$ gave the best result (Table 1, entry 8). Other copper catalysts such as CuBr, CuCl, CuO, $CuBr_2$, $Cu(acac)_2$, and $Cu(OTf)_2$ were inferior to $Cu(OAc)_2$ (Table 1, entries 2–7). Given the large amount of **3a'a** produced in the reaction, we reasoned that higher reaction temperature and an atmosphere of molecular oxygen would probably improve the oxidative aromatization to minimize the amount of **3a'a**. To our delight, after careful examinations, we found that the reaction could be finished in 3 h at evaluated temperature under $O_2$ in a sealed tube. Moreover, the reaction was clean and afforded **3aa** in 93 % yield (Table 1, entry 10). Next, solvent screening indicated that **3a'a** was obtained as the major product in dichloromethane and 1,2-dichloroethane (DCE) (Table 1, entries 11 and 12). In contrast, lower yield of **3aa** was observed when the reactions were conducted in *N,N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), toluene, acetonitrile, and THF (Table 1, entries 13–17). Notably, the use of a stoichiometric amount of $Cu(OAc)_2$ resulted in much lower yield (Table 1, entry 19).

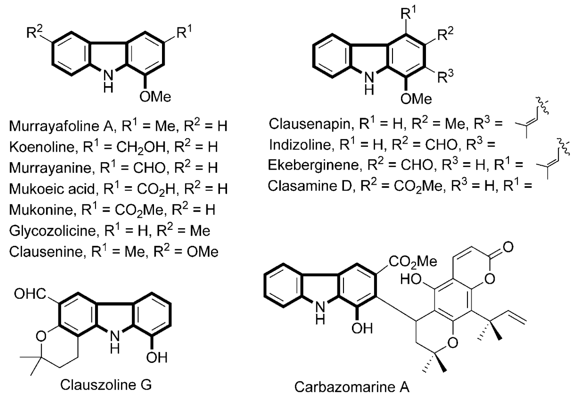


Scheme 2. Substrate scope. Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), $Cu(OAc)_2$ (0.05 mmol), in 1,4-dioxane (3 mL) with $O_2$ in a sealed tube at 80 °C for 3 h. Yields of isolated product are given. [a] Reaction time is 8 h.

With the optimized reaction conditions in hand, we next examined the substrate scope. An array of anilines and diazo substrates were subjected to this cascade procedure (Scheme 2). Generally, the electron-rich anilines delivered the corresponding 2-arylaminophenols in higher yields than the electron-deficient anilines even with shorter reaction time. The *ortho*-substituted anilines displayed lower reactivity than *para* and *meta*-substituted anilines (Scheme 2, **3ab**, **3ae**, **3ak**, **3al** and **3bo**). In addition, *N*-methyl substituted aniline (**2p**) was also tolerated in the reaction and gave **3ap** in 59 % yield. For the diazo substrates investigated, the substituents did not affect the reactivity significantly. Even for the more sterically hindered diazo cyclohexenone, the reactions still proceeded smoothly to afford the desire diarylamines in moderate to high yields (Scheme 2, **3ca**, **3cd**, **3ch**).

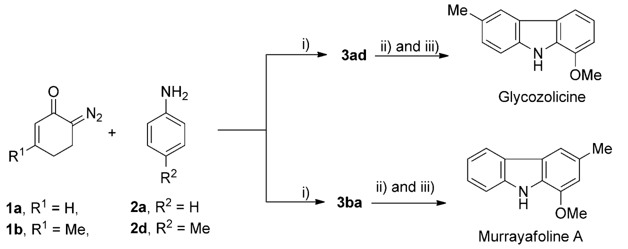
1-Oxygenated carbazole alkaloids have been found mainly in *Rutaceae* family plants such as *Murraya*, *Clausena*, and others (Scheme 3).[13] These alkaloids have received considerable attention due to their diverse and significant biological activities. Thus much effort has been paid toward a general and flexible approach to access this 1-oxygenated carbazole scaffold.[17]

Using our newly established methodology, we pursued a simple and efficient route to two natural 1-oxygenated car-



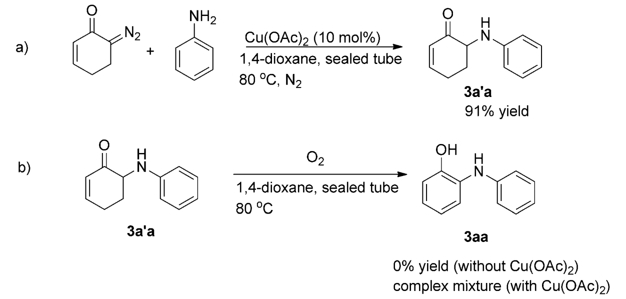
Scheme 3. Natural 1-oxygenated carbazole alkaloids.

bazole alkaloids (glycozolicine and murrayafoline A) on a gram scale (Scheme 4). It was easy to prepare the key diarylamine intermediates **3ad** and **3ba** in high yields. After methylation and palladium-catalyzed annulation, glycozolicine was obtained in 67 % yield[17a] and 76 % yield[17b] in three steps, murrayafoline A in 60 % yield[17a] and 42 % yield.[17b] Obviously, this approach can be employed to prepare other 1-oxygenated carbazole alkaloids.



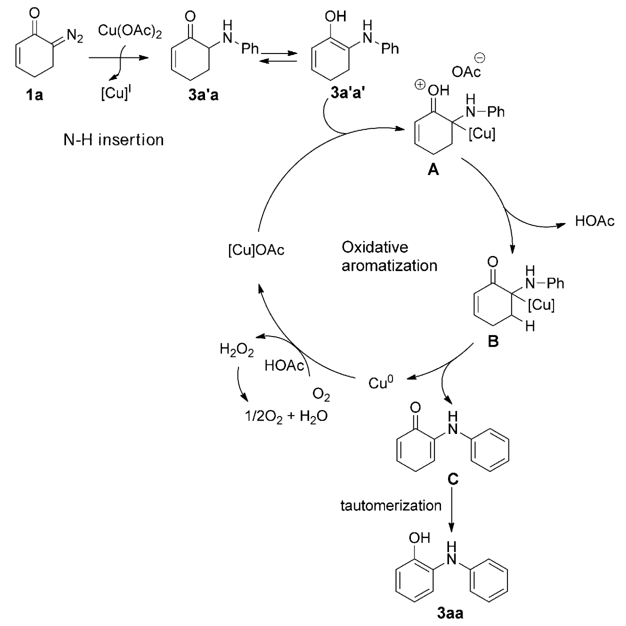
Scheme 4. Synthesis of glycozolicine and murrayafoline A on a gram scale. Reaction conditions: i) **1** (20 mmol), **2** (10 mmol), $Cu(OAc)_2$ (1 mmol), $O_2$, 1,4-dioxane, sealed tube, 80°C, 3 h. ii) MeI, $K_2CO_3$, $Me_2CO$, reflux, 3 h. iii) A: $Pd(OAc)_2$, HOAc, 140°C, 10 h. B: $Pd(OAc)_2$ (5 mol %), $K_2CO_3$ (10 mol %), pivalic acid, 110°C, 14 h.

To further understand the reaction process, we conducted control experiments (Scheme 5). Under a nitrogen atmosphere, **3a′a** was isolated as the sole product (Scheme 5 a). In addition, when **3a′a** was subjected to standard reaction conditions in the absence of $Cu(OAc)_2$, no **3aa** was detected (Scheme 5 b). In addition, the reaction gave a complex mixture when the $Cu(OAc)_2$ was added (Scheme 5 b). As described in Table 1, the use of a stoichiometric amount of $Cu(OAc)_2$ gave **3a′a** in very low yield (Table 1, entry 19). These experiments revealed that the formation of **3a′a** served as the key step during the cascade process. Moreover, the actual active copper species was not $Cu(OAc)_2$, which could explain why a large amount of $Cu(OAc)_2$ led to a much lower yield and the stepwise oxidation of **3a′a** gave a complex mixture of products.



Scheme 5. Control experiments.

As reported by Kochi and Salomon, although $Cu^{II}$ complexes are highly active catalysts in reactions of diazo compounds, those catalytic systems involve prior reduction from $Cu^{II}$ to $Cu^{I}$ by the diazo substrates.[18] The actual catalytically active copper species is $Cu^{I}$ in copper carbenoid chemistry.[4,8d,18] So a plausible reaction mechanism is proposed in Scheme 6. The first catalytic step is Cu-mediated NHI to afford the insertion intermediate **3a′a**. Secondly, **3a′a′** is generated through tautomerization of **3a′a**; subsequent electrophilic addition of [Cu]OAc produces intermediate **A**. Elimination of HOAc gives intermediate **B**, which undergoes deprotonation to deliver intermediate **C** and $Cu^0$ species. Finally, intermediate **C** would quickly tautomerize to its more stable isomer **3aa**, while the $Cu^0$ species could be reoxidized to a higher oxidative state in the presence of molecular oxygen to complete the second catalytic cycle.



Scheme 6. Proposed reaction mechanism.

In summary, we have demonstrated here a novel and efficient strategy for the synthesis of 2-arylaminophenols. A variety of aniline derivatives with different substituents afforded the desired phenols in moderate to high yields. Notably, this one-pot cascade procedure involves a copper-carbene mediated N–H insertion and an oxidative dehydrogenative aromatization under an atmosphere of molecular oxygen. Also, this approach featured the application of cheap $Cu(OAc)_2$ as the catalyst, a very simple procedure, very high efficiency, and molecular oxygen as green oxidant. Furthermore, based on this newly established methodology, two naturally occurring 1-oxygenated carbazole alkaloids, glycozolicine and murrayafoline A have been prepared in three steps from the diazo substrates.

## Experimental Section

*Typical Procedure for Copper-Catalyzed N–H Insertion and Oxidative Aromatization Cascade*

A 25 mL Schlenk tube was charged with copper(II) acetate (10 mol %), evacuated, and refilled with molecular oxygen (three cycles) by using a balloon. Aniline (0.5 mmol), 6-diazo-2cyclohexenone (1 mmol), and 1,4-dioxane (3 mL) were added by syringe. Then the balloon was removed and the tube was sealed, and the reaction mixture was stirred at 80°C for 3–8 h. After the mixture was cooled to room temperature, solvents were removed under vacuum. The residue was purified by column chromatography on silica gel and eluted with petroleum ether and ethyl acetate to give the pure product.

## Acknowledgements

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**Keywords:** aromatization · copper · diazo compounds · domino reactions · homogeneous catalysis

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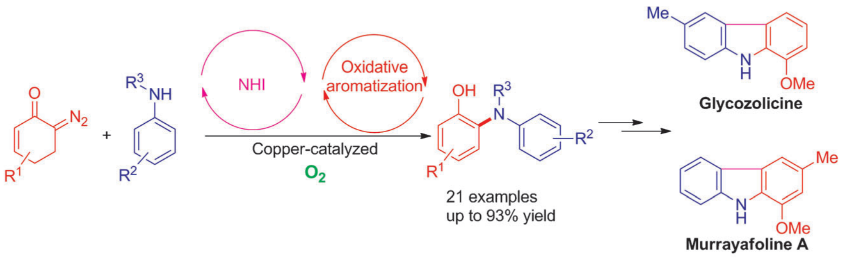

**Copper falls**: A copper-catalyzed cascade reaction of N−H insertion and oxidative aromatization yields 2-arylaminophenols. This newly established methodology also allows efficient access to natural 1-oxygenated carbazole alkaloids, such as glycozolicine and murrayafoline A.

**Homogeneous Catalysis**

*Dong Ding, Xiaobing Lv, Jian Li, Guangyang Xu, Bing Ma, Jiangtao Sun** ▮▮▮▮–▮▮▮▮

**Copper-Catalyzed N−H Insertion and Oxidative Aromatization Cascade: Facile Synthesis of 2-Arylaminophenols**