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Copper-mediated *ortho* C—H primary amination of anilines

Tai-Jin Cheng [a,b], Xing Wang [a,b], Hui Xu [a,*], Hui-Xiong Dai [a,b,*]

[a] Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Shanghai 201203, China
[b] University of Chinese Academy of Sciences, Beijing 100049, China

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ABSTRACT

We report herein a copper-mediated *ortho* C—H primary amination of anilines by using cheap and commercially available benzophenone imine as the amination reagent. The protocol show good functional group tolerance and heterocyclic compatibility. Late-stage diversification of drugs demonstrate the synthetic utility of this protocol.

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Primary anilines are important structural motifs in organic synthesis, and commonly found in natural products and pharmaceuticals.[1]. Thus, development of an efficient and practical approach to introduce a primary amino into the target molecular is highly desirable in organic synthesis [2]. Direct C—H primary amination is the most straightforward way. Without chelating group assistance, in 2016, Tung [3a] and Nicewicz [3b] independently developed photocatalyzed C—H bond primary amination by employing ammonia and ammonium carbamate as amino source. Zhang developed a radical amination by using $TMSN_3$ as the amino source [4]. Falck [5a], Morandi [5b], Jiao [5c], and Seko [5d] reported the Rh-, Fe-, and Cu-catalyzed electrophilic amination. However, these non-directed protocols often suffer poor regioselectivities, and a mixture of aniline isomers were formed (Scheme 1a).

Directing-group assisted C—H functionalization is a reliable approach to regioselectively introduce a functional group in the *ortho*, *meta*, and even remote *para* positions of the arene [6]. By employing 8-aminoquinoline, and oxazoline amides as the directing group, Tan [7a], Gui [7b], Bolm [7c], Chang [7d] and our group [7e] reported Cu- and Ni-catalyzed C—H primary amination of aryl carboxylic acid by employing ammonia, NaN_3, oxime, and dibenzothiophene sulfoximine as the amino source (Scheme 1b-1). In 2016, Uchiyama [8] demonstrated a new strategy to introduce primary amine into arene *via* directed deprotonative cupration of aromatic C—H bond and subsequent amination using $BnONH_2$. In 2014, Zhu [9] reported *ortho* primary amination of 2-phenylpyridine-type substrate using $TMSN_3$ as the amino source (Scheme 1b-2). Despite these undisputable achievements, *ortho* C—H primary amination of aniline has not been demonstrated yet. In connection with our interest in copper-catalyzed C—H functionalization [10] and development of new primary amination reagents [7e], herein, we report copper-mediated *ortho* C—H primary amination of anilines by employing safe and commercially available benzophenone imine as the amino source (Scheme 1c).

Aqueous ammonia, amide and imine are often employed as the amino source in the metal-catalyzed C—H amination [3–5,7–9]. Thus, we commenced our studies by treating **1a**, aqueous ammonia **2a** with 0.2 equiv. $Cu(OAc)_2$ in 3 mL toluene at 80 °C (Table 1, entry 1). However, no desired product was obtained. Next, we screened various amino sources, including amide, sulfamide, imine, and oxime. To our delight, imine **2d** afforded the desired product **3a** in 11% yield after the hydrolysis (entries 2–5). Among varieties of copper salts investigated, CuCl was the optimal and could improve the yield to 21% (entries 6–8). Increase the loading of CuCl to 1 equiv. could significantly improve the yield to 51% (entry 9). DMSO was also effective, albeit in lower yield (entry 10). When DMF and MeOH were employed in the reaction, no desired product was obtained (entries 11 and 12). Lowering or elevating the reaction temperature to 60 and 100 °C could not improve the yield (entries 13 and 14). Copper-promoted dimerizations of benzophenone imine were inevitably formed during the optimization process [11], promote us to further screen the imine equivalent and the CuCl loading (see supporting information). Finally, we could improve the yield to 85% in the presence of 1.5 equiv. of CuCl and 2.5 equiv. of benzophenone imine **2d** (entry15).

* Corresponding authors at: Chinese Academy of Sciences Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Shanghai 201203, China (H.-X. Dai).

E-mail addresses: xuhui2018@simm.ac.cn (H. Xu), hxdai@simm.ac.cn (H.-X. Dai).

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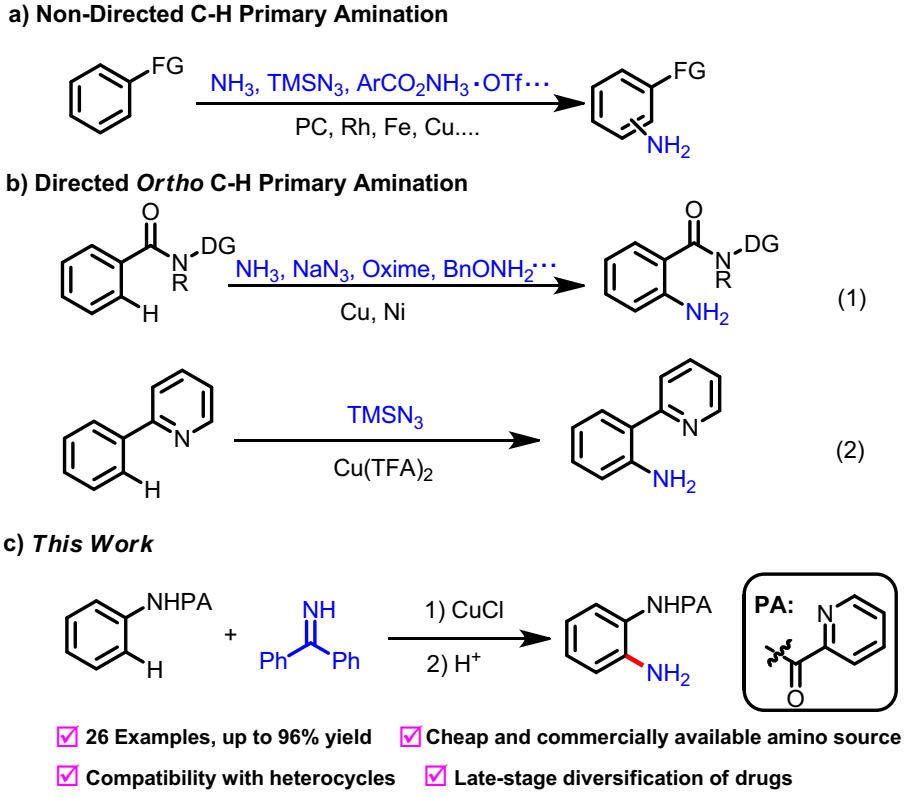
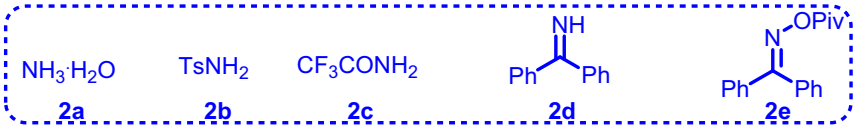


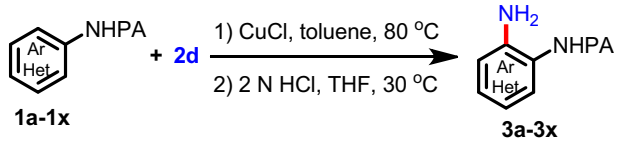
Scheme 1. Dirtect C—H primary amination reactions.

Table 1
Optimization of the reaction conditions.[a]



Having the optimal reaction condition in hand, we began to explore the substrate scope (Table 2). 4-Methyl and 4-phenyl substituted **1b** and **1c** gave the aminated product in a moderate yields. Various substrate bearing electron-rich substitutes at the *para* position afforded the desired product **3d**-**3g** in moderate to good yield. 4-Halogen substituted substrates were compatible in the reaction, furnishing the desired product **3h**-**3j** in moderate to good yields. When 4-CF_3 and 4-CO_2Me substituted **1k** and **1l** were employed, the desired product **3k** and **3l** were obtained in 44% and 46% yields, respectively. When substrates bearing -Me, -OMe, -F, and -Cl at the *meta* position of aniline were employed, C—H primary amination occurred at the less hinder C-6 positions, giving the desired products **3m**-**3p** in 50–84% yields. Substrate **1q** afforded the corresponding product **3q** in excellent yield. α-Naphthylamine **1r** and β-Naphthylamine **1s** were also tested, furnishing the aminated product **3r** and **3s** in 60% and 82% yields, respectively. Remarkably, this protocol show good heterocyclic compatibilities. Heterocycles, including indole, benzothiophene, benzothiazole, quinoline and quinoxaline were well tolerated, affording the desired products **3t-3x** in 41–93% yields.

Table 2
Substrate scope of aromatic anilines.



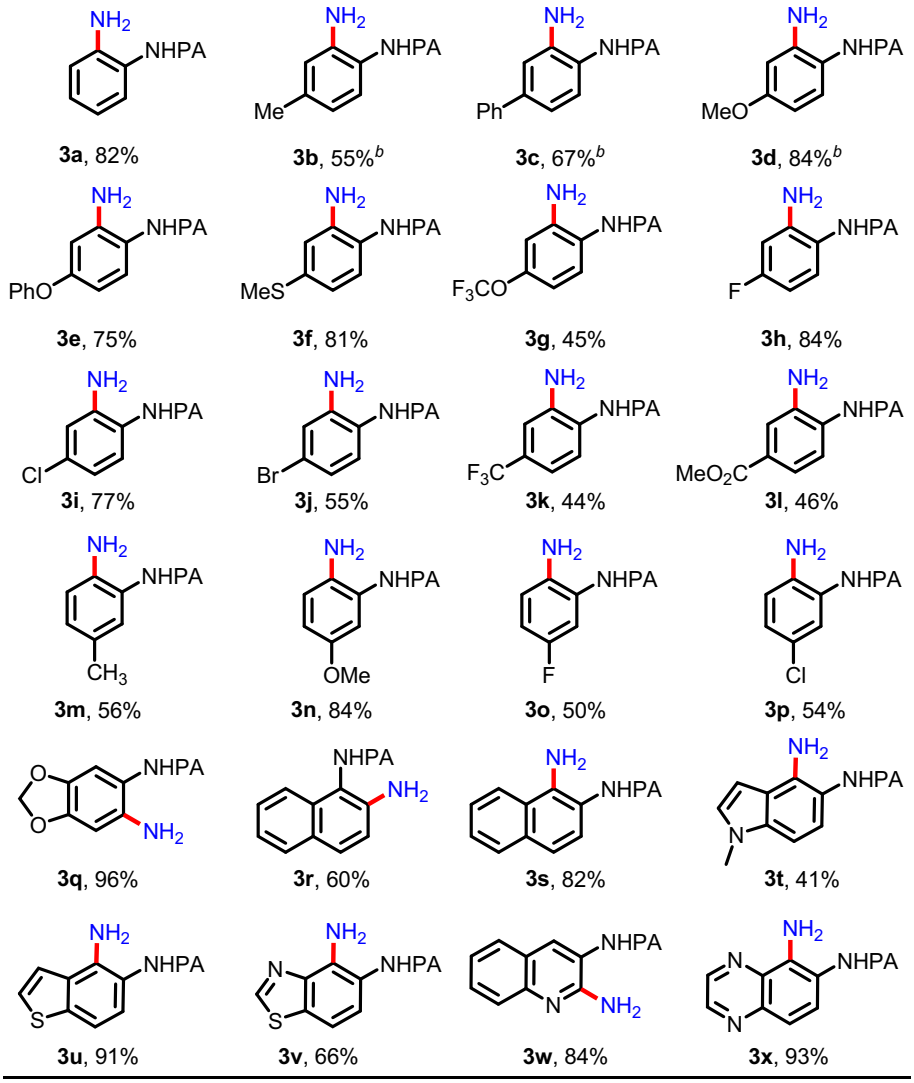
To demonstrate the synthetic utility, we applied this protocol to the late-stage diversification of medicinal drugs. To our delight, Mesalazine **1y**, and Chlorphenesin **1z** could be facilely aminated, furnishing the desired product **3y** and **3z** in 45% and 72% yields, respectively (Table 3).

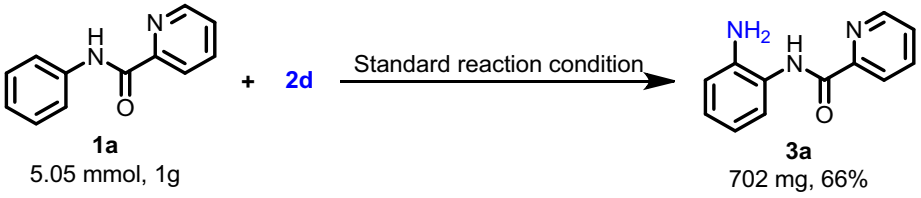
Furthermore, to showcase the synthetic practicality, gram-scale experiment was carried out by using substrate **1a** (1.0 g) under standard reaction condition, affording the corresponding product **3a** in 66% yield (Scheme 2).

For a better understanding of the mechanism of copper catalyzed C—H primary amination, some control experiments were carried out (Scheme 3). The addition of radical scavenger TEMPO had no impact on the yield, which indicated that the radical process was not involved in the amination reaction (Scheme 3-a) [12]. Both inter- and intermolecular kinetic isotope competition experiment gave a K_H/K_D value of 1.0, indicating that C—H cleavage was not the rate-limiting step.

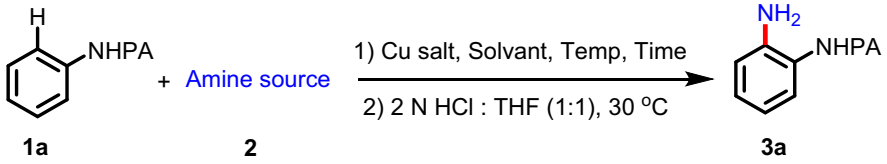
Finally, the 1,2-diaminobenzene **4** was obtained in 48% yield by removing the picolinamide directing group of **3a**.

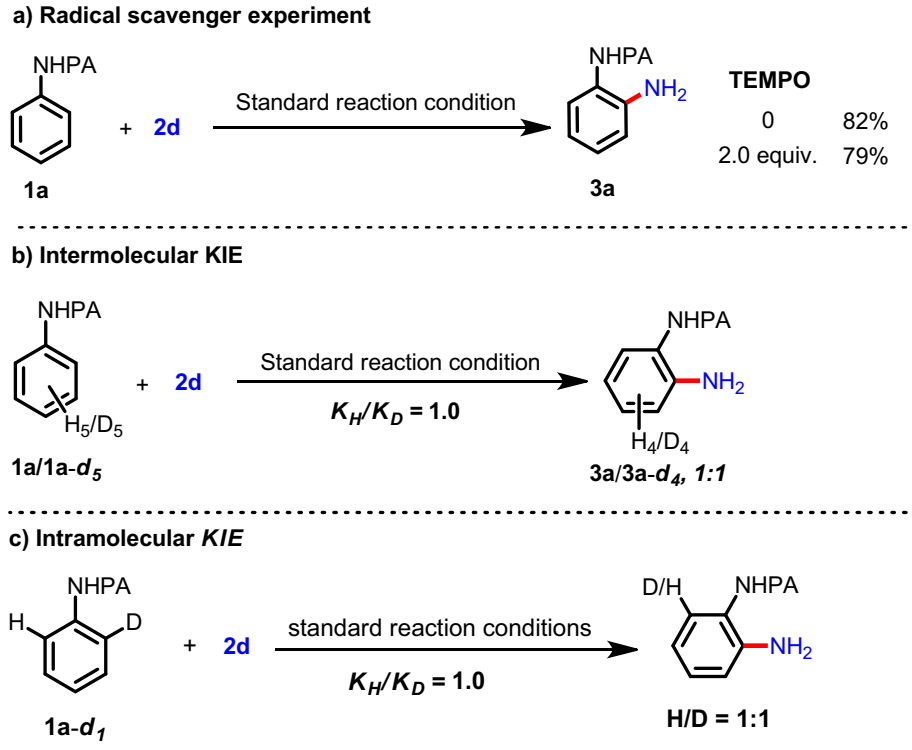
Table 3
Late-stage diversification of medicinal drugs.





Scheme 2. Gram-scale experiment.





Scheme 3. Mechanism studies.

In summary, we developed a copper-mediated *ortho* C—H primary amination of aniline by using cheap and commercially available benzophenone imine as the amino source. A variety of functional groups were well tolerated, affording the desired product in moderate to excellent yields. Heterocycles, including indole, benzothiophene, benzothiazole, quinoline, and quinoxaline were well compatible. Late-stage diversification of medicinal drugs and gram-scale experiment were carried out, demonstrating the synthetic utility of this protocol. Further mechanism investigations are currently ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153099.

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