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Copper-Catalyzed Electrophilic Ortho C(sp^2)−H Amination of Aryl Amines: Dramatic Reactivity of Bicyclic System

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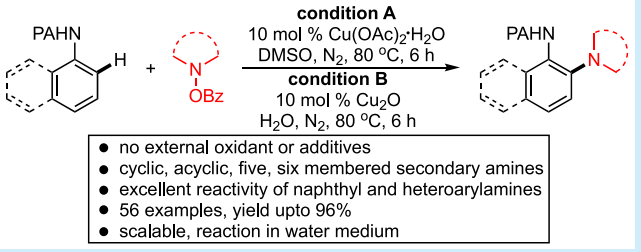
Supporting Information

ABSTRACT: A practical copper-catalyzed, 2-picolinamide-directed *ortho* C−H amination of anilines with benzoyl-protected hydroxylamines has been disclosed that proceeds smoothly without any external stoichiometric oxidant or additives. Remarkably, besides anilines, bicyclic naphthyl or heterocyclic amines furnished amination products with five- and six-membered cyclic and acyclic amines at the *ortho* position selectively. This electrophilic C−H amination also proceeds smoothly in water under slightly modified reaction conditions.



Efficient construction of C−N bonds represents one of the mainstays of research in organic synthesis over the last decades, because of the exponential use of nitrogen-containing molecules in pharmaceutical, medicinal, and materials science.[1] Following the pioneer works of Buchwald and Hartwig regarding palladium-catalyzed C−N bond formation from aryl halides and amines,[2] an impressive array of Earth-abundant, inexpensive copper-catalyzed C−N coupling reactions have been explored.[3] A mechanistically distinct copper-catalyzed/mediated oxidative C−N coupling using organometallic reagents has also been developed under mild conditions.[4] A paradigm shift from transition-metal-catalyzed cross-coupling with organometallic reagents to direct C−H amination strategy has been observed in the last decades. In this vein, the research groups of Yu and Chatani independently reported copper-mediated C−H amination of 2-arylpyridines.[5] Remarkably, the Daugulis group expanded the scope of C−H amination using removable, bidentate directing groups.[6] Recently, the Chang group also reported copper-mediated C−H amination with aqueous ammonia.[7]

2-Aminoanilide moiety is ubiquitously found in drug candidates for the treatment of cancer, Alzheimer's disease, wet age-related macular degeneration (wet AMD), and infectious diseases.[8] In 2014, the research groups of Rodríguez and Chen independently reported copper-catalyzed, 2-picolinamide-directed ortho C−H amination of aniline.[9] However, stoichiometric amount of expensive PhI(OAc)$_2$ was used as an oxidant, which generates PhI as a byproduct. More recently, an electrochemical synthesis of C−H amination of the same substrate was reported by the Mei group, using tetrabutylammonium iodide (TBAI) as a redox mediator.[10] However, all these protocols are limited to the six-membered cyclic amines only. Acyclic amines, pyrrolidine (<5% yield), etc. were ineffective and bicyclic 1-naphthylamine was a moderately effective (∼50% yield) substrate under these protocols.

As an alternative to oxidative C−H/N−H coupling, an umpolung strategy employing R_2N^+ species is emerging for electrophilic amination under mild conditions.[11] In this direction, palladium,[12] rhodium,[13] ruthenium,[14] and iron[15] catalysis has been explored where a high-valent metal center is believed to be involved in the catalytic cycle. Although copper-catalyzed electrophilic amination using organometallic reagents has been well-explored,[16] electrophilic C−H amination by a copper catalyst is limited to the electron-deficient systems in nondirected fashion.[17] A copper-mediated electrophilic C−H amination with oximes to primary amines was reported by the Yu group.[18] To the best of our knowledge, copper-catalyzed directed electrophilic C−H amination has not been reported.

We report here, a practically useful and general methodology for the *ortho* C−H amination of aryl amines using *O*-benzoylhydroxylamines without any stoichiometric external oxidant (Scheme 1). Surprisingly, we observed the superior reactivity of the naphthylamines, which were inferior substrates in previous methods.

To optimize the reaction condition, we chose 2-picolinamide protected aniline **1a** and *O*-benzoyl hydroxylmorpholine **2a** as model substrates, which is summarized in Table 1. After several screenings, we found that, when **1a** was heated at 80 °C for 6 h under a nitrogen atmosphere with 2.5 equiv of **2a** in the presence of 10 mol % of Cu(OAc)$_2$·H$_2$O in dimethylsulfoxide (DMSO), the desired *ortho* aminated product was isolated in 94% yield. No product was formed

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Scheme 1. Copper-Catalyzed C−H Amination of Anilines

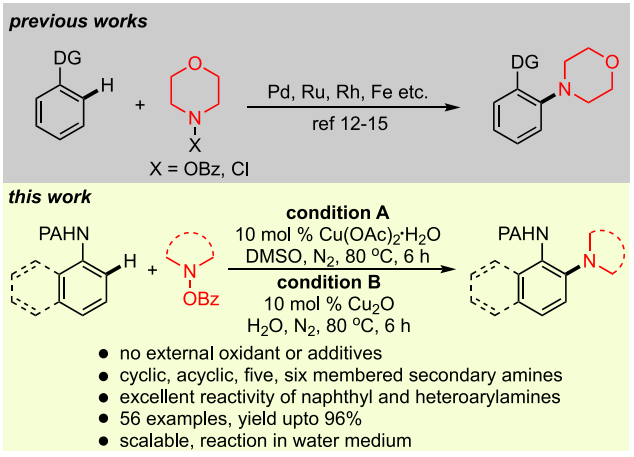
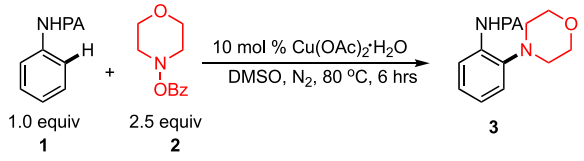


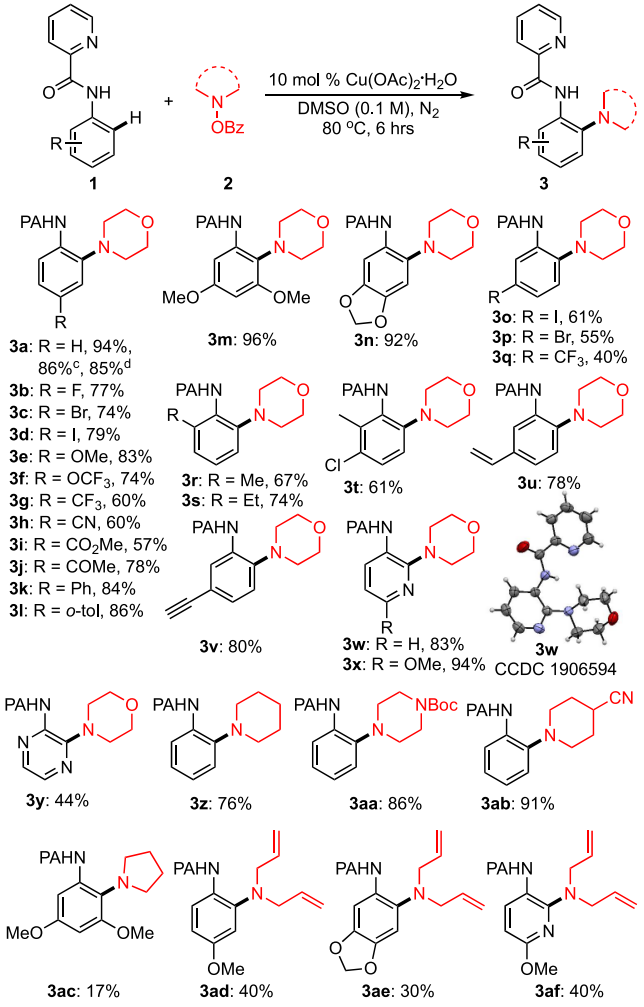
Table 1. Optimization of the Reaction Conditions[a,b]



entry	deviation from optimized condition	yield[b] (%)
1	none	94
2	no $Cu(OAc)_2.H_2O$	nr
3	$Cu(OTf)_2$ instead of $Cu(OAc)_2·H_2O$	76
4	CuOAc instead of $Cu(OAc)_2.H_2O$	84
5	Cu_2O instead of $Cu(OAc)_2·H_2O$	78
6	Cu powder instead of $Cu(OAc)_2·H_2O$	85
7	O_2 atm instead of N_2	72
8	air instead of N_2	65
9	25 °C instead of 80 °C	51
10	1.0 equiv of **2**	40
11	3.5 equiv of **2**	95
12	morpholine/Bz_2O_2 instead of **2**	50

[a]All reactions were performed in 0.2 mmol scale. [b]Yields referenced here are overall isolated yields.

Scheme 2. Substrate Scope with Monocyclic (Het)aromatic Anilides[a,b]



[a]Reactions were performed in 0.2 mmol scale. [b]Yields refer to isolated pure compounds. [c]Reaction performed in gram scale. [d]10 mol % Cu powder was used.

in the absence of a copper catalyst. $Cu(OTf)_2$, Cu_2O provided amination product in lower yields. Interestingly, inexpensive copper powder that had been dissolved in the course of reaction was also able to provide amination product in 85% yield, demonstrating the superior reactivity of the electrophilic amine surrogate. When the reaction was performed under an air or oxygen atmosphere, the yield was decreased, presumably because of decomposition via overoxidation of the amination product. The reaction at room temperature provided 51% of the desired product. The reaction with copper nanoparticle (~50 nm) and lower catalyst loading (i.e., 5 mol %) Cu powder provided yields of 65%−70%.

Under the optimized reaction conditions, we examined the substrate scope (Scheme 2). Aniline moieties containing fluoro, bromo, iodo at the *para* position (**3b**−**3d**, see Scheme 2) gave moderate yields under the optimized reaction conditions. As expected, electron-rich substrates furnished better yields than electron-deficient anilines. Electron-donating methoxy, phenyl, *O*-tolyloxy substitution at the *para* position (**3e**, **3k**, **3l**; see Scheme 2) provided good yields. On the other hand, electron-withdrawing trifluoromethoxy, trifluoromethyl, cyano substitution at the same position gave moderate yields (**3f**−**3h**, see Scheme 2). Ester and keto groups are found to be tolerable under this condition, providing moderate yields of the desired product (**3i**−**3j**, see Scheme 2). *meta*-Dimethoxy-, methylene dioxy-substituted anilines gave excellent yields (**3m**, **3n**; see Scheme 2). Iodo, bromo substitution at the *meta* position afforded lower yields than their corresponding *para* substitution (**3o**, **3p**; see Scheme 2). Vinylic group and terminal alkyne group also survived under the optimized condition providing very good yields (**3u**, **3v**; see Scheme 2). Remarkably, sterically congested *ortho* methyl-, ethyl-substituted anilines also furnished moderate yields, which were poor substrates in the previous reports (**3r**−**3t**, see Scheme 2). This method was also applicable to the heterocyclic amines. For example, 3-amino pyridine derivatives yielded desired product in excellent yields (**3w**, **3x**; see Scheme 2) and the amination at the 2-position was confirmed by X-ray crystallography (**3w**, CCDC 1906594), whereas 2-amino pyridine was ineffective. Picolinamide of 2-aminopyrazine also provided amination product, albeit in moderate yield (**3y**, see Scheme 2). Other six-membered amines such as piperidine, N-Boc-protected piperazine, 4-cyano-piperidine also provided the amination

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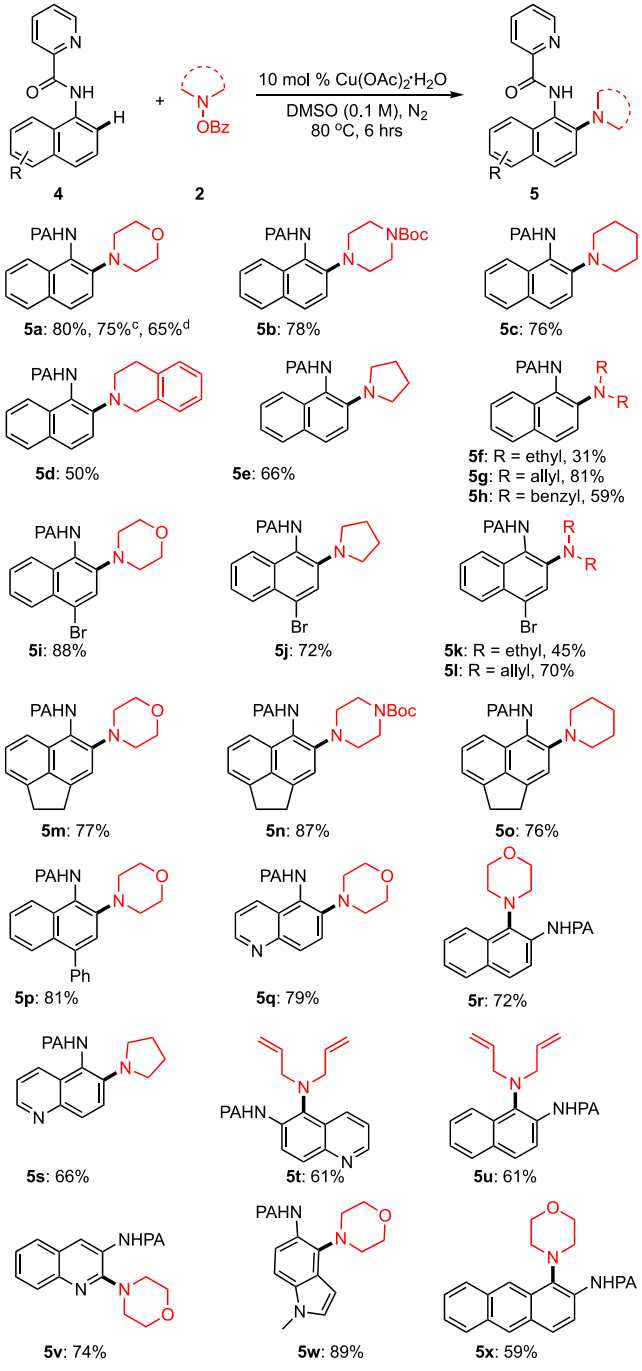
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope with Polycyclic (Het)aromatic Anilides[a,b]

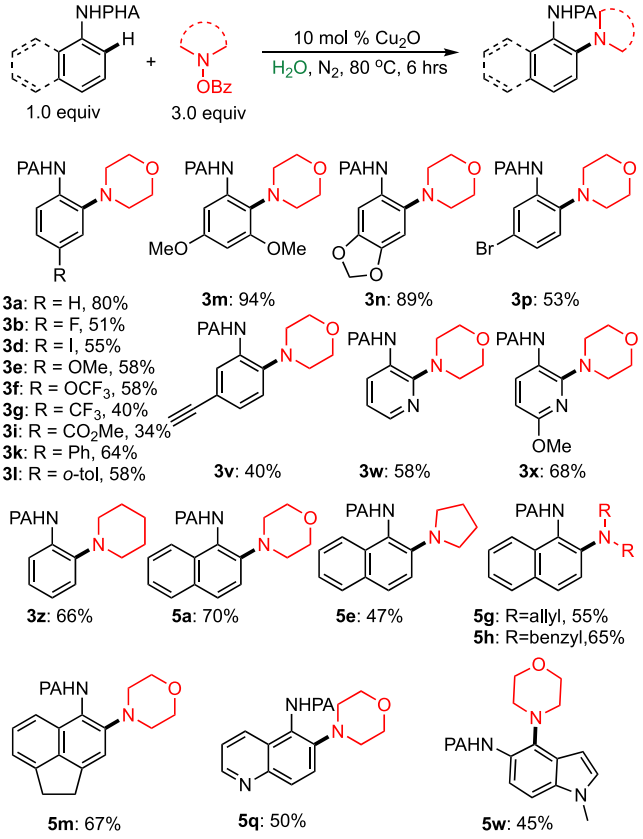


[a]Reactions were performed in 0.20 mmol scale. [b]Yields refer to isolated pure compounds. [c]Reaction performed in gram scale. [d]10 mol % Cu powder was used.

products in good to excellent yields (**3z**–**3ab**, Scheme 2). Besides six-membered cyclic amines, this method is also applicable for five-membered cyclic amines **3ac** and acyclic amines, although the yields are not satisfactory (**3ad**–**3af**).

Next, we turn our attention to examine the scope of conjugated naphthylamines which were inferior substrates in the previous reports (yields of ∼50%). Gratifyingly, 1-naphthylamine furnished 80% yield of the *ortho* amination product under the optimized condition (**5a**, see Scheme 3).

Scheme 4. Electrophilic C–H Amination in Water[a,b]



[a]Reactions were performed in 0.2 mmol scale. [b]Yields refer to isolated pure compounds.

Other six-membered amines were also effective to furnish moderate to high yields (**5b**–**5d**, see Scheme 3). Remarkably, this bicyclic system also exhibits superior reactivity to five-membered pyrrolidine (**5e**, **5j**, **5s**; see Scheme 3) and acyclic amines (**5f**, **5g**, **5h**, **5k**, **5l**, **5t**, **5u**; see Scheme 3) providing good to high yields. Substituted naphthylamines (**5i**–**5p**, Scheme 3) were also effective furnishing comparable yields of the amination product. Heterobicycles such as quinoline (**5s**, **5v**) and indole (**5w**) were also proven to be excellent substrates. Tricyclic 2-amino anthracene was less reactive to some extent, yielding 59% amination product (**5x**).

To demonstrate practicability of this present method further, we performed the amination reaction in water as an environmentally benign and green solvent (Scheme 4).[19] Gratifyingly, carboxamide-protected anilines and naphthalenes provided the corresponding *ortho* amination product using copper(I) oxide in lieu of copper(II) acetate (for detail optimization, see the Supporting Information). While electron-rich substrates (**3m**, **3n**; see Scheme 4) furnished comparable yields to DMSO, the electron-deficient substrates (**3g**, **3i**; see Scheme 4) afforded moderate yields. Other bicycles (**5a**, **5e**, **5g**, **5h**, **5m**) and heterocycles (**3w**, **3x**, **5q**, **5w**) also underwent amination reaction in water, providing moderate to good yields. To note, nucleophilic-free amines were ineffective under this condition to provide the corresponding amination product.

To understand the mechanism of this copper-catalyzed electrophilic amination, we performed several control experiments (Scheme 5). From a competitive experiment between **1a**

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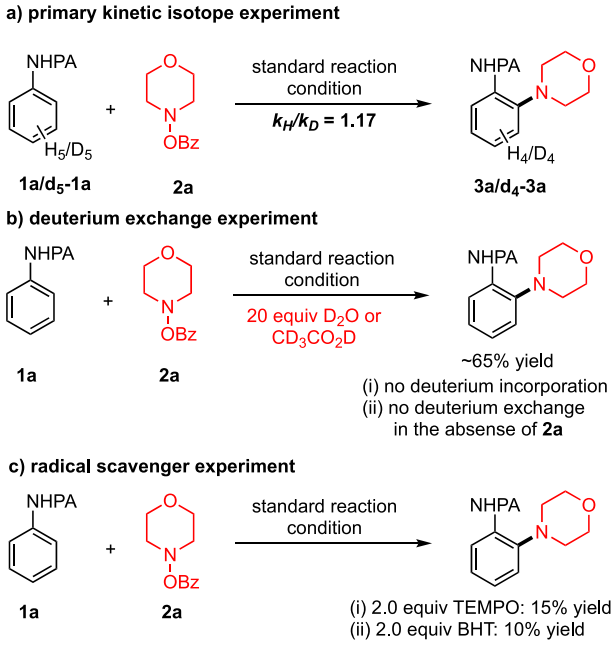
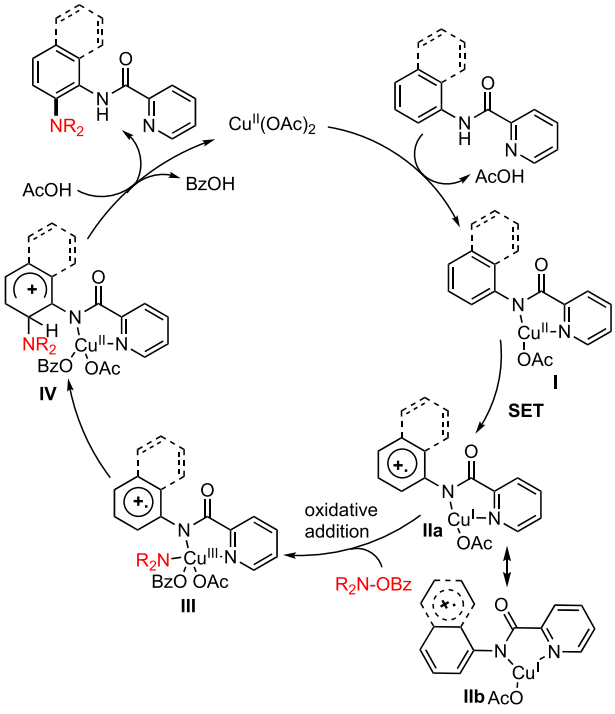
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Control Experiments



Scheme 6. Plausible Catalytic Cycle

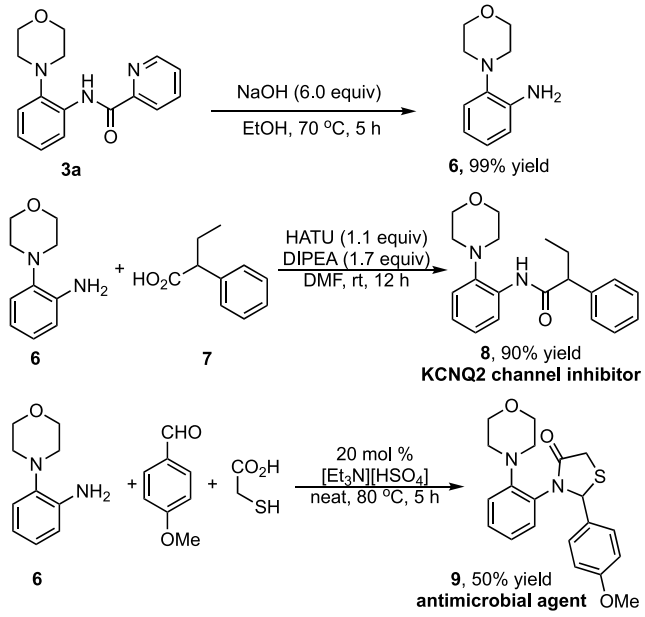


and d_5-**1a**, the primary kinetic isotope effect k_H/k_D was determined to be 1.17, which indicates that C−H bond cleavage may not be involved in the rate-limiting step (Scheme 5a). When substrate **1a** was subjected to the reaction conditions in the presence of 20.0 equiv D_2O or CD_3COOD with or without an amine source, no *ortho* H−D exchange occurred, suggesting that no reversible *ortho* C−H insertion happened (Scheme 5b). The addition of radical scavengers such as 2.0 equiv of TEMPO and BHT in the reaction medium suppressed the reaction significantly, indicating a probable radical pathway (Scheme 5c). Furthermore, when **1a** was heated for 1 h in the presence of a copper catalyst in DMSO, followed by the addition of an amine source, and stirring was continued for 5 h; the corresponding amination product was obtained in comparable yields. However, the reverse addition sequence yielded no product. It indicates that, initially, chelation of substrate with copper in bidentate fashion occurs to generate complex-**I**, followed by one electron transfer to generate the Cu(I) complex (**IIa**). This single electron transfer mechanism is further supported by the fact that naphthyls are susceptible for diverse amines than the corresponding anilines, presumably because of better resonance stabilization. Inversely, oxidative addition followed by chelation may not be operative.

From these control experiments and previous literature reports,[20] a plausible mechanistic cycle is proposed (Scheme 6). Initial coordination of copper with bidentate 2-picolinamide may generate complex **I**. Subsequently, one-electron reduction of complex **I** lead to the formation of copper(I) complex **II**, which might be better resonance-stabilized in the case of naphthalenes. This Cu(I) complex may undergo oxidative addition to *O*-benzoylhydroxylamines to generate a high-valent Cu(III) species (**III**). Amine transfer to the arenes, followed by deprotonation, may provide the desired C−H amination product and copper(II) for the subsequent runs.

The electrophilic amination was also performed in gram-scale and the 2-picolinamide directing group was removed by excess NaOH−ethanol under reflux condition (Scheme 7). Amide coupling with the free diamine, **6** with **7** furnished a

Scheme 7. Directing Group Deprotection and Product Derivatization



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Org. Lett. XXXX, XXX, XXX−XXX

KCNQ2 channel inhibitor.[21] Furthermore, a three-component coupling in neat condition provided an antimicrobial agent.[22]

In conclusion, we have developed a mild copper-catalyzed 2-picolinamide directed electrophilic *ortho*-amination of anilines and naphthylamines with *O*-benzoylhydroxylamines. The reaction proceeds smoothly without any external oxidants or additives. Notably, bicyclic anilines were also effective substrates to a broad scope of dialkylamines under this electrophilic amination strategy, which is a remarkable discovery, compared to the existing methods. The amination has also been demonstrated in water, providing an environmentally benign methodology. Thus, we anticipate that this practical electrophilic amination will be highly applicable in academia and industrial research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01546.

Experimental procedures, spectroscopic data, X-ray crystallography data, ^{1}H and ^{13}C NMR spectra for all synthesized compounds (PDF)

Accession Codes

CCDC 1906594 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX