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Copper(II) mediated C-8 amination of 1-naphthylamide derivatives with acyclic and cyclic amines

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ABSTRACT

A simple and facile copper(II) mediated protocol for C-8 amination of 1-naphthylamide derivatives is reported here. Picolinamide and its derivatives were used as a bidentate directing group for the C-8 amination reaction. Various substituted naphthylamide derivatives with numerous cyclic and acyclic amines proceed in good yields under mild conditions. Air was used solely as an oxidant.

Introduction

Functionalized 1-naphthyl amine moiety represents an important structural unit having the potential use in pharmaceuticals, functional materials and also served as a ligand system [1]. During the last decade, considerable efforts have been made for the synthesis of functionalized naphthalenes *via* direct C—H functionalization approach [2]. Among them, bidentate chelation controlled strategy for regioselective functionalization of 1-nathylamine scaffolds achieved significant progress in recent years [3]. For the 1-naphthylamide system catalytic regioselective functionalization of C2-H, C4-H and C8-H has been explored by many groups using Daugulis introduced picolinamide (PA) directing group [4].

Among these, notable progress has been accomplished for the C8-H functionalization of 1-naphthylamide moiety such as alkylation [5], arylation [6], alkenylation [7] chalcogenation [8], amination [9], acylation [10], etherification [11], esterification [12], cyanation [13] using various transition metal-catalyzed reaction. Direct C—N bond formation reactions are important in organic synthesis, as the prevalence of nitrogen-containing molecules in numerous pharmaceutical, medicinal, synthetic intermediates, and functional materials [14]. The directing group assisted C—H bond amination of various arenes has been well explored [15]. In terms of picolinamide directed C—H amination of naphthalene, Wu and co-workers first reported the palladium-catalyzed C8-H amination of naphthalene moiety with simple secondary cyclic aliphatic amines (Scheme 1a) [9]. Very recently, the same group reported the copper-catalyzed amination using a super stoichiometric amount of di-*tert*-butyl peroxide (DTBP) as an oxidant with a large excess (30 equivalent) of amines (Scheme 1b) [16]. In 2017, Punniyamurthy and co-workers reported copper-catalyzed amination of naphthalene with azoles using picolinamide (PA) directing group with silver carbonate as additive and NMO as an oxidant [17]. Aminations of similar naphthalene moiety using preactivated benzoyl protected hydroxylamine as an aminating agent were reported by Jana and co-workers (Scheme 1c) [18]. Thus, the development of a simple and efficient protocol for regioselective aminations of naphthalene under external oxidant free conditions is demanding. In continuation, our effort on bidentate directing group directed regioselective functionalization of 8-aminoquinoline derivatives at C2, C5 sites [19], and 1-naphthylamine derivatives at C4 site [20]. Herein, we report a simple and useful Cu(II) mediated methodology for the C8-amination of naphthylamine with both cyclic and acyclic amines, and using simple air as an external oxidant.

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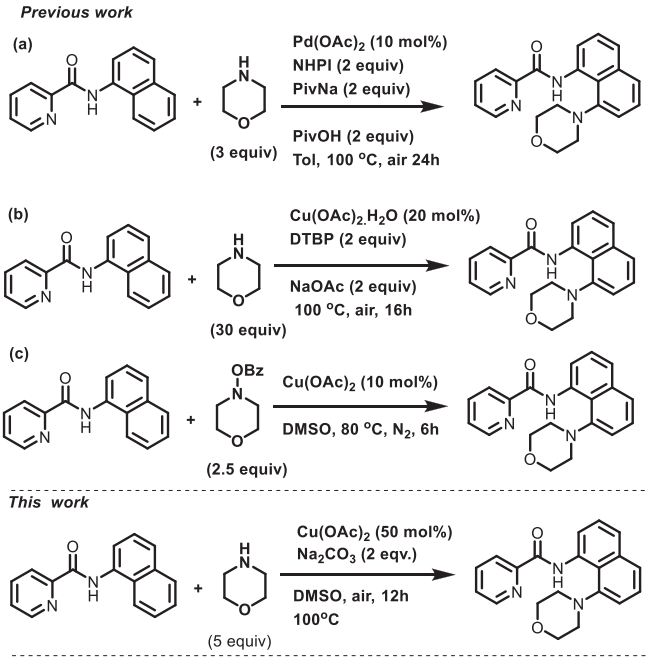


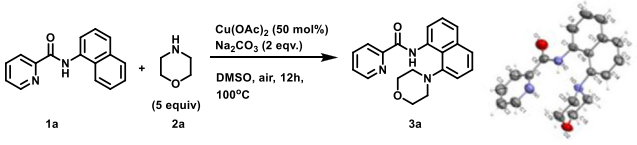
Scheme 1. Picolinamide directed C-8 amination of naphthalene.

Results and discussion

We began our studies using N-(naphthalene-1-yl) picolinamide (**1a**) and morpholine (**2a**) as a model substrate to optimize the reaction condition, as summarized in Table 1. After, various screenings, we identified that **1a** reacted with **2a** (5 equiv.) in presence of 50 mol% $Cu(OAc)_2$ with Na_2CO_3 (2 equiv) as a base in DMSO (0.5 ml) solvent at 100 °C for 12 h provided the desired C8-aminated product in 74% isolated yield (Table 1, entry 1). Furthermore, the structure of compound **3a** was characterized by single-crystal X-ray crystallography. An equivalent amount of catalyst loading decreases the yield (63%, entry 2). Other copper salts e.g. Cu $(OTf)_2$ and $CuBr_2$ provided a lower yield of the aminated product (entries 3–4). Altering the base to sodium acetate diminished the yield (entry 5), sodium carbonate was found superior to other bases (supporting information). The use of external oxidants like $PhI(OAc)_2$ and DTBP was not beneficial (entries 6 and 7). In the absence of a catalyst, no product was obtained (entry 8). Lowering of the catalyst loading and reaction temperature was unsuccessful, resulted in diminished yield (entry 9–10). The use of pure oxygen instead of air gave a similar yield to the product (entry 11). In absence of the sodium carbonate, yield drops to 23% indicate the importance of the base in the reaction. The reaction with 2 equiv. of amine lowered the yield of the desired product (entry 13). To improve the product yield variation of other reaction parameters such as temperature, solvent, catalyst loading, etc. was unsuccessful (see supporting information).

Under the optimized reaction conditions, we then explored the substrate scope of the various amines with naphthylamide derivatives (Table 2). A wide range of secondary cyclic amine was investigated, various 4-substituted piperidines proceed well, and moderate to good yields of the desired product were obtained (3b-3e). 5-membered pyrrolidine also proceeds well and generates the desired product in moderate yields (3f). To our delight acyclic amine, *N*-methyl benzylamine also worked well, which was not reported earlier by any catalytic system, gave a similar yield of the aminated product (43%, 3g). However, amination with diethylamine was not successful, maybe due to the low boiling point (54–

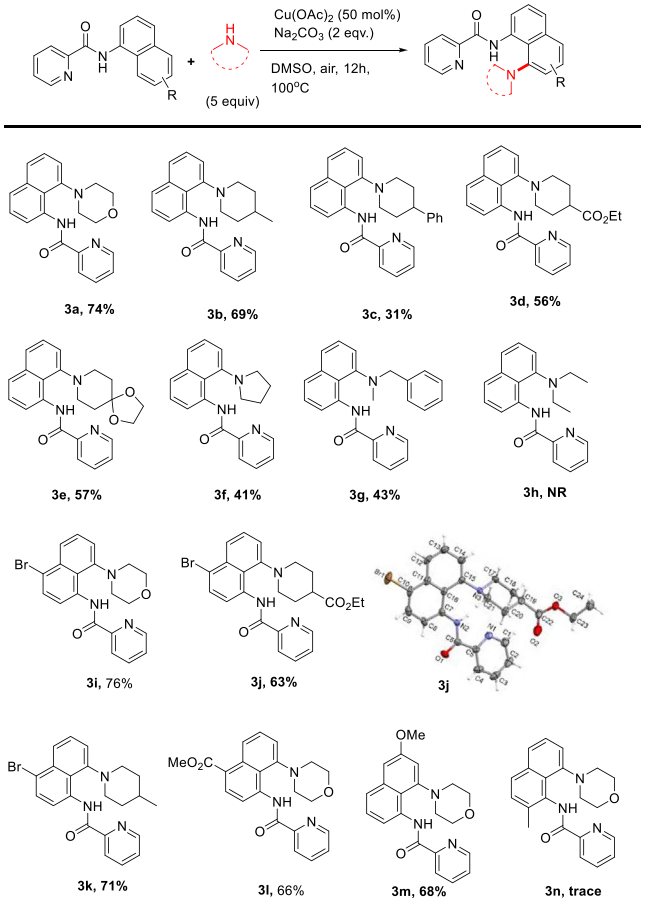
Table 1
Optimization of reaction condition.[a]



Entry	deviation from optimized condition	Yield (%)[b]
1	No	74
2	$Cu(OAc)_2$ (1 equiv) instead of (50 mol%)	63
3	$Cu(OTf)_2$ instead of $Cu(OAc)_2$	63
4	$CuBr_2$ (1 equiv) instead of (50 mol%)	36
5	NaOAc instead of Na_2CO_3	35
6	$PhI(OAc)_2$ as an external oxidant (2 equiv)	35
7	DTBP as an external oxidant (2 equiv)	44
8	Without $Cu(OAc)_2$	nr
9	$Cu(OAc)_2$ (25 mol%) instead of (50 mol%)	58
10	80 °C instead of 100 °C	56
11	Pure oxygen atmosphere instead of air	74
12	Without Na_2CO_3	23
13	With 2 equiv of 2a instead of 5 equiv	36

[a] 1a (0.2 mmol), 2a (5 equiv.), $Cu(OAc)_2$ (50 mol%), Na_2CO_3 (2 equiv.), and DMSO (0.5 ml) at 100 °C, for 12 h, in a reaction tube under air.
[b] Isolated yields.

Table 2
Substrate scope of 1-naphthylamides.



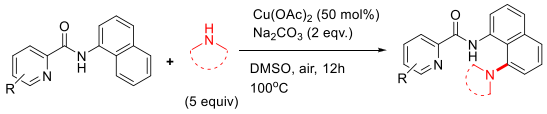
Reaction condition: 1 (0.2 mmol), 2 (5 equiv.), $Cu(OAc)_2$ (50 mol%), Na_2CO_3 (2 equiv.), and DMSO (0.5 ml) at 100 °C, for 12 h, in a reaction tube under air.

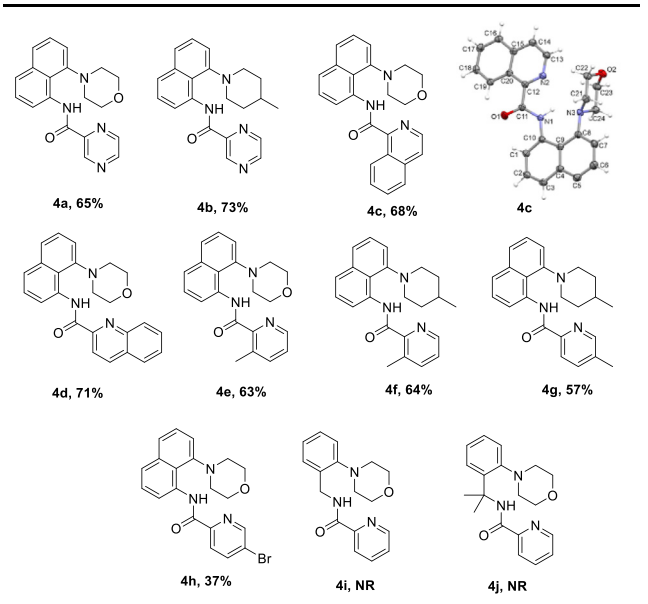
56 °C) of the amine. Reaction with various functional groups such as bromo, ester, methoxy, methyl-substituted in different positions naphthalene proceeds smoothly afforded the desired product in good yields (3i-3 m). The structure of compound 3j was further confirmed by the single-crystal X-ray crystallography. 2-methyl substituted naphthalene moiety found to be unreactive might be due to the steric effect of the methyl group (3n). Next, the role of directing group for amination was investigated. Several analogous and substituted picolinamide were explored as described in Table 3. Interestingly, when pyrazine was used instead of pyridine, the presence of an additional N –atom does not have any effect, the reaction proceeds smoothly and the desired product was obtained in good yields (4a-4b). Isoquinoline and quinoline were also similarly effective as a directing group (4c-4d), the structure of 4c was further characterized by X-ray crystallography. C-3 methyl, C-5-methyl, and C-5 bromo substituted pyridine are well tolerated and the desired aminated product was obtained in moderate to good yields (4e-4h). However, picolinamide attached with benzylamine or cumylamine are unreactive under the optimized condition, which might be due to the non-planner (sp^3) structure of the moiety.

To demonstrate the potential application of our methodology, several experiments were carried out as described in Scheme 2. A gram scale reaction of the standard substrate proceeded successfully without affecting the yield. Selective removal of the directing group with NaOH in ethanol to afford 8-morpholinonaphthalen-1-amine showcased the synthetic utility of our protocol.

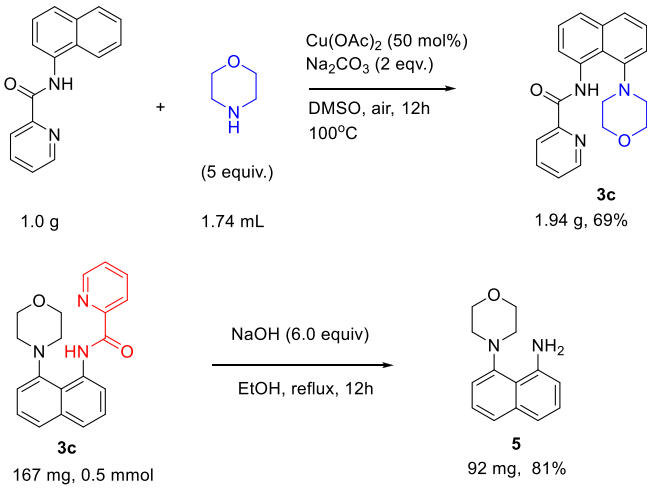
Next, the sequential C—H functionalization of the substrate1-naphthyl amide moiety (**1a**) was carried out to synthesize various substituted naphthalene in a regioselective manner with our developed methodologies (Scheme 3). In path A, C8-selective amination was carried out with our newly developed methodology

Table 3
Substrate scope with analogous and substituted picolinamides.

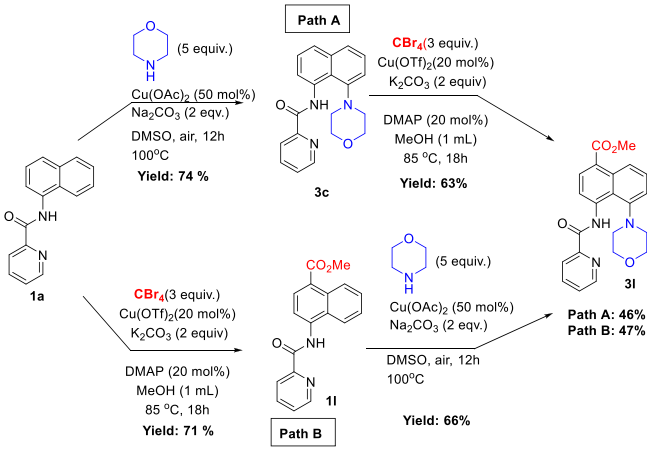




Reaction condition: 1 (0.2 mmol), 2 (5 equiv.), $Cu(OAc)_2$ (50 mol%), Na_2CO_3 (2 equiv.), and DMSO (0.5 ml) at 100 °C, for 12 h, in a reaction tube under air.



Scheme 2. Gram scale synthesis and removal of directing group.



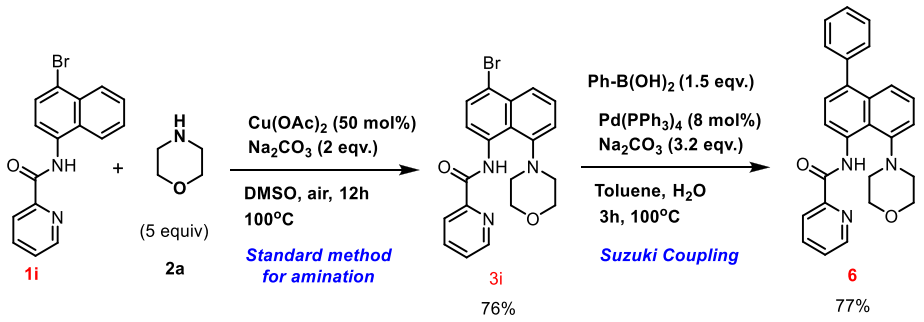
Scheme 3. Sequential C—H functionalization of the 1-naphthylamide moiety.

in the 1st step, to get intermediate 3c, which was carboxylated by our previously developed methodology [20] at C4 position. In path B, the C—H functionalization sequence was reversed, initially carboxylation at the C4 position, and next, amination was carried out, a similar overall yield was obtained.

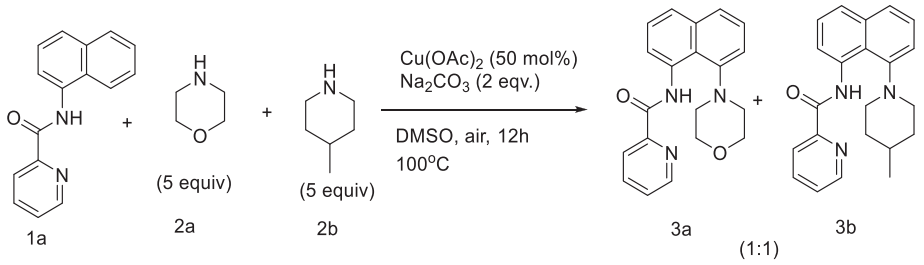
Further, the 4-bromo substituted naphthyl amide derivative (3i) was efficiently coupled with phenylboronic acid (Scheme 4) [21], thus late-stage functionalization to get an arylated product is feasible.

An intermolecular competitive amination reaction with morpholine and 4-methyl piperidine was carried out (Scheme 5) and produced almost 1:1 of both aminated products, indicates the pKa of amines does not have any effect in the reaction.

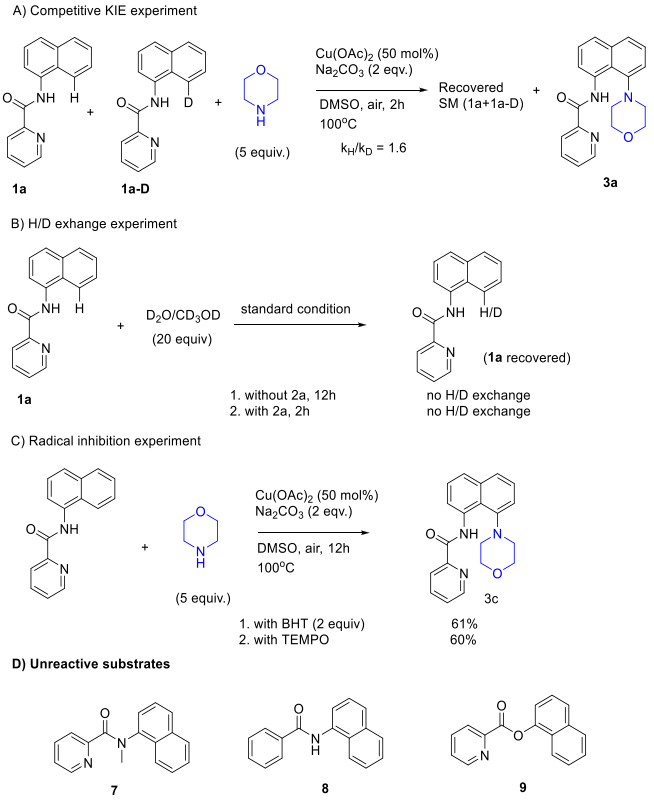
To investigate the reaction mechanism, we have carried out a few control experiments. First, the competitive reaction with 1a and 1a-D was carried out for 2 h, k_H/k_D was determined to be 1.6, which indicates the C—H bond cleavage might be the rate-determining step (scheme 6a). Next, we have performed the H/D exchange experiment (Scheme 6b), no H/D exchange was observed in recovered starting material in the presence and absence of the amine (2a), indicates the irreversibility of C—H bond activation. Finally, the reaction was carried out with the presence of radical scavengers such as TEMPO [(2,2,6,6-Tetramethylpiperidin-1-yl) oxyl] and BHT (butylated hydroxyl toluene) which does not have



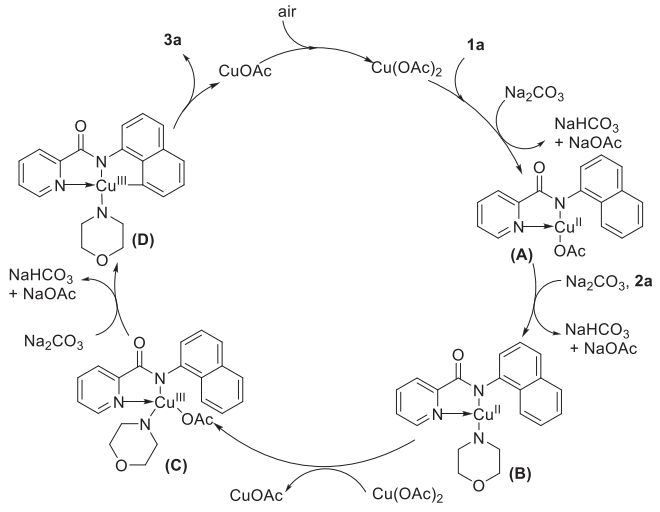
Scheme 4. Product derivatization.



Scheme 5. Intermolecular competitive amination.



Scheme 6. Control experiments for mechanistic investigation.



Scheme 7. Proposed mechanism.

a significant effect on the reaction, indicates that the reaction might not proceed through a radical mechanism (Scheme 6c).

Finally, to get some insight into the co-ordination of the substrate with copper, we have carried out the reaction with a few designed substrates (7–9), as expected no aminated products were obtained (Scheme 6d). These results indicate that N, N bidentate ligand like picolinamide (DG) is crucial for this reaction.

Based on the aforementioned outcome and in combination with previous reports [9,14,22], a plausible mechanism is proposed as shown in Scheme 7. Initially, the coordination of 1a with copper acetate took place in the presence of a base leads a chelated intermediate A. followed by the substitution with morpholine (2a) gives intermediate B. Next, intermediate B oxidized by $Cu(OAc)_2$ to produce Cu^{III} intermediate C, which then leads to naphthyl *peri* C—H cupration to generate cyclometalated Cu^{III} intermediate D. Finally, reductive elimination afforded product 3a and Cu(I) species. Which is oxidized by air to Cu(II) and continues the cycle.

Conclusion

In summary, we have developed a simple copper-catalyzed regioselective C8 amination of 1-naphthylamine using picoli-

namide and analogous amide as a directing group. The amination works well with both cyclic and acyclic amines. Moreover, no sacrificial external oxidant was used, air was used as a sole oxidant. This amination method showed very good functional group tolerance, and easy to scale up. Deprotection of directing group, late-stage functionalization, and sequential C—H functionalization of 1-naphthyl amide moiety to polysubstituted naphthalene showcased the applicability of our developed methodology.

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.

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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.2021.152858.

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