Organic LETTERS

Letter

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Copper-Catalyzed Carboxamide-Directed *Ortho* Amination of Anilines with Alkylamines at Room Temperature

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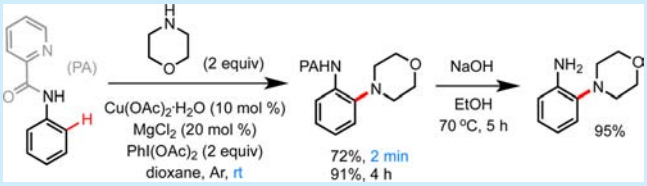
Supporting Information

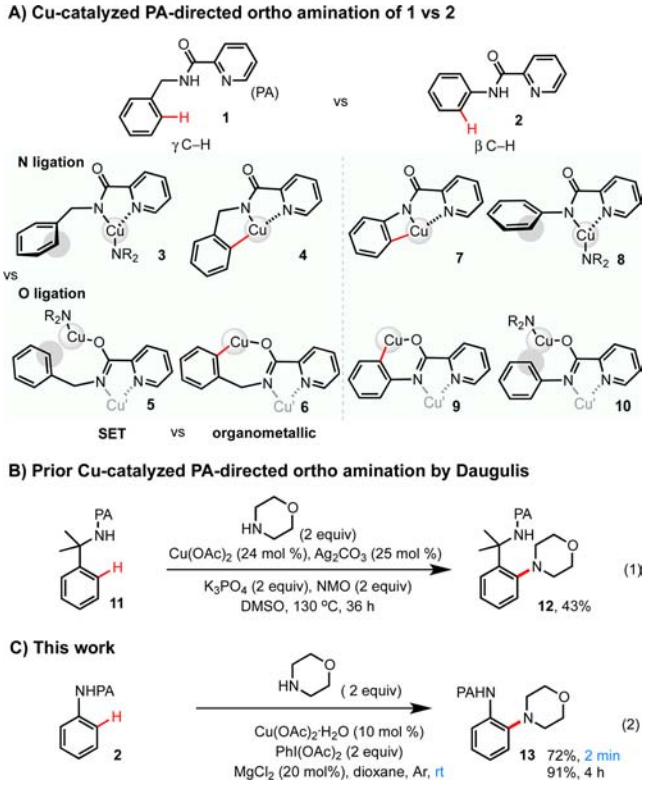
ABSTRACT: In this report, a highly efficient method for the room temperature installation of alkyl amino motifs onto the ortho position of anilines via Cu-catalyzed carboxamide-directed amination with alkylamines is described. This method offers a practical solution for the rapid synthesis of complex arylamines from simple starting materials and enables new planning strategies for the construction of arylamine-containing pharmacophores. A single electron transfer (SET)-mediated mechanism is proposed.



Arylamines and heteroarylamines are important structural units in pharmaceutical agents and organic materials.[1] Over the past decade, transition-metal-catalyzed amination of C−H bonds has emerged as an attractive new strategy for Ar−N bond construction.[2] In particular, reactivity enabled by cheap and abundant copper catalysts has attracted great interest.[3−12] In 2006, the laboratory of Yu[5] reported a Cu-catalyzed intermolecular amination of the nonacidic *ortho* C−H bonds of 2-phenylpyridine with tosylamine.[6] Recently, the laboratory of Daugulis[11a] has shown that the nonacidic ortho C−H bonds of *N*-quinolyl benzocarboxamides can be directly coupled with alkylamines, providing a useful Cu-catalyzed C−H amination method facilitated by a removable auxiliary. Herein, we describe a highly efficient and broadly applicable method for the room temperature installation of cyclic alkylamino motifs onto the ortho position of aniline substrates via Cu-catalyzed carboxamide-directed amination.[13]

Recently, our laboratory has focused on investigating the picolinamide (PA) directing group, first introduced by Daugulis, for use in palladium-catalyzed C−H functionalization reactions.[14−16] In these studies, we found that the ortho C(sp^2)−H bonds of *N*-benzyl picolinamides (e.g., **1** in Scheme 1A) can be readily transformed into a variety of functional groups under palladium catalysis. We postulated that *N,N*-PA-chelated 5-membered palladacycle intermediates (analogous to organometallic Cu complex **4**) were involved in these Pd-catalyzed C−H functionalization reactions. In contrast with *N*-quinolyl benzocarboxamides, *N*-benzyl picolinamides seemed to be much more challenging substrates for Cu-catalyzed C−H amination. In a prior report by Daugulis, only two examples of conformationally constrained α-gem-dimethyl benzylamine substrates (e.g., **11**) could be aminated in moderate yield (Scheme 1B).[11a] Our own attempts with unsubstituted benzylamine **1** did not afford any γ ortho-aminated product under the same reaction conditions. This disparate reactivity between AQ (aminoquinoline) and PA-coupled substrates led us to reexamine the mechanistic model for this Cu-catalyzed PA-directed ortho functionalization reaction. While 5-membered

Scheme 1. Cu-Catalyzed PA-Directed Ortho Amination of Arenes



N,N-PA-chelated metallacycle intermediates (e.g., **4**) have been invoked in many Pd- and Cu-catalyzed C−H functionalization reactions, we suspected that the imidate O-atom of the Cu-chelated PA moiety might also be able to bind Cu to

Received: February 12, 2014
Published: March 4, 2014

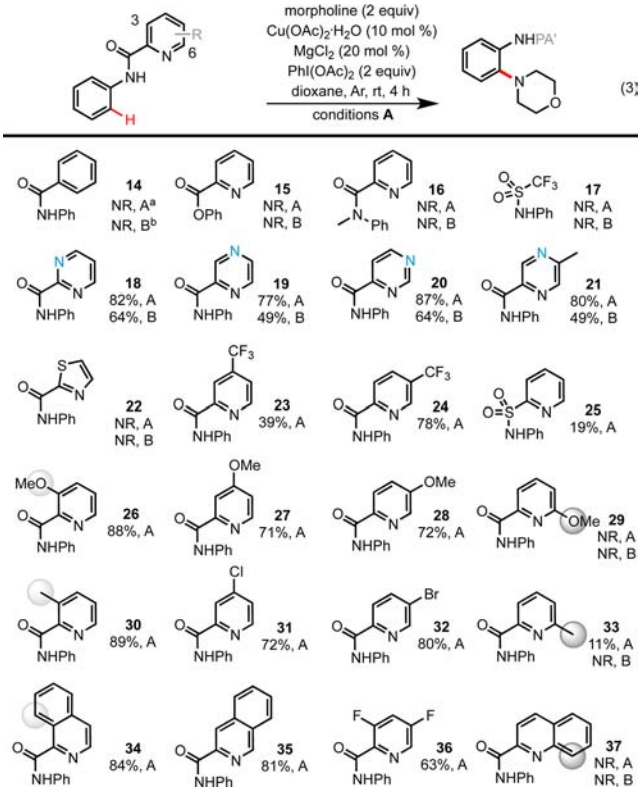
effect ortho C−H amination (see **6**).[17,18] In comparison with ortho amination of benzylamine through a 7-membered metallacycle intermediate (e.g., **6**),[19] ortho C−H functionalization of aniline substrates (see **2**) may proceed more easily through a 6-membered *O*-ligated metallacycle (e.g., **9**). In addition to organometallic pathways, electron-transfer-mediated mechanisms could also provide viable pathways for PA-directed ortho amination of anilines (see **8**, **10**), as invoked in Yu's 2-phenylpyridine system.[5,20] If so, ortho amination of anilines may be favored due to the more compact conformation of the reaction intermediates (see **3** vs **8**, **5** vs **10**)[21] and their electron-rich arene moiety.

Prompted by our new mechanistic model, we attempted the Cu-catalyzed amination of **2** with morpholine (eq 2, Scheme 1C; see Supporting Information (SI) for the detailed screening conditions). We were delighted to find that 2 equiv of phenyliodonium diacetate $PhI(OAc)_2$,[22] 2 equiv of morpholine, and 20 mol % of $Cu(OAc)_2{\cdot}H_2O$ in dioxane at 90 °C gave desired product **13** in 86% yield. An ortho-diaminated product was formed in trace quantities. Lowering the catalyst loading to 10 mol % $Cu(OAc)_2{\cdot}H_2O$ provided a decreased yield (72%). Interestingly, the addition of 20 mol % $MgCl_2$ largely restored the amination yield.[23] To our surprise, the amination reaction also proceeded very quickly at rt to give a 72% yield in 2 min and a 91% isolated yield in 4 h. No product was formed in the absence of the Cu catalyst.

To probe the mechanism of this Cu-catalyzed C−H amination reaction and evaluate the scope of directing groups, we next surveyed a range of ester and amide-linked auxiliary groups under the standard conditions **A** at rt (eq 3, Scheme 2). Simple benzamide **14**, phenolic ester **15**, *N*-methylated amide **16**, and sulfonamides (e.g., **17**) did not undergo the desired C−H amination reaction, indicating the critical roles of both amide *NH* and the ortho pyridine *N*. On the other hand, the parent picolinamide motif demonstrated remarkable tolerance for substitution on the pyridine ring while still facilitating Cu-catalyzed ortho amination. For instance, pyrimidines **18** and **20** as well as pyrazine **19** containing an additional N-atom on the pyridine ring gave a good to excellent amination yield. Sterically bulky substituents on the 3, 4, and 5 positions of the pyridine ring are very well tolerated. In contrast, substrates bearing substituents at position 6 are unreactive under the standard conditions (e.g., **29**, **33**, **37**). All of these picolinic acid analogues are available commercially and are frequently employed as building blocks in structure and activity relationship (SAR) studies in medicinal chemistry.

As shown in Scheme 3, anilines substituted with a variety of functional groups such as OBn, *NH*Boc, ester, and all of the halogens were well tolerated under the standard reaction conditions. Even free OH groups are tolerated (see **54**, **58**). In general, electron-rich substrates are more reactive. For example, near-quantitative yields of **47** could be obtained at rt in 5 min (conditions C). Electron-deficient substrates (e.g., **41**, **48**) and even a pyridine substrate (e.g., **42**) also worked well. The amination reactions were sensitive toward the sterics of the targeted C−H bond; the less hindered ortho position was preferentially aminated in the case of substrates bearing meta-substitutents (see **44**−**46**). As shown in Scheme 3B, 6-membered cyclic secondary amines were excellent substrates for this reaction. A variety of functional groups and substituents on the amine substrate were well tolerated, including the sulfide group on thiomorpholine (see **51**). In comparison, 5-membered

Scheme 2. Evaluation of PA Analogues As Directing Groups[a]



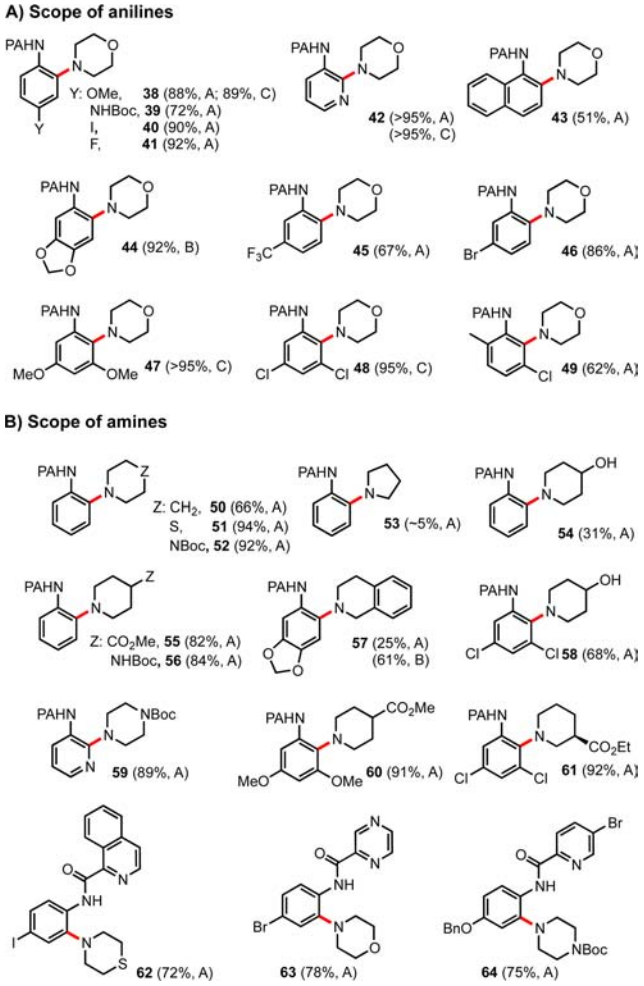
[a]Isolated yields on 0.2 mmol scale under the standard conditions A (rt, 4 h). [b] Conditions B: 90 °C, 4 h.

pyrrolidine, e.g. **53**, and acyclic amines, e.g. diethylamine, were unreactive (<10%) under these reaction conditions.[24]

The mechanistic details of these Cu-catalyzed ortho amination reactions are unclear. The differing reactivity of naphthalene substrate **65**, which contains both β and γ' C−H bonds, in three different Cu-catalyzed C−H functionalization systems may provide mechanistic insight (Scheme 4A). Subjecting **65** to our room temperature $PhI(OAc)_2$-oxidized conditions gave exclusively β-aminated product **43**, along with unreacted starting material. No γ'-aminated product **70** was obtained. Little conversion of **65** was observed under the previously reported Cu-catalyzed, NMO-mediated, and Ag-promoted amination conditions at 110 °C.[11a] In contrast, a recent study[11d] by Daugulis reported that the C−H alkoxylation of **65** with phenols under Cu-catalyzed conditions gave primarily the γ' functionalized product **66**.[25] A recent study by Miura showed that the C−H heteroarylation of **65** with benzoxazole under Cu-facilitated conditions gave exclusively γ' functionalized product **67**.[12b] In addition, our control experiments indicated that the addition of radical scavengers, e.g. TEMPO or galvinoxyl, inhibited the reaction (see SI). The lack of KIE (~1.0) between **2** and D_5-substituted substrate **70** indicates that C−H cleavage is not the rate-limiting step (Scheme 4B). Whereas organometallic pathways involving 5-membered N,N-bidentate metallacycle intermediates (e.g., **68**) have been proposed for Miura's C−H heteroarylation,[12,20] an aromatic substitution-type pathway mediated by stepwise single electron transfer (SET) is very likely to be operative in our system (see **69**).[26] The exact binding mode of the PA group and the oxidation state of the reactive Cu species (Cu^{II} or Cu^{III})[7,20,27] is still unclear.

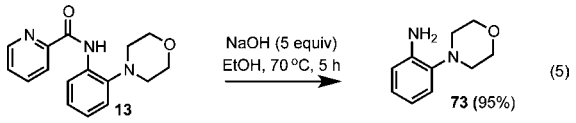
dx.doi.org/10.1021/ol500464x | Org. Lett. 2014, 16, 1764−1767

Scheme 3. Substrate Scope of Anilines and Amines[a]



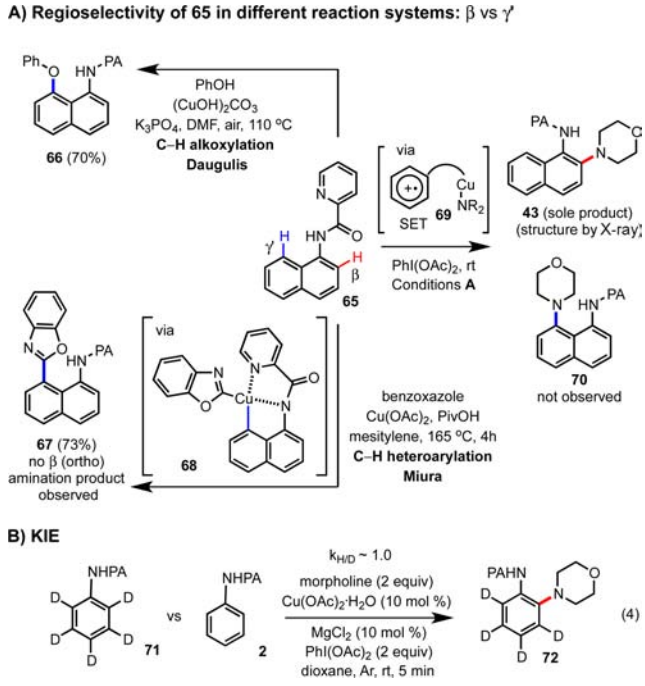
[a]Isolated yields on a 0.2 mmol scale under the standard conditions. A: rt, 4 h. B: 90 °C, 4 h. C: rt, 5 min.

The PA group of the aminated products can be easily removed under simple basic conditions due to the electron-deficient pyridine ring. For example, treatment of **13** with 5 equiv of NaOH in EtOH at 70 °C gave aniline **73** in high yield (eq 5).



In summary, we have developed a highly efficient method to selectively install alkyl amino motifs onto the ortho position of aniline substrates via Cu-catalyzed and carboxamide-directed amination at rt. These reactions are operationally simple and robust, avoid the use of sensitive and expensive reagents, and possess a broad substrate scope for both anilines and directing groups. The picolinamide group can be used as a protecting group to facilitate the synthesis of complex ortho-diaminated arenes from readily available aniline starting materials. A broad range of picolinamide derivatives and related motifs can be potentially used as "smart" building blocks/directing groups for the synthesis of arylamine-containing pharmacophores.

Scheme 4. Mechanistic Considerations



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, X-ray crystallographic analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully thank the Pennsylvania State University, NSF (CAREER CHE-1055795), and ACS-PRF (51705-DN11) for financial support of this work.

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dx.doi.org/10.1021/ol500464x | *Org. Lett.* 2014, 16, 1764−1767