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Electrooxidative Amination of sp^2 C−H Bonds: Coupling of Amines with Aryl Amides via Copper Catalysis

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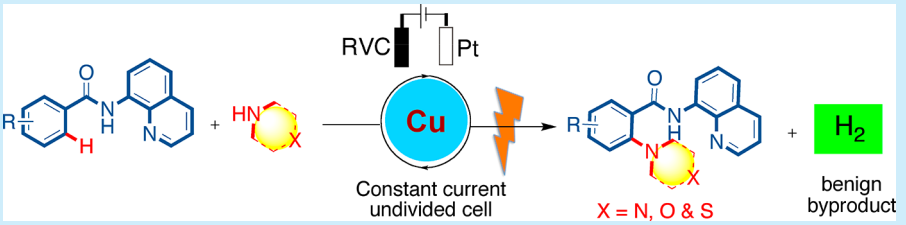
Supporting Information

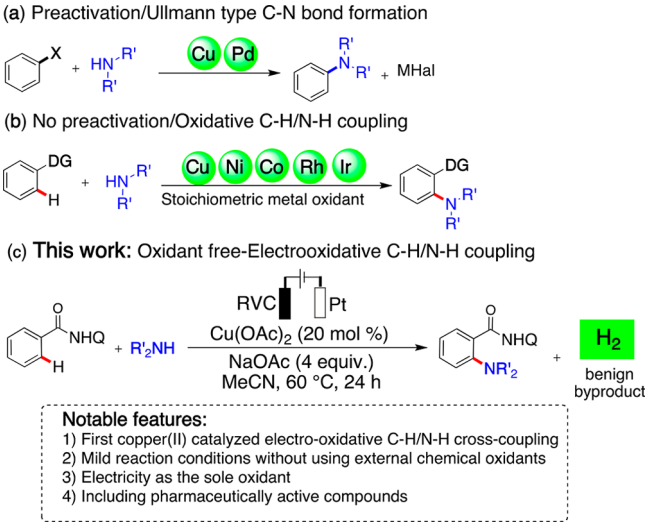


ABSTRACT: Metal-catalyzed cross-coupling reactions are among the most important transformations in organic synthesis. However, the use of C−H activation for sp^2 C−N bond formation remains one of the major challenges in the field of cross-coupling chemistry. Described herein is the first example of the synergistic combination of copper catalysis and electrocatalysis for aryl C−H amination under mild reaction conditions in an atom-and step-economical manner with the liberation of H_2 as the sole and benign byproduct.

The efficient construction of C−N bonds is important in organic chemistry due to the presence of nitrogen-containing motifs in a wide range of natural products, pharmaceuticals, and functional materials.[1−4] There are a number of notable routes to the formation of sp^2 C−N bonds, including the Buchwald−Hartwig reaction, Ullmann coupling, and Chan−Lam amination that use prefunctionalized organometallic reagents, organic halides, or pseudohalides as coupling partners (Scheme 1a).[5−16]

From step- and atom-economy standpoints, approaches to functionalized aromatic amine derivatives that make use of otherwise unreactive C−H bonds in direct amination is most desirable, especially if avoiding the use of prefunctionalized coupling partners.[17−21] Recent years have seen tremendous effort being focused on the direct C−H/N−H cross-coupling. To date, Cu^{II}, Ni^{II}, Co^{III}, Ir^{III}, and Rh^{III} catalysts have been used to facilitate C−H amination reactions with both primary and secondary and primary amines (Scheme 1b).[22−39] Despite these undisputable advances, direct C−H aminations largely require sacrificial terminal oxidants, which lead to undesired metal byproducts. For example, the first copper-promoted directed amination of $C(sp^2)$−H bonds was realized by Yu using O_2 as a terminal oxidant.[40] Later, Chen reported copper-catalyzed carboxamide directed *ortho*-amination of anilines with alkylamines using $PhI(OAc)_2$ as the oxidant.[41] Daugulis subsequently described a method for copper-catalyzed, direct amination of sp^2 C−H bonds of benzoic acid derivatives.[42,43] This reaction employed a $Cu(OAc)_2$ catalyst in conjunction with Ag_2CO_3 as a cocatalyst and O_2 as a co-oxidant. In spite of the above excellent developments, the establishment of efficient strategies for direct C−H aminations, ideally with mild external oxidant-free catalyst systems, is highly desirable.

Scheme 1. Transition-Metal-Catalyzed C−H Amination Reactions: (a) Ullmann-Type C−N Bond Formation Reactions; (b) Direct Oxidative C−H/N−H Coupling; (c) External Oxidant-Free Metalloelectrocatalysis for C−H/N-H coupling



The synergistic merger of electrocatalysis and transition metal catalysis (metalloelectro catalysis) has gained significant momentum in synthetic organic chemistry and has even been employed in the development of C−H activation reac-

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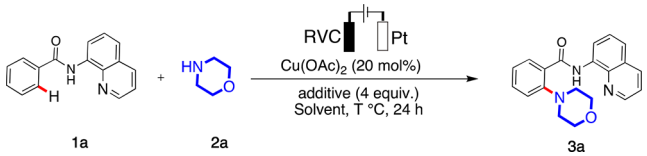
tions.[44−51] We perceived that metalloelectrocatalysis might provide an opportunity to realize transition-metal-catalyzed oxidative C−H amination under external oxidant-free conditions based upon results from a range of other metalloelectrocatalysis studies.[52−58] For example, Jutand and co-workers described a Pd-catalyzed electrochemical dehydrogenative Heck reaction.[59] Later, Kakiuchi and co-workers developed a Pd-catalyzed aromatic C−H halogenation via anodic oxidation.[60] Mei and co-workers reported a Pd-catalyzed direct electrochemical oxygenation.[61] More recently, Ackermann and Lei independently developed very interesting cobalt(II)-catalyzed electrooxidative C−H amination.[62,63] However, copper-catalyzed electrooxidative C(sp^2)−H/N−H cross-coupling has not yet been achieved.[64] Herein, we demonstrate the potential of copper(II) catalysis in electrooxidative C−H/N−H cross-coupling between amides and various secondary amines including pharmaceutically active compounds (Scheme 1c).

We initiated our studies by probing various reaction conditions for the envisioned copper-catalyzed electrochemical C−H amination (Table 1). Preliminary experiments identified

Table 1. Optimization Studies[a]



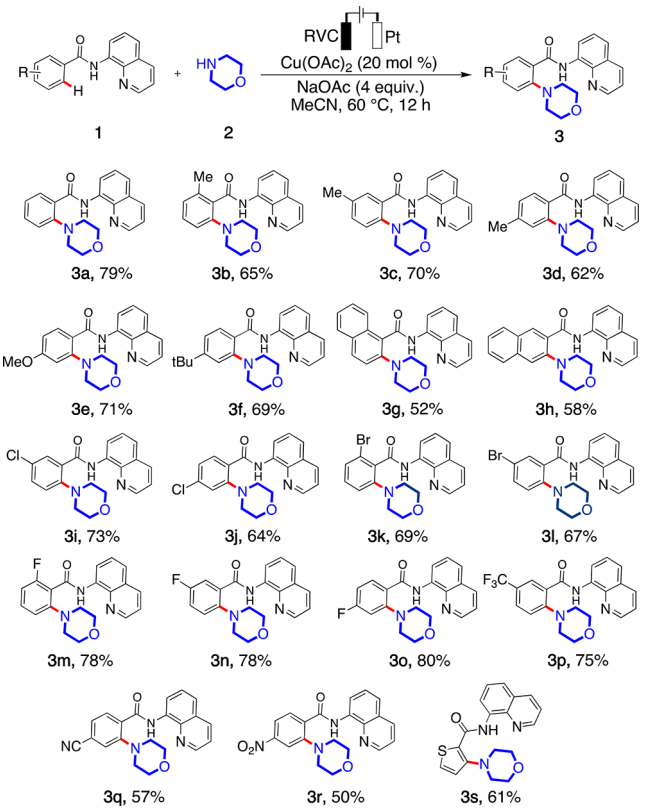
entry	solvent	additive	T (°C)	yield (%)[b]
1	DMF	NaOAc	80	15
2	DMSO	NaOAc	80	–
3	DCE	NaOAc	80	–
4	HFIP	NaOAc	80	–
5	MeCN	NaOAc	80	68
6	MeCN	NaOPiv	80	11
7	MeCN	KOAc	80	50
8	MeCN	NaOAc	60	79[c]
9	MeCN	NaOAc	60	79[d]
10	MeCN	NaOAc	60	–[e]
11	MeCN	–	60	–[f]
12	MeCN	NaOAc	60	–[g]

[a]Reaction conditions: undivided cell, **1a** (0.4 mmol), **2a** (1.2 mmol), $Cu(OAc)_2$ (20 mol %), base (4.0 equiv), solvent (13 mL), 60 °C, 2 mA, 12 h, RVC electrode (1.0 × 1.5 cm), Pt-plate electrode (1.5 cm × 1.5 cm). [b]Isolated yield. [c]$Cu(OAc)_2$ (10 mol %). [d]Under air. [e]Without electricity. [f]Without additive. [g]Without copper catalyst. RVC = reticulated vitreous carbon.

$Cu(OAc)_2$ as an effective catalyst for the C−H amination of the amide **1a** derived from 8-aminoquinoline.[65] From a series of representative solvents (entries 1−5), acetonitrile was found to provide the most optimal results (entry 5). It is noteworthy that, to the best of our knowledge, this constitutes the first example of the use of copper catalysis in conjunction with an electrochemical C−H activation with secondary amines. NaOAc proved to be the ideal additive (entries 6−7). The observed comparable efficacy under an atmosphere of ambient air (entries 8 and 9) confirmed the robustness of the electrocatalysis. Control experiments were used to verify the critical roles of the electricity, the copper catalyst, and the additive (entries 10−12).

With the optimized copper(II) catalyst for the electrooxidative C−H/N−H functionalizations in hand, we examined the scope of benzamides (**1a**−**1s**) ammenable to reaction with morpholine **2a** (Scheme 2). Gladly, the reaction tolerated a

Scheme 2. Scope of Amides



range of substrate substituents, affording the corresponding products in moderate to good yields (55−80%), relative to the unsubstituted benzamide **1a**, which afforded the desired product in good yield (79%). Generally, the reactivity of electron-deficient substrates (**1k**−**1t**) were lower than in the case of electron-rich substrates (**1b**−**1h**). It was notable that, in each case, only monoaminated products were observed. Moreover, in the case of the *meta*-substituted benzamides (**1c**, **1i**, **1l**, and **1n**), C−H functionalization was observed to take place exclusively at the less hindered position, highlighting the reaction's good regioselectivity. Gratifyingly, 1- and 2-napthamide (**1g**−**1h**) were also applicable under the standard conditions, yielding the desired products (**3g**−**3h**) in good yield. This transformation also tolerates halogenated substituents, notably the bromo and fluoro groups, which are otherwise apt to participate in nucleophilic amination reactions.[66,67] In addition, we were pleased to find that the heterocyclic thiophene amide **1s** was also aminated (**3s**) in moderate yields (61%).

To further explore the scope of this copper(II) catalyzed electrooxidative amination reaction, a series of secondary amines were tested. As seen in Scheme 3, the reaction of substrate **1f** with a range of cyclic six-membered ring secondary amines was explored with piperidine and a series of its derivatives containing either electron-withdrawing or -donating substituents using the optimized electrooxidative conditions, which yielded the aminated products in 55−88% yield (**4b**−**4k**), highlighting the broad functional group compatibility of

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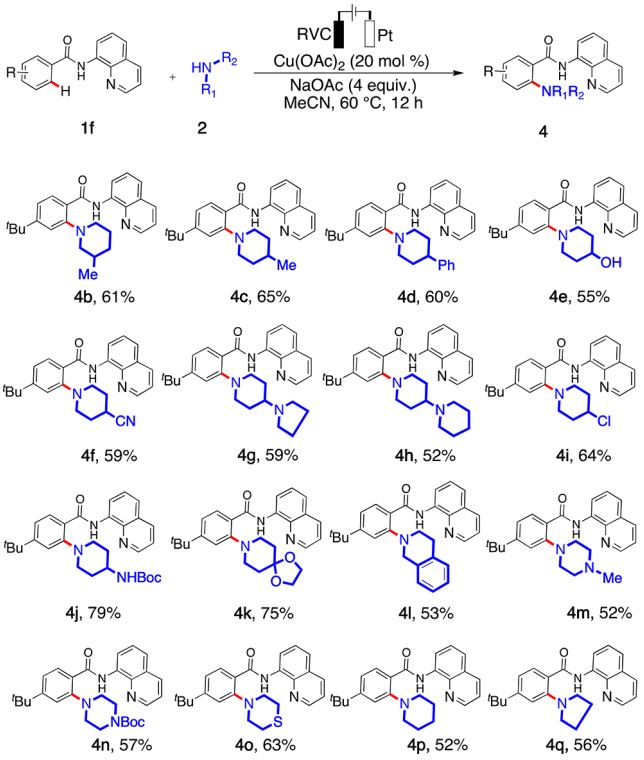
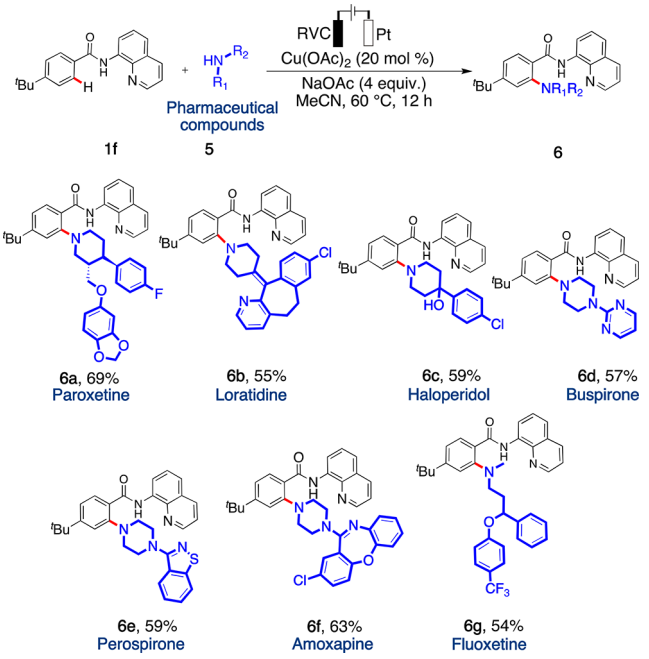
Scheme 3. Scope of Amines



Scheme 4. Synthetic Utility

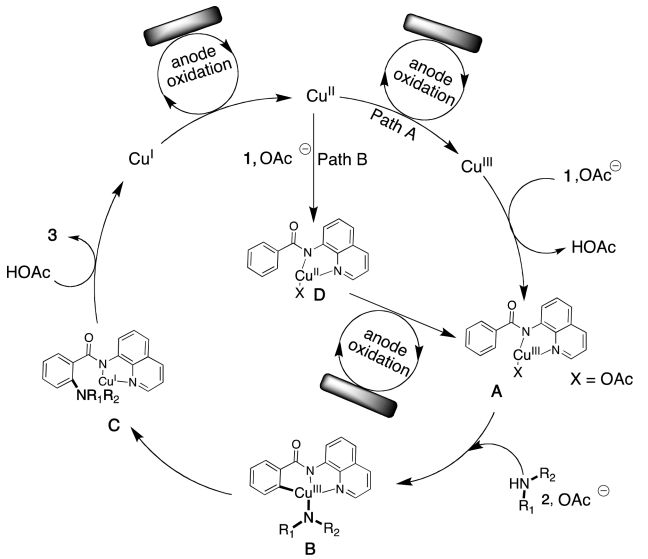


the reaction. Moreover, the coupling of **1f** with tetrahydroisoquinoline also gave the corresponding aminated product **4l** in 70% yield. Medicinally privileged protected piperizine derivatives could also be used in the reaction, as is evidenced throught the formation of **4m** and **4n**. Notably, the coupling of thiomorpholine under metalloelectrocatalysis conditions was successful and furnished the aminated product **4o** in 63% yield. Finally, pyrrolidine and piperidine could be cross-coupled, furnishing products **4p**–**4q** in moderate yields.

We anticipate that this copper(II) catalyzed electrooxidation should find wide application in medicinal chemistry, and accordingly wanted to demonstrate that coupling fragments of established significance could be performed (Scheme 4). The examples presented in Scheme 4 consist of a series of amines containing active pharmaceutical ingredients (APIs), or closely related derivatives thereof, that can be effectively used in this reaction. For example, reaction with the series of complex substituted piperidine derivatives (**5a**–**5e**) proceeded well, leading to the incorporation of amine fragments belonging to the antidepressant Paroxetine (**6a**), Loratidine (antihistamine, **6b**), Clopidogrel (antiplatelet agent, **6c**), and Haloperidol (antipsychotic/antimotility, **6c**). Piperazines that feature in the anti-Parkinsonian compound Piribedal (**6d**), and atypical antipsychotics Perospirone and Ziprasidone (**6e**) all performed well, as was also the case for the piperazine moiety that constitutes the API in the antidepressant Amoxapine, **6f**. We were also able to employ the acylic *N*-methylamine containing the API of the antidepressant Fluoxetine **6g**. Notably, the use of *N*-alkyl amines is reported to have limited compatibility in reported C–H amination reactions.[62,63] However, this elegant copper(II)–metalloelectrocatalysis strategy provides a method to incorporate *N*-alkylamines under mild reaction conditions using electricity as a green oxidant.

Based on the observed reactivities and previous reports on transition-metal-directed C–H activations and oxidative functionalizations with hydrogen evolution without the use of external chemical oxidants for recycling the catalysts, we propose an electrooxidative C–H amination that proceeds through a Cu^{II}/Cu^{III} catalytic cycle (Scheme 5),[62−64,68,69]

Scheme 5. Possible Mechanisms



where Cu(II) was oxidized to Cu(III) at the anode which then reacts with amide **1** in the presence of NaOAc to form intermediate **A**. Subsequent coordination of amine **2** to intermediate **A** affords **B**. A subsequent reductive elimination of the intermediate **B** delivers the final product **3**, which is followed by anodic oxidation to complete the catalytic cycle, thus avoiding the use of expensive terminal oxidants (Path A). Alternatively, the amide **1** could react with Cu(II) to form **D**,

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which on further oxidation at the anode yields complex **A** (Path B).

In summary, copper-catalyzed coupling of synthetically versatile aryl amides with various aliphatic amines has been enabled under mild conditions in the absence of an external oxidant. This has been achieved through a synergistic merging of electrocatalysis with copper(II) organometallic chemistry employing electricity as the only oxidant and generating hydrogen as the sole byproduct. The newly developed methodology is tolerant of variation in both reaction partners and proceeds in the presence of basic heteroatoms and several heterocyclic scaffolds. They potential for using this methodology in late-stage functionalization in drug development is highlighted by its use in the derivatization of a number of pharmaceutically active compounds. Finally, we anticipate that this new cross-dehydrogenative cross-coupling strategy will provide a useful, complementary approach to C−N bond-forming reactions while also expanding upon the repertoire of transformations mediated by base metal catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00003.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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