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Electrochemically Enabled Chan−Lam Couplings of Aryl Boronic Acids and Anilines

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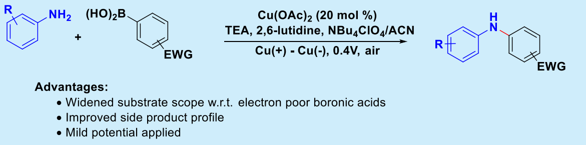
Supporting Information

ABSTRACT: The Chan−Lam reaction remains a highly utilized transformation for C−N bond formation. However, anilines remain problematic substrates due to their lower nucleophilicity. To address this problem, we developed an electrochemically mediated Chan−Lam coupling of aryl boronic acids and amines utilizing a dual copper anode/cathode system. The mild conditions identified have enabled the preparation of a wide range of functionalized biarylanilines in good yields and chemoselectivities.

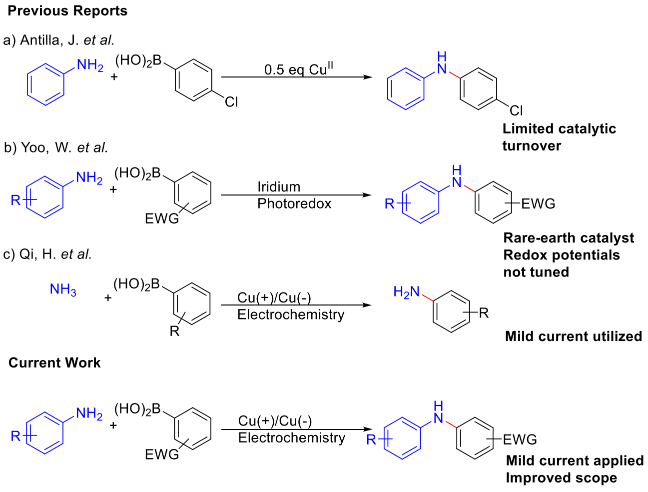


The formation of carbon−nitrogen bonds via metal-catalyzed cross-coupling reactions has been one of the most impactful classes of reactions in recent decades due to their ability to provide robust access to a wide-range of medicinally relevant molecules. As a result, these reactions are commonly utilized in industry.[1−5] A method for N,O-arylation was developed by Chan[6], Lam[7] (N-arylation) and Evans[8] (O-arylation) that allowed for the formation of carbon−heteroatom bonds using boronic acid coupling partners, which are widely available due to the popularity of Suzuki coupling.[9] Despite the wide availability of the reaction components and the ability to access medicinally relevant compounds, the Chan−Lam coupling remains relatively underutilized in the synthetic community[11,13,15−17] due to slow rates, stoichiometric copper, water sensitivity, side-product formation, incompatibility with boronic ester coupling partners and consumption of the boronic acid partner.[10]

In particular, anilines are problematic substrates when used in the Chan−Lam coupling due to their low nucleophilicity resulting in the slow formation of the catalytically active copper complexes.[10,11] In addition, there are several substrates in the literature that have been identified to be challenging.[12,13] For instance, the coupling of anilines with electron-deficient boronic acids are generally characterized by yields consistent with little to no catalytic turnover (Scheme 1a).[12] Despite recent advances in the mechanistic understanding[10,14] and general synthetic methodology to achieve these transformations, electron-deficient boronic acids remain challenging substrates for traditional Chan−Lam methodologies.[11,13,15−17]

Inspired by a report on the electrochemical conversion of aryl boronic acids to either primary anilines or phenols (Scheme 1c) using ammonia or water, respectively,[18] we envisioned that the drawbacks of the Chan−Lam reaction described previously could be solved by developing an electrochemical version of the reaction and testing it for traditionally difficult substrates (e.g., electron-deficient boronic acids and anilines). In addition, the application of a well-tuned and mild electrochemical current would allow us to broaden the substrate scope as compared to the photochemical method to substrates such as aryl iodides, which are reduced by the photoexcited Ir(ppy)$_3$ (Scheme 1b, vide infra).[11] Finally, we aimed to elucidate the mechanism by which our conditions may enable the reaction to proceed.

Scheme 1. Chan−Lam Coupling through Electron-Poor Cu^{II}



Herein, we report an electrochemically enabled protocol that achieves improved yields for these historically difficult products. To ensure the practicality of this method, we constrained our optimization to a reaction time of less than 1 day at room temperature with a catalytic amount of copper and readily available starting materials.

A summary of the most relevant preliminary results is depicted in Table 1 using aniline **1a** and boronic acid **2a** and inexpensive and widely available Cu(OAc)$_2$. Inspired by the reaction conditions for the electrochemical conversion of aryl boronic acids to either primary anilines or phenols,[18] a dual

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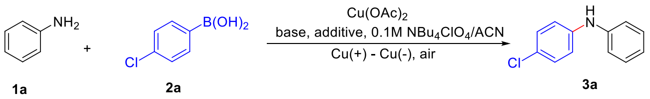
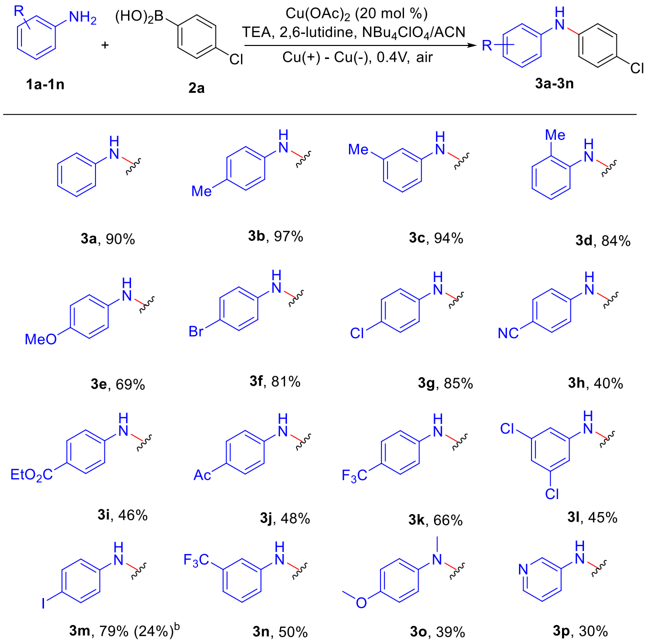
Table 1. Optimization of the Electrochemical Chan−Lam Coupling of 1a and 2a.[a,b]



entry	V	base (1.2 equiv)	additive (0.2 equiv)	yield (%)
1	0.40	–	–	21[c]
2	0.40	–	–	45
3	0.40	–	–	60[d]
4	0.30	–	–	nd[e]
5	0.35	–	–	nd[e]
6	0.45	–	–	39
7	0.50	–	–	42
8	0.40	2,6-lutidine	–	65
9	0.40	2,6-lutidine	TEA	98
10	0.40	2,6-lutidine	DIPEA	45
11	0.40	TEA	–	80
12	–	2,6-lutidine	TEA	54
13	–	2,6-lutidine	TEA	47[f]
14	0.40	2,6-lutidine	TEA	<5[g]

[a] Reaction conditions: aniline **1a** (0.55 mmol), **2a** (0.71 mmol), 0.1 M NBu_4ClO_4/ACN (4 mL), additive (0.11 mmol, 0.2 equiv), base (0.66 mmol, 1.2 equiv), $Cu(OAc)_2$ (0.11 mmol, 20 mol %), rt, undivided cell, air, 20 h. [b] Yields determined by NMR integration using 1,4-dinitrobenzene as an internal standard. [c] Reaction run under nitrogen in degassed ACN. [d] Reaction run under O_2 balloon. [e] Current unable to flow. [f] Heated to 35 °C. [g] $Cu(OAc)_2$ omitted.

Scheme 2. Aniline Substrate Scope with Boronic Acid 2a[a]



[a] Reaction conditions: aniline **1a** (0.55 mmol), **2a** (0.71 mmol), 0.1 M NBu_4ClO_4/ACN (4 mL), Et_3N (0.11 mmol, 0.2 equiv), 2,6-lutidine (0.66 mmol, 1.2 equiv), $Cu(OAc)_2$ (0.11 mmol, 20 mol %), rt, undivided cell, air, 20 h. [b] See the SI for procedure.

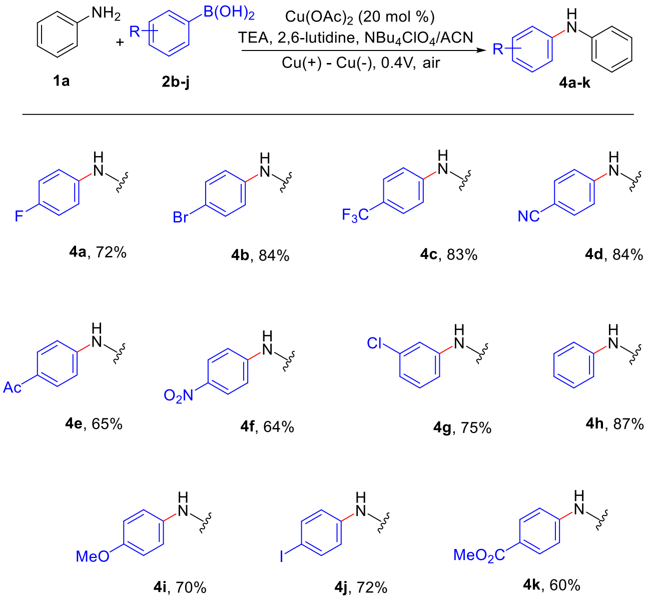
copper anode/cathode system was utilized.[19] The current was cycled every 10 min in order to avoid electrode spoiling, and a constant voltage of 0.4 V was applied over 24 h resulting a 21% yield (entry 1). Subsequently, initial results indicated that running the reaction under oxygen or air atmosphere was crucial for the efficiency of our electrochemical coupling resulting in 45% and 60% yields, respectively (entries 2 and 3). Increasing the voltage to 0.5 V resulted in a messier reaction profile (entry 7) with no improvement in yield (42%), whereas voltage lower than 0.4 V resulted in a loss of current soon after electrolysis was initiated (entries 4 and 5). We found that the use of 2,6-lutidine significantly increased our yields to 65% (entry 8). A further increase in yield was observed with the addition of triethylamine (98%, entry 9). This could be explained by helping with acceleration of the rate of the Chan−Lam reaction through the generation of an improved active catalyst complex and a greater rate of Cu^I/Cu^{II} oxidation.[10] Furthermore, the more nucleophilic Et_3N (TEA) was preferred versus DIPEA (entry 10), suggesting the beneficial role of TEA to break up the copper paddlewheel complex. Interestingly, 2,6-lutidine and TEA both appear to be necessary for efficient reactivity, and using Et_3N alone resulted in decreased yield (80%, entry 12). Finally, control experiments were performed. When no current was applied at room temperature or at 35 °C, lower yields were obtained showcasing the benefits of using electrochemical versus classic Chan−Lam conditions (entries 12 and 13). The omission of the copper acetate ablated catalytic activity (<5%, entry 14), showing the reaction is not mediated by the electrodes directly. Overall, C−N coupling was accomplished in a simple undivided cell setup at room temperature overnight.

With our optimal conditions identified, we sought to demonstrate the scope of this method on a variety of anilines and boronic acids (Scheme 2). First, we explored the substrate scope with respect to anilines coupling with boronic acid **2a**. As expected, electron-rich anilines **3a−e** performed quite well. Additionally, anilines bearing a *para*-halogen performed well under the reaction conditions (**3f**, **3g**, and **3m**). Under photoredox conditions,[11] aryl iodides are partially reduced, resulting in reduced yields (24%) when compared to this mild electrochemical procedure (79%) which showed no dehalogenation (3m). Electron-deficient anilines **3h−k,n** and aminopyridine **3p** were coupled in moderate yields, likely due to the poor nucleophilicity of the aniline starting materials slowing of the generation of the active Cu^{II} complex.[10] Finally, *N*-methylaniline-derived **3o** also proceeded in modest yield, likely due to increased steric hindrance.

We next endeavored to understand our substrate scope with respect to boronic acid coupling with aniline **1a** (Scheme 3). All substrates, including electron-poor boronic acids, yielded product in good to excellent yields. This supports the role of aniline in generating the active Cu^{II} complex.[10] Once again, Chan−Lam amination was selectively achieved for aryl iodide **4j**. In addition, the conversion of electron-poor **4f** was achieved in good yield due to the mild potential employed, which is well below the predicted redox potential of the nitro group ($E_{1/2}^{red} = -1.19$ V vs SCE).[20] We have shown that with our mild electrochemical method a wider range of substrates can be achieved with yields comparable to those of the previous state of the art.

Finally, we were interested in evaluating the mechanism by which our applied voltage was mediating the Chan−Lam coupling. In our CV studies, no oxidative peak was observed within the relevant range, suggesting that it is unlikely that direct oxidation of the Cu^{II} to the Cu^{III} intermediate, required for reductive elimination, occurred (SI Figure 1). A hint of the mechanism could be found by analyzing the structures and abundance of the byproducts (SI Figure 5); the electro-

Scheme 3. Boronic Acid Substrate Scope with Aniline 1a[a]



[a]Reaction conditions: aniline (0.55 mmol), **2a** (0.71 mmol), 0.1 M NBu_4ClO_4/ACN (4 mL), Et_3N (0.11 mmol, 0.2 equiv), 2,6-lutidine (0.66 mmol, 1.2 equiv), $Cu(OAc)_2$ (0.11 mmol, 20 mol %), rt, undivided cell, 20 h.

chemical process showed decreased formation of the phenol, known to arise from a Cu^I-mediated process.[10]

In order to probe the redox behavior of the reaction mixture CV was performed (see the SI for full discussion and spectra). We observed a quasi-reversible deposition ($E_{1/2}^{red}$ = −0.35 V vs Ag/AgCl) of an impure Cu^0/perchlorate film on the electrode surface[21] but no direct oxidation of the soluble Cu^I. Using this finding, we propose the electrochemical refining mechanism shown in Figure 1, where the less stable Cu^I generated during the reaction is plated to the cathode, diminishing side product formation. When the current is reversed after 10 min, the copper previously deposited as an impure film is oxidized back to Cu^I at the new anode. The Cu^I can then either be oxidized back to Cu^{II} by oxygen or plated to the new cathode.[22−24] Beyond this step, the catalytic cycle is identical to that previously reported.[10] The initial Cu^{II} complex **I** is broken up by the aniline to form **II** before transmetalation of with the boronic acid coupling partner to form intermediate **III**. This Cu^{II} complex is then oxidized to Cu^{III} via disproportionation to form **IV**. Finally, reductive elimination step yields the desired product and a Cu^I species **V** that is either oxidized by oxygen or plated to the cathode as discussed previously.

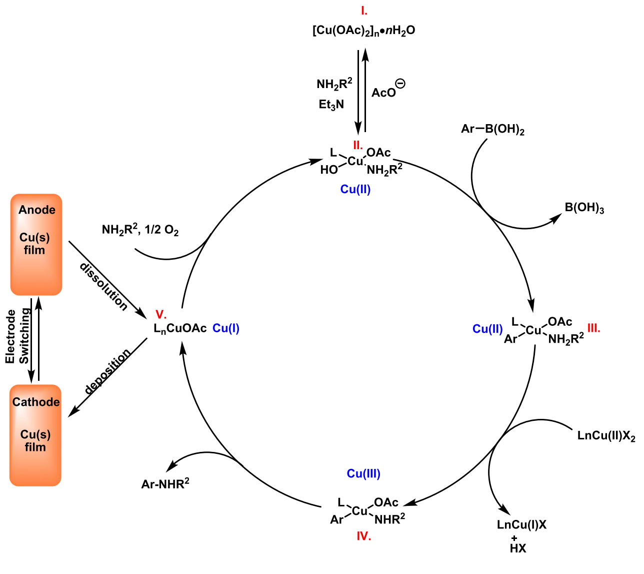


Figure 1. Proposed mechanism.

In summary, a new methodology has been developed to allow access to traditionally challenging Chan−Lam substrates under mild conditions. In comparison to previous methods, this protocol has shown a broadened scope. Additionally, we have made steps to elucidate the mechanism, identifying a possible electrochemical refining process that limits side-product formation and slows unproductive starting material consumption. Further investigations into the scope and applications of this process are currently underway in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01434.

> Additional experiments (controls and reaction optimization); ^1H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(24) See the SI for a detailed mechanistic discussion and investigation.