Cross-Coupling

Cu(OTf)$_2$-Mediated Cross-Coupling of Nitriles and N-Heterocycles with Arylboronic Acids to Generate Nitrilium and Pyridinium Products

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Abstract: Metal-catalyzed C–N cross-coupling generally forms C–N bonds by reductive elimination from metal complexes bearing covalent C- and N-ligands. We have identified a Cu-mediated C–N cross-coupling that uses an additive N-ligand in the bond-forming event, which, in contrast to conventional methods, generates reactive cationic products. Mechanistic studies suggest the process operates via transmetalation of an aryl organoboron to a Cu$^{II}$ complex bearing neutral N-ligands, such as nitriles or N-heterocycles. Subsequent generation of a putative Cu$^{III}$ complex enables the oxidative C–N coupling to take place, delivering nitrilium intermediates and pyridinium products. The reaction is general for a range of N(sp) and N(sp$^2$) precursors and can be applied to drug synthesis and late-stage N-arylation, and the limitations in the methodology are mechanistically evidenced.

Introduction

Transition metal-mediated C-N cross-coupling is an essential synthetic method, used extensively throughout the chemical industry for the synthesis of pharmaceuticals, agrochemicals, natural products, and materials$^{[1-8]}$. The development of new or improved processes for C–N bond construction remains a continual inspiration for metal-based reaction development. Despite a broad diversity and subtlety in the mechanism of these methods, the basic premise of the reaction involves a series of individual mechanistic steps, e.g., oxidative addition, transmetalation, and/or deprotonation, to allow access to a key metal complex bearing formally anionic, covalently bound C- and N-ligands (Scheme 1a). This complex undergoes reductive elimination to deliver a neutral product, which is produced regardless of whether the catalysis itself is electroneutral (e.g., the Buchwald-Hartwig or Ullmann-Goldberg reactions) or oxidative (e.g., the Chan-Lam reaction)$^{[6-9]}$.

In these processes, the N-ligand originates from a precursor amine or amine-derived substrate bearing at least one functionalizable N–H, which undergoes deprotonation at some stage in the reaction mechanism to deliver the required anionic N-ligand. This limits the scope of established processes to substrates with at least one N–H.

However, it should be noted that the direct N-arylation of substrates without a functionalizable site is known. N-arylation of nitriles and N-heterocycles has been achieved with or without transition metal activators, for example, using diaryliodonium salts$^{[10,11]}$. With Cu-promoted processes$^{[10,11]}$, these are mechanistically ambiguous, with no evidence for
a metal-centered reductive elimination. These processes have also been rationalized as direct arylation using the increased electrophilicity of the aryl transfer reagent via Lewis acid activation. More specifically, while CuI has been shown to slightly accelerate aryl transfer with diarylidoiums, these processes also proceed effectively without CuI consistent with observed general reactivity of this class of reagents and related reactive aryl transfer reagents, such as arylazidonium salts.

Here, we report the discovery, mechanistic rationale, example scope, and limitations of a Cu-mediated C-N cross-coupling method that promotes reductive elimination to neutral N-ligands, such as nitriles and N-heterocycles generating reactive cationic products (Scheme 1b).

Results and Discussion

During investigations to rationalize the reactivity of CuII sources in standard Chan-Lam reactions, the amide product 3a was identified in good yield when the reaction of arylboronic acid 1 with aniline was attempted with Cu(OTf)2 (4 equiv) in MeCN (Scheme 2a). A similar observation was made by Sanford during studies of fluorodeboronation, which also used stoichiometric Cu(OTf)2 (4 equiv) in MeCN (Scheme 2b). We were intrigued by this observation since hydrolysis of MeCN to acetamide followed by Chan-Lam-type N-arylation seemed unlikely—we have previously attempted Chan-Lam arylations of amides using Cu(OTf)2, and found this to be problematic (vide infra). Consequently, we sought to understand the origin of this coupling process.

Control experiments indicated the possibility of an alternative pathway. The Chan-Lam arylation of acetamide 6 using Cu(OTf)2 in PhMe does not provide the N-aryl product. Instead, the products of arylboronic acid oxidation and protodeboronation were observed and represented the almost complete mass balance (Scheme 3a)—protodeboronation was also noted as an issue in Sanford’s study and is a common problem for Cu-mediated reactions of organoborons. Separate experiments (Table S1) indicated that the same conditions did not lead to nitrile hydrolysis. The competition reaction of 1 with acetamide and DCCN in the presence of Cu(OTf)2 led to the deuterated acetamide product 3b exclusively, further supporting the absence of a Chan-Lam pathway and indicating selectivity for nitrile (Scheme 3b).

To rationalize these initial observations, we considered a reaction pathway that proceeded via formation of a nitrilium intermediate formed by Cu-mediated N-arylation of the nitride. N-arylation of nitriles is known using highly reactive aryl transfer agents, such as iodonium and diazonium salts; however, oxidative coupling of nitriles with arylboronic acids is unknown. Accordingly, we sought to establish if an oxidative coupling pathway was operational.

Treatment of Cu(OTf)2 with H2O in MeCN leads to a stable and isolable complex CuII(OTf)2(H2O)(MeCN)2 (10a, Scheme 3c). Heating this complex with 1 lead to the observed acetamide 3a, which we propose proceeds through nitrilium 11a, suggesting possible formation and involvement of 10a in the reaction.

Nitrilium ions are highly reactive electrophiles capable of a variety of bond forming processes with nucleophiles; however, extensive experimentation to intercept the proposed nitrilium 11a were unsuccessful and afforded a mixture of amide and returned starting material (Tables S2 and S3). We therefore attributed amide formation to hydrolysis of the nitrilium with H2O present in the reaction mixture, arising either from boroxine formation from 1 or Cu-bound H2O in 10a–H2O could not be excluded in preparation of stoichiometric Cu(OTf)2, nitrile complexes as noted above.

Independent preparation of stable nitrilium 11c and treatment with 10a led to instantaneous hydrolysis, high-

Scheme 2. Observations of Cu-mediated nitrile arylation. [a] Determined by HPLC. ArI = p-PhC6H4; Tf = trifluoromethylsulfonyl.

Scheme 3. Control reactions. ArI = p-PhC6H4; ArII = p-(F3CO)C6H4.
lighting the lability of Cu-bound H$_2$O (Scheme 3d). To probe the origin of H$_2$O in the acetamide product, we undertook labelling experiments. Addition of H$_2^{18}$O to the reaction of 10a with 1 led to 41% $^{18}$O incorporation in the product 3c, consistent with the $^{18}$O:10$^{18}$O stoichiometry (Scheme 3e). Preparation of 18$^{18}$O-labelled complex 10b was successful; however, the $^{18}$O incorporation could not be quantified due to lability of the dative ligands. Indeed, despite obtaining crystal structure data of 10a and 10b (identical), HRMS analyses were uniformly unsuccessful. Use of 10b in the absence of additional H$_2$O gave 3c in comparable yield to the reaction of 10a and with 60% $^{18}$O incorporation (Scheme 3f).

The inability to trap the nitrilium by any nucleophile other than H$_2$O in solution, a Cu aquo species (e.g., 10a/10b), or from a Cu$^+$ complex liberated after reductive elimination (e.g., 13, Scheme 3f).

To further substantiate this nitrilium proposal, HRMS analysis of reaction mixtures identified a series of mass ions that allowed the following mechanism to be proposed (Scheme 4).[25]

We propose that Cu(OTf)$_2$ forms 10a (crystal structure obtained from reaction mixtures). Loss of TIOH and H$_2$O gives 14a—mass ions consistent with [14a·MeCN] (14b) and [14a·H$_2$O] (14c) were found. Transmetalation then gives 16a (16b found), possibly via a pathway consistent to the Chan-Lam amination (15).[26] Disproportionation of 16a gives the key Cu$^{III}$ intermediate 17a with [17a·TfO$^-$] (17b) found,[26–28] allowing formation of the nitrilium product 11 (11b found). Mass ions consistent with the proposed Cu$^+$ aquo complex 18a were detected (18b), consistent with the quenching proposal outlined in Scheme 3f. Stoichiometric Cu(OTf)$_2$ was exclusively effective—other Cu sources failed to promote the reaction (Table S7). Extensive investigation failed to allow this process to operate with catalytic Cu(OTf)$_2$—the addition of terminal oxidants led to issues of organoboron oxidation and rendering Cu turnover (Scheme 4, dotted line) irrelevant (Table S9). The same turnover issues in systems using Cu(OTf)$_2$ and CuOTf have been observed in C-F bond formation by Sanford[27] and Hartwig,[29] respectively, where 3–4 equivalents of Cu were necessary for reaction efficiency. This problem remains unresolved for many Cu(OTf)$_2$-based processes.[30]

The proposed nitrilium ions were observable by HRMS; however, the inability to intercept the proposed nitrilium with other nucleophiles was unsatisfactory. Specifically, this invites further scrutiny of the proposed key C–N bond forming event in Scheme 4—the potential for an on-metal hydrolysis cannot be excluded. We therefore sought to demonstrate the C–N bond forming process using a system that would allow unambiguous identification C–N bond formation produced from reductive elimination to a neutral N-ligand on Cu$^{III}$.

Treatment of Cu(OTf)$_2$ with DMAP allowed formation of Cu$^{III}$(OTf)$_2$(DMAP)$_3$ (19) and its structure unambiguously confirmed by X-ray (Scheme 5).

Complex 19 is similar to the nitrile complex 10a; however, this can be prepared without aquo ligands. Under the same reaction conditions used in Scheme 3c, 19 leads to a similar C–N bond formation giving N-aryl pyridinium 20 and in similar yield to the nitrile process. 20 was characterized unambiguously by spectroscopy and X-ray, providing strong support for C–N cross-coupling via Cu$^{III}$. We propose this reaction to follow a similar course to that proposed in Scheme 4. Single electron pathways via oxidation of DMAP by Cu$^{III}$ were proposed to be unlikely based on oxidation potentials and EPR analysis (vide infra).[33–35]

Despite evidence for the feasibility of reductive elimination from (aryl)Cu$^{III}$ complexes yielding N-aryl ammonium products,[36,37] the equivalent N(sp$^3$) cross-coupling under the conditions reported here did not afford the desired C–N(sp$^3$) bond. We attribute this to competing amine oxidation by Cu$^{II}$.[38] this was substantiated by EPR studies, which showed quenching of Cu$^{II}$ and, in the case of N-methylpyrrolidine, a radical species could be observed (Scheme 6a). Addition of tertiary amines to the optimized DMAP N-arylation process
had variable effects on the observed yield (Scheme 6b). For example, PhNMME, almost completely reduced CuII and lowered yield of 21 by approximately half; however, n-butylaziridine reduced approx. 25% of CuII yet had no impact on the yield of 21. Little reduction of CuII by TEMEDA was observed by EPR and the arylation reaction was instead impaired by formation of a series of novel but unreactive bidentate complexes (Scheme S12). As expected, DMAP did not significantly reduce CuII.

Moreover, in the presence of unsubstituted anilines, an alternative oxidative coupling pathway becomes evident via formation of 1,2-diarylhydrazines (22) and azobenzenes (23) (Scheme 6c). This is clearly mechanistically related to previously reported Cu-mediated N-N coupling reactions.8-10 Consistent with these previous reports, our EPR data suggests that these processes proceed via single electron oxidation of the aniline by CuII; however, importantly, the resulting aminium radical does not appear to be free in solution and attempts to intercept these species were universally unsuccessful (Table S6). In contrast to a previously proposed mechanism,10 our data suggests formation of the N–N bond at the metal or within the solvent cage. This would deliver the symmetrical hydrazine product, consistent with previous observations.8-10 As an adjunct to the main work described here, additional control experiments have shown facile oxidation of the hydrazine to the azobenzene by Cu(OTf)2 aligning with the experimental data observed across these separate studies (Scheme S14).8-10

Following optimization (Tables S7–S11), a general process was developed for the coupling of aryloboronic acids with nitriles and N-heterocycles—a selection of products is provided in Scheme 7 (for additional substrates see Scheme S15).10 The process tolerates a variety of functional groups on both the nitrile and aryloboronic acid, with standard structural and electronic variations examined in this example scope. The nitrilium process is an unusual amidation protocol (essentially an aryl Ritter reaction) providing a new approach to this ubiquitous motif; however, the heterocycle N-arylation process allows access to products that cannot be made easily using any established method, providing novel opportunities for synthetic design. In general, the scope of the boronic acid was very good for aryloboronic acids, with some lower yields observed using heteroaromatic species consistent with established limitations with these substrates.10 Alkyloboronic acids were tolerated only in the N-heterocycle process (e.g., product 45); no desired products were observed in the equivalent nitrilium reactions. For the nitrilium process, the C-N cross-coupling could be achieved using the nitrile as solvent where practical (e.g., for MeCN, EtCN), otherwise PhMe was the preferred medium for both the nitrilium and N-heterocycle processes. While generally effective, solubility issues can present with certain aryloboronic acids in PhMe resulting in lower yields (e.g., 29–31). With regards the N-heterocycle process, the reaction was broadly tolerant to the nature of the heterocycle, although higher yields were obtained with more electron-rich compounds, which may be expected based on the oxidative coupling process. The issue of lower yields with substrates bearing ortho-substitution was replicated (e.g., 27 and 40) and is again consistent with observations in Cu-mediated oxidative coupling processes.10

As discussed above for the nitrile process, stoichiometric Cu(OTf)2, was also needed for the heterocycle process, which perhaps offers some explanation for the lack of observable reinsertion into the N-aryl pyridinium products. Additional demonstrations of utility are provided in Scheme 7c-g. The C-N coupling process can be applied to the N-arylation of non-aryl N(Sp2) including the common organic base DBU as well as the Lewis base organocatalyst (--)-tetramisole to afford compounds 52 and 53, respectively (Schemes 7c and d).

The ability to induce direct N-arylation of N-heterocycles allows a significantly shorter route to non-symmetrical NHCS by N-arylation of N-aryl imidazoles such as 54, which proceeds via the expected complex 55 to deliver imidazolium salt 56 (Scheme 7e; see also 50 and 51 in Scheme 7b for alkyl/aryl imidazolium).11 Lastly, the process can be used in synthesis, for example using the nitrilium process to access pharmaceutically relevant amides, such as the Tolvaptan intermediate 57 (Scheme 7f) and for late-stage functionalization, for example N-arylation of the agrochemical Pyriproxyfen, giving product 58 (Scheme 7g).

**Conclusion**

In summary, the data provided establishes a framework for oxidative C-N cross-coupling of aryloboronic acids with neutral N-ligands. Importantly, mechanistic data supports
a Cu\textsuperscript{III}-based process and is distinct from Lewis acid-assisted N-arylations using reactive aryl transfer electrophiles (e.g., iodoniums). This expands the scope of oxidative coupling, allowing access to new products. The broader implications are that, assuming specific metal-centered mechanistic events can be appropriately controlled, neutral N-ligands may be effective partners for cross-coupling more generally within transition metal catalysis, providing new opportunities for reaction design.\cite{48}

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**Conflict of interest**

The authors declare no conflict of interest.
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