Spectroscopic studies of the Chan-Lam amination: A mechanism-inspired solution to boronic ester reactivity

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ABSTRACT: We report an investigation of the Chan-Lam amination reaction. A combination of spectroscopy, computational modeling, and crystallography has identified the structures of key intermediates and allowed a complete mechanistic description to be presented, including off-cycle inhibitory processes, the source of amine and organoboron reactivity issues, and the origin of competing oxidation/protodeboronation side reactions. Identification of key mechanistic events has allowed the development of a simple solution to these issues: manipulating Cu(I)→Cu(II) oxidation and exploiting three synergistic roles of boric acid has allowed the development of a general catalytic Chan-Lam amination, overcoming long-standing and unsolved amine and organoboron limitations of this valuable transformation.

1. INTRODUCTION

Transition metal-mediated C-N bond formation is an essential transformation that enables the preparation of valuable aryl amine products. Copper-catalyzed processes such as the Ullmann2 and Chan-Lam3,4 reactions are both particularly valuable and widely practiced (Scheme 1). The Ullmann reaction has seen significant development, particularly in the context of ligand design to allow milder reaction conditions and overcoming reactivity issues with aryl chloride electrophiles. Where the Ullmann reaction follows the characteristic transition metal-catalyzed nucleophile/electrophile coupling, the Chan-Lam amination is unique, coupling two nucleophiles, an aryl organoboron compound and an amine, usually under mild oxidative conditions (air or O2).4

(a) Cu-catalyzed amination (Ullmann)

(b) Cu-catalyzed oxidative amination (Chan-Lam)

Scheme 1. Cu-catalyzed C-N bond formation.

2. GOALS OF THIS STUDY

A major limitation of the Chan-Lam amination has been the lack of general reactivity using aryl boronic acid pinacol (BPin) esters, especially with aryl amines. While conversion of BPin to the boronic acid is relatively straightforward, ary1 BPin are more readily accessed, especially by modern transition metal-catalyzed methodologies. In addition, BPin are often more stable than boronic acids, where protodeboronation can be problematic for several substrate classes. There have been several approaches to improving ary1 BPin reactivity, including the use of additives to achieve boron species interconversion in situ and the use of substrates bearing Cu-ligating groups that are seemingly more reactive.6.10

The origin of these reactivity differences is unknown and a purely steric argument was unsatisfactory: Chan-Lam-type amination of specific BPin species have been reported10 and ary1 BPin are competent in numerous other transition metal-catalyzed reactions. More broadly, the utility of the Chan-Lam amination is hampered by significant problems with byproduct formation and the mechanism of the amination remains elusive,11 although a seminal study of the related etherification process by Stahl has provided a solid foundation for understanding these Cu-based oxidative coupling reactions.12

Here we report a spectroscopic investigation of the Chan-Lam amination reaction, providing a complete mechanistic description, including off-cycle inhibitory processes, the source of amine and organoboron substrate reactivity issues, and the origin of competing oxidation/protodeboronation side reactions. This knowledge has been leveraged to provide a simple solution to the catalytic Chan-Lam amination of both boronic acids and BPin esters with alkyl and aryl amines.

3. PREVIOUS WORK

Seminal studies by Stahl have provided key insight into the mechanism of the related etherification process, using a boronic acid dimethyl ester in MeOH as the benchmark process (summarized in Scheme 2).12

Stahl’s process begins from a Cu(II) species (I) that undergoes transmetallation with boronic ester 2 to deliver ary1 Cu(II) species 4, releasing byproduct 3. Stahl proposed 9 as a resting state with turnover-limiting transmetallation proceeding via 10. Oxidation of 4 to Cu(III) complex 6 occurs via disproportionation with a second equivalent of 1, liberating Cu(I) complex 5. Reductive elimination of ether product 7 gives 5, which is reoxidized to 1 using O2, HX, and X–B(OOMe)2 to complete the cycle. While there are several fundamental differences between the etherification process and the amination reaction, this key study provides important data that proved highly informative for assembling a complete mechanistic description of the amination reaction (vide infra).
Scheme 2. Summarized version of Stahl’s etherification mechanism and proposed catalyst resting states/pre-transmetallation intermediates.

4. RESULTS

4.1 Reaction Profiles and Identification of Byproducts. Control experiments were performed to evaluate the performance of the Chan-Lam amination using representative members of two amine classes, piperidine (12, alkyl) and aniline (14, aryl), and two organoboron compounds, boronic acid (11a) and BPin ester (11b).

(a) Chan-Lam amination of 11a/11b with alkyl amine 12

(b) Chan-Lam amination of 11a/11b with aryl amine 14

(c) Reaction profile for reaction of 11a with 12 under standard conditions

Under standard conditions (1 equiv amine, 2 equiv organoboron reagent, 1 equiv Cu(OAc)₂; see Scheme 3 and ESI) using 12 as the amine coupling partner (Scheme 3a), boronic acid 11a is converted to product 13a in 87% yield while the corresponding BPin 11b provides 28% yield. Using 14 as the amine component with 11a gives product 15a in 92% yield and 16% yield using 11b (Scheme 3b).

Several byproducts were identified including phenol 16, protodeboronation product 17, and oxidative homocoupling product 18. A reaction profile for the reaction in Scheme 3a is given in Scheme 3c. Protodeboronation was comparable to amination, while competing oxidation delivers 16 and, as [16] increases, competing Cu-catalyzed etherification delivers 18.

Table 1 provides the full product distribution for the reaction of amines 12 and 14 with 11a. These values are based on the organoboron reagent (2 equiv vs. 1 equiv amine) in order to fully appraise the extent of byproduct formation.

Table 1. Product distribution in the amination of boronic acid 1a with piperidine (12) and aniline (14).

<table>
<thead>
<tr>
<th>Entry</th>
<th>EtN (equiv)</th>
<th>SM</th>
<th>Product</th>
<th>Byproducts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11a</td>
<td>13a/15a</td>
<td>16</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>32</td>
<td>66</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>2</td>
<td>76</td>
<td>7</td>
</tr>
<tr>
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<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>65</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3</td>
<td>97</td>
<td>13</td>
</tr>
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</table>

Reagents and conditions from Scheme 3 unless otherwise stated.

Using amine 2:

<table>
<thead>
<tr>
<th>Entry</th>
<th>EtN (equiv)</th>
<th>SM</th>
<th>Product</th>
<th>Byproducts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>11a</td>
<td>13a/15a</td>
<td>16</td>
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<tr>
<td>6</td>
<td>0</td>
<td>46</td>
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<td>10</td>
<td>3</td>
<td>1</td>
<td>93</td>
<td>10</td>
</tr>
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Under especially dry reaction conditions, the quantity of 16 and 18 can be lowered significantly and homocoupling of the organoboron component can be observed, giving tetraphenyl 19 (Scheme 4). Homocoupling was only observed under atypical (strictly anhydrous) reaction conditions and was significantly less problematic than oxidation and protodeboronation.

Scheme 4. Observation of organoboron homocoupling. Isolated yields.

4.2 Assessment of Inhibitors. The addition of AcOH and AcOK has been observed to inhibit the related etherification process. The reactions of amines 12 and 14 with boronic acid 11a were assessed in the presence of added AcOH, AcOK, as well as pinacol in order to probe any inhibitory effects and assist in establishing similarities with the etherification reaction (Figure 1).
AcOH inhibited the amination of both 12 and 14 (Chart a). AcOK inhibited only the reaction of 14 (Chart b, red line) and was found to be beneficial to efficiency for the reaction using 12 (Chart b, blue line). Pinacol was found to inhibit both amination reactions, with a stronger effect on the reaction of 14 than that of 12 (Chart c).

4.3 Identification and Analysis of Cu(II) Complexes. 4.3.1 EPR Analysis of Paddlewheel Dissociation. \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) is used as standard in the majority of Chan-Lam amination reactions. The effect of the amine and organoboron components on \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) was examined by EPR (Figure 2). The fluid solution EPR spectrum of \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) in MeCN only shows a minor trace of a monocupper(II) species, with the paddlewheel structure intact in solution as evinced by a frozen solution spectrum (150 K) that is characteristic of the \(S = 1\) complex. Treatment of \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) with piperidine (12) immediately results in a deep blue solution. EPR confirmed the dissociation of the paddlewheel dimer to a monomolecular species: the characteristic four-line signal resulting from the hyperfine coupling of the \(S = 1/2\) Cu(II) \(d^9\) centre with its nuclear spin \(I = 3/2\) of the 63,65% Cu isotopes (100% abundant). A similar effect is exhibited upon treatment of \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) with aniline (14); however, the effect is notably weaker, only becoming significant at increased [14]. In contrast to the effect of the amine, treatment of the paddlewheel dimer with only organoboron compounds 11a or 11b gave no observable change to the EPR spectrum.

Figure 2. X-band EPR spectrum of \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) (a) in MeCN, after treatment with (b) 14 or (c) 12, and (d) showing concentration effect of 14, recorded at 293 K. Simulations of (b) and (c) are depicted by the red trace.

4.3.2 Structural Characterization of Cu(II) Complexes. Aging the Chan-Lam reaction of 12 with 11b delivered two different diffraction-quality crystals. The hexa-acetate paddlewheel 20 is similar to \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) with AcO replacing \(\text{H}_2\text{O}\) at the axial sites and the resulting anionic charge balanced by piperidinium ions. The tetracopper complex 21, contains two bridging oxo units, four bridging acetates, two terminal acetates, and four neutral piperidine ligands (Figure 3).

Independent preparation of both 20 and 21 was also possible on gram scale (Scheme 5). Treatment of \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) with piperidinium acetate in MeCN at \(-20^\circ\text{C}\) delivered 20 as green crystals in 11% yield, while treatment of \([\text{Cu(OAc)}_{4}] \cdot 2\text{H}_2\text{O}\) with piperidine in PhMe at room temperature provided the large blue crystals of 21 in 29% yield. Both complexes were found to be stable at room temperature over a period of weeks.

Figure 3. Isolated complexes. \(\text{R}_2\text{NH}\) = piperidine.

4.3.3 HRMS Identification of Cu(II) Complexes in Solution. High-resolution mass spectrometry (HRMS) was used to identify organometallic complexes in solution. Aliquots from the reaction of 11b and 12 were analyzed and mass ions consistent with several proposed reaction-relevant structures were detected (Figure 4).

Two amine-ligated Cu(II) complexes, 22 and 23 (Figure 4a), were identified in relatively high abundance. The proposed structures of these two complexes are clearly related both to each other and to the tetracopper complex 21 (Figure 3). Mass ions consistent with proposed pre-transmetallation intermediate structural isomers 24 and 25 were detected (Figure 4b), as well as the corresponding proposed post-transmetallation complex 26 (Figure 4c). A Cu(II)(Pin) complex 27 was also observed (Figure 4d).

4.4 Oxidation of Cu(I)→Cu(II). In the etherification process, Stahl has shown that oxidation of Cu(I)→Cu(II) takes place using molecular oxygen and additional Cu(I), with the requirement of acid (HX) and BX (see Scheme 2). The oxidation of Cu(I)OAc to Cu(II)X₂ under air can be readily monitored by UV-Vis spectroscopy, allowing assessment of additives (Figure 5).

Chart a shows the oxidation in the presence of specific reaction-relevant additives but in the absence of amine substrates. In the absence of any additive, CuOAc persists – no oxidation was observed by simply stirring in MeCN under air. Similarly, no oxidation was seen in the presence of Et₃N alone. However, oxidation was relatively rapid in the presence of AcOH. Oxidation was slower in the buffered system using both AcOH and Et₃N.

Figure 5. Oxidation of Cu(I) to Cu(II) in the presence of reaction-relevant additives monitored by UV-Vis spectroscopy. Cu(OAc)₂ was used as an illustrative Cu(II) reference in (a).

Similar trends were observed when the same analysis was repeated in the presence of piperidine (12) and aniline (14) (Chart b). The Cu(I) oxidation was generally more rapid in the presence of 12 than 14, including in the presence in the presence of Et₃N, although this was marginal.

5. DISCUSSION

5.1 Organoboron Reactivity Differences and Byproduct Formation. The differences in reactivity between alkyl and aryl amines (12 and 14, respectively), and boronic acids and BPIN esters (11a and 11b, respectively) can be clearly observed in the benchmark reactions (Scheme 3). Reactions of 11a are generally successful while those with 11b are significantly less efficient.

With regards to byproduct formation, in the benchmark reaction of 11a with 12 and 14 (Scheme 3 and Table 1), while formation of the desired products (13a and 15a, respectively) can be excellent (e.g., entries 3, 5, 8, and 10), there were some immediate observations: (1) the addition of Et₃N was beneficial, efficiency markedly improved with 1 equivalent but was optimum with 3 equivalents (e.g., entries 1-3 and 5, entries 6-8 and 10). This is consistent with previous studies. The improvement in yield is not due to inhibition of side reactions but rather improvement in general reactivity – starting material (11a) persisted in the absence of Et₃N, product distribution remained approximately constant (e.g., entry 6 vs. entry 7); (2) Molecular sieves are beneficial to lower production of the oxidation product 16 (e.g., entry 3 vs. entry 4, entry 8 vs. entry 9). This is consistent with the ¹⁸O labeling experiments of Lam demonstrating that oxidation arises from H₂O and observations by Evans on the effect of molecular sieves (3).

The most significant observation was the extent of the production of side products 16-18. Oxidation can be tempered with molecular sieves but production of 16 persisted at ca. 5-10% while 18 varied from 12-25%. Protodeboronation was also a significant issue, with 50-68% yield of 17 generated throughout. Accordingly, even for high yielding reactions (e.g., entry 5) approximately half of the total yield of 11a was consumed in side reactions, explaining the necessity for superstoichiometric quantities of 11a. Organoboron homocoupling (Scheme 4) was found to be minimal and was not
further considered. In summary, amination is marginally competitive with side reactions under these standard conditions.

The primary goal of this study was to establish a mechanistic description of the Chan-Lam amination in order to solve these specific reactivity and byproduct formation issues, potentially allowing the development of a more general catalytic protocol for the amination of boronic acids and BPin substrates.

5.2 Entry to Catalysis. 5.2.1 Paddlewheel Dissociation, Reformation, and Reaction Inhibition. Paddlewheel complexes are unreactive in Cu-catalyzed oxidative coupling reactions and must undergo dissociation as the first mechanistic event.13 In etherification reactions, paddlewheel dissociation is promoted in the alcoholic media.12,14 However, alcoholic media are not feasible in the amination reaction due to chemoselectivity issues (amination vs. etherification).9

EPR studies (Figure 2) demonstrated that [Cu(OAc)$_2$]$_2$2H$_2$O can be readily dissociated using alkyl amine 12 but less readily by aryl amine 14. 14 was only able to induce a comparable level of dissociation of the paddlewheel when the concentration was >10 fold greater than that of 12. This highlights an immediate reactivity difference between the amine classes (Scheme 3): dissociation of the paddlewheel dimer is dependent on Lewis basicity.

The competitive nature of this key event was reinforced by the additive experiments (Figure 1). AcOK promotes reformation of dinuclear Cu(II) species from mononuclear complexes.12 Piperidine (12) induces denucleation even in the presence of additional AcOK (Figure 1, Chart b, blue line), while aniline (14), as a poorer ligand, does not (Figure 1, Chart b, red line), thus generating significantly less monomeric species (Scheme 6).17

Scheme 6. Competitive vs. non-competitive denucleation of [Cu(OAc)$_2$]$_2$2H$_2$O with 12 and 14.

AcOH displays a similar inhibitory effect to that of AcOK, promoting reformation of dinuclear Cu(II) species but with an additional inhibitory function. Piperidine is able to induce denucleation in the presence of AcOK (Figure 1, Chart b) but not in the presence of AcOH (Figure 1, Chart a) due to N-protonation, thereby necessitating the addition of a base (e.g., Et$_3$N). Indeed, treatment of 11a or 11b with 20 under reaction-like conditions led to 50% and 6% yield of 13a, respectively (Scheme 7) – less effective than standard conditions (see Scheme 3).


In contrast, exposing 11a or 11b to 21 under reaction-like conditions gave 13a in 76% and 18% yield, respectively (Scheme 8) – very similar to the typical yield for these substrates under standard conditions (87% and 28%, respectively, see Scheme 3). Unfortunately, complexes derived from 14 were not isolated preventing a similar evaluation.


These experiments indicate that one of the roles of Et$_3$N in Chan-Lam aminations is to sequester HX, generating sufficient amine freebase to drive denucleation of paddlewheel species and allow the formation of reactive amine-ligated Cu(II) complexes, such as 21.

Together, these data (1) support the requirement for paddlewheel dissociation as a first key mechanistic event, (2) demonstrate that reactivity differences between amine classes begin at this initial event, and (3) provide an explanation for the reactivity increase in the presence of Et$_3$N.

5.2.2 Organoboron Reactivity Differences: Reaction Inhibition by Pinacol. The disparity in reactivity between 11a and 11b can be attributed to the presence of pinacol, which has a notable inhibitory effect on the amination reaction of 11a using both 12 and 14, with a greater effect on the latter (see Figure 1, Chart c).

Importantly, this inhibitory function does not appear to be driven by differences in rates of transmetallation.15 Indeed, pinacol has an immediate inhibitory function as shown in Scheme 9. The reaction of 11a with 14 proceeds to deliver 92% of 15a over 16 h, with 41% conversion to 15a over 6 h. When the reaction is allowed to take place for 6 h before addition of pinacol and then allowed a further 12 h, conversion to 15a is commensurate with the 6 h time point.


Under reaction-like conditions (without amine or Cu(OAc)$_2$), treatment of 11a with pinacol gave 46% of 11b over 16 h (Scheme 10). This slow esterification cannot account for the levels of inhibition observed in reactions of 11b.

Scheme 10. Esterification of 11a with pinacol. Determined by HPLC analysis.

This suggests that the observed inhibitory effect (Figure 1, Chart c) was not necessarily due to formation of 11b, but rather due to some other interaction of pinacol. Various diols are known to form complexes with Cu(II), including derivatives of pinacol.16 While a crystalline structure of a Cu(II)pinacol complex was not obtained, NMR and HRMS analysis confirmed the presence of Cu(II)(pinacol)$_2$ in solution in both isolated experiments and in samples from amination reaction mixtures using 11b (Scheme 11). Accordingly, we believe the observed BP complex reactivity issues in the Chan-Lam amination are due to catalyst inhibition by pinacol, generated either by hydrolysis of the organoboron starting material (e.g., 11b) or of the organoboron byproduct following the transmetallation event.

Scheme 11. Formation of Cu(II)(pinacol)$_2$ complex 27 observed by NMR and HRMS.

5.2.3 Solution Structure of the Mononuclear Cu(II) Species. Important to our goals in this study was to attempt to provide an understanding of the ligands on any Cu-based species. To achieve
this, we used a combination of HRMS analysis coupled with computational modeling. Mass ions were identified from the benchmark reactions using 11b and 12, and the potential structures, and their interconversion, were rationalized by modeling to assist in assembling a proposed mechanism.

Mass ions consistent with Cu(II) complex 22 and dinuclear complex 23 were identified (Figure 4). Significantly, the isolated tetracopper complex 21 appears to be a dimer of 23, which itself is a dimer of 22 (Scheme 12). 21 is competent in the amination reaction (Scheme 8) suggesting that 21, 22, and 23 are in equilibrium and that 22 is the mononuclear complex produced following dissociation of [Cu(OAc)Cl2]2+2H2O with 21 a resting state/reservoir.

In relation to the proposed structure of 22, calculations reveal this complex and its amide isomer 28 are isoenergetic. However, we posit 22 as the likely structure based on the structure of 21 and previous observations.20

5.3 Transmetallation. HRMS analysis of the 11b reaction mixture allowed detection of mass ions consistent with proposed isostructural Cu(II) complexes 24 and 25 (Figure 4), which is consistent with a pre-transmetallation intermediate arising from ligation of 11b to 22 (Scheme 13).

Complex 24 is consistent with the resting state proposed by Stahl (9, Scheme 2),12 however, molecular modeling of these proposed structural isomers suggests 25 was 12.4 kcal mol−1 more stable than 24. Accordingly, whether or not 24 has a role is unclear. However, HRMS also allowed detection of a post-transmetallation intermediate 26 (Figure 4 and Scheme 14). In agreement with Stahl, a molecular modeling comparison of transmetallation via a 4-membered transition state beginning from 25 and the 6-membered transition state beginning from 24 favored the 4-membered transition state by 17.7 kcal mol−1. The production of the expected boron byproduct, HO–BPi, could be observed by 11B NMR (see ESI).

More holistically, a 4-membered oxo-metal transmetallation pathway is consistent with organoboron transmetallation in other transition metal-catalyzed coupling reactions. For example, within Suzuki-Miyaura cross-coupling using Pd and Ni,12,23 and Rh-catalyzed conjugate addition.25 Accordingly, there is potentially an elegant symmetry and generality in the transmetallation of organoboron compounds to these metal species.

5.4 Reductive Elimination: C-N vs. C-O. Based on Stahl’s mechanism,12 following transmetallation, oxidation via disproportionation generates a Cu(III) intermediate that undergoes reductive elimination to give the product and a Cu(I) species. While not detected,24 a proposed structure of this Cu(III) intermediate 29, based on the structure of 26, allowed investigation of the reductive elimination event (Scheme 15).

Computational modeling of reductive elimination from 29 also favors C-N bond formation over C-O bond formation by 36.9 kcal mol−1. This is consistent with the work of Fensterbank.20b Accordingly, we do not believe that formation of phenol side products arises from competitive reductive elimination of 29 but from other processes (vide infra).

5.5 (Re)Oxidation of Cu(I). 5.5.1 Completion of the Catalytic Cycle. Completion of the catalytic cycle requires reoxidation of Cu(I) to Cu(II). Stahl has shown that this takes place using molecular oxygen and additional Cu(I), with the requirement of acid (HX) and BX3 (see Scheme 2).12 As proposed above, Cu(I)OAc is the product of the reductive elimination event (Scheme 15). Evaluation of the oxidation of Cu(I)OAc to Cu(II)X in the presence of various reaction-relevant additives was informative, highlighting the fundamental effects of the amine components (Figure 5).

The requirement for HX is consistent with our observations (Figure 5, Chart a). In the presence of only Et3N, no oxidation takes place and in the presence of AcOH, oxidation is relatively rapid. With both AcOH and Et3N, oxidation proceeds more slowly. When the same analysis is repeated in the presence of piperidine (12) and aniline (14) (Figure 5, Chart b), the same trends are observed but, notably, the Cu(I) oxidation is more rapid in the presence of 12 than 14, highlighting a second difference between the amine classes.25 Oxidation was comparably slow for both amines in the presence of Et3N.

These observations point to two fundamental roles for Et3N: (1) to sequester AcOH in order to avoid (re)formation of inactive paddlewheel complexes (e.g., 20) and (2) the resulting salt (Et3N+AcOH) provides the necessary H+ to promote Cu(I) oxidation. This promotes reaction efficiency consistent with previous observations.3 Similarly, the amine substrates have two essential roles beyond acting as the coupling partner: (1) to induce dissociation of paddlewheel complexes and (2) to promote Cu(I) oxidation. That oxidation is more rapid in the presence of 12 vs. 14 indicates that oxidation takes place from an amine-ligated Cu(I) complex. This, then, allows access directly to Cu(II) complex 22 (Scheme 16).

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5.5.2 Cu(I) and Byproduct Generation. The (re)oxidation event of Cu(I) to Cu(II) has important ramifications on amination reaction performance, specifically with respect to by-product generation. Oxidation to deliver 16 and protodeboronation to deliver 17 are problematic and both of these processes are known to
be facilitated by Cu(I) species more than Cu(II). Indeed, treatment of 11a with CuOAc delivers 40% oxidation (16) and 56% protodeboronation (17) while the corresponding reaction with CuOAc$_2$ gives 9% and 63%, respectively (Scheme 17). Accordingly, we believe that oxidation issues arise primarily through the side reactions of Cu(I) species generated after reductive elimination prior to reoxidation to Cu(II). Protodeboronation was equally problematic for both Cu(I) and Cu(II) in these control experiments. However, additional data (vide infra) suggests that protodeboronation takes place when the reaction is unable to take any alternative course (e.g., amination), such as in this control reaction. Consequently, we believe that a slow Cu(I)-Cu(II) oxidation will lead to increased levels of side reactions.

**Scheme 17.** Comparison of Cu(I) vs. Cu(II) on oxidation/protodeboronation of 11a. Determined by HPLC analysis.

5.6 Proposed Mechanism for the Chan-Lam Amination. Based on previous work by Stahl on the etherification process and the isolated stoichiometric experiments detailed above, a complete mechanistic description of the Chan-Lam amination can be proposed (Scheme 18).

![Scheme 18. Proposed mechanism of the Chan-Lam amination.](image)

$[\text{Cu(OC\text{ac})}_2]_2 \cdot 2\text{H}_2\text{O}$ undergoes deenucleation by action of the amine to a mononuclear Cu(II) complex 22, which exists in equilibrium with its dimer, 23, and tetramer, 21, derivatives. This initial amine-driven deenucleation event is essential to catalysis and can be inhibited by action of AcO$^-$ and AcOH, both of which promote reformation of paddlewheel species. AcOH simultaneously inhibits deenucleation by protonation of the amine, giving the hexa-acetate paddlewheel 20. Engagement of the organoboron component leads to transmetallation via 4-membered transition state 25 to deliver Cu(II) species 26. Oxidation to Cu(III) via disproportionation gives complex 29. A selective C-N reductive elimination liberates the desired amine product and a Cu(I)OAc species 32. Completion of the catalytic cycle is achieved via oxidation to Cu(II) in the presence of O$_2$ and HX and is promoted in the presence of the amine substrate. Side product generation is a function of this reoxidation event: a slow oxidation provides sufficient opportunity for Cu(I)-promoted oxidation and protodeboronation.

The origin of substrate reactivity issues has been identified: (1) the reactivity issue of aryl amines (e.g., 14) compared to their alkyl counterparts (e.g., 12) is a function of the Lewis basicity – decumplexation of the paddlewheel dimer is more readily achieved with 12 vs. 14. In addition, the reoxidation event from Cu(I) to Cu(II) is slower with 14 vs. 12. (2) BPin substrates are problematic due to catalyst inhibition by pinacol (generating 27) produced as a byproduct during the reaction.

5.7 Development of a General Chan-Lam Amination. Based on the above discussion, there are three key events that must be controlled to resolve the substrate reactivity and side product issues associated with the Chan-Lam amination: (1) sequestration of AcO$^-$/AcOH; (2) removal of free pinacol; and (3) promotion of Cu(I) oxidation. These are not intuitively/simply solved since AcOH is both beneficial and inhibitory (vide supra). However, based on our previous work, a straightforward solution was offered using a byproduct of the Chan-Lam amination, boric acid, in combination with inverting the conventional organoboron:amine stoichiometry.

B(OH)$_3$ reversibly forms borates with AcO$^-$/AcOH and forms stable boric acid esters with diols, including pinacol (Scheme 19a). Control experiments also demonstrated that B(OH)$_3$ promotes oxidation of Cu(I) to Cu(II) more effectively than 12/14 in the presence of AcOH and Et$_3$N (Scheme 19b vs. Figure 5).

![Scheme 19. (a) Reversible borate formation with B(OH)$_3$ and AcOH/AcOK and HOBPin formation](image)

In addition, based on the findings above, Cu(I) oxidation is dependent on [amine]. Increasing [amine] would be expected to facilitate Cu(I) oxidation and lower byproduct generation. Increased [amine] would also have a second beneficial effect by driving deenucleation of paddlewheel complexes.

This simple change in stoichiometry was found to be effective, leading to a significant improvement in reaction profile – yield of desired product increased while overall byproduct generation was decreased (Scheme 20).

![Scheme 20. Impact of amine stoichiometry on side product formation. Determined by HPLC analysis using an internal standard.](image)

Based on all of this, in the context of the Chan-Lam reaction using stoichiometric Cu(OAc)$_2$, upon replacing the conventional organic base (Et$_3$N) directly with B(OH)$_3$ and inverting the organoboron:amine stoichiometry, the Chan-Lam amination can be improved considerably (Scheme 21). On comparison with the reaction profile shown in Scheme 3c, a dramatic improvement in product distribution is apparent and in a significantly improved timeframe (2 h vs. 16 h).
More importantly, we have found that the use of B(OH)\_2 as a promoter could be used to allow the development of a generally effective catalytic Chan-Lam amination of aryl BPin that was broadly effective for both alkyl and aryl amines (Scheme 22a and 22b, respectively; see ESI for optimization).\(^{29}\) Comparable levels of efficiency were noted for BPin vs. boronic acid as well as catalytic vs. stoichiometric Cu(OAc)\_2 (see 13a and 15a). The same reaction conditions were also effective within etherification and thiolation (Scheme 22c). It should be noted that while these conditions operate effectively across reaction partners of broadly varied electronic and structural variety, ortho-substitution on the aryl component generally results in poorer yields when using secondary or bulky primary amines, for example, the yield of 13g was notably lower than that of 13o and 13r.


<table>
<thead>
<tr>
<th>Scheme 22. B(OH)_2-promoted catalytic Chan-Lam reaction of ArBPin: Application. Isolated yields using FlashMaster® purification system.</th>
<th>(\text{Ar} \rightarrow \text{BPin} (1 \text{ equiv}))</th>
<th>(\text{R}^1 \rightarrow \text{XH} (2 \text{ equiv}))</th>
<th>Cu(OAc)_2 (20 mol%), B(OH)_2 (2 equiv)</th>
<th>MeCN, 4 Å MS, 80 °C, O_2, 24 h</th>
<th>(\text{Ar} \rightarrow \text{X}^1 \rightarrow \text{R}^1)</th>
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</thead>
<tbody>
<tr>
<td>A) Alkyl amines</td>
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</tr>
<tr>
<td>1a</td>
<td>70%, 84%, (^a) 81% (^b)</td>
<td>13b</td>
<td>90%</td>
<td>13c</td>
<td>82%</td>
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<tr>
<td>13d</td>
<td>77%</td>
<td>13e</td>
<td>71%</td>
<td></td>
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</tr>
<tr>
<td>13f</td>
<td>85%</td>
<td>13g</td>
<td>36%</td>
<td></td>
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<tr>
<td>13h</td>
<td>74%</td>
<td><strong>13i</strong></td>
<td>81%</td>
<td></td>
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</tr>
<tr>
<td>13j</td>
<td>77%</td>
<td>13k</td>
<td>67%</td>
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<tr>
<td>13l</td>
<td>81%</td>
<td>13m</td>
<td>81%</td>
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<td>13n</td>
<td>86%</td>
<td>13o</td>
<td>75%</td>
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</tr>
<tr>
<td>13p</td>
<td>CF(_3)</td>
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<tr>
<td>13q</td>
<td>64%</td>
<td>13r</td>
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<td><strong>13s</strong></td>
<td>90%</td>
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<td>73%</td>
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<td><strong>13u</strong></td>
<td>94%</td>
<td><strong>13v</strong></td>
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<td>62%</td>
<td><strong>13x</strong></td>
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B) Aryl amines

To further validate the applicability of our developed method on a molecule of higher molecular weight and increased functionality, we assessed the developed reaction conditions within the synthesis of the tyrosine-kinase inhibitor Imatinib (Gleevec\textsuperscript{®}, 41, Scheme 19).\(^{30}\) Formation of the required BPin compound was achieved over three steps via an acylation/alkylation sequence.
using dichloride 36 and amines 37 and 38. Subsequent Miyaura borylation of 39 gave BPin 40. Application of the developed reaction conditions towards Chan-Lam amination of 40 gave access to 41 in 67% isolated yield on 0.5 g scale.


6. CONCLUSIONS

In summary, investigation of the Chan-Lam amination has allowed a complete mechanistic description to be assembled. Spectroscopic analyses have provided insight into the course of the reaction with a formative identification of key reactive intermediates. This has allowed the origin of three specific issues (BPin reactivity, aryl amine reactivity, and side reactions (oxidation, protodeboronation)) to be determined. In addition, synergistic promotive effects of boric acid were identified and have been leveraged to overcome these issues, providing the first generally efficient BPin Chan-Lam amination conditions proceeding under non-basic reaction conditions. We believe these findings will allow more general uptake and application of this valuable C-N bond forming reaction.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, assay details and spectra, characterization data for all compounds. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions
The manuscript was written through contributions of all authors.

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ABBREVIATIONS

EPR, electron paramagnetic resonance; HPLC, high performance liquid chromatography; NMR, nuclear magnetic resonance; Pin, pinacolato; RT, room temperature.

REFERENCES

† Modeled at the B3LYP/def2-TZVP level of theory with solvent effects included using COSMO. cis/trans isomers were evaluated but were isoenergetic within the experimental limits. See SI for full details.

For a study of organoboron homocoupling using Cu(I) and Cu(II), see: Demir, A. S.; Reis, O.; Emrullahoglu, M. J. Org. Chem. 2003, 68, 10130–10134.

[17] The formation of aniline-Cu(II) complexes derived from [Cu(OAc)]**:2H2O is typically achieved in alcoholic solvents (e.g., MeOH) in order to provide sufficient mononuclear Cu(OAc)2 (see ref 16). For example, see: (a) Van Heuvelen, A.; Goldstein, L. J. Phys. Chem. 1968, 72, 481–485. In contrast, alkyl amine complexes of are more readily formed. For example, see: (b) Narain, G. Can. J. Chem. 1965, 44, 895–898.


[28] For a discussion, see ref 27e and references therein.

[29] It should be noted that B(OH)3 was also found to promote speciation equilibria with 11b, but this was found to be rather slow under the reaction conditions (see ESI).

Chemotypes influence key mechanistic events

Catalyst inhibition

Side products

Deactivation

• Effective C-X bond formation
• B(OH)$_3$ promotion
• 57 examples