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# Exploiting the Bis-Nucleophilicity of α-Aminoboronates: Copper-Catalyzed, Intramolecular Aminoalkylations of Bromobenzoyl Chlorides

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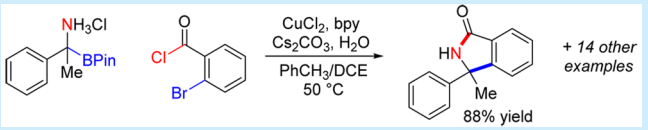
Supporting Information

**ABSTRACT:** α-Aminoboronate salts are interesting examples of heteroatomic species containing adjacent nucleophilic centers. We have developed an acylation/arylation reaction using 2-bromobenzoyl chlorides as bis-electrophiles that harnesses the nucleophilicity of both positions, leading to isoindolinones. The reactions proceed under mild conditions via an intramolecular, Cu-catalyzed $sp^3-sp^2$ coupling, giving products in up to 95% yield. These conditions enable arylation of α,α-disubstituted aminoboronates, which are difficult to accomplish using methods based on less abundant and more expensive transition metals.

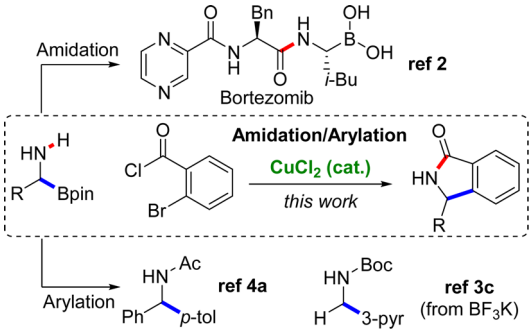



α-Aminoboronates are stable heteroatomic bis-nucleophiles that are finding wider use as methods to access them broaden.[1] The nitrogen's reactivity is essentially unchanged compared to standard amines, and coupling of aminoboronates to carboxylic acids is used routinely, for example, in the synthesis of boronic acid-based protease inhibitors such as bortezomib.[2] However, reactions of the nucleophilic C−B bond in, for example, Suzuki coupling, are made more difficult by the adjacent nitrogen atom. This is likely due to a combination of factors including a higher barrier to transmetalation at $sp^3$-centers, increased steric hindrance around the reactive carbon atom, and facile competitive protodeboronation via 1,2-boryl migration. Nevertheless, advances in transition metal-catalyzed C−C bond forming reactions of aminoboronates have been achieved. Molander has performed extensive studies on aromatic aminomethylations using a variety of substituted $R_2NCH_2BF_3K$ salts by Pd- or photoredox/Ni-catalysis.[3] Pd-catalyzed aminobenzylations of branched aminoboronates were pioneered by the group of Suginome.[4] Additionally, Rh(I)-catalyzed additions to carbonyls were reported by Ellman,[5] and transition metal-free arylations of cyclic aminoboronates were recently disclosed by Aggarwal.[6]

Inspired by this precedent, we reasoned that reactions that exploit the geminal nucleophility of both the nitrogen atom and the C−B bond in aminoboronates could be useful, so long as a suitable bis-electrophilic partner was identified. Herein, we describe the one-pot amidation/arylation of aminoboronates with 2-halobenzoyl chlorides as a means of preparing isoindolinones (Scheme 1).[7] Key to this transformation was the discovery of a mild Cu-catalyzed coupling reaction that enabled intramolecular $sp^3-sp^2$ arylation without relying on more expensive and less abundant transition metals.

With the expectation that amidation would precede benzylic arylation in the proposed domino process, initial optimization focused on identifying conditions for the Suzuki coupling step using bromobenzamide **1a** (Table 1). Extensive screening of Pd

**Scheme 1. Use of Doubly Nucleophilic Aminoboronates in Cu-Catalyzed Cyclizations**




sources, ligands, bases, and solvent systems failed to provide any of the expected product, isoindolinone **2a** (entry 1). However, a screen of additives revealed that Cu(I) salts were effective in promoting the desired coupling (entry 2). Surprisingly though, a control experiment revealed that the coupling occurred in the absence of a Pd source and that **2a** was obtained in essentially identical yield with only the Cu additive (entry 3). Further investigation showed that Cu(II) salts were more effective promoters (entry 4), and subsequent optimization was carried out using this metal oxidation state. Performing the reaction at lower temperature slowed down competitive protodeboronation and led to cleaner reaction profiles, but decreased the solubility of the catalyst and amide **1a**. Addition of a chelating ligand, 2,2′-bipyridine (bpy), improved Cu(II) availability (entry 5), while the use of DCE or THF as a cosolvent increased the solubility of amide **1a** (entries 6 and 7). As a probe of reactivity and functional group compatibility, couplings were attempted within the halogen series (entries 8−10). While iodide **1b** coupled with

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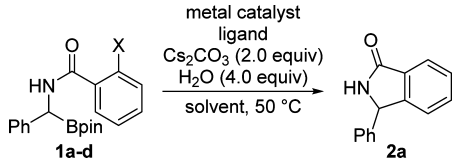
**Table 1. Optimization of Reaction Conditions for Conversion of Amidoboronate 1a into Isoindolinone 2a**




| entry | X | metal (equiv) | ligand (equiv) | solvent | yield 2a[a] |
|---|---|---|---|---|---|
| 1[b] | Br | $Pd(OAc)_2$ (0.05) | X-Phos (0.1) | $PhCH_3$ | 0 |
| 2[b] | Br | $Pd(OAc)_2$ (0.05) CuCl (1.0) | X-Phos (0.1) | $PhCH_3$ | 45 |
| 3[b] | Br | CuCl (1.0) | | $PhCH_3$ | 44 |
| 4[b] | Br | $CuCl_2$ (1.0) | | $PhCH_3$ | 65 |
| 5 | Br | $CuCl_2$ (1.0) | bpy | $PhCH_3$ | 29 |
| 6 | Br | $CuCl_2$ (1.0) | bpy | $PhCH_3$/DCE | 85 |
| 7 | Br | $CuCl_2$ (1.0) | bpy | $PhCH_3$/THF | 53 |
| 8 | I | $CuCl_2$ (1.0) | bpy | $PhCH_3$/THF | 51 |
| 9 | Cl | $CuCl_2$ (1.0) | bpy | $PhCH_3$/THF | 0 |
| 10 | F | $CuCl_2$ (1.0) | bpy | $PhCH_3$/THF | 0 |

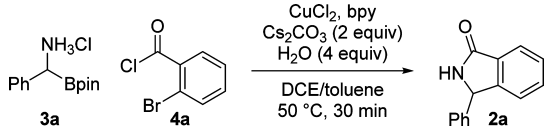
[a]Yield determined by $^1H$ NMR relative to an internal standard of 1,3,5-trimethoxybenzene. [b]Reaction performed at 70 °C.

essentially the same efficiency as bromide **1a** (entry 8), the corresponding chloride **1c** and fluoride **1d** gave no isoindolinone **2a** (entries 9 and 10). Considering the wider availability of aryl bromides relative to iodides, further investigation was carried out using bromo derivatives.

Having successfully identified conditions for the challenging C−C bond forming step, further improvements in the method were sought. This had two main aims, the first being to avoid the low yielding isolation of amide **1a** by forming it in situ during the coupling reaction from aminoboronate salt **3a** and benzoyl choride **4a**. Further experiments proved this to be facile since the basic conditions required for the coupling also promoted *N*-acylation; the overall yield of **3a** improved to 85% via the one-pot procedure versus an overall yield of 42% when amide **1a** was isolated before coupling (entry 1). With a simple procedure in hand, reactions using catalytic amounts of $CuCl_2$ were examined next. We were pleased to find that the catalyst loading could be reduced easily, with reactions at 50 mol % (entry 2) and 10 mol % (entry 3) being equally effective. To the best of our knowledge, these results are the first examples of base metal-catalyzed C−C bond forming reactions of aminoboronates.

Somewhat surprisingly, the catalytic conditions were also higher yielding than couplings using stoichiometric $CuCl_2$.

**Table 2. Catalytic, One-Pot Amidation/Arylation of Aminoboronate 3a**

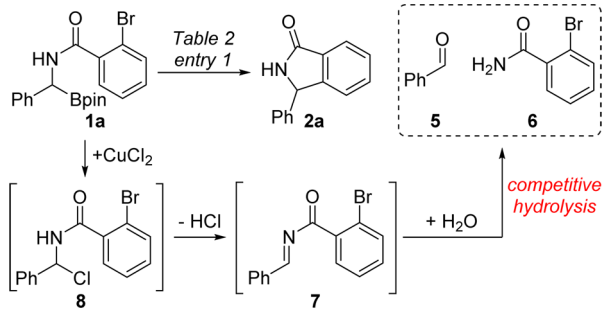



| entry | equiv of $CuCl_2$ | equiv of bpy | yield 2a (%)[a] |
|---|---|---|---|
| 1 | 1.0 | 2.0 | 85 (42)[b] |
| 2 | 0.5 | 1.0 | 85 |
| 3 | 0.1 | 0.2 | 93 |

[a]Isolated yield. [b]Yield in brackets is for reaction over two steps from **3a** using isolated amide **1a**

Analysis of the crude reaction mixtures showed that this was due to reduced levels of undesired side-products, which were identified as benzaldehyde (**5**) and 2-bromobenzamide (**6**). The origin of these side-products was traced to hydrolysis of imine **7**, which was identified by LCMS analysis as a minor intermediate in the coupling of benzamide **1a** (Scheme 2). A

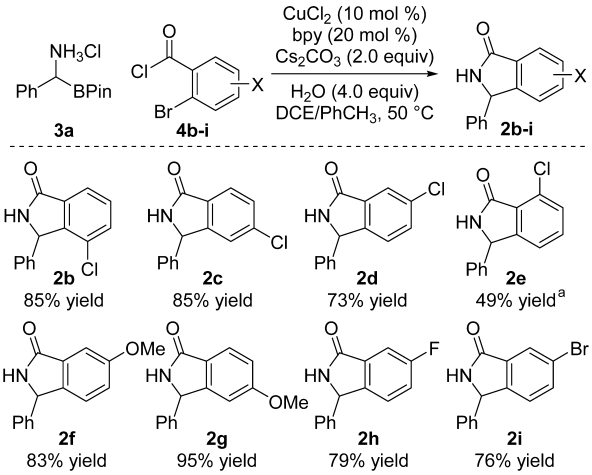
**Scheme 2. Competitive Hydrolysis via Imine Intermediates Suppressed by Catalytic Coupling Conditions**




plausible explanation for imine formation is C−B bond chlorination by $CuCl_2$,[8] followed by elimination of HCl from the resulting $\alpha$-chloroamide **8**. By performing the coupling with a catalytic amount of $CuCl_2$, formation of side-products **5** and **6** was minimized, and the desired pathway predominated to favor coupling to **2a**.

With a high yielding and catalytic method to couple aminoboronate **3a** in hand, the scope of the reaction was examined with substituted acid chlorides **4b−i** (Scheme 3). Since

**Scheme 3. Catalytic Cyclization of Aminoboronate 3a and Diverse Benzoyl Chlorides 4b−i**




[a]Reaction performed with $CuCl_2$ (1.0 equiv) and bpy (2.0 equiv); see Supporting Information for details.

aryl chlorides did not themselves react under the coupling conditions, this useful functional handle could be introduced at any position of the ring, including ortho to the reactive bromide group (**2b−e**). Electron-donating groups were compatible, with conjugation into both the bromide (**2f**) or carboxyl (**2g**) groups. As expected based on the results of Table 1, entry 10, a fluoroaromatic was equally tolerated (**2h**). Of particular note was the formation of brominated product **2i**, where cyclization occurred exclusively at the 2-Br group, and no products resulting



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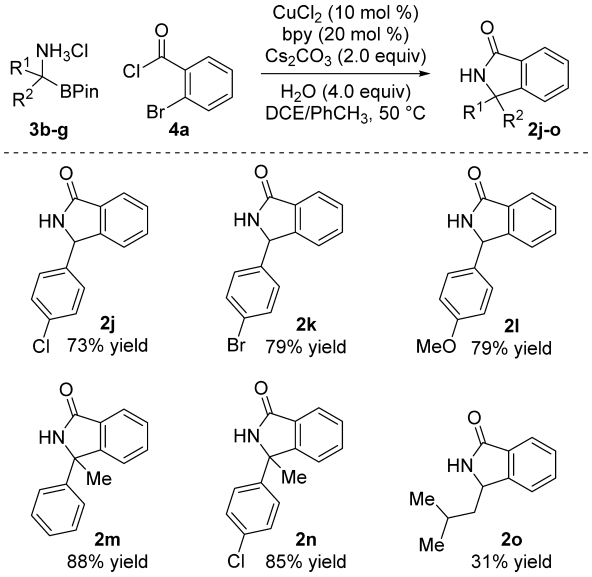
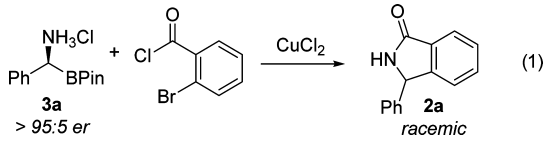
from intermolecular coupling at the 5-Br substituent were detected.

The reaction performed equally well starting from aminoboronates other than **3a** (Scheme 4).[9] As was the case with the benzoyl chloride substituents, halogen substitution including bromide was compatible with the reactions conditions (**2j** and **2k**), as were electron-donating groups (**2l**).[10] More importantly, the Cu-catalyzed arylation enabled the formation of 3,3-disubstituted isoindolinones **2m** and **2n** by coupling of quaternary aminoboronates.[11] To the best of our knowledge, these are the first examples of arylation of fully substituted aminoboronates or Cu-catalyzed couplings of quaternary boronates. The importance of an adjacent aromatic ring in the aminoboronate partner was highlighted by the formation of alkyl-substituted **2o**, which coupled in low yield with a large amount of protodeboronated side-products.

**Scheme 4. Catalytic Cyclization of Aminoboronates 3b−g with Benzoyl Chloride 4a**



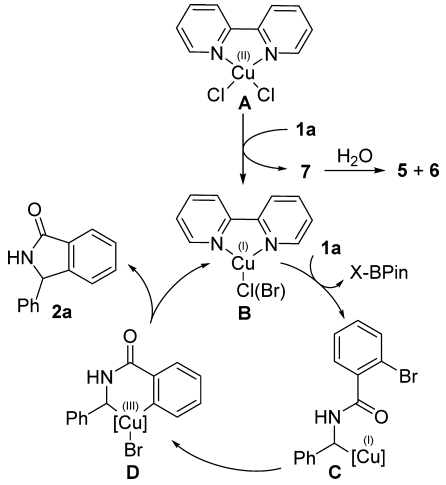

Cu-promoted cross-couplings are emerging as a viable alternative to precious metal-catalyzed processes.[12] While Cu-catalyzed couplings of aminoboronates have not previously been described, observations made during the course of this work point toward a likely mechanism for the arylation reaction. First, complete racemization of enantioenriched aminoboronate **3a** occurred in formation of product **2a**, suggesting that a configurationally unstable intermediate formed during the reaction (eq 1). Second, the coupling likely proceeded via initiation at the C−B bond rather than the aryl halide since other C−Br groups in both partners were well-tolerated (**2i** and **2k**). Third, the C−C bond formed via a cross-coupling mechanism involving oxidative addition into the weaker C−Br bond rather than a $S_NAr$ or ipso radical substitution;[13] otherwise, aryl fluorides and chlorides would be competent electrophiles (Table 1, entries 9 and 10).[14]




(1)

Based on the literature precedent for Cu(I)-catalyzed Suzuki-coupling of arylboronates and the seminal recent studies of Giri,[15] we propose the mechanism shown in Scheme 5. To access the catalytically active Cu(I) oxidation state, the Cu(II)-precatalyst **A** is reduced by a sacrificial amount of boronate **1a**. Following that, C−B transmetalation would generate benzylic Cu(I) intermediate **C**, which should racemize readily especially after the loss of chelation from the carbonyl oxygen that would be necessary to bring the bromide group proximate to the metal center.[16] Following oxidative addition to form Cu(III) intermediate **D**, reductive elimination would give the product **2a** and regenerate the Cu(I) catalyst **B**.

**Scheme 5. Proposed Mechanism for Cu-Catalyzed Arylation**




To conclude, we have described the use of stable and readily available aminoboronate salts as bisnucleophiles in the preparation of isoindolinones. This was made possible by the discovery of a novel $sp^3-sp^2$ cross-coupling reaction catalyzed by a cheap and abundant copper complex. This work provided the first examples of intramolecular coupling of aminoboronates as well as the first arylation of quaternary derivatives. We have also demonstrated the use of aminoboronates in domino processes that involve both of the geminal reactive groups, which we hope will prove useful in other transformations.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00586.

Experimental details and characterization data for preparation of isoindolinones and precursor aminoboronate salts(PDF)

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### Notes

The authors declare no competing financial interest.

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(9) Aminoboronate salts were conveniently prepared by HCl deprotection of the corresponding *t*-butanesulfinamides; see Supporting Information and ref 1c.

(10) We were unable to test more electron-withdrawing substituents such as *p*-CF3 due to the instability of the precursors to the deprotection/protonation step that generates the amine salts.

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