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The Elusive Metal-Free Primary Amination of Arylboronic Acids: Synthetic Studies and Mechanism by Density Functional Theory

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Abstract

Herein, we disclose the first *metal-free* synthesis of primary aromatic amines from arylboronic acids, a reaction that has eluded synthetic chemists for decades. This remarkable transformation affords structurally diverse primary arylamines in good chemical yields, including a variety of halogenated primary anilines that often cannot be prepared *via* transition metal-catalyzed amination. The reaction is operationally simple, requires only a slight excess of aminating agent, proceeds under neutral or basic conditions and, importantly, it can be scaled up to provide multigram quantities of primary anilines. Density functional calculations reveal that the most likely mechanism involves a facile 1,2-aryl migration and that the presence of an *ortho* nitro group in the aminating agent plays a critical role in lowering the free energy barrier of the 1,2-aryl migration step.

Primary aromatic amines are a prominent class of compounds found in a wide variety of natural products and as key components of pharmaceuticals, agrochemicals, dyes and polymers.¹ They are most commonly prepared *via* catalytic hydrogenation or metal-mediated reductions of aromatic nitro compounds,² direct substitution of aryl halides with ammonia at high pressure and temperature³ and, transition metal catalyzed amination of aryl halides with ammonia or its surrogates (Figure 1, A & B).⁴ However, these transformations often have several drawbacks, for example, the concomitant formation of undesired diaryl amines, the use of strong bases, and the requirement for sometimes costly ligands. During the past decade, significant advances have been made in the area of copper-catalyzed oxidative amination of arylboronic acids which offer practical access to a wide variety of *N*-substituted arylamines (e.g., Chan-Lam coupling).⁵ More recently, the transition metal-catalyzed (Pd, Ni or Cu) electrophilic amination of various organometallic reagents⁶ (e.g., Li, Zn and B) as well as the direct C-H amination of aromatic rings⁷ have received considerable attention for the preparation of *N,N*-dialkyl anilines. Surprisingly, the synthesis of primary arylamines from arylboronic acids and derivatives has proven to be far more challenging.⁸ For example, Fu and co-workers have only recently achieved the cross-coupling of arylboronic acids with aqueous ammonia in the presence of copper(I) oxide (Figure 1, C).^{8a}

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Notes

The authors declare no competing financial interest.

Supporting Information

Complete experimental procedures and characterization data including ¹H and ¹³C NMR spectra, further computational details and full reference 18b. This material is available free of charge via the Internet at <http://pubs.acs.org>.

All of the aforementioned achievements are mediated by transition metals. From a practical point of view, non-metal processes are much preferred, especially in the pharmaceutical industry where the removal of undesired metal contamination can be expensive.⁹

Moreover, certain functional groups are incompatible with transition metals; for example, the preparation of mono- and polyhalogenated anilines^{6e} is often not possible under transition metal catalysis due to competing cross-coupling processes.

Our recent studies¹⁰ on the hydroxylation of arylboronic acids by *N*-tertiary amine oxides prompted us to investigate if a similar strategy, *via* a leaving group-initiated 1,2-aryl migration,¹¹ would also work for the preparation of primary arylamines (Scheme 1). However, it was clear that achieving the metal-free amination would be significantly more challenging, since it is well-known that common electrophilic aminating agents (e.g., hydroxylamine-*O*-sulfonic acid and alkyl azides) do not affect boronic acids and their esters.¹² These aminating agents require the presence of substantially more electrophilic boron derivatives, such as borinic acids, borinic esters or dichloroboranes.¹³ Indeed, a thorough literature search revealed only a handful of recent methods that can convert the C(sp²)-B bond of arylboronic acids and derivatives to the corresponding C(sp²)-N bond in the absence of transition metals.¹⁴ For instance, boronic acids can be exchanged for highly electron-deficient nitrogen functional groups (i.e., nitro and nitroso groups) *via* an aromatic *ipso* substitution mechanism.^{14a,14d,14f} There were also two reports in which electrophilic aminating agents (e.g., organic azides and *N,N*-dialkyl-*O*-benzoyl hydroxylamines) reacted with arylboronic acids^{14b} and arylboroxines,^{14g} respectively, albeit under very harsh reaction conditions (>130 °C), to afford the corresponding *N*-monosubstituted as well as *N,N*-disubstituted anilines. Finally, excess lithiated methoxyamine (3 equiv) was found to aminate aryl pinacol boronates, although the scope of this transformation is mostly limited to electron rich substrates and base-sensitive functional groups are apparently not compatible with the reaction conditions.^{14e} Herein, we disclose a metal-free, mild, operationally simple and practical approach to access primary arylamines by the direct amination of arylboronic acids (Scheme 1, **II**).

At the outset, we assessed the reactivity of various potential aminating reagents towards arylboronic acids (Table 1). We hypothesized that the ideal reagent should possess two key structural features: (a) an NH₂ group that is nucleophilic enough to attack the boronic acid and electrophilic enough to accept the migrating aryl group; (b) a weak N-N or N-O bond that upon cleavage facilitates the departure of the leaving group. Attempted amination of 2-naphthylboronic acid **1a** with different hydrazine derivatives (**3–5**) did not yield the desired primary aryl amine (entries 1–3). Surprisingly, hydroxylamine-*O*-sulfonic acid (HSA, **6**) and *O*-mesitylenesulfonyl-hydroxylamine (MSH, **7**), both of which are effective for the conversion of trialkylboranes to alkylamines,¹⁵ also did not transfer the NH₂ group to **1a** (entries 4–5). Gratifyingly, the reaction with *O*-(2,4-dinitrophenyl)-hydroxylamine (DPH, **8**) furnished the expected primary 2-naphthylamine **2a** in good isolated yield (entry 6). Importantly, aminating reagent **8** is conveniently prepared *via* Charett's two-step procedure,¹⁶ and is stable at 0 °C for several months without appreciable decomposition.¹⁷ With DPH **8** selected as the preferred aminating reagent, we next investigated the effect of solvents on the transformation **1a–2a**. The choice of solvent was critical for success. Among the examined solvents, only DCE and toluene gave rise to the expected product (**2a**), with the latter resulting in a higher yield (70% *vs* 76%). Many common solvents such as THF, dioxane, methanol, acetonitrile, DMF and DMSO were apparently unsuitable for the transformation. At 25 °C, the amination was slow to complete (>2 d), however, raising the temperature to 50 °C led to the full consumption of **1a** in 24 hours.

With the optimized reaction conditions in hand, we turned to explore the scope of substrates (Table 2). Pleasingly, these conditions were compatible with a variety of substituents, regardless of their electronic or steric properties. Toluene as the solvent worked for most substrates, however, in some cases the use of other solvents proved more advantageous (entries 10, 11, 13 & 16). Boronic acids featuring fused aromatic rings furnished the aminated products in good yields (entries 1–4). Generally, the amination of substrates with electron-donating groups (Ph, Me, *i*-Pr and MeO) resulted in good product yields (entries 6–10). The presence of the strongly electron-withdrawing CF₃, CN and CO₂Me groups in **1j–l** required extended reaction times (up to 4 days) to reach full conversion (entries 11–13) and, in one case the reaction temperature had to be raised to 100 °C. Single or multiple halogen substituents (F, Cl, Br and I, **1m–t**), at the *ortho*, *meta* and *para*-positions, were also well-tolerated in the transformation (entries 14–22). However, polyhalogenated substrates **1s** and **1t** required heating to 100 °C in order to undergo primary amination (entries 21 & 22). The steric bulk of *ortho* substituents also did not prevent the amination of substrates **1h** and **1i** (entries 9 & 10). In the case of the 2,4,6-trimethyl-phenylboronic acid (**1i**) the yield of **2i** was only moderate, however, a single *i*-Pr group in the *ortho* position did not substantially impact the yield of primary aniline **2h** (entry 9). Most substrates could be transformed under mild conditions without any additives. However, in a few special cases, the addition of a base, such as Cs₂CO₃, was beneficial for the reaction. For instance, the base slightly improved the isolated yield of 2-naphthylamine **2a** (entry 2), or significantly shortened the reaction time (24 h vs 96 h) and also reduced the required reaction temperature (25 vs 50 °C) for **1r** (entry 20). For unknown reasons, *N*-acyl substituted boronic acids do not undergo primary amination under the optimized reaction conditions. In addition, substrates containing unprotected nitrogen atoms (e.g., indole, pyrrole), sulfur atoms (e.g., thiophene) and carbonyl groups (e.g., aryl ketones) are not compatible with the reaction conditions. These findings were not very surprising since pyridines and pyrroles are known to undergo *N*-primary amination in the presence of aminating agent **8**.¹⁶ We were pleased to find, however, that an oxygen-containing heteroaromatic boronic acid such as **1u** was smoothly aminated to afford **2u** in good isolated chemical yield (entry 23).

To understand the mechanism and novel reactivity of reagent **8**, we have used the M06-2X density functional method¹⁸ to calculate possible transition states and pathways for reaction with PhB(OH)₂. We first examined possible radical pathways since the computed N-O bond dissociation free energy (BDFE) of reagent **8** is relatively small (29.9 kcal/mol). However, all pathways considered result in radical Wheland-type intermediates that have ΔG values greater than ~40 kcal/mol. We explored concerted mechanisms that begin from the B-N dative bond complex (**Complex-8**, Figure 2). From this slightly endergonic complex the lowest energy concerted pathway involves the 1,2-aryl migration transition state, **TS-1**, that has a $\Delta G^\ddagger$ of 28.0 kcal/mol relative to separated PhB(OH)₂ and **8**.¹⁹ In **TS-1** the Ph-B bond is stretched to 1.75 Å and the Ph-N bond is formed at 2.03 Å. There is also simultaneous N-OAr bond cleavage (1.85 Å) and shortening of the B-N bond (1.52 Å). The product resulting from **TS-1** is the (PhNH₂)B(OH)₂(OAr) complex, which is highly exergonic with $\Delta G_{\text{rxn}} = -72.0$ kcal/mol.

To understand why reagent **8** provides a facile 1,2-migration pathway, we investigated the impact of the NO₂ groups in stabilizing **TS-1**. Removal of only the *para*-NO₂ group increases $\Delta G^\ddagger$ by 4.4 kcal/mol. Surprisingly, removal of only the *ortho*-NO₂ group increases $\Delta G^\ddagger$ by 12.2 kcal/mol. This shows that the *ortho*-NO₂ group is key in providing a low barrier for 1,2-aryl migration because it both stabilizes the developing aryl oxide anion and participates in a hydrogen bonding interaction with one of the amino NH bonds.

In accordance with no product formation, reagents **3–5** have $\Delta G^\ddagger$ values that range from 54–66 kcal/mol for aryl migration. Reagents **6** and **7** have $\Delta G^\ddagger$ values of 31.1 and 31.6 kcal/

mol, respectively. In general there is a connection between these barrier heights and the N-N and N-O bond strengths of the aminating agents. For reagents **3**, **4**, and **5** the N-N BDFEs are 82.1, 74.1, and 68.4 kcal/mol, respectively. Reagents **6** and **7** with N-O bonds have BDFEs of 52.7 and 49.4 kcal/mol. All of these BDFEs are significantly larger than the N-O BDFE of reagent **8**. However, there is clearly no direct linear correlation between barriers and BDFEs.

We have already established that electron deficient amination reagents lower the 1,2-aryl migration barrier. To examine the electronic effects of the aryl boronic acid we calculated $\Delta G^\ddagger$ values for *para* substituted versions. This analysis showed that electron-donating groups lower the barrier for migration. This is likely due to facilitating intramolecular attack of the N-O antibond and stabilization of the electron deficient nitrogen as the anionic OAr group is displaced.

Next, we explored if representative commercially available boronic acid derivatives would also undergo primary amination using **8** (Table 3). To our delight, both 2-naphthyltrifluoroborate **3a** as well as 2-naphthylboronic ester **3b** were converted to the corresponding primary 2-aminonaphthalene **2a** when water was used as a co-solvent in the reaction. In both cases, use of Cs₂CO₃ as an additive improved the isolated yield of **2a**.

Encouraged by the results above, the amination reaction was subsequently conducted on a gram scale, demonstrating its practicality (Scheme 2). When substrates **1a** and **1r** were primary aminated either in the presence or absence of Cs₂CO₃, the corresponding anilines were obtained in similar chemical yields.

In summary, the first *metal-free amination* of aromatic boronic acids leading to primary arylamines, a reaction that has eluded synthetic chemists for decades, was demonstrated. The transformation is operationally simple, proceeds under mild conditions and, affords structurally diverse primary aniline products in good chemical yield. It is especially noteworthy that a variety of halogenated primary anilines, that often cannot be prepared *via* the transition metal-catalyzed amination of the corresponding arylboronic acids and aryl halides, are also readily produced using this method while obviating the formation of undesired *N*-polyarylated products. In addition, the reaction can be readily scaled up to gram-scale, thereby offering a practical route for the production of structurally diverse primary arylamines. The exploration of related transformations and several powerful aminating agents is currently under way in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 17. Aminating agent **8** is commercially available from Corvinus Chemicals, LLC in multi-gram quantities with >99% purity (corvinuschemicals@gmail.com).
 18. (a) All calculations were performed in Gaussian 09 with the M06-2X/6-31G(d,p) functional and basis set in conjunction with the SMD solvent model for toluene. All structures were confirmed as minima or saddle points through normal mode analysis and free energies are reported at 298 K Frisch MJ, et al. Gaussian 09, revision A.02. Gaussian, Inc Wallingford, CT 2009. Zhao Y, Truhlar DG. *Theor Chem Acc.* 2008; 120:215. Zhao Y, Truhlar DG. *Acc Chem Res.* 2008; 41:157. [PubMed: 18186612] Marenich AV, Cramer CJ, Truhlar DG. *J Phys Chem B.* 2009; 113:6378. [PubMed: 19366259]
 19. (a) As a comparison, the $\Delta G^\ddagger$ values computed for **TS-1** using the B3LYP, ω B97-XD, and BMK functionals with the 6-31G(d,p) basis set are 26.1, 28.7 and 30.2 kcal/mol, respectively. Becke AD. *J Chem Phys.* 1993; 98:5648. Boese AD, Martin JML. *J Chem Phys.* 2004; 121:3405.

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Figure 1.

Approaches to primary aromatic amines from aryl halides and aromatic boronic acids/derivatives.

Figure 2.
1,2-Aryl migration transition state. (Bond lengths in Å)

I. Hydroxylation of Arylboronic Acids with Tertiary Amine N-Oxides **II. Amination of Arylboronic Acids with Electrophilic Aminating Agents** **Scheme 1.**

Hydroxylation and Amination of Arylboronic Acids via Leaving-Group-Initiated 1,2-Aryl Migration

Scheme 2.

Primary Amination of Arylboronic Acids on a Gram-Scale Using Aminating Agent DPH (8).

Table 1

Potential Aminating Agents for the Conversion of 1a to 2a.

Entry ^a	Aminating Agent	Yield ^c (%)
1		0
2		0
3		0
4 ^b		0
5 ^b		0
6		70

Table 2

Scope of Metal-Free Amination Using DPH (8).

<div> $\text{Ar-B(OH)}_2 \text{ (1)} \xrightarrow{\text{8 (1.1 equiv)}} \text{Ar-NH}_2 \text{ (2)}$ </div>						
Entry ^a	Substrate	T (°C)	Cs ₂ CO ₃ (equiv)	Time (h)	Product	Yield ^c (%)
1		50	N/A	24		76
2		25	1.2	24		82
3		50	N/A	24		84
4		50	N/A	24		61
5		50	N/A	24		80
6		50	N/A	24		62
7		50	N/A	20		80
8		50	N/A	4		72
9		50	N/A	48		67

<div>Ar-B(OH)₂ 1</div> <div>8 (1.1 equiv)</div> <div>Ar-NH₂ 2</div>						
Entry ^a	Substrate	T (°C)	Cs ₂ CO ₃ (equiv)	Time (h)	Product	Yield ^c (%)
10		25 (DCE)	1.2	48		42
11		100 (THF, sealed tube)	N/A	96		51
12		80	N/A	96		78
13		50 (CH ₃ CN)	1.2	24		88
14		50	N/A	48		82
15		50	N/A	24		83
16		50 (Dioxane)	N/A	24		60
17		50	N/A	24		54
18		50	N/A	48		66

<div>Ar-B(OH)₂ 1</div> <div>8 (1.1 equiv)</div> <div>Ar-NH₂ 2</div>						
Entry ^a	Substrate	T (°C)	Cs ₂ CO ₃ (equiv)	Time (h)	Product	Yield ^c (%)
19		50	N/A	96		80
20		25	1.2	24		86
21		100	N/A	30		56
22		100	N/A	72		54
23		50	1.2	20		66

^a Performed on 0.2 mmol scale (0.2 M solution) in toluene unless shown otherwise;^b 1.5 equiv of reagent 8;^c Isolated yield.

Table 3

Arylboric Acid Derivatives as Substrates Using Aminating Agent DPH (8).

Entry ^a	Substrate	T (°C)	Cs ₂ Co ₃ (equiv)	Time (h)	Product	Yield ^b (%)
1		50 (toluene:H ₂ O = 5:1)	1.2	30		74
2		100 (dioxane:H ₂ O = 5:1)	1.2	3		73

^a Performed on 0.2 mmol scale (0.2 M solution) in the solvent shown;^b Isolated yield.