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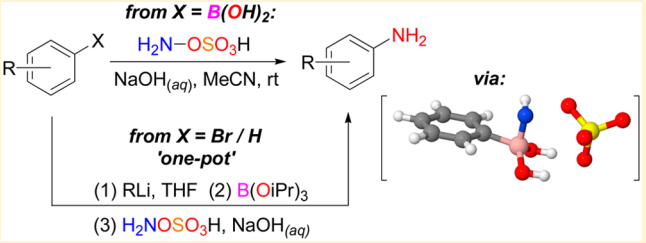
Transition-Metal-Free Access to Primary Anilines from Boronic Acids and a Common $^{+}NH_2$ Equivalent.

Samantha Voth, Joshua W. Hollett, and J. Adam McCubbin*

Department of Chemistry, University of Winnipeg, 599 Portage Avenue, Winnipeg, Manitoba Canada, R3B 2E9

Supporting Information

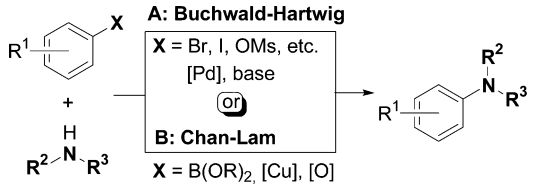
ABSTRACT: Diversely substituted anilines are prepared by treatment of functionalized arylboronic acids with a common, inexpensive source of electrophilic nitrogen (H_2N-OSO_3H, HSA) under basic aqueous conditions. Electron-rich substrates are found to be the most reactive by this method. However, even moderately electron-poor substrates are well tolerated under the room temperature conditions. Sterically hindered substrates appear to be equally effective compared to unhindered ones. Highly electron-deficient substrates afford product in very low yields at room temperature, but moderate to good yields are obtained at refluxing temperatures. Our method is also amenable to electrophilic amination of several common boronic acid derivatives (e.g., pinacol esters). We demonstrate that it can be combined with metal−halogen exchange reactions or a variety of directed ortho metalation protocols in a "one-pot" sequence for the synthesis of aromatic amines with unique substitution patterns. DFT studies, in combination with experimental results, suggest that the reaction occurs via base-mediated activation of HSA, followed by 1,2 aryl B−N migration. This mode of activation appears to be critical for the success of the reaction and allows, for the first time, a general, electrophilic amination of boronic acids at ambient temperature.



INTRODUCTION

The formation of C−N bonds constitutes one of the most important transformations in organic synthesis, due primarily to the large proportion of medicinally relevant structures, dyes, and materials that contain amines.[1] In this context, the highly successful palladium-catalyzed Buchwald−Hartwig coupling of aryl halides with amines has received enormous attention in recent decades (Scheme 1A).[2] In efforts to avoid the use of costly palladium catalysts, similar methods developed more recently have employed copper[3] and nickel-based[4] catalysts. The preparation of secondary and tertiary anilines using all of these catalysts has been well established, but the mild, efficient synthesis of primary anilines remains a significant challenge. Ammonia equivalents, such as imines, TMS_2N−metal salts, and those containing other cleavable protecting groups are often employed but are inefficient from a step- and atom-economy perspective.[5] Only recently have methods been developed in which simple ammonium salts can be used in place of these equivalents.[6]

Scheme 1. Transition-Metal-Catalyzed Aminations



Alternative methods, including the copper-catalyzed oxidative coupling of arylboronic acids with amines and their derivatives (Chan−Lam coupling, Scheme 1B)[7] have found success in the context of secondary and tertiary aniline synthesis. However, similarly to other metal-catalyzed methods there are, to date, few reports on the preparation of primary aromatic amines by these methods.[8]

By comparison to metal-catalyzed methods, transition-metal-free arylative amination methods are much more rare.[9] They are typically limited in scope and rely on harsh reaction conditions. For example, the amination of aryl Grignard reagents with chloramines is useful for the preparation of tertiary anilines only.[10] However, such protocols are a useful addition to the arsenal of methods for preparing anilines, in that they avoid the use of expensive and often-toxic transition metal complexes. Indeed, removal of metal waste from final products is critical yet often difficult and expensive, especially in an industrial context.[11]

The development of hydroboration−amination reactions has led to the efficient preparation of aliphatic amines, without the need for transition metal catalysts in the amination step.[12] On the other hand, the oxidation of arylboronic acids with peroxide has found significant utility in the synthesis of phenols, particularly those with unusual substitution patterns and in the context of preparing complex molecules.[13] The simplicity of this method, its reliability when used in situ, and a lack of

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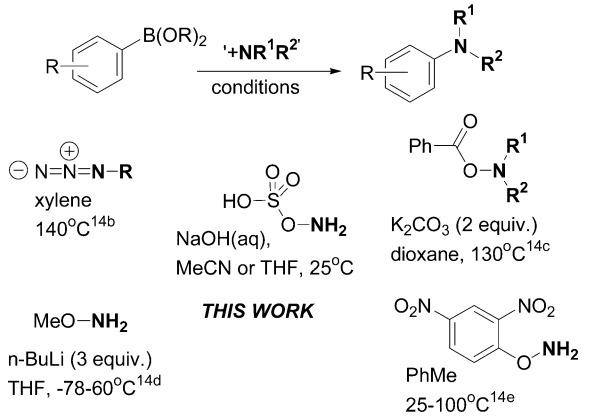
comparable alternatives have certainly contributed to its widespread use. A similarly simple and convenient method for amination of arylboronic acids would therefore be highly desirable.

In very recent years, several reports on the electrophilic amination of boronic acids (or their derivatives) have emerged (Scheme 2).[14] Such methods are appealing in that they avoid

Scheme 2. Transition-Metal-Free Amination of Boronic Acids



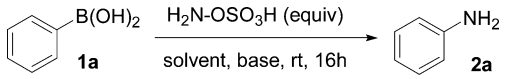
the use of transition metals and, in most cases, the need for strongly nucleophilic/basic reagents. Development of effective electrophilic amination processes for arylboronic acids has been hampered by the high stability of these compounds as compared to alkyl boranes generated via hydroboration.[12] Indeed, all of the methods reported to date require elevated temperatures to produce the desired products. Furthermore, to our knowledge, only a single such method has been reported for the preparation of primary anilines.[14e] Misconceptions regarding the reactivity of some of the most common and widely available electrophilic aminating agents have likely contributed to this lack of mild, simple, and readily accessible methods of this type. Indeed, the lack of reactivity of hydroxylamine-*O*-sulfonic acid (HSA) toward arylboronic acids has been directly stated.[14e,15] Such statements may be strictly true of the neutral reagent; however, the possibility of in situ activation should not be ruled out.

As part of our efforts to build upon the utility of boronic acids in the transition-metal-free synthesis of useful products,[16] we report herein a convenient, operationally simple, room temperature method for the preparation of primary anilines using HSA and other common reagents.

RESULTS AND DISCUSSION

Guided by the peroxide-mediated oxidation analogy,[13] typically performed in the presence of both base and water, we began our investigation by treating phenylboronic acid (**1a**) with HSA under a variety of conditions (Table 1). Early experiments confirmed that basic aqueous conditions were indeed necessary to achieve appreciable conversion to aniline **2a**. The use of aqueous alcohol mixtures with NaOH afforded **2a** after 16 h at ambient temperature in moderate to good conversion (entries 1–3). The use of DMF as a solvent provided no further improvement (entry 4), but both THF and acetonitrile produced **2a** in comparably good conversions (entries 5, 6). By increasing the proportion of the aminating agent, a further increase in conversion was observed; these proved to be the

Table 1. Optimization of Amination Conditions



entry	equiv	solvent[a]	base[b]	conversion (%)[d]
1	1.2	MeOH/H_2O	NaOH	36
2	1.2	i-PrOH/H_2O	NaOH	60
3	1.2	*t*-BuOH/H_2O	NaOH	76
4	1.2	DMF/H_2O	NaOH	69
5	1.2	THF/H_2O	NaOH	81
6	1.2	MeCN/H_2O	NaOH	83
7	1.5	MeCN/H_2O	NaOH	92
8	1.5	MeCN	NaOH	8
9	1.5	H_2O	NaOH	32
10	1.5	MeCN/H_2O	Na_2CO_3	40
11	1.5	MeCN	NaOH[c]	55
12	1.5	MeCN/H_2O	KOH[c]	48
13	1.5	MeCN/H_2O	LiOH[c]	53

[a]0.1 M concentration of **1a** (0.5 mmol); binary solvents in 1:1 ratio (v:v). [b]5 equiv of base used. [c]3 equiv of base used. [d]Conversion determined by ^{1}H NMR.

optimal conditions (entry 7). In the absence of water or organic solvent, conversion to **2a** was poor (entries 8, 9). The use of a weak base similarly depressed conversion (entry 10), as did reducing the amount of NaOH used (entry 11). Two other hydroxide bases were tested (entries 12 and 13) at reduced concentrations, affording the product in similar yields to that shown in entry 11, indicating a lack of counterion effect for this reaction.

We next investigated the scope of this reaction by subjecting a variety of simple arylboronic acids to the optimized conditions: 1.0 mmol of **1** and 1.5 mmol of HSA in 0.1 M concentration in a 1:1 mixture of CH_3CN/1.0 M $NaOH_{(aq)}$ at room temperature (Table 2). The prototypical substrate **1a** afforded the corresponding aniline **2a** in very good isolated yield (entry 1). Similarly, electron-rich **1b** afforded **2b** (entry 2). The introduction of a strongly electron-withdrawing CF_3 substituent in **1c** caused a marked decrease in reactivity; **2c** was isolated in low yield upon reaction at room temperature (entry 3). However, heating the mixture to reflux for 5 h resulted in moderate yield of the desired product (entry 4). Substrates bearing nitro, carbonyl, and related substituents (e.g., ketones, esters, or nitriles) were found to be incompatible with the reaction conditions and resulted in either no reaction at room temperature or complex mixtures of products under refluxing conditions. Aliphatic boronic acids and their pinacol esters were found to be similarly incompatible.

The similarly high yields obtained for the *p*- (**2d**, entry 5) and *o*-methyl derivatives (**2e**, entry 6), as well as the 2-naphthyl derivative **2f** and its 1-substituted analogue **2g** (entries 7 and 8) suggest that steric influences have little effect on the reaction. Indeed, even the highly sterically hindered *o*-isopropyl derivative **1h** reacted efficiently under the optimized conditions to afford the desired product **2h** in high yield (entry 9). The relative position of a methoxy group had only a very modest effect on yield. *m*-Methoxy derivative **2i** (entry 10) was isolated in only slightly decreased yield as compared to its *o*- (**2j**, entry 11) and *p*- (**2b**, entry 2) isomers.

All three dimethoxy arylboronic acid derivatives (**1k**, **1l**, and **1m**) tested performed very well under the reaction conditions, with **2k**, **2l**, and **2m** isolated in high to near-quantitative yields

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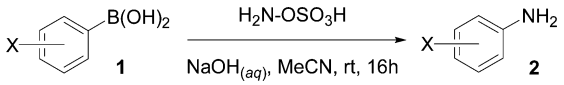
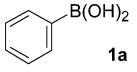
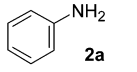
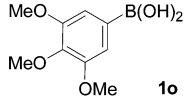
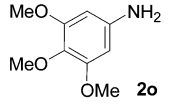
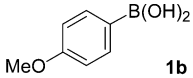
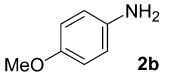
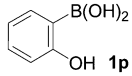
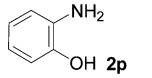
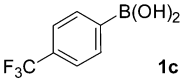
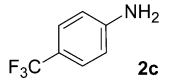
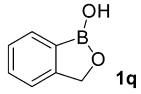
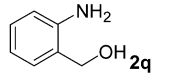
Table 2. Amination Scope



Entry	1	2	Yield[a]	Entry	1	2	Yield[a]
1	 1a	 2a	88%	16	 1o	 2o	88%
2	 1b	 2b	86%	17	 1p	 2p	80%
3	 1c	 2c	11%	18	 1q	 2q	74%
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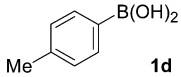
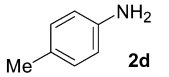
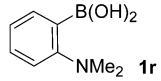
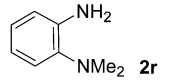
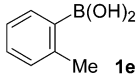
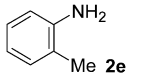
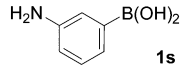
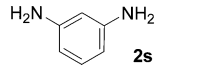
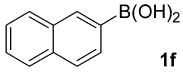
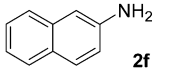
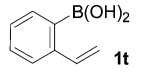
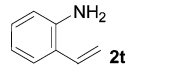
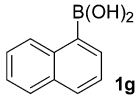
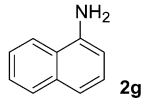
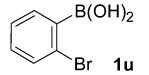
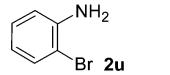
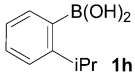
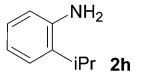
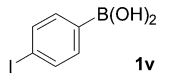
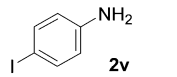
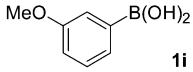
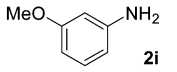
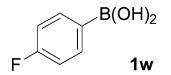
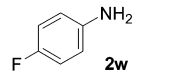
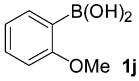
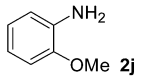
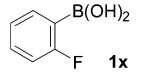
5	 1d	 2d	90%	19	 1r	 2r	75%
6	 1e	 2e	87%	20	 1s	 2s	90%
7	 1f	 2f	92%	21	 1t	 2t	77%
8	 1g	 2g	81%	22	 1u	 2u	70%
9	 1h	 2h	85%	23	 1v	 2v	74%
10	 1i	 2i	78%	24	 1w	 2w	69%
11	 1j	 2j	80%	25	 1x	2x	78%
12	1k	2k	97%	26	1y	2y	87%
13	1l	2l	99%	27	1z	2z	90%
14	1m	2m	82%	28	1aa	2aa	81%
15	1n	2n	90%	29	1ab	2ab	89%

[a]Isolated yields for reaction of 1.0 mmol of **1** with 1.5 equiv of HSA in 5 mL of CH_3CN and 5 mL of 1 M $NaOH_{(aq)}$ solution. [b]Reaction run at reflux for 5 h.

(entries 12−14). Methylenedioxy-substituted **1n** and the 3,4,5-trimethoxy derivative **1o** performed similarly well, affording the corresponding products **2n** and **2o** in excellent yields (entries 15 and 16). These results suggest that, at least for electron-rich substrates, this method is useful for the preparation of highly substituted primary anilines, several with substitution patterns that are complementary to those that could be achieved by electrophilic aromatic substitution.

o-Phenol derivative **1p** and borocycle **1q**, which is presumably hydrolyzed to the boronic acid-substituted benzylic alcohol under the reaction conditions, smoothly afforded products **2p** and **2q** in good yields (entries 18 and 19). These results indicate that both alcohols and phenols are tolerated well under the amination conditions. Similarly, the good yields obtained for reaction of both the *o*- and *m*-amino (**1r** and **1s**) substituted boronic acids to afford **2r** and **2s**, respectively (entries 19 and 20), suggest the suitability of this

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J. Org. Chem. 2015, 80, 2545−2553

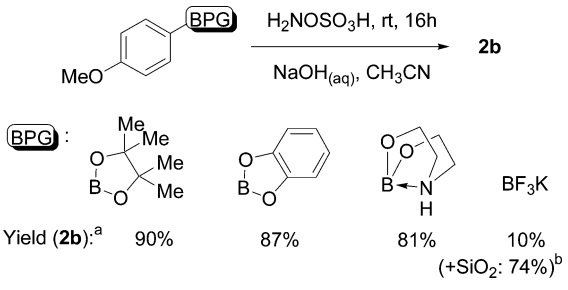
method for the synthesis of a variety of aromatic diamines. Styrene derivative **1t** also reacted cleanly under these conditions to afford **2t** in good yield (entry 21), indicating tolerance of alkene functionality.

Halogenated aromatics are an attractive target for transition-metal-free amination reactions, in that they are incompatible with metal-catalyzed methods.[14a] In this pursuit, we next tested several bromo-, iodo-, and fluoro-substituted phenylboronic acids under our electrophilic amination conditions. Gratifyingly, both 2-bromo (**1u**) and 4-iodo (**1v**) phenylboronic acid substrates reacted cleanly under our conditions to form products **2u** and **2v** in good yields (entries 22 and 23). In view of the prominence of both amino and fluoro groups in pharmaceuticals, we next tested the fluorinated substrates **1w** and **1x**; both reactions afforded the desired products, **2w** and **2x**, in good yields (entries 15 and 16). The reactivity of all four of the halogenated substrates suggests that, in contrast to highly electron-poor derivatives (e.g., **1c**, entry 3) that require elevated temperatures to afford products in acceptable yields, our room temperature conditions are well suited to not only electron-rich and electron-neutral substrates but moderately electron-poor ones as well.

Heterocyclic boronic acids have proven to be challenging substrates for this type of reaction, due to their propensity to undergo undesired side reactions.[17] All attempts to react electron-poor (e.g., 4-pyridineboronic acid) or electron-rich (e.g., 3-furanboronic acid) heterocyclic derivatives resulted in complex mixtures of products. However, quinolineboronic acid **1z** was found to react smoothly to afford **2z** in excellent yield (entry 27). This result, along with those reported in entries 19 and 20, suggests that HSA is chemoselective under the reaction conditions, in that no N–N bond formation was observed even in the presence of nucleophilic nitrogen substituents. Finally, to demonstrate further the applicability of our method for the synthesis of more highly substituted primary anilines, we tested two further trisubstituted derivatives (**1aa** and **1ab**) under the amination conditions. Clean formation of the desired products (**2aa** and **2ab**, respectively) was observed, in good to very good yields (entries 28 and 29).

In view of the fact that many methods for the synthesis and purification of arylboron compounds result in their formation as boronic esters or other derivatives,[15] we next tested our amination conditions on some of the most common protected boronic acids (Scheme 3). We were pleased to observe that under the standard reaction conditions, pinacol, catechol, and diethanolamine esters of arylboronic acid **1b** all reacted to form the desired aniline **2b** in very good to excellent yields.

Scheme 3. Amination of Boronic Acid Derivatives

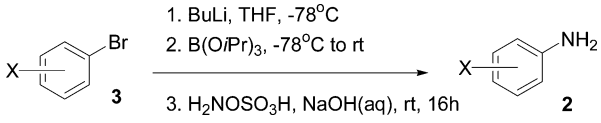


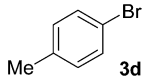
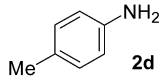
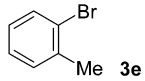
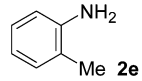
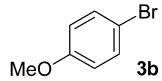
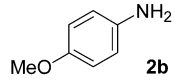
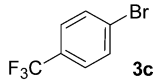
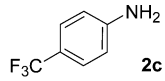
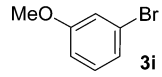
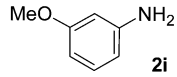
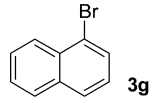
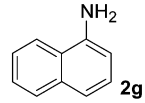
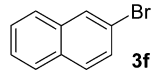
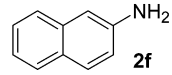
[a]Isolated yields for reaction of 1.0 mmol of the boronic acid substrate with 1.5 equiv of HSA in 5 mL of CH_3CN and 5 mL of 1 M $NaOH_{(aq)}$ solution. [b]1.00 g of silica added to the reaction.

Interestingly, potassium trifluoroborate derivative failed to react under the standard conditions to any appreciable extent. However, the addition of excess silica gel, a fluorophilic reagent known to facilitate trifluoroborate hydrolysis,[18] resulted in formation of the desired product, albeit in moderate yield.

A significant advantage of the peroxide-induced oxidation of boronic acids is that it can be used as part of a one-pot method to convert easily generated aryllithium species to phenols.[13] Our investigation into the potential use of our amination conditions in an analogous process to this are summarized in Table 3. Encouraged by the observation during optimization

Table 3. One-Pot Li–Br Exchange/Amination



Entry	3	2	Yield[a]
1	 **3d**	 **2d**	91%
2	 **3e**	 **2e**	84%
3	 **3b**	 **2b**	90%
4	 **3c**	 **2c**	24%
5	 **3i**	 **2i**	78%
6	 **3g**	 **2g**	76%
7	 **3f**	 **2f**	87%

[a]Isolated yields for reaction of 1.0 mmol of **3** with 1.05 equiv of *n*-BuLi in THF (5 mL) followed by addition of HSA (1.5 equiv) in 5 mL of 1 M $NaOH_{(aq)}$ solution.

that THF is an equally effective solvent to acetonitrile in the amination reaction (Table 1, entries 5 and 6), we subjected **3d** to typical lithium–halogen exchange conditions in THF, followed by triisopropyl borate quench and then an aqueous solution of aminating agent and NaOH upon warming the mixture to room temperature. Gratifyingly, we observed the formation of **2d** in high yield (entry 1).

The *o*-methyl derivative **3e** performed similarly (entry 2) and afforded **2e** in comparable yield to that starting from pure boronic acid (Table 2, entry 4). The one-pot protocol also afforded electron-rich **2b** and electron-poor **2c** (entries 3 and 4) in comparable yields to the simple amination procedure, which suggests that it is the amination step, rather than the lithiation step that is yield-limiting. *m*-Methoxy (**3i**) and naphthyl derivatives (**3g** and **3f**) also underwent the reaction to afford **2i**, **2g**, and **2f**, respectively, in very good to excellent yields.

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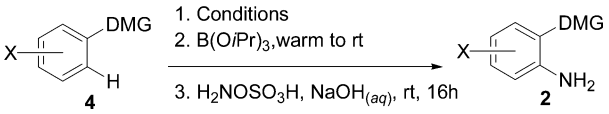
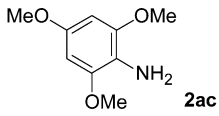
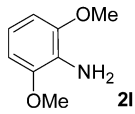
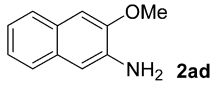
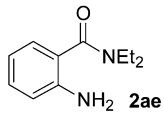
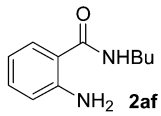
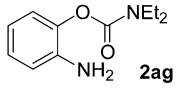
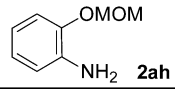
Another potential advantage of this amination protocol would be the regioselective preparation of products with substitution patterns difficult to achieve by other means. The Directed *o* Metalation (D*o*M) reaction is effective toward this end, particularly with respect to providing complimentarity to electrophilic aromatic substitution products.[19] Methods for introducing the amino functionality using D*o*M have so far been limited to transition-metal-containing electrophiles, or those of a highly reactive/toxic nature.[20] We therefore began testing the compatibility of our amination procedure with established metalation conditions and directed metalation groups (DMGs) (Table 4). Various methoxy-arenes, lithiated

Table 4. One-Pot DoM/Amination



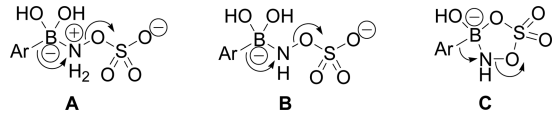
Entry	Conditions	2	Yield
1	*n*-BuLi, THF, 0°C	 **2ac**	83%
2	*n*-BuLi, THF, 0°C	 **2l**	69%
3	*n*-BuLi, THF, 0°C	 **2ad**	77%
4	*s*-BuLi, TMEDA, THF, -78°C		0%
5		 **2ae**	0%[b]
6	*t*-BuLi, THF, -78°C	 **2af**	40%[b]
7	*t*-BuLi, THF, -78°C	 **2ag**	66%
8	*n*-BuLi, THF, 0°C	 **2ah**	93%

[a]Isolated yields for reaction of 1.0 mmol of **4** in 5 mL of THF under the indicated conditions, followed by addition $B(OiPr)_3$ (1.5 equiv) and then HSA (1.5 equiv) in 5 mL of 1 M $NaOH_{(aq)}$ solution. [b]Amination reaction run at reflux for 16 h.

using *n*-BuLi, proved to be compatible with our aminating conditions and afforded products **2ac**, **2l**, and **2ad** in good to very good yields (entries 1−3). The products **2l** and **2ad** have complementary substitution patterns to those that would be afforded by classical methods (e.g., electrophilic nitration/reduction). In contrast, attempts to apply the one-pot sequence to *N*,*N*-diethylphenylamide (entries 4 and 5) failed to produce any of the desired product **2ae**. This may be due to a combination of steric and electronic effects or to incompatibility of the amination conditions with TMEDA. Contrastingly, lithiation of a secondary amide with *t*-BuLi, followed by boronation and amination at reflux afforded **2af**, albeit in low yield (entry 6). Strongly directing oxygen-based groups appear to be more effective in this one-pot reaction. *o*-Amino carbamate **2ag** was afforded in moderate yield under room temperature amination conditions (entry 7). The readily cleavable OMOM directing group proved to be most effective in promoting amination in our study; **2ah** was isolated in high yield (entry 8).

To further understand our electrophilic amination reaction, we initiated computational studies on the mechanism for the conversion of simple boronic acid **1a** to aniline **2a** using wave function and density functional methods.[21] In light of previous mechanistic work on related systems,[14c,e] and by analogy to the related 1,2-migration mechanism of peroxide-mediated oxidation of boronic acids,[22] we propose three possible mechanisms for the key reaction step of electrophilic amination using HSA under basic conditions: A, B, and C (Scheme 4). Given the

Scheme 4. Proposed Modes of Aryl B−N Migration



polar nature of the species, we reasoned that the migration step occurs in the aqueous phase of the biphasic reaction mixtures.[23] Transition states of reasonable energy were identified for all three proposed mechanisms.

For the dipolar reaction via mechanism A, in which HSA is monodeprotonated, **TSA-1a** was found to have $\Delta G^{\ddagger}$ = 200.3 kJ/mol (Scheme 5). This result is consistent with calculations performed previously for a similar reaction pathway.[24] The cyclic transition state structure of path C leads to a barrier similar to that of path A, $\Delta G^{\ddagger}$ = 191.3 kJ/mol and is omitted from Scheme 5 for clarity. Contrastingly, for the dianionic mechanism B, in which HSA is deprotonated twice, **TSB-1a** was found to have a much lower activation energy ($\Delta G^{\ddagger}$ = 103.6 kJ/mol) relative to the starting materials. This result, in combination with our experimental investigation, suggests that sufficiently basic conditions are critical for facile 1,2-aryl B−N migration to occur. Excess base may be required to drive the initial equilibrium between the reactants and **C1B-1a** sufficiently toward the complex so that migration occurs at a sufficient rate at ambient temperature to achieve good yields within the 16 h reaction time. Furthermore, these results suggest that in situ deprotonative activation of the HSA reagent is a viable alternative to using organoboron species that are more electrophilic than aryl boronic acids.[12] Interestingly, our calculations also reveal a 2-fold hydrogen bonding arrangement between one of the sulfate oxygens and the two OH hydrogens of the borate moiety (O···H distances of 1.98 and 2.16 Å). These interactions may serve to organize the transition state as well as to further increase electron density on the boron atom, thus promoting aryl B to N transfer. Following migration for both pathways, highly exergonic formation of complexes **C2A-1a** and **C2B-1a** occurs. These complexes would be expected to

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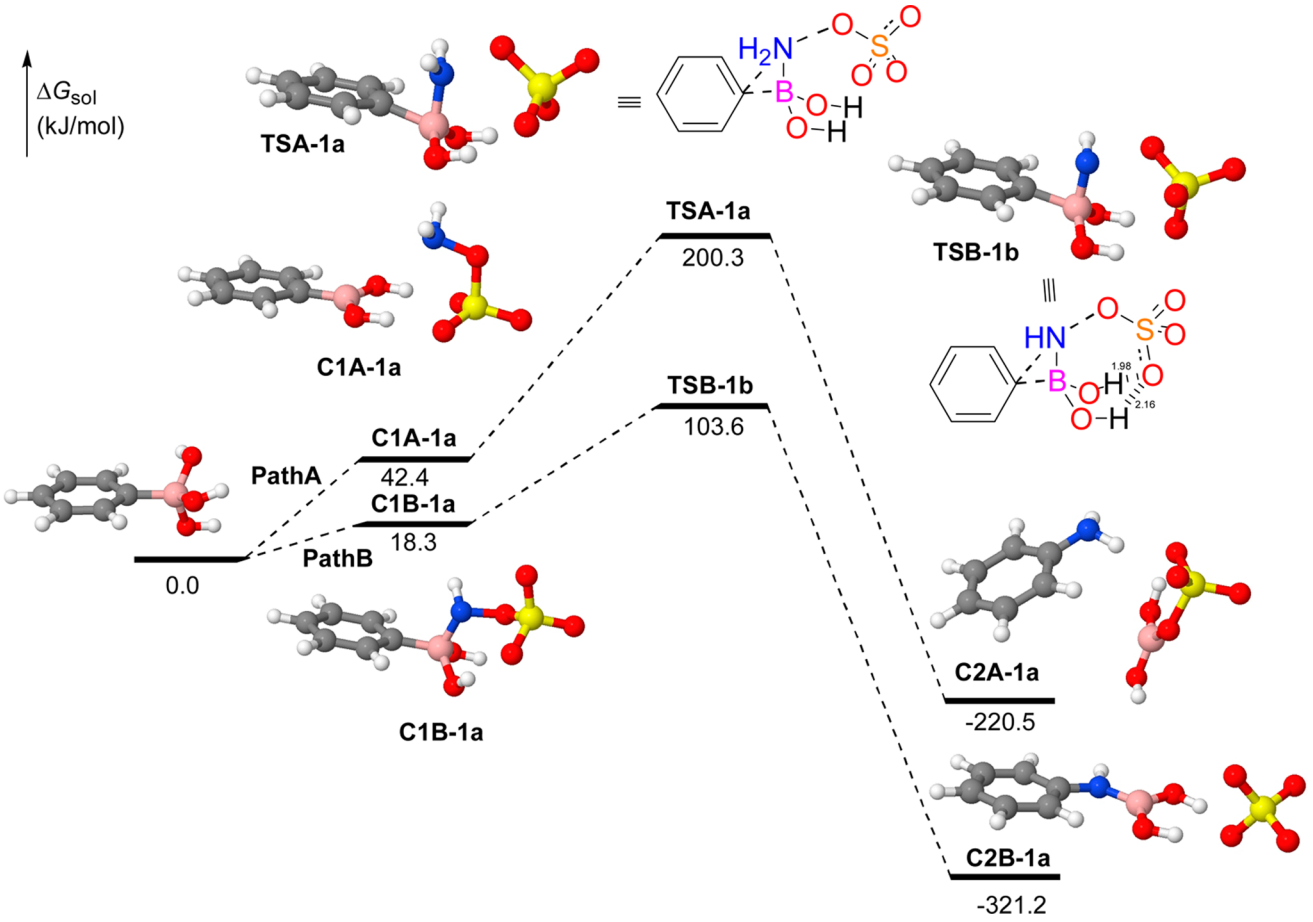
Scheme 5. Reaction Pathways A and B for 1a and 2a

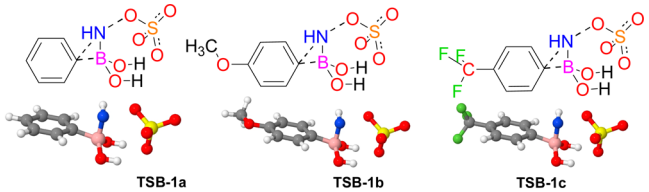


hydrolyze readily under the reaction conditions to form the free aniline **2a**.

Comparison of the calculated reaction pathway B for our electrophilic amination under basic conditions to that of the best previously reported electrophilic amination reaction[14e] is consistent with the success of our method at ambient temperature. Using *O*-(2,4-dinitrophenyl)hydroxylamine, the lowest energy pathway has $\Delta G^{\ddagger}$ = 117 kJ/mol relative to starting materials. Our calculations on pathway B reveal a $\Delta G^{\ddagger}$ that is more than 13 kJ/mol lower in energy.

Finally, to further probe the mechanism of our reaction and provide a rationale for the superior reactivity of electron-rich substrates as compared to electron-poor ones at ambient temperature, we calculated transition state energies for the conversion of **1b** to **2b** and **1c** to **2c** (**TSB-1b** and **TSB-1c**, respectively, Table 5). Consistent with our experimental observations, for the reaction of electron-rich substrate **1b**, the calculated $\Delta G^{\ddagger}$ was 9 kJ/mol lower in energy than that for **1a**, and that for electron-poor substrate **1c** was 4 kJ/mol higher. The calculated activation energies for the conversion of **1a** to **2a**, **1b** to **2b**, and **1c** to **2c** via pathway B correspond to relative rates of 1.0, 37.8, and 0.2, respectively, at 25 °C. These results are at least in qualitative agreement with the reactivity observed experimentally.

Table 5. Calculated Transition State Structures



	TSB-1a	TSB-1b	TSB-1c
$\Delta G^{\ddagger}_{sol}$ (kJ/mol):	104	95	108
Rel. Rate (25°C):	1.0	37.8	0.2
Yield (Exp.)	88%	86%	11%

CONCLUSIONS

We have developed a simple, mild, transition-metal-free method for the synthesis of primary anilines from boronic acids. The reaction uses common, inexpensive, commercially available reagents and affords products, in the large majority of cases, in good to near quantitative yields. It is most effective for electron-rich substrates, but electron-neutral or moderately electron-poor substrates are also well tolerated under ambient conditions. Highly electron-deficient substrates require refluxing conditions. Our results suggest that steric effects have little impact on the progress of the reaction. This method is amenable to "one-pot" methods in combination with metal–halogen exchange and various D*o*M protocols that provide efficient access to unusually substituted primary anilines via a simple and atom-economical "$^{+}NH_2$" equivalent and compares favorably to the analogous peroxide-mediated oxidation of aryl boronic acids. Computational studies, in combination with experimental results, suggest that the reaction occurs via base-mediated activation of HSA, followed by hydrogen bond-assisted 1,2 aryl B–N migration. This mode of activation appears to be critical for the success of the reaction and allows,

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J. Org. Chem. 2015, 80, 2545–2553

for the first time, general electrophilic amination of boronic acids at ambient temperature.

EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded using a 400 spectrometer at 400 and 100 MHz, respectively. NMR shifts are reported relative to a TMS or $CDCl_3$ internal standard. Flash chromatography was performed using silica gel Si 60 (40−63 μm). Tetrahydrofuran (THF) was distilled from sodium−benzophenone ketyl. All other solvents were purchased as ACS reagents and used without further purification. Solutions of *n*-BuLi in hexanes and *t*-BuLi in pentane were titrated periodically. A −78 °C bath refers to a mixture of dry ice in acetone, and a 0 °C bath refers to an ice/water slush. All other chemicals were purchased and used as received.

General Procedure A for Amination of Boronic Acids and Derivatives (Table 1, Scheme 3). To a vial containing the boronic acid (**1**, 1.0 mmol) in MeCN (5 mL) was added HSA (1.5 equiv, 170 mg), followed by NaOH solution (1 M, 5 mL). The vial was capped, and the biphasic mixture was stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O (30 mL, saturated $NH_4Cl_{(aq)}$ for products containing acidic functional groups) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified (if necessary) by flash chromatography (EtOAc/hexanes) to afford the amine product (**2**). Compounds **2a** (82 mg, 88%),[25] **2b** (106 mg, 86%),[26] **2c** (92 mg, 57%),[27] **2d** (96 mg, 90%),[26] **2e** (93 mg, 87%),[28] **2f** (132 mg, 92%),[25] **2g** (116 mg, 81%),[25] **2h** (115 mg, 85%),[28] **2i** (96 mg, 78%),[25] **2j** (99 mg, 80%),[29] **2k** (149 mg, 97%),[30] **2l** (152 mg, 99%),[31] **2m** (126 mg, 82%),[32] **2n** (123 mg, 90%),[33] **2o** (161 mg, 88%),[34] **2p** (87 mg, 80%),[35] **2q** (91 mg, 74%),[36] **2r** (102 mg, 75%),[37] **2s** (97 mg, 90%),[28] **2t** (92 mg, 77%),[37] **2u** (120 mg, 70%),[38] **2v** (162 mg, 74%),[39] **2w** (77 mg, 69%),[40] **2x** (87 mg, 78%),[29] **2y** (168 mg, 87%),[41] **2z** (103 mg, 90%),[42] **2aa** (151 mg, 81%),[43] and **2ab** (122 mg, 89%)[44] were prepared by this method and had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

General Procedure B for One-Pot Metal−Halogen Exchange−Boronation−Amination (Table 4). To an oven-dried 25 mL round-bottom flask, cooled to rt under Ar, were added the aryl bromide (**3**, 1.0 mmol) and freshly distilled THF (5.0 mL). The solution was cooled to −78 °C under Ar, and to it was added a solution of *n*-BuLi in hexanes (1.6 M, 1.05 equiv, 0.66 mL), dropwise via syringe. The resulting mixture was stirred for 30 min at −78 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The reaction mixture was allowed to warm to rt over 30 min, and then NaOH solution (1M, 5.0 mL) was added, followed by HSA (1.5 equiv, 170 mg) in one portion. The resulting biphasic mixture was stirred at ambient temperature for 16 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified (if necessary) by flash chromatography (EtOAc/hexanes) to afford the amine product (**2**). Compounds **2d** (98 mg, 91%),[26] **2e** (90 mg, 84%),[28] **2b** (111 mg, 90%),[26] **2c** (39 mg, 24%),[27] **2i** (96 mg, 78%),[25] **2g** (109 mg, 76%),[25] and **2f** (125 mg, 87%)[25] were prepared by this method and had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

*2,4,6-Trimethoxyaniline (**2ac**).*[45] To an oven-dried 25 mL round-bottom flask, cooled to room temperature under Ar atmosphere, were added 1,3,5-trimethoxybenzene (168 mg, 1.0 mmol) and THF (5 mL). The mixture was cooled to 0 °C, and to it was added *n*-BuLi (1.2 equiv, 0.75 mL), dropwise via syringe as a 1.6 M solution in hexanes. The mixture was stirred for 1 h at 0 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The ice−water bath was removed and the mixture allowed to warm to room temperature. A freshly prepared solution of HSA (1.5 equiv, 170 mg) in 1 M aqueous NaOH (5 mL) was added, and the resulting biphasic mixture stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes) to afford the amine product (**2ac**: 152 mg, 83%), which had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

*2,6-Dimethoxyaniline (**2l**).*[31] To an oven-dried 25 mL round-bottom flask, cooled to room temperature under Ar atmosphere, were added 1,3-dimethoxybenzene (138 mg, 1.0 mmol) and THF (5 mL). The mixture was cooled to 0 °C, and to it was added *n*-BuLi (1.2 equiv, 0.75 mL), dropwise via syringe as a 1.6 M solution in hexanes. The mixture was stirred for 1 h at 0 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The ice−water bath was removed and the mixture allowed to warm to room temperature. A freshly prepared solution of HSA (1.5 equiv, 170 mg) in 1 M aqueous NaOH (5 mL) was added and the resulting biphasic mixture stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes) to afford the amine product (**2l**: 106 mg, 69%), which had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

*2-Amino-3-methoxynaphthalene (**2ad**).*[46] To an oven-dried 25 mL round-bottom flask, cooled to room temperature under Ar atmosphere, were added 2-methoxynaphthalene (158 mg, 1.0 mmol) and THF (5 mL). The mixture was cooled to 0 °C, and to it was added *n*-BuLi (1.2 equiv, 0.75 mL), dropwise via syringe as a 1.6 M solution in hexanes. The mixture was stirred for 1 h at 0 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The ice−water bath was removed and the mixture allowed to warm to room temperature. A freshly prepared solution of HSA (1.5 equiv, 170 mg) in 1 M aqueous NaOH (5 mL) was added and the resulting biphasic mixture stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes) to afford the amine product (**2ad**: 133 mg, 77%), which had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

*2-Amino-N-butylphenylcarboxamide (**2af**).*[47] To an oven-dried 25 mL round-bottom flask, cooled to room temperature under Ar atmosphere, were added *N*-butylphenylcarboxamide (177 mg, 1.0 mmol) and THF (5 mL). The mixture was cooled to −78 °C, and to it was added *t*-BuLi (1.2 equiv, 0.75 mL), dropwise via syringe as a 1.6 M solution in pentane The mixture was stirred for 1 h at −78 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The dry ice−acetone bath was removed and the mixture allowed to warm to room temperature. A freshly prepared solution of HSA (1.5 equiv, 170 mg) in 1 M aqueous NaOH (5 mL) was added and the resulting biphasic mixture heated to reflux for 16 h. The reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes) to afford the amine product (**2af**: 77 mg, 40%), which had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

*2-Amino-N,N-diethylphenyl-O-carbamate (**2ag**).*[48] To an oven-dried 25 mL round-bottom flask, cooled to room temperature under Ar atmosphere, were added *N,N*-diethylphenyl-*O*-carbamate (193 mg, 1.0 mmol) and THF (5 mL). The mixture was cooled to −78 °C, and to it was added *t*-BuLi (1.2 equiv, 0.75 mL), dropwise via syringe as a 1.6 M solution in pentane. The mixture was stirred for 1 h at −78 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The dry ice−acetone bath was removed and the mixture allowed to warm to room temperature. A freshly prepared solution of HSA (1.5 equiv, 170 mg) in 1 M aqueous NaOH (5 mL) was added, and the resulting biphasic mixture was stirred at room temperature for 16 h. The reaction mixture was cooled to room temperature, diluted with H_2O, and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes) to afford the amine product (**2ag**: 137 mg, 66%), which had ^{1}H and ^{13}C NMR data that matched with that reported in the literature.

*2-Methoxymethoxyaniline (**2ah**).*[49] To an oven-dried 25 mL round-bottom flask, cooled to room temperature under Ar

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J. Org. Chem. 2015, 80, 2545−2553

atmosphere, were added methoxymethoxybenzene (138 mg, 1.0 mmol) and THF (5 mL). The mixture was cooled to 0 °C, and to it was added *n*-BuLi (1.2 equiv, 0.75 mL), dropwise via syringe as a 1.6 M solution in hexanes. The mixture was stirred for 1 h at 0 °C, and then to it was added $B(OiPr)_3$ (1.5 equiv, 0.35 mL). The ice−water bath was removed and the mixture allowed to warm to room temperature. A freshly prepared solution of HSA (1.5 equiv, 170 mg) in 1 M aqueous NaOH (5 mL) was added and the resulting biphasic mixture stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O and extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexanes) to afford the amine product (**2ah**: 142 mg, 93%), which had ^1H and ^{13}C NMR data that matched with that reported in the literature.

■ ASSOCIATED CONTENT

Supporting Information

Complete characterization data including ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: a.mccubbin@uwinnipeg.ca.

Notes

The authors declare no competing financial interest.

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