Hydroxylamines

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# Metal- and Base-Free Room-Temperature Amination of Organoboronic Acids with *N*-Alkyl Hydroxylamines

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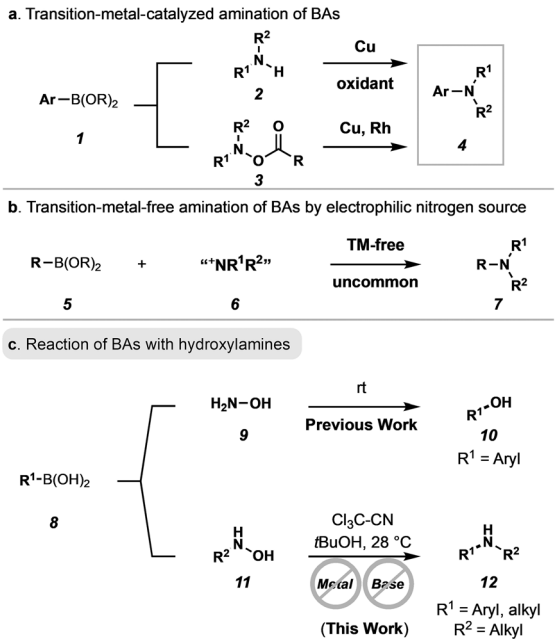
***Abstract:*** *We have found that readily available N-alkyl hydroxylamines are effective reagents for the amination of organoboronic acids in the presence of trichloroacetonitrile. This amination reaction proceeds rapidly at room temperature and in the absence of added metal or base, it tolerates a remarkable range of functional groups, and it can be used in the late-stage assembly of two complex units.*

As amines are ubiquitous in pharmaceuticals, agrochemicals, functional materials, and natural products,[1] methods for making C–N bonds are highly important in chemistry. For example, the advent of transition-metal-catalyzed C–N cross-coupling reactions[2] has largely addressed the difficulty of building $C_{aryl}$–N bonds, and profoundly influenced many fields such as medicinal chemistry, materials science, and chemical biology. However, in addition to the required basic reaction conditions, one drawback of these methods is the use of transition metals (TMs), whose removal, if required, can be cumbersome and expensive. TM-free methods for making $C_{aryl}$–N bonds are frequently needed in various disciplines, and actively pursued by the synthetic community, but have remained underdeveloped.[3]

Organoboronic acid derivatives (BAs) are a fundamental class of intermediates in synthesis because of their synthetic versatility and their compatibility with many functional groups.[4] Moreover, BAs are readily available from commercial sources and can be prepared by a large and increasing number of synthetic methods.[5] Recently, tremendous efforts have been devoted to the conversion of BAs into amines. Classic examples include the Chan–Lam–Evans reaction,[6] in which BAs undergo oxidative couplings with amines to give anilines (Scheme 1 a, **1** + **2** → **4**). Additionally, the groups of Lei, Liebeskind, Lalic, and others have reported on the amination of BAs with *N*-chloro amides or *N*-alkyl hydroxylamine derivatives in the presence of copper- or rhodium-based catalysts (Scheme 1 a, **1** + **3** → **4**).[7] Notably, reactions




***Scheme 1.*** Methods for the conversion of boronic acids into (aryl) amines.

converting BAs into amines are unconventional in that the C atom in the resulting C–N bond could be viewed as a nucleophile.[8] With recent developments, methods in this category have become important alternatives to produce amines. However, the aforementioned reactions also require the participation of transition metals.

TM-free methods for the conversion of BAs into amines under mild conditions would be of importance in chemistry (Scheme 1 b, **5** + **6** → **7**). Whereas TM-free amination reactions of the more Lewis acidic organoboron reagents, such as dihaloboranes, dialkyl borinates, and trialkyl boranes, by electrophilic nitrogen sources are known,[9,10] aminations of BAs are less common[3a,b] and usually require harsh reaction conditions. For instance, *N*,*N*-dialkyl *O*-benzoyl hydroxylamines and organic azides have been used to aminate aryl boroxines and aryl boronic acids, respectively, but only at high temperatures (> 130 °C).[11] Lithiated methoxyamine is an effective amination reagent for aryl and alkyl pinacol boronates.[12] However, the high basicity of this reagent limits the variety of compatible functional groups. The groups of Kürti and Falck reported the elegant use of *O*-(2,4-dinitrophenyl)hydroxylamine as an aminating agent for aryl boronic acids under mild conditions.[13] Nevertheless, as pointed out by the authors, aryl boronic acids containing

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*N*-acyl or carbonyl groups, or those with unprotected N atoms (e.g., indoles) or S atoms, are not suitable substrates. Moreover, this reaction gives primary anilines as the products, and thus cannot be used to build up molecular complexity. Most recently, the conversion of BAs into diaryl amines was reported.[3b]

In continuation of our interest in developing novel methods for the synthesis of amines,[14] we herein report a mild transformation (Scheme 1c, **8** + **11**→**12**) that converts BAs into secondary amines at ambient temperature (28 °C) and in the absence of added metal or base. Our method employs readily available *N*-alkyl hydroxylamines **11** as the electrophilic nitrogen source. Remarkably, while the parent hydroxylamine (**9**) has been used as an oxygen-transfer agent that converts aryl boronic acid derivatives into phenols (**8** + **9**→**10**),[15] we establish in this work that *N*-alkyl hydroxylamine **11** is an effective reagent for the amination of BAs (**8**) in the presence of a stoichiometric amount of trichloroacetonitrile ($CCl_3CN$). This process was adopted for the amination of both aryl and alkyl boronic acids. Moreover, the amination of alkyl boronic acids was found to be stereoretentive. This method tolerates a remarkable range of functional groups, including amides, ketones, esters, unprotected alcohols, and carboxylic acids. The reaction is operationally simple, and can be performed open to air. The generality of this method was demonstrated by its application in the preparation of products containing peptide side chains or carbohydrate motifs.

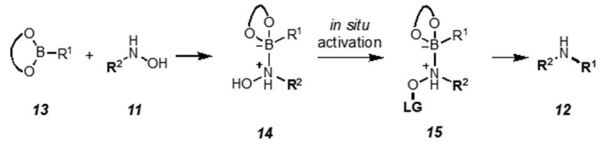
Our proposed strategy to achieve the amination of BAs is outlined in Table 1a (**13** + **11**→**12** via **14**/**15**). We wondered whether *N*-alkyl hydroxylamines could be turned into an effective aminating reagent to deliver an *N*-alkyl group. Given the ready availability of both reaction partners, if successful, this method might well be applicable in the late-stage coupling of complex units through C–N bond formation. *N*-Alkyl hydroxylamines are compatible with BAs, which we attributed to the poor leaving group ability of the free hydroxy group (cf. **11** or **14**). We surmised that we could facilitate the B-to-N migration of the $R^1$ group in **14** through activating the N–O bond by installing a leaving group on the O atom in situ (cf. **15**). This in situ activation strategy would obviate the need for isolating potentially unstable intermediates, permit a rapid screen of various activation conditions, and enhance the chance of identifying an efficient transformation.

Guided by this plan, we investigated the model reaction between phenylboronic acid (**16**) and *N*-benzyl hydroxylamine (**17**), as shown in Table 1b. After mixing **16** and **17** in $CH_2Cl_2$, we tested various conditions that would likely activate the O atom in **17**. Conventional reagents such as $Ac_2O$, MsCl, or $Tf_2O$ gave no observable product (entries 1–3). The use of Py·$SO_3$ did not effect this transformation either (entry 4). Our initial success resulted from the use of $CCl_3CN$:[16] In the absence of any additional base and at ambient temperature, the desired *N*-benzyl aniline was produced in 71% yield (entry 5). A further screen of reaction conditions (entries 6–10) revealed *t*BuOH to be the optimal solvent, in which **18** was formed in near-quantitative yield (entry 10). In sharp contrast, the use of other alcoholic solvents, such as *i*PrOH (entry 9), led to no observable product, highlighting the significant impact of solvent on the reaction outcome. Importantly, we found that this reaction could be performed open to air (entry 11). Lastly, this reaction was run on 7 mmol scale, yielding 1.18 g of **18** in 92% yield within 20 min (entry 12). Among all boronic acid derivatives tested, we found that 2,4,6-triphenylboroxine gave similar results to **16**, while others, such as phenylboronic acid pinacol ester (PhBpin) or potassium phenyltrifluoroborate ($PhBF_3K$), were unreactive (results not shown).

We next explored the substrate scope of this transformation (Figure 1). The reaction displays significant scope with respect to the organoboronic acid partner (Figure 1a). Both electron-rich (**19k**–**19m**, **19r**–**19s**) and electron-deficient (**19e**, **19n**–**19q**) aryl groups were tolerated. Substitution at the *ortho* (**19f**–**9h**), *meta* (**19i**, **9j**), or *para* position (**19a**–**19e**) was possible. Not surprisingly, aryl halides were stable under the reaction conditions (**19a**–**19d**), providing opportunities for further derivatization. Various functional groups, including ketone (**19n**), ester (**19m, 19mq**), nitro (**19o**), free carboxylic acid (**19p**), free phenol (**19r**), and free indole (**19x**) moieties, were all tolerated. Aryl boronic acids bearing fused (**19t**) and heterocyclic ring systems (**19u**–**19aa**) reacted smoothly in this reaction. Furthermore, a boronic acid derived from estrone was efficiently aminated (**19ab**). It is important to note that the amination of alkyl boronic acids/esters seems more challenging.[12] Nevertheless, we found that our method could be employed for the amination of alkyl boronic acids as

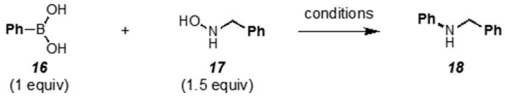
***Table 1:*** Amination of organoboronic acids: Proposed strategy and optimization of the reaction conditions.[a]

a. Our proposed in situ activation strategy to achieve amination of BAs




13 11 14 15 12

b. Condition optimization for a model transformation




16 (1 equiv) 17 (1.5 equiv) 18

| Entry | Activating agent | Solvent | *T* [°C] | Yield[a] [%] |
|---|---|---|---|---|
| 1 | $Ac_2O$, $Et_3N$ | $CH_2Cl_2$ | 25–80 | < 5 |
| 2 | MsCl, $Et_3N$ | $CH_2Cl_2$ | 25–80 | < 5 |
| 3 | $Tf_2O$, $Et_3N$ | $CH_2Cl_2$ | 25–80 | < 5 |
| 4 | Py·$SO_3$ | $CH_2Cl_2$ | 25–80 | < 5 |
| 5 | $CCl_3CN$ | $CH_2Cl_2$ | 28 | 71 |
| 6 | $CCl_3CN$ | toluene | 28 | 70 |
| 7 | $CCl_3CN$ | $CH_3CN$ | 28 | 40 |
| 8 | $CCl_3CN$ | THF | 28 | 48 |
| 9 | $CCl_3CN$ | *i*PrOH | 28 | < 5 |
| 10 | $CCl_3CN$ | *t*BuOH | 28 | 99 |
| 11[c] | $CCl_3CN$ | *t*BuOH | 28 | 99 |
| 12[d] | $CCl_3CN$ | *t*BuOH | 28 | 92[b] |

[a] Unless otherwise noted, all reactions were performed on 0.2 mmol scale. The yields were determined by $^1$H NMR analysis with 1,3,5-trimethylbenzene as the internal standard. [b] Yield of isolated product. [c] Reaction mixture open to air. [d] With 7 mmol of **16**, 20 min.

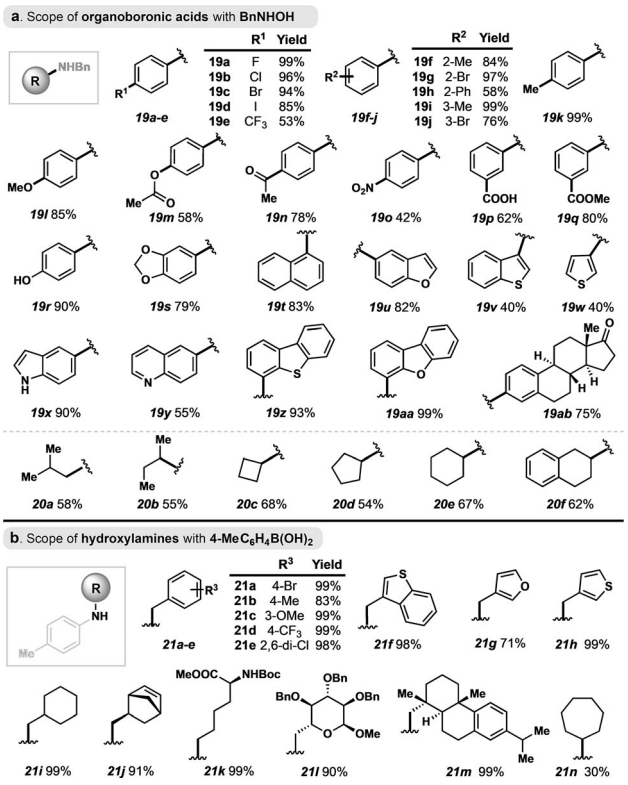



***Figure 1.*** Substrate scope. Reaction conditions: Boronic acid (0.3 mmol), hydroxylamine (0.45 mmol), and $CCl_3CN$ (0.45 mmol) in *t*BuOH (0.5 ml) at 28 °C for 1–8 h. Yields of isolated products are given. For **19p** and **19x**, the yields were determined by $^1$H NMR analysis with 1,3,5-trimethylbenzene as the internal standard. For **20a**–**20f**, the boronic acids were used in excess (2.0–3.0 equiv). Products **20a**–**20f** were isolated as the corresponding tosyl amides. Yields of isolated products are given. See the Supporting Information for details.

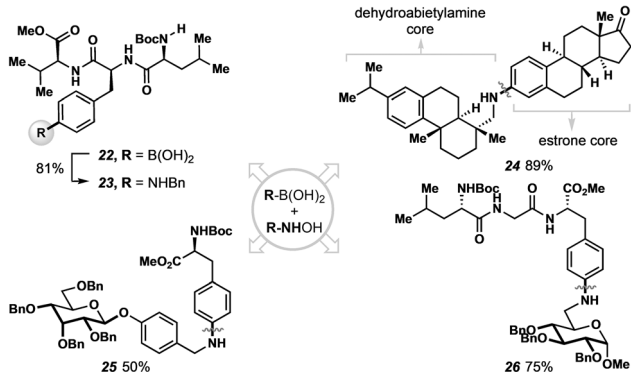


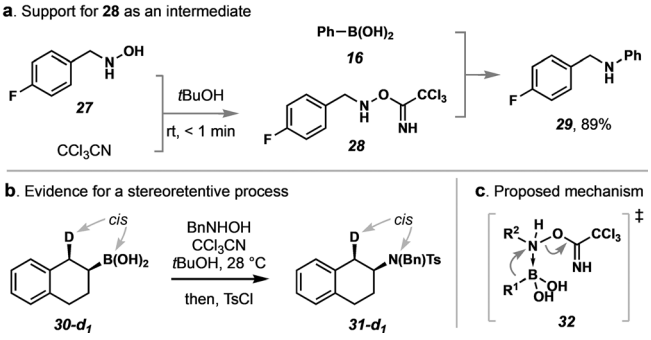

***Figure 2.*** Synthetic applications. Unless otherwise noted, the reactions were performed on 0.15 mol scale. See the Supporting Information for details.

well (**20a**–**20f**). Our process is unique in that it proceeds under almost neutral conditions.

Hydroxylamines with various functional groups participate in this reaction as well (Figure 1b). For instance, those with aryl rings of different electronic properties (**21a**–**21e**) and with heteroaryl substituents (**21f**–**21h**) are suitable substrates. Functional groups including aryl halides (**21a**), alkenes (**21j**), and esters (**21k**) were accommodated, too. The hydroxylamines derived from lysine (**21k**), glucose (**21l**), and the natural product dehydroabietylamine (**21m**) can all be employed as efficient aminating agents in this reaction. The use of *N*-cycloheptyl hydroxylamine gave the corresponding amine **21n**, albeit in modest yield.

To further show the utility of this method, we conducted the reactions shown in Figure 2. An aryl boronic acid embedded in a tripeptide backbone was aminated in high yield (**22**→**23**). In addition, this method was successfully used to unite a dehydroabietylamine scaffold with a steroidal moiety under metal- and base-free conditions (**24**). Lastly, we also applied this method in the coupling of hydroxylamines with carbohydrate backbones with an amino acid derivative (**25**) and with a tripeptide (**26**). The broad substrate scope, tolerance of air and moisture, and operational ease of this method are key to the success of the above-mentioned reactions. Given these attractive features, we anticipate that this method might be adopted in other complex settings, including in the construction of chemical libraries.

We then carried out various experiments to gain mechanistic insight into this reaction (Scheme 2). *N*-Alkyl hydroxylamines react with trichloroacetonitrile to give the corresponding *O*-imino hydroxylamines.[16] We monitored the reaction of **27** and trichloroacetonitrile in *t*BuOH by $^{19}$F NMR spectroscopy, and found that **28** was formed in almost quantitative yield within 1 min (Scheme 2a). Moreover, mixing phenylboronic acid (**16**) with **28** gave the expected product **29** in high yield. These results suggest that the real aminating agent of our reaction could be **28**.[17] We further prepared a monodeuterated compound **30**-$d_1$ and subjected it to our standard reaction conditions (Scheme 2b). We isolated **31**-$d_1$ after protection of the resulting amine with a tosyl group. We found that the deuterium atom in **31**-$d_1$ is positioned *cis* relative to the amide group, suggesting that the amination of **30**-$d_1$ proceeds with stereoretention. Based on this information, we surmise that our reaction proceeds via a transition-state structure such as **32**, in which the migration of the $R^1$ group from the B to the N atom results in the expulsion of the trichloroimidate group (Scheme 2c). We propose that the relaxation of the imidate in **32** to an amide group contributes to the lowering of the activation energy of this process.




***Scheme 2.*** Mechanistic studies.

In conclusion, we have developed a mild method for the amination of organoboronic acids with *N*-alkyl hydroxylamines in the presence of trichloroacetonitrile. Salient features of this reaction include that 1) it converts organoboronic acids into the corresponding secondary amines in the absence of added metal or base, 2) it employs readily available starting materials, 3) it is operationally simple, occurs rapidly at room temperature, and can be performed open to air, and 4) it tolerates a broad scope of functional groups, and can be used in the late-stage coupling of two complex substrates. Experimental studies provided insight into the mechanism of this reaction. Further applications of this method in the preparation of synthetically relevant amines are currently being studied.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** amination · amines · boronic acids · hydroxylamines · trichloroacetonitrile

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# Communications

**Hydroxylamines**

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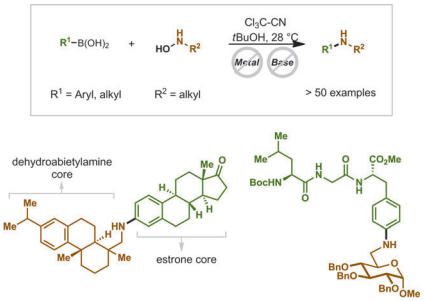
Metal- and Base-Free Room-Temperature Amination of Organoboronic Acids with *N*-Alkyl Hydroxylamines




**The amination** of organoboronic acids was achieved through the use of *N*-alkyl hydroxylamines in the presence of trichloroacetonitrile but in the absence of added metal or base. This reaction features a remarkably broad substrate scope and can be applied to the late-stage coupling of two complex units.