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A Protocol for Direct Stereospecific Amination of Primary, Secondary, and Tertiary Alkylboronic Esters

Emma K. Edelstein, Andrea C. Grote[#], Maximilian D. Palkowitz[#], and James P. Morken^{*}

Department of Chemistry, Boston College, Chestnut Hill, MA 02467

[#] These authors contributed equally to this work.

Abstract

The direct, stereospecific amination of alkylboronic and borinic esters can be conducted by treatment of the organoboron compound with methoxyamine and potassium *tert*-butoxide. In addition to being stereospecific, this process also enables the direct amination of tertiary boronic esters in an efficient fashion.

Graphical Abstract

Keywords

Organoboron; Asymmetric Synthesis; Amination; Chiral Amines; Stereochemistry

Although a number of synthetic methods have been developed that target construction of stereodefined alkylamines, efficient access to stereodefined tertiary carbinamines remains a most challenging task. Recently, access to enantioenriched alkylamines has been made possible through metal-free amination of boron reagents.¹ Although early examples of this transformation include the amination of trialkylboranes,² several recent examples detail the amination of boronic acids,³ borinic esters,⁴ boroxines,⁵ and dichloroboranes.⁶ Despite this progress, direct amination of common alkylboronic esters remains a challenge, with the only effective process being one developed by our laboratory that employs lithiated methoxyamine as a reactive reagent (Scheme 1, eq 1).⁷ While this method is efficient and

^{*}corresponding author. morken@bc.edu.

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stereospecific, it is cumbersome to implement, limited to reactions of primary and secondary boronic esters, and it requires the use of a large excess of *n*-BuLi and methoxyamine to generate the amination reagent. Indeed when we attempted to employ this reaction for the reaction in equation 2, <5% amination was observed. Herein, we report a modified amination process (eq 3) that is not only experimentally simple and avoids the use of pyrophoric reagents, but also extends to the stereospecific amination of tertiary alkyl boronic esters. Importantly, there are currently no methods available that directly convert tertiary boronic esters into the corresponding amine in a stereospecific fashion and thus this process fills an important gap in synthetic methods.⁸

In connection to borylation methods under study in our laboratory, we recently attempted the conversion of tertiary alkylboronic esters into α -tertiary amines. Preliminary experiments focused on stereospecific amination using lithiated methoxyamine as an amination reagent. Using previously described reaction conditions (Scheme 1, eq 2; deprotonation of methoxyamine at $-78\text{ }^{\circ}\text{C}$, followed by addition of the alkylboronic ester and warming to $60\text{ }^{\circ}\text{C}$), this process failed to deliver useful quantities of the amine-derived reaction products. Considering the proposed mechanism of this process (Scheme 2A), it was considered that with a congested tertiary boronic ester, the lithiated methoxyamine (**A**) may be unable to coordinate efficiently to the electrophilic *tert*-alkylboronic ester and that, upon heating, the uncoordinated amination reagent may decompose to nitrene prior to formation of the “ate” complex (**B**). To avoid decomposition of the lithium nitrenoid species at elevated temperatures, we considered amination conditions that do not require the use of a preformed anionic nitrogen reagent. Instead, it was considered that use of neutral methoxyamine, in conjunction with an alkoxide base, might enable an alternate mechanistic manifold wherein the weak base is only able to deprotonate the amination reagent once the nitrogen atom is acidified by coordination to the boron center (**D**, Scheme 2B). By avoiding the intermediacy of free lithium nitrenoid species, it was considered that the amination reagent might survive at higher temperatures required for more challenging aminations.

Previous studies in our laboratory suggested that potassium *tert*-butoxide can serve as a competent base to effect amination of alkyl pinacol boronates with methoxyamine as the aminating reagent.⁷ Although low conversion and low isolated yields (16%) in the amination of *n*-octylB(pin) were observed, the observation that the product was formed at all suggested that the soft deprotonation strategy depicted in Scheme 2B can operate. Further experiments aimed at optimizing amination of *n*-octylB(pin) with KOtBu and methoxyamine revealed that increasing the reaction temperature ($80\text{ }^{\circ}\text{C}$) and using toluene/THF as the reaction solvent, resulted in complete conversion and good yield; after Boc protection to ease product purification, the protected amine derivative could be isolated in good yield (85%)⁹ With effective conditions in hand we explored the scope of the reaction with primary and secondary boronic esters (Scheme 3).

As depicted in Scheme 3, while alkyl pinacol boronic esters were smoothly converted to the corresponding amine, it was also found that other boronic esters such as neopentylglycol (**2**) and 1,3-dimethylpentane-1,3-diol (**3**) derivatives, as well as a borinic ester (**15**) also engaged in the amination reaction. Functional groups such as an arene, pyridine, silane, and benzyl- and silyl-protected alcohols were also tolerated in the process and were converted to the

Boc-protected amine derivatives in good yield. Similar to the process employing preformed lithated methoxyamine, the process employing soft deprotonation in Scheme 3 is stereospecific and proceeds without detectable loss of enantiomeric purity when nonracemic organoboron compounds were employed as substrates (**10-16**). The observation that the reaction is stereoretentive provides further compelling evidence that the reaction proceeds *via* a 1,2-metallate shift, consistent with the proposed mechanism in equation 4. Unlike the process employing lithiated methoxyamine, it was noted that a benzylic boronic ester suffers greatly diminished yield with the conditions of Scheme 3: with substrate **14**, significant amounts of protodeboration products were formed, in addition to the amination product. Lastly, it should be noted that attempts to directly prepare substituted amines by use of N-methylmethoxyamine in place of methoxyamine have, so far, been unsuccessful.

Having determined that efficient amination of primary and secondary organoboron compounds can be accomplished with methoxyamine and potassium *tert*-butoxide, we sought to determine whether the reaction would be effective with more challenging tertiary boronic esters. Using the same conditions that were employed for primary and secondary organoboron reagents, it was found that amination of tertiary boronates could indeed occur; however, the process occurred with only moderate conversion (70%) of starting material. Increasing the amount of methoxyamine and KO*t*Bu to 3.0 and 5.0 equivalents respectively, resulted in complete conversion of starting material, and the desired α -tertiary amines or Boc-protected derivatives could be isolated in good yield (**21** and **23**, Scheme 4). Gratifyingly, the aminations of tertiary boronic esters were also stereospecific and gave the desired amines without erosion of enantioselectivity. Sterically encumbered tertiary centers such as those with an *iso*-propyl substituent and substrates containing protected aryl and alkyl ether groups were also successfully converted into the amine. A highly congested tertiary center, however, such as that with an adjacent *tert*-butyl substituent (**24**), did not undergo amination, and the starting material was fully recovered. Similar to the case with secondary substrates, tertiary benzylic boronic esters (i.e. **25**) did not give any desired amination product, with the starting material undergoing non-stereospecific conversion to the proto-deboration product (**26**).

In terms of reaction mechanism, the ^{11}B NMR spectrum of the boronic ester is unchanged upon addition of methoxyamine alone, whereas addition of KO*t*Bu and methoxyamine gives a resonance consistent with *tert*-butoxide binding to the boronic ester. Thus, it is plausible that the *tert*-butoxide-derived “ate” complex is formed reversibly and reaction occurs either with a small equilibrium concentration of the deprotonated amine, or through deprotonation of a low equilibrium concentration of the adduct formed between methoxyamine and the boronic ester (*via* **E**, Scheme 2b). Similar to computational experiments on hydroxylamine sulfonic acid amination¹⁰, we do not expect amination to occur by rearrangement directly on compound **D** (Scheme 2b).

To probe the utility of the amination process for preparative scale chemistry and to study conditions that might be employed routinely by practicing synthetic chemists, we conducted the experiments described in Scheme 5. In the first experiment (eq 3), we conducted a gram scale amination of TBDPS-protected substrate **8**. As shown, this reaction proceeded as efficiently as the smaller scale experiment presented in Scheme 3. In a second experiment

(eq 4), we conducted a gram-scale amination of cyclohexylB(pin) in the open atmosphere. In addition, rather than employing solid KO^tBu dispensed in a glovebox, a syringe-transferred 1 M THF solution of potassium *tert*-butoxide was employed. In this experiment, only a modest diminution in yield was obtained relative to the experiment in Scheme 3.

In summary, we have described a simple protocol for the direct amination of a range of alkylboronic esters in an efficient and stereospecific fashion. Collectively, these experiments suggest that the amination of alkylboronic esters using MeONH₂/KO^tBu can be a broadly useful reaction for the construction of amine derivatives.

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Supplementary Material

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Acknowledgment

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- (8). Aggarwal has accomplished the stereospecific amination of tertiary boronic esters employing multistep route that involves conversion of the boronic ester to a trifluoroborate, chlorination to provide the dichloroborane, and then reaction with benzylazide. See: Ref. 6b.
- (9). Procedure: In an glove box, a 2-dram vial equipped with magnetic stir bar was charged with potassium *tert*-butoxide (5.0 equiv). The vial was sealed with a septum cap and was removed from the glove box. Toluene and methoxyamine (1.96 M in THF, 3.0 equiv) were added *via* syringe. Subsequently, the alkyl boronic ester (1.0 equiv) was added as a solution in toluene to achieve a final substrate concentration of 0.2 M. The vial was sealed with tape, and left to stir for 16 hours at 80 °C behind a blast shield. The reaction mixture was then cooled to room temperature before Boc₂O (5.0 equiv) and saturated NaHCO₃ were added. After stirring under N₂ at 80 °C for 5 hours, the mixture was cooled to room temperature, water was added and the mixture and extracted three times with ethyl acetate. Drying (Na₂SO₄), filtration, and purification on silica gel delivered the final product.²²²⁴Product from **10**: ¹H NMR (600 MHz, CDCl₃) δ 7.32–7.26 (m, 2H), 7.24–7.14 (m, 3H), 4.29 (br s, 1H), 3.82 (br s, 1H), 2.76 (br m, 2H), 1.52–1.91 (m, 15H), 0.87 (t, *J* = 6.7 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 155.6, 138.5, 129.7, 128.4, 126.3, 79.1, 51.7, 41.5, 34.0, 28.5, 28.3, 22.7, 14.2. IR (neat) ν_{max} 3339.4 (m), 2958.1 (m), 2928.4 (m), 2857.0 (w), 1699.6 (m), 1683.0 (s), 1524.6 (s), 1454.7 (w), 1363.5 (m), 1251.4 (s), 1169.2 (s), 1045.4 (m), 1014.2 (m), 743.3 (w), 699.0 (m) cm⁻¹. HRMS (DART+) for C₁₇H₂₈NO₂ [M+H]⁺ calculated: 278.2120, found: 278.2107. [α]_D²⁰ –15.953 (c = 0.890, CHCl₃, *l* = 50 mm). **10**¹³₃max¹⁷²⁸²₂₀Product from **19**: ¹H NMR (600 MHz, CDCl₃) δ 7.36–7.30 (m, 4H), 7.30–7.26 (m, 1H), 4.50 (s, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 1.62 (p, *J* = 6.5 Hz, 2H), 1.47 (br s, 2H), 1.43–1.33 (m, 4H), 1.08 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 138.7, 128.5, 127.8, 127.6, 73.0, 70.4, 49.7, 44.9, 30.5, 30.3, 21.3. IR (neat) ν_{max} 2935.3 (br), 2860.1 (w), 1453.9 (w), 1362.9 (m), 1100.0 (s), 841.9 (br), 733.0 (s), 696.4 (s) cm⁻¹. HRMS (DART+) for C₁₄H₂₃NO [M+H]⁺ calculated: 222.1858, found: 222.1852.**19**¹³₃max⁻¹₁₄₂₃⁺
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Scheme 1.
Amination of Alkylboronic Esters.

Scheme 2.
Prospective Mechanisms for Boronic Ester Amination.

Scheme 3.

Substrate Scope in the Amination of Primary and Secondary Alkylboronic Esters. (a)
Experiment conducted with 5 equiv. MeONH₂ and 7 equiv KO^tBu.

Scheme 4.

Amination of Tertiary Boronic Esters. (a) Using work-up procedure A, the primary amine was isolated. (b) Using work-up procedure B, the product was isolated as the Boc-protected amine.

Scheme 5.
Preparative Amination Reactions.