A divalent protecting group for benzoxaboroles†

Brett VanVeller,‡ Matthew R. Aronoff‡,a and Ronald T. Raines*ab

1-Dimethylamino-8-methylaminonaphthalene is put forth as a protecting group for benzoxaboroles. The ensuing complex is fluorescent, charge-neutral, highly stable under basic conditions, stable to anhydrous acid, and readily cleavable in aqueous acid to return the free benzoxaborole.

Oxaborole heterocycles are boronic acids that are receiving much attention for applications in drug discovery, synthetic methodology, molecular recognition, and biotechnology. Benzoxaborole (1; Fig. 1), which is characterized by a phenyl ring fused to a five-membered oxaborole, is the most widely employed oxaborole pharmacophore in medicinal chemistry.

Compared to phenylboronic acid, the annulated benzylic alcohol in 1 confers high stability, low pKa, and superior polyol-binding (1 → 2) under physiological conditions (i.e., water near neutral pH), favorable attributes for applications that entail binding to carbohydrates.

The vacant p-orbital on boron—essential for complexation with polyols—can confound multistep synthetic routes and the purification/isolation of derivatives. This issue is compounded further by the commercial availability of countless elaborately functionalized boronic acids but only a small number of simple benzoxaboroles. Our interest in benzoxaboroles for the cellular delivery of chemotherapeutic agents and other pharmacological applications drove us to develop a protecting group for 1 that would enhance its synthetic utility.

A variety of successful protecting group strategies have been developed to modulate the undesired reactivity of boronic acids. A common example is a pinacol ester (3), which sterically shields the p-orbital from reaction. Similarly, Suginome and coworkers demonstrated the reduced reactivity of boronic acids in a complex with 1,8-diaminonaphthalene (4). An often-employed strategy developed by Molander and coworkers capitalizes on the fluoro-affinity of boron to form a trifluoroborinate salt (5). While highly stable, these salts are incompatible with chromatography, limiting their utility in multistep synthetic routes. Burke and coworkers have popularized a trivalent N-methyliminodiacetic acid (MIDA) ligand for boronic acids that coordinates the vacant p-orbital with atrialkylamine through a dative bond to give a charge-neutral complex (6). The trivalent MIDA group is not, however, suitable for protecting 1, which can coordinate to only two ligands. Divalent protecting

---

**Fig. 1** Structure of free benzoxaborole (1), its complexation with a polyol (2), and other general structures of protected boronic acids (3–6) and their unsuitable complexes (7–9) with 1.
groups like 3 and 4 are also not appropriate for 1 because they would lead to anionic complexes (7 and 8). Likewise, fluoride protection would yield an anionic difluoroborate salt (9).

We sought to apply the principle of charge neutrality, as demonstrated by the efficacious MIDA protecting group, to the divergent protection of benzoazaboroles. Inspired by the strong complexes that simple boronic acids form with 1,8-diaminonaphthalene (4), we devised a protecting group based on 1,8-bis(dimethylamino)naphthalene (10) to generate charge-neutral complexes with 1 that maintain a Lewis basic site to promote acid-mediated cleavage (Scheme 1). We found that complexes 11a–e were fluorescent, stable to basic conditions, moderately stable to anhydrous acid, and readily deprotected under aqueous acidic conditions.

Following a previous report, 1,8-bis(dimethylamino)naphthalene was monodemethyalted to give 1-dimethylamino-8-methylaminonaphthalene (10) in one step of >90% yield without chromatography. After azeotropic removal of water, 1a–e and 10 readily formed complexes 11a–e (Scheme 1). Excess 10 was necessary for high yields, but unreacted 10 was re-isolated quantitatively by chromatography (Fig. 2B, inset). Formation of the complex generated a tetrahedral boron center (1c → 11c) that was stereogenic—the benzylic protons of 1 became nonequivalent (Fig. 2A) and served as signature of complex formation. The complex was characterized with X-ray crystallography (Fig. 2C).

Next, we investigated the generality of our protecting group design. First, we investigated a small library of compounds similar to 10 for protection of 1a (see ESI†). Only 10, however, led to complexes that were stable during chromatography. α-Amino acids (which resemble divalent versions of MIDA) are known to form stable complexes with dialkyl boranes (i.e., borinic acids). We found these complexes to be too fragile for effective protection of 1. From these data, we conclude that the stability of complexes 11a–e stems from both the rigid structure imposed by the diaminonaphthalene ring and the strongly donating nitrogen ligands. The ease of purification also relies on coordinating the vacant p-orbital through a dative bond supplied by the dimethyl amine ligand to create a charge-neutral complex. Finally, we note that 11a–e are highly fluorescent (11a, Φ = 0.45, Fig. 2B and inset) allowing for easy tracking of product derivatives (11–18) during multi-step synthesis and purification using a standard long-wave (365 nm) bench-top lamp. Complex 11a was subjected to a screen of conditions to determine its stability (Table 1, representative time points, see ESI† for kinetic traces and further discussion). In general, 11a is deprotected readily under aqueous acidic conditions (entries 1–3), but exhibits modest (i.e., kinetic) stability under anhydrous acid (entries 4–6) (Table 1). This sensitivity to acid affirms an aspect of our design—protonation of the methylamino group leads to weaker binding and allows for hydrolytic cleavage. In contrast, 11a is highly stable under basic conditions (entries 7–10). This reactivity indicates that protecting group 10 is well suited for solid-phase peptide synthesis, in which amino acids are coupled under basic conditions and subsequently cleaved from a solid-support using acid. Finally, the complex tolerated strong reducing reagents, such as LiAlH₄ (entry 11). We do note that oxidative conditions were not compatible with 11b and lead to complex mixtures. This sensitivity is not surprising due to the electron-rich nature of the diaminonaphthalene moiety, which is prone to oxidation.

![Scheme 1 Protection of benzoazaborole derivatives.](image)

![Table 1 Screening of the stability of 11a under various conditions*](image)

*Average of two experiments at 0.1 M 11a with 4-bromo-2,6-dimethylphenol as an internal standard. Analyzed with LC-MS. Analyzed with 1H NMR spectroscopy.
To explore further the stability of the protecting group, we evaluated 11b, 11d, and 11e under a series of synthetic transformations (Scheme 2 and 3, see ESi† for 11b). As expected, the complex was able to tolerate reducing conditions such as H₂/Pd (11e → 12). Conversion of 12 to trflate 13 and subsequent Suzuki–Miayaura coupling using an XPhos palladacyclic pre-catalyst,¹⁹ provided 14 in high yield. Notably, 10 prevented reaction at the benzoxaborole center.¹⁸ Recent data suggest that Suzuki–Miayaura reactions necessitate a vacant boron p-orbital,²¹ validating our protecting group design.²²

The base stability of the complex allowed for Buchwald–Hartwig C–N cross-coupling of the protected boron center to give 15 from 11d.²³ As noted above, protecting group 10 is compatible with organic amine bases associated with peptide bond formation reagents to provide 16 in high yield (94%). In comparison, a similar peptide coupling reaction attempted with unprotected 1d provided only a 23% yield of the amide 18. Notably, in both the Pd-catalyzed and peptide-coupling reactions, the methylamino groups in 11d are unreactive. Finally, evincing the utility of the protecting group under anhydrous acid, selective deprotection of the amino group in 16 with HCl gave 17 in good yield (78%), while the benzoxaborole moiety could be deprotected selectively with aqueous acetic acid to return 18 (Scheme 2).

In conclusion, benzoxaborole 1 has become a privileged entity in medicinal chemistry and for carbohydrate recognition. Its continued development will rely on the efficiency of its derivatization. We have demonstrated the stability and utility of 1 and other benzoxaboroles when protected with 10. Protecting group 10 occupies the vacant p-orbital on boron while creating charge neutrality in the final product. Its complexes are formed readily and are compatible with synthetic reagents and separation/purification techniques employed commonly in multi-step syntheses to enable or improve the efficiency of manipulating benzoxaborole.

![Scheme 2](image)

Scheme 2 Synthetic evaluation of protected benzoxaborole derivatives; yields are isolated but not optimized.

**Acknowledgements**

We are grateful to Dr Ilia Guzei for X-ray diffraction analysis of complex 11a. B.V. was supported by postdoctoral fellowship 289613 (CIHR). This work was supported by grant R01 GM044783 (NIH), and made use of the National Magnetic Resonance Facility at Madison, which is supported by grants P41 RR002301 and P41 GM066326 (NIH).

**Notes and references**


22 Attenuating the reactivity of boronic acids by rehybridization of the boron center from sp2 to sp3 using a dative nitrogen ligand was demonstrated initially by Burke and coworkers (ref. 12a).