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Functional Group Compatibility of the Oxidation-Resistant Benzoxaborolone Pharmacophore

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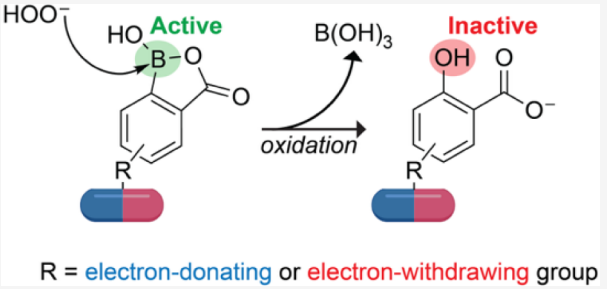
ABSTRACT: Benzoxaborolone, or 2-carboxyphenylboronic acid, forms a stable borolactone that engenders 10^4-fold greater stability toward oxidation than more commonly used phenylboronic acids and benzoxaboroles. Importantly, this stability could enhance the pharmacological activity of boron-based small molecules. Here, we experimentally and computationally examined the impact of pendant electron-donating and electron-withdrawing groups on the oxidative stability of benzoxaborolone. We find that oxidation is faster with electron-donating groups and slower with electron-withdrawing groups, though the changes are $<10^2$-fold. The effects are explicable by physical organic principles of aromatic activation/deactivation. The results demonstrate that even substituted benzoxaborolones are much more resistant to oxidation than common boronic acids and provide guidance for their continued development as pharmacophores.



INTRODUCTION

An empty p-orbital makes all the difference. This atomic feature of boron has been leveraged by synthetic and medicinal chemists for decades, enabling the design of reagents that serve as catalysts or protecting groups for a variety of biomolecular transformations, as well as reversible, covalent small-molecule inhibitors targeting Lewis bases in proteins.[1−12] Notably, the clinical success of the proteosome inhibitor, bortezomib, in hematological malignancies led to focused efforts in drug discovery to design boronic acid−based therapeutics.[13] Yet, since the approval of bortezomib over two decades ago, only four more boronic acid−based drugs have entered the clinic. A serious problem is that the Lewis acidic character of boron that enables therapeutic efficacy also renders these molecules highly susceptible to oxidative deboronation, leading to the release of boric acid and an inactivated pharmacophore. Although aryl boronic acids such as phenylboronic acid (PBA) and benzoxaborole (BL) offer slightly greater stability than does the alkyl boronic acid in bortezomib, biological environments are unforgivingly redox-centric, and the oxidative deboronation of these groups by reactive oxygen species (ROS) is an eventual certainty. This vulnerability can be particularly acute in environments of metabolic dysfunction, where most pharmaceutical compounds operate. For this reason, however, boronic acids are useful as ROS sensors in biological settings.[14]

To circumvent this roadblock in chemotherapeutic development, we put forth an oxidation-resistant aryl boronic acid with 10^4-fold greater stability to oxidative deboronation over PBA and BL (Figure 1A).[15] Drawing inspiration from the cyclic ester that spontaneously forms in BL,[19] we placed a carboxy group *ortho* to the boronic acid to induce a similar cyclization to form a borolactone-containing boronic acid derivative, benzoxaborolone (BOL). The ensuing shift in orbital overlap and electron density on the boron increases the Lewis acidity of the boron and lowers its pK_a, causing a dramatic shift in equilibrium toward the anionic, tetrahedral boron species (Figure 1B). In turn, the orbital geometry between the boron and the carboxy group prevents stabilization of the electron deficiency that the boron encounters during B−C bond breaking during oxidation, deterring this reaction (Figure 1C). As suggested by the difference in cLog*P* values (Figure 1A), a BOL pharmacophore lends greater hydrophilic character than does PBA or BL, offering medicinal chemists increased freedom for scaffold modification. Further, unlike aryl and alkyl boronic acids, which are generally stored under $N_2(g)$ or Ar(g) at either 4 °C or −20 °C, benzoxaborolones are bench stable and do not require flushing with $N_2(g)$ or Ar(g) for

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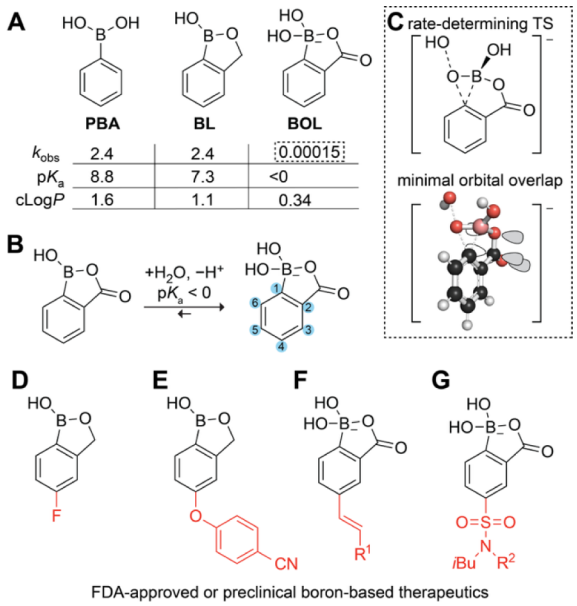

Figure 1. (A) Second-order rate constants (M^{-1} s^{-1}) for oxidation by H_2O_2,[15] experimentally determined pK_a values (Figure S1),[15] and calculated Log$P$ values. (B) Equilibrium between trigonal planar and tetrahedral species of boron in BOL.[15] (C) Minimal orbital overlap between the boron and the carboxy group slows oxidation.[15] (D) FDA-approved antifungal agent.[16] (E) FDA-approved PDE4 inhibitor.[17] (F) Preclinical transthyretin stabilizer.[15] (G) Preclinical HIV-1 protease inhibitor.[18]

storage. In addition, benzoxaborolones do not form boroxines through dehydration.

Having identified this stable boron-based pharmacophore, we have begun to design, synthesize, and study the stability and activity of BOL-based inhibitors of protein targets known to be inhibited by less oxidatively stable boronic acid drugs.[15] In doing so, an important consideration arose—does the electron-withdrawing (EW) or electron-donating (ED) nature of a substituent on the phenyl moiety of BOL impact oxidative stability? A variety of ED/EW substituents are present on the phenyl moieties of both FDA-approved and preclinical boron-based drugs, including EW sulfonamide, fluoro, and phenoxy groups and ED alkenes (Figure 1D–G). Herein, we sought to evaluate the impact of EW and ED substituents on the stability of the BOL pharmacophore, both experimentally and computationally, and to inform medicinal chemists on linkage selection for the incorporation of BOL into pharmaceutical leads. Further, the borolactone scaffold presents synthetic challenges, and we provide a blueprint for the synthesis of BOL-containing molecules using a diversity of borylation and deprotection strategies.

RESULTS AND DISCUSSION

Synthetic Strategies. We generated a panel of benzoxaborolones with EW and ED groups at the C4 or C5 position, as defined in Figure 1B, with the boron-bound carbon as C1 and depicted explicitly in Scheme 1 and Figure S2. The panel included commercially available EW fluoro- and chloro-substituted BOL. We synthesized trifluoromethyl- and nitro-substituted benzoxaborolones to expand the range of EW effects. To evaluate increasing ED effects, we synthesized methyl- and methoxy-substituted BOL.

Due to their long-standing use in organic chemistry as substrates for cross-coupling reactions, boronic acids have been synthesized via numerous methods.[20,21] Nevertheless, the presence of the EW *ortho* carboxy group presents a new challenge for boron installation and deprotection that is relatively untouched by the literature. The EW *ortho* carboxy group is not only an additional reaction center that requires the installation and removal of protecting groups, but also imparts a steric and electronic influence on the reactivity of C1 for borylation. The combination of a borylation reaction and protection and deprotection strategy for all synthetic benzoxaborolones reported herein was chosen empirically based on the isolation of products with a yield and purity sufficient for experimental studies of oxidation. Synthetic procedures were facilitated by the use of 10-hydroxybenzo[*h*]quinolone as a stain for benzoxaborolones after thin-layer chromatography.[22]

For substituents *para* to the carboxylic acid, a directed *ortho* metalation[23,24] was used for borylation *ortho* to the carboxy group, as in the syntheses of compounds **6b** (C5−OCH_3), **8b** (C5−CH_3), and **12b** (C5−CF_3) (Scheme 1). A symmetric aryl substrate for borylation is required to avoid a mixture of products with this strategy. The more commonly used Miyaura borylation[25,26] strategy proved useful in the synthesis of compounds **7c** (C4−OCH_3), **9d** (C5−CH_3), **10d** (C4−CH_3), **14c** (C5−NO_2), and **15c** (C5−NO_2), but these reactions require large amounts of a costly palladium catalyst, proceed slowly, and often require several purification steps. A Grignard-type borylation strategy[27] was used for the synthesis of compound **13c** (C4−CF_3), which, like the directed *ortho* metalation strategy, is rapid and requires less extensive workup. This strategy has the added benefit, as does the Miyaura borylation, of functioning with both symmetric and non-symmetric benzoic acid starting materials. A methyl ester or *tert*-butyl ester was chosen as the carboxylic acid protecting group (R^2 in Scheme 1A,B). A methyl ester protecting group was not compatible with the directed *ortho* metalation strategy but facilitated removal with a weak base such as sodium bicarbonate, which limits base-mediated deboronation. We found that the protection of the carboxylic acid as a *tert*-butyl ester was compatible with all three borylation strategies. When employing the directed *ortho* metalation strategy, an isopropyl borate substrate was used as the borate donor. These isopropyl protecting groups on the boron were easily removed by anhydrous acid in an organic solvent. A pinacol borate donor was employed in the Miyaura and Grignard-type borylation strategies. Three previously reported pinacol borate deprotection strategies worked with differing degrees of success, depending on the substrate and, specifically, its solubility in the deprotection conditions. The pinacol borate was either oxidized via sodium periodate,[28] hydrolyzed via transesterification with methyl boronic acid,[29] or transformed into a trifluoroborate intermediate that could be isolated and transformed (via fluoride capture) into the boronic acid (Scheme 1B,C and Supporting Information).[30]

A principal challenge in the synthesis of these compounds is protodeboronation during borylation, which can dramatically reduce product yields. Additionally, oxidative deboronation or protodeboronation occurs to varying degrees during pinacol boronate deprotection and acid- or base-mediated deprotection of the carboxylic ester protecting group. We found that the unprotected arylboronic acid with a protected 2-carboxy ester is highly susceptible to oxidation and should be flushed

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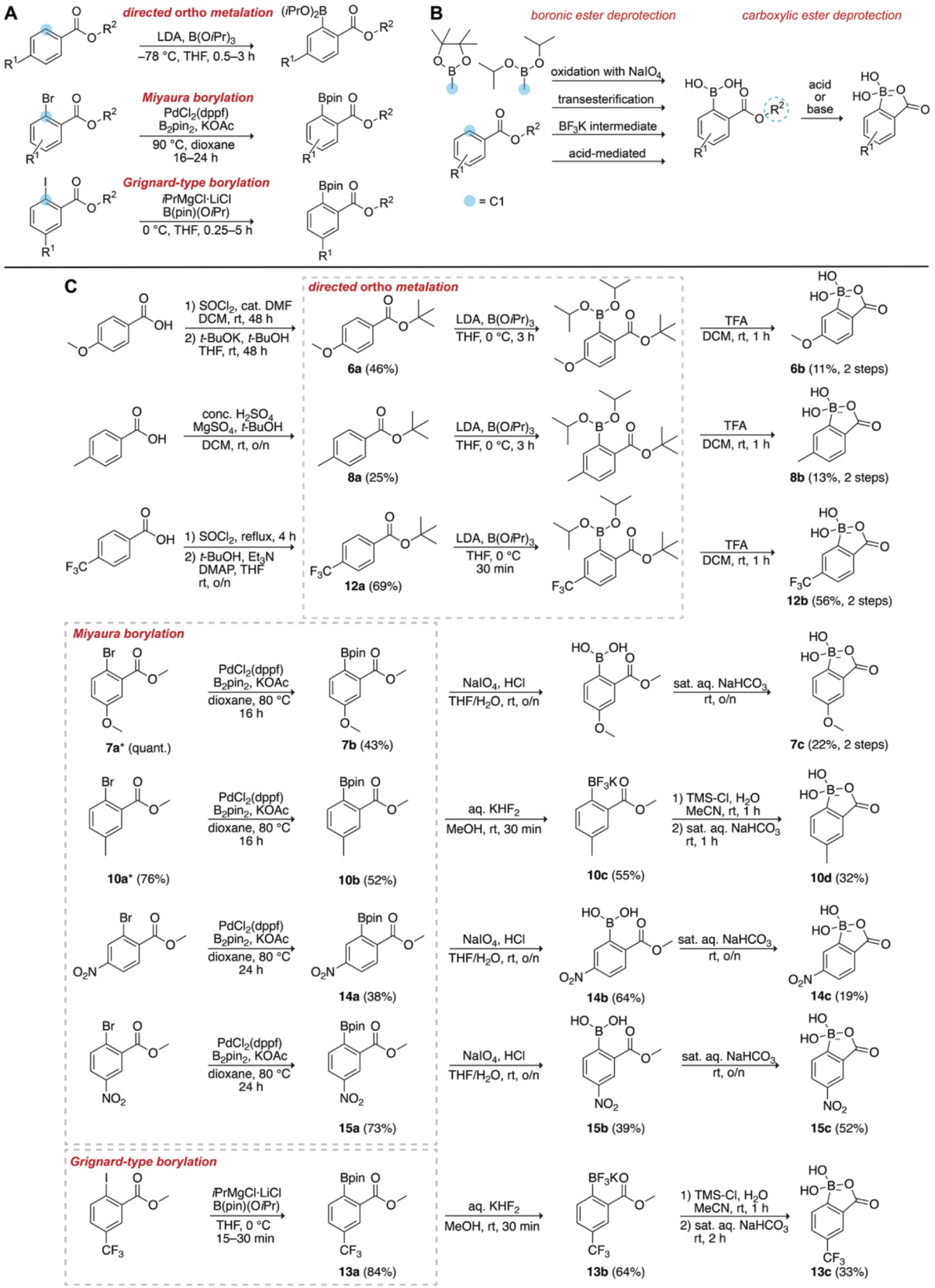
Scheme 1. Borylation Strategies (A) and Ester-Deprotection Strategies (B) for the Synthesis of Benzoxaborolones (C)[a]



[a]Esters 7a and 10a were prepared by Fischer esterification of the cognate acids as described in the Supporting Information.

with an inert gas and stored at −20 °C. Whereas the acid or base carboxylic ester deprotection conditions can lead to protodeboronation, rapid ester deprotection and concurrent cyclization of the carboxylic acid with the boron leads to a

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highly stable configuration. The deprotected boronic acid derivative is poorly compatible with silica chromatography due to strong interactions with stationary phase hydroxy groups. Hence, reversed-phase purification should be used to purify these polar hydrophilic benzoxaborolones. Altogether, these synthetic hurdles can culminate in low yields of benzoxaborolones, as evident in Scheme 1C, which reports unoptimized isolated yields.

Oxidation Kinetics. The experimental rates of oxidation by H_2O_2 for each substituted BOL were determined by UV spectroscopy as reported previously.[15] H_2O_2 was chosen as the oxidant because it is the most biologically abundant ROS[31,32] and therefore most relevant for pharmaceutical development. Moreover, H_2O_2 is not a free-radical oxidant, which simplifies experimental analyses. In addition, the mechanism of H_2O_2-mediated oxidation of aryl boronic acids is well-known.[33] H_2O_2 is an ambiphilic oxidant, having two-electron electrophilic reactivity in the O−O bond and nucleophilic character from the adjacent nonbonding orbitals of two oxygens, contributing an α-effect.[14,34,35] When the boron p-orbital reacts with the nucleophilic peroxy anion species, the B−C bond in turn becomes nucleophilic in the anionic tetrahedral boronate geometry and will engage in a 1,2-shift with the bound peroxy group, breaking the electrophilic O−O bond. The transition state for the rate-limiting step of this mechanism involves a concerted breakdown of the B−C bond and formation of the B−O bond, in which the developing p-orbital is stabilized by electron donation from the other two boron-bound oxygens. With benzoxaborolone, this stabilization is significantly reduced, slowing the 1,2-shift (Figure 1C).[15]

The oxidation product, salicylic acid, has a characteristically strong absorbance between 275 and 300 nm,[36] whereas this absorbance is nearly absent in BOL (Figure 2). The rate of

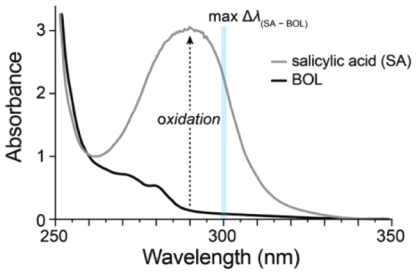

Figure 2. Absorbance spectrum of benzoxaborolone (BOL) and its salicylic acid (SA) oxidation product in 0.10 M sodium phosphate buffer, pH 7.4, at room temperature.

oxidation has been shown to be second-order with respect to the boronic acid derivative and H_2O_2 concentrations.[37,38] Using known concentrations of each reagent along with experimentally determined extinction coefficients of oxidation (Table S1 and Figures S3 and S4), we measured the increase in absorbance over time to derive second-order rate constants for oxidation by H_2O_2 (Table S1). The rate constants had a range of ~40-fold, from 1.9×10^{-5} M^{-1} s^{-1} for compound **8b** to 7.3×10^{-4} M^{-1} s^{-1} for compound **2**. A representative subset of the data, plotted relative to the rate of oxidation (k_{rel}) of benzoxaborolone itself, is shown in Figure 3A.

As expected, the presence of ED groups on C4 or C5 of the aryl ring increases k_{rel}, whereas the presence of EW groups on C4 or C5 of the aryl ring decreases k_{rel} (Figure 3A). This trend can be explained by both the inductive and mesomeric effects of ED and EW groups on the partial positive charge that develops on C1 during the breakdown of the B−C bond during oxidation (Figure 3B). ED groups reduce the magnitude of the developing partial positive charge on C1 during oxidation, stabilizing the transition state. In contrast, EW groups increase the magnitude of the partial positive charge on C1, destabilizing the transition state.

An ED methoxy group on C4 leads to a higher reaction rate relative to its C5-substituted counterpart, likely due to additional electron density on C1 from mesomeric donation (Figure 3B). An ED methyl group on C5 minimally donates electron density to C1 through mesomeric effects (Figure 3B) and must rely on donation through induction into the π-system, and possibly hyperconjugation into a neighboring electron-deficient sp^2 carbon. The methyl group on C5 is more electron-donating through induction than is the methoxy group, leading to greater stabilization of the transition state and faster oxidation, as we observed experimentally.

EW groups on C4 have the opposite effect, with both inductive and mesomeric effects withdrawing electron density from C1 and destabilizing the transition state. EW groups on C5 rely solely on inductive effects, albeit stronger than those imposed by EW groups on C4. The weaker inductive effect, combined with mesomeric contributions of EW groups on C5, is likely similar in magnitude to the lone inductive effects by C4 EW groups. Yet, the value k_{rel} when a fluoro group is on C5 is notably lower than when the fluoro group is on C4. On C4, a fluoro group destabilizes the transition state of oxidation through inductive effects, but these effects are slightly counteracted by weak mesomeric donation. A fluoro group on C5, however, more strongly influences C1 reactivity through inductive effects alone, consistent with the observed difference. Smaller but similar consequences are observed for chloro groups. Trifluoromethyl and nitro groups are both strongly EW, influencing C1 through inductive effects. Unlike a trifluoromethyl group, a nitro group can withdraw additional electron density through mesomeric effects, which we observe experimentally in a comparison of the two nitro-containing compounds. Based on these data, it is also possible that the k_{rel} observed for the EW groups tested is nearing the lower limit of k_{rel} that is achievable for BOL oxidation by H_2O_2.

In our analysis (Figure 3B), we only consider the influence of ED and EW groups on C1. These substituents likely affect the oxidative stability of benzoxaborolone through inductive and mesomeric effects on the carboxy group on C2 as well. Thus, a second mechanism for stabilization/destabilization is likely at play, precluding a traditional Hammett analysis.[39−41] In one scenario, these substituents might alter the stability of the B−O ester bond. A weaker B−O ester bond could increase the pK_a of the boronic acid and shift the population from tetrahedral to trigonal boronic acids.

To investigate this and any other impacts of the ED or EW groups on the electron density of the boron, we performed proton decoupled ^{11}B NMR analyses of each compound in a 1:1 mixture of deuterated phosphate buffer/CD_3CN with a pD of 7.2. The traditional boron NMR standard $BF_3{\cdot}OEt_2$ is not amenable to aqueous solvent systems due to its rapid and hazardous hydrolytic decomposition. Instead, a small amount of boric acid was used to provide a reference ^{11}B signal.

In each spectrum, we observed two distinct peaks: one for the boric acid reference (20 ppm) and one for the tetrahedral benzoxaborolone (8.08−12.36 ppm), summarized in Table S3. The absence of an additional peak around 28−32 ppm, which

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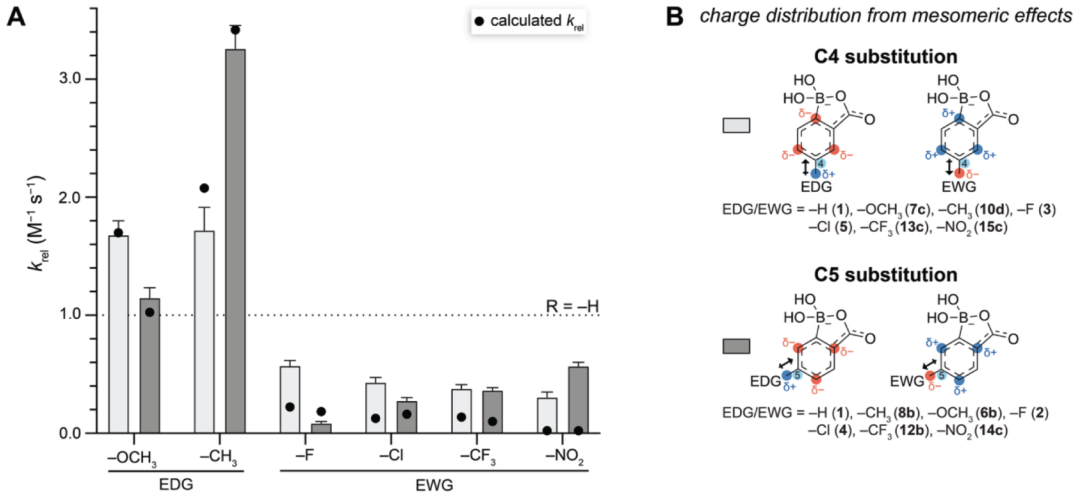

Figure 3. (A) Bar graph of k_{rel} values for the H_2O_2-mediated oxidation of benzoxaborolones. Values are the mean ± SE for three replicates. Computationally predicted k_{rel} values are indicated with black circles. (B) Expected mesomeric electron delocalization depending on substituent type (ED or EW) and location (C4 or C5).

is typically observed for trigonal boronic acids, confirms the strength of the B−O ester bond and the dominance of the tetrahedral boron. EW groups could deshield the boron and produce downfield shifts, whereas ED groups could shield the boron and produce upfield shifts. We did not observe any trends in the ^{11}B NMR spectra that reflect this scenario, consistent with the multifaceted effects of EW and ED groups on this molecular system.

To frame the data in terms of biological relevance and to answer the question as to whether ED/EW groups could substantially influence the stability of the benzoxaborolone pharmacophore in small molecules, we must compare these rates of oxidation to those of widely used aryl boronic acids. We determined the rate constant of oxidation of 4-nitrophenylboronic acid (**16**) by H_2O_2. This rate constant was compared to the rate of oxidation for BOL functionalized with a nitro group on C4 (**15c**). We found that the rate constant for the oxidation of 4-nitrophenylboronic acid by H_2O_2 is >10^4-fold greater than that of its cognate benzoxaborolone (Figure 4). This difference far exceeds that observed between benzoxaborolones functionalized with different ED and EW groups (Figure 3).

Computational Analyses. Finally, we used density functional theory to calculate the free energy of activation ($\Delta G^{\ddagger}$) for the oxidation transition state (Figure 1C) of all of the benzoxaborolones that were assessed experimentally. We used these values of $\Delta G^{\ddagger}$ to derive values of k_{rel} for the substituted benzoxaborolones relative to BOL itself. (Table S2). Gratifyingly, the computationally derived k_{rel} values corresponded well to the experimentally determined values (Figure 3).

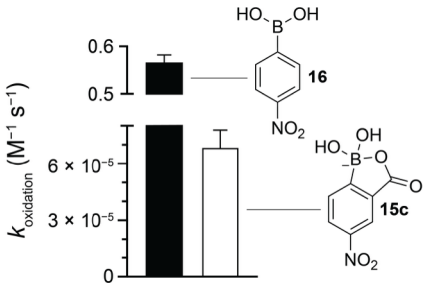

Figure 4. Bar graph of $k_{oxidation}$ values for the H_2O_2-mediated oxidation of 4-nitrophenylboronic acid (**16**) and its cognate benzoxaborolone (**15c**), which differ by 8.3 × 10^3-fold. Values are the mean ± SE for 3 replicates.

CONCLUSIONS

Benzoxaborolones have recently been developed as oxidatively stable aryl boronic acids with high applicability for development as versatile pharmacophores. Herein, we have shown that the chemical characteristics for the point of attachment of benzoxaborolone to other molecular scaffolds have a small but predictable impact on their oxidative stability. Generally, ED groups increase the rate of oxidation, whereas EW groups decrease that rate. Further, we demonstrate a variety of synthetic routes to prepare these recently developed aryl boronic acids, taking care to navigate the additional challenges presented by the *ortho* carboxy group.

MATERIALS AND METHODS

See the Supporting Information.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.5c01467.

Procedures for the synthesis and analysis of all compounds, Tables S1−S3, Figures S1−S4, and computational Gibbs free energies and optimized Cartesian coordinates (PDF)

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Notes

The authors declare no competing financial interest.

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