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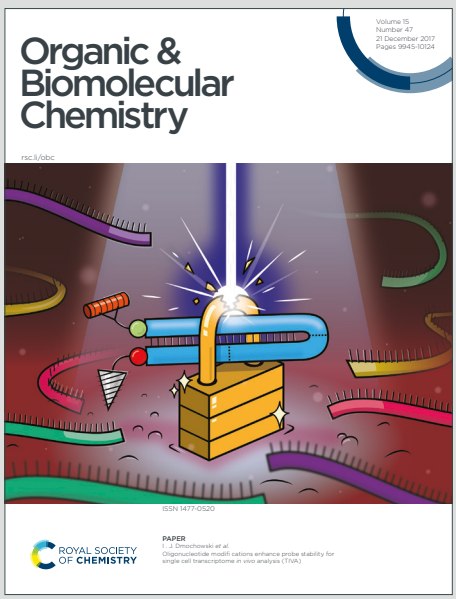

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ARTICLE

Synthesis and physicochemical evaluation of phosphorus(III) and phosphorus(V) substituted benzoxaboroles

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ABSTRACT: This study presents a one-pot synthesis of phosphorus(III) benzoxaboroles using hypophosphorous acid to yield H-phosphinates. These H-phosphinates, together with their phosphonate congeners, were systematically evaluated for their physicochemical properties, including pK_a, diol-binding affinity, and oxidative stability in buffer. The presence of the phosphorus atom as either phosphorus(III) or phosphorus(V) provided high aqueous water solubility. The results demonstrated that the nature of the phosphorus substituent significantly influenced the acidity and binding behavior of the benzoxaborole core. Notably, the phosphorus(III) derivatives exhibited strong diol binding and exceptional oxidative resistance. Overall, this work introduces new H-phosphinyl and phosphoryl substituents to tune organoboron properties for use as sensors, therapeutics, or chemical probes.

INTRODUCTION

Alkyl boronic acids and benzoxaboroles offer unique opportunities in drug discovery due to their ability to form reversible covalent bonds with biological targets, enabling precise modulation of target activity.[1] The proteasome inhibitor bortezomib was approved to treat multiple myeloma and functions by interacting with a nucleophilic threonine residue.[2,3] The fungal leucyl-^{t}RNA synthetase inhibitor, tavaborole, was approved to treat topical fungal infections and functions by coordinating to the 2,3-ribosyl diol.[4] The phosphodiesterase-4 inhibitor crisaborole, was approved to treat atopic dermatitis. [5] The evolution from boronic acids to benzoxaboroles underscores the benefits of exploring diverse boron-containing functionalities. This progression not only refines pharmacodynamic drug properties, but also highlights boron's versatility in drug discovery and future promise in discovering treatments for unmet medical needs.[6]

The capacity of boron-containing functionality to form reversible covalent bonds with diols also drives applications in biosensing, diagnostics, therapeutics,[7,8] and catalysis (**Figure 1**).[9] This binding mechanism involves nucleophilic attack by vicinal diol oxygen atoms on the electron-deficient boron center, generating a cyclic boronate ester.[10,11] Many boron-containing systems have been devised to monitor glucose concentrations in a biological context for diabetes management,[8,12,13] and several have been commercialized.[14,15]

Despite their utility, boronic acids face significant stability challenges in biological environments. These challenges arise primarily from two decomposition pathways: protodeboronation and oxodeboronation. Protodeboronation proceeds via pH-dependent mechanisms—acid-catalyzed electrophilic substitution (B replaced by H), or base-catalyzed hydrolysis of the boronate anion at high pH.[16] Oxodeboronation is the dominant degradation route in physiological systems, where oxidative C–B bond cleavage yields the corresponding alcohol.[17,18] To address oxidative stability—a critical property for biological applications—strategies focusing on boron's electronic and geometric properties have been developed.[18] In this work, we explore the effects of substituting the benzoxaborole ring with phosphorus substituents.

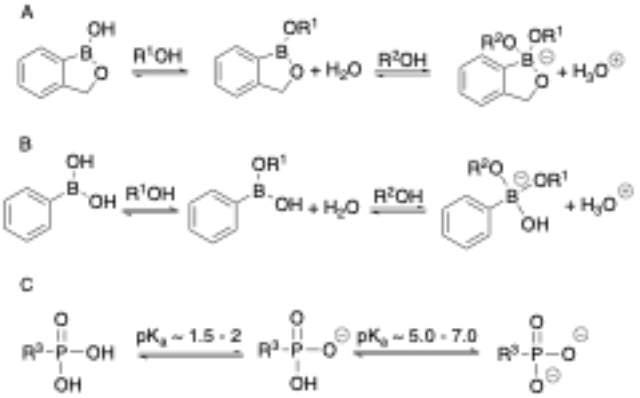

Figure 1. Lewis acidity of organoboron acids with alcohols, when pH < pK_a. A) benzoxaborole; B) phenylboronic acid. R^1-R^2 linked for diols, C) Brønsted acidity of phosphonic acids. R^3 for alkyl or aryl.

When discussing the acidity of boronic acids, it's essential to distinguish between Brønsted acidity—the ability to donate a proton (H^+)[19]—and Lewis acidity, which involves the boron atom acting as an electron pair acceptor.[20] This Lewis acid–base equilibrium has an associated apparent pK_a, which reflects the solution-phase acidity of the boron center[21] — not proton donation, but rather its affinity for nucleophilic attack.[22] The pK_a being discussed in this work corresponds to the Lewis acidity of boronic acids—specifically, the equilibrium between the neutral boronic acid and its anionic boronate form in aqueous solution. Ultimately, it is the Lewis acidic behavior of the boron center that is being investigated, not a Brønsted acid dissociation, which is not commonly observed in boronic acids.[9]

Hypophosphorous acid (H_3PO_2) and its salts serve as versatile reducing agents in organic synthesis, leveraging their reactive P–H

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bonds to enable hydride transfer or radical-based mechanisms under mild conditions.[23,24,25] Beyond reduction chemistry, recent breakthroughs exploit H_3PO_2 as a multifunctional synthon for sustainable organophosphorus synthesis. These advances enable microwave-assisted hydrophosphinylation of unactivated alkenes for rapid P–C bond formation[26], Brønsted acid-mediated Meyer-Schuster metal-free rearrangements of propargylic alcohols to access enones[27], stereoselective separation of phosphinic acid diastereomers via cyclic adduct formation[28], and solvent-free Phospha-Mannich reactions under microwave irradiation to efficiently synthesize bioactive α-aminophosphinic acids[29]—collectively highlighting H_3PO_2 dual role as a synthon and reaction mediator for green, high-yield methodologies in pharmaceutical applications.

Herein, we report the use of hypophosphorus acid in the synthesis of benzoxaborole derivatives functionalized with phosphorus in the phosphorus(III) (H-phosphinate) oxidation state. The compounds, together with phosphorus(V) congeners, were evaluated for their pK_a, diol-binding, and oxidative properties, to inform pharmacodynamic potential.[30,31,32]

RESULTS AND DISCUSSION

SYNTHESIS

The general procedure for the synthesis of boronic acid phosphorus(III) species via reaction of formylphenyl boronic acid derivatives with hypophosphorus acid is outlined in **Figure 2**. The hypophosphorus acid-mediated cyclization was initially investigated using formylphenylboronic acid, which underwent efficient cyclization to afford the benzoxaborole-phosphorus(III) species in excellent yield (99 %). Reaction progress was monitored by thin-layer chromatography (TLC). Following completion, the crude product was characterized directly by ^{1}H and ^{31}P NMR. The spectra indicated the formation of the product in high purity without the need for chromatographic purification. The ^{1}H NMR spectrum exhibited complete disappearance of the aldehyde proton resonance (δ ~9.8 – 10.2 ppm), consistent with conversion of the aldehyde to the benzoxaborole scaffold. Concurrently, the ^{31}P NMR spectrum revealed a distinct doublet at δ 23.86 ppm ($^1J_{PH}$ = 532 Hz), indicative of a P–H moiety in the PIII species. The observed coupling constant aligns with literature-reported values for H-phosphinates ($^1J_{PH}$ ≈ 515 – 520 Hz).[7] This spectroscopic evidence corroborates the formation of the target phosphorus(III) benzoxaborole structure. A proposed mechanism is outlined in **Figure 2C**.

Subsequent evaluation of the substrate scope demonstrated that electron-donating substituents (e.g., -OMe) and the 4-chloro derivative on the aryl ring of formylphenylboronic acid afforded the corresponding benzoxaborole-phosphorus(III) products in high yields (75 - 99 %). By contrast, substrates bearing fluorine atoms (e.g., 3- or 6-fluoro) exhibited diminished yields (40 - 65 %), attributed to incomplete cyclization or partial hydrolysis during aqueous workup. Notably, all reactions proceeded with high functional group tolerance, and products were isolated in moderate to excellent yields (40 - 98 %) without requiring chromatographic purification. Reaction times were not optimized for the less reactive substrates.

NMR spectroscopic analysis of the product in deuterated water (D_2O) revealed a slow proton - deuterium exchange for the hydrogen atom directly bonded to phosphorus (**Figure 3**). This dynamic process induced a characteristic 1 : 1 : 1 splitting pattern in the ^{31}P NMR spectrum, arising from scalar coupling between phosphorus and deuterium. This spectroscopic evidence corroborates the presence of a P–H bond within the benzoxaborole framework, confirming the successful formation of the H-phosphinate-benzoxaborole. The retention of coupling under aqueous conditions further underscores the stability of the P–H bond in this moiety.

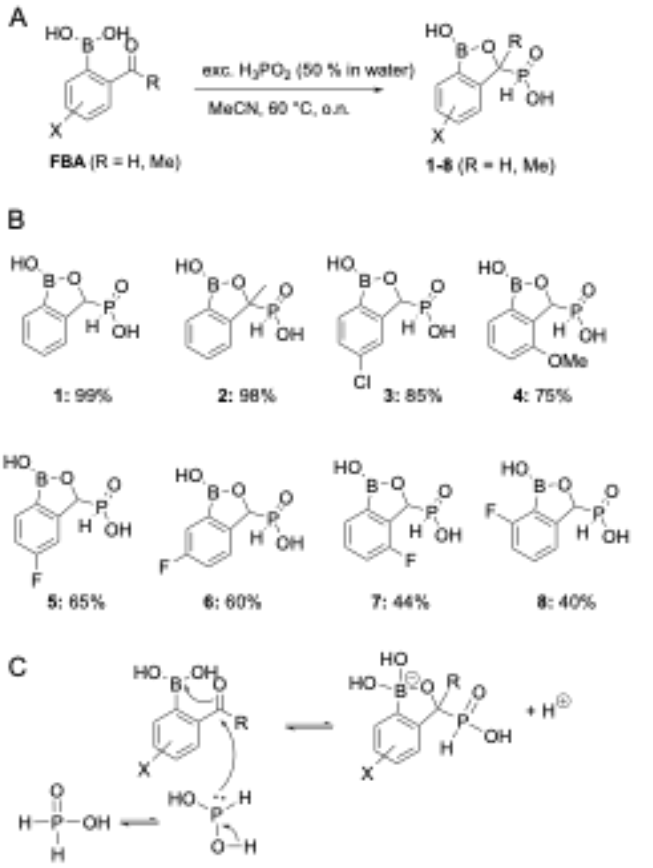

Figure 2. (A) One-pot synthesis of benzoxaborole derivatives containing a phosphorus(III) Functionality, (B) reaction scope, (C) proposed mechanism including the equilibrium forms of hypophosphorus acid.

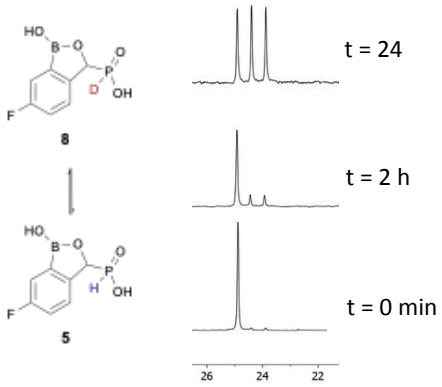

Figure 3. ^{31}P NMR spectra P-H / D exchange of compound **6** (66 mM in D_2O) over 24 h.

In addition to the hypophosphorous acid-mediated cyclization approach, we have established a series of synthetic steps to access benzoxaborole-derived compounds functionalized with phosphorus-based groups in the +5 oxidation state (**Figure 4**). These phosphorus(V)-containing derivatives were designed as structural

analogs of the earlier phosphorus(III) species to enable comparative analysis of their behaviour in systematic evaluations of physicochemical characteristics (e.g., pK_a and oxidative behaviour) and their binding affinity for diol-containing substrates.

Our initial efforts targeted the development of novel dealkylation products derived from diethyl phosphonate benzoxaborole **9**, a key intermediate synthesized via a Pudovik reaction between 2-formylphenylboronic acid and diethyl phosphite using K_2CO_3 (**Figure 1**).[32] To evaluate boron's compatibility with trimethylsilyl (TMS) halide-mediated dealkylation of phosphonate esters within the same molecular framework, we investigated the reactivity of diethyl phosphonate **9** under standard desilylation conditions. While TMS halides (e.g., TMSBr, TMSCl) are well-established for mild deprotection of phosphonate alkyl esters[33–35], their application in boron-containing systems remains unexplored. Treatment of **9** with TMSBr in anhydrous dichloromethane efficiently cleaved the ethyl groups via sequential nucleophilic displacement, generating a transient silyl phosphonate intermediate. Subsequent hydrolysis under controlled acidic conditions (pH 4 – 5, H_2O / THF) afforded the corresponding phosphonic acid in 98 % yield. The reaction mixture was adjusted to pH 9 prior to lyophilization, preserving the benzoxaborole scaffold.

Additionally, TMSCl with NaI (in situ generation of TMSI) also effected mono dealkylation of **9** (75 % yield) to furnish **10**. Both phosphonic acid derivatives were synthesized to systematically assess (i) the influence of ionizable phosphonic acid groups on the pK_a of the benzoxaborole moiety, (ii) diol-binding affinity via Alizarin Red S / dopamine titration, and (iii) oxidative stability under physiological conditions.[18]

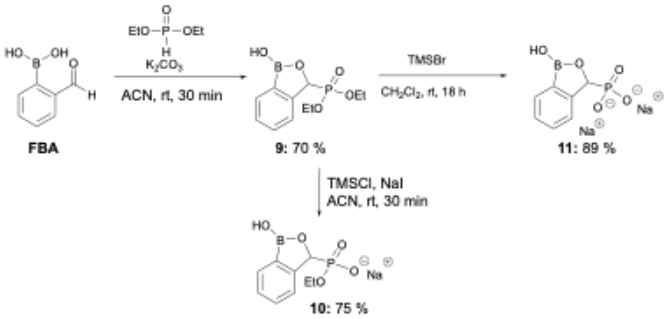

Figure 4. Synthesis of benzoxaborole derivatives containing a phosphorus(V) functionality.

PHYSICOCHEMICAL MEASUREMENTS

PK_A STUDIES

The physicochemical behavior of the synthesized phosphorus substituted benzoxaboroles (**1**, **9** - **11**) was examined first by systematic investigation of their pK_a values, focusing on the ionizable boron and phosphorus functionality. These compounds feature distinct Lewis and Brønsted acidic sites: (i) the benzoxaborole moiety (B–OH) and (ii) the phosphonic/phosphinic acid group (P–OH).

The coordination state of boron—whether sp^2 (trigonal planar) or sp^3 (tetrahedral)—fundamentally governs the reactivity and stability of boronic acids. In their native sp^2-hybridized form, boronic acids exhibit electrophilic character due to the vacant p orbital, transitioning to an sp^3-hybridized state, enabling interactions with nucleophiles such as diols or amines, which drive inhibition, sensing and catalysis.[2,8,10,18,20,22,36]

Prior studies report pK_a values of 6–9 for arylboronic acids, 7–8 for benzoxaboroles.[37,38] Phosphonic acids exhibit two ionizable functionalities. The first deprotonation typically occurs at a pK_a of 1.5–2.0, while the second deprotonation occurs at a higher pK_a, generally in the range of 5.0–7.0.[39–41] In contrast, H-phosphinic acids, which contain only one ionizable functionality, display a single pK_a value typically in the range of 1.5–2.0.[39,41] The pK_a investigation would provide insight into the proximity effects of the different ionisable functionality.

Solutions of each compound (10 mM) were adjusted to pH 3-10 by titrating deuterated HCl and NaOH (1M and 5 M). ^{1}H, ^{11}B and ^{31}P NMR spectra were recorded for each compound ranging from pH values 3 – 10 (**Figure 5**). For each ^{1}H spectrum, the least ambiguous signal was chosen to determine the chemical shift at that pH, which was then plotted against the pH. For ^{11}B and ^{31}P spectra only one signal was observed, which was plotted similarly. Using a non-linear fit (Grafit, Erithacus Software) yielded the pK_a values of each compound. Due to the use of deuterated solutions a correction factor of 0.42 was applied to all obtained values to yield the pK_a in H_2O.[42–44]

Compound **9** (**Figure 5A**), contains only a single Lewis acidic group, the boronic acid. All three nuclei exhibited the same pK_a of 5.77 (**Table 1**), indicating that nuclei remote from the boron atom report the ionization change. This compound is the most acidic benzoxaborole evaluated, herein, and is one of the more acidic benzoxaboroles reported.[38]

Compound **1** (**Figure 5B**) contains, in addition to the ionizable benzoxaborole, one ionizable group on the phosphinic acid, which has a pK_a around 2 for a phosphorus(III) species. Given the pH range examined, this phosphinic acid would remain ionized throughout our study. Thus, the change in phosphorus chemical shift reports on the ionization at boron. The ^{1}H and ^{31}P NMR measurements resulted in essentially identical pK_a values (7.7) whilst the boron pK_a was determined to be 7.3. However, given the difficulty assigning chemical shifts to the boron resonance either side and at neutral pH, due to the broad signal, rationalizing the discrepancy between the ^{11}B and ^{1}H / ^{31}P data using chemical inference is likely inconsequential.

Compound **10**, a monoethyl phosphonate with a phosphorus(V) oxidation state, was found to be the least acidic benzoxaborole, with pK_a values ranging from 8.2 to 8.5. As with **1** and **11**, interpretation is complicated by discrepancies between the ^{11}B and ^{31}P NMR data - likely due to challenges in assigning the broad ^{11}B chemical shifts. The substantial increase in pK_a by more than two pH units between **9** and **10** is attributable to the ionization already present on the phosphorus(V) species (**Table 1**).

Compound **11 (Figure 5C**) features two ionizable phosphorus (V) groups in addition to the benzoxaborole scaffold. pK_a values were determined to be between 6.32 and 6.62. Counterintuitively, the acidity of **11** sits between that of **10** and **9**. Two molar equivalents of deuterated HCl and NaOH were consumed during this ionization, indicating that both the phosphonate and benzoxaborole were ionized, again the broad 11B NMR signals precluded determination of the order of ionization at boron or phosphorus.

Taken together, these pK_a findings demonstrate that the nature of the phosphoryl functionality modulates the benzoxaborole ionisation over 2.5 pH units, providing a new mechanism to tune the acidity of the benzoxaborole.

Table 1: pK_a values determined from pH titration experiments using NMR spectroscopy[a,b]

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Compound	^{1}H NMR	^{11}B NMR	^{31}P NMR
1	7.68 ± 0.03	7.280 ± 0.027	7.69 ± 0.03
9	5.77 ± 0.09	5.77 ± 0.08	5.76 ± 0.08
10	8.46 ± 0.08	8.20 ± 0.09	8.51 ± 0.11
11	6.44 ± 0.05	6.32 ± 0.11	6.619 ± 0.061

[a] Errors represent mean ± standard deviation. [b] Correction of 0.42 pH units applied to account for D_2O.[42–44]

DIOL BINDING STUDIES

Investigations into the ability of the phosphorus-substituted benzoxaboroles to bind diols commenced with an Alizarin Red S (ARS) binding assay, first developed by Wang and Springsteen to measure association constants of boronic acids with diols.[11,37,45] Thus, solutions of ARS (0.1 mM, in PBS 0.1 M, pH 7.4) were titrated with boronic acid derivatives (0.05–2 mM in 0.1 M PBS, pH 7.4). Binding interactions were monitored via UV-Vis spectroscopy by observing a shift in absorbance from 520 nm to 460 nm, causing a visible colorimetric shift from red to yellow. Association constants (K_a) were calculated from data at 460 nm using Thordarson's approach[46,47] as we have undertaken previously.[48,49]

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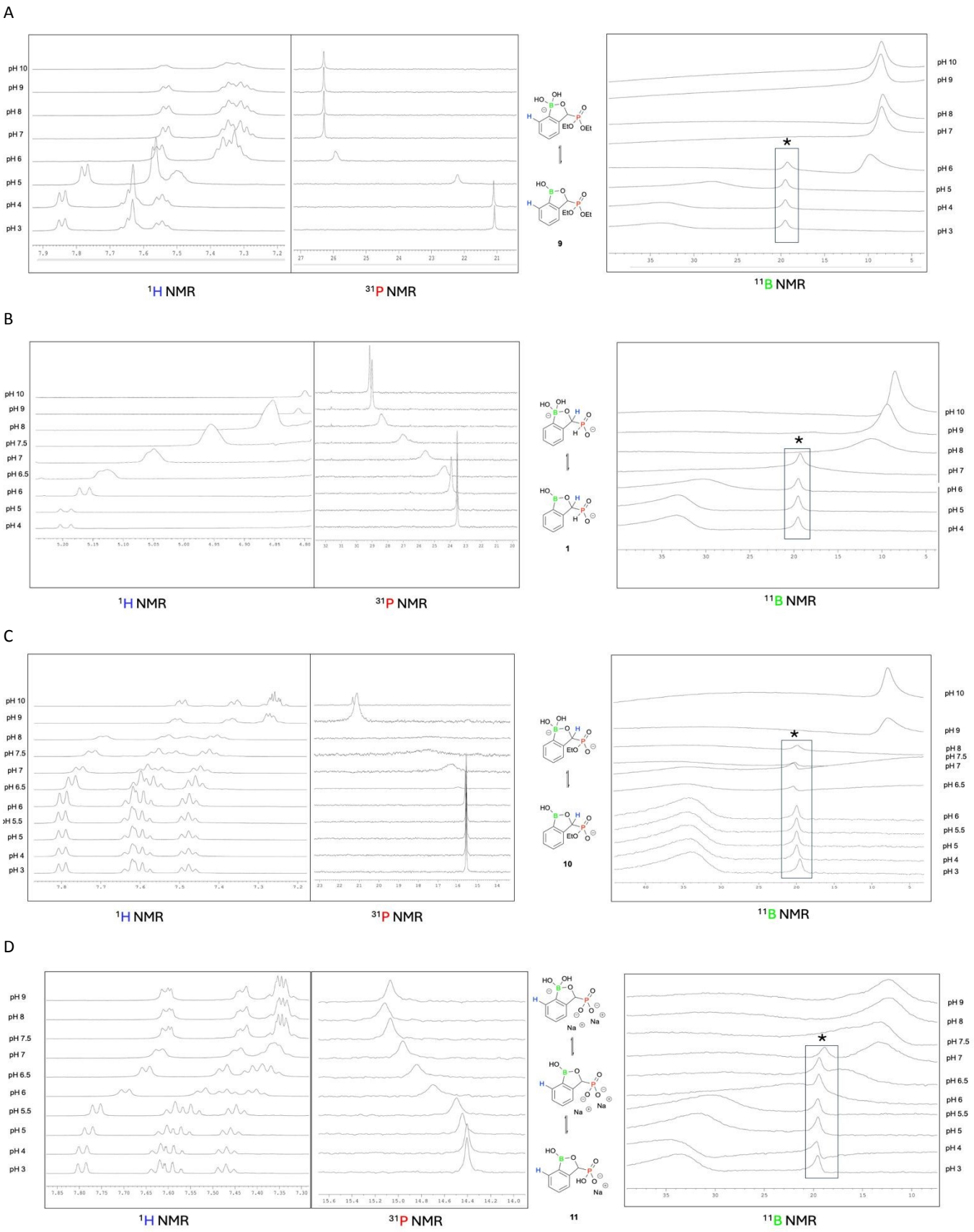

Figure 5. pH-titrations: ^{1}H, ^{11}B and ^{31}P NMR (A) **9**, (B) **1**, (C) **10** and (D) **11** *Boric acid

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The ARS binding assay demonstrated diol-binding interactions between the benzoxaboroles and ARS, with the magnitude of binding varying significantly depending on the benzoxaborole (**Table 2**). The two control compounds, phenylboronic acid and benzoxaborole, bound with significant affinity, consistent with literature reports.[45,50] Of the phosphorus-substituted benzoxaboroles, the most potent was **1**, the phosphorus(III) derivative, with an affinity approximately $^1/_3$ that of benzoxaborole. The next most potent was **9**, the phosphorus(V) diethyl ester derivative, with an affinity of $^1/_6$ that of benzoxaborole. **10** and **11** did not demonstrate any interaction with ARS under these assay conditions. This result seemed counterintuitive, given that both the more sterically hindered **9,** and the less sterically hindered **1,** showed binding, despite the phosphoryl functionality being on the opposite side of the benzoxaborole ring. Both **10** and **11** have anionic charge associated with them at physiological pH (through the phosphonic acid), and potentially there could exist an electrostatic repulsion between the phosphonic acid and the sulfonic acid present on ARS. Few reports describe the ARS assay involving methylene-substituted benzoxaboroles, and potentially this indicates that there are limitations to the utility of the ARS assay.

In order to determine whether the benzoxaborole **10** and **11** bound a representative diol, an alternative binding assay was devised utilizing dopamine (**Figure 6, Table 2**). Dopamine (DA) contains a catechol functionality, similar to that of ARS, and also a primary amine that is protonated at physiological pH, ensuring aqueous solubility. Thus, dopamine was switched for ARS, and titrated with increasing concentrations of phosphorus-substituted benzoxaboroles.

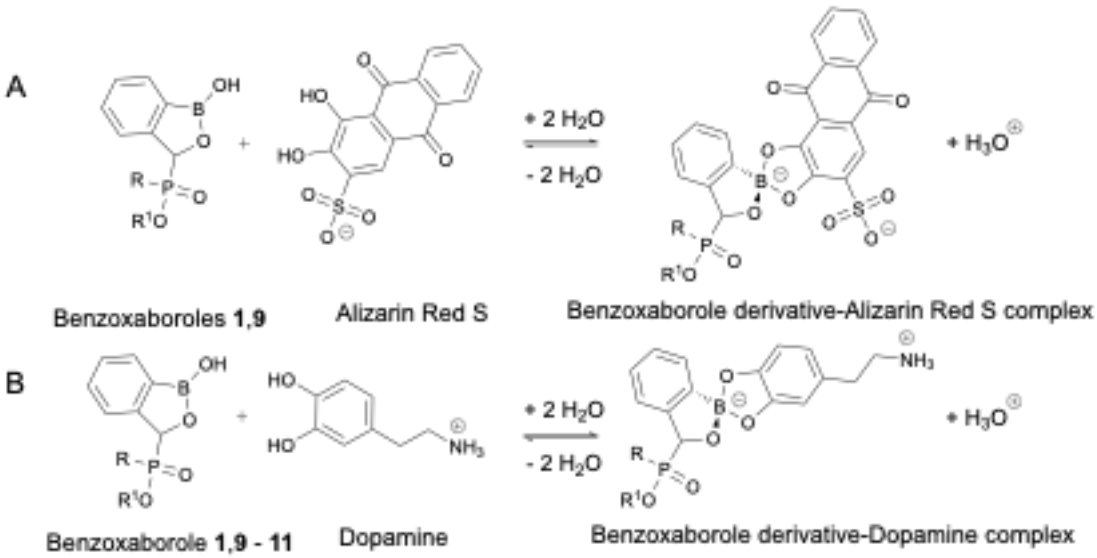

Figure 6. Binding equilibria between benzoxaborole derivatives and (A) alizarin Red S and (B) dopamine[a]

[a]Binding studies were carried out in 0.1 M PBS (pH 7.4)

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Table 2: UV-Vis association constants, K_a, for the binding of boronic acids to ARS and dopamine, and oxidative deboronation constants[a]

Compound	K_a (ARS) (M^{-1})	K_a (DA) (M^{-1})	Oxidation k_{obs} (M^{-1} s^{-1})
PBA	3230 ± 610	130.66 ± 5.22	2.4 ± 0.19
Benzoxaborole	3200 ±1300	297.78 ±6.14	2.6 ± 0.14
1	1010 ± 370	1270 ± 170	0.81 ± 0.13
9	590 ± 150	1130 ± 110	0.395 ± 0.087
10	[b]	540 ± 39	1.615 ± 0.033
11	[b]	486 ± 19	2.459 ± 0.094

[a] Errors represent mean ± standard deviation. [b] No absorbance change was observed, thus no association constant was calculated.

Association constants for dopamine-boronic acid complexes were again calculated via the Thordarson method using the 270 nm absorbance maximum observed in UV-Vis spectra (200-400 nm). To correct for background absorbance, reference spectra (200-400 nm) of each boronic acid compound and dopamine (10 mM stock) were acquired. The absorbance of the free, diluted boronic acid present in the complex solutions was subsequently calculated from these reference spectra, thus accounting for dilution and background absorbance. With this assay, all six compounds demonstrated binding (**Table 2**). Phenyl boronic acid and benzoxaborole bound with approximately 100 M^{-1} to dopamine. Whereas **9**, by contrast, bound with approximately 4 times the affinity of benzoxaborole. The greatest affinity was observed with **1**, with an order of magnitude greater affinity than phenyl boronic acid or benzoxaborole. Notably **10** demonstrated binding in this assay, with an affinity twice that of phenyl boronic acid, whilst **11** also demonstrated binding, with a affinity comparable to that of **10**. Given that **11** has two formal negative charges, whereas **10** has only one at the pH of the assay, the electrostatic interaction between the protonated ammonium ion in dopamine and the phosphonic acid does not significantly enhance binding.

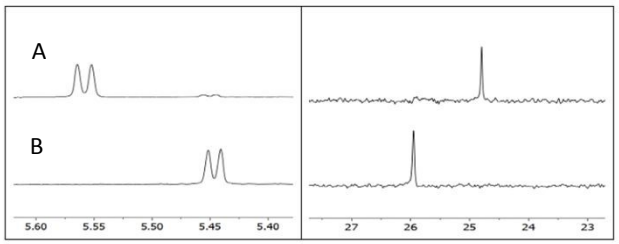
Our UV-titrations demonstrate that the magnitude of benzoxaborole – diol binding is maximal in the presence of either a phosphorus(III) species appended to the benzoxaborole or in the presence of a phosphorus(V) non-charged phosphonate. However, upon ionization of the phosphorus(V) species, there is a reduction in the magnitude of diol binding.

Further evidence for the binding of benzoxaborole derivatives to dopamine was obtained from ^{1}H and ^{31}P NMR spectroscopy under physiological conditions (0.1 M PBS, pH 7.4, **Figure 7**) by measuring the spectra in the presence and absence of dopamine. In these NMR assays, all compounds qualitatively demonstrated diol binding. Specifically, for compound **9**, dopamine binding induced a downfield shift of the characteristic methylene doublet from 5.45 ppm to 5.56 ppm in the ^{1}H NMR spectrum (**Figure 7A and B**). Additionally, a significant upfield shift from 26.0 ppm to 24.8 ppm was observed in the ^{31}P NMR spectrum upon dopamine binding (**Figure 7A and B**). These NMR spectral changes corroborate the binding interactions observed by UV-Vis spectroscopy for the phosphorus(V) phosphonate. Changes to the chemical shift of the methylene protons and ^{31}P nucleus were observed for **1** (**Figure 7C-E**), with a 1:1 complex (**Figure 7D**) demonstrating a slow-exchange equilibrium resulting in equimolar intensities for free and bound complexes. Although compounds **10** and **11** did not show observable binding to ARS and exhibited less potent binding affinity for dopamine, changes in the ^{1}H and ^{31}P spectra upon dopamine addition confirmed their interaction. Upon addition of dopamine, the methylene protons in **10** (**Figure 7FG**) exhibited a chemical shift change and a measurable change to the ^{31}P signal was also observed, consistent with complex formation. The methylene protons in **11** were obscured by the residual HOD signal. Therefore we focused our attention on the aromatic region, where as a result of dopamine addition, a new resonance appeared at 7.40, concomitant with a decrease in the signal at 7.74 (**Figure 7HI**). Thus, changes to the ^{1}H and ^{31}P spectra of these compounds function as a readout for the binding interaction between the diol and benzoxaborole.

OXIDATIVE STABILITY

The final physicochemical property investigated was that of susceptibility towards oxidation. Oxidative deboronation involves ROS-mediated cleavage of carbon-boron bonds, yielding alcohols and boric acid, while protodeboronation entails base-induced proton transfer without oxidation.[18,51] Oxidative processes dominate in biological systems, whereas protodeboronation is favored in electron-deficient or sterically hindered boronic acids under alkaline conditions.[17,51]

To assess the oxidative stability of the boronic acid derivatives under physiological conditions, time-dependent degradation studies were conducted under controlled oxidative conditions (**Figure 8**).[18] Solutions of the boronic acids (0.25 - 1.0 mM) were treated with hydrogen peroxide (5 mM) in aqueous buffer (PBS, pH 7.4), and the oxidation process was monitored via UV-Vis spectroscopy by tracking the characteristic absorbance increase at 270 nm, corresponding to the formation of phenolic oxidation products. The reaction kinetics were analyzed by measuring the time-dependent increase of absorbance over a time interval of 6 min.



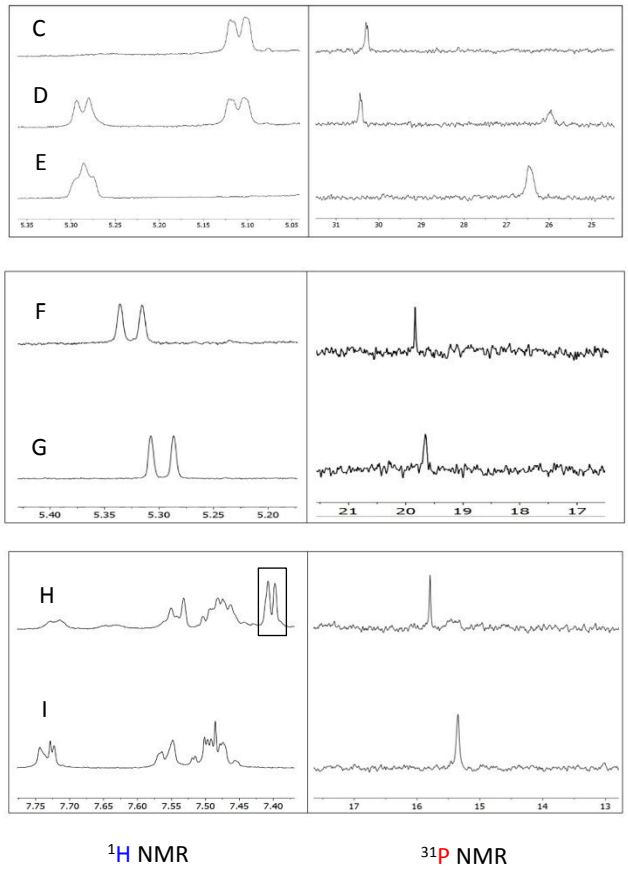


Figure 7. Change in chemical shift for ^{1}H and ^{31}P NMR for benzoxaborole derivatives upon dopamine binding in PBS 0.1 mM, pH 7.4. (A) **9** (0.01 M) with dopamine (0.02 M), (B) **9** (0.01 M), (C) **1** (0.01 M) with dopamine (0.02 M), (D) **1** (0.01 M) with dopamine (0.04 M), (E) **1**, (F) **10** (0.01 M) with dopamine (0.02 M), (G) **10**, (H) **11** (0.01 M) with dopamine (0.02 M), (I) **11** (0.01 M).

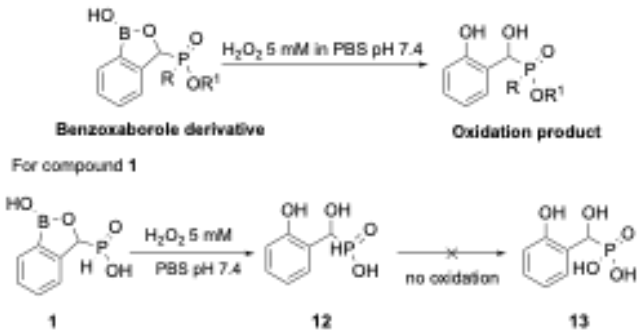


Figure 8. Oxidation of benzoxaborole derivatives containing a phosphorus(III) and phosphorus(V) Functionality

This methodology enabled quantitative comparison of oxidative stability across the boronic acid series. The data provide the first insight into phosphorus (V) or (III) features that enhance or mitigate oxidative susceptibility in organoboron compounds. All of the compounds were subject to deboronation (benzoxaborole ring cleavage) under assay conditions. This was confirmed through inspection of ^{11}B NMR spectra and the formation of boric acid. The phosphorus-substituted benzoxaboroles were more oxidatively stable than either benzoxaborole or phenyl boronic acid (**Table 2**). The rates of oxidative deboronation spanned an order of magnitude for the four compounds. We initially hypothesized that the phosphorus(III)-containing derivative might undergo oxidation to a phosphorus(V) species in addition to deboronation (**Figure 8**). However, our data indicated that there was no phosphorus(III) oxidation during the assay. The ^{11}B NMR indicated deboronation, whilst the ^{31}P spectrum of the oxidized compound remained essentially unchanged at 23.7 ppm (dd, $^1J_{PH}$ = 525.63 Hz, **Figure 9A and C and S60**), even under prolonged exposure to hydrogen peroxide. The presence of a doublet-of-doublets in the ^{31}P (H-coupled) spectrum confirmed that the phosphorus(III) moiety remained intact (**Figure 9B).** Compound **9** was the most resistant to oxidative deboronation. This stability may be attributed to the absence of ionizable phosphoryl functionality and the significant steric bulk provided by the two ethyl esters. The next most stable compound was the phosphorus(III) derivative, with the least steric bulk around the phosphorus atom. The next most stable was **10**, with a single ethyl ester at phosphorus. The most reactive was **11**, the doubly ionized phosphonic acid, with comparable oxidative deboronation to PBA and benzoxaborole. This demonstrates that charge around the phosphorus atom does not protect the benzoxaborole from oxidative deboronation.

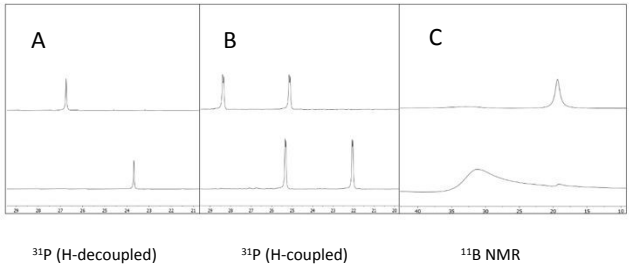


Figure 9. Oxidation of **1** as observed by ^{11}B and ^{31}P NMR. Top spectra: oxidized **1**, bottom spectra **1**; (A) ^{31}P (H-decoupled), (B) ^{31}P (H-coupled), and (C) ^{11}B NMR spectra.

Oxidative stability towards deboronation has been demonstrated through two different approaches with these phosphorus-substituted benzoxaboroles. The phosphorus(V) species, as a diethyl ester derivative, offers significant stability in comparison to benzoxaborole. Alternatively, the phosphorus(III) species also provides oxidative stability, and is, under the assay conditions, resistant to oxidation at phosphorus.

CONCLUSIONS

We successfully developed a versatile one-pot methodology for the synthesis of benzoxaborole derivatives incorporating phosphorus(III) directly from hypophosphorus acid. The reaction demonstrated broad substrate scope including electron-donating, electron-withdrawing, or halogen substituents on the aromatic ring. Products were isolated in good yield and purity without necessitating chromatography. From pK_a titrations, the ^{1}H, ^{11}B and ^{31}P NMR nuclei directly report the pK_a of the benzoxaborole. The pK_a values spanned 2.5 pH units, indicating that the choice of phosphoryl substituent appended to the benzoxaborole greatly influences the acidity.

All phosphorus(III) or phosphorus(V)-substituted benzoxaboroles demonstrated diol binding through UV-Vis titrations and ^{1}H and ^{31}P NMR equilibria, with the choice of phosphoryl substituent influencing the magnitude of binding. The interactions observed herein were more significant than those between boronic acids and phosphate as investigated by James and co-workers.[52] All

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phosphorus-substuted benzoxaboroles demonstrated enhanced oxidative stability, with the most resistant compound being an order of magnitude more stable than either benzoxaborole or phenyl boronic acid. The phosphorus(III) functionality remained resistant towards oxidation under the conditions, demonstrating utility for biological systems.

Collectively, this work establishes new synthetically accessible water-soluble phosphorus(III) or phosphorus(V) phosphorus-substituted benzoxaboroles platforms with tuneable properties, enabling future applications in chemical biology, sensing, and therapeutic development.

Author contributions

E.O.: investigation, methodology, data curation, writing original draft, formal analysis, supervision. M.B.: Investigation. D.L.J.: conceptualization, resources, supervision, writing - review and editing.

Conflicts of interest

There are no conflicts to declare.

Data availability

The materials, methods and data supporting this article have been included as part of the ESI.†

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The materials, methods and data supporting this article have been included as part of the ESI.†

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