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Research Article

General Access to *C*-Centered Radicals: Combining a Bioinspired Photocatalyst with Boronic Acids in Aqueous Media

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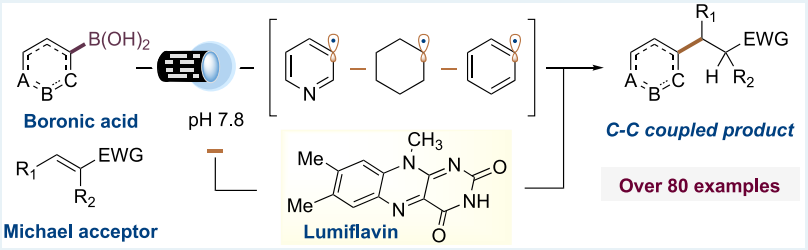

ABSTRACT: *Carbon*-centered radicals are indispensable building blocks for modern synthetic chemistry. In recent years, visible light photoredox catalysis has become a promising avenue to access *C*-centered radicals from a broad array of latent functional groups, including boronic acids. Herein, we present an aqueous protocol wherein water features a starring role to help transform aliphatic, aromatic, and heteroaromatic boronic acids to *C*-centered radicals with a bioinspired flavin photocatalyst. These radicals are used to deliver a diverse pool of alkylated products, including three pharmaceutically relevant compounds, via open-shell conjugate addition to disparate Michael acceptors. The mechanism of the reaction is investigated by computational studies, deuterium labeling, radical-trapping experiments, and spectroscopic analysis.

KEYWORDS: *radical, biocompatible, photoredox catalysis, flavin, boronic acid*

C-centered radicals (namely, $sp^2C\bullet$ and $sp^3C\bullet$) are useful intermediates in the preparation of natural products, pharmaceuticals, and agrochemicals.[1] Owing to their broad utility, a number of powerful photocatalytic platforms—including C−H or C−halogen abstraction, single-electron oxidation or reduction, and energy transfer—have evolved to convert molecules containing both innate (i.e., carboxylic acids, alkenes, alcohols, halides, and C−H bonds) and synthetic (i.e., phthalimides, oxalates, diazonium salts, and silicates) functional groups into chemically reactive *C*-centered radicals.[2] In many instances, these photocatalytic paradigms offer a milder and more sustainable route to *C*-centered radicals[3] as compared to complementary procedures employing stoichiometric reagents (e.g., tin hydrides,[4] manganese(III) acyloxy derivatives,[5] trialkylboranes,[6] and borohydrides[7] or other metal salts[8]). Furthermore, use of photocatalysts enables *C*-centered radicals to be parlayed with a more diverse pool of acceptor molecules through redox-neutral processes, thereby expanding their applications in chemical synthesis.[9] For these reasons, development of photocatalytic strategies to access *C*-centered radicals from commercially available or easily installed functional groups has become an active area of research.

Recently, use of photocatalysts for controlled oxidation of boronic acids (ubiquitous reagents in organic synthesis[10] and substituents in many biologically active molecules[11]) and trifluoroborates[12] to yield *C*-centered radicals has been explored. In the case of boronic acids, coordinately saturated iridium photocatalysts (i.e., $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$)[13] and organic photocatalysts (i.e., 10-(3,5-dimethoxyphenyl)-9-mesityl-1,3,6,8-tetramethoxyacridin-10-ium BF_4 and phenanthrene)[14] are employed in place of standard metal salts (Mn^{3+}, Ag^{1+}, $Fe^{2+/3+}$, Ni^{2+}, Bi^{3+})[15] to facilitate formation of aryl and alkyl radicals, which can be subsequently captured by an array of Michael acceptors to afford C−C coupled products. Unfortunately, these photocatalysts are only mildly effective on their own and call for addition of strong ionic bases (NaOH)[14b] or Lewis bases (DMAP)[16] to assist boronic acid oxidation through formation of labile boronate or amino−boryl complexes, respectively. These additives can potentially hinder the scope of boronic acids. In alkaline media (pH 11−13), many boronic acids, including several classes of heterocycles, are prone to protodeboronation by Kuivila (base-catalyzed) and Perrin (specific-base catalyzed) mechanisms. Base-mediated protodeboronation can likewise occur via concentration-dependent autocatalysis or by a direct reaction with water (often with more basic heterocycles).[17] These

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mechanisms can be accelerated in the presence of UV−vis light.[18] Lewis bases can compete with the oxidation of electron-deficient boronic acids by reductively quenching the photocatalyst.[19] Whether by these constraints or others, established photocatalytic methods have yet to demonstrate wide success with heteroaromatic boronic acids (i.e., *N*-, *O*-, and *S*-containing).[20] Discovery of a more comprehensive method might well enhance the utility of boronic acids in chemical synthesis and drug development.

With a focus on the present conundrum of generality, we gathered that a photocatalyzed method that avoids the use of exogenous activating reagents could minimize boronic acid decomposition or undesirable side reactions and permit mild access to *C*-centered radicals. To this end, boronic acids are known to form Lewis base adducts with water and/or low concentrations of boronate salts at physiological pH.[21] These electron-rich intermediates should be more susceptible to single-electron oxidation. A catalytic system that leverages water as a primary solvent might, therefore, obviate the need for ionic- or amine-base activation altogether (Figure 1). Furthermore, by generating *C*-centered radicals in aqueous

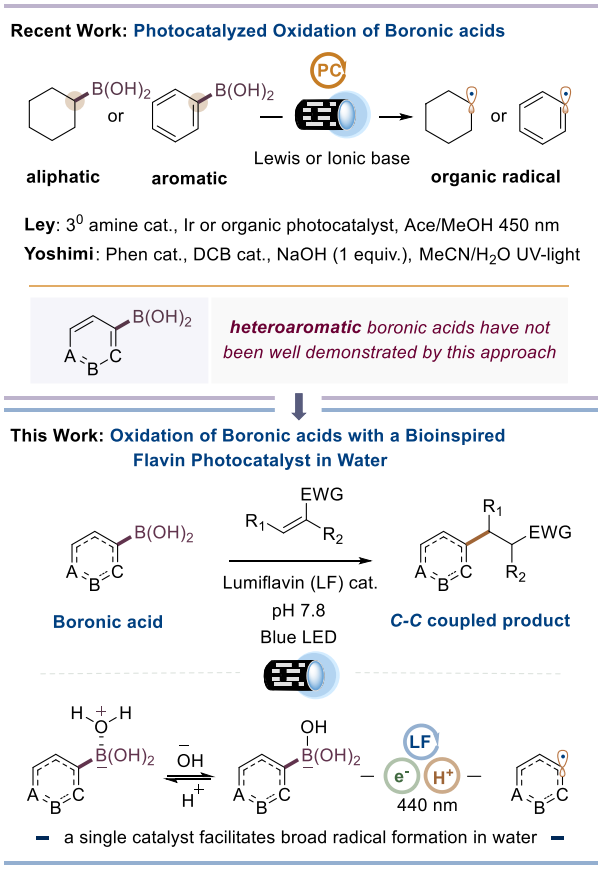

Figure 1. General access to *C*-centered radicals using a bioinspired flavin photocatalyst and boronic acids in water.

media, hydrogen-atom abstraction from solvent (BDE of H_2O = 119 kcal mol^{-1})[22]—a prevalent background reaction of *C*-centered radicals in organic solvents such as MeCN (BDE = 97 kcal mol^{-1})[23] and THF (BDE = 92 kcal mol^{-1})[24]—might also be deterred. To test our proposed strategy, identification of a photocatalyst that is both suitably oxidizing and water compatible along with a reactive probe molecule to quantify formation of *C*-centered radicals is deemed essential to our design plan. Initially, we found inspiration from nature in the way of flavin monooxygenases. This family of flavoenzymes houses a conserved flavin cofactor which is able to transform aromatic boronic acids to aromatic alcohols harnessing molecular O_2.[25] As photocatalysts, flavin cofactors have also been shown to act as single-electron photo-oxidants[26] or reductants[27] in deaerated water under visible light irradiation. Intrigued by their open-shell reactivity and ability to oxidize boronic acids under biocompatible conditions, we postulated that a flavin-derived cofactor might be an ideal photocatalyst to access radicals in a highly general manner. Once formed, we surmised that the radicals could engage a Michael acceptor to furnish a stable conjugate addition product, an overall process hereafter referred to as deborylative−alkylation. Now, we disclose our recent findings in which a flavin-based photocatalyst, lumiflavin (LF), can be used to convert an array of commercially available heteroaromatic, aromatic, and aliphatic boronic acids to valuable alkylated products under innocuous, biocompatible, and general conditions with visible light.

To begin our investigations, we examined heteroaromatic (*N*-containing) boronic acids, being less explored in previous reports. We selected pyridine-3-boronic acid (stable to protodeboronation; $t_{0.5}$ > 1 week, pH 12, 70 °C)[17] as a prototypical heterocycle and diethyl ethylidenemalonate (DEEM) as a Michael acceptor. Accordingly, a mixture of Michael acceptor and excess pyridine-3-boronic acid was irradiated in the presence of various flavin photocatalysts using 10 mM phosphate buffer with 5% (v:v) DMF as solvent. In the case of lumiflavin, we observed small quantities of the desired 3-alkylpyridine product following 16 h of irradiation (40W blue LED). We also observed formation of 3-hydroxypyridine as a minor byproduct along with large amounts of unaltered pyridine-3-boronic acid. Anodic substitution reactions of aromatic organoboron compounds have previously been documented.[28] In the absence of any residual oxygen, the propensity for flavin photocatalysts to perform two sequential single-electron oxidation events[29] might well lead to an aryl cation which can be trapped by water or OH^- under our reaction conditions. Interestingly, increased amounts of 3-hydroxypyridine were found in the case of less effective flavin photocatalysts. In line with these results, we suspected that 3-hydroxypyridine might act as a poison through competitive oxidation ($E_p^{ox} \approx 0.9$ V vs SCE in H_2O pH 7.4)[30] in lieu of the less readily oxidized 3-pyridineboronic acid (for reference, phenylboronic acid is E_p^{ox} = 2.55 V vs SCE and potassium phenyltrifluoroborate is E_p^{ox} = 1.95 V vs SCE).[31] Indeed, adding 10 mol % or 1 equiv of 3-hydroxypyrdine to our standard reaction mixture resulted in no product formation and no consumption of pyridine-3-boronic acid. At this point, we gathered that modifying the pH of the reaction and changing the organic cosolvent could ameliorate background aryl−alcohol formation and enhance reaction efficiency. By adjusting the reaction to pH 7.8 with ammonium formate buffer and using methyl acetate (5% v:v), formation of alcohol could be substantially diminished and the yield of alkylated pyridine improved to 11%. Sufficient quantities of pyridine-3-boronic acid still remained. Increasing the amount of organic cosolvent beyond 5% (v:v) or using pure organic solvents with extensively dried boronic acids and ammonium formate gave considerably lower yields, identifying the essential role of water as a solvent. Use of $(Ir[dF(CF_3)ppy]_2(dtbpy)PF_6)$ or 9-mesityl-10-methylacridinium perchlorate as alternative photo-

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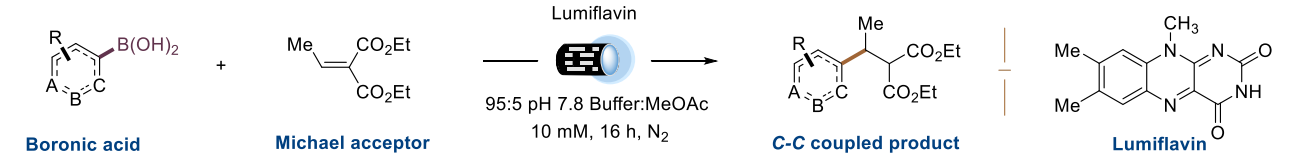
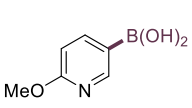
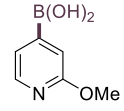
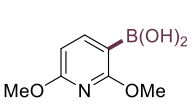
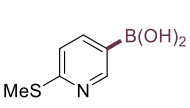
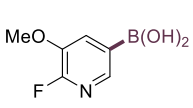
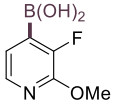
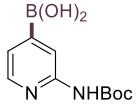
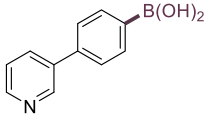
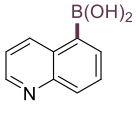
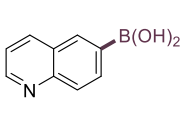
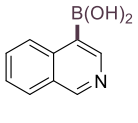
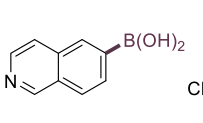
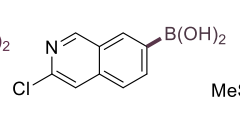
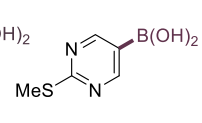
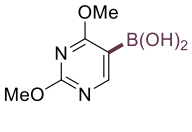
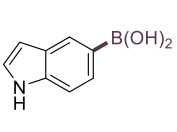
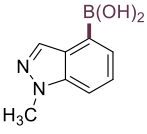
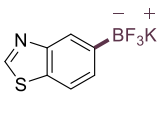
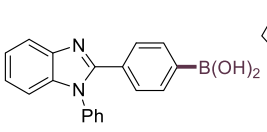
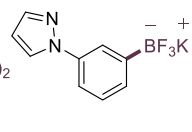
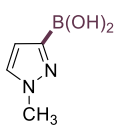
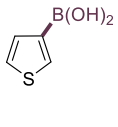
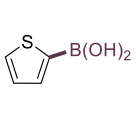
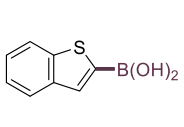
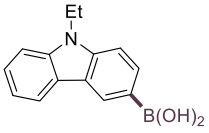
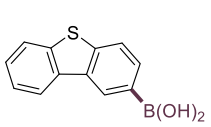
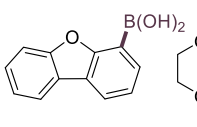
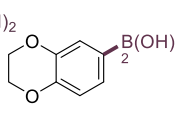
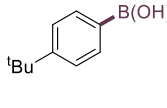
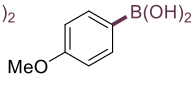
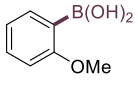
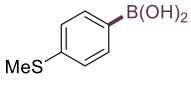
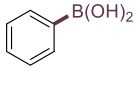
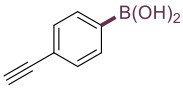
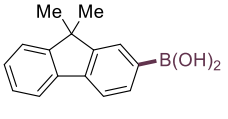
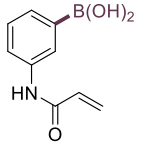
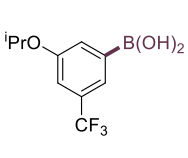
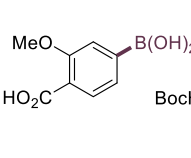
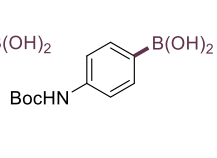
Table 1. Boronic Acid Scope for Flavin-Catalyzed Deborylative−Alkylation[a]



 **1** (61%)	 **2** (80%), (58%)[b] (66%)[c]	 **3** (45%)	 **4** (41%)	 **5** (51%)	 **6** (54%)	 **7** (42%)
 **8** (76%), (64%)[c]	 **9** (45%)	 **10** (40%)	 **11** (35%)	 **12** (57%)	 **13** (68%), (78%)[c]	 **14** (42%)
 **15** (37%)	 **16** (64%)	 **17** (51%)	 **18** (59%)	 **19** (41%)	 **20** (50%)	 **21** (28%)
 **22** (51%)	 **23** (42%)	 **24** (54%)	 **25** (62%)	 **26** (51%)	 **27** (57%)	 **28** (77%), (68%)[c]

• + 12 examples (see Supporting Information) •

 **29** (71%), (68%)[b]	 **30** (80%)	 **31** (36%)	 **32** (63%)	 **33** (41%)	 **34** (52%)	 **35** (58%)
 **36** (43%)	 **37** (53%)	 **38** (66%)	 **39** (50%)	**40** (60%)	**41** (62%), (57%)[c]	**42** (58%)

• + 13 examples (see Supporting Information) •

43 (15%)[d]	**44** (32)[b]	**45** (54%)[b]	**46** (59%)[b], (52%)[c]	**47** (61%)[b] **48** (22%)[b]	**49** (49%)[b]

[a]All reactions were performed using 0.026 mmol of boronic acid, 30 mol % of lumiflavin, and 10 equiv of diethyl ethylidenemalonate. Reactions were degassed with N_2 and irradiated for 16 h with four, 40 W blue LEDs in a solution of pH 7.8 (ammonium formate) H_2O and MeOAc (95:5, 10 mM overall concentration). Isolated yields are in parentheses. See Supporting Information for full experimental details and additional substrates. [b]Isolated yield using 3 equiv of Michael acceptor. [c]Reactions were performed at 0.63 mmol scale with respect to boronic acid. [d]Yield reported by crude ^{1}H NMR using dibromomethane (1 equiv) as an internal standard.

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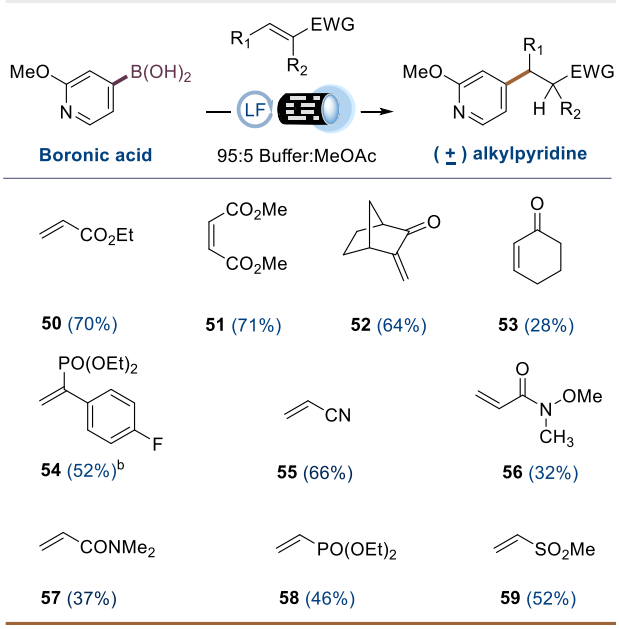
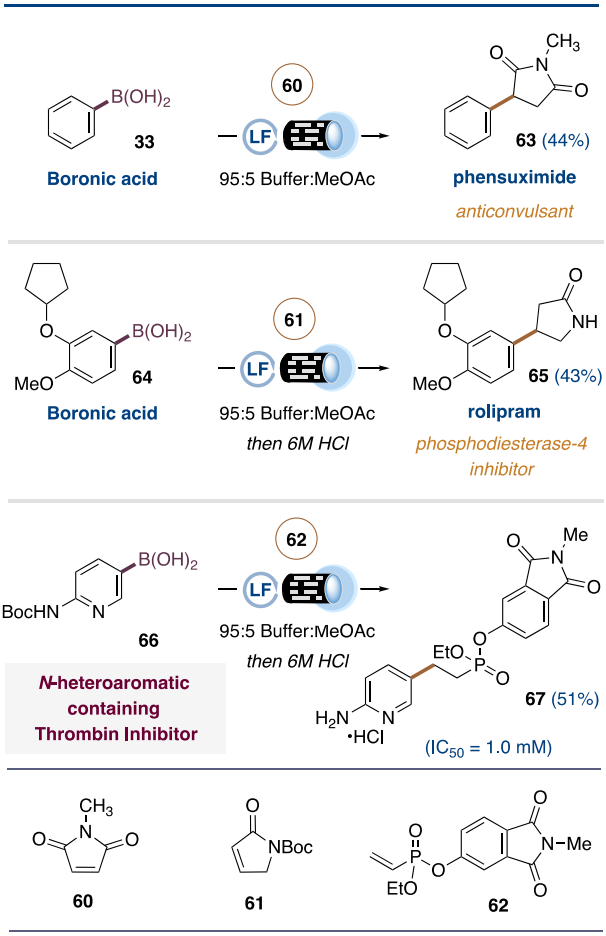
Table 2. Scope of Michael Acceptors[a]



[a]For products **50**−**53** and **55**−**59**, the reactions were performed using 0.026 mmol of boronic acid, 30 mol % of lumiflavin, and 10 equiv of Michael acceptor. The reactions were degassed with N_2 and irradiated for 16 h with four, 40 W blue LEDs in a solution of pH 7.8 (ammonium formate) H_2O and MeOAc (95:5, 10 mM overall concentration). [b]The reaction was performed using 0.026 mmol of **54**, 30 mol % of lumiflavin, and 2 equiv of boronic acid. Isolated yields are in parentheses.

Scheme 1. Drug Synthesis[a]



[a]For the synthesis of **63**, the reaction was performed using 0.026 mmol of Michael acceptor (**60**), 30 mol % of lumiflavin, and 2 equiv of boronic acid (**33**). For product **65**, the reaction was performed using 0.0026 mmol of boronic acid, 30 mol % of lumiflavin, and 10 equiv of Michael acceptor. For the synthesis of **67**, the reaction was performed using 0.026 mmol of boronic acid (**66**), 30 mol % of lumiflavin, and 2 equiv of Michael acceptor (**62**). All of the reactions were degassed with N_2 and irradiated for 16 h with four, 40 W blue LEDs in a solutions of pH 7.8 (ammonium formate) H_2O and MeOAc (95:5, 10 mM overall concentration). Isolated yields are in parentheses.

catalysts gave only trace amounts of alkylated product under our optimized conditions (a similar result was found for other heteroaromatic boronic acids). Despite our best efforts to improve this reaction further, we were unable to increase the yield of 3-alkylpyridine. We hypothesized that the diminished yield could be due to the limited nucleophilicity of the 3-pyridyl radical. To examine this theory, we subjected the more readily oxidized sodium trihydoxy(pyridine-3-yl)borate salt to our reaction conditions.[28,31] The yield of the reaction was comparable. Employing the more nucleophilic radical precursor, 6-methoxy-3-pyridineboronic acid (**1**), afforded a significant increase in reaction efficiency to 26% yield. Use of excess Michael reagent (10 equiv) improved the reaction of **1** to an optimal 61% isolated yield.

Considering the importance of electronics to boronic acid reactivity, we decided to explore the scope of our reaction to a myriad of heterocyclic boronic acids (Table 1). (It is important to note that in some cases the boronic acid was not commercial; in these instances, the trifluoroborate derivative was used instead—compounds **18**, **20**, **46**, **47**, and **49**.) Among those surveyed, fluoro-, ether-, and thioether-containing pyridine boronic acids were efficient substrates for deborylative−alkylation (compounds **1**−**6**, yields 41−80%). Our methodology was likewise successful with other nitrogenous heterocycles including quinolines, isoquinolines, pyrimidines, indoles, indazoles, benzimidazoles, and pyrazoles (compounds **9**−**17** and **19**−**21**, yields 28−68%). In all cases, increased amounts of Michael acceptor (10 equiv) afforded optimal yields for heteroaromatic boronic acids, likely proceeding through highly reactive sp^2 radicals. On scale (0.63 mmol), the reaction performed well as demonstrated by **2**, **8**, **13**, **28**, **41**, and **46**.

Satisfied by the generality of our method to nitrogenous heterocycles, we next assessed a series of boronic acids derived from common therapeutic scaffolds, e.g., benzothiazoles (compound **18**, antitumor, antimicrobial, and antidiabetic),[32] dibenzothiophenes (compound **26**, keratolytic),[33] and dibenzofurans (compound **27**, anti-inflammatory).[34] In all cases, alkylated products were obtained in moderate yields (51−59%) and with excellent chemoselectivity. Finally, we examined aromatic and aliphatic boronic acids (Table 1). To our delight, aromatic systems proved competent substrates, affording yields of alkylated products between 36% and 80% yield, including an ortho-substituted boronic acid **31** and a well-established anticancer warhead **36**.[35] Electron-deficient phenylboronic acids (4-CF_3, 4-F, 4-CN, and 4-$COCH_3$) gave lower yields (5−26% ^{1}H NMR yields data not shown), presumably being less nucleophilic and harder to oxidize. In

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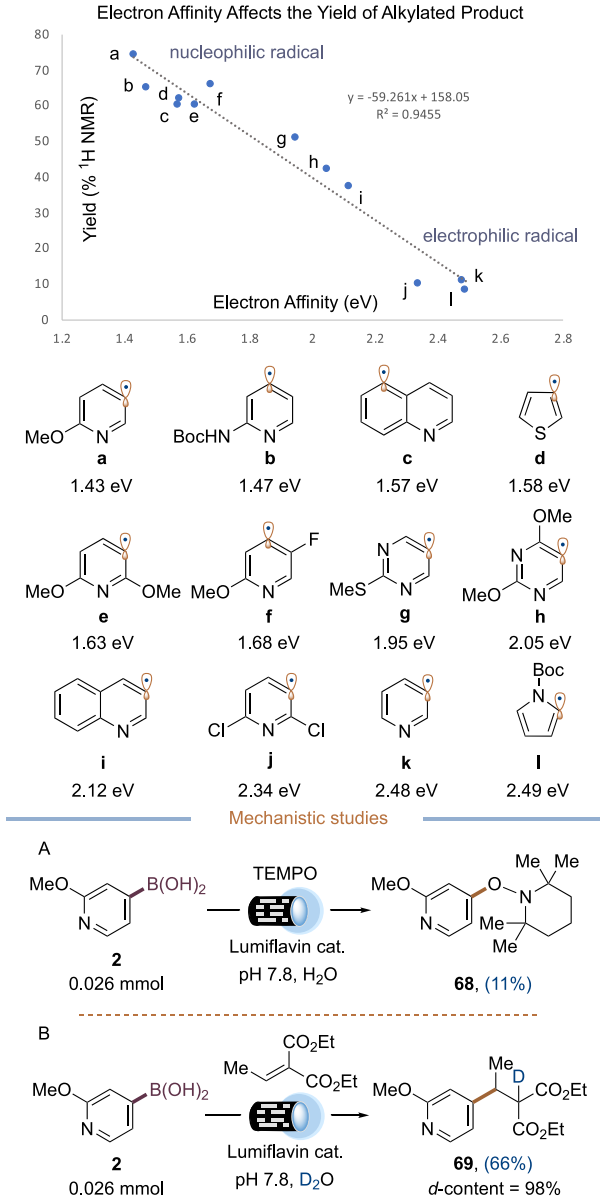
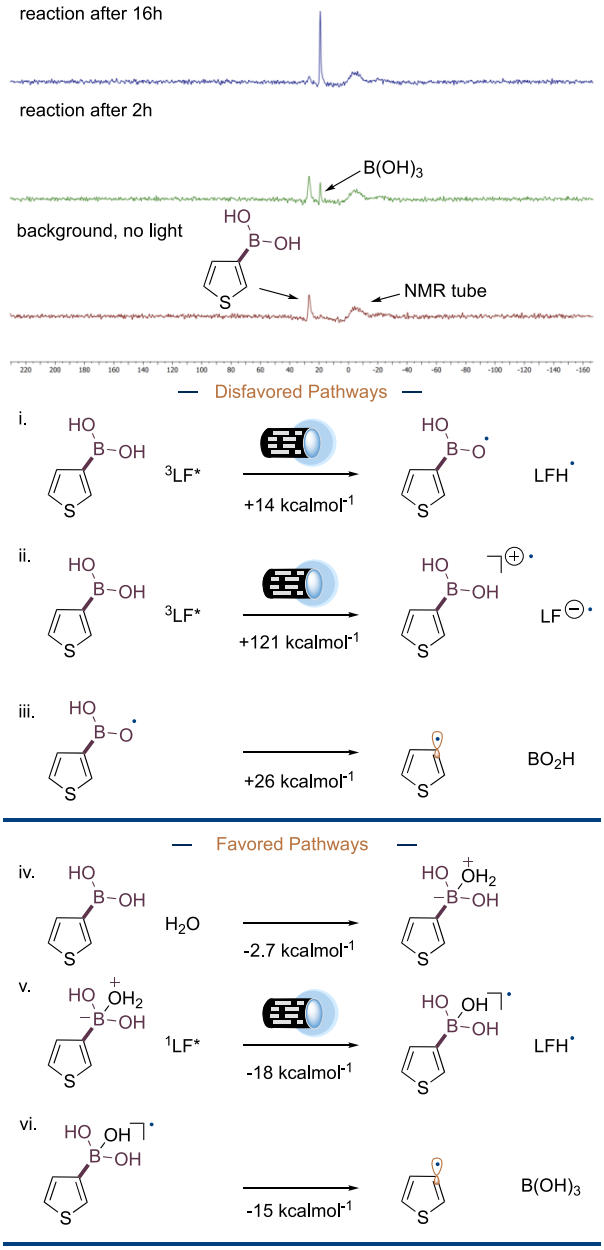


Figure 2. Computational and experimental studies into the open-shell mechanism.

the case of aliphatic boronic acids—cyclic, linear, and heteroatom containing—each proved to be viable substrates for deborylative−alkylation. Unlike aromatic systems, we found that 3 equiv of Michael acceptor gave comparable yields to the use of 10 equivalents, a result consistent with the greater nucleophilicity of sp^3 radicals. To our surprise, methylboronic acid **43** was a promising candidate for conjugate addition. Access to methyl radicals represents a particularly attractive avenue for introducing methyl groups into drug molecules,[36] and its direct generation from a boronic acid has not been achieved prior to our report.

Concluding our survey of disparate boronic acids, we turned our attention to the use of alternative Michael acceptors in our reaction (Table 2). Conjugated esters, ketones, and amides worked well in addition to a vinyl sulfone, acrylonitrile, and vinylphosphonate using **2** as the radical precursor (compounds **50**−**59**, yields 28−71%). No polymerization was observed for these Michael acceptors. Styrenes, propiolates, vinyl boronates, and vinylsilanes were not effective. The poor efficiency of these

Scheme 2. Photocatalyzed Oxidation of Boronic Acids



alkenes is attributed to the inability of lumiflavin to reduce the radicals formed in these systems following open-shell conjugate addition.[37] Nevertheless, by employing *N*-methylmaleimide **60** as a Michael acceptor, we successfully prepared the anticonvulsant drug phensuximide **63** (44% yield) in one step from phenylboronic acid **33**. By employing the commercially available boronic acid **64** and *N*-Boc-3-pyrrolin-2-one **61**, we synthesized the FDA-approved phosphodiesterase-4 (PDE4) inhibitor rolipram **65** in 43% yield. Finally, starting from 2-*N*-Boc-aminopyridine-5-boronic acid **66** and the phthalimide Michael acceptor **62**, we prepared the thrombin inhibitor **67** in 51% yield.[38] These results highlight the application of our methodology to prepare three medicinally significant compounds (Scheme 1).

To provide some insight into the mechanism of our reaction, we undertook preliminary computational experiments. As evidenced by Figure 2, the nucleophilicity of the proposed radical intermediate, obtained from optimized open-shell

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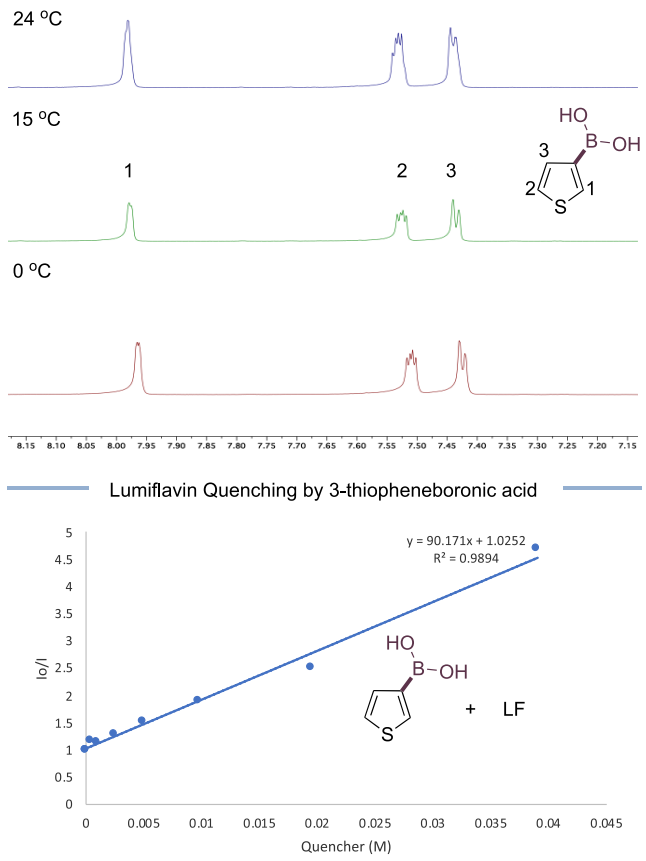

Figure 3. Low-temperature ^{1}H NMR and Stern–Volmer studies.

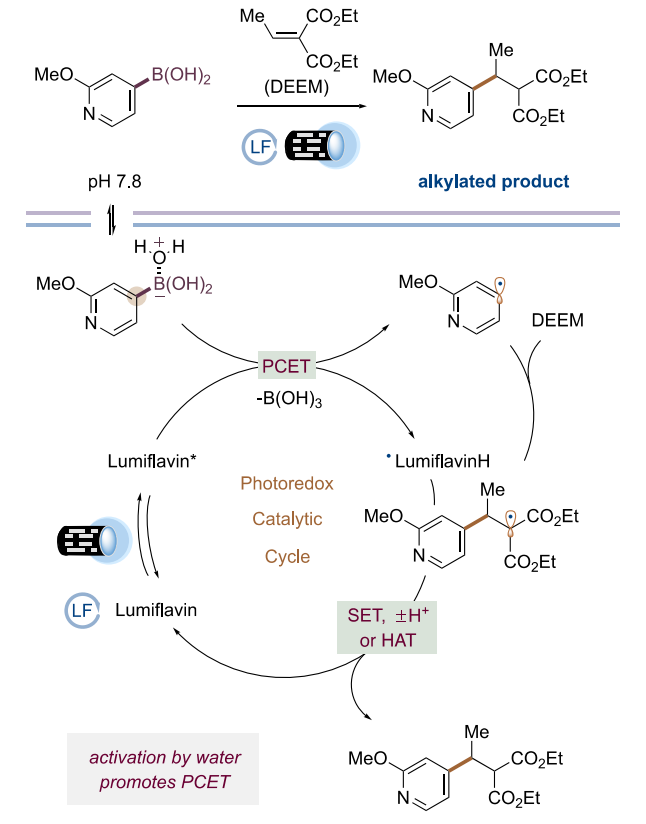

Figure 4. Proposed mechanism for the flavin-catalyzed deborylative–alkylation of boronic acids.

structures at B3LYP/6-311G+*[39] and corrected using weighted averages from neutral and protonated states of heterocycles in water, agreed with the observed efficiency of the reaction (by ^{1}H NMR analyses). Radical intermediates with electron affinities of ≤2.0 eV are suitable substrates for alkylation under our optimized reaction conditions. This trend only provides a first approximation as other factors such as (i) partial acid-catalyzed protolysis via a Kuivila mechanism,[40] (ii) specific-base-mediated protolysis through a Perrin mechanism,[41] or (iii) additional protolysis and disproportionation processes as summarized by Lloyd–Jones[17] may well influence the yields for unique heteroaromatic boronic acids. However, our analysis does correctly account for substrates that performed less admirably, including pyridine-3-boronic acid, which computationally gives rise to a highly electrophilic radical (2.48 eV) following oxidative deborylation.[42] In all, this computational model not only provides a convenient tool for predicting substrate competence but also garners initial support for the existence of radical intermediates in our reaction.

To further explore the intermediacy of radicals, we performed a radical-trapping experiment in the presence of TEMPO and a deuterium-labeling study in D_2O. Reaction of **2** in the absence of diethyl ethylidenemalonate and with 2 equiv of TEMPO afforded 11% of the *O*-pyridyl-TEMPO coupling product **68** (Figure 2A). This result indicates that a free heteroaromatic radical is oxidatively generated by the lumiflavin photocatalyst. To probe the involvement of this radical in the C–C bond-forming event, we reacted **2** with diethyl ethylidenemalonate using our optimized procedure and D_2O as solvent (Figure 2B). If the heteroaryl radical engages with our Michael acceptor via single-electron conjugate addition, we anticipate formation of a stabilized α-malonyl radical. This radical is easily reduced to the corresponding anion by single-electron reduction ($E^{\circ\prime} \approx 0.7$ V vs SCE),[43] an achievable potential from the reduced state of the lumiflavin photocatalyst ($E^{\circ\prime} \approx -0.46$ V vs SCE at pH 7 for flavins).[44] The resultant anion would be protonated by solvent to complete the catalytic cycle. Delivery of a proton from reduced lumiflavin semiquinone may also be possible and cannot be excluded. If solvent is involved in the final protonation event, replacing H_2O with D_2O should lead to the α-deuterated product **69**. As expected, we found that reaction of **2** in D_2O produced deuterium-enriched **69** in 66% yield (98% *d*-content). To dismiss any chance that **69** was formed by keto–enol tautomerization from the protonated congener, we subjected *H*-**69** to a pH 7.8 D_2O solution for 16 h with blue light irradiation. No deuterium incorporation was observed.

Finally, we explored the radical formation step. We used ^{11}B NMR to determine the identity of the boronic acid species formed during the reaction (Scheme 2). For this series of studies 3-thiopheneboronic acid was employed due to its greater solubility in D_2O. Performing our standard reaction in the absence of light gave only a single peak centered at 27 ppm, corresponding to monomeric 3-thiopheneboronic acid. No boronate was evident after 16 h of stirring in the dark. An identical observation was found for other heteroaromatic boronic acids (compounds **2**, **9**, **15**, and **21**) despite their limited solubility in D_2O. The absence of any conjugate addition product was also noted by ^{1}H NMR. When the reaction was irradiated with 440 nm light, a new peak at 19 ppm formed, identified as boric acid. This signal could be recapitulated by the combination of boronic acid, lumiflavin,

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and 440 nm irradiation in D_2O. Addition of diethyl ethylidenemalonate to the irradiated mixture afforded the α-deuterated conjugate addition product. Inclusion of TEMPO (2 equiv) gave a TEMPO-trapped adduct, identified by mass spectrometry. In accordance with these findings we find the following. (1) Formation of an oxidatively labile boronate salt is unlikely, at least on the ^{11}B NMR time scale. Thus, the *C*-centered radical does not appear to be generated through an intermediate boronate. (2) Formation of a discrete Lewis base adduct between lumiflavin and the boronic acid is unlikely, not having been observed by ^{11}B NMR or ^{1}H NMR. To further rule out formation of a photocatalyst−boronic acid complex, we used UV−vis spectroscopy. No change in the UV−vis spectrum of lumiflavin was observed upon titration with the boronic acid in water. Previous work by Wolf[45] and Fukuzumi[46] showed that coordination of Lewis acids to flavins results in a characteristic blue shift of the flavin absorption and fluorescence maximum. The absence of any distinct shift in our reaction argues against complex formation and indicates that this adduct is not responsible for generating the *C*-centered radical (Figure S6).

Finding no evidence for the formation of a discrete boronate or photocatalyst−boronic acid complex to assist radical formation, we examined the direct oxidation of 3-thiopheneboronic acid by photoexcited lumiflavin using computations. Thermodynamic energies for triplet lumiflavin, lumiflavin radical anion, and 5*H*-lumiflavin radical were taken from previous work by Platz.[47] First, we envisioned that the reaction could proceed through a boronyl radical formed via direct hydrogen-atom abstraction from the boronic acid and/or proton-coupled electron transfer (PCET) by triplet lumiflavin (Scheme 2, i). Alternatively, we imagined electron transfer (Scheme 2, ii) followed by deprotonation. The resultant boronyl radical could fragment to give a *C*-centered radical and BO_2H, which hydrolyzes to boric acid (Scheme 2, iii). HAT or PCET (+14 kcal mol^{-1}) and SET (+121 kcal mol^{-1}) were predicted to be unfavorable. Fragmentation of the boronyl radical was also predicted to be unfavorable (+26 kcal mol^{-1}).

To offset the unfavorable reactivity of triplet lumiflavin, we postulated the involvement of singlet photoexcited lumiflavin. Experimental measurements by Muller[48] determined an energy difference of 2.79 eV between the ground and the singlet excited state of lumiflavin in water. A similar value (ca. 3.05 eV) was obtained by quantum chemical calculations as summarized by Schapiro.[49,50] Considering the singlet excited state, direct oxidation of the boronic acid is still predicted to be unfavorable (+102 kcal mol^{-1}). Singlet lumiflavin has been shown to oxidize aromatic compounds ≤2.0 V vs SCE via SET.[51] Aromatic, heteroaromatic, and aliphatic boronic acids often have potentials ≥ 2.0 V vs SCE, leading to an unfavorable electron tranfer.[31] Interestingly, exothermic coordination of a molecule of water to the boronic acid (Scheme 2, iv, −2.7 kcal mol^{-1}) is predicted to facilitate a favorable PCET or HAT event, but not SET, from singlet lumiflavin (Scheme 2, v, −18 kcal mol^{-1}). These mechanisms are unfavorable in the case of triplet lumiflavin (+7.4 kcal mol^{-1}). (Even though PCET, SET, and HAT from triplet lumiflavin may be endothermic, generation of the *C*-centered radical is still a favorable process overall (−10.3 kcal/mol^{-1}), suggesting that catalysis through the triplet state may still occur.) Formation of *C*-centered radicals from trisubstituted borane−water complexes was originally proposed by Wood.[52] Complexation of H_2O to trialkylboranes results in substantial weakening of the O−H bond (86 kcal mol^{-1} compared to 116 kcal mol^{-1} for uncomplexed H_2O by ab initio calculations), enabling H-atom abstraction. The derived C_S-symmetric radical readily dissociates to form an alkyl radical and $Alkyl_2BOH$. Use of aqueous solvent in our reaction may therefore entice the coordination of water to the Lewis acidic boronic acid, promoting H-atom abstraction or PCET by singlet lumiflavin. A HAT mechanism is less feasible due to an inherent electronic mismatch between the electrophilic *N*-centered radical of photoexcited lumiflavin and the O−H bond of water, favoring the PCET mechanism. Abstraction of a single electron from the aqua−boryl complex would increase the acidity of the O−H bond of the coordinated water, allowing for deprotonation by the reduced lumiflavin semiquinone ($pK_a \approx 8.4$).[53] The resulting boronyl radical fragments to give the reactive *C*-centered radical and boric acid (Scheme 2, vi, −15 kcal mol^{-1}).

To probe formation of an aqua−boryl complex, we performed low-temperature ^{11}B NMR and ^{1}H NMR experiments. In cooling a solution of 3-thiopheneboronic acid in D_2O from 25 to 0 °C, the boronic acid was found to retain its monomeric form (Figure 3). The ^{11}B spectra revealed considerable broadening of the boronic acid signal but afforded no new signals. Temperatures below 0 °C gave similar results. A slight upfield shift of the boronic acid aromatic protons was also observed upon cooling. Weak coordination of a water molecule to the boronic acid could stabilize the boronic acid monomer at low temperatures and cause a buildup of electron density on the Lewis acidic boronic acid. This weak dative interaction is expected to be in rapid equilibrium and could contribute to ^{11}B peak broadening.[21] In contrast, solvation of the boronic acid in a less coordinating solvent, d_6-acetone, resulted in extensive aggregate formation at low temperatures and a general deshielding of the aromatic and boronic acid proton signals. While these experiments do not provide definitive evidence for water coordination, they do indicate that water significantly affects the boronic acid coordination sphere.

In hopes to elucidate a potential PCET mechanism involving an aqua−boryl complex, we performed a Stern−Volmer quenching experiment and a deuterium-labeling experiment. Excitation of lumiflavin in an aqueous solution of 3-thiopheneboronic acid resulted in considerable quenching of lumiflavin (Figure 3), indicating that a favorable electron transfer between the boronic acid and the photocatalyst is possible in water. Direct quenching from water was not observed by Stern−Volmer, relegating a mechanism based on the intermediacy of hydroxy radicals formed by water oxidation. Quenching of 3-pyridineboronic acid by lumiflavin was also observed by Stern−Volmer (Figure S7), suggesting that formation of *N*-heterocyclic radicals occurs through a similar mechanism. To examine proton transfer we prepared d_2-phenylboronic acid−$PhB(OD)_2$. If proton transfer occurs from a coordinated water molecule, reaction of d_2-phenylboronic acid with lumiflavin in H_2O should afford BO_3D_2H and N5-*H*-lumiflavin semiquinone. Unfortunately, rapid exchange of water with the boronic acid caused significant scrambling of the deuterium atoms. While this innate exchange did limit our ability to probe proton transfer from a coordinated water molecule, we were able to study deuterium transfer between ground state lumiflavin and d_2-phenylboronic acid in anhydrous solvents ($CHCl_3$, CH_3CN, dioxane, DCM, acetone). Deuteration of the basic *N*-5 nitrogen was not observed. A mechanism involving deprotonation of the boronic

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acid by ground state lumiflavin followed by photocatalyzed oxidation is therefore improbable.

From our collective data, we propose the following mechanism for deborylative−alkylation: (1) coordination of water to the boronic acid, (2) photoexcitation of the lumiflavin photocatalyst by 440 nm light gives rise to excited lumiflavin which abstracts an electron and a proton from the aqua−boryl complex, (3) fragmentation of the resulting open-shell intermediate releases the heteroaryl radical, (4) expedient capture of the heteroaryl radical via open-shell conjugate addition (1.8×10^8 M^{-1} s^{-1} for phenyl radical)[54] to diethyl ethylidenemalonate, and (5) reduction of the α-malonyl radical by SET, HAT, or PCET from LFH• forges the desired alkylated product and regenerates the ground state photocatalyst (Figure 4).

In conclusion, we present a general catalytic platform to access diverse heteroaromatic radicals as well as aromatic and aliphatic radicals from commercial boronic acids using an under-explored and cofactor-derived flavin photocatalyst in aqueous media. We demonstrate the ability of these radicals to engage Michael acceptors via single-electron conjugate addition. Finally, we show that water acts as a key solvent and potential reagent for radical generation and open-shell alkylation. Further investigations to harness the aqueous compatibility of this reaction and the unique properties of flavin photocatalysts for applications to more biologically relevant substrates (i.e., peptides and proteins) are presently underway and forthcoming.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03422.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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