Unlocking the Accessibility of Alkyl Radicals from Boronic Acids through Hydrogen-bond Assisted Organophotoredox Activation

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Supporting Information Placeholder

ABSTRACT: Despite their prevalence in organic synthesis, the application of boronic acids (BAs) as alkyl radical precursors in visible-light assisted photocatalyzed reactions has been limited by their high oxidation potential. This study demonstrates the remarkable ability of amide solvents viz. DMA (N,N-dimethylacetamide) to participate in hydrogen-bonding interactions with BAs, thus enabling the modulation of their oxidation potential towards the generation of alkyl radicals. The developed protocol is simple, robust and demonstrates broad applicability for alkylation, allylation and elimination reactions in batch and continuous flow. The application towards dehydroalanine allows the synthesis of unnatural amino acids. Furthermore, the chemo-selective generation of radical species from BAs, in the presence of boronic ester-containing molecules, is now feasible, endorsing plausible boron-selective (bio-) orthogonal modifications.

1. Introduction

Free radicals are involved as reaction intermediates in various chemical and biological processes.[1] Since the last decade, considerable attention has been paid to explore and understand the role of different functionalities towards alkyl radical generation.[1a] The identification of suitable alkyl radical sources has remained a longstanding goal in the field of photoredox catalysis, with the aim to offer a wide assortment and to obtain chemoselectivity in the generation of these open shell reactive species. In this direction, the visible-light photoredox generation of alkyl radicals from organoboron species has proven to be a remarkable tool for the preparation of high-valued organic compounds.[2] Since the pioneering work of Molander[3] and Akita[4a], trifluoroborates (synthesized from BAs or boronic esters) have been extensively exploited in various kinds of organic transformations, primarily because of their bench stability and low oxidation potential (~1.2 V *vs* SCE).[3] In recent years, the search for appropriate alternatives has been compensated by other boronic acid (BA) derivatives such as boronic esters, boroxines and their metal-salts (*viz.* boracene-based alkylborate lithium salts).[5-7] This late development can be ascribed to the photocatalytically unachievable high oxidation potential of BA (derivatives) (>2.0 V *vs* SCE) (Figure 1a).[6] To overcome this challenge, two predominant strategies have been employed in the last few years: the use of a mild oxidant like acetoxybenziodoxole (BI-OAc)[8] or a Lewis-base adduct formation (Figure 1b)[6a] to activate the BA derivatives (boronic esters/boroxines) towards the generation of carbon-centered radicals. Nonetheless, these approaches

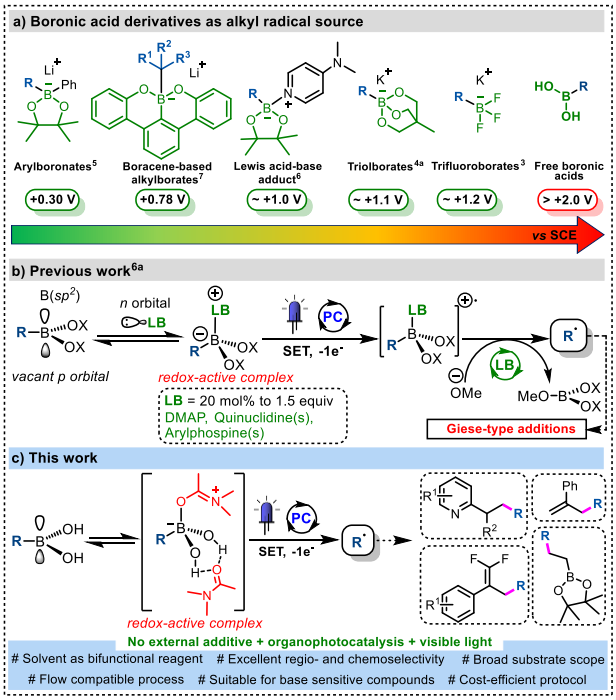


Figure 1: State of the art for the photoactivation of boronic acid (derivatives).

still suffer from limitations, such as: 1) the use of an external oxidant narrows down the synthetic applicability; 2) the pres-

ence of a strong Lewis-base severely restricts the selective activation of sp^2-hybridized BAs in the presence of other sp^2-hybridized organoboron species; 3) the fast protonation of carbanionic species abates the chances of intramolecular reactions.[4] To overcome some of the drawbacks, the recent work of Bloom and co-workers has demonstrated the use of a PCET process using water as solvent and activating agent for the generation of radicals for a broad variety of aromatic boronic acids. However, the aliphatic counterpart only afforded low to moderate yield (15-61%).[18b] Despite these limitations, the employment of BAs offers several advantages. As evident from literature, BAs are one of the most omnipresent classes of reagents in modern organic synthesis, enabling different types of C-C and C-heteroatom bond formations.[9-10] Moreover, the last decade has witnessed a substantial growth in the application of boron-based molecules in therapeutic areas (*viz.* ixazomib, tavaborole and crisaborole),[11] chemosensing, material chemistry, and biomedical engineering, keeping their commercial availability high.[12-13] The unique properties of BAs are due to a vacant *p*-orbital centered on the B-atom which readily establishes reversible dative bonds with *O*- and *N*- nucleophiles.

Inspired by their ubiquity and chemical tunability, herein we report a straightforward additive free mode of BA activation for the successful generation of alkyl radicals, avoiding any exogenous activating agent. In light of the role of amide based solvents in modulating the reactivity of BA derivatives, as reported by Aggarwal[14] and Studer[15], and aware of the ability of these solvents to engage in H-bonding interaction with BAs[16], we anticipated the possibility of modulating BA reactivity *via* weak hydrogen-bond interactions with a suitable solvent under mild photocatalyzed conditions (Figure 1c). The presented mode of activation is broadly applicable to generate carbon-based radicals and further engage in the functionalization of electron-deficient alkenes *via* Giese-type addition, allylation and elimination reactions.

2. Result and Discussion

Reaction Optimization. We began our investigation with 2-vinyl pyridine as electron deficient alkene and cyclopentyl boronic acid as C-centered radical source. The choice of 2-vinyl pyridine as radical acceptor was dictated by the omnipresence of the pyridine scaffold in pharmaceuticals, agrochemicals and natural products.[17] The reaction mixture was irradiated with 14 W blue LEDs in the presence of an organic photocatalyst (4CzIPN) in dry DMA (0.1 M). To our delight, the desired product was obtained in 77% yield (Table 1, Entry 1). Among different dry amide solvents tested, DMA and NMP (*N*-methyl-2-pyrrolidone) gave the highest yields (80% and 82%, respectively). DMPU (*N*, *N*′-dimethylpropyleneurea), a cyclic urea having similar nucleophilicity as compared to DMA, resulted in a lower yield. This outcome could be due to higher steric hindrance around the carbonyl oxygen.

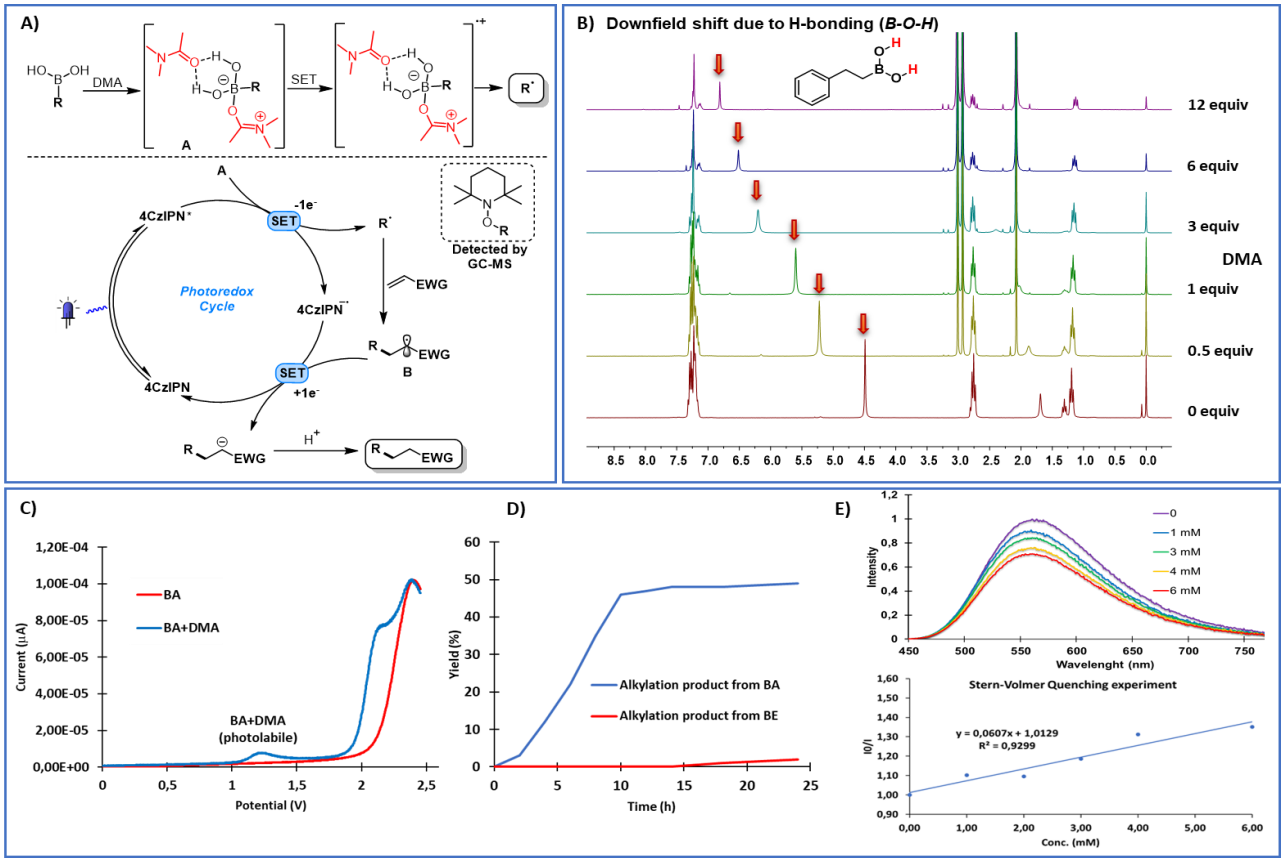
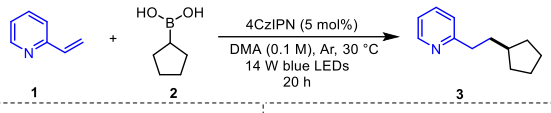
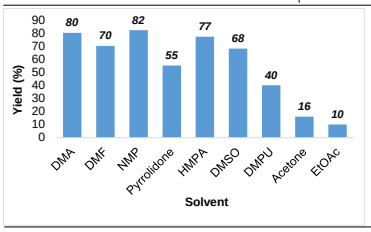


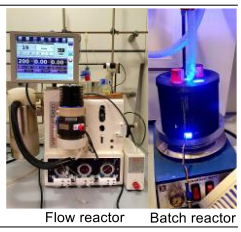
Figure 2: Hydrogen-bonding interactions makes direct photo-activation of BAs possible: A) Design plan and mechanistic proposal; B) ^{1}H-NMR measurements with increasing amount of DMA confirm the role of H-bonding interactions; C) Lowering of oxidation potential of phenyl ethyl BA demonstrated *via* CV measurements (by cyclovoltametry; redox potential shown for free BA and measured for the complex; BA:DMA ratio: 1:5, measurements performed in degassed ACN); D) The resulted time-dependent chemoselective activation of cyclopentyl BA in comparison to the cyclohexyl boronic acid pinacol ester counterpart for the alkylation of 2-vinyl pyridine under the optimal conditions; E) Fluorescence quenching experiment and Stern-Volmer plot confirm the exited state of PC is quenched by cyclopentyl BA-DMA complex.

Table 1: Optimization of reaction conditions.[a]



Batch			Flow			
Entry	Deviation from above	Yield (%)[b]	Entry	Solvent	Resident time (min)	Yield (%)[b]
1	None	80 (77)	6	DMA	50 min	45
2	No PC/light	0	7	DMA	100 min	25
3	TEMPO	0	8	DMA:ACN (1:1)	50 min	76
4	Under air	30	9	DMA:ACN (1:4)	50 min	87
5	H_2O:DMA (9:1)	68	10	DMA:Acetone (1:1)	50 min	25





[a] All reactions were carried out using boronic acid **2** (0.22 mmol, 1equiv), 2-vinyl pyridine **1** (0.33 mmol, 1.5 equiv), [b] Yields were determined by 1H-NMR using 3,5,6 trimethoxybenzaldehyde as internal standard. Isolated yields in parentheses.

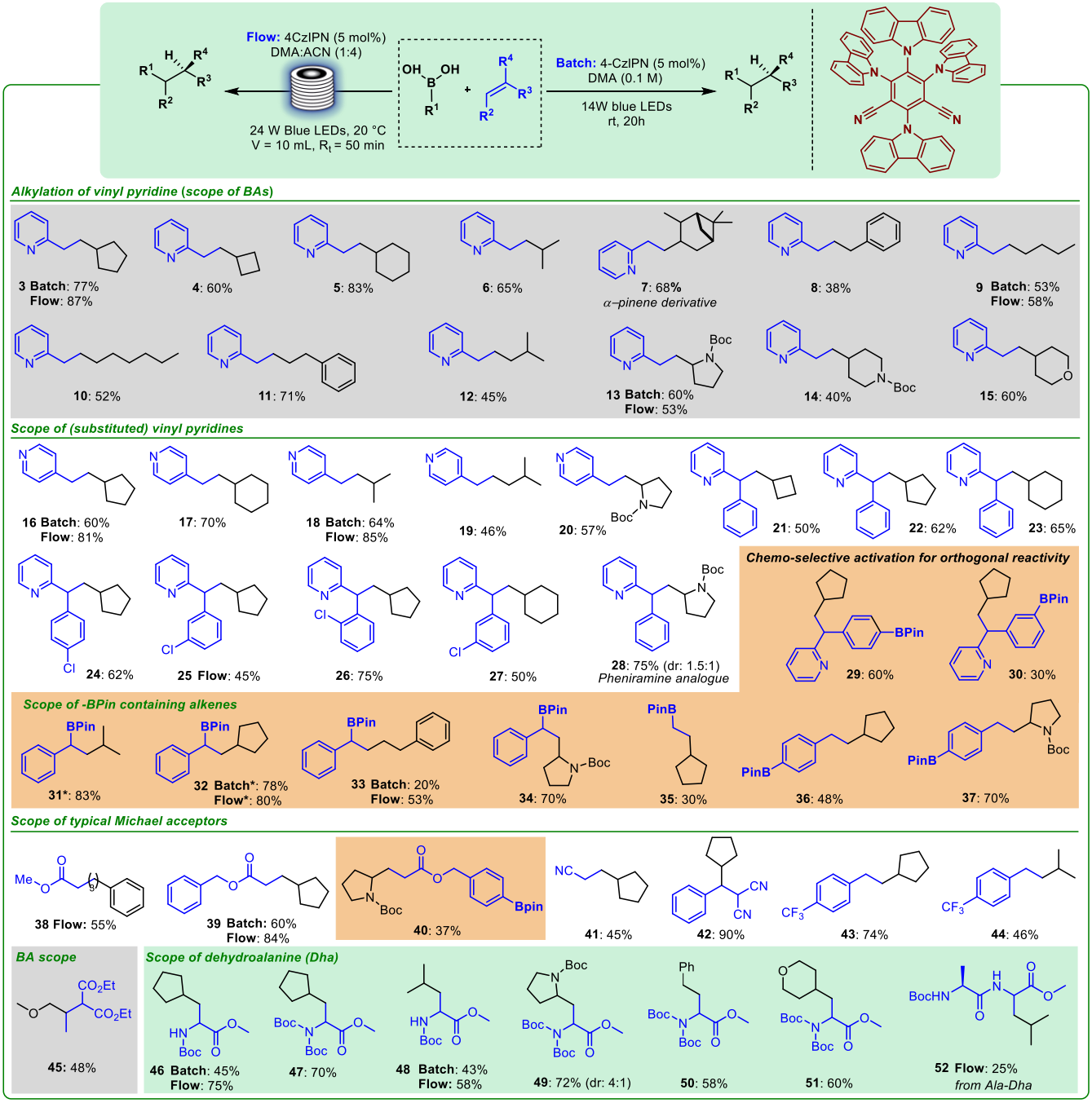
Further, control experiments (Table 1, Entry 2-4) proved that the photocatalyst, an oxygen-free atmosphere and irradiation with blue light, are essential for this transformation (see SI for full optimization). To enable this reaction manifold under aqueous conditions or in a biocompatible manner, we also performed the reaction with a mixture of water and DMA (Entry 5). Interestingly, we obtained 68% yield of desired product. This preliminary result is intriguing, as it shines light on the possibility of performing the same reaction in a more sustainable manner.[18]

In an attempt to improve the reaction efficiency and scalability, we tried the optimized reaction conditions in a photo-flow reactor (Vapourtec UV-150).[19] The translation of the optimal conditions in flow, with a residence time of 50 and 100 min, only afforded the desired product in 45% and 25% yield, respectively (Entry 6,7). Unfortunately, GC-MS and NMR analysis of the reaction showed major formation of a dimer of 2-vinyl pyridine with other unidentified side products. This result could be assigned to the high viscosity of DMA, which can inhibit the diffusion of radicals from one solvent cage to another solvent cage and therefore increase the chance of formation of side products.[20] In order to increase the reaction efficiency, a mixture of different solvents and DMA was evaluated (Entry 8-10). Pleasingly, a 1:4 mixture of DMA in ACN resulted in being the optimal condition, affording **3** in 87% yield (Entry 9). In contrast, working with similar conditions in batch only yielded 16% product **3** (after 1 h irradiation), thus evidently suggesting a close connection between photo-flow reactors and reaction efficiency.

Mechanistic investigations. To gain further insight into the mechanism underlying the observed reactivity, we performed cyclic voltammetry (CV) analysis (Figure 2C). Notably, in the presence of DMA, a new oxidation peak appeared at 1.13 V (*vs* SCE in ACN). This outcome is due to the formation of an electron rich boronate intermediate,[6] probably facilitated by hydrogen bonding interactions between the BA and the weakly nucleophilic DMA (H-bond acceptor basicity (β) = 0.76).[21] The initial observations were further strengthened by NMR spectroscopy (Figure 2B). Indeed, gradually increasing the concentration of DMA, the -OH peak of phenyl ethyl boronic acid showed a clear downfield shift (spectrum recorded in $CDCl_3$). In addition, the signals of the -CH_2- protons close to the boron center also showed a slight upfield shift (spectrum recorded in acetone-d_6, for more detailed information, see SI, Figure S8), an additional proof of the formation of an electron rich boronate intermediate in the presence of DMA. Next, we used ^{31}P-NMR probe to evaluate the Lewis acid and hydrogen bond contributions of BA in the current activation mode.[22] For this purpose, a mixture of HMPA (hexamethylphosphoramide) and phenyl ethyl boronic acid (1:1) in CD_2Cl_2 was used. We observed a downfield shift of HMPA in ^{31}P-NMR, indicating strong binding interactions with boronic acid. The same experiment with phenyl ethylboronic acid pinacol ester resulted in a minor downfield shift in ^{31}P-NMR (SI, Figure S9). These data support the strong contribution of hydrogen bonding in the case of free BAs. Subsequently, fluorescence quenching experiment elucidated the SET step between the excited state photocatalyst and our proposed transient intermediate **A** (Figure 2E). Though no appreciable quenching was detected in the presence of DMA and BA alone, a stronger quenching of the excited state photocatalyst was observed by the mixture of DMA and BA (see SI Figure S4-S6). In the light of these observations, the proposed mechanism is illustrated in Figure 2A. Upon excitation with blue LEDs, the photocatalyst in its excited state oxidizes complex **A** to generate an alkyl radical, which is then trapped by an electron deficient alkene in a Giese-type fashion. Following radical addition, intermediate **B** undergoes a single electron reduction from the reduced form of the photocatalyst, thus forming a carbanion, which can then be protonated or involved in an E1cb elimination step, affording the desired product.

Competitive boron-selective experiment. Understanding the importance of obtaining selective activation in the presence of different boron-based species,[4] we have demonstrated that a chemoselective activation (BAs *vs* Bpins) is quite achievable (Figure 2D). Despite the chemical similarities between BAs and esters as well as their similar oxidation potentials, we established the faster reaction kinetics of cyclopentyl BA over cyclohexyl boronic esters in a competitive experiment. In the presence of both the species in the reaction mixture, the hydrogen bonding interactions selectively increase the electrophilicity of the boron center in BAs over boronic esters and facilitate the formation of a redox-active complex. This unique platform therefore enables the unprecedented chemo-selective generation of radical species from BAs in the presence of –Bpin containing molecules, endorsing plausible (bio)orthogonal modifications under mild reaction conditions.

Alkylation scope. Having evaluated the reaction conditions and aware of the reactivity of different alkyl radicals, we then decided to explore various alkyl BAs towards Giese type addition reaction. In most of the cases, both cyclic and acyclic secondary BAs provided the desired product in good yield, whilst we observed a slight decrease in yield when moving to smaller ring sizes, particularly in the case of the cyclobutyl system, probably due to the destabilization of the resultant radical (Scheme 1, **3-6**).[23]



Scheme 1: **Scope of Giese-type addition**: The values indicate the yield of the isolated products. Conditions unless otherwise noted: BA **1** (1 equiv, 0.44 mmol), alkene **2** (1.5 equiv, 0.66 mmol), 4-CzIPN (5 mol%), DMA (0.1 M), 20 h, irradiating with blue LEDs (14 W). *NMR yield.

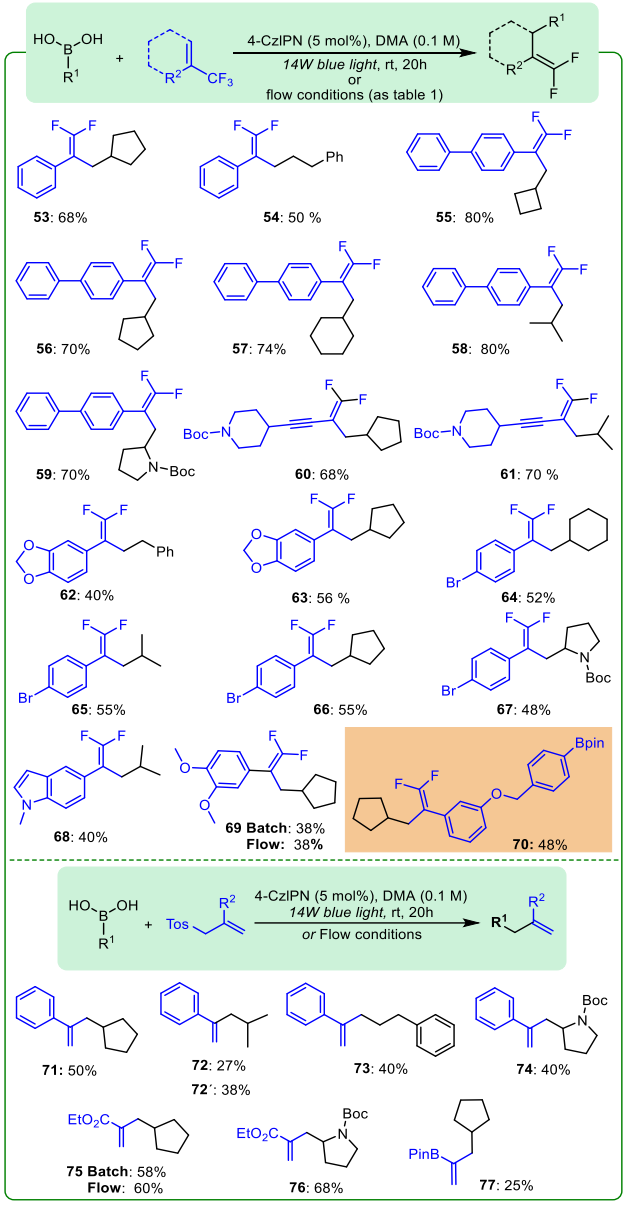
Moreover, the BA derived from *α*-pinene, an abundant natural terpene, could be notably employed as radical source as well (**7**) without observing structural rearrangements in this complex scaffold. Afterwards, primary alkyl BAs and benzyl BA were successfully coupled with both 2-vinyl pyridine and the less reactive 4-vinyl pyridine (**8-12**, **19**) in good to moderate yields. Our methodology was likewise successful with heteroatomic BAs like *N*-Boc protected pyrrolidine, *N*-Boc protected piperidine and tetrahydropyran containing BAs, (**13-15, 20**), providing moderate to good yields. A similar result was obtained with methoxy methyl boronic acid (**45**). Unfortunately, tertbutyl BA was found to be less reactive (15%) under the reported conditions (see SI for details).

4-Vinyl pyridine, despite being less reactive, underwent the alkylation as well, affording the related products in moderate to good yields (**16-18**). A significant increase in the product formation could be pleasingly achieved when performing the same reaction in continuous flow (**16** and **18**). We next turned our attention to delineate the scope of differently substituted alkenyl pyridines. 2-(1-Phenylvinyl)pyridine successfully reacted with cyclobutyl, cyclopentyl, cyclohexyl BA to give the desired products in 50%, 62%, and 65% yield, respectively (**21-23**). Chloro-substituted vinyl pyridines smoothly underwent this Giese-type addition as well to deliver the desired products in good yields (**24-27**). *N*-Boc protected pyrrolidine boronic acid was also employed to form the antihistamine

pheniramine analogue **28** in 75% yield. These results are noticeable, considering that similar transformations become otherwise problematic in traditional metal catalyzed reactions. Our approach was also successfully employed for the selective activation of BAs in the presence of-BPin containing molecules (**29**-**37**), a result otherwise difficult to obtain because of the similar oxidation potential of these two boron species.[7,24] In addition, as underlined by Aggarwal,[25] the synthesis of benzylic pinacol boronic ester derivatives, as for the case of **31**-**34**, is challenging under photochemical conditions due to a fast (photo)catalysed protodeborylation process in the presence of a base. In the case of **33**, a continuous-flow approach was particularly beneficial to increase the yield, as a result of the shorter reaction time and hence increased efficiency.

To further broaden our scope, a wide range of Michael acceptors was tested. The Giese-products were obtained in good to moderate yield (**38**-**52**). The product formation was conditioned by the electrophilicity of the alkene, thus providing an excellent yield in the case of 2-benzylidinemalononitrile (**42**) and a lower yield in the case of acrylonitrile (**41**). It is worth mentioning that, in the case of benzyl acrylate (**39**), flow conditions were found to be particularly beneficial, with a lower formation of byproducts probably derived from the labile benzylic scaffold.[26] We next turned our attention to the functionalization of dehydroalanine (Dha), an aminoacidic residue whose unsaturated backbone can serve as radical acceptor. Indeed, in recent years, the seminal work by Davis' group on 'post-translational mutagenesis' using dehydroalanine residue as free-radical trapping, has inspired many researchers to install side chains on peptides and proteins, employing several radical sources to engage in this transformation.[27a] In this context, we decided to utilize our methodology for the functionalization of protected Dha, affording a variety of structurally modified *unnatural* protected amino acids and the protected amino acid leucine itself in good yields (**46**-**51**). As already highlighted by Molander, the *N*-(Boc, Boc) protection of Dha results in higher reactivity because of the lower electron density on the alkene moiety in comparison with the singly *N*-Boc protected Dha.[27b] Interestingly, the Dha containing dipeptide **52** could be functionalized as well in flow (no desired product could be observed in batch), unveiling the possibility for the selective modification of peptide residues in complex organic and biologically relevant structures.

Elimination scope. We then further proved the versatility of this protocol by applying it to intramolecular radical–polar crossover elimination reactions, *viz*. defluorinative alkylation and allylation reactions. Under the conditions reported by Ley's group,[6] the fast protonation of the intermediate carbanion limits the applicability for elimination reactions. Xu and co-workers circumvented the problem employing a non-protic solvent (DCM), but still using a Lewis base in a defluorinative alkylation method.[29] Pleasingly, under our additive free conditions, the same E1cb-type fluoride elimination predominated over protonation and delivered the desired *gem*-difluroalkene. This moiety is indeed interesting, because of its ability to act as carbonyl mimicking group,[28] with higher stability towards *in vivo* metabolism. We therefore evaluated the scope with respect to a broad variety of trifluoromethylalkenes using primary and secondary boronic acids. Alkyne bearing substrates (Scheme 2, **60, 61**) underwent the reaction smoothly, without observing the concomitant addition of the radical on the alkyne

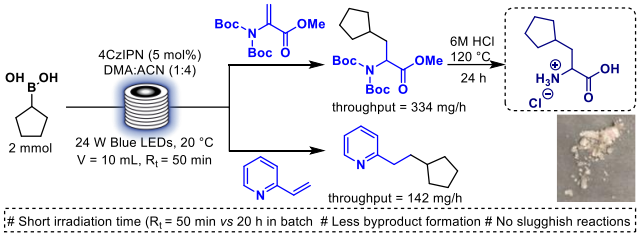


Scheme 2: Defluorinative alkylation and allylation scope. The values indicate the yield of the isolated products. Conditions unless otherwise noted for defluorinative alkylation BA (1.5 equiv, 0.66mmol), alkene (1.0 equiv, 0.44 mmol), 4-CzIPN (5 mol%), DMA (0.1 M), 20 h, blue LEDs (14 W). Conditions unless otherwise noted for allylation reactions: BA (1 equiv, 0.44 mmol), alkene (1.5 equiv, 0.66 mmol), 4-CzIPN (5 mol%), DMA (0.1 M), 20 h, irradiating with blue LEDs (14 W). Flow conditions as mentioned in Table 1.

moiety. Interestingly, we could functionalize heteroaromatic styryl systems bearing the indole moiety (**68**) and a benzo[d][1,3]dioxole group (**62, 63**) under mild reaction conditions. In addition, a -BPin substituted styryl system could also be successfully alkylated in moderate yield without the loss of the pinacolborate scaffold (**70**). With a similar elimination mechanism, allylation reactions were performed as well

(**71**-**77**). The desired allylated products were obtained in moderate yield in the case of phenyl allyl sulphone (**71**-**74**), while increased yields could be achieved installing a more electron-withdrawing group such as an ethyl ester in the starting material (**75** and **76**). The competitive protonation step especially lowered the yield in the case of **72**, where the Giese product was predominantly formed (**72´**).

Reaction scale-up. Having demonstrated the wide applicability of this reaction manifold, we sought to prove its robustness *via* performing large scale continuous-flow reaction. Increasing the reaction scale to 2 mmol in flow in a 10 mL reactor, the alkylated product from 2-vinyl pyridine was afforded in 68% yield (throughput = 142 mg/h), opening the possibility to achieve a successful scale-up. The same reaction in batch could only afford 6.09 mg/h. Similarly, the 2 mmol reaction employing Dha as radical acceptor, delivered the unnatural amino acid presented in Scheme 3 in 75% yield (throughput: 334 mg/h). These results clearly show the superiority of flow chemistry for an efficient scale up of photochemical reactions.



Scheme 3: Reaction Scale-up.

Conclusion. In conclusion, we have demonstrated that the oxidation potential of alkyl boronic acids can be tuned by means of a hydrogen bond-assisted activation with an amide based solvent, allowing for the possibility of performing a wide variety of reactions. This remarkable result enables for the first time the selective generation of radical species from boronic acids in the presence of boronic esters, giving rise to the possibility of further functionalization and construction of complex scaffolds. Continuous-flow chemistry also played a fundamental role in the attempt to decrease the otherwise long reaction times and obtain better yields. Considering the presented results, we believe that this expedient approach will be of great utility for the efficient employment of boronic acids as a radical source in the growing field of photoredox catalysis.

ASSOCIATED CONTENT

Supporting Information

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Author Contributions

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Notes

The authors declare no competing financial interest.

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