REVIEW

Uncovering the potential of boronic acid and derivatives as radical source in photo(electro)chemical reactions

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Abstract: The chemistry of boron compounds has been profoundly investigated in the last decades, leading to ubiquity in many synthetic applications as well as biologically active molecules. Since the advent of photoredox catalysis, an upsurge in the discovery of suitable radical precursors has been witnessed, and boron is becoming a protagonist in this field. Despite many studies focused on trifluoroborates, the use of boronic acids and esters have received much less attention in this regard. Because of their high oxidation potential, the development of methods to enable their involvement in photocatalyzed reactions is only recent. Nonetheless, this review summarizes novel strategies developed to unlock their role as radical precursors in photochemical reactions and discloses the potential that boronic acids and esters own, when their intrinsic chemical properties are exploited.

1. Introduction

Since its recognition as an enabling tool to form challenging C-C and C-heteroatom bonds in mild and sustainable conditions, photoredox catalysis has been in the spotlight of the synthetic community.[1–4] The central role that this field is gradually achieving relies on the remarkable possibility to employ visible light to generate open shell species in a selective manner. Upon excitation, photocatalysts are able to interact with suitable radical precursors, whom redox potential lies in the redox window of the photocatalyst itself.[2] Photons, therefore, become traceless reagents and their employment in photoredox reactions enable the gradual formation of radical species, avoiding the use of harmful UV radiations, toxic tin containing radical initiators and high temperature.[5] As a consequence, the interest to develop novel synthetic strategies has spiked and researchers have developed different strategies to overcome the limitations related to the field. In particular, in depth studies on the photochemical properties of organic dyes or metal based photocatalysts, and advancement in the analytical techniques have allowed to fine tune their properties.[6] Also, employment of the photo-flow reactors has provided the solution to the limitations related to light penetration and scale-up of photochemical reactions.[7–9] The choice of suitable radical sources has markedly been of central importance, with the aim to offer both a wide assortment and high selectivity to the chemists approaching the photoredox catalysis field, allowing for unprecedented functional group tolerance and applicability.[3,5] In the radical precursor landscape, boron-based species have begun to play a predominant role.[10–13] Their chemical stability and versatility, together with an environmentally benign character and low toxicity, have been the reasons of their broad exploitation in Suzuki-Miyaura cross-coupling reactions, and render them appealing substrates for photochemical reactions.[14] In particular, since 1969, boranes have become a convenient radical source under light irradiation and many procedures have been developed in absence of tin-containing reagents. Indeed, the electron deficiency of the boron atom and the possibility to engage in strong B-X bonds (BDE (B-O) for $(EtO)_3B$ = 519 kJ/mol) was discovered early and deeply explored in radical reactions employing highly energetic UV irradiation as energy source.[15] However, the autoxidation of boranes is no longer regarded as a convenient photochemical radical generation method. Of late, the development of greener alternatives has allowed to surpass these protocols and has broadened the synthetic application of boron-containing species.[10] In 2012, Akita's group reported the use of trifluoroborates as radical precursors in a photocatalyzed reaction.[16] In this foremost example, trifluoroborates were first employed as α-heteroatom methyl radical precursors and thereafter as primary, secondary and tertiary alkyl radical sources in a Giese-type addition reaction. Two years later, Molander and co-workers disclosed the first dual catalytic pathway for a cross-coupling reaction by exploiting a single electron transmetalation step and employing trifluoroborates as radical precursors.[17] After these pioneering works, a plethora of novel protocols exploiting the reactivity of trifluoroborates has appeared.[11,18,19]

Organotrifluoroborates are tetrahedral, non-Lewis acidic species, where the sp^3-hybridized boron atom engages in strong B-F bonds, impeding the reactions that would occur through the interaction between a nucleophile and the empty *p*-orbital on boron.[20] After their discovery in the 1960s, trifluoroborates have become convenient substrates in the Suzuki-Miyaura reaction because of their ease of preparation, bench stability and the possibility to be employed as protected forms of boronic acids and esters, avoiding sluggish reactions and the formation of byproducts related to the earlier introduced less stable boron species. Notably, what also makes trifluoroborates extremely convenient reagents in photoredox reactions is their medium to low oxidation potential, matching most of the redox values of the commonly employed photocatalysts.[10]

Serena Pillitteri received her Master's degree with *summa cum laude* in *Pharmaceutical Chemistry and Technology* at the University of Turin (Italy) in 2019. Her undergraduate thesis focused on novel approaches for the generation of C-based radicals from boronic acids and derivatives under photocatalyzed conditions and was conducted under the guidance of Prof. Erik Van der Eycken and Dr. Upendra K. Sharma at KU Leuven (Belgium). After her master thesis, she joined PhD in the same group as a FWO-researcher. Her research interests focus on the application of visible light photoredox catalysis in continuous flow and on the development of novel synthetic methodologies for the generation of C-based radicals.

Prabhat Ranjan received his PhD degree in Chemistry (Marie Skłodowska-Curie fellow) from KU Leuven, Belgium, in 2021 under the guidance of Prof. Erik Van der Eycken. During his PhD, he gained expertise on enabling technologies in organic synthesis through short research stays at Prof. Rafael Luque's lab (Spain) and Prof. Giancarlo Cravotto's group (Italy). Currently, he is working as a Postdoctoral researcher at the *Aachen Maastricht University for Biomass* under the guidance of Prof. Romano Orru. His research interests lie in the area of photocatalysis, flow chemistry, heterogeneous catalysis and green chemistry.

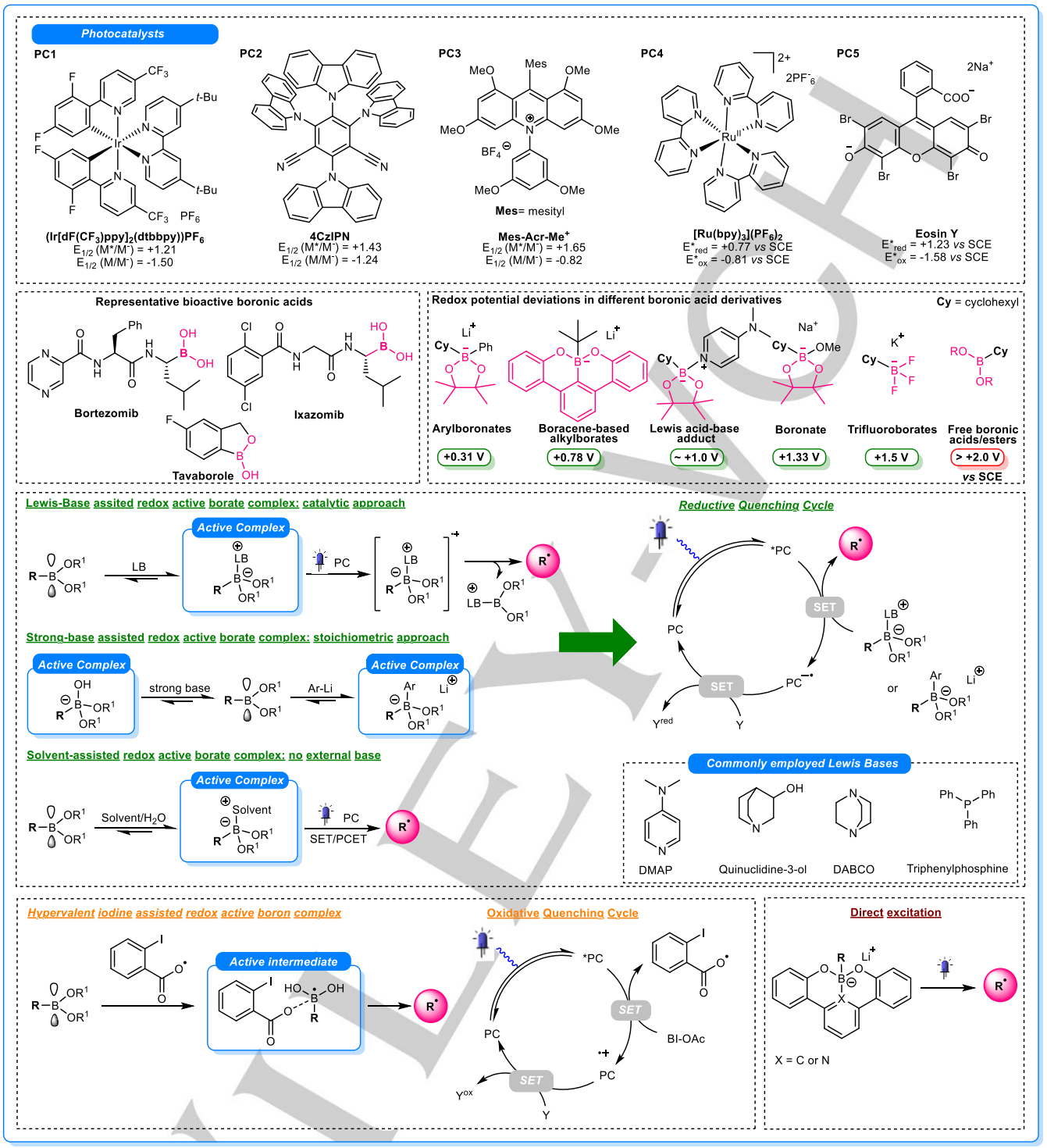


Figure 1. The background and radical generation pathways involving boronic acid (derivatives).

While the reactivity of trifluoroborates has been widely investigated, the interest in the use of other boron species as radical precursors in photocatalyzed reactions has only recently arisen. This late exploration lies in the fact that the oxidation potential of boronic acids and esters is considerably high, and the use of strong oxidants has usually been a straightforward mean to achieve the formation of radical species.[21] Nonetheless, to circumvent issues related to the low solubility of trifluoroborates in organic solvents and the ensuing difficulty in the use of flow systems to boost the photochemical reaction efficiency, a diverse array of activation modes has been developed. In most of the cases, the inherent chemical nature of boronic esters and boronic acids, *i.e.* their Lewis acidity, was exploited. In these species, boron is sp^2 hybridized and shows a trigonal planar geometry, with the vacant *p*-orbital perpendicular to the plane. This empty orbital is responsible for the Lewis acidic character of boronic esters, boronic acids and their trimeric form (boroxines).[22] These are, in fact, susceptible to electron donation from Lewis bases, resulting in the formation of a tetrahedral "-ate" complex that shows different chemical features from its precursors. In general, through different interaction strategies with the empty *p*-orbital, boronic acids and esters have become, in the last years,

viable radical precursors. This review is therefore intended to present these activation strategies and to enlighten the synthetic potential of these techniques, whose very recent development leaves the challenges of the field worth investigating. For the sake of clarity, we have divided the activation methods into three principal sections: radical generation through a reductive or an oxidative quenching cycle, direct excitation of boronic acid (derivatives) (**Figure 1**). Further hints regarding the electrochemical generation of radical species have also been provided.

2. Radical generation through a reductive quenching cycle

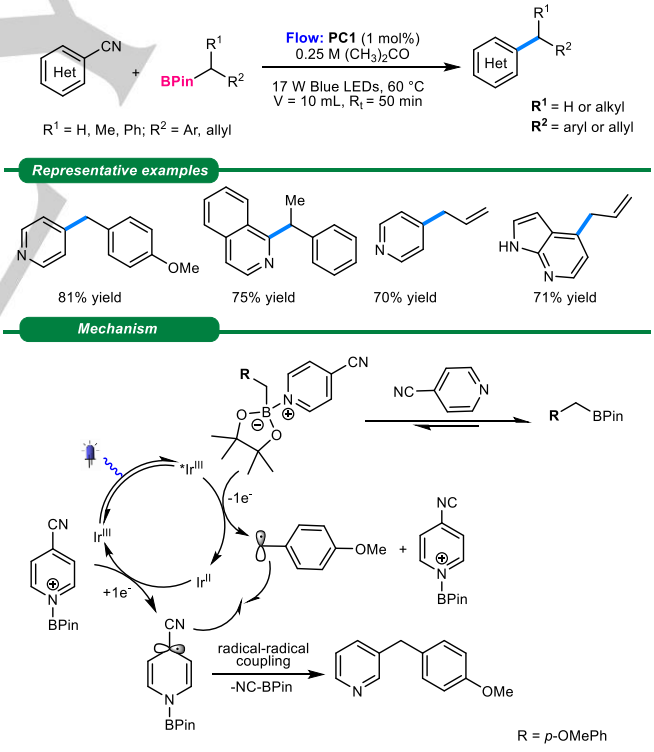
2.1. Lewis-base activation of boronic acids and esters

In a reductive quenching cycle, the photocatalyst in its excited form behaves like an oxidant and is able to abstract an electron from a donor. The radical intermediate thus generated then undergoes further reactions. Concurrently, to complete the catalytic cycle, the turnover of the reduced form of the photocatalyst is accessed through a second single electron transfer (SET) process. The electron is therefore donated either to a sacrificial oxidant or to a reaction intermediate (redox-neutral reactions).[2]

Erik V. Van der Eycken is a full Professor of Organic Chemistry and Head of the Division of Molecular Design & Synthesis at KU Leuven, Belgium. He received his PhD-degree (1987) in organic chemistry from the University of Ghent, Belgium. He spent time as visiting scientist at the University of Graz (2002) with Prof. C. O. Kappe, at The Scripps Research Institute (La Jolla, USA) (2003) in the group of K. B. Sharpless, and at Uppsala University (2004) with Prof. M. Larhed and Prof. A. Hallberg. The main focus of his research is the development of new synthetic methodologies in combination with enabling techniques.

Upendra K. Sharma received his PhD (2011) from CSIR-Institute of Himalayan Bioresource Technology, Palampur, India. Thereafter, he worked as an assistant professor for a short period at the National Institute of Technology, Jalandhar, India. In 2013, he joined the research group of Prof. Erik Van der Eycken at the University of Leuven, Belgium followed by postdoctoral stints with Prof. Steven Ley (University of Cambridge), Prof. Timothy Noël (University of Eindhoven) and Prof. Shu-Li You (SIOC, China). In 2020, he joined KU Leuven as a senior research-expert. His research interests include new reaction methodologies employing photoredox catalysis, C-H functionalizations and flow chemistry.

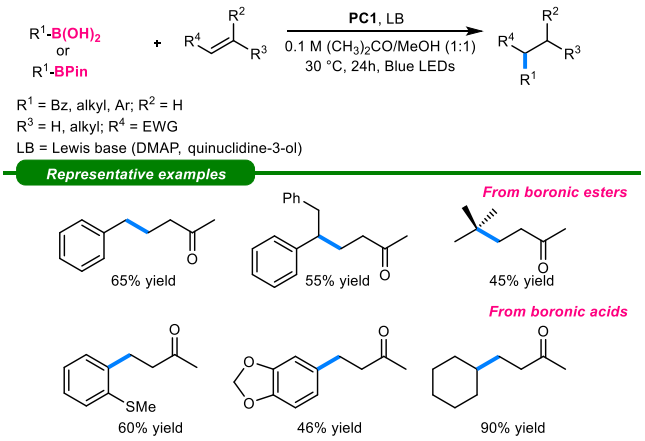
Among the oxidative carbon radical precursors, the employment of boronic esters remained underexplored until 2016, when for the first time Ley's group disclosed a novel activation mode of benzyl boronic acid pinacol esters in a photocatalyzed process (**Scheme 1**).[23] In their report, the formation of an acid-base adduct between the boronic ester and a Lewis base (pyridine or 4-(dimethylamino)pyridine (DMAP)) was found to be the underlying reason enabling the formation of a benzyl radical. Indeed, the electron-rich boronate complex is susceptible to oxidation and subsequent rearrangement to form the benzyl radical intermediate. In silico calculations and NMR complexation studies were conducted to validate the hypothesis. Employing Molander's conditions[17], the dual Ir/Ni catalyzed cross-coupling reaction performed well in the presence of activated benzyl boronic esters. In comparison to the corresponding trifluoroborates reported by Molander, slightly lower yields were obtained. An added value to this procedure was that photo-flow reactors could be easily employed, avoiding the common clogging issues related to the use of trifluoroborates or carboxylates as radical precursors. In the same report, the authors applied the aforementioned mode of activation to obtain the arylation of benzyl and allyl boronic esters using cyanopyridines as both activating agents and reagents. In this transformation, the excited photocatalyst first oxidizes the activated boronic ester and then reduces the cyanopyridine. The persistent radical formed can then engage in a radical-radical coupling with the previously generated benzyl or allyl radical, forming the desired product.



Scheme 1. Activation of boronic esters applied in a photoredox catalyzed $C(sp^2)$-$C(sp^3)$ cross-coupling reaction in a flow reactor.

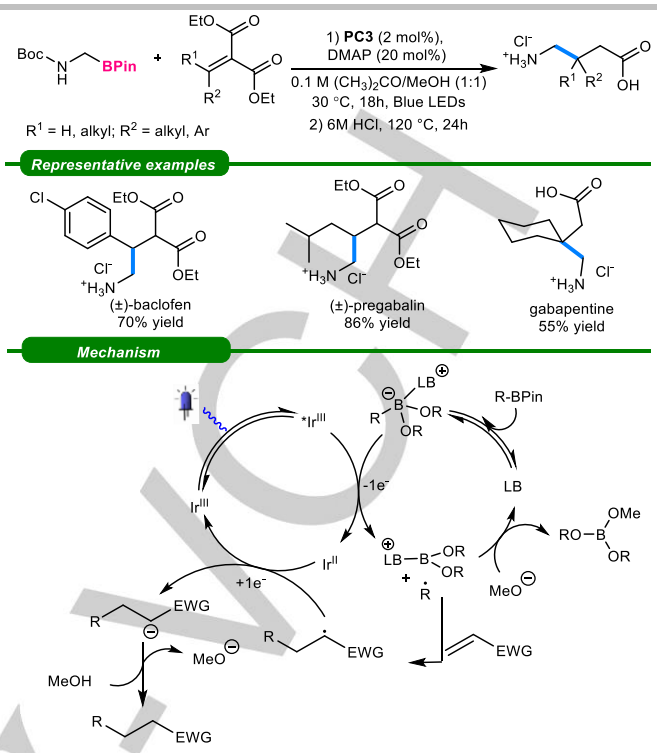
In 2017, in light of Denmark's concept of Lewis-base catalysis[24], the same group implemented the previously presented method to generate not only benzyl, but also unstabilized alkyl and aryl radicals that further reacted in a Giese-type addition with electron-deficient alkenes (**Scheme**

2).[25] The interaction between the Lewis acidic boron center and a carefully chosen Lewis base caused the desired alteration in the redox properties of the boron species and enhanced their reactivity, a behavior that can be ascribed to the Lewis-base catalysis theory thoroughly described by Denmark.[24] After a broad screening, the authors succeeded in the use of a catalytic amount of a Lewis base (quinuclidine-3-ol or DMAP) in the activation step.

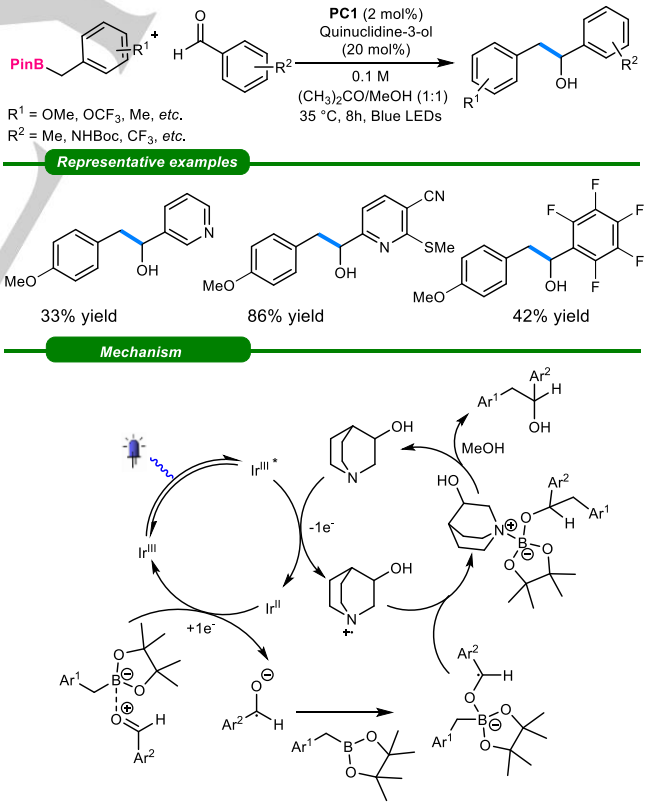


Scheme 2. Lewis base-catalyzed activation of boronic acids and boronic esters and application in a Giese-type addition reaction.

In the proposed mechanism, the redox-active complex undergoes a single electron oxidation step, followed by the addition on electron-poor olefins. This radical intermediate is then reduced by the photocatalyst and the resulting anion is protonated by a protic solvent, *i.e.* methanol. The authors propose that the methoxide thus formed is responsible for the regeneration of the Lewis base catalyst. Unfortunately, this catalytic platform could not be applied to aromatic boronic esters, but this limitation led the authors to explore the use of different boron species. Electron rich aryl boronic acids were found to be reactive under their conditions, allowing to broaden the range of applicability of this innovative reaction manifold. The authors later demonstrated through NMR complexation experiments that the reactive species in solution were not the free boronic acids, but their trimeric form (boroxines), that could be subjected to the same mode of activation. In light of this result and in the attempt to further expand the scope of this transformation, primary and secondary alkyl boronic acids were also employed and proved to be reactive. An additional attractive feature of this protocol is its applicability in the synthesis of biologically active drug molecules. Indeed, soon after the first report, the same group employed Boc-protected α-amino boronic ester in a coupling reaction with easily available diethyl malonate-derived olefins, providing, after a deprotection, hydrolysis and decarboxylation step in the presence of HCl, the desired APIs belonging to the γ-amino butyric acid (GABA) derived drug family (**Scheme 3**).[26] Moreover, the use of a large-scale flow system enabled the synthesis of 8 mmol/h of these drug molecules. This report stands out from the previous methodologies because of the utilization of an organic photocatalyst (acridinium based, **Figure 1**, PC3), that solves the problem of metal (Ir and Ru mainly) contamination in the production of APIs.



Scheme 3. Activation of Boc-protected amino boronic esters.

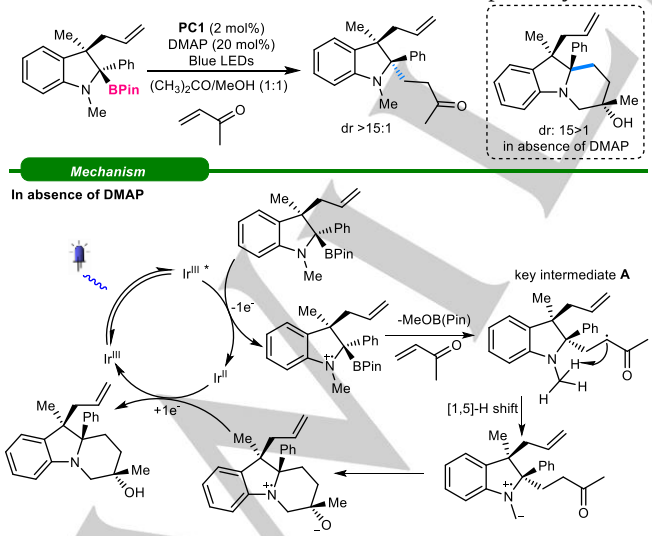


Scheme 4. Photoredox coupling of benzyl boronic esters with carbonyl-containing compounds.

When performing the reaction with the aforementioned conditions, employing aldehydes/ketones as radical acceptors, the result obtained was intriguing. Indeed, Ley and co-workers reported that only benzylic BPin esters could undergo the reaction, delivering the desired addition product in the presence of aldehydes, ketones and a small number of preformed imines (**Scheme 4**).[27] While in the previous protocol DMAP worked optimally in most of the cases, in this work only a moderate yield was achieved, and the efficiency of DMAP was surpassed by quinuclidine.

The authors therefore rationalized this result considering that the excited photocatalyst can first oxidize quinuclidine and be then regenerated after the single electron reduction of the carbonyl moiety, activated through the interaction with benzyl boronic ester. It was also proposed that the acyl radical can then interact with the boron center or alternatively, the generated activated complex (by the interaction between carbonyl moiety and boronic ester) is directly reduced to form a common radical intermediate. In the last step, this intermediate is oxidized by the quinuclidine radical, thus regenerating the Lewis base and leading to the final product. Despite the novelty, the scope of this transformation remains limited to benzyl boronic esters, but allows the functionalization of carbonyl moieties, a remarkable result considering the propensity of the intermediate alkoxy radicals towards back electron transfer or homolytic C-C *β*-scission. The reaction also performed exceptionally in flow and the scale-up afforded 1.69 g of the product in a 10 h run.

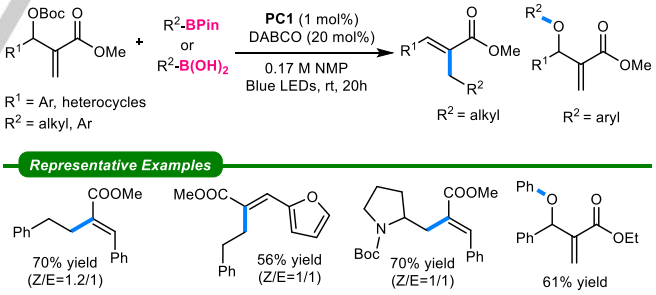
Inspired by these seminal reports, Ready and Panda functionalized chiral indolines with adjacent quaternary stereocenters employing Ley's conditions for the activation of the -BPin moiety (**Scheme 5**).[28] In their work, they observed interesting results that helped to enrich the understanding and the applicability of the previously described activation method. In particular, the tertiary boronic ester moiety, upon activation, gave rise to a radical species that underwent the addition onto the radical acceptor (methyl vinyl ketone). The desired product was afforded with high diastereoselectivity (dr > 15:1). Moreover, the authors noticed the additional formation of an annulated compound together with the 1,4-addition product in the absence of DMAP, as a result of a different mechanistic pathway.



Scheme 5. Photocatalytic radical functionalization of indolines containing a -BPin moiety.

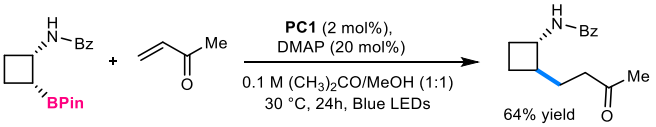
Surprisingly, this unexpected structure could be formed exclusively and diastereoselectively in the absence of DMAP. Mechanistically, the formation of this product was rationalized considering that the -BPin moiety is adjacent to the nitrogen of the indole scaffold, a missing structural element in Ley's compounds. The Ir photocatalyst in its excited state is thus able to engage in the single-electron oxidation of the indoline nitrogen, that after subsequent rearrangement and loss of the boryl group forms a tertiary radical. At this stage, the radical attacks methyl vinyl ketone, generating the key intermediate **A**, that can either be reduced and undergo the final protonation step or can be involved in a 1,5-hydrogen atom transfer with the *N*-methyl group and form the annulated product (Scheme 5). In their mechanistic studies, the authors noticed that a fine-tuning of the reaction conditions could lead to distinct outcomes. Despite the role of DMAP remaining unclear, a higher loading of the Lewis base was found to favor the reduction of the *α*-keto radical intermediate, probably by direct reduction. The high level of diastereoselectivity observed was related to the presence of a stereocenter at C3. Indeed, the tertiary carbon radical formed after the SET step is achiral, and it was therefore concluded and further demonstrated that the methyl/allyl stereocenter causes steric effects.

In 2019, Xu and co-workers utilized the same activation strategy to couple alkyl boronic acids or esters with Baylis-Hillman derivatives, generating *α,β*-unsaturated carbonyl compounds (**Scheme 6**).[29] As highlighted in their report, the synthesis of trisubstituted alkenes remains highly dependent on the use of harsh conditions. Nevertheless, employing DABCO as the activating Lewis base, they were able to form the desired products in good to moderate yield. While primary and secondary boronic acids were both reactive, the product obtained when employing aryl boronic acids was different than the expected one. The authors suggest that this outcome could be due to the rapid oxidation of boronic acids to phenols in the reaction conditions, and their subsequent involvement in S_N2'-S_N2' reaction.



Scheme 6. Functionalization of Baylis-Hillman products with Lewis base activated boronic acids/esters under photocatalyzed conditions.

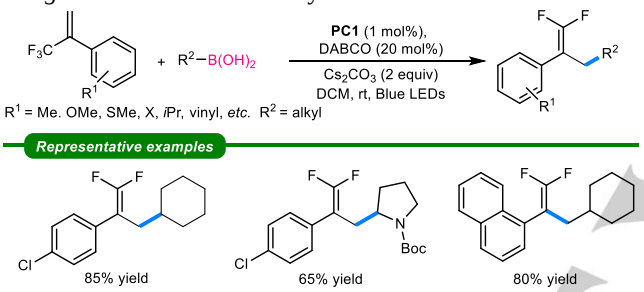
In the same year, Liu and co-workers demonstrated the versatility of -BPin containing cyclobutanes obtained through 1,2-azaborine photoisomerization.[30] The DMAP-mediated activation of the boronic acid pinacol ester moiety resulted in the functionalization of 1,2-substituted cyclobutene without loss of this constrained structure (**Scheme 7**).



Scheme 7. 1,2-substituted -BPin bearing cyclobutene functionalization through photocatalysis and Lewis-base activation of the boronic ester moiety.

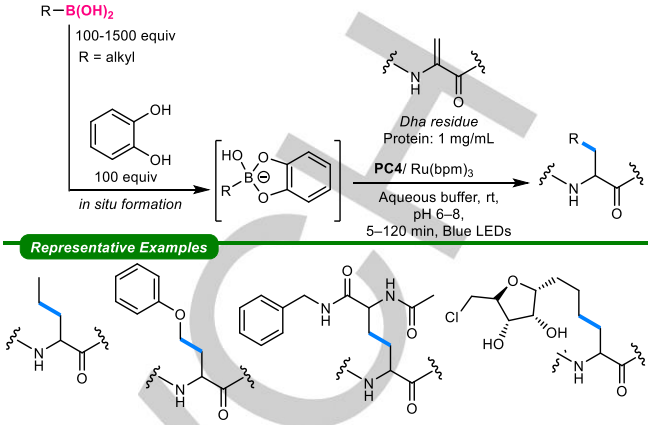
In 2020, the Lewis base-mediated activation strategy was successfully employed in the synthesis of *gem*-difluoroalkenes (**Scheme 8**)[31], already recognized biologically relevant moieties as bioisosteres of the carbonyl group.[32] As a result, their synthesis has received increasing attention, and many radical sources (potassium organotrifluoroborates, *α*-trimethylsilylamines, silicates and Hantzsh esters) have been used in combination with *α*-trifluoromehtylstyrene as radical acceptor because of its high electrophilicity.

In this report, primary and secondary alkyl boronic acids were used as coupling partners, and variously substituted *α*-trifluoromehtylstyrenes were successfully subjected to the reaction conditions. The authors confirmed the necessity of the Lewis base (DABCO) and Cs_2CO_3 as an additive, and they proposed a radical-polar crossover mechanism. The anionic intermediate formed after photocatalyst turnover, a common element in all the described methods, is then involved in an elimination step (instead of protonation) to obtain the formation of a *gem*-difluoroalkene moiety.



Scheme 8. Coupling of Lewis-base activated alkyl boronic acids with *α*-(trifluoromethyl)styrenes.

In the same year, the generation of radical species from boronic acids was skillfully addressed by Davis, Gouverneur and co-workers in the post-translational modification of proteins (**Scheme 9**).[33] The challenges related to the modification of peptides and proteins are well recognized, and, to avoid the difficulties related to the incorporation of unnatural amino acids during biosynthetic processes, the need for mild and selective reaction conditions has been a longstanding target. In this context, the authors elegantly employed catechol as an activating agent to form a boronic acid catechol ester, whose oxidation potential measured by cyclic voltammetry was found to be compatible even with weak oxidizing Ru photocatalysts ($Ru(bpy)_3$ ($^*E_{ox}$ = +0.77) or $Ru(bpm)_3$ ($^*E_{ox}$ = +0.99)) at sub-stoichiometric concentration. The use of catechol alkylboronic esters as radical precursors is already well established[34,35], but their employment in photocatalyzed reactions has been elusive. In their report, the authors suggested that the higher strength of B-O bonds in comparison to C-B bond is the driving force for the formation of a complex and its subsequent oxidation. The recovery of catechol in aqueous media allowed its use in a catalytic amount. Subjecting dehydroalanine (Dha) pre-functionalized proteins to the previously described conditions, different side chains could be installed, and a wide variety of functional groups for further functionalization was tolerated. Unfortunately, the authors highlighted the impossibility to achieve the addition of methyl groups or the use of aromatic radicals.



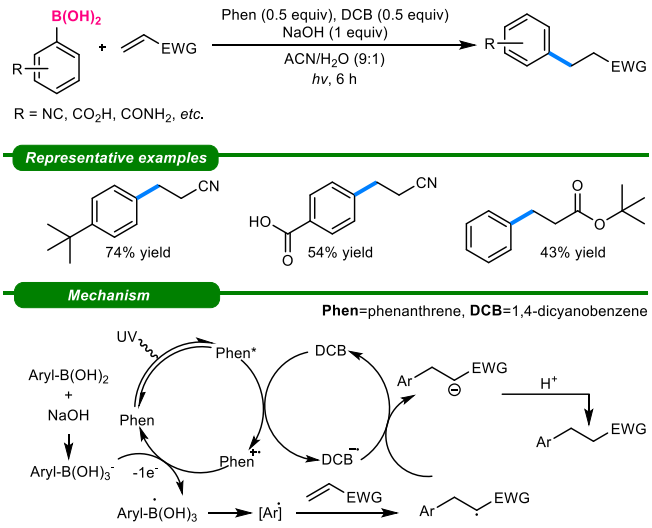
Scheme 9. Light-driven post-translational installation of alkyl groups through photochemical activation of *in situ* generated boronic acid catechol esters.

2.2 Activation of boronic acids and esters through charged nucleophiles and strong bases

The generation of redox-active complexes between boronic acids/esters and charged nucleophiles or strong bases has also been thoroughly investigated, leading to the development of expedient strategies to exploit the intrinsic properties of boronic acids/esters as radical precursors.

The first example was presented in 2018 by Yoshimi's group, who reported a photo-Meerwein type arylation strategy, where aryl radicals could be conveniently formed from boronic acids.[36] Though aryl diazonium salts have usually been the preferential source of aryl radicals in this kind of reaction[37], their inherent instability and toxicity hinder many synthetic perspectives. In this regard, Yoshimi and co-authors exchanged the use of these unstable compounds with easily available, more stable and non-toxic boronic acids (**Scheme 10**).

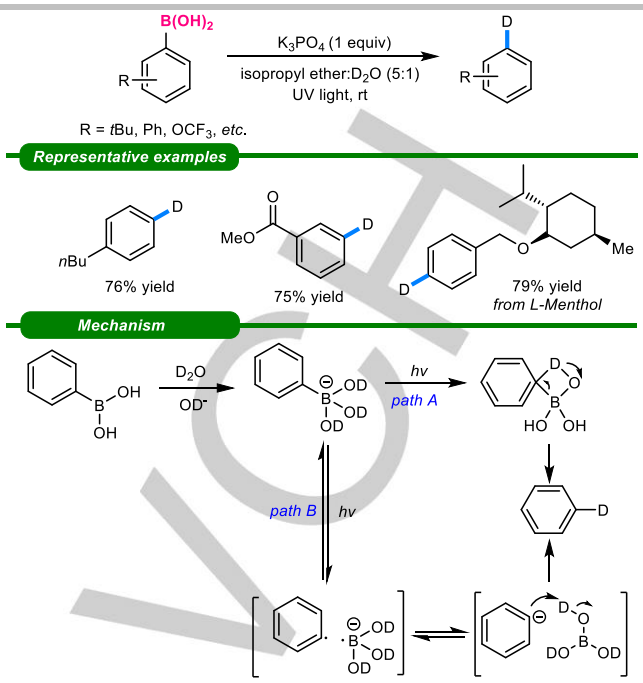
In their strategy, the addition of 1 equivalent of NaOH is necessary to form the redox-active borate, which is subsequently oxidized by a combination of the photosensitizers phenanthrene (Phen) and 1,4-dicyanobenzene (DCB) under UV light irradiation (100 W high-pressure mercury lamp). Under the same conditions, phenyl boronic acid pinacol esters and triphenyl borane, as well as phenyl triolborate and phenyl trifluoroborate (both in the absence of NaOH) showed less activity. Following a Giese-type mechanism, the procedure led to higher yields in the case of electron-rich boronic acids, while lower product formation was observed in the presence of electron-withdrawing groups on the aromatic ring, a predictable behavior caused by the slower addition rate of electron-poor aromatic radicals on electron-poor olefins. At this stage, the authors underlined the need of a higher concentration of radical acceptor (5 equiv). Considering the reactivity of aryl radicals, a hydrogen atom transfer (HAT) event from the solvent is indeed expected and highly probable. The high concentration of electron-withdrawing alkene was therefore intended to limit the formation of the reduced product rather than the desired one. The high amount of the photocatalysts (10 mol%) was justified to reduce the rate of oligomerization arising from the high amount of alkene added.



Scheme 10. Photo-Meerwein type arylation of electron-poor olefins.

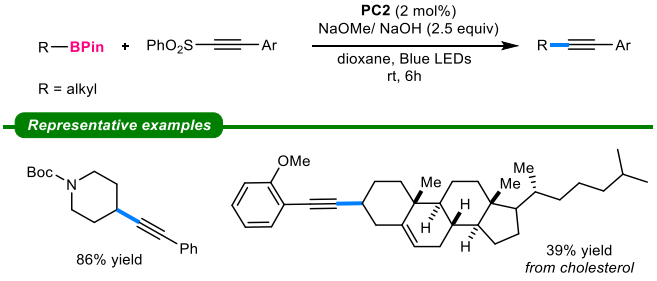
In 2020, Zeng and co-workers employed a similar activation mode to perform a deborylation-deuteration reaction.[38] It is widely recognized that deuterated molecules play a central role in many scientific fields, including medicinal chemistry.[39] Nonetheless, the development of practical photocatalyzed deuteration reactions is still underexplored. In this context, the authors presented a robust strategy to synthesize deuterated compounds from boronic acids using a cheap deuterium source (D_2O) without the need of metal catalysts or high temperature (**Scheme 11**). Noteworthy, in the presence of K_3PO_4 and UV light, it was possible to achieve the deuteration of a wide variety of aromatic boronic acids, regardless of the electronic properties of the substituents. In fact, aryl boronic acids containing both electro-donating and electro-withdrawing groups could be deuterated. The optimized conditions successfully delivered the deuterated products with a wide range of substrates, even in the presence of heteroatoms, free hydroxyl group, and amide groups, allowing to deuterate natural products such as a Vitamin E derivative and *L*-menthol derivatives. Unfortunately, alkyl boronic acids were found to be unreactive because of the impossibility to excite them even with a 254 nm UV irradiation. Mechanistically, the authors propose that upon the formation of a boronate complex in the presence of a base and subsequent excitation a four membered transition state is formed, followed by deborylation and deuterium incorporation. Alternatively, the authors do not exclude that the light can promote a C-B bond homolytic cleavage of the boronate complex, leading to the formation of a phenyl radical and a boric acid radical anion. After electron exchange, a phenyl anion and boric acid are formed. At this stage, the aryl anion can either abstract deuterium from boric acid or from D_2O to generate the final deuterated product with a remarkable level of deuterium incorporation.

The alkynylation of boronic acid pinacol esters was accomplished by Liu and co-workers in 2020 (**Scheme 12**).[40] In this work, the boron center was activated towards single-electron oxidation through the addition of an excess of NaOMe or NaOH.



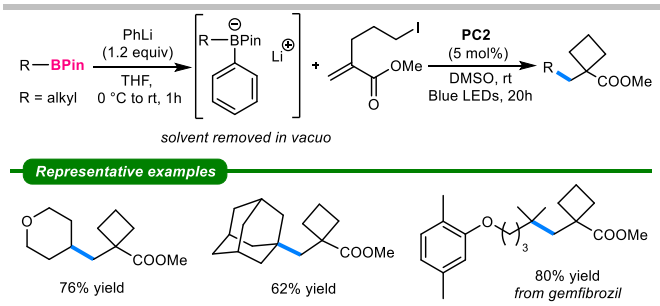
Scheme 11. Photochemical deuteration of aryl boronic acids.

The alkynylation was accessed *via* a radical addition/elimination pathway using phenylsulfones as radical acceptors. The reaction conditions proved to be widely applicable, and only a change from NaOMe to NaOH was required in the case of tertiary boronic acid pinacol esters, as a result of the increased steric hindrance of tertiary carbon centers, which precluded the possibility of complexation with the acetate group. Regioselectivity in the presence of two distinct boron centers was achieved as well, giving rise to the possibility of further functionalization of the derived products. Overall, the method proved to be versatile and applicable to natural product derived structures.



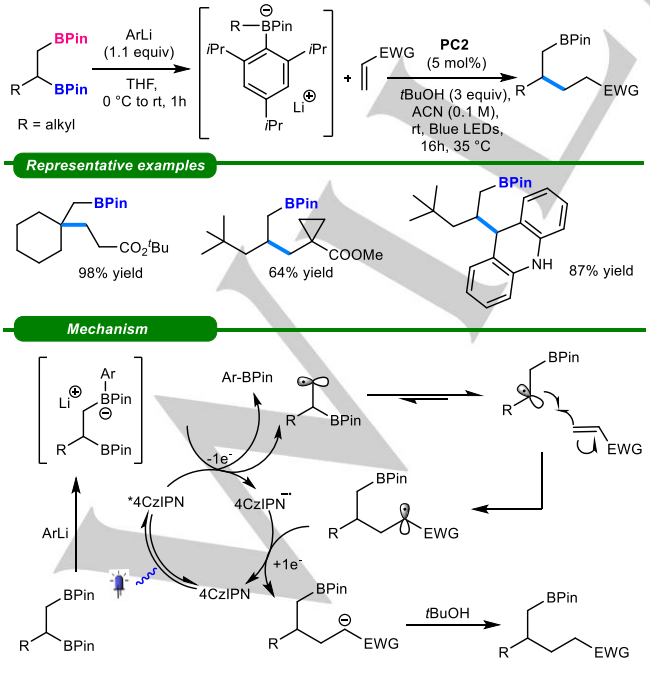
Scheme 12. Photo-induced alkynylation of alkyl pinacol boronates.

In 2019, Aggarwal and co-workers reported the synthesis of cyclobutanes through a deboronative radical addition-polar cyclisation pathway.[41] In this case, the activation of the boron center towards single-electron oxidation was achieved through the use of organolithium reagents, whose high nucleophilicity allows to form a complex with the boronic ester moiety (**Scheme 13**).

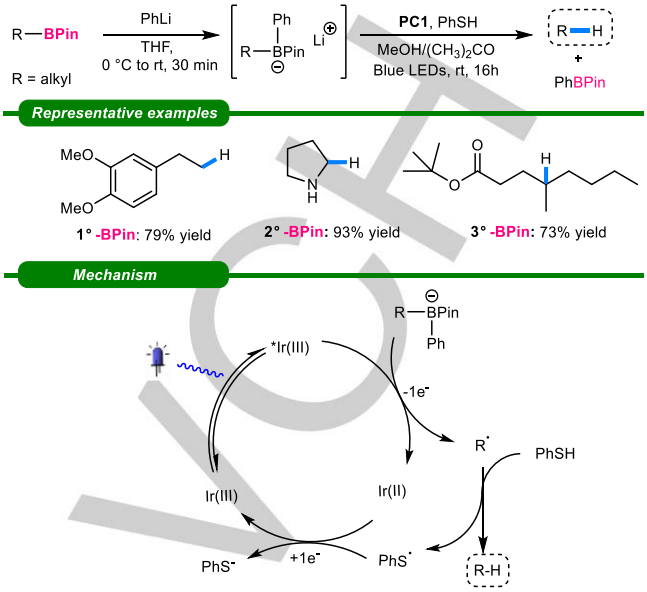


Scheme 13. Photoredox catalyzed synthesis of cyclobutanes through a deboronative radical addition-polar cyclization.

This complex shows an incredibly low reduction potential (0.31 V *vs* SCE in ACN) that renders it susceptible to oxidation by all the commonly employed photocatalysts, a remarkable decrease considering the high oxidation potential of free boronic acid pinacol esters. The removal of the solvent (Et_2O) and recovery of the complex allowed the authors to employ anhydrous conditions in the subsequent step. Indeed, in the absence of water, an S_N2 4-*exo-tet* cyclization is favored over the protonation usually ending in a Giese-type addition process, leading to the formation of the chemically constrained, but biologically highly valuable cyclobutane ring. The process showed high group tolerance and allowed to employ primary, secondary and tertiary boronic esters as radical source. Interestingly, the authors propose two different mechanistic scenarios, where the use of ACN as a solvent enables a radical polar crossover, with the formation of a carbanion to close the photocatalytic cycle and a subsequent S_N2 step to achieve the cyclobutanation. This mechanism is supported by a control experiment performed in the presence of 5% of water, where only the Giese adduct could be formed. On the contrary, mechanistic studies performed in DMSO allowed to state that a radical cyclization is more prone to happen, and the liberating iodine radical can be reduced and thus regenerate the photocatalyst.



Scheme 14. 1,2-Boron shift of β-boryl radicals obtained from bis-boronic esters.



Scheme 15. Photoredox catalyzed protodeboronation of pinacol boronic esters.

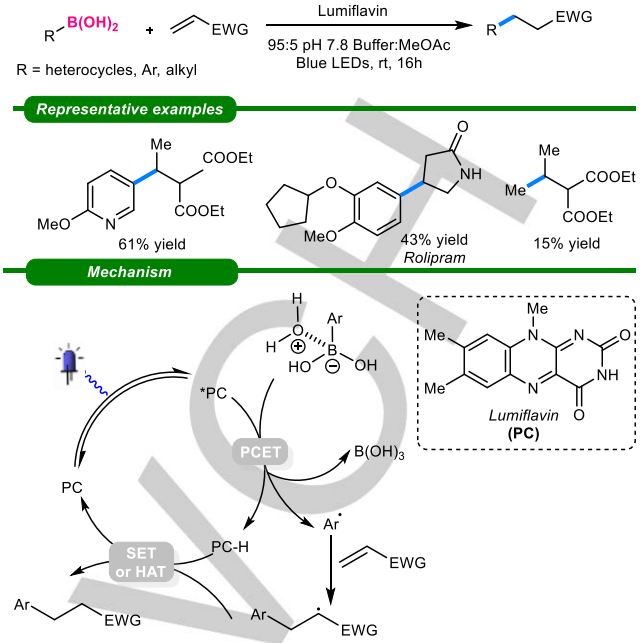
The same group also reported the mono-functionalization of 1,2-bis-boronic esters under photocatalyzed conditions **(Scheme 14)**.[42] Aryl lithium reagents were once again employed to activate the boron center towards single-electron oxidation. In this work, the authors reported the selective formation of the boronate complex at the less hindered position, followed by single-electron oxidation and generation of an unstable primary radical. At this stage, they hypothesize a 1,2-boron shift, that led to the formation of the thermodynamically more stable secondary radical, which was further reduced with the concomitant regeneration of the photocatalyst. A slight variation of the optimal reaction conditions allowed to tune the reactivity of the anionic species, providing the protonated, transannulated or the allylated product. The unconventional 1,2-boron shift was demonstrated through DFT calculations and deep mechanistic investigations, which enabled to confirm the thermodynamically driven pathway towards the functionalization of the more hindered position in the presence of two or three boronic acid pinacol ester groups. In addition, the migration step was found to be stereospecific.

In the same year, Studer and co-workers accomplished, for the first time, an efficient photocatalytic protodeboronation strategy of primary, secondary and tertiary boronic esters (**Scheme 15**).[43] The employed boronic esters where subjected to the activation strategy introduced by Aggarwal,[41] using phenyl lithium in diethyl ether to form the redox active complex. The authors reported the impossibility to obtain the protodeboronated product employing a Lewis base instead of phenyl lithium as activating agent. Pairing this protocol with a Matteson-CH_2-homologation step, an *anti*-Markovnikov alkene hydromethylation was achieved, providing the synthetic foundation for the successful synthesis of various natural products. In the proposed mechanism, the excited photocatalyst is able to oxidize the preformed boronate complex, that upon rearrangement gives rise to an alkyl radical and phenyl boronic

acid pinacol ester as byproduct. The alkyl radical then abstracts a hydrogen from thiophenol, thus forming the desired product and a thiyl radical, which is responsible for the regeneration of the photocatalyst. Beside its novelty, the method was also applicable to enantioenriched boronic esters, as this transformation was found to be highly stereospecific.

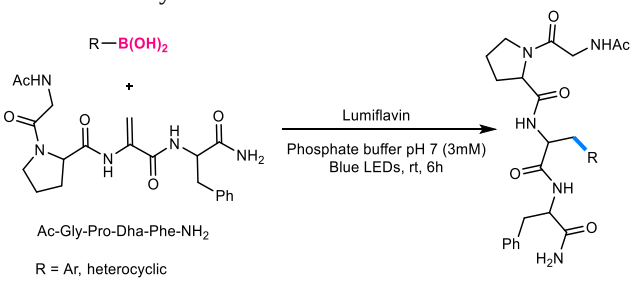
2.3 Activation of boronic acids with solvent/weak base

An interesting strategy, able to combine photoredox catalysis and biocompatibility in the use of boronic acids as radical precursors, was developed by Bloom and co-workers in 2020 (**Scheme 16**).[44] This example stands out from previous works because of the bioinspired catalytic mechanism involved in the transformation. In their report, the authors aim to avoid the use of external Lewis bases as well as strong ionic bases, which can either directly engage in the single electron reduction of the photocatalyst or can favor a protodeboronation pathway of the boronic acids. The authors therefore introduced a biologically inspired photocatalyst (lumiflavin) in aqueous media to achieve the formation of heteroaryl, aryl and alkyl radicals, which further engage in a Michael addition pathway to form a wide variety of arylated or alkylated products, including three drug molecules. In their extensive mechanistic studies, they revealed the central involvement of water in the activation of boronic acids and subsequent photochemical generation of radicals, otherwise impossible by a direct SET (single electron transfer), HAT (hydrogen atom transfer) or PCET (proton coupled electron transfer) step from free boronic acids. DFT calculations revealed that a water molecule can exothermically coordinate to the boron center. Upon coordination, the O-H bond strength significantly decreases, allowing a PCET with the singlet lumiflavin to happen. Indeed, the single-electron oxidation of the aqua-boryl complex renders the proton of the coordinated water more acidic and susceptible to abstraction from the radical lumiflavin semiquinone. This cardinal step is then followed by rearrangement and formation of boric acid as a byproduct, together with radical species, later involved in the Giese-type reaction pathway. The authors suggest that the radical intermediate arising after the radical addition on the electron poor alkene can be either involved in a HAT step with the photocatalyst or in a SET process followed by protonation from the solvent. The novelty of the method relies on the remarkable possibility to generate radicals from aryl boronic acids without the need of activating agents, with the benefit of using biologically compatible reaction conditions (a water-soluble flavin derived photocatalyst in a water solution at pH 7.8, with a low addition of an organic solvent).



Scheme 16. Biocompatible generation of radicals from boronic acids in aqueous media.

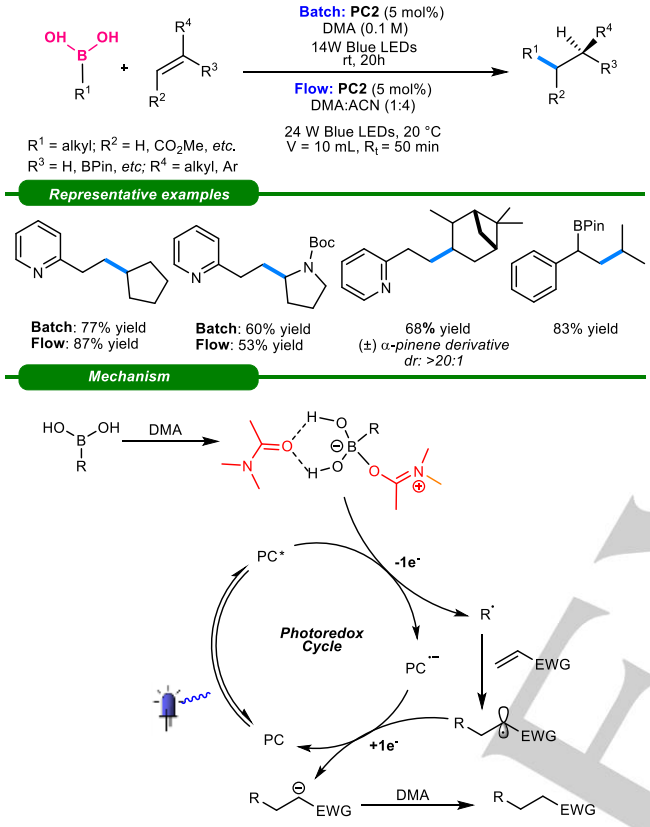
The same group further applied this method to peptide modification, to synthesize non-proteogenic amino acids (NPAA), that often reveal to be important modulators of peptide-based drug activity or in peptide probes (**Scheme 17**). With a different structure from natural amino acids, these provide a broader range of chemical interactions that can help to improve the bioactive properties of the structures under study. Using a high-throughput method and lumiflavin as a biocompatible photocatalyst, the authors employed a 96-well array with 445 nm blue LEDs to test aromatic, heteroaromatic and aliphatic boronic acids as radical precursors to attack a dehydroalanine (DHA) containing short peptide. A parallel purification method was also employed, enabling to perform a thrombin inhibition experiment to evaluate the bioactivity of the obtained products. Interestingly, when applied to a longer peptide bearing potentially interfering amino acids chains, the DHA residue was the only modified residue, and only boronic acids acted as radical precursors, affording the desired peptide in 50% conversion. The transformation therefore features broad applicability and chemoselectivity.



Scheme 17. Biocompatible generation of radicals from boronic acids and non-proteinogenic amino acid synthesis.

A complementary strategy for the solvent-mediated activation of aliphatic boronic acids was presented last year by our group.[45]

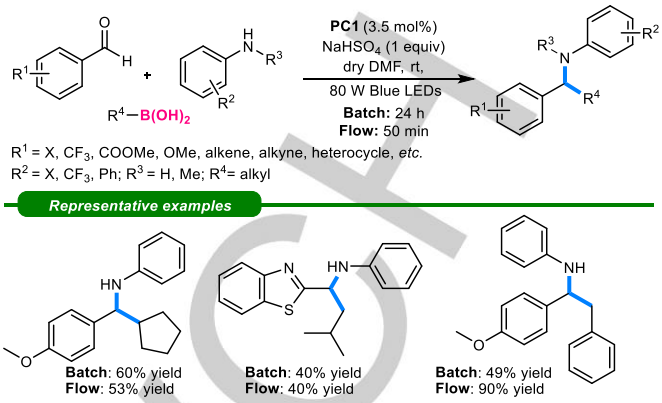
The ability of DMA was exploited to modulate the oxidation potential of boronic acids through its hydrogen bonding abilities, enabling radical generation without the need of external activators (**Scheme 18**). The optimal reactions conditions were applied to the Giese-type reaction, allylation and defluorination reactions. This strategy could be applied to the functionalization of dehydroalanine as well, leading to the synthesis of unnatural amino acids. Another relevant element was the possibility to achieve the orthogonal functionalization of boronic acids in the presence of BPin-containing starting materials, opening the way to further functionalization.



Scheme 18. Accessibility of alkyl radicals from boronic acids through solvent-assisted organophotoredox activation.

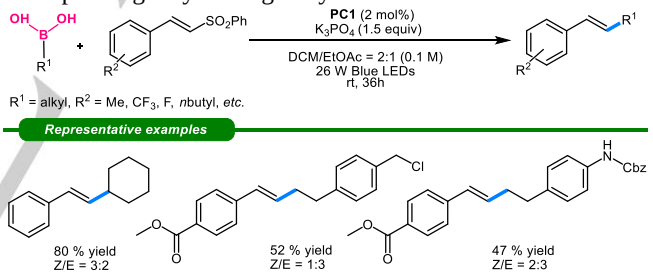
The translation of batch conditions to flow led to a drastic reduction of reaction times, with a residence time of 50 min found sufficient to obtain comparable yields. In some cases, the shorter irradiation time resulted in less byproduct formation and increased yield. The mechanism of this transformation, supported by several mechanistic investigations, follows the Giese-type addition pathway, with the hydrogen bonding and Lewis acid-base interactions between boronic acids and DMA as driving force for radical generation.

Following the activation method described above, a photoredox catalyzed Petasis reaction was also performed, to achieve the formation of secondary and tertiary amines.[46] In contrast to the traditional Petasis reaction, this protocol did not need any activating group on the starting material, avoiding substrate limitations, and it could be applied to alkyl boronic acids, expanding the scope from vinyl and (hetero)aryl boronic acids.[47] This multicomponent reaction manifold developed by our group was also amenable to flow conditions. Again, the implementation of batch conditions under continuous flow appeared to be a winning strategy to increase the reaction throughput in shorter time (**Scheme 19**).



Scheme 19. Visible light-mediated Petasis reaction using boronic acid.

Recently, Wang *et al.* presented a different approach to form alkyl radicals from boronic acids (**Scheme 20**).[48] In this case, they observed through quenching experiments that benzensulfinates are able to activate boronic acids towards single-electron oxidation. Following the pathway of a redox-neutral elimination, the authors found broad applicability of the reaction conditions, that could be applied to variously substituted benzensulfinates and to primary and secondary alkyl boronic acids. Unfortunately, the E/Z ratio could not be controlled. Alkynyl sulfones could be employed as well, affording the corresponding alkynes in good yield.



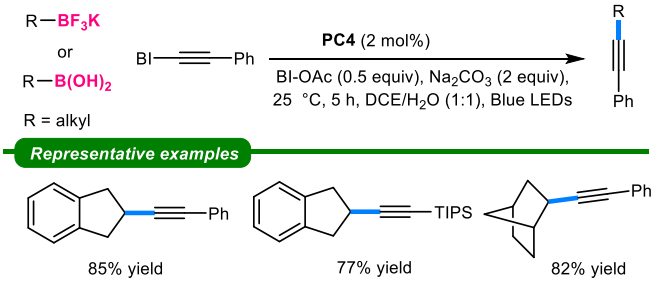
Scheme 20. Alkenylation of alkyl boronic acids without an external Lewis base as activator.

3. Radical generation through an oxidative quenching cycle.

A different strategy to tackle the formation of radical species from boron acid derivatives has addressed the use of mild iodine containing oxidants, harnessing the interaction between the two species or the direct involvement of the oxidant in the photocatalytic cycle. In contrast to the previous section, the quenching of the excited photocatalyst happens through an oxidation step which often involves the iodine reagents in the presented examples. This first step is then followed by catalyst reduction and turnover through the donation of one electron (**Figure 1**). In the examples added to this section, a common active form of the boron species could not be identified, as different mechanistic scenarios were envisioned in each report.

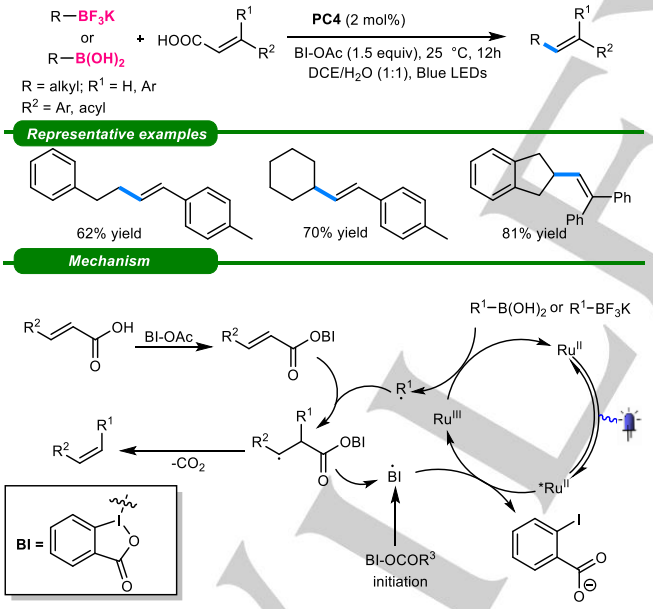
In 2014, Chen's group introduced for the first time the use of benziodoxole derivatives (*i.e.* BI-OH or BI-OMe) in a

deboronative alkynylation reaction, where a range of variously substituted BI-alkynes was functionalized with primary, secondary and tertiary alkyl groups derived from the corresponding trifluoroborates and, notably, from boronic acids as well (**Scheme 21**).[49]



Scheme 21. Deboronative alkynylation of BI-OAc activated alkynes.

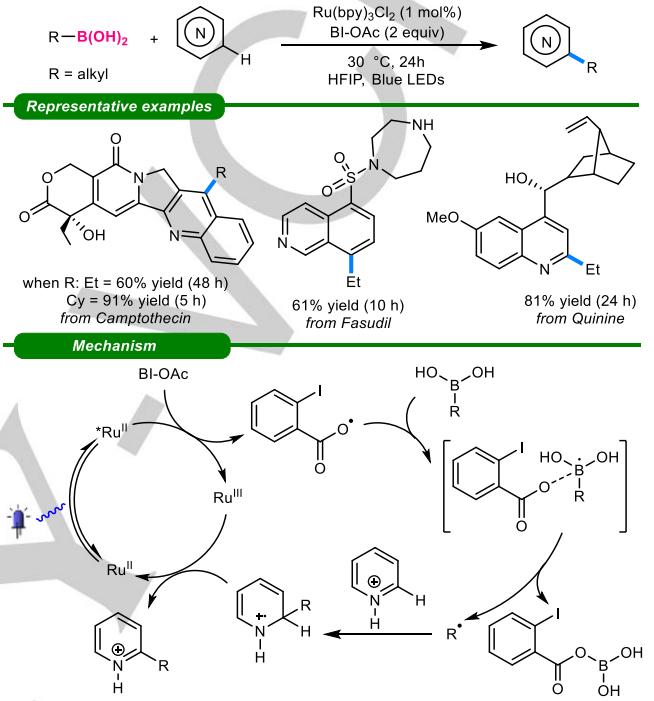
A year later, the same group employed a similar strategy in a Csp^2-Csp^3 radical alkenylation reaction.[50] In both the reports, a common mechanistic pathway was conceived, where either BI-OH (or BI-O•) or the benzoiodoxole vinyl carboxylic acid complex are able to oxidatively quench the photocatalyst in an initiation step. The regeneration of the photocatalyst is then achieved through a SET step with the radical precursor (trifluoroborates or boronic acids). The alkyl radical is then further involved in an alkynylation or a decarboxylation alkenylation process, leading to the formation of the desired product (**Scheme 22**).



Scheme 22. Deboronative alkenylation enabled by an hypervalent iodine reagent.

The mild conditions developed in both reports allow the functionalization of differently substituted starting materials, avoiding the need of harsh conditions and protecting groups. Primary, secondary and tertiary radicals could be successfully employed. Notably, the authors also developed biocompatible conditions to perform the reactions, using a pH 7.4 phosphate saline buffer in the presence of different biomolecules, including aminoacids, oligosaccharides, nucleic acids and remarkably, bacterial lysates. Despite the presence of variously substituted oxidation sensitive functional groups, the reaction proved to be chemoselective and robust, unlocking the possibility to develop biocompatible manifolds, an objective that is gradually becoming predominant in synthetic chemistry.

In 2016, the BI-OAc-mediated activation of boron species was employed by Chen and Liu in a Minisci C-H alkylation of *N*-heteroarenes.[51] Boronic acids were the preferential source of primary and secondary alkyl radicals (**Scheme 23**).

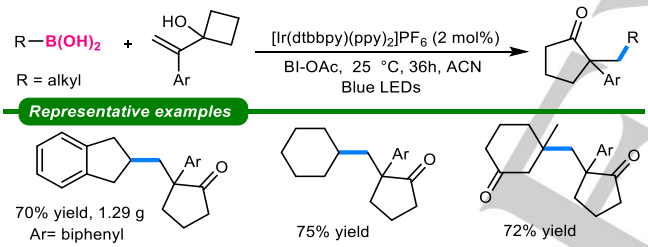


Scheme 23. Photoredox catalyzed Minisci C-H alkylation of *N*-containing heterocycles with boronic acids and hypervalent iodine.

The functional group tolerance and the mildness of the optimized conditions allowed to functionalize various biologically relevant heterocycles, including quinine (bearing a free hydroxyl group), the less reactive caffeine and in-use drugs such as the anticancer camptothecin and the antiviral famciclovir, paving the way for a highly tolerant strategy for late-stage functionalization. To achieve the transformation, together with $[Ru(bpy)_3]Cl_2$ as photocatalyst, BI-OAc was added as a mild oxidant to help the formation of alkyl radicals from boronic acids. The authors shed light on the possible reaction mechanism through control experiments and DFT calculations. They propose that the interaction between the employed mild oxidant and boronic acid is the driving force for the formation of radical species. As compared to Chen's reports, this work deeply investigates the role of BI-radical in the generation of alkyl radicals from boronic acids, proposing a different mechanistic scenario from the previous work. This was demonstrated by adding 1 equivalent of ortho-iodobenzoyl peroxide to the reaction mixture. Even in the absence of the photocatalyst, the alkylated product was formed in 38% yield, demonstrating that benzoyloxy radical can interact with boronic acids. This hypothesis was substantiated by computational studies, which suggested that $[Ru(bpy)_3]Cl_2$ in its excited state can reduce BI-OAc, leading to the formation of a radical intermediate, that subsequently undergoes a

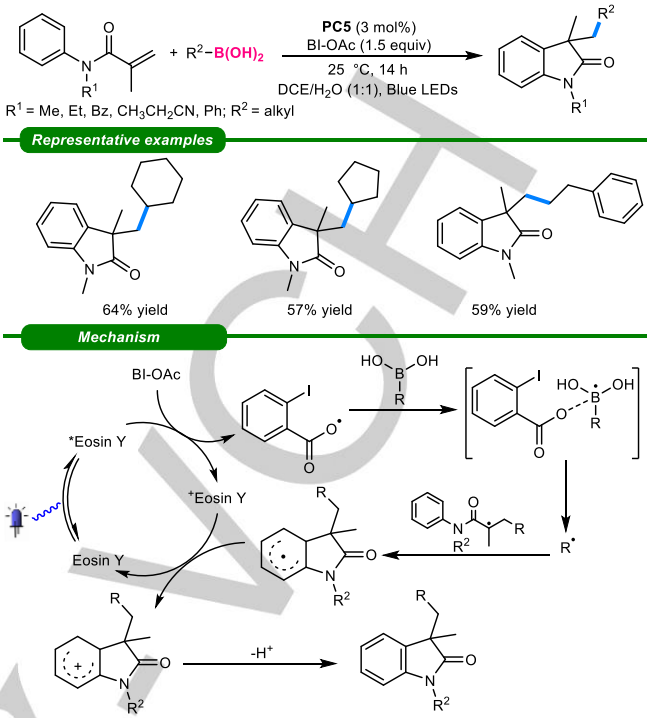
rearrangement (I-O bond cleavage) with the release of an acetate anion and an oxygen-based radical. This radical can interact with the boron atom to form an intermediate "-ate" anion that then rearranges to form the desired alkyl radical. The reaction mechanism then follows the classical pathway of the Minisci reaction, with the addition of the alkyl radical to the *N*-heteroaromatic protonated scaffold, forming a radical intermediate which is then oxidized by the photocatalyst. This step leads to the generation of the final product and the closure of the photocatalytic cycle.

In 2018, a similar approach was employed to build ketones bearing an α-quaternary carbon center, employing allylic alcohols as starting materials and boronic acids as alkylating agents (**Scheme 24**).[52] In the reaction mechanism, a crucial role was played by BI-OAc, both in the photocatalytic cycle and as activator of the allylic alcohol. The authors proposed that the excited $[Ir(dtbbpy)(ppy)_2]PF_6$ is quenched by BI-OAc through an oxidative quenching cycle, which leads to the formation of an Ir^{IV} species. The oxidized form of the photocatalyst is then involved in the oxidation of boronic acid and in the generation of an alkyl radical, which can attack the BI-OAc/allylic alcohol complex. After the oxidation of this intermediate and the formation of a cation, a semi-pinacol rearrangement takes place, generating the final product. The optimal conditions were applicable on a modest number of substrates, nevertheless showing a high functional group tolerance. Interestingly, the gram-scale reaction between cyclopentyl boronic acid and vinyl cyclobutanol afforded 1.29 g of the correspondent product (70% yield).



Scheme 24. Alkyl boronate addition/rearrangements to allylic alcohols.

Wang, Han and co-workers further explored this strategy to achieve the formation of 3,3-disubstituted oxindoles through a deboronative alkyl-arylation of acrylamides.[53] Owing to the central role that this scaffold holds in pharmaceutical chemistry, the authors successfully employed the already known combination of BI-OAc and boronic acids under photochemical conditions, using Eosin Y (PC5) as the photocatalyst (**Scheme 25**). The radical intermediate underwent an intramolecular radical C-H functionalization, affording the cyclic species which was subsequently subjected to oxidation and deprotonation to afford the desired product and the regeneration of the catalyst. Exploring the scope, the authors underlined the possibility to use a variety of primary and secondary boronic acids, but unfortunately, aryl boronic acid did not work under these reaction conditions probably due to lower stability of aryl radicals. With respect to the acrylamides, notable group tolerance was observed, with the generation of a mixture of regio-isomers in the case of *meta* substitutions. Overall, the presented method showed relatively broad applicability, avoiding the use of the harsh conditions traditionally necessary to generate the same scaffold.

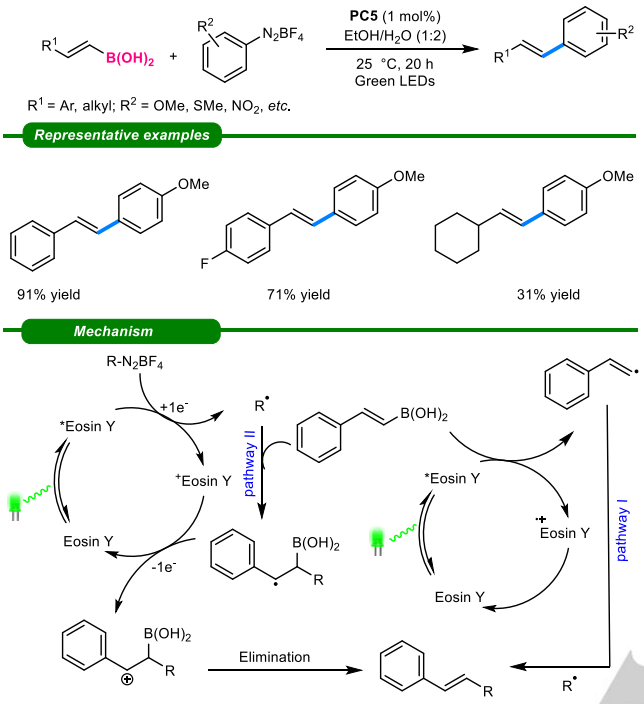


Scheme 25. Deboronative alkylarylation of acrylamides with boronic acids.

A different approach in the generation of radicals from boronic acids was presented in 2020 by Wu and co-workers (**Scheme 26**).[54] They developed a convenient alternative to the traditionally employed methodologies to synthesize stilbenes, whose ubiquitous presence in natural and biologically active molecules is well recognized. In contrast to the usually employed quite harsh conditions, the authors proposed the employment of an organic photocatalyst (Eosin Y, PC5) in a mixture of EtOH and water at room temperature. These mild conditions also allowed the safe employment of diazonium salts, in combination with the non-toxic and easy to handle boronic acids, to achieve the formation of *E*-stilbenes.

The reaction showed tolerance to different functional groups and a reasonable decrease in yield when going from *para* to *meta* to *ortho* substitution. Alkyl boronic acids were found to be less reactive. Mechanistically, through EPR studies and control experiments, the authors suggested that upon excitation Eosin Y (PC5) is able to reduce aryl diazonium salts and generate a reactive aryl radical. The next step is the generation of a vinyl radical from boronic acids, which then undergoes a radical-radical coupling with the aromatic radical. Based on the lifetime difference of vinyl and phenyl radicals, the authors proposed that the persistent radical effect is responsible for the formation of the desired product through radical-radical coupling. The homocoupling from both the radical sources could be detected as byproducts, according to the substitution pattern and the deriving self-reaction rate constants. Alternatively, having found a molecular weight correspondent to the TEMPO adduct *via* GC-MS, the authors suggested that the aryl radical can also undergo a radical addition on the *E*-styrene boronic acid. The radical intermediate arising can then be subjected to an elimination following an oxidation step, generating the final product. The authors also pin-pointed the different regio-selectivity in the

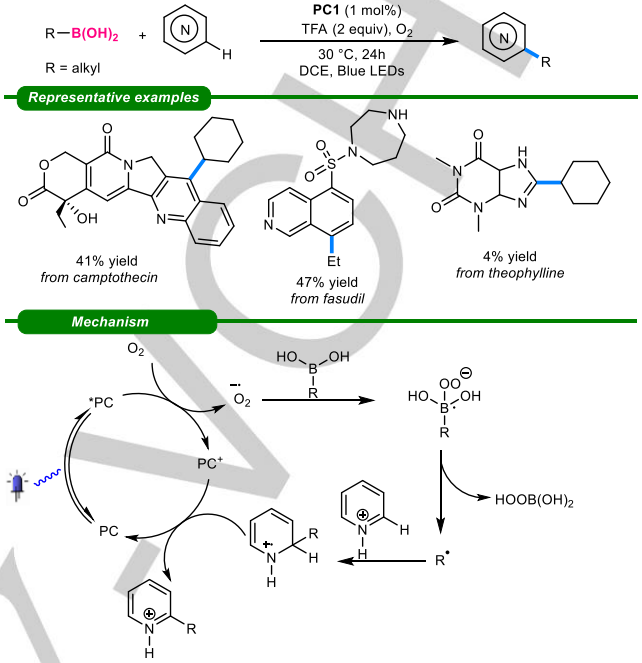
presence of $Ru(bpy)_3Cl_2$, where *Z*-stilbenes become the main product. After careful monitoring of the reaction conditions, they were able to confirm the photochemical reason for the observed isomerization, excluding the involvement of a cross-coupling mechanism.



Scheme 26. Synthesis of stilbenes through cross-coupling of alkenyl boronic acids and diazonium salts.

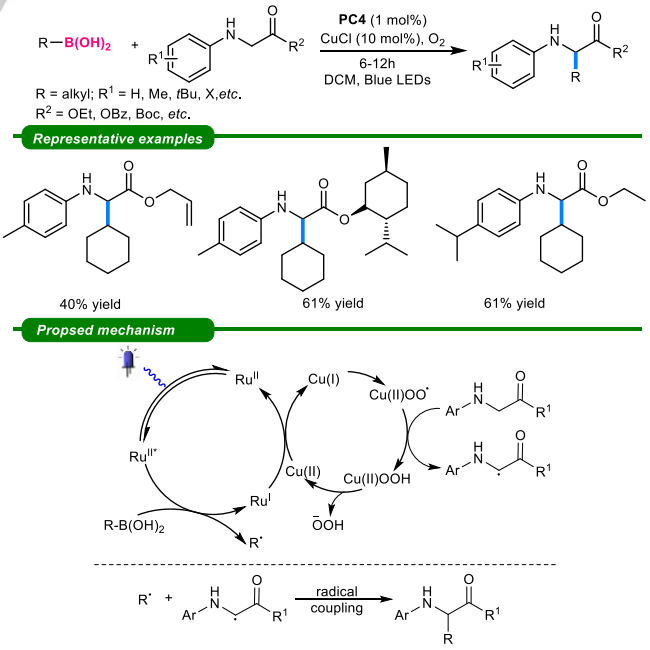
The affinity of O_2, in the form of superoxide radical anion, towards boronic acids/boronic esters is well known.[13] The development of hydroxylation strategies of boronic acids under aerobic conditions has therefore flourished over the years, and renewed attention has arisen with the introduction of photoredox catalysis. Since 2012, metal based photocatalysts[55], together with organic photosensitizers[56], have been employed for the mild and green generation of the superoxide radical anion, thus leading to the formation of phenols form aryl boronic acids. Over the years, the application of heterogeneous catalysts have broadened the spectrum of convenient photocatalysts[57,58], with the application to alkyl boronic acids for the formation of aliphatic alcohols as well.[59]

Being the hydroxylation of boronic acids out of the scope of this review, we decided to limit our selection to synthetic protocols achieving radical generation from boronic acids through the mediation of a superoxide radical, generated by means of a photocatalyst. In 2020, Wang and co-workers reported a molecular oxygen-mediated Minisci reaction, where boronic acids were employed as radical precursors to achieve the alkylation of electron deficient heteroarenes.[60] In the proposed mechanism, radical generation is proceeded *via* the formation of a superoxide radical anion following an oxidative quenching cycle of the designated photocatalyst. The highly reactive oxygen species further interacts with boronic acid to extrude, as a result, a nucleophilic alkyl radical, involved in the attack of the electron-poor nitrogen containing heterocycle. The catalytic cycle is ended by the oxidation and deprotonation of the intermediate (**Scheme 27**). This protocol appears benign in its utilization of non-toxic reactants and for the use of O_2 as the sole oxidant. It was successfully applied to the derivatization of drugs, including fasudil, etofibrate and theophylline as examples. The reaction scale-up (up to 6 mmol) also afforded the desired product in 81% yield.



Scheme 27. Minisci reaction employing boronic acids an radical source and O_2 as oxidant.

Soon after, the *α*-akylation of glycine under photocatalyzed aerobic conditions was also accomplished, enabling the synthesis of a broad variety of unnatural amino acids, including interesting natural product derived scaffolds.[61] Primary and secondary boronic acids were solely employed as radical source. Radical generation was obtained under O_2 atmosphere, in combination with a Ru and Cu catalyst.

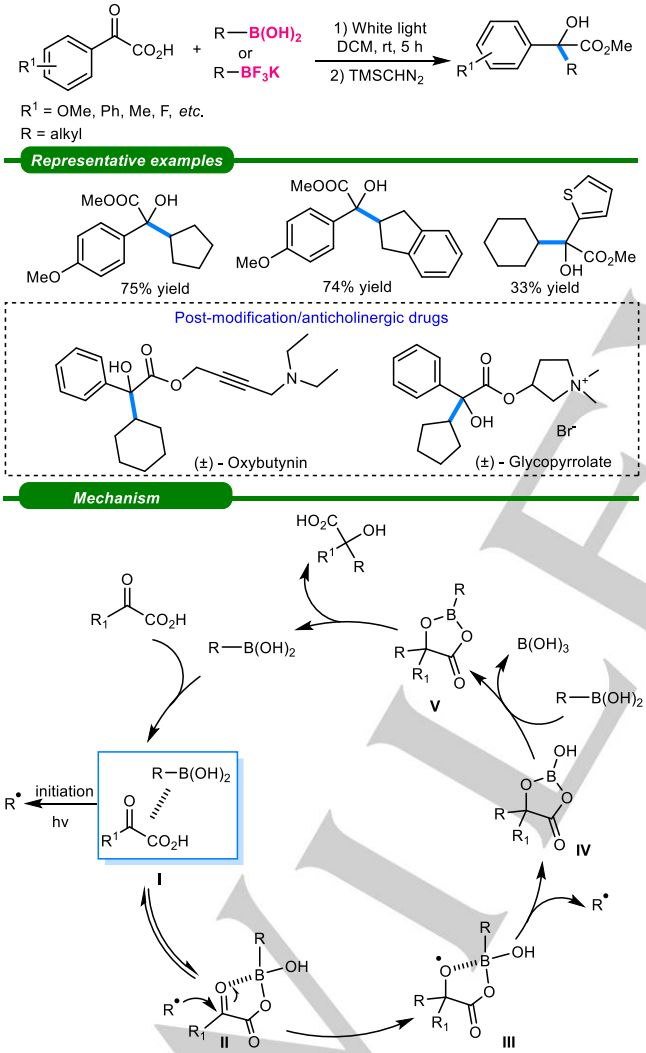


Scheme 28. Alkylation of glycine for the synthesis of unnatural amino acids.

Notably, authors noticed that while an atmospheric pressure of O_2 was the essential requirement for the reaction to happen, the photocatalyst and Cu-catalyst could be omitted, with a concurrent decrease in yield. These observations support the role of O_2 as either oxidant or as activator of boronic acids to access radical formation. Alternatively, the peroxide radical could also be involved in the Cu-mediated HAT step to form radicals from glycine (**Scheme 28**).

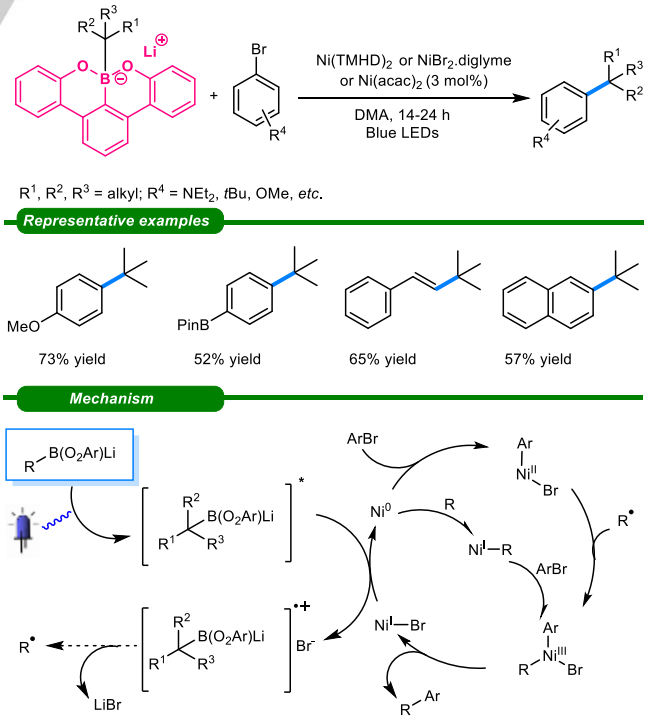
4. Direct excitation of boronate complexes

Recently, there has been an upsurge of elegant strategies to obtain the formation of radicals from boron species without the need of a photocatalyst. In this regard, visible light absorbing precursors have been ingeniously employed, exploiting the Lewis acidity of the boron atom and its propensity to interact with a nucleophilic counterpart.



Scheme 29. Boron activation through the formation of a complex with α-ketoacids.

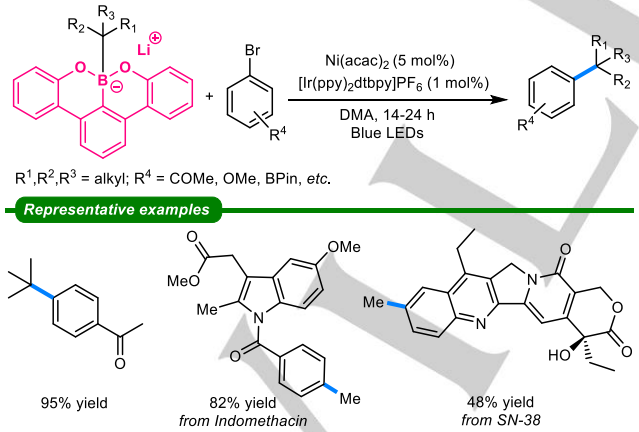
In 2019, Chen and co-workers serendipitously disclosed that boronic acids and *α*-ketoacids form a visible light absorbing complex which, upon irradiation, undergoes fragmentation and release of an alkyl radical (**Scheme 29**).[62]
This radical can then easily attack the carbonyl group and lead to the formation of lactates. The radical addition to ketones is a challenging transformation because of the propensity of the alkoxy radical intermediate to rearrange and cleave the newly formed C-C bond. The inventiveness of this method therefore relies on the stabilization that the boron center provides to the ketoacids and the arising radical intermediates, preventing from *β*-elimination. Mechanistically, the authors reported that the photoexcited Lewis acid-base pair **I** or the boron anhydride **II** lead to the formation of a radical, which then attacks a carbonyl center, affording the boron-containing radical intermediate **III**. This intermediate is prevented from *β*-elimination, but its rearrangement determines a C-B bond cleavage, with the formation of another radical for chain propagation. An ester exchange reaction with the alkyl boronic acid then allows the formation of the intermediate **IV** and the liberation of boric acid as a by-product. The final hydration of intermediate **V** delivers the product and releases the alkyl boronic acid for the following catalytic cycle.
Cyclic and acyclic secondary boronic acids were successfully employed, as well as primary and benzyl boronic acids. The inertness of tertiary boronic acids was justified by their steric hindrance that does not allow to form the complex. Considering the ketoacidic counterpart, variously substituted ketoacids underwent the reaction, and in particular, a homoserine derived ketoacid was functionalized as well, suggesting the possibility to employ these mild conditions in bioconjugation reactions. Notably, the reaction performed in flow afforded 1.69 g (75% yield) of the corresponding lactate, the precursor of the anticholinergic drugs oxybutynin and glycopyrrolate.
A new reaction manifold through an innovative activation method was presented by Ohmiya and co-workers in 2020 (**Scheme 30**).[63] In their report, they aimed to bypass the necessity of a photocatalyst through the use of boracene (8,9-dioxa-8a-borabenzo [*fg*]-tetracene). This planar, π-conjugated and robust scaffold was functionalized with primary, secondary and tertiary alkyl groups which, being deviated from the boracene plane and generating a borate complex, could serve as a radical precursor.



Scheme 30. Generation of radicals through the direct excitation of boracene-based alkylborates.

The installation of these side groups to form the active borate complex was achieved through organolithium reagents, Grignard reagents or *in situ* lithiation of alkyl halides by lithium di-*tert*-butylbiphenylide (LiDBB). These boracene derived radical precursors proved to be widely applicable in many known radical reaction pathways, including Giese-type additions, decyanoalkylations, nickel catalyzed cross-coupling reactions (three-component vicinal alkylarylation of alkenes). This broad applicability is ascribed to the ability of the boracene derived borate complex to absorb visible light (absorption maximum at 370 nm) and to act as a strong reductant in its excited state (approximated redox potential ($E_{(Boracene^{\bullet+}/Boracene^{*})}$ = -2.2 V). The authors therefore propose that two reaction pathways can be devised, where either a direct homolytic C-B bond cleavage or a single electron reduction step involving the reactive counterpart (an electron-withdrawing alkene, cyanopyridine or nickel catalyst) can afford the radical generation. It is necessary to underline that in either of the involved reaction pathways, boracene could be recovered. Radical generation was accomplished from primary, secondary and tertiary borate complexes. The methylation of medicinally relevant scaffolds, such as indomethacin and coumarin, was obtained as well in good yields (80% and 76% respectively). In addition, the authors highlighted the better results obtained in comparison to the Ni/Ir combination employed by Molander's group while using electron-rich aryl halides as coupling counterparts.

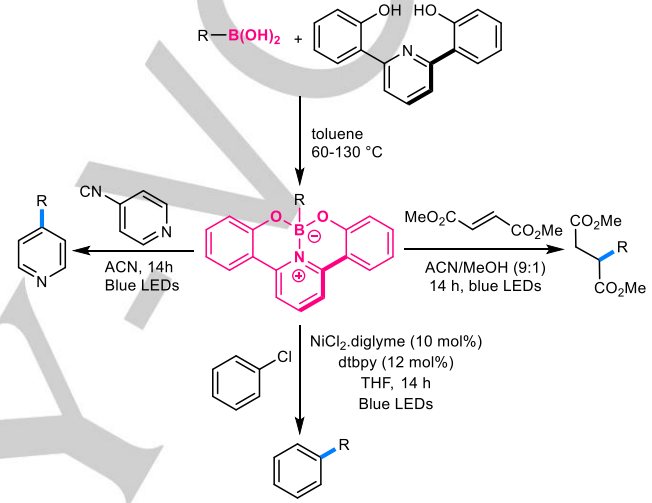
The same group also presented a variation of the previously discussed nickel catalyzed cross-coupling reaction[63], where the addition of an iridium photocatalyst sharply increased the reaction efficiency (**Scheme 31**).[64] The product yield was found to be higher in many cases and the reaction times were considerably decreased even under the irradiation of a Micro Photochemical Reactor, which has a weaker spectral irradiance in comparison to the most frequently used irradiation sources.



Scheme 31. Direct excitation and Ir involvement in the radical generation from boracene.

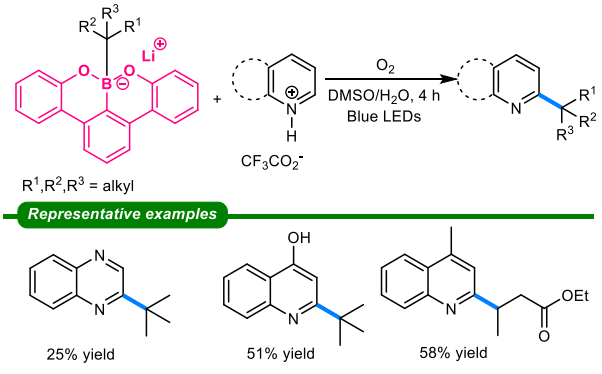
The better results upon the addition of an iridium catalyst are possible because the borate complex is not only able to act as a strong reductant through direct excitation, but can also undergo a single electron reduction step in its ground state. Its oxidation potential is indeed matching with many iridium containing photocatalysts (+0.78 V *vs* SCE in ACN). Despite these results, the authors reported that the addition of the metal photocatalyst was not successful in three-component reactions.

In 2021, Ohmiya's group also reported the direct photo-excitation of 2,2′-(pyridine-2,6-diyl)diphenol (PDP) based-borates to generate alkyl radicals.[65] PDP based borates can be directly synthesized from boronic acids or trifluoroborate salts. Similar to their previous reports, the PDP-based borates were subjected to different reaction conditions, affording the Giese-products, the decyanoalkylation of 4-cyanopyridine and photoredox/Ni-catalyzed alkylation of aryl chlorides (**Scheme 32**). Later on, this strategy was also employed in the direct photoexcitation of PDP-based borates in the well-known Minisci reaction to develop a green approach for the functionalization of heterocyclic scaffolds (**Scheme 33**).[66] In comparison with Chen and Liu's approach,[51] the optimized conditions afforded lower functional group tolerance with diminished yields.

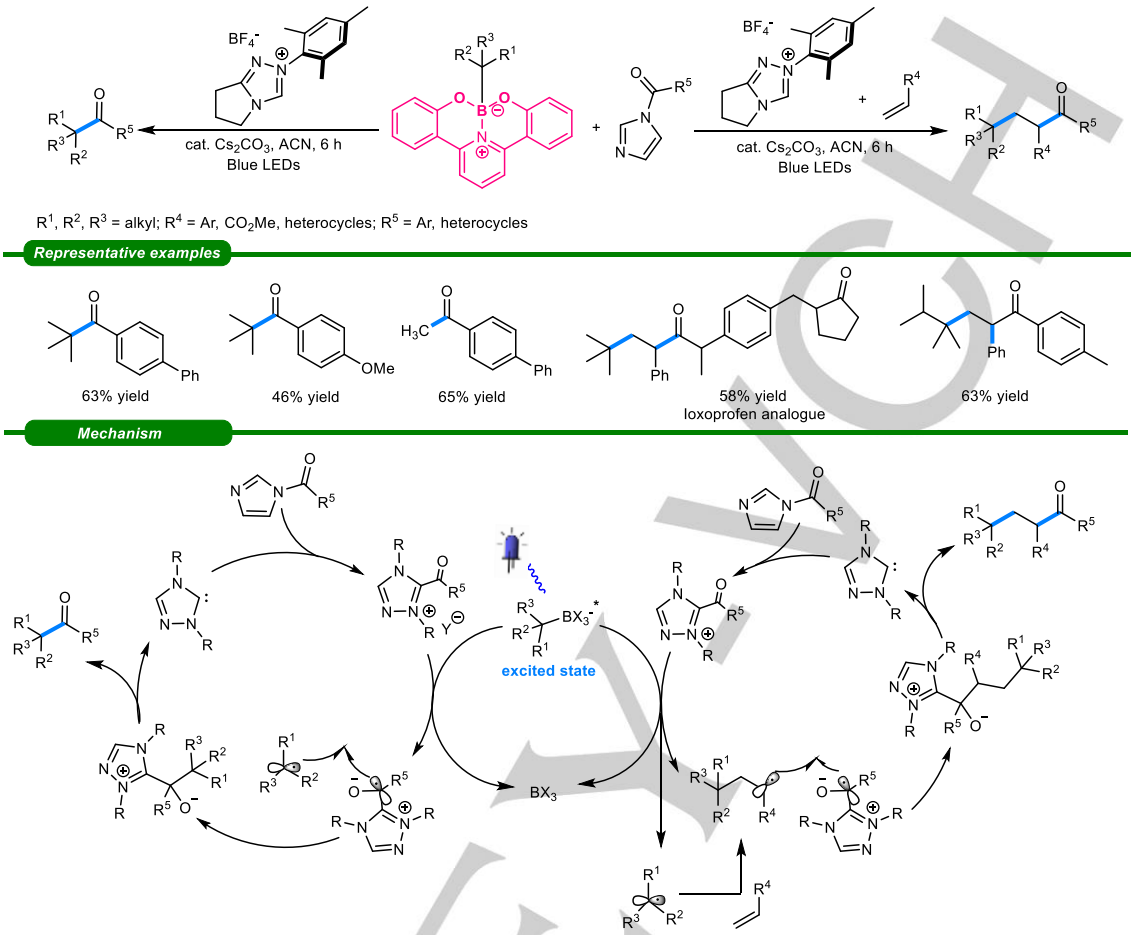


Scheme 32. Alkyl radicals via the direct photoexcitation of 2,2'-(pyridine-2,6-diyl)diphenol-based borates.

In 2021, the combination of *N*-heterocyclic carbene (NHC) catalysis and the direct excitation of borates were applied to the cross-coupling of alkyl borates and acyl imidazoles, and to the alkylacylation of alkenes, leading in both cases to the formation of ketones (**Scheme 34**). In the light of the mechanistic investigations performed, upon formation of an intermediate acyl azolium (through *in situ* condensation of the acyl imidazole and NHC), a SET between the excited borate and the acyl azolium happens. The alkyl and ketyl radicals derived from this step then combine in a radical coupling process, leading to the final product. Alternatively, the alkyl radical can first attack a styrene-based alkene, generating a radical intermediate that further reacts in a similar radical coupling step with the ketyl radical.

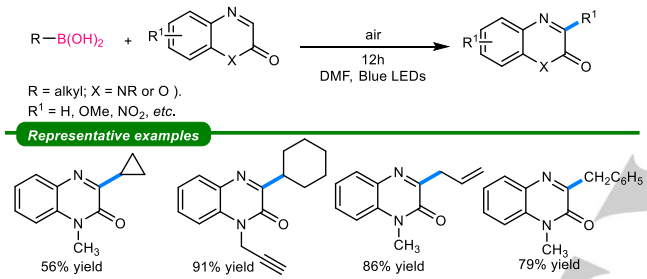


Scheme 33. Direct excitation of borate enabling Minisci reaction.



Scheme 34. Photoredox and *N*-heterocyclic carbene catalysis using alkylborates.

This strategy proved to be highly versatile, allowing the radical coupling of a persistent ketyl radical with tertiary, but notably also primary and secondary alkyl radicals. As previously mentioned, the photoactive borate complexes were derived from the corresponding trifluoroborate salts or boronic acids. Methyl and deuteriomethyl radicals could also be formed, despite giving low to moderate yields. The multicomponent dicarbofunctionalization also allowed the use of widely substituted styrene derivatives, including heterocyclic scaffolds. The formation of an excitable complex was also observed by Li and co-workers in 2021.[67] In this report, a switchable reactivity under aerobic or anaerobic conditions was found, amplifying the potential synthetic outcomes of this transformation. Quinoxalin-2(1 *H*)-ones were the designated starting materials, due to their ubiquitous presence in natural products and drugs. Upon visible-light irradiation, the alkylation of this scaffold with secondary, tertiary and benzyl alkyl boronic acids was obtained. In particular, alkylquinoxalin-2(1 *H*)-ones and 3,4-dihydroquinoxalin-2(1 *H*)-ones were obtained under anaerobic and aerobic conditions respectively in good yields. Aryl boronic acids and boronic acid pinacol esters, with the exception of specific substrates, were found unreactive (**Scheme 35**).

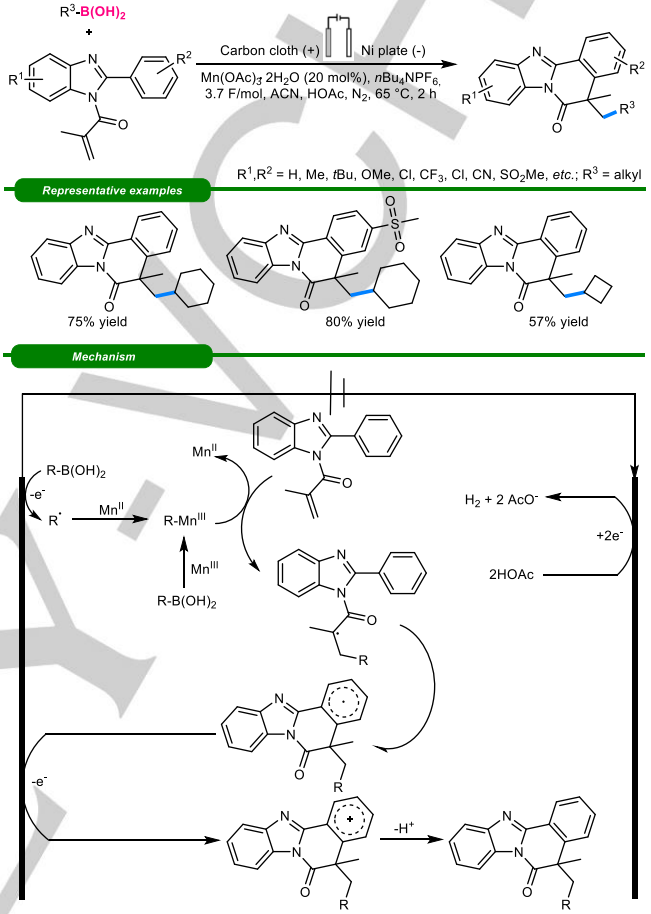


Scheme 35. Synthesis of alkylquinoxalin-2(1*H*)-ones and 3,4-dihydroquinoxalin-2(1 *H*)-ones through switchable conditions.

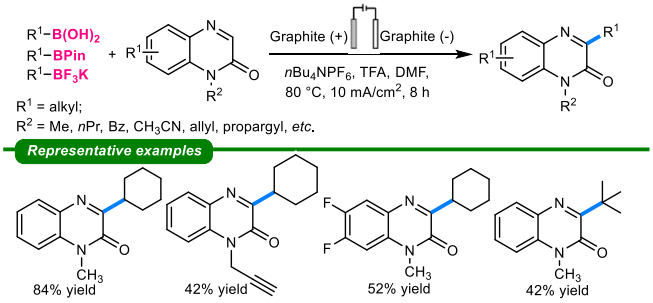
5. Electrochemistry as future challenge

The renaissance that electrochemistry has recently witnessed relies on the potential that this technique offers as a complementary green and mild alternative to photoredox catalysis.[66,67] The employment of boronic acids and derivatives in this field is only recent, as the limited number of reports on the topic are available. We therefore intend to present here few relevant examples that will serve as starting point for future implementation.

The first electrochemical radical generation from boronic acids only appeared in 2020. In this report, benzo[4,5]imidazo[2,1-a]-isoquinolin-6(5*H*)-one derivatives were synthesized, subjecting the starting materials (alkyl boronic acids and *N*-substituted 2-arylbenzoimidazoles) to a 15 mA current for 2 h, in the presence of $Mn(OAc)_3•2H_2O$ as a catalyst.[70] Under the optimal conditions, this radical cascade cyclization reaction was amenable to a wide range of *N*-substituted 2-arylbenzoimidazoles, and only the *p*-substituted 2-phenyl rings bearing electro-donating groups delivered the desired product albeit in lower yield. Primary and secondary boronic acids could be successfully employed. After careful evaluation of the mechanistic scenario, the authors propose that $Mn(OAc)_3•2H_2O$ forms a complex with the boronic acid, which helps the alkyl radical to attack the *N*-substituted 2-arylbenzoimidazole. This leads to the formation of a Mn^{II} catalyst and a carbon radical intermediate that further cyclizes and then undergoes anodic oxidation and deprotonation to form the final product. Simultaneously, since the direct anodic oxidation of Mn^{II} is difficult to achieve, the authors propose that the single-electron oxidation of boronic acids is more probable, followed by its reaction with Mn^{II} and the formation of the alkyl radical-Mn^{III} complex (**Scheme 36**).



Scheme 36. Electrochemical synthesis of benzo[4,5]imidazo[2,1-a]-isoquinolin-6(5*H*)-one derivatives.



Scheme 37. Electrochemical alkylation of quinoxaline-2(1*H*)-ones.

In 2021, a further electrochemical strategy for the direct anodic oxidation of boronic acids, boronic esters and trifluoroborates was devised.[71] The authors highlighted the challenges to achieve the direct oxidation of boron containing species, due to their high oxidation potential that can lead to radical

dimerization or overoxidation. In this case, the alkylation of quinoxalin-2(1*H*)-ones was performed. Primary, secondary and tertiary boronic acids, together with cyclic and tertiary boronic esters and trifluoroborates could all be employed. Different substituents on the *N*-atom were also tolerated. The authors also enlightened the possibility to use a battery as power supply instead of a specialized DC device (**Scheme 37**).

6. Conclusions and future perspectives

For years, the photochemical generation of radical species from boronic acids and esters has been neglected, surpassed by the use of strong oxidants or trifluoroborates in convenient strategies for the purpose. Nonetheless, the mild conditions for the generation of these reactive species from non-toxic and easy to handle reagents, together with their involvement in more sustainable transformations, have been longstanding goals that still represent the cutting-edge of organic chemistry. The upsurge in the development of novel reaction pathways involving boronic acids and boronic esters is therefore justified by this purpose, and photoredox catalysis offers the ideal platform to achieve this aim. The inherent chemical properties of the boron atom have represented the starting point for the development of straightforward synthetic pathways. Indeed, a broad number of examples presented in this review focuses on the formation of a complex between boronic acids/esters and Lewis bases to unlock their reactivity. The use of charged nucleophiles and strong bases has also been used for the same reason, allowing to perform photocatalytic reactions through a reductive quenching cycle. Moreover, the formation of strong B-O bonds has been the underlying motif that has enabled to form radical species through an oxidative quenching cycle in the presence of hypervalent iodine reagents. In addition, the direct excitation of boronate complexes, either with less applicable UV irradiation or with the more sustainable visible light, has also allowed to obtain encouraging results.

Despite the innovation that all the presented reports have brought, more digging of the field is needed in order to further explore the potentials that boronic acids and esters own. Indeed, a general strategy with the same efficiency in the generation of both alkyl and aryl radicals is still missing and despite the efforts to circumvent this issue, many limitations can still be observed. The increase in the employment of these species in photo-flow reactors also needs to be addressed, as boronic acids/esters constitute a valuable alternative to charged substrates which often cause clogging issues in the presence of less polar organic solvents. The possibility to *in situ* generate and directly utilize boronic acids/esters in flow reactors is therefore highly desirable, enabling the possibility to directly engage these species in photochemical reactions under photo-flow conditions. This underexplored strategy would overcome the limitations in the synthesis and isolation of these boron containing species, a problem that has hindered a wider applicability of the discussed strategies. The role of enabling technologies still needs to be enhanced in order to fully exploit the potentials of the already developed and future methodologies. A complementary development that only accounts for preliminary studies is the introduction of more biocompatible conditions. Given the non-toxic properties of these reagents and the mildness that photoredox catalysis guarantees, deeper studies in this direction will surely afford valuable and more applicable results. As evident from the scarce number of examples reported here, electrochemical processes involving the generation of radicals from boron containing species is also a promising field, that will allow the exploration of more reactivity platforms. This review is therefore intended to shed light on the wide synthetic possibilities that the use of boronic acids/esters as radical precursors offer for fruitful future implementations.

Author Contributions

SP and PR wrote the manuscript. EVdE and UKS revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflicts of interest

The authors declare that there is no conflict of interest.

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Keywords: Boronic acids • Photoredox catalysis • Alkyl radicals • Boronic esters • Flow chemistry

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Entry for the Table of Contents

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This review focuses on the activation modes that have been developed in recent years to achieve photochemical and electrochemical radical generation from boronic acid (derivatives). Despite their unattainable oxidation potential, different approaches enable the formation of alkyl and aryl radicals, rendering these species a viable and easily available radical source.

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