Light-driven four-component reaction with boronic acid derivatives as alkylating agents: an amine/imine mediated activation approach

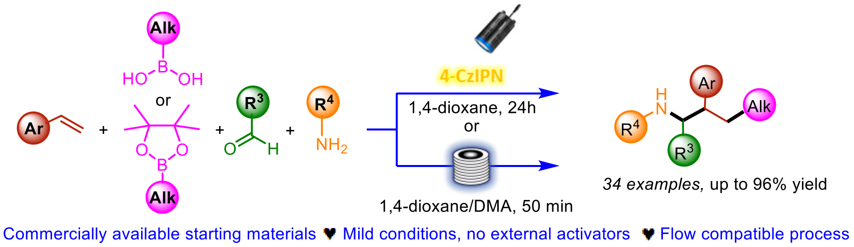
Laura Y. Vázquez-Amaya,[†] Brecht Dootselaere,[†] Gerardo M. Ojeda-Carralero,[‡] Serena Pillitteri[†], Erik V. Van der Eycken,[†,§] Upendra K. Sharma[*,†]

[†]Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven Celestijnenlaan 200F, B-3001 Leuven, Belgium

[‡]Department of General and Inorganic Chemistry, Faculty of Chemistry, University of Havana, Zapata y G, Havana 10400, Cuba.

[§]People's Friendship University of Russia (RUDN University), Miklukho-Maklaya street 6, RU-117198 Moscow, Russia.

Supporting Information Placeholder



ABSTRACT: Herein, we describe a one-pot aminoalkylation of styrene derivatives with boronic acids (BAs) and boronic acid pinacol esters as radical precursors for the synthesis of complex secondary amines, in moderate to high yields through a mild and easily accessible organophotoredox-catalytic four-component reaction. Additionally, we report for the first time in a photoredox process, the activation of alkyl boronic acids derivatives by imines, which play a dual role in the reaction as both substrate and Lewis base activator. The protocol's applicability was greatly enhanced by its successful adaptation to photo-flow reactors.

Photoredox-catalyzed multicomponent reactions (MCRs) are photoinduced one-pot cascade transformations involving at least three components, where the majority of the atoms of the starting materials are incorporated into the final product.[1] In these reactions, visible light initiates a cascade reaction through the excitation of a photocatalyst involving the generation of highly active open-shell species *via* single-electron transfer processes (SET). Due to the rapid achievement of high levels of complexity and diversity in combination with the characteristic mild conditions of photoredox catalysis, photocatalyzed MCRs hold a privileged position in synthetic chemistry. In this sense, they are often recognized as powerful tools not only for the generation of chemical diversity but also for the functionalization and modification of complex molecular architectures.[2]

Nonetheless, regio- and chemoselectivity issues are intrinsic challenges associated with MCRs, and as a result, photocatalyzed MCRs with four or more components are rather uncommon. Consequently, the development of new reactions with more than three components is always highly valuable to the synthetic community. Some recently developed photoredox-catalyzed four-component protocols include the functionalization/decoration of *N*-heterocycles,[3] the synthesis of trifluoro,[4] and sulfone-containing complex molecules (Figure 1a).[5] In that respect, Opatz and co-workers reported a photoredox-catalyzed four-component one-pot sulfonylation/aminoalkylation using styrene derivatives, aromatic amines, aldehydes, and sodium sulfinates as radical precursors.[6] This protocol furnished substituted γ-sulfonylamines in moderate to good yields (Figure 1c). Although the reaction is highly atom-economic and operationally simple, its scope was limited to the generation of mostly arylated scaffolds. Conversely, reactions involving the installation of distally functionalized or entirely unfunctionalized alkyl fragments would be desirable as a strategy to further diversify the skeleton of complex secondary amines with complementary functionalities.

In this context, free alkyl boronic acids and boronic esters constitute a highly homogenous source of alkyl radicals for photocatalyzed processes, which has been constantly overlooked due to their high oxidation potential. Strategies designed to overcome this challenge include the use of oxidants[7] or external activators namely bases,[8] ArLi,[9] and more recently solvent assisted-activation approaches (Figure 1b).[10] In this sense, our research group has been actively involved in the development of a strategy to generate alkyl radicals from free boronic acids (BAs) under mild photoredox conditions through the activation *via* H-bonding interactions with amide base solvents.[10b] The strategy found later an application on a photoredox-catalyzed Petasis reaction for the synthesis of secondary amines.[11]

Interestingly, in the latter report when the amide base solvent (DMF) was substituted by 1,4-dioxane, the reaction was still

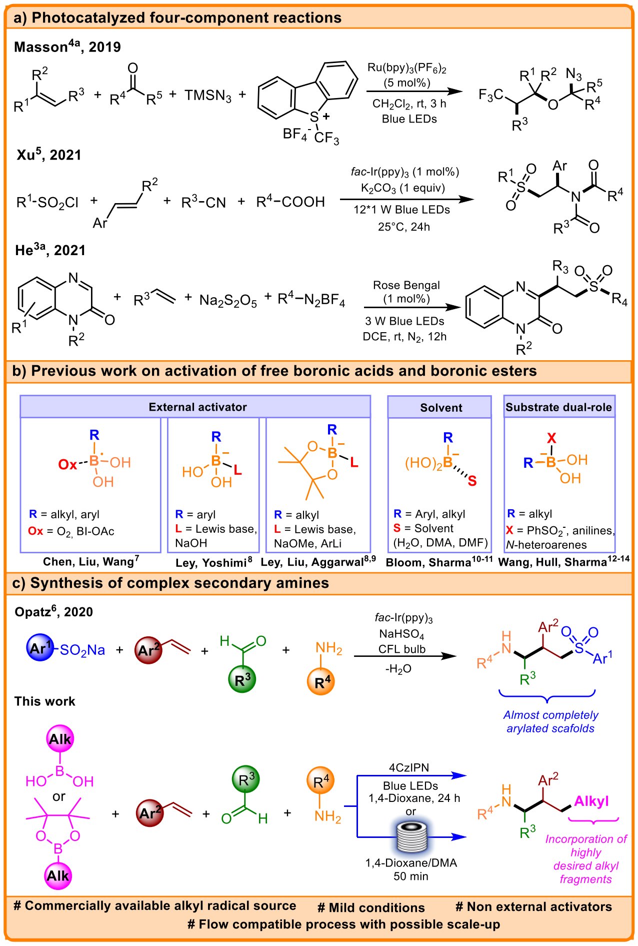
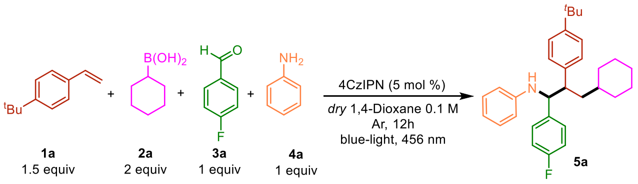


Figure 1: A) Recent examples of photocatalyzed 4-CR. B) Boronic acid derivatives activation approaches and C) Our work.

Table 1: Optimization of the reaction conditions.[a]



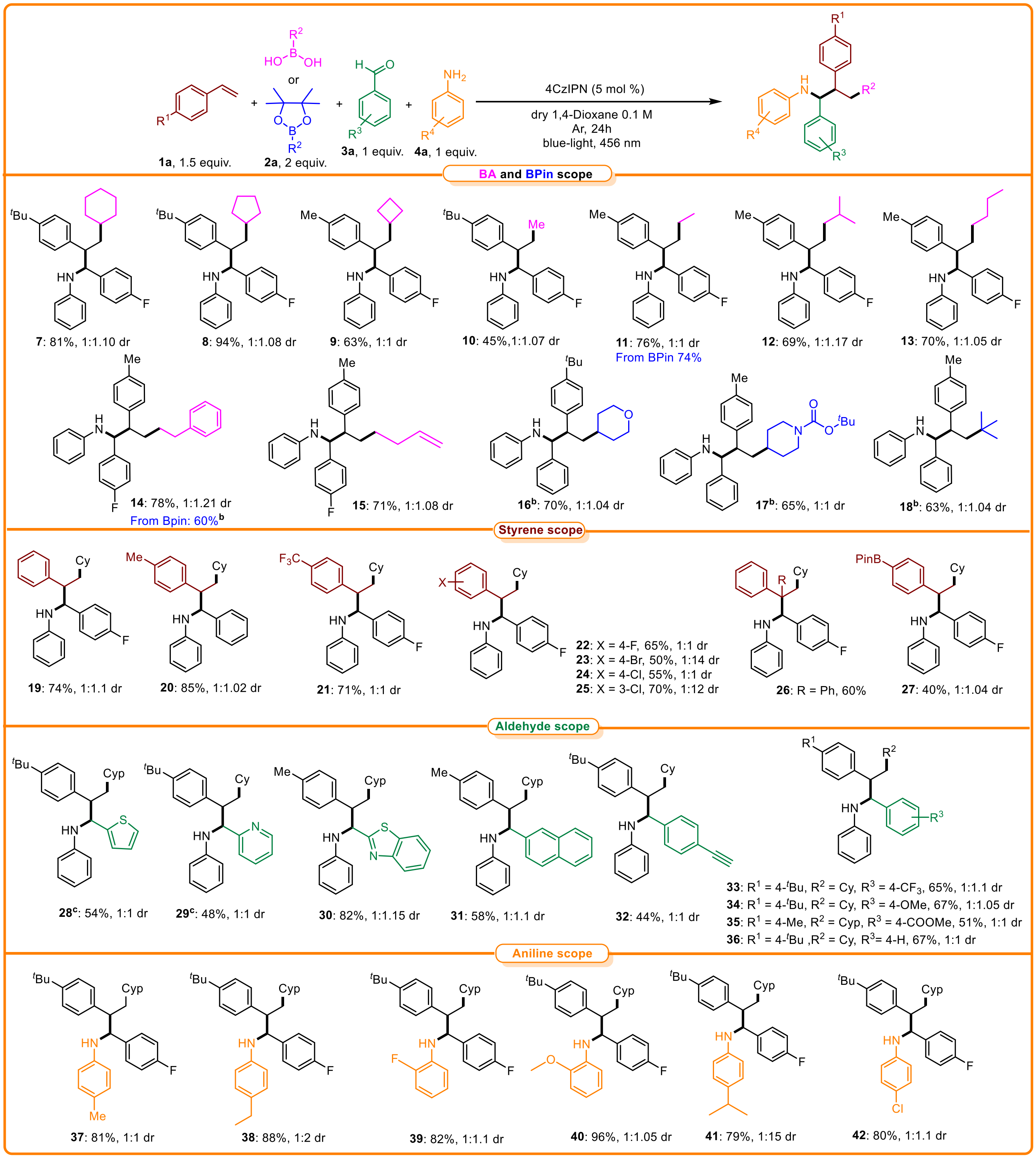
entry	variations	**6a** (%)[c]
1	None	81
2	2 equiv of **1**, 1.5 equiv of **2**, 4 equiv of **3**, 4 equiv of **4**	75
3[b]	DMA/DMF	35/38
4[b]	$NaHSO_4$, $NaHSO_4/H_2O$	trace/trace
5[b]	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (3.5 mol%)	72
6[b]	$Ru(bpy)_3Cl_2.6H_2O$ (3.5 mol%)	trace
7[b]	$Mes\text{-}Acr\text{-}Me^+$ (3.5 mol%)	trace
8	No 4CzIPN	n.d.
9	No light	n.d
10	No inert atmosphere	54
11	20% water	65
12	2 equiv of Cy-BPin	80

[a] All reactions were carried out using BA (0.4 mmol, 1.5 equiv), 4-*t*-butylstyrene (0.6 mmol, 1.5 equiv), 4-fluorobenzaldehyde (0.2 mmol, 1 equiv), aniline (0.2 mmol, 1 equiv), PC, solvent (0.1M), under blue LEDs irradiation. [b] Same equiv as in entry 2. [c] Isolated yield.

found to take place, albeit in a low yield. This interesting outcome suggested a different activation pathway for the BAs, presumably involving whether the aniline present in the medium as previously described[12] or even more interestingly the imine formed *in situ*. In this sense, BAs activation strategies in radical chemistry involving the dual role of a substrate in the reaction as reactant and activator have been previously reported, including the use of benzenesulfinates,[13] anilines,[12] and more recently *N*-heteroarenes by our research group.[14] On the other hand, Lewis base-Lewis acid interactions between BAs derivatives and imines have received little attention in this context, and to our knowledge, this type of interaction has not been exploited in photoredox or radical chemistry.[15]

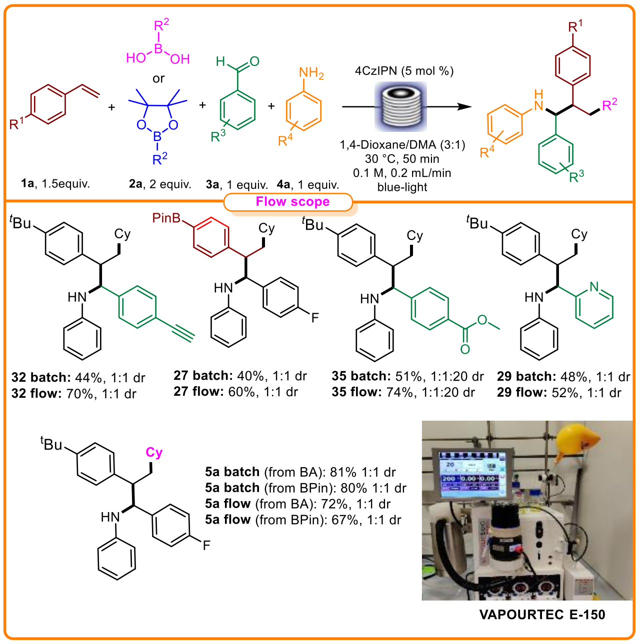
Intrigued by our early observation we became interested in the development of an easily accessible one-pot alkylative/aminoalkylation reaction of styrenes with boronic acid derivatives for the synthesis of complex secondary amines without the use of an external activator, in which the aniline or the transiently formed imine could serve a dual role in the reaction as both a substrate and a Lewis base activator. We started our investigation by using boronic acids as a radical source, although we later expanded the protocol to include boronic pinacol esters. Initial experiments were carried out using cyclohexyl (Cy) boronic acid (2.0 equiv), 4-*t*-butylstyrene (1.0 equiv), 4-fluorobenzaldehyde (4 equiv), aniline (4 equiv), and 4CzIPN as the photocatalyst (5 mol%) in dry 1,4-dioxane. The reaction mixture was then irradiated for 12 h under blue-light. To our delight the desired product **5a** was obtained selectively over the Petasis product in 75% yield (Table 1, Entry 2). We then tried using amide-based solvents (DMA and DMF) as the occurrence of both activation methods (solvent *vs* substrate) could synergistically promote the generation of the desired alkyl radicals.[14] However, the desired product was obtained only in poor yields (Table 1, entry 3). Notably, the addition of $NaHSO_4$ proved futile for the reaction, as the desired product was observed only in traces even after the addition of water to improve solubility (Table 1, entry 4). These results could preliminarily indicate the involvement of free imines as Lewis bases in the boronic acid activation step. Next, various photocatalysts were tested, revealing that 4CzIPN is the most efficient one for our system (entries 1, 5-7). Thereafter, different stoichiometric combinations were explored, finding that the use of 1.5 equiv of styrene, 1 equiv of amine, 1 equiv of aldehyde, and 2 equiv of boronic acid was the best combination for the devised reaction giving the product in yield of 81% ((Table 1, Entry, also see SI).

Control experiments were further performed, confirming the need for both photocatalyst and light, as the reaction did not proceed in the absence of any of them (Table 1, entries 8, 9). On the other hand, the lack of an inert atmosphere and the addition of water were detrimental to the reaction, affording a reduced amount of desired product (54% and 65% yield, Table 1, entries 10, 11). Moreover, the robustness of the protocol was successfully expanded to the use of boronic acid pinacol esters,



Scheme 1. Scope of the reaction. ^{a}Reaction conditions: **1a** (0.3 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), **2a** (0.2 mmol), 5 mol% of 4CzIPN in 1,4-dioxane stirring under blue light with fan cooling 30-35 ºC for 12 h. ^{b} 48 h. ^{c} Yields obtained with preformed imine (3-CR).

as the use of Cy-BPin provided the desired product in 80% yield without any further modifications to the established protocol (Table 1, entry 12). With the optimized conditions in hand, we investigated the extent of the scope of the reaction (Scheme 1). First, a variety of boronic acid (derivatives) was tested. To our delight secondary, tertiary and even non-stabilized primary boronic acid derivatives were suitable for our protocol, affording the desired products in good to excellent yields (**7-18**). Different alkyl fragments were easily incorporated in the molecular structure/back bone, including a methyl (**10**) alkyl group, unreactive in previous reports, which was installed in moderate yield (45% from BA), allowing for the possibility of methylation. In addition, we successfully incorporated a *t*-butyl alkyl (**18**, 63% yield, from BPin) chain, as well as diverse size cycloalkanes including cyclohexyl, cyclopentyl (Cyp) (**8**, 94% yield) and cyclobutyl (**9**, 63% yield) rings. Notably, the incorporation of -



Scheme 2. Photocatalyzed 4-CR under photo-flow conditions. The values indicate the yield of the isolated products. Conditions unless otherwise noted: BA (0.4 mmol), 4-*t*-Butylstyrene (0.3 mmol), 4-fluorobenzaldehyde (0.2 mmol), aniline (0.2 mmol), 4-CzIPN (5 mol%), 0.2 mL/min, reactor volume: 10 mL, residence time: 50 min, irradiating with blue LEDs (40 W).

hetereoaromatic fragments (**16**,**17**), phenethyl (**14**, from BA and BPin), and allyl (**15**) moieties was also feasible, which opens the possibility to perform further modifications. For the styrene component of the reaction, both electron-donating (**20**) and electron-withdrawing groups (**21-25**) were well tolerated forming the expected product in good yields.

Remarkably, the reaction proceeded smoothly with the sterically hindered diphenylethylene derivative furnishing the desired product **26** in a moderate 60% yield. The platform also enabled the chemoselective generation of radical species from BAs in the presence of a -Bpin-containing molecule (**27**), allowing possible orthogonal modifications. In addition, the incorporation of heteroarenes (**28-30**) and an alkyne fragment (**32**) was also accomplished on the aldehyde fragment affording the corresponding products in good yields. Due to slow *in situ* imine formation in the case of compound **28-29**, the products of these reactions were obtained in a three-component fashion with a preformed imine (see SI). We found that the electronic effects of different groups on the aniline moiety have little influence on the outcome of the reaction as all the products were obtained in high to excellent yield (**37-42**). Moreover, the mild conditions of our protocol allowed protecting groups (such as a Boc-group) to remain untouched during the transformation (**17**).

We further expanded the applicability of our photocatalyzed 4-CR by adapting the protocol to a photo-flow reactor. Recently, it has been shown that the combination of flow chemistry with photoredox-catalyzed processes offers various benefits, including faster reactions, fewer byproduct formation, and scaling-up possibilities.[16] After a few modifications to the initial protocol (see SI for more details), we applied the optimized conditions to some sensitive substrates that afforded moderate yields under batch conditions. Pleasantly, the flow protocol was highly beneficial for such transformations, allowing higher yields to be obtained in a fraction of the time compared to the batch process

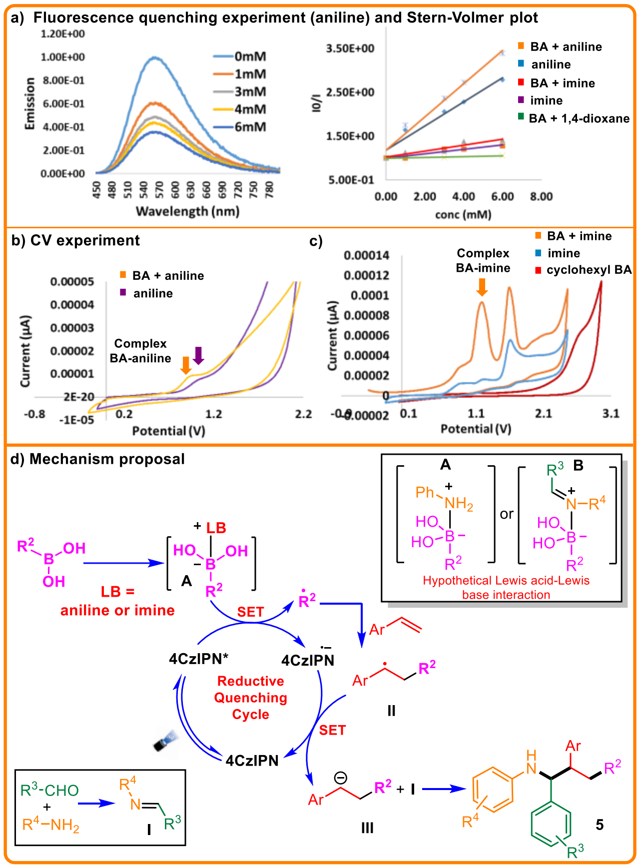


Figure 2. a) Fluorescence quenching experiment in the presence of aniline and Stern-Volmer plot for luminescence quenching of BA-1,4-dioxane, BA-imine, imine, aniline, and BA-aniline. b, c) Cyclic voltammetry experiment (0.1 M of reagents in acetonitrile using AgCl/Ag as reference electrode). d) Proposed mechanism.

(Scheme 2). The continuous-flow conditions were especially effective in the case of products **27** and **32** since a remarkable increase in the yield was observed (70% and 60% yield respectively), as probably long irradiation times promote the degradation of the products in batch conditions.

Finally, to gain insight into the mechanism of the reaction, fluorescence quenching experiments were carried out resulting in a stronger quenching of the excited state of the photocatalyst by the mixture BA-aniline as compared to the mixture BA-imine, which confirmed that aniline is the primary activator for BAs in our system (Figure 2a). In addition, cyclic voltammetry (CV) experiments showed the formation of a new peak at 0.78 V (*vs* SCE in ACN), which supports the formation of the previously described Lewis base-Lewis acid (LB-LA) complex between aniline and BAs (Figure 2b).[12] Moreover, the mixture of boronic acid-1,4-dioxane was also analyzed to rule out the activation of the BA through interactions with the solvent (Figure 2a, Stern-Volmer plot). Despite the obtained results that revealed the complex between BA-aniline as the primary quencher, it was evident from the formation of the products **28** and **29** and from quenching experiments (Figure 2a, Stern-Volmer plot) that the activation of BAs by imines is actually feasible. Intrigued by these results we further investigated this interaction. In that sense, the model reaction was carried out in a 3-CR fashion with the preformed imine (*E*)-1-(4-fluorophenyl)-*N*-phenylmethanimine. Pleasantly, we found that the desired product **5a** was obtained in 78% yield, which confirms that indeed, an imine can activate free alkyl BAs as efficiently as aniline (for more details see SI). To further support the latter finding, CV experiments were performed. Notably, we observed the formation of a new peak at 1.05 V (*vs* SCE in ACN) when the mixture BA-imine was analyzed (Figure 2c). This result validates our hypothesis in relation to the formation of an oxidizable complex through a LB-LA interaction between the free BA and imines, resulting in a decrease in the oxidation potential, which in turn explains the formation of the products **28** and **29**. On the other hand, an experiment of radical trapping *via* TEMPO confirmed the formation of the alkyl (R) radical (detected by GC-MS) from the BA precursor (see SI). Based on the obtained results a plausible mechanism for the photocatalyzed multicomponent reaction is proposed. (Figure 2d). First, the PC undergoes excitation upon irradiation with blue light, followed by the oxidation of the complex BA-aniline and/or BA-imine leading to the formation of the alkyl radical R^2. Next, the radical is trapped by the styrene forming the intermediate **II**, which can undergo single electron reduction from the reduced form of the photocatalyst, affording the carbanion **III**. Finally, intermediate **III** attacks the transient formed imine **I**, giving rise to the desired product **5**. In conclusion, we successfully developed a one-pot aminoalkylation of styrenes with BA derivatives for the synthesis of complex secondary amines in moderate to high yields through a mild and easily accessible photoredox-catalyzed four-component reaction in batch and continuous flow. The scope of the reaction is robust as a variety of alkyl fragments were easily incorporated. Interestingly, we found that imines can play an active role in the activation of alkyl BAs in photoredox processes. This contribution constitutes a valuable addition to the portfolio of free BAs derivatives activation strategies.

AUTHOR INFORMATION

Corresponding Author

Upendra K. Sharma − Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), B-3001 Leuven, Belgium; orcid.org/0000-0001-7489-2337; Email: usharma81@ gmail.com, upendrakumar.sharma@kuleuven.be.

ACKNOWLEDGMENT

L.Y.V.-A. thankful to BOF-IDN/20/014G project for a PhD scholarship. G. M. O. C. is grateful to VLIR-UOS for financial support of a Flemish-Cuba cooperation project (CU2018TEA458A101). S. P. is thankful to the FWO for obtaining a PhD scholarship (S. P. grant No. 11H0121N). The publication has been prepared with the support of the ''RUDN University Strategic Academic Leadership Program'' (recipient E. V. V. d. E.; writing and supervision).

REFERENCES

(1) (a) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. Multicomponent reactions: advanced tools for sustainable organic synthesis. *Green Chem*. **2014**, *16*(6), 2958–297; (b) Ruijter E.; Scheffelaar R.; Orru R. V. A. Multicomponent reaction design in the quest for molecular complexity and diversity. *Angew. Chem., Int. Ed.*, **2011**, *50*, 6234–6246; (c) Ruijter, E.; Orru, R. V. A. Multicomponent reactions–opportunities for the pharmaceutical industry. *Drug Discovery Today: Technol*. **2013**, *10*, e15–e20.

(2) (a) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem., Int. Ed*. **2018**, *57*, 10034−10072. (b) Coppola, G. A.; Pillitteri, S.; Van der Eycken, E. V.; You, S. L.; Sharma, U. K. Multicomponent reactions and photo/electrochemistry join forces: atom economy meets energy efficiency. *Chem. Soc. Rev*. **2022**, *51*, 2313-2382 (c) Yadav, P.; Anagha Varma, A; Punnya, A. J.; Gopinath, P. Photoredox-mediated Multicomponent Reactions. *Asian J. Org. Chem*., **2022**, *11*(10), e202200390; (d) Younus, H. A; Al-Rashida, M.; Hameed, A; Uroos, M.; Salar, U.; Rana, S.; Khan, K. M. Multicomponent reactions (MCR) in medicinal chemistry: a patent review (2010-2020). *Expert Opin Ther Pat*. **2021**, *31*(3), 267-289.

(3) a) Lv, Y.; Luo, J.; Lin, M.; Yue, H.; Dai, B.; He, L. A visible-light photoredox-catalyzed four-component reaction for the construction of sulfone-containing quinoxalin-2 (1 H)-ones. *Org. Chem. Front*. **2021**, *8* (19), 5403-5409. b) Lv, Y.; Luo, J.; Lin, M.; He, L.; Yue, H.; Liu, R.; Wei, W. Metal-Free Multi-Component Sulfur Dioxide Insertion Reaction Leading to Quinoxalin-2-One-Containing Vinyl Sulfones under Visible-Light Photoredox Catalysis. *Adv. Synth. And Catal.*, **2021**, *363*(22), 5122-5128.

(4) (a) Levitre, G.; Dagousset, G.; Anselmi, E.; Tuccio, B.; Magnier, E.; Masson, G. Four-component photoredox-mediated azidoalkoxy-trifluoromethylation of alkenes. *Org. Lett*. **2019**, *21* (15), 6005–6010. (b) Zhou, X.; Li, G.; Shao, Z.; Fang, K.; Gao, H.; Li, Y.; She, Y. Four-component acyloxy-trifluoromethylation of arylalkenes mediated by a photoredox catalyst. *OBC*, **2019**, *17*(1), 24-29.

(5) Guo, S. Q.; Yang, H. Q.; Wang, A. L.; Jiang, Y. Z.; Xu, G. Q.; Luo, Y. C.; Chen, Z. X.; Xu, P.F. Divergent Ritter-type amination via photoredox catalytic four-component radical-polar crossover reactions. *Green Chem.* **2021**, *23* (23), 9571–9576.

(6) Kammer, L. M.; Krumb, M.; Spitzbarth, B.; Lipp, B.; Kühlborn, J.; Busold, J.; Mulina, O. M.; Terentev, A. O.; Opatz, T. Photoredox-catalyzed four-component reaction for the synthesis of complex secondary amines. *Org. Lett*. **2020**, *22* (9), 3318–3322.

(7) (a) Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. Visible-light-induced chemoselective deboronative alkynylation under biomolecule-compatible conditions. *J. Am. Chem. Soc.*, **2014**, *136*(6), 2280-2283. (b) Huang, H.; Jia, K.; Chen, Y. Hypervalent iodine reagents enable chemoselective deboronative/decarboxylative alkenylation by photoredox catalysis. *Angew. Chem., Int. Ed*. **2015**, 54, 1881−1884. (c) Li, G.-X.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. Photoredox-mediated Minisci C−H alkylation of N- heteroarenes using boronic acids and hypervalent iodine *Chem. Sci*. **2016**, *7* (10), 6407−6412; (d) Zhang, L.; Liu, Z.-Q. Molecular oxygen-mediated Minisci-type radical alkylation of heteroarenes with boronic acids. *Org. Lett*. **2017**, *19* (24), 6594–6597; (e) Dong, J.; Yue, F.; Song, H.; Liu, Y.; Wang, Q. Visible-light-mediated photoredox minisci C–H alkylation with alkyl boronic acids using molecular oxygen as an oxidant. *Chem. Commun*. **2020**, *56* (83), 12652–12655; (f) Pillitteri, S.; Ranjan, P.; Van der Eycken, E.; Sharma, U. K. Uncovering the Potential of Boronic Acid and Derivatives as Radical Source in Photo(electro)chemical Reactions, *Adv. Synth. Catal.*, **2022**, *364*, 1643–1665; (g) Marotta, A.; Adams, C. E.; Molloy, J. J.; The Impact of Boron Hybridisation on Photocatalytic Processes, *Angew. Chem. Int. Ed*. **2022**, e202207067.

(8) a) Lima, F.; Kabeshov, M. A.; Tran, D. N.; Battilocchio, C.; Sedelmeier, J.; Sedelmeier, G.; Schenkel, B.; Ley. S. V. Visible Light Activation of Boronic Esters Enables Efficient Photoredox C (sp2)–C (sp3) Cross-Couplings in Flow. *Angew. Chem. Int. Ed*. **2016**, 55, 14085–14089. b) Lima, F.; Sharma, U. K.; Grunenberg, L.; Saha, D.; Johannsen, S.; Sedelmeier, J.; Van der Eycken, E. V.; V. Ley, S. A Lewis base catalysis approach for the photoredox activation of boronic acids and esters. *Angew. Chem. Int. Ed*. **2017**, *56* (47), 15136–15140; (c) Iwata, Y.; Tanaka, Y.; Kubosaki, S.; Morita, T.; Yoshimi, Y. A strategy for generating aryl radicals from arylborates through organic photoredox catalysis: photo-Meerwein type arylation of electron-deficient alkenes. *Chem. Commun*. **2018**, *54* (10), 1257−1260; (d) Shi, D.; Xia, C.; Liu. C. Photoinduced transition-metal-free alkynylation of alkyl pinacol boronates. *CCS Chemistry*, **2021**, *3* (6), 1718-1728.

(9) (a) Shu, C.; Noble, A.; Aggarwal, V. K. Photoredox-Catalyzed Cyclobutane Synthesis by a Deboronative Radical Addition–Polar Cyclization Cascade. *Angew. Chem. Int. Ed*. **2019**, *58* (12), 3870–3874; (b) Clausen, F.; Kischkewitz, M.; Bergander, K.; Studer, A. Catalytic protodeboronation of pinacol boronic esters: formal anti-Markovnikov hydromethylation of alkenes. *Chem. Sci*. **2019**, *10* (24), 6210–6214.

(10) (a) Chilamari, M.; Immel, J. R.; Bloom, S. General access to C-centered radicals: combining a bioinspired photocatalyst with boronic acids in aqueous media. *ACS Catal*. **2020**, *10* (21), 12727–12737; (b) Ranjan, P.; Pillitteri, S.; Coppola, G.; Oliva, M.; Van der Eycken, E. V.; Sharma, U. K. Unlocking the accessibility of alkyl radicals from boronic acids through solvent-assisted organophotoredox activation. *ACS Catal*. **2021**, *11* (17), 10862–70.

(11) Oliva, M.; Ranjan, P.; Pillitteri, S.; Coppola, G. A.; Messina, M.; Van der Eycken, E. V.; Sharma, U. K. Photoredox-catalyzed multicomponent Petasis reaction in batch and continuous flow with alkyl boronic acids. *iScience*. **2021**, *24* (10), 103134.

(12) Gockel, S. N.; Lee, S.; Gay, B.L.; Hull, K.L. Oxidative three-component carboamination of vinylarenes with alkylboronic acids. *ACS Catal*. **2021**,*11* (9), 5166-5171.

(13) Yue, F.; Dong, J.; Liu, Y.; Wang, Q. Visible-light-mediated alkenylation of alkyl boronic acids without an external Lewis base as an activator. *Org. Lett*. **2021**, *23* (7), 2477-2481

(14) Pillitteri, S.; Ranjan, P.; Ojeda-Carralero, G. M.; Vázquez-Amaya, L. Y.; Alfonso-Ramos, J. E.; Van der Eycken, E. V.; Sharma, U. K. Merging dual photoredox/cobalt catalysis and boronic acid (derivatives) activation for the Minisci reaction. *Org. Chem. Front.*, **2022**, *9*, 6958-6967.

(15) a) Bishop, J. A., Lou, S.; Schaus, S. E. Enantioselective addition of boronates to acyl imines catalyzed by chiral biphenols. Angewandte Chemie, **2009**, *121*(24), 4401-4404; (b) Hutin, M.; Bernardinelli, G.; Nitschke, J. R. An iminoboronate construction set for subcomponent self-assembly. *Chem. Eur. J*. **2008**, *14*(15), 4585-4593; (c) Galbraith, E.; Kelly, A. M.; Fossey, J. S.; Kociok-Koehn, G.; Davidson, M. G.; Bull, S. D.; James, T. D. Dynamic covalent self-assembled macrocycles prepared from 2-formyl-aryl-boronic acids and 1, 2-amino alcohols. *NJC*, **2009**, *33*(1), 181-185; (d) Cal, P. M.; Vicente, J. B.; Pires, E.; Coelho, A. V.; Veiros, L. F.; Cordeiro, C.; Gois, P. M. Iminoboronates: a new strategy for reversible protein modification. *J. Am. Chem. Soc*. **2012**, *134*(24), 10299-10305; (e) Gutiérrez-Moreno, N. J.; Medrano, F.; Yatsimirsky, A. K. Schiff base formation and recognition of amino sugars, aminoglycosides and biological polyamines by 2-formyl phenylboronic acid in aqueous solution. *OBC*, **2012**, *10*(34), 6960-6972.

(16) (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. Continuous-flow technology—a tool for the safe manufacturing of active pharmaceutical ingredients. *Angew. Chem. Int. Ed*. **2015**, *54*, 6688–6728; (b) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of continuous-flow photochemistry in organic synthesis, material science, and water treatment. *Chem. Rev*. **2016**, *116*, 10276–10341; (c) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. The hitchhiker's guide to flow chemistry. *Chem. Rev*. **2017**, 117, 11796–11893.