Merging dual photoredox/cobalt catalysis and boronic acid (derivatives) activation for the Minisci reaction

Serena Pillitteri, Prabhat Ranjan, Gerardo M. Ojeda-Carralero, Laura Y. Vázquez Amaya, Javier E. Alfonso-Ramos, Erik V. Van der Eycken, Upendra K. Sharma*

[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium, upendrakumar.sharma@kuleuven.be; u Sharma81@gmail.com

[b] Aachen Maastricht Institute for Biobased Materials (AMIBM), Maastricht University, Urmonderbaan 22, 6167 RD Geleen, The Netherlands.

[c] Peoples’ Friendship University of Russia (RUDN University), Miklukho-Maklaya street 6, 117198 Moscow, Russia

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

[e] Laboratory of Computational and Theoretical Chemistry, Faculty of Chemistry, University of Havana, Zapata y G, Havana 10400, Cuba.

Abstract: The merger of open-shell and closed-shell organometallic chemistry steps has enabled multiple effective cross-coupling pathways. Here we report a visible-light promoted photoredox-cobalt catalyzed Minisci reaction of N-heteroarenes under mild and sustainable conditions, employing various boronic acids and derivatives as alkyl radical precursors. This study demonstrates the prominent ability of the Co co-catalyst to promote the oxidation step of the photocatalytic cycle following a reductive quenching pathway, thus avoiding the use of stoichiometric (inorganic) oxidants. This feature enables the straightforward application of photoflow conditions, particularly attractive for an easy scale-up and to enhance the efficiency of the reaction (throughput: 0.78 mmol/h in flow vs 0.02 mmol/h in batch). Furthermore, the process is predominantly selective towards the C2-alkylation of quinolines, and a mechanistic rationale has been provided with both experimental and DFT calculation support. The developed protocol demonstrates broad applicability for the alkylation of different N-heteroarenes under suitable homogeneous conditions for a flow-compatible Minisci reaction.
Introduction

The past decade has witnessed tremendous growth in the realm of photoredox catalysis, inspired by the vision of enabling chemistry and chemical synthesis with visible-light irradiation.\(^1,2\) With the photons as traceless reagent, radical processes have assumed a renewed role, and the unpredictability closely associated with the generation of single-electron species has turned into a trustworthy way to functionalize organic molecules under mild and sustainable conditions.\(^3,4\) In particular, the excitation of a photocatalyst (PC), followed by single electron transfer (SET) or hydrogen atom transfer (HAT) events has allowed the facile generation of alkyl radicals, further involved in the functionalization of a broad variety of molecular architectures.\(^3,5,6\) Such conceptually simple transformations become of vital importance when considering the untapped chemical space for drug discovery and even late-stage functionalization of medicinally relevant (bio)molecules.\(^7,8\) Higher chances of generating biologically active scaffolds are also associated with the installation of saturated bonds, thus increasing the odds of successful ligand-receptor binding and improving drug-like properties.\(^9\)

The Minisci reaction, which allows the direct C-H bond functionalization of pyridine-based heteroarenes through a radical pathway, is a powerful method to synthesize alkyl-substituted heterocycles.\(^10\) Under conventional alkyl radical generation processes, metal catalysts, high temperatures and excessive amounts of oxidants are generally involved,\(^11\) leading to sustainability and safety concerns.

In order to avoid these limitations, several methods to generate alkyl radicals have recently emerged through the aid of photoredox catalysis.\(^3\) Among many, activated N-hydroxyphthalimide redox-active esters (synthesized from carboxylic acids) appear to be particularly suitable for the Minisci reaction, avoiding the use of further stoichiometric oxidants to close the catalytic cycle and generate the final product.\(^11\) Among reported examples, Molander’s pioneering work employing electron-rich alkyltrifluoroborate salts to generate alkyl radicals is noteworthy.\(^12\) However, this method requires a stoichiometric inorganic oxidant (potassium persulfate), which might be incompatible with flow conditions due to poor solubility.

On the contrary, few sporadic reports employing boronic acids (BAs) (direct precursors of trifluoroborates) in the Minisci
reaction have appeared (Figure 1A), while boronic esters have not been reported as alkyl radical precursors for the Minisci reaction, despite their ease of synthesis. Overall, the unattainable oxidation potential of these species has hindered their utilization as suitable radical precursors. Only recently, expedient strategies have been devised for this purpose, including our previous work on free boronic acid activation under photo-flow conditions, which relied on the mediation of amide based solvents to form alkyl radicals (Figure 1B). The application of these strategies is nevertheless mostly limited to redox-neutral additions on activated alkenes and a few related reactions. On the other hand, the Minisci reaction of boronic acids and derivatives is still largely dependent on stoichiometric use of oxidants ranging from K$_2$S$_2$O$_8$, O$_2$, and benziodoxole, with the latter following an oxidative quenching pathway.

In recent years, the introduction of metals in dual photoredox-metal mediated reactions has also undergone widespread growth, because of the ability of transition metals (Ni, Cu, Fe, Co, Pd, etc.) to efficiently participate in SET events, resulting in the merger of open-shell and closed-shell-elementary organometallic steps. In this context, we questioned if it might be possible to merge photoredox Minisci-type activation employing various boronic acids and derivatives with a cooperative cobaloxime co-catalyst to replace the stoichiometric use of oxidants (Figure 1C). We further recognized that this system might be suitable, from a flow chemistry point of view, to overcome the issues related to the use of stoichiometric inorganic oxidants (i.e. clogging) and to deal with scale-up issues.

Table 1: Optimization of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from the standard conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>50 mol% TFA</td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv of TFA</td>
<td>97%</td>
</tr>
<tr>
<td>4</td>
<td>1.2 equiv cy-Bpin, acetone</td>
<td>80%</td>
</tr>
<tr>
<td>5</td>
<td>1 equiv cy-BF$_3$K</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>No TFA</td>
<td>40%</td>
</tr>
<tr>
<td>7</td>
<td>No 4CzIPN or Co(dmglH)(dmglH)$_2$Cl$_2$</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>No blue LEDs</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>No inert atmosphere</td>
<td>93%</td>
</tr>
<tr>
<td>10</td>
<td>Addition of water: DMA/water (95:5)</td>
<td>10%</td>
</tr>
</tbody>
</table>

*a* All reactions were carried out using BA (0.2 mmol, 1 equiv), isoquinoline (0.3 mmol, 1.5 equiv), PC, Co co-catalyst, solvent (0.1 M), under blue LED irradiation (14 W). *b* Isolated yield. 48 h.

Results and Discussion

**Reaction Optimization.** We began our investigation using boronic acids as the radical source but aiming to later expand the scope to boronic acid pinacol esters and trifluoroborate salts. While trifluoroborates need no additional activation, the high potential needed for the oxidation of boronic acids and their pinacol esters impedes oxidation by any common photocatalyst. An external activator becomes therefore necessary to generate radicals from these species. In the light of our previous work and literature precedents, we were aware of the possibility to activate boronic acids to SET through solvent mediated interactions, without excluding the probable involvement of heterocyclic substrates as Lewis base, thus
leading to the formation of a Lewis acid-base adduct with the boronic acids.\textsuperscript{37} We therefore postulated that the occurrence of both activation methods could stir the reaction for the generation of the desired alkyl radical. We commenced our study by irradiating a mixture of cyclopentyl BA, isoquinoline, 4CzIPN (5 mol\%) as photocatalyst, Co(dmgH)(dmgH\textsubscript{2})Cl\textsubscript{2} (5 mol\%) and trifluoroacetic acid (TFA, 50 mol\%) for 48 h. We were delighted to obtain 82\% yield (Table 1, Entry 2). The catalyst choice proved to be the best combination for the devised reaction (see SI for more details). Interestingly, we observed nearly quantitative conversion when adding one (Table 1, Entry 1) or two equivalents of TFA (Table 1, Entry 3), as a result of the double role of the acid in lowering the activation energy for the radical attack (see DFT mechanistic studies in the SI) and in facilitating H\textsubscript{2} release in the cobalt cycle. After careful screening of more conditions, 20 h of irradiation were found to be sufficient to obtain the desired product, employing only one equivalent of acid (Table 1, Entry 1). In the attempt to extend the scope to the employment of boronic acid pinacol esters and trifluoroborates, small adjustments to the reaction conditions were applied (Table 1, Entry 4 and 5). Control experiments confirmed the necessity of both the photocatalyst and the cobalt co-catalyst, as the reaction did not proceed in the absence of any of them (Table 1, Entry 7). When left in the dark, no conversion of the starting materials was observed (Table 1, Entry 8). The addition of TEMPO allowed us to confirm a radical mechanism. To explore the robustness of this reaction platform, we sought to study the effect of water and the lack of inert atmosphere. While dry solvents were not required, the use of the solvent mixture DMA/water (95:5) was found to be detrimental for the reaction, giving rise to a reduced amount of desired product (10\% yield, Table 1, Entry 10), together with photocatalyst decomposition and increased byproduct formation. On the other hand, the lack of inert atmosphere did not affect the reaction outcome, proving the robustness of the reaction for further implementation on an industrial scale (Table 1, Entry 9).

**Scope and limitations of the reaction.** To prove the viability of the method, the optimal conditions were then tested on a variety of boronic acid (derivatives) and heterocyclic structures. First, secondary boronic acid (derivatives) were tested, affording the desired products in good to excellent yield. Cyclopentyl, cyclohexyl and cyclobutyl rings were easily installed (Scheme 1, 1-3). Indene boronic acid pinacol ester also worked well (5), and similar results could be pleasingly obtained with a difluorocyclohexyl moiety (6). To our delight, the naturally occurring (\textpm)-\textalpha-pinene moiety (4) could be coupled as well without any structural rearrangements. This reaction platform was also amenable to bridged alkanes (i.e. norbornyl ring and adamantyl ring, privileged scaffold in the development of relevant drug molecules\textsuperscript{38} (7,18). The acyclic secondary isopropyl and sec-butyl groups afforded the desired product in good yield (8-9). Despite their intrinsic instability, primary boronic acids and their trifluoroborate salts successfully delivered the corresponding Minisci products. The short-chained ethyl and propyl boronic acid gave the expected product (10,11, albeit in lower yield in the
case of propyl boronic acid), and the same happened with butyl (12), phenylethyl (14) and iso-butyl (15) boronic acid. A but-1-enyl moiety (13) also reacted moderately, retaining the terminal alkene, which could potentially undergo further functionalization. Octyl trifluoroborate was also found reactive, despite the lower yield (16). Unfortunately, primary boronic esters were not suitable substrates for radical generation and only the starting material was recovered. When subjecting benzyl boronic acid (19) to the optimal conditions, the product could only be isolated in 20% yield, and the concomitant formation of unidentified side products was observed. Tertiary boronic esters reacted smoothly, but in moderate yield, under the reported conditions (17-18); in addition to the adamantly moiety mentioned before, a tert-butyl group was also coupled. Heterocyclic boronic acid (derivatives) also proved to be successful radical sources, and a tetrahydropyran moiety, together with N-Boc-protected piperidine (one of the most common scaffolds found in drugs) were coupled in good yields (20-21).

Next, we sought to explore the broadness of the heterocyclic counterpart. A range of diversely substituted isoquinolines was tested, and the yield spanned from good to moderate. A variety of substituents were tolerated, including benzyl (24), methyl ester (25), bromo (26) and cyano (27). In the case of halogen substituted quinolines and isoquinolines, the side products from dehalogenation were also observed. A lower yield was obtained in the case of a free hydroxyl bearing isoquinoline (30). After these experiments, we applied our best conditions to quinoline derivatives, but we observed a sharp decrease in yield. Surprised by this unexpected result, we further optimized the reaction conditions, observing that a change in the solvent led to a drastic increase in yield (for the full optimization table, see SI). Solvents with low polarity performed better. In line with the reported ability of the combination between nonpolar solvents (toluene) and TFA to shift the selectivity to the C2 position of quinolines, we subjected non-substituted quinoline to the modified conditions (31). We pleasingly observed a net increase in the yield (75%), with a concomitant predominance of the C2-alkylated product (ratio C2:C4 = 4:1). The prevalence of C2-alkylated products was also observed in the case of 3-bromo quinoline (33) and 7-methyl quinoline (35). The reaction also proved to be amenable to phenanthridine, phthalazine, imidazo[1,2-b]pyridazine and benzothiazole (36-39). Pyridines, on the other hand, showed lower reactivity. This is reflected in the low yield of the alkylation product when employing protected desloratadine as a substrate (40,43). The antifungal drug quinoxyfen was alkylated in good yield (42), and the alkylation of parvaquone and probenecid derivatives were accomplished as well (41, 44).
Scheme 1. Scope of the reaction.4 The values indicate the yield of the isolated products. Radical precursors other than BA are specified. Conditions unless otherwise stated: BA (1 equiv 0.4 mmol), heterocycle (1.5 equiv 0.6 mmol), 4CzIPN (5 mol%), Co(dmgH)(dmgH)Cl₂ (5 mol%), DMA (0.1 M), TFA (1 equiv), 14W blue light room temp, 20h.

1: 98%  2: 68%  3: 87% (BA) 80% (BPin) 78% (BF₃K)
4: 60% (BPin)  5: 40%  6: 60% (BPin)  7: 62% (BF₃K)
8: 49%  9: 70% (BF₃K)  10: 56%  11: 20%  12: 59%  13: 42%  14: 55%
15: 49%  16: 31% (BF₃K)  17: 35% (BPin)  18: 50% (BPin)  19: 20%  20: 63% (BPin)  21: 62% (BPin)

22: 89%  23: 30%  24: 81%  25: 40%  26: 27%  27: 30%  28: <10 %
29: <10%  30: 20%  31: 75% Ratio C₂:C₄ = 4:1  32: 83%  33: 28% Ratio C₂:C₄ = 6:1  34: 56%
35: 48% Ratio C₂:C₄ = 4:1  36: 69%  37: 60%  38: 33%  39: 51%  40: 22%

41: 30% from paroxetine  42: 52% from quinolin  43: 20% from desloratadine  44: 26% from prbenzene
Application under photo-flow conditions.
With the final aim to render the devised reaction scalable, we decided to implement this reaction manifold in a photo-flow reactor. The robustness and tolerability to air and moisture that the reaction features suits well for practical flow applications. The combination of flow chemistry with photoredox catalyzed processes has shown several benefits, given the better light penetration and mixing properties, in addition to increased reaction efficiency and often decreased by-product formation.\textsuperscript{45–47} Surprisingly, considering the relevance of the Minisci reaction to functionalize common scaffolds in drugs and the necessity to scale-up industrially applicable reactions, only few examples of Minisci reactions performed in photo-flow reaction setups can be found. In 2015, Stephenson and co-workers first applied the Minisci mechanism in flow to achieve the trifluoromethylation of electron-rich or slightly electron-deficient heterocycles, observing minimal reactivity of the pyridine scaffold, as a result of the nature of the trifluoromethyl radical and its challenging formation from readily available feedstock.\textsuperscript{48} Beside trifluoromethylation strategies,\textsuperscript{49,50} limited in the scope of heterocyclic scaffolds, the carboxylic acid derived redox-active esters were utilized as radical source, with low atom economy and still limited applications.\textsuperscript{51,52} In the light of the reaction mechanism, stoichiometric oxidants are not required for these transformations, therefore avoiding plausible clogging issues in a flow setup. Despite the advancement in the topic, a broader scope in the radical precursors landscape remains so far a challenge. To this end, the net oxidative protocol here devised enables the avoidance of stoichiometric insoluble oxidants or inorganic bases, substituted by a catalytic amount of a Co-based co-catalyst, which does not pose clogging issues in a flow setup. When the optimal conditions of our protocol were translated to a Vapourtec-UV 150 photo-flow reactor, the desired product was isolated in 64% yield within a residence time of 50 min (Scheme 2, Entry 2).

The reaction was performed in a 10 mL volume reactor, equipped with 1.23 mm PFA tubing. In the same time frame, the corresponding batch reaction only afforded traces of the desired compound.

\begin{table}
\centering
\begin{tabular}{|l|c|c|}
\hline
Entry & Deviation from the standard conditions & Yield (%)  \\
\hline
1 & None & 80%  \\
2 & DMA & 64%  \\
3 & DMA/ACN (1:1) & 51%  \\
4 & 2 mol% Co(dmgH)(dmgH₂)Cl₂ & 74%  \\
5 & 0.4 mL/min (flow rate) & 50%  \\
\hline
\end{tabular}
\end{table}

Scheme 2. The Minisci reaction under photo-flow conditions.\textsuperscript{9} The values indicate the yield of the isolated products. Conditions unless otherwise noted: BA (1 equiv 0.4 mmol), heteroarene (1.5 equiv 0.6 mmol), 4-CzIPN (5 mol%), Co(dmgH)(dmgH₂)Cl₂ (5 mol%), DMA/ACN (1:1) (0.1 M), DMA/ACN (1:1), TFA (1 equiv) in 10 mL reactor, equipped with 1.23 mm PFA tubing.
0.2 mL/min, reactor volume: 10 mL, residence time: 50 min, irradiating with blue LEDs (40 W). A flow rate of 0.1 mL/min was employed, with a residence time of 100 min.

This result clearly pinpoints the increased efficiency of a continuous-flow approach. The conditions were further optimized, and after several variations, we noticed that the use of a solvent mixture (DMA/ACN 1:1), as in our previous report was sufficient to increase the yield up to 80% (Entry 1, see SI for more details), keeping a residence time of 50 min and a flow rate of 0.2 mL/min. The optimized conditions were then applied to more substrates, affording yields consistent with the batch conditions, in a steadily decreased time frame. Impressively, in the case of benzyl boronic acid (19) the desired product was obtained in 56% yield (while the corresponding batch reaction only afforded 20% yield). In addition, isoquinolines bearing electro-donating groups performed better under continuous-flow conditions (28-29), as a result of the lower irradiation time, which avoids side product formation, otherwise experienced under batch conditions. In the latter case, the reaction was sluggish and decomposition products were observed. Under photo-flow conditions, at a flow rate of 0.05 mL/min, the product could be easily isolated in 90% yield (28). Similarly, isoquinoline-6-carbonitrile performed better in flow conditions (27).

To explore the robustness of this protocol, a large-scale synthesis of the alkylated isoquinoline under photo-flow conditions was performed as well. The low amount of catalysts and the minimal expense for the starting materials and catalysts render the presented method viable for the large-scale synthesis. A 10-fold increase in the reaction scale (4 mmol over 0.4 mmol) led to a 65% yield (513 mg obtained in 200 min). This result showcases the potential to efficiently scale-up the reaction, that would otherwise be less effective in batch, requiring longer irradiation times to overcome the limitations caused by inefficient light penetration in bigger reactors.

**Mechanistic investigations.** Thereafter, we sought to elucidate the mechanistic scenario underlying the observed reactivity. For this purpose, we conducted mechanistic experiments and confirmed the results obtained through DFT calculations. Hypothesizing an oxidation step involving boronic acids and aware of Ley’s and our group’s work on the Lewis acid-base interaction between boronic esters and DMAP, we wondered if the interaction between boronic acids and heterocyclic molecules could lead to a reduced oxidation potential and therefore to a radical generation as well.

We first measured the oxidation potential resulting from the mixture of boronic acid and isoquinoline. The reduction in boronic acid redox potential in the presence of dimethylacetamide (DMA) has already been proven by cyclic voltammetry. Similarly, as shown in Figure 2B, a lowered oxidation peak at 1.01 V (vs SCE) arises from the mixture of cyclohexyl boronic acid and isoquinoline, supporting our hypothesis (for more information see SI). This value lies in the redox window of the employed photocatalysts. DFT calculations confirmed the experimental result. Under the reaction conditions, isoquinoline exists in equilibrium in free, protonated and hydrogen-bonded forms (see SI for more details). Free isoquinoline and cyclopentyl boronic acid are involved in a parallel equilibrium forming the
corresponding Lewis acid-base adduct (Figure 2B). This adduct has 1.71 Å of B-N bond distance and 106° between the B-N and B-O bonds, very close to the value of 109° (sp³ hybridization) for tetrahedral geometry. Upon oxidation, the C-B bond elongates to 2.89 Å and is almost fully broken in the resultant radical cation; meanwhile, the bond angle increases up to 115° and the B atom now is better described as trigonal planar (sp² hybridization). The cyclopentyl ring has a large radical character, largely centred on the C atom previously bonded to the B atom (see SI for the spin densities). In the following dissociation step, the C-B bond completely breaks and releases the cyclopentyl radical. This process proceeds spontaneously with a Gibbs energy change of -5.79 kcal/mol and drives the equilibrium towards the formation of the product. It was found that the (calculated) redox potential required for the oxidation of the adduct is about 1.0 V lower than the oxidation potential of the free boronic acid, which is supported the CV measurements.

**Figure 2. Proposed mechanism and mechanistic investigations.** A) Proposed mechanism. B) Cyclic voltammetry experiment (0.2 mM of cyclohexyl boronic acid and isoquinoline in acetonitrile using AgCl/Ag as reference electrode). The potential of the redox-active complex is highlighted in blue. C) Reaction kinetics at different Co-cocatalyst concentrations. D) Light-dark experiment.

Once demonstrated the possible generation of the required electron rich boronate complex (the Lewis acid-base adduct), we focused our attention on determining whether a reductive quenching pathway could be confirmed. As reported in previous literature, the reduction
potential of Co(dmgH)(dmgh2)Cl2 (-0.49 V)\textsuperscript{29} is compatible with the redox window of the photocatalyst employed for this transformation (4CzIPN\textsuperscript{+}/4CzIPN\textsuperscript{*} = -1.04 V).\textsuperscript{53} We therefore performed fluorescence quenching studies. These studies revealed to be not conclusive. Strong quenching of 4CzIPN happened in the presence of Co(dmgH)(dmgh2)Cl2. Nevertheless, a comparison with the quenching rate of the boronic acid-isoquinoline complex could not be made, as a result of an energy transfer mechanism between the heterocyclic structure and the PC itself, that led to a decrease in the emission of the PC in the sole presence of the heterocycle (see SI for more details).\textsuperscript{54} In this scenario, being unclear if the boronate complex was responsible for the first oxidation step in the hypothesized mechanism, kinetic studies were conducted. The reaction was performed under increasing concentrations of the cobalt co-catalyst to understand its effect on the reaction rate. As shown in Figure 2C, the reaction rate decreased in the presence of higher amount of co-catalyst. This behavior could be related to a possible detrimental interaction between PC and the cobalt catalyst.\textsuperscript{55} Being the oxidation potential of the utilized cobalt complex matching the redox window of the PC, at higher concentrations, the engagement between the two catalysts could hinder radical formation, as the sharp decrease in the reaction rate would suggest. This behavior therefore endorses our hypothesis of a reductive quenching cycle involving radical formation from boronic acid (derivatives) as the first catalytic step. We therefore conjectured that, upon photocatalyst excitation, a single electron oxidation of the boronic acid (or derivatives) occurs, thus leading to the radical generation, followed by the radical attack on the protonated heterocyclic core, according to the general mechanism of the Minisci reaction (Figure 2A). At this stage, the intervention of the Co co-catalyst becomes essential to complete the catalytic cycle and form the final product. The reaction between the Co\textsuperscript{II} complex (generated upon PC mediated reduction of the Co\textsuperscript{III} species) and the radical intermediate then results in a formal $\beta$-hydride elimination that affords the desired product, together with the formation of a Co\textsuperscript{III}-H species.\textsuperscript{30,56,57} In the acidic reaction medium, Co\textsuperscript{III}-H undergoes H\textsubscript{2} loss, followed by Co\textsuperscript{III} to Co\textsuperscript{II} reduction and concomitant photocatalyst turnover.\textsuperscript{29,58,59} To confirm the photocatalytic mechanism, we further performed a light-dark experiment to define the nature of our reaction. As visible from Figure 2D, the graph suggests a photochemical mediated mechanism. The experimentally found quantum yield of 0.64 (see SI for more details) corroborates this assumption.

Further DFT calculations clarified the reasons for the experimentally observed regioselectivity. Single point calculations for the neutral and ionized molecules allowed to obtain the radical Fukui function and the dual descriptor.\textsuperscript{60,61} It was found that even when both quinoline and isoquinoline possess several reactive sites, the reactivity becomes more localized after the interaction with acid (C1 and C4 of isoquinoline, and C2 and C4 of quinoline (Figure 3), see SI for all the results found). The same trend was observed for the Lewis acid-base complexes of the nitrogen heterocycles with the boron-containing species employed in this reaction. Then we analyzed the effects on the reaction energetics.
Earlier Baran’s group found that the effect of acids on the regioselectivity of the Minisci reaction is higher for nucleophilic radicals, such as the ones employed in the present study. Therefore, we calculated the Gibbs energy for the radical addition step in the presence and absence of acid (Figure 3A). For isoquinoline, the addition on C1 is favored over the addition at C4 for both the free molecule (\(\Delta \Delta G^\ddagger = -1.9\) kcal/mol) and the hydrogen-bonded form (\(\Delta \Delta G^\ddagger = -5.8\) kcal/mol). For quinoline, only the addition of acid slightly drives the selectivity towards the C2 position (\(\Delta \Delta G^\ddagger = 0.3\) kcal/mol for the free molecule, while \(\Delta \Delta G^\ddagger = -2.0\) kcal/mol for the hydrogen-bonded form). Aiming to pinpoint the underlying causes of such energetic changes, the different contributions to the activation barriers were studied within the framework of the Distortion-Interaction (Activation-Strain) model. It was found that, overall, the main reason of the experimentally observed regioselectivity is the large increase in the energy of interaction between the nucleophilic alkyl radical and the electrophilic hydrogen-bonded (iso)quinoline (Figure 3B, see SI for more details). Non-covalent interactions (NCI) analysis of the transition state corresponding to the radical addition at the C2 position of the quinoline (TS-C2) revealed weak attractive interactions. As represented in Figure 3C, two non-classical hydrogen bonds between the O-atoms of the trifluoracetate counter ion and two C-H bonds of the cyclopentyl ring are established, contributing to the stabilization of the transition state and a further decrease of the activation barrier. Previous experimental studies also showed that acid catalysis in nonpolar solvents (e.g. toluene) drive the radical substitution towards the C2 position of pyridines and quinolines. Our results suggest that the main reason for this behavior might be the formation of favorable interactions between the radical that is adding and the counterion in the hydrogen-bonded species (the most abundant in a nonpolar acidic reaction media). Such kind of cooperative mechanism have been previously proposed to occur, for example, in the chiral phosphoric acid catalyzed enantioselective Minisci reaction.

**Figure 3. Regioselectivity for the addition of cyclopentyl radical to (iso)quinoline explained.** A) Energy profile of the reactions. Calculations of the Gibbs energies were performed at the theoretical level UB3LYP-D3/def2-TZVP/SMD(toluene). B) Distortion-Interaction analysis. C) Non-covalent Interaction analysis for the transition state corresponding to protonated and hydrogen-bonded isoquinoline. An RGB color scale set from -0.005 a.u. to 0.005 a.u. is used to differentiate between repulsive (red), weak (green) and attractive (blue) non-covalent interactions.

**Conclusions**

In conclusion, a robust dual photoredox/Co catalyzed Minisci type reaction employing boronic acids and their derivatives (pinacol esters and trifluoroborates) as radical source
has been developed. The applicability of the presented synthetic strategy proved its high efficiency in batch and under continuous-flow conditions. The flow-compatible homogeneous conditions, in the absence of (poorly soluble) stoichiometric oxidants enabled the introduction of a flow reactor, therefore drastically reducing the reaction time. DFT calculations in combination with experimental studies allowed to elucidate the reaction pathway, allowing to understand the role of the reaction parameters in controlling the regioselectivity.

Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: SP, PR and UK; methodology: SP; DFT calculation: JEAR and GMOC; experimentation: SP, LYVA, GMOC and PR; draft manuscript preparation: SP, PR, GMOC, LYVA, JEAR, EVDE, UKS.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

SP (experiments and writing) is thankful to the FWO for obtaining a PhD scholarship (SP grant No. 11H0121N). GMOC is grateful to VLIR-UOS for financial support of a Flemish-Cuba cooperation project (CU2018TEA458A101). 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). GMOC and JEAR are grateful to Ana Lilian Montero-Alejo for her valuable suggestions. JEAR acknowledges CITMA for financial support (project PN223LH010-02X), Cuba. Powered@NLHPC: This research was partially supported by the supercomputing infrastructure of the NLHPC (ECM-02), Chile.

References


**Entry for the Table of Contents**

Boronic acid (derivatives) activation for the Minisci reaction via dual photoredox/ cobalt catalysis in batch and under continuous-flow.

Institute and/or researcher Twitter usernames:

@KU Leuven, @upen14