

Journal Pre-proofs

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Use of acridinium-based photocatalyst in the Giese-type coupling of arylboronic acids with electron poor olefins

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ABSTRACT

The development of a visible light-mediated Giese-type reaction using arylboronic acids as aryl radical source is described. The synthetic protocol capitalizes on the employment of environmentally benign metal-free catalyst to forge Csp²-Csp³ bonds. Applications of the methodology to the synthesis of aminoesters and the anti-inflammatory drug nabumetone, either in batch or in flow, are also reported.

Key words: Visible light photocatalysis, boronic acids, Giese reaction, metal free, nabumetone

1. Introduction

Visible light-mediated photocatalysis has emerged as an extremely useful synthetic strategy in many organic transformations and the utility of this technology in the pharmaceutical field has gained tremendous attention in recent years.¹ The mild reaction conditions involved matched the

actual industrial attitude in exploiting simpler and environment-friendly chemical transformations, especially when the catalytic system can capitalize on non-toxic and cheap metal-free ingredients.² Aiming at exploiting boronic acid as the radical source in a Giese-type reaction, we focused on arylboronic acids, as photoredox coupling involving alkylboronic acids is well precedented in the literature.^{3,4,5} Moreover, several examples employing alkyltrifluoroborates as radical source has been reported by Akita and coworkers using different catalysts.⁶

Arylboronic acids⁷ are widely known for their use in organic synthesis, mainly in transition metal-catalyzed generation of carbon-carbon bonds (Suzuki-Miyaura reaction, Cham-Lam reaction etc).⁸ Other less popular applications involve, for instance, their employment in the multi-component Petasis reaction for the preparation of amines.⁹ The widely recognized value as reagents of arylboronic acids led to their broad availability either from commercial sources or by simple synthetic protocols. Recently, their application in photoredox catalysis has unveiled a new scope of these intermediates.³ However, while their employment in oxidative cycles¹¹ or in combination with a second catalyst¹² has been deeply investigated, the use of arylboronic derivatives in a reductive cycle is less explored due to the unfavorable redox potential. Limited examples regarding boronic acids as aryl radical precursor can be found.¹³ Excellent works by Yoshimi,³ Ley⁴ and Bloom¹⁴ have shown that photoredox catalysis allows the generation of transient aryl radicals from arylboronic acids through a single-electron reduction process, prompting us to focus our efforts in expanding the scope and limitation of the alkene counterpart in combination with an acridinium catalyst.

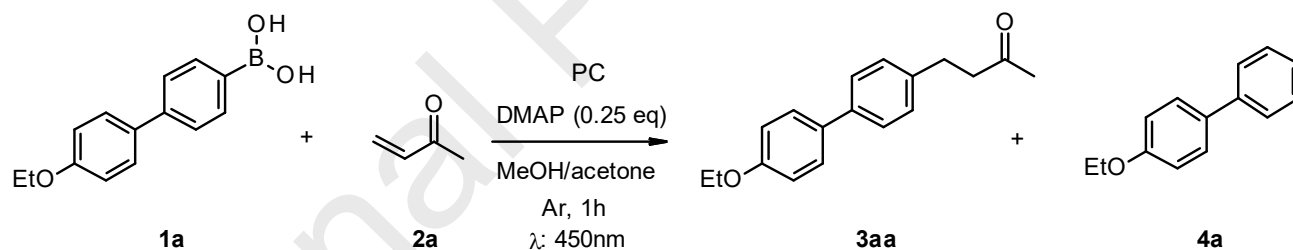
In this account we report our results in investigating the Giese-type photoredox coupling of arylboronic acids with several electron-poor olefins, thus expanding our knowledge on this kind of transformation.

2. Result and discussion

Our exploration started by using 4-ethoxybiphenyl-4'-boronic acid (**1a**) as a model since it allows, differently from simpler phenylboronic acids, to quickly monitor the progression of the chemical reaction with methyl vinyl ketone (MVK, **2a**), used as a pilot olefin, through UV detection. In order to select the catalyst, Ley's reaction conditions^{4b} were applied. The reaction outcome was analyzed after 1 h irradiation at 450 nm (PhD Photoreactor M2) (Table 1, Entries 1-12). Eleven

different catalysts were investigated. The reaction resulted in a complete conversion with $[\text{Ir}\{\text{dFCF}_3\text{ppy}\}_2(\text{bpy})]\text{PF}_6$,^{15a} (**PC1**, entry 2), Mes-Acr⁺BF₄⁻ (10-(3,5-dimethoxyphenyl)-9-mesityl-1,3,6,8-tetramethoxyacridin-10-ium tetrafluoroborate, Mes-Acr)^{15b} (**PC3**, entry 4) and 4-CzIPn (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene)^{15c} (**PC4**, entry 5), while partial transformations were observed with the three flavine-based catalysts (riboflavin tetraacetate (RFTA, **PC5**), riboflavin (**PC6**) and lumiflavin (**PC7**), entries 6-8). Moreover, only unreacted starting material **1a** resulted from the use of Ru(bpy)₃(PF₆)₂ (**PC2**), fluorescein (**PC8**, entry 9), anthracene/1,4-dicyanobenzene (**PC9**, entry 10) as well as two xanthene-derived (rose Bengal (**PC10**) and Eosin Y (**PC11**), entries 11-12) catalysts. Thus, Mes-Acr was selected to further investigate scope and limitations of this reaction as it was the best performing among the metal-free scrutinized catalysts. It has to be underlined that side-product 1-ethoxydiphenyl (**4a**) was always detected, albeit in different amounts, with all the catalysts, and that the efficiency of the aryl radical addition was mainly related to the properties of the olefin rather than the nature of the catalyst employed.

Table 1. Optimization of the reaction conditions: selection of the catalyst



Entry	Photocatalyst (PC)	mol %	1a (%) ^a	3aa (%) ^a	4a (%) ^a	Ratio (3aa/4a)
1	No catalyst	-	100	-	-	
2	$[\text{Ir}\{\text{dFCF}_3\text{ppy}\}_2(\text{bpy})]\text{PF}_6$ (PC1)	2.5	-	60	40	1.5
3	Ru(bpy) ₃ (PF ₆) ₂ (PC2)	2.5	100	-	-	
4	Mes-Acr (PC3)	2.5	-	67	33	2
5	4CzIPN (PC4)	2.5	-	49	51	1
6	RFT (PC5)	10	20	48	32	1.5
7	Riboflavin (PC6)	10	68	20	13	1.5
8	Lumiflavin (PC7)	10	48	38	14	2.7
9	Fluorescein (PC8)	10	100	-	-	
10	Anthracene/DCB (PC9)	10	100	-	-	

11	Rose Bengal* (PC10)	2.5	100	-	-	
12	Eosin Y* (PC11)	2.5	100	-	-	

Solvents employed were previously degassed by bubbling argon for 15 minutes

^a Normalized percentages were evaluated by HPLC/MS as AUC at $\lambda=254$ nm

* Also irradiated with green led light

After identifying the best photocatalyst, further reaction conditions analysis (see Supporting Information Table 1S) firmly confirmed the already reported^{4b} degassed methanol/acetone (1/1) mixture as the most appropriate, as well as the superior performance of the blue 450 nm wavelength (see Supporting Information Table 2S) in achieving the desired Giese-type product.

Interestingly, by exposing the reaction mixture to direct sunlight irradiation, the complete disappearance of the starting material was observed within 4 hours, however with a much less efficient formation of the desired product due to presence of several (uncharacterized) impurities.

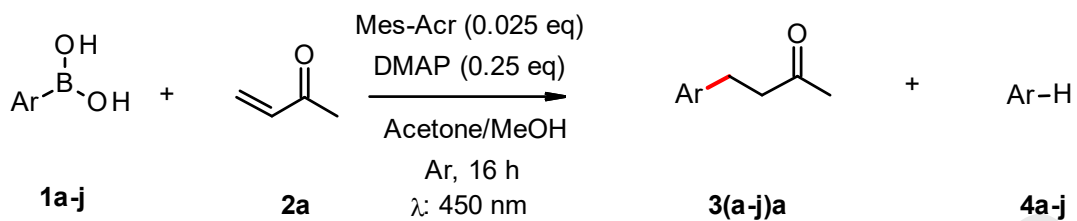
Among a small set (8 compounds, see Supporting Information Table 3S) of organic bases tested, none of them proved to be superior to DMAP and 3-quinuclidinol (sub-stoichiometric amount; both 0.25 equivalents), thus confirming Ley *et al.* previous observations.^{4b} The main limitation of this synthetic protocol is linked to its overall lack of atom economy, as it requires 4 equivalents of olefin to be efficiently accomplished. Efforts in diminishing the excess of enone either provide lower yields or worsen the **3aa/4a** ratio (Supporting Information, Table 4S).

Mechanistically, we confirmed that the reaction between **1a** and **2a** is completely inhibited in the presence of TEMPO (see Supporting Information Scheme 1S) and, through deuterium labelling experiments, we showed that MeOH is responsible for the quenching of carbanion intermediate (see Supporting Information Scheme 2S).

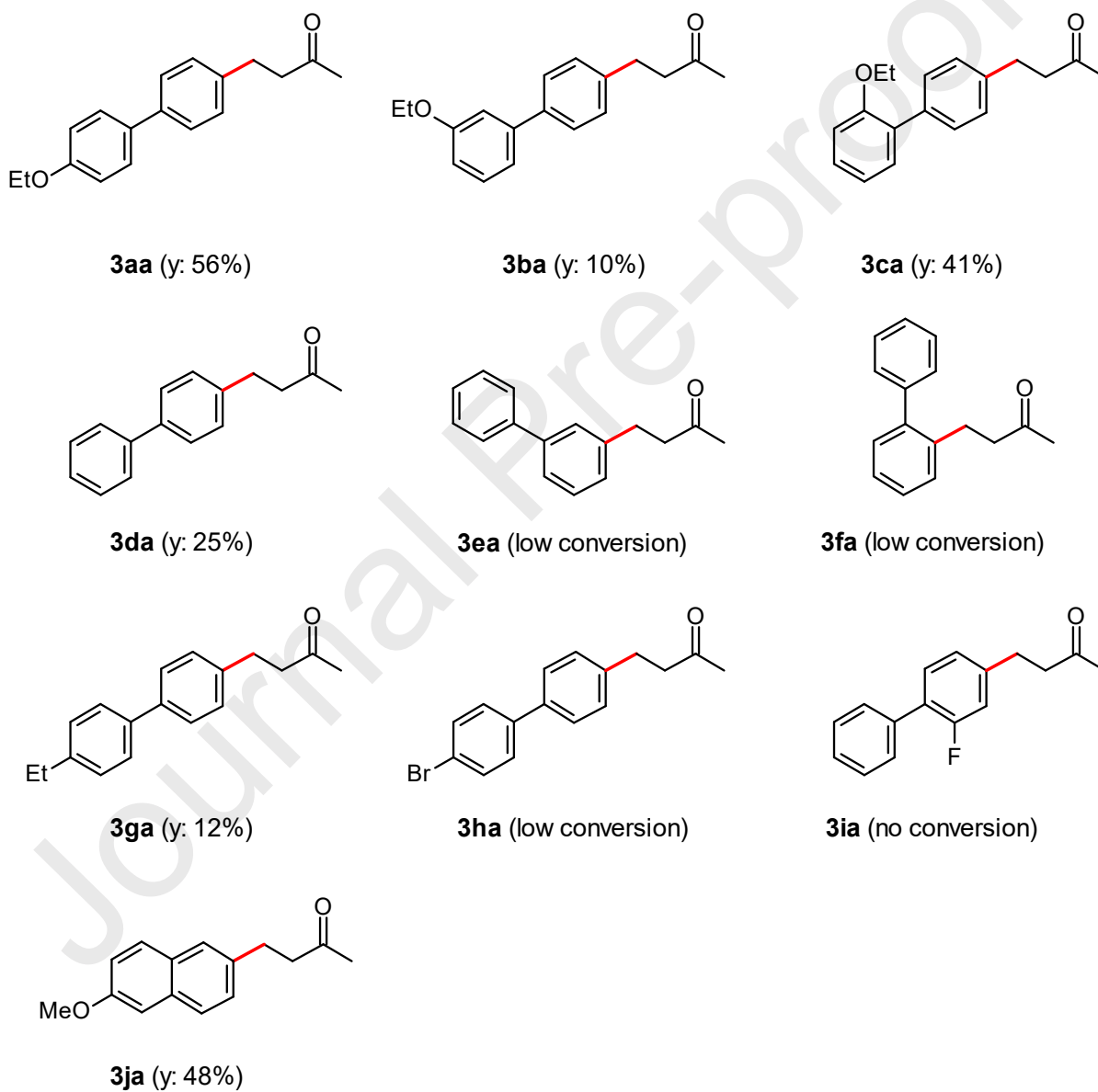
Conventional light switch on/off experiments were also performed to confirm that the reaction is not just a simple radical chain process (see Supporting Information Table 5S).

All these results are in agreement with Ley's proposed reaction mechanism (see Supporting Information Scheme 3S).^{4a}

The optimized reaction protocol was then systematically applied to different arylboronic acids (Scheme 1, **1a-j**), thus confirming the need for an electron-donating group onto the boronic counterpart in the 2' or 4' position for the reaction to proceed (Scheme 1, compare products **3(a-d)a**, **3ga** and **3ja** with **3ea**, **3fa**, **3ha** and **3ia**). Reactions with **1e**, **1f** and **1i** were also performed with either **PC1** and **PC4** but no conversion was detected.

Scheme 1. General reaction scheme for boronic acids

Products synthesized and their isolated yields:

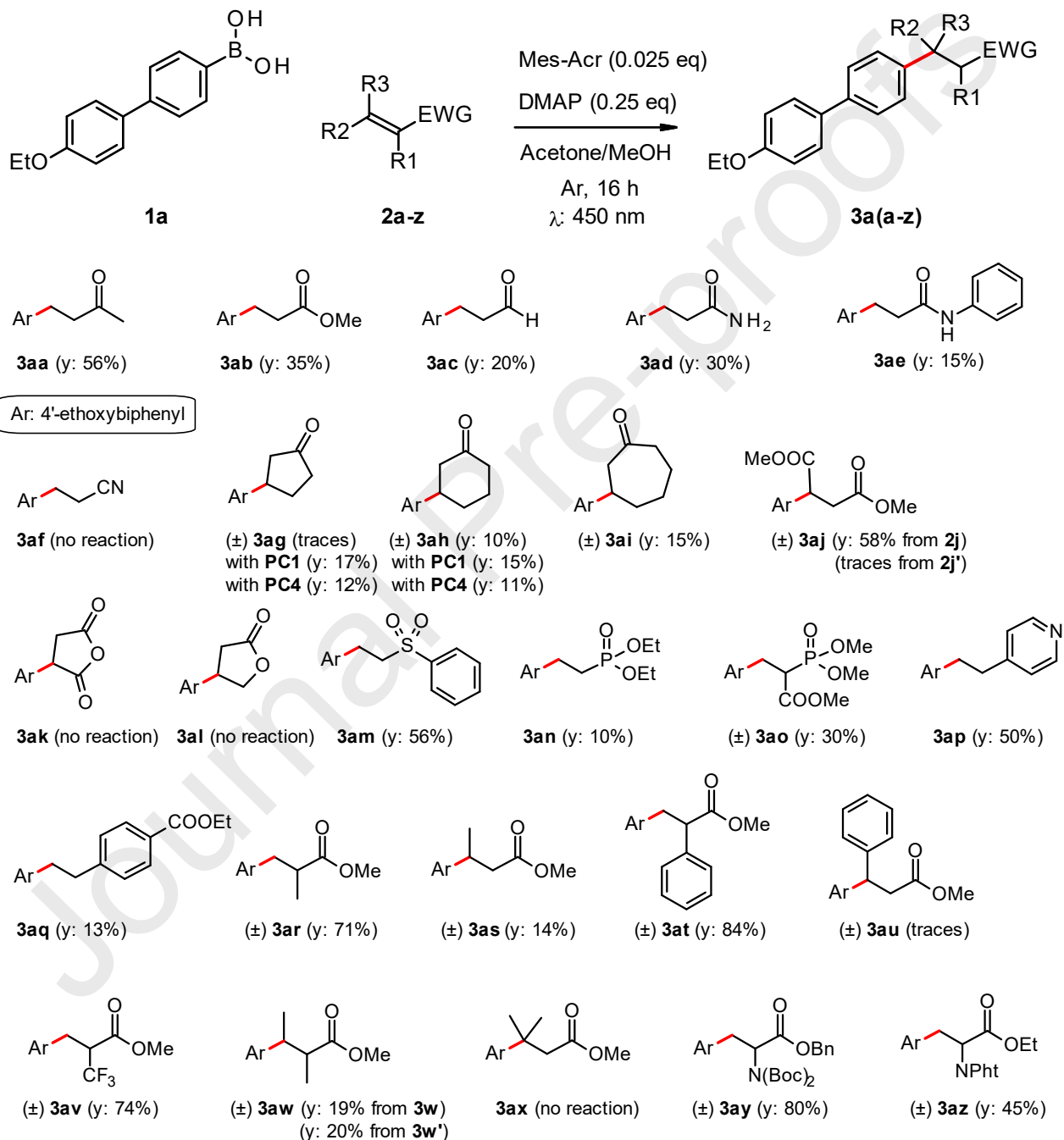


To expand the scope of the alkene counterpart, different electron-poor alkenes were examined (Scheme 2, **2a-z**). Reactions were performed with the prototype boronic acid **1a** by irradiating the mixture for 16 hours. A full conversion was observed with unsubstituted terminal alkenes (Scheme 2, products **3a(a-e)**), whose nature has an impact on the target/byproduct (**3a(a-d)/4a**) ratio, which ranges from 2 (MVK **2a**) to 0.4 (acrolein **2c**). On the other hand, cyclic olefins reacted either much less efficiently, as in the case of cyclohexanone (**2h**) and cycloheptanone (**2h**) or did not allow to isolate any appreciable amount of final product, as for cyclopentanone (**2g**) and γ -crotonolactone (**2l**). Unexpectedly, reaction with maleic anhydride (**2k**) only delivered compound **4a**. Addition of acrylonitrile (**2f**) to the reaction mixture gave immediately a turbid suspension probably due to the reactant polymerization.¹⁶ Differences were observed between dimethyl maleate (**2j**) and dimethyl fumarate (**2j'**) in the preparation of **3aj**, as the former gave the expected product in good yield (y: 58%, **3aj/4a** ratio: 1.4) while the reaction with the latter was much more sluggish, resulting in the preferential formation of the protodeboronation product (ratio **3aj/4a**, 0.8). Steric hindrance and stabilization of the intermediate alkyl radical (**D**, Supporting Information, Scheme 1S) influenced the outcome of the reaction: while 2-methyl acrylate (**2r**) reacted smoothly affording the expected product **3ar** with an excellent 71% yield, 3-methyl acrylate (**2s**) gave **3as** in only 14% yield and methyl 3-methylbut-2-enoate (**2x**) did not react at all. The combination of steric and electronic effects emerged even much more dramatically by comparing the reactivity of regioisomeric phenylacrylates. Thus, preparation of **3at** proved to be straightforward (84% yield, **3at/4a** ratio 4.2), while isomeric **3au** was barely detectable in the reaction mixture.

Some other electron-withdrawing containing alkenes were investigated: phenylvinylsulfone (**2m**) and 4-vinylpyridine (**2p**) (**3am**, y: 56%; **3ap**, y: 50%) performed nicely, while diethylvinylphosphonate (**2n**) and 4-styryl ethylacetate (**2q**) poorly reacted (**3an**, y: 10%; **3aq**, y: 13%). Furthermore, unsubstituted styrene gave only traces of the expected product. The introduction of a second electron-withdrawing group on the alkene moiety had a positive effect, since trimethylphosphonoacrylate (**2o**) gave **3ao** with 30% isolated yield, compared to the mono substituted analog diethylvinylphosphonate (**2n**), which produced **3an** in only 10% yield. Similarly, an improved yield was observed in the case of **3av** (74%) compared to **3ab** (35%). To note, similar yield and diastereomeric ratio were obtained from the methyl angelate (**2w**) and methyl tiglate (**2w'**), which delivered the same product (**3aw**) in 19% (dr: 0.62/1) and 20% (dr: 0.58/1) yield, respectively. It is worth noting that the reaction of cyclopentenone (**2g**) with **PC1**

and **PC4** gave the expected product, albeit in low yields (17% and 12%, respectively). On the other hand, attempt in improving the yield of **3ah** by using **PC1** or **PC4** did not substantially ameliorate the outcome of the reaction (15% with **PC1** and 11% with **PC4**).

Scheme 2. General reaction scheme for vinyl acceptors



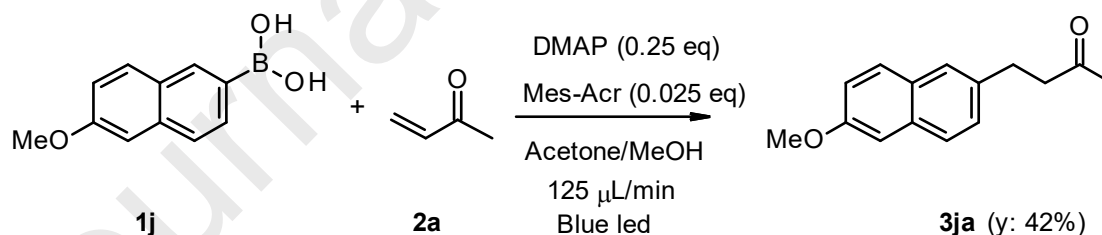
The bis-Boc- (**2y**) or the phtalimido- (**2z**) protected 2-aminoacrylate derivatives as unsaturated counterpart should potentially give access to racemic 3-aryl-aminoesters as reported by others.¹⁷ Thus, by applying the standard protocol (Scheme 2), some preliminary results proved the feasibility of the approach, allowing to isolate protected aminoesters **3ay** and **3az** in modest yield. Further investigations are needed to consolidate these observations.

To demonstrate the potential of this procedure, the reaction of (6-methoxy-2-naphtalenyl)boronic acid (**1j**) with **2a** generated the well-known nonsteroidal anti-inflammatory drug nabumetone (**3ja**)¹⁸ in a single step and in an acceptable yield. The reaction was also performed in a flow-system (see Supporting Information).

The use of flow chemistry technique to overcome the issues associated with the scaling-up of photoredox reactions in batch is well known¹⁹ and confirmed by us while increasing the reaction scale (from 0.2 to 0.5 mmoles of limiting reagent **1j**) in the synthesis of nabumetone **3ja**. In fact, while scaling-up the reaction in batch resulted in a significant drop (from 48 to 32%) of the isolated yield, this latter remained constant no matter the scale involved (42%) by performing the reaction in flow (Scheme 3).

Overall, the flexibility of this Giese-type reaction protocol would potentially be of interest for early-stage drug discovery programs.

Scheme 3. Synthesis of nabumetone



3. Conclusions

We investigated the engagement of arylboronic acids with different electron-poor olefins in a Giese-type reaction under photochemical conditions. The resulting protocol,²⁰ which capitalizes on the use of cheap metal-free photocatalysts and DMAP as Lewis base activator, was sufficiently robust and, despite the moderate isolated yields, quite wide-in-scope with an easy set-up, thus reinforcing previous data on the use of aryl boronic acids as radical sources in Giese-type reactions. The reaction protocol can be performed either in-batch and in-flow and was applied to the

preparation of a simple anti-inflammatory drug. The overall features of this transformation further corroborate the exquisite environmental benignity of photocatalysis, as prophetically anticipated by Ciamician more than a century ago.²¹

Acknowledgments

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- 20) General procedure: unless otherwise noted, the reactions were performed under Schlenk conditions using an over dried 5-mL microwave vial equipped with a rubber septum. The appropriate boronic acid (0.20 mmol, 1.0 equiv.), photocatalyst (0.025 equiv.), and base (0.25 equiv.) were added. Next, the vial was evacuated and purged with argon three times. The corresponding olefin (4.0 equiv.) was then added. Degassed solvent (2 mL) was added, and the reaction mixture irradiated for the indicated time and assayed by HPLC/MS. Next, the reaction was concentrated under reduced pressure and the crude mixture was purified by column chromatography (AcOEt/hexane).
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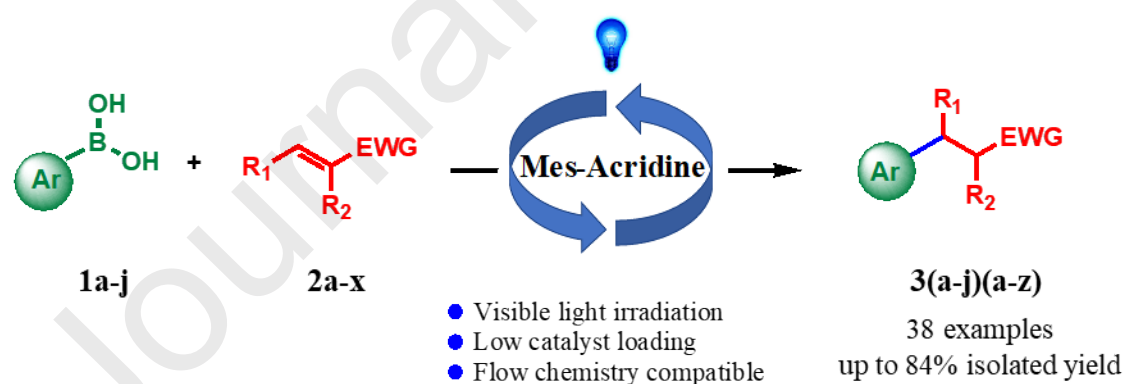
Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:



Graphical Abstract



ABSTRACT

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