



Photocatalysis and photochemistry in organic synthesis

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Negishi-coupling-enabled synthesis of α -heteroaryl- α -amino acid building blocks for DNA-encoded chemical library applications

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Full Research Paper

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Abstract

Amino acids are vital motifs in the domain of biochemistry, serving as the foundational unit for peptides and proteins, while also holding a crucial function in many biological processes. Due to their bifunctional character, they have been also used for combinatorial chemistry purposes, such as the preparation of DNA-encoded chemical libraries. We developed a practical synthesis for α -heteroaryl- α -amino acids starting from an array of small heteroaromatic halides. The reaction sequence utilizes a photochemically enhanced Negishi cross-coupling as a key step, followed by oximation and reduction. The prepared amino esters were validated for on-DNA reactivity via a reverse amidation–hydrolysis–reverse amidation protocol.

Introduction

DNA-encoded chemical library (DEL) technology is a powerful tool for hit identification [1,2]. DELs are chemically synthesized libraries in which every member is covalently attached to a unique DNA sequence serving as a molecular “barcode” [3]. The success of this technology ultimately relies on the quality and diversity of the libraries. DEL synthesis must employ DNA-compatible reactions; hence it operates under a limited set of conditions [4,5]. DELs are typically produced via split-and-pool combinatorial chemistry methods. Using bifunctional building blocks (BBs) can quickly increase the diversity of these molecular libraries [6]. Hence, DEL practitioners constantly seek access to novel building blocks [7].

Amino acids (AAs) are vital motifs in the domain of biochemistry, serving as the foundational unit for peptides and proteins, while also holding a crucial function in many biological processes [8]. Non-canonical amino acids (NCAs) are widely used in medicinal chemistry [9]. Not surprisingly, they also find broad use as bifunctional building blocks (BBs) for DELs. In an early example, an 800-million-members DEL utilized Fmoc-amino acids as primary diversity elements [10].

The pursuit of achieving the efficient synthesis of α -amino acids has been an ongoing challenge since 1850, marked by the initial report of the Strecker condensation [11]. The Strecker synthesis

and the related Bucherer–Bergs hydantoin formation remains the most employed approach for producing this family of substrates [12]. Despite its effectiveness, this approach requires hazardous cyanides and harsh conditions for the subsequent hydrolysis of the nitrile or the hydantoin. Additionally, it carries significant limitations in its scope, reducing its overall applicability.

A different approach for the synthesis of α -amino acids involves the formation of dehydroamino acids and subsequent hydrogenation [13,14]. More recently, there have been reports of techniques that utilize phase transfer catalysts (PTCs) to alkylate glycine derivatives [15,16]. A range of less widely applicable strategies have been developed as well [17–22].

The above-mentioned methods focus on the synthesis of α -alkyl-amino acids. Moving to α -aryl-amino acids, the Clayden group published an excellent asymmetric α -arylation method to access quaternary amino acids with high enantiomeric purity [23]. The synthesis of formally glycine-derived tertiary α -aryl-amino acids is much less developed. The most common strategy for obtaining these substrates is by lithiation of an aromatic ring followed by coupling with a glycine derivative (Scheme 1a). For example, this approach was applied to the synthesis of *N*-substituted pyrazoles and poly-substituted isothiazoles [24,25]. Glycine derivatives can be reacted with indoles using copper catalysis or metallophotoredox catalysis [26]. Le et al. reported the use of the same approach for imidazo[1,2-

a]pyridines [27,28]. However, the selectivity of these photoredox reactions is driven by the structural properties of the heteroaromatic ring. During the preparation of this article, the Meggers group published an outstanding enantioselective iron-catalyzed α -amination pathway (Scheme 1b) [29]. The method is widely applicable to a broad range of substrates, however, it utilizes a catalyst that is not commercially available and small heteroaromatic rings are underrepresented in the scope.

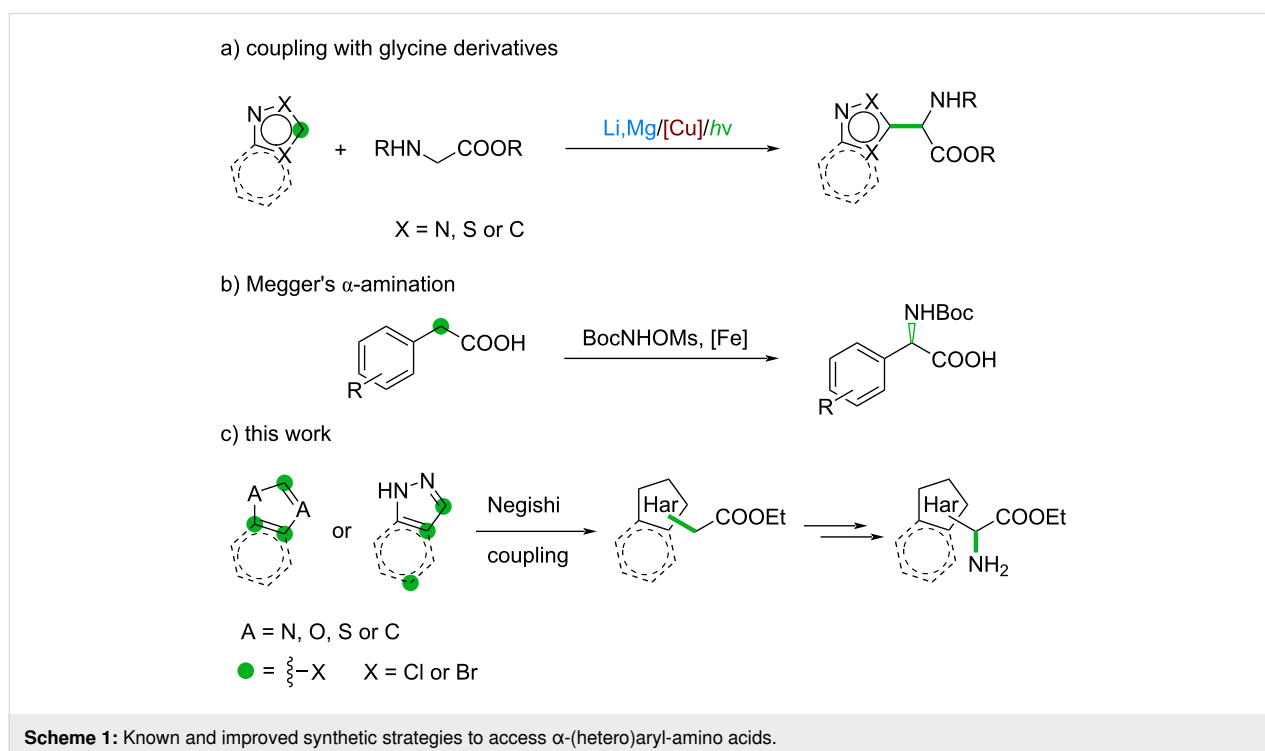
Recognizing the importance of small heteroaromatic rings and the amino acid motif in medicinal chemistry [30–33], and aiming to expand our in-house DEL BB collection, we sought to develop a synthetic route capable of providing a broad range of α -heteroaryl- α -amino acids in a cost-effective manner (Scheme 1c).

Herein, we describe the synthesis and on-DNA validation of non-canonical α -heteroaryl- α -amino acids. We envisioned that α -heteroaryl acetates accessed through Negishi coupling can be used as key intermediates towards NCAs (Scheme 1c). Indeed, oximation of these motifs followed by reduction gave access to the desired NCAs.

Results and Discussion

Negishi cross-coupling step

The Negishi reaction provides convenient access to compounds featuring C(sp²)–C(sp³) bonds. However, the general view is



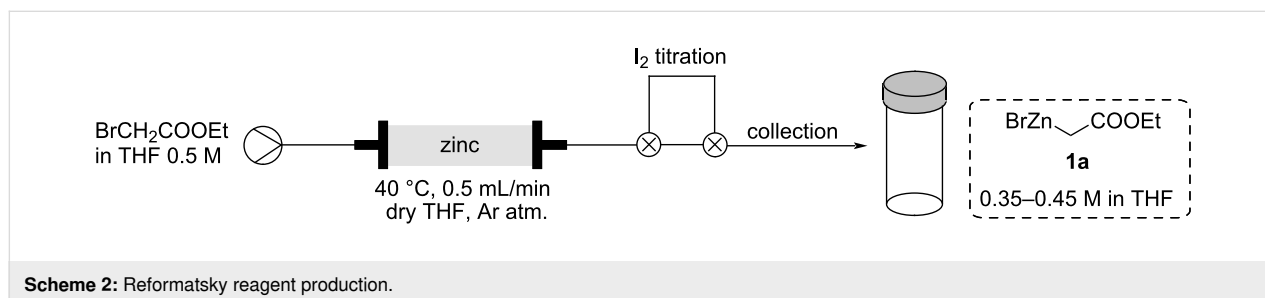
that this transformation is less reliable than its orthogonal counterpart, the Suzuki reaction. Recent years have seen significant developments in Negishi reaction methodologies [34–39]. In particular, Alcazar et al. developed continuous flow protocols for both the generation of alkylzinc halides and for the subsequent Negishi cross-coupling reaction [40–44]. We successfully adapted Alcazar's protocols for the synthesis of otherwise challenging heteroaryl–alkyl connections (see Table S1 in Supporting Information File 1). We decided to explore the potential of this methodology for the formation of α -heteroarylacetates. In particular, we were curious to see whether this methodology translates well for five-membered heteroarene substrates (e.g., thiazoles, pyrazoles, imidazoles) which are usually underrepresented in the peer-reviewed literature in comparison to phenyl groups or their six-membered counterparts (e.g., pyridines, pyrimidines) [42]. Furthermore, the increasing importance of small heteroaromatic rings containing nitrogen, sulfur and/or oxygen in medicinal chemistry is well depicted by the list of recently approved drugs by the FDA [31]. Fezolinetant (an NK3 receptor antagonist) and quizartinib (FLT3 inhibitor) are just a couple of examples among the drugs reaching the market in the last year.

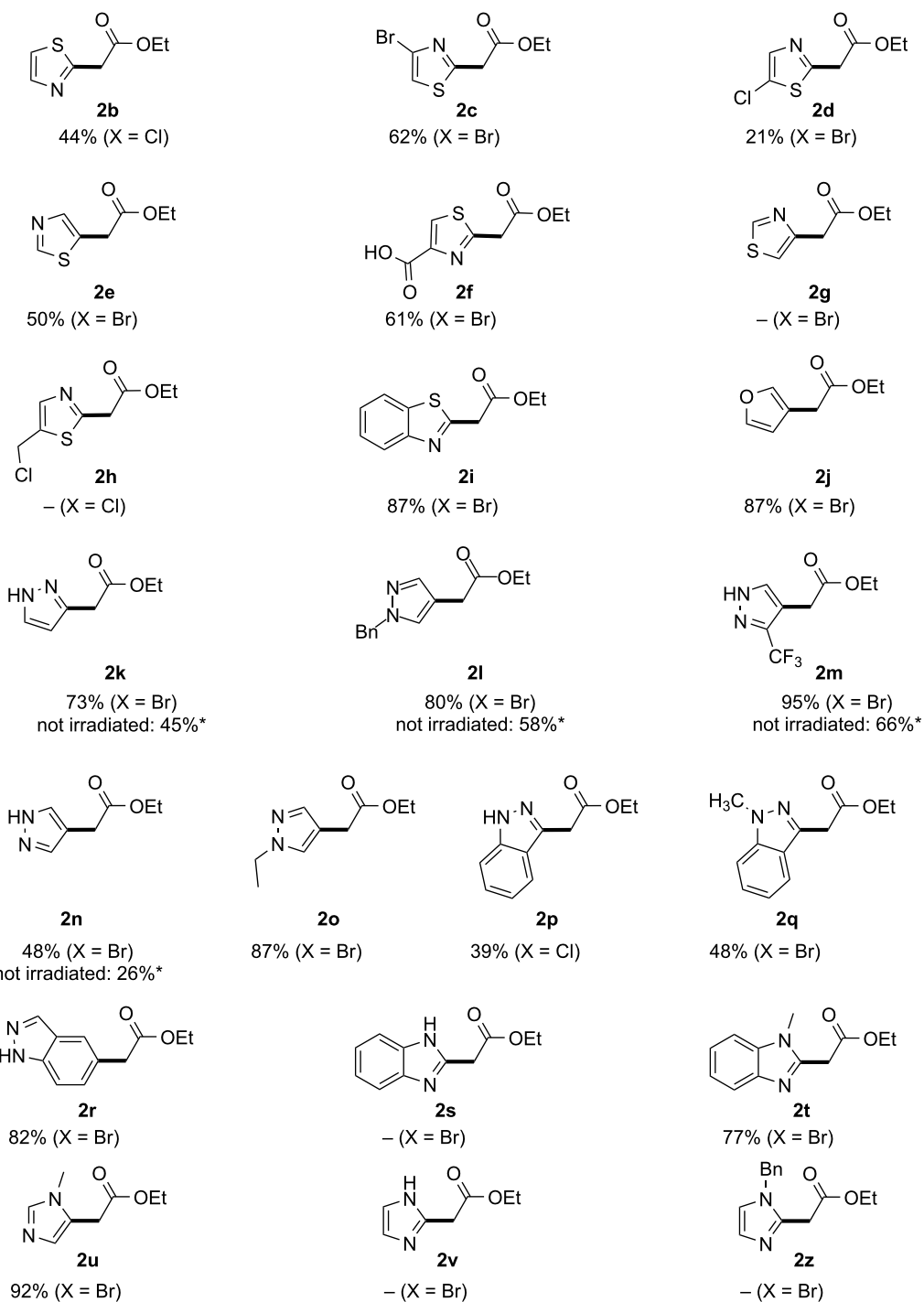
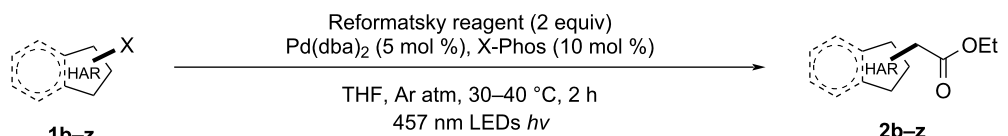
As shown in Scheme 2, ethyl (bromozinc)acetate (**1a**) was synthesized in flow by pumping a solution of ethyl 2-bromoacetate through a pre-activated zinc column (see page 11 in Supporting Information File 1) [44]. The Reformatsky reagent could be obtained in yields varying from 70 to 90% depending on the activation state of the column. The yield of the reaction was determined by titration with iodine (see page 11 Supporting Information File 1), affording final concentrations between 0.35 to 0.45 M in THF. The solution can be stored in the fridge under argon for one week before being used in the Negishi reaction. With concentrations above 0.4 M we observed crystallization of ethyl (bromozinc)acetate at the bottom of the vial after a few hours of storage in the fridge. The solid can be easily re-dissolved by gentle heating, and without affecting the product concentration and integrity.

After a brief screening, Pd(dba)₂ and X-Phos (in a 1:2 ratio) were selected as the catalyst system for the Negishi reaction

(Supporting Information File 1). Preliminary experiments were carried out with and without blue light irradiation in the PhotoCube™ photoreactor [45]. These experiments revealed that while the conversion of imidazoles and pyrazoles benefits from irradiation, thiazoles seem to be largely unaffected by the presence of light (see pages 5 and 6 in Supporting Information File 1). In the case of indazoles, increased reaction rates were observed in the presence of light, but the overall yield was the same for the dark and irradiated experiments. Although these reactions are typically complete within 4 h in the dark, irradiation with blue light halves the reaction time for many compounds. Overall, these observations are in line with those of Alcazar et al. [43]. In their work, the authors demonstrated the formation of a complex between palladium and the organozinc reagent which is absorbing in the blue region. This complex then accelerates the oxidative addition of the aryl halide to the metal, which is usually the rate-limiting step for palladium-catalyzed cross-couplings. Based on these results we decided to perform all Negishi reactions under blue light irradiation.

With the optimized conditions in hand, we proceeded with the investigation of the heteroaryl halide scope in batch (Scheme 3). Thiazoles proved to be challenging substrates typically affording the desired products in moderate yields (**2b–h**). While 2-chlorothiazole led to the production of **2b** in 44% yield, 2-bromo-5-chlorothiazole only afforded 21% yield (**2d**). Grati-fyingly, the reaction selectively proceeded in position 2 of the ring. Position 4 seems to be inert to the Negishi coupling conditions as illustrated by substrates **2c** and **2g**. Somewhat surprisingly, LCMS analysis indicated that **1g** did not go through oxidative addition and remained unreacted. Formation of **2h** did not occur, however, we observed the formation of unidentified side products. Interestingly, the presence of a free carboxylic group is well tolerated (**2f**). Benzothiazole **1i** proved to be an excellent substrate for this reaction, leading to the desired acetate **2i** in high yield. A similar result was obtained for the furanyl derivative **2j**. Pyrazoles were the only substrate class which clearly benefited from light irradiation (**2k–o**), displaying not just a shorter reaction time but also higher yields. Even unprotected pyrazoles (**2k**, **2m**, **2n**) performed well, showing that *N*-protection is not mandatory for this transformation.





Scheme 3: Scope of ethyl heteroarylacetates. Isolated yields are given. *Dark reactions were carried out for 4 h.

3-Bromo- and 3-chloroindazoles offered moderate yields (39% and 48% for **2p** and **2q**, respectively), while 5-substituted **2r** was isolated with 82% yield. In contrast to pyrazoles and indazoles, benzimidazoles and imidazoles required the protection of the aromatic NH group (**2s** vs **2t**; **2v** vs **2u**). Reactions with unprotected imidazoles **1s** and **1v** led to immediate formation of a precipitate upon addition of the Reformatsky reagent. Surprisingly, **1z** did not afford the expected product (**2z**).

The synthesis of the Reformatsky reagent can be combined with the Negishi cross-coupling step in a continuous flow manner [41–43]. Continuous flow chemistry offers superior control over reaction parameters compared to traditional batch methods. This approach leads to reproducible reactions, improved safety features, and it can facilitate high-throughput screening and rapid optimization [46,47]. Homogenous heating and mixing in flow reactors can lead to higher reaction rates and yields. In terms of photochemistry, continuous flow setups provide enhanced light irradiation as well [48,49]. These advantages make flow chemistry a powerful tool for chemical synthesis and industrial applications [50,51].

To assess the advantage of moving from batch to flow, the production of compounds **2b** and **2i** was carried out with the telescoped approach. Despite the difference in the yield being minimal, the rate of the transformation showed a significant improvement under continuous flow conditions, leading to reaction completion within 30 minutes (Scheme 4).

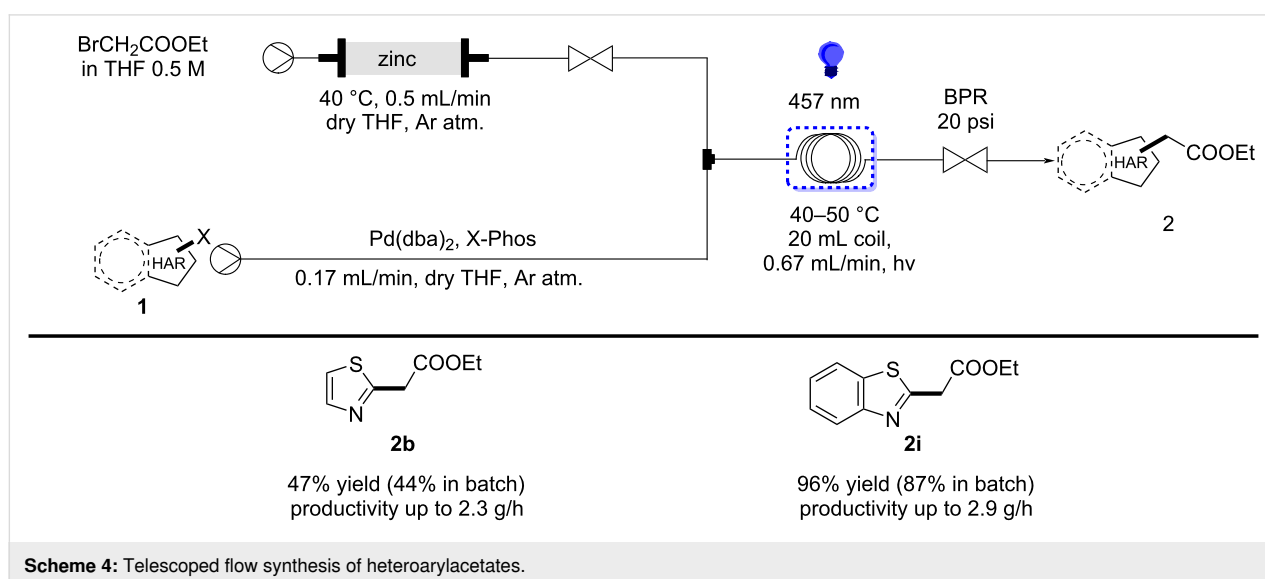
Oxime formation

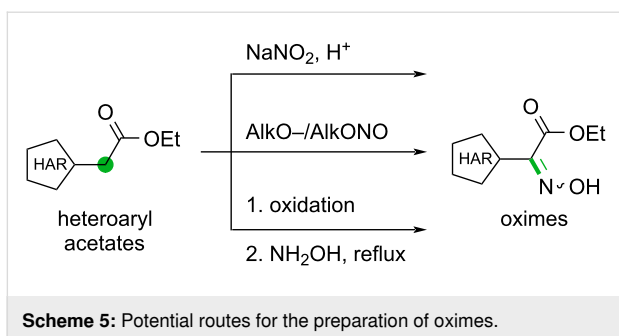
Once the ethyl heteroarylacetates scope was completed we turned our attention to the incorporation of the amino group. There are precedents for α -aminations, but we were not able to

find a method suitable for our needs [52,53]. Benzylic bromination followed by nucleophilic substitution offers a general approach for the introduction of the nitrogen atom [54–56]. Consequently, the continuous flow Wohl–Ziegler bromination of **2b** was attempted [57]. Even though we could observe excellent LCMS-conversion for the mono-brominated compound, we encountered several problems related to the stability of the product (see Supporting Information File 1).

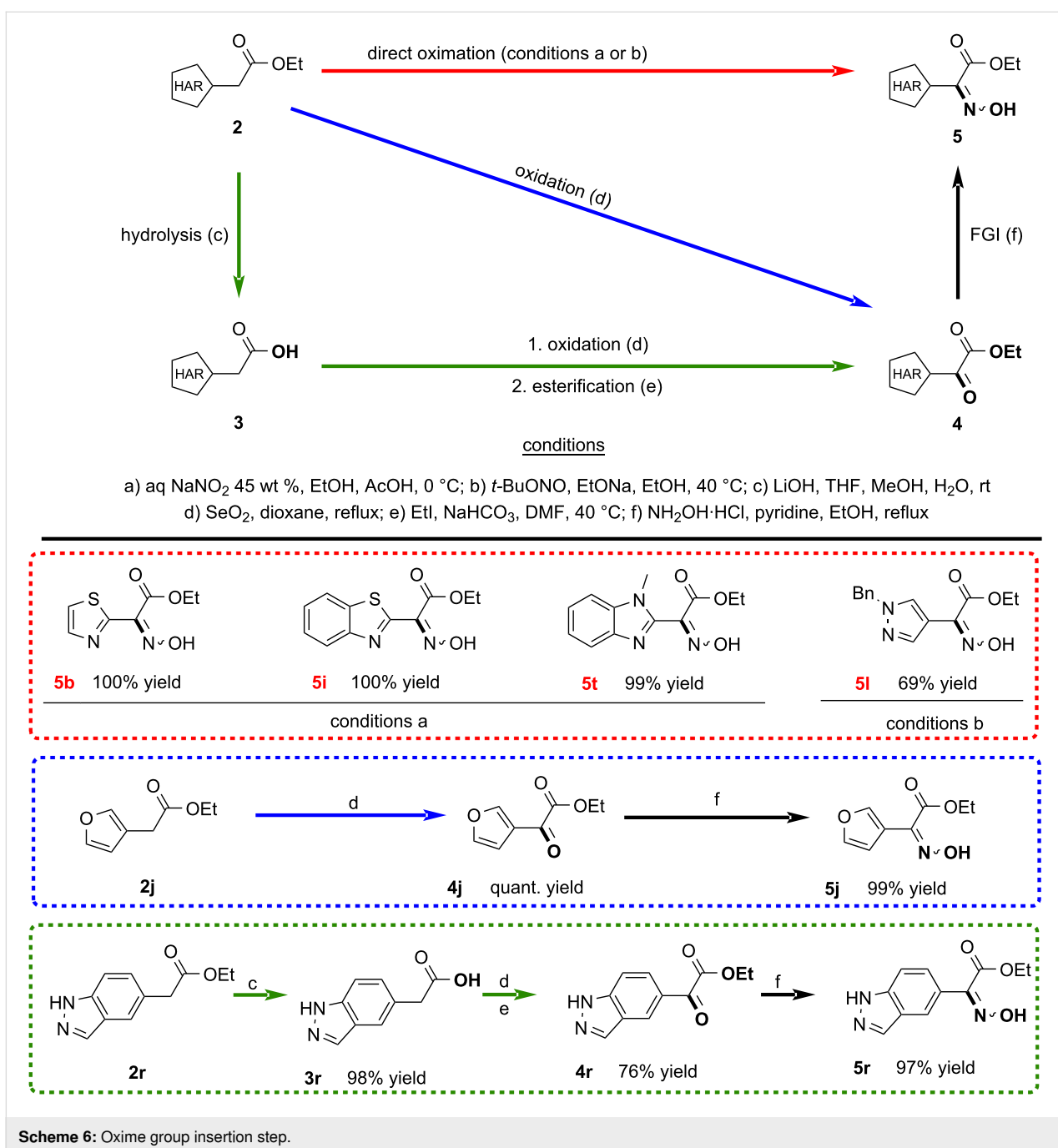
To circumvent these issues, we came across the possibility of inserting an oximino group into the benzylic position which can then be converted into an amino group by reduction. We reasoned that increasing the sp^2 fraction and the rigidity of the whole structure will lead to increased stability of these derivatives. The first exploratory attempts demonstrated the easy preparation and the high bench stability of the oxime derivatives, therefore we opted to proceed using this route. In this study, we explored three distinct approaches commonly employed for the introduction of the oximino group into a molecule. The first approach is based on the generation of the nitrosonium ion from sodium nitrite under acidic conditions (Scheme 5, top) [58,59]. Additionally, another very common method involves the employment of a strong base, typically sodium ethoxide or methoxide, in combination with an alkyl nitrite to promote the incorporation of the oximino group (Scheme 5, middle) [60,61]. Furthermore, a widely adopted strategy involves the conversion of a carbonyl group to an oxime through condensation with hydroxylamine (Scheme 5, bottom) [62–64].

In order to develop a synthetic approach applicable to several different substrates, we decided to screen the three methods on one example from each type of heteroaryl halides. According to





our experimental results, thiazole **2b**, benzothiazole **2i** and benzimidazole **2t** react very well with sodium nitrite in an acidic environment (Scheme 6, red section). Among the various subclasses of compounds, pyrazole **2l** exhibited a high reactivity using *t*-BuONO and EtONa in ethanol (Scheme 6, red section). On the other hand, no reaction was observed with indazoles and furans using the first two conditions, requiring the formation of the ketoesters **4j** and **4r** first, followed by the functional group interconversion (FGI) with $\text{NH}_2\text{OH}\cdot\text{HCl}$ (Scheme 6, blue and green sections).



The Riley oxidation of the furanyl derivative **2j** proceeded smoothly yielding **4j** in quantitative yield. However, obtaining compound **4r** presented some challenges due to the resistance of ester **2r** towards conventional oxidation methods (see Table S5 in Supporting Information File 1). Consequently, a multi-step process involving ester hydrolysis and subsequent re-esterification was necessary to achieve the desired ketoester.

Reduction of the oximes

Oximes are commonly reduced to the corresponding amines using either palladium on activated carbon and hydrogen gas [65–68], or with zinc and a Brønsted acid as source of hydrogen [68,69]. Both methods were tested and after a brief optimization process, zinc dust and HCl in a mixture of EtOH/dioxane proved to be the best conditions in order to maximize the yield and limit the amino ester instability issues (see Table S6 in Supporting Information File 1). By slightly adjusting the reaction time and the temperature, all oxime derivatives underwent reduction to yield the corresponding amine. The amino esters were effectively safeguarded against degradation through the immediate formation of the HCl salt or by Boc-protection. This procedure allowed us to obtain all the protected amino acids in a yield that varies from 56 to 74% (Scheme 7).

Gram scale experiment

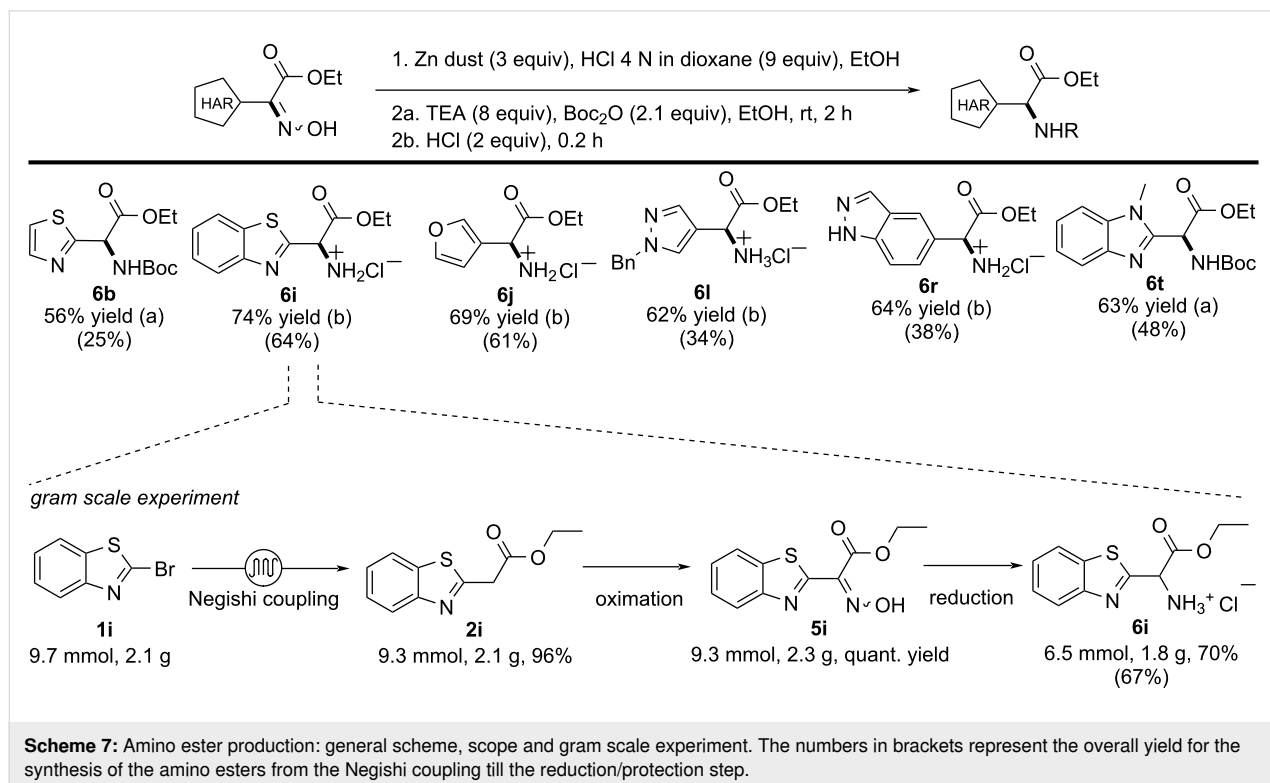
With the optimized synthetic route, we were able to reach the final targets in good to excellent overall yields (from 25% to

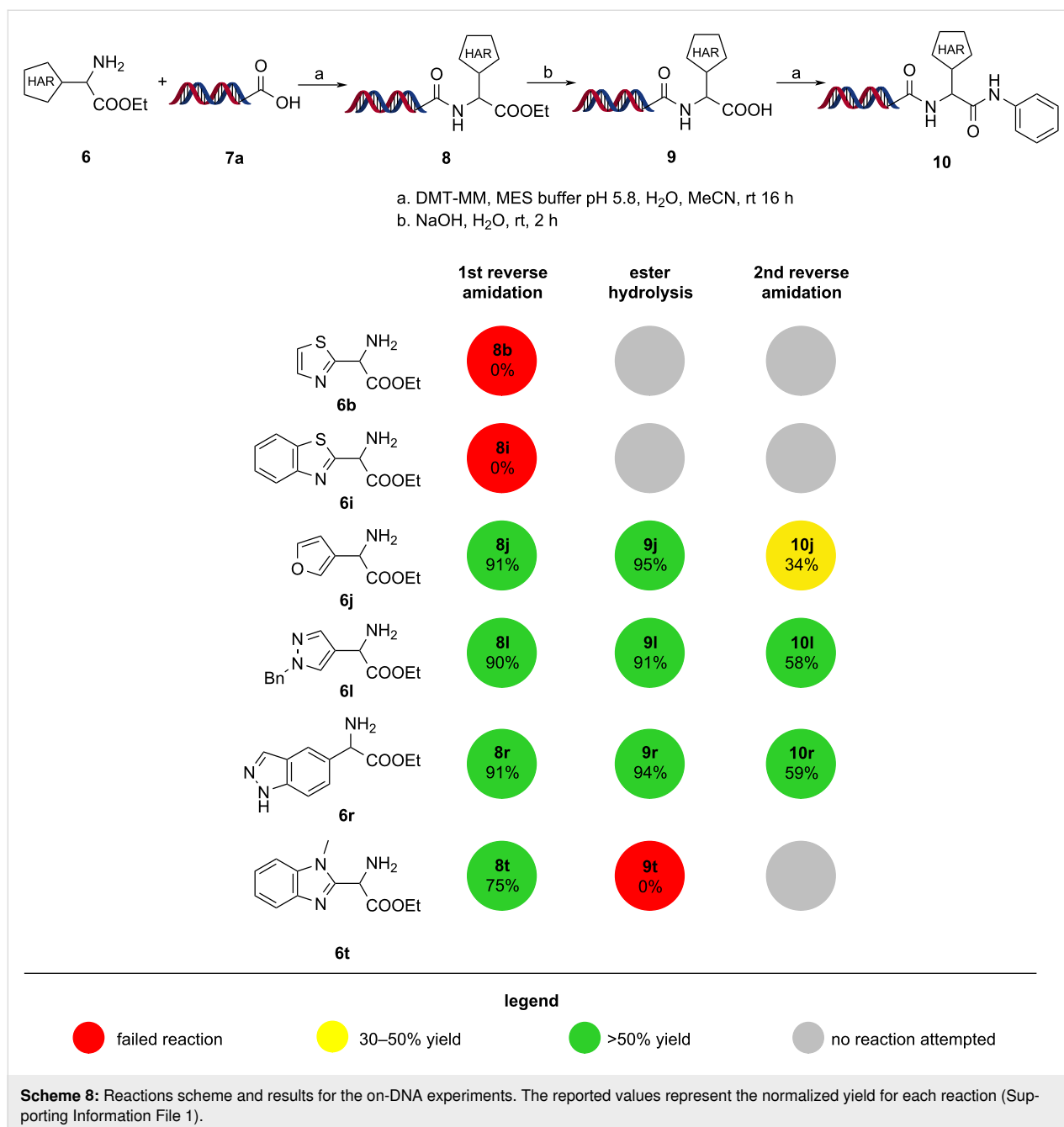
64%, see Scheme 7). To test the robustness of our approach, the synthesis of compound **6i** was carried out on gram scale starting from 2.1 g of 2-bromobenzothiazole (**1i**). The gram scale production showed comparable results to those obtained in the small-scale procedure, leading to the formation of 1.8 g (67% overall yield) of the final product **6i** (Scheme 7, bottom).

On-DNA validation

Due to the large complexity of DELs, there is only limited opportunity to track the efficiency of individual reactions during library synthesis. Therefore, BBs need to pass validation before being used in library synthesis settings. For these bifunctional amino esters, we performed a three-step validation where they were first attached to carboxylic acid functionalized DNA headpiece **7a** (first reverse amidation). Next, the ester was hydrolyzed to obtain acid **9**, and finally, a second reverse amidation with aniline afforded **10**.

Both the reverse amidation and the ester hydrolysis were performed following literature protocols [70,71]. In these experiments, compounds **6b** and **6i** proved to be unstable under on-DNA conditions as they failed to form esters **8b** and **8i**. Closely related structures, such as α -aminobenzothiazol-2-ylacetic acid is known to undergo decarboxylation at room temperature [72]. Compound **8t** underwent decarboxylation during the hydrolysis step. Compounds **6j**, **6l** and **6r** passed validation in moderate to good yields (Scheme 8).





Conclusion

In conclusion, by taking advantage of the recent advances in the Negishi cross-coupling reaction we obtained a broad range of heteroarylacetates starting from heteroaromatic halides. One compound from each subclass of medicinal chemistry-relevant substrates (thiazoles, pyrazoles, etc.) was used for the preparation of α -heteroaryl- α -amino esters via the insertion of an oxime group and subsequent reduction step. The procedure relies solely on readily available and widely used reagents, rendering our approach well-suited for both industrial and academic settings. The synthesized amino esters were engaged in a three-

step on-DNA validation protocol, demonstrating their possible application for DEL production.

Supporting Information

Supporting Information File 1

Experimental part and NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-168-S1.pdf>]

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

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Development of a flow photochemical process for a π -Lewis acidic metal-catalyzed cyclization/radical addition sequence: in situ-generated 2-benzopyrylium as photoredox catalyst and reactive intermediate

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Abstract

A flow photochemical reaction system for a π -Lewis acidic metal-catalyzed cyclization/radical addition sequence was developed, which utilizes in situ-generated 2-benzopyrylium intermediates as the photoredox catalyst and electrophilic substrates. The key 2-benzopyrylium intermediates were generated in the flow reaction system through the intramolecular cyclization of *ortho*-carbon-yl alkynylbenzene derivatives by the π -Lewis acidic metal catalyst AgNTf_2 and the subsequent proto-demetalation with trifluoroacetic acid. The 2-benzopyrylium intermediates underwent further photoreactions with benzyltrimethylsilane derivatives as the donor molecule in the flow photoreactor to provide 1*H*-isochromene derivatives in higher yields in most cases than the batch reaction system.

Introduction

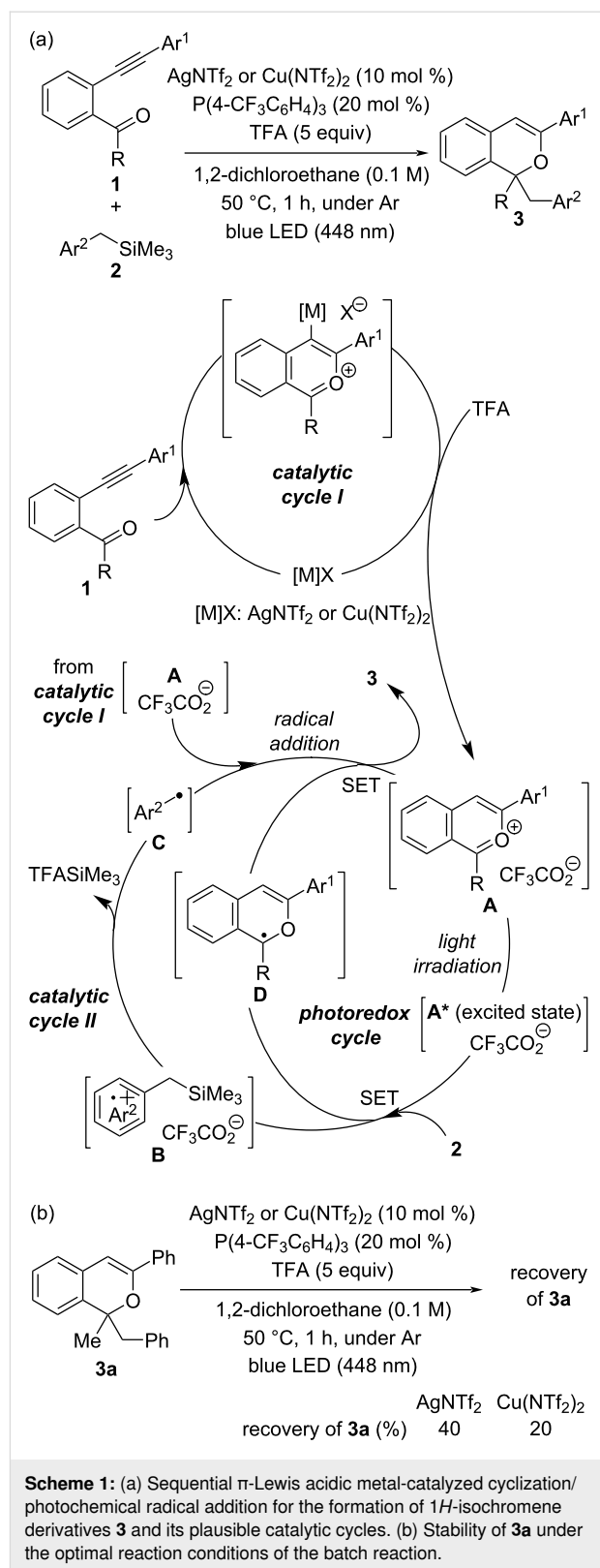
Flow chemistry has been actively studied in recent years as a method to run a reaction continuously using a flow path or tube, rather than in a flask [1-16]. This method has attracted much attention because, unlike a batch reaction system, it allows for rapid generation of unstable chemical species by controlling parameters such as flow velocity and mixing properties, and in

some cases makes it possible to achieve reactions that are difficult to perform using batch chemistry [17-21]. In general, efficient two-phase mixing and heat transfer, as well as ease of scale-up, are the advantages of using a flow system. In addition, reproducibility in a liquid-liquid flow system is improved because the flow velocity and temperature can be precisely con-

trolled by using a syringe pump and a temperature control unit, respectively. Moreover, as the reaction mixture continues to flow and the reaction can be quenched immediately when necessary, the decomposition of an unstable product under the reaction conditions can be avoided [22–25]. Furthermore, when a photoreaction is performed in a flow system, there is an advantage that the light irradiation efficiency [26–29] is increased. Thus, the flow photochemical process is crucial and beneficial to product formation.

Recently, we reported a sequential transformation consisting of a π -Lewis acidic metal-catalyzed cyclization [30–45] and subsequent photochemical radical addition [46–54], which affords 1*H*-isochromene derivatives **3** through three catalytic cycles (Scheme 1a) [55]: catalytic cycles I and II and a photoredox cycle of the photocatalyst [56,57] (see Supporting Information File 1 for the overall catalytic cycles). In catalytic cycle I, the key cationic components, 2-benzopyrylium intermediates **A**, are generated in situ by the activation of the alkyne moiety of *ortho*-carbonyl alkynylbenzene derivatives **1** in the presence of the π -Lewis acidic metal catalyst [M]X [AgNTf₂ or Cu(NTf₂)₂] and subsequent intramolecular cyclization followed by protodemetalation with trifluoroacetic acid (TFA). In catalytic cycle II, photoexcitation of the generated 2-benzopyrylium intermediates **A** under light irradiation facilitates single-electron transfer (SET) from benzyltrimethylsilane derivatives **2** as the donor molecule, initiating further radical reactions through the formation of radical cations **B**. Nucleophilic arylmethyl radicals **C**, which are generated from radical cations **B** by desilylation, undergo an addition reaction with 2-benzopyrylium intermediates **A**, giving rise to the corresponding radical cation. Catalytic cycle II is completed through a SET from **D**, a reduced form of the photoredox catalyst 2-benzopyrylium intermediates **A**, to the generated radical cation, affording 1*H*-isochromene derivatives **3**. The photoredox cycle is also completed with the regeneration of cations **A** through SET from **D**.

The most distinctive feature of this sequential transformation is that the in situ-generated 2-benzopyrylium intermediates **A** are used not only as an electrophile but also as a photoredox catalyst. However, as this reaction is carried out under relatively harsh conditions (i.e., light irradiation, use of an excess amount of TFA), the stability of products **3** was a concern. Indeed, subjecting product **3a** to the optimal reaction conditions with either AgNTf₂ or Cu(NTf₂)₂ resulted in the significant degradation of **3a**, although the degradation of **3a** was partially suppressed when AgNTf₂ was used (Scheme 1b). Accordingly, we envisioned that the characteristics of the flow photochemical process, i.e., efficient light irradiation and immediate separation of the formed product from the reaction system, would be suitable for this sequential reaction. Here, we report the results



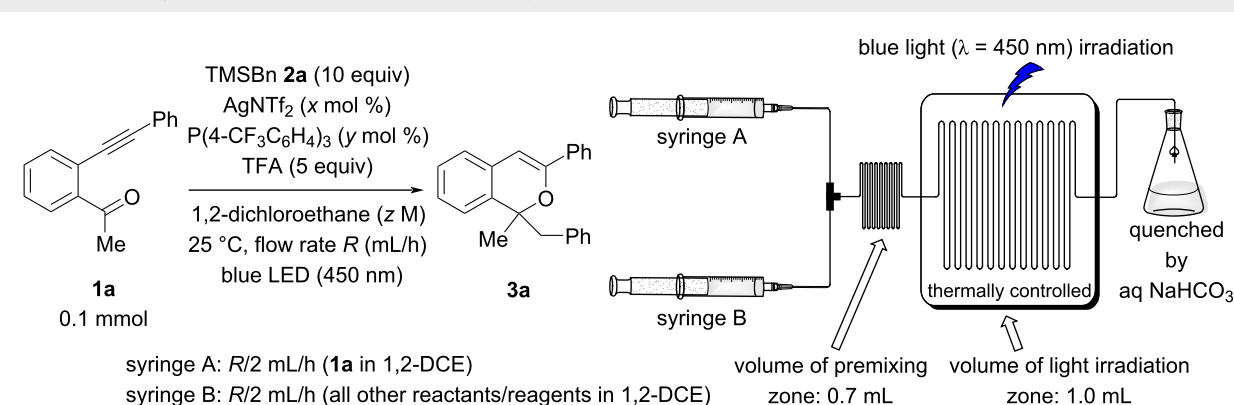
of our investigation on the use of a flow photochemical reaction system to improve the yield of the present sequential transformation.

Results and Discussion

At the outset of our studies to optimize the flow reaction conditions, we employed AgNTf_2 as the π -Lewis acidic metal catalyst because of its high solubility in 1,2-dichloroethane (1,2-DCE) [58] and ability to partially suppress the degradation of the product formed (Scheme 1b). When designing a flow reaction system for the present sequential transformation, we considered the fact that the transformation involves three catalytic cycles. In particular, given that catalytic cycle I (see Scheme 1a) generates, e.g., key cationic components, 2-benzopyrylium intermediates **A** without light irradiation, it is necessary to ensure that the reaction time of catalytic cycle I is not affected by the timescale of the flow reaction. Therefore, we adopted a dual syringe system in which two solutions are mixed before being introduced into the photoreactor (volume: 1.0 mL) (Table 1, top right). After several trials, we decided to fill syringe A with *o*-alkynylacetophenone **1a** and syringe B with AgNTf_2 , $\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$, benzyltrimethylsilane (**2a**, TMSBn), and TFA (see Supporting Information File 1 for details). At this

time, the volumes of the solutions placed in the two syringes were adjusted to be approximately the same. The initial conditions of the flow reaction were based on those of the batch reaction [0.1 mmol of **1a**, 10 μmol (10 mol %) of AgNTf_2 , 20 μmol (20 mol %) of $\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$, 1.0 mmol (10 equiv) of **2a**, and 0.5 mmol (5 equiv) of TFA under light irradiation (blue LED: $\lambda_{\text{max}} = 448 \text{ nm}$) at 50 °C for 1 h in 1 mL (total volume) of 1,2-DCE] [55] with a flow rate of 3 mL/h (light irradiation time: 20 min in the flow reaction, 1 h in the batch reaction). As shown in Table 1, product **3a** was obtained in moderate yield (entry 1: 42%, cf. batch reaction: 76%). Lowering the reaction temperature to 25 °C reduced the yield (Table 1, entry 2: 35%), but decreasing the amount of the phosphine ligand from 20 mol % to 5 mol % markedly improved the yield (Table 1, entry 3: 53%). Even when the flow rate was increased from 3 mL/h to 24 mL/h (light irradiation time was shortened from 20 min to 2.5 min), the yield of **3a** was maintained (Table 1, entry 4: 53%). Under these conditions, no improvement in yield was observed when the premixing zone (0.7 mL) was provided

Table 1: Screening of reaction conditions in the flow reaction system^a.



Entry	AgNTf_2 ($x \text{ mol } \%$)	$\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$ ($y \text{ mol } \%$)	Conc. of 1a ($z \text{ M}$)	Flow rate (R mL/h)	Premixing zone (mL)	Yield of 3a (%) ^b	Recovery of 1a (%) ^b
1 ^c	10	20	0.1	3	none	42	0
2	10	20	0.1	3	none	35	22
3	10	5	0.1	3	none	53	1
4	10	5	0.1	24	none	53	0
5	10	5	0.1	24	0.7	52	9
6	5	2.5	0.1	24	none	26	14
7	5	2.5	0.1	24	0.7	49	0
8	5	2.5	0.05	24	0.7	61	0
9	2	1	0.05	24	0.7	28	28
10 ^d	5	2.5	0.05	24	0.7	77	0

^aUnless otherwise noted, all reactions were carried out in a flow photochemical reactor (volume: 1.0 mL, $\lambda_{\text{max}} = 450 \text{ nm}$) using a dual syringe system, as shown in the table scheme. Syringe A: 0.1 mmol of **1a** in 1,2-DCE (0.55 mL). Syringe B: AgNTf_2 , $\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$, TMSBn (**2a**), and TFA in 1,2-DCE (0.45 mL); ^bYield was determined by NMR analysis using 1,1,2,2-tetrabromoethane as an internal standard; ^cAt 50 °C. ^dReaction was conducted on a 0.5 mmol scale. Syringe A: 0.5 mmol of **1a** in 1,2-DCE (5.4 mL). Syringe B: 25 μmol (5 mol %) of AgNTf_2 , 12.5 μmol (2.5 mol %) of $\text{P}(4\text{-CF}_3\text{C}_6\text{H}_4)_3$, 5 mmol (10 equiv) of TMSBn (**2a**), and 2.5 mmol (5 equiv) of TFA in 1,2-DCE (4.6 mL).

(Table 1, entry 5: 52%); however, the effect of adding the premixing zone was remarkable when the amount of AgNTf₂ was reduced by half (5 mol %; Table 1, entry 6 vs entry 7: 26% vs 49%). These results suggest that the generation of 2-benzopyrylium intermediates **A**, (i.e., catalytic cycle I) requires a certain reaction time (at this flow rate: ca. 2 min). Moreover, the yield of **3a** was improved when the concentration of **1a** was lowered from 0.1 M to 0.05 M (Table 1, entry 8: 61%). Meanwhile, further reducing the catalyst loading from 5 mol % to 2 mol % resulted in a significant decrease in yield (Table 1, entry 9: 28%). When the reaction was scaled up from 0.1 mmol to 0.5 mmol of **1a** in consideration of the dead volume of the flow reactor, the product **3a** was obtained in markedly improved yield (Table 1, entry 10: 77%) [59] which was comparable to that of the batch reaction (76%). Notably, however, the present flow reaction was performed at 25 °C (batch: 50 °C) with half the amount of AgNTf₂ (flow: 5 mol %, batch: 10 mol %), and the light irradiation time was shortened to only 2.5 minutes (batch: 1 h). Thus, under the optimal conditions

(Table 1, entry 10), the flow reaction system proved extremely useful for improving the efficiency of the present photochemical sequential transformation.

With the optimal flow reaction conditions in hand, we next investigated the scope of substrates **1** by introducing a series of substituents to the terminal phenyl group. The results of the batch reaction system are also shown for comparison in Table 2 (right-hand side) [55]. As expected, the use of the flow reaction system significantly increased yields, although the yields obtained in the reactions of substrates having an electron-donating methoxy group were low to moderate regardless of the substitution pattern (Table 2, entries 1, 2, and 6). Indeed, when a methoxy group was introduced at the *para*-position, product **3b** was obtained in low yield (Table 2, entry 1: 14%). Because this yield was lower than that obtained in the batch reaction (48%), the flow reaction conditions for **1b** were thoroughly reconsidered (see Supporting Information File 1 for details). As a result, extending the premixing time and the light irradiation time

Table 2: Scope of substrates^a.

Reaction conditions:
 AgNTf₂ (5 mol %)
 P(4-CF₃C₆H₄)₃ (2.5 mol %)
 TFA (5 equiv)
 1,2-dichloroethane (0.05 M)
 25 °C, flow rate (24 mL/h)
 blue LED (450 nm)

Reaction setup:
 syringe A: 12 mL/h (**1** in 1,2-DCE)
 syringe B: 12 mL/h (all other reactants/reagents in 1,2-DCE)

Entry	1	R ¹	R ²	R ³	R ⁴	R ⁵	3	Yield of 3 (%) ^b	Batch reaction using AgNTf ₂ . Yield of 3 (%) ^{b,c}
1	1b	MeO	H	H	H	H	3b	14	48 ^d
2 ^e	1b						3b	54	
3	1c	Me	H	H	H	H	3c	76	21
4	1d	Br	H	H	H	H	3d	57	10
5	1e	CF ₃	H	H	H	H	3e	77	65
6	1f	H	MeO	H	H	H	3f	39	40
7	1g	H	Me	H	H	H	3g	75	50
8	1h	H	Br	H	H	H	3h	68	63
9	1i	H	CF ₃	H	H	H	3i	65	42
10	1j	H	H	Me	H	H	3j	76	72
11	1k	H	H	H	F	H	3k	79	–
12	1l	H	H	H	H	F	3l	75	–

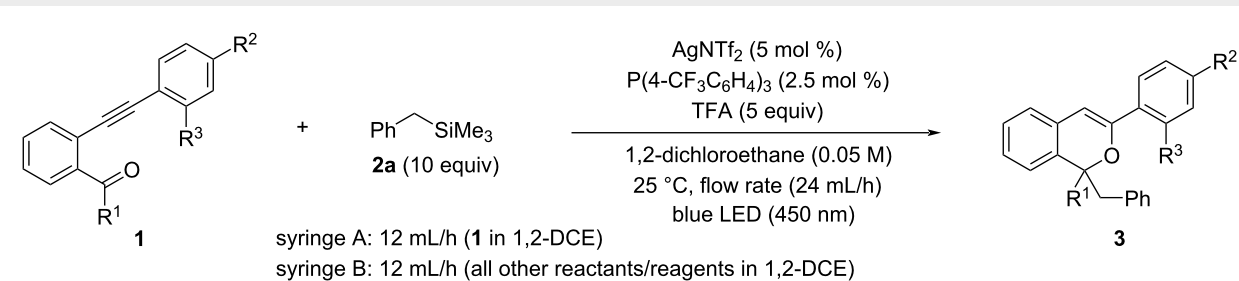
^aUnless otherwise noted, all reactions were carried out in the flow photochemical reactor (volume: 1.0 mL, λ_{max} = 450 nm) having a 0.7 mL premixing zone using a dual syringe system with a flow rate of 24 mL/h (12 mL/h for each syringe) at 25 °C. Syringe A: 0.5 mmol of **1** in 1,2-DCE (5.4 mL). Syringe B: 25 μmol (5 mol %) of AgNTf₂, 12.5 μmol (2.5 mol %) of P(4-CF₃C₆H₄)₃, 5 mmol (10 equiv) of TMSBn (**2a**), and 2.5 mmol (5 equiv) of TFA in 1,2-DCE (4.6 mL). ^bYield was determined by NMR analysis using 1,1,2,2-tetrabromoethane as an internal standard. Substrates **1** were not recovered in all cases. All products **3** were isolated before structural assignment. ^cBatch reaction conditions (see ref. [55]): Unless otherwise noted, all reactions were carried out using blue LED (λ_{max} = 448 nm), 0.1 mmol of **1**, 1.0 mmol (10 equiv) of TMSBn (**2a**), 10 μmol (10 mol %) of AgNTf₂, 20 μmol (20 mol %) of P(4-CF₃C₆H₄)₃, and 5 equiv of TFA in 1,2-DCE (1.0 mL: 0.1 M of **1**) at 50 °C for 1 h. ^dAt 0 °C for 6 h. ^eThe flow photochemical reactor having a 1.1 mL premixing zone using a dual syringe system with a flow rate of 6 mL/h (3 mL/h for each syringe).

(Table 2, entry 2) led to an improved yield; the obtained yield was higher than that of the batch reaction system even when half the amount of AgNTf₂ was used with the temperature reduced to 25 °C (flow: 54% vs batch: 48%). Meanwhile, the reaction of substrate **1c** having a methyl group as a weak electron-donating group at the *para*-position afforded product **3c** in high yield (Table 2, entry 3: 76%). In addition, the reaction of **1d** having a bromo group resulted in a moderate yield, but with a significant improvement compared with the batch reaction (Table 2, entry 4: 57% vs 10%). The reaction of **1e** substituted with a strong electron-withdrawing trifluoromethyl group afforded the product **3e** in high yield (Table 2, entry 5: 77%), again confirming the high efficiency of the flow reaction system (batch: 54%). Next, the effects of the substituent at the *meta*-position were investigated. Substrate **1f** having a methoxy group afforded compound **3f** in only moderate yield (Table 2, entry 6: 39%), similar to the batch reaction (40%). The reactions of substrates having a methyl, bromo, or trifluoromethyl group gave the corresponding products **3g–i**, respectively, in good yields (Table 2, entries 7–9). The *ortho*-methyl-substituted substrate **1j** was also compatible, affording product **3j** in good yield (Table 2, entry 10: 76%). This yield was comparable to that of the substrate having a methyl group at the *para*- or *meta*-position, despite the steric hindrance of the *ortho*-substituent

(Table 2, entry 10 vs entries 3 and 7). When a fluoro group was introduced to the tethering phenyl backbone, a high yield was obtained regardless of whether it was introduced at the 6- or 7-position (Table 2, entries 11 and 12).

Next, the effects of a carbonyl substituent, instead of a methyl ketone substituent, were investigated (Table 3). First, the reaction was performed with phenyl ketone **1m**, but product **3m** was obtained in low yield (Table 3, entry 1: 7%). This yield was lower than that obtained in the batch reaction (30%), and because 28% of **1m** were recovered, the flow reaction conditions were further examined (see Supporting Information File 1 for details). Although the yield of **3m** was improved to 19% (Table 3, entry 2) by increasing the temperature of the premixing zone from room temperature to 50 °C and reducing the flow rate from 24 mL/h to 6 mL/h (light irradiation time was extended from 2.5 min to 10 min), it did not exceed the yield of the batch reaction. In contrast, aldehyde **1n** having a simple phenyl group gave product **3n** in good yield (Table 3, entry 3: 72%). Because the yield of this flow reaction was better than that of the batch reaction (65%), the reactions of aldehydes with a series of substituents introduced to the terminal phenyl group were further investigated (Table 3, entries 4–7). Aldehydes having an electron-donating methyl group and an electron-with-

Table 3: Sequential transformation of phenyl ketone **1m** and aldehydes **1n–r**^a.

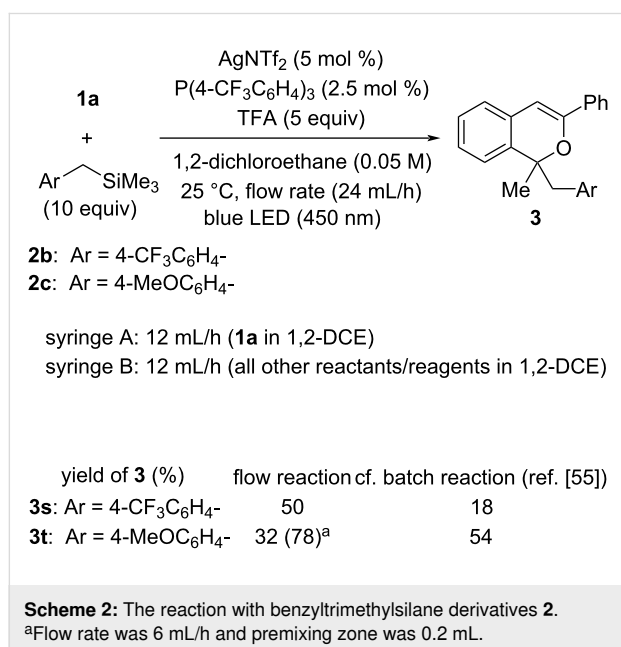


Entry	1	R ¹	R ²	R ³	3	Yield of 3 (%) ^b	Recovery of 1 (%) ^b	Batch reaction using AgNTf ₂ . Yield of 3 (%) ^c
1	1m	Ph	H	H	3m	7	29	30
2 ^{d,e}	1m				3m	19	0	
3	1n	H	H	H	3n	72	0	65 ^f
4	1o	H	Me	H	3o	82	5	–
5	1p	H	Br	H	3p	75	0	34 ^f
6	1q	H	CF ₃	H	3q	63	18	–
7 ^e	1r	H	H	Me	3r	73	8	–

^aUnless otherwise noted, all reactions were carried out in the flow photochemical reactor (volume: 1.0 mL, λ_{max} = 450 nm) having a 0.7 mL premixing zone using a dual syringe system with a flow rate of 24 mL/h (12 mL/h for each syringe) at 25 °C. Syringe A: 0.5 mmol of **1** in 1,2-DCE (5.4 mL). Syringe B: 25 μmol (5 mol %) of AgNTf₂, 12.5 μmol (2.5 mol %) of P(4-CF₃C₆H₄)₃, 5 mmol (10 equiv) of TMSBn (**2a**), and 2.5 mmol (5 equiv) of TFA in 1,2-DCE (4.6 mL). ^bYield was determined by NMR analysis using 1,1,2,2-tetrabromoethane as an internal standard. All products **3** were isolated before structural assignment. ^cBatch reaction conditions: unless otherwise noted, reactions were carried out using 0.1 mmol of **1**, 1.0 mmol (10 equiv) of TMSBn (**2a**), 10 μmol (10 mol %) of AgNTf₂, 20 μmol (20 mol %) of P(4-CF₃C₆H₄)₃, and 5 equiv of TFA in 1,2-DCE (1 mL: 0.1 M of **1**) at 50 °C for 1 h. ^dThe flow photochemical reactor having a 0.5 mL premixing zone using a dual syringe system with a flow rate of 6 mL/h (3 mL/h for each syringe). ^eThe temperature of the premixing zone was increased to 50 °C. ^fThe reaction was performed using 0.05 M of **1** and 2.5 equiv of TFA for 2 h.

drawing bromo group at the *para*-position of the phenyl moiety gave products **3o** and **3p**, respectively, in high yields (Table 3, entries 4 and 5). The aldehyde **1q** bearing a strong electron-withdrawing trifluoromethyl group at the *para*-position gave product **3q** in moderate yield (Table 3, entry 6: 63%), with the recovery of substrate **1q** (18%). The reaction of *ortho*-methyl-substituted aldehyde **1r** afforded the product **3r** in high yield when the temperature of the premixing zone was increased to 50 °C (Table 3, entry 7: 73%).

The scope of donor molecules **2b** and **2c** having an electron-withdrawing trifluoromethyl group and an electron-donating methoxy group [60,61] at the *para*-position of the benzyltrimethylsilane, respectively, was also investigated in the present flow reaction system (Scheme 2). As expected, the flow reaction of **2b** having a trifluoromethyl group afforded product **3s** in higher yield (50%) than that of the batch reaction (18%) under the optimal reaction conditions. In contrast, in the flow reaction of **2c** having a methoxy group, product **3t** was obtained in a markedly lower yield (32%) than that of the batch reaction (54%). However, extending the light irradiation time by reducing the flow rate from 24 mL/h to 6 mL/h (light irradiation time: 24 mL/h = 2.5 min, 6 mL/h = 10 min) significantly improved the yield of **3t** (78%), presumably because of the retardation of the desilylation process (from **B** to **C** in Scheme 1a).



Conclusion

We have demonstrated a flow reaction system for a π -Lewis acidic metal-catalyzed cyclization/photochemical radical addition sequence, affording, in most cases, the *1H*-isochromene de-

rivatives in higher yields than the batch reaction system, even with the amount of the π -Lewis acidic metal catalyst reduced by half. In the present sequential transformation, the key cationic species, 2-benzopyrylium intermediates, were generated in situ through the AgNTf₂-catalyzed intramolecular cyclization of *ortho*-carbonyl alkynylbenzene derivatives and subsequent proto-demetalation with TFA. Further photoreactions of 2-benzopyrylium intermediates with benzyltrimethylsilane derivatives as the donor molecule were conducted in the flow photoreactor. We confirmed that the flow reaction system is an excellent method for improving the efficiency of the present sequential transformation, avoiding product degradation under photochemical reaction conditions. Further investigation of other flow photochemical reactions using in situ-generated organic cations is in progress in our laboratory.

Supporting Information

Supporting Information File 1

The exploratory investigation, experimental procedures, and characterization data.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-173-S1.pdf>]

Supporting Information File 2

Copies of NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-173-S2.pdf>]

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Author Contributions

Masahiro Terada: conceptualization; funding acquisition; methodology; project administration; resources; supervision; visualization; writing – original draft; writing – review & editing. Zen Iwasaki: data curation; formal analysis; investigation; validation; visualization. Ryohei Yazaki: data curation; formal analysis; investigation. Shigenobu Umemiya: data curation; formal analysis; investigation; methodology; supervision; writing – review & editing. Jun Kikuchi: conceptualization; funding acquisition; investigation; methodology; project administration; supervision; visualization; writing – review & editing.

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

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58. Cu(NTf₂)₂ which was also the effective catalyst in our batch system (ref. [55]) did not solve well in 1,2-DCE.
59. Benzyltrimethylsilane (**2a**), which was not consumed in the corresponding radical reaction, was almost completely recovered.
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Photoredox-catalyzed intramolecular nucleophilic amidation of alkenes with β -lactams

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Abstract

The direct nucleophilic addition of amides to unfunctionalized alkenes via photoredox catalysis represents a facile approach towards functionalized alkylamides. Unfortunately, the scarce nucleophilicity of amides and competitive side reactions limit the utility of this approach. Herein, we report an intramolecular photoredox cyclization of alkenes with β -lactams in the presence of an acridinium photocatalyst. The approach uses an intramolecular nucleophilic addition of the β -lactam nitrogen atom to the radical cation photogenerated in the linked alkene moiety, followed by hydrogen transfer from the hydrogen atom transfer (HAT) catalyst. This process was used to successfully prepare 2-alkylated clavam derivatives.

Introduction

Access to nitrogen radicals for the functionalization of alkenes is a field under active investigation [1-4], as it gives the possibility to directly introduce nitrogen into an alkyl chain (alkene carboamination) to obtain valuable nitrogen-containing molecules [5,6]. Among several N-centered radicals, such as aminyl, amidyl, or iminyl radicals, N-heterocyclic amidyl radicals were largely underinvestigated despite their importance as intermediates or relevant N-heterocyclic products in medicinal chemistry [7-10].

Recently, photoredox catalysis has emerged as a novel area of research [11,12], particularly focusing on innovative approaches to synthesize natural or bioactive compounds [13]. In the carboamination of alkenes, amides are used in photoredox cyclizations under proton-coupled electron transfer (PCET) conditions [14-17]. An alternative method to generate N-amidyl radicals uses activated N–O amide derivatives capable of generating amidyl radicals through fragmentation [18,19]. The direct formation of amidyl radicals in the presence of a carbon alkyl

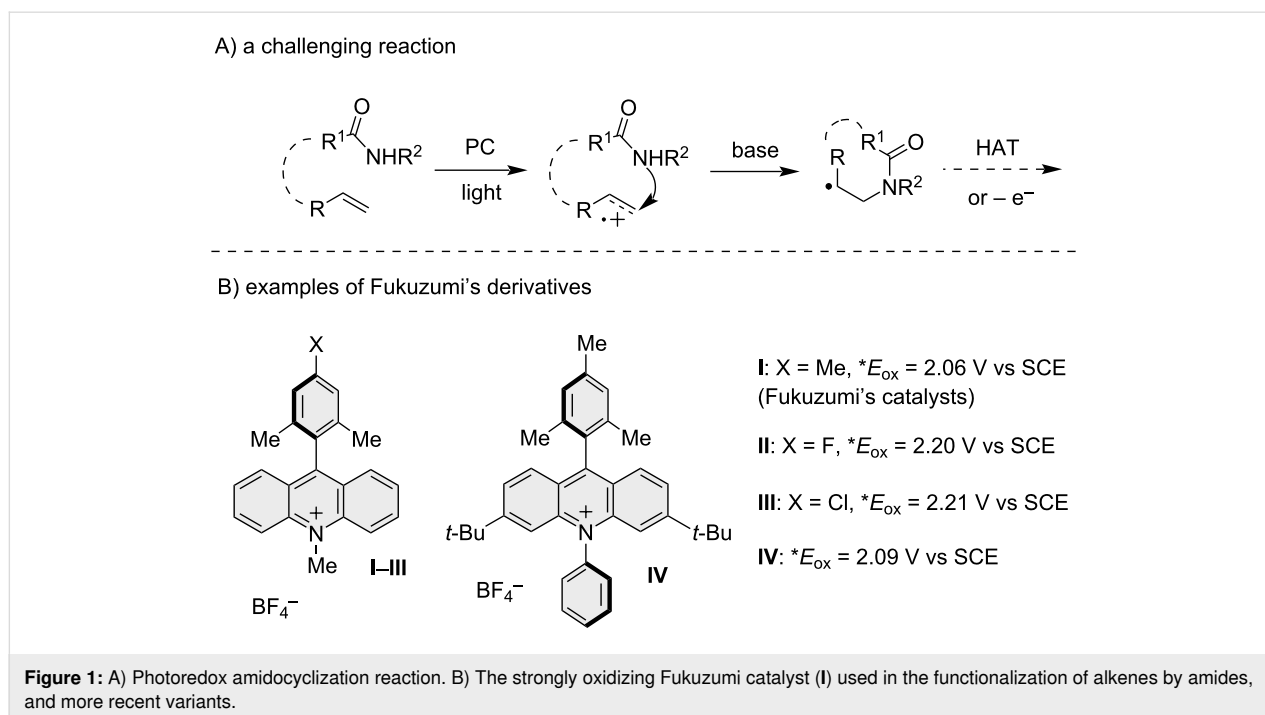
chain could lead to a competitive 1,5-hydrogen atom transfer (1,5-HAT) [20–22], limiting the direct functionalization of amides with alkenes under photoredox conditions. Another viable approach for amide functionalization through photoredox catalysis involves the nucleophilic addition, in the presence of base, of an amide to a radical cation obtained by oxidation of an unfunctionalized alkene moiety (Figure 1A) [23–25]. The nucleophilic attack of the nitrogen atom on the oxidized C=C double bond results in the formation of a radical intermediate after deprotonation. This radical intermediate can proceed through various pathways (e.g., HAT, oxidation) to yield the desired final product.

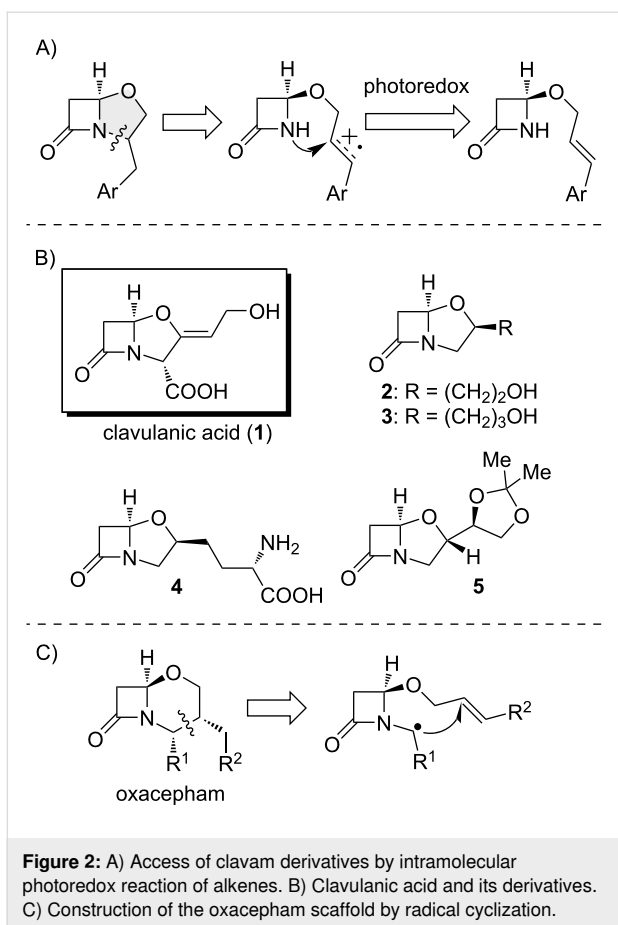
In the functionalization of amides with alkenes under oxidative conditions, the oxidation potential of the alkene plays a pivotal role in the oxidation to a radical cation through photoredox catalysis [26]. Alkenes that are less functionalized possess a higher oxidation potential, necessitating the use of potent photocatalysts (PC) that act as oxidants in the excited state [27]. The direct functionalization of amides with alkenes has been a relatively underexplored area in research, as evidenced by the limited number of examples reported in the literature. An interesting observation was made by the Nicewicz group during their investigation of the hydrofunctionalization reaction of unsaturated amides and thioamides [28]. They have found that the oxygen atom of the amide group, rather than the nitrogen atom, acted as a nucleophile, leading to the formation of 2-oxazolines and 2-thiazolines. Another recent example of intramolecular nucleophilic attack induced by photocatalytic oxidation

was reported by Yoon et al. with tosylamide derivatives [29]. Specifically, amides were employed in a photoredox cyclization process using a strong photooxidative acridinium catalyst such as the Fukuzumi catalyst (**I**, Figure 1B) [30,31]. Through tailored molecular design, it is possible to enhance the oxidation capability of these catalysts, enabling the utilization of less reactive alkenes and even aromatic molecules such as toluene [32].

Until now, heterocyclic amides such as β -lactam compounds have not been employed in alkene carboaminations. However, photoredox catalysis could be applied to a suitable β -lactam intermediate decorated with an alkene moiety to achieve N–H addition and cyclization to the fused bicyclic system of clavams (Figure 2A).

Clavulanic acid (**1**, Figure 2B) belongs to the family of clavam β -lactam compounds and is well known as a potent β -lactamase inhibitor [33,34]. It is produced by the filamentous bacterium *Streptomyces clavuligerus*, but in low yield. Various clavams **2–5** have been identified (Figure 2B), either through isolation as natural metabolites or obtained by synthetic methods [35–43]. The inhibitory activity of β -lactamases is exhibited by those congeners with a (3*R*,5*R*)-configuration, such as clavulanic acid (**1**), whereas clavams with other configurations are not lactamase inhibitors, although some of these have antifungal or antibacterial properties [35]. In the literature, oxacepham scaffolds, the 6-membered fused bicyclic analog of clavams, were prepared from appropriately substituted unfused precursors by





intramolecular C-radical addition to alkene functionalities [44]. The utilization of radical conditions has prevented the effective nucleophilic opening of the lactams.

Notably, all reported structures have alkyl or aryl substituents in position 3 of the clavam ring. Conversely, clavams substituted

with alkyl chains at the 2-position, to the best of our knowledge, have not been previously reported and are absent from common organic compound databases. To explore potential biological effects, a simple and modular approach to these molecules is thus required. Based on this, we decided to use photoredox chemistry to access 2-alkylclavams through a simplified synthetic pathway. We investigated the intramolecular nucleophilic addition of the nitrogen atom of the β -lactams to photooxidized alkenes (Figure 2A), and our findings are presented in this study.

Results and Discussion

The initial phase of our investigation involved the synthesis of suitable starting compounds for the following oxidative cyclization. For this purpose, a series of 4-alkoxy- β -lactams containing an alkene group was readily synthesized starting from commercially available 4-acetoxy-2-azetidinone (**6**) by nucleophilic displacement of the 4-acetoxy group with allylic alcohols promoted by Zn(OAc)₂ (see compounds **8a–h**, Scheme 1) [45]. Similarly, enantiopure derivatives **10c–f** were synthesized from the commercially available β -lactam **9**, a key intermediate for the industrial preparation of carbapenems.

Starting from the reaction conditions reported by Nicewicz and Morse [28], we optimized the conditions with compound **8c** as the model substrate for the photoredox cyclization (Table 1). The reaction was carried out in DCM with acridinium PC **IV** (5 mol %), 50 mol % of PhSSPh as HAT catalyst, and lutidine (50 mol %) as the base.

Upon 72 hours of irradiation with a blue light at 456 nm, the product **11c** was obtained in a satisfactory yield as a mixture of diastereoisomers in a 1.4:1 ratio (Table 1, entry 1). Assignment of the relative configurations as *cis* or *trans* was achieved by

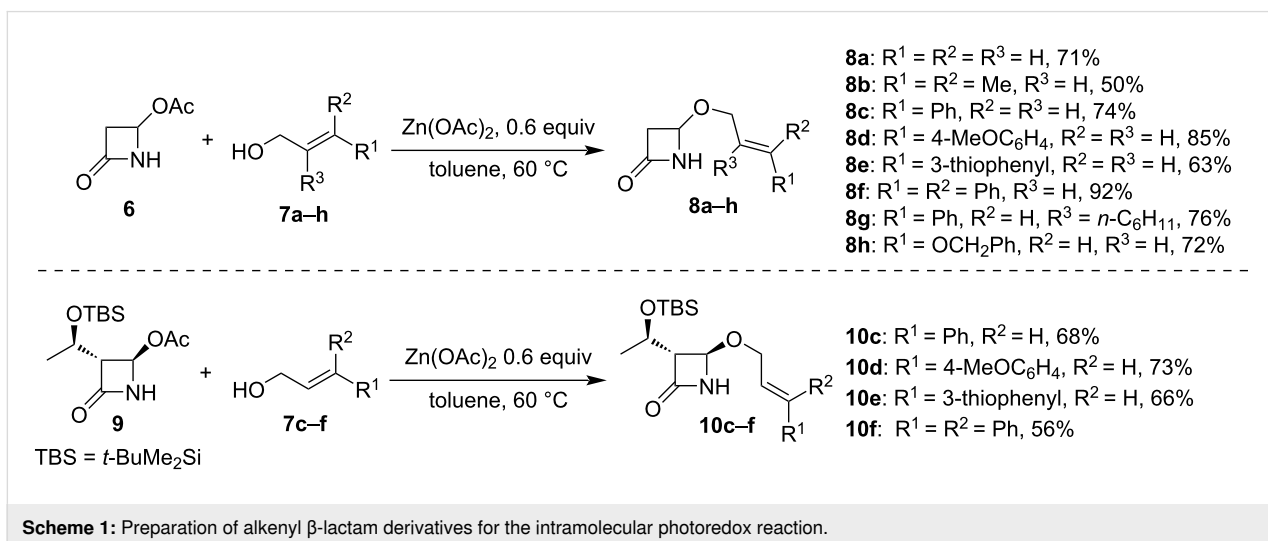
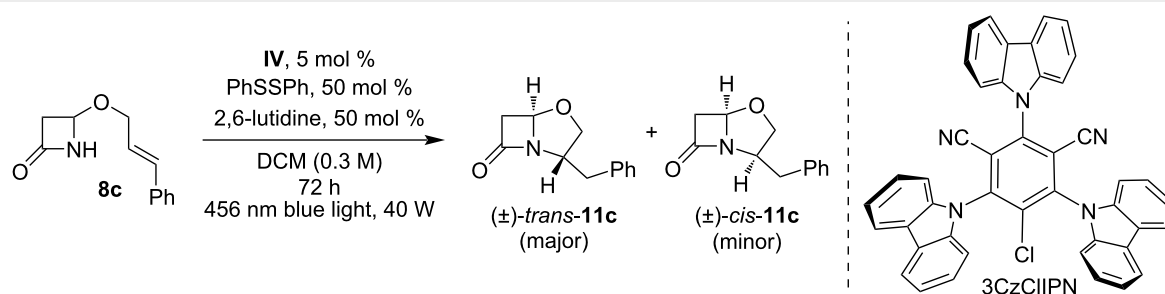


Table 1: Intramolecular cyclization of β -lactams induced by photoredox conditions.^a

entry	deviation from standard conditions	conversion to 11c , % ^{b,c}	dr ^d
1	—	72 (70)	1.4:1
2	absence of IV	0	—
3	absence of light	0	—
4	reaction time 14 h	traces	—
5	20 mol % PhSSPh, 20 mol % 2,6-lutidine	49	1.4:1
6	DMF solvent	0	—
7	MeCN solvent	68	1.4:1
8	DCE solvent	49	1.4:1
9	I instead of IV	60	1.4:1
10	3CzClIPN instead of IV	0	—

^aThe reactions were conducted under irradiation with a Kessil blue light (40 W) for 72 hours on a 0.05 mmol scale. ^bConversion determined by ¹H NMR analysis of the crude reaction mixture. ^cIn parentheses: isolated yield after purification by flash column chromatography. ^d*Trans/cis* dr determined by ¹H NMR analysis on the crude reaction mixture.

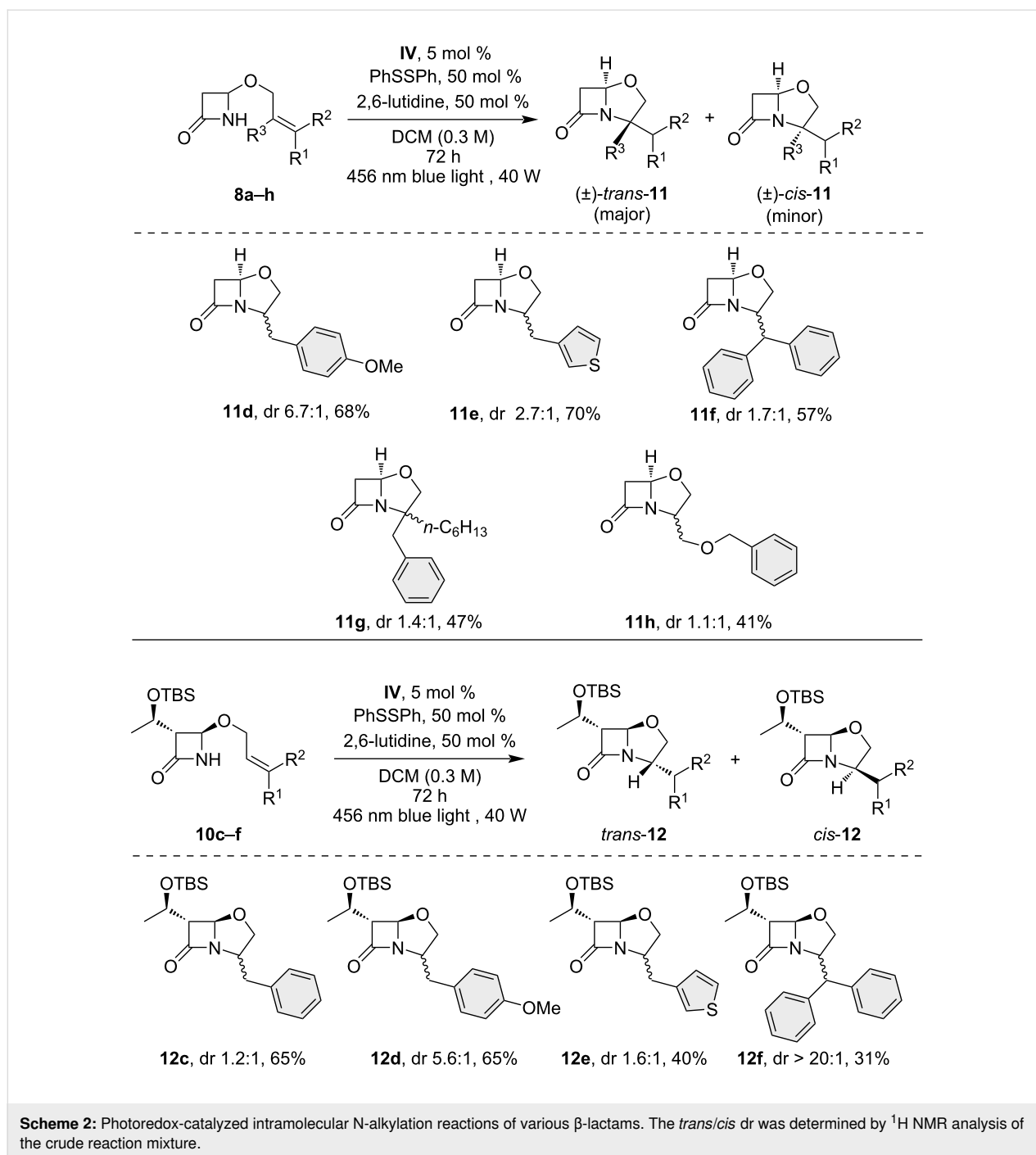
¹H NMR analysis, considering the chemical shifts of the proton in the α -position of the β -lactam nitrogen atom and the geminal protons in the benzylic position (see Supporting Information File 1). The difference in the chemical shifts of these protons in the two isomers could be attributed to the influence of the anisotropy of the neighboring carboxy group of the β -lactam and could be correlated with the configuration at the bridgehead stereocenter [46]. This analysis revealed the preferred formation of the *trans*- over the *cis*-isomer.

The optimal PC for the reaction was acridinium salt **IV** (Table 1, entry 1), while the Fukuzumi catalyst (**I**), commonly employed by Nicewicz et al., was less effective (Table 1, entry 9). 3CzClIPN, an organic dye belonging to the class of thermally activated delayed fluorescence (TADF) dyes commonly employed nowadays in photoredox catalysis [47], was tested in our reaction. This dye was chosen due to its oxidizing properties, and it ranks among the most oxidizing agents within this class of compounds ($E_{1/2}[^*PC/PC^{\bullet-}] = +1.56$ V vs SCE) [48], but it proved ineffective in our reaction (Table 1, entry 10). The reaction was successfully conducted in various solvents, such as DCM, DCE, and MeCN (Table 1, entries 1, 7, and 8). However, DMF failed to yield the desired product (Table 1, entry 6). Shortening the reaction time to 14 hours resulted in minimal product formation (Table 1, entry 4), while reducing the amount

of PhSSPh and lutidine to 20 mol % led to a lower yield (Table 1, entry 5).

With the optimized reaction conditions in hand, we submitted the previously prepared 4-alkoxy- β -lactam substrates **8a–h** to photoredox conditions (Scheme 1), and the salient results are reported in Scheme 2. Unfortunately, the substrates **8a,b** displayed low reactivity due to their significantly higher oxidation potential compared to the excited photoredox catalysts (>2.5 V vs SCE) [49]. However, other derivatives exhibited a satisfactory product yield ranging from moderate to good. Substrate **8d** exhibited an enhancement in reaction diastereoselectivity, resulting in the isolation of product **11d** with a dr of 6.7:1 in favor of the *trans*-diastereoisomer. Remarkably, the formation of a fully substituted quaternary center was possible, as observed for the product **11g**, where the *trans*-diastereoisomer was favored.

In this study, enantiopure 3-(1'-(*tert*-butyldimethylsilyl)ethyl)- β -lactams **10c–f** were also tested. Products **12c–f** were obtained with moderate to good yield, underscoring the feasibility of the methodology for the C3-substituted β -lactam moiety. The configuration at the newly formed stereocenter in the five-membered ring was attributed by ¹H NMR analysis for **11c**. Moreover, the configuration was also confirmed by NOE studies on



the two isolated diastereoisomers, which confirmed the preferred *trans*-isomer formation (see Supporting Information File 1).

Analysis of the dr values revealed that the diastereoselectivity of the nucleophilic attack of the β -lactam on the radical cationic intermediate was influenced by stereoelectronic factors. Compounds unsubstituted at position C-3 of the β -lactam ring, **11d–h**, showed modest stereoselectivity with a higher dr (6.7:1)

for compound **11d**, which has an electron-donating methoxy group on the phenyl substituent. Derivatives with a 3-OTBS side chain, **12c–e**, displayed moderate diastereoselectivity, except for the higher diastereoselectivity achieved for **12f** (dr 20:1), probably due to steric effects, albeit at the expense of a reduced isolated yield.

Across all tested substrates, nucleophilic attack predominantly occurred at the homobenzylic position, leading to the regiose-

lective formation of clavam derivative with 2-benzylic substitution due to aryl stabilization of the radical intermediate (see mechanistic discussion below).

We briefly investigated whether this protocol could be adapted to other lactams, allowing for a practical synthesis of bicyclic structures. The resulting bicyclic lactam substrate could serve as a foundation to access pyrroloisoquinoline alkaloids [50,51]. The model substrate **14** was synthesized in a two-step process starting from succinimide (Scheme 3). Through a simple reaction in toluene at 80 °C in the presence of Zn(OAc)₂, the hemiaminal derivative **13** underwent substitution with cinnamyl alcohol, resulting in the isolation of **14** with a satisfactory yield. Under optimized reaction conditions, the photocatalytic cyclization occurred by producing *trans*-**15** in 35% yield as the single diastereoisomer.

For the reaction mechanism, we propose a mechanistic hypothesis according to the study by Nicewicz and Nguyen (Figure 3) [23]. The incorporation of electron-donating groups into the acridinium core, as in catalyst **IV**, enhances charge transfer by stabilizing the mesityl moiety. Conversely, the introduction of *tert*-butyl groups increases the life time of the excited state [52–56]. As a consequence, the PC **IV** is a strong oxidant in the excited state and displays unique oxidizing properties ($E_{1/2}[*PC^+/PC^*] = +2.09$ V vs SCE) [55,56]. The $*PC^+$ species can oxidize the unsaturated lactam, thereby producing the corresponding radical cation intermediate **A**. The low stabilization by amide-bond resonance of the cyclic four-membered β -lactam [57,58] ensures a good nucleophilicity of the nitrogen atom to

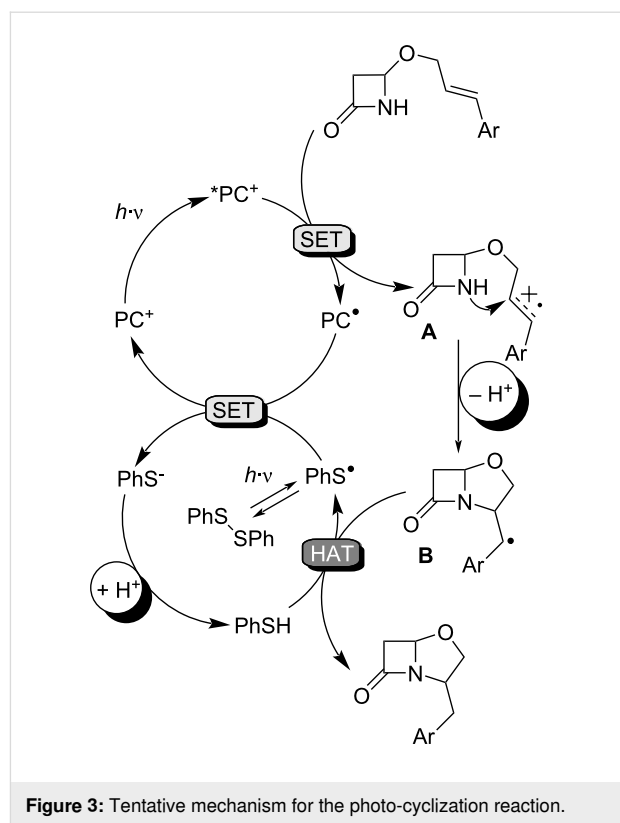
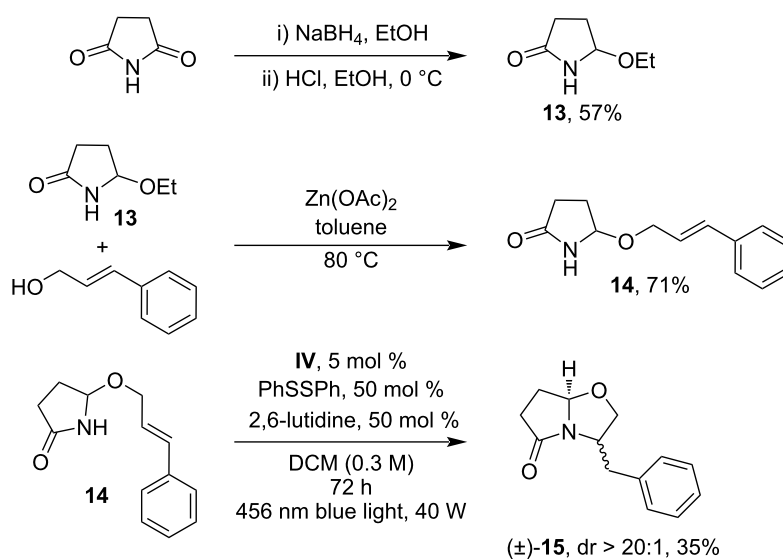


Figure 3: Tentative mechanism for the photo-cyclization reaction.

efficiently attack the radical cation **A**, giving the bicyclic radical intermediate **B**. Amide is an ambident nucleophile, and oxygen attack of radical cation **A** is also conceivable to give the corresponding imidate [28]. In our reaction, O-addition is disfavored due to the formation of an unsaturated four-membered ring as



Scheme 3: Synthesis of the model substrate **14** and its photoredox-catalyzed intramolecular N-alkylation reaction. The *trans/cis* dr was determined by ¹H NMR analysis of the crude reaction mixture.

final product, characterized by significant ring strain [59]. Under light irradiation, PhSSPh is in equilibrium with the corresponding thiyl radical, which is subsequently reduced to thio-phenolate by PC[•], originating from the reduction of *PC⁺. The reduction potential of PhS⁻/PhS[•] ($E_{p_{red}} = +0.45$ V vs SCE) [60,61] is sufficient to oxidize the radical form of **IV** (PC[•]/PC⁺ = -0.57 V vs SCE) [55,56]. Finally, PhS⁻ is protonated and HAT from thiophenol to **B** furnishes the final product, closing the HAT cycle. Additionally, lutidine acts as a proton shuttle between the lactam NH unit and thiophenolate.

Conclusion

To conclude, we have employed a photoredox methodology to access clavam and pyrrolyloxazole intermediates, showing the possibility of using the nucleophilic nitrogen atom of β -lactams under photoredox conditions. The acridinium catalyst **IV** was able to oxidize the C=C double bond present in the substrates to access the corresponding radical cation. The reaction shows high regioselectivity and good to moderate diastereoselectivity with satisfactory yield. The limitation, which will be further addressed by a more powerful catalyst, is related to the unreactivity of unsubstituted alkenes due to their higher oxidation potential. Biological studies concerning the new derivatives will also be a subject of future investigations.

Supporting Information

Supporting Information File 1

Reaction optimization studies, general experimental procedures, product isolation and characterization, spectroscopic data for new compounds, and copies of NMR spectra.

[<https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-210-S1.pdf>]

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Data Availability Statement

All data that supports the findings of this study is available in the published article and/or the supporting information of this article.

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