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Visible-Light Photoredox Catalytic Direct *N*-(Het)Arylation of Lactams

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Lactam rings are essential structural motifs in organic chemistry, widely present in natural products and clinically important drugs, such as antibiotics and antiepileptics. Existing methods for synthesizing *N*-functionalized lactams often require harsh conditions, toxic reagents, or complex catalytic systems. Here, we report a mild and efficient photochemical approach for generating *N*-centered radicals, enabling straightforward *N*-heteroarylation of lactams. This versatile method enables the synthesis of a range of *N*-(het)arylated lactams and is effective even in aqueous media, facilitating the functionalization of biomolecules. Furthermore, the photochemical reaction is easily scalable under continuous flow conditions, making it highly suitable for large-scale applications.

Introduction

Lactam rings are fundamental structural motifs in organic chemistry, appearing widely in natural products and clinically important drugs, including antibiotics and antiepileptics (Figure 1A).[1,2] Numerous methods for functionalizing lactam rings, especially at the nitrogen center, have been extensively explored. Common approaches often begin with commercially available lactam rings, which are then modified through reactions such as Ullmann-type couplings. However, these methods frequently require harsh conditions and elevated temperatures, limiting their broader applicability in synthetic organic chemistry.[3,4] Alternative strategies include the closure of the lactam ring using isocyanide-based multicomponent reactions with a Ugi-like mechanism[5] intramolecular insertion of iridium nitrenes into C–H bonds[6] and photoredox 5-*exo*-trig cyclizations[7] (Figure 1B). Moreover, same related work in the field of the light-mediated synthesis of *N*-aryl lactones and *N*-aryl imides is present in the literature.[8] Despite these advances, developing mild and efficient methods for synthesizing *N*-functionalized lactams remains a significant challenge, especially for pharmaceutical applications.

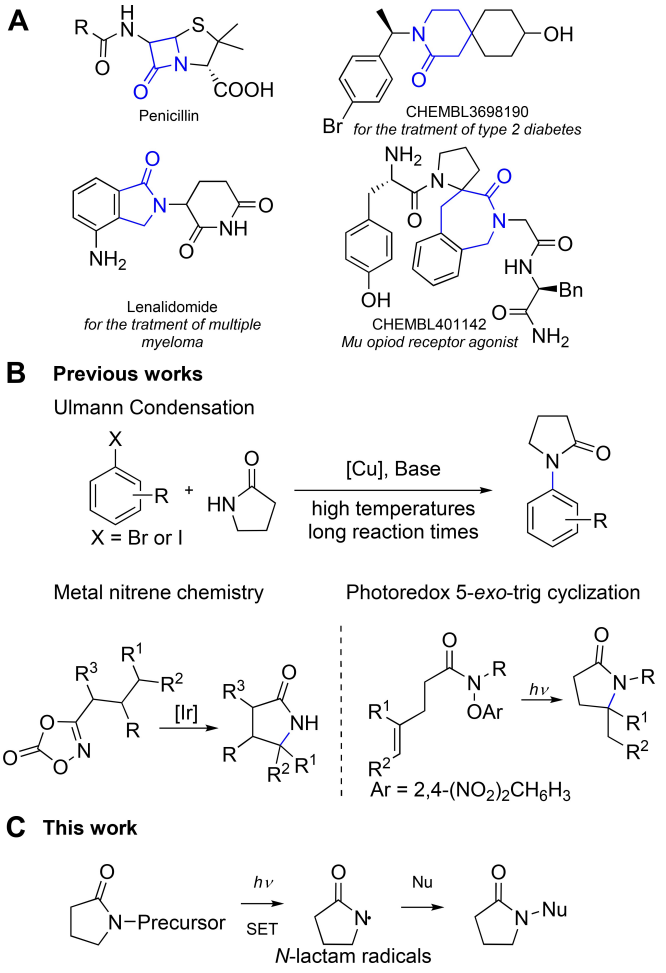

Figure 1. A) Selected examples of biologically active molecules containing β-, γ-, δ- and ε-lactam units. B) Previous literature on the synthesis and functionalization of lactams C) Our approach for generating *N*-lactam radicals.

We hypothesized that radical chemistry and photoredox catalysis could provide new avenues for addressing these

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challenges by enabling the formation of *N*-lactam radicals - an emerging class of nitrogen radicals (Figure 1C). Over the past decade, the organic chemistry community has increasingly embraced photocatalysis as a transformative tool, allowing for the mild generation of reactive intermediates. This approach has facilitated the development of innovative synthetic transformations previously unattainable with traditional methods.[9,10]

Various precursors for nitrogen-centered radical[11–14] generation have been explored relying on the cleavage of N-O,[7,15,16] N-halogen,[17,18] N-N[19] and N-H[20] bonds. Among the numerous nitrogen radical precursors in the literature, we selected three distinct approaches to generate suitable starting materials for *N*-lactam radical formation (Figure 2). The first strategy builds on the pioneering work by MacMillan and co-workers,[15] which demonstrated the use of nitrogen-centered radicals generated from *N*-(aryl-sulphonyl-oxy)amides to achieve enantioselective α-amination of aldehydes (Figure 2a). The second approach, developed by Leonori and co-workers[7] in 2016, introduced *O*-aryl hydroxylamides as nitrogen radical precursors, enabling mild and metal-free amidyl and carbamyl radical additions to arenes and heteroarenes (Figure 2b). In the third strategy, Studer and co-workers[19] utilized pyridinium salts as amidyl radicals precursors with a ruthenium-based photocatalyst and blue light irradiation to achieve high yields in the amidation of arenes and heteroarenes (Figure 2c).

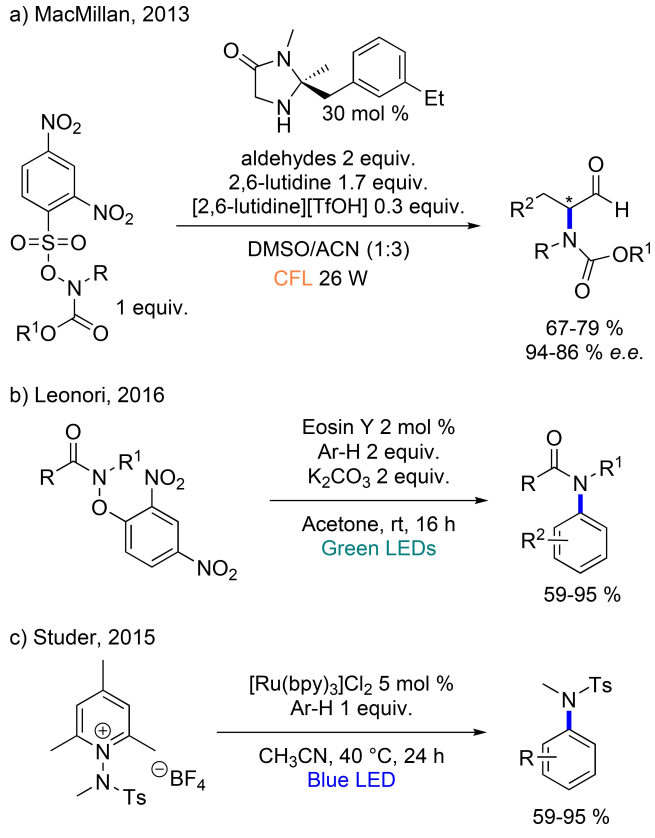


Figure 2. a) Enantioselective α-amidation of aldehydes; b) *O*-aryl hydroxylamides for the addition of amidyl radicals to arenes and heteroarenes; c) Pyridinium ions for the addition of amidyl radicals to arenes and heteroarenes.

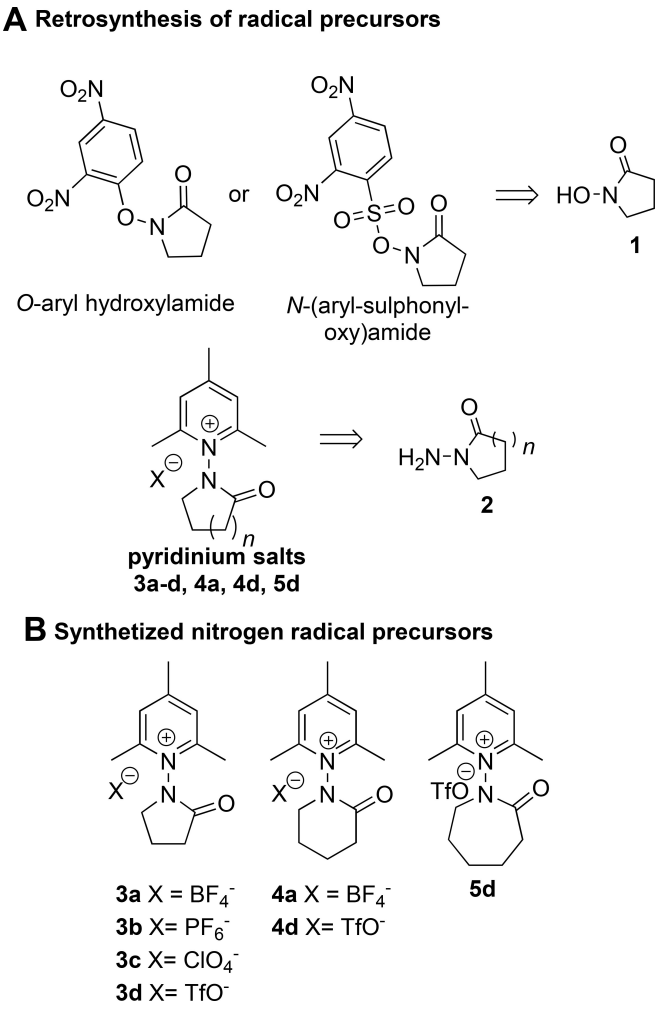
Results and Discussion

Nitrogen radical precursors synthesis and optimisation of reaction conditions

As outlined in the retrosynthetic approach in Scheme 1 and based on previous literature reports,[7,15,19] three potential precursors were considered for generating the desired *N*-centered lactam radicals. During our initial investigations, we found that synthesizing pyridinium-based precursors[18] was relatively straightforward, as they could be derived from the known hydrazide **2**.[21]

The general synthesis of precursors **3a-d**, **4a**, **4d** and **5d** is reported in Section 3 of the Supporting Information.

We then examined the properties and characteristics of the γ-*N* lactam precursors **3a-d**. Cyclic Voltammetry (CV) measurements in DMA were carried out to determine the reduction potential of these molecules under the reaction conditions. The CVs revealed an irreversible reduction peak at −0.8/-0.75 V vs Ag/Ag^+ ($GC^+|Pt^-$), which is consistent with the values reported



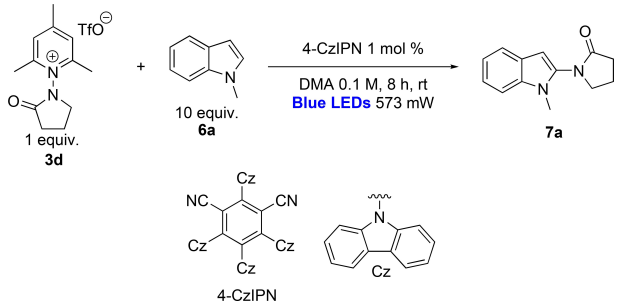
Scheme 1. A) Retrosynthetic strategy for the synthesis of *N*-lactam radical precursors. B) Synthetized nitrogen radical precursors.

in the literature for known pyridinium salts (Supporting Information, Section 3.3).[19]

Next, we tested the nitrogen radical precursors in a model reaction[7,19] involving the regiospecific addition of the *N*-lactam radical to 1-methylindole **6a** under blue light irradiation at room temperature. Following an extensive screening of the catalysts and solvents, 4CzIPN (1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) and DMA were identified as the optimal choices (see Section 4 in the Supporting Information for further details). The key optimization results for this reaction are summarized in Table 1.

It is to be noted here that, although $Ir(ppy)_3$ and $Ru[bpy_3]Cl_2$ (Table 1, Entry 3 and Entry 7) can also be used for the photochemical reaction, 4CzIPN was selected for further studies due to its pure organic nature. The stoichiometry of the reaction was found to be important (Table 1, Entry 4): while using 1.0 equivalent of 1-methylindole **6a** resulted in 32% yield of the desired product, increasing the amount to 10 equivalents significantly improved the yield, leading to 80% isolated yield of product **7a** after chromatography column. The remaining unreacted 9 equivalents of 1-methylindole **6a** are fully recovered. Both **3a** and **3d** precursors, with BF_4^- and TfO^- as counterions respectively, produced product **7a** with almost identical yields (Entry 5). Lowering the reaction temperature (Entry 6) led to a decrease in the yield. Control experiments confirmed the essential roles of both light and the photocatalyst in the transformation (Entries 8–10). Notably, the reaction conditions are remarkably simple: the desired product was obtained in excellent isolated yield by merely mixing the reaction partners in air, followed by irradiation under a nitrogen atmosphere in the presence of a photocatalyst.

Table 1. Optimization of the reaction conditions and control reactions.



Entry	Modification from above	Yield (%)
1	none	80
2	DMSO instead of DMA	42
3	$Ir(ppy)_3$ instead of 4CzIPN	78
4	1 equiv. of 1-methylindole **6a**	32
5	**3a** instead of **3d**	80
6	0 °C instead of rt	50
7	$[Ru(bpy)_3]Cl_2$ and Green LEDs (167 mW) instead of 4CzIPN and Blue LEDs	78
8	no light	< 1
9	no 4CzIPN	< 1
10	no light, 60 °C	< 1

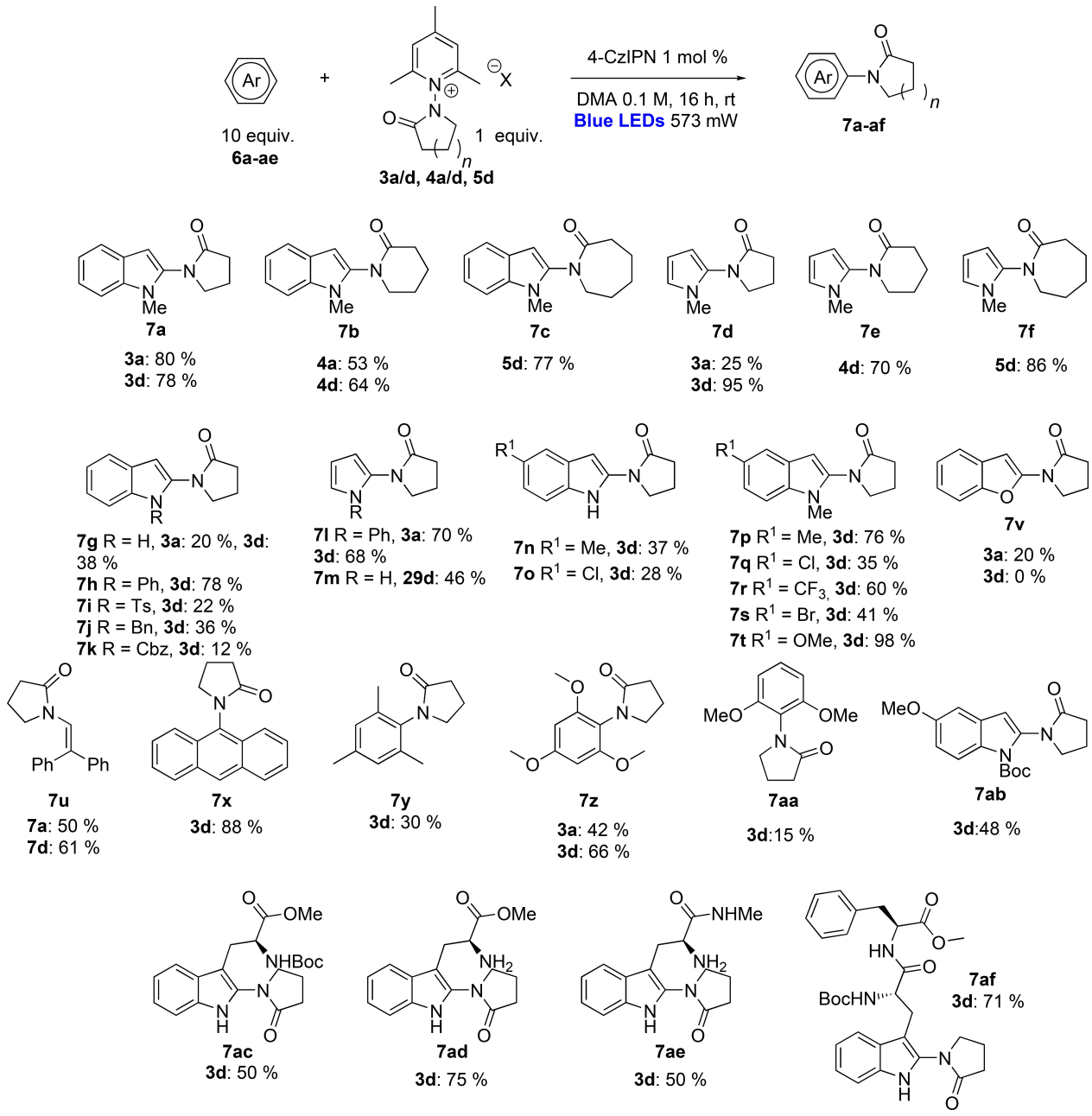
Substrate Scope

With the optimized reaction conditions in hand, we then extensively explored the scope of the $C(sp^2)$-N bond-forming reaction using various lactams (γ-, δ-, and ε-*N*-lactams) with a range of arenes and, more importantly, heteroarenes (Scheme 2). Initially, we evaluated the performance of **3a**, **3d**, **4a**, **4d**, and **5d** on both 1-methylindole **6a** and 1-methylpyrrole **6d**. To our delight, the corresponding products **7a-f**[22] were successfully isolated in good to excellent yields, ranging from 64% to 95%. Notably, when indole or pyrrole without *N*-protection was used, the reactions proceeded well, yielding products **7g** and **7m** in synthetically useful yields. Additionally, a range of *N*-protected indoles with easily removable groups gave the desired products **7h-k**, with the Ph-protection group outperforming others, resulting in 78% isolated yield for the corresponding product. Further investigations into the effect of substituents at the 5-position of the indole ring demonstrated that electron-withdrawing groups resulted in decreased yields (**7q**, **7r**, **7s**), whereas electron-donating groups significantly enhanced the yields (**7p**, **7t**). The synthetic transformations were not limited to functionalized indoles and pyrroles; other functionalized arenes and heteroarenes also successfully served as reactant partners giving the desired products, albeit with low to modest isolated yields depending on the (hetero)arene used. For instance, electron-rich arenes such as 1,3,5-trimethylbenzene and 1,3,5-trimethoxybenzene afforded the corresponding products **7u-z** in good yields. Additionally, 1,1-diphenylethylene served as a viable reaction partner, and, to our delight, anthracene was functionalized, yielding the desired product **7x** in an excellent 88% isolated yield.

The applicability of this synthetic method became even more evident when we explored its use with biologically relevant molecules as reaction partners. To our delight, employing Boc-OMe–L-tryptophan, NH_2-OMe–L-tryptophan, and NH_2-NHMe–L-tryptophan yielded the desired products **7ab**, **7ac**, and **7ad** in 50%, 75%, and 50% yields, respectively. Additionally, the dipeptide Boc-Trp-Phe-OMe also performed well, producing the desired product **7ae** in 70% yield. This highlights the selectivity of our approach for the most electron-rich group in the substrates, demonstrating the method's potential for functionalizing complex biomolecules.

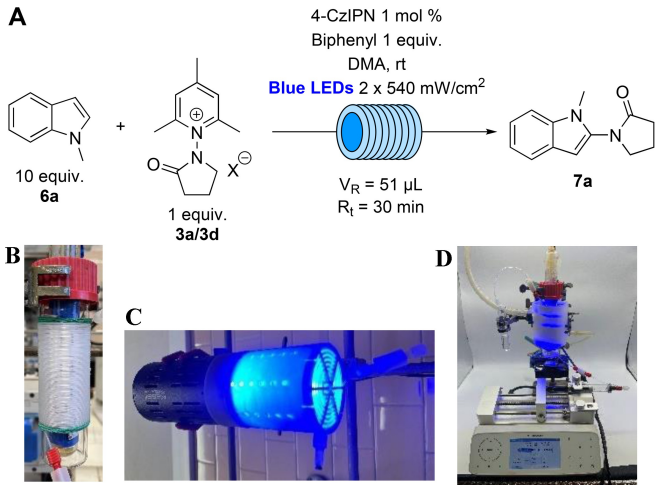
γ-N Lactam Addition in Flow Conditions

Given the well-established benefits of light-driven transformations in continuous flow,[23] we explored the regioselective addition of γ-*N*-lactam radical to 1-methylindole **6a** using custom-made photoredox coil reactors (Scheme 3A; for device specifications, see Supporting Information, Section 6).



Scheme 2. Reaction Scope. Isolated yields are reported unless otherwise noted.

The radical precursor **3a**, biphenyl as an internal standard and all the reagents were charged in a single syringe and pumped into the coil (HPFA, 0.01" as internal diameter, 100 cm, 51 μL) wrapped around a homemade photoreactor built with a Blue LED strip (Scheme 3B). A key observation was the significant effect of the counterion on the overall reaction performance. Among the tested precursors, **3d** proved to be the most effective under flow conditions, minimizing precipitate formation, a challenge observed with other precursors (see Supporting Information for further details).[24] After reaction screening, it was found that the photochemical reaction can be conducted using various light sources. For instance, employing a Kessil lamp with a cylindrical 3D-printed support (6.5 cm length, 6 cm width, and a 6 cm diameter disk for spiral placement of the coil; details in the Supporting Information; Scheme 3C) allowed us to achieve product **7a** in 76% yield with 30 minutes of residence time. In an alternative setup using photoreactor **PR-3**[25] with LED strips on both the inner and outer sides (Scheme 3D), product **7a** was obtained in 82% yield with the same residence time. Based on these results we

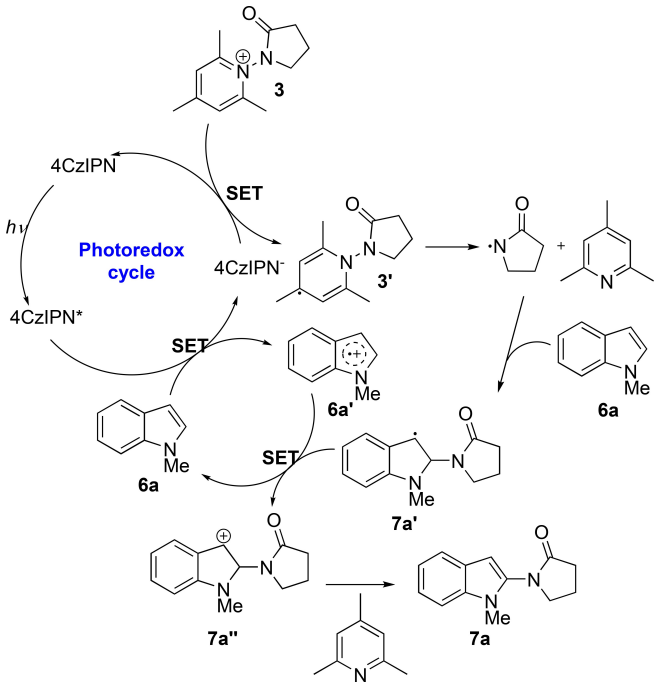


Scheme 3. A) γ-*N*-lactam addition to 1-methylindole **6a** under flow conditions. B) Sublimator photoreactor **PR-1** C) Kessil Lamp setup. D) Sublimator unit + 3D printed setup photoreactor **PR-3**.

decided to continue the flow parameter investigation using the photoreactor **PR-3** described in Scheme 4C. Using a PFA coil reactor with 0.02" as internal diameter (25 cm, 51 µL) we obtained **7a** in 86% yield. Then, we tested several concentrations (see details in Supporting Information, Section 6.2) obtaining **7a** in 87% yield with 0.2 M concentration with a slight improvement of the productivity in comparison with the batch (0.019 mmolh-1 vs 0.016 mmolh-1, Table 2). In the end, we accomplished to lower 1-methylindole **6a** equivalents to 5 without affecting the yield.

A scale-up of the reactor was also realized, increasing the reactor volume from 51 µL to 1381 µL (PFA, 0.02" internal diameter, 670 cm). Under the same conditions (0.2 M, 30 min residence time), we obtained product **7a** in 86% isolated yield, thus improving considerably the productivity (0.47 $mmolh^{-1}$).

Table 2 outlines the productivity metrics and space-time yield (STY) for the three different setups: batch, flow at 51 µL, and flow at 1381 µL reactor volume. These results underscore the better efficiency of the continuous flow process. While the batch reaction achieved a STY of 0.016 $mmol\,h^{-1}\,mL^{-1}$, the 51 µL and 1381 µL flow reactors demonstrated a remarkable 21-fold increase, reaching 0.35 $mmol\,h^{-1}\,mL^{-1}$ under identical 30-minute conditions.



Scheme 4. Mechanism proposal.

In Water Investigation

To further extend the applicability of our radical addition methodology, we explored its use in aqueous media, with results summarized in Table 3.

Notably, product **7a** was obtained in 34% yield when the reaction was conducted in tap water (Table 2, Entry 2). The yield increased to 44% with the addition of meglumine, an amino sugar (Entry 4).[26] We hypothesize that this improvement is due to either enhanced solubility of 1-methylindole **6a** in water or the amino group acting as a base. Subsequent experiments confirmed that the latter was the primary factor, as using dibutyl amine or Cs_2CO_3 in tap water improved the yield to 50% (Entries 10 and 11). Remarkably, this approach also facilitated the functionalization of pharmaceutically relevant compounds, such as NH_2-OMe–L-tryptophan, in aqueous media, yielding the desired product **7ac** in a satisfactory 25% isolated yield.

Mechanistic Investigations

To gain insight into the mechanism of the photocatalytic reaction, both mechanistic and computational studies were

Table 2. Productivity and Space Time Yield (STY); *1.0 equivalent of **3d**, 5.0 equivalents of 1-methylindole **6a**, 1 mol% of 4CzIPN, DMA 0.2 M, rt, 8 h, Blue LEDs 573 mW.

Entry	Yield (%)	Productivity ($mmolh^{-1}$)	Rel. Factor	STY ($mmolh^{-1}ml^{-1}$)	Rel. Factor
batch	65*	0.016	1	0.016	1
51 µL	87	0.019	1.2	0.35	22
1.38 mL	86	0.47	29	0.34	21

Table 3. γ-*N* lactam addition to 1-methylindole **6a** in water

Entry	Solvent	Additive (equiv.)	GC Yield (%)
1	Distilled H_2O	-	29
2	Tap water	-	34
3	Distilled H_2O	Meglumine (1)	33
4	Distilled H_2O	Meglumine (2)	44
5	Distilled H_2O	Meglumine (3)	27
6	Distilled H_2O	Meglumine (5)	23
7	Distilled H_2O	Meglumine (10)	27
8	Distilled H_2O	Glucose (2)	12
9	Distilled H_2O	Sorbitol (2)	8
10	Tap water	Dibutyl amine (2)	48
11	Tap water	Cs_2CO_3 (2)	50

conducted. We measured the quantum yield (ϕ = 1 %), indicating the absence of a radical chain propagation mechanism or a really inefficient one.[27] Additionally, the color change in the reaction mixture—from yellow before irradiation to deep orange afterward—suggests the formation of other absorbing species that compete with the photocatalyst, and diminish the quantum efficiency in the course of the reaction. The effect of each reaction component on the photoluminescence of 4CzIPN was also examined. A 10 μM solution of 4CzIPN in DMA was prepared, and its lifetime was measured under air-equilibrated conditions (τ_{prompt} = 21.4 ns, τ_{delay} = 707 ns). Upon incremental addition of precursor **3d** and 1-methylindole **6a**, we recorded the corresponding lifetime decay. To assess the influence of counterions on electron transfer, NaOTf was added to the solution, showing almost no effect on the photocatalyst's luminescence (Stern–Volmer quenching rate constant, k_q = 7.5×10^4 $M^{-1}s^{-1}$). The photoluminescence lifetime of 4CzIPN decreased with increasing concentrations of both 1-methylindole **6a** and precursor **3d**, indicating that 1-methylindole **6a** directly quenches the photocatalyst, while precursor **3d** exhibits a milder quenching effect. The quenching rates from the Stern-Volmer plot revealed that 1-methylindole **6a** quenches 4CzIPN significantly faster ($k_q = 7.13\times10^6$ $M^{-1}\cdot s^{-1}$) than the nitrogen radical precursor **3d** ($k_q = 2.5\times10^5$ $M^{-1}\cdot s^{-1}$). Notably, the reaction still proceeded in the presence of substrates like mesitylene ($k_q = 1.9\times10^4$ $M^{-1}s^{-1}$), which weakly quench 4CzIPN fluorescence. The quenching efficiency of the mesitylene is significantly lower than that of the nitrogen radical precursor **3d** (about 10 times) or 1-methylindole **6a**. However, as under the reaction conditions the mesitylene is used in a tenfold excess, quenching rates of the amide and the mesitylene become equal. Therefore, despite different quenching constants as derived from Stern Volmer experiments, two distinct mechanistic scenarios may operate in parallel.

Density functional theory (DFT) calculations were employed to assess the electrophilicity of *N*-lactam radicals. As illustrated in Figure 3, the electrophilicity increases with decreasing ring size, though all radicals fall within the category of moderate

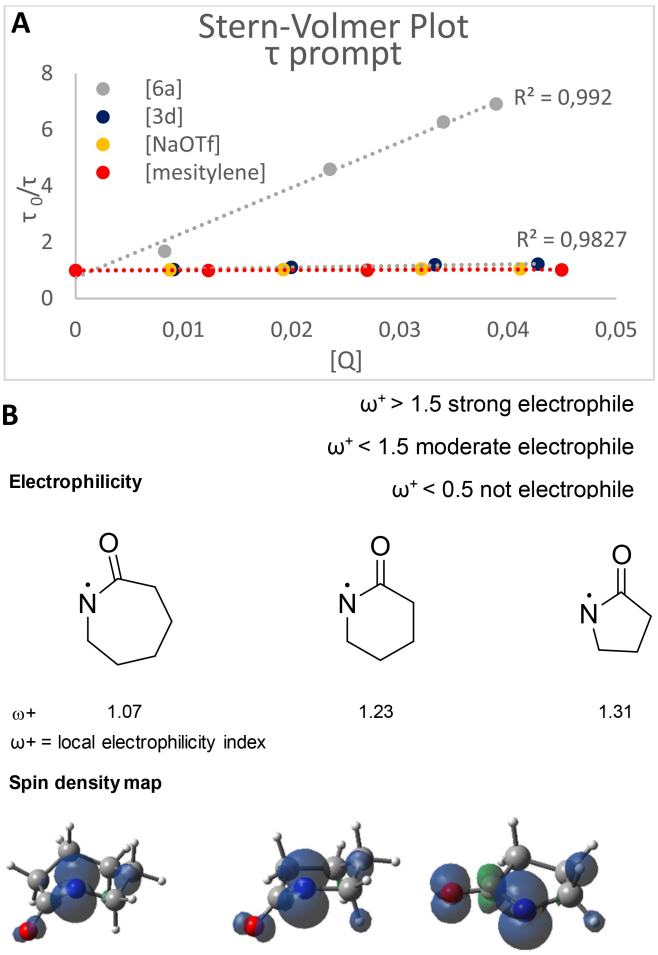


Figure 3. A) Summary Plot of the Stern-Volmer Studies. B) Electrophilicity calculations. ω^+ = local electrophilicity index.

electrophiles, with ω^+ values (local electrophilicity index) ranging from 0.5 to 1.5.[7]

Based on the experimental data, we propose a reaction mechanism (Scheme 4). Blue light (451 nm) excites the 4CzIPN photocatalyst, which oxidizes 1-methylindole **6a** via single-electron transfer (SET). The reduced 4CzIPN radical anion ($4CzIPN^{\bullet-}$) then reduces precursor **3**, regenerating the photocatalyst. The resulting intermediate **3′** undergoes fragmentation, releasing 2,4,6-collidine and generating the *N*- lactam radical. This radical reacts with another molecule of 1-methylindole **6a**, forming radical intermediate **6a′**, which is subsequently oxidized to carbocation **6a″**. Finally, loss of a proton from **6a″** is facilitated by aromatization and yields the desired product. For arene substrates exhibiting low photocatalyst quenching, the excited state of the photocatalyst can reduce the radical precursor, generating a reactive *N*-centered radical. This radical reacts with the arene to form an intermediate radical, which is then oxidized, completing the photocatalytic cycle. Upon proton release, the desired product is formed.

Conclusions

In conclusion, we have developed a mild and efficient method for the direct *N*-(het)arylation of lactams using a diverse range of arenes and heteroarenes. The reaction allows the synthesis of various *N*-(het)arylated lactams and works in aqueous media, allowing the functionalization of biomolecules. Moreover, the photochemical reaction can be easily scaled under continuous flow conditions, making it suitable for large-scale applications. We believe this work advances *N*-lactam radical chemistry, providing a versatile and scalable tool for synthetic chemists aiming to achieve *N*-functionalized lactams under mild, metal-free conditions.

Experimental Section

General Procedure for the Photocatalytic addition of Lactam Radicals to Heteroarenes and Arenes

Into a 7 ml vial, the nitrogen radical precursor **3a**, **3d**, **4a**, **4d** or **5d** (1 equiv., 0.2 mmol), 1.6 mg of 4-CzIPN (1 mol%) and the heteroarenes (10 equiv., 2 mmol) were introduced. The vial was sealed with a septum cap and three nitrogen-vacuum cycles were done. 2 ml of DMA were added and other three nitrogen-vacuum cycles were performed. The reaction mixture was irradiated for 16 hours with Blue LEDs (451 nm, 573 mW) using the Plate photoreactor. After that the DMA was removed under reduced pressure and the crude was purified with flash column chromatography on silica gel.

Supporting Information

The Supporting Information contains synthetic procedures, spectra, crystallographic data, computational studies and additional comments. This information is available free of charge.

Deposition Numbers https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.2024043852402309 (for **3a**), https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.2024043852402310 (for **3d**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe http://www.ccdc.cam.ac.uk/structures Access Structures service. The authors have cited additional references within the Supporting Information.[28,41]

Author Contributions

M.F. Boselli and N. Intini: investigation, writing original draft, contribution to conceptualization; M. Fattalini investigation; I. Ghosh supervision, writing review; B. König supervision and review/editing; A. Puglisi and M. Benaglia methodology, supervision, conceptualization, and review/editing. All authors contributed to the discussion on the study and edited the manuscript.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Flow Chemistry · Lactams · Photocatalysis · Radical Reactions

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[22] The large difference in yields observed in the reaction scope (Scheme) could be ascribed to a difference in reaction rate between precursors **3 a** and **3 d** (Supporting Information Section 4.1): if the starting material appears to be unstable under the reaction conditions, like 1-methylpyrrole **6 d**, slow kinetics will cause its degradation before the reaction can occur, whereas faster kinetics allow the desired product to be obtained in excellent yields (compound **7 d**). On the other hand, when the starting material remains stable under the reaction conditions, the product yields derived from the two precursors are equal (compound **7 a**).
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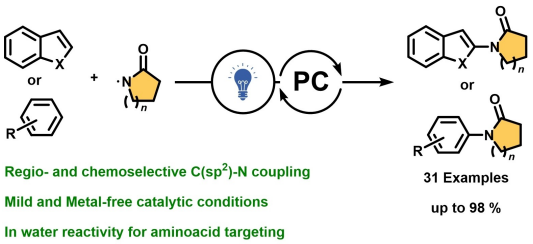

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Visible-Light Photoredox Catalytic Direct *N*-(Het)Arylation of Lactams

Lactam rings can be introduced to a diverse range of arenes and heteroarenes employing our mild and efficient photoredox method. The *N*-(het)arylation of lactams also works in aqueous media, allowing the functionalization of biomolecules. Moreover, the photochemical reaction can be easily scaled under continuous flow conditions, making it suitable for large-scale applications.