Brønsted base assisted photoredox catalysis: Proton coupled electron transfer for remote C-C bond formations via amidyl radicals

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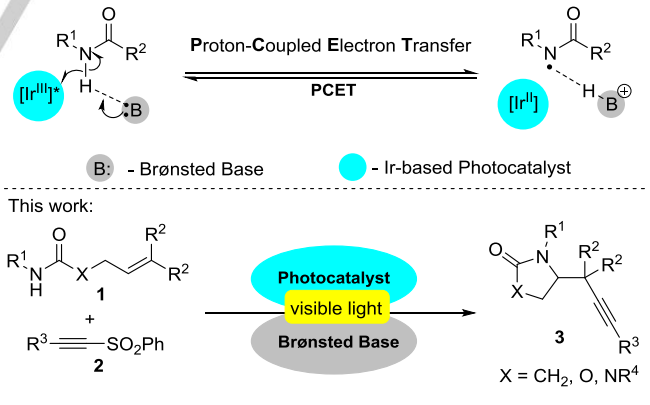
Abstract: The synthesis of alkyne and alkene decorated lactams has been achieved through a photoredox initiated radical cascade reaction. The developed Brønsted base assisted photoredox catalyzed intramolecular 5-exo-trig cyclization/intermolecular radical addition/elimination reaction provides facile access to functionalized γ-lactams, with good functional group tolerance and high yields.

γ-Lactams (pyrrolidin-2-ones) constitute an important class of biologically active compounds which are particularly relevant for the pharmaceutical and medicinal chemistry.[1] The presence of the γ-lactam core structure in a wide range of naturally occurring as well as a multitude of synthetic bioactive molecules, has stimulated the development of improved methods which provide access to this valuable structural motif.[2] Ring expansion of β-lactams, intramolecular cyclizations, cycloaddition reactions and intermolecular cascade or sequential reactions constitute the main general approaches for the synthesis of γ-lactams.[2] Well-established cyclization methods for the synthesis of this important class of *N*-heterocycles include intramolecular cyclization of amino acid derivatives via amide bond formation and intramolecular cyclization of amides either via C-C bond formation or via *N*-alkylation with N-C bond formation. Approaches based on N-C bond formation comprise basically the intramolecular *N*-alkylation of substrates bearing a suitably located leaving group and the addition of amidyl radicals to pendant alkenes. Amidyl radicals[3] have attracted increasing attention, in particular as highly reactive intermediates for the synthesis of *N*-heterocyclic structures. Traditionally, amidyl radicals can be accessed via reductive cleavage of N-X (X = Cl, Br, I), N-N, N-C, N-O or N-S bonds under harsh reaction conditions or via oxidative cleavage of N-H amide bonds in the presence of strong oxidants. Nevertheless, with the recent increasing advances in photoredox catalyzed reactions,[4] a more convenient and practical alternative for the homolytic cleavage of N-H bonds in amides has appeared. Neutral, *N*-centered amidyl radicals have been elegantly obtained through a proton-coupled electron transfer (PCET)[5,6] process in which the substrate is activated through a photoredox catalyst (Scheme 1 top). The amidyl radicals[7-9] obtained thereby have been successfully applied in 1,5-hydrogen atom transfer reactions with subsequent functionalization of the γ-position[7d-f] and in intramolecular cyclization reactions.[7a-c] The cyclization reactions designed to date, involve reduction of the resulting radical intermediate or addition to a radical acceptor. This however inevitably decreases the number of functional groups on the final product that could serve as site for subsequent functionalization. In order to retain the functional group introduced with the radical acceptor, a suitable radical leaving group on the radical acceptor might be a feasible solution. For example, the presence of a sulfonyl group in the acceptor, would lead to the product while releasing a sulfonyl radical,[10,11] which would continue its role for the photocatalyst regeneration,[11h] while retaining the functional group of the reactant (Scheme 1 bottom).

With these considerations in mind, we started our research,[12] aiming at the synthesis of functionalized γ-lactam derivatives. Herein, we report our successful development of Brønsted base assisted visible light photoredox catalyzed intramolecular 5-exo-trig cyclization / intermolecular radical addition / elimination cascade reaction.



Scheme 1. Proton-coupled Electron Transfer (PCET) as promoter for cascade reactions.

Initial experiments were conducted with substrates **1a** and **2a**, catalyst **4a** and $NBu_4(OMe)_2PO_2$ as base in solvents of different polarity (Table 1, entries 1-4) and the desired product **3a** could be obtained in up to 62% when the reaction was performed in toluene (entry 1). However, in all these cases (entries 1-4) side reactions resulted in impurities that were inseparable from the desired product. When switching to DMF as solvent, no reaction occurred (Table 1, entry 5). When trifluorotoluene was used instead, a clean reaction was

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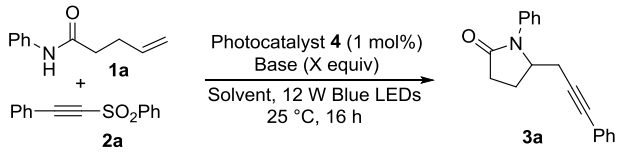
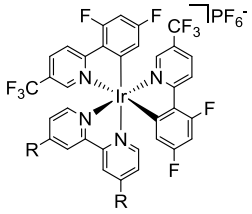
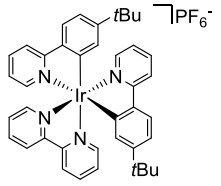
observed, giving the desired product **3a** in 66% yield (Table 1, entry 6). Thus, further optimization was performed in trifluorotoluene as solvent.

Table 1. Optimization of reaction condition.[a]

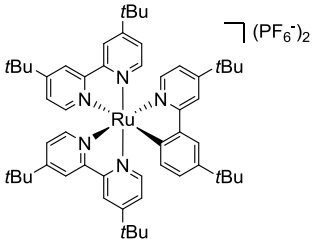




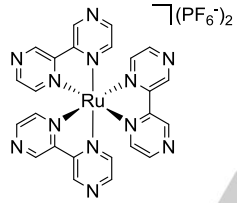
4a: R = H, Ir(dF-CF$_3$-ppy)$_2$(bpy)(PF$_6$)
4b: R = *t*Bu, Ir(dF-CF$_3$-ppy)$_2$(dtbbpy)(PF$_6$)



4c: Ir(dtbppy)$_2$(bpy)(PF$_6$)



4d: Ru(dtbppy)$_3$(PF$_6$)$_2$



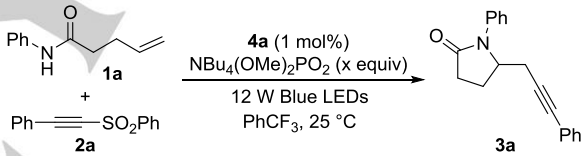
4e: Ru(bpz)$_3$(PF$_6$)$_2$

Entry	Solvent	Base (x equiv.)	PC 4	Yield (%)[b]
1	Toluene	$NBu_4(OMe)_2PO_2$ (0.4)	**4a**	62
2	THF	$NBu_4(OMe)_2PO_2$ (0.4)	**4a**	38
3	DCM	$NBu_4(OMe)_2PO_2$ (0.4)	**4a**	27
4	Acetone	$NBu_4(OMe)_2PO_2$ (0.4)	**4a**	56
5	DMF	$NBu_4(OMe)_2PO_2$ (0.4)	**4a**	0
6	$PhCF_3$	$NBu_4(OMe)_2PO_2$ (0.4)	**4a**	66
7	$PhCF_3$	K_3PO_4 (2.0)	**4a**	0
8	$PhCF_3$	Cs_2CO_3 (2.0)	**4a**	0
9	$PhCF_3$	Pyridine (0.4)	**4a**	0
10	$PhCF_3$	2,6-Lutidine (0.4)	**4a**	0
11	$PhCF_3$	DMAP (0.4)	**4a**	34
12	$PhCF_3$	$NBu_4(OMe)_2PO_2$ (0.4)	**4b**	0
13	$PhCF_3$	$NBu_4(OMe)_2PO_2$ (0.4)	**4c**	0
14	$PhCF_3$	$NBu_4(OMe)_2PO_2$ (0.4)	**4d**	0
15	$PhCF_3$	$NBu_4(OMe)_2PO_2$ (0.4)	**4e**	0

[a] Standard conditions: **1a** (0.1 mmol), **2a** (2 equiv.), photocatalyst (PC) **4** (1 mol%), base (x equiv.), solvent (1 mL), 16 h, under Ar at 25 °C, irradiation with 12 W blue LEDs. [b] NMR yield of **3a** with CH_2Br_2 as internal standard.

Next, the effect of various bases on the reaction outcome was evaluated. Inorganic bases such as K_3PO_4 and Cs_2CO_3 did not give any conversion (Table 1, entries 7-8). The reaction hardly occurred after switching to organic bases, as both pyridine and 2,6-lutidine gave no conversion (Table 1, entries 9-10), and DMAP provided a low yield of 34% (Table 1, entry 11). This confirmed the importance of the Brønsted bases for the homolytic N-H bond activation. Different photocatalysts were evaluated as well in order to improve the yield further. Interestingly, apart from photocatalyst **4a** all other catalysts proved inactive (Table 1, entries 12-15). This could be due to the redox potentials of the photocatalysts in which only photocatalyst **4a** is a perfect match for the intermediary amide/base pair. Subsequently the influence of both reaction time and amount of base on the reaction outcome was evaluated and the results are summarized in Table 2. Decreasing the amount of base from 0.4 to 0.2 equiv., led to a decrease in the reaction efficiency and the product was obtained in a lower yield of 43% (Table 2 entry 2 vs. entry 1). The efficiency increased dramatically upon extending the reaction time from 16 to 24 hours, providing the product in 82% yield (Table 2, entry 3). The yield increased slightly to 88% and 89% with increasing the amount of base to 0.6 and 1.0 equivalent respectively (Table 2, entries 4-5). Furthermore, when 1.1 equiv. of phosphate base was used, the yield increased to 92% (entry 6). The model reaction ran smoothly also on a 0.2 mmol scale, providing the desired product **3a** in 88% yield (entry 7).

Table 2. Effect of base amount and reaction time on reaction efficiency.[a]

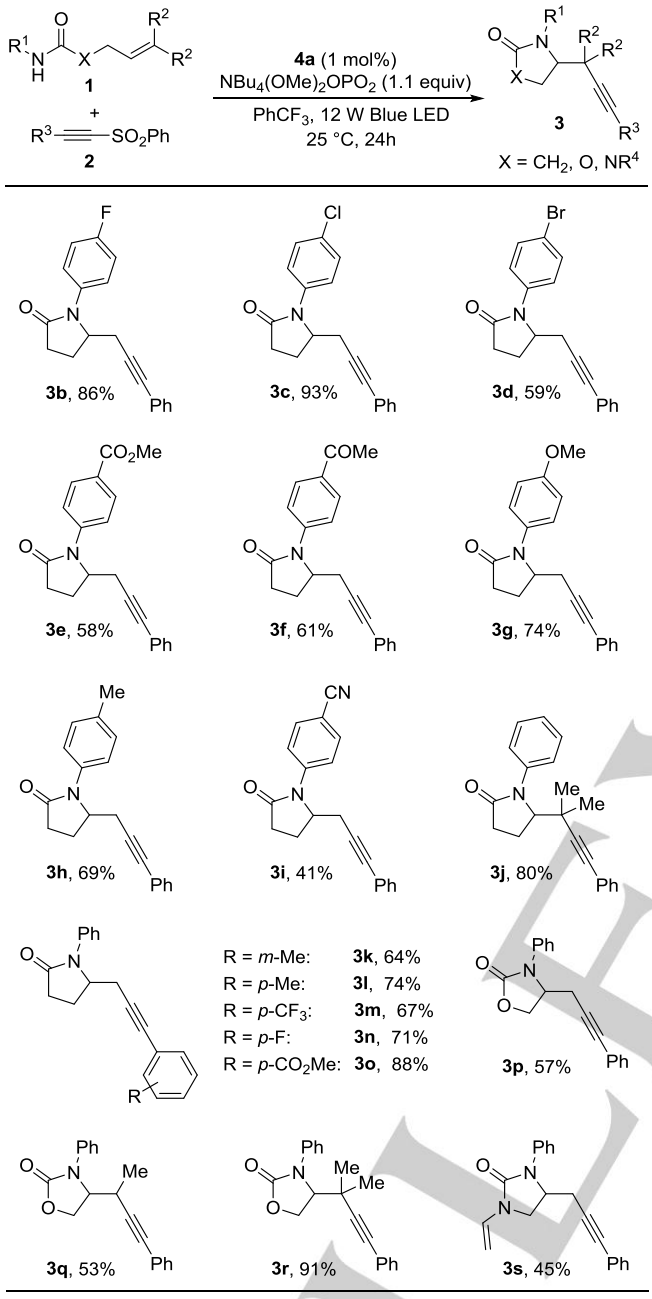


Entry	$NBu_4(OMe)_2PO_2$ (x equiv)	Time (h)	Yield (%)[b]
1	0.4	16	66
2	0.2	16	43
3	0.4	24	82
4	0.6	24	88
5	1.0	24	89
6	1.1	24	92[c]
7[d]	1.1	24	88[c]

[a] Standard conditions: **1a** (0.1 mmol), **2a** (2 equiv) photocatalyst **4a** (1 mol%), $NBu_4OP(O)(OMe)_2$ (x equiv), $PhCF_3$ (1 mL), 24 h, under Ar at 25 °C, irradiation with 12 W blue LEDs. [b] NMR yield of **3a** with CH_2Br_2 as internal standard. [c] Yield after purification. [d] Reaction with 0.2 mmol **1a**.

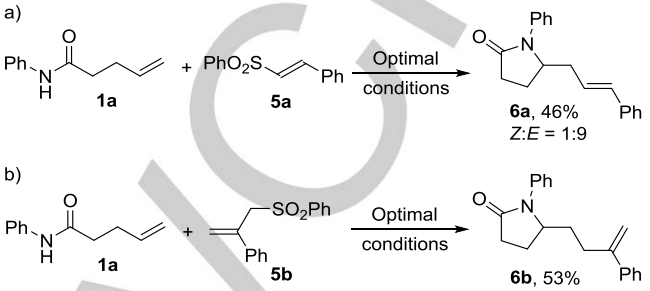
With the optimized conditions in hand, the scope of the reaction with respect to the structure of both substrates was investigated (Table 3). Good yields were obtained for a variety of different substrates **1b-i** upon varying the aryl substituent of the amide group. Various substrates bearing either an electron-withdrawing or an electron-donating group in the *para*-position of the aryl group are tolerated under the reaction conditions. It is noteworthy that functional groups such as Br, ester, ketone and ether could be tolerated under the reaction conditions and gave products also in good yields.

Table 3. Substrate scope.[a],[b]



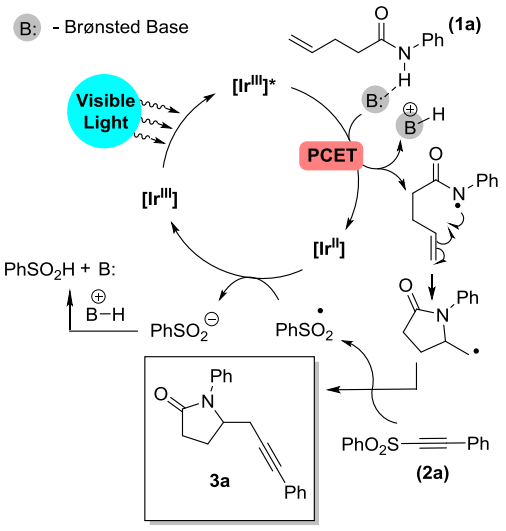
[a] Standard conditions: **1** (0.2 mmol), **2** (2 equiv), photocatalyst (PC) **4a** (1 mol%), $NBu_4OP(O)(OMe)_2$ (1.1 equiv), $PhCF_3$ (2 mL), 24 h, under Ar at 25 °C, irradiation with 12 W blue LEDs. [b] Yield after purification.

The reaction also proceeded well when the terminal alkene was changed to an internal alkene (**1j**), providing the corresponding product **3j** in 80% yield. Good to high yields were obtained also by switching to other alkyne substrates. Alkyne **2b** having a methyl group in the *meta*-position of the aryl group, afforded the product **3k** in 64% yield. For alkynes **2c-f** bearing aromatic groups with substituents in the *para*-position, the yields were high (**3l-o**, 67-88%) for both electron-rich as well as electron-poor radical acceptors. In addition to amide substrates, carbamates proved also to be compatible for such a reaction.[13] As shown in Table 3, good to high yields could be obtained (**3p-r**) for the reaction with terminal and internal alkenes. An urea derivative was also tested and gave the product **3s**. These examples emphasize the applicability of this method to diverse substrates, leading to products with multiple functional groups, which could be further manipulated for different purposes.



Scheme 2. Extension of substrate scope: alkenes as radical acceptor.

Furthermore, the reaction is applicable to alkenes as radical acceptor. When E-alkene **5a** was used, the product **6a** was obtained as a mixture of Z- and E-alkene in a ratio of 9:1, as E/Z alkene isomerism could readily occur under photocatalytic conditions[10] (Scheme 2a). When terminal alkene **5b** was used as radical acceptor instead, the reaction was clean, giving only product **6b** (Scheme 2b). These examples show that alkenes can also be employed as a radical acceptor for this methodology. With regard to the whole substrate scope a wide variety of products bearing different functional groups could be obtained in good to high yields. The method gives access to different lactams, cyclic carbamates and urea derivatives that have not been reported before and which are the potential for further derivatization.



Scheme 3. Proposed mechanism of the visible light photoredox catalyzed intramolecular 5-exo-trig cyclization / intermolecular radical addition / elimination reaction.

Regarding the reaction mechanism, a plausible proposal is depicted in Scheme 3. With the aid of a suitable Brønsted base, the amide **1a** can undergo SET, cleaving the N–H bond homolytically to generate an amidyl radical. Intramolecular addition to the pendant olefin results in the formation of a γ-lactam bearing an alkyl radical. Alkyne **2a** can intercept this radical intermediate to form product **3a** via an addition/elimination mechanism extruding •SO_2Ph. Subsequently, the •SO_2Ph radical can accept one electron from [Ir^{II}], regenerating the catalyst. The resulting phenyl sulfonyl anion ($PhSO_2^-$) is protonated by the $[B\text{-}H]^+$ to yield benzene sulfinic acid and release the free Brønsted base (B:) that can participate in the next catalytic cycle.

In summary, an efficient method for the synthesis of alkyne and alkene decorated lactams by employing a Brønsted base assisted visible light photoredox catalyzed intramolecular 5-exo-trig cyclization/intermolecular radical addition/elimination reaction was developed. The feasibility to retain functional groups on the radical acceptor by introducing a sulfonyl group is successfully proven by the products obtained. The method developed is widely applicable, affording products in good to high yields for a broad range of substrates, with high functional group tolerance starting from readily available amides. This provides the first reported access to these core structures, which will be useful for further functionalization into valuable fine chemicals. Further attempts of exploring such concepts are currently ongoing in our laboratories and will be reported in due course.

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Keywords: photoredox catalysis • Brønsted base • lactam derivatives • sulfonyl radical • PCET

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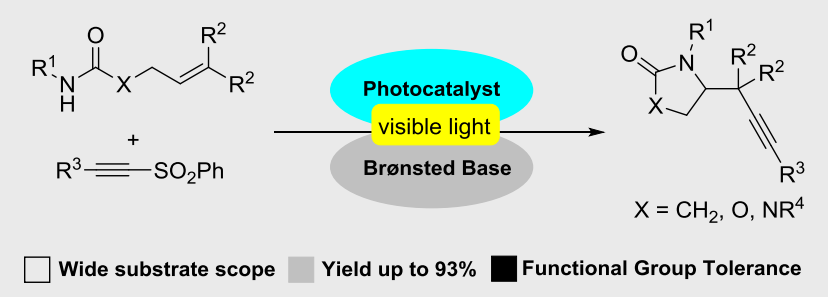

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Brønsted base assisted photoredox catalysis: Proton coupled electron transfer for remote sp^3-alkylations via amidyl radicals

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A Brønsted base assisted photoredox catalyzed intramolecular 5-exo-trig cyclization / intermolecular radical addition / elimination cascade reaction which provides facile access to a broad range of functionalized γ-lactams, with good functional group tolerance and good to high yields, was developed.