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Photocatalytic C–H Functionalization of Nitrogen Heterocycles Mediated by a Redox Active Protecting Group

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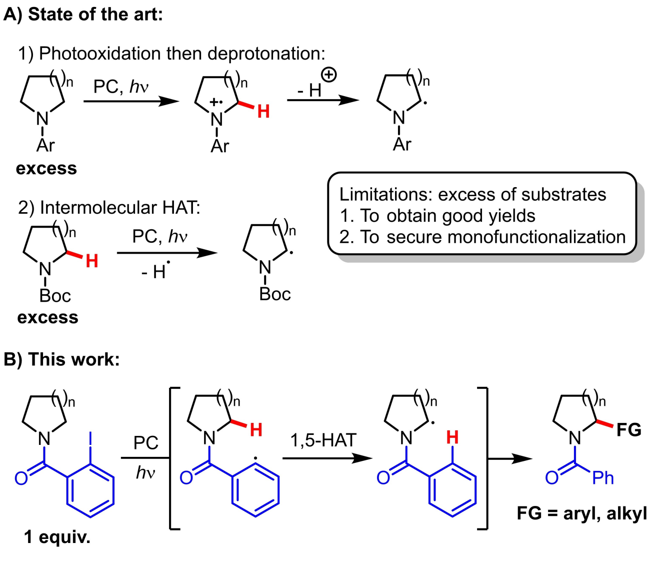
Dedicated to Prof. Burkhard König on the occasion of his 60th birthday; Tanguy Saget was nominated to be part of this collection by EurJOC Board Members Geraldine Masson and Corinne Gosmini.

Herein, we report a photocatalytic strategy for the C–H functionalization of saturated azaheterocycles under mild conditions with only one equivalent of starting material. Our strategy is based on a redox active benzamide protecting group that is activated *via* a halogen-atom transfer (XAT) process to trigger the formation of an α-amino radical. This nucleophilic radical intermediate was then engaged in Giese additions and radical cross couplings to afford C–H alkylated and arylated products.

Introduction

Saturated nitrogen-containing heterocycles are ubiquitous structural motifs in natural products and bioactive compounds.[1] Along this line, a recent study revealed that piperidines, piperazines and pyrrolidines are among the most represented structural motifs within pharmaceuticals approved by the U.S. Food and Drug Administration (FDA).[2] Because of their prevalence, the development of novel methods in heterocyclic chemistry is of paramount importance. In this respect, catalytic strategies targeting the C–H functionalization of azaheterocycles represent an ideal way to obtain a variety of molecularly diverse analogs starting from a single and readily available heterocyclic precursor.[3]

Photoredox catalysis[4] has recently emerged as a powerful tool for the C–H functionalization of organic compounds mediated by low-energy visible light.[5] When applied to azaheterocycles, these reactions lead to α-functionalized derivatives through the formation of nucleophilic α-amino radicals that are mainly obtained *via* two distinct mechanisms: 1) photooxidation of an amine followed by α-deprotonation[6] or 2) intermolecular Hydrogen Atom Transfer (HAT)[7] (Scheme 1A). In both cases, the use of an excess of heterocyclic precursors (typically 3–5 equivalents) is often required in order to obtain useful yields, either because of a poorly efficient intermolecular HAT or to avoid chemoselectivity issues leading to the polyfunctionalization of the substrate on both sites adjacent to the nitrogen atom.[8] This aspect is far from ideal in terms of atom economy and can hamper the purification of the functionalized products or prevent the use of complex/expensive nitrogen heterocycles. To tackle this issue, we investigated a strategy relying on an entropically favored intramolecular HAT[9] enabled by a redox active protecting group and we focused on tertiary amides derived from cheap and readily available 2-iodobenzoic acid (Scheme 1B). Indeed, we reasoned that the generation of an aryl radical resulting from the cleavage of the C–I bond would trigger a 1,5-HAT[10] to



Scheme 1. Photocatalytic α-functionalization of azaheterocycles.

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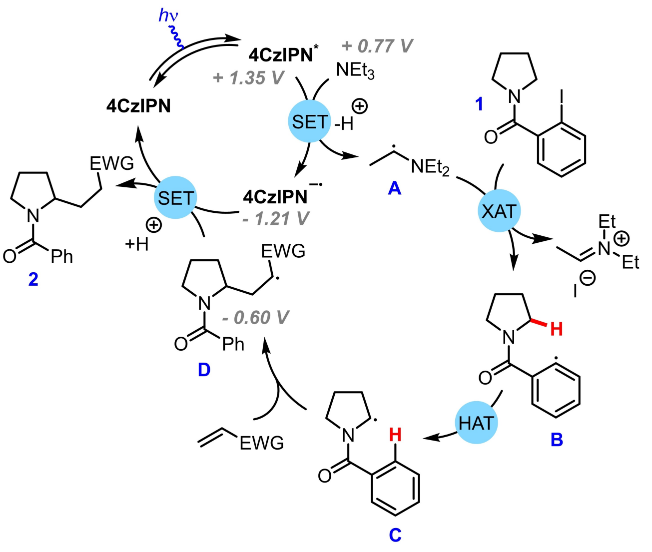
generate the desired α-amino radical that could be engaged in several downstream transformations (Scheme 1B). The obtained products would then be unreactive under the reaction conditions because they are devoid of a C–I bond, thus preventing polyfunctionalization of the substrate. This redox active protecting group strategy has already some precedents in photocatalysis, but so far the cleavage of the C–X bond required either strongly reducing photocatalysts[11] or transition metals,[12] thus restricting the scope of transformations available for the resulting α-amino radical. Herein, we report a complementary approach relying on halogen-atom transfers (XAT)[13] mediated by a readily available organic photocatalyst and enabling the introduction of alkyl and aryl substituents.[14]

The generation of aryl radicals through XAT does not require the use of strongly reducing species as matching redox potential are not relevant anymore. However, XAT-based activation has long been associated with the use of toxic/expensive tin or silicon reagents. Recently, the groups of Doyle and Leonori demonstrated that α-amino radicals derived from trialkylamines are convenient halogen abstractors.[15] Importantly, they allow the facile generation of aryl radicals with common photocatalysts under visible light.[15c] Based on this hypothesis, we investigated photocatalytic XATs for the α-alkylation of saturated azaheterocycles according to the catalytic cycle depicted in Scheme 2. An excited photocatalyst would oxidize a trialkyl amine leading to species **A** after deprotonation, which then could react with **1** and trigger the formation of aryl radical **B** through XAT. Radical **B** would undergo a thermodynamically favored 1,5-HAT enabling the formation of nucleophilic radical **C** that would add to a Michael acceptor to afford **D**. Reduction of **D** by the radical-anion of the photocatalyst would close the photocatalytic cycle affording the alkylated product **2** after proton transfer.



Scheme 2. Proposed catalytic cycle for the C–H alkylation of azaheterocycles.

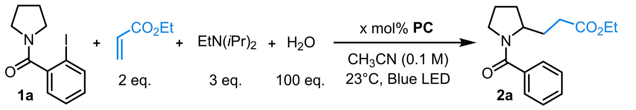
Results and Discussion

To investigate the feasibility of the envisioned reaction, we focused on readily available and versatile donor-acceptor cyanoarene organophotocatalysts[16] that are potent photooxidants whose reducing properties can be finely tuned by simple structural modification. We started our studies with the alkylation of *N*-(*o*-iodobenzoyl)-pyrrolidine **1 a** with ethyl acrylate in the presence of triethylamine ($E_{ox}=+0.77$ V versus SCE),[15c] water and a catalytic amount of **4CzIPN** ($E_{1/2}$ (PC*/PC$^{\bullet-}$)$=+1.35$ V versus SCE).[16b] The reaction proceeds nicely in several solvents (Table S1, entries 1–4), and acetonitrile was selected as the optimal solvent because it led to cleaner reaction mixtures. The addition of water is beneficial for the reaction (Table S1, entries 5–6) but is not mandatory (entry 7) and it can be replaced by a catalytic amount of a carboxylic acid (entry 8). The positive influence of a protic additive could result from the facilitated protonation of the carbanion after the reduction of intermediate **D** ($E_{red}=-0.60$ V versus SCE)[17] by the radical anion of **4CzIPN** ($E_{1/2}$ (PC/PC$^{\bullet-}$)$=-1.21$ V versus SCE).[16b] Importantly, the use of Hünig's base (EtN(iPr)$_2$) instead of triethylamine led to a significantly higher yield (Table 1, entry 1–2). As anticipated, the presence of a trialkyl amine is required for this process and its removal led to full recovery of the starting material (entry 3). Lowering the catalyst loading to 1 mol% was detrimental (entry 4), and other common cyanoarene photocatalysts such as **4DPAIPN** or **3DPA2FBN** proved to be less efficient than **4CzIPN** for this transformation (entries 5–6). Control experiments revealed that both light and the photocatalyst are required to observe the desired reactivity (entry 7–8) and that the reaction can be carried out under air albeit with a slightly reduced yield (entry 9). Of note, lowering the amount of ethyl acrylate or EtN(iPr)$_2$ also led to reduced yields.

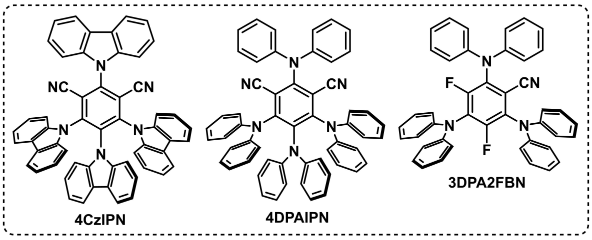
Tanguy Saget carried out his PhD in the group of Prof. Nicolai Cramer at ETH Zürich in the field of enantioselective C–H activation. In 2014, he joined the group of Prof. Barry Trost at Stanford University to work on enantioselective Mannich reactions. He then got trained in organocatalysis with Prof. Jean Rodriguez at Aix-Marseille University and in photocatalysis with Prof. Burkhard König at the university of Regensburg. In 2020, he joined the "Institut de Chimie des Substances Naturelles" at Gif-sur-Yvette as a CNRS researcher to work on the development of catalytic and selective C–H functionalization reactions.

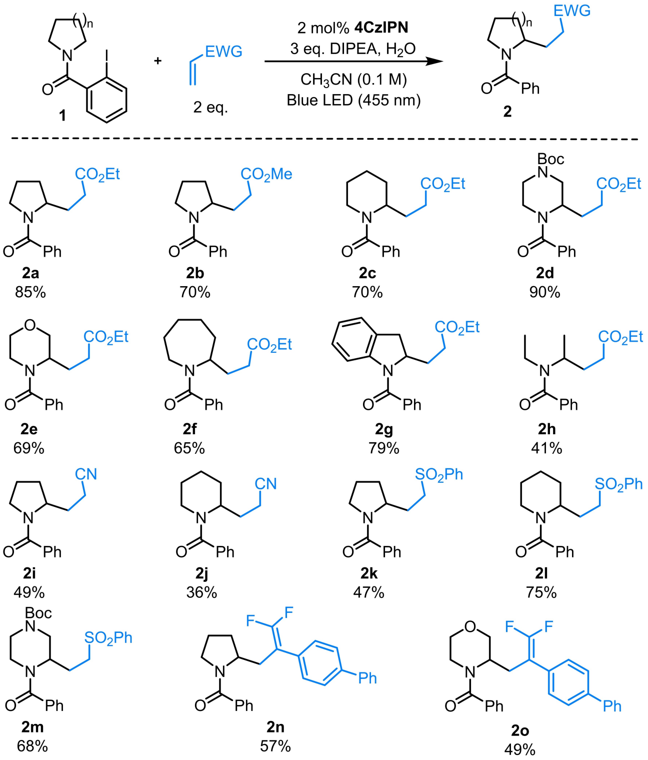
With the optimized conditions (Table 1, entry 9), we then studied the scope of the reaction regarding the heterocycles and the Michael acceptors that can be engaged in our process (Scheme 3). Gratifyingly, a range of azaheterocycles were successfully alkylated in good yields with acrylates (**2 a**–**2 g**). In addition, the alkylation could also be performed with an acyclic substrate (**2 h**). To further study the scope of alkylating partners, a preference was given to the piperidine-, piperazine- and pyrrolidine-motifs as these heterocycles are the most repre-

Table 1. Reaction optimization.



entry	conditions	yield
1	2 mol% **4CzIPN**	85%
2	2 mol% **4CzIPN**, NEt$_3$ instead of EtN(iPr)$_2$	67%
3	2 mol% **4CzIPN**, no EtN(iPr)$_2$	0%
4	1 mol% **4CzIPN**	63%
5	2 mol% **4DPAIPN**	37%
6	2 mol% **3DPA2FBN**	35%
7	no photocatalyst	0%
8	entry 1, no LED	0%
9	entry 1, under air	62%



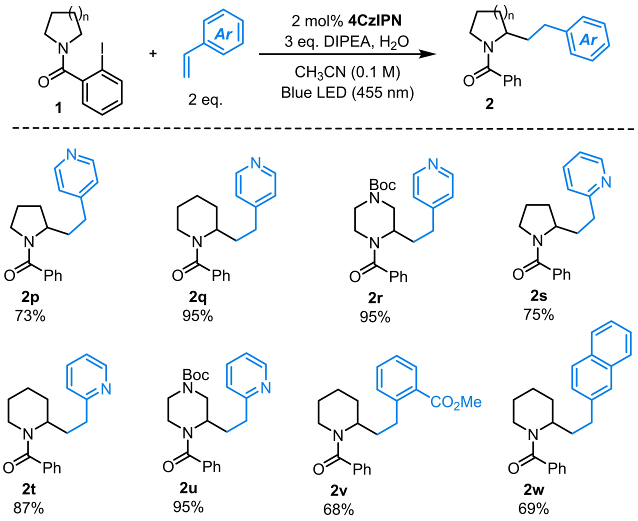


Scheme 3. Scope of the alkylation reaction with Michael acceptors.

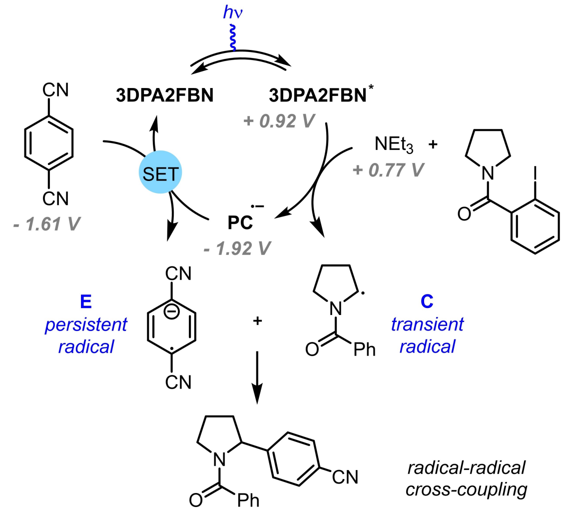
sented within pharmaceuticals.[2] Along this line, we investigated the use of other Michael acceptors such as acrylonitrile and vinyl sulfone that afforded the corresponding alkylated products in useful to good yields (**2i**–**2m**). Interestingly, the use of a trifluoromethyl-substituted acceptor led to the corresponding *gem*-difluoroalkenes (**2n**–**2o**).[18] In this case, the reduction of intermediate **D** (see the catalytic cycle in scheme 2) triggers a fluoride elimination *via* a E1cB type mechanism. Importantly, the *gem*-difluoroalkene motif is a carbonyl bioisostere that is frequently found in agrochemicals and pharmaceuticals.[19]

Styrenes also proved to be successful alkylating reagents (Scheme 4) and particularly styrenes substituted with an electron-poor aromatic such as 2- and 4-vinylpyridines (**2p**–**2u**) and an *ortho*-benzoate derived styrene (**2v**). Of note, a neutral styrene could also be used as exemplified with product **2w**. In this case, an increased catalyst loading of 4 mol% was required to avoid the formation of side-products probably resulting from a kinetically slow reduction of intermediate **D**.

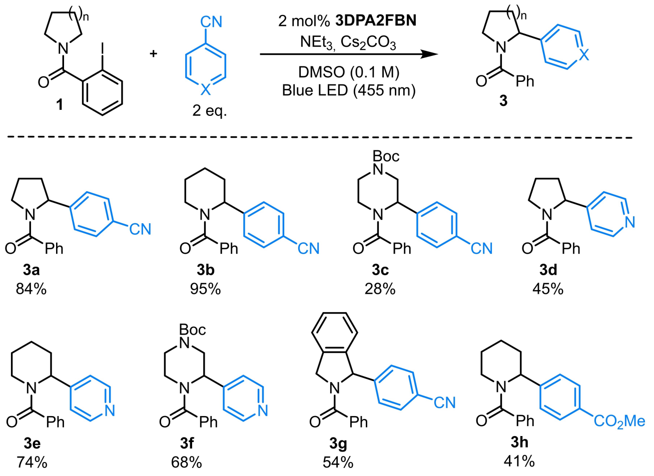
With an efficient C–H alkylation protocol in hand, we then investigated the development of a C–H arylation method. To this purpose, we focused on the use of dicyanoarenes as arylating reagents[20] according to the hypothesis described in Scheme 5. In a similar fashion to the alkylation reaction, photoinduced oxidation of the trialkyl amine triggers the



Scheme 4. Scope of the alkylation reaction with styrenes.



Scheme 5. Proposed catalytic cycle for the C–H arylation with cyanoarenes.



Scheme 6. Scope of the arylation reaction with cyanoarenes.

formation of radical intermediate **C** and the radical anion of the photocatalyst. Thus, the latter could reduce 1,4-dicyanobenzene ($E_{red} = -1.61$ V versus SCE)[21] to produce a persistent radical **E** that could couple with transient radical **C**. This would afford the arylation product after the elimination of cyanide. After some optimization, we found an efficient catalytic system for the arylation of substrate **1a** with 1,4-dicyanobenzene (see the SI for optimization). The reaction proceeds well with **3DPA2FBN** ($E_{1/2}$ (PC/PC$^{\bullet -}$) $= -1.92$ V versus SCE)[16c] as photocatalyst and the addition of an inorganic base such as Cs_2CO_3 was important to obtain high yields.

The scope of the reaction was briefly studied with 1,4-dicyanobenzene or 4-cyanopyridine as arylating reagents (Scheme 6). The corresponding arylated products were obtained in moderate to good yields with several azaheterocyclic partners (**3a**–**3f**). In addition, an isoindoline substrate that was not competent for the alkylation reaction could be arylated in good yield (**3g**). Finally, methyl 4-cyanobenzoate was also successfully used as arylating agent (**3h**).

Conclusions

In conclusion, we reported a photocatalytic strategy for the selective α-mono-functionalization of azaheterocycles as limiting reagents. Our strategy relies on a redox active protecting group that is activated *via* a photo-mediated XAT under blue light irradiation to trigger a 1,5-HAT enabling the efficient generation of the key α-aminoradical intermediate. This intermediate was engaged in Giese reactions to afford α-alkylated products as well as in radical-radical cross-couplings with persistent radicals to give α-arylated products. Overall, this methodology enables an efficient and selective peripheral editing to produce a small library of substituted valuable azaheterocycles that are prevalent in pharmaceuticals.

Experimental Section

A vial equipped with a stirring bar was charged with the corresponding azaheterocycle (0.20 mmol, 1.0 equiv.), a Michael acceptor (0.40 mmol, 2.0 equiv.) and 4CzIPN photocatalyst (3.1 mg, 2.0 mol%). Acetonitrile (2 mL, 0.1 M), DIPEA (105 μL, 3.00 equiv.) and H_2O (200 μL, 100 equiv.) were sequentially added and the vial was sealed. After freeze-pump-thaw degassing, the reaction mixture was vigorously stirred for 16 h in front of a blue LED in a photoreactor equipped with a water-cooling system. The mixture was then diluted with EtOAc (30 mL) and washed with HCl 1 N (×3) and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude was then purified by flash column chromatography on silica gel to afford the corresponding alkylated product.

Supporting Information

Additional references cited within the Supporting Information.[22]

Acknowledgements

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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: azaheterocycles · C–H functionalization · halogen atom transfer · hydrogen atom transfer · photoredox catalysis

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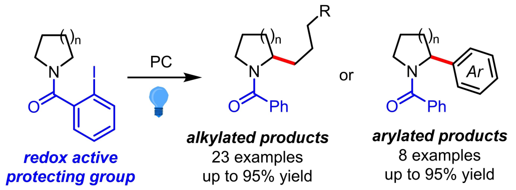

Herein, we report a photocatalytic strategy to efficiently access functionalized azaheterocycles starting from one equivalent of an heterocyclic precursor incorporating a redox active benzamide protecting group. Activation of the protecting group triggered an intramolecular 1,5-HAT leading to α-aminoradical intermediates that were engaged in Giese additions or radical cross couplings to respectively afford alkylated or arylated products.

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Photocatalytic C–H Functionalization of Nitrogen Heterocycles Mediated by a Redox Active Protecting Group