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Photoinduced Decarboxylative Azidation of Cyclic Aminoacids

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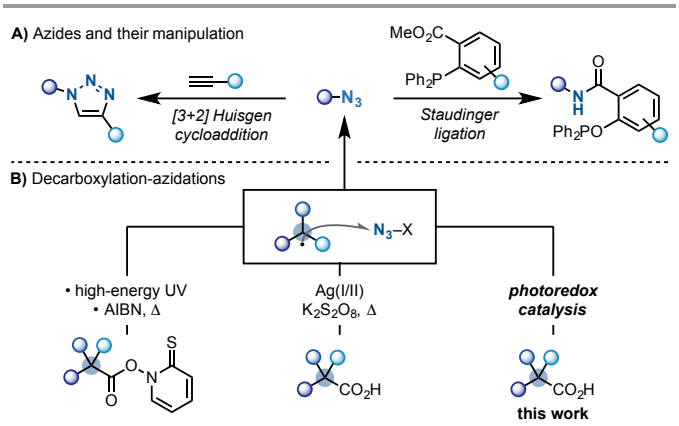
The direct decarboxylative azidation of cyclic α-amino acids has been achieved via visible light-mediated organo-photoredox catalysis. This synthetic strategy allows the simple preparation of azide-contaning building blocks and has been used in the selective modification of *N*-terminal proline residues of two di-peptides.

The azide is among the most important functional groups in organic chemistry, regularly used in research programs aimed at drug discovery, chemical biology and material science.[1] This relevance stems from the ease by which organic azides can be converted into amines and amides (Staudinger reduction/ligation) as well as triazoles (click-chemistry dipolar cycloaddition) (Scheme 1A).[2]

In general, alkyl azides are prepared by nucleophilic substitution of (pseudo)halides[3d], Mitsunobu reaction[3e] on alcohols, or alkene hydro-azidation[3a-c,g,f]. More recently methods for direct sp^3 C–H azidation[4a-b] have been developed using radical strategies based on Mn[4c] and Fe[4d] systems. These approaches have enabled the modification of very complex substrates via the functionalization of the most activated sp^3 C–H bonds (i.e. the functionalization of tertiary centres over secondary). Radical approaches targeting the azidation of specific but non-activated sp^3-carbons have generally relied in the preparation of Barton-type esters and their following decarboxylation-azidation using high-energy UV-light or AIBN at elevated temperature.[5] More recently, Li[6a] and Jiao[6b] have reported the direct oxidative conversion of carboxylic acids into alkyl azides using silver(I/II) catalysts and strong oxidants (e.g. $K_2S_2O_8$) in stoichiometric amounts.

As carboxylic acids represent a very versatile feedstock for the generation of alkyl radicals using photoredox catalysis,[7] we were surprised to realise that no methodology has been developed for their engagement in sp^3-C azidation. The realisation of this transformation would provide high complementarity to current methods both in terms of substrate scope and functional group compatibility given the mild conditions normally associated to visible-light photoredox catalysis. In this report, we describe the development of the first photoredox decarboxylative-azidation process. The methodology described here utilises low cost and readily available organic dyes as photocatalysts and it has been found particularly useful for the modification of cyclic aminoacids and di-peptides.



Scheme 1. A) Most used reactions of organic azides in bio-organic chemistry. B) Decarboxylative azidation procedures involving the generation of alkyl radicals.

Our proposed reaction manifold is based on a classical photoredox reductive quenching cycle where visible light-excitation of a photocatalyst (**PC** → ***PC**) leads to the SET (single electron transfer) oxidation of a carboxylate starting material (**A**) (Scheme 2).[8] Following a fast decarboxylation process, the resulting alkyl radical (**B**) can be intercepted by an N_3-containing SOMOphile (N_3–Y) to give the desired product **C**. Examples of commercially available N_3-SOMOphiles are the Zhdankin reagent[9] (**D**) and aryl sulfonyl azides (**E**, **F**), which have been shown to efficiently transfer the azide group to alkyl radicals.[10] A final SET between the radical generated upon

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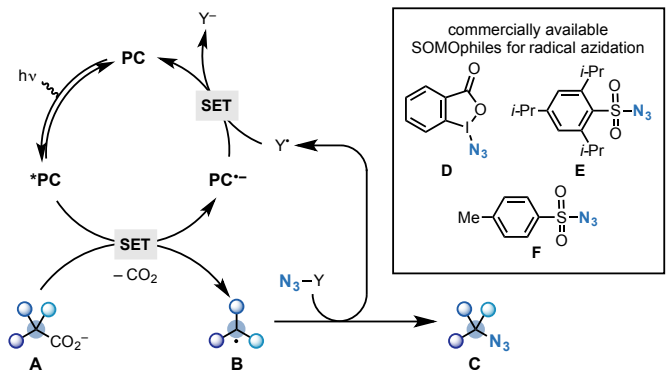
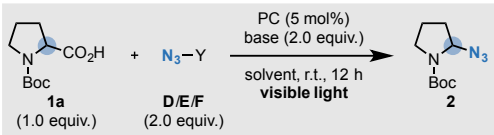
azide-transfer ($Y^{\bullet}$) and the reduced photocatalyst ($PC^{\bullet-}$) would close the photoredox cycle ensuring catalytic activity.



Scheme 2. Proposed photoredox cycle for decarboxylate azidation.

To assess our hypothesis, we started by investigating the reaction of SOMOphiles **D–F** with *N*-Boc-proline **1a** as the carboxylic acid (**1a**-Cs E^{ox} = +0.95 V vs SCE in CH_3CN) and several photocatalysts. At the outset we decided to restrict our photocatalyst screening to organic dyes as they are considerably less expensive and commercially available on larger scale.[11] As illustrated in Scheme 3, we were pleased to find out that using **E** as the SOMOphile, rhodamine 6G ($*E^{red}$ = +1.18 V vs SCE in CH_3CN)[12] as the photocatalyst and K_2CO_3 as the base in DCE under green LEDs irradiation, **2** was obtained in a promising 36% yield (entry 1).



Entry	PC	Base	N_3–Y	solvent	light	yield (%)
1	rhodamine 6G	K_2CO_3	**E**	DCE	green LEDs	36
2	rhodamine 6G	$NaHCO_3$	**E**	DCE	green LEDs	51
3	rhodamine 6G	$CsHCO_3$	**E**	DCE	green LEDs	55
4	rhodamine 6G	CsOBz	**E**	DCE	green LEDs	90
5	rhodamine 6G	TMG	**E**	DCE	green LEDs	85
6	rhodamine 6G	CsOBz	**F**	DCE	green LEDs	50
7	rhodamine 6G	CsOBz	**D**	DCE	green LEDs	15
8	rhodamine 6G	CsOBz	**E**	CH_2Cl_2	green LEDs	51
9	rhodamine 6G	CsOBz	**E**	CH_3CN	green LEDs	54
10	rhodamine 6G	CsOBz	**E**	THF	green LEDs	72
11	rhodamine 6G	CsOBz	**E**	DMF	green LEDs	30
12	methylene blue	CsOBz	**E**	DCE	blue LEDs	32
13	riboflavine	CsOBz	**E**	DCE	blue LEDs	39
14	mesityl acridinium	CsOBz	**E**	DCE	blue LEDs	11
15	4CzIPN	CsOBz	**E**	DCE	blue LEDs	34
16	eosin Y	CsOBz	**E**	DCE	green LEDs	15
17	–	CsOBz	**E**	DCE	green LEDs	–
18	rhodamine 6G	–	**E**	DCE	green LEDs	–
19	rhodamine 6G	CsOBz	**E**	DCE	–	–

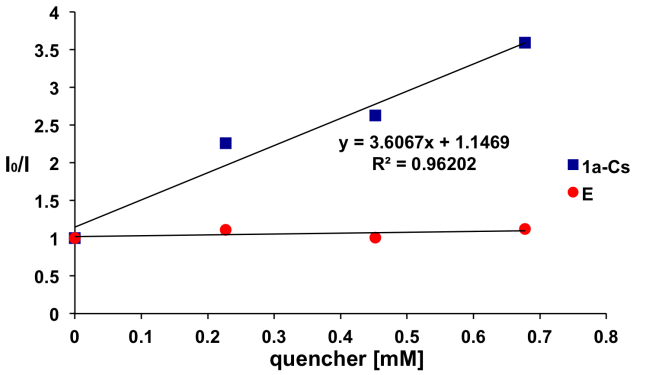
Scheme 3. Optimization of the decarboxylative azidation using **1**. B) Luminescence-quenching experiments.

We then screened several bases and found that by using the more soluble CsOBz and tetramethyl guanidine (TMG), the yield was improved to 90% and 85% respectively (entries 2-5). Under these conditions the other azidating reagents **F** (entry 6) and **D** (entry 7) provided **2** in considerably lower yields. Other solvents (entries 8–11) and commonly used organo-photocatalysts (entries 12-16) were evaluated but they generally provided **2** with lower efficiency.

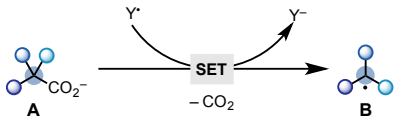
Control experiments confirmed the requirement for light, photocatalyst and base (entries 17–19).

Our mechanistic proposal is further supported by luminescence-quenching studies (Stern-Volmer analysis) that revealed **1**-Cs (k_q = 2.1 10^9 M^{-1} s^{-1}) and not **E** to quench the excited state of rhodamine 6G (Scheme 4A). Unfortunately, quantum yield measurement has not been possible due to the lack of green-light actinometers. As a result, we cannot exclude the presence of radical chain propagations resulting, for example, by the direct oxidation of **A** by $Y^{\bullet}$ (Scheme 4B).

A) Stern-Volmer analysis



B) Possibility for radical chain propagation

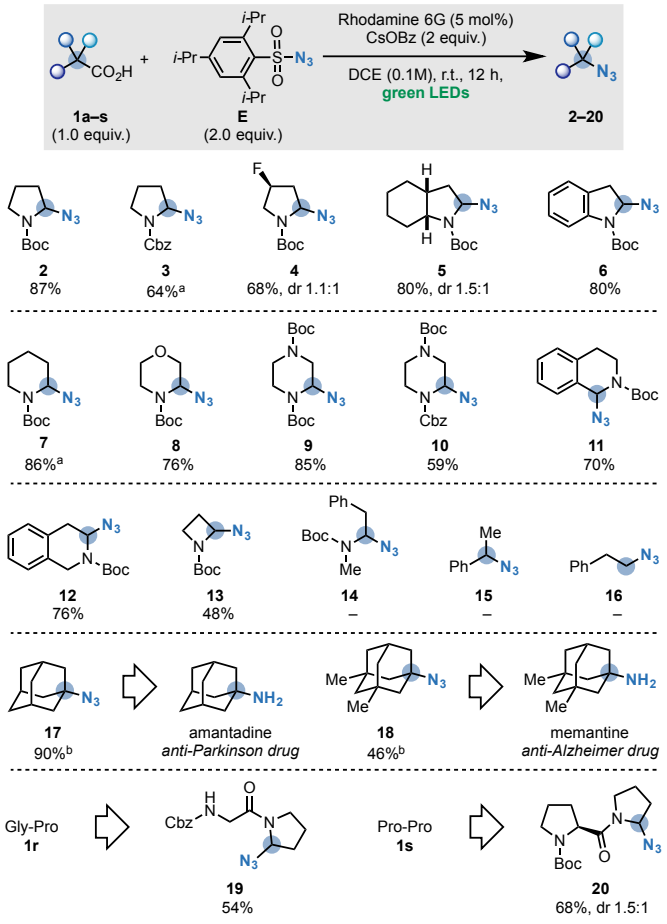


Scheme 4. Luminescence-quenching experiments.

With the optimised reaction conditions in hand, we evaluated the scope of the process (Scheme 5). Replacing the *N*-Boc protecting group with the *N*-Cbz on proline was possible and we obtained **3** in good yield. Fluorinated pyrrolidines are common motifs in drugs for the treatment of diabetes (e.g. bisegliptin)[13] and we successfully prepared C-2-azidated building block **4** in good yield but low dr. The octahydroindole-2-carboxylic acid core is found in many ACE inhibitors like perindopril and was used (following *N*-Boc protection) to access **5** in high yield. The chemistry could also be used to obtaine C-2 azidated-*N*-Boc-indoline **6**. Six-membered-ring *N*-Boc-aminoacids were evaluated next and we successfully engaged pipecolic acid (giving **7**) as well as substrates based on morpholine (**8**) and protected piperazine (**9** and **10**) heterocycles. Decarboxylative-azidation of tetrahydro-isoquinoline carboxylic acids was possible and enabled the preparation of building blocks functionalised at C-1 (**11**) and C-3 (**12**) positions. Saturated four-membered ring *N*-heterocycles

are frequently used in medicinal chemistry programmes and we successfully applied the reaction to the C-2-azidation of *N*-Boc-azetidine (**13**).[14] Extension of this methodology to non-cyclic aminoacids is a current limitation of the protocol and despite extensive re-optimization of the process we did not manage to achieve the decarboxylative-azidation of, for example, protected phenylalanine (**14**).

Secondary and primary carboxylic acids are sometimes difficult to engage in oxidative decarboxylative protocols and cannot be used as starting materials in this strategy. Tertiary substrates however are amenable as demonstrated by the formation of **17** and **18** which can be used to access derivatives of amantadine and memantidine, two blockbuster drugs for the treatment of the Parkinson and Alzheimer diseases respectively. In this case however, optimum yields were obtained using mesityl acridinium[15] as the photocatalyst.



Scheme 5. Scope of the reaction. [a] TMG was used as the base. [b] $MesAcrBF_4$ was used as the photocatalyst.

To showcase the utility of this methodology we evaluated its applicability in the late-stage modification of terminal proline residues embedded in peptide structures.[13] Pleasingly, commercially available Cbz-Gly-Pro-OH (**1r**) and Boc-Pro-Pro-OH (**1s**) dipeptides were competent substrate and provided the azidated products **19** and **20** in good yields but low dr in the case of **20**. To the best of our knowledge this is the first example of late-stage modification of peptides by decarboxylation-azidation.

Conclusions

In conclusion, we have developed the first visible-light mediated process that enables the preparation of organic azides by oxidative decarboxylation. The methodology has been successfully applied to the synthesis of several novel α-*N*-Boc-amino-azides building blocks and the late-stage functionalization of dipeptides.

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Conflicts of interest

There are no conflicts to declare.

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