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Chichibabin pyridinium synthesis *via* oxidative decarboxylation of photoexcited α-enamine acids†

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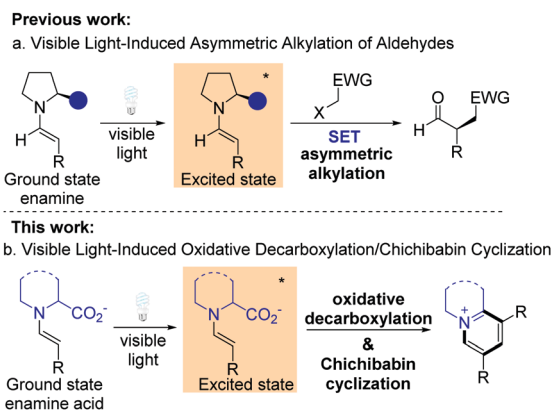
A visible light-induced decarboxylative Chichibabin pyridinium synthesis between α-amino acids and aldehydes was developed. When the *in situ* generated α-enamine acids were photoexcited, they were oxidized by aerobic oxygen to give radical cation species. After decarboxylation and further oxidation, the generated iminium undergoes Chichibabin cyclization to afford pyridiniums. This photochemical protocol enables the synthesis of various tetra-substituted pyridiniums and related natural products in one-step.

The carbon–carbon bond formation through oxidative decarboxylation offers a concise strategy for direct transformation of structurally diverse carboxylic acids to various compounds. Significant developments of decarboxylation of Csp^1- and Csp^2-linked carboxylic acids have been achieved in the last decade to access various valuable product classes along with multifaceted reaction pathways.[1] In the meantime, the direct oxidative decarboxylation of Csp^3-linked carboxylic acids was found to be more challenging and mostly relied on strong oxidants, such as potassium persulfat.[2]

α-Amino acids as a specific kind of Csp^3-linked carboxylic group adjacent to an amine group, can undergo decarboxylative 1,3-dipolar cyclization, or 1,5- and 1,7-electrocyclizations at high temperature *via* azomethine ylide intermediates by formation with aldehydes.[3] They also enable decarboxylative electrophilic coupling with various nucleophiles,[4] or oxidative decarboxylative cyclization with oxidants at high temperature.[5] The photochemical strategy enables decarboxylation of α-amino acids under mild conditions. The directly oxidative decarboxylation of α-amino acids by a photocatalyst was achieved to couple with a broad scope of cyanoarenes or Michael acceptors.[6] On combination of the photocatalyst with a nickel catalyst, the amino acids were able to couple with different aryl halides or sulfonates into valuable benzylic amines, or with vinyl halides for decarboxylative olefination.[7]

Recently, Melchiorre and co-workers reported that electron-rich enamines, which were *in situ* generated by condensation of amines and aldehydes in the ground state, could reduce organic halides *via* visible light induced single electron transfer (SET) to realize the asymmetric alkylation of aldehydes (Scheme 1a).[8] This novel photochemical strategy unveiled the ability of enamines to act as photosensitizers, which provide new reactivity frameworks for designing visible light-driven transformation. Here we reported that the photoexcited enamines derived from α-amino acids could undergo an oxidative decarboxylation followed by a Chichibabin cyclization to afford highly substituted pyridiniums (Scheme 1b).

Our initial investigations were conducted by irradiation of the mixture of proline **1a** and phenylacetaldehyde **2a** in $CHCl_3$ using household CFL bulbs as the light source. The pyridinium **3a** was only obtained in 5% yield, while the Aldol condensation product was obtained as the main by-product (Table 1, entry 1). We found that when NaOTf was added as an additive, the



Scheme 1 Photochemical activation of an *in situ* generated enamine: (a) visible light-induced asymmetric alkylation of aldehydes; and (b) visible light-induced decarboxylative Chichibabin pyridine synthesis.

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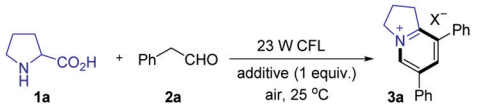
Table 1 Optimization of photochemical decarboxylative Chichibabin pyridine synthesis



Entry	Amine	Additive	Solvent	Light	Yield[a] (%)
1	**1a**	None	$CHCl_3$	23 W CFL	5
2	**1a**	NaOTf	$CHCl_3$	23 W CFL	53
3	**1a**	$NaBF_4$	$CHCl_3$	23 W CFL	47
4	**1a**	NaI	$CHCl_3$	23 W CFL	83
5	**1a**	KI	$CHCl_3$	23 W CFL	75
6	**1a**	NaI	MeOH	23 W CFL	15
7	**1a**	NaI	PhMe	23 W CFL	38
8	**1a**	NaI	DMSO	23 W CFL	59
9[b]	**1a**	NaI	$CHCl_3$	In dark	0
10[c]	**1a**	NaI	$CHCl_3$	23 W CFL	0
11	Pyrrolidine	NaI	$CHCl_3$	23 W CFL	0
12	**1a**	NaI	$CHCl_3$	Blue LEDs	78

[a] Reported yields were based on **1a** and determined by chromatography isolation. [b] Reaction was conducted in the dark on reflux. [c] Reaction was conducted under argon.

pyridinium **3a** was isolated in 53% yield (entry 2). Moreover, $NaBF_4$ was also found as a practicable additive to afford product **3a** in 47% yield. Further optimization identified that NaI was the most effective additive to inhibit the formation of the Aldol condensation product and the visible light-induced decarboxylative cyclization product **3a** was isolated in 83% yield (entry 4). A lower yield was obtained when KI was utilized as the salt additive. Other salts (*i.e.* NaBr, NaCl, or KBr) were also evaluated but only a trace amount of the cyclization product was isolated. The effects of salt additives on inhibition of the competitive Aldol condensation were further confirmed by conducting the reaction in the dark. As shown in Fig. S13 (see the ESI†), the formation of the Aldol product was significantly decreased when NaOTf, $NaBF_4$, or NaI was added to the reaction mixture. Different solvents (for example MeOH, PhMe, or DMSO, entries 6–8) were also screened but resulted in poorer conversions. The photochemical nature of this decarboxylation was incontestably proved as essentially no pyridinium product was detected when the controlled experiments were performed in the dark even on reflux (entry 9). Since the photoreaction was an oxidative decarboxylative process, air as an oxidant was necessary for this reaction, otherwise, no product was observed under argon (entry 10). We used pyrrolidine instead of proline to conduct the reaction and confirmed the indispensability of the carboxylic acid moiety of proline for the photochemical decarboxylative cyclization (entry 11). Changing the light source from CFL to a blue LED also afforded the pyridinium **3a** in 78% yield (entry 12). A gram scale reaction was conducted under the optimal conditions and the product **3a** was obtained in 69% yield.

To probe the possible photochemical mechanism, the UV-vis experiments were conducted. A significant optical absorption was observed in the visible light spectrum after mixture of proline with phenylacetaldehyde in DMSO (Fig. 1a). The same optical absorption (two curves completely overlapped) was also observed for the pre-prepared enamine **I** from

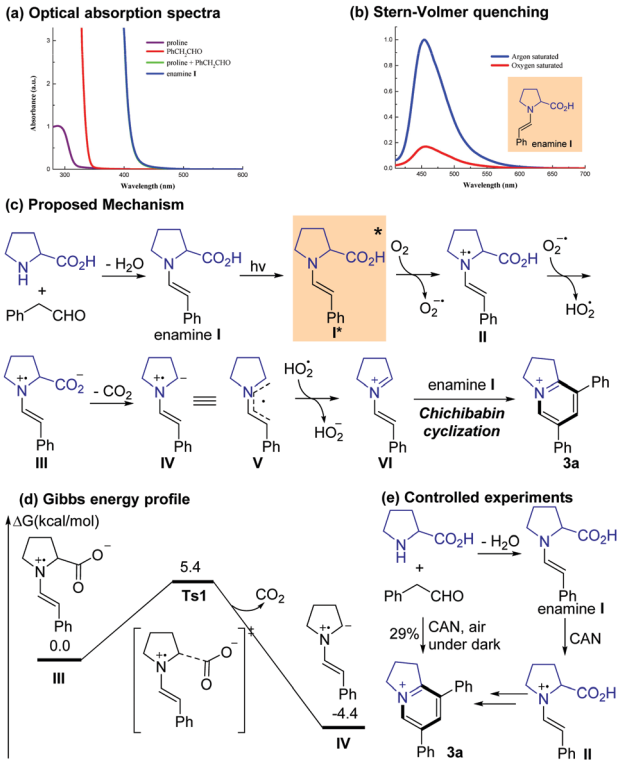


Fig. 1 (a) Optical absorption spectra recorded in DMSO in 1 cm path quartz cuvettes. (b) Quenching of the enamine **I** emission in the presence of oxygen. (c) Proposed mechanism. (d) Gibbs energy profile of the decarboxylation reaction. (e) Controlled experiments by oxidation of enamine with CAN.

proline and phenylacetaldehyde, which verified that the *in situ* generated enamine was responsible for the visible light absorption. The Stern–Volmer quenching studies showed that the excited state of enamine **I** was efficiently quenched by oxygen, revealing that the single electron transfer (SET) process was between the photoexcited enamine **I** and oxygen (Fig. 1b). In addition, the thermodynamic feasibility of the photo-induced SET was analyzed by the oxidation–reduction potentials. The ground-state potential E(**II**/**I**) was determined to be 0.60 V *vs.* SCE in DMSO. Therefore, the redox potential of the excited enamine **I*** was calculated to be −2.11 V at 450 nm (*vs.* SCE, see the ESI,† for details).[8a,9]

On the basis of these results, a proposed mechanism is depicted in Fig. 1c. The *in situ* generated enamine **I** reaches its electronically excited state **I*** under visible light irradiation. Then a single electron transfer between excited state **I*** and molecular oxygen occurs, as suggested by the quenching experiment, to afford radical cation **II**. After deprotonation, the radical **III** undergoes a decarboxylation to give radical **IV**. DFT calculations suggest that the activation free energy from this species is merely 5.4 kcal mol^{-1}, indicating a very fast process (Fig. 1d). The radical **IV**, which is a resonance structure of **V**, is further oxidized by the hydroperoxyl radical to yield the iminium **VI**. Then the iminium **VI** undergoes a Chichibabin pyridine synthesis[10] with another molecule of enamine **I** to furnish the compound **3a**. To verify that the photochemical

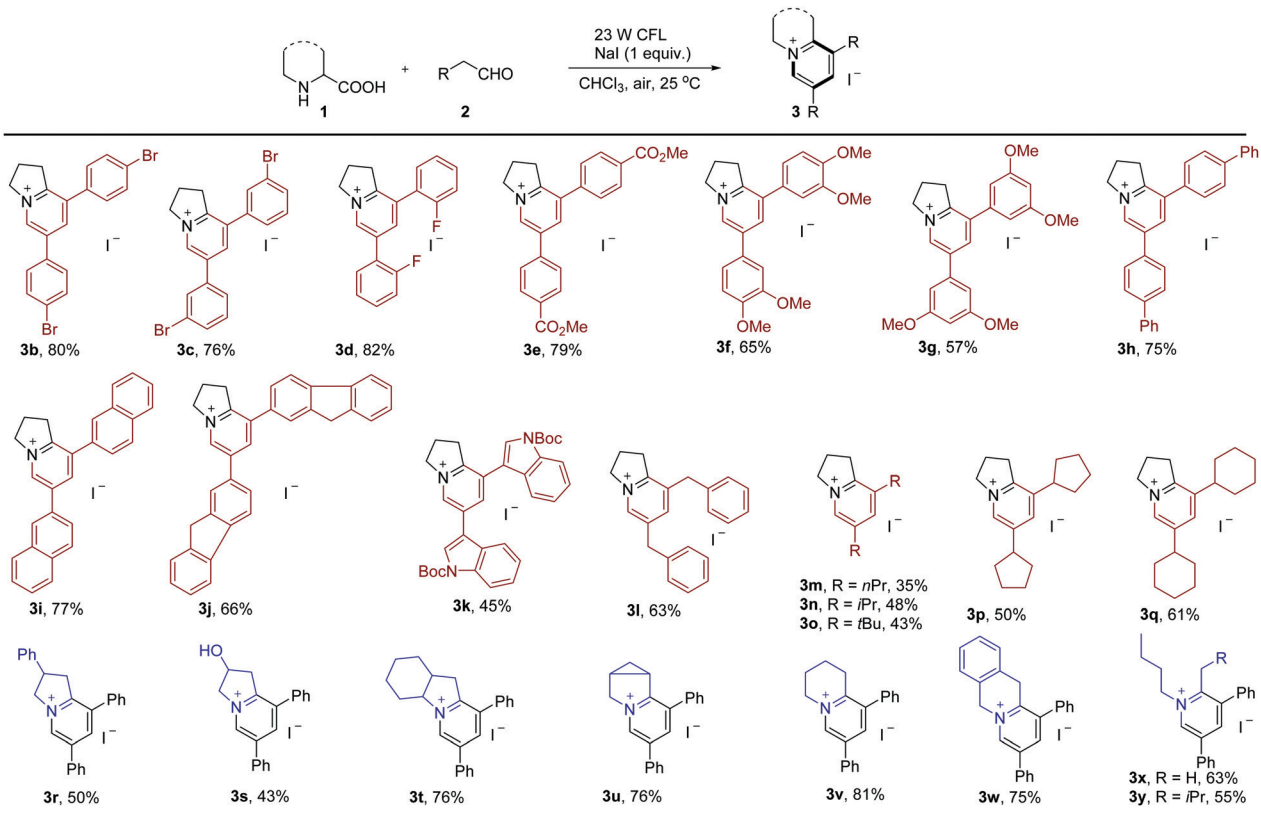
generation of radical cation **II** is the key step for the pyridinium formation, an alternative protocol by oxidation with CAN was performed.[11] As expected, the corresponding pyridinium **3a** was afforded in 29% yield (Fig. 1e).

With the optimized conditions established, we then evaluated the synthetic potential of the photochemical oxidative decarboxylation/Chichibabin pyridine synthesis strategy by varying the structures of α-amino acids and aldehydes. Different electron-withdrawing substitution patterns were observed at the aromatic moiety on the phenyl ring (Schemes 2a, **3b–3e**). The presence of electron-donating substituents on the aromatic ring somewhat lowered the reactivity (**3f** and **3g**). Biphenyl or fused aryls of aldehydes were well tolerated, regardless of their position, and ethylal also underwent the decarboxylative 1,6-annulation in good yields (**3h–3j**). Indole-substituted pyridinium **3k** was also smoothly afforded in receivable yield through this photochemical Chichibabin cyclization. The reactivity of different aliphatic aldehydes with proline was also examined (Scheme 2b). Owing to the electron donating abilities of the alkyl chain, only moderate yields were obtained for aliphatic aldehydes (**3l–3q**). Remarkably, bulky substitutions, even the highly hindered 3,3-dimethylbutyraldehyde, were well tolerated and afforded the product **3o** in 43% yield.

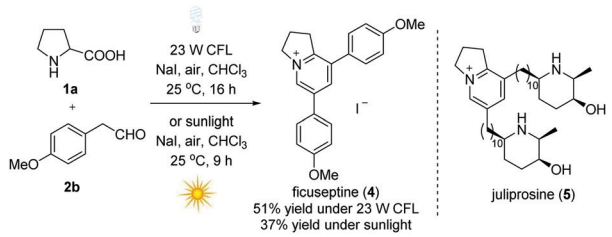
The scope of the α-amino acids to demonstrate the generality of the photochemical decarboxylative annulation was also explored (Scheme 2c). Both the phenyl and hydroxyl proline derivatives were competent substrates, thus enabling the generation of products **3r** and **3s**. The utilization of fused-ring proline derivatives resulted in the tricyclic pyridinium salts **3t** and **3u** in good yields. Similarly, the six-membered pipecolic acids were also the ideal substrates for the annulation (**3v** and **3w**). After the modification of the non-cyclic α-amino acids by alkylation, for example the butylated alanine or leucine, the corresponding tetra-substituted pyridiniums **3x** and **3y** were afforded in moderate yields.

Several tetra-substituted pyridiniums were also identified from natural resources. Ficuseptine **4** was isolated from the leaves of *Ficus septica* with significant antibacterial and antifungal activity.[12] Juliprosine **5** was discovered from *Prosopis juliflora* by Hesse and co-workers.[13] We postulated that these natural products might be directly produced from proline and aldehyde *via* photochemical Chichibabin pyridinium synthesis under sunshine irradiation and non-enzymes were involved in the biosynthesis. To confirm our hypothesis, a mixture of proline and *p*-anisylacetaldehyde was irradiated under sunshine and the ficuseptine **4** was harvested in 37% yield after 9 h (Scheme 3). These interesting results showed that some of the natural products might be produced by photochemical reactions instead of by enzymatic catalysis.

In conclusion, we have probed and shown that the photochemical activity of an *in situ* generated electron-rich enamine enables oxidative decarboxylation under irradiation by household CFL bulbs at ambient temperature. The salient feature of the strategy involves the formation of three new bonds



Scheme 2 Evaluation of the scope of the visible light-induced decarboxylative Chichibabin pyridine synthesis.



Scheme 3 Visible light-induced oxidative decarboxylative Chichibabin pyridinium synthesis of ficuseptine.

(one C–N and two C–C bonds) by a cascade visible light-induced decarboxylative Chichibabin pyridine synthesis and provides a straightforward method to prepare highly functionalized pyridiniums.

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Conflicts of interest

There are no conflicts to declare.

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