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Iminyl-Radicals via Oxidation of α-Imino-oxy Acids: Photoredox-Neutral Alkene Carboimination for the Synthesis of Pyrrolines

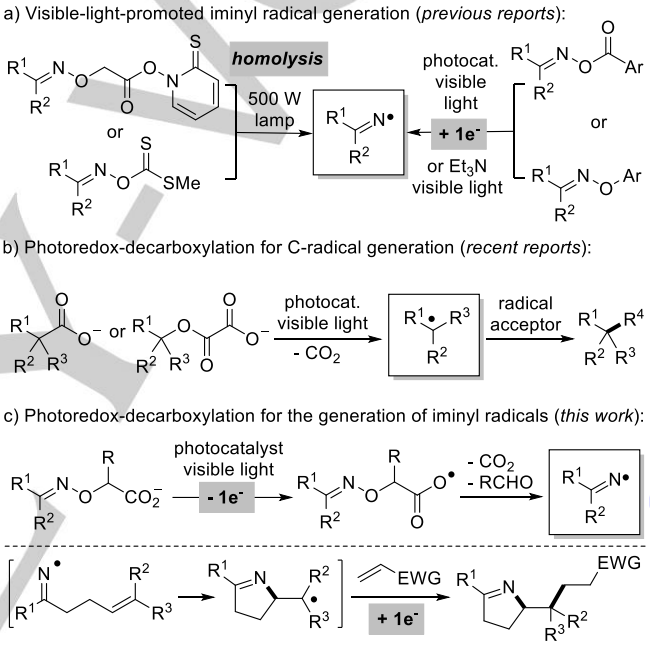
Heng Jiang and Armido Studer*

Dedication ((optional))

Abstract: The visible-light-promoted decarboxylation of α-imino-oxy propionic acids for the generation of iminyl radicals has been accomplished through the use of $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ as a photoredox catalyst. Different from visible-light promoted homolysis and single-electron-reduction of oxime derivatives, this strategy provides a novel catalytic cycle for alkene carboimination through a sequence comprising N-radical generation, iminyl radical cyclization, intermolecular conjugate addition to a Michael acceptor, and single electron reduction to afford various pyrroline derivatives in an overall redox-neutral process. The indolizidine alkaloid skeleton could be easily constructed from a pyrroline derivative prepared by this synthetic method.

Iminyl radicals are valuable reactive intermediates that can be used for the construction of various heterocycles.[1] They can be generated from oxime derivatives but often harsh conditions such as UV irradiation or high temperature[2] are required. Generation of iminyl radicals using visible light would enlarge the synthetic value of these N-radicals.[3] Along these lines, visible-light induced homolysis of thiohydroxamic esters or ketoxime xanthates have been achieved (Scheme1, a, left).[4] Recently, there has been progress using the photoredox strategy to generate iminyl radicals through single electron reduction of oxime derivatives (Scheme 1, a, right).[5],[6] However, the photoredox approach to generate iminyl radicals *via* single-electron-oxidation of oxime derivatives has not been reported to date.

Photoredox-decarboxylation to oxidatively generate C-radicals from carboxylic acids or oxalates has been investigated by several groups (Scheme 1, b)[7] and cascades comprising C-C,[7a-7k] C-N,[7l] C-X,[7m] C-S,[7n] C-B,[7o] C-F[7p],[7q] and C-H[7r],[7s] bond formation have been developed. We envisioned that iminyl radicals should also be accessible by the photoredox-decarboxylation strategy form readily available α-imino-oxy acids (Scheme1, c). This proposal was further supported by the known decarboxylation of α-imino-oxy acids to iminyl radicals using stoichiometric $K_2S_2O_8$, where, however the strongly oxidizing and harsh conditions restrict its applicability and practicability.[8] In our suggested photoredox-decarboxylation, single electron transfer (SET) oxidation of an α-imino-oxy acid should lead to the corresponding carboxyl radical that upon sequential CO_2 and aldehyde fragmentation should give an iminyl radical. Radical cylization will allow constructing N-heterocycles. The photoredox-strategy demands a SET reduction step in the cascade and we suggested to trap the cyclized C-radical with a Michael acceptor where the adduct radical should be readily SET reduced.[9] The overall sequence is redox-neutral and an additional radical reducing reagent is not required, further increasing economy of the suggested cascade.



Scheme 1. Visible-light-promoted iminyl radical generation.

We chose α-imino-oxy acetic acid **1a** as the model substrate in combination with methyl acrylate (**2a**) as the radical acceptor. **1a** is readily prepared from the corresponding ketone by oxime ether formation (see Supporting Information). Pleasingly, blue LED light irradiation of a DCE solution containing **1a**, **2a**, $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ (**A**, 1 mol%) as a photocatalyst and K_3PO_4 as a base for 16 h afforded the desired pyrroline **3a** in 31 yield (Table 1, entry 1). The use of other potassium or sodium salts such as K_2CO_3, KOAc, NaOAc, and $NaHCO_3$ provided worse results (Table 1, entries 2-5). However, with cesium salts yield further improved and CsF afforded **3a** in 56% yield (Table 1, entries 6-8). Other photoredox catalysts such as $Ir(ppy)_2(dtbbpy)PF_6$ (**B**), $Ru(bpy)_3(PF6)_2$ (**C**) and acridinium (**D**) did not catalyze this transformation (Table 1, entries 9-11). Next, the R-substituent of the acid was varied and with 2-imino-oxy propionic acid **2b** (R = Me), pyrroline **3a** was obtained in 79% yield (Table 1, entry 12). The improved efficiency is likely caused by the acceleration of the iminyl radical generation (faster aldehyde expulsion). 2-Imino-oxy phenylacetic acid **2c** (R = Ph) provided a slightly worse result (Table 1, entry 13). In control

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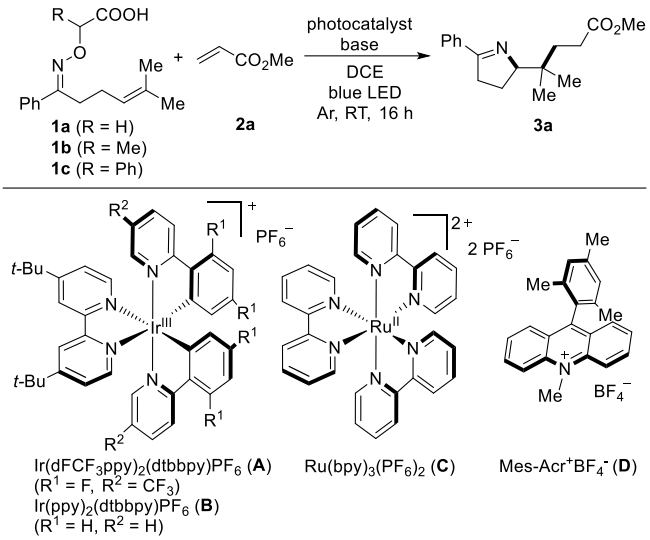
experiments, product **3a** was not formed in the absence of either photocatalyst or CsF (Table 1, entries 14, 15) and this cascade did not proceed in the dark (Table 1, entry 16).

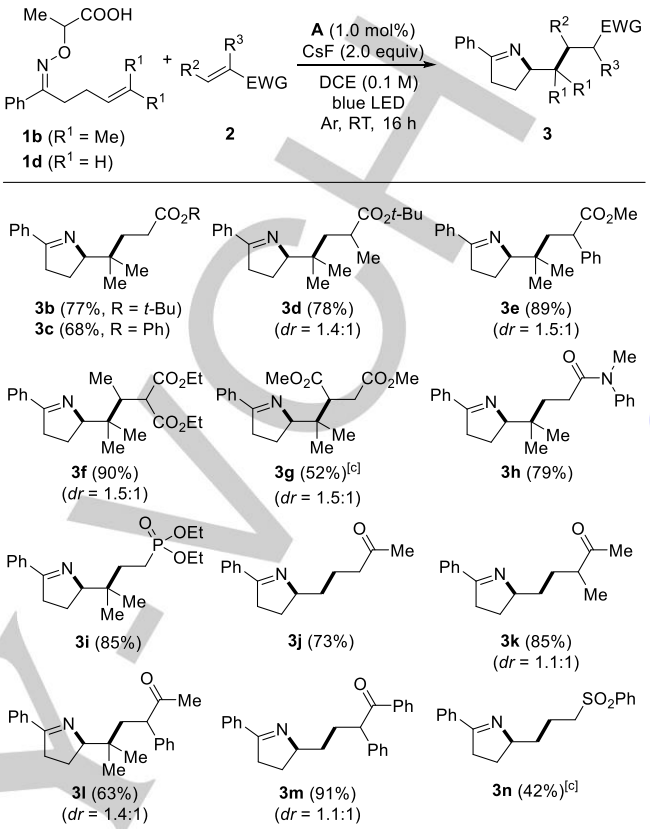
Table 1. Reaction optimization.



entry[a]	PC	base	R	yield (%)[b]
1	**A**	K_3PO_4	H	31
2	**A**	K_2CO_3	H	27
3	**A**	KOAc	H	17
4	**A**	NaOAc	H	N.D.
5	**A**	$NaHCO_3$	H	N.D.
6	**A**	Cs_2CO_3	H	49
7	**A**	CsOAc	H	47
8	**A**	CsF	H	56
9	**B**	CsF	H	N.D.
10	**C**	CsF	H	N.D.
11	**D**	CsF	H	N.D.
12	**A**	**CsF**	**Me**	**79 (73)[c]**
13	**A**	CsF	Ph	53
14	**–**	CsF	Me	N.D.
15	**A**	**–**	Me	N.D.
16[d]	**A**	CsF	Me	N.D.

[a] Reaction conditions: A mixture of **1** (0.1 mmol, 1.0 equiv), **2a** (0.6 mmol, 3.0 equiv), photocatalyst (0.001 mmol, 1.0 mol%), base (0.2 mmol, 2.0 equiv) in DCE (1.0 mL, 0.1 M) was irradiated by a 10 W blue LED at room temperature for 16 h. [b] The yield was determined by ^{1}H NMR analysis using CH_2Br_2 as an internal standard. [c] Isolated yield at 0.2 mmol scale. [d] The reaction was conducted in the dark.

Table 2. Variation of the radical acceptor.[a],[b]



[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), photocatalyst **A** (0.002 mmol, 1.0 mol%), CsF (0.4 mmol, 2.0 equiv) in DCE (2.0 mL, 0.1 M) was irradiated by a 10 W blue LED at room temperature for 16 h. [b] Isolated yields. [c] 0.004 mmol photocatalyst **A** was used.

With the optimal conditions in hand, we examined the scope by first varying the radical acceptor (Table 2). Various α,β-unsaturated esters were competent coupling partners affording pyrrolines **3b**-**3g** in moderate to good yields showing that substituents at the α and β-position of the ester acceptor are tolerated. As expected, diastereoselectivity was not controlled. α,β-Unsaturated amides and a phosphonate worked very well to give the pyrrolines **3h** and **3i** in high yields. We examined the reactivity of α,β-unsaturated ketones and found that for such acceptors, cascades were also efficient using precursor **1d** that results upon cyclization in a primary alkyl radical. Methyl vinyl ketone, substituted congeners therefrom and a phenyl vinyl ketone worked well in combination with **1d** and **3j**-**3m** were isolated in good to excellent yields (63-91%). Phenyl vinyl sulfone could also be used as an acceptor, albeit yield for the target **3n** was slightly lower (42%).

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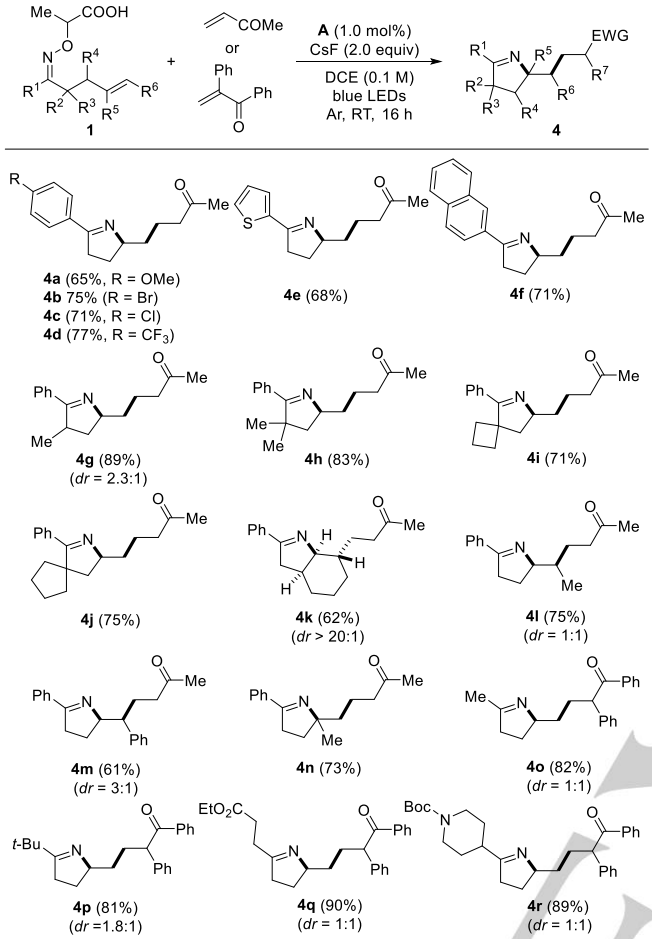
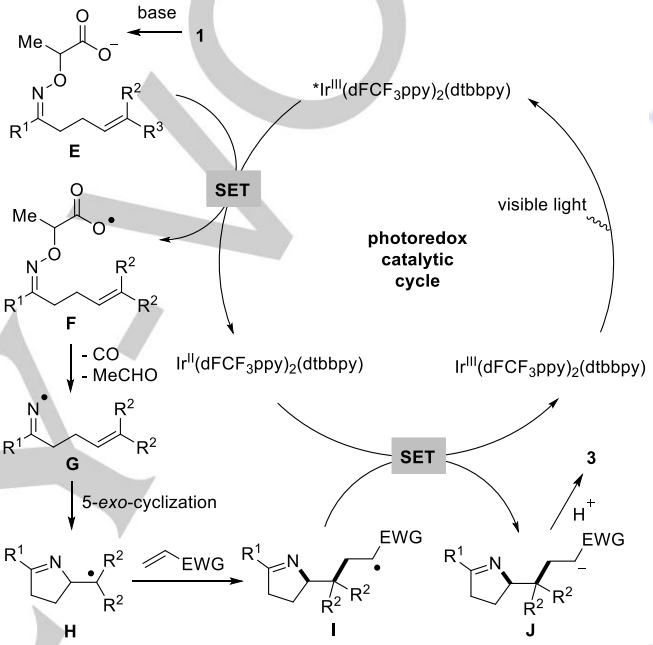
Table 3. Variation of the α-iminyl-oxy acids.[a],[b]



[a] Reaction conditions: A mixture of **1** (0.2 mmol, 1.0 equiv), **2** (0.6 mmol, 3.0 equiv), photocatalyst **A** (0.002 mmol, 1.0 mol%), base (0.4 mmol, 2.0 equiv) in DCE (2.0 mL, 0.1 M) was irradiated by a 10 W blue LED at room temperature for 16 h. [b] Isolated yields.

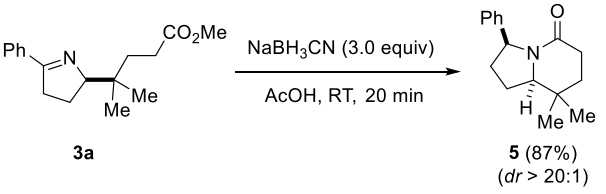
We then investigated the scope with respect to the iminyl radical precursor using methyl vinyl ketone or α-styryl phenyl ketone as acceptors (Table 3). The phenyl group in the oxime ether could be replaced by electron rich or electron poor *para*-substituted phenyl groups and the pyrrolines **4a**-**4d** were obtained in good yields. 2-Thienyl or 2-naphthyl were also tolerated as R^1-substituents to afford **4e** and **4f** in 68% and 71% yield. Oxime ethers bearing substituents R^2 and R^3 at the α-position of the C=N double bond were good substrates (see **4g**-**4j**) but the 1,3-stereoinduction in the cyclization was low (see **4g**). The alkene moiety in the oxime ethers can also be charged with additional substituents R^3 and R^4 (**4k**-**4n**) and reaction occurred with complete stereoselectivity using the cyclohex-2-enyl-methyl oxime ether as an N-radical precursor (see **4k**). However, for the non-cyclic substrates, selectivity was low (see **4l**, **4m**). Importantly, cascade works also efficiently with alkyl substituted oxime ethers as documented by the preparation of pyrrolines **4o**-**4r**.

The proposed mechanism of the cascade is depicted in Scheme 2. Photo-excitation of $Ir^{III}(dFCF_3ppy)_2(dtbbpy)PF_6$ by visible light leads to the excited $*Ir^{III}(dFCF_3ppy)_2(dtbbpy)PF_6$ complex that is SET reduced by carboxylate **E**, formed by deprotonation of substrate **1**, to generate the carboxyl radical **F** along with $Ir^{II}(dFCF_3ppy)_2(dtbbpy)PF_6$. Sequential fragmentation of CO_2 and acetaldehyde from **F** generates the iminyl radical **G**. 5-*exo*-Cyclization provides C-radical **H** that then further reacts *via* intermolecular conjugate addition to give the corresponding electrophilic adduct radical **I**. The photoredox cycle is closed through SET reduction of **I** by $Ir^{II}(dFCF_3ppy)_2(dtbbpy)PF_6$ to provide **J**, thereby regenerating the ground-state photocatalyst $Ir^{III}(dFCF_3ppy)_2(dtbbpy)PF_6$. Protonation of **J** eventually affords the isolated pyrroline **3**.



Scheme 2. Proposed mechanism.

The pyrroline derivatives that are readily accessed using our alkene carboimination conjugate addition pathway are valuable precursors for the construction of the core skeleton of indolizidine alkaloids. This is documented in Scheme 3 by the highly stereoselective $NaBH_3CN$ reduction of pyrroline **3a** and subsequent lactamization to give indolizidine derivative **5** in 87% overall yield.



Scheme 3. Synthetic application.

In conclusion, we have applied α-imino-oxy propionic acids as readily accessible and highly efficient precursors for the generation of iminyl radicals upon SET oxidation. This approach has been used to develop a photoredox neutral carboimination of α-imino-oxy proponic acids with Michael acceptors to give

valuable pyrrolines in good to excellent yields. The cascade comprises a C-N and a C-C bond formation and uses an Ir-photoredox catalyst. Reactions proceed under mild conditions and a wide range of functional groups are tolerated. We have further shown that the products of the radical cascade are valuable synthetic building blocks for the construction of the core skeleton of indolizidine alkaloids.

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Conflict of Inerest

The authors declare no conflict of interest.

Keywords: iminyl radicals • photoredox chemistry • decarboxylation • redox-neutral • pyrroline derivatives

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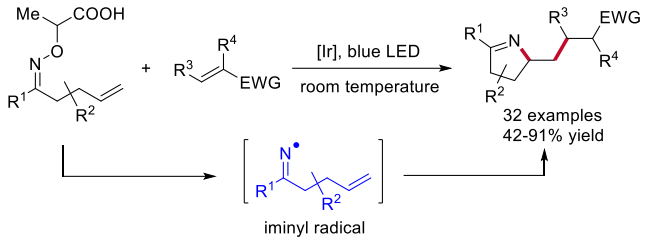

A redox-neutral radical cascade of α-imino-oxy propionic acids with various Michael acceptors using Ir-photoredox catalysis to give valuable pyrrolines is presented. These cascades comprise oxidative iminyl radical generation followed by cyclizing carbominination and subsequent intermolecular radical conjugate addition.

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Iminyl-Radicals via Oxidation of α-Imino-oxy Acids - Photoredox-Neutral Alkene Carboimination for the Synthesis of Pyrrolines