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# Visible-Light-Promoted Carboimination of Unactivated Alkenes for the Synthesis of Densely Functionalized Pyrroline Derivatives

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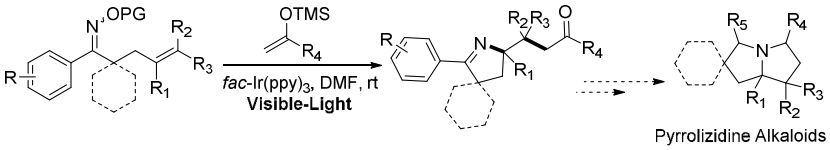
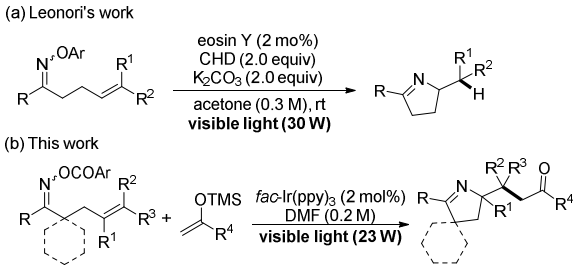
**ABSTRACT:** An efficient strategy which integrates visible-light-induced iminyl-radical formation with carboimination of unactivated alkenes has been developed for the easy access of densely functionalized pyrroline derivatives. With *fac*-[Ir(ppy)$_3$] as photoredox catalyst, the acyl oximes were converted into iminyl radical intermediates by one electron reduction, which evolve through a cascade of intramolecular cyclization, intermolecular carbon radical trapping to give the functionalized pyrrolines. The utilization of silyl enol ethers as coupling partners not only allows the introduction synthetically useful ketone functionalities but also render catalyst regeneration without any external reductants. This protocol is characterized by its mild reaction conditions and the tolerance of a broad range of functionalities.




**KEYWORDS:** *N-heterocycles, pyrroline, photoredox catalysis, visible light, iminyl radicals*

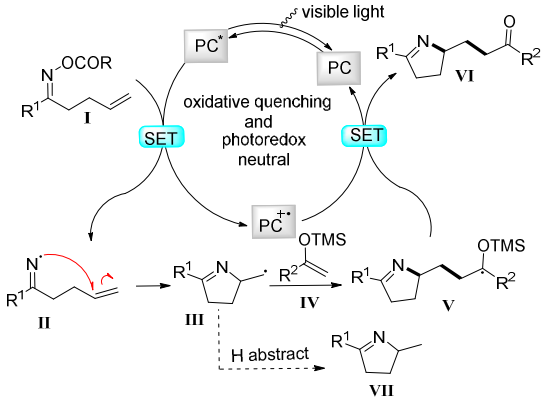
N-centered radicals (NCRs) have been showing their increasing synthetic potential for the creation of C–N bonds which represent as the centrality in alkaloids synthesis, yet they have not received adequate attentions form the synthetic community as compared with the congener of carbon radicals.[1] Arguably, the frequently employed methods for NCRs generation often rely on the deprotonative oxidation of N–H containing motifs using stoichiometric amount of external strong oxidants; spin transfer type addition of more easily accessible parent radicals to unsaturated nitrogen-containing functional groups and the homolytic scission of a weak N–X bond containing entities.[1a] Among all these strategies, the homolytic cleavage of N-O bond in hydroxy amine derivatives enables an efficient and facile generation NCRs from readily available starting materials.[2] Therefore, tremendous efforts from the synthetic chemists have been directed toward this particular scenario by making use of diverse initiation mode, including either transition-metal catalysis[3], microwave heating[4] or UV irradiation[5]. While much progress in this vein has been made during the past decade, there, however, still remained considerable limitations such as relying on the use of toxic and hazardous reagents, elevated temperatures as well as narrow substrate scope. Therefore, it is still a long way from being widely applicable for the construction of complex molecular skeletons despite the synthetic potential of NCRs and a mild, selective and general protocol for the generation of NCRs from readily available bulk starting materials would unarguably be in high demand.




**Scheme 1. Pyrroline construction employing oxime derivatives**

The visible-light promoted organic transformations, which gain energy from photons and enable reactions to occur under very mild conditions, have been attracting increasing attentions from synthetic organic chemists since the seminal work of MacMillan, Yoon and Stephenson.[6] By resorting to either organic or metallic photoactive sensitizers, a large variety of intriguing

transformations, which otherwise would be of formidable challenge with traditional synthetic protocols, were successfully accomplished.[7] Beyond all doubt, the boom of photocatalysis, to some extent, led to a renaissance of this paticular chemistry respect to NCRs because of the redox activity of photocatalysts which enable the production of these active species under very mild reaction conditions.[8] To be more specific, elegant works pertaining to iminyl radical as the pivotal intermediate generated via photocatalysis have been reported by the groups of Leonori[9] and Yu[10], which enables the ease of C–N bonds or N-heterocycles construction.

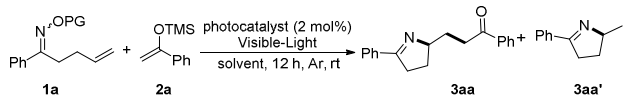



**Scheme 2. Proposed reaction mechanism**

Pyrroline represents as a core structural motif which is widely present in naturally occurring compounds and pharmaceuticals. As such, the quest for the development of effective methods for the synthesis of densely functionalized pyrroline derivatives is actively pursued in the past several years.[11] Quiet recently, by using *O*-aryl oxime as substrate, Leonori developed a photocatalytic hydroimination protocol for construction of pyrroline skeleton (Scheme 1a).[9] Despite these significant developments, there still remain ample room for further improvement especially in terms of reaction diversity, applicability and practicality. With our continuing interest in C-N bonds and *N*-heterocycles construction,[12] we would like to report our recent advancement in visible-light-promoted carboimination of unactivated alkenes for the construction of densely functionalized pyrroline derivatives.

As outlined in Scheme 2, the catalytic cycle is envisioned to start with the excitation of a photocatalyst PC to its excited state PC*. Oxidative quenching of PC* via reduction of oxime derivative **I** would generate the key iminyl radical intermediate **II**, which inclines to undergo 5-exo-cyclization to produce pyrroline species **III** containing a primary carbon-centred radical. At this stage, the carbon radical **III** is envisioned to be trapped by silyl enol ether **IV** to deliver α-oxygen radical **V**, which would ultimately furnish the desired product **VI** through single electron transfer and desilylation processes, while simultaneously regenerating the active catalyst PC. It should also be pointed out that the premature generation of hydroimination product **VII** via hydrogen transfer between **III** and reaction media shall never be overlooked.

**Table 1. Optimization of reaction condition**[a]



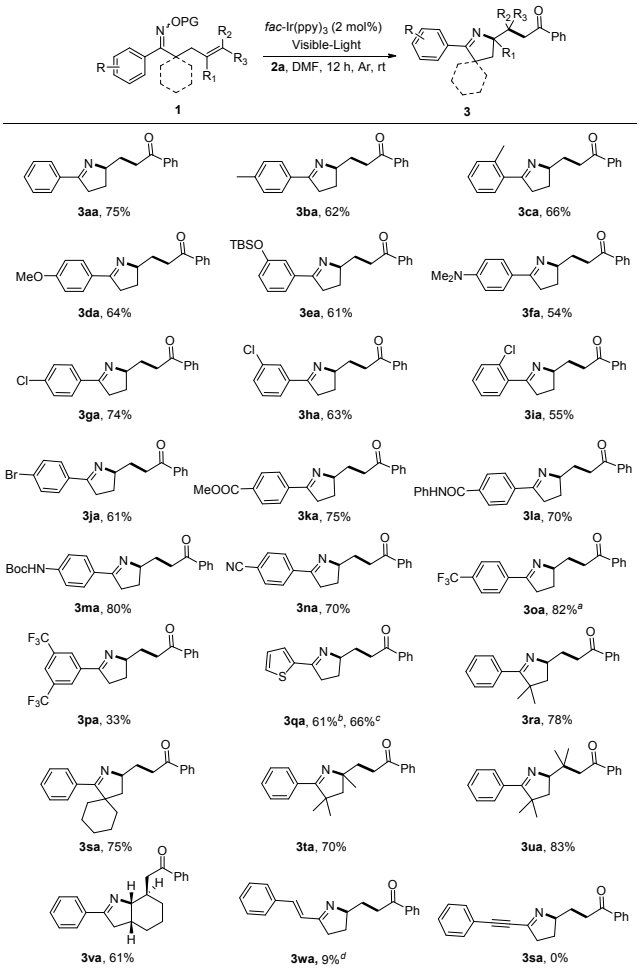

| Entry | photocatalyst | solvent | Yield (%)(**3aa**/**3aa'**) |
|---|---|---|---|
| 1 | *fac*-Ir(ppy)$_3$ | DMF | 54/24 |
| 2 | *fac*-Ir(ppy)$_3$ | DMA | 38/43 |
| 3 | *fac*-Ir(ppy)$_3$ | DMPU | trace |
| 4 | *fac*-Ir(ppy)$_3$ | NMP | 11/55 |
| 5 | *fac*-Ir(ppy)$_3$ | $CH_3CN$ | 15/9 |
| 6[b] | *fac*-Ir(ppy)$_3$ | DMF | 86/12 |
| 7[c] | *fac*-Ir(ppy)$_3$ | DMF | 62/9 |
| **8**[b,d] | ***fac*-Ir(ppy)$_3$** | **DMF** | **85(75)**[e]**/9** |
| 9[b,d] | Ru(bpz)$_3$(PF$_6$)$_2$ | DMF | 14/0 |
| 10[b,d] | DCA | DMF | trace |
| 11[b,d] | Cu(dap)$_2$Cl | DMF | 0 |
| 12[b,d,f] | *fac*-Ir(ppy)$_3$ | DMF | 0 |
| 13[b,d] | — | DMF | 0 |

[a]Unless otherwise noted, the reactions were carried out at room temperature under Ar atmosphere using **1a** (*E*/*Z* mixture, 0.1 mmol), **2a** (0.2 mmol), photocatalyst (0.002 mmol) in solvent (1 mL) for 12 h with yields being determined by $^1$H NMR using mesitylene as internal standard. [b]**2a** (0.3 mmol). [c]**2a** (0.4 mmol). [d]Solvent (0.5 mL). [e]Isolated yield. [f]No light. DCA = 9,10-dicyanoanthra-cene. DMPU = 1,3-dimethyl -3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone. PG = 4-(trifluorome-thyl)benzoyl.

Considering the more oxidizing ability of electron deficient *O*-acyl oxime, which was envisioned to furnish iminyl radical more readily via one electron reduction, the coupling between **1a** and 1-phenyl-1-trimethylsilyloxyeth-ylene **2a** was chosen as the model reaction and the representative experiment results are summarized in Table 1. It was pleasing to find that when using *fac*-Ir(ppy)$_3$ as photocatalyst and DMF as solvent, the expected carboimination product **3aa** was obtained in 54% yield as well as the hydroimination **3aa'**, which was assumed to be produced via hydrogen atom abstraction form the solvent, in 24% yield (Table 1, entry 1). With the aim of suppressing such accompanying hydroimination process, various solvents were examined, which, however, provided no more positive results than that of DMF (Table 1, entries 2-5). To our delight, the reaction efficacy could be further enhanced by using 3 equiv **2a**, whereas **3aa'** was still produced in 12% yield (Table 1, entry 6). By adjusting the concentration of reacation, the yield of desired product **3aa** could be further improved to 85% yield with minimal amounts of the byproduct **3aa'** being formed (Table 1, entries 7, 8). Different kinds of photocatalysts were also examined, which, however, proved to be not efficacious for such transformation (Table 1, entries 9-11). Control experiments revealed the indispensability of both light and photocatalyst in this transformation, without either, no desired product could

be obtained but the recovered starting material (Table 1, entries 12, 13).

**Table 2. Reaction scope of acyl oximes**

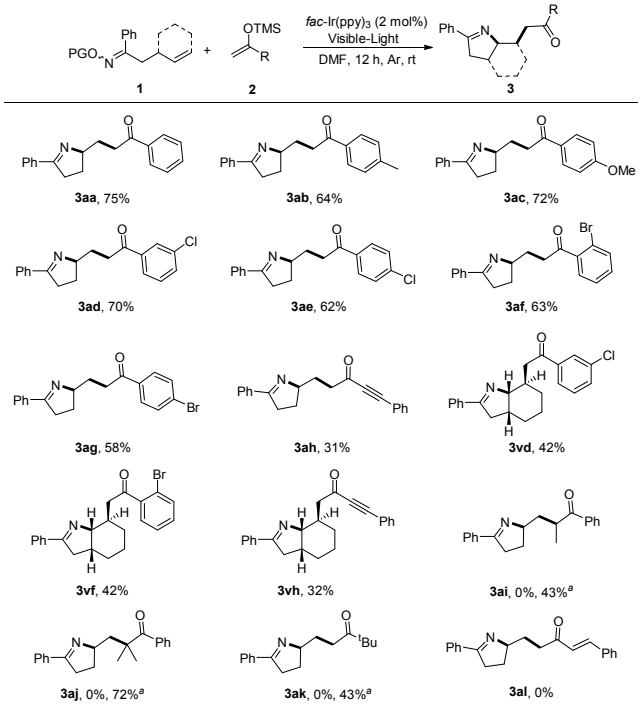



See the Supporting Information for the detailed reaction conditions. [a]Run in 24 h. [b]*E*-configuration substrate. [c]*Z*-configuration substrate. [d]Yield determined by $^1$H NMR using mesitylene as internal standard. PG = 4-(trifluoro methyl)benzoyl.

With the optimized conditions obtained, the reaction generality with respect to *O*-acyl oximes **1** was investigated with **2a** as model coupling partner and the results were summarize in Table 2. It was found that this reaction shown a nice compatiblity of a large variety of functionalities and enabled diverse substitution patterns with respect to the starting oxime derivative to be well accommodated. Generally, the desired pyrroline products were obtained in moderate to high yield (33-82%) irrespective of the position and electronical property of substituents on the phenyl moiety (**3aa-pa**) and heterocyclic substrate was also amenable to this transformation (**3qa**). Furthermore, oxime substrates that contain α-substituents also worked smoothly to deliver desired products in good yields (**3ra, 3sa**). As expected, the cyclization also worked smoothly in the cases of substrates with either di- or tri-substituted alkene pendent, affording the desired products in good yields (**3ta**, **3ua**). Notably, when **1v** was employed, the reaction proceeded selectively to afford only one diastereoisomer in acceptable yield. While aromatic ketone derived substrates worked well, notable limitations with respect to the substrate scope still remain. For example, alkyl, alkenyl and alkynyl based substrates as well as imidothioate derivative were all not appropriate for such transformation and the exact reason for the incompetence of these substrates is currently not clear.

To further probe the reaction generality, the reactions between oxime derivatives and various silyl enol ethers were carried out and the examination results were listed in Table 3. With respect to α-aryl silyl enol ether, substrates with both electron-withdrawing and electron-donating functional groups on the aryl substituents all worked smoothly to afford desired products in moderate to good yields. Pleasingly, the halogen substituents were proved to be well adapted to this reaction condition, thus furnishing the opportunity of further synthetic elaboration via traditional cross-coupling methodologies (**3ad**-**3ag**). It is worth mentioning that this transformation was not restricted to aryl derived silyl enol ethers. Substrates incorporating alkynyl substituents were also found to be competent reaction partners as demonstrated in the case of **3ah**. Though somewhat diminished reactivity was observed in this case, the synthetic potential of thus incorporated alkynyl moiety in **3ah** would make such transformation very appealing. Furthermore, the variation of silyl enol ether was also feasible when reacting with **1v**, thus offering an effective synthetic pathway for the easy access of hexahydro-3*H*-indole derivatives that containing three contiguous stereogenic centers (**3vd**-**3vh**). Unfortunately, tri- and tetra-substituted silyl enol ethers were not suitable for such transformation, with no desired

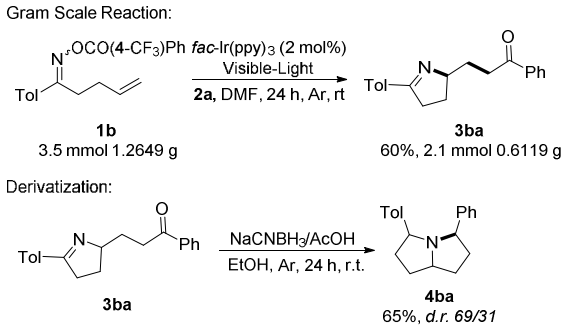
**Table 3. Reaction scope of silyl enol ethers**




See the Supporting Information for the detailed reaction conditions. [a]Yield of hydroimination product, determined by $^1$H NMR using mesitylene as internal standard. PG = 4-(trifluoromethyl)benzoyl.

products but only hydroimination byproducts being obtained in these cases (**3ai**, **3aj**). In addition, alkyl and alkenyl derived silyl enol ethers were also proved to be inappropriate (**3ak** and **3al**).

In order to assess the practicality of this transformation, a gram-scale reaction between **1b** and **2a** was carried out and the desired product **3ba** was obtained in comparable yield to that of small scale version.[13] As a continuing attempt to further showcase the synthetic potential of these pyrroline derivatives thus obtained, synthetic elaboration was carried out with product **3ba**. By making use of imine and ketone functionality incorporated, the reductive cyclization worked smoothly to the deliver the hexahydro-*1H*-pyrrolizine alkaloid **4ba**, which is ubiquit- ous and represents as a core structure motif in numerous bioactive natural products[14], albeit with moderate diastereoselectivity (Scheme 3).




**Scheme 3. Gram scale reaction and synthetic derivatization**

In conclusion, a novel strategy for the expedient synthesis of pyrroline derivatives was discovered. This reaction cascade takes place through intramolecular 5-exo-cyclization of iminyl radical, which is generated by virtue of visible-light-promoted mesolysis of *O*-acyl oxime derivatives, followed by intermolecular interception of thus formed carbon-centred radical with silyl enol ether derivatives. Furthermore, this transformation exhibited high reaction efficiency and accommodated a vide spectrum of synthetically useful functionalities, thus providing a competent synthetic route for the pyrroline derivative construction. Further investigation to extend the reaction scope is ongoing in our laboratory and will be reported in the due course.

## ASSOCIATED CONTENT

**Supporting Information**.

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.xxxxxxxxx.

Experimental procedures and compound characterization (PDF)

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### Notes

The authors declare no competing financial interest.

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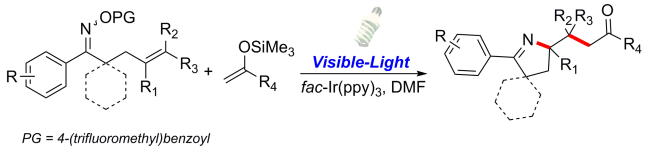


*PG = 4-(trifluoromethyl)benzoyl*

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