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Photocatalytic Radical Trifluoromethylation/Cyclization Cascade: Synthesis of CF_3-Containing Pyrazolines and Isoxazolines

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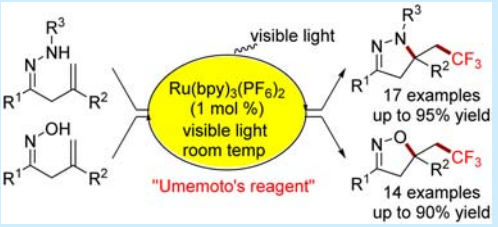
Supporting Information

ABSTRACT: A general visible light induced photoredox-catalyzed radical trifluoromethylation/cyclization cascade of β-aryl-β,γ-unsaturated hydrazones and oximes is described. The protocol enables an efficient access to various densely functionalized and biologically important CF_3-containing dihydropyrazoles and isoxazolines with generally high yields.

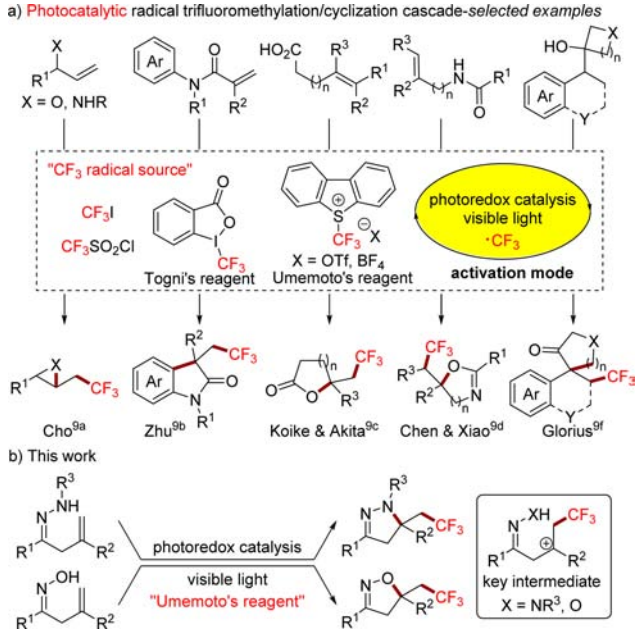


The visible light induced photocatalysis using photosensitizers to activate organic molecules has been established as a powerful protocol for triggering new chemical reactions in organic synthesis.[1] Employing the unique activation modes of such types of catalysis, numerous versatile methodologies have been disclosed by many research groups for efficient transformations of a vast array of carbon feedstocks into useful chemicals. Among these processes, a great deal of research effort has been directed toward photoredox-catalyzed alkene difunctionalizations that form C−C or C−X (X = heteroatom) bonds, given the abundance and ready availability of alkenes and their derivatives.[2−6] In this field, the photocatalytic radical-mediated addition/cyclization across a carbon−carbon double bond provides an attractive platform for construction of various biologically important and functionalized carbo- and heterocycles.

Since the pioneering works on the photocatalytic radical trifluoromethylation of aldehydes and enolsilanes reported by MacMillan,[7] a range of elegant photocatalytic CF_3 radical-mediated addition/cyclization reactions have been developed for synthesis of various biologically important CF_3-containing carbo- and heterocycles when the alkene substrates have suitable nucleophilic pendants or radical acceptors.[8,9] As such, a wide variety of allylic alcohols and amines,[9a] *N*-arylacrylamides,[9b] and alkenoic acids[9c] were facilely transformed into the corresponding CF_3-substituted three-, five, six-, and seven-membered oxygen and/or nitrogen heterocycles with good yields and selectivities (Scheme 1a).

In this regard, our group has also reported an efficient photocatalytic radical trifluoromethylation/cyclization cascade reaction of *N*-allylamides using visible light, providing a practical access to diversely functionalized CF_3-substituted oxazolines and benzoxazines.[9e] Recently, the Glorius group disclosed a photocatalytic tandem trifluoromethylation/ring expansion of cycloalkanol-substituted styrenes for efficient synthesis of CF_3-containing cyclic ketone derivatives.[9f] In these reactions, the CF_3 radical and β-CF_3-substituted carbocations, generated through a single-electron transfer (SET) process, were proposed to be involved as key intermediates. In view of the wide occurrence of the CF_3 moiety in heterocycle-based pharmaceuticals and agrochemicals and its unique physical and biological properties,[10] it is still highly desirable to develop new protocols for incorporation of the CF_3 group into carbo- and heterocycles.[11]

Scheme 1. Visible Light Induced Photoredox-Catalyzed Alkene Difunctionalization and Reaction Design



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Pyrazolines and isoxazoles are an important class of heterocycles because of their remarkable biological activities and versatile synthetic utility.[12] In particular, CF_3-substituted dihydropyrazoles and isoxazoles have recently been proven to exhibit remarkable biological activities (Figure 1).[13] Despite

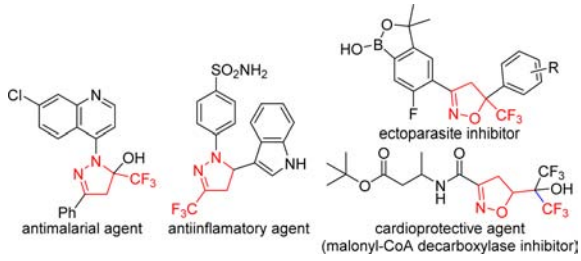


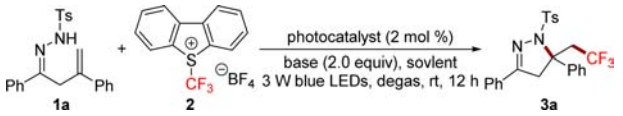
Figure 1. Examples of biologically active CF_3-containing dihydropyrazoles and isoxazolines.

some recent advances, however, efficient methods to introduce the CF_3 group into dihydropyrazoles and isoxazoles are still scarce.[14] On the basis of our recent studies on visible light induced photocatalytic hydroamination and oxyamination of *β,γ*-unsaturated hydrazones,[15] we envisioned that the *β,γ*-unsaturated hydrazones and oximes might also be applicable to the synthesis of attractive CF_3-containing dihydropyrazoles and isoxazoles when the addition of CF_3 radical to the alkene moiety is preferred to the generation of *N*-centered hydrazonyl radicals. Herein, we describe a successful introduction of such a strategy (Scheme 1b).

Ont he basis of the wide use of Umemoto's and Togni's reagents in trifluoromethylation reactions, we initially chose these reagents as privileged CF_3 radical sources.[16] When a mixture of *β,γ*-unsaturated hydrazone **1a** and Umemoto's reagent in degassed MeCN was irradiated by 3 W blue LEDs at rt using 2 mol % of *fac*-Ir(ppy)$_3$ as photocatalyst, the expected radical trifluoromethylation/cyclization cascade indeed occurred to give the product **3a** in 67% yield (entry 1, see Scheme 3 for X-ray structure of **3a**).[17] Encouraged by this result, we continued to optimize other parameters to further improve the yield. A simple survey of reaction media and inorganic bases demonstrated that the combination of $NaHCO_3$ with MeCN gave rise to the best effect (entries 2−5). We then evaluated several other photocatalysts with different reduction potentials and identified Ru(bpy)$_3$(PF$_6$)$_2$ as a superior catalyst with **3a** being obtained in 72% yield (entry 8). Interestingly, only a 48% yield was observed in the absence of $NaHCO_3$ (entry 9). Control experiments without photocatalyst or light irradiation confirmed that the present reaction is a photocatalytic process (entries 10 and 11). Further screening of concentration, CF_3 radical sources, and catalyst loading resulted in the optimal conditions: 1 mol % of Ru(bpy)$_3$(PF$_6$)$_2$ as photocatalyst, $NaHCO_3$ (2.0 equiv) as base, and Umemoto's reagent (1.1 equiv) in 2.0 mL of CH_3CN (0.05 M) at rt (entry 15).

With the optimized reaction conditions established, a range of *β,γ*-unsaturated hydrazones were first examined to explore the substrate scope (Scheme 2). It was found that diverse variation of the hydrazone moiety (R^1) proved to be possible. For example, a range of substrates with various electron-donating (e.g., Me) and electron-withdrawing groups (e.g., CF_3, Br, CN) on the phenyl ring participated in the reaction to afford the corresponding products **3b−e** in good yields. As shown in the synthesis of pyrazoline **3f**, the substitution patterns have no obvious effect on the reaction. Moreover, a substrate with a 2-naphthyl also reacted

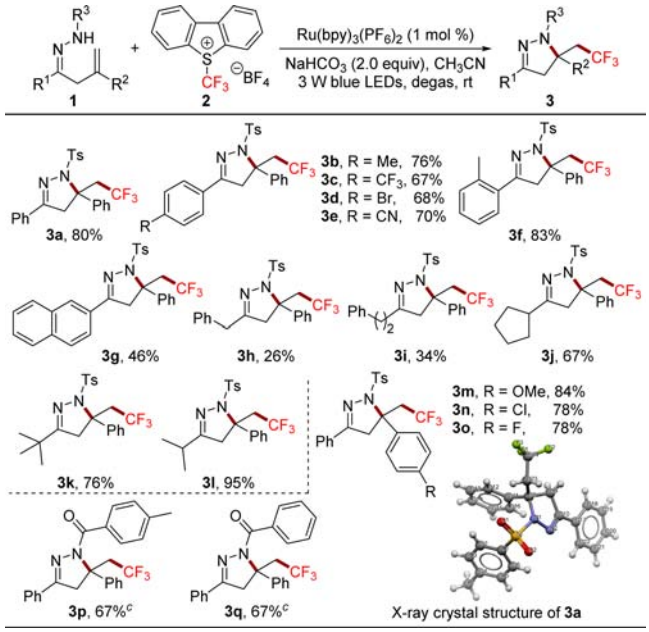
Table 1. Condition Optimization[a]



entry	solvent	base	photocatalyst	yield[b] (%)
1	MeCN	$NaHCO_3$	*fac*-Ir(ppy)$_3$	67
2	CH_2Cl_2	$NaHCO_3$	*fac*-Ir(ppy)$_3$	50
3	$CHCl_3$	$NaHCO_3$	*fac*-Ir(ppy)$_3$	61
4	MeCN	K_2CO_3	*fac*-Ir(ppy)$_3$	43
5	MeCN	K_2HPO_4	*fac*-Ir(ppy)$_3$	38
6	MeCN	$NaHCO_3$	Ru(bpy)$_3$Cl$_2$·6H$_2$O	57
7	MeCN	$NaHCO_3$	Ir(ppy)$_2$(dtbbpy)PF$_6$	52
8	MeCN	$NaHCO_3$	Ru(bpy)$_3$(PF$_6$)$_2$	72
9	MeCN		Ru(bpy)$_3$(PF$_6$)$_2$	48
10	MeCN	$NaHCO_3$		trace
11[c]	MeCN	$NaHCO_3$	Ru(bpy)$_3$(PF$_6$)$_2$	trace
12[d]	MeCN	$NaHCO_3$	Ru(bpy)$_3$(PF$_6$)$_2$	76
13[d,e]	MeCN	$NaHCO_3$	Ru(bpy)$_3$(PF$_6$)$_2$	trace
14[d,f]	MeCN	$NaHCO_3$	Ru(bpy)$_3$(PF$_6$)$_2$	trace
15[d,g]	MeCN	$NaHCO_3$	Ru(bpy)$_3$(PF$_6$)$_2$	83

[a]**1a** (0.10 mmol), **2a** (0.11 mmol), photocatalyst (2 mol %), and base (0.20 mmol) in 1.0 mL of solvent at rt under irradiation by 3 W blue LEDs for 12 h. [b]Isolated yield. [c]Without visible light. [d]2.0 mL of CH_3CN was used. [e]Togni's reagent was used. [f]CF_3SO_2Cl was used. [g]Performed with 1 mol % of Ru(bpy)$_3$(PF$_6$)$_2$.

Scheme 2. Scope of *β,γ*-Unsaturated Hydrazones[a,b]



[a]**1** (0.30 mmol), **2** (0.33 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (1 mol %), $NaHCO_3$ (0.60 mmol) in MeCN (6.0 mL) at rt under irradiation by 3 W blue LEDs for 12−18 h. [b]Isolated yield. [c]48 h.

well to give a 46% yield of **3g**. Notably, this protocol could also be applied successfully to a range of linear and branched aliphatic *β,γ*-unsaturated hydrazones **1h−l**; and the desired products **3h−l** were obtained in moderate to high yields. We then proceeded to examine the possible structural variation of alkene moiety (R^2). Again, a series of electron-donating (e.g., OMe) and electron-withdrawing groups (e.g., Cl, F) on the phenyl ring were well tolerated, with the expected products **3m−o** being obtained in

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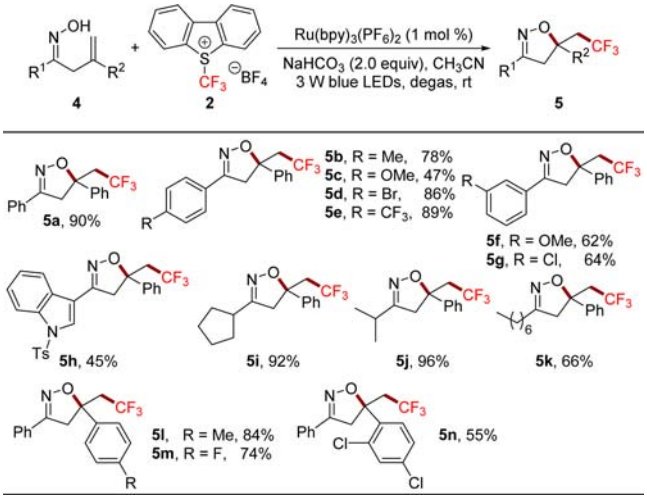
78−84% yield. As demonstrated in the synthesis of pyrazolines **3p,q**, benzoic protecting groups could also be introduced into the nitrogen atom with prolonged reaction time, which should be useful from the viewpoint of medicinal chemistry. The limitation of the present method is the required incorporation of a aryl group into the alkene moiety, which might serve to stabilize the β-CF_3-substituted carbocation intermediate generated during the reaction.[9]

The β,γ-unsaturated oximes have recently been applied to efficient synthesis of isoxazolines by Han using stoichiometric amounts of TEMPO as the radical initiator via oxime radicals.[18] Thus, we attempted to extend our catalytic strategy to a range of β,γ-unsaturated oximes **4** (Scheme 3). Under the standard

Scheme 3. Scope of β,γ-Unsaturated Oximes[a,b]

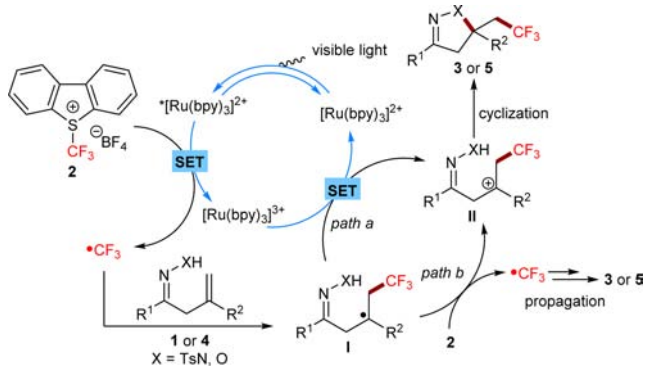


[a] **4** (0.30 mmol), **2** (0.33 mmol), $Ru(bpy)_3(PF_6)_2$ (1 mol %), $NaHCO_3$ (0.60 mmol) in MeCN (6.0 mL) at rt under irradiation by 3 W blue LEDs for 12−18 h. [b] Isolated yield.

conditions, all the substrates with electron-neutral, electron-rich (e.g., Me, OMe), and electron-deficient (Br, Cl, CF_3) functional groups at the *para*- or *meta*-position of the arene of the hydrazone moiety were well tolerated, giving **5a−g** in generally good yields. The 3-indolyl group could also be incorporated into the product isoxazoline **5h**. Once again, the reactions with aliphatic β,γ-unsaturated oximes **4i−k** proceed smoothly to give products **5i−k** in 66−92% yield. As further shown in the synthesis of isoxazolines **5l−n**, various structural variations of the alkene moiety also proved to be feasible. Notably, while some hydrazones and oximes existed as mixtures of *E*/*Z* isomers with respect to the C═N bond, these isomeric substrates could interconvert easily in solution even without irradiation.

Based on the previous literature[3,9] and our own study,[4c,9e,15] we propose a plausible catalytic cycle for the present reaction as depicted in Scheme 4, although the mechanistic details remain to be explored. Upon irradiation by visible light, the ground-state photocatalyst $[Ru(bpy)_3]^{2+}$ is first excited to the excited state $*[Ru(bpy)_3]^{2+}$ species, which then serves as a reductant to reduce the Umemoto's reagent by a SET process with release of a highly reactive CF_3 radical. Subsequently, the CF_3 radical undergoes a radical addition to the alkene of unsaturated hydrzones and oximes to give the new radical intermediate **I**, which was further oxidized to β-CF_3-substituted carbocation intermediate **II** by the strongly oxidizing $[Ru(bpy)_3]^{3+}$ species (path a). However, an alternative pathway involving the

Scheme 4. Proposed Catalytic Cycle



conversion of radical **I** into carbocation **II** by radical chain propagation cannot be excluded at the current stage. A final nucleophilic cyclization leads to the formation of the corresponding products **3** or **5**.[19]

In conclusion, we have developed an efficient and mild photocatalytic radical trifluoromethylation/cyclization cascade of β,γ-unsaturated hydrazones and oximes using visible light. The reaction enable the synthesis of a wide range of CF_3-containing dihydropyrazoles and isoxazolines in high yields. Our laboratory is currently working on the adaption of this strategy in order to develop the enantioselective variant.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02118.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

X-ray crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) CCDC 1412788 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

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