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# Metal-Free Radical Trifluoromethylation of β-Nitroalkenes through Visible-Light Photoredox Catalysis<sup>‡</sup>

Received 00th January 20xx, Accepted 00th January 20xx Siba P. Midya,<sup>1,2†</sup> Jagannath Rana,<sup>1,2†</sup> Thomas Abraham,<sup>1</sup> Bhaskaran Aswin,<sup>1</sup> and Ekambaram Balaraman<sup>\*,1,2</sup>

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Catalytic method for functional group interconversion is immensely important in modern science. Here, we report an efficient catalytic conversion of nitroalkenes to highly stereoselective 1-trifluoromethylalkenes at room temperature. This unprecedented metal-free photocatalytic strategy is simple and operates under visible-light irradiation using the commercially available CF<sub>3</sub> source.

The trifluoromethyl group (-CF<sub>3</sub>) constitutes a very important chemical entity found in pharmaceuticals, agrochemicals, and material sciences mainly because of its excellent metabolic stability and excessive lipophilicity.<sup>1-2</sup> Undoubtedly, the introduction of the CF<sub>3</sub> group into organic scaffolds can change the physical properties of molecular substances, such as solubility, membrane permeability.<sup>3</sup> Consequently, immense efforts have been devoted to incorporating the trifluoromethyl group into organic molecules. Despite a significant breakthrough on trifluoromethylation of arenes,<sup>4</sup> examples that describe the synthesis of 1-trifluoromethylalkenes is very limited in the contemporary science.40,5 Transition-metal catalyzed trifluoromethylation of vinylboronic acids have independently been developed by Liu,<sup>6</sup> Shen,<sup>7</sup> and Buchwald.<sup>8</sup> However, considering the difficulties in the preparation of vinylboronic acids and their derivatives, Hu<sup>9</sup> and Liu<sup>10</sup> et al., reported the transition-metal catalyzed decarboxylative trifluoromethylation of  $\alpha$ , $\beta$ -unsaturated carboxylic acids using the Togni reagent and Langlois reagents, respectively. Recently, trifluoromethylation of  $\beta$ -nitroalkenes promoted by a stoichiometric amount of iron(III)salts at 120 °C using the Togni reagent as CF<sub>3</sub>-source was reported.<sup>11</sup> In this context, a new efficient method for constructing Cvinvi-CF3 bonds,

possessing broad substrate scope under mild reaction conditions is highly desired and synthetically very demanding.



In recent times, a visible-light mediated photoredox catalysis is emerging has a powerful synthetic tool in chemical sciences. MacMillan and co-workers developed an elegant approach to trifluoromethylation of arenes under visible light irradiation at room temperature using the Ru-based polypyridyl complex as a photoredox catalyst and CF<sub>3</sub>SO<sub>2</sub>Cl as a source of trifluoromethyl group.<sup>12</sup> Subsequently, fewer methods were developed for trifluoromethylation under visible-light photoredox catalysis.<sup>13</sup> However, the use of expensive metal catalysts (Ru and Ir), and the problems involved in removing potential toxic metal impurities from the final product are some common concerns. Hence, development of alternative metal-free trifluoromethylation performed under mild and practical conditions is highly desirable and very demanding. Here, we report an operationally simple, efficient transitiontrifluoromethylation of βmetal-free stereoselective nitroalkenes using the commercially available

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trifluoromethylating source. To the best of our knowledge, no example of the room temperature metal-free catalyzed direct formation of the  $C_{vinyl}$ -CF<sub>3</sub> bond has been reported under photoredox conditions.



We began our direct stereoselective trifluoromethylation of  $\beta$ nitroalkenes with an evaluation of a range of photoredox catalysts, solvents, light source, and additives using (E)-1methoxy-4-(2-nitrovinyl)benzene 1a as a benchmark substrate. The commercially available and relatively economical CF<sub>3</sub>SO<sub>2</sub>Cl (2) was used as a CF<sub>3</sub>-source (Table 1). Upon visible-light irradiation in the presence of catalytic amount of photoredox catalyst and  $K_2HPO_4$  as additive under argon atm at room temperature enabled (E)-selective 3a in 74% yield (Table 1, entry 2). A series of photoredox catalysts was examined, and among them, eosin-Y was found to be an optimal photocatalyst for this transformation (Table 1, entries 1-6). The necessity of each of the key reaction components (photoredox catalyst, additive and light source) was demonstrated (Table 1, entries 7-9). Significantly, the choice of additive was found to have a dramatic effect on the yield of 3a and with K<sub>2</sub>HPO<sub>4</sub> proving to be optimal for the present strategy (Table 1, entries 1, and 10-12). We believe that a weakly Lewis basic nature of  $K_2HPO_4$  would facilitate the formation of  $CF_3$ radical.  $^{\rm 12\text{-}13}$  We have observed that the use of  $\rm CH_3CN$  as the reaction medium was found to provide an excellent yield of 3a. Further screening using common solvents, including apolar arenes (toluene and o-xylene), or polar Et<sub>2</sub>O and DMSO proved ineffective. Notably, other commonly employed solvents in photoredox catalysis, such as DMF, MeOH, THF and DCE afforded the product 3a in 0%, 31%, 39% and 27% respectively (Table 1, entries 13-15). While trace amounts of the product were formed in the absence of additive; no reaction was observed in the absence of photoredox catalyst as well as upon exclusion of light (Table 1, entries 7-9). Other commercially available trifluoromethylating reagents (Langlois reagent, Togni reagent, CF<sub>3</sub>CO<sub>2</sub>Na and (CF<sub>3</sub>CO)<sub>2</sub>O; see Scheme 2b) were examined and among them, CF<sub>3</sub>SO<sub>2</sub>Cl was found to be effective for this transformation. Reactions in the dark and

at increased temperature (60 °C) didn't yield the desired product, which excludes homolytic bond cleavage of the starting material to trifluoromethyl radical under these conditions. Notably, no *Z*-isomer was observed under our standard conditions ( $^{19}$ FNMR spectroscopy). Table 1. Optimization of the reaction conditions.<sup>a</sup>

MeO	NO <sub>2</sub> + CF₃ 1a	cat. (5 addi SO <sub>2</sub> CI <u>visible</u> Ar atm <b>2</b>	mol%) tive light h, RT MeO	CF <sub>3</sub>
Entry	Catalyst	Solvent	Additive	Yield (%) <sup>b</sup>
1.	Ru(bipy) <sub>3</sub> Cl <sub>2</sub>	MeCN	K <sub>2</sub> HPO <sub>4</sub>	51
2.	Eosin-Y	MeCN	$K_2HPO_4$	74 (66%) <sup>c</sup>
3.	Rose Bengal	MeCN	K <sub>2</sub> HPO <sub>4</sub>	68
4.	Rodamin-B	MeCN	$K_2HPO_4$	36
5.	Alizarine-S	MeCN	K <sub>2</sub> HPO <sub>4</sub>	67
6.	Fluorecene	MeCN	K <sub>2</sub> HPO <sub>4</sub>	12
7.	Eosin-Y	MeCN	-	trace
8.	-	MeCN	K <sub>2</sub> HPO <sub>4</sub>	NR
9.	Eosin-Y	MeCN	K <sub>2</sub> HPO <sub>4</sub>	NR <sup>d</sup>
10.	Eosin-Y	MeCN	KH <sub>2</sub> PO <sub>4</sub>	33
11.	Eosin-Y	MeCN	K₃PO4	NR
12.	Eosin-Y	MeCN	CsOAc	NR
13.	Eosin-Y	DMF	K <sub>2</sub> HPO <sub>4</sub>	NR
14.	Eosin-Y	MeOH	K <sub>2</sub> HPO <sub>4</sub>	31
15.	Eosin-Y	THF	K <sub>2</sub> HPO <sub>4</sub>	39
16.	Eosin-Y	DCE	K <sub>2</sub> HPO <sub>4</sub>	27

<sup>*a*</sup>Unless otherwise noted, the reaction performed under an inert atmosphere of argon. Reaction conditions: **1a** (0.125mmol), CF<sub>3</sub>SO<sub>2</sub>Cl (0.3mmol), photocatalyst (5 mol%), additive (0.3 mmol) and solvent (0.5 mL) under visible-light irradiation at room temperature for 32 h. <sup>*b*</sup>Yield determined by GC using *m*-xylene as an internal standard. <sup>*c*</sup>Reaction under direct sun-light. <sup>*d*</sup>Reaction performed under dark condition. NR = No reaction.

Having identified optimal conditions for a metal-Free, roomtemperature, radical trifluoromethylation of  $\beta$ -nitroalkenes, we sought to define the scope of  $\beta$ -nitroalkenes **1**. As shown in Table 2, the present metal-free catalyzed the direct formation of Cvinvl-CF3 bond strategy displayed high functional-group tolerance and proved to be an efficient method for the preparation of E-selective 1-trifluoromethylalkene in good to excellent yields (up to 81%) under very mild conditions. Notably, the addition of the trifluoromethyl radical is viable when aromatic substituents are present, due to the easy formation of benzyl radicals. Thus, the present strategy is highly applicable to  $\beta$ -nitrostyrene derivatives. The  $\beta$ nitrostyrene bearing electron-donating groups at the meta and para position of the phenyl ring, such as methyl, methoxy and offered proceeded smoothly and thiomethyl the corresponding 1-trifluoromethylalkenes in good yields (Table 2, products 3a-3c, 3i-3j, and 3m). Various halides substitutes are also well tolerated and gave the desired product in good yields (products 3e in 70%, 3f in 63%, 3k in 67%, and 3l in 66%). Indeed, electron-withdrawing group substituted βnitroalkene showed better reactivity and to afford the expected (E)-1-trifluoromethylalkenes (3h) in 81% yield. These results indicate that the electronic nature of the nitroalkenes has considerable influence on our room-temperature metalfree trifluoromethylation strategy. However, a substituent at the ortho position of the phenyl ring (1-methoxy-2-(2Published on 31 May 2017. Downloaded by University of Arizona on 31/05/2017 13:31:37

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nitrovinyl)benzene) gave desired CF<sub>3</sub>-product in very poor yield (~6% yield) with 87% recovery of starting material, which could be explained by steric reasons. The reaction of 2-nitrovinyl naphthalene also proceeded well, yielding the desired product up to 64% yield. Thus, the reaction of 1n-1p under optimal conditions gave the corresponding (E)-1-trifluorometylated products 3n (60%),3o (59%), and 3p (64%), respectively. We further applied the optimized reaction conditions to different heterocyclic, substituted nitroalkenes and are amenable to this trifluoromethylation protocol. Thus, treatment of 1q and 1r optimal conditions gave under the expected trifluoromethylated product 3q in 66% and 3r in 65% yields. Notably, under optimal condition aliphatic and arylaromatic nitroalkenes (1s-1t) failed to yield the corresponding trifluoromethyled products, due to less stability of the carboncentred radical (see Scheme 5).

Table 2. Stereoselectivetrifluoromethylation of  $\beta$  -nitroalkenes under metal-free photoredox catalysis.



<sup>a</sup>Unless otherwise noted, the reaction performed under an inert atmosphere of argon. Reaction conditions: **1a-t** (0.25mmol), **2** (0.625mmol), eosin-Y (5 mol%), K<sub>2</sub>HPO<sub>4</sub> (0.625mmol), and CH<sub>3</sub>CN (1 mL)under visible-light irradiation at room temperature. <sup>b</sup>Average yields of two independent reactions. <sup>c</sup>GC yield. <sup>d</sup>Based on <sup>19</sup>F NMR. n. d: not detected.

To our delight, we have successfully shown the scalability and practical viability of this catalytic protocol under standard conditions.<sup>14</sup> To gain an insight into the course of the reaction, we conducted a series of control experiments (Scheme 4). When we performed the reaction in the presence of the radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), the reaction was completely inhibited. To our delight, performing the reaction in the presence of eosin-Y, CF<sub>3</sub>SO<sub>2</sub>Cl, and TEMPO under standard conditions yielded the trifluoromethyl-TEMPO product, which was detected on GC-MS. These results indicate that radical reaction pathway could

be involved in the catalytic cycle. Furthermore, the yield of **3a** was completely dropped when no photoredox catalyst was present in the reaction and/or under dark conditions (Table 1, entries 8-9). A competition experiment with a different electronic substituent (*para* position of the phenyl ring) on  $\beta$ -nitroalkenes revealed that electron-withdrawing groups facilitate the reaction. This finding can be rationalized regarding stabilization of the benzylic radical by strong electron-withdrawing group (Scheme 4c). Notably, under an optimal condition, other alkenes such as styrene,  $\beta$ -bromo, and  $\beta$ -carboxy-styrene failed to yield the product **3a**. This result clearly indicates that denitration is very crucial in the catalytic cycle and the nitro radical does not facilitate the radical chain process.<sup>15</sup>



In the cyclic voltammetric study, the observed reduction potential of  $\beta$ -nitroalkene (**1d**) (-0.968 V and -0.848 V vs. SCE)<sup>14</sup> is quite lower than the reduction potential of triflyl chloride (-0.81 V vs. SCE).<sup>12</sup> Furthermore, the Stern-Volmer fluorescence quenching experiment illustrates that the excited state of eosin-Y\* is quenched in the presence of triflyl chloride (**2**) The Stern-Volmer constant of **2** and  $\beta$ -nitroalkene (**3d**) are 71 x 10<sup>-3</sup> and 3.4 x 10<sup>-3</sup>, respectively (Figure 2).<sup>14</sup> These results clearly support the oxidative quenching pathway in the catalytic cycle.



Figure 2. Eosin-Y emission quenching with CF<sub>3</sub>SO<sub>2</sub>Cl and 4-fluoro-nitroalkene.

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Based on preliminary results and known literature, 12-13,15 a plausible mechanism for the trifluoromethylation of  $\beta$ nitroalkenes is shown in Scheme 5. The photocatalyst eosin-Y absorbs light in the visible region ( $\lambda_{max}$  = 539 nm) to give a photoexcited singlet state, <sup>1</sup>eosin-Y\*, which undergoes intersystem crossing to form the long-lived triplet state <sup>3</sup>eosin-Y\*. The reaction proceeds first via single-electron reduction (SET) of triflyl chloride (2,  $E_{1/2}^{red} = -0.81$  V vs. SCE) by the  $^3$ eosin-Y\*. The radical anion of  ${f 2}$  immediately collapsed and generates a more stable  $CF_3^{\bullet}$  radical with the release of  $SO_2$ and chloride, which is an entropically driven process.<sup>12</sup> The radical addition of trifluoromethyl radical to β-nitroalkene derivatives 1 produces carbon-centred radical (D). Subsequently, oxidation of the radical intermediate **D** by the Eosin-Y radical cation (C) to afford the expected 1trifluoromethylalkene 3, assisting in the elimination of NO<sub>2</sub> and thus regenerates the photoredox catalyst.<sup>15</sup>



#### Conclusions

In summary, a room-temperature trifluoromethylation of  $\beta$ nitrostyrenes under visible-light metal-free photoredox catalysis is disclosed. The reaction operates under mild conditions with no generation of copious metal waste and can thereby be scaled up in large-scale synthesis. The broad substrate scope, as well as functional group tolerance (ether, thioether, halides and nitro) with an excellent selectivity of this process, makes it attractive for facile synthesis of 1trifluoromethylalkenes of high utility in various research areas.

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