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Four-Component Photoredox-Mediated Azidoalkoxy-trifluoromethylation of Alkenes

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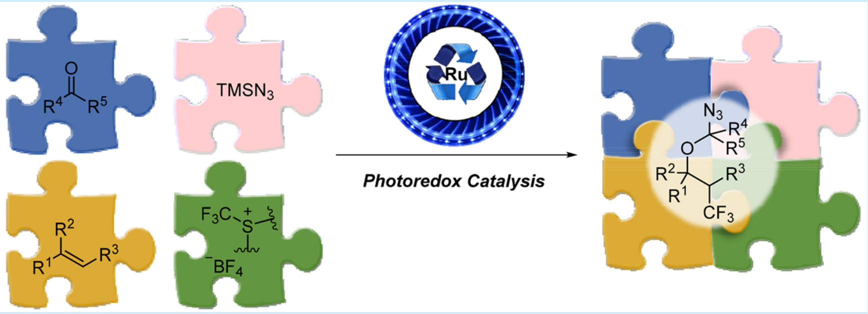
Supporting Information

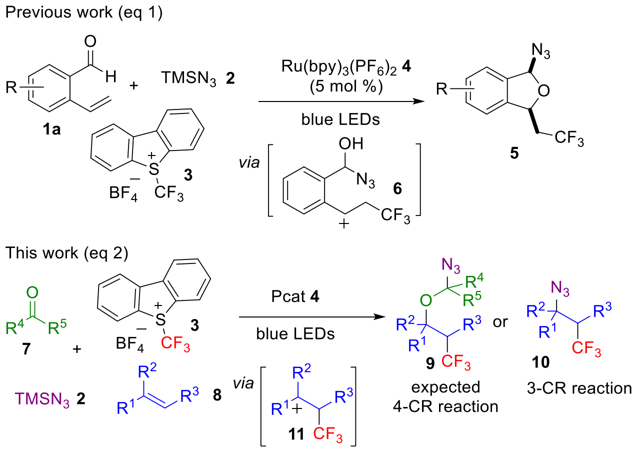


ABSTRACT: We report herein an efficient four-component photoredox-catalyzed reaction. Under the optimized conditions using [Ru(bpy)$_3$(PF$_6$)$_2$] as the photocatalyst, a wide range of terminal and internal alkenes can efficiently undergo azidoalkoxy-trifluoromethylation in the presence of Umemoto's reagent, carbonyl compound, and TMSN$_3$, giving rise to original and highly complex molecules in a single operation.

The trifluoromethyl (CF$_3$) group is an important structural motif in a large number of pharmaceuticals, agrochemicals, and organic materials. Many research efforts have been made to develop new efficient methods to incorporate the CF$_3$ group in the past years.[1] Among the various approaches, the photocatalyzed multicomponent trifluoromethylation reactions (PMCTRs) of alkenes have emerged as a powerful and ecofriendly methodology from the viewpoint of safety, simplicity, and efficiency.[2−4] In addition, this strategy offers access to diverse trifluoromethylated compounds in a single step with high synthetic efficiency from three simple and easily available reagents. In such a process, two bonds are formed with the simultaneous incorporation of the CF$_3$ group with hydrogen,[5] oxygen,[6] nitrogen,[6e,7] halogen,[8] or carbon[6e,9] into the alkenes. Despite the diversity, as far as we know, there are few examples[7a,10] in which more than three components have been incorporated into the alkenes in order to generate more elaborate trifluoromethylated products. The development of such photocatalyzed multicomponent reactions is a challenging task since one has to consider not only the reactivity match of the components but also the reactivity of the intermediates generated *in situ* and their compatibility.

Our group has previously developed a novel three-component photoredox-mediated synthesis of CF$_3$-containing phthalans through an initial nucleophilic addition of azide to vinylbenzaldehydes and a subsequent intramolecular oxytrifluoromethylation (Scheme 1).[11] Based on this precedent and our previous work,[6e,j,7b,8e,9c,12] we questioned whether a four-component reaction, in which both carbonyl and alkene

Scheme 1. Synthetic Approach of Four-Component Azidoalkoxy-Trifluoromethylation of Alkenes



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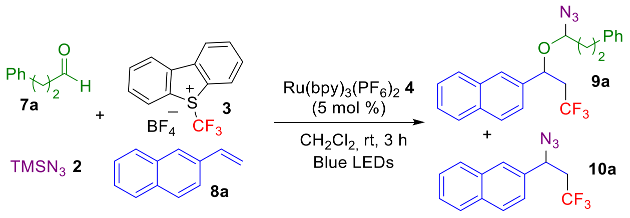
functionalities would not be linked together, could be achieved. This PMCTR might provide a facile route to highly functionalized azidoalkoxy-trifluoromethylated compound **5** through a sequence of C−CF_3, C−N, and C−O bond-forming processes. Although conceptually appealing, the execution of this four-component reaction is quite challenging. Indeed, $TMSN_3$ has a high propensity to trap the *β*-trifluoromethylated carbocation **11** to form azidotrifluoromethylated compounds **10**.[1k,3,6e,7b,e,13] In addition, the *α*-azido alcohol which is reversibly generated from aldehyde and an azide anion is a short-lived species.[14] For the reaction to succeed, the trapping of **11** by the *in situ* generated *α*-azido alcohol has to occur at a much faster rate than its trapping by the azide ion.

To test the feasibility of the proposed four-component reaction, $TMSN_3$ (**2**, 2 equiv) was added to a mixture of 2-vinylnaphthalene (**8a**, 1 equiv) and phenylpropionaldehyde (**7a**, 1 equiv) in DCM, in the presence of $Ru(bpy)_3(PF_6)_2$ **4** under blue LED light (Table 1). Our initial experiment failed, affording only the azidotrifluoromethylated three-component product **10a** in 65% yield. Gratefully, when 2 equiv of $TMSN_3$ and 3 equiv of aldehyde **7a** were employed, we did isolate the four-component adduct **9a** as a mixture of two diastereoisomers (36% yield), together with **10a** (25% yield). Based on this encouraging result, we speculated that the yield could be further improved by adjusting the stoichiometry of $TMSN_3$ and phenylpropionaldehyde (**7a**). Indeed, after a careful screening, 5 equiv of $TMSN_3$ and 6 equiv of **7a** were optimal for obtaining satisfactory yield of the desired four-component product **9a**. In this condition, the formation of three-component product **10a** was minimized (10%). Interestingly, when a catalyst such as $SnCl_2$[14b] or TfOH[14g] was added, lower yield of **9a** was obtained (entries 6−7).

Table 1. Survey of Reaction Conditions for the Photocatalyzed Azidoalkoxy-Trifluoromethylation of 7a[a]

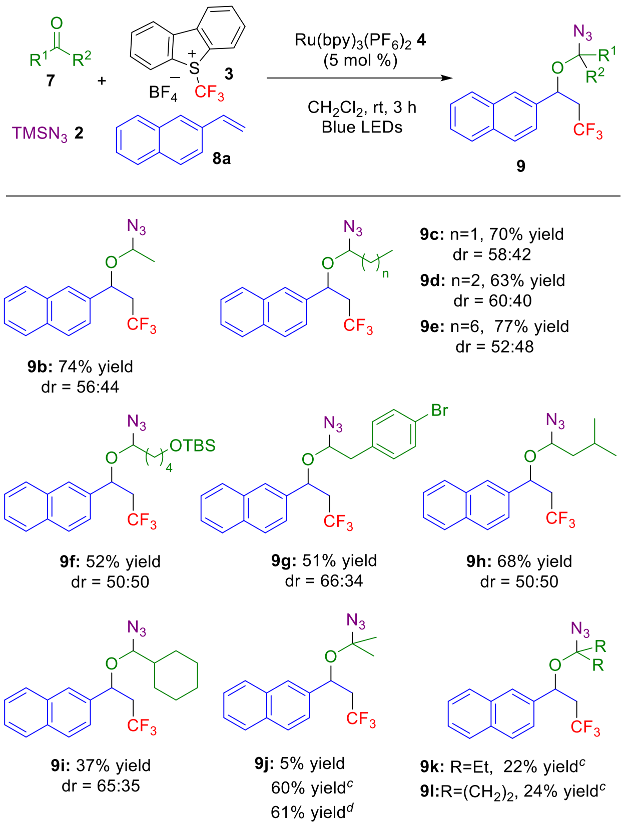


entry	*y* equiv of **2**	*z* equiv of **7a**	yield **9a** (%)[b]	yield **10a** (%)[b]
1	2	1	0	65
2	2	3	36	25
3	3	4	19	37
4	5	6	61	10
5	5	5	39	30
6[c]	5	6	18	37[e]
7[d]	5	6	20	35[e]
8[f]	5	6	-	-
9[g]	5	6	-	-
10[h]	5	6	14	13

[a]General conditions: **3** (0.15 mmol), **8a** (0.10 mmol), **2** (0.y mmol), **7a** (0.z mmol), and **4** (0.05 equiv) in distilled CH_2Cl_2 (2.0 mL) irradiated under blue LEDs at rt for 2.5 h. [b]Yields referred to chromatographically pure product and 56:44 dr were determined by ^1H NMR analysis. [c]With 10 mol % of $SnCl_2$. [d]With 1 mol % of TfOH. [e]Formation of *gem*-diazide 10% yield. [f]Without photocatalyst. [g]Without light. [h]With Umemoto triflate salt.

Having identified the optimal conditions, we next investigated the scope of this four-component azidoalkoxy-trifluoromethylation by varying the structure of carbonyl components. As shown in Scheme 2, linear aldehydes **7b−e** were all compatible, leading to the respective adducts in decent yields (up to 77% yield) with moderate diastereoselectivities. *β*-Branched aldehydes participated effectively in the four-component reaction, leading to compound **9h** in 68% yield, while *α*-branched aldehydes were much less reactive (**9i**, 37% yield). It is also worth noting that the process was compatible with aldehydes bearing functional groups such as halogen or silyl ether, affording the expected products **9f** and **9g** in 52 and 51% yields, respectively.[15] However, the four-component reaction with acetone **7j** as a partner did not proceed, and only the three-component product **10a** was observed. We found after further optimization that the three-component undesired reaction was minimized when the amount of $TMSN_3$ was reduced to 1.5 equiv. Pleasingly, the reaction was scaled up without any decrease in the yield. However, hindered ketones such as pentan-3-one and cyclobutanone led to much lower yields (**9k** and **9l**) with concurrent increase of **10a**.[16]

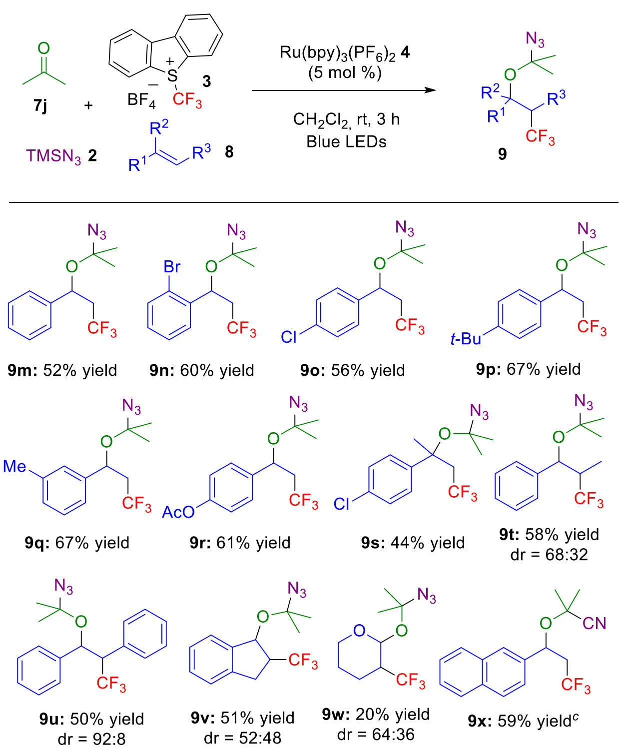
Scheme 2. Scope of Carbonyl Compounds[a,b]



[a]General conditions: **3** (0.15 mmol), **8a** (0.10 mmol), **2** (0.50 mmol), **7** (0.60 mmol), and **4** (0.05 equiv) in distilled CH_2Cl_2 (2.0 mL) irradiated under blue LEDs at rt for 2.5 h. [b]Yields refer to chromatographically pure products. The dr's were determined by ^1H NMR analysis in all cases. [c]With 1.5 equiv of **2**. [d]Reaction performed with 1 mmol of **8a**.

We next examined the scope of this four-component reaction by varying the structure of alkenes (Scheme 3). A variety of substituents such as bromine, chlorine, methyl, *tert*-

Scheme 3. Scope of Alkene Compounds[a,b]

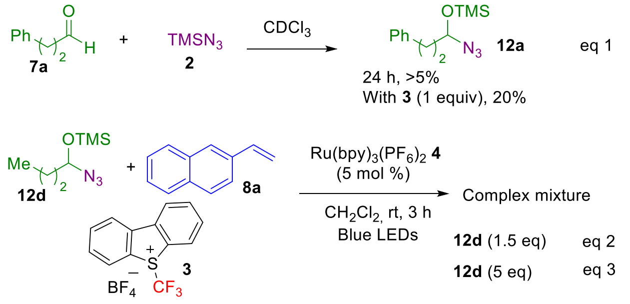


[a] General conditions: **3** (0.15 mmol), **8** (0.10 mmol), **2** (0.15 mmol), **7j** (0.60 mmol), and **4** (0.05 equiv) in distilled CH_2Cl_2 (2.0 mL) irradiated under blue LEDs at rt for 2.5 h. [b] Yields refer to chromatographically pure products. The dr's were determined by ^{1}H NMR analysis in all cases. [c] Reactions performed with TMSCN (0.15 mmol) as a nucleophile.

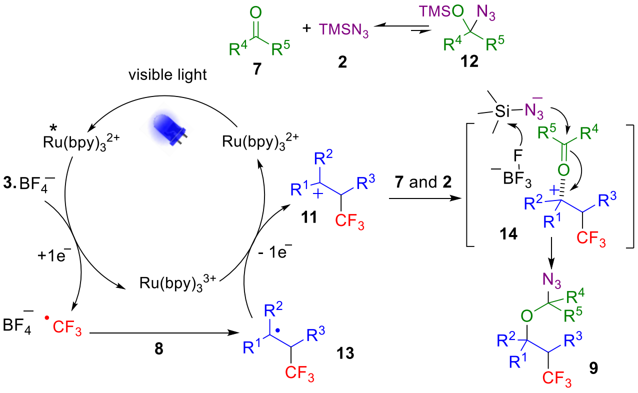
butyl, and acetate at different positions of the aromatic ring of styrenes were tolerated, affording the expected four-component adducts **9m−s** in up to 67% yield. 1,1-Disubstituted alkene was also compatible with this transformation, providing the desired trifluoromethylated tertiary azido-ether **9s** in 44% yield. Remarkably, this process could also be successfully extended to internal alkenes. For instance, *trans-β*-methylstyrene, stilbene, as well as cyclic indene smoothly reacted to afford the corresponding azidoalkoxy-trifluoromethylated products **9t−9v**, respectively, in 58−51% yields, with diastereomeric ratios from 52:48 to 92:8. It is also worth noting that only small amounts of three-component trifluoromethylated azides **10a** were isolated in all cases (<10%), thus pointing out the high selectivity in favor of the four-component transformation. On the other hand, the reaction was not limited to styrenes as dihydropyran was azidoalkoxytrifluoromethylated, furnishing the corresponding product **9w** albeit with moderate yield.[17] To our delight, TMSCN could be efficiently used instead of $TMSN_3$, leading to cyanoalkoxy-trifluoromethylation of **9w** in 59% yield.

In order to understand the mechanism of the current four-component reaction, a set of control experiments were performed (see Supporting Information). The conversion of aldehyde **7a** into the corresponding trimethylsilylated azohydrin **12a** (Scheme 4) was studied by ^{1}H NMR monitoring of a reaction mixture containing **7a** and $TMSN_3$ in DCM. It revealed that in both cases the addition of $TMSN_3$ was very slow, and only a trace of **12a** was observed after 24 h. When the same reaction was carried out in the presence of the Umemoto's reagent **3**, a slightly better conversion was noted. Also, when the preformed trimethylsilylated azohydrin **12d**[14c] prepared by the reported procedure was used, the expected azidoalkoxytrifluoromethylated product **9d** was not formed, and only a complex mixture was obtained. These results suggest that the four-component reaction is unlikely to proceed via a nucleophilic addition of **12** to **11**. On the basis of the above results as well as other reports,[2−11] a plausible reaction mechanism is shown in Scheme 5. First, irradiation with visible light excites $Ru(bpy)_3^{2+}$ into a strong reductant species $^*Ru(bpy)_3^{2+}$, which performs a single electron transfer (SET) to generate $\cdot CF_3$ from Umemoto's reagent **3** (see Supporting Information for Stern−Volmer experiments and for ST/EPR experiments).[4,6−9,11]

Scheme 4. Control Experiments



Scheme 5. Plausible Reaction Mechanism



Subsequent regioselective addition of electrophilic $\cdot CF_3$ to alkene **8** leads to the radical species **13**, which can be further oxidized into cation **11** by SET from $Ru(bpy)_3^{3+}$. Then, the corresponding cation **11** can act as an electrophilic species assisting the nucleophilic attack of $TMSN_3$ to carbonyl compound **7** with the tetrafluoroborate counteranion acting as the source of fluoride ion.[18] To support this assumption, an additional experiment using Umemoto triflate salt **3b** was performed (Table 1, entry 10) where only a little amount of **9a** (14%) and **10a** (13%) was recovered.

In conclusion, we have successfully developed an efficient azidoalkoxy-trifluoromethylation reaction. A wide range of terminal and internal alkenes as well as a variety of carbonyl compounds are compatible with this MCR, affording the corresponding trifluoromethylated compounds in up to 77% yield. Importantly, this radical/cationic process represents an efficient and straightforward example of four-component photoredox-mediated reaction. Extension of this new concept

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of photoredox MCTR is currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

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> Experimental procedures, characterization data, and NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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