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Visible-Light-Induced Trifluoromethylation of Allylic Alcohols

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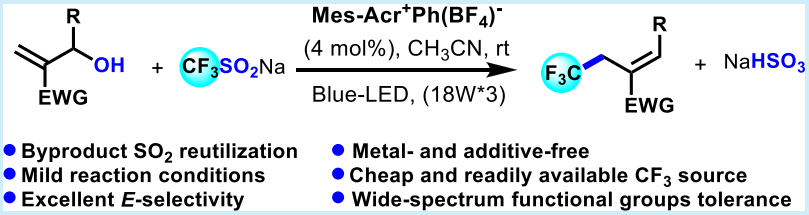
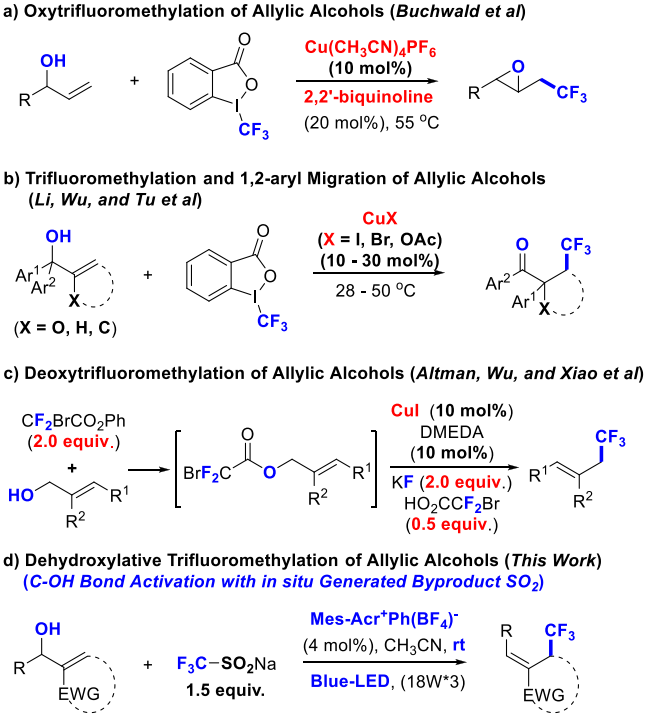


ABSTRACT: An organic photoredox-catalyzed dehydroxylative trifluoromethylation of allylic alcohols was developed in an environmentally benign manner. In this reaction, the readily available CF_3SO_2Na was selected as the trifluoromethylation reagent. The *in situ* generated byproduct SO_2 was reutilized to activate C−OH bond, which enabled this dehydroxylative trifluoromethylation to be performed conveniently. A variety of multifunctionalized CF_3-allylic compounds were obtained in high yields and excellent stereoselectivity.

The incorporation of a CF_3 group into organic molecules has a profound impact on their physical and biological properties and thus has gained increasing attention from pharmaceutical, agrochemical,[1] and materials industries.[2] In particular, CF_3-containing allyl compounds are versatile precursors.[3] However, in the few carefully tailored C(allyl)−CF_3 bond construction methods, harsh reaction conditions, superstoichiometric quantities of transition metals, and additional toxic or expensive reagents[4] were usually required. Recently, copper-catalyzed allylic trifluoromethylations of terminal alkenes were reported by Buchwald,[5a] Liu,[5b] Wang,[5c] and Qing[5d] independently for preparing monosubstituted allyl-CF_3 compounds[5] in high efficiency. Allylsilanes[6] or allylic acetates[7] were also identified as suitable feedstocks to afford CF_3-containing di- or tri-substituted olefins by Sodeoka and Singh, respectively.

Targeting minimal waste and high sustainability, the direct dehydroxylative trifluoromethylation of commercially available allylic alcohols is highly sought-after and represents a much greener, atom- and step-economical approach for C(allyl)−CF_3 bond construction. Despite the inherently strong C−OH bonds[8] and versatile reactivity of allylic alcohols,[9,10] some impressive transformations, such as oxytrifluoromethylation[9] or neophyl rearrangement,[10] were developed. For instance, an amazing intramolecular oxytrifluoromethylation of allylic alcohols was realized by Buchwald[9a] (Scheme 1a). With 1,1-diaryl allylic alcohols, Li and Wu[10a] and Tu[10b] independently reported powerful trifluoromethylation-initiated radical 1,2-aryl migration[10] (Scheme 1b). In contrast, deoxy-trifluoromethylation of allylic alcohols was still a challenging task and typically required multistep transformations and suffered from a variety of limitations.[11] With extensive efforts, a promising one-pot sequential trifluoromethylation of allylic alcohol via an *in situ*

Scheme 1. Trifluoromethylation of Allylic Alcohols



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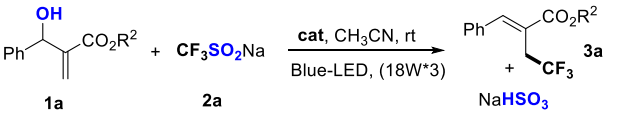
decarboxylative procedure[12] was pioneered by Altman[12a−c] with excellent regioselectivity in the presence of copper catalysts (Scheme 1c). Consequently, the exploration of metal-free and inexpensive photocatalytic procedures[13] for the dehydroxylative trifluoromethylation of allylic alcohols was enthusiastically pursued. With our continuous interest in C−OH bond cleavage and related green transformation,[14] we developed an organic photoredox-catalyzed dehydroxylative trifluoromethylation of electron-withdrawing group activated allylic alcohols (Scheme 1d), which would be complementary work to previous investigations. The desired product equipped with ester groups provided facile access to distinct molecules that previous methods could not generate. In this reaction, readily available CF_3SO_2Na[15] was selected as the trifluoromethylation reagent. Under organic photoredox catalysis, *in situ* generated byproduct SO_2 was reutilized to activate the C−OH bond, which enabled the reaction to occur through an S_N2' process under mild conditions.

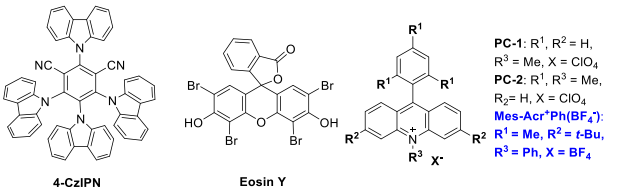
In an attempt to access the desired allyl-CF_3 compounds (**3a**), allylic alcohol (**1a**) and CF_3SO_2Na (**2a**) were selected as the model substrates. At room temperature, a variety of photoredox catalysts were screened in CH_3CN solvent (Table 1). After 24 h, only a trace amount of **3a** or even no **3a** was

Table 1. Screening Reaction Conditions[a]



entry	cat.[e] (mol %)	t (h)	**3a** (%)[b]	E/Z[c]
1	eosin Y (1)	24	0	
2	$Ru(bpy_3)Cl_2$ (1)	24	*f*	
3	$Ru(bpy_3)(PF_6)_2$ (1)	24	*f*	
4	PC-1 (1)	24	32	95/5
5	PC-2 (1)	24	26	>99/1
6	Mes-Acr$^+$Ph(BF_4^-) (1)	24	68	>99/1
7	Mes-Acr$^+$Ph(BF_4^-) (2)	10	67	>99/1
8	**Mes-Acr$^+$Ph(BF_4^-) (4)**	**4**	**73**	>99/1
9	4-CzIPN (1)	1.5	77	90/10
10[d]	Mes-Acr$^+$Ph(BF_4^-) (4)	4	0	

[a]Experimental conditions: **1** (0.3 mmol), **2a** (0.45 mmol), and **cat** were mixed in CH_3CN (4.5 mL) under blue-LED (18w*3). [b]Isolated yield. [c]Determined by crude ^1H NMR. [d]Without light sources. [e]



[f]Trace.

detected when $Ru(bpy_3)Cl_2$, $Ru(bpy_3)(PF_6)_2$, and Eosin Y were selected as the catalysts (Table 1, entries 1−3). To our delight, acridinium ion photoredox catalysts[16] PC-1 (Table 1, entry 4) and PC-2 (Table 1, entry 5) delivered **3a** in moderated yields with high E/Z ratios. Mes-Acr$^+$Ph(BF_4^-) gave a more positive result in terms of higher yield and ratio of isomers E/Z (Table 1, entry 6). Increasing the catalyst loading (Table 1, entries 7 and 8) enabled the transformation to be finished in 4 h with **3a** isolated in 73% yield (Table 1, entry 8). In the presence of catalyst 4-CzIPN,[13a,b,17] **3a** was obtained in higher yield, while the isomer ratio was as low as 90/10 (E/Z). Further investigation revealed that the reaction was sensitive to the solvent. Only diminished desired products were obtained when CH_3CN was replaced by other solvents such as DMF, THF, toluene, etc. (for details, see Supporting Information (SI), Table S1).

Subsequently, the generalizability of this reaction was evaluated using a variety of allylic alcohols (Scheme 2). Allylic alcohols with a wide variety of substituents on phenyl ring were found compatible with this transformation, delivering corresponding allylic CF_3 in good to high yields. Functional groups such as halide, CF_3, CN, NO_2, and CHO were well tolerated. Both electron-withdrawing (**3b−3h**) and electron-donating (**3i−3k**) aryl substituted allylic alcohols were amenable to this protocol. The positions of the substituents (at the *para* or *meta* positions) on the phenyl ring have limited effects on the overall transformation (**3b−3s**). In addition to monosubstituted versions, allylic alcohols with multiple substituents on the aromatic ring were compatible with the reaction (**3t**, **3u**). Fused-aromatic allylic alcohols could be utilized in this reaction, generating **3v** in a high yield. Moreover, allylic alcohols bearing heteroaryl substituents, such as pyridien-2-yl (**3w**) and thiophen-2-yl (**3x**) were also well tolerated well. In addition, methyl (2*E*,4*E*)-5-phenyl-2-(2,2,2-trifluoroethyl)-penta-2,4-dienoate (**3aa**) can be obtained by selecting cinnamenyl α-substituted allylic alcohols, albeit the yield was slightly lower. Besides aryl substituted allylic alcohols, alkyl substituted versions also worked well under identity conditions (**3ab**, **3ac**). Double trifluoromethylation was performed well by using ethyl 3-(4-(2-(ethoxycarbonyl)-1-hydroxyallyl)phenyl)-2-hydroxybut-3-enoate (**3ad**). The structure of **3ad** was determined by X-ray analysis (**3ad**, CCDC 2071921). Remarkably, γ-blocked allylic alcohols also could also participate into this transformation, albeit affording **3ae** with a lower yield. Further investigation indicated that the electron-withdrawing group on the β-position of allylic alcohol was crucial to this transformation (**3af−3ah**). For instance, no reaction occurred when 2-methyl-1-phenylprop-2-en-1-ol was selected as the substance (**3ag**). Moreover, an alkynyl group on the phenyl ring was compatible with the reaction conditions, affording **3ai** in 57% yield. This observation allowed for further functionalization with a Cu-catalyzed click reaction. Moreover, the reaction could also be performed at gram scale, with **3a** (72%, 1.76 g) and **3ai** (44%, 1.01 g) isolated in comparable yield. Without other notice (**3s**, **3x**, and **3af**), the final product was detected with excellent *E*-selectivity. Unfortunately, this catalytic system was found inefficient to primary allylic alcohols, such as methyl (*E*)-2-(hydroxymethyl)-3-phenyl acrylate or (*E*)-2-nitro-3-phenylprop-2-en-1-ol (for details, see SI).

The reproducibility of this protocol was also evaluated by using the methodologies reported by Glorius et al.[18] Factors such as concentration, oxygen level, scales, water level, temperature, and light intensity was screened and compared with the standard condition (for details, see SI, Sensitivity assessment). Among these parameters, except for the higher temperature having limited effect on this transformation, all the other variations caused only negligible changes. Therefore, this investigation indicated this reaction has good reproducibility.

The synthetic utility of this transformation was then preliminarily studied. We initially examined late-stage trifluoromethylation toward several allylic alcohols bearing biologically active skeletons. As is shown in Scheme 3, L-

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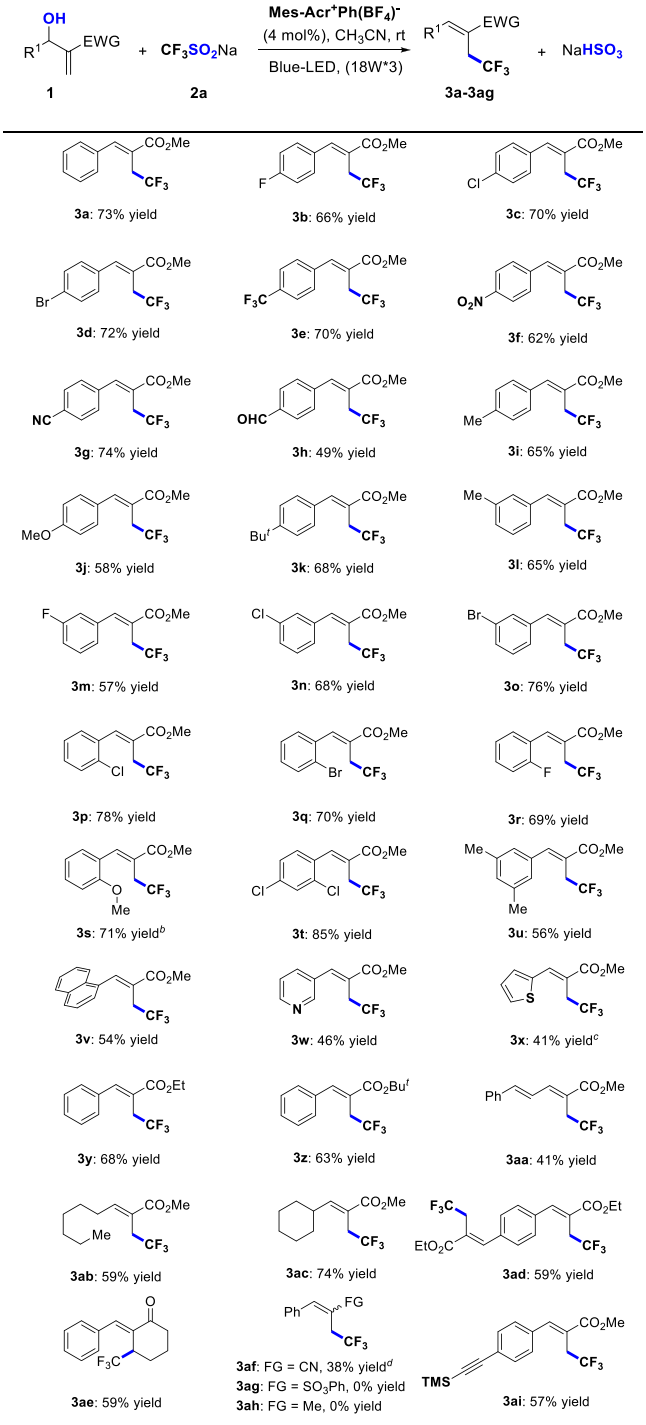
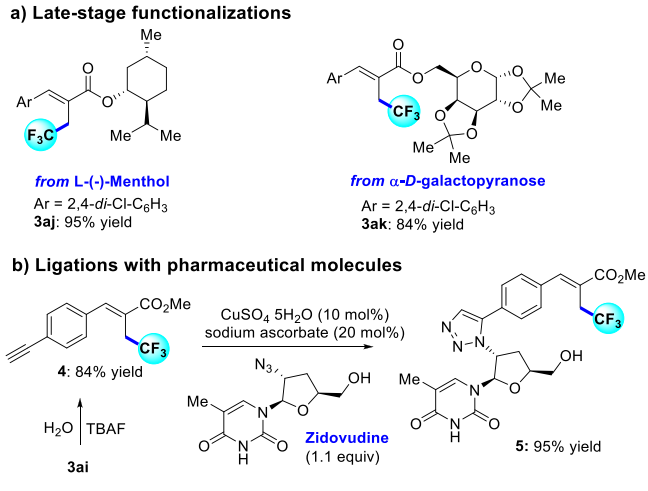
Scheme 2. Dehydroxylative Trifluoromethylation of Allylic Alcohols[a]



[a]Experimental conditions: **1** (0.3 mmol), **2a** (0.45 mmol), and Mes-Acr$^+$Ph(BF_4^-) (4.0 mol %) in CH_3CN (4.5 mL) under blue-LED (18w*3) at room temperature. Isolated yield. Unless noted, only one isomer was detected. [b]The ratio of E/Z = 98/2. [c]The ratio of E/Z = 97/3. [d]The ratio of Z/E = 82/18.

(−)-menthol (**3aj**) and α-D-galactopyranose (**3ak**) could be conveniently incorporated into the desired allylic CF_3 skeletons. The corresponding products **3aj** and **3ak** were generated in high to excellent yields. These results further highlighted the utility of this protocol in pharmaceutical-related investigations. Subsequently, the ligation of pharmaceutical molecules was investigated. As for **3ai**, the TMS moiety could be removed conveniently, and then the allylic compound **4** was successfully ligated with an antiviral drug (zidovudine) through Cu-catalyzed azide−alkyne cycloaddition, producing a new compound, **5**, in 95% yield.

Scheme 3. Late-Stage Functionalization and Ligation of Pharmaceutical Molecules



To get more insight into the reaction mechanism, we conducted Stern−Volmer fluorescence quenching experiments (for details, see SI). A 505 nm fluorescence initiated by Mes-Acr$^+$Ph(BF_4^-) was observed when the sample excited was 464 nm. The fluorescence intensity dramatically decreased when CF_3SO_2Na (**2a**) was introduced. The linear relationship between I_0/I and the concentration of **2a** indicated that **2a** was an efficient quencher of excited Mes-Acr$^+$Ph(BF_4^-). In sharp contrast, the addition of allylic alcohol **1a** has little effect on fluorescence intensity. These results revealed that excited Mes-Acr$^+$Ph(BF_4^-) oxidized **2a** rather than allylic alcohol **1a**. Then, we speculated that a single electron transfer (SET) process was involved between **2a** and Mes-Acr$^+$Ph(BF_4^-) in this transformation.

Next, more control experiments were carried out. Under standard reaction conditions, **2a** was reacted with radical scavenger 2,2,6,6-tertmethylpiperidin-1-yl-oxidanyl (TEMPO). As detected by ^{19}F NMR and HRMS, the related radical generated from **2a** was trapped by TEMPO delivering adducts **6** and **7** (Scheme 4a, top). To gain insight into the role of SO_2, a control experiment was also conducted. As expected, **6** and **7** were still observed when DABCO was introduced to absorb the in situ generated SO_2.[19] This result proved DABCO has limited effect on the generation of CF_3 containing radicals (Scheme 4a, bottom). However, the model reaction of **1a** with **2a** was completely inhibited when DABCO was added (Scheme 4b, top). All these results guided us to the conclusion that SO_2 was crucial for the C−OH bond activation. Moreover, TEMPO can totally shut down the model dehydroxylative trifluoromethylation process with **6**, **7**, and **8** detected by HRMS. Furthermore, the radical mechanism of this protocol was also proven by the electron paramagnetic resonance (EPR) investigation (Scheme 4c). The parameters observed here for the spin adduct are g_{factor} = 2.0072, a(N,NO) = 13.69 G, and a(H,−(CF_3)CH) = 15.45 G. The spin Hamiltonian parameters observed for this spin adduct are in good agreement with the literature values for a CF_3 radical.[20]

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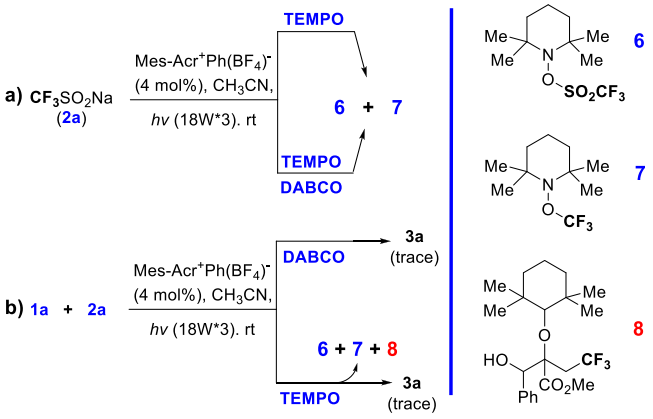
Scheme 4. Mechanism Investigations



Based upon the investigations, we proposed the plausible reaction mechanism shown in Scheme 4d. The reaction initiated with the SET of sodium trifluoromethanesulfinate (**2a**) by photoexcited Mes-Acr$^+$Ph(BF_4^-) (**PC***) to give CF_3SO_2 radical[21] and reduced Mes-Acr$^+$Ph(BF_4^-) (**PC**$^{\bullet-}$). The decomposition of radical CF_3SO_2 afforded key CF_3 radical and SO_2. Subsequently, the radical addition of CF_3 to the double bond[5,21] of allylic alcohols delivered intermediate **A**, in which the C−OH bond was activated with the in situ generated SO_2. The process was also supported by our control experiments (Scheme 4a,b). Then, the intermediate **A** reacted with **PC**$^{\bullet-}$ via a SET process[7] to form intermediate **B** with the regeneration of catalyst Mes-Acr$^+$Ph(BF_4^-) (**PC**).

In summary, we developed a Mes-Acr$^+$Ph(BF_4^-)-catalyzed dehydroxylative trifluoromethylation of allylic alcohols in an environmentally benign manner. In this reaction, the readily available CF_3SO_2Na was selected as the trifluoromethylation reagent. The *in situ* generated byproduct SO_2 can be reutilized for C−OH bond activation and served as a key factor for dehydroxylative trifluoromethylation to occur under mild conditions. A variety of multifunctionalized allylic compounds could be obtained in excellent stereoselectivities and good to excellent yields with wide-spectrum functional group tolerance. This investigation also sheds light on dehydroxylative trifluoromethylation with respect to a variety of alcohols, although at this stage, only the MBH alcohols could be used.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01767.

Experimental procedures, screening reaction conditions, analytical data for all new compounds (**3a**−**3ak**, **4**, and **5**), NMR spectra for the products, and X-ray data for **3ad** (PDF)

Accession Codes

CCDC 2071921 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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