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Three-component Oxytrifluoromethylation of Alkenes: Highly Efficient and Regioselective Difunctionalization of C=C Bonds Mediated by Photoredox Catalysts**

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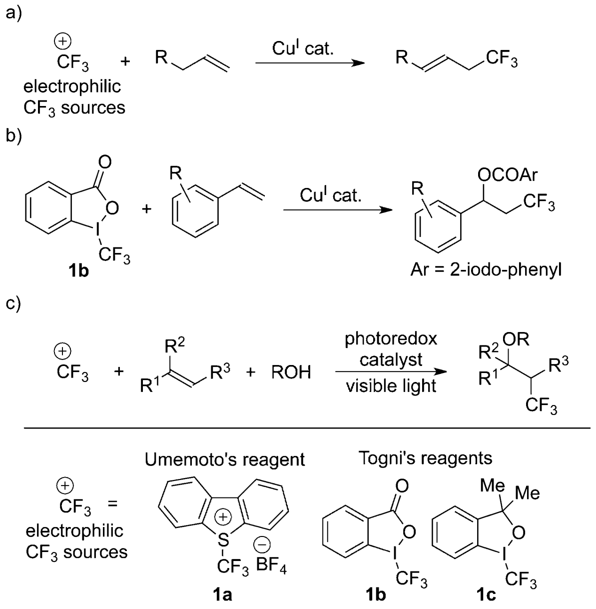
Organofluorine compounds continue to increase in importance in the pharmaceutical and agrochemical fields as well as in the materials science field.[1] In particular, the trifluoromethyl (CF_3) group is considered to be a useful structural motif in many biologically active molecules because it can often influence chemical and metabolic stability, lipophilicity, and binding selectivity.[2] Thus, the development of new methodologies for highly efficient and selective incorporation of a CF_3 group into diverse skeletal structures has attracted great interest of synthetic chemists.[3] The strategies for trifluoromethylation can be classified into three types, that is, nucleophilic, electrophilic, and radical trifluoromethylation. The electrophilic and radical transformations using Umemoto's reagent **1a** (*S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate),[4] and Togni's reagents **1b** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one) and **1c** (1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole)[5] have attracted attention because the reagents are easy to handle in terms of shelf-stable solid chemicals at room temperature.[6]

Trifluoromethylation of aromatic compounds is a hot research area and effective methods have been established.[7] In contrast, it is apparent that trifluoromethylation of simple alkenes is still developing.[8–11] Recently, Parsons and Buchwald,[8a] Liu et al.[8b] and Wang et al.[8c] reported copper-mediated allylic trifluoromethylation with electrophilic trifluoromethylating reagents, thus leading to allylic CF_3 compounds (Scheme 1 a). The detailed reaction mechanism involving a Cu/CF_3 species, and the question as to whether they proceed through a radical or nonradical pathway, is open to further discussion. During preparation of this manuscript, Szabó and co-workers reported a copper-catalyzed benzoyloxytrifluoromethylation with Togni's reagent **1b** (Scheme 1 b).[11] In contrast, recent studies by the groups of MacMillan,[12a,b] Stephenson,[9d,e] and others[12c,d] proved the conversion of CF_3I and CF_3SO_2Cl into the CF_3 radical ($^{\bullet}CF_3$) by photoredox catalysis. For the past few years, photoredox catalysis using the well-defined ruthenium(II) polypyridine derivatives (e.g. $[Ru(bpy)_3]^{2+}$) and the relevant cyclometalated iridium(III) complexes has been regarded as a valuable synthetic tool for redox reactions on the basis of their visible-light-driven single-electron transfer (SET).[13–15] We envisioned that electrophilic trifluoromethylating reagents such as Umemoto's reagent **1a** and Togni's reagents (**1b**, **c**) could also serve as precursors to the CF_3 radical in the presence of photoredox catalysts. In addition, we expected difunctionalization of alkenes through a SET photoredox process (Scheme 1 c). Although it is known that selective difunctionalization of an alkene is an extremely powerful chemical transformation, only a limited number of reports involving trifluoromethylation have been shown.[9–11] Herein, we report novel three-component intermolecular oxytrifluoromethylation of alkenes. Highly efficient (usually 2–4 h) and regioselective incorporation of a CF_3 group and a variety of O functionalities such as hydroxy, alkoxy, and carboxy



Scheme 1. Transition-metal-catalyzed trifluoromethylation of alkenes with electrophilic trifluoromethylating reagents (**1a**–**c**). a) Cu^I-mediated allylic trifluoromethylation reported by Parsons and Buchwald,[8a] Liu et al.,[8b] and Wang et al.[8c]. b) Cu^I-mediated benzoyloxytrifluoromethylation reported by Szabó and co-workers.[11] c) This work: three-component oxytrifluoromethylation by photoredox catalysis

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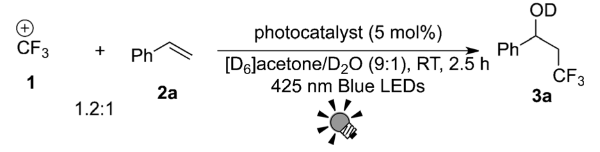
groups to C═C bonds has been achieved by photoredox catalysis under visible-light irradiation (Blue LEDs) and sunlight at room temperature.

We initially examined the photocatalytic hydroxytrifluoromethylation of styrene (**2a**) with 1.2 equivalents of **1a** or **1b**, **c** using 5 mol% of the photoredox catalyst [*fac*-Ir(ppy)$_3$][16] in a mixture of [D$_6$]acetone and D$_2$O (9:1) under visible-light irradiation (Blue LEDs: $\lambda_{max} = 425$ nm; Table 1, entries 1–3). The experiments confirmed the formation of deuterated 3,3,3-trifluoro-1-phenyl-1-propanol (**3a**) in every case, however, the choice of the trifluoromethylating reagent turned out to be crucial for efficiency and chemoselectivity. Umemoto's reagent **1a** afforded the alcohol **3a** with high chemo- and regioselectivity in 97% yield as determined by ^{1}H NMR spectroscopy (entry 1). Even when the catalyst loading was reduced to 0.5 mol% in a preparative scale experiment, **3a** was obtained in 88% yield upon isolation. In contrast, Togni's reagents **1b**, **c** provided a mixture of **3a** and olefinic by-products. Another photocatalyst, [Ru(bpy)$_3$](PF$_6$)$_2$, also promoted the present reaction in a manner similar to [*fac*-Ir(ppy)$_3$] (entry 4). Notably, the product **3a** was not obtained either in the dark or in the absence of the photoredox catalyst (entries 5 and 6), thus strongly supporting the involvement of the photoexcited species of the photoredox catalyst in the reaction.

Table 1: Optimization of photocatalytic hydroxytrifluoromethylation of styrene (**2a**).[a]

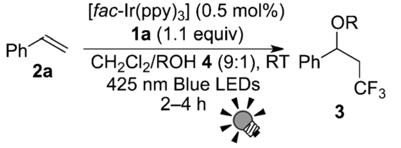


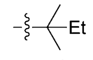
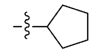
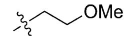
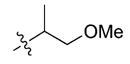
Entry	CF$_3$ reagent	Photocatalyst	Yield [%][b]
1	**1a**	[*fac*-Ir(ppy)$_3$]	97 (88[c])
2	**1b**	[*fac*-Ir(ppy)$_3$]	62
3	**1c**	[*fac*-Ir(ppy)$_3$]	4
4	**1a**	[Ru(bpy)$_3$](PF$_6$)$_2$	96
5[d]	**1a**	[*fac*-Ir(ppy)$_3$]	0
6	**1a**	none	0

[a] Reaction conditions as indicated. [b] Yield determined by NMR spectroscopy. [c] Yield of isolated product from preparative scale reaction; see the Supporting Information. [d] In the dark. bpy = 2,2′-bipyridine, LED = light-emitting diode, ppy = 2-phenylpyridine.

Next, we investigated other O nucleophiles (ROH; **4**) such as alcohols and carboxylic acids (Table 2). All reactions were conducted in dry CH$_2$Cl$_2$/ROH because the present hydroxytrifluoromethylation is so efficient that it can be promoted by a trace amount of water in the acetone solvent.[17] As a result, alkoxytrifluoromethylation and carboxytrifluoromethylation smoothly proceeded not only to introduce a CF$_3$ group to an alkene but also to construct ether and ester functionalities. Reactions of **2a** with primary (**4a–c** and **4g**) and secondary (**4d**,**f**) alcohols produced the expected CF$_3$-substituted ethers **3aa–ad**, **3af**, and **3ag** in good yields (entries 1–4, 6, and 7). The sterically hindered tertiary alcohol *tert*-amyl alcohol (**4e**), resulted in a low yield of **3ae** (entry 5). The reaction of 1-methoxy-2-propanol (**4h**) gave the product in 87% yield as a mixture of two diastereomers (1:1; entry 8). Acetic acid (**4i**) and propionic acid (**4j**) afforded the corresponding CF$_3$-containing esters **3ai** and **3aj** in 74 and 72% yield, respectively (entries 9 and 10). These results indicate that the present photocatalytic oxytrifluoromethylation leads to the efficient and regioselective reactions, regardless of the O nucleophiles.

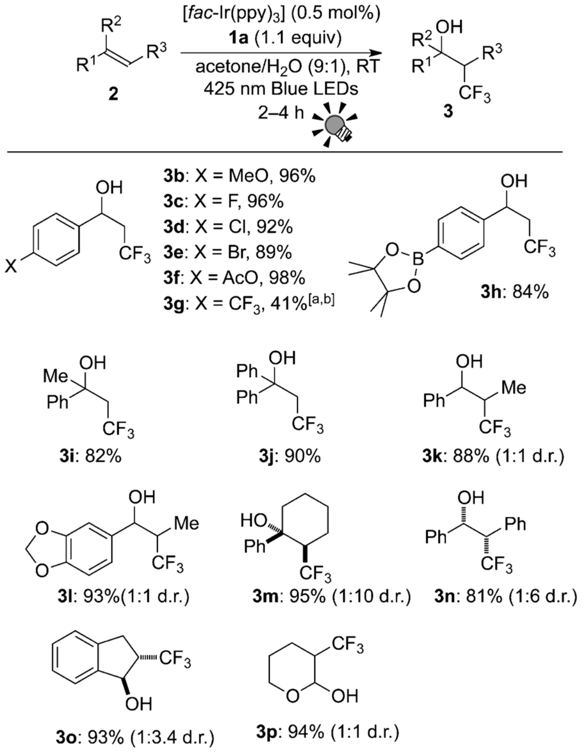
Table 2: Photocatalytic oxytrifluoromethylation of styrene **2a**.[a,b]



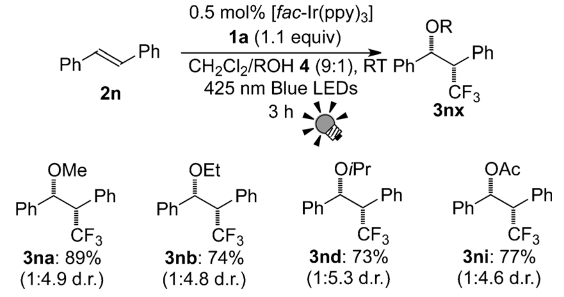
Entry	4	R	Yield [%][c]
1	**4a**	Me	**3aa**: 78 (99[d])
2	**4b**	Et	**3ab**: 75
3	**4c**	*n*Pr	**3ac**: 76
4	**4d**	*i*Pr	**3ad**: 84
5	**4e**		**3ae**: 51
6	**4f**		**3af**: 72
7	**4g**		**3ag**: 74
8	**4h**		**3ah**: 87 (1:1 d.r.)
9	**4i**	COMe	**3ai**: 74
10	**4j**	COEt	**3aj**: 72

[a] For reaction conditions, see the Supporting Information. [b] Yields of the isolated products are lower than those determined by NMR spectroscopy because of the volatility of the products. [c] Yield of isolated products. [d] Yield was determined by ^{1}H NMR spectroscopy using tetraethylsilane as an internal standard.

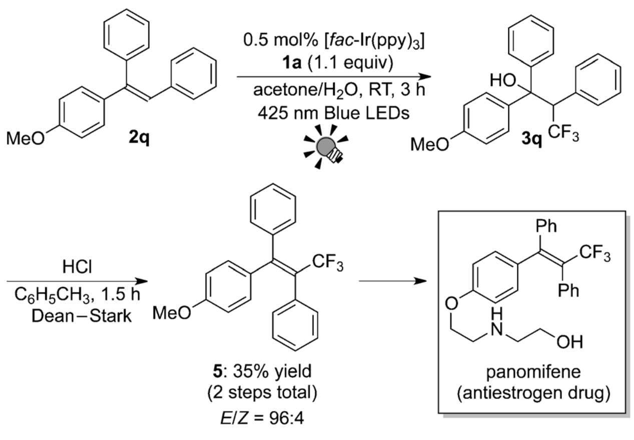
The scope and limitations of the present photocatalytic hydroxytrifluoromethylation are summarized in Scheme 2. Styrenes with the electron-donating substituent MeO (**2b**) on the benzene ring smoothly produced the corresponding three-component coupling product **3b** in 96% yield after 2.5 hours. In addition, this reaction can be applied to styrenes bearing halogen atoms such as F (**2c**), Cl (**2d**), and Br (**2e**), an ester group such as AcO (**2f**), a boronic acid ester such as Bpin (**2h**), and an acetal group (**2l**). The corresponding alcohol products **3c–f**,**h**[18] and **l** were obtained in good yields (84–98%) without any loss of the functional groups. In particular, the Br and Bpin functionalities can serve as potential handles for additional transformations. In contrast, substrates with a strongly electron-withdrawing group such as CF$_3$ (**2g**) on the benzene ring resulted in a low yield. Styrenes with α-alkyl and α-aryl substituents (**2i** and **j**) afforded the corresponding alcohols **3i** (82%) and **3j** (90%), respectively. Next, to expand the scope, internal alkenes were examined. The reaction of *trans*-β-methylstyrene (**2k**) gave the single regioisomer **3k** as a mixture of two diastereomers (1:1 d.r.) in 88% yield, and has the 1,1,1-trifluoroisopropyl skeleton used as modifications of amino acids and biologically active compounds.[19] Remarkably, the reaction of the trisubstituted alkene 1-phenylcyclohexene (**2m**) proceeded in a highly regio- and diastereoselective manner (1:10 d.r.), that is, the



Scheme 2. The scope and limitations of the present hydroxytrifluoromethylation. Yield are given as yields of isolated products. For reaction conditions, see the Supporting Information. [a] Yield was determined by ^{1}H NMR spectroscopy using tetraethylsilane as an internal standard. [b] Irradiation time = 8 h.



Scheme 3. Studies on diastereoselective oxytrifluoromethylation of *trans*-stilbene (**2n**).



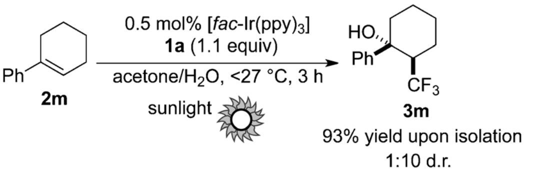
Scheme 4. Application to synthesis of CF_3-containing tetrasubstituted alkene: panomifene.

CF_3 and hydroxy groups were introduced in an *anti* fashion, in 95% yield. The reactions of *trans*-stilbene (**2n**) and indene (**2o**) also showed a moderate diastereoselectivity. Furthermore, the electron-rich alkene 3,4-dihydro-2*H*-pyran (**2p**) can be used in this photocatalytic system. However, the simple linear alkene 1-octene did not react at all.[20] These results show that the present hydroxytrifluoromethylation is regiospecific for both terminal and internal electron-rich alkenes. In addition, the featured effectiveness of styryl substrates and electron-rich alkenes supports the involvement of the electron-deficient CF_3 radical in this reaction.

Stereoselective difunctionalization of alkenes is the next stage for this work. Before advancing to stereocontrolled reactions, we tested diastereocontrolled reactions by changing the O nucleophiles. Based on the results summarized in Scheme 2, **2n** was chosen as a substrate because diastereoselective hydroxytrifluoromethylation of **2n** was observed to a certain extent. As a result, oxytrifluoromethylation with O nucleophiles such as MeOH, EtOH, *i*PrOH, and AcOH exhibited similar d.r. values (1:4.6–5.3) as shown in Scheme 3. These results suggest the reactions proceed through the common 3,3,3-trifluoro-1,2-diphenylpropyl intermediate having the same configuration.

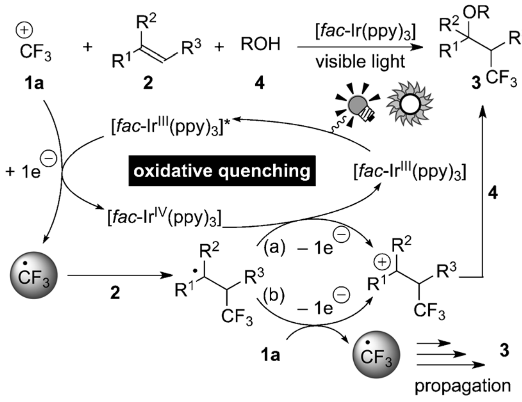
Encouraged by the highly efficient and selective hydroxytrifluoromethylation of the trisubstituted alkene **2m**, we expanded this transformation to the reaction of the 1,1,2-triphenylethylene derivative **2q** (Scheme 4). The hydroxytrifluoromethylation of **2q** and sequential dehydration gave the key intermediate **5** for the preparation of panomifene, which is reported to exhibit antiestrogenic activity and is a well-known drug for the treatment of breast cancer.[21] Indeed, the CF_3-containing tetrasubstituted alkene **5** was obtained in 35% yield. This result suggests we can easily access to the corresponding CF_3-containing alkenes by the consecutive hydroxytrifluoromethylation and dehydration processes.

Finally, it was found that the present photocatalytic hydroxytrifluoromethylation can harness sunlight as a light source. It should be noted that sunlight induced the reaction with an efficiency and selectivity similar to that for the irradiation with Blue LEDs [Eq. (1)].



(1)

On the basis of the experimental results, a plausible reaction mechanism is shown in Scheme 5. First, irradiation of visible light excites [*fac*-Ir^{III}(ppy)$_3$] to [*fac*-Ir^{III}(ppy)$_3$]*. Luminescence quenching experiments support the SET process between [*fac*-Ir^{III}(ppy)$_3$]* and **1a** (see the Supporting Information). Choice of the CF_3 source is key in the present photocatalytic transformation. We showed that use of **1b**, **c** instead of **1a** leads to loses in efficiency and selectivity.



Scheme 5. A plausible reaction mechanism.

Electrochemical analysis of the CF_3 sources provides a reasonable explanation with respect to efficiency. Cyclic voltammograms for **1a**,**b**, and **c** contain irreversible reduction waves at −0.75 V, −1.34 V, and −1.49 V (vs Cp_2Fe in CH_3CN), respectively. These data indicate that **1a** is reduced more easily than **1b** and **c**, thus leading to generation of $^{\bullet}CF_3$. Addition of $^{\bullet}CF_3$ to the alkenes **2** gives the alkyl radical intermediate, which is oxidized by the [*fac*-Ir^{IV}(ppy)$_3$] formed by the SET process (path a in Scheme 5). Subsequent nucleophilic attack of **4** on the carbocation intermediate produces the three-component coupled product **3**. We cannot rule out radical chain propagation mechanism (path b), but the present transformation requires continuous irradiation of visible light (see Figure S8 in the Supporting Information), thus suggesting that chain propagation is not a main mechanistic component.

In conclusion, we have developed the first visible-light-driven three-component oxytrifluoromethylation of alkenes using the photoredox catalyst [*fac*-Ir(ppy)$_3$]. This highly efficient (usually 2–4 h) and regioselective (100% in all cases) radical transformation of alkenes proceeds even at room temperature under sunlight (under mild reaction conditions) and makes use of a broad range of O nucleophiles such as alcohols, carboxylic acids, and water. In addition, these reactions are operationally easy. Furthermore, this photocatalytic reaction was used in the synthesis of the antiestrogen drug panomifene from the corresponding triarylalkene. Importantly, Umemoto's reagent turns out to be crucial for efficient and selective reaction. The additional development of this method in the directed synthesis of pharmaceuticals and agrochemicals is a continuing effort in our laboratory.

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[18] The molecular structure of **3h** is shown in the Supporting Information. CCDC 887925 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/data_request/cif.

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