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Visible-light-induced synthesis of a variety of trifluoromethylated alkenes from potassium vinyltrifluoroborates by photoredox catalysis†

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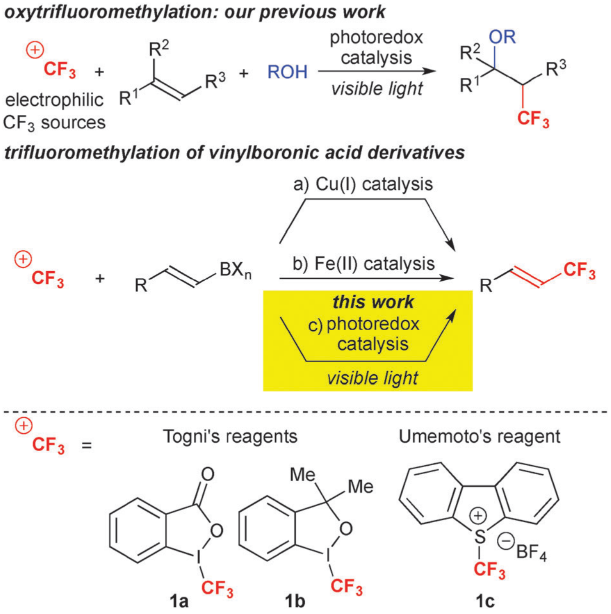
A facile synthesis of trifluoromethylated alkenes by the radical-mediated trifluoromethylation of vinyltrifluoroborates has been developed. Togni's reagent serves as a CF_3 radical precursor in the presence of the photoredox catalyst $[Ru(bpy)_3](PF_6)_2$ under visible light irradiation. This new photocatalytic protocol can be applicable to a wide variety of vinylborates containing electronically diverse substituents and hetero-aromatics.

The trifluoromethyl (CF_3) group is a useful structural motif in many biologically active molecules as well as materials.[1,2] Thus, the development of new methodologies for highly efficient and selective incorporation of a CF_3 group into diverse skeletons has attracted great interest of synthetic chemists.[3] Over the past few years, a variety of transition-metal-catalyzed trifluoromethylations of aromatic molecules have been well developed.[4] On the other hand, effective construction of $C_{alkenyl}$–CF_3 bonds is significantly more limited although trifluoromethylated alkenes are promising building blocks for pharmaceuticals, agrochemicals and functional materials.[2a,3b,5–7]

The strategies for trifluoromethylation using electrophilic trifluoromethylating ($^+CF_3$) reagents such as Togni's reagents **1a** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one), **1b** (1-trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benzioxodole) and Umemoto's reagent **1c** (*S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate) have attracted great attention because the reagents are easy-to-handle chemicals in terms of being shelf-stable solid compounds at room temperature.[8–10] Over the past few years, several catalytic synthetic methods for construction of $C_{alkenyl}$–CF_3 bonds with "$^+CF_3$" reagents have been reported.[11] The groups of Shen and Liu have shown non-stereoselective trifluoromethylation of vinylboronic acids by Cu(I) catalysis (Scheme 1a).[11a,b] Furthermore, Buchwald and co-workers reported an Fe(II)-catalyzed stereoselective trifluoromethylation of vinyltrifluoroborates (Scheme 1b).[11c] In addition, there are a few reports on copper-mediated trifluoromethylation of α,β-unsaturated carboxylic acids,[11d] alkynes[11e] and enamides.[11f] These methods, however, exhibit limited substrate scopes with respect to hetero-aromatics and functional groups. Therefore, a new protocol for construction of $C_{alkenyl}$–CF_3 bonds with broad scope as well as in an efficient and stereoselective manner is highly desirable.



Scheme 1 Photoredox-catalysed trifluoromethylation using electrophilic trifluoromethylating reagents (**1a–c**).

Recently, there have been several reports on radical trifluoromethylation by photoredox catalysis, which is regarded as a useful redox tool for organic compounds *via* single electron transfer (SET) in the presence of well-defined ruthenium(II) polypyridine complexes (*e.g.* $[Ru(bpy)_3]^{2+}$) and the relevant cyclometalated iridium(III) derivatives under visible light irradiation,[12–16] and conventional trifluoromethyl radical ($^\bullet CF_3$) sources such as CF_3SO_2Cl **1d** and gaseous CF_3I were used. These "$^\bullet CF_3$" precursors, however, require operational carefulness and special apparatus. In contrast, we have previously

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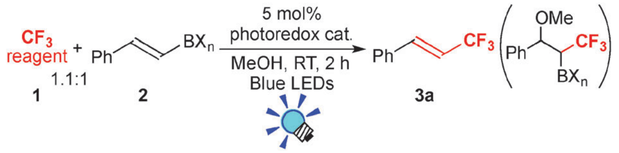
reported the photoredox-catalyzed oxytrifluoromethylation of alkenes with “$^{+}CF_3$” reagents based on usual laboratory techniques and equipment.[14c] Importantly, easy-to-handle “$^{+}CF_3$” reagents can serve as “$^{\bullet}CF_3$” precursors in the presence of photoredox catalysts under visible light irradiation.

Herein we disclose highly efficient and stereoselective deboronated trifluoromethylation of vinyltrifluoroborates with commercially available and air-stable Togni's reagent **1a** by visible-light-driven photoredox catalysis (Scheme 1c). In particular, this new photocatalytic protocol is effective in the selective and large-scale synthesis of (*E*)-trifluoromethylated alkenes bearing a π-electron-deficient hetero-aromatic moiety, which are difficult to access by previous catalytic systems.

We initially examined the photocatalytic trifluoromethylation of (*E*)-styrylboronic acid derivatives **2** with 1.1 equiv. of Togni's reagent **1a** as the CF_3 source in the presence of 5 mol% photoredox catalyst $Ir(ppy)_3$[17] in MeOH under visible light irradiation (blue LEDs: λ_{max} = 425 nm) for 2 h. Every entry resulted in formation of β-trifluoromethylstyrene **3a** (Table 1, entries 1–3). As a result, the choice of the boron auxiliary turned out to be crucial for better yield and selectivity. The reaction of potassium (*E*)-styryltrifluoroborate **2a** afforded the product **3a** with an *E*/*Z* ratio of 94/6 in 85% yield (entry 3). In contrast, the substrates with $B(OH)_2$ and Bpin groups gave mixtures of **3a** and methoxytrifluoromethylated by-product. Next, examination of the CF_3 reagents revealed that **1a** is the best choice in terms of yield and selectivity. The use of **1b** and **1c** provided product **3a** in good yields, but did not improve the *E*/*Z* selectivity (entries 4 and 5). A typical CF_3 radical source **1d** gave a mixture of product **3a**, styrene and unidentified by-products (entry 6). Finally, the Ru photocatalyst $[Ru(bpy)_3](PF_6)_2$ also promoted the present reaction, providing the product **3a** with excellent *E*/*Z* selectivity (98/2) in 81% yield upon 5 h irradiation (entry 7). Notably, the product **3a** was not obtained at all either in the dark or in the absence of the photoredox catalyst (entries 8 and 9), strongly supporting that the photoexcited species of the photoredox catalyst play key roles in the reaction.

Table 1 Optimization of photocatalytic trifluoromethylation of (*E*)-styrylboronic acid derivatives **2**

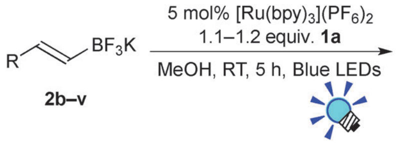


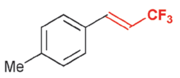
Entry	CF_3 reagent	BX_n	Photoredox catalyst	*E*/*Z*[a]	Yield[a]/%
1	**1a**	$B(OH)_2$	$Ir(ppy)_3$	57/43	53
2	**1a**	Bpin	$Ir(ppy)_3$	54/46	36
3	**1a**	BF_3K **2a**	$Ir(ppy)_3$	94/6	85
4	**1b**	BF_3K **2a**	$Ir(ppy)_3$	90/10	83
5	**1c**	BF_3K **2a**	$Ir(ppy)_3$	85/15	79
6[b]	CF_3SO_2Cl **1d**	BF_3K **2a**	$Ir(ppy)_3$	99/1	27
7[c]	**1a**	BF_3K **2a**	$[Ru(bpy)_3](PF_6)_2$	98/2	81
8	**1a**	BF_3K **2a**	none	—	0
9[d]	**1a**	BF_3K **2a**	$[Ru(bpy)_3](PF_6)_2$	—	0

ppy = 2-phenylpyridine, bpy = 2,2′-bipyridine. For reaction conditions, see the ESI.[a] Yields and *E*/*Z* ratios were determined by ^1H and ^{19}F NMR spectroscopies. [b] CD_3CN was used as solvent. [c] Reaction time = 5 h. [d] In the dark.

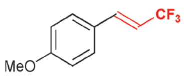
The scope and limitations of the present photocatalytic trifluoromethylation of vinyltrifluoroborates are summarized in Table 2. (*E*)-Styrylborates with electron-donating substituents, Me (**2b, l**) and MeO (**2c**), smoothly produced the corresponding β-CF_3-styrene products with high *E*/*Z* selectivities in good yields (**3b, c, l**). In addition, this reaction can be applied to vinylborates bearing a variety of electron-withdrawing functional groups, F (**2i**), Cl (**2d**), Br (**2e**), CF_3 (**2f, j**), OCF_3 (**2g**), CN (**2h**), and NHBoc (**2k**). The corresponding trifluoromethylated alkene products (**3d–k**) were obtained without deterioration by the functional groups with excellent *E*/*Z* selectivities (>94/<6) in high yields (68–93%). This broad applicability of vinylborates is remarkable. The above-mentioned Buchwald's catalytic system is ineffective for electron-deficient substrates.[11c]

Table 2 The scope of the present trifluoromethylation of vinylborates[a,b]

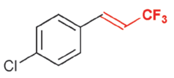




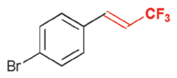
3b: 81%
E/*Z* = 92/8



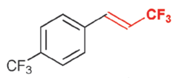
3c: 88%
E/*Z* = 99/1



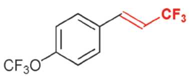
3d: 72%
E/*Z* = 94/6



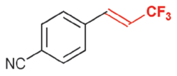
3e: 81%
E/*Z* = 95/5



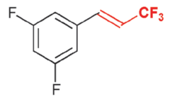
3f: 79%[c,d]
E/*Z* = 98/2



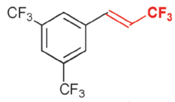
3g: 69%
E/*Z* = 95/5



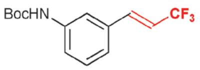
3h: 78%
E/*Z* = 96/4



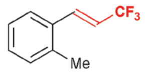
3i: 68%
E/*Z* = 96/4



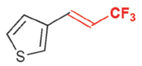
3j: 81%[c,d]
E/*Z* = 97/3



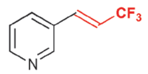
3k: 93%
E/*Z* = 94/6



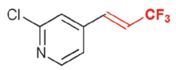
3l: 70%
E/*Z* = 95/5



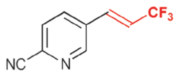
3m: 63%[e,f]
E/*Z* = 96/4



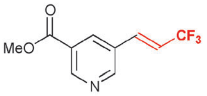
3n: 68%
E/*Z* = 97/3



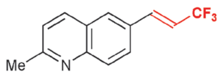
3o: 56%
E/*Z* = 98/2



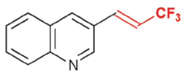
3p: 66%
E/*Z* = 98/2



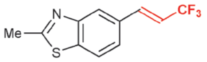
3q: 70%
E/*Z* = 98/2



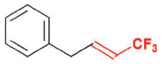
3r: 69%
E/*Z* = 97/3



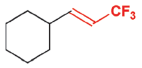
3s: 71%
E/*Z* = 98/2



3t: 82%
E/*Z* = 97/3

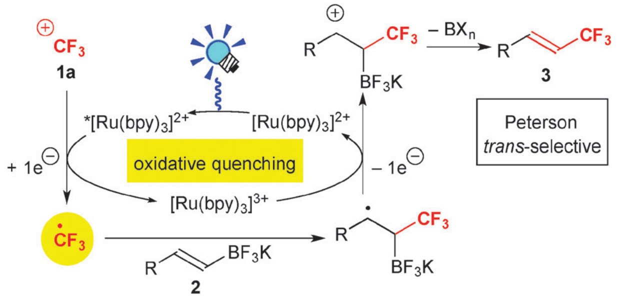


3u: 60%
E/*Z* = 63/37



3v: 79%[g]
E/*Z* = 73:27

For reaction conditions, see the ESI. [a] Isolated yields. [b] *E*/*Z* ratios were determined by ^1H and ^{19}F NMR spectroscopies of the crude product mixtures. [c] Photocatalyst $Ir(ppy)_3$ (0.5 mol%) was used. [d] Reaction time = 2 h. [e] 1.1 equiv. of vinylborate with respect to **1** was used. [f] Protodeboronated by-product was obtained in 2% yield. [g] NMR yield.



Scheme 2 A plausible reaction mechanism.

Next, vinylborates containing heteroaryl groups such as thiophene, pyridine, quinoline and benzothiazole were examined. Hetero-aromatic substrates are relevant to pharmaceuticals and agrochemicals because hetero-arenes are ubiquitous structures in biologically active compounds.[18] Remarkably, the photocatalytic reactions of **2m–t** gave the corresponding CF_3-substituted alkenes **3m–t** with excellent *E*/*Z* selectivities (>96/<4) in good yields (56–82%). The catalytic formation of $C_{alkenyl}$–CF_3 bonds connected with π-electron-deficient hetero-aromatics has not been so far reported,[11] thus the present photocatalytic protocol might be attractive from the viewpoint of regio- and stereoselective introduction of a CF_3 group into these scaffolds. Furthermore, alkylvinylborates (**2u** and **v**) can also be applicable to this photocatalytic system with moderate selectivities and good yields (**3u** and **v**).

As a demonstration of scalability of this transformation, the trifluoromethylation of **2s** was carried out on a gram scale. As a result, the trifluoromethylated alkene with quinoline moiety **3s**, which is a herbicide-related molecule,[7] was obtained in good yield (64%, 1.06 g) with excellent *E*/*Z* selectivity (>99/<1) (see the ESI†).

A plausible reaction mechanism based on a SET photoredox process (oxidative quenching) is shown in Scheme 2. According to our previous report,[14c,19] $^{\bullet}CF_3$ can be generated from 1e-reduction of electrophilic Togni's reagent **1a**. $^{\bullet}CF_3$ reacts with a C=C bond of vinylborates **2** to give β-borato-stabilized radical intermediates[20] in a regioselective manner. Subsequent 1e-oxidation by the high-oxidation state photocatalyst $[Ru(bpy)_3]^{3+}$ produces β-borato cation intermediates. Finally predominant Peterson elimination of the boron-based group with *trans*-selectivity provides (*E*)-trifluoromethylated alkenes **3**.[21] However we could not rule out the possibility that a mechanism including radical chain propagation occurs.

In conclusion, we have developed a new and facile visible-light-induced synthesis of a variety of trifluoromethylated alkenes using a Ru photoredox catalyst. Togni's reagent **1a** plays an important role as a CF_3 radical source. This photocatalytic system allows easy access to (*E*)-trifluoromethylated alkenes bearing electron-deficient moieties such as π-electron-deficient hetero-aromatics. We expect this protocol to be of broad utility in the synthesis of biologically active organofluorine molecules.

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