Direct C–H trifluoromethylation of di- and trisubstituted alkenes by photoredox catalysis

Ren Tomita, Yusuke Yasu, Takashi Koike* and Munetaka Akita*

Abstract

Background: Trifluoromethylated alkene scaffolds are known as useful structural motifs in pharmaceuticals and agrochemicals as well as functional organic materials. But reported synthetic methods usually require multiple synthetic steps and/or exhibit limitation with respect to access to tri- and tetrasubstituted CF₃-alkenes. Thus development of new methodologies for facile construction of C–Calkenyl–CF₃ bonds is highly demanded.

Results: The photoredox reaction of alkenes with 5-(trifluoromethyl)dibenzo[b,d]thiophenium tetrafluoroborate, Umemoto’s reagent, as a CF₃ source in the presence of [Ru(bpy)]²⁺ catalyst (bpy = 2,2’-bipyridine) under visible light irradiation without any additive afforded CF₃-substituted alkenes via direct C–Calkenyl–H trifluoromethylation. 1,1-Di- and trisubstituted alkenes were applicable to this photocatalytic system, providing the corresponding multisubstituted CF₃-alkenes. In addition, use of an excess amount of the CF₃ source induced double C–H trifluoromethylation to afford geminal bis(trifluoromethyl)alkenes.

Conclusion: A range of multisubstituted CF₃-alkenes are easily accessible by photoredox-catalyzed direct C–H trifluoromethylation of alkenes under mild reaction conditions. In particular, trifluoromethylation of triphenylethene derivatives, from which synthetically valuable tetrasubstituted CF₃-alkenes are obtained, have never been reported so far. Remarkably, the present facile and straightforward protocol is extended to double trifluoromethylation of alkenes.

Introduction

The trifluoromethyl (CF₃) group is a useful structural motif in many bioactive molecules as well as functional organic materials [1-6]. Thus, the development of new methodologies for highly efficient and selective incorporation of a CF₃ group into diverse skeletons has become a hot research topic in the field of organic synthetic chemistry [7-12]. Recently, radical trifluoro-
methylation by photoredox catalysis [13-23] with ruthenium(II) polypyridine complexes (e.g., [Ru(bpy)3]2+ (bpy: 2,2’-bipyridine)), the relevant Ir cyclometalated complexes (e.g., fac-Ir(ppy)3 (ppy: 2-phenylpyridine)) and organic dyes has been developed; the trifluoromethyl radical (CF3) can be easily generated from conventional CF3 radical precursors such as CF3I, CF3SO2Cl and CF3SO2Na through visible-light-induced single-electron transfer (SET) processes [24-32]. On the other hand, we have intensively developed trifluoromethylations of olefins by the Ru and Ir photoredox catalysis using easy-handling and shelf-stable electrophilic trifluoromethylating reagents [33-36] (+CF3) such as Umemoto’s reagent (1a, 5-(trifluoromethyl)dibenzo[b,d]thiophenium tetrafluoroborate) and Togni’s reagents (1b (1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one) and 1c (3,3-dimethyl-1,3-dihydro-1,2-benziodoxole) [37-41]. It was found that electrophilic trifluoromethylating reagents (+CF3) can serve as more efficient CF3 radical sources under mild photocatalytic reaction conditions. In addition, the putative β-CF3 carbocation intermediate formed through SET photoredox processes is playing a key role in our reaction systems (vide infra).

Trifluoromethylated alkenes, especially multi-substituted CF3-alkenes (3,3,3-trifluoropropene derivatives), have attracted our attention as fascinating scaffolds for agrochemicals, pharmaceuticals, and fluorescent molecules (Scheme 1) [3,42-45].

Conventional approaches to CF3-alkenes require multiple synthetic steps [46-54]. In contrast, “trifluoromethylation” is a promising protocol to obtain diverse CF3-alkenes easily. Several catalytic synthetic methods via trifluoromethylation have been developed so far [38,55-62]. Most of these reactions require prefunctionalized alkenes as a substrate (Scheme 2a). Additionally, only a limited number of examples for synthesis of tri/tetra-substituted CF3-alkenes have been reported so far. Recently, the groups of Szabó and Cho described trifluoromethylation of alkenes, leading to trifluoromethylated alkenes but the application to the synthesis of tetrasubstituted CF3-alkenes is not well documented (Scheme 2b) [63,64]. Another straightforward approach is direct C–H trifluoromethylation of alkenes (Scheme 2c). The groups of Loh, Besset, Cahard, Sodeoka and Xiao showed that copper catalysts can induce a C–H trifluoromethylation of alkenes by electrophilic CF3 reagents (+CF3) [65-69]. In addition, Cho et al. reported that the reaction of unactivated alkenes with gaseous CF3I in the presence of a Ru photocatalyst, [Ru(bpy)3]2+, and a base, DBU (diazabicyclo[5,4,0]undec-7-ene) produced CF3-alkenes through iodotrifluoromethylation of alkenes followed by base-induced E2 elimination [70]. To the best of our knowledge, however, the development of synthetic methods for tri- and tetrasubstituted CF3 alkenes through Calkenyl-H trifluoromethylation of simple alkenes have been left much to be desired.

Previously, we reported on the synthesis of CF3-alkenes via sequential photoredox-catalyzed hydroxytrifluoromethylation and dehydration (Scheme 3a) [37] and photoredox-catalyzed trifluoromethylation of alkenylborates (Scheme 3b) [38]. These results prompted us to explore photoredox-catalyzed C–H trifluoromethylation of di- and trisubstituted alkenes (Scheme 3c). Herein we disclose a highly efficient direct C–H trifluoromethylation of di- and trisubstituted alkenes with easy-handling and shelf-stable Umemoto’s reagent 1a by visible-light-driven photoredox catalysis under mild conditions. This photocatalytic protocol allows us easy access to a range of multi-substituted trifluoromethylated alkenes. In addition, our methodology can
be extended to a double trifluoromethylation of 1,1-disubstituted alkenes.

Scheme 3: Our strategies for synthesis of CF₃-alkenes.

Results and Discussion
The results of investigations on the reaction conditions are summarized in Table 1. We commenced examination of photocatalytic trifluoromethylation of 1,1-diphenylethene 2a with 1 equivalent of Umemoto’s reagent 1a in the presence of 5 mol % fac-Ir(ppy)₃, a photoredox catalyst, and 2 equivalents of K₂HPO₄, a base, in [D₆]-DMSO under visible light irradiation (blue LEDs: λ_max = 425 nm) for 2 h. As a result, 3,3,3-trifluoro-1,1-diphenylpropene (3a) was obtained in an 82% NMR yield (Table 1, entry 1). The choice of CF₃ reagents turned out to be crucial for the yield of 3a. Togni’s reagents 1b and 1c gave 3a in lower yields (Table 1, entries 2 and 3). We also found that DMSO is suitable for the present reaction (Table 1, entries 4–6). Other solvent systems gave substantial amounts of the hydroxytrifluoromethylated byproduct, which we reported previously [37]. In addition, the present C–H trifluoromethylation proceeds even in the absence of a base (Table 1, entry 7). Another photocatalyst, [Ru(bpy)₃](PF₆)₂, also promoted the present reaction, providing the product 3a in an 85% NMR yield (Table 1, entry 8). The Ru catalyst is less expensive than the Ir catalyst; thus, we chose the Ru photocatalyst for the experiments onward. Notably, product 3a was obtained neither in the dark nor in the absence of photocatalyst (Table 1, entries 9 and 10), strongly supporting that the photoexcited species of the photoredox catalyst play key roles in the reaction.

The scope and limitations of the present photocatalytic trifluoromethylation of alkenes are summarized in Table 2. 1,1-Diphenylethenes with electron-donating substituents, MeO (2b), and halogens, Cl (2c) and Br (2d), smoothly produced the corresponding trisubstituted CF₃-alkenes (3b–d) in good yields.

Table 1: Optimization of photocatalytic trifluoromethylation of 1,1-diphenylethene 2a.

| Entry | Photocatalyst | CF₃ reagent | Solvent | Base | NMR yield (%) |
|-------|---------------|-------------|---------|------|---------------|
| 1     | fac-Ir(ppy)₃  | 1a          | [D₆]-DMSO | K₂HPO₄ | 82            |
| 2     | fac-Ir(ppy)₃  | 1b          | [D₆]-DMSO | K₂HPO₄ | 17            |
| 3     | fac-Ir(ppy)₃  | 1c          | [D₆]-DMSO | K₂HPO₄ | 47            |
| 4     | fac-Ir(ppy)₃  | 1a          | CD₂CN   | K₂HPO₄ | 57            |
| 5     | fac-Ir(ppy)₃  | 1a          | CD₂Cl₂  | K₂HPO₄ | 27            |
| 6     | fac-Ir(ppy)₃  | 1a          | [D₆]-acetone | K₂HPO₄ | 29            |
| 7     | fac-Ir(ppy)₃  | 1a          | [D₆]-DMSO | none  | 81            |
| 8     | [Ru(bpy)₃](PF₆)₂ | 1a        | [D₆]-DMSO | none  | 85            |
| 9     | none          | 1a          | [D₆]-DMSO | none  | 0             |
| 10b   | [Ru(bpy)₃](PF₆)₂ | 1a        | [D₆]-DMSO | none  | 0             |

*For reaction conditions, see the Experimental section. bIn the dark.
Table 2: The scope of the present trifluoromethylation of alkenes.\(^{a,b}\)

| Trifluoromethylated products 3a–m | R\(^2\) | R\(^1\) | R\(^3\) | 1a | 1b | 1c | 1d | 1e | 1f | 1g | 1h | 1i | 1j | 1k | 1l | 1m |
|----------------------------------|--------|--------|--------|----|----|----|----|----|----|----|----|----|----|----|----|----|
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\(^{a}\)For reaction conditions, see the Experimental section. \(^{b}\)Isolated yields. \(^{c}\)NMR yields. \(^{d}\)E/Z ratios were determined by \(^{19}\)F NMR spectroscopy of the crude product mixtures. \(^{e}\)2,6-Lutidine (2 equiv) was added as a base.

In the reactions of unsymmetrically substituted substrates (2e–h), products were obtained in good to moderate yields but consisted of mixtures of E and Z-isomers. Based on the experimental results, the E/Z ratios are susceptible to the electronic structure of the aryl substituent. Reactions afforded the major isomers, in which the CF\(_3\) group and the electron-rich aryl substituent are arranged in E-fashion. In addition, the present photocatalytic reaction can be tolerant of the Boc-protected amino group (2f) or pyridine (2h). Moreover, a substrate with an alkyl substituent, 2,4-diphenyl-4-methyl-1-pentene (2i), was also applicable to this transformation, whereas the reaction of 1,2-disubstituted alkenes such as trans-stilbene provided complicated mixtures of products.

Next, we extended the present C–H trifluoromethylation to trisubstituted alkenes. The reactions of 1,1-diphenylpropene derivatives 2j and 2k (E/Z = 1/1) afforded the corresponding tetrasubstituted CF\(_3\)-alkenes 3j and 3k in 82% and 59% (E/Z = 74/26) yields, respectively. Triphenylethenes 2l and 2m (only E-isomer) are also applicable to this photocatalytic C–H trifluoromethylation. Remarkably, the E-isomer of 3m is a key intermediate for the synthesis of panomifene, which is known as...
an antiestrogen drug [71,72]. These results show that the present protocol enables the efficient construction of a C\textsubscript{alkenyl}-CF\textsubscript{3} bond through direct C–H trifluoromethylation of 1,1-disubstituted and trisubstituted aryl alkenes.

During the course of our study on the C–H trifluoromethylation of 1,1-diarylethenes 2, we found that a detectable amount of bis(trifluoromethyl)alkenes 4 was formed through double C–H trifluoromethylation. In fact, the photocatalytic trifluoromethylation of 2a, b and d with 4 equivalents of Umemoto’s reagent 1a in the presence of 5 mol % of [Ru(bpy)\textsubscript{3}]PF\textsubscript{6}\textsuperscript{2-} with irradiation from blue LEDs for 3 h gave geminal bis(trifluoromethyl)ethene (4a, b and d) in 45, 80 and 24% NMR yields, respectively (Scheme 4). Substituents on the benzene ring significantly affect the present double trifluoromethylation. Reaction of the electron-rich alkene 2b afforded 1,1-anisyl-2,2-bis(trifluoromethyl)ethene (4b) in a better yield than other alkenes 2a and 2d. Additionally, we found that photocatalytic trifluoromethylation of CF\textsubscript{3}-alkene 3d in the presence of an excess amount of Umemoto’s reagent 1a produced bis(trifluoromethyl)alkenes 4d in a better yield (56% yield) compared to the above-mentioned one-pot double trifluoromethylation of 2d.

A possible reaction mechanism based on SET photoredox processes is illustrated in Scheme 5. According to our previous photocatalytic trifluoromethylation [37-41], the trifluoromethyl radical (·CF\textsubscript{3}) is generated from an one-electron-reduction of electrophilic Umemoto’s reagent 1a by the photoactivated Ru catalyst, *{[Ru(bpy)\textsubscript{3}]}^{2+}*. ·CF\textsubscript{3} reacts with alkene 2 to give the benzyl radical-type intermediate 3’ in a regioselective manner. Subsequent one-electron-oxidation by highly oxidizing Ru species, {[Ru\textsuperscript{III}(bpy)\textsubscript{3}]^{3+}}, produces β-CF\textsubscript{3} carbocation intermediate 3\textsuperscript{+}. Finally, smooth elimination of the olefinic proton, which is made acidic by the strongly electron-withdrawing CF\textsubscript{3} substituent, provides trifluoromethylated alkene 3. Preferential formation of one isomer in the reaction of unsymmetrical substrates is attributed to the population of the rotational conformers of the β-CF\textsubscript{3} carbocation intermediate 3\textsuperscript{+}. Our experimental result is consistent with the previous report [71], which described E-selective formation of the tetrasubstituted CF\textsubscript{3}-alkene 3m via a β-CF\textsubscript{3} carbocation intermediate. In the presence of an excess amount of CF\textsubscript{3} reagent 1a, further C–H trifluoromethylation of CF\textsubscript{3}-alkene 3 proceeds to give bis(trifluoromethyl)alkene 4.

We cannot rule out a radical chain propagation mechanism, but the present transformation requires continuous irradiation of visible light (Figure 1), thus suggesting that chain propagation is not a main mechanistic component.
Conclusion
We have developed highly efficient C–H trifluoromethylation of alkenes using Umemoto’s reagent as a CF3 source by visible-light-driven photoredox catalysis. This reaction can be applied to multi-substituted alkenes, especially, 1,1-disubstituted and trisubstituted aryl alkenes, leading to tri- and tetrasubstituted CF3-alkenes. The present straightforward method for the synthesis of multisubstituted CF3-alkenes from simple aryl alkenes is the first report. In addition, we can extend the present photocatalytic system to double trifluoromethylation. Further development of this protocol in the synthesis of bioactive organofluorine molecules and fluorescent molecules is a continuing effort in our laboratory.

Experimental
Typical NMR experimental procedure (reaction conditions in Table 1)
Under N2, [Ru(bpy)3](PF6)2 (1.1 mg, 1.3 μmol), Umemoto’s reagent 1a (8.5 mg, 25 μmol), 1,1-diphenylethylene (2a, 4.3 μL, 25 μmol), SiEt4 (~1 μL) as an internal standard, and [D6]-DMSO (0.5 mL) were added to an NMR tube. The reaction was carried out at room temperature (water bath) under irradiation of visible light (placed at a distance of 2–3 cm from 3 W blue LED lamps: hν = 425 ± 15 nm).

General procedure for the photocatalytic C–H trifluoromethylation of alkenes (reaction conditions in Table 2)
A 20 mL Schlenk tube was charged with Umemoto’s reagent 1a (102 mg, 0.3 mmol, 1.2 equiv), [Ru(bpy)3](PF6)2 (4.3 mg, 2 mol %), alkene 2 (0.25 mmol), and DMSO (2.5 mL) under N2. The tube was irradiated for 2 h at room temperature (water bath) with stirring by 3 W blue LED lamps (hν = 425 ± 15 nm) placed at a distance of 2–3 cm. After reaction, H2O was added. The resulting mixture was extracted with Et2O, washed with H2O, dried (Na2SO4), and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (eluents: hexane and diethyl ether) to afford the corresponding product 3. Further purification of 3c and 3d by GPC provided pure 3c and 3d.

Procedures for the photocatalytic double C–H trifluoromethylation of 1,1-bis(4-methoxyphenyl)ethylene (2b)
A 20 mL Schlenk tube was charged with Umemoto’s reagent 1a (340 mg, 1.0 mmol, 4 equiv), [Ru(bpy)3](PF6)2 (10.7 mg, 5 mol %), 2b (60 mg, 0.25 mmol), and DMSO (5 mL) under N2. The tube was irradiated for 3 h at room temperature (water bath) with stirring by 3 W blue LED lamps (hν = 425 ± 15 nm) placed at a distance of 2–3 cm. After reaction, H2O was added. The resulting mixture was extracted with Et2O, washed with H2O, dried (Na2SO4), and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel (eluents: hexane and hexane/Et2O = 29:1) to afford 4b as a product mixture with 3b. Further purification by GPC provided pure 4b in 44% isolated yield (42 mg, 0.11 mmol). Isolated yield was much lower than the NMR yield because of the difficulty of separation of 3b and 4b.

Supporting Information
Supporting information features experimental procedures and full spectroscopic data for all new compounds (3c, 3d, 3f, 3g, 3h, 3i, 3k, 4a, and 4d).

Supporting Information File 1
Experimental procedures and NMR spectra. [http://www.beilstein-journals.org/bjoc/content/ supplementary/1860-5397-10-108-S1.pdf]

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And see references for the bioactivity therein.

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