Combining Photoredox-Catalyzed Trifluoromethylation and Oxidation with DMSO: Facile Synthesis of α-Trifluoromethylated Ketones from Aromatic Alkenes^{**}

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Dedicated to Dr. Teruo Umemoto

Abstract: Trifluoromethylated ketones are useful building blocks for organic compounds with a trifluoromethyl group. A new and facile synthesis of ketones with a trifluoromethyl substituent in the α -position proceeds through a one-pot photoredox-catalyzed trifluoromethylation–oxidation sequence of aromatic alkenes. Dimethyl sulfoxide (DMSO) serves as a key and mild oxidant under these photocatalytic conditions. Furthermore, an iridium photocatalyst, fac-[Ir(ppy)₃] (ppy = 2-phenylpyridine), turned out to be crucial for the present photoredox process.

he trifluoromethyl group prevails in pharmaceutical and agrochemical compounds as well as in functional organic materials.^[1,2] Therefore, the development of new methods for the efficient and selective incorporation of a CF₃ group into diverse molecular architectures has become an important research topic in synthetic organic chemistry.^[3] Trifluoromethylated carbonyl compounds are versatile building blocks for the synthesis of a wide variety of fluorinated compounds.^[4] In general, electrophilic or radical trifluoromethylation of enolates, which were prepared from the corresponding carbonyl compounds in advance, provides access to valuable $\alpha\text{-trifluoromethylated carbonyl compounds.}^{[5]}$ A few other unique methods have also been reported,^[6-9] but examples of the "direct" oxidative trifluoromethylation (keto-trifluoromethylation) of alkenes, which are abundant and commonly used feedstocks, have been limited thus far.^[10] Xiao and coworkers reported the keto-trifluoromethylation of styrenes with an S-(trifluoromethyl)diphenylsulfonium salt and air in the presence of an excess amount of the reducing agent, HOCH₂SO₂Na. However, the α -CF₃-substituted ketones were obtained in low yields (Scheme 1a). More recently, Maiti et al. described a catalytic system consisting of AgNO₃ and $K_2S_2O_8$ that is effective for the oxidative trifluoromethy-

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Scheme 1. Keto-trifluoromethylation of alkenes.

lation of alkenes with the Langlois reagent, CF_3SO_2Na , and air (Scheme 1b). For both processes, the involvement of a trifluoromethyl radical ('CF₃) was proposed, and it was implied that the outcome of the reaction is significantly affected by the methods that are used for the generation of the CF₃ radical and oxidation.

Recently, radical trifluoromethylation by photoredox catalysis has emerged; visible-light-driven single-electron transfer (SET) processes are enabled by the well-known ruthenium(II) polypyridine complexes (e.g., $[Ru(bpy)_3]^{2+}$; bpy = 2,2'-bipyridine) and the corresponding cyclometalated iridium(III) derivatives (e.g., *fac*-[Ir(ppy)₃]; ppy=2-phenylpyridine).^[5k,m,11-13] Our efforts have been devoted to the development of a photoredox-catalyzed difunctionalization of C=C bonds^[13] in the presence of electrophilic trifluoromethylating reagents $({}^{+}CF_3)$, such as Togni's reagent (1a) or Umemoto's reagent (1b). In these reactions, a key intermediate is the β -CF₃-substituted carbocation that is generated from SET photoredox processes, and which undergoes subsequent nucleophilic attack to produce difunctionalized products. This is a powerful method for the difunctionalization of alkenes without isolation of the intermediate. We hypothesized that combining the photoredox-catalyzed trifluoromethylation and Kornblum (DMSO) oxidation^[15] of the β-CF₃-substituted carbocation would enable the development of a facile and new approach to the synthesis of α -trifluoromethylated ketones by keto-trifluoromethylation (Scheme 1c), which is the subject of the present contribution.

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Our strategy provides us with an operationally simple procedure as well as a highly regioselective and efficient transformation. Furthermore, it has been revealed that an alkoxysulfonium species, which is a well-known intermediate in DMSO oxidation,^[16] smoothly produces an α -CF₃-substituted ketone without treatment with any base under photoredox reaction conditions.

We initially examined the photocatalytic reaction of styrene (**2a**) with Togni's reagent **1a** (1.05 equiv) and the iridium photoredox catalyst *fac*-[Ir(ppy)₃]^[17] (5 mol%) in [D₆]DMSO under visible-light irradiation (blue LEDs: $\lambda_{max} = 425$ nm) for two hours. To our surprise, the α -CF₃-substituted ketone **3a** was directly formed in 58% yield together with β -trifluoromethylstyrene (**4a**, 35% yield; entry 1, Table 1).

Table 1: Optimization of the photocatalytic keto-trifluoromethylation of styrene (2a).^[a]

	۲ Ph 🔨 - 2a	Obtocatalyst (5 mol%) [®] CF ₃ (1.05 equiv) [D ₆]DMSO, RT, 2 h 425 nm blue LEDs	O Ph CF ₃ + 3a Ph	4a ⊕ O-S(CD ₃) ₂ CF ₃ 5a
Entry	CF ₃ reagent	Photocatalyst	Yield of 3 a [%] ^[b]	Yield of 4a [%] ^[b]
1	la	fac-[lr(ppy) ₃]	58	35
2	1b	fac-[lr(ppy) ₃]	59	22
3	la	[Ru(bpy) ₃](PF ₆) ₂	5	0
4	1 b	[Ru(bpy) ₃](PF ₆) ₂	76 (5 a); 38 ^[c]	20
5 ^[d]	la	fac-[lr(ppy)₃]	0	0
6	la	-	0	0

[a] For detailed reaction conditions, see the Supporting Information. [b] Yields were determined by ¹H NMR spectroscopy using Si(Et)₄ as an internal standard. [c] Yield after treatment of the product mixture with NEt₃ (10 equiv). [d] In the dark. bpy=2,2'-bipyridine, LED=light-emitting diode, ppy=2-phenylpyridine.

When Umemoto's reagent 1b was used in place of 1a, a similar product mixture (3a: 59%, 4a: 22%) to that of the reaction with Togni's reagent 1a (entry 2) was obtained. The ruthenium photoredox catalyst $[Ru(bpy)_3](PF_6)_2^{[18]}$, in contrast, did not promote the present direct keto-trifluoromethylation of 2a very well (entries 3 and 4). The use of Togni's reagent 1a resulted in low conversion (12%; entry 3). Remarkably, the use of Umemoto's reagent 1b gave alkoxysulfonium salt 5a in 76% yield instead of 3a with concomitant formation of β -trifluoromethylstyrene (4a) in 20% yield (entry 4). When the salt **5a**, the key intermediate of the DMSO oxidation,^[16] was treated with NEt₃, the desired α -CF₃-substituted ketone **3a** was formed in 38% yield (entry 4). For entries 1 and 2, ketone 3a was formed in the absence of a base, as is the case in the Kornblum oxidation. On the basis of these results, we have developed the direct keto-trifluoromethylation of alkenes using the iridium photocatalyst without addition of a base. Notably, product 3a was not obtained either in the dark or in the absence of the photocatalyst (entries 5 and 6), strongly supporting that the photoexcited species of the photoredox catalyst plays key roles in the reaction.

The scope of the present photocatalytic keto-trifluoromethylation is summarized in Table 2. Styrene (2a) and styrene derivatives bearing CO₂Me (2b) and NHBoc groups (2c; Boc = tert-butoxycarbonyl) on the aryl ring produced the α -

Table 2: Scope of the photocatalytic keto-trifluoromethylation.^[a,b]



[a] For detailed reaction conditions, see the Supporting Information. [b] Yields of isolated products. [c] Reaction conducted on a gram scale. For details, see the Supporting Information. [d] **1a** (1.30 equiv) was used. [e] *fac*-[Ir(ppy)₃] (5 mol%) and **1a** (1.5 equiv) were used. [f] *fac*-[Ir(ppy)₃] (5 mol%), **1a** (2.0 equiv), 5 h.

CF₃-substituted ketones (3a-3c) in moderate yields (36-60%) because of concomitant formation of β -trifluoromethylstyrene derivatives **4**. In contrast, styrenes with electrondonating substituents, such as methyl (2d) and acetoxy groups (2e), and (E)- β -methylstyrene (2f) suppressed the formation of the side product **4** to a significant extent. As a result, the corresponding CF₃-substituted ketones were obtained in good yields (3d-f; 69-78%).

Furthermore, β -methylstyrene derivatives with electrondonating groups on the aromatic ring (2g and 2h) smoothly afforded the corresponding products 3g and 3h in a regiose-

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lective fashion and in 87% and 81% yield, respectively. To demonstrate the scalability of the present photocatalytic reaction, the keto-trifluoromethylation of 2g was carried out on a gram scale, and the product 3g was isolated in 84% yield (1.31 g). Halogen (2i–2k), hydroxy (2l), boronic ester (Bpin; 2m), and pyridyl groups (2n) did not hinder the reaction (45-84%). Alkenes with bulky mesityl or cyclohexyl substituents (20 and 2p), cyclic alkenes (2q and 2r), and *trans*-stilbene (2s) were also suitable substrates for this transformation (45– 74%). Furthermore, the present catalytic system was amenable to the reaction of β -disubstituted alkenes (2t and 2u). The corresponding α -CF₃-substituted ketones that bear a quaternary carbon atom were obtained in $28\,\%$ and $56\,\%$ yield, respectively (3t and 3u). The reactions of some alkenes, such as 1-octene and vinylcyclohexane, resulted in an inseparable mixture of products. These results show that aromatic alkenes with a variety of functional groups, such as halogen, ester, acetal, boronic ester, hydroxy, and pyridyl groups, can be applied to the present photocatalytic ketotrifluoromethylation, leading to the corresponding α -CF₃substituted ketones in a highly regioselective fashion.

To gain insight into the reaction mechanism, we conducted some control experiments. As mentioned above, the reaction of (E)- β -methylstyrene **2f** gave a better yield than that of styrene **2a** because formation of CF₃-substituted alkene **4** was suppressed. Therefore, we conducted the reaction of **2f** with Umemoto's reagent **1b** in the presence of [Ru(bpy)₃](PF₆)₂ (5 mol%). As a result, quantitative formation of a diastereomeric mixture of alkoxysulfonium salt **5f** was observed by NMR spectroscopy. In light of these results, side product **4** is possibly formed before formation of **5**. Subsequent treatment of **5f** with sodium benzoate (2.0 equiv; method A) or further photoreaction with addition of *fac*-[Ir(ppy)₃] (5 mol%; method B) provided **3f** in 78% and 84% yield, respectively (yields determined by NMR spectroscopy; Scheme 2 a). When *fac*-[Ir(ppy)₃] (5 mol%) was added at the beginning of the reaction, a product mixture of 3f (31% NMR yield) and 5f (49% NMR yield) was obtained after ten minutes, and elongated reaction times (30 min) enabled the formation of **3 f** in 74% yield as the sole product. A cyclic voltammogram for alkoxysulfonium salt 5 f exhibited a broad irreversible reduction wave at -1.07 V (vs. $[Cp_2Fe]$ in MeCN; Cp = cyclopentadienyl), which is close to the reduction potential of the photoexcited $[Ru(bpy)_3]^{2+}$, indicating that **5f** cannot be easily reduced by the photoexcited $[Ru(bpy)_3]^{2+}$, but only by the photoexcited fac-[Ir(ppy)₃].^[17,18] These results suggest that the action of benzoate or the iridium photocatalyst can induce the formation of the corresponding ketones 3 from the alkoxysulfonium intermediates 5. Furthermore, to our surprise, the reactions of α -cyclohexylstyrene 2v and α -methylstyrene 2wafforded 3a in 79% and 44% yield, respectively; these transformations proceed through a C-C bond cleavage process. In the case of the reaction of 2v, the eliminated alkyl group was detected as the cyclohexyldimethylsulfonium salt 6v (Scheme 2b). These remarkable C-C bond cleavage processes likely stem from β -scission of the tertiary alkoxy radical intermediate. These results suggest that photoredox catalysis is playing two crucial roles in the present photocatalytic keto-trifluoromethylation: 1) formation of the β -CF₃-substituted carbocation intermediate,^[13] and 2) formation of the reactive alkoxy radical intermediate from the alkoxysulfonium intermediate 5.

On the basis of these results, a possible reaction mechanism was proposed by combining photoredox-catalyzed trifluoromethylation and oxidation with DMSO (Scheme 3). First, irradiation with visible light excites fac-[Ir^{III}(ppy)₃] (**Ir**^{III}) into fac-[Ir^{III}(ppy)₃]* (***Ir**^{III}), which undergoes SET reduction of the electrophilic trifluoromethylating reagent (⁺CF₃) **1** to generate the CF₃ radical ([•]CF₃), accompanied by formation of the highly oxidized fac-[Ir^{IV}(ppy)₃]* (**Ir**^{IV}) species. Addition of the CF₃ radical to alkene **2** provides radical intermediate **5**'. A second SET oxidation event of **5**'



Scheme 2. Control experiments. [a] Method A: Sodium benzoate (2 equiv) was added at RT, and the reaction mixture stood for two hours; method B: *fac*-[Ir(ppy)₃] (5 mol%) was added, and the reaction mixture was irradiated with visible light (425 nm blue LEDs) at RT for one hour. Yields were determined by ¹H NMR spectroscopy using Si(Et)₄ as an internal standard.



Scheme 3. A proposed reaction mechanism.

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should occur concurrently with reduction of \mathbf{Ir}^{IV} to the \mathbf{Ir}^{III} ground state, leading to the β -CF₃-substituted carbocationic intermediate 5^+ . Nucleophilic attack of DMSO to 5^+ affords alkoxysulfonium intermediate 5. In the reaction with Togni's reagent 1a, o-iodobenzoate, which is the byproduct of the reduction of 1a, should serve as the base. A reaction similar to Kornblum oxidation proceeds to give product 3 (path a).^[19] On the other hand, the strong reducing agent *Ir^{III} can affect the reduction of 5, which leads to the formation of alkoxy radical 3' (path b), especially in the reaction with Umemoto's reagent 1b. Subsequent SET oxidation preceded by 1,2hydrogen atom shift $^{[20]}$ or $\beta\text{-scission}$ of the alkoxy radical $\boldsymbol{3'}$ furnishes the product 3. In the reactions of 2v and 2w, the alkyl groups (R) cannot be removed with the help of a base. This observation is therefore regarded as unequivocal evidence for the hypothesis that at least in the case of α -substituted styrene derivatives, the photoredox mechanism is operating for the conversion of 5 into 3 via 3'.

In conclusion, we have developed a new method for the synthesis of α -CF₃-substituted carbonyl compounds by combining photoredox-catalyzed trifluoromethylation and oxidation mediated by an alkoxysulfonium ion. The iridium photocatalyst *fac*-[Ir(ppy)₃], which can be a strong reducing agent, plays key roles in achieving the direct keto-trifluoromethylation of a C=C bond in a regioselective manner. Furthermore, this iridium-catalyzed reaction is a new type of base-free DMSO oxidation. The present method also enabled the transformation of alkenes with a variety of functional groups into the corresponding α -CF₃-substituted ketones. The development of new photocatalytic multifunctionalization processes that include trifluoromethylation is currently underway in our laboratory.

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Communications

Keto-Trifluoromethylation

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Combining Photoredox-Catalyzed Trifluoromethylation and Oxidation with DMSO: Facile Synthesis of α -Trifluoromethylated Ketones from Aromatic Alkenes



Valuable α -CF₃-substituted ketones can be synthesized from aromatic alkenes by combining photoredox-catalyzed trifluoromethylation and oxidation with DMSO. The iridium photocatalyst *fac*-[Ir(ppy)₃] (ppy=2-phenylpyridine) plays key roles in this keto-trifluoromethylation. SET = single electron transfer.

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