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# Keto-Difluoromethylation of Aromatic Alkenes by Photoredox Catalysis: Step-Economical Synthesis of $\alpha$ -CF<sub>2</sub>H-Substituted Ketones in Flow

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ABSTRACT: A step-economical method for synthesis of  $\alpha$ -CF<sub>2</sub>H-substituted ketones from readily available alkene feedstocks has been developed. Radical difluoromethylation of aromatic alkenes combining DMSO oxidation and photoredox catalysis is a key to the successful transformation. Electrochemical analysis, laser flash photolysis (LFP), and density functional theory (DFT) calculations reveal that *N*-tosyl-*S*-difluoromethyl-*S*-

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phenylsulfoximine serves as the best CF<sub>2</sub>H radical source among analogous sulfone-based CF<sub>2</sub>H reagents. The present photocatalytic keto-difluoromethylation has been applied to flow synthesis and easily scaled up to gram-scale synthesis within reasonable reaction time. Furthermore, potentials of the  $\alpha$ -CF<sub>2</sub>H-substituted ketones for useful synthetic intermediates are shown, *e.g.*, synthesis of the CF<sub>2</sub>H-containing  $\alpha$ -hydroxyamide with the same carbon skeleton as that of the anticonvulsant active CF<sub>3</sub>-analogue, is disclosed. Additionally, mechanistic studies are also discussed in detail.

KEYWORDS: photoredox catalysis, difluoromethylation, alkene difunctionalization, radical reaction, flow synthesis

## **1. INTRODUCTION**

Organofluorine compounds are of strong interest for researchers in the fields of pharmaceuticals, agrochemicals, and organic functional materials.<sup>1</sup> In particular, fluorinated ketones are regarded as notable compounds because they can be utilized for bioactive molecules as themselves, valuable fluorine-containing building blocks, and other materials.<sup>2</sup> For the past several years, various strategies for catalytic synthesis of  $\alpha$ -CF<sub>3</sub>-substituted ketones have been developed.<sup>3</sup> Representative synthetic methods from alkenes, alkynes,  $\beta$ -ketoacids, and activated carbonyl compounds are shown in Scheme 1a. On the other hand, the difluoromethyl (CF<sub>2</sub>H) group has recently attracted great

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interest as a useful structural motif because it serves as a bioisostere of alcohol and thiol.<sup>4</sup> However, synthesis of  $\alpha$ -CF<sub>2</sub>H-substituted ketones through catalytic difluoromethylation<sup>5</sup> has not been reported yet. In 2012, Mikami and co-workers reported on difluoromethylation of lithium enolate through substitution of fluoroform, which focused on synthesis of  $\alpha$ -CF<sub>2</sub>H-substituted amides and esters. Only one example of  $\alpha$ -CF<sub>2</sub>H-substituted ketone that bears a quaternary carbon atom was reported (Scheme 1b).<sup>6</sup> In 2017, the group of Paquin developed multi-step synthesis of  $\alpha$ -CF<sub>2</sub>Hsubstituted ketones from alkynes (Scheme 1c).<sup>7</sup> Development of novel operationally simple and step-economical synthetic methods is associated with exploration of CF<sub>2</sub>Hcontaining drugs.

ΟН

.CF<sub>2</sub>H





Herein, we report on the first example of photoredox-catalyzed keto-

*difluoromethylation*, *i.e.*, a single-step synthesis of  $\alpha$ -CF<sub>2</sub>H-substituted ketones from

alkenes (Scheme 1d). Previously, we reported on efficient generation of  $\beta$ -CF<sub>2</sub>Hsubstituted carbocationic species **A** by the Ir photocatalytic reaction of aromatic alkenes **2** with *N*-tosyl-*S*-difluoromethyl-*S*- phenylsulfoximine (**1a**). <sup>8,9,10</sup> The in-situ DMSOtrapping reaction of **A** involved in so-called Kornblum oxidation<sup>11</sup> is expected to lead to synthetically useful  $\alpha$ -CF<sub>2</sub>H-substituted ketones **3** in one-pot operation (Scheme 2).



Scheme 2. Contents Highlighted in this Article

In addition to the synthetic studies, laser flash photolysis (LFP) and density functional theory (DFT) calculations are performed to gain new mechanistic insights into the  $CF_2H$  radical generation process promoted by electron transfer from the excited Ir species (\* $Ir^{III}$ ) to the reagent **1a**. Furthermore, photocatalytic flow synthesis, synthetic applications of the obtained  $CF_2H$ -ketone, and basic mechanistic studies are also discussed in detail.

## 2. RESULTS AND DISCUSSION

## 2.1. Optimization of Photocatalytic Keto-Difluoromethylation of Alkenes: NMR-scale Experiment.

We commenced the reaction of 4-methylstyrene (2a) with the  $CF_2H$  reagent 1a in DMSO- $d_6$  in the presence of fac-[Ir(ppy)<sub>3</sub>] (5 mol%) under visible light irradiation (425 nm). То  $\alpha$ -CF<sub>2</sub>H-ketone 3,3-difluoro-1-(4our delight, the desired product, methylphenyl)propanone (3a), was obtained in an 87% NMR yield together with a small amount of CF<sub>2</sub>H-alkene 4a (4% NMR yield) (entry 1 in Table 1). Examination of other sulfone-based CF<sub>2</sub>H reagents ( $1b^{12a}$ ,  $1c^{12b}$ , and  $1d^{12d}$ )<sup>12</sup> and commonly used photocatalysts ([Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> and [Ir(ppy)<sub>2</sub>(dtbbpy)](PF<sub>6</sub>) (bpy: 2,2'-bipyridine, dtbbpy: 4,4'-di-*tert*-butyl-2,2'-bipyridine)) revealed that the combination of fac-[Ir(ppy)<sub>3</sub>] and the phenylsulfoximine reagent 1a was the best for the present transformation (entries 2-6). Next, the reaction was applied to 4-methoxystyrene (2b). Unfortunately, the desired ketone **3b** was obtained only in a 41% NMR yield and a considerable amount of the corresponding CF<sub>2</sub>H-alkene **4b** was formed (39% NMR yield). Usually DMSO oxidation proceeds via the reactive ylide species, which is formed from deprotonation of an alkoxysulfonium intermediate, to afford the carbonyl product. Then, we explored addition of a base to promote the deprotonation (entries 10-12). As a result, sodium benzoate suppressed the formation of by-product **4b** to give *keto-difluoromethylated* product **3b** in a 75% NMR yield. The reaction did not proceed at all either in the dark or in the absence

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3	of the photocatalyst (entries 7, 8, 13, and 14). These results suggest that the photoexcited
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6	fac-[Ir(ppy) <sub>3</sub> ] is involved in the reaction.
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Scale<sup>a</sup>





8 <sup>e</sup>	2a	fac-[Ir(ppy) <sub>3</sub> ]	1a	_	0	0
9	2b	<i>fac</i> -[Ir(ppy) <sub>3</sub> ]	1a	_	41	39
10	2b	<i>fac</i> -[Ir(ppy) <sub>3</sub> ]	1a	PhCO <sub>2</sub> Na	75	4
11	2b	<i>fac</i> -[Ir(ppy) <sub>3</sub> ]	1a	NEt <sub>3</sub>	13	17
12	2b	fac-[Ir(ppy) <sub>3</sub> ]	1a	K <sub>2</sub> CO <sub>3</sub>	-f	-f
13	2b	none	1a	PhCO <sub>2</sub> Na	0	0
14 <sup>e</sup>	2b	<i>fac</i> -[Ir(ppy) <sub>3</sub> ]	1a	PhCO <sub>2</sub> Na	0	0

<sup>*a*</sup>Reaction conditions: A mixture of photocatalyst (0.75 µmol, 5 mol%), **1** (15 µmol, 1 equiv.), **2** (18 µmol, 1.2 equiv.), and additional base (15 µmol, 1 equiv.) in DMSO-*d*<sub>6</sub> (0.46 mL) was irradiated by 3 W blue LEDs ( $\lambda = 425 \pm 15$  nm) at room temperature. <sup>*b*</sup>Reported reducing power ( $E^*_{ox}$  V vs. Cp<sub>2</sub>Fe) in the parenthesis. [ $E^*_{ox}$  vs. Cp<sub>2</sub>Fe] = [ $E^*_{ox}$  vs. SCE] – 0.41.<sup>13 c</sup>Yields were determined by <sup>1</sup>H NMR spectroscopy. <sup>*d*</sup>Yields were determined by <sup>19</sup>F NMR spectroscopy. <sup>*e*</sup>In the dark. <sup>*f*</sup>Complicated mixture.

## 2.2. Evaluation of CF<sub>2</sub>H-Sulfone Derivatives 1 as CF<sub>2</sub>H Radical Precursors.

As mentioned above, **1a** turned out to be the best difluoromethylating reagent for the present *keto-difluoromethylation*. On the other hand, the group of Hu reported that **1d** also serves as a  $CF_2H$  radical precursor by the action of photoredox catalysis.<sup>12c</sup> Thus, we examined properties and reaction of the related  $CF_2H$  reagents **1** by means of cyclic voltammetry (CV), LFP and DFT calculations.

2.2.1. Cyclic voltammetry of the CF<sub>2</sub>H reagents **1**.

Irreversible broad reduction waves were observed in the CV traces for the  $CF_2H$  reagents

(1a: -2.26 V, 1b: -2.50 V, 1c: -2.31 V, 1d: -1.79 V vs. Cp<sub>2</sub>Fe in DMSO) as shown in Figure

1. According to the literature,<sup>13</sup> the reduction power  $(E^*_{ox})$  of *fac*-[Ir(ppy)<sub>3</sub>] in the photoexcited state is -2.14 V, indicating that CF<sub>2</sub>H reagents except **1b** could be smoothly reduced by the excited Ir photocatalyst.



**Figure 1**. Cyclic voltammograms of the  $CF_2H$  reagents (**1a**–**d**). Measurements were performed for DMSO solutions ([sample] = 2.0 mM, [(NBu<sub>4</sub>)PF<sub>6</sub>] = 0.10 M) with a platinum disk (working electrode), a platinum wire electrode (counter electrode), and a Ag/AgNO<sub>3</sub>

#### ACS Catalysis

reference electrode under  $N_2$  at room temperature. The scan rate was 100 mV/s. Ferrocene (Cp<sub>2</sub>Fe) was used as a reference.

## 2.2.2. Laser flash photolysis.

To gain mechanistic insights into the variable yields of **3** dependent on **1**, firstly, the quenching rate constants ( $k_{\alpha}$ ) of the electronically excited state fac-[Ir(ppy)<sub>3</sub>]\* by the CF<sub>2</sub>H reagents (**1a**–**d**) were evaluated. The observed decay rates ( $k_{obs}$ ) of phosphorescence from fac-[Ir(ppy)<sub>3</sub>]\* in the presence of different concentrations of each reagent **1** are determined by the LFP method. The phosphorescence decay (excited at 355 nm and monitored at 780 nm in DMSO at 295 K) of fac-[Ir(ppy)<sub>3</sub>]\* in the presence of **1a** is shown as an example (Figure 2a, for data on the other reagents, see the Supporting Information). The CF<sub>2</sub>H reagents except **1b** significantly shortened the lifetime. The obtained  $k_{obs}$  values are plotted against concentrations of each reagent **1** and compiled into Figure 2b. Their quenching rate constants ( $k_a$ ) were determined from the slopes in Figure 2b to be 6.7 x  $10^7 \text{ M}^{-1}\text{s}^{-1}$  (1a),  $1.7 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$  (1b),  $1.3 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$  (1c), and  $2.0 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$  (1d). In addition, transient absorption spectroscopic analyses with **1a** suggest that the present phosphorescence decay was not caused by an energy transfer process but by a SET process from *fac*-[Ir(ppy)<sub>3</sub>]\* (see the Supporting Information).<sup>14</sup>

NTs

CF<sub>2</sub>H

CEAH

0.05



Figure 2. (a) Measurements of phosphorescence decay (excited at 355 nm and monitored at 780 nm in DMSO at 295 K) of fac-[Ir(ppy)<sub>3</sub>]\* in the presence of the CF<sub>2</sub>H reagent **1a**. (b) Evaluation of the quenching rate constants  $(k_q)$  of fac- $[Ir(ppy)_3]^*$  by each of **1a**–**d**.

## 2.2.3. DFT calculations.

(a) transition state analysis for generation of  $\cdot CF_2H$  from **1a** 



**Scheme 3**. Reaction Diagrams for Formation of the CF<sub>2</sub>H radical from Anionic Radicals of the CF<sub>2</sub>H Reagents (**1a** and **1d**)

Secondly, transition state analysis for the generation of the CF<sub>2</sub>H radical from the corresponding anionic radical species [1]·- was performed by DFT calculations (UB3LYP/6-31G(d)/SMD-DMSO level of theory)<sup>15</sup>. Anionic radical species [1]·- should be formed by 1e-reduction of **1**. Subsequent carbon–sulfur bond cleavage process leads to generation of the CF<sub>2</sub>H radical. During refinement of the anionic radical of **1a**, it spontaneously decomposes without substantial activation energy to generate the CF<sub>2</sub>H radical (Scheme 3a). In contrast, the reactions of the other reagents (**1b–d**) should overcome the transition

states though not so significant ( $\Delta E_a$ : 5.41 kJ mol<sup>-1</sup>(**1b**), 23.5 kJ mol<sup>-1</sup> (**1c**), and 36.2 kJ mol<sup>-1</sup> (**1d**)). In addition, calculations suggest that the CF<sub>2</sub>H radical generation from **1c** and **1d** is thermodynamically unfavorable ( $\Delta E$ : –13.7 kJ mol<sup>-1</sup>(**1b**), 4.99 kJ mol<sup>-1</sup> (**1c**), and 19.7 kJ mol<sup>-1</sup> (**1d**)) as is shown for **1d** in Scheme 3b (for data on the other reagents, see the Supporting Information).

In brief summary, **1d** is most susceptible to 1e-reduction among the reagents **1a–d**, but **1a** serves as a better CF<sub>2</sub>H radical source as mentioned above (section 2.1 Table 1 (entries 1–4)). These results suggest that, for the CF<sub>2</sub>H radical precursors, efficient S–C bond homolysis of the electronically activated species, *i.e.*, anionic radical species, is a more important factor than the lower reduction potential and the faster quenching rate.

# 2.3. Photocatalytic Keto-Difluoromethylation of Alkenes: Preparative-Scale Flow Synthesis.

As it was found that *keto-difluoromethylation* proceeds smoothly on NMR-scale experiments (Table 1), we conducted preparative scale experiments next. In addition, to prove synthetic utilities of the  $\alpha$ -CF<sub>2</sub>H-ketones (section 2.4.), gram-scale synthesis is essential. Thus, we adopted the MiChS flow photoreactor L-1 (M) with a single lane (2 mm in width, 1 mm in depth, 1.35 m in length: total volume 2.7 mL) covered with quartz.<sup>16</sup>

2.3.1. Scope of keto-difluoromethylation.

Page 15 of 39

#### ACS Catalysis

The scope of the present flow synthesis of the CF<sub>2</sub>H-ketones is summarized in Table 2. Styrenes with *p*-substituents such as Me (2a), H (2c), <sup>t</sup>Bu (2d), and halogens (F (2e), Cl (2f), and Br (2g)) underwent base-free keto-difluoromethylation in flow (residence time  $t_{R}$  = 30 min.) to give the products in good yields (**3a**, **3c–g**: 43–67%) (entries 1, 3–7 in Table 2). In addition, ester (2h), aldehyde (2k), and pyridyl (2l) groups are compatible with the present reaction system (3h: 66%, 3k: 44%, 3l: 15%) (entries 8, 11, 12). Reactions of electron-rich styrene derivatives with p-substituents such as OMe (2b), O<sup>t</sup>Bu (2i), and two alkoxy substituents (2j) in the presence of sodium benzoate (1 equiv.) gave the corresponding CF<sub>2</sub>H-ketones without significant deterioration of the yields (**3b**: 69%,<sup>17</sup> **3i**: 49%, 3j: 66%) (entries 2, 9, 10). Furthermore, the present reaction systems could be also applied to internal alkenes such as *trans*-stilbene (2m), isosafrole (2n), indene (2o), and 2-methylindene (2p) (3m: 31%, 3n: 64%, 3o: 47%, 3p: 33%) but they needed longer residence time (entries 13–16). It should be noted that the reactions of aliphatic alkene, 4-phenyl-1-butene, and electron-deficient alkenes, acrylonitrile and methyl acrylate, did not afford the corresponding difluoromethylated products at all. These results suggest that the present photocatalytic system is useful for the reaction of aromatic alkenes with a variety of functional groups such as ether, carbonyl, halogens and pyridyl groups. Noticeably, it was found that most of  $CF_2H$ -ketones **3** easily underwent dehydrofluorination (see below) upon purification by silica gel column chromatography.<sup>18</sup> Thus, automated flash column chromatography was performed for purification.





Entry	Substrate <b>2</b>	Product <b>3</b>		
	R	R CF <sub>2</sub> H		
1	<b>2a</b> : R = Me	<b>3a</b> : 67%		
2 <sup>c</sup>	<b>2b</b> : R = MeO	<b>3b</b> : 69% <sup>17</sup>		
3	<b>2c</b> : R = H	<b>3c</b> : 51%		
4	<b>2d</b> : R = <sup><i>t</i></sup> Bu	<b>3d</b> : 65%		
5	<b>2e</b> : R = F	<b>3e</b> : 53%		
6	<b>2f</b> : R = Cl	<b>3f</b> : 56%		
7	<b>2g</b> : R = Br	<b>3g</b> : 43%		
8	<b>2h</b> : R = AcO	<b>3h</b> : 66%		
9 <sup>c</sup>	<b>2i</b> : R = <sup><i>t</i></sup> BuO	<b>3i</b> : 49%		
10 <sup>c</sup>	MeO BnO	MeO BnO CF <sub>2</sub> H		
	2ј	<b>3j</b> : 66%		
11	H	H CF <sub>2</sub> H		



<sup>*a*</sup>A mixture of photocatalyst (15  $\mu$ mol, 5 mol%), **1a** (0.30 mmol, 1 equiv.), **2** (0.36 mmol, 1.2 equiv.) in DMSO (9.2 mL) was placed in a syringe, and was pumped into the photoreactor at a rate of 5.4 mL/h (residence time t<sub>R</sub> = 30 min.) using a syringe pump. The reactor was irradiated by blue LED lamps (405 nm (3.85 mW x 20), 450 nm (20 mW x 20), 470 nm (20 mW x 20)) at room temperature. <sup>*b*</sup>Isolated yields. <sup>*c*</sup>Sodium benzoate (1 equiv.) was added. <sup>*d*</sup>1.1 equiv. of **1a** were used. <sup>*e*</sup>1.7 equiv. of **1a** were used.

# 2.3.2. Gram-scale synthesis in flow and batch.

The flow system is highly beneficial for large-scale photoreaction because a thin lane enhances transmittance of light to cause efficient light absorption.<sup>16</sup> We conducted the

gram-scale synthesis of **3b** in flow ( $t_R = 20$  min.) (Scheme 4). As a result, **3b** was obtained in a 67% yield (1.44 g) after irradiation for 21 h. When the batch reaction (200 mL-Schlenk tube) was examined on the same scale, 3b was isolated only in a 22% isolated yield even after prolonged reaction time, 24 h. In addition, a part of the CF<sub>2</sub>H reagent **1a** still remained unreacted (89% conversion). Furthermore, we observed formation of byproducts, which were not detected for the NMR-scale experiments (section 2.1.). Enol benzoate **5b** (vide infra) was detected as a major by-product (13%) together with CF<sub>2</sub>Halkene 4b (6%). Then, we investigated the stability of the product 3b in the presence of sodium benzoate. The reaction of **3b** with 2 equiv. of sodium benzoate gave **5b** in a 77% yield in a highly E-selective manner (Scheme 5a). Further investigation about the action of triethylamine on **3b** disclosed formation of *E*-3-fluoropropenone **6b** in a 76% isolated yield (Scheme 5b). Furthermore, 5b was formed in a 71% yield by the reaction of the isolated **6b** with 1 equiv. of sodium benzoate. These results suggest that the  $CF_2H$ -ketones **3** are so unstable under basic reaction conditions as to undergo dehydrofluorination.<sup>18</sup> These side reactions are remarkable, especially in the case of the prolonged reaction of the batch system. On the other hand, the flow system can shorten the residence time  $(t_R)$ , resulting in prevention of the secondary reactions of the product **3**.



<sup>a</sup>For detailed reaction conditions, see the Supporting Information.

Scheme 4. Application to Gram-Scale Synthesis<sup>a</sup>



Ar = 4-methoxyphenyl. <sup>a</sup>Yields are isolated values.

Scheme 5. Stability of the Product Under Basic Conditions<sup>a</sup>

# 2.4. Synthetic Applications of the CF<sub>2</sub>H-Ketone.

To explore usefulness of the CF<sub>2</sub>H-ketones as fluorine-containing building blocks, some fundamental reactions with respect to the product **3b** were investigated (Scheme 6). (a) Reduction with NaBH<sub>4</sub> afforded the corresponding CF<sub>2</sub>H-containing alcohol **7b** in an 89%

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yield. (b) Asymmetric reduction by 1 equiv. of oxazaborolidine catalyst ((S)-Me-CBS catalyst)<sup>19</sup> at 0 °C produced optically active CF<sub>2</sub>H-alcohol ((R)-**7b**) in a 73 % yield with >99% ee. (c)  $\alpha$ -Bromoketone **8b** was synthesized by bromination with [BnNMe<sub>3</sub>](Br<sub>3</sub>) (58% vield).20 (d) The carbonyl group was protected by treatment with ethylenedioxybis(trimethylsilane) in the presence of the Bi(OTf)<sub>3</sub> catalyst at room temperature<sup>21</sup> to give the acetal product **9b** in a 56% yield. (e) Silylcyanation<sup>22</sup> afforded cyanohydrin derivative **10b** (79%). Subsequent (f) hydration of **10b** followed by (g) desilvlation led to the CF<sub>2</sub>H-containing  $\alpha$ -hydroxyamide product **13b**, a CF<sub>3</sub> analogue of which is an anticonvulsant compound.<sup>23,24</sup> The CF<sub>2</sub>H-containing cyanohydrin **11b** was also obtained from desilylation of **10b** (87% yield). These results suggest that the CF<sub>2</sub>Hketones **3** can serve as promising building blocks for  $CF_2H$ -containing compounds under appropriate reaction conditions.



Ar = 4-methoxyphenyl. <sup>*a*</sup>Isolated yields. For detailed reaction conditions, see the Supporting Information. (a) NaBH<sub>4</sub> (1.1 equiv.), EtOH, rt, 3 h. (b) (S)-Me-CBS cat (1.0 equiv.),

BH<sub>3</sub>•SMe<sub>2</sub> (2.0 equiv.), THF, 0°C, 1 h. (c) [BnNMe<sub>3</sub>](Br<sub>3</sub>) (1.4 equiv.), CH<sub>2</sub>Cl<sub>2</sub>/MeOH, 50 °C, 48 h. (d) TMSOCH<sub>2</sub>CH<sub>2</sub>OTMS (1.8 equiv.), Bi(OTf)<sub>3</sub> (1 mol%), MeOH, rt, 20 h. (e) ZnI<sub>2</sub> (1 equiv.), TMSCN (2.5 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, rt, 24 h. (f) InCl<sub>3</sub> (5 mol%), acetaldoxime, toluene, 45 °C, 3 days. (g) 1 M HCl, MeOH.

Scheme 6. Synthetic Applications of the CF<sub>2</sub>H-Ketone 3b<sup>a</sup>

# 2.5. Mechanistic Studies.

On the basis of the previous reports,<sup>3j,9,11,25</sup> plausible reaction mechanisms are illustrated in Scheme 7. The reaction sequence involving the first SET photoredox process mediated by the Ir photocatalyst produces  $\alpha$ -CF<sub>2</sub>H-substituted carbocationic intermediate **A**, which undergoes nucleophilic attack of DMSO to afford an alkoxysulfonium intermediate **B**. Deprotonation from **A** gives CF<sub>2</sub>H-alkene by-product **4**. Conversion of **B** into the CF<sub>2</sub>Hketone **3** may follow the two possible pathways: (i) Kornblum-type oxidation *via* the ylide species **C** under basic conditions and (ii) the second SET photoredox processes *via* an alkoxy radical intermediate **D**. In the present section, (a) detection of the CF<sub>2</sub>H radical, (b) involvement of the photoredox processes rather than radical chain processes, and (c) details of DMSO oxidation processes will be discussed.



**Scheme 7**. Plausible Reaction Mechanisms

# 2.5.1. The CF<sub>2</sub>H radical trap experiment.

The radical trapping experiment with TEMPO gave CF<sub>2</sub>H–TEMPO in an 86% NMR yield

(Scheme 8), supporting involvement of the  $\cdot CF_2H$  radical in the present reaction.



<sup>a</sup>The reaction conditions were identical to those of entry 1 in Table 1 except for addition of TEMPO.

# Scheme 8. Radical Trap Experiment<sup>a</sup>

#### **ACS** Catalysis

2.5.2. Photoredox processes vs. radical chain processes.

To clarify involvement of radical chain processes (noncatalytic reduction of **1a** by **E**), (i) an intermittent light irradiation experiment and (ii) determination of the quantum yield of the reaction were carried out. As shown in Figure 3, the present photocatalytic reaction proceeded only during the visible light irradiation periods. In addition, the quantum yield of the photocatalytic *keto-difluoromethylation* of **1a** with **2a** was 0.28 (Scheme 9). These results indicate that the present reaction does not proceed through radical chain processes as a main component, but through photoredox processes.



**Figure 3**. Intermittent light irradiation experiment. <sup>*a*</sup>The reaction conditions were identical to those of entry 1 in Table 1 except for light irradiation.



<sup>a</sup>For detailed procedures, see the Supporting Information.

Scheme 9. Determination of Quantum Yield<sup>a</sup>

# 2.5.3. Detection of dimethylsulfides.

In general, DMSO oxidation accompanies formation of dimethylsulfide. Monitoring the reaction in the presence of sodium benzoate (entry 10 in Table 1) by <sup>1</sup>H NMR spectroscopy revealed that the CF<sub>2</sub>H-ketone **3b** was formed from alkene **2b** without detection of any intermediates such as the alkoxysufonium salt **B** shown in Scheme 7. Furthermore, the characteristic quintet signal at 2.00 ppm ( ${}^{2}J_{HD} = 1.8$  Hz) indicates formation of dimethylsulfide- $d_{5}$  (Figure 4). In contrast, under the base-free reaction conditions (entry1 in Table 1), the signal of dimethylsulfide- $d_{5}$  was not detected by <sup>1</sup>H NMR spectroscopy, indicating formation of dimethylsulfide- $d_{6r}$ , which was confirmed by GC-MS analysis of the

### ACS Catalysis

reaction mixture (Scheme 10) (see the Supporting Information). These results indicate that the reaction in the presence of base (entry 10 in Table 1) follows Kornblum oxidation (path (i) in Scheme 7). For path (ii), see the next section.



Figure 4. <sup>1</sup>H NMR spectra of the reaction of **2b** in the presence of PhCO<sub>2</sub>Na. <sup>a</sup>The reaction

conditions were identical to those of entry 10 in Table 1. Ar = 4-methoxyphenyl.



<sup>a</sup>The reaction conditions were identical to those of entry 1 in Table 1. Ar = 4-methylphenyl.

Scheme 10. Detection of Dimethylsulfide in Keto-Difluoromethylation under Base-free

Conditions

2.5.4. Reaction of  $\alpha$ -alkylstyrene.

It should be noted that the reaction of  $\alpha$ -cyclohexylstyrene (**2q**) gave the parent  $\alpha$ -CF<sub>2</sub>H-ketone **3c** in an 65% NMR yield, resulting from C–C bond cleavage (Scheme 11). Elaborative examination revealed that the eliminated cyclohexyl group was converted into the corresponding dimethylsulfonium salt **14**, which was characterized by NMR and ESI-MS spectroscopies (see the Supporting Information). The present C–C bond cleavage process should follow  $\beta$ -scission of alkoxy radical **D** formed by 1e-reduction of **B** and O– S bond homolysis, and the resultant cyclohexylradical is converted to **14** through 1eoxidation processes and reaction with dimethylsulfide-*d*<sub>6</sub>. The reduction potential of the styrene derivative **B** was estimated by the theoretical method<sup>26</sup> to be *E*<sub>calc</sub> = –0.43 vs. Cp<sub>2</sub>Fe in MeCN, suggesting that *fac*-[Ir(ppy)<sub>3</sub>]\* can reduce **B** (see the Supporting Information). These results support occurrence of the reaction pathway (path(ii) in Scheme 7) involving alkoxy radical.



**Scheme 11**. Reaction of  $\alpha$ -Alkylstyrene.

## **3. CONCLUSION**

We have developed the first example of operationally simple and step-economical synthesis of  $\alpha$ -CF<sub>2</sub>H-substituted ketones from readily available aromatic alkenes through *keto-difluoromethylation* mediated by photoredox catalysis. The combination of the *fac-*[Ir(ppy)<sub>3</sub>] catalyst and *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**1a**) turns out to be a key to the successful transformation. Efficient radical generation depends not only on redox balance between the excited photocatalyst and the precursor relevant to 1e-reduction but also on the easiness of the homolytic bond cleavage process from the resultant anionic radical species. In addition, the flow system is efficient for gram-scale production of the CF<sub>2</sub>H-ketone **3** because of (i) efficient of light absorption and (ii) prevention of the secondary reactions of the product. The additive effect of sodium benzoate reveals occurrence of two mechanisms for the present *keto-difluoromethylation*.

The obtained  $CF_2H$ -ketone is regarded as a promising synthetic intermediate for  $CF_2H$ containing molecules because it can be applied to typical transformation of the carbonyl group such as reduction,  $\alpha$ -bromination, and cyanation. Further studies on photocatalytic difluoromethylation are underway in our laboratory.

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## Notes

The authors declare no competing financial interest.

# ASSOCIATED CONTENT

# **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization, crystallographic data of **3b**, photo- and electro-chemical experiments, laser flash photolysis, control experiments, DFT calculations and <sup>1</sup>H, <sup>13</sup>C, and <sup>19</sup>F NMR spectra (PDF)

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# ABBREVIATIONS

DMSO, dimethyl sulfoxide; LHMDS, lithium hexamethyldisilazide; DDQ, 2,3-dichloro-5,6dicyano-*p*-benzoquinone; Me-DAST, N,N-dimethylaminosulfur trifluoride, ppy, 2pyridylphenyl; bpy, 2,2'-bipyridine; dtbbpy, 4,4'-di-tert-butyl-2,2'-bipyridine; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl; <sup>*t*</sup>Bu, tertiary butyl; <sup>*n*</sup>Bu, normal butyl; Bn, benzyl; Me, methyl; Ph, phenyl; TMS, trimethylsilyl; Tf, trifluoromethanesulfonyl; Ts, *p*-toluenesulfonyl; CV, cyclic voltammetry; SET, single electron transfer; DFT, density functional theory; LED, light-emitting diode.

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