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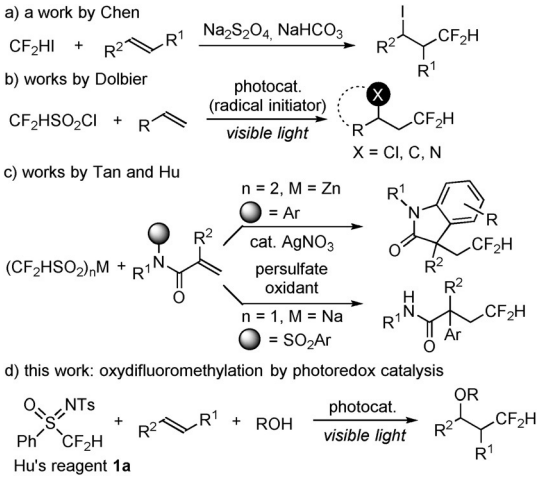
Photocatalysis

Oxydifluoromethylation of Alkenes by Photoredox Catalysis: Simple Synthesis of CF_2H-Containing Alcohols

Yusuke Arai, Ren Tomita, Gaku Ando, Takashi Koike,* and Munetaka Akita*[a]

Abstract: We have developed a novel and simple protocol for the direct incorporation of a difluoromethyl (CF_2H) group into alkenes by visible-light-driven photoredox catalysis. The use of *fac*-[Ir(ppy)$_3$] (ppy = 2-pyridylphenyl) photocatalyst and shelf-stable Hu's reagent, *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine, as a CF_2H source is the key to success. The well-designed photoredox system achieves synthesis of not only β-CF_2H-substituted alcohols but also ethers and an ester from alkenes through solvolytic processes. The present method allows a single-step and regioselective formation of C(sp^3)–CF_2H and C(sp^3)–O bonds from C=C moiety in alkenes, such as hydroxydifluoromethylation, regardless of terminal or internal alkenes. Moreover, this methodology tolerates a variety of functional groups.



Scheme 1. Direct difluoromethylation of alkenes for the construction of C(sp^3)–CF_2H bond.

Organofluorine compounds continue to increase in importance in the fields of pharmaceuticals, agrochemicals and functional materials, because installation of fluorine atoms frequently influences the medicinal action as well as the chemical and physical properties.[1] Thus, considerable research efforts have been made so far towards the development of new methodologies for the selective incorporation of fluorine atoms or fluoroalkyl groups. There have been great advances in catalytic methods for the fluorination and trifluoromethylation in the past few years.[2,3] In contrast, simple and widely applicable introduction of a difluoromethyl (CF_2H) group to various carbon skeletons is still underdeveloped,[4] even though the CF_2H group is an intriguing structural motif, especially in medicinal chemistry.[5,6] In the past decade, multistep strategies for the preparation of CF_2H-containing compounds, that is, incorporation of a difluoroalkyl unit (CF_2-PG: PG = a protective group) into the carbon skeletons followed by deprotection, have been well-developed. However, a direct difluoromethylation is still highly desirable.[5,7]

Alkenes are fundamental carbon feedstock and functionality, but the direct difluoromethylation of alkenes has been limited.[8] In 1994, Chen and co-workers reported a radical iododifluoromethylation using CF_2HI, which is a gaseous and hard to prepare reagent (Scheme 1 a).[8a] More recently, Dolbier and co-workers exploited CF_2HSO_2Cl as a difluoromethyl radical source and developed alkene difluoromethylation, for example, chloro-, carbo- and aminodifluoromethylation (Scheme 1 b).[8b–e] Furthermore, the groups of Tan and Hu developed a silver-catalyzed intramolecular carbodifluoromethylation with difluoromethylsulfinate salts, $(CF_2HSO_2)_nM$, such as $(CF_2HSO_2)_2Zn$ and CF_2HSO_2Na (Scheme 1 c).[8f,g]

For the past several years, our group has been extensively developing a photoredox-catalyzed trifluoromethylative difunctionalization[9,10] of alkenes and alkynes using electrophilic trifluoromethylating reagents, such as Umemoto's[11] and Togni's reagent.[12] We envisaged that the appropriate choice of a difluoromethylating reagent could open an unprecedented photoredox-catalyzed difluoromethylation of alkenes. Herein, we describe the first example of a photocatalytic oxydifluoromethylation of alkenes with shelf-stable and easy-to-handle *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**1 a**), so-called Hu's reagent, which has been previously reported to be a useful difluorocarbene source by Hu and co-workers (Scheme 1 d).[13,14]

[a] *Y. Arai, R. Tomita, G. Ando, Dr. T. Koike, Prof. Dr. M. Akita*
Chemical Resources Laboratory
Tokyo Institute of Technology
R1-27, 4259 Nagatsuta, Midori-ku, Yokohama 226-8503 (Japan)
E-mail: koike.t.ad@m.titech.ac.jp
makita@res.titech.ac.jp

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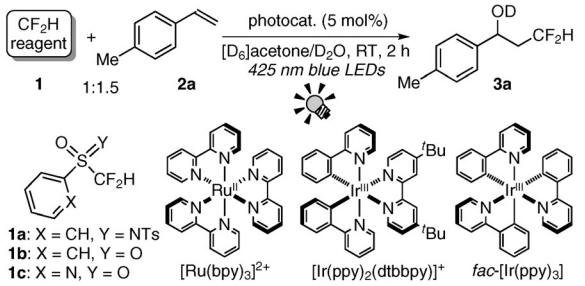
Table 1. Optimization of the photocatalytic hydroxydifluoromethylation of 4-methylstyrene (**2a**).[a]



Entry	Photocatalyst	CF_2H reagent **1**	Yield of **3a** [%][b]
1	*fac*-[Ir(ppy)$_3$]	**1b**	0
2	*fac*-[Ir(ppy)$_3$]	**1c**	29
3	*fac*-[Ir(ppy)$_3$]	**1a**	88
4	[Ru(bpy)$_3$][PF$_6$]$_2$	**1a**	0
5	[Ir(ppy)$_2$(dtbbpy)][PF$_6$]	**1a**	0
6[c]	*fac*-[Ir(ppy)$_3$]	**1a**	0
7	none	**1a**	0

[a] For detailed reaction conditions, see the Supporting Information. [b] Yields were determined by ^{1}H NMR spectroscopy using Si(Et)$_4$ as an internal standard. [c] In the dark. LED = light-emitting diode.

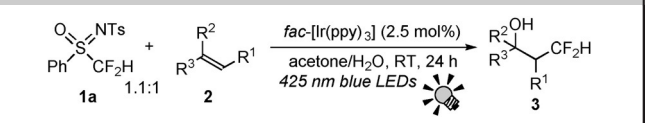
This protocol allows us simple and versatile access to a wide range of CF_2H alcohols through regioselective installation of the CF_2H group and an oxygen nucleophile onto alkenes.

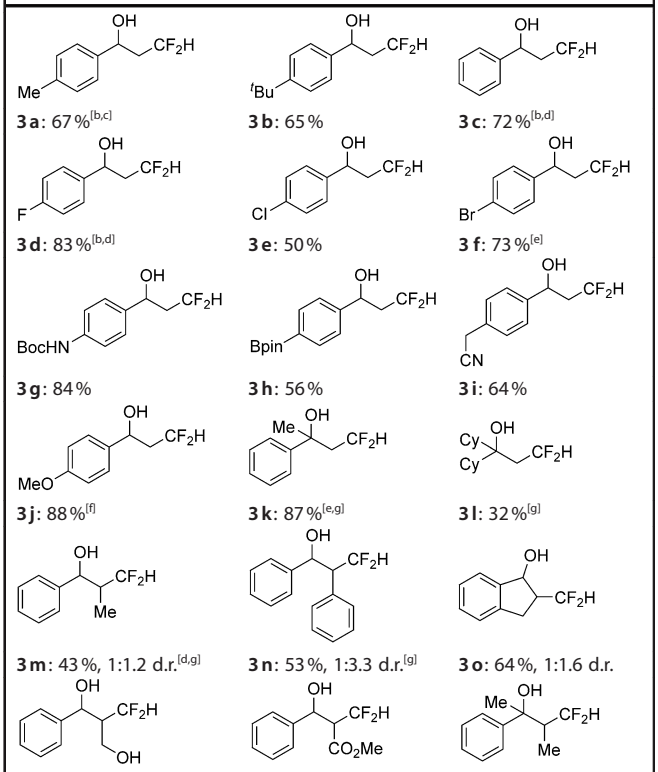
We initially explored CF_2H reagent **1** for the photocatalytic hydroxydifluoromethylation of 4-methylstyrene (**2a**) at room temperature under visible-light irradiation with blue LEDs (λ_{max} = 425 nm; Table 1). Taking account of the reaction conditions of the photocatalytic hydroxytrifluoromethylation reported by us,[10a] we conducted the reaction in a mixed solvent system of [D$_6$]acetone and D$_2$O (9:1) in the presence of *fac*-[Ir(ppy)$_3$] (ppy = 2-pyridylphenyl) (5 mol%), which serves as a strong reducing agent when photoexcited ($E_{1/2}$ = −2.14 V versus. [Cp$_2$Fe]).[15] Under these reaction conditions, sulfone-based commercially available CF_2H reagents, CF_2HSO_2Ph (**1b**) and CF_2HSO_2Py (**1c**; Py = 2-pyridyl), were tested (entries 1 and 2). Reagent **1b** was scarcely converted. In contrast, **1c** gave the corresponding CF_2H alcohol **3a** in 29% NMR yield together with a mixture of unidentified products. Encouraged by these results, we continued to examine the analogous CF_2H reagent (sulfoximine-based CF_2H reagent **1a**).[16] To our delight, hydroxydifluoromethylation proceeded in a regioselective manner to afford 3,3-difluoro-1-tolylpropanol (**3a**) as a sole regioisomer in 88% NMR yield (entry 3). Next, the examination of typical photocatalysts revealed that *fac*-[Ir(ppy)$_3$] was the best catalyst (entries 3–5).[15] Finally, the present photocatalytic reaction did not proceed at all either in the dark or in the absence of photocatalyst (entries 6 and 7), indicating that photoactivated species is involved in the present transformation.

The scope of the present photocatalytic hydroxydifluoromethylation of alkenes is summarized in Table 2. Styrenes with various functional groups on the benzene ring, such as alkyls (**2a**, **b**), halogens (**2d**–**f**), Boc-protected amino (**2g**), boronic acid ester (**2h**), and cyanomethyl (**2i**) groups, smoothly produced the corresponding CF_2H-containing alcohols (**3a**–**i**) in good yields (50–84%, 2–24 h). In contrast, the reaction of styrene with an electron-donating group on the benzene ring, 4-methoxystyrene (**2j**), required longer time, but the corresponding product **3j** was obtained in good yield (88%, 72 h). In addition, α-methylstyrene (**2k**) and the aliphatic alkene, 1,1-dicyclohexylethene (**2l**), were also successfully applied to the present photocatalytic reaction, leading to the corresponding CF_2H alcohols (**3k**, **l**) in 87 and 32% yields, respectively.

Furthermore, the present photocatalytic system enables the difluoromethylation of internal alkenes, including a trisubstituted alkene. Reactions of β-methylstyrene (**2m**), *trans*-stilbene (**2n**), indene (**2o**), *trans*-cinnamyl alcohol (**2p**), *trans*-cinnamic acid methyl ester (**2q**), and α,β-dimethylstyrene (**2r**; *E*/*Z* = 1:5.6) afforded the corresponding difluoromethylated products (**3m**–**r**) in 43–67% yields as sole regioisomers but mixtures of diastereomers. It should be noted that the present photocatalytic system with Hu's reagent **1a** is compatible for a wide vari-

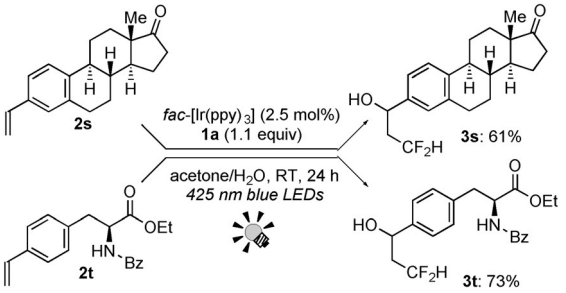
Table 2. Scope of the photocatalytic hydroxydifluoromethylation.[a]



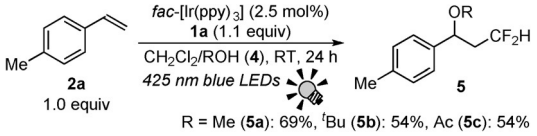


[a] For detailed reaction conditions, see the Supporting Information; diastereomer ratios (d.r.) were determined by ^{1}H NMR spectra of crude reaction mixtures; yields were obtained after purification. [b] Ir photocatalyst (0.5 mol%) was used. [c] Reaction time = 2 h. [d] The ratio of **2** and **1a** was 1.5:1; yields were calculated on the basis of starting **1a**. [e] Ir photocatalyst (5 mol%) was used. [f] Reaction time = 72 h. [g] Reaction time = 36 h.

ety of functionalities, such as hydroxyl, *N*-protected amino, halogens, nitrile, ester, and boronic acid ester groups. Moreover a regiospecific addition of the CF_2H and OH groups, regardless of terminal or internal alkenes, is particularly significant. These results prompted us to investigate reactions of more structurally complex substrates. It was found that the present reaction system was amenable to the hydroxydifluoromethylation of vinylestrone (**2s**) and vinyl-*N*-benzoyl-L-tyrosine ethyl ester (**2t**), leading to the corresponding difluoromethylated alcohols (**3s**: 61%; **3t**: 73%; Scheme 2). These results suggest that the present protocol would be valuable for the late-stage difluoromethylation in a synthetic process.



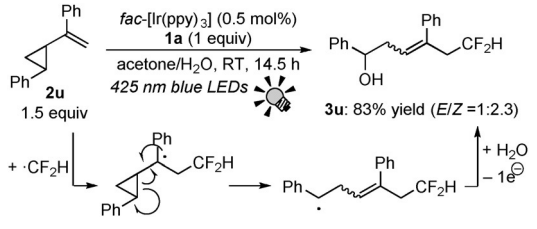
Scheme 2. Direct difluoromethylation of alkenes with estrone and amino acid skeleton.



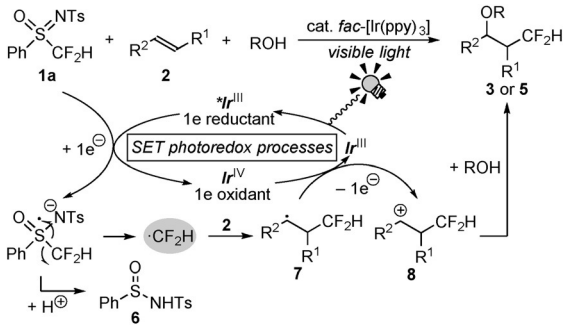
Scheme 3. Oxydifluoromethylation of 4-methylstyrene (**2a**): simple synthesis of CF_2H ester and CF_2H ethers.

Next, we examined other oxygen nucleophiles, ROH (**4**), such as alcohols and carboxylic acids, for the reaction of 4-methylstyrene (**2a**; Scheme 3). All reactions were conducted in dry CH_2Cl_2/ROH (9:1). It turned out that the alkoxydifluoromethylation and carboxydifluoromethylation smoothly proceeded regioselectively not only to introduce a CF_2H group but also to construct ether and ester functionalities onto the C=C bond. Reactions with MeOH (**4a**) and *t*BuOH (**4b**) gave the corresponding CF_2H ethers **5a** and **5b** in 69 and 54% yields, respectively. Carboxylic acid substrate **4c** produced CF_2H-containing ester **5c** in 54% yield.

To gain insight into the reaction mechanism, the reaction of 1-phenyl-2-(1-phenylethenyl)cyclopropane (**2u**) was examined (Scheme 4). As a result, the difluoromethylated alcohol **3u** was obtained in 83% yield (E/Z = 1:2.3) through a ring-opening process of the cyclopropane unit. In addition, when photocatalytic hydroxydifluoromethylation of **2a** was conducted in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO), which is a radical scavenger, the hydroxydifluoromethylation was completely inhibited (See the Supporting Information for details). These results suggest that radical intermediates are involved in the present photocatalytic reaction.



Scheme 4. Photocatalytic hydroxydifluoromethylation of 1-phenyl-2-(1-phenylethenyl)cyclopropane (**2u**).



Scheme 5. A plausible reaction mechanism.

On the basis of these observations and our previous reports,[10] a plausible reaction mechanism is shown in Scheme 5. First, the photocatalyst ***Ir***^{III} is excited by visible light to give the excited species *Ir^{III}. The formed excited species *Ir^{III} serves as a strong one-electron reductant to undergo single-electron transfer (SET) to Hu's reagent **1a**, leading to generation of the highly oxidized species ***Ir***^{IV}. Reduced **1a** fragmentizes into the CF_2H radical and sulfinamide **6**. The generated CF_2H radical reacts with alkene **2** in a regioselective manner to afford the stabilized radical intermediate **7**, which is then oxidized by the strongly oxidizing species ***Ir***^{IV} to generate α-CF_2H carbocationic intermediate **8** together with regeneration of the photocatalyst ***Ir***^{III} of the ground state. Finally, the carbocationic intermediate **8** undergoes solvolysis by ROH to produce oxydifluoromethylated products **3** or **5**.

In conclusion, we have developed a novel photoredox-catalyzed oxydifluoromethylation of alkenes. The present work is the first report to use Hu's reagent, *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**1a**), as a CF_2H radical precursor. Visible-light-driven photoredox catalysis by the Ir photocatalyst, *fac*-[Ir(ppy)$_3$], has opened a new possibility of radical difluoromethylation by the difluorocarbene source **1a**. The designed redox-neutral reaction system enables step-economical synthesis of β-CF_2H-substituted alcohols, ethers, and esters under mild reaction conditions. Remarkably, the present photocatalytic difluoromethylation system exhibits excellent functional group compatibility. A development of new synthetic methods for organofluorine compounds through a photoredox-catalyzed fluoroalkylation is currently underway in our laboratory.

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Keywords: alcohols · fluorine · homogeneous catalysis · iridium · photochemistry

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