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Photoredox-Catalyzed Bromodifluoromethylation of Alkenes with (Difluoromethyl)triphenylphosphonium Bromide

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Ⓢ *Supporting Information*

ABSTRACT: Under visible-light photoredox conditions, difluoromethyltriphenylphosphonium bromide was used as the precursor of the CF_2H radical for bromodifluoromethylation of alkenes. The presence of catalytic $CuBr_2$ resulted in the selective formation of the bromodifluoromethylated products.

The selective introduction of fluorinated moieties into organic molecules often affects their physicochemical and biological properties.[1] Among various fluorinated moieties, the difluoromethyl group (CF_2H) is an intriguing structural motif, which can bring about some useful effects, such as the enhancement of binding affinity and lipophilicity.[2] Furthermore, this group is considered isosteric and isopolar with OH and SH.[3] Therefore, the CF_2H group plays increasingly important role in drug discovery.[4]

Traditionally, difluoromethylated compounds were prepared by the deoxyfluorination of aldehydes with SF_4 or DAST ((*N*,*N*-diethylamino)sulfur trifluoride).[5] However, these reactions suffer from poor functional group tolerance and harsh reaction conditions. Recently, much effort has been devoted to the developments of new methods for the incorporation of a CF_2H group into organic molecules via electrophilic,[6] nucleophilic,[7] and radical[8] approaches. Among these three strategies, radical difluoromethylation is more attractive. In 1994, Chen reported the first example of direct radical transfer of a CF_2H unit in the context of additions to alkenes or alkynes using HCF_2I (**A**) as the difluoromethylating reagent.[9] However, HCF_2I is not commercially available and operationally problematic (Figure 1). In 2012, Baran's group developed a new reagent **B**, $Zn(SO_2CF_2H)_2$, for the radical difluoromethylation of heteroarenes.[8a,b] Reagent **B** was also applied in the decarboxylative difluoromethylation of α,β-unsaturated carboxylic acids[8c] and difluoromethylation−cyclization reactions of arylacrylamides.[8d] Hu disclosed that $NaSO_2CF_2H$ (**C**) was a CF_2H radical precursor for the silver-catalyzed cascade difluoromethylation/aryl migration/SO_2 extrusion of conjugated *N*-arylsulfonylated amides.[8e] Over the past 3 years, Dolbier and co-workers have reported a series of radical difluoromethylations of unsaturated bonds using HCF_2SO_2Cl (**D**) as the CF_2H radial sources.[8f−k] Recently, Koike and Akita developed a photocatalytic oxidifluoromethylation of alkenes with *N*-tosyl-*S*-(difluoromethyl)-*S*-phenylsulfoximine (**E**).[8l] Hu and Ni reported the radical difluoromethylation of isocyanides with 2-[(difluoromethyl)sulfonyl]benzo[*d*]thiazole (**F**) under visible-light photoredox catalysis.[8m] Although much progress has been made in the direct difluoromethylation via a radical process, these reagents **B**−**F** were all prepared from gaseous HCF_2Cl through several steps.[10] Thus, the development of the easily available and handled radical difluoromethylating reagents is still highly desirable.

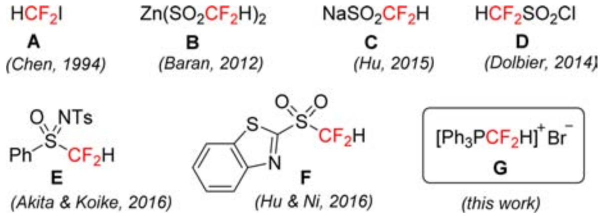

Figure 1. Radical difluoromethylating reagents.

(Difluoromethyl)triphenylphosphonium bromide (**G**) was prepared by Burton as early as in 1985 by mixing PPh_3, CF_2Br_2, and H_2O in THF.[11] Normally, this reagent was used as the precursor of difluoromethylene phosphonium ylide (Scheme 1a).[12] Inspired by recent achievements of photoredox-catalyzed

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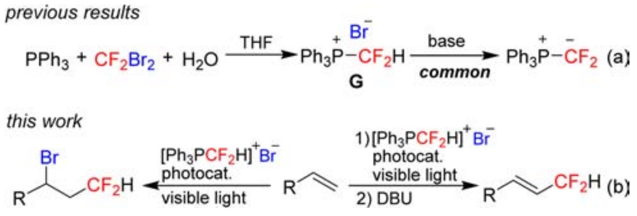
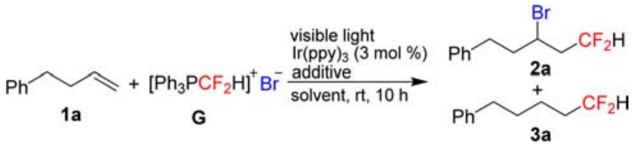
Scheme 1. Synthesis and Application of Reagent G



fluoroalkylation reactions,[13,14] we hypothesized that reagent **G** might find new applications under visible light irradiation. On the other hand, the development of new methods for the simultaneous incorporation of a CF_2H group and another functional group (H,[8k,14d] C,[7f,8d–f] N,[8i] O,[8i,l] Cl,[8f,g] and I[9]) into alkenes has received great attention recently. However, bromodifluoromethylation of alkenes has not been reported yet. Herein, we describe the bromodifluoromethylation of alkenes with reagent **G**. Moreover, this protocol was further applied for the preparation of CF_2H-containing alkenes via an addition/elimination process (Scheme 1b).

Initially, the reaction conditions were optimized using 4-phenyl-1-butene (**1a**) as the model substrate and reagent **G** as the CF_2H source (Table 1). Among the common photocatalysts including $Ru(bpy)_3Cl_2$, $Ir(ppy)_3$, Methylene Blue, and Eosin Y, only $Ir(ppy)_3$ could trigger this reaction (entries 1–4).

Table 1. Optimization of Reaction Conditions[a]



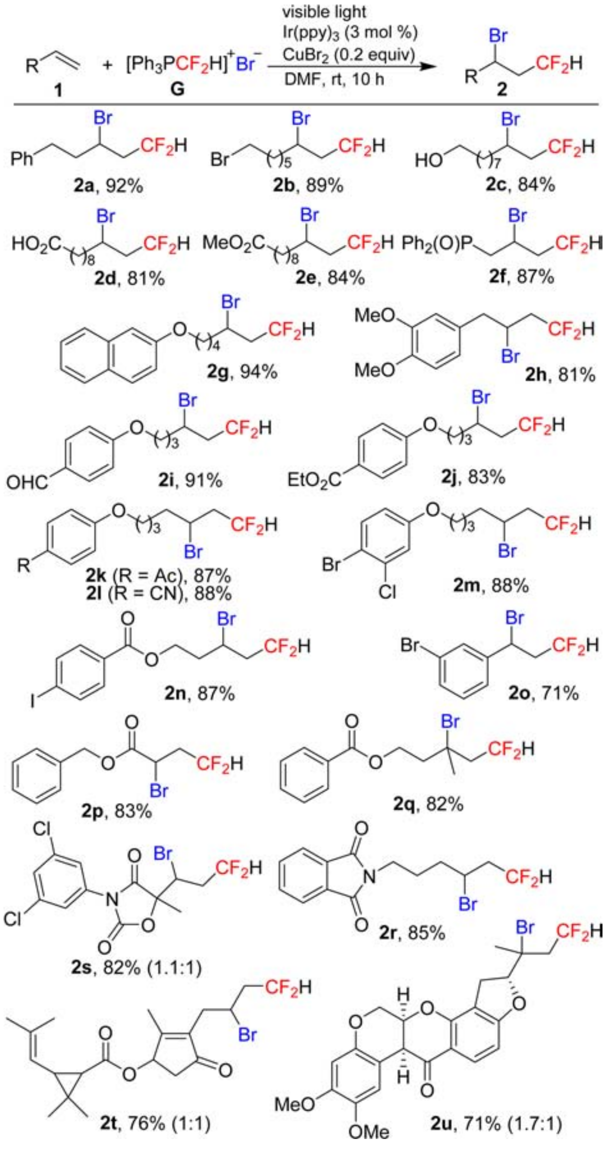
entry	photocat.	solvent	additive	yield[b] (**2a**/**3a**, %)
1	$Ru(bpy)_2Cl_2$	THF		0/0
2	$Ir(ppy)_3$	THF		4/57
3	Methylene Blue	THF		0/0
4	Eosin Y	THF		0/0
5	$Ir(ppy)_3$	MeCN		5/39
6	$Ir(ppy)_3$	DMSO		36/4
7	$Ir(ppy)_3$	DMF		82/10
8	$Ir(ppy)_3$	DMAc		76/12
9	$Ir(ppy)_3$	DMF	$K_2S_2O_8$	80/16
10	$Ir(ppy)_3$	DMF	$PhI(OAc)_2$	76/18
11	$Ir(ppy)_3$	DMF	$Cu(OAc)_2$	87/trace
12	$Ir(ppy)_3$	DMF	$CuBr_2$	93/trace
13	$Ir(ppy)_3$	DMF	$CuSO_4{\cdot}5H_2O$	92/trace
14[c]	$Ir(ppy)_3$	DMF	$CuBr_2$	0/0

[a] Reaction conditions: **1a** (0.1 mmol), difluoromethyltriphenylphosphonium bromide (0.3 mmol), photocatalyst (0.003 mmol), additive (0.02 mmol), solvent (1.0 mL), visible light, rt, under N_2, 10 h. [b] Yields determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard. [c] $CuBr_2$ (0.12 mmol).

However, the bromodifluoromethylated compound **2a** was formed in extremely low yield in THF along with the hydrodifluoromethylated compound **3a**[14d] as the major product (entry 2). Then, different solvents were screened to improve the yield of **2a** (entries 5–8). Among them, DMF was superior to other solvents, giving product **2a** in 82% yield and byproduct **3a** in 10% yield (entry 7). To inhibit this byproduct, different additives were explored (entries 9–13). Oxidants such as $K_2S_2O_8$ and $PhI(OAc)_2$ had negative effects on the selective formation of **2a** (entries 9 and 10). The catalytic amount of copper salts, including $Cu(OAc)_2$, $CuBr_2$, and $CuSO_4{\cdot}5H_2O$, could effectively inhibit the formation of **3a** (entries 11–13). Among them, $CuBr_2$ was optimal to provide the desired **2a** in the highest yield of 93% (entry 12). Surprisingly, there was no reaction when the stoichiometric $CuBr_2$ was used (entry 14).

With the optimal reaction conditions in hand, we next expanded the substrate scope of this visible light induced bromodifluoromethylation of alkenes. A variety of terminal alkenes **1** could be converted into the corresponding products **2** in moderate to excellent yields (Scheme 2). Various functional groups, including alcohols, ethers, aldehydes, carboxylic acids, esters, alkyl bromides, and phosphide oxides, were well tolerated (**1b**–**l**). Notably, substrates bearing chloro, bromo,

Scheme 2. Substrate Scope of Bromodifluoromethylation of Alkenes[a]



[a] Reaction conditions: **1** (0.5 mmol), (difluoromethyl)-triphenylphosphonium bromide (1.5 mmol), $Ir(ppy)_3$ (0.015 mmol), $CuBr_2$ (0.1 mmol), DMF (5.0 mL), visible light, rt, under N_2, 10 h, isolated yields.

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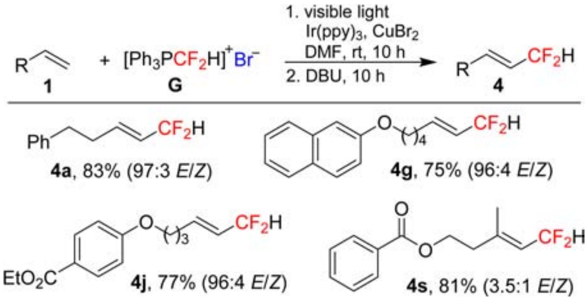
and iodo substituents on the arene rings are also compatible (**1m**,**o**). It was noteworthy that this reaction allowed the direct bromodifluoromethylation of styrene **1o** and α,β-unsaturated ester **1p** to afford the corresponding products **2o** and **2p** in good yields. Moreover, the geminally disubstituted alkene **1q** also exhibited good reactivity. Furthermore, bromodifluoromethylation of one fungicide (vinclozolin, **1s**) and two insecticides (allethrin, **1t**, and rotenone, **1u**) proceeded smoothly to give products **2s**−**u** in good yields, respectively. The current protocol was also applied to the preparation of CF_2H-containing alkenes via a one-pot addition/elimination process. As shown in Scheme 3, alkenes **1** underwent bromodifluoromethylation followed by dehydrobromination[13g,15] to give the difluoromethylated alkenes **4** in good yields.

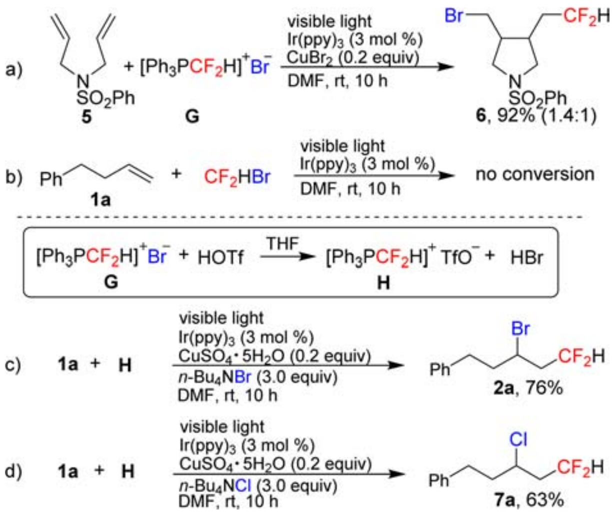
Scheme 3. Difluoromethylation of Alkenes[a]



[a]Reaction conditions: **1** (0.5 mmol), (difluoromethyl)-triphenylphosphonium bromide (1.5 mmol), $Ir(ppy)_3$ (0.015 mmol), $CuBr_2$ (0.1 mmol), DMF (5.0 mL), visible light, rt, under N_2, 10 h, then DBU (3.0 mmol), 10 h, isolated yields.

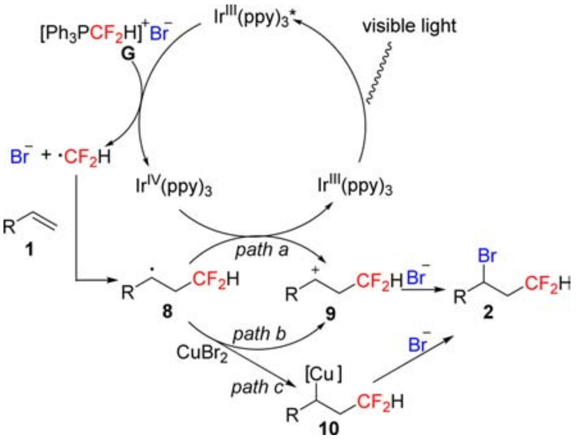
To gain insight into the reaction mechanism, we conducted a series of experiments. First, when diene **5** was subjected to the standard reaction conditions, the cyclized product **6** was obtained in excellent yield with low dr value (Scheme 4a). This result revealed that the CF_2H radical was involved in this transformation. Furthermore, the reaction of **1a** with CF_2HBr did not take place, which excluded the possibility of CF_2HBr as the active intermediate (Scheme 4b). To determine how the bromine was introduced, a new CF_2H-containing phosphonium salt **H** was prepared, and then the difluoromethylation of **1a** with **H** in the presence of n-Bu_4NBr or n-Bu_4NCl (Scheme 4c,d) was investigated. Both bromo- and chlorodifluoromethylated products **2a** and **7a** were formed in good yields, which indicated that bromine was introduced through a nucleophilic attack of bromide anion.[16] All these results suggested that a radical/cationic process was probably involved in this transformation.

Scheme 4. Mechanistic Investigations



Based on the mechanistic studies, a plausible reaction mechanism was proposed in Scheme 5. Initially, the irradiation of visible light excited $Ir^{III}(ppy)_3$ to $Ir^{III}(ppy)_3$*. Then, a single-electron-transfer (SET) from $Ir^{III}(ppy)_3$* to (difluoromethyl)-triphenylphosphonium bromide **G** generated the CF_2H radical, which was subsequently added to alkene **1** for the formation of radical intermediate **8**.[14d] The intermediate **8** was oxidized into carbocation **9** by the SET from $Ir^{IV}(ppy)_3$ (path a). Finally, the nucleophilic trapping of carbocation **9** by bromide anion afforded the bromodifluoromethylated product **2**. Alternatively, the reaction of radical intermediate **8** and $CuBr_2$ might give either carbocation **9** (path b) or an alkylcopper species **10** (path c),[17] which then was transformed into the final product **2**. Currently, the exact role of the copper salt for promoting this reaction remains unclear.

Scheme 5. Proposed Reaction Mechanism



In conclusion, we have disclosed that (difluoromethyl)-triphenylphosphonium bromide **G** might be the most easily available and handled radical difluoromethylating reagent up to now. The reaction of alkenes with this reagent under photoredox catalysis afforded previously unknown bromodifluoromethylated compounds. Considering the importance of the Br and CF_2H functional groups, this protocol has potential application in organic synthesis and medicinal chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00935.

Experimental procedures, characterization data, and copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) For the preparation of reagent **B**, see ref 8a. For the preparation of reagent **C**, see ref 8e. For the preparation of reagent **D**, see ref 8f. For the preparation of reagent **E**, see: Zhang, W.; Wang, F.; Hu, J. *Org. Lett.* **2009**, *11*, 2109. For the preparation of reagent **F**, see ref 8m.

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