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Visible-light-induced radical hydrodifluoromethylation of alkenes†

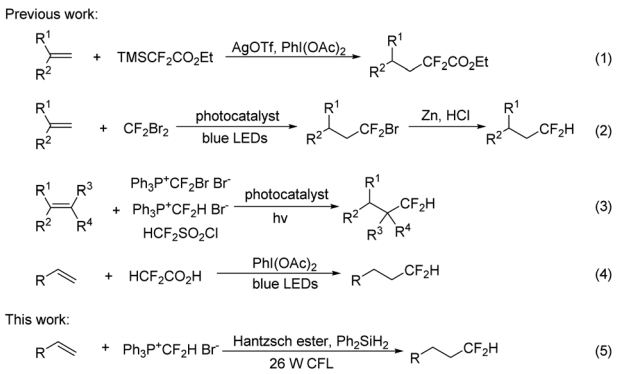
Jiao Yu,[a] Jin-Hong Lin,[a] Yu-Cai Cao[b] and Ji-Chang Xiao*[a]

Described here is the radical-mediated hydrodifluoromethylation of alkenes that occurs under transition-metal-free conditions by using the phosphonium salt $[Ph_3P^+CF_2H]Br^-$ under the irradiation of 26 W household compact fluorescent light. The reaction lends itself to a convenient protocol for the installation of a C–CF_2H bond while maintaining good functional group tolerance.

The difluoromethyl group (HCF_2) has received increasing attention in drug design, because it is a lipophilic hydrogen-bond donor and can act as a bioisostere of an OH or SH unit.[1] The past few decades have seen the emergence of many HCF_2-containing pharmaceuticals and agrochemicals, such as eflornithine, deracoxib, sedaxane, isopyrazam, bixafen, and thiazopir.[2] The high demand for HCF_2-substituted biologically active compounds has prompted the development of efficient methods for the incorporation of a HCF_2 group into organic molecules.

The straightforward strategies for HCF_2 incorporation include the insertion of difluorocarbene into X-H bonds[3] (X = C, N, O, S, *etc.*) and direct difluoromethylation with a HCF_2 reagent.[2,4] Difluorocarbene insertion is highly effective for the installation of an XCF_2H moiety (X = N, O, or S), but for the formation of a C–CF_2H group by this strategy, a reactive substrate or a strong base has to be used.[5] Over the last few years, a large number of direct difluoromethylation approaches have been developed, such as nucleophilic,[6] radical,[7] electrophilic[8] and transition-metal-promoted reactions,[9] enabling convenient construction of C–CF_2H bonds. However, the reported methods usually suffer from the use of a transition metal that may limit their biomedical applications, or difluoromethylation reagents that are volatile or difficult to prepare. In addition, a further tedious procedure may be required to remove the undesired auxiliary group X from XCF_2 moieties to form HCF_2-products. It is therefore highly desirable to develop mild protocols for direct difluoromethylation under transition-metal-free conditions by using an easy-to-handle reagent.

Hydrodifluoromethylation of alkenes is an attractive approach for the installation of a Csp^3–CF_2H bond. In 2014, Hao described a hydrodifluoromethylation of terminal alkenes with $TMSCF_2CO_2Et$, a process in which an excess of silver source is essential (Scheme 1, eqn (1)).[10] In 2015, Qing disclosed a two-step sequence involving visible-light-induced hydrobromodifluoro-methylation with ozone-depleting CF_2Br_2 and the subsequent reductive debromination to convert the $BrCF_2$ to HCF_2 groups (Scheme 1, eqn (2)).[11] Shortly after, they further reported the hydrodifluoromethylation using phosphonium reagents, $[Ph_3P^+CF_2Br\ Br^-]$[12] and $[Ph_3P^+CF_2H\ Br^-]$,[13] under photocatalytic conditions (eqn (3)). Dolbier *et al.* found that the photocatalyzed hydrodifluoromethylation with HCF_2SO_2Cl could also occur well (eqn (3)).[14] Gouverneur reported a visible-light-promoted hydrodifluoromethylation of alkenes with HCF_2CO_2H (eqn (4)).[15] This operationally simple reaction did not require a photocatalyst, affording the hydrodifluoromethylation products in good yields. Although the above approaches are quite efficient, their synthetic utility



Scheme 1 Hydrodifluoromethylation of alkenes.

[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Science, 345 Lingling Road, Shanghai 200032, China. E-mail: jchxiao@sioc.ac.cn*
[b]*State Key Laboratory of Polyolefins and Catalysis, Shanghai Key Laboratory of Catalysis Technology for Polyolefins, Shanghai Research Institute of Chemical Industry Co. Ltd, China*

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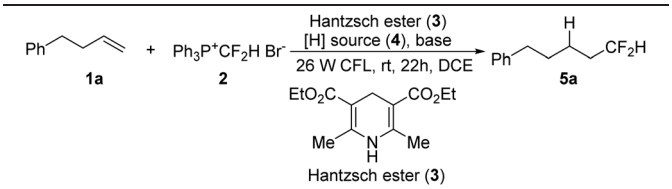
may be compromised by the disadvantages such as the need for an additional step to remove an auxiliary group,[10,11] or the use of an expensive photocatalyst[12–14] or a strong oxidant.[15] In continuation of our studies on fluoroalkylation,[6d,16] we investigated the feasibility of performing direct hydrodifluoromethylation of alkenes under radical mediated conditions. Herein, we report the visible light induced hydrodifluoromethylation of alkenes using the phosphonium salt $[Ph_3P^+CF_2H]Br^-$ under the irradiation of with 26 W household compact fluorescent light (CFL) (eqn (5)).

We have previously shown that the phosphonium salt, $[Ph_3P^+CF_2H]Br^-$ (**2**),[6d] could be easily prepared from the phosphobetaine $Ph_3P^+CF_2CO_2^-$, a reagent developed by us,[17] *via* a convenient decarboxylative protonation. Since salt **2** could be reduced to generate a difluoromethyl radical,[18] various reducing agents were examined in our initial attempts at the hydrodifluoromethylation of alkene **1a** with **2** (Table 1, entries 1–4). However, almost no desired product was detected by using metals as reducing agents (entries 1–3). We then probed Hantzsch ester **3**, as it was known to act as an efficient reducing agent when irradiated with visible light.[19] To our delight, 16% yield was obtained by irradiating the reaction with household 26 W CFL in the presence of a Hantzsch ester (entry 4). A brief survey of the reaction solvents (entries 4–7) revealed that 1,2-dichloroethane (DCE) was a superior choice (entry 7). The yield was increased in the presence of $NaHCO_3$ (entry 8 *vs.* 7), but other bases seemed ineffective (entries 9–12 *vs.* 7). Apparently, a hydrogen source was needed in this hydrodifluoromethylation reaction. The 41% yield (entry 8) indicated that one of the reagents used also served as a hydrogen source. Since it was difficult to increase the yield further, a second hydrogen source was then added (entries 13–16). The use of Ph_2SiH_2 increased the yield to 50% (entry 14). The molar ratios of the reagents were screened (entries 17–20). An increase in the yield was observed by increasing the loading of phosphonium salt **2** (entry 20).

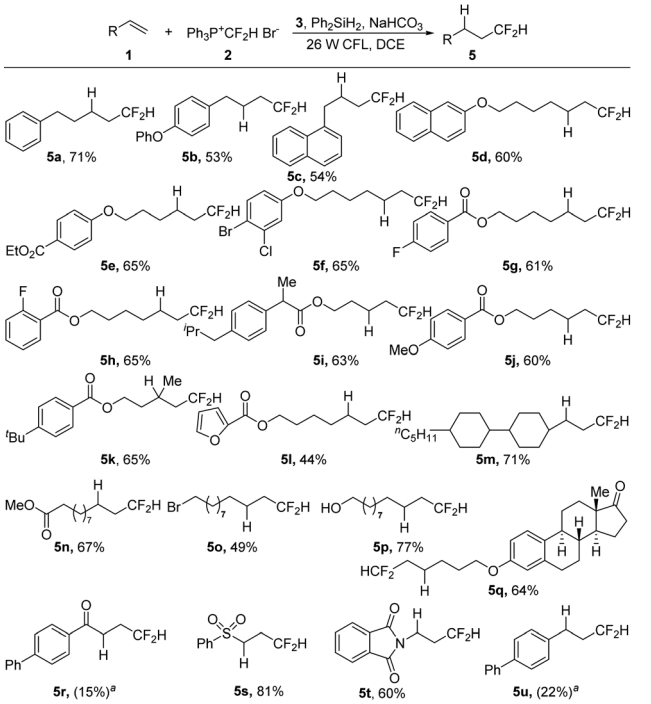
With the optimized reaction conditions in hand (Table 1, entry 20), we then investigated the substrate scope of the visible-light-induced hydrodifluoromethylation of alkenes (Scheme 2). The process could be applied to a wide range of alkenes, and various functional groups could be tolerated, including ester, carbonyl, halides, heterocycles, hydroxyl, sulfonyl, and imide groups. Besides monosubstituted alkenes, disubstituted terminal alkenes could also be converted smoothly into the desired products (**5k**). However, in the case of trisubstituted alkenes, low regioselectivity was observed, and complex mixtures were obtained. For substrates with electron-

Table 1 Optimization of the reaction conditions[a]



Entry	[H] source	Base	Ratio[b]	Yield[c] (%)
1[d,e]	—	—	1 : 3 : 3 : 0 : 0	ND
2[d,f]	—	—	1 : 3 : 3 : 0 : 0	Trace
3[d,g]	—	—	1 : 3 : 3 : 0 : 0	ND
4[d]	—	—	1 : 3 : 3 : 0 : 0	16
5[h]	—	—	1 : 2 : 2 : 0 : 0	4
6[i]	—	—	1 : 2 : 2 : 0 : 0	25
7	—	—	1 : 2 : 2 : 0 : 0	28
8	—	$NaHCO_3$	1 : 2 : 2 : 0 : 4	41
9	—	KH_2PO_4	1 : 2 : 2 : 0 : 4	17
10	—	CH_3COOK	1 : 2 : 2 : 0 : 4	28
11	—	$Na_2C_2O_4$	1 : 2 : 2 : 0 : 4	16
12	—	Cs_2CO_3	1 : 2 : 2 : 0 : 4	28
13	$(TMS)_3SiH$	$NaHCO_3$	1 : 2 : 2 : 4 : 4	15
14	Ph_2SiH_2	$NaHCO_3$	1 : 2 : 2 : 4 : 4	50
15	Et_3SiH	$NaHCO_3$	1 : 2 : 2 : 4 : 4	45
16	Bu_3SnH	$NaHCO_3$	1 : 2 : 2 : 4 : 4	6
17	Ph_2SiH_2	$NaHCO_3$	1 : 2 : 2 : 4 : 2	31
18	Ph_2SiH_2	$NaHCO_3$	1 : 3 : 2 : 4 : 4	57
19	Ph_2SiH_2	$NaHCO_3$	1 : 4 : 2 : 4 : 4	70
20	Ph_2SiH_2	$NaHCO_3$	1 : 4 : 2 : 2 : 4	71

[a] Reaction conditions: **1a** (0.2 mmol), **2**, **3**, **4** and base in 1,2-dichloroethane (3.5 mL) under the irradiation of household 26 W CFL at room temperature for 22 h. [b] Molar ratio of **1a**:**2** : **3** : **4** : base. [c] The yields were determined by ^{19}F NMR; ND = not detected. [d] CH_3CN was used as the reaction solvent. [e] Mg was used as the reductant instead of a Hantzsch ester. [f] Zn was used as the reductant instead of a Hantzsch ester. [g] Fe was used as the reductant instead of a Hantzsch ester. [h] DMF was used as the reaction solvent. [i] DCM was used as the reaction solvent.

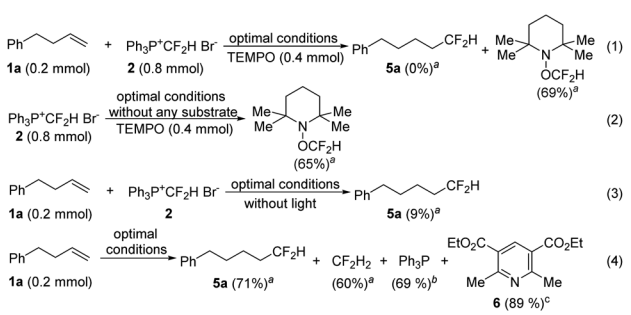


Scheme 2 Hydrodifluoromethylation of alkenes. Isolated yields. Reaction conditions: Substrate **1** (0.5 mmol), salt **2** (4 equiv.), Hantzsch ester (2 equiv.), Ph_2SiH_2 (2 equiv.), and $NaHCO_3$ (4 equiv.) in DCE (9 mL) under the irradiation of 26 W household CFL at room temperature for 22 h. [a] The yields of **5r** and **5u** were determined by ^{19}F NMR spectroscopy.

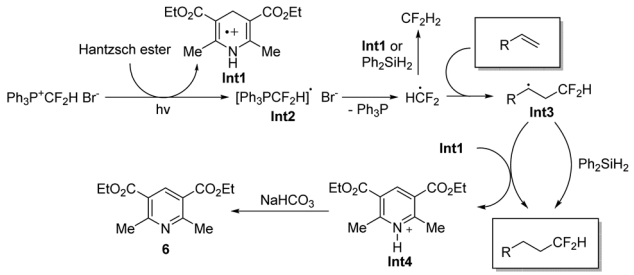
withdrawing carbonyl and sulfonyl groups, although the carbonyl-substituted alkene showed a low reactivity (**5r**), the sulfonyl alkene was transformed into the desired product in a good yield (**5s**). While the reaction of an enamine derivative gave the product in a good yield (**5t**), the hydrodifluoromethylation of an aryl alkene under the present reaction conditions led to a low conversion (**5u**).

More experimental evidence was collected to gain insight into the mechanism of this hydrodifluoromethylation reaction. The addition of a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl), completely suppressed the formation of the desired product, and the TEMPO-CF_2H byproduct was produced in 69% yield (Scheme 3, eqn (1)). The TEMPO-CF_2H adduct was also detected from the reaction run in the absence of a substrate (eqn (2)), indicating that a radical mechanism is operative. The desired product was generated in a very low yield when the reaction was conducted in the dark (eqn (3)), suggesting that light is essential for this process. After the reaction was complete, CF_2H_2, Ph_3P and pyridine **6** were produced as the byproducts (eqn (4)). In particular, Ph_3P and **6**, formed from $[Ph_3P^+CF_2H]Br^-$ and the Hantzsch ester, respectively, were isolated in high yields, indicating that $[Ph_3P^+CF_2H]Br^-$ was reduced while the Hantzsch ester was oxidized in the reaction. The Stern–Volmer luminescence quenching experiments revealed that the phosphonium salt $[Ph_3P^+CF_2H]Br^-$ could quench the excited Hantzsch ester (see the ESI† for experimental details), suggesting that electron transfer between these two reagents might have occurred.

On the basis of the above results, we proposed the reaction mechanism as shown in Scheme 4. Under the irradiation of light, a single electron transfer from the Hantzsch ester to the phosphonium salt $[Ph_3P^+CF_2H]Br^-$ generates radical cation **Int1** and $[Ph_3PCF_2H]^\bullet$ radical. The release of Ph_3P from $[Ph_3PCF_2H]^\bullet$ radical provides $HCF_2^\bullet$, which is easily trapped by an alkene to form intermediate **Int3**. The $HCF_2^\bullet$ radical may also be quenched by **Int1** or Ph_2SiH_2 to give CF_2H_2. Radical **Int3** would abstract a hydrogen atom from Ph_2SiH_2 or radical cation **Int1** to deliver the desired product **5**. The reaction of **Int3** with **Int1** leads to the formation of pyridinium cation **Int4**, which is neutralized by $NaHCO_3$ to afford compound **6**.



Scheme 3 Mechanistic investigations. [a] The yields were determined by ^{19}F NMR spectroscopy based on **1a** (0.2 mmol); [b] isolated yield based on $[Ph_3P^+CF_2H\ Br^-]$; [c] isolated yield based on the Hantzsch ester.



Scheme 4 The proposed mechanism.

Conclusions

In summary, we developed an efficient radical-mediated hydrodifluoromethylation of alkenes using easily available phosphonium salt $[Ph_3P^+CF_2H]Br^-$ with the irradiation of 26 W household CFL under transition-metal-free conditions. This operationally simple reaction offers a convenient protocol for the installation of a C sp^3–CF_2H bond. With good functional group tolerance, this approach may find applications in the synthesis of biologically active HCF_2-containing molecules.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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