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Visible Light/Tertiary Amine Promoted Synergistic Hydroxydifluoroacetamidation of Unactivated Alkenes under Air

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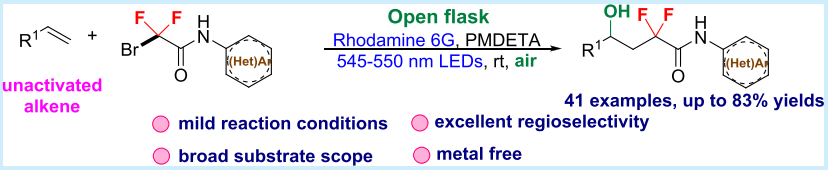
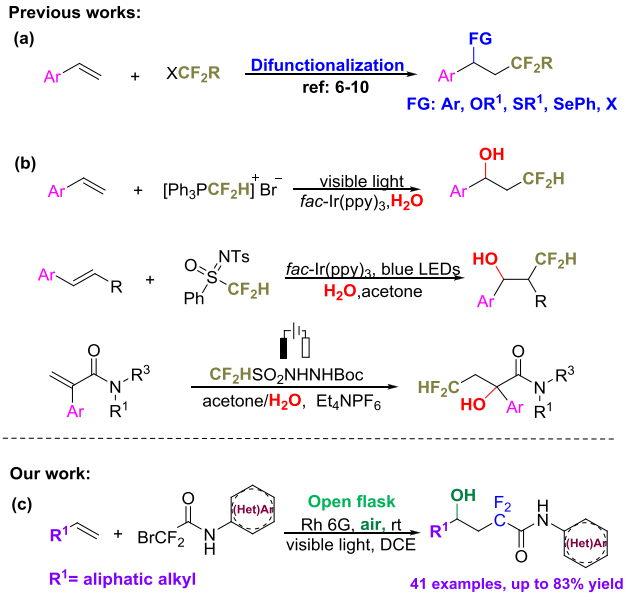


ABSTRACT: An efficient and novel method for regioselective hydroxydifluoroacetamidation of alkenes with bromodifluoroacetamides has been achieved via a tandem radical pathway mediated by photoredox catalysis under metal-free conditions. This transformation proceeded smoothly in the presence of Rhodamine 6G, affording a series of α,α-difluoro-γ-hydroxyacetamides in moderate to excellent yields. The significant advantages of this protocol are the low-cost photocatalyst, readily available starting materials, synthetic convenience, and wide functional group compatibility.

The difluoromethylene (CF_2) group is a privileged structural motif in pharmaceuticals,[1] pesticides,[2] and materials science[3] because it can dramatically affect the physical, chemical, and biological properties of organic molecule.[4] Over the past few years, the significance of difluoroalkyl compounds has inspired chemists to develop novel methods for the construction of C−CF_2 bonds.[5] Among these, difunctionalization of alkenes is regarded as one of the most powerful tools for the synthesis of difluoroalkylated compounds as it can realize the rapid synthesis of structurally diverse molecules. By employing this strategy, difluoroalkylation of alkenes has been well-established, accompanied by simultaneous γ-functionalization such as arylation,[6] oxylation,[7] thiolation,[8] benzeneselenolation,[9] and halogenation (Scheme 1, a).[10] According to the existing reports, synthesis of CF_2R-containing molecules via difunctionalization of styrene-type alkenes has been studied extensively, while it would be more interesting to achieve difluoroalkylation of unactivated alkenes, like aliphatic olefins.

Alcohol, which is considered as a reactive center for functional group interconversions, plays a vital role in organic synthesis,[11] and thus, preparation of alcohols from simple starting materials is one of the key transformations in organic reactions. In the past several years, a few strategies for selective hydroxydifluoroalkylation of styrene have been established for the synthesis of CF_2R-containing alcohols (Scheme 1, b).[12] For example, Qing[12a] and Akita[12b] respectively developed a convenient method for synthesis of CF_2H-containing alcohol via visible light induced hydroxydifluoromethylation of styrene by employing water as the nucleophile. Recently, Xu[12c] reported a mild method for preparation of α-hydroxy amides

Scheme 1. Introduction of the RCF_2 Group into Alkenes



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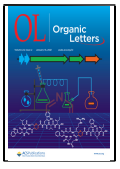

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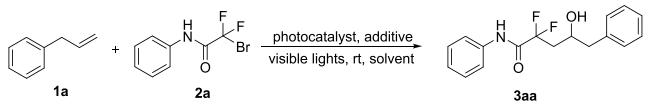
through hydroxydifluoromethylation of electron-deficient alkene (acrylamides) mediated by electrochemical catalysis. Although several successful strategies have been disclosed, the more difficult task of hydroxydifluoroalkylation of unactivated aliphatic alkene still remained elusive, which could be explained by the unfavored oxidation of the aliphatic carbon radical to the corresponding carbocation.

Our group has widely developed green and efficient methods for photoredox catalyzed C−H functionalization in the past several years.[13] As our pioneering works for difluoroalkylation, $BrCF_2R$-type derivatives were demonstrated to be easily activated under photocatalytic conditions to generate the difluoroalkyl radical while eliminating a bromide anion. Meanwhile, dioxygen, which is known as an ideal cheap and environmentally friendly oxidant, could act as a potential hydroxy source because it is capable of interacting with a carbon-centered radical.[14] We speculated that the carbon radical generated through radical addition between $\cdot CF_2R$ and aliphatic alkene would be initially trapped by O_2 rather than being oxidized to the carbocation, which is crucial for achieving the hydroxydifluoroalkylation of unactivated alkene. Herein, we describe the first example of an aerobic hydroxydifluoroacetamidation of aliphatic alkenes with bromodifluoroacetamides mediated by photoredox catalysis via employing inexpensive Rhodamine 6G as a photocatalyst.

Initially, we employed allylbenzene (**1a**) and the easily prepared 2-bromo-2,2-difluoro-*N*-phenylacetamide (**2a**) as model substrates to evaluate the reaction parameters such as the photocatalyst, solvent, and additive. Satisfactorily, the desired product **3aa** was obtained in 31% yield when the reaction was carried out in the presence of Na_2-Eosin Y and PMDETA in DCE with irradiation of a 10 W 545−550 nm LED for 12 h (Table 1, entry 1). Subsequently, various photocatalysts, including Eosin B, Eosin Y, Rose Bengal, *fac*-$Ir(ppy)_3$, Acr^+-$MesClO_4^-$, Rhodamine 6G, $Ru(bpy)_3Cl_2$, and methylene blue were also studied (Table 1, entries 2−9). Among them, the Rhodamine 6G exhibited a better catalytic efficiency, and the yield of **3aa** could be dramatically increased to 56% (Table 1, entry 7). A series of commonly available solvents such as DCM, CH_3CN, DMSO, and DMF was then tested for this reaction, but none of them could give a better result compared with DCE (Table 1, entries 10−13). To our delight, the isolated yield of **3aa** was increased to 76% when the allylbenzene was employed as solvent (Table 1, entry 14). The effects of other additives were then examined, and the results showed that DIPEA only could give a much lower yield, while DMAP, DBU, and DABCO were not effective at all (Table 1, entries 15−18). The further optimization for the yield of product based on alkene was also studied, and the result revealed that the product could be obtained only in a yield of 25% when the ratio of **1a** and **2a** was adjusted to 1:2 (Table 1, entry 19). Control experiments indicated that photocatalyst, visible light, and organoamine were all indispensable for this transformation (Table 1, entries 20−22).

With the optimized conditions in hand, the substrate scope of this visible-light-induced aerobic hydroxydifluoroacetamidation of alkenes was investigated, and this method exhibited good substrate compatibility and remarkable selectivity. As shown in Scheme 2, the allylbenzene with electron-donating (methyl or methoxy) or electron-withdrawing (fluoro) groups on the benzene ring were all suitable for this reaction, giving the α,α-difluoro-γ-hydroxy-acetamides (**3ba**−**3da**) in moderate to good yields. In addition, the effect of carbon chain length on

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	photocatalyst	additive	solvent	yields[b] (%)
1	Na_2-Eosin Y	PMDETA	DCE	31
2	Eosin B	PMDETA	DCE	27
3	Eosin Y	PMDETA	DCE	36
4	Rose Bengal	PMDETA	DCE	34
5	*fac*-$Ir(ppy)_3$	PMDETA	DCE	50
6	Acr^+-$MesClO_4^-$	PMDETA	DCE	48
7	Rhodamine 6G	PMDETA	DCE	56
8	$Ru(bpy)_3Cl_2$	PMDETA	DCE	N.D.
9	methylene blue	PMDETA	DCE	trace
10	Rhodamine 6G	PMDETA	DCM	52
11	Rhodamine 6G	PMDETA	CH_3CN	36
12	Rhodamine 6G	PMDETA	DMSO	24
13	Rhodamine 6G	PMDETA	DMF	15
14[c]	Rhodamine 6G	PMDETA		76
15[c]	Rhodamine 6G	DIPEA		22
16[c]	Rhodamine 6G	DMAP		N.D.
17[c]	Rhodamine 6G	DBU		N.D.
18[c]	Rhodamine 6G	DABCO		N.D.
19[d]	Rhodamine 6G	PMDETA	DCE	25
20[c,e]		PMDETA		N.D.
21[c,f]	Rhodamine 6G			N.D.
22[c,g]	Rhodamine 6G			N.D.

[a](1) Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.6 mmol), **2a** (0.2 mmol), additive (0.4 mmol), and photocatalyst (1 mol %) in solvent (2 mL) under air atmosphere, irradiated by a 10 W LED for 12 h; (2) 545−550 nm for Na_2-Eosin Y, Eosin B, Eosin Y, Rose Bengal, Rhodamine 6G; 400−405 nm for Acr^+-$MesClO_4^-$, *fac*-$Ir(ppy)_3$; 455−460 nm for $Ru(bpy)_3Cl_2$. [b]Isolated yield based on **2a**. [c]**1a** (2 mL). [d]**1a** (0.2 mmol), **2a** (0.4 mmol). [e]Without photocatalyst. [f]Without organoamine. [g]Without light.

this reaction was also studied. The results showed that the examined olefins, including but-3-en-1-ylbenzene, pent-4-en-1-ylbenzene, and hex-5-en-1-ylbenzene, all exhibited moderate reactivity in this transformation (**3ea**−**3ga**), affording the corresponding products in 52 to 59% yields. The naphthalene substituted alkene **1h** also worked well, delivering the desired product **3ha** in 71% yield. It was noteworthy that the normal aliphatic olefin without a benzene ring, such as pent-1-ene, hex-1-ene, and oct-1-ene, still led to the desired product in moderate yields (**3ia**−**3ka**). Apart from the chain alkene, cyclic alkene (cyclohexene) was also viable for this protocol, giving the product **3la** in a yield of 48%. Furthermore, functionalized aliphatic alkenes containing a hydroxy or bromo group were then employed for this transformation. Screening revealed that free hydroxyl group was compatible with the reaction conditions, and the corresponding product **3ma** was obtained in a yield of 54%. Accidentally, alkenes with the easy leaving group, such as 5-bromopent-1-ene, gave the five-membered cyclic ether **3na** in 57% yield via the elimination of hydrogen bromide caused by intramolecular substitution, and the anticipated hydroxydifluoroacetamidation product was not observed. A range of styrenes bearing either an electron-donating (methoxy) or electron-withdrawing (chloro) group on the aryl ring also could be transformed into the corresponding hydroxydifluoroacetamidation products **3oa**,

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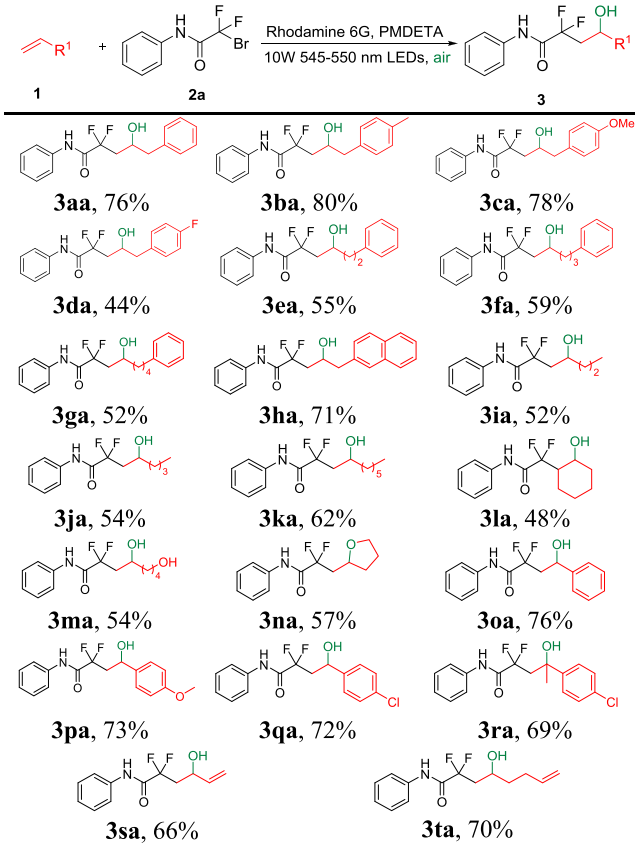
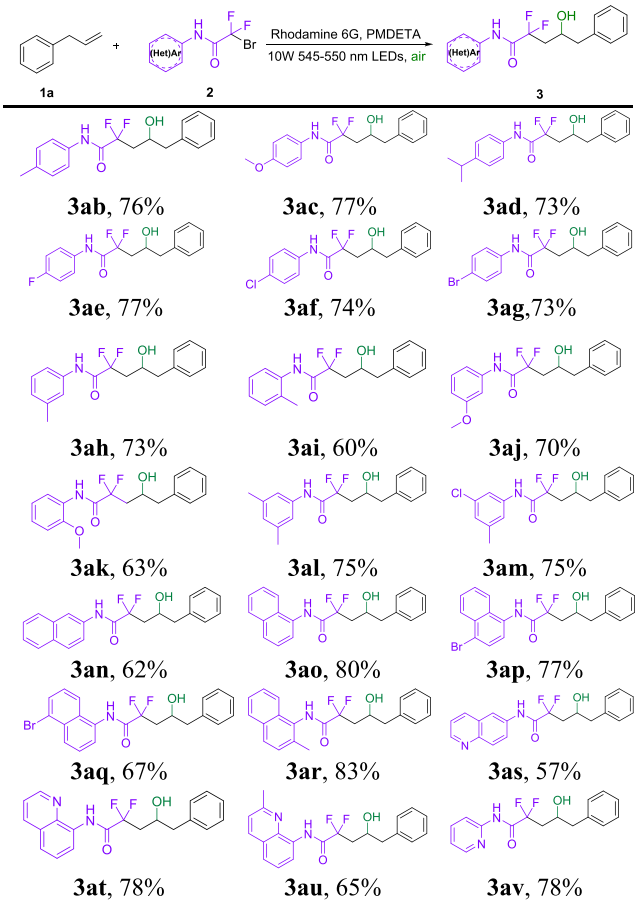
Scheme 2. Substrate Scope of Alkenes[a]



[a]Reaction conditions: **1** (2 mL), **2a** (0.2 mmol), Rhodamine 6G (1 mol %, 0.002 mmol), and PMDETA (0.4 mmol) was irradiated with an LED (545−550 nm) in air atmosphere at room temperature for 12 h. Isolated yields.

Scheme 3. Substrate Scope of Bromodifluoroacetamides[a]



[a]Reaction Conditions: **1a** (2 mL), **2** (0.2 mmol), Rhodamine 6G (1 mol %, 0.002 mmol) and PMDETA (0.4 mmol) was irradiated with a LED (545−550 nm) in air atmosphere at room temperature for 12 h. Isolated yields.

3pa, and **3qa** in 76, 73, and 72% yields, respectively. The α-substituted alkene α-methylstyrene reacted smoothly, affording the desired product **3ra** in a yield of 69%. Conjugated diene **1s** was readily converted to the desired α,α-difluoro-γ-hydroxyacetamides product **3sa** in moderate yield. Additionally, the photocatalytic protocol presented herein was also easily extended to nonconjugated diene **1t**, which demonstrated its wide substrate tolerance.

After the scope of alkenes was examined, a variety of N-aryl bromodifluoroacetamides was then investigated via the hydroxydifluoroacetamidation with allylbenzene **1a** under the standard conditions, and the results are summarized in Scheme 3. It was found that the substrates bearing either electron-donating (methyl, methoxy, isopropyl) or electron-withdrawing (fluoro, chloro, bromo) groups on the para-position of the benzene ring all could produce the corresponding products in moderate to good yields (**3ab**−**3ag**). The effect on the position of substituents on the phenyl was then studied, and the results showed that either *meta*-substituted or *ortho*-substituted derivatives all exhibited good tolerance for this reaction, providing the products **3ah**−**3ak** in 60−73% yields. The bromodifluoroacetamides with multisubstituents on the phenyl ring also worked well to give the corresponding products **3al** and **3am** in satisfied yields. Subsequently, several other aryl groups were demonstrated to be tolerated well for this transformation. For example, compounds **2n**−**2r** bearing a naphthalene group afforded the difunctionalization products (**3an**−**3ar**) in moderate to good yields. In addition, we found that substrates **2s**−**2u** with quinoline moieties also could work satisfactorily, affording the products **3as**−**3au** in 57−78% yields. Finally, the pyridinyl-containing compound **2v** was tested for this reaction, and the desired product **3av** was obtained in a satisfactory yield.

To gain insights into the mechanism of this reaction, some control experiments were performed (Scheme 4). A radical scavenger, 2,6-*di*-*tert*-butyl-4-methyphenol (BHT), was first applied to the standard reaction system, and the transformation was totally inhibited (Scheme 4, a). Subsequently, a similar result was obtained when another radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was employed in same reaction system, and to our delight, the adduct between TEMPO and RCF_2 radical was successfully detected by ESI- MS (Scheme 4, b). These results suggested that the reaction might proceed via a radical mechanism. In addition, this transformation could not proceed well when it was conducted under N_2 atmosphere, indicating that oxygen was crucial for this reaction (Scheme 4, c, d). The Stern−Volmer fluorescence quenching experiments revealed that the excited Rhodamine 6G was quenched by PMDETA, while 2-bromo-2,2-difluoro-*N*-phenylacetamide **2a** exhibited much less of an effect (Figure S4−S5, see Supporting Information).

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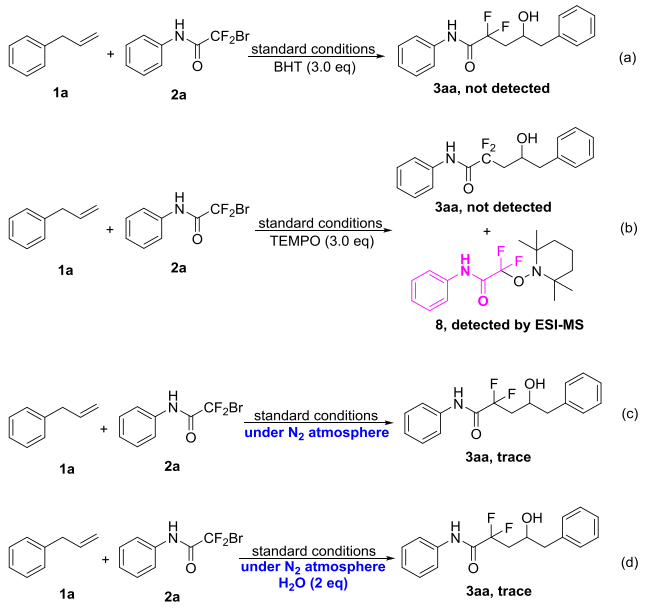
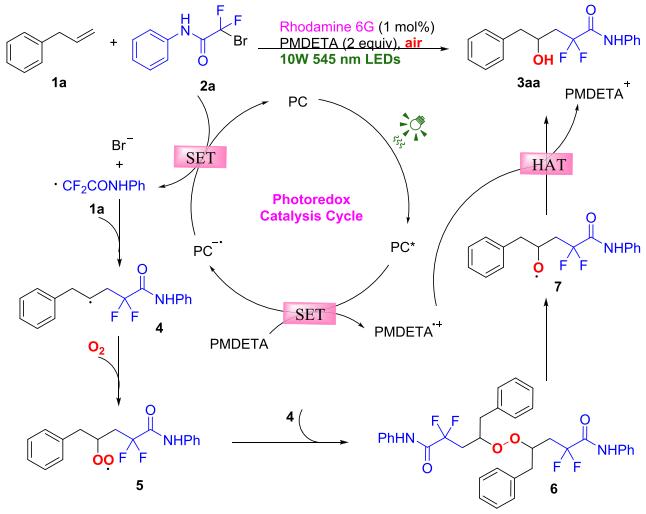
Scheme 4. Radical Inhibitor Experiment



According to the above-mentioned observations and previous literature reports,[15] we could speculate a plausible mechanism for this reaction as follows (Scheme 5). Irradiation

Scheme 5. Proposed Mechanism



of a photocatalyst (PC) with visible light generated the excited catalyst PC*, which was reductively quenched by the sacrificial electron donor PMDETA to give $PMDETA^{\cdot+}$, accompanied by the reduction of PC* to $PC^{\cdot-}$. **2a** could abstract an electron from the reduced Rhodamine 6G to form a difluoroacetamide radical and a bromide anion, accompanied by reoxidation of $PC^{\cdot-}$ to its ground state. The difluoroacetamide radical subsequently performed addition to allylbenzene **1a** to afford the carbon-centered radical **4**, which could be further trapped by the oxygen molecule and transformed into peroxyl radical **5**. The following radical coupling between **5** and **4** furnished the peroxide species **6**, which immediately underwent the homolysis of the O−O bond to provide the oxygen-centered radical **7**. It is assumed that the radical **7** could be finally converted into the desired product **3aa** after abstracting a hydrogen atom from $PMDETA^{\cdot+}$.

In summary, we succeeded in developing a synthetically valuable method for the hydroxydifluoroacetamidation of unactivated alkenes by employing a photocatalytic system under metal-free conditions, affording novel access to α,α-difluoro-γ-hydroxyacetamides. This transformation proved to be compatible with a wide range of aliphatic alkenes, and bromodifluoroacetamides bearing various functional groups also exhibited good tolerance. Furthermore, this protocol featured mild conditions, low cost, excellent regioselectivity, and simple operation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04216.

Experimental details and spectroscopic data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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