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Visible light promoted fluoroalkylation of alkenes and alkynes using 2-bromophenol as a catalyst†

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We report a new protocol for the fluoroalkylation of alkenes and alkynes by using 2-bromophenol as a catalyst. This reaction can be tailored for different reaction modes by altering the base and solvent, which feature a wide substrate scope and excellent functional group tolerance with high chemo- and regioselectivities. We further propose a mechanism involving an electron donor–acceptor (EDA) complex.

Fluorinated organic compounds can alter metabolic stability, lipophilicity, and electronic properties. Thus, they play privileged roles in pharmaceuticals, agrochemicals, and functional materials,[1] and the development of simple methods enabling the efficient construction of fluorine-containing molecules is an important topic of continuous scientific endeavor.[2]

Alkenes and alkynes are ubiquitous feedstock materials, and thus fluoroalkylation of unsaturated C–C bonds is an attractive method for accessing fluorine containing compounds. Traditionally, this methodology was achieved *via* radical initiators such as peroxide,[3] $Na_2S_2O_4$,[4] Et_3B,[5] and UV light.[6] However, these reactions have a limited substrate scope. In the past 10 years, many powerful strategies have been developed to realize such transformations with high yields and broad substrate scopes.[7,8] Among them, fluoroalkylation involving visible light promoted reactions serve as an ideal strategy. In these protocols, reactions are usually performed *via* photo-excited catalysts such as Ru/Ir metal complexes and organic dyes.[8,9] More recently, noncovalent interaction initiated radical fluoroalkylation driven by electron donor–acceptor (EDA) complexes[10,11] has attracted our great attention and prompted us to discover new catalytic systems.

Phenols are commercially available raw materials that have a lone pair of electrons in the hydroxyl group; therefore, they can combine with fluoroalkyl iodides to form donor–acceptor complexes.[11a] Thus, we reason that phenols can serve as promising catalysts for the discovery of unprecedented transformations. Here, we demonstrate a 2-bromophenol catalyzed fluoroalkylation of alkenes and alkynes. The advantages of this method are high efficiency, excellent functional group tolerance and synthetic simplicity.

According to our hypothesis, allylbenzene **1a** and ethyl iododifluoroacetate **2a** were initially chosen as model substrates for atom transfer radical addition (ATRA) difluoroalkylation. No desired product was observed when the reaction was performed with **1a** (1.0 equiv.), **2a** (2.0 equiv.) and K_2CO_3 (2.0 equiv.) in 1,4-dioxane at room temperature under blue LED irradiation for 16 hours (Table 1, entry 1). To our delight, the expected photochemical transformation could be realized smoothly when a catalytic amount of phenol (0.1 equiv.) was added and afforded the desired ATRA product **3a** in 68% yield (Table 1, entry 2). An evaluation of different alkali metal bases revealed that KOAc was the optimal choice and the yield of **3a** could be improved to 73% (Table 1, entry 5). With this preliminary result in hand, the improvement in the reaction efficiency was investigated by screening phenols as catalysts (Table 1, entries 7–9; for details, see the ESI†). The yield of **3a** was improved to 85% in the presence of 2-bromophenol (Table 1, entry 7). This provided a significantly higher yield than the other analogous phenols examined. The reaction medium was proved to be the crucial factor for an efficient system; when the reaction was conducted in 1,2-dichloroethane, yields up to 92% can be obtained (Table 1, entry 12). The yield of **3a** decreased slightly when the loading of 2-bromophenol was reduced to 0.05 equiv. (Table 1, entry 13). A control experiment was carried out by performing the reaction in the dark; no reaction occurred, demonstrating the photochemical nature of this transformation (Table 1, entry 14). An additional study was conducted in the absence of base; only 7% yield was achieved (Table 1, entry 15). 44% yield was obtained without any catalyst (Table 1, entry 16). A comparable yield was

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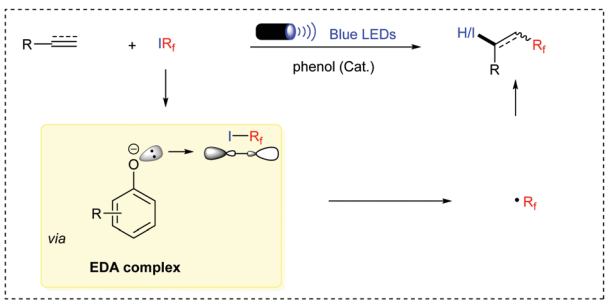
Table 1 Representative results for the optimization of the visible-light promoted difluoroalkylation of allylbenzene (**1a**)[a]

Entry	Catalyst (x mol%)	Base	Solvent	Yield[b] (%), **3a**
1	—	K_2CO_3	Dioxane	—
2	PhOH (10)	K_2CO_3	Dioxane	68
3	PhOH (10)	Cs_2CO_3	Dioxane	64
4	PhOH (10)	Na_2CO_3	Dioxane	31
5	PhOH (10)	KOAc	Dioxane	73
6	PhOH (10)	NaOAc	Dioxane	60
7	2-Br-C_6H_4OH (10)	KOAc	Dioxane	85
8	4-Br-C_6H_4OH (10)	KOAc	Dioxane	74
9	2-Me-C_6H_4OH (10)	KOAc	Dioxane	63
10	2-Br-C_6H_4OH (10)	KOAc	MeCN	65
11	2-Br-C_6H_4OH (10)	KOAc	Toluene	12
12	2-Br-C_6H_4OH (10)	KOAc	DCE	92 (88)
13	2-Br-C_6H_4OH (5)	KOAc	DCE	79
14[c]	2-Br-C_6H_4OH (10)	KOAc	DCE	—
15	2-Br-C_6H_4OH (10)	—	DCE	7
16	—	KOAc	DCE	44
17[d]	2-Br-C_6H_4OH (10)	KOAc	DCE	87

[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv.), **2a** (0.6 mmol, 2.0 equiv.), catalyst (0.03 mmol, 0.1 equiv.), solvent (2.0 mL), 12 W blue LEDs (430–490 nm), room temperature, 16 h. [b] The NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard and the number in parentheses is an isolated product yield. [c] The reaction was performed without light. [d] A 450–455 nm blue LED was used.

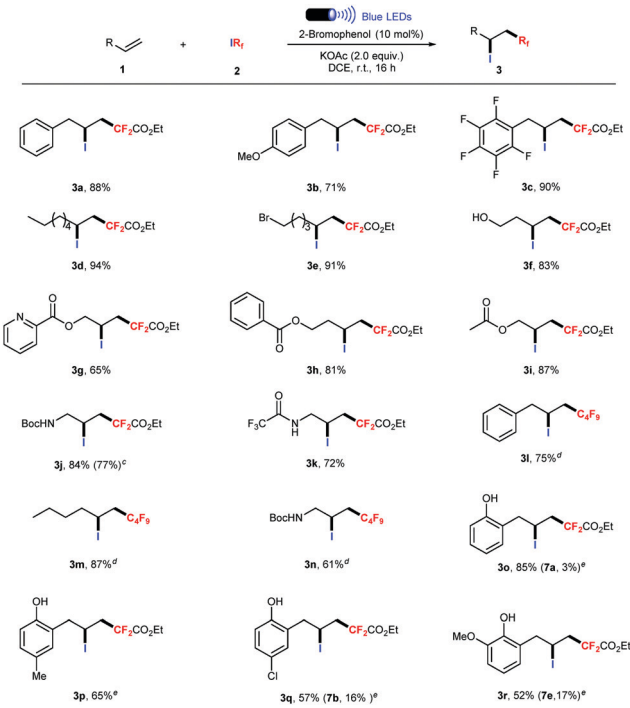
still obtained when short-wavelength LEDs were used as light sources (for details, see the ESI†). These results suggest that acetate anions ($^-$OAc) might also act as an electron donor group (Scheme 1).

With the optimized reaction conditions in hand, the scope of this photochemical atom transfer radical addition was next evaluated using abundant and structurally diverse terminal alkenes. The reaction exhibited excellent functional group tolerance. Terminal alkenes containing methoxyl, fluoride, hydroxyl, ester, and even bromo substituents were generally compatible with the reaction and provided difluoroalkylated ATRA products in good to excellent yields (Table 2, **3b–i**). A major benefit of this mild, convenient visible-light-mediated ATRA procedure is the synthesis of analogues of biologically important fluorinated amino acids in good yields (Table 2, **3j** and **k**). These results demonstrate the synthetic utility of this protocol. This reaction system is also amenable to the use of other commercial perfluoroalkyl iodides



Scheme 1 New protocol designed for the fluoroalkylation of alkenes and alkynes.

Table 2 Scope of the 1,2-addition reaction of fluoroalkyl iodides to alkenes[a,b]



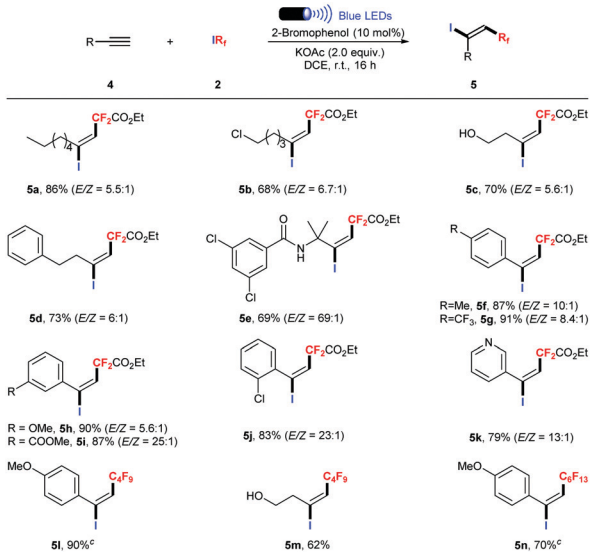
[a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.6 mmol, 2.0 equiv.), 2-bromophenol (0.03 mmol, 0.1 equiv.), KOAc (0.6 mmol, 2.0 equiv.), DCE (2.0 mL), 12 W blue LEDs (430–490 nm), 16 h. [b] Yields of the isolated products. [c] K_2CO_3 was used as a base and the reaction was performed on a 10 mmol scale in 40 mL DCE, 40 h. [d] Cs_2CO_3 (0.6 mmol, 2.0 equiv.) as a base. [e] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2a** (0.6 mmol, 2.0 equiv.), KOAc (0.6 mmol, 2.0 equiv.), dioxane (2.0 mL), and 12 W blue LEDs (430–490 nm), 16 h.

such as C_4F_9I, and the corresponding products can be obtained in moderate to good yields when the base is changed to Cs_2CO_3 (Table 2, **3l–n**). Importantly, the reliability and scalability of this protocol can also be demonstrated by gram-scale synthesis of **3j** (77%, 3.17 g). Based on the results above, we reason that allylphenol could be fluoroalkylated smoothly without adding any other phenols as catalysts. Therefore, the direct fluoroalkylation of allylphenols was then investigated (Table 2, **3o–r**), and moderate to good yields can still be obtained.

The substrate scope can also be extended to a variety of terminal alkynes with good functional group tolerance. Many important functional groups, such as halides, hydroxyls, amides, aldehydes, esters and pyridyls, underwent the current process smoothly (Table 3, **5a–k**). Moreover, we found that the transformation presented good stereoselectivity when C_4F_9I and $C_6F_{13}I$ were employed, to provide the desired products in good yields.

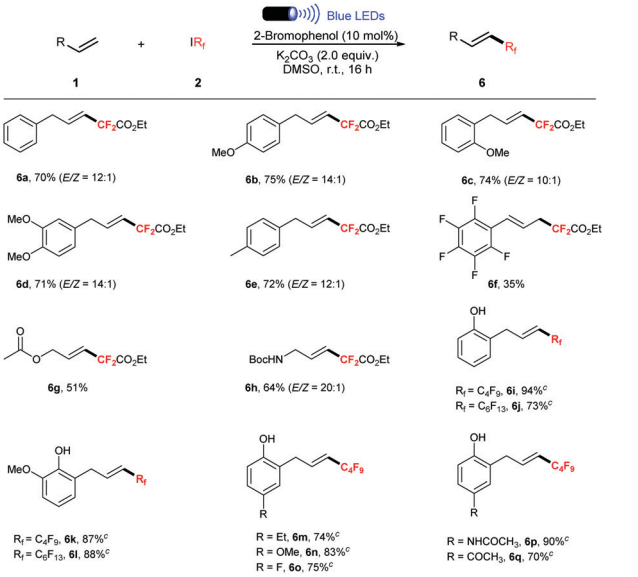
To our delight, a Heck-type reaction occurred when allylbenzene was treated with ethyl iododifluoroacetate **2a** with DMSO solvent.[8d] Good yields can be obtained when electron-rich allylbenzenes were treated (Table 4, **6a–e**). The yield diminished and only a double-bond shifted product was observed when electron-deficient allylpentafluorobenzene was used as the substrate (Table 4, **6f**). Aliphatic olefins were also suitable substrates, and

Table 3 Scope of the 1,2-addition reaction of fluoroalkyl iodides to alkynes[a,b]



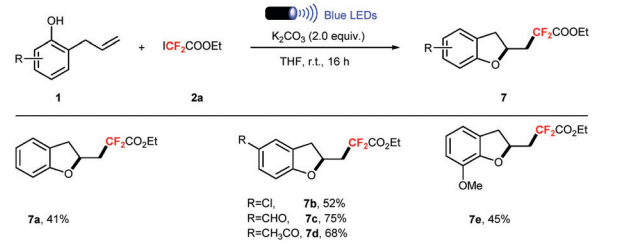
[a] Reaction conditions: **4** (0.3 mmol, 1.0 equiv.), **2** (0.6 mmol, 2.0 equiv.), 2-bromophenol (0.03 mmol, 0.1 equiv.), KOAc (0.6 mmol, 2.0 equiv.), DCE (2.0 mL), 12 W blue LEDs (430–490 nm), 16 h. [b] Yields of the isolated products. [c] K_2CO_3 was used as a base.

Table 4 Scope of the Heck-type reaction of fluoroalkyl iodides with alkenes[a,b]



[a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.6 mmol, 2.0 equiv.), 2-bromophenol (0.03 mmol, 0.1 equiv.), K_2CO_3 (0.6 mmol, 2.0 equiv.), DMSO (2.0 mL), 12 W blue LEDs (430–490 nm), 16 h. [b] Yields of the isolated products. [c] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.6 mmol, 2.0 equiv.), KOAc (0.9 mmol, 3.0 equiv.), DCM/DMSO (v/v = 3 : 1), 12 W blue LEDs (430–490 nm), 14 h.

Table 5 Direct cross-coupling of 2-allylphenol with ethyl iododifluoroacetate[a,b]



[a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2a** (0.6 mmol, 2.0 equiv.), K_2CO_3 (0.6 mmol, 2.0 equiv.), THF (2.0 mL), 12 W blue LEDs (430–490 nm), 16 h. [b] Yields of the isolated products.

fluorinated amino acids (**6h**) can be easily synthesized *via* this strategy in moderate yield. Interestingly, the reaction can also proceed smoothly without addition of any other phenols as catalysts when using allylphenols as substrates, perfluoroalkyl iodides as fluoroalkyl sources and DCM/DMSO (3 : 1) as solvent, which exhibited excellent functional group tolerance and high chemo- and stereo-selectivities (Table 4, **6i–q**). No reaction occurred when the phenolic hydroxyl group was protected or in the absence of hydroxyls. These results further demonstrate the important role of the phenolic hydroxyl group in such transformations (for details, see the ESI†). Finally, cyclization products could be selectively obtained in moderate to good yields in the presence of K_2CO_3 and THF when **2a** was treated with 2-allylphenol (Table 5).[12]

To better understand the mechanism of this transformation, a series of additional experiments were conducted (for details, see the ESI†). Radical inhibition experiments were performed first. No desired product was observed when the radical scavenger TEMPO (100 mol%) was added under the standard reaction conditions, suggesting that a radical pathway might be involved in this transformation. Radical clock experiments were then performed, and the ring opening compound was formed with or without **1a**. Optical absorption spectra of the reactants found that the absorption was obviously strengthened when **2a**, KOAc and 2-bromophenol were mixed, indicating that non-covalent interactions occurred between phenols and **2a**. Moreover, almost no visible light absorption was observed when 2-bromophenol was tested; therefore, radicals generated from the excited phenol can be preliminarily excluded.[13] Finally, HPLC experiments indicated that the concentration of 2-bromophenol remained nearly constant in the reaction process (for details, see the ESI†).

Based on these preliminary results and previous reports,[8,14] a plausible mechanism is proposed in Fig. 1 for this transformation. Initially, the EDA complex was generated between phenol and fluoroalkyl iodides in the presence of a base. The fluoroalkyl radical was then generated under irradiation of blue LEDs. The subsequent regioselective addition of $^{\bullet}$Rf to alkenes (**1**) led to the carbon-radical intermediate **A**. The newly formed radical then abstracted an iodine atom from R_fI to afford the desired product **3** and regenerated the Rf radical. Alternatively, cation species **B** was generated *via* a SET process from intermediate **A**, and the fluoroalkylated product **6** was obtained by further deprotonation. This pathway was further confirmed *via* treatment of the preformed **3a** with K_2CO_3 (2.0 equiv.) in DMSO (2 mL), and product **6a** was formed in 48% yield with low

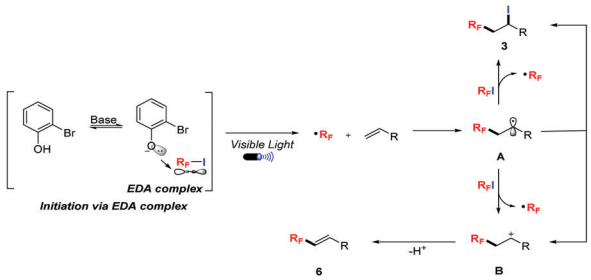


Fig. 1 Proposed reaction mechanism.

chemoselectivity after 16 h at room temperature (for details, see the ESI†). These values are much different from the results shown in Table 4.

In conclusion, the first example of visible light promoted intermolecular fluoroalkylation of alkenes and alkynes using 2-bromophenol as a catalyst has been developed. The notable features of this reaction include mild reaction conditions, synthetic simplicity, and excellent functional group compatibility, therefore providing an efficient methodology for the preparation of diversified fluorinated compounds that have important applications in life sciences and functional materials.

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Conflicts of interest

There are no conflicts to declare.

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