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A General and Green Fluoroalkylation Reaction Promoted *via* Noncovalent Interactions between Acetone and Fluoroalkyl Iodides

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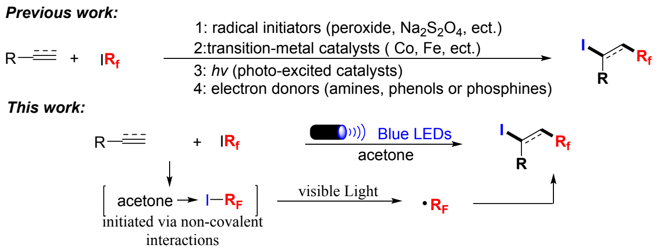
Abstract: The first example of visible light promoted fluoroalkylation reactions initiated via noncovalent interactions between acetone and fluoroalkyl iodides is presented. The reaction system features synthetic simplicity, mild reaction conditions without any photoredox catalyst, and high functional group tolerance. A wide range of substrate scopes such as alkenes, alkynes and (hetero)arenes were all compatible with the reaction system.

Fluorinated compounds have attracted much attention as candidates for pharmaceuticals and functional materials because of their superior lipophilicity, binding selectivity, bioavailability, and metabolic stability compared to their nonfluoroalkylated analogs.[1] Consequently, to meet the increasing demand for these materials in the life sciences and materials science, the development of more practical, economical and environmentally friendly methods enabling the efficient construction of the fluorine-containing organic compounds has been one of the most important research topics in organofluorine chemistry.

In the past ten years, numerous methods have been developed to synthesize fluoroalkylated compounds with high efficiency, and major improvements were made via transition-metal catalysts or photo-excited catalysts.[2] Very recently, noncovalent interactions (EDA complexes or halogen bond) initiated radical fluoroalkylations have emerged as an attractive and useful strategy to directly introduce fluorinated groups into organic molecules.[3] In such transformations, the noncovalent interaction usually occurred between excess amounts of amines or substrates and R_FI. We envision that the noncovalent interaction might also occur between the solvent and R_FI, and a radical intermediate could be generated under the irradiation of visible light If the driven force is strong enough, thus leading to the discovery of unprecedented transformations.

Acetone is one of the most common solvents. We assumed that a noncovalent interaction between the carbonyl group and C-I bond might occur, which could induce radical intermediates under the irradiation of visible light. To test the hypothesis above, we began our investigations by treating alkenes with R_FI in acetone to study the atom transfer radical addition (ATRA) reaction. Usually, this protocol was realized by using radical initiators, such as peroxide,[4] $Na_2S_2O_4$,[5] Et_3B,[6] or UV light[7]. Recently, transition-metal[8] and photoredox catalysis[9] have emerged as more effective alternatives, and the utilization of amines,[10] phenols[11] or phosphines[12] as catalysts has also been developed in the past several months (Scheme 1). Herein, we report the first example of visible light promoted fluoroalkylation reactions via noncovalent interactions between solvent and R_FI. A variety of substrate scopes such as alkenes, alkynes and (hetero)arenes were all compatible with the reaction system.



Scheme 1 Methods for 1,2-Addition of Fluoroalkyl Iodides to Alkenes and Alkynes.

Accordingly, we conducted this reaction by treating tert-butyl allylcarbamate **1a** and ethyl iododifluoroacetate **2a** (1.5 equiv) as model substrates. To our delight, 74% yield of the desired product **3a** was obtained when the reaction was performed

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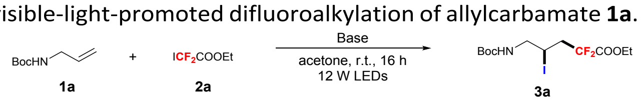
with K_2CO_3 (1.0 equiv.) in acetone and irradiated by blue LEDs for 16 hours. Further optimization of the inorganic bases demonstrated that other bases were less effective, and the desired product **3a** was isolated in 93% yield when 2.0 equiv. of K_2CO_3 was used (Table 1, entries 1-4). No desired product was observed when control experiments were carried out in the dark, confirming the photochemical nature of the transformation (Table 1, entry 5). To our surprise, the product **3a** at 49% yield was still obtained without bases (Table 1, entry 6). Finally, various short-wavelength LEDs were used as light sources to examine the influence of optical wavelength on the reaction, comparable yields were still obtained when LEDs with wavelengths between 425-475 nm were used, and the yields decreased with longer wavelengths (Table 1, entries 7-11). For other ketones, 82% yield was still obtained when 3-pentanone was used, and no reaction was observed using ketones with larger substituents (Table 1, entries 12-14). Those results indicate that the interactions between the solvent and fluoroalkyl iodides were decreased with the increase of the steric hindrance. Other solvents were also examined (Table 1, entries 15-18), no reaction occurred when the reaction performed in dioxane or toluene, and 68% yield was obtained when MeCN used as the solvent. The major products come from atom transfer radical addition-elimination (ATRE) reaction when conducted in DMA or DMSO. We reason noncovalent interactions also occurred between those solvent and R_FI (Table 1, entries 17-18, for details, see ESI).

Table 1. Representative results for the optimization of the visible-light-promoted difluoroalkylation of allylcarbamate **1a**. [a]



Entry	LEDs (nm)	Solvent	Base (equiv.)	Yield % [b]
1	Blue (430-490)	acetone	K_2CO_3 (1)	74
2	Blue (430-490)	acetone	KOAc (1)	64
3	Blue (430-490)	acetone	K_2CO_3 (2)	99 (93)
4	Blue (430-490)	acetone	Na_2CO_3 (2)	81
5	-----	acetone	K_2CO_3 (2)	0
6	Blue (430-490)	acetone	-----	49
7	Blue (450-455)	acetone	K_2CO_3 (2)	93
8	Blue (470-475)	acetone	K_2CO_3 (2)	91
9	Blue (490-495)	acetone	K_2CO_3 (2)	72
10	Green (510-515)	acetone	K_2CO_3 (2)	67
11	Green (545-550)	acetone	K_2CO_3 (2)	52
12	Blue (430-490)	S-1	K_2CO_3 (2)	82
13	Blue (430-490)	S-2	K_2CO_3 (2)	0
14	Blue (430-490)	S-3	K_2CO_3 (2)	0
15	Blue (430-490)	Dioxane	K_2CO_3 (2)	0
16	Blue (430-490)	MeCN	K_2CO_3 (2)	68
17	Blue (430-490)	DMA	K_2CO_3 (2)	26
18	Blue (430-490)	DMSO	K_2CO_3 (2)	5

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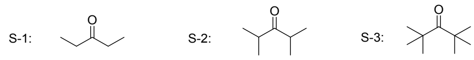
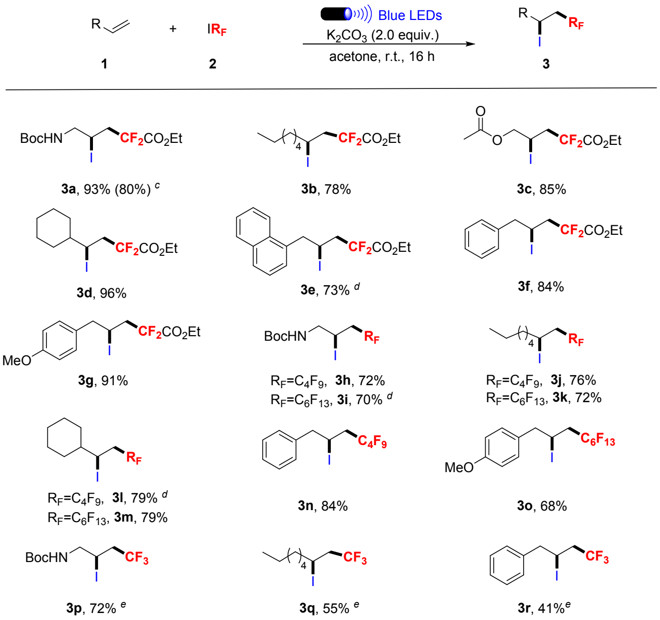


[a] Reaction conditions (unless otherwise specified): **1a** (0.3 mmol, 1.0 equiv.), **2a** (0.45 mmol, 1.5 equiv.), acetone (2.0 mL), room temperature, 16 h. [b] NMR yield determined by ^{19}F NMR using fluorobenzene as internal standard and number in parenthese is yield of isolated product.

With the optimized reaction conditions in hand, the scope of this photochemical atom transfer radical addition was evaluated using an abundant structurally diverse terminal alkenes.[10] As shown in Table 2, functional groups such as amine, esters naphthyl and methoxy were well-tolerated and provided difluoroalkylated ATRA products in good to excellent yields (Table 2, **3a-g**). This reaction system is also amenable to the use of other commercial perfluoroalkyl iodides, such as C_4F_9I and $C_6F_{13}I$, and the corresponding products were obtained in moderate to good yields (Table 2, **3h-o**). CF_3I was less reactive, moderate to good yields could be provided when 5.0 equiv. of CF_3I was used (Table 2, **3p-r**). Remarkably, when the reaction was performed on a gram scale (**3a**), an 80% yield was still obtained, demonstrating the synthetic utility of the protocol.

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** (0.45 mmol, 1.5 equiv.), K_2CO_3 (0.6 mmol, 2.0 equiv.) in acetone (2.0 mL), room temperature, 12 W blue LEDs (430-490 nm), 16 h. [b] Yield of isolated product. [c] **1a** (10 mmol, 1.0 equiv.), **2a** (15 mmol, 1.5 equiv.), K_2CO_3 (2.0 equiv.), acetone (40 mL), room temperature, 24 W Blue LED (430-490 nm), 48 h. [d] **2** (2.0 equiv.) was used. [e] CF_3I (5.0 equiv.) was used.

Then, we extended the substrate scope to a variety of terminal alkynes. Many important functional groups, such as halide, cyano, methoxy trifluoromethyl and even nitro

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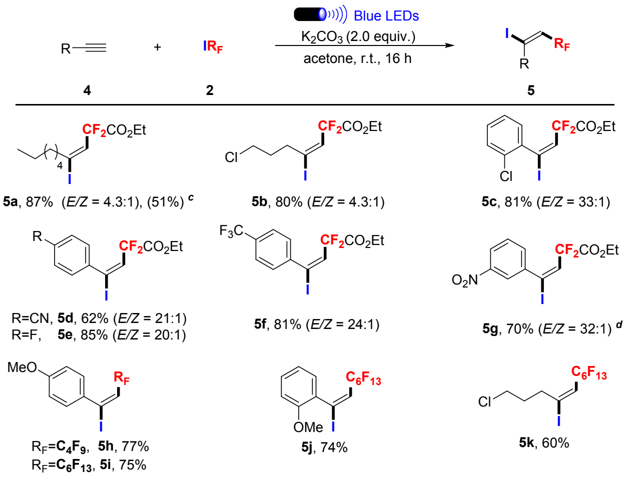
underwent the process smoothly (Table 3). For aliphatic alkynes, high yield with low stereoselectivity was provided (Table 3, **5a**-**b**). Phenylacetylenes were suitable substrates, and high stereoselectivity could be obtained (Table 3, **5c**-**g**). Moreover, we found that the transformation presented good reactivity when C_4F_9I and $C_6F_{13}I$ were employed, and provided the desired products in good yields (Table 3, **5h**-**k**).

Table 3. Scope of the 1,2-Addition Reaction of Fluoroalkyl Iodides to Alkynes. [a,b]

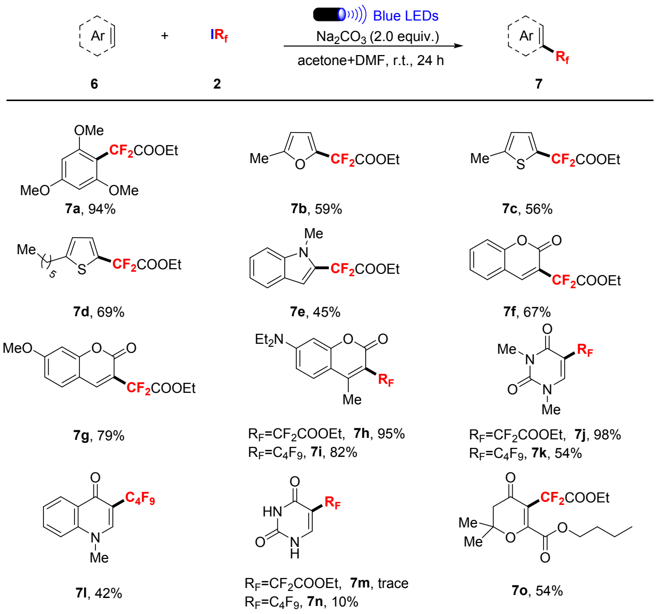


[a] Reaction conditions: **1** (0.3 mmol, 1.0 equiv.), **2** (0.45 mmol, 1.5 equiv.), K_2CO_3 (0.6 mmol, 2.0 equiv.) in acetone (2.0 mL), room temperature, 12 W blue LEDs (430-490 nm), 16 h. [b] Yield of isolated product. [c] Without K_2CO_3. [d] **2** (2.0 equiv.) was used.

Encouraged by the results of the 1,2-addition of R_FI to alkenes and alkynes, we proceeded to investigate direct fluoroalkylation of arenes.[13] Pleasingly, by using DMF as a co-solvent, a wide range of arenes and heteroarenes underwent the catalyst-free fluoroalkylation smoothly. 94% yield was obtained when 1,3,5-trimethoxybenzene was treated (Table 4, **7a**). Five membered heteroarenes such as furan, thiophene and pyrrole were relatively inert reaction partners, and only moderate yields were given (Table 4, **7b-e**). Coumarins and 1,3-dimethyluracil were also suitable substrates for this transformation, delivering the desired products in good to excellent yields (Table 4, **7f-h, 7j**). In addition, the C-H perfluoroalkylation of heteroarenes with C_4F_9I was also investigated, and moderate to good yields were still obtained (Table 4, **7i, 7k-l**). Unprotected uracil failed to give satisfactory results (Table 4, **7m-n**), which indicated the mechanism of this transformation is different from our previous report.[3f] Moreover, butopyronoxyl was also a suitable substrate, and 54% yield was obtained (Table 4, **7o**).

To gain insight into the mechanism of this transformation, a series of experiments were conducted. The reaction was suppressed by the addition of a radical scavenger TEMPO (100 mol%) and only 15% yield of **3a** was obtained, which suggests that the involvement of radical intermediates is likely during the reaction (for details, see ESI). A radical clock experiment employing alpha-cyclopropylstyrene **8** as a substrate produced the ring-opening product **9** in 82% yield (for details, see ESI). Optical absorption spectra of the reactants found that the absorption was clearly strengthened when **2a** and acetone were mixed, and those results indicate that non-covalent interactions occurred between acetone and **2a** (Figure 1, for details, see ESI). In addition, this conclusion was further confirmed by a Job's plot. Finally, the light-dark experiment was performed using alternative intervals of light and dark, and the formation of the product was both feasible during periods of irradiation and dark, which is suggestive of a radical chain process (for details, see ESI).

Table 4. Direct Fluoroalkylation of Arenes and Heterocycles. [a,b]



[a] Reaction conditions: **6** (0.3 mmol, 1.0 equiv.), **2** (0.9 mmol, 3.0 equiv.), Na_2CO_3 (0.6 mmol, 2.0 equiv.), acetone (1.0 mL) + DMF (1.0 mL), room temperature, 12 W blue LEDs (430-490 nm), 24 h. [b] Yield of isolated product.

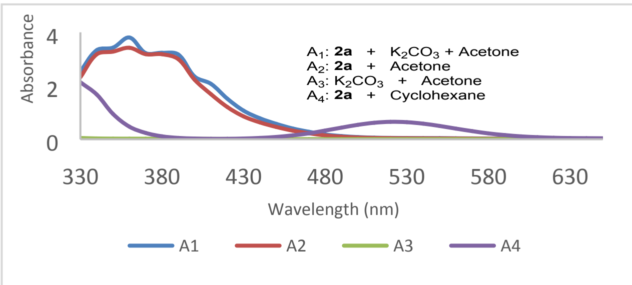
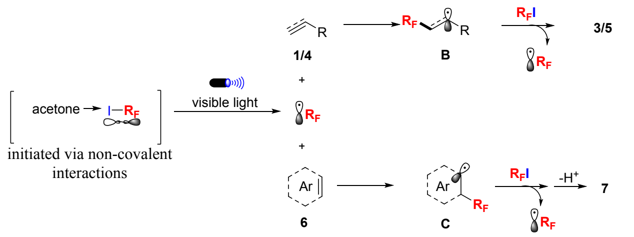


Figure 1 Optical absorption spectra studies.

Based on these preliminary results, a plausible mechanism for this transformation was proposed in Scheme 2. First, the EDA complex was generated between acetone and the fluoroalkyl iodides in the presence of base. Then, a fluoroalkyl radical was generated under the irradiation of blue LEDs. Subsequent regioselective addition of •R_F to alkenes or alkynes (**1** or **4**) lead to the carbon-radical intermediate (**B**), which abstracted an iodine atom from R_FI to afford the desired product **3** or **5** and regenerated the R_F radical. For arenes, cation species were generated via a SET process from an intermediate **C**, and the fluoroalkylated products (**7**) were obtained by further deprotonation.



Scheme 2 Proposed a Plausible Reaction Mechanism.

In summary, we have developed a simple, mild, and efficient protocol for photochemical fluoroalkylation reactions via noncovalent interactions between acetone and fluoroalkyl iodides. The significant advantages of this method are high atom economy, excellent functional group tolerance, and synthetic simplicity, thus providing a facile route for further application in pharmaceuticals and life sciences. Mechanistic studies indicate that the reaction was initiated via non-covalent interactions between acetone and carbon-iodine bonds.

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Conflicts of interest

There are no conflicts to declare.

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