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Photoinduced, copper-catalyzed three components cyanofluoroalkylation of alkenes with fluoroalkyl iodides as fluoroalkylation reagents[†]

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In the past few years, Ru and Ir catalyzed photoredox radical coupling reactions have been widely applied in organic synthesis. In contrast, the applications of Cu catalysts in photoredox organic transformations were limited. We here report the first example of photoinduced, Cu-catalyzed three component cyanofluoroalkylation of alkenes by directly using fluoroalkyl iodides as fluoroalkylation reagents.

The introduction of fluoroalkyl groups, such as trifluoromethyl (-CF₃) and perfluoroalkyl (R_f, (-C_nF_{2n+1}, $n \ge 2$)), into organic molecules always leads to drastic enhancement of their solubility, metabolic stability, and bioavailability.¹ In this context, the developments of efficient processes for the construction of C-CF3 and C-R_f bonds have been significant issues in organic synthesis. Atom transfer radical addition (ATRA) reactions provide efficient ways to construct two vicinal carbon-carbon or carbon-heteroatom bonds in a single step from easily available alkene substrates. Among them, three-component ATRA reactions represent the most atom- and step-economical methods for difunctionalization of alkenes, and have received much attention.²

The transition metal catalyzed^{3a,b} or photoinduced⁴ two component ATRA of fluoroalkyl iodides (CF₃I and R_fI) across alkyl substituted alkenes has been disclosed to generate new C-CF₃/C-R_f and C-I bonds in one step (Scheme 1). In view of synthetic efficiency, it is ideal to add -CF₃ (or -R_f) and a carbonbased functional group across alkenes in a single synthetic operation as a three component reaction. However, when fluoroalkyl iodides are used in the ATRA of alkenes, the fluoroalkyl radicals and I[•] are simultaneously formed by the homolytic cleavage of the CF₃-I or R_f-I bonds, which subsequently add to alkenes through radical propagation pathways. It is difficult to suppress the coupling of I[•]

(1) Two Components ATRA Type lodofluoroalkylation of Alkenes



(2) Our Work: Three Components ATRA Type Cyanofluoroalkylation of Alkenes

$$R \longrightarrow + \frac{I - CF_3}{or} + TMSCN \xrightarrow{hv (254 \text{ nm}), \text{ cat. Cu}}_{DIPEA, \text{ rt}} R \xrightarrow{CN}_{CF_3} (R_t)$$

 $\checkmark \text{ cheap and feedstock reagents used}$

 $\checkmark \text{ effective for both C-CF_3 and C-Rf bonds formation}$

 $\checkmark R = aryl, heteroaryl, and alkyl$

 $\checkmark Rf = C_4F_9, C_6F_{13}, C_8F_{17}, \text{ and } CF_2CO_2Et$

 $\checkmark \text{ general and mild}$

Scheme 1 ATRA type fluoroalkylation of alkenes.

with the alkyl radical intermediates and push the reactions into a three component ATRA fashion. So far, several examples of Pd or Cu catalyzed three component ATRA to alkynes by directly using fluoroalkyl iodides as fluoroalkyl radical precursors have been reported,^{3c-g} and reports on the three component ATRA of CF₃I or R_fI to structurally diversified alkenes are very few.⁵

To avoid the interference of Iº generated from fluoroalkyl iodides, an alternative strategy for introducing a fluorine-containing motif (-CF₃) into alkenes and realizing the three component ATRA is using Togni's or Umemoto's reagents.⁶ However, all these reagents are expensive or require multistep synthesis. More importantly, the reactions were restricted in trifluoromethylation,7 whereas other highly interesting F-containing groups, such as difluoroalkyl and perfluoroalkyl, cannot be introduced. Compared with Togni's and Umemoto's reagents, fluoroalkyl iodides and related compounds, especially CF₃I, are much cheaper, easily available for various fluoroalkyl groups, and more practical for large-scale synthesis.8 Despite these benefits, the use of CF₃I and R_fI for three component ATRA of alkenes has scarcely been explored. More importantly, general methods of three component ATRA of alkenes for constructing both C-CF3 and C-Rf are highly desirable but not yet realized.



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In the past few years, Ir- and Ru-catalyzed photoredox reactions have widely been applied in organic synthesis, especially in radical coupling reactions.⁹ In contrast, Cu has scarcely been used as a photoredox catalyst for organic transformations.¹⁰ Very recently, Fu, Peters, and Ackermann reported the copper salt catalyzed radical couplings of organic halides under UV light promotion.¹¹ Inspired by these precedents, we envisioned that, under UV light irradiation, by using a suitable single electron reductant, the conversion of CF₃I (or R_fI) to ${}^{\circ}$ CF₃ (or ${}^{\circ}$ R_f) and I⁻ could be realized through the Cu-catalyzed oxidative quenching cycle without the assistance of Ru or Ir photocatalysts.^{4d,12} More importantly, we assumed that the rapid reduction of CF₃I to I⁻ could suppress the radical propagations in competing two component iodofluoroalkylation of alkenes and facilitate the desired three component reaction.

Nitriles are widely known as an important class of organic compounds, which are found in numerous pharmaceuticals, agricultural chemicals, and optoelectronic materials. In 2014, Liu and co-workers reported the first example of Cu-catalyzed cyanotrifluoromethylation of alkenes using Togni's reagent.^{7c} Later, remarkable progress has been achieved in the enantioselective cyanotrifluoromethylation by the same group.^{7d} We here report the first example of photoinduced, Cu-catalyzed cyanofluoroalkylation of alkenes using fluoroalkyl iodides as fluoroalkylation reagents. The reactions were effective for both C-CF₃ and C-R_f bond formation.

We initiated the investigation by using C_4F_9I (1a, 3 equiv.), 4-methylstyrene (2a), and TMSCN (3, 3 equiv.) as model substrates, dry CH_3CN as solvent, and CuI (10 mol%) as the catalyst. The reaction mixture was irradiated under a 25 W UVC (254 nm) compact fluorescent light bulb¹³ at room temperature. *tert*-Amines were reported as single electron transfer

agents for reducing Cu^{II} to Cu^I in photoinduced oxidative quenching cycles.¹⁴ To our delight, when DIPEA (3 equiv.) was employed, the desired product 4a was obtained in 31% yield without the formation of iodofluoroalkylation product 4aa (Table 1, entry 1, see the ESI[†] for details). Introducing 2 equiv. of H_2O dramatically increased the yield to 61% (entry 2). 365 nm UV light was not as effective as 254 nm (entry 3). A variety of copper species, including cuprous salts (CuCl, CuBr, CuTc, Cu(MeCN)₄PF₆, and Cu₂O) and cupric salts (Cu(acac)₂, Cu(OAc)₂, CuF₂, CuCl₂, Cu(OH)₂, and CuSO₄) was carefully examined, which indicated that both Cu(I) and Cu(II) worked well (entries 4-6). It gave the best result (87%) when $Cu(OAc)_2$ was used (entry 5). Significant formation of 4aa was observed during the survey of amines (Et₃N, DBU, pyridine, Et₂NH, TMEDA, DMAP, and DABCO, entry 7). When other solvents (DMF, THF, toluene, dioxane, or DMSO) were used, the yield did not improve (entry 8). Further varying the amount of DIPEA indicated that 4 equiv. was optimal (entry 9). The control experiment showed that only a trace amount of 4a was obtained without $Cu(OAc)_2$ (entry 10). In the absence of DIPEA, only iodofluoroalkylation occurred (entry 11). The reaction was carried out at room temperature for 24 h or 80 °C for 12 h without light, and no desired product was observed (entry 12).

With the optimal conditions in hand, we set out to explore the scope of the reaction. We first studied the substrate generality in terms of aromatic alkenes with different substituents (Table 2). To our delight, substrates bearing electron-donating and electronwithdrawing groups were compatible with the current transformations (**4a–4o**). It was worth noting that a series of functional groups, such as $-Bu^t$, $-OCH_3$, -F, $-CF_3$, -OAc, and -CN, were all tolerated. Compared to terminal alkenes, the internal alkenes **2p** exhibited slightly lower reactivity (**4p**, 48%), but in good diastereoselectivity

Table 1	Optimization of reaction conditions ^a			
	C ₄ F ₉ l +	+ TMSCN + TMSCN conditions	CN C4F9 4a C4F9 4a 4a	
Entry	Catalyst	Amine	Solvent	$\text{Yield}^{b} (\%) (4a/4aa)$
1	CuI	DIPEA	CH ₃ CN	31/0
2^{c}	CuI	DIPEA	CH ₃ CN	61/0
3^d	CuI	DIPEA	CH ₃ CN	25/0
4	Other Cu(1) catalysts instead of CuI	DIPEA	CH ₃ CN	57/0-64/0
5	$Cu(OAc)_2$	DIPEA	CH ₃ CN	87/0
6	Other $Cu(II)$ catalysts instead of $Cu(OAc)_2$	DIPEA	CH ₃ CN	59/0-68/0
7	$Cu(OAc)_2$	Other amines instead of DIPEA	CH ₃ CN	4/30-66/0
8	$Cu(OAc)_2$	DIPEA	Other solvents instead of CH ₃ CN	3/0-55/0
9 ^e	$Cu(OAc)_2$	DIPEA	CH ₃ CN	92(91)/0
10	$Cu(OAc)_2$	DIPEA	CH ₃ CN	Trace
11	$Cu(OAc)_2$	DIPEA	CH ₃ CN	0/12
12^{f}	$Cu(OAc)_2$	DIPEA	CH ₃ CN	0

^{*a*} Unless otherwise noted, the reactions were carried out by using **2a** (0.1 mmol), **1a** (3.0 equiv.), **3** (3.0 equiv.), amine (3.0 equiv.), solvent (1.0 mL), and catalyst (10 mol%), under N₂, and stirred at room temperature for 2 hours under UV light irradiation. ^{*b*} ¹H NMR yields with anisole as internal standard. ^{*c*} 2.0 equiv. of H₂O was added here and after. ^{*d*} 25 W, 365 nm UVC. ^{*e*} 4.0 equiv. of DIPEA was used; isolated yield in parentheses. ^{*f*} No light, 24 h at rt or 12 h at 80 °C, respectively.

 Table 2
 Cyanofluoroalkylation reaction of alkenes^{a,b}



^a All reactions were conducted in a 0.4 mmol scale. ^b Isolated yields.

(>20:1). The substrate scopes were then expanded to alkylsubstituted alkenes. A range of alkenes with various substituents was all suitable for this reaction (**6a–6h**). Functional groups, such as keto, imide, *-O*-benzoyl, *-O-tert*-butyldiphenylsilyl, and *-O*-P(O)Ph₂, were tolerated (**6c**, **6e**,¹⁵ and **6f–6h**). Complex molecules containing alkenyl groups, namely cinchonine derivatives **5i** and estrone derivatives **5j**, afforded products with excellent yields (**6i**, 76%; **6j**, 89%).

To further explore the substrate scopes, a variety of fluoroalkyl iodides were examined, including the feedstock agent CF₃I (Table 3). To our delight, CF₃I, ICF₂CO₂Et, C₆F₁₃I, and C₈F₁₇I all reacted smoothly with uniformly good yields (**8a–8l**).



^a All reactions were conducted in a 0.4 mmol scale. ^b Isolated yields.



Scheme 2 Synthetic applications.



The results indicated the general ability of this reaction to introduce various fluoroalkyl groups by directly using feedstock reagents.

The cyanofluoroalkylated products are versatile synthetic intermediates and could be used to prepare fluoroalkylated compounds, such as amine **9** and carboxylic acid **10** in good yields (Scheme 2, eqn (1)). In addition, the 10 mmol scale reactions also proceeded smoothly with high yields (eqn (2)).

To gain some mechanistic insight, several experiments were carried out (Scheme 3). The reaction was completely shut down by 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO). Meanwhile, the radical trapping product 11 was isolated in 45% yield, which indicated the formation of a fluoroalkyl radical (eqn (1)). Addition of butylated hydroxytoluene (BHT) led to a dramatic decrease of the yield (eqn (2)). These results indicated that a radical pathway could be involved. In the reaction, the iodofluoroalkylation product might possibly form as an intermediate which could then couple with TMSCN to give the cyanofluoroalkylation product. This prompted us to carry out several control reactions. In the absence of TMSCN, no iodoperfluoroalkylation product was observed (eqn (3)).¹⁶ Without DIPEA, 4a was not formed, whereas 4aa was isolated in 12% yield, which indicated the crucial role of amine in this multicomponent reaction (eqn (4)). Interestingly, under standard conditions, 4aa could react with TMSCN and formed 4a in 87% yield. These control experiments indicated that even if the iodofluoroalkylation product is a suitable precursor and participant as an intermediate in this transformation cannot be completely ruled out, it seems unlikely to be involved in the main operating pathway.



Based on these investigations and previous reports, a plausible mechanism was proposed (Scheme 4).^{7c,d} Firstly, the rapid ligand exchange delivered a Cu^{II} species, which was reduced by the electron rich *tert*-amine and formed an amine radical cation and Cu^{I.14} Under UV light irradiation, Cu^I was excited to its triplet state [Cu^I]*.¹¹ The following oxidative quenching step converted R_fI into ${}^{\bullet}R_{f}$ and I⁻ along with recycling of Cu^{II.10} Meanwhile, ${}^{\bullet}R_{f}$ attacked alkene to give the radical intermediate **A**. Then, it reacted with Cu^{II}(CN)_n and formed a Cu^{III} species, **B**. The subsequent reductive elimination provided the desired cyanofluoroalkylation product. It should be noted that both Cu^I and Cu^{II} salts showed good catalytic activities (Table 1, entries 4 and 6). These results indicated that the catalytic cycle could be initiated either from Cu^{II} or from Cu^I. Unstable species TMS⁺ and I⁻ undergo rapid hydrolysis and then neutralized by amine, which promoted a complete conversion.¹⁷

In conclusion, the first example of photoinduced, Cu-catalyzed three component cyanofluoroalkylation of alkenes was disclosed. The reactions were effective for the introduction of both perfluoroalkyl and trifluoromethyl groups by directly using the fluoroalkyl iodides. A 25 W UVC compact fluorescent light bulb irradiation was sufficient for functionalization of a broad range of simple and complex alkenes at room temperature. Compared with previously reported cyanotrifluoromethylation of alkenes, our method showed significant advantages: (i) using less costly and feedstock CF₃I instead of expensive Togni's or Umemoto's reagent is more practical for large-scale synthesis; and (ii) besides CF₃, a variety of fluoroalkyl groups ($-C_4F_9$, $-C_6F_{13}$, $-C_8F_{17}$, and $-CF_2CO_2Et$) could be introduced with high yields.

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Conflicts of interest

There are no conflicts to declare.

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