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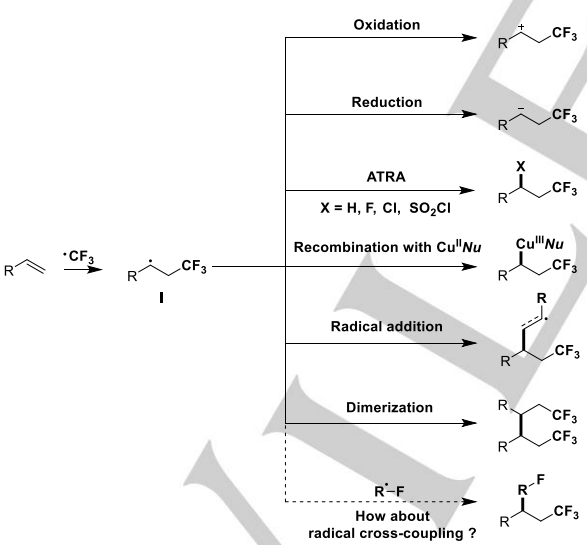
Trifluoromethylation and Monofluoroalkenylation of Alkenes Through Radical–Radical Cross-Coupling

Qiang Wang, Yi Qu, Hao Tian, Yuxiu Liu, Hongjian Song, and Qingmin Wang*

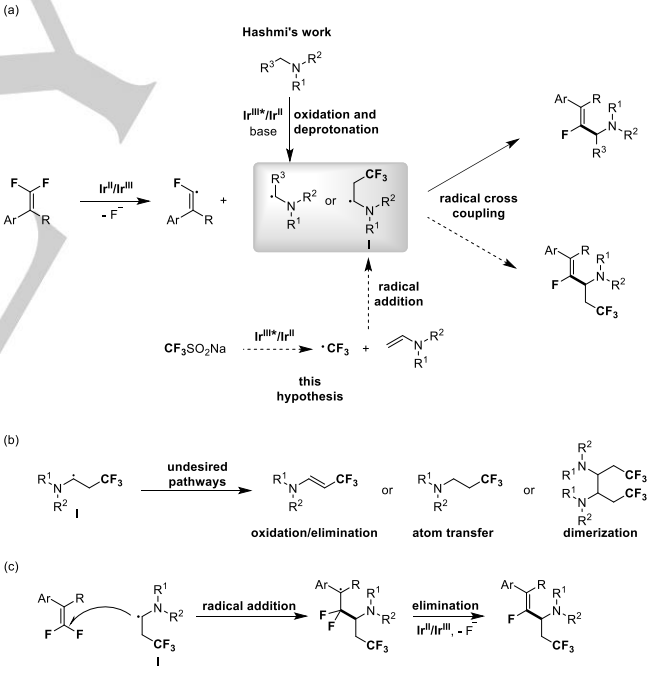
Abstract: *The first visible-light-induced trifluoromethylation and monofluoroalkenylation of simple alkenes via a challenging radical–radical cross-coupling step was achieved. This method provided a mild, step-economical and redox-neutral route to privileged two different fluorinated difunctionalized allyl compounds. The utility of this method is illustrated by late-stage modification of medically important molecules.*

Owing to the small size and high electronegativity of fluorine and the unique chemical and physical properties of fluorine-containing structural motifs, fluorinated organic compounds have widely application in pharmaceutical and agrochemical fields.[1] Nowadays, about 20–25% of pharmaceuticals and 30–40% of agrochemicals in the market are estimated to be molecules containing fluorine.[2] Therefore, great efforts have been made to develop highly efficient and selective methods for constructing diverse fluorine-containing compounds.[3] However, these methods are often limited to introduce only one fluorine atom or one fluorine-containing group into organic molecules, and this is obviously not enough for the research and development of modern medicine and pesticides. So, it's an urgent task for chemists to exploit an efficient and step-economical route to introduce two different fluorine-containing groups into one organic molecule at the same time.[4]



Scheme 1. The radical trifluoromethylative difunctionalization of alkenes.

The radical trifluoromethylative difunctionalization of alkenes is one of the most efficient methods for enriching the library of fluorine-containing compounds. Basically, all these reactions experience a common trifluoromethylated alkyl radical intermediate **I** (Scheme 1), which can undergo several different pathways to afford diverse trifluoromethylated products. These pathways include single electron transfer (SET) oxidation,[5] reduction,[6] atom transfer reaction[4d,7], recombination with metal species,[8] radical addition[9] and dimerization.[10] However, the radical-radical cross-coupling of intermediate **I** with another radical species has not been explored. We hypothesized that combining intermediate **I** with another fluorine-containing radical would provide an efficient, step-economical route to two different fluorinated difunctionalized molecules.



Scheme 2. The radical trifluoromethylation and monofluoroalkenylation of alkenes.

Monofluoroalkenes are important structural motifs in materials and medicinal chemistry,[11] and they can be synthesized from readily available *gem*-difluoroalkenes by defluorinative nucleophilic addition.[12] But these transformations always require strong nucleophiles and harsh reaction conditions which limit the scope of the reaction. Recently, chemists have realized photoinduced defluorinative cross-coupling reactions to afford monofluoroalkenes by using difluoroalkenes as substrates.[13] For example, the group of

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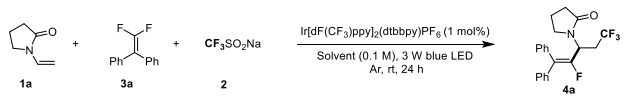
Hashmi reported the monofluoroalkenylation of dimethylamino compounds through radical–radical cross-coupling of *α*-aminoalkyl radicals with monofluoroalkenyl radicals derived from *gem*-difluoroalkenes (Scheme 2a). Based on this, we wondered if the cross-coupling of trifluoromethylated *α*-aminoalkyl radicals with monofluoroalkenyl radicals was also possible. If so, it would give us a chance to recombine intermediate **I** and monofluoroalkenyl radicals to afford both trifluoromethylated and monofluoroalkenylated molecules (Scheme 2a). In this assumption, the trifluoromethylated *α*-aminoalkyl radicals could be obtained through addition of trifluoromethyl radical to enamine compounds (Scheme 2a). Nevertheless, this hypothesis still faces some difficulties. For example, the trifluoromethylated *α*-aminoalkyl radicals may also undergo other competitive reactions as described above (Scheme 2b) without obtaining the target cross-coupling products or reducing the yields. With these questions in mind, we studied this reaction.

Table 1. Optimization of conditions for radical trifluoromethylation and monofluoroalkenylation.

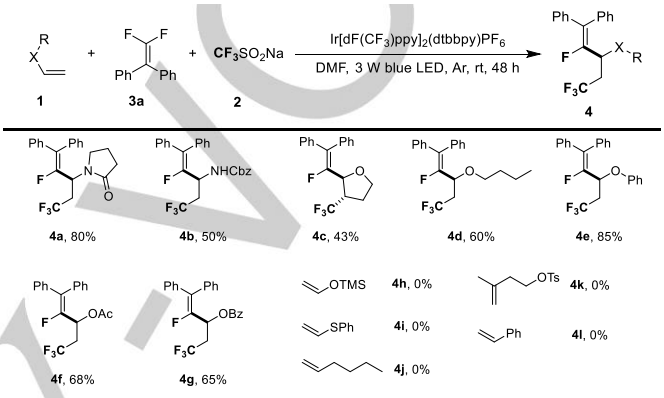


Entry	**1a**[a]	**2**[a]	**3a**[a]	Solvent	Yield [%][b]
1	1	2	1.2	DMF	30
2	1	3	1.5	DMF	39
3	2	4	1	DMF	71
4	2	6	1	DMF	72
5	3	6	1	DMF	74
6	3	6	1	DMSO	65
7	3	6	1	DMA	66
8	3	6	1	MeCN	trace
9[c]	3	6	1	DMF	82
10[c,d]	3	6	1	DMF	0
11[c,e]	3	6	1	DMF	0

[a] Chemical equivalent. [b] Determined by ^{19}F NMR spectroscopy with (trifluoromethyl)benzene as an internal standard. [c] 48 h. [d] Without photocatalyst. [e] Without irradiation.

To optimize the reaction conditions, we chose commercially available *N*-vinyl-2-pyrrolidone (**1a**) as radical receptor, CF_3SO_2Na (**2**) as trifluoromethyl radical source and *gem*-difluoroalkene **3a** as monofluoroalkenyl radical source. As shown in Table 1, the proposed trifluoromethylation and monofluoroalkenylation was indeed feasible during an initial test with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as photosensitizer and a 3 W blue LED as the light source (entry 1). This can be rationalized by the strong oxidation potential of photosensitizer's long-lived (2.3 μs) excited state ($E_{1/2}[*Ir^{III}/Ir^{II}]$ = +1.21 V vs. SCE) and the strong reducing ability of the corresponding Ir^{II} complex ($E_{1/2}[Ir^{III}/Ir^{II}]$ = -1.37 V vs. SCE).[14] Regarding these values, both SET oxidation of **2** ($E_{1/2}^{ox}$ = 1.05 V vs. SCE)[15] and SET reduction of **3a** ($E_{1/2}^{red}$ = -1.04 V vs. SCE)[13a] are thermodynamically feasible. Next, when the chemical equivalent of **2** and **3a** were both increased, the yield was not significantly improved (entry 2). Moreover, we found that substrate **1a** was fully consumed but substrate **3a** had a large surplus under these conditions. The main side products were trifluoromethylated derivatives of **1a** as we mentioned above in Scheme 2b. These results strongly supported the existence of trifluoromethylated *α*-aminoalkyl radical **I** in this system. In order to completely consume **3a**, we increased the ratios of easily available **1a** and **2** to **3a**, and the yield was improved to 71% (entry 3). A further screening of the equivalents of these substrates revealed that 3 equivalents of **1a** and 6 equivalents of **2** was the optimal choice (74% yield, entry 5). Then changing the solvent to DMSO, DMA, or MeCN did not further improve the results (entries 6–8). But when the reaction time extended to 48 hours, we obtained the best yield (82%, entry 9). Finally, in the absence of a photocatalyst or light (entries 10 and 11), no reaction occurred, which indicated that both the photocatalyst and irradiation were essential.

Table 2. Substrate scope with regard to the radical receptors. [a,b]



[a] Reaction conditions: **1** (0.6 mmol), **2** (1.2 mmol), **3a** (0.2 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol) in DMF (2 mL) irradiated with a 3 W blue LED bulb at rt under Ar for 48 h after being degassed. [b] Yields of isolated product are given.

With the optimal conditions established, we first explored the substrate scope with respect to different radical receptors (Table 2). The results revealed that the substituents on the alkenes have a large effect on the reaction efficiency. Substrate bearing a free N–H bond went smoothly to afford the final product **4b**. In addition, the reaction of different types of vinyl ethers and vinyl esters **1c**–**1g** all furnished the desired products with moderate to good yields (43–85%), whereas the OTMS and SPh substituted ethylene, **1h** and **1i**, respectively, failed to give the desired product. Additionally, this reaction did not tolerate non-heteroatom substituted alkenes as a complex mixture of products were obtained in the cases of **1j**–**1l**, even though the starting materials were consumed. These experimental results indicated that the nitrogen or oxygen substituted vinyl structural motif is crucial for this transformation. We speculated that replacement of the *α*-aminoalkyl radicals or *α*-oxyalkyl radicals by simple alkyl radicals is unfavorable for the radical recombination process because of their different lifetimes and reactive tendency.[13a, 16]

We then examined various tetrasubstituted *gem*-difluoroalkenes with **1e** as radical receptor (Table 3). A range of substrates (**3b**–**3j**), including those with two phenyl rings containing electron-donating or electron-withdrawing groups, as well as a fluorene ring, afforded **5b**–**5j** in 50–85% yields. Furthermore, substrate bearing a methyl substituent on the alkene also gave out the final product in moderate yield (**5k**).

Table 3. Substrate scope with regard to the tetrasubstituted *gem*-difluoroalkenes.[a,b]

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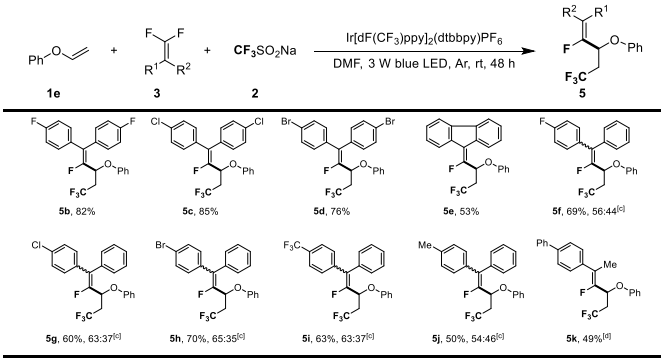
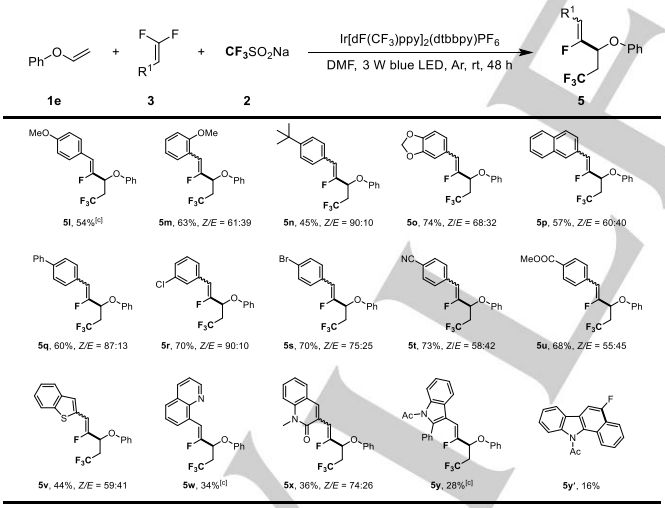


[a] Reaction conditions: **1e** (0.6 mmol), **2** (1.2 mmol), **3** (0.2 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol) in DMF (2 mL) irradiated with a 3 W blue LED bulb at rt under Ar for 48 h after being degassed. [b] Yields of isolated product are given. [c] *Z*/*E* or *E*/*Z* ratios were determined by ^{1}H NMR spectroscopy. [d] Only *Z* configuration of the product was isolated.

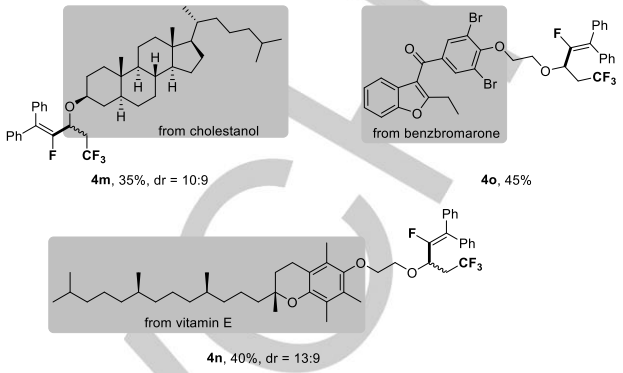
Next, we turned our attention to the trisubstituted *gem*-difluoroalkenes (Table 4). We found substrates bearing an electron-donating or electron-withdrawing substituent at different positions (*meta* or *para*) on the phenyl rings, all smoothly afforded the corresponding products in good yields with different *Z*/*E* selectivity (**5l**–**5u**). Moreover, we also evaluated some heterocyclic substituted substrates, the reactions could also be carried out smoothly despite in lower yields (**5v**–**5y**). Notably, for indole derived *gem*-difluoroalkene **3y**, the reaction gave access to a by-product **5y′** which containing carbazole structure. This result indicated that monofluoroalkenyl radical intermediate might be formed in this reaction.

Table 4. Substrate scope with regard to the trisubstituted *gem*-difluoroalkenes.[a,b]



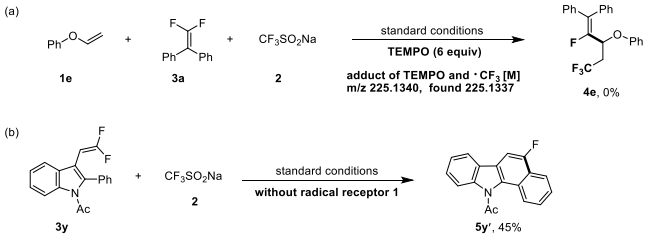
[a] Reaction conditions: **1e** (0.6 mmol), **2** (1.2 mmol), **3** (0.2 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol) in DMF (2 mL) irradiated with a 3 W blue LED bulb at rt under Ar for 48 h after being degassed. [b] Yields of isolated product are given and *Z*/*E* ratios were determined by ^{1}H NMR spectroscopy. [c] Only *Z* configuration of the product was isolated.

The challenging late-stage modification of medically important molecules is indispensable for the development of innovative methods. As depicted in Scheme 3, the vinyl derivatives of some bioactive molecules, such as cholestanol, vitamin E and benzbromarone were tolerated to this reaction (**4m**–**4o**). The successful incorporation of the trifluoromethyl and monofluoroalkenyl motif into such bioactive compounds could help to improve their bioactivities and other properties. These examples demonstrate that this step-economical method represent a powerful late-stage strategy to introduce two different fluorine-containing groups into bioactive molecules.



Scheme 3. Late-stage trifluoromethylation and monofluoroalkenylation of bioactive molecules.

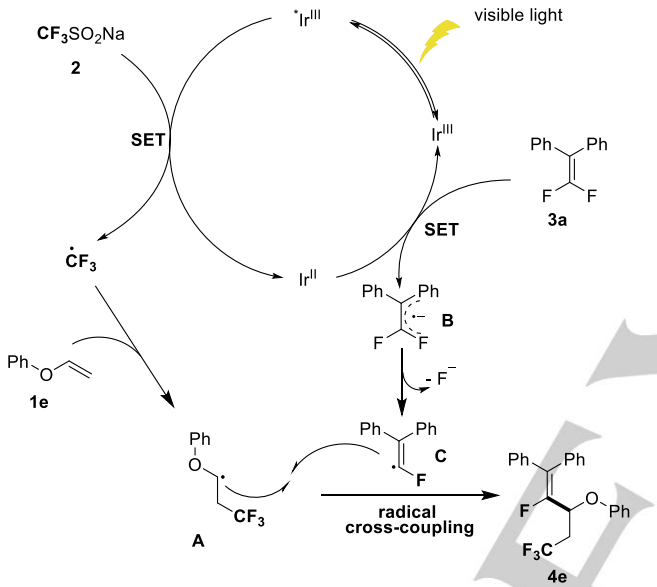
To gain more insight into the mechanism of this transformation, we carried out a series of control experiments (Scheme 4). When the reaction was carried out in the presence of a radical scavenger (2,2,6,6-tetramethyl-1-piperidinyl-oxy, TEMPO), none of the desired product formed (Scheme 4a). Moreover, the detection of TEMPO-CF_3 adduct indicated that this reaction might proceed through a radical pathway. There were two possible pathways for the reaction, involving either radical–radical cross-coupling or radical addition/elimination (see the Supporting Information). In the substrate expansion section in table 4, indole derived substrate **3y** obtained its own defluorinative cyclization by-product at a 16% yield under standard reaction conditions. Here, when the radical-radical cross-coupling was blocked by removing the radical receptor **1e**, the yield of this by-product was increased to 45% (Scheme 4b). We thought that the by-product **5y′** was most likely to be obtained by intramolecular radical cyclization of monofluoroalkenyl radical which formed via photoinduced defluorination process. These results strongly imply the involvement of monofluoroalkenyl radical in this reaction. What's more, the trifluoromethylated by-products generated in above conditional optimization proved the existence of *α*-aminoalkyl radical **I** in this reaction. Therefore, an addition/elimination process is less likely, and the subsequent generation of carbon-carbon bond is more likely formed by free radical coupling.



Scheme 4. Mechanistic studies.

On the basis of the above-described mechanistic experiments and previous work,[13a] we propose the mechanism

shown in Scheme 5 by taking substrates **1e** and **3a** as examples. Under visible-light irradiation, the photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ is photoexcited to the strongly oxidizing complex $*Ir[dF(CF_3)ppy]_2(dtbbpy)^+$. Then this species undergoes SET by accepting one electron from CF_3SO_2Na to generate CF_3 radical and Ir^{II} complex. The CF_3 radical selectively combines with the electron-rich olefin **1e** to obtain the *α*-oxyalkyl radical intermediate **A**. On the other hand, subsequent SET reduction of *gem*-difluoroalkene **3a** by Ir^{II} complex would complete the photoredox catalytic cycle and generate radical anion **B**, which might be prone to undergo C–F bond fragmentation to generate monofluoroalkenyl radical **C**. Finally, according to the "persistent-radical effect",[17] the selective cross-recombination of the less reactive *α*-oxyalkyl radical **A** with the more reactive monofluoroalkenyl radical **C** could afford product **4e**.



Scheme 5. Proposed reaction mechanism.

In summary, we have developed an unprecedented trifluoromethylation and monofluoroalkenylation reaction of simple alkenes through an efficient, step-economical, and redox-neutral route to privileged allyl compounds by photoredox catalysis. Mechanistic investigations indicate a radical–radical cross-coupling reaction of *α*-aminoalkyl radicals or *α*-oxyalkyl radicals with monofluoroalkenyl radicals. The mild reaction conditions, broad substrate scope, excellent functional-group tolerance and efficient one-step two fluorinated difunctionalization strategy open up an opportunity for performing challenging late-stage modification of complex medically molecules. Further application of this method to modify more bioactive molecules and evaluation of the bioactivities of these modified compounds are underway in our laboratory.

Acknowledgements

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Keywords: trifluoromethylation • monofluoroalkenylation • photoredox • radical coupling • late-stage functionalization

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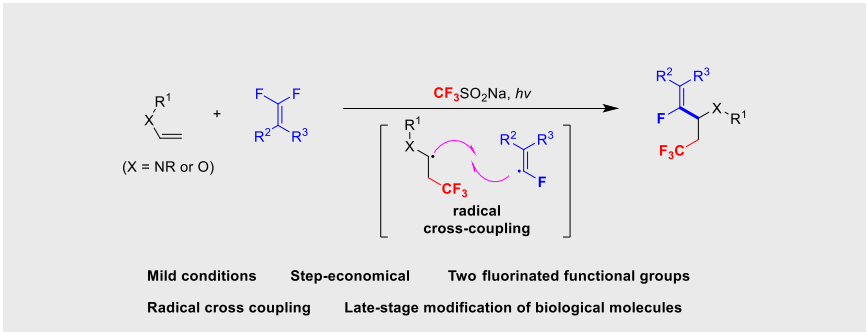

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