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Visible-Light-Promoted Regioselective 1,3-Fluoroallylation of *gem*-Difluorocyclopropanes

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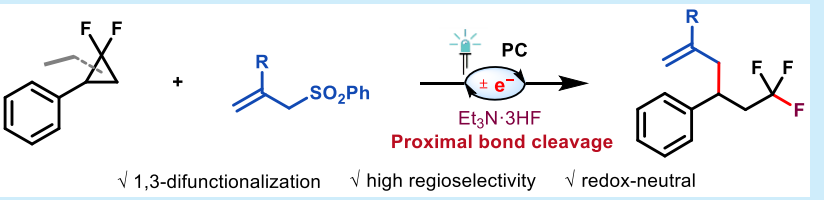
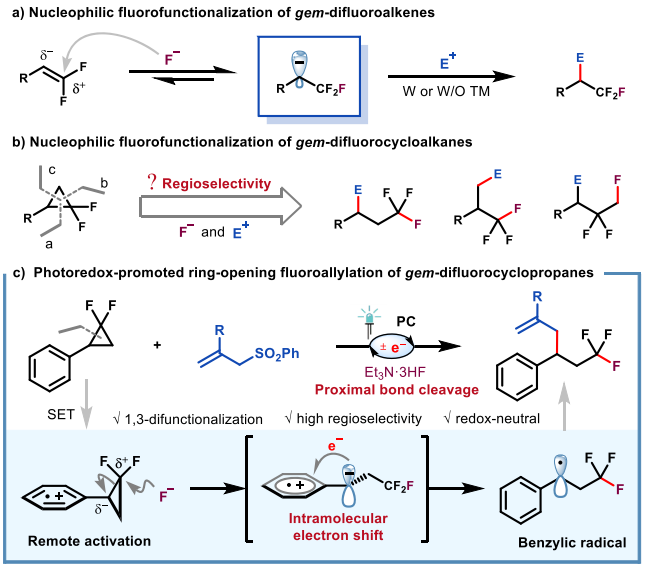


ABSTRACT: A strategically novel protocol for ring-opening functionalization of aryl *gem*-difluorocyclopropanes (F_2CPs), which allows an expedient construction of CF_3-containing architectures via visible-light-promoted F-nucleophilic attack manifold, was disclosed. Single electron oxidation of F_2CPs was ascribed as the critical step for the success of this transformation by prompting F-nucleophilic attack, as well as the ensuing C−C bond scission. The observed intriguing regioselectivity for fluoroincorporation in this reaction was rationalized by invoking the cation-stabilization property of *gem*-difluorine substituents and also the thermodynamic gains acquired from forming CF_3 functionality. By using cost-effective fluorination reagent and readily available substrates, a broad collection of structurally diversified α-allyl-β-trifluoromethyl ethylbenzene derivatives could be obtained in generally good yields. Further mechanistic investigations proved the engagement of a benzylic radical intermediate in this transformation.

The exploration of efficient synthetic protocols for the smooth incorporation of fluorine and fluorine-containing groups into organic architectures was demonstrated to be of vital importance, especially from the consideration of development of new drugs, agrochemicals, and advanced materials.[1] The fact that ∼30% of marketed pharmaceuticals and agrochemicals are organofluorine compounds, in no small part, underscores the value of synthetic method development in this area.[2] In this context, the accomplishment of expedient introduction of trifluoromethyl (CF_3) functional group represents as a remarkably appealing direction, in view of the ubiquitous of this functionality in drug molecules, for example, Prozac, Efavirenz, and Sorafenib.[3] Accordingly, over the past decade, considerable endeavors from the synthetic community have formulated a palette of diverse but enabling protocols to fulfill this objective. While notable advancement has been attained, the majority of attention, however, has been focused on either direct trifluoromethylation using CF_3 reagents or synthetic elaboration using CF_3-contaning templates.[4,5] Given this situation, the continuing exploration of strategically novel synthetic methods for easing the access of CF_3-containing frameworks, especially those that simultaneously allow rapid assembly of molecular complexity, is still highly desirable.

While pursuing complementary alternatives, we have recently casted a strategy of "F-nucleophilic addition induced functionalization of *gem*-difluoroalkenes" (Scheme 1a).[6] The regioselective attack of exogenous nucleophilic fluoride onto electropositive difluorine-substituted carbon atom allows the ready assembly of CF_3 group, while the ensuing elaboration of

Scheme 1. Nucleophilic Fluorofunctionalization of *gem*-Difluoroalkenes and *gem*-Difluorocyclopropanes



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the nascent carbon anion/radical species ultimately achieves 1,2-difunctionalization.[7] Based on these achievements, we posited whether it is possible to further expand the potential applicability of this strategy, for example, enabling ring-opening 1,3-fluorofunctionalization of *gem*-difluorocyclopropanes (F_2CPs). In principle, the successful development of this homologous reaction would build up a new dimension for the expedient construction of structurally complicated CF_3-decorated frameworks that is not easily acquired by resorting to previously known regimes. Although seemingly enticing, the relative inertness of cyclopropane ring compared with alkene π-system would pose a remarkable challenge, much less the realization of exquisite site-selectivity, with respect to C−C bond cleavage (Scheme 1b).

The exploitation of avenues that enable regioselective ring-opening functionalization of F_2CPs has aroused much interest from synthetic chemists.[8] Although diverse efficacious strategies for the activation of cyclopropane ring have been put forward, most of the reported protocols still fall short of general applicability, such that specific neighboring activating groups are always required.[9−11] In this vein, the regioselective functionalization of alkyl- or aryl-based F_2CPs, which are devoid of extra activating elements, still proved to be nontrivial. Notably, by capitalizing on tactics including hypervalent iodine catalysis and bromine radical-engaged homolytic-substitution, as well as C−C bond cleavage through low-valent palladium insertion, elegant examples were reported by the groups of Jacobsen, Kawasaki-Takasuka, and Fu.[12−14] Notwithstanding these notable progresses, the aforementioned works mainly focus on monofunctionalization, despite the fact that rapid construction of molecular complexity is more favored for difunctionalization reactions. With our continuing interest in fluorine chemistry,[15] we would like to report our recent progress in regioselective 1,3-carbofluorination of aryl F_2CPs (Scheme 1c). The notable features as well as the underlying reasons, with regard to the present work are as follows: (i) by resorting to photoredox catalysis, the aryl group readily undergoes single-electron oxidation, with the in-situ-generated aryl radical cation segment enabling a remote activation of the attached F_2CPs motif toward exogenous fluoride attack;[16] (ii) the positive charge in aryl moiety is effectively delocalized to F_2CPs through hyperconjugation effect, thus resulting in an enrichment of positive charge on *gem*-difluorine substituted carbon atom, because of the p-electron-donating ability of F atoms; (iii) beside the cation-stabilization capacity of *gem*-difluorine substituents, which secure a high regioselectivity concerning the fluoride attack, extra thermodynamic gains could be anticipated by the formation of CF_3 groups.[9a,b,17]

Before we started to validate our hypothesis, the redox potential of 1-(2,2-difluorocyclopropyl)-4-methoxybenzene (**1a**) was determined using cyclic voltammetry, which was identified around +1.68 V (vs SCE in MeCN). Based on this assessment, initial attempts of the reaction between **1a** and ethyl 2-((phenylsulfonyl)methyl)acrylate (**2a**) was performed using different photocatalysts. (For optimization details, see the Supporting Information.) We were pleased to find that the desired product **3a** could be isolated in 16% yield, when using $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}d(CF_3)bpy)](PF_6)$ (PC-II, E_{Red} = +1.69 V vs SCE in MeCN) as the catalyst and Py·9HF as the fluorine source (Table 1, entry 1).[18] Among the nucleophilic fluoride tested, $Et_3N{\cdot}3HF$ was revealed to be the best choice, which resulted in the generation of **3a** in 31%,

Table 1. Optimization of Reaction Conditions[a]

entry	fluoride	solvent	yield[b] (%)
1	Py·9HF	dioxane	16
2	AgF	dioxane	NR
3	KF	dioxane	NR
4	CsF	dioxane	NR
5	$BF_3{\cdot}OEt_2$	dioxane	5
6	$Et_3N{\cdot}3HF$	dioxane	31
7	$Et_3N{\cdot}3HF$	MeCN	30
8	$Et_3N{\cdot}3HF$	DCE	43
9	$Et_3N{\cdot}3HF$	$PhCF_3$	36
10	$Et_3N{\cdot}3HF$	acetone	23
11	$Et_3N{\cdot}3HF$	DCE	89 (74)[c]
12	$Et_3N{\cdot}3HF$	DCE	NR[d]
13	$Et_3N{\cdot}3HF$	DCE	NR[e]

[a]Standard reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), PC-II (2.0 mol %, 0.002 mmol), $Et_3N{\cdot}3HF$ (2.0 equiv, 0.2 mmol), dioxane (0.5 mL) under N_2 atmosphere while irradiating with 8 W blue LEDs for 12 h. [b]Yield was determined by ^{19}F NMR with $PhOCF_3$ as the internal standard. [c]DCE (0.25 mL) and the reaction time was 48 h. Isolated yield was given in parentheses. [d]Without photocatalyst. [e]Without light irradiation.

whereas other metallic fluorides proved unsuitable for this transformation (Table 1, entries 2−6). Further enhancement of reaction efficiency was observed when substituting DCE for dioxane as the reaction media, while no further yield increase was gained with other reaction solvents (Table 1, entries 7−10). Pleasingly, by further prolonging the reaction time to 48 h along with increasing the reaction concentration, full consumption of starting materials was observed and the NMR yield of desired product could be increased to 89% (Table 1, entry 11). Furthermore, control experiments clearly indicated that both photocatalyst and light irradiation were indispensable to the success of this reaction and no any product was obtained with the omission of either (Table 1, entries 12 and 13).

With the optimized reaction conditions in hand, the exploration of substrate scope, with respect to aryl F_2CPs, was subsequently pursued and the representative results are compiled in Scheme 2. The para position of the aryl group decorated with electron-donating alkoxyl or aryloxyl functionalities were all tolerated and moderate to good yields could be obtained with these substrates (**3a**−**3c**). Although there were more recalcitrant toward SET oxidation, the less electron-rich substrates bearing a phenyl or alkyl group were also amenable to this reaction and delivered the desired products **3d** in 54% and **3e** in 49% yield, respectively, when using Fukuzumi salt as the catalyst. Notably, substrate **3f**, which is decorated with propargyl ether, also participated in this fluoroallylation reaction readily, with the propargyl group remaining intact throughout this transformation. In addition, heterocycle-containing aryl F_2CPs also turned out to be amenable, as showcased by the example of **3g**. With the activation of methoxy group at the para-position, a set of additional substituents differs in electronic property were accommodated such as F, Cl, Br, Me, Ph, and OMe (**3h**−**3l**, **3n**, **3o**). Interestingly, while **1a** reacted efficiently, its ortho-OMe-

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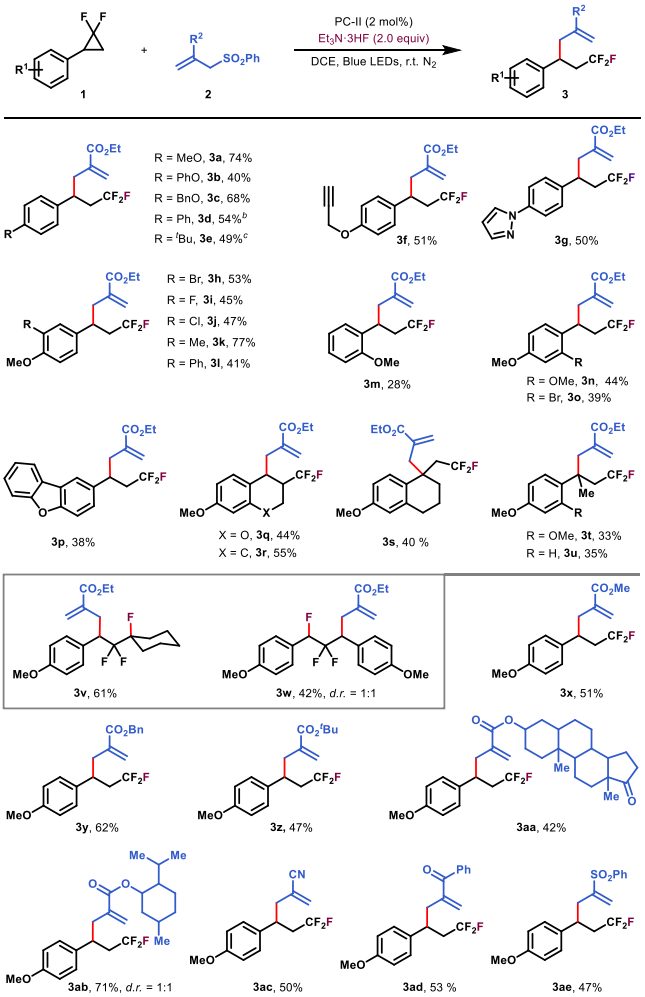
Scheme 2. Substrate Scope of 1,3-Fluoroallylation of *gem*-Difluorocyclopropane[a]

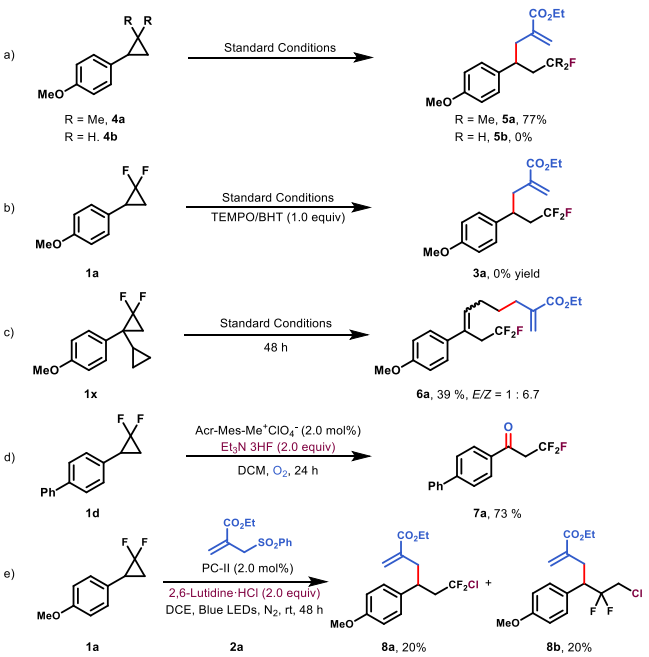


[a]Standard conditions:**1** (0.2 mmol), **2a** (0.6 mmol), PC (2.0 mol %, 0.002 mmol), $Et_3N{\cdot}3HF$ (2.0 equiv, 0.4 mmol), DCE (0.5 mL) under N_2 atmosphere and irradiated with 8 W blue LEDs at indicated times. Isolated yield. [b]9-Mesityl-2,7-dimethyl-10-phenylacridin-10-ium tetrafluoroborate was used as a photocatalyst. [c]3,6-Di-*tert*-butyl-9-mesityl-10-phenylacridin-10-ium tetrafluoroborate as a photocatalyst.

derived congener **1m** participated in this reaction much less readily, with only 28% yield of desired product **3m** being obtained. We believe that the discrepancy in reactivity could be rationalized by invoking the distinct magnitude of activation on the cyclopropane ring, because of the disparity of positive charge distribution on these two aryl radical cation systems. Of note, heterocyclic substrates such as that derived from dibenzofuran was also applicable, albeit giving rise to the desired product **3p** in moderate yield. To our pleasure, benzocyclane-derived F_2CPs also readily engaged in this reaction to afford the desired products **3q** and **3r** in good yields. Note that this reaction could be successfully extended to 1,1-disubstituted F_2CPs, which enables the smooth generation of desired products with adjacent all-carbon quaternary center either in cyclic or acyclic systems (**3s**−**3u**). Much more intriguingly, when aryl F_2CPs that contain additional alkyl or aryl substituents on the neighboring C-3 atom were subjected to the standard reaction conditions, the fluoride had a tendency to attack the C-3 position, accompanied by the distal C−C bond cleavage (**3v**, **3w**). This regioselectivity divergence could be rationalized by assuming that *gem*-difluorine group is less inclined to stabilize the adjacent positive charge compared with either dialkyl or aryl substituents. The generality of allyl sulfone was also interrogated by using 1-(2,2-difluorocyclopropyl)-4-methoxybenzene (**1a**) as the modern substrate. A series of 2-alkoxycarbonyl substituted allyl sulfones reacted smoothly to yield the corresponding products in good yields (**3x**−**3z**). Note that cholesterol (**3aa**)- and menthol (**3ab**)-derived allyl sulfone also engaged in this transformation without any issues. Furthermore, other electron-withdrawing functional groups such as cyano (**3ac**), benzoyl (**3ad**), and phenyl sulfone (**3ae**) also proved to be compatible in this reaction, thus providing the desired products in good yields. Notably, relatively lower yields were obtained except for **3a**, which might be attributed to the increased oxidation potential in some cases. However, the exact reason is unclear at the present stage.

Stern−Volmer measurement verified that only substrate **1a** positively quenched the excited state of photocatalyst. To shed more light on the reaction mechanism, a set of control experiments were further performed. Structurally analogous nonfluorinated cyclopropanes **4a** and **4b** were tested under standard conditions. It was found that **4a** featuring *gem*-dimethyl groups worked well, while **4b** remained intact (Scheme 3a). This result emphasizes the enabling effect of

Scheme 3. Control Experiments



the electron-donating substituent. Furthermore, the transformation was totally inhibited when 1.0 equiv of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) or 2,6-di*tert*-butyl-4-methylphenol (BHT) was added (Scheme 3b). A radical-clock experiment was also conducted by subjecting **1x** into the optimized reaction conditions, which led to the generation of 1,6-difunctionalization product **6a** in 39% yield (Scheme 3c). These experiments indicated that benzyl radical was involved as reactive intermediate in this transformation. Further proof of benzyl radical production came from control experiment using O_2 as the radical trap, which indeed led to the formation of

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anticipated of oxofluorination product in 73% yield (Scheme 3d).[19] Apart from fluoride, other nucleophilic halogen sources were also investigated. 2,6-Lutidine·HCl was demonstrated as a viable nucleophile to furnish the ring-opening products **8a** and **8b** in 40% yield (see Scheme 3e). In addition, light on/off experiment demonstrated that continuous light irradiation was essential for the progress of the reaction.

In summary, we have successfully developed a conceptually novel protocol for ring-opening 1,3-fluoroallylation of aryl F_2CPs by taking advantage of photoredox catalysis. The in-situ-generated aromatic radical cation acted as the key activating element, which engender a remote electronic activation on an otherwise inert difluorocyclopropane ring system toward exogeneous fluoride attack. The regioselectivity of fluorine incorporation, as well as thus-accompanied C−C bond cleavage, is delicately controlled by the cation-stabilization capacity of substituents on the cyclopropane. Furthermore, the successful development of this reaction not only expands the applicability of "F-nucleophilic addition induced functionalization" but also provides a convenient pathway for the construction of α-allyl-β-trifluoromethyl ethylbenzene derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03268.

Experimental details and full spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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