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Defluoroalkylation of *gem*-Difluoroalkenes with Alcohols via C−F/C−H Coupling

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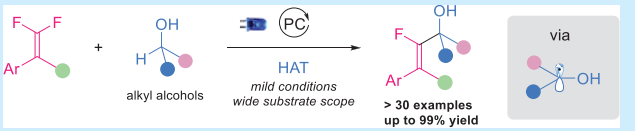
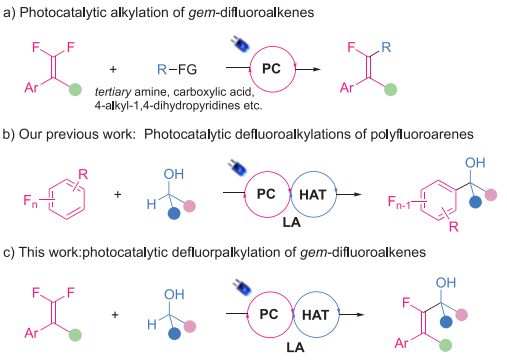
ABSTRACT: A feasible and effective method to synthesize α-fluoroalkenyl alcohols was reported. With the cooperation of photoredox and hydrogen atom transfer (HAT) processes, defluoroalkylations of *gem*-difluoroalkenes occurred smoothly with alcohols under visible-light irradiation. Notably, the protocols feature broad scopes, mild conditions, and validity for the late-stage functionalization of bioactive molecule derivatives. Mechanistic studies suggested that the reaction occurred through the radical coupling of the alkyl radical and the fluoroalkenyl radical.



Monofluoroalkenes as peptide bond isosteres exhibited versatile applications for pharmaceutical development.[1] C−F activation of easily accessible *gem*-difluoroalkenes provided a straightforward pathway for the synthesis of monofluoroalkenes.[2] With the development of visible-light-induced organic synthesis,[3] a series of cross-coupling reactions between *gem*-difluoroalkenes and other reaction partners via a radical-involved process have been reported to access functionalized monofluoroalkenes (Scheme 1a).[4] For C−F alkylation of *gem*-difluoroalkenes, Hashimi and Xie developed the seminal work with tertiary amine as the alkyl source via photoredox pathways.[4a] Afterward, alkyl carboxylic acid,[4b−e] 4-alkyl-1,4-dihydropyridines,[4f] and alkylsulfones[4i] were used as the alkylation reagents to achieve the alkylated monofluoroalkenes. However, the majority of these coupling reactions proceeded with prefunctionalized starting materials via direct photoredox functional group transformations. The reactivity is heavily restricted by their redox properties, leading to narrow applications and undermining the atom economy. Thus, alkylation via direct inert C−H activation of alkyl sources could become an efficient strategy to be involved in the C−F functionalization of *gem*-difluoroalkenes. Inert C−H bond activations through the cooperation of photoredox catalysis and hydrogen atom transfer (HAT) catalysis have become a powerful strategy to produce alkyl radicals for alkylations via radical addition or substitution reactions.[5] Recently, Wang developed the seminal work for the α-monofluoroalkenylation of amines and ethers utilizing this strategy.[6] Afterward, Deng also reported an excellent work on C−H/C−F bond coupling of ethers with *gem*-difluoroalkenes through the cooperation of photoredox catalysis and halide reagents as the HAT catalysts.[7] However, the utilization of ether substrates as the solvent or at high temperature led to limited scope and low efficacy. Above all, the constructions of alkylated monofluoroalkenes via direct C−H/C−F bond coupling were still undeveloped, and it was challenging to develop efficient catalytic systems for this transformation.

Scheme 1. Defluorofunctionalizations of *gem*-Difluoroalkenes



Recently, we developed a series of defluorofunctionalization reactions of multifluorinated substrates,[4k,8] including the defluoroalkylations of polyfluoroarenes with alcohols through Lewis-acid-promoted C−H/C−F bond coupling under visible-light irradiations via a radical addition pathway (Scheme 1b).[8b] Considering the low cost of alcohols and the wide application of α-fluoroalkenyl alcohol derivatives as bioactive compounds,[9] herein we assumed that the coupling of alcohol α-C−H and C−F bonds from *gem*-difluoroalkenes might occur utilizing similar strategies to deliver α-fluoroalkenyl alcohol products. Notably, the redox properties of polyfluoroarenes and *gem*-

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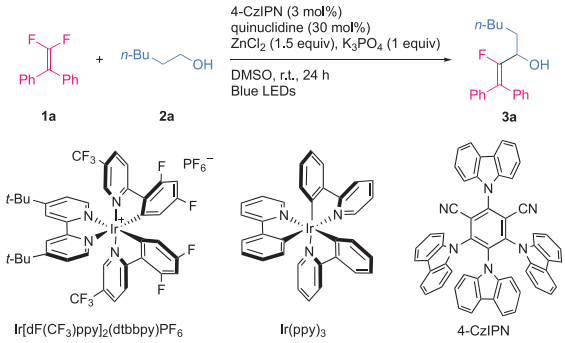
difluoroalkenes are distinctive, suggesting the different radical involving pathways.

We began our investigations by carrying out reactions of diphenyl *gem*-difluoroalkene (**1a**) and hexan-1-ol (**2a**) with the goal of optimizing the reaction conditions (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



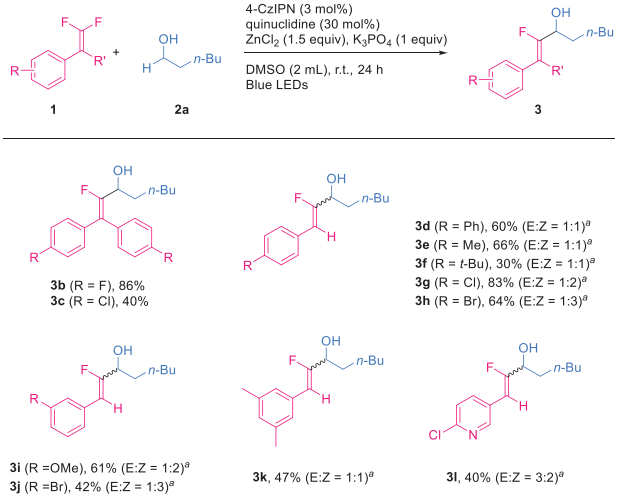
.	deviation	yield (%)[b]
1	none	92 (87)[c]
2	$Ir(ppy)_3$	0
3	$Ir(ppy)_2(dtbbpy)PF_6$	0
4	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	15
5	0.5 equiv of K_3PO_4	30
6	1 equiv of $ZnCl_2$	17
7	w/o 4-CzIPN, quinuclidine, or $ZnCl_2$	0
8	w/o light	0
9	w/o K_3PO_4	26

[a]General reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3 equiv), 4-CzIPN (0.003 mmol, 3 mol %), quinuclidine (0.03 mmol, 30 mol %), $ZnCl_2$ (0.15 mmol, 1.5 equiv), K_3PO_4 (0.1 mmol, 1.0 equiv), and DMSO (2 mL). [b]Yields of **3a** were determined by analysis of the crude ^1H NMR spectra using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yields were shown in the parentheses.

Pleasingly, the desired α-fluoroalkenyl alcohol product (**3a**) was achieved and isolated in 87% yield with the catalytic system consisting of 4-CzIPN (3 mol %), quinuclidine (30 mol %), $ZnCl_2$ (1.5 equiv), and K_3PO_4 (1 equiv) under blue LED irradiation in DMSO at room temperature after 24 h (entry 1). Notably, iridium complexes such as $Ir(ppy)_3$, $Ir(ppy)_2(dtbbpy)PF_6$, and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ instead of 4-CzIPN led to sluggish reactions (entries 2−4). Decreasing the number of equivalents of K_3PO_4 or $ZnCl_2$ induced much lower yields (entries 5 and 6). In addition, the yields decreased substantially without 4-CzIPN, quinuclidine, light, $ZnCl_2$, or K_3PO_4 (entries 7 and 8), indicating that these components were all essential for this transformation.

With the optimal conditions established, we first explored the scope of *gem*-difluoroalkenes (**1**) using hexan-1-ol (**2a**) as the reaction partner (Scheme 2). Symmetric diaryl *gem*-difluoroalkenes bearing fluoro and chloro substituents were both alkylated smoothly to give the products (**3b−3c**) in 86% and 40% yields, respectively. For alkene substrates derived from aryl aldehydes, the reaction conditions were slightly modified with LiCl instead of $ZnCl_2$ (see Supporting Information). Substituents such as phenyl, methyl, and *t*-butyl groups at the *para*-position of arenes on *gem*-fluoroalkenes had no obvious influence on the reactivity and delivered the alkylation products in moderate to good yields (**3d−3f**) with *E*/*Z* selectivity up to 3:1. Notably, C−F bonds

Scheme 2. Alkylation of *gem*-Difluoroalkenes

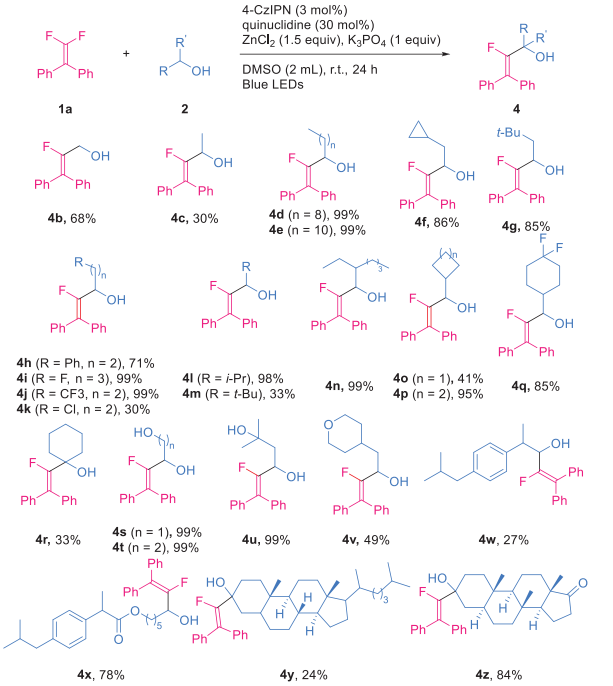


[a]LiCl (1.5 equiv) was used instead of $ZnCl_2$.

instead of C−Cl and C−Br bonds were selectively cleaved in the substrates to produce the monofluoroalkenes in good yields (**3g** and **3h**). Defluoroalkylations occurred smoothly with substrates decorated with *meta*-substituents such as methoxy, bromo, and dimethyl groups to produce the desired products (**3i−3j**) in good yields. Luckily, the pyridinyl alkene could also be a good candidate for this transformation to produce the defluoroalkylation products in 40% yields (**3l**).

A variety of alcohols (**2**) could also be monofluoroalkenylated with diphenyl-*gem*-difluoroalkene (**1a**) under standard conditions (Scheme 3). Simple linear alkyl alcohols, such as methanol, ethanol, 1-decanol, and 1-dodecanol, were fluoroalkenylated at the α-position to produce the products in good to excellent yields (**4b-4e**). Sterically hindered β-alkyl-substituted alcohols gave the monofluoroalkenylation products

Scheme 3. α-Fluoroalkenylations of Alcohols



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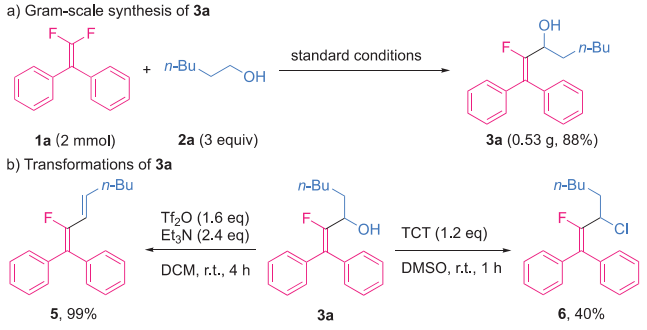
in excellent yields (**4f**–**4g**). Functional groups, such as phenyl, fluoro, chloro, and trifluoromethyl groups, were compatible with this transformation (**4h**–**4k**). Notably, the alcohols bearing the sterically hindered or cyclic α-alkyl groups were also workable for α-monofluoroalkenylation to afford the products (**4l**–**4q**) in 33%–99% yields. The monofluoroalkenylation of the cyclic secondary alcohols, i.e., cyclohexanol, occurred smoothly to deliver the desired products (**4r**), albeit in only 33% yields. To our delight, diols including ethane-1,2-diol, propane-1,3-diol, and 3-methylbutane-1,3-diol were selectively monoalkenylated to give the monofluoroallyl alcohol products (**4t**–**4u**) in great yields. For 4-(2-hydroxyethyl) tetrahydropyran, we were glad to observe the regioselective α-C–H fluoroalkenylation of the hydroxyl group to give the products (**4v**) in 49% yields. Impressively, the protocol was successfully applied to the monofluoroalkenylations of complex natural products and pharmaceutical derivatives with alcohol functionalities. The hydrogenated ibuprofen could be α-monofluoroalkenylated to afford the corresponding product in moderate yields (**4w**). Meanwhile, alcohols linked with ibuprofen could also be selectively monofluoroalkenylated at the α-position of the hydroxy group to deliver the product (**4x**) in 78% yields. Notably, the direct monofluoroalkenylation of β-cholestanol and epiandrosterone worked well to give the derivatives (**4y** and **4z**) in moderate to good yields.

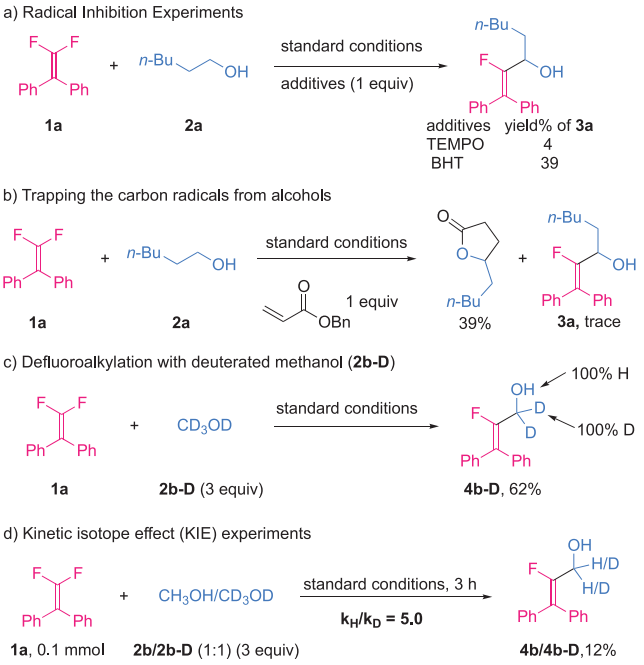
To further demonstrate the synthetic utility of this protocol, the gram-scale production of **3a** from **1a** and **2a** under standard conditions was carried out leading to 88% yields (Scheme 4a). Treatment of the product (**3a**) with Tf_2O afforded the dehydroxylated product, fluorinated diene (**5**), in 99% yields and excellent stereoselectivity.[10] The hydroxy group in the product (**3a**) could also be transformed to chlorine (**6**) using cyanuric chloride (TCT) in 40% yields (Scheme 4b).[11] These transformations of the hydroxyl groups on the products provided feasible strategies for the synthesis of various monofluoroalkene derivatives that could not be achieved via conventional methods.

Scheme 4. Gram-Scale Synthesis and Transformations of 3a



To verify the mechanism for α-monofluoroalkenylations of alcohols, a series of experiments were carefully designed (Scheme 5). When radical inhibitors, such as TEMPO or BHT, were added to the reaction mixture under standard conditions, only 4% or 30% of **3a** was obtained, respectively, suggesting that the reaction occurred via a radical pathway (Scheme 5a). Then, benzyl acrylate as a radical trapper was introduced to the coupling reaction. Under standard conditions, the desired products were not detected, while the radical addition and esterification product was observed in 39%

Scheme 5. Mechanistic Experiments



yield, indicating the presence of the alcohol α-carbon radical (Scheme 5b). Interestingly, D4-methanol (**2b-D**) could be monofluoroalkenylated with *gem*-difluoroalkenes (**1a**) to give the α-deuterated alcohols (**4b-D**) in 62% yields without H–D exchanges at the α-position but with exclusive H–D exchange on the hydroxyl group (Scheme 5c), illustrating the existence of the alkoxide intermediate. The competition reaction of **2b** and **2b-D** with **1a** was conducted to figure out a KIE value of 5.0, suggesting that the α-C–H activation of alcohols could be the rate-determining step (Scheme 5d).[12] The CV tests showed that the oxidative potential of the quinuclidine (E^{ox} = +1.01 V vs SCE in DMSO) was lower than that of the excited photocatalyst (**PC^n***: 4-CzIPN*) (E(**PC^n***/**PC^{n-1}**) = +1.35 V vs SCE in CH_3CN), while the reductive potential of *gem*-difluoroalkenes (E^{red} = −0.91 V vs SCE in DMSO) was higher than **PC^{n-1}** (E(**PC^{n-1}**/**PC^n**) = −1.21 V vs SCE in CH_3CN).[13] In addition, Stern–Volmer quenching studies were conducted. The quenching effect of quinuclidine was much stronger than that of alcohols (**2a**) and could be further enhanced by the addition of K_3PO_4 (see the Supporting Information). Therefore, we concluded that the initial step of the reaction was the reductive quenching of the excited photocatalyst with quinuclidine, and *gem*-difluoroalkenes could be reduced by the reductive state of the photocatalyst (**PC^{n-1}**). The quantum yield (0.36) was also determined to exclude the radical chain mechanism.[14]

Based on these experiments' results and literature reports,[8,13] we propose the plausible catalytic cycles for this transformation (Scheme 6). Under the irradiation of blue light, the **PC^n** was first photoexcited to **PC^n***. Then, reductive quenching occurred for **PC^n*** with quinuclidine to deliver the quinuclidinyl N-radical cation and **PC^{n-1}**. At this stage, the reaction between alcohol and $ZnCl_2$ occurred to give the alkoxide zinc intermediate (**int-I**). HAT of the α-C–H bond of **int-I** with the quinuclidine radical cation then delivered the alkyl radical (**int-II**). Meanwhile, it was followed by fluoride elimination to produce the alkenyl radical (**int-III**) and recover the **PC^n**. Afterward, the cross-recombination of **int-II** with **int-**

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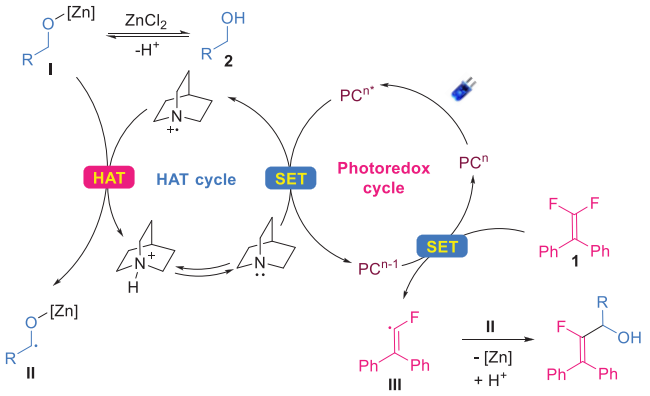
Scheme 6. Plausible Catalytic Cycles



III resulted in the formation of products (**3** or **4**) after protonation.

In summary, a visible-light-promoted defluorinative alkylation of *gem*-difluoroalkenes was successfully achieved using alcohols as the alkyl source under mild conditions via C−H and C−F coupling reactions. The reaction was triggered by the Lewis-acid-assisted photoredox and HAT dual catalytic systems through a radical coupling pathway. This protocol represents one of the most feasible strategies to construct α-fluoroalkenyl alcohol with easily accessible starting materials and provides a green and efficient method for the synthesis of functional fluoroalkenes.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03982.

Experimental procedures, mechanistic experiments, and characterization data for all compounds (PDF)

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Author Contributions

M.W. and W.X. designed this project. C.X., H.H., B.Y., and Q.S. conducted the experiments. C.X. and W.X. analyzed the data and prepared the Supporting Information. M.W., W.X., and C.X. analyzed the data and prepared the manuscript.

Notes

A patent (CN202211134212.X) on the presented chemistry was deposited.

The authors declare no competing financial interest.

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