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Letter

Photoredox-Mediated Mono- and Difluorination of Remote Unactivated Methylene C(sp^3)−H Bonds of *N*-Alkyl Sulfonamides

Zhiqiang Deng, Zhenxiang Zhao, Gang He, and Gong Chen*

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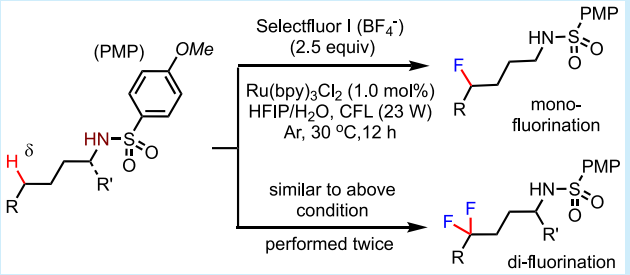
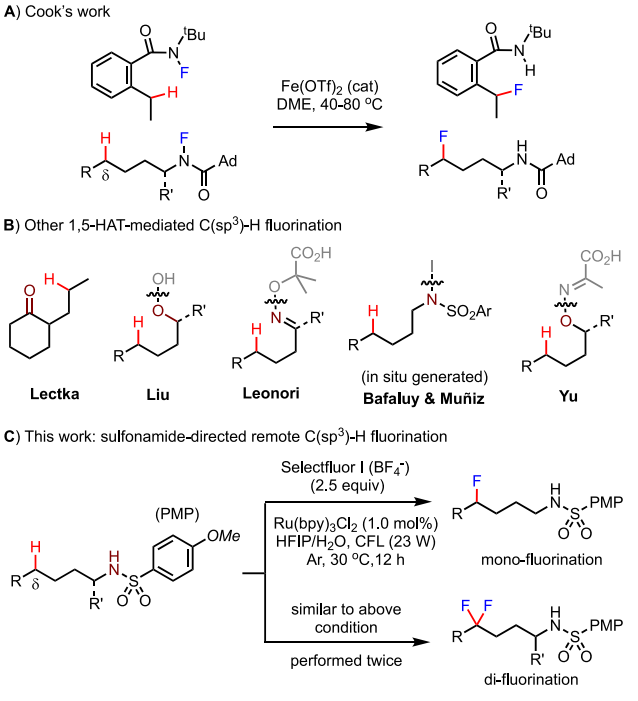
ABSTRACT: A photoredox-mediated δ-C(sp^3)−H fluorination of sulfonyl-protected primary alkylamines with Selectfluor is developed. The reaction can proceed in excellent monofluorination selectivity for amine substrates without α substituent. For α-substituted substrates, a slightly modified reaction conditions with two rounds of operation gives the δ,δ-difluorination products in good yield. Mechanistic studies suggest SET oxidation of sulfonamide group directly generates the key sulfonamide N radical intermediate, which triggers a 1,5-HAT process to form the δ alkyl radical.



Radical-mediated alkyl C−H functionalization reactions have been widely used to incorporate fluorine atom or fluorine-containing moieties into various organic molecules.[1−3] Among the different types of radical reactions, the intramolecularly directed approach via an 1,5-hydrogen atom transfer (1,5-HAT) process of heteroatom-centered radical intermediates has proven to be a reliable strategy to selectively functionalize the unactivated alkyl C−H bond at a remote position.[4] While the strategy has long been used to install chlorine, bromine, and iodine as in the classic Hofmann−Loffler−Freytag (HLF) reaction and other heteroatoms and carbon moieties, the corresponding fluorination reaction is relatively underdeveloped.[5−8] In 2016, Cook first demonstrated that presynthesized *N*-fluorocarboxamide precursors can undergo efficient C−H fluorination at the δ position via an amidyl radical intermediate under the catalysis of Fe(OTf)$_2$.[7a] Later, the groups of Lectka,[8a] Liu,[8b] Leonori,[8c] and Yu[8d] reported ketone, O, or iminyl radical intermediates can also direct the δ C−H fluorination via 1,5-HAT with suitable fluorination reagents. Very recently, the group of Bafaluy and Muñiz reported that sulfonamides can undergo remote C−H fluorination via an in situ generated *N*-iodosulfonamide intermediate.[8e] Herein, we report a new photoredox-mediated method for δ-C(sp^3)−H fluorination of sulfonyl protected primary alkyl amines with Selectfluor reagent (Scheme 1C). The reaction can proceed in good to excellent monofluorination selectivity for amine substrates without an α substituent. For α-substituted substrates, a slightly modified condition with two rounds of operation gave δ,δ-difluorination products in good yield and with high selectivity.

We previously reported a photoredox-mediated method for δ-C(sp^3)−H heteroarylation of sulfonyl-protected primary alkyl amines with *N*-heteroarenes using benziodoxole acetate oxidant.[9,10] It was found that the sulfonamide group can be

Scheme 1. Radical-Mediated Remote C−H Fluorination of Aliphatic Amines via 1,5-HAT



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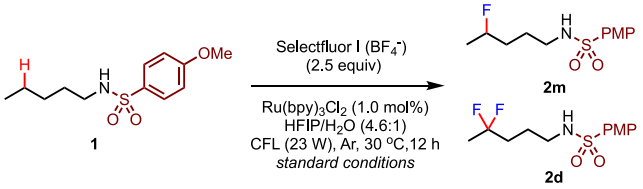
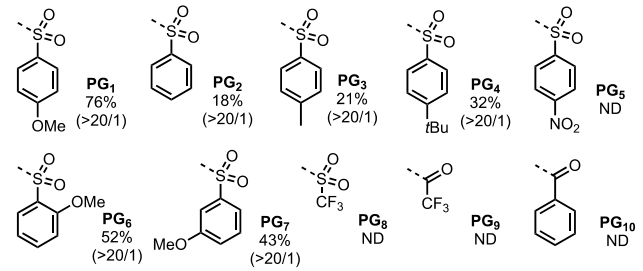
directly oxidized by single electron transfer (SET) to generate an N-radical, which triggers the subsequent 1,5-HAT and Minisci-type arylation.[9,11] Encouraged by these results, we wondered whether a similar alkyl radical via 1,5-HAT can be trapped by suitable fluorination reagents to give the fluorination product. As shown in Table 1, we were pleased to find that reaction of *p*-methoxyphenyl (PMP) sulfonyl pentylamine **1** with 2.5 equiv of Selectfluor I (BF_4) and 1.0 mol % of $Ru(bpy)_3Cl_2$ photocatalyst under the irradiation of household compact fluorescent lamp (CFL, 23 W) in the mixed solvents of hexafluoroisopropanol (HFIP)[12] and water (4.6/1) at 30 °C for 12 h gave the desired monofluorination product **2m** along with a small amount of difluorination **2d** in 70% isolated yield (entry 1). The mono- and difluorination products are difficult to separate by silica gel chromatography. The HFIP/H_2O ratio had a significant impact to the mono- vs difluorination selectivity. Changing the ratio of HFIP/H_2O from 4.6:1 to 1:1 gave comparable yield of **2** but dramatically reduced monoselectivity (entry 3). Replacing HFIP with trifluoroethanol (TFE) gave lower yield (entry 4). Use of other organic solvents such as CH_3CN and acetone caused significantly lower reactivity (entries 5 and 6). The substituent on the phenyl ring of the arylsulfonamide protecting group (PG) had a significant impact to the reactivity. For example, replacing the 4-methoxy group ($\mathbf{PG_1}$) with a 4-methyl group ($\mathbf{PG_3}$) gave 21% of the fluorination product. Use of trifluoromethyl sulfonamide ($\mathbf{PG_8}$), trifluoromethylacetamide ($\mathbf{PG_9}$), and benzamide ($\mathbf{PG_{10}}$) gave no desired product. Selectfluor I (BF_4^-) served as the best fluorination reagent (entries 7–12). Photocatalyst and visible light irradiation were critical (entries 13–16). The addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl or oxidanyl (TEMPO) reagent abolished the reaction (entry 18).

Table 1. Reaction Optimization of δ C–H Fluorination of N-Protected Pentylamine

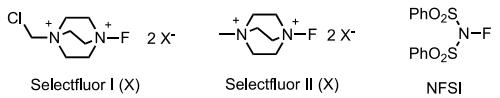


entry	change from the standard conditions (equiv of reagents)	yield of 2[a] (2m/2d) (%)
1	No change	76 [70[b]] (>20:1)
2	HFIP/H_2O (4.6:1 → 5.5:1)	70 (>20:1)
3	HFIP/H_2O (4.6:1 → 1:1)	67 (2.5:1)
4	HFIP is replaced with TFE	50 (11.8:1)
5	HFIP is replaced with CH_3CN	25 (19:1)
6	HFIP is replaced with acetone	22 (>20:1)
7	2 equiv of Selectfluor I (BF_4^-) is used	69 (>20:1)
8	3 equiv of Selectfluor I (BF_4^-) is used	80 (>20:1)
9	Selectfluor I (OTf^-) is used	70 (>20:1)
10	Selectfluor II (BF_4^-) is used	75 (19.7:1)
11	Selectfluor II (OTf^-) is used	43 (>20:1)
12	Selectfluor is replaced with NFSI	ND
13	0.5 mol % of $Ru(bpy)_3Cl_2$ is used	64 (>20:1)
14	1.5 mol % of $Ru(bpy)_3Cl_2$ is used	66 (>20:1)
15	without $Ru(bpy)_3Cl_2$	ND
16	in darkness	ND
17	under air	41 (>20:1)
18	2.0 equiv of TEMPO is added	ND

Yields of 2 and the corresponding analogs with different N protecting groups (PG) under the standard conditions[a]



Structure of F^+ reagents:



[a]Yields were based on ^1H NMR analysis of the crude reaction mixture at a 0.2 mmol scale. The ratio of **2m**/**2d** was measured by ^{19}F NMR. [b]Isolated yield. ND: not detected.

The scope of amines was then examined under the optimized conditions **A** and **B** with different ratios of HFIP and H_2O solvents (Scheme 2). Primary amines with both linear and cyclic alkyl scaffolds can work. Most linear alkyl amines proceeded with excellent δ regioselectivity (δ: other isomers >20:1) (e.g., **4**–**7**) under conditions **A** using a 4.6:1 mixture of HFIP and H_2O. Notably, the reaction of hexylamine **3** gave a moderate regioselectivity. Besides the δ methylene C–H bonds, fluorination at the more inert δ methyl group can also work albeit in lower yield. Conditions **B** using 1:1 mixture of HFIP and H_2O gave slightly higher yield (see **8**). Fluorination of the δ tertiary C–H of **9** proceeded in moderate yield along with the formation of 20% of cyclized pyrrolidine byproduct. In comparison to **1**, substrate bearing a α-methyl substitunt showed higher reactivity and gave significantly more difluorination product **10d** under conditions **A**. A 1.1:1 ratio of mono- vs difluorination product was obtained under conditions **B**. Similarly, **16** bearing an α-substituent was significantly more reactive than **14**. Fluorination of δ methylene C–H bonds of cyclic scaffolds proceeded in varied yield and selectivity. For example, the reactions of cyclooctylamine and cyclododecylamine gave **12** and **13** in 60% and 50% yield, respectively. Small amounts of difluorination products of cyclooctylamine at both the δ and δ′ positions were obtained and can be readily separated from the monofluorination product by silica gel column chromatography. δ-Methyl fluorination of α-amino acid substrates gave the corresponding fluorinated product in low to moderate yield under conditions **B** (**17**–**19**).

Methods for selective double C–H fluorination of unactivated methylene groups remain scarce.[7b,8d,13] We were pleased to find that reaction of **20** under slightly modified condition **B** with 3.5 equiv of Selectfluor I (BF_4) and 0.5 mol % of $Ru(bpy)_3Cl_2$ gave **10** in a 1.4:1 ratio of di- and monofluorination (d/m) (Scheme 3). Furthermore, subjecting the purified product to the same fluorination treatment gave **10d** with excellent selectivity and in good overall yield. As exemplified by **21d** and **23d**, the two-round protocol worked well for α-substituted alkyl amines, forming the otherwise difficult-to-access products in good yield and with excellent difluoroselectivity.[14]

As shown in eq 1, the *p*-methoxyphenylsulfonyl group in product **4** can be cleanly removed by the treatment of SmI_2/

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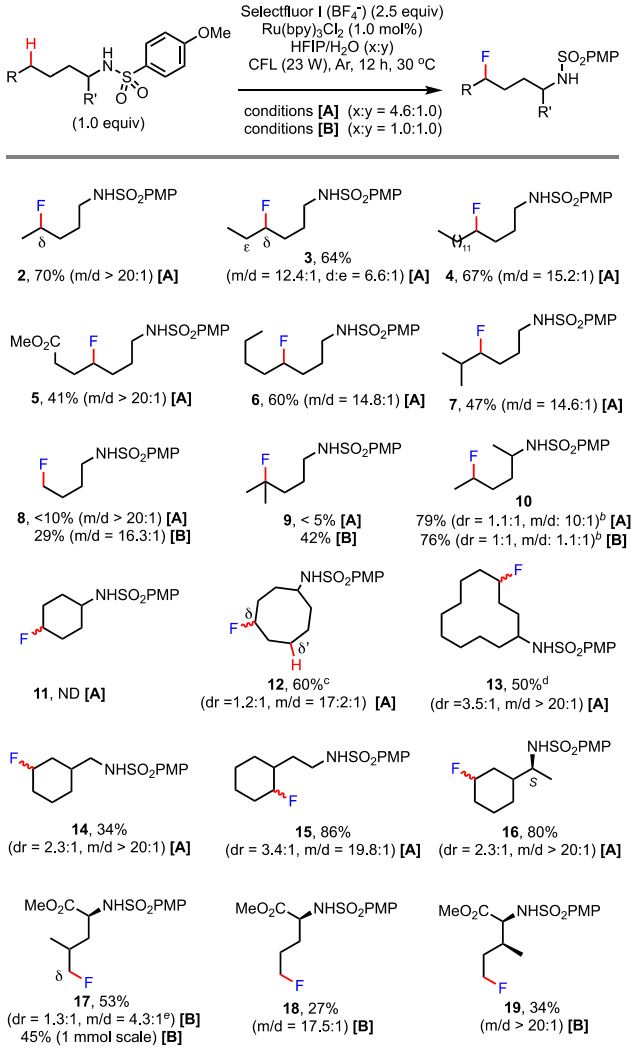
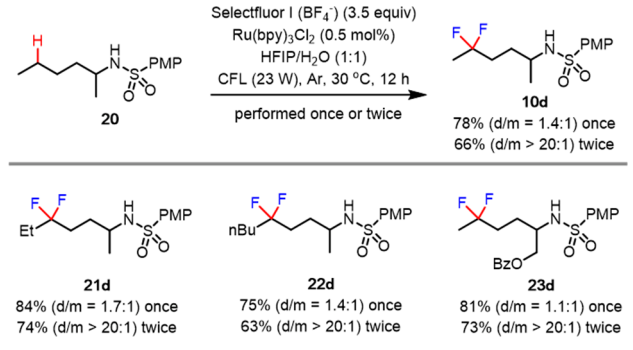
Scheme 2. Scope of Aliphatic Amines[a]

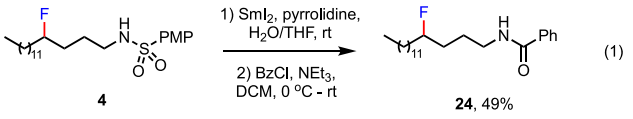


[a]Isolated yield on a 0.2 mmol scale. Unless otherwise specified, excellent δ regioselectivity (δ: other regioisomers >20:1) was obtained. m/d: mono vs difluorination product at δ position. [b]0.5% mmol of $Ru(bpy)_3Cl_2$ was used. [c]8% of δ,δ'-difluorination byproduct was also obtained. [d]The two diastereomers can be separated. [e]Difluorination on the same methyl group.

Scheme 3. δ, δ-Difluorination of α-Substituted Aliphatic Amine[a]



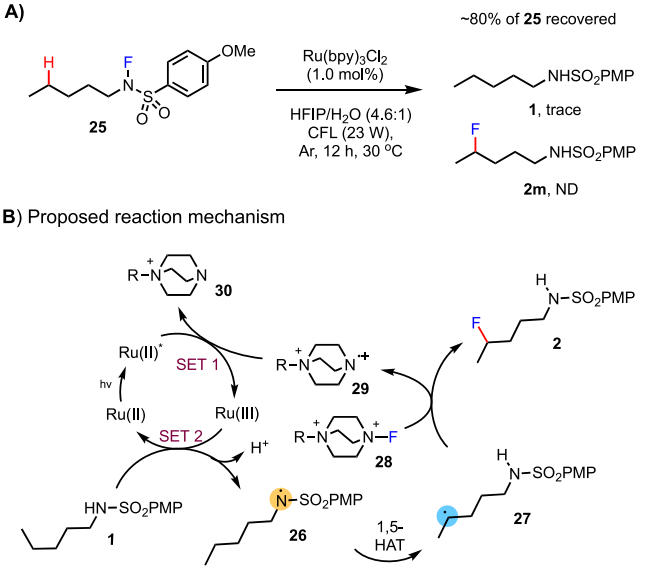
[a]Isolated yield on a 0.2 mmol scale. The ratio of d/m was measured by ^{19}F-NMR. Yields were based on the initial nonfluorinated amines.



pyrrolidine/H_2O in THF at rt.[15] Capping of the resulting free amine with benzoyl chloride gave product **24** in 49% yield over two steps.

As shown in Scheme 4A, the treatment of *N*-fluorosulfonamide intermediate **25** under our typical photoredox conditions

Scheme 4. Mechanistic Consideration



in the absence of Selectfluor reagent did not form any δ-fluorination product **2m**. Based on this evidence and the related work by Knowles, Rovis, and our group, the following mechanism is proposed for this reaction system (Scheme 4B).[9,11] Upon photoexcitation, Ru(II) can be oxidized by Selectfluor or its derived intermediate via SET to form a Ru(III) species. The sulfonamide substrate **1** can be directly oxidized by Ru(III) via SET or proton-coupled electron transfer process to form N-radical **26** and Ru(II).[16] Compound **26** undergoes 1,5-HAT to generate C-centered radical **27**, which reacts with F^+ species **28** to give the fluorination product **2** and **29**.

In summary, we have developed a radical-mediated δ-C(sp^3)–H fluorination reaction of *N*-sulfonyl primary alkyl amines with Selectfluor reagent under photoredox catalysis. The reaction can proceed in good yield and with excellent monofluorination selectivity for amine substrates without α substituent. For α-substituted substrates, δ, δ-difluorination products can be obtained in good yield and with high selectivity using a two-round protocol. Mechanistic studies suggest that photoredox oxidation of a sulfonamide group directly generates the key sulfonamide N radical intermediate, which triggers the subsequent 1,5-HAT and radical trapping with Selectfluor. This reaction offers a useful method to prepare mono- and difluorinated alkyl amines from simple precursors.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01020.

Details for mechanistic investigation; copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Gong Chen − *State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China;* orcid.org/0000-0002-5067-9889; Email: gongchen@nankai.edu.cn

Authors

Zhiqiang Deng − *State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Zhenxiang Zhao − *State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China*

Gang He − *State Key Laboratory and Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, China;* orcid.org/0000-0002-9064-3418

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c01020

Notes

The authors declare no competing financial interest.

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