OL Organic Letters

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N-Activation of 2-PySO$_2$CF$_2$H for Electrophilic Difluoromethylthiolation of Electron-Rich Heteroarenes

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Cite This: https://doi.org/10.1021/acs.orglett.5c01431 Read Online

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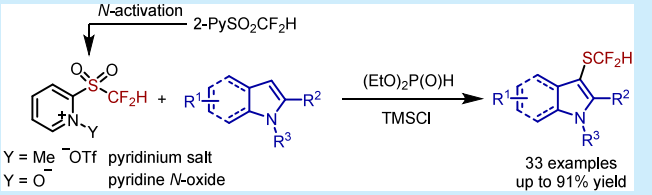
ABSTRACT: Difluoromethyl 2-pyridyl sulfone (2-PySO$_2$CF$_2$H) is a readily accessible, cost-effective, and versatile reagent with broad applications in fluoroalkylation and fluoroolefination. Here, we unveil a novel application of 2-PySO$_2$CF$_2$H in electrophilic difluoromethylthiolation. Key to this advance is the strategic *N*-activation of 2-PySO$_2$CF$_2$H to generate stable *N*-methylpyridinium salt and pyridine *N*-oxide derivatives. When synergistically combined with (EtO)$_2$P(O)H/TMSCl, these activated sulfones facilitate efficient difluoromethylthiolation of electron-rich heteroarenes, such as indoles and pyrroles. This research not only introduces a new strategy for electrophilic difluoromethylthiolation but also provides new insights into the mechanism of (EtO)$_2$P(O)H/TMSCl-mediated difluoromethylthiolation reactions.



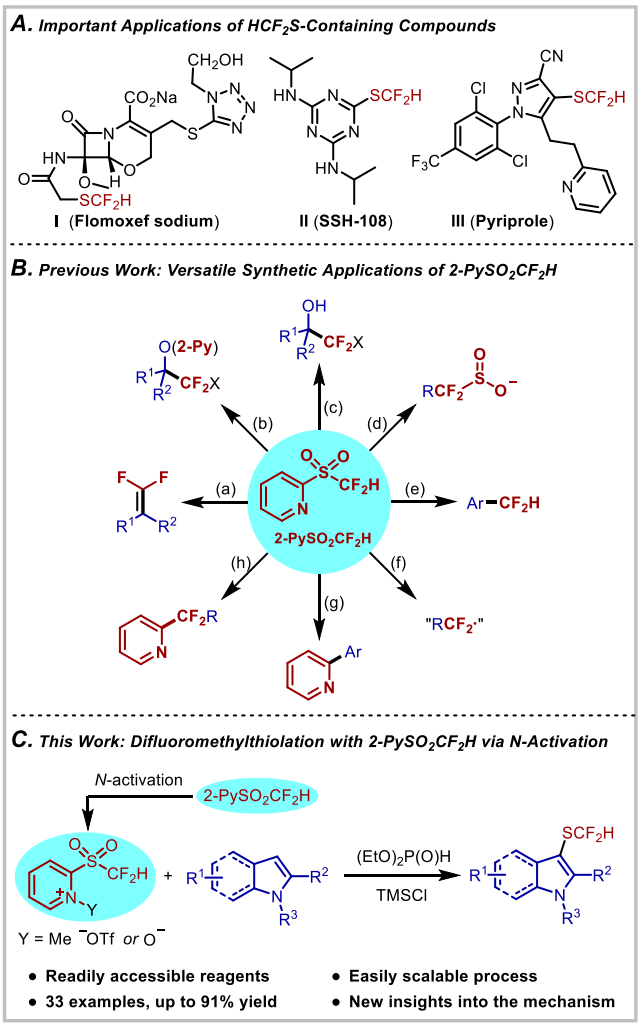
The strategic incorporation of fluorine atoms or fluorinated functionalities represents a cornerstone of molecular design, offering profound enhancements to the physicochemical profiles and bioactivity of organic compounds.[1] Among various fluorine-containing groups, the difluoromethylthio (SCF$_2$H) group has gained considerable interest due to its potential to improve the pharmacokinetics of lead compounds.[2] On the one hand, its moderate lipophilicity (Hansch parameter π_R = 0.68, positioned between CF$_3$, π_R = 0.88, and CH$_3$, π_R = 0.56)[3] and balanced electronegativity (Hammett constant σ_p = 0.37, falling between CF$_3$, σ_p = 0.54, and CF$_2$H, σ_p = 0.32)[4] to optimize druglike properties such as lipophilicity and binding affinity. On the other hand, as a bioisostere, it maintains hydrogen-bond donating ability akin to thiols, hydroxyls, and amines while exhibiting increased lipophilicity.[2] To date, several molecules containing the SCF$_2$H group have received regulatory approval for pharmaceutical or agrochemical applications. Notable examples include the β-lactamase-resistant oxcephalosporin antibiotic Flomoxef sodium (**I**),[5] the herbicide SSH-108 (**II**),[6] and the pesticide Pyriprole (**III**)[7] (Scheme 1A).

Traditional synthetic routes to difluoromethylthiolated compounds predominantly rely on difluorocarbene insertion chemistry,[8] wherein transient difluorocarbene (:CF$_2$) intermediates—generated from precursors such as TMSCF$_2$Br,[9] ClCF$_2$H,[10] or CHF$_3$,[11]—formally insert into S−H bonds. While effective, this strategy suffers from inherent limitations in substrate scope due to the restricted availability and compatibility of thiol precursors. Over the past decade, the direct introduction of SCF$_2$H has gained significant attention due to its step economy and operational simplicity. In this context, a diverse range of difluoromethylthiolation reagents have been developed to enable the efficient and selective incorporation of the SCF$_2$H group into various molecular frameworks.[12] Generally, these reagents can be categorized into two groups: the SCF$_2$H-type reagents and the S-(O)$_x$CF$_2$H-type reagents (x = 1, 2). The latter category includes NaSO$_2$CF$_2$H,[13] RS(O)CF$_2$H,[14] ClS(O)CF$_2$H,[15] ClSO$_2$CF$_2$H,[16] 2-BTSO$_2$CF$_2$H (2-BT = benzo[*d*]thiazol-2-yl),[17] and difluoromethanesulfonyl iodine(III) ylides.[18] These reagents introduces the SCF$_2$H group via electrophilic pathways that involve the in-situ removal of oxygen atom(s) from the sulfur center.[19] Considering that NaSO$_2$CF$_2$H, ClSO$_2$CF$_2$H, and 2-BTSO$_2$CF$_2$H can also serve as radical difluoromethylation reagents,[20] we envisioned that developing fluoroalkylthiolation methods using readily available sulfur-based fluoroalkylation reagents would be of great synthetic value. This approach can simplify the toolbox for introducing structurally diverse fluorinated motifs.

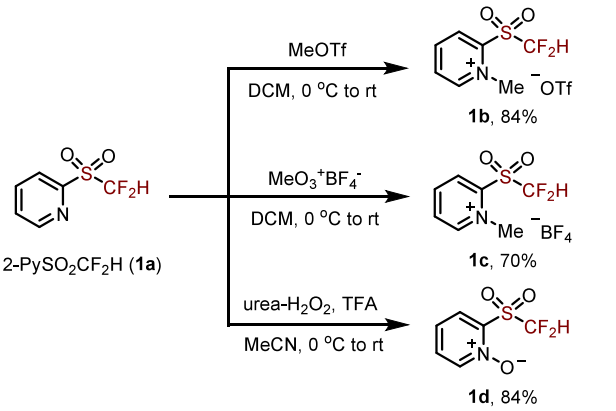
Difluoromethyl 2-pyridyl sulfone (2-PySO$_2$CF$_2$H, the so-called Hu reagent) is a bench-stable, readily available and cost-effective reagent first introduced by our group.[21] It has been established as a versatile tool for *gem*-difluoroolefination (Scheme 1B, a),[22] formal nucleophilic halodifluoromethylation of carbonyl compounds (Scheme 1B, b and c),[23] (sulfinato)-difluoromethylation (Scheme 1B, d),[24] and metal catalyzed aromatic difluoromethylation (Scheme 1B, e).[25] Additionally, it can serve as a precursor for difluoroalkyl radicals (Scheme

Received: April 10, 2025
Revised: May 3, 2025
Accepted: May 7, 2025

Scheme 1. Significance of the SCF_2H Group and Synthetic Applications of 2-$PySO_2CF_2H$



Scheme 2. Methods for *N*-Activation of 2-$PySO_2CF_2H$ (1a)



1B, f)[26] and as an aryl-heteroaryl cross coupling partner (Scheme 1B, g).[27] More recently, the development of ligand coupling reactions involving heteroaryl fluoroalkyl sulfones has further expanded its utility, making it an effective reagent for accessing 2-difluoroalkylpyridines (Scheme 1B, h).[28] Although difluoromethylthiolation using electron-deficient 2-$BTSO_2CF_2H$ has been reported,[17] the application of 2-$PySO_2CF_2H$ for difluoromethylthiolation has never been previously disclosed due to its relatively low reactivity. Herein, we present a strategic activation protocol for difluoromethylthiolation with 2-$PySO_2CF_2H$, achieved through either *N*-methylation or *N*-oxidation of the pyridyl ring to activate the sulfone followed by in situ reduction (Scheme 1C). The synthetic utility of this approach is demonstrated through the electrophilic difluoromethylthiolation of indoles.

Our research began with the activation of 2-$PySO_2CF_2H$ (**1a**) to form a pyridinium salt or pyridine *N*-oxide (Scheme 2). Treatment of **1a** with methyl triflate[29] or trimethyloxonium tetrafluorobarate provided the pyridinium salts **1b** and **1c**, respectively. Oxidation of **1a** with urea-H_2O_2 complex in the presence of trifluoroacetic acid provided the pyridine *N*-oxide **1d**. All three compounds (**1b**−**1d**) were obtained as stable solids. Notably, in the case of **1b**, the crude product obtained after removal of the volatile components from the reaction mixture could be used directly (see **3j** in Scheme 3).

With compounds **1b**−**1d** in hand, we first examined their difluoromethylthiolation ability using indole (**2a**) as a model substrate (Table 1), under conditions similar to those previously used for the reaction of 2-$BTSO_2CF_2H$, employing $(EtO)_2P(O)H$/TMSCl as the promotor and MeCN as the solvent at 80 °C.[17] When 2.0 equiv of *N*-methylated sulfone **1b** were combined with 4.0 equiv of $(EtO)_2P(O)H$/TMSCl, the reaction proceeded efficiently, affording 3-difluoromethylsulfanylindole (**3a**) in an excellent yield of 93% (Table 1, entry 1). Changing the counterion from triflate to tetrafluorobarate has little impact on the reaction outcome (Table 1, entry 2). Interestingly, the *N*-oxide derivative of 2-$PySO_2CF_2H$ (**1d**) also facilitated difluoromethylthiolation (Table 1, entry 3), albeit with a somewhat lower yield compared to **1b** and **1c**. In contrast, when examining sulfone **1a** alongside its derivatives **1b**−**1d**, we found that **1a** failed to participate in the reaction (Table 1, entry 4), highlighting the crucial role of pyridine ring activation. The reactivity order of **1a**, **1b**, and **1d** (**1b** > **1d** > **1a**) is consistent with their first reduction potential values (**1a**: −1.79 V; **1b**: −0.42 V; **1d**: −1.49 V versus Ag/AgCl in CH_3CN). The combination of a phosphine and a chloride source is crucial for the reaction, with $(EtO)_2P(O)H$/TMSCl identified as the optimal choice (Table 1, entries 5−10). Solvent screening showed that MeCN was more effective than toluene, DMF, and THF (Table 1, entries 11−13). High temperature is essential for the reaction, as lowering the reaction temperature significantly hinders its progress (Table 1, entries 14 and 15). Finally, a survey on reagent loading showed that reducing the amounts of **1b**/$(EtO)_2P(O)H$/TMSCl resulted in a lower yield (Table 1, entry 16), likely due to the competitive formation of $(EtO)_2P(O)SCF_2H$ (**4**).[17]

Under the optimized conditions (Table 1, entry 1), the scope of difluoromethylthiolation of electron-rich heteroarenes with **1b** was investigated, as illustrated in Scheme 3. This methodology demonstrates exceptional substrate generality, successfully accommodating 1-, 2-, and 1,2-substituted indoles with diverse functional groups on the benzene ring, including halogens (F, Cl, Br, I), alkyl, methoxy, ester, and cyano moieties. The protocol delivers 3-difluoromethylthiolated indoles in synthetically useful yields (30−91%), showcasing robust compatibility with both electron-donating and electron-withdrawing substituents (**3a**-**3k**, **3m**-**3ae**). Additionally, 3-substituted indoles, such as 3-methylindole, proved to be viable substrates, furnishing the 2-difluoromethylthiolation product in

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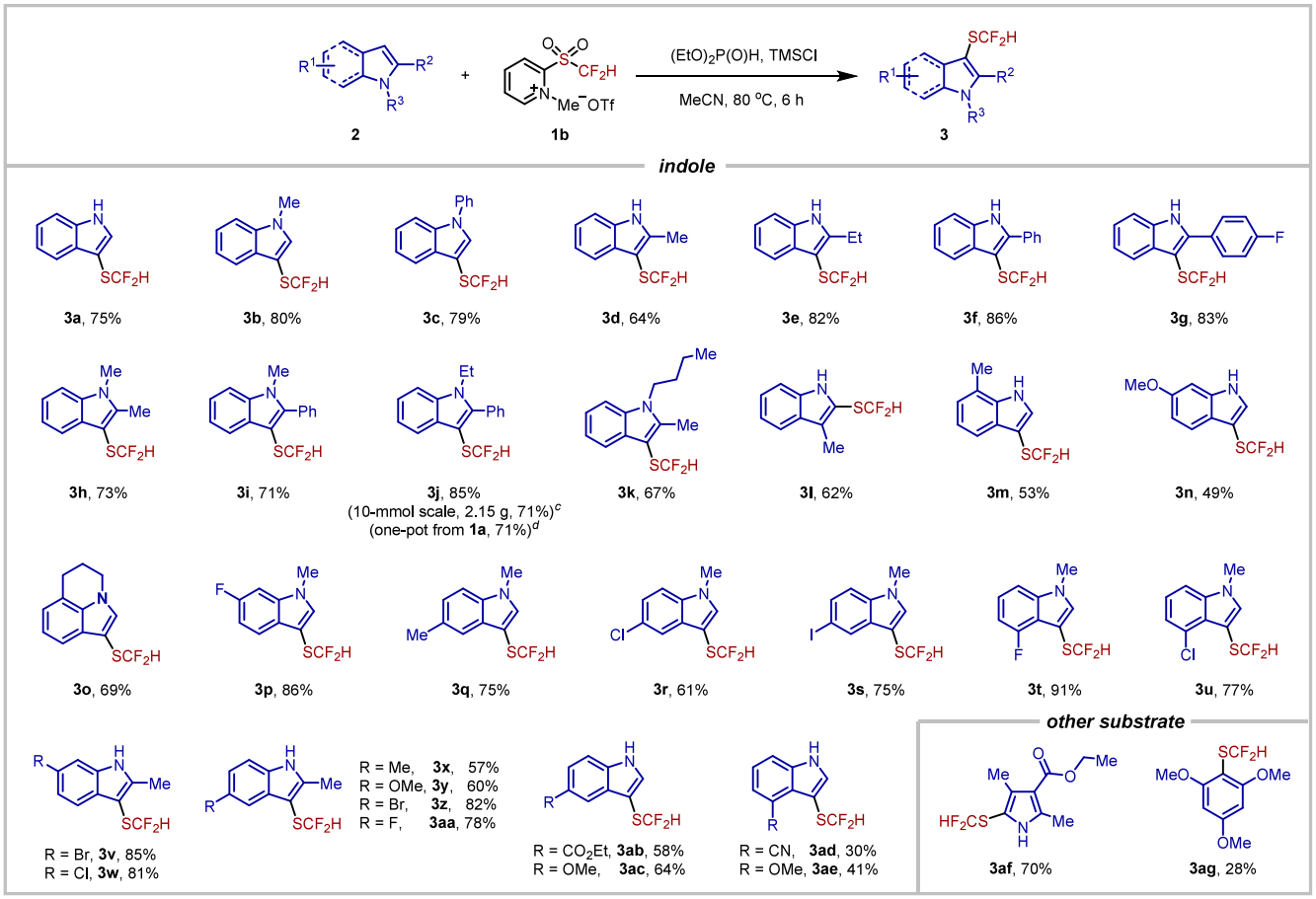
Scheme 3. Substrate Scope[a,b]



[a]Reaction conditions: **2** (0.5 mmol, 1.0 equiv), **1b** (1.0 mmol, 2.0 equiv), $(EtO)_2P(O)H$ (2.0 mmol, 4.0 equiv), TMSCl (2.0 mmol, 4.0 equiv), MeCN (3.0 mL). [b]Isolated yield. [c]18 h. [d]*N*-activation of **1a**, followed by difluoromethylthiolation, in a one-pot process.

62% yield (**3l**). Furthermore, our results indicate that both strong electron-donating and strong electron-withdrawing groups on the benzene ring of NH-indoles reduce the yield of the corresponding difluoromethylthiolation products (**3ab**-**3ae** Vs **3a**), with electron-withdrawing groups causing a more pronounced decrease (**3ab**, **3ad**). Similarly, a substituted pyrrole also underwent difluoromethylthiolation smoothly, affording the corresponding product in 70% yield (**3af**). The electron-rich arene 1,3,5-trimethoxybenzene also underwent the reaction, albeit in only 28% yield (**3ag**). Additionally, this method was successfully applied to a gram-scale reaction (**3j**).

To gain insights into the mechanism of the current difluoromethylthiolation reaction with sulfone **1b** in the presence of $(EtO)_2P(O)H$ and TMSCl, a series of experiments were conducted to elucidate the possible pathways. Initially, we monitored the reaction progress using ^{19}F NMR analysis with fuoroindole **2aa** as the substrate (Scheme 4; see the Supporting Information for details). Two key intermediates, **A** and **B**, were identified. At first, **1b** was rapidly consumed, forming intermediate **A** (Scheme 4, a and b), which then reacted quickly with **2aa** to generate intermediate **B**, accompanied by the formation of side intermediate **C** (Scheme 4, b and c). Intermediate **B** was slowly converted to the desired product **3aa** (Scheme 4, b-f), while intermediate **C** gradually transformed into side-product $(EtO)_2P(O)SCF_2H$ (**4**). During this process, fluorine substitution on the indole ring was beneficial for identifying **B** as the key intermediate.

To further investigate the reaction pathways and elucidate the structures of the key intermediates, we conducted some control experiments (Scheme 5A). It was found that the reaction between **1b** and TMSCl, in the absence of other reactants, rapidly produced intermediate **A**. Since a separate reaction between HCF_2SO_2Na and TMSCl also yielded **A**, we assigned its structure as HCF_2SO_2TMS (**5**). Additionally, *N*-methyl-2-chloropyridinium salt (**6**) was detected as a by-product of the reaction between **1b** and TMSCl. To determine the structure of intermediate **B**, the reaction was quenched before completion. The isolated intermediate **B** was characterized as sulfoxide **7aa**. Further control experiments using isolated **7aa** showed that both $(EtO)_2P(O)H$ and TMSCl were essential for the reduction of the sulfoxide intermediate to the corresponding sulfide, **3aa**. Besides, according to the ^{19}F NMR data and the mass balance of the transformation of **5**, intermediate **C** was assigned as HCF_2SO_2H (**8**).

Based on the experimental results and previous reports, a plausible reaction mechanism for the difluoromethylthiolation of indoles with the activated sulfone reagent **1b** and $(EtO)_2P(O)H$/TMSCl is proposed in Scheme 5B. Initially, sulfone **1b** reacts with TMSCl rapidly to generate the trimethylsilyl ester, HCF_2SO_2TMS (**5**), and the heteroaromatic chlorination product, *N*-methyl-2-chloropyridinium salt **6**, most probably proceeding via chloride ion catalysis. Subsequently, HCF_2SO_2TMS (**5**), acting as an electrophilic sulfinylating agent, undergoes a quick reaction with indole **2** to

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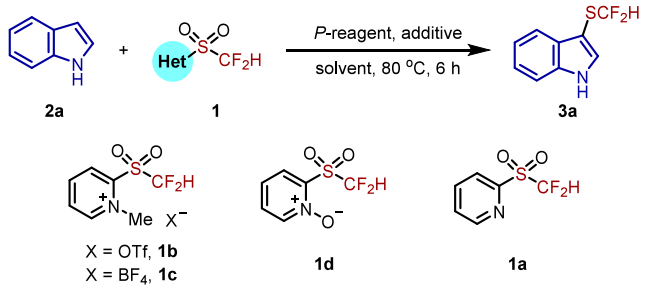
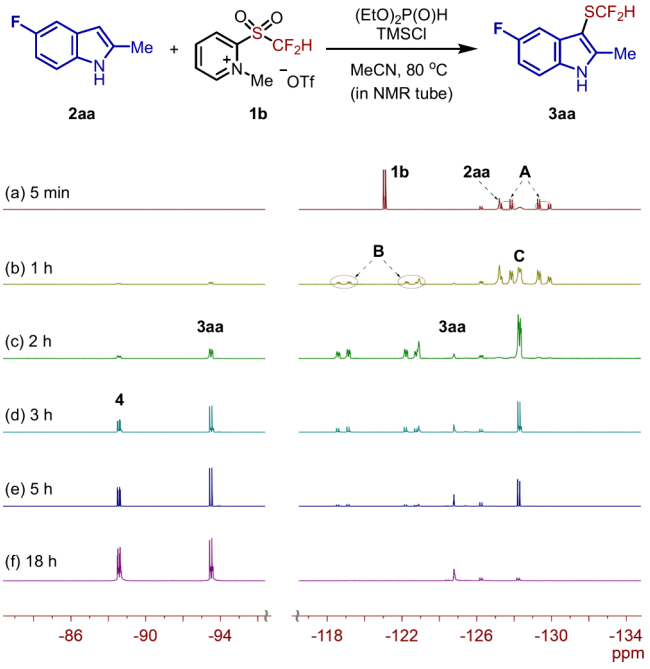
Table 1. Optimization of the Reaction Conditions[a]



entry	1	*P*-reagent	additive	solvent	yield, 3a (%)
1	**1b**	$(EtO)_2P(O)H$	TMSCl	MeCN	93
2	**1c**	$(EtO)_2P(O)H$	TMSCl	MeCN	92
3	**1d**	$(EtO)_2P(O)H$	TMSCl	MeCN	78
4	**1a**	$(EtO)_2P(O)H$	TMSCl	MeCN	0
5	**1b**	$(EtO)_2P(O)H$	-	MeCN	0
6	**1b**	$(MeO)_2P(O)H$	TMSCl	MeCN	73
7	**1b**	Ph_3P	TMSCl	MeCN	74
8	**1b**	-	TMSCl	MeCN	0
9	**1b**	$(EtO)_2P(O)H$	nBu_4NCl	MeCN	64
10	**1b**	Ph_2PCl	-	MeCN	69
11	**1b**	$(EtO)_2P(O)H$	TMSCl	THF	33
12	**1b**	$(EtO)_2P(O)H$	TMSCl	DMF	50
13	**1b**	$(EtO)_2P(O)H$	TMSCl	toluene	84
14[c]	**1b**	$(EtO)_2P(O)H$	TMSCl	MeCN	80
15[d]	**1b**	$(EtO)_2P(O)H$	TMSCl	MeCN	57
16[e]	**1b**	$(EtO)_2P(O)H$	TMSCl	MeCN	84

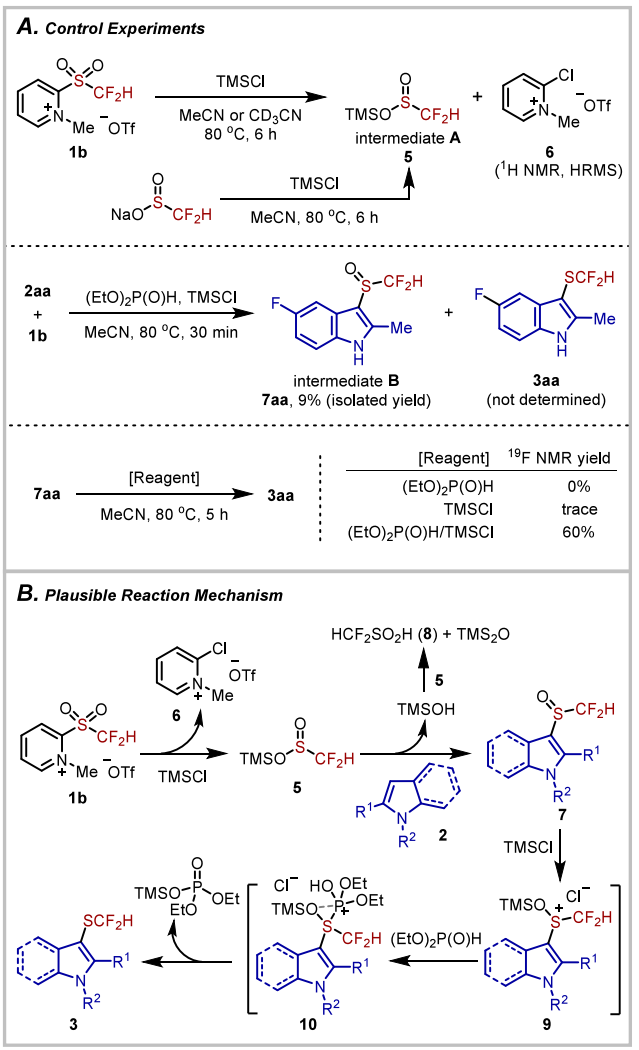
[a]Reaction conditions: **2a** (0.3 mmol, 1.0 equiv), **1** (0.6 mmol, 2.0 equiv), *P*-reagent (1.2 mmol, 4.0 equiv), additive (1.2 mmol, 4.0 equiv), solvent (2.0 mL). [b]Yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [c]60 °C. [d]40 °C. [e]**1b** (0.45 mmol, 1.5 equiv), $(EtO)_2P(O)H$ (0.9 mmol, 3.0 equiv), TMSCl (0.9 mmol, 3.0 equiv).

Scheme 4. ^{19}F NMR Monitoring of the Reaction



form difluoromethyl sulfoxide **7**, with TMSOH released as a byproduct. Finally, by activation with TMSCl, sulfoxide **7** undergoes deoxygenation by $(EtO)_2P(O)H$, yielding difluoromethyl sulfide **3**.[30] During the reaction, the byproduct TMSOH readily reacts with **5** to generate hexamethyldisiloxane (TMS_2O) and HCF_2SO_2H (**8**). HCF_2SO_2H (**8**), which is less reactive toward indole **2**, gradually reacts with excess $(EtO)_2P(O)H$ to form $(EtO)_2P(O)SCF_2H$ (**4**) (for details, see the Supporting Information).

Scheme 5. Mechanism Consideration



In summary, we have developed a novel approach for electrophilic difluoromethylthiolation using the cost-effective and readily available 2-$PySO_2CF_2H$. This strategy involves N-activation of the pyridine ring, forming pyridinium salt or pyridine N-oxide derivatives that serve as bench-stable reagents. The method enables the introduction of the SCF_2H group into electron-rich heteroarenes, such as indoles and pyrroles, in the presence of $(EtO)_2P(O)H$/TMSCl. Mechanistic studies suggest that the reaction proceeds via TMSCl-promoted formation of a difluoromethyl sulfoxide followed by its deoxygenation, a previously undisclosed major pathway in prior $(EtO)_2P(O)H$/TMSCl-mediated difluoromethylthiolation reactions.[17,13b] Ongoing research is focused on further exploring the synthetic potential of *N*-activation derivatives of 2-$PySO_2CF_2H$.

https://doi.org/10.1021/acs.orglett.5c01431
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■ 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.5c01431.

Experimental procedures, ^{1}H, ^{19}F, and ^{13}C NMR characterization data, cyclic voltammetry studies, mechanistic studies, copies of NMR spectra, associated references (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 22261132514 and 22271299), the Strategic Priority Research Program of the Chinese Academy of Sciences (No. XDB0590000), the Natural Science Foundation of Shandong Province (No. ZR2023LFG003), and the Shandong Dongyue Polymer Materials Co., Ltd.

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https://doi.org/10.1021/acs.orglett.5c01431
Org. Lett. XXXX, XXX, XXX−XXX