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Transition-Metal-Free Electrophilic Fluoroalkanesulfinylation of Electron-Rich (Het)Arenes with Fluoroalkyl Heteroaryl Sulfones via C(Het)–S and S=O Bond Cleavage

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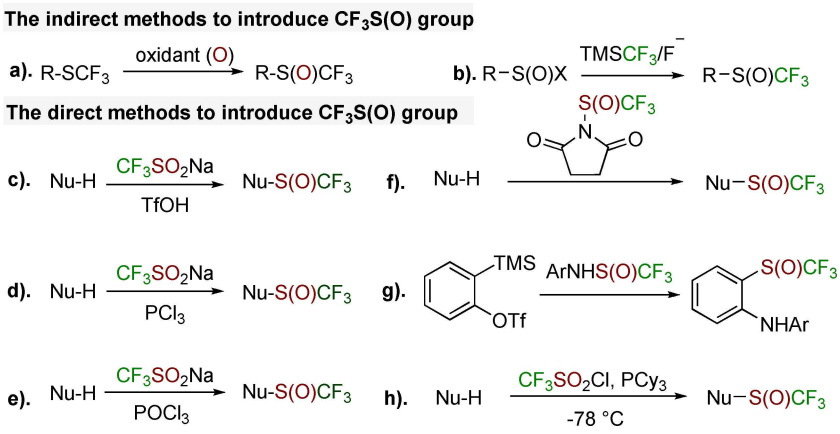
Abstract: A novel $Ph_2P(O)Cl$-mediated direct fluoroalkanesulfinylation of electron-rich (het)arenes using fluoroalkyl heteroaryl sulfones as the R_fSO source ($R_f = C_4F_9$, CF_2Cl, CF_2Br, and CF_2COOEt) was developed. This is the first example where 2-$HetSO_2R_f$ performs as the R_fSO synthon in organic synthesis via both C(Het)–S and S=O bond cleavage.

Keywords: fluoroalkanesulfinylation; fluoroalkyl heteroaryl sulfones

In recent years, the introduction of fluoroalkyl groups into molecules has been of growing interest due to their high lipophilicity and electron-withdrawing character.[1] Sulfoxide, an oxidized form of thioether, also plays a significant role in organic synthesis[2] and medicinal chemistry.[3] In this context, fluoroalkyl sulfoxides have become a subject of special interest owing to the combination of two chemical moieties. In terms of electron-withdrawing character, $CF_3S(O)$ has a much higher Hammett substituent constant than the SCF_3 and the CF_3 group,[4] and the enhancement of biological activity has also been found in some $CF_3S(O)$-containing compounds, such as the insecticide fipronil and its analogues.[5] Furthermore, the "intermediate valence" character of the $CF_3S(O)$ group enables it to prepare other fluorinated moieties, such as trifluoromethylsulfoximine $CF_3SO(NH)$,[6] trifluoromethylsulfone CF_3SO_2, trifluoromethylthio CF_3S, and so on.

The traditional methods for the construction of $CF_3S(O)$ moiety involve the monooxidation of CF_3S (Scheme 1a)[7] and the nucleophilic trifluoromethylation of sulfinyl halides or sulfinic esters with $TMSCF_3$ (Scheme 1b).[8] Compared with these indirect methods, the direct method to introduce $CF_3S(O)$ group into molecule is more attractive. However, traditional direct methods need the use of trifluoromethanesulfinyl halides $CF_3S(O)X$ (X = F, Cl), which suffers from high toxicity, volatility and poor stability.[9] Therefore, a new, easily accessible, scalable and shelf-stable trifluoromethanesulfinylation reagent is highly desirable. In previous years, a few direct methods have been reported using Langlois reagent CF_3SO_2Na in the presence of TfOH,[10] PCl_3[11] or $POCl_3$[12] (Scheme 1c–e). In 2003, 1-(trifluoromethanesulfinyl)-pyrrolidine-2,5-dione was also developed as a direct trifluoromethanesulfinylation reagent by Bertrand's group (Scheme 1f).[9b] Two years later, Larock's group reported an intermolecular S–N addition of trifluoromethanesulfinamides to arynes for the preparation of *ortho*- trifluoromethanesulfinyl anilines (Scheme 1g).[13] Recently, Cahard's group reported the direct trifluoromethanesulfinylation of hereroarenes using the CF_3SO_2Cl/PCy_3 (Cy = cyclohexyl) system at low temperature (−78 °C) (Scheme 1h).[14]

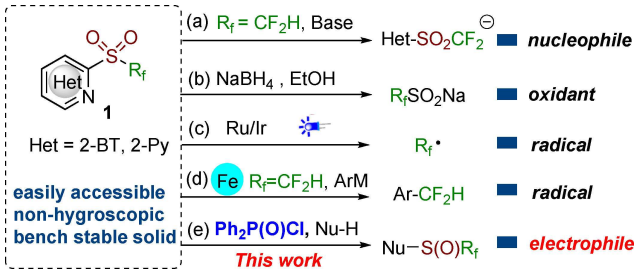
Fluoroalkyl heteroaryl sulfones **1** are easy to prepare, bench-stable and non-hygroscopic solid, allowing for widespread use in the pharmaceutical and fluorine chemical fields.[15] Previously, 2-$PySO_2CF_2H$



Scheme 1. Previous work of trifluoromethanesulfinylation.

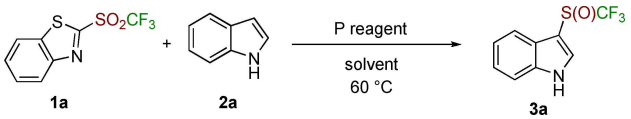
(Hu reagent) was employed as a robust *gem*-difluoroolefination and formal nucleophilic halodifluoromethylation reagent (Scheme 2a),[16] and 2-BTSO$_2$R$_f$ have been used as fluoroalkanesulfinate precursors (Scheme 2b).[17] Hu's group also reported the visible light mediated radical fluoroalkylation of isocyanides with 2-BTSO$_2$R$_f$ (Scheme 2c).[18] In addition, the iron-catalyzed difluoromethylation of ArM (M = Mg, Zn) with 2-PySO$_2$CF$_2$H was disclosed more recently (Scheme 2d).[19] However, despite great advances in nucleophilic and radical fluoroalkylation with fluoroalkyl heteroaryl sulfones **1**, while to the best of our knowledge, compound **1** as electrophile has not yet been reported. Consistent with our ongoing research on this field, we herein report an efficient method for the direct electrophilic fluoroalkanesulfinylation of electron-rich (het)arenes with 2-BTSO$_2$R$_f$ (R$_f$ = C$_4$F$_9$, CF$_2$Cl, CF$_2$Br, and CF$_2$COOEt) (Scheme 2e).

Our initial attempt began by employing compound indole **2a** as the model substrate with 2-BTSO$_2$CF$_3$ **1a** and Ph$_2$PCl/TMSCl in MeCN (1.0 mL) at 60 °C under a N$_2$ atmosphere.[20] Gratifyingly, the desired trifluoromethanesulfinylation product **3a** was isolated in 55% yield after 1 h (Table 1, entry 1). Further solvent screening proved that MeCN was more favorable than others, including THF, toluene and DCM (Table 1,



Scheme 2. The applications of fluoroalkyl heteroaryl sulfones.

Table 1. Optimization of reaction conditions.[a]



Entry	P reagent	Additive	Solvent	**3a**[b]
1	Ph$_2$PCl	TMSCl	MeCN	55
2	Ph$_2$PCl	TMSCl	THF	17
3	Ph$_2$PCl	TMSCl	toulene	43
4	Ph$_2$PCl	TMSCl	DCM	0
5[c]	Ph$_2$PCl	TMSCl	MeCN	29
6	Ph$_2$PCl	–	MeCN	56
7	(EtO)$_2$P(O)H	–	MeCN	41
8	(EtO)$_2$PCl	–	MeCN	0
9	POCl$_3$	–	MeCN	30
10	**Ph$_2$P(O)Cl**	–	MeCN	94[d]
11	(MeO)$_2$P(O)Cl	–	MeCN	54

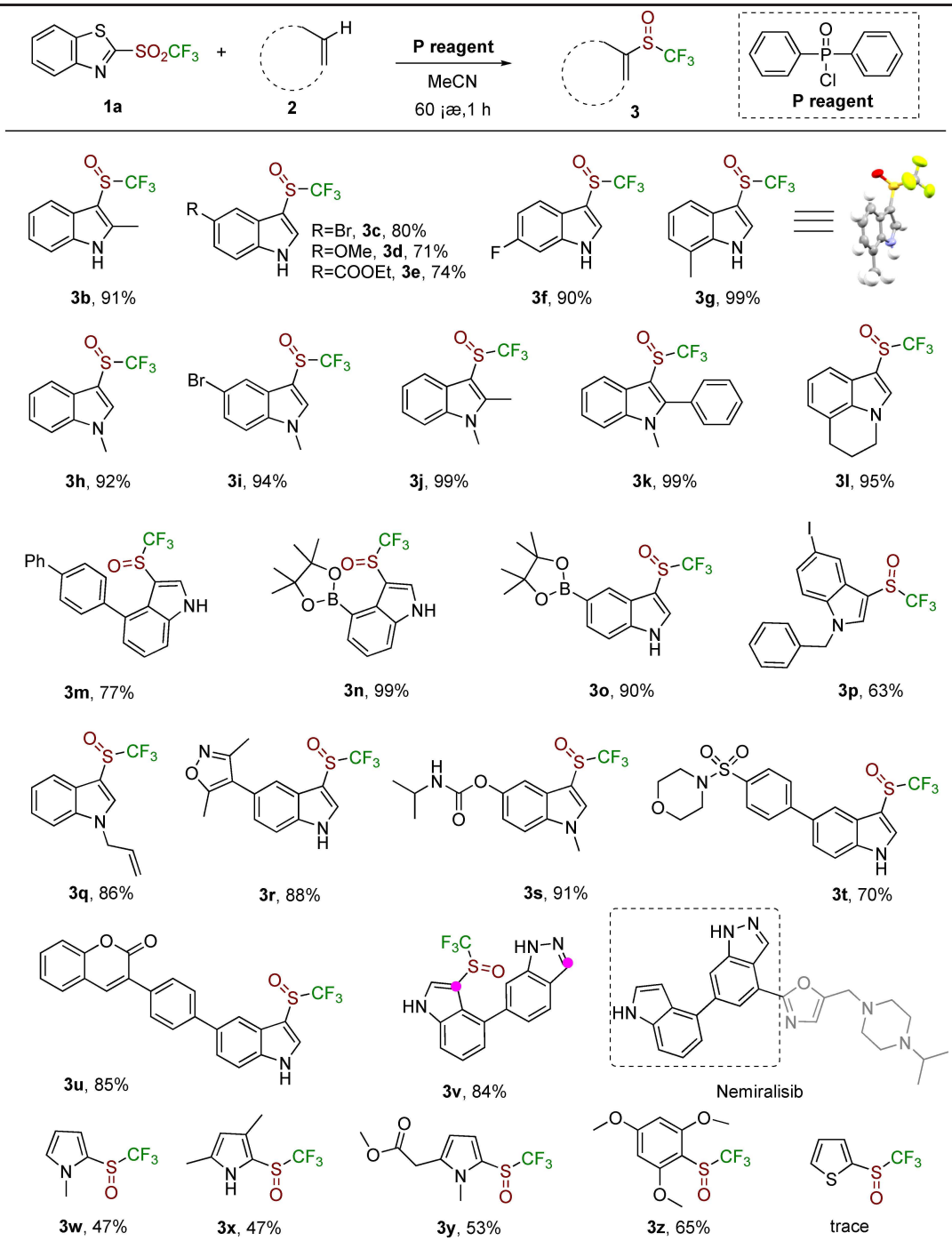
[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.2 mmol, 1.0 equiv.), P reagent (0.2 mmol, 1.0 equiv.), additive (150 mol%), solvent (1 mL), N$_2$, 60 °C, 1 h.
[b] Yields were determined by ^{19}F NMR using PhCF$_3$ as an internal standard.
[c] 90 °C for 1 h.
[d] Isolated yield.

entries 2–4). Elevating the temperature to 90 °C decreased the yield of **3a** to 29% (Table 1, entry 5). The removal of TMSCl did not affect the yield of **3a** obviously, indicating TMSCl was not necessary in this reaction (Table 1, entry 6). Then, several other reducing agents, including (EtO)$_2$P(O)H, (EtO)$_2$PCl, POCl$_3$, Ph$_2$P(O)Cl and (MeO)$_2$P(O)Cl were employed to replace Ph$_2$PCl in this reaction (Table 1, entries 7–11). Among these reagents, Ph$_2$P(O)Cl proved to be the best choice and produced a 94% yield of product **3a**. Therefore, the best result was obtained with a combination of 1.0 equiv. of **1a** and indole with

1.0 equiv. $Ph_2P(O)Cl$ in MeCN at 60 °C for one hour to furnish **3 a** in 94% yield (Table 1, entry 10).

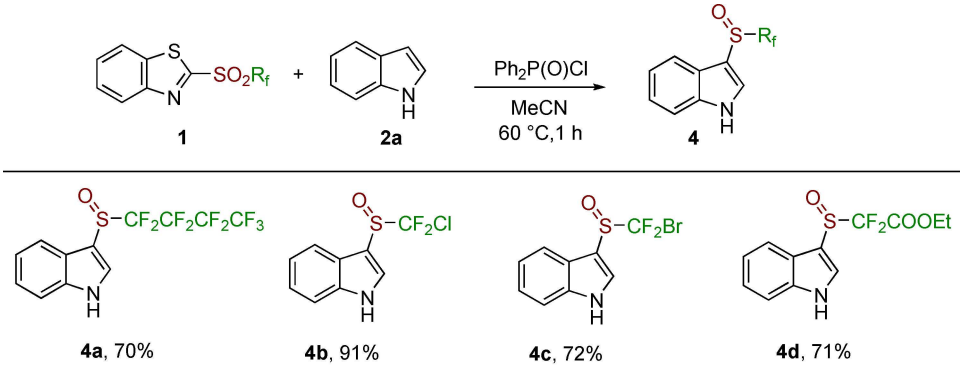
With optimized reaction conditions in hand, we explored the substrate scope with various indole derivatives. The data in Table 2 showed that all these reactions proceeded smoothly and both electron-withdrawing and electron-donating substituted indoles can produce corresponding 3-trifluromethanesulfinyl indoles with good to excellent yields (63–99%), indicating good tolerance of different substituents and positions on indoles. In addition, various functional groups on the indole ring demonstrate good compati-

Table 2. Trifluoromethanesulfinylation of electron-rich (het)arenes.[a]



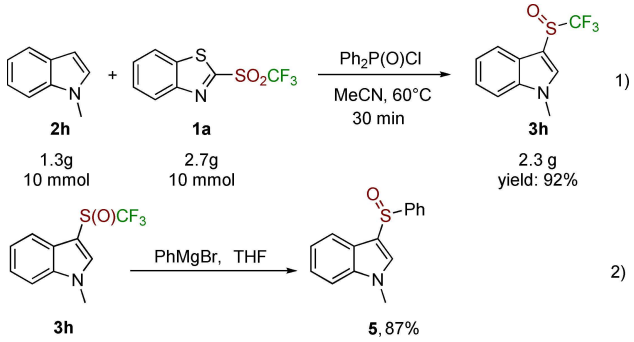
[a] Reaction conditions: **1 a** (1.0 mmol, 1.0 equiv.), **2** (1.0 mmol, 1.0 equiv.), $Ph_2P(O)Cl$ (1.0 mmol, 1.0 equiv.), MeCN (5 mL), N_2, 60 °C for 1 h. Isolated yields.

Table 3. Fluoroalkanesulfinylation of indole.[a]



[a] Reaction conditions: **1** (1.0 mmol, 1.0 equiv.), **2a** (1.0 mmol, 1.0 equiv.), $Ph_2P(O)Cl$ (1.0 mmol, 1.0 equiv.), MeCN (5 mL), N_2, 60 °C for 1 h. Isolated yields.

bility, including phenyl **2k**, biphenyl **2m**, borate **2n** and **2o**, benzyl **2p**, alkenyl **2q**, antipyrine **2r**, carbamate **2s**, sulfonamide **2t** and chromene **2u**, with good to excellent yields of corresponding indole derivatives **3k**–**3u**. Notably, the reaction of **1a** with 6-(1*H*-indol-4-yl)-1*H*-indazole **2v**, the active scaffold of selective PI3 K δ inhibitor Nemiralisib,[21] showed excellent selectivity for indole over indazole to achieve 84% yield of **3v** under the standard conditions. To further expand the substrate scope of the trifluoromethanesulfinylation reaction, other electron-rich arenes including 1-methyl-1*H*-pyrrole **2w**, 2,4-dimethyl-1*H*-pyrrole **2x**, methyl 2-(1-methyl-1*H*-pyrrol-2-yl)acetate **2y**, 1,3,5-trimethoxybenzene **2z**, and thiophene were tested. As expected, reactions with substituted pyrroles and 1,3,5-trimethoxy benzene can produce the corresponding trifluoromethanesulfinylated products **3w**–**3z** in moderate to good yields, while thiophene only gave a trace amount of product. However, β-keto esters, oxindoles, and 3-methylindole were not suitable substrates in this reaction (see the SI). In addition, the structure of **3g** was confirmed by single crystal X-ray analysis (see the SI).[22]

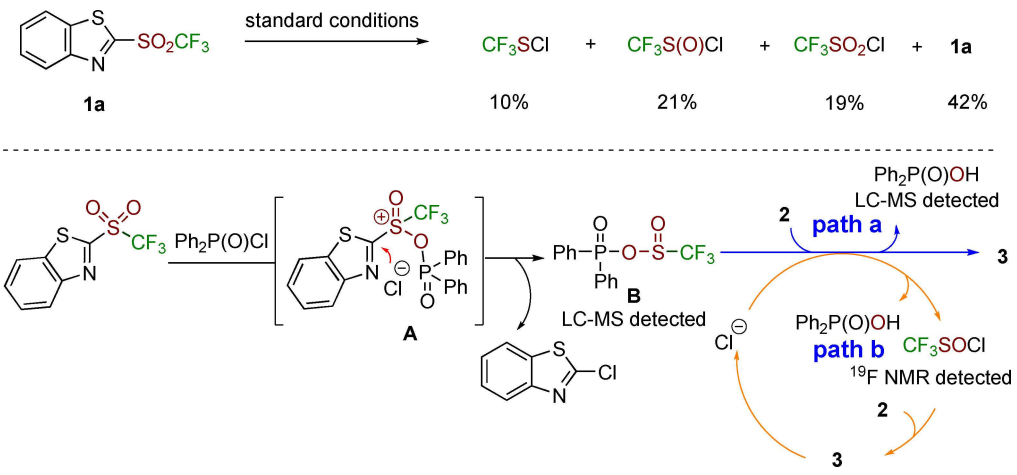


Scheme 3. The synthetic application of reaction.

Then, other fluoroalkyl heteroaryl sulfones (2-$BTSO_2R_f$) with different R_f groups were used for this transformation. The corresponding products **4a**–**d**, which bearing $C_4F_9S(O)$, $BrCF_2S(O)$, $ClCF_2S(O)$ and $EtOOCCF_2S(O)$ groups were obtained in good to excellent yields under standard conditions (70–91%, Table 3).

To further demonstrate the synthetic application of this protocol, a gram-scale synthesis was conducted (Scheme 3, eq 1). When 10 mmol of 1-methyl-1*H*-indole **2h** was reacted with 10 mmol of **1a**, the product **3h** can be obtained with excellent yield of 92%. In addition, since the CF_3 group can be readily substituted by a nucleophile,[23] and the trifluoromethanesulfinylation can serve as an effective approach to introduce a sulfoxide S(O) group. For example, the nucleophilic reaction of PhMgBr with **3h** gave the corresponding sulfoxide **5** in excellent yield (Scheme 3, eq 2).

We then turned our attention on the mechanistic features of this reaction. Simply heating 2-$BTSO_2CF_3$ **1a** and $Ph_2P(O)Cl$ in acetonitrile at 60 °C for 1 h gave CF_3SOCl (21%, δ =--−77.32 ppm), CF_3SO_2Cl (19%, δ = −76.13 ppm) and CF_3SCl (10%, δ = −46.56 ppm), respectively, which were detected by ^{19}F NMR spectroscopic analysis (Scheme 4). According to previous report that CF_3SOCl can convert to CF_3SCl and CF_3SO_2Cl by self-disproportionation,[24] this result indicates that CF_3SOCl may be an intermediate in this reaction. Furthermore, the formation of CF_3SOCl is also supported by the on line ^{19}F NMR analysis (see the Supporting Figure 2). On the base of the above-mentioned experiments and literature reports,[20,25] a plausible mechanism for this reaction was proposed as follow (Scheme 4). First, the oxygen of 2-$BTSO_2CF_3$ attacks the phosphorus center of $Ph_2P(O)Cl$ to get intermediate **A**, which was converted to $Ph_2P(O)OS(O)CF_3$ **B** (detected by LCMS; see SI, Supporting Figure 3) through the elimination of 2-chloro-benzothiazole. Then, indole reacts directly with $Ph_2P(O)OS(O)$



Scheme 4. Preliminary mechanistic study and proposed mechanism.

CF_3 **B** via electrophilic trifluoromethanesulfinylation process to generate product **3** (path a). Meanwhile, the $Ph_2P(O)OS(O)CF_3$ **B** can be nucleophilic attacked by chloride anion to get a reactive species CF_3SOCl, which reacts with indole to afford the target product (path b).

In conclusion, we have developed an unprecedented application of fluoroalkyl heteroaryl sulfones as efficient electrophilic $R_fS(O)$ sources. Under mild conditions, a range of substituted electron-rich (het) arenes can be converted smoothly into $CF_3S(O)$ decorated products with these reagents in good to excellent yields. Considering the readily available reagents and mild conditions (see the SI, Supporting Table 1), the described protocol promises more applications in medicinal chemistry and related fields.

Experimental Section

General Procedure for Fluoroalkanesulfinylation of Electron-Rich (Het)Arenes (3 a–3 z, 4 a–4 d)

A mixture of fluoroalkyl heteroaryl sulfone **1** (1.0 mmol, 1.0 equiv.) and (het)arene (1.0 mmol, 1.0 equiv.) were added to a dry Schlenk tube. The tube was evacuated and backfilled with pure N_2 for 3 times. Then, $Ph_2P(O)Cl$ (212 μL, 1.0 mmol, 1.0 equiv.) and dry MeCN (5.0 mL) were added with syringe under N_2 atmosphere. Then the mixture was stirred at 60 °C for 1 h. After the reaction was complete, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel by using a mixture of petroleum ether/EtOAc as an eluent to provide the desired products **3** or **4**.

Acknowledgements

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