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Nucleophilic (Phenylsulfonyl/arylthio)difluoromethylation of Aldehydes with $TMSCF_2Br$: A Three-Component Strategy

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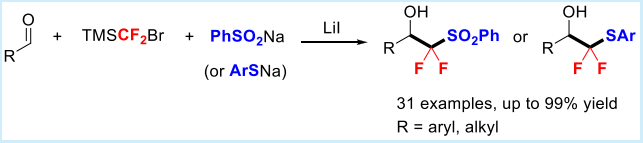
Supporting Information

ABSTRACT: An efficient method for nucleophilic (phenylsulfonyl/arylthio)difluoromethylation of aldehydes with $TMSCF_2Br$ was developed. The reaction proceeds through in situ generation of difluorocarbene, which is captured by $PhSO_2Na$ or ArSNa to form the corresponding $PhSO_2CF_2^-$ or $PhSCF_2^-$ anions, followed by nucleophilic addition to aldehydes to give the desired difluoromethylated products.



Because of the unique physicochemical and biological properties of lightly fluorinated organic compounds, the selective incorporation of fluorine atom(s) or fluorine-containing groups into organic molecules have attracted great attention in life science- and material science-related realms.[1] Among various fluorinated moieties, difluoromethylene (CF_2) group is of particular interest, because it is known to be isosteric to ethereal oxygen atom.[2] On the other hand, sulfur-containing fluoroalkyl groups have attracted much attention in recent years, because the introduction of sulfur-containing functionalities can further change the properties of the molecules;[3] therefore, many bioactive compounds contain fluoroalkylthio or fluoroalkylsulfonyl moieties. For example, compound **A** is a PDE4 (phosphodiesterase-4) inhibitor,[4] and compound (−)-**B** shows potent antifungal activity against *Candida albicans* in vivo for both oral and intravenous administrations[5] (see Figure 1).

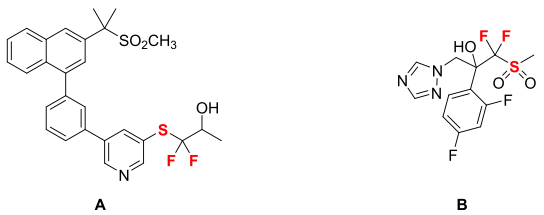


Figure 1. Bioactive compounds containing $-SCF_2-$ fragments.

Because of the importance of $-SCF_2-$ fragments, many methods have been developed to incorporate them into organic molecules,[6] but these methods are mainly dependent on the use of $PhSO_2CF_2X$ or $PhSCF_2X$ (X = H, TMS, Br, I) reagents. As a result, one end of the S atom is fixed to phenyl group, which is difficult to change to other groups. To meet the demand of pharmaceutical development, an efficient method to introduce the $-SCF_2-$ group that can easily tune the structure of two ends of the $-SCF_2-$ group is highly desired.

Difluorocarbene is an ideal reaction intermediate to incorporate CF_2 into organic molecules. Although many difluorocarbene reagents have been developed thus far, most of these reagents were focused on (1) the [2 + 1] cycloaddition reactions with alkenes and alkynes, (2) difluorocarbene insertion into Y−H (Y = heteroatoms) bonds to achieve the introduction of CF_2H functionality, and (3) transformation of carbonyls into difluoromethylidene ($=CF_2$).[7] However, using difluorocarbene to achieve CF_2 incorporation in multicomponent cascade reaction has not attracted much attention; only some examples have been reported by the Dilman group with limited nucleophiles.[8] Therefore, it is highly desirable to use difluorocarbene as an efficient synthetic intermediate for CF_2 incorporation into various types of molecules.

Our group has been focusing on sulfur-based fluoroalkylation chemistry and difluorocarbene chemistry.[6c,d,7e,9] In the past decade, tremendous efforts have been made in the development of new (phenylsulfonyl/phenylthio)-difluoromethylation reagents and reactions.[6] Among these reactions, nucleophilic addition of $PhSO_2CF_2^-$ or $PhSCF_2^-$ anion to carbonyl compounds (such as aldehydes) is an important way to synthesize α-difluorocarbinols (see Scheme 1a). To achieve the valuable $-SCF_2-$ group introduction with two tunable ends, we envisioned that difluorocarbene could be used to accomplish the (arylsulfonyl/arylthio)-difluoromethylation reaction if a proper S-nucleophile is used to capture the in situ formed difluorocarbene to form the corresponding difluorocarbanion, which could then attack an electrophile. Herein, we report our new strategy to achieve

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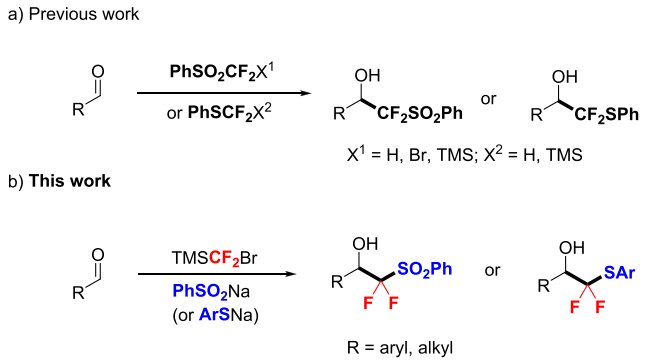
Scheme 1. Different Strategies for (Phenylsulfonyl/phenylthio)difluoromethylation of Aldehydes: (a) Previous Work and (b) This Work



(phenylsulfonyl/arylthio)difluoro- methylation of aldehydes using difluorocarbene as the CF_2 source (see Scheme 1b).

Our work started with using 2-naphthaldehyde **1a** as the model substrate, $PhSO_2Na$ as the nucleophile, and $TMSCF_2Br$, a versatile difluorocarbene reagent developed by us that can generate difluorocarbene under various mild conditions,[8k,p,9k,10] as the CF_2 source. In the initial studies, we tried to use a catalytic amount of *n*-Bu_4NBr to initiate the generation of difluorocarbene at 100 °C. Although $TMSCF_2Br$ was completely consumed, only a trace amount of the desired product **2a** was detected (see Table 1, entries 1−3). We reasoned that the aldehyde might be not sufficiently electrophilic, and adding a metal salt as a Lewis acid to activate the carbonyl group might be helpful to the reaction. Gratifyingly, when LiBr was used instead of *n*-Bu_4NBr, **2a** was formed in 13% yield (Table 1, entry 4). When the reaction proceeded at room temperature, a significant improvement of reaction efficiency was observed, with **2a** being formed in 49% yield, together with 28% yield of protonation product **4** (Table 1, entry 5). The higher efficiency might attribute to the higher stability of the in-situ-formed $PhSO_2CF_2^-$ anion at room temperature than that observed at 100 °C. Screening of the equivalent of LiBr showed that a substoichiometric amount of the LiBr was sufficient to promote the reaction, with 0.7 equiv of LiBr giving the best results (Table 1, entries 5−7). When the reaction proceeded at 0 °C for 2 h, moderate yield was obtained, but the conversion of $TMSCF_2Br$ was only 90%, and a new byproduct $PhSO_2CF_2TMS$ was observed in 20% yield (Table 1, entry 8). Prolonged reaction time could achieve complete conversion of $TMSCF_2Br$, and the yield of **2a** was increased to 83% (Table 1, entries 9 and 10). Using other Lewis acids showed that LiI could increase the yield to some extent, while $MgCl_2$ was inferior to that of LiBr (Table 1, entries 11−13). Because of the fact that the byproduct $PhSO_2CF_2TMS$ was observed when the reaction was conducted at 0 °C, while this byproduct was not observed at or above room temperature, we envisioned that if we could transform this byproduct to the desired product, the reaction efficiency could be further improved. When we performed the reaction at 0 °C for 2 h and then raised the temperature to room temperature to react for additional 6 h, the yield was finally increased to 96% (see Table 1, entries 14 and 15).

With the optimal conditions (Table 1, entry 15) in hand, the substrates scope of this difluorocarbene-involved cascade reaction was explored. The results are shown in Scheme 2. Aromatic aldehydes bearing electron-withdrawing groups and

Table 1. Optimization of Reaction Conditions[a]

entry	Lewis acid, LA	temperature, T (°C)	reaction time, t (h)	**2a**[b] (%)	$PhSO_2CF_2H$ **4** (%)	$PhSO_2CF_2TMS$ **5** (%)
1[c,d]	–	100	2	trace	trace	n.d.
2[c,e]	–	100	2	trace	trace	n.d.
3[c]	–	100	2	trace	trace	n.d.
4	LiBr[f]	100	2	13	6	n.d.
5	LiBr[f]	rt	2	49	28	n.d.
6	LiBr	rt	2	59	21	n.d.
7	LiBr[g]	rt	2	35	14	n.d.
8	LiBr	0	2	50 (90)	19	20
9	LiBr	0	4	73 (92)	15	17
10	LiBr	0	8	83	13	8
11	LiCl	0	8	83	21	13
12	LiI	0	8	87	17	3
13	$MgCl_2$	0	8	19	9	n.d.
14[h]	LiI	0	2	84	6	22
15[i]	LiI	0	2	96	5	6

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), $TMSCF_2Br$ (2.0 equiv), LA (0.7 equiv), THF (1 mL). Yields were determined by ^{19}F NMR spectroscopy, using $PhOCF_3$ as an internal standard. n.d.= not detected. [b]The conversion of $TMSCF_2Br$ is given in the parentheses; if not, the conversion is >99%. [c]0.1 equiv of *n*-Bu_4NBr was used instead of LiBr. [d]$PhCH_3$ was used as the solvent. [e]CH_3CN was used as the solvent. [f]LiBr (1.0 equiv) was used. [g]LiBr (0.5 equiv) was used. [h]After reacted at 0 °C for 2 h, the mixture was slowly warmed to room temperature (rt) and stirred for 2 h. [i]After reacted at 0 °C for 2 h, the mixture was slowly warmed to rt and stirred for 6 h.

electron-donating groups, as well as halogens, are all well compatible under the reaction conditions, giving good yields of the corresponding products (**3a**−**3l**). When cinnamaldehyde was used as the substrate, the desired product **3m** was formed in 70% yield, and no difluorocyclopropane byproduct was observed by ^{19}F NMR spectroscopy. Heteroaromatic aldehydes are also suitable substrates; for example, 5-bromo-2-furaldehyde and 4-bromothiophene-2-carboxaldehyde reacted under the standard reaction conditions could give the corresponding products **3n** and **3o** in 74% and 91% yields, respectively. It is noteworthy that both nonenolizable and enolizable aldehydes exhibited good reactivity, and good to excellent yields of products were obtained (**3p**−**3t**). Unfortunately, under the standard reaction conditions, when 4-bromoacetophenone (a simple ketone) was used as a substrate, no desired (phenylsulfonyl)difluoromethylated carbinol product was formed.

Encouraged by the successful (phenylsulfonyl)-difluoromethylation of aldehydes using $TMSCF_2Br$ as the CF_2 source, we turned our attention to arylthio)-difluoromethylation, which might be achieved by using the same strategy with ArS^- as the nucleophile. After a quick modification of reaction parameters (for details, see the Supporting Information), the best conditions were obtained: 1 equiv of aldehyde **1**, 2 equiv of ArSH, NaH used as the base, LiI as the Lewis acid, and DMF as the solvent; the reaction proceeded at 0 °C for 3 h. A series of aromatic thiols and

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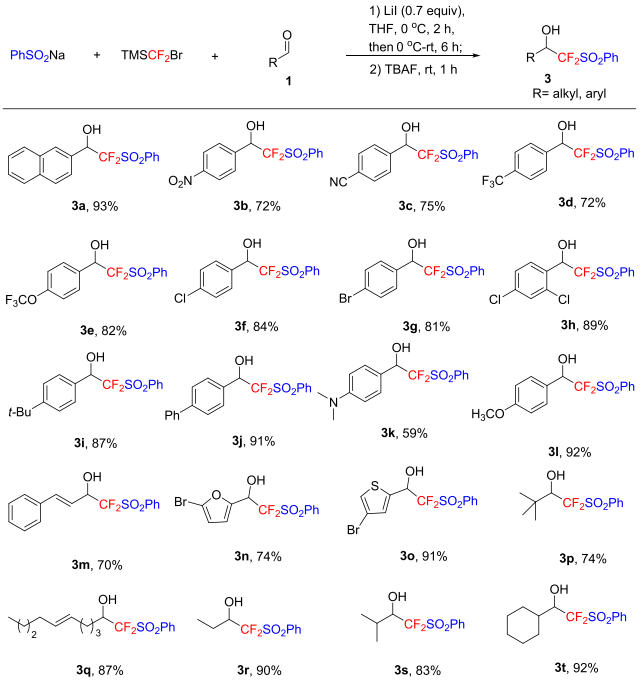
Scheme 2. (Phenylsulfonyl)difluoromethylation of Aldehydes with $TMSCF_2Br$[a]

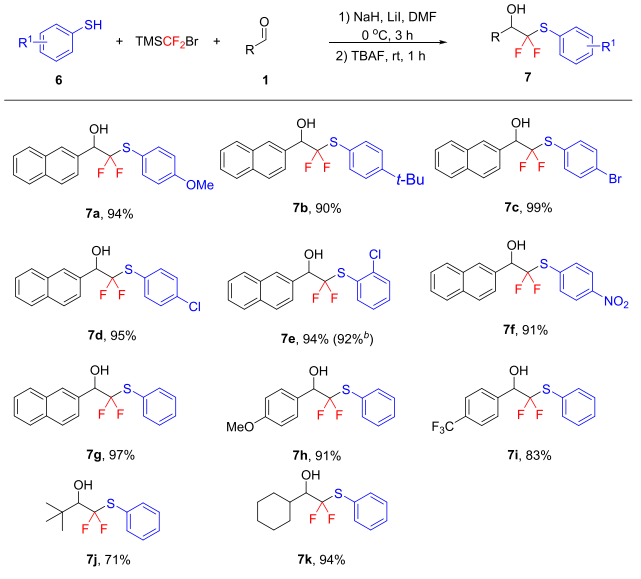


[a]Reaction conditions: **1** (0.4 mmol, 1.0 equiv), $TMSCF_2Br$ (2.0 equiv), $PhSO_2Na$ (3.0 equiv), THF (2 mL), TBAF (2.5 equiv). Yields were isolated yields.

aldehydes could be used to accomplish the desired transformation (see Scheme 3). For aromatic thiols, whether electron-donating or electron-withdrawing groups on the aromatic rings, the desired products could be formed in excellent yields (**7a**–**7f**). The reaction efficiency was also not sensitive to the positions where substituents located on the aromatic rings (**7d** and **7e**). The reaction with **6e** was also performed on a 1 mmol scale, and an excellent yield (92%) of **7e** was still obtained. When PhS^- was used as a nucleophile, different aromatic aldehydes all showed high reactivity (**7g**–**7i**). When nonenolizable aliphatic aldehyde (trimethylacetaldehyde) was used as a substrate, the desired product could be formed in 71% yield (**7j**). Note that, although NaH was used as the base to generate ArS^-, enolizable aldehyde was also compatible to the reaction conditions, and the desired product (**7k**) was formed in 94% yield.

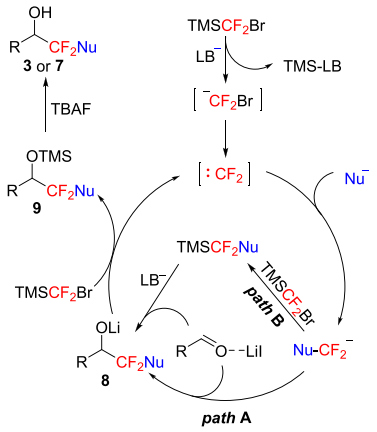
A plausible reaction mechanism is shown in Scheme 4. The activation of $TMSCF_2Br$ by a Lewis base activator (LB^- = $PhSO_2^-$, PhS^-, or **8**) generates CF_2, which is trapped by a nucleophile (Nu^- = $PhSO_2^-$ or PhS^-) to give a difluorinated carbanion, $NuCF_2^-$. This carbanion undergoes nucleophilic addition to the LiI-activated aldehyde, giving the alkoxide **8** (cheme **4**, path A). Alternatively, the reaction between $NuCF_2^-$ and $TMSCF_2Br$ gives $TMSCF_2Nu$, which then reacts with aldehydes (under the activation of a Lewis base activator) to yield **8** (Scheme 4, path B). The reaction of **8** with $TMSCF_2Br$ affords **9**, together with the generation of difluorocarbene. Desilylation of **9** by using TBAF gives the final products **3** or **7**. Path B cannot be ruled out, as $TMSCF_2Nu$ can be observed as a byproduct during the reaction.

Scheme 3. (Arylthio)difluoromethylation of Aldehydes with $TMSCF_2Br$[a]



[a]Reaction conditions: **1** (0.4 mmol, 1.0 equiv), $TMSCF_2Br$ (2.0 equiv), **6** (2.0 equiv), NaH (2.5 equiv), DMF (4 mL), TBAF (2.5 equiv). Yields were isolated yields. [b]Performed on 1 mmol scale of **1**.

Scheme 4. Proposed Mechanism for (Phenylsulfonyl/Arylthio)difluoromethylation of Aldehydes with $TMSCF_2Br$



In conclusion, we have developed a new strategy to accomplish the (phenylsulfonyl/arylthio)difluoromethylation of aldehydes. This three-component protocol allows the rapid introduction of (phenylsulfonyl/arylthio)difluoromethyl groups into aldehydes using commercially available $TMSCF_2Br$ as the CF_2 source, and $PhSO_2^-$ or ArS^- as the nucleophiles, which avoids multistep preparation of $PhSO_2CF_2X$ or $PhSCF_2X$ (X = H, Br, TMS) reagents in advance. Moreover, different arylthio groups could be introduced by simply using different aromatic thiols. The ability of simultaneous change of two ends of the $-SCF_2-$ group shows great potential of this method for rapid construction of various substituted SCF_2-containing analogues, which is beneficial for drug development and late-stage modification of bioactive molecules. Further efforts to explore the synthetic utility of this new strategy are currently ongoing in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03520.

Experimental procedures and characterization data for products (PDF)

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Notes

The authors declare no competing financial interest.

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