

N-Tosyl-S-difluoromethyl-S-phenylsulfoximine: A New Difluoromethylation Reagent for S-, N-, and C-Nucleophiles

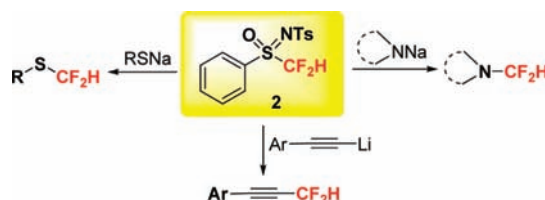
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ABSTRACT



The first α -difluoromethyl sulfoximine compound, **2**, was successfully prepared by using the copper(II)-catalyzed nitrene transfer reaction. Compound **2** was found to be a novel and efficient difluoromethylation reagent for transferring the CF₂H group to S-, N-, and C-nucleophiles. Deuterium-labeling experiments suggest that a difluorocarbene mechanism is involved in the current difluoromethylation reactions.

Selective incorporation of fluorine atom(s) or fluoroalkyl group(s) (such as CF₃, CF₂H, and CH₂F) into organic molecules has become a trend in the life-sciences-related applications.¹ Many studies showed that the fluorine atom(s) or fluoroalkyl group(s) can bring about many beneficial effects in a biologically active molecule, such as the enhancement of metabolic stability, lipophilicity, and bio-availability or an increase of binding affinity, as well as an improvement of membrane permeability through changing the basicity of the drug molecule.² Among the fluoroalkyl groups, the difluoromethyl (CF₂H) group is of particular interest, given the fact that the CF₂H moiety is known to be isosteric and isopolar to a carbinol (CH₂OH) unit and also, as a lipophilic group, can act as a hydrogen donor through

hydrogen bonding.³ Despite the increasing importance of the CF₂H group in medicinal chemistry and drug discovery, and in contrast to trifluoromethylations, mild and efficient difluoromethylation methods are relatively sparse.^{4–6} Compared with both nucleophilic and free radical difluoromethylations,^{4,5} electrophilic difluoromethylation is more challenging regarding the efficiency and generality.⁶ Both S-(difluoromethyl)diarylsulfonium salt^{6a} and a hypervalent iodine(III)-

(1) (a) Bégue, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Weinheim, 2008. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004.

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(3) (a) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2006**, *44*, 5882. (b) Prakash, G. K. S.; Weber, C.; Chacko, S.; Olah, G. A. *Org. Lett.* **2007**, *9*, 1863. (c) Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626.

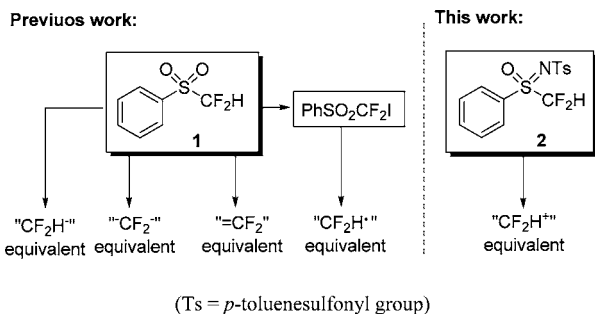
(4) For selected examples of nucleophilic difluoromethylation methods, see: (a) Beier, P.; Alexandrova, A. V.; Zibinsky, M.; Prakash, G. K. S. *Tetrahedron* **2008**, *64*, 10977. (b) Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 786. (c) Li, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2489. (d) Ni, C.; Hu, J. *Tetrahedron Lett.* **2005**, *46*, 8273. (e) Prakash, G. K. S.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 1361. (f) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Org. Lett.* **2004**, *6*, 4315. (g) Yudin, A. K.; Prakash, G. K. S.; Deffieux, D.; Bradley, M.; Bau, R.; Olah, G. A. *J. Am. Chem. Soc.* **1997**, *119*, 1572. (h) Hagiwara, T.; Fuchikami, T. *Synlett* **1995**, 717.

(5) For selected examples of radical difluoromethylation methods, see: (a) Cao, P.; Duan, J.-X.; Chen, Q.-Y. *J. Chem. Soc., Chem. Commun.* **1994**, 737. (b) Li, Y.; Liu, J.; Zhang, L.; Zhu, L.; Hu, J. *J. Org. Chem.* **2007**, *72*, 5824. (c) Li, Y.; Li, H.; Hu, J. *Tetrahedron* **2009**, *65*, 478. (d) Reutrakul, V.; Thongpisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913.

$\text{CF}_2\text{SO}_2\text{Ph}$ compound^{6b} have been reported as direct CF_2H^+ - and $\text{PhSO}_2\text{CF}_2^+$ -transferring reagents, but the scope of their applicability was shown to be limited. There are more reports on the difluorocarbene-based difluoromethylations using reagents such as CHClF_2 , CF_2Br_2 , $\text{FSO}_2\text{CF}_2\text{COOH}$, difluorodiazirine, chlorodifluoromethyl ketones and sulfones, among others.^{6c–g} However, the fact that a large excess of a difluorocarbene precursor is generally required in the reactions makes it highly desirable to develop more efficient difluoromethylation methods.

Previously, we were extensively involved in nucleophilic fluoroalkylations using a series of fluorinated organosulfur reagents.⁷ In particular, difluoromethyl phenyl sulfone ($\text{PhSO}_2\text{CF}_2\text{H}$, **1**) was found to be a versatile nucleophilic difluoromethylation reagent (via its deprotonated form $\text{PhSO}_2\text{CF}_2^-$), thanks to the excellent modulating ability of the phenylsulfonyl group on both the stability and nucleophilicity of the $\text{PhSO}_2\text{CF}_2^-$ anion species (Scheme 1).^{3a,4b,7} $\text{PhSO}_2\text{CF}_2\text{H}$

Scheme 1. Synthetic Applications of Difluoromethylated Sulfone **1** and Sulfoximine **2**



has been successfully used in the organic synthesis as a difluoromethyl anion equivalent (CF_2H^-),^{3a,4b,f,7} a selective difluoromethylene dianion equivalent ($^-\text{CF}_2^-$),⁸ and a difluoromethylidene equivalent ($=\text{CF}_2$).⁹ Furthermore, $\text{PhSO}_2\text{CF}_2\text{H}$ can also be indirectly used in free radical difluoromethylation through a simple conversion to $\text{PhSO}_2\text{CF}_2\text{I}$ (a $\text{CF}_2\text{H}^\bullet$ equivalent).^{5b,c} Despite these “chemical chameleon” behaviors of $\text{PhSO}_2\text{CF}_2\text{H}$ reagent (Scheme 1), the use of $\text{PhSO}_2\text{CF}_2\text{H}$ in efficient electrophilic difluoromethylation (as a CF_2H^+ equivalent) remains a challenging task.¹⁰ We envisioned that this problem may be solved by using a potentially chiral analogue of $\text{PhSO}_2\text{CF}_2\text{H}$, that is,

(6) For selected examples of electrophilic difluoromethylation methods, see: (a) Prakash, G. K. S.; Weber, C.; Chacko, S.; Olah, G. A. *Org. Lett.* **2007**, *9*, 1863. (b) Zhang, W.; Zhu, J.; Hu, J. *Tetrahedron Lett.* **2008**, *49*, 5006. (c) Zheng, J.; Li, Y.; Zhang, L.; Hu, J.; Meuzelaar, G. J.; Federsel, H.-J. *Chem. Commun.* **2007**, 5149. (d) Zhang, L.; Zheng, J.; Hu, J. *J. Org. Chem.* **2006**, *71*, 9845. (e) Langlois, B. R. *J. Fluorine Chem.* **1988**, *41*, 247. (f) Chen, Q.-Y.; Wu, S.-W. *J. Org. Chem.* **1989**, *54*, 3023. (g) Iseki, K.; Asada, D.; Takahashi, M.; Nagai, T.; Kobayashi, T. *Tetrahedron Asymmetry* **1996**, *7*, 1205.

(7) For an account, see: Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921.

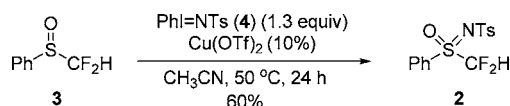
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N-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**2**) (Scheme 1). Sulfoximines have been widely used in organic synthesis, but the fluorinated sulfoximines still remain a relatively poorly studied class of compounds.¹¹ Recently, fluorinated Johnson reagent was developed by Shibata and co-workers for the electrophilic trifluoromethylation of carbon nucleophiles.^{12a} To the best of our knowledge, however, although both *S*-trifluoromethyl and *S*-monofluoromethyl sulfoximes have been known,¹² the *S*-difluoromethyl sulfoximines (such as **2**) have never been reported. Herein, we disclose the preparation of *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**2**) and the use of **2** as a novel “ CF_2H^+ ” equivalent in difluoromethylation of *S*-, *N*-, and *C*-nucleophiles.

Our initial preparation of *S*-difluoromethyl sulfoximine by oxidative imination^{12b,d} of difluoromethyl phenyl sulfoxide (**3**) using hydrazoic acid (generated in situ from NaN_3 and concentrated sulfuric acid or oleum) was not successful. After a careful survey of different methods, we synthesized the first *S*-difluoromethyl sulfoximine compound **2** in 60% yield by the treatment of **3** with 1.3 equiv of $\text{PhI}=\text{NTs}$ (**4**) in the presence of 10 mol % of copper(II) triflate (Scheme 2).

Scheme 2. Preparation of Sulfoximine **2** from Sulfoxide **3**



Compound **2** is a colorless crystalline solid, and its X-ray single crystal structure was characterized by us (see Supporting Information).






















With compound **2** in hand, we were able to explore its reactivity with a series of nucleophiles in detail. Arylthiolates (ArSNa), derived from a facile deprotonation of arylthiols **5** with NaH , were found to readily react with 1.2 equiv of **2** at 60 °C. As shown in Table 1, the difluoromethylation of thiophenol (**5a**) gave difluoromethyl phenyl sulfide **6a** in excellent yield (94%, entry 1), while other arylthiols **5b–f** were difluoromethylated by reagent **2** in satisfactory yields (61–78%, entries 2–6). Even the aliphatic thiol **5g** was also successfully difluoromethylated (entry 7). Interestingly, both *S*- and *N*-difluoromethylated products **6ha** and **6hb** were obtained in the reaction with benzo[*d*]thiazole-2-thiol (**5h**) (entry 8). Furthermore, heteroarylthiol **5i** was also difluoromethylated in 57% yield (entry 9). It is noteworthy that,

(10) Previously, $\text{PhSO}_2\text{CF}_2\text{H}$ has been recognized as a poor electrophilic difluoromethylation agent (via difluorocarbene mechanism), see: (a) Hine, J.; Porter, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 6178. (b) See ref 6c.

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Table 1. Difluoromethylation of *S*-Nucleophiles with **2**

$\text{R-SH} \xrightarrow[2) \text{ 2 (1.2 equiv), 60 }^\circ\text{C, 14 h}]{1) \text{ NaH (1.1 equiv), DMF, rt, 0.5 h}} \text{R-S-CF}_2\text{H}$ <div style="text-align: center;"> 5 6 </div>			
entry	substrate	product	yield (%) ^a
1			94 ^b
2			76
3			61
4			78 ^b
5			61 ^b
6			62
7			57 ^b
8			27
			44
			71
9			57
10 ^c			71

^a Isolated yield. ^b Determined by ¹⁹F NMR spectroscopy using PhCF₃ as internal standard. ^c NaH was not used.





















without an additional base, sodium 4,6-dimethylpyrimidine-2-thiolate (**5j**) was also smoothly difluoromethylated by reagent **2** in 71% yield (entry 10).

Next, we examined the scope of the N-difluoromethylation reaction with reagent **2**. The results are summarized in Table 2. By using similar conditions as for Table 1, a wide range of imidazole derivatives were readily difluoromethylated in moderate to good yields (entries 1–4, 6, 9). It was found that phenyltetrazole (**7e**) and benzotriazole (**7g**) could be difluoromethylated with reagent **2** (entries 5 and 7). When **7h** was subjected to the difluoromethylation with **2**, product **8h** was obtained in low yield (entry 8).

Thereafter, we applied the reagent **2** in the difluoromethylation of phenylacetylene derivatives (Table 3). It showed that lithium acetylides derived from **9a–9e** smoothly reacted with reagent **2** to give the desired C-difluoromethylated products **10a–10e** in moderate to good yields (Table 3). Electrophilic difluoromethylation of acetylene derivatives was generally difficult, and our current methodology with reagent **2** represents a good alternative to the previously known Freon-based approaches.¹³

To gain some insights into the current S-, N-, and C-difluoromethylations with reagent **2**, we carried out several deuterium-labeling experiments (Scheme 3). When sodium phenylthiolate (**5a'**) was treated with **2** in D₂O–DMF at 60 °C for 14 h, both PhSCF₂H (**6a**) and PhSCF₂D (**6a'**) were

Table 2. Difluoromethylation of *N*-Nucleophiles with **2**

$\text{Nucleophile} \xrightarrow[2) \text{ 2 (1.2 equiv), 60 }^\circ\text{C, 14 h}]{1) \text{ NaH (1.1 equiv), DMF, rt, 0.5 h}} \text{Nucleophile-CF}_2\text{H}$ <div style="text-align: center;"> 7 8 </div>			
entry	substrate	product	yield (%) ^a
1			72
2			60
3			61
			
4			45
5			37
			
			70
6			53
7			40
8			26
9			54 ^b






^a Isolated yield. ^b Determined by ¹⁹F NMR spectroscopy using PhCF₃ as internal standard.

formed in 80% overall yield with a ratio **6a:6a'** = 1:6 (eq 1). It should be mentioned that in this reaction, although unreacted **2** was recovered, no deuterium-labeled derivative of **2** [PhSO(NTS)CF₂D] was observed, which suggests there was no H/D exchange occurring with reagent **2** under the reaction conditions. In the presence of NaOD in D₂O–DMF at 60 °C, no H/D exchange was observed with reagent **2** in a period of 14 h (eq 2). We also noticed that product **6a** was unable to undergo H/D exchange either in the presence of PhSNa/D₂O/DMF or in the presence of prepared *N*-phenylsulfinyl-*p*-toluenesulfonamide anion **11**¹⁴ and D₂O/DMF (eq 3). These experimental results rule out the possibility of the involvement of an S_N2 or free radical

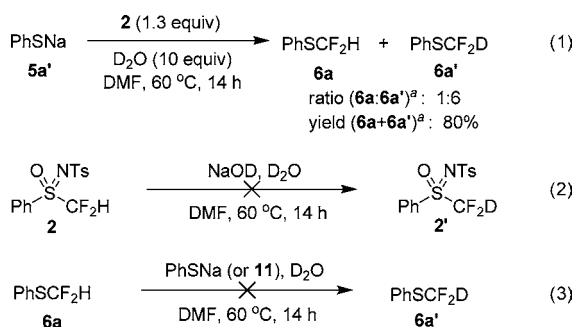
(13) (a) Konno, T.; Kitazume, T. *Chem. Commun.* **1996**, 19, 2227. (b) Xiao, L.; Kitazume, T. *Tetrahedron Asymmetry* **1997**, 8, 3597.

(14) Johnson, C. R.; Katekar, G. F. *J. Am. Chem. Soc.* **1970**, 92, 5753.

Table 3. Difluoromethylation of C-Nucleophiles with **2**

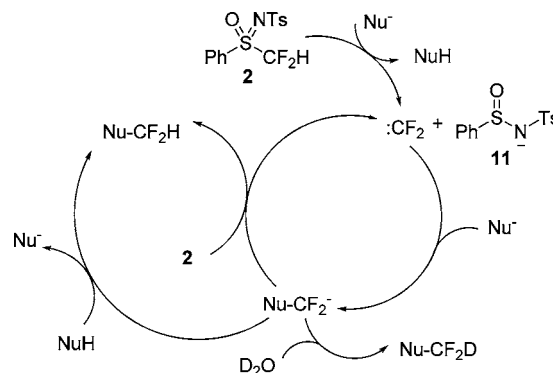
$\text{Ar}-\text{C}\equiv\text{CH} \xrightarrow[0^\circ\text{C}, 0.5\text{ h}]{1) n\text{BuLi (1.0 equiv)}} \text{Ar}-\text{C}\equiv\text{CF}_2\text{H}$ <p style="text-align: center;">9 10</p>					
$\text{Ar}-\text{C}\equiv\text{CH} \xrightarrow[-78\text{ to }0^\circ\text{C}, 6\text{ h}]{2) \textbf{2} (0.5\text{ equiv})} \text{Ar}-\text{C}\equiv\text{CF}_2\text{H}$					
entry	product	yield (%) ^a	entry	product	yield (%) ^a
1		87	4		47
2		46	5		78
3		73			

^a Determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard and calculated on the basis of the amount of reagent **2** used.

Scheme 3. Deuterium-Labeling Experiments

^a Determined by ¹⁹F NMR spectroscopy.

mechanism as a major pathway in the current electrophilic difluoromethylation with **2** and suggest that the difluoromethylation of S-, N-, and C-electrophiles proceeded via a difluorocarbene mechanism (as shown in Scheme 4). The nucleophiles (such as S-, N-, and C-anions) can act as a base to deprotonate **2**, which generates difluorocarbene species and anion **11** in a fast process. The expected PhSO(NTs)CF₂[−] anion (**12**) is likely to be a highly unstable species, since both the deuteration of **12** by D₂O (eqs 1 and 2) and electrophilic quenching of **12** by benzaldehyde were not successful. Nucleophiles (Nu[−]) react with difluorocarbene intermediate to generate NuCF₂[−], and the latter could be protonated by **2** or NuH to give difluoromethylated products NuCF₂H. In the presence of D₂O, a deuteriated product (NuCF₂D) can be produced (Scheme 4).

Scheme 4. Proposed Reaction Mechanism

In summary, we have successfully prepared the first α-difluoromethyl sulfoximine compound, **2**, by using the copper(II)-catalyzed nitrene transfer reaction. Compound **2** was found to be a novel and efficient difluoromethylation reagent for transferring CF₂H group to S-, N-, and C-nucleophiles. Our deuterium-labeling experiments suggest that a difluorocarbene mechanism was involved in the current difluoromethylation reactions with reagent **2**. Not only do our results present a novel and practically useful synthetic method for many potential applications; the remarkably different reactivity patterns between reagent **2** (as an electrophilic fluoroalkylation reagent) and the previously well-known PhSO₂CF₂H (**1**, as a nucleophilic fluoroalkylation reagent) also provides important insights into the unique chemical reactivities of fluorinated sulfoximines. Further exploration of fluorinated sulfoximine chemistry is currently underway in our laboratory.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic information files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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