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

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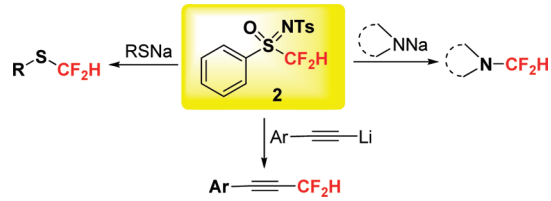
ABSTRACT



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 CF_2H 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 CF_3, CF_2H, and CH_2F) 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 bioavailability 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 (CF_2H) group is of particular interest, given the fact that the CF_2H moiety is known to be isosteric and isopolar to a carbinol (CH_2OH) unit and also, as a lipophilic group, can act as a hydrogen donor through hydrogen bonding.[3] Despite the increasing importance of the CF_2H 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) Bégué, 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.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science 317*, 1881. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637. (d) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (e) Prakash, G. K. S.; Chacko, S. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 793.

(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.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913.

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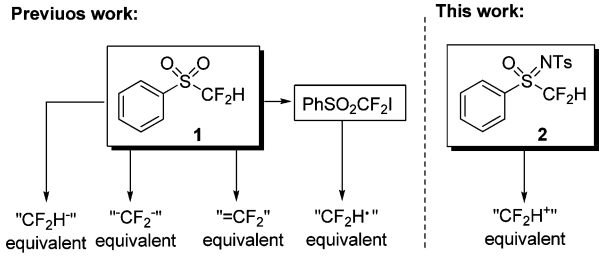
CF_2SO_2Ph compound[6b] have been reported as direct CF_2H^+- and $PhSO_2CF_2^+$-transferring reagents, but the scope of their applicability was shown to be limited. There are more reports on the difluorocarbene-based difluoromethylations using reagents such as $CHClF_2$, CF_2Br_2, FSO_2CF_2COOH, difluorodiazirine, 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 ($PhSO_2CF_2H$, **1**) was found to be a versatile nucleophilic difluoromethylation reagent (via its deprotonated form $PhSO_2CF_2^-$), thanks to the excellent modulating ability of the phenylsulfonyl group on both the stability and nucleophilicity of the $PhSO_2CF_2^-$ anion species (Scheme 1).[3a,4b,7] $PhSO_2CF_2H$ has been successfully used in the organic synthesis as a difluoromethyl anion equivalent (CF_2H^-),[3a,4b,f,7] a selective difluoromethylene dianion equivalent ($^-CF_2^-$),[8] and a difluoromethylidene equivalent ($=CF_2$).[9] Furthermore, $PhSO_2CF_2H$ can also be indirectly used in free radical difluoromethylation through a simple conversion to $PhSO_2CF_2I$ (a $CF_2H^\bullet$ equivalent).[5b,c] Despite these "chemical chameleon" behaviors of $PhSO_2CF_2H$ reagent (Scheme 1), the use of $PhSO_2CF_2H$ 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 $PhSO_2CF_2H$, that is, *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.

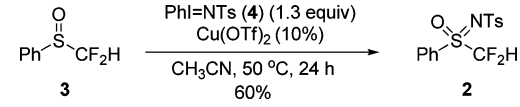
Scheme 1. Synthetic Applications of Difluoromethylated Sulfone **1** and Sulfoximine **2**



(Ts = *p*-toluenesulfonyl group)

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 PhI=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 nucelophiles 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 difluoromethy 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,

(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.

(8) Prakash, G. K. S.; Hu, J.; Mathew, T.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 5216.

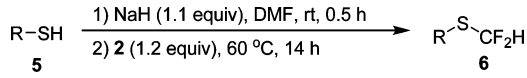
(9) Prakash, G. K. S.; Hu, J.; Wang, Y.; Olah, G. A. *Angew. Chem., Int. Ed.* **2003**, *43*, 5203.

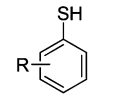
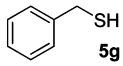
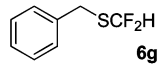
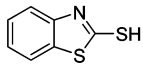
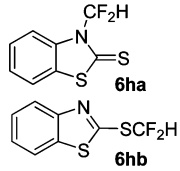
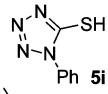
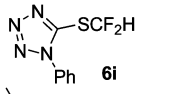
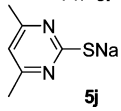
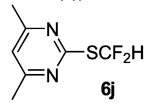
(10) Previously, $PhSO_2CF_2H$ has been recognized as a poor electrophilic difluoromethylation agent (via difluorocarbene mechanism), see: (a) Hine, J.; Porter, J. J. *J. Am. Chem. Soc.* **1960**, *82*, 6178. (b) See ref 6c.

(11) See reviews: (a) Reggelin, M.; Zur, C. *Synthesis* **2000**, 1. (b) Okamura, H.; Bolm, C. *Chem. Lett.* **2004**, *33*, 482. (c) Harmata, M. *Chemtracts−Org. Chem.* **2003**, *16*, 660.

(12) (a) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465. (b) Kondratendo, N. V.; Radchenko, O. A.; Yagupol'skii, L. M. *Zh. Org. Khim.* **1984**, 2250. (c) Magnier, E.; Wakselman, C. *Synthesis* **2003**, 565. (d) Boys, M. L.; Collington, E. W.; Finch, H.; Swanson, S.; Whitehead, J. F. *Tetrahedron Lett.* **1988**, *29*, 3365. (e) Adachi, K.; Ishikara, S. JP 20030388769, 2003.

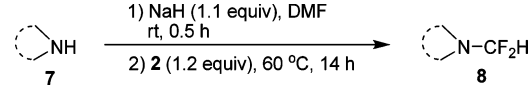
Table 1. Difluoromethylation of *S*-Nucleophiles with **2**

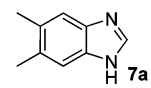
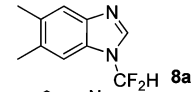
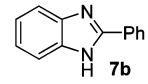
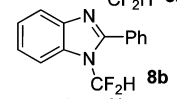
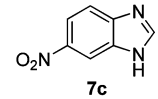
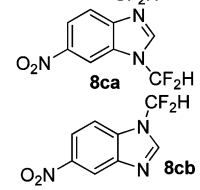
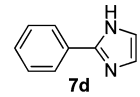
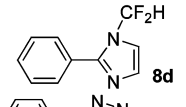
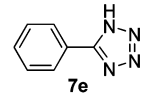
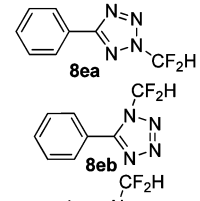
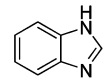
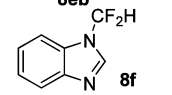
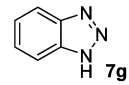
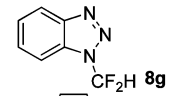
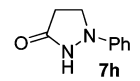
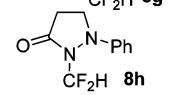
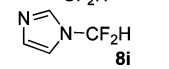


entry	substrate	product	yield (%)[a]
1	 (**5a-5f**)	 (**6a-6f**) **6a** R = H	94[b]
2		**6b** R = *p*-NO_2	76
3		**6c** R = 2, 5-MeO	61
4		**6d** R = 2, 6-Cl	78[b]
5		**6e** R = *p*-Me	61[b]
6		**6f** R = *o*-MeO	62
7	 **5g**	 **6g**	57[b]
8	 **5h**	 **6ha** / **6hb**	27 / 44 → 71
9	 **5i**	 **6i**	57
10[c]	 **5j**	 **6j**	71

[a] Isolated yield. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. [c] NaH was not used.

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



entry	substrate	product	yield (%)[a]
1	 **7a**	 **8a**	72
2	 **7b**	 **8b**	60
3	 **7c**	 **8ca** / **8cb**	61
4	 **7d**	 **8d**	45
5	 **7e**	 **8ea** / **8eb**	37 / 33 → 70
6	 **7f**	 **8f**	53
7	 **7g**	 **8g**	40
8	 **7h**	 **8h**	26
9	 **7i**	 **8i**	54[b]

[a] Isolated yield. [b] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard.

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).

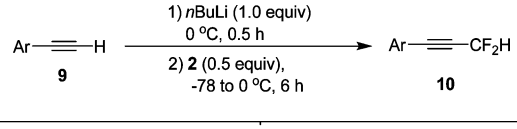
Thereafter, we applied the reagent **2** in the difluoromethylation of phenylacetylene derivatives (Table 3). It showed that lithium acetylides derived from **9a**−**9e** smoothly reacted with reagent **2** to give the desired C-difluoromethylated products **10a**−**10e** in moderate to good yields (Table 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]

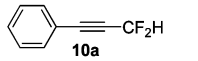
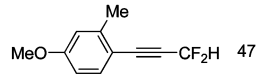
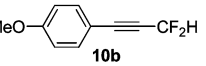
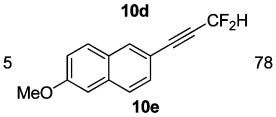
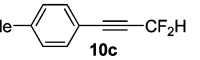
To gain some insights into the current S-, N-, and C-difluoromethylations with reagent **2**, we carried out several deuterium-labeling experiments (Scheme 3). When sodium phenylthiolate (**5a′**) was treated with **2** in D_2O−DMF at 60 °C for 14 h, both $PhSCF_2H$ (**6a**) and $PhSCF_2D$ (**6a′**) were 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)CF_2D] was oberved, which suggests there was no H/D exchange occurring with reagent **2** under the reaction conditions. In the presence of NaOD in D_2O−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 $PhSNa/D_2O$/DMF or in the presence of preprepared *N*-phenylsulfinyl-*p*-toluenesulfonamide anion **11**[14] and D_2O/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.

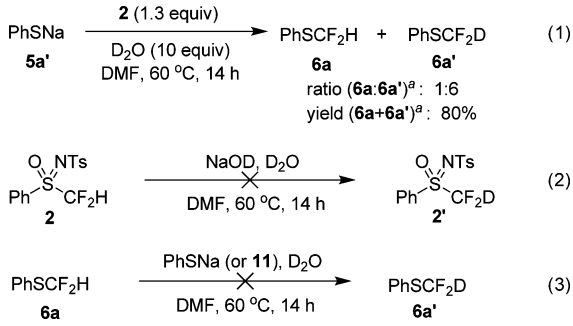
Table 3. Difluoromethylation of *C*-Nucleophiles with **2**



entry	product	yield (%)[a]	entry	product	yield (%)[a]
1	 **10a**	87	4	 **10d**	47
2	 **10b**	46	5	 **10e**	78
3	 **10c**	73			

[a] Determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard and calculated on the basis of the amount of reagent **2** used.

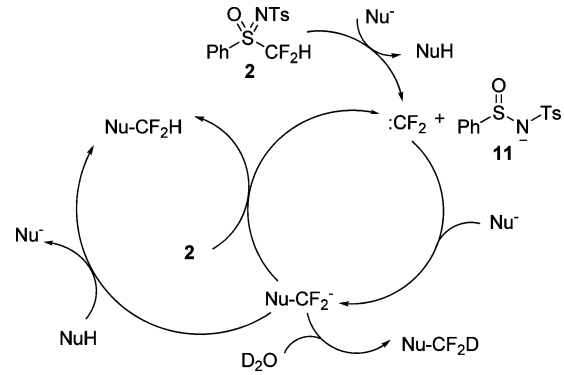
Scheme 3. Deuterium-Labelling Experiments



[a] Determined by ^{19}F 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 $PhSO(NTs)CF_2^-$ anion (**12**) is likely to be a highly unstable species, since both the deuteriation of **12** by D_2O (eqs 1 and 2) and electrophilic quenching of **12** by benzaldehyde were not successful. Nucleophiles (Nu^-) react with difluorocarbene intermediate to generate $NuCF_2^-$, and the latter could be protonated by **2** or NuH to give difluoromethylated products $NuCF_2H$. In the presence of D_2O, a deuteriated product ($NuCF_2D$) 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 CF_2H 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 $PhSO_2CF_2H$ (**1**, as an nucleophilic fluoroalkylation reagent) also provides important insights into the unique chemical reactivities of fluorinated sulfones and 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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