Chlorodifluoromethyl phenyl sulfone: a novel non-ozone-depleting substance-based difluorocarbene reagent for *O*- and *N*-difluoromethylations†‡

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Chlorodifluoromethyl phenyl sulfone, a previously unknown compound that can be readily prepared from non-ODS-based precursors, was found to act as a robust difluorocarbene reagent for *O*- and *N*-difluoromethylations.

Selective introduction of fluorine atoms or fluorine-containing moieties into organic molecules is well-recognized as a powerful strategy to modulate the target molecules' physical, chemical and biological properties.[1] As a result, the development of mild, efficient and environmentally friendly fluorination and fluoroalkylation methods is highly useful for life science- and material science-related research.[1,2] One major effort in the field is to develop new non-ODS-based fluoroalkylation methods (ODS = ozone-depleting substances) to replace the conventional ODS-based ones.[3] For instance, most of the currently known difluorocarbene reagents for *O*- and *N*-difluoromethylations (Fig. 1), such as chlorodifluoromethane and chlorodifluoroacetic acid derivatives, are either ODS themselves or derived from ODS-based precursors.[4–6] Furthermore, although *S*-(difluoromethyl)diarylsulfonium tetrafluoroborate was developed as a new electrophilic difluoromethylating agent, this reagent could not transfer the difluoromethyl group to phenols and secondary amines.[7] 2-Chloro-2,2-difluoroacetophenone (**1**) was developed by us as a non-ODS-based difluorocarbene reagent for *O*-difluoromethylation of phenol derivatives.[4] However, the fact that a large excess of reagent **1** ($\geqslant$5 equiv.) was generally required in reactions[4] has driven us to seek more efficient non-ODS-based difluorocarbene reagents. In this communication, we disclose our recent success in developing chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$, **2**) as a robust non-ODS-based difluorocarbene reagent for *O*- and *N*-difluoromethylations.

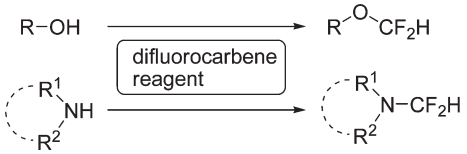
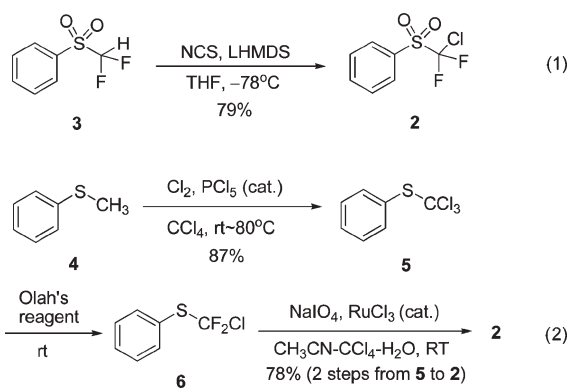


Fig. 1 *O*- And *N*-difluoromethylations with difluorocarbene reagents.

Fluorinated sulfones have increasingly become a class of highly useful compounds in nucleophilic fluoroalkylations,[8] but the reports on their use as difluorocarbene reagents are rare.[9] Chlorodifluoromethyl phenyl sulfone (**2**) is a previously unknown compound. Initially, we prepared compound **2** in 79% yield through a nucleophilic (phenylsulfonyl)difluoromethylation reaction between difluoromethyl phenyl sulfone (**3**) and *N*-chlorosuccinimide (NCS, 3.4 equiv.) in the presence of lithium hexamethyldisilazide (LHMDS, 2.5 equiv.) in THF at −78 °C (Scheme 1, eqn (1)). To achieve a non-ODS-based practical synthesis of compound **2**, we developed a three-step synthesis of **2** with good yield starting from readily available and inexpensive thioanisole (**4**). The synthetic procedures include chlorination with Cl_2, selective fluorination with Olah's reagent (HF–pyridine, molar ratio = 10 : 1), and oxidation with $NaIO_4$ (Scheme 1, eqn (2)).

With compound **2** in hand, we carried out the *O*-difluoromethylation reactions by using phenol (**7a**) as a model compound. The results are summarized in Table 1. Potassium hydroxide (25 wt% in H_2O) was used both as a base to deprotonate phenol (**7a**) and as an activating agent for reagent **2** to generate $:CF_2$ species. It was found that the reaction between phenol **7a** and reagent **2** (in a sealed pressure tube) was successful in different solvent systems (such as THF–H_2O, DME–H_2O, and CH_3CN–H_2O) at 50–80 °C. CH_3CN–H_2O (7 : 2 v/v) was found to be the best solvent system for the reaction (Table 1, entries 6–10). Decreasing or increasing the reaction temperature did not show a significant impact on the product yield (entries 6–8). The optimal product yield (72%) was obtained when the reaction proceeded at 50 °C for 5 h with reactant ratio **7a** : **2** : KOH = 1 : 2.3 : 11



Scheme 1 Synthesis of difluorocarbene reagent **2**.

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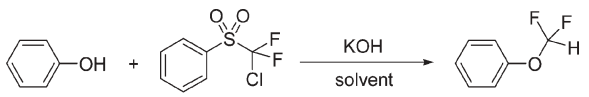
‡ Electronic supplementary information (ESI) available: Experimental details and characterization data. See DOI: 10.1039/b713156a

Table 1 Survey of reaction conditions



7a **2** **8a**

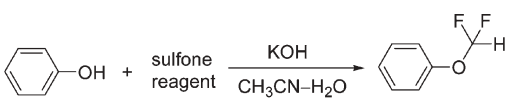
Entry[a]	Reactant ratio (**7a** : **2** : KOH)	Solvent	Temperature/ °C	Time/h	Yield (%)[b]
1	1 : 2 : 11	Dioxane–H_2O	50	4	13
2	1 : 2 : 11	H_2O	50	4	0[c]
3	1 : 2 : 11	THF–H_2O	80	4	56
4	1 : 2 : 11	DME–H_2O	80	6	64
5	1 : 2 : 16	DME–H_2O	60	6	63
6	1 : 2 : 11	CH_3CN–H_2O	50	4	68
7	1 : 2 : 11	CH_3CN–H_2O	60	4	65
8	1 : 2 : 11	CH_3CN–H_2O	80	4	67
9	1 : 2 : 5.5	CH_3CN–H_2O	60	6	68[d]
10	1 : 2.3 : 11	CH_3CN–H_2O	50	5	72
11	1 : 2 : 11	CH_3CN	50	4	38[e]
12	1 : 2 : 11	CH_3CN–H_2O	50	4	0[f]

[a] Typical reaction procedures: **7a** (1 mmol), KOH (25 wt% in H_2O, 2 mL, *ca.* 11 mmol), 7 mL of organic solvent (except entry 5) and **2** were mixed in a pressure tube at rt, and the tube was sealed. The reaction mixture was heated to the desired temperature for a certain time. [b] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard. [c] Even when the phase transfer catalyst tris[2-(2-methoxyethoxy)ethyl]amine was added, no product was observed. [d] Half amount of KOH (25 wt% in H_2O, 1 mL, *ca.* 5.5 mmol) was applied. [e] Anhydrous KOH (instead of aqueous solution) was used. [f] K_2CO_3 (instead of KOH) was used as a base.

(entry 10). It was evident that water played an important role in the current difluorocarbene reaction; when the reaction was carried out under anhydrous conditions, a poor product yield (38%) was obtained (entry 11). However, the reactions in water alone or in the presence of a phase transfer catalyst (tris[2-(2-methoxyethoxy) ethyl]amine) could not give any desired product (entry 2). Furthermore, we found that potassium carbonate was not a suitable base (to replace KOH) for the reaction (entry 12).

Thereafter, we compared the reactivity of reagent **2** with those of other potential difluorocarbene reagents, including bromodifluoromethyl phenyl sulfone **9**, iododifluoromethyl phenyl sulfone **10**, difluoromethyl phenyl sulfone **3**,[8,9] and trifluoromethyl phenyl sulfone **11** (see Table 2). It was found that compounds **9**, **10** and **3** were also able to act as difluorocarbene reagents for *O*-difluoromethylation of phenol, while compound **11** did not show any

Table 2 Difluoromethylation with different sulfone reagents



7a **8a**

Entry[a]	Sulfone reagent	Yield (%)[b]
1	$PhSO_2CF_2Cl$ (**2**)	72
2	$PhSO_2CF_2Br$ (**9**)	70
3	$PhSO_2CF_2I$ (**10**)	25
4	$PhSO_2CF_2H$ (**3**)	23
5	$PhSO_2CF_3$ (**11**)	0

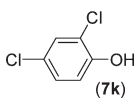
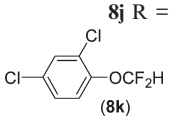
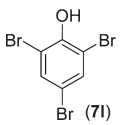
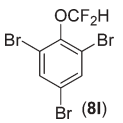
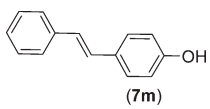
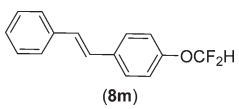
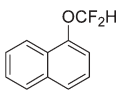
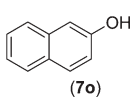
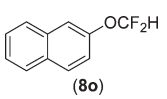
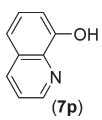
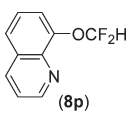
[a] For all cases, the reactant conditions were similar to those of entry 10 in Table 1. [b] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard.

difluorocarbene character under similar reaction conditions (in the case of compound **11**, CF_3H was formed as a major product). As shown in Table 2, compound **2** showed the highest reactivity among these five fluorinated sulfones.

Next, we carefully examined the scope of the *O*- and *N*-difluoromethylation reaction with reagent **2**. The results are summarized in Table 3 and Table 4. It was found that by using the **2**–KOH–CH_3CN–H_2O system, a wide range of phenol derivatives were readily difluoromethylated in good to excellent yields with a simple experimental procedure (Table 3). It is particularly remarkable that, although only 2.3 equiv. of reagent **2** were used, the product yields were still notably higher than those of the reported reactions using 5 equiv. of $PhCOCF_2Cl$ reagent.[4] Furthermore, the present difluoromethylation reaction was also found to be applicable to *N*-heterocyclic compounds **12a**–**12e** to give difluoromethylated products **13a**–**13e** in satisfactory product yields (see Table 4), which broadens the synthetic application of reagent **2**.

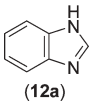
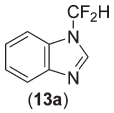
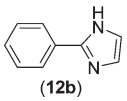
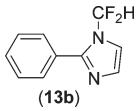
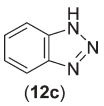
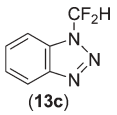
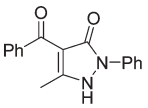
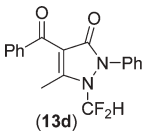
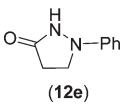
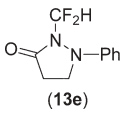
The synthetic application of reagent **2** was further demonstrated in the synthesis of the compounds **16** and **17**, which are highly useful intermediates for making pharmacologically active

Table 3 *O*-Difluoromethylation with reagent **2**

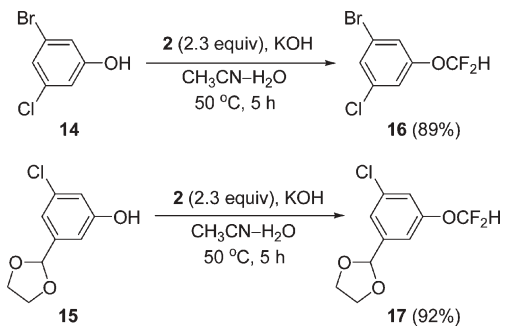
Entry[a]	Substrate	Product	Yield (%)[b]
1	 (**7a**–**7j**)	 (**8a**–**8j**) **8a** R = H	72[c]
2		**8b** R = *o*-I	79
3		**8c** R = *p*-I	70
4		**8d** R = *p*-Br	74
5		**8e** R = *p*-Cl	65
6		**8f** R = *o*-NO_2	93
7		**8g** R = *p*-NO_2	96
8		**8h** R = *p*-*t*Bu	77
9		**8i** R = *p*-Ph	87
10		**8j** R = *o*-OCH_3	70[c]
11	 (**7k**)	 (**8k**)	83
12	 (**7l**)	 (**8l**)	95
13	 (**7m**)	 (**8m**)	94
14	 (**7n**)	 (**8n**)	79
15	 (**7o**)	 (**8o**)	81
16	 (**7p**)	 (**8p**)	93

[a] For all cases, the reactant conditions were similar to those of entry 10 in Table 1. [b] Isolated yields. [c] Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as internal standard due to the volatile nature of the product.

Table 4 *N*-Difluoromethylation with reagent **2**

Entry[a]	Substrate	Product	Yield (%)[b]
1	 (**12a**)	 (**13a**)	86
2	 (**12b**)	 (**13b**)	66
3	 (**12c**)	 (**13c**)	69
4	 (**12d**)	 (**13d**)	58
5	 (**12e**)	 (**13e**)	44

[a] For all cases, the reactant conditions were similar to those of entry 10 in Table 1. [b] Isolated yield.



Scheme 2 Synthesis of compounds **16** and **17**.

compounds. As shown in Scheme 2, the reaction between **2** and 3-bromo-5-chlorophenol (**14**) smoothly gave product **16** in 89% isolated yield. When the same procedure was applied to precursor **15**, product **17** was obtained in 92% yield (Scheme 2). It is important to mention that the present new difluoromethylation method can be easily used in relatively large-scale reactions. For example, when 9.28 g (44 mmol) of compound **14** were treated with 2.0 equiv. of reagent **2** under similar reaction conditions, product **16** was obtained in 85% yield.

In summary, we have successfully developed a non-ODS-based preparation of chlorodifluoromethyl phenyl sulfone (**2**). Compound **2** was found to be a novel and efficient difluorocarbene reagent for *O*- and *N*-difluoromethylation of phenols and *N*-heterocycles. The present synthetic methodology was successfully applied to the synthesis of two highly useful intermediates, **16** and **17**, which are both relevant for the preparation of pharmaceutically interesting compounds. The present synthetic methodology promises to act as a useful synthetic tool for many other applications.

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