Fluorine Chemistry

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A Remarkably Efficient Fluoroalkylation of Cyclic Sulfates and Sulfamidates with $PhSO_2CF_2H$: Facile Entry into β-Difluoromethylated or β-Difluoromethylenated Alcohols and Amines**

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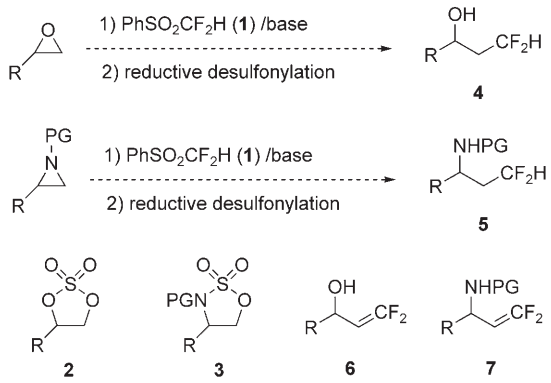
Fluorine is increasingly recognized as a remarkable element in the life sciences, based on the fact that incorporation of one or a few fluorine atoms in an organic molecule can often dramatically alter its stability, lipophilicity, bioavailability, and biopotency. Currently, "as many as 30–40% of agrochemicals and 20% of pharmaceuticals on the market are estimated to contain fluorine".[1] Fluorination and fluoroalkylation are the two major synthetic methods to introduce fluorine atoms or fluorine-containing moieties into organic molecules.[2] While nucleophilic, electrophilic, and radical trifluoromethylations have been extensively studied over the past 30 years, the systematic exploration of the analogous difluoromethylations and difluoromethylenations has emerged more recently.[3] The difluoromethyl functionality (CF_2H) can act both as a more lipophilic biostere of the carbinol group (CH_2OH) and as a hydrogen donor through hydrogen bonding,[3b,4] while 1,1-difluoroalkenyl functionality can be used as a biostere of the carbonyl group with a different reactivity pattern.[3i,5] In some cases, the difluoromethylated compounds exhibit increased bioactivity compared with their trifluoromethylated counterparts.[6]

Previously, we successfully synthesized both α-difluoromethyl alcohols and α-difluoromethylamines from carbonyl compounds and imines by using a direct nucleophilic difluoromethylation strategy, orchestrated by $TMSCF_2SO_2Ph$ and $PhSO_2CF_2H$ (**1**).[3a,b,d] However, the synthesis of β-difluoromethyl alcohols and β-difluoromethylamines was found to be more challenging. We studied the reactions between $PhSO_2CF_2^-$ and epoxides (or aziridines), but the expected products, the β-difluoromethyl alcohols **4** (or amines **5**), were not observed (Scheme 1).[7] We ascribed the difficulty of this ring-opening reaction to be the "negative fluorine effect", that is, fluorine substitution on the carbanion center will dramatically decrease its nucleophilicity towards electrophiles.[7] Although the negative fluorine effect was weakened by using $(PhSO_2)_2CHF$, and both the β-monofluoromethyl alcohols and amines were successfully prepared in one step, this method was still not suitable for the synthesis of β-difluoromethyl alcohols **4** and amines **5**.[7] We surmised that this problem might be solved by using the more electrophilic epoxide and aziridine equivalents, the 1,2-cyclic sulfates **2** and sulfamidates **3** (Scheme 1), to react with $PhSO_2CF_2^-$. Compounds **2** and **3** represent a versatile class of functionalized and often enantiomerically pure electrophiles,[8] and their application in organic synthesis has been widely studied, especially since the development of osmium-catalyzed asymmetric dihydroxylation and aminohydroxylation reactions by Sharpless and co-workers.[9] However, the nucleophilic fluoroalkylation of 1,2-cyclic sulfates and sulfamidates have scarcely been reported, with the only successful example being the trifluoromethylation of 1,2-cyclic sulfates with CF_3I/TDAE (TDAE = tetrakis(dimethylamino)ethylene) to give a β-trifluoromethyl alcohol in moderate yields (43–62%).[10] Herein we disclose a remarkably efficient and highly regioselective fluoroalkylation of both 1,2-cyclic sulfates **2** and sulfamidates **3** using difluoromethyl phenyl sulfone (**1**)[3] as the fluoroalkylating agent. In addition to its high efficiency and the simple experimental procedures involved, the major advantage of this synthetic methodology is that it allows facile entry to both β-difluoromethylated and β-difluoromethylenated alcohols (**4** and **6**) and amines (**5** and **7**, Scheme 1), which are important building blocks for drug design and for the synthesis of bioactive target molecules.[11]



Scheme 1. Initial attempted preparation of β-difluoromethyl alcohols **4** and β-difluoromethylamines **5**. PG = protecting group.

In a first trial, we chose propane 1,2-cyclic sulfate **2a**, which is readily prepared from propane-1,2-diol according to

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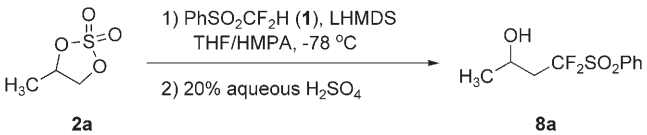
the procedure of Gao and Sharpless,[9a] as a model compound. The initial reaction of the anion $PhSO_2CF_2^-$ (generated in situ from $PhSO_2CF_2H$ and LHMDS) with **2a** was carried out in THF/HMPA at −78 °C over 2 h (molar ratio **2a**/**1**/LHMDS 1.2:1:1.2), and the (phenylsulfonyl)difluoromethylated product **8a** was obtained in 77 % yield after subsequent hydrolysis (Scheme 2). A brief optimization of the reaction conditions revealed that an excellent yield (98 %) of product **8a** was obtained when the ratio of reactants was **2a**/**1**/LHMDS 1.0:1.1:1.2 and the reaction time reduced (less than 30 min, Scheme 2). The addition of HMPA significantly enhanced



2a/**1**/LHMDS 1.2:1.0:1.2, 77% yield
2a/**1**/LHMDS 1.0:1.1:1.2, 98% yield

Scheme 2. (Phenylsulfonyl)difluoromethylation of 1,2-cyclic sulfate **2a**. HMPA = hexamethyl phosphoramide, LHMDS = lithium hexamethyldisilazanide.

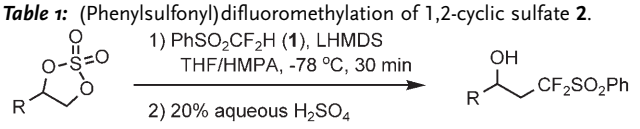
both the reaction rate and the yield. The propane 1,2-cyclic sulfite (the precursor to the preparation of **2a**) was also examined as a substrate under the similar reaction conditions. However, no product **8a** was formed, and longer reaction times resulted in the decomposition of the $PhSO_2CF_2H$ reagent.

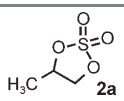
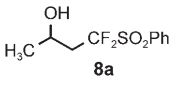
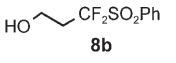
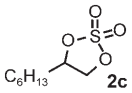
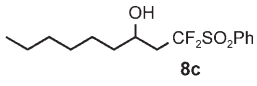
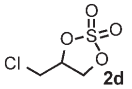
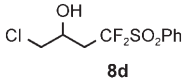
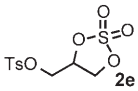
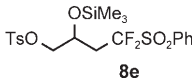
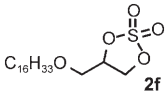
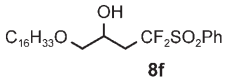
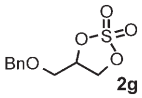
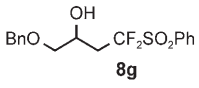
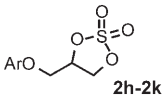
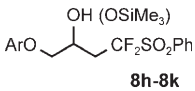
We examined the scope of the nucleophilic (phenylsulfonyl)difluoromethylation of **2** with **1** under these optimized reaction conditions (Table 1). The reaction proved to be general and highly regioselective, with the $PhSO_2CF_2^-$ ion attacking at the less-hindered-carbon atom of the cyclic sulfates **2** to provide the secondary alcohols **8**. In all cases, as shown in Table 1, the yields of **8** were excellent (87–99 %). The reaction was found to be compatible with other functional groups such as OTs and Cl (Table 1, entries 4 and 5), which shows the high reactivity of $PhSO_2CF_2^-$ towards cyclic sulfates **2**. Notably, high reaction rates meant that in all cases the reaction had reached completion as soon as the dropwise addition of the base (LHMDS) had finished (usually within 30 min at −78 °C). The nucleophilic fluoroalkylation of 1,2-cyclic sulfates **2** with **1** was remarkable, especially when compared with the previously reported nucleophilic trifluoromethyations of **2** using CF_3I/TDAE which proceed in much lower yields (< 62 %).[10]

We also investigated the reaction of 1,3-cyclic sulfate **9** with $PhSO_2CF_2^-$ as shown in Scheme 3. We found that compound **9** showed lower reactivity towards $PhSO_2CF_2^-$, and a longer reaction time (8 h) was required to afford the γ-difluoroalkylated product **10** in 63 % yield.

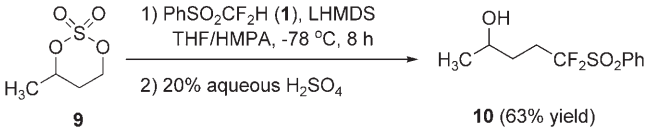
Encouraged by these results, we predicted that the 1,2-cyclic sulfamidates **3** could also undergo the nucleophilic ring-opening reaction with $PhSO_2CF_2^-$. Thus, the optically pure 1,2-cyclic sulfamidates **3** were prepared from the corresponding amino alcohols. A variety of structurally diverse 1,2-cyclic sulfamidates **3** were found to react readily with $PhSO_2CF_2^-$

Table 1: (Phenylsulfonyl)difluoromethylation of 1,2-cyclic sulfate **2**.



Entry	Sulfate **2**	Product **8**	Yield [%][a]
1	 **2a**	 **8a**	98
2	 **2b**	 **8b**	94
3	 **2c**	 **8c**	94
4	 **2d**	 **8d**	89
5	 **2e**	 **8e**	92[b]
6	 **2f**	 **8f**	87
7	 **2g**	 **8g**	99
	 **2h-2k**	 **8h-8k**	
8	Ar = Ph (**2h**)	Ar = Ph (**8h**)	93
9	Ar = *p*-$MeOC_6H_4$ (**2i**)	Ar = *p*-$MeOC_6H_4$ (**8i**)	99
10	Ar = *o*-$MeOC_6H_4$ (**2j**)	Ar = *o*-$MeOC_6H_4$ (**8j**)	97[b]
11	Ar = *m*-MeC_6H_4 (**2k**)	Ar = *m*-MeC_6H_4 (**8k**)	94[b]

[a] Yield of isolated product. [b] Purified after silylation of the hydroxy group. Bn = benzyl, Ts = toluene-4-sulfonyl.

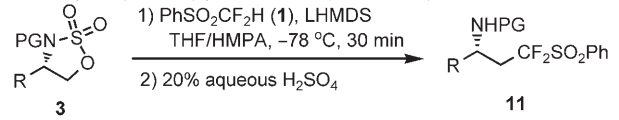


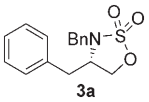
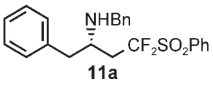
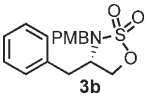
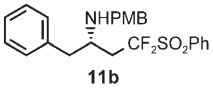
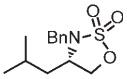
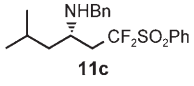
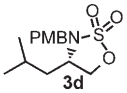
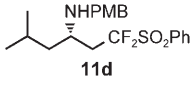
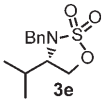
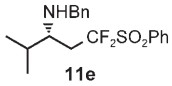
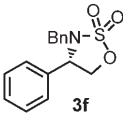
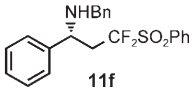
Scheme 3. (Phenylsulfonyl)difluoromethylation of 1,3-cyclic sulfate **9**.

with high regioselectivity under similar reaction conditions as for **2**, and the corresponding homochiral β-(phenylsulfonyl)-difluoromethylated amines **11** were obtained in 90–99 % yields (Table 2). Stereochemical deterioration at the stereogenic center is negligible as demonstrated by the high *ee* value (> 99.5 %) determined for product **11a** by HPLC on a chiral stationary phase (see the Supporting Information).

To demonstrate the synthetic utility of this highly efficient fluoroalkylation reaction, β-(phenylsulfonyl)difluoromethyl

Table 2: (Phenylsulfonyl)difluoromethylation of cyclic sulfamidates **3**.

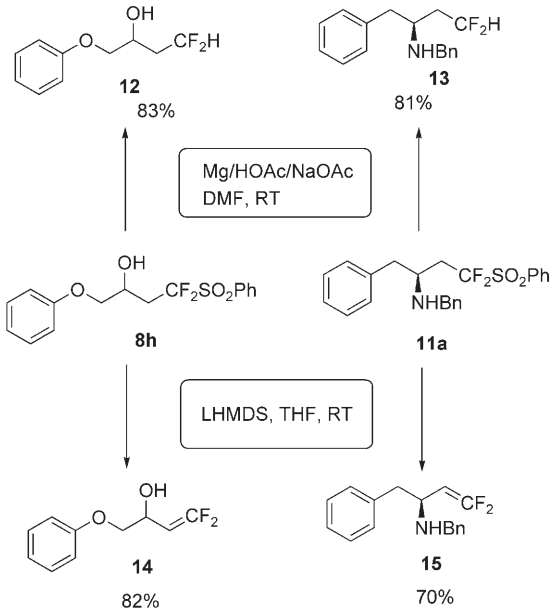


Entry	Sulfamidate **3**	Product **11**[a]	Yield [%][b]
1	 **3a**	 **11a**	96
2	 **3b**	 **11b**	98
3	 **3c**	 **11c**	99
4	 **3d**	 **11d**	98
5	 **3e**	 **11e**	93
6	 **3f**	 **11f**	90

[a] An *ee* value of >99.5% was determined for **11a** by using HPLC analysis on a chiral stationary phase. The configurations of other products **11b–f** were assigned based on the fact that no racemization occurred during the reactions. [b] Yield of isolated product. PMB = *para*-methoxybenzyl.

alcohol **8h** and amine **11a** were further transformed into their corresponding β-difluoromethylated and β-difluoromethylenated products **12–15** (Scheme 4), by taking advantage of the property of the sulfone functionality as a "chemical chameleon".[12] Reductive desulfonylations of **8h** and **11a** were carried out in DMF solution at room temperature by using our previously developed Mg/HOAc/NaOAc system.[3a] The corresponding β-difluoromethylated alcohol **12** and amine **13** were obtained in 83% and 81% yield, respectively (Scheme 4). Another important transformation of **8h** and **11a** is the base-mediated α,β-elimination of a molecule of phenylsulfinic acid to give the corresponding β-difluoromethylenated alcohol **14** and amine **15** in 82% and 70% yield, respectively.

In summary, we have demonstrated a highly regioselective synthesis of β-difluoromethylated and β-difluoromethylenated alcohols and amines using a nucleophilic difluoromethylation strategy. Nucleophilic (phenylsulfonyl)difluoromethylation of 1,2-cyclic sulfates and sulfamidates with difluoromethyl phenyl sulfone affords the corresponding β-(benzenesulfonyl)difluoromethylated products **8** and **11** in excellent yields. Upon selective desulfonylation, compounds **8** and **11** can be readily transformed into β-difluoromethylated and β-difluoromethylenated alcohols and amines, which are highly useful building blocks for many applications in the life sciences.



Scheme 4. Prepration of β-difluoromethylated and β-difluoromethylenated alcohols **12** and **14**, and amines **13** and **15**. DMF = *N*,*N*-dimethylformamide.

Experimental Section

Typical procedure for the nucleophilic difluoromethylation of 1,2-cyclic sulfates using difluoromethyl phenyl sulfone: A solution of LHMDS (1.0 M, 1.2 mmol) in THF (1.2 mL) was added over 10 min to a 20-mL Schlenk flask containing **2a** (138 mg, 1.0 mmol) and **1** (211 mg, 1.1 mmol) in THF (5 mL) and HMPA (0.5 mL) at −78 °C under N_2. The reaction mixture was stirred at this temperature for another 20 min, and then 20% aqueous sulfuric acid (5 mL) was added. The mixture was stirred at room temperature overnight, and then extracted with Et_2O (10 mL × 3). The combined organic phase was washed with saturated $NaHCO_3$ solution and then dried over $MgSO_4$. After removal of volatile solvents under vacuum, the crude product was purified by column chromatography through silica gel to give **8a** as a colorless oil (245 mg, 98% yield).

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Keywords: cyclic sulfates · fluorine · fluoroalkylation · nucleophilic addition · sulfamidates

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