Synthetic Methods

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S-((Phenylsulfonyl)difluoromethyl)thiophenium Salts: Carbon-Selective Electrophilic Difluoromethylation of β-Ketoesters, β-Diketones, and Dicyanoalkylidenes**

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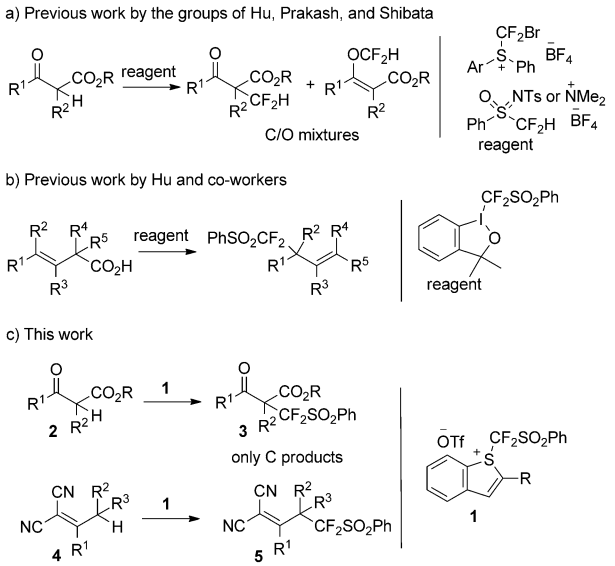
Abstract: *S-((Phenylsulfonyl)difluoromethyl)thiophenium salts were designed and prepared by a triflic acid catalyzed intramolecular cyclization of ortho-ethynyl aryldifluoromethyl sulfanes. The thiophenium salts were found to be efficient as electrophilic difluoromehtylating reagents for introduction of a CF_2H group to sp^3-hybridized carbon nucleophiles such as of β-ketoesters and dicyanoalkylidenes. The (phenylsulfonyl)difluoromethyl group can be readily transformed into CF_2H under mild reaction conditions. Enantioselective electrophilic difluoromethylation was also achieved in the presence of bis(cinchona) alkaloids.*

The search for new drugs using organofluorine compounds has great potential since more than 20% of the pharmaceuticals and agrochemicals on the market, including a couple of top-ten drugs, contain fluorine in their structures.[1] Thus, the functionalization of organic molecules with fluorinated moieties has been a key strategy in drug development. Among fluorinated functional groups, the difluoromethyl (CF_2H) group has clear advantages: it is isosteric and isopolar to a hydroxy (OH)[2] and thiol (SH)[3] unit. The CF_2H group can also act as a more lipophilic hydrogen donor than OH and NH groups through hydrogen bonding,[1n,4–6] thus making it an interesting moiety with respect to the design of bioactive molecules. In contrast to the enormous progress of trifluoromethylation research within of the last few years, methodology for the introduction of the CF_2H group is relatively sparse.[5–10] Shelf-stable reagents for electrophilic difluoromethylation are one of the most powerful tools for this purpose, as they provide direct functionalization of target molecules and can be implemented with high reproducibility, even at on small scale. As part of our research program towards the development of biologically active organofluorine compounds, we required reagents suitable for the difluoromethylation of C_{sp^3}-centered nucleophiles, since they produce medicinally important difluoromethylated molecules having a quaternary carbon center. While reagents for electrophilic difluoromethylation of carbon and heteroatom nucleophiles have been reported,[6,7h,i,k,u,8a] the difluoromethylation of C_{sp^3}-centered nucleophiles remains an area of limited success. Recently, we reported shelf-stable reagents, *S*-(bromodifluoromethyl)diaryl sulfonium salts,[7p] for electrophilic difluoromethylation of C_{sp^3}-centered nucleophiles including β-ketoesters and dicyanoalkylidenes. We also reported the difluoromethylation of β-ketoesters using a difluoromethylsulfoxinium salt.[7o] In contrast to the monofluoromethylation[11] and trifluoromethylation,[12] all the β-ketoesters gave a mixture of C- and O-difluoromethylation products in good yields with poor to modest regioselectivities (C/O = 6:4 to 8:2, Scheme 1a).[7o,p] For the reaction of 1,3-diones, only O-difluoromethylation products were selectively obtained.[7s] Mikami and co-workers recently developed a nice protocol[8e] for the α-difluoromethylation of lithium enolates using fluoroform (CF_3H) as the difluoromethylating reagent to furnish α-difluoromethyl carbonyl compounds. However, the scope of substrates was limited to amides, ketones, and esters and merely achieved low to moderate yields. Additionally, no example was shown for carbon-selective difluoromethylation of β-ketoesters and 1,3-diketones, both of which are problematic because of the ease with which they are enolized. To



Scheme 1. Difluoromethylation and (phenylsulfonyl)difluoromethylation of C_{sp^3}-centered nucleophiles. Tf = trifluoromethanesulfonyl.

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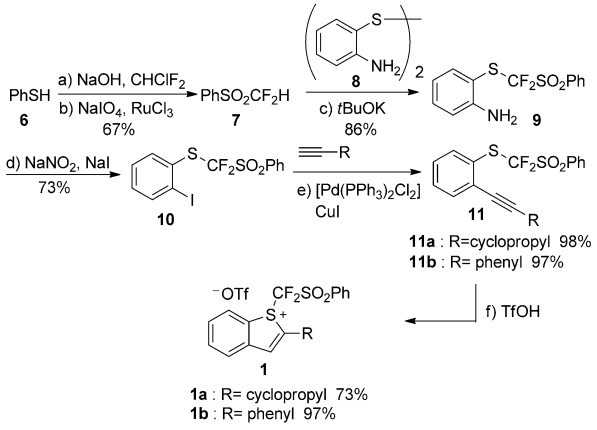
achieve the previously unsuccessful selective C_{sp^3} difluoromethylation of β-ketoesters, difluoromethylation should take place under a more electrophilic pathway rather than that of radical or carbene, and the reactive species for the difluoromethylation should be softer. Incidentally, Hu and coworkers developed a hypervalent-iodine-type reagent for electrophilic (phenylsulfonyl)difluoromethylation of thiols.[8a] This reagent is also applicable for the allylic (phenylsulfonyl)difluoromethylation under copper catalysis to provide C_{sp^3}–CF_2SO_2Ph products (Scheme 1b).[7q] Since Hu's reagent has a somewhat radical-type character because of the hypervalent iodine structure, it required modification to be more electrophilic for the selective C_{sp^3} difluoromethylation of β-ketoesters. We disclose herein the novel electrophilic reagents, *S*-(phenylsulfonyldifluoromethyl)thiophenium salts (**1**), for this purpose. With the reagents **1**, β-ketoesters and 1,3-diketones **2** are selectively functionalized with a difluoromethyl group at the C_{sp^3} centers in high to excellent yields under mild reaction conditions, thus providing **3** which has a quaternary carbon center. None of the undesired O–CF_2SO_2Ph products were isolated. Allylic (phenylsulfonyl)difluoromethylation of dicyanoalkylidenes **4** was also achieved with **1** to provide the allylic C_{sp^3}–CF_2SO_2Ph products **5** (Scheme 1c). The CF_2SO_2Ph group can be readily transformed into CF_2H under mild reaction conditions. Preliminary results for asymmetric variant of this reaction are also discussed (up to 55% *ee*).

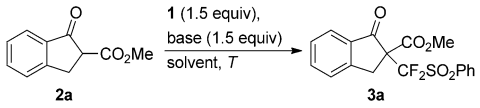
The reagents **1** were synthesized by the procedure shown in Scheme 2. The difluoromethyl sulfone **7** was prepared from benzenethiol (**6**) in two steps, and reacted with **8** to furnish the aniline **9**. After treatment of **9** with $NaNO_2$ and NaI under acidic conditions, **9** was converted into the iodide **10**, and subsequent Sonogashira cross-coupling afforded the alkyne **11**. Finally, the target *S*-(phenylsulfonyldifluoromethyl)thiophenium salts **1** were successfully prepared in excellent yields by cyclization of **11** in the presence of triflic acid.

The potential for electrophilic (phenylsulfonyl)difluoromethylation of the β-ketoesters **2** by **1** was next examined. We began our investigation with methyl indanone-2-carboxylate (**2a**) as a model substrate for (phenylsulfonyl)difluoromethylation (Table 1). The reaction was carried out with 1.5 equiv-



Scheme 2. Synthesis of *S*-(phenylsulfonyldifluoromethyl)thiophenium salts (**1**). See details in the Supporting Information.

Table 1: Electrophilic (phenylsulfonyl)difluoromethylation of **2a** with the salts **1**.[a]



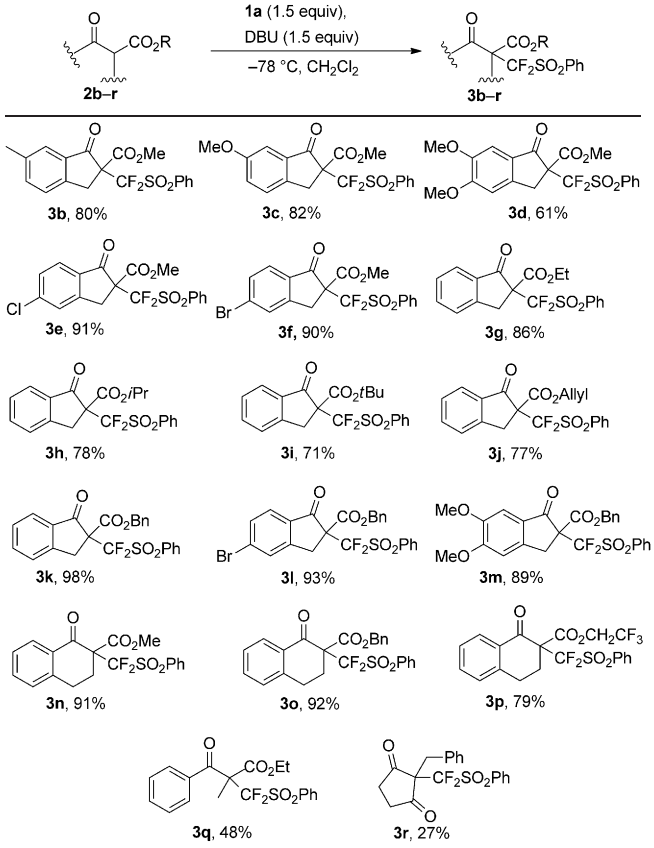
Entry	1	Base	Solvent	*T* [°C]	Yield [%][b]
1	**1a**	DBU	CH_2Cl_2	−78	99
2	**1b**	DBU	CH_2Cl_2	−78	87
3	**1a**	DBU	CH_3CN	−40	83
4[c]	**1a**	DBU	CH_2Cl_2	−78	83
5	**1a**	P1	CH_2Cl_2	−78	74
6	**1a**	K_2CO_3	CH_2Cl_2	−78	14

[a] The reaction was carried out with 0.1 mmol of substrate **2a**. For detailed reaction conditions, see the Supporting Information. [b] Yields of isolated products. [c] Used 1.2 equivalents of **1a**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, P_1 = phosphazene base P1-*tert*-butyl-tris(tetramethylene).

alents of **1a** or **1b** in the presence of 1.5 equivalents of DBU in dichloromethane at −78 °C (entries 1 and 2). As expected, **1a** gave only the C_{sp^3}–CF_2SO_2Ph product **3a** in 99% yield without any undesired O–CF_2SO_2Ph product. The phenyl reagent **1b** also proceeded nicely to afford **3a** in 87% yield. We next examined the effects of temperature and solvent. The yield decreased to 83% in acetonitrile at −40 °C (entry 3). When 1.2 equivalents of DBU were used, the yield decreased slightly to 83% (entry 4). The base was also screened, and when P1 was used instead of DBU it gave a lower yield of 74% (entry 5), whereas the inorganic base K_2CO_3 provided **3a** in only 14% yield (entry 6). The complete carbon selectivity could be explained in terms of the electrophilic softness of difluoromethyl cation increase caused by the phenylsulfonyl moiety.

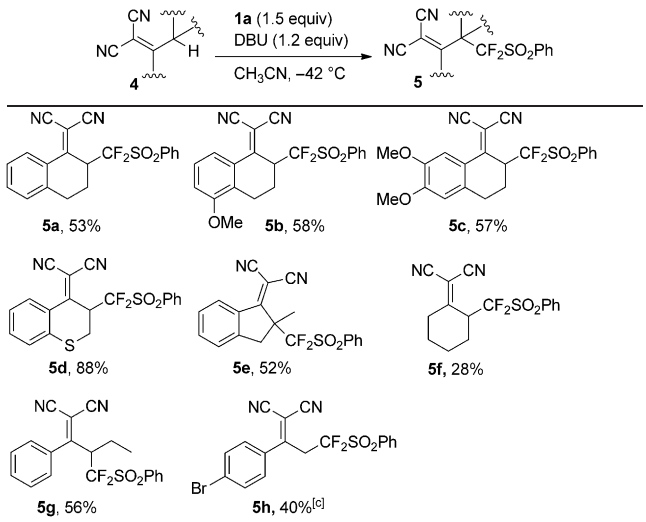
Under the optimum reaction conditions, we explored the substrate scope (**2b–r**; Table 2). A wide range of both indanone carboxylates and tetralone carboxylates were evaluated and furnished the corresponding C_{sp^3}–CF_2SO_2Ph products **3b–p**, having a quaternary carbon center. Methyl indanone carboxylates with both an electron-donating group (**2b–d**) and an electron-withdrawing group (**2e**,**f**) on the benzene ring reacted smoothly with **1a** to provide the corresponding products **3b–d** and **3e**,**f** in good to excellent yields. A variety of alkyl indanone carboxylates **2g–i** were efficiently transformed into the desired products **3g–i** in high to excellent yields. The allyl indanone carboxylate **2j** proceeded well to give **3j** in 77% yield. Benzyl indanone carboxylate without a substituent (**2k**) or with electron-withdrawing and electron-donating groups on benzene ring (**2l**,**m**) were good substrates for difuoromethylation with **1a**, thus affording **3k–m** in excellent yield. Tetralone carboxylates **2n–p** were also found to be good substrates for (phenylsulfonyl)difluoromethylation and furnished the products **3n–p** in good to excellent yields. It is noteworthy that even the less reactive acyclic β-ketoester **2q** afforded the corresponding difluoromethylated compound in moderate yield. We next examined the difluoromethylation of 1,3-diketones which, is more challenging since they selectively afford O–CF_2H products. Interestingly, the 1,3-diketone **2r** was selectively converted into the corresponding C_{sp^3}–CF_2SO_2Ph product **3r**

Table 2: Scope of the substrates **2** when using **1a**.[a,b]



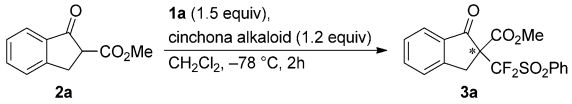
[a] Reaction conditions: **2** (0.1 mmol) was treated with DBU (0.15 mmol) for 15 to 20 min in CH_2Cl_2 at room temperature. The reaction mixture was cooled then to −78 °C and **1a** (0.15 mmol) was added, maintained for 30 min at the same temperature, then warmed to room temperature. [b] Yields of the isolated products.

Table 3: Allylic (phenylsulfonyl)difluoromethylation of the dicyanoalkylidenes **4** with **1a**.[a,b]



[a] Reaction conditions: **4** (0.1 mmol) was treated with DBU (0.12 mmol) for 15 to 20 min in CH_3CN at room temperature. The reaction mixture was then cooled to −42 °C and **1a** (0.15 mmol) was added, maintained for 30 min at the same temperature, then warmed to room temperature. [b] Yields of the isolated products. [c] Determined by ^{19}F NMR spectroscopy.

Table 4: Preliminary results of enantioselective (phenylsulfonyl)difluoromethylation of **2a** using **1a**.[a]



Entry	Cinchona alkaloid	Yield [%][b]	*ee* [%]
1	quinine	27	(+)-26
2	quinidine	29	(−)-19
3	cinchonine	19	(−)-15
4	cinchonidine	15	(+)-17
5	$(DHQ)_2PYR$	48	(+)-55
6	$(DHQ)_2AQN$	63	(+)-49
7[c]	$(DHQ)_2PYR$	50	(+)-50
8[c]	$(DHQ)_2AQN$	62	(+)-44
9	$(DHQD)_2AQN$	52	(−)-42

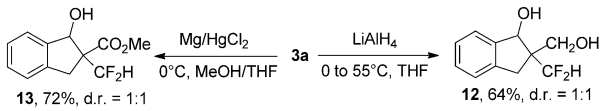
[a] The reaction was carried out with 0.1 mmol of substrate **2a**. For detailed reaction conditions, see the Supporting Information. [b] Yields of the isolated products. [c] Used 0.6 equivalents of cinchona alkaloid.

in 27% yield without any formation of the $O-CF_2SO_2Ph$ product, however, the reaction conditions need further optimization to improve the yield. The low yields for **3q** and **3r** were not improved by the use of stronger bases such as guanidines and phosphazenes.

The new reagent **1** can also be used in the electrophilic allylic (phenylsulfonyl)difluoromethylation of tetralone-derived dicyanoalkylidenes **4a–c** under similar reaction conditions, thus affording the corresponding allylic C_{sp^3}-CF_2SO_2Ph compounds **5a–c** in good yields (Table 3). The hetero-cyclodicyanoalkylidene **4d** and indanone-derived cyclodicyanoalkylidene **4e** were efficiently transformed into **5d** (88%) and **5e** (52%), respectively. The hexanone-derived aliphatic dicyanoalkylidene **4f** afforded **5f** in 28% yield. Excitingly, the acyclic substrates **4g** and **4h** were also found to be good substrates under the same reaction conditions, although product **5h** was unstable.

Enantioselective (phenylsulfonyl)difluoromethylation of **2a** was briefly investigated in the presence of cinchona alkaloids (Table 4). Quinine, quinidine, cinchonine, and cinchonidine gave **3a** in low yields with low enantioselectivities of up to 26% *ee* (entry 1–4). Bis(cinchona) alkaloids, such as $(DHQ)_2PYR$, $(DHQ)_2AQN$, and $(DHQD)_2AQN$ were found to be better for the enantioselective transformation (entries 5–8). Moderate yields (up to 63%) and enantioselectivities (up to 55% *ee*) of **3a** were observed in the presence of $(DHQ)_2PYR$ and $(DHQ)_2AQN$, respectively (entries 5 and 6). Interestingly, reducing the amount of $(DHQ)_2PYR$ and $(DHQ)_2AQN$ to 0.6 equivalents showed little influence on this transformation an gave almost the same yields and enantioselectivities (entries 7 and 8). The antipode of **3a** was obtained in the presence of a pseudo-enantiomer, $(DHQD)_2AQN$, to give **3a** in 42% *ee* and 52% yield (entry 9).

The product **3a** was conveniently transformed into the compound **12** in 64% yield by reduction with $LiAlH_4$ in THF.



Scheme 3. Reduction of **3a** to the compounds **12** and **13**. THF = tetrahydrofuran.

It was also converted into **13** in 72% yield by reduction with $Mg/HgCl_2$ (Scheme 3).

In conclusion, we have developed the novel electrophilic difluoromethylating reagents *S*-(phenylsulfonyldifluoromethyl)-thiophenium salts (**1**). These reagents are highly efficienct in the difluoromethylation of C_{sp^3} nucleophiles. A wide range of β-ketoesters and diketones are nicely and selectively converted into the corresponding products **3** in good to excellent yields under mild reaction conditions with none of the undesired $O-CF_2SO_2Ph$ products being isolated. The electrophilic allylic (phenylsulfonyl)difluoromethylation of dicyanoalkylidenes also succeeded with **1**. It should be noted that sulfur and fluorine are always a very good combination for the development of novel reagents for fluorine chemistry and our reagents represent another successful addition to this collection.[13] Studies to expand the scope of reagents and to develop applications are in progress, and includes the improvement of the enantioselective difluoromethylation.

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