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Fluoromethylene Transfer from Diarylfluoromethylsulfonium Salts: Synthesis of Fluorinated Epoxides

Janis Veliks*[a], and Armands Kazia[a]

Abstract: Diarylfluoromethyl sulfonium salts are efficient fluoromethylene transfer reagents equivalent to fluorocarbene, which is difficult to access. This was demonstrated by the development of a monofluorinated Johnson-Corey-Chaykovsky reaction with ketones and aldehydes, delivering uncommon 2-unsubstituted fluoroepoxides. This is the first evidence for the feasibility of sulfur fluoromethylylide and its action as a reaction intermediate.

The abundance of organofluorine compounds in medicinal and agrochemical portfolios has fueled enormous progress in the development of new synthetic methodologies in the area of fluorine chemistry.[1] However, direct monofluoromethylene (:CHF) transfer remained underdeveloped due to an extreme instability of fluorocarbenoids[2] and a limited availability of suitable reagents (Figure 1. A). Furthermore, computational studies predict that diazofluoromethane is not a viable species[3] (Figure 1. B). Freons of type $CHFX_2$ may be used as fluorocarbene precursors, but they are expensive, difficult to handle and restricted due to their ozone depleting properties.[4] To overcome this issue several indirect methods for accessing the fluoromethylene synthon have been developed which require extra synthetic steps, such as reduction of halofluoro- or phenylsulfide moieties.[5] Another successful example is the fluorinated sulfoximine reagent developed by Hu and coworkers.[6] The aforementioned reagents are suitable for the fluoromethylenation of alkenes, with only a single example of direct monofluoromethylene (:CHF) transfer to a carbonyl moiety known to date[7]. Availability of solid, bench stable reagents for this purpose would be of great value in the areas of medicinal[1b], agrochemical and material[8] chemistries.

Sulfur ylides may be used as carbene equivalents[9] and are central in the Johnson-Corey-Chaykovsky reaction.[10] We envisioned the use of sulfur ylides for fluoromethylene transfer, however, only decomposition of fluoromethyldimethyl sulfonium tetrafluoroborate has been reported.[11] Additionally, the lack of data on the ability of fluoromethylsulfonium salts to generate sulfur ylides and participate in Johnson-Corey-Chaykovsky reactions raised doubts over their suitability for the proposed transformation. Olah and co-workers have shown that *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**1**) is a bench stable and remarkably versatile reagent for the monofluoromethylation of various nucleophiles.[12] We were intrigued as to whether fluormethylsulfonium salt **1** could be used to generate sulfur fluoromethylylide, for participation in the Johnson-Corey-Chaykovsky fluoromethylenation.

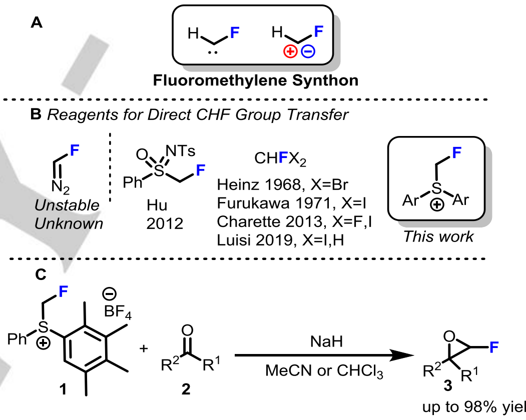

Figure 1. **A** Fluorocarbene and fluoromethylene synthon. **B** Reagents for the direct fluoromethylenation. **C** Fluoromethylenation of aldehydes and ketones.

Luisi very recently succeeded in monofluormethylenation of ketones to furnish 2-unsubstituted fluoroepoxides using lithiated fluoroiodomethane[7] (Figure 1. B). However, fluoroiodomethyllithium reaction with aldehydes and acetophenone derivatives does not afford fluoroepoxides. The closely related fluorinated sulfoximines developed by Hu and co-workers [6a-c] are capable of direct monofluoroalkenyl (:CRF, where R = Alk) transfer to ketones *via* a carbanion intermediate to deliver substituted fluoroepoxides. Monofluoromethylene transfer (:CHF) has not been demonstrated using the Hu reagent, and aldehydes are not tolerated under the reported reaction conditions as well. Other synthetic routes to fluorinated epoxides include: a) oxidation of vinyl fluorides;[13] b) base promoted cyclization of fluorohalohydrines;[14] c) Darzens type reaction with carbonyl compounds;[15] d) nucleophilic substitution of bromoepoxide with fluoride source.[16] Fluorinated epoxides are known to be of inherently low stability and tend to undergo 1,2-fluorine migration,[6a] limiting access to these compounds. Here we disclose the first example of fluoromethylsuflonium salt **1** as a competent flurомethylene transfer reagent, and its ability to participate in a fluorinated Johnson-Corey-Chaykovsky

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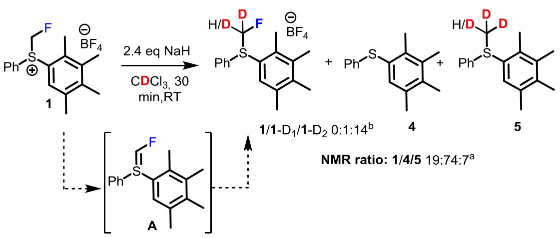
reaction under mild conditions, giving access to uncommon 2-unsubstituted fluoroepoxides.

Initial attempts to trap sulfur fluoromethyl ylide **A** involved treating sulfonium salt **1** with *n*-buthyllithium and subsequently quenching with deuterated benzoic acid or D_2O. However, only decomposition of sulfonium salt **1** with a loss of fluoride was observed. When reagent **1** was treated with NaH in $CDCl_3$ the ^1H and ^{19}F NMR spectra showed the formation of a deuterated sulfonium salt **1**-D_1/D_2 in addition to the decomposition products **4** and **5** (Scheme 1). This unprecedented deuteration of sulfonium salts in $CDCl_3$ suggests fluoromethylylide **A** as probable intermediate.



Scheme 1. Deuteration of **1** *via* sulfur fluoromethyl ylide **A**. NMR ratio determined by $^1H^{[a]}$ and ^{19}F NMR[b].

This result motivated further exploration of sulfonium salt **1** as a competent fluoromethylene group transfer reagent.

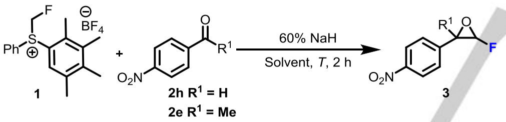
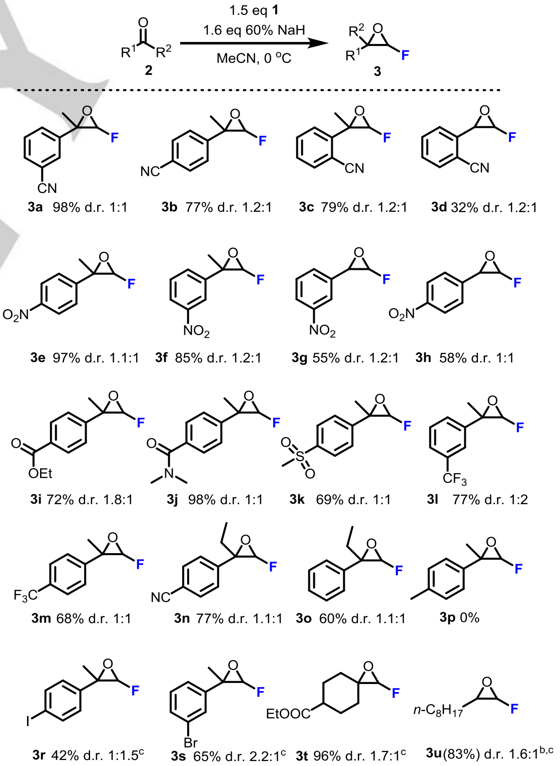


Table 1. Reaction Optimization.

entry[a]	**1/2/base**	R^1	Solvent[b]	*T* °C	Yield of **3** [%] [d]	d.r.
1	1/1/1.1[c]	H	THF	-78	0	-
2	1/1/1.5	H	1,4-dioxane	RT	57	1.7:1
3	1/1/1.5	H	CH_2Cl_2	RT	55	1.4:1
4	1/1/1.5	H	THF	RT	52	1.2:1
5	1/1/1.5	H	DMF	RT	0	-
6	1/1/1.5	H	$CHCl_3$	RT	81	1:1
7	1/1/1.5	H	MeCN	RT	83	1.4:1
8	1.1/1/1.5	Me	MeCN	RT	54	1.3:1
9	1.5/1/1.6	Me	MeCN	RT	72	1:1
10	1.5/1/1.6	Me	MeCN	0	96(97)	1:1
11	2.0/1/2.2	Me	MeCN	0	87	1:1

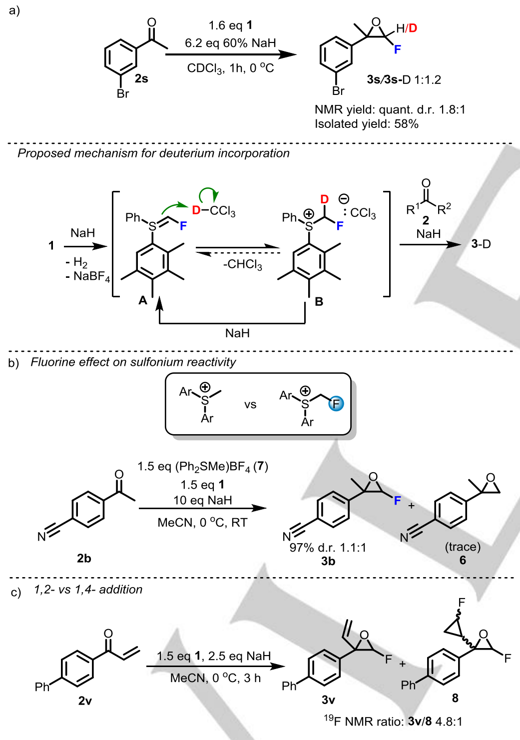
[a] Reaction conditions: To a mixture of **1** (0.138 mmol) and **2** in a solvent (0.05 M) under Ar atmosphere was added 60% NaH (in paraffin oil). The solvent was evaporated under reduced pressure and the crude reaction mixture was analysed by ^1H and ^{19}F NMR. [b] Anhydrous solvents. [c] 1.1 eq *n*-BuLi, 20 min, -78 °C, then **2**, 18 h, -78 °C to RT. [d] Determined by ^{19}F NMR using CF_3COOEt as internal reference. Isolated yields in parenthesis.

p-Nitrobenzaldehyde **2h** was selected as a model substrate to test the feasibility of monofluoromethylenation using sulfonium salt **1**. Our initial attempt to generate the desired ylide in THF using *n*-BuLi followed by the addition of **2h** was not successful (Table 1, entry 1). Gratifyingly, when sulfonium salt **1** and aldehyde **2h** were combined in 1,4-dioxane followed by NaH addition, the desired product **3h** was observed in moderate yield (entry 2). Solvent screening (Table 1, entry 2 to 7) identified acetonitrile as the optimal solvent. When, under the same conditions, *p*-nitroacetophenone **2e** was used as substrate (entry 8) the reaction proceeded with moderate yield but incomplete conversion. Higher loading of **1** (entry 9) and lower temperature (entry 10) gave the optimal reaction conditions. Further increasing the loading of sulfonium salt **1** was not beneficial, giving a slight decrease in yield (entry 11). The optimal reaction conditions therefore consist of treating **2e** with **1** (1.5 eq) and NaH (1.6 eq) in MeCN at 0 °C, giving the desired product with excellent yield as a mixture of diastereomers. Typically, the reaction is complete within 3 to 4 hours.



Scheme 2. Scope of the monofluoromethylenation. ^{a}Isolated yields unless otherwise stated. ^{b}Yield was determined by ^1H NMR using 1.0 eq of EtOAc as an internal reference. ^{c}Conditions: 2.0 eq **1**, 4.0 eq NaH, $CHCl_3$ (0.1 M), 0 °C, 1-5 h.

After establishing reaction conditions for the Johnson-Corey-Chaykovsky fluoromethylenation, the substrate scope was investigated (Scheme 2). The reaction conditions are compatible with variety of aryl substituted ketones and aldehydes **2**. Functional groups such as nitro, cyano, ester, amide, trifluoromethyl and sulfone are tolerated, affording products **3a-n** in moderate to high yields. Electron withdrawing groups are known to increase the stability of fluorinated epoxides,[6a] meaning a range of compounds could be chromatographically isolated on silica gel pretreated with Et_3N[6c] or alumina. To our surprise, ketone **2o** with an unsubstituted phenyl ring gave product **3o** in a good isolated yield after chromatography. Substrates bearing electron donating groups on the aryl ring did not afford the desired products (see **3p**) due to instability of the corresponding epoxides. Halogenated acetophenones efficiently participate in this reaction with $CHCl_3$ as solvent, giving products **3r** and **3s** in moderate to good yields. In addition, linear and cyclic aliphatic ketones or aldehydes participate well in the reaction, giving good to high yields of **3t** and **3u,** respectively. The substrate scope is broad and mainly limited by the stability of the resultant fluoroepoxides **3** rather than the fluoromethylenation itself, as the decomposition products originating from fluoroepoxide **3** are always observed for unproductive substrates.[17]



Scheme 3. Reactivity and properties of sulfonium salt **1**.

To corroborate our indirect observation of ylide formation in $CDCl_3$ (Scheme 1) we have investigated whether deuterium can be transferred from $CDCl_3$ *via* ylide to the fluorinated epoxide **3**. Indeed, when fluoromethylenation of ketone **2s** was performed in the $CDCl_3$, deuterium incorporation into fluoroepoxide **3s**/**3s**-D was observed in a ratio of 1:1.2 (Scheme 3a). This suggests that formation of fluoromethylylide is a fast and possibly reversible process in chloroform, competing with nucleophilic attack of ylide at the carbonyl group. Chloroform-*d* could act either reversibly as an acid, exchanging proton to deuteron *via* intermediate **B,** or alternatively ylide **A** could be regenerated by a second reaction of **B** with another equivalent of NaH. (Scheme 3a).

In order to probe the influence of fluorine on the reactivity of sulfonium salts we performed a competition experiment whereby fluoromethyl sulfonium salt **1** and methyldiphenylsulfonium tetrafluoroborate (**7**) were reacted with ketone **2b** delivering fluorinated epoxide **3b** in excellent yield (Scheme 3b). Only traces of nonfluorinated epoxide **6** were observed by ^{1}H NMR. This demonstrates the positive effect of fluorine on the reactivity of sulfonium salts compared to their nonfluorinated counterparts. This could be attributed to higher acidity of the fluromethyl group compared to the methyl group of sulfonium salts. Fluorine could also increase the nucleophilicity of the ylide intermediate **A**. This offers a rationale as to why competing decomposition of **1** to deliver nonfluorinated sulfonium salt **5** (Scheme 1) does not have a detrimental effect on chemoselectivity of the reaction.

Vinyl substituted ketone **2v** has been used to probe selectivity towards 1,2-addition versus 1,4-addition (Scheme 3c). Fluoromethylenation proceeds preferably at the carbonyl moiety to give fluoroepoxide **3v**. However, a complex mixture of cyclopropanated diastereomers **8**–which could originate from the conjugate addition–can be observed by ^{19}F NMR as well.

In summation, we have demonstrated the first evidence for the feasibility of sulfur fluoromethylylide, generated from diarylfluoromethylsulfonium tetrafluroborate, as a reaction intermediate. This resulted in the development of an efficient and general method for the formation of uncommon 2-unsubsituted fluoroepoxides, highlighting the unexplored and vast potential of fluoromethylsulfonium salts as direct fluoromethylene transfer reagents. With this, we offer a bench stable, easy to operate and efficient synthetic equivalent to the otherwise very challenging fluorocarbene synthon.

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Finnancial support by ERDF project Nr.1.1.1.5/17/A/003. Prof. Dr. Aigars Jirgensons for scientific advise. Renāte Melngaile, Artūrs Sperga for the synthesis of **1**. LIOS analytical service for NMR and elemental analysis. Dr. Stephen Hyde for proofreading.

Keywords: Johnson-Corey-Chaykovsky reaction • fluoromethylenation • sulfur fluoromethylylide • fluorinated epoxides • Fluoromethylene transfer

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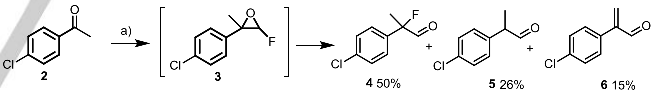
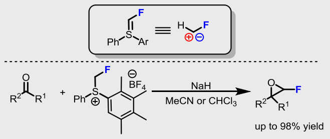


a) 1.5 eq **1**, 1.6 eq NaH, MeCN, 0 °C, 4 h. Yields determined by ^1H NMR using 1.0 eq CF_3COOEt as internal reference.

COMMUNICATION

Sulfur fluoromethylylide in action: Diarylfluoromethyl sulfonium salts are efficient fluoromethylene transfer reagents. This was demonstrated by the development of a monofluorinated Johnson-Corey-Chaykovsky reaction with ketones and aldehydes, delivering uncommon 2-unsubstituted fluoroepoxides. This is the first evidence for the feasibility of sulfur fluoromethylylide and its action as a reaction intermediate.



up to 98% yield

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