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Diastereoselective Monofluorocyclopropanation Using Fluoromethylsulfonium Salts

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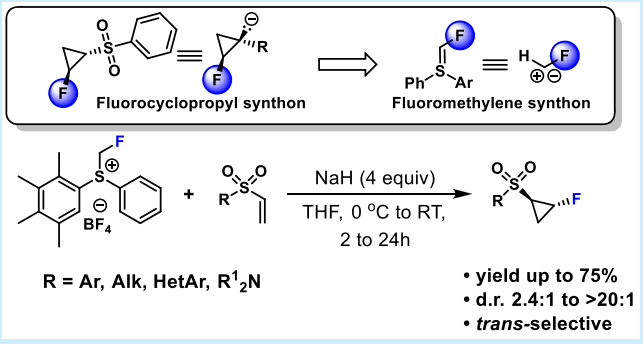
Supporting Information

ABSTRACT: Diarylfluoromethylsulfonium salts, alternatives to freons or advanced fluorinated building blocks, are bench stable and easy-to-use sources of direct fluoromethylene (:CHF) transfer to alkenes. These salts enabled development of a *trans*-selective monofluorinated Johnson−Corey−Chaykovsky reaction with vinyl sulfones or vinyl sulfonamides to access synthetically challenging monofluorocyclopropane scaffolds. The described method offers rapid access to monofluorinated cyclopropane building blocks with further functionalization opportunities to deliver more complex synthetic targets diastereoselectively.



The cyclopropyl moiety and fluorine atom can be commonly found in drug molecules.[1] Often both of these functionalities add to the physicochemical properties of potential drug molecules in terms of metabolic stability, lipophilicity, and pharmacokinetics.[2] However, the combination of these two moieties into a fluorocyclopropyl moiety is rather rare and much less studied.

A prominent example of a drug molecule containing a fluorocyclopropane motif is the broad spectrum antibiotic Sitafloxacin[3a] (Figure 1A). The recently approved constituent of combination drug to combat hepatitis C virus, Glecaprevir[3b] illustrates that the combination of multiple fluorines and cyclopropanes improves overall profile. In addition, fluorocyclopropyl groups containing Tyk2 JH 2 kinase inhibitors show promising results for the treatment of psoriasis and Crohn's disease.[3c]

Thus, there is a clear need for novel and direct monofluoromethylene (:CHF) transfer methodologies utilizing available substrates and user-friendly reagents. Nevertheless, the intriguing world of small and strained cycles rarely meet together with fluorine due to the limited accessibility of suitable reagents, lack of concise synthetic routes and stability issues of the reactive intermediates.[4] Availability and versatility of various alkenes bearing electron-withdrawing groups would be an ideal platform for the synthesis of monofluorocyclopropanes. Diazofluoromethane would be an atractive source of fluorocarbene, however, it has been predicted to be an unstable species (Figure 1B).[5] Fluorocarbene generated from either low boiling, expensive, or environmentally concerning freons of type $CHFX_2$,[6] gave mixed results in terms of the reactivity and efficiency. To overcome these issues, several indirect methods have been developed to access fluorinated cyclopropanes.[7] Hu's fluorinated sulfoximines have shown to be a direct monofluoromethylenation reagent[8] of alkenes. However, the application of the aforementioned reagent beyond Weinreb amide has not been demonstrated. Other methods accessing monofluorocyclopropanes involve different bond forming approaches, such as, carbenoid addition to vinyl fluorides[9] or fluorination of already existing cyclopropane derivatives.[10] In general, access to α-unsubstituted fluorcyclopropanes suffers from limitation of current synthetic methods. In addition, current methods deliver primarily *cis*-products.[11]

Fluorocarbenoids, generally considered as extremely unstable and difficult to access, have shown recent progress in terms of feasibility and synthetic utility.[12] Our work has demonstrated that bench stable and solid diarylfluoromethyl sulfonium reagents can efficiently transfer the monofluoromethylene group to ketones and aldehydes delivering α-fluoroepoxides under mild conditions.[13] Pursuing research in this direction, we report an efficient protocol for the *trans*-diastereoselective Johnson-Corey-Chaykovsky fluoromethylenation of vinyl sulfones and vinyl sulfonamides using *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**1**), now a commercially available reagent,[14] to deliver novel fluorocyclopropane derivatives.

This method delivers monofluorocyclopropane derivatives decorated with functional groups offering an access to the fluorinated building blocks relevant to medicinal chemistry.

We began the investigations with the fluorocyclopropanation of arylvinylsulfones **2** because vinyl sulfones are potent Michael acceptors.[15] Morevoer, fluorocyclopropylsulfones and sulfonamides[16] emerged as new scaffolds in medicinal chemistry. In

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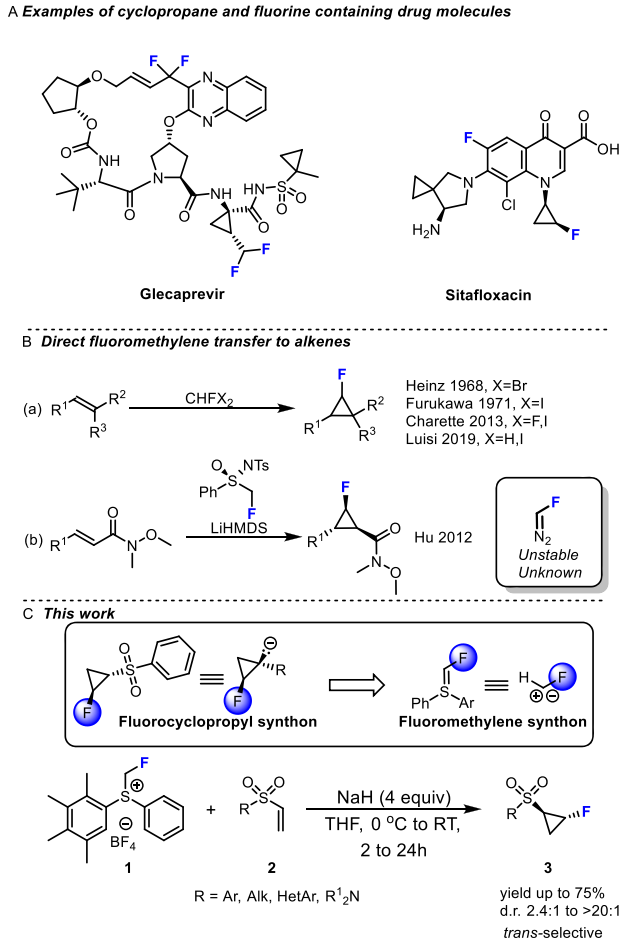

Figure 1. (A) Drug molecules containing both the cyclopropyl moiety and a fluorine atom. (B) Direct methods for monofluoromethylenation of alkenes. (C) Johnson–Corey–Chaykovsky fluorocyclopropanation.

addition, we were attracted to the idea of the potential utility of further functionalization at the α-position of the sulfone group.[17]

Initial attempt to perform the reaction of the fluoromethylsulfonium salt **1** with phenylvinylsulfone **2a'** in chloroform-*d* allowed quick identification of the formation of the desired fluorocyclopropane **3a'** by ^{1}H and ^{19}F NMR albeit in low yield (Table 1, entry 1). Solvent screening identified THF as the optimal solvent (Table 1, entries 2–6). Further dilution or concentration did not give any improvement (entries 7–8). Performing the reaction at lower temperature increased reaction time from 3 to 24 h as well as gave incomplete conversion and lower product **3a'** yield but very high diastereoselectivity (entry 9). Adjusting the amount of sulfonium salt **1** and addition of the base in one portion (entry 10) gave the highest overall yield and the most versatile conditions for the broad spectrum of substrates (vide infra). The final reaction conditions therefore consist of treating **2a'** with **1** (2.0 equiv) and NaH (4.0 equiv) in THF at room temperature giving desired fluorocyclopropylsulfone **3a'** in very good yield with *trans*/*cis* 4.4:1 selectivity.

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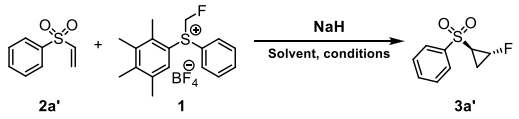
Table 1. Optimization Experiments[a]



no.	**2a'**/**1**/NaH	solvent (c, M)	t (h)	yield **3a'** (%)[b]	d.r. trans/cis
1	1/1/1.5	$CDCl_3$ (0.1)	3	26[c]	6:1
2	1/2/2.2	MeCN (0.05)[f]	18	43	4:1
3	1/1.6/4[d]	$CHCl_3$ (0.1)	20	71	5:1
4	1/1.6/4[d]	1,4-diox (0.1)	20	75	3:1
5	1/1.6/4[d]	CH_2Cl_2 (0.1)	24	76	4:1
6	1/1.6/4[d]	THF (0.1)	3	85	6:1
7	1/1.6/4[d]	THF (0.05)	3	67	9:1
8	1/1.6/4[d]	THF (0.2)	3	78	6:1
9	1/1.6/4[d]	THF (0.1)[f]	24	75	18:1
10	**1/2/4**[e]	**THF (0.1)**	**2.5**	**86**	**4.4:1**

[a]To a mixture of **2a'** (0.1 mmol) and **1** under an Ar atmosphere was added anhydrous solvent followed by 60% NaH in paraffin oil. The reaction mixture was stirred at rt for the indicated time unless otherwise stated. The crude reaction mixture was analyzed by ^{1}H NMR. [b]^{1}H NMR yield determined using EtOAc (1.0 equiv) as an internal reference. [c]67% deuterated product. [d]Stepwise addition of NaH. [e]NaH added in one portion. [f]0 °C to rt.

After identification of optimal reaction conditions, the reaction scope was investigated (Scheme 1). The reaction conditions tolerate a range of substituted arylvinyl sulfones **2** as substrates delivering fluorocyclopropanes **3** with good yields of chromatographically purified *trans*-products. The reaction conditions turned out to be robust giving similar results for large variety of fluorocyclopropylarylsulfones **3**. Such functionalities as ester, nitrile and nitro-groups are tolerated under the reaction conditions. Cycloalkyl **2a** and benzylic **2u** vinylsulfones are tolerated giving the desired fluorocylclopropanes **3a** and **3u** with moderate yields and diastereoselectivities. Heterocyclic substrates **2r**, **2s**, **2v** work well under the reaction conditions. Noteworthy, is that the benzothiazole derivative **3x** forms with excellent diastereoselectivity but low yield. Sulfonamide functionality is abundant in many drug molecules[18] including Glecaprevir (Figure 1, A). To our delight, vinyl sulfonamides **2aa–ad** also participate in the reaction with fluoromethyl sulfonium salt **1**. Reaction proceeds with longer reaction time and performs best at lower temperature affording fluorocyclopropyl sulfonamides **3aa–ad** in moderate yields. The product **3ad** shows selectivity toward the vinyl sulfone moiety in the presence of another double bond.

The fluorocyclopropanation reaction of vinylsulfones **2** can be easily upscaled to gram scale (Scheme 2). The desired fluorocyclopropyl sulfone **3a'** was obtained with excellent yield and good diastereoselectivity. Both diastereomers can be easily separated chromatographically giving access to both *cis*- and *trans*- diastereomers. This motivated investigating on the use of the compound **3a'** as a nucleophilic fluorocyclopropane building block - a platform for the further functionalization.

An alkylation at the α-position of **3a'** offers an access of more advanced monofluorocyclopropyl- containing products **4** (Scheme 2). The alkylation of fluorocyclopropane **3a'** gave selectively *trans*-products **4** in good yields. We were pleased to see that aldehydes are competent electrophiles as well, to give product **4d'** as a 1:1 mixture of diastereomers while completely retaining *trans*- configuration at α-position. The high diaster-

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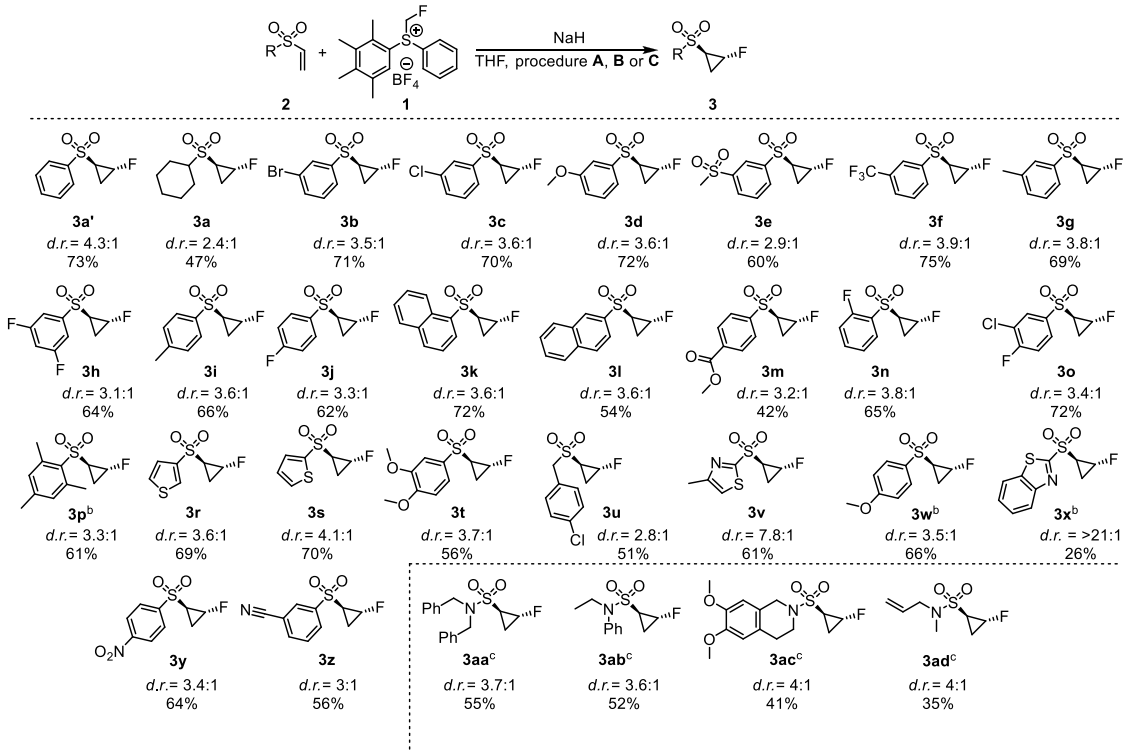
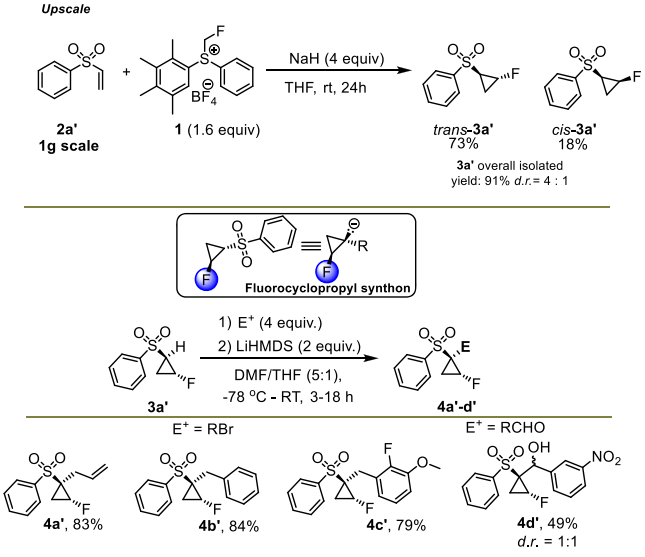
Scheme 1. Reaction Scope of the Fluorocyclopropanation[a]

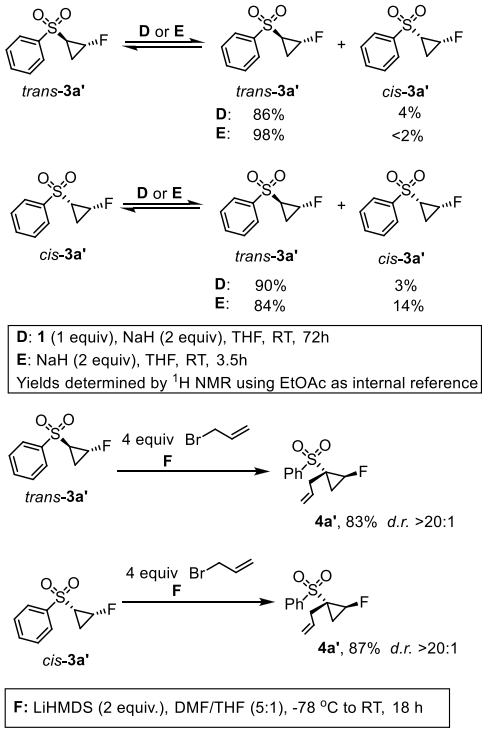


[a]**Procedure A: 2** (0.20 mmol, 1.0 equiv), **1** (2 equiv), 60% NaH (4.0 equiv), dry THF (0.1 M), rt, 2 to 3 h, unless otherwise stated. Isolated yields for *trans*-**3** products; *d.r.* determined by ^{1}H or ^{19}F NMR of the crude reaction mixture. [b]**Procedure B: 2** (0.20 mmol, 1.0 equiv), **1** (3 equiv), 60% NaH (4.0 equiv), dry THF (0.1 M), rt, 24 h [c]**Procedure C: 2** (0.20 mmol, 1.0 equiv), **1** (3 equiv), 60% NaH (5.0 equiv), dry THF (0.2 M), rt, 24 h.

Scheme 2. Upscale and α-Functionalization of Fluorocyclopropyl Sulfone 3a′



Scheme 3. Mechanistic Experiments



eoselectivity affording compounds **4** renders **3a′** a valuable fluorocyclopropylgroup containing building-block.

To gain deeper insight into the origin of the diastereoselectivity observed in the fluorocyclopropanation reaction we pursued mechanistic investigations. Both isolated *cis*-**3a′** or *trans*-**3a′** diastereomers exposed repeatedly to the conditions mimicking the reaction (Scheme 3, conditions **D**) or stirred with the base alone (conditions **E**) in THF afforded *trans*-**3a′** product with *d.r.* ∼ 15:1 without significant decomposition even after 3 days. When both *cis*-**3a′** or *trans*-**3a′** were exposed to the alkylation conditions (conditions **F**) with allylic bromide, both

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diastereomers afforded the same *trans*-**4a**′ product suggesting the involvement of a thermodynamically more stable *trans*-carbanion. The geometry of sulfone stabilized carbanion is known to be nonplanar[19] providing bases for highly stereoselective process.

Computational studies were carried out to identify mechanistic details of the reaction process for the fluorocyclopropanation reaction. Initially, addition of ylide to the activated double bond can afford *syn*- or *anti*- betaines $\mathbf{A^1}$ and $\mathbf{A^2}$, which subsequently undergo rotation, to form $\mathbf{B^1}$ and $\mathbf{B^2}$ (Figure 2, A),

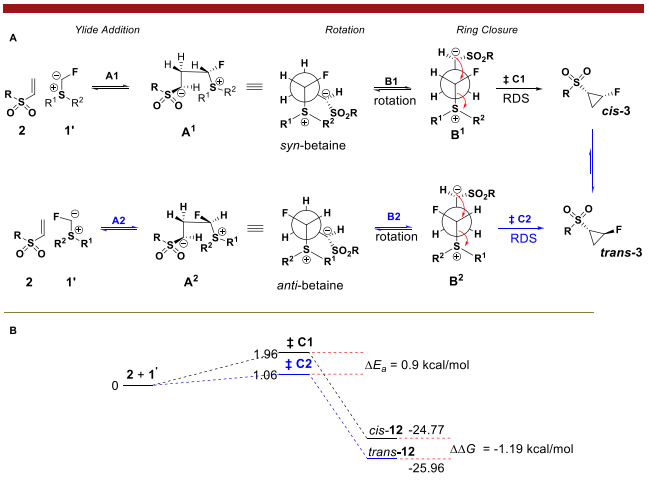

Figure 2. (A) Proposed reaction mechanism. (B) B97D/Def2-TZVPPD (THF)//B97D/Def2-TZVPP (THF) calculated reaction profile for (R = 3-MePh−, $R^1 = R^2$ =Me−). Energetics (including ZPE) in kcal/mol.

respectively.[20] For both pathways, calculations support an attenuated steric model in the transition state, with the ring closing being ‡**C1** and ‡**C2** as the stereoselective steps and formation of *trans* product 0.9 kcal/mol lower in energy than for *cis*-product (Figure 2, B). The calculated thermodynamics also indicates that the *trans*-product is more stable by 1.19 kcal/mol. These results suggest that initially the reaction is kinetically controlled with selectivity consistent with TS energy differentiation, while at longer times thermodynamic equilibration sets in and the energy difference of the products determines the stereoisomeric outcome.

The calculations also show that substituents at the aryl ring have minor influence on the diastereoselectivity of the reaction (see SI, p 41), which is in agreement with experimental results (Scheme 1).

In conclusion we have demonstrated that bench stable and accessible diarylfluoromethyl sulfonium salts are competent fluoromethylene transfer reagents to deliver functionalized monofluorocyclopropanes in Johnson−Corey−Chaykovsky reaction with vinyl sulfones and vinyl sulfonamides. This shows that an active intermediate, sulfur fluoromethylylide, offers an efficient and alternative way to tackle chemistry currently performed mostly by fluorocarbene and fluorocarbenoid chemistry. The synthetic utility of fluorocyclopropylarylsulfones spans from the possibility to introduce the fluorocyclopropane substructure in more complex products to favorable stereoselectivity offering facile access to *trans*-products as opposed to more common *cis*-selective transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02867.

Experimental details, computational data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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