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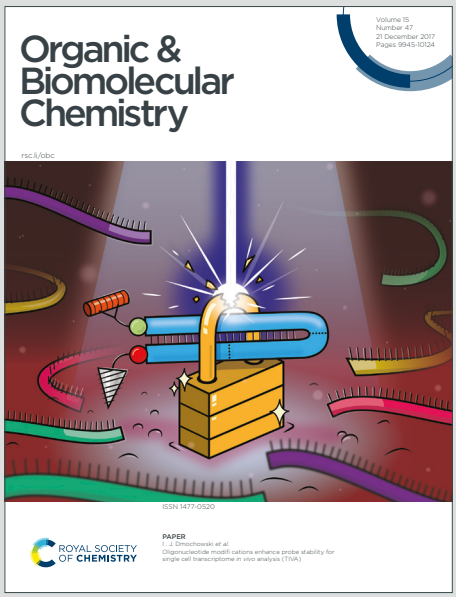

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ARTICLE

Johnson–Corey–Chaykovsky Fluorocyclopropanation of Double Activated Alkenes: Scope and Limitations

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Johnson-Corey-Chaykovsky fluorocyclopropanation of double activated alkenes utilizing *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate is an efficient approach to obtain a range of monofluorocyclopropane derivatives. So far, fluoromethylsulfonium salts display the broadest scope for direct fluoromethylene transfer. In contrast to more commonly used fluorohalomethanes or freon derivatives, diarylfluoromethylsulfonium salts are bench stable, easy-to use reagents useful for the direct transfer of a fluoromethylene group to alkenes giving access to the challanging products - fluorocyclopropane derivatives. An interplay between reactivity of starting materials and stability of formed fluorocyclopropanes determines the outcome of the process.

Introduction

The fluorine atom is commonly found in many pharmaceuticals[1] and agrochemicals[2] due to its unique ability to improve the range of molecular properties. For instance, bioisosteric replacement of hydrogen with fluorine often enhances pharmacophysical properties of drug candidates[3]. On the other hand, a cyclopropane moiety can be found both in natural products and many pharmaceutical drugs[4]. Cyclopropane can act as configurationally stable bioisosteric replacement of a double bond and, in general, it can improve metabolic stability, lipophilicity and solubility of the potential drug candidate. The fluorocyclopropanes[5]– a combination of both chemical entities – cyclopropylgroup and fluorine, is less common, however, is a very interesting substructure to be used in medicinal chemistry for drug discovery. This is exemplified by fluorocyclopropyl-containing pharmaceuticals, such as Sitafloxacin[6], Tyk2 JH 2 kinase inhibitors[7]. Upon lead optimization the fluorine test, where fluorine atom is introduced in various positions of an active molecule is a routine nowadays[8]. However, incorporation of a fluorine atom into a cyclopropane moiety poses many synthetic challenges. Direct fluorination of cyclopropane requires pre-functionalized cyclopropanes[9]. An alternative approach towards these structures is the use of vinylfluorides which are exposed to carbenoid chemistry[10]. Much more perspective from a versatility point of view is direct fluorocarbene or fluorocarbenoid addition to alkenes. For this transformation, freons ($CHFX_2$)[11] or fluoromethylsulfoximine reagents[12] are currently used. These methods, though, used even on a large scale[13], constitute considerable drawbacks, such as the use of low boiling, or environmentally concerning reagents, or suffer from limited substrate scope. Until recently, fluorocarbenoid species were considered a very unstable and difficult to work with species[14a]. However, recent progress has showed feasibility and even remarkable stability of the fluorocarbenoid species to be effectively used in synthesis[14].

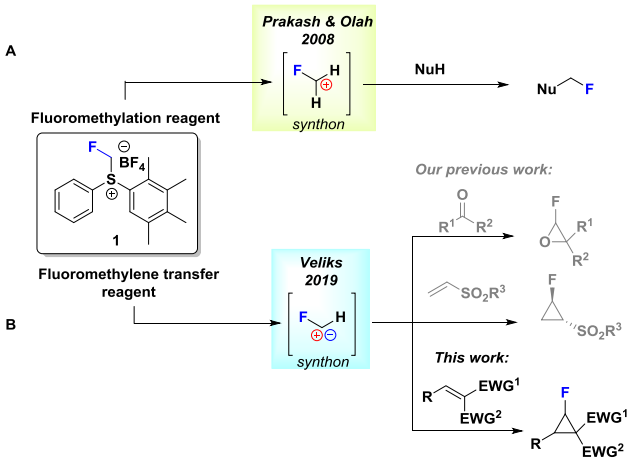

Fig. 1 Fluoromethylsulfonium reagent **1** for: **A** Fluoromethylation; **B** fluoromethylene transfer.

Our recent work has demonstrated that an alternative to halomethane or freon is the solid, bench stable and easy-to-use *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (**1**) (Fig. 1). This sulfur fluromethylylide precursor, originally developed for electrophilic fluoromethylation[15] (CH_2F-), can be used efficiently as a fluoromethylene transfer (CHF=) reagent to ketones, aldehydes[16a], vinylsulfones and vinylsulfonamides[16b]. Pursuing our research program on fluoromethylene transfer chemistry we aimed to investigated scope and limitation of

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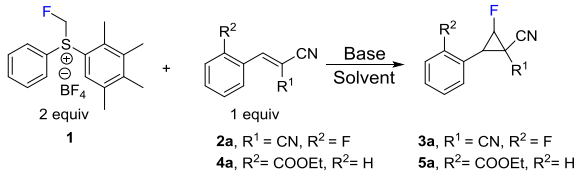
fluoromethylsulfonium reagent **1** for the synthesis of fluorocyclopropane derivatives. Herein, we demonstrate that fluoromethylsulfonium salt **1** is a highly efficient and user friendly reagent for the Jonhnson-Corey-Chaykovsky fluorocyclopropanation of double activated alkenes.

Results and discussion

Initially, for the fluorocyclopropanation reaction arylidene malononitrile **2a** was selected as a model substrate. It was encouraging to observe the formation of the desired fluorocyclopropane **3a** under the initially selected, non-optimized reaction conditions (Table 1, entry 1). After solvent screening (entries 1-4) 1,4-dioxane turned out to be the most efficient reaction media (entry 4) and NaH was identified as an optimal base (entry 4 *vs* 5) affording the fluorocyclopropanated product **3a** with moderate ^{1}H NMR yield. Unfortunately isolation of the dicyano- substituted fluorocyclopropanes **3a** was unsuccessful due to instability of the formed products. In turn, the fluorocyclopropanation of ethyl benzylydenecyanoacetate **4a** was found to be highly efficient (Table 1). The resulting cyanoacetate derived fluorocyclopropane **5a** turned out to be a stable and chromatographically isolable product which was obtained in excellent yield. After adjustment a concentration (entries 6-8) of the optimal reaction conditions are as follows: to a solution of **4a** (1 equiv) and **1** (2 equiv) in dry 1,4-dioxane (0.17 M of **1**) under Ar atmosphere 60% NaH (4 equiv) was added at room temperature. Under the optimized reaction conditions a substrate scope was further investigated (Scheme 1).

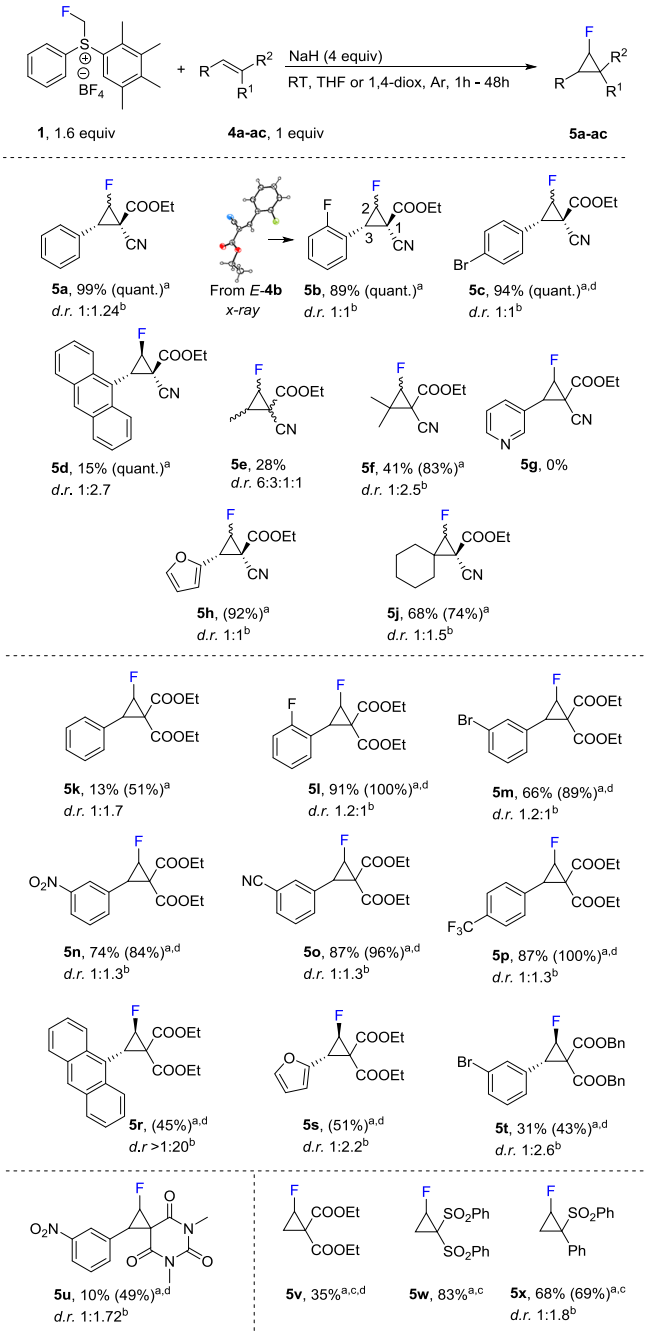
Table 1 Optimization of fluorocycolpropanation reaction of arylidene malononitrile **2a**



Nr.	Base (equiv)	Solvent[d]	SM	Yield **3a,5a**, %[c]	*d.r. cis/trans*
1.	NaH (2.5)[a]	$CDCl_3$	**2a**	15	1/1.28
2.	NaH (2.5)[a]	THF	**2a**	44	1/1.35
3.	NaH (2.5)[a]	MeCN	**2a**	17	1/1.08
4.	NaH (2.5)[a]	1,4-diox	**2a**	55	1/1
5.	*n*-BuLi (2.2)[b]	THF	**2a**	18	1/1.12
6	NaH (4)[a]	1,4-diox	**4a**	85	1/1.7
7	**NaH (4)[a]**	**1,4-diox**[e]	**4a**	**100 (99)**	**1/1.24**
8	NaH (4)[a]	1,4-diox[f]	4a	95	1/1.2

[a] Addition at RT. [b] Addition at -78 °C, then warmed to RT. [c] ^{1}H NMR yield determined using 1 equiv EtOAc as internal standart (Isolated yield). [d] Sulfonium reagent **1** conc. 0.17 M. [e] 0.11 M. [f] 0.082 M.

The aryl substituted fluorocyclopropyl-cyanoesters **5a-d** were formed with high isolated yields as a mixture of diastereomers.



Scheme 1. Substrate scope for Johnson–Corey–Chaykovsky fluorocyclopropanation reaction. Reaction conditions: To a solution of **4** (0.21 mmol, 1 equiv), **1** (1.6 equiv) in 1,4-dioxane (3 mL) under Ar atmosphere was added NaH (60 % in paraffin

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oil, 4.0 equiv) at RT unless otherwise stated. The reaction mixture was stirred at RT till completion (TLC control). [a] Isolated yields (NMR yields using 1.0 equiv. of EtOAc as an internal reference). [b] d.r. determined for the crude reaction mixture. [c] Reaction performed at 0 °C. [d] THF used as a solvent.

As shown on the example of product **5b**, the original configuration at the positions C-1 and C-3 was transferred from a starting material alkene *E*-**4b** which applies to all aryl-substituted fluorocyclopropanes **5a-d**, **5h** in a cyanoester series. This results in the formation of only two diastereomers instead of 4 possible. Sterically demanding anthracenyl derivative **5b** was formed in excellent NMR yield and increased d.r albeit it could only be isolated with low yield due to its poor stability. This suggests that steric bulk at the position C-1 in the resulting cyclopropane can improve the stereoselectivity at the fluorine bearing center (C-2). The alkyl-substitution of cyanoesters **4e,f,j** is compatible with the fluorocyclopropanation protocol giving products **5e,f,j** in low to good isolated yields. However, the sterically small methyl substitution does not provide transfer of the stereochemistry of the double bond geometry into the product. Methyl- substituted fluorocyclopropane **5e** was obtained as a mixture of all four diastereomers.

Pyridine as a substituent was not compatible with the reaction conditions, despite the full conversion of the starting material **4g** the formation of fluorocyclopropanation product **5g** was not observed. The limitation of the fluorocyclopropanation are substrates containing electron rich aromatic double bond substituents due to obvious instability of the reaction products. The furan derivative **4h** efficiently undergoes fluoromethylene transfer as detected by NMR, however, the product **5h** decomposed upon chromatographic purification.

Arylidene malonate derivatives **4k-t** are well suited substrates for the fluorocyclopropanation reaction giving the products **5k-t** in low to very good yields as a mixture of diastereomers. Electron withdrawing groups (**4n,o,p**) and halogen (**4l,m**) on the aryl moiety of the arylydene malonates **4** furnished good to excellent yields of the fluorocyclopropanes **5**. Olefins with electron rich aryl groups and unsubstituted phenyl substituents (**5k, 5r, 5s**) gave products with moderate NMR yields which were prone to decompose upon isolation. This observation is in line with the stability and kinetics of donor-acceptor (D-A) cyclopropanes where generally electron donating groups increase the cyclopropane cleavage rate[18].. The barbituric acid derivative **4u** involves readily in fluorocyclopropanation reaction affording the fluorocyclopropane **5u** with good NMR yield, however, the isolated yield of the product is rather low.

Further, we investigated cyclopropanation of β-unsubstituted substrates **4v-x**. β-Unsubstituted substrates participate readily in the fluorocyclopropanation process giving stable, isolable products **5v-x** in moderate to high yields.

As a fluorocyclopropane **5k** with unsubstitued phenyl group at cyclopropane was prone to decomposition we opted to alter the ester functionality (Fig. 2 A). This eventually led to the finding that the benzyl esters **5ab** are stable products compared to the other esters **5y,k,z,aa** broadening their potential application.

In order, to summarize the scope and limitations of the current fluorocyclopropanation of activated alkenes using fluoromethylsulfonium salt **1** we compared the reactivity of various monosubstituted Michael acceptors (Fig. 2 B and C) with double activated ones. The reactivity is well correlated with electrophylicities[19] of the corresponding activated Michael acceptors. The phenylvinyl sulfoxide does not react, however, the corresponding sulfone readily involves in the reaction[16a] setting the boundary of the utility of this reaction. Double activated arylidene and methylidene derivatives are a good fit for this reaction. Stronger EWG groups facilitate the fluorocyclopropanation reaction (Fig. 2 C), however, in the case of arylidene derivatives the decreased stability of the formed products can be observed. The EWG groups on the aryl-ring contribute to the improved stability of the fluorocyclopropanes, but those with EDG are of poor stability. The balance between reactivity and stability illustrate the landscape and scope of the process under discussion.

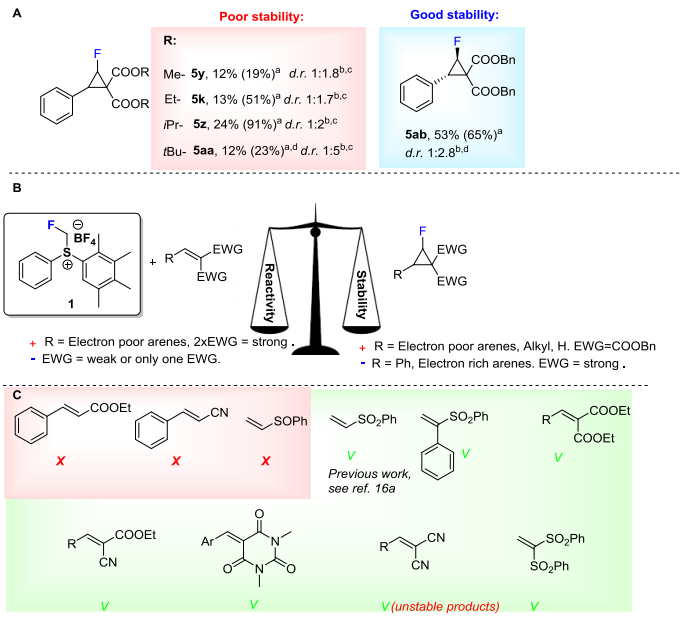
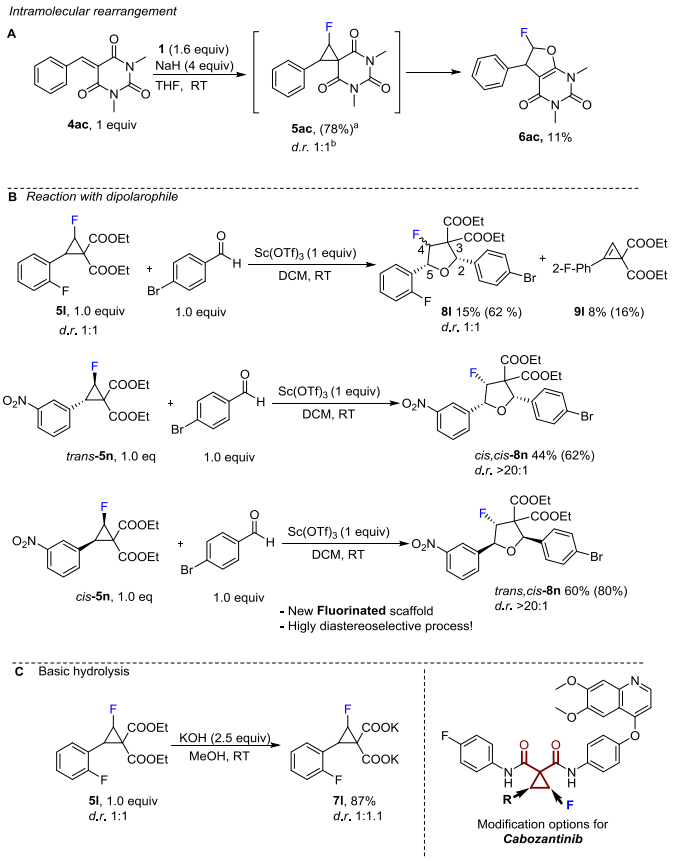


Fig. 2 Scope and limitations of the Johnson-Corey-Chaykovsky fluorocyclopropanation reaction. **A** An ester group influence on the reactivity and stability of phenylsubstituted cyclopropanes **5**. Standard reaction conditions unless otherwise stated. [a] Isolated yields (NMR yields using 1.0 equiv. of EtOAc as an internal reference). [b] d.r. determined for the crude reaction mixture. [c] Solvent – dry MeCN. [d] Solvent – dry THF. **B** The balance of reactivity and stability parameters of the flurocyclopropanation process. **C** The influence of substitutents on the reactivity of Michael acceptors: (x) no reaction; (v) suitable substrates.

In order to get a clearer understanding of the parameters for successful fluorocyclopropanation, we performed several control experiments (Scheme 2). For example, benzylidene barbiturate **4ac** readily participated in fluorocyclopropanation

reaction giving good NMR yield of the corresponding cyclopropane **5ac**, however, upon chromatographic isolation only 5-membered rearrangement product **6ac** was obtained (Scheme 2A). Donor-acceptor cyclopropanes are known to involve in various ring-extension reactions[18]. The substrate **5ac** displays an example of intramolecular rearrangement process which is in line with Mayr's[20] observations where arylidene barbiturates in Corey-Chaykovsky reaction give similar 5-membered product. This is explained to proceed via initial formation of a cyclopropane intermediate rather than the *O*-attack to the betaine intermediate of the Corey-Chaykovsky reaction which is in line with our observations. Utilization of D-A cyclopropane[21] properties of fluorocyclopropanes **5** opens perspective for the further synthetic application of these scaffolds. Under unoptimized conditions, fluorocyclopropane **5l** involved in $Sc(OTf)_3$ mediated [3+2] ring-extension reaction with *p*-bromobenzaldehyde as a dipolarophile to give new fluorinated furan scaffold **8l** (Scheme 2 B). The process appeared to be highly diastereoselective with respect to stereocentres at C-2- and C-5 as only 2 diastereomers of **8l** were observed.



Scheme 2 Properties and further functionalization options of fluorocyclopropanes **5**.

Cyclopropene **9l** was detected as the major side product of this transformation. In order to probe the observed stereochemical outcome, isolated *trans*-**5n** and *cis*-**5n** fluorocyclopropanes were exposed to the corresponding ring extension reaction affording only single diastereomers *cis,cis*-**8n** and *trans,cis*-**8n** correspondingly. It is noteworthy that the rotation across the C(4)-C(5) bond takes place resulting in inversion of relative configuration of fluorine and aryl- substituents of fluorofuranes **8** which is in a good agreement with the previously proposed [3+2] cycloaddition reaction mechanism[21a]. Interestingly that fluorocyclopropane **5** scaffold displays remarkable stability under strongly basic conditions. Ester **5l** can be readily hydrolyzed by using KOH (Scheme 2 C) to give salt **7l** in a good isolated yield. This opens an avenue for the potential synthesis of a fluorocyclopropyl analogues of biologically active compounds[22].

Conclusions

We have demonstrated that diarylfluoromethylsulfonium salt **1** can be efficiently used for fluoro-Johnson-Corey-Chaykovsky reaction to afford a range of fluorocyclopropane **5** derivatives. We have investigated scope and limitations of the fluorocyclopropanation reaction which displays the balance between reactivity of substrates and stability of the products. The fluorocyclopropane derivatives **5** are an interesting class of chemical entities with potential application in medicinal chemistry and as well as the intermediates to access new monofluorinated scaffolds by involving them in further reactions.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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