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COMMUNICATION

Fluorine containing cyclopropanes: Synthesis of aryl substituted all-*cis* 1,2,3-trifluorocylopropanes, a facially polar motif

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The synthesis of substituted all-*cis*-1,2,3-trifluorocylopropanes are described for the first time. The three fluorines located on each of the cyclopropyl carbons with a stereochemistry where they are all on the same face of the cyclopropane, imparts a significant polarity to the molecule, and the inherent conformational rigidity and lowering of Log P makes this motif attractive for exploration as a substituent for pharmaceuticals and agrochemicals research.

Fluorine is widely used in bioactive pharmaceutical and agrochemical products to refine pharmacokinetic profiles as a lead compound is progressed through development.[1] Although the incorporation of fluorine is synonymous with increasing lipophilicity, this is almost entirely confined to the replacement of an aryl or heterocyclic hydrogen by –F or -CF_3 and higher levels of fluorination.[2] Selective fluorination generally increases polarity, particularly where there are adjacent geminal and vicinal hydrogens, which become polarised due to the electronegative fluorine and therefore aliphatic fluorination actually lowers Log P values.[2d] This adds another attractive feature associated with the introduction of fluorine in the arena of bioactives discovery, where Log P values require to be contained as a lead compound is developed. An extreme example of this polarity phenomenon is found in 1,2,3,4,5,6-all-*cis* hexafluorocyclohexane **1**, a molecule with a fluorine on each of the six carbons, and with a stereochemistry where all the fluorines are on one face of the ring.[3a] Cyclohexane **1** is among the most polar aliphatic motifs known. It has attracted significant attention in its ability to coordinate both anionic and cationic species to the hydrogen and fluorine faces respectively, and it has clear prospects in supramolecular chemistry.[4] The potential for derivatives of cyclohexane **1** in drug discovery is in its infancy, but looks attractive as the ring should coordinate electropositive and electronegative substituents on proteins. These prospects have improved recently as substituted ring systems are now available due to direct hydrogenation of pentafluoroaryl substrates[3b] to the corresponding all-*cis* 1,2,3,4,5-pentafluorocyclohexyl derivatives.

With this background we became interested in preparing derivatives of all-*cis*- 1,2,3-trifluorocylopropane **2**. Progressing from a cyclohexane to a cyclopropane reduces the carbon count and with that the lipophilicity and unlike cyclohexane, cyclopropane has a rigid conformation which favours entropic factors in binding to proteins (Fig 1a). Similar to the properties of cyclohexane **1**, cyclopropanes such as **2** are predicted to have the unusual property of facial polarity[4] with different coordinating preferences for the fluorine and hydrogen faces.

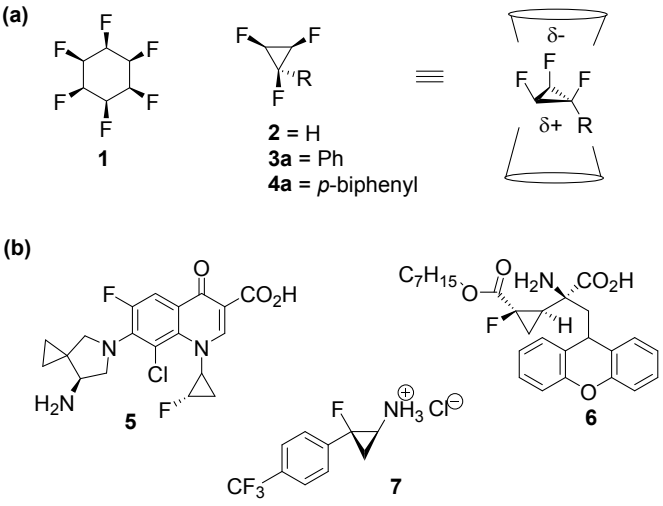

Figure 1. (a) Facially polarised fluorocycloalkanes. (b) Fluorocyclopropanes in medicinal chemistry.

More generally the cyclopropyl ring has been used widely in drug development programmes.[5] As a subset, some fluorinated cyclopropanes have featured in medicinal chemistry however examples are confined almost exclusively to mono-fluorinated cyclopropanes (Fig 1b).[6] Fluorocyclopropyl-amines are the most common variant of this class such as the cyclopropane found in the 6-fluoroquinolone antibiotic sitafloxin **5**, and LY-341,495 **6** a selective orthosteric antagonist.[7] There has been extensive exploration by Haufe and coworkers into the

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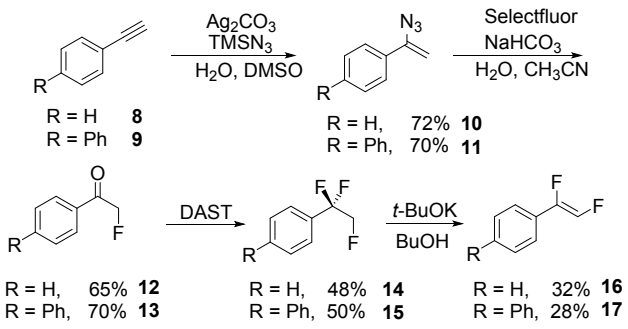
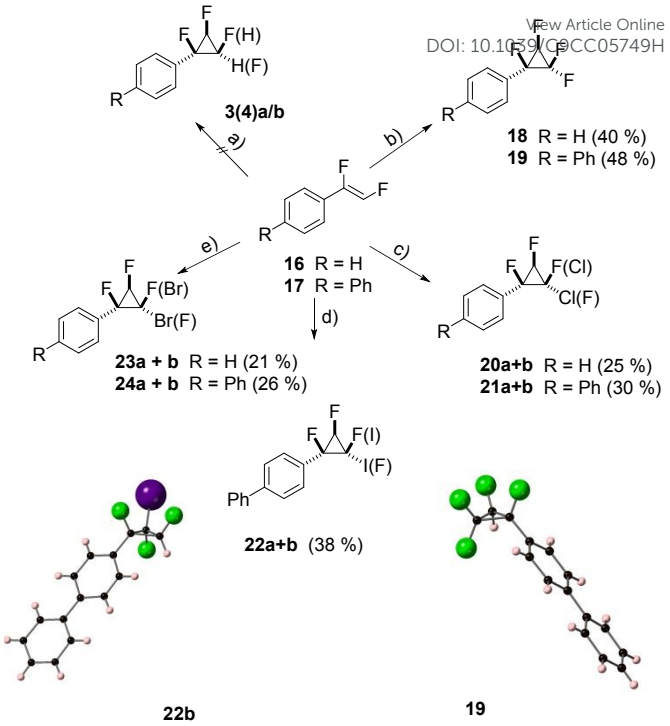
synthesis, physical chemistry and bioactivity of monofluorinated phenylcyclopropylamines such as **7**, particularly as candidate monoamine oxidase inhibitors.[8] Jubault's lab have made recent contributions to the synthesis of more highly functionalised monofluorocyclopropanes.[9] Good methods have developed to prepare *β,β*-difluorocyclopropanes through difluorocarbene addition to olefins,[10] and a very wide range of such compounds have been prepared, and this category of fluorinated cyclopropane dominates entries in the chemical and patent literature. Vicinal *α,β*- or *β,β'*-di-fluorocyclopropanes are rarely quoted, where the fluorines are located on two adjacent carbons, rather than as a CF_2 group. Again there are some patent claims to vicinal difluoro cyclopropanes, but examples in the primary literature are confined to theory studies where properties are computationally predicted.[11] The focus of this study was to explore synthesis routes to substituted all-*cis*-1,2,3-trifluorocyclopropanes **3a** and **4a**. We are not aware of any derivatives of all-*cis* 1,2,3-trifluorocyclopropanes **2** having been reported, however both isomers of the unsubstituted parent 1,2,3,-trifluorocyclopropane, **2a** and **2b** have been prepared at analytical levels.[12] The isomers emerge as minor products of the ozonolysis of *cis*-1,2-difluoroethene. Analytical samples of each isomer were secured by preparative gas chromatography and their integrity and stereochemistry was assigned by vibrational and microwave spectroscopy.[12a] In this paper we report the first preparations of derivatives of all-*cis*-1,2,3-trifluorocyclopropanes. In this context the phenyl **3a** and *para*-biphenyl **4a** derivatives, as well as their *trans* isomers **3b** and **4b** are reported. We also compare the relative polarity (Log Ps) of the phenyl derivative **3a** and **3b** to other selectively fluorinated phenylcyclopropanes and demonstrate that **3a** is the most polar of the series.

Our synthesis approach to the all-*cis*-1,2,3-cyclopropane motif envisaged either direct monofluorocarbene (:CHF) or fluorohalocarbene (:CFX) addition to (*Z*)-*α,β*-difluorostyrene **16** or the corresponding *p*-biphenyl-(*Z*)- *α,β*-difluorostyrene **17**. The *p*-biphenyl series was developed to render products less volatile and crystalline. The required styrenes were prepared from *α*-fluoroketones **12** and **13** following the protocol of Leroy.[13] The *α*-fluoroketones were prepared efficiently from vinyl azides **10** and **11**[14a] using recent methodology developed by Wu,[14b] and they were then treated with DAST to generate the aryltrifluoroethyl products **14** and **15**. A stereoselective base (tBuOK) induced hydrogen fluoride elimination from **14** and **15**, gave the required (*Z*)-*α,β*-difluorostyrenes **16** and **17**, with the fluorines in the required *syn* arrangement.[13] The route is summarised in Scheme 1.

At the outset we explored reactions of **16** and **17** with monofluorocarbene (:CHF) generated from $CHFI_2$[15], to try to generate **3a/b** and **4a/b** directly, but these reactions were unsuccessful presumably because these olefins are poor



Scheme 1 Route to (*Z*)-*α,β*-difluorostyrenes.



Scheme 2. Fluorocarbene reactions and X-ray structures of **19** and **22b**. *Conditions*: a) $CHFI_2$, $ZnEt_2$, PE, 0 °C; b) $TMSCF_3$, NaI, THF, reflux; c) $CFCl_3$, $TiCl_4$, $LiAlH_4$, THF, 0-RT; d) $CHFI_2$, TEBAB (Benzyltriethylammonium Bromide), $NaOH{\cdot}H_20$, DCM, 0-RT; e) $CHFBr_2$, TEBAB, $NaOH{\cdot}H_20$, DCM, 0-RT

nucleophiles and the CHF carbene is not so electrophilic. Consistent with this, the more electrophilic fluorohalocarbenes (:CXF, where X = Cl, Br and I) all successfully reacted with (*Z*)-*α,β*-difluorostyrenes **16** and **17** at room temperature, and also with the less electrophilic carbene (:CF_2), generated from the Ruppert-Prakash (TMS-CF_3) reagent[16] but at high temperature. This gave the various trifluorohalocyclopropanes **18 - 24**. In the case of the chlorocyclopropanes **20** and **21** the required :CClF carbene was generated from $CFCl_3$, using the method of Dolbier,[17] and the iodo- **22** and bromo- cyclopropanes **23** and **24** were generated from $CHFI_2$ and $CHFBr_2$ [18] derived fluorohalo carbenes respectively, following the methods developed by Weyerstahl *et al.*[19,20] For these reactions it proved necessary to prepare the required haloform precursors $CHFI_2$ and $CHFBr_2$ as they are not commercially available. These reactions are summarised in Scheme 2.

Given that the monofluorocarbene reactions with **16** and **17** were unsuccessful and the fluorohalocarbene additions were more fruitful, our approach towards the target 1,2,3-trifluorocyclopropanes **3** and **4** envisaged reductive removal of the non-fluorine halogen from the product cyclopropanes **20** - **24**. In the first instance reductive removal of the chlorine from cyclopropanes **20** and **21** was investigated. The individual **a** (fluorines all *cis*) and **b** (fluorine *trans*) isomers of **20** and **21** were not easily separated and the mixture was explored in each case for dehalogenation (Bu_3SnH/AIBN).[20] In the event this required high temperatures and led to product mixtures, although containing the desired cyclopropanes (as determined by ^{19}F-NMR) but with significant levels of unidentifiable products. Due to this poor selectivity, attention turned to the iodo cyclopropanes **22a/b**. Isomers **22a** and **22b**, were separated and treated individually. Each could be reduced at a

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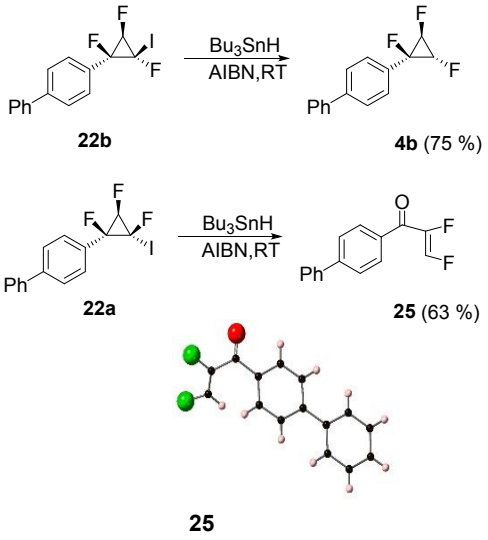
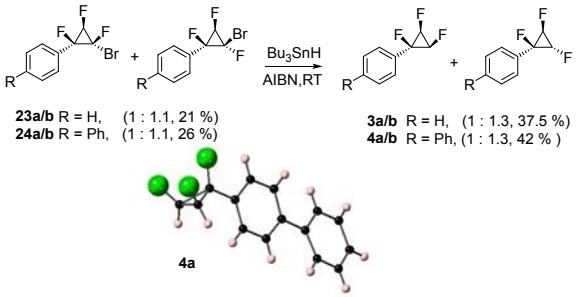


Scheme 3. Reductive deiodination of cyclopropanes **22a** and **22b**.

lower temperature than the corresponding chlorocyclopropanes. The *trans* isomer **22b** resulted in *trans*-1,2,3-trifluorocyclopropane **4b** with retention of stereochemistry, however the *cis*-isomer **22a** lead to the formation of the α,β-unsaturated ketone **25** as the only isolatable product, the nature of which was confirmed by X-ray structure analysis (Scheme 3).

Due to the inability to access *cis*-1,2,3-trifluorocyclopropane **4a** from the iodine series, attention turned to the bromocyclopropanes **23** and **24**. The isomer mixture of **23a** and **23b** was also subjected to reductive dehalogenation to generate the anticipated 1,2,3-trifluorocylopropanes **3a** and **3b** (scheme 4). These product isomers could be readily separated by chromatography. The all-*cis* isomer **3a** has characteristic second order ^{1}H- and ^{19}F-NMR spectra associated with the symmetry of the nuclei on the cyclopropane ring (see SI). A similar reduction was carried out on isomers **24a** and **24b**, which gave rise to the all-*cis* isomer **4a** and the *trans* isomer **4b** respectively. In the case of **4a** a suitable crystal was selected for X-ray structure analysis as illustrated in Scheme 4. This confirmed the all-*cis* configuration of the three C-F bonds.

It was anticipated that the all-*cis* phenyl-1,2,3-trifluorocyclopropane **3a** would display a significant polarity relative to phenylcyclopropane **29**, following from our previous observations with all–*cis* multifluorocyclohexanes.[21] A calculated electrostatic surface



Scheme 4. Reductive debromination and structure of all-*cis* trifluorocyclopropane **4a**.

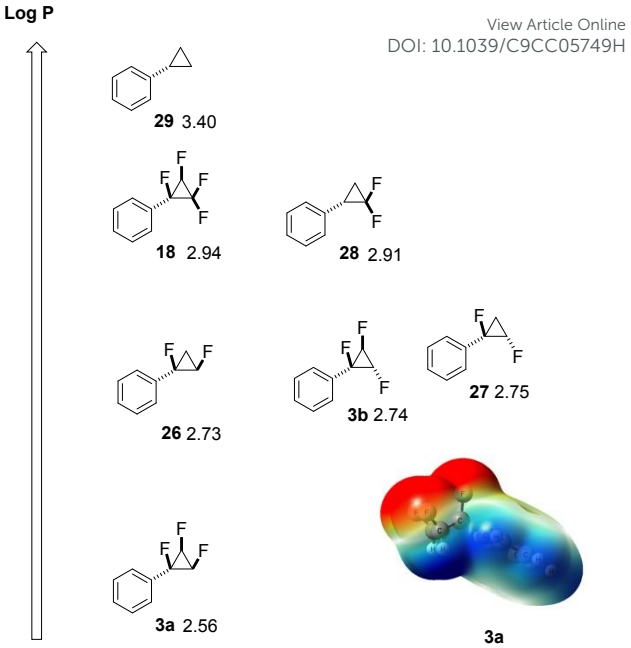


Figure 2. Log P values of selectively fluorinated phenylcyclopropanes (approximately scaled), and an electrostatic surface potential map of **3a**.

potential map of **3a** is shown in Figure 2 and this clearly illustrates the different electrostatic profile on each face of the cyclopropane ring. To explore polarity in the context of bioactives discovery Log P values for the selectively fluorinated cyclopropanes **3a**, **3b, 26**-**28**[22] as well as phenylcyclopropane **29** as a reference, were evaluated experimentally by reverse phase HPLC on a C_{18} coated silica column, a method which has been widely validated.[23] The selected phenyl cyclopropanes are directly compared as they differ only by the degree of fluorination on the cyclopropane ring. From this analysis it emerged that all of the partially fluorinated cyclopropanes **3a**, **3b, 26**-**28** are more polar than phenylcyclopropane **29** itself consistent with the fluorine polarising geminal, and to a lesser extend vicinal, hydrogens around the ring. The all *cis*-1,2,3- trifluorocyclopropane **3a** (Log P 2.56) is the most polar of the series, and more polar than the *trans* isomer **3b** (Log P 2.74) where in the latter case the *anti* fluorine is compromising the overall polarity. Notably cyclopropanes **18** and **28** which contain CF_2 groups are significantly more lipophilic than those with their fluorines in fluoromethylene (CHF) groups, indicating that geminal CHF hydrogens are particularly polarised and contribute significantly to lowering Log P.

In conclusion, all-*cis*-1,2,3-trifluorocyclopropanes **3a** and **4a** have been prepared by halofluorocarbene addition to α,β-difluorostyrenes, and then by removal of the non-fluoro halogen by reductive dehalogenation. The study was stimulated by a recognition that the facially polarised characteristics of such a cyclopropyl ring system could offer unique polar properties for an alicyclic ring. This tendency was demonstrated by evaluation of Log P's across a series of selectively fluorinated phenylcyclopropanes where the all *cis* isomer **3a** was the least hydrophobic of the series. The study reports the first synthetic access to cyclopropanes of this class and demonstrates attractive characteristics for optimizing pharmacokinetic profiles in bioactive discovery programmes.

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Conflicts of interest

There are no conflicts to declare.

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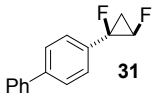
22. The synthesis of compounds **26** and **27** are described in the Supplementary Information. The stereochemistry of these vicinal difluorocyclopropanes was established after a synthesis and X-ray structure analysis of biphenyl-*cis*-1,2-difluorocyclopropane **31**.



31

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