Organo-fluorine chemistry

Edited by David O'Hagan
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It is a great pleasure to be able to introduce this Themed series on organo-fluorine chemistry in the *Beilstein Journal of Organic Chemistry*. The introduction of fluorine into organic molecules is widely practiced particularly when tuning the properties of molecules for specialist functions. Of particular prominence is the role fluorine substitution finds in pharmaceutical development [1], and selective fluorination has made a major contribution to the bioactivity of a wide range of agrochemical products [2]. Organo-fluorine compounds have also found a significant role in soft materials chemistry such as liquid crystals, photoresist polymers and self-assembling monolayers [3].

Allied to this breadth of activity is a steady development in the number and range of fluorination reagents and methodologies. DAST/Deoxofluor, HF:amine reagents and TBAF have secured a central role in the armory of organic chemists and the ready availability and improvements in their formulations are allowing these reagents to be incorporated beyond the research lab and into process development. Indeed micro-reactor technology is enabling elemental fluorine to be used in large scale organo-fluorine production [4]. The introduction in the early 1990's of air stable electrophilic fluorinating reagents such as Selectfluor [5] has been revolutionary and has opened up many new methods for fluorine introduction, and provided the foundation for intense research efforts into asymmetric fluorinations leading now to some exquisite catalytic asymmetric methodologies [6].

The changes in behaviour of a molecule after the introduction of a fluorine atom continue to be unpredictable, and understanding such behaviour remains a driver in organo-fluorine research [7]. Investigations into the stereoelectronic influence of fluorine and the nature of weak interactions between fluorine and other substituents remains an active area of research and for example important insights into how fluorinated drugs interact with proteins are emerging as a result of accumulating crystallographic data of protein-drug interactions [8]. Exploring the role and nature of fluorous molecules has been an intense area of research internationally [9], one which has had a relatively short lead time since the seminal paper of Horváth and Rábai in 1994 [10]. In the area of medical imaging, positron emission tomography (PET) has undergone a step change in growth across all developing countries, with an exponential increase in the installation of PET cameras and cyclotrons to generate isotope for labelling ligands and diagnostic probes. $^{18}$F is an important isotope in PET because it has a relatively long half life ($t_{1/2} = 110$ min) and methods for introducing fluorine, appropriate to PET synthesis are in demand and will continue to grow. So the field is active and exciting and it is in that context that the...
BJOC feels it appropriate to profile a themed series in the area. Contributions to the series come from an international grouping of noted experts in fluorine chemistry and we are delighted that they have agreed to contribute their papers for such a successful launch.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.4.11
Stereoselective synthesis of (2S,3S,4Z)-4-fluoro-1,3-dihydroxy-2-(octadecanoyl-amino)octadec-4-ene, [(Z)-4-fluoroceramide], and its phase behavior at the air/water interface

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Full Research Paper

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Abstract

Background
Sphingolipids belong to the most important constituents of the membranes of eukaryotic cells. As intermediates in sphingolipid metabolism, sphingosine and its N-octadecanoyl-derivative, ceramide, exhibit a variety of biological functions. These compounds play a crucial role in many essential biological processes such as cell growth, cell differentiation, cell recognition and apoptosis. More specifically, sphingolipids are crucial e.g. for the function of the skin because they contribute to the formation of the water permeability barrier consisting of a highly organized multilaminar lipid matrix of free fatty acids, cholesterol and ceramides containing additional hydroxyl groups in the sphingosin part and longer fatty acid amide functions.

Results
In a short synthetic route (2S,3S)-4-fluorosphingosine and 4-fluoroceramide, the fluorinated analogues of the natural products, D-erythro-sphingosine and ceramide, have been prepared. The key step of the synthetic sequence is an asymmetric aldol reaction of (Z)-2-fluorohexadec-2-enal, prepared in three steps from tetradecanal, with an enantiopure N-protected iminoglycinate. Deprotection of the imino function and reduction of the ester group led to the 4-fluorosphingosine, which on acetylation with stearoyl chloride gave 4-fluoroceramide. After careful HPLC purification of the latter compound its phase behavior was investigated by Langmuir film balance technique and compared to that of natural ceramide. While the isotherms are quite similar in shape, they differ significantly in the starting point of increasing film pressure (56 or 67 Å²/molecule) and in the film collapse pressure (38 or 56 mN/m) for ceramide and 4-fluoroceramide, respectively. Moreover, the hysteresis curves are very different. While consecutive isothermic compression – expansion cycles are reversible for the 4-fluoro derivative, substantial substance loss into the subphase or irreversible formation of multi-layers was observed for natural ceramide.
Conclusions

Asymmetric aldol reaction proved to be successful for the preparation of enantiopure 4-fluoroceramide. Surface/pressure isotherms and hysteresis curves of ceramide and its 4-fluoro derivative showed that the presence of fluorine leads to stronger intermolecular interactions between the hydrophobic chains of neighboring molecules, and therefore to increasing stability of the monolayer of 4-fluoroceramide at the air water interface.

Introduction

Sphingolipids belong to the most important constituents of the membranes of eukaryotic cells. As intermediates in the sphingolipid metabolism, sphingosine (1a) and its N-octadecanoyl-derivative, ceramide (1b) (Figure 1), exhibit a variety of biological functions [1,2]. They play a major role as intracellular signal molecules (second messengers) and mediate signals for essential processes such as cell growth, cell differentiation, cell recognition and apoptosis [3-9]. Moreover, sphingosine is known as an inhibitor of protein kinase C [10,11]. The dynamic balance between ceramide, sphingosine and sphingosine-1-phosphate seems to be decisive for cell growth or apoptosis [12, 13]. The specific initiation of apoptosis by suitable derivatives of these signal molecules is discussed as a new method for treatment of numerous diseases [1,14,15], and of cancer in particular [16-18].

A few years ago Herdewijn et al. showed that fluorinated ceramide and dihydroceramide analogues with chain length C_{12} and a fluorine atom instead of the OH group at C(3) exhibit significantly higher apoptosis activity in different cell cultures as compared to their non-fluorinated parent compounds [19]. Furthermore, L-threo-3-fluorodihydroceramides with short chain amido groups at C(2) were identified as moderate inhibitors of the dihydroceramide desaturase [20]. Several other fluorinated C_{12} sphingosine and sphinganine analogues inhibited the sphingosine kinase [21] and the corresponding fluorinated C_{18} derivatives were shown to be inhibitors of the protein kinase C [22]. Recently, a D-erythro-1-deoxy-1-fluoroceramide analogue was shown to inhibit the formation of sphingomyeline and glycosylceramide in cultured murine neurons, but only in high concentrations (100 μM) [2]. Moreover, sphingolipids are crucial, e.g. for the function of the skin because they contribute to the formation of the water permeability barrier consisting of a highly organized multilaminar lipid matrix of free fatty acids, cholesterol and ceramides containing additional hydroxyl groups in the sphingosine part and longer fatty acid amide functions [23]. The function of the additional free OH group seems to be the formation of additional hydrogen bridges, which enhance the rigidity of the intercellular lipid aggregates and hence decrease the transepidermal water loss [24,25].

Several of the biological properties of sphingosines and ceramides (e.g. sphingomyelinase activity) were assigned to the OH group in the 3-position. While the primary OH group is functionalized with a carbohydrate, a phosphate, sulfate, etc. the 3-OH group is free for various interactions with other constituents of the cell membrane such as cholesterol or proteins [1,26]. The nature of these interactions among other factors depends on the hydrogen bond donating and hydrogen bond accepting properties of the hydroxyl group. Consequently, placement of electron donating or electron accepting substituents close to this group will modify these properties and hence will change the physical, chemical as well the physiological properties of the fluorinated analogues compared to their natural parents. Recently we have demonstrated the effect of a fluorine substituent in the 4-position on the phase behavior at the air/water interface of diastereomeric enantiopure 2-azido-4-fluoro-3-hydroxystearates [27], the precursors of the enantiomers of both diastereomeric 4-fluoro-4,5-dihydroceramides, which we synthesized recently [28].

We became interested in studying the properties and report in this paper the stereoselective synthesis of (Z)-2-amino-4-fluorooctadec-4-ene-1,3-diol (4-fluorosphingosine, 1b) and (Z)-2-octadecanoylamo-no-4-fluorooctadec-4-ene-1,3-diol (4-fluoroceramide, 2b) having the D-erythro-configuration (25,35) and the trans-configured C(4)-C(5) double bond of the natural compounds 1a and 2a (Figure 1). Our first investigations on the phase behavior at the air/water interface of 4-fluoroceramide (2b) and its non-fluorinated analogue 2a by Langmuir film balance measurements are also presented.
Results and Discussion

Our synthetic sequence started from (ethoxycarbonylfluoro-methyl)triphenylphosphonium bromide and tetradecanal, from which \((Z)-2\text{-fluorohexadecan-2-enal} \ (3)\) was prepared in three steps according to a synthetic route we developed recently for the preparation of long chain \(\alpha\)-fluoro-\(\alpha,\beta\)-unsaturated carboxylic acid esters [29] and fluorinated 2,4-dienecarboxylic acid esters [30]. The key step of the synthesis is an asymmetric aldol reaction of the fluorinated aldehyde 3 with the enantiopure iminoglycinate 4 (Scheme 1). The latter building block has already been used for the preparation of several \(\gamma\)-fluoro-\(\alpha\)-amino acids [31]. This methodology, utilizing the corresponding ethyl iminoglycinate instead of 4, was previously applied for the synthesis of natural D-erythro-sphingosine (1a) [32], deuterium and tritium labeled sphingosines [33] and various other non-fluorinated sphingosine, sphinganine and phytosphingosine derivatives [34].

The aldol reaction was carried out with a small excess of the iminoglycinate 4 (1.1 equiv) and in the presence of 1.6 equiv \(\text{ClTi(OEt)}_3\) [35] and 2.0 equiv of \(\text{Et}_3\text{N}\). After 13 h at 0 °C the reaction provided the desired tert-butyl imino acid ester 5 as a mixture with the ethyl imino acid ester 6 (formed due to a partial transesterification of 4 with the titanium reagent) and four non-identified compounds (among them most likely diastereomers of the title compounds) in a ratio of 57:28:7:1:2:5, respectively, as detected by \(^{19}\text{F}\) NMR spectra. The ratio between the major products 5 and 6 was determined to be 65:35. The starting aldehyde 3 (12% from the crude product) was also found in the isolated mixture. Extension of the reaction time or increasing the reaction temperature to r.t. to achieve complete conversion of 3 was not successful. In this case, according to the ESI-MS spectra, besides the iminoglycinate 4, its analogue with ethoxy group as well 2-hydroxypinan-3-one were also present in the crude product. During the purification by column chromatography a partial cleavage of the C(2)-C(3) bond (retro-aldol reaction) and partial elimination of the auxiliary occurred. Therefore no pure compounds were isolated (for analytical investigations an 88:12 mixture of compounds 5 and 6 was applied) and the crude product was used in the following reaction without purification.

For both major products, 5 and 6, the D-erythro-configuration of the stereogenic centers is most probable, considering the reaction mechanism we propose in Scheme 2. Moreover, the \(^{\text{H}}\text{H}\) coupling constants between the protons at C(2) and C(3), which were determined to be 7.8 Hz and 7.7 Hz for 5 and 6, respectively, support this assignment. The \(^{\text{H}}\text{F}\) coupling constants between the fluorine atom and the vinylic proton and between the fluorine and the proton next to the OH group in the \(^{1}\text{H}\) NMR. For the tert-butyl imino acid ester 5 \(J = 37.6\) Hz and 19.8 Hz, respectively, were found. The appropriate coupling constants in case of the ethyl imino acid ester 6 were determined from the \(^{19}\text{F}\) NMR (because the signals do overlap in \(^{1}\text{H}\) NMR) to be 38.3 Hz and 18.7 Hz, respectively.

The crude product obtained from the aldol reaction was partially deprotected with 15% aq solution of citric acid for 68 h at r.t. \(^{19}\text{F}\) NMR analysis of the crude product showed the formation of three major compounds, which were identified as the tert-butyl imino acid ester 7, the carboxylic acid 8 and the ethyl amino acid ester 9 in a ratio of 31:25:44. Because of partial decomposition on silica gel compounds 8 and 9 could not be isolated in pure form. The D-erythro-configuration was confirmed by the \(^{\text{H}}\text{H}\) coupling constants for the proton at C(2) in \(^{1}\text{H}\) NMR, which are 5.0 Hz for compound 7 and 4.7 Hz for compound 9. These values correlate well with the corres-
Scheme 2: Mechanism of the aldol reaction.

The crude product mixture of the hydrolysis was used in the following reduction without purification. The reduction with 8.0 equiv excess of NaBH₄ at 0 °C for 28 h gave the desired 4-fluorosphingosine (1b) and a small amount of a non-identified product (ratio 97:3 ¹⁹F NMR). Also 24% of non-converted tert-butyl ester 7 and traces of non-identified products were present in the reaction mixture. Because of the observed instability of 1b, no chromatographic purification was performed. The crude product was treated with stearoyl chloride (1.3 equiv) in a mixture of THF and 50% aq solution of AcONa. According to the ¹⁹F NMR spectra the N-octadecanoyl derivative of compound 7, a non-identified trace compound and the desired 4-fluoroceramide (2b) were present in a ratio 27:1:72, respectively. Other non-identified products (together 34%) with ¹⁹F NMR chemical shifts between δ –115.0 ppm and δ –124.3 ppm were also detected in the mixture. A part (0.1 g) of the crude product was purified by HPLC (CHCl₃:MeOH, 98:2) in order to isolate 4-fluoroceramide (2b) as a white solid in 76% purity and 30% yield. For analytical investigations the described substances were prepared similarly and purified by column chromatography giving compounds with 61–99% purity (for details see Supporting Information File 1). For the investigations of the phase behavior of 4-fluoroceramide (2b) at the air/water interface a >99% pure compound was used.

The diastereoselectivity of the aldol reaction, described above, is controlled by the formation of a titanium enolate, which may follow the mechanism we propose in Scheme 2.

The iminoglycinate 4 is deprotonated with Et₃N to the resonance stabilized anion I. ClTi(OEt)₃ coordinates the carbonyl oxygens of 4 and 3 in a six membered Zimmermann-Traxler transition state II. The resulting structure of the titanium alcoholate III shows the erythro-configuration of the tert-butyl amino acid ester 7 and its derivatives 8 and 9. The absolute configuration (2S,3S) of the products is controlled by the chiral auxiliary.

In recent years several studies on cell membrane lipid models suggested that ceramide could act indirectly as a messenger by modulation of membrane properties. The membrane lipids (mostly sphingomyelin) together with cholesterol are organized in small domains, known as rafts, stabilized by hydrogen bonds.
among the polar head groups and van der Waals interactions of the hydrophobic chains. The presence of lipid domains is thought to be involved in receptor-mediated signal transduction. Due to its ability to form large hydrogen bonded networks, because its polar head groups can act both as acceptor and as a donor, ceramide, when added or generated in situ in the membrane, can segregate from the other lipids and cause coalescence of the small lipid raft domains to give highly ordered ceramide-enriched domains. Moreover, due to the small size of its polar head group ceramide can displace the raft-associated cholesterol [36-39].

In this context, having the fluorinated analogue 2b of ceramide in hand, we were interested to compare its phase behavior at the air/water interface to that of the corresponding non-fluorinated compound 1b in order to study the effect of the fluorine atom on the arrangement of the molecules at the water surface. Using Langmuir film balance, the molecular area/surface pressure isotherms (π–A isotherms) shown in Figure 3 were measured at 20 °C.

The curve progression is very similar for both compounds and also correlates with the π–A isotherms of C18 ceramide and some of its analogues measured from Löfgren and Pascher at 22 °C [40], as well with the π–A isotherms of the 4-position fluorinated dihydroceramide analogues [41] and of C16 ceramide [42]. Both isotherms run over a large interval parallel to the X axis. At 56 Å²/molecule for 2a and at 67 Å²/molecule for 2b the surface pressure starts to increase. In the case of fluorinated ceramide 2b the film collapses at substantially higher pressure (56 mN/m) than 2a (38 mN/m), which refers to an increasing stability of the film due to the presence of fluorine. The change of the temperature to 10 °C or 30 °C does not cause any dramatically different curve course for both substances. But a significant difference in the molecules behavior is observed while measuring three consecutive isotherm cycles of compression and expansion (Figure 4).

The isotherm of 2b shows only a slight shift of the compression curves to higher pressures while the curves of 2a move significantly to smaller molecular area after every cycle. Thus, there is no loss of substance into the subphase in case of the fluorinated compound 2b, while molecules of 2a go partly into the subphase or form multi-layers irreversibly. It seems that the molecules of 4-fluoroceramide (2b) interact more strongly with their hydrophobic parts due to the presence of fluorine, which might form intermolecular hydrogen bridges to the vinylic proton of the next molecule. Similar effects were observed in compressed monolayers of ethyl (Z)-2-fluorooctadec-2-enoate [29] and ethyl (2E,4Z)-4-fluorooctadeca-2,4-dienoate [43]. Moreover, a very short C–H···F–C distance (2.30 Å) was observed in crystalline state for (Z)-2-amino-4-fluorododec-4-enecarboxylic acid [44].
Conclusion

In this paper a short diastereo- and enantioselective synthetic route was presented for the preparation of the first analogues 1b and 2b, fluorinated in 4-position, of the natural signaling molecules sphingosine (1a) and ceramide (2a) with the required D-erythro-configuration (2S,3S) of the stereogenic centers and a Z configured C(4)-C(5) double bond. It is noteworthy that the presence of both, the fluoride atom and the ester moiety, close to the C(2)-C(3) bond decreases considerably the stability of this bond due to the strong electron withdrawing power of both substituents, which finally leads to a cleavage of the bond during chromatographic purification or at elevated temperature, as was observed in case of amino acid esters 5 and 6. This might hold for the overall instability and sensitivity against several factors of the fluorinated analogues reported here comparing to their non-fluorinated parent compounds. This complicates the synthesis and purification of these compounds.

By Langmuir film balance measurements we demonstrated that the presence of the fluoride in 4-fluoroceramide (2b) leads to stronger intermolecular interactions between the hydrophobic chains of neighboring molecules, comparing to the non-fluorinated parent compounds, and therefore to higher stability of the monolayer formed at the air/water interface. This unique behavior of the 4-fluoroceramide molecules provides the basis for further development of the morphology of the monolayer and possible formation of multi-layers, as well as for biological investigations such as the expected apoptosis activity of 2b.

Supporting Information

Supporting Information File 1
General methods, synthesis of the compounds and spectroscopic structure assignment.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-12-S1.doc](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-12-S1.doc)

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The definitive version of this article is the electronic one which can be found at:

doi:10.3762/bjoc.4.12
Trifluoromethyl ethers – synthesis and properties of an unusual substituent

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Abstract

After nitrogen, fluorine is probably the next most favorite hetero-atom for incorporation into small molecules in life science-oriented research. This review focuses on a particular fluorinated substituent, the trifluoromethoxy group, which is finding increased utility as a substituent in bioactives, but it is still perhaps the least well understood fluorine substituent in currency. The present review will give an overview of the synthesis, properties and reactivity of this important substituent.

Introduction

Nowadays, fluorine containing compounds are synthesized in pharmaceutical research on a routine basis and about 10% of all marketed pharmaceuticals contain a fluorine atom. There has been an enormous increase in the use of fluorine containing compounds for medicinal applications. For example, nine of the 31 new chemical entities approved in 2002 contain one or several fluorine atoms. According to the World Drug Index (WDI), there are 128 fluorinated compounds with US trade names. Even more fluorinated drugs are predicted to be developed in the near future, as fluoro-organic compounds continue to attract attention in the field of chemistry and biochemistry [1].

Fluorine as a substituent in active ingredients plays a significant and increasingly important role. Currently about 15% of the pesticides listed in the 13th edition of the Pesticide Manual contain at least one fluorine atom. The biggest group of fluorinated pesticides are the compounds containing a trifluoromethyl group (mainly at aromatic rings), followed by aromatic compounds containing an isolated fluorine atom (one and more). However, according to the 12th and 13th edition of the pesticide manual only five pesticides containing OCF₃-groups are so far registered (see Figure 1). The proinsecticide Indoxacarb acting as a voltage-gated sodium channel (vgSCh) modulator, the insect growth regulant (IGR) Triflumuron, the plant
growth regulator Flurprimidol, the inhibitor of the respiratory chain and succinate dehydrogenase (SD) Thifluzamide as well as the inhibitor of acetolactate synthase (ALS) Flucarbazone-sodium. It was estimated that the number of fluorinated compounds currently under development represent some 35–50% of the all active ingredients under development [2].

One or several fluorine atoms as substituents at specific sites in an organic compound can dramatically alter its chemical and biological nature. In fact, the incorporation of fluorine into a bioactive compound allows a simultaneous change in the electronic, lipophilic and steric parameters, all of which can influence both the pharmacodynamic and pharmacokinetic properties of the candidate [3].

What is so particular about fluorine? Due to its comparable size, the fluorine atom (1.47 Å) can mimic a hydrogen atom (1.20 Å) or a hydroxy group (1.40 Å) in a bioactive compound with respect to steric requirements at receptor sites. Its high electronegativity (4.0 according to the Pauling scale) can have a pronounced influence on the reactivity pattern of a molecule. The most common reason for incorporating fluorine into a molecule is to reduce the rate of oxidative metabolism. However, the increased oxidative stability of fluorinated molecules has nothing to do with the greater strength of the carbon-fluorine bond relative to the carbon-hydrogen bond. In fact, biological oxidation does not involve the homolysis of C–H or C–F bonds. More relevant are the bond energies and heats of formation of H–O and C–O bonds relative to those of F–O bonds. As the latter are unfavorable all alternative mechanisms avoiding attack at fluorine always apply in biological systems [4].

Moreover, the presence of fluorine atoms in biologically active molecules can enhance their lipophilicity and thus their uptake and transport. In particular, the trifluoromethyl group (–CF₃) confers increased stability and lipophilicity in addition to its high electronegativity [5-9]. However, another fluorinated substituent, the trifluoromethoxy group, is becoming more and more important in both agrochemical research and pharmaceutical chemistry [10,11].

The trifluoromethoxy group is perhaps the least well understood fluorine substituent. When asked to draw up a list of textbook substituents, hardly anyone would consider associating such an "exotic entity" like trifluoromethoxy to the lasting popularity of the carboxyl, acetyl, formyl, nitro, amino, hydroxyl and sulfo groups. Nevertheless, the occurrence of OCF₃-substituted organics, the majority of which are aromatic compounds, has significantly increased in the recent years [12].

In the 1950s and 1960s the successful development of α-fluorinated ethers as volatile, non-toxic, non-explosive and fast-acting inhalation anesthetics was quickly followed by applications of anti-inflammatory agents. Investigations of the anesthetic properties of α-fluorinated ethers were undertaken on the rational basis that replacement of the hydrogen atom in already known "anesthetic molecules" by fluorine should result in derivatives having improved thermal stabilities relative to the inhalation anesthetics in common use at that time (cyclopropane and

![Figure 1: OCF₃-bearing pesticides.](image-url)
ether), like the halo ether anesthetic Fluoroxene (Fluoromar®, F₃C-H₂C-O-CH=CH₂). Numerous analogues [13] were prepared and evaluated (Table 1). Meanwhile, cyclic analogues bearing the fluorinated 1,3-dioxolanes moiety [14] have largely replaced Fluoroxene in its clinical use. Many anesthetics currently used are powerful positive allosteric modulators of GABAA[15].

Numerous new OCF₃ containing compounds have been prepared, clinically evaluated and in many cases marketed as drugs with enhanced effectiveness, often coupled with diminished side-effects [10]. Between 2004 and 2007 the number of structures bearing an OCF₃-substituent has more than doubled (from 30,000 to 74,514). They are documented in 18,000 literature references (SciFinder Scholar), most being patent applications (~11,000), but also in close to 7000 research articles. In contrast, trifluoromethoxy substituted heterocycles are relatively rare, although numerous structures are protected by patent applications.

**Review**

**Preparation of Trifluoromethyl Ethers**

Nucleophilic substitution

The first aryl trifluoromethylethers were prepared by L. Yagupol'skii in 1955 starting from substituted anisoles [16]. The displacement of chlorine by fluoride was realized with anhydrous hydrogen fluoride or with antimy trifluoride in the presence of antimy pentachloride (Scheme 1 and Table 2) [16-19].

The photochlorination which works well with electron-deficient anisoles cannot be applied to anisole itself. In fact, halogen attack on the phenyl ring proceeds more easily than radical chlorination of the methyl group. Louw and Franken could show that with elemental chlorine, photostimulated in refluxing tetrachloromethane, essentially tetrachloromethylenisole is obtained [20]. The fluorination of the trichloromethyl ether succeeds then easily as shown above. The chlorination/fluorination sequence described above can be simplified by producing the trichloromethyl aryl ethers without isolation and through in situ conversion into the final trifluoromethyl aryl ethers. As Feiring could show more recently, the phenol is heated together with tetrachloromethane, anhydrous hydrogen fluoride and catalytic amounts of boron trifluoride to a closed pressure vessel under autogeneous pressure up to 150 °C [21]. However, substrates containing ortho substituents capable of hydrogen bonding to the hydroxy group are not suitable starting materials. The stoechiometric use of tetrachloromethane lowers the yield and milder conditions afford essentially chlorodifluoromethoxy derivatives (Scheme 2 and Table 3).

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**Table 1: α-Fluorinated ethers used as Anesthetics.**

| Entry | α-Fluorinated ethers | b.p. [°C] | Common names | Brand names |
|-------|----------------------|-----------|--------------|-------------|
| 1     | F₂HC-O-CHFCF₃        | 12.4 ± 25.0 | Desflurane   | Suprane®    |
| 2     | F₂HC-O-CHClCF₃       | 48.5 ± 0.0  | Isoflurane   | Forane®     |
| 3     | F₂HC-O-(CF₃)₂        | 49.5 ± 25.0 | Sevoflurane  | Sevoflurane®|
| 4     | F₂HC-O-CF₂-CHFCI     | 59.9 ± 25.0 | Enflurane    | Ethrane®    |
| 5     | F₂HC-O-HF-CF₂-CF₂    | 60.9 ± 25.0 | BAX 3224     | Synthane®   |
| 6     | H₂C-O-CF₂-CFBr       | 87.0 ± 25.0 | Roflurane    | DA 893      |
| 7     | H₂C-O-CF₂-CHCl₂      | 105.0 ± 0.0 | Methoxyflurane | Pentrane® |

**Scheme 1: Preparation of trifluoromethyl ethers via a chlorination/fluorination sequence.**

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**Table 2: Synthesis of ArOCF₃ compounds starting from substituted anisoles.**

| Anisole       | ArOCCl₃ | Yield (%) | ArOCF₃ | Yield (%) |
|---------------|---------|-----------|--------|-----------|
| 4-ClC₆H₄OMe  | 4-ClC₆H₄OCCl₃ | 77       | 4-ClC₆H₄OCF₃ | 80        |
| 2-ClC₆H₄OMe  | 2-ClC₆H₄OCCl₃ | 69       | 2-ClC₆H₄OCF₃ | 40        |
| 4-FC₆H₄OMe   | 4-FC₆H₄OCCl₃ | 66       | 4-FC₆H₄OCF₃ | 58        |
| 2,4-Cl₂C₆H₃OMe | 2,4-Cl₂C₆H₃OCCl₃ | 70   | 2,4-Cl₂C₆H₃OCF₃ | 20        |
| 4-NCC₆H₄OMe  | 4-NCC₆H₄OCCl₃ | 50       | 4-NCC₆H₄OCF₃ | 20        |
| 4-Cl(O)CC₆H₄OMe | 4-Cl(O)CC₆H₄OCCl₃ | 83 | 4-Cl(O)CC₆H₄OCF₃ | 69        |
Yarovenko and Vasil’eva developed an approach based on the readily accessible, although highly toxic aryl chlorothionoformates \(1\). They can be cleanly converted by chlorination into trichloromethyl aryl ethers \([17]\). This step is then followed by fluorination using antimony trifluoride and a catalytic amount of antimony pentachloride (Scheme 3). The latter compounds can be obtained directly when treated with molybdenum hexafluoride \([22]\). Unfortunately, the high percutaneous toxicity of the chlorothionoformates \(1\) prohibited any industrial exploitation so far.

W. Sheppard described in 1964 the syntheses of aryl trifluoromethylethers \([23]\) by reaction of \(SF_4\) with aryl fluoroformates. However, this approach implied the use of highly toxic reagents and the fluoroformates were rarely isolated (Scheme 4 and Table 4).

### Fluorodesulfurization methods

Recently, an elegant method towards trifluoromethyl ethers based on an oxidative desulfurization-fluorination has been disclosed by Hiyama \([24-27]\). When dithiocarbonates \(2\), xanthogenates are exposed to a huge excess of hydrogen fluoride-pyridine and 1,3-dibromo-5,5-dimethylhydantoin, trifluoromethyl ethers form in moderate to excellent yields (Scheme 5 and Table 5).

What makes this procedure attractive is its applicability to the conversion of aliphatic alcohols into trifluoromethyl alkyl...
Scheme 4: Preparation of trifluoromethyl ethers via fluoroformates.

Table 4: Preparation of aryl trifluoromethyl ethers by two-step method from phenols.

| Phenol (mol)     | COF₂ (mol) | SF₄ (mol) | ArOCF₃    | Yield (%) |
|------------------|------------|-----------|------------|-----------|
| C₆H₅OH (2.5)     | 3.0        | 2.5       | C₆H₅OCF₃  | 62        |
| 4-O₂N-C₆H₄OH (1.0) | 1.5        | 1.5       | 4-O₂N-C₆H₄OCF₃ | 81        |
| 4-ClC₆H₄OH (0.25) | 0.38       | 0.28      | 2-ClC₆H₄OCF₃ | 58        |
| 2-ClC₆H₄OH (0.25) | 0.38       | 0.28      | 2-ClC₆H₄OCF₃ | 17        |
| 4-FC₆H₄OH (0.13) | 0.22       | 0.16      | 4-FC₆H₄OCF₃ | 42        |
| 4-MeC₆H₄OH (1.0) | 1.35       | 1.2       | 4-MeC₆H₄OCF₃ | 9         |

Reactions run in "Haselloy-lined" pressure vessel of 140, 240, or 1000 mL. capacity at autogenous pressure. Normal heating pattern was 1 h at 100 °C followed by 2 to 3 h at 140 °C (or higher temperatures above phenol melting point) for the COF₂ reaction; 2 h successively at 100, 140, or 150 °C, and 160 or 175 °C for the SF₄ reaction.

Scheme 5: Oxidative desulfurization-fluorination toward trifluoromethyl ethers.

Table 5: Oxidative desulfurization-fluorination towards ROCF₃ compounds.

| Xanthogenate 2 | Fluoride source (mol) | N-halo imide (mol) | ArOCF₃ | Yield (%) |
|----------------|-----------------------|--------------------|--------|-----------|
| 4-n-Pr-C₆H₄ | 70% HF/Py (40) | DBH (3) | 4-n-Pr-C₆H₄OCF₃ | 81        |
| 4-n-Hex-C₆H₄ | 70% HF/Py (80) | DBH (3) | 4-n-Hex-C₆H₄OCF₃ | 58        |
| 4-PhCH₂OC₆H₄ | 70% HF/Py (80) | DBH (4) | 4-PhCH₂OC₆H₄OCF₃ | 56        |
| 4-Br-C₆H₄ | 70% HF/Py (80) | DBH (3) | 4-Br-C₆H₄OCF₃ | 62        |
| Ph-CH₂CH₂CH₂ | 70% HF/Py (80) | DBH (3) | Ph-CH₂CH₂CH₂OCF₃ | 75        |
| n-C₁₆H₃₃ | 70% HF/Py (80) | DBH (3) | n-C₁₆H₃₃OCF₃ | 95        |

Mol amounts of HF/Py (70%) or tetrabutylammonium dihydrogen trifluoride (TBAH₂F₃) for 1 mol of 2. aMol amounts of 1,3-dibromo-5,5-dimethylhydantoin (DBH) or N-bromosuccinimide (NBS). bIsolated yield.
ethers provided that the alcohol is primary rather than benzylic, secondary or tertiary (in which case the reaction fails). The mechanism is based on the nucleophilic attack of the carbon-sulfur bond on a positively charged halogen which makes subsequently the nucleophilic substitution by a fluoride possible (Scheme 6). Under modified reaction conditions, for example by using TBAH₂F₃ instead of HF-pyridine, the transient mono-thioacetals 3 can be isolated [24].

**CF₃-Transfer agents**

Umemoto reported recently in detail on the preparation of O-(trifluoromethyl)dibenzofuranium salts 4 [28-31] and their use as CF₃-transfer agents based on studies of Yagupol'skii [32]. The direct O- and N-trifluoromethylation of alcohols, phenols, amines, anilines and pyridines under mild conditions was described. However, the difficulty in the use of these reagents is the in situ preparation by photochemical decomposition of the corresponding 2-(trifluoromethoxy)biphenyl-2'-diazonium salts at −100 °C (Scheme 7) [28]. The major drawback of this method is the necessity to work at very low temperature and on small scale.

Togni managed very recently to circumvent these difficulties by using hypervalent iodine compounds such as 5 [33-35]. When 2,4,6-trimethylphenol was treated with the hypervalent iodine compound depicted below, the corresponding trifluoromethyl ether was obtained beside C-trifluoromethylation products (Scheme 8).

Alkyl trifluoromethyl ethers, still a rarity, have so far been prepared by the reaction of alkyl fluoroformates with sulfur tetrafluoride [36], the trifluoromethyl transfer from O-(trifluoromethyl)dibenzofuranium hexafluoroantimonate 4 [37] and the addition of trifluoromethyl hypofluorite (FOCF₃) to olefins [38].

The introduction of the trifluoromethoxy substituent into carbohydrates was realized using tris(dimethylamino)sulfonium
trifluoromethoxide (TASOCF₃) as OCF₃-transfer reagent [39]. This compound can be prepared by reaction of carbonyl fluoride with tris(dimethylamino)sulfonium difluorotrimethylsilicate in anhydrous THF at −75 °C (Scheme 9) [40]. The trifluoromethoxide anion is a relatively poor nucleophile. However, when reacted with primary triflate esters of carbohydrates, the anion displaced the triflate under mild conditions.

However, although aromatic trifluoromethyl ethers are well known and have many applications in pharmaceutical and agricultural domains, aliphatic trifluoromethyl ethers are still rare and difficult to make [41]. Methyl (trifluoromethoxy)acetate for example has been prepared [42] using the carbonyl fluoride/sulfur tetrafluoride method cited above [36]. Recent advances in the fluorodesulfurization reaction [24,41,43-45] enabled the preparation of some aliphatic trifluoromethyl ethers under mild conditions.

Properties
What makes the introduction of OCF₃ into pharmaceutically relevant compounds particularly intriguing is their unique electron distribution. The geminal combination of an alkoxy or arylxy group with a fluorine atom offers the possibility of bonding/non-bonding resonance which can be formally expressed by the superposition of a covalent and an ionic limiting structure (Figure 2).

Structure
The anomeric effect reveals itself by a lengthening of the acceptor bond and a shortening of the donor bond. The differences are nevertheless small at least as far as the carbon-fluorine bond is concerned which in general is elongated by just 0.02 Å. In contrast, anomerically active carbon-oxygen bonds may shrink by almost 0.1 Å. The stable tris(dimethylamino)sulfonium (TAS) trifluoromethoxide (see Scheme 9 for structure) [40] represents an extreme case. The three carbon-fluorine bonds are stretched by approximately 0.07 Å and the carbon-oxygen bond contracted by 0.21 Å relative to trifluormethanol [40] and by 0.21 Å relative to methanol [46].

The geminally 1,1-difluorinated 2,3,4,6-tetra-O-acetyl-1-deoxy-D-glucopyranose (6, Figure 3) [47] exhibits unequivocally non-identical C-F bond lengths, according to crystallography. The difference of 1.5 hundredth of an Å falls in the expected range.

The effect of replacing a methyl by a trifluoromethyl moiety on bond length is dependent upon the electronegativity of the atom to which the substituent is attached [49] and reflects the "anomeric effect" shown above [50]. The lengthening of the acceptor bond and the shortening of the donor bond are small, as far as the carbon fluorine bond are concerned. However the carbon-oxygen bond may decrease by almost one tenth of an Å (Table 6).

A fluorine substituent can lead to a change in the preferred molecular conformation. For example, methoxybenzenes
Table 6: Effect of substituting a trifluoromethyl group for methyl on different heteroatoms.

| Atom/group Y-CX₃ (X = H, F) | Allred-Rochow Electronegativity | C-Y bond length in Å | Δr = r(CF₃)−r(CH₃) in Å |
|-----------------------------|---------------------------------|----------------------|------------------------|
| P-(CX₃)                    | 2.06                            | 1.844                | 1.904                  | +0.060                 |
| H-(CX₃)                    | 2.20                            | 1.099                | 1.102                  | +0.003                 |
| I-(CX₃)                    | 2.21                            | 2.139                | 2.138                  | −0.001                 |
| S-(CX₃)                    | 2.44                            | 1.805                | 1.819                  | +0.014                 |
| Se-(CX₃)                   | 2.48                            | 1.945                | 1.980                  | +0.035                 |
| Br-(CX₃)                   | 2.74                            | 1.939                | 1.923                  | −0.016                 |
| Cl-(CX₃)                   | 2.83                            | 1.781                | 1.752                  | −0.029                 |
| N-(CX₃)                    | 3.07                            | 1.458                | 1.426                  | −0.032                 |
| O-(CX₃)                    | 3.50                            | 1.416                | 1.369                  | −0.047                 |
| F-(CX₃)                    | 4.10                            | 1.385                | 1.319                  | −0.066                 |

without ortho substituents favor a planar conformation. However, Roche researchers by searching trifluoromethoxybenzenes without ortho substituents in the Cambridge Structural Database, found that none of the entries has the –OCF₃ group in the plane of the phenyl ring (Figure 4). From six compounds, five entries have a dihedral angle C-C-O-C of around 90° and one compound showed a skew conformation (dihedral angle C=C/OCF₃: 36°) [51].

Lipophilicity

On the basis of its electronic properties, which are close to those of a chlorine or a fluorine atom [52], the trifluoromethoxy group has been referred to as a super- [53] or a pseudo-halogen [54]. The advantage of incorporating a trifluoromethoxy group into a molecule can be described in terms of its properties. The trifluoromethoxy group is both more electron withdrawing and lipophilic than its methoxy analogue.

The fluorinated carbon adjacent to an oxygen atom increases lipophilicity as shown by the high value of the OCF₃ hydrophobic substituent parameter. While both trifluoromethyl and trifluoromethoxy substituents invariably boost the lipophilicity (Table 7), single fluorine atoms may alter this parameter in either direction. If the halogen occupies a vicinal or homovical position with respect to a hydroxy, alkoxy or carbonyl oxygen atom, it enhances the solvation energy in water more than in organic solvents (such as 1-octanol or chloroform) and hence lowers the lipophilicity [51]. It appears that the OCF₃ substituent is far more lipophilic (π = +1.04) than the halogens and lies between a CF₃ (π = +0.88) and a SCF₃ (π = +1.44) group. It may thus replace advantageously a fluorine atom (π = +0.14) in most molecules with the benefit of increased lipid solubility.

Table 7: Electronegativities and Hydrophobic Parameters for various substituents.

| Atom/group | Pauling Electronegativity | Hydrophobicity π [55,56] |
|------------|--------------------------|--------------------------|
| H          | 2.1                      | 0.00                     |
| F          | 4.0                      | 0.14                     |
| Cl         | 3.0                      | 0.71                     |
| Br         | 2.8                      | 0.86                     |
| I          | 2.5                      | 1.12                     |
| CH₃        | 2.3                      | 0.56                     |
| C(CH₃)₂     | 2.3                      | 1.98                     |
| CF₃        | 3.5                      | 0.88                     |
| OCH₃       | 2.7                      | −0.02                    |
| OCF₃       | 3.7                      | 1.04                     |
| SCF₃       | −                       | 1.44                     |
| C₆H₅       | −                       | 1.96                     |
| SF₅        | −                       | 1.23                     |

Acidity of trifluoromethyl ethers

As described previously, the trifluoromethoxy group is at the same time a strong electron-withdrawing substituent due to the three fluorine atoms and a π-donating substituent due to the oxygen lone pairs. Yagupolskii [57,58] and Sheppard [53,59] provided detailed data on the pKₐ-values of benzoic acids and phenols which reveal that the trifluoromethoxy group is a moderately electron-withdrawing moiety which resembles a
chlorine atom. The pK_a values are lowered by the trifluoromethoxy group by 0.5 – 1.0 units [60-62].

Reactivity
The OCF_3 group is thermally and chemically resistant to attack by acids, bases, organometallic reagents and oxidizing/reducing agents [23,36]. When substituted on an aromatic ring, the trifluoromethoxy group exhibits similar electron withdrawing behavior to the alkoxy group but also acts to deactivate the aromatic ring system [53].

Electrophilic Aromatic Substitution
Trifluoromethoxybenzene, for example, undergoes nitrations considerably (up to 5 times) more slowly than benzene. The electrophilic substitution occurs selectively at the ortho and para position. This means the inductive electron-withdrawing effect compromises the attack of the electrophile, but is counterbalanced, to some extent, by the capacity of the ether oxygen to act through resonance as an electron donor. This antagonistic behavior is well known for chloro and bromo substituents. The trifluoromethoxy substituent has a pronounced preference for the para substitution. Unless the para position is occupied, ortho isomers are formed only in small amounts (≤ 10%) without any trace amounts of the meta isomers [52,63,64].

When nitrations are carried out under standard conditions, the ortho/para ratio changes with the number of fluorine atoms as depicted in Scheme 10 [52,65,66]. At temperatures in the range of 25 – 50 °C, double nitrations can be achieved. The resulting 2,4-dinitrophenyl ethers are isolated in moderate to excellent yield [29,66,67].
The para-directing effect of a trifluoromethoxy group surpasses even that of an amide function. N-Acetyl-3-(trifluoromethoxy) aniline is nitrated mainly at the 6-position and to a minor extent (10%) at the 4-position (Scheme 11) [19]. N-Acetyl-4-(trifluoromethoxy)aniline reacts at the 3-position (again meta with respect to the nitrogen function and ortho to the trifluoromethoxy group!).

The pronounced preference for para substitution of (trifluoromethoxy)benzene [52,63,64] holds for most electrophilic aromatic substitutions, in particular sulfonation [64], bromination [52], chloromethylation [68] and acylation [52,64]. Attack at the meta position has so far been observed only with the isopropylation and ethylation of (trifluoromethoxy)benzene (to the extent of 9 and 31%, respectively) [52].

**Organometallic Reactions**

Some very versatile methodology functionalizing trifluoromethoxy substituted aromatics is based on the synthesis-oriented organometallic chemistry. The metal is introduced into a substrate in general by either one of two favorite methods, the permutational interconversion of halogen against metal or hydrogen against metal and subsequently replaced by an electrophile [69,70].

Trifluoromethoxybenzene reacts with sec-butyllithium in the presence of N,N,N',N'-tetramethylethylenediamine (“TMEDA”) smoothly under hydrogen/metal permutation (“metalation”) as shown in Scheme 13 [72].

The three isomeric bromo(trifluoromethoxy)benzenes react easily with butyllithium in diethyl ether at −75 °C to generate the corresponding aryllithium (Scheme 12) species which can be trapped by a variety of electrophiles furnishing a diversity of new products (Table 8) [71,72].

4-Trifluoromethoxybiphenyl can be metalated using the Schlosser superbase LIC-KOR made by combining butyllithium (LIC) with potassium tert-butoxide (KOR) in tetrahydrofuran at −100 °C. Upon trapping with molecular iodine, 3-iodo-4-trifluoromethoxybiphenyl was isolated in 90% yield [73]. Under the same conditions as employed with trifluoromethoxybenzene, 1- and 2-trifluoromethoxynaphthalene

**Scheme 12:** Bromine/lithium exchange of bromo(trifluoromethoxy) benzenes.

**Scheme 13:** Metalation of (trifluoromethoxy)benzene.

**Scheme 14:** Metalation of (trifluoromethoxy)naphthalenes.
undergo selective lithiation at the 2- and 3-position, respectively (Scheme 14) [74].

Both the trifluoromethyl and the trifluoromethoxy group are strongly electron-withdrawing groups and both have a far-reaching activating effect [74]. In an intramolecular competition on 1-trifluoromethoxy-4-(trifluoromethyl)benzene it has been shown, that lithiation next to the OCF$_3$ substituent is favoured, probably due to steric reasons. In fact, 1-trifluoromethoxy-4-(trifluoromethyl)benzene (Scheme 15) affords 2-trifluoromethoxy-5-(trifluoromethyl)benzoic acid after lithiation and carboxylation [75].

The OCF$_3$ group reveals a powerful π-polarization as it acidifies not only the ortho but also the meta and para positions strongly. Therefore, metatation of 2- and 4-(trifluoromethoxy) anisole occurs preferentially or exclusively at the methoxy-neighboring position. However, proton abstraction at the trifluoromethoxy-adjacent sites becomes dominant when sec-butyllithium in the presence of $N,N,N',N''$-pentamethyldiethylenetriamine (PMDTA) is employed. 3-Trifluoromethoxyanisole undergoes deprotonation always at the doubly activated 2-position (Scheme 17). The trifluoromethoxy group enhances the kinetic acidity of anisole by a factor of 3 if in the

![Scheme 15: Competition between -CF$_3$ and -OCF$_3$ in Metalation reactions.](image)

When the OCF$_3$ substituent is in competition with fluorine, as in fluoro(trifluoromethoxy)benzenes, the fluorine-adjacent positions are always metalated (Scheme 16) [75].

![Scheme 16: Competition between -F- and -OCF$_3$ in Metalation reactions.](image)
Scheme 18: Metalation of Bromo(trifluoromethoxy)benzenes.

orthoposition, 300 if in the para position and almost 2000 if in the metaposition [76].

The long-range effect of the trifluoromethoxy group was rationalized by Schlosser et al. by a synergy between two kinds of electronic perturbations. The electronegativity of nitrogen, oxygen, or a halogen atom pulls electrons in all σ-bonds towards the heteroelement. This σ-polarization diminishes with the distance. On the other hand, the substituent affects the π-electron cloud by attracting the whole sextet as one toward itself if it is both tetravalent and electrondeficient, e.g. trifluoromethyl or trimethylammonio groups. Alternatively, the π-cloud will remain, as in chlorobenzene, or even be pushed away from lone-pair carrying substituents (with progressively increasing strength from fluorine to alkoxy to dialkyaminio). In this way, π-electron density can accumulate at the meta and para positions, where it counterbalances the σ-polarization. The trifluoromethoxy group has a slightly smaller σ-inductive effect than fluorine or a trifluoromethyl substituent. Its π-donating capacity is inferior to the one of the methoxy group, and even inferior to that of a fluorine atom. As a result, these two effects confer its electronic individuality to the trifluoromethoxy group. While acidifying ortho-positions only moderately, its anionstabilizing effect is important at meta- and para-positions (Figure 5) [76].

By contrast, bromo(trifluoromethoxy)benzenes are metalated at −100 °C by bases such as LDA at a position next to the oxygen substituent (Scheme 18) [74].

At temperatures above −75 °C, lithium bromide elimination generates didehydro(trifluoromethoxy)benzenes ("arynes"). These short-lived species can be trapped with furan to form the corresponding Diels-Alder cycloadducts (Scheme 19) [74].

Trifluoromethoxy substituted anilines require protection of the amino function. The BOC-protected ortho and para isomer gives the 3- and 4-(trifluoromethoxy)anthranilic acid after metalation with tert-butyllithium, followed by carboxylation (Scheme 20) [71]. When the amino function is protected instead of a BOC group by a silyl group, 3-trifluoromethoxy-N-(trimethylsilyl)aniline is metalated in position 2. However, 3- and 4-trifluoromethoxy-N,N-bis(trimethylsilyl)aniline are metalated at the oxygen-adjacent position [71].
Conclusion

In the life science field, single fluorine atoms, trifluoromethyl or trifluoromethoxy groups are used to tailor $pK_a$ values, to facilitate cell membrane penetration and to increase the metabolic stability of compounds. These features of fluorine contribute to the critical “bioavailability” of therapeutically active compounds. The growing interest and utility of the trifluoromethoxy-substituent in drugs and agrochemical products, presents challenging synthetic strategies which are increasing being tackled in industrial and academic research programmes.

Acknowledgments

We thank the Ministère de la Recherche of France and are grateful to the CNRS and Bayer CropScience for a PhD grant to BM.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjr.4.13
DBFOX-Ph/metal complexes: Evaluation as catalysts for enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones

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Preliminary Communication

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Keywords:
fluorination; enantioselective; nickel; Lewis acid; catalyst

Abstract

We examined the catalytic enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones 1 with N-fluorobenzenesulfonimide (NFSI) by DBFOX-Ph/metal complexes under a variety of conditions. After optimization of the metal salts, solvents and additives, we found that the fluoro-2-thiazolidinones 2 were obtained in good to high yields with moderate to good enantioselectivities (up to 78% ee) when the reaction was carried out in the presence of DBFOX-Ph (11 mol%), Ni(ClO₄)₂·6H₂O (10 mol%) and 2,6-lutidine (0 or 1.0 equiv) in CH₂Cl₂.

Background

Enantioselective electrophilic fluorination represents an important and straightforward strategy for C-F bond formation at a carbon stereocenter, providing easy access to chiral fluoro-organic compounds [1,2]. Due to the significance of chiral fluoro-organic compounds, such as fluorinated quinolones [3,4] and liquid crystals [5], in pharmaceutical and material sciences considerable effort has been dedicated to this issue for decades [6-17]. As a consequence, a variety of procedures have been developed to increase the yields and enantioselectivities of electrophilic fluorination reactions. Stoichiometric approaches based on cinchona alkaloid/Selectfluor® combinations [18-32], chiral ligand/metal-catalyzed [33-57] or organocatalytic [58-64] procedures for enantioselective fluorination are major advances in recent years. The discovery that chiral ligands/metals can catalyze electrophilic fluorination with conventional fluorinating reagents has had a large impact on synthetic organic chemistry, because of the availability of commonly used classes of ligands for asymmetric catalysis, such as, TADDOLs [37,39,41,47], BINAPs [38,40,43,44,46,49,51,53,55-57] and bis(oxazoline) [33,34,36,42,45]. Of particular importance are
BINAP ligands. Sodeoka et al. have used the latter ligands in asymmetric fluorination of a wide range of substrates, including β-keto esters, β-keto phosphonates, oxindoles [38,40,43,51,53,56,57]. They have also recently reported the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with their NiCl₂-BINAP/R₃SiOTf-lutidine (trinary system, up to 87% yield and selectivity) [57]. Although the enantioselectivities are moderate to good in these examples (63–79% ee), the results are quite impressive because the fluorination proceeds even in the absence of base (entries 1 and 2). That is, both Ni(ClO₄)₂-DFFOX-Ph (unary system, entries 1 and 2) and Ni(ClO₄)₂-DFFOX-Ph/lutidine (binary system, entries 3–6) are moderately effective in the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with N-fluorobenzenesulfonylimide (NFSI) (Figure 1).

**Results and Discussion**

Our previous studies of the DBFOX-Ph/Ni(II)-catalyzed enantioselective fluorination of β-keto esters have shown that the optimal reaction conditions require NFSI as the fluorine source and a catalytic amount of Ni(ClO₄)₂·6H₂O in CH₂Cl₂ at room temperature. Therefore, we first attempted the reaction of 1a with the same conditions and found that the desired fluorinated product 2a was obtained in 42% yield with 69% ee (Table 1, entry 1). The reaction at higher temperature (40 °C) improved the yield to 62% with slightly lower enantioselectivity (63% ee, entry 2). The reaction time in these experiments was shortened by the addition of 1 equiv of 2,6-lutidine to 2a in 87% yield with 66% ee at room temperature (entry 3). Both yield and selectivity were improved to 90% and 74% ee when the reaction was performed at 0 °C (entry 4). The highest ee value of 2a was obtained at −20 °C, but resulted in a decrease in yield (24%, 79% ee, entry 5). Changing the metal salts did not improve the results (entries 6 and 7). The absolute stereochemistry of 2a was determined by comparing the optical rotation and HPLC analysis with the literature values [57]. Although the enantioselectivities are moderate to good in these examples (63–79% ee), the results are quite impressive because the fluorination proceeds even in the absence of base (entries 1 and 2).

**Table 1: Optimisation of the Conditions for DBFOX-Ph/Ni(II)-Catalysed Enantioselective Fluorination of 3-(2-Phenylacetyl)-2-thiazolidinone (1a)**

| Run | Metal salt | 2,6-Lutidine (equiv) | Temp (°C) | Time (d) | Yield (%) | ee (%) |
|-----|------------|----------------------|-----------|----------|-----------|--------|
| 1   | Ni(ClO₄)₂·6H₂O | none | 62 °C | 20 h | 42 | 69 |
| 2   | Ni(ClO₄)₂·6H₂O | none | 40 | 4 d | 62 | 63 |
| 3   | Ni(ClO₄)₂·6H₂O | 1.0 | rt | 17 h | 87 | 66 |
| 4   | Ni(ClO₄)₂·6H₂O | 1.0 | 0 | 20 h | 90 | 74 |
| 5   | Ni(ClO₄)₂·6H₂O | 1.0 | −20 | 4 d | 24 | 79 |
| 6   | Ni(ClO₄)₂·6H₂O | 1.0 | rt | 4 d | 55 | 72 |
| 7   | Zn(OAc)₂ | 1.0 | rt | 3 d | NR | - |
| 8   | Cu(OTf)₂ | 1.0 | 0 | 2 d | NR | - |
| 9   | Ni(ClO₄)₂·6H₂O | 1.0 | 0 | 2 d | 33 | 15%

For detailed reaction conditions, see Supporting Information File 1. Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of 2a was determined by comparison with the optical rotation and HPLC analysis in the literature [57]. NR: No reaction. For detailed reaction conditions, see Supporting Information File 1. Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of 2a was determined by comparison with the optical rotation and HPLC analysis in the literature [57]. NR: No reaction. For detailed reaction conditions, see Supporting Information File 1. Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of 2a was determined by comparison with the optical rotation and HPLC analysis in the literature [57]. NR: No reaction.
Table 2: Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/Ni(II)\textsuperscript{a}.

| Entry | \( Ar \) | \( 2a \) | Time (h) | Yield (%) | ee (%) |
|-------|---------|---------|---------|---------|-------|
| 1     | Ph      | 2a      | 20      | 90      | 74    |
| 2     | \( \text{C}_6\text{H}_4\text{-o-OMe} \) | 2b      | 48      | 96      | 78    |
| 3     | \( \text{C}_6\text{H}_4\text{-m-OMe} \) | 2c      | 24      | 94      | 66    |
| 4     | \( \text{C}_6\text{H}_4\text{-p-OMe} \) | 2d      | 24      | 90      | 65    |
| 5     | \( \text{C}_6\text{H}_4\text{-o-Me} \) | 2e      | 48      | 69      | 78    |
| 6     | \( \text{C}_6\text{H}_4\text{-m-Me} \) | 2f      | 48      | 75      | 73    |
| 7     | \( \text{C}_6\text{H}_4\text{-m-Me} \) | 2g      | 48      | 75      | 77    |
| 8     | \( \text{C}_6\text{H}_4\text{-p-Me} \) | 2h      | 48      | 60      | 62    |
| 9     | \( \text{C}_6\text{H}_4\text{-p-Br} \) | 2i      | 48      | 77      | 56    |
| 10    | 1-Naphthyl | 2j      | 48      | 85      | 59    |
| 11    | 2-Naphthyl | 2k      | 48      | 90      | 60    |

\textsuperscript{a}For detailed reaction conditions, see Supporting Information File 1. Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of \( 2a \) was determined by comparison with the optical rotation and HPLC analysis in the literature [57]. Others were tentatively assigned by comparing the signs of their optical rotations to that of \( 2a \).

The DBFOX-Ph/Ni(OTf)_2-6H_2O catalysis for fluorination showed high generality for various 3-(2-arylacetyl)-2-thiazolidinones \( 1a-k \) in good to high yields with moderate to good enantioselectivities. The results are summarized in Table 2. The fluorination reaction was not very sensitive to substitution in the position of the phenyl group and the desired products with methoxy or methyl groups at the \( o \), \( m \), or \( p \)-position of the benzene ring were obtained in 65–78% ee (entries 2–7). The reactions of fluoro or bromo-substituted \( 1h, i \) and bulky-substituted \( 1j, k \) afforded the desired products \( 2h-k \) in good yields with slightly lower enantioselectivities (56–62% ee, entries 8–11).

The \( R \)-enantioselection of \( 2 \) can be explained by assuming an octahedral complex coordinated with a water molecule for DBFOX-Ph/Ni(II)/1 as shown in Scheme 1. In the complex, the \( Si \) face is shielded by one of the phenyl groups of DBFOX-Ph so that NFSI approaches from the \( Re \) face of the substrates (Scheme 1). Since a major difference in ee values of \( 2 \) was not observed for the fluorination reaction of \( 1 \) with NFSI in the presence or absence of 2,6-lutidine (entries 1–3, Table 1), 2,6-lutidine presumably just accelerates the tautomerization of \( 1 \) to its enol form.

Conclusion

This research has demonstrated that DBFOX-Ph/Ni(II) catalysis can be used for the catalytic enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with or without 2,6-lutidine to afford chiral 2-fluoro-2-arylacecyl derivatives in good to high yields with moderate to good enantioselectivities of up to 78% ee. The Box-Ph ligand was not effective for this reaction. Our best ee value is slightly lower than that of Sodeoka’s report [57]; this is presumably due to the low activity...
of our catalyst system which requires higher reaction temperature conditions (0 °C vs. -20 °C [57]). Racemization of the products 2 during the fluorination reaction was ruled out since no racemization was observed when 2a was stirred overnight under the same fluorination conditions. Further studies to improve the enantioselectivity of DBFOX-Ph/metal catalysis in enantioselective fluorination are under way.

Supporting Information

Supporting Information File 1
Experimental methods. General methods, general procedure for the enantioselective catalytic fluorination, spectral data of 2, copies of 1H, 13C and 19F-NMRs and HPLC charts of 2
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-16-S1.doc]

Acknowledgments
Support was provided by KAKENHI (19390029), by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology Japan (19020024).

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Efficient 1,4-addition of α-substituted fluoro(phenylsulfonyl)methane derivatives to α,β-unsaturated compounds

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Abstract

The 1,4-addition of a monofluoromethyl nucleophile to a variety of α,β-unsaturated compounds has been achieved under mild conditions using either phosphines or potassium carbonate at room temperature. α-Substituted fluoro(phenylsulfonyl)methane easily undergoes Michael addition to α,β-unsaturated ketones, esters, nitriles, sulfones, as well as propynoates at room temperature to yield the corresponding adducts in moderate to excellent yields.

Background

Compounds with a monofluoromethyl moiety are of great importance with regards to isostere-based drug design [1-4]. Consequently, synthesis of new functionalized α-monofluorine-substituted active methylene derivatives has attracted considerable attention particularly in the field of medicinal chemistry [5, 6]. One of the major interests in our group has focused on developing new fluorination reagents or fluorinated building blocks for preparation of fluorine-substituted compounds [7-13]. As part of our ongoing effort to extend the applications of fluorine-containing (phenylsulfonyl)methane derivatives, we envisaged that fluoro(phenylsulfonyl)methane, α-substituted by nitro, cyano, ester, or acetyl would be useful for the synthesis of functionalized monofluoromethylated compounds, which would undergo various transformations. New synthetic methods for the synthesis of α-substituted fluoro(phenylsulfonyl)methane derivatives under mild reaction conditions, using convenient starting materials, are still desirable.

Fluorinated carbanions are in principle "hard" nucleophiles that readily undergo 1,2-addition with Michael type acceptors instead of 1,4-addition [14-16]. Different strategies have been employed to achieve 1,4-addition, which is still perceived to be
a challenge. For instance, Yamamoto [17] and Röschenthaler [18,19] have made use of bulky aluminum Lewis acids to protect the carbonyl of Michael acceptors and thus successfully transferred the trifluoromethyl anion generated from the "Ruppert-Prakash reagent" (TMS-CF$_3$) in a 1,4-manner rather than the favored 1,2-addition. Portella et al. [20] have shown that 1,4-addition of difluoroenoxysilanes to enones can be used to introduce difluoromethylene moiety while Kumadaki and coworkers [21,22] have used bromodifluoroacetate with a copper catalyst to introduce the CF$_2$ functionality. There also exist few reports on the 1,4-addition of monofluoromethylene moieties to α,β-unsaturated compounds [23,24]. Takeuchi and coworkers [25] have shown that α-fluoronitroalkanes can undergo 1,4-addition to methyl vinyl ketone and acrylonitrile to afford the dialkylated products.

Results and Discussion

Herein, we disclose the facile reaction of fluoro(phenylsulfonyl)methane derivatives and various Michael acceptors. We first began with the preparation of nitro, cyano, ester, or acetyl-substituted (phenylsulfonyl)methanes from the corresponding (phenylthio)methane derivatives, the precursors of α-substituted fluoro(phenylsulfonyl)methane derivatives. Oxidation of (nitromethyl)(phenyl)sulfide with aqueous hydrogen peroxide [H$_2$O$_2$, 30% (wt)] was attempted in acetic acid at room temperature. Tuning the conditions by using 4-fold excess of H$_2$O$_2$ afforded 90% yield of (nitromethylsulfonyl)benzene overnight (Table 1, entry 1) [26-28]. 2a–c and 2e were prepared in 76–91% yields under the optimized condition and used without further purification [30-34]. Interestingly, the oxidation of 1d gave a mixture of 2d and methylsulfonylbenzene in a ratio of 2:1. Hence, compound 2d was synthesized from another known procedure [29]. Fluorobis(phenylsulfonyl)methane 3f was prepared following a literature procedure by fluorinating bis(phenylsulfonyl)methane, which is commercially available [11].

Our strategy for the preparation of monofluoro methane was to use commercially available Selectfluor® [35] as the electrophilic fluorine source. The monofluorination of (nitromethylsulfonyl)benzene with Selectfluor® under the improved conditions [36] [treatment of (nitromethylsulfonyl)benzene (6.75 mmol) with NaH (6.75 mmol) in THF (25 mL) followed by Selectfluor® (6.75 mmol) in 15 mL of DMF at 0 °C] gave [fluoro(nitro)methylsulfonyl]benzene 3a in 62% isolated yield (Table 1, entry 1). A doublet was observed at δ −142.16 ppm in the $^{19}$F NMR spectrum of 3a, which matched our previously reported result [11]. Other fluoro(phenylsulfonyl)methane derivatives were synthesized in 45–61% yields under similar conditions (Table 1, entries 2–5).

### Table 1: Oxidation of sulfides and monofluorination of sulfones.

| Entry | R   | Yield (%) | Yield (%) |
|-------|-----|-----------|-----------|
| 1     | NO$_2$ | 90 | 62 |
| 2     | CN   | 76 | 45 |
| 3     | CO$_2$Et | 83 | 56 |
| 4     | COMe | b | - |
| 5     | CH=CH$_2$ | 91 | - |

*a*isolated yield, *b*2d was prepared according to ref. [29], *c*no product obtained
Alkylation of 3a–d, 3f is reported to be a challenge because the combined carbanion-stabilizing abilities of the two strong electron-withdrawing groups are not sufficient to overcome the well-known carbanion destabilization by the adjacent fluorine [25]. With this in mind, we first opted to use phosphines as nucleophilic catalysts. Concerning applications of 3a–d, and 3f in constructing the carbon-carbon bond, a reaction of [fluoro(nitro)methylsulfonyl]benzene with methyl vinyl ketone was first tested in the presence of PPh$_3$ (50 mol%) in THF at room temperature under argon. Interestingly, 5-fluoro-5-nitro-5-(phenylsulfonyl)pentan-2-one (5a) was obtained in 93% yield as the sole product, which was characterized by $^{1}H$, $^{13}C$, $^{19}F$ NMR, and HRMS. In the $^{19}$F NMR spectrum of 5a, two doublets at δ = -125.94 ppm were observed. As it is known, fluoro substitution can cause problems in transformations, since fluoride can also act as a leaving group. Notably, fluorine-free

Table 2: PMe$_3$-catalyzed reaction of fluoro(phenylsulfonyl)-substituted methane derivatives with methyl vinyl ketone and ethyl acrylate.

| Entry | R$_1$ | R$_2$ | Product | Time (h) | Yield$^a$ (%) |
|-------|-------|-------|---------|----------|--------------|
| 1     | NO$_2$ | Me    | ![Image of 5a](image.png) | 40       | 93           |
| 2     | CN    | Me    | ![Image of 5b](image.png) | 22       | 90           |
| 3     | CO$_2$Et | Me | ![Image of 5c](image.png) | 24       | 75           |
| 4     | PhSO$_2$ | Me | ![Image of 5d](image.png) | 17       | 91           |
| 5     | NO$_2$ | OEt   | ![Image of 5e](image.png) | 72       | 64           |
| 6     | CN    | OEt   | ![Image of 5f](image.png) | 72       | 60           |
| 7     | CO$_2$Et | OEt | ![Image of 5g](image.png) | 116      | 71           |
| 8     | PhSO$_2$ | OEt | ![Image of 5h](image.png) | 67       | 88           |

$^a$isolated yield
products were not detected in the course of above-mentioned Michael reactions, under the reaction conditions.

We then screened various electronically and sterically different phosphines such as PPh\textsubscript{3}, Bu\textsubscript{3}P, (iPr)\textsubscript{3}P and PMe\textsubscript{3}. Initial experiments revealed that the catalytic activity of phosphines and phosphine loading (varying from 20\% to 50\%) efficiently promoted the Michael reaction. With 50 mol\% catalyst loading, the reaction rates were approximately 2- to 3-fold faster than the corresponding 20 mol\% PPh\textsubscript{3} catalyzed reactions. A dramatic increase in the efficiency of the reaction came from the usage of less bulkier phosphine, PMe\textsubscript{3} (20 mol\%), which led to the best result (Table 2, entry 1).

Having established optimal conditions, we then investigated the scope of various substrates in the reaction (Table 2). Methyl vinyl ketone reacted with 3a, 3b, 3c, or 3f to furnish the corresponding products in good to excellent yields, respectively, except in the case of 1-fluoro-1-(phenylsulfonyl)propane-2-one (3d) (Table 2, entries 1–4). Compound 3d gave complex results due to the reactions of the two types of active acidic \(\alpha\)-Hs adjacent to the carbonyl group in the molecule.

When ethyl acrylate was subjected to similar reaction conditions, the yields of the products were 60–88\% after prolonged reaction time. Compared to methyl vinyl ketone, the reaction rates were slow due to the somewhat lower reactivity of ethyl acrylate (Table 2, entries 5–8). All products obtained were characterised by \(^{19}\text{F}, ^{1}\text{H}, ^{13}\text{C}\) NMR spectra, as well as HRMS. In addition, base-sensitive functional groups such as cyano, nitro, and ester were well tolerated during the course of the reaction. The failure of \((E)\)-pent-3-en-2-one to undergo the Michael reaction under these conditions demonstrates that the reaction is not tolerant of substituents at the terminal position of the double bond due to steric effects.

On the basis of the above mentioned results, a proposed mechanism for the formation of 5a–h is outlined in Scheme 1. Trialkylyphosphine catalysed Morita-Baylis-Hillman reaction is well studied by a number of groups [37-39]. Addition of PMe\textsubscript{3} to alkene 4 generates the dipolar intermediate. The latter abstracts a proton from the \(\alpha\)-fluoro-substituted methylene derivative 3, followed by an intermolecular \(S_N2\) reaction to furnish the desired product 5 and the release of PMe\textsubscript{3} (Scheme 1). The mechanism supports the fact that the less steric hindered catalyst PMe\textsubscript{3} is more efficient than PPh\textsubscript{3}, Bu\textsubscript{3}P or (iPr)\textsubscript{3}P.

In addition, the presence of electron withdrawing groups such as the phenylsulfonyl group can be exploited to generate a carb-anion that can act as a “soft” nucleophile [40,41]. The phenylsulfonyl group delocalises the electron density on the fluorinated carb-anion center, which makes the resulting nucleophile softer and more suitable for 1,4-addition with Michael acceptors. Hence, we explored the possibility of a base induced Michael addition reaction. Among the various bases and solvent combinations that we explored, the \text{K}_2\text{CO}_3/DMF system was found to be very efficient both in terms of conversions as well as reaction times.

The reactions were carried out at room temperature and the completion observed within 2 h. The reaction was found to be versatile for various \(\alpha,\beta\)-unsaturated compounds such as ketones, esters, nitriles and sulfones (Table 3). In case of \(\alpha,\beta\)-unsaturated aldehydes the reaction was found to be not clean.

Scheme 1: Reaction mechanism for phosphine catalyzed 1,4-addition to \(\alpha,\beta\)-unsaturated compounds.
Table 3: K$_2$CO$_3$/DMF catalyzed 1,4-addition to α,β-unsaturated esters, ketones, sulfone, nitriles and propynoates.

| Entry | R   | Substrate | Product (5/6) | Yield$^a$ |
|-------|-----|-----------|---------------|-----------|
| 1     | PhSO$_2$ | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 70        |
| 2     | PhSO$_2$ | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 70        |
| 3     | PhSO$_2$ | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 71        |
| 4     | PhSO$_2$ | $\text{PhSO}_2$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 90        |
| 5     | PhSO$_2$ | $\text{PhSO}_2$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 79        |
| 6     | PhSO$_2$ | $\text{PhSO}_2$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 60        |
| 7     | PhSO$_2$ | $\text{PhSO}_2$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 54 (1:2)  |
| 8     | NO$_2$   | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 45        |
| 9     | COOEt    | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 65$^b$    |
| 10    | PhSO$_2$ | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 76 (2:3)$^c$ |
| 11    | PhSO$_2$ | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 60 (1:1)$^c$ |
| 12    | NO$_2$   | $\text{HCOO}$ | (PhSO$_2$)$_2$FC$_\text{}$O$\text{}$O$\text{}$ | 46$^d$    |

$^a$isolated yield, $^b$NMR yield (based on $^{19}$F NMR), $^c$cis : trans ratio, $^d$only trace amount of cis isomer observed
and too many fluorine peaks appeared in the $^{19}$F NMR even when the reaction was carried out at low temperatures. On the other hand, α,β-unsaturated nitriles underwent a second Michael addition of the product 6h. Both fluoro(bisphenylsulfonyl)methane and fluoronitro(phenylsulfonyl)methane were added to propynoates under similar conditions. As expected, a mixture of both cis and trans products were obtained as shown in Table 3 (entries 10–11). Interestingly, in the case of fluoronitro(phenylsulfonyl)methane only the trans isomer 61 was obtained in an appreciable amount while the cis product was observed only in traces.

During our study, we observed that the steric factor affects the addition of the pronucleophile to the Michael acceptor. Substitution at the α-position of the Michael acceptor affects the reactivity of the nucleophile generated by the K$_2$CO$_3$/DMF system. The reaction of fluoro(bisphenylsulfonyl)methane with methyl crotonate was found to give only 50% conversion based on $^{19}$F NMR after 36 h and methyl cinnamate did not react at all at room temperature using the K$_2$CO$_3$/DMF system. Methyl cinnamate was found to give only 50% conversion based on $^{19}$F NMR after 36 h and methyl cinnamate did not react at all at room temperature using the K$_2$CO$_3$/DMF system. The reaction of fluoro(bisphenylsulfonyl)methane with methyl crotonate was found to give only 50% conversion based on $^{19}$F NMR after 36 h and methyl cinnamate did not react at all at room temperature using the K$_2$CO$_3$/DMF system.

In summary, a convenient protocol for the preparation of α-substituted fluoro(phenylsulfonyl)methane derivatives has been described and its subsequent use in 1,4-addition to α-substituted fluoro(phenylsulfonyl)methane derivatives has been demonstrated. Further applications of fluoro(phenylsulfonyl)methane including stereocontrolled synthesis will be reported in due course.

Acknowledgments
Support of our work by the Loker Hydrocarbon Research Institute is gratefully acknowledged.

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Supporting Information
Supporting Information File 1
Experimental procedures, full spectroscopic data and spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-17-S1.doc]

Supporting Information File 2
Spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-17-S2.doc]
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Understanding the mechanism of Pd-catalyzed allylic substitution of the cyclic difluorinated carbonates

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Abstract

We present a mechanistic investigation of Pd-catalyzed allylic substitution of cyclic gem-difluorinated carbonates ¹ and ⁴, previously employed in the synthesis of ³',³'-difluoro-²'-hydroxymethyl-⁴',⁵'-unsaturated carbocyclic nucleosides in 17 steps. The substitution features a reversal of regioselectivity caused by fluorine.

Background

Carbocyclic nucleosides (CNAs), in which the furanose oxygen atoms of the ⁴'-oxonucleosides are substituted by CH₂, have received considerable attention because they exhibit greater metabolic stability toward nucleoside phosphorylases and higher lipophilicity, two properties that are potentially beneficial in terms of increased in vivo half life, oral efficiency and cell wall penetration [¹,²]. Based on CNA skeletons, ₁,₂-disubstituted carbocyclic nucleosides (OTCs) recently attracted more and more attention [³-⁹], especially after De Clercq et al. found that some OTCs showed moderate to good activity against murine leukemia cells L1210/0, human T-lymphocyte cells Molt4/C8, and CEM/0 via topological substructural approach to molecular design (TOSS-MODE) [¹⁰]. As part of our ongoing and continual efforts to prepare potential bioactive fluorinated nucleosides, our group recently described the stereoselective synthesis of ³',³'-difluoro-⁴',⁵'-unsaturated OTCs ²–₃ and ⁵ [¹¹]. The whole synthesis highlighted the stereoselective Reformatskii-Claisen rearrangement, ring-closing metathesis (RCM), and Pd-catalyzed allylic substitution, in which the regioselectivity was reversed from that of nonfluorinated substrates. This reversed regioselectivity caused by fluorine interests us greatly. Herein, we present a mechanistic investigation of Pd-catalyzed allylic substitution of cyclic gem-difluorinated carbonates.

Results and Discussion

On installation of pyrimidine bases into the gem-difluorinated allylic carbonates ¹ and ⁴, our group found that the γ-substitution products ², ³ and ⁵ were surprisingly generated exclusively in good yields, respectively, when the compounds ¹ and ⁴...
reacted with suitably protected nucleobases 3-benzyloxyuracil and 3-benzylothymine in the presence of a catalytic amount of Pd(PPh₃)₄ at 60 °C in THF (Scheme 1) [11]. The exclusive regioselectivities of Pd-catalyzed allylic alkylation (Pd-AA) reactions were very interesting. Although Konno et al. have reported that the electron-withdrawing fluoroalkyl groups would alter the regioselectivities of acyclic allylic alkylation compared with their non-fluorinated counterparts [12-17], their reactions mostly concerned the Pd-catalyzed regio- and stereoselective formate reduction of fluorine-containing allylic mesylates. To the best of our knowledge, the effect of gem-difluoromethylene group on Pd-catalyzed cyclic allylic substitution has never been addressed so far. The regioselectivity was totally different from those of nonfluorinated substrates [18].

Unexpected and specific regioselectivity of Pd-catalytic asymmetric reactions of the gem-difluorinated allylic intermediates 1 and 4 prompted us to investigate further the mechanism of these reactions. Currently, one of the most direct tactics for mechanistic investigation of Pd-AA reaction was built on the analysis of crystal structure and ¹³C NMR spectroscopy of Pd-π-allyl complex [19,20]. The orientation of attack of nucleophiles on the Pd-π-allyl complex could be illustrated via examining the ¹³C NMR chemical shifts of three carbon atoms attached to the palladium. According to the model of DeShong et al. [21], it was anticipated that a symmetrical Pd-π-allyl complex should be temporarily generated once the compounds 1 or 4 were treated with palladium catalyst. Thus, α-substitution products should be afforded considering the steric effects. However, only γ-substitution products 2–3 and 5 were isolated in our case, which, in our opinion, resulted from the specific electron-withdrawing property of the gem-difluoromethylene group. To further validate our hypothesis and the proposed model of DeShong et al., we decided to explore the crystal structure and ¹³C NMR of the corresponding Pd-π-allyl complex.

In 2000, Bäckvall and co-workers investigated the X-ray structures for cis and trans isomers of [(1,2,3-η)-4-acetoxy-2-cyclohexen-2-yl]palladium chloride dimers [22]. They found that the X-ray structure of trans-trans dimer displayed asymmetric allyl-palladium bonding where the Pd-C3 bond was shorter than the Pd-C1 bond. Their study provided the first direct evidence for the presence of electronic interaction in the Pd-catalytic asymmetric allylic reactions of 1-acetoxy-4-chloro-2-cyclohexene. Based on their study, we first converted the precursor compound 6 to the γ-chloro-substituted compound 7 in 78% yield by treatment with NCS / PPh₃ in THF at 0 °C (Scheme 2). Using the stereodivergent method of Kurosawa et al. [23], trans-trans dimer 8 and cis-cis dimer 9 were prepared in 74% and 86% yield by treatment of the chloride 7 with Pd(dba)₂ using toluene and DMSO as the solvent, respectively.

To our delight, the crystal of trans-trans dimer 8 was suitable for X-ray analysis (Figure 1). It was clear that 1,2-bis(benzyloxy)ethyl moieties in dimer 8 occupied the positions trans to the corresponding palladium atoms. Also obvious was that allyl-palladium bonding in trans-trans dimer 8 was almost symmetric: within experimental error, there was not much difference between the Pd1-C2 bond length 2.105 Å (11) and Pd1-C4 bond length 2.118 Å (9), and between the Pd1-C4-C3 bond angle 68.9° (6) and Pd1-C2-C3 bond angle 69.2° (7) (Table 1). Thus, as expected from the proposed model [21], the symmetrical Pd-π-allyl complex was generated. According to the X-ray structure of the trans-trans dimer 8, it was clear that C4 position was more shielded than the C2 position, which should guide the attack of nucleophiles from the C2 position.

Scheme 1: Pd-catalyzed allylic substitution of the gem-difluorinated allylic carbonates 1 and 4.
Scheme 2: Synthesis of trans-trans dimer 8 and syn-syn dimer 9.

However, we only isolated the product resulting from the attack of nucleophiles from C4 position, which, in our opinion, was totally attributed to the strong electron-withdrawing property of neighboring gem-difluoromethylene group. $^{13}$C NMR spectroscopy of the trans-trans dimer 8 unambiguously demonstrated that C2 (t, δ = 73.2) experienced higher field than C4 (s, δ = 81.4), which was also ascribed to the strong electron-withdrawing property of the CF₂ group. Taking all the above analysis together, it seems that the CF₂ group’s strong electron-withdrawing property leads to a higher density of positive charge at the C4 position of the π-allyl palladium, which predominantly promotes attack of the nucleophile on C4 even when the C4 position is more hindered than the C2 position.

Interestingly, we also found that treatment of the trans-trans dimer 8 with PPh₃ / 3-benzoylthymine sodium at rt provided the nucleoside analogue 5 in 30% yield. No product was detected when PPh₃ was absent (Scheme 3). Thus, we think that the reaction occurred involving the monopalladium complex 10. The complex 10 resulted from the depolymerization of the dimer 8 caused by PPh₃. With this thought in mind, we attempted to isolate and characterize the monopalladium complex. Unfortunately, we found that exposure of the trans-trans dimer 8 to PPh₃ / AgSbF₆ afforded the monopalladium complex 11, which was too unstable to be isolated (Scheme 4). Neither did substitution of PPh₃ by dppe deliver our desired complex 12 but gave instead the palladium complex 13, whose structure was confirmed by X-ray structure analysis. In our opinion, the reason we failed to isolate the monopalladium complex was also due to the presence of gem-difluoromethylene group. That is, in the absence of nucleophiles, the dimer 8 tended to lose the cyclopentanyl ligand upon treatment.

Table 1: Selected bond lengths (Å), bond angle (°) and chemical shifts of $^{13}$C NMR spectroscopy of the trans-trans dimer 8.

| bond      | bond length (Å) | bond angle (°) | $^{13}$C NMR chemical shift (δ, ppm) |
|-----------|-----------------|----------------|-------------------------------------|
| Pd1-C2    | 2.105 (11)      |                |                                     |
| Pd1-C4    | 2.118 (9)       |                |                                     |
| Pd1-C4-C3 |                | 68.9° (6)      |                                     |
| Pd1-C2-C3 |                | 69.2° (7)      |                                     |
| C2         |                |                | 73.1 (t, $J$ = 19.3 Hz)             |
| C4         |                |                | 81.4 (s)                            |
with PPh₃ or dppe, because the CF₂ group made the Pd-π-allyl too electron-deficient. That was why we could isolate the palladium complex 13 as the only product.

In conclusion, we have investigated the reaction mechanism of Pd-catalyzed allylic substitution of cyclic gem-difluorinated intermediates in detail via the crystal structure and ¹³C NMR spectroscopy of the Pd-π-allyl complex. We found that the Pd-catalyzed reactions of cyclic gem-difluorinated allylic carbonates 1 and 4 proceeded via the symmetric Pd-π-allyl bonding and highly regioselective γ-substitution resulted from the neighboring gem-difluoromethylene group. We propose that the present work opens a new avenue for the further insight into the Pd-catalyzed allylic substitution reactions.

Supporting Information

Supporting Information File 1
Experimental Section and Characterization Data of Compounds
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-18-S1.doc]

Acknowledgments

The financial support of our research in this area by National Natural Science Foundation of China, the Program for Changjiang Scholars, Innovative Research Team in University and Shanghai Municipal Scientific Committee was greatly acknowledged.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.4.18
Synthesis of new triazole-based trifluoromethyl scaffolds
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Abstract
Trifluoromethyl propargylamines react with various azide derivatives to afford 1,4-disubstituted 1,2,3-triazoles through a Huisgen 1,3-dipolar cycloaddition. The reaction is catalyzed by a Cu(I) species in acetonitrile, and the corresponding products are obtained in good yields. This process thus offers an entry to new trifluoromethyl peptidomimetics as interesting scaffolds.

Background
The 1,2,3-triazole system has widespread uses, and it has been considered as an interesting component in terms of biological activity [1-5]. Although the use of heterocyclic moieties in peptidomimetics has been widely reported [6], the application of 1,2,3-triazoles in the field of conformational studies has occurred only recently [7-13]. In particular, Angelo and co-workers [8,12] reported the synthesis of triazole foldamers able to adopt specific protein-like conformations. On the other hand, it is well known that the introduction of fluorine atoms or a fluoroalkyl group can greatly modify the physico-chemical features and thus the biological properties of a molecule (resistance to metabolic oxidation and hydrolysis, modification of pKa, hydrophobicity,...) [14-17]. Furthermore, the development of CF3-containing scaffolds has gained a real interest especially in the peptidomimetic area [18-21]. In continuation of our interest in the synthesis of original trifluoromethyl compounds [22-26], and in order to study the influence of trifluoromethyl groups on the conformation of peptidomimetics, we decided to explore the preparation of trifluoromethyl triazole derivatives. Herein we turn our attention to the synthesis of new triazoles from trifluoromethyl propargylamines using the Huisgen 1,3-dipolar cycloaddition [27-29].

Results and Discussion
The synthetic approach depicted in Scheme 1 shows that the desired compounds could be easily obtained via a 1,3-dipolar cycloaddition from the corresponding propargylamines which are obtained using an efficient procedure from the trifluoromethyl imines previously described by our group [30-32].

The copper(I)-catalyzed 1,3-dipolar cycloaddition [33-38] of organic azides and alkenes (also called “click chemistry”)
resulting in the formation of 1,2,3-triazoles has become an increasingly attractive area [39]. According to the literature [33-38], the Cu(I) species can be used directly (e.g. Cul), or generated by oxidation of a Cu(0) or reduction of a Cu(II) species. Catalysis by the Cul is known to yield exclusively the 1,4-disubstituted regioisomer [33,34]. First, the N-(p-methoxyphenyl)-1-(trifluoromethyl)propargylamine was reacted with benzyl azide in the presence of CuI (10 mol%) and showed good reactivity with completion of the reaction within 24 h, whereas the use of CuSO₄/Na ascorbate afforded the cycloadduct in low yield. The reaction was then carried out with different propargylamines (N-(p-methoxyphenyl) and N-benzyl) and various azides at room temperature in acetonitrile within 24 h which afforded the compounds 2a-i with good yields (63-92%) after purification by column chromatography. The results are summarized in Table 1.

As expected the new triazoles were formed in a fully regioselective manner affording the 1,4-regioisomer as highlighted from NOE experiments on compound 2c (Figure 1). A strong correlation was observed between the hydrogen H₄ and H₈ respectively. The structure of the other compounds 2a-i was assigned by analogy with 2c.

In our goal to study the influence of the CF₃ group on the conformation of peptidomimetics, we applied our strategy to the enantiopure trifluoromethyl-propargylamine 3 bearing the removable (R)-phenylglycinol chiral auxiliary (Scheme 2) [30-32].

The reaction was carried out under the same condition with azidoacetic acid methyl ester and afforded the cycloadduct 4 in good yield (79%) and as a single isomer without any racemization. This compound can easily afford the free amino ester which is a promising trifluoromethyl building block for the synthesis of new triazole-based trifluoromethyl oligomers.

Table 1: Copper(I)-catalyzed synthesis of 1,4-disubstituted triazoles

| Entry | R₁     | R₂         | Product | Yield (%)   |
|-------|--------|------------|---------|-------------|
| 1     | -PMP  | -Bn       | 2a      | 82          |
| 2     | -PMP  | -CH₂COPh  | 2b      | 76          |
| 3     | -PMP  | -CH₂OOC(CH₃)₃ | 2c  | 73          |
| 4     | -PMP  | -CH₂CO₂CH₃ | 2d      | 83          |
| 5     | -PMP  | -CH₂CH₂OH  | 2e      | 87          |
| 6     | -Bn   | -Bn       | 2f      | 75          |
| 7     | -Bn   | -CH₂COPh  | 2g      | 63          |
| 8     | -Bn   | -CH₂CO₂CH₃ | 2h      | 92          |
| 9     | -Bn   | -(CH₂)₂OH | 2i      | 73          |

aPMP: p-methoxyphenyl, Bn: benzyl. bYield after flash purification.

Figure 1: Experimentally found NOE correlation for compound 2c.
Conclusion
In summary, this paper describes the synthesis of new trifluoromethyl triazole scaffolds from readily accessible propargylamines and azides through a copper (I) catalyzed 1,3-dipolar cycloaddition. The triazole derivatives were obtained in good yields and will be useful intermediates for further synthesis of new fluorinated foldamers and their conformational feature studies.

Supporting Information
Supporting Information File 1
General methods, synthetic procedure and spectroscopic data of 2a-i and 4.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-19-S1.doc]

Acknowledgments
Claire Troufflard is gratefully acknowledged for NMR experiments. Central Glass is thanked for kind gift of fluoral hydrate and azides. We thank Julien Legros for helpful discussions. Central Glass is thanked for kind gift of fluoral hydrate and azides. We thank the European Community for the financial support (Marie Curie Early Stage training Fellowship of the European Community’s Sixth Framework Programme: contract MEST-CT-2004-515968). We thank Julien Legros for helpful discussion.

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doi:10.3762/bjoc.4.19
Enantioselective nucleophilic difluoromethylation of aromatic aldehydes with Me$_3$SiCF$_2$SO$_2$Ph and PhSO$_2$CF$_2$H reagents catalyzed by chiral quaternary ammonium salts

Chuanfa Ni, Fang Wang and Jinbo Hu*

Abstract

Background
Although the nucleophilic difluoromethylation of aldehydes, ketones, and imines has been realized with PhSO$_2$CF$_2$H and related reagents, there are still no reports on the enantioselective nucleophilic reactions.

Results
With a chiral quaternary ammonium salt as the catalyst and KOH as the base, we describe the first enantioselective difluoromethylation of aromatic aldehydes with PhSO$_2$CF$_2$H or Me$_3$SiCF$_2$SO$_2$Ph. The enantioselectivity is substrate-dependent and for 2-chlorinated benzaldehyde an ee up to 64% was obtained.

Conclusion
These results provide some insights into the enantioselective nucleophilic difluoromethylation chemistry, which will stimulate further progress in this field.

Background
Because of the unique properties of fluorine, selective introduction of fluorine atom(s) or fluorine-containing moieties into organic molecules often dramatically alter their stability, lipophilicity, bioavailability, and biopotency. It is estimated that as many as 30–40% of agrochemicals and 20% of pharmaceuticals on the market contain fluorine [1,2]; as a result, fluorine is highlighted as the second most utilized hetero-element (after nitrogen) in life science-oriented research [3]. Nucleophilic fluorooalkylation, typically involving the transfer of a fluorinated carbanion ($R_f^-$, the fluorine substitution being commonly

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Beilstein Journal of Organic Chemistry 2008, 4, No. 21.
doi:10.3762/bjoc.4.21
Received: 29 February 2008
Accepted: 18 June 2008
Published: 26 June 2008

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on the carbanion center) to an electrophile, represents one of the major methods for the synthesis of organofluorine compounds [4-18]. In recent years, a few methods have been reported for the enantioselective introduction of a trifluoromethyl group into aldehydes and ketones with Ruppert-Prakash reagent, (trifluoromethyl)trimethylsilane, Me₃SiCF₃ and other reagents [19-29]. Although one-step nucleophilic difluoromethylation with R₂SiCF₂H is challenging regarding generality and efficiency [30], we found that both PhSO₂CF₂H and Me₃SiCF₂SO₂Ph can be used as general and efficient nucleophilic difluoromethylation reagents [11,12,31]. We have successfully synthesized both α-difluoromethyl alcohols and β-difluoromethyl alcohols by using these two reagents [12,16,31]. Moreover, we have described a highly diastereoselective nucleophilic difluoromethylation method with N-(tert-butylsulfinyl)iminines using PhSO₂CF₂H as a difluoromethylation reagent [13]. However, enantioselective introduction of the difluoromethyl group has not been previously reported.

As a class of versatile catalysts for asymmetric synthesis, cinchona alkaloids and their derivatives can catalyze an amazing array of synthetically important reactions, providing access to chiral products of high enantiopurity [32,33]. Several examples have been reported on the enantioselective incorporation of trifluoromethyl [23-28] or monofluoromethyl group [34] into organic molecules catalyzed by chiral quaternary ammonium salts. In the course of our research on the fluoride ion-induced difluoromethylation of carbonyl compounds with Me₃SiCF₂SO₂Ph, we found that the counterion of the fluoride source played an important role in tuning the fluoroalkylation reactivity towards aldehydes and ketones, i.e. aldehydes showed higher reactivity than ketones [12]. In connection with our studies on selective fluoroalkylation reactions, herein we disclose the first example of catalytic enantioselective difluoromethylation reaction of aromatic aldehydes with Me₃SiCF₂SO₂Ph or PhSO₂CF₂H in the presence of a cinchona alkaloid-based chiral quaternary ammonium salt.

**Table 1: Asymmetric nucleophilic difluoromethylation of aromatic aldehydes with PhSO₂CF₂SiMe₃.**

| entry[a] | carbonyl compound | Initiator [mol%] | solvent  | yield [%][b] | ee [%][c] |
|----------|-------------------|-----------------|----------|-------------|----------|
| 1        | PhCHO             | 4 (5)           | THF      | 91          | 14       |
| 2        | PhCHO             | 4 (5)           | CH₂Cl₂   | 64          | 9        |
| 3        | PhCHO             | 4 (5)           | Et₂O     | 67          | 27       |
| 4        | PhCHO             | 4 (5)           | PhCH₃    | 65          | 36       |
| 5        | PhCHO             | 4 (10)          | PhCH₃    | 60          | 47       |
| 6        | 2-NapCHO          | 4 (10)          | PhCH₃    | 64          | 26       |
| 7        | p-MeOCH₂CH₂CHO    | 4 (10)          | PhCH₃    | 50          | 25       |
| 8[d]     | PhCOCH₃           | 4 (10)          | PhCH₃-CH₂Cl₂ (2:1, vs) | 97 | 10       |

[a] Unless noted, reactions were carried out at 1.0 mmol scale. To a mixture of 1 (1.0 equiv) and 4 (x mol%) in 2 mL of toluene at −78 °C, 2 (1.2 equiv, dissolved in 2 mL of toluene) was added dropwise over 2 hours. The reaction mixture was then stirred at the same temperature for additional 3 hours.
[b] Isolated yield of the pure product.
[c] Enantioemic excess was determined by HPLC analysis using a chiral column.
[d] The reaction was carried out at 0.25 mmol scale. 2 (4.0 equiv) in 0.5 mL PhCH₃-CH₂Cl₂ was added in 5 minutes to the reaction mixture of 1 and 4 at −78 °C. The mixture was then stirred at the same temperature for another 12 hours.
reported to be a relatively effective catalyst in the reaction between Me$_3$SiCF$_3$ and aromatic aldehyde [23]. When the reaction was carried out in THF solvent at $-78$ °C, the reaction proceeded smoothly to afford the desired product in 91% yield with poor enantioselectivity (Table 1, entry 1). After a quick survey of the reaction solvent, the enantioselectivity was improved when toluene was used as solvent (Table 1, entries 1–4). It turned out that the least polar solvent (toluene) was an appropriate solvent for the reaction, while the use of polar solvents such as THF, Et$_2$O and CH$_2$Cl$_2$ gave the product with relatively lower enantioselectivity. The increase of the catalyst loading was able to improve the enantioselectivity further. When 10 mol% of 4 was used, the ee was improved to 47% (Table 1, entry 5). However, when 2-naphthaldehyde or 4-methoxybenzaldehyde was used as the substrate, in each case lower ee was observed (Table 1, entries 6 and 7). Although catalyst 4 was ineffective in the catalysis of the nucleophilic difluoromethylation of ketones in toluene, the reaction could proceed smoothly when CH$_2$Cl$_2$ was added as a co-solvent. The tetrasubstituted difluoromethylated aryl alcohol was formed in 97% yield with 10% ee (Table 1, entry 8).

**Enantioselective nucleophilic difluoromethylation of aromatic aldehydes with PhSO$_2$CF$_2$H**

In 1989, Stahly reported the nucleophilic difluoromethylation of aromatic aldehydes with PhSO$_2$CF$_2$H under the phase transfer condition using Aliquat 336 (a commercially available quaternary ammonium salt) as the phase transfer catalyst [35]. With most aldehydes, the reaction affords moderate to excellent yields of products. Moreover, unlike the Me$_3$SiCF$_2$SO$_2$Ph-based reactions, the reaction with PhSO$_2$CF$_2$H is not water-sensitive [34]. The use of PhSO$_2$CF$_2$H as a robust fluoroalkylating agent [11] has aroused our interest in developing its application in enantioselective difluoromethylation reactions. Thus, we decided to evaluate the ability of known chiral ammonium salts to promote the enantioselective difluoromethylation of aldehydes with PhSO$_2$CF$_2$H. In a preliminary study, we examined the reaction with the chiral quaternary ammonium salt 6a (see Scheme 1) as the phase transfer catalyst at room temperature, with 30% NaOH as the base and toluene as the solvent. After 12 h, the reaction afforded the desired product in 93% yield with a modest but significant enantioselectivity of 22% (Table 2, entry 1). When solid powdered KOH was used as the base, the ee could be slightly improved (Table 2, entry 2). Better enantioselectivity (47% ee) was observed on lowering the reaction temperature to $-40$ °C (Table 2, entry 3). However, at $-78$ °C, the reaction did not proceed.

Using toluene as the solvent and solid KOH as the base, we scanned four 4-trifluoromethylphenyl ammonium salts derived from quinine (QN), quinidine (QD), cinchonine (CN), and cinchonidine (CD) at different reaction temperatures. We found the structure of the cinchona alkaloid had some influence on the enantioselectivity. When a cinchonine or quinidine derivative was used, the main isomer was obtained as (+)-3a, and CN 6a was superior to QD 7a. The optimized reaction temperature was $-40$ °C (Table 2, entries 2 and 3). For quinine derivative 8a, it is interesting that a high temperature was beneficial for the enantioselectivity and (−)-3a was obtained as the main isomer. When the reaction was conducted at $-40$ °C, the reaction proceeded with moderate yield and poor enantioselectivity due to the low solubility of the catalyst in toluene (Table 2, entries 5 and 6). For CD derivative 9a, the enantioselectivity was slightly lower than 8a at rt (Table 2, entry 7). As reported, cinchonine derivatives and quinine derivatives yield products with the opposite configuration [32]. From the above screening, the quaternary salts 6a and 8a derived from the CN and QN were selected as the catalysts for further study.

Subsequently, the solvent effect was examined with catalyst 8a in the presence of solid KOH as the base at room temperature. It was shown that the use of toluene as a reaction medium remarkably improved the enantioselectivity. When THF or CH$_2$Cl$_2$ was used, the complete loss of enantioselectivity was observed.

**Scheme 1: Structure of chiral quaternary ammonium salts.**

|   |   |   |   |   |
|---|---|---|---|---|
| 6a | A = H, Ar = 4-CF$_3$-C$_6$H$_4$, X = Br |
| 6b | A = H, Ar = Ph, X = Cl |
| 6c | A = H, Ar = 9-anthracenyl, X = Cl |
| 6d | A = OMe, Ar = 4-CF$_3$-C$_6$H$_4$, X = Br |
| 7a | A = OMe, Ar = 4-CF$_3$-C$_6$H$_4$, X = Br |
| 7b | A = OMe, Ar = Ph, X = Cl |
| 7c | A = OMe, Ar = 2,3,4,5-Cl$_4$H$_2$, X = Br |
| 7d | A = H, Ar = 4-CF$_3$-C$_6$H$_4$, X = Br |
In general, the chemical yields were chosen due to its generality towards other aldehydes such as benzaldehyde was almost equally effective when tested, although the two types of cinchona alkaloids were catalysts. As shown in Table 3, the results are shown in Table 3. Encouraged by these results, we further examined the influence of substituents on the chiral phase transfer catalysts. As shown in Table 2, the different substituents showed some influence on the enantioselectivity. The electron-withdrawing group CF\textsubscript{2}H under various conditions. (Table 2, entries 10 and 11). Moreover, KOH gave the best results in enantioselectivity in comparison with the other metal hydroxides, such as CsOH and RbOH (Table 2, entries 8 and 9). Encouraged by these results, we further examined the influence of substituents on the chiral phase transfer catalysts. As shown in Table 2, the different substituents showed some influence on the enantioselectivity. The electron-withdrawing group CF\textsubscript{2}H at C-4 position of the benzyl ring afforded the product with good ee, though the unsubstituted one gave a significantly low ee (Table 2, entries 12 and 14). Although the 9-anthracenylmethyl and 2,3,4-trifluorobenzyl functionality were found to be quite useful for asymmetric alkylation of tert-butylglycinate Schiff base [36] or asymmetric synthesis of \(\alpha,\beta\)-epoxysulfones [37], they were not as effective as 4-trifluoromethylphenyl functionality in the current asymmetric reaction (Table 2, entries 13, 15 and 16).

In the light of these results, we next examined the substrate scope of this enantioselective difluoromethylation reaction with catalyst \(6a\) or \(8a\), and the results are shown in Table 3. Although the two types of cinchona alkaloids \(6a\) and \(8a\) are almost equally effective when benzaldehyde was tested, \(6a\) was chosen due to its generality towards other aldehydes such as 4-chlorobenzaldehyde \(1b\). In general, the chemical yields were good to excellent, except in the case of 4-tert-butylbenzaldehyde \(1k\), where a moderate yield was obtained (although the reaction was performed at rt) (Table 3, entry 13). It is obvious that the enantioselectivity was dependent on the substrate structure. It is interesting that the aldehydes with halogen substitution (Table 3, entries 3, 5–9) showed better enantioselectivity than those with methyl and methoxy substituents (Table 3, entries 11,12). Among the halogenated benzaldehydes that were tested, the reaction with 2-chlorobenzaldehyde showed an enantiomeric excess up to 64% (Table 3, entry 7). The enantiomeric excess obtained from 2-naphthaldehyde was also modest (23% ee) (Table 3, entry 14).

The absolute configuration of the alcohol (+)-3a (Table 3, entry 1) was determined to be \(S\) by comparing the optical rotation with that of the corresponding difluoromethyl alcohol (after desulfonylation) with the known data (Scheme 2) [38]. For other alcohols, the stereochemistry was tentatively determined by \(^{19}\text{F}\) NMR analysis of the corresponding Mosher's esters comparing with (+)-3a [39].

**Conclusion**

In conclusion, we have described the first chiral quaternary ammonium salts catalyzed enantioselective difluoromethyla-

![Table 2: Enantioselective difluoromethylation of benzaldehyde with PhSO\textsubscript{2}CF\textsubscript{2}H under various conditions.](image-url)
Table 3: Asymmetric nucleophilic difluoromethylation of aromatic aldehydes with PhSO₂CF₂H.

| entry[a] | aromatic aldehyde | PTC T [°C] | time [h] | yield [%][b] | ee [%][c] |
|----------|-------------------|-----------|----------|-------------|----------|
| 1        | 1a: Ar=C₆H₅ -    | 6a        | −40      | 48          | 3a: 67   | 47 (S)[d] |
| 2        | 1a: Ar=C₆H₅ -    | 8a        | 25       | 2           | 3a: 94   | 46 (R)[e] |
| 3        | 1b: Ar=4-Cl-C₆H₄ - | 6a      | −40      | 48          | 3b: 74   | 52 (S)[f] |
| 4        | 1b: Ar=4-Cl-C₆H₄ - | 8a      | 25       | 1           | 3b: 91   | 23 (R)[f] |
| 5        | 1c: Ar=2,4-Cl-C₆H₄ - | 6a      | −20      | 48          | 3c: 95   | 54 (S)[f] |
| 6        | 1d: Ar=3-Cl-C₆H₄ - | 6a      | −20      | 48          | 3d: 83   | 46 (S)[f] |
| 7        | 1e: Ar=2-Cl-C₆H₄ - | 6a      | −20      | 48          | 3e: 92   | 64 (S)[f] |
| 8        | 1f: Ar=4-F-C₆H₄ - | 6a      | −20      | 48          | 3f: 93   | 41 (S)[f] |
| 9        | 1g: Ar=4-Br-C₆H₄ - | 6a      | −20      | 48          | 3g: 95   | 36 (S)[f] |
| 10       | 1h: Ar=4-FCF₃-C₆H₄ - | 6a     | −20      | 48          | 3h: 68   | 36 (S)[f] |
| 11       | 1i: Ar=2-Me-C₆H₄ - | 6a      | −20      | 48          | 3i: 77   | 11        |
| 12       | 1j: Ar=4-MeO-C₆H₄ - | 6a      | −20      | 48          | 3j: 80   | 12        |
| 13       | 1k: Ar=4-tBu-C₆H₄ - | 6a     | 25       | 12          | 3k: 58   | 4         |
| 14       | 1l: Ar=2-naphthyl- | 6a      | −20      | 48          | 3l: 72   | 23 (S)[f] |

[a] All reactions were carried out at 0.25 mmol scale with 1 (1.2 equiv) and 5 (1.0 equiv) in 1.5 mL toluene.
[b] Isolated yield of the pure product.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column (Chiralcel AD-H, OD or IC).
[d] The absolute configuration was determined to be S after chemical derivatization.
[e] The absolute configuration was determined to be R by comparing the retention time on chiral HPLC.
[f] The absolute stereochemistry was tentatively determined by ¹⁹F NMR analysis of the corresponding Mosher's esters comparing with (S)-3a.

Scheme 2: Determination of the absolute configuration of (+)-3a.

The easy preparation of the chiral cinchonium salts and the convenient experimental procedure make the reaction operationally simple. These results provide some insights into enantioselective nucleophilic difluoromethylation chemistry, which will stimulate further progress in this field.
Supporting Information

Supporting Information File 1
Full experimental details and compound characterization data for all new compounds described.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-21-S1.doc]

Acknowledgments
We gratefully acknowledge the National Natural Science Foundation of China (20502029, 20772144), Shanghai Rising-Star Program (06QA14063), and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) for financial support.

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Perhalogenated pyrimidine scaffolds. Reactions of 5-chloro-2,4,6-trifluoropyrimidine with nitrogen centred nucleophiles

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Abstract

Background
Highly functionalised pyrimidine derivatives are of great importance to the life-science industries and there exists a need for efficient synthetic methodology that allows the synthesis of polysubstituted pyrimidine derivatives that are regioselective in all stages to meet the demands of RAS techniques for applications in parallel synthesis. 5-Chloro-2,4,6-trifluoropyrimidine may be used as a scaffold for the synthesis of polyfunctional pyrimidine systems if sequential nucleophilic aromatic substitution processes are regioselective.

Results
Use of 5-chloro-2,4,6-trifluoropyrimidine as a core scaffold for the synthesis of functionalised pyrimidine systems is assessed in reactions with a small range of nitrogen centred nucleophiles. Mixtures of products arising from nucleophilic aromatic substitution processes are formed, reflecting the activating effect of ring nitrogen and the steric influences of the chlorine atom.

Conclusions
5-Chloro-2,4,6-trifluoropyrimidine is not an ideal scaffold for analogue synthesis or for multiple substitution processes because purification must be performed to remove the 2-substituted regioisomer from the mixture before further reactions can be carried out. However, 4-amino derivatives can be isolated in acceptable yields using this methodology.
Introduction

Highly functionalised pyrimidine derivatives are of great importance to the life-science industries and, indeed, many pyrimidine derivatives have been used for various medicinal applications (Figure 1) [1-3].

Synthesis of pyrimidine rings most commonly involves cyclocondensation reactions of amidine, guanidine or thiourea derivatives with either 1,3-diketone or 1,3-diester systems [4,5]. However, many of these reactions are not regiospecific and, furthermore, there is an added difficulty of synthesizing a range of structurally related pyrimidine analogues by parallel synthesis or rapid analogue synthesis (RAS) techniques [6,7] due to the limited range of non-cyclic polyfunctional precursors available. These limitations have, in part, provided added impetus for drug discovery programmes to develop effective synthetic methodologies towards multiply substituted systems from simple readily accessible pyrimidine scaffolds [8]. Consequently, pyrimidine core scaffolds that bear multiple functionality, which may be transformed into a widely diverse range of functionalised derivatives by a sequence of efficient and regioselective reactions, are becoming increasingly important [6,7]. In particular, the attachment of amino groups to the pyrimidine nucleus by formation of carbon-nitrogen bonds is a highly desirable process but one of the most difficult to achieve in practice.

Pyrimidines are electron-deficient aromatic systems and, when halogenated, become very useful substrates for a variety of nucleophilic aromatic substitution (S\textsubscript{N}Ar) processes [9] and, since numerous chloropyrimidines are commercially available, there have been many reports of synthetic strategies concerned with creating pyrimidine-based libraries from halogenated core scaffolds. For example, recently, synthesis of an inhibitor of the cyclin-dependent kinase was developed [10] (Scheme 1) starting from 2,4,6-trichloropyrimidine as the core scaffold. However, as regioisomeric products are formed in both nucleophilic aromatic substitution stages, separation of the isomers is required after each step, making adoption of this scaffold for analogue synthesis less likely.

There remains, therefore, a requirement for efficient synthetic methodology that allows the synthesis of polysubstituted pyrimidine derivatives that are regioselective in all sequential nucleophilic aromatic substitution stages to meet the demands of RAS techniques for applications in parallel synthesis.

We are exploring the use of polyhalogenated heteroaromatic systems [11-13] as potential heteraryl core scaffolds for analogue synthesis of polyfunctional heterocyclic systems [14-16]. Polyhaloaromatic systems act as useful scaffolds because, in principle, several or all halogen atoms can be displaced by nucleophiles, giving rise to a wide range of heteroaromatic systems and, in this context, we have used a range of perfluorinated heteroaromatic molecules as synthetically versatile building blocks for the creation of new molecular scaffolds for drug discovery [14-17]. In this paper, we describe the reactivity of 5-chloro-2,4,6-trifluoropyrimidine (1) with a range of representative nitrogen centred nucleophiles, with the aim of exploring the regioselectivity of these nucleophile aromatic substitution processes in order to assess the utility of the system as a scaffold for pyrimidine analogue synthesis. Whilst 1 is commercially available and has been known for some time, only a limited number of reactions have been reported (e.g. with ammonia to give the 4-amino derivative [18]) despite the fact that 1 is used widely in the fibre reactive dye industry [19]. However, a systematic study of the reactivity of this potentially

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**Figure 1:** Pharmaceuticals with pyrimidine sub-units.
valuable scaffold with other nitrogen nucleophiles has not been reported.

**Results and Discussion**

A series of reactions between 5-chloro-2,4,6-trifluoropyrimidine (1) and a range of primary and secondary amines were carried out in acetonitrile at 0 °C in the presence of DIPEA as a hydrogen fluoride scavenger and these results are collated in Table 1. All of the reactions were monitored via $^{19}$F NMR and the isomer ratios measured by $^{19}$F NMR integration from samples taken from the reaction mixture.

Reaction of 1 with ammonia results in two isomeric products, as observed by $^{19}$F NMR analysis of the reaction mixture which displayed two distinctive peaks (−48.18 and −69.47 ppm) for the 4-substituted isomer and one peak (−65.44 ppm) for the 2-isomer in a 9 : 1 ratio, the chemical shifts being consistent with previous studies [18]. Similarly, reaction of 1 with ethylamine gives two isomers in an 8 : 1 ratio by $^{19}$F NMR as shown by the appearance of two fluorine signals (−47.48 and −70.83 ppm) and one signal (−63.59 ppm) corresponding to the 4- and 2-amino isomers respectively. Distillation afforded the 4-isomer in good yield. Other reactions gave a mixture of products which were identified by $^{19}$F NMR as described above and, in all cases, the major product could be isolated by either recrystallisation, or column chromatography. All products were fully characterised and $^{19}$F NMR analysis of the crude reaction mixtures gave the ratio of products observed.

Furthermore, when 1 was reacted with the difunctional nucleophile benzamidine, nucleophilic substitution of the fluorine at the 4- and the 2-position in a 40 : 1 ratio occurred (Scheme 2). The main product 3g was isolated by recrystallisation from acetonitrile and characterised by X-ray crystallography (Figure 2).

In all cases, therefore, the major product obtained arises from substitution of the fluorine atom at the 4-position which is the most activated site para to ring nitrogen and further activated by the adjacent chlorine atom, consistent with previous observations for reactions involving perfluorinated heterocycles [13]. However, as the steric requirement of the nucleophile increases, the amount of product arising from substitution at the less activated 2-position is increased, reflecting the steric hindrance of substitution at the more activated 4-position by the larger chlorine atom located at the adjacent 5-position.

Reaction of the related 2,4,6-trifluoropyrimidine with ammonia is reported [20] to give two products in a 4 : 1 ratio and a primary amine, ethanolamine, gave a 2 : 1 ratio of products. Therefore, reactions of 1 with nitrogen centred nucleophiles are more selective than 2,4,6-trifluoropyrimidine despite the increased steric influence of the chlorine atom to nucleophilic attack. This can be rationalised by the fact that the electron-negative chlorine atom activates the site ortho to itself towards nucleophilic attack and this partly compensates for steric factors in these reactions.
Table 1: Reactions of amine nucleophiles with 5-chloro-2,4,6-trifluoropyrimidine (1).

| R₁R₂NH | Products (isolated yield) | Ratio 3 : 4 |
|--------|---------------------------|-------------|
| NH₃    | 3a, 57%; 4a, 9 : 1        |             |
| EtNH₂  | 3b, 57%; 4b, 8 : 1        |             |
| NH₂    | 3c, 47%; 4c, 5 : 1        |             |
| C₆H₅NH₂| 3d, 41%; 4d, 5 : 1        |             |
| NH₂    | 3e, 49%; 4e, 3 : 1        |             |
| NH     | 3f, 49%; 4f, 3 : 1        |             |

a Isolated yield of major products 3. Minor products 4 were not isolated.
b Ratio of 3 : 4 in crude product mixture by ¹⁹F NMR analysis.
Consequently, it becomes clear that 5-chloro-2,4,6-trifluoropyrimidine (1) is not an ideal scaffold for analogue synthesis or for multiple substitution processes because purification must be performed to remove the 2-substituted regiosomer from the mixture before further reactions can be carried out. However, 4-amino derivatives can be isolated in acceptable yields using this methodology and, indeed, these systems could be used as scaffolds for further analogue synthesis.

Experimental

Typical Procedure: Synthesis of N-Benzyl-5-chloro-2,6-difluoropyrimidin-4-amine (3d)

A solution of 5-chloro-2,4,6-trifluoropyrimidine (0.5 g, 3 mmol), benzylamine (0.32 g, 3 mmol) and DIPEA (0.39 g, 3 mmol) in acetonitrile (50 cm$^3$) was stirred at 0 °C for 2 h after which time $^{19}$F NMR indicated 100% conversion with the formation of N-benzyl-5-chloro-2,6-difluoropyrimidin-4-amine (3d) (~45.80 and ~67.84 ppm) and N-benzyl-5-chloro-4,6-difluoropyrimidin-2-amine (4d) (~48.09 ppm) in a 5 : 1 ratio. The reaction solvent was evaporated and the crude product partitioned between DCM (3 x 40 cm$^3$) and water (40 cm$^3$). The organic layer was separated, dried (MgSO$_4$) and evaporated to dryness to give a crude product containing 3d and 4d as a yellow solid (0.54 g). Recrystallisation from n-hexane yielded N-benzyl-5-chloro-2,6-difluoropyrimidin-4-amine (3d) (0.31 g, 41%) as a white solid; mp 57–59 °C; IR (neat, ν cm$^{-1}$): 3408, 3281, 2364, 2169, 1739, 1612, 1528, 1447, 1349, 1129, 695; (Found: C, 51.7; H, 3.1; N, 16.6; C$_{11}$H$_8$ClF$_2$N$_3$ requires: C, 51.7; H, 3.15; N, 16.4%); δ$_H$ (CDCl$_3$) 4.74 (2H, d, $^2$J$_{HH}$ 5.8, CH$_2$), 7.39 (5H, m, Ar-H); δ$_C$ (CDCl$_3$) 46.2 (s, CH$_2$), 93.1 (dd, $^2$J$_{CF}$ 21.4, $^4$J$_{CF}$ 8.0, C-5), 128.1 (s, Ar-CH), 128.4 (s, Ar-CH), 129.2 (s, Ar-CH), 136.9 (s, Ar-CH), 159.3 (dd, $^1$J$_{CF}$ 222, $^3$J$_{CF}$ 22.1, C-2), 162.6 (dd, $^1$J$_{CF}$ 13, $^3$J$_{CF}$ 5.4, C-4), 164.5 (dd, $^1$J$_{CF}$ 236.2, $^3$J$_{CF}$ 18.7, C-6); δ$_F$ (CDCl$_3$) ~45.8 (1F, s, C-6), ~67.9 (1F, s, C-2); m/z (El$^+$) 255 ([M$^+$], 40%), 218 (10), 178 (12).

All other experimental procedures and data are presented in Supporting Information File 1 which accompanies this paper.

Supporting Information

Supporting Information File 1
Experimental procedures and data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-22-S1.doc]

Acknowledgments

We thank EPSRC for funding (DTA studentship to ELP), GSK Pharmaceuticals for their support of this work and Prof. Judith Howard and Dr Dmitrii Yufit for X-ray crystallography.

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.4.22
Synthesis of deep-cavity fluorous calix[4]arenes as molecular recognition scaffolds

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Abstract

Several lower-rim perfluoroalkylated (fluorous) calix[4]arenes have been synthesized by O-alkylation of the parent calix[4]arene. The compounds are formed in the cone conformation. They are soluble in several fluorous solvents and show promise for use in sensing, selective extractions and other applications.

Introduction

Calixarenes [1] are one of the most useful types of macrocyclic scaffolds. Since first reported by Zinke and Ziegler [2], calix[4]arenes have been used for a variety of molecular recognition, nanotechnology, and supramolecular applications. These have included nanowires [3], self organized nanostructures [4] chiral supramolecular assemblies [5], as well as sensors for cations [6,7], anions [8] and neutral organic molecules [9]. The versatility of the calixarene scaffold is a result of its preorganized cavity [10], which consists of four phenolic units connected by methylene bridges. Synthetic advances over the last several decades [1] have produced methodology to append various functional groups to the aromatic rings. These groups are selected to interact with specific guest molecules [11].

Calix[4]arenes can exist in four possible conformations: cone (Figure 1), partial cone, 1,2, and 1,3 alternates [1]. Although small groups (Me, Et) on the lower rim allow for interconversion between conformers, large groups prevent interconversion [12]. Reactions that lock the conformation result in a mixture of conformers; however, methods exist to enhance the formation of a single conformer [12]. Of the four possible conformations, the cone is the most desirable for molecular recognition and
sensing applications because it has the largest available surface area for host-guest interactions [10]. With appropriate functionality and conformation, the calixarene can be tailored to bind preferentially with specific target guest molecules.

Fluorous chemistry [13] has become an increasingly popular field as a result of the multitude of applications that it has provided across the disciplines of chemistry. Fluorocarbons are extraordinarily non-polar and are at once both hydrophobic and lipophobic [14-16]. Fluorous liquids preferentially dissolve fluorous compounds and represent a unique class of selective solvents. These solvents have recently engendered powerful methods for separations [17] that have been used in applications ranging from recyclable reagents [18] to the total synthesis of natural products [19]. Fluorous compounds are the basis for highly selective ion sensors that show promise by virtue of their low level of biofouling [20]. Recently, it was shown that simple fluorous compounds act as molecular receptors for selective extraction of organic substrates into a fluorous liquid phase via hydrogen bonding [21].

Combining the selective nature of fluorous chemistry with the extensive molecular recognition capabilities of calixarenes should generate a scaffold for selective molecular receptors, yet few reports exist that detail the synthesis and applications of fluorous calixarenes [22-26]. There are no reports of studies of solubilities of such calixarenes in fluorous solvents. The work reported herein is focused on synthesizing fluorous calixarenes that are easily functionalized for selective molecular recognition and extraction of various analytes.

Results and Discussion

The initial target was calixarene tetra-ether 3a bearing four perfluorohexyl groups insulated by propylene spacers. To begin, the tert-butyl groups were removed from commercially available 4-tert-butylcalix[4]arene 1, providing calix[4]arene 2. Using NaH/DMF, conditions known to favor reaction in the cone conformation [12], 2 was alkylated with 3-(perfluorohexyl)propyl iodide to give cone conformer 3a as the dominant tetraalkylated product in 61% yield after recrystallization (Scheme 1). However, 3a did not exhibit the desired solubility properties and did not dissolve in perfluorinated solvents (Table 1). Therefore, to increase the fluorine content of the calixarene scaffold, 2 was treated with 3-(perfluorooctyl)propyl iodide to provide 3b as the dominant tetraalkylated product, which was isolated in the cone conformation in 61% yield after recrystallization. Unlike the tetra-perfluorohexyl product 3a, we were not able to get exact mass data for 3b or other tetra-perfluorooctyl products. These compounds are otherwise well characterized and structures and purities are secure (see Supporting Information File 1).

The solubility of 3b was explored in a variety of organic and fluorous solvents (Table 1). As with many calixarenes, 3b was highly soluble in chloroform, and in fluorophilic solvents such as THF and diethyl ether.

Similarly, 3b was soluble in fluorous solvents, FC-72 (perfluorohexanes), FC-75 (perfluoro-(2-perfluorobutyl)tetrahydrofuran), FC-77 (perfluoroctanes), HFE-7100 (methyl nonafluorobutyl ether), HFE-7500 (3-ethoxy-1,1,1,2,3,4,4,5,5,6,6,6-dodecafluoro-2-trifluoromethylhexane), and F-626 (1H,1H,2H,2H-perfluorooctyl 1,3-dimethylbutyl ether) at a 1mM or greater concentration [28,29]. Compound 3b also showed solubility in CO2 at a 2 wt % concentration, 3500 psi, and room temperature due to the presence of fluorous tails [26].

To expand the versatility of this scaffold, rim functionalization was explored. Halogenated calix[4]arenes have been shown to participate in a variety of organometallic processes, particularly

Scheme 1: Preparation of 3a and 3b.

\[
\begin{align*}
\text{OH} & \quad \text{AlCl}_3 \quad \text{PhOH} \quad \text{PhMe} \\
\text{Bu} & \quad \text{4} \\
\text{OH} & \quad \text{NaH} \quad \text{I-R}_{\text{ref}} \quad \text{DMF} \\
\text{H} & \quad \text{4} \\
\text{OR}_{\text{ref}} & \quad \text{3a: } R_{\text{ref}} = (\text{CH}_2)_{2}\text{C}_6\text{F}_{13} \quad 61\% \\
& \quad \text{3b: } R_{\text{ref}} = (\text{CH}_2)_{2}\text{C}_8\text{F}_{17} \quad 61\%
\end{align*}
\]
Table 1: Solubility of 3a and 3b in fluorous solvents.

| Solvent | FC-72 | FC-75 | FC-77 | HFE-7100 | HFE-7500 | F-626 |
|---------|-------|-------|-------|-----------|-----------|-------|
| 1 mM    | –     | –     | –     | +         | +         | +     |
| 2 mM    | –     | –     | –     | +         | +         | +     |
| 5 mM    | –     | –     | –     | +         | +         | +     |
| 10 mM   | –     | –     | –     | +         | +         | +     |

[a] 3a and 3b were heated in solvent until a clear solution formed. This was allowed to cool to room temperature and stand. 3a and 3b were determined to be soluble at the recorded concentration if no precipitate was observed after 24 h. [b] 3a recrystallized upon cooling overnight.

The reactivity of 5 in the Kumada cross-coupling reaction was next investigated. Treatment of 5 with PdCl₂(dppf) followed by phenylmagnesium bromide provided the biaryl 6 as the only observed product in 75% yield (Scheme 3).

With simple cross coupling accomplished, coupling with a functionalized phenyl ring was investigated. Therefore, 5 was treated with an excess of Grignard 7 in the presence of PdCl₂(dppf) to provide a mixture of two inseparable compounds, the target biaryl 8, and the dimer of 7, as observed by NMR spectroscopy. Without separation, the two compounds were carried on to the subsequent TBS cleavage with TBAF to provide the free tetrol 9 after column chromatography in 69% yield over two steps (Scheme 4).

The conformations of these new fluorous calixarenes are important to understand for projected applications. The cone conformation of 3b was supported by peak symmetry observed in similar examples [8,31] by ¹H NMR spectroscopy. Accordingly, the derived products should also have cone conformations. Crystals of 5 were grown by slow evaporation from a palladium catalyzed cross coupling reactions, including Kumada, Negishi, and Suzuki processes which can be used to append aromatic rings onto the molecule [30,31]. Therefore, 3b was treated with N-bromosuccinimide (NBS) in methyl ethyl ketone (MEK) [32] to give the bromide 4 in 87% yield. Correspondingly, 3b was treated with silver trifluoroacetate [32] in the presence of iodine providing iodide 5 in 72% yield on a 1 mmol scale (Scheme 2). Results for the iodination were scale dependent; near quantitative yields could be obtained on 0.1 mmol scale preparations, while 1 mmol scale preparations showed diminished yields due to product occlusion with the precipitation of silver iodide.

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solution in THF, and one of these provided the X-ray structure in Figure 2.

Two crystallographically independent calixarene molecules made up the asymmetric unit, each molecule having a similar calix[4]arene ring and differing in the number and location of the gauche bonds in the (perfluoroctyl)propyl chains. The asymmetric unit also contained one molecule of THF. Like other reported calixarenes [33], 5 exists in a pinched cone conformation with $C_2v$ cavity symmetry in the solid state. Its cavity volume is about 81 Å$^3$.

Although the calixarenes 3–5 have an inherent cavity in this conformation, the cavity volume and surface area are small, thus limiting the scope of possible host-guest interactions. Increasing the depth of the cavity by coupling 5 with aromatic rings to give 9 allows for host-guest interactions involving larger substrates. This modification increases the versatility of the scaffold and the variety of host-guest interactions that can occur in ion binding [8] and capsule formation [34]. Likewise, introduction of hydrogen bonding groups like those of 9 are crucial for achieving interactions with various substrates [35, 36].

Coupling an aromatic ring onto the upper-rim of the fluorous calixarene led to an increase in fluorescence emission (as observed qualitatively on TLC). An increase in fluorescence emission was observed with 7, 8, and 9 as compared to the single aryl ring analogs, and allows for better applications of the scaffold as a sensor [8,37].

Conclusion

Deep-cavity functionalized fluorous calix[4]arenes that are locked in the cone conformation have been synthesized. These molecules are soluble in several fluorous solvents, and show promise as fluorescent sensors. Introducing the hydroxyl func-
tionality onto these molecules provides a scaffold with a deep cavity and hydrogen bonding functional groups for molecular recognition interactions.

Supporting Information

Supporting Information File 1
Experimental Procedures, Characterization Data and Copies of Spectra
[http://www.beilstein-journals.org/bjoc/content-supplementary/1860-5397-4-36-S1.pdf]

Supporting Information File 2
Crystal structure data for 5.
[http://www.beilstein-journals.org/bjoc/content-supplementary/1860-5397-4-36-S2.txt]

Acknowledgments
We are grateful to the National Institutes of Health and the National Science Foundation (CHE0615952) for funding.

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