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Organo-fluorine chemistry II

David O'Hagan

Editorial

Address:
School of Chemistry, University of St Andrews, Fife, KY16 9ST, United Kingdom

Email:
David O'Hagan - do1@st-andrews.ac.uk

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It is a pleasure to be able to introduce this second Thematic Series on 'organo-fluorine chemistry' within the *Beilstein Journal of Organic Chemistry*. The series now embeds the subject firmly as a special interest area of the journal. The first series in 2008 presented contributions representing a wide range of organic fluorine chemistry [1-10] and this series continues that trend exploring the synthesis and properties of a new range of organo-fluorine compounds. Contributions have been received from research groups in Australia, China, Germany, Japan, North America, Ukraine and the United Kingdom, representing a particularly international research community.

The introduction of fluorine remains an important specialism in organic chemistry for modulating the physical properties of molecules involved in programmes ranging from bioorganic chemistry to performance materials. Consequently fluorinated organics are of major commercial significance to the pharmaceuticals, agrochemicals, materials and polymer industries with the fluorine fine chemicals industry servicing these industrial sectors. New innovations and insights into the synthesis and the nature and behaviour of organo-fluorine compounds continue to intrigue and this Thematic Series offers a glimpse into the level of activity in the area.

I am delighted that all of the authors have agreed to submit such high quality contributions to render this Thematic Series substantial and make it such a success.

David O'Hagan

St. Andrews, April 2010

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Synthesis of *gem*-difluoromethylenated analogues of boronolide

Jing Lin[1], Xiao-Long Qiu[2] and Feng-Ling Qing*[1,2]

Full Research Paper

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Address:
[1]College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China and [2]Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Email:
Feng-Ling Qing* - flq@mail.sioc.ac.cn

* Corresponding author

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Abstract

The straightforward synthesis of four *gem*-difluoromethylenated analogues **4**–**7** of boronolide is described. The key steps of the synthesis include the concise preparation of the key intermediates **12a**–**b** through the indium-mediated *gem*-difluoropropargylation of aldehyde **9** with the fluorine-containing building block **11** and the efficient construction of α,β-unsaturated-δ-lactones **15a**–**b** via BAIB/TEMPO-procedure.

Introduction

(+)-Boronolide (**1**), isolated from the bark and branches of *Tetradenia fruticosa* [1] and from the leaves of *Tetradenia barberae* [2], has been used as a traditional medicine in Madagascar and South Africa [2-4]. In addition, a partially deacetylated analogue **2** and the totally deacetylated analogue **3** have also been obtained from *Tetradenia riparia* [3,5], a Central African species traditionally employed by the Zulu as an emetic, and whose leaf infusions have also been reported to be effective against malaria [2,4]. Boronolide (**1**) and its analogues **2**–**3** feature an interesting polyacetoxylated (or polyhydroxyl) side chain and an α,β-unsaturated-δ-lactone moiety, making them an attractive target for total syntheses [6-16] since many natural products with a wide range of biological activity contain these structural elements. Noteworthily, structure–activity relationships have demonstrated that the α,β-unsaturated-δ-lactone moiety plays a key role in the bioactivity of many natural products. This is due to the fact that this unit is an excellent potential Michael acceptor for nucleophilic amino acid residues of the natural receptors interacting with these compounds [16-18]. Considering the similarity in size of fluorine and hydrogen atoms, the strong electron-withdrawing property of *gem*-difluoromethylene group (CF_2) [19,20] and our continual efforts to prepare *gem*-difluoromethylenated analogues of natural products containing α,β-unsaturated-δ-lactone moiety [21-24], we intended to introduce a CF_2 group to α,β-unsaturated-δ-lactone of boronolide at the γ-position (Figure 1). We envisioned that the resulting γ,γ-difluoromethylenylated–α,β-unsaturated conjugated double bond would be much more electron-deficient and therefore a better candidate to enhance the reactivity of the conjugated double bond as an acceptor with minimum steric change. In this article we describe the concise synthesis of *gem*-difluoromethylenated analogues **4**–**7** of boronolide.

Results and Discussion

The retrosynthetic analysis of the target molecules **4**–**7** is outlined in Scheme 1. We envisioned that the key γ,γ-*gem*-difluoromethylenated α,β-unsaturated-δ-lactone scaffold could be constructed via an oxidation–cyclization reaction of intermediate **A** according to our published procedures [22]. *cis*-Selective reduction of homopropargyl alcohol **B** would provide the homoallylic alcohol **A**. The alcohol **B** could be obtained via an indium-mediated reaction of the fluorine-containing building block **C** and the protected aldehyde **D**, which in turn could be readily prepared by the reported procedure. Three chiral centres in our target molecules would be derived from D-glucono-δ-lactone, and the last one could be constructed by diastereoselective propargylation of the aldehyde.

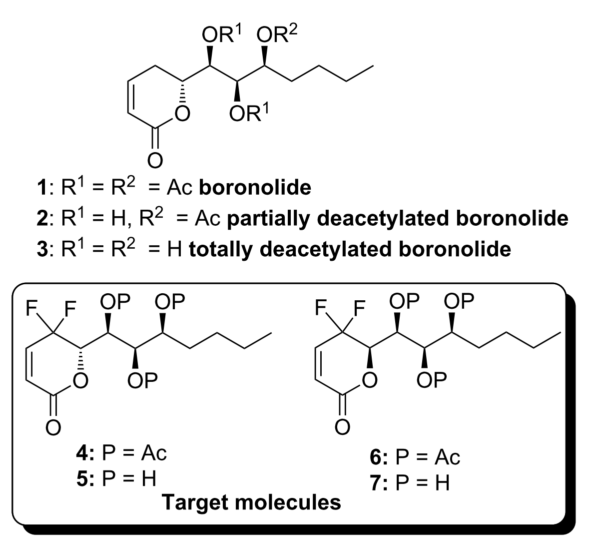
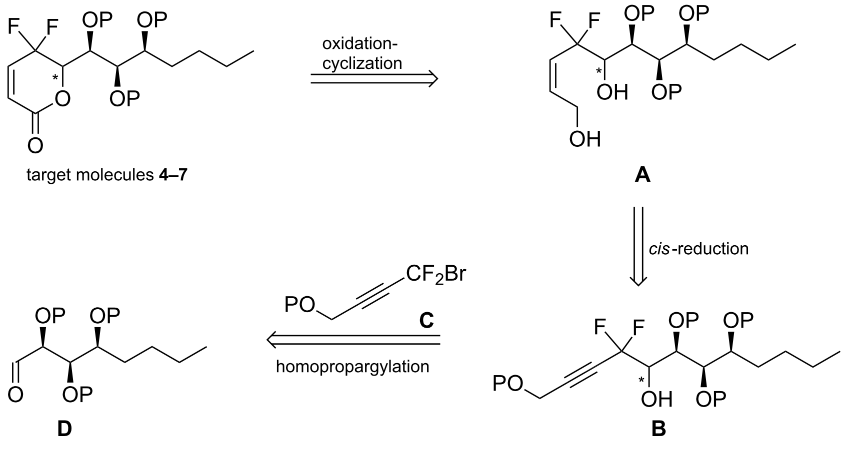
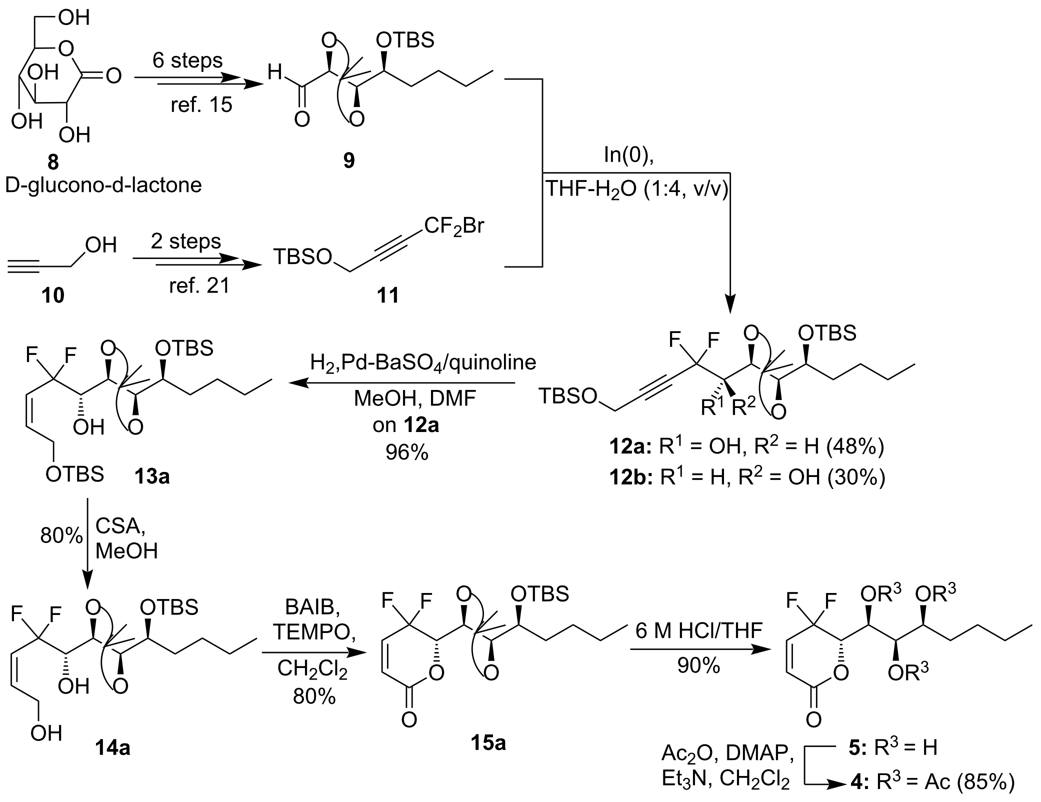


Figure 1: Boronolide (**1**), boronolide analogues **2**–**3** and *gem*-difluoromethylenated analogues **4**–**7**.

According to the retrosynthetic analysis our synthesis embarked from aldehyde **9**, which was prepared from commercially available D-glucono-δ-lactone (**8**) in six steps, based on the reported route [15] (Scheme 2). The synthesis of the fluorine-containing intermediate **11** was accomplished from propargyl alcohol (**10**) by our improved procedure [22]. With these two key fragments in hand, we focused our efforts on the *gem*-difluoropropargylation reaction. Utilizing Hammond's reaction conditions [25], we were pleased to find that treatment of aldehyde **9** with compound **11** in the presence of indium with THF–H_2O (1:4, v/v) as solvent smoothly gave the expected product **12a** in 48% yield and **12b** in 30% yield. More pleasing was the fact that the diastereomers **12a** and **12b** could be easily separated by silica gel chromatography. The assignment of the stereochemistry of the formed alcohol groups in **12a** and **12b** was based on the comparison of the ^{19}F NMR spectra of compounds **5** and **6** with those of our synthesized *gem*-difluoromethylenated goniodiols. The absolute configuration of the formed alcohol was determined by X-ray crystallographic analysis [23]. Initial attempts to convert the triple bond in compound **12a** into the *cis* double bond via hydrogenation in the presence of Lindlar catalyst were



Scheme 1: Retrosynthetic analysis of target molecules **4**–**7**.



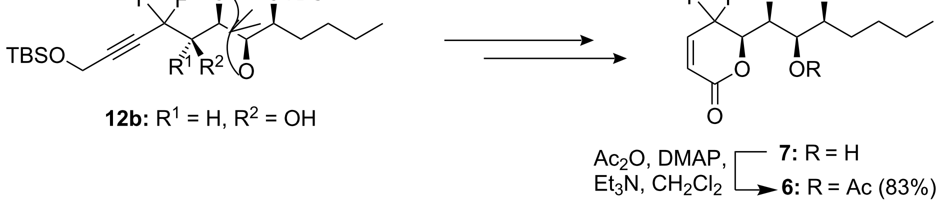
Scheme 2: Synthesis of target molecules **4–5**.

unsuccessful. Even with the addition of quinoline, these reactions only resulted in inseparable mixtures. Fortunately, hydrogenation proceeded well by means of Pd–BaSO$_4$–quinoline system [26], leading to the expected alcohol **13a** in 96% yield. Subsequent selective removal of the primary TBS group in **13a** with D-camphor-10-sulfonic acid (CSA) yielded the diol **14a** in 80% yield. As expected, treatment of compound **14a** with 0.2 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 3.0 equiv of [bis(acetoxy)iodo]benzene (BAIB) in dichloromethane at room temperature afforded the desired α,β-unsaturated-δ-lactone **15a** in 80% yield. Exposure of compound **15a** to a solution of 6 M HCl in aqueous THF removed the protecting groups smoothly, and the deacetylated boronolide derivative **5** was obtained in 90% yield. Additionally, *gem*-difluoromethylenated boronolide **4** was prepared in good yield via treatment of compound **5** with Ac$_2$O/DMAP/Et$_3$N.

Using similar reaction conditions, *gem*-difluoromethylenated boronolide analogues**6**–**7** were also synthesized from the intermediate **12b** (Scheme 3).

Conclusion

In summary, we accomplished a concise synthesis of the *gem*-difluoromethylenated analogues of boronolide **4**–**7**. Our approach featured the preparation of separable key diastereoisomers **12a**–**b** from the indium-mediated *gem*-difluoropropargyla-



Scheme 3: Synthesis of target molecules **6–7**.

tion of aldehyde **9** with fluorine-containing building block **11** and the efficient construction of α,β-unsaturated-δ-lactones **15a**–**b** via the BAIB/TEMPO-procedure.

Supporting Information

Supporting information features synthesis and characterization of *gem*-difluoromethylenated analogues of boronolide:

Supporting Information File 1

Synthesis, characterization of concerned compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-37-S1.pdf]

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The C–F bond as a conformational tool in organic and biological chemistry

Luke Hunter

Review

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Address:
School of Chemistry, The University of Sydney, NSW 2006, Australia

Email:
Luke Hunter - luke.hunter@sydney.edu.au

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Abstract

Organofluorine compounds are widely used in many different applications, ranging from pharmaceuticals and agrochemicals to advanced materials and polymers. It has been recognised for many years that fluorine substitution can confer useful molecular properties such as enhanced stability and hydrophobicity. Another impact of fluorine substitution is to influence the conformations of organic molecules. The stereoselective introduction of fluorine atoms can therefore be exploited as a conformational tool for the synthesis of shape-controlled functional molecules. This review will begin by describing some general aspects of the C–F bond and the various conformational effects associated with C–F bonds (i.e. dipole–dipole interactions, charge–dipole interactions and hyperconjugation). Examples of functional molecules that exploit these conformational effects will then be presented, drawing from a diverse range of molecules including pharmaceuticals, organocatalysts, liquid crystals and peptides.

Review

General aspects of the C–F bond

Fluorine is a small atom, with an atomic radius intermediate between that of hydrogen and oxygen (Table 1). The small size of fluorine means that it can be incorporated into an organic molecule as a replacement for hydrogen without dramatically affecting the overall molecular size. However, fluorine is the most electronegative element in the periodic table, consequently the C–F bond is highly polarised and in this sense it is a dramatic change from a C–H bond [1,2]. In the highly polarised C–F bond, the fluorine atom bears a partial negative charge and the carbon atom bears a partial positive charge, and these charges attract each other. Hence, the C–F bond has significant ionic character; it is a very short and strong bond. The fluorine atom has three lone pairs, but because of fluorine's high electronegativity these lone pairs are tightly held by the nucleus and are therefore quite unreactive (fluorine is only a very weak H-bond acceptor, for example). Another consequence of the highly polarised nature of the C–F bond is a low-energy σ* antibonding orbital, which is located behind the carbon atom in the plane of the C–F bond. This vacant orbital can accept electron density from nearby electron-donating groups such as lone pairs or σ-bonds and the importance of this will be discussed in the next section. Overall, the C–F bond can be thought of as short, strong, polarised and unreactive.

Table 1: Properties of some common elements and of their bonds to carbon [2,3].

	H	**F**	O	N	C	Cl	Br
Van der Waals radius (Å)	1.20	**1.47**	1.52	1.55	1.70	1.75	1.85
Pauling electronegativity	2.1	**4.0**	3.5	3.0	2.5	3.2	2.8
Length of single bond to carbon (Å)	1.09	**1.40**	1.43	1.47	1.54	1.77	1.97
Strength of bond to carbon (kcal/mol)	98	**105**	84	70	83	77	66

Conformational effects associated with C–F bonds

Dipole–dipole interactions

We now have a picture of the C–F bond as a highly polarised unit containing a hard, partially negative fluorine atom. This picture suggests that the C–F bond should interact with its environment principally through electrostatic (dipole–dipole and charge–dipole) interactions. Such interactions can indeed be observed in an intermolecular sense, where, for example, fluorine-containing drug molecules can bind their receptor with the fluorine atom oriented towards a partial positive charge such as an amide carbon or an acidic hydrogen in a protein receptor (**1** and **2**, Figure 1a) [4,5]. However, it should be emphasised that such intermolecular electrostatic interactions are quite weak: for example, the C–F···H–O interaction (**2**) is at most one-quarter as strong as a "normal" hydrogen bond [2].

In contrast, electrostatic interactions can also occur within an organofluorine molecule and these can be substantially stronger. For example, in α-fluoroamides (e.g. **3**, Figure 1a) there is a strong preference for the C–F bond to align antiparallel to the C=O bond, a conformation in which the C–F dipole opposes the amide dipole. An analogous effect exists with other α-fluorocarbonyl compounds, but the effect decreases with the decreasing dipole moment of the carbonyl group (**4**–**6**, Figure 1a) [2].

As well as stabilising certain conformations, dipole–dipole interactions can also be responsible for destabilising other conformations. For example, in 1,3-difluoroalkanes (e.g. **7**, Figure 1a) there is an energetic penalty associated with the conformation in which the two C–F bonds are aligned parallel [6,7]. Molecules containing 1,3-*syn* fluorine substituents will therefore prefer to twist in order to avoid parallel 1,3-C–F dipoles. An alternative explanation for the 1,3-difluoro repulsion effect invokes a steric clash between the fluorine atoms, but since fluorine is a small atom, the dipole repulsion argument is more convincing.

Charge–dipole interactions

Electrostatic interactions associated with the C–F bond become more pronounced when a neighbouring group bears a formal

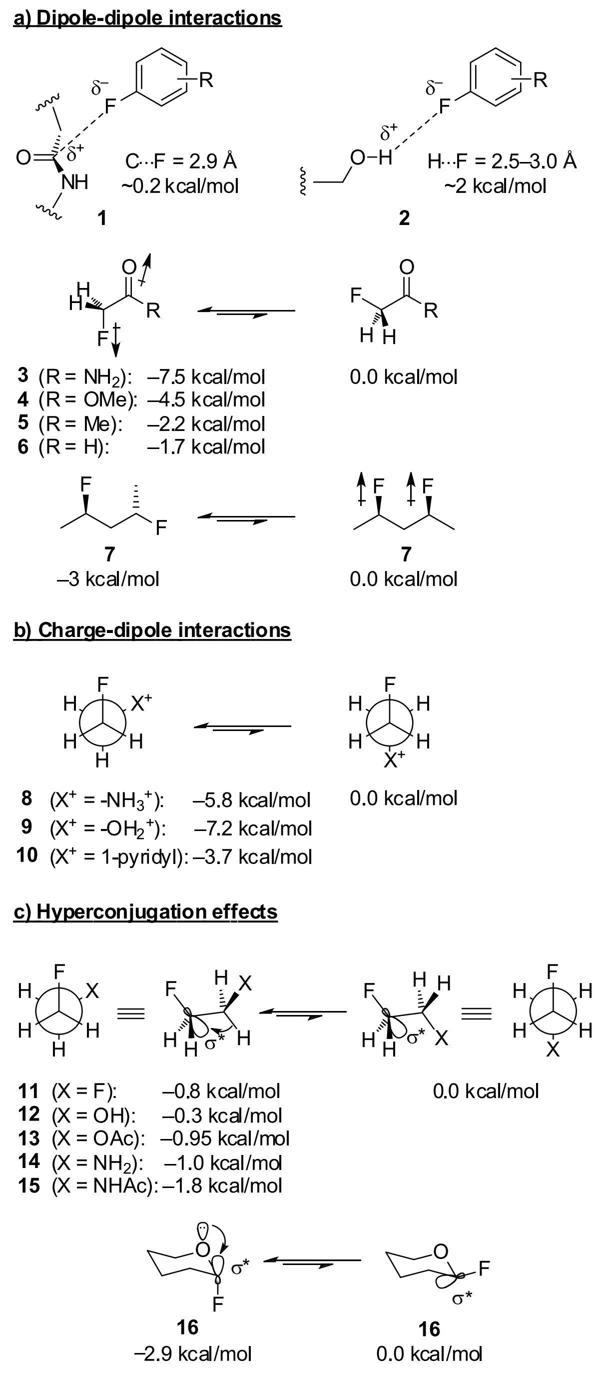


Figure 1: Conformational effects associated with C–F bonds.

charge [8]. For example, in the 2-fluoroethylammonium ion (**8**) and protonated 2-fluoroethanol (**9**) (Figure 1b), the *gauche* conformers are strongly preferred because these bring the (partially negative) fluorine atoms close to the formally positively-charged oxygen or nitrogen [9]. It is possible to envisage an intramolecular hydrogen bond helping to stabilise the *gauche* conformers of **8** and **9**, but the *gauche* preference is also maintained in systems such as **10** (Figure 1b) which cannot accommodate a hydrogen bond [10], confirming that the charge–dipole interaction is more important than any weak H-bonding in these systems.

Hyperconjugation effects

Consider the well-studied molecule 1,2-difluoroethane (**11**, Figure 1c). There are two possible staggered conformers, with the fluorine atoms either *gauche* or *anti*. NMR and molecular modelling studies have shown that the *gauche* conformer is lower in energy, which is perhaps a surprising result since the fluorine atoms might reasonably be expected to repel each other. What effect overrides the difluoro repulsion and stabilises the *gauche* conformer?

There is a vacant low-energy σ^* antibonding orbital associated with each C–F bond (Figure 1c). In the *gauche* conformer of **11**, both σ^*_{CF} orbitals are aligned with adjacent C–H bonds, which can donate electron density into the σ^*_{CF} orbitals in a process known as hyperconjugation [1,2]. Feeding electron density into an antibonding orbital in this way is equivalent to partially breaking the bond, so when hyperconjugation occurs the C–F bonds of **11** become longer and less covalent in character. However the bonds are still strong because the fluorine atoms have now become even more negative, so they are more strongly attracted to the partially positive carbon atoms. Overall, hyperconjugation is a stabilising effect and thus will lower the energy of the *gauche* conformer of **11**. In contrast, in the *anti* conformer of **11** each σ^*_{CF} orbital is now aligned with an adjacent C–F bond, which is highly polarised and less electron releasing than a C–H bond and hence hyperconjugation does not occur.

The *gauche* effect is only a subtle conformational influence compared with the dipole–dipole and charge–dipole interactions described earlier. Nevertheless, the *gauche* effect is very general and applies in many other systems in addition to 1,2-difluoroalkanes. For example, compounds containing F–C–C–O and F–C–C–N also experience this effect (**12**–**15**, Figure 1c) [9,11-13]. In general, more electronegative substituents give rise to stronger *gauche* effects. It should be noted that there are other explanations for the *gauche* effect in addition to the hyperconjugation argument presented above. For example, the "bent bond" theory [11] is an alternative explanation for the *gauche* preference of compounds **11**–**15** (Figure 1c). However, the hyperconjugation argument is more widely cited today [2] and will be exclusively quoted in this review.

The examples of hyperconjugation presented thus far (**11**–**15**, Figure 1c) all feature σ-bonds as the electron-donating groups. However, hyperconjugation can also occur with other electron donors such as lone pairs [1,14] or π-systems [15]. In each case, conformations which align the electron-donating group with the σ^*_{CF} orbital will be favoured (e.g. **16**, Figure 1c).

In summary, fluorine atoms influence the conformation of organic molecules through dipole–dipole interactions, charge–dipole interactions and hyperconjugation effects. All of these influences can be rationalised by considering that the C–F bond is short, strong and highly polarised. The remainder of this review will focus on examples of *shape-controlled functional molecules* that exploit the C–F bond as a conformational tool.

Bioactive small molecules

Despite being the most abundant halogen in the Earth's crust, fluorine is almost completely absent from natural products chemistry [16]. However, in contrast to the paucity of fluorinated molecules in nature, there are many *synthetic* (non-natural) organofluorine compounds with valuable biological activity. Of these, an interesting subset exploit the C–F bond specifically as a conformational tool and some examples of such molecules are examined below.

Fluorinated pharmaceuticals

A drug will bind its protein target with maximal affinity if it is pre-organised into the correct conformation prior to binding and this can be achieved in certain cases by judiciously incorporating fluorine atoms into the drug [4,17]. This concept is illustrated in structure–activity relationship studies of Indinavir (**17**, Figure 2), an HIV protease inhibitor developed by Merck. It is a functionalised pseudopeptide containing a central hydroxyethylene moiety in place of a scissile peptide bond. X-ray crystallography shows that **17** binds to HIV protease with its central carbon chain in an extended zigzag conformation [18]. To further investigate this binding mode, the fluorinated Indinavir analogues **18** and **19** were synthesised (Figure 2) [19]. Analogue **18** was shown to be equipotent with Indinavir (**17**), whereas the diastereomeric fluorinated analogue **19** was 14-fold less potent. The difference in potency between the fluorinated analogues can be attributed to the F–C–C–O *gauche* effect, which either reinforces (**18**) or destabilises (**19**) the bioactive extended chain conformation.

Another conformational effect of fluorine substitution is revealed in compounds **20** and **21** (Figure 3). These molecules

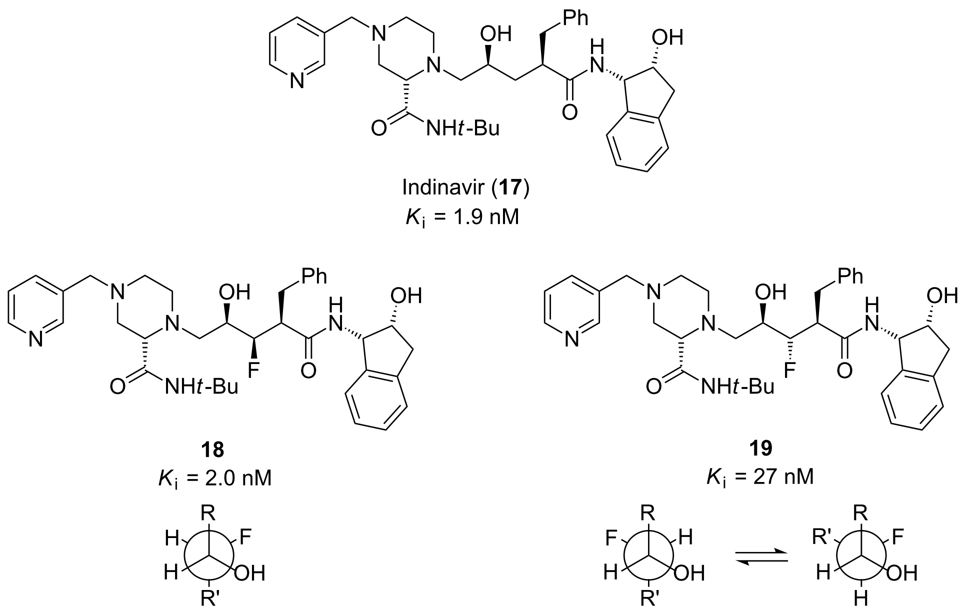


Figure 2: HIV protease inhibitor Indinavir (**17**) and fluorinated analogues **18** and **19**. In analogue **18** the *gauche* effect reinforces the active zigzag conformation, whereas in analogue **19** the *gauche* effect competes against the zigzag conformation resulting in conformational disorder.

are inhibitors of cholesteryl ester transfer protein, and are therefore of potential value in the treatment of coronary heart disease [20]. Alkoxyphenyl substituents (such as the ethoxy group of **20**) are known to align in the plane of the aryl ring (Figure 3). This is perhaps a surprising result given the additional steric demand of the in-plane conformation, but it can be rationalised by considering that the ether oxygen is sp^2 hybridised [4] which allows its p-orbital to enter into conjugation with the aryl π-system. In contrast, the ether oxygen of the fluorinated analogue **21** is sp^3 hybridised, which allows the two lone pairs to donate electron density into the two σ^*_{CF} antibonding orbitals. As a result there is less conjugation between the oxygen lone pairs and the aryl π-system, so there is nothing to counteract the steric demand of an in-plane conformation, and thus the fluoroalkyl ether of **21** prefers an orthogonal orientation. In the case of inhibitor **21**, the orthogonal orientation of the fluorinated sidechain results in more efficient binding to the target protein, translating into an 8-fold increase in potency relative to the non-fluorinated analogue **20**.

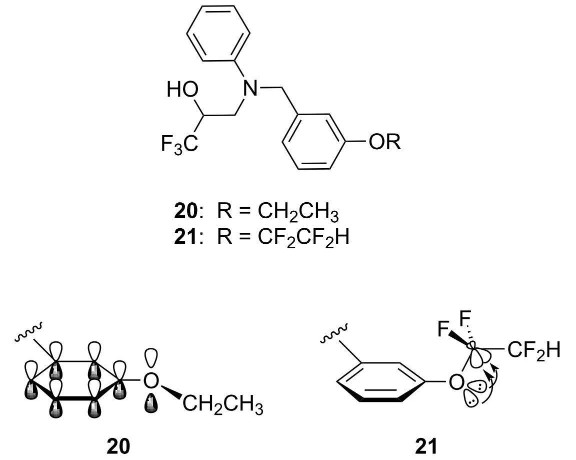


Figure 3: Cholesteryl ester transfer protein inhibitors **20** and **21**. In the fluorinated analogue **21**, $n_O \rightarrow \sigma^*_{CF}$ hyperconjugation leads to an out-of-plane orientation of the fluoroalkyl sidechain, resulting in improved binding affinity.

There has been a large amount of research into fluorinated nucleoside analogues as potential treatments for cancer and viral infection [21,22]. Fluorine is an obvious choice for incorporating into sugar-modified nucleoside analogues, since fluorine can be considered a reasonable mimic of either a hydrogen atom or a hydroxyl group. Fluorine atoms have a strong influence on both the electronic and the conformational properties of the sugar moiety, and these effects are illustrated in a series of antiviral compounds **22–25** (Figure 4) [23]. Dideoxy adenosine (**22**) is an inhibitor of HIV reverse transcriptase, but its clinical use is hampered by low hydrolytic stability. This problem can be overcome by incorporating a fluorine atom in the C2′ position (**23** and **24**, Figure 4). The enhanced acid-stability of **23** and **24** is due to the fluorine atom inductively destabilising the glycosyl carbonium ion hydrolytic intermediate. Interestingly however, fluorinated isomer **23** is inactive against HIV reverse transcriptase, whereas the diastereomeric compound **24** maintains the potency of the parent compound **22**. This result can be explained by the effect of the fluorine atoms on the molecular conformations of **23** and **24** [24]. In isomer **23**, the fluorine atom aligns *gauche* to the ring oxygen, resulting in a C3′-*endo* ring pucker which is not recognised by HIV reverse transcriptase [24,25]. By contrast, in isomer **24** the fluorine once again aligns *gauche* to the ring oxygen, but this leads to a C3′-*exo* ring pucker which is known to be optimal for biological activity. This effect can be explored further by incorporating a second fluorine atom at the C3′ position (**25**, Figure 4). If the C3′ stereochemistry is appropriate, the C3′-*exo* ring pucker can be further reinforced, with both fluorines aligned *gauche* to the ring oxygen (note that a potential difluoro *gauche* effect is overridden in this case) [24,26].

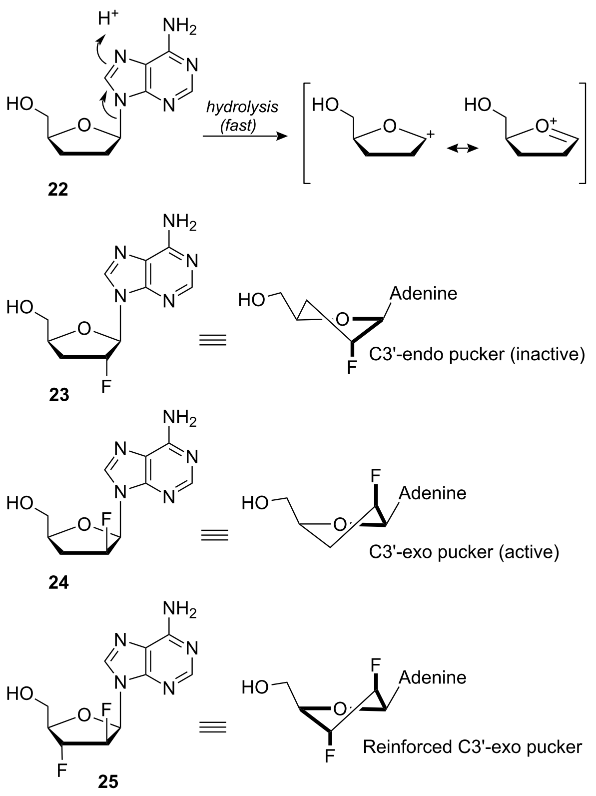


Figure 4: HIV reverse transcriptase inhibitor **22** and acid-stable fluorinated analogues **23**–**25**. The F–C–C–O *gauche* effect influences the ring conformations of **23**–**25**.

Dihydroquinidine (**26**, Figure 5) is a highly active anti-malarial alkaloid. It has conformational degrees of freedom about the C9–C4′ and C8–C9 bonds, and some information about the bioactive conformation of **26** can be obtained from the fluorinated analogues **27** and **28** (Figure 5) [27]. Although there is a reduction in potency upon replacing the hydroxyl group of **26** with a fluorine atom, the fluorinated analogues **27** and **28** nevertheless maintain anti-malarial activity in the nanomolar range. Interestingly, **27** and **28** have quite similar activities (only a two-fold difference in potency). A possible interpretation of this result is that the bioactive conformation is as illustrated in Figure 5, since both isomers **27** and **28** benefit from a *gauche* F–C–C–N^+ alignment in this conformation. Such an analysis is reinforced by NMR data which clearly show that **27** and **28** adopt the illustrated conformations about the C8–C9 bond in methanol solution.

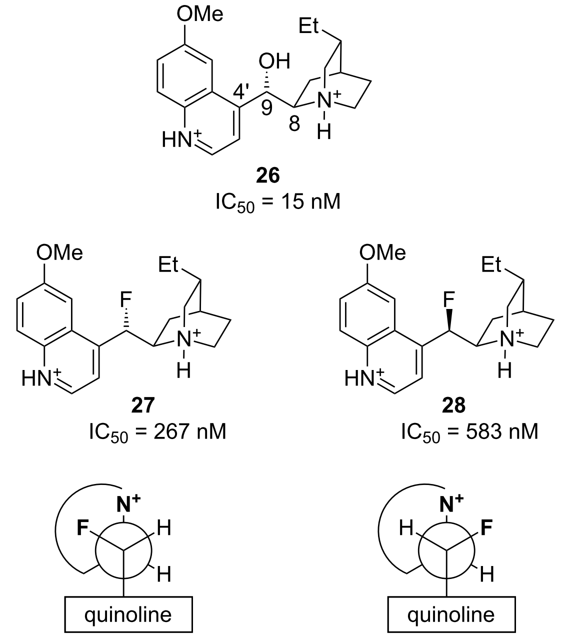


Figure 5: Dihydroquinidine (**26**) and fluorinated analogues **27** and **28**. Newman projections along the C9–C8 bonds of **27** and **28** show the proposed bioactive conformation.

Biological probes

γ-Aminobutyric acid (GABA, **29**, Figure 6) is an important neurotransmitter molecule. It is quite a flexible molecule, with 3 rotatable C–C bonds. GABA (**29**) binds to several different proteins, including various (GABA)-gated ion channels and the metabolising enzyme GABA-aminotransferase. In order to rationally design drugs that are specific for individual GABA-binding proteins, it is necessary to know the conformation that the flexible molecule GABA adopts when binding that particular protein. One method to gain this information is to investigate the fluorinated GABA analogues (*R*)-**30** and (*S*)-**30** (Figure 6) [28]. Each of (*R*)-**30** and (*S*)-**30** can adopt three possible staggered conformations about the C3–C4 bond, but because of a charge–dipole attraction between the fluorine and nitrogen atoms, these staggered conformations have different energies. Comparison of the binding affinities of (*R*)-**30** and (*S*)-**30** for a particular protein can therefore give information on the binding conformation of the natural ligand. For example, (*R*)-**30** and (*S*)-**30** are found to bind with equal affinity to the $GABA_A$ synaptic receptor [28]. This suggests that the extended conformer ("**b**" in Figure 6) is the relevant binding mode since both (*R*)-**30** and (*S*)-**30** benefit from a *gauche* F–C–C–N$^+$ alignment in this conformation, and therefore have approximately equal energies. In contrast, (*R*)-**30** is found to bind with more than 10-fold higher affinity than (*S*)-**30** to the metabolising enzyme GABA-aminotransferase [29]. This suggests that a bent conformer ("**c**" in Figure 6) is the relevant binding mode in this case, since (*R*)-**30** benefits from a *gauche* F–C–C–N$^+$ alignment in conformer "**c**" whereas (*S*)-**30** does not.

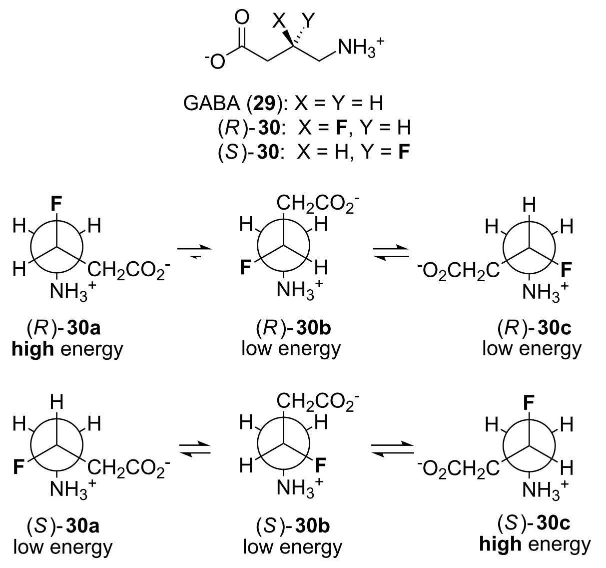


Figure 6: The neurotransmitter GABA (**29**) and fluorinated analogues (*R*)-**30** and (*S*)-**30**. Newman projections of (*R*)-**30** and (*S*)-**30** along the C3–C4 bond show the three possible staggered conformations ("**a**", "**b**" and "**c**").

In a similar vein, some information about the bioactive conformation of the insect pheromone **31** may be obtained by investigating the fluorinated analogues (*R*)-**32** and (*S*)-**32** (Figure 7) [30]. When (*R*)-**32** and (*S*)-**32** are compared in their ability to attract the relevant insect (the European corn borer, *Ostrinia nubilalis*), (*S*)-**32** is reported to possess similar biological activity to the parent non-fluorinated pheremone **31**, whereas (*R*)-**32** is inactive. This would suggest the bioactive conformation shown in Figure 7. However, this interpretation is speculative since the biological assay data is only preliminary, and the *gauche* effect in this system is relatively subtle (~1 kcal/mol).

Capsaicin (**33**, Figure 8) is a vanilloid natural product responsible for the pungency of chilli peppers. Its natural production is thought to protect the chilli pepper from predatory mammals. Capsaicin (**33**) binds to the pain receptor TRPV1, a non-selective cation channel that also responds to heat and acidic pH. Somewhat counterintuitively, capsaicin has been used for many years as a traditional medicine for the treatment of pain and there is considerable interest today in the production of capsaicin analogues as new analgesics. However, the binding mode of capsaicin (**33**) to the receptor TRPV1 is not known in full detail. The fluorinated analogues (*R*)-**34** and (*S*)-**34** (Figure 8) provide valuable information [31]. Due to the α-fluoroamide effect, the two enantiomers are expected to project the alkyl chain in different directions from the molecular axis, so the relative binding efficiency of (*R*)-**34** and (*S*)-**34** should inform on the binding conformation of natural capsaicin (**33**). It emerges that both enantiomers bind TRPV1 with similar affinity to capsaicin itself and this suggests that the alkyl chain projects roughly along the molecular axis when bound to TRPV1 since both enantiomers can approximate this conformation equally well [31]. This interpretation is in agreement with a previous study which made inferences from X-ray crystallography of a related receptor [32].

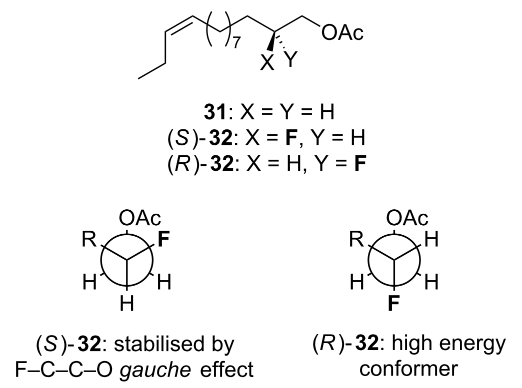


Figure 7: The insect pheromone **31** and fluorinated analogues (*S*)-**32** and (*R*)-**32**. The proposed bioactive conformation is shown in Newman projections.

Organocatalysts

So far we have seen that the C–F bond can be a valuable tool for medicinal chemists seeking to control the molecular con-

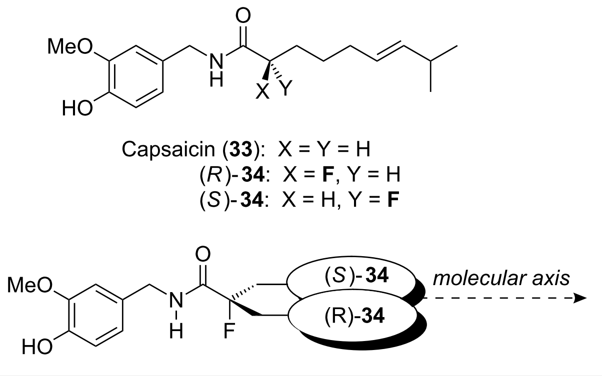


Figure 8: Capsaicin (**33**) and fluorinated analogues (*R*)-**34** and (*S*)-**34**.

formation of drugs and bioprobes. This section will show that the C–F bond is also emerging as a useful tool in the field of catalysis. Recent reports have shown that organocatalysts can be conformationally "fine-tuned" by fluorine substitution for improved activity and selectivity.

Pyrrolidine **35** (Figure 9) is a highly selective catalyst for the epoxidation of α,β-unsaturated aldehydes (e.g. **36**) [33]. In the first step of the reaction, aldehyde **36** and pyrrolidine **35** react together to form the iminium ion **37**. This has a LUMO-lowering effect (analogous to Lewis-acid activation of **36**) which makes **37** more reactive towards nucleophiles [34]. In intermediate **37**, the fluorine atom aligns *gauche* to the positively-charged nitrogen atom (Figure 9, inset), resulting in a phenyl group shielding the top (*re*) face of the alkene. Hydrogen peroxide consequently attacks from the bottom (*si*) face, leading to epoxide **38** with high enantioselectivity. In a control experiment, the related organocatalyst 2-(diphenylmethyl)pyrrolidine (containing a hydrogen atom instead of the fluorine atom of **35**) also catalyses the same reaction but with lower enantioselectivity suggesting that the fluorine atom of **35** helps to rigidify the activated intermediate and thereby enhances selectivity.

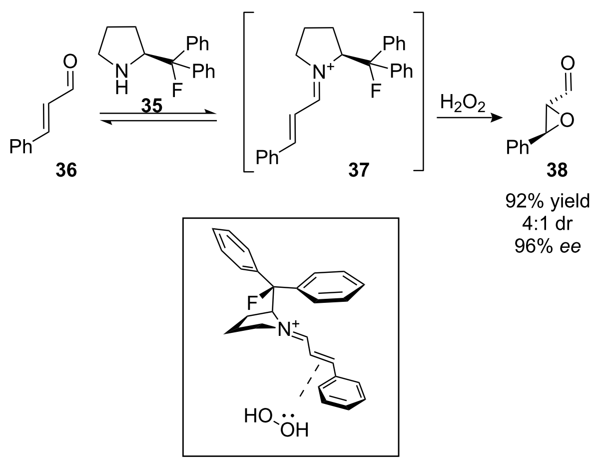


Figure 9: Asymmetric epoxidation reaction catalysed by pyrrolidine **35**. Inset: the geometry of the activated iminium ion intermediate **37** is stabilised by a *gauche* F–C–C–N^+ alignment.

Another fluorinated organocatalyst has recently featured in the first example of an asymmetric transannular aldol reaction (Figure 10) [35]. (*S*)-proline (**39**) is able to catalyse this reaction with moderate enantioselectivity and a similar result is observed with *cis*-4-fluoroproline (**40**). However, a notable improvement in enantioselectivity is obtained with the diastereoisomeric catalyst *trans*-4-fluoroproline (**40**). The authors of this study report that further work to elucidate this fluorine effect is ongoing. Fluorine atoms are known to influence the conformation of pyrrolidine rings through the F–C–C–N *gauche* effect (see this review's section on collagen for a further discussion of this effect in the context of fluorinated peptides). It is interesting to speculate whether a Cγ-*exo* proline ring shape, reinforced by the F–C–C–N *gauche* effect, could be partly responsible for the high enantioselectivity of catalyst **41**. As an illustration of the importance of this work, catalyst **41** has already been put to good use in a total synthesis of the natural product (+)-hirsutine (**46**, Figure 10), with the key transannular aldol reaction (**44**→**45**) proceeding in high yield and with impressive enantioselectivity [35].

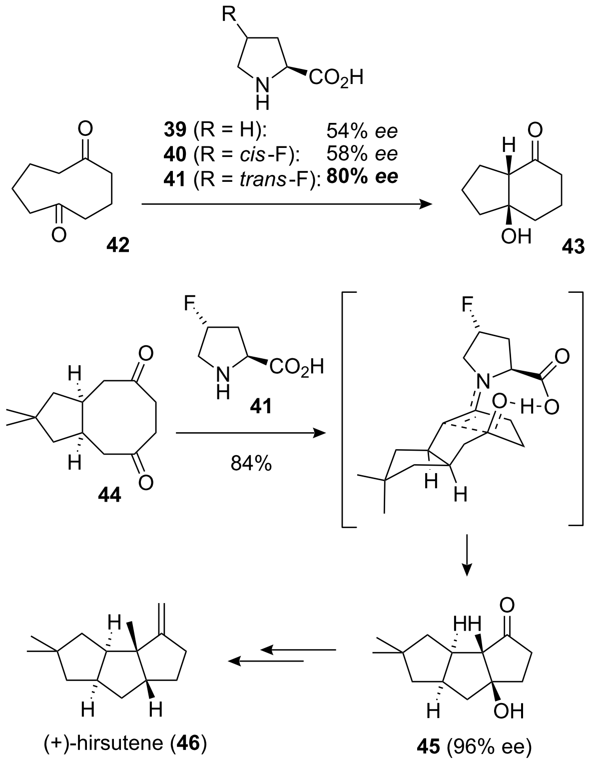


Figure 10: The asymmetric transannular aldol reaction catalysed by *trans*-4-fluoroproline (**41**), and its application to the total synthesis of (+)-hirsutene (**46**).

Fluorine-substituted organocatalysts are also useful in the asymmetric Stetter reaction (Figure 11) [36]. *N*-Heterocyclic carbene **49** was identified as a promising first-generation catalyst for the Stetter reaction between aryl aldehydes (e.g. **47**) and nitroalkenes (e.g. **48**). Superficially, it seems that the bulky isopropyl group of **49** is solely responsible for the enantioselectivity of this reaction. However, the shape of the bicyclic ring system might also play a role and this idea can be explored by comparing catalyst **49** with the fluorinated analogues **50**–**52**. The parent catalyst **49** adopts a Cγ-*endo* ring conformation, which is favoured because of the pseudoequatorial orientation of the bulky isopropyl group. In catalyst **50** the Cγ-*endo* conformation is maintained (this time reinforced by hyperconjuga-

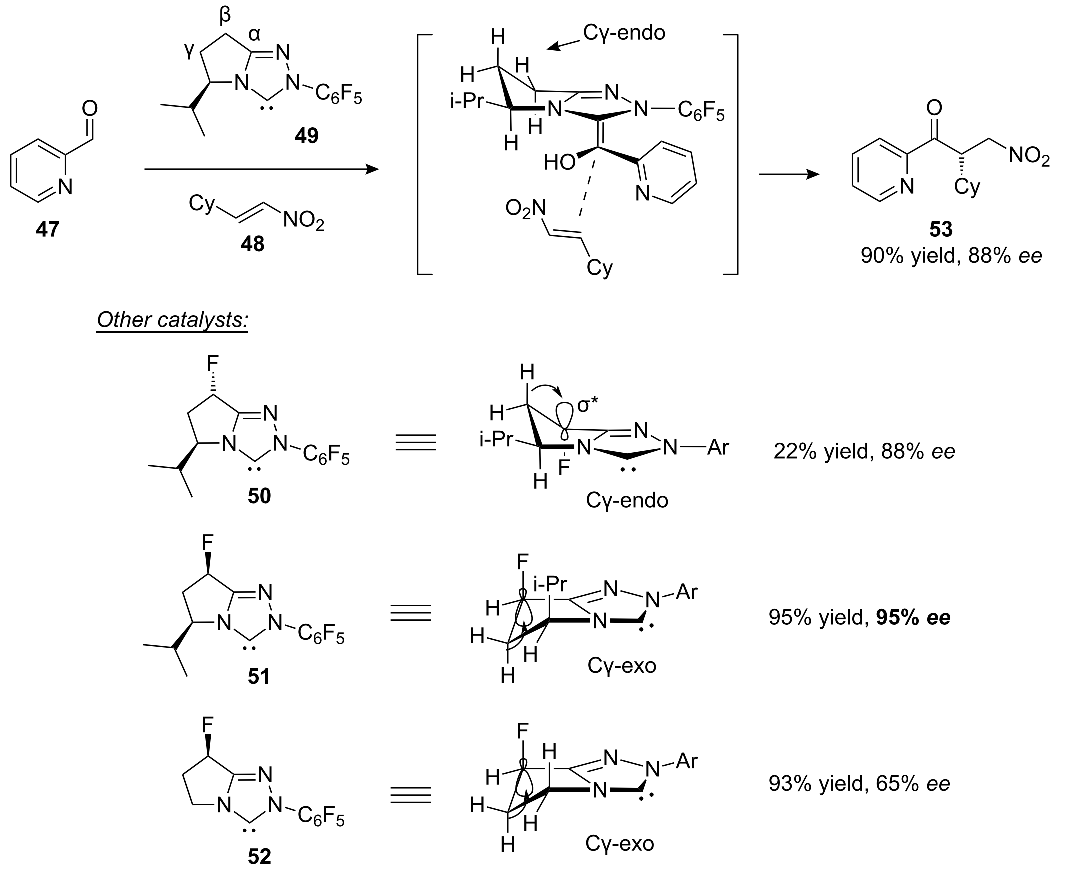
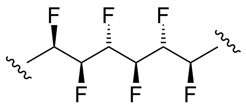


Figure 11: The asymmetric Stetter reaction catalysed by chiral NHC catalysts **49**–**52**. The ring conformations of **50**–**52** are influenced by $\sigma_{CH}\rightarrow\sigma^*_{CF}$ hyperconjugation. Cy = cyclohexyl.

tion) and the enantioselectivity of the reaction is unchanged. In contrast, catalyst **51** adopts a Cγ-*exo* conformation. This seems surprising because the bulky isopropyl group is now forced into a pseudoaxial position, but the steric clash is more than compensated for by hyperconjugation. Catalyst **51** is found to be significantly more enantioselective than **50**, suggesting that the Cγ-*exo* ring shape could be responsible for the improvement. Consistent with this, catalyst **52** is still capable of a reasonable level of asymmetric induction despite lacking the isopropyl group. The enantioselectivity of catalyst **52** is achieved solely through the Cγ-*exo* ring shape (assuming zero steric effects associated with the small fluorine atom). Overall, this work illustrates the great potential of using the C–F bond as a conformational tool in the development of new and improved organocatalysts.

Multi-vicinal fluoroalkanes

We have already seen that in 1,2-difluoroethane (**11**, Figure 1c) the two vicinal C–F bonds align *gauche* to one another. What happens if there is a longer carbon chain containing several vicinal fluorine atoms? This gives rise to a new type of compound termed a "multi-vicinal fluoroalkane" (e.g. **54**, Figure 12), which is conceptually intermediate between alkanes and perfluoroalkanes [37]. Multi-vicinal fluoroalkanes are interesting systems for studying stereoelectronic effects such as the *gauche* effect and they also have potential applications in materials science, for example, as novel liquid crystals.



54

Figure 12: A multi-vicinal fluoroalkane.

A distinguishing feature of compounds such as **54** is their stereochemical complexity. It is necessary to control these stereocentres during synthesis so that the conformational properties of different diastereoisomers can be compared. This has been explored with compounds containing up to six vicinal fluorines [37-39] and it emerges that the conformations of these compounds are governed by two main considerations: parallel 1,3-C–F bonds are avoided, and *gauche* 1,2-C–F bonds are favoured. For example, consider the all-*syn* hexafluoroalkane **55** (Figure 13) [39]. This molecule cannot adopt a zigzag conformation because this would incur multiple 1,3-difluoro repulsions. Instead, **55** adopts a helical shape in which each pair of vicinal fluorines is aligned *gauche* but no 1,3-difluoro repulsion is present. In contrast, the diastereoisomeric compound **56** *does* adopt the zigzag conformation (Figure 13). This affords three out of a possible five 1,2-difluoro *gauche* alignments, while the different stereochemistry of the molecule prevents 1,3-difluoro repulsion from occurring.

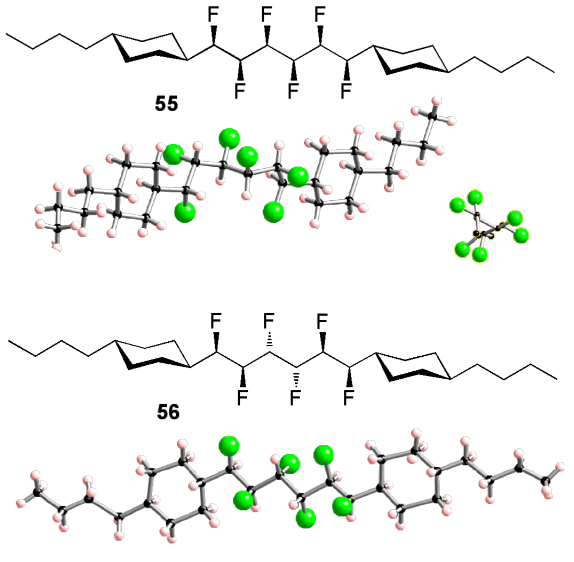
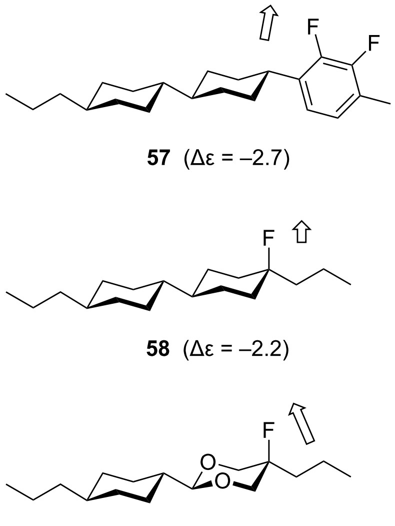


Figure 13: X-ray crystal structures of diastereoisomeric multi-vicinal fluoroalkanes **55** and **56**. The different conformations can be explained by (i) the avoidance of 1,3-difluoro repulsion and (ii) a preference for 1,2-difluoro *gauche* alignments.

Knowledge of the conformational behaviour of multi-vicinal fluoroalkanes has informed the design of novel liquid crystals. A liquid crystal is a fluid phase in which there is some orientational ordering of the molecules. Liquid crystal display (LCD) technology requires rod-shaped molecules that have a dipole moment perpendicular to the long axis of the molecule, and this is often achieved by incorporating fluorinated subunits into the liquid crystal molecule (Figure 14) [40]. In most cases (e.g. **57** and **58**), the fluorine atoms act not as conformational control elements but simply as polar substituents. However, note that in the more sophisticated compound **59**, the ring oxygens also contribute to the dipole moment in addition to reinforcing the molecular conformation with two F–C–C–O *gauche* alignments [41].



57 (Δε = –2.7)

58 (Δε = –2.2)

59 (Δε = –4.7)

Figure 14: Examples of fluorinated liquid crystal molecules. Arrows indicate the orientation of the molecular dipole moments, which are quantified in the negative dielectric anisotropy values, Δε.

With a developing knowledge of the behaviour of multi-vicinal fluoroalkanes it has been possible to develop new liquid crystals containing several fluorine atoms, in which the fluorine atoms affect the molecular conformation as well as the molecular dipole moment. The difluoro compound **60** (Figure 15) can be viewed as a conceptual progression from the axially fluorinated liquid crystal **58**. NMR and modelling data show that the fluoroalkyl chain of **60** adopts a zigzag conformation in which the two C–F bonds are aligned *gauche* to one another [42]. Hence, both fluorine atoms are presented on the same face of the molecule, resulting in a substantial molecular dipole moment as measured in the large negative dielectric anisotropy value (Δε). This system can be extended to incorporate a third vicinal fluorine atom (**61**, Figure 15). Disappointingly however, the trifluoro analogue **61** seems to offer no improvement over the difluoro analogue **60** (almost identical values of Δε). This is because the conformation of **61** is affected by 1,3-difluoro repulsion. The fluoroalkyl chain of compound **61** cannot adopt the zigzag conformation because of this repulsion effect and hence the three fluorine atoms are not all presented on the same face of the molecule. This problem is overcome in the next-generation compound **62** (Figure 15) [39]. X-ray crystallography reveals that the fluoroalkyl chain of **62** adopts the desired zigzag conformation, which maximises the number of fluorine *gauche* alignments, with the insulating ethyl spacer preventing 1,3-difluoro repulsion. Interestingly, the X-ray structure of **62** reveals a slight twisting distortion about the molecular axis, possibly reflecting strain associated with a very high dipole moment caused by the orientation of all four fluorine atoms on the same face of the molecule. Overall, this

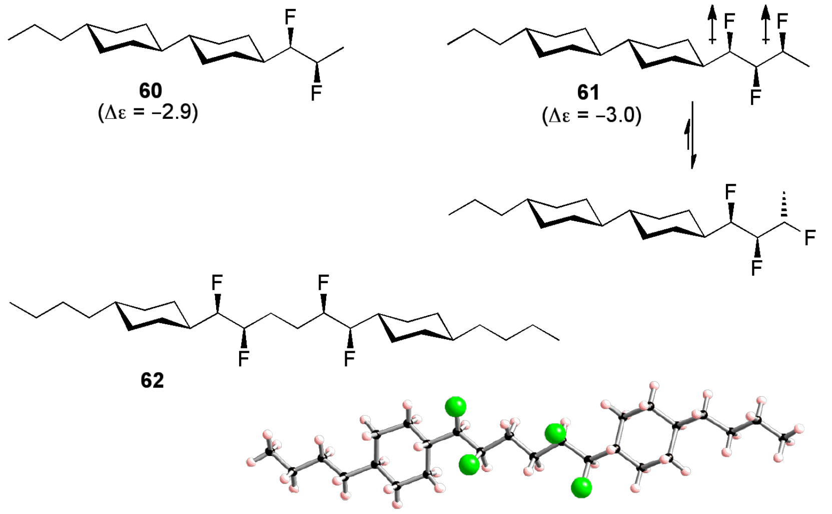


Figure 15: Di-, tri- and tetra-fluoro liquid crystal molecules **60**–**62**.

work illustrates that a basic knowledge of the conformational preferences of multi-vicinal fluoroalkanes can have a valuable bearing on the design of functional materials.

Peptides and proteins

Some of the most notable examples of exploiting the C–F bond as a conformational tool come from the world of peptides and proteins. The presence of amide functional groups in the peptide backbone provides a good opportunity to exploit the α-fluoroamide effect and the F–C–C–N *gauche* effect [43]. The concept of controlling peptide conformation using fluorine atoms is exciting because the conformation of a peptide critically affects its biological activity and consequently, there are many potential applications in medicinal chemistry and biotechnology.

Collagen

Collagen is the most abundant protein in animals. It is a structural protein responsible for the tensile strength of connective tissue. Collagen fibrils consist of a tight bundle of three parallel protein strands wound into a triple helix (Figure 16). Each protein strand is made of ~300 repeats of the sequence Xaa-Yaa-Gly, where Xaa is often proline (**39**) and Yaa is often 4(*R*)-hydroxyproline (**63**). The triple helix is partly held together by backbone hydrogen bonds and for many years it was thought that the hydroxyl groups of the 4(*R*)-hydroxyproline residues (**63**) contributed to the stability of collagen by providing extra hydrogen bonding. However, this theory was thrown into doubt when a collagen mimic was synthesised in which the 4(*R*)-hydroxyproline residues (**63**) were replaced with 4(*R*)-fluoroproline (**41**) [44]. Despite being unable to participate in inter-strand hydrogen bonding, the 4(*R*)-fluoroproline residues were found to greatly increase the stability of the collagen triple helix. How could this be?

It emerges that rather than hydrogen bonding, the source of stability derives from conformational changes imparted by the fluorine substituent of **41** (Figure 16). For most peptide bonds, the *trans* conformation is strongly preferred and indeed an all-*trans* arrangement is required for the collagen strands to assemble into the triple helix. However, peptide bonds adjacent to proline residues have only a very slight *trans* preference, meaning that the *cis* isomer is also significantly populated in solution. In 4(*R*)-fluoroproline (**41**), the electronegative fluorine atom exerts an inductive “pull” which lowers the C(O)–N bond order [46]. This reduces the energy barrier to *cis*/*trans* isomerisation, allowing the peptide strand to pre-organise into the required all-*trans* conformation and thereby facilitating triple helix formation. More importantly, the fluorine substituent also affects the conformation of the proline ring (Figure 16). In unsubstituted proline residues **39**, the pyrrolidine moiety adopts a Cγ-*endo* ring pucker. In contrast, 4(*R*)-fluoroproline (**41**) exhibits a Cγ-*exo* pucker which is stabilised by a fluorine-amide *gauche* alignment [47]. There are several consequences of this, including further stabilising the *trans* amide through subtle mechanisms [48,49]. Crucially, the Cγ-*exo* pucker also means that the C–F bond is projected in such a way that it aligns anti-parallel to three proximal C=O dipoles in the triple helix [47]. Thus, the fluorinated collagen mimic reveals that it is dipole–dipole interaction rather than hydrogen bonding that gives collagen its great stability.

Opioid receptor-binding peptides

The hexapeptide Tyr-D-Ser-Gly-Phe-Leu-Thr, known as the enkephalin-related peptide, binds to the δ-opioid receptor. Opioid receptor-binding peptides are of interest because of their biological roles in analgesia as well as in respiratory, gastrointestinal and cardiovascular functions [50]. However,

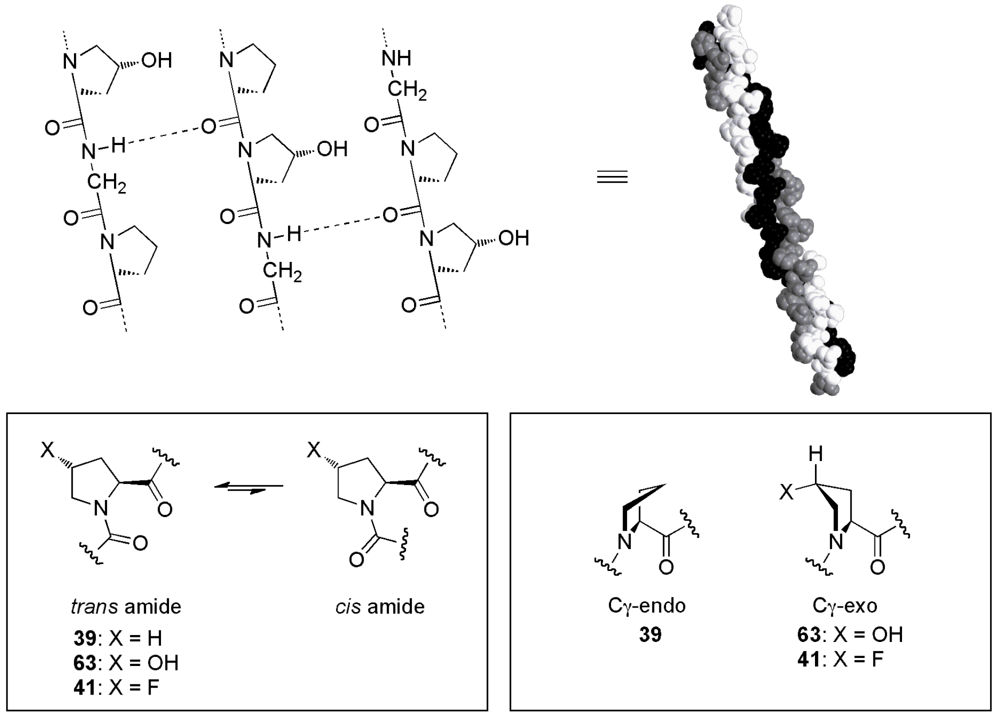


Figure 16: Collagen mimics of general formula (Pro-Yaa-Gly)$_{10}$ where Yaa is either 4(*R*)-hydroxyproline (**63**) or 4(*R*)-fluoroproline (**41**). The fluorinated isomer is more stable, due to an increased preference for the *trans* amide bond and the Cγ-*exo* pyrrolidine ring pucker. The illustrated collagen triple helix structure is from PDB code 1CAG [45].

their mechanism of action is difficult to elucidate, partly because these linear peptides are conformationally flexible. In order to gain information about the bioactive conformation, fluorine chemistry can be used to modify the peptides' conformational behaviour. For example, there is an interesting contrast between the enkephalin-related peptide derivative **64** and its fluorinated analogue **65** (Figure 17) [51,52]. The NOESY spectrum of peptide **64** reveals long-range through-space interactions, suggesting a folded conformation possibly reinforced by a Tyr-O$\underline{\text{H}}$···Thr-$\underline{\text{O}}$H hydrogen bond. In contrast, analogue **65** contains an electron-withdrawing trifluoromethyl group, which lowers the H-bond acceptor ability of the adjacent hydroxyl group. The NOESY spectrum of **65** reveals no long-range interactions, suggesting that the crucial Tyr–Thr hydrogen bond is disrupted and that a linear peptide conformation is preferred.

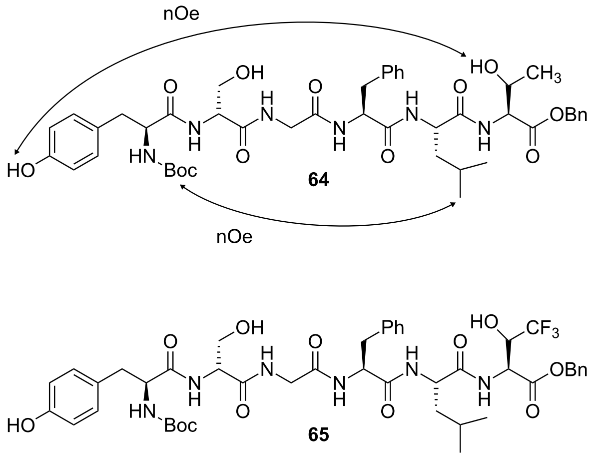


Figure 17: Enkephalin-related peptide **64** and the fluorinated analogue **65**. The electron-withdrawing trifluoromethyl group of **65** disrupts a key hydrogen bond, leading to a different conformation as determined by NOESY experiments.

Fluorinated β-peptides

β-Peptides are unnatural polymers composed of β-amino acids, which have an extra -CH_2- group relative to natural α-amino acids (Figure 18). Despite the increased conformational freedom of β-peptides, they can nevertheless assemble into well-defined secondary structures such as helices, sheets and turns [53]. Certain β-peptidic structural motifs have been developed as effective mimics of biologically important α-peptides [54] and this holds great therapeutic promise because β-peptides are not recognised by hydrolase enzymes so have much longer half-lives in vivo [55].

One way to control the conformation of β-peptides is to incorporate fluorine atoms into the peptide backbone. This concept is

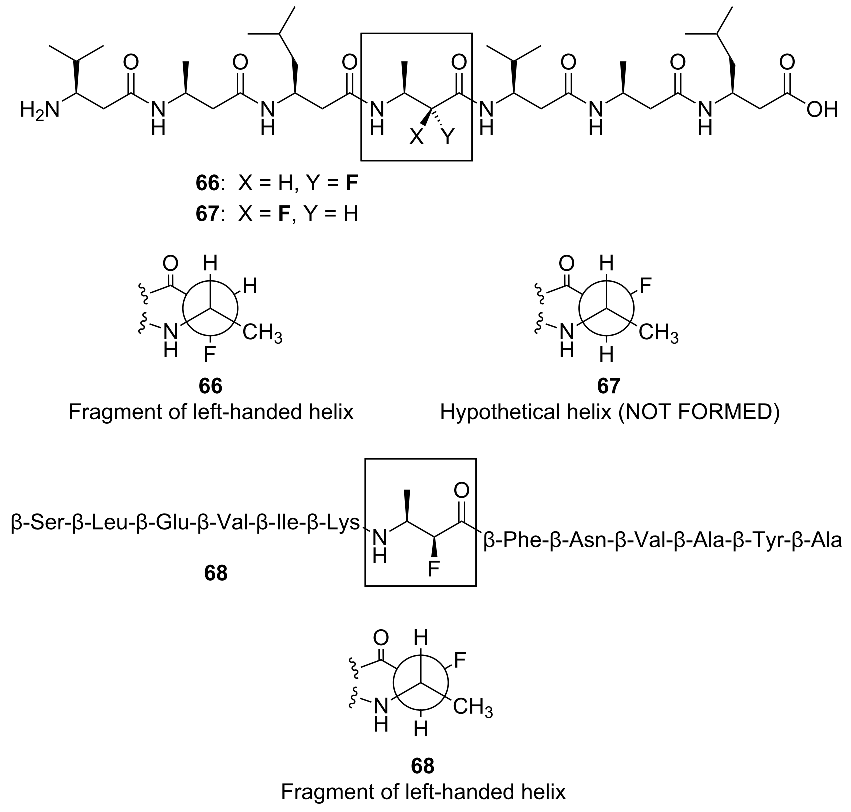


Figure 18: The C–F bond influences the conformation of β-peptides. β-Heptapeptide **66** adopts a helical conformation, reinforced by the α-fluoroamide effect and a fluorine-amide *gauche* alignment. In isomeric β-heptapeptide **67**, the helical conformation is disrupted by the fluorine atom. The disruptive effect of fluorine is overridden in the longer helix-forming β-tridecapeptide **68**.

elegantly illustrated by the diastereoisomeric β-peptides **66** and **67** (Figure 18) [56]. The β-amino acid sequence of **66** and **67** is known to promote the formation of a left-handed helix and this helical conformation can be either reinforced or destabilised by a fluorine substituent. In the case of β-peptide **66**, the fluorine atom aligns antiparallel to the adjacent C=O bond and *gauche* to the adjacent amide nitrogen, and this reinforces the helical conformation of the β-peptide. In contrast, the helical conformation of β-peptide **67** cannot accommodate these favourable alignments, so in this case the fluorine atom has a helix-breaking effect.

Interestingly, there is a limit to the conformational directing power of the C–F bond, as demonstrated by the longer β-tridecapeptide **68** (Figure 18) [57]. In this more extended system, the stronger propensity for helix formation overrides the conformational influence of the C–F bond, which is forced into a high-energy orientation orthogonal to the adjacent C=O bond. Nevertheless, taken together, the results with β-peptides (Figure 18) show that a single C–F bond can have a dramatic impact on peptide conformation.

Future directions

Recent results obtained with β-peptides illustrate that promising biological activity can be achieved with unnatural peptides [54]. This opens the door to a new area of research into more exotic amino acids containing several vicinal fluorine atoms. This would allow a greater variety of molecular shapes to be created, governed by the conformational rules known to operate in multi-vicinal fluoroalkanes in addition to the α-fluoroamide effect and the fluorine-amide *gauche* effect. Progress has been made towards this goal with the synthesis of pseudopeptides containing a difluorosuccinate core (**69** and **70**, Figure 19) [58,59]. In each of pseudopeptides **69** and **70**, the two fluorine atoms align antiparallel to the adjacent C=O bonds and *gauche* to one another, leading to different backbone conformations in the two diastereoisomers.

Building upon these promising results, a logical next step is to pursue the synthesis of non-symmetrical amino acids containing two or more vicinal fluorine atoms. Such fluorinated amino acids could be useful building blocks for the synthesis of shape-controlled bioactive pseudopeptides. Studies towards this goal

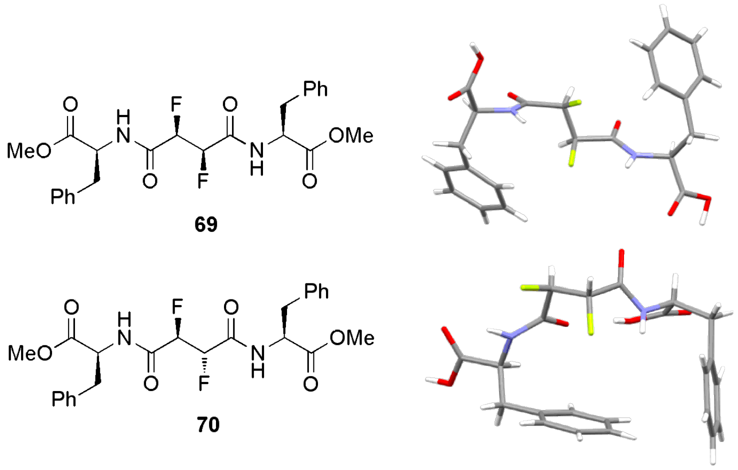


Figure 19: The conformations of pseudopeptides **69** and **70** are influenced by the α-fluoroamide effect and the fluorine *gauche* effect.

are underway in the author's laboratory, and details of these investigations will be reported in due course.

Conclusion

The conformations of organofluorine compounds are influenced by a number of stereoelectronic effects associated with the C–F bond, including dipole–dipole interactions, charge–dipole interactions and hyperconjugation. Knowledge of these conformational effects allows the properties of functional molecules to be optimised through selective fluorination chemistry. This concept has been demonstrated in diverse areas including medicine, catalysis, materials science and biotechnology. It is hoped that the examples highlighted in this review have persuaded the reader of the great usefulness of the C–F bond as a conformational tool in organic and biological chemistry.

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Preparation, structures and preliminary host–guest studies of fluorinated *syn*-bis-quinoxaline molecular tweezers

Markus Etzkorn[*1], Jacob C. Timmerman[1], Matthew D. Brooker[1], Xin Yu[2] and Michael Gerken[2]

Preliminary Communication

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Address:
[1]Department of Chemistry, The University of North Carolina at Charlotte, 9201 University City Blvd., Charlotte, NC 28223, USA and [2]Department of Chemistry and Biochemistry, University of Lethbridge, Lethbridge, AB T1K 3M4, Canada

Email:
Markus Etzkorn[*] - metzkorn@uncc.edu

* Corresponding author

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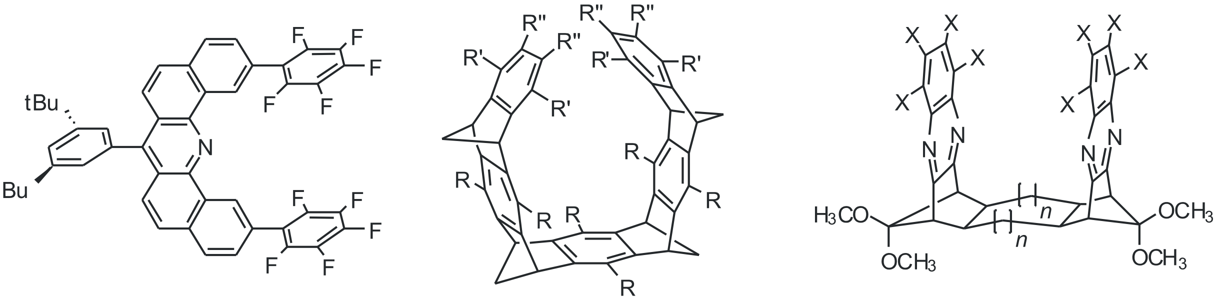
Abstract

A series of polycyclic frameworks with fluorinated *syn*-facial quinoxaline sidewalls has been prepared as potential molecular tweezers for electron-rich guest compounds. Our synthetic route to the cyclooctadiene-derived scaffolds **16a**–**d** takes advantage of the facile isolation of a novel spirocyclic precursor **9b** with the crucial *syn*-orientation of its two alkene moieties. The crystal structure of **16c** displays two features typical of a molecular tweezer: inclusion of a solvent molecule in the molecular cleft and self-association of the self-complementary scaffolds. Furthermore, host–guest NMR studies of compound **16c** in solution show chemical exchange between the unbound and bound electron-rich guest, *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylenediamine.

Introduction

A broad variety of structurally diverse molecular tweezers, i.e., scaffolds in which a tether unit connects two *syn*-oriented aromatic pincers, are well-established as devices for the molecular recognition of mostly electron-deficient guest compounds [1-10]. Conversely, molecular tweezers with a binding cleft that displays an inverted electrostatic potential could thus find application in sensing of electron-rich guests, or even anions [11-13]. Possible frameworks include the seemingly trivial fluorinated analogues of known frameworks (Scheme 1), but so far only a few groups have investigated these intriguing target compounds: Korenaga and Sakai optimized the synthetic access to fluorinated acridine-based molecular tweezers **1** and determined association constants for the complexation of electron-rich arenes [14,15]. Hermida-Ramón and Estévez calculated the structures and electrostatic potentials of belt-shaped compounds **2a**–**c** and predicted the complexation of halide anions in the cavity of **2c** [16-18].



1

2a [R = F, R' = R'' = H]
2b [R = R' = F, R'' = H]
2c [R = R' = R'' = F]

3 [*n* = 1; X = H]

4a [*n* = 2 ; X = H]
4b [*n* = 2 ; X = F]

Scheme 1: Fluorinated molecular tweezers.

Intrigued by Chou's communication on the spectroscopic properties of non-fluorinated bis-quinoxalines of type **3** and **4a** [19], we targeted on the corresponding fluorinated derivatives – in particular compound **4b** with its large binding cleft.

In this paper, we present the synthesis and characterization of these synthetically more challenging derivatives. Furthermore, we discuss structural features of a cyclooctadiene-derived scaffold of type **4b** and report preliminary spectroscopic data on their association with electron-rich guest compounds.

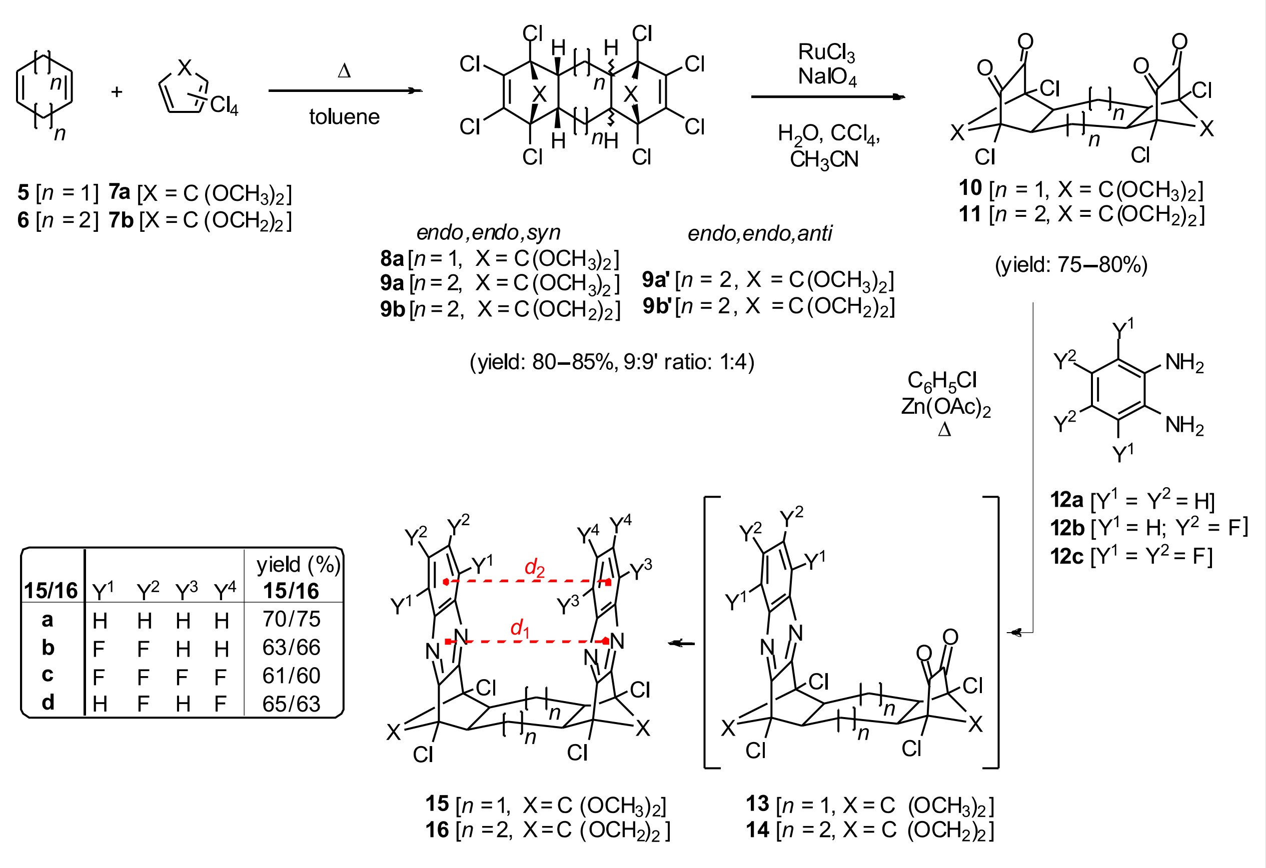
Results and Discussion

Synthesis of fluorinated bis-quinoxalines

The general route [19] to bis-quinoxaline targets (Scheme 2) utilizes a twofold Diels–Alder reaction of a cycloalkadiene (**5**,**6**) with cyclopentadienone derivatives (**7**), subsequent oxidation of the *syn*-diene intermediates (**8**,**9**) to their corresponding tetraketones (**10**,**11**) and condensation of the latter with *o*-phenylenediamine derivatives (**12**) to obtain the *syn*-bis-quinoxaline target compounds (**15**,**16**). This synthetic route is flexible with regard to the tether size (cyclohexane vs cyclooctane) and modifications in the pincer sidewalls (degree of fluorination).

Although only the larger cyclooctadiene-derived scaffolds **16a**–**d** could function as molecular tweezers, we also synthesized the fluorinated cyclohexadiene-derived compounds **15b**–**d** with their smaller π-π–distances. A Diels–Alder reaction of cyclohexadiene (**5**) with ketal **7a** furnished exclusively the *syn*-bis-adduct **8a** [20] which was then converted to the canary-yellow tetraketone **10** by Khan's original $RuCl_3$-catalyzed oxidation protocol [21-23] since Chou's "optimized" procedure was somewhat capricious in our hands. The twofold condensation with di- or tetrafluoro-*o*-phenylenediamine (**12b**,**c**) [24,25] provided access to the novel fluorinated species **15b**–**c** in acceptable yields (60–70%). This last reaction required harsh conditions and delivered a dark crude product with unspecified tarry material after heating the substrates for several days to 115 °C (^{1}H and ^{19}F NMR control). Occasionally, the condensation reaction did not lead to complete conversion of the tetraketone precursor **10** and produced a separable mixture of the mono- and bis-condensation products **13** and **15**, respectively. The isolated mono-adducts **13a** (or **13b**) could then be converted to the symmetrical target **15a** (or **15c**) or, upon condensation with the appropriate *o*-phenylenediamine derivative **12c** (or **12a**), to scaffold **15b** with only one fluorinated quinoxaline subunit.

The synthetic access to cyclooctadiene-derived scaffolds is complicated by the lack of selectivity in the twofold Diels–Alder reaction of diene **6** and led to a mixture of the *syn*- and *anti*-bis-adducts in a 1:4 ratio [26,27]. Since the separation of the crucial *syn*-isomer **9a** from *anti*-compound **9a′** by repeated recrystallization did not furnish the pure *endo*,*endo*,*syn*-isomer **9a** in our hands, we focused on the new spirocyclic derivative **9b**. Thus, reaction of the spiro-ketal **7b** [28] with cyclooctadiene (**6**) furnished a mixture of **9b** and **9b′** in excellent yield in the same ratio of isomers as observed in the previous case. Again, the *endo*,*endo*,*syn*-isomer **9b** could not be satisfactorily separated from the *endo*,*endo*,*anti*-isomer **9b′** by chromatography, but gram-amounts of the crucial *syn*-isomer **9b** were readily obtained after repeated recrystallization from hot diethyl ether. The assignment of both *syn*- and *anti*-isomers was initially based on ^{1}H NMR spectroscopic analogies to the bis-methoxyketals, i.e., the small low-frequency shift of the bridgehead proton resonances of the *anti*-adduct (Δδ = 0.20 ppm). The X-ray structure determination of target compound **16c** confirmed indirectly the correct assignment of isomers **9b** and **9b′** (vide infra). Oxidation of **9b** with Khan's original protocol [21-23] and condensation of the resulting tetraketone **11** with *o*-phenylenediamine **12a** or the fluorinated derivatives **12b**–**c** resulted in the new non-fluorinated parent



15/16	Y^1	Y^2	Y^3	Y^4	yield (%) 15/16
a	H	H	H	H	70/75
b	F	F	H	H	63/66
c	F	F	F	F	61/60
d	H	F	H	F	65/63

Scheme 2: Synthesis of non-fluorinated and fluorinated *syn*-bis-quinoxalines.

compound **16a** and the three fluorinated scaffolds **16b**–**c**, respectively. All new *syn*-bis-quinoxalines were purified by flash-chromatography on silica gel and obtained as off-white powders in 60–75% yield after recrystallization from methanol. Considering the low nucleophilicity of the fluorinated amine building blocks **12b**–**c**, our yields in the condensation reaction are quite good (71–86% for each condensation step) and any modification of the reaction conditions by other reported procedures [29-32] did not significantly alter the outcome. It should be noted that all fluorinated bis-quinoxalines are stable compounds which do not show any decomposition over extended periods of time; loss of fluorine has only been observed under typical nucleophilic aromatic substitution conditions.

Although the new compounds, in particular the cyclohexadiene-derived species **15b**–**c**, were reasonably soluble in dipolar aprotic solvents (DMSO, DMF) or halogenated aromatic solvents (C_6H_5Cl), they only displayed poor solubility in several standard organic solvents ($CHCl_3$, CH_2Cl_2, CH_3OH, C_6H_6, CH_3CN). Their full characterization and some preliminary host–guest studies of the cyclooctadiene-derived frameworks could however, be carried out in dilute chloroform, acetonitrile and methylene chloride solutions. The spectroscopic characteristics of **15a** and several non-fluorinated derivatives have been described elsewhere [19] and the NMR spectroscopic data for **15b**–**c** (**16a**–**d**) are only altered by the absence of the corresponding proton resonances, the additional coupling of fluorine with either the arene protons in **15c** (**16c**) or the aromatic carbon atoms, and the more complex signal structure of the spirocyclic ketal in **16a**–**d**. The UV–vis spectra (available in the Supporting Information File 1) display the expected electronic transitions for quinoxaline derivatives [33-35], i.e., a prominent π,π^* transition with λ_{max} between 236–245 nm and a lower intensity n,π^* transition with λ_{max} between 312–316 nm with a poorly resolved vibrational structure. The spectra of the cyclohexadiene-derived scaffolds **15** and the cyclooctadiene-derived frameworks **16** are very similar. Within each series we could not observe a gradual blue-shift for the electronic transitions as the degree of fluorination increased from **15a** (**16a**) to **15c** (**16c**), a result that is in accord with Chou’s UV–vis data for differently substituted bis-quinoxaline scaffolds that abstain from clear trends as the electronic-withdrawing character of the substituents were altered [19]. The ESI-mass spectra (acetonitrile, acetic acid) of all new *syn*-bis-quinoxalines show the correct isotopic pattern of the protonated molecules and, interestingly, display mass clusters for the protonated "dimers" of compounds **15b** and **16b**. Nevertheless, any interpretation of the nature of these latter species (proton-bridged "dimer", protonated π-π–aggregate, protonated self-associated "dimer") requires further investigation and cannot be easily transferred to the solution- or solid-state structures of the neutral tweezer compounds [36].

Structures

We were able to grow single crystals of the octafluoro compound **16c** from acetonitrile or chloroform solutions suitable for X-ray structure determination (Table 1, Figure 1). In each case, the crystals contained residual ethyl acetate from the purification step, indicating strong binding of the ethyl acetate molecule inside the binding cleft of **16c**. Compound **16c** crystallizes, with an ethyl acetate solvent molecule, in the monoclinic system (space group: $P2_1/n$) and displays bond lengths and angles in the expected ranges. The ethyl acetate displays a small degree of orientation disorder (11.8%). Figure 1a shows a thermal ellipsoid image of **16c** and Figure 1b depicts the packing within a unit cell setting. The large binding pocket of *syn*-bis-quinoxaline **16c** provides enough space to allow the association with solvent (ethyl acetate) and, through "dimer formation", with the pincer sidewall of a second tweezer molecule. The "dimer" association of fluorinated molecular tweezers in the solid state has been observed for the acridine-derived scaffold **1** [15] and is quite common in many other molecular tweezer scaffolds [1-10]. Compound **16c** shows the typical orientation of fluorine substituents of one pincer sidewall over the arene subunit of another tweezer (substituent distances to arene plane: 3.283 Å, 3.315 Å), interpreted as the attractive interaction between fluorine substituents with the electron-depleted fluoroarene subunit [37,38]. The centroid-centroid distances (d_1, d_2) and the bite angle between the two quinoxaline sidewalls of the binding pocket in fluorinated framework **16c** differ only slightly from the parameters of the non-fluorinated compound **4a**, although the latter does not include any solvent in the cleft and, furthermore, lacks the interpenetrating self-association displayed in

Table 1: Crystallographic details for **16c** and related non-fluorinated compounds.

	16c	**4a** [19]	**3** [19]
crystal system	monoclinic	monoclinic	orthorhombic
space group	$P2_1/n$	$P2_1/c$	$Pbcn$
R [%]	3.79	3.16	3.70
d_1 [Å]^a	8.144	7.907	4.686
d_2 [Å]^a	10.004	9.641	4.135
bite angle [°]^b	46.68	45.03	−14.41

^{a}defined in Scheme 2.
^{b}a negative bite angle defines U- vs. V-shaped tweezers.

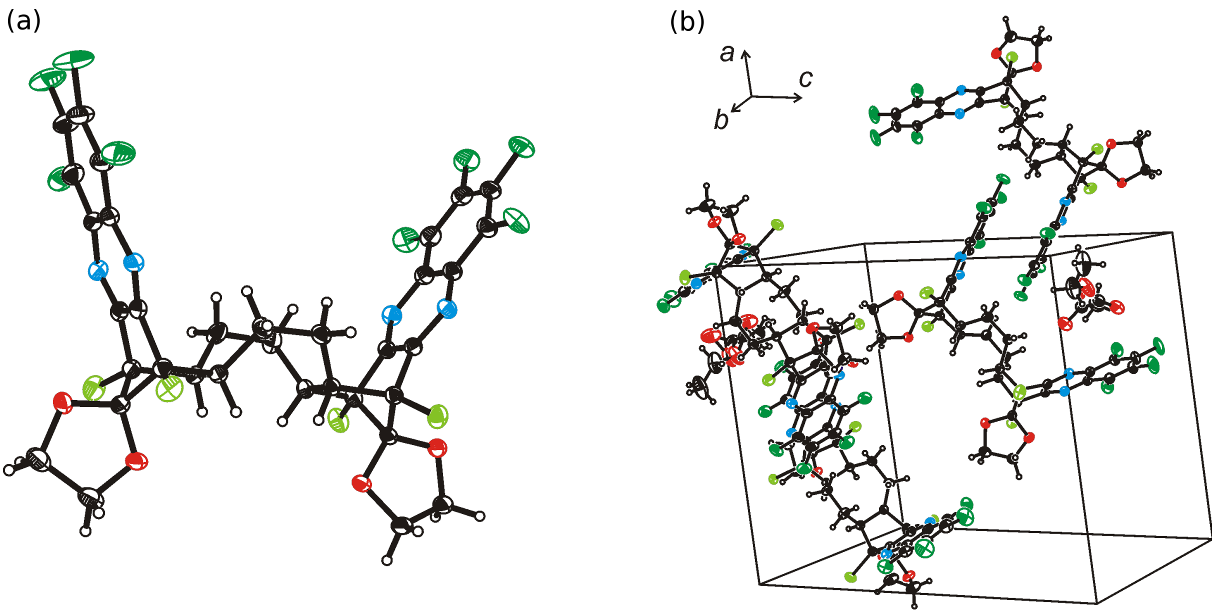
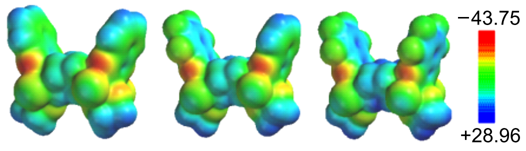


Figure 1: (a) Thermal ellipsoid image of the tweezer molecular **16c** in the structure **16c** · $CH_3CO_2C_2H_5$; thermal ellipsoids are drawn at the 50% probability level. (b) View of the packing of **16c** in the unit cell (two $CH_3CO_2C_2H_5$ molecules are omitted for clarity). [$C_{34}H_{20}Cl_4F_8N_4O_4$ · $CH_3CO_2C_2H_5$, MW = 930.44, monoclinic, space group $P2_1/n$, a = 15.3990(12) Å, b = 14.0635(11) Å, c = 17.7148(14) Å, β = 94.6470(10)°, V = 3823.8(5) Å^3, Z = 4, d_{calc} = 1.616 g cm^{-3}, T = 153(2) K, λ = 0.71073 Å, 44247 reflections measured, 9378 unique (R_{int} = 0.017), final R_1 [$I > 2\sigma(I)$] = 0.0343 and R_1 = 0.0403 (wR_2 = 0.0952) for all data; CCDC deposit # 786086.

16c [19]. Conversely, **4a** shows π-π–interaction of two adjacent molecules by stacking two pincer sidewalls, each from the outside (U···U geometry).

Host–Guest Chemistry

Although none of the reported cyclooctadiene-derived *syn*-bis-quinoxaline scaffolds [19] has been established as a molecular tweezer, the general architecture with two *syn*-oriented aromatic sidewalls and a large π-π–distance does allow the accommodation of guest compounds as demonstrated in the crystal structure of **16c**. Whilst most molecular tweezers have a typical cleft size of ca. 7 Å, several functional larger systems have been reported [39,40]. Figure 2 shows the electrostatic potential surfaces of compounds **16a**–**c**, depicting the inversion of the electrostatic potential in the pincer subunits upon increasing the degree of fluorination.



16a **16b** **16c**

Figure 2: Electrostatic potential surfaces of **16a–c** (Spartan 06 [41]: B3LYP/6-31G*//B3LYP/6-31G*; legend in kcal/mol).

NMR titration experiments with electron-rich arenes (1,4-dimethoxybenzene, 1,3,5-trimethoxybenzene, *N*,*N*-dimethylaniline, *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylenediamine) were carried out in deuterated methylene chloride solution for the four cyclooctadiene-derived species **16a**–**d**. Interestingly, only the octafluoro-derivative **16c** showed line-broadening of the ^{1}H resonances for one guest compound, i.e., *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylenediamine, at various host–guest ratios (Figure 3). No changes in chemical shift of the quinoxaline ^{19}F resonances were observed in the ^{19}F NMR spectra. Upon cooling the NMR samples the guest's aromatic and methyl ^{1}H resonances sharpened only to less broad signals. Titration of **16c** with other electron-rich aromatic guest compounds (1,4-dimethoxybenzene, 1,3,5-trimethoxybenzene, *N*,*N*-dimethylaniline) under the same conditions showed only the original host and guest resonances in the ^{1}H NMR spectra without any line broadening, which indicates that there was no interaction between these three molecules with the tweezer's cavity. It is important to note that from the entire series of compounds, only the highly fluorinated scaffold **16c** shows chemical exchange between the unbound and bound guest, *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylenediamine. While this facile exchange is certainly due to the large binding cleft, the effect of eight fluorine substituents on the electrostatic potential within the cleft is paramount in the facilitation of this interaction between host and guest.

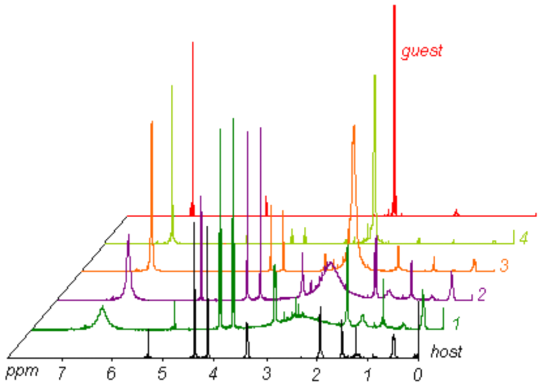


Figure 3: ^{1}H NMR spectra (CD_2Cl_2, 500 MHz) of **16c** (host [black]) upon titration with *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylenediamine (guest [red]); host concentration: 0.01M; host–guest ratio: 1:2 (1), 1:5 (2), 1:10 (3), 1:20 (4).

Korenaga and Sakai have already noted that *N*,*N*,*N′*,*N′*-tetramethyl-*p*-phenylendiamine displays a stronger association constant with molecular tweezer **1** when compared to several other electron-rich aromatic guest compounds. This behavior was explained by the large magnitude of the former guest's quadrupole moment [15].

With our preliminary NMR titrations we could demonstrate that scaffold **16** can indeed associate with an external guest compound in solution if the host and guest units are matched appropriately. Further experiments employing complementary analytical techniques, e.g., isothermal calorimetry, as well as additional investigations of the host–guest chemistry with suitable, larger guest compounds, will provide detailed thermodynamic parameters of the host–guest association, and possibly a better host–guest match, respectively.

Conclusion

The synthesis of fluorinated *syn*-bis-quinoxalines (**15b**–**c**, **16b**–**c**) was successfully accomplished by a three-step procedure, utilizing the new, readily isolable spirocyclic *syn*-derivative **9b** as an entry towards the larger cyclooctadiene-derived scaffold **16**. The crystal structure of **16c** clearly demonstrates that *syn*-bis-quinoxaline frameworks can function as molecular tweezers. Furthermore, preliminary NMR spectroscopic titration experiments with the octafluoro-*syn*-bis-quinoxaline **16c** prove the interaction of an external, electron-rich guest with the molecular tweezer's cavity in solution.

Supporting Information

Supporting Information File 1

Experimental details and characterization data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-39-S1.pdf]

Supporting Information File 2

Crystallographic data of *syn*-bis-quinoxaline **16c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-39-S2.pdf]

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Chemical aminoacylation of tRNAs with fluorinated amino acids for in vitro protein mutagenesis

Shijie Ye, Allison Ann Berger, Dominique Petzold, Oliver Reimann,
Benjamin Matt and Beate Koksch*

Preliminary Communication

Address:
Department of Biology, Chemistry and Pharmacy, Freie Universität Berlin, Institute of Chemistry and Biochemistry – Organic Chemistry, Takustrasse 3, 14195 Berlin, Germany; Tel.: 0049-30-83855344; Fax: 0049-30-83855644

Email:
Beate Koksch* - koksch@chemie.fu-berlin.de

* Corresponding author

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Abstract

This article describes the chemical aminoacylation of the yeast phenylalanine suppressor tRNA with a series of amino acids bearing fluorinated side chains via the hybrid dinucleotide pdCpA and ligation to the corresponding truncated tRNA species. Aminoacyl-tRNAs can be used to synthesize biologically relevant proteins which contain fluorinated amino acids at specific sites by means of a cell-free translation system. Such engineered proteins are expected to contribute to our understanding of discrete fluorines' interaction with canonical amino acids in a native protein environment and to enable the design of fluorinated proteins with arbitrary desired properties.

Introduction

Over the past two decades, the interest in engineering proteins containing site-specific synthetic amino acids with novel functionalities has grown considerably. The utility of chemically aminoacylated suppressor transfer RNAs (tRNAs) combined with cell-free translation systems in producing proteins that contain non-canonical amino acids was reported independently from each other by Schultz and Chamberlin [1,2]. Their methodology is based on the following observations: 1) the central intermediate molecule in protein translation, the aminoacyl-tRNA (aa-tRNA) produced in the cell by specific tRNA synthetases (aaRSs) can be semi-synthesized; 2) a nonsense codon TAG can replace an amino acid-encoding codon at a desired position and can be recognized by the corresponding mutated orthogonal suppressor tRNA during the translation (Figure 1).

The key intermediates in this methodology are the suppressor aminoacyl-tRNAs. Due to the great number of reactive groups

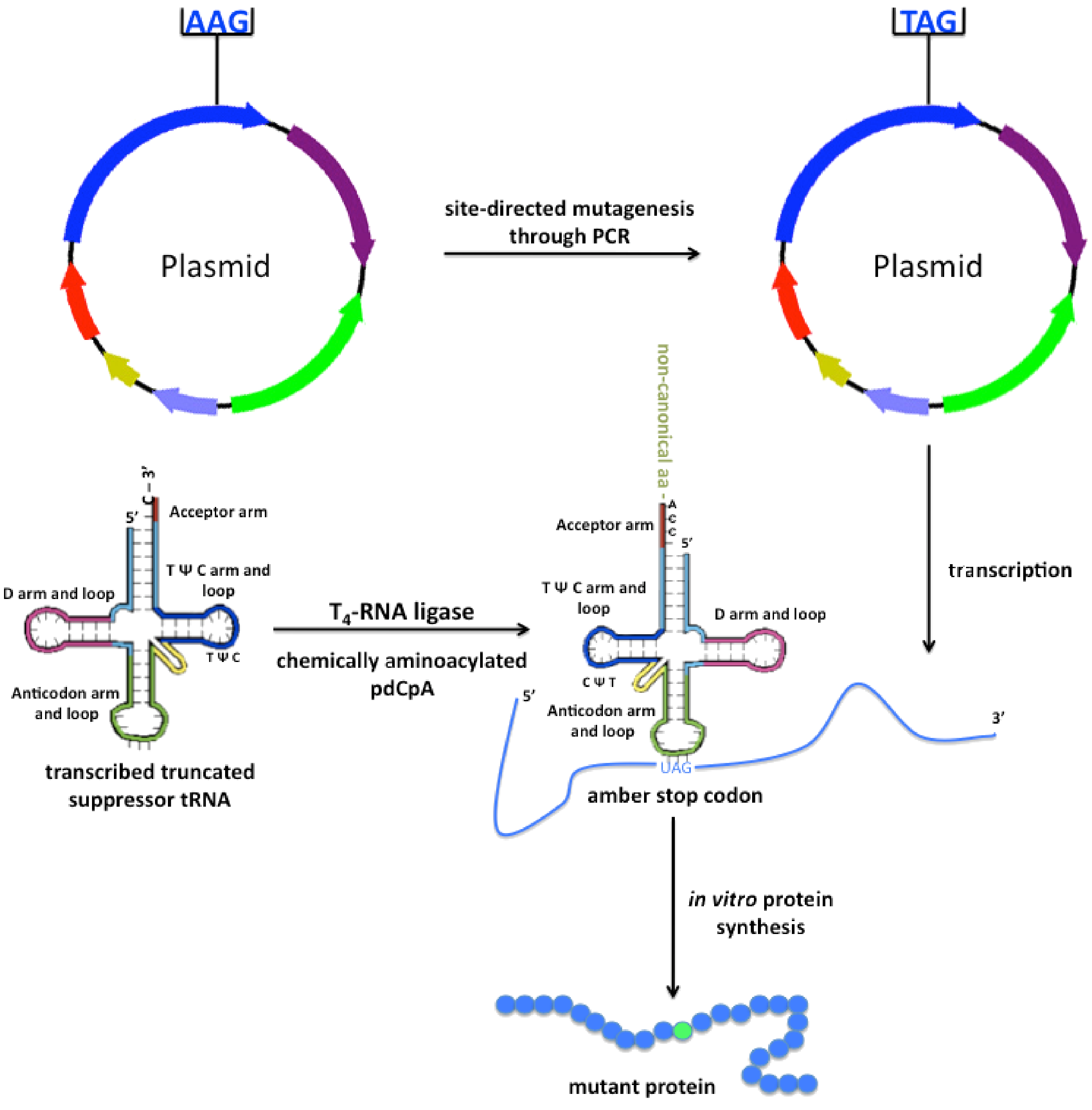


Figure 1: General strategy of using a chemically aminoacylated suppressor tRNA and an in vitro translation system to produce proteins which contain non-canonical amino acids (based on Noren et al. [1]). An amber stop codon, TAG, is introduced site-specifically into the protein-encoding gene, replacing an amino acid-encoding codon. The hybrid dinucleotide pdCpA is chemically aminoacylated with the non-canonical amino acid of interest and ligated to the appropriately truncated suppressor tRNA (tRNA-CA). Non-natural mutant proteins are produced by means of an in vitro protein synthesis system.

in the tRNA molecule, direct chemical acylation is not possible. Hecht and co-workers developed a procedure in which N^{α}-protected amino acids were used to chemically aminoacylate the dinucleotide pCpA. Subsequent enzymatic ligation to truncated tRNAs (without the 3′-terminal CA dinucleotide) yielded the desired AA-tRNAs [3]. More recently, this approach was optimized and the chemistry simplified by Schultz and co-workers. By using the hybrid dinucleotide pdCpA and activation of the amino acid as the cyanomethyl ester, selective coupling to the 2′- or 3′-hydroxyl group of the terminal adenosine was possible [4,5]. Since the N^{α}-aminoacyl moiety is not stable under the ligation conditions, the N^{α}-amino group of amino acid was either protected beforehand as the 6-nitroverastryloxycarbonyl (NVOC) derivative, a moiety which can be removed photochemically after the ligation, or left unprotected. However, in both cases low yields resulted. Lately, Hecht and co-workers reported the use of the *N*-(4-pentenoyl) protecting group as suitable for preparing a variety of misacylated tRNAs [6-9]. Removal of this group is achieved under mild chemical conditions by treatment with iodine solution; it has also been used in the preparation of caged proteins.

Fluorine is the most electronegative element and has a van der Waals radius of 1.47 Å [10]. Thus, substitution of a C–H bond with a C–F bond dramatically changes the electronic properties of the given molecule but exerts only a minor steric effect [11]. Due to the unique properties of the fluorine atom, the incorporation of amino acids which contain fluorinated side chains into peptides and proteins is becoming increasingly popular for the rational design of biopolymers and materials with novel biological properties. For example, certain fluorinated analogues of hydrophobic amino acids have been incorporated into the hydrophobic core of peptides, oligomers and proteins, leading to a significant increase in the thermal stability of the structure [12-15]. The introduction of fluoroalkyl groups into proteins can also enhance the hydrophobicity of the molecule, enabling better diffusion across the membranes [16]. Koksch and co-workers have developed a model peptide system based on the coiled-coil folding motif. They used it to show that the impact of fluorine substitution on structure and stability is strongly dependent on the position and the number of fluorine atoms within the peptide chain [17-19]. Finally, due to the high NMR sensitivity of fluorine, the incorporation of fluorinated amino acid analogues into proteins provides the opportunity for probing the structure and dynamics that play a role in protein–protein and protein–ligand interaction, and metabolic processes [20,21].

We report here the chemical and enzymatic aminoacylation of the yeast phenylalanine suppressor tRNA with a series of fluoroalkylated amino acids for site-specific protein mutagenesis (Figure 2). (*RS*)-2-amino-2-methyl-3,3,3-trifluoropropanoic acid (α-(Tfm)Ala) [22], (*S*)-ethylglycine (Abu) and two of its fluorinated analogues, (*S*)-2-amino-4,4-difluorobutanoic acid (DfeGly) [23] and (*S*)-2-amino-4,4,4-trifluorobutanoic acid (TfeGly) [24], were synthesized in the appropriate protected activated form and used to chemically aminoacylate $tRNA^{Phe}{}_{CUA}$ by means of the hybrid dinucleotide pdCpA and enzymatic ligation.

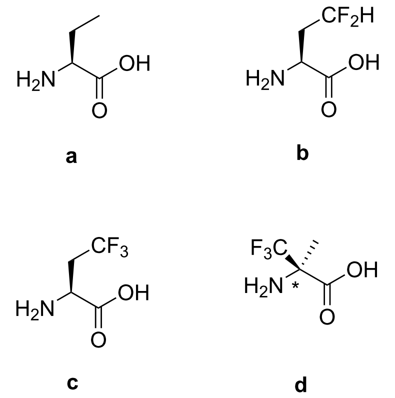


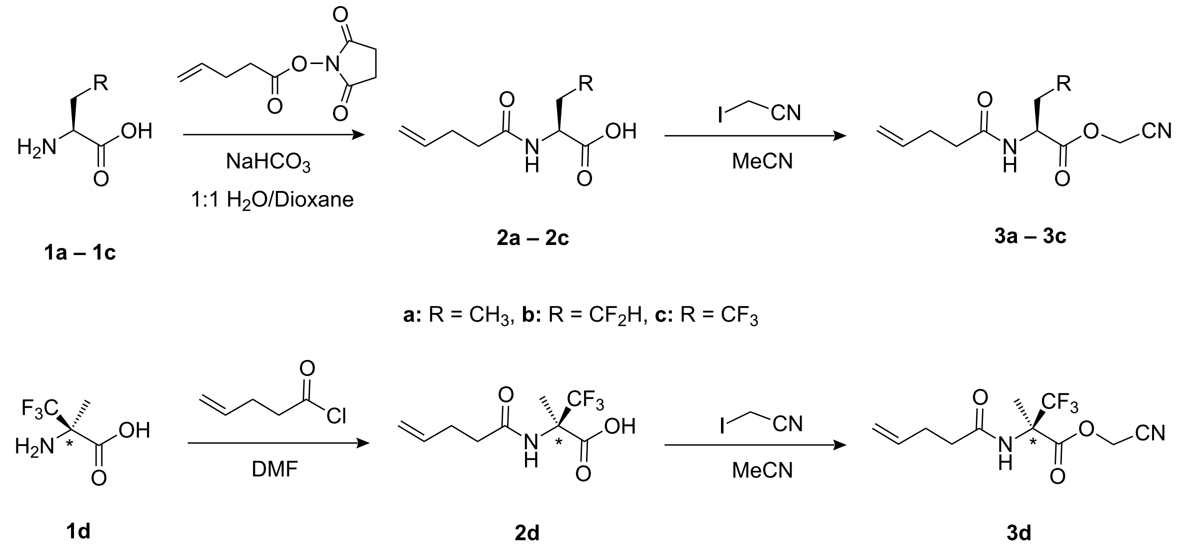
Figure 2: Structures of non-canonical amino acids. **a.** (*S*)-ethylglycine, **b.** (*S*)-2-amino-4,4-difluorobutanoic acid, **c.** (*S*)-2-amino-4,4,4-trifluorobutanoic acid, **d.** (*RS*)-2-amino-2-methyl-3,3,3-trifluoropropanoic acid.

Results and Discussion

Syntheses of *N*-(4-pentenoyl) amino acid cyanomethyl esters

The aminoacylation of a suppressor tRNA is the first step to incorporate non-canonical amino acids into proteins. Several strategies have been developed to accomplish this [4-7,25-27]. We chose a combination of chemical and enzymatic aminoacylation which relies on the hybrid dinucleotide pdCpA and the T4-RNA ligase-mediated coupling to it to give a truncated suppressor tRNA. The N^{α}-amino groups of the amino acids were protected with the 4-pentenoyl group and the amino acids were activated as their corresponding cyanomethyl esters (Scheme 1).

The *N*-(4-pentenoyl) protection of Abu and its fluorinated analogues DfeGly and TfeGly, and the preparation of their cyanomethyl esters were performed as described by Hecht and co-workers [7,9]. In the first step, the amino acid was treated with *N*-(4-pentenoyloxy)succinimide and in the second step treatment with iodoacetonitrile gave the desired compound in yields ranging from 59 to 81%. Due to the strong electron-withdrawing character of the C–F bond, the CF_3 substituent in the α-position in α-(Tfm)Ala influences considerably the reactivity of both the amino and carboxylic groups; there is also a steric effect in this case. The amino group of α-(Tfm)Ala is generally protected by treatment with highly reactive mixed anhydrides or acid chlorides [28]. Thus, the *N*-(4-pentenoyl)-α-(Tfm)Ala was synthesized by means of 4-pentenoyl chloride. We investigated the reaction both in pyridine and DMF as the solvent, in the case of DMF, 4-dimethylaminopyridine (DMAP) was added as base. Although, pyridine also behaves as a base (pK_a 5.21), higher yields were achieved with DMAP in DMF. The synthesis of *N*-(4-pentenoyl)-TfmAla cyanomethyl ester was achieved



Scheme 1: General scheme for the synthesis of an *N*-(4-pentenoyl) amino acid cyanomethyl ester.

in an overall yield of 22%. The syntheses of *N*-(4-pentenoyl) amino acid cyanomethyl esters are summarized in Table 1.

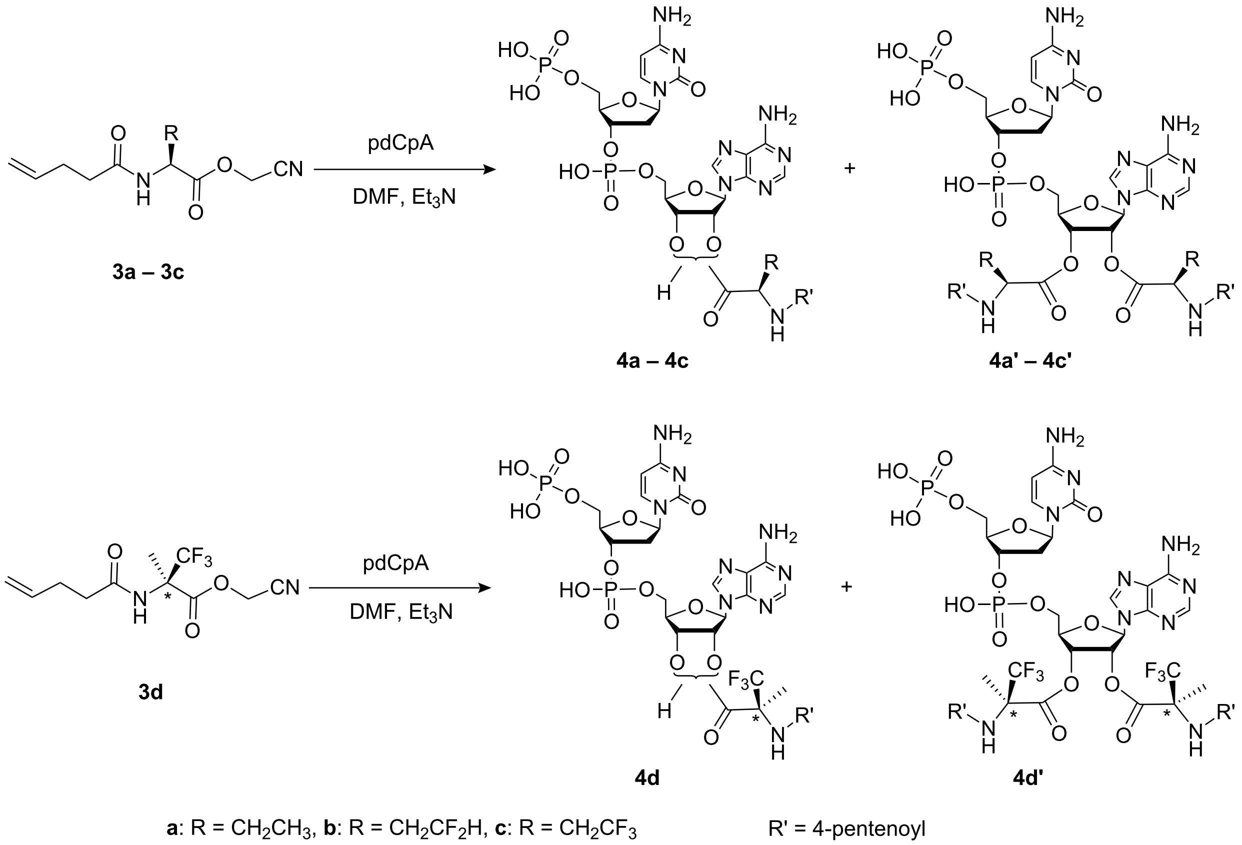
Syntheses of 2′(3′)-*O*-[*N*-(4-pentenoyl)aminoacyl]-tRNAs and bis-2′,3′-*O*-[*N*-(4-pentenoyl)aminoacyl]-tRNAs

Chemical aminoacylation of pdCpA [4] was carried out using an N-protected amino acid activated as cyanomethyl ester in anhydrous DMF, and gave yields ranging from 40 to 90% (Scheme 2). The tetra-*n*-butylammonium (TBA) counter-ion is required to increase the solubility of pdCpA in DMF. Schultz and co-workers have reported that a ratio of 1:10 of TBA-pdCpA:activated ester results in the highly selective mono-acylation of the 2′,3′-hydroxyl groups of the adenosine ribose ring [5]. However, due to the expense of fluorinated amino acid analogues, we performed the aminoacylation reaction using a ratio of 1:2 or 1:3 TBA-pdCpA:activated ester at 40 °C overnight. Both mono-acylated and bis-acylated products were detected and purified by HPLC in the cases of Abu, TfeGly, and α-(Tfm)Ala, whereas only the mono-acylated product of DfeGly was observed. In general, longer incubation times and higher temperatures resulted in higher yields and increased amounts of bis-acylated products. A systematic investigation by Hecht and co-workers showed that such tandem activated tRNAs can also participate efficiently in the prokaryotic- and eukaryotic-based cell-free translation system. Both activated amino acids present in bis-acylated tRNAs can be recognized by the ribosome and incorporated into proteins [29,30]. pdCpA bearing Abu or the fluorinated amino acid analogue were efficiently ligated to the truncated suppressor $\text{tRNA}^{\text{Phe}}{}_{\text{CUA}}$ by treatment with T4-RNA ligase and were analyzed using denatured acidic PAGE (Figure 3) [31]. Thus, both our mono- and bis-acylated tRNAs are suitable for in vitro protein mutagenesis.

Table 1: Syntheses of *N*-(4-pentenoyl) amino acid cyanomethyl esters.

	Yield of protection and activation (%)	^{19}F-NMR: δ (ppm)^a	Mass $(M+H)^+$ (*m/z*) (calculated)
Abu (**3a**)	81	—	225.1263 (224.1161)
DfeGly (**3b**)	59	−116.46 (tdd, 1F, *J* = 320.0 Hz, *J* = 58.6 Hz, *J* = 17.1 Hz), −115.70 (tdd, 1F, *J* = 320.0 Hz, *J* = 58.6 Hz, *J* = 17.1 Hz)	261.1045 (260.0972)
TfeGly (**3c**)	75	−62.98 (t, 3F, *J* = 9.8 Hz)	279.0929 (278.0878)
TfmAla (**3d**)	22	−76.227 (s, 3F)	279.0929 (278.0878)

[a] s: singlet, t: triplet (See Supporting Information File 1).



a: R = CH_2CH_3, **b**: R = CH_2CF_2H, **c**: R = CH_2CF_3 R' = 4-pentenoyl

Scheme 2: General scheme of synthesis of mono-2′(3′)-*O*-[*N*-(4-pentenoyl)aminoacyl]-pdCpAs and 2′-3′-bis-*O*-[*N*-(4-pentenoyl)aminoacyl]-pdCpAs.

Conclusion and Outlook

The efficient chemical and enzymatic synthesis of three novel fluorinated aminoacyl-pdCpAs and Abu-pdCpA and their corresponding charged tRNAs is reported. These aminoacyl-tRNAs can be used for site-specific protein mutagenesis in a cell-free protein synthesis system and will enable a systematic investigation of the structural and dynamic behavior of fluorine within a native protein environment.

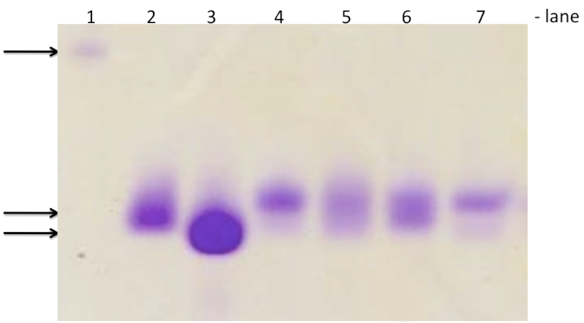


Figure 3: Denaturing PAGE of ligation products of truncated suppressor tRNA and fluorinated aminoacyl-pdCpAs and Abu-pdCpA. Lane 1: RNA Marker 100 bp, Lane 2: transcribed full-length $tRNA_{CUA}$, Lane 3: transcribed truncated $tRNA_{CUA}$-C_{OH}, Lane 4: Abu-$tRNA_{CUA}$, Lane 5: DfeGly-$tRNA_{CUA}$, Lane 6: TfeGly-$tRNA_{CUA}$, Lane 7: α-(Tfm)Ala-$tRNA_{CUA}$. Amino groups are *N*-(4-pentenoyl) protected. Visualized by using Stains-all (Sigma-Aldrich®).

Supporting Information

Supporting information features detailed information on experimental procedures and compound characterization.

Supporting Information File 1

Experimental procedures and compound characterization
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-40-S1.pdf]

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Prins fluorination cyclisations: Preparation of 4-fluoro-pyran and -piperidine heterocycles

Guillaume G. Launay, Alexandra M. Z. Slawin and David O'Hagan*

Full Research Paper

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Address:
School of Chemistry and Centre for Biomolecular Sciences, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, United Kingdom

Email:
David O'Hagan* - do1@st-andrews.ac.uk

* Corresponding author

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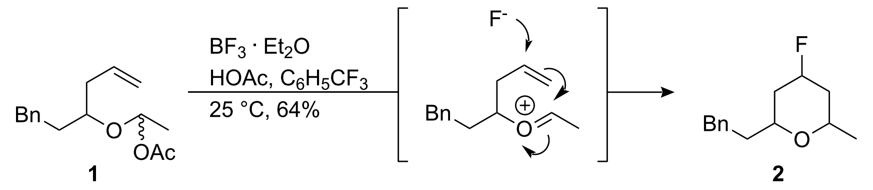
Abstract

The Prins reaction was investigated using $BF_3 \cdot OEt_2$ as a Lewis acid. It has been recently demonstrated, that if $BF_3 \cdot OEt_2$ is used in stoichiometric amounts then these reactions generate fluorinated products where the $BF_3 \cdot OEt_2$ contributes fluoride ion to quench the intermediate carbocations. In this study oxa- and aza-Prins reactions for the synthesis of 4-fluoro-pyrans and -piperidines were investigated. The products were obtained in good yields, but only with moderate diastereoselectivity. These Prins fluorination reactions can be accelerated under microwave conditions. The study extends the Prins fluorination methodology for the generation of the C–F bond in heterocycles.

Introduction

Selective incorporation of the C–F bond into organic molecules can impart useful and attractive properties to performance materials [1-3]. To this end there are a useful but relatively limited range of fluorination reagents and methodologies available to synthetic organic chemistry, and novel methods for introducing fluorine into organic molecules continue to be valuable [4]. In this paper we focus on extending the scope of the Prins fluorination reaction as a synthetic methodology. The Prins reaction is a well established strategy for the synthesis of pyrans [5-7]. This cyclisation reaction, which occurs between a homoallylic alcohol and an aldehyde, is generally promoted by a Lewis acid. When $BF_3 \cdot OEt_2$ is used as the Lewis acid, then fluoride ion from the reagent can become incorporated into the product generating a C–F bond and a new stereogenic centre. Liberation of fluoride ion from $BF_3 \cdot OEt_2$ has, for example, been observed in epoxide ring opening reactions [8,9]. This was first recognised in a Prins reaction as an unexpected side reaction by Al-Mutairi et al. [10,11] and was noted separately by Jaber et al. [12] and subsequently by Kataoka et al. [13]. For example, homoallylic alcohol **1** was converted to pyran **2** with a high diastereoselectivity (Scheme 1) [12]. Most recently, oxa-, aza- and thia-Prins fluorination cyclisations have been carried out using ionic liquid hydrogen fluoride salts ($Et_4NF \cdot 5HF$) as the reaction medium, without the requirement for $BF_3 \cdot OEt_2$

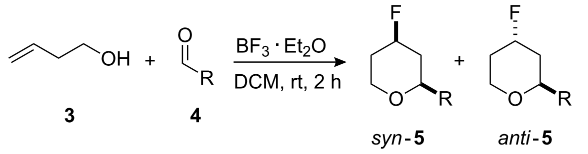


Scheme 1: The C–F bond forming Prins reaction leading to 4-fluoropyrans [10].

[14,15]. These reactions with fluoride follow from the much more commonly observed Prins reactions of halides ($\mathrm{Cl^-}$, $\mathrm{Br^-}$ and $\mathrm{I^-}$) other than fluoride in the quenching of the intermediate oxonium intermediate [16-22].

We have explored C–F bond formation by the $\mathrm{BF_3{\cdot}OEt_2}$/Prins reaction further. In this paper we report that a wide range of 4-fluorotetrahydropyrans can be prepared by reaction of homoallylic alcohols with different aldehydes with $\mathrm{BF_3{\cdot}OEt_2}$ as the fluoride source. This Prins methodology was extended to the aza-Prins reaction using *N*-tosyl-homoallylic amines to generate the corresponding 4-fluoropyrrolidines. In general, these reactions leading to both the 4-fluorotetrahydropyrans and 4-fluoropyrrolidines occur with good to high conversions, however the diastereoselectivities are modest, particularly in the aza-Prins cases. This study also demonstrates that the conversions and reaction times can be improved using microwave conditions.

Table 1: Prins fluorination reaction of homoallylic alcohol (**3**) with various aldehydes **4** giving substituted fluoropyrans **5**. Reaction conditions: $\mathrm{BF_3{\cdot}OEt_2}$ (1 equiv), but-3-en-1-ol (1 equiv), aldehyde (1 equiv), DCM, rt, 2 h.



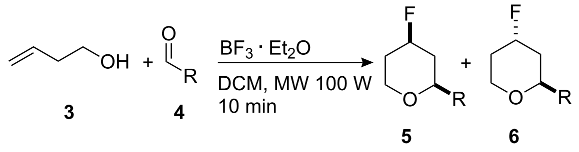
pyran	aldehyde	conversion	d.r. (*syn/anti*)
5a	4-nitrobenzaldehyde	67%	1.9/1
5b	2-fluorobenzaldehyde	66%	4.5/1
5c	3-fluorobenzaldehyde	66%	3.4/1
5d	4-fluorobenzaldehyde	66%	4.5/1
5e	2-bromobenzaldehyde	65%	5.4/1
5f	3-bromobenzaldehyde	73%	3.8/1
5g	4-bromobenzaldehyde	90%	4.8/1
5h	2-methoxybenzaldehyde	<5%	1.3/1
5i	4-methoxybenzaldehyde	20%	2.4/1
5j	2,3,6-trimethoxybenzaldehyde	no reaction	/
5k	hexanal	76%	2/1
5l	2-methylcinnamaldehyde	<5%	/

Results and Discussion

The oxa-Prins fluorination reaction: Oxa-Prins fluorination reactions were investigated with but-3-en-1-ol (**3**) and a range of substituted benzaldehydes **4**. Electron withdrawing groups on the aromatic ring led to the more efficient reactions (Table 1, entries a–g) to generate 4-fluoropyrans **5** with conversions of 65–73%. Diastereoselectivities were however, modest with d.r's of between 1.9 : 1 and 5.4 : 1. With electron donating groups on the aromatic ring (Table 1, entries h–j), the reactions were inefficient and conversions dropped dramatically. The saturated aliphatic aldehyde, hexanal (entry k), resulted in a good conversion, although the corresponding 4-fluoropyran products were obtained with poor diastereoselectivity (2 : 1). In the case of 2-methylcinnamaldehyde (entry l), the conversion was poor.

Microwave – oxa-Prins: The Prins fluorination reactions were then investigated under microwave conditions (Table 2 and Scheme 3). Reaction times were significantly reduced to 10 min and, in general, the conversions were higher than under the more classical conditions. The diastereoselectivity appears to decrease a little, and in some cases there is an inversion in the major diastereoisomer, e.g., with 4-methoxybenzaldehyde.

Table 2: Prins fluorination microwave (100 W, 50 °C, 10 min) reactions using homoallylic alcohol (**3**), an aldehyde and $\mathrm{BF_3{\cdot}OEt_2}$ in DCM.



entry	aldehyde	d.r. (**5**/**6**)	conversion
5a	4-nitrobenzaldehyde	1.5/1	53%
5e	2-bromobenzaldehyde	3/1	92%
5f	3-bromobenzaldehyde	1.8/1	93%
5g	4-bromobenzaldehyde	2.3/1	83%
5i	4-methoxybenzaldehyde	1/1.2	41%
5k	hexanal	1.8/1	91%
5m	benzaldehyde	3.4/1	66%

A series of low temperature studies was carried out in an attempt to improve the diastereoselectivity. When the temperature was lowered to −20 °C (Table 3) the diastereoselectivity increased from ~2/1 to 10/1 and generally in good yields, but with a significant increase in the reaction time. Lowering the temperature below −20 °C did not lead to a significant improvement.

Table 3: Prins fluorination reaction with alcohol **3** and aldehydes at −20 °C. Reaction conditions: $BF_3{\cdot}OEt_2$ (1 equiv), but-3-en-1-ol (**3**) (1 equiv), aldehyde (1 equiv), DCM, −20 °C, 5 h.

entry	aldehyde	d.r. (**5**/**6**)	conversion
5a	4-nitrobenzaldehyde	10/1	61%
5k	hexanal	10/1	66%
5m	benzaldehyde	10/1	59%

In order to confirm the configuration of the major diastereoisomer, an X-ray structure analysis was carried out on the major diastereoisomer produced in the low temperature reaction between alcohol **3** and 4-nitrobenzaldehyde. The X-ray confirmed that the major diastereoisomer is *syn*-**5a** as shown in Figure 1.

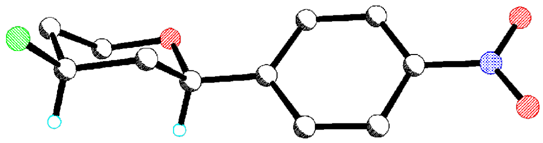
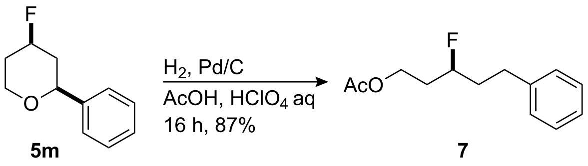


Figure 1: X-ray crystal structure of *syn*-**5a**.

In order to elaborate one of the Prins fluorination products, pyran **5m** was subjected to hydrogenolysis [23] as illustrated in Scheme 2. This resulted in the efficient conversion to the corresponding open chain compound 3-fluoro-5-phenylpentyl acetate (**7**).

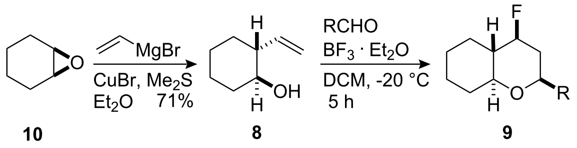


Scheme 2: Ring opening hydrogenation of an oxa-Prins product.

The structural diversity of the Prins fluorination reaction was extended using 2-vinylcyclohexan-ol (**8**) as a substrate. Vinylcyclohexanol **8** was prepared by treatment of cyclohexene oxide (**10**) with vinylmagnesium bromide in the presence of CuBr/DMSO as illustrated in Table 4 [24]. This gave a single diastereoisomer of **8** which was used in the Prins fluorination reactions.

Prins fluorination reactions, at −20 °C, with cyclohexanol **8** using benzaldehyde and 4-nitrobenzaldehyde gave rise to the corresponding bicyclic products **9** with good diastereoselectivity (10/1) and in moderate yields (Table 4).

Table 4: Prins reactions using vinylcyclohexanol **8** and an aldehyde at −20 °C. Reaction conditions: $BF_3{\cdot}OEt_2$ (1 equiv), 2-vinylcyclohexanol (**8**) (1 equiv), aldehyde (1 equiv), DCM, −20 °C, 5 h.



	aldehyde	*syn/anti*	yield of *syn*-**9**
9a	benzaldehyde	10/1	59%
9b	4-nitrobenzaldehyde	10/1	57%

The X-ray crystal structure of the predominant bicyclic diastereoisomer was determined and the *syn*-stereoisomer **9b**, as shown in Figure 2, was confirmed as the major product of this Prins reaction.

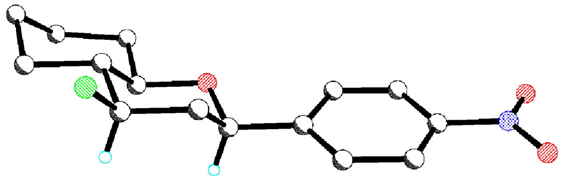
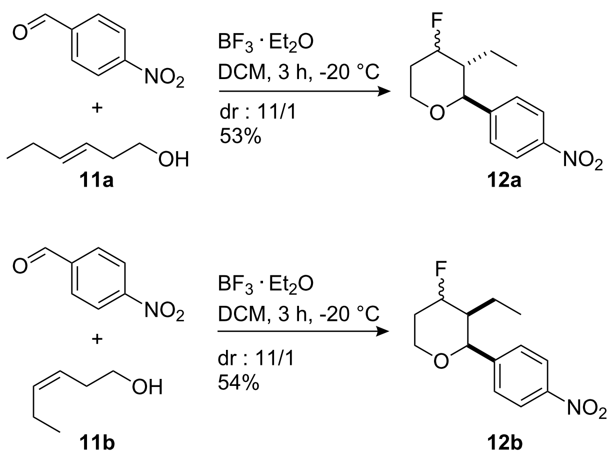


Figure 2: X-ray crystal structure of the major bicyclic tetrahydropyran diastereoisomer **9b**.

It is interesting to note that when (*E*)- and (*Z*)-hex-3-en-1-ol (**11a**) and (**11b**) were used as substrates, the double bond stereochemistry is retained. Only two diastereoisomers were observed in the products, differing only in the orientation of the fluorine. In general, these reactions gave good diastereoselectivities in moderate to good yields (Scheme 3).

Aza-Prins fluorination reaction

The aza-Prins reaction is less well known but has been exploited, e.g., in tandem reactions in alkaloid synthesis [25,26]. Recently, it has been used to incorporate a halogen atom at the 4 position of a piperidine ring as reported by Carballo et al. [16], and most recently an example incorporating fluorine at the 4-position of a piperidine using $Et_4NF{\cdot}5HF$



Scheme 3: Reaction using (*E*)-**11a** and (*Z*)-**11b** hex-3-en-1-ols with 4-nitrobenzaldehyde to generate 4-fluorotetrahydropyrans **12**.

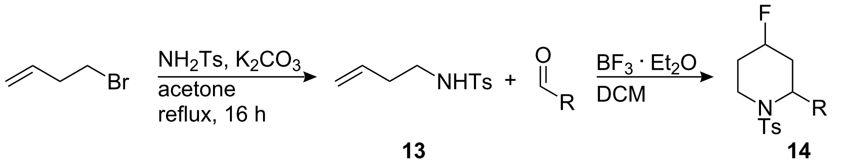
has been reported [14,15]. We have extended this study to explore more fully the aza-Prins fluorination reaction of homoallylamine **13**. Several amine protecting groups such as benzoyl and Boc were examined, but only the *N*-tosyl homoallylamine **13** proved to be a useful substrate as illustrated in Table 5. The tosylamine **13** was prepared (41% yield) by the reaction of 1-bromobut-3-ene with *N*-tosylamine in the presence of potassium carbonate. The yields and diastereoselectivity of the aza-Prins reactions with a variety of aldehydes were comparable to the oxa-Prins reactions, but longer reaction times were required (typically 36 h). The reactions are summarised in Table 5. In contrast to the oxa-Prins reactions, lowering the temperature of the reaction had no measurable influence on the diastereoselectivity (Table 5, entry 4a).

All the aldehydes used in the study (Table 5) gave universally poor diastereoselectivities, however the conversions were generally good except in the case of where a relatively strong electron donating group was present on the aromatic ring (e.g. **14h**, Table 5). There was no reaction with the α,β-unsaturated aldehyde, 2-methylcinnamaldehyde (**14i**). In the case of aliphatic aldehydes (**14b**, **14j**, **14k**), the conversions were high, but again the diastereoselectivity was poor.

Microwave – aza-Prins: Following the observation of reduced reaction times in the oxa-Prins under microwave conditions, it was of interest to investigate the aza-Prins fluorination reaction under microwave conditions, particularly as these reactions were much slower.

In the event, the microwave reactions proved to be very efficient giving products with improved conversions after 30 min as shown in Table 6. Despite this improvement in rate, there was no significant improvement in the diastereoselectivity of the reaction products. This should be contrasted with the study using an HF containing ionic liquid ($Et_4NF·5HF$) in place of $BF_3·OEt_2$, where diastereoselectivities for similar aza-Prins reactions where around 7:1 to 10:1 in favour of the *syn*-products [14,15].

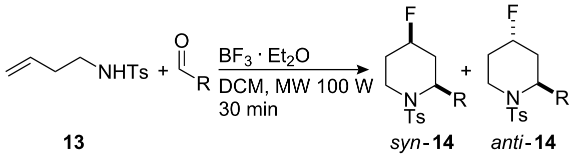
Table 5: Aza-Prins reaction between *N*-homoallyl-*N*-tosylamine (**13**) and aldehydes **14** in the presence of $BF_3·OEt_2$. Reaction conditions (except entry 2): Amine **13** (1 equiv), aldehyde (1 equiv), $BF_3·OEt_2$ for 36 h at rt; yield refers to the isolation of both stereoisomers in each case except for entry **14j** and **14k** where the yields refer to the isolation of diastereoisomer mixture.



entry	aldehyde	(*syn/anti* **14**)	conversion
14a	4-nitrobenzaldehyde	1/1	65%
14a[a]	4-nitrobenzaldehyde	1/1	71%
14b	hexanal	2/1	75%
14c	4-bromobenzaldehyde	1/1	71%
14d	3-bromobenzaldehyde	2/1	61%
14e	2-bromobenzaldehyde	1/1.6	50%
14f	4-fluorobenzaldehyde	1.8/1	70%
14g	3-fluorobenzaldehyde	2/1	67%
14h	4-methoxybenzaldehyde	2.5/1	23%
14i	2-methylcinnamaldehyde	no reaction	–
14j	acetaldehyde	1/1	73%
14k	isobutyraldehyde	1/1	82%

[a] Low temperature reaction (−20 °C, 48 h)

Table 6: aza-Prins reaction under microwave conditions. Reaction conditions: amine **13** (1 equiv), aldehyde (1 equiv), $BF_3{\cdot}OEt_2$, microwave 100 W, 50 °C, 30 min.



entry	aldehyde	*syn/anti*	conversion
14a	4-nitrobenzaldehyde	1.3/1	61%
14b	hexanal	1.9/1	83%
14c	4-bromobenzaldehyde	1.9/1	68%
14f	4-fluorobenzaldehyde	1.5/1	63%
14i	acetaldehyde	1.2/1	77%
14k	isobutyraldehyde	1.9/1	83%

The crystal structure of the minor *anti*-diastereoisomer of the piperidine product **14d** was determined and is shown in Figure 3.

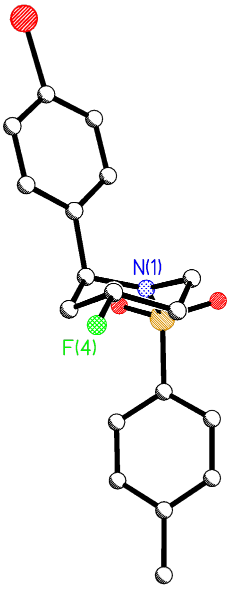


Figure 3: X-ray crystal structure of the minor *anti*-piperidine product **14d**.

Conclusion

Selective methods for fluorination are finding increasing utility in pharmaceutical, agrochemicals and fine chemicals research. The $BF_3{\cdot}OEt$ mediated oxa- and aza-Prins fluorination extends the methodologies available for the synthesis of C–F bonds, particularly concomitant with *O*- and *N*-heterocycle assembly. In general the diastereoselectivities are poor in these reactions, however they can be improved in the oxa-Prins case by lowering the temperature of the reactions to −20 °C. Both these oxa- and aza-Prins reactions can be significantly accelerated under microwave conditions.

Supporting Information

Supporting Information File 1

Experimental and characterisation details of synthesised compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-41-S1.pdf]

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9,10-Dioxa-1,2-diaza-anthracene derivatives from tetrafluoropyridazine

Graham Pattison[1], Graham Sandford[*1], Dmitrii S. Yufit[2],
Judith A. K. Howard[2], John A. Christopher[3] and David D. Miller[3]

Full Research Paper

Address:
[1]Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, United Kingdom, [2]Chemical Crystallography Group, Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, U.K. and [3]GlaxoSmithKline R&D, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom

Email:
Graham Sandford* - Graham.Sandford@durham.ac.uk

* Corresponding author

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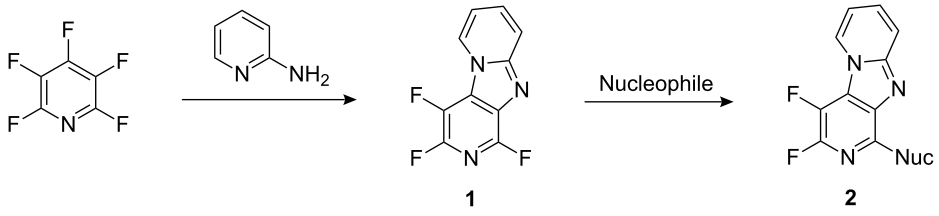
Abstract

Reaction of tetrafluoropyridazine with catechol gives a tricyclic 9,10-dioxa-1,2-diaza-anthracene system by a sequential nucleophilic aromatic substitution ring annelation process, further extending the use of perfluoroheteroaromatic derivatives for the synthesis of unusual polyfunctional heterocyclic architectures. The tricyclic scaffold reacts with amines and sodium ethoxide providing a short series of functional 9,10-dioxa-1,2-diaza-anthracene systems.

Introduction

Drug discovery programmes are continually searching for viable synthetic routes to highly novel classes of heterocyclic compounds with the aim of exploring chemical 'drug-like' space [1] and uncovering valuable biological activity for hit-to-lead generation of new chemical entities by parallel synthesis techniques. The wide variety of relatively simple heterocyclic structural types that have not been synthesised [2], the relatively low level of structural diversity in all known organic structures [3] and, indeed, the perceived lack of structural diversity in pharmaceutical companies' compound collections have often been suggested to be among the bottlenecks in drug discovery programmes [4]. Methodology for the ready synthesis of new organic frameworks is still required and, in this context, heterocyclic scaffolds based on novel molecular archi-



Scheme 1: Synthesis of novel tricyclic heterocycles from pentafluoropyridine.

tecture that bear multiple functionality and can be rapidly processed into many analogues by parallel synthesis are particularly valuable [5,6].

In a continuing research programme, we have demonstrated that perfluorinated heteroaromatic derivatives are very useful starting scaffolds for the synthesis of a variety of heteroaromatic [7], [5,6] and [6,6]-bicyclic [8-11], and polycyclic heterocyclic systems [12]. Perfluoroheteroaromatic derivatives are either commercially available or can be accessed by halogen-exchange processes by reaction of the corresponding perchloroheteroaromatic system and potassium fluoride [13]. No special techniques for handling perfluoroheteroaromatic compounds are required, apart from the usual laboratory precautions, because these systems are generally volatile, colourless liquids. We established that highly novel tricyclic scaffolds, such as the relatively uncommon dipyrido[1,2-*a*:3′,4′-*d*]imidazole system **1**, could be synthesised from pentafluoropyridine in a single step [12], exemplifying our general strategy for the synthesis of highly novel classes of polyfunctional heterocyclic compounds. Several dipyrido[1,2-*a*:3′,4′-*d*]imidazole analogues **2** were prepared by the displacement of the remaining ring fluorine atoms by nucleophilic aromatic substitution processes (Scheme 1).

We were interested in further expanding the use of highly fluorinated heterocycles for the preparation of novel heterocyclic structures and focussed upon the synthesis of ring fused systems that could be derived from the reaction of tetrafluoropyridazine (**3**) with catechol (**4**). In principle, two possible systems **5** and **6** may be formed depending upon the regioselectivity of the nucleophilic aromatic substitution processes (Scheme 2).

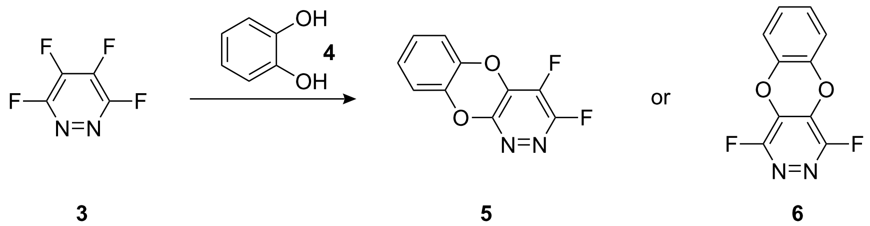
Both **5** and **6** have ring fluorine atoms present that may, in principle, be displaced by nucleophiles which could lead to the synthesis of many analogues of these systems. The dioxa-1,2-diaza-anthracene (or 3,4-difluorobenzo[5,6][1,4]dioxino[2,3-*c*]pyridazine also referred to as benzodioxinopyridazine) systems are very rare heterocyclic structures and only a handful of analogues based upon this molecular skeleton have been synthesised, mainly by the reaction of chlorinated pyridazines with catechol [14-16].

In this paper, we describe the synthesis of dioxa-1,2-diaza-anthracene derivatives by the sequential reaction of commercially available tetrafluoropyridazine with catechol, and a short series of nucleophiles.

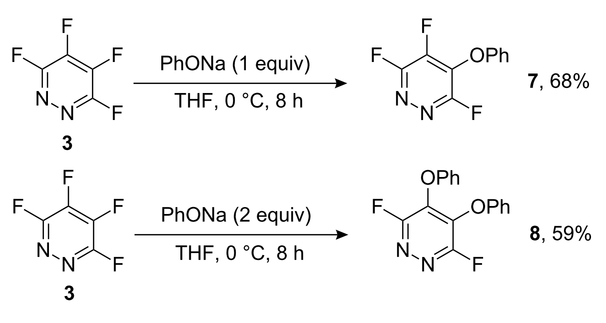
Results and Discussion

Initially, we carried out reactions of tetrafluoropyridazine (**3**) with one and two equivalents of sodium phenoxide as a model substrate for catechol (Scheme 3).

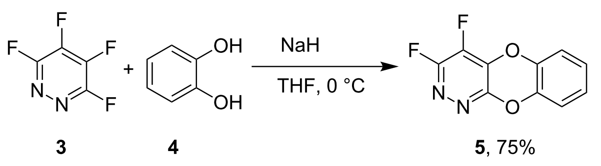
Reaction of one equivalent of sodium phenoxide with (**3**) gave product **7** arising from substitution of fluorine located at the site *para* to activating ring nitrogen, consistent with earlier studies involving reactions between tetrafluoropyridazine and various nucleophiles [13]. Similarly, reaction of two equivalents of



Scheme 2: Synthetic route to dioxa-diaza-anthracene derivatives.



Scheme 3: Reactions of tetrafluoropyridazine **3** with sodium phenoxide.



Scheme 4: Synthesis of dioxa-1,2-diaza-anthracene scaffold **5**.

sodium phenoxide gave the 4,5-diphenoxy derivative **8** by displacement of both fluorine atoms that are attached to the sites *para* to ring nitrogen atoms.

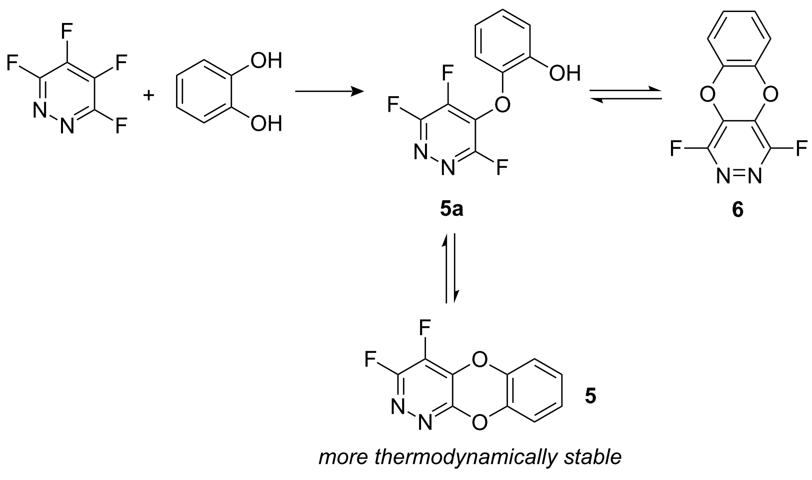
In contrast, however, reaction of catechol (**4**) with tetrafluoropyridazine (**3**) under similar reaction conditions gave the tricyclic system **5** arising from displacement of the 3- and 4-fluorine atoms as the sole product according to a ^{19}F NMR analysis of the crude reaction mixture (Scheme 4). The ^{19}F NMR displays two resonances at −96.4 and −151.9 ppm in accord with structure **5**, whereas if the symmetrical 4,5-disubstituted product **6** had been formed only one resonance in the ^{19}F NMR spectrum at ca. −88 ppm (cf. **8**) would have been observed.

It seems reasonable to assume that initial substitution occurs at the 4-position of **3**, analogous to the reaction between **3** and phenoxide, to give intermediate **5a**. At this point, we would expect cyclisation to occur at position 5 to give product **6**, again by analogy to the outcome of reaction between **3** and excess phenoxide. However, since nucleophilic aromatic substitution reactions are frequently reversible [13], conversion of **6** must occur via intermediate **5a** and lead to the most thermodynamically stable product **5** (Scheme 5).

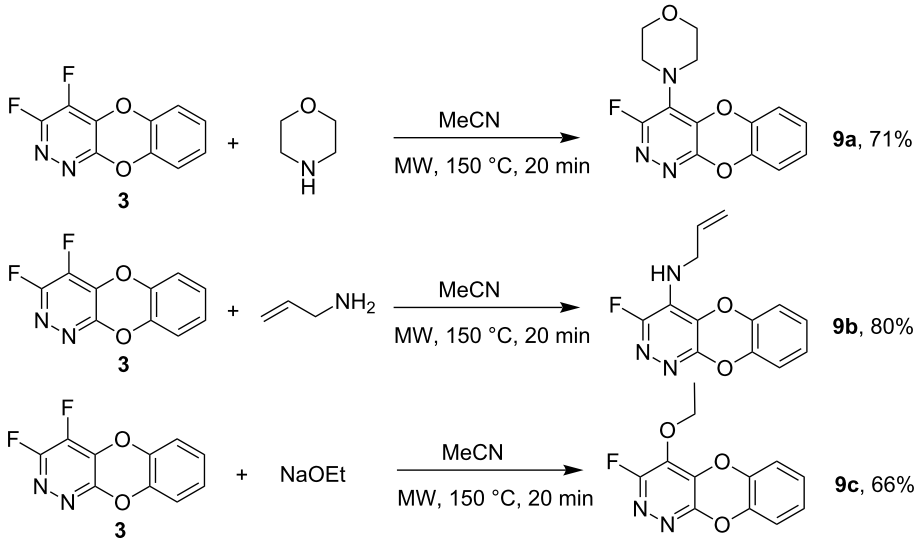
The utility of the dioxa-1,2-diaza-anthracene system **5** as a scaffold for array synthesis was assessed in representative reactions with a short series of nucleophiles (Scheme 6).

Nucleophilic substitution of fluorine at the 4-position occurs regiospecifically to afford products **9a–c** according to ^{19}F NMR analysis of the corresponding reaction mixtures. The ^{19}F NMR resonances located at ca. −90 ppm are characteristic of fluorine atoms located at sites *ortho* to a ring nitrogen atom. X-ray crystallography of the allylamino derivative **9b** (Figure 1), and a comparison of NMR spectral data, confirms the structures of these analogues.

The geometrical parameters of the molecule **9b** are close to expected values. The molecules of **9b** in the crystal are linked together by N–H···N hydrogen bonds in chains, parallel to the [101] direction and $\pi\cdots\pi$ stacking interactions (shortest interatomic distance C5···C3 is 3.336 Å), and short C–H···O



Scheme 5: Mechanism of formation of **5**.



Scheme 6: Reactions of dioxa-1,2-diaza-anthracene scaffold **5** with nucleophiles.

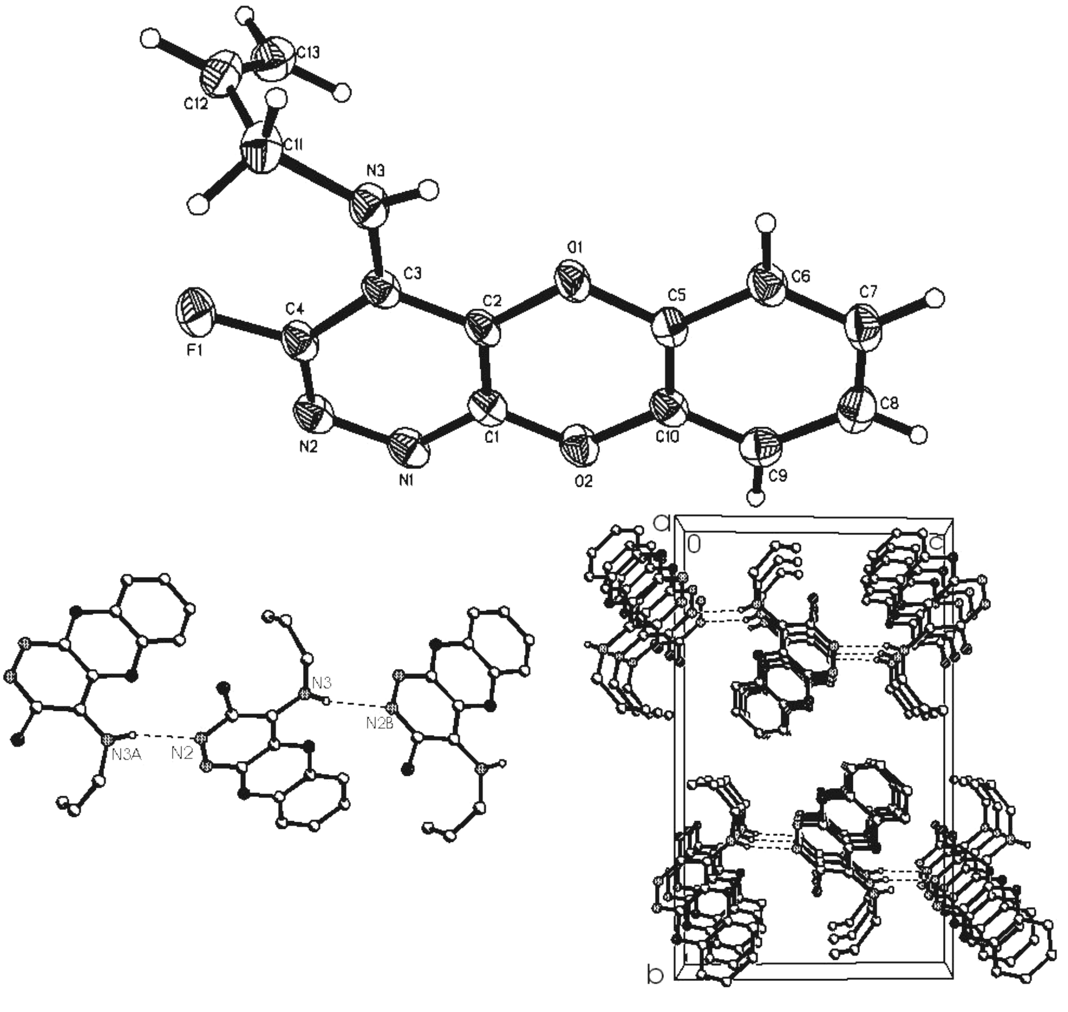


Figure 1: Molecular structure of 4-allylamino-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (**9b**).

contacts (C···O 3.387 Å) bind adjacent chains in the [100] and [010] directions, respectively.

Again, the regiospecificity of these reaction processes occurs because of the activating effect of ring nitrogen directly opposite the site of nucleophilic substitution.

Conclusions

A small range of dioxa-1,2-diaza-anthracene analogues **5** and **9** have been synthesised from tetrafluoropyridazine in two efficient steps, further expanding the application of highly fluorinated heterocycles for the synthesis of rare heterocyclic architectures.

Experimental

Synthetic procedures for the preparation of all the new compounds described in this paper are given below.

Reactions of tetrafluoropyridazine (**3**) with sodium phenoxide

3,4,6-Trifluoro-5-phenoxypyridazine (**7**)

Phenol (0.17 g, 1.81 mmol) was dissolved in THF (20 mL) and added to sodium hydride (0.07 g, 1.8 mmol, 60% dispersion in mineral oil) which was cooled to 0 °C and stirred. Tetrafluoropyridazine (**3**) (0.25 g, 1.64 mmol) was added slowly and the mixture stirred at 0 °C for 8 h. The solvent was evaporated and the crude material partitioned between dichloromethane (25 mL) and water (25 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 25 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated in vacuo to provide a crude yellow material. Column chromatography on silica gel using hexane:ethyl acetate (4:1) as elutant gave 3,4,6-trifluoro-5-phenoxypyridazine (**7**) (0.25 g, 68%) as a colourless oil; Anal. Calcd for $C_{10}H_5F_3N_2O$: C, 53.1; H, 2.2; N, 12.4%. Found: C, 53.2; H, 2.5; N, 12.2. ^{1}H NMR (200 MHz, $CDCl_3$, δ_H): 7.04–7.42 (5H, m, ArH); ^{19}F NMR (188 MHz, $CDCl_3$, δ_F): −86.2 (1F, dd, $^5J_{FF}$ = 31.2 Hz, $^4J_{FF}$ = 23.7 Hz, F-6), −94.5 (1F, dd, $^5J_{FF}$ = 31.2 Hz, $^3J_{FF}$ = 23.7 Hz, F-3), −140.4 (1F, dd, $^3J_{FF}$ = 23.7 Hz, $^4J_{FF}$ = 23.7 Hz, F-4); MS (ES$^+$) *m/z*: 227 ([MH]$^+$, 100%).

3,6-Difluoro-4,5-diphenoxypyridazine (**8**)

Using the procedure described above, phenol (0.32 g, 3.45 mmol), sodium hydride (0.138 g, 3.45 mmol, 60% dispersion in mineral oil), tetrafluoropyridazine (0.25 g, 1.64 mmol) and THF (20 mL) gave 3,6-difluoro-4,5-diphenoxypyridazine (**8**) (0.29 g, 59%) as a white solid; mp 123–124 °C; Anal. Calcd for $C_{16}H_{10}F_2N_2O_2$: C, 64.0; H, 3.4; N, 9.3%. Found: C, 63.7; H, 3.5; N, 9.2. ^{1}H NMR (700 MHz, $CDCl_3$, δ_H): 6.80 (2H, d, $^3J_{HH}$ = 7.7, H-2′), 7.09 (1H, t, $^3J_{HH}$ = 7.7, H-4′), 7.23 (2H, t, $^3J_{HH}$ = 7.7, H-3′); ^{13}C NMR (175 MHz, $CDCl_3$, δ_C): 116.4 (s, C-2′), 124.9 (s, C-4′), 129.7 (s, C-3′), 137.2 (dd, $^2J_{CF}$ = 20.6, $^3J_{CF}$ = 12.9, C-4), 155.2 (s, C-1′), 160.1 (dd, $^1J_{CF}$ = 251.2, $^4J_{CF}$ = 6.8, C-3); ^{19}F NMR (658 MHz, $CDCl_3$ δ_F): −88.2 (s); MS (ES$^+$) *m/z*: 301 ([MH]$^+$, 100%).

Synthesis of 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**)

Catechol (0.80 g, 7.2 mmol) was dissolved in THF (20 mL) at 0 °C under an argon atmosphere with stirring and added to sodium hydride (0.35 g, 14.5 mmol, 60% dispersion in mineral oil). Tetrafluoropyridazine (1.00 g, 6.6 mmol) was added dropwise and the mixture stirred at 0 °C for 8 h. After this period, the solvent was evaporated, and the crude material redissolved in dichloromethane (25 mL) and water (25 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 25 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and evaporated to provide a crude yellow material. Crystallisation from acetonitrile gave 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**) (1.09 g, 75%) as white solid; mp 146–148 °C; Anal. Calcd for $C_8H_{11}FN_4O$: C, 54.1; H, 1.8; N, 12.6%. Found: C, 54.0; H, 1.9; N, 12.6. IR, ν_{max}/cm^{-1}: 1015, 1035, 1094, 1115, 1260, 1416, 1464, 1490, 1568, 1654; ^{1}H NMR (400 MHz, $CDCl_3$, δ_H): 7.13–7.06 (4 H, m, ArH); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C): 117.0 (s, C-5), 118.1 (s, C-6), 126.0 (s, C-7), 126.8 (s, C-8), 133.4 (dd, $^2J_{CF}$ = 6.3 Hz, $^3J_{CF}$ = 6.3 Hz, C-4*a*), 136.8 (dd, $^1J_{CF}$ = 278.0 Hz, $^2J_{CF}$ = 30.0 Hz, C-4), 138.6 (s, C-8a), 140.3 (s, C-9a), 154.5 (s, C-10a), 156.9 (dd, $^1J_{CF}$ = 290 Hz, $^2J_{CF}$ = 8.0 Hz, C-3); ^{19}F NMR (376 MHz, $CDCl_3$, δ_F): −96.4 (1F, d, $^3J_{FF}$ = 25.8 Hz, F-3), −151.9 (1F, d, $^3J_{FF}$ = 25.9 Hz, F-4); MS (EI$^+$) *m/z*: 222 ([M]$^+$, 10%), 138 (43), 74 (66), 63 (67), 50 (100).

Reaction of 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**) with morpholine

3-Fluoro-4-(morpholin-4-yl)-9,10-dioxa-1,2-diaza-anthracene (**9a**)

A mixture of 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**) (0.20 g, 0.90 mmol), morpholine (0.16 mL, 1.80 mmol) and acetonitrile (2 mL) were placed in a 0.5–2 ml microwave vial under an argon atmosphere and subjected to microwave irradiation at 150 °C for 20 min. The mixture was partitioned between dichloromethane (20 mL) and water (20 mL) and the organic layer separated. The aqueous layer was then extracted with dichloromethane (3 × 20 mL) to give a crude yellow material. Column chromatography on silica gel using hexane:ethyl acetate (2:1) as eluent gave 3-fluoro-4-(morpholin-4-yl)-9,10-dioxa-1,2-diaza-anthracene (**9a**) (0.18 g, 71%) as white crystals; mp 207–208 °C; Found: [MH]$^+$, 290.09345. $C_{14}H_{12}FN_3O_3$ requires: [MH]$^+$, 290.09355; ^{1}H NMR (700 MHz, $CDCl_3$, δ_H): 3.44 (4H, t, $^3J_{HH}$ = 4.4 Hz, H-2′), 3.84 (4H, t, $^3J_{HH}$ = 4.4 Hz, H-3′), 6.94 (1H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.01 (1H, tm, $^3J_{HH}$ = 7.6 Hz, ArH), 7.06 (2H, m, ArH); ^{13}C NMR (175 MHz, $CDCl_3$, δ_C): 50.4 (d, $^4J_{CF}$ = 4.0 Hz, C-2′), 67.3 (s, C-3′), 116.5 (s, C-5), 117.7 (s, C-8), 125.2 (s, C-6), 125.9 (s, C-7), 126.0 (d, $^2J_{CF}$ = 25.4 Hz, C-4), 134.6 (d, $^3J_{CF}$ = 8.9 Hz, C-4*a*), 139.4 (s, C-8*a*), 140.9 (s, C-10*a*), 153.7 (s, C-9*a*), 159.0 (d, $^1J_{CF}$ = 237.7 Hz, C-3); ^{19}F NMR (658 MHz, $CDCl_3$, δ_F): −86.4 (s); MS (ES$^+$) *m/z*: 290 ([MH]$^+$, 100%).

Reaction of 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (5) with allylamine

4-Allylamino-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (9b)

Using the procedure described above, 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**) (0.15 g, 0.67 mmol), allylamine (0.10 mL, 1.35 mmol) and acetonitrile (2 mL) gave 4-allylamino-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (**9b**) (0.14 g, 80%) as white crystals; mp 175–177 °C; Anal Calcd for $C_{13}H_{10}FN_3O_2$: C, 60.2; H, 3.9; N, 16.2%. Found: C, 60.3; H, 4.0; N, 16.3. ^{1}H NMR (500 MHz, DMSO-d_6, δ_H): 4.04 (2H, t, $^3J_{HH}$ = 5.1 Hz, NCH_2), 5.10 (1H, dd, $^3J_{HH}$ = 10.3 Hz, $^2J_{HH}$ = 1.5 Hz, $=CH_2$), 5.17 (1H, dd, $^3J_{HH}$ = 17.2 Hz, $^2J_{HH}$ = 1.5 Hz, $=CH_2$), 5.94 (1H, ddt, $^3J_{HH}$ = 17.2 Hz, 10.2, 5.1, -CH=), 6.96 (1H, br t, $^3J_{HH}$ = 5.1 Hz, NH), 7.07 (3H, m, ArH), 7.12 (1H, m, ArH); ^{13}C NMR (125 MHz, DMSO-d$_6$, δ_C): 45.7 (d, $^4J_{CF}$ = 2.5 Hz, NCH_2), 115.3 (s, $=CH_2$), 116.4 (s, C-5), 117.0 (s, C-6), 124.6 (d, $^2J_{CF}$ = 28.2 Hz, C-4), 125.1 (s, C-7), 125.2 (s, C-8), 127.2 (d, $^3J_{CF}$ = 9.6 Hz, C-4*a*), 136.1 (s, CH=), 139.4 (s, C-8*a*), 140.5 (s, C-10*a*), 152.3 (s, C-9*a*), 155.2 (d, $^1J_{CF}$ = 230.4 Hz, C-3); ^{19}F NMR (470 MHz, DMSO-d_6, δ_F) −93.7 (s); MS (ES$^+$) *m/z*: 323 ([M+MeCN+Na]$^+$, 100%), 260 ([MH]$^+$, 68), 219 (69).

Crystal data for **9b**: $C_{13}H_{10}FN_3O_2$, M = 259.24, monoclinic, space group $P2_1/n$, a = 4.9065(1), b = 19.5663(4), c = 11.8180(2) Å, β = 94.25(1)°, U = 1131.44(4) Å^3, F(000) = 536, Z = 4, D_c = 1.5220 mg·m^{-3}, μ = 0.117 mm^{-1} (Mo Kα, λ = 0.71073 Å), T = 120.0(2) K. 14166 reflections were collected on a Bruker SMART 6000 diffractometer (ω-scan, 0.3°/frame) yielding 2875 unique data (R_{merg} = 0.0615). The structure was solved by direct method and refined by full-matrix least squares on F^2 for all data using Olex2 software. All non-hydrogen atoms were refined with anisotropic displacement parameters, H-atoms were located on the difference map and refined isotropically. Final $wR_2(F^2)$ = 0.1275 for all data (212 refined parameters), conventional R(F) = 0.0439 for 1918 reflections with $I \geq 2\sigma$, GOF = 0.985. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-764716.

Reaction of 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (5) with sodium ethoxide

4-Ethoxy-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (9c)

Using the procedure described above, 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**) (0.10 g, 0.45 mmol), sodium ethoxide (0.06 g, 0.90 mmol) and ethanol (2 mL) gave 4-ethoxy-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (**9c**) (0.07 g, 66%), as white crystals; mp 131–133 °C; Anal Calcd for $C_{12}H_9FN_2O_3$: C, 58.1; H, 3.7; N, 11.3%. Found: C, 58.0; H, 3.7; N, 11.2. ^{1}H NMR (500 MHz, $CDCl_3$, δ_H): 1.49 (3H, t, $^3J_{HH}$ = 7.0 Hz, CH_3), 4.52 (2H, qd, $^3J_{HH}$ = 7.0 Hz, $^5J_{HF}$ = 1.4 Hz, OCH_2), 7.00–7.11 (4H, m, ArH); ^{13}C NMR (125 MHz, DMSO-d$_6$, δ_C): 15.7 (s, CH_3), 70.6 (d, $^4J_{CF}$ = 3.9 Hz, OCH_2), 116.7 (s, C-5), 117.8 (s, C-6), 125.4 (s, C-7), 126.1 (s, C-8), 133.6 (d, $^2J_{CF}$ = 27.2 Hz, C-4), 135.1 (d, $^3J_{CF}$ = 8.2 Hz, C-4*a*), 139.2 (s, C-8*a*), 140.7 (s, C-10*a*), 154.0 (d, $^4J_{CF}$ = 1.5 Hz, C-9*a*), 158.2 (d, $^1J_{CF}$ = 239.5 Hz, C-3); ^{19}F NMR (470 MHz, $CDCl_3$, δ_F) −92.4 (s); MS (ES$^+$) *m/z*: (249 ([MH]$^+$), 100%).

Supporting Information

Supporting Information with ^{1}H NMR and ^{13}C NMR spectra for 3,4,6-trifluoro-5-phenoxypyridazine (**7**), ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra for 3,6-difluoro-4,5-diphenoxypyridazine (**8**), 3,4-difluoro-9,10-dioxa-1,2-diaza-anthracene (**5**), 3-fluoro-4-(morpholin-4-yl)-9,10-dioxa-1,2-diaza-anthracene (**9a**), 4-allylamino-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (**9b**), 4-ethoxy-3-fluoro-9,10-dioxa-1,2-diaza-anthracene (**9c**).

Supporting Information File 1

NMR spectra of all synthesized compounds **7, 8, 5** and **9a–9c**
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-45-S1.pdf]

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Acid catalyzed cyclodimerization of 2,2-bis(trifluoromethyl)-4-alkoxy-oxetanes and -thietanes. Synthesis of 2,2,6,6-tetrakis(trifluoromethyl)-4,8-dialkoxy-1,5-dioxocanes and 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane

Viacheslav A. Petrov*[1] and Will Marshall[2]

Full Research Paper

Address:
[1]DuPont Central Research and Development (publication No 8966), Experimental Station, PO Box 800500, Wilmington DE 19880-0500, United States and [2]DuPont Corporate Center for Analytical Sciences, Experimental Station, PO Box 800500, Wilmington DE 19880-0500, United States

Email:
Viacheslav A. Petrov* - viacheslav.a.petrov@usa.dupont.com

* Corresponding author

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cyclodimerization; electrophilic [4 + 4] cyclodimerization; fluorinated oxetanes; fluorinated thietanes; reaction with alcohols; reaction with H_2SO_4

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Abstract

Treatment of 2,2-bis(trifluoromethyl)-4-R-oxetanes (R = C_2H_5O, n-C_3H_7O, n-C_4H_9O) with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 solvent results in spontaneous electrophilic [4 + 4] cyclodimerization with the formation of the corresponding 2,2,6,6-tetrakis(trifluoromethyl)-4,8-dialkoxy-1,5-dioxocanes, isolated in 31–42% yield. The structures of two products (R = C_2H_5O and n-C_3H_7O) were established by single crystal X-ray diffraction. The corresponding oxetane carrying the bulky t-C_4H_9O group has different reactivity towards $BF_3{\cdot}OEt_2$, slowly producing a mixture of two acyclic, unsaturated products.

Clean and spontaneous reaction with alcohols is another interesting transformation of oxetanes described in this paper. The reaction leads to high yield formation of the corresponding acetals $(CF_3)_2C(OH)CH_2CH(OR)OR'$.

Structurally related 2,2-bis(trifluoromethyl)-4-R-thietanes (R = i-C_3H_7O, t-C_4H_9O and C_2H_5O) have different reactivity towards electrophiles. They are totally inert to the action of $BF_3{\cdot}OEt_2$ and rapidly react with a protic acid (H_2SO_4) forming the same product, 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane in 35–50% yield. The structure of this product was established by single crystal X-ray diffraction.

Introduction

Polyfluorinated 2,2-bis(trifluoromethyl)-4-alkoxy-oxetanes and -thietanes are readily available materials, prepared by [2 + 2] cycloaddition of vinyl ethers with hexafluoroacetone [1-3] or hexafluorothioacetone [4,5], respectively. Although both groups of compounds have been known for over 40 years, reports on their chemical transformations are limited. Among the reported reactions of oxetanes are hydrolysis of 2,2-bis(trifluoromethyl)-4-alkoxyoxetanes **1** leading to the formation of 4,4,4-trifluoro-3-(trifluoromethyl)-3-hydroxybutanal [1,6] and thermal or acid catalyzed isomerization of 2,2-bis(trifluoromethyl)-4-*n*-butoxy-oxetane into (*E*)-4-*n*-butoxy-1,1,1-trifluoro-2-(trifluoromethyl)but-3-en-2-ol [2].

Some compounds containing two 2,2-bis(trifluoromethyl)oxetane units, such as bis-4,4-(trifluoromethyl)oxetan-2-yl ether, were reported to undergo Lewis acid catalyzed polymerization [3].

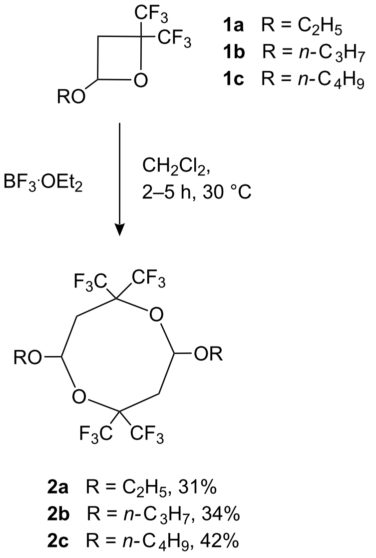
Known reactions of 2,2-bis(trifluoromethyl)-4-alkoxythietanes (R = CH_3O and C_2H_5O) include the formation of 4-(4,4-bis(trifluoromethyl)thietan-2-yloxy)-2,2-bis(trifluoromethyl)thietane on treatment with H_2SO_4 [4], thiophilic ring opening by the action of alkyl magnesium or lithium reagents [4], the recently reported oxidation with selective formation of the corresponding S-oxides [7], and an unusual reductive ring expansion leading to the corresponding dihydrothiophenes [7].

As part of a program to identify new, readily available fluorinated monomers, we have carried out a comparative study of the reactivity of 2,2-bis(trifluoromethyl)-4-alkoxy- oxetanes and -thietanes towards acids. The results of this study are reported in this paper.

Results and Discussion

In sharp contrast to the reported isomerization of 2,2-bis(trifluoromethyl)-4-alkoxyoxetanes catalyzed by protic acids [2], the reaction of oxetanes **1a**–**c** with a catalytic amount of *Lewis acid* leads to a completely different reaction course. The addition of boron trifluoride etherate catalyst to a solution of the oxetane in dichloromethane resulted in a spontaneous and mildly exothermic reaction. A very interesting feature of this process is the appearance of highly intensive blue or blue-green colour upon the addition of the first drop of the catalyst. The colour of the reaction mixture rapidly changes to dark red and finally to brown and, at this stage, usually the formation of a precipitate is observed. The solid products **2a**–**c** were isolated in moderate yields after filtration of the cold reaction mixture and washing of the filter cake with water. Analytically pure samples were prepared by crystallization from hexane. ^{1}H, and ^{13}C NMR and IR spectroscopic data show the absence of a C=C bond in all of the isolated products. Due to the fact, that ^{1}H and ^{19}F NMR spectra of **2a**, **b** (see Supporting Information File 1, Table 1, Entries 1, 2) and starting oxetanes **1a**, **b** have a similar appearance, spectroscopic data were not sufficient for an unambiguous assignment of the structure. Consequently, structure assignments for **2a** and **2b** were made based on single crystal X-ray diffraction data (see Supporting Information File 2).

Both compounds were found to have a symmetrical 2,2,6,6-tetrakis(trifluoromethyl)-1,5-dioxocane core with a trans-orientation of two alkoxy groups located at positions 4 and 8 (Scheme 1 and Figure 1 for structure of **2a** and **2b**, Supporting Information File 2 for single crystal X-ray data).



1a R = C_2H_5
1b R = n-C_3H_7
1c R = n-C_4H_9

2a R = C_2H_5, 31%
2b R = n-C_3H_7, 34%
2c R = n-C_4H_9, 42%

Scheme 1: Electrophilic [4 + 4] dimerization of oxetanes **1a–c** under action of $BF_3{\cdot}OEt_2$ catalyst.

Since ^{1}H, ^{13}C and ^{19}F NMR spectra of compound **2c** were similar to the NMR spectra of **2a**, **b**, it is assumed that compound **2c** also has a 2,2,6,6-tetrakis(trifluoromethyl)-1,5-dioxocane structure.

Despite the fact that yields of 1,5-dioxocanes **2a**–**c** in the reaction of oxetanes with $BF_3{\cdot}OEt_2$ are modest, the process itself is simple, reproducible and provides easy access to this new group of stable polyfluorinated 1,5-dioxocanes. It should also be pointed out, that examples of electrophilic [4 + 4] cycloaddi-

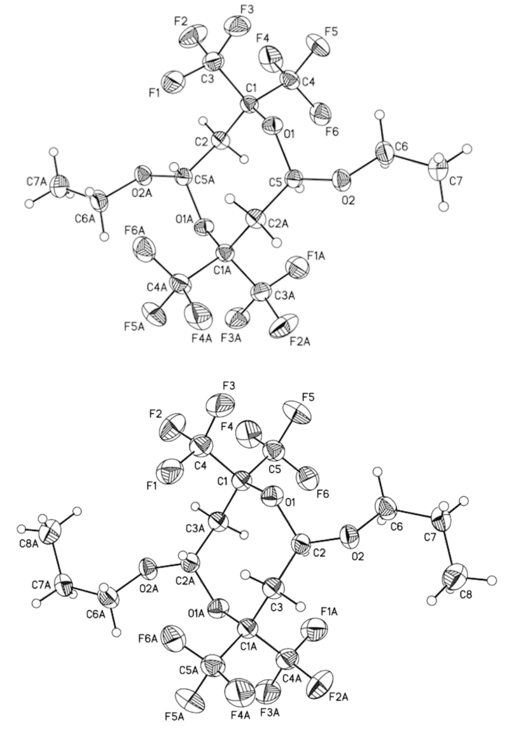
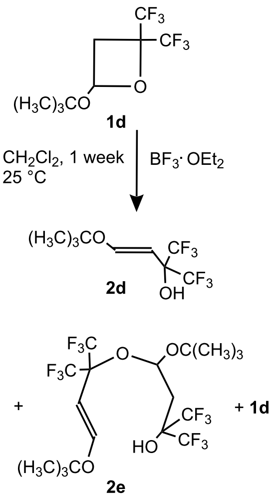


Figure 1: ORTEP drawing of compounds **2a** and **2b** with thermal ellipsoids drawn to the 50% probability level.

tion reactions are extremely rare and limited to two examples: the reaction of the oxetane (derived from the cycloaddition of 1,1-dimethoxyethylene and 2,2-dimethylcyclopropanone), leading to a stable hydrocarbon 1,5-dioxocane [8] and the formation of the corresponding fluorinated 1,5-dioxocane intermediate [9,10] observed in the isomerization of 2-ethoxy-4-(perfluoropropan-2-ylidene)oxetane [11,12].

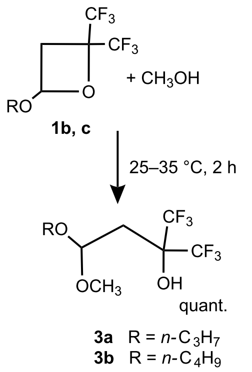
The chemical behavior of oxetane **1d** carrying the bulky t-C_4H_9O substituent is different to **1a–c**. The addition of $BF_3{\cdot}OEt_2$ as catalyst to a solution of **1d** in CH_2Cl_2 is not exothermic and results only in a faint blue-greenish color in this case. In sharp contrast to the reaction of oxetanes **1a–c** with $BF_3{\cdot}OEt_2$, this process is rather slow (85% conversion after 1 week at 25 °C) and it leads to the formation of a mixture of olefinic products **2d** and **2e** (Scheme 2).



Scheme 2: Reaction of **1d** with $BF_3{\cdot}OEt_2$.

A sample of pure **2d** was isolated by fractional distillation of the reaction mixture under reduced pressure. The structure of the olefin **2d** was established by single crystal X-ray diffraction analysis (see Supporting Information File 2).

Hydrocarbon oxetanes were reported to react with alcohols under relatively mild conditions [13]. It is interesting, that electron deficient oxetanes **1** also have similar reactivity and rapidly react with alcohols in the absence of the catalyst. The reaction leads to a ring opening with the formation of the corresponding acetals of 4,4,4-trifluoro-3-(trifluoromethyl)-3-hydroxybutanal. For example, the addition of **1b** or **1c** to an excess of methanol results in a fast and mildly exothermic reaction, leading to selective formation of acetals **3a** or **3b**, respectively (Scheme 3).

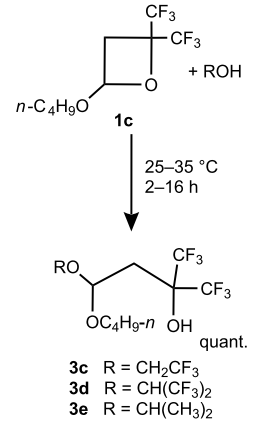


Scheme 3: Reaction of 2,2-bis(trifluoromethyl)-4-alkoxyoxetanes **1b**, **c** with methanol.

Since the vacuum distillation of **3b** lead to decomposition, the isolation of similar products in an analytically pure form was not attempted. However, removal of excess alcohol after the reaction was complete by washing with water afforded products of reasonable purity (96–98%) in >95% yield.

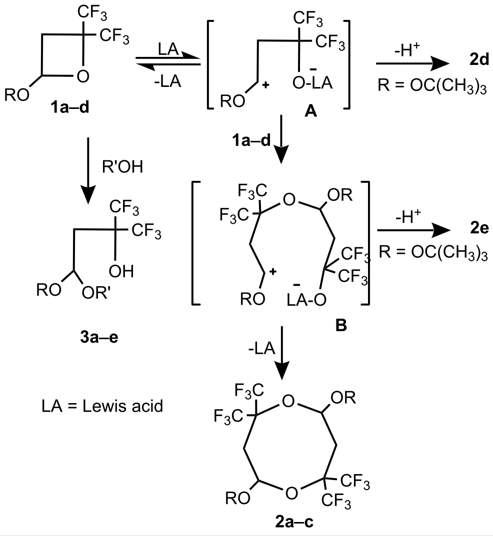
Although kinetic measurements were not carried out in this study, it appears that the reaction time and the exothermicity of the reaction of oxetanes correlates with the acidity of the corresponding alcohol. For example, in contrast to a mildly exothermic reaction of **1b**, **c** with methanol ($pK_a = 15.5$ [14,15])

the interaction of **1c** with more acidic CF_3CH_2OH (pK_a = 12.4, 12.8 [15]) or $(CF_3)_2CHOH$ (pK_a = 9.3 [16]) is significantly more exothermic, leading to products **3c** and **3d**, respectively. All reactions were completed within 1–2 h at ambient temperature. On the other hand, the reaction of **1c** with the less acidic $(CH_3)_2CHOH$ (pK_a= 17.1 [15]) was significantly slower taking >10 h for completion at ambient temperature, as monitored by ^{19}F NMR, and led to acetal **3e** (Scheme 4).



Scheme 4: Reaction of oxetane **1c** with alcohols.

A mechanism for the reaction of these fluorinated oxetanes with Lewis acids and alcohols, is presented by Scheme 5.



Scheme 5: Putative mechanism for the reaction oxetanes **2a–d** with $BF_3 \cdot OEt_2$ and alcohols.

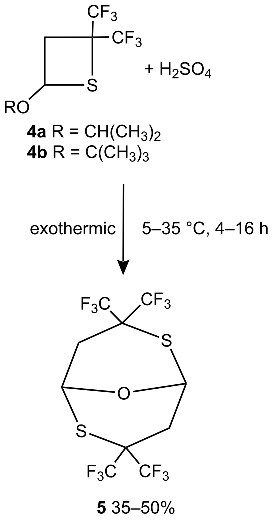
Coordination of the Lewis acid with the oxetane ring oxygen results in the formation of stabilized zwitterion **A**, which probably exists in equilibrium with the starting material. The reaction of **A** with a second mole of oxetane then leads to the formation of zwitterion **B**, which can undergo intramolecular cyclization with formation of 1,5-dioxocanes **2a–c**. The Lewis acid liberated in this process is free to carry out the next catalytic cycle. It should be pointed out, that recently a zwitterion similar to **B** was observed in the isomerization of the cycloadduct of bis(trifluoromethyl)ketene and ethyl vinyl ether [9,10].

In the case of oxetane **1d**, the main channel of the reaction involves stabilization of intermediates **A** and **B** by H^+ elimination, leading to the formation of olefins **2d** and **2e**, respectively. Such a distinct difference in the reactivity of **1d** may be a result of steric hindrance of the carbocationic center in intermediates **A** or **B**, created by the bulky $(CH_3)_3CO$-group, which favors elimination and the formation of olefins **2e** and **2d.**

The addition of alcohols to oxetanes **1a–c** probably involves the protonation of the oxetane ring oxygen atom as the first step, followed by ring opening and addition of the alkoxy anion. This mechanism agrees well with the observed order of reactivity of alcohols, with the acidic alcohols being more reactive towards the oxetane. It should be pointed out, however, that an alternative mechanism involving the “concerted” addition of the alcohol to the oxetane cannot be ruled out at this point.

Despite the structural similarity shared with oxetanes, thietanes **4a–c** display a totally different reactivity (Scheme 6, Scheme 7).

For example, no reaction was detected between thietane **4a** and an excess of either methanol or hexafluoroisopropanol (25 °C, 16 h, NMR) and both **4a** and **4b** were found to be inert towards $BF_3 \cdot OEt_2$ (25 °C, 10 h, CH_2Cl_2, NMR). However, the addition of compounds **4a** or **4b** to concentrated H_2SO_4 resulted in an



Scheme 6: Reaction of thietanes **4a**, **b** with H_2SO_4 to generate **5**.

exothermic reaction and formation of a product, which, after single crystal X-ray diffraction analysis, was shown to be 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane (**5**) (Scheme 6, Figure 2, Supporting Information File 2).

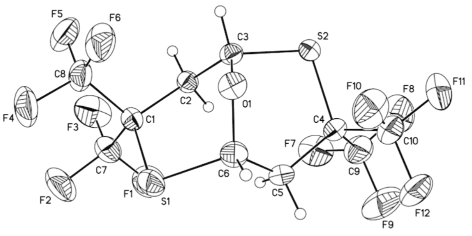
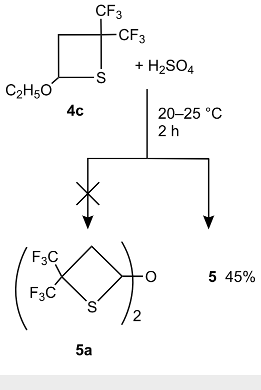


Figure 2: ORTEP drawing of **5** with thermal ellipsoids drawn to the 50% probability level.

A solid product with similar melting point (91–92 °C) was observed earlier [4] in the reaction of thietanes **4** (R = CH_3 and C_2H_5) with concentrated H_2SO_4. Based on a combination of ^1H, ^{19}F NMR, mass spectrometry and elemental analysis data, the structure of 4-[4,4-bis(trifluoromethyl)thietan-2-yloxy]-2,2-bis(trifluoromethyl)thietane **5a** was proposed for that product [4].

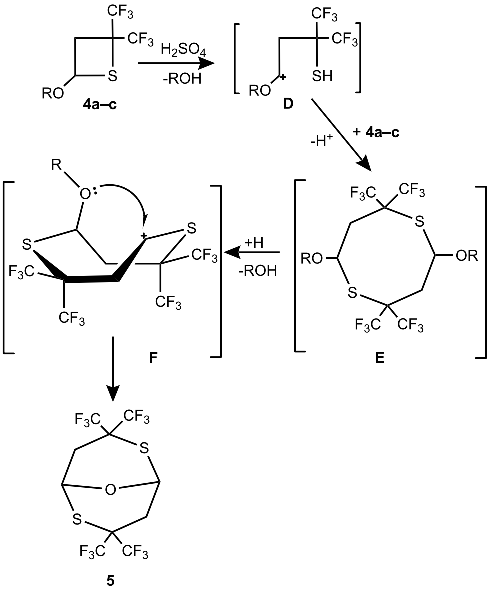
In order to clarify this result, thietane **4c** (R = C_2H_5) was treated with H_2SO_4 (Scheme 7) under conditions similar to those reported previously [4]. A solid product was isolated in 45% yield, which had a similar melting point and identical ^1H, ^{19}F NMR spectra to that reported for **5a** (see Supporting Information File 1, Table 1, Entry 11 and footnotes f,h), but also identical to the analytical data for compound **5** prepared from oxetanes **4a** and **4b**.



Scheme 7: Reaction of **4c** with H_2SO_4.

Since all experimental data obtained for the reaction of thietanes **4a–c** with H_2SO_4 in this work are consistent, it is concluded that the main product of this reaction is dithiocin **5**, rather than the isomeric ether **5a**, proposed in reference [4].

A possible mechanism describing the formation of compound **5** is depicted by Scheme 8.



Scheme 8: Putative mechanism for the formation bicyclic ether **5**.

Protonation of the thietane sulfur of **4**, followed by ring opening, results in the formation of an oxygen stabilized carbocation **D**. Electrophilic attack of **D** at the sulfur of the second thietane molecule and loss of H^+ would lead to the formation of intermediate **E**, structurally similar to cyloadducts **2a–c**. However, the process does not stop at this stage. Protonation of the alkoxy group of **E**, followed by the elimination of alcohol leads to the cyclic cation **F**, which further undergoes cyclization through intramolecular electrophilic attack on oxygen of the alkoxy group, resulting in the formation of 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane (**5**).

Conclusion

Despite the structural similarity, 2,2-bis(trifluoromethyl)-4-alkoxy-oxetanes and thietanes have very different reactivity towards Lewis and protic acids. While the reaction of 2,2-bis(trifluoromethyl)-4-R-oxetanes (R = C_2H_5, n-C_3H_7, n-C_4H_9) with $BF_3{\cdot}OEt_2$ results in the fast formation of the corresponding 2,2,6,6-tetrakis(trifluoromethyl)-1,5-dioxocanes **2a–c**, the corresponding thietanes **4b**, **c** (R = i-C_3H_7, t-C_4H_9) are inert towards this Lewis acid, but rapidly react with concentrated H_2SO_4 with the formation of bicyclic 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane **5**. Reinvestigation of a previously reported reaction of **4c**, (R = C_2H_5) with

H_2SO_4, led us to the conclusion, that the product formed in this process has the structure 3,3,7,7-tetrakis(trifluoromethyl)-9-oxa-2,6-dithia-bicyclo[3.3.1]nonane (**5**), rather than 4-[4,4-bis(trifluoromethyl)thietan-2-yloxy]-2,2-bis(trifluoromethyl)-thietane (**5a**) as proposed earlier [4].

Supporting Information

Supporting Information File 1

Experimental details and analytical data for compounds **2a**–**2e**, **3a**–**3e** and **5**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-46-S1.pdf]

Supporting Information File 2

X-ray data for compounds **2a**, **2b**, **2d** and **5**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-46-S2.cif]

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Synthesis of fluorinated δ-lactams via cycloisomerization of *gem*-difluoropropargyl amides

Satoru Arimitsu[1] and Gerald B. Hammond[*2]

Full Research Paper

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Address:
[1]Department of Chemistry, Kyoto University, Kyoto, Japan and
[2]Department of Chemistry, University of Louisville, Louisville,
Kentucky 40292, United States

Email:
Gerald B. Hammond[*] - gb.hammond@louisville.edu

* Corresponding author

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Abstract

gem-Difluoro-1,7-enyne amides are suitable building blocks for the synthesis of difluorodihydropyridinones via a ring-closing metathesis reaction, and of 4,4-difluoro-3-oxoisoquinolines through a ring-closing metathesis–enyne metathesis tandem reaction. These products, in turn, undergo a Diels–Alder reaction to yield heterotricyclic systems in moderate to good yields.

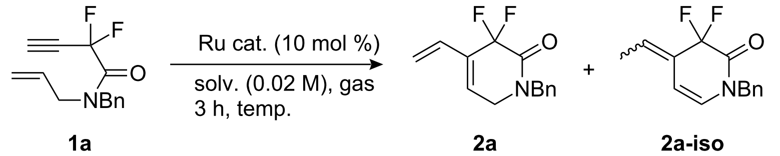
Introduction

It has been estimated that as many as 25% of all synthetic pharmaceutical drugs contain an amide bond [1]. Commonly, β- and γ-lactams are present in many natural products and pharmaceuticals, and the introduction of a *gem*-difluoromethylene moiety has been reported to improve their biological activities. For example, a *gem*-difluoro-γ-lactam can inhibit γ-lactamase, which is responsible for bacterial resistance to γ-lactam antibiotics [2-4]. Additionally, α,α-difluoro lactams are precursors of some biologically active compounds [5-8]. Our group's entry in this arena started as a collaboration with Professor Fustero and resulted in the syntheses of fluorinated β- and γ-lactams [9-13]. This sparked our interest in the synthesis of larger-ring lactams, with six to eight members, because nitrogen-containing medium-size heterocyclics are found in many natural products as part of fused cyclic structures. In their pioneering work on middle-range lactams bearing fluorine(s), Fustero et al. developed a ring-closing metathesis of α,α-difluoro-1,*n*-dienyl amides to furnish the corresponding α,α-difluorinated lactams [14]. The synthesis of medium-size heterocycles by a metathesis reaction is quite relevant, as demonstrated by its extensive application to multi-fused heterocyclics [15-19]. We postulated that functionalized fluorinated enyne amides could be used for the synthesis of a chemically diverse suite of δ-lactams because enynes are suitable partners in ring-closing metathesis reactions or cycloisomerizations. An additional benefit of using enynes in metathesis reactions is that the resulting diene product could be further elaborated using a Diels–Alder reaction to construct bi- or tricyclic ring systems [20].

Results and Discussion

Initially, we investigated the enyne metathesis reaction of fluorinated enyne **1a** with commercially available ruthenium carbene complexes, the Hoveyda–Grubbs second-generation catalyst being the most reactive (entries 1–3, Table 1). The reaction at 110 °C gave **2a-iso** as the major compound, probably through the isomerization of **2a** (entry 3, Table 1) [14]. The latter (**2a**) was isolated when the reaction was carried out at 70 °C in toluene (entry 4, Table 1). Other solvents did not give good yields or selectivities (entries 5 and 6, Table 1). From experimentation, it became clear that ethylene gas was crucial for driving this reaction forward (compare entry 4 with 7, Table 1) [21]. 2,6-Dichloro-1,4-benzoquinone, which has been reported to prevent isomerization [22], gave disappointing results (entry 8, Table 1). When our optimized conditions were applied to other fluorinated 1,7-enynes we isolated the desired lactams (entries 1–3, Table 2). Higher temperatures were required with internal alkynes (entries 2–5, Table 2), where isomerization occurs and the enyne ester **1d** did not yield satisfactory results. Interestingly, although enyne ketone **1e** gave a good ^{19}F NMR yield (97%) of the desired diene **2e**, we could only isolate the *ortho*-fluorophenol **3** in good yield after silica gel chromatography. This unexpected result could have positive synthetic repercussions, as *ortho*-fluorophenol is a moiety that has attracted attention because it is present in some bioactive compounds [23-25].

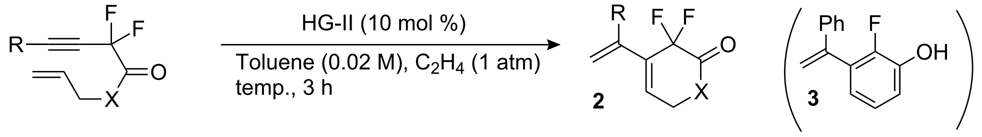
Table 1: Screening reaction conditions for the enyne metathesis of **1a**.



Entry	Solvent	Ru cat.	Gas	Temp. (°C)	Yield of products (%)[a] **1a/2a/2a-iso**
1	Toluene	G-I	C_2H_4	110	53/0/0
2	Toluene	G-II	C_2H_4	110	0/34/0
3	Toluene	HG-II	C_2H_4	110	0/6/66 (60)[b]
4	Toluene	HG-II	C_2H_4	70	0/85 (70)/0
5	1,2-DCE[c]	HG-II	C_2H_4	70	No rxn.
6	THF	HG-II	C_2H_4	70	30/25/0
7	Toluene	HG-II	Argon	70	28/34/0
8	Toluene	HG-II	C_2H_4[d]	110	0/20/11

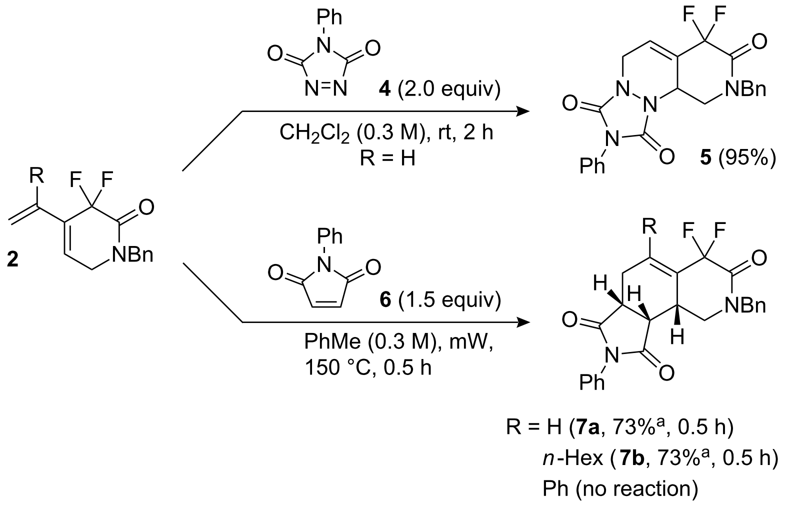
[a] Yield was determined by ^{19}F NMR and the value in parentheses is the isolated yield.
[b] **2a-iso** was isolated as an *E*/*Z* mixture (*E*/*Z* = 3/1).
[c] 1,2-Dichloroethane.
[d] 20 mol % of 2,6-dichloro-1,4-benzoquinone was used.

Table 2: Metathesis reaction of fluorinated 1,7-enyne carbonyl compounds.



Entry	X	R	Temp. (°C)	Yield of **2** (%)[a]
1	NBn	H (**1a**)	70	70 [85] (**2a**)
2	NBn	*n*-Hex (**1b**)	110	52 [78] (**2b**)
3	NBn	Ph (**1c**)	110	69 [95] (**2c**)
4	O	Ph (**1d**)	110	— [33][b] (**2d**)
5	C	Ph (**1e**)	110	— [97][c] (**2e**)

[a] The yields in brackets were determined by ^{19}F NMR.
[b] Isolation of **2d** was unsuccessful due to the complex mixture that had been formed.
[c] Compound **3** was isolated in 84% after silica gel chromatography.

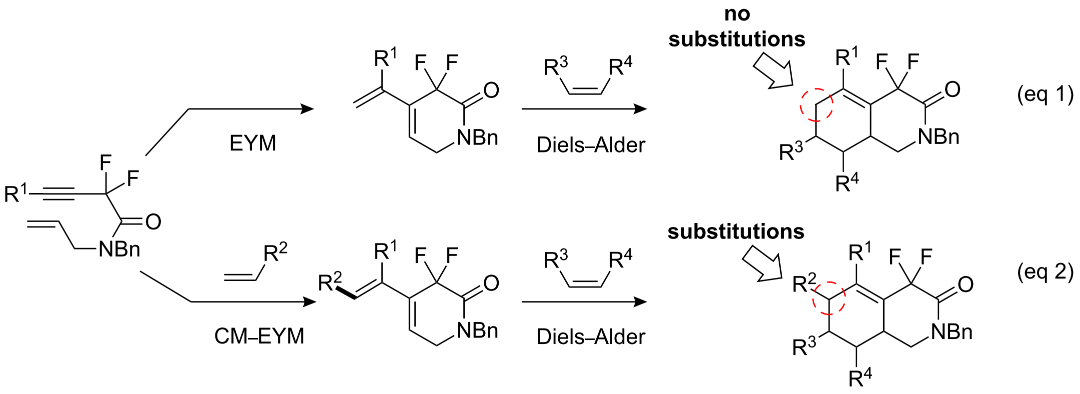


Scheme 1: Diels–Alder reaction of diene **2** with **4** and **6**. [a]The other isomers of **7a** and **7b** were isolated in 8% and 20% yield, respectively.

Dienes **2a** and **2b** were used in Diels–Alder reactions with **4** and **6** to produce **5** and 4,4-difluoroisoquinolin-3-one derivatives **7**, respectively, in excellent yield and good stereoselectivity (Scheme 1). Phenyl-substituted diene **2c** gave no reaction, even after a longer reaction time. The stereochemistry of **7a** and **7b** was determined by COSY and NOESY experiments.

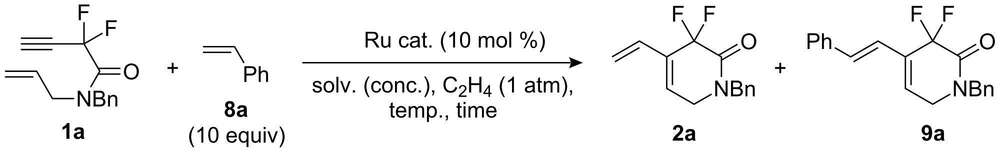
Recently, various tandem reactions with ruthenium complexes have become popular in organic chemistry because Ru(II) complexes are capable of catalyzing additional reactions [26,27]. Since our enyne metathesis reaction of fluorinated 1,7-enynes does not permit substitution at the 6-position of the resultant *gem*-difluoroisoquinolinone (eq 1, Scheme 2), we examined a potential cross metathesis–enyne metathesis tandem-type reaction (CM–EYM reaction). In theory, if the terminal vinyl group of diene **2** can be modified by a tandem metathesis reaction, this would permit the synthesis of multi-substituted *gem*-difluoroisoquinolinones through a subsequent Diels–Alder reaction (eq 2, Scheme 2) [28].

In this regard, we screened various ruthenium carbene complexes using 1,7-enyne amide **1a** and styrene **8a** as a model reaction and found that the Hoveyda–Grubbs second-generation catalyst gave the best mass balance of products **2a** and **9a** (entry 3, Table 3). We obtained better results when the reaction was carried out in a sealed pressure reaction vessel (compare entries 3 and 4, Table 3). More interestingly, the choice of solvent had a tremendous effect on the selectivity between **2a** (EYM product) and **9a** (CM–EYM product) (entries 4–8, Table 3). Methylene chloride was found to be the best solvent (entry 5, Table 3). Other reaction factors were also examined carefully; higher concentrations reduced the yield and selectivity slightly (entries 9 and 10, Table 3). Lower reaction temperature (50 °C) resulted in no conversion (entry 11,



Scheme 2: Synthetic concept toward multi-substituted *gem*-difluoroisoquinolinones.

Table 3: Screening of CM–EYM tandem reaction.



Entry	Ru cat.	Solvent	Conc. (M)	Temp. (°C)	Time[a] (h)	Yield of products **2a**/**3a** (%)[b]
1[c]	G-I	Toluene	0.02	110	1.5	Complex
2[c]	G-II	Toluene	0.02	110	1.5	23/17
3[c]	HG-II	Toluene	0.02	110	3	34/46
4	HG-II	Toluene	0.02	110	3	33/37
5	HG-II	CH_2Cl_2	0.02	110	24	0/68 (67)[d]
6	HG-II	1,2-DCE	0.02	110	24	26/24
7	HG-II	THF	0.02	110	24	4/28
8	HG-II	1,4-Dioxane	0.02	110	24	9/32
9	HG-II	CH_2Cl_2	0.05	110	24	0/56
10	HG-II	CH_2Cl_2	0.1	110	24	8/32
11	HG-II	CH_2Cl_2	0.02	50	24	No reaction
12[e]	HG-II	CH_2Cl_2	0.02	110	24	18/30

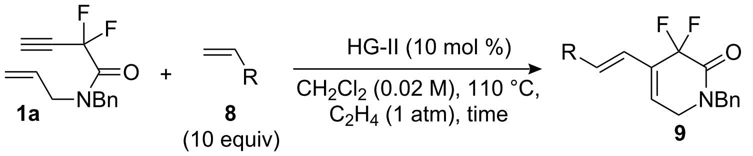
[a] Time was determined by TLC and/or GC–MS.
[b] The yield and ratio of products were determined by ^{19}F NMR.
[c] The reaction was carried out without a pressure vessel.
[d] The value in parentheses is the isolated yield.
[e] The reaction was carried out under argon.

Table 3), and the reaction produced a mixture of **2a** and **9a** in lower yield in the absence of ethylene gas (entry 12, Table 3).

These optimized reaction conditions were applied to other vinyl compounds **8** (Table 4). After 4-substituted aryl alkenes gave the desired product **9** in moderate yields with excellent selectivity (*E*-major) (entries 3 and 4, Table 4), it then became clear that steric hindrance and the electronic deficiency of alkenes **8** decrease the efficiency of the tandem reaction; the non-tandem product **2a** being formed instead (entries 2 and 6, Table 4). Allyl acetate **8f** gave the desired product only when toluene was employed as solvent (entry 6, Table 4).

The stereochemistry of the terminal double bond of **9** was determined by comparing coupling constants of vinyl protons of compound **2a**. The coupling constants of *trans*-protons (Ha–Hc)

Table 4: CM–EYM tandem reaction with fluorinated 1,7-enyne **1a** and alkene **8**.



Entry	R	Time (h)[a]	Isolated yields of **9** [*E*/*Z*][b] + **2a** (%)
1	Ph (**8a**)	24	67 [1/0] (**9a**) + 0
2	3-MeO-C_6H_4 (**8b**)	24	36 [1/0] (**9b**) + 15
3	4-MeO-C_6H_4 (**8c**)	24	33 [1/0] (**9c**) + trace
4	4-Cl-C_6H_4 (**8d**)	24	43 [1/0] (**9d**) + trace
5	4-F-C_6H_4 (**8e**)	27	33 [1/0] (**9e**) + 19
6[c]	CH_2OAc (**8f**)	3	31 [1/0] (**9f**) + 31

[a] Time was determined by TLC and/or GC–MS.
[b] The ratio of products was determined by ^{1}H and/or ^{19}F NMR.
[c] Toluene was used instead of CH_2Cl_2.

and *cis*-protons (Ha–Hb) on a double bond are $J = 17.5$ Hz and $J = 11.0$ Hz, respectively (Figure 1).

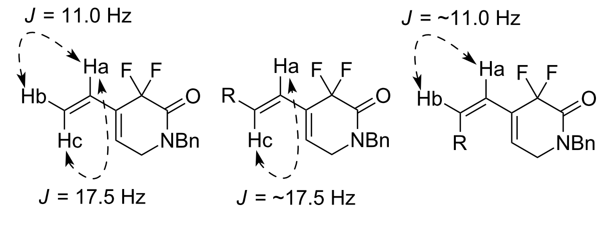
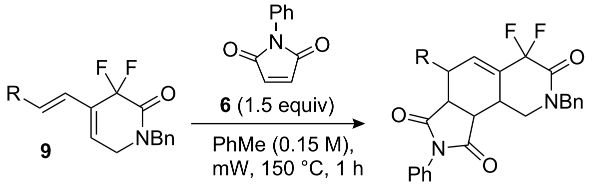


Figure 1: Comparison of coupling constant of vinyl protons.

As expected, the Diels–Alder reaction with *N*-phenylmaleimide **6** gave 6-substituted *gem*-difluoroisoquinolinones efficiently with slight stereoselectivity (Scheme 3).



R = Ph; 52%^{a} (**10a**)
= CH_2OAc; 60%^{a} (**10b**)

Scheme 3: Diels–Alder reaction with **9** and **6**. ^{a}Combined yield of two isomers.

In summary, *gem*-difluoro-1,7-enyne carbonyl derivatives are useful reaction partners in enyne metathesis cycloisomerization and CM–EYM tandem reactions catalyzed by ruthenium carbene complexes. The resulting diene products can be elaborated further using a Diels–Alder reaction.

Supporting Information

Supporting Information File 1

Synthesis of fluorinated δ-lactams via cycloisomerization of *gem*-difluoropropargyl amides
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-48-S1.pdf]

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(a similar approach with non-fluorinated building blocks has been reported).

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The definitive version of this article is the electronic one which can be found at:
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Beilstein Journal
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Synthesis and crystallographic analysis of *meso*-2,3-difluoro-1,4-butanediol and *meso*-1,4-dibenzyloxy-2,3-difluorobutane

Bruno Linclau*, Leo Leung, Jean Nonnenmacher and Graham Tizzard

Full Research Paper

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Address:
School of Chemistry, University of Southampton, Highfield,
Southampton SO17 1BJ, UK

Email:
Bruno Linclau* - bruno.linclau@soton.ac.uk

* Corresponding author

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Abstract

A large-scale synthesis of *meso*-2,3-difluoro-1,4-butanediol in 5 steps from (*Z*)-but-2-enediol is described. Crystallographic analysis of the diol and the corresponding benzyl ether reveals an *anti* conformation of the vicinal difluoride moiety. Monosilylation of the diol is high-yielding but all attempts to achieve chain extension through addition of alkyl Grignard and acetylide nucleophiles failed.

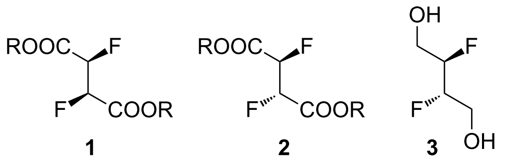
Introduction

Selective fluorination of bioactive compounds is a widely employed strategy for the modification of their properties [1]. Fluorine atoms can be introduced to modulate the pK_a of adjacent acidic and basic functional groups as well as the lipophilicity, chemical and metabolic stability of the compound. Recent exciting reports describe weak but stabilising interactions between a C–F moiety and protein residues, which is certain to have implications in drug design [2,3]. Further important applications include molecular imaging using ^{18}F [4], and modification of high-performance materials [5].

In recent years, the vicinal difluoride motif has received increasing attention due to the conformational properties instilled by the 'gauche effect' [6], which results in the vicinal difluoro *gauche* conformation being more stable than the corresponding *anti* conformation [7-9]. O'Hagan has demonstrated that vicinal difluoride substitution along a hydrocarbon chain of a fatty acid leads to conformational rigidity or disorder depending on the relative stereochemistry of the fluorine atoms, which originates from the enforcing or opposing fluorine *gauche* and hydrocarbon *anti* low-energy conformations [10]. As an extension, multi-vicinal tri- to hexafluorinated chains have been synthesised [11-16], which revealed yet another effect on the conformational behaviour, i.e. that conformations containing parallel 1,3-C–F bonds are destabilised. As an application, liquid crystals have been prepared containing a vicinal difluoride motif [14,17,18].

Efficient stereodefined synthesis of vicinal difluoride moieties is not straightforward. Direct methods include fluorination of alkenes with F_2 [19], XeF_2 [20], or hypervalent iodine species [21]. Such approaches often display poor stereoselectivity or result in rearrangement products. Treatment of 1,2-diols with SF_4 [22,23], DAST [24], or deoxofluor [25] also leads to vicinal difluorides. Reaction with vicinal triflates has also been successful in some cases [7,26]. A common two-step method involves opening of an epoxide to give the corresponding fluorohydrin [27], followed by the conversion of the alcohol moiety to the fluoride [28]. Another two-step method is halofluorination of alkenes and subsequent halide substitution with silver fluoride [9,29,30].

The introduction of multiple fluorine atoms is often a cumbersome process, and in many cases a fluorinated building block approach [31,32] is more efficient. Known vicinal difluoride containing building blocks include (racemic) C_2-symmetric and *meso*-2,3-difluorosuccinic acids (or esters) **1**,**2** (Figure 1) [9,22,23,33,34].



1 **2** **3**

Figure 1: Vicinal difluoride containing building blocks.

Herein we describe the first synthesis of *meso*-2,3-difluoro-1,4-butanediol **3** as a further simple vicinal difluoride building block as well as its successful monosilylation, and our attempts to employ **3** for the synthesis of fluorinated hydrocarbons.

Results and Discussion

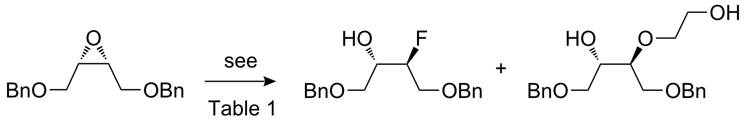
Synthesis

The synthesis of **3** was achieved from *meso*-epoxide **4**, which was obtained from (*Z*)-2-butene-1,4-diol in excellent yield according to the published two-step sequence [35]. The optimisation of the reaction of **4** with fluoride sources is shown in Table 1.

Reaction with Olah's reagent [29] proceeded in excellent yield (Table 1, entry 1), however, the product was isolated as a mixture of isomers, which were not further characterised. Reaction with potassium hydrogen difluoride in ethylene glycol [36,37] gave the fluorohydrin in only modest yield (entry 2). Interestingly, the product arising from epoxide ring opening by ethylene glycol, **6**, was isolated in 50% yield. The addition of molecular sieves (entry 3) led to complete conversion to **6** (TLC analysis). No reaction took place when DMSO (entry 4) or DMF/18-crown-6 were used as solvents [38,39] (entry 5). With $Bu_4NH_2F_3$ as the fluoride source [40,41], 11% of the desired product (together with some elimination byproducts) was obtained when xylene was used as solvent (entry 6). However, reaction with a mixture of $Bu_4NH_2F_3$ and KHF_2 in the absence of solvent [42-44] led to an excellent 91% yield of the desired product **5** albeit after a relatively long reaction time (entry 8).

The subsequent conversion to **3** is shown in Scheme 1. Treatment of **5** with DAST in DCM at reflux temperature only gave **7** in 29% yield (not shown). A slight improvement (40% yield) was obtained when the reaction was conducted in hexane or toluene, but a procedure in which DAST was added to a solution of **5** in toluene at room temperature, followed by the add-

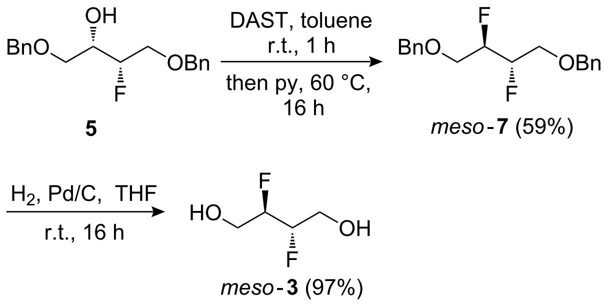
Table 1: Conversion of epoxide **4** to the fluorohydrin.



meso-**4** *rac*-**5** *rac*-**6**

Entry	Reaction conditions	$\mathbf{5}^a$	$\mathbf{6}^a$	$\mathbf{4}^a$
1	HF•py (70% HF), r.t., 3 h	80^b	–	–
2	KHF_2, ethylene glycol, 150 °C, 3 h	34	50	–
3	KHF_2, ethylene glycol, mol. Sieves, 150 °C, 3 h	–	^{c}	–
4	KHF_2, DMSO, 150 °C, 16 h	–	–	^{d}
5	KHF_2, DMF, 18-crown-6, reflux, 16 h	–	–	^{d}
6	$Bu_4NH_2F_3$ (1 equiv), xylene, reflux, 3 d	11	–	57
7	$Bu_4NH_2F_3$ (1 equiv), KHF_2 (1 equiv), 130 °C, 16 h	71	–	–
8	$Bu_4NH_2F_3$ (1 equiv), KHF_2 (1 equiv), 115 °C, 2.5 d	91	–	–

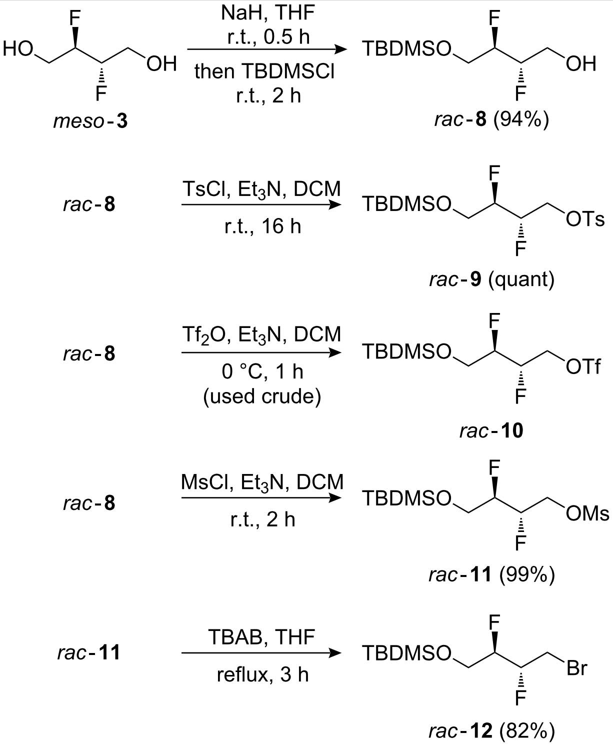
[a] Isolated yield.
[b] Mixture of isomers.
[c] Complete conversion to **6** (TLC analysis).
[d] No reaction observed.



Scheme 1: Synthesis of *meso*-2,3-difluoro-1,4-butanediol.

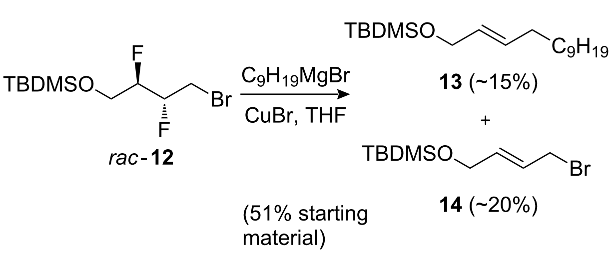
ition of pyridine [28] and heating the reaction mixture for a prolonged period gave the desired vicinal difluoride in good yield. Nevertheless, while this procedure was deemed sufficiently safe to conduct at about the 50 mmol scale, further upscaling with a more thermally stable fluorinating reagent such as deoxofluor [45], Fluolead [46], or aminodifluorosulfinium tetrafluoroborate [47] would be recommended. Subsequent alcohol deprotection gave the target compound in almost quantitative yield in multigram quantities.

The potential of **3** as a building block, in particular for the construction of longer aliphatic chains of varying length, was investigated next. Thus (Scheme 2), the diol moiety in **3** was monoprotected as a silyl ether, and the remaining alcohol group was activated as the corresponding tosylate **9**, triflate **10**, mesylate **11**, and bromide **12** as precursors for chain extension. Nucleophilic substitution of similar tosylates with phenolate nucleophiles has been previously described [18]. Reaction of **9**–**12** with a number of carbon nucleophiles was investigated.



Scheme 2: Monoprotection of **3**, and activation of the remaining alcohol.

Unfortunately, reaction of **9**–**12** with alkyl Grignard and acetylide reagents did not lead to the desired chain extension. Reaction of **9** or **10** with a sodium or lithium acetylide led to decomposition, while **12** did not react under these conditions. Treatment of **11** with $C_9H_{19}MgBr/CuBr$ was unsuccessful, whilst surprisingly, when **12** was subjected to this reagent combination (Scheme 3), the defluorinated reaction products **13** and **14** were obtained. We have not yet deduced an acceptable explanation for this unexpected result.



Scheme 3: Reaction of **12** leading to defluorinated products.

Crystallographic analysis

Compounds **7** and **3** yielded colourless crystals suitable for study by single crystal X-ray diffraction [48]. The dibenzyl ether **7** crystallises in the monoclinic $P2_1/c$ space group with half a molecule of **7** in the asymmetric unit. The molecule possesses crystallographic inversion symmetry. Two conformers are present in the crystal (55:45) which differ only in the sign of the torsion angle of the rings (Figure 2). The disparity in the amounts of each conformer present gives rise to the disorder observed in the crystal structure.

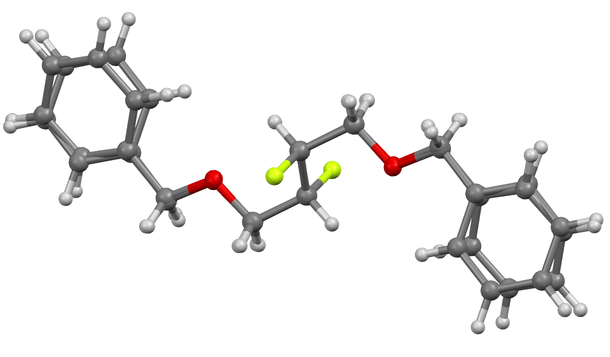


Figure 2: Molecular overlay of both conformers of **7**.

The vicinal difluoro group adopts an *anti* conformation with the F–C–C–F dihedral angle exactly 180°, which manifests itself in the crystallographic inversion centre. Nevertheless, each benzyloxy group does adopt a *gauche* conformation with its adjacent fluoro substituent where the F–C–C–O dihedral angle is 71.5°. Although strong H-bonding interactions are absent within the crystal, each molecule displays eight short contacts less than the sum of the van der Waals radii to its four nearest neighbours; three C–F···H–C contacts (2.554 Å, 2.581 Å and 2.637 Å) for each fluorine, and a pair of C–H···π contacts (2.662 Å to centroid of ring). The hydrogen atoms involved in the C–F contacts are an aromatic proton, the C<u>H</u>F and a C<u>H</u>HOBn proton (Figure 3).

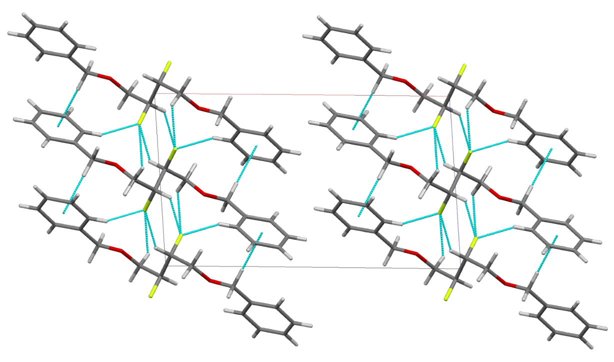


Figure 3: Crystal packing of **7** viewed along the b axis. Short contacts (see text) are shown in light blue.

The diol **3** crystallises in the tetragonal space group $I4_1/a$ with half a molecule of **3** in the asymmetric unit. This molecule also displays crystallographic inversion symmetry. In common with **7**, the vicinal difluoro group of **3** adopts an *anti* conformation with a symmetry-constrained dihedral angle of 180°, and the hydroxyl groups adopt *gauche* conformations with the adjacent fluoro atoms with F–C–C–O dihedral angles of 66.8° (Figure 4).

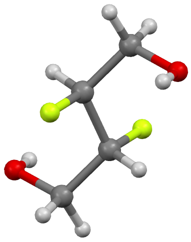


Figure 4: Crystal structure of **3**.

There is strong hydrogen bonding between the hydroxyl groups of the molecule with each hydroxyl group acting both as donor and acceptor (O–H···O: 2.685 Å, 170.1°). The hydrogen bonded molecules are arranged helically about the crystallographic 4_1 screw axes. Thus the crystal structure comprises of alternating left and right handed hydrogen bonded helical constructs with each molecule part of two adjacent helices (Figure 5).

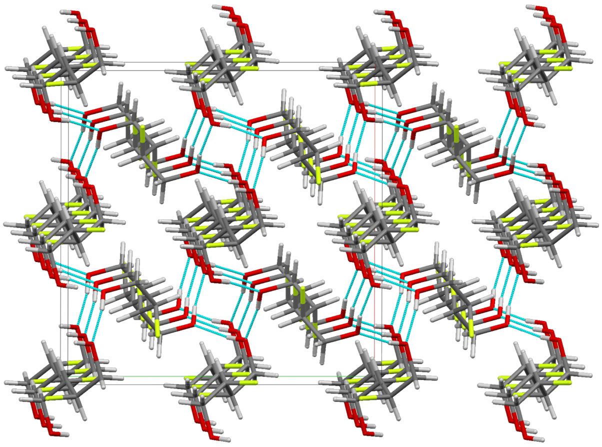


Figure 5: Crystal packing of **3** viewed along the c axis. H-bonds are shown in light blue.

Examination of the Cambridge Structural Database [49] (V5.31, November 2009) revealed three more *meso*-*vic*-difluoro compounds: 1,2-difluoro-1,2-diphenylethane, 2,3-difluorosuccinic acid and 2,3-difluorosuccinate benzylamide, all reported by O'Hagan [9]. Of these, only difluorosuccinic acid crystallises with the vicinal difluoro group in the expected *gauche* conformation, whilst both other structures, in common with the structures described in this work, contain the vicinal difluoro group in an *anti* conformation. The conformation of vicinal difluorides in solution can also be deduced from NMR studies. Schlosser has reported that the $^3J_{\text{H-F}}$ is around 22 Hz when the fluorines are in the *syn* configuration, because of a preferred *gauche* conformation, and around 14 Hz when in the *anti* configuration, because there is no overall preferred conformation [28]. Unfortunately, we were unable to extract $^3J_{\text{H-F}}$ values from the second order signals in both the ^{1}H and ^{19}F NMR spectra of **3** and **7**, however, analysis of the coupling constants in **11** revealed two $^3J_{\text{H-F}}$ values of 10.1 and 9.6 Hz ($^3J_{\text{F-F}}$ 13.5 Hz). Walba et al. have reported the $^3J_{\text{H-F}}$ values of a very similar *syn*-1-hydroxy-4-aryloxy-2,3-difluorobutane system to be around 22.0 Hz [17]. Hence, this value is indeed much higher than the $^3J_{\text{H-F}}$ values for **11**, from which it can be concluded that the gauche effect in **11** (*anti*) is operating in solution.

Conclusion

The synthesis of *meso*-2,3-difluoro-1,4-butanediol **3** was achieved in 5 steps from (*Z*)-1,4-butenediol in 40% overall yield on a multigram scale. A high-yielding (94%) monosilylation was also achieved, but all attempts for chain extension met with failure. Crystallographic analysis revealed that the vicinal fluorine atoms in **3** and its dibenzyl ether **7** are in the *anti* conformation.

Experimental

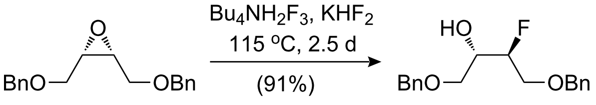
^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Bruker DPX400 or AV300 spectrometer as indicated. Low resolution ES mass and EIMS were recorded on a Waters ZMD and Thermoquest TraceMS quadrupole spectrometers, respectively. Infrared spectra were recorded as neat films on a Nicolet Impact 380 ATR spectrometer. Melting points were recorded on a Gallencamp Melting Point Apparatus and are uncorrected.

Column chromatography was performed on 230–400 mesh Matrex silica gel. Preparative HPLC was carried out using a Biorad Biosil D 90-10, 250 × 22 mm column eluting at 20 mL min^{-1}, connected to a Kontron 475 refractive index detector. Reactions were monitored by TLC (Merck) with detection by $KMnO_4$ or anisaldehyde stains.

Reaction solvents were dried before use as follows: THF and Et_2O were distilled from sodium/benzophenone; CH_2Cl_2 and Et_3N were distilled from CaH_2; toluene was distilled from sodium.

X-ray data crystal structure analyses: Suitable crystals were selected and data collected on a Bruker Nonius Kappa CCD Area Detector equipped with a Bruker Nonius FR591 rotating anode (λ(MoKα) = 0.71073 Å) at 120 K driven by COLLECT [50] and processed by DENZO [51] software and corrected for absorption by using SADABS [52]. The structures were determined in SHELXS-97 and refined using SHELXL-97 [53]. All non-hydrogen atoms were refined anisotropically with hydrogen atoms included in idealised positions with thermal parameters riding on those of the parent atom.

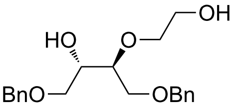
syn-1,4-Bis(benzyloxy)-3-fluorobutan-2-ol (**5**)



meso-**4** *rac*-**5**

KHF_2 (9.57g, 123 mmol) was added to a mixture of epoxide **4** (17.4 g, 61.3 mmol) and $Bu_4NH_2F_3$ (10.6 g, 35.2 mmol) and the mixture stirred at 115 °C for 2.5 days. Et_2O (300 mL) was added and the solution poured into sat. $NaHCO_3$ (200 mL). The organic layer was washed successively with sat. $NaHCO_3$ (100 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether 10% to 20%) to afford fluorohydrin **5** as a colourless oil (17.0 g, 91%). IR ν_{max} (cm^{-1}) 3062 w, 3030 w, 2993 w, 2858 w, 1496 w, 1453 m, 1369 w, 1088 s; ^{1}H NMR (400 MHz, $CDCl_3$) 7.42–7.20 (10H, m, ArH), 4.74 (1H, ddt, *J* = 47.5, 5.5, 3.5 Hz, CHF), 4.60 (1H, d, *J* = 12.0 Hz, $C\underline{H}_aH_bPh$), 4.58 (1H, d, *J* = 12.0 Hz, $C\underline{H}_cH_dPh$), 4.56 (1H, d, *J* = 12.0 Hz, $CH_a\underline{H}_bPh$), 4.54 (1H, d, *J* = 12.0 Hz, $CH_c\underline{H}_dPh$), 4.04 (1H, dm, *J* = 22.0 Hz, $C\underline{H}OH$), 3.80 (1H, ddd, *J* = 23.0, 11.0, 4.0 Hz, $C\underline{H}_aH_bOBn$), 3.76 (1H, ddd, *J* = 24.0, 11.0, 5.0 Hz, $CH_a\underline{H}_bOBn$), 3.63 (1H, ddd, *J* = 10.0, 5.0, 1.0 Hz, $C\underline{H}_cH_dOBn$), 3.59 (1H, ddd, *J* = 10.0, 6.5, 1.0 Hz, $CH_c\underline{H}_dOBn$), 2.61 (1H, bd, *J* = 4.0 Hz, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 137.9 (C_{Ar}), 137.7 (C_{Ar}), 128.6 (CH_{Ar}), 128.0 (CH_{Ar}), 127.9 (CH_{Ar}), 91.8 (d, *J* = 175.0 Hz, CHF), 73.9 (CH_2Ph), 73.7 (CH_2Ph), 70.37 (d, *J* = 5.5 Hz, CH_2OBn), 70.34 (d, *J* = 20.0 Hz, CHOH), 69.8 (d, *J* = 23.0 Hz, CH_2OBn) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) −204.3 (1F, dq, *J* = 46.7, 23.4) ppm; ES$^+$ *m*/*z* (%) 327 ((M+Na)$^+$, 100); HRMS (ES$^+$) for $C_{18}H_{21}FO_3Na$ (M+Na)$^+$: Calcd 327.1367; Measured 327.1364.

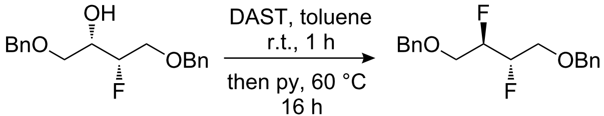
Data for *syn*-3-(2-hydroxyethyl)-1,4-bis(benzyloxy)butan-2-ol (**6**)



rac-**6**

Colourless oil. IR ν_{max} (cm^{-1}) 3399 br, 3062 w, 3030 w, 2863 w, 1496 w, 1483 m, 1091 s; ^{1}H NMR (400 MHz, $CDCl_3$) 7.40–7.27 (10H, m), 4.54 (4H, s), 3.87 (1H, q, *J* = 5.5 Hz), 3.78–3.60 (7H, m), 3.58 (1H, dd, *J* = 10.0, 5.0 Hz), 3.51 (1H, dd, *J* = 9.5, 6.0 Hz), 3.25–2.30 (2H, br, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 137.9 (C_{Ar}), 137.7 (C_{Ar}), 128.61 (CH_{Ar}), 128.59 (CH_{Ar}), 128.01 (CH_{Ar}), 127.99 (CH_{Ar}), 127.92 (CH_{Ar}), 79.4 (CHO), 73.7 (CH_2Ph), 73.6 (CH_2Ph), 73.2 (CH_2O), 71.0 (CH_2O), 70.9 (CHOH), 70.6 (CH_2O), 62.3 (CH_2O) ppm; ES$^+$ *m*/*z* (%) 715 ((2M+Na)$^+$, 20); HRMS (ES$^+$) for $C_{20}H_{26}O_5Na$ (M+Na)$^+$: Calcd 369.1672; Measured 369.1667.

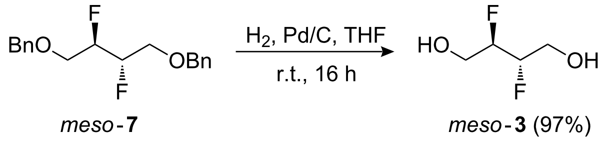
meso-1,4-Bis(benzyloxy)-2,3-difluorobutane (**7**)



5 *meso*-**7** (59%)

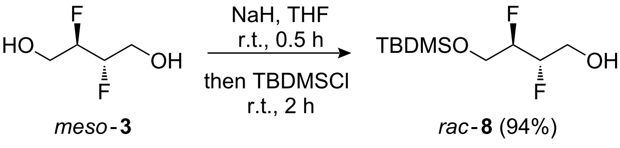
DAST (9.6 mL, 72.7 mmol) was added to a solution of fluorohydrin **5** (17.0 g, 55.9 mmol) in toluene (75 mL) and the mixture stirred at r.t. for 5 min. Pyridine (11.9 mL, 145 mmol) was then added and the solution stirred at 70 °C for a further 16 h. The reaction mixture was cooled, poured into sat. $NaHCO_3$ (100 mL) and Et_2O (100 mL). The organic layer was washed successively with sat. $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was quickly purified by column chromatography (EtOAc/petroleum ether 0% to 5%) to afford a mixture which was recrystallised from hot petroleum ether. The filtrate was concentrated and recrystallised again from hot petroleum ether. The recrystallisation process was carried out for a third time to afford difluoride **7** as a white crystalline solid (overall yield 10.1 g, 59%). mp 56–57 °C; IR ν_{max} (cm^{-1}) 3058 w, 3030 w, 2916 w, 2878 w, 1607 w, 1496 w, 1449 m, 1137 s, 1048 s; ^1H NMR (400 MHz, $CDCl_3$) 7.40–7.27 (10H, m, ArH), 4.96–4.78 (2H, m, CHF × 2), 4.61 (4H, s, CH_2Ph × 2), 3.88−3.71 (4H, m, CH_2OBn) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 137.8 (C_{Ar} × 2), 128.6 (CH_{Ar} × 4), 128.0 (CH_{Ar} × 2), 127.8 (CH_{Ar} × 4), 90.0 (dd, J = 175.5, 27.5 Hz, ABX, $^{13}\underline{C}HF$-^{12}CHF × 2), 73.8 (CH_2Ph × 2), 68.4 (m, ABX, $^{13}\underline{C}H_2CHFCHF$ × 2) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) −198.7 ppm; ES^+ m/z (%) 329 ($(M+Na)^+$, 100); HRMS (ES^+) for $C_{18}H_{20}F_2O_2Na$ $(M+Na)^+$: Calcd 329.1324; Measured 329.1319.

meso-2,3-Difluorobutane-1,4-diol (**3**)



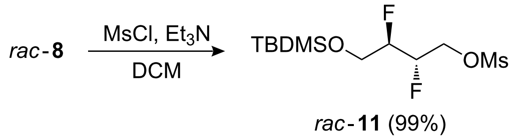
Pd/C (5%; 13.9 g, 6.5 mmol) was added to a solution of difluoride **7** (10.0 g, 32.7 mmol) in THF (108 mL) and the mixture stirred at r.t. for 16 h under a H_2 atmosphere (balloon). The suspension was filtered through celite, washed with MeOH and concentrated in vacuo. The crude product was purified by column chromatography (acetone/petroleum ether 30% to 50%) to afford diol **3** as a white crystalline solid (4.0 g, 97%). mp 99–101 °C; IR ν_{max} (cm^{-1}) 3329 br, 2936 br, 1647 br, 1042 s; ^1H NMR (400 MHz, $CDCl_3$) 4.85–4.70 (2H, m, CHF × 2), 4.08–3.83 (4H, m, CH_2OH × 2), 1.92 (2H, t, J = 6.5 Hz, OH × 2) ppm; ^{13}C NMR (100 MHz, acetone-d_6) 92.6 (dd, J = 173.0, 26.0 Hz, ABX, $^{13}\underline{C}HF$-^{12}CHF × 2), 61.2 (m, ABX, $^{13}\underline{C}H_2CHFCHF$ × 2) ppm; $^{19}F\{^1H\}$ NMR (282 MHz, acetone-d_6) −200.5 ppm; HRMS (ES^+) for $C_4H_8F_2O_2Na$ $(M+Na)^+$: Calcd 149.0385; Measured 149.0384.

anti-4-*tert*-Butyldimethylsilanyloxy-2,3-difluorobutan-1-ol (**8**)



NaH (60% dispersion in mineral oil; 1.40 g, 34.9 mmol) was added to a solution of diol **3** (4.0 g, 31.7 mmol) in THF (64 mL) and the mixture stirred at r.t. for 30 min. TBDMSCl (5.26 g, 34.9 mmol) was then added and the solution stirred at r.t. for a further 2 h. The reaction mixture was quenched with H_2O (150 mL) and extracted with Et_2O (200 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (neat petroleum ether, then acetone/petroleum ether 10%) to afford silyl ether **8** as a colourless oil (7.14 g, 94%). IR ν_{max} (cm^{-1}) 3354 br, 2954 m, 2930 m, 2858 m, 1254 s, 1055 s; ^1H NMR (400 MHz, $CDCl_3$) 4.84–4.58 (2H, m, CHF × 2), 4.03–3.76 (4H, m, CH_2O × 2), 2.47 (1H, br, OH), 0.91 (9H, s, $SiC(CH_3)_3$), 0.09 (6H, s, $SiCH_3$ × 2) ppm; $^1H\{^{19}F\}$ NMR (400 MHz, $CDCl_3$) 4.77 (1H, ddd, J = 6.0, 5.0, 3.0 Hz, CHF), 4.69 (1H, dt, J = 6.1, 3.5 Hz, CHF) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 90.8 (dd, J = 170.5, 21.0 Hz, CHF), 90.5 (dd, J = 178.5, 30.5 Hz, CHF), 61.7 (dd, J = 21.5, 5.0 Hz, CH_2O), 61.3 (dd, J = 21.5, 5.0 Hz, CH_2O), 25.9 ($SiC(\underline{C}H_3)_3$), 18.4 (SiC), −5.38 (CH_3), −5.43 (CH_3) ppm; ^{19}F NMR (376.5 MHz, $CDCl_3$) −201.6 (d, J = 13.0 Hz), −201.9 (d, J = 13.0 Hz) ppm; ES^+ m/z (%) 263 ($(M+Na)^+$, 100); HRMS (ES^+) for $C_{10}H_{22}F_2O_2SiNa$ $(M+Na)^+$: Calcd 263.1249; Measured 263.1256.

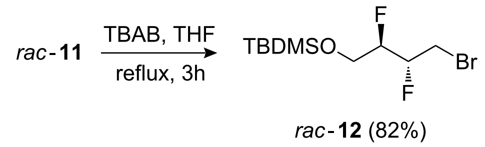
anti-4-*tert*-Butyldimethylsilanyloxy-2,3-difluorobutyl methanesulfonate (**11**)



MsCl (3.39 mL, 43.8 mmol) was added to a mixture of alcohol **8** (7.0 g, 29.2 mmol) and Et_3N (6.6 mL, 46.7 mmol) in DCM (64 mL) and the mixture stirred at r.t. for 2 h. The reaction mixture was cooled to 0 °C, filtered, washed with cold Et_2O/petroleum ether 1:1 and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford mesylate **11** as a colourless oil (9.29 g, 99%). [TLC monitoring should be performed using DCM/petroleum ether 6:4 until the complete consumption of the starting material, which has the same R_f value as the product when eluted with EtOAc/petroleum ether.] IR ν_{max} (cm^{-1}) 2955 m, 2931 m, 2858 m, 1473 w, 1360 s, 1256 m, 1178 s, 836 vs; ^1H NMR (400 MHz, $CDCl_3$) 4.98 (1H, ddtd, J = 46.9, 10.1, 6.6, 2.0 Hz, $C\underline{H}CH_2OS$), 4.68 (1H, dddt, J = 46.0, 9.6, 6.6, 3.3 Hz, $\underline{C}HCH_2OSi$), 4.62 (1H, ddt, J = 26.8, 12.1, 2.0 Hz, $C\underline{H}_aH_bOS$), 4.49 (1H, dddd, J = 25.3, 12.1, 6.1, 2.0 Hz, $CH_a\underline{H}_bOS$), 3.98 (1H, dddd, J = 18.5, 12.5, 3.5, 2.5 Hz, $C\underline{H}_aH_bOSi$), 3.87 (1H, dddd, J = 30.5, 12.5, 3.5, 2.5 Hz, $CH_a\underline{H}_bOSi$), 3.06 (3H, s, SCH_3), 0.91 (9H, s, $SiC(CH_3)_3$), 0.09 (6H, s, $SiCH_3$ × 2) ppm; $^1H\{^{19}F\}$ NMR (400 MHz, $CDCl_3$) 4.98 (1H, td, J = 6.1, 2.0 Hz, $C\underline{H}CH_2OS$), 4.68 (1H, dt, J = 6.6, 3.0 Hz, $C\underline{H}CH_2OSi$) ppm;

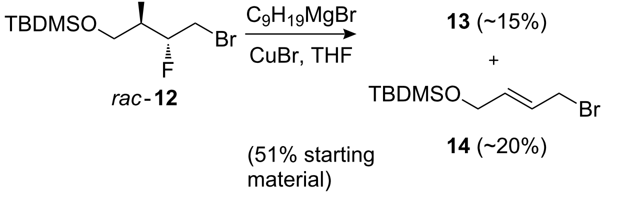
^{13}C NMR (100 MHz, CDCl$_3$) 90.2 (dd, J = 176.5, 27.0 Hz, $\underline{C}HCH_2OSi$), 87.5 (dd, J = 177.0, 27.5 Hz, $\underline{C}HCH_2OS$), 67.8 (dd, J = 21.0, 6.0 Hz, CH_2OS), 61.3 (dd, J = 21.5, 4.5 Hz, CH_2OSi), 37.7 (SCH_3), 25.9 ($SiC(\underline{C}H_3)_3$), 18.4 (SiC), −5.4 (CH_3), −5.5 (CH_3) ppm; ^{19}F{^{1}H} NMR (282 MHz, CDCl$_3$) −198.6 (d, $^3J_{F\text{-}F}$ = 13.5 Hz), −202.0 (d, $^3J_{F\text{-}F}$ = 13.5 Hz) ppm; ES$^+$ *m/z* (%) 341 ((M+Na)$^+$, 10); HRMS (ES$^+$) for $C_{11}H_{24}F_2O_4SSiNa$ (M+Na)$^+$: Calcd 341.1025; Measured 341.1030.

anti-4-Bromo-2,3-difluoro-1-*tert*-butyldimethylsilanyloxybutane (**12**)



TBAB (9.94 g, 30.8 mmol) was added to a solution of mesylate **11** (8.91 g, 28.0 mmol) in THF (28 mL) and the mixture stirred at reflux for 3 h. The reaction mixture was concentrated in vacuo and the crude product purified by column chromatography (EtOAc/petroleum ether 0% to 25%) to afford bromide **12** as a yellow oil (6.95 g, 82%). IR ν_{max} (cm^{-1}) 2954 w, 2930 w, 2886 w, 2858 w, 1472 w, 1464 w, 1256 m, 836 vs, 778 s; ^{1}H NMR (400 MHz, CDCl$_3$) 4.90 (1H, ddtd, J = 46.0, 12.0, 6.5, 3.0 Hz, $C\underline{H}F$), 4.66 (1H, dddt, J = 46.0, 9.0, 6.5, 3.5 Hz, $C\underline{H}F$), 3.99 (1H, dddd, J = 19.5, 12.0, 3.0, 2.5 Hz, $C\underline{H_a}H_b$), 3.89 (1H, dddd, J = 30.5, 12.5, 4.0, 3.0 Hz, $CH_a\underline{H_b}$), 3.75 (1H, dddd, J = 23.5, 12.0, 3.0, 1.5 Hz, $C\underline{H_c}H_d$), 3.63 (1H, dddd, J = 24.0, 12.0, 6.0, 2.0 Hz, $CH_c\underline{H_d}$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.10 (6H, s, $SiCH_3 \times 2$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) 91.0 (dd, J = 176.5, 27.0 Hz, $\underline{C}HF$), 88.1 (dd, J = 177.0, 28.0 Hz, CHF), 61.3 (dd, J = 21.5, 4.0 Hz, CH_2OSi), 30.4 (dd, J = 22.0, 4.5 Hz, CH_2Br), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 (SiC), −5.5 (CH_3), −5.6 (CH_3) ppm; ^{19}F NMR (282 MHz, CDCl$_3$) −192.6 (d, J = 15.0 Hz), −201.3 (d, J = 13.0 Hz) ppm; EI *m/z* (%) 245 ((M-*t*Bu)$^+$, 5), 303 and 305 (1:1, M$^+$, 10).

(*E*)-1-*tert*-Butyldimethylsilanyloxytridec-2-ene (**13**) and (*E*)-1-bromo-4-*tert*-butyldimethylsilanyloxybut-2-ene (**14**)



$C_9H_{19}MgBr$ (1.42 mL, 0.6M, solution in Et_2O, 0.852 mmol) was added to a mixture of CuBr (137 mg, 0.955 mmol) in THF (1.2 mL). The mixture was then transferred to a solution of bromide **12** (140 mg, 0.462 mmol) in THF (1.2 mL) at 0 °C, warmed to r.t. and stirred for 3 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (10 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (DCM/petroleum ether 0% to 20%) to afford alkene **13** [54] as a mixture of isomers (1:11) as a yellow oil (24.1 mg, ~15%) and alkene **14** as a yellow oil (26.2 mg, ~20%) along with 72.0 mg (51%) of the starting bromide **12**.

Alkene **13**: IR ν_{max} (cm^{-1}) 2955 w, 2924 s, 2854 m, 1463 w, 1378 w, 834 s, 774 s; ^{1}H NMR ((*E*)-isomer only, 400 MHz, CDCl$_3$) 5.64 (1H, dtt, J = 15.5, 6.5, 1.5 Hz, $C\underline{H}$=CH), 5.53 (1H, dtt, J = 15.0, 5.0, 1.0 Hz, CH=$C\underline{H}$), 4.13 (2H, dq, J = 5.5, 1.5 Hz, CH_2O), 2.06–2.00 (2H, m, CH_2), 1.40–1.21 (16H, m, $CH_2 \times 8$), 0.92 (9H, s, $SiC(CH_3)_3$), 0.93–0.86 (3H, m, CH_3), 0.08 (6H, s, $SiCH_3 \times 2$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) 131.8 ($\underline{C}$H=CH), 129.3 (CH=$\underline{C}$H), 64.3 (CH_2O), 32.4 (CH_2), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.2 ($SiC(\underline{C}H_3)_3$), 22.9 (CH_2), 18.6 (SiC), 14.3 (CH_3), −4.9 ($SiCH_3 \times 2$) ppm; EI *m/z* (%) 255.3 ((M-*t*Bu)$^+$, 57); HRMS (ES$^+$) for $C_{19}H_{40}OSiNa$ (M+Na)$^+$: Calcd 335.2746; Measured 335.2741.

Alkene **14**: Our spectra were in accord with literature copies of the spectra [55]: ^{1}H NMR (400 MHz, CDCl$_3$) 5.99−5.79 (2H, m, $C\underline{H}$=$C\underline{H}$), 4.21 (2H, ddd, J = 4.0, 2.5, 1.5 Hz, CH_2), 3.98 (2H, ddd, J = 7.5, 2.0, 1.0 Hz, CH_2), 0.92 (9H, s, $SiC(CH_3)_3$), 0.08 (6H, s, $SiCH_3 \times 2$) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) 134.7 ($\underline{C}$H=CH), 125.8 (CH=$\underline{C}$H), 62.6 (CH_2O), 32.4 (CH_2Br), 25.9 ($SiC(\underline{C}H_3)_3$), 18.4 (SiC), −5.3 ($SiCH_3 \times 2$); EI *m/z* (%) 207 and 209 ((M-*t*Bu)$^+$, 31, 1:1); HRMS (EI$^+$) for $C_6H_{12}O^{79}BrSi$ (M-*t*Bu)$^+$: Calcd 206.9835; Measured 206.9841.

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Shelf-stable electrophilic trifluoromethylating reagents: A brief historical perspective

Norio Shibata*[1], Andrej Matsnev[1] and Dominique Cahard*[2]

Review

Address:
[1]Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan and [2]UMR 6014 CNRS – C.O.B.R.A. Université et INSA de Rouen, 1 rue Tesnière, 76130 Mont Saint Aignan, France

Email:
Norio Shibata* - nozshiba@nitech.ac.jp; Dominique Cahard* - dominique.cahard@univ-rouen.fr

* Corresponding author

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Abstract

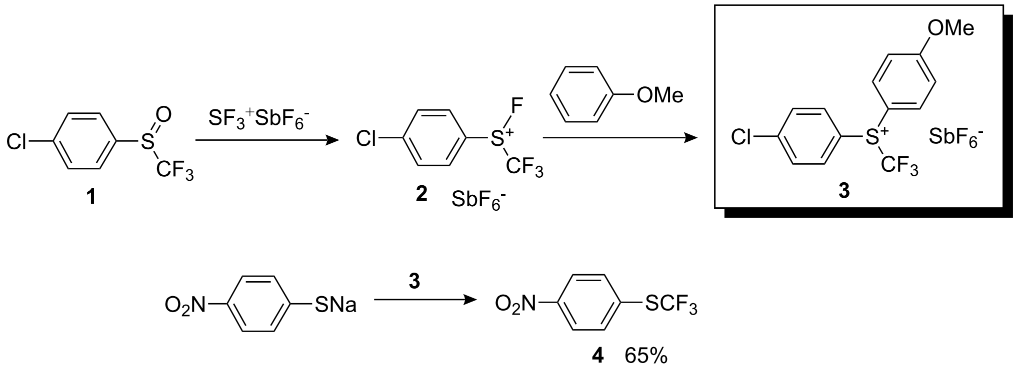
Since the discovery by Yagupolskii and co-workers that *S*-trifluoromethyl diarylsulfonium salts are effective for the trifluoromethylation of thiophenolates, the design and synthesis of electrophilic trifluoromethylating reagents have been extensively researched in both academia and industry, due to the significant unique features that trifluoromethylated compounds have in pharmaceuticals, agricultural chemicals, and functional materials. Several effective reagents have been developed by the groups of Yagupolskii, Umemoto, Shreeve, Adachi, Magnier, Togni and Shibata. Due to the high stability and reactivity of these reagents, a series of Umemoto reagents, Togni reagent and Shibata reagent are now commercially available. In this review, we wish to briefly provide a historical perspective of the development of so-called "shelf-stable electrophilic trifluoromethylating reagents", although this field is in constant development.

Review

The chemistry of fluoro-organic compounds is one of the areas of the life sciences that have developed most rapidly over the last 50 years, despite the fact that fluorine is "foreign" to the organic chemistry of life since not more than a dozen of compounds containing fluorine atom(s) have been found in nature [1,2]. It is a gross understatement to say that introduction of fluorine into organic molecules often leads to significant changes in their physical, chemical and biological properties [3]. The specific physical and chemical properties of fluorine in fluorine containing compounds, especially its strong electronegativity, lipophilicity and reaction ability, differ dramatically from those of other halogens and thus lead to changes in the interaction between the molecule and components in the surrounding biological environment [4]. Fluorine has now a prestigious position especially in the design of biologically active compounds, and indeed, nearly 20% of human medicines and 35% of agrochemicals on the market contain one or more fluorine atoms [5]. Among the increasingly powerful methods that have been developed for the direct introduction of fluorine into organic compounds, trifluoromethylation is one of the most direct and straightforward strategies in the synthesis of fluorine-containing organic compounds. Efficient transfer of the trifluoromethyl group from a reagent to a target molecule is key for the reaction, and the reagents are classified according to their radical, nucleophilic or electrophilic character. Radical trifluoromethylation can be achieved from various sources of trifluoromethyl radicals that include trifluoromethyl iodide, trifluoromethylacetyl and trifluoromethylsulfonyl derivatives, *S*-trifluoromethyl xanthates and others [6]. These reagents are well-suited for trifluoromethylation of aromatics, heteroaromatics and unsaturated double bonds [7]. Nucleophilic trifluoromethylation probably represents the most versatile and actively studied methodology available for the purpose of direct trifluoromethylation. The success of this methodology is greatly indebted to the availability of the reagents. The best known reagent for nucleophilic trifluoromethylation is “Ruppert’s reagent”, trifluoromethyltrimethylsilane (Me_3SiCF_3), which, under catalysis, produces a trifluoromethyl anion capable of reacting with various electrophiles [6,8-10]. Despite the fact that the idea of a reagent in which the perfluoroalkyl group could be positively charged would appear at first to be nonsensical, in 1984 Yagupolskii and co-workers discovered that *S*-(trifluoromethyl)diarylsulfonium salts are effective for the electrophilic trifluoromethylation of thiophenolates. Since this pioneering work, the design and synthesis of electrophilic trifluoromethylating reagents have been extensively investigated. Historically, the chalcogenium salts developed by Umemoto and co-workers are the most widely used reagents for effective trifluoromethylation of a wide range of nucleophiles. Typical reagents are the *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate and triflate, both of which are commercially available. More recently, in 2006, Togni and co-workers reported a new family of hypervalent iodine(III)-CF_3 reagents as mild electrophilic trifluoromethylating agents suitable for reactions with carbon- and heteroatom-centered nucleophiles. These reagents further demonstrated generality in trifluoromethylation of a wide range of nucleophiles including the trifluoromethylation of aliphatic alcohols and these are now commercially available. In 2008, we reported a novel fluorinated Johnson-type reagent for electrophilic trifluoromethylation of carbon-centered nucleophiles. This reagent has demonstrated high efficiency in trifluoromethylation of cyclic β-ketoesters and dicyanoalkylidenes and is now commercially available. We also disclosed an easy-access to extended Yagupolskii-Umemoto type reagents, *S*-(trifluoromethyl)thiophenium salts, through triflic acid-catalyzed intramolecular cyclization of *o*-ethynylaryltrifluoromethylsulfanes. A series of *S*-(trifluoromethyl)benzo[*b*]thiophenium salts have also demonstrated high ability for trifluoromethylation of β-ketoesters and dicyanoalkylidenes to yield the trifluoromethylated products with a quaternary carbon center, even if the substrates have a rather unreactive acyclic system. In this review, we wish to briefly provide a historical perspective of the development of so-called “shelf-stable electrophilic trifluoromethylating reagents”, although, as noted in the introduction, this field is in constant development.

First electrophilic trifluoromethylating reagent

In 1984, Yagupolskii and co-workers successfully achieved electrophilic trifluoromethylation by means of a diaryl(trifluoromethyl)sulfonium salt, $Ar_2S^+CF_3\ SbF_6^-$ (**3**) [11]. This trifluoromethylating reagent was obtained by treatment of aryltrifluoromethyl sulfoxide **1** with $SF_3^+\ SbF_6^-$ and subsequent reaction of the fluoro(trifluoromethyl) arylsulfonium salt **2** with electron-enriched arenes. Reagent **3** reacted with sodium *p*-nitrothiophenolate to give the corresponding trifluoromethyl sulfide **4** in 65% yield (Scheme 1). The substitution proceeded smoothly although electron-donating substituents on **3** partially

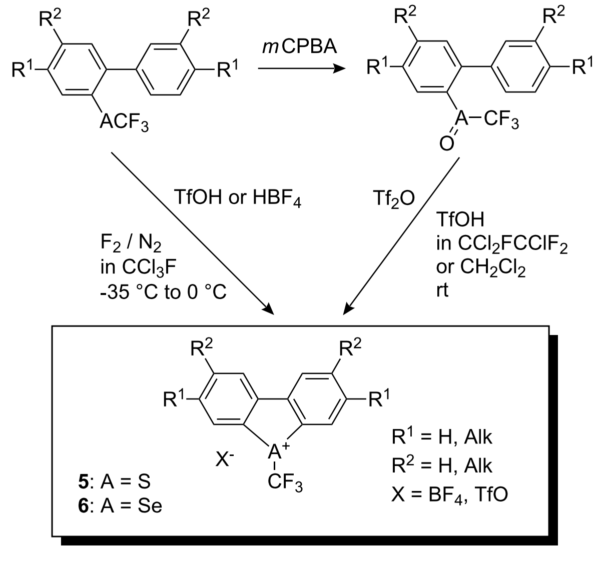


Scheme 1: Preparation of the first electrophilic trifluoromethylating reagent and its reaction with a thiophenolate.

neutralize the positive charge on the sulfur atom and thus significantly reduce the electrophilicity of the sulfonium moiety.

Umemoto reagents: (Trifluoromethyl)dibenzothio-, seleno- and telluro-phenium salts

In order to find reagents with a wider scope of application, Umemoto and co-workers developed new electrophilic trifluoromethylating reagents i.e. (trifluoromethyl)dibenzoheterocyclic salts with electron-donating and electron-withdrawing substituents in benzene rings for fine tuning of their electrophilicity [12-14]. (Trifluoromethyl)dibenzothio- and selenophenium salts **5** and **6**, respectively, were synthesized either by oxidation of the starting sulfides (or selenides) with *m*-chloroperbenzoic acid followed by cyclization of the corresponding sulfoxides (or selenoxides) either with triflic anhydride or by direct fluorination with 10% F_2/N_2 in the presence of one equivalent of triflic acid or HBF_4 (Scheme 2).

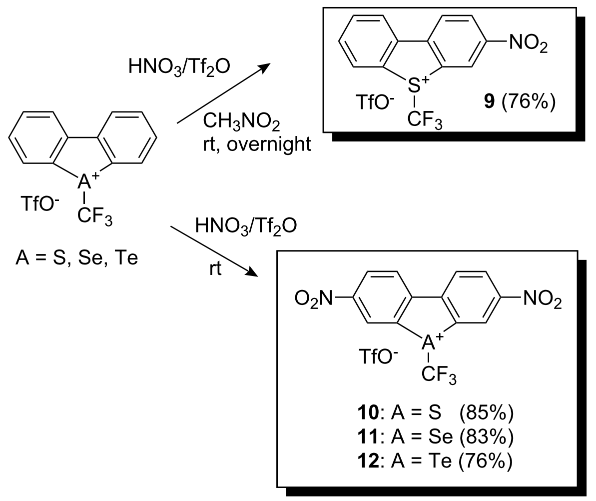


Scheme 2: Synthetic routes to *S*-CF_3 and *Se*-CF_3 dibenzochalcogenium salts.

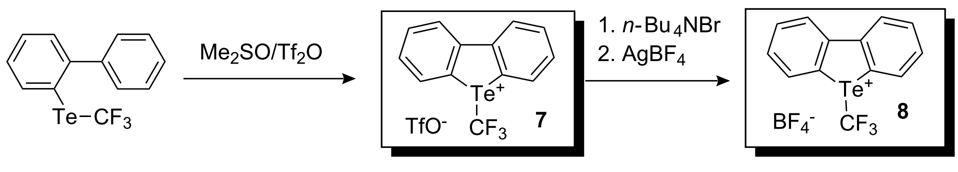
The tellurophenium salt **7** was synthesized in high yield by treatment of telluride starting material with an equimolar mixture of triflic anhydride and DMSO at 0 °C. Anion exchange was easily accomplished with silver tetrafluoroborate to afford **8** (Scheme 3) [13].

To increase the electrophilicity of salts **5**–**8**, the salts were nitrated with nitronium triflate generated in situ from nitric acid and triflic anhydride [12]. For example, mononitro-substituted thiophenium salt **9** was obtained after overnight stirring with nitronium triflate in nitromethane at room temperature, whereas treatment for 3 days in the absence of solvent gave the dinitro-substituted thiophenium salt **10**. Similar treatment of selenophenium and tellurophenium analogs for 3 h and 1 h, respectively led to dinitro-substituted products **11** and **12** in high yields (Scheme 4).

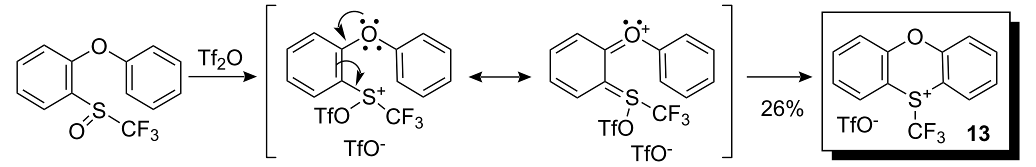
In addition to the reagents described above, Umemoto and co-workers synthesized the phenoxathiinium salt **13** by treating 2-phenoxyphenyl trifluoromethyl sulfoxide with triflic anhydride (Scheme 5). The reaction proceeded very slowly and in



Scheme 4: Nitration of (trifluoromethyl)dibenzochalcogenium salts.



Scheme 3: Synthesis of (trifluoromethyl)dibenzotellurophenium salts.

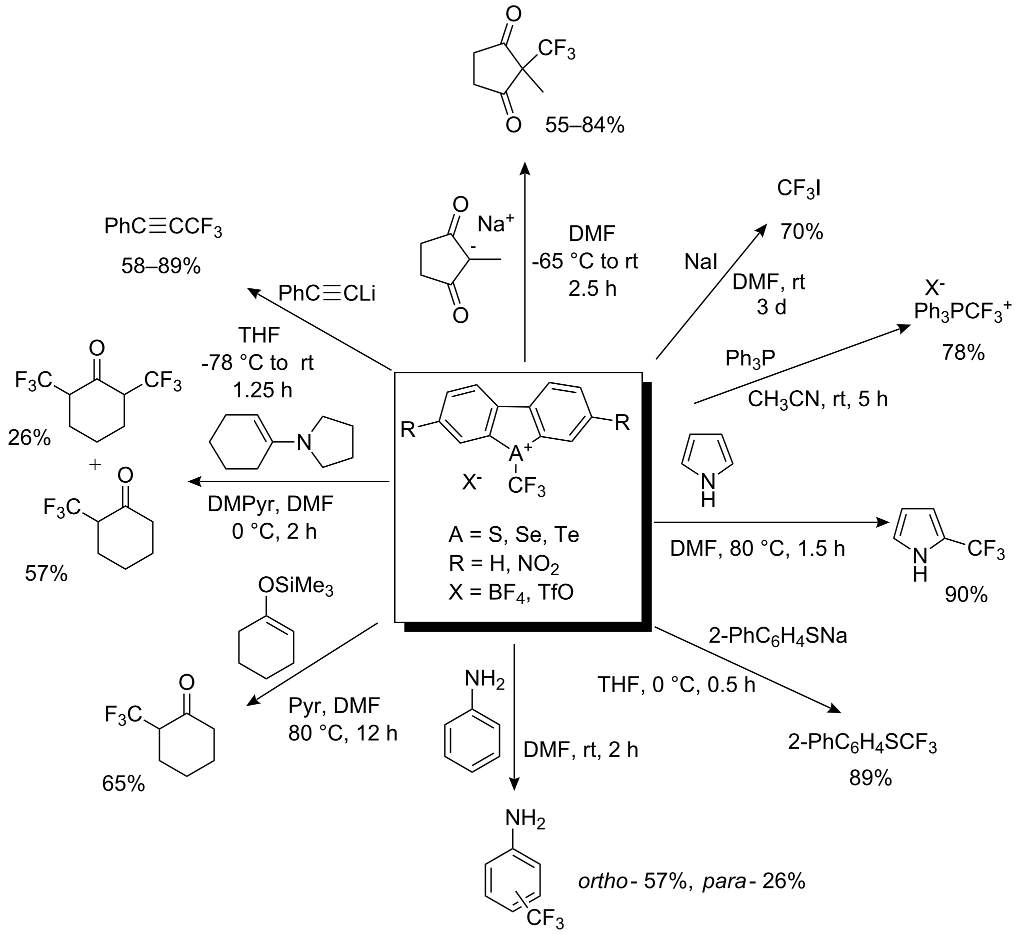


Scheme 5: Synthesis of a sulphonium salt with a bridged oxygen.

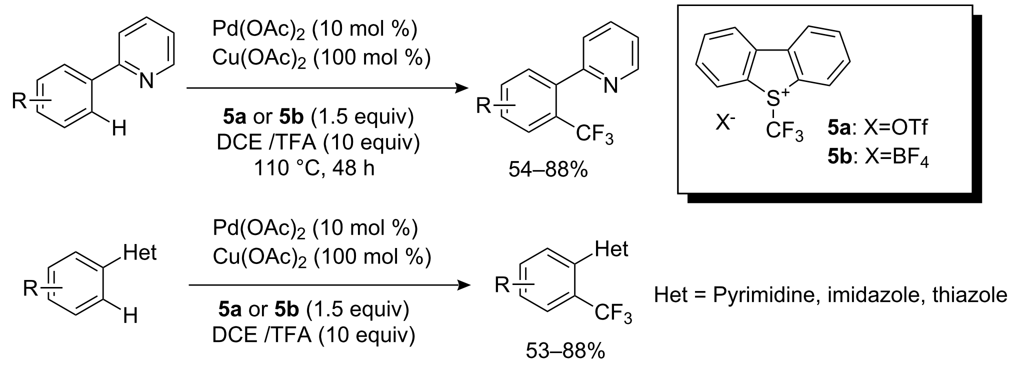
low yield (6 days, 26%), presumably because of the stabilization of a cationic sulfur atom in the intermediate by the electron-donating ether moiety [13].

The relative trifluoromethylating power of chalcogenium salts increased in the order Te < Se < S while nitro-substituted reagents showed higher reactivity than non-nitrated reagents [14]. Matching the power of the trifluoromethylating agent with the nucleophile (carbanion, silyl enol ether, enamine, phenol, aniline, phosphine, thiolate) made trifluoromethylation possible as illustrated in Scheme 6.

Just prior to submission of this manuscript, an interesting paper concerning trifluoromethylation of aromatics with Umemoto reagents by Yu and co-workers appeared [15]. 2-Pyridine substituted arenes were converted to the corresponding tri-



Scheme 6: Reactivity of (trifluoromethyl)dibenzochalcogenium salts.

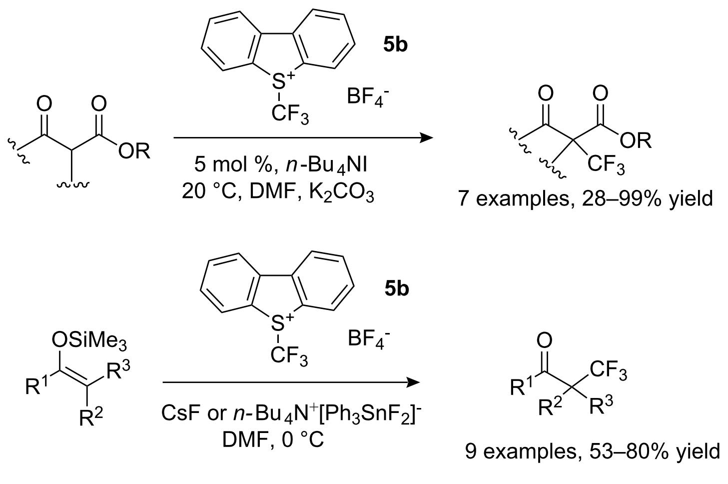


Scheme 7: Pd(II)-Catalyzed *ortho*-trifluoromethylation of heterocycle-substituted arenes by Umemoto's reagents.

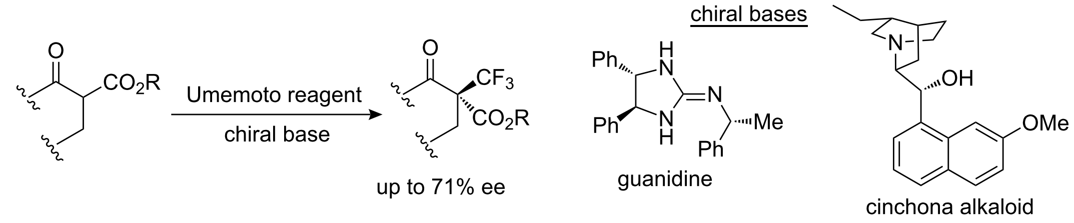
fluoromethylated arenes by treatment with Umemoto reagents, **5a** or **5b**, in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ at 110 °C in a mixture of dichloroethane (DCE) and 10 equiv of trifluoroacetic acid (TFA). Arenes having other heterocycles such as thiazole, imidazole, or pyrimidine also reacted under the same conditions to give *ortho*-trifluoromethylated arenes in good yields (Scheme 7). Togni's reagent (**37**, see later in the text) could be used for this reaction, although product yields were as low as 11%.

The reaction conditions for trifluoromethylation of silyl enol ethers and β-ketoesters were reinvestigated by one of us (D.C.) with reagents of type **5** in order to provide milder conditions. Indeed, cyclic and acyclic β-ketoesters were efficiently trifluoromethylated with *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate in the presence of a phase-transfer catalyst to afford the corresponding α-substituted α-trifluoromethyl β-ketoesters in good to excellent yields. In a second approach, **5** and tetrabutylammonium difluorotriphenylstannate were used for efficient electrophilic trifluoromethylation of various silyl enol ethers to give the corresponding α-trifluoromethyl ketones in good to high yields (Scheme 8) [16].

The α-substituted α-trifluoromethyl β-ketoesters feature a stereogenic carbon center that would be interesting to control. Chiral trifluoromethylating reagents are not currently known, with the exception of compound **18** (see Scheme 14 later in the text); however, no enantioselection was observed with this reagent. Umemoto was first to report, in 1994, an enantioselective electrophilic trifluoromethylation of a ketone enolate mediated by a chiral borepin derived from a binaphthol with *S*-(trifluoromethyl)dibenzothiophenium tetrafluoroborate **5b**.



Scheme 8: Mild electrophilic trifluoromethylation of β-ketoesters and silyl enol ethers.



Scheme 9: Enantioselective electrophilic trifluoromethylation of β-ketoesters.

The best enantiomeric excess was 45% for 20% yield [17]. In 2008–2009, we found that chiral nonracemic cinchona alkaloids and guanidines act as Brønsted bases to generate ammonium or guanidinium enolates for the enantioselective electrophilic trifluoromethylation of β-keto esters with Umemoto reagents with good enantioselectivities in the range 60–71% (Scheme 9) [18,19].

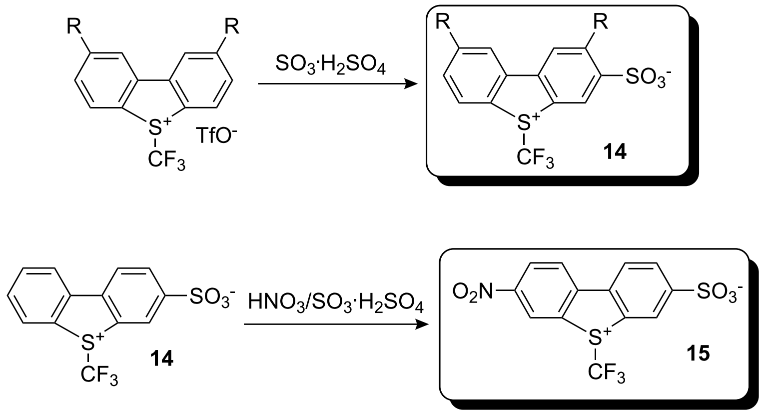
The reagents so far described lead to by-products (dibenzothio-, seleno-, and tellurophene) after the trifluoromethylation reaction that are sometimes difficult to separate from the desired trifluoromethylated products. To overcome this drawback, Umemoto and co-workers synthesized sulfonated analogs of (trifluoromethyl)dibenzochalcogenium salts by sulfonation with fuming sulfuric acid. Further nitration of sulfonate **14** led to a more reactive nitro-substituted derivative **15** (Scheme 10). These reagents allow easy separation of by-products from the desired trifluoromethylated products by simple filtration or washing [20].

Since it was of interest to find an attractive synthetic method to make these reagents commercially available, Umemoto and co-workers developed a new route appropriate for the large-scale preparation of *S*-(trifluoromethyl)dibenzothiophenium salts. For instance, 2-(phenyl)phenyl trifluoromethyl sulfoxide was converted into the corresponding sulfonium salt by treatment with an excess amount of 60% $SO_3 \cdot H_2SO_4$ at 0 °C followed by hydrogen sulfate anion exchange with tetrafluoroborate or triflate ion (Scheme 11). Increasing the reaction temperature during cyclization led to the corresponding water soluble 3-sulfonate analog **14** [21].

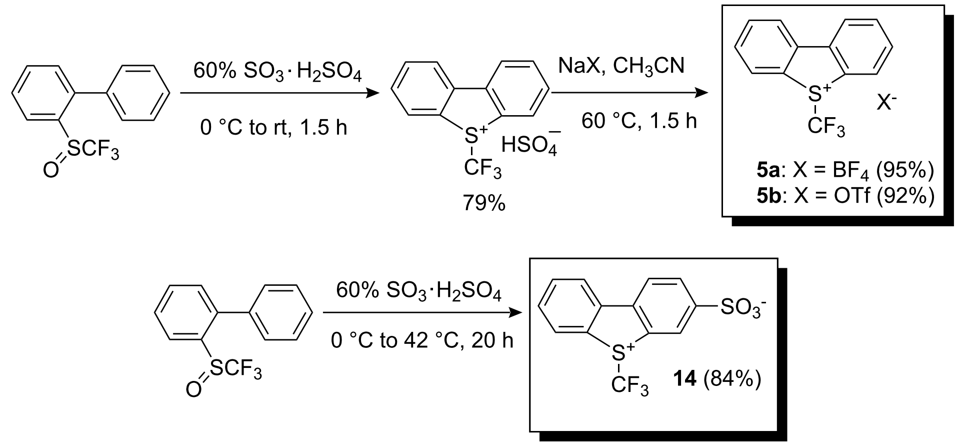
Extended Yagupolskii–Umemoto-type reagents

In 2010 a novel method for synthesis of *S*-(trifluoromethyl)sulfonium salts was developed by Shibata and co-workers. The new approach allowed access to Yagupolskii- and Umemoto-like compounds that are benzothiophenium salts rather than dibenzo analogs. *Ortho*-ethynylaryl- and alkyl-trifluoromethylsulfanes were cyclized under strong acidic conditions with triflic acid to give the corresponding sulfonium salts in 64–94% yields (Scheme 12). It should be noted, that in the presence of gold or copper salts no cyclization occurs [22].

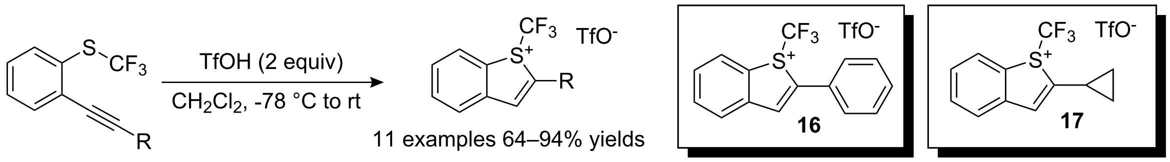
A number of sulfonium salts were obtained, in particular **16** and **17**, which were evaluated as trifluoromethylating agents for β-ketoesters and dicyanoalkylidenes. The cyclopropyl-substituted reagent **17** gave slightly better yields than the phenyl-substituted reagent **16** and much higher yields than the commercially available Umemoto or Togni reagents in trifluoro-



Scheme 10: Preparation of water-soluble *S*-(trifluoromethyl)dibenzothiophenium salts.



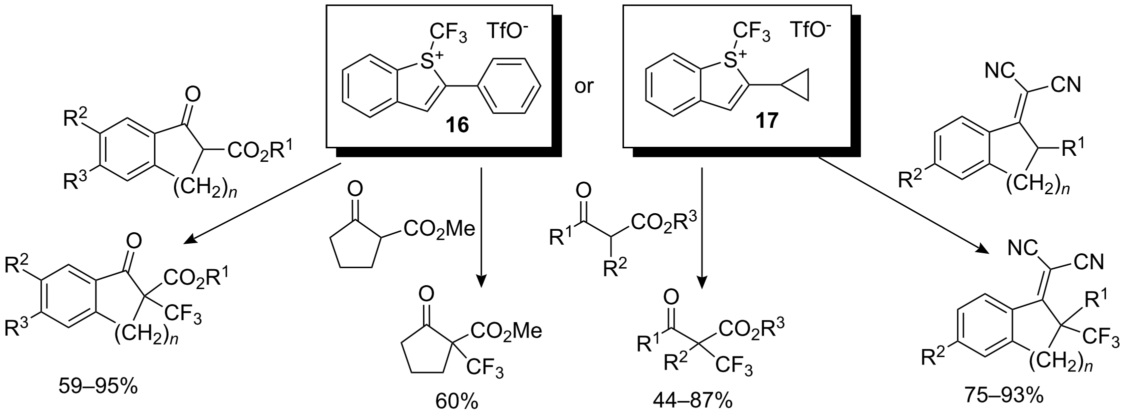
Scheme 11: Method for large-scale preparation of *S*-(trifluoromethyl)dibenzothiophenium salts.



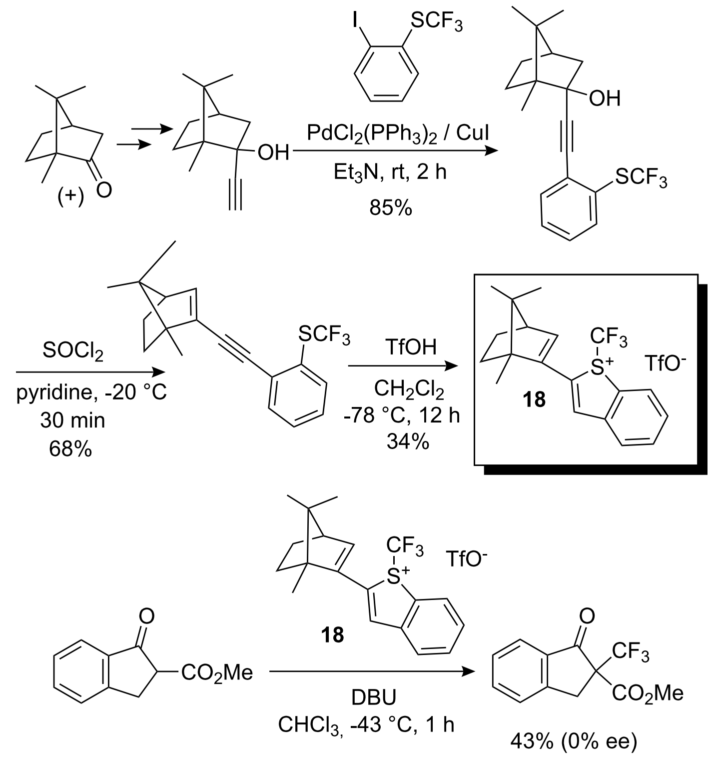
Scheme 12: Triflic acid catalyzed synthesis of 5-(trifluoromethyl)thiophenium salts.

methylation reactions. Of particular interest, the vinylogous trifluoromethylation of dicyanoalkylidenes afforded an access to allylic trifluoromethylated compounds (Scheme 13). All the reactions were carried out in acetonitrile at −43 °C to room temperature in the presence of a base: DBU or *tert*-butylimino-tri(pyrrolidino)phosphorane (1.2 to 2.2 equivalents).

One of the potential advantages of *S*-(trifluoromethyl)benzothiophenium salts is the ease with which the thiophene 2-position can be modified by chiral groups thus giving the possibility to achieve enantioselective trifluoromethylation of prochiral substrates. This is one of the important issues that is only partially solved in fluoro-organic chemistry. Therefore,



Scheme 13: Trifluoromethylation of β-ketoesters and dicyanoalkylidenes by *S*-(trifluoromethyl)benzothiophenium salts.



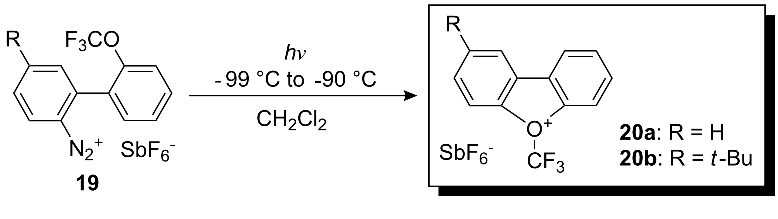
Scheme 14: Synthesis of chiral *S*-(trifluoromethyl)benzothiophenium salt **18** and attempt of enantioselective trifluoromethylation of a β-ketoester.

chiral reagent **18** was designed and synthesized from (1*R*)-(+)-camphor as shown in Scheme 14. Reagent **18** was obtained as a 1:1 mixture of diastereoisomers originating from the chirality at the sulfur atom. The trifluoromethylation of a β-ketoester by **18** was then carried out in the presence of DBU to furnish the trifluoromethylated β-ketoester in 43% yield but as a racemate (Scheme 14) [22].

O-(Trifluoromethyl)oxonium salts

All the previously described reagents allow trifluoromethylation only of soft nucleophiles and there is no possibility of preparing *N*-CF_3 or *O*-CF_3 compounds by direct trifluoromethylation via these compounds. *O*-Trifluoromethyl oxonium salts were anticipated to act as a useful source of the highly electrophilic trifluoromethyl group but until the work of Umemoto and co-workers initiated in 1994 and published as a full paper in 2007 [23], their synthesis remained problematic. *O*-(Trifluoromethyl)dibenzofuranium salts **20a**,**b** are thermally unstable compounds that are obtained by photochemical decomposition at very low temperature of diazonium salts **19** (several synthetic steps are required to obtain such precursors including the construction of the CF_3O-aryl moiety) (Scheme 15).

The trifluoromethyloxonium salts decompose to yield CF_4 and dibenzofuran derivatives from −70 °C. Decomposition of the salts is rapid at –30 °C. However, reaction with *O*- and *N*-centered nucleophiles was possible with in situ generated trifluoromethyloxonium salts obtained by irradiation of **19** with



Scheme 15: Synthesis of *O*-(trifluoromethyl)dibenzofuranium salts.

a high-pressure mercury lamp at low temperature in dichloromethane; other chalcogenium salts lead to *C*-trifluoromethylation.

Reagent **20b** with a *t*-Bu substituent was especially suitable for this process due to its high solubility in dichloromethane and was selected for investigating the trifluoromethylating activity in reactions with various *O*- and *N*-nucleophiles. Scheme 16 illustrates the type of substrates that could be efficiently subjected to electrophilic trifluoromethylation with **20b**. Alcohols were smoothly trifluoromethylated at low temperature in the presence of 2-chloropyridine or di(*iso*-propyl)ethylamine as an acid acceptor to give corresponding *O*-trifluoromethylated products in high yields. Primary and secondary amines also reacted with **20b** to afford *N*-CF_3 products in good yields. Tertiary amines as well as pyridines gave quaternary ammonium and pyridinium salts, respectively.

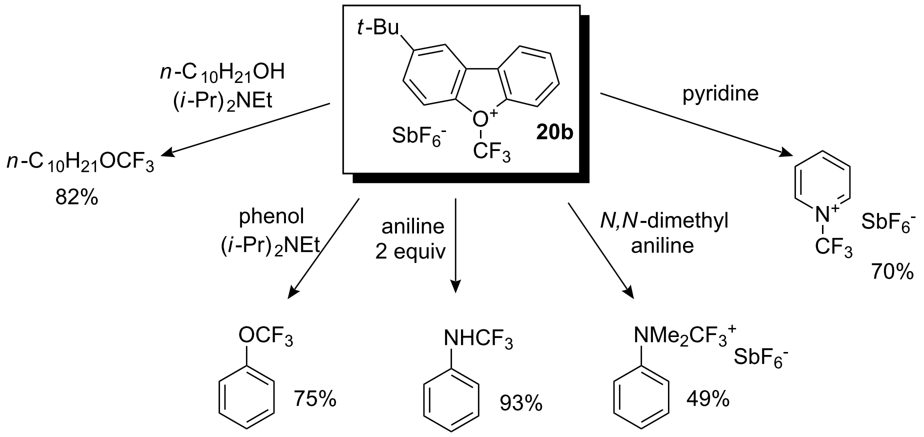
Electrophilic trifluoromethylation could also be achieved by thermal decomposition of 2-(trifluoromethoxy)biphenylyl-2′-diazonium salts such as **19a** (R=H) through in situ generation of a trifluoromethyloxonium salt. The yield of trifluoromethylated products was highly dependent on the counteranion as observed in the trifluoromethylation of phenol (Scheme 17) [23].

The synthetic application of thermally prepared *O*-(trifluoromethyl)dibenzofuranium hexafluoroantimonate from **19a** with various nucleophiles is illustrated in Scheme 18.

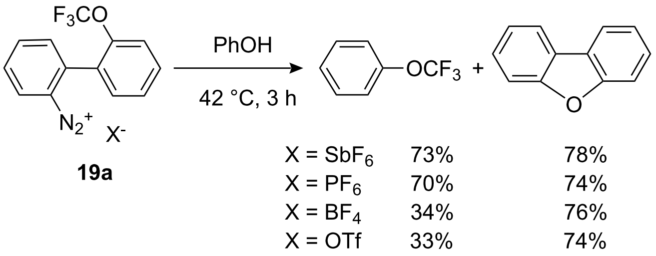
In both photochemical and thermal reactions only *O*- and *N*-trifluoromethylated products were observed. *O*-CF_3 reagents are the actual source of trifluoromethyl cation because of their ability to trifluoromethylate hard nucleophiles in contrast to other chalcogenium salts that react only with soft nucleophiles. However, this method suffers from several shortcomings, thus rendering it difficult to exploit.

S-(Trifluoromethyl)diarylsulfonium salts

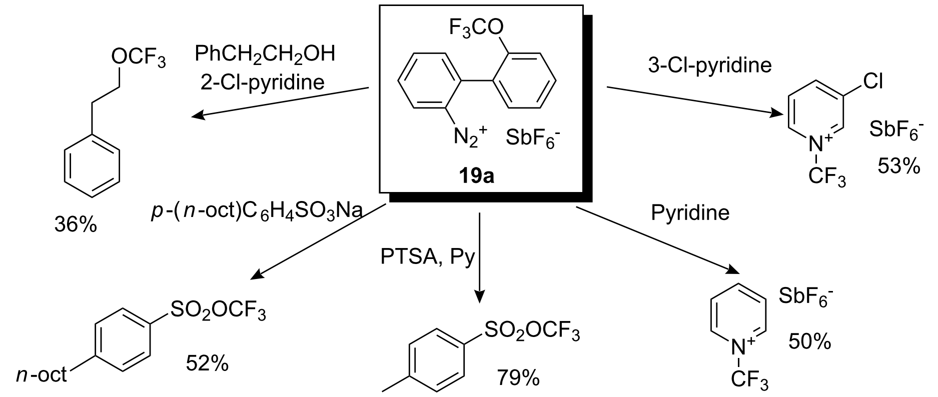
In 1998, Shreeve and co-workers developed a simpler method for the preparation of Yagupolskii-type reagents i.e. non-heterocyclic trifluoromethyldiarylsulfonium triflates. By treating phenyl trifluoromethylsulfoxide with benzene or its derivatives



Scheme 16: Photochemical *O*- and *N*-trifluoromethylation by **20b**.



Scheme 17: Thermal *O*-trifluoromethylation of phenol by diazonium salt **19a**. Effect of the counteranion.

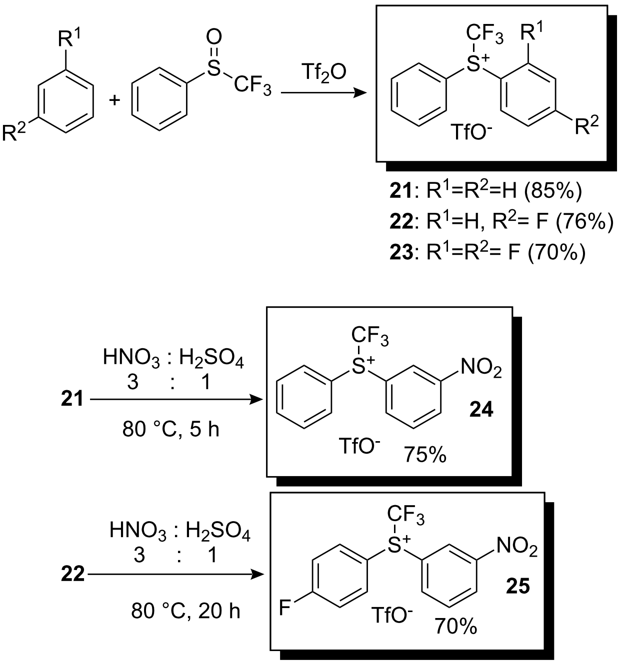


Scheme 18: Thermal *O*- and *N*-trifluoromethylations.

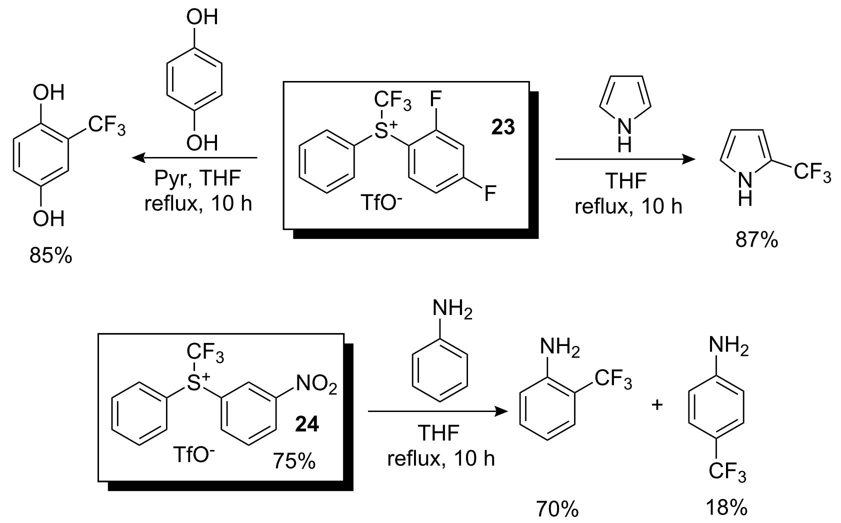
(fluorobenzene and 1,3-difluorobenzene) in triflic anhydride at room temperature for 12 h *S*-(trifluoromethyl)diphenylsulfonium triflate **21** and its derivatives, **22** and **23**, were obtained in good yields via intermolecular condensation (Scheme 19) [24]. The products were easily purified by column chromatography and recrystallization. To increase the reactivity towards nucleophiles, a nitro group was introduced in the meta-position of the benzene ring by a conventional nitration reaction.

Shreeve and co-workers used these reagents for the trifluoromethylation of aromatic systems [24]. After optimization of reaction conditions, they found that the best result for the trifluoromethylation of aniline with reagent **24** led to a mixture of 2-trifluoromethylaniline and 4-trifluoromethylaniline in a 4:1 ratio. *p*-Hydroquinone was trifluoromethylated with **23** to produce 2-trifluoromethyl-*p*-hydroquinone in 85% yield, whereas 2-trifluoromethylpyrrole was obtained from pyrrole in 87% yield with the same trifluoromethylating reagent (Scheme 20).

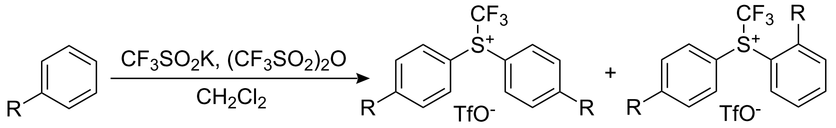
In 2006, the group of Blazejewski and Magnier presented a one-pot synthesis of Shreeve's reagents, *S*-(trifluoromethyl)diarylsulfonium salts, by reacting an aromatic compound with potassium triflinate in triflic anhydride and dichloromethane at



Scheme 19: Method of preparation of *S*-(trifluoromethyl)diphenylsulfonium triflates.



Scheme 20: Reactivity of some *S*-(trifluoromethyl)diarylsulfonium triflates.



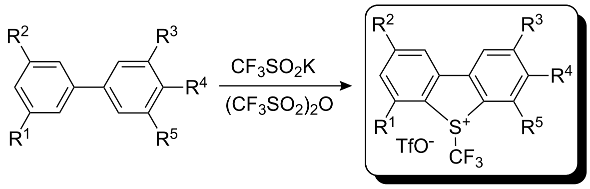
R	yield, %	yield, %
Me	62	11
H	60	0
Cl	50	0
F	46	0
OCF_3	15	0

Scheme 21: One-pot synthesis of *S*-(trifluoromethyl)diarylsulfonium triflates.

room temperature via the advantageous in situ formation of the aryl trifluoromethylsulfoxide (Scheme 21). The yields of the *S*-(trifluoromethyl)diarylsulfonium salts were moderate to good [25].

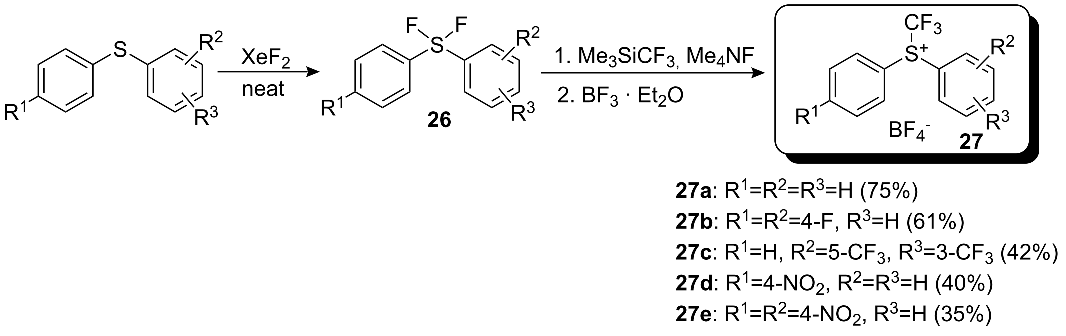
The same group later reported an improved experimental protocol that does not require solvent and gives better yields, up to 77% [26]. In this work, it was stressed that the purity of trifluoromethanesulfinate salts is an essential factor for the success of this reaction; low purity of the latter decreased the yield of the desired sulfonium salt. Starting from biphenyls, the method is applicable to the synthesis of Umemoto's type reagents; yields strongly depend on the presence or absence of substituents in the aromatic rings (Scheme 22).

Recently Yagupolskii and co-workers proposed a new route for the synthesis of *S*-(trifluoromethyl)diarylsulfonium salts by transformation of the nucleophilic trifluoromethylating reagent, CF_3SiMe_3, into an electrophilic one [27]. This method opens up the possibility for the preparation of various reagents with electron-withdrawing substituents even in the para-position of aromatic compounds. The difluorosulfurane **26**, obtained from the corresponding sulfide by treatment with xenon difluoride,



R^1	R^2	R^3	R^4	R^5	yield, %
H	H	H	H	H	12
H	Me	H	H	Me	15
Me	Me	H	H	H	36
Me	Me	Me	H	Me	46
Me	Me	H	NO_2	H	27

Scheme 22: One-pot synthesis of Umemoto's type reagents.



27a: R^1=R^2=R^3=H (75%)
27b: R^1=R^2=4-F, R^3=H (61%)
27c: R^1=H, R^2=5-CF$_3$, R^3=3-CF$_3$ (42%)
27d: R^1=4-NO$_2$, R^2=R^3=H (40%)
27e: R^1=R^2=4-NO$_2$, R^3=H (35%)

Scheme 23: Preparation of sulfonium salts by transformation of CF$_3^-$ into CF$_3^+$.

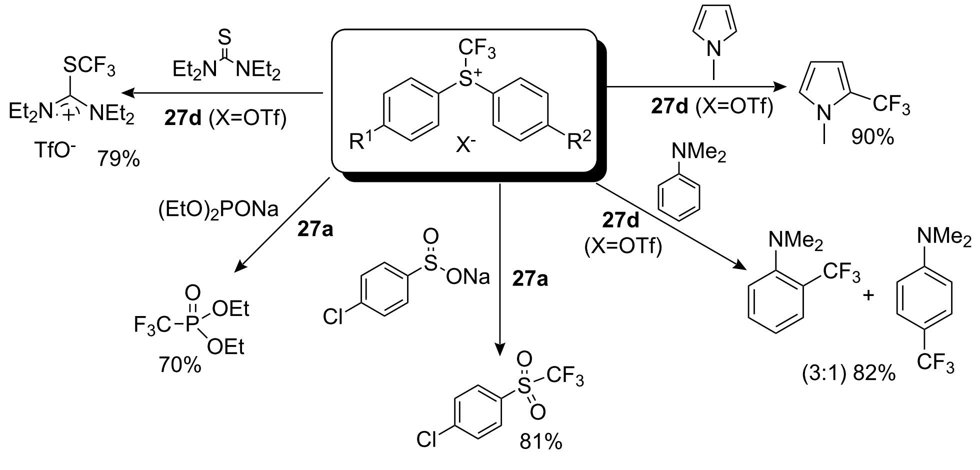
was reacted first with Me$_3$SiCF$_3$ in the presence of fluoride ions and then with boron trifluoride to give the trifluoromethylsulfonium salt **27** (Scheme 23).

The reactivity of these new sulfonium salts was investigated by examining their reactions with different nucleophiles (Scheme 24). Reagents **27d** and **27e** showed the best reactivity. The reaction with sodium iodide to yield CF$_3$I was studied. Compound **27a** reacted only when heated, whilst the reactions with **27d** and **27e** were completed at room temperature after 6 h and 3 h, respectively. For further investigation of trifluoromethylation ability, reagents **27a** and **27d** (X=OTf or BF$_4$) were selected. Reactions with *N*-methylpyrrole and *N*,*N*-dimethylaniline gave similar results to those observed using Shreeve reagents. The authors demonstrated the possibility of trifluoromethylation of sulfur-containing compounds with a partial negative charge on the sulfur atom. Thus, tetraethylthiourea reacted with **27d** (X=OTf) to give tetraethylamino(trifluoromethylthio) carbenium triflate. The reaction of **27a** (X=OTf) with sodium diethoxyphosphinate and sodium *p*-chlorophenylsulfinate led to diethyl trifluoromethanephosphonate and *p*-chlorophenyltrifluoromethylsulfone, respectively (Scheme 24).

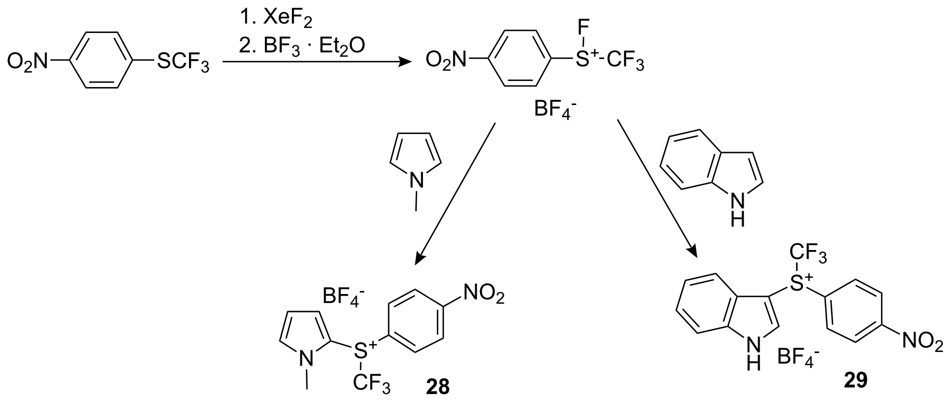
Interestingly, the method was developed for the synthesis of heteroaromatic diarylsulfonium salts. Thus, *p*-nitrophenyl trifluoromethyl sulfide was reacted first with xenon difluoride in the absence of solvent and then with boron trifluoride. The addition of an electron-rich heterocycle gave products **28** and **29** (mixtures of 2- and 3-substituted adducts; yields not provided) (Scheme 25). However, the trifluoromethylating ability of these compounds has not yet been investigated.

Neutral *S*–CF$_3$ reagents

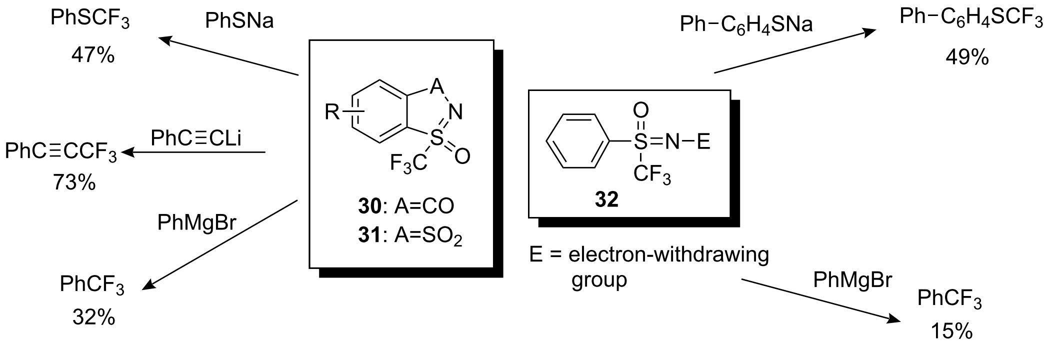
The first neutral reagents for electrophilic trifluoromethylation were synthesized by Adachi and co-workers at Daikin laboratories in 2003. 1-Oxo-1-trifluoromethyl-1λ^6-benzo[*d*]isothiazol-3-one (**30**), and 1-trifluoromethyl-benzo[1,3,2]dithiazole 1,3,3-trioxide (**31**) as well as acyclic sulfoximines **32** were synthesized as new trifluoromethylating agents (Scheme 26). It was



Scheme 24: Selected reactions with the new Yagupolskii reagents.



Scheme 25: Synthesis of heteroaryl-substituted sulfonium salts.



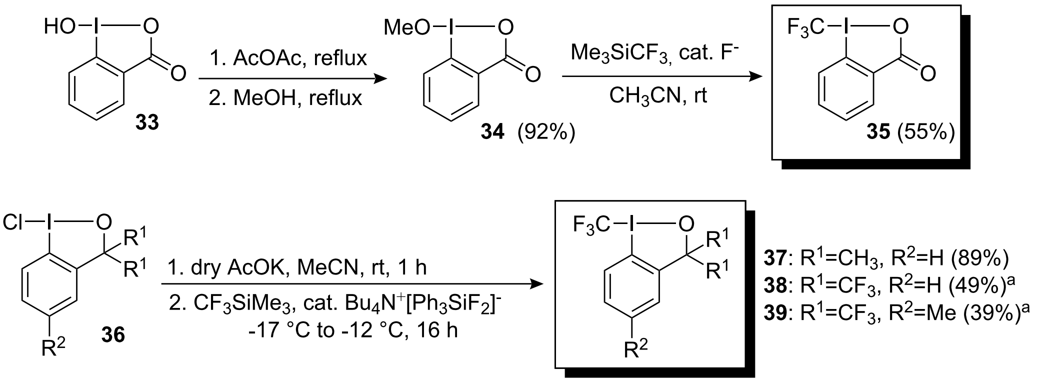
Scheme 26: First neutral *S*-CF$_3$ reagents.

possible to trifluoromethylate carbanions, enamines, and thiolate anions with these reagents, albeit in low to moderate yields [28].

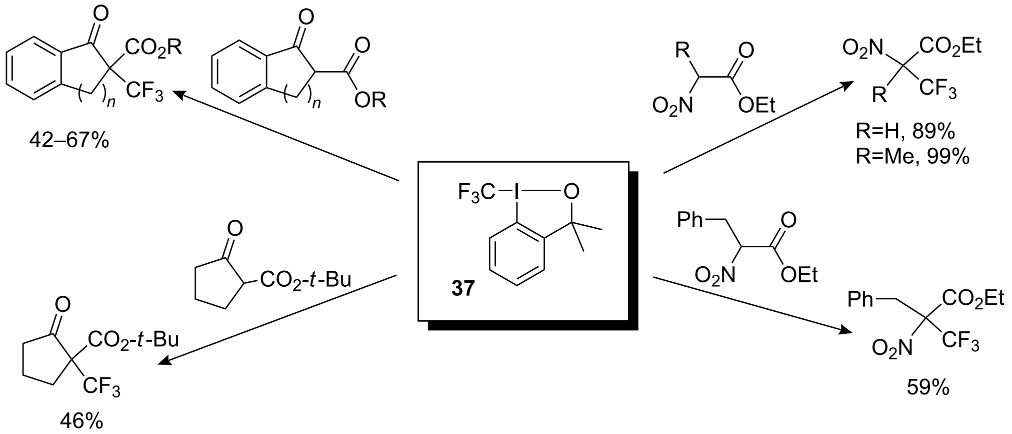
Neutral hypervalent iodine(III)–CF$_3$ reagent

Initial attempts by Yagupolskii and Umemoto to synthesize iodonium salts with a trifluoromethyl group were unsuccessful. Whilst iodonium salts including *p*-tolylperfluoroalkyliodonium chlorides, perfluoroalkylphenyliodonium triflates (FITS) and perfluoroalkylphenyliodonium hydrogen sulfates (FIS) have been reported as perfluoroalkylating agents, they do not function as trifluoromethylating agents [29-31]. The reason is the required synthetic intermediates have low stability compared to the intermediates with R$_f$ groups with more than one carbon atom. In 2006 Togni and co-workers reported a new family of hypervalent iodine compounds in which the CF$_3$ group is bonded directly to the iodine atom. The overall synthetic protocol depends on a formal umpolung of the CF$_3$ group since nucleophilic ligand displacement with CF$_3^-$ at the hypervalent iodine atom is carried out during the synthesis of these CF$_3^+$ donor reagents. For example, reaction of the methyl ester of 2-iodosylbenzoic acid **34**, with Me$_3$SiCF$_3$ in the presence of a catalytic amount of fluoride ions in CH$_3$CN at ambient temperature gave 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one (**35**) in 55% yield (Scheme 27) [32]. Reagents **37**–**39** were preferentially obtained in an improved, practical, one-pot procedure by substitution of chloro substituent in **36** by an acetoxy group followed by fluoride catalyzed substitution with Ruppert's reagent (Scheme 27) [33]. These reagents are shelf-stable, non-explosive under ambient conditions but should not be heated as solid materials.

These new electrophilic trifluoromethylating reagents were initially evaluated in reactions with carbonyl compounds such as β-keto esters and α-nitro esters. In particular, reagent **37** was found to be an effective trifluoromethylating agent. Under phase-transfer catalysis the β-keto esters derived from indanone, tetralone and pentanone in the presence of **37** gave the corresponding trifluoromethylated product in 42–67% yields. The new reagents showed a clear advantage in the reaction with α-nitro esters; the reaction proceeded smoothly in CH$_2$Cl$_2$ in the presence of a catalytic amount of CuCl$_2$ (Scheme 28) [33].



Scheme 27: Synthesis of Togni reagents. [a]Yield for the two-step procedure.



Scheme 28: Trifluoromethylation of *C*-nucleophiles with **37**.

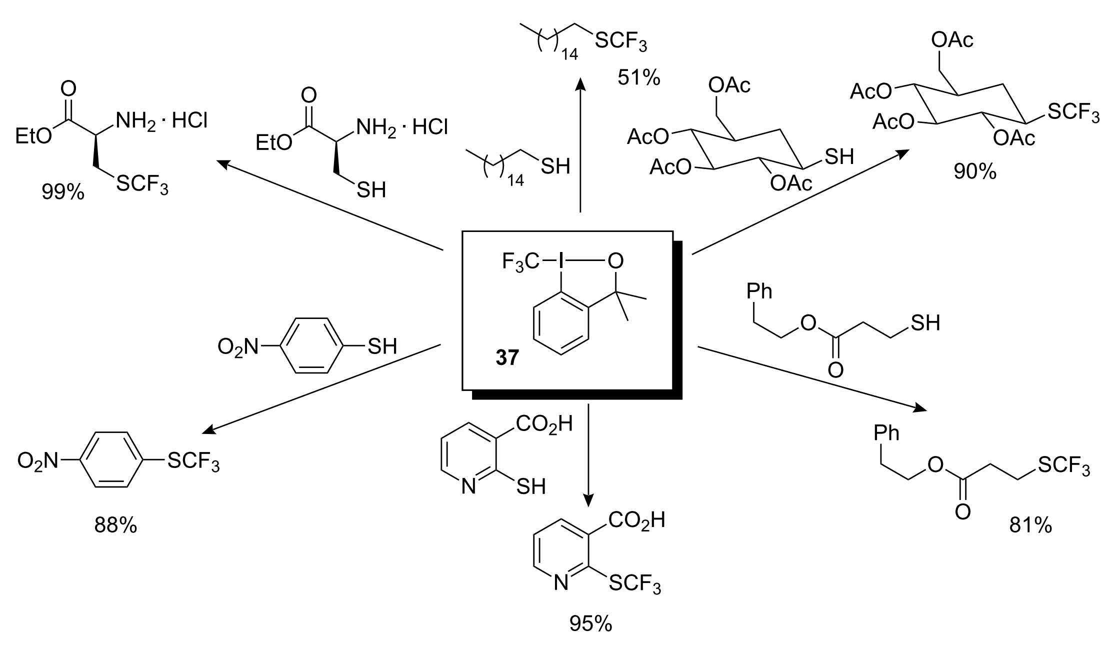
Interestingly, 2-(2-iodophenyl)propan-2-ol formed as by-product in the reactions of **37** with the substrates could be isolated and recycled.

The same group studied the reactivity of hypervalent iodine–CF_3 reagents with different types of sulfur-, phosphorus- and oxygen-centered nucleophiles. Firstly, it was demonstrated that sulfur-centered nucleophiles react with hypervalent iodine–CF_3 reagents. Thus, both aromatic and aliphatic thiols underwent *S*-trifluoromethylation smoothly in the presence of 1.1 equiv of **37** to afford the corresponding products in 51–99% yields (Scheme 29) [33]. The reaction outperforms other methods for synthesis of the SCF_3 motif and shows high functional-group tolerance, and has particular application for the synthesis of sugar and amino acid derivatives.

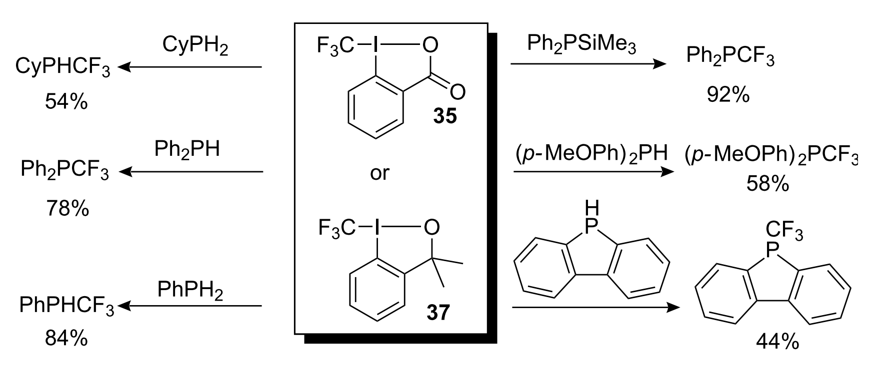
Reagents **35** and **37** have been identified as mild and efficient trifluoromethylating reagents for primary and secondary aryl- and alkylphosphines. Both reacted with equal efficiency at −78 °C to rt without any added base since the reagents generate base in situ (a carboxylate from **35** and an alcoholate from **37**). *P*-Trifluoromethyl phosphines were formed in moderate to high yields from either diarylphosphines or *P*-trimethylsilylated derivatives under the same reaction conditions (Scheme 30). By contrast, the corresponding lithium and potassium phosphides ($MPPh_2$) gave only trace amounts of the trifluoromethylated product [34,35].

The reaction of phenols with reagent **35** was investigated. From 2,4,6-trimethylphenol, the expected 1,3,5-trimethyl-2-(trifluoromethoxy)benzene was obtained only in poor yields in the range 4–15%. The trifluoromethylation was carried out in the presence of sodium hydride in DMF at different temperatures and occurred preferentially at the ortho- and para-positions of the aromatic ring (Scheme 31). Other substituted phenols were used as substrates under conditions yielding only *C*-trifluoromethylated products [36].

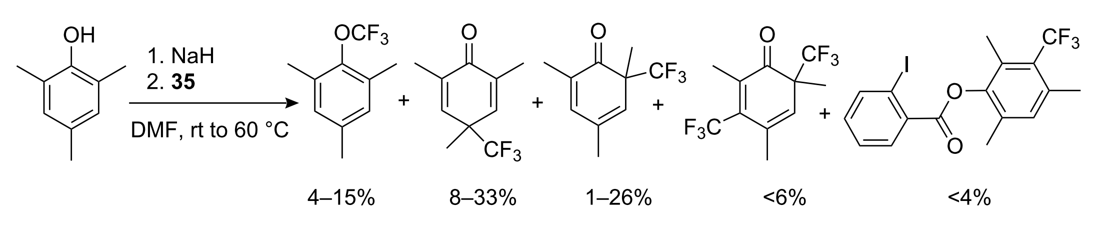
Although *O*-trifluoromethylation of phenols still remains an unsolved problem, the trifluoromethylation of aliphatic alco-



Scheme 29: Selected examples of trifluoromethylation of *S*-nucleophiles with **37**.

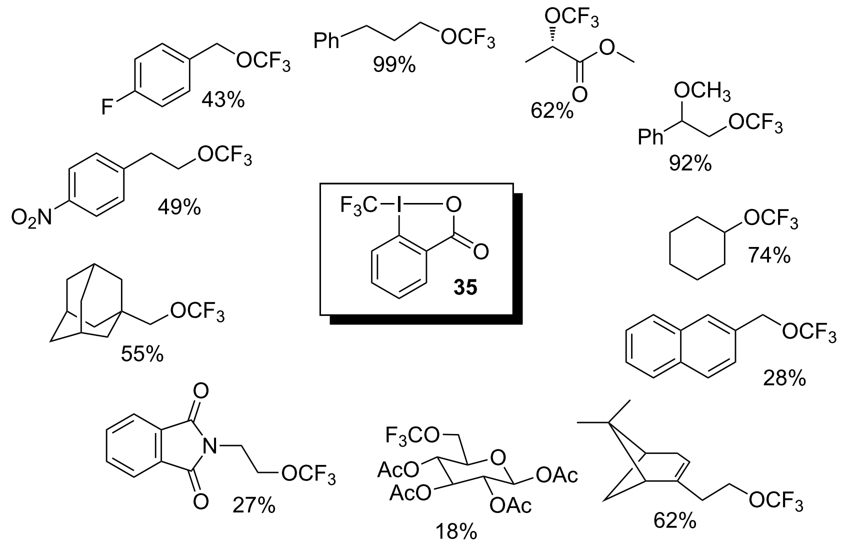


Scheme 30: Selected examples of trifluoromethylation of *P*-nucleophiles with **35** and **37**.



Scheme 31: Trifluoromethylation of 2,4,6-trimethylphenol with **35**.

hols is now possible as a result of the efforts of Togni and co-workers who discovered that the transfer of a CF_3 group to an alcohol oxygen atom could be achieved in the presence of zinc (II) salts. Thus, 1-pentanol was quantitatively converted to the corresponding trifluoromethyl ether, which was obtained in high yield, by treatment with reagent **35** in the presence of $Zn(OTf)_2$ or $Zn(NTf_2)_2$. An even higher yield of the trifluoromethyl ether resulted when the alcohol was used both as substrate and solvent in the presence of a catalytic amount of zinc salt. After optimisation of reaction conditions, different alco-



Scheme 32: Examples of *O*-trifluoromethylation of alcohols with **35** in the presence of 1 equiv of $Zn(NTf_2)_2$.

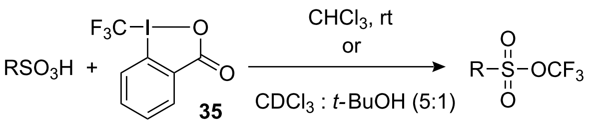
hols were subjected to the *O*-trifluoromethylation reaction. The reaction proceeded smoothly when primary and secondary aliphatic alcohols were used (Scheme 32). Alcohols such as *t*-BuOH, as well as phenols, could not be *O*-trifluoromethylated [37].

Further investigations into the trifluoromethylating ability of **35**, revealed that sulfonic acids undergo *O*-trifluoromethylation to give the corresponding trifluoromethyl sulfonates in good to high yields under facile reaction conditions, i.e., in chloroform, overnight, at ambient temperature (Scheme 33). The reagent **35** is activated by the Brønsted acidity of the sulfonic acids. No reaction took place with *p*-toluenesulfonate salts or with substrates having an internal base moiety such as 4-aminobenzenesulfonic acid [38].

The first highly enantioselective electrophilic trifluoromethylation of aldehydes has only very recently been reported by MacMillan by using a combination of organocatalysis with Togni's reagent **37** [39]. This report appeared only just after a photolytic approach, also reported by MacMillan, that employs $CF_3^{\bullet}$ radical generated from CF_3I [40]. However, the reaction with bench-stable Togni's reagent is mechanistically distinct from the previous radical approach (Scheme 34). In accord with a similar mechanism proposed by Togni [37], the resulting λ^3-iodane species **40** undergo rapid reductive elimination with stereoretentive CF_3 transfer. High enantioselectivities in the range 93–97% were measured for the corresponding alcohols because of post-reaction racemization of aldehydes. Although the scope of this asymmetric reaction is limited to aldehydes, the level of enantioselectivity is superior to that obtained in the enantioselective trifluoromethylation of β-ketoesters.

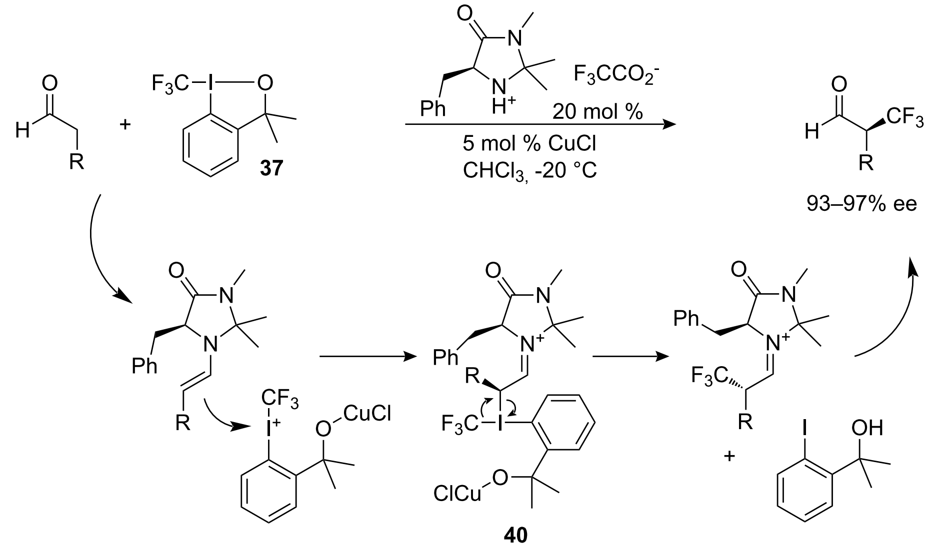
Fluorinated Johnson's type reagent

In 2008, a novel type of electrophilic trifluoromethylating agent, a trifluoro analog of Johnson's methyl-transfer reagent **41**, was synthesized by Shibata and co-workers. Transfer of the CF_3 group from **42** to various substrates proceeds via nucleophilic attack at the CF_3 group with elimination of *N*,*N*-dimethylbenzenesulfinamide. The synthetic route to the sulfoximinium salt **42** starts from phenyl trifluoromethyl sulfoxide as depicted



substrate	yield, %
2-Naphthalenesulfonic acid	67
(±)-10-Camphorsulfonic acid	75
4-Nitrobenzenesulfonic acid	76
4-Chlorobenzenesulfonic acid	60
Benzenesulfonic acid	42
4-Methylbenzenesulfonic acid	51
4-Ethylbenzenesulfonic acid	32
4-Hydroxybenzenesulfonic acid	45
4-Methoxybenzenesulfonic acid	75

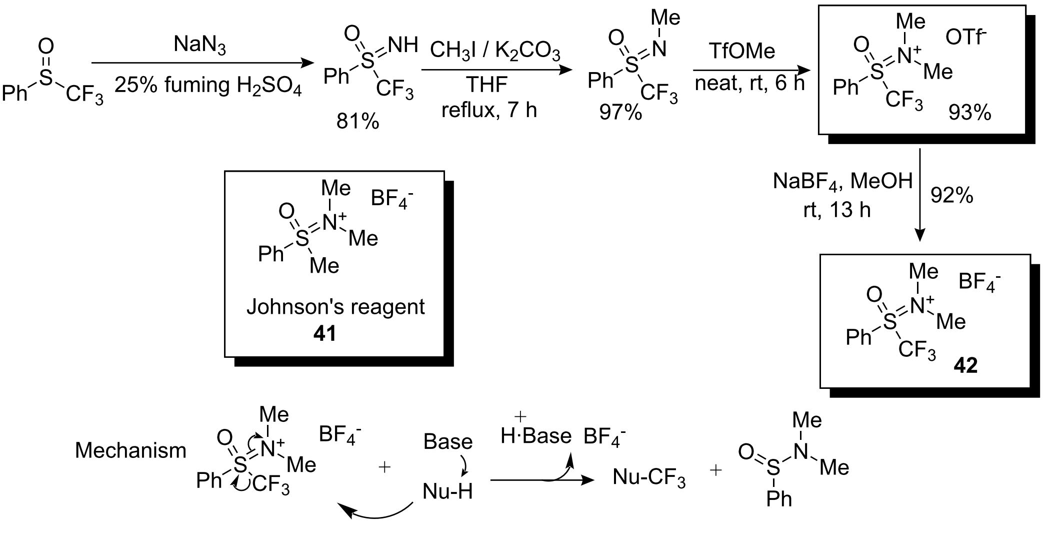
Scheme 33: Formation of trifluoromethyl sulfonates from sulfonic acids and **35**.



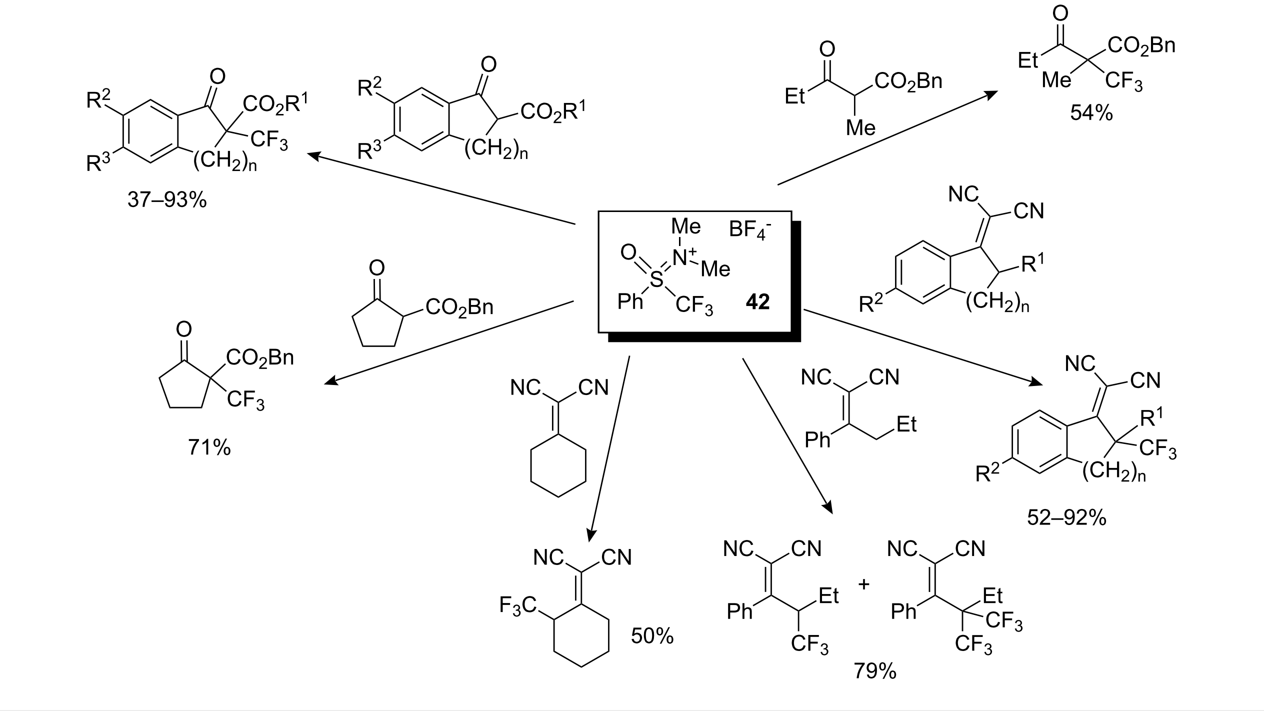
Scheme 34: Organocatalytic α-trifluoromethylation of aldehydes with **37**.

in Scheme 35. The triflate salt is an ionic liquid at room temperature whereas the tetrafluoroborate **42** is obtained as colorless crystals.

An initial series of experiments to optimize the reaction conditions for efficient trifluoromethyl group transfer to indanone carboxylate were found to be the use of DBU as base and dichloromethane as solvent at room temperature. Guanidine bases, such as TMG or TBD, and phosphazene bases P^1-*t*-Bu or P^2-Et were equally effective. The trifluoromethylation reaction did not take place with either pyridine or triethylamine. Transfer of trifluoromethyl group from **42** to various β-ketoesters and dicyanoalkylidenes was investigated. β-Ketoesters such as indanone, tetralone and oxocyclopentane carboxylates gave the corresponding trifluoromethylated products in 52–92% yields (Scheme 36). In the case of an acyclic ester, a good yield was achieved only in the presence of the phosphazene base P^2-Et. When the reaction was carried out in the presence of nitrobenzene there was no decrease in the yield of the desired product. Consequently, this process was classified as electrophilic trifluoromethylation. The first example of vinylogous trifluoromethylation of dicyanoalkylidenes was also reported with reagent **42** (Scheme 36). The corresponding trifluoromethylated dicyanoalkylidenes were obtained in good to high



Scheme 35: Synthesis of reagent **42** and mechanism of trifluoromethylation.



Scheme 36: Trifluoromethylation of β-ketoesters and dicyanoalkylidenes with **42**.

yields (50–92%) preferentially in the presence of P^1-*t*-Bu as base in CH_2Cl_2 at room temperature for 1 h [41]. Reagent **42** is now commercially available in Japan.

Conclusion

We have discussed the synthesis and reactivity of shelf-stable electrophilic trifluoromethylating reagents. Since the initial report in 1984 this field has been increasingly active, however, there are still high challenges due to the current limitations of these reagents. A broader substrate scope is highly desirable in order to cover reactions of both hard and soft nucleophiles. Mechanistic studies with appropriate analytical tools should be conducted in order to obtain more insight on the transfer of the electrophilic CF_3 group. A bimolecular nucleophilic substitution, S_N2 type mechanism, is often suggested, although a single electron transfer mechanism cannot be ruled out depending on the reagent and reaction conditions. Of special interest is the question of asymmetric trifluoromethylation: Is it possible to induce stereoselectivity by electrophilic trifluoromethylation with the aid of an optically active trifluoromethylating reagent? Both our research groups are currently attempting to provide an answer to this question. It is the authors' hope that this review will stimulate chemists to conduct further research that lead to the design of new reagents and to optimize the present ones for selective electrophilic trifluoromethylation of a wider range of substrates.

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of Organic Chemistry

Aromatic and heterocyclic perfluoroalkyl sulfides. Methods of preparation

Vladimir N. Boiko

Review

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Address:
Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya St. 5, 02094 Kiev, Ukraine

Email:
Vladimir N. Boiko - boikovolodymyr@yandex.ru

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Abstract

This review covers all of the common methods for the syntheses of aromatic and heterocyclic perfluoroalkyl sulfides, a class of compounds which is finding increasing application as starting materials for the preparation of agrochemicals, pharmaceutical products and, more generally, fine chemicals. A systematic approach is taken depending on the mode of incorporation of the SR_F groups and also on the type of reagents used.

Review

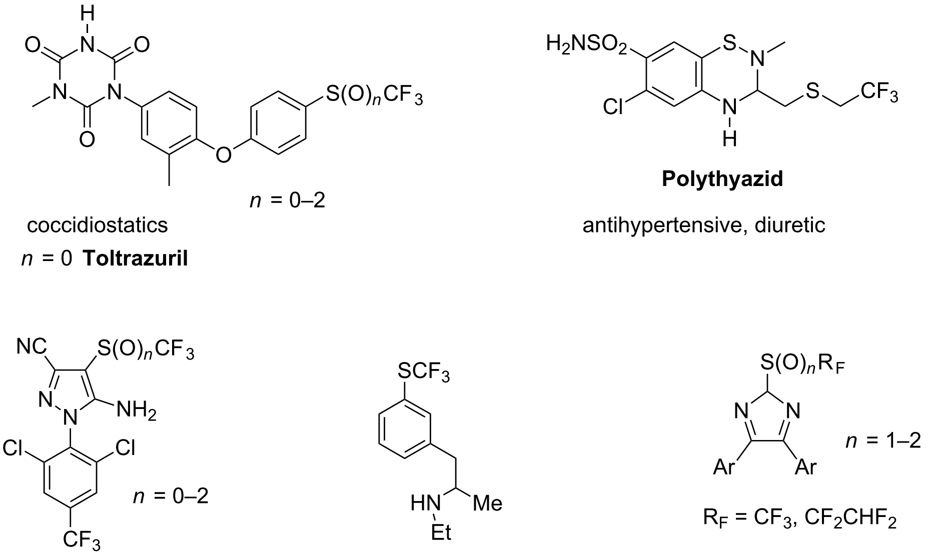
1. Introduction

Perfluoroalkyl sulfides of aromatic and heterocyclic compounds have been an important aspect in the general development of organofluorine chemistry over the last twenty years.

Alkyl aryl sulfides containing partly fluorinated aliphatic moieties have been widely used for a number of years. Their methods of preparation, for example, by the reaction of thiols with fluoro-olefins or with chloropolyfluoroalkanes are well known and have been widely used. In contrast, sulfides with fully fluorinated aliphatic chains have been limited to trifluoromethylated compounds. This was due to the unique preparation (at that time) of such compounds by means of two consecutive reaction steps: the chlorination of the side chain followed by replacement of the chlorine atoms by fluorine. This procedure enabled only the preparation of CF_3S-derivatives because it is not possible to synthesize perchloroalkylated aromatic sulfides larger than CCl_3S. This is currently still the case. Iodoperfluoroalkanes as perfluoroalkylating agents have only emerged rather recently.

New synthetic procedures to access this class of compounds have appeared which make use of novel intermediates. Thus, single-electron oxidation or reduction enables the generation of perfluoroalkyl radicals. Two-electron reduction of perfluoroalkyl iodides generates perfluoroalkyl carbanions, which may be stabilized by organophosphorus and organosilicon ligands and even by dimethylformamide.

One of the driving forces for the synthesis of perfluoroalkyl sulphides is the high lipophilic properties of perfluoroalkylthio



coccidiostatics

n = 0–2

n = 0 **Toltrazuril**

Polythyazid

antihypertensive, diuretic

insecticides

n = 0–2

n = 1 **Fipronil**

nervous anorexia treatment

n = 1–2

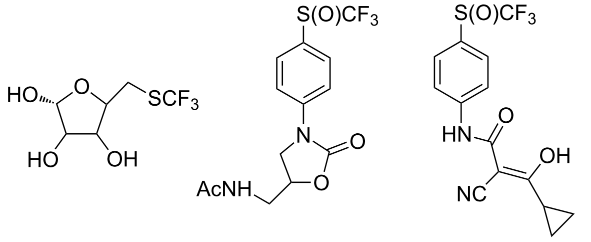
$R_F = CF_3, CF_2CHF_2$

anti-inflammatory

Figure 1: Examples of industrial fluorine-containing bio-active molecules.

groups (the greatest Hansch constant $\pi = 1.44$, belongs to SCF_3 group [1]), which increases the ability of such molecules to cross lipid membranes and creates opportunities for the modification of known and new drugs. Thus this group is a useful substituent in agrochemicals and pharmaceuticals [2-4]. Examples of bioactive compounds containing SCF_3, $SOCF_3$ and SO_2CF_3 groups are shown in Figure 1 and Figure 2.

The synthesis of a large number of potential hypotensive agents containing SR_F and SO_2R_F groups of the 1,4-dihydropyridine class and also of Losartan (Dup 753) analogues which are used clinically for the treatment of cardiovascular diseases have also been developed [5,6] (Figure 3).



antimalarial
antipneumonia

antibacterial

antihypertensive
anti-arthritic

Figure 2: $CF_3(S)$- and $CF_3(O)$-containing pharmacologically active compounds.

Losartan analogues

$R = C_4H_9$; $R' = SCF_3, SC_2F_5, SC_3F_7, OC_2F_5, SO_2C_3F_7$

$R = SC_2F_5, SC_3F_7, SC_4F_9$; $R' = H$

Nifedipin analogues

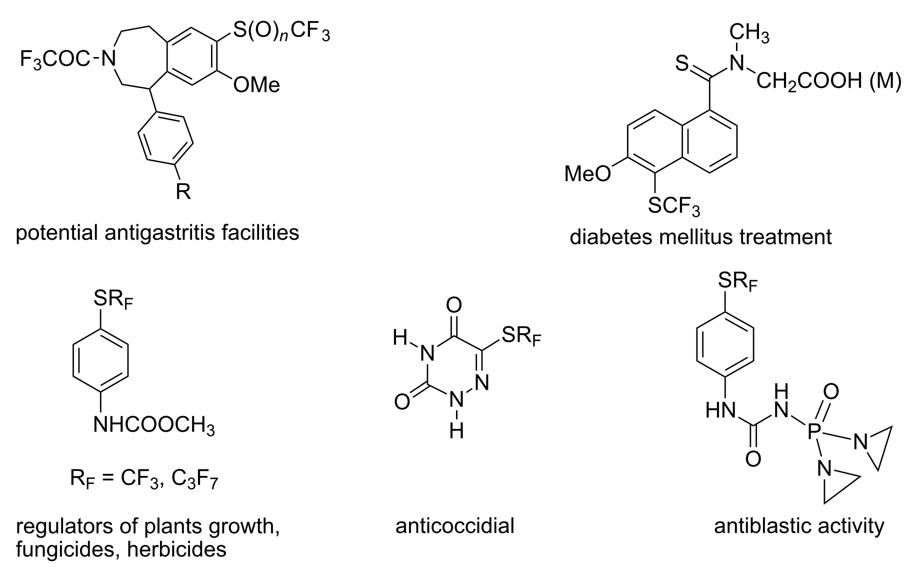
$R = CF_3, OCHF_2, SCHF_2, SO_2CHF_2, SO_2CF_3$

Figure 3: Hypotensive candidates with SR_F and SO_2R_F groups – analogues of Losartan and Nifedipin.

Other patented compounds containing perfluoroalkyl thio substituents are illustrated in Figure 4 and Figure 5 along with their pharmacological functions [7-11].

These examples represent only a small number of the vast array of organic compounds with SR_F, SOR_F or SO_2R_F groups which display pharmacological activity and interest in such analogues continues to grow.

Previous reviews in this area are either dated [19] or focus on specialist aspects such as perfluoroalkyl radicals [20-22], fluorinated carbanions [23], organometallic compounds [24,25], per-



potential antigastritis facilities

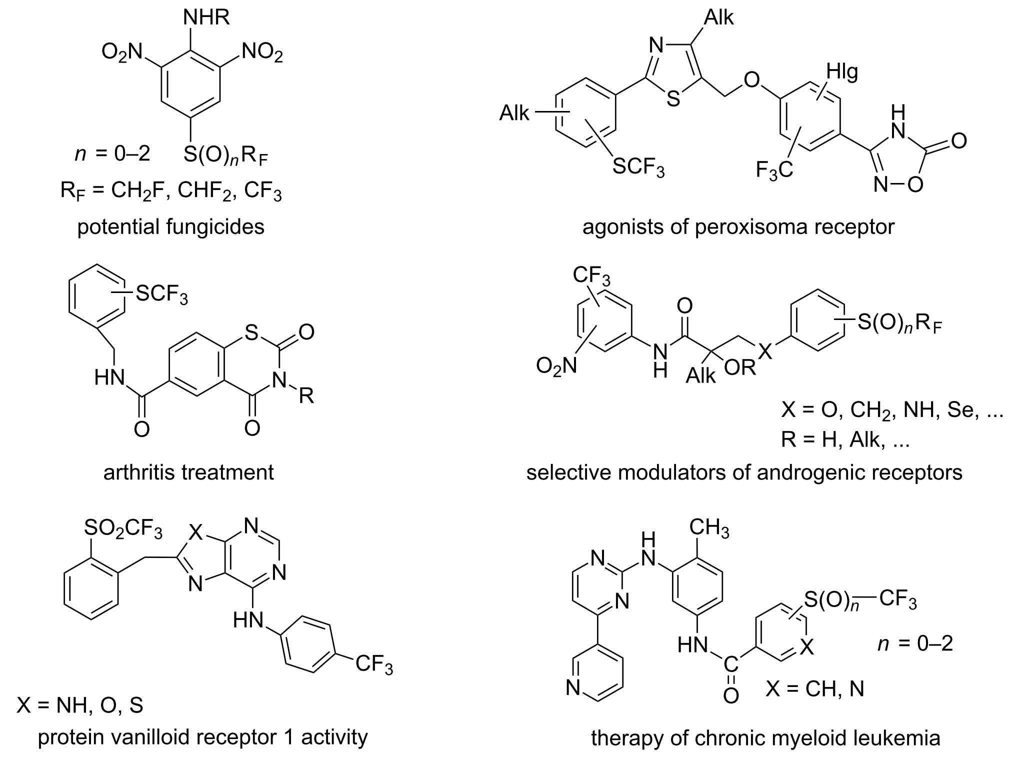
diabetes mellitus treatment

regulators of plants growth, fungicides, herbicides

anticoccidial

antiblastic activity

Figure 4: The variety of the pharmacological activity of R_FS-substituted compounds.



potential fungicides

agonists of peroxisoma receptor

arthritis treatment

selective modulators of androgenic receptors

protein vanilloid receptor 1 activity

therapy of chronic myeloid leukemia

Figure 5: Recent examples of compounds containing $R_FS(O)_n$-groups [12-18].

fluoroalkyl sulfenyl halides [26], perfluoroalkyl silicon reagents [27-32], the trifluoromethylthio anion [29] or electrophilic perfluoroalkylating agents [33]. Others are devoted to particular methods such as trifluoromethylation initiated by sodium dithionite [34] or the electrochemical introduction of fluoroalkyl groups in organic molecules [35]. Moreover, many of the reviews on the subject are very general [28,30,32,36].

The present work reviews synthetic methods employed to prepare aromatic and heterocyclic perfluoroalkyl sulfides and is systematized depending on the mode of constructing the SR$_F$ groups and also on the nature of the starting materials.

1. The halogenation of SAlk-derivatives with subsequent replacement of the halogen atoms by fluorine.
2. The introduction of SR$_F$-moieties into aromatic compounds by both electrophilic and nucleophilic reagents.
3. Various modes of perfluoroalkylation of organosulfur compounds including cationic, anionic, radical and ion-radical variants.

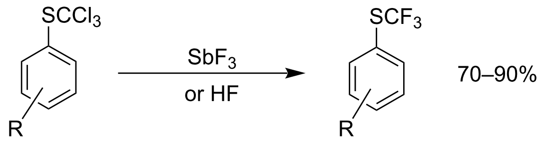
2. Substitution of halogen atoms by fluorine in aryl-α-polyhalogenoalkyl sulfides

Substitution of the halogen atoms in SAlk$_{Hlg}$ groups (mainly chlorine) using antimony trifluoride [37], is the oldest method of perfluoroalkylsulfide preparation and is still commercially significant.

The reaction is carried out by heating a mixture of aryl trichloromethyl sulfide with an excess of SbF$_3$ in the absence of a solvent. For industrial processes, dry hydrogen fluoride is used as the fluorinating agent (Scheme 1).

The presence of halogen atoms and electron-withdrawing groups such as NO$_2$, CF$_3$ or COCl in the aromatic ring of trichlorothioanisole does not influence the fluorination and the reaction is not hindered by bulky ortho-substituents e.g., phthalic acid imide [53] or *N*-substituted anilines [54]. Other reactive substituents, for example 3-SCCl$_3$ or 4-COCl are also fluorinated and form 1,3-bis(SCF$_3$) benzene [38-40] and 4-SCF$_3$-benzoic acid fluoride, respectively [55].

The use of hydrogen fluoride has some advantages. Due to its low boiling point (+19.4 °C) and good solubility in water, excess HF is easily removed from the reaction mixture. Unlike HF, reactions with SbF$_3$ can be carried out in glass. The SbF$_3$ must be freshly sublimed and used in a corrosion-proof vessel. Attempts to use less aggressive fluoride ion sources, e.g., KF/18-Crown-6 in CH$_3$CN or KF/Bu$_4$N$^+$ Cl$^-$ under phase-transfer conditions, have been unsuccessful [56].



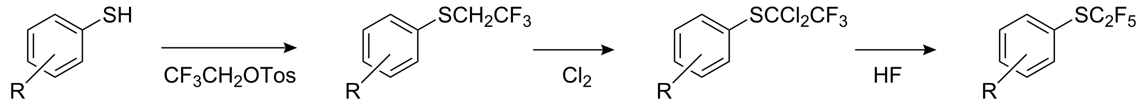
R = H, 4-CH$_3$, 3-Cl, 3-CF$_3$, 2,4-Cl$_2$, 2,5-Cl$_2$, 3,4-Cl$_2$, 2-Cl-4-NO$_2$, 4-Cl-3-NO$_2$, 3-CF$_3$-4-NO$_2$ [a]; R = 4-C$_2$H$_5$ [b]; R = 4-CHCl$_2$ [c]; R = 3-Br, 4-Br [d]; R = 3-NO$_2$, 4-NO$_2$ [e]; R = 2-Cl, 4-Cl [f]; R = 2-F, 4-F [g]; R = 2-Cl-5-CF$_3$ [h]; R = 4-SCF$_3$ [i]; R = 2-phthalimido [j]; R = 4-NR^{1}R^2 [k]

Scheme 1: Fluorination of ArSCCl$_3$ to corresponding ArSCF$_3$ derivatives. For references see: [a][38-43]; [b][41,42]; [c][43]; [d][44]; [e][38-43,45-47]; [f][38-43,48,49]; [g][49,50]; [h][51]; [i][52]; [j][53]; [k][54].

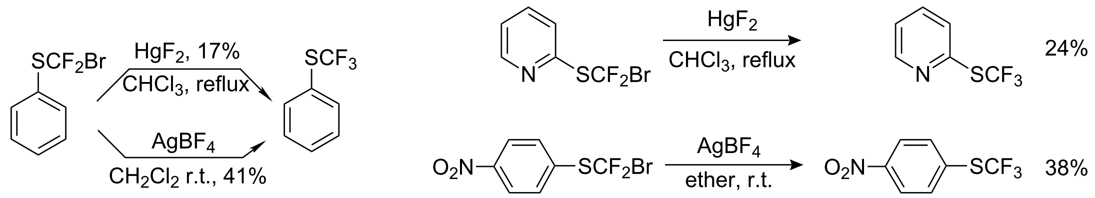
The method does not give access to longer perfluoroalkyl sulfides because the required aryl perchloroalkyl sulfide precursors are not easily accessible [57,58]. However, pentafluoroethyl ethers of various thiophenols (or phenols) can be obtained by the more sequential process as shown in Scheme 2 [59].

Use of mixed (Cl/F) polyhalogenofluoro alkanes as partial fluorinated alkylating agents generates the corresponding sulfides which are appropriate precursors for subsequent conversion to perfluoroalkyl thioethers. For example, α,α-difluoro polyhalogenoalkyl sulfides and α,α-dichlorotrifluoroethyl sulfide can be obtained by reaction of thiophenols with dihalogenodifluoro methanes [60-62], per(halogenofluoro) ethanes [60,63,64] and 2,2,2-trifluorotrichloroethane.

The Cl- and Br-substituents can then be replaced by fluorine without use of HF or SbF$_3$ [61]. As shown in Scheme 3 [65], bromine to fluorine exchange is possible by the use of other heavy metal fluorides, and even by silver tetrafluoroborate under mild conditions.



Scheme 2: Preparation of aryl pentafluoroethyl sulfides.



Scheme 3: Mild fluorination of the aryl SCF_2Br derivatives.

The halex-method allows the selective preparation of α,α-difluoroalkyl aryl sulfides (and also ethers, sulfoxides and sulfones) as intermediate products in the synthesis of herbicides [66,67]. Interestingly, the reaction of anhydrous hydrogen fluoride with aryl α,α,β-trichloroisobutyl sulfide at 20 °C leads only to substitution of the α-chlorine atoms, whilst at a higher temperature and pressure a more complete fluorination with rearrangement is observed [67] (Scheme 4).

Hydrogen fluoride/fluoride complexes such as H_2F_3 stabilized on a polymer [68] show even greater selectivity. For example, only one chlorine atom of the α,α-dichloromethylene group of benzyl alkyl sulfide is substituted by the reagent (Scheme 5).

$$PhCH_2SCCl_2COOMe \xrightarrow{H_2F_3/polymer} PhCH_2SCFClCOOMe$$

Scheme 5: Monofluorination of α,α-dichloromethylene group.

Thus, halogen atoms replacement by fluorine is an effective and cheap method for preparing aromatic and heterocyclic perfluoroalkyl sulfides. Application of the appropriate conditions allows control and a degree of selectivity thus making this method an important industrial process.

3. Introduction of the aryl SR_F moiety

3.1. Electrophilic introduction of SR_F groups

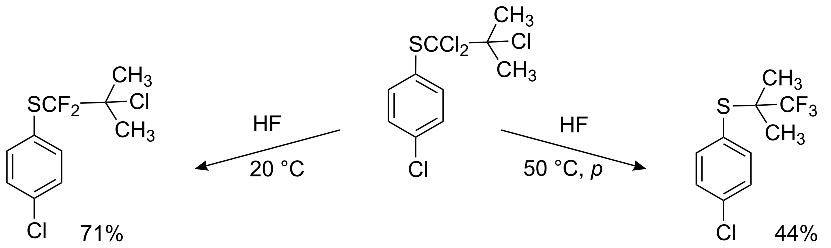
Perfluoroalkyl sulfenyl chlorides react with electron rich aromatic and heterocyclic compounds, to give SR_F derivatives. Thus, phenol, *o*-hydroquinone and their derivatives react with CF_3SCl to yield *p*-hydroxyaryl trifluoromethyl sulfides (Scheme 6).

R = H (26%), 2-OH (54%), 2-Me (53%), 3-Me (67%), 3-Cl (42%)

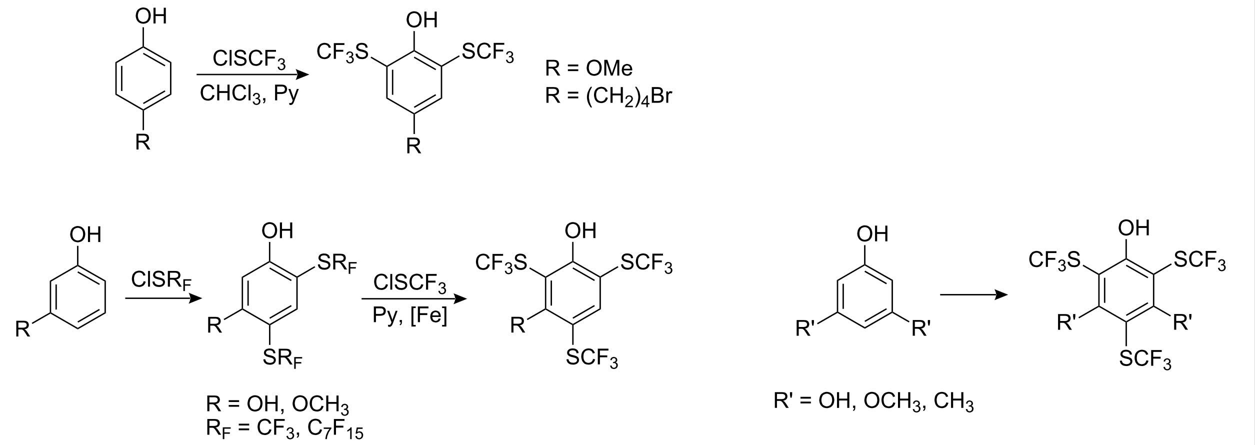
Scheme 6: Electrophilic substitution of phenols with CF_3SCl [69].

The best yields are achieved when electron-donating substituents are present on the ring. In the case of *m*-cresol and *m*-chlorophenol a small degree of *o*-substitution was observed. Phenol is a poor substrate in the reaction (Scheme 6) however, when $FeCl_3$ was used as a catalyst the yield of *p*-$HOC_6H_4SCF_3$ was increased, albeit only slightly (30%). A significant improvement in yield occurs (72%) when the reaction is conducted with pyridine in chloroform and at ambient temperatures (0–20 °C) [70,71]. Under these conditions and with electron-donating substituents in the phenol, two and even three perfluoroalkylthio groups can be introduced (Scheme 7).

Forcing conditions are required for the introduction of three CF_3S-groups. This can be achieved either by activation with iron powder under pressure (or by conduction the reaction in a



Scheme 4: HF fluorinations of aryl α,α,β-trichloroisobutyl sulfide at various conditions.



Scheme 7: Introduction of SCF_3 groups into activated phenols [71-74].

steel autoclave) or by the presence of two donor groups in meta-positions [71].

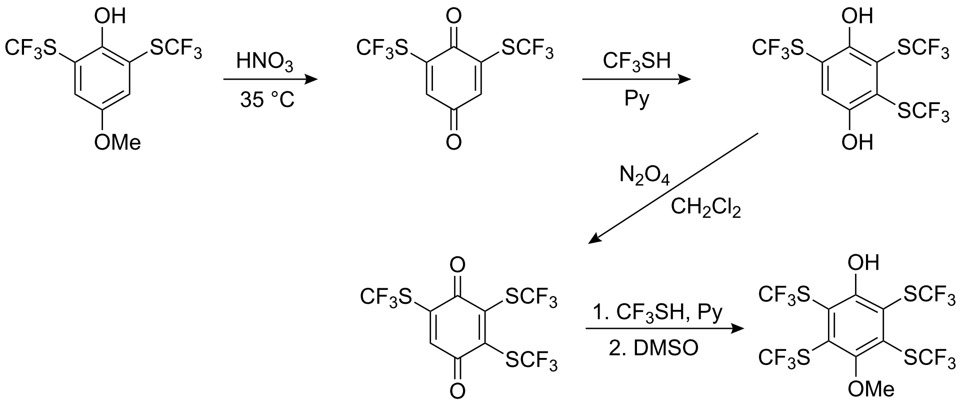
For *p*-hydroquinone, reaction with CF_3SCl in the presence of pyridine results only in the formation of a chlorohydroquinone pyridinium species [72], and neutral conditions are required in this case [69]. For the synthesis of poly(SCF_3) substituted *p*-hydroquinones, Scribner oxidized 2,6-bis(SCF_3)-4-methoxyphenol to generate 2,6-bis(SCF_3)-1,4-benzoquinone. The addition of CF_3SH in the presence of pyridine to the bis-compound gave 2,3,5-tris(SCF_3)hydroquinone [72] which could be subsequently converted into tetrakis(SCF_3)-1,4-hydroquinone (Scheme 8).

Unlike *p*-hydroquinone, resorcinols and phloroglucinols perhaps surprisingly react with R_FSCl [75] to generate mono-perfluoroalkyl thio derivatives. With iron powder as a catalyst bis(SR_F)-derivatives can be obtained (Scheme 9).

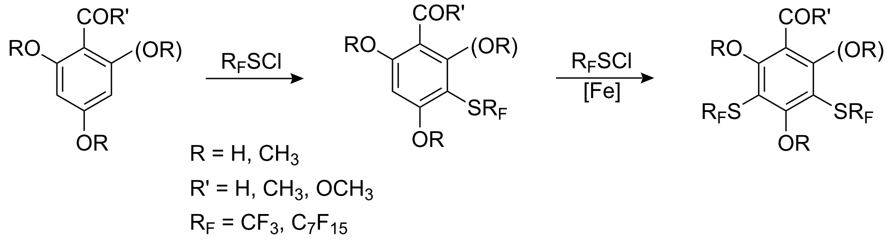
Similarly, methyl benzoates and benzaldehydes with two and especially three hydroxyl groups form bis(CF_3S)-substituted derivatives without of catalyst.

Analogous reactions are observed with aniline. However, since reaction takes place in the first instance on the amino group [74,76], for the introduction of SCF_3 group into the aromatic ring the amino function must be protected. Mono-*N*-substitution is insufficient: *N*-methyl aniline, *N*-(SCF_3)aniline and *N*(Ac)-*m*-toluidine all yield mainly *N*-(SCF_3)-derivatives, and only a small amount of aromatic CF_3S-substitution is observed [74]. The best results are achieved [70,74] with *N*,*N*-bis-substituted aniline (Scheme 10).

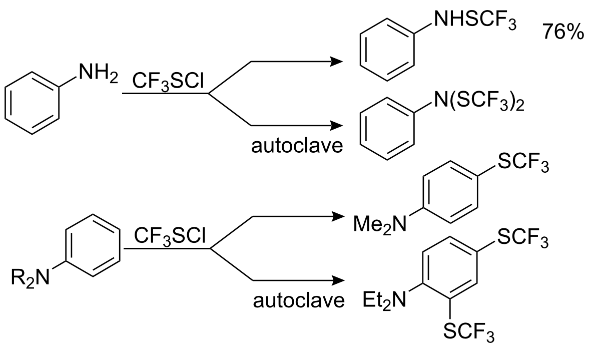
The introduction of strong electron-donating meta groups significantly activates the aromatic nuclei not only for *N*,*N*-bis-substituted anilines but also for *N*-monosubstituted substrates and even those with a free NH_2 group (Scheme 11).



Scheme 8: Preparation of tetrakis(SCF_3)-4-methoxyphenol [72].



Scheme 9: The interactions of resorcinol and phloroglucinol derivatives with R_FSCl.



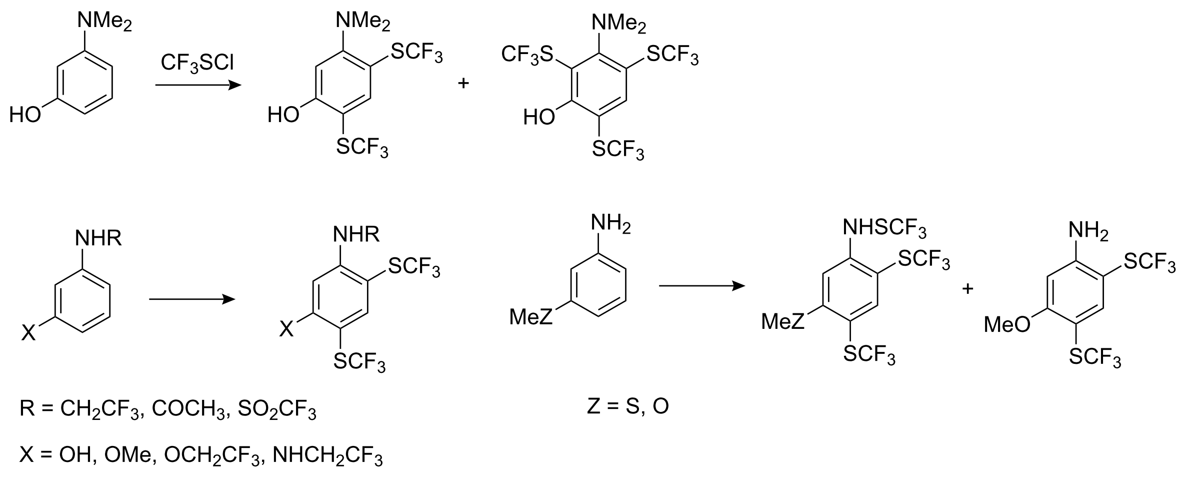
Scheme 10: Reactions of anilines with CF_3SCl.

In naphthalene and benzophenone derivatives only those rings containing hydroxy or amino groups undergo perfluoroalkylsulfanylation [74,75]. Other electron-donating substituents on the aromatic ring are not so activating for reaction with CF_3SCl. For example, thiophenol [76] forms only phenyltrifluoromethyl disulfide [70]. The presence of a methyl group and halogens requires high temperatures (100–200 °C) and the presence of catalysts (HF or BF_3) for reaction and yields of the corresponding aryltrifluoromethyl sulfides are only 25–60%. Both toluene and halobenzenes lead to mixtures of isomers [70].

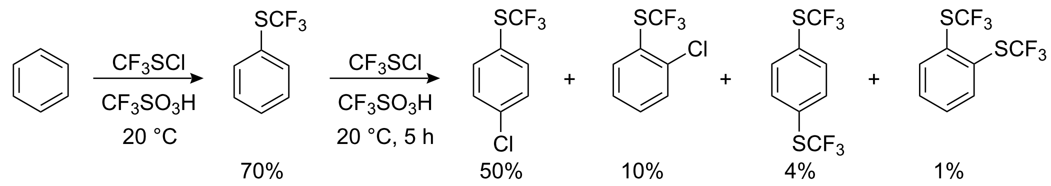
Benzene undergoes trifluoromethylsulfanylation with trifluoromethanesulfonic acid as a catalyst even at 20 °C. However, further reaction of the resultant phenyltrifluoromethyl sulfide leads mainly to chlorination with only minor amounts of bis-(CF_3S) products (Scheme 12).

Aryl magnesium [78] and -mercury [79] compounds have been employed for the introduction of CF_3S groups. Such reactions proceed in ether or THF at low temperatures; however, the yields of aryltrifluoromethyl sulfides do not exceed 50–60% and are accompanied with halogenated side-products (Scheme 13).

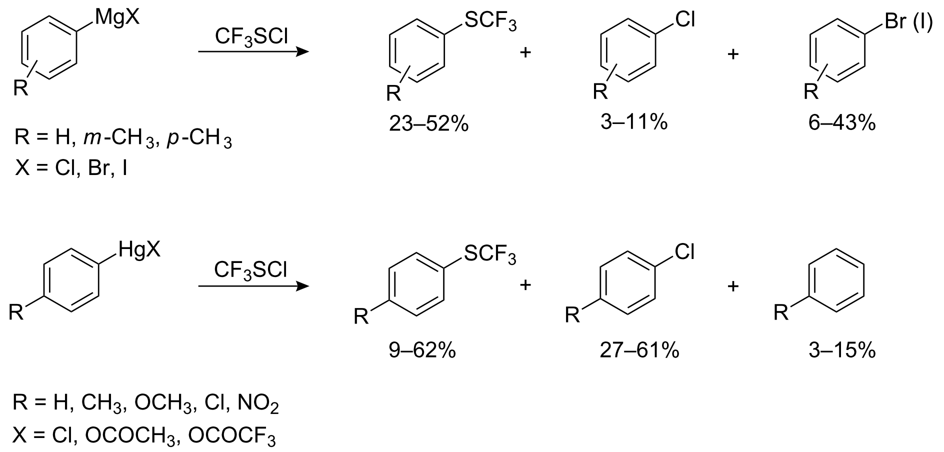
Among heterocyclic systems, pyrroles are the best substrates for reaction with trifluoromethyl-, difluorochloro- and dichlorofluoromethyl sulfenyl chlorides. Their reactivity exceeds that of benzene and its organometallic derivatives [80]. An excess of reagent gives bis-(SCF_3) pyrrole derivatives as shown in Scheme 14.



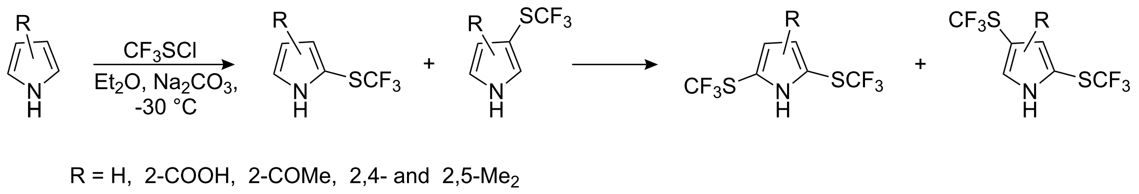
Scheme 11: Trifluoromethylsulfanylation of anilines with electron-donating groups in the meta position [74].



Scheme 12: Reaction of benzene with CF_3SCl/CF_3SO_3H [77].



Scheme 13: Reactions of trifluoromethyl sulfenyl chloride with aryl magnesium and -mercury substrates.



Scheme 14: Reactions of pyrroles with CF_3SCl.

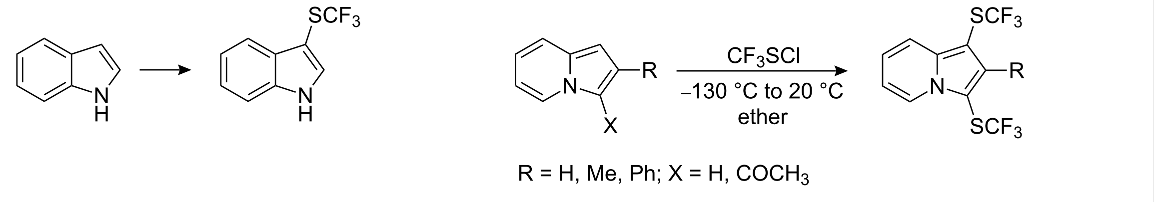
Condensed pyrroles also react readily with CF_3SCl. Indole undergoes substitution, as expected, at the 3-position [80], while indolizine and some of its derivatives give 1,3-bis(SCF_3)-substituted products, in some cases, in quantitative yield [81]. It is interesting to note that not only hydrogen, but also an acetyl group in the 1-position is substituted (Scheme 15).

However, no reaction occurs when there are two electron-withdrawing groups in the five-membered indolizine ring (e.g. R = Ph, and X = COPh or NO_2). By contrast, in the case of 1-benzyl-2-methyl indolizine [81] both the pyrrole and the aromatic ring of the benzyl group undergo trifluoromethylsulfanylation. Only *N*-substitution occurs in the case of carbazole [80].

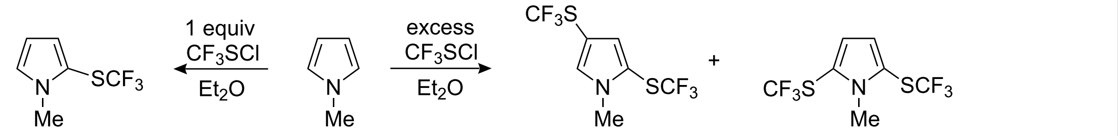
N-Methylpyrrole can be variously substituted depending on the conditions as illustrated in Scheme 16.

Heating *N*-methylpyrrole in $CHCl_3$/Py affords the 2-SCF_3 derivative along with a small amount of 3-SCF_3-*N*-methylpyrrole [83]. Attempted selective introduction of the second SCF_3 group at −30 °C with $C_4F_9SO_3H$ to 2-trifluoromethylsulfanylpyrrole was unsuccessful and gave a mixture of 2,4- and 2,5-isomers [87].

Unlike pyrroles, furan, thiophene and selenophene react with CF_3SCl only in the presence of catalysts. For selenophene [84] and thiophenes [85] $SnCl_4$ is sufficient, whilst furans require more forcing conditions usually involving prolonged heating



Scheme 15: Trifluoromethylsulfanylation of indole and indolizines.

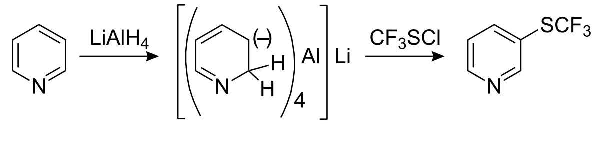


Scheme 16: Reactions of *N*-methylpyrrole with CF_3SCl [80,82].

(20 h at 60 °C) and in pyridine for activation [83,84] (Scheme 17).

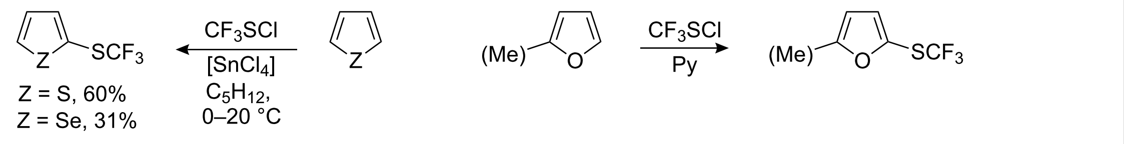
Similarly, some five membered heterocycles with two heteroatoms [*N*-Ac- and *N*-(SO_2Alk)-thiazoles, 1-Me-2-SCH_2CF_3- and 1,2-Me_2-imidazoles] undergo single trifluoromethylsulfanylation on heating (60 °C) with CF_3SCl in a pyridine-chloroform mixture [83]. Interestingly, unlike 1,2-dimethylimidazole, the sulfanylation of 2,4-dimethylthiazole under the same conditions occurs twice on the same 2-methyl group (Scheme 18).

Pyridine is too deactivated for trifluoromethylsulfanylation under classical conditions and to achieve substitution it is first of all necessary to convert pyridine to an anionic hydride σ-complex by reduction with $LiAlH_4$ [86]. The reaction with CF_3SCl then proceeds with difficulty [84] and mono-substituted 3-trifluoromethylsulfanyl pyridine is formed in low yield along with small amounts of the 3,5-bis(SCF_3) derivative (~1%) (Scheme 19).

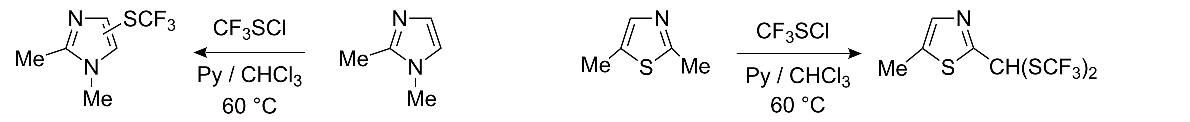


Scheme 19: Trifluoromethylsulfanylation of pyridine requires initial hydride reduction.

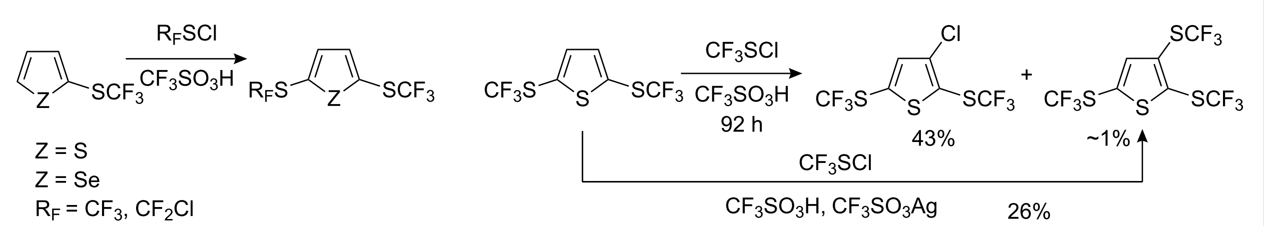
Introduction of additional R_FS-groups into heterocyclic compounds (except for pyrrole and its derivatives) occurs in the presence of perfluoroalkanesulfonic acids (Scheme 20). Incorporation of the second fluoroalkylsulfanyl group into thiophenes [85] and selenophene [84] is possible in the presence of CF_3SO_3H. However, reaction of CF_3SCl with 2,5-bis(SCF_3) thiophene in presence of CF_3SO_3H gives the 3-chloro-derivative as the major product. 2,3,5-Tris(SCF_3) thiophene is accessible if CF_3SO_3H is added as its Ag-salt [77]. Such reactions can also be successfully carried out on pyrroles (Scheme 21).



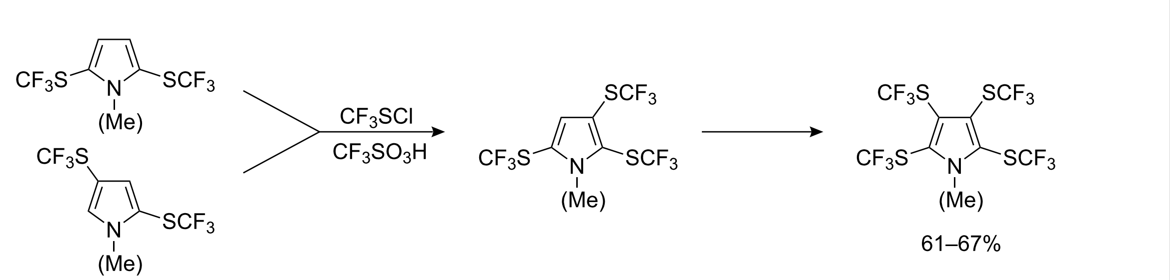
Scheme 17: Reactions of furan, thiophene and selenophene with CF_3SCl.



Scheme 18: Trifluoromethylsulfanylation of imidazole and thiazole derivatives [83].

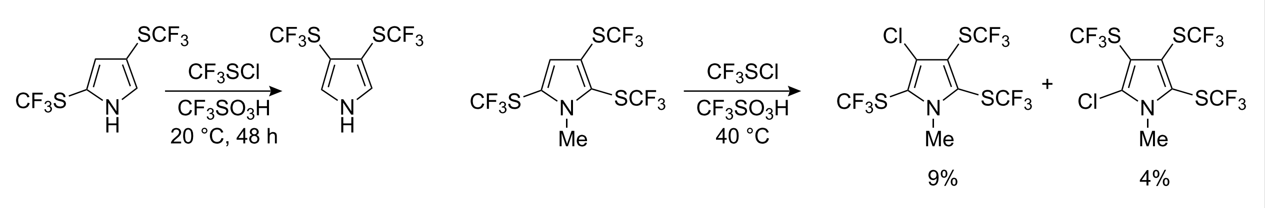


Scheme 20: Introduction of additional R_FS-groups into heterocyclic compounds in the presence of CF_3SO_3H.



Scheme 21: Introduction of additional R_FS-groups into pyrroles [82,87].

Prolonged reaction times lead to chlorinated products as well as products that arise from migration of the CF_3S-groups (Scheme 22).

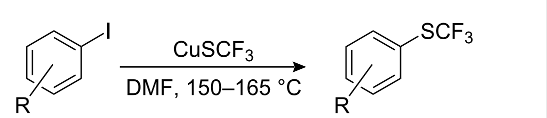


Scheme 22: By-products in reactions of pyrroles with CF_3SCl [82].

Thus, the reaction of perfluoroalkanesulfenyl chlorides with electron-rich aromatic and heterocyclic compounds offers an effective and comparatively straightforward method for the introduction of one or more SR_F groups. The reactions are more problematic however, for electron deficient substrates where competing halogenation, reduction and isomerization products often result from perfluoroalkylthiolation reactions.

3.2. Nucleophilic introduction of SR_F groups

Anionic salts of type $R_FS^- M^+$ and their heavy metal complexes have been known for many years [88], however their application to the synthesis of aromatic perfluoroalkyl sulfides is comparatively recent. For example, trifluoromethylthiomercury and trifluoromethylthiosilver react with aliphatic halogenides to generate aliphatic and benzylic trifluoromethyl sulfides [89-92]. It is well known that the reaction of non-activated aryl halides with phenols, thiophenols and amines are catalyzed effectively by copper (Ullmann reaction). L. M. Yagupol’skii [93-97] developed a related protocol for trifluoromethylsulfanylation of aromatic and heterocyclic compounds using trifluoromethylthiocopper (Scheme 23).



R = H (55%); 4-CH_3 (30%); 2- and 4-NO_2 (75%);
2-CHO-3,5-$(SCF_3)_2$; 2,3- and 3,4-$(COOEt)_2$

Scheme 23: Reaction of aromatic iodides with $CuSCF_3$ [93,95].

The reaction is carried out by heating in a polar solvent (e.g. DMF, quinoline or *N*-methyl pyrrolidone) and the substrate can contain electron-donating or electron-withdrawing groups. Electron-withdrawing groups activate the iodo atom and consequently, give better yields (70–75%). 2-Trifluoromethylsulfanylpyridine, 6-trifluoromethylsulfanylquinoline [93] and 1-trifluoromethylsulfanylnaphthalene [97] are obtained in good yields (60–70%) by this method. Multiple aromatic iodine substituents result in multiple substitution by SCF_3 (Scheme 24).

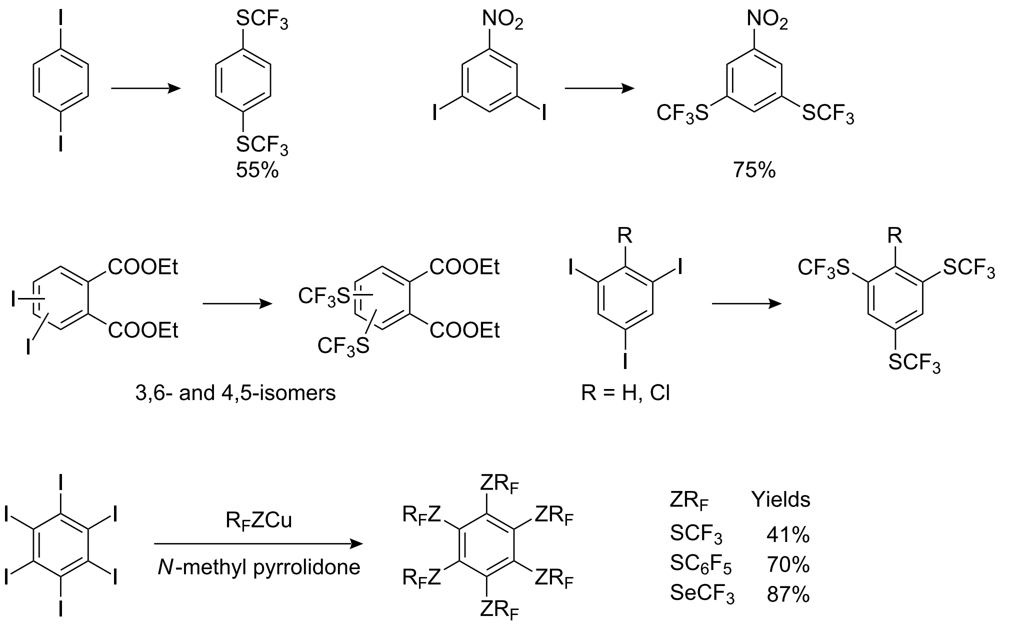
In the cases of triiodo derivatives, the yields generally do not exceed 30%. Thus, the synthesis of 1,3,5-tris(SCF_3)benzene is more efficient via 3,5-bis(SCF_3)-iodobenzene [93]. Hexaiodobenzene reacts with $CuSCF_3$ to form hexakis(trifluoromethylsulfanyl)benzene in modest yield (41%). However, with $CuSC_6F_5$ and $CuSeCF_3$ the corresponding hexa-substituted thio- and seleno-derivatives are obtained in yields of 70–90% [96].

It should be noted that the interaction of $CuSCF_3$ with aromatic iodides is sometimes accompanied by side-reactions. For example, the introduction of CF_3S groups into 2,6-diiodo-4-nitrochlorobenzene and 2,6-diiodo-4-nitroanisole involve simultaneous reduction and substitution (Scheme 25).

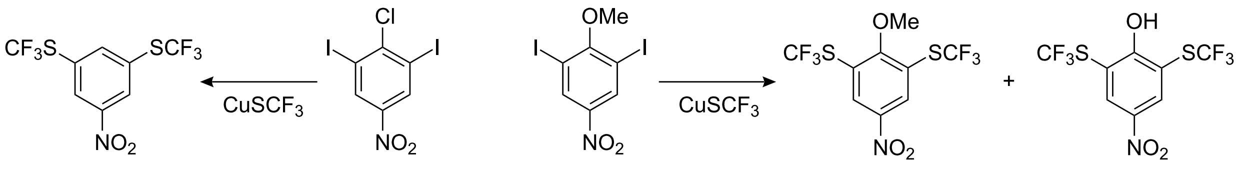
Trifluoromethylthiocopper is obtained by reaction of CuBr with $AgSCF_3$ [93,99], the latter is generated from silver fluoride and carbon disulfide [90,100].

To simplify the process, Remy [101,102] suggested carrying out the synthesis of aryltrifluoromethyl sulfides by generation $CuSCF_3$ (from trifluoromethylthio mercury and -copper) in situ with the aryl halides. This not only reduces the number of steps but also increases the overall efficiency (Scheme 26).

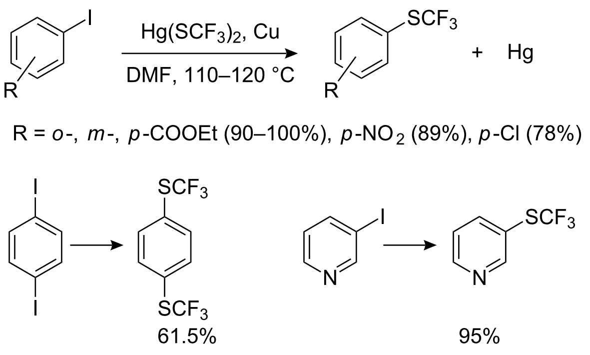
Aryl bromides can also be used but require higher temperatures (150–190 °C) and more polar solvents. Under such forcing conditions compounds containing both electron-withdrawing and electron-donating groups can now be used effectively. In the case of *p*-bromo-*N*,*N*–dimethylaniline an excess (3 equiv) of the reagent was used. Aromatic chlorides do not react under



Scheme 24: Reaction of aromatic iodides with R_FZCu (Z = S, Se), $R_F = CF_3$, C_6F_5 [93,95,96].



Scheme 25: Side reactions during trifluoromethylsulfanylation of aromatic iodides with CF_3SCu [98].



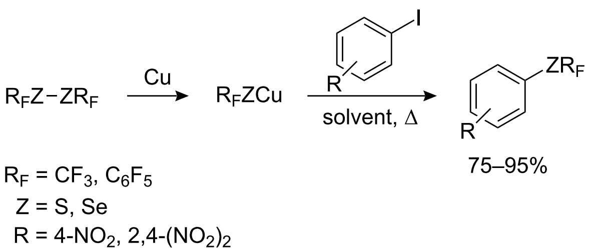
Scheme 26: Reactions with in situ generated $CuSCF_3$.

these conditions. Thus, this method allows the selective substitution of different halogens by varying the temperature.

Since the original work on trifluoromethylthiocopper and trifluoromethylthiomercury [93,95,96,101,102], other nucleophilic reagents and new methods have been developed. For example, Clark et al. have used $CuSCF_3$ adsorbed onto Al_2O_3 [100], whilst Munavalli et al. have employed the acetonitrile adduct $CF_3SCu{\cdot}CH_3CN$ [103] for the reaction with *m*-iodobenzoic acid and its methyl ester [104].

Bulky perfluoroalkylthiocopper reagents, derived from 2,2,4,4-tetrakis(CF_3)-1,3-dithietane, hexafluoropropene and alcohols in the presence of KF or CuBr, have been also used for reaction with substituted iodobenzenes (Scheme 27).

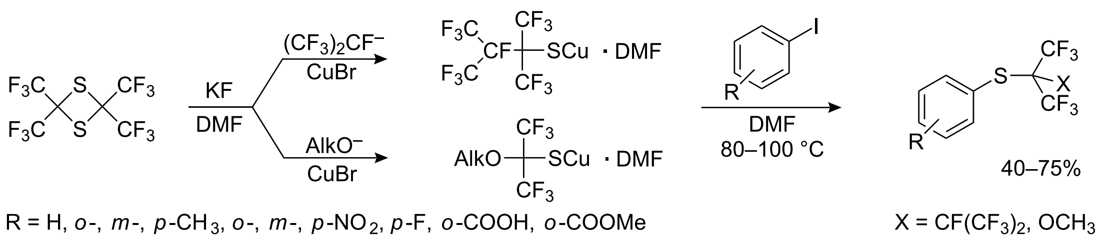
A variety of perfluoroalkyl- and perfluoroarylcopper mercaptides and selenides have become more accessible, prepared by cleavage of the corresponding disulfides and diselenides with copper powder [94]. The resultant R_FZCu reagents complexed with DMF or *N*-methylpyrrolidone, are quite stable and can be stored without decomposition, can be used for the production of aryltrifluoromethyl-, arylpentafluorophenyl sulfides and -selenides from the corresponding iodobenzenes (Scheme 28) [94].



Scheme 28: In situ formation and reaction of R_FZCu with aryl iodides.

The compounds shown in Figure 6 have been synthesized by this method.

An alternative approach for the generation of CF_3SCu involves heating of methyl fluorosulfonyl difluoroacetate in polar aprotic solvents to generate difluorocarbene, which in the presence of CuI and sulfur, forms trifluoromethylthiocopper [106]. Subsequent reaction with aryl halides results in the corresponding trifluoromethylsulfanyl derivatives (Scheme 29).



Scheme 27: Perfluoroalkylthiolation of aryl iodides with bulky R_FSCu [105].

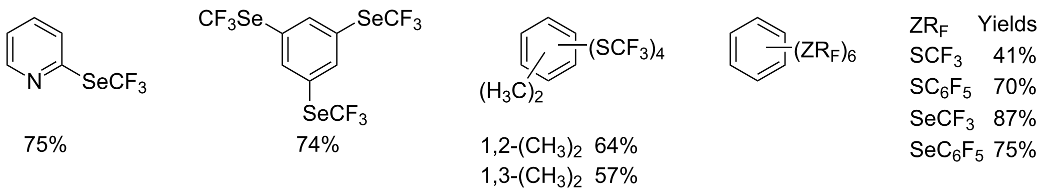
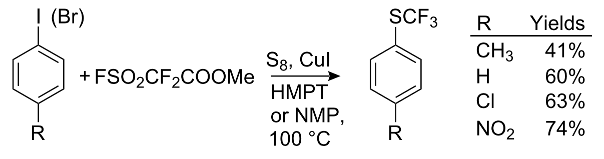


Figure 6: Examples of compounds obtained using in situ generated R_FZCu methodology [94].

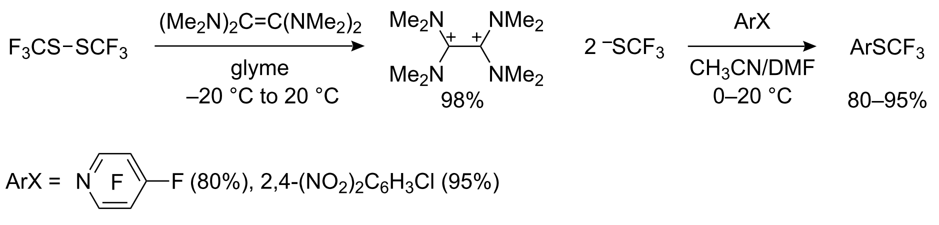


Scheme 29: Introduction of SCF_3 group into aromatics via difluorocarbene.

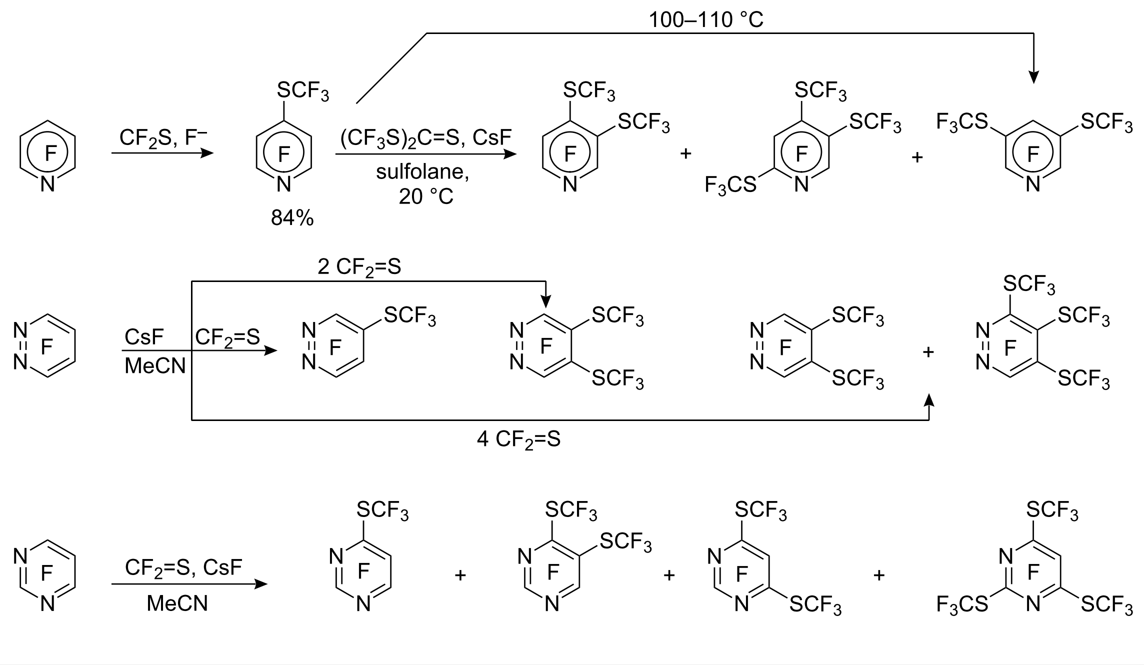
Reduction of bis(perfluoroalkyl)disulfides with tetrakis(dimethylamino)ethylene produces tetrakis(dimethylamino)ethylene dication stabilized perfluoroalkyl thiolates. In contrast to the corresponding potassium and tetramethylammonium salts [29], this compound is stable and can be isolated in a pure state [107], and reacts with activated aryl halides to form the corresponding trifluoromethyl sulfides often in quantitative yields (Scheme 30).

Dmowski and Haas used the reaction of thiocarbonyl difluoride with metal fluorides, to generate the trifluoromethylthiolate anion [108] for introduction into activated perfluoroheterocyclic compounds. Thus, reaction of CF_2S/CsF with pentafluoropyridine under mild conditions gave the 4-substituted product [109]. However, for the subsequent introduction of additional SCF_3 groups this system is not suitable due to effective self-condensation of thiocarbonyl difluoride (CF_2=S) at higher concentrations. For this purpose the trimer of thiocarbonyl difluoride, bis(trifluoromethyl)trithiocarbonate $(CF_3S)_2C$=S, is more stable and reacts with CsF in sulfolane to generate CF_3S^- anions [110]. However, the use of this reagent leads to mixtures of products (Scheme 31).

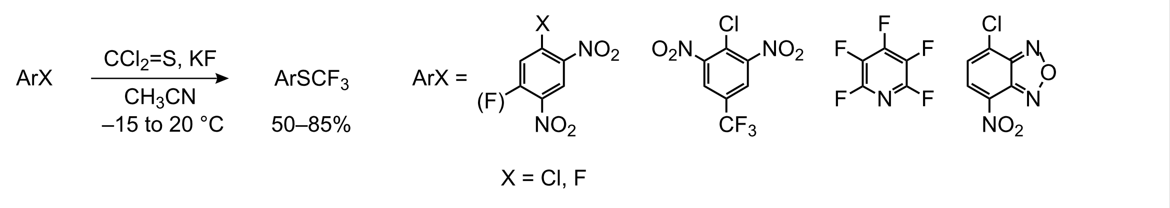
Whilst reaction of CF_2=S/CsF (or its trimer) with tetrafluoropyridazine allows for the selective formation of mono-, di- and tri-(SCF_3) substituted products, the analogous reaction with tetra-



Scheme 30: Tetrakis(dimethylamino)ethylene dication trifluoromethyl thiolate as a stable reagent for substitution of aromatic halides.



Scheme 31: The use of CF_2=S/CsF or $(CF_3S)_2C$=S/CsF for the introduction of CF_3S groups into fluorinated heterocycles.



Scheme 32: One-pot synthesis of $ArSCF_3$ from ArX, CCl_2=S and KF.

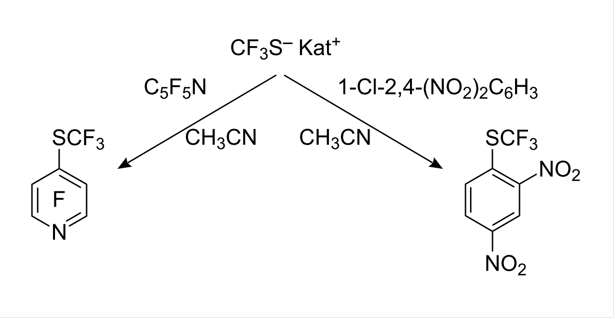
fluoropyrimidine results in a mixture of polyfluoropyrimidine derivatives [111] (Scheme 31). Interestingly, the reaction of $(CF_3S)_2C$=S/CsF with *C*,*N*-bis(pentafluorophenyl) imidoyl chloride leads to introduction of the SCF_3 group into the pentafluorophenyl ring along with substitution of the imidoylic chlorine atom [112].

A considerable improvement of this method was developed by Clark et al. [113]: No preliminary preparation of difluorothiophosgene or its trimer is necessary, the required reagents being generated in situ (from thiophosgene and KF). The reaction with activated aromatic compounds is shown in Scheme 32.

The less reactive 2-Cl-5-NO_2 benzonitrile forms the CF_3S-derivative in only 49% yield after many hours reflux and 2-F-5-NO_2 benzonitrile is a by-product despite the use of a 100% excess of thiophosgene.

The use of Me_4NF in place of KF for the generation of the CF_3S^- anion in reactions with 2,4-dinitrofluorobenzene and pentafluoropyridine increases the yields of the corresponding trifluoromethyl sulfides to 90–96% [29,114]. However, with other substrates this method can be problematic due to competing side reactions.

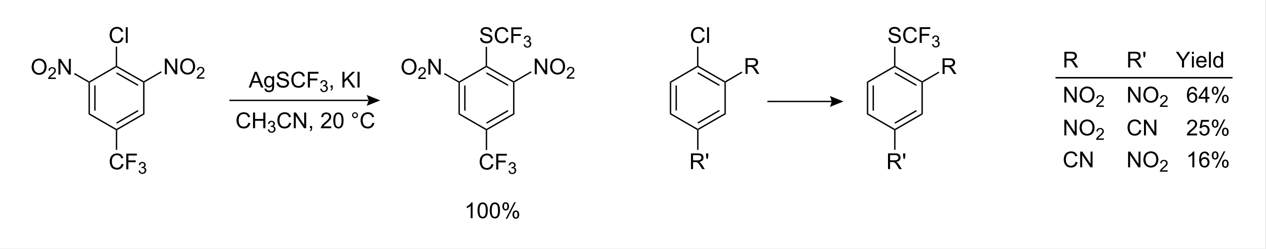
A new method for the preparation of trifluoromethylthiolate anion involves the reaction of Me_3SiCF_3 with sulfur in the presence of a fluoride ion source [115]. The salts obtained by this method are considerably more thermally stable than those previously reported [29,110,114]. They can be treated with boiling ether or CS_2 to remove excess sulfur and readily react at room temperature with inorganic, aliphatic and activated aromatic halides with the formation of trifluoromethyl sulfides (Scheme 33).



Scheme 33: Reaction of aromatics with CF_3S^- Kat^+ [115].

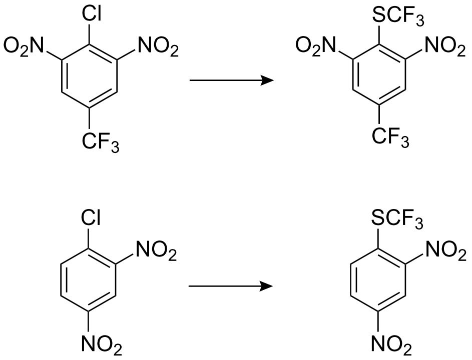
It has already been noted that trifluoromethylthiomercury and trifluoromethylthiosilver cannot be used for the preparation of aryltrifluoromethyl sulfides, as they react only with aliphatic halides [89-92]. However, it is known [116,117], that $Hg(SCF_3)_2$ forms a complex with KI which decomposes with the formation of an unstable anion "$^-SCF_3$". Based on this observation, Adams and Clark used a mixture of trifluoromethylthiosilver and KI (or Bu_4NI) as a source of trifluoromethylthiolate anion for nucleophilic introduction of the trifluoromethylsulfanyl moiety into aromatic molecules [118]. Of the metal halides investigated for this reaction, the best results were obtained with KI and Bu_4NI, whilst NaI, NaBr, and KF were ineffective. Some of these reactions are illustrated in Scheme 34.

This reagent can displace a range of activated halides, particularly bromides and iodides. For the reaction of 2,4-



R	R'	Yield
NO_2	NO_2	64%
NO_2	CN	25%
CN	NO_2	16%

Scheme 34: Reactions of activated aromatic chlorides with $AgSCF_3$/KI.



Yields of $ArSCF_3$ using $CuSCF_3$, KI	 $Hg(SCF_3)_2$, KI
89%	100%
0%	26%

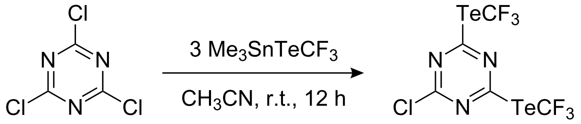
Scheme 35: Comparative $CuSCF_3$/KI and $Hg(SCF_3)_2$/KI reactions.

$(NO_2)_2C_6H_3X$ with $AgSCF_3$/KI, the reactivity of the halogens occurs in the reverse sequence: F (26%) < Cl (52%) < Br (85%) < I (97%) [118]. Presumably, coordination of the complex anionic nucleophile $K^+[Ag(SCF_3)I]^-$ with aryl halide accelerates the reaction.

Trifluoromethylthiocopper and trifluoromethylthiomercury also participate in analogous reactions, $CuSCF_3$ is less active than $AgSCF_3$ whilst $Hg(SCF_3)_2$ displays increased reactivity as indicated in Scheme 35 [118].

It should be noted that the tellurium reagent, $Me_3SnTeCF_3$, is capable of introducing the $TeCF_3$ group into activated heteroaromatics [119]. In the reaction shown (Scheme 36) the use of three equivalents resulted in the introduction of only two $TeCF_3$ groups.

The Sandmeyer reaction is used widely to introduce functionality into aromatic compounds. However, early attempts using trifluoromethylthiosilver as the nucleophile were not encouraging [120] with yields below 30% accompanied with deaminated side products (up to 38%). The use of trifluoromethylthiocopper was rather unsuccessful. However, with diazonium salts generated with *tert*-butyl nitrite in acetonitrile in the presence of $CuSCF_3$ and BF_3 better results were obtained [121]. Yields of the resulting aryltrifluoromethyl sulfides improved (~40–70%). The best results were observed with isolated tetrafluoroborate diazonium salts (Scheme 37), although the presence of electron-donating and bulky ortho-substituents in the aromatic ring led to reduced yields.

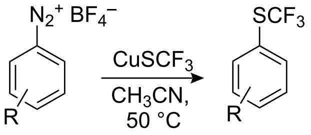


Scheme 36: $Me_3SnTeCF_3$ – a reagent for the introduction of the $TeCF_3$ group.

4. Perfluoroalkylation of aromatic sulfur compounds

Perfluoroalkyl iodides have not generally been considered as alkylating agents. Unlike R-X they show anomalous behavior in their reactions with nucleophiles. For example, the reaction of CF_3I with alkali gives fluoroform (CHF_3) and potassium hypoiodide (KIO) [122]. The interaction of organolithium compounds with perfluoroalkyl iodides [123-126] does not result in combination of the two alkyl species (R_F and R), but in transmetallation (Scheme 38).

Such reactivity has been explained by the reverse polarization of the C–I bond in the fluorinated substrates. Because of the greater electronegativity of CF_3 over iodine (3.3 for CF_3 and



R	Yield $ArSCF_3$
2-, 3-, 4-NO_2, 2-CN, 3-CF_3, 2-Cl-4-NO_2, 3-Cl, 2-NO_2-5-Cl	91–98%
2-NO_2-4-Cl	60%
3-CH_3	17%
2-CH_3	7%
2-Ph	3%

Scheme 37: Sandmeyer reactions with $CuSCF_3$.

$$CF_3I + KOH \longrightarrow CHF_3 + KOI$$

$$R_FI + RLi \longrightarrow R_FLi + RI$$

$$R_F = C_nF_{2n+1}\ (n = 1–8),\ CF(CF_3)_2$$

$$R = Me, Bu, Ph$$

Scheme 38: Reactions of perfluoroalkyl iodides with alkali and organolithium reagents.

2.5 for the atom of iodine [127,128]), the iodine acquires a partial positive charge:

$$\overset{\delta-}{F_3C}–\overset{\delta+}{I} \qquad \overset{\delta+}{H_3C}–\overset{\delta-}{I}$$

Nevertheless, Haszeldine et al., were able to carry out the perfluoroalkylations of alkylthiols. Prolonged heating of polyfluoroalkyl iodides with the sodium methylthiolate at 100–110 °C in DMSO lead to the formation of methyl polyfluoroalkyl sulfides [129]. The halophilic generated carbanion (R_F^-) in turn reacted with the sulfenyl iodide to generate a thioether. However, R_FCH_3 and R_FH, are also obtained as by-products, which may be a result of homolytic decomposition of the perfluoroalkyl iodides at high temperature [130,131]. Similarly, reactions of R_FI with sodium thiophenoxide (like other aromatics such as halogenated benzenes [132] or aromatic heterocycles [133]) resulted in the introduction of the perfluoroalkyl radical into aromatic rings with the formation of a mixture of isomeric R_F-compounds.

4.1. Ion-radical perfluoroalkylation

4.1.1. Interaction of S-, Se- and Te-phenols, and diaryl disulfides with perfluoroalkyl iodides in liquid ammonia under UV irradiation

Kornblum's work on nucleophilic substitution in alkyl halides [134-137] and Bunnett's reactions with non-activated aromatic substrates [138-142] (under UV irradiation) introduced the concept of the nucleophilic radical substitution mechanism ($S_{RN}1$). The essence of this approach consists of the generation of the anionic radical $RHlg^{-•}$, its decomposition to a radical $R^•$ ($Alk^•$ or $Ar^•$) followed by reaction with a nucleophile.

Although perfluoroalkyl iodides have a reversed polarity, and in spite of their tendency to undergo homolytic decomposition under UV irradiation, it is probable that they are also able to react with thiolate anions by a similar mechanism. Indeed, they react readily with aliphatic, aromatic and heterocyclic thiols [143-146], and with seleno- [147] and tellurophenols [148] under UV irradiation with formation of corresponding perfluoroalkyl sulfides, -selenides and -tellurides. The original method required liquid ammonia as the solvent and Pyrex glassware. Thiophenol and its derivatives containing both, electron-donating and electron-withdrawing substituents are easily transformed to the corresponding arylperfluoroalkyl sulfides in high yields (Table 1).

α,ω-Diiodoperfluoroalkanes react at both reaction centers with the formation of bis(SAr)–derivatives containing perfluoroalkylene bridges [144,146] in yields of 80–96%.

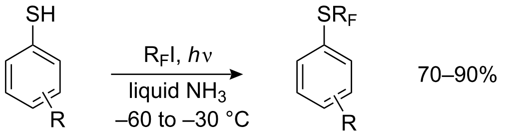
With the exception of 4-nitrothiophenol, the reactions are independent of the type of substituents. Unlike many thiophenoxides which bear electron-withdrawing substituents (*p*-Cl, 2,4-Cl_2, *o*-SO_2CHF_2 and even *p*-SO_2CF_3), sodium 4-nitrothiophenoxide affords 4,4′-dinitrodiphenyl disulfide under these conditions. Conversion to 4-nitrophenyl trifluoromethyl sulfide (60% yield) requires prolonged irradiation in a quartz ampoule at 30–45 °C [143]. The length of the perfluoroalkyl iodide chain has no influence, although lower yields were observed using CF_3I in comparison with other iodoperfluoroalkanes. A branching R_FI chain results in lower yields of the corresponding sulfides (10–15%). In the case of tertiary perfluorobutyl iodide, thiophenols are quantitatively transformed into diaryl disulfides. Such behavior of branched perfluoroalkyl iodides can be explained by the facile generation of the $I^•$ radical both as a consequence of their homolytic decomposition [155] and the decomposition of in situ generated radical anions [156]: $i\text{-}R_FI^{-•} \rightarrow i\text{-}R_F^- + I^•$. The radical $I^•$ (or I_2) oxidizes the ArS^- anion to disulfide.

Diaryl disulfides may also be used as substrates. Although they can be trifluoromethylated directly [157], unlike dialkyl disulfides [130,131] the yields generally do not exceed 40% (except for nitro derivatives 4-NO_2 – 58%, 2-NO_2 – 72%). The preliminary breaking of the S–S bond can be carried out very mildly and selectively [9], without affecting other functional groups (Scheme 39).

Perfluoroalkylthioanilines are accessible in a one-pot perfluoroalkylation reaction of dinitrodiphenyl disulfides [158,159] (Scheme 40). This method gives good yields of the desired products, higher than those from the perfluoroalkylation of amino thiophenols.

Seleno- [147] and telluro phenols [148] also react with perfluoroalkyl iodides under UV irradiation. Subsequently, it was shown that ArSeNa and ArTeNa react with perfluoroalkyl halides without irradiation to generate $R_F^•$ radicals which react with olefins [160,161]. Irradiation of polymercapto derivatives of benzene and CF_3I in liquid ammonia gives poly(trifluoromethylsulfanyl) compounds in high yields (Table 2).

Table 1: Interaction of thiophenols with perfluoroalkyl iodides in liquid ammonia under UV irradiation.



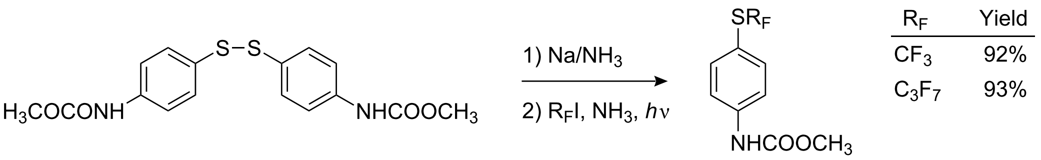
R	R_F	Yields of $ArSR_F$, %	Ref.
H	CF_3	76	[143]
	C_2F_5, *n*-C_3F_7, *iso*-C_3F_7	84, 81, 76	[144]
4-NH_2	CF_3	87	[146]
2-NH_2	CF_3	71	[143]
4-OH	CF_3	69.5	[143]
2-OCH_3	CF_3	86	[98]
4-Cl	CF_3	72	[146]
	C_2F_5, *n*-C_3F_7, *iso*-C_3F_7	84, 83, 65	[144]
2-SO_2CHF_2	CF_3	69	[143,146]
4-SO_2CF_3	CF_3	78	[143,146]
4-NO_2	CF_3	2.7[a]	[143,146]
		63[b]	[143,146]
2,4-Cl_2	CF_3	87	[149]
	C_3F_7	89	[149]
2-COOH	CF_3	90	[150]
3- and 4-$COOCH_3$	CF_3, *n*-C_3F_7, *iso*-C_3F_7	70–80	[151]
3- and 4-F	CF_3, *n*-C_3F_7	80–90	[152]
	iso-C_3F_7	72–75	[152]
4-$NHCOCH_3$	CF_3	96	[153]
4-$NHCOOCH_3$	CF_3, *n*-C_3F_7	88 (92[c]), 82 (93[c])	[9]
	C_2F_5, C_4F_9	62, 55	[154]

[a] In a quartz flask.
[b] In a quartz ampoule at 30–45 °C.
[c] With preliminary reduction of 4,4′-bis(MeOCONH)diaryl disulfide and without the isolation of corresponding thiophenol.

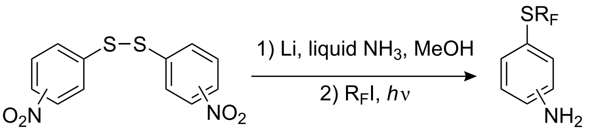
However, the reaction of 2,4,6-trimercaptochlorobenzene with CF_3I generates a mixture of compounds A, B, C and D as illustrated in Scheme 41. Reducing the irradiation time from 30 to 5 min does not change the product composition.

Control experiments indicate that aniline (B) is not derived from either chloro- (A) and iodo- (C)-sulfides, and iodo-product (C) is not formed from chlorosulfide (A). It is known [164] that photochemical nucleophilic aromatic substitution is promoted by electron-donating groups. Therefore, it appears most likely that the sulfides (B), (C) and (D) are produced as a consequence of loss of chloride from the intermediate radical anion as shown in Scheme 42.

Such side reactions explain the decrease of trifluoromethylation efficiency with the number of thiol groups present in a series of thiolated chlorobenzenes. The yields are 72% for 4-SH- [146], 64% for 2,4-$(SH)_2$- [143] and 37% for 2,4,6-$(SH)_3$- [163].



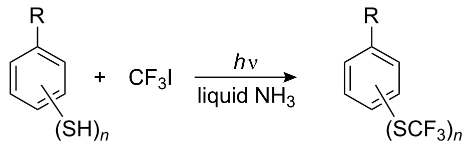
Scheme 39: Perfluoroalkylation with preliminary breaking of the disulfide bond.



Position of NH_2	R_F	Yield
o-	CF_3	85%
m-	CF_3	85%
p-	CF_3	75%
p-	C_3F_7	75%

Scheme 40: Preparation of R_FS-substituted anilines from dinitrodiphenyl disulfides.

Table 2: UV irradiation of polymercapto benzenes with CF_3I in liquid NH_3.

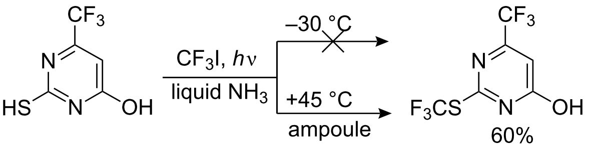


R	Position of $(SH)_n$ and $(SCF_3)_n$	Yield	Ref.
Cl	2,4-	64%	[143]
COOH	3,5-	89%	[162]
CH_3	2,4,6-	90%	[163]
NH_2	2,4,6-	88%	[163]
OH	2,4,6-	69%	[163]

4.1.2. Perfluoroalkylation of heterocyclic thiols

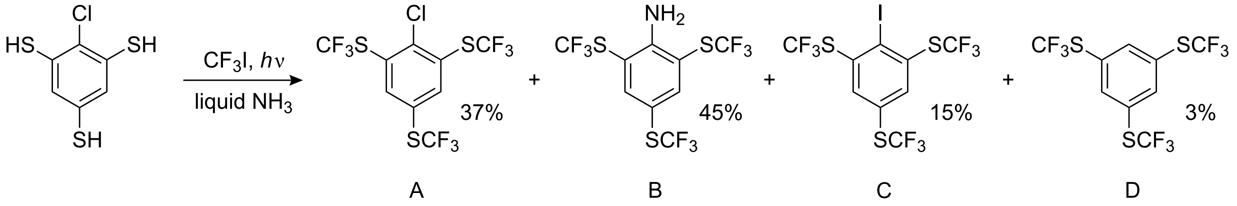
Heterocyclic thiol form *S*-perfluoroalkyl derivatives when irradiated in liquid ammonia in the presence of iodoperfluoroalkanes. The type of heterocyclic ring and the position of the thiol group influences the reaction. More electron-deficient heterocycles require longer irradiation times (Table 3).

It appears that 4-hydroxypyrimidine-2-thiol does not react with CF_3I under standard conditions. Similar to the reaction of 4-nitrothiophenol noted above [143,146], this reaction requires more forcing conditions. Other 4-hydroxypyrimidine-2-thiols behave similarly. The irradiation of an ammoniacal solution of 2-mercapto-4-oxy-6-trifluoromethylyrimidine with CF_3I must be conducted in a Pyrex ampoule at 30–45 °C to produce the *S*-trifluoromethyl derivative (Scheme 43).

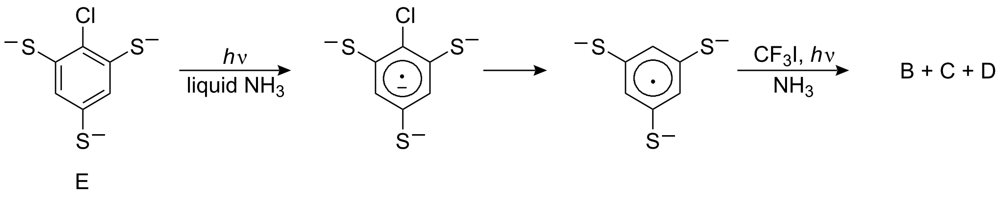


Scheme 43: Trifluoromethylation of 2-mercapto-4-hydroxy-6-trifluoromethylyrimidine [145].

Apparently, the reaction of these hydroxymercapto heterocyclic derivatives is complicated by stabilization of sulfur centred radicals as illustrated in Scheme 44.



Scheme 41: Photochemical trifluoromethylation of 2,4,6-trimercaptochlorobenzene [163].

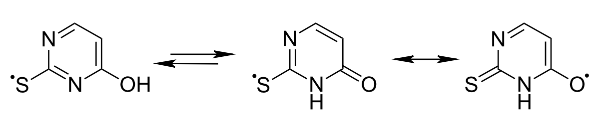


Scheme 42: Putative process for the formation of B, C and D.

Table 3: *S*-Perfluoroalkylation of heterocyclic compounds under UV irradiation of heterocycles thiols R-Het-SH in liquid ammonia.

R	R_F	Reaction conditions	Yield of products, %	Ref.
2-(SCF_3)-Benzothiazole				
H	CF_3	−60 to −33 °C, 90 min	87.5	[143]
2-(SR_F)-Benzimidazoles				
H	CF_3	−50 to −33 °C, 4 h	51	[165]
	C_1–C_4	Pyrex ampoule, 30 °C, 5 h	63–80	[154]
5-Cl	C_2F_5	liquid NH_3, THF, 10 h	56	[166]
5-(SR_F)-Benzimidazoles[a]				
2-Bu	CF_3 C_3F_7	liquid NH_3, ampoule, 25–40 °C, 10 h	20–39	[154]
5-(SR_F)-6-Azauracil				
H	CF_3	−33 °C, 45 min	77	[10]
	C_3F_7		76	
2-(SCF_3)-Pyrimidines				
4,6-(CH_3)$_2$	CF_3	−33 °C, 60 min	82	[154]
4-SH	CF_3		61[b]	[154]
4-SH-6-CH_3	CF_3		58[b]	[154]
4-OH-6-CF_3	CF_3	Pyrex ampoule, 30–45 °C, 5 h	59	[154]
4,6-Me_2-5-OH	CF_3	−30 °C, 4 h,	89	[154]

[a] Received from 5-SZn salts, poorly soluble in liquid ammonia.
[b] The 2,4-bis(SCF_3)-derivatives.



Scheme 44: Deactivation of 2-mercapto-4-hydroxypyrimidines *S*-centered radicals.

In the case of 2-mercapto-5-hydroxypyrimidines, no tautomeric keto form such as that shown in Scheme 44 is possible and consequently, are perfluoroalkylated without any problems, e.g., 2-mercapto-5-hydroxy-4,6-dimethyl pyrimidine [145].

In summary, heterocyclic thiols react with perfluoroalkyl iodides with considerably more difficultly than aromatic thiols.

4.1.3. Photochemical perfluoroalkylation in organic solvents under phase transfer conditions

Liquid NH_3 is a key reaction medium for the reaction of organic thiols with perfluoroalkyl iodides under UV irradiation. However, other solvents have been investigated including alcohols, acetone, acetonitrile, dioxane, THF, DMF, DMSO, HMPA and so on. Polar aprotic solvents emerge as the best. Biphasic reactions with water work well, particularly with diethyl ether and benzene (Table 4).

Heterocyclic thiolates react more slowly with perfluoroalkyl iodides than thiophenoxides both in liquid ammonia and in organic solvents. Besides, in reactions with heterocyclic thiolates, as well as with thiophenoxides, CF_3I is a poorer electrophile than C_3F_7I - even under biphasic conditions.

4.1.4. Interaction of thiols with perfluoroalkyl bromides

Although brominated perfluoroalkanes are cheaper and more readily available than the corresponding iodides, they react more slowly in thioether forming reactions. In general, monobrominated perfluoroalkanes do not react. However, dibromodifluoromethane, bromochlorodifluoromethane as well as 1,2-dibromotetrafluoroethane [170,171] do react with metal phenoxides and thiophenoxides via halophilic mechanisms [64], and almost always lead to mixtures of bromo and chloro containing products of mono- and di-substitution.

Table 4: Reaction of thiophenols RC_6H_4SH and mercapto heterocycles with R_FI under UV irradiation in organic solvents and biphasic conditions.

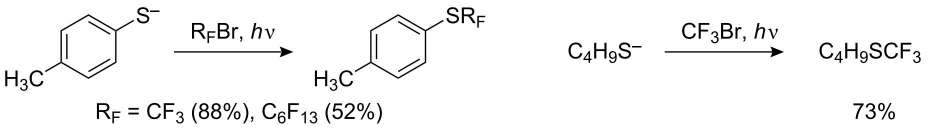
R	R_F	Base	Solvent	Conditions	Yields of $ArSR_F$, %	Ref.
			Thiophenols			
H	CF_3	PhSNa	CH_3OH or acetone	0–5 °C, 30 min	57.5 or 79	[143]
			CH_3CN		89	[143]
		NaOH	CH_3OH or acetone	0–5 °C, 30 min	43 or 49	[143]
			CH_3CN		72	[143]
	$CF(CF_3)_2$	Et_3N	CH_3CN	0 °C, 30 min	88	[104]
	CF_3	NaOH	Et_2O/H_2O	$(Et)_3BzN^+Cl^-$, 20–25 °C, 30 min	54	[167]
	C_3F_7				78	[167]
4-Cl	C_3F_7	$ArSNa^a$	CH_3OH or CH_3CN	20 °C, 30 min	61 or 81	[144]
	CF_3	NaOH	Et_2O/H_2O	$(Et)_3BzN^+Cl^-$, 20–25 °C, 30 min	61	[167]
	C_3F_7				85	
	i-C_3F_7				60	
	C_6F_{13}				71	
	C_3F_7		C_6H_6/H_2O		68	[167]
4-CH_3	CF_3, C_3F_7	NaOH	Et_2O/H_2O	$(Et)_3BzN^+Cl^-$, 20–25 °C, 30 min	58, 83	[167]
	C_3F_7		C_6H_6/H_2O^b		67	[167]
4-OCH_3	CF_3	NaOH	Et_2O/H_2O		52	[167]
4-CO_2CH_3	C_3F_7	NaOH	Et_2O/H_2O		71	[167]
4-NH_2	CF_3	NH_4OH	NH_4OH	−60 to 25 °C	95	[168]
			2-Mercapto heterocycles[c]			
Heterocycle	R_F	Base	Solvent	Conditions	Yield	Ref.
Benzothiazole	$Cl(CF_2)_4$	NaH	DMF	70 °C, 10 h	41.2	[169]
	$Cl(CF_2)_6$	NaH	DMF	70 °C, 10 h	61.6[d]	[169]
	C_6F_{13}	NaH	DMF	70 °C, 10 h	53.6	[169]
	C_8F_{17}				71.6	
Benzimidazole	$Cl(CF_2)_4$	NaH	DMF	70 °C, 10 h	40.6[e]	[169]
	$Cl(CF_2)_6$	NaH	DMF	70 °C, 10 h	38.2	[169]
	C_6F_{13}, C_8F_{17}	NaH	DMF	70 °C, 10 h	77.6, 78.2	[169]
Benzoxazole	$Cl(CF_2)_6$	NaH	DMF	70 °C, 10 h	15.0	[169]

[a] At ArSH + Et_2NH or Et_3N for 3 h, the yields are 37% and 28%, respectively.
[b] In CH_2Cl_2/H_2O or $CHCl_3/H_2O$ the yields are 50% and 55%, respectively.
[c] Yields of products are resulted taking into account a conversion of R_FI.
[d] In presence of $(t\text{-Bu})_2N\text{-}O^\bullet$ the yield is 18.6%.
[e] In presence of $(t\text{-Bu})_2N\text{-}O^\bullet$ the yield is 8.6%.

Their lower reactivity [88] is largely due to the greater dissociation energy of the C–Br bond (55 kcal/mol for CF_3Br) compared to C–I (28 kcal/mol for CF_3I) [172]. In addition, CF_3Br has a higher reduction potential than CF_3I and prefers to receive two rather than one electron on reduction [173].

Nevertheless, it was found [174] that UV irradiation of thiolates in liquid ammonia or dimethylformamide with perfluoroalkyl bromides does result in the formation of the corresponding perfluoroalkyl sulfides as shown in Scheme 45. Thiols with electron-donating substituents give reasonable yields, whilst *p*-chlorothiophenol produces the corresponding trifluoromethyl sulfide in low yield (~3–5%), although better yields are obtained when iodide salts are used as catalysts [175].

Wakselman et al., have shown [176] that liquid $C_6F_{13}Br$ reacts with thiolates without any irradiation, whereas bubbling gaseous CF_3Br through a DMF solutions of thiolates at 20 °C or heating such mixtures in an autoclave (80 °C) does not produce trifluoromethyl sulfides. Reactions between thiophenoxides and



Scheme 45: Perfluoroalkylation of thiolates with CF_3Br under UV irradiation.

CF_3Br are successful if carried out under pressure (CF_3Br 2–3 atm) in DMF at 20 °C [176-178]. However, even under these conditions only thiols containing electron-donating groups in the para-position give high yields. All ethers (Table 5), even those with electron-donating groups in the ortho- and meta-positions show very poor reactivity.

The best results arise from a combination of two factors – a pressure of CF_3Br and UV irradiation [158,179]. Results are given in Tables 6–8. In these cases the influence of the solvent is obvious. For example, *p*-chlorothiophenol reacts poorly with CF_3Br and 4-chloro-4′-trifluoromethylsulfanyldiphenyl sulfide is obtained as a byproduct presumably as the result of photo-substitution of chlorine in 4-trifluoromethylsulfanylchorobenzene by an $S_{RN}1$ mechanism. HMPA suppressed this side-reaction (similar to iodobenzene with potassium diethyl phosphite [180]) and promoted trifluoromethylation (Table 6).

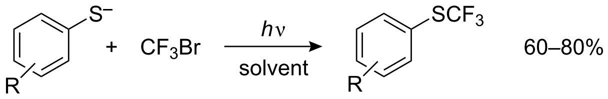
The reaction solvent is important and the yield of the trifluoromethylated product decreases in the following sequence: HMPA > DMF > CH_3CN > *N*-methyl pyrrolidone > sulfolane [179] (Table 6). The efficiency of the combined influence of irradiation and pressure of CF_3Br is presented in Table 7.

As can be seen from the data in (Table 6 and Table 7), in spite of increased product yields in general, the selectivity remains

Table 5: Yields of CF_3Br reaction with thiophenoxides in DMF at 20 °C under pressure (2–3 atm) [178].

Substituents in thiophenols	H	4-CH_3	4-OCH_3	3-OCH_3	2-OCH_3	3-NH_2	4-Cl	3-CF_3	4-NHAc
Yields of $ArSCF_3$, %	62	75	83	40	7	23	34	13	9

Table 6: Reactions of thiophenoxides with CF_3Br under UV irradiation and pressure of reaction gas [179].



R	Solvent	Base	*p* (atm)	*T* (°C)	Irradiation time, (h)	Conversion of ArSH, (%)	Isolated yields of $ArSCF_3$ (%)
4-CH_3	DMF	Et_3N	4–5	10–13	1.5		82
4-NH_2	DMF	Et_3N	4.5–6	10–20	2		76.4
3-NH_2	HMPA	morpholine	3–4	17–19	3.25		63.5^a
4-NHCOMe	DMF	Et_3N	3.5	19	2.7		69
4-$NHCO_2Me$	DMF	Et_3N	4.5–5	15–25	1.2	63	55.5
	HMPA	morpholine	2–5	8–10	2.5	73	83.6
4-Cl	CH_3CN	Et_3N	3–3.5	15–18	2.8	53	43^a
	DMF	Et_3N	3–3.5	14	1.2	100	48^a
	HMPA	Et_3N	4	8–10	1	100	69
	HMPA	morpholine	3–4	14–16	3.5	97	62.5
	HMPA	morpholine	3–4.5	29–30	3	36	46
	Sulfolane	morpholine	3.5	23	2	19.5	5.4
	N-Methyl pyrrolidone	morpholine	3.5	17	2.2	35.5	14.3

^{a}Determined by GLC.

Table 7: Comparison of $RC_6H_4SCF_3$ yields, obtained under a pressure of CF_3Br with and without UV irradiation (DMF, p = 3–5 atm, T = 10–20 °C).

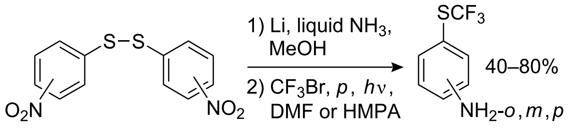
R	Irradiation time, h	Yields of $RC_6H_4SCF_3$, %	
		Irradiation	Without irradiation[a]
$4\text{-}CH_3$	1.5	82	75
$3\text{-}NH_2$	2.2	56	23
	4	72.5	
$4\text{-}NHCOCH_3$	2.7	69	9
4-Cl	1.2	48	34

[a] According to [178] (DMF, p = 2–3 atm, 3 h, 20 °C)

about the same. The best results are found with thiophenols, containing electron-donating substituents in the para-position. It is possible to increase the effectiveness of the *p*-chlorothiophenol reaction to ~70% by suppression of by-product formation ($4\text{-}Cl\text{-}C_6H_4SC_6H_4SCF_3\text{-}4$) and by using HMPA as solvent.

Trifluoromethylation of easily oxidizable aminothiophenols can be conducted by a modified procedure. The required thiophenoxides are prepared directly prior to irradiation by reduction of the corresponding dinitrophenyl disulfides with Li/liquid NH_3 (Table 8), in much the same way as the described above for R_FI [158,159].

Table 8: Preparation of aminophenyl trifluoromethyl sulfides with CF_3Br (3–7 atm) and UV irradiation with preliminary reduction of dinitrodiphenyl disulfides [179].



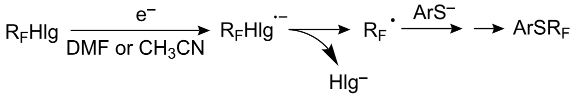
Location of NO_2 (NH_2)	Solvents	p (atm)	T (°C)	Irradiation time, h	Yields of products, %
o-	DMF	4.6–6	10–13	7.75	40.9
m-	DMF	3–3.5	8–10	2.2	56[a]
	DMF	3–6	10–14	4	72.5[a]
	DMF	4–6	12–19	6.8	80.8
	HMPA	3–5	8–10	3	71.8[a]
p-	DMF	5–6	15–20	5	80.3

[a] Isolated as the acetyl derivative.
Due to greater UV stability of CF_3Br compared to CF_3I, it is possible to increase the irradiation time, with a beneficial effect on the product yield.

4.1.5. Other methods of initiating

From the knowledge that the reaction mechanism is a single-electron transfer process involving $R_F^{\bullet}$ radicals, alternative methods to photochemical initiation have been developed (see sections 4.1.1.–4.1.4.), e.g., the electrochemical reduction of perfluoroalkyl halogenides [173,181]. In the presence of thiolate anions the resulting electrophilic radicals react [182,183] to give aryl perfluoroalkyl sulfides (Table 9).

Table 9: Formation of aryl perfluoroalkyl sulfides by electrochemical initiated reactions of ArS^- with R_FHlg.



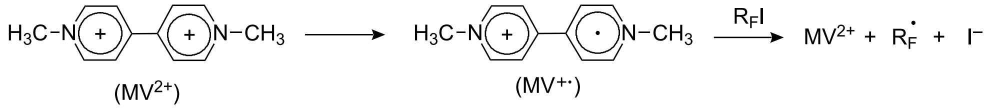
Reagents		Yield of $ArSR_F$, %		Ref.
ArS^-	R_FHlg	On substrate	On current	
p-$CH_3C_6H_4S^-$	CF_3I	55	300	[182]
p-$CH_3C_6H_4S^-$	C_3F_7I	77	270	[182]
p-$CH_3C_6H_4S^-$	CF_3Br	40[a]	200	[182]
p-$CH_3C_6H_4S^-$	$C_8F_{17}Br$	63	360	[182]
p-$ClC_6H_4S^-$	CF_3I	75	250	[182]
p-$ClC_6H_4S^-$	CF_3Br	61[b]	98	[182]
p-$ClC_6H_4S^-$	C_3F_7I	82	450	[182]
p-$ClC_6H_4S^-$	CF_3I	60	300	[181]
p-$CH_3OCONHC_6H_4S^-$	CF_3I	33	160	[181]
Thiazole-2-S^-	$C_6F_{13}I$	64[c]		[184]

[a] With a carbon-glass electrode a yield is 77%.
[b] With a carbon-glass electrode.
[c] In the presence of *p*-$O_2NC_6H_4CN$.

The good yields for electrochemical perfluoroalkylation (especially > 100% electrochemical yield) are consistent with a radical-chain process.

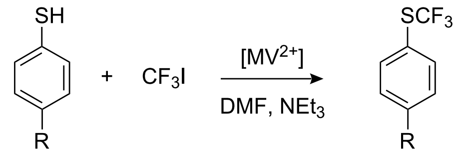
Perfluoroalkyl iodides are better substrates than the bromides which give lower yields in these electrochemical reactions (Table 9). Such electrochemically initiated reactions are described in detail in a review [35].

Another method of catalytic generation of $R_F^{\bullet}$ radicals involves electron-transfer from a nucleophile to a perfluoroalkyl halide, in this case using the dimethyl dipyridinium salt (methylviologen, MV^{2+}) as a catalyst. This dication is initially reduced to a radical cation, which then transfers an electron to a perfluoroalkyl iodide [185] to generate $R_F^{\bullet}$ (Scheme 46). A small amount of MV^{2+} (7% relative to ArSH) is sufficient for quantitative transformation of thiols into aryl perfluoroalkyl sulfides (Table 10).



Scheme 46: Catalytic effect of methylviologen for $R_F^\bullet$ generation.

Table 10: Catalysis of trifluoromethylation by methylviologen [186].



R	MV^{2+}, %	Yields of $ArSCF_3$,%	
		With MV^{2+}	Without MV^{2+}
H	6.5	91.2	3
Cl	7.0	100.0	5
NO_2	7.9	9.2	–
NHCOOMe	6.9	88.5	11

It should be noted that over-reduction of such halides will generate R_F^- anions rather than the desired $R_F^\bullet$ radicals. For example, tetrakis(dimethylamino)ethylene reacts with R_FI to form the perfluoroalkyl anion which acts as a nucleophilic R_F-alkylation agent for organic and inorganic substrates [187].

The use of any catalyst in the case of perfluoroalkyl iodides is of more theoretical interest, although the method can be applied in the case of poorly reactive thiophenols. In general these reactions work well (see section 4.1.6.) in common organic solvents or under biphasic conditions [188,189]. Reactions with perfluoroalkyl bromides are more sluggish. Only compounds with long perfluoroalkyl chains such as $C_6F_{13}Br$ [178] react readily with thiolates. In the reaction of gaseous CF_3Br with thiophenols special procedures are required (see section 4.1.4.): UV irradiation [174], pressure [178] and electrochemical stimulation [182]. Moreover, thiophenols with electron-donating substituents in the para-position give the best results. Combined pressure and irradiation [158,179] improved yields only slightly and requires special equipment. A detailed study of catalytic stimulation in reactions of bromo- and chloro-containing freons R_FX with thiols is necessary.

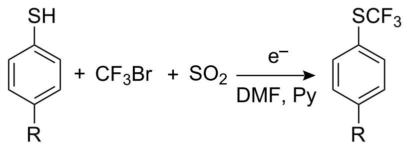
The decreased reactivity of CF_3Br as compared to CF_3I can be explained, first of all, by the higher reduction potential (−2.07 V against −1.52 V for CF_3I on a glass-carbon cathode), and secondly, by the fact that the $CF_3^\bullet$ radical has a reduction potential (−1.80 V) close to that of CF_3Br [173]. Thus trifluoromethyl bromide in reactions with nucleophiles or on a cathode surface accepts two electrons and is transformed to CF_3^- and therefore does not react with thiolates. The $SO_2^{-\bullet}$ radical anion can act as an electron mediator in such reactions. This radical anion, generated by chemical [190-193] or electrochemical [194,195] methods, causes a single-electron reduction of CF_3Br with the formation of the necessary trifluoromethyl radical. Thus, the influence of $SO_2^{-\bullet}$ sources ($Na_2S_2O_4$, $HOCH_2SO_2Na$ or SO_2 in presence Zn and Na_2HPO_4 or HCOONa) on trifluoromethyl bromide in DMF in the presence of diaryl disulfides [193,196] leads to the formation of the corresponding trifluoromethyl sulfides, often in high yields (Scheme 47).

$$\text{RS-SR} + CF_3Br \xrightarrow[\text{DMF}]{[SO_2^{-\bullet}]} RSCF_3 \quad 65–90\%$$

R = Ph, Bu, CH_2COOEt, 2-NH_2-3-(2,4,6-$Cl_3C_6H_2$)$^{-5}$-CN-pyrazolyl

Scheme 47: $SO_2^{-\bullet}$ catalyzed trifluoromethylation.

Related transformations with various $SO_2^{-\bullet}$ sources involving R_FI and CF_2ClBr, $CFCl_2$-CF_2Cl in the reactions with diaryl disulfides [197] and diselenides have been reported [198]. Electrochemical studies involving the $SO_2^{-\bullet}$ radical anion prove that the electron transfer to CF_3Br takes place at a reduction potential of the mediator between −0.9 and −1.0 V which prevents the transfer of a second electron to $CF_3^\bullet$ and the generation of CF_3^- [199]. Therefore electrochemical reduction in the presence of sulfur dioxide allows the trifluoromethylation of thiophenols with the less reactive, but more readily available trifluoromethyl bromide (Scheme 48).



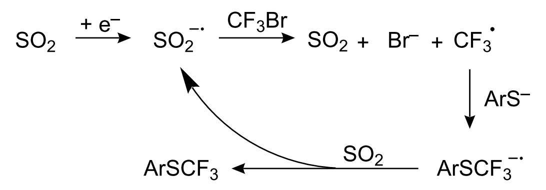
R	Yield
$NHCO_2Me$	94%
H	78%
Br	64%
Cl	60%
NO_2	24%

Scheme 48: Electrochemical reduction of CF_3Br in the presence of SO_2 [199,200].

Although 4-nitrothiophenol is a very poor substrate (see section 4.1.1. and Table 11), it reacts with perfluoroalkyl iodides to afford 4-perfluoroalkylsulfanylnitrobenzenes in presence of

NaH in DMF in almost quantitative yields [201], presumably via “hydride” catalysis.

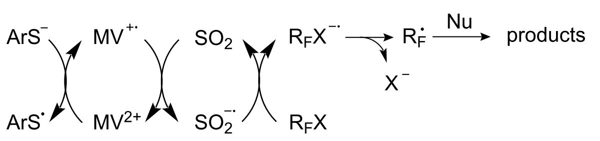
The catalytic influence of SO_2 on the reaction of ArS^- with CF_3Br is not limited to the activation of the initial bromide. Sulfur dioxide can oxidize the radical anion $ArSCF_3^{-\bullet}$, i.e., it can affect the rate determining step of the process [189] (Scheme 49).



Scheme 49: Participation of SO_2 in the oxidation of $ArSCF_3^{-\bullet}$.

This dual influence of sulfur dioxide contributes to the overall efficiency of these reactions.

By comparing the possibility of two mediators (SO_2 and MV), Koshechko et al., [202] have shown that the radical cation $MV^{+\bullet}$ ($E_p = -0.4$ V) easily reduces SO_2 ($E_p = -0.9$ V) to its radical anion which in turn activates CF_3Br. Thus, a combination of both mediators generates an electron transfer cascade (Scheme 50).



Scheme 50: Electron transfer cascade involving SO_2 and MV.

Thus, bubbling CF_3Br into a solution of thiophenol or thiocresol in DMF containing pyridine, SO_2 and a catalytic amount of MV^{2+} 2 I^-, results in the formation of the corresponding aryl trifluoromethyl sulfides in moderate to good yields (40–70%) [202].

Similar reactions with SO_2, where KI or I_2 were used instead of MV^{2+} have been carried out [202], however, the yields of $PhSCF_3$ were reduced. The catalytic effect of iodide ion was discovered from UV irradiation of a reaction mixture of *p*-chlorothiophenol with CF_3Br in different solvents [175].

The MV^{2+}/SO_2 system is effective for reactions with Freons, particularly those with C–Cl bonds such as Freon-113 (CF_2Cl-$CFCl_2$) [202].

A good example of the catalytic properties of SO_2 has recently been shown in the reaction of 1,2-dibromotetrafluoroethane with thiophenoxides [203]. It is known that these reactions $ArSCF_2CF_2Br$ and a significant amount of $ArSCF_2CF_2H$ are produced. The presence of SO_2 in the reaction promotes a $S_{RN}1$ process which results in quantitative yields of $ArSCF_2CF_2Br$ without the byproduct $ArSCF_2CF_2H$.

4.1.6. Spontaneous perfluoroalkylation of thiols without initiators

Since Feiring reported in 1984 that reactions of thiolate anions and perfluoroalkyl iodides can occur spontaneously without any initiator [188], the method has been extensively investigated and the reaction conditions optimized (Table 11 and Table 12). Reactions times, for example, are shortened with heating (60–70 °C) [204].

Later it was found that these types of reaction can be made to proceed considerably easier and quicker (Table 12). In acetonitrile or DMF the majority of thiophenolates react rapidly with C_3F_7I at room temperature (from 10–15 min to 2–3 h). However, for spontaneous reaction many factors are involved such as carrying out the reaction in the dark, temperature, solvent etc. This is discussed in more detail in section 4.1.7.

4.1.7. Reaction mechanism

The stages of *S*-perfluoroakylation [22,35,143,188,208] can be represented as follows (Scheme 51):

$$\begin{aligned}
&ArS^- + R_FX \longrightarrow ArS^\bullet + [R_FX]^{-\bullet} && (1)\\
&[R_FX]^{-\bullet} \longrightarrow R_F^\bullet + X^- && (2)\\
&R_F^\bullet + ArS^- \longrightarrow \left[ArS^\bullet + R_F^-\right] \longrightarrow ArSR_F^{-\bullet} && (3)\\
&[ArSR_F]^{-\bullet} + R_FX \longrightarrow ArSR_F + [R_FX]^{-\bullet} && (4)
\end{aligned}$$

Scheme 51: Four stages of the $S_{RN}1$ mechanism for thiol perfluoroalkylation.

The peculiar behavior of 4-nitrothiophenol [143,146] and 4-hydroxypyrimidine-2-thiol [145] unlike the more electronegative *p*-SO_2CF_3- and *o*-SO_2CHF_2-thiophenols [143] is presumably related to the ability of the nitro- and carbonyl groups to stabilize the mercapto-radicals in the radical ion pairs [$^\bullet O_2NArS + R_F^-$] and [$^\bullet O{=}CArS + R_F^-$]. As a result, these radicals are less reactive, although at higher temperatures an increase in their activity is observed.

The participation of radicals is supported by the fact that the addition of nitrobenzene [178] or di-*tert*-butylnitroxide [169]

Table 11: Reactions of thiols RC_6H_4SH and HetArSH with R_FI in organic solvents and in biphasic conditions without initiators.

R	SH, ($SCat^+$)	R_F	Base	Reaction conditions	Yields of $ArSR_F$, %	Ref.
				Thiophenols		
H	SNa	C_8F_{17}	—	DMF, 25 °C, 17 h	90	[188]
H	SNa	C_8F_{17}	—	DMF, 25 °C, 17 h + norbornene	77	[188]
H	SNa	C_8F_{17}	—	DMF, 25 °C, 17 h + styrene	0	[188]
H	SNa	$CF(CF_3)_2$	—	DMF, 25 °C, 17 h	76	[188]
H	$SNBu_4$	C_6F_{13}	—	CH_2Cl_2/H_2O, 40 °C, 4 h	48	[188]
H	$SNBu_4$	C_6F_{13}	—	C_6H_6/H_2O, 25 °C, 2.5 h	76[a]	[188]
H		$R(CF_2)_n$		DMF, conditions are not presented	56–87	[205]
4-NH_2	SH	C_2F_5	K_2CO_3	DMF, 10 °C	84	[206]
4-F	SNa	$C_{10}F_{21}$	—	DMF, 70 °C, 1 h	97	[204]
4-F	SNa	$CF_2)_4I$	—	DMF, 25 °C,12 h, 60 °C, 1 h	86[b]	
4-Cl	SNa	$(CF_2)_8I$	—	DMF, 50 °C, 6 h		
H	SH	C_4F_9	NaH	DMF, 20–25 °C, 17–18 h	66	[201]
4-CH_3	SH	C_4F_9	NaH	DMF, 20–25 °C, 17–18 h	77	[201]
4-OH	SH	C_4F_9	NaH	DMF, 20–25 °C, 17–18 h	30	[201]
4-Cl	SH	C_4F_9	NaH	DMF, 20–25 °C, 17–18 h	83	[201]
4-NO_2	SH	C_4–C_8	NaH	DMF, 20–25 °C, 17–18 h	93–99	[201]
F_5	SCu	CF_2=CF	—	DMAC, 70 °C, 20 h	65	[207]
F_5	SCu	C_8F_{17}		DMAC, 70 °C, 20 h	0	[207]
H	SeNa	CF_3Br		EtOH, 20 °C, 2 h, olefins	2–60	[160]
H	SeNa	C_4F_9I–$C_8F_{17}I$		EtOH, 20 °C, 2 h, olefins		[160]
				Heterocyclic thiols		
Heterocycle		R_F	Base	Reaction conditions	Yields	Ref.
2-SH-benzothiazole		C_3F_7	NEt_3	DMF, 55–60 °C, 3–48 h	Traces	[189]
		C_3F_7	NEt_3	DMF, 20–22 °C, 120 h	59	[189]
		$Cl(CF_2)_{4–6}$	NaH	DMF, 70 °C, 10 h	0–4.5[c]	[169]
2-SH-benzimidazole		$Cl(CF_2)_{4–6}$	NaH	DMF, 70 °C, 10 h	0–3[d]	[169]
8-SNa-quinoline		C_3F_7	NEt_3	DMF, 20–22 °C, 24 h	72	[189]

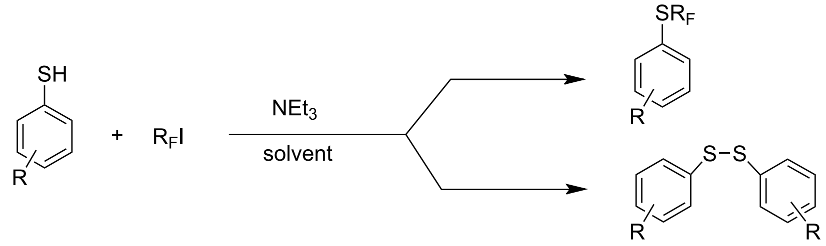
[a] In the presence of norbornene and styrene the yields are 30% and 0%, respectively.
[b] α, ω-Bis(SAr)perfluoroalkanes.
[c] 8.5% conver. R_FI.
[d] ~3% conver. R_FI.

inhibits the reaction. The addition of olefins such as norbornene or styrene [188] has a similar effect and perfluoroalkyl derivatives of these olefins have been identified in the reaction products. The formation of radicals in the reaction of PhSeNa with perfluoroalkyl halides ($PhSe^\bullet$ and $R_F^\bullet$) has been firmly established from their interception by unsaturated compounds [160].

Further confirmation of a radical mechanism was obtained by studying the reaction without an initiator (Table 12 and Table 13). The decrease of reaction temperature, carrying out the reaction in the absence of light, the presence of electron-withdrawing substituents in the thiol ring and use of low-polar solvents all led to lower $ArSR_F$ yields. Also replacement of C_3F_7I for CF_3I leads to a slower reaction and reduced yields of aryl perfluoroalkyl sulfides. In spite of heptafluoropropyl iodide being a stronger oxidant than CF_3I [182,209], greater amounts of diaryl disulfides are obtained only with CF_3I. The factors listed above influence the yields of diaryl disulfides in a different way. They either do not change (in darkness), or they even slightly increase (from 3–4 to 12–13%).

These observations point towards the rate determining step of the reaction [189]. Two steps (Scheme 51), i.e., the rapid fragmentation of the radical anion $R_FX^{-\bullet}$ (Equation 2) [173] and recombination of the electrophilic radical $R_F^\bullet$ with the ArS^- anion (Equation 3) are fast and cannot therefore be rate limiting.

Table 12: Reaction conditions of thiophenoxides $RC_6H_4S^-$ Et_3NH^+ with R_FI without irradiation [189].

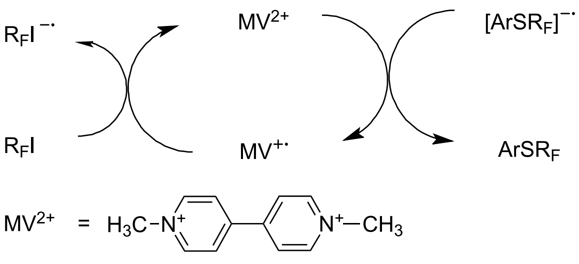


Entry	R	R_F	Solvent	*T* (°C)	*t* (h)	Yields (%)		
						$ArSR_F$	ArS-SAr	ArSH
1	H	C_3F_7	DMF	19–20	2	83	3	—
2	4-$NHCO_2CH_3$	C_3F_7	DMF	21–22	20 min	89	3	—
3[a]	4-$NHCO_2CH_3$	C_3F_7	DMF	21–22	1	60	4	12
4	4-$NHCO_2CH_3$	CF_3	DMF	21–22	1	70	9	—
5	4-$NHCO_2CH_3$	C_3F_7	DMF	0–5	3	17	12	30
6	4-$NHCO_2CH_3$	CF_3	DMF	0–22	5	30	7	54
7	4-$NHCO_2CH_3$	C_3F_7	HMPA	0–5	3	0	12	50
8	4-$NHCO_2CH_3$	C_3F_7	HMPA	21–22	2	75	3	—
9	4-$NHCO_2CH_3$	C_3F_7	CH_3CN	21–22	0.5	98	Traces	—
10	4-$NHCO_2CH_3$	C_3F_7	dioxane	21–22	2	82	2	—
11	4-$NHCO_2CH_3$	C_3F_7	THF	21–22	1.5	64	10	—
12	2-NH_2	C_3F_7	CH_3CN	21–30[b]	10 min	84	-	—
13	2-NH_2	CF_3	DMF	23–24	1	66	7	—
14	4-OCH_3	C_3F_7	CH_3CN	22–40[b]	10 min	88	6	—
15	4-Cl	C_3F_7	DMF	22	2	72	3	—
16	4-Cl	C_3F_7	CH_3CN	21–22	3	40	12	9
17	4-COOH	C_3F_7	DMF	22–30[b]	10 min	72	Traces	Traces
18	4-$COOCH_3$	C_3F_7	DMF	20	3	39	13	Traces
19	4-NO_2[c]	C_3F_7	DMF	50–55	5	Traces	6	80

[a] In the dark.
[b] Spontaneous warming.
[c] Sodium thiophenoxide.

Since all experimental factors (light, temperature, solvent etc.) have an inverted influence on the yields of disulfides, it can be assumed that Equation 1, the generation of $ArS^\bullet$ is also not limiting. Therefore electron transfer from the radical anion $[ArSR_F]^{-\bullet}$, Equation 4, seems to be the most likely.

Homogeneous catalysis by the methyl viologen (MV) [186] supports this. This catalyst can oxidize the radical anion $[ArSR_F]^{-\bullet}$ via its dication (MV^{2+}) [200,202], accelerating the last step (Scheme 52).



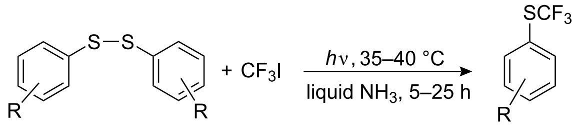
Scheme 52: A double role of MV in the catalysis of R_FI reactions with aryl thiols.

4.2. Radical perfluoroalkylation

Synthetic methods for aryl perfluoroalkyl sulfides via $R_F^\bullet$ radicals are now described. Prolonged UV irradiation of CF_3I solutions with diaryl disulfides in liquid ammonia results in the formation of the corresponding aryl trifluoromethyl sulfides (Table 13).

For diaryl disulfides the $CF_3^\bullet$ radical can attack either the sulfur atom or the aromatic ring, [132,210] and thus give rise to undesired side products. Arylperfluoroalkyl sulfides are formed also in a reverse strategy from aliphatic disulfides and aryl radicals. For example, during irradiation of bis(trifluoromethyl) disul-

Table 13: UV irradiation of CF_3I with diaryl disulfides in a sealed quartz tube [157].



R	*t* (h)	Yield of $ArSCF_3$ (%)
H		12[a]
4-Cl	5	36.5[a]
$4-NO_2$	25	58
$2-NO_2$	12	72

[a] Extracted from mixtures.

fide and pentafluoroiodobenzene [211] the product mixture contains $C_6F_5SCF_3$, $C_6F_5SSCF_3$, CF_3I as well as $(CF_3S)_2$ with $(CF_3)_2S$ suggesting the following reaction mechanism (Scheme 53).

N-Trifluoromethyl-*N*-nitrosobenzene sulfonamide has been used as a source of $CF_3^•$ radicals. This reagent (obtained by reaction of CF_3NO, NH_2OH and benzenesulfonic acid chloride) reacts with organic disulfides under irradiation or on mild heating to give the corresponding trifluoromethyl sulfides (Scheme 54).

The *N*- trifluoromethylnitrososulfonamide of trifluoromethane sulfonic acid reacts similarly with aliphatic disulfides [214]. Interaction of CF_3NO with aryl sulfonamides generates relatively stable trifluoromethyl azosulfonyl arenes $ArSO_2N{=}NCF_3$, which decomposed on heating to $CF_3^•$ radicals which react with organic disulfides to form trifluoromethyl sulfides [215] (Scheme 55).

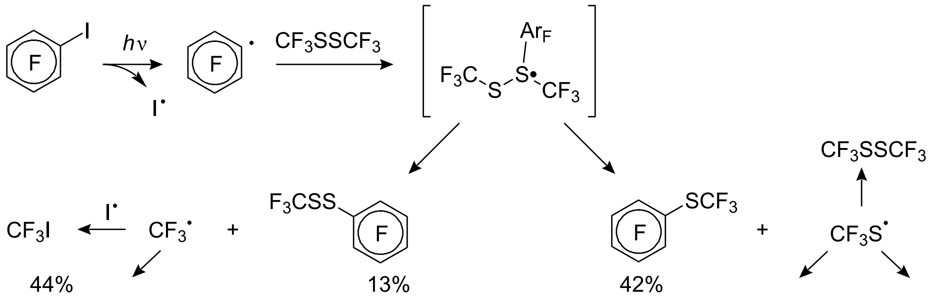
$$RS{-}SR \; + \; ArSO_2N{=}NCF_3 \xrightarrow{80\text{–}95\ °C} RSCF_3$$

R = C_6H_5 31%
R = CH_2COOH 37%

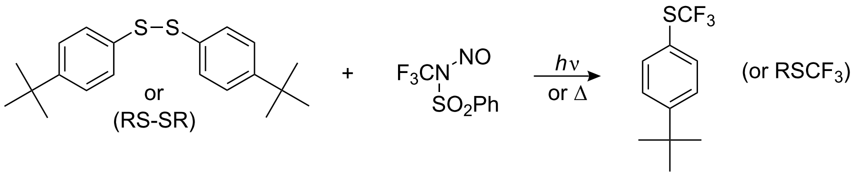
Scheme 55: Radical trifluoromethylation of organic disulfides with $ArSO_2N{=}NCF_3$.

Barton has shown [216] that the irradiation of thiohydroxamic esters of perfluorocarboxylic acids generates $R_F^•$ radicals which in the presence of olefins give addition products. However, in the absence of radical traps they attack the sulfur to yield, for example, *S*-perfluoroalkyl derivatives of pyridine (Scheme 56).

Decarboxylation of non-fluorinated carboxylic acid esters proceeds in a similar manner to afford 2-pyridyl sulfides. However, in the presence of $C_6F_{13}I$ the reaction follows a different course where the perfluorinated radical attacks sulfur with the formation of the fluorinated sulfide [217] (Scheme 57).

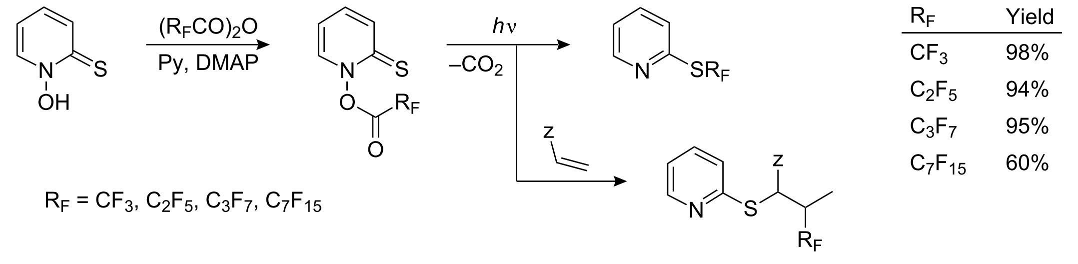


Scheme 53: Photochemical reaction of pentafluoroiodobenzene with trifluoromethyl disulfide.



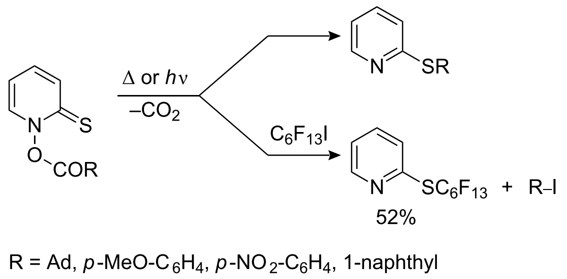
R = CH_2COOH, CH_2COOBu, etc.

Scheme 54: *N*- Trifluoromethyl-*N*-nitrosobenzene sulfonamide – a source of $CF_3^•$ radicals [212,213].



R_F	Yield
CF_3	98%
C_2F_5	94%
C_3F_7	95%
C_7F_{15}	60%

Scheme 56: Barton's *S*-perfluoroalkylation reactions [216].



Scheme 57: Decarboxylation of thiohydroxamic esters in the presence of $C_6F_{13}I$.

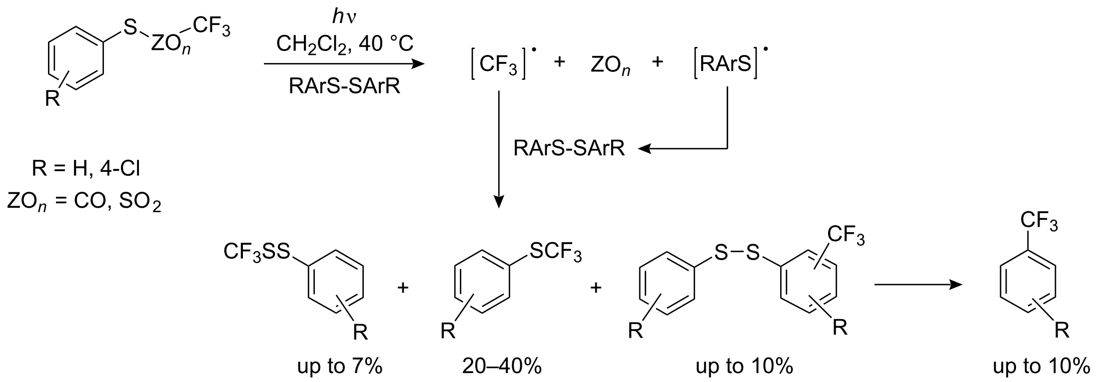
The irradiation of thioesters of trifluoroacetic and trifluoromethanesulfonic acids in refluxing methylene chloride results in their decarbonylation (or desulfonation in the case of CF_3SO_2SR) with the production of $CF_3^•$ radicals, which then react with diaryl- or dialkyl disulfides (Scheme 58).

The formation of aryl trifluoromethyl sulfides from thioesters of trifluoroacetic acid occurs in rather better yields (30–40%) than from the corresponding esters of trifluoromethanesulfonic acid (20–30%). Alkyl thioesters of trifluoroacetic and trifluoromethanesulfonic acids form $AlkSCF_3$ in higher yields (up to 80%). As shown in Scheme 58, the $CF_3^•$ radical can attack at several sites. Phenyl selenide esters of trifluoromethanesulfonic acid react analogously [218].

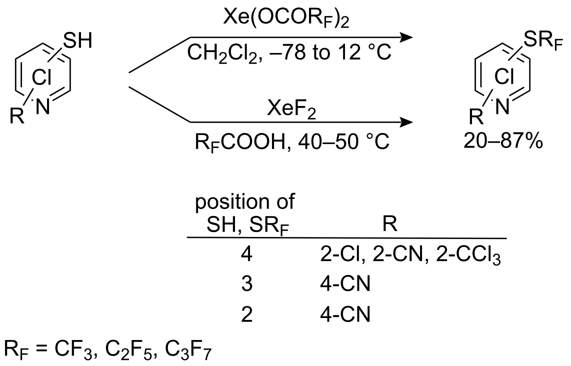
The photochemical decomposition of trifluoromethanesulfonic and carboxylic thioesters affords $CF_3^•$ radicals which can be used to prepare trifluoromethyl sulfides [219].

Xenon difluoride has been used to initiate oxidative decarboxylation of perfluorocarboxylic acids for $R_F^•$ generation and with aromatic and heterocyclic compounds the perfluoroalkyl groups can also become incorporated into the aromatic ring [220]. Nevertheless, Sipyagin et al., have employed this method for the perfluoroalkylation of thiols such as polychloropyridine thiols [221]. Two different methods were used: the action of preformed xenon carboxylates (method A) or treatment of a pyridinethiol solution in R_FCOOH directly with xenon difluoride (method B). A range of isomeric perfluoroalkyl sulfides was obtained (Scheme 59).

Similar reactions have been carried out with tetrafluoropyridine 4-thiol [224] and its corresponding disulfide [225,226] (40–50% yield). The formation of *S*-perfluoroalkyl derivatives with performed xenon carboxylates from nitro aromatic disulfides was also successful (Scheme 60).



Scheme 58: Reactions of thioesters of trifluoroacetic and trifluoromethanesulfonic acids in the presence of aromatic disulfides [218].



Scheme 59: Perfluoroalkylation of polychloropyridine thiols with xenon perfluorocarboxylates or XeF_2 [222,223].

Perfluoroalkylsulfinic acids can also be used for oxidative decomposition. For example, careful treatment of sodium trifluoromethylsulfinate with *tert*-butyl hydroperoxide in the presence of an organic disulfide gives the corresponding trifluoromethyl sulfide [228,229]. Aliphatic disulfides react well to give $AlkSCF_3$ but problems arise with aromatic disulfides due to attack of the $CF_3^{\bullet}$ radical on the aromatic rings. For example, diphenyl disulfide is converted only in 13% yield. The S/C ratio reflecting the amount of trifluoromethylation on sulfur and on the aryl ring depends on the solvent. In CH_3CN it is 36:64, while in aqueous CH_3CN it is 60:40. Dichlorodiphenyl disulfide gives the best ratio in favor of the sulfide in aqueous acetonitrile [228].

One final method of $CF_3^{\bullet}$ radical generation involves the interaction of $Bi(CF_3)_3/Cu(OCOCH_3)_2$ with thiophenolate (Scheme 61).

$$PhS^{-}\ {}^{+}NBu_4 \xrightarrow{Bi(CF_3)_3/CuAc_2} PhSCF_3 + PhSSPh$$

Scheme 61: $Bi(CF_3)_3/Cu(OCOCH_3)_2$ trifluoromethylation of thiophenolate [230].

The above methods for the synthesis of aryl perfluoroalkyl sulfides all generate electrophilic $R_F^{\bullet}$ radicals which prefers to react at nucleophilic reaction centers such as S^{-}, C=S or $S^{\bullet}$. In the case of diaryl disulfides [228] the regioselectivity of attack is less controlled due to ring delocalization.

4.3. Anionic perfluoroalkylation

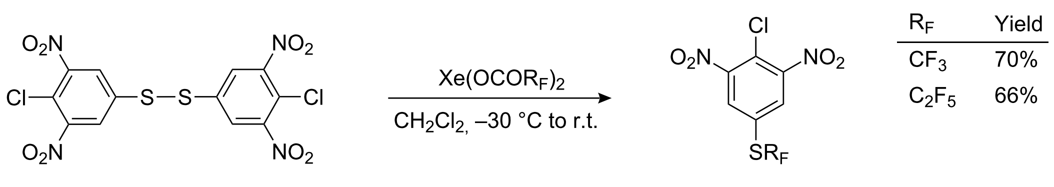
This method of perfluoroalkylation involves the reaction of aromatic or heterocyclic sulfur compounds with perfluoroalkyl anions, stabilized by suitable ligands, or with a reagent that generates such an anion.

Perfluoroalkyl anions are extremely unstable. For example, the CF_3 anion decomposes at −100 °C with the elimination of F^{-} and formation of difluorocarbene, which reacts further or dimerizes [123]. Nevertheless, in the last two decades nucleophilic perfluoroalkylation of organic compounds has expanded. The problem of R_F-lithium anion stability in synthesis has been reviewed [24]. Trifluoromethylated reagents of heavy metals and their application in organic synthesis were considered by Barton [25], whilst perfluoroalkylated [31,32] and trifluoromethylated [27,28,30] organosilicon compounds have attracted considerable interest. However, despite the large body of literature involving the use of such reagents, the synthesis of aryl perfluoroalkyl sulfides is restricted to anionic attack on sulfenyl chlorides and thiocyanates.

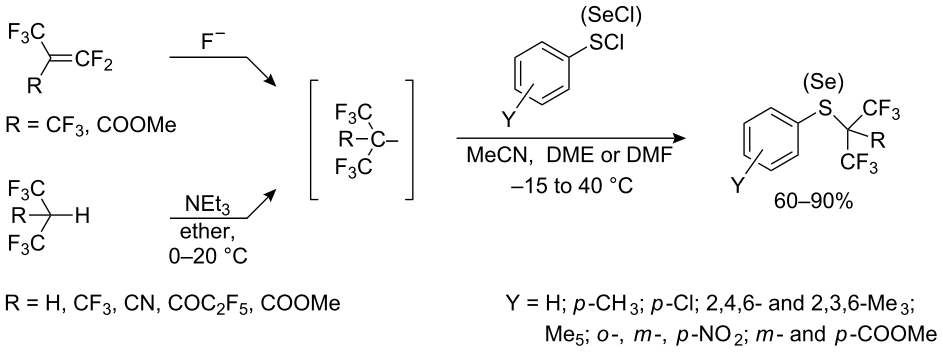
Various methods for the synthesis of aryl perfluoroalkyl sulfides, depending on the mode of generation of the perfluoroalkyl anion, are described below.

4.3.1. "R_F^{-}" from a perfluorinated olefins

Relatively stable tertiary perfluoroalkyl carbanions can be prepared by addition of fluoride ion to fluoroolefins [151,231-234] or by the deprotonation of monohydroperfluoroalkanes or their derivatives [235,236] as shown in Scheme 62. Most processes involve generating the hexafluoroisopropyl carbanions with a third stabilizing group such as CF_3 [151,231,232,236], C_3F_7 [233,234], as well as CN, COC_2F_5, COOMe [232,236]. Reactions of the resulting salts with aryl



Scheme 60: Interaction of $Xe(OCOR_F)_2$ with nitroaryl disulfide [227].



Scheme 62: Reaction of fluorinated carbanions with aryl sulfenyl chlorides.

sulfenyl (or aryl selenyl) chlorides yield perfluoro- or polyfluoroalkyl sulfides (selenides).

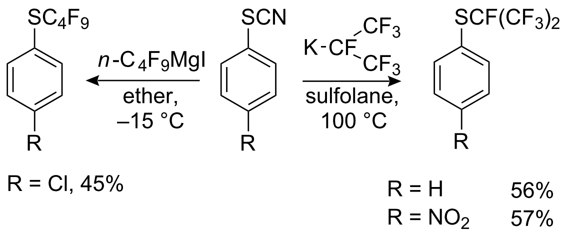
The $[C_3F_7(CF_3)_2C]^-$ anion, obtained from isomeric dimers of perfluoropropylene in the presence of KF or CsF, reacts with sulfenyl chlorides and selenyl chlorides to afford the corresponding sulfides and selenides bearing a tertiary perfluorohexyl group [233].

In the reaction of R_F^- carbanions with sulfenyl chlorides high yields of sulfides are obtained when either electron-withdrawing or electron-donating substituents are present on the aryl ring. The yields of isomeric nitrophenyl perfluoro-*tert*-butyl sulfides decrease, the closer the nitro group is to the sulfur atom: *p*-NO_2 – 86%, *m*-NO_2 – 78% [231] and *o*-NO_2 – 68% [232]. Both secondary and tertiary anions react [236] but nature of the counter ion is important. Thus, cesium or potassium perfluoro *tert*-butyl alkyls obtained by the addition of CsF or KF to perfluoroisobutene, give high yields of $ArSC(CF_3)_3$ [151,231,232], while the same anion, generated by deprotonation of nonafluoroisobutane $(CF_3)_3CH$ with NEt_3 gives $PhSC(CF_3)_3$ in low yield ~20% [236].

In the reaction of methyl perfluoromethacrylate with PhSCl in the presence of fluoride ion, prolonged stirring gave two sulfides as shown in Scheme 63, illustrating the competition between halides (F^- and Cl^-) for fluoroolefin addition [232].

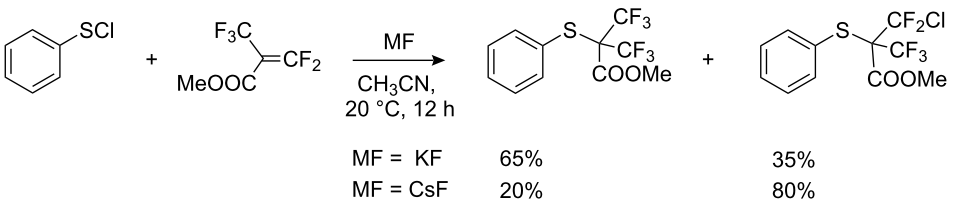
4.3.2. "R_F^-" from perfluoroalkyl halogenides

In a similar manner to alkylhalides, perfluorinated alkylhalides also form organometallic derivatives which can be used for the synthesis of perfluoroalkyl sulfides. The effectiveness of such reagents depends largely on the counterion which is illustrated below for reactions with organic thiocyanates (Scheme 64). Potassium perfluoroisopropyl (generated from CF_2=$CFCF_3$ and KF) reacts with phenyl- and *p*-nitrophenyl thiocyanates in sulfolane at 100 °C, whilst the Grignard reagent (*n*-C_4F_9MgI) reacts at subzero temperatures.



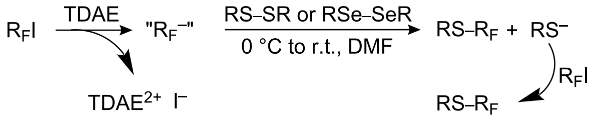
Scheme 64: Reactions of ArSCN with potassium and magnesium perfluorocarbanions [237].

Cuprates react with benzyl thiocyanate but require more forcing conditions, i.e., 100 °C [237], whereas in situ generated zinc reagents R_FZnX react with thiocyanates at 20 °C in pyridine [238].



Scheme 63: Reaction of methyl perfluoromethacrylate with PhSCl in the presence of fluoride.

Recently, it has been shown that tetrakis(dimethylamino)ethylene (TDAE) can undergo a two-electron transfer to perfluoroalkyliodides to generate R_F^- anions [187] which react with organic disulfides to afford perfluoroalkyl sulfides in high yields [239,240]. The economy of this method, as distinct from previous methods [196,241-248], lies in the fact that the thiolate released by the first nucleophilic attack on the disulfide reacts directly with a second equivalent of perfluoroalkyliodide, to form a second equivalent of the desired perfluoroalkyl sulfide (Scheme 65). This approach thus combines two principles of trifluoromethylation, i.e., nucleophilic attack of the R_F-anion on the disulfide and reaction of a radical anion with a thiol as noted in section 4.1.



$R_F = CF_3, C_2F_5, C_4F_9$

R	Yields of RSR_F
Ph	93% (99% $PhSeCF_3$)
4-Py	95–100%
2-Py	90%
n-Bu	88%

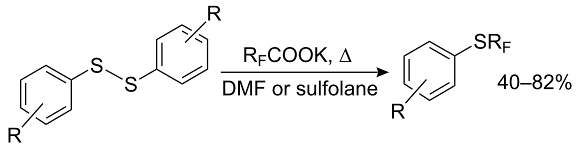
Scheme 65: Reactions of R_FI with TDAE and organic disulfides [239,240].

4.3.3. “R_F^-” from perfluorocarboxylic acids

A simple method for the generation of metal derivatives of perfluoroalkyl carbanions by the decarboxylation of alkali salts of perfluorocarboxylic acids, has also been used. For example, heating potassium perfluoroalkyl carboxylates in the presence of diaryl disulfides in DMF or sulfolane leads to the formation of the corresponding aryl perfluoroalkyl sulfides as summarized in Table 14.

Disulfides of pyridine [242], pyrimidine and naphthalene [249] have also been used in such reactions. The use of this method for longer perfluorocarboxylic acids leads to product mixtures that result from chain isomerism and cyclisation [250,251] (Scheme 66).

Table 14: Perfluoroalkylation of aryl disulfides by decarboxylation of perfluorocarboxylates.



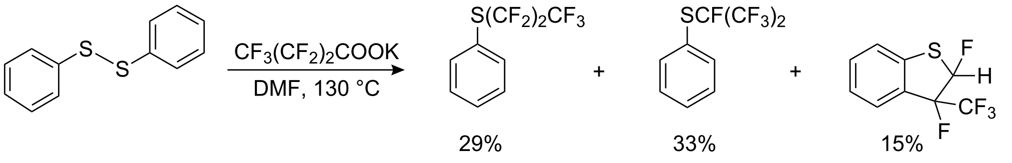
R	R_F	Solvent	*T* (°C)	Yield of $ArSR_F$ %	Ref.
H	CF_3	DMF	140	84	[245]
H	CF_3	sulfolane	180–230	56	[242]
4-Me	CF_3	sulfolane	180–230	51	[242]
4-Cl	CF_3	sulfolane	180–230	56	[242]
4-F	CF_3	sulfolane	180–230	82	[242]
2-Br	CF_3	sulfolane	180–230	48	[242]
4-OMe	CF_3	sulfolane	180–230	50	[242]
H	C_2F_5	DMF	145	70	[245]
4-Me	C_2F_5	DMF	145	50	[245]
4-NO_2	C_2F_5	DMF	145	42	[245]

Polyhalogenated carboxylic acids containing fluorine together with other halogens can also alkylate disulfides. However, the results strongly depend on the structure of halogenated alkyl group. The method is successful for potassium trichloroacetate but not for difluorochloroacetate. In the latter case the corresponding sulfide $PhSCF_2Cl$ was found but only in trace amounts whilst $PhSCCl_3$ is obtained in 80% yield [245]. The mixed haloalkyl anions appear to be less stable.

The stability and reactivity of perfluoroalkyl anions largely depend on the solvents used. For example, CF_3MgI [252-254] and CF_3Li [123,255-258] in diethyl ether are unstable even at low temperatures, but in coordinating solvents such as sulfolane, *N*-methylpyrrolidone, HMPA and especially, in DMF, the CF_3^- anion does not decompose so readily and can be used as a nucleophilic reagent [259].

4.3.4. “CF_3^-” from trifluoromethane (fluoroform)

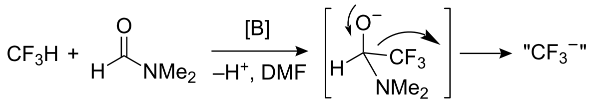
Trifluoromethane (fluoroform) has been used as a source of the trifluoromethyl anion. Trifluoromethane is a waste product of



Scheme 66: Decarboxylation of perfluorocarboxylates in the presence of disulfides [245].

Teflon manufacture and it is of interest as a raw material for organofluorine chemistry [260]. However, its application has been restricted by the low stability of the CF_3^- anion [123,252-255].

The CF_3^- anion has greater stability when the counter ion is a bulky ammonium ion, and in the presence of pyrrolidone it reacts with aldehydes and ketones [261]. This suggests that an intermediate gem-aminoalcoholate is involved. The method is improved with DMF, which is also thought to form a stable aminoalcoholate intermediate (Scheme 67) [243,262,263].



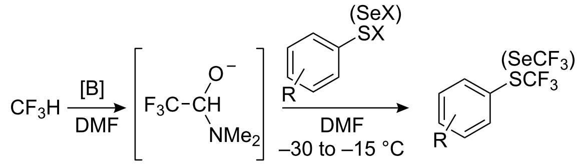
Scheme 67: Organization of a stable form of "CF_3^-" anion in the DMF.

This mechanism is supported by the observation that equivalent reactions do not occur in THF or DMSO [263]. Furthermore, the intermediate CF_3 aminoalcoholate has been trapped in its protonated form and as hydrated trifluoroacetaldehyde by the action of acids, as well as trapped as a silyl ether [243]. The deprotonation of fluoroform has been applied successfully for the synthesis of aromatic trifluoromethyl sulfides and selenides, as summarized in Table 15.

Langlois et al. have used silylated amines in the presence of fluoride ion to promote fluoroform deprotonation [244]. For example, with $(Me_3Si)_3N$ such reactions were possible in both DMF and THF. In the latter case stabilization of the CF_3^- anion and its reaction with disulfide probably involves a transition state complex such as that depicted in Scheme 68.

In the case of trifluoromethylation of aliphatic disulfides, silazanes are the preferred reagents. However, in the case of diaryl disulfides, e.g., diphenyl disulfide, the significant formation of byproducts occurs and, $PhSN(TMS)_2$ (46%) and $PhSCHF_2$ (23%) are main reaction products. Other CF_3 aminomethanols have been synthesized by Langlois et al. [264] (Figure 7).

Table 15: Reaction of the CF_3^- anion derived from fluoroform with S-derivatives of thiophenols.



B	R	X	Yield, %	Ref.
t-BuOK	H	SPh	80	[243]
t-BuOK	H	SO_2Ph	90	[243]
t-BuOK	4-NO_2	Cl	60	[243]
$LiN(TMS)_2/NH(TMS)_2$	H	SPh	4	[244]
$N(TMS)_3/Me_4NF$	H	SPh	6	[244]
t-BuOK	H	SPh	82	[244]
$N(TMS)_3/Me_4NF$	H	SePh	61[a]	[244]
t-BuOK	H	SePh	77[a]	[244]

[a] $PhSeCF_3$.

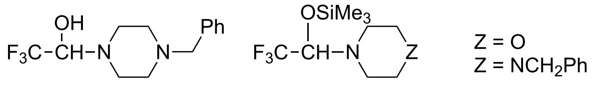
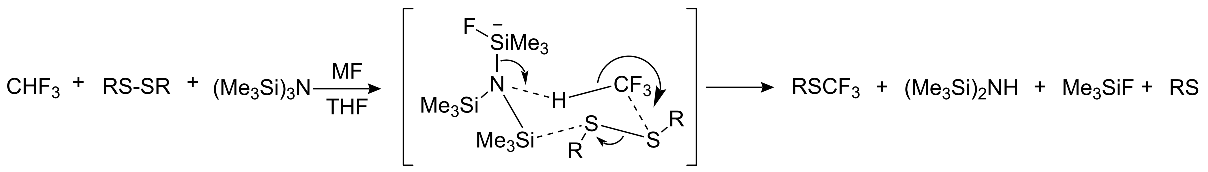


Figure 7: Other examples of aminomethanols [264].

Trifluoromethylation of disulfides by the first of them was efficient, for example, 87% in the case of $PhSCF_3$ but less efficient for diselenides ($PhSeCF_3$ 45%) [246]. The reaction failed with bis(4-chlorophenyl) disulfide and dioctyl disulfide where only by-products were generated.

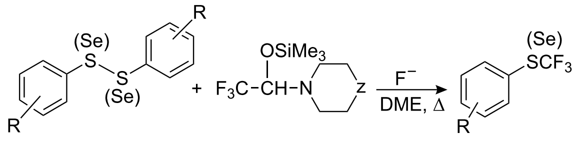
Silylated hemiaminals are more suitable for CF_3^- transfer (Table 16), although high reaction temperatures (60–80 °C) are required.

The use of F^- anion as an alkaline agent (De-Shopge reagent, Bu_4N^+ $Ph_3SiF_2^-$) in place of a strong base (*t*-BuOK) allows trifluoromethylation of aliphatic disulfides.



Scheme 68: Silylated amines in the presence of fluoride can deprotonate fluoroform for reaction with disulfides [244].

Table 16: Reactions of silylated hemiaminals with disulfides [246].



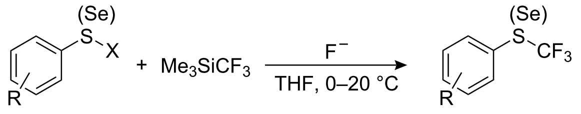
R	S (Se)	Z	“F$^-$”	*T*, °C	Yield, %
H	S	O	CsF	80	50
H	S	O	TBAT[a]	80	90
H	S	NCH_2Ph	TBAT	60	78
H	S	NCH_2Ph	TBAT	80	95
4-Cl	S	NCH_2Ph	TBAT	80	95
H	Se	NCH_2Ph	TBAT	80	92
4-Cl	Se	NCH_2Ph	TBAT	80	75

[a] TBAT: $Bu_4N^+ Ph_3SiF_2^-$.

4.3.5. “CF_3^-” anion from trifluoromethyl silanes

Perfluoroalkyltrialkyl silanes in the presence of fluoride ion generate reactive R_F carbanions which have been used widely in synthesis [27,28,30-32,265]. For example, Ruppert’s reagent, CF_3SiMe_3 [266] and its tin analogue (CF_3SnMe_3) have been used for the nucleophilic introduction of a CF_3 group to electrophilic sulfur for the preparation of trifluoromethyl sulfoxides and sulfones [267-269]. Trifluoromethyl trimethylsilane has also been used for the synthesis of aromatic trifluoromethyl sulfides and selenides (Table 17).

Table 17: Trifluoromethylation of sulfur and selenium compounds with Ruppert’s reagent.



X	F$^-$	R	Yield, %	Ref.
Cl	TASF[a]	H	59	[270]
Cl	TASF	4-Cl	72	[270]
Cl	TASF	$4\text{-}NO_2$	69	[270]
Cl	Bu_4NF	$4\text{-}NO_2$	14	[241]
SPh	Bu_4NF	H	32 (43[b])	[241]
CN	Bu_4NF	H	70 (58[b])	[271]
CN	Bu_4NF	$4\text{-}NO_2$	58	[271]
CN	Bu_4NF	$2,4\text{-}(OMe)_2$	30	[271]

[a] $TASF = (Me_2N)_3S^+ Me_3SiF_2^-$.
[b] $ArSeCF_3$.

Reactions proceed easily in THF or light hydrocarbon solvents and the reaction can also be extended to aliphatic and heterocyclic [271] sulfur-trifluoromethylations. The data (Table 17) indicate that the source of the F^- anion exerts an important influence on the reaction of sulfenyl chlorides with CF_3SiMe_3 [267]. For example, in the presence of TASF *p*-nitrophenyl trifluoromethyl sulfide is formed in almost 70% yield, while the use of $Bu_4N^+ F^-$ (even 2 equiv) under identical conditions gives only a 14% yield. In addition, in the reaction of diaryl disulfides with CF_3SiMe_3 it has been shown [241] that the best results are obtained when the Bu_4NF is added with a syringe-pump rather than by ordinary dropwise addition.

Such trifluoromethylation reactions with CF_3SiMe_3 can also be catalysed with cyanide ion. However, this also results in competing side reactions where the cyanide attacks the disulfide directly and is especially problematic in the case of aliphatic disulfides [271].

4.3.6. “CF_3-anion” from $ArSOCF_3$ and $ArSO_2CF_3$

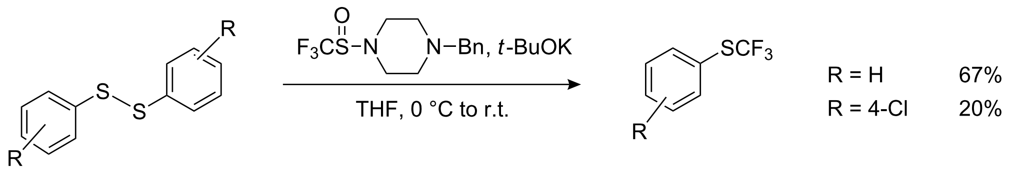
Aryl trifluoromethyl sulfones react with CH_3ONa to generate sodium arylsulfonates and fluoroform [272], and with Grignard reagents to generate aryl alkyl- or diaryl sulfones [273]. Also nucleophilic substitution of the pentafluoroethyl group can be induced in bis(pentafluoroethyl) sulfone by various nucleophiles [274]. Prakash et al. have adapted this chemistry for nucleophilic trifluoromethylation. Both phenyl trifluoromethyl sulfone or the corresponding sulfoxide on treatment with *t*-BuOK in DMF generate a CF_3-adduct similar to that formed during fluoroform deprotonation [243,263], which is a useful trifluoromethylating agent for aldehydes, ketones and disulfides [248]. An example is shown in Scheme 69.

$$\text{PhS-SPh} \xrightarrow[\text{DMF, –30 °C to r.t.}]{PhSO_2CF_3/t\text{-BuOK}} \underset{87\%}{PhSCF_3}$$

Scheme 69: Trifluoromethylation of diphenyl disulfide with $PhSO_2CF_3$/*t*-BuOK.

On the other hand, under the same reaction conditions methyl trifluoromethyl sulfone does not function as a trifluoromethylating agent, whilst esters and amides of trifluoromethane sulfinic acid are good trifluoromethyl transfer agents [247] (Scheme 70).

However, trifluoromethylation strategies with aryl trifluoromethyl -sulfoxides, -sulfones, -sulfinates, and amides have to compete with cheaper reagents such as fluoroform, trifluoroacetic acid derivatives and trifluoromethyl halogenides. For the synthesis of aryl trifluoromethyl sulfides, it should be noted that these are prepared from sulfones, which are in turn synthesized from the same sulfides.

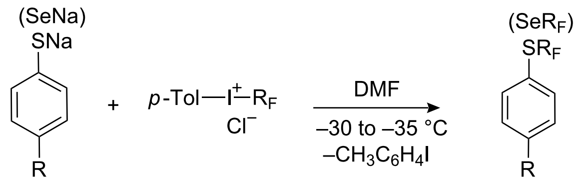


Scheme 70: Amides of trifluoromethane sulfinic acid are sources of CF_3^- anion.

4.4. Cationic perfluoroalkylation

Aryl perfluoroalkyl iodonium reagents as perfluoroalkylating agents were first developed by Yagupolski et al. [275]. Unlike perfluoroalkyl iodides, tolyl perfluoroalkyl iodonium chlorides react easily with sodium thiophenolates and selenophenolates at low temperature to form the corresponding aryl perfluoroalkyl sulfides and selenides as summarized in Table 18.

Table 18: Interaction of tolyl perfluoroalkyl iodonium chlorides with sodium thiophenolates and selenophenolate [275].



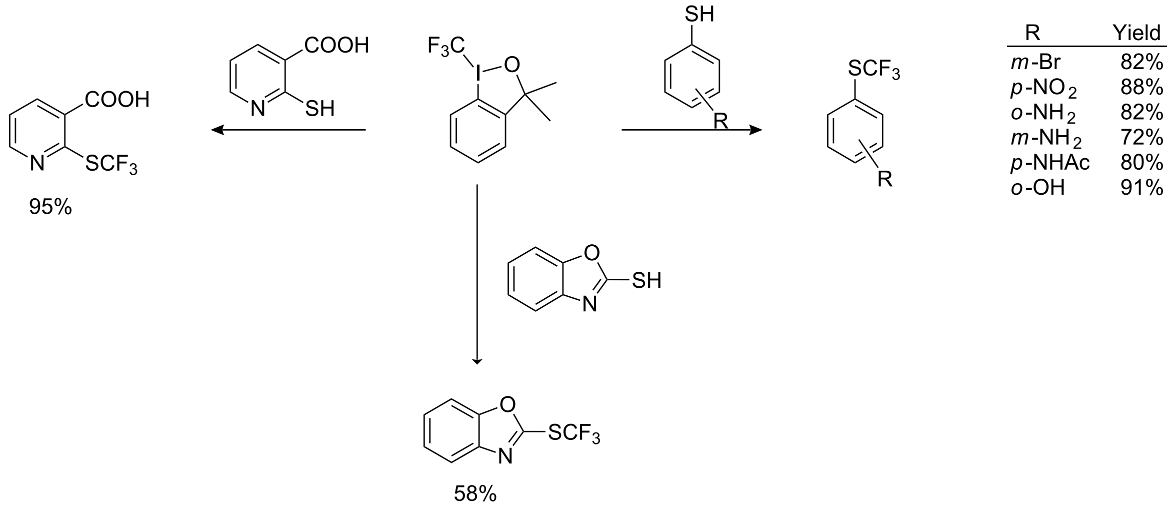
R	R_F	Yields, % (GLC) of	
		$ArSR_F$	$ArSeOR_F$[a]
H	C_3F_7	61 (81)	87
CH_3	C_3F_7	71 (96)	–
NO_2	C_3F_7	34 (56)	–
H	C_6F_{13}	41	45

[a]After chlorination and subsequent hydrolysis of corresponding selenides.

These iodonium salts even react with sodium *p*-nitrothiophenolate and while C_3F_7I does not react without some initiation [189] the C_3F_7 containing salts (Table 18) react readily. The yields of *p*-$O_2NC_6H_4SR_F$ ($R_F = C_3F_7$ and C_6F_{13}) are increased to a quantitative level by the use of iodonium tetrafluoroborate salts [276] instead of chlorides.

Similarly, perfluoroalkyl phenyl iodonium trifluoromethanesulfonates (FITS reagents) react with thiolates [277]: Perfluoroalkylation is selective for sulfur even in the presence of other functional groups (e.g. OH, NHMe, COOH, COOAlk). The preparation and application of R_F iodonium salts has been reviewed [33]. However, CF_3 iodonium salts were not discussed, presumably due to their low stability.

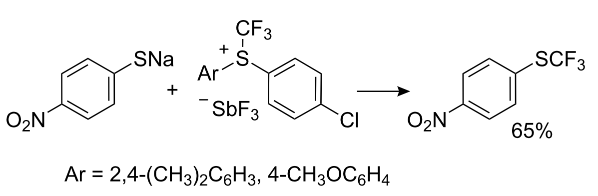
A "hyper-valent" iodine (III) compound containing a trifluoromethyl group, first synthesized in 2006 [278], appears to be quite stable. This moisture-sensitive reagent reacts with aromatic, heterocyclic and aliphatic thiols at low temperature (−78 °C) with the formation of the corresponding SCF_3 derivatives in high yields (Scheme 71).



Scheme 71: Trifluoromethylation of various thiols using "hyper-valent" iodine (III) reagent [279].

However, this attractive methodology has some drawbacks in that its synthesis involves four steps and trifluoromethylation products must be purified by chromatography to remove a side-product – 2-iodophenyl dimethyl carbinol.

Unlike iodonium salts, onium salts of the group VI elements appear to be more stable with CF_3 group. Diaryl R_F-sulfonium salts, where $R_F = CF_3$, are readily synthesized from aryl trifluoromethyl sulfoxides [280]. Reaction of these reagents with sodium *p*-nitrothiophenolate affords the trifluoromethyl sulfide in good yield (Scheme 72).



Scheme 72: Trifluoromethylation of *p*-nitrothiophenolate with diaryl CF_3 sulfonium salts [280].

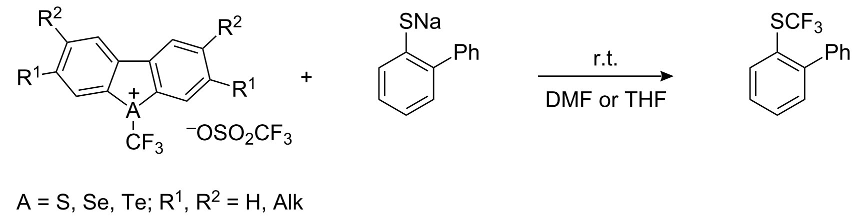
It should be noted that for perfluoroalkylation is it necessary to use the diaryl sulfonium salts and not aryl alkyl sulfonium salts, since reaction of $PhS^+(CH_3)CF_3\ BF_4^-$, with *p*-nitrothiophenolate yields the SCH_3 compound not the SCF_3 derivative [280]. Subsequently, diaryl thiophenium, -selenophenium and -tellurophenium reagents have been developed with perfluoroalkyl groups attached to S, Se and Te [33,281,282] which can transfer perfluoroalkyl fragments to nucleophilic centers. In particular, the dibenzo (CF_3)S-, (CF_3)Se- and (CF_3)Te-phenium systems have been investigated. For example, $S(CF_3)$dibenzothiophenium triflate (A = S) reacts with sodium thiolate in DMF to give the *S*-trifluoromethyl derivative in high yield. The related selenophenium salt (A = Se) appears to be more effective in trifluoromethyl transfer (Scheme 73).

The same general reactivity is also observed in reactions of these reagents with aliphatic thiols. Dibenzoselenophenium triflate (A = Se, R^1 and R^2 = H) reacts much better with sodium dodecyl thiolate (yield of $C_{12}H_{25}SCF_3$ is 87%) than the sulfur analogue (yield 47%) [283,284].

On the whole R_F onium compounds are powerful perfluoroalkylating agents [33,281], however they are rather exotic reagents which require to be synthesized by multi-stage methods as illustrated in Scheme 74.

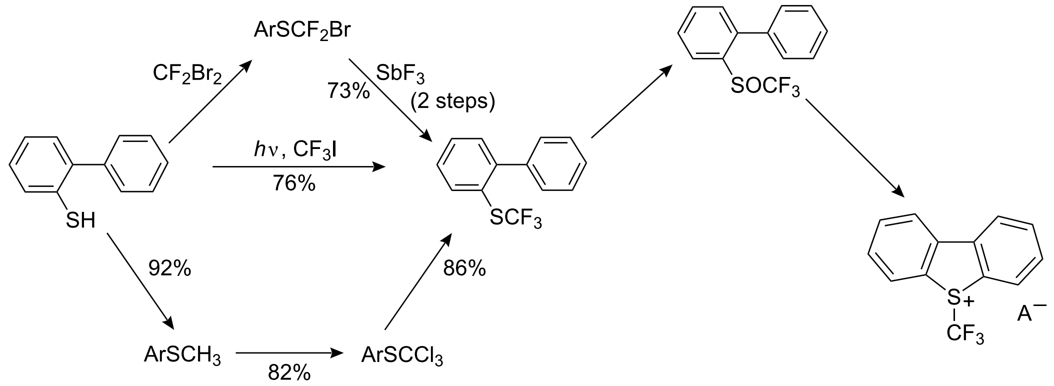
Conclusion

A summary of the known methods for the synthesis of aromatic and heterocyclic perfluoroalkyl sulfides are presented. These



A	R^1, R^2	Yield
S	H	78%
Se	H	89%

Scheme 73: Trifluoromethyl transfer from dibenzo (CF_3)S-, (CF_3)Se- and (CF_3)Te-phenium salts to thiolates [283].



Scheme 74: Multi-stage paths for synthesis of dibenzo-CF_3-thiophenium salts [61].

involve perfluoroalkylation of thiols by single electron transfer, nucleophilic and electrophilic methods. The variety of methods reflects the level of interest chemists have given to generating this class of fluorine containing organic compounds. As a class of compounds, perfluoroalkyl sulfides find increasing utility in agrochemical and pharmaceutical applications.

A concise review concerning the preparation of selectively fluorinated ethers, thioethers, amines and phosphines was published [285] during preparation of this manuscript.

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