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Review

Fluoro-Pummerer rearrangement and analogous reactions

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Dedicated to Professor David O'Hagan with best wishes on the occasion of winning the ACS Award for Creative Work in Fluorine Chemistry.

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Oxidative desulfurization–fluorination
Trifluoromethyl compounds

ABSTRACT

Fluorine containing compounds hold huge promise for pharmaceuticals and agrochemicals due to their specific therapeutic potency or pesticide properties. Therefore, the development of selective and efficient methods for the introduction of fluorine or fluorinated groups into organic molecules is one of the most important tasks in organofluorine chemistry today.

Oxidative fluorinations of sulfur compounds like the fluoro-Pummerer rearrangement and analogous transformations such as oxidative desulfurization–fluorination reactions reveal mild, selective and efficient pathways toward mono-, di- or trifluorinated organic compounds. This article summarizes the synthetic approaches as well as the scope and limitations of fluoro-Pummerer rearrangements, oxidative desulfurization–fluorination, as well as the oxidative desulfurization–di- and trifluorination reactions. Application of these oxidative fluorination methods gives rise to various α-fluorinated sulfides, *gem*-difluorides and trifluoromethylated compounds.

Contents

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1. Introduction

Considering the enormous impact of fluorinated molecules on medicinal and materials chemistry, the development of new methods for the introduction of one or more fluorine atoms into organic molecules is one of the most important tasks of current organofluorine chemistry [1]. The introduction of fluorine atoms into biologically active substances is known to modify their pharmacological properties and their therapeutic potency. The particular properties of fluorine, such as high electronegativity, relatively small size, low polarisability of the C–F-bond and, in many cases, increased lipophilicity of fluorine containing organic molecules can have considerable influence in a biological environment [2,3]. Many different, very efficient and selective synthetic approaches have been developed in recent years [4]. In general organofluorine compounds can be prepared following two strategies: the building block methods and the direct fluorination of target structures.

Building blocks are small fluorinated organic molecules like fluorinated organometallics, fluorinated carbonyl compounds, including α,β-unsaturated ones, as well as fluorinated alkenes and oxiranes, which are incorporated into target molecules by appropriate chemical transformations [5–8]. Fluorine-containing carbenium ions, fluoroalkyl radicals, fluoro substituted carbenes or carbenoids and fluorinated carbanions are reactive intermediates for the synthesis of fluoroorganics. Various kinds of building blocks have been developed and a considerable number of them is commercially available now [9,10].

Procedures for direct fluorination of organic molecules can be divided into electrophilic and nucleophilic fluorination methods. Due to the electrophilic character of fluorine, electrophilic fluorination procedures belong to the most important methods for the introduction of fluorine into organic molecules [11]. Besides elemental fluorine many electrophilic fluorinating reagents like fluoroxytrifluoromethane (CF_3OF) [12], perchloryl fluoride [13,14], xenon difluoride [15], nitrogen oxide fluorides [16] and several other hypofluorites [17,18] have been developed in the last fifty years. The key compounds for the establishment of electrophilic fluorination in organic chemistry have been *N*-fluoroimides [19] like *N*-fluoro-bis[(benzene)sulfonyl)]imide (NSFI) [20] and *N*-fluoro-bis[(trifluoromethyl)sulfonyl]imide [21,22], *N*-fluorosultams [23], *N*-fluoropyridinium salts like Umemoto's reagent [24,25] and Selectfluor® [26]. Despite innovative developments in this field of fluorination the selective electrophilic fluorination still remains a difficult task due to side reactions and substrate restrictions.

Another important method for the synthesis of fluorinated organic molecules is the introduction of fluoride. The most feasible nucleophilic fluorinating reagents are hydrogen fluoride (HF) and its aqueous solutions. Anhydrous HF easily adds to double bonds of olefins leading to fluoroalkanes, while aqueous hydrofluoric acid is not able to react with olefins. More easily to handle are amine/HF reagents like pyridine·9HF (Olah's reagent), triethylamine/HF or melamine/HF, which form stable ammonium fluorides in a polymeric network of HF molecules, and are conveniently used to substitute secondary and tertiary OH-groups, or halogens [27]. Fluoride reagents like Bu_4NF (TBAF), $Bu_4NH_2F_3$, $(R_2N)_3SF_2SiMe_3$ and Ph_4PF enable the substitution of halogen atoms and sulfonates in aromatic and aliphatic substrates [28–30]. Hydroxy, carbonyl and carboxyl groups can be converted to fluorinated moieties using sulfur tetrafluoride (SF_4) [31,32] and (diethylamino)sulfur trifluoride (DAST) [33]. Due to toxicity and moisture sensitivity of SF_4 and thermal instability of DAST these reagents have to be handled carefully. Analogous, but more stable SF_3-reagents like Desoxofluor® [34], Fluorinox® [35], Morpholino sulfur trifluoride [36], Fluolead™ [37] were also applied for nucleophilic fluorination reactions. For many substrates also bromine trifluoride (BrF_3) has been used [38,39].

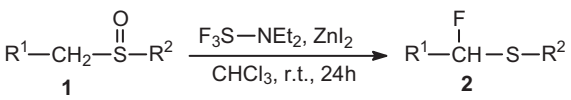
Modification of nucleophilic fluorinating reagents for more convenient handling is often attended with a loss of reactivity. Therefore, electrophilic activation of the substrate by an oxidant can be an effective method to facilitate the nucleophilic attack of fluoride of modified HF reagents. These reagents are frequently used in halofluorination reactions [40] and epoxide ring opening [41]. Hereunto, the oxidative fluorination of sulfides or sulfoxides with electrophiles in the presence of different fluorinating reagents revealed numerous advantages for the α-fluorination of these compounds. Especially, the Pummerer and Pummerer-type reactions have found various applications in α-fluorination of sulfides. The products, α-fluoro sulfides, have been proved to be valuable in modifying biologically active molecules and serving as useful synthetic intermediates [42]. Powerful and easy to handle reagents have been developed for the Pummerer-type α-fluorination of sulfides [43].

2. α-Fluorination of sulfides and sulfoxides *via* fluoro-Pummerer rearrangement

2.1. Application of DAST and DAST-related fluorinating reagents

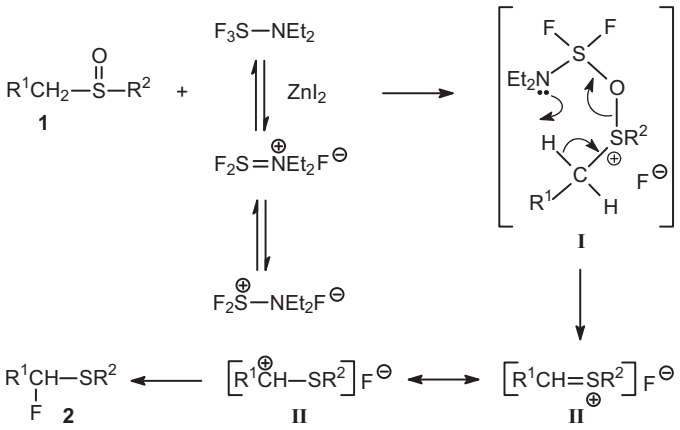
The original fluoro-Pummerer rearrangement of sulfoxides was first described by McCarthy et al. in 1985 using the combination of DAST and a catalytic amount of ZnI_2 [44]. Under these reaction conditions the authors were able to synthesize α-fluoro sulfides **2** in good yields starting from alkyl aryl sulfoxides **1** (Scheme 1) [45].

The mechanism of this fluorine insertion reaction is similar to that of the Pummerer rearrangement [43,46]. Formation of a carbenium/sulfonium ion **II** from the adduct of a sulfoxide with DAST (**I**) can be rationalized by a six-membered transition state in which nitrogen acts as a base. The intermediate ion **II** is then attacked by the liberated fluoride ion to give the α-fluorinated sulfide **2**. The Lewis acid ZnI_2 is catalyzing this reaction by forming a reactive sulfiminium ion from DAST (Scheme 2).

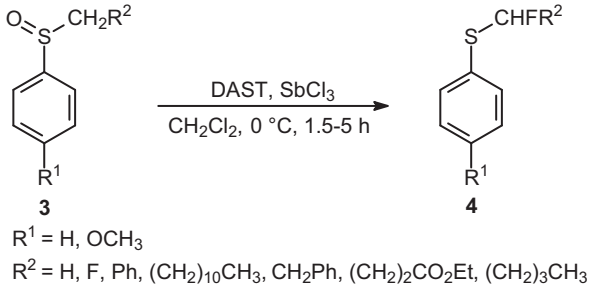


$R^1 = CH_3(CH_2)_{14}$, $PhthNCH_2$, $EtO_2C(CH_2)_2$, $NC(CH_2)_2$, $PhCH_2$, Ph
R^2 = Ph, 4-MeO-Ph

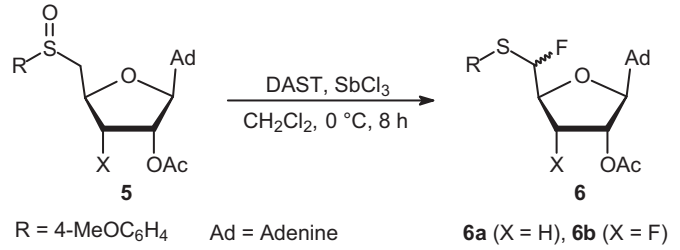
Scheme 1. Synthesis of α-fluoro sulfides with DAST and a catalytic amount of ZnI_2.



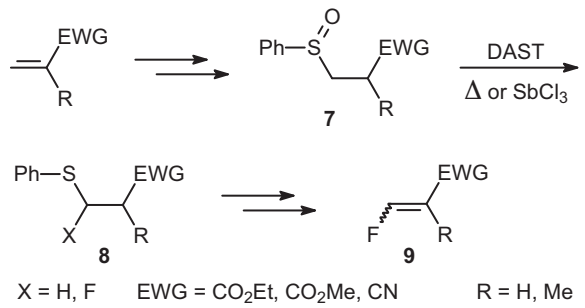
Scheme 2. Mechanism of the fluoro-Pummerer rearrangement with DAST and ZnI_2.



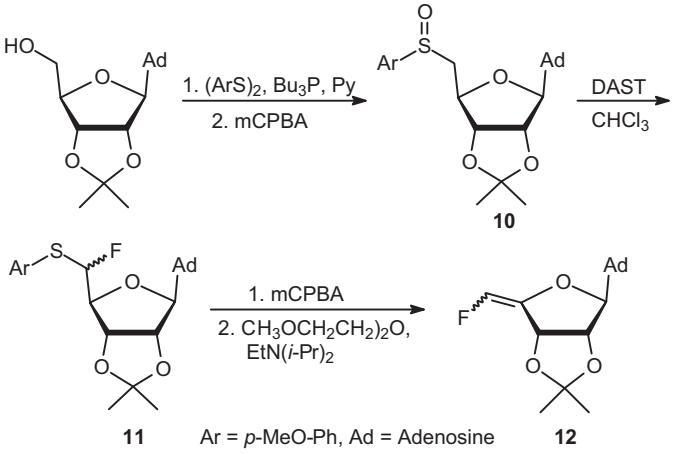
Scheme 3. Synthesis of α-fluoro sulfides **4** from sulfoxides **3** with DAST under $SbCl_3$ catalysis.



Scheme 4. Preparation of fluorinated deoxyadenosine derivatives **6** with DAST/$SbCl_3$.



Scheme 5. Synthesis of β-fluoro-α,β-unsaturated esters and nitriles **9**.



Scheme 6. Synthesis of (*E*)- and (*Z*)-5′-fluoroalkene carboxylic nucleosides **12** *via* fluoro-Pummerer rearrangement.

However, several attempts to apply McCarthy's DAST/ZnI_2 procedure, *e.g.* to diastereomeric sulfoxides derived from 2′3′-di-*O*-acetyl-5′-*S*-phenylthioadenosine [47], protected 5′-methylthioadenosine sulfoxide [48], or methyl phenyl sulfoxide [49] resulted in highly predominant deoxygenation at the sulfur atom without fluorination.

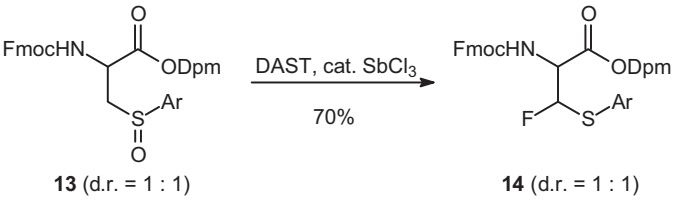
To avoid this side reaction, Boys and co-workers omitted the catalyst ZnI_2 [49], Sufrin et al. used dimethylaminosulfurtrifluoride (meDAST) [48] and Wnuk and Robins replaced ZnI_2 by antimony(III)-chloride ($SbCl_3$). In this way for the preparation of α-fluorosulfides **4**, the ratio of sulfoxide **3**/DAST could significantly be reduced and the reaction time was shortened to 1.5–5 h [50] (Scheme 3).

Many examples of successful implementation of the later modified α-fluorination method were published. Wnuk and Robins applied this method for the preparation of 5′-*S*-(alkyl and aryl)-5′-fluoro-5′-thioadenosines **6a** [51] and 3′-fluoro-3′-deoxyadenosines **6b** [52] (Scheme 4).

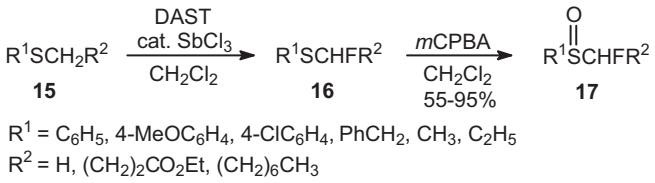
Sampson and Krishnan achieved the synthesis of β-fluoro-α,β-unsaturated esters and nitriles **9** as Michael acceptors *via* DAST/$SbCl_3$-mediated fluoro-Pummerer rearrangement of β-substituted sulfoxides **7**. In contrast to the complete conversion of β-carboalkoxy functionalized sulfoxides to the desired α-fluoro sulfides **8** (X = F), the formation of significant amounts of deoxygenation products **8** (X = H) was observed in addition to the fluorodeoxygenation of β-cyano-substituted sulfoxides **7** [53] (Scheme 5).

McCarthy et al. utilized this method also for the preparation of fluoromethyl phenyl sulfone (a reagent for the synthesis of fluoroalkenes) [54] and therefore for the synthesis of (*E*)- and (*Z*)-5′-fluoroalkene carboxylic nucleosides **12** *via* fluoro-Pummerer rearrangement, oxidation of the α-fluoro sulfide **11** and pyrolysis to the (*E*)- and (*Z*)-fluoro olefins **12** [55]. During the design of a competitive inhibitor of *S*-adenosyl-L-homocysteine hydrolase (SHD hydrolase) the *p*-anisylidine group of the isopropylideneadenosine sulfide allowed the fluoro-Pummerer reaction to proceed without a catalyst [56] (Scheme 6).

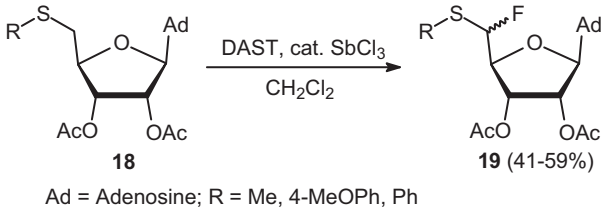
In addition, this method was applied by van der Donk *et al.* to synthesize Michael acceptors that serve as enzyme inhibitors and



Scheme 7. Fluoro-Pummerer rearrangement of **13** in the synthesis of *erythro*- and *threo*-3-fluoro-3-phenylthio alanine **14**.



Scheme 8. Direct α-fluorination of sulfides **15** with DAST and subsequent oxidation of **16** to form **17**.



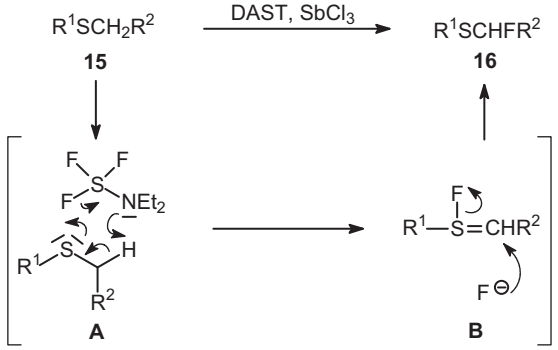
Scheme 9. Reaction of sulfide derived nucleosides **18** with DAST and $SbCl_3$.

active site affinity labels. *Erythro*- and *threo*-3-fluoro-3-phenylthio alanine **14** were prepared from serine (Scheme 7). They also proved that the configuration of the sulfur atom in the sulfoxide **13** has no influence on the diastereoselectivity of the fluoro-Pummerer reaction [57]. This is consistent with the proposed reaction of a fluoride ion onto a thiocarbenium intermediate formed upon reaction of the sulfoxide [56].

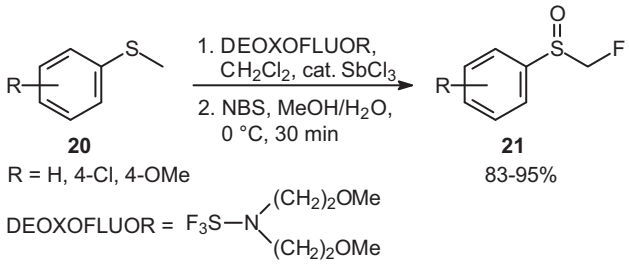
In 1993, Wnuk and Robins succeeded in the direct α-fluorination of sulfides with DAST or DAST/antimony(III)-chloride [58]. Therefore, oxidation of sulfides to sulfoxides was unnecessary. Even with deactivating *p*-chloro substituents and the use of only 1.2 equiv of DAST and 0.05–0.07 equiv of $SbCl_3$, the transformation of sulfides **15** with DAST afforded the α-fluoro sulfides **16**. Larger quantities of antimony(III)-chloride inhibited the α-fluorination and gave dark product mixtures. However, in general the α-fluorinated sulfides **16** are not stable and were oxidized with *m*CPBA to sulfoxides **17** (Scheme 8).

Sulfides **18** derived from nucleosides did react in the same way to form **19** [58] (Scheme 9).

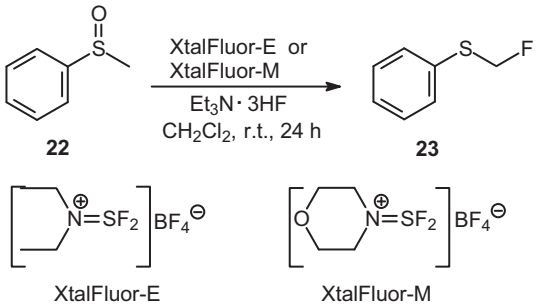
The mechanism of the α-fluorination is suggested to proceed from compounds of type **15** *via* a six-membered transition state **A** with transfer of fluorine from DAST to the sulfur atom of the sulfide and abstraction of an α-proton by the basic nitrogen function. An intermolecular three-centered fluorine rearrangement or conjugate nucleophilic attack by external fluoride on intermediate **B** completes the transformation to the α-fluoro sulfide **16** (Scheme 10).



Scheme 10. Mechanism of the fluoro-Pummerer rearrangement with DAST and $SbCl_3$ starting from sulfides **15**.



Scheme 11. Fluorination of sulfides **20** with deoxofluor and oxidation to **21**.



Scheme 12. Synthesis of α-fluoro sulfides **23** with XtalFluor-E and XtalFluor-M.

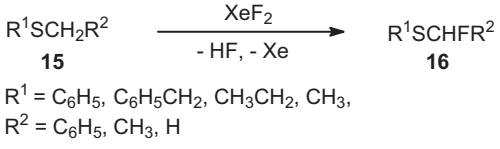
Drawbacks of this fluorination method are high costs, thermal instability of DAST and α-fluorosulfides at elevated temperatures.

Deoxofluor® [bis(2-methoxyethyl)aminosulfur trifluoride], which is thermally more stable than DAST, was found to react in an analogous manner with sulfides and sulfoxides producing α-fluoro sulfides. Good yields were obtained from various alkyl aryl sulfides **20** and sulfoxides in dichloromethane containing 0.01 equiv of $SbCl_3$ (Scheme 11). Most of the α-fluoro sulfides were not stable under standard purification techniques and were transformed to sulfoxides **21** or sulfones by oxidation with *N*-bromosuccinimide (NBS) and water or *m*CPBA, respectively [59,60].

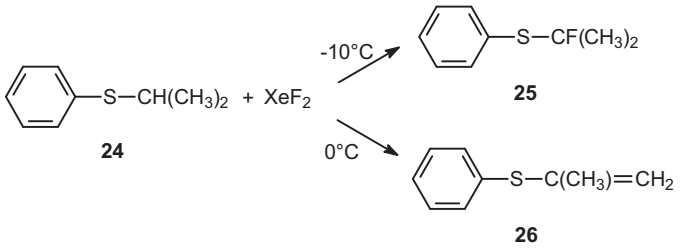
The recently developed crystalline fluorinating reagents diethylamino-difluorosulfinium tetrafluoroborate (XtalFluor-E) and morpholinodifluorosulfinium tetrafluoroborate (XtalFluor-M) enable the conversion of methyl phenylsulfoxide **22** to the α-fluoro sulfide **23** in the presence of 4 equiv triethylamine trishydrogenfluoride ($Et_3N{\cdot}3HF$) in good yields [61] (Scheme 12).

2.2. Application of electrophilic fluorinating reagents

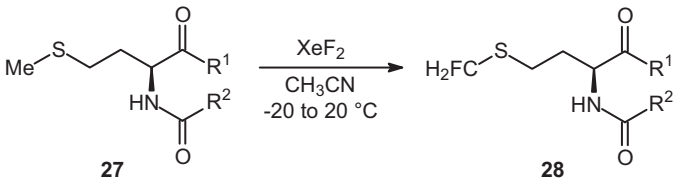
An alternative method for the preparation of α-fluoro sulfides **16** is the reaction of sulfides **15** with xenon difluoride. The reaction of methyl phenyl sulfide in dichloromethane with anhydrous HF and XeF_2 to fluoromethyl phenyl sulfide **23** was described by Zupan back in 1976 already. With a second equiv of XeF_2 further fluorination led to difluoromethyl phenyl sulfide [62]. One year later Marat and Janzen reported the direct α-monofluorination of sulfides with xenon difluoride. Substituents like methyl, ethyl, isopropyl and benzyl permitted the reaction with xenon difluoride to α-monofluorinated sulfides [63] (Scheme 13).



Scheme 13. Fluorination of sulfides **15** with xenon difluoride.

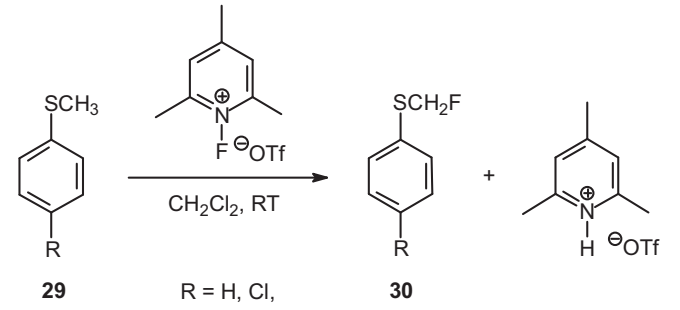


Scheme 14. Competing formation of the α-fluoro sulfide **25** and the olefin **26**.



R^1 = OCH_3, OC_6H_4 (*p*-NO_2), $NHCH_2C(O)OCH_2CH_3$
R^2 = CF_3, $OC(CH_3)_3$, $OCH_2C_6H_5$

Scheme 15. Fluorination of methionylglycine derivatives with XeF_2.



Scheme 16. Fluoro-Pummerer rearrangements with *N*-fluoropyridinium triflate.

Depending on temperature, the reaction of the isopropyl phenyl sulfide **24** showed HF-elimination as a competing reaction. At −10 °C the formation of the α-fluoro sulfide **25** was preferred, whereas at 0 °C the olefin **26** was formed predominantly (Scheme 14) [63].

This method was as applicable for the mild, fast and efficient α-fluorination exclusively at the methyl group of N-protected methionines and methionylglycine derivatives **27** to form compounds **28** [64] (Scheme 15).

However, utilization of xenon difluoride is limited because of its high price. Moreover, for preparation of the acid labile α-fluoro sulfides treatment with bis(trimethylsilyl)amine is needed to remove the formed hydrogen fluoride.

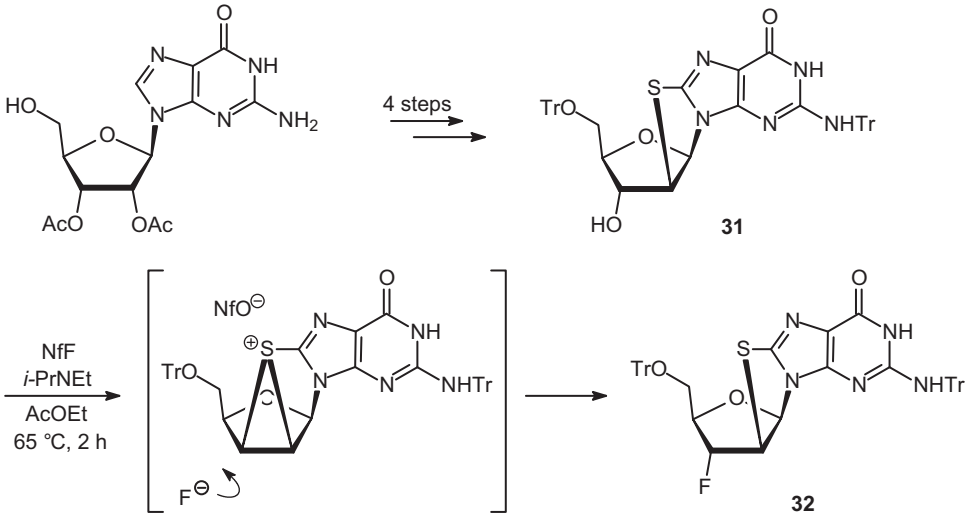
Umemoto et al. developed different, easy to handle *N*-fluoropyridinium salts for fluoro-Pummerer rearrangements of sulfides to α-fluoro sulfides [65]. Aryl α-fluoromethyl sulfides **30** and alkyl α-fluoromethyl sulfides with longer alkyl chains can be prepared using *N*-fluoro-2,4,6-trimethylpyridinium triflate in dichloromethane (Scheme 16). In contrast, no α-fluoro sulfides were formed in polar solvents like tetrahydrofuran and acetonitrile. Unsymmetrical dialkyl sulfides, like methyl dodecyl sulfide, resulted in fluorination of the methyl group, exclusively.

The α-fluorination of sulfides with *N*-fluoropyridinium salts is suggested to proceed *via* a two-step mechanism, starting with an oxidative fluorination of sulfur, followed by deprotonation and fluoro-Pummerer-like rearrangement of the fluorine to the α-carbon. Due to the instability of the intermediates, Umemoto as well as Zupan [62] failed to detect the intermediate S–F-compounds by ^{19}F NMR technique. Therefore, the detailed mechanism is not clearly confirmed.

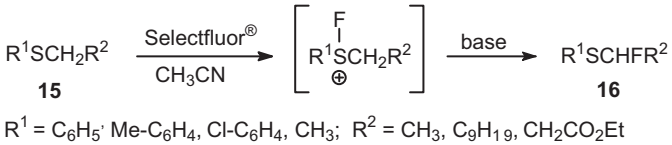
Maruyama et al. reported the 3′-α-selective fluorination of an 8,2′-thioanhydronucleoside **31** using perfluorobutanesulfonyl fluoride (NfF) in the presence of *i*-Pr_2NEt, which is comparable to a fluoro-Pummerer rearrangement [66]. While the reaction with DAST gave a complex mixture, the NfF reaction was selective to give **32**. Sulfur facilitates the attack of the fluoride ion. Therefore, the retentive fluorination of the intermediate sulfonium ion preferred the 3′α rather than the 2′α position (Scheme 17).

It has also been found that sulfides **15** possessing α-hydrogens react rapidly with Selectfluor® (F-TEDA-BF_4) in CH_3CN at room temperature forming the fluorosulfonium salt, which conceivably underwent a Pummerer-like rearrangement on treatment with triethylamine or DBU to produce the α-fluoro sulfides **16** (Scheme 18).

This process was applicable to a variety of alkyl and aryl sulfides forming the α-fluoro sulfides in moderate yields with the ease of the reaction being highly dependent on the nucleophilicity of the sulfur atoms. Ethyl (methylthio)acetate gave the product resulting from deprotonation of the more acidic methylene proton, while the unsymmetrical sulfide, methyl *n*-nonyl sulfide afforded the fluorination product, expected from a kinetically preferred



Scheme 17. 3′-α-Selective fluorination of 8,2′-thioanhydronucleoside **31** using NfF.



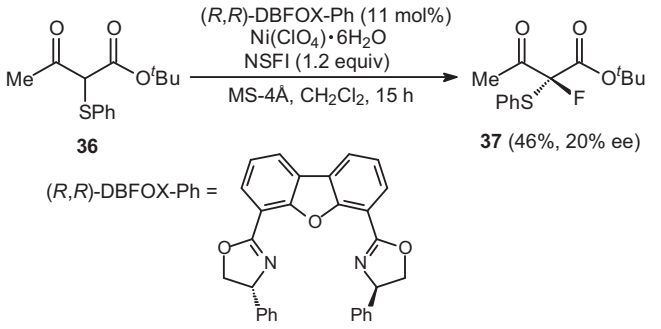
Scheme 18. Fluorination of sulfides with Selectfluor®.

deprotonation of the methyl group. Due to instability to standard chromatographic purification methods most of the α-fluoro sulfides were not isolated, but oxidized to the corresponding sulfoxide (with NBS, H_2O) or sulfone (with *m*CPBA) [67].

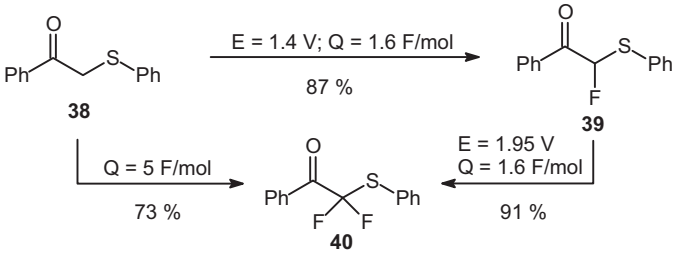
Attempted α-fluorination of β-ketosulfides **33** using Selectfluor® in the presence of sodium carbonate in dry acetonitrile, under argon atmosphere, resulted in the isolation of the corresponding diaryl disulfides **35**. However, GC–MS analysis prior to purification showed the presence of the desired monofluorinated products **34**. This evidence suggests that the β-ketosulfides are indeed fluorinated through Pummerer mechanism and then decompose to disulfides. Other products were not identified (Scheme 19) [68].

Shibata et al. attempted a catalytic enantioselective fluorination of an α-sulfenylated β-ketoester **36** with *N*-fluorobenzenesulfonimide (NSFI) in the presence of $Ni(ClO_4)_2{\cdot}6H_2O$, (*R*,*R*)-4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX-Ph) in dichloromethane. In contrast to the catalytic enantioselective fluorination of β-ketoesters, oxindoles, malonates and oxathiazolidinones with DBFOX-Ph, the level of enantioselectivity in the α-fluorination reaction to form **37** was low (46% yield, 20% ee) (Scheme 20) [69].

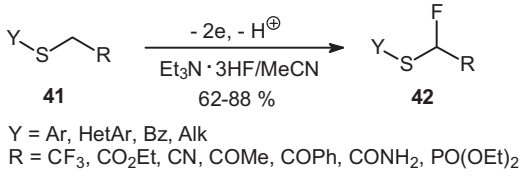
Finally the authors succeeded in the synthesis of α-fluoro-α-sulfenyl-β-ketoesters in good yields and high enantiomeric excess up to 93% *via* the reverse pathway by enantioselective α-sulfenylation of α-fluorinated-β-ketoesters with the DBFOX-Ph/Ni(II) complex [69].



Scheme 20. Enantioselective fluorination of α-phenyl-β-ketoesters mit NFSI catalyzed by DBFOX-Ph/Ni(II).



Scheme 21. Electrochemical α-fluorination with $Et_3N{\cdot}3HF$.



Scheme 22. Anodic fluorination of alkyl and aryl sulfides.

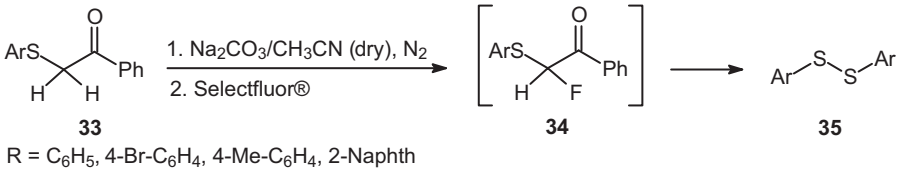
2.3. Electrochemical partial fluorination

A very successful method for the introduction of fluoride *via* fluoro-Pummerer rearrangement is the selective anodic oxidation in the presence of $Et_3N{\cdot}3HF$. The electrochemical partial fluorination is very attractive because one fluorine atom can be selectively introduced into organic molecules in one step under safe and mild conditions at room temperature. Brigaud and Laurent reported on anodic α-fluorination of sulfides such as **38** having electron-withdrawing ester and benzoyl groups using $Et_3N{\cdot}3HF$ as supporting electrolyte to form **39**. By increasing the potential during the electrolysis the difluorinated sulfides **40** were obtained (Scheme 21). However, the authors failed to fluorinate simple alkyl sulfides [70]. Simonet et al. achieved the electrochemical fluorination of alkyl aryl sulfides with strongly electron-withdrawing groups in the aryl ring [71].

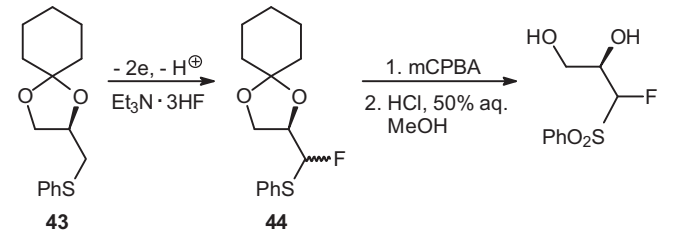
Fuchigami and coworkers systematically examined the anodic fluorination of various types of alkyl and aryl sulfides **41** [72,73]. Selective electrochemical fluorination to form **42** of phenyl 2,2,2-trifluoroethyl sulfide [74], α-(phenylthio)acetate and related organosulfur compounds, bearing electron withdrawing groups was successful in acetonitrile containing $Et_3N{\cdot}3HF$ (Scheme 22) [75].

The supporting fluoride source strongly affected the fluorination and anhydrous conditions are necessary due to the nucleophilicity decrease of fluoride in the presence of water. The anodic fluorination proceeded by way of a Pummerer-type mechanism *via* a fluorosulfonium cation [76]. Thus, if R was an electron-withdrawing group, the deprotonation of the intermediate fluorosulfonium cation (see Scheme 18) was significantly facilitated. Consequently, the fluorination of the carbenium/sulfonium ion intermediate proceeded efficiently.

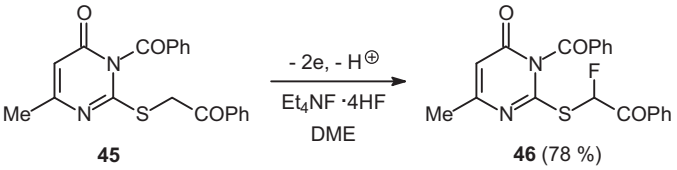
Regio- and diastereoselective electrochemical fluorinations of various heteroatom compounds such as **43** to form **44** (and downstream chemistry) [77], but also including other heterocycles [78,79] have been successful using $Et_3N{\cdot}nHF$ as a fluoride source (Scheme 23).



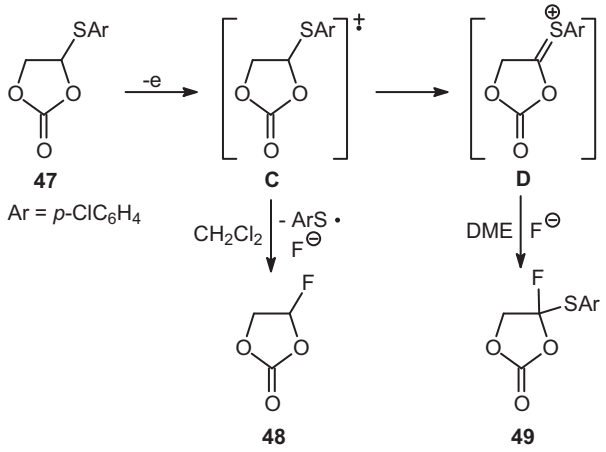
Scheme 19. Attempted fluorination of β-ketosulfides using Selectfluor®/Na_2CO_3.



Scheme 23. Regio- and stereoselective electrochemical fluorination of a spiro acetal based phenyl sulfide **43**.



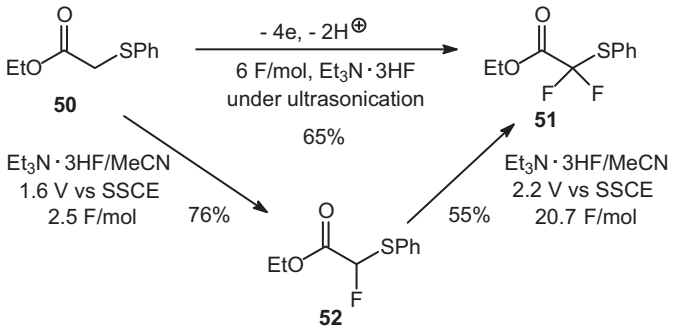
Scheme 24. Electrochemical fluorination of heterocyclic sulfides **45** in DME.



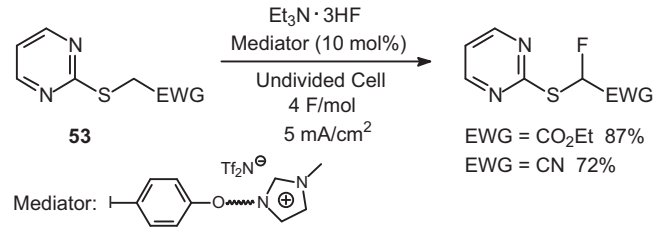
Scheme 25. Effect of DME in anodic fluorination reactions.

Moreover, Fuchigami *et al.* found that ethereal solvents such as 1,2-dimethoxyethane (DME) were much more suitable for electrochemical fluorination of heterocyclic sulfides like **45** than dichloromethane or acetonitrile [80] (Scheme 24).

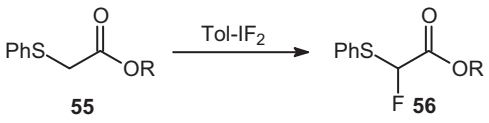
The use of DME markedly increased the selectivity and yields of fluorination reactions of **47** because DME stabilizes the anodically generated radical cation **C** and facilitates the formation of the sulfonium ion **D**. Therefore, α-fluorination of **D** proceeded to form **49** without desulfurization in DME, while desulfurization–fluorination to give **48** took place in dichloromethane [81,82] (Scheme 25).



Scheme 26. Stepwise and direct anodic difluorination under ultrasonication.



Scheme 27. Indirect electrochemical fluorination of **53** using an iodoarene mediator.



Scheme 28. α-Fluorination of α-phenylsulfanyl acetates **55** with DFIT.

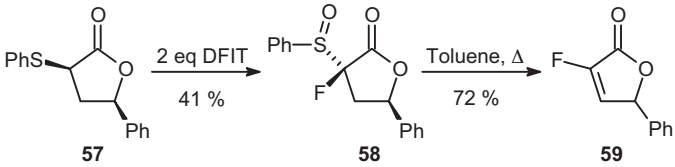
Noel et al. carried out the first anodic α-fluorination of sulfides in solvent-free $Et_3N{\cdot}3HF$ and obtained the desired α-fluorinated products in moderate yields [83]. Fuchigami and coworkers improved the solvent free anodic fluorination using ultrasonication. In this way, the reaction of ethyl α-(phenylthio)acetate **50** in $Et_3N{\cdot}3HF$ proceeded smoothly to provide the α-fluoro sulfides **51** in high yield and with high current efficiency. Anodic difluorination of the substrate to form **52** was also achieved either stepwise or directly under ultrasonication [84] (Scheme 26).

To avoid passivation of the anode, Fuchigami et al. developed an indirect electrochemical fluorination system, employing a task-specific ionic liquid with an iodoarene moiety as the mediator in HF reagents and improved the reaction efficiency for a variety of electrochemical fluorinations [85]. A polymer-supported iodobenzene (PSIB) mediator was also effective for indirect anodic fluorination of **53** in HF reagents such as $Et_3N{\cdot}3HF$ [86] (Scheme 27).

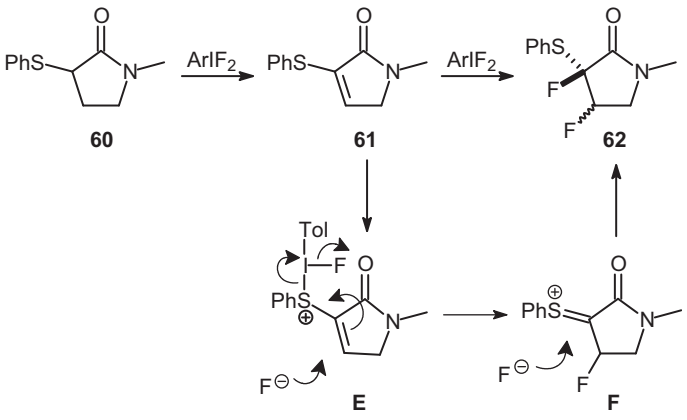
2.4. Application of hypervalent difluoroiodotoluene (DFIT)

The readily prepared crystalline, hypervalent fluorinating reagent difluoroiodotoluene (DFIT), soluble in organic solvents, offers an exceptionally mild method for the α-fluorination of sulfides [87]. α-Phenylsulfanyl acetates **55** were fluorinated in the α-position to give **56** in good yields upon treatment with only one single equiv of DFIT in dichloromethane (Scheme 28). A second fluorination was also possible with the α,α-difluoro sulfide being formed using two equiv of DFIT. The addition of a third equiv led to the α,α-difluoro sulfoxide after aqueous work up.

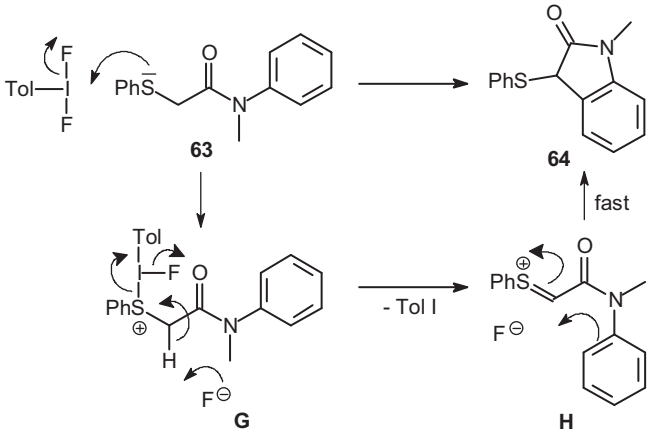
Treatment of the racemic *cis*-disubstituted γ-lactone with one equiv of DFIT gave the α-fluoro sulfide as a single diastereomer. Due to a highly concerted transition state involving simultaneous deprotonation and nucleophilic attack, the fluoride was inserted *cis* to the bulky phenyl group [88]. With two equiv of DFIT the α-fluoro sulfoxide **58** was formed after hydrolysis, which can be converted to the vinyl fluoride **59** through thermal elimination of sulfenic acid (Scheme 29) [89].



Scheme 29. Synthesis of vinyl fluoride **59**.



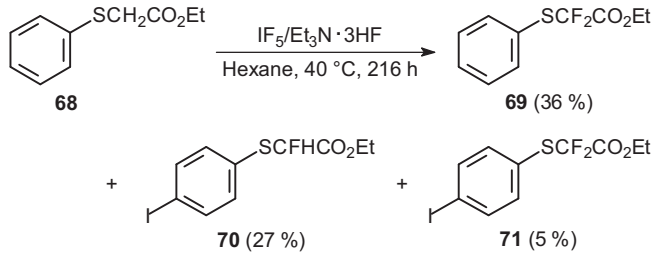
Scheme 30. Additive-Pummerer reaction for a DFIT activated sulfide.



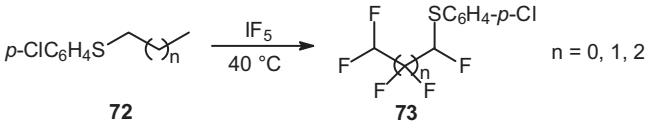
Scheme 31. Competing cyclization in the reaction of α-phenylsulfanyl acetanilides **63** with DFIT.

In contrast to γ-lactones, sulfur containing lactams **60** undergo a second deprotonation at β-position upon treatment with 1 equiv of DFIT producing α-phenylsulfanyl-α,β-unsaturated lactams **61**. A second equiv of DFIT leads to α,β-difluorinated compounds **62**. An initial Pummerer reaction generates the α,β-unsaturated derivative **61**, followed by a so-called additive-Pummerer reaction [90]. In the additive-Pummerer reaction, two molecules of the nucleophile add across the double bond of an α,β-unsaturated sulfide to generate the saturated α,β-difluorinated sulfide **62**. Scheme 30 shows an additive-Pummerer mechanism for a DFIT-activated sulfide *via* the proposed intermediates **E** and **F** [91,92].

As in the case of esters, α-fluorination of allylic α-phenylsulfanyl acetamides with difluoroiodotoluene takes place in good overall yields. The use of a second equiv of DFIT provided a simple one-pot method for α,α-difluorination. However, α-phenylsulfanyl acetanilides **63** can undergo a competing cyclization reaction to form **64** at temperatures higher than 0 °C *via* intermediate **G**, due to π-participation of the aromatic ring in intermediate **H**. In all substrates the formation of the initial iodosulfonium salt occurs at 0 °C. However, the formation of either α-fluoro sulfides, or sulfoxides or cyclized products **64** is strongly influenced by the substituents next to the amide nitrogen atom [93] (Scheme 31).



Scheme 33. Fluorination of ethyl (phenylthio)acetate (**68**) using $IF_5/Et_3N{\cdot}3HF$.



Scheme 34. Polyfluorination of alkyl arylsulfides **72** with IF_5.

2.5. $IF_5/Et_3N{\cdot}3HF$ and IF_5 as reagents

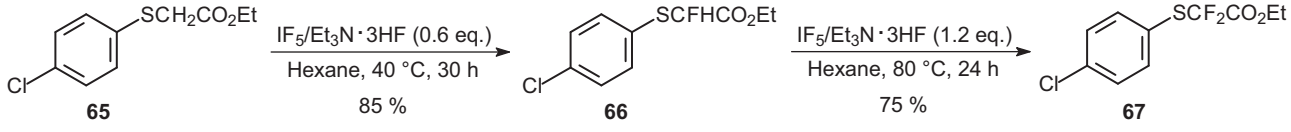
Yoneda et al. depicted that the novel fluorinating reagent $IF_5/Et_3N{\cdot}3HF$ allows selective mono- and difluorination of sulfides bearing various electron withdrawing groups, such as ester, amide, ketone, nitrile, sulfone or trifluoromethyl moieties by choosing the reaction conditions [94]. The monofluorination product **66** of (*p*-chlorophenylthio)acetate (**65**) was selectively obtained by carrying out the reaction at 40 °C using 0.6 molar amount of $IF_5/Et_3N{\cdot}3HF$. The reaction of compound **66** with a 1.2 molar amount of $IF_5/Et_3N{\cdot}3HF$ at 80 °C afforded the difluorinated product **67** (Scheme 32). The latter product was also obtained from (*p*-chlorophenylthio)acetate (**65**) directly using 1.2 equiv of the reagent [95].

Starting from *para*-unsubstituted ethyl (phenylthio)acetate (**68**) with $IF_5/Et_3N{\cdot}3HF$ in hexane at 40 °C besides the expected difluoro(phenylthio)acetate (**69**), also the mono- and difluorinated (*p*-iodophenylthio)acetates **70** and **71** were isolated (Scheme 33). The iodination of the aromatic ring takes place by the interhalogen IF, which was formed by disproportionation of the generated IF_3 to IF_5 and IF during the reaction [95].

Because regenerated IF_5 (by disproportionation of IF_3) is used for fluorination of the substrate again, more than one fluorine atom of IF_5 is transferred. Thus, a 2 molar amount of IF_5 is not necessary to obtain the difluorinated product in good yields [95].

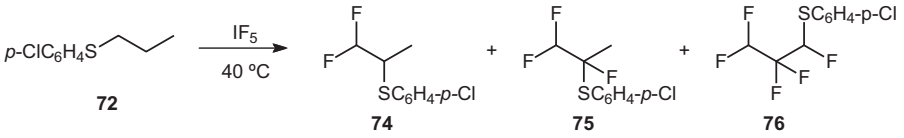
Treatment of alkyl *p*-chlorophenyl sulfides **72** with 2.4 equiv of IF_5 led to compounds **73** by polyfluorination of the alkyl chain accompanied by migration of the arylthio group. Fluorine atoms were not only introduced to the α-position but also to the β-position of the sulfur group. The ω-carbon remained difluorinated. Polyfluorination proceeded *via* the migration of the arylthio group from the inner to the terminal carbon during the reaction. Therefore fluorination took place at all carbons where the arylthio group had been attached [96] (Scheme 34).

The reaction of *p*-chlorophenyl propyl sulfide **72** ($n = 1$) with IF_5 in heptane under reflux led to **75** by selective introduction of three fluorine atoms into the alkyl chain. When **72** ($n = 1$) was allowed to react with 1.2 equiv of IF_5 under reflux for 1 h the arylthio group migrated once and a mixture of difluoro and trifluoro substituted



Scheme 32. Mono- and difluorination of (*p*-chlorophenylthio)acetate (**65**) with $IF_5/Et_3N{\cdot}3HF$.

Table 1
Reactions of *p*-chlorophenyl propyl sulfide **72** with IF_5 under various conditions.[a]



72 74 75 76

IF_5 [eq.]	Reaction time [h]	Yield [%][b]		
		74	**75**	**76**
1.2	1	43	17	0
2.4	1	0	74	0
2.4	6	0	72	5
2.4[c]	48	0	0	72

[a] If not otherwise mentioned the reaction was carried out in heptane under reflux.
[b] Isolated yield based on the starting sulfide.
[c] The reaction was carried out in hexane at 40 °C in a tight screw capped vessel.

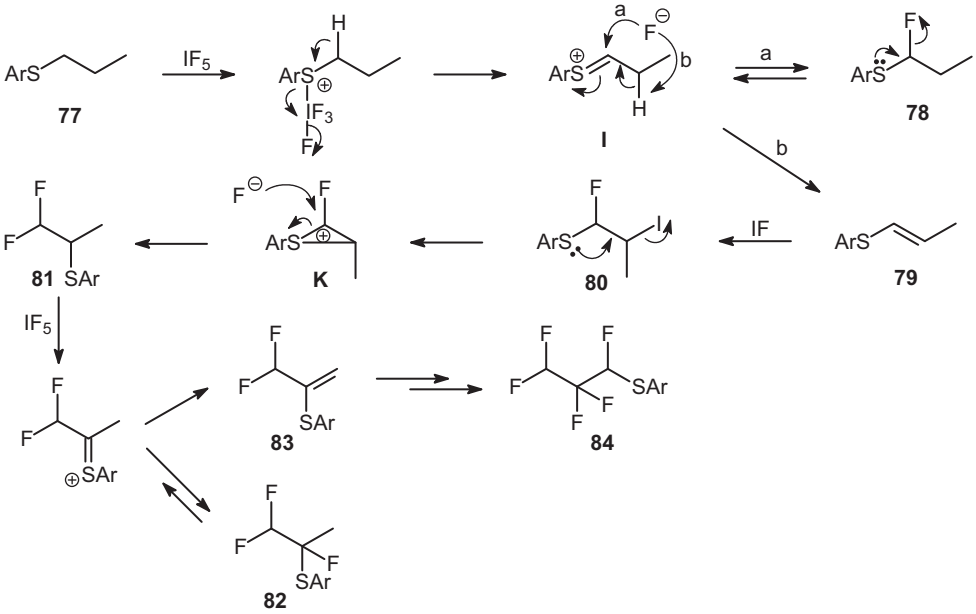
sulfides **74** and **75** was obtained (Table 1). By using of 2.4 equiv of IF_5 the trifluorinated sulfide **75** was formed selectively. If the reaction was carried out in hexane at 40 °C in a tight-screw capped vessel, the arylthio group migrated twice and after 48 h the pentafluorinated product **76** was obtained as main product.

Various other alkyl aryl sulfides were converted into corresponding trifluorides with IF_5 in refluxing heptane. In addition, Hara et al. observed that the *p*-substituents of the aryl group have a significant effect on the reaction time and the equiv of IF_5 needed for the reaction. Electron-donating substituents accelerated the reaction and only 1.2 equiv of IF_5 were enough to obtain the trifluorinated product. The presence of electron-withdrawing groups retarded the reaction and longer reaction times and larger excess of IF_5 were required to complete the reaction [97].

The proposed reaction mechanism of the polyfluorination reaction is depicted in Scheme 35 using phenyl propyl sulfide (**77**) as an example: Initially iodination of sulfur gives the sulfonium intermediate **I**, which reacts to give the mono-fluorinated product **78** or the vinylic sulfide **79**. Addition of the *in situ* generated IF to the later compound affords the vicinal iodofluoride **80**. By anchimeric assistance of the sulfur function, iodide is eliminated under formation of episulfonium ion **K**. Fluorination at the terminal carbon yielded the geminal difluoride **81** by migration of the arylthio group into the 2-position. Repeated oxidative fluorination at the α-carbon to sulfur gave the trifluorinated sulfide **82**. The alternative formation of the vinylic sulfide **83** is slow due to its high oxidation potential (1.65 V) and the low electron density at the sulfur atom. This reaction can be accelerated at 98 °C to form the pentafluorinated sulfide **84** [97] (Scheme 35).

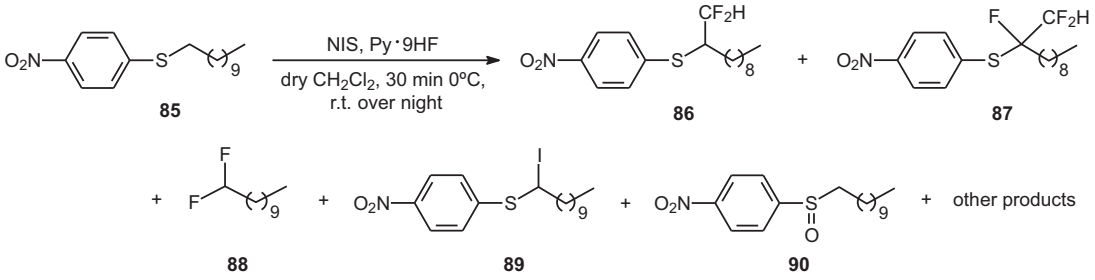
2.6. Application of oxidants and nucleophilic fluorinating reagents

Seeking for methods for the selective introduction of one or more fluorine atoms into the activated α-positions of alkyl aryl sulfides, we discovered reactions similar to those described in the former paragraph. The initial reaction of *p*-nitrophenyl undecyl sulfide (**85**) with NIS and Olah's reagent (Py·9HF) was not selective and gave mixtures of di- and trifluoro sulfides **86** and **87** and a geminal difluoroalkane **88** depending on the molar ratio of substrate and reagents (Table 2). In addition, the α-iodonated sulfide **89** and the fluorine free sulfoxide **90** were identified in the crude product mixture.



Scheme 35. Mechanism of the formation of polyfluorinated aryl sulfides.

Table 2
Reaction of *p*-nitrophenyl undecyl sulfide (**85**) with NIS and Olah's reagent under various conditions.



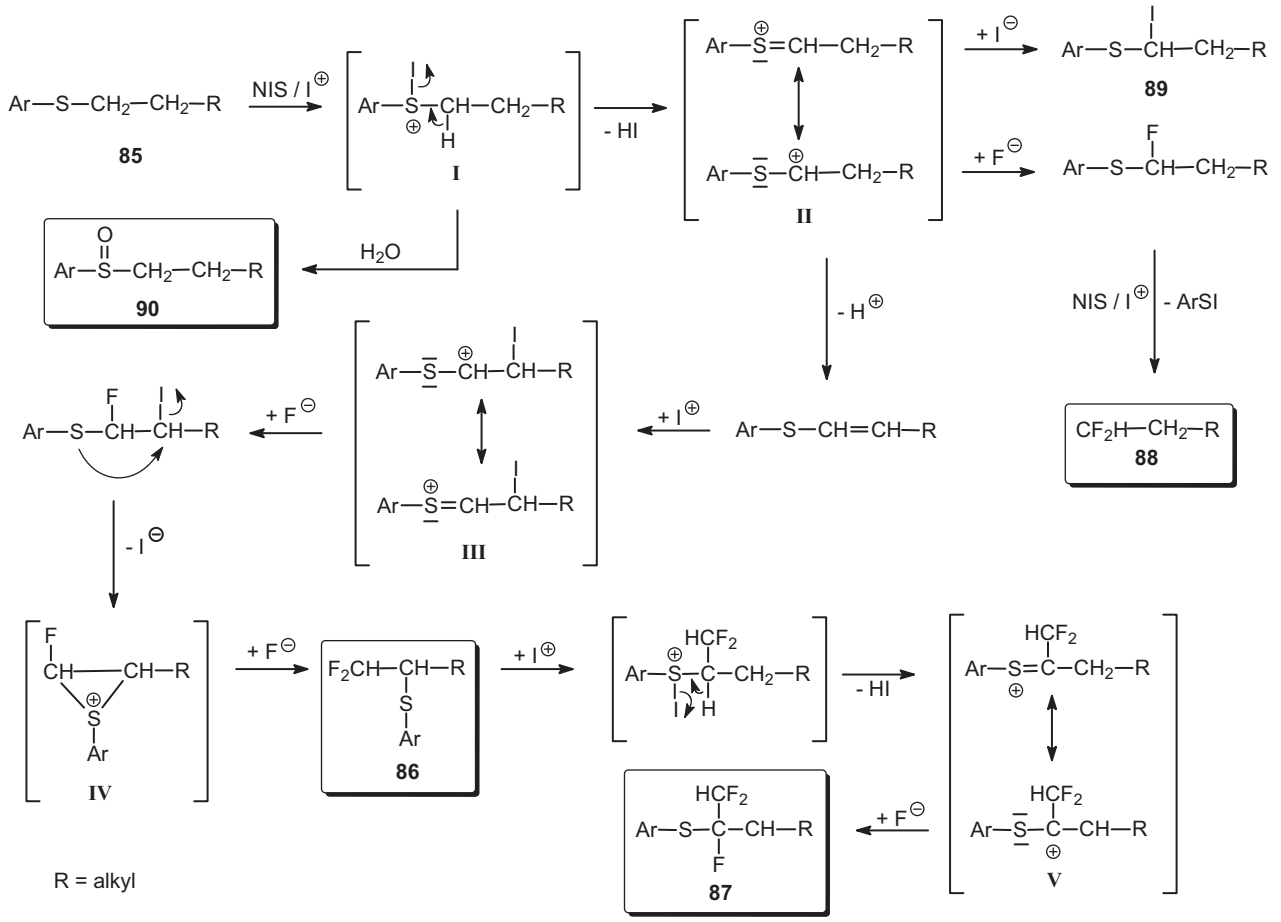
85 **86** **87** **88** **89** **90**

NIS (eq.)	Py·9HF (eq.)	Crude product mixture (GC %)						
		85	**86**	**87**	**88**	**89**	**90**	**Others**
1.1	2.2	55	12	–	–	2	28	3
2.2	4.4	33	42	1	–	2	19	3
4.4	4.4	–	41	23	6	7	11	12
6.0	6.0	–	3	43	14	–	12	28

The mechanism of formation of the di- and trifluoro sulfides **86** and **87** is similar to the one proposed by Hara et al. With an increasing excess of the reagents compound **86** reacts further to give **87**. Moreover, with excess of NIS/Py·9HF also the *gem*-difluoroalkane **88** is formed *via* oxidative desulfurization–difluorination (Scheme 36) [98].

Treatment of alkyl aryl sulfides with electron-withdrawing substituents like fluorine, oxygen, carbonyl or carboxyl in β-position under the conditions of the desulfurization–difluorination approach (2 equiv of DBH/6 equiv of Py·9HF) did not lead exclusively to the geminal difluorides of type **88**. The reaction of arylthioacetates **91** bearing a carboxyl function in α-position to the potential fluorination position, led to difluorinated arylthioacetates **92** (Table 3). The reaction with the *p*-methoxy substituted sulfide (entry 5), however, did not proceed selectively [99].

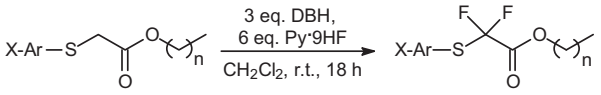
The suggested mechanism of the formation of the alkyl-2-arylthio-2,2-difluoroacetates **92** involves two fluoro-Pummerer-like rearrangements [99].



85 **I** **II** **89** **90** **III** **88** **IV** **86** **87** **V**

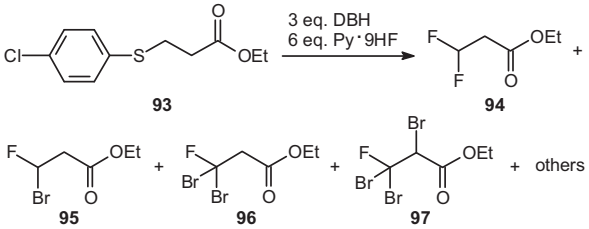
Scheme 36. Suggested mechanism for the formation of the fluorinated sulfides.

Table 3
Synthesis of alkyl 2-arylthio-2,2-difluoroacetates **92**.



X = F, Cl, NO_2, MeO, Me
n = 1, 7

Entry	X	*n*	Yield [%]
1	*p*-NO_2	1	77
2	*p*-Cl	1	72
3	*p*-F	1	65
4	*p*-Me	1	71
5	*p*-OMe	1	Traces
6	*p*-NO_2	7	25
7	*p*-Cl	7	67
8	*p*-Me	7	52

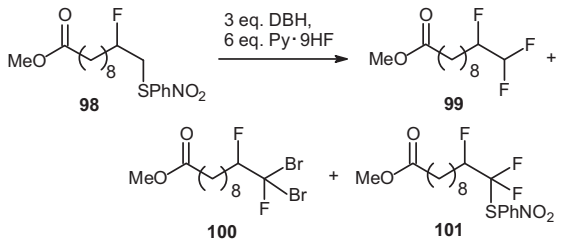


Scheme 37. Oxidative desulfurization–difluorination of ethyl 3-(arylthio)propionate (**93**).

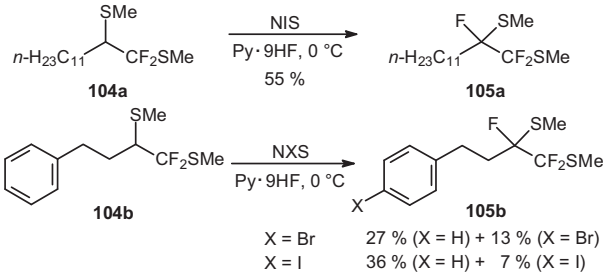
The conversion of ethyl 3-(arylthio)propionate (**93**) having a CH_2-group between the reaction center and the ester group with 3 equiv of DBH and 6 equiv of Olah's reagent did not lead to ethyl 3-arylthio-3,3-difluoropropionate. Instead a mixture of desulfurization–difluorination product **94** and desulfurization–polybromination products **95–97** was formed (Scheme 37).

The reaction of the β-fluorinated alkyl aryl sulfide **98** with DBH and Olah's reagent gave a mixture of the trifluoride **99**, the dibromodifluoride **100** and the trifluorinated sulfide **101** in a ratio of 1:1.2:2 (Scheme 38) [99].

These results showed that neither the electron-withdrawing effect of an ester group nor that of a fluorine atom in β-position to the reactive center is sufficient to prevent the desulfurization step, but decelerated the reaction rate and directed the reaction toward oxidative desulfurization–difluorination and desulfurization–polybromination [99]. Formation of the brominated compounds



Scheme 38. Oxidative desulfurization–difluorination of methyl 11-(arylthio)-10-fluoroundecanoate (**98**).

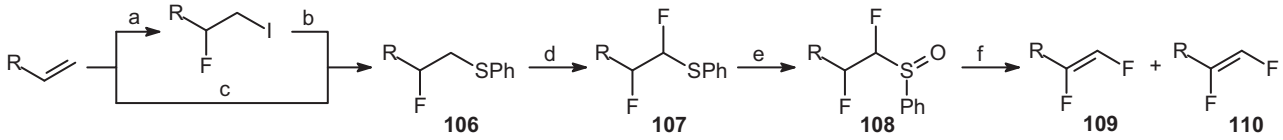


Scheme 39. Fluorination of 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethane derivatives **104** using the reagent combination of NXS/Olah's reagent.

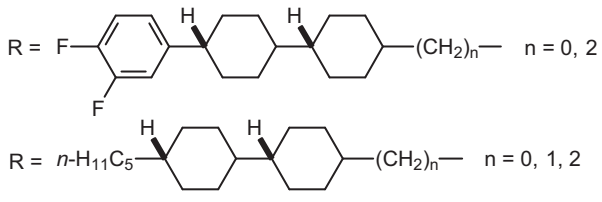
proceeded *via* addition of a bromide instead of a fluoride to the respective intermediates. Bromide ions are formed by HBr-elimination from the intermediate **I** (compare Scheme 36) or by reaction of the bromonium ion donor with the fluorinating reagent analogous to a mechanism postulated by Guerrero et al. for bromofluorination reactions of olefins with NBS and tetrabutylammonium bifluoride (*n*-$Bu_4NH_2F_3$, $TBAH_2F_3$) as a mild, safe and stable fluorinating reagent [100].

Hiyama et al. combined 1,3-dibromo-5,5-dimethylhydantoin (DBH) as an electrophile with $TBAH_2F_3$ to enhance the synthetic utility of fluoro-Pummerer rearrangements. In this way various organic sulfides **102** were readily fluorinated to give α-fluorosulfides **103** in dichloromethane in 20 min (Table 4, entries 1–4) [101]. The fluoro-Pummerer rearrangement was also applicable to 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethanes **104**. The substrates were converted selectively into trifluoro sulfides **105** (Table 4, entries 5–9) [102].

Also Py·9HF was employed as a fluorinating agent in combination with electrophiles like NIS and NBS. In the presence of a phenyl ring (**104b**), in addition to the fluoro-Pummerer rearrangement products (**105b**), minor amounts of halogenation products at the phenyl ring were formed (Scheme 39).

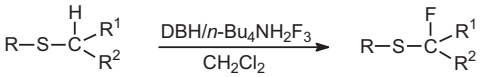


a: NIS (1 mol), *n*-$Bu_4NH_2F_3$ (3 mol), CH_2Cl_2, r.t.
b: PhSH (1.2 mol), NaH, (1.1 mol), THF, 0 °C to r.t.
c: *N*-PhS-Phthalimide (1 mol), Py·9HF (10 mol), CH_2Cl_2, r.t.
d: DBH (1 mol), *n*-$Bu_4NH_2F_3$ (3 mol), CH_2Cl_2, r.t., 30 min
e: *m*CPBA (1.1 mol), CH_2Cl_2, -30 °C, 3 h
f: *o*-Xylene, 170 °C

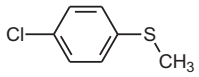
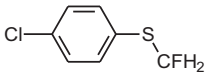
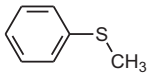
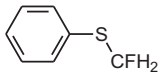
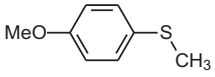
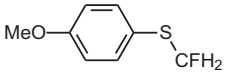
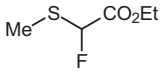
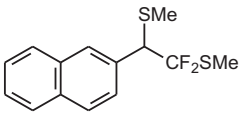
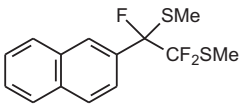
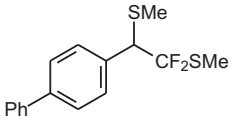
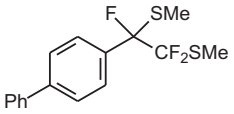
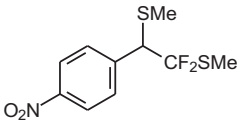
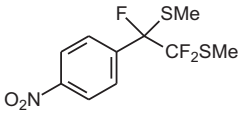
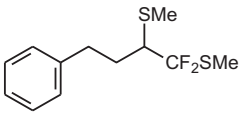
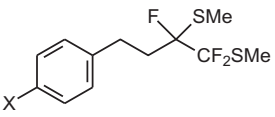
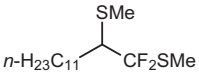
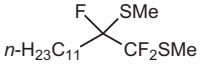


Scheme 40. Synthesis of *vic*-difluoro olefins **109** and **110**.

Table 4
Fluorination of organic sulfides.



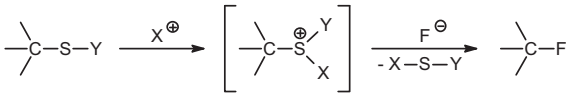
102,104 **103, 105**

Entry	**102,104**	Conditions (equiv)	**103,105**	Yield [%]
1		DBH (1.4), *n*-$Bu_4NH_2F_3$ (1.4), r.t.		90
2		DBH (1.4), *n*-$Bu_4NH_2F_3$ (1.4), r.t.		52
3		DBH (1.4), *n*-$Bu_4NH_2F_3$ (1.4), r.t.		59
4		DBH (2.5), *n*-$Bu_4NH_2F_3$ (3.5), r.t.		46
5		DBH (2.5), *n*-$Bu_4NH_2F_3$ (3.5), r.t.		55
6		DBH (2.5), *n*-$Bu_4NH_2F_3$ (3.5), r.t.		33
7		DBH (2.5), *n*-$Bu_4NH_2F_3$ (3.5), r.t.		70
8		DBH (2.5), *n*-$Bu_4NH_2F_3$ (3.5), r.t.		72
9		DBH (2.5), *n*-$Bu_4NH_2F_3$ (3.5), r.t.		35

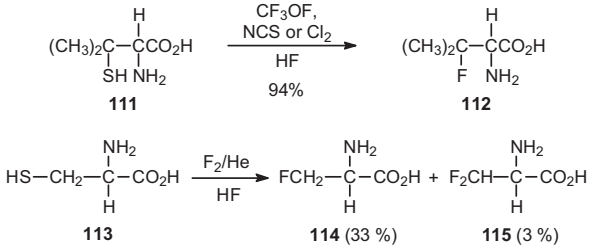
This method was applied for the synthesis of *vic*-difluoro olefins **109** and **110** for liquid crystalline materials. The fluoro-Pummerer rearrangement of the β-fluoroalkyl phenyl sulfide **106** with DBH and $TBAH_2F_3$ gave the α,β-difluoroalkyl phenyl sulfides **107** in high yields as 1:1 diastereomeric mixtures. Subsequent oxidation to the sulfoxides **108** and thermolysis in xylene afforded mixtures of *cis*- and *trans*-difluoro olefins **109** and **110** [103,104] (Scheme 40).

3. Desulfurization–fluorination

In contrast to the oxidative α-fluorination of sulfides in the fluoro-Pummerer rearrangements, the oxidative desulfurization–fluorination in net is a nucleophilic substitution of the sulfur function by a fluoride. The basic idea involves the activation of the C–S bond by an electrophile, followed by a nucleophilic substitution with fluoride [105] (Scheme 41).



Scheme 41. Concept of the oxidative desulfurization–fluorination.



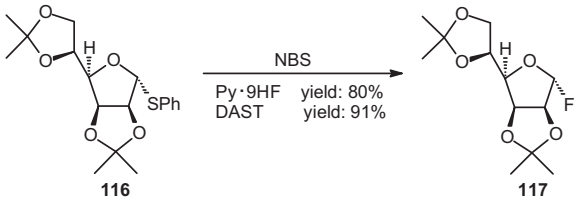
Scheme 42. Oxidative desulfurization–fluorination using CF_3OF, NCS or Cl_2, respectively, F_2/He in liquid HF.

3.1. Application of oxidants and nucleophilic fluorinating reagents

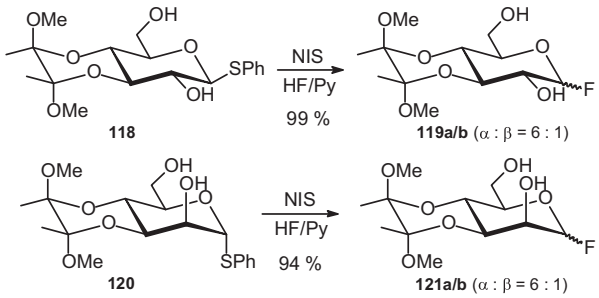
The first desulfurization fluorination reaction was described by Kollonitsch et al. using hazardous reagent combinations. 2-Aminothiols and mercapto amino acids were successfully converted into aminoalkyl fluorides and fluorinated amino acids in liquid hydrogen fluoride solution with fluoroxytrifluoromethane (CF_3OF), chlorine, *N*-chlorosuccinimide (NCS), or a fluorine–helium mixture, respectively. The reaction of D-penicillamine (**111**) in liquid HF at −78 °C with CF_3OF gave 3-fluoro-D-valine (**112**) in 94% yield, while primary amino thiols, such as cysteine (**113**), by reaction with the more powerful oxidizer F_2/He gave 3-fluoroalanine (**114**) and a minor amount of difluoroalanine (**115**) [106] (Scheme 42).

In due course the original hazardous combination of reagents (CF_3OF and/or F_2/He) [106] were replaced by more convenient reagents such as *N*-bromosuccinimide (NBS)/Olah's reagent (Py·9HF) or DAST. Nicolaou et al. applied these two different methods to prepare glycosyl fluorides **117** from phenylthio glycosides **116** demonstrating the efficiency of this transformation. The use of NBS/DAST showed slightly better yields than the combination NBS/Py·9HF [107] (Scheme 43).

The transformation of 1-(phenylthio)glycosides **118** and **120** into glycosyl fluorides **119** and **121** was reported by López and coworkers to proceed with halonium ions supplied from NIS, NBS or bis(2,4,6-collidine)iodonium perchlorate (IDCP) in the presence of HF-pyridine or $Et_3N{\cdot}3HF$ in dichloromethane at low temperature. Studies of selected 1-(phenylthio)-glycosides illustrated that the combination NIS/HF-pyridine was more potent in provoking the reaction of thioglycosides, while NIS/$Et_3N{\cdot}3HF$ was more tolerant of acid-sensitive functionalities. However, large



Scheme 43. Oxidative desulfurization–fluorination with NBS/Olah's reagent and NBS/DAST.



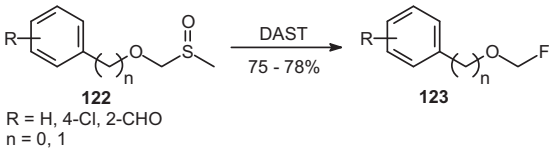
Scheme 44. Desulfurization–fluorination reaction of 1-(phenylthio)glycosides with NIS/HF-pyridine.

excess of the HF-pyridine reagent (20–40 equiv) or triethylamine trishydrofluoride (40–120 equiv) was needed and moderate stereoselectivity was observed [108] (Scheme 44).

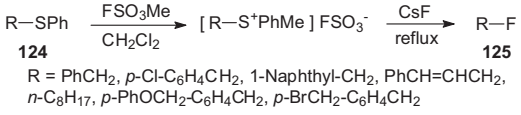
Benneche et al. reported the synthesis of α-fluoro ethers **123** from α-alkoxy sulfoxides **122** by replacement of the sulfinyl group with fluorine using DAST (Scheme 45). The α-alkoxy group in the sulfoxide plays a very important role for this reaction to succeed, because without an α-alkoxy group or any group that can stabilize the carbocation, sulfoxides give rise to the fluoro-Pummerer reaction resulting in the formation of α-fluoro sulfides [109].

Combinations of methyl fluorosulfonate and cesium fluoride as well enabled desulfurization–fluorination reaction. Several phenyl sulfides **124** were converted selectively into the corresponding fluorides **125** without affecting the coexisting phenoxy or bromine substituents [110] (Scheme 46).

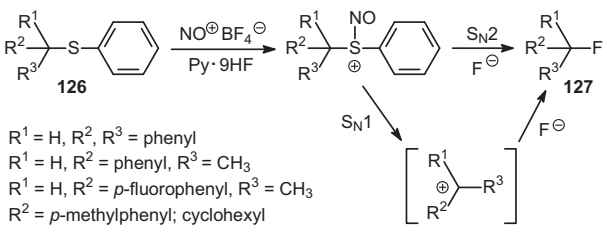
The reagent combination of nitrosonium tetrafluoroborate ($NOBF_4$) and Py·9HF showed excellent desulfurization–fluorination potencies. Monofluorides **127** and *gem*-difluorides were obtained in good yields from the corresponding phenyl sulfides **126** or dithiolane derivatives, respectrively. Limitations of this



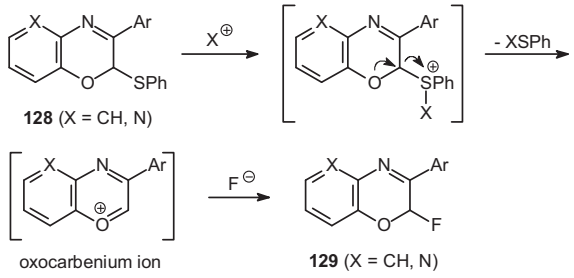
Scheme 45. Desulfurization–fluorination of α-alkoxy sulfoxides **122** with DAST.



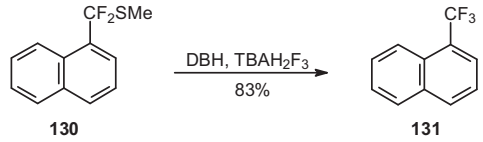
Scheme 46. Fluorodesulfurization with FSO_3Me and CsF.



Scheme 47. Desulfurization–fluorination with $NOBF_4$ and Py·9HF.



Scheme 48. Mechanism of the selective desulfurization–fluorination of benzo- and pyrido-oxazine derivatives **128**.



Scheme 49. Preparation of 1-trifluoromethylnaphtahlene (**131**) from 1-[difluoro-(methylthio)methyl]naphthalene (**130**) using DBH and $TBAH_2F_3$.

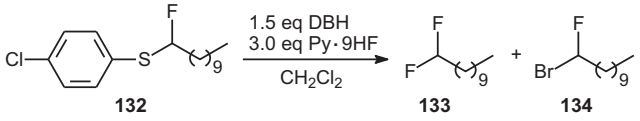
reagent have been found in the fluorination reaction of phenyl cyclohexyl sulfides, which gave low yield of fluorocyclohexane [111] (Scheme 47).

Fuchigami et al. achieved the selective desulfurization–fluorination of benzo- and pyrido-oxazine derivatives using different *N*-halosuccinimides as oxidizing reagent in the presence of $Et_3N{\cdot}3HF$ (25 equiv). The reactions were carried out in dichloromethane requiring only 30 min reaction time. A possible mechanism for the selective desulfurization–fluorination is illustrated in Scheme 48. An active halonium ion, derived from *N*-halosuccinimide reacts with the phenylthio group of **128**, followed by elimination of the phenylthio group to generate an oxocarbenium ion, which reacts with fluoride to provide the corresponding monofluorinated products **129** [112] (Scheme 48).

Hiyama et al. converted α,α-difluoro(methylthio)methyl substituted aromatic compounds **130** to the corresponding trifluormethyl derivatives **131** by treatment with DBH and *n*-$Bu_4N^+H_2F_3^-$ by desulfurization–fluorination (Scheme 49). Only trifluoromethyl substituted aromatics have been synthesized by this method so far [113].

Starting from α-fluorinated sulfides *gem*-difluorides were obtained applying oxidative desulfurization–fluorination conditions (DBH/Py·9HF). *p*-Chlorophenyl-(1-fluoroundec-1-yl)sulfide (**132**), as a model compound, was reacted with 1.5 equiv of DBH and 3 equiv of Olah's reagent to give 1,1-difluoroundecane (**133**) and 1-bromo-1-fluoroundecane (**134**) in a ratio of 95:5. By microwave irradiation the amount of fluorinating reagent and the reaction time could be reduced to 1.1 equivequiv and 40 min (Table 5) [98].

Table 5
Oxidative desulfurization–fluorination of *p*-chlorophenyl-(1-fluoroundec-1-yl)sulfide (**132**).



Entry	DBH (eq.)	Py·9HF (eq.)	Reaction conditions	**133**	**134** (GC %)[a]
1	1.5	3.0	20 h, r.t.	95	5
2	1.5	2.0	40 min, 45 °C, 100 W	90	10
3	1.5	1.1	40 min, 45 °C, 100 W	93	7

[a] The ratio is calibrated to 100%, <5% impurities.

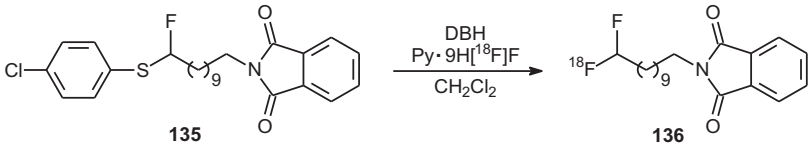
On the basis of this latter transformation a new radiofluorination protocol was developed. The [^{18}F]radiolabeled difluoride [^{18}F]**136** was synthesized from the α-fluorosulfide **135** by combination of DBH and carrier added Py·9H[^{18}F]F. Maximum radiochemical yield (rcy) of 9% was achieved with 8 fold excess of Py·9H[^{18}F]F (Table 6) [98].

By treatment of different *para*-substituted 2-arylthio-2,2-difluoroacetates **137** with an electrophile (DBH, NIS, NCS), applying a large excess of Py·9HF and heating to 45 °C, the corresponding trifluorides **138** were obtained. The use of NCS as an electrophile avoided the formation of the chlorodifluoride **139b** (X = Cl). Depending on the substituents of the arylthio group, the reaction was possible with lower amounts of fluorinating reagent and in shorter reaction time (Table 7) [99]. This method might be developed to an appropriate method for ^{18}F-labeling of medicinally relevant ligands for the positron emission tomography (PET).

3.2. Application of electrophilic fluorinating reagents

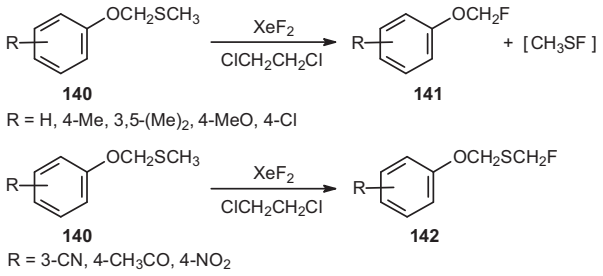
Similarly to the α-fluorination of sulfides, xenon difluoride was also applied for the synthesis of fluoromethoxybenzenes **141** by cleavage of the *O*,*S*-acetal **140**. The desulfurization–fluorination reaction proceeded well, provided the aromatic ring was

Table 6
Radiofluorination of 4-chlorophenyl-(1-fluoro-11-*N*-phthalimidylundec-1-yl)sulfide (**135**) with DBH and carrier-added Py·9H[^{18}F]F.

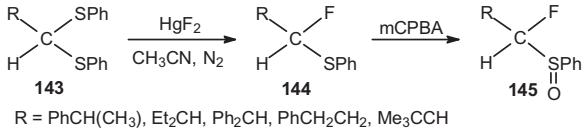


Entry	Py·9H[^{18}F]F [μl]	CH_2Cl_2 [μl]	Product	Rcy[a,c] [%]	Rcp[b,c] [%]
1–3	2.5	150	[^{18}F]**135**	6.9 ± 1.5	78 ± 3
4–6	5.0	300	[^{18}F]**136**	9.0 ± 1.4[d]	65 ± 14
7–9	10.0	150	[^{18}F]**136**	5.5 ± 0.4[d]	61 ± 24

[a] Rcy: radiochemical yield (decay corrected).
[b] Rcp: radiochemical purity of the prepurified (C18 cartridge) reaction solution determined by HPLC.
[c] Values are the mean ± standard deviation of three experiments.
[d] [^{18}F]**135** was formed as a by-product with 0.5% rcy.



Scheme 50. Synthesis of α-fluoro ethers with XeF_2.



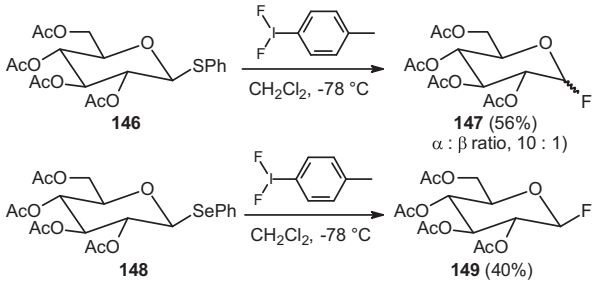
Scheme 51. Oxidative desulfurization–fluorination with HgF_2.

non-substituted or contained electron-donating groups. Strong electron-withdrawing substituents led to α-fluorinated products **142** in the course of a fluoro-Pummerer rearrangement [114] (Scheme 50).

The use of HgF_2 as electrophile and fluoride source in anhydrous acetonitrile allowed oxidative desulfurization–fluorination reaction of thioacetals **143**. Due to their instability, the α-fluoro sulfides **144** were subsequently oxidized to α-fluoro sulfoxides **145** [115] (Scheme 51).

3.3. Application of hypervalent difluoroiodotoluene (DFIT)

The hypervalent fluorinating reagent difluoroiodotoluene (DFIT) was efficiently applied for the α-fluorination of sulfides (see Section 2.4). This reagent has also been used for oxidative desulfurization–fluorination reactions. Thus, treatment of β-thio- **146** and β-selenoglycosides **148** with DFIT led to the formation of the corresponding glycosyl fluorides in moderate to good yield. In the absence of neighboring group participation by substituents at C-2, the thioglycoside derivatives reacted preferentially by S_N2 like inversion of the configuration to form **147**, while selenoglycosides exhibiting a tendency for S_Ni like retention of the configuration leading to **149** [116] (Scheme 52).



Scheme 52. Fluorodesulfurization of thioglycosides and selenoglycosides using DFIT.

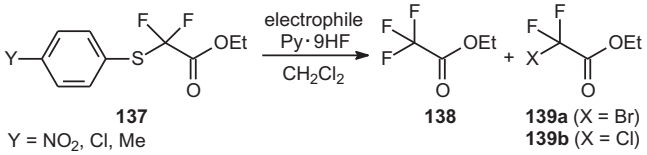
3.4. Electrochemical partial desulfurization–fluorination

Similarly to the oxidative desulfurization fluorination of dithioacetals with NBS and DBH in the presence of fluoride ions [105], Fuchigami and coworkers attempted indirect anodic fluorination using a Br^-/Br^+ redox mediator. However, the reaction with anodically generated mixed positive bromine species containing F^- resulted in low efficiency for the formation of difluorinated products. Thus, it was found that anodically generated bromofluorides such as Br_2F^- and BrF_2^- were efficient species for oxidative desulfurization/monofluorination of dithioacetals **150** to form **151** (Scheme 53) [117].

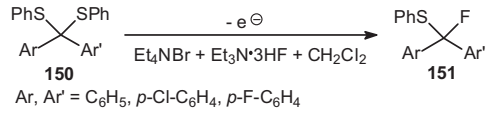
3.5. Enzyme catalyzed desulfurization–fluorination

Organofluorine compounds are very rare in nature [118] and only few enzymes seem to be involved in carbon-fluorine bond formation. A decade ago, O'Hagan et al. reported that in *Streptomyces cattleya* a fluorinase is involved in C–F bond formation catalyzing the conversion of *S*-adenosyl-L-methionine (SAM, **152**) and fluoride into 5′-fluoro-5′-desoxy-adenosine (5′-FDA) [119]. This fluorinase (5′-fluoro-5′-deoxyadenosine synthase, 5′-FDAS, E.C. 2.5.1.63) has been purified to homogeneity [120] and, besides its academic importance, became very attractive as a novel biocatalyst to explore its potential application for [^{18}F]-labeling of adenosine derivatives. First enzymatic radiolabeling approaches for the production of [^{18}F]-5′-FDA (**153**) using wild type fluorinase and [^{18}F]HF showed that the process, although successful, was inefficient with a radiochemical yield (rcy) of ~1% [121]. By the use of over-expressed fluorinase and elevated temperature of 35 °C the

Table 7
Oxidative desulfurization–fluorination of ethyl 2-arylthio-2,2-difluoroacetates **137**.



Entry	Electrophile (eq.)	Py·9HF (eq.)	Y	Temperature (°C)/time (h)	Products (^{19}F NMR)		
					137	**138**	**139**
1	DBH (3.0)	20.0	NO_2	30 min, 0 °C; 18 h, 40 °C	–	100	–
2	DBH (3.0)	20.0	NO_2	6.5 h, 40 °C	3	88	9
3	DBH (3.0)	10.0	NO_2	20 h, 45 °C	12	76	12
4	DBH (3.0)	5.0	NO_2	20 h, 45 °C	38	55	7
5	DBH (3.0)	10.0	Cl	3 h, 45 °C	–	68	32
6	DBH (3.0)	10.0	Me	7 h, 45 °C	–	66	8
7	NCS (3.0)	1.1	Me	18 h, 45 °C	–	75	–



Scheme 53. Indirect anodic desulfurization/monofluorination of dithioacetals **150** using a Br^-/Br^+ mediator.

radiochemical yields for [^{18}F]-5′-FDA production from [^{18}F]fluoride was improved dramatically up to 95%. By addition of L-amino acid oxidase (E.C. 1.4.3.2) the equilibrium of the reversible desulfurization–fluorination reaction was pulled toward [^{18}F]-5′-FDA (**153**). Additionally, in this coupled enzyme system the synthesis of [^{18}F]-5′-fluoro-5′-deoxyinosine ([^{18}F]-5′-FDI, **154**) and [^{18}F]-5-fluoro-5-deoxy-D-ribose ([^{18}F]-5-FDR, **155**) was accomplished in good radiochemical yields [122] (Scheme 54).

4. Oxidative desulfurization–difluorination

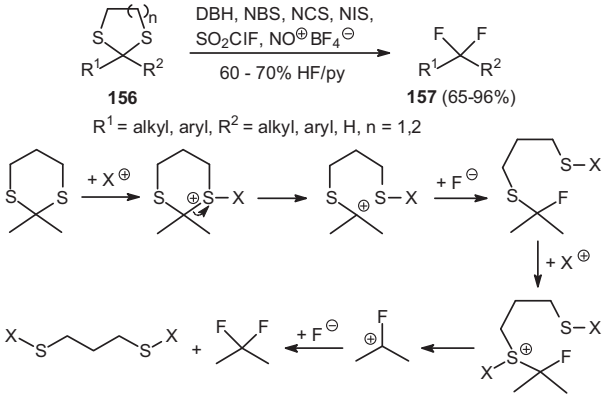
Recently the difluoromethyl group, which is isopolar and almost isosteric to a carbonyl group, came into the focus because of its biological properties. Several compounds bearing this moiety are metabolically more stable than the original biologically active molecules and/or are potent enzyme inhibitors [123]. Consequently, a variety of methods for their preparation have been described [124]. Among them the oxidative desulfurization–difluorination approach provides an efficient method for the synthesis of *gem*-difluorinated organic compounds [105,125].

4.1. Oxidative desulfurization–difluorination of dithiolanes and dithianes

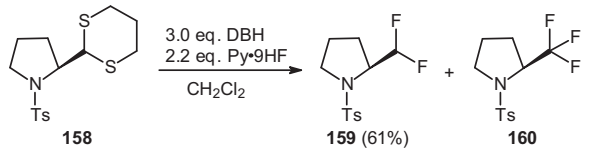
Cyclic dithioacetals derived from aryl and alkyl aldehydes and ketones **156** were smoothly converted to *gem*-difluorides **157** using reagent combinations consisting of an oxidant such as DBH, NBS, NIS [126–128], SO_2ClF [129] or $NO^+[BF_4]^-$ [111] and Py/HF, which are more easy to handle than the CF_3OF/HF-combination constituted by Kollonitsch et al. [106] or a mixture of elemental iodine and fluorine [130] or BrF_3 [131]. Recently, the combination of BrF_3 and pyridine was shown to be a suitable reagent for this type of reactions, while BrF_3 alone led to aromatic bromination or tarring [132]. The mechanism of the desulfurization–difluorination reaction is based on the ability of sulfur and later of fluorine to stabilize the formed α-carbocations till capture by fluoride (Scheme 55).

Direct difluorination of an L-prolinal derived 1,3-dithiane was achieved recently. Starting from the 1,3-dithiane substituted *N*-tosyl-L-pyrrolidine **158** the selective synthesis of (2*S*)-2-difluoromethyl-*N*-tosylpyrrolidine (**159**, 61%), beside minor amount of trifluoride **160**, was achieved by treatment with DBH and Py·9HF [133] (Scheme 56).

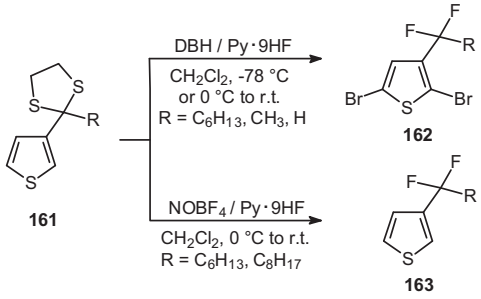
A drawback of using of DBH and NBS is the *in situ* formed BrF, which gives rise to side reactions such as bromination of



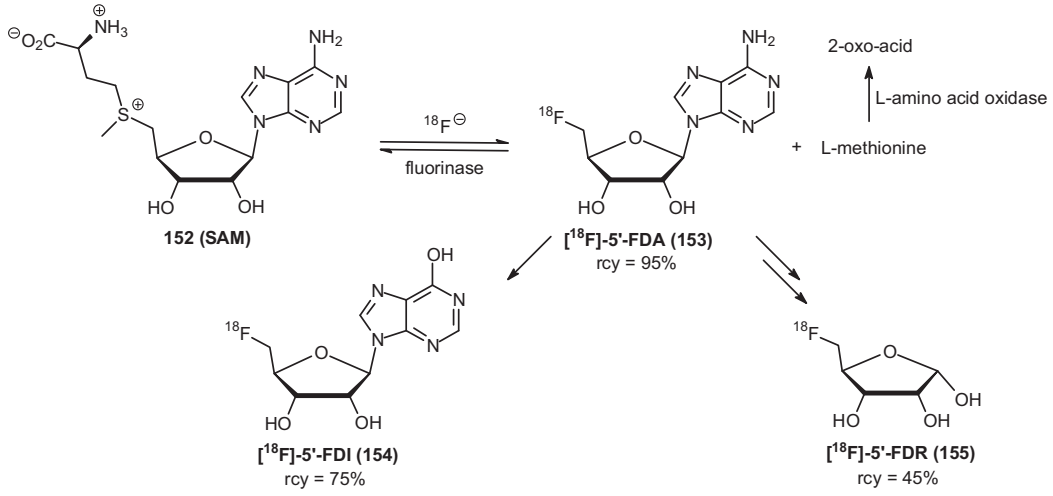
Scheme 55. Oxidative desulfurization–difluorination of dithioacetals **156**.



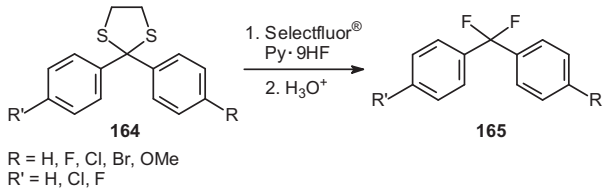
Scheme 56. Desulfurization–difluorination of (2*S*)-2-(1,3-dithian-2-yl)-*N*-tosylpyrrolidine (**158**).



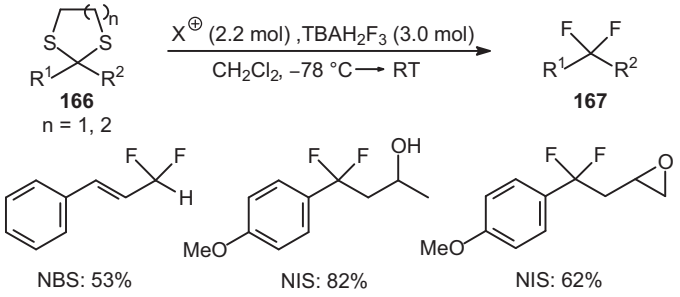
Scheme 57. Desulfurization–fluorination of dithiolane substituted thiophene derivatives **161**.



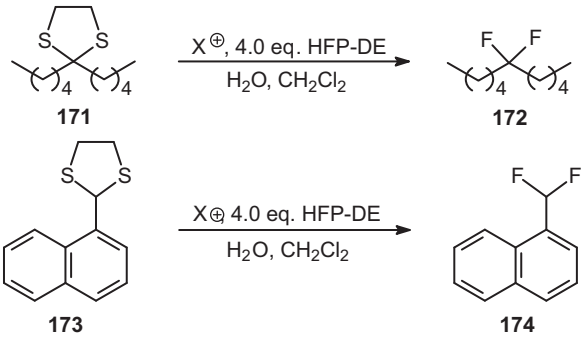
Scheme 54. Enzymatic ^{18}F-radiolabeling using fluorinase and [^{18}F]HF.



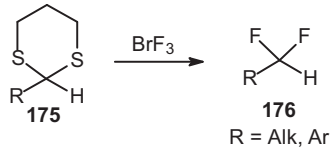
Scheme 58. *gem*-Difluorination of 2,2-diaryl-1,3-dithiolanes **164** with Selectfluor® and Py·9HF.



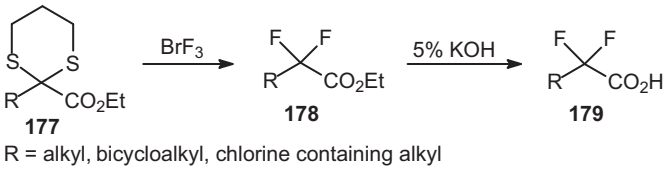
Scheme 59. Desulfurization–difluorination with NXS and $TBAH_2F_3$.



Scheme 61. *gem*-Difluorination of 1,3-dithiolanes **171** and **173** with HFP-DE and NIS or DBH.



Scheme 62. Reactions of dithianes **175** with BrF_3 leading to difluoromethyl derivatives **176**.



Scheme 63. Synthesis of α,α-difluoro acids **179**.

electron-rich aromatic rings [126]. The application of SO_2ClF (or SO_2Cl_2) in Olah's reagent was as well limited to 1,3-dithiolanes of benzophenone derivatives due to competing chlorination reactions [129]. With NO^+ as an electrophilic species, ketone-derived 1,3-dithiolanes with electron-rich aromatic groups were converted to the corresponding *gem*-difluorides [111]. While the use of DBH transformed 1,3-dithiolane substituted thiophene derivatives **161** to 2,5-dibromo-3-(difluoroalkyl)thiophenes **162**, the reaction with $NO^+[BF_4]^-$ cleanly produced 3-difluoroalkylated products **163** in moderate yields [134,135] (Scheme 57).

Treatment of 2,2-diaryl-1,3-dithiolanes **164** with the reagent combination of Selectfluor® and Olah's reagent under mild conditions gave *gem*-difluorinated compounds **165** in moderate yields (Scheme 58) [136].

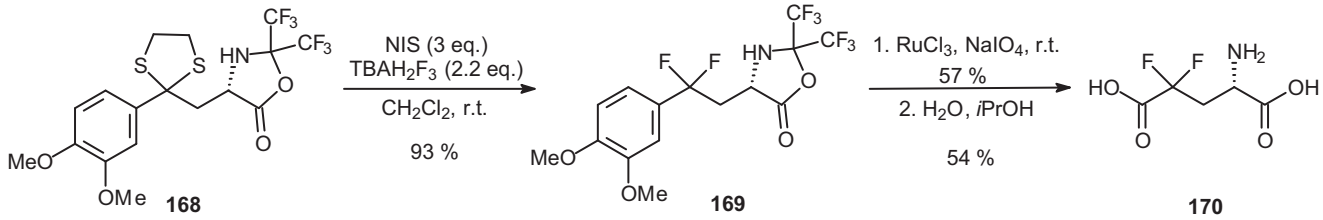
With $TBAH_2F_3$ as fluorinating reagent oxidative desulfurization–difluorination of cyclic dithioacetals **166** proceeded under milder conditions to form **167**. Functional groups like C=C double bonds, alcohols, and oxiranes were tolerated (Scheme 59) [137].

Furthermore, this strategy was applied to the synthesis of difluoroglutamic acid **170** from **168** *via* the intermediate structure **169** (Scheme 60) [125].

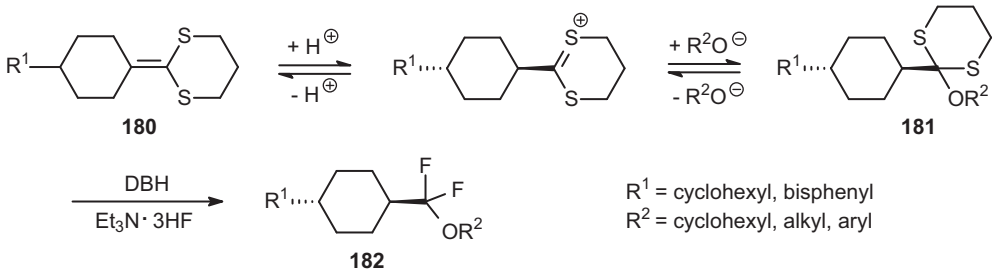
Shimizu et al. used DBH or NIS as electrophiles and utilized a hexafluorpropene-diethylamine complex (1,1,2,3,3,3-hexafluoropropyl-*N*,*N*-diethylamine, HFP-DE, Ishikawa's reagent) for the *in situ* generation of HF by reaction with 1 equiv. of water. This reaction was applicable to 1,3-dithiolanes of ketones **171** and aromatic aldehydes **173** (Scheme 61) [138].

p-(Difluoroiodo)toluene (DFIT) [139] as well as bromine trifluoride (BrF_3) [38,39], which efficiently combine electrophile and fluoride in one reagent, also proved their applicability for desulfurization–difluorination reactions. DFIT was able to convert 1,3-dithiolanes and 1,3-dithianes of diaryl ketones to *gem*-difluoro compounds in good yields [139]. The electrophilic bromine in BrF_3 forms a complex around basic heteroatoms, especially sulfur. Such complexation is accompanied by a closer distance of the naked and therefore nucleophilic fluoride to the potential reaction center and reduces the prospects of unselective radical brominations and fluorinations. The reaction of 2-alkyl-1,3-dithiane derivatives **175** for 1–2 min with BrF_3 afforded the corresponding 1,1-difluoromethyl alkanes **176** in 60–75% yield (Scheme 62). The reaction proceeded well also with α,ω-bis-dithianes, with dithianes bearing tertiary centers and with dithianes derived from polycyclic ketones [131].

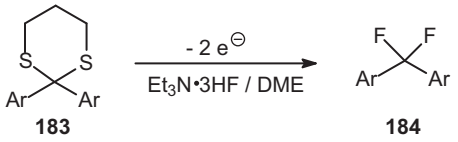
In order to prepare α,α-difluoro carboxylic acids **179**, 2-alkyl-2-ethoxycarbonyl-1,3-dithianes **177** were treated with a 3-fold excess of BrF_3 and the formed ethyl 2,2-difluoroalkanoates **178** were hydrolyzed in good yields (Scheme 63). While a large array of functional groups is tolerant to the reaction, ketones required protection of the carbonyl group, usually accomplished by transforming it to the corresponding acetal [140]. In a similar



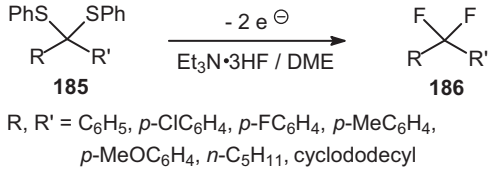
Scheme 60. Synthesis of difluoroglutamic acid **170**.



Scheme 64. Acid catalyzed alkoxylation and subsequent oxidative desulfurization–difluorination of ketene dithioacetals **181**.



Scheme 65. Anodic *gem*-difluorination of 1,3-dithiolanes **183**.



Scheme 66. Anodic difluorination of acyclic dithioacetals of ketones **185**.

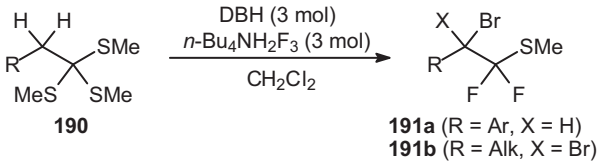
manner the synthesis of β,β-difluorocarboxylic acids was achieved with BrF_3 [141].

Kirsch et al. succeeded in the synthesis of difluoroxymethylene-bridged liquid crystals *via* "oxidative alkoxydifluorodesulfuration" of dithianylium salts [142,143]. The reaction of ketene dithioacetals **180** with alcohols and subsequent desulfurization–fluorination of **181** with DBH and $Et_3N{\cdot}3HF$ at −70 °C afforded α,α-difluoroalkylethers **182**. Pentafluoroethylation of *O*-nucleophiles was possible with 2-trifluoromethyl-1,3-dithianylium triflates in combination with desulfurization–fluorination reaction [144] (Scheme 64).

4.2. Anodic desulfurization–difluorination of dithioacetals

Replacement of the chemical oxidant by an anode and therefore electrochemical oxidation of the sulfur displays an alternative method for the oxidative desulfurization/difluorination of 1,3-dithiolanes of ketones **183** with $Et_3N{\cdot}3HF$ to form **184** [145,146] (Scheme 65).

Anodic *gem*-difluorination of bis(phenylthio)acetals of aromatic ketones **185** was carried out by Fuchigami et al. in the presence of $Et_3N{\cdot}3HF$ providing *gem*-difluoro compounds **186** in good yields, while the fluorination of bis(phenylthio)acetals of aliphatic ketones was less efficient. It was found that the difluorination was strongly affected by substituents at the phenyl ring. Electron-withdrawing groups promoted the anodic difluorination, while electron-donating groups significantly interfered with the difluorination (Scheme 66) [145].

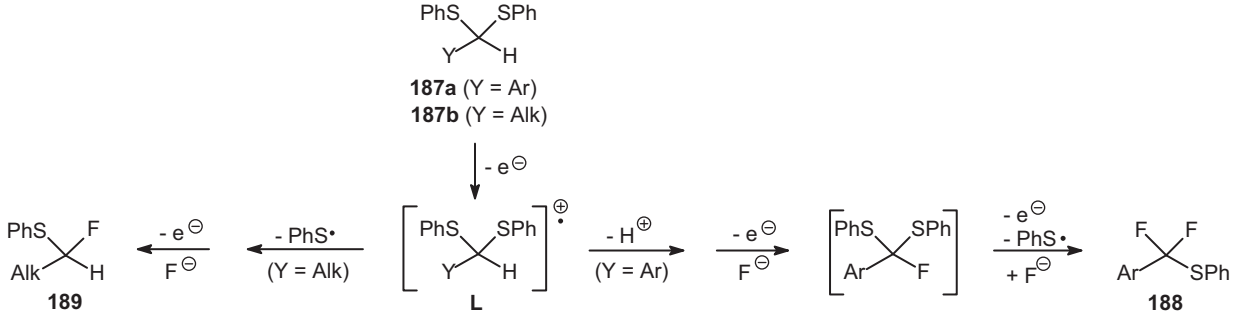


Scheme 68. Brominative difluorination of orthothioesters **190**.

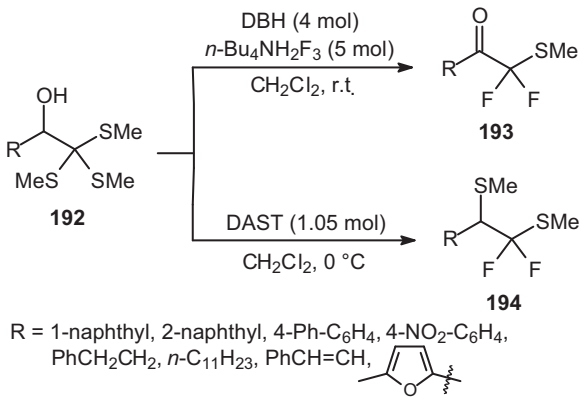
In contrast to bis(phenylthio)acetals of aromatic ketones, corresponding dithioacetals of aromatic and aliphatic aldehydes **187** gave either *gem*-difluoro sulfides **188** and monofluoro sulfides **189**, respectively. Thus, aromatic aldehyde-derived dithioacetals **187a** (Y = Ar) were converted into sulfides **188** containing a difluoromethyl group. Aliphatic aldehyde derived dithioacetals **187b** (Y = Alk) underwent C–S bond cleavage selectively and monofluorinated sulfides **189** were formed. This behavior can be explained by easier deprotonation of the cation radicals **L** (see Scheme 67) derived from the aromatic dithioacetals **187a** due to higher acidity of the α-proton. Therefore, the aryl compound **187a** underwent fluoro-Pummerer rearrangement in the first step and subsequent desulfurization–fluorination to α,α-difluorosulfide **188**, while the aliphatic compound gave the monofluorinated product **189** by an oxidative desulfurization–fluorination reaction [145].

4.3. Oxidative desulfurization–difluorination of trithio orthoesters

The reagent combination DBH and $TBAH_2F_3$ was applied for the desulfurization–difluorination of cyclic dithioacetals [137] (see Section 4.1). Upon treatment of trithio orthoesters **190** with this reagent combination, difluorination took place along with β-bromination (R = aryl) to form **191a** (X = H) or dibromination (R = alkyl) to form **191b** (X = Br) depending on the kind of substituent R (Scheme 68). No trifluorination occurred even after prolonged reaction time [147].



Scheme 67. Anodic fluorination of aldehyde-derived aryl and alkyl dithioacetals **186**.



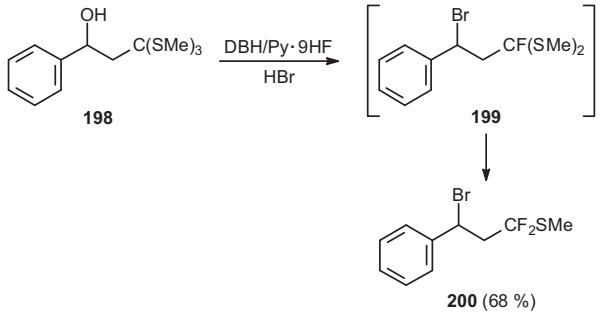
Scheme 69. Oxidative desulfurization–difluorination of 2,2,2-tris(methylthio)ethanols **192** with DBH and $TBAH_2F_3$ or DAST.

β-Hydroxy trithio orthoesters **192** were converted into difluoro(methylthio)methyl ketones **193** and/or 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethanes **194**, depending on the reagent used. Treatment with DBH and $TBAH_2F_3$ yielded the α,α-(difluoromethyl)-α-methylthio ketone **193** *via* oxidation of sulfur of two methylthio groups by Br^+, nucleophilic substitution of the C–S bonds by fluoride and oxidation of the hydroxyl group. On the other hand, when the trithio orthoester **192** was treated with DAST, 2-substituted 1,1-difluoro-1,2-bis(methylthio)ethanes **194** were obtained *via* deoxygenation, rearrangement, fluorination and oxidative desulfurization–fluorination. However, in both reaction pathways trifluorination and bromofluorination of intermediate C=C bonds was not observed. Ketone derived substrates gave complex product mixtures [102,148] (Scheme 69).

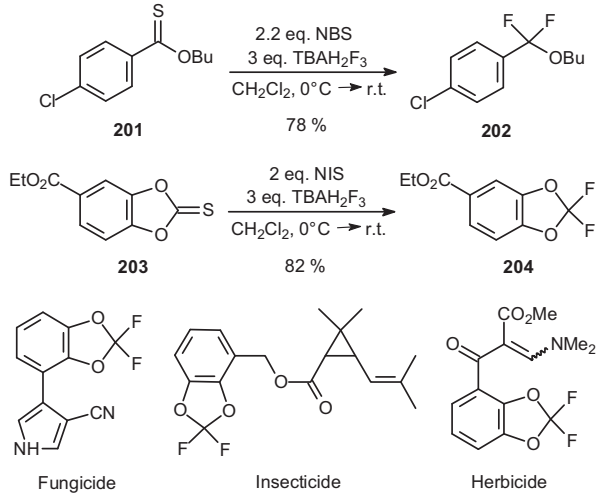
β,β-Difluoro-β-(methylthio)carbonyl compounds **197** were prepared by desulfurization–fluorination reaction of β,β-bis(methylthio)carbonyl compounds **195** with $Hg(OCOCF_3)_2$ and pyridine·6HF in good yields. The reaction proceeds *via* hydrogen fluoride addition to dithioacetals **195** giving β-fluoro-β,β-bis(methylthio)ketones **196**, which were then converted to the final product **197** by desulfurization–fluorination caused by $Hg(OCOCF_3)_2$ as electrophile and the amine/HF reagent as fluoride source. Bromofluorination of the double bond of the β,β-bis(methylthio)carbonyl compounds **195** occurred, when DBH or NBS were used as electrophiles (Scheme 70) [149].

The reaction of the 3-hydroxy-3-phenyltrithio orthoester (**198**) (formed from corresponding epoxides and the lithium salt of trithio orthoformiate) with DBH and Olah's reagent led to stepwise replacement of one (**199**) or two methylthio groups by fluoride (**200**) (Scheme 71) [150].

Starting from thioesters **201** or thiocarbonates **203** difluoro alkylethers **202** or difluoromethylenedioxy compounds **204** were



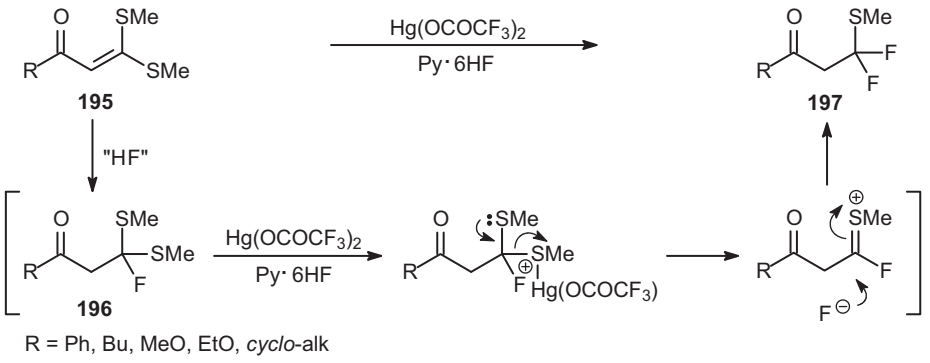
Scheme 71. Fluorination of 3-hydroxy trithio orthoester **198** with DBH/Olah's reagent.



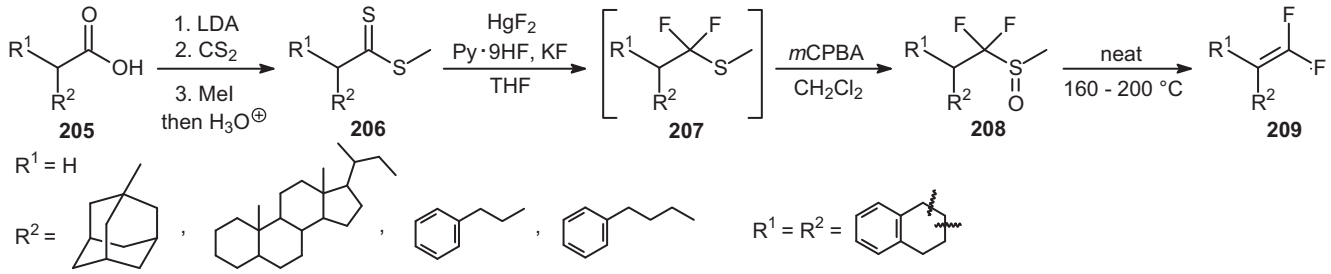
Scheme 72. Synthesis of difluoroalkyl ethers **202** and difluoromethylenedioxy compounds **204**.

synthesized by reaction with NBS (or NIS) and $TBAH_2F_3$. A collection of bioactive substances prepared by this fluorination approach are depicted in Scheme 72 [151]. Also deoxofluor in the presence of a catalytic amount of $SbCl_3$ [152] or Py·BrF_3 [132] were applicable for the oxidative desulfurization–difluorination of thiocarbonyl compounds.

McCarthy et al. discovered a new route for the synthesis of 1,1-difluoroolefins **209** from carboxylic acids **205**. The key step involved the conversion of a dithioester **206** to an α,α-difluoro sulfide **207** with HgF_2 and Olah's reagent. Compound **207** was oxidized to sulfoxide **208** and eliminated to **209** in high yields (Scheme 72) [153] (Scheme 73).



Scheme 70. Preparation of β,β-difluoro-β-(methylthio)carbonyl compounds **197**.



Scheme 73. Synthesis of 1,1-difluoroolefins **209** from carboxylic acids **205**.

4.4. Oxidative desulfurization–difluorination of sulfides

Different ω-substituted alkyl aryl sulfides **210** were directly transformed to terminal 1,1-difluoroalkanes **211** using the reagent combination of DBH and Olah's reagent. As a competing reaction, introduction of a bromide formed in the first reaction step or by reaction of DBH and Olah's reagent [99] led to the *gem*-bromofluorides **212** as a minor product. Higher reaction temperatures (30–45 °C) and longer reaction times were necessary to complete the conversion of the sulfides with less electron-withdrawing or with electron-releasing substituents in the *para*-position of the phenyl ring (Table 8) [98,154].

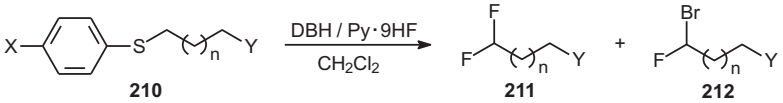
These oxidative desulfurization–difluorination reactions of alkyl aryl sulfides **210** involve the oxidation of the α-carbon of sulfur (fluoro-Pummerer reaction) and a subsequent nucleophilic substitution of the arylthio group by fluoride (Scheme 74). Thus, during the difluorination reaction the α-carbon is oxidized from the oxidation state of an alcohol to that of an aldehyde. By then, such an oxidation step was not observed in desulfurization–fluorination reactions. In contrast, both the anodic and other chemical desulfurization–fluorination reactions do need thioacetals or aldehyde derived starting materials to form geminal difluorides of type **211**. While the oxidative attack takes place at the sulfur atom, the α-carbon to sulfur retains its oxidation state [39,126,129,137,138,145].

Applying this oxidative desulfurization–difluorination approach (3 equiv of DBH, 6 equiv of Py·9HF) to the (2*S*)-prolinol derived *p*-chlorophenyl sulfide **213** gave (2*S*)-2-difluoromethyl pyrrolidine **214** (33% yield), (2*S*)-dibromofluoromethyl pyrrolidine **215** (13% yield) and 3-fluoro-*N*-tosylpiperidine **216** (16% yield). Lowering both the amounts of electrophile and fluorinating reagent gave the dibromofluoride **215** exclusively. Increasing the amount of Olah's reagent implicated the formation of the ring expanded monofluoro substituted piperidine, monobrominated in *meta*-position at the tosyl group (Scheme 75) [133].

Subjection of an *N*-phthalimide protected *S*-phenylcysteine derivative **217** to the standard oxidative desulfurization–difluorination conditions did afford only traces of the expected 3,3-difluoro-alanine derivative **218**. The reaction led mainly to α,α-dibromo-α',α'-difluoroalkylamide **219** exhibiting an unique, so far not known structure motif by formal loss of a phenylthiomethyl group (Scheme 76). The formation of this product is suggested to involve a sulfur assisted deoxygenation-difluorination of an imino oxygen, mediated by the close proximity of one of the carbonyl oxygens of the phthalimido moiety to the sulfur, and a haloform reaction-like carbon–carbon bond fission as key steps [133].

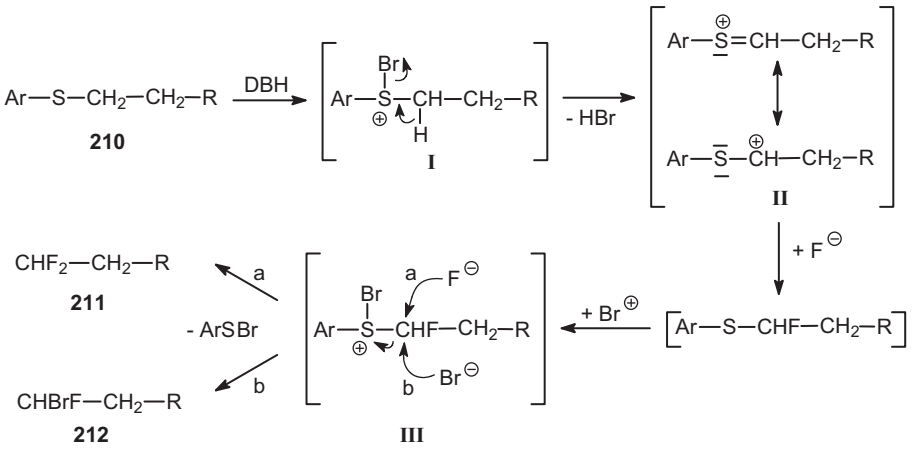
Recently, another desulfurization–difluorination of benzyl sulfides **220**, having an electron-withdrawing group in α-position, such as an ester, a ketone, a nitrile, or an amide with IF_5 in hexane or dichloromethane (Scheme 77) [155]. A Pummerer-type

Table 8
Oxidative desulfurization–difluorination of various ω-substituted alkyl aryl sulfides **210**.

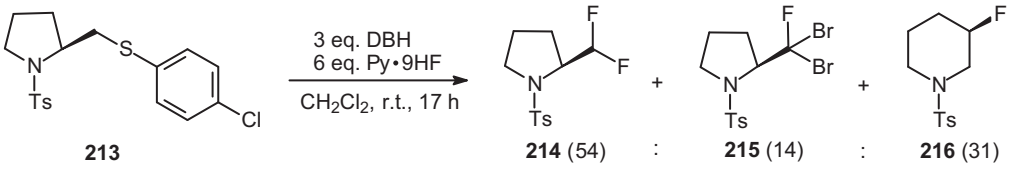


Entry	**210**	X	Y	*n*	Reaction conditions	Crude product (GC %)[a]		Yield [%][b]
						211	**212**	
1	**a**	NO_2	Br	10	2 h, r.t.	81	19	68
2	**b**	Cl	Br	10	5 h, 30 °C	87	13	–[c]
3	**c**	F	Br	10	5 h, 30 °C	93	7	92
4	**d**	CH_3	Br	10	29 h, r.t.	86	14	–[c]
5	**e**	NO_2	Br	9	2 h, r.t.	86	14	86
6	**f**	NO_2	Br	3	20 h, r.t.	52	48	51
7	**g**	F	Br	3	20 h, r.t.	75	25	42
8	**h**	NO_2	Br	13	20 h, r.t.	48	52	23
9	**i**	NO_2	COOMe	8	4.5 h, r.t.	60	40	54
10	**j**	Cl	COOMe	8	18 h, r.t.	95	5	80
11	**k**	F	COOMe	8	18 h, r.t.	80	20	–[c]
12	**l**	Cl	OMe	9	18 h, r.t.	94	6	93
13	**m**	Cl	PhthN	9	18 h, r.t.	88	12	88
14	**n**	Cl	$OPhNO_2$	10	18 h, r.t.	96[d]	4	38[d]

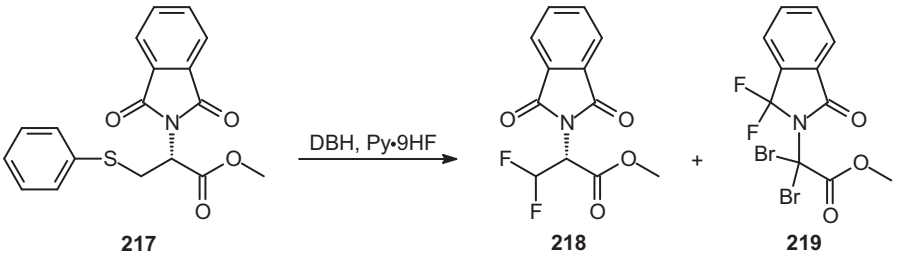
[a] The ratio is calibrated to 100%. Approximately 10% of unidentified byproduct was also found by GC of the crude product mixture after aqueous workup.
[b] Isolated yield of difluoride **211**.
[c] Aliquots for reaction control were taken; no yields determined.
[d] Compound **211n** with monobrominated phenyl ring (ratio by ^{19}F NMR).



Scheme 74. Suggested mechanism of formation of *gem*-difluorides **211** and *gem*-bromofluorides **212**.



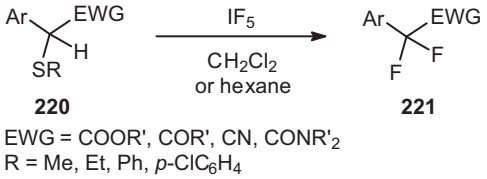
Scheme 75. Oxidative desulfurization–fluorination of (2*S*)-prolinol derived sulfide **213**.



Scheme 76. Formation of α,α-dibromo-α',α'-difluoroaklylamide **219**.

fluorination and a desulfurization–fluorination reaction occurred successively to give *gem*-difluoro compounds **221** selectively. The desulfurization reaction was successful with methyl sulfides, as well as aryl sulfides with 1-naphthyl, bromophenyl and phenyl groups. The presence of an aryl group, stabilizing the carbocation, generated by the elimination of the sulfur group and accelerating the desulfurization reaction, seemed to be critical for the desulfurizing difluorination reaction. When butyl methylthioacetate was subjected to reaction with IF_5, the Pummerer-type difluorination reaction proceeded without desulfurization to give butyl α,α-difluoro-α-methylthioacetate selectively [155].

Later this method was applied to (1-aryl-1-hydroperfluoroalkyl)sulfides **223**, obtained by Friedels-Crafts reaction from (1-chloro-1-hydroperfluoroalkyl)sulfides **222**. As the perfluoro group in the α-aryl sulfides **223** is a strong electron-withdrawing group,

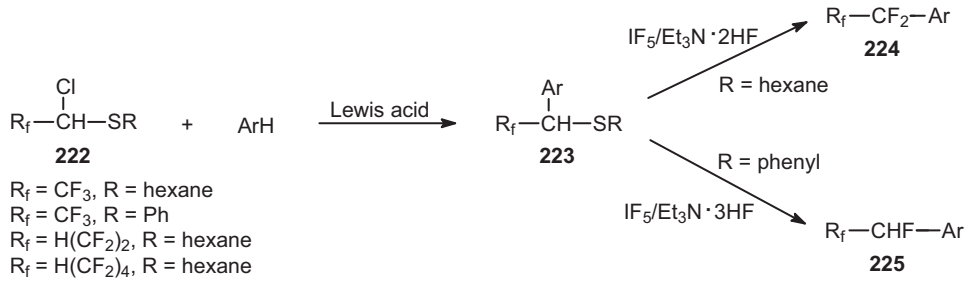


Scheme 77. Desulfurization–difluorination reaction of benzyl sulfides **220** using IF_5.

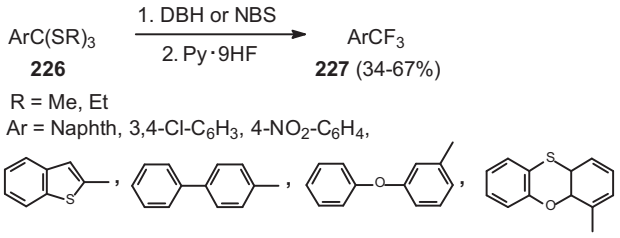
subsequent desulfurization–difluorination with $IF_5/Et_3N{\cdot}nHF$ allowed the introduction of perfluoroethyl, hexafluoropropyl and decafluoropentyl groups to various aromatic compounds. Depending on the quality of the leaving sulfanyl group, monofluorination or difluorination took place. Due to a better leaving ability of the phenylsulfanyl group, initially desulfurization–fluorination reaction took place to afford **225**. Starting sulfide **222** bearing a hexylsulfanyl leaving group led to the difluorinated product **224** *via* hydrogen substitution and substitution of the alkylsulfanyl group by fluoride. The monofluorinated product **225** was formed as a minor by-product of these reactions (Scheme 78). Additionally selective perfluoroethylation of uracil at the 5-position was performed in this way [156].

5. Oxidative desulfurization–trifluorination

Organic molecules bearing a trifluoromethyl group often exhibit high lipophilicity and increased metabolic stability compared to the parent compounds with a methyl moiety. Incorporation of this group into a molecule generally modifies the biochemical properties, while the steric distortion to the methyl group is not too big. Therefore, a variety of trifluoromethylated pharmaceuticals and agrochemicals have been developed in recent years. Besides different methods for the introduction of the whole CF_3 group into organic molecules [157]



Scheme 78. Synthesis of perfluorinated aromatic compounds **224** and **225** with $IF_5/Et_3N{\cdot}nHF$.



Scheme 79. Preparation of trifluoromethyl compounds **227** by treatment of aromatic trithio orthoesters **226** with DBH or NBS and Olah's reagent.

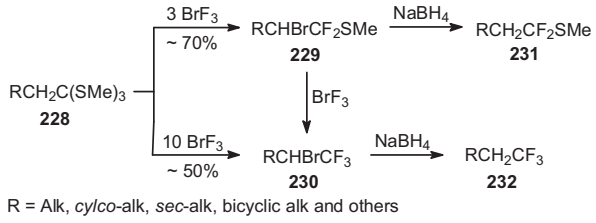
the oxidative desulfurization–trifluorination approach can be utilized for the construction of CF_3 groups in strategic positions of various molecules [38,105,125].

5.1. Oxidative desulfurization–trifluorination of trithio orthoesters

First applications of the oxidative desulfurization–trifluorination reaction to orthothioesters were described by McCarthy et al. in 1986. Aromatic trifluoromethyl compounds **227** were prepared by treatment of aromatic trithio orthoesters **226** with DBH or NBS and Olah's reagent in moderate yields (Scheme 79). Trifluorination of the trithio orthoesters takes place *via* three succeeding oxidative desulfurization–fluorination reactions, starting with the activation of the C–S bond by the halonium species and followed by a nucleophilic substitution with fluoride.

The hypervalent bromine trifluoride is also applicable for the construction of the CF_3 group. Reaction of trithio orthoesters **228** with 3 equiv of BrF_3 resulted mainly in the introduction of two fluorine atoms to form **229**. When using 10 equiv of BrF_3 all three sulfur atoms were substituted by fluoride and **230** was isolated. The more CF bonds are formed the stronger and less basic the remaining carbon–sulfur bonds become. Therefore, the reaction requires higher concentration of BrF_3 to proceed. The products obtained in this way can be reduced to bromine free compounds **231** and **232** using $NaBH_4$ (Scheme 80) [158].

Starting from the aliphatic trithio orthoester **233** the construction of an [^{18}F]-labeled trifluoride **235** was achieved using 2 equiv DBH and 7 equiv [^{18}F]-HF·pyridine for the introduction of [^{18}F]fluoride in the first reaction step. Another 4 equiv of DBH and 140 equiv of pyridine/HF were needed for the conversion of **234** to the trifluoro compound **235**. The decay corrected radiochemical yield of the [^{18}F]-labeled product **235** was as low as approximately 1.6% in 25 min [159] (Scheme 81).

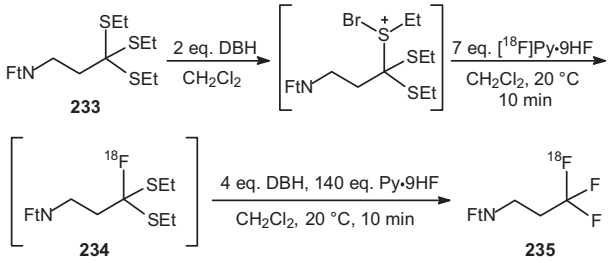


Scheme 80. Reactions of tris(methylthio)alkanes **228** with BrF_3.

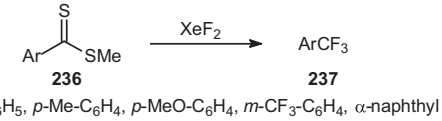
5.2. Oxidative desulfurization–trifluorination of dithioesters

As early as in 1990, Zupan and Bregar reported that treatment of aromatic dithiocarboxylic acid derivatives **236** with xenon difluoride gave trifluoromethylated aromatic compounds **237** in 40–77% yield (Scheme 82) [160].

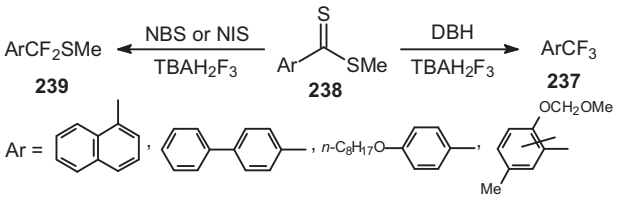
This type of compounds was also obtained by oxidative desulfurization–trifluorination reaction of methyl arenedithiocarboxylates **238** using DBH and $TBAH_2F_3$. In contrast, the use of NBS or NIS instead of DBH afforded difluoro(methylthio)methyl substituted aromatics **239** (Scheme 83). In case of electron rich aromatic substrates additional bromination of the ring occurred. The difluorinated products **239**, assumed to be intermediates of the desulfurization–trifluorination reaction, could be converted into the corresponding trifluorides **237** in a second desulfurization fluorination reaction [113].



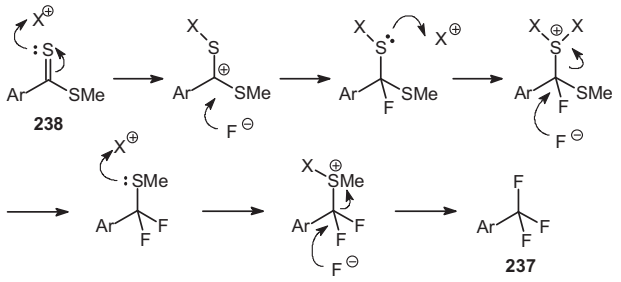
Scheme 81. Synthesis of [^{18}F]substituted [^{18}F]-*N*-phthalimido-3,3,3-trifluoropropylamine (**235**) by desulfurization/[^{18}F]fluorination of a trithio orthoester **233**.



Scheme 82. Conversion of aromatic dithiocarboxylic acids to trifluoromethylated aromatics with XeF_2.



Scheme 83. Oxidative desulfurization–fluorination of methyl arenedithiocarboxylates **238**.

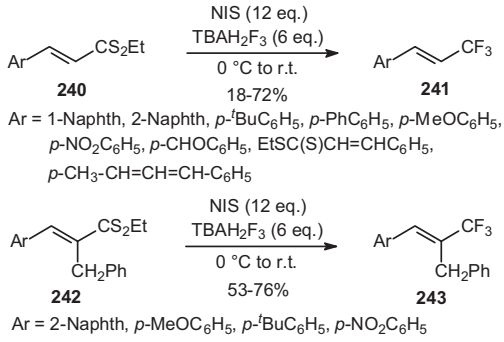


Scheme 84. Assumed mechanism of formation of trifluoromethyl aryl compounds **237** from **238**.

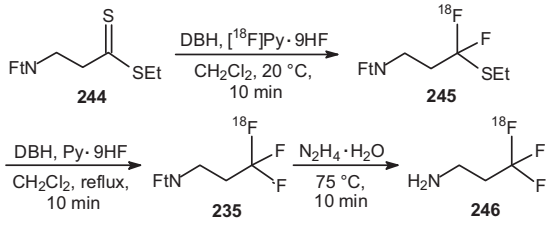
Thus, the supposed mechanism (Scheme 84) of formation of trifluoromethyl compounds is similar to the pathway discussed for the trithio orthoesters.

Likewise dithiocinnamates **240** and its 2-benzyl derivatives **242** were successfully adopted for oxidative desulfurization–trifluorination reactions using NIS and $TBAH_2F_3$ to give 3,3,3-trifluoropropenyl aromatic compounds **241** and **243**, respectively. Halogenation of the aromatic ring and halofluorination of the C=C double bond did not take place under these conditions. Electron-donating groups accelerated the trifluorination reaction, while substrates with electron-withdrawing groups gave difluorinated products, which did not give the trifluoromethyl compounds even after prolonged reaction time or with excess of reagents, due to the reduced electron density at the reaction center (Scheme 85) [161].

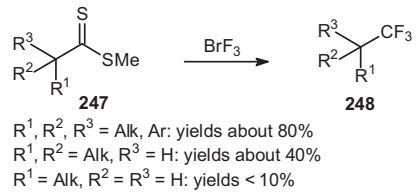
This type of reaction was also applied for radiolabeling of trifluoromethyl groups. Accordingly [^{18}F]trifluoropropylamine (**247**) was prepared in three steps from ethyl *N*-phthalimido-3-aminopropane dithioate (**244**) by repeated oxidative desulfurization-[^{18}F]-fluorination reactions with DBH and Py/[^{18}F]HF *via* **245** and hydrazinolysis of the resulting [^{18}F]-*N*-phthalimido-3-trifluoropropylamine **235** within 70 min in approximately 5% radiochemical yield (Scheme 86) [162].



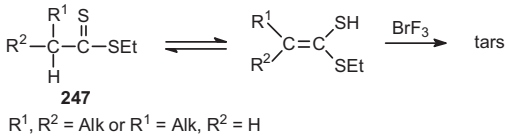
Scheme 85. Oxidative desulfurization–trifluorination of dithiocinnamates **240** and **242**.



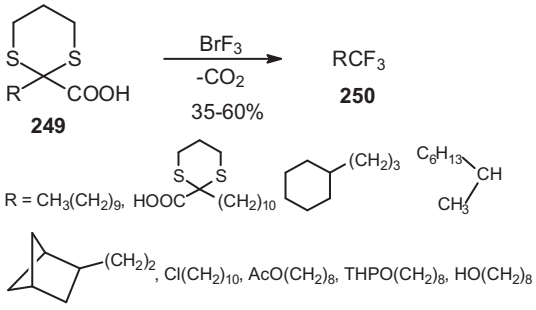
Scheme 86. Synthesis of [^{18}F]trifluoropropylamine (**246**) by desulfurization [^{18}F]fluorination of dithioester **244**.



Scheme 87. Oxidative desulfurization–trifluorination of dithioesters **247** with BrF_3.



Scheme 88. Mechanism of side reactions with BrF_3.



Scheme 89. Decarboxylative desulfurization–trifluorination reactions of 2-(1,3-dithianyl)-carboxylic acid derivatives **249**.

The reaction of dithioesters **247** with BrF_3 gave high yields of **248** (about 80%) when tertiary or deactivated in the aromatic ring compounds were used. The yields are lower with secondary ones (about 40%) and less than 10% for primary dithioesters (Scheme 87) [163].

Secondary and primary dithioesters **247** are prone to tautomerize to the enedithiol structure giving rise to a variety of competing reactions with BrF_3 resulting in tars (Scheme 88) [163].

The application of the desulfurization–fluorination conditions with BrF_3 to various 2-(1,3-dithianyl)carboxylic acid derivatives **249** led to unique decarboxylative desulfurization–trifluorination reactions yielding trifluoromethyl substituted compounds **250** (Scheme 89) [164].

5.3. Oxidative desulfurization–trifluorination of dithiocarbonates and dithiocarbamates

The oxidative desulfurization–trifluorination approach using reagent combinations of *N*-haloimides and fluorinating reagents like $TBAH_2F_3$ or other amine/HF reagents as well as BrF_3 can be efficiently transferred to various dithiocarbonates and dithiocarbamates to synthesize trifluoromethyl ethers [165] and trifluoromethylamine derivatives [166]. These reactions have been extensively reviewed in several articles [38,105,125] and will not be discussed in this review.

Acknowledgements

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