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Review

New trends in the chemistry of α-fluorinated ethers, thioethers, amines and phosphines

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Dedicated to the memory of Professor L. M. Yagupol'skii, a pioneer in fluorine chemistry.

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ABSTRACT

Fluorine, the most electronegative element plays nowadays a key role in pharmaceutical, agrochemical and material sciences. About 20% of all pharmaceuticals and about 30% of agrochemicals under development or recently introduced on the market contain fluorine. However, when one examines the relevant structures more closely, one quickly recognizes a structural monotony. The same fluorine bearing aromatic or heterocyclic "cores" appear over and over again. The search for novel molecules having "emergent" fluorinated groups and the development of an efficient access toward them is a challenging task for industrial as well as academic laboratories. For example, the trifluoromethoxy group finds increased utility as a substituent in bioactives, but it is still perhaps the least well understood fluorine substituent in currency. The present review will give an updated overview on the synthesis of α-fluorinated ethers, thioethers, amines and phosphines.

Contents

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1. Introduction

As "a small atom with a big ego" [1], fluorine plays increasingly important roles in many fields such as agrochemical, medicinal and pharmaceutical research and material science [2,3].

The last 30 years were marked by an increased use of fluorinated compounds as well in agrochemical research as in pharmaceutical chemistry. Although mainly single fluorine atoms or a trifluoromethyl group have been introduced in various molecules, the introduction of (difluoromethoxy)- or (trifluoromethoxy)aryl fragments into crop production products were realized. The successful use of α-fluorinated ethers, thioethers, and amines in active ingredients for modern agrochemicals is witnessed by various commercial products like insecticides, fungicides, plant growth regulators, and herbicides.

According to the 12th and 13th edition of the pesticide manual [4], five pesticides containing OCF_3-groups are so far registered. The proinsecticide *Indoxacarb* [5] acting as a voltage-gated sodium channel (vgSCh) modulator, the insect growth regulant (IGR) *Triflumuron* [4,6], the plant growth regulator *Flurprimidol* [7], the inhibitor of the respiratory chain and succinate dehydrogenase (SD) *Thifluzamide* [8] as well as the inhibitor of acetolactate synthase (ALS) *Flucarbazone-sodium* (Fig. 1) [9].

The difluoromethoxy function can be found in the volted-gated sodium channel modulator *Flucythrinate* [10]. Among the fungicides, one has to mention *Tetraconazole* [11] and the protein kinase inhibitor *Fludioxonil* [12], bearing a difluoromethylenedioxo unit. *Primisulfuron-methyl* [13], a selective fluorosulfonylurea herbicide bears two difluoromethoxy subunits (Fig. 2).

The trifluoromethyl sulfoxide-containing arylaminopyrazole *Fipronil* (Fig. 3) [14,15], launched in 1993 by Rhone-Poulenc, is one of the most important non-competitive GABA antagonist in insects.

There has also been an enormous increase of α-fluorinated ethers and thioethers in medicinal chemistry. However, examples of trifluoromethyl ethers in pharmaceutical chemistry are still quite rare [16,17]. They were rapidly used as volatile, non-toxic, non-explosive and fast-acting inhalation anaesthetics and anti-inflammatory agents. Numerous new α-fluorine containing compounds have been prepared, marketed as drugs with enhanced effectiveness often coupled with diminished side-effects. Today, significant application areas for α-fluorinated ether are analgesics, anaesthetics, cardiovascular drugs, respiratory drugs, psychopharmacologic drugs, neurological drugs, gastrointestinal drugs and anti-infective therapeutics.

For example the difluoromethoxy bearing *Riodipine* [18] is known as Ca^{2+} antagonist with antihypertensive and anti-anginal effects. The cardio protective *Celikalim* is a putative K^+ channel activator [19]. The difluoromethoxy-substituted *Roflumilast* [20] is a specific PDE4 inhibitor being developed for the potential treatment of asthma and chronic obstructive pulmonary disease (COPD). The OCF_3-containing piperidine *CP-122,721* [21–23], an antagonist at the neurokinin-1 (NK_1) receptor, has a 400-fold higher activity than its non-fluorinated parent compound (CP-99,994). *Riluzole*, a OCF_3-substituted 2-amino-benzothiazole, is the first drug approved for treatment of Amyotropic Lateral Sclerosis, to treat schizophrenia and other neurological diseases [24]. (−)-*Pantoprazole* [25–27], an irreversible proton pump inhibitor, reached its first market worldwide for acute treatment of gastric and duodenal ulcers and gastroesophageal reflux disease (Fig. 4).

As α-fluorinated thioethers one has to mention the *meta*-SCF_3-substituted 2-phenylethylamines like *Tiflorex* [28] used to treat anorexia nervosa. *Triflamizole* [29,30] and *Triflumidate* [31], bearing a $-SO_2CF_2CHF_2$ and a $-SO_2CF_3$ moiety, respectively, are used for their anti-inflammatory activity. *Flomoxef sodium* [32] is a $SCHF_2$-

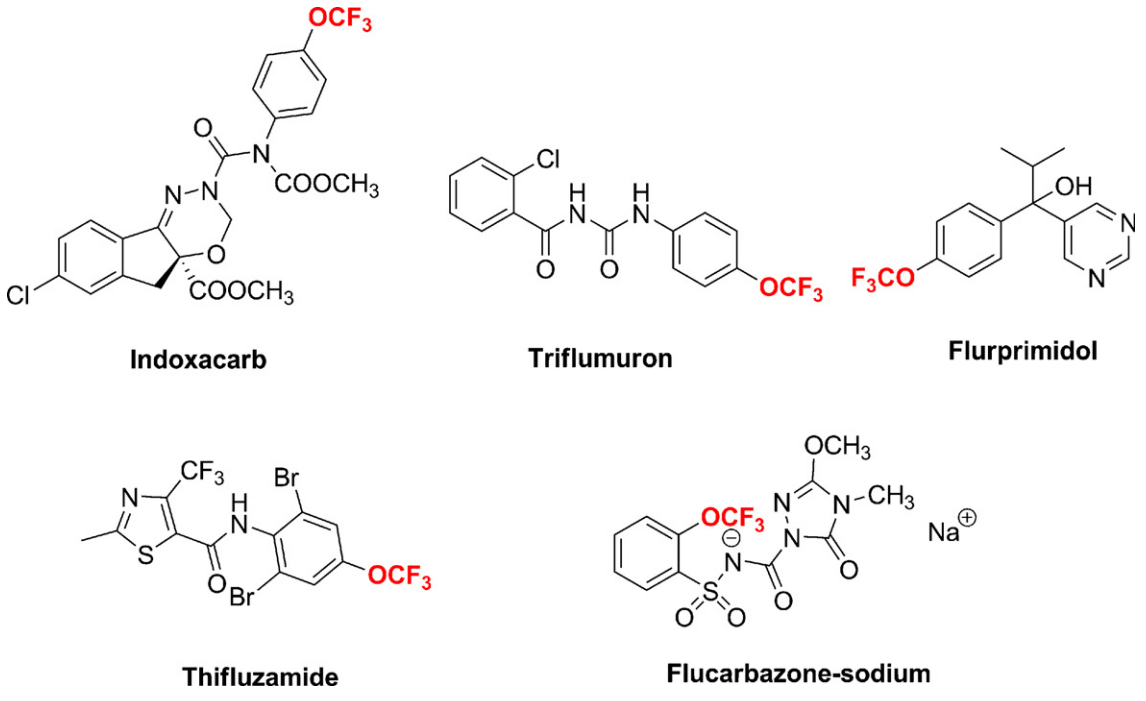


Fig. 1. OCF_3-bearing agrochemicals.

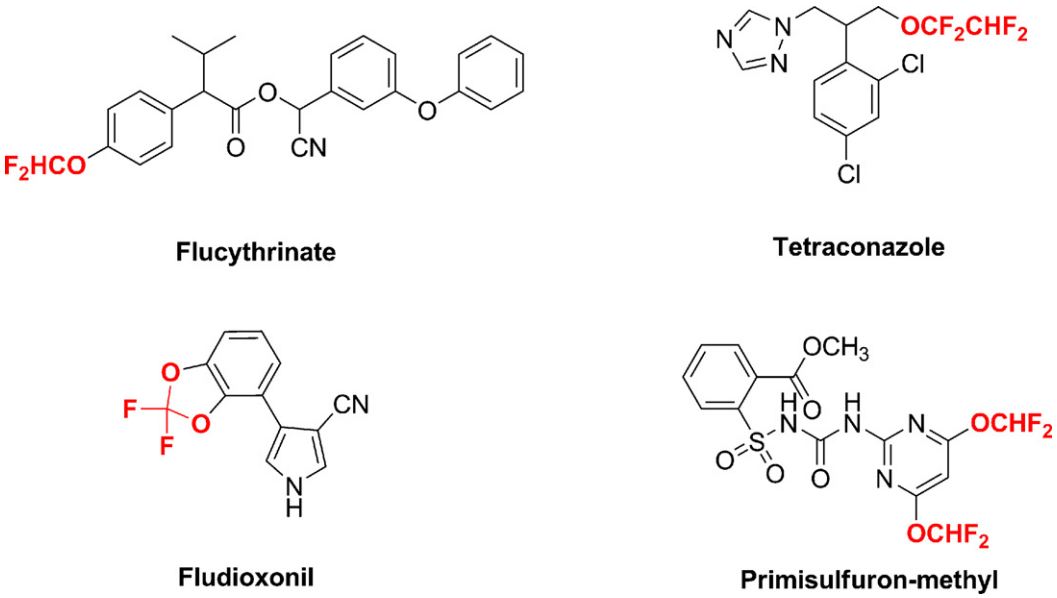


Fig. 2. $OCHF_2$-bearing agrochemicals.

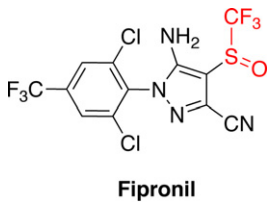


Fig. 3. Fipronil as an example of a *S*-perfluoroalkyl substituted agrochemical.

substituted β-lactamase-resistant oxcephalosporin antibiotic (Fig. 5).

In the field of α-fluorinated amines, the perfluorotripropylamine, $N(CF_2–CF_2–CF_3)_3$, *Perfluamine* (Fluosol DA®) can be mentioned, which acts as a so-called plasma volume expander, an oxygen carrying agent for erythrocyte substitution (blood substitute) [33].

What is the reason, why α-fluorinated ethers, thioethers and amines become more and more interesting from an industrial point of view? Without pointing out the often reported virtues of fluorine introduction in bioactives [34,35], we wish to insist on the

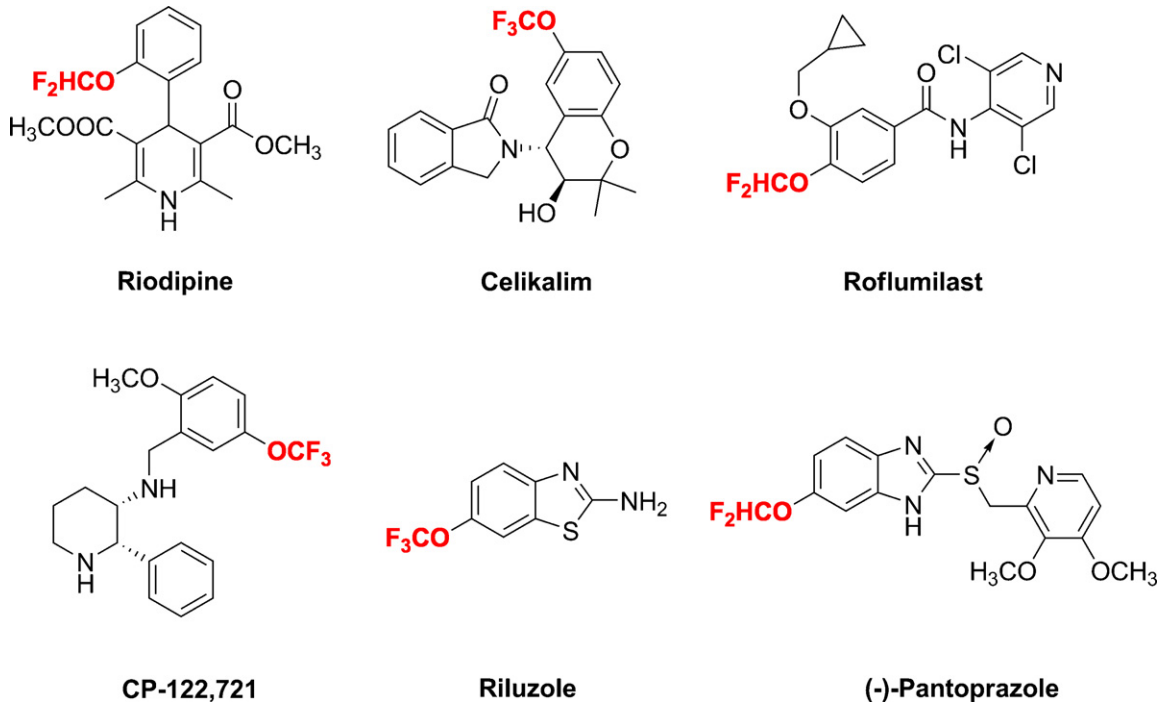


Fig. 4. α-Fluorinated ethers as pharmaceuticals.

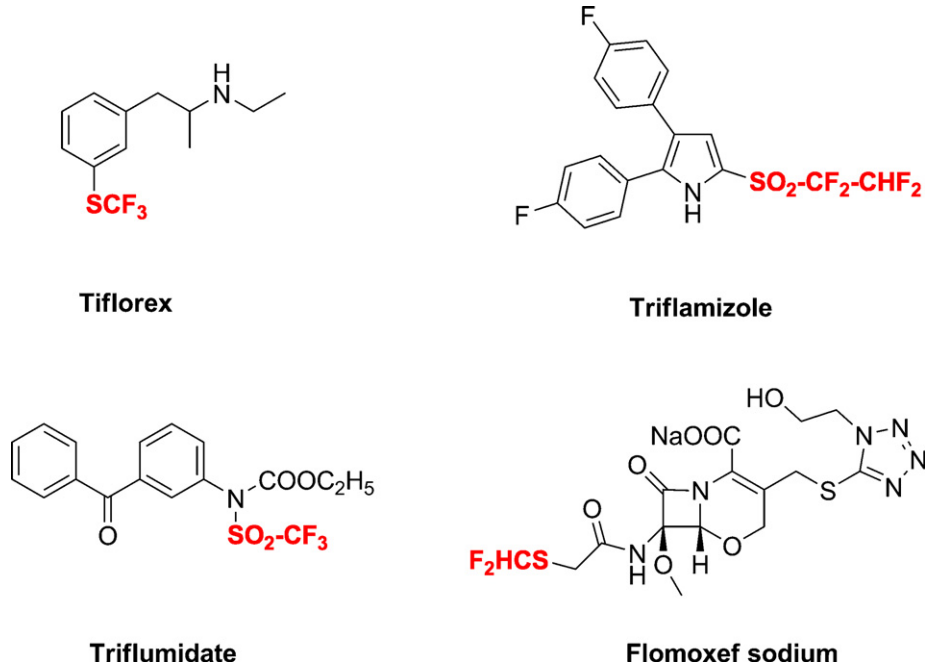


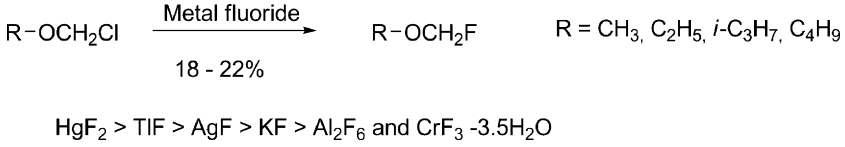
Fig. 5. α-Fluorinated thioethers as pharmaceuticals.

Fig. 6. Anomeric effect of α-fluorinated ethers.

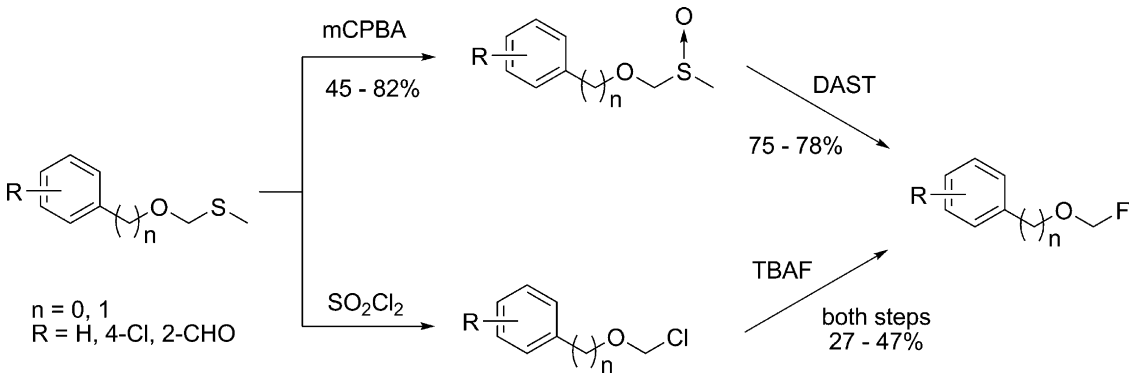
particularly intriguing unique electron distribution. The geminal combination of an alkoxy or aryloxy group with a fluorine atom offers the possibility of bonding/non-bonding resonance which can be formally expressed by the superposition of a covalent and an ionic limiting structure. This phenomenon which reveals itself by a lengthening and weakening of the carbon–halogen bond and a shortening and strengthening of the carbon–oxygen bond is known as the *anomeric effect* (Fig. 6) [16]. The oxygen atom may be replaced by any other donor element, in particular by sulphur or nitrogen.

On the basis of its electronic properties, which are close to those of chlorine or a fluorine atom [36], the trifluoromethoxy group has been referred to as a super- [37] or a pseudo-halogen [38].

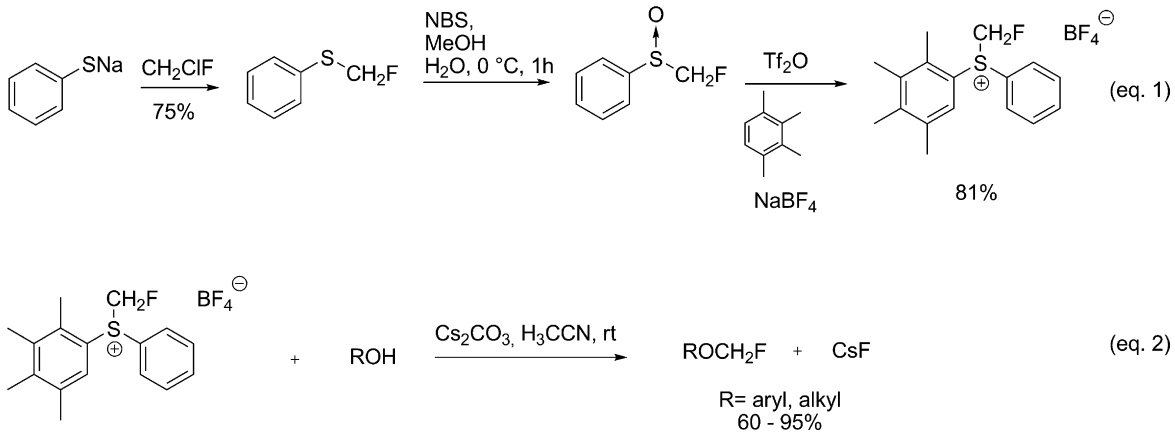
The fluorinated carbon adjacent to an oxygen atom increases lipophilicity as shown by the high value of the OCF_3 hydrophobic substituent parameter [39,40]. While both trifluoromethyl and trifluoromethoxy substituents invariably boost the lipophilicity, single fluorine atoms may alter this parameter in either direction. If the halogen occupies a vicinal or homovicinal position with respect to a hydroxy, alkoxy or carbonyl oxygen atom, it enhances the solvation energy in water more than in organic solvents (such as 1-octanol or chloroform) and hence lowers the lipophilicity [41]. It



Scheme 1.



Scheme 2.



Scheme 3.

appears that the OCF_3 substituent is far more lipophilic (π = +1.04) than the halogens and lies between a CF_3 (π = +0.88) and a SCF_3 (π = +1.44) group. It may thus replace advantageously a fluorine atom (π = +0.14) in most molecules with the benefit of increased lipid solubility.

For reasons of thematic coherence the scope of the present review restricts itself to review the synthesis of α-fluorine bearing ethers, sulphides, amines and phosphines. *N*-Fluoro-, difluoro- and trifluoromethylated heterocycles will not be discussed in this review. A detailed description of the steric and electronic properties of these groups [16], their medicinal application [17] and reactivity [42] was recently reviewed in detail and will not be presented here.

2. Preparation of α-fluorinated ethers, thioethers, amines and phosphines

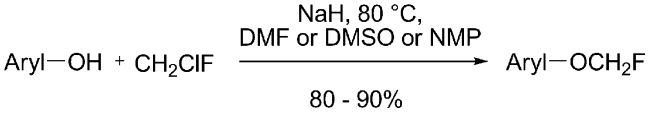
2.1. α-Fluoromethyl ethers

Fluoromethyl ethers can be obtained from chloromethyl ethers by nucleophilic substitution with metal fluoride. The difficulty is in finding a metal fluoride which will exchange its fluorine for halogen at a temperature low enough so as to minimize the decomposition of both the reactant and product. Mercuric fluoride was found to exchange its fluorine for the α-chlorine in some halogenated ethers. Compounds of the type $Cl_3CCHFOR$ and H_2CFOR were prepared (Scheme 1) [43,44].

α-Fluoro ethers can also be made in good yields from α-alkoxy sulfoxides by replacement of the sulfinyl group using diethylaminosulphur trifluoride (DAST; Scheme 2) [43].

Without the α-alkoxy group in the sulfoxide for stabilization of the intermediate carbocation, α-fluoro thioethers are obtained *via* a Fluoro-Pummerer reaction (see following section) [45,46].

Compared with electrophilic trifluoromethylation and difluoromethylation (see below), much less has been known about electrophilic monofluoromethylation (the electrophilic transfer of 'CH_2F^-' building block). Prakash disclosed recently an efficient access to monofluoromethylated ethers using *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate as electrophilic monofluoromethylation reagent (Scheme 3, Eq. (1)) [47]. This reagent was prepared *via* the nucleophilic substitution ($S_{RN}1$) reaction of liquefied CH_2FCl with sodium thiophenolate. The unstable monofluoromethyl sulphide was, without isolation, oxidized to the corresponding sulfoxide using *N*-bromosuccinimide. Its subsequent Friedel–Crafts type reaction with 1,2,3,4-tetramethylbenzene initiated by trifluoromethanesulfonic anhydride and treatment with $NaBF_4$-salt affords the *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate in good yield. The fluoromethylation of alcohols proceeds smoothly in acetonitrile at room temperature with good yields (Scheme 3, Eq. (2)).



Scheme 4.

Recently, the use of chlorofluoromethane as a useful electrophilic monofluoromethylating agent for a variety of *O*-nucleophiles has been reported (Scheme 4) [48]. Although previously several electrophilic monofluoromethylations of oxygen-, sulphur-, nitrogen-, and carbon nucleophiles have been reported with CH_2FI [49–51], CH_2FBr [52–58], CH_2FCl [56,59–61], or CH_2FOSO_2R (R = CF_3, CH_3, tolyl) [55,62] as monofluoromethylating agents, their use was restricted to ^{18}F-labelling.

Benzyl alcohol and its analogues with a non-activated benzene ring were transformed to fluoromethoxy derivatives by reaction with XeF_2. In the course of the reaction, the phenyl group migrates from carbon to oxygen (Scheme 5) [63].

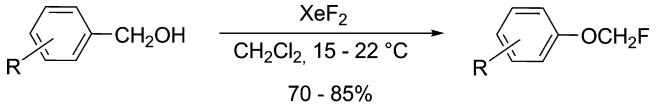
Similarly, substituted fluoromethoxybenzenes were prepared by cleavage of *O*,*S*-acetals, readily obtained by reaction of the phenols with chloromethyl methyl thioether under basic conditions, with xenon difluoride [64]. The cleavage reaction works well with unsubstituted, electron-donor or weak electron-acceptor substituted aromatic rings (Scheme 6).

Finally, replacement of the carboxylic acid function with fluorine by means of xenon difluoride also affords fluoromethyl ethers (Scheme 7) [65,66].

Ochiai reported very recently on the reaction of benzyl alcohol with difluoro-λ^3-bromane (Scheme 8, Eq. (1)). Oxidation to benzaldehyde competes with the more facile oxidative 1,2-phenyl rearrangement that produces fluoromethyl phenyl ether (Scheme 8, Eq. (2)) [67].

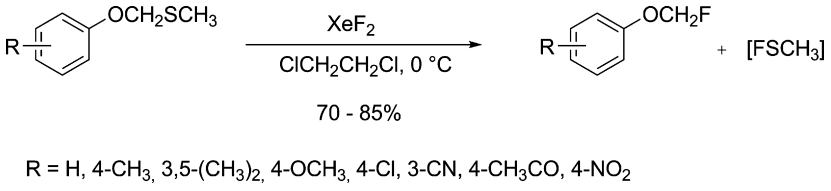
2.2. α-Fluoromethyl thioethers

Fuchigami reported on the regioselective anodic monofluorination of various aryl and alkyl fluoroalkyl sulphides where fluorine

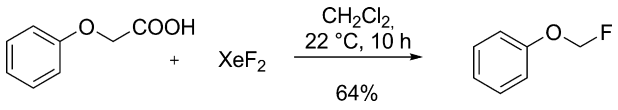


R = H, *o*-, *m*-, *p*-NO_2, p-CF_3, *m*-F

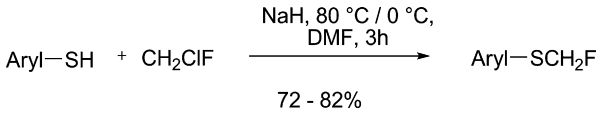
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 9.

was exclusively (aryl sulphides) or preferentially (alkyl sulphides) introduced at the position α to the fluoroalkyl group [68].

The cleavage of *O,S*-acetals by means of xenon difluoride, as described in Section 2.1, may afford α-fluorothioethers when strong electron-withdrawing groups are present on the aromatic ring [64].

Analogously to fluoromethyl ethers, fluoromethyl thioethers are obtained by nucleophilic substitution of chloromethyl sulphides with potassium fluoride [69].

Chlorofluoromethane was also successfully employed in the electrophilic monofluoromethylation of *S*-nucleophiles as described above for *O*-nucleophiles (Scheme 9) [48].

Umemoto could show that *N*-fluoropyridinium salts, most preferably the *N*-fluoro-2,4,6-trimethylpyridinium triflate afford satisfactorily α-fluoro thioethers (Scheme 10) [70].

The reaction of DAST with sulfoxides and sulphides bearing α-hydrogen atoms can also furnish these compounds (Scheme 11) [71]. In this very interesting Fluoro-Pummerer reaction, DAST activates a sulfoxide for fragmentation, similar to the Pummerer reaction, and fluoride then attacks the electrophilic intermediate affording monofluoromethylated sulphides which can be reoxidized to sulfoxides [46,72].

DEOXOFLUOR reacts with sulphides in a manner analogous to DAST to produce α-fluorothioethers [73]. Excellent yields were obtained on fluorination of various aryl–alkyl and dialkyl sulphides in CH_2Cl_2 containing 0.01 equiv of $SbCl_3$ catalyst (Scheme 12) [74]. Most of the α-fluorothioethers are not stable to standard purification techniques and were oxidized to the sulfoxides or sulfones prior to isolation [75].

Upon treatment under oxidative desulfurization–fluorination conditions ($Bu_4NH_2F_3$ and 1,3-dibromo-5,5-dimethylhydantoin), organic sulphides undergo also a Pummerer-type rearrangement, followed by fluorination, to give α-fluoro sulphides (Scheme 13) [76].

The α-fluorination of thioethers can also be realized, as it was shown by Lal, with Selectfluor. It has been found that sulphides possessing α-hydrogens afford rapidly with F-TEDA-BF_4 (Selectfluor) a fluorosulfonium salt which undergoes a Pummerer-like rearrangement on treatment with base (triethylamine or DBU) to produce the α-fluoro thioethers (Scheme 14) [77].

Hara could show that the novel fluorinating agent IF_5-Et_3N-3HF allows selective mono- and difluorination by choosing the reaction conditions. Various substrates have been studied carrying electron-withdrawing groups such as ester, amide, ketone, nitrile, sulfones or trifluoromethyl. Because more than one fluorine atom on IF_5 is used, a large excess amount of the reagent is not necessary, even for difluorination reactions (Scheme 15) [78–80].

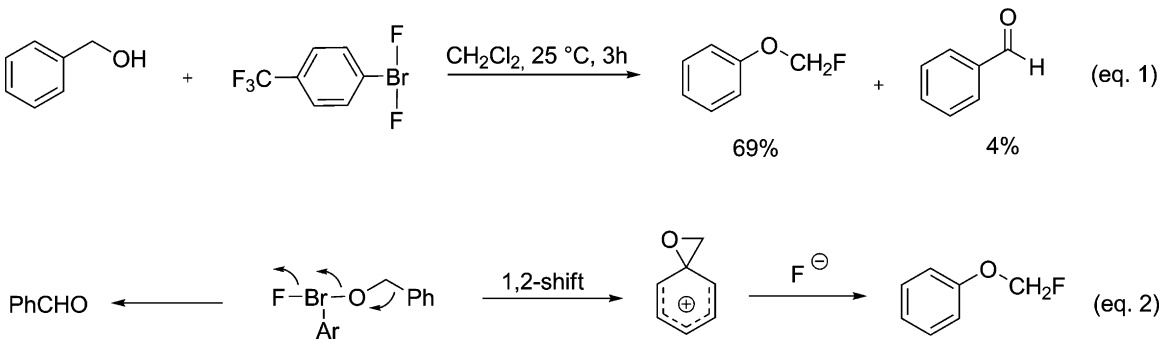
2.3. α-Fluoromethyl amines

As outlined in Section 2.1 for α-fluoromethyl ethers (Scheme 3, Eq. (2)), fluoromethyl amines can be prepared using *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate (Scheme 16) [47].

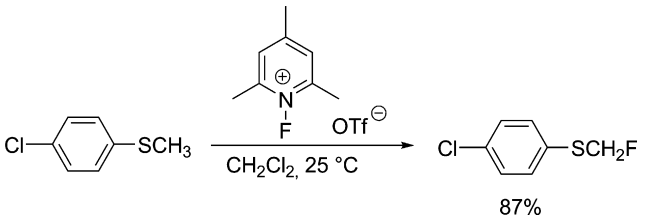
2.4. α-Fluoromethyl phosphines

Triphenylphosphine and/or trialkylphosphines (R = Et, Bu, Oc) react with fluorotrihalomethanes in a three-to-one ratio to produce fluorinated phosphoranium salts in excellent yields (Scheme 17). The mechanism of formation of fluorinated phosphoranium salts is a series of halophilic reactions similar to that of non-fluorine-containing phosphoranium salts [81].

Hydrolysis of the fluorinated phosphoranium salts takes place under mild reaction conditions to produce an equivalent of phosphine oxide and (fluoromethyl)phosphonium salt (Scheme 18) [82].



Scheme 8.



Scheme 10.

As for *O*- and *N*-nucleophiles, triphenylphosphine could be converted into the monofluoromethylated phosphonium salt according to the method described by Prakash (Scheme 19) [47].

(Fluoromethyl)phosphonium salts have also been prepared *via* fluorination of $[Ph_3P^+–CH_2OH]BF_4^-$ with DAST (Scheme 20) [45].

3. Preparation of α-difluorinated ethers, thioethers, amines and phosphines

3.1. α-Difluoromethyl ethers

Difluoromethyl aryl ethers are most conveniently prepared by reaction of the appropriate phenolate with chlorodifluoromethane in the presence of a base such as sodium hydroxide which generates an intermediate difluorocarbene (Scheme 21) [83–85].

α,α-Difluoroethyl aryl ethers and α,α-difluorobenzyl aryl ethers can be prepared by oxidative desulfurization–fluorination [86] of the corresponding xanthogenates or from substituted benzaldehydes by fluorination with sulphur tetrafluoride, bromination and subsequent condensation with phenolate [87].

The reaction of trifluoromethyl zinc bromide ($Zn(CF_3)Br·2CH_3CN$) [88–90] and bis(trifluoromethyl) cadmium ($Cd(CF_3)_2·2CH_3CN$) [91] affords in a convenient procedure difluoromethyl ethers from primary, secondary and tertiary aliphatic alcohols. However, these compounds revealed to be unstable and to decompose in the course of few hours. In contrast, phenols can be conveniently difluoromethylated (Scheme 22, Eq. (1)). The reaction mechanism was suggested to be a successive substitution of fluorine for the phenoxy group, with the primary substitution of one fluorine atom being the carbenoid step (Scheme 22, Eq. (2)). The fluorine abstraction is accelerated by using Lewis acids like $BF_3·OEt_2$. This procedure was successfully applied in the *O*-difluoromethylation of several monosaccharides (Scheme 22, Eq. (3)) [92].

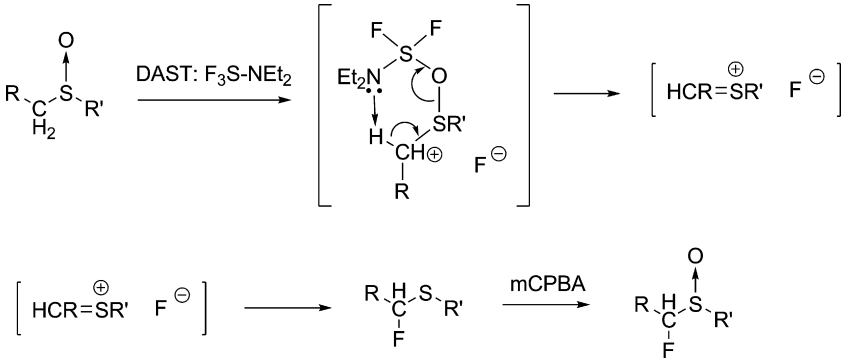
α,α-Difluoroalkyl alkyl ethers have been obtained by the fluorodesulfurization of the corresponding thionoesters. Bis(2-methoxyethyl)aminosulphur trifluoride (DEOXOFLUOR) has been recommended as the reagent of choice for this purpose (Scheme 23) [75,93].

Benzaldehyde and ring non-activated derivatives could be converted with XeF_2 in the presence of excess of HF into the corresponding difluoromethoxy benzene derivatives via migration of the penyl ring (Scheme 24).

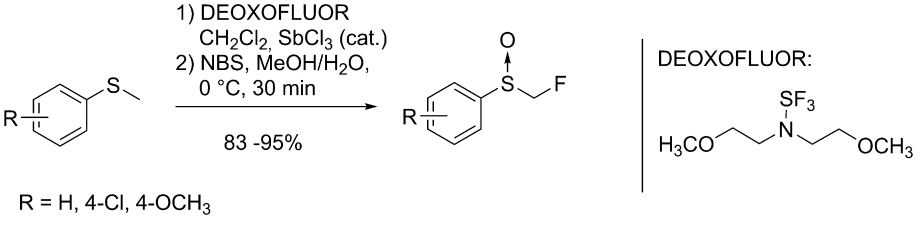
Aryldioxydifluoromethane is prepared *via* a chlorine/fluorine exchange, usually accomplished with antimony trifluoride, on the corresponding dichloro precursor, obtained by radical chlorination. The sequence starting with the conversion of pyrocatechol into 1,3-benzodioxole and the bromination of the latter and leading *via* 5-bromo-2,2-dichloro-1,3-benzodioxole to 5-bromo-2,2-difluoro-1,3-benzodioxole is representative in this respect (Scheme 25) [94–97].

The structurally related 1,1,3,3-tetrafluoro-2-benzofurans and 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxines are made analogously. The readily available precursor 2-benzofurans and 2,3-dihydro-1,4-benzodioxines are perchlorinated at the heterocyclic ring before being subjected to the chlorine/fluorine exchange [98–100].

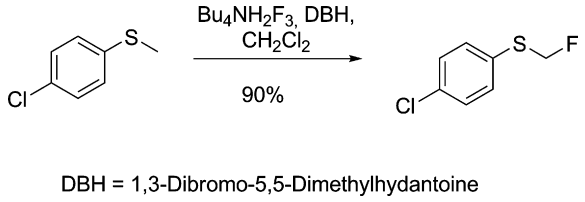
One major effort in modern fluorine chemistry is to develop new non-ODS-based fluoroalkylation methods (ODS = ozone-depleting substances) in order to replace the conventional ODS-based ones. For instance, most of the currently known difluorocarbene reagents for *O*- and *N*-difluoromethylations, such as chlorodifluoromethane and chlorodifluoroacetic acid derivatives, are either ODS themselves or derived from ODS-based precursors. Zheng and co-workers introduced 2-chloro-2,2-difluoroacetophenone as a non-ODS-based difluorocarbene reagent for *O*-difluoromethylation of phenol derivatives (Scheme 26, Eq. (1)) [101].



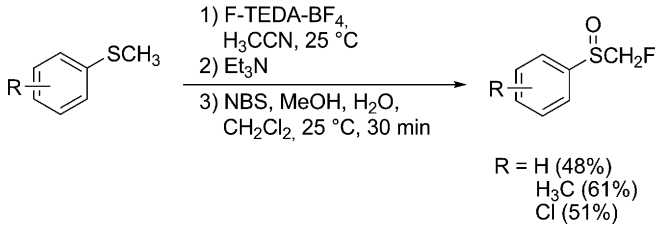
Scheme 11.



Scheme 12.



Scheme 13.



Scheme 14.

More recently, the same authors reported on a more efficient non-ODS-based difluorocarbene reagent for *O*- and *N*-difluoromethylations, chlorodifluoromethyl phenyl sulfone ($PhSO_2CF_2Cl$; Scheme 26, Eq. (2)) [102].

3.2. α-Difluoromethyl thioethers

As phenols, thiophenols react in the presence of sodium hydroxide with chlorodifluoromethane to give difluoromethyl aryl sulphides, *via* the intermediate formation of chlorodifluoromethylsodium and difluorocarbene [83].

α,α-Difluoroalkyl alkyl thioethers have also been obtained by the fluorodesulfuration with DEOXOFLUOR of the corresponding thionothioesters as described previously for *O*-nucleophiles [75,93].

Trifluoromethyl zinc bromide was also used for the preparation of *S*-difluoromethylethers [89].

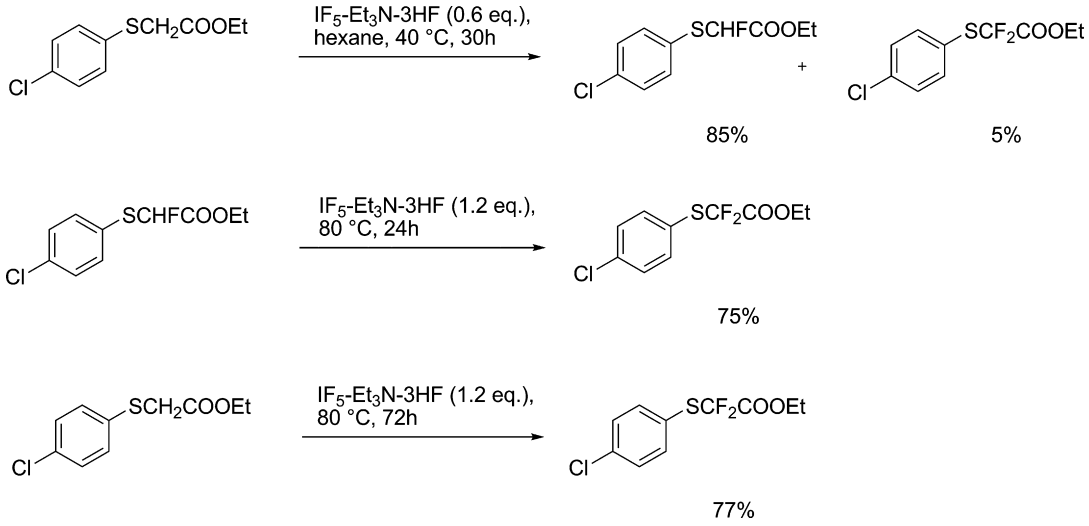
The first electrophilic (phenylsulfonyl)difluoromethylation with a hypervalent iodine(III)-CF_2SO_2Ph reagent was very recently reported by Hu (Scheme 27) [103]. The hypervalent iodine(III)-compound has been prepared by selective nucleophilic reaction using $PhSO_2CF_2SiMe_3$ (Scheme 27, Eq. (1)). The (phenylsulfonyl)-difluoromethylation proceeds with good yield (about 75%) in CH_2Cl_2 at −78 °C on a range of sulphur nucleophiles (Scheme 27, Eq. (2)).

3.3. α-Difluoromethyl amines

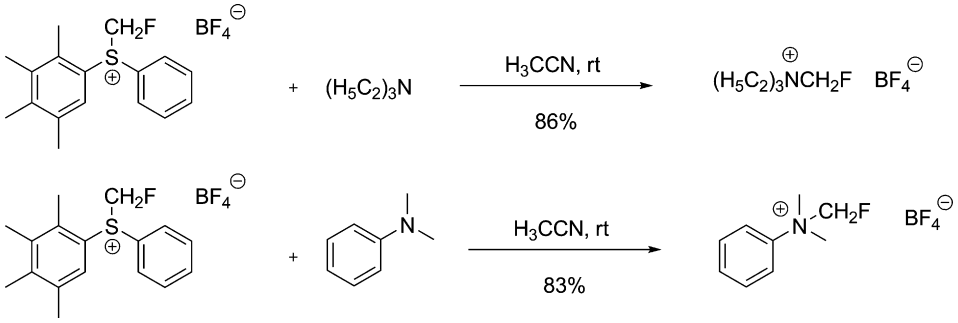
As a rule, compounds having a difluoromethyl group at exocyclic nitrogen atom readily undergo hydrolysis, so that they were not obtained by direct difluoromethylation [104].

Difluoromethylamines like difluorobenzyl(dimethyl)amine (DBDA) are readily used as fluorinating agents to replace hydroxyl groups in alcohols and carboxylic acids by fluorine atoms. Their first synthesis required the highly toxic sulphur tetrafluoride.

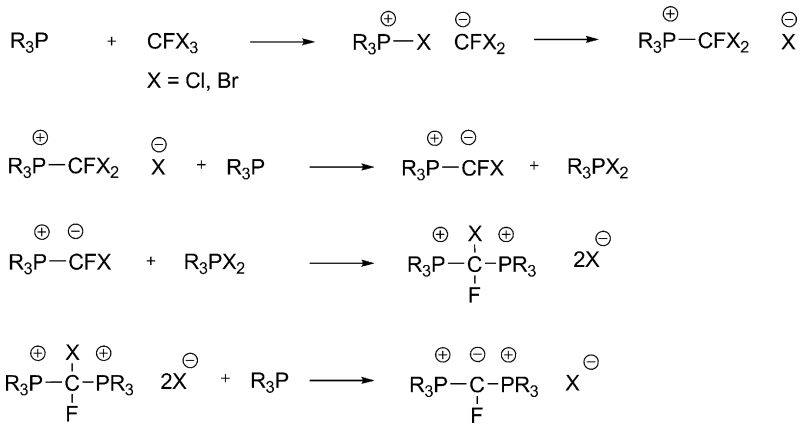
An approach toward difluoromethyldimethylamine has been developed by Arnold based on the reaction of *N*,*N*-dimethylformamide with phosgene and subsequent treatment with anhydrous hydrogen fluoride (Scheme 28) [105].



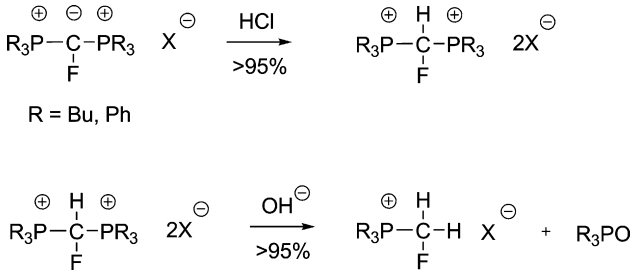
Scheme 15.



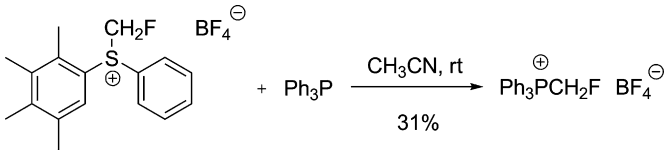
Scheme 16.



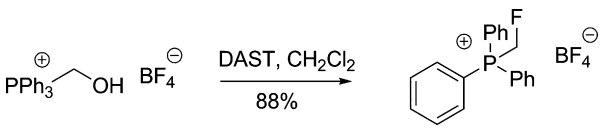
Scheme 17.



Scheme 18.



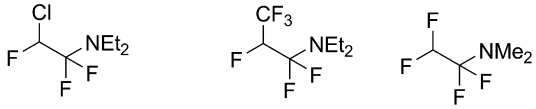
Scheme 19.



Scheme 20.

The synthesis was simplified by using fluorophosgene or oxalylfluoride affording directly the desired difluoromethylamines [106].

N,*N*-Diformylanilines, prepared by reaction of formanilide *N*-sodium salts with acetic-formic anhydride, afforded with PCl_5 and



Yarovenko reagent **Ishikawa reagent** **DuPont**

Fig. 7.

$POCl_3$ *N*,*N*-bis(dichloromethyl)anilines which can be converted by Cl/F-exchange into the corresponding bis(difluoromethyl)anilines (Scheme 29) [104].

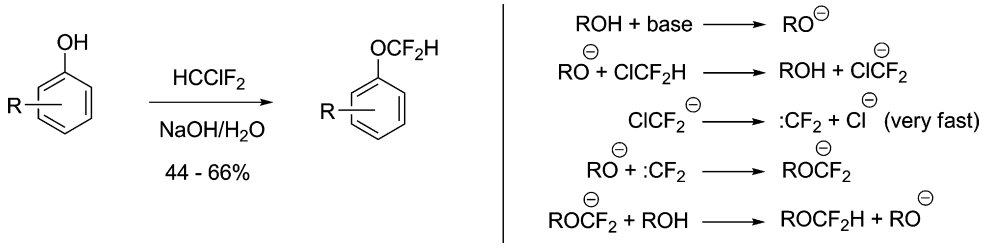
Reactions of sulfonamides RSO_2NHR' with chlorodifluoromethane and solid alkali gave the corresponding difluoromethylated derivatives $RSO_2N(CHF_2)R'$ [107]. In this case, the strong electron-acceptor group at the exocyclic nitrogen atom enhances the stability.

Like α,α-difluoroalkyl ethers and -thioethers, α,α-difluoroalkyl amines have been obtained by the fluorodesulfurization with DEOXOFLUOR of the corresponding thionoamides [75,93].

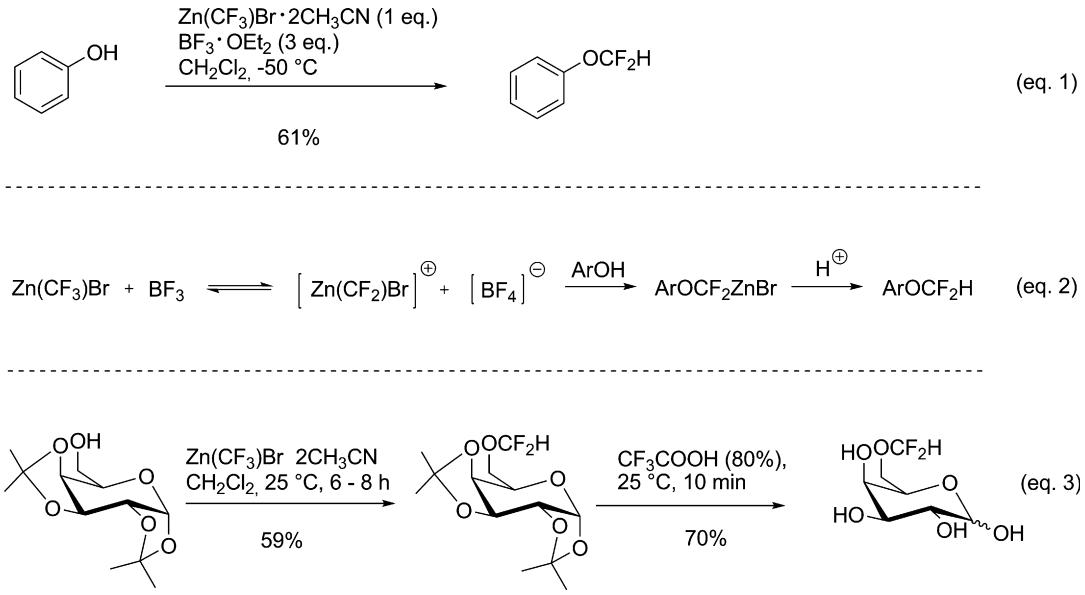
In recent years various deoxofluorinating agents have been developed which are more selective and can be easily handled. In this respect, the Yarovenko agent [108], 2-chloro-1,1,2-trifluoroethyldiethylamine, the Ishikawa agent [109], hexafluoropropyldiethylamine, and 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine [110] are difluoromethylamine derivatives which convert efficiently alcohols to fluorides (Fig. 7).

More recently, Hayashi reported on the synthesis of 2,2-difluoro-1,3-dimethylimidazolidine (DFI, Scheme 30, Eq. (1)) [111] which converts alcohols to monofluorides and aldehydes and ketones to *gem*-difluorides under mild conditions. Moreover, DFI can be recovered after the fluorination reaction in form of DMI. Its synthesis and recycling are depicted in Scheme 30, Eq. (2).

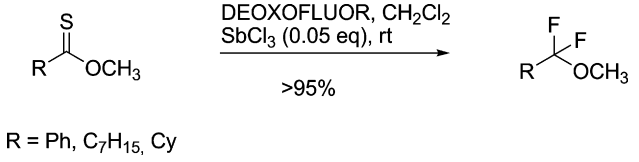
Analogously to the *O*- and *S*-difluoromethylation, amines can be difluoromethylated using trifluoromethyl zinc bromide [112].



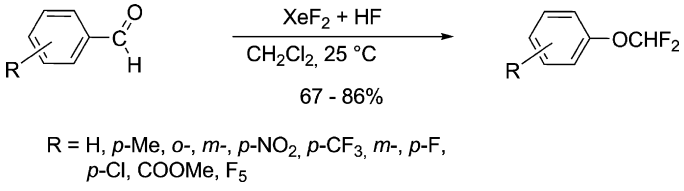
Scheme 21.



Scheme 22.



Scheme 23.



Scheme 24.

S-(Difluoromethyl)diarylsulfonium tetrafluoroborate was developed as a new electrophilic difluoromethylating agent (Scheme 31). However, this reagent cannot transfer the difluoromethyl group to phenols and secondary amines [113].

3.4. α-Difluoromethyl phosphines

Prakash tested the reactivity of *S*-difluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate toward phosphorus nucleophiles. In the case of triphenyl phosphine, only 15% conversion after 1 day of stirring at room temperature was observed. However, in the presence of at least 15% of di*iso*propylazodicarboxylate (DIAD), 100% conversion was achieved in 16 h. Other phosphines worked equally well under similar conditions (Scheme 32) [113].

The alkylation of the *H*-phosphinate ($CH_3C(OEt)_2P(O)$-$(OEt)H$), the "Ciba-Geigy reagent", with difluorochloromethane can be used to prepare the corresponding difluoromethylphosphinate (Scheme 33) [114].

Fild and co-workers reported on the synthesis of Ph_2PCF_2Br from Ph_2PSiMe_3 and CF_2Br_2 [115]. Ph_2PCF_2H can be prepared as the major product by the reaction of Ph_2PCF_2Br with $NaBH(OMe)_3$ as nucleophilic reagent (Scheme 34) [116].

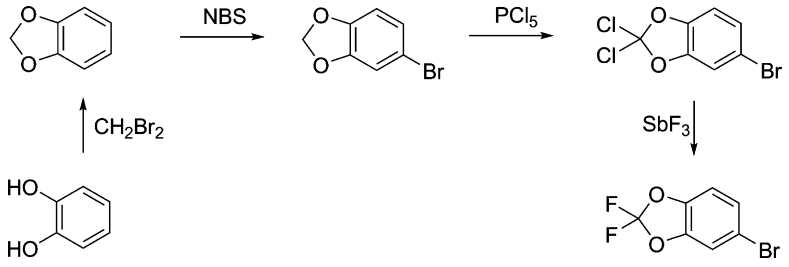
As previously described for ethers, thioethers and amines, trifluoromethyl zinc bromide was shown to convert triphenylphosphine into the adduct $Ph_3P(CF_2H)^+\ Br^-$ [89,117].

4. Preparation of α-trifluorinated ethers, thioethers, amines and phosphines

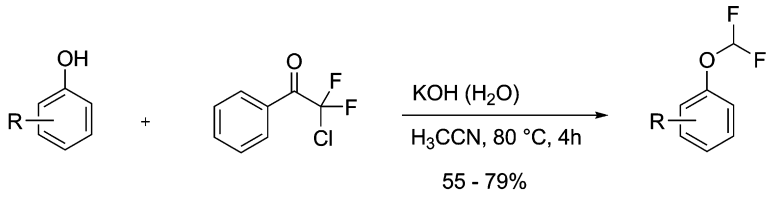
4.1. α-Trifluoromethyl ethers

Yagupol'skii prepared in 1955 the first aryl trifluoromethyl ethers from substituted anisols [118]. The substitution of chlorine by fluorine was realized with anhydrous hydrogen fluoride or with antimony trifluoride (Swart's reagent) in the presence of antimony pentachloride (Scheme 35) [118–121].

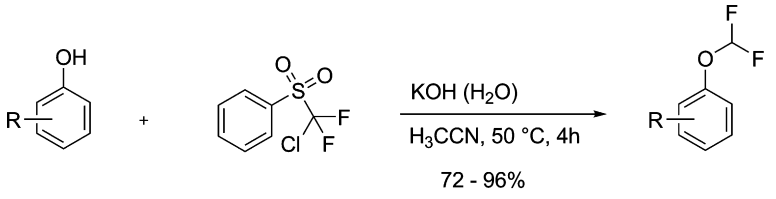
Louw and Franken could convert anisole into trichloromethyl anisole by photochlorination with elemental chlorine in



Scheme 25.



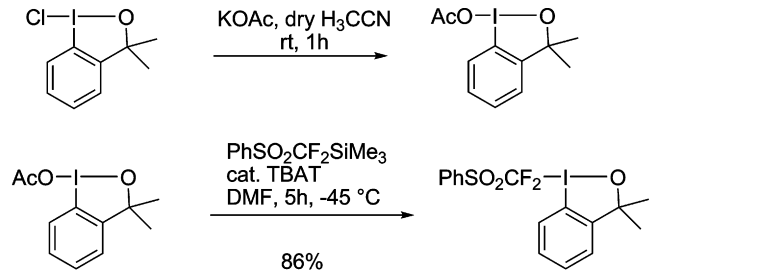
(eq. 1)



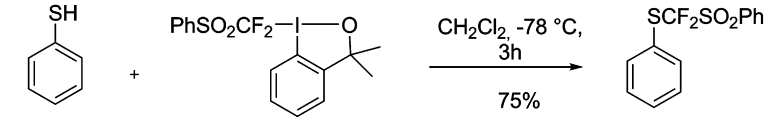
(eq. 2)

R = H, *o*-I, *p*-I,*p*-Br, *p*-Cl, *o*-NO_2, *p*-NO_2, *p*-tBu, p-Ph, *o*-OCH_3

Scheme 26.

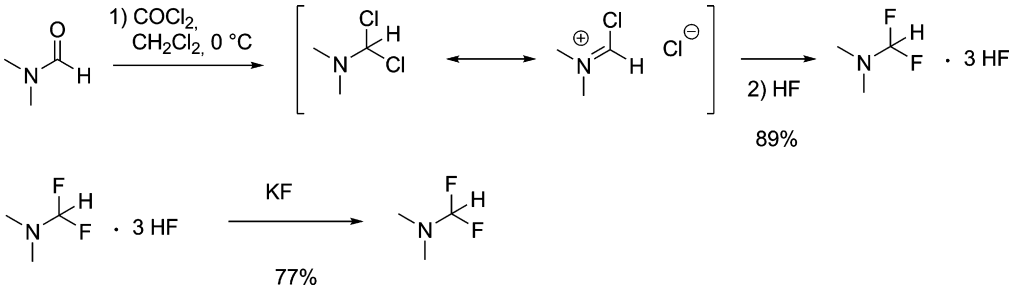


(eq. 1)

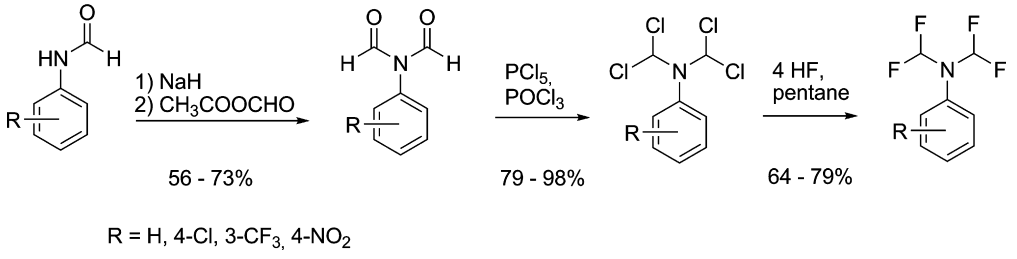


(eq. 2)

Scheme 27.

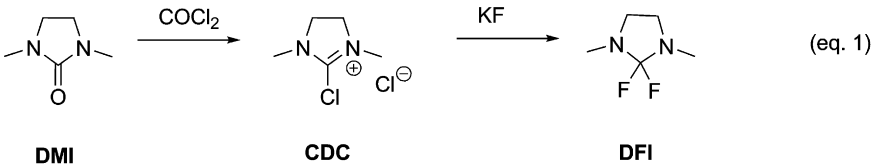


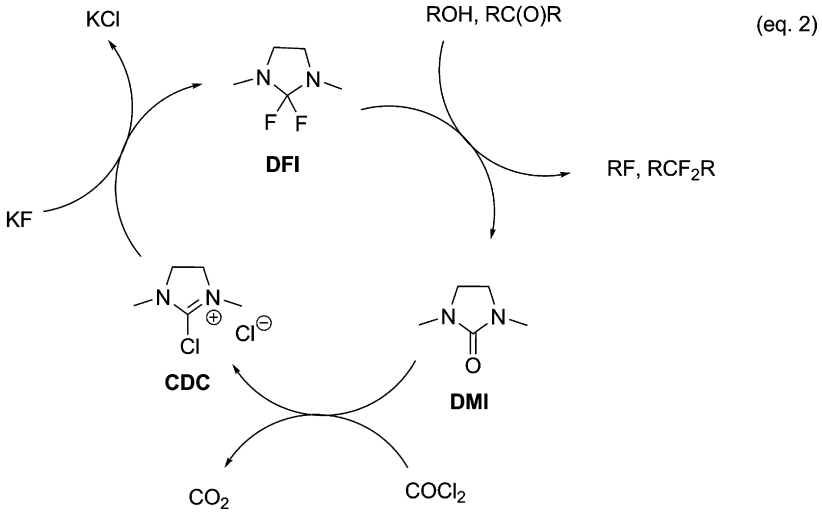
Scheme 28.



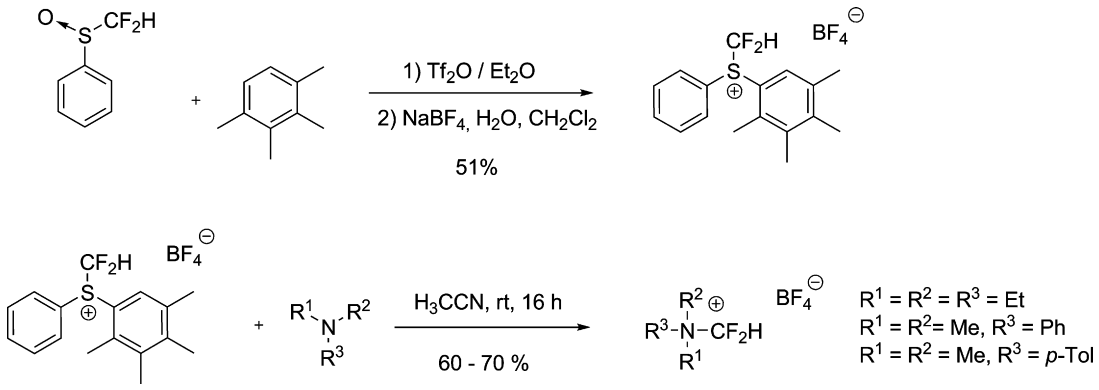
R = H, 4-Cl, 3-CF_3, 4-NO_2

Scheme 29.





Scheme 30.



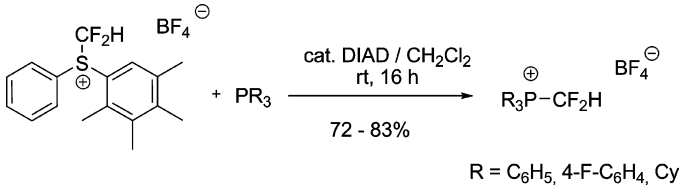
Scheme 31.

refluxing tetrachloromethane [122]. Feiring could show more recently, that the trichloromethyl aryl ethers can be *in situ* converted into the final trifluoromethyl aryl ethers. In fact, the phenol is heated together with tetrachloromethane, anhydrous hydrogen fluoride and catalytic amounts of boron trifluoride in a closed pressure vessel under autogeneous pressure up to 150 °C (Scheme 36) [123].

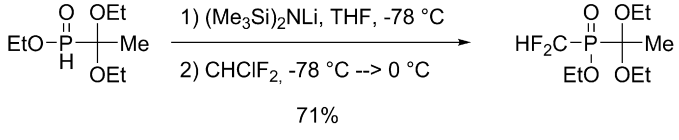
Yarovenko and Vasil'eva developed an approach based on aryl chlorothionoformates. They can be cleanly converted by chlorination into trichloromethyl aryl ethers (Scheme 37) [119]. This step is then followed by fluorination using antimony trifluoride and a catalytic amount of antimony pentachloride.

Sheppard described in 1964 the syntheses of aryl trifluoromethylethers [124] by reaction of SF_4 with aryl fluoroformates (Scheme 38).

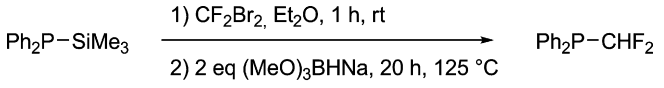
Hiyama et al. developed the oxidative desulfurization–fluorination of dithiocarbonates (xanthogenates) by treatment with



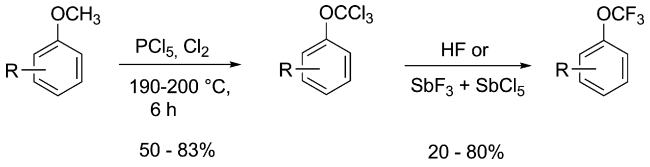
Scheme 32.



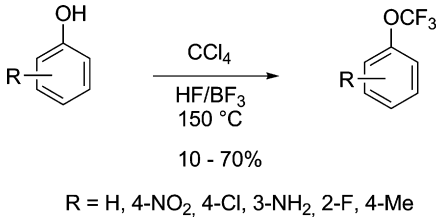
Scheme 33.



Scheme 34.



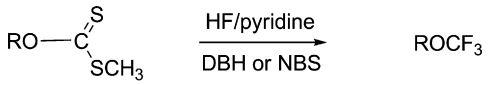
Scheme 35.



Scheme 36.

1,3-dibromo-5,5-dimethylhydantoin (DBH) or *N*-bromosuccinimide (NBS) and a huge excess of 70% hydrogen fluoride-pyridine (Olah's reagent, up to 80 equivalents). The corresponding trifluoromethyl ethers are formed in moderate to excellent yields (Scheme 39). When the reaction was conducted with tetrabutylammonium dihydrogen trifluoride ($TBAH_2F_3$) instead of hydrogen fluoride-pyridine, the intermediate difluoromethylthioacetal was obtained in good yields [125–128].

What makes this procedure attractive is its applicability to the conversion of aliphatic alcohols into trifluoromethyl alkyl ethers. The reagent consisting of 70% HF/pyridine and a halonium oxidant converts R–OCS_2CH_3 into either R–OCF_3 (R = primary) or R–F (R = secondary, tertiary or benzylic) whereas 50% HF/pyridine converts R–OCS_2CH_3 (R = secondary) into R–OCF_3 [129]. The mechanism is based on the nucleophilic attack of the carbon–



R = 4-Pr-C_6H_4-, 4-Hex-C_6H_4-, 4-$PhCH_2O$-C_6H_4-, 4-Br-C_6H_4-, Ph-$CH_2CH_2CH_2$-, $C_{16}H_{33}$-

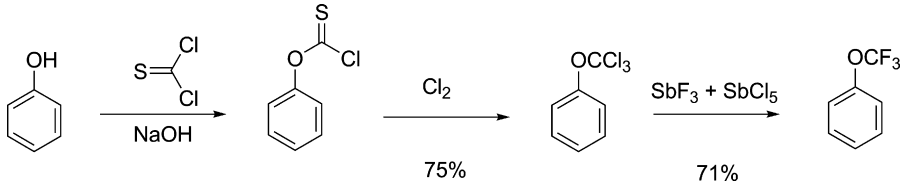
Scheme 39.

sulphur bond on a positively charged halogen which makes subsequently the nucleophilic substitution by a fluoride possible (Scheme 40). Under modified reaction conditions, for example by using $TBAH_2F_3$ instead of HF-pyridine, the transient monothioacetals can be isolated [126].

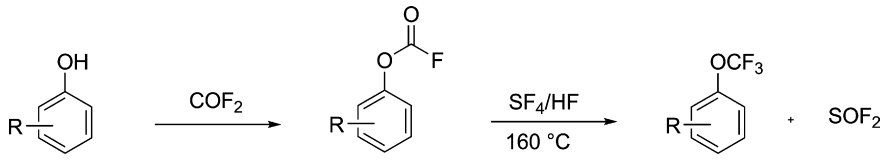
Umemoto reported recently in detail on the preparation of *O*-(trifluoromethyl)dibenzofuranium salts [130–133] and their use as CF_3-transfer agents based on studies of Yagupol'skii [134]. The direct *O*- and *N*-trifluoromethylation of alcohols, phenols, amines, anilines and pyridines under mild conditions was described (Scheme 41). However, the difficulty in the use of these reagents is the *in situ* preparation by photochemical decomposition of the corresponding 2-(trifluoromethoxy)biphenylyl-2′-diazonium salts at −100 °C.

Alkyl trifluoromethyl ethers, still a rarity, have so far been prepared by the reaction of alkyl fluoroformates with sulphur tetrafluoride [135], the trifluoromethyl transfer from *O*-(trifluoromethyl)dibenzofuranium hexafluoroantimonate [136], the addition of trifluoromethyl hypofluorite ($FOCF_3$) to olefins [137] and the oxidative desulfurization–fluorination of xanthates [125–128]. Although the oxidative desulfurization–fluorination is the most widely used procedure for the synthesis of primary $AlkOCF_3$ derivatives on laboratory and semi-industrial scale, all these transformations, require either highly toxic reagents like concentrated HF solutions or SF_4, an operation with huge excesses of highly toxic and flammable carbon disulphide, methyl iodide and HF/Pyridine, or the *in situ* generation of highly reactive reagents from precursors already containing a trifluoromethoxy group.

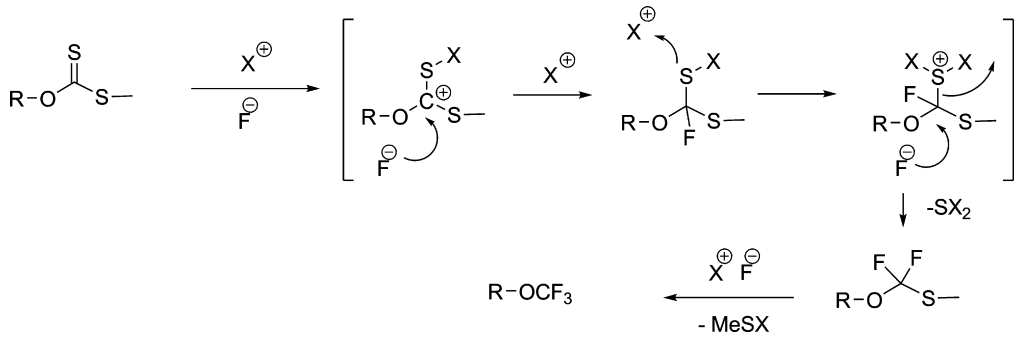
Togni reported recently on the synthesis and use of hypervalent iodine compounds [138] and their use as electrophilic trifluoromethylation reagents. Contrary to *C*-, *S*- [139], and *P*-nucleophiles [140], the *O*-trifluoromethylation undergoes sluggishly. When 2,4,6-trimethylphenol was treated with this reagent, the desired product was only obtained in 15% yield (Scheme 42, Eq. (1)). The major products were a mixture of *C*-trifluoromethylated derivatives [141].



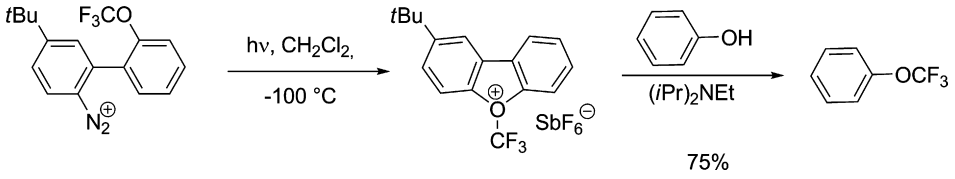
Scheme 37.



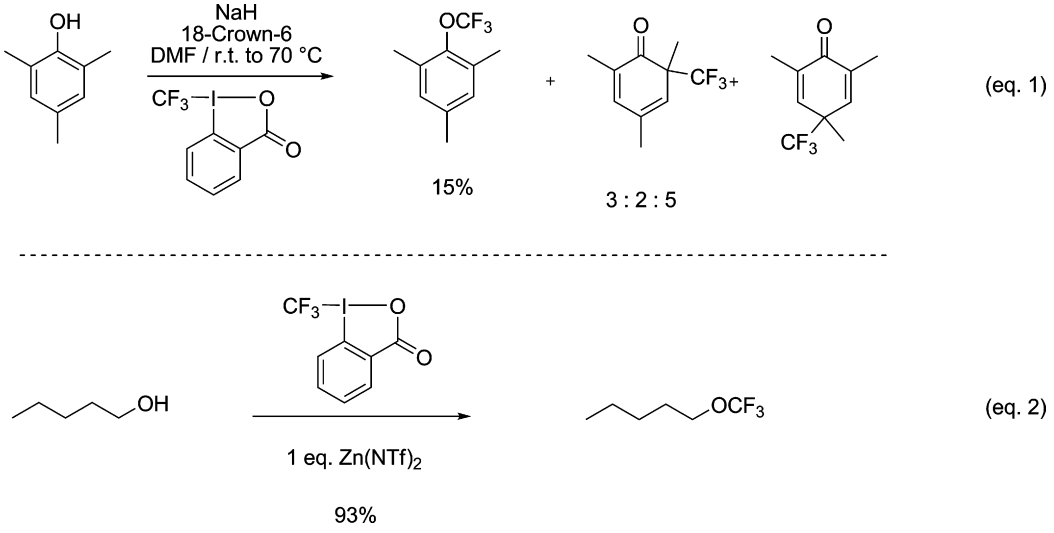
Scheme 38.



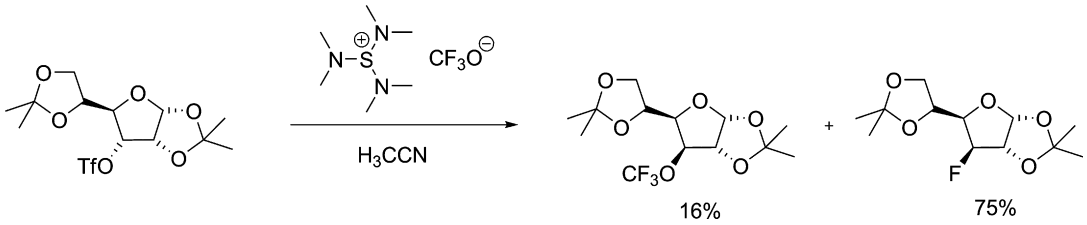
Scheme 40.



Scheme 41.



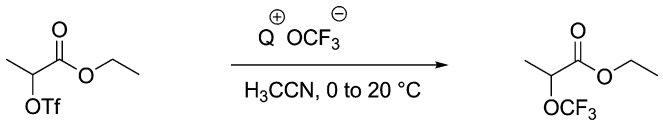
Scheme 42.

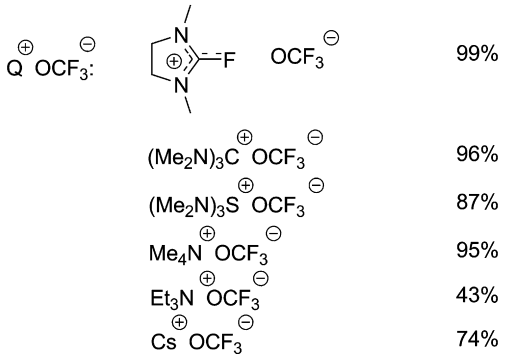


Scheme 43.

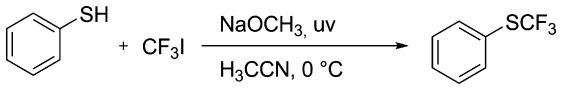
However, a great step forward was realized very recently by the same authors, when the transfer of trifluoromethyl group from a hypervalent iodine reagent to an aliphatic alcohol was realized upon activation by zinc bis(triflimide). This constitutes a straightforward method for the preparation of trifluoromethoxy alkyl derivatives, compounds otherwise difficult to access (Scheme 42, Eq. (2)) [142].

The introduction of the trifluoromethoxy substituent into carbohydrates was realized using *tris*(dimethylamino)sulfonium trifluoromethoxide ($TASOCF_3$) as OCF_3-transfer reagent (Scheme 43) [143]. This compound can be prepared by reaction of carbonyl fluoride with *tris*(dimethylamino)sulfonium difluorotrimethylsilicate in anhydrous THF at −75 °C [144]. The trifluoromethoxide anion is a relatively poor nucleophile. When reacted with primary triflate esters of carbohydrates, the anion displaced the triflate under mild conditions. However, an operation with carbonyl difluoride limits the laboratory application.





Scheme 44.



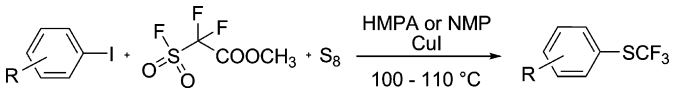
89%

Scheme 45.

Kolomeitsev reported very recently on a convenient access to trifluoromethanolates from trifluoromethyl trifluoromethanesulfonate, $CF_3OSO_2CF_3$ (TFMT) and their application as trifluoromethoxy carriers in nucleophilic displacement reactions (Scheme 44) [145].

4.2. α-Trifluoromethyl thioethers

$S_{RN}1$ reaction of aryl thiolates with trifluoromethyl iodide or bromide was the first synthesis of trifluoromethyl sulphides. This method, first reported by Yagupolskii using CF_3I and UV irradiation [146], and by Wakselman and Tordeux using CF_3Br [147], has proved to be generally useful when using aryl thiolates but less efficient when using alkyl thiolates (Scheme 45).



Scheme 47.

The other popular method involves the reaction of trifluoromethyl anion (generated *in situ* by various methods) with aryl and alkyl disulphides (Scheme 46) [148–151].

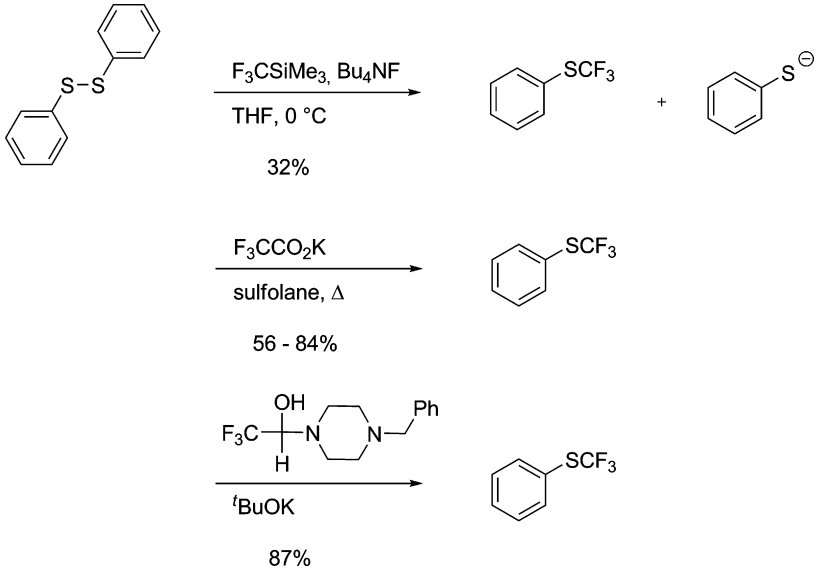
As described previously for trifluoromethyl ethers, Umemoto reported on the trifluoromethylation of thiols with *S*-(trifluoromethyl)dibenzothiophenium triflate affording the corresponding trifluoromethyl thioethers in medium to good yield [130].

Otherwise, trifluoromethyl phenyl thioethers and ring-substituted analogs are readily made from iodo- or bromoarenes, methyl difluoro(fluorosulfonyl)acetate and elemental sulphur in the presence of cuprous iodide in hexamethylphosphoric triamide (HMPA) or *N*-methylpyrrolidone (NMP) as depicted in Scheme 47 [152].

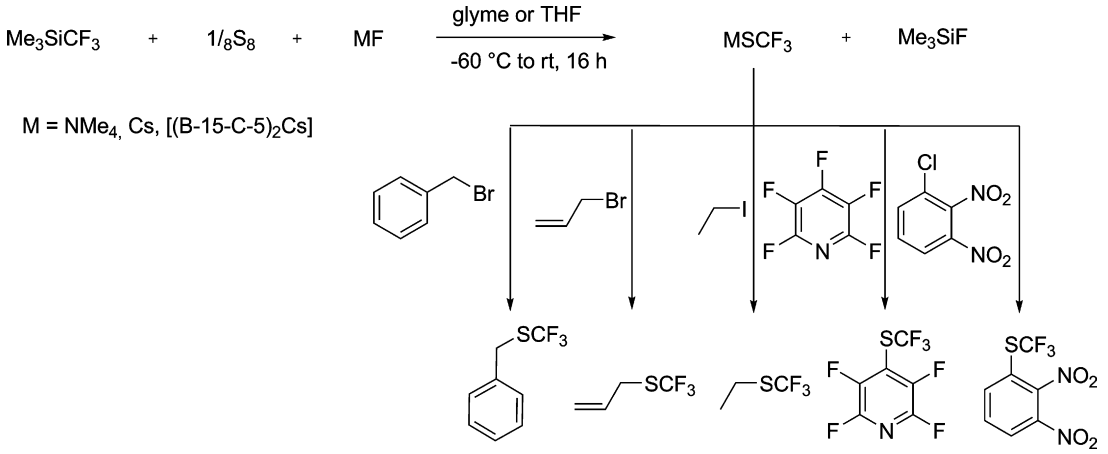
Tyrra and Naumann reported on the synthesis of $[NMe_4]SCF_3$, $CsSCF_3$ and $[(B\text{-}15\text{-}C\text{-}5)_2Cs]SCF_3$ (B-15-C-5: benzo-15-crown-5) from reactions of the corresponding fluorides, trimethyl(trifluoromethyl)silane, Me_3SiCF_3, and elemental sulphur. The properties of these compounds as nucleophilic SCF_3-transfer reagents were studied with a variety of organic, organometallic and inorganic compounds (Scheme 48) [153].

Langlois disclosed that trifluorothioacetates ($CF_3CO–S–R$, from $(CF_3CO)_2O$ and thiols) as well as trifluoromethanethiosulfonates ($CF_3SO_2–S–R$ from CF_3SO_2Na, RSSR, and Br_2) can be formally decarbonylated or desulfonylated, respectively, provided that they are photolyzed at 40 °C in the presence of 1 equiv of the corresponding disulphide or diselenide. Trifluoromethyl sulphides were obtained, and the added disulphide recovered after reaction (Scheme 49) [154].

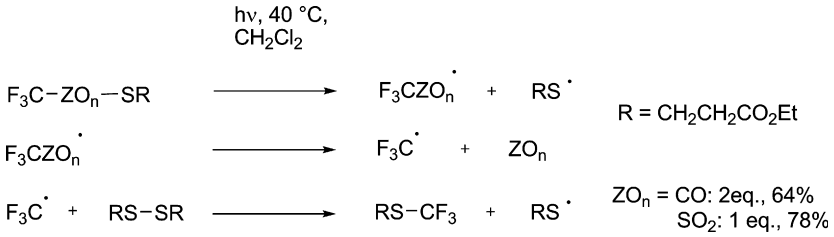
Langlois reported also on a cheap strategy towards benzyl trifluoromethyl sulfone which implies the intermediate formation of benzyl trifluoromethyl sulphide (Scheme 50). Benzyl trichloromethyl sulphide was easily prepared from benzyl thiocyanate, chloroform and sodium hydroxide under phase transfer conditions. Subsequent conversion into the trifluoromethyl sulphide was achieved by halogen exchange with HF/Pyridine (Olah's reagent) [155]. When benzyl trifluoromethyl sulfone was treated



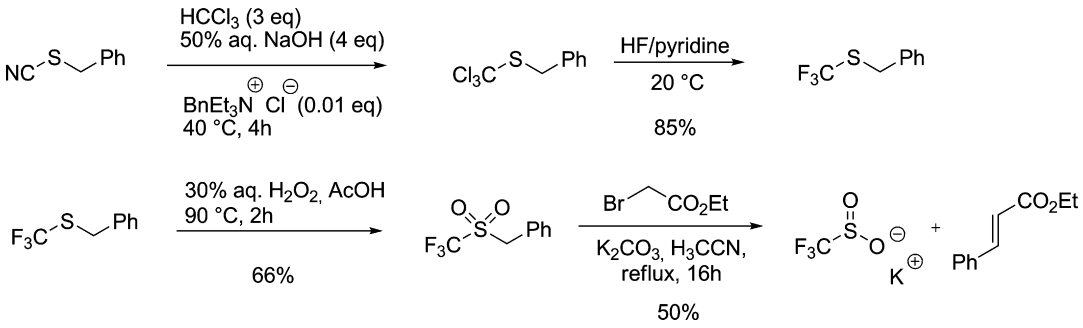
Scheme 46.



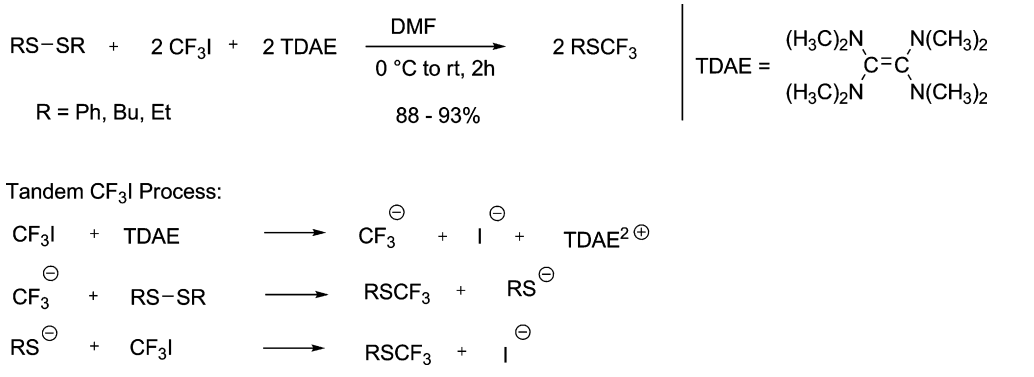
Scheme 48.



Scheme 49.



Scheme 50.

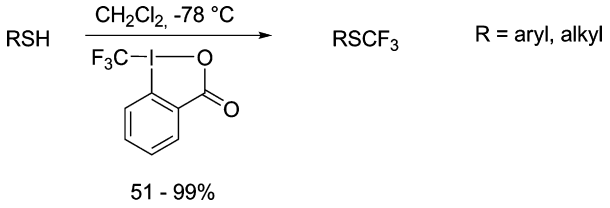


Scheme 51.

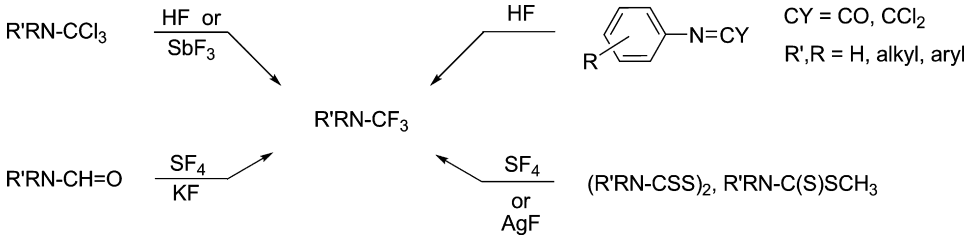
with ethyl bromoacetate, potassium triflinate was obtained in high purity and satisfactory yield.

Sodium or potassium trifluormethanesulfinates (triflinates) are highly valuable compounds as they can be precursors for trifluoromethanesulfonic acid.

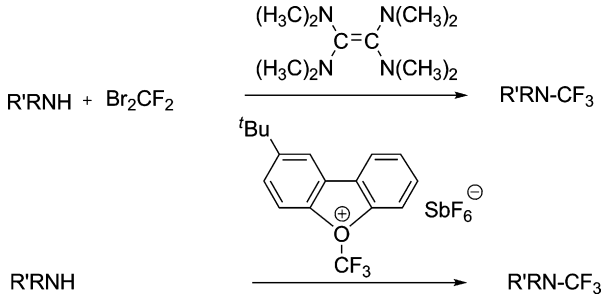
A new atom-economic procedure for preparation of trifluoromethyl thioethers was reported by Dolbier, wherein now both halves of aryl- and alkyldisulphides are able to be utilized with high efficiency (Scheme 51). When alkyl or aryl disulphides are reduced by the organic reducing agent tetrakis-(dimethylami-



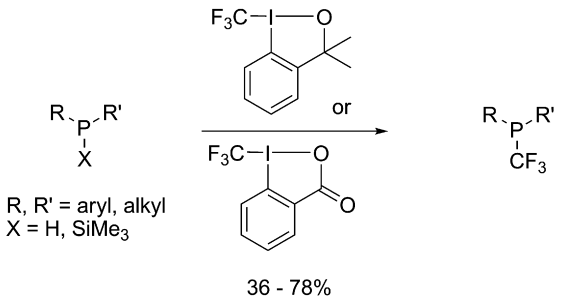
Scheme 52.



Scheme 53.



Scheme 54.

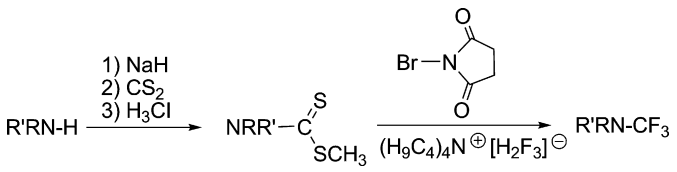


Scheme 57.

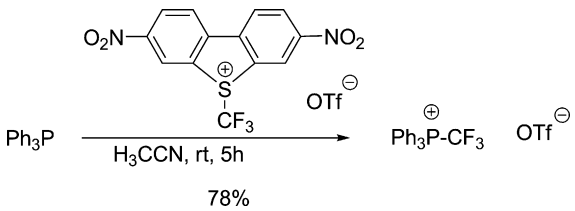
no)ethylene (TDAE), the CF_3I forms a reagent anion that converts disulphides into their trifluoromethyl thioethers [156,157].

In all these previous methods, an SCF_3 substituent was introduced into organic molecules by direct transfer of the SCF_3 moiety [153], or by the delivery of a CF_3 fragment to an appropriate sulphur atom by a nucleophilic, or, more often, a radical reaction [154,156,157].

Togni found that both aromatic and aliphatic thiols undergo *S*-trifluoromethylation selectively and smoothly in the presence of 1.1 equivalent of hypervalent CF_3-iodine(III) reagents to afford the products in good to excellent yields (Scheme 52) [139].



Scheme 55.



Scheme 56.

4.3. α-Trifluoromethyl amines

N-Trifluoromethyl substituted amines can be prepared by chlorine/fluorine exchange with hydrogen fluoride or antimony trifluoride applied to *N*-(trichloromethyl)amines [158], thiuram disulphides and sulphur tetrafluoride [159,160] or silver fluoride [161], *N*,*N*-dialkylformamides and sulphur tetrafluoride in the presence of potassium fluoride [160] and arylisocyanates or phosgene arylimines with hydrogen fluoride (Scheme 53) [162].

Less frequently employed are the reaction of secondary amines with dibromodifluoromethane in the presence of tetrakis(dimethylamino)ethylene (TDAE) [163] or with *O*-(trifluoromethyl)-dibenzofuranylium hexafluoroantimonate (Scheme 54) [132].

When secondary amines were converted into dithiocarbamates, their oxidative fluorodesulfurization with excess *N*-bromosuccinimide and tetrabutylammonium dihydrogen trifluoride gave the trifluoromethylamines in good to excellent yields (Scheme 55) [127].

4.4. α-Trifluoromethyl phosphines

Trifluoromethylated triphenylphosphonium salt has been prepared by Umemoto by means of *S*-(trifluoromethyl)dibenzothionium salts as electrophilic trifluoromethylation reagent (Scheme 56) [130].

A direct, mild and efficient trifluoromethylation of primary and secondary phosphines was achieved with easily accessible, cheap hypervalent iodine compounds acting as electrophilic CF_3-transfer reagents (Scheme 57) [140].

5. Conclusion

"Fluorine leaves nobody indifferent. . .. As a substituent it is rarely boring, but always good for a surprise. . .. Apparently the smallest halogen emits several kinds of electronic effects which. . . may counterbalance or amplify each other" [164]. The present review updates the synthesis of so-called emergent fluorinated substituents like α-fluorinated ethers, thioethers, amines and phosphines which are becoming more and more important in agrochemical, medicinal and pharmaceutical research as well as in material sciences. This is due to their particular stereoelectronic properties, their unusual chemical reactivity and their possible contribution to biorelevant parameters like metabolic stability and lipophilicity.

In other words, fluorine is an important tool to modulate the properties of biologically active substances and α-fluorinated ethers, thioethers, amines and phosphines will without any doubt play a major role in the future evolution of the field.

Acknowledgments

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