Selective Fluorinations by Reagents Containing the OF Group

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Received November 9, 1995 (Revised Manuscript Received March 18, 1996)

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Shlomo Rozen was born in 1942 in Bulgaria and immigrated to Israel as a small child. He received his B.Sc., M.Sc., and Ph.D. from the Hebrew University of Jerusalem, under the supervision of the late Ernst D. Bergmann, the pioneer of fluorine chemistry in Israel, and I. Shahak. He spent three years in the Research Institute for Medicine and Chemistry, Cambridge, MA, with D. H. R. Barton, R. H. Hesse, and M. M. Pechet, where he began work with elemental fluorine. In 1976 he joined the School of Chemistry at the Tel Aviv University where he assumed the position of Professor of Chemistry in 1989. On multiple occasions during the last 15 years he has held the position as visiting scientist at the Central Research Department of the Du Pont Company. His main goal in chemistry is to demonstrate that elemental fluorine is a very useful reagent in general organic chemistry, as well as in fluorine chemistry, and chemists should discard their unjustified fear and prejudice against this long-known but somewhat neglected element. He has published more than 140 papers and patents in most of which F_2 is the starting point.

Introduction

For more than a century[1] organofluorine chemistry has regularly used numerous variations of nucleophilic fluorination processes.[2] The field of electrophilic fluorination started to emerge during the late 1950s and early 1960s with the employment of perchloryl fluoride ($FClO_3$), which was used to fluorinate electron-rich sites.[3] While its use declined rapidly because of safety problems, the known,[4] but practically never used fluoroxytrifluoromethane, CF_3OF, started to take off following the pioneering work of Barton and Hesse.[5] In late 1970s a large body of work with this reagent had been reviewed by Hesse[6] and Mukhametshin,[7] but soon afterward the number of publications with CF_3OF dropped sharply since its commercial production encountered problems. Some works describing mono- and bishypofluorites with higher perfluoroalkyl chains have also appeared,[8] but these reagents did not gain much popularity since usually they were not commercially available and required F_2 and special conditions for their synthesis. At that time mentioning elemental fluorine was enough to deter most organic chemists since it was "well known" that fluorine is dangerous, or at least is very nonselective. Generally, it was considered wise to leave work with this most reactive halogen to inorganic chemists although a few organic chemists insisted on trying despite its bad reputation. It was Merritt[9] who showed 30 years ago that when handled properly, F_2 could be added across some double bonds. Later, Barton and the author of this review, who worked as a postdoctoral fellow with this great chemist, showed that both CF_3OF and fluorine are capable of activating some "impossible sites" in certain steroids, although F_2 was found to be more efficient.[10] Eventually we fully developed the field and outlined the mechanism of this rare electrophilic reaction on saturated sites.[11] This work offered one of the best examples and proofs for Olah's three-center−two-electron nonclassical carbonium ion postulation, associated with most electrophilic reactions on sp^3-hybridized carbons.[12] Fluorine was shown to be surprisingly easy to handle which made it possible to explore several avenues for using this element to make a whole series of secondary reagents used for various types of fluorinations. The present number of laboratories which work with elemental fluorine is much greater than it was some 20 years ago and more and more chemists now look upon this halogen with curiosity and interest rather than with fear and distrust.

We will review here some of the chemistry concerning reagents possessing the OF moiety, usually prepared in situ from F_2. With the notable exception of CF_3OF most other reagents in this category are neither isolated nor purified prior to their reactions with a substrate, but their existence and structure have been proven beyond doubt.

The Chemistry of CF_3OF

As mentioned in the Introduction, the flood of papers on CF_3OF has become a trickle since the

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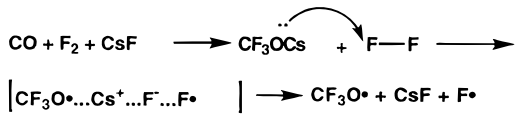
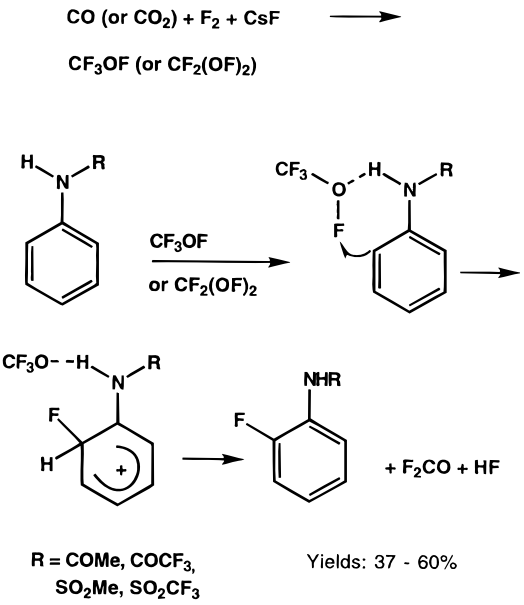
Scheme 1



Scheme 2

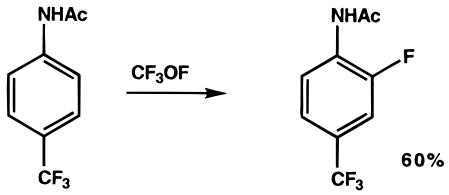


beginning of the 1980s. Its users could be divided into two groups, those who bought CF_3OF after it reappeared commercially with a very high price tag and frequently a long delivery time, and those who made it by somewhat the similar technique Cady developed in the 1940s.[4a] This consisted of reacting F_2 and CsF with CO and CO_2 forming CF_3OF and $CF_2(OF)_2$, respectively. At the beginning it was believed that the formation of these hypofluorites was of ionic nature but later it was argued by Mukhametshin that the process consisted of the generation of the trifluoromethoxy radicals formed by a one-electron transition (Scheme 1).[13]

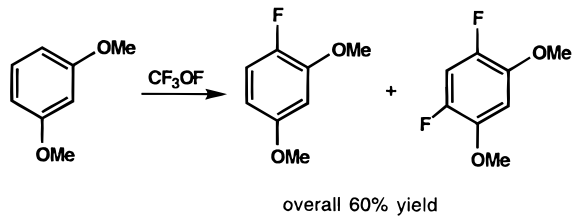
Fifolt made both hypofluorites in a continuous-stream process and reacted them with aromatic derivatives, especially anilines. The reaction, carried at 0 °C for about 2 h, resulted in a mixture of *o*- and *p*-fluoroanilines. With aprotic nonpolar solvents, however, the preference for ortho substitution was considerably enhanced. A complex formation between the aniline derivative and CF_3OF was assumed (Scheme 2). It was found that the relative activity of the studied substituted anilines is of the following order: $PhNHSO_2CH_3 > PhNHCOCF_3 \approx PhNHCOCH_3 \approx PhNHSO_2CF_3$. With particular substrates, these fluorinating agents are of practical synthetic utility, e.g., 2-fluoro-4-(trifluoromethyl)aniline was produced in relatively high yield by fluorinating the intermediate 4-(trifluoromethyl)acetanilide (Scheme 3).[14]

With benzene, anisoles, and toluenes, mono- and bis-electrophilic fluorination was observed, but generally in low yields and conversions. Aromatic fluorination was also reported by Belanger, who reacted CF_3OF with 1,3-dimethoxybenzene (Scheme 4),[15] and by Chambers, who reacted it with metal aryl, especially mercury, derivatives to obtain monofluoro derivatives in good yields (Scheme 5).[16]

Scheme 3

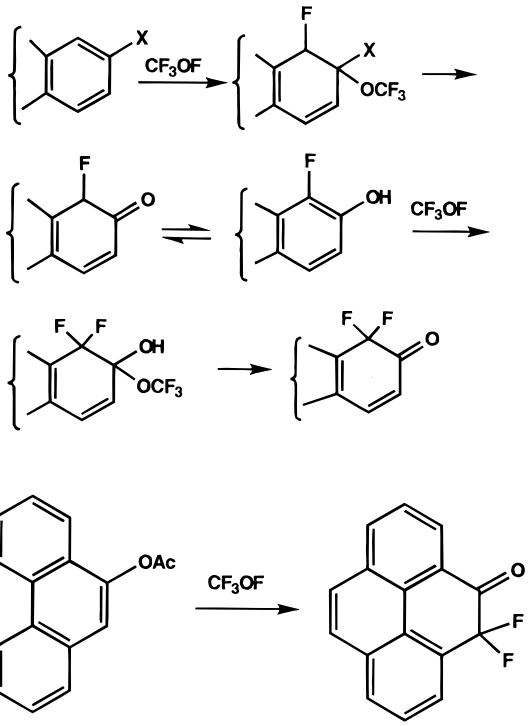


Scheme 4



Scheme 5

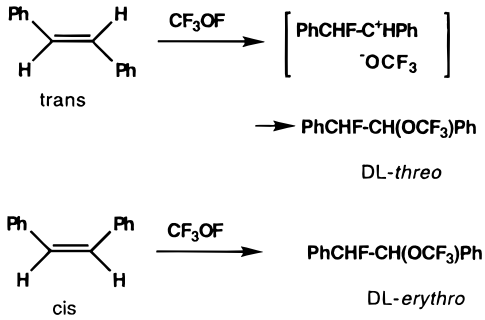
Scheme 6



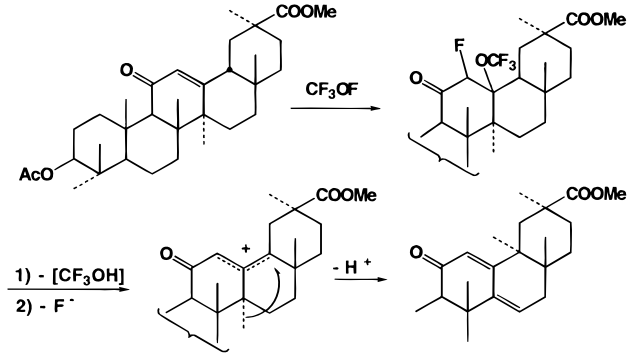
Patrick found that even at −78 °C, the main side reaction of activated aromatic molecules,[17] as well as of polycyclic aromatics such as coronene,[18] was the addition of CF_3OF across the most electron-rich π region of the ring to form unsaturated fluoro and difluoro ketones (Scheme 6). If large excess of fluoroxytrifluoromethane was used the remaining double bonds also reacted to give a complex mixture which was difficult to separate.

As early as 1959, Cady conducted a few experiments by reacting CF_3OF with simple organic molecules such as methane, chloroform, and ethylene under UV irradiation.[19] A few years later Barton and Hesse started to systematically introduce CF_3OF to organic chemistry and have shown that it could add across many double bonds in an ionic mode. The recorded stereochemistry was mainly syn[20] and the regiochemistry indicated that the oxygen-bound fluo-

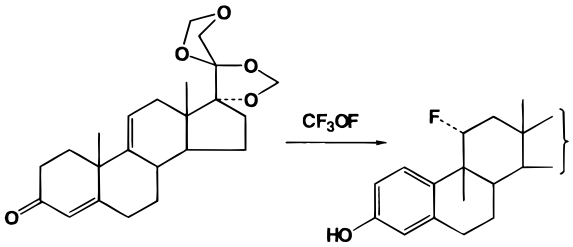
Scheme 7



Scheme 8



Scheme 9

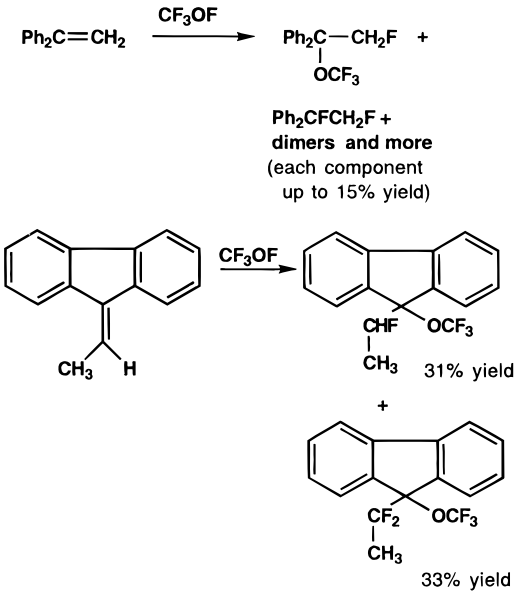


rine was electrophilic in nature. The syn addition is typical of most reactions with electrophilic fluorine since they proceed through the very unstable α-fluorocarbocation which collapses before the anion has a chance to diffuse out of the reaction cage (Scheme 7). Regio- and stereoselective addition was recorded also with complex molecules such as glycyrrhetic acid where the decomposition of the adduct led to a rare 1,3-sigmatropic methyl shift (Scheme 8).[21] In some special cases, where a relatively stable α-fluorocarbocation is formed, a cationic rearrangement is observed at −78 °C, which further supported the ionic notion (Scheme 9).[22]

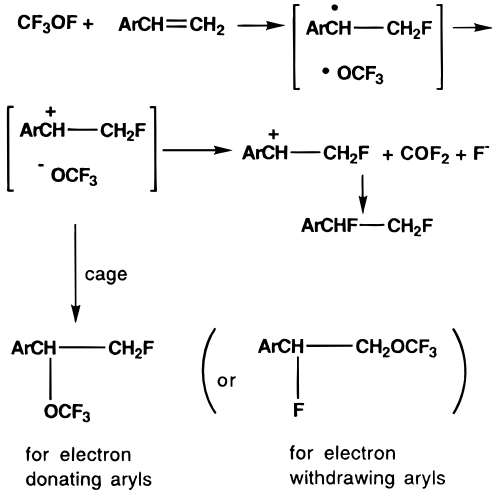
Patrick's work on the addition of the fluoroxytrifluoromethane to 1,1-diphenylethene and 9-ethylidenefluorene (Scheme 10),[23] and the corresponding Hammett ρ values of the reaction of CF_3OF with various styrenes at −78 °C (Scheme 11),[24] pointed to a tandem radical−ionic addition mechanism despite the low dipole moment of 0.3 D this reagent possesses. Thus the regioselectivity demonstrated is characteristic of an electrophilic fluorination and the difluoro adducts, found in many reactions of CF_3OF with olefins, were the result of a secondary process in which the CF_3O anion quickly decomposed to the more stable pair of difluorophosgene and fluoride anion (Scheme 11).

DesMarteau showed, however, that with concentrated solutions or with neat olefins (usually simple

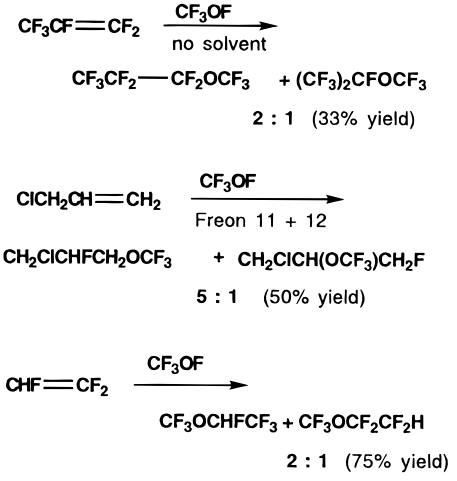
Scheme 10



Scheme 11

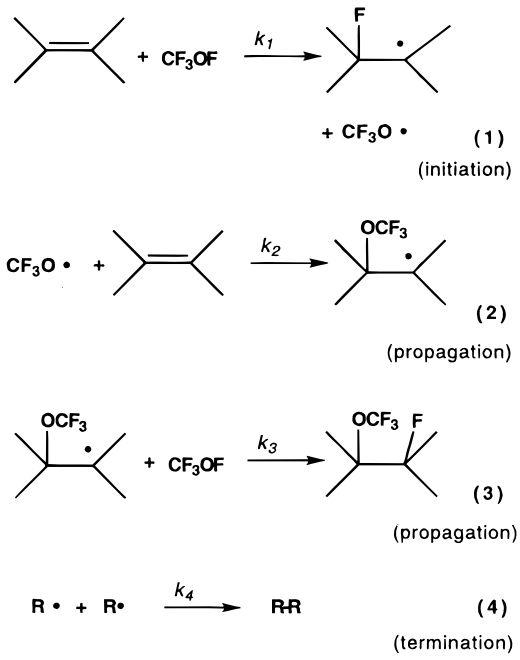


Scheme 12



and electron-depleted ones) CF_3OF reacts in a radical mode with low stereo- and regioselectivity (Scheme 12). In most cases the starting temperatures of the reactions were as low as −160 °C and gradually raised to room temperature in about 20 h.[25] Sekiya warmed similar olefins from −110 to 20 °C for 20 h, in order to prepare several potentially biologically

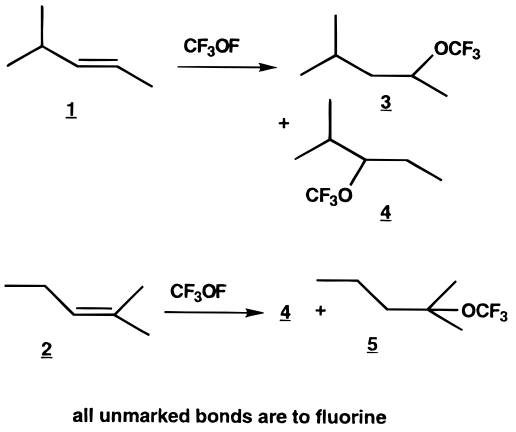
Scheme 13



interesting trifluoromethyl ethers.[26] The radical mechanism was supported by kinetic studies of the thermal reaction (+20 to +75 °C) between CF_3OF with hexafluoropropene[27] and trichloroethene.[28] Very recently, the radical mechanism in the above cases was strongly reinforced through Navarrini and Russo's work who measured the kinetics of the addition to a series of electron-poor olefins in unpolar solvents at temperatures as low as −105 °C.[29] They determined the rate constants of the initiation, chain-propagation, and the termination steps (Scheme 13). This work clearly concluded that in radical-encouraging conditions, the CF_3OF reacted after being homolytically cleaved. The ultimate proof for the existence of such mechanism was the observation of intermediate radicals by EPR technique recently reported by the Italian group who added fluoroxytrifluoromethane to HFP (hexafluoropropene) dimers and other perfluoroalkenes.[30] It should be noted that the selectivity of the addition to dimer **1** was remarkable and the ratio of **3**/**4** was 24. This is explained by sterical considerations which make the secondary radical $(CF_3)_2CFC^{\bullet}FCF(CF_3)(OCF_3)$ much more stable than the isomeric $(CF_3)_2CFCF(OCF_3)C^{\bullet}FCF_3$. The ratio of the products **4**/**5** obtained from the other HFP (**2**) was only 2.3 (Scheme 14).

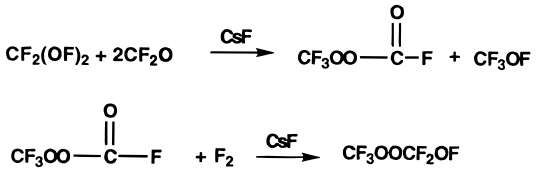
An interesting reaction with a much less known homolog of CF_3OF, the fluoroxydifluoromethyl trifluoromethyl peroxide (CF_3OOCF_2OF) with 1,2-dichloro-1,2-difluoroethylene was reported recently.[31] This hypofluorite could be made from $CF_2(OF)_2$ in very good yield and is safe to handle (Scheme 15). The reaction itself, carried at −60 °C, leads to 4,5-dichloro-2,2,4,5-tetrafluoro-1,3-dioxolane (Scheme 16). Similar compounds could also be obtained in good yields starting with $CF_2(OF)_2$ at temperatures of around −80 °C, although in this case they are always accompanied by the corresponding difluoro adduct (Scheme 16).[32] Such fluorodioxolanes are promising starting materials for new polymers resembling the somewhat difficult to make Teflon AF.

Scheme 14

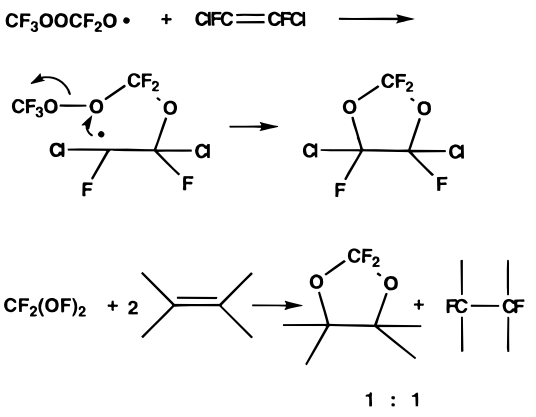


all unmarked bonds are to fluorine

Scheme 15



Scheme 16



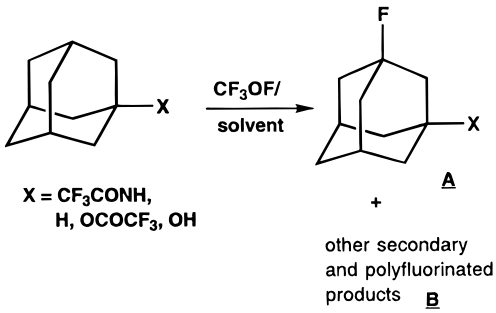
up to 95% combined yield

Regardless of the olefin, solvent, and temperature, the mode of the reaction of CF_3OF under irradiation is always a radical one. Barton and Hesse examined such reactions in the 1970s when adamantane and 1,2-cyclohexanedicarboxylic acid were fluorinated. They concluded that the radical process is usually not very regioselective and in the presence of radical inhibitors the overall rate of fluorination was moderately slowed down, but the enhancement of the selectivity was striking (Scheme 17).[33]

Radical reactions initiated by strong UV light were also recorded by Kollonitsch who passed CF_3OF at −78 °C for 19 h through D-alanine dissolved in liquid HF. The $CF_3O^{\bullet}$ radicals obtained this way were considered to be the chain carrier (Scheme 18).[34] Katzenellenbogen irradiated CF_3OF as a way to convert carbonyls, via their dithiolane derivatives, into the important CF_2 moiety (Scheme 19).[35]

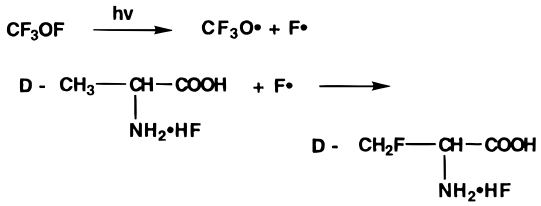
Synthesis of fluorosugars was a main goal for many medicinal chemists and CF_3OF was used for this purpose soon after Barton and Hesse started to experiment with this reagent. Hesse found that at −78 °C CF_3OF in $CFCl_3$ could be added to glucal to give four adducts, two α- and β-CF_3OF and two α- and β-difluoro ones (α-D-glucopyranosides and β-D-

Scheme 17

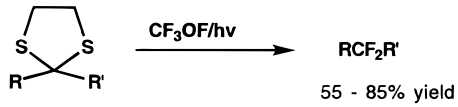


solvent	A:B
$CFCl_3/C_6Cl_6$	0.6
$CFCl_3/O_2$	11
$CFCl_3/PhNO_2$	12.5
$CHCl_3$	13

Scheme 18

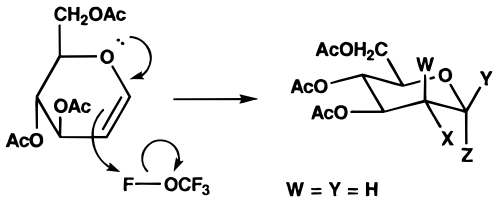


Scheme 19



R = R' = C_5H_{11}
R = $C_{11}H_{23}$, R' = H
R = R' = Cholesteryl
R = R' = Ph
R = Ar, R' = H

Scheme 20



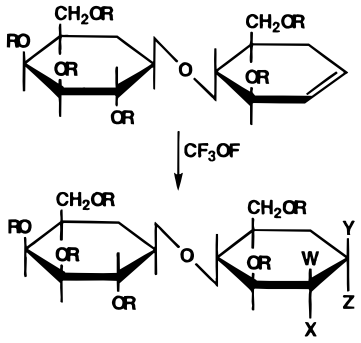
W = Y = H
X = F, Z = OCF_3 26%
X = Z = F 34%

X = Z = H
W = F, Y = OCF_3 6%
W =Y = F 8%

mannopyranosides) (Scheme 20).[36] Several similar works with similar results have appeared,[37] including fluorination of lactal and related disaccharides, which after 4 h at 0 °C formed 2-deoxy-2-fluorolactose and 2-deoxy-2-fluorodisaccharides (Scheme 21).[38] Various *gem*-difluorosugars, which frequently are biologically important,[39] were also obtained by treating monofluoroolefinic sugars with CF_3OF through an ionic mechanism (Scheme 22).[40]

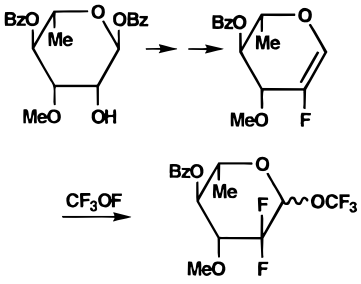
Fluoroxytrifluoromethane was also used for fluorination of other biologically interesting compounds such as various pyrimidines. In 1972 Barton showed that uracil, cytosine, thymine, and others, could be directly fluorinated with CF_3OF at temperatures from −78 to 25 °C in very good yields, using aqueous

Scheme 21

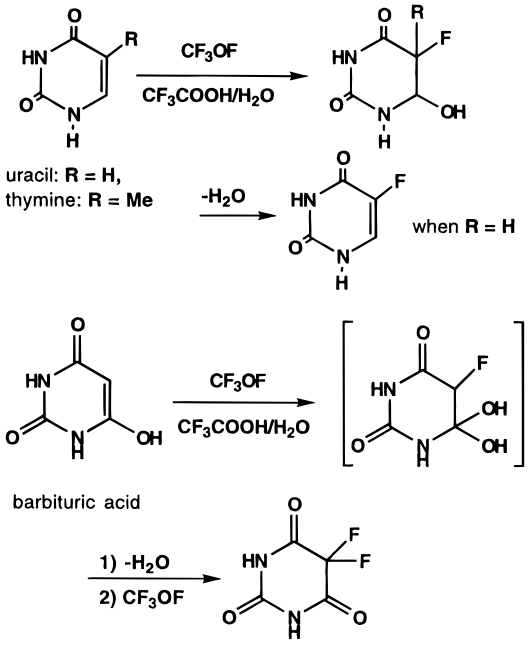


W = F; Y = OCF_3; X = Z = H
+
W = Y = F; X = Z = H
+
X = F; Z = OCF_3; W = Y = H
+
X = Z = F; W = Y = H

Scheme 22

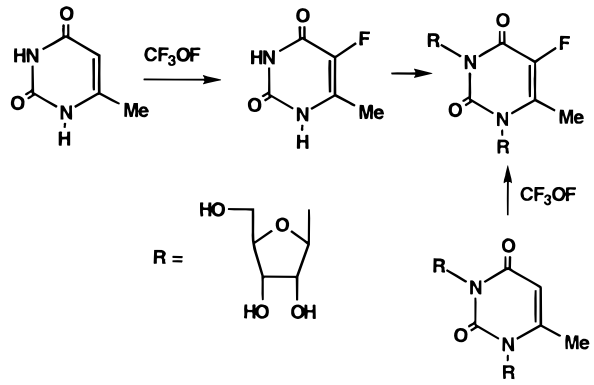


Scheme 23

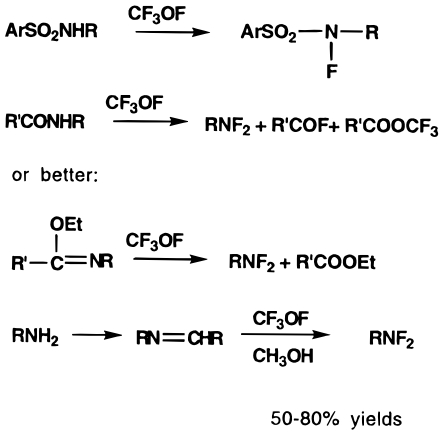


trifluoroacetic acid as a solvent. They all added the elements of F and OH with consequent loss of a water molecule by gentle heating wherever possible. The monoadduct of barbituric acid, after a spontaneous lost of water, reacts faster than the starting material and one could isolate only the difluorobarbituric acid which resulted from reaction with 2 mol/equiv of CF_3OF (Scheme 23).[41] Later Miyashita repeated this work and made several additional 5FU derivatives,[42] providing an important ingredient of several fluorine containing nucleosides.[43] It should be noted, how-

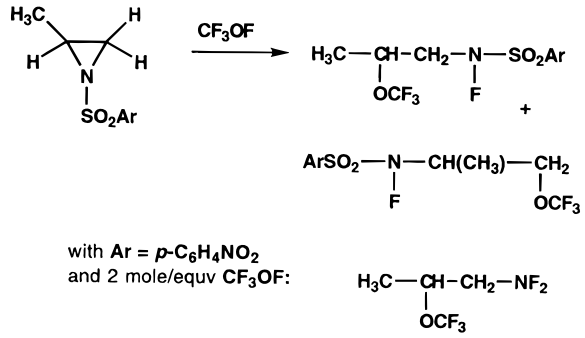
Scheme 24



Scheme 25



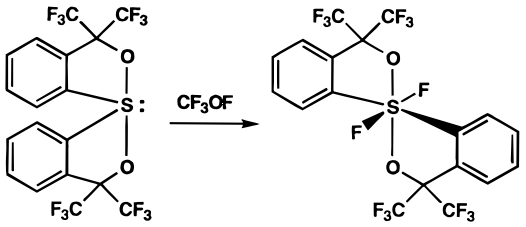
Scheme 26



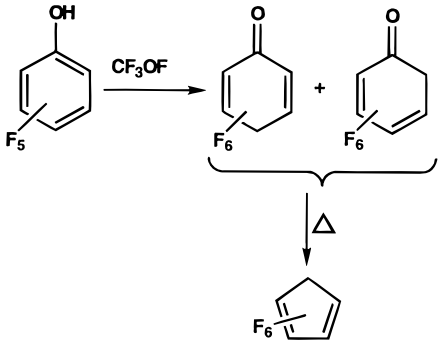
ever, that in many cases the fluorination step could be carried out even on the nucleoside level as shown in the case of uridine (Scheme 24).[41,44]

Fluoroxytrifluoromethane was used in several occasions for constructing compounds possessing the N−F moiety a family of reagents which recently found many uses in fluoroorganic chemistry. As in many other subfields which are using CF_3OF, Barton and Hesse were pioneers here as well. They reacted arylsulfonamides and other amides at room temperature with this reagent, obtaining the corresponding $ArSO_2NF$ and RNF_2 derivatives.[45] The yields of RNF_2 compounds could be considerably increased when Schiff bases, especially these of adamantylamine, were reacted with CF_3OF at 0 °C (Scheme 25).[46] A somewhat different route for making NF derivatives with CF_3OF was devised by Basselier[47] who used aziridines as substrate to form both NF- and NF_2-containing materials in good yields (Scheme 26).

Scheme 27



Scheme 28

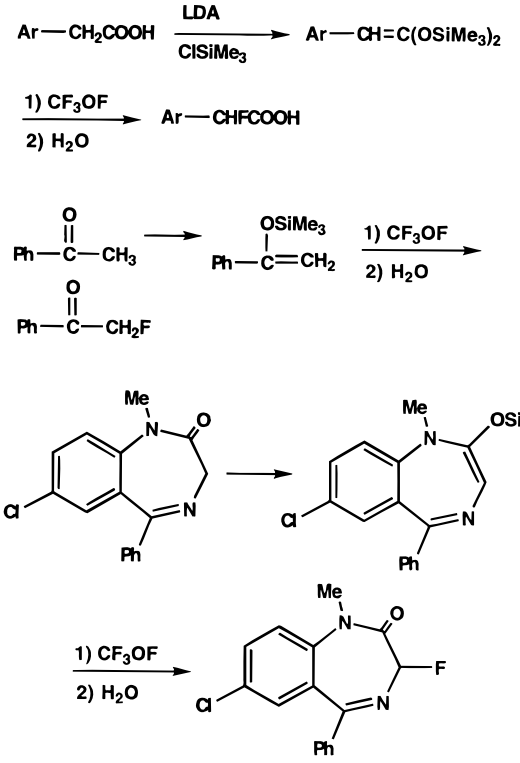


CF_3OF played a role also in fluorinating other heteroatoms such as sulfur. J. C. Martin reacted it with his unique persulfurane system, oxidatively adding two fluorine atoms to the central sulfur at −80 °C forming *t,t,t*-3,3,3′,3′-tetrakis(trifluoromethyl)-1,1′-spirobi[3*H*-2,1-benzoxathiole] 1,1-difluoride (Scheme 27).[48] It should be noted that the bulk of the reactions in this work have been conducted with BrF_3, but CF_3OF gave similar results. Lemal used this reagent to oxidize pentafluorophenol to hexafluorocyclohexadienone as an important step in his elegant synthesis of hexafluorocyclopentadiene (Scheme 28).[49]

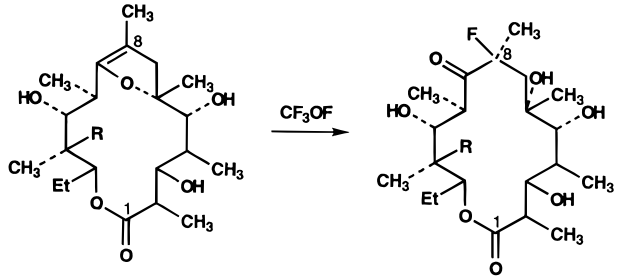
The area where CF_3OF found its most intense use, however, continued to be its reaction with various enols, forming the α-fluorocarbonyl moiety through electrophilic fluorination. Hesse summarized in his excellent review most of the early work on this subject.[6] Middleton[50] successfully developed an alternative route to α-fluoro acids,[51] which proved to be good also for esters, ketones, aldehydes, and amides. He reacted CF_3OF with silyl enol ethers at −70 °C and got in one step the corresponding α-fluorocarbonyl derivatives in 70−90% yield (Scheme 29). Toscano used erythromycin internal enol ether to prepare by this way fluoroerythromycin[52] with outstanding biological properties (Scheme 30). It should be noted that CF_3OF reacts with the enol moiety faster than with a free hydroxyl group so the latter does not have to be protected if large excess of the hypofluorite could be avoided. Fluoroxytrifluoromethane was also used for turning nortestosterone into 2-fluoroestradiol[53] and for introducing fluorine into the important 16 position of 17-ketosteroids (Scheme 31).[54]

The notion of electrophilic fluorination was a bit confusing and there were some who referred to the oxygen-bound fluorine as a positive fluorine, F^+. Christe clarified the problem by comparing the electronegativity of the fluorine with the groups it is attached to showing that there is no such species,[55] at least not in the ground state. Still it does not mean that there is no electrophilic fluorine as proved

Scheme 29



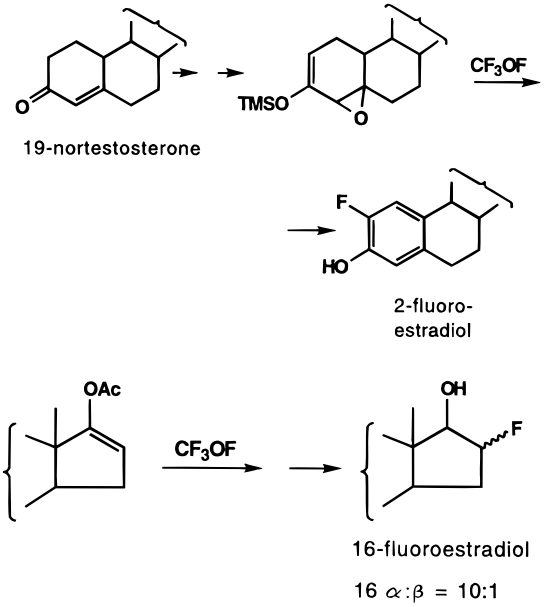
Scheme 30



R = OH; H

(8S)-8-fluoroerythronolide
(a precursor to (8S)-8-fluoro-erythromycin)

Scheme 31



19-nortestosterone

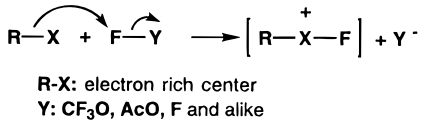
2-fluoro-estradiol

16-fluoroestradiol

16 α:β = 10:1

by many reactions. What this term really means is that the oxygen-bound fluorine is susceptible to nucleophilic attack from an electron-rich center. The

Scheme 32



R-X: electron rich center
Y: CF_3O, AcO, F and alike

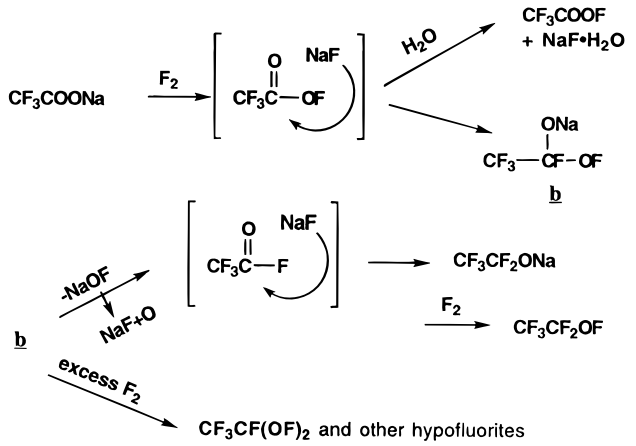
whole process is aided by the fact that the adjacent group is usually a relatively good leaving one and it is accepted now to symbolize an electrophilic fluorine by the "F^+" symbol (Scheme 32).[56]

Higher Perfluoroalkyl and Perfluoroacyl Hypofluorites

The literature of the early 1980s dealing with this category concentrates mainly on CF_3CF_2OF, CF_3-COOF, and in a few cases on higher perfluoroacyl hypofluorites, R_fCOOF. Not much has been done with these classes of compounds in the last 10 years or so, mainly because several easier ways have been developed for electrophilic fluorination.

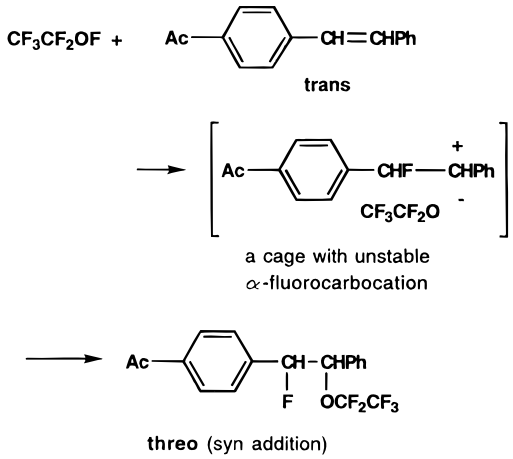
In general, these hypofluorites were made by reacting fluorine, usually diluted with nitrogen, with a suspension of sodium trifluoroacetate, or potassium salts of higher perfluoro acids, in inert solvents. An oxidizer is formed whose nature is mainly governed by the form of the salt used and the concentration of the fluorine in nitrogen. With dry salt and a low F_2 concentration the main oxidizer seemed to be fluoroxypentafluoroethane, CF_3CF_2OF,[57] while increasing fluorine concentration encourages a higher proportion of bishypofluorites. Similar results were obtained by Mulholland who eliminated the solvent and used a column of dry, solid CF_3COONa through which he passed F_2, thus obtaining CF_3CF_2OF, CF_3-$CF(OF)_2$, CF_3OF, and $CF_2(OF)_2$. These experiments were repeated with ^{18}F-^{19}F fluorine gas, having positron emitting tomography (PET) experiments in mind.[58] If, however, the salt is hydrated, the fluoride ion in the NaF which is first formed loses its nucleophilic power and mainly trifluoroacetyl hypofluorite, CF_3COOF, results (Scheme 33).[59]

Scheme 33

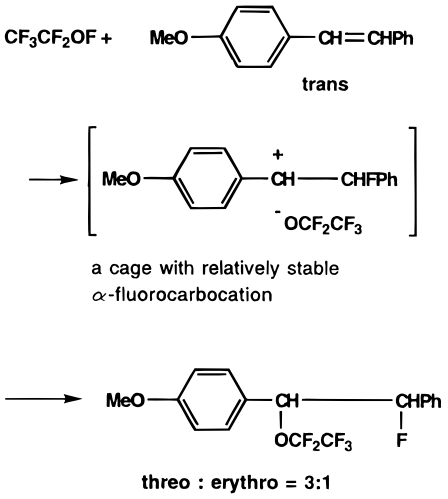


As with CF_3OF, fluoroxypentafluoroethane possesses an electrophilic fluorine and adds across double bonds with excellent regioselectivity and good *syn*-stereoselectivity. The reason for this stereoselectivity, common to all addition reactions with electrophilic fluorine, is the formation of a caged pair of ions, one of them being the extremely unstable

Scheme 34



Scheme 35



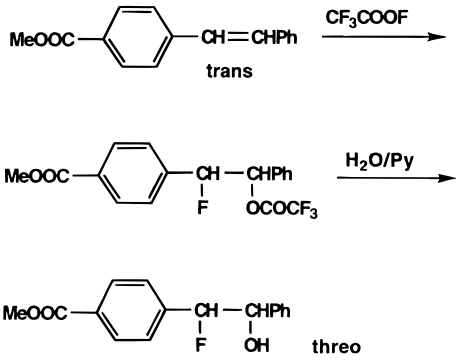
α-fluorocarbocation. This instability is responsible for the immediate collapse of the ion pair in the cage to the corresponding product before rotation around the central C−C bond can take place leading inevitably to the syn addition (Scheme 34). If on the other hand, the α-fluorocarbocation involved is somehow stabilized, there is a good chance for some diffusion out of the cage and the recombination of the ions leads to products resulting from either syn or anti addition mode (Scheme 35).[57]

Trifluoroacetyl hypofluorite was usually added across double bonds in better yields than CF_3CF_2OF, but with similar regio- and stereospecificity (syn addition). The trifluoroacetoxy group is easily hydrolyzed by aqueous pyridine at room temperature thus offering a good route to the important fluorohydrin moiety (Scheme 36).[60]

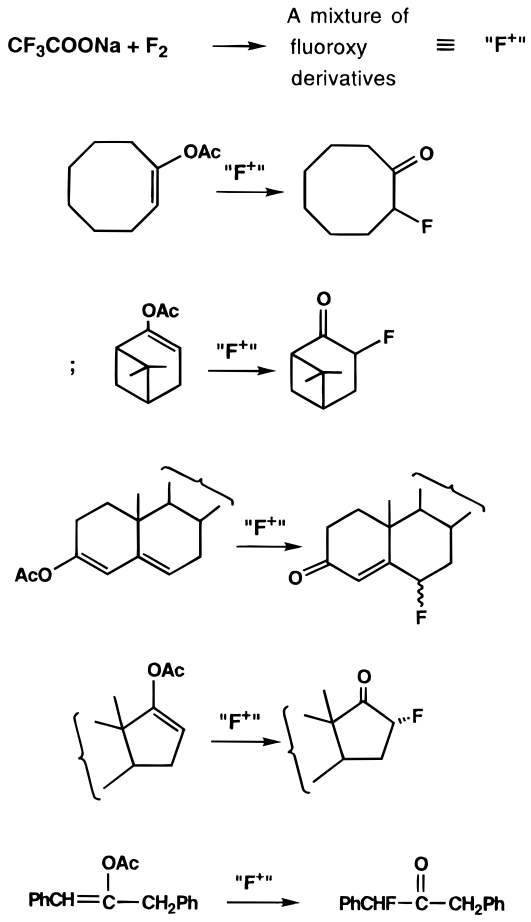
Regardless of the exact reaction conditions, the fluoroxy group is common to all the oxidants produced in the reaction between F_2 and CF_3COONa. Thus when the formation of the α-fluoro carbonyl moiety is the goal, the mixture of the various reagents can be regarded as a single homogeneous electrophilic fluorinating agent ("F^+"). The reaction of this mixture with all kinds of enol derivatives produces the corresponding α-fluorocarbonyls in yields usually exceeding 90% (Scheme 37).[58]

Higher homologs of trifluoroacetyl hypofluorites, made from potassium salts of higher perfluorocarboxylic acids, are indefinitely stable in $CFCl_3$ solution

Scheme 36



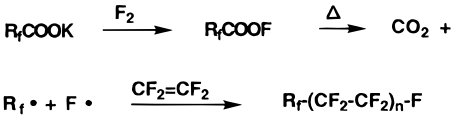
Scheme 37



at 0 °C. These solutions can therefore serve as "off the shelf" electrophilic sources and react with enol acetates to form α-fluoro ketones in the same manner as does CF_3COOF. Their uniqueness, however, lies in their ability to serve as radical initiators for polymerization of fluoroolefins. Thus, unlike the commonly used persulfate initiator which creates a sizable proportion of undesired oxygen-containing end groups, catalytic amounts of $C_8H_{17}COOF$, for example, efficiently polymerize tetrafluoroethylene forming high molecular weight polymers with practically no detectable oxygenated terminal groups (Scheme 38).[61]

It should be mentioned that recently Gambaretto and co-workers studied solvent effects on some reactions of F_2 and certain aromatics (phenols and ArH).[62] They suggested that the active species are various hypofluorites resulting from an initial reaction between the solvent and the fluorine. Their hypothesis

Scheme 38

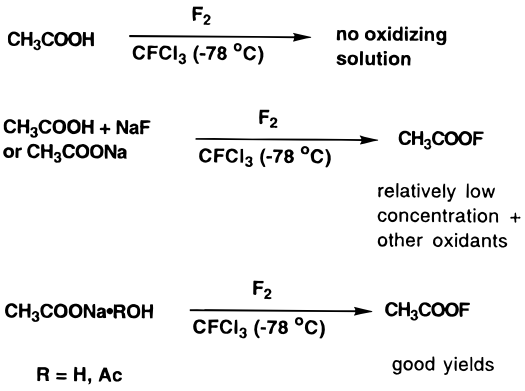


was that CF_3COOF, CF_3CF_2OF, CF_3CH_2OF, and CH_3OF were formed, but no experimental evidence was found to support this notion.

Acetyl Hypofluorite and Higher Homologs

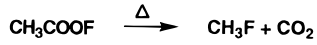
Acetyl hypofluorite is a good example of the fate of some legends and myths. It was long believed that molecules with the fluoroxy moiety could be reasonably stable only if they contained a perfluorinated alkyl residue; otherwise it was thought that they would disintegrate via an immediate vicinal HF elimination. A student in our group, who was trying in vain to dissolve F_2 in acetic acid (no oxidative solution was formed) following a claim in the literature on this subject,[63] was unaware of this reasoning. In one experiment he added NaF to a mixture of acetic acid and $CFCl_3$ and obtained a low concentration of oxidizers. The same happened when he replaced the sodium fluoride with carefully dried sodium acetate. When reacted with olefins, this solution gave several products including one which suggested an addition of the elements of F and OAc. Remembering the difference between the parallel reactions with dry and wet CF_3COONa (see above),[58] we decided to repeat the reaction with a suspension in $CFCl_3$ of sodium acetate solvated with either H_2O or AcOH. A much higher concentration of an oxidant was obtained and the reactions with olefins, which were much cleaner this time, indicated that we were dealing mainly with acetyl hypofluorite, AcOF, the first member of a new family of acyl hypofluorites (Scheme 39).[64]

Scheme 39

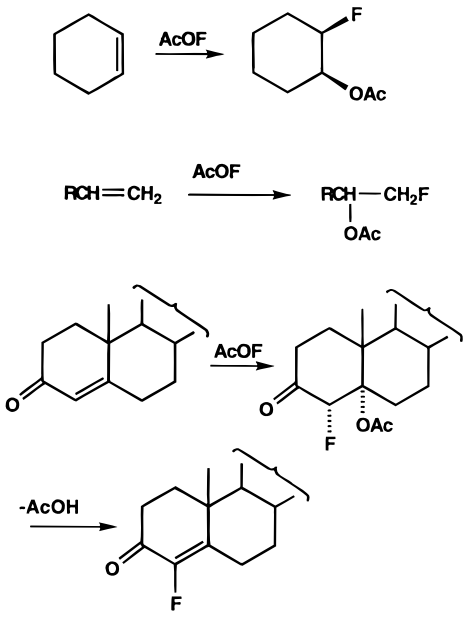


This hypofluorite proved to be quite stable in polar solutions with a half-life time of about 2 h at room temperature offering a reasonable time for reactions with organic substrates. At the beginning it was not clear whether it was a true molecule which gave these reactions or a series of processes starting with electrophilic fluorine from some source, followed by attack from the nucleophilic acetoxy group present in the reaction mixture. The ^{19}F and ^{1}H NMR strongly supported the existence of AcOF. When it was prepared in the absence of AcOH the ^{19}F NMR showed a slightly broad signal at +168 ppm ($^4J_{HF}$ = 3.6 Hz), a very characteristic chemical shift for a fluoroxy group.[7] The ^{1}H NMR revealed the methyl group of the AcOF resonating at 2.12 ppm (d, $^4J_{HF}$ = 3.6 Hz). The thermal decomposition of the AcOF was also studied by GC specially equipped for gas examination. Only methyl fluoride and CO_2 were obtained quantitatively (Scheme 40).[65]

Scheme 40



Scheme 41

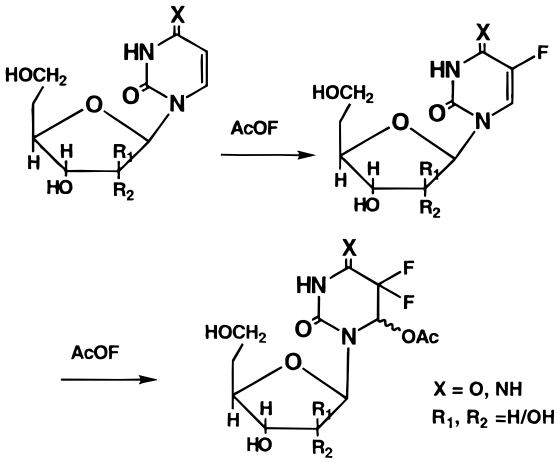


It was Appelman, however, who came up with the ultimate proof for the existence of AcOF.[66] He succeeded in isolating it in pure form and measuring its mp of −96 °C and bp of ∼53 °C. He also recorded its MS, IR, and Raman spectra. It should be noted here that isolation and purification of AcOF should be attempted only by a well-trained person, since it may explode when in a pure form.[67]

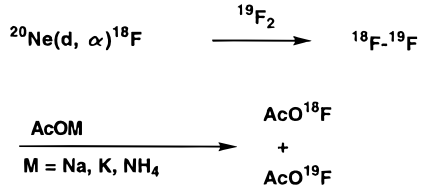
One of the characteristic reactions of AcOF is addition across many types of double bonds including benzylic, isolated aliphatic, and steroidal (Scheme 41). In all cases a full regioselectivity was observed, indicating that acetyl hypofluorite has an electrophilic fluorine. A good stereospecificity leading to syn addition was also recorded further supporting the ionic mechanism of the reaction.[68] Most reactions were completed with good yields and the formation of *cis*-2-acetoxyfluorocyclohexane from cyclohexene in 60% yield can serve as an example (Scheme 41). However, identifiable factors such as high temperatures and nonpolar solvents, and frequently unidentified ones such as minor impurities, can trigger radical decomposition of AcOF and change the course of the reaction. Visser[69] described the formation of a complicated mixture when reacting cyclohexene with acetyl hypofluorite. All compounds which he identified, including the above-described adduct, were obtained in very low yields. This prompted the author to suggest a radical mechanism for all acetyl hypofluorite addition reactions.

Visser also reacted AcOF with uracil and cytosine using water and/or acetic acid as solvents.[70] Although a single electron-transfer mechanism was

Scheme 42



Scheme 43



proposed here as well, there was no strong evidence for it. Indeed, in another paper which described one or two consecutive additions of AcOF to some unprotected uracil- and cytosine-based nucleotides, syn addition characteristic of an ionic mechanism involving an α-fluorocarbocations was observed (Scheme 42).[71]

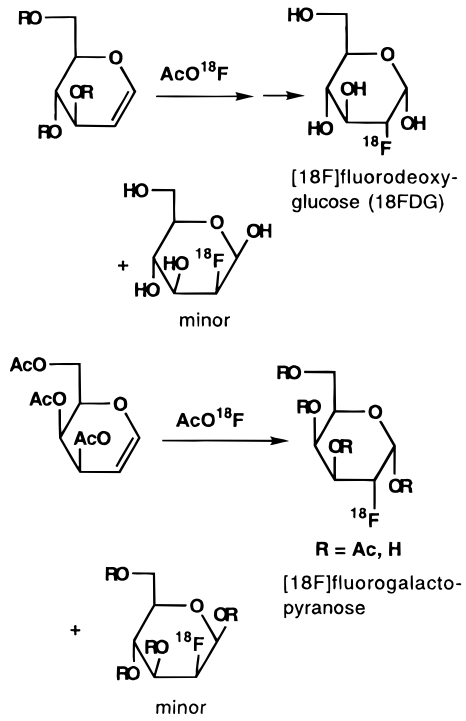
Diksic performed a similar reaction and found that an external acetate can also be incorporated in the 6 position of the uracil molecule.[72] This excluded concerted four-center mechanism, which at the time served as a popular alternative explanation for the syn addition phenomenon.

One of the main forces in the development of acetyl hypofluorite chemistry was the rapidness of its preparation which made it suitable for work with the positron-emitting isotope ^{18}F which has a half-life of 110 min. Although the specific activity was never very high, its easy preparation from neon (Scheme 43), and its fast reactions with double bonds made this reagent very attractive for positron-emitting tomography (PET) studies. Several variations for its preparation have consequently emerged including replacing the sodium acetate with ammonium acetate,[70] and the development of the "dry column" method by Ehrenkaufer and Jewett which consisted of passing gaseous F_2, or $^{18}F-^{19}F$, through a column packed with solvated AcOK·2AcOH.[73]

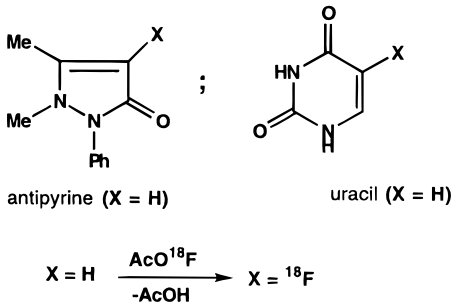
This development prompted intensive research on adding AcOF to various olefinic sugars, the synthesis of [^{18}F]fluorodeoxyglucose (18FDG) being especially emphasized. Vyplel reported good yields of *syn*-fluoroacetoxy sugars.[74] The elements of F and AcO could be found on either the α or β side of the molecule (Scheme 44). It was found that some anti addition could also be detected when working with polar solvents, but nonpolar ones reduced this to less than 4%.[75]

The great biological importance of fluorosugars, especially for antiviral treatments, is beyond the

Scheme 44



Scheme 45



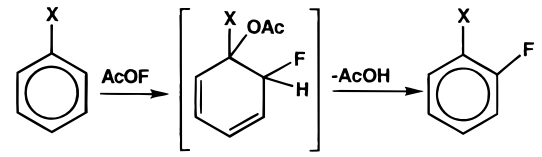
scope of this review, but we mention Vyplel's work on proving that many enzymatic processes will treat fluorosugars as practically natural substrates. He prepared such sugars using AcOF and mixed them with certain lipid saccharides in the presence of lipid synthase demonstrating easy reversible transfer of the lipid chain to the fluorosugar.[76]

Labeled acetyl hypofluorite was also used for fluorination of antipyrine and uracil. The corresponding radioactive fluoro derivatives resulted through an addition elimination mechanism (Scheme 45).[77]

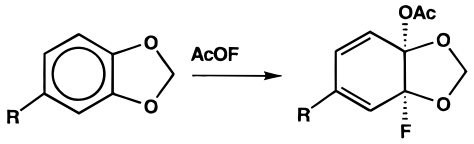
Because acetyl hypofluorite carries an electrophilic fluorine, it was only natural to check it for its ability to fluorinate aromatic compounds. It was found that activated rings produced mainly the ortho fluoro derivative in yields of up to 85%.[56] The dominant ortho substitution was a result of the addition of AcOF across the most electron-rich region of the aromatic ring. A subsequent spontaneous elimination of AcOH restored the aromaticity, but in cases where this last step was not possible, the resulting cyclohexadiene reacted very rapidly with the reagent and tars were obtained. Only in certain cases, and with careful monitoring, could the corresponding adducts be isolated (Scheme 46).

The reaction was used to prepare many types of biologically interesting derivatives including fluoro-

Scheme 46

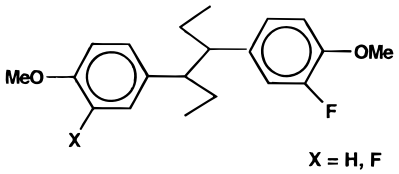


X = OR, NHCOR



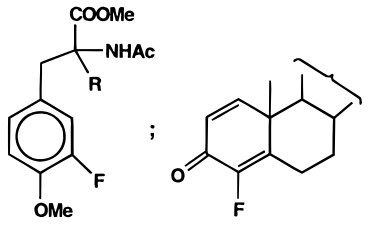
R = H, CHO

Scheme 47



X = H, F

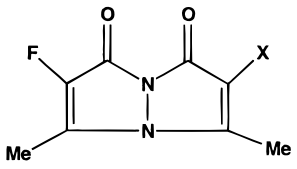
fluorohexestrol



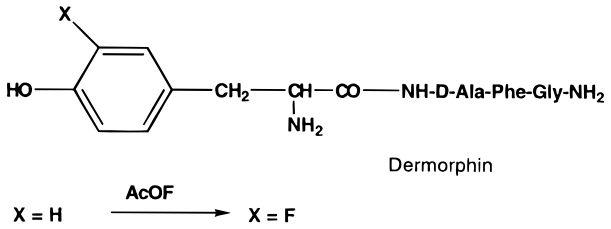
R = H, CH_2F

fluorotyrosine derivatives

Scheme 48



fluorobimane

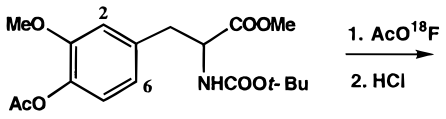


Dermorphin

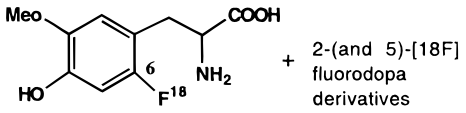
hexestrols, various 4-fluorosteroids, fluorotyrosines,[78] and their important α-fluoromethyl derivatives (Scheme 47).[79] Other compounds such as 6-fluorosteroids, fluorobimans,[80] and fluorinated opiatic peptides similar to dermorphin were also easily obtained (Scheme 48).[81]

Aromatic rings more activated than tyrosine, such as catechol derivatives, are more difficult to fluorinate since, as already mentioned, AcOF tends to add across the most electron-rich area, which in this case is between the two adjacent hydroxyls. Nevertheless,

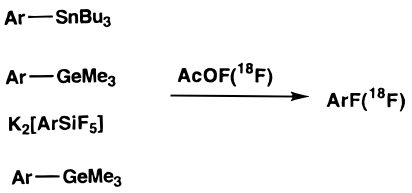
Scheme 49



protected dopa



Scheme 50



because of the importance of dopa derivatives, attempts have been undertaken to react them with radiolabeled $AcO^{18}F$. The yields were relatively low, but two main fluorodopamine compounds were isolated and identified as 2-fluoro and the more important 6-fluorodopamine (Scheme 49). The latter is metabolized in the brain to corresponding fluorodopa derivatives.[82]

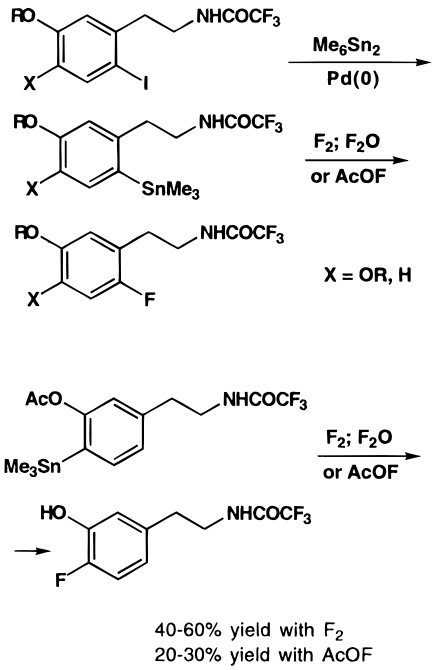
The frequently low yields obtained in these fluorinations of very electron-rich aromatic compounds encouraged exploration of other routes. Adam was the first to successfully try reacting AcOF with aromatic tin derivatives resulting in the corresponding aryl fluorides in excellent yields.[83] Other heteroatoms such as silicon[84] and germanium[85] were also employed for this purpose (Scheme 50).

Very recently Satyamurthy used similar substitutions for the synthesis of 6-fluorodopamine, and 6- and 4-fluoro-*m*-tyramine. He chose to replace the trimethyltin moiety with the fluorine atom by using acetyl hypofluorite as well as other fluorinating agents such as fluorine and oxygen difluoride (Scheme 51).[86] This study is a prelude to the attempts to prepare these important derivatives with the ^{18}F isotope with the highest possible radioyield for use in PET studies.

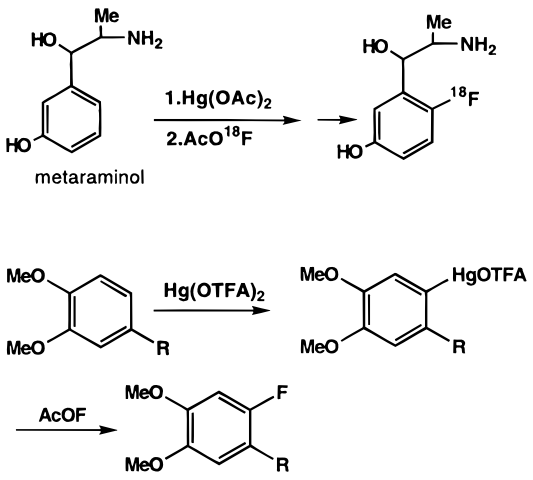
Visser used mercury as the metal atom. He found that with arylmercury acetates, ArHgOAc, the best results could be achieved with acetic acid used as a solvent.[87] As in most of the other reactions he described, a radical cation mechanism was also proposed here.[88] This type of exchange reaction was used for fluorination of the para (to the hydroxyl group) position of the biologically important neurotransmitter, metaraminol,[89] and for various catechol derivatives (Scheme 52),[90] especially dopa (Scheme 53).[91] Also fluorinated were compounds in the benzodiazepine family which strongly affect the central nervous system (Scheme 54).[92]

The cleavage of the carbon metal bond is not confined to aromatics only and was found to be of a general nature. It was proven that the exchange reaction proceeds through an electrophilic attack of the fluorine on the electrons of the C−M bond itself, an attack which is bound to lead to a full retention of configuration (Scheme 55).[93]

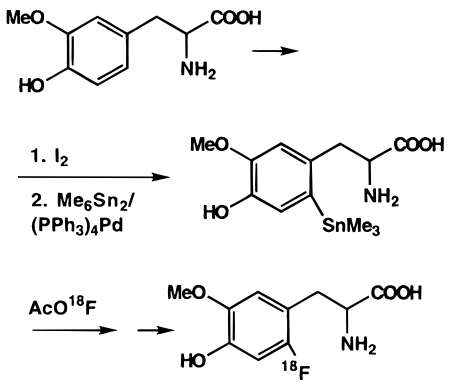
Scheme 51



Scheme 52

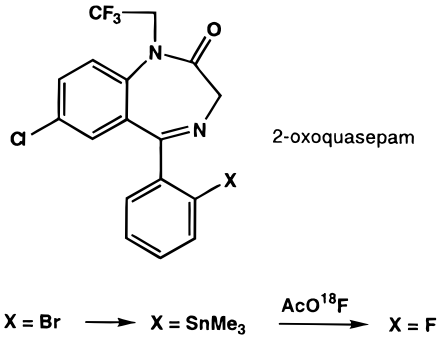


Scheme 53

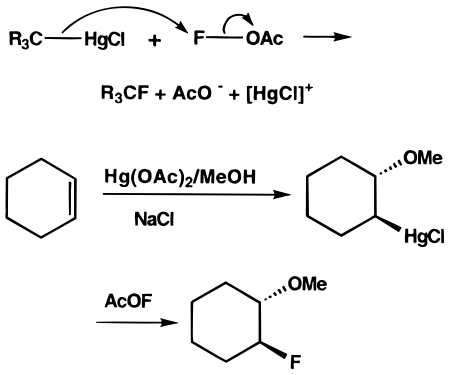


As with other hypofluorites, acetyl hypofluorite reacts smoothly with electron-rich olefins, such as enol acetates, to produce the expected α-fluorocarbonyls (Scheme 56).[94] In most cases lithium enolates of monocarbonyl derivatives made with LDA could also be fluorinated although the released diethylamine had to be distilled out prior to the reaction with AcOF (Scheme 57).[95] This hypofluorite also

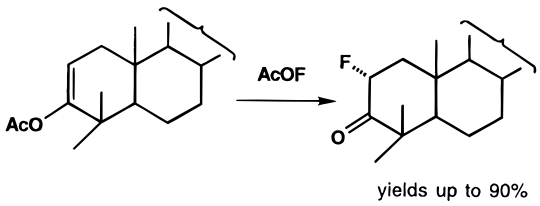
Scheme 54



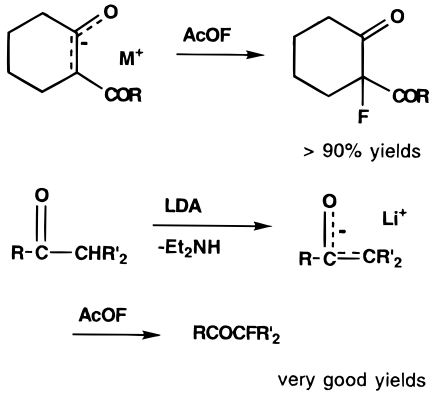
Scheme 55



Scheme 56



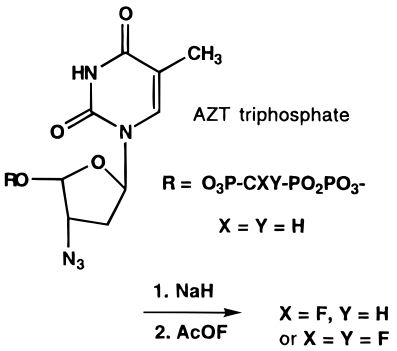
Scheme 57



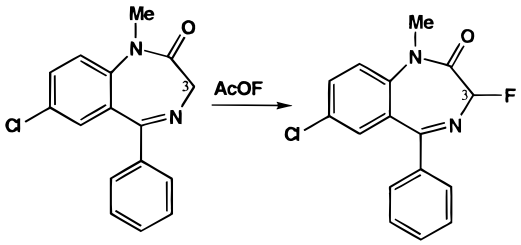
reacts very efficiently with 1,3-dicarbonyl compounds or their easy to make enolates (Scheme 57).[96]

The reaction proceeds well with other easily enolizable carbonyl derivatives as well and the methylene phosphonate moiety in an analog of the AZT drug (Scheme 58) can serve as an example. It is interesting to mention that while the resulting fluoro derivative is less potent than AZT itself, it is much more active than the parallel CH_2 derivative.[97] The high electron density in the 3 position of diazepam was the basis for its easy fluorination at this position without the intermediacy of an enol derivative (Scheme 59).[98] In most cases—but not all (see the previous reference for example)—the parallel reac-

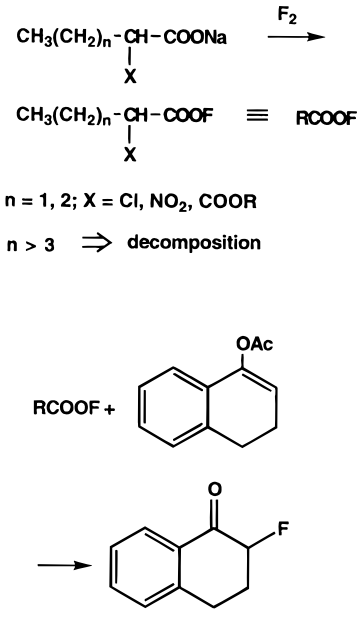
Scheme 58



Scheme 59



Scheme 60



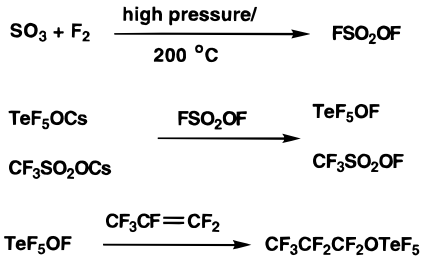
tions with F_2, CF_3OF, or CF_3COOF resulted only in tars or in very low yields of the expected monofluoro derivatives.

The question of whether AcOF is the only fluorooxy compound with a fluorine-free alkyl residue was addressed. It was reported that there are some higher homologs,[99] although their number seems to be limited. If the alkyl chain in these hypofluorites is too long there are many conformations where an alkyl hydrogen may be near the oxygen-bound fluorine, apparently triggering HF and CO_2 elimination followed by uncontrollable fragmentation. As expected, the higher acyl hypofluorites possess an electrophilic fluorine and react with enol acetates to form α-fluoro ketones (Scheme 60).

Hypofluorites Bonded to the Sulfur Atom

Although some of the reagents in this category such as SF_5OF were known for many years, their use in

Scheme 61

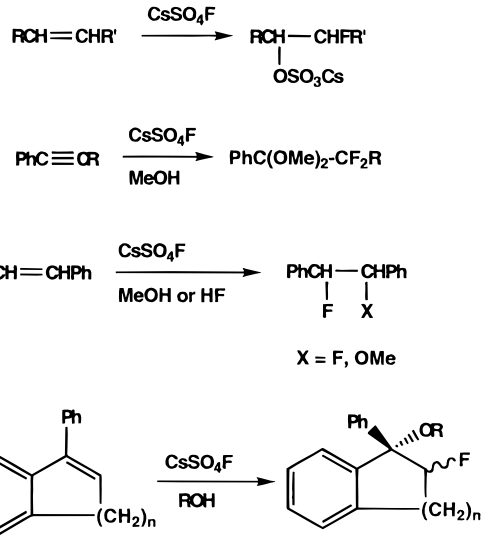


organic chemistry has been limited since they are not commercially available. Chemists who are in a position to prepare such reagents in their laboratory are usually interested in their physical properties and inorganic reactions, while most organic chemists would be too intimidated to make them. The author is not aware of a single synthetic organic work with SF_5OF in the last 10 or so years. Christe prepared the tellurium analog TeF_5OF by using fluorosulfuryl hypofluorite, FSO_2OF, as a fluorinating agent[100] and demonstrated the electrophilicity of the oxygen-bound fluorine by performing a few reactions with simple perfluoroolefins. Recently Appelman used a similar procedure to prepare, isolate and characterize for the first time, trifluoromethanesulfonyl hypofluorite, CF_3SO_2OF, a hypofluorite derivative in which the sulfur atom is attached to a carbon (Scheme 61).[101] It should be noted that fluorosulfuryl hypofluorite itself is still a reagent used very rarely. It is prepared from SO_3 and F_2 either by using high pressure and temperature or catalytically at 160−180 °C at atmospheric pressure. Although no organic reactions with CF_3SO_2OF were reported, the ^{19}F NMR shows a peak at +238 ppm for the OF moiety, clearly indicating the electrophilicity of the oxygen-bound fluorine (see discussion in the last section). It should be noted, however, that great care should be exercised when working with this compound since it is potentially explosive and was involved in tragic accidents.

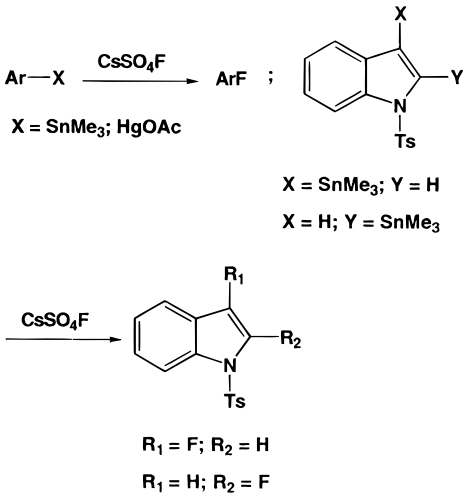
Among the sulfur-bound hypofluorites cesium fluorooxysulfate, $CsSO_4F$, is an exception in the sense that quite a few synthetic organic reactions were performed with it. Appelman was the first to prepare, isolate, and fully characterize both $CsSO_4F$ and $RbSO_4F$ by passing fluorine through M_2SO_4 (M = Cs, Rb) solutions.[102] Its advantages are the possibility of storage and its relative mild reactions, but on the other hand it is produced only in minute amounts at a time (its reactions with various substrates are usually on the 1 mmol scale) since it tends to explode under mild pressure.[102,103] It has been added to olefins and, in absence of nucleophilic solvents, forms a vicinal fluoro−sulfoxy cesium salt although the stereospecifity is quite low.[104] In the presence of solvents such as MeOH or HF, vicinal fluoromethoxy or difluoro derivatives were obtained with some syn addition preference.[105] The reaction was also used to add the elements of F and OR across several indene derivatives with yields of up to 70% and is believed to proceed via a radical cation mechanism.[106] Addition to acetylenes was also attempted resulting in *gem*-difluoro ketals (Scheme 62).[107]

Cesium fluorooxysulfate has often been used for aromatic fluorinations. Two main approaches have been employed, substituting a heteroatom attached to the ring or a direct attack on the nucleus. Cham-

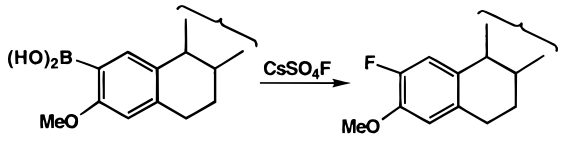
Scheme 62



Scheme 63



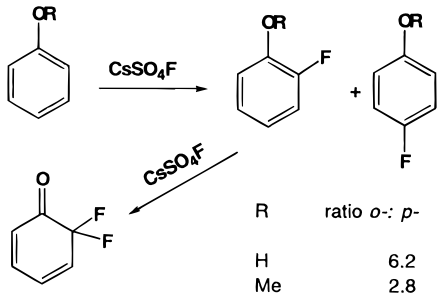
Scheme 64



bers found that replacing trimethyltin is more efficient than with any other aromatic tin derivative.[108] Arylmercury compounds were also successfully used for this purpose in general[109] and for the synthesis of both 2- and 3-fluoroindanols in particular (Scheme 63).[110] Arylboronic acids were similarly fluorinated. Thus 2-(dihydroxyboryl)-3-*O*-methylestrone[111] produced only 2-fluoroestrones avoiding the usual mixture of 2- and 4-fluoroestrones obtained by many other methods (Scheme 64).[112]

Appelman reacted phenols and other activated aromatics to form mainly *o*-fluoro derivatives accompanied by some para isomers, the ratio of ortho to para being usually around 4. The corresponding difluoro ketones were also formed from an addition reaction of the reagent to the fluoro derivatives formed in the first stage (Scheme 65). Appelman studied also the effect of acidic catalysts on the reaction using HF, H_2SO_4, BF_3, CF_3SO_3H, FSO_3H, and $SbF_5{\cdot}FSO_3H$ on the reaction of $CsSO_4F$ with toluene, nitrobenzene, and naphthalene in acetonitrile. In general the stronger the acid the stronger the catalytic effect was with the exception of H_2SO_4 when naphthalene served as a substrate. Low yields of monomeric oxygenated products were also found along with considerable oxygen- and fluorine-containing dimers and higher polymers. These results were interpreted in terms of acid-catalyzed electrophilic fluorination followed by free radical-induced oxidative coupling.[102,113] Zupan used BF_3 as a catalyst for room temperature fluorinations of alkoxy-substituted benzene and naphthalene derivatives, which took up to 6 h to complete, and reported similar results. He found however that with the more bulky alkoxy groups the fluorination at the ortho position tended to be distracted and the ratio of ortho to para fluorination decreased considerably (Scheme 65).[103,114] Zupan also applied $CsSO_4F$ for 4 h at room temperature to fluorinate unactivated polyaromatic compounds such as naphthalene, phenanthrene, and pyrene. The last two compounds did not require BF_3 for their reactions with $CsSO_4F$ and what is more a very diluted reagent should be used to avoid a sharp drop of the yields and formation of unidentified polymeric compounds (Scheme 66).[115] It should be noted that Patrick performed similar aromatic fluorinations with $CsSO_4F$ but did not observe any secondary addition leading to a difluorocarbonyl derivative.[116]

Scheme 65



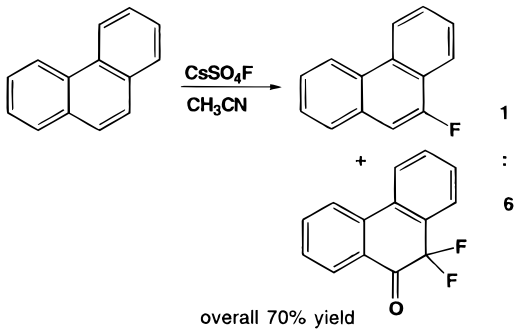
R	ratio *o*-: *p*-
H	6.2
Me	2.8
n-Bu	1.8
EtCHMe	1.2

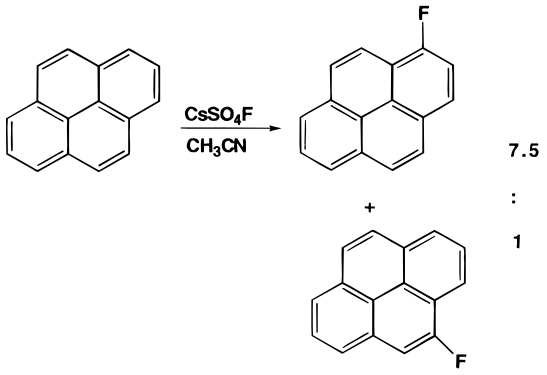
A third quite surprising reaction leading to aryl fluorides was reported by Zupan who reacted various α-substituted benzyl alcohols with $CsSO_4F$ (Scheme 67). The mechanism of this reaction is unknown as yet but the yields are good especially with compounds having an electron-donating ring.[117] Under radical conditions various alkyl benzenes were fluorinated on the benzylic position in 50−60% yield (Scheme 67).[118] When oxygen was added during the reaction, the radical pathway became insignificant and mostly the aromatic ring was fluorinated. A non-benzenoidic aromatic porphyrin derivative reacted as well to form mainly 5-fluoroporphyrin (Scheme 68) accompanied by some di- and trifluoro derivatives.[119]

Being an oxidizing agent, $CsSO_4F$ was used to transform primary alcohols, as well as aromatic aldehydes to the corresponding acyl fluorides[120] and certain secondary alcohols to the respective ketones (Scheme 69).[121] In contact with this reagent, various N-substituted uracils and barbituric acid derivatives form 5-fluoro-6-alkoxyuracils accompanied by some 5,5-difluoro derivatives (Scheme 70).[122]

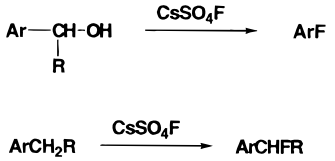
Few attempts have been made to harness the electrophilic power of cesium fluorooxysulfate to fluorinate enol derivatives, but it seems that better

Scheme 66

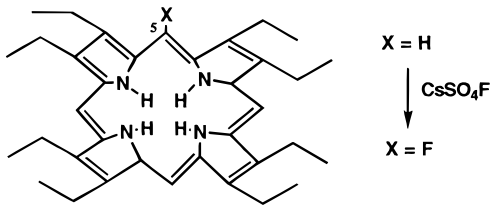




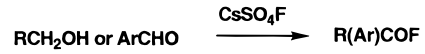
Scheme 67



Scheme 68



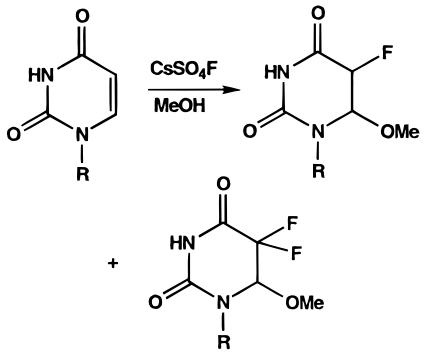
Scheme 69



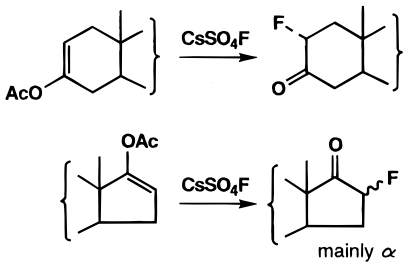
results could be obtained with other agents as may be judged from Kobayashi's work where 2-fluorocholestenone was made from the enol acetate en route to 2-fluorovitamin D.[123] An enol acetate on ring D also reacted to produce a 16-fluoroestrone (Scheme 71).[124] Cesium fluorooxysulfate was used to fluorinate the enol form of 1,3-dicarbonyls, affording mainly the expected 2-fluoro derivative (Scheme 72).[125]

Having an electrophilic fluorine, cesium fluorooxysulfate was also tested for its ability to substitute tertiary unactivated hydrogens,[126] as fluorine itself does in such a remarkable manner.[11] Some tertiary fluorination did take place, especially when the relatively highly reactive adamantane was used as a substrate, but the yields were quite low and some radical fluorination on secondary carbons was also

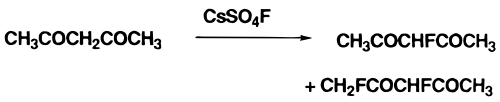
Scheme 70



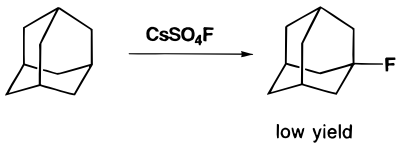
Scheme 71



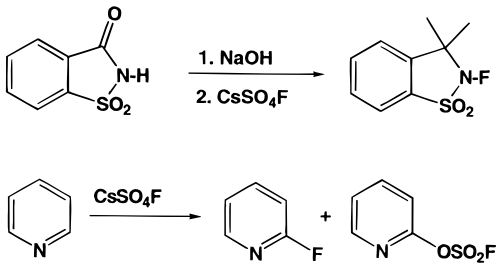
Scheme 72



Scheme 73



Scheme 74



observed despite the addition of radical scavengers (Scheme 73).

Recently this reagent was used for preparation of NF compounds, although usually the sodium salt had first to be prepared in order to react satisfactorily with $CsSO_4F$. Phtalimides and saccharin are just two examples[127] for making stable NF derivatives, while *N*-fluoropyridine rearranged to 2-fluoropyridine accompanied by some 2-fluorosulfonate derivative (Scheme 74).[128]

Fluoroxy Reagents Not Containing Electrophilic Fluorine

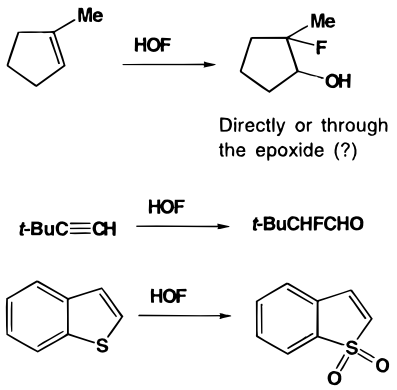
All the hypofluorites mentioned so far have an electrophilic fluorine and have been used primarily for fluorination purposes. Contrary to these the oxygen-bound fluorine in the reagents discussed

below enjoys a much higher electron density and behaves more as a nucleophile. Consequently, the oxygen atom itself becomes a strong electrophile governing quite a few unique reactions. We will cover in this section reactions which lead to fluorine containing products only.

HOF and Its Acetonitrile Complex

Hypofluorous acid was first prepared by Appelman, and in his first account on 1973, he pointed out that like many other fluorinating agents and procedures, HOF was believed to be an impossible to make species.[129] He dubbed this phenomenon as "auto-hypnosis"; once chemists accept some "fact" they stop bothering to confirm it. Appelman made mixtures of HOF/HF in batches of 30−50 mg, by passing fluorine over ice and storing the reaction mixtures at −78 °C.[130] The ^{19}F NMR indicated that the fluorine is quite shielded and resonates at +20 ppm,[131] a relatively high field compared to other reagents with an O−F bond. He later published a detailed study on the kinetics and mechanism of this reaction and the effect of F_2 on the produced HOF.[132] In his thorough research, Appelman also measured the Raman spectra of solid HOF and DOF revealing a zigzag chain arrangement.[133] From an X-ray study of a single crystal of HOF it was found that the oxygen atom, rather than the fluorine, is involved in the hydrogen bonding, while the halogen sticks out of the chain line.[134] Appelman tried a few organic reactions with HOF, but for the most part they were impractical because of the short half-life time of HOF at room temperature and of the minute amounts (~1 mmol) which could be generated in a batch mode. Still, it was demonstrated that when added to olefins it produced fluorohydrins, with regiochemistry confirming the nucleophilicity of the fluorine atom (Scheme 75).[135] At that stage the authors were not

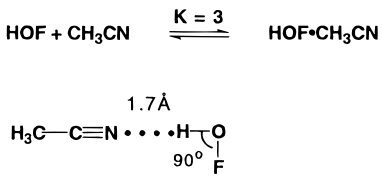
Scheme 75



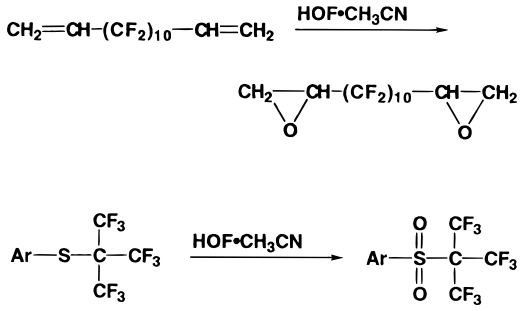
sure if the fluorohydrin derivatives were formed directly during the reaction between HOF and the olefin or they resulted from a secondary reaction between the unsolvated HF and an intermediate epoxide. HOF was also reacted with a few acetylenes (Scheme 75)[135] resembling the Merritt reactions of F_2O with triple bonds.[136] Although the scale and the yields were very low, the potential to oxidize sulfides and naphthalene could already be detected even in this early stage (Scheme 75).[137]

In the mid-1980s we were experimenting with the possible interaction between fluorine and acetonitrile

Scheme 76



Scheme 77



and noticed that when the CH_3CN was carefully dried no oxidative solution developed. Only some of the methyl hydrogens were slowly substituted by fluorine, probably via unavoidable radical reactions. When, however, the acetonitrile was used without special drying an oxidative solution was formed which increased in concentration with increasing water content in the reaction mixture.[138] Subsequently we had several indications that a complex between HOF and acetonitrile was being formed.[139] Additional studies indeed proved this hypothesis and measurements showed that the equilibrium constant of the complexation reaction is 3 and the formation enthalpy −14.3 kJ.[140] The solid structure was elucidated by X-ray crystallography, showing a linear arrangement between the nitrogen, hydrogen, and the oxygen, while the H−O−F bond forms a 90° angle. The distance between the nitrogen and the hydrogen atoms is 1.7 Å, permitting weak hydrogen bonding responsible for the complexation (Scheme 76).[141]

This complex has a great advantage over free HOF, since it is relatively stable at room temperature (half-life time more than an hour) and can be conveniently made in concentrations of up to 1 molar. HOF·CH_3-CN has not found much use as a fluorinating agent and therefore will not be reviewed here in detail. We will mention however, that it is an excellent oxygen-transfer agent and in many instances more efficient than dimethyldioxirane.[142] It is a superior epoxidizing and oxidizing agent even for electron-poor, fluorine-containing olefins[143] and sulfides (Scheme 77).[144]

Alkyl Hypofluorites

As with acetyl hypofluorite, methyl hypofluorite was a hypothetical molecule until recently. Early theoretical studies[145] did not support its possible existence, since in principle HF elimination seemed to be a very favorable process. On the basis of our success with acetyl hypofluorite, we decided to conduct some experiments to see if a molecule of MeOF could exist, at least in solutions. Addition of the elements of CH_3O and F across a double bond is not in itself compelling evidence for the existence of a CH_3OF molecule, since this has been accomplished

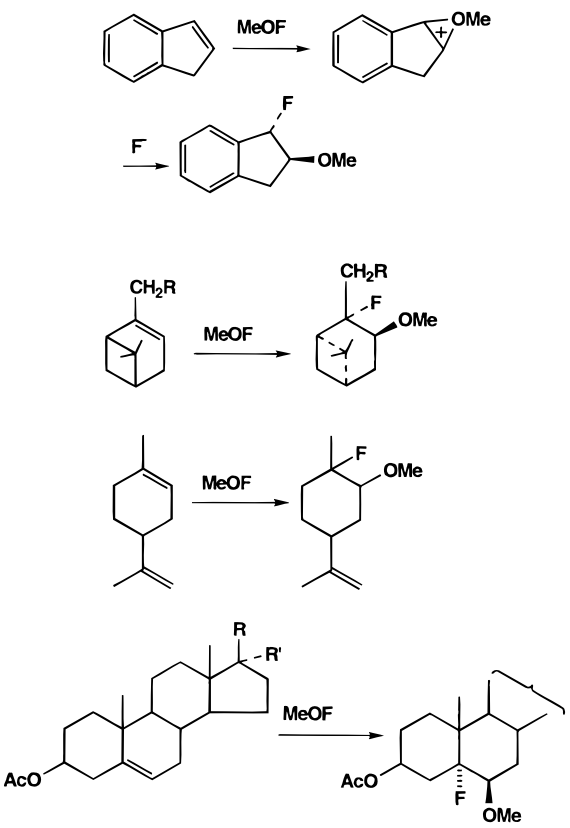
by using methanol as a solvent in reactions of olefins or acetylenes with a source of electrophilic fluorine such as F_2, CF_3OF, $FClO_3$, $CsSO_4F$, or XeF_2.[146] Of special interest in this respect was Shellhamer's work. He seemed to have successfully generated MeOF evidenced by reacting olefins with XeF_2/MeOH.[147] Later however, it was recognized that the reactive intermediate involved was the unique MeOXeF.[148]

Our first set of experiments aimed at forming MeOF was conducted with elemental fluorine passed through a suspension of sodium methoxide in $CFCl_3$ at −78 °C, but nothing which might have hinted toward the formation of methyl hypofluorite was detected. Similar negative results were obtained when fluorine was bubbled through a dilute solution of MeOH in $CFCl_3$ at −78 °C. Somewhat more encouraging signs emerged when F_2 was passed through cold neat MeOH, but it seemed that after a short time several oxidative species were formed, and reaction with olefins were not very clean to say the least. After observing the stabilizing effect acetonitrile had on HOF (see above), we passed F_2 through a MeOH/CH_3CN mixture and got an oxidizing solution which seemed to be mainly MeOF.[149] Its addition to olefins was such that the MeO group acted as an electrophile. The ^{19}F NMR +120.3 ppm (q, $^3J_{HF}$ = 45 Hz), ^1H NMR 4.51 ppm (d, $^3J_{HF}$ = 45 Hz), and ^{13}C NMR 70.3 ppm ($^2J_{CF}$ = 11 Hz) were in agreement with the structure of MeOF. The observed $^3J_{HF}$ is the highest coupling constant of this type of which we are aware. In order to finally prove the structure of this molecule, it was isolated in a pure form by a series of cold tube to cold tube distillations. The pure sample of MeOF was thus obtained with a mp of −142 °C and, through an extrapolation of the vapor pressure, its boiling point was calculated to be −32.6 °C. The mass spectrum shows a prominent molecular ion peak at *m/e* 50 (M^+, 70%) and 29 (HCO^+, 100%) originating from formaldehyde, the main thermal decomposition pathway.[150] This new molecule broke a long-standing record for the smallest organic molecule which had not yet been made. Prior to its preparation, MeHe, MeOHe, and MeOF were the three smallest organic compounds waiting to be introduced to the extremely rich world of organic chemistry.

Unlike HOF·CH_3CN, methyl hypofluorite was used for both methoxylation processes[151] and reactions which resulted in fluorine incorporation into the target molecule. Similar to the hypofluorous acid complex, however, the fluorine was not the electrophilic end of the reagent. The methoxylium group ("MeO^+") assumes this role.[152]

When MeOF was reacted with indene, *trans*-1-fluoro-2-methoxyindene was obtained. The anti addition is characteristic of this reagent since, unlike electrophilic fluorine, the electrophilic methoxylium species is capable of forming a bridged oxonium intermediate (Scheme 78). MeOF was also successfully added to strained bicyclic pinene derivatives and to several steroids. It is more sensitive to electronic factors than steric ones and with limonene for example, it reacted selectively with the more hindered but electron richer endocyclic double bond.

Scheme 78



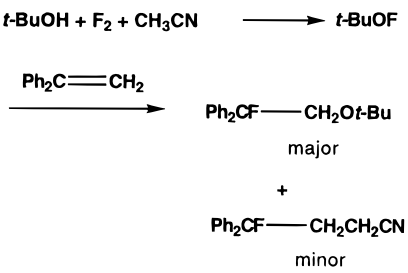
Enones and other electron-poor olefins do not react with MeOF (Scheme 78).[153]

Recent theoretical studies elaborate on methyl hypofluorite's structure and its relative stability. Apeloig was able to carry out ab initio calculations and extract from them NMR and IR data which well agreed with the actual experimental values. He also predicted a C−O−F angle of around 105° and a length of 1.45 Å for the O−F bond. The two most favorable decomposition pathways seem to be through radical decomposition to $MeO^\bullet + F^\bullet$, and through one-step HF elimination, both with the same activation free energy of 38 kcal/mol.[154]

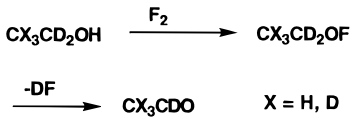
There is a link between the ^{19}F NMR chemical shift and the electrophilic character of the oxygen-bound fluorine, but this is still not completely established. It appears that the borderline is somewhere between +160 and +120 ppm, since all oxygen-bound fluorine atoms acting as electrophiles resonate at or lower than 160 ppm, while the nucleophilic OFs could be found at 120 ppm and toward a higher field. This criterion holds also for the second member of the alkyl hypofluorite family, *tert*-butyl hypofluorite, whose fluorine atom resonates at +67 ppm. *t*-BuOF was prepared similarly to MeOF and when isolated it proved to be a white solid melting at −94 °C with a bp of around +40 °C. It adds across some double bonds mainly in an anti mode, forming principally the adduct in which the *tert*-butoxylium species acts as an electrophile. The major byproduct of this reaction is the incorporation of the acetonitrile residue from acetonitrile which serves as a solvent. A γ-fluoronitrile derivative is formed through a not yet completely understood mechanism (Scheme 79).[155]

The success of preparing MeOF and *t*-BuOF could not be repeated with other alcohols. Attempts to

Scheme 79



Scheme 80



make EtOF, PrOF, CF_3CH_2OF, $(CF_3)_2CHOF$, and alike failed and the only results were formation of HF and decomposition of the alcohols. Apparently adjacent CH bond strengths are an important factor in alkyl hypofluorite stability, and we tried to check alcohols with deuterium atoms α to the OH group. Reacting an acetonitrile solution of CD_3CD_2OD with fluorine indeed formed an oxidative solution, and spectral evidence clearly points to the formation of the desired CD_3CD_2OF. Any attempt, however, to react this oxidant with electron-rich centers, such as various types of double bonds including enol derivatives, resulted in its immediate decomposition with no affect on the organic substrate. When the deuterated hypofluorite is warmed to 20 °C it quickly decomposes, and the oxidative power disappears along with the deuterium signals in ^2D NMR at 1.28 and 4.75 ppm for the CD_3 and CD_2OF groups, respectively. Two new peaks at 2.0 and 9.8 ppm suggest that the decomposition product is CD_3CDO, obtained via DF elimination from the hypofluorite. Similar results were also obtained with CH_3CD_2OD (Scheme 80).[156]

Recent Reviews on Fluorination Methods Involving the OF Moiety

We have noted at the beginning of this review the excellent but early reviews of Hesse and Mukhametshin covering the CF_3OF chemistry until 1977[6] and 1980,[7] respectively. In 1986 Purrington wrote a review on F_2 and various hypofluorites and their role in organic chemistry,[157] and Rozen published several monographs including an *account* of his research with fluorine and various hypofluorites.[158] Mann covered selected literature dealing with hypofluorites,[159] while Firnau concentrated on the synthesis of ^{18}F-containing compounds and their synthesis with AcOF.[160] Yagupolskii reviewed the synthesis of optically active aromatic amino acids mainly phenyl alanine and tyrosine where the aromatic fluorine was introduced with acetyl and other hypofluorites.[161] In 1992 Wilkinson published a review in this journal describing many fluorinating methods with a respectable proportion devoted to hypofluorites including $CsSO_4F$.[162] Recently Resnati wrote a review which concentrated mainly on the synthesis and bioactivity of chiral fluorine-containing compounds and described electrophilic fluorination procedures with F_2, CF_3OF, and AcOF. Finally two books which are of great help to the fluoroorganic community should also be mentioned. The first is *New Fluorinating Agents in Organic Synthesis* edited by German and Zemskov,[163] and the most recent one is the *Chemistry of Organic Fluorine Compounds II* edited by Hudlicky and Pavlath.[164]

Conclusion

More than 40 years have passed from the preparation of the first carbon-containing hypofluorite, CF_3OF, to the latest, *t*-BuOF. During this period fluorine chemistry underwent an unprecedented revolution, moving from an esoteric corner to the center stage of organic chemistry. Seebach[165] and others predict a bright future to this branch of chemistry. More than 6% of all the compounds appearing in *Chemical Abstracts* possess a CF bond.[166] The hypofluorite group has had a very important role in this remarkable advance. It helped to introduce many new concepts to the reasoning methodology of the organofluorine chemist. Some of these concepts were also new and useful to organic chemistry in general. Electrophilic fluorination, which in the beginning was considered almost a contradiction in terms, is now widely used and has bred other useful reagents, such as the family of NF-possessing compounds. Some of the hypofluorites have helped to create another notion, of the electrophilic oxygenated species, with a yet to be revealed potential. We believe that the field of fluoroxy compounds will continue to grow very strongly and organofluorine, as well as general chemistry, will only benefit from this.

Acknowledgments

Some parts of the research presented in this review were supported by the Israel Science Foundation administrated by the Israel Academy of Science and Humanities.

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CR941147+