Attaching the Fluorine Atom to Organic Molecules Using BrF₃ and Other Reagents Directly Derived from F₂

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ABSTRACT

Elemental fluorine is a starting point for nucleophilic fluorinations (e.g., BrF_3), radical fluorinations (e.g., F_2 under irradiation), and electrophilic fluorinations (e.g., AcOF). All three categories are represented in this Account. Bromine trifluoride, although commercially available, can be readily made from the elements and is a very good source for naked nucleophilic fluoride ions. To minimize radical reactions, an anchor has to be installed in the molecules with which it reacts. Such an anchor is constituted of a soft base such as nitrogen and especially sulfur atoms. This reagent was used for constructing compounds with a CF_2, CF_3, CHF_2, or CF_2COOH group in specific sites. F_2 itself was used for completing perfluorination of various polyfluoroethers, while the electrophilic acetyl hypofluorite is an excellent tool for introducing a single fluorine atom into organic molecules such as carboxylic acids and nitro compounds.

Introduction

Elemental fluorine is an amazing entity especially when used in organic chemistry. It can play variable roles at will. If there is a need for a source of radical fluorine species, F_2 is ready;[1] if one desires to work in an electrophilic mode, F_2 is an excellent choice;[2] and if the idea is to perform a nucleophilic fluorination with active naked fluoride, F_2 would still be a very good candidate. What is even more amazing is the fact that this most reactive element of the periodic table can perform some of the most exacting regio- and stereoselective reactions in chemistry.[3] But F_2 is not only used for fluorination purposes, as it also serves as a tool for constructing difficult or impossible to make fluorine-free compounds,[4,5] making it a versatile reagent indeed. This Account, though,

will mostly revolve around some *fluorination* methods not mentioned in our previous Account[6] and Chemical Reviews paper.[7]

Fluorine-containing materials are, of course, very valuable in our life. Numerous fluoropolymers,[8] fluorooligomers, and perfluorinated molecules[9] are very important in material science. Small fluorine-containing molecules such as the new HFCs and blowing agents with zero ozone-depleting potentials, surfactants, lubricants, dyes, etc., are one of the pillars of any modern society. Probably the most important of all, are the many drugs, anesthetics, artificial blood constituents, and agriculturally important materials that are either in use or in every stage of the development ladder. While the scope of this Account does not allow us to elaborate on these families of compounds and their applications, we would like to point to Seebach's review published a 15 years ago, but still relevant today, emphasizing the role of fluoroorganic chemistry and categorizing it among the few areas with a bright future, which probably will continue to attract substantial research efforts and resources.[10] In this Account, we will mention different types of fluorination reactions, all based on the same starting point—F_2.
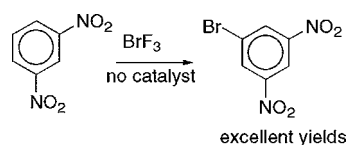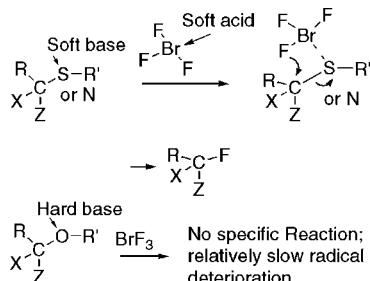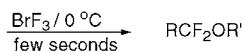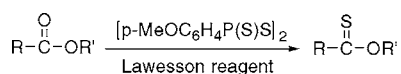
A. Nucleophilic Fluorinations with Bromine Trifluoride—BrF₃

The biggest handicap of bromine trifluoride was, and still is, the mythical fears and prejudice associated with it, as was the situation with F_2 20 years ago. These fears are based on its strong and frequently uncontrolled reactivity with water and oxygenated solvents. All its reactions could, however, be carried out with solvents such as $CHCl_3$, $CFCl_3$, CCl_4, CH_2Cl_2, or perfluoroethers. BrF_3 is commercially available but can also be readily prepared in the laboratory by passing fluorine through bromine at about +5 °C. It can be stored indefinitely in Teflon vessels.

Till recently, very few organic works with BrF_3 were published. Martin used it for fluorination of sulfur and tellurium atoms in certain organic derivatives.[11] Lemal needed it for his elegant synthesis of hexafluorocyclopentadiene,[12] and Boguslavskaya and Yagupolskii used it for substituting bromine atoms with fluorine.[13,14] The reagent's main use, however, lies in the preparation of modern anesthetics, such as sevoflurane and desflurane, where chlorine or bromine atoms and sometimes even hydrogens are replaced by fluorine.[15–17]

Bromine trifluoride is essentially a nucleophilic fluorinating agent. It possesses nonsolvated and hence very reactive fluorides along with a strong electrophilic bromine. This last quality made BrF_3 an excellent brominating agent of very deactivated aromatic compounds (Scheme 1)[18] but also presented certain problems for reactions with compounds having activated aromatic rings. The electrophilic bromine is also a soft acid, a pivotal feature in our main line of research with this reagent.

Shlomo Rozen was born in 1942 in Bulgaria and arrived in 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 pioneer of fluorine chemistry in Israel, the late Ernst D. Bergmann, and I. Shahak. He spent 3 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 started working with elemental fluorine. In 1976, he joined the School of Chemistry at the Tel Aviv University were he assumed the position of Professor in 1989. In 1999, he became a Josef Kryss professor in Organic Chemistry and held the position of the Head of the School of Chemistry from 1997 until 2001. He is the recipient of the "Teva Founders" award, of the 2005 ACS Award for Creative Work in Fluorine Chemistry, and of the Israel Chemical Society 2004 Award. For many years, he was a visiting scientist at the Central Research Department of the DuPont Company in Delaware. His main goal in chemistry is to demonstrate that elemental fluorine can be a very useful reagent in fluorine chemistry, as well as in general organic chemistry, and chemists should discard their unjustified fear and prejudice against this long known but somewhat neglected element.

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Scheme 1. Aromatic Electrophilic Bromination with BrF₃

$$\text{1,3-dinitrobenzene} \xrightarrow[\text{no catalyst}]{BrF_3} \text{1-bromo-2,4-dinitrobenzene}$$

excellent yields

Scheme 2. General Mechanism for Reactions of BrF₃ with Sulfur- and Nitrogen-Containing Compounds

Soft base / Soft acid →

$$R\underset{\underset{Z}{\overset{|}{X-C}}}{\overset{}{\underset{}{}}}\overset{}{\text{S-R' or N}} \quad + \quad F-Br\cdots F \longrightarrow$$

$$\longrightarrow \underset{\underset{Z}{\overset{|}{X-C}}}{R}\text{-C-F}$$

Hard base

$$R\underset{\underset{Z}{\overset{|}{X-C}}}{}\text{O-R'} \quad \xrightarrow{BrF_3} \quad \text{No specific Reaction; relatively slow radical deterioration}$$

Scheme 3. Preparation of α,α-Difluoroethers

$$R-\overset{O}{\overset{\|}{C}}-OR' \xrightarrow[\text{Lawesson reagent}]{[p\text{-MeOC}_6H_4P(S)S]_2} R-\overset{S}{\overset{\|}{C}}-OR'$$

$$\xrightarrow[\text{few seconds}]{BrF_3 / 0\ °C} RCF_2OR'$$

1	R = 1-Ad; R' = Me	(95%)
2	R = Octyl; R' = Et	(70%)
3	R = 4-methylcyclohexyl; R' = Et	(90%)
4	R = Ph; R' = Me	(70%)

A.1. Common Features of BrF₃ Reactions with Sulfur- and Nitrogen-Containing Compounds.

Since both sulfur and nitrogen atoms are relatively soft bases, they can complex the softly acidic bromine in BrF₃ and place the naked nucleophilic fluorides close to the electrophilic carbon positioned α to the heteroatom. In most cases, the fluoride will then substitute the sulfur or nitrogen to form a new C−F bond (Scheme 2). It is worth mentioning that such complexation is less favorable with the hard base oxygen and no clean ionic reactions were observed with it.

A.1.1. Reactions of BrF₃ with Sulfur-Containing Organic Molecules. A.1.1.1. Reactions with Thioesters and Orthothioformates.

Reacting BrF₃ with esters did not produce any main identifiable product, but replacing the carbonyl oxygen with a sulfur atom altered the outcome completely. When thioesters were reacted for a few seconds with BrF₃, the corresponding α,α-difluoroethers were obtained in good yields.[19] The formation of α,α-difluoromethylene(1-adamantyl)methyl ether (**1**) proceeded in 95% yield. 1,1-Difluorooctylethyl ether (**2**) was obtained in 70% yield and 1,1-difluoromethyl-1-(4-methylcyclohexyl)ethyl ether (**3**) in 90% yield. The fast reaction between the thiocarbonyl and BrF₃ is demonstrated in the case of *O*-methyl thionobenzoate, which produced α,α-difluorobenzyl methyl ether (**4**) in 70% yield with no appreciable bromination on the aromatic ring (Scheme 3).

This reaction led us to experiment also with dithionic esters to convert them to the CF₃ derivatives. The reaction
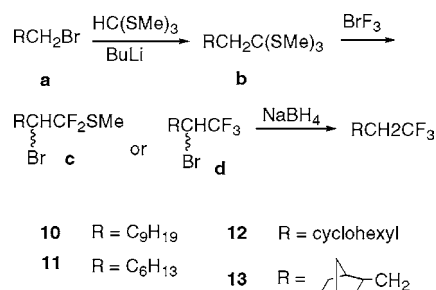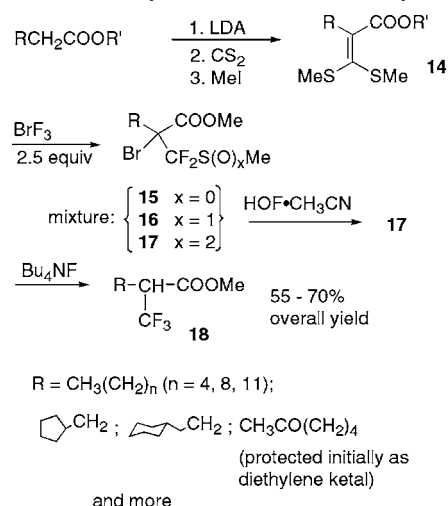
Scheme 4. ArCOOH to ArCF₃

$$Ar-\overset{O}{\overset{\|}{C}}-OH \xrightarrow[\text{2. EtSH}]{\text{1. SO}_2\text{Cl}} Ar-\overset{O}{\overset{\|}{C}}-SEt$$

$$\xrightarrow[\text{(Lawesson reagent)}]{[p\text{-MeOC}_6H_4P(S)S]_2} Ar-\overset{S}{\overset{\|}{C}}-SEt$$

$$\xrightarrow{BrF_3} ArCF_2SEt \xrightarrow{BrF_3} ArCF_3$$

Ar = 4-NCC₆H₄ (75%); 4-ClC₆H₄ (70%);
2-ClC₆H₄ (70%); 3-BrC₆H₄ (75%);
4-CF3C₆H₄ (65%)
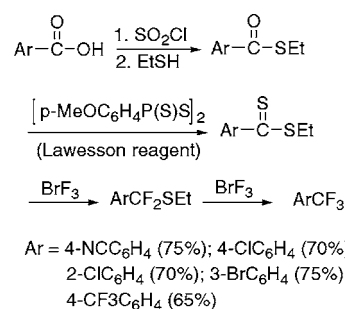
Scheme 5. From ROH to ROCF₃

$$RCH_2OH \xrightarrow[\text{3. MeI}]{\substack{\text{1. NaH} \\ \text{2. CS}_2}} RCH_2O-\overset{S}{\overset{\|}{C}}-SMe \xrightarrow{BrF_3}$$

a → **b**

RCH₂OCF₃   **c**

CF₃O(CH₂)₁₁OCF₃   **9d** (78%)

5	R = CH₃(CH₂)₆	(82% for c)
6	R = CH₃(CH₂)₈	(89% for c)
7	R = CH₃(CH₂)₁₀	(80% for c)
8	R = ⬡-CH₂	(84% for c)
9	R = MeSSCO(CH₂)₁₁	
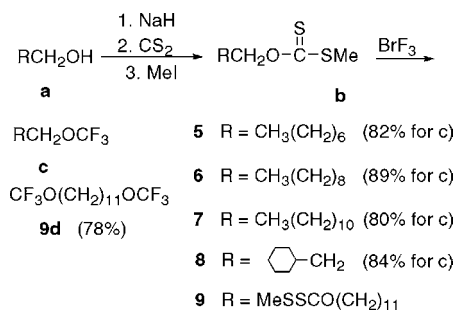
does work, but apparently only with aromatics.[20] The first step is the formation of the CF₂ moiety resulting in ArCF₂-SR, but increasing the BrF₃/substrate ratio resulted in the replacement of the last sulfur atom by a third fluorine atom forming the desired CF₃ group (Scheme 4).

The next logical step was to attach the sulfur-containing group to alcohols to prepare trifluoromethyl ethers. Such aromatic ethers are not easily prepared but still are well-known and have many applications in the pharmaceutical and agricultural domains.[21] Aliphatic trifluoromethyl ethers, however, are very rare and even more difficult to make. Xanthates, which are usually prepared in high yields from the corresponding alcohols, seemed to be a good choice. Reacting them with BrF₃ produced the corresponding trifluoromethyl ethers in very good yields. *n*-Octanol (**5a**) through its xanthate (**5b**) was reacted with BrF₃ to form octyl trifluoromethyl ether (**5c**) in 82% yield. Similarly, the xanthates of *n*-decanol (**6b**), *n*-dodecanol (**7b**), and 2-cyclohexylethanol (**8b**) and the dixanthate of the 1,12-dodecanediol (**9b**) were converted to the corresponding trifluoromethyl ethers **6c**, **7c**, **8c**, and **9d** with 89%, 80%, 84%, and 78% yield, respectively (Scheme 5).[22]

The trifluoromethyl group has a profound influence on the biological activity of organic molecules often associated with its ability to increase the lipophilicity of the compound. Its high electronegativity and extra stability have contributed to its ever-rising popularity.[23] To synthesize alkyltrifluoromethyls, we developed a method to substitute the halogen in alkyl halides with the CF₃ moiety using BrF₃.

Reacting 1,1,1-tris(methylthio)undecane (**10b**), made readily from bromodecane (**10a**), with a 3-fold excess of BrF₃ resulted in the 1-methylthio-2-bromo-1,1-difluoroundecane (**10c**) in 70% yield, while with a 10-fold excess, one obtains 2-bromo-1,1,1-trifluoroundecane (**10d**) in 60% yield. The bromine atom, invariably found at the α-posi-
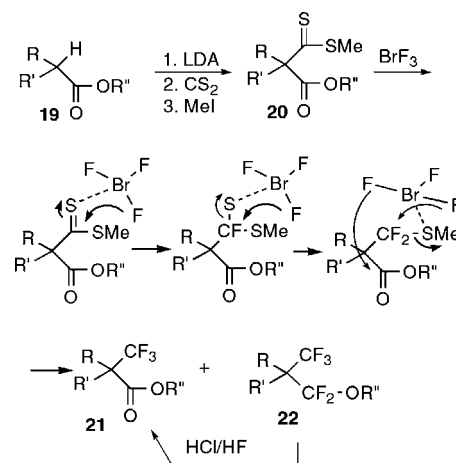
Scheme 6. From RBr to RCF$_3$

RCH$_2$Br $\xrightarrow[\text{BuLi}]{\text{HC(SMe)}_3}$ RCH$_2$C(SMe)$_3$ $\xrightarrow{\text{BrF}_3}$

a   **b**

RCHCF$_2$SMe   RCHCF$_3$ $\xrightarrow{\text{NaBH}_4}$ RCH2CF$_3$
Br **c**   or   Br **d**

10	R = C$_9$H$_{19}$	**12**	R = cyclohexyl
11	R = C$_6$H$_{13}$	**13**	R = (norbornyl)–CH$_2$

Scheme 7. The Synthesis of α-Trifluoromethyl Acids

RCH$_2$COOR' $\xrightarrow[\text{2. CS}_2]{\text{1. LDA}}$ (3. MeI) →

R–C(COOR')=C(SMe)(MeS) **14**

$\xrightarrow[\text{2.5 equiv}]{\text{BrF}_3}$ R–C(COOMe)(Br)–CF$_2$S(O)$_x$Me

mixture: { **15** x = 0; **16** x = 1; **17** x = 2 } $\xrightarrow{\text{HOF·CH}_3\text{CN}}$ **17**

$\xrightarrow{\text{Bu}_4\text{NF}}$ R–CH(CF$_3$)–COOMe **18**   55 – 70% overall yield

R = CH$_3$(CH$_2$)$_n$ (n = 4, 8, 11);

(cyclopentyl)–CH$_2$; (cyclohexyl)~CH$_2$; CH$_3$CO(CH$_2$)$_4$
(protected initially as diethylene ketal)
and more

Scheme 8. The Synthesis of Secondary and Sterically Hindered α-Trifluoromethyl Acids

R–CH(R')–C(=O)–OR" **19** $\xrightarrow[\text{2. CS}_2]{\text{1. LDA}}$ (3. MeI) → R–C(R')(C(=S)SMe)–C(=O)OR" **20** $\xrightarrow{\text{BrF}_3}$

[mechanism structures]

→ R–C(R')(CF$_3$)–C(=O)–OR" **21**   +   R–C(R')(CF$_3$)–CF$_2$–OR" **22**

$\xrightarrow{\text{HCl/HF}}$

a) R = R' = cyclooctyl, R" = Et; b) R = R' = Pr, R" = Et;

c) R = t-Bu, R' = H, R" = Bu;

d) R = (norbornyl)~CH$_2$, R' = H, R" = Me

tion, could be easily replaced with hydrogen in very good yields by treating the products with NaBH$_4$. The reaction between BrF$_3$ and the tris(methylthio) derivatives can be applied to a number of aliphatic chains with similar results.[24] A few examples are given in Scheme 6.

It was surprising to find out that no general method for introducing the important CF$_3$ group into the important α position of a *given* carboxylic acid was ever developed. Bromine trifluoride closed this gap.[25] One of the best methods to place a sulfur atom on the α-position of an ester is to react its corresponding enolate with CS$_2$ followed by MeI. We have prepared several 2-carbomethoxy-1,1-bis(methylthio)-1-alkenes, **14**, which were reacted with BrF$_3$ for less than a minute. Mixtures were obtained consisting of methyl 2-bromo-2-[difluoro(methylthio)methyl]alkanoates, **15**, the respective sulfoxides, **16**, and traces of the sulfones, **17**. The mixtures were not resolved but treated "as is" with HOF·CH$_3$CN at room temperature, transferring all sulfur-containing compounds to the corresponding sulfones, **17**, in just a few minutes.[26] These sulfones were reacted with Bu$_4$NF[27] eliminating both bromine and sulfone groups to give the target α-trifluoromethylalkanoates **18** in overall yields of up to 70% based on the starting esters (Scheme 7). It should be emphasized that this method is very suitable for introducing the important isotope ^{18}F into the CF$_3$ group for research and diagnostics with positron emitting tomography (PET).

A.1.1.2. Reactions with Methyl Sulfide Derivatives. With secondary and sterically hindered acid derivatives, the reaction takes a somewhat different course from that
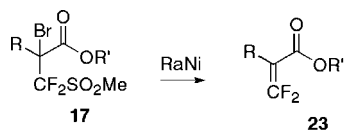
described in Scheme 7.[28] The protocol with ethyl cycloheptylcarboxylate (**19a**) can serve as an illustrative example for placing the CF$_3$ group at the α-position. When **19a** was reacted with LDA, CS$_2$, and MeI, methyl 2-carboethoxydithiocycloheptanoate (**20a**) was obtained in very good yield. The reaction with BrF$_3$ took a few seconds, and the desired ethyl 2-trifluoromethylcycloheptanoate (**21a**) was formed, although in 35% yield only. It was, however, accompanied by an additional major product (45% yield), which proved to be 1-(ethoxydifluoromethyl)-1-trifluoromethylcycloheptane (**22a**).

These results indicate that while the electrophilic bromine is complexed around the sulfur atoms, the nucleophilic fluorides get close not only to them, but also to the adjacent ester carbonyl moiety forming, in addition to the CF$_3$ group, the corresponding α,α-difluoroether. This ether is not very stable and when treated with an aqueous-alcoholic mixture of HCl/HF for a few hours regenerated the ester moiety in higher than 80% yield, raising the overall yield of **21a** to 70% (Scheme 8).

Similarly, the aliphatic ethyl 2-propylpentanoate (**19b**), butyl 3,3-dimethylbutanoate (**19c**), and methyl 2-norbornyl acetate (**19d**) were converted to **20b−d**, which when reacted with BrF$_3$ formed both 2-trifluoromethylcarboxylates (**21b−d**), and the pentafluoro derivatives (**22b−d**). All compounds of type **22** were successfully converted to the respective **21**s in good yields.

Fluoroacrylic esters are of interest in the fields of coating, polymerization, special optical properties, and more.[29] However, the known methods of preparing β,β-difluoroacrylates are limited.[30,31] We found that the difluoromethyl sulfones, **17**, described in Scheme 7, can also serve as a good starting point for making these acrylic derivatives by treating them with Raney nickel, eliminating both the bromine atom and the sulfone group. Methyl 2-alkyl-β,β-difluoroacrylates (**23**) were eventually formed

Scheme 9. The Synthesis of Difluoroacrylates
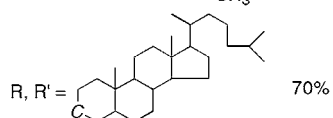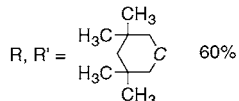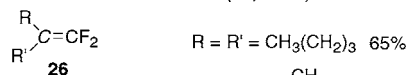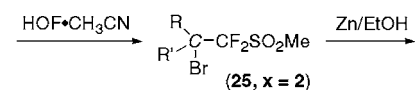
R = CH₃(CH₂)₇CH₂ ; R' = Me   (75%)

R = cyclopentyl-CH₂ ; R' = Me   (65%)

R = Cl~CH₂ ; R' = Me   (55%)

R = ~O~CH₂ ; R' = Et   (50%)

R = (ester)~O~CH₂ ; R' = Et   (55%)

R = (ketone)~CH₂ ; R' = Me (55%)

Scheme 10. The Preparation of α,α-Difluoroolefins from Carbonyls

R = R' = CH₃(CH₂)₃   65%

R, R' = (dimethylcyclohexyl)   60%

R, R' = (steroid)   70%
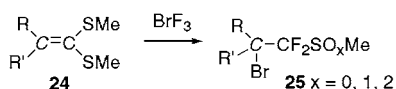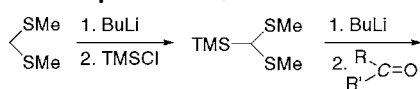
in 55−80% overall yield. Many functional groups, such as halogens, carbonyls, or hydroxyls are tolerated as demonstrated by some representative cases shown in Scheme 9.[32]
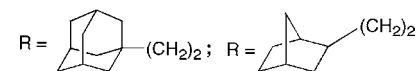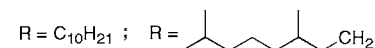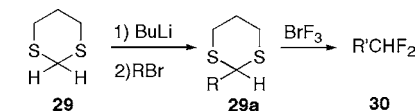
Terminal difluoroalkenes are of interest in organic chemistry since they serve as starting materials for various fluorine-containing products and polymers, as well as for enzyme inhibitors or pesticides.[33,34] Consequently, new methods for the synthesis of 1,1-difluoroalkenes have become a highly desirable goal. Here too, BrF₃ can be the reagent of choice.

The reaction of the lithium salt of the commercial bis-(methylthio)methane with TMSCl and ketones or aldehydes produces 2-alkyl-1,1-bis(methylthio)alkenes (**24**).[35] Reacting these derivatives with BrF₃ gave oily mixtures that contained the bromo difluoro derivatives **25** ($x = 0$) as the main product along with some of the corresponding sulfoxide and sulfone derivatives (**25**, $x = 1$ and 2, correspondingly, Scheme 10). The mixture was reacted with the HOF·CH₃CN complex, and the resulting **25** ($x = 2$) was treated with activated Zn eliminating both the

Scheme 11. The Preparation of Difluoroolefins from Alkyl Halides

$HC(SMe)_3 \xrightarrow[\text{2. } RCH_2Br]{\text{1. BuLi}} RCH_2C(SMe)_3$

27 x = 0, 1, 2

28 70 − 75% overall yield

R = CH₃(CH₂)₇CH₂ ; R = (bicyclic)-CH₂

R = Cl(CH₂)₄CH₂
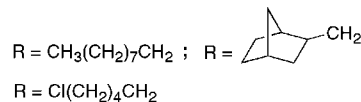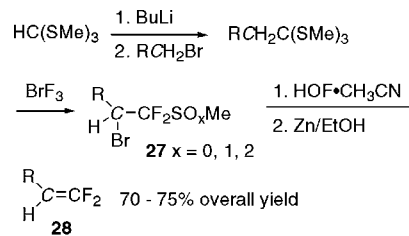
Scheme 12. The Preparation of the Difluoromethyl Moiety

29 $\xrightarrow[\text{2) RBr}]{\text{1) BuLi}}$ **29a** $\xrightarrow{BrF_3}$ R'CHF₂ **30**

R = C₁₀H₂₁ ;   R = (branched alkyl)-CH₂
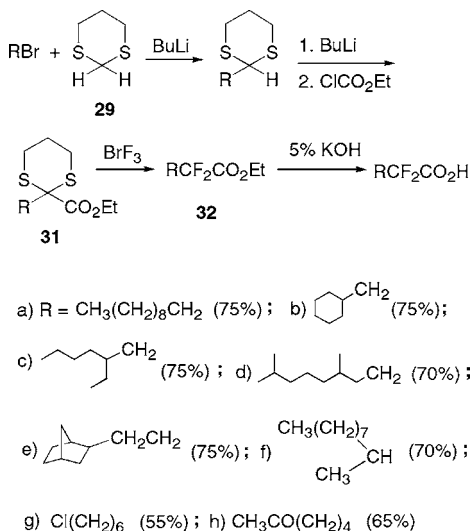
R = (adamantyl)-(CH₂)₂ ;   R = (bicyclic)-(CH₂)₂

sulfone and the bromine atom forming 1,1-difluoro-2,2-dialkylethenes (**26**) in 65−70% yield.[36] Several examples of this reaction are shown in Scheme 10.

Alkyl halides are also suitable starting materials for the preparation of 1,1-difluoroolefins. We have already shown that when reacted with the commercial tris(methylthio)-methane, 1-alkyl-1,1,1-tris(methylthio)alkane derivatives were produced (compounds **b** in Scheme 6). Reacting those with bromine trifluoride, followed by HOF·CH₃CN oxidation, led to materials of type **27**. Again elimination of both the sulfone group and the bromine atom with Zn produced the desired 1,1-difluoroalkenes (**28**) in 70−75% overall yield (Scheme 11). It should be noted that using primary alkyl halides or aldehydes will result in similar products.

A.1.1.3. Reactions with Dithiane Derivatives. Another useful sulfur-containing anchor for bromine trifluoride proved to be the dithiane moiety. The construction of the difluoromethyl group, CHF₂, is illustrative. This group often contributes special biological properties to organic molecules. Apart from its high lipophilicity similar to the CF₃ group, it also is able to act as a hydrogen donor, through hydrogen bonding,[37] and is actively pursued for enhancing biological activities.[38]

The lithium salt of cyclic 1,3-dithiane (**29**) is readily accessible and can react with alkyl halides to form the corresponding 2-alkyl-1,3-dithianes **29a**. When such compounds were reacted for 2−5 min under mild conditions with BrF₃, we were able to isolate the corresponding 1,1-difluoroalkane (**30**) in 55−75% yield. A few examples are shown in Scheme 12.[39]

The fact that α,α-difluoroketones can serve as enzyme inhibitors[34] prompted the development of several synthetic routes for constructing a difluoromethylene group adjacent to carbonyls and especially to the carboxylic

Scheme 13. The Preparation of α,α-difluorocarboxylates

a) R = CH$_3$(CH$_2$)$_8$CH$_2$ (75%); b) [cyclohexyl]—CH$_2$ (75%);

c) [structure]—CH$_2$ (75%); d) [structure]—CH$_2$ (70%);

e) [bicyclic]—CH$_2$CH$_2$ (75%); f) CH$_3$(CH$_2$)$_7$ / CH$_3$ CH (70%);

g) Cl(CH$_2$)$_6$ (55%); h) CH$_3$CO(CH$_2$)$_4$ (65%)

Scheme 14. Fluorodecarboxylations

a) R = CH$_3$(CH$_2$)$_8$CH$_2$; b) R = [cyclohexyl]—(CH$_2$)$_3$
   (75%)   (60%)

c) R = [bicyclic]—(CH$_2$)$_2$; d) R = Cl(CH$_2$)$_{10}$
   (60%)   (55%)

e) R = THPO(CH$_2$)$_8$Br $\xrightarrow{\text{1) BuLi/ }\mathbf{29}}$ **31** $\xrightarrow{\text{1) AcCl/ AcOH}}$
                              2) BuLi/CO$_2$ 2) BrF$_3$

   34 R = AcO(CH2)8 (50%)

f) [structure] HOOC—(CH$_2$)$_{10}$—COOH $\xrightarrow[\text{- CO}_2]{\text{BrF}_3}$ CF$_3$(CH$_2$)$_{10}$CF$_3$

Scheme 15. Radical Chain Fluorodecarboxylation

Initiation:

RCF$_2$COOH $\xrightarrow[\text{BrF}_2 \cdot \text{+ F} \cdot]{\text{BrF}_3}$ HF + CO$_2$ + RCF$_2$·

35 R = CH$_3$(CH$_2$)$_9$

Propagation:

RCF$_2$· + BrF$_3$ ⟶ RCF$_3$ (**34**) + BrF$_2$·

BrF$_2$· + RCF$_2$COOH ⟶ RCF$_2$· + CO$_2$ + HF + BrF

moiety. One of the most common methods for making such compounds was developed by Burton and is based on variations of the Reformatsky reaction using halodifluoroacetic acid.[40] Here too, bromine trifluoride can play an important role, and after a few experiments, a new and easy route for the synthesis of the α,α-difluorocarboxylates from commercially available alkyl bromides, cyclic 1,3-dithiane (**29**), and BrF$_3$ was developed.[41]

Thus, alkyl halides were reacted with the lithium salt of **29** followed by ethyl chloroformate to produce 2-alkyl-2-ethoxycarbonyl-1,3-dithianes (**31**). When this derivative was reacted for 1−2 min at 0 °C with BrF$_3$, the expected ethyl 2,2-difluoroalkanoates (**32**) were formed in 65−75% yield. The reaction could be applied to a wide variety of alkyl halides such as straight chains of any length, alkyls that contain relatively labile tertiary hydrogens, bicyclic compounds, secondary alkyl halides, chlorine-containing substrates, and even ketones (**a**−**g**), although the latter have to be protected prior to the reactions with BuLi. The difluoroester derivatives could eventually be hydrolyzed to the corresponding α,α-difluoroacids in nearly quantitative yields, by refluxing them with 5% KOH in EtOH/H$_2$O for 1 h (Scheme 13).

The above synthesis presented an opportunity to develop yet another method for the construction of the CF$_3$ group using difluoroacids, either as substrates or intermediates, via a Hunsdiecker-like reaction. Although one of the oldest procedures in organic chemistry for halodecarboxylation, only XeF$_2$ was able to induce fluorodecarboxylations, in special cases.[42] BrF$_3$ proved to be a very good reagent for such transformations as well. 2-Decyl-1,3-dithiane-2-carboxylic acid (**33**) was reacted with BrF$_3$ producing 1,1,1-trifluoroundecane (**34a**) in 60% yield in a matter of 1 min. Several different types of compounds (**a**−**e**) were successfully tested as well, including alcohols protected as tetrahydropyranyls (THP, **e**) for the initial reaction with BuLi. The protecting THP was then replaced by the acetyl group, which was stable to the fast reaction with BrF$_3$. The reaction with the disubstituted
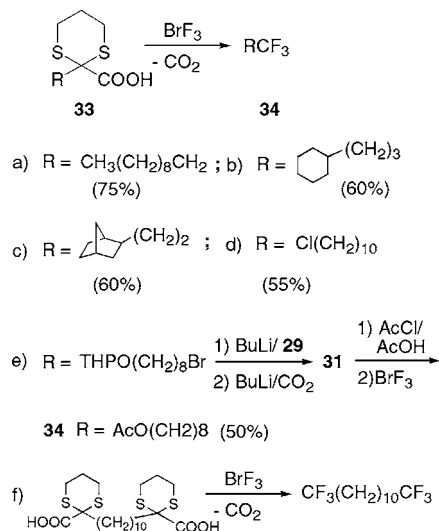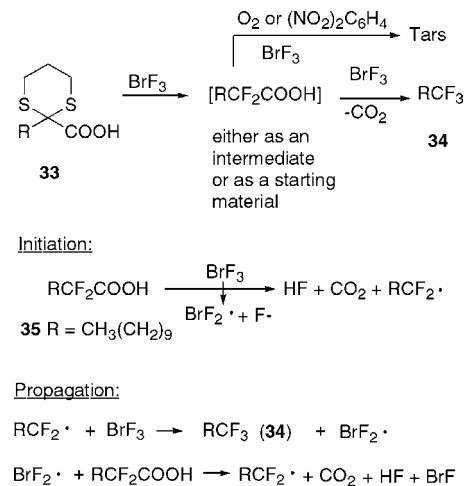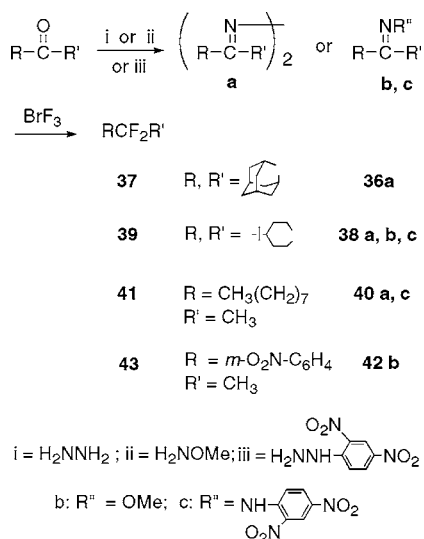
1,10-dibromodecane also proceeded as expected and 1,1,1,12,12,12-hexafluorododecane (**f**) was formed (Scheme 14).[43]

It should be noted that the fluorodecarboxylation step is of a radical nature. When the reaction was carried out under either an oxygen-rich atmosphere or in the presence of dinitrobenzene, the radical chain process was interrupted and practically no trifluoromethylated compounds were formed. Additional support for this mechanism was found in reactions with α,α-difluoro acids. Thus, for example, when α,α-difluorododecanoic acid (**35**, R = CH$_3$(CH$_2$)$_9$) was reacted with BrF$_3$ 1,1,1-trifluoroundecane (**34**, R = CH$_3$(CH$_2$)$_9$) was formed in 60% yield. For comparison, no such reaction takes place with the corresponding dodecanoic acid itself. This is due to the higher stability of the difluoromethylene radical, compared to the nonfluorinated counterpart, which better sustains a chain reaction with BrF$_3$ forming eventually the CF$_3$ group (Scheme 15).
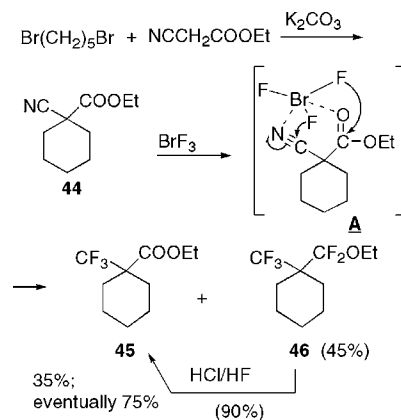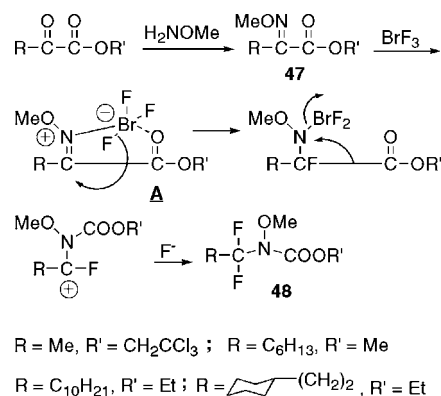
A.1.2. Reactions of BrF$_3$ with Nitrogen-Containing Organic Molecules. In the past, we had used quite extensively iodine monofluoride, made directly from I$_2$ and F$_2$, for aromatic iodination[44] and transferring ketones

Scheme 16. From Ketones to the CF$_2$ Group

i = H$_2$NNH$_2$; ii = H$_2$NOMe; iii = H$_2$NNH—

b: R" = OMe; c: R" = NH—

Scheme 17. Reactions of BrF$_3$ with Nitrilocarboxylates

Scheme 18. Reactions of BrF$_3$ with Pyruvates

R = Me, R' = CH$_2$CCl$_3$; R = C$_6$H$_{13}$, R' = Me

R = C$_{10}$H$_{21}$, R' = Et ; R = —(CH$_2$)$_2$, R' = Et

through their hydrazones to the corresponding CF$_2$ group.[45] IF, however, has to be prepared for each reaction, and what is more, it does not react with some C=N derivatives such as azines, methyl oxime ethers, and the like. These disadvantages do not exist with BrF$_3$. Adamantanyl azine (**36a**), easily prepared from the parent adamantanone and hydrazine, was reacted with BrF$_3$ forming immediately 2,2-difluoroadamantane (**37**) in 95% yield. Also, 4-*tert*-butyl-cyclohexanone, through its azine (**38a**) as well as its oxime methyl ether **38b** or DNP **38c**, was converted to the 4,4-difluoro-*tert*-butylcyclohexane (**39**) in good yields. Similar results were obtained with aliphatic straight-chain ketones such as 2-decanone whose azine **40a** and DNP **40c** both transformed to 2,2-difluorodecane **41** in a matter of seconds. With deactivated aromatic ketones such as the oxime methyl ether of *m*-nitroacetophenone (**42b**), the reaction also resulted in 90% yield of the desired *m*-nitro-(1,1-difluoroethyl)benzene (**43**) (Scheme 16).[46]

While the complexation of BrF$_3$ with the basic hydra-zone's nitrogen atoms led to very good results, its com-plexation with the nitrile moiety is weaker providing higher chances for destructive radical reactions. Still, there are certain types of nitriles that react relatively cleanly. The nitrogen atom in such compounds has to be assisted by an additional electron-donating element, for example, in 1-cyano-1-carboethoxycyclohexane (**44**) made from ethyl cyanoacetate and 1,5-dibromopentane. The naked nucleophilic fluorides attack the nitrile carbon leading eventually to ethyl 1-trifluoromethyl cyclohexanoate (**45**) in 35% yield. Since, however, the ester's carbonyl is in the right proximity (intermediate **A** in Scheme 17) to the fluorides, it also reacts with the complexed BrF$_3$ forming the additional derivative 1-(ethoxydifluoromethyl)-1-tri-fluoromethylcyclohexane (**46**) in 45% yield. This major product could be hydrolyzed in high yield to produce the trifluoromethyl ester **45** raising effectively its overall yield to more than 70%.[47] This pattern of reactions resembles very much the one described in Scheme 8.

Not all carbonyl derivatives behaved as expected. In our quest for new synthetic ways to make α,α-difluoro-carboxylic acids (see Scheme 13), we have tried to use pyruvic acids as starting materials since it is possible to selectively make the corresponding oxime methyl ethers **47** (Scheme 18). Such materials were then subjected to reactions with BrF$_3$ forming products that were not the anticipated α,α-difluoroesters, but proved eventually to be *N*-(1,1-difluoroalkyl)-*N*-methoxy carbamates **48** (50–70% yields).[48] The driving force for this novel C−C−N to C−N−C rearrangement that leads to a new type of molecule can be attributed, among other factors, to the relative stability of the fluorocarbocation intermediate. It should be noted that adding radical chain inhibitors such as dinitrobenzene, having oxygen present, or conducting the reaction under complete darkness does not change the outcome, reducing the possibility of any radical-involving mechanism.

Dimethyl 2-oxoglutarate (**49**) provided an interesting insight into the rearrangement process. When its methyl oxime ether **50** (prepared with both isotopes ^{14}N and ^{15}N) was reacted with bromine trifluoride, two main products were isolated and purified. The minor one was the expected by now rearranged compound methyl *N*-(3-carbomethoxy-1,1-difluoropropyl)-*N*-methoxy carbamate (**51**), but the major derivative proved to be a very unusual "doubly rearranged" product methyl *N*-(4,4-difluoro-4-methoxybutanoyl)-*N*-methoxy carbamate (**52**) (structure confirmed by X-ray and ^{15}N NMR; Scheme 19).

Bromine trifluoride is a mild oxidizer that gets its oxidizing power from the electrophilic bromine. As other oxidizers of this category, it starts the process by being

Scheme 19. Reactions of BrF₃ with Oxoglutarate
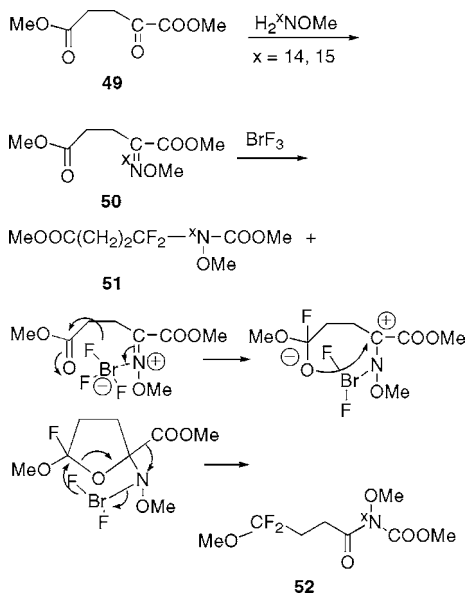
Scheme 20. Reactions of BrF₃ with Alcohols
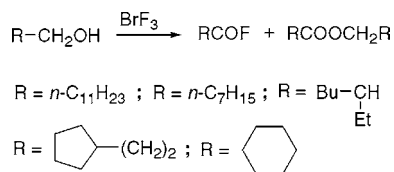
**Scheme 21. Formation of Sulfonyl Fluorides**
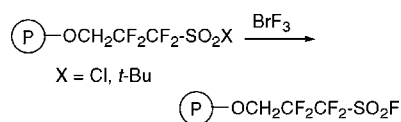
attracted to the electrons of the electron-rich C−H bonds α to an etheric or alcoholic oxygen.[49] Thus, while BrF₃ will not oxidize aromatic aldehydes,[18] it reacts with primary alcohols producing acyl fluorides in good yields (70−85%) accompanied by the symmetrical corresponding esters, which resulted from a secondary reaction of the acyl fluoride with the starting alcohol (Scheme 20).[50]

Apart from making acyl fluorides, BrF₃ was used for forming the important sulfonyl fluorides of partially fluorinated monomers and polymers for ion-exchange resins. The reaction proceeded successfully in good yields, with either the respective sulfonyl chlorides or the corresponding *t*-Bu-sulfones (Scheme 21).[51]

B. Radical Fluorinations with F₂

Perfluoropolyethers exhibit high thermal stability, excellent chemical resistance, and low surface energy and have found applications as lubricants, elastomers, and heat transfer fluids under demanding conditions. These materials are usually prepared by various polymerization processes of fluorine-containing monomers. An alternate synthetic strategy involving direct fluorination of hydrocarbon ethers has been reported by Lagow.[52]

We have prepared several oligomers and polymers whose Achilles' heel, however, was the number of protons

Scheme 22. Radical Fluorination of Polyfluorinated Ethers
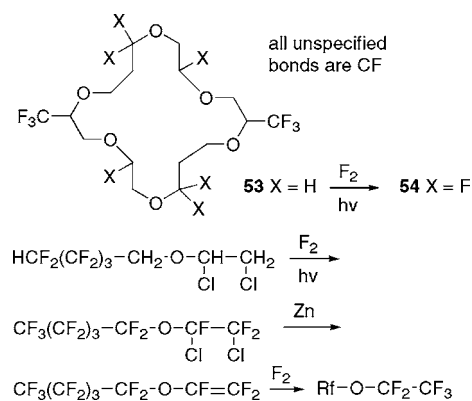
still present. If these compounds were to be heavy duty lubricants, for example, the presence of any hydrogen is undesirable. The obvious solution is replacing them with fluorine atoms, and it appears that the best chance for such transformation lies in radical fluorination.

The cyclic dimer **53**, which contains six hydrogen atoms, can serve as an example. About 10-fold excess of fluorine (per hydrogen) was passed through the reaction mixture while it was irradiated with a medium-pressure mercury lamp. After full conversion was achieved, the cyclic product **54** was isolated by distillation in very good yield.[53] This procedure will not affect other bonds such as a carbon−chlorine one and therefore was used also for making perfluorovinyl ether monomers.[54] If needed, such double bonds could easily be fluorinated by F₂ (Scheme 22).[55]
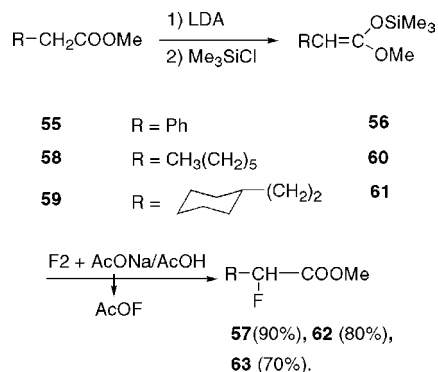
C. Electrophilic Fluorinations with AcOF (Made Directly from F₂)

The basic chemistry of electrophilic fluorinations with both F₂ and AcOF was already reviewed by us.[4b,6,7] We are presenting here only two topics that were not included in these reviews. This completes the picture portraying elemental fluorine as a source for nucleophilic, radical, and electrophilic fluorination processes.
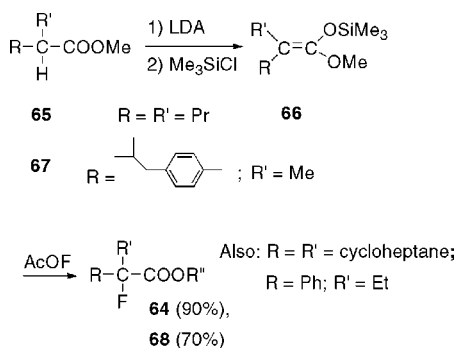
The interest in fluorocarboxylic acids started to rise in the 1950s when it was found that straight-chain ω-fluoroacids with an even number of carbons are almost as toxic as fluoroacetic acid itself. Soon after, a considerable interest was focused on various fluoroacids and especially on α-fluoro ones. The main method for their preparation was based on the displacement of a leaving group α to the carboxylate moiety using different sources of nucleophilic fluorides. Because of the basicity of the fluoride ion, however, such an approach resulted in elimination reactions or various rearrangements along with the desired α-fluoroacids. These two types of side reactions become dominant whenever α- or β-branched carboxylic acids were the target molecules.[56] These limitations encouraged development of alternative, specific multistep routes, which usually resulted in low overall yields.

The electrophilic fluorine in acetyl hypofluorite is free from all the above disadvantages and was instrumental

Scheme 23. Electrophilic Fluorination of Carboxylic Acids

$$R-CH_2COOMe \xrightarrow[\text{2) Me}_3\text{SiCl}]{\text{1) LDA}} RCH=C\begin{smallmatrix}OSiMe_3\\OMe\end{smallmatrix}$$

55	R = Ph	**56**
58	R = CH$_3$(CH$_2$)$_5$	**60**
59	R = ⬡–(CH$_2$)$_2$	**61**

$$\xrightarrow[\text{AcOF}]{F_2 + \text{AcONa/AcOH}} R-CH-COOMe$$
$$\underset{F}{|}$$

57 (90%), **62** (80%), **63** (70%).

Scheme 24. Electrophilic Fluorination of Branched Carboxylic Acids

$$R-\underset{H}{\overset{R'}{C}}-COOMe \xrightarrow[\text{2) Me}_3\text{SiCl}]{\text{1) LDA}} \underset{R}{\overset{R'}{>}}C=C\begin{smallmatrix}OSiMe_3\\OMe\end{smallmatrix}$$

65   R = R' = Pr   **66**

67   R = (isobutylphenyl) ; R' = Me

$$\xrightarrow{\text{AcOF}} R-\underset{F}{\overset{R'}{C}}-COOR''$$

Also: R = R' = cycloheptane;
R = Ph; R' = Et
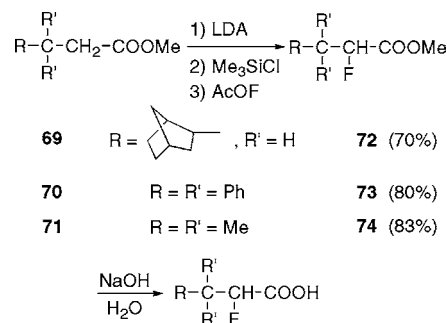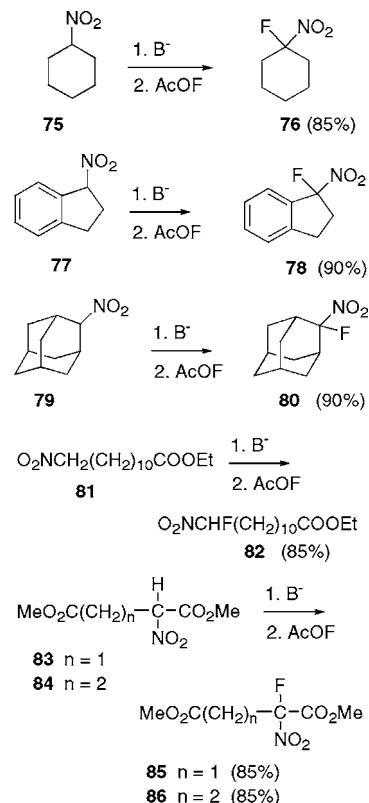
64 (90%),
68 (70%)

in introducing this halogen into the α position of practically any desirable acid.

Methyl phenylacetate (**55**) was converted to its trimethylsilyl ketene acetal (**56**) and then reacted with AcOF for a few minutes forming **57** in 90% yield. Nonbenzylic carboxylic acids are also suitable, and methyl octanoate (**58**) or methyl 4-cyclohexylbutanoate (**59**) can serve as examples. Their trimethylsilyl ketene derivatives **60** and **61** are easy to make and consecutive reactions with AcOF produce methyl 2-fluorooctanoate (**62**) and methyl 2-fluoro-4-cyclohexylbutanoate (**63**) in high yields (Scheme 23).[57]

The power of this method is demonstrated with branched carboxylic acids, which cannot be prepared by nucleophilic fluorination. Methyl 2-propyl-2-fluoropentanoate (**64**) was synthesized in 90% yield, from methyl 2-propylpentanoate (**65**), which was first converted to its trimethylsilyl ketene acetal **66**, and AcOF. Ibuprofen, 2-(4-isobutylphenyl) propionic acid (**67**), is a powerful analgesic drug. It required only two steps to make methyl 2-fluoro-2-(4-isobutylphenyl) propionate (**68**) in 70% yield by reacting AcOF with the corresponding trimethylsilyl ketene acetal. Several other examples are also shown (Scheme 24).

Another group of α-fluorocarboxylic acids that cannot be prepared by conventional nucleophilic fluorination methods consists of compounds branched at the β-position sterically preventing the typical formation of the S$_N$2 transition state. These obstacles could be easily eliminated if electrophilic fluorination with AcOF is employed. Methyl 2-norbornaneacetate (**69**), methyl 3,3,3-triphenylpropionate (**70**), and methyl 3,3,-dimethylbutyrate (**71**) exhibit strong steric hindrance on the α position of the carboxylic

Scheme 25. Electrophilic Fluorination of the Neopentyl Type of Carboxylic Acids

$$R-\underset{R'}{\overset{R'}{C}}-CH_2-COOMe \xrightarrow[\substack{\text{2) Me}_3\text{SiCl}\\\text{3) AcOF}}]{\text{1) LDA}} R-\underset{R'}{\overset{R'}{C}}-\underset{F}{\overset{}{CH}}-COOMe$$

69	R = (norbornyl) , R' = H	**72**	(70%)
70	R = R' = Ph	**73**	(80%)
71	R = R' = Me	**74**	(83%)

$$\xrightarrow[\text{H}_2\text{O}]{\text{NaOH}} R-\underset{R'}{\overset{R'}{C}}-\underset{F}{\overset{}{CH}}-COOH$$

Scheme 26. Electrophilic Fluorination α to a Nitro Group

75		**76** (85%)
77		**78** (90%)
79		**80** (90%)

$$O_2NCH_2(CH_2)_{10}COOEt \xrightarrow[\text{2. AcOF}]{\text{1. B}^-}$$
81

$$O_2NCHF(CH_2)_{10}COOEt$$
82 (85%)

$$MeO_2C(CH_2)_n-\underset{NO_2}{\overset{H}{C}}-CO_2Me \xrightarrow[\text{2. AcOF}]{\text{1. B}^-}$$

83 n = 1
84 n = 2

$$MeO_2C(CH_2)_n-\underset{NO_2}{\overset{F}{C}}-CO_2Me$$

85 n = 1 (85%)
86 n = 2 (85%)

group. They were, however, readily converted to the corresponding trimethylsilyl ketene acetals and then reacted with AcOF to form in minutes methyl 2-fluoro-3-(2-norbornyl)propionate (**72**), methyl 2-fluoro-3,3,3-triphenylpropionate (**73**), and methyl 2-fluoro-3,3,-dimethylbutyrate (**74**), all in good yields. The free α-fluorocarboxylic acids could also be obtained by basic hydrolysis (5% NaOH in EtOH/H$_2$O at 70 °C for about an hour) in nearly quantitative yields. (Scheme 25).

Although not every anionic center is suitable for a fruitful reaction with acetyl hypofluorite, the one vicinal to a nitro group seems to work fine. Nitrocyclohexane (**75**), for example, formed 1-fluoro-1-nitrocyclohexane (**76**) in 85% yield after treatment with base and AcOF. Other examples are benzylic nitro compounds such as 1-nitroindane (**77**), which formed 1-fluoro-1-nitroindane (**78**), and 2-nitroadamantane (**79**), converted to 2-fluoro-2-nitroadamantane (**80**), both in 90% yield.

A somewhat surprising result was observed with molecules possessing two potential anionic centers exemplified by ethyl 12-nitrododecanoate (**81**). After treatment with excess of either sodium ethoxide or sodium hydride followed by addition of AcOF, only the fluoronitro derivative **82** was formed in 85% yield. No fluorine incorporation into the 2 position was observed. This does not mean, however, that the position α to the carboxylic group cannot be fluorinated. Dimethyl nitrosuccinate (**83**) and dimethyl nitroglutarate (**84**) reacted smoothly to give the *gem*-fluoronitromethylene moiety α to the carboxylic group (**85** and **86**, respectively, both in 85% yield) (Scheme 26).[58]

Conclusions

Elemental fluorine and its immediate offspring are quite amazing and versatile tools in organic chemistry. Their main problem is the fear they inspire in many chemists. This fear is unjustifiable, and if elementary precautious are taken, the work with F_2 and its secondary reagents is relatively simple. *Still one should remember that fluorine and BrF_3 are very corrosive materials. They should be used in well ventilated areas and, in the case of BrF_3, in the absence of oxygenated solvents.* If elementary precautions and common sence are practiced, work with these reagents is relatively simple, and we have had no bad experiences working with them.

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