

Recent Advances in the Selective Formation of the C-F Bond

JOHN A. WILKINSON

Loker Hydrocarbon Institute and Department of Chemistry, University of Southern California, Los Angeles, California 90089

Received October 17, 1991 (Revised Manuscript Received March 17, 1992)

Contents

I. Introduction	505
II. Nucleophilic Sources of Fluorine	506
A. Alkali Metal Fluorides	506
B. AgF/CuF ₂	507
C. Tetraalkylammonium Fluorides	507
D. PPHF	508
E. Alkyl Amine Hydrogen Fluorides	509
F. TASF	510
G. HgF ₂	510
H. ZnF ₂	511
I. SiF ₄	511
J. BrF ₃	511
K. SF ₄	511
L. DAST	512
M. Fluoroalkylamine Reagents (FAR)	513
N. XeF ₂	514
O. Aromatic Hypervalent Iodine Fluorides	514
III. Electrophilic Sources of Fluorine	515
A. F ₂	515
B. Acetyl Hypofluorites	516
C. CsSO ₄ F	516
D. N-F Electrophilic Fluorinating Reagents	517
IV. Electrochemical Fluorination	517



John Wilkinson was raised in England and obtained his first degree at the University of Sussex in chemistry-by-thesis under the supervision of F. McCapra. After 3 years in industry he went to Imperial College, London where he obtained his Ph.D. for work entitled *Oxidation and Selective Fluorination of Organic Compounds using Organo-Hypervalent Iodine Species* under the supervision of W. B. Motherwell. He is currently an SERC NATO postdoctoral fellow with George Olah at the Loker Hydrocarbon Institute, University of Southern California. His research interests are organofluorine chemistry, buckminsterfullerenes, and synthetic methods.

I. Introduction

Of the 10 million compounds registered in the American Chemical Society's *Chemical Abstracts*, a staggering 6.2% contain compounds possessing a C-F bond.¹ The importance of such compounds can be exemplified by the pictorial graphs (Figures 1 and 2), which indicate the intense activity in the area of organofluorine chemistry.²

These figures reflect the interest of scientists, both industrial and academic, in utilizing fluorine to alter the physical and chemical properties of organic compounds. It is now well known that the introduction of fluorine into organic compounds increases thermal and oxidative stability, alters electronic effects, increases lipophilicity, and also closely mimics hydrogen in steric requirements.

Organofluorine compounds have been used as lubricants, coatings for cooking utensils, propellants, refrigerants, solvents, fire extinguisher agents, inhalation anesthetics, drugs, blood substitutes, dyes, liquid crystals, surfactants, and textile chemicals and in the production of agrochemicals.³

The preparation of organofluorine compounds remains a difficult area, and since fluorine itself is so reactive and difficult to control alternative methods of incorporating fluorine into organic molecules are required. The problem is enhanced when the specific incorporation of fluorine in a regio- and stereoselectivity controlled way is required. Incorporation of fluorine

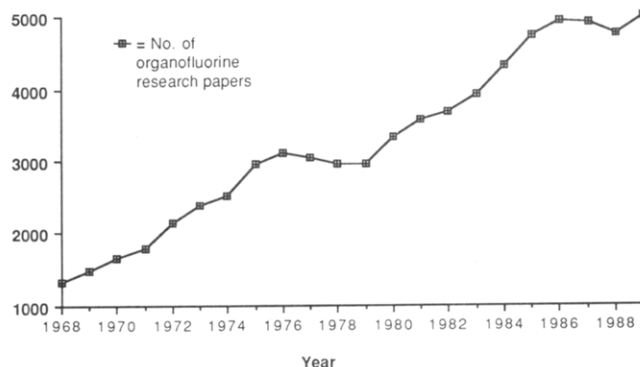


Figure 1. The increase in the number of published research papers on organofluorine compounds from 1968 to 1989.

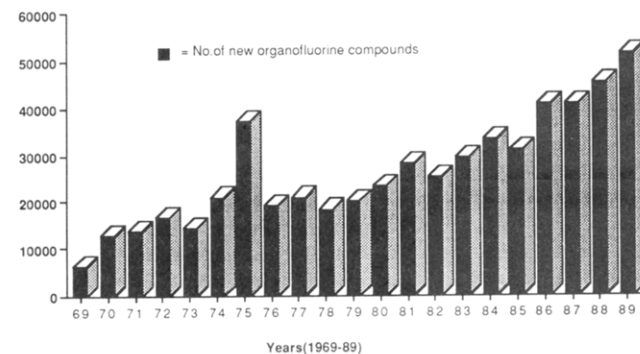


Figure 2. The rise in the number of published novel organofluorine compounds prepared during the period 1969 to 1989.

selectively into organic compounds is of great importance to the chemical industry and has consequently provided a great challenge to academic and industrial researchers alike to overcome this problem. There are now many different ways of carrying out this process and so, appropriately, this review highlights the most recent research methods and covers the work published in the years 1987–1990, for the selective incorporation of fluorine into organic compounds.

II. Nucleophilic Sources of Fluorine

Incorporation of fluorine into organic molecules by nucleophilic substitution with the fluoride anion remains a difficult area. The small size of F^- (radius is 1.36 Å) and its low polarizability encourages F^- to behave as a base rather than a nucleophile. Indeed F^- has been successfully used as a mild base in organic synthesis.⁴

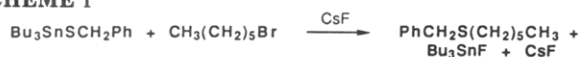
Nucleophilic substitution of halogens with F^- was first achieved in 1863 by Borodine,⁵ and since that time many reagents have been developed to overcome problems such as poor solubility, substitution versus elimination in nucleophilic displacement reactions, lowering of toxicity and price, and also increasing the stability of the fluorinating agents. While major advances have been achieved much good work remains to be done. Recent research has focused on the following reagents.

A. Alkali Metal Fluorides

These "classical" fluorinating agents have been used to substitute fluorine for other halogens in a variety of compounds such as alkyl halides, aromatic halides, and halo compounds such as α -halo esters, nitriles, and amides and ω -halo compounds such as ω -halo alcohols esters and nitriles. The main driving force is the formation of the thermodynamically favorable C–F bond (107 kcal/mol). The fluorinations are often carried out in high boiling solvents which aid solubility of the ionic fluorides or in anhydrous solvents. Under these conditions stray hydrogen bonds which are easily formed due to the high hydration energy (123 kcal/mol) of F^- are greatly diminished. This encourages the formation of unsolvated fluoride anions or, as Liotta succinctly put it,⁶ "naked fluoride". Crown ethers have also been used to solvate inorganic fluorides by complexation. In this form ionic fluorides are soluble in nonpolar solvents, such as benzene.

In a recent paper Harpp⁷ has shown that CsF when "capped" with 18-C-6 or dibenzo-24-C-8 displayed enhanced nucleophilicity compared to CsF alone. The rate enhancement was measured by following the fluorodestannylation of benzyl (tributyltin) sulfide with cesium fluoride (Scheme 1).

SCHEME 1



In their study 18-C-6, which fails to completely envelope cesium ions due to its small ring size, formed edge or sandwich complexes⁸ with CsF (Scheme 2).

When compared to dibenzo-24-C-8 ether a crown ether which completely encompasses cesium ions, an increased rate factor of 5 and 7 was respectively found. This system has advantages over TBAF (tetrabutyl-

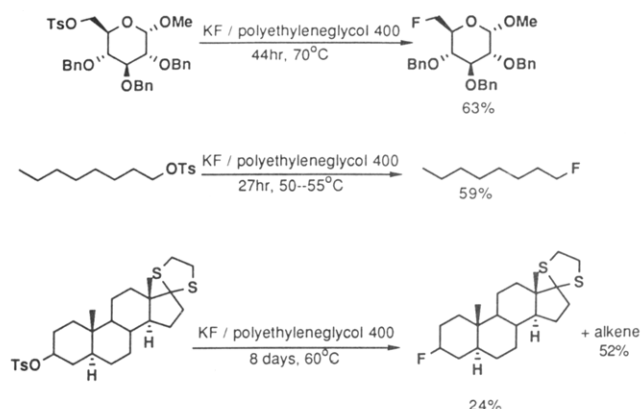
SCHEME 2



ammonium fluoride), since anhydrous conditions are easily obtained. The authors concluded that a qualitative order of nucleophilic fluoride anion is of the order; TBAF (anhydrous) > CsF/24-C-8-CsF (18-C-6)_n > KF/18-C-6.

Solvation of metal cations is not just limited to crown ethers but can be extended to using donor solvents such as glycols and glymes.⁹ The latest investigations in this area have found that from a large selection of glycols and glymes, polyethylene glycol 400 appears to be the most attractive due to its low cost and low toxicity and its ability to dissolve some inorganic salts.¹⁰ With use of this glycol as a solvent (with and without cosolvents), efficient monofluorination has been achieved using mild temperatures and potassium fluoride as a nucleophilic source of fluorine. Some representative examples are shown in Scheme 3.

SCHEME 3

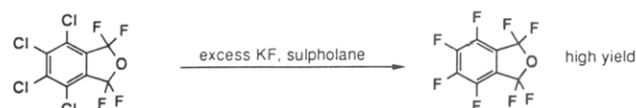


In some cases, such as 17,17-(1,2-ethanediyldithio)-3 α -(tosyloxy)-5 α -androstane, a high yield of the alkene (52%) instead of monofluorination (24%) was obtained.

Another interesting area of research is the use of supported KF reagents. Here, the reactivity of KF is improved by dispersion on suitable supports, and this increases the reagents surface area, for example KF and alumina, silica, and zeolites have all been used.¹¹

Alternative support systems which cut down internal hydrogen bonding of F^- to the support would be expected to greatly increase the reactivity of F^- . In recent years KF supported on CaF_2 has been shown to have enhanced reactivity.¹² A further innovation which clarifies the need for non-hydroxylated supports is the recent work by Liu using polymer supported KF.¹³ The dispersion of KF on a cross-linked polystyrene support showed increased yields of fluorination from acyl chlorides compared to KF/ CaF_2 and KF alone. Finally aromatic fluorinations using KF on polychlorinated substrates have been investigated by Wielgat.¹⁴ (Scheme 4).

SCHEME 4



B. AgF/CuF₂

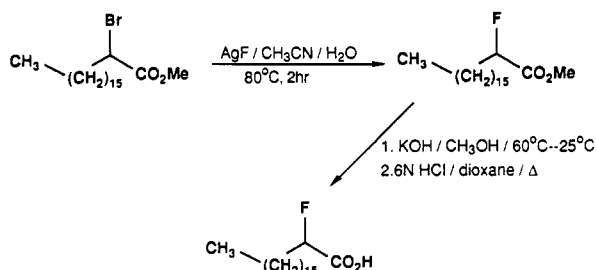
Silver(I) fluoride is a commercially available, colorless, deliquescent solid which melts at 435 °C and dissolves in water and aqueous ammonia. It was first used by Moissan in 1897¹⁵ for fluorination of organic compounds. It is a popular fluorinating reagent because of its high selectivity and its low basicity (compared to alkali metal fluorides such as KF) and this latter property minimizes elimination over substitution and generally gives cleaner reaction products than the more traditional nucleophilic sources of fluorine. Its main use is in selective halogen exchange reactions, e.g. RI → RF. Its disadvantages are its high cost and that 2 mol of reagent are required to 1 mol of substrate (Scheme 5).

SCHEME 5



Recent work has centered on increasing the nucleophilicity of the reagent by modification with added water or inorganic salts. Water is generally thought to inhibit the nucleophilicity of F⁻ due to hydrogen bonding, but in contrast, high yields of fluorination have been achieved by using "wet" AgF, a modification of a former fluorination procedure.¹⁶ Thus 2-fluorostearic acid was formed in 84% yield from the bromide whereas under anhydrous conditions a reduced yield of 10–15% resulted (Scheme 6). By comparison TBAF, TBAF on

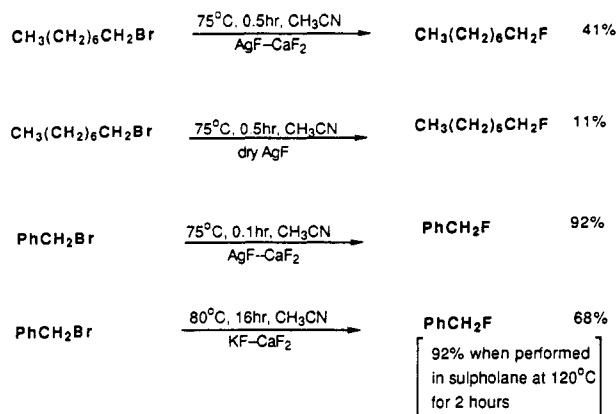
SCHEME 6



silica gel, RbF, CsF, and KF/18-C-6 gave approximately equal amounts of olefin and fluoro derivative, highlighting the increased basicity of these reagents compared to aqueous AgF.¹⁷ The effect of small amounts of water in enhancing the reactivity of AgF is not fully understood, but it does support the recent work of Clark and co-workers who have found that incomplete drying of KF supported on CaF₂ increases the reactivity of this reagent.¹⁸ Modification of this reagent by replacing KF with AgF has led to the use of AgF/CaF₂ mixtures by Ando.¹⁹ These give superior results to KF/CaF₂ and CsF/CaF₂, although the presumably high cost of the reagent could outweigh the increase in yield when used on a large scale. Some comparative examples are shown in Scheme 7. A natural extension of this work, encompassing the research of Clark, Ando, and Yoneda, would be the use of "wet" AgF/CaF₂ as a highly potent source of F⁻. Recently AgF has been used in combination with BF₃ to make *gem*-difluorides from *gem*-diiodides.²⁰

Finally Cu₂O/anhydrous HF mixtures have been used in halogen exchange fluorination reactions for making cyclo and tertiary alkyl fluorides.²¹ With primary halides, elimination was the major pathway, but this has been overcome by using a deep purple solid which was isolated from Cu₂O and anhydrous HF at low temper-

SCHEME 7

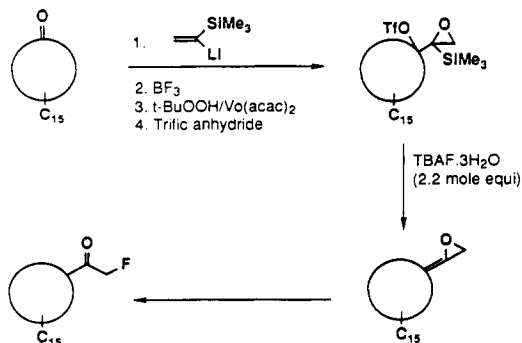


atures, and is thought to be of the composition CuF·0.5H₂O.²² This compound is stable at room temperature and when used in combination with 2,2'-bipyridine or collidine gave high yields of primary alkyl fluorides. This halogen exchange reaction was found to be superior to the more traditional reagents such as spray-dried KF or anion resins.

C. Tetraalkylammonium Fluorides

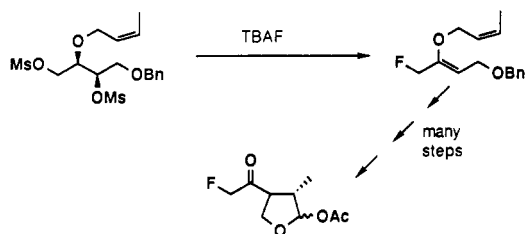
Tetraalkylammonium fluorides were invented to overcome problems with using alkali metal fluorides by (i) providing a soluble source of F⁻ and (ii) replacing the M⁺ ion with a bulky organic cation, thereby reducing ion pairing and enhancing the nucleophilicity (and basicity) of F⁻. TBAF (tetrabutylammonium fluoride), TMAF (tetramethylammonium fluoride), TEAF (tetraethylammonium fluoride), and BTMAF (benzyltrimethylammonium fluoride) have all been used as sources of F⁻, with TBAF receiving the most attention. "Anhydrous" TBAF is a commercially available extremely hygroscopic substance. Its major disadvantage is the presence of trace amounts of water which often produces varying results. The reagent is prepared by neutralization of tetraalkylammonium hydroxide with aqueous HF to give TBAF·3H₂O. From this, anhydrous TBAF is obtained by heating to 50 °C at 15 mm and then storing over P₂O₅ in a vacuum desiccator for 24 h.²³ An improved procedure using a higher vacuum and lower temperatures which prevents thermal decomposition of TBAF has been introduced.²⁴ Despite efforts to produce the anhydrous material, wet TBAF has also been used successfully to prepare fluorinated compounds. Recently hydrated TBAF has been used to make a range of α -fluoromethyl ketones via allene epoxides²⁵ (Scheme 8). Here, surprisingly, F⁻ competes

SCHEME 8



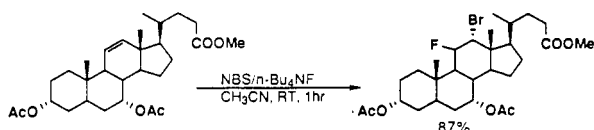
effectively against a 2 mol excess of $H_2O!$ TBAF has also been used to make (\pm)-fluorobotryodiplodin, a mycotoxin with antileukemic properties, via an elimination-substitution reaction²⁶ (Scheme 9).

SCHEME 9



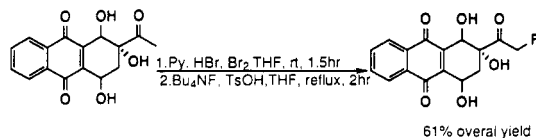
The reagent has also been used successfully in the bromo fluorination of olefins, e.g. using 3 equiv of NBS and TBAF, the fluorinated steroid was formed in 87% yield,²⁷ whereas no bromofluorination occurred with NBS/RbF or NBS/CsF (Scheme 10).

SCHEME 10



TBAF has also been found to give high yields of fluorinated products when used on organic halides in the absence of solvent.²⁸ The reagent has recently been used to make novel 14-fluoroanthracyclines, which were found to have significant cytotoxic activity against P388 murine leukemia in vitro and in vivo.²⁹ In this case TBAF was activated by using *p*-toluenesulfonic acid. The authors suggested that this mixture could be forming tetrabutylammonium hydrogen bifluoride (TBABF) as the active species, in situ, which is known to be a potent source of fluoride anion (Scheme 11).

SCHEME 11

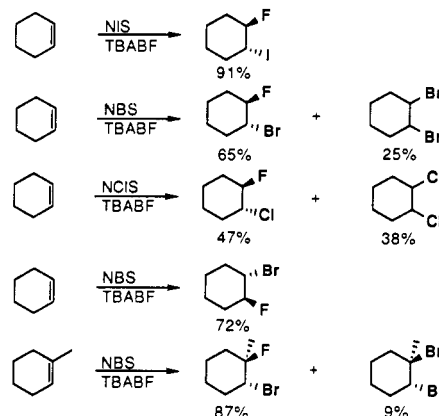


TBABF ($Bu_4N^+HF_2^-$) recently introduced as a new source of "naked" fluoride ion³⁰ is prepared by passing a solution of ammonium bifluoride through an Amberlite IRA 40 exchange resin, until the effluent gives no reaction to silver nitrate solution. After washing and drying under vacuum, a solution of tetrabutylammonium chloride in CH_3CN is passed through the column, and after removal of solvent and drying at 80 °C at 0.1 Torr for 24 h, dry TBABF is obtained. Various aliphatic, benzyl, and α -halo ketones were fluorinated in comparable or better yields than with other sources of F^- .

Further work using TBABF has concentrated on the halofluorination of alkenes.³¹ These were obtained in good yields by treatment of the alkene with NBS and TBABF in dichloromethane. However, unlike the NBS/TBAF reaction mentioned earlier, a major side product was the formation of vicinal dibromides. This was thought to be due to free-radical side reactions from the in situ formation of tetrabutylammonium tribromide. By using NIS, these side products were sup-

pressed and high yields of halofluorinated products were obtained. The reagent seems particularly good with cyclic and acyclic trisubstituted olefins (Scheme 12).

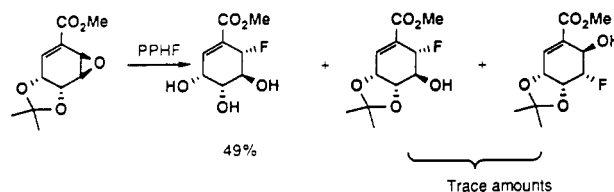
SCHEME 12



D. PPHF

Anhydrous hydrogen fluoride (AHF) is one of the cheapest and most popular fluorinating agents but due to its corrosive nature and low boiling point (19 °C) alternatives are required. This problem has largely been overcome by "taming" AHF in suitable donor solvents, initially with THF and later more successfully with triethylamine and pyridine from which PPHF was made. Polypyridinium hydrogen fluoride (PPHF), commonly known as Olah's reagent is a commercially available stable liquid. It has the molecular composition 1py:9HF (30% py:70% HF w/w) and has successfully been used to replace AHF, as detailed in Olah's first report³² and updated recently.³³ It has mainly been used to fluorinate secondary and tertiary alcohols,³⁴ alkenes,³⁴ and alkynes³⁵ and in halogen exchange reactions.³⁶ It has also been used recently to incorporate fluorine into shikimic acid derivatives via allylicly assisted ring opening of an epoxide.³⁷ Under these conditions removal of the isopropylidene groups occurred concomitantly with fluorination (Scheme 13).

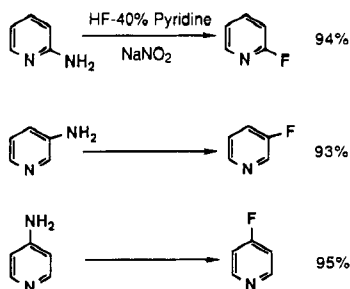
SCHEME 13



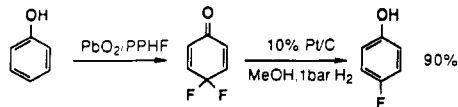
The reaction has also been effectively applied to the fluorination of aromatic compounds via a modified Balz-Schiemann reaction.³⁸ A recent addition to this work by Yoneda³⁹ has demonstrated that this process can be applied successfully to the fluorination of pyridines (Scheme 14).

Fluorination of arenes has also been achieved using PPHF in combination with electrolysis or with inorganic oxidants.⁴⁰ For example, upon reacting phenol with PbO_2 /PPHF a 30% yield of the difluoro dienone was obtained, which on subsequent hydrogenation gave a 90% yield of 4-fluorophenol. Other phenols, oxidants, and fluoride sources were also used and gave similar results (Scheme 15).

SCHEME 14

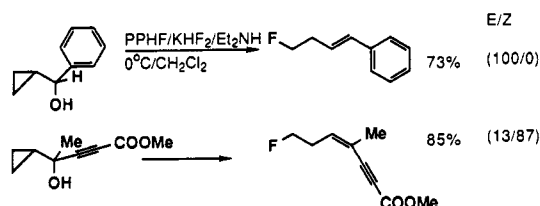


SCHEME 15



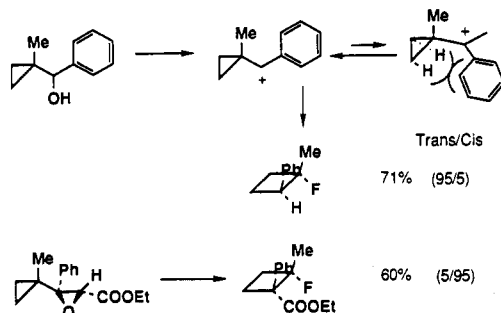
PPHF has also been used for the fluorination of polyaromatic hydrocarbons in conjunction with *N*-bromoacetamide.⁴¹ The reagent has also been used to form fluorocyclobutanes and homoallylic fluorides from cyclopropanemethanols via a modified Julia rearrangement⁴² (Scheme 16). With 1-substituted cyclo-

SCHEME 16



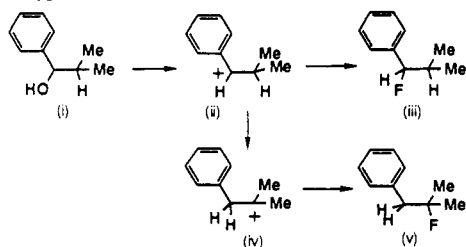
propanemethanols, fluorocyclobutanes were formed (Scheme 17). Beguin has demonstrated that fluoro-

SCHEME 17



dehydroxylation of several substituted benzyl alcohols can occur regioselectively depending on the HF content of PPHF⁴³ (Scheme 18).

SCHEME 18



At high HF concentrations, v dominated, and at low HF concentrations iii was only produced. Deuterium labeling showed that hydrogen transfer occurred between ii and iv at high HF concentration, and this was

attributed to the cation intermediate iv being stabilized by long HF polymeric chains present in high concentrations of HF/pyridine mixtures.

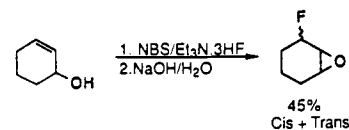
Olah has recently shown that PPHF in combination with NBS can be used to convert hydrazones to *gem*-difluorides.⁴⁴

Finally a polymeric version of PPHF has been used by Zupan to produce high yields of iodofluorinated alkenes from phenyl-substituted alkenes.⁴⁵ The polymer resins could be easily recovered and reused several times.

E. Alkyl Amine Hydrogen Fluorides

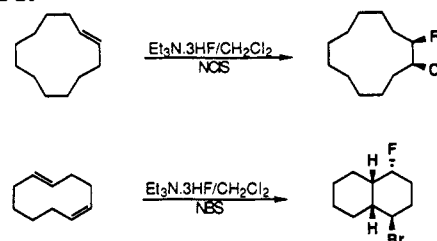
Et₃N·3HF, originally introduced by Franz,⁴⁶ is also a popular source of F⁻ and it is less corrosive than PPHF. It has recently been used for the bromo-fluorination of allylic alcohols.⁴⁷ Treatment of the fluorobromohydrins with aqueous sodium hydroxides generates epifluorohydrins (Scheme 19).

SCHEME 19



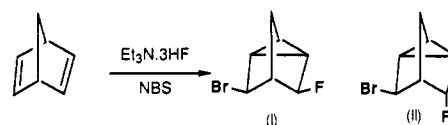
Halofluorination has also been achieved with NCIS and NIS⁴⁸ (Scheme 20).

SCHEME 20



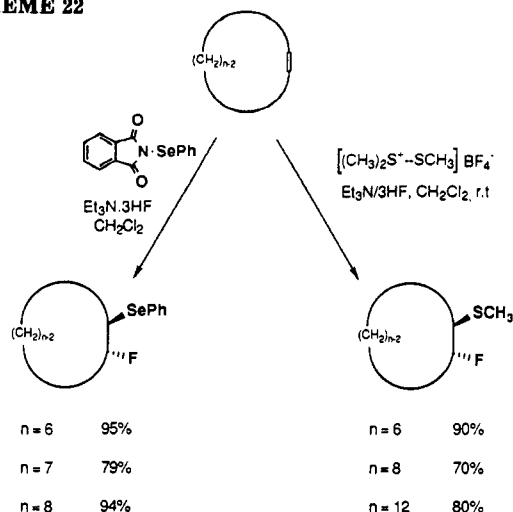
An investigation of NBS/Et₃N·3HF on norbornadiene⁴⁹ has been reexamined by Laurent.⁵⁰ Compounds i and ii have been shown by a combination of ¹H + ¹³C NMR and by independent synthesis to be the major products in this reaction resulting from *exo* attack of the bromonium ion and quenching with F⁻ (Scheme 21).

SCHEME 21

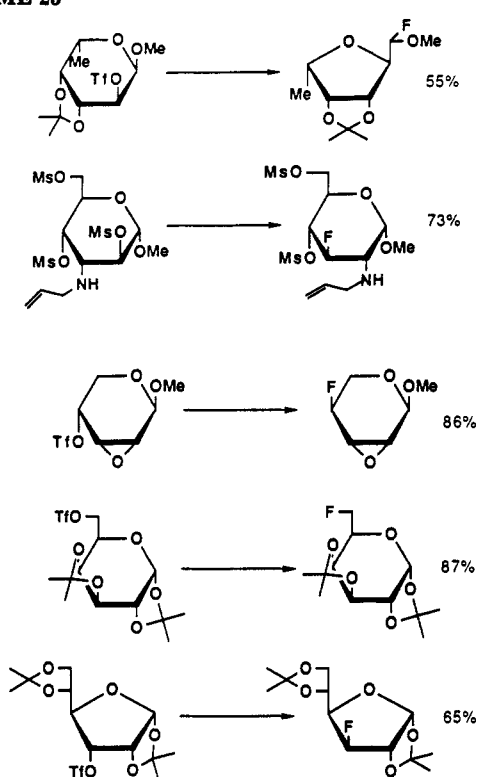


β -Fluoroalkyl methyl thioethers have been prepared by addition of dimethyl(methylthio)sulfonium fluoroborate (DMTSF) and Et₃N·3HF across olefins.⁵¹ The corresponding β -fluoro selenides were formed in higher yields from *N*-phenyl selenophthalimide⁵² (Scheme 22). Et₃N·3HF has also been recently used to prepare some fluoro sugars although in some cases rearrangement occurred^{53,54} (Scheme 23).

SCHEME 22

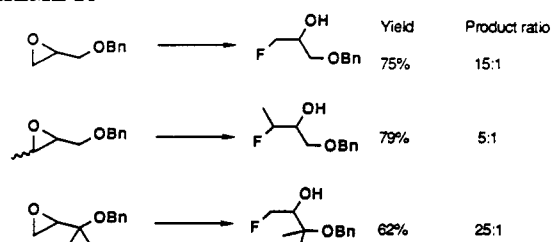


SCHEME 23



$\text{Et}_2\text{NH}\cdot 3\text{HF}$ is also a good source of F^- and has been used with great success in the regioselective ring opening of epoxides.⁵⁵ Addition of F^- to generate the corresponding fluorohydrins was generally found to occur from the least hindered carbon (Scheme 24).

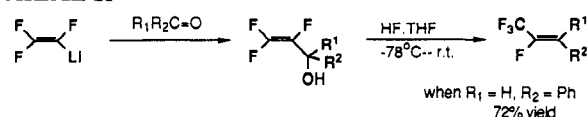
SCHEME 24



$\text{THF}\cdot\text{HF}$, first reported by Hirschmann⁵⁶ in 1956, has recently been revived as a fluorinating medium. A series of tetrafluoro-substituted alkenes were synthesized

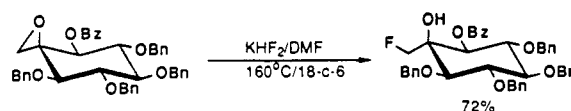
using this cheap source of fluorinating agent⁵⁷ (Scheme 25).

SCHEME 25



HF has also been used on a polymer support for the fluorination of α -bromo ketones.⁵⁸ Different polymer F^- species were prepared and a significant increase was noted in the nucleophilicity compared to basicity on transcending the series P^+F^- , P^+HF_2^- , $\text{P}^+\text{H}_2\text{F}_3^-$. HF_2^- in the form of KHF_2 was also used recently to prepare fluorinated inositol derivatives via an epoxide ring opening⁵⁹ (Scheme 26).

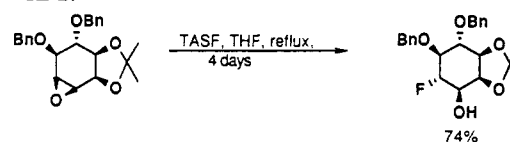
SCHEME 26



F. TASF

Tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) was introduced by Middleton in 1976 as a highly nucleophilic source of fluorine.⁶⁰ Since then many different so called TAS reagents have been developed, with TASF receiving the most attention.⁶¹ Ley has recently used it for the preparation of fluorinositol derivatives⁶² (Scheme 27).

SCHEME 27

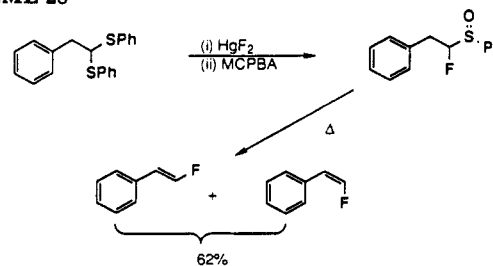


TASF has also been used for the fluoride ion catalyzed generation and carbonyl addition of α -halo carbanions derived from α -halo organosilicon compounds.⁶³

G. HgF_2

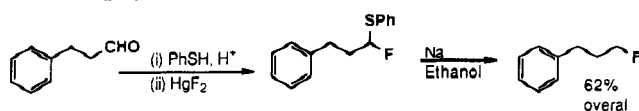
Mercury(II) fluoride is an ionic crystalline solid that is easily hydrolyzed and is insoluble in many organic solvents.⁶⁴ It has been traditionally used for replacing bromine with fluorine in organic halides.⁶⁵ However it has been recently used effectively in the formation of α -fluoro sulfoxides and vinyl fluorides⁶⁶ (Scheme 28).

SCHEME 28



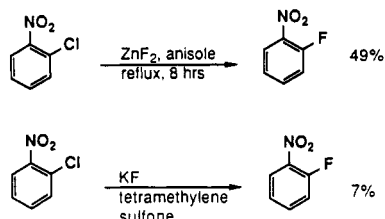
This methodology was extended to produce a new method for the preparation of alkyl fluorides⁶⁷ (Scheme 29).

SCHEME 29


 H. ZnF_2

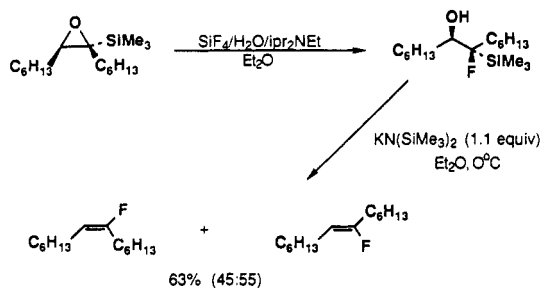
ZnF_2 is a highly toxic, colorless solid made by the action of fluorine on zinc, zinc oxide, zinc bromide, and zinc sulfide.⁶⁸ This infrequently used fluorinating agent has recently shown some promise in the fluorination of aromatic compounds⁶⁹ (Scheme 30).

SCHEME 30


 I. SiF_4

A new fluorinating system utilizing $\text{SiF}_4/\text{Bu}_4\text{NF}$ has been developed by Shimizu and Yoshioka and used in the ring opening fluorination of epoxides.⁷⁰ This work has been extended to α,β -epoxysilanes whereby β -fluoro- β -silyl alcohols were produced without elimination of the silicon moiety in contrast to $\text{Et}_3\text{N}\cdot 3\text{HF}$, PPHF, $\text{BF}_3\cdot\text{Et}_2\text{O}$, and KHF_2 which all gave desilylated products⁷¹ (Scheme 31).

SCHEME 31

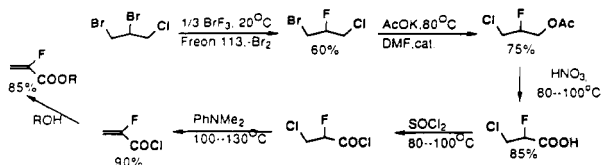


Subsequent Peterson olefination gave an excess of the sterically preferred trans product.

 J. BrF_3

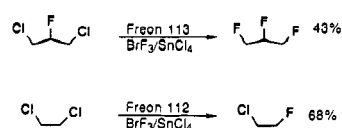
Bromine trifluoride, a yellow green liquid, bp 126 °C, adds to unsaturated, aryl C-H or carbon-halogen bonds.⁷² Recent work has centered on replacing bromine and chlorine with fluorine using BrF_3 in the synthesis of α -fluoroacrylic acid derivatives via bromochloroalkanes⁷³ (Scheme 32).

SCHEME 32



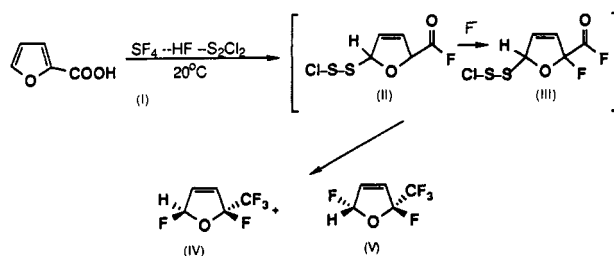
In the presence of Lewis acids (SnCl_4 , SbCl_5) in a freon solvent further fluorinations occur⁷⁴ (Scheme 33).

SCHEME 33


 K. SF_4

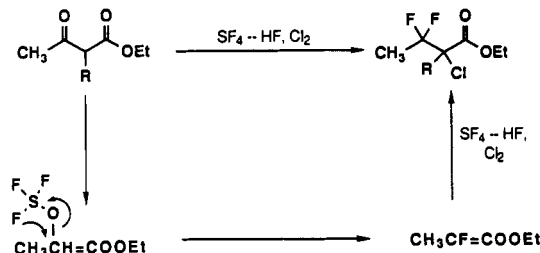
SF_4 is a commercially available gas with a boiling point of -40 °C, and with a toxicity similar to that of phosgene, it must be handled with caution. Most of the reactions require special apparatus since the fluorinations are carried out at elevated temperatures (100–200 °C depending on the substrate) and high pressures in stainless steel vessels, usually with added HF or BF_3 . SF_4 has been used for the conversion of ketones and aldehydes to *gem*-difluoro compounds, carboxylic acids to the trifluoromethyl group, and alcohols to alkyl fluorides. The chemistry and reactions of SF_4 have been reviewed several times in the past.^{75–78} Recent work has centered on using SF_4/HF in combination with S_2Cl_2 . This system has been used to fluorinate double bonds via S_2ClF generated in situ⁷⁹ and has now been applied to the fluorination of furan derivatives.⁸⁰ In the case of furan-2-carboxylic acid (I), compounds IV and V were formed in high yields supposedly via intermediates II and III (Scheme 34).

SCHEME 34



With SF_4 alone only monofluorination of furan-2-carboxylic acids occurred⁸¹ to give furan-2-carbonyl fluoride which underwent resinification on prolonged heating. Similar reactions have occurred using Cl_2 instead of S_2Cl_2 .⁸² The $\text{SF}_4\text{-HF-Cl}_2$ system has also been used to functionalize a range of acetoacetate ester derivatives⁸³ and α,β -unsaturated esters and acids⁸⁴ (Scheme 35). SF_4 alone usually converts α,β -unsaturated esters to *gem*-difluoro compounds and α,β -unsaturated acids to the CF_3 moiety, while leaving the carbon-carbon double bond untouched.⁸⁵ The reaction of diketene with SF_4/HF , gives the fluorinated compound in 70% yield⁸⁶ (Scheme 36).

SCHEME 35



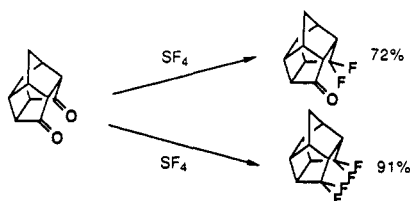
rated esters to *gem*-difluoro compounds and α,β -unsaturated acids to the CF_3 moiety, while leaving the carbon-carbon double bond untouched.⁸⁵ The reaction of diketene with SF_4/HF , gives the fluorinated compound in 70% yield⁸⁶ (Scheme 36).

SCHEME 36



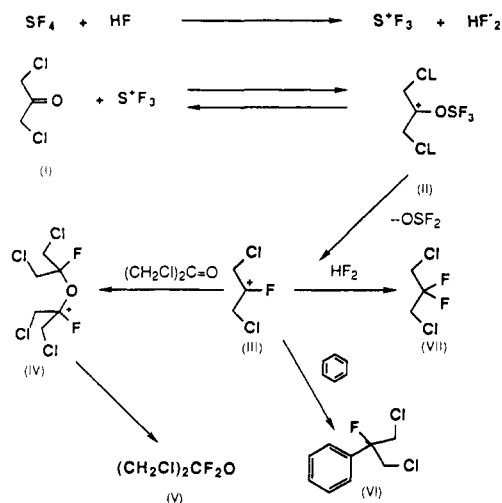
With dicarbonyl compounds it is possible to selectively mono or difluorinate each carbonyl group⁸⁷ (Scheme 37).

SCHEME 37



In some cases SF_4 forms α,α -difluoro ethers as side products in the fluorination of ketones. A recent investigation into the mechanism of these side products using 1,3-dihaloacetone has resulted in the mechanism suggested in Scheme 38.⁸⁸

SCHEME 38



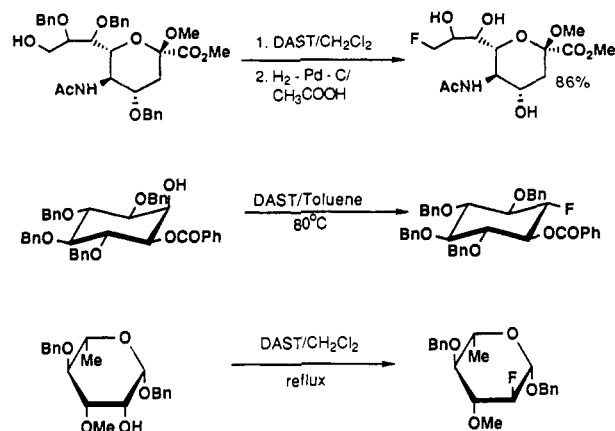
The existence of intermediate III was demonstrated by trapping out the fluorine stabilized carbocation with benzene, giving compound VI. Hence, by using added HF in SF_4 fluorinations, the formation of *gem*-difluoro derivatives over α,α -difluoro ethers is encouraged. Finally, SF_4 has also been used recently to convert 1,3-glycols into fluoroalkyl fluoro sulfites.⁸⁹

L. DAST

DAST [(diethylamido)sulfur trifluoride] has become one of the most important fluorinating agents of this century. This is mainly due to the innovative and pioneering work of the Du Pont group led by Middleton.⁹⁰ Its success is due to the fact that it can mimic the chemistry of SF_4 while avoiding the problems of high pressure and toxicity associated with the use of SF_4 . It is a commercially available liquid which can be used at convenient temperatures in standard laboratory equipment. DAST is mainly used to fluorinate alcohols and carbonyl groups, although a recent comprehensive review has listed many other important transformations.⁹¹ The majority of research on DAST and its reactions in the last few years has centered on the conversion of alcohols to fluorides. DAST has been used to make *N*-acetyl-9-deoxy-9-fluoroneuraminic acid,⁹² (-)-1*L*-1-deoxy-1-fluoro-*myo*-inositol⁹³ and 2,2-difluorooleandrose,⁹⁴ via the following intermediates (Scheme 39).

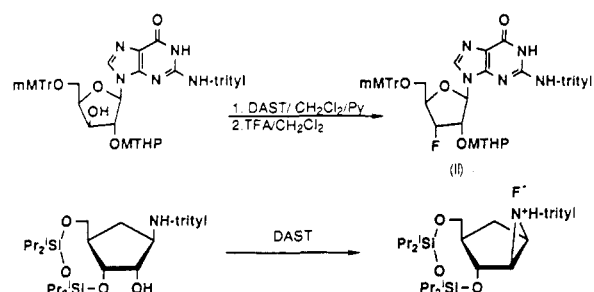
Some 5-membered rings have also been fluorinated, such as II (Scheme 40), a new potent antiviral agent,⁹⁵

SCHEME 39



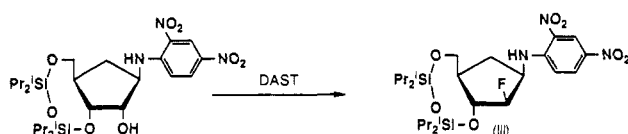
and III (Scheme 41) a fluorinated synthon for fluorocarbocyclic nucleosides,⁹⁶ in the latter example initially only an aziridinium species was isolated (Scheme 40).

SCHEME 40



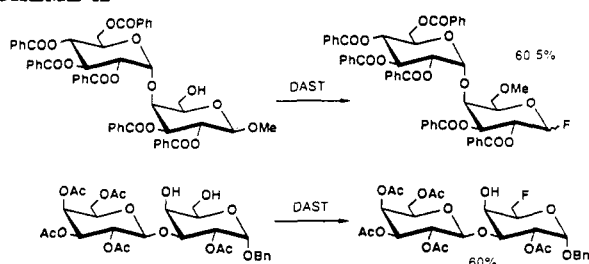
However changing to a less basic amino group resulted in the normal inversion of configuration expected from DAST fluorinations on secondary alcohols (Scheme 41). These authors also demonstrated the compatibility of DAST with an azide-substituted carbocycle.

SCHEME 41



Attempted preparation of the 6-fluoro derivatives of methyl β -D-galabioside gave the rearranged 1-fluoro derivative,⁹⁷ but in the fluorination of mucin-type oligosaccharides, the 6 position was fluorinated in 60% yield⁹⁷ (Scheme 42).

SCHEME 42

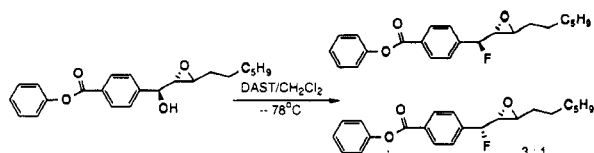


Similarly α -monofluoro- and α,α -difluorothymidine have recently been prepared, using DAST, for their possible antiviral and antitumor properties.⁹⁹

In the preparation of some novel chiral fluorinated ferroelectric liquid crystals Walba has demonstrated that DAST can fluorinate primary alcohols, α to an

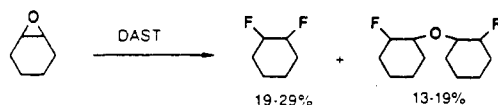
epoxide, with predominant retention of configuration¹⁰⁰ (Scheme 43).

SCHEME 43



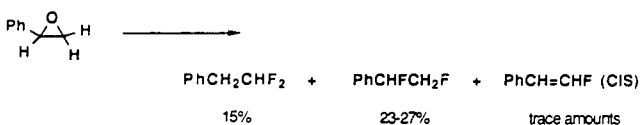
However in the absence of an OH group DAST will react with epoxides, as a recent example by Hudlicky shows, to form *gem*-difluorides, vicinal difluorides, and bis(*m*-fluoroalkyl) ethers¹⁰¹ (Scheme 44).

SCHEME 44



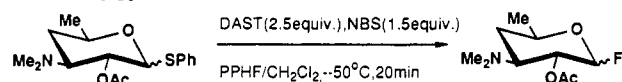
Presumably the *gem*-difluoride is formed via the acid catalyzed rearrangement of the epoxide to give phenyl acetaldehyde which is subsequently fluorinated (Scheme 45). Extending Nicolaou's recent work on the

SCHEME 45



fluorination of thioglycosides,¹⁰² Suzuki has found that some thioglycosides failed to react effectively with the DAST/NBS system.¹⁰³ Competitive attack of NBS to both PhS and Me₂N groups was thought to have been the problem in this case. On adding PPHF a 77% yield of the fluoroglycoside was achieved (Scheme 46).

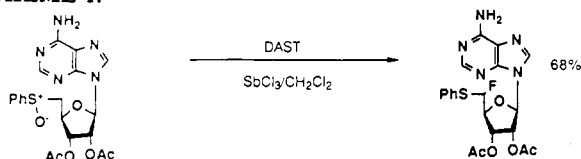
SCHEME 46



Robins and Wnuk have successfully fluorinated an adenosine derivative by reaction of DAST on a sulfoxide moiety to produce an α -fluorinated sulfide.¹⁰⁴

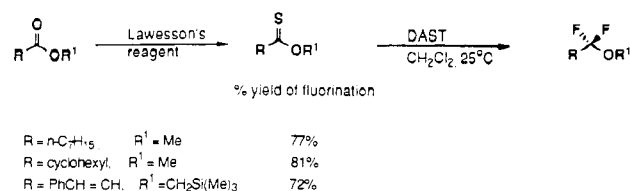
This follows on from the original work of DAST on sulfoxides by McCarthy,¹⁰⁵ in this case however, the addition of SbCl₃ as a Lewis acid catalyst instead of ZnI₂ was needed for efficient fluorination (Scheme 47).

SCHEME 47

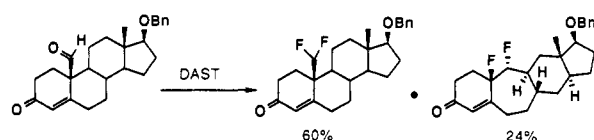


Further work on conversion of carbonyl derivatives to fluoro compounds has focused on the reactions of esters with this reagent. DAST has recently been used for the preparation of α,α -difluoro ethers, from thioesters, normal esters being unreactive or giving side products.¹⁰⁶ A mechanism similar to that for the conversion of aldehydes and ketones to *gem*-difluorides has been proposed (Scheme 48). Mann has used DAST recently to fluorinate steroidal aldehydes.¹⁰⁷ In the process an interesting rearrangement also occurred which was elucidated by ¹³C NMR and X-ray crystallography (Scheme 49). Finally, Middleton has used

SCHEME 48

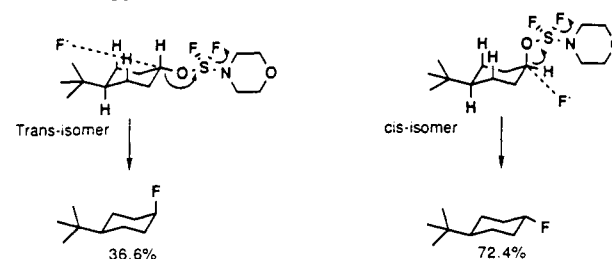


SCHEME 49



morphoDAST (4-morpholinosulfonium trifluoride) to fluorinate cyclohexanols.¹⁰⁸ This reagent gives higher yields than DAST, and in this particular case the *cis* alcohol gave a higher yield than the *trans* alcohol, via an S_N2 pathway (Scheme 50).

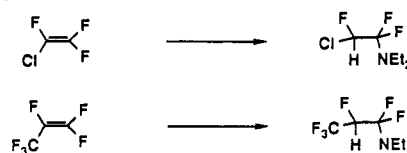
SCHEME 50



M. Fluoroalkylamine Reagents (FAR)

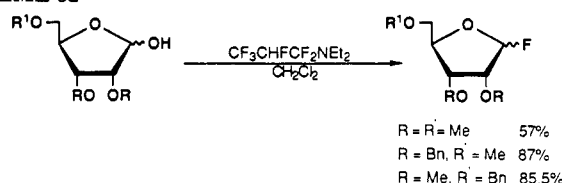
FAR have been used for replacement of OH and carbonyl groups with fluorine.¹⁰⁹ There are two frequently used FARs that dominate research in this area, the first is known as Yarovenko's reagent¹¹⁰ (chloro-1,1,2-trifluoroethylamine) and the second being Ishikawa's reagent¹¹¹ [2-(trifluoromethyl)-1,1,2-trifluoroethylamine] (Scheme 51).

SCHEME 51



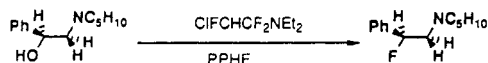
Ishikawa's reagent has been used recently to produce anomeric fluorides in good yields¹¹² (Scheme 52).

SCHEME 52



Yarovenko's reagent has been used in combination with Olah's reagent to fluorinate amino alcohols with retention of configuration, presumably via anchimeric assistance from the adjacent pentyl amino group¹¹³ (Scheme 53).

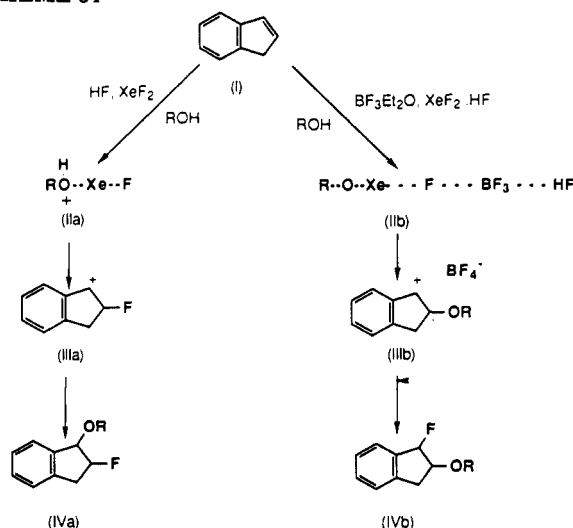
SCHEME 53



N. XeF₂

The xenon fluorides were discovered almost 30 years ago,¹¹⁴ shortly after it was shown that the inert gas could undergo chemical reactions if the correct conditions and reagents were used.¹¹⁵ In the same year xenon difluoride was also prepared¹¹⁶ and has proved to be one of the most useful fluorinating agents and the most stable (an exception is the recent innovation of "taming" XeF₆ by forming an adduct with graphite to form C₁₀XeF₆ intercalater¹¹⁷). Xenon difluoride has been used in the fluorination of alkenes,^{118,119} in fluorodecarboxylation,¹²⁰ in the fluorination of thioethers,¹²¹ and in the fluorination of aromatic¹²² and aliphatic¹²³ compounds. The reactions of XeF₂ with organic compounds has been reviewed by Filler.¹²⁴ Many of the reactions with XeF₂ require the addition of Lewis acids or proton donors such as BF₃ and HF. These are thought to coordinate with the fluorine lone pairs and enhance the electrophilicity of XeF₂, encouraging the formation of radical cations or nucleophilic attack on fluorine. Recent work has centered on replacing one of the fluorine groups with an alcohol¹²⁵ or carboxylic acid¹²⁶ group. Thus, instead of the usual 1,2 difluorination with XeF₂, these new species can be used to monofluorinate double bonds in a regiospecific way (Scheme 54). In the case of alcohols, the resulting

SCHEME 54



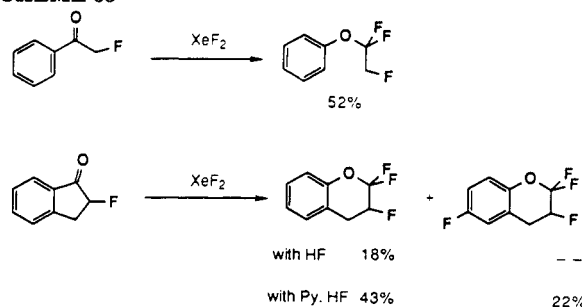
ROXeF species can react through oxygen or fluorine depending on the reaction conditions. When R = CH₃, with added BF₃·Et₂O, I reacted via an electrophilic oxygen species IIb to give a mixture of *cis*- and *trans*-2-methoxy-1-fluoroindan (IVb). With added HF, I reacted via an electrophilic fluorine species IIa to give *cis*- and *trans*-1-methoxy-2-fluoroindan (IVa). When more acidic alcohols were used¹²⁷ (R = CF₃) IVb predominated, without added BF₃·Et₂O. (In the absence of any

indan, oxidation of the alcohol was found to occur.) A free radical reaction pathway was thought unlikely since no change in the reaction time or product distribution was found to occur upon addition of a free-radical inhibitor and a predominance of *cis* to *trans* was found. (The *trans* product would be preferred in a free-radical pathway due to the steric requirements of the chain transfer step.)

An interesting application of this work would be the reaction of ROXeF with various substituted glycals. By modifying the reaction conditions fluorine sugars substituted at the 2 or 3 position could be obtained, which would be useful in biological studies. XeF₂ also reacts with ketones via their enol acetates.¹²⁸ With silyl enol ethers α -fluoro ketones were formed.^{129,130}

Zupan¹³¹ has recently shown that XeF₂ reacts with aryl-substituted ketones to give rearranged difluoro-substituted ethers. By using BF₃ as a catalyst, enhanced aromatic fluorination in preference to skeletal rearrangements occurred (Scheme 55). Here BF₃ seems

SCHEME 55



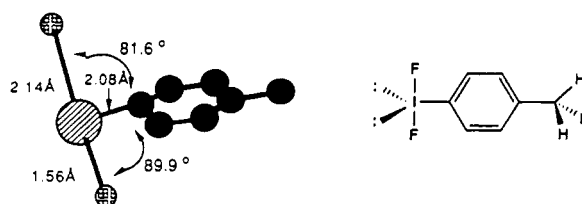
to enhance the electrophilicity of fluorine, which is in contrast to the previous studies on alkenes mentioned earlier.

Fluorination of nitro compounds and imidazole *N*-oxides has been studied recently, for which free-radical mechanisms have been invoked.¹³² Finally studies in XeF₂ with Grignard reagents gave solvent-derived products as well as coupled products; however, no fluorinated compounds were formed.¹³³

O. Aromatic Hypervalent Iodine Fluorides

These compounds are easily prepared from the corresponding chlorides and are relatively stable. For example the 4-methyliodobenzene difluoride derivative can be conveniently stored at 0 °C for many months. It possesses a bent T-shaped geometry around iodine as shown recently for the first time by X-ray diffraction¹³⁴ which appears to be typical of these compounds in general (Scheme 56). Although these compounds

SCHEME 56

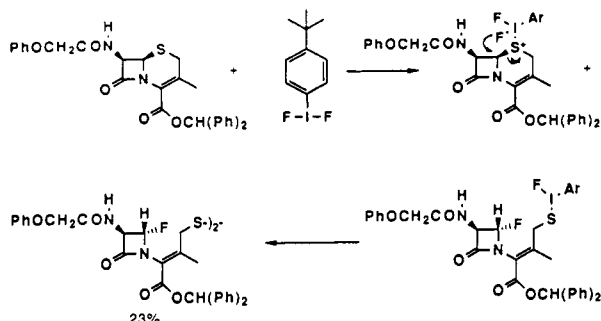


were first made over a 100 years ago¹³⁵ they have only recently been investigated as possible fluorinating agents.¹³⁶⁻¹⁴⁴

Motherwell has recently shown that *p*-*tert*-butyl-iodobenzene difluoride efficiently fluorinates steroids

when used in conjunction with an electron-transfer agent. A one electron transfer mechanism has been implicated.¹⁴⁵ The same reagent has also been used by the group to fluorinate cephalosporins¹⁴⁶ (Scheme 57).

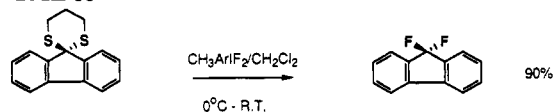
SCHEME 57



This is the first case of nucleophilic substitution on a carbon-centered iodonium-sulfonium intermediate with fluoride anion. The reaction is presumably facilitated by formation of the azetidinium ion intermediate by azetidine C-S heterolysis.

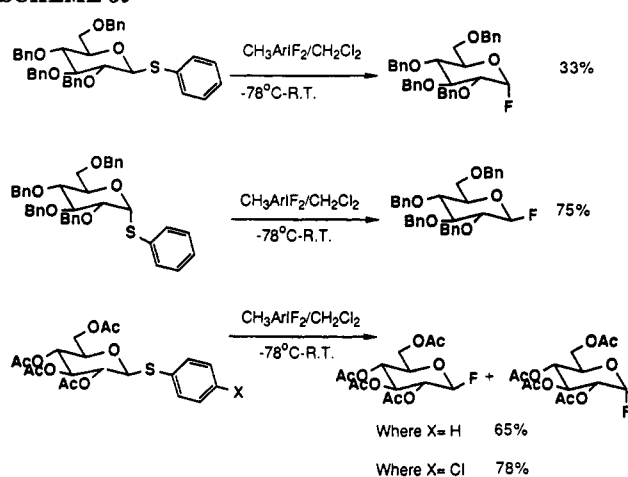
This work has been extended to the synthetically useful formation of *gem*-difluorides in high yields from dithianes¹⁴⁷ (Scheme 58).

SCHEME 58



Similarly the efficient formation of fluoro carbohydrates from phenyl thioglycosides under relatively mild conditions has been achieved with this reagent.¹⁴⁸ Higher yields were obtained when *p*-chloro substituents were present on the aromatic ring of the glycoside. An S_N2 displacement at the anomeric center is implied with some of the substrates which lack neighboring group participants at the C-2 position (Scheme 59).

SCHEME 59



III. Electrophilic Sources of Fluorine

These reagents have been developed for introducing fluorine at centers of high electron density, and they therefore offer an interesting alternative where nucleophilic and free radical sources of fluorine have proved inefficient or have failed. The ability of fluorine to behave as an electrophile is not easily achieved since fluorine is the most electronegative element. Ingenious

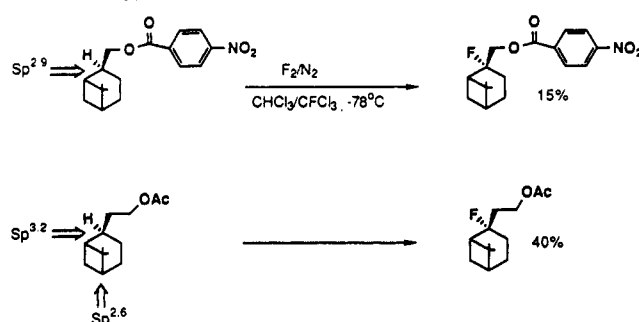
ways of overcoming this problem have been achieved by either withdrawing electronic charge from fluorine through inductive effects or by the presence of an excellent leaving group adjacent to fluorine, or by a combination of these effects. CF₃OF, FClO₃, CF₃CF₂OF, CF₃COOF, CH₃COOF, CF₃COOF, N-F reagents, CsS-O₄F, and F₂ itself have all been used as sources of F⁺. An obvious extension to this list would be CF₃SO₃F which has not appeared as another contender despite CF₃SO₃Cl and CF₃SO₃Br being excellent sources of positive halogen.¹⁴⁹

Some of the more recent developments in this area are included below.

A. F₂

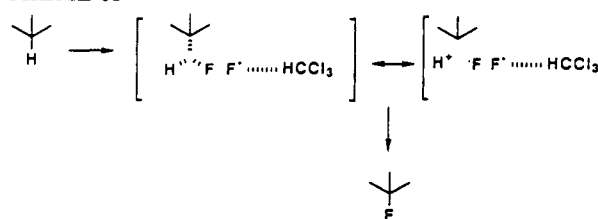
Although fluorine can behave as a free-radical source of fluorine under different conditions it can also behave as an electrophile. Barton and Rozen have both shown that F₂ diluted with N₂ can fluorinate electron-rich C-H bonds.^{150,151} Recently Rozen has extended this work to other systems which contain electronegative substituents¹⁵² (Scheme 60).

SCHEME 60



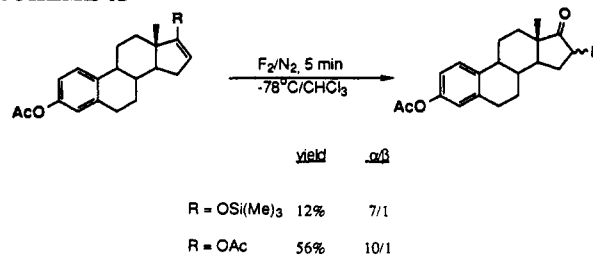
Fluorine in this system selectively reacts with the C-H bonds which contain the highest p-orbital contribution (hybridization) as indicated by CNDO and PRDDO computer calculations. Since fluorination occurs with retention of configuration, absence of eliminations, rearrangements, and partial inversions of configuration, a pentacoordinate carbonium ion mechanism has been suggested¹⁵³ (Scheme 61).

SCHEME 61



Fluorine has also been used to make an a fluoro-carbonyl derivative via the silyl enol ether and the enol acetate of estrone¹⁵⁴ (Scheme 62).

SCHEME 62

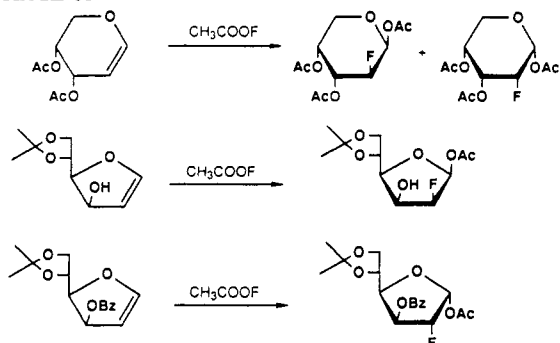


Other fluorinating agents were also used including CF_3OF , CsCO_4F , and XeF_2 . XeF_2 gave exclusively the α isomer in 44% yield, where $\text{R} = \text{OSi}(\text{Me})_3$. F_2/N_2 has also been used to fluorinate substituted pyridines in reasonably good yields. In the case of 4-isopropyl pyridine a 47% yield of 2-fluoro-4-isopropyl pyridine was obtained.¹⁵⁵

B. Acetyl Hypofluorites

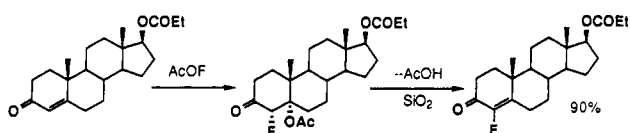
CF_3COOF was the first acyl hypofluorite to be made,¹⁵⁶ and this has been used to good effect in organic and polymer chemistry by Rozen.¹⁵⁷ CH_3COOF has recently been used to fluorinate glycols of pentopyranoses and hexo- and pentofuranoses.¹⁵⁸ Syn addition occurred with all the glycols, with the stereospecificity of addition to furanoid glycols being governed by the nature of the C-3 substituent (Scheme 63).

SCHEME 63

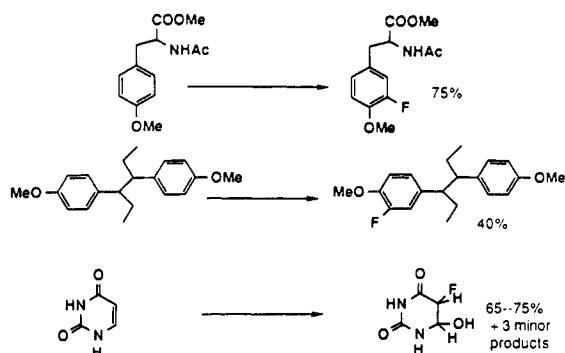


CH_3COOF has also been used to fluorinate steroids, tyrosine, hexestro, and uracil derivatives^{159,160} (Schemes 64 and 65). Other derivatives of acetyl hypofluorite

SCHEME 64

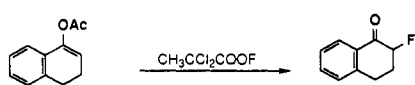


SCHEME 65



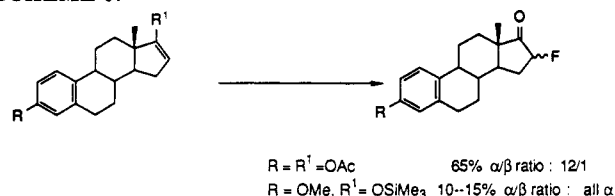
have been made recently and it was found that reasonable stability could be achieved providing at least one electron-withdrawing group was at the α position and that lengthy alkyl chains were avoided.¹⁶¹ For example, when sodium 2,2-dichloropropionate was reacted with F_2 , 2,2-dichloropropionyl hypofluorite was formed and this reacted with the enol acetate of tetralone to give the α -fluoro derivative in 85% yield (Scheme 66).

SCHEME 66



CF_3OF was first prepared by Cady in 1957.¹⁶² Barton and Hesse pioneered the early work on this reagent and demonstrated that it was a more powerful electrophile than FCIO_3 .¹⁶³ As mentioned briefly in the section on fluorine apart from F_2 and XeF_2 , CF_3OF adds to siloxystrone and estrone diacetate to give α -fluoro ketones¹⁶⁴ (Scheme 67).

SCHEME 67

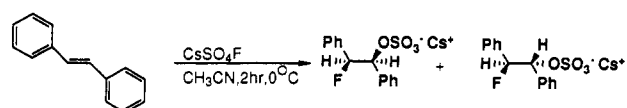
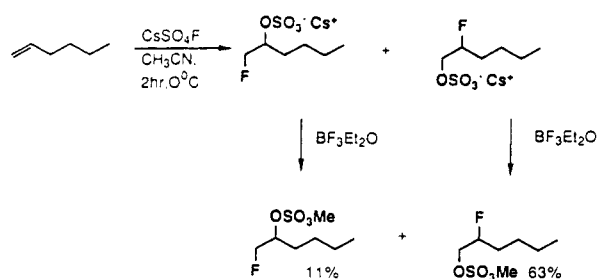


CF_3OF has also been used to introduce ^{18}F into sugar derivatives via their glycols in high yields.¹⁶⁵

C. CsSO_4F

This is a new solid electrophile fluorinating agent introduced by Appleman in 1979;¹⁶⁶ however, it must be used with caution since under certain conditions it is explosive. It has been used for the fluorination of aromatic systems,¹⁶⁷ and the α fluorination of ketones,¹⁶⁸ but recent work has centered on addition to alkanes and alkenes (Scheme 68).

SCHEME 68

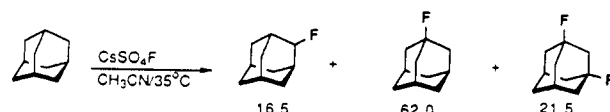


Zefirov has demonstrated that CsSO_4F reacts with alkenes, showing a preference for anti Markovnikov products from syn addition.¹⁶⁹

This suggests that the electrophilic center in CsSO_4F is oxygen rather than fluorine in these reactions, this is in contrast to previous studies by Zupan on CsSO_4F with indene where F^+ was implicated as the electrophilic species.¹⁷⁰

CsSO_4F has also recently been shown to react with saturated hydrocarbons.¹⁷¹ Adamantane, for example, was fluorinated in over 40% yield giving a mixture of products in which the addition of a free-radical inhibitor had no effect on the reaction rate or product distribution. Other alkanes were also fluorinated (Scheme 69).

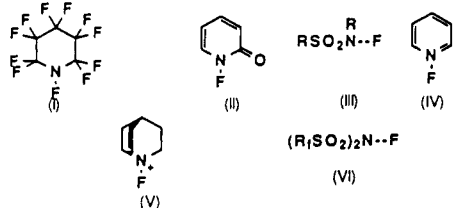
SCHEME 69



D. N-F Electrophilic Fluorinating Agents

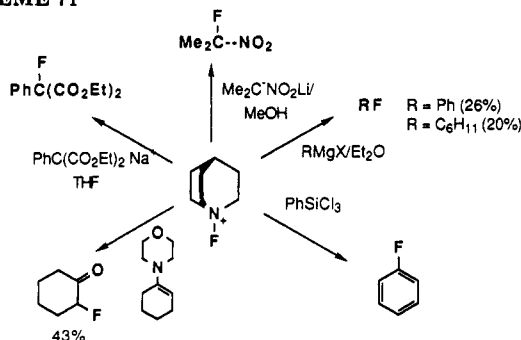
The compounds were developed to overcome the problems associated with the more traditional sources of electrophilic fluorine which are more explosive, hygroscopic, gaseous, and toxic. These new reagents are often more stable and selective, and many are solids and therefore easier to handle. The range of compounds which have been developed include, *N*-fluoroperfluoropiperidine (I) (1964, Banks¹⁷²), dihydro-*N*-fluoro-2-pyridone (II) (1983, Purrington¹⁷³), *N*-fluoro-*N*-alkyl sulfonamides (III) (1984, Barnette¹⁷⁴), *N*-fluoropyridinium salts (IV) (1986 Umemoto¹⁷⁵), *N*-fluoroquinuclidinium salts (V) (1986, Banks¹⁷⁶), and *N*-fluoroperfluoroalkyl sulfonamides (VI) (1987, Des-Marteau¹⁷⁷) (Scheme 70).

SCHEME 70



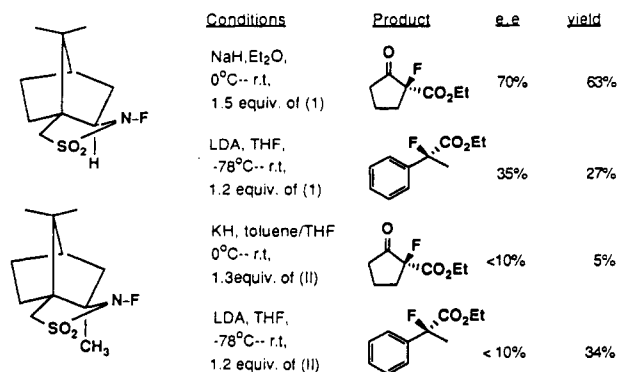
These reagents have been used to fluorinate aromatic rings, Grignards, lithium salts, enolates, etc. A recent paper by Banks has shown that *N*-fluoroquinuclidinium fluoride, one of the more successful N-F fluorinating agents, can fluorinate a wide array of electron-rich substrates¹⁷⁸ (Scheme 71).

SCHEME 71



N-Fluorosultams have been recently made by Lang, and these have been used for the first time to achieve enantioselective fluorination of metal enolates¹⁷⁹ (Scheme 72).

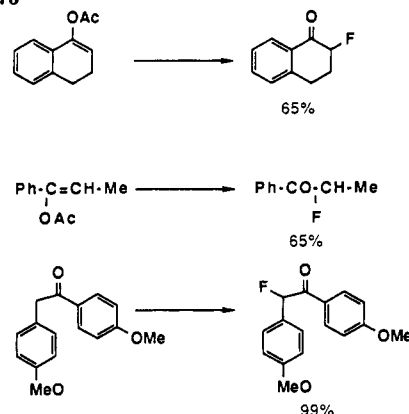
SCHEME 72



IV. Electrochemical Fluorination

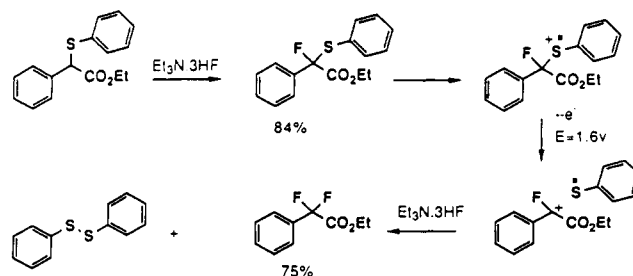
This classical fluorination technique is difficult to employ for selective fluorinations and was traditionally used to make polyfluorinated organic compounds.¹⁸⁰ Recently however Laurent has successfully applied this technique to the α fluorination of ketones¹⁸¹ and benzylic compounds¹⁸² by carrying out the electrolysis in the presence of Et₃N·3HF (Scheme 73).

SCHEME 73



This work has been extended to the oxidative fluorination of sulfides and offers an interesting alternative to DAST for such transformations.¹⁸³ Monofluorides or *gem*-difluorides can be produced by adjusting the potential during the electrolysis. A radical cation mechanism, which seems reasonable has been invoked to explain product formation (Scheme 74).

SCHEME 74



Acknowledgments. I thank Dr. W. B. Motherwell and Professor G. A. Olah for their comments and suggestions and to the Science and Engineering Research Council for an SERC NATO postdoctoral fellowship.

Registry No. F₂, 7782-41-4.

References

- (1) The 10 millionth registry substance was recorded in February 1990.
- (2) (a) This information was obtained from various CAS searches, courtesy of David Walsh, Chemical Abstracts Service, STN International, Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 4WF U.K. (b) A referee pointed out that a similar display of fluorine data has been presented recently; see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* 1990, 29, 1320 (footnote 90).
- (3) (a) For a recent comprehensive guide to the industrial applications of organofluorine compounds, see: Banks, R. E., Sharp, D. W. A., Tatlow, J. C., Eds. *Fluorine: The First Hundred Years*; Elsevier Sequoia: New York, 1986. (b) For previous reviews concerning general organofluorine chemistry, see: Mann, J. *Chem. Soc. Rev.* 1987, 16, 381 and references therein.
- (4) Clark, J. H. *Chem. Rev.* 1980, 80, 429.
- (5) Borodine, A. J. *Liebigs, Ann. Chem.* 1863, 126, 58.
- (6) Liotta, C. L.; Harris, P. H. *J. Am. Chem. Soc.* 1974, 96, 2250.
- (7) Gringras, M.; Harpp, D. N. *Tetrahedron Lett.* 1988, 29, 4669.

- (8) Edge sandwich complexes with cesium salts have been implicated before, see ref 4 and references therein.
- (9) Graham, D. P. *J. Org. Chem.* 1966, 31, 955.
- (10) Badone, D.; Jommi, G.; Pagliarin, R.; Tavecchia, P. *Synthesis* 1987, 920.
- (11) Ando, T.; Brown, S. J.; Clark, J. H.; Cork, D. G.; Hanafusa, T.; Ichihara, J.; Miller, J. M.; Robertson, M. S. *J. Chem. Soc., Perkin Trans. 2* 1986, 1133 and references therein.
- (12) (a) Clark, J. H.; Hyde, A. J.; Smith, D. K. *J. Chem. Soc., Chem. Commun.* 1986, 791. (b) Ichihara, J.; Matsuo, T.; Hanafusa, T.; Ando, T. *J. Chem. Soc., Chem. Commun.* 1986, 793.
- (13) Liu, H. *J. Fluorine Chem.* 1989, 43, 429.
- (14) (a) Dmowski, W.; Wielgat, J. *J. Fluorine Chem.* 1988, 41, 241. (b) Dmowski, W.; Wieglat, J. *Bull. Pol. Acad. Sci. Chem.* 1989, 36 (5-6), 195.
- (15) Moissan, H. *Le Fluor et ses Composés*; Steinheil: Paris, 1900.
- (16) Tarnhauser, P.; Pratt, R. J.; Jensen, E. V. *J. Am. Chem. Soc.* 1956, 78, 2658.
- (17) Pogany, S. A.; Zentner, G. M.; Ringeisen, C. D. *Synthesis* 1987, 718.
- (18) (a) Clark, J. H.; Hyde, A. J.; Smith, D. K. *J. Chem. Soc., Chem. Commun.* 1986, 791. (b) Ando, T. *J. Chem. Soc., Chem. Commun.* 1986, 793.
- (19) Ando, T.; Cork, D. G.; Fujita, M.; Kimura, T.; Tatsuno, T. *Chem. Lett.* 1988, 1877.
- (20) Bloodworth, A. J.; Bowyer, K. J.; Mitchel, J. C. *Tetrahedron Lett.* 1987, 28, 5347.
- (21) Yoneda, N.; Fukuhara, T.; Yamagishi, K.; Suzuki, A. *Chem. Lett.* 1985, 1693.
- (22) Yoneda, N.; Fukuhara, T.; Yamagishi, K.; Suzuki, A. *Chem. Lett.* 1987, 1675.
- (23) Kent, P. W.; Young, R. C. *Tetrahedron* 1971, 27, 4057.
- (24) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* 1984, 49, 3216.
- (25) Kabat, M. M. *J. Fluorine Chem.* 1989, 42, 435.
- (26) Nakahara, Y.; Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* 1988, 29, 2325.
- (27) Maeda, M.; Abe, M.; Kojima, M. *J. Fluorine Chem.* 1987, 34 (3-4), 337.
- (28) Bram, G.; Loupy, A.; Pigeon, P. *Synth. Commun.* 1988, 18 (14), 1661.
- (29) Matsumoto, T.; Ohsaki, M.; Matsuda, F.; Terashima, S. *Tetrahedron Lett.* 1987, 28, 4419.
- (30) Bosch, P.; Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *Tetrahedron Lett.* 1987, 28, 4733.
- (31) Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* 1989, 54, 4294.
- (32) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* 1972, 44, 3872.
- (33) Olah, G. A.; Shih, J. G.; Prakash, G. K. S. Fluorine containing reagents in organic chemistry. In *Fluorine: The First Hundred Years*; Banks, R. E., Sharp, D. W. A., Tatlow, J. C., Eds.; Elsevier Sequoia: New York, 1986; pp 377-396.
- (34) Olah, G. A.; Nojima, M.; Kerekes, I. *Synthesis* 1973, 786.
- (35) See ref 1.
- (36) (a) Olah, G. A.; Shih, J. G.; Singh, B. P.; Gupta, B. G. B. *Synthesis* 1983, 713. (b) Olah, G. A.; Shih, J. G.; Krishnamurthy, V. V.; Singh, B. P. *J. Am. Chem. Soc.* 1984, 106, 4492.
- (37) Campbell, M. M.; Sainsbury, M.; Bowles, S.; Davies, G. *Tetrahedron Lett.* 1989, 30, 28, 3711.
- (38) See ref 1.
- (39) Yoneda, N.; Suzuki, A.; Fukuhara, T. *J. Fluorine Chem.* 1988, 38, 435.
- (40) Meurs, J. H. H.; Sopher, D. W.; Eilenberg, W. *Angew. Chem., Int. Ed. Engl.* 1989, 28 (7), 927.
- (41) Mirsadeghi, S.; Prasad, G. K. B.; Whittaker, N.; Thakker, D. R. *J. Org. Chem.* 1989, 54, 3091.
- (42) Shimizu, M.; Yoshioka, H.; Kanemoto, S. *Bull. Chem. Soc. Jpn.* 1989, 62, 2024.
- (43) Beguin, C. G.; Dahbi, A.; Hamman, S. *J. Chem. Res.* 1989, 128.
- (44) Surya Prakash, G. K.; Prakash Reddy, V.; Li, Xing-Ya; Olah, G. A. *Synlett* 1990, 594.
- (45) Zupan, M.; Gregorcic, A. *Bull. Chem. Soc. Jpn.* 1987, 60, 3083.
- (46) Franz, R. *J. Fluorine Chem.* 1980, 15, 423.
- (47) Baklouti, A.; Chehidi, I.; Chaabount, M. M. *Tetrahedron Lett.* 1989, 30 (24), 3167.
- (48) Laurent, A.; Haufe, G.; Alvernhe, G. *Synthesis* 1987, 562.
- (49) Zupan, M.; Gregorcic, A. *Tetrahedron* 1977, 33, 3243.
- (50) Laurent, A.; Anker, D.; Alvernhe, G.; Haufe, G.; Beguin, C. *Tetrahedron* 1988, 44, 3551.
- (51) Haufe, G.; Alvernhe, G.; Anker, D.; Laurent, A.; Saluzzo, C. *Tetrahedron Lett.* 1988, 29 (19), 2311.
- (52) Anker, D.; Saluzzo, C.; Alvernhe, G.; Haufe, G. *Tetrahedron Lett.* 1990, 31 (5), 663.
- (53) Baer, H. H.; Mateo, F. H.; Siemsen, L. *Carbohydr. Res.* 1989, 187, 67.
- (54) Anker, D.; Pico, D. *Carbohydr. Res.* 1987, 166, 309.
- (55) Poulter, C. D.; Muelbacher, M. *J. Org. Chem.* 1988, 53, 1026.
- (56) Hirschmann, R. F.; Miller, R.; Wood, J.; Jones, R. E. *J. Am. Chem. Soc.* 1956, 78, 4956.
- (57) Dolbier, W. R., Jr.; Gray, T. A.; Ohnishi, K. *Synthesis* 1987, 956.
- (58) Cousseau, J.; Albert, P. *J. Org. Chem.* 1989, 54, 5380.
- (59) Yang, S. S.; Min, J. M.; Beattie, T. R. *Synth. Commun.* 1988, 18 (9), 899.
- (60) Middleton, W. J. U.S. Pat. 3940402, 1976; *Chem. Abstr.* 1976, 85, 6388j.
- (61) (a) Farnham, W. B.; Harlow, R. L. *J. Am. Chem. Soc.* 1981, 103, 4608. (b) Webster, O. W.; Hertler, W. R.; Sogah, D. Y.; Farnham, W. E.; RajanBabu, T. *J. Am. Chem. Soc.* 1983, 105, 5706.
- (62) Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfield, F.; Vidal, A. *Tetrahedron Lett.* 1989, 30, 3557.
- (63) Fujita, M.; Obayashi, M.; Hujama, T. *Tetrahedron Lett.* 1988, 44, 4135.
- (64) Cotton, F. A.; Wilkinson, G., Eds. *Advanced Inorganic Chemistry*; Interscience: New York, 1972; p 517.
- (65) (a) Henne, A. L. *J. Am. Chem. Soc.* 1937, 59, 1200. (b) McBee, E. T.; Hass, H. B.; Bittenbender, W. A.; Weesner, W. E.; Toland, W. G.; Hausch, W. R.; Frost, L. W. *Ind. Eng. Chem.* 1947, 39, 409.
- (66) Purrington, S. T.; Pittman, J. H. *Tetrahedron Lett.* 1987, 28, 3901.
- (67) Purrington, S. T.; Pittman, J. H. *Tetrahedron Lett.* 1988, 29, 6851.
- (68) Durrant, P. J., Durrant, B., Eds. *Introduction to Advanced Inorganic Chemistry*; Longman: New York, 1972; p 495.
- (69) Momotake, H. *Jpn. Kokai Tokkyo Koho JP*, 63, 284, 135, [88, 284, 135], 1988; *Chem. Abstr.* 1989, 110, 134341k.
- (70) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* 1988, 29, 4101.
- (71) Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* 1989, 29, 967.
- (72) Sheppard, W. A.; Sharts, C. M., Eds. *Organic Fluorine Chemistry*; 1969, Benjamin, W. A., Inc: New York, 1969; p 57.
- (73) Boguslavskaya, L. S.; Chuvatkin, N.; Morozova, T. V.; Pan-teleeva, I. Yu.; Kartashov, A. V.; Sineokov, A. P. *Zh. Org. Khim.* 1987, 28, 1173.
- (74) Kartashov, A. V.; Chuvatkin, N. N.; Boguslavskaya, L. S. *Zh. Org. Khim.* 1988, 24, 2522.
- (75) Smith, W. C. *Angew. Chem., Int. Ed. Engl.* 1962, 1, 467.
- (76) Boswell, G. A.; Ripka, W. C.; Schriber, R. M.; Tullock, C. W. *Org. React. (New York)* 1974, 1, 21.
- (77) Wang, C. L. *J. Org. React. (New York)* 1985, 34, 319.
- (78) Dmowski, W. *J. Fluorine Chem.* 1986, 32, 2555.
- (79) Muratov, N. N.; Mohamed, N. M.; Kunshenko, B. V.; Alekseeva, L. A.; Yagpolskii, L. M. *Zh. Org. Khim.* 1986, 22 (5), 964-969.
- (80) Kunshenko, B. V.; Il'nitskii, S. O.; Motnyak, L. A.; Lyalin, V. V.; Yagupolskii, L. M. *Zh. Org. Khim.* 1987, 23 (4), 833.
- (81) Lyalin, V. V.; Grigorash, R. V.; Alekseeva, A. L.; Yagupolskii, L. M. *Zh. Org. Khim.* 1975, 11 (5), 1086.
- (82) Kunshenko, B. V.; Il'nitskii, S. O.; Motnyak, L. A.; Lyalin, V. V.; Burmakov, A. I.; Yagupolskii, L. M. *Bull. Chim. Fr.* 1986, 6, 974.
- (83) Kunshenko, B. V.; Mohamed, N. M.; Il'nitskii, S. O. *Zh. Org. Khim.* 1987, 23 (8), 11678.
- (84) Hasek, W. R.; Smith, W. C.; Engelhart, V. A. *J. Am. Chem. Soc.* 1960, 82 (3), 543.
- (85) Kunshenko, B. V.; Makhamed, N. M.; Muratov, N. N.; Yagupolskii, L. M. *Zh. Org. Khim.* 1988, 24 (4), 705.
- (86) Bloshchita, F. A.; Burmakov, A. I.; Yagupolskii, L. M. *Zh. Org. Khim.* 1988, 24 (7), 1558.
- (87) Aleksandrov, A. M.; Sorochinskii, A. E.; Petrenko, A. E.; Kukhar, V. P. *Zh. Org. Khim.* 1988, 24 (1), 149.
- (88) Wielgat, J.; Domogaala, Z.; Kolinski, R. *J. Fluorine Chem.* 1987, 35, 643-652.
- (89) Hassanein, S. M.; Burmakov, A. I.; Bloshchitsa, F. A.; Yagupolskii, L. M. *Zh. Org. Khim.* 1988, 24 (8), 1633.
- (90) Middleton, W. J. *J. Org. Chem.* 1975, 54, 574.
- (91) Hudlicky, M. *Org. React. (New York)* 1988, 515, 35.
- (92) Sharma, M.; Petrie, C. R., III; Korytnyk, W. *Carbohydr. Res.* 1988, 175, 25.
- (93) Kozikowski, A. P.; Xia, Y.; Rusnak, J. M. *J. Chem. Soc., Chem. Commun.* 1988, 1301.
- (94) Bliard, C.; Herczegh, P.; Olesker, A.; Lukacs, G. *J. Carbohydr. Chem.* 1989, 8 (1), 103.
- (95) Imbach, J. L.; Puech, F.; Gosselin, G. *J. Chem. Soc., Chem. Commun.* 1989, 955.
- (96) Roberts, S. M.; Biggadike, K.; Borthwick, A. D.; Evans, D.; Exall, A.; Kirk, B. E.; Stephenson, L.; Youds, P. *J. Chem. Soc., Perkin Trans. 1* 1988, 549.
- (97) Magnusson, G.; Kihlberg, J.; Frejd, T.; Jansson, K. *Carbohydr. Res.* 1988, 176, 287.
- (98) Matta, K. L.; Thomas, R. L.; Abbas, S. A. *Carbohydr. Res.* 1987, 165, 14.

- (99) Watanabe, K. A.; Matulic-Adamic, J. *Chem. Pharm. Bull.* 1988, 36 (4), 1554.
- (100) Walba, D. M.; Razavi, H. A.; Clark, N. A.; Parmar, D. S. *J. Am. Chem. Soc.* 1988, 110, 8686.
- (101) Hudlicky, M. *J. Fluorine Chem.* 1987, 36 (4), 373.
- (102) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* 1986, 106, 4189.
- (103) Suzuki, K.; Maeta, H.; Matsumoto, T.; Tsuchihashi, G. I. *Tetrahedron Lett.* 1988, 29, 3571.
- (104) Robins, M. J.; Wnuk, S. F. *Tetrahedron Lett.* 1988, 29, 5729.
- (105) McCarthy, J. R.; Peet, N. P.; Le Tourneau, M. E.; Inbasekaran, M. *J. Am. Chem. Soc.* 1985, 107, 735.
- (106) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* 1990, 55, 768.
- (107) Mann, J.; Pietrzak, B. *J. Chem. Soc., Perkin Trans. 1* 1987, 385.
- (108) Middleton, W. J.; Mange, K. C. *J. Fluorine Chem.* 1989, 43, 405.
- (109) Sharts, C. M.; Sheppard, W. A. Modern Methods to Prepare Monofluoroaliphatic Compounds. *Org. React. (New York)* 1974, Chapter 2, 21, 125.
- (110) Yarovenko, N. N.; Raksha, M. A. *J. Gen. Chem., USSR, (Engl. Transl.)* 1959, 29, 2125.
- (111) Ishikawa, N.; Takaoka, A.; Iwakiri, H. *Bull. Chem. Soc. Jpn.* 1979, 52, 3377.
- (112) Araki, Y.; Kobayashi, N.; Ishido, Y. *Carbohydr. Res.* 1987, 171, 125.
- (113) Hamman, S.; Beguin, C. G. *J. Fluorine Chem.* 1987, 37, 343.
- (114) Claassen, H. H.; Selig, H.; Malm, J. G. *J. Am. Chem. Soc.* 1962, 84, 3593.
- (115) Bartlett, N. *Proc. Chem. Soc.* 1962, 218.
- (116) Hoppe, R.; Mattauch, H.; Rodder, K. M.; Dahne, W. *Angew. Chem., Int. Ed. Engl.* 1962, 1, 599.
- (117) Selig, H.; Rabinovitz, M.; Agranat, I.; Lin, C. H.; Ebert, L. *J. Am. Chem. Soc.* 1976, 98, 1601.
- (118) Shieh, T. C.; Feit, E. D.; Chernick, C. L.; Yang, N. C. *J. Org. Chem.* 1970, 35, 4020.
- (119) Zupan, M.; Pollak, A. *J. Chem. Soc., Chem. Commun.* 1973, 845.
- (120) Patrick, T. B.; Jokri, K. K.; White, D. H. *J. Org. Chem.* 1988, 48, 4159.
- (121) Janzen, A. F. *J. Fluorine Chem.* 1983, 22, 557.
- (122) Anand, S. P.; Quaterman, L. A.; Christian, P. A.; Hyman, H. H.; Filler, R. *J. Org. Chem.* 1975, 40, 3796.
- (123) (a) Podkhalyuzin, A. T.; Navarova, M. P. *J. Org. Chem., USSR* 1975, 11, 1547. (b) Zupan, M. *J. Fluorine Chem.* 1976, 8, 305.
- (124) Filler, R. *Isr. J. Chem.* 1978, 71, 17.
- (125) Shellhamer, D. F.; Curtis, C. M.; Dunham, R. H.; Hollingsworth, D. R.; Ragains, M. L.; Richardson, R. E.; Heasley, V. L.; Shackelford, S. A.; Heasley, G. E. *J. Org. Chem.* 1985, 50, 2751.
- (126) (a) Gregoric, A.; Zupan, M. *J. Org. Chem.* 1979, 44, 4120. (b) Shustov, L. D.; Lyvnovskaya-Gurova, L. B.; Fomin, O. P.; Nikolenko, L. N. *Zh. Obshch. Khim.* 1976, 49, 918. (c) Eisenberg, E.; Desmarteau, D. D. *Inorg. Nucl. Chem. Lett.* 1970, 6, 29.
- (127) Shellhamer, D. F.; Carter, S. L.; Dunham, R. H.; Graham, S. N.; Spitsbergen, M. P.; Heasley, V. L.; Chapman, R. D.; Druelinger, M. L. *J. Chem. Soc., Perkin Trans. 2* 1989, 2, 159-65.
- (128) Zajc, B.; Zupan, M. *J. Org. Chem.* 1982, 47, 573.
- (129) Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* 1982, 23, 1165.
- (130) Filler, R. J.; Cantrell, G. L. *J. Fluorine Chem.* 1985, 27, 35.
- (131) Zajc, B.; Zupan, M. *J. Org. Chem.* 1990, 55, 1099.
- (132) (a) Martynov, I. V.; Brel', V. K.; Uranov, V. I.; Pomytkin, I. A.; Aleinikov, N. N.; Kashtanov, S. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1988, 2, 466-7 (in Russian). (b) Grigorev, I. A.; Starichenko, V. F.; Kirilyuk, I. A.; Volodarski, L. B. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1989, 4, 933-7. (c) Tselinski, I. V.; Melnikov, A. A.; Trubitsin, A. E. *Zh. Org. Khim.* 1987, 23 (8), 1657. (d) Grigorev, I. A.; Volodarski, I. B.; Starichenko, V. F.; Kirilyuk, I. A. *Tetrahedron Lett.* 1989, 30, 751.
- (133) Bregar, Z.; Stavber, S.; Zupan, M. *J. Fluorine Chem.* 1989, 44 (2), 187-93.
- (134) Wilkinson, J. A. Oxidation and Selective Fluorination of Organic Compounds using Organo-hypervalent Iodine Species. Ph.D. Thesis, Imperial College: University of London, 1991.
- (135) Willgerodt, C. *Die Organischen Verbindungen mit mehrwertigen Jod*; Ferdinand Enke Verlag: Stuttgart, 1914.
- (136) (a) Dimroth, O.; Bockemuller, W. *Ber. Deut. Chem. Ges.* 1931, 64, 516. (b) Garvey, B. S., Jr.; Halley, L. F.; Allen, C. F. H. *J. Am. Chem. Soc.* 1937, 59, 1827. (c) Badger, G. M.; Stephens, J. F. *J. Chem. Soc.* 1956, 3637.
- (137) See ref 19a.
- (138) Bornstein, J.; Borden, M. R.; Nunes, F.; Tarlin, H. I. *J. Am. Chem. Soc.* 1963, 85, 1609.
- (139) Carpenter, W. *J. Org. Chem.* 1966, 3, 2688.
- (140) Zupan, M.; Gregoric, A. *Bull. Chem. Soc. Jpn.* 1976, 50, 517.
- (141) Zupan, M.; Pollak, A. *J. Chem. Soc., Chem. Commun.* 1975, 715.
- (142) Zupan, M. *Collect. Czech. Chem. Commun.* 1977, 42, 266.
- (143) Tsushima, T.; Kawada, K.; Tsuji, T. *Tetrahedron Lett.* 1982, 23, 116.
- (144) Martin, J. C.; Amey, R. L. *J. Org. Chem.* 1979, 44, 1779.
- (145) Motherwell, W. B.; Edmunds, J. J. *J. Chem. Soc., Chem. Commun.* 1989, 881.
- (146) Motherwell, W. B.; Edmunds, J. J. *J. Chem. Soc., Chem. Commun.* 1989, 1348.
- (147) Motherwell, W. B.; Wilkinson, J. A. *Synlett* 1991, 191.
- (148) Motherwell, W. B.; Caddick, S.; Wilkinson, J. A. *J. Chem. Soc., Chem. Commun.* 1991, 674.
- (149) DesMariseau, D. D. *J. Am. Chem. Soc.* 1978, 100, 340.
- (150) Barton, D. H. R.; Alker, D.; Hesse, R. H.; Lister-James, J.; Maxwell, R. E.; Pecket, M. M.; Rozen, S.; Takeshita, T.; Toh, H. T. *Nouv. J. Chim.* 1980, 4, 239.
- (151) (a) Rozen, S.; Gal, C. *Tetrahedron Lett.* 1984, 25, 449. (b) Rozen, S.; Gal, C. *J. Org. Chem.* 1987, 52, 2769.
- (152) Rozen, S.; Gal, C. *J. Org. Chem.* 1988, 53, 2803.
- (153) Pentacoordinated carbonium ion intermediates was first suggested by Professor Olah as intermediates for electrophilic substitution on saturated carbon. For a detailed discussion, see: Olah, G. A.; Prakash, G. K. S.; Williams, R. E.; Field, L. D.; Wacle, K. *Hypercarbon Chemistry*; Wiley: New York, 1987.
- (154) Patrick, T. B.; Mortezaia, R. *J. Org. Chem.* 1988, 53, 5153.
- (155) Van Der Puy, M. *Tetrahedron Lett.* 1987, 28, 255.
- (156) Cady, G. H.; Gard, G. L. *Inorg. Chem.* 1965, 4, 594.
- (157) (a) Rozen, S.; Menahem, Y. *J. Fluorine Chem.* 1980, 16, 19. (b) Rozen, S.; Lerman, O. *J. Org. Chem.* 1980, 45, 672. (c) Barnette, W. E.; Wheland, R. C.; Middleton, W. J.; Rozen, S. *J. Org. Chem.* 1985, 50, 3698.
- (158) Dax, K.; Glanzer, B. I.; Schulz, G.; Vyplel, H. *Carbohydr. Res.* 1987, 162, 13.
- (159) Rozen, S.; Lerman, O.; Hebel, D. *Bull. Soc. Chim.* 1986, 6, 861.
- (160) Visser, G. W. M.; Herder, R. E.; De Kanter, F. J. J.; Herscheid, J. D. M. *J. Chem. Soc., Perkin Trans. 1* 1988, 1203.
- (161) Rozen, S.; Hebel, D. *J. Org. Chem.* 1990, 55, 2621.
- (162) Cady, G. H.; Porter, R. F. *J. Am. Chem. Soc.* 1957, 79, 5625.
- (163) (a) Barton, D. H. R.; Godinho, L. S.; Hesse, R. H.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* 1968, 804. (b) Barton, D. H. R.; Ganguly, A. K.; Hesse, R. H.; Loo, S. N.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* 1968, 806. (c) Barton, D. H. R.; Danks, L. J.; Ganguly, A. K.; Hesse, R. H.; Tarzia, G.; Pechet, M. M. *J. Chem. Soc., Chem. Commun.* 1968, 227.
- (164) See ref 6.
- (165) Oberdorfer, F.; Traving, B. C.; Maier-Borst, W.; Hull, W. E. *J. Labelled Compd. Radiopharm.* 1988, 25 (5), 465.
- (166) Appleman, E. H.; Basil, L. J.; Thompson, R. C. *J. Am. Chem. Soc.* 1979, 101, 3384.
- (167) Zupan, M.; Stavber, S. *J. Chem. Soc., Chem. Commun.* 1981, 148.
- (168) Zupan, M.; Stavber, S. *J. Chem. Soc., Chem. Commun.* 1981, 795.
- (169) Zefirov, N. S.; Zhdankin, V. V.; Koz'min, A. S.; Fainzilberg, A. A.; Gakh, A. A.; Ugrak, B. I.; Ramaniko, S. V. *Tetrahedron* 1988, 44, 6505.
- (170) Zupan, M.; Stavber, S. *J. Org. Chem.* 1987, 919.
- (171) Zupan, M.; Stavber, S. *Tetrahedron* 1989, 45, 2737.
- (172) Banks, R. E.; Cheng, W. M.; Haszeldine, R. N. *J. Chem. Soc.* 1962, 3407.
- (173) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* 1983, 48, 761.
- (174) Barnette, W. E. *J. Am. Chem. Soc.* 1984, 106, 452.
- (175) Umamoto, T.; Tomita, K. *Tetrahedron Lett.* 1986, 27, 3271.
- (176) Banks, R. E.; DuBoisson, R. A.; Tsiliopoulos, E. *J. Fluorine Chem.* 1986, 32, 461.
- (177) DesMariseau, D. D.; Singh, S.; Zuberi, S. S.; Witz, M.; Huang, H. N. *J. Am. Chem. Soc.* 1987, 109, 7194.
- (178) Banks, R. E.; DuBoisson, R. A.; Morton, W. D.; Tsiliopoulos, E. *J. Chem. Soc., Perkin Trans. 1* 1988, 10, 2805.
- (179) Differding, E.; Lang, R. W. *Tetrahedron Lett.* 1988, 29, 6087.
- (180) For a review, see: Nagase, S. *Fluorine Chem. Rev.* 1967, 1, 77.
- (181) (a) Laurent, E.; Tardivel, R.; Thiebault, H. *Tetrahedron Lett.* 1983, 24, 903. (b) Laurent, E.; Marquet, E.; Tardivel, R.; Thiebault, H. *Bull. Soc. Chim.* 1986, 6, 955.
- (182) Laurent, E.; Marquet, B.; Tardivel, R. *Tetrahedron* 1989, 45, 4431.
- (183) Brigaud, T.; Laurent, E. *Tetrahedron Lett.* 1990, 31, 2287.
- (184) Tatlow, J. C.; Plevy, R. G.; Bailey, J. *J. Fluorine Chem.* 1987, 37, 1.