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THE COMBINATION OF HYDROGEN FLUORIDE WITH ORGANIC BASES AS FLUORINATION AGENTS

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1. INTRODUCTION

In view of the rapidly growing role of organo-fluorine compounds, particularly in material and pharmaceutical science, the synthesis of organo-fluorine compounds is becoming increasingly important. Introduction of fluorine[1] at a late stage in synthesis often produces technical and economical problems. One of the major problems in the organo-fluorine chemical industry is the cost of synthetic processes employing organo-fluorine compounds. Although fluorine itself is an inexpensive element, fluorinating agents such as diethylamino sulfurtrifluoride (DAST), which is a highly effective fluorination agent to convert hydroxyl groups into fluoro-substituents, are usually very expensive.[1,] The

CAUTION: All precautions which apply to the use of AHF should likewise be applied to the use of AHF·Amine solutions The recommended procedure for an HF burn is to sluice with water, pack with ice and obtain medical attention as quickly as possible.[5]

utilization of anhydrous hydrogen fluoride (AHF), which is not expensive and is readily available is obviously among the most attractive fluorinating agents. AHF has a strong ability for the fluorination of various compounds, particularly of organic halides, by exchange either alone, or more often in conjunction with antimony or mercury salts. These processes are used industrially in large quantities to produce chlorofluorocarbons, invariably by replacement of chlorine in a chlorocarbon by fluorine.[2] However, AHF is an extremely hazardous chemical due to its low boiling point (19.5°C) and high toxicity.[3a] Thus, reactions using AHF are invariably accompanied by severe handling difficulties and undesirable side reactions. In order to overcome these difficulties, an AHF solution of Lewis base organic compounds, which contain an atom having a pair of electrons such as ketones, amines, alcohols, ethers and so on, has been employed widely as a convenient reagent for fluorination reactions.

This Report will be devoted to a description of AHF-organic base reagents as fluorination agents for organic molecules.

2. PROPERTIES OF AHF AND AHF-BASES

AHF is a colorless, pungent smelling mobile liquid between −85 and +19.6°C, which forms thick fumes in contact with moist air. Compared with the other hydrogen halide homologues—hydrogen chloride, hydrogen bromide, and hydrogen iodide—AHF has a higher boiling point and wider temperature range in the liquid state. AHF can dissolve many inorganic and organic substances. AHF is a very strong acid and it forms salts with very weakly basic nitrogen and oxygen compounds.

The HF molecule has a high polarity and associates strongly to form molecular aggregates. It shows a very high dielectric constant.[3] However, when compared to associated liquids such as water, the values of its surface tension and viscosity are small, similar to those of an unassociated liquid. Judging from these facts, the HF molecule is considered to form intermolecular associates by hydrogen bonding. The one dimension association state based on an interaction of dissociated ions is shown in the following equation[3a]

$$2HF = H_2F^+ + F^-.$$

Organic bases form stable solutions with AHF. The amount of HF which can combine with the base forming stable HF · Base solutions is dependent on temperature and the bases employed (Fig. 1).[6] Preparation of solutions by the addition of AHF to pyridine or triethylamine is accompanied

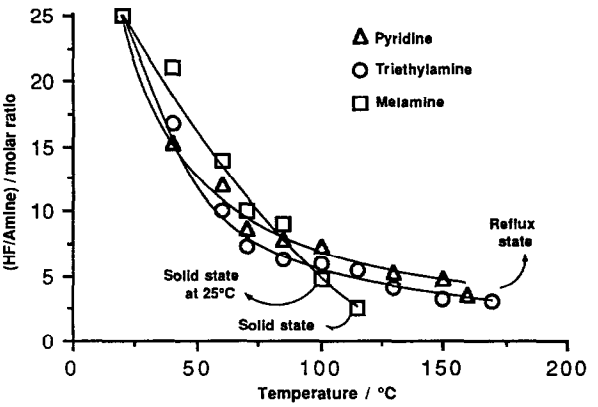


Fig. 1 The amount of HF to combine with amines to form stable HF · Amine solutions at various temperatures

by vigorous heat evolution. Solutions of about 9–10 equiv of HF to 1 equiv of organic bases are stable up to 60°C. Raising the temperature results in the elimination of HF to decrease the HF/Base molar ratio. About 6 equiv of HF can combine with these bases at 100°C. On the other hand, solid melamine can be gradually dissolved in AHF without any vigorous exothermic reaction and the resulting HF-Melamine solution (HF · Mel) can contain about 14 equiv of HF to 1 equiv of melamine. This complex is remarkably stable at atmospheric pressure and up to 60°C, and can be stored under ordinary conditions. However, at temperatures higher than 80°C, HF · Mel solution releases HF, and a white crystalline solid composed of Melamine · 2HF was obtained at 110°C. Pyridine and triethylamine (R_3N) can retain 5 equiv of HF under similar conditions, and the refluxing solution at 160–170°C has a composition of 3 moles of HF to one mole of pyridine or R_3N. $Et_3N \cdot 3HF$ is distillable *in vacuo*, can be handled without hazard, and does not corrode bosilicate glass.[7] Tetraethylammonium trihydrogen tetrafluoride ($Et_4NF \cdot 3HF$; TEAF) can be prepared as white hygroscopic crystals by the addition of AHF to tetraethylammonium iodide and evaporation at 20°C and at 160°C for 6 h, then dried over P_4O_{10} for 20 h at 1 mmHg.[65]

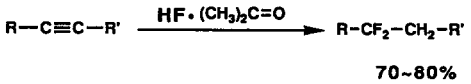
The formation of solid complexes of Pyr · nHF ($n = 1 \sim 8$) at low temperature ($-1 \sim -124$°C) was studied by difference thermal analysis and X-ray powder diffraction. In the complex, the base is not protonated by the acid and the hydrogen bond F–H···N can be identified. The remaining structures were found to contain pyridinium cations and complex $H_{n-1}F_n^-$ anions.[4] Pyr · nHF was suggested to be in equilibrium with a small amount of free hydrogen fluoride. The presence of polyhydrogen fluoride species in Pyr · 9HF was indicated by the ^{19}F NMR spectrum, in which each fluorine atom is surrounded by four hydrogen atoms.[9]

3. HYDROFLUORINATION

Hydrofluorination of alkenes or alkynes with AHF is always accompanied by difficulties such as the handling of AHF, the need for pressure equipment, and undesirable polymerization of the substrate. The use of less volatile solutions of AHF with an oxygenated compound such as acetone was the first attempt to carry out the hydrofluorination of acetylenes. The corresponding difluorides expected from Markovnikov's rule were obtained (70–80%; Scheme 1).[8]

The HF · Pyr solution composed of 30%(wt/wt)pyridine – 70%(wt/wt)AHF, was first used in the fluorination of some functional groups in steroids by Bergstrom.[50] Olah later established that this HF · Pyr solution contains about 9 equiv of HF to 1 equiv of pyridine. It was a convenient agent for fluorination reactions such as hydrofluorination of alkenes (Olah's reagent).[1k,9]

HF · Organic base such as amine, ketone or ether solutions, are strongly hygroscopic, and such solutions after absorbing moisture exhibit remarkably low fluorination activity. Activity of HF · Mel solution (14(Mel) : 86(AHF) in wt/wt%) in the hydrofluorination of alkene, on the other hand, was reported to surpass other HF · Amine reagents including the Olah's reagent, as is summarized in Table 1.[10] This solution is also superior to other HF · Base solutions with regard to not only hydrofluorination activity for alkenes, but in relation to its preparation and handling ease.[12] In the hydrofluorination of alkenes using HF · Amine solutions, it is necessary to quench the agent by adding a large amount of water and neutralizing with inorganic bases such as $NaHCO_3$. This results in the destruction of the agent. However, HF · Mel in pentane or CCl_4 gives a liquid–liquid two phase mixture which is a highly convenient agent for alkenes. It is also a suitable system for repeated



Scheme 1

Table 1. Hydrofluorination of alkenes with HF · Amine

Alkene	Amine	Amount of amine wt/%	React condts	Conv of alkene/%	Yield of RF/%	Hydrofluorination selectivity/%
Cyclohexene	—	0	C	98	71	72
Cyclohexene	Et_3N	51	A	12	12	100
Cyclohexene	$BuNH_2$	29	A	37	37	100
Cyclohexene	Aniline	34	A	50	50	100
Cyclohexene	Pyridine	30	A	28	28	100
Cyclohexene	Pyridine	30	BD	22	22	100
Cyclopentene	Pyridine	30	B	65	65	100
Cyclohexene	Melamine	14	A	88	88	100
Cyclohexene	Melamine	3	C	95	89	94
Cyclohexene	Melamine	14	B	98	98	100
Cyclohexene	Melamine	23	C	46	40	87
Cyclohexene	Melamine	14	BD	98	98	100

React Condts, AHF (150 mmol) and an Alkene (5 mmol) in 3 ml THF
A React. Temp (T) 0°C, Time(t) 10 min B T = 0°C, t = 60 min
C: T = 0°C, t = 5 min D. HF containing 1 wt% water

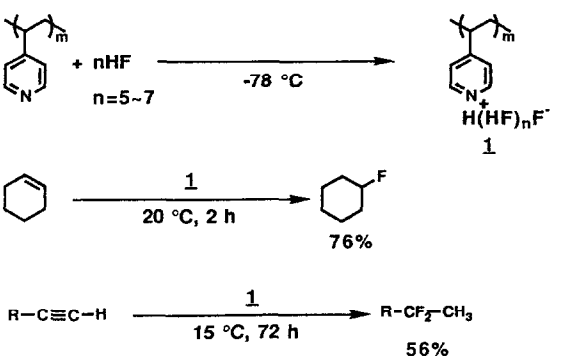
use (Table 2).[11] In contrast with rapid deterioration of activity of HF · Pyr solvent systems, HF · Mel solutions can be used repeatedly without decrease of activity, by using it with co-solvents such as pentane or CCl_4.

Cross-linked poly-4-vinylpyridine (in bead form) reacts readily with AHF at −78°C without the use of solvent giving stable polyhydrogen fluoride **1** as shown in Scheme 2.[20] This solid polymeric poly (hydrogen fluoride) was used as a fluorinating agent for the hydrofluorination of alkenes and

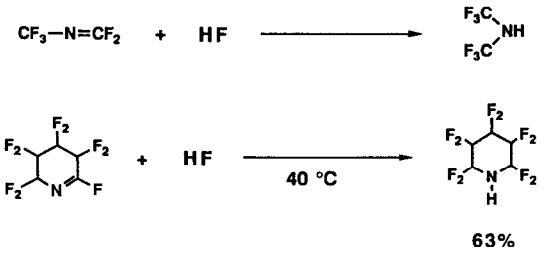
Table 2 Repeated use of HF · Pyr and HF · Mel in the hydrofluorination of cyclohexene

Number of repeated use of HF · Base	Yield of RF/% HF · Pyr	HF · Mel
1	70	99
2	48	96
3	39	98
4	—	94

React Condts · Temp 0°C, Time 10 min
Co-solvent CCl_4 or Pentane



Scheme 2



Scheme 3

alkynes affording the corresponding alkylfluorides in good yields (56–81%) at temperatures of 0–20°C for 1–72 h. The advantages of this method are easy handling and extremely convenient work-up.

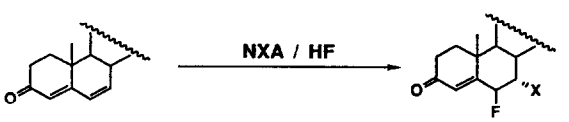
Polymer-supported dihydrogen trifluoride (Polymer-$H_2F_3^-$ or $P^+F^- \cdot nHF$), as well as tetrabutyl ammonium dihydrogen trifluoride $(Bu)_4N^+H_2F_3^-$, promotes addition of HF to carbon–carbon triple bonds activated by nitrile, ester, ketone or aldehyde groups under mild conditions affording the *Z*- and *E*-isomers of fluoroalkenes.[88] $P^+F^- \cdot nHF$ was prepared by the reaction of the commercial resins (Amberlyst A 26 etc.) in fluoride form P^+F^- with an aqueous HF-KHF_2 or 2HF-KF.

1H-Decafluoropiperidine is prepared by the hydrofluorination of perfluoro-2,3,4,5-tetrahydropyridine with AHF (Scheme 3). This is analogous to that used to prepare bis-trifluoromethylamine.[21]

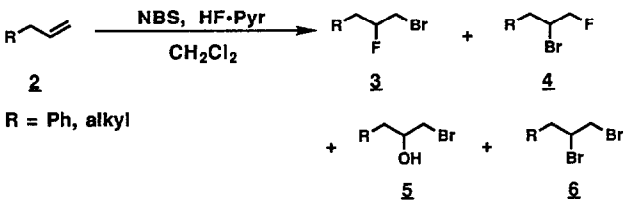
4. HALOFLUORINATION

Olefin halofluorination involves the *in situ* generation of ClF, BrF, or IF by treatment of a solution of fluoride ion in an acidic medium with a source of the electrophilic halogen (X) and subsequent addition of X–F to the olefin.[28] Halofluorination of terminal olefins can proceed rapidly and efficiently with KF or CsF with NBS and strong acids such as sulfuric acid. In contrast with heterogeneous reactions with metal fluoride salt/acid, the homogeneous reactions of alkenes with N-halogenated amides (NXA ; X = Cl, Br, I) and AHF in the presence of an organic proton acceptor such as 5% EtOH in $CHCl_3$ or THF were successfully performed yielding *vic*-fluorohaloalkanes[22,23] (Scheme 4). This reaction has considerable utility for the preparation of bromofluorosteroids.[24]

Terminal olefins **2** afford the Markovnikov **3** and the anti-Markovnikov-type products **4** (10 to 1 ratio, 50–60%) together with some of halohydrin **5** and the halogen addition product **6** using N-bromosuccinimide (NBS)[26,27] in the presence of HF · Pyr and CH_2Cl_2 (Scheme 5). Compound **5** is formed only when excess NBS and water are both present. Compound **6** forms slowly only when the source of the electrophilic halogen is present in excess over fluoride. N-Iodosuccinimide (NIS), NBS, and 1,3-dibromo-5,5-dimethylhydantoin (DBH) are used as the source of the electrophilic halogen. The reaction rate increases in that order. The reaction can proceed using an excess of HF · Pyr at room temperature or even at −20°C within a few minutes. These are much milder conditions than those normally used in hydrofluorination. This can be explained by the fact that



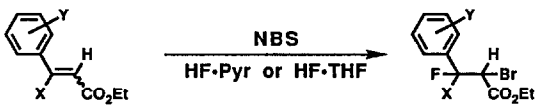
Scheme 4



Scheme 5.

the olefin (a soft base) is being activated by a halogen cation (a soft acid) towards the reaction with fluoride ion (a hard base). In the hydrofluorination, however, the activating species, the proton (a hard acid) prefers to interact with fluoride ion (a hard base) rather than with olefin. This would impede the reaction by the non-productive hard acid–hard base (proton–fluoride ion) interaction.[26] The reaction is much more efficient in solvents that lack non-bonding electrons such as aliphatic and aromatic hydrocarbons, and chlorinated methane solvents. The rates appear to correlate with the solvent dielectric constant. No halofluorination of terminal olefins takes place in THF but THF can be used successfully in other halofluorinations.[28]

Bromofluorination of substituted ethyl cinnamates with NBS in HF · Pyr solution or HF · THF (several molar ratios) gives Markovnikov-type regioselectivity (Scheme 6). The stereoselectivity depends upon the following factors: the nature of the substituent, the solvent (pyridine or THF) and the HF-solvent molar ratio (Table 3).[25]

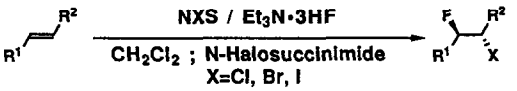


Scheme 6

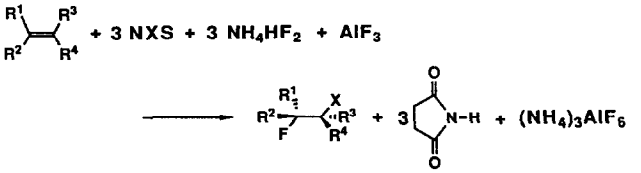
Table 3. Bromofluorination of substituted ethyl cinnamates[a] with NBS in HF · Pyr or HF · THF

Substrate[a]	Product[a]	HF · Pyr/HF (wt%) 53%	70%	82%	HF · THF/HF (wt%) 50%		67%
7E	11e[b]	—	100	100	—		100
8E	12e	100	100	100	100		50
9E	13e	100	50	—	50		—
8Z	12t[c]	52	26	10	11		—
10Z	14e	75	75	—	—	DF[d]	—
10E	14t	45	40	—	—	DF	—

[a] See Scheme 6
[b] *erythro.*
[c] *threo*
[d] Difluorides Ar-$CF_2CHBrCO_2Et$ are produced.



Scheme 7.



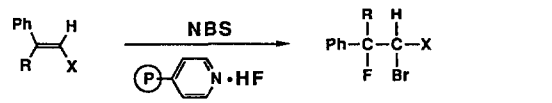
Scheme 8

The combination of an N-halosuccinimide and triethylamine tris-hydrofluoride, $(Et)_3N \cdot 3HF$,[7] is a convenient and effective reagent for the halofluorination of alkenes (Scheme 7). This permits working at room temperature in normal glass apparatus. The anti-addition reaction proceeds stereospecifically.

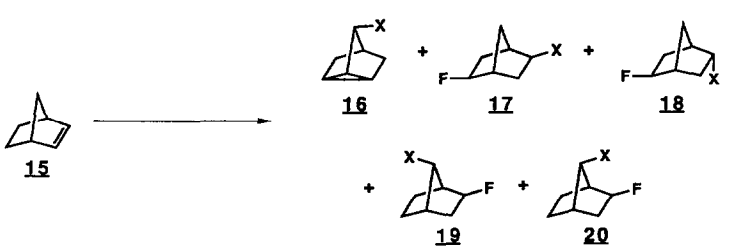
Halofluorination of alkenes is performed stoichiometrically in the presence of $NH_3 \cdot 2HF$ ($NH_4^+ \cdot HF_2^-$) and AlF_3 (Scheme 8). Sonication is helpful in this reaction.[86]

Polymer-supported HF, prepared by the reaction of HF with crosslinked poly(styrene-co-4-vinyl-pyridine) containing 40–50 mol% of 4-vinylpyridine, was effective in the bromofluorination of various phenyl-substituted olefins with NBS in CH_2Cl_2.[30] The reaction proceeds with Markovnikov type regioselectivity (Scheme 9).

Fluorination and halofluorination of norbornene **15** with xenon difluoride or NCS or NBS take place readily in the presence of polymer-supported HF. A large increase in halonortricyclane formation is observed as compared against the reaction in the presence of HF·Pyr (Scheme 10; Table 4).



Scheme 9



Scheme 10.

Table 4. Product distributions in the reaction of norbornene with XeF_2 or NXS using polymer-supported-HF or HF·Pyr[a]

		Product[a] distribution/%				
	X[a]	**16**	**17**	**18**	**19**	**20**
XeF_2+[A][b]	F	71	4	6	11	8
XeF_2+[B][b]	F	14	10	19	35	22
NCS[c]+[A]	Cl	76	trace		3	21
NCS+[B]	Cl	26	2	3	31	38
NBS[d]+[A]	Br	81	trace		5	14
NBS+[B]	Br	20	3	5	37	35

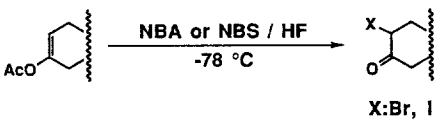
[a] See Scheme 10.
[b] [A] Polymer-supported-HF, [B] HF·Pyr
[c] N-Chlorosuccinimide
[d] N-Bromosuccinimide

Poly-4-vinylpyridine poly(hydrogen fluoride) (Scheme 2) was also demonstrated to have good results for the bromofluorination of alkenes (70–81%) at 0–20°C for 1–72 h.[20]

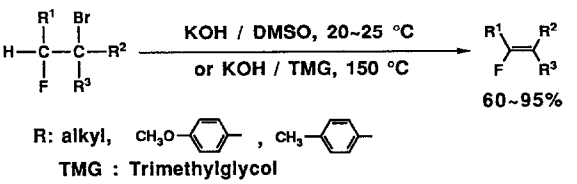
The enol acetate function in steroids affords the corresponding 2α-bromo-3-ketones after treatment with NBS and AHF under low temperature conditions (Scheme 11). This indicates that diaxial addition of Br–F does not operate for the enol acetate of a C-3-ketone in the steroid series.[24]

Products in the halofluorination of unsaturated hydrocarbons are of interest as intermediates for the synthesis of a large variety of fluoroorganic compounds. The β-halosubstituent is a useful functionality for elimination or substitution reactions. Thus, *vic*-bromofluoroalkanes are converted to vinylfluoride by treatment with KOH/DMSO at 20–25°C or KOH/tri-methyleneglycol at 150°C (Scheme 12).[31]

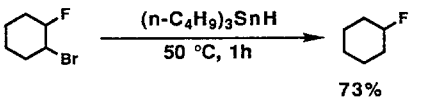
When bromofluoroalkanes were treated with a reducing agent such as tributyltin hydride, $(n\text{-}C_4H_9)_3SnH$, selective replacement of bromine by hydrogen may be accomplished in good yields (Scheme 13).[32]



Scheme 11



Scheme 12



Scheme 13

5. HYDROFLUORINATION ACCOMPANYING RING OPENING

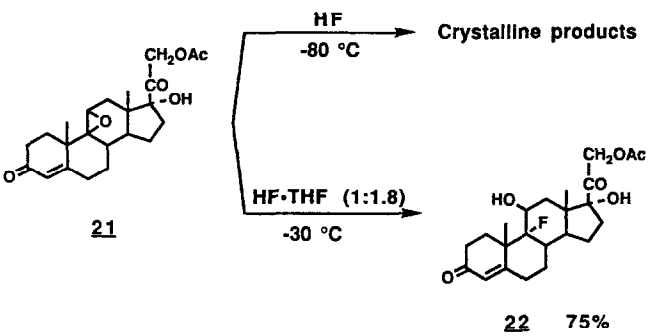
5.1. *Oxiranes, epoxynitriles*

HF Addition to epoxides is a very clean and good method for preparing α,β-fluoroalcohols. ANF Alone, however, is not an adequate source of fluoride ion for the ring opening reaction of epoxides. In fact (Scheme 14), the treatment of epoxides such as **21** with AHF at −80°C for 4.5 h gives by-products such as major crystalline products.[33,34] On the other hand, the reaction with AHF in the presence of THF (AHF/THF = 1.79 molar ratio; −30°C) affords 9α-fluoro-4-pregnene-11β,-17α,21-triol 3,20-dione 21-acetate **22** and its 1-dehydro analogue (75%).[33] Compound **22** is of pharmacological importance since it possesses about ten times the glucocorticoid activity of hydrocortisone acetate.[34]

Phenyl substituted epoxides **23** are converted to the corresponding fluoroalcohols **24** and **25** with HF · Base at 95–140°C for 2–12 h (Scheme 15).[35] Benzylic carbon was predominantly bonded with fluorine giving **24**, but the formation of **25** was also observed. *trans*-Addition takes place giving products of structure *erythro*- from *trans*-**23** and *threo*- from *cis*-**23** respectively. Among HF · Base such as NH_4F, $NH_4F \cdot HF$, $(CH_3)_2NH \cdot HF$, $(CH_3)_3N \cdot 2HF$, $(Et)_3N \cdot 3HF$, $((CH_3)_2CH)NH_2 \cdot nHF$; (n = 1, 1.8) and $((CH_3)_2CH)_2NH \cdot nHF$; (n = 2, 3) employed in the reaction of **23** (R_1 = H, R_2 = H), diisopropylamine · 3HF gave the desired reaction most rapidly affording **24** and **25** (ratio 75:25; 70%).[35] The combination of NH_4HF_2 and porous AlF_3 is a useful solid reagent for epoxide opening reaction under sonication to give fluorohydrins.[86b]

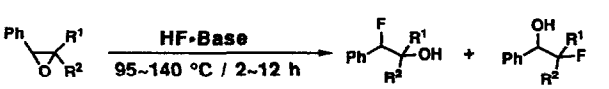
By using $(iPr)_2NH \cdot 3HF$, the synthesis and structures of the fluoroalcohols produced in the reaction of epoxy-indane and epoxy-1,2-tetralin was also studied (Scheme 16).[36]

2-Fluorotosylates **26**, which can be readily obtained by the reaction of the corresponding oxiranes with $(CH_3)_3N \cdot 2HF$ followed by the treatment of tosylchloride–pyridine, participated in substitution



21 22 75%

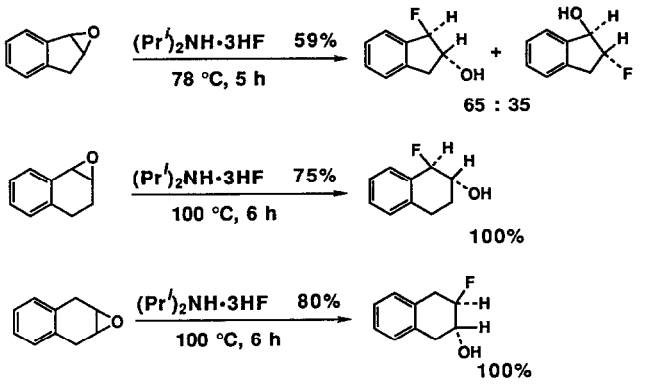
Scheme 14



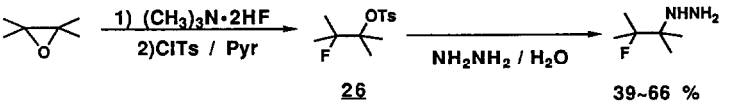
23 24 25

R^1; H, CH_3, Ph
R^2; H, CH_3

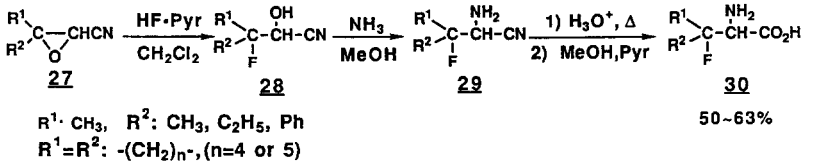
Scheme 15.



Scheme 16



Scheme 17



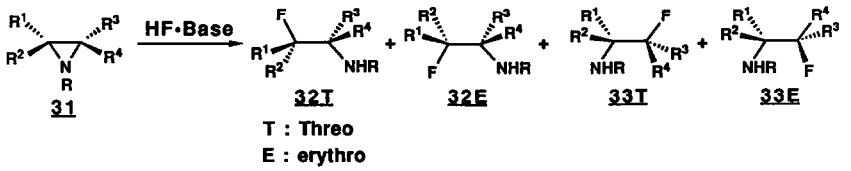
Scheme 18

of the tosylate group (Scheme 17).[37] 2-Fluoroalkylhydrazines were obtained by the reaction of NH_2–NH_2 with **26**.

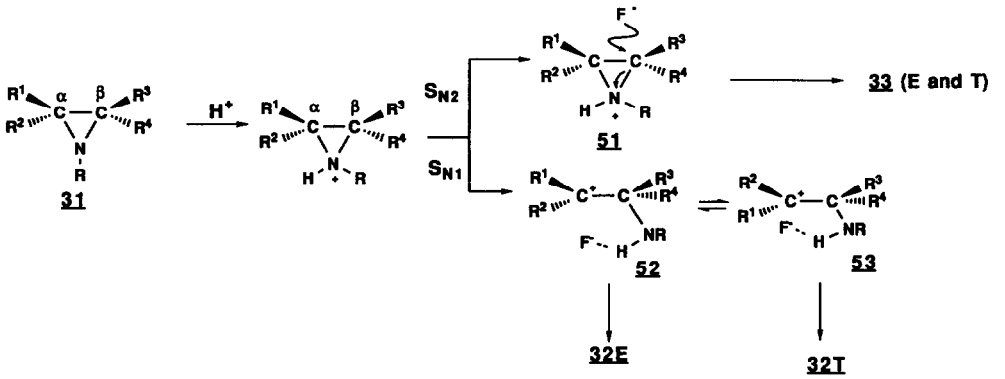
Ring opening of glycidonitriles **27** by HF · Pyr leads to fluorocyanohydrins **28**. Treatment of **28** with ammonia in MeOH gives the α-amino-β-fluoro-nitriles **29**, which upon acidic hydrolysis affords the β-fluoro-α-amino acids **30** in good yields (Scheme 18).[38]

5.2. *Aziridines*

Ring-opening of aziridines **31** by the addition of HF provides a convenient route to α,β-fluoro-amines **32T** (*threo*) and **32E** (*erythro*), and **33T** and **33E** (Scheme 19; Table 5).[39–41] These fluoro-amines are very stable compared with the corresponding chloro-amine analogues:[42] they exhibit biological activity on the central nervous system. This reaction has been performed in the mytomycin series.[39b] The reaction of secondary aziridines with AHF or HF · Pyr usually takes place cleanly under mild conditions (room temperature for a few hours). The regiochemistry, the diastereoisomer distribution, and the stereospecific ring-opening of aziridines **31** which are observed (Table 5), are highly dependent on the structure of **31** and the nature of the fluorinating reagent. These results are rationalized by an S_N1/S_N2 type mechanism (Scheme 20).[39] Fluorine attack is generally directed on the carbon more capable of stabilizing the charge of the initially formed carbocation **52** giving



Scheme 19

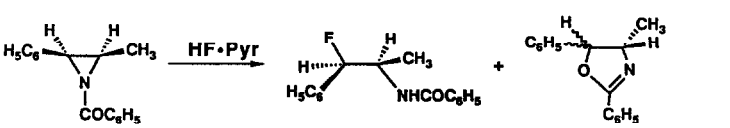


Scheme 20

32 preferentially. However, two ring-opening pathways occur to afford **32** and **33** in the reaction of **36** and **38** with HF·Pyr, and **37** with AHF as exceptions, although **37** with Pyr·HF gives **32** exclusively (Table 5). Fluoride attack at the less substituted carbon of the aziridines **31** may be accounted for by a S_N2-like mechanism on the aliphatic secondary or primary carbon of the ring in **51**.[39,45]

The presence of an alkyl group on the nitrogen of aziridine such as **35** decreases the reaction rate and higher temperature is required to obtain the corresponding fluoro-amine. On the other hand, N-activated aziridines such as **42C**, give oxazolines **46** as the main product and the desired N-benzoyl fluoro-amines **45** as minor products in HF·Pyr as shown in Scheme 21. However, preferential formation of N-activated fluoro-amines are observed in the reaction of **39** using NR_3·HF with regioselective enhancement compared to that of **38** (Table 5).

The preferential formation of oxazolines **46** in the reaction of **42C** with HF·Pyr indicates that HF·Pyr is either too strongly acidic or is an insufficiently nucleophilic agent to be effective in the desired fluorination reaction. On the other hand, **42T** with NR_3·nHF (n = 3, 2.5, 2), which are less

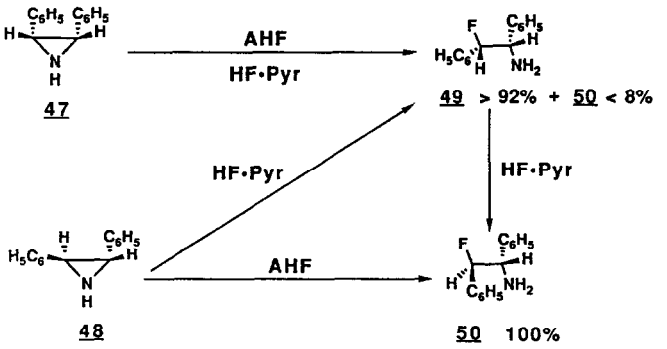


Scheme 21.

Table 5. Reaction of aziridines with HF or HF · Base[a]

Aziridine 31[a]						Fluorinating condt.			Product distribution %							
										32[a]		33[a]		O[d]		
R^1	R^2	R^3	R^4	R	X[e]	Agent	Temp. °C	Time h	Total yield%	32T[b]	32E[c]	33T[b]	33E[c]	46	Ref
Ph	Et	H	H	H	**34**	$Et_4NF \cdot 3HF$[f]	20		60		100		0			40
Ph	Et	H	H	H	**34**	Pyr · HF	20	1	70		100		0			45
Ph	H	H	H	Et	**35**	Pyr · HF	70	1	47		100		0			45
Ph	H	CH_3	Et	H	**36**	Pyr · HF	50	70	85	56	14	27	3			39
Ph	CH_3	CH_3	H	H	**37**	AHF	20	18	83	49	35	16				39
Ph	CH_3	CH_3	H	H	**37**	Pyr · HF	50	70	100	61	39	0				39
CH_3	H	H	H	H	**38**	Pyr · HF	70	20	83		65	35				39
CH_3	H	H	H	COPh	**39**	$NR_3 \cdot 3HF$	50	5	85		100	0				39
Ph	H	CH_3	H	H	**40C**[g]	AHF	20	5	poor		—	—				39
Ph	H	H	CH_3	H	**40T**[h]	AHF	15	0.3	25	80	20	0				39
Ph	H	Ph	H	COPh	**41C**[g]	$NR_3 \cdot 2.5HF$	50	4	69		68	0		32 **C**[g]		39
Ph	H	H	Ph	COPh	**41T**[h]	$NR_3 \cdot 2.5HF$	20	3	5		26	0		74 **T**[b]		39
H	Ph	H	Ph	COPh	**42C**[g]	Pyr · HF	20	5	79		Some	0		99 **T**[h]/**C**[g] · 52/48		39
H	Ph	Ph	H	COPh	**42T**[h]	$NR_3 \cdot 3HF$	20	6	60	68	32	0		Some		39
Ph	H	CH_3	H	CO_2Et	**43**	$NR_3 \cdot 2.5HF$	20	6	67	92	8	0		Some		39
Ph	H	CH_3	H	CO_2tBu	**44**	$NR_3 \cdot 2.5HF$	20	6	63	100	0	0		Some		39

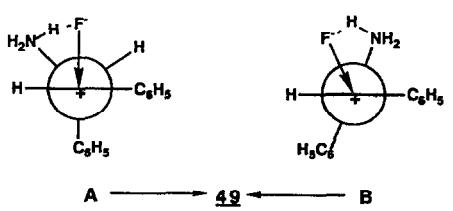
[a] See Schemes 19 and 20
[b] *threo.*
[c] *erythro*
[d] Oxazoline, see Scheme 21.
[e] Compound number, see text
[f] With BF_3-Et_2O.
[g] *cis.*
[h] *trans*



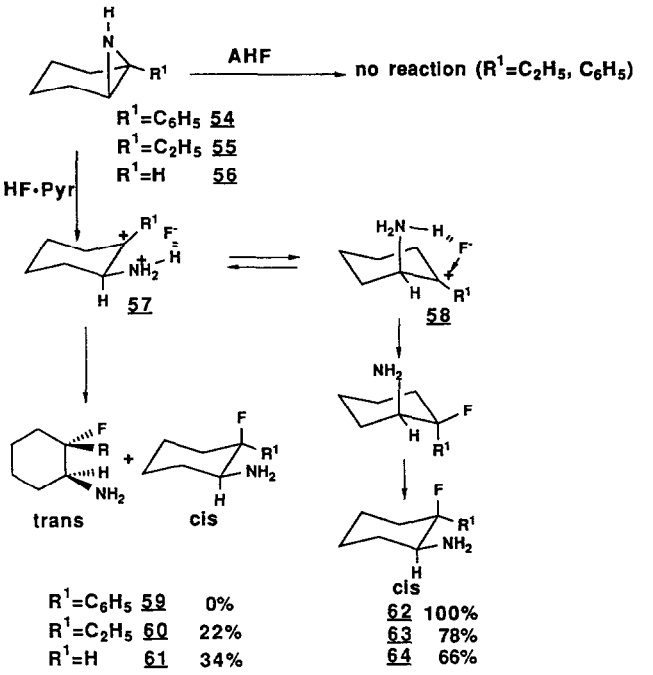
Scheme 22

acidic and more nucleophilic, can improve the yields of fluorinated products along with formation of much smaller amounts of oxazolines under similar conditions. The fundamental difference in behavior between HF · Pyr and AHF is observed in the stereochemistry of the reaction of secondary aziridines **47** and **48** (Scheme 22). The reaction of the *cis*-compound **47** using AHF gives the *threo*-fluoro-amine **49** as the major product, whereas the *trans*-isomer **48** affords only the *erythro*-compound **50**. In these cases, the partially ring-open aziridinium ion **51** in Scheme 20 is the reactive intermediate, and it undergoes a backside attack by the fluoride anion. In contrast, these two aziridines **47** and **48** with HF · Pyr give the *threo*-isomer **49** as major product. This was accounted for by the formation of a cation which rotates to its most stable conformation **A** or **B**, (Scheme 23), before reacting with fluoride anion delivered by the ammonium group. This explanation is in agreement with the formation of carbocation intermediates **52** or **53** (Scheme 20).

Further differences between AHF and HF · Pyr are observed in the reactivity of bicyclic aziridines such as 7-azabicyclo[4.1.0]heptanes **54**, **55** and **56** in Scheme 24. These aziridines are inert to AHF and are recovered quantitatively. In contrast, they react with HF · Pyr, which has a greater ionizing power compared to that of AHF and readily leads to the carbocation **57**. Compound **54** produces only *cis*-fluoro-amine **62** exclusively through the preferred conformation **58** because of the steric interactions between the phenyl group borne by the sp^2 carbon and the amine function at the axial position. The complexation of nitrogen with HF is followed by *cis* addition of the fluoride ion in relation to the amine group. Similarly, **55** is opened to a carbocation by HF · Pyr, whose conformational equilibrium is shifted to a high degree in the direction of conformer **58** with a small population of the conformer **57**. The latter conformer, in which the dihedral angle Et–CCN falls to zero, provides the *cis*- (**63**; 78%) and *trans*-fluoro-amines (**60**; 22%). Compound **56** yields a mixture of *cis*-**64** and *trans*-fluoro-amines **61**: the former is totally isomerized to the *trans*-compound at the end of the reaction in HF · Pyr. Isomerization of **59** to **62**, and of **64** to **61** results from thermodynamic



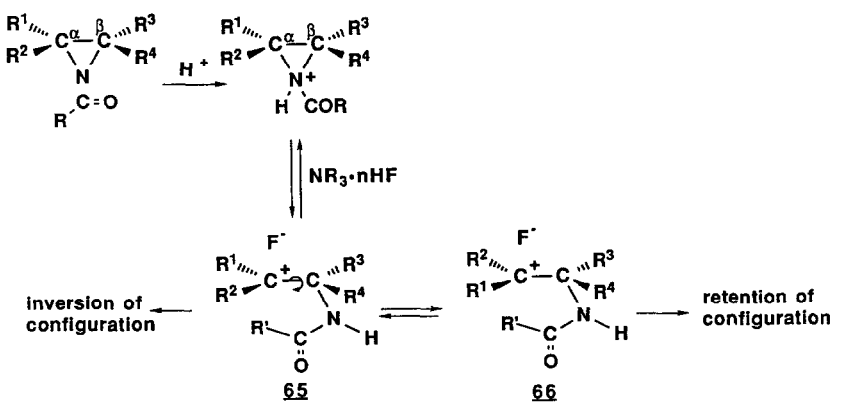
Scheme 23



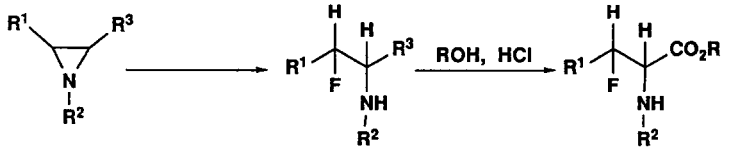
Scheme 24.

control under the same conditions. An equilibrium between the two conformers **57** and **58**, which correspond to **A** and **B** in Scheme 23, is rapidly reached affording a mixture of **63** and **60** in a 78 : 72 ratio.

Product compositions and configurations in the reaction of *cis* and *trans* epimino-cyclohexanes using HF·Pyr accompany their ring opening involving F addition *trans* to the NH_2 group.[43] Diastereoisomeric aziridines **41C** or **41T** in $NR_3 \cdot nHF$ predominantly afford **32** (Table 5). Each isomer, **41C** or **41T**, also gives rise to oxazolines in variable yields with the retention of configuration. This is explained by steric decompression during the course of cyclization. The results are accounted for by carbocation mechanisms involving formation of the intermediates **65** and **66** (Scheme 25). The steric hindrance due to the N-acyl group explains the exclusive formation of the *trans*-compounds.



Scheme 25



R^1 = H, Me, Ph, p-Cl-Ph

R^2 = H, Bu^t, $PhCH_2$

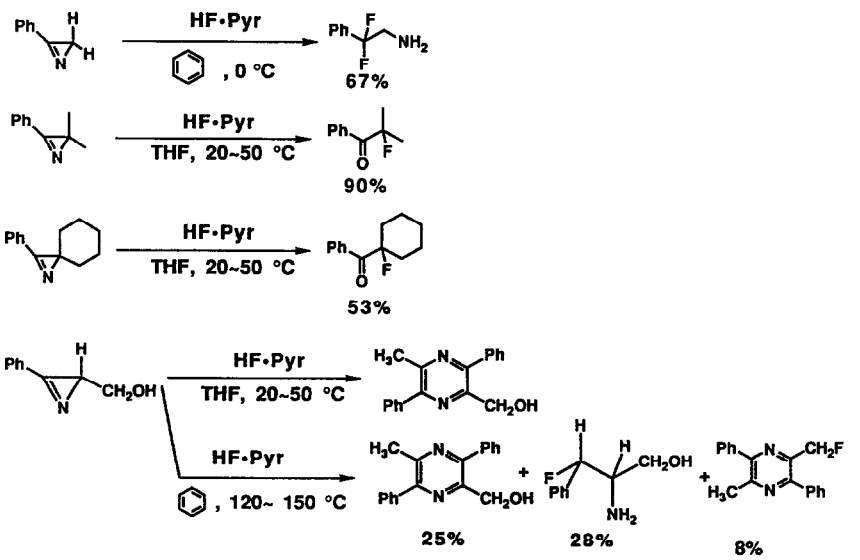
R^3 = CN, $CONH_2$

Scheme 26

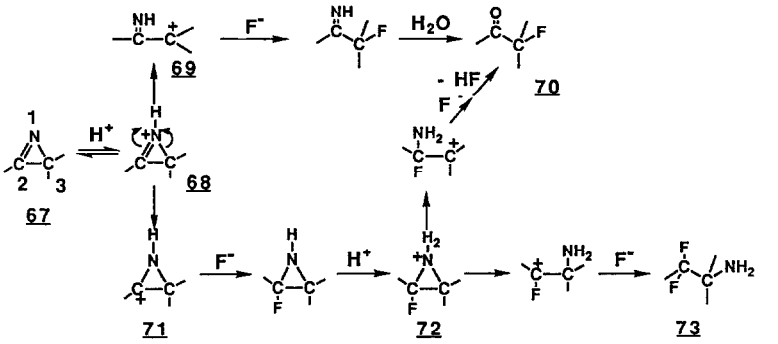
The reaction of *cis*-cyano-2- and *cis*-amido-2-aziridines in HF·Pyr affords β-fluoro-α-aminoacids and esters in good yields (Scheme 26).[45] The addition of HF is highly regioselective for both substrates in HF·Pyr. *threo*-β-Fluoro-α-aminoacid amides are exclusively obtained from *cis*-2-amido-aziridines. *cis*-2-Cyanoaziridines give mixtures of *threo*- and *erythro*-2-amino-3-fluoronitriles (57 : 43).

5.3 *Azirines*

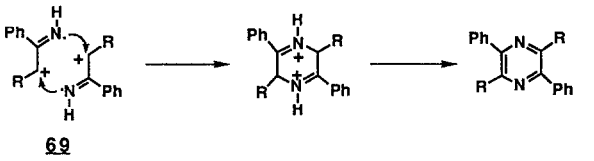
Addition of HF to azirines leads to the formation of difluoroamines or α-fluoroketones.[45,46] 1-Aziridines with no substitution at their 3 position such as 2-phenyl-1-azirine give only β,β-difluoroamines (Scheme 27).[47] On the other hand, 3-substituted 1-aziridines give, after hydrolysis, α-fluoroketones in the presence of HF·Pyr. 1-Azirines appeared to be more reactive toward HF·Pyr than their aziridine homologues.[44] 1-Phenyl-3-hydroxymethyl azirine gives pyrazines along with difluoroamines and α-fluoropropiophenone. Product distribution and yields can be made to vary by changes in additives (THF or benzene) to HF·Pyr. Yields are improved when using a more nucleophilic fluorinating reagent obtained by the addition of Et_3N to HF·Pyr.[46] A mechanism is suggested (Scheme 28). 1-Azirines **67** add a proton readily giving the azirinium ions **68**. From such intermediates **68**, the reaction is likely to proceed by two main pathways, one of which leads to



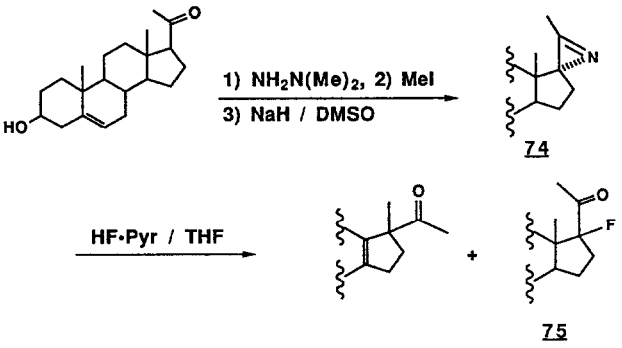
Scheme 27.



Scheme 28



Scheme 29



Scheme 30

α-fluoroketones **70**, while the other affords β,β-difluoro-amines **73**. 3-Substituted 1-azirines may give the stabilized carbonium ion **69** with electron donating alkyl or phenyl groups at the 3-position. This may lead to the predominant formation of α-fluoroketones. The formation of pyrazines is explained by the reaction of the intermediates **69** (Scheme 29).

1-Azirines substituted by an electron withdrawing group such as carboxyl and not substituted at their 3-position, can afford intermediates **72** via the carbonium ions **71** yielding β,β-difluoro-amines **73**. The presence of a fluorine on the azirinic ring of intermediates **72** would have an effect of considerably increasing the positive charge of the aziridinyl carbon. Consequently, an increase of the cycle bond-breaking rate would be observed compared with that of the aziridines.

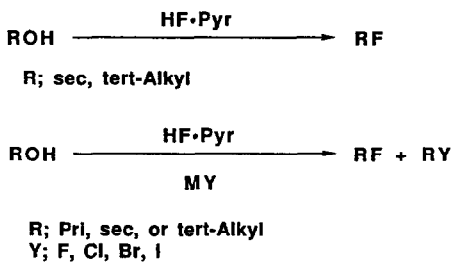
The synthesis of the α-fluoropregnenone **75** (Scheme 30), was successfully carried out by applying this reaction to the corresponding azirine **74**. This proceeds via a cationic intermediate **69** (Scheme 28).

6. FLUORODEHYDROXYLATION

Tertiary and secondary alcohols are readily fluorinated in HF · Pyr (Scheme 31).[9] The fluorides may be conveniently separated from the reaction media by extraction with cyclohexane or heptane, which forms an immiscible upper layer into which the fluorides are extracted. Primary alcohols are unreactive with HF · Pyr. However, the reaction proceeds smoothly in the presence of added NaF. It may be considered that monomeric fluoride ion is a strong nucleophile, whereas polymeric $F^-(HF)x$ is a very weak one. The presence of other halide ions such as chloride, bromide, or iodide ion gave the corresponding alkyl halides in high yields. The S_N2 nature of the reactions was demonstrated by the preparation of neopentyl halides from neopentyl alcohol without any rearrangement to 2,3-dimethyl-2-halopropanes.

HF · 14% Melamine is reported to be superior to the HF · organic amine reagents including HF · Pyr (Table 6).[12]

The effect of the mole fraction of $HF(X_{HF})$ in HF · Pyr on the regioselectivity of fluorination of benzylic alcohols **76** (Scheme 32) was reported[18] as follows: for (i) at $X_{HF} < 0.83$, the α-fluoro compound **77** was the only product; (ii) at $0.83 < X_{HF} < 0.87$, mixtures of **77** and a rearranged product **78** were observed; and (iii) at $X_{HF} > 0.87$, **78** was the only product. The influence of the composition of HF · Pyr is shown in detail in Fig. 2. Hydrogen displacement from the β-carbon in the carbocation (**I**) to the α-carbon takes place most readily at $X_{HF} = 0.85$ to form (**II**) since an equimolar mixture of **77** and **78** was observed. The reactivity and the rearrangement thresholds were

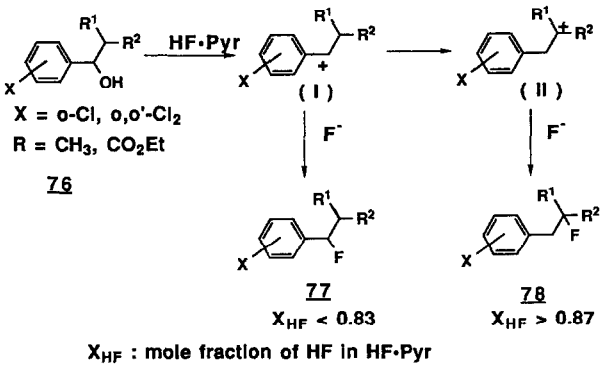


Scheme 31

Table 6 Fluorination of alcohols with HF-Pyridine or HF-Melamine

Alcohol[a]	React. Temp /°C	React. Time/h	Yield of RF% HF · Pyr[b]	HF · Mel[c]
2-Propanol	50	3	30	—
2-Propanol	20	1	—	81
2-Butanol	20	3	70	—
2-Butanol	0	1	—	70
2-Methyl-2-propanol	0	1	50	—
2-Methyl-2-propanol	0	1/4	—	39
Cyclopentanol	0	1	32	—
Cyclopentanol	−20	1	—	55
2,3-Dimethyl-2-butanol	0	1	10	—
2,3-Dimethyl-2-butanol	−20	1	—	69
3-Ethyl-3-pentanol	0	1	—	94

[a] 5 mmol of alcohol dissolved in 3 ml of THF.
[b] 30 wt% Pyridine, HF; 150 mmol.
[c] 14 wt% Melamine, HF, 150 mmol



Scheme 32

both shifted towards high HF content when electron-withdrawing substituents are introduced into the benzyl alcohols. Thus, the reaction of **76** with R = COOEt, or X = *o*–Cl or *o,o'*–Cl_2 does not produce any H-migration, even at the highest HF molar ratios. Both diastereoisomers of **76** with R = COOEt [(**76E**) = α-*R**, β-*S** and (**76T**) = α-*R**, β-*R**] resulted in the same molar composition of the fluoro product **77** [**77E** (α-*R**, β-*R**): **77T** (α-*R**, β-*S**) = 60:40]. These stereochemical results eliminate the possibility of an S_N2 mechanism for fluoride replacement of H_2O in the conjugated acid of the benzylic alcohol **76**, and suggest a loss of water to generate the carbocation (**I**), which then reacts with fluoride ion giving the substitution product **77** or undergoes a rearrangement into a second carbocation (**II**) which subsequently reacts with fluoride ion to give the rearranged fluoride **78** (Scheme 32). When the HF molar ratio is increased, an increase in the amount of transposition products from **76** at the expense of substitution products **77** can be explained as being due to a stabilization of the cationic intermediate (**II**) because long HF polymeric chains occur in mixtures which have a high HF content.

The reaction of methanol and of dimethyl ether with AHF leads to the formation of methyl fluoride at temperatures from 375 to 425°C in high yields in the presence of AlF_3 catalyst.[49] At temperatures above 425°C, thermal decomposition of substrates takes place predominantly. A

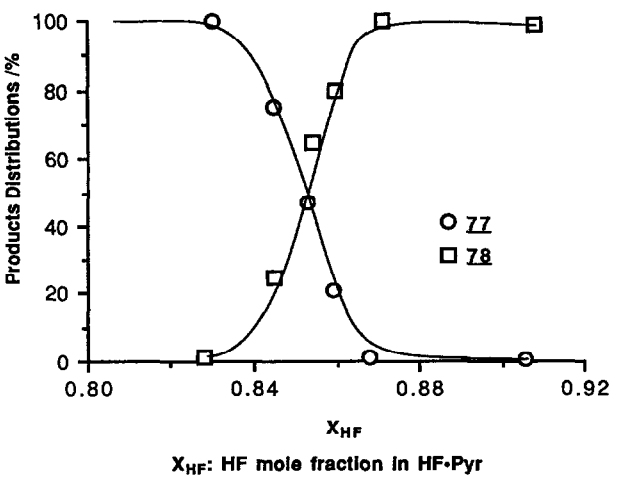


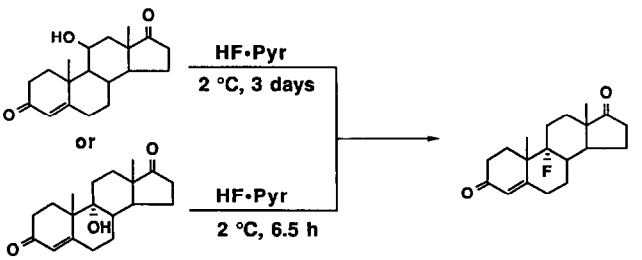
Fig 2 Influences of the mole fraction of HF in HF · Pyridine solution on the fluorodehydroxylation of **76**

similar reaction of the other alcohols and phenols did not occur to afford alkyl fluorides and fluorobenzene, but gave only ethylenic hydrocarbons.

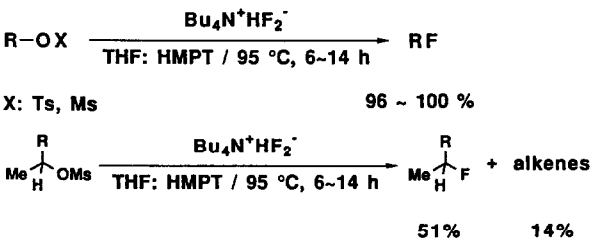
The treatment of a 9α- or 11β-hydroxy or 9(11)-dehydro steroid with a 70% HF in pyridine in an ice bath for a long time resulted in the introduction of fluorine at 9α (Scheme 33).[50]

Tetrabutylammonium bifluoride (TBABF) is useful for the transformation of primary alcohols to the corresponding RF through the intermediate tosylates and mesylates (Scheme 34).[51] The corresponding trifluoroacetates do not give RF. Reaction with mesylates of secondary alcohols led to a marked decrease in the yield of the expected fluoride with the formation of a considerable amount of alkenes.

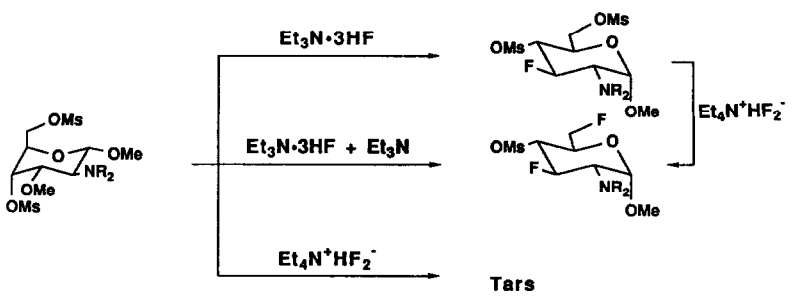
In the reaction of Ph-$(CH_2)_3$-OMe with Amine·HF to obtain Ph-$(CH_2)_3$-F, fluorination reactivity was demonstrated to be $Et_4N^+HF_2^- \gg Et_3N \cdot 3HF/Et_3N > Et_3N \cdot 3HF \gg Et_3N \cdot HF$.[52] Thus, $Et_3N \cdot 3HF/Et_3N$ was successfully used as a neutral nucleophilic fluorinating reagent in the synthesis of α,β-aminofluorosugars, to obtain 3,6-difluoroglucosamine in one step (Scheme 35).[52] An equilibrium between $Et_3N \cdot 3HF$ and $Et_3N \cdot 2HF$ was proposed with this new fluorination reagent as



Scheme 33.



Scheme 34.



Scheme 35

shown in the following Equations

$$Et_3N \cdot 3HF + 2Et_3N \rightarrow 3[Et_3N \cdot HF]$$

$$2[Et_3N \cdot 3HF] + Et_3N \rightarrow 3[Et_3N \cdot 2HF].$$

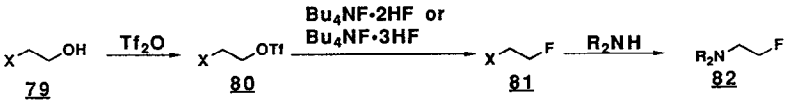
Substitutions of the methanesulfonic group in *n*-octyl methanesulfonate by fluoride ion associated with tetrahexylammonium cation Q^+ were investigated[56] as shown in the following Equation

$$R\text{-}SO_2OMe + (Hexyl)_4N^+F^- \rightarrow RF + (Hexyl)_4N^+MeSO_3^-$$

R: Primary alkyl.

Nucleophilicity and basicity, in other words, the fluorination reactivity of the fluoride anion of $(hexyl)_4N^+F^-$ is affected in solvents of low polarity by specific solvation of a limited number of water molecules (Table 7). Thus, nucleophilicity and basicity enhancements of $Q^+F^- \cdot nH_2O$ was found to be about 3 orders of magnitude by reducing the anion hydration state (n) from 8 to 0. Such nucleophilicity and basicity enhancements are not a linear function of hydration state (n) of $Q^+F^- \cdot nH_2O$ but exponentially increase by diminishing n. The basicity of the fluoride ion is much more affected by specific solvation than is its nucleophilicity. Partially hydrated quaternary fluoride such as $Q^+F^- \cdot nH_2O$ (n = 4) still has a nucleophilic reactivity substantially higher than that of the AHF, namely, $Q^+(HF)F^-$ and dihydrogen trifluoride $Q^+(HF)_2F^-$ (17 and 2000 times). The following reactivity scale was provided in the study of quaternary ammonium poly (hydrogen fluorides) $Q^+(HF)n \cdot F^-$, where n = 1, 2: $F^- \gg HF_2^- > H_2F_3^-$.

The preparation of fluoro-substituted amines **82** and amides has been done by the reactions involving fluoride ion displacement of haloalkyl trifluoromethanesulfonate (triflate), followed by fluoroalkylation of the heteroatom system (amine or amide) by the fluoroalkyl halide (Scheme 36).[57] The displacement reaction of haloalkyl triflates **80** which are derived from the corresponding alcohols **79**, with fluoride ion, takes place with $Bu_4NF \cdot 2HF$ or $Bu_4NF \cdot 3HF$ affording the corresponding fluorides **81**. Yields (25–100%) of **81** depend on the agents and solvents. Quantitative yields are obtained at room temperature within seconds in *o*-DCB, CH_3CN, and THF with *n*-$Bu_4NF \cdot 3HF$.



79 80 81 82

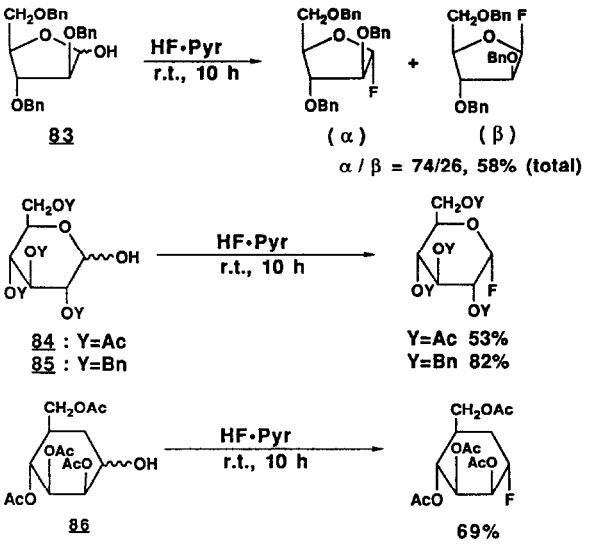
Scheme 36

Table 7 Effect of the specific hydration of fluoride ion on its basicity for the elimination reaction of $hexyl_4N^+F^- \cdot nH_2O$ in PhCl[a]

$Hexyl_4N^+F^- \cdot nH_2O$	$10^5k^c, s^{-1}$	k_{rel}
6 0	—[b]	—
4 6	0 005	1
3 2	0 035	7
2 4	1 7	340
2 0	9 5	1900
1 7	38	7600
0	$1\ 17 \times 10^5$	$2\ 34 \times 10^7$

[a] 60° C

[b] No elimination



Scheme 37

This provides the prospect of the synthesis of F-18 labelled products: dry and reactive *n*-Bu_4NF can be produced from [^{18}F]fluoride ion. However, the displacement reaction of **80** does not proceed in the presence of HF · Pyr.

The reaction of fully acetylated carbohydrates with AHF in a platinum vessel was reported to give glycosyl fluorides. However, this reaction is not capable of extension to general use, because the severe conditions sometimes cause undesired side-reactions such as removal of protective groups or structural change.[53] On the other hand, as shown in the following Equation, appropriately protected sugars are converted readily to 1-fluoro-derivatives by the reaction using HF · Pyr[54]

$$\text{Glucosyl-OR} + \text{HF} \cdot \text{Pyr} \rightarrow \text{Glucosyl-F}$$

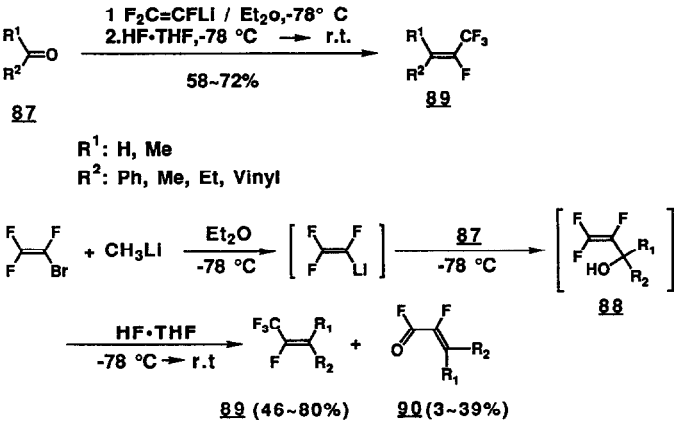
R: H, Ac Bn.

The reaction of penta-O-acetyl-β-D-glucopyranose, which has a participating acetoxyl group at the 2-position gave a mixture of the α- and β-fluorides in which the latter predominated. Under forcing conditions, the kinetically favored β-isomer isomerizes to a more stable α-isomer.

The replacement of the anomeric hydroxyl group of partially protected monosaccharides by fluorine can also be accomplished by the use of HF · Pyr at room temperature for 10 h, without prior activation of the substrate (Scheme 37).[55] The addition of acetone, dichloromethane or collidine to HF · Pyr is capable of affecting the reactions in the following manner. Acetone is equally effective in most reactions. The reaction of **83** requires the use of acetone or CH_2Cl_2–collidine {1 : 1 (v/v)}. In the case of **84**, the addition of collidine is disadvantageous, whereas in the case of **85** the best results are obtained using acetone–collidine {1 : 1 (v/v)}. Compound **86** gives good results by treatment with only HF · Pyr.

7. HYDROFLUORINATION OF POLYFUNCTIONAL COMPOUNDS

Unsaturated compounds with some functional groups such as OH, may undergo skeletal rearrangement.[13] Thus, 1,1,1,2-tetrafluoro-2-alkenes **89** can be prepared in the hydrofluorination of trifluoroallylic alcohols **88**, which are readily prepared from the reaction of trifluorovinyllithium



Scheme 38

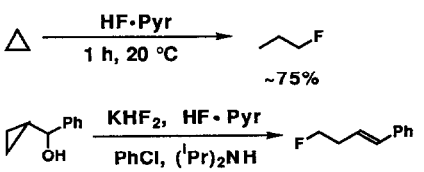
with appropriate ketones or aldehydes **87** in the presence of HF·THF solution (Scheme 38). The formation of α-fluoro-α,β-unsaturated acid fluorides **90** is always observed together with the formation of **89**. The reaction is accompanied by a rearrangement of allylic alcohols **88** to afford, almost exclusively, the *Z* isomer of **90**. The yields of desired product **89** are effected by the composition of HF·THF solution and are optimal with a 5 : 1 ratio of HF/THF (Table 8). The relative steric size of R_1 versus R_2 in **88** can determine the stereochemistry of the products **89**. The larger substituent prefers to end up *trans* to the CF_3 group.

Treatment of cyclopropanes with HF·Pyr gives fluoropropanes.[14] A cyclopropylmethanol, on the other hand, gave the corresponding homoallylic fluoride selectively by the treatment with HF·Pyr in chlorobenzene–diisopropylamine solution in the presence of KHF_2 (Scheme 39).[15]

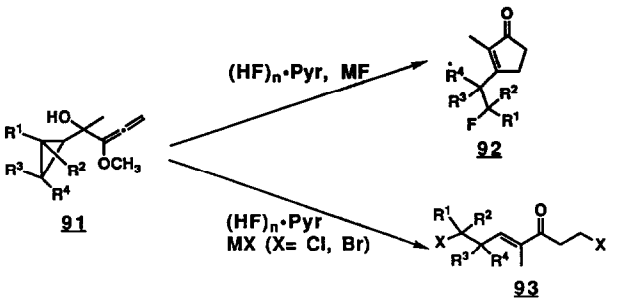
Table 8 Effect of the HF/THF ratio on the reaction of **88**[a]

Molar ratio of substrates			React	Yield of products%	
88	THF	HF	time/h	**89**	**90**
1	10	10	2	55	39
1	10	10	24	55	22
1	10	25	4	46	3
1	10	50	4	72	8
1	10	50	72	80	6
1	10	100	4	53	9

[a] R_1 = Ph, R_2 = H, see Scheme 38



Scheme 39



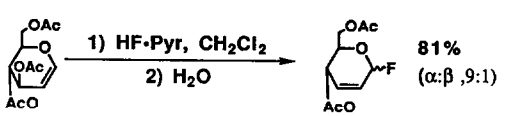
Scheme 40

HF · Pyr itself or ethereal solvents hinder the selectivity of formation of homoallylic fluorides. Ethers are also commonly used as organic bases in AHF. HF · Et_2O, however, undergoes condensations to form complex by-products in this reaction. Diisopropylamine and KHF_2 were considered to activate HF · Pyr in such a way that the amine dissociates the aggregate of HF molecules. This generates a less aggregated fluoride ion. At the same time KHF_2 increases the nucleophilicity of the fluoride ion.

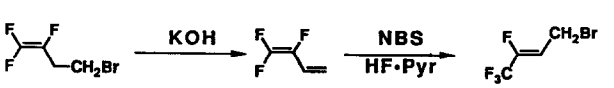
Treatment of cyclopropyl methoxyallenyl carbinols **91** with HF · Pyr in CH_2Cl_2 at 0°C in the presence of fluorides such as NaF gave 3-fluoroethyl-2-cyclopenten-1-ones **92** (23–65%; Scheme 40).[16] In the absence of metal fluorides, the reaction becomes complex and affords **92** in low yield (< 10%). NaF and KHF_2 give better results among the fluorides (NaF, KHF_2, KF, CsF, SnF_2, NH_4F, *n*-Bu_4NF). Organic solvents such as CH_2Cl_2, $CHCl_3$, CCl_4, and PhCl gave the desired product in good yields, whereas EtOH, DMF, CH_3CN, AcOEt, THF, Et_2O, and *n*-C_5H_{12} provided poor yields. Thus, a delicate control of the nucleophilicity and the acidity of HF · Pyr by the metal fluorides and the solvents is the key to successful application of this modification to highly functionalized substrates. Metal fluorides appear to increase the nucleophilicity of fluoride ion and to lower the acidity of AHF. Metal chloride or bromide give the non-annulated dihalogenoenones **93** as a sole product.

Treatment of appropriate glycals with AHF or saturated solution of AHF in benzene yielded unstable products,[17] whereas HF · Pyr gives the Ferrier rearranged products[18] (Scheme 41).[19] Only when the ester protecting groups at C-3 and C-4 are *trans* does the rearrangement proceed. When the groups at C-3 and C-4 are *cis* then other reactions predominate to form unknown products.

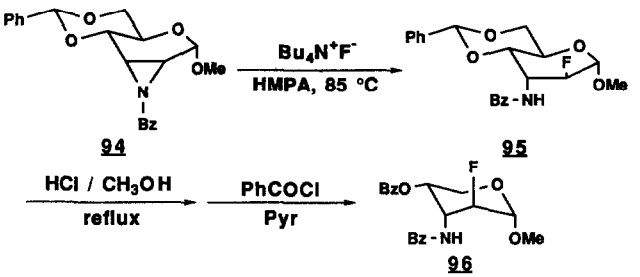
Trifluorobutadiene, which can be obtained in the reaction of 4-bromo-1,1,2-trifluoro-1-butene with potassium hydroxide, reacts with NBS and HF · Pyr in CH_2Cl_2 to give 1-bromo-3,4,4,4-tetrafluorobutene-2 (52%)[85] (Scheme 42).



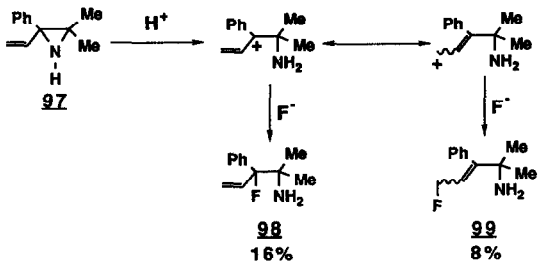
Scheme 41.



Scheme 42.



Scheme 43.



Scheme 44

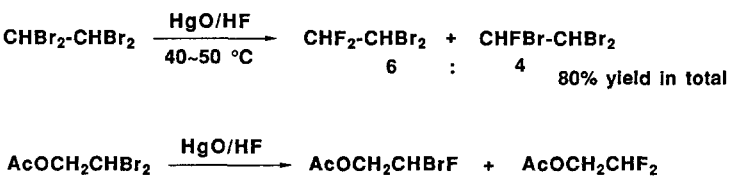
The formation of only one fluoro-amine derivative was reported when an N-benzoyl aziridine in the sugar series is treated with Bu_4NF.[87] For example, N-benzoylepi-imine **94**, which has OMe and an aziridine ring, gives 2-fluoro-α-D-altropyranoside **95** (Scheme 43). Debenzylidenation of **95** followed by benzoylation affords the 2-fluoroglycopyranoside **96**.

Phenyl-vinyl aziridine **97** reacts with HF·Pyr to give the α,β-fluoroallyl amine **99** together with the usual α,β-fluoro-amine **98** (Scheme 44).[40]

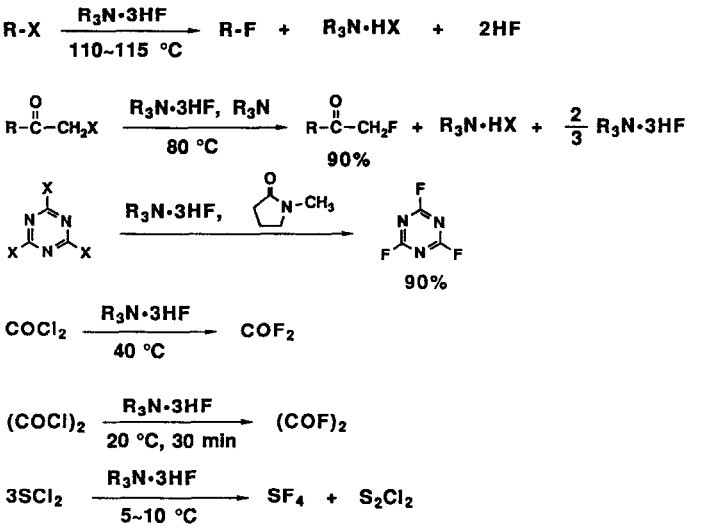
8. HALOGEN-EXCHANGE FLUORINATION

Halogen-exchange fluorination of aliphatic halides is generally carried out using KF under basic conditions. However, the reaction of cyclo and tertiary alkyl halides is usually subjected to preferential elimination giving olefinic compounds. In contrast, Cu_2O-HF·Organic base such as THF and Et_2O is usually successful as a highly reactive halogen exchange fluorination reagent (Table 9).[61] However, application of this reagent to primary alkyl halides gave low yields (20%) of the corresponding fluoride together with considerable amounts of isomeric secondary alkyl fluorides.

Metal oxides can be converted into metal fluorides, which are useful fluorinating reagents, by treatment with AHF. Thus, organic halogenated compounds with HgO give the corresponding fluorides in the presence of AHF at 40–50°C (Scheme 45).[60] On the other hand, the deep purple



Scheme 45



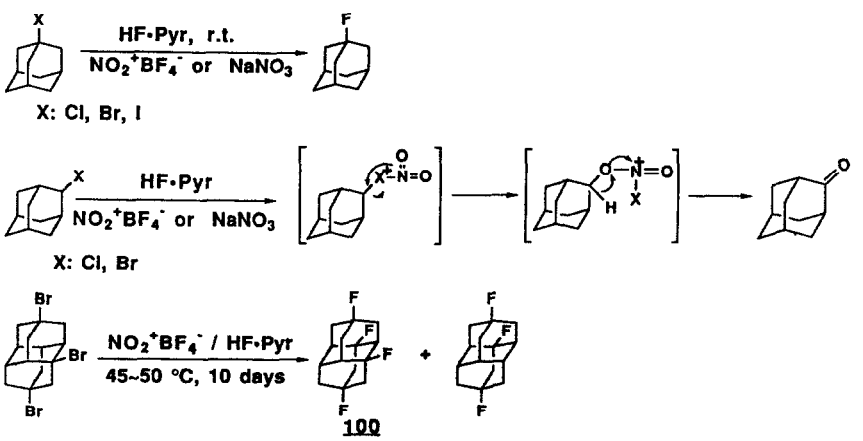
Scheme 46

semicrystalline precipitates, which were obtained by the treatment of Cu_2O with HF and calcination at 100°C or higher were highly effective halogen-exchange fluorination reagents for primary alkyl halides in the presence of pyridine.[62] This method is superior to other known halogen-exchange fluorination methods (Table 9).

$R_3N \cdot 3HF$ is a convenient reagent for the nucleophilic replacement of chlorine or bromine atoms by fluorine (Scheme 46). This reagent gives homogeneous reaction mixtures often leading to high yields under very mild conditions.[7]

Tetrabutylammonium bifluoride $Bu_4N^+HF_2^-$ (TBABF) can be prepared by the reaction of ammonium bifluoride (NH_4HF_2) with Bu_4NCl. This reagent is a stable and easily available source of fluoride anion in the nucleophilic substitution of RX to afford RF (Table 9).[51]

The HF·Pyr reagent does not convert tertiary alkyl halides to the corresponding fluorides. However, in the presence of a halide abstracting agent such as nitronium tetrafluoroborate, HF·Pyr can then act as the suitable fluoride donor.[58] Thus, bridgehead adamantyl and diamantyl halides undergo halogen exchange fluorination in the presence of $NO_2^+BF_4^-$ with HF·Pyr (Scheme 47).

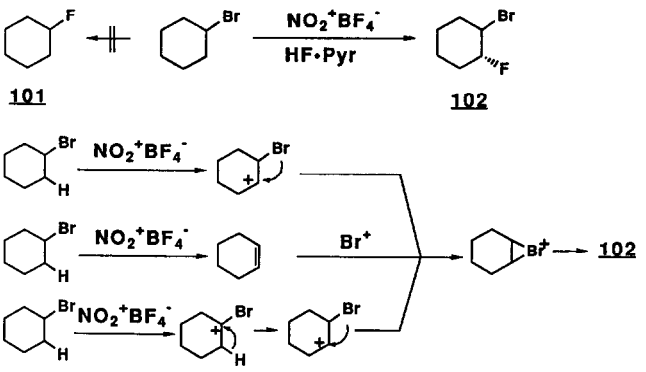


Scheme 47

Table 9 The halogen-exchange fluorination of RX

Substrate RX	Fluorination conditions: Agent	Solvent	Time h	Temp °C	Conversion %	Product distribution/%: RF	Alkene	Other	Ref
1-Bromodecanen	$Bu_4N^+HF_2^-$	THF-HMPT	3	95	100	88		12[e]	51
1-Iodooctadecane	$Bu_4N^+HF_2^-$	THF-HMPT	2 5	95	100	76	24		51
1-Iodooctadecane	$Bu_4N^+HF_2^-$	CH_3CN	7	80	70	86	14		51
1,10-Dibromodecane	$Bu_4N^+HF_2^-$	THF-HMPT	3.5	95	100	76	2	22[f]	51
Benzylbromide	$Bu_4N^+HF_2^-$	THF-HMPT	4	95	100	100			51
PhCOCH2Cl	$Bu_4N^+HF_2^-$	THF-HMPT	4 5	95	100	100			51
p-NO_2PhCl	$Bu_4N^+HF_2^-$	THF-HMPT	57	95	70	100			51
1-Bromooctane	KF	DEG[c]	23	135		48	Ethers and Alkenes		89
1-Bromooctane	Anion-Exchange Resin		20	86	94	87	13		90
2-Bromooctane	Anion-Exchange Resin		25	86	94	21	79		90
1-Bromooctane	KF[a]		3 5	160	87	74	17	9[g]	91
2-Bromooctane	KF[a]		5	160	72	0	89	11[g]	91
1-Bromooctane	KF[b]		230	83	100	92	8		92
2-Bromooctane	KF[b]		150	83	100	32	68		92
1-Bromooctane	CuF_2	CH_3CN	128	82	90	98	2		93
1-Bromooctane	CuF[d]	2,2′-Bipyridine	0 75	130	85	98	2		62
Cyclohexyl-Cl	KF[a]		70	125	100	0	100		91
Cyclohexyl-Cl	HF-THF		2	50	0				61
Cyclohexyl-Cl	HF-Cu_2O		2	30	100	0	0	Oligomers	61
Cyclohexyl-Br	HF-THF-Cu_2O		1	20	95	96	4		61
Adamantyl-Br	HF-THF-Cu_2O		0 25	25	100	100			61
2-Chloro-2-methylbutane	HF-Et_2O-Cu_2O		0.5	20	97	100			61
2-Chloro-2,4-dimethylpentane	HF-Et_2O-Cu_2O		1 5	0	83	100			61
1-Chloro-1-methylcyclopentane	HF-Et_2O-Cu_2O		0 1	0	75	100			61

[a] With phase-transfer catalyst
[b] 18-Crown-6-complex-kF
[c] Diethylene glycol
[d] Prepared from Cu_2O and HF, and calcined at 100°C
[e] Unknown
[f] $Br(CH_2)_{10}F$.
[g] Alcohols



Scheme 48

Under the same conditions, secondary 2-haloadamantanes gave 2-adamantanone, instead of the halogen-fluorine exchange product. 1,4,7,9-Tetrafluorodiamantane **100** is formed unexpectedly in the reaction of 1,4,9-tribromodiamantane with excess $NO_2^+BF_4^-$/HF·Pyr reagent, together with 1,4,9-trifluorodiamantane. The fluorine atoms at the 1, 4, and 9 positions are obviously introduced through halogen exchange reaction with nitronium ion acting as the bromide abstracting agent. The nitronium ion is also capable of attacking the tertiary bridgehead C–H bond at C_7 to bring about hydride abstraction forming C_7 bridgehead carbocation, which in turn is quenched by fluoride from pyridinium polyhydrogen fluoride reagent affording **100**.

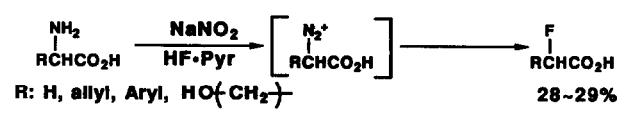
1-Chlorohexane did not give any fluorinated product, when treated with an equivalent of $NO_2^+BF_4^-$ in an excess of HF·Pyr at −5°C for 15 h. However, iodocyclohexane gave 1-fluorocyclohexane (30%) under similar conditions. Secondary alkyl and cycloalkyl bromide such as 1-bromocyclohexane, on the other hand, did not give the expected halogen exchange product **101**, but gave the *trans* vicinal bromofluoroproduct **102**, (69%) (Scheme 48). A mechanistic pathway for the formation of such β-fluorination products is suggested to involve the acyclic bromonium ion as a reaction intermediate which is formed by α-hydride abstraction of starting bromides by the nitronium ion which is a good hydride abstracting agent. 1-Bromo-1-deuteriocyclohexane gave the product **102** with no deuterium in the product.[59]

9. DEAMINATIVE FLUORINATION

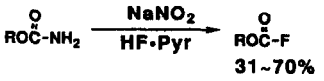
α-Amino acids give 2-fluorocarboxylic acids in moderate yields by reaction with $NaNO_2$ in HF·Pyr solution (Scheme 49).[9] This reaction with glutamine (R:–$CH_2CH_2(CO)NH_2$) was unsuccessful.

The reaction of alkyl carbamates in HF·Pyr with $NaNO_2$ results in the formation of the corresponding fluoroformates at room temperature (Scheme 50).[9]

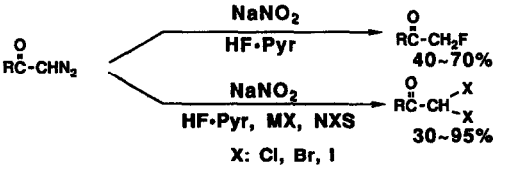
Reactions of diazoketones (Scheme 51) with HF·Pyr yields the corresponding fluoroketones or fluoroalkanes.[9] In the presence of added MX or NXS, α-halogenated ketones and haloalkanes are produced.



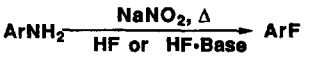
Scheme 49.



Scheme 50



Scheme 51.



Scheme 52

The Balz–Schiemann reaction of arenediazonium tetrafluoroborate salts (ArN_2BF_4) derived from aminoarenes ($ArNH_2$), is known to be the most convenient and practical method available for a controlled, regiospecific introduction of fluorine into aromatic rings.[71] However, the isolation and controlled decomposition of ArN_2BF_4 is a troublesome synthetic procedure so the reproducibility of yields of the desired ArF is at times poor. A few attempts have been made to improve this two-step process using HF. This provides a convenient one-pot diazotization and fluorodediazoniation of $ArNH_2$ affording ArF in fairly good yields (Scheme 52).[72] The yields of ArF are greatly influenced by the substituents on the aromatic nucleus, and tarry matter is sometimes formed in considerable amounts. Recently, this procedure has been substantially improved to produce ArF in high yields by the use of HF with bases.[9,73–75] The functions of bases in the HF solution has been studied recently to enhance the diazotization of anilines.[77] Thus, since substrate $ArNH_2$ itself can play a role as base, the yields of ArF are greatly influenced by the ratio of $HF/ArNH_2$ in the reaction (Fig. 3). As shown (Table 10), the procedure has been further improved to produce ArF in high yields compared to those obtained in the Schiemann reaction[94] by the use of HF with bases such as pyridine.[74] The amount of pyridine in HF is important (Fig. 4). Fluoro-dediazoniation of

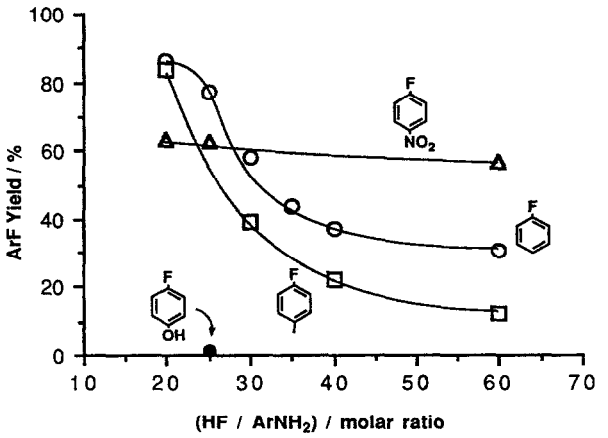


Fig. 3 Diazotization and fluoro-dediazoniation of $ArNH_2$ in HF

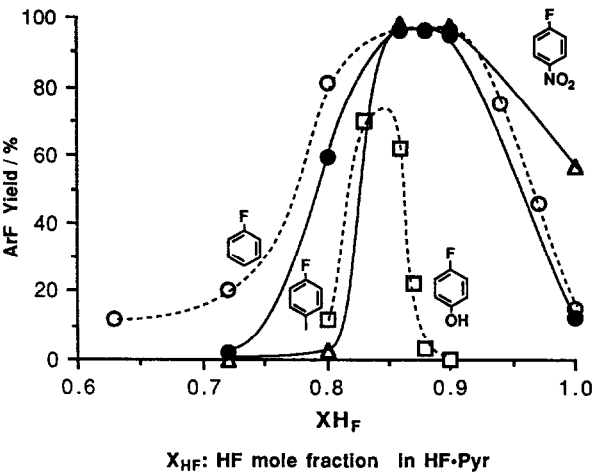
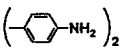
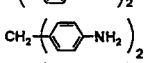
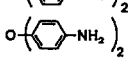


Fig 4 Diazotization and fluoro-dediazoniation of $ArNH_2$ in HF·Pyr solution

Table 10 Diazotization[a] and dediazoniation[b] of $ArNH_2$ using 30–45% Pyr·HF at atmospheric pressure

Substrate		Dediazoniation Temp./°C[b]	ArF Yield/%[c]	The Schiemann React. Yield/%[c]
		55	99	51-90
	o-	55	99	45-65
	m-	70	98	69-87
	p-	70	98	70
	o-	150	17 (83)[d]	31-64
	m-	55	87	32-52
	p-	130	71	47-73
	o-	160	72	83
	m-	80	98	60-65
	p-	110	92	63
	o-	90	72	7
	m-	80	95	5
	p-	100	89	32
	o-	90	76	-
	m-	90	95	64-80
	p-	80	85	-
		100	80	44-80
		100	95	58
		100	95	10

[a] 0°C for 15 min.
[b] 30–60 min.
[c] Based on $ArNH_2$ [94]
[d] Irradiation for 18 h at 13°C [95]

Table 11 Fluoro-dediazoniation rate constants of PhN_2BF_4 in HF · Pyridine solutions[a]

HF/Pyridine mole ratio	$k \times 10^5$ s^{-1}
36	3 80
16	3.02
9	2 12
6	1 54
4	0 88

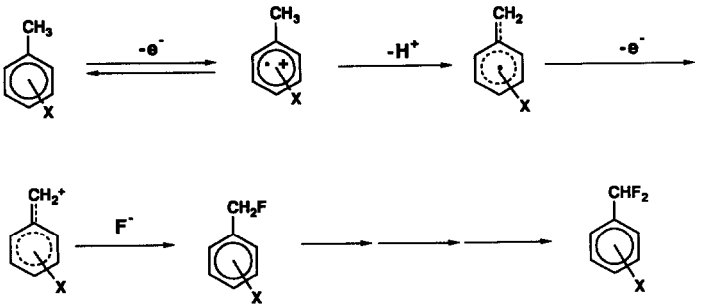
[a] Reaction conditions · PhN_2BF_4, 5 mmol, HF, 450 mmol, 20°C

diazonium cations, takes place readily and exclusively without the formation of undesirable products in HF or HF · Base. Such bases serve to slow down the rate of decomposition of PhN_2BF_4 salts (Table 11).[77]

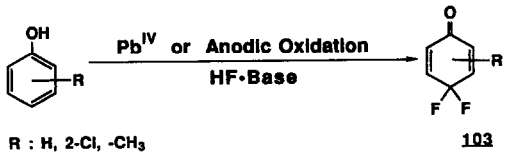
10. OXIDATIVE FLUORINATION

HF · Base is a source of fluoro-substituents in the oxidative fluorination of aromatic hydrocarbons. Aryl cations or aryl radical cations are formed oxidatively which then react with fluoride ions *in situ* with the formation of F–C bonds. Toluene derivatives bearing electro-negative substituents are cleanly fluorinated on the methyl group by reaction with PbO_2 or NiO_2 in HF.[67] Aromatic cation radicals are proposed as intermediates (Scheme 53).[68]

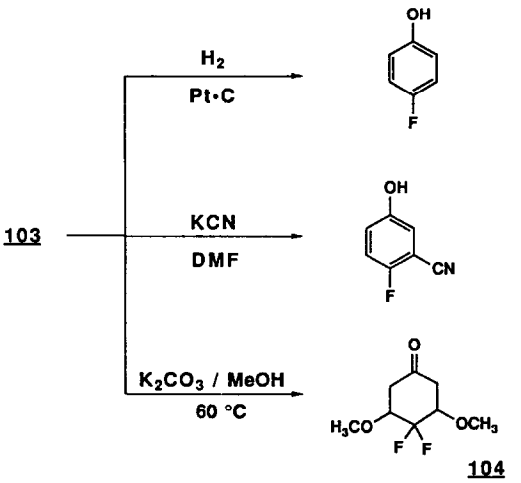
Phenols are converted into the dienone **103** in an HF · Base in the presence of stoichiometric amounts of lead(IV) compounds or by anodic oxidation (Scheme 54). Interestingly, without the addition of bases **103** is not formed, but only polymers. Compound **103** can be converted to



Scheme 53



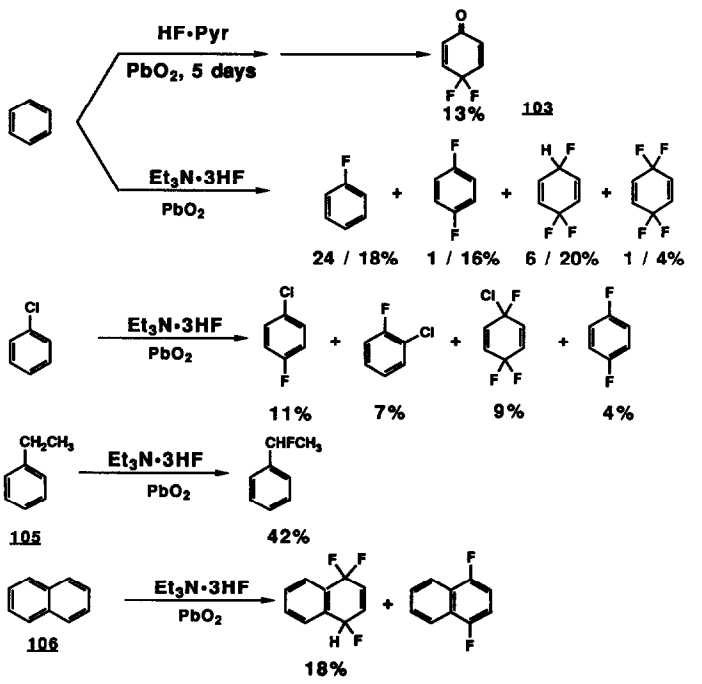
Scheme 54



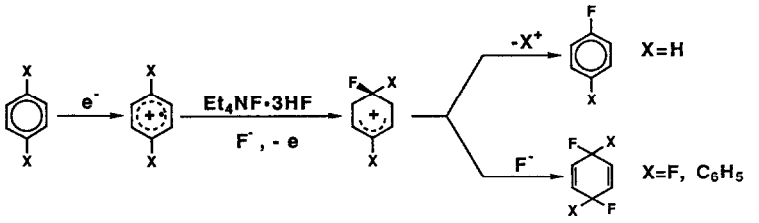
Scheme 55

p-fluorophenol by hydrogenation, 2-fluoro-5-hydroxybenzonitrile by a Michael addition with CN^-, and to compound **104** by the addition of methoxide (Scheme 55).

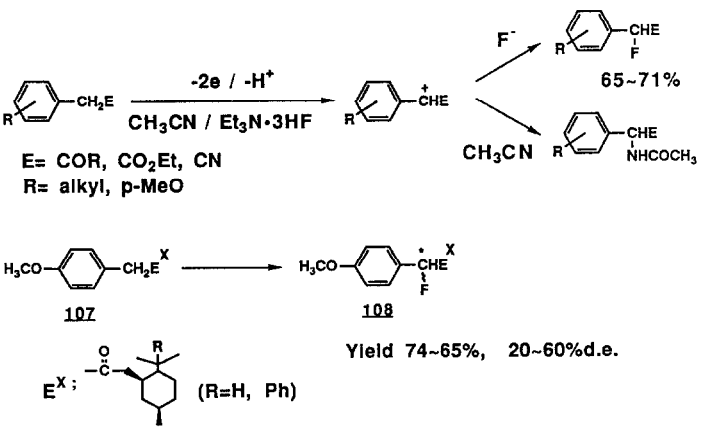
Benzene reacts with PbO_2 in HF·Pyr to yield **103** very slowly (Scheme 56). However, in the presence of $Et_3N \cdot 3HF$ as a fluoride ion source, non-activated aromatics such as **105** and **106** can afford fluorinated products.[78] Products from the electro-chemical oxidation of aromatic compounds



Scheme 56



Scheme 57

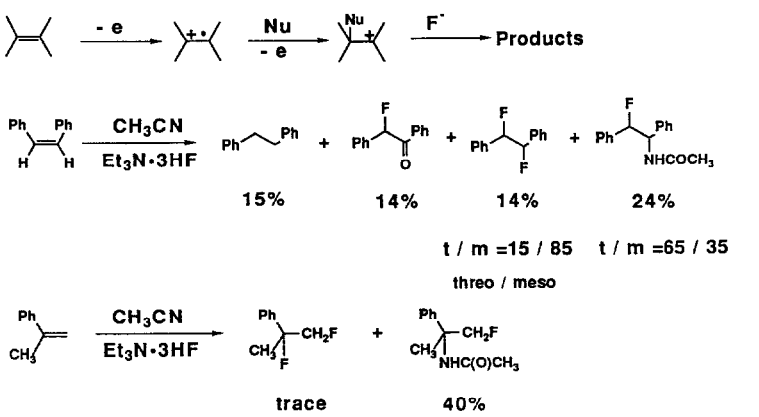


Scheme 58

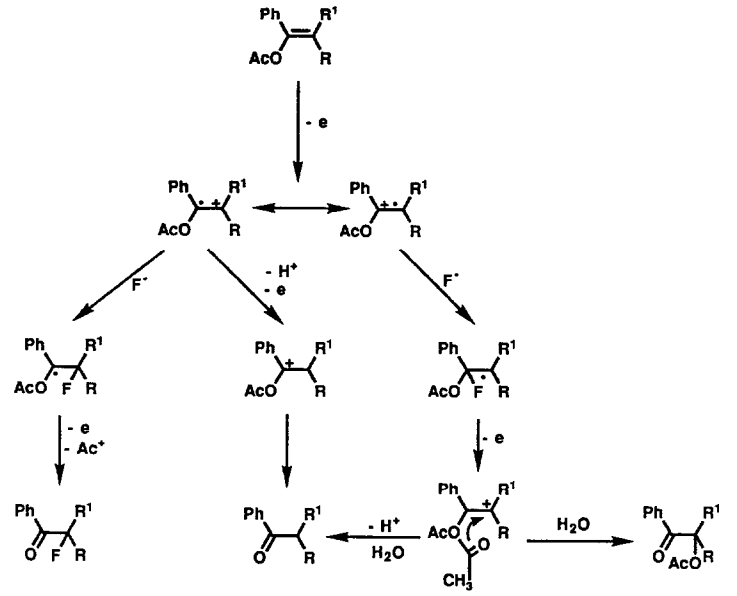
are derived by initial oxidation of the aromatic substrate followed by subsequent reaction with F^- (Scheme 57).[65]

Benzylic ketones, esters and nitriles yield the corresponding monofluoro- or difluoro-compounds by anodic oxidation in $CH_3CN/Et_3N \cdot 3HF$ that proceeds through an α-carbonyl or an α-cyano carbocation (Scheme 58).[66] Regioselective fluorination of benzylic derivatives **107** takes place to produce **108** at the platinum anode in $Et_3N \cdot 3HF/CH_3CN$.[79]

Olefinic compounds also afford fluorinated products during oxidation at the platinum anode in the presence of $Et_4NF \cdot 3HF/CH_3CN$.[80] Thus, styrenes afford fluorinated products (Scheme 59).



Scheme 59

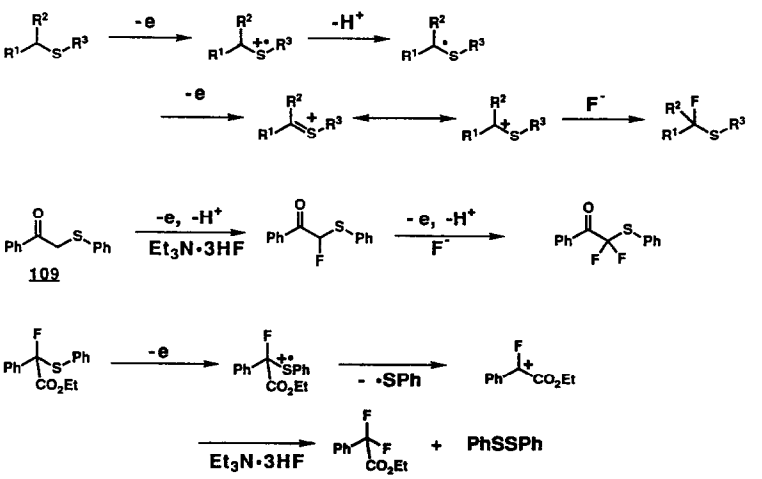


Scheme 60

2-Fluoropyridine can be synthesized (22%) by electro-chemical fluorination of pyridine at a Pt anode at 2.5 V vs Ag/Ag^+ (0.1 M) with 0.5 M $Me_4NF \cdot 2HF$ in CH_3CN.[81] At lower $Me_4NF \cdot 2HF$ concentrations and at lower applied potentials, the reaction rate is decreased whereas at higher potentials the supporting electrolyte/solvent system decomposes.

The anodic oxidation of enol esters and enol ethers in $CH_3CN/Et_3N \cdot 3HF$ solutions gives mainly the fluoroketone or the acetoxyketone (Scheme 60). The enol ether cation-radicals seem to be less reactive towards $H_2F_3^-$ ions than the corresponding enol ester cation-radicals.[82]

Compound **109** with an electron-withdrawing group in the β position affords fluorocompounds by sulfide electrochemical oxidation using $Et_3N \cdot 3HF$ (Scheme 61). The reaction proceeds via sulfonium ions followed by the addition of a fluoride ion.[83]



Scheme 61

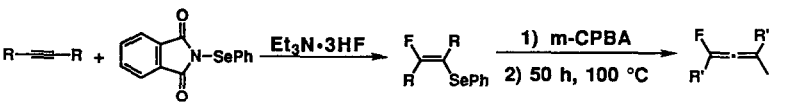
11. MISCELLANEOUS

The electrophilic *trans*-addition of the elements of benzene-selenylfluoride towards C–C triple bonds is achieved by reaction of N-phenylselenophthalimide and $Et_3N \cdot 3HF$ with alkynes (Scheme 62).[84]

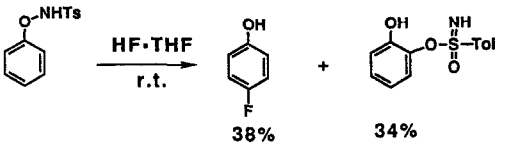
Nucleophilic aromatic fluoride substitution of N-tosyl-O-phenylhydroxylamine produces *p*-fluorophenol (38%) using HF·THF, which is an excellent source of nucleophilic fluoride ion (Scheme 63)[63].

Aromatic *ortho* thioesters can be converted to aromatic trifluoromethyl compounds by reaction with DBH or NBS followed by HF·Pyr (Scheme 64).[64]

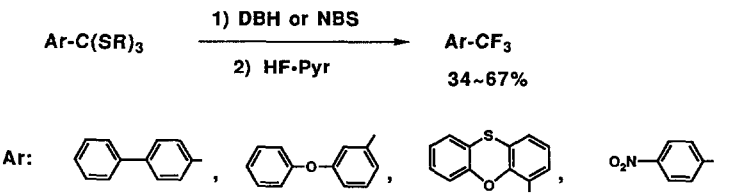
Aryl trifluoromethyl ethers are prepared by reacting selected phenols with CCl_4 in HF (Scheme 65).[69] Mild catalysis of the reactions with BF_3 or SbF_3 was reported. However, KF decreases the acidity of the medium and this results in lower conversion. An acid-catalyzed nucleophilic attack on CCl_4 was proposed[69] for the reaction pathway (Scheme 66). An electron-transfer pathway, which might be facilitated by the highly polar nature of HF solvent,[78] may also be proposed (Scheme 65).



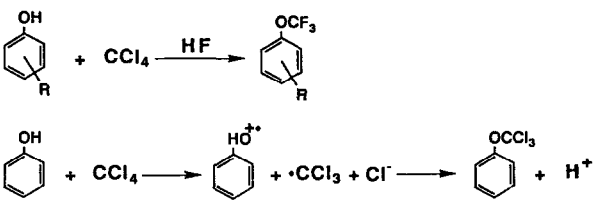
Scheme 62



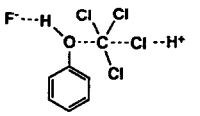
Scheme 63



Scheme 64



Scheme 65



Scheme 66

12. FINAL REMARKS

AHF in conjunction with various Lewis bases enhances the effective availability of nucleophilic fluoride ion in organic fluorination reactions. The reduced volatility of the reaction medium allows higher reaction temperatures at atmospheric pressure and this leads to easier handling. No quantitative analysis can be offered for the relation between the enhancement of nucleophilicity of fluoride ion and Lewis bases employed in AHF.

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