The Application of Elemental Fluorine in Organic Synthesis

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I. Introduction

In commemoration of the 100th anniversary of Moissan's discovery of fluorine gas,[1] and with the ever growing interest in fluorinated organic molecules for biomedical applications, a review of the methods of fluorination in organic synthesis is appropriate. Much has been accomplished since Bockemuller first showed the potentially selective nature of fluorine as demonstrated in his fluorination of aliphatic carboxylic acids.[2] Since that time, many new selectively fluorinated organic molecules have been made available from elemental fluorine, including some that are useful intermediates in the synthesis of other non-fluorinated compounds.[3]

There have been a number of publications that deal in part with selective fluorination using elemental fluorine,[4-11] but since 1961[8] there have been no comprehensive compilations. This paper will concentrate on the more recent developments. The direct fluorination of ureas, carbamates, amines, nitro compounds, carboxylate salts, anhydrides,[4] and the commercially unavailable halogen monofluorides[12] have been previously reviewed and will be updated accordingly. Perfluorination reactions, although at times synthetically useful, are too broad a subject and are best left to a separate review.

Until the 1960's, elemental fluorine had been considered too reactive and dangerous to be practical for the fluorination of organic molecules. Fluorine is such a strong oxidizing agent that it reacts with almost any organic compound, usually exothermically, and often with explosive results.[4] The poor solubility of fluorine results in reactions that proceed at the liquid–gas interface.[13] This behavior, coupled with the exothermic nature of the reaction, allows localized hot spots to form which can promote unwanted side reactions.[14] To minimize this effect, solutions of fluorine diluted with inert gases such as nitrogen or argon are usually employed to provide more control and selectivity.[15] Synthetic applications have greatly increased with the commercial availability of these diluted solutions and also with the development of various moderating agents.

II. Addition of Fluorine to π Bonds

A. C=C

1. Alkenes

The addition of fluorine to various alkenes is summarized in Table I. Under appropriate reaction conditions, elemental fluorine exhibits reactions that are associated with electrophilic processes[16] in which substrates act as nucleophiles towards fluorine. Merritt[17-20] first recognized the electrophilic nature of F_2 in his investigation of the addition to alkenes. Fluorination of *cis*-stilbene with 1 equiv of F_2 at low pressure and temperature in fluorocarbon solvents resulted in products which show that the syn mode of addition predominated. Merritt[18] ruled out a free-radical pathway

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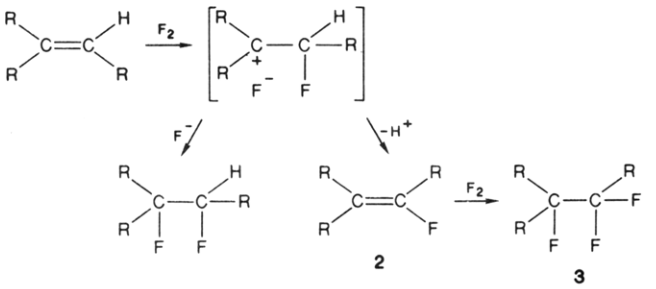
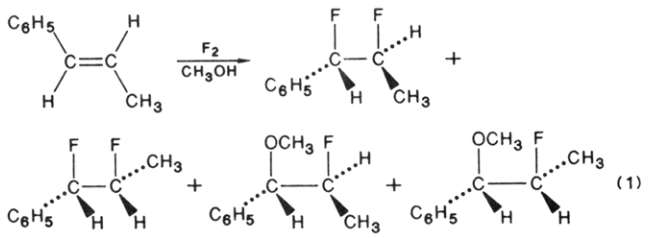
based on the observed selectivity and the reaction conditions and proposed a concerted pathway to account for the experimental observations. However, a mechanism that proceeds by way of a tight ion pair,

SCHEME I



such as that proposed for acetyl hypofluorite[21] and fluoroxytrifluoromethane[22] additions, is more reasonable (Scheme I). The unstable α-fluoro carbocation gives rise to the vinyl fluoride (**2**) by loss of a proton or adds fluoride to give the vicinal difluoride (**1**). The vinyl fluoride was the precursor to the trifluoro products (**3**) observed (entries 2, 5, 6, and 13), as shown by the further fluorination of 1,1-diphenyl-2-fluoroethylene (entry 3). Propenylbenzenes (entries 5 and 6), which would lead to a less stabilized intermediate than the other compounds studied, produced the smallest amount of the trifluoride.[20] Further support for the mechanism is found in the fluorination of *trans*-1-phenylpropene in methanol at −78 °C[20] which gave 44% *threo* and 7% *erythro* difluoro adducts. In addition, a 49% mixture of the solvent incorporated *erythro*- and *threo*-1-methoxy-1-phenyl-2-fluoropropanes was observed (eq 1). Under the same conditions, *cis*-1-



(1)

phenylpropene gave 12% *threo* and 38% *erythro* adducts and 50% of the ethers.

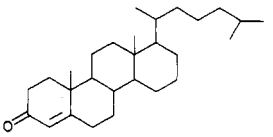
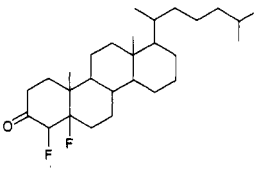
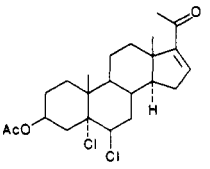
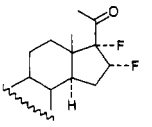
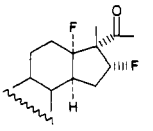
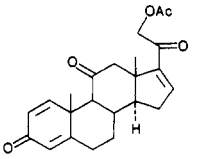
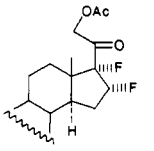
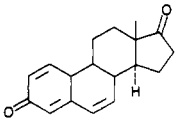
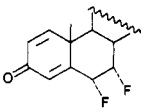
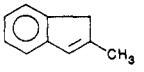
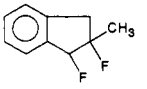
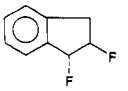
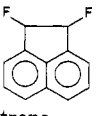
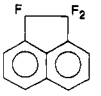
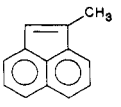
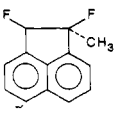
Direct addition of fluorine to steroidal olefins has also been studied[19,23] (entries 7–10). The 16α-fluoro-17β-methyl adduct of entry 8 was assumed to be formed by Kagi–Miescher rearrangement.[23] The vicinal product of entry 8, the 16α,17α-difluoro adduct, displayed the expected syn addition of fluorine to the double bond. Addition was directed to the α face of the substrate because of the sterically hindered nature of the β face.

2. Heterocycles

Generally, $CFCl_3$ is the solvent of choice for many selective fluorinations; however solubility sometimes proves to be a problem. Purines and pyrimidines exhibit poor solubility in $CFCl_3$ and require an alternative solvent. Acetic acid has been found to be an ideal solvent, although on occasion other solvents such as methylene chloride,[25] hydrofluoric acid,[26] water,[27] and pyridine[28] have been used. The latter solvents give lower product yields and are not generally employed. However, in the case of 2-pyrimidinone a 38% yield of the 5-fluoro adduct was formed in liquid HF whereas only 5–10% was obtained in acetic acid.[26]

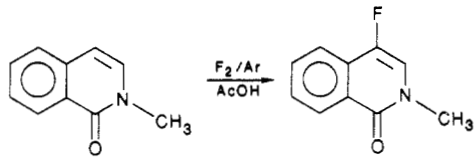
The isoquinoline ring system could not be fluorinated, but fluorination of the related 2-methylisocarbostyril

TABLE I. Addition of Fluorine to Alkenes in Freon

entry	substrate	product	% yield	ref
1	*trans*-EtOCOCH=CHCO$_2$Et	EtOCOCHFCHFCO$_2$Et	<10	24
2	Ph$_2$C=CH$_2$	Ph$_2$CFCH$_2$F	14	18
		Ph$_2$C=CHF	78	
		Ph$_2$CFCHF$_2$	8	
3	Ph$_2$C=CHF	Ph$_2$CFCHF$_2$	93	18
4	*cis*-PhCH=CHPh	*meso*-PhCHFCHFPh	79	18
		dl-PhCHFCHFPh	16	
5	*trans*-PhCH=CHCH$_3$	PhCHFCHFCH$_3$ *erythro:threo* 31:69	80–90	20
		PhCHFCF$_2$CH$_3$	<3	
6	*cis*-PhCH=CHCH$_3$	PhCHFCHFCH$_3$ *erythro:threo* 78:22	80–90	20
		PhCHFCF$_2$CH$_3$	<3	
7			60–70	19
8			40	20
			12	
9			10	23
10			10[a]	23
11		 (cis and trans)	43	17
12			32	17
13				
		trans	11	
		cis	35	17
				
14			20	17

[a] In CF_3CH_2OH.

(4) was successful.[29] In acetic acid, a 54% yield of the 4-fluoro compound was isolated as shown in eq 2.

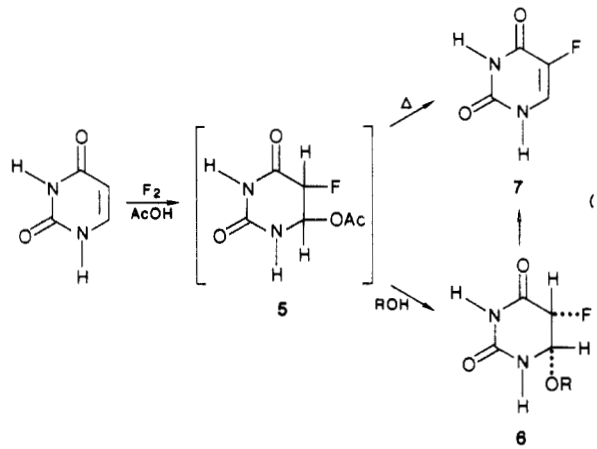


(2)

4

Similarly, 1-methyl-5-fluoro-2-pyridone was prepared in 43% yield from 1-methyl-2-pyridone.[29]

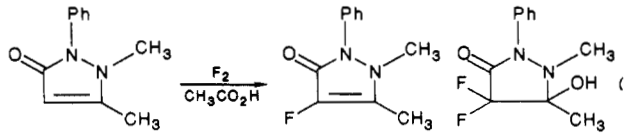
A nitrogen-diluted solution of fluorine reacted with pyrimidines for the synthesis of 5-fluorouracil, 6-fluorothymine, and many other important biochemical derivatives.[25-28,30-41] In the synthesis of 5-fluorouracil, Cech[25] proposed that the reaction was initiated by syn addition of fluorine across the double bond, followed by solvent assisted elimination of F^-. In acetic acid, an unstable acetoxy intermediate (**5**) is formed in this manner (eq 3). The addition of an alcohol to the reaction mixture, both prior to and after the evaporation of solvent, gave the corresponding stable 5-fluoro-6-alkoxy-5,6-dihydrouracil derivative (**6**). NMR experiments and a crystal structure show that the orientation of the fluorine is cis with respect to the alkoxy group.[42] The alkoxy derivatives can be readily transformed to 5-fluorouracil (**7**) as indicated in eq 3. Yields for the fluorination of a number of substrates ranged from 50% to quantitative.[30] Recently, Visser et al.[41] have investigated the products of the reaction of F_2 and acetyl hypofluorite with cytosine as well as uracil using ^{18}F as a tracer. In addition, many nucleosides of uracil derivatives have been fluorinated in the same manner with high yields.[25,28,31,32,34,40]



(3)

5 6 7

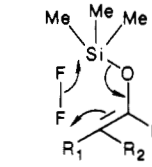
Antipyrine (**8**), a lipophilic compound that has been shown to have a high uptake by the brain, can be selectively fluorinated in an aqueous medium[27] or in glacial acetic acid to give the 4-fluoro derivative (**9**).[43] The preparation of its radiolabeled fluorinated analogue is expected to serve as a means for measurement of regional cerebral blood flow.[43] In glacial acetic acid significant amounts of the 4,4-difluoro adduct (**10**)[44]



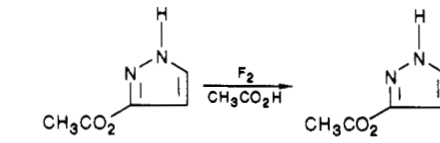
(4)

8 9 10

SCHEME II



were also formed, increasing with increased fluorine to substrate ratios (eq 4). In a related reaction, fluorination of 3-carbomethoxypyrazole (**11**) with fluorine in acetic acid at 20 °C led to the formation of 4-fluoro-3-carbomethoxypyrazole (**12**) in 75% yield based on a 20% conversion of the starting material (eq 5).[45]



(5)

11 12

3. Enol Derivatives

In an attempt to prepare α-fluorocarbonyl compounds, a number of enol derivatives have been fluorinated; the results are compiled in Table II. For example, fluorination of the enolized 3-substituted pyruvate esters with 10% fluorine in nitrogen (entries 2–6), gave the α-fluorinated ketone derivatives in yields as high as 70%. Attempts to fluorinate the related free acid, sodium salt, and trimethylsilyl enol ether (entry 7) were unsuccessful.[46] Direct fluorination of unenolized pyruvates was also unsuccessful and yielded complex product mixtures.[46]

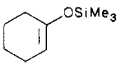
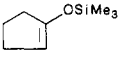
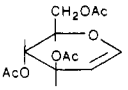
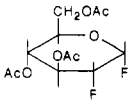
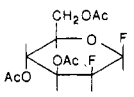
Purrington et al.[47] were able to prepare a number of α-fluoroaldehydes and ketones (entries 8–17) from trimethylsilyl derivatives in relatively short reaction times (3.5 h). The reactions were run in $CFCl_3$ with 5% fluorine in nitrogen at −78 °C. The silylated enol of the substrate readily lost innocuous, volatile trimethylsilyl fluoride to give the α-substituted product. The reaction may proceed via a six-membered cyclic transition state as shown in Scheme II.

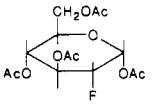
Silyl enol ethers of methyl ketones tended to give overfluorinated products and required shorter reaction times (2 h) as well as ultrapure silyl enol ether to obtain the monosubstituted product.[47] Fluorination of silyl ketene acetals (entry 19) has also been performed.[48]

Direct fluorination of enol acetates has not proven to be a good route to α-fluorocarbonyl compounds. Rozen[49] reported that this reaction gave complex mixtures with no definite isolatable products. However, the simplest case, vinyl acetate[24] gave a 12.5% yield of α-fluoroacetaldehyde after hydrolysis (entry 1).

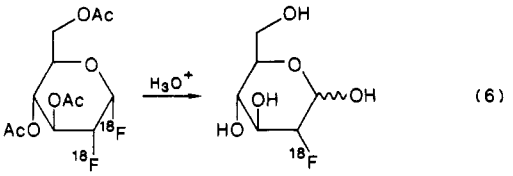
The addition of elemental fluorine to double bonds has found applications in many other areas of organic chemistry, including the synthesis of modified carbohydrates.[50-54] Fowler et al.[50] have observed the syn addition of fluorine (2.5% in argon) to 3,4,6-tri-*O*-acetyl glucal, in $CFCl_3$ at −78 °C for the preparation of 1,2-difluorides (entry 18). When the fluorination was performed in acetic acid, 3,4,6-tri-*O*-acetyl-2-deoxy-2-fluoro-α-D-glucopyranosyl acetate was also formed.[51] 2-Deoxy-2-[^{18}F]fluoro-D-glucose (**14**), a compound that is used as a tracer for glucose metabolism in man, has

TABLE II. Addition of Fluorine to Enol Derivatives

entry	substrate	product	% yield	ref
1	CH_2=CHOCOCH$_3$	$CH_2FCHFOCOCH_3$[a] + CH_2FCHO[a]	20	24
	R_2CH=C(OH)CO_2R_1	$R_2CHFCOCO_2R_1$		
2	R_1 = Et, R_2 = Ph	R_1 = Et, R_2 = Ph	40	46
3	R_1 = Me, R_2 = Ph		50–60	46
4	R_1 = Me, R_2 = *p*-PhCl		65	46
5	R_1 = Et, R_2 = *p*-PhNO$_2$		46	46
6	R_1 = Et, R_2 = *n*-PrCO		70	46
7	PhCH=C(OSiMe$_3$)CO_2CH_3	PhCHFCOCO$_2$CH$_3$	0	46
8	PhCH=CHOSiMe$_3$	PhCHFCHO	72	47
9	$CH_3(CH_2)_4$CH=CHOSiMe$_3$	$CH_3(CH_2)_4$CHFCHO	70	47
10	PhC(CH$_3$)=CHOSiMe$_3$	PhCF(CH$_3$)CHO	52	47
11	Ph$_2$C=CHOSiMe$_3$	Ph$_2$CFCHO	57	47
12	PhCH$_2$CH=CHOSiMe$_3$	PhCH$_2$CHFCHO	70	47
13	PhC(OSiMe$_3$)=CHCH$_3$	PhCOCHFCH$_3$	59	47
14			78	47
15			73	47
16	PhC(OSiMe$_3$)=CH$_2$	PhCOCH$_2$F	61	47
17	PhCH=C(OSiMe$_3$)Ph	PhCHFCOPh	64	47
18		 	40[b] 26	50
19	PhCH=C(OEt)OSiMe$_3$	PhCHFCO$_2$Et	71	48

[a] Aqueous workup. [b] In acetic acid,  is also formed (ref 51).

been prepared by acid hydrolysis of the difluoride (**13**) in approximately 20% overall yield, (eq 6).[50] When



(6)

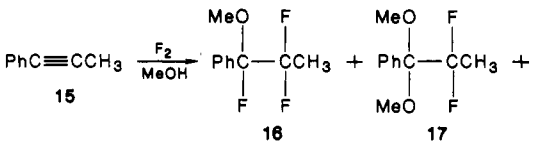
13 **14**

using $^{18}F_2$, an 8% radiochemical yield of **14** was obtained in only 110 minutes, a time equivalent to the half-life of ^{18}F.[54]

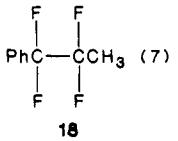
B. C≡C

Addition of elemental fluorine to alkynes at −78 °C under the conditions used for the olefin addition reactions[17-19] gave various products depending on the nature of the solvent used.[55] When $CFCl_3$ (or Freon 11) was employed, the acetylenic compounds were tetrafluorinated. Reducing the amount of fluorine to less than a stoichiometric amount did not produce any difluoro adduct. However, the reaction of substituted tolanes with fluorine produced complex product mixtures including *cis*- and *trans*-α,α′-difluorostilbenes.[56] Rearrangement products including 1,2,2-trifluoro-1,2-diarylethanes, 1,2,2,2-tetrafluoro-1,1-diarylethanes, and 1,1-difluoro-2,2-diarylethenes were observed. Although the 1,1,2,2-tetrafluoroethanes were the major products at −78 °C, the others predominated at 0 °C. McEwen and co-workers[56] believe that the reaction proceeds by way of a fluorovinyl radical with a partial positive charge on carbon based on product distribution, a small negative ρ, and inhibition of fluorination by oxygen.

Merritt[55] observed a number of products when the fluorination was run in methanol. 1-Phenyl-1-propyne (**15**) gave the trifluoro ether (**16**, 57%) and the dimethyl ketal (**17**, 20%) as well as the tetrafluoro adduct (**18**, 23%) (eq 7). The products from solvent incorporation,



15 **16** **17**

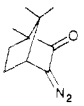
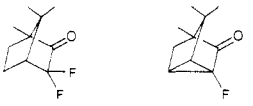
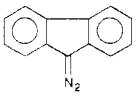
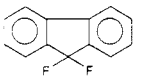
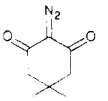
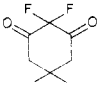
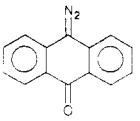
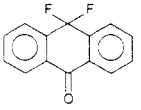
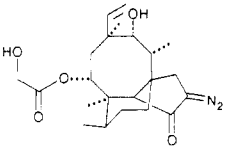
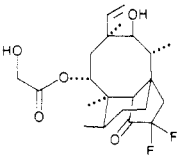


(7)

18

where the alkoxy group(s) substituted only at the position that would support a positive charge demonstrates the polar nature of the addition. Compounds of types **16** and **17** were readily hydrolyzed with a 10% solution of sulfuric acid at 50 °C to give α,α-difluoro ketones.

TABLE III. Geminal Fluorination of Diazo Compounds

entry	substrate	product(s)	% yield	ref
1	*t*-BuCOCN$_2$H	*t*-BuCOCHF$_2$	14–15	59
2		 7:3	low	59
3	Ph$_2$C=N$_2$	Ph$_2$CF$_2$	71	58
4			88	58
5			80	58
6			94	58
7	PhCOCN$_2$Ph	PhCOCF$_2$Ph	79	58
8	(EtOCO)$_2$C=N$_2$	(EtOCO)$_2$CF$_2$	70	58
9			65	58
10			31	11

C. C=N

1. Imines

The low-temperature fluorination of benzaldehyde imines with elemental fluorine gave α,α-difluoro secondary fluoramines and α-fluoramines, as shown in eq 8.[57] An electrophilic process was postulated for the

$$\mathrm{PhCH{=}NR} \xrightarrow{F_2} \underset{\mathbf{19}}{[\mathrm{PhCHFNFR}]} \rightarrow \underset{\mathbf{20}}{\mathrm{PhCF{=}NR}} + \underset{\mathbf{21}}{\mathrm{PhCF_2NFR}} \quad (8)$$

addition that resulted in the intermediate vicinal difluoride (**19**). The weak N–F bond (64.5 kcal/mol) coupled with the relative acidity of the benzylic proton resulted in dehydrofluorination even at −78 °C to produce compound **20**. A second mole of fluorine added to **20** giving the trifluorinated compound **21**.

The α,α-difluorofluoramines could be purified by chromatography on an untreated silica gel column. However, when the silica gel was first dried under vacuum at 160 °C, conversion to the *N*-fluoroimine (**22**) was observed in 25% yield (eq 9). Hydrolysis of the trifluoro adducts led to *N*-fluoro-*N*-alkylbenzamides (**23**) as shown in eq 10.[57]

$$\underset{\mathbf{21}}{\mathrm{PhCF_2NFR}} \rightarrow \underset{\mathbf{22}}{\mathrm{PhCF{=}NF}} \quad (9)$$

$$\underset{\mathbf{21}}{\mathrm{PhCF_2NFR}} \xrightarrow{H_2O} \underset{\mathbf{23}}{\mathrm{PhCONFR}} \quad (10)$$

2. Diazo and Related Compounds

Geminal difluorides have been prepared from diazo compounds as shown in Table III. The reaction of fluorine diluted with nitrogen in Freon 11 at −70 °C proceeds for a variety of diazo compounds, however, fluorination was always adjacent to either an aromatic ring or a carbonyl group.[11,58,59] Neither the carbonyl functionality nor any of the C–H bonds were affected in the reactions, suggesting that a free radical pathway for the reaction was unlikely. In addition, the enthalpy for the reaction, calculated to be −154 kcal/mol, may explain the selectivity observed. The mechanism in Scheme III might be considered.

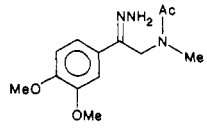
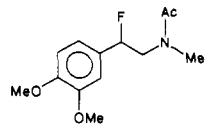
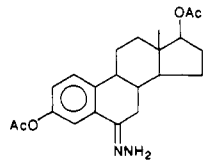
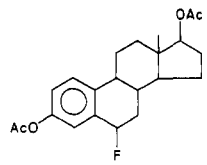
In a related reaction, a number of aryl ketone hydrazones (Table IV) have been shown to react with dilute molecular fluorine to form monofluoro and geminal difluoro derivatives.[60] Oxidation of the hydrazone gave a diazo intermediate, which was found to react with a molecule of HF (generated during the oxidation) to form the monosubstituted product or with elemental fluorine to produce the geminal difluoride. The hydrazones of benzaldehyde, cyclohexanone, and cyclopentanone did not give fluorinated products.

III. Nitrogen Derivatives

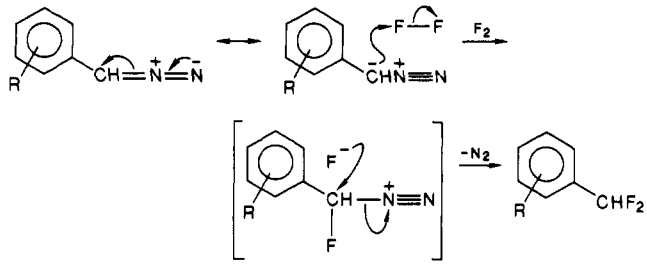
A. Isocyanates

Merritt[61] found that alkyl isocyanates, unlike imines, did not add fluorine to the double bond. Initial side

TABLE IV. Fluorination of Aryl Ketone Hydrazones

entry	substrate	products	% yield	ref
1	$Ph_2C{=}NNH_2$	Ph_2CHF	11	60
		Ph_2CF_2	69	
2	$Ph(CH_3)C{=}NNH_2$	$PhCHFCH_3$	45	60
		$PhCF_2CH_3$	34	
3	$PhCH_2CPh{=}NNH_2$	$PhCHFCH_2Ph$	45	60
		$PhCF_2CH_2Ph$	38	
4			15	60
5			38	60

SCHEME III



chain fluorination was followed by loss of fluorophosgene (COF_2) and fluorination on nitrogen as shown for *n*-propyl isocyanate in Scheme IV. The product mixture was complicated by the reaction of the isocyanate with HF. *N*-Propylcarbamyl fluoride (**24**) was found to be the precursor of *N*-fluoro-*N*-propylcarbamyl fluoride (**25**) and could be excluded when a strong HF scavenger such as sodium carbonate was employed.[61]

B. Isonitriles

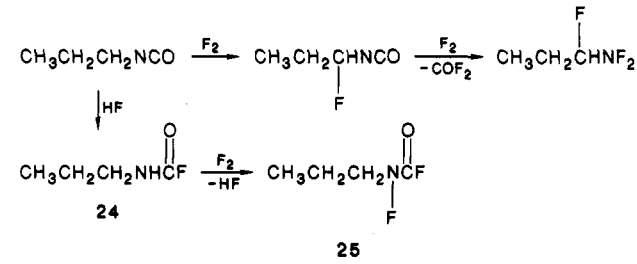
The reaction of organic isonitriles[62] was shown to give primarily aza analogues of fluorophosgene (**26**) which were used in situ due to the susceptibility to hydrolysis. Traces of HF in the reaction mixture resulted in addition and dimerization products (**27**) and (**28**) (eq 11).

$$RN{\equiv}C \xrightarrow{F_2} \underset{\mathbf{26}}{[RN{=}CF_2]} \rightarrow \underset{\mathbf{27}}{RNHCF_3} + \underset{\mathbf{28}}{RN{=}CFNRCF_3} \quad (11)$$

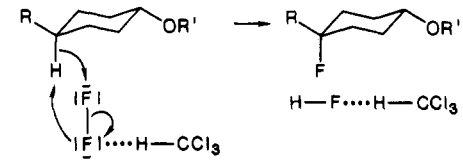
C. Amides

Since the Grakauskas review,[4] only two papers have addressed the fluorination of amides. Difluoramino carboxylic acids have been prepared from their corresponding lactams with elemental fluorine.[63,64] The NF_2 group is thought to be a better isostere for CH_3 than CH_2F in the preparation of fatty acid cardiac imaging agents, because it introduces less polarity into the aliphatic chain as indicated by chromatography.[63] For example, 15-difluoraminopentadecanoic acid (**30**) was prepared by treating the corresponding lactam (**29**) in

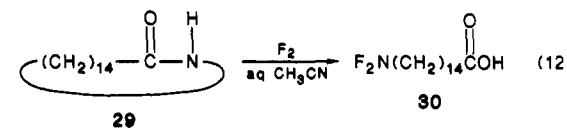
SCHEME IV



SCHEME V



acetonitrile/water (9:1) with a fluorine (2% in nitrogen) in 50% yield (eq 12—isolated as the methyl ester for



analytical purposes). Jewett and Ehrenkaufer found that hydrolysis of the difluoramine group at pH 8 was slow with respect to the half-life of ^{18}F.[63]

IV. Substitution at Unactivated C–H Positions

In a process reminiscent of the reaction between ozone and hydrocarbons,[65] dilute elemental fluorine has been shown to selectively replace tertiary hydrogens with retention of configuration for a number of unactivated substrates.[3,66-75] The reactivity of the tertiary C–H bond in electrophilic substitution has also been observed by Olah during the deuterolysis of alkanes with superacids.[76]

The fluorinations were conducted at low temperatures with varying amounts of chloroform in Freon to take advantage of the slight differences in the electron densities of the C–H bonds and optimize product yields. In unstrained molecules the electron density at a tertiary hydrogen is greater than that at secondary or primary so the hydrogen is more vulnerable to substitution. The mechanism proposed for this substitution is illustrated in Scheme V. Chloroform can also act as a free-radical scavenger,[68] which helps prevent overfluorination. When a nonpolar reaction medium was used (pentane or $CFCl_3$ for example), radical processes interfered and complicated product mixtures resulted.[67] The products of fluorination of various substrates are compiled in Tables V and VI.

Electron withdrawing substituents decrease electron density in molecules and affect the fluorination of nearby tertiary positions. When the tertiary position is β to an ester, the yield of fluorinated product was about half that obtained when it was γ (Table V, entries 22 and 28). Since inductive effects fall off rapidly with distance, field effects may play an important role. Although entries 23 and 24 (Table V) both show about 60% fluorination, the reaction was significantly slower

TABLE V. Tertiary Hydrogen Fluorinations Resulting In Mainly One Product

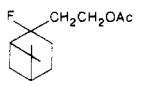
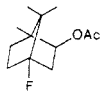
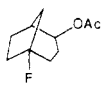
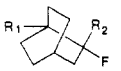
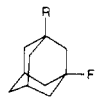
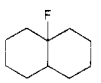
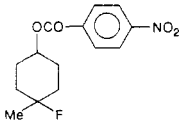
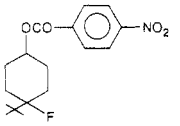
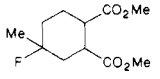
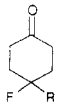
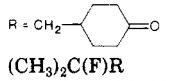
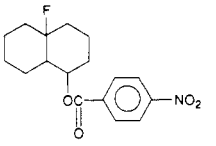
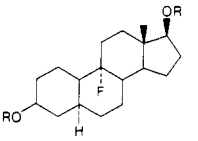
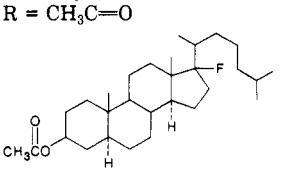
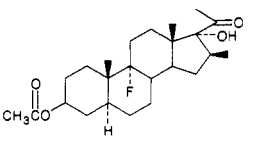
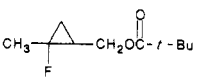
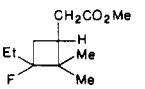
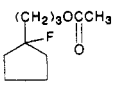
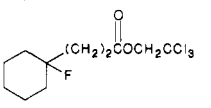
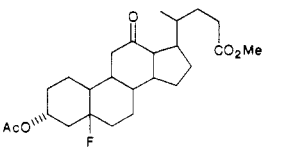
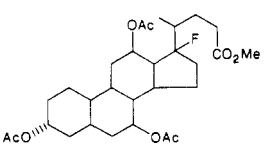
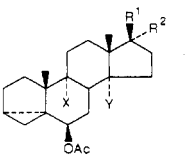
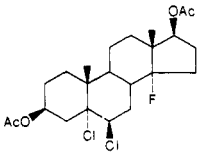
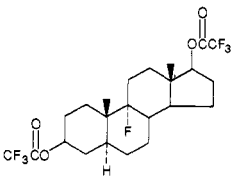
entry	product	% yield	ref
1		40	66
2		20	66
3		75	66
4		20	66
			
5	$R_1 = R_2 = H$	50	66
6	$R_1 = OMe$, $R_2 = Et$	20	66
			
7	R = H	71–90	73, 75
8	R = OH	70	66
9	R = p-$O_2CC_6H_4NO_2$	90	66
10	R = $NHCOCF_3$	83	73, 75
11		70	67
			
12	cis	80	67
13	trans	90	67
14	$CH_3CH_2C(CH_3)(F)(CH_2)_5CH_3$	60	67
			
15	*trans*-Me + p-$OCOC_6H_4NO_2$	60	68
16	*cis*-Me + p-$OCOC_6H_4NO_2$	65	68
			
17	*trans*-*t*-Bu + p-$OCOC_6H_4NO_2$	50	68
18	*cis*-*t*-Bu + p-$OCOC_6H_4NO_2$	83	68
19		25	74
			
20	R = CH_3	20	74
21		10	74
	$(CH_3)_2C(F)R$		
22	R = $(CH_2)_2CO_2CH_2CCl_3$	55	69
23	R = $(CH_2)_3CH(CH_3)OCOC_6H_4NO_2$-$p$	65	69
24	R = $(CH_2)_2OCOC_6H_4NO_2$-p	60	69
25	R = $(CH_2)_3CH(CH_3)(CH_2)_2OCOC_6H_4NO_2$-$p$	30	69
26	R = $(CH_2)_2O_2CCCl_3$	65	69
27	R = $(CH_2)_2OCH_2O(CH_2)_2OCH_3$	20	69
28	R = $CH_2CO_2CH_2CCl_3$	25–30	69
29		<50	67
	$MeO_2C(CH_2)_mC(Me)(F)(CH_2)_nCO_2Me$		
30	$m = n = 1$	2	74
31	$m = 1$, $n = 2$	10	74
	$CH_3CO_2(CH_2)_mC(CH_3)(F)(CH_2)_nO_2CCH_3$		
32	$m = n = 2$	37	74
33	$m = 2$, $n = 3$	3	74
			
34	R = $CF_3C{=}O$	34	3, 75
35	R = $CH_3C{=}O$	50	3
36		25	3, 70
37		50	3, 75
38		0	71
39		30	71
40		40	71
41		60	71
42		30	71
43		25	72
44		25	72
			
45	$R^1 = COCH_3$, $R^2 = X = H$, $Y = F$	37	75
46	$R^1 = R^2 = O$, $X = F$, $Y = H$	20	75

TABLE V (Continued)

entry	product	% yield	ref
47		27	75
48		34	75

for the compound where the tertiary hydrogen was closer to the electron-withdrawing group. When there were two tertiary positions within the molecule, as with 3,7-dimethyl-1-octyl-*p*-nitrobenzoate (entry 25, Table V), only fluorination at the more remote tertiary position was observed.

In Table VI, two or more monofluorinated products were observed because there were two or more tertiary hydrogens available for substitution. The reaction generally only gave a monofluorinated product even when two tertiary centers were available in the molecule. Once substituted, the electronegative fluorine decreased the electron density available at the other tertiary position (Table VI, entries 4 and 5).

The p character of the C–H bond in rings varies with ring size due to differing amounts of bond strain. This is exemplified by the increasing reactivity of tertiary hydrogens as ring size increases from three to six carbons, entries 38–41 (Table V). Competition from radical fluorination was significant in larger ring systems due to the increased ratio of nontertiary to tertiary hydrogens (entry 42). Molecular fluorine also reacted with unactivated polycyclic compounds selectively fluorinating tertiary bridgehead positions (entries 2, 4, 7–10).

Susceptibility of ethers to oxidation by fluorine (entry 27) resulted in decreased hydrogen substitution as well as carbonyl-containing byproducts.[69]

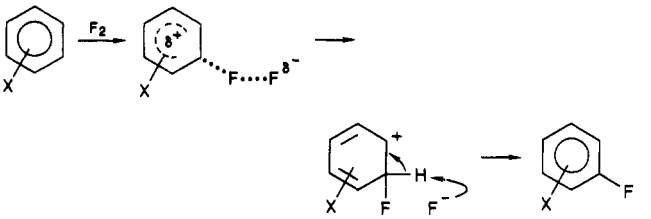
The substitution of tertiary hydrogens with fluorine has been extended to fluorination of various steroids (entries 34–37). Monofluorination has been accomplished at the C-5 (β), C-14 (α), and C-17 (α) positions of bile acids,[72] the C-9 center in corticoids, the C-14 position in cardenolides, and the C-17 for conversion of plant sterols into steroids of biomedical interest.[3] The highly polar transition state and substituent inductive effects at proximal and/or remote sites to two or more tertiary hydrogens can be used to predict the fluorination products.[3]

V. Electrophilic Aromatic Substitution

A. Evaluation of F^+ as a Reactive Intermediate

The development of fluorinating agents that have a tendency to follow electrophilic patterns of substitution with a variety of substrates has prompted the question, "Does the fluoronium (F^+) ion exist?" The many examples of syn addition of fluorine to double bonds[17-19] suggest the absence of a fluoronium ion. Olah and co-workers,[77] have ruled out a bridged fluoronium species in the equilibration of the 2,3-dimethyl-3-fluoro-2-butyl cation in superacid solution on the basis of spectral observations. Christie[78,79] theorizes that the fluoronium ion cannot exist because no group of atoms,

SCHEME VI



even those containing fluorine, should have a greater electronegativity than fluorine, the most electronegative atom. However, Cartwright and Woolf[80] argue that the existence of NF_4^+ and XeF^+ salts infer the presence of positive fluorine. With regard to monofluorination of aromatic rings, theoretical studies have compared the stability of a bridged fluoronium ion and an open protonated fluorobenzene. Hehre and Hiberty[81] have shown that a bridged fluoronium ion intermediate would lie at an energy maximum, some 20.5 kcal/mol higher than a protonated fluorobenzene.

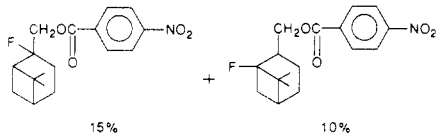
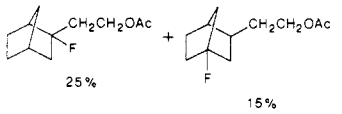
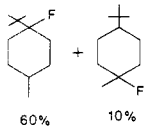
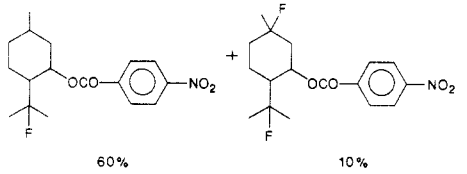
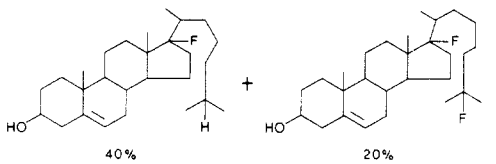
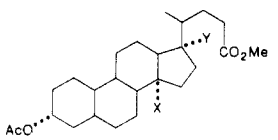
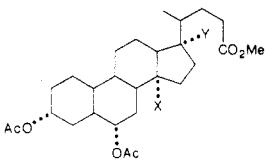
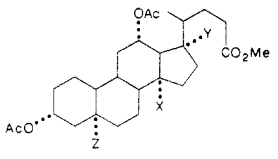
B. Reaction of Aromatic Substrates

Early attempts to substitute aromatic rings with elemental fluorine were plagued with problems. The introduction of dilute solutions of molecular fluorine has greatly enhanced the ability to control reactions of this type. Cacace et al.[13] have performed aromatic substitutions on a variety of aromatic rings with molecular fluorine (<0.76% F_2 in N_2), at low conversions (0.01%), near the lower limit of analytical sensitivity. The reactions run in $CFCl_3$ at −78 °C show first-order kinetics under these conditions, dependent only on the amount of aromatic substrate present.[13,82] Fluorination positions on substituted benzene rings mimicked the pattern generally observed for electrophilic aromatic substitution.[13,83] A plot of the partial rate factors vs. σ^+ constants for polar aromatic substitution gave a ρ^+ value of −2.45 (correlation coefficient of 0.993), supporting the proposed mechanism shown in Scheme VI. For these low-temperature reactions, radical processes could be discounted.

Grakauskas[83] was able to fluorinate several aromatic compounds on a synthetically useful scale. The substitution pattern also suggested electrophilic addition. The reactions were generally run in acetonitrile at −20 °C, and for methyl benzoate gave 74% *p*-, *o*-, *m*-fluorobenzoates (1:3:5, respectively).

Sams et al.[14] have utilized molecular sieves to minimize the possibility of secondary reactions with F_2. As a result, polymer formation that has been commonly observed with increasing conversion to product was absent. After optimization of the reaction conditions (−78 °C, no solvent), Sams obtained almost 20% *o*- and *p*-difluorobenzenes from fluorobenzene.

TABLE VI. Tertiary Hydrogen Fluorinations Resulting in Two or More Products

entry	product mixtures	ref
1	 15% + 10%	66
2	 25% + 15%	66
3	 60% + 10%	67
4	 60% + 10%	67
5	$(CH_3)_2C(F)(CH_2)_3CH$-$(CH_3)(CH_2)_3CH(CH_3)$-$(CH_2)_3CH(CH_3)_2$ (25%) + $(CH_3)_2CH(CH_2)_3C(F)$-$(CH_3)(CH_2)_3CH(CH_3)$-$(CH_2)_3CH(CH_3)_2$ (25%)	67
6[a]	 40% + 20%	3, 70
7	 X = F, Y = H; 15% X = H, Y = F; 40%	72
8	 X = H, Y = F; 15% X = F, Y = H; 25%	72
9	 X = Z = H, Y = F; 10% Y = Z = H, X = F; 10% X = Y = H, Z = F; 10%	72

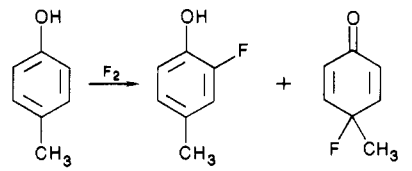
[a] Dichloride was treated with fluorine, followed by reduction with Zn and alkaline hydrolysis.

Misaki[84,85] has monofluorinated a variety of oxygenated aromatic substrates in high yields using molecular fluorine (11% in nitrogen). Fluorination of a 10% solution of phenol at −20 °C, at 10% conversion to the monofluorinated product gave fluorophenols with an ortho to para product ratio of 22:1. However, at greater conversions (51–56%), under identical reaction conditions the ortho to para ratio was 3.6:1, an indication that there was some further reaction of the ortho product with time. Apparently, as the conversion increased, some of the ortho isomer was changed to an unidentified polymeric material, an experimentally observed byproduct. Temperature also seemed to have an effect on the isomeric ratios. Misaki found that at 10% conversion and at 10 °C, phenol yielded only a 10:1 ortho to para ratio. In addition, at lower temperatures greater conversions and fewer sunsequent reactions were observed.

TABLE VII. Fluorination of Substituted Phenols RPhOH in CH_3CN

R	T, °C	% conversion	products, %	ref
2-CH_3	−20	70.8	(4-F) 27.5; (6-F) 22.5	84
3-CH_3	−20	67.7	(4-F) 20.7; (2-F + 6-F) 46.4	84
4-CH_3	−20	78.0	(**32**) 38.4; (**33**) 23.1	84
4-CO_2H	−10	63.3	(2-F) 59.4; (2,6-F_2) 14.4	85
2-CO_2H	−10	79.0	(4-F) 55.9; (4,6-F_2) 21.0	85
2-CHO	−10	62.9	(4-F) 32.1; (6-F) 22.1, (4,6-Fe_2) 5.1	85
4-Ph	−10	–	(2-F) 50.1; (2,6-F_2) 21.5	85
H	−20	56.1	(2-F) 38.9; (4-F) 10.7	84

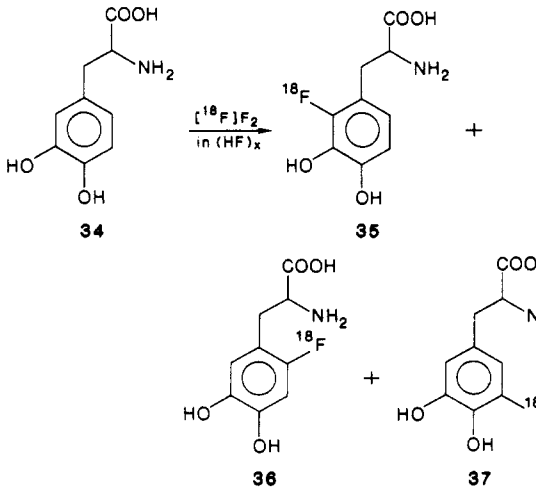
Misaki[84] also investigated the fluorination of the various substituted phenols. Those results are summarized in Table VII. *p*-Cresol (**31**) produced a very interesting side product in addition to the expected *o*-fluoro derivative (**32**) (eq 13). 4-Fluoro-4-methyl-



31 **32** **33** (13)

2,5-cyclohexadienone (**33**) was observed in yields as high as 42.1% in tetraglyme at −20 °C. Interestingly, he[85] observed fluorination of salicylaldehyde, but oxidation and fluorination of salicyl alcohol. Misaki has also used anhydrous HF as a solvent for the fluorination of several phenolic compounds.[85] Salicyclic acid gave a 72.6% yield of 3-fluoro salicylic acid, while phenyl salicylate gave a mixture of 3- and 5-fluorophenyl salicylates in 88.6% yield.

When radiolabeling was applied to L-dopa (**34**) to measure the metabolism of the neurotransmitter dopamine in the brain, a 0.5% solution of $[^{18}F]F_2$ at −65 °C in HF gave a 5.8% chemical yield and a 3.0% radiochemical yield of 6-[^{18}F]fluoro-L-dopa (**35**) (eq 14).[86]



34 **35** **36** **37** (14)

Major byproducts were the 2-fluoro and 5-fluoro-L-dopa in 12% (**36**) and 1.7% (**37**) yields, respectively. Liquid

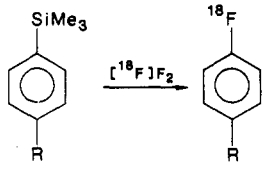
TABLE VIII. Fluorination of Organometallic Compounds in $FCCl_3$ with F_2 at -78 °C

MArR		% yield,	
M	R	radiochem (chem)	ref
$Sn(n\text{-}Bu)_3$	$3,4(OCH_3)_2$	56	87
$Sn(n\text{-}Bu)_3$	$4\text{-}OCH_3$	72	87
$Sn(n\text{-}Bu)_3$	$4\text{-}CH_3$	82	87
$Sn(n\text{-}Bu)_3$	$3\text{-}CH_3$	58	87
$Sn(n\text{-}Bu)_3$	$2\text{-}CH_3$	54	87
$Sn(n\text{-}Bu)_3$	H	72	87
$Sn(n\text{-}Bu)_3$	4Cl	>95	87
$Sn(n\text{-}Bu)_3$	4F	>95	87
$SiMe_3$	H	20 (23)	90
$SiMe_2Bu$	H	21 (24)	90
$SiMePh_2$	H	14 (16)	90
$SiMe_3$	4-CN	14 (16)	90
$SiMe_3$	4-Cl	14 (16)	90
$Sn(n\text{-}Bu)_3$	H	38 (70)	89, 91
$SnPh_3$	H	8 (15)	89, 91
$SiPh_3$	H	(2.4)	89
$PbPh_3$	H	(0)	89
HgPh	H	(26)	89
$SiMe_3$	H	24.5	88
$SiMe_3$	$4\text{-}CH_3$	27.9	88
$SiMe_3$	$4\text{-}OCH_3$	21.3	88
$SiMe_3$	4-Cl	21.5	88
$SiMe_3$	$4\text{-}SiMe_3$	21.6	88
HgPh	H	(40)	92

HF was chosen to minimize the oxidation of L-dopa which is initiated by the deprotonation of the hydroxyl group.

The use of fluorine to cleave aryl metal bonds is summarized in Table VIII. $[^{18}F]F_2$ gave exceptional radiochemical yields for the *p*-chloro and *p*-fluoro tin substrates (>95%).[87] Yields of the aryl fluoride were generally higher when the reaction was run in CCl_4 at 0 °C rather than $CFCl_3$ at -78 °C.

A number of aryltrimethylsilanes have been successfully substituted at the ipso position with both radioactive elemental fluorine ($[^{18}F]F_2$)[88-90] (eq 15) and



(15)

acetyl hypofluorite ($CH_3COO^{18}F$).[87,88] (See section VIII.A.1). Reaction yields were generally low (under 30%) and gave various F for H substitutions. In general, $[^{18}F]F_2$ gave the higher radiolabeled product yields, a result that was attributed to the milder electrophilic character of the acetyl hypofluorite. In addition, the reaction was much cleaner with F_2 as a reagent. The substitution ratios for fluorination at silicon vs. hydrogen were dependent on the substituent para to the leaving trimethylsilyl group. When the group was strongly ring activating, F for H substitution increased relative to silyl substitution.

VI. Metathetical Reactions

Rozen has found that elemental fluorine (1.5% in nitrogen) reacts with both iodo- and bromoadamantanes in $CFCl_3$ to give the corresponding fluoro derivative in yields as high as 99%.[93] 1-Bromoadamantan-4-one, 3,5-dimethyl-1-bromoadamantane and methyl (3-bromo-1-adamantyl)acetate were fluorinated by a metathetical process to give the fluoro adducts in 95%, 97%, and 90% yields, respectively. The intermediacy of a stable adamantyl cation was postulated because tertiary fluorides were formed in higher yields than secondary fluorides. Further, solvent incorporation of an ethoxy and hydroxy group was observed when ethanol or water was present in the halogenated solvent. When 2-iodoadamantane reacted with fluorine in methylene chloride, 47% 2-chloroadamantane was isolated in addition to 50% 2-fluoroadamantane.[93] In previous work, Barton et al. observed debromination upon fluorinating a 5,6-dibromide steroid;[3] however, fluorine for bromine substitution was not mentioned. The 5,6-dichloro derivative of the same steroid did not dechlorinate, but underwent substitution at a remote tertiary hydrogen. This result is consistent with Rozen's observation that 1-chloroadamantane and other chloro compounds do not react with elemental fluorine.

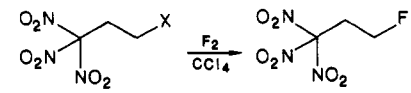
The mechanism postulated for the reaction requires oxidation of the halogen in secondary haloadamantanes and tertiary bromoadamantanes. Tertiary iodoadamantanes, however, are easily ionized to a stable carbocation and could react with fluoride ion generated from the reaction of the iodo nucleophile with fluorine.[93]

In a related reaction, L-cysteine and 2-(diethylamino)ethanethiol have been successfully fluorinated and simultaneously desulfurized in 33% and 25%, respectively.[94] The reaction was carried out in liquid HF saturated with gaseous BF_3 at -78 °C. L-Cysteine (**38**) afforded 3-fluoro-L-alanine (**39**) in 33% yield along with 3% difluoro byproduct (**40**) (eq 16). The mechanism

$$\underset{\mathbf{38}}{HSCH_2CH(NH_2)CO_2H} \xrightarrow[HF]{F_2/He} \underset{\mathbf{39},\ 33\%}{FCH_2CH(NH_2)CO_2H} + \underset{\mathbf{40},\ 3\%}{F_2CHCH(NH_2)CO_2H} \quad (16)$$

for the reaction was thought to proceed via oxidation of the sulfur followed by fluoride ion displacement of SF_3^+ which is known to exist in liquid HF.[95]

1-Bromo- and 1-iodo-3,3,3-trinitropropane underwent a metathetical reaction with elemental fluorine in anhydrous CCl_4 at 0 °C to give the 1-fluoro-3,3,3-trinitropropane in yields as high as 90% (eq 17).[96] The



(17)

X = Br, I

mechanism for the reaction was presumed to be free radical because formation of the dimer, 1,1,1,6,6,6-hexanitrohexane, was also observed.

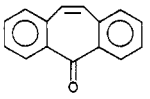
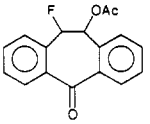
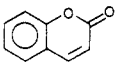
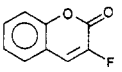
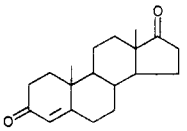
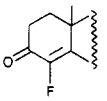
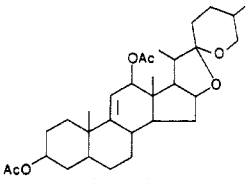
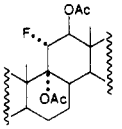
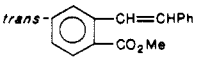
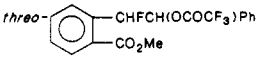
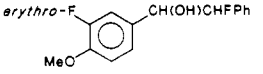
VII. Preparation of Commercially Unavailable Fluorinating Reagents

A. Organo Fluoroxy Compounds

1. Acyl Hypofluorites

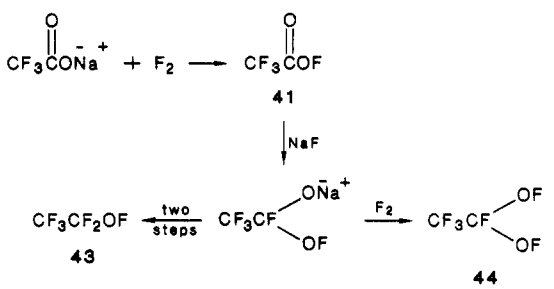
The research impetus in hypofluorite chemistry has recently changed focus from CF_3OF to the acyl hypofluorites (CH_3COOF, CF_3COOF) and cesium fluoroxysulfate ($CsSO_4F$). The chemistry and properties of CF_3OF, the only commercially available hypofluorite,

TABLE IX. Reaction of Alkenes with Acyl Hypofluorites

entry	substrate	product	hypofluorite	% yield	ref
1	*trans*-PhCH=CHPh	*threo*-PhCHFCHPhOAc	CH_3COOF	50	102, 123
		erythro isomer		7	
2	*cis*-PhCH=CHPh	*threo*-PhCHFCHPhOAc	CH_3COOF	1	102, 123
		erythro isomer		51	
3	*trans*-*p*-MeOPhCH=CHPh	*threo*-*p*-MeOPhCH(OAc)CHFPh[a]	CH_3CCOF	42	123
		erythro isomer		15	
4	*trans*-*p*-MeOPhCH=CHMe	*threo*-*p*-MeOPhCH(OAc)CHFCH$_3$[b]	CH_3COOF	57	123
		erythro isomer		13	
5		 cis	CH_3COOF	60	123
6	$C_{10}H_{21}CH=CH_2$	$C_{10}H_{21}CH(OAc)CH_2F$	CH_3COOF	30	123
7	*trans*-PhCH=CHCO$_2$Et	*threo*-PhCH(OAc)CHFCO$_2$Et	CH_3COOF	57	123
8	*cis*-PhCH=CHCO$_2$Me	*erythro*-PhCH(OAc)CHFCO$_2$Me	CH_3COOF	50	123
9	*trans*-PhCH=CHCOPh	*threo*-PhCH(OAc)CHFCOPh	CH_3COOF	70	123
10			CH_3COOF	55	123
11			CH_3COOF	95	123
12			CH_3COOF	64	123
13			CH_3COOF	90	123
14	*trans*-PhCH=CHPh	*threo*-PhCHFCH(OH)Ph	CF_3COOF	62	105
15	*cis*-PhCH=CHPh	*erythro*-PhCHFCH(OH)Ph	CF_3COOF	58	105
16	*trans*-PhCH=CHPh-*p*-CO$_2$Me	*threo*-PhCH(OH)CHFPh-*p*-CO$_2$Me	CF_3COOF	80	105
17	*cis*-PhCH=CHPh-*p*-CO$_2$Me	*erythro*-PhCH(OH)CHFPh-*p*-CO$_2$Me	CF_3COOF	25	105
18	*trans*-PhCH=CHPh-*p*-COMe	*threo*-PhCH(OH)CHFPh-*p*-COMe	CF_3COOF	28	105
19	*trans*-PhCH=CHPh-*p*-Cl	*threo*-PhCH(OH)CHFPh-*p*-Cl	CF_3COOF	32	105
		threo-PhCHFCH(OH)Ph-*p*-Cl		32	
20			CF_3COOF	40	105
		erythro isomer		14	
21	*trans*-PhCH=CHPh-*p*-OMe		CF_3COOF	57	105
		threo isomer		14	
22	*trans*-PhCH=CHPh-*p*-Me	PhCHFCH(OH)Ph-*p*-Me PhCH(OH)CHFPh-*p*-Me	CF_3COOF	48	105
		PhCHFCH(OH)Ph-*p*-Me		8	105

[a] In addition 5% *threo*- and 14% *erythro*-1-acetoxy-1-(3-fluoro-4-methoxyphenyl)-2-fluoro-2-phenylethane was formed. [b] In addition, 15% of a mixture of *threo*- and *erythro*-1-acetoxy-1-(3-fluoro-4-methoxyphenyl)-2-fluoropropane was isolated.

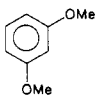
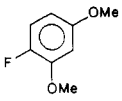
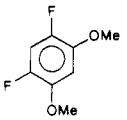
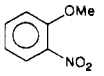
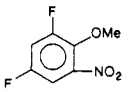
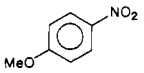
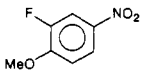
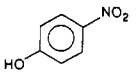
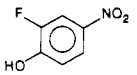
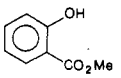
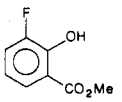
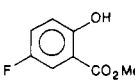
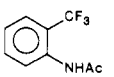
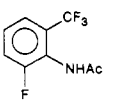
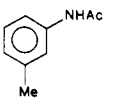
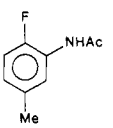
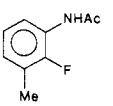
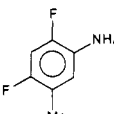
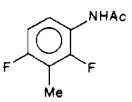
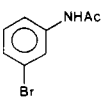
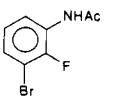
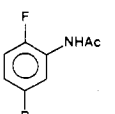
SCHEME VII

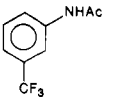
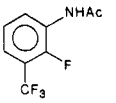
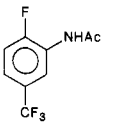
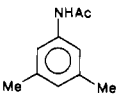
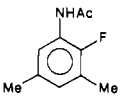
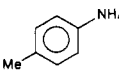
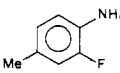
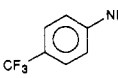
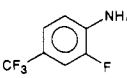
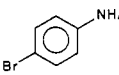
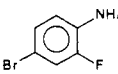
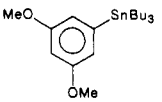
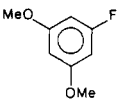


were reviewed in 1978 by Hesse[97] and will not be discussed. Recent synthetic studies with CF_3OF have involved reactions with diarylethenes,[98] diazo compounds,[59] steroids,[23] arenes,[99] and silyl enol ethers.[6,100]

Cady prepared and characterized trifluoroacetyl hypofluorite, CF_3COOF (**41**), in 1953,[101] but hypofluorite chemistry did not move to the forefront until 1981 when Rozen discovered a general synthetic procedure for acetyl hypofluorite, CH_3COOF (**42**).[16,102,103] The synthesis of trifluoroacetyl hypofluorite (**41**) from sodium trifluoroacetate[104-107] as well as perfluoroalkyl hypofluorites[108] (**43** and **44**) is outlined in Scheme VII. Compounds **43** and **44** formed in the absence of moisture or acid have synthetic utility similar to that of **41** and **42**. Rozen and Barnette extended the solution preparation to the formation of stable long-chain

TABLE X. Aromatic Substitution by Acyl Hypofluorites

entry	substrate	product(s)	% yield	ref
1	PhOMe	2-FPhOMe	77	16
		4-FPhOMe	8	
2			39	16
			55	
3[a]	PhOEt	2-FPhOEt	46	16
		4-FPhOEt	6	
4[b]	$2R_1OPhOR_2$	–	–	16
5			42	16
6			47	16
7			62	16
8[c]			9	16
			14	
9[d]	PhNHAc	2-FPhNHAc	55	16
		4-FPhNHAc	8	
10	$PhNHCOCF_3$	$2\text{-}FPhNHCOCF_3$	57	16
11	PhNHCO-*t*-Bu	2-FPhNHCO-*t*-Bu	52	16
12	2-MePhNHAc		0	16
13	2-BrPhNHAc		0	16
14			62	16
15			32	16
			28	
			11	
			10	
16			25	16
			47	

entry	substrate	product(s)	% yield	ref
17			34	16
			28	
18			67	16
19			85	16
20			72	16
21			65	16
22			68[e]	87
23	$4\text{-}MeOPhSnBu_3$	4-MeOPhF	78[e]	87
24	$4\text{-}MePhSnBu_3$	4-MePhF	72[e]	87
25	$3\text{-}MePhSnBu_3$	3-MePhF	71[e]	87
26	$2\text{-}MePhSnBu_3$	2-MePhF	57[e]	87
27	$PhSnBu_3$	PhF	72[e]	87
28	$4\text{-}ClPhSnBu_3$	4-ClPhF	68[e]	87
29	$4\text{-}FPhSnBu_3$	4-FPhF	73[e]	87
30	PhOMe	2-FPhOMe	64	121, 127
		4-FPhOMe	21	
31	4-MeOPhHgOAc	4-MeOPhF	65	121, 127
32	PhNHAc	2-FPhNHAc	44	121, 127
		4-FPhNHAc	22	
33	4-AcOHgPhNHAc	4-FPhNHAc	60	121, 127
34	PhOH	2-FPhOH	45	121, 127
		4-FPhOH	30	
35	2-HOPhHgCl	2-HOPhF	53	121, 127
36	4-HOPhHgCl	4-HOPhF	47	121, 127
37	PhH	PhF	18	121, 127
38	PhHgCl	PhF	55	121, 127
39	$PhCH_3$	$2\text{-}FPhCH_3$	8	121, 127
		$3\text{-}FPhCH_3$	1	
		$4\text{-}FPhCH_3$	4	
		$PhCH_2F$	1	
40	PhHgOAc	PhF	58	121, 127
41	$PhSiMe_3$	PhF	10[e,f]	88
42	$4\text{-}MePhSiMe_3$	4-MePhF	13[e,f]	88
43	$4\text{-}MeOPhSiMe_3$	4-MeOPhF	9[e,f]	88
44	$4\text{-}ClPhSiMe_3$	4-ClPhF	15[e,f]	88
45	$4\text{-}BrPhSiMe_3$	4-BrPhF	14[e,f]	88
46	$4\text{-}MeCOPhSiMe_3$	4-MeCOPhF	6[e,f]	88
47	$4\text{-}AcOPhSiMe_3$	4-AcOPhF	16[e,f]	88
48	$4\text{-}Me_3SiPhSiMe_3$	$4\text{-}FPhSiMe_3$	16[e,f]	88
49	$K_2[PhSiF_5]$	PhF	20[e]	135
50	$K_2[PhCH_2SiF_5]$	$PhCH_2F$	6[e]	135
51	$K_2[4CH_3PhSiF_5]$	$4\text{-}CH_3PhF$	18[e]	135
52	$PhNH_2$	$2\text{-}FPhNH_2$	3.5	127
		$4\text{-}FPhNH_2$	2.5	
53	$4\text{-}AcOHgPhNH_2$	$4\text{-}FPhNH_2$	4	127
54	$3\text{-}AcOHgPhNH_2$	$3\text{-}FPhNH_2$	19	127
55	PhCl	2-FPhCl	5	127
		4-FPhCl	5	
56	L-dopa	6-F L-dopa	4[e]	122

[a] 50% conversion. [b] $R_1 = R_2 = Me$; $R_1 = Me$, $R_2 = Ac$; $R_1 = R_2 = Ac$; $R_1 = Me$, $R_2 = OCOCF_3$; $R_1 = Me$, $R_2 = i\text{-}Pr$. No definite monofluoro products; only tars were observed. [c] 70% conversion. [d] 80% conversion. [e] Radiochemical yield from $CH_3CO_2{}^{18}F$. [f] Ring fluorination also observed.

TABLE XI. Reaction of Hypofluorites with Derivatives of Various Carbonyl Compounds

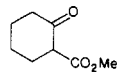
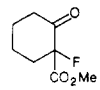
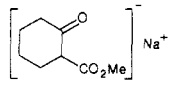
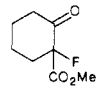
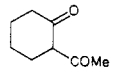
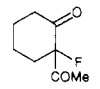
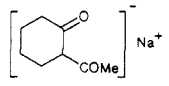
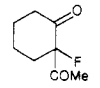
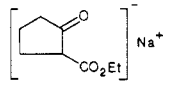
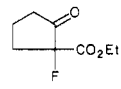
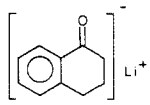
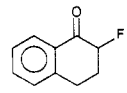
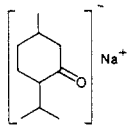
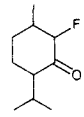
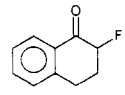
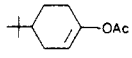
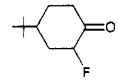
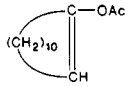
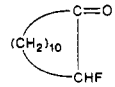
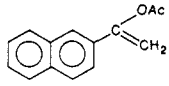
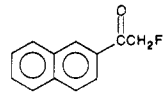
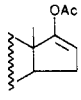
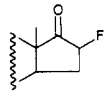
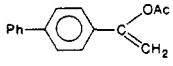
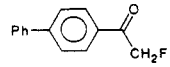
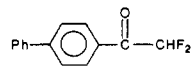
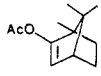
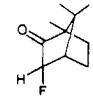
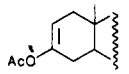
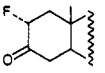
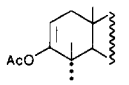
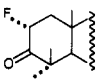
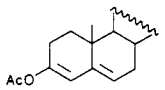
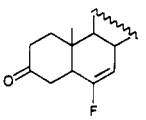
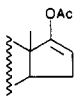
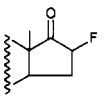
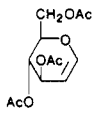
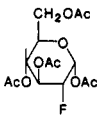
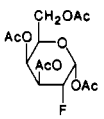
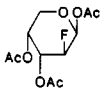
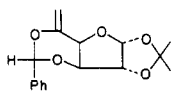
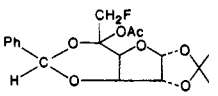
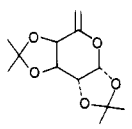
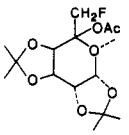
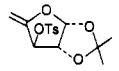
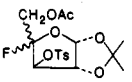
entry	substrate	product	% yield	ref
1	$EtOCOCOCH_2CO_2Et$	$EtOCOCOCHFCO_2Et$	65[a]	120
2	$[EtOCOCOCHCO_2Et]^-Na^+$	$EtOCOCOCHFCO_2Et$	75[a]	120
3	$MeCOCH_2CO_2Et$	$MeCOCHFCO_2Et$	72[a]	120
4	$[MeCOCHCO_2Et]^-Na^+$	$MeCOCHFCO_2Et$	81[a]	120
5			30[a]	120
6			60[a]	120
7			30[a]	120
8			90[a]	120
9			92[a]	120
10	$[CH(CO_2Me)_2]^-Na^+$	$CHF(CO_2Me)_2$	52[a]	120
11	$[EtC(CO_2Et)_2]^-Na^+$	$EtCF(CO_2Et)_2$	77[a]	120
12	$PhCOCH_2Li$	$PhCOCH_2F$	75[a]	123
13	$2\text{-}C_{10}H_7COCH_2Li$	$2\text{-}C_{10}H_7COCH_2F$	55[a]	123
14			86[a]	123
15	$n\text{-}BuCOCHLiCH_2CH_2CH_3$	$n\text{-}BuCOCHFCH_2CH_2CH_3$	54[a]	123
16	$n\text{-}C_6H_{13}CHLiCO_2Et$	$n\text{-}C_6H_{13}CHFCO_2Et$	67[a]	123
17			37[a] (ax) 40[a] (eq)	123 123
18			85[b,c] (eq)	104, 106, 107, 109
19			43[c] (trans) 29[c] (cis)	106, 107
20			87[c]	107
21			45[c]	106, 107
22			85[c]	104
23	$PhCH{=}C(OAc)CH_2Ph$	$PhCHFCOCH_2Ph$	50[c]	106
24		 	62[c] 29[c]	106
25			65[c]	106

TABLE XI (Continued)

entry	substrate	product	% yield	ref
26			80[c]	106
27			40–50[c] 60[b]	106 109
28			85[b,c]	106, 109
29			27[c] (α) 43[c] (β)	106
30			85[c]	106
31			78[a]	118, 119
32			84[a]	118, 119
33			96[a]	119
34			53[a]	119
35			83[a]	119
36			71[a]	119

[a] Acetyl hypofluorite. [b] Oxidizing solution obtained from F_2 + $C_7F_{15}CO_2K$. [c] Hypofluorite formed from CF_3CO_2Na + F_2.

fluoroxy compounds such as $CF_3(CF_2)_7OF$, $CF_3(CF_2)_6CF(OF)_2$, and $CF_3(CF_2)_6COOF$, which were obtained as a mixture from $CF_3(CF_2)_6COOK$. The mixture proved somewhat stable for extended periods and exhibits similar chemistry.[109,110]

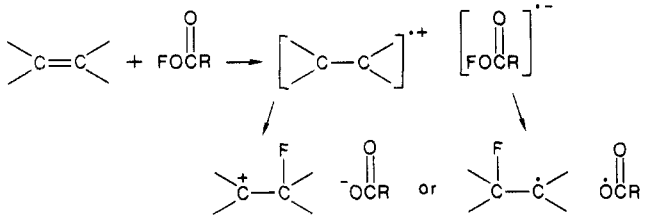
Rozen's procedure for the preparation of CH_3COOF (**42**) consisted of bubbling fluorine gas, diluted to 5–10% concentration with nitrogen, through a mixture of sodium acetate in glacial acetic acid and $CFCl_3$ at −78 °C. The yields of **42** were 50–80% and reactions were conducted on a 30–50 mmol scale. It is noteworthy that acetyl hypofluorite is the first hypofluorite prepared that is not perfluorinated.

Rozen's procedure has been extended to the use of ammonium and other alkali metal salts, especially in the preparation of fluorine-18 labeled **42**.[51,88,111] Jewett has developed a method for the preparation in a gas-solid phase system which permits the separation of gaseous **42** from contaminants and is followed by condensation in a solvent suitable for subsequent reactions ($CFCl_3$, CH_3COOH, CH_2Cl_2, CH_3OH, hexane, DMF). Jewett's procedure is useful for the preparation of the fluorine-18 labeled hypofluorite.[112–114] Because radiolabeled F_2 contains only one ^{18}F atom, the preparation of $CH_3COO^{18}F$ is accompanied by nonradiolabeled species. Thus, radiochemical specific activities of the resulting products are low to moderate, but not high.

Acetyl hypofluorite has generally been prepared and used in situ. Adam has reported that an explosion occurred on condensation.[115] Spectral characterizations of **42** have been determined by Rozen[116] for solution preparations. Appelman[117] has also characterized the hypofluorite by spectral methods on pure samples prepared by Jewett's gas-phase synthesis.

The reactions of CH_3COOF (**42**) with a wide number of substrates have been investigated by Rozen and many other workers.[16,21,51,87,88,102,103,118–130] There have been relatively few investigations on CF_3COOF or the other acyl hypofluorites.[105–108,114] The reaction products are subject to strong solvent and temperature effects and may indicate the involvement of some radical processes as observed for trifluoromethyl hypo-

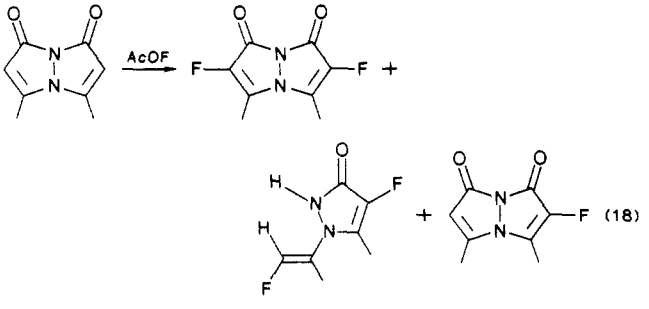
SCHEME VIII



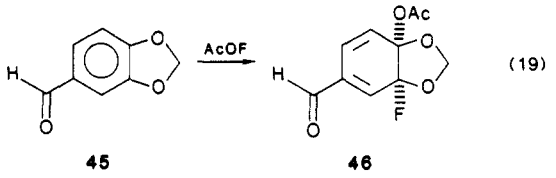
fluorite.[131-134] Thus, with extrapolation to acyl hypofluorite chemistry, reactions of **41** and **42** may be viewed as electrophilic processes in which the substrate alkene or arene serves as a nucleophile, but radical processes may also be operational. An initial one-electron transfer step, as indicated in Levy's work and for which precedence exists in SET reactions of fluorocarbons,[133] would allow a second step in which either a fluoride ion or radical is transfered (Scheme VIII).

The reactions of acyl hypofluorites, with nucleophilic olefinic and aromatic substrates have proven of great synthetic utility for the introduction of a single fluorine atom at a predictable site in the substrate. Numerous alkene substrates have shown remarkable stereoselective syn additions with both **41** and **42**. High regioselectivity introducing the fluorine atom at the nucleophilic site and the acylate function at the site predicted for the more stable carbocation, has also been observed. Fluorohydrin derivatives were formed in 20–90% yields (Table IX). *Trans*-stilbenes gave *threo* products; and *cis*-stilbenes gave *erythro* products with high stereoselectivity (entries 1–4, 14–22). That a higher degree of stereoselectivity is observed with CF_3COOF rather than CH_3COOF has been ascribed to the fact that $CF_3CO_2^-$ is a harder anion than $CH_3CO_2^-$. (Table IX, compare entries 1 and 14.) Thus, it reacts more rapidly with the hard α-fluoro carbocation of the tight ion pair.[21] In the presence of stilbenes with activated rings, both addition to the double bond and fluorination ortho to the activating (OCH_3) group are observed[21,102,104,105,107,108] (entries 3 and 4).

Heterocyclic substrates have received very limited attention in reactions with acyl hypofluorites. A study of the reaction of bimane with CH_3COOF by Rozen and Kosower proved interesting as shown (eq 18).[125]



The reaction of various aromatic substrates with **41** or **42** are compiled in Table X. In the fluoroaromatic derivatives produced, the fluorine atom was generally ortho to the substituent, although mixtures were routinely obtained (entries 15–17). The best results were obtained when activating substituents (OCH_3, OH, NHAc) were present. The ortho substitution by fluorine arose from an addition–elimination sequence at the electron-rich site in the substrate.[16,103,121] In the case of piperonal (**45**), isolation and characterization of an addition product (**46**) in 55% yield serves as evidence for the process[16] (eq 19).

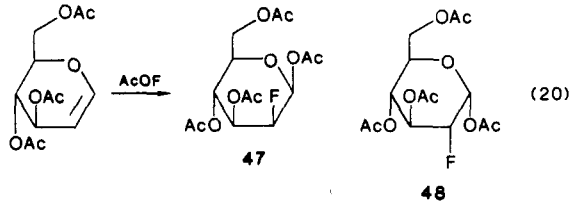


45 **46**

Investigations of aryl metallic compounds have shown that substituents other than hydrogen on an aromatic ring may be replaced by fluorine during reaction with CH_3COOF. Such studies have application in the preparation of fluorine-18 ring-substituted aromatic derivatives. Adam showed that the aryl–tin bond in several substrates was readily converted to an aryl–fluorine bond in 57–78% radiochemical yield from $CH_3COO^{18}F$ (entries 22–29).[87] Visser discovered that the aryl–mercury bond was specifically converted to the aryl–fluorine function in 47–65% yield in a process adaptable to fluorine-18 chemistry (entries 31–40).[121] Ward prepared 2-fluoroestradiol on a large scale by reaction of a 2-trifluoroacetyl mercury estradiol derivative with CH_3COOF.[136] The aryl–silicon bond of both arylsilanes and aryl silicates are converted specifically to the aryl–fluorine function.[88,135] In the case of aryl silanes a high degree of replacement of aryl–H bonds accompanied this reaction. Shiue observed radiochemical yields of 5–15% and Si/H substitution ratios from 12.9/1 to 0.9/1 (entries 41–48).[88]

The lithium enolates of ketones were found to react smoothly with CH_3COOF to yield α-fluoroketones (37–86%) as shown in Table XI. Other alkali metals were useful but yields tended to be lower, while unactivated ketones reacted poorly.[120,123] Enol acetates were also excellent substrates, and α-fluorocarbonyl compounds formed in 50–90% yield. Steroidal enol acetates with a wide range of structural complexity have also been used (entries 22,27–30).[6,21,104,106,107,114]

Several workers have investigated the fluorination of vinyl ether derivatives of carbohydrates with emphasis on the preparation of fluorine-18 labeled sugars (entries 31–36).[51,109,118,119,124,127-130] Bida[130] first observed the solvent-dependent formation of 2-deoxy-2-fluoro-D-mannose (**47**), a side product in the preparation of 2-deoxy-2-fluoro-D-glucose (**48**). Shiue found that **47** was formed in 4% yield in low polarity solvents ($CFCl_3$, CCl_4) but in 20% yield in high polarity solvents (HOAc, CH_3OH, DMF)[124] (eq 20). The size of the substituent on the hydroxyl had no effect on the relative yields.[126]

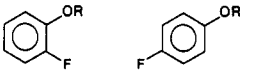
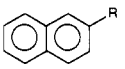
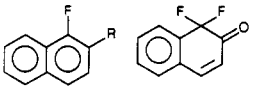
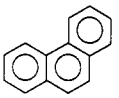
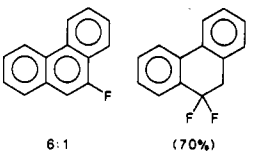
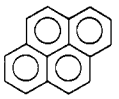
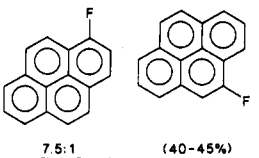
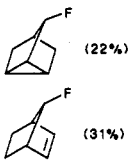
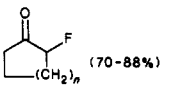
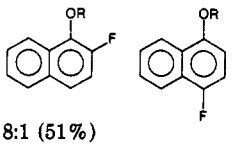


47 **48**

2. Fluoroxysulfate Salts

Although it had been known for some time that bubbling fluorine gas through an aqueous solution of sodium sulfate gave an oxidizing solution,[137] only in 1981 did Appelman discover that the use of cesium or

TABLE XII. Fluorinated Products Obtained Using $CsSO_4F$

entry	substrate	$CsSO_4F$:substrate	product[a] (% yield)	ref
				
1	R = H	1:1	6.2:1 (70–80%)	140
2	R = Me	1:1	2.8:1 (70–80%)	140
3	R = *n*-Bu	1:1	1.8:1 (70–80%)	140
4	R = 2-Bu	1:1	1.2:1 (70–80%)	140
				
5	R = H	1.3:1	5:1 (38–42%)	141
6	R = OH	1:1	4.9:1 (60–80%)	140
7	R = OMe	1:1	2.8:1 (60–80%)	140
8	R = OEt	1:1	2.6:1 (60–80%)	140
9	R = O-*i*-Pr	1:1	1.6:1 (60–80%)	140
10	C_6H_6	2:1	C_6H_5F (30–35%)	141
11		2:1	 6:1 (70%)	141
12		1.3:1	 7.5:1 (40–45%)	141
13	$Ph_2C{=}CH_2$	1.2:1	$Ph_2C{=}CHF$ (70%)	144
14		1.2:1	 (22%) (31%)	144
15	$PhC(CH_3)C{=}CH_2$	1.2:1	$PhC(CH_2F){=}CH_2$ (30%) $PhC(CHF_2){=}CH_2$ (32%)	144
16	 n = 1-4	1.2:1	 (70–88%)	144
				
17	R = H	1:0.7	8:1 (51%)	142
18	R = Me	1:0.7	3.5:1 (50%)	142
19	R = Et	1:0.7	3:1 (50%)	142
20	R = *i*-Pr	1:0.7	1.8:1 (51%)	142
21	R = H	1:1.6	6.2:1 (72%)[b]	142
22	R = Me	1:1.6	3.9:1 (83%)[b]	142
23	R = Et	1:1.6	6.9:1 (79%)[b]	142
24	R = *i*-Pr	1:1.6	6.9:1 (71%)[b]	142
25	PhNHAc	1:1	2-FPhNHAc (75%) 4-FPhNHAc (11%)	142
26	$PhCH_3$	1.4:1	2-$FPhCH_3$ (31%) 3-$FPhCH_3$ (4%) 4-$FPhCH_3$ (8%)	142
27	$PhNO_2$	1.4:1	2-$FPhNO_2$ (6%) 3-$FPhNO_2$ (16%) 4-$FPhNO_2$ (3%)	139

[a] And product ratio. [b] From 6–23% difluorination was observed.

rubidium sulfate led to the isolation of solid, relatively stable anionic hypofluorites, cesium fluoroxysulfate and rubidium fluoroxysulfate[138,139] (eq 21). Cesium fluoroxysulfate was prepared easily in 2–5-g batches and stored in the cold for long periods without significant loss of activity. $CsSO_4F$ has detonated occasionally on contact with metal surfaces, and should be handled in small quantities. The initial chemistry of $CsSO_4F$, described by Appelman, showed that $CsSO_4F$ is espe-

$$M_2SO_4 + F_2 \rightarrow MSO_4F + MF \qquad (21)$$

M = Cs or Rb

TABLE XIII. Use of *N*-Fluoro Compounds for Fluorination

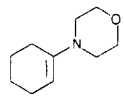
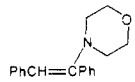
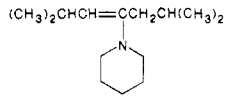
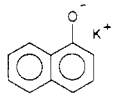
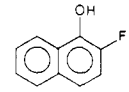
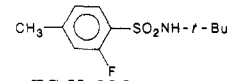
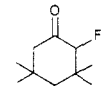
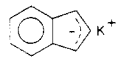
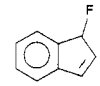
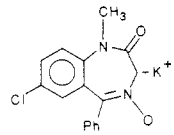
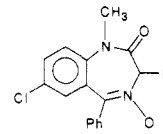
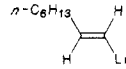
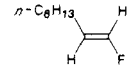
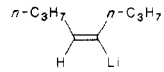
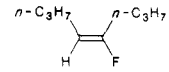
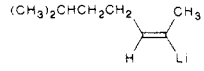
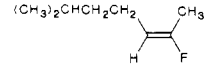
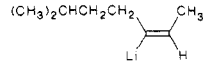
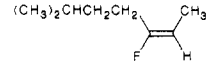
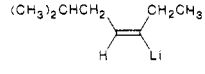
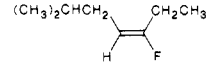
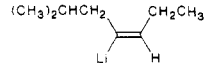
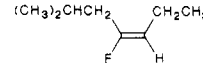
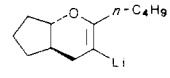
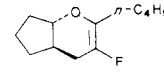
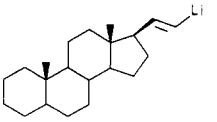
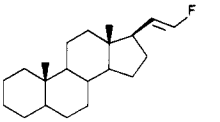
entry	substrate	reagent	product	% yield	ref
1	$PhC(CO_2Et)_2^-Na^+$	*a*	$PhCF(CO_2Et)_2$ $PhCFHCO_2Et$	20–39 0–5	145
2	$PhCH_2C(CO_2Et)_2^-Na^+$	*a*	$PhCH_2CHFCO_2Et$	30–33	145
3	$CH_3C(CO_2Et)_2^-Na^+$	*a*	$CH_3CF(CO_2Et)_2$	17	145
4	$CH(CO_2Et)_2^-Na^+$	*a*	$F_2C(CO_2Et)_2$ $HCF(CO_2Et)_2$	5 9	145
5	PhMgBr	*a*	PhF	15	146
6	c-$C_6H_{11}MgBr$	*a*	c-$C_6H_{11}F$	11	146
7	$CH_3(CH_2)_5CH(MgBr)CH_3$	*a*	$CH_3(CH_2)_5CHFCH_3$	5	146
8		*a*		36–44	146
9		*a*	PhCHFCOPh	11–33	146
10		*a*	$(CH_3)_2CHCHFCOCH_2CH(CH_3)_2$	23	146
11	$PhC(CO_2Et)_2^-Na^+$	*b*	$PhCF(CO_2Et)_2$	81	147
12	$CH_3C(CO_2Et)_2^-Na^+$	*b*	$CH_3CF(CO_2Et)_2$	53	147
13	PhMgBr	*c*	PhF	50	147
14		*c*		60	147
15	p-$CH_3C_6H_4SO_2N$-t-Bu^-Li^+	*d*		55	147
16	$PhOMe^-Li^+$	*d*	3-FC_6H_4OMe	24	147
17		*d*		35	147
18	$[PhCOCHCH(CH_3)_2]^-K^+$	*d*	$PhCOCHFCH(CH_3)_2$	81	147
19	$CH_3(CH_2)_{13}MgBr$	*d*	$CH_3(CH_2)_{13}F$	15	147
20		*d*		31	147
21	$(CH_3)_2CNO_2^-$-n-Bu_4N^+	*c*	$(CH_3)_2CFNO_2$	83–87	147
22	$[Ph_2CCO_2]^{2-}2Li^+$	*d*	Ph_2CFCO_2H	69	147
23		*d*		52	147
24		*e*		71	148
25		*e*		76	148
26		*e*		85	148
27		*e*		75	148
28		*e*		75	148
29		*e*		88	148
30		*e*		83	148
31		*e*		74	148

TABLE XIII (Continued)

entry	substrate	reagent	product	% yield	ref
32		e		80	148

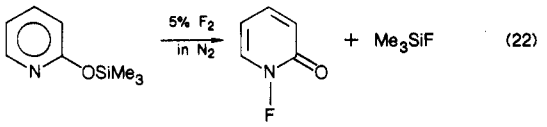
[a] *N*-Fluoro-2-pyridone. [b] *N*-Fluoro-*N*-neopentyl-*p*-toluenesulfonamide. [c] *N*-Fluoro-*N*-*tert*-butyl-*p*-toluenesulfonamide. [d] *N*-Fluoro-*N*-*exo*-2-norbornyl-*p*-toluenesulfonamide. [e] *N*-*tert*-Butyl-*N*-fluorobenzenesulfonamide.

cially useful as a fluorination agent for aromatic substrates.[138,139] Although presently unknown, $CsSO_4{}^{18}F$ should be as easily prepared as $CH_3COO^{18}F$ and thus, enhance the scope of radiofluorination methods.

Fluorinations using $CsSO_4F$ are summarized in Table XII. Zupan used $CsSO_4F$ reactions catalyzed by BF_3 in the fluorination of a wide range of aromatic derivatives (entries 1–6). Mixtures of fluoro isomers were obtained (entries 7–9).[140–143] Electron-withdrawing substituents such as trifluoromethyl or carbomethoxy gave only small product conversions to the meta product (see entry 27). Aniline and *N*,*N*-dimethylaniline only gave tars at −20 °C. Zupan observed a direct relation between product yields and the ratio of cesium fluoroxysulfate to substrate for naphthalene derivatives (entries 5–9, 17–24). Appelman suggested the mechanism in Scheme IX to account for observations of both electrophilic and radical character in the reactions of $CsSO_4F$ with aromatics.[138] Zupan also communicated that alkenes and enol acetates fluorinated at room temperature with $CsSO_4F$ (entries 13–16).[144]

B. *N*-Fluoro Compounds

N-Fluoro-2-pyridone[145,146] and various *N*-fluoro-*N*-alkylsulfonamides[147] have been shown to be useful fluorinating reagents, under very mild conditions. The results of fluorinations using these reagents are compiled in Table XIII. *N*-Fluoro-2-pyridone is prepared from the direct fluorination of 2-(trimethylsiloxy)-pyridine with molecular fluorine (eq 22). The driving



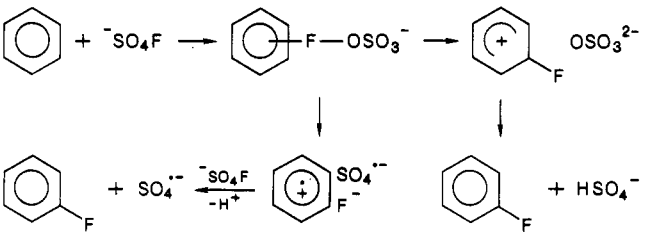
(22)

force for fluorination with the pyridone may be rearomatization of the pyridine nucleus. Barnette prepared *N*-fluoro-*N*-alkylsulfonamides by treatment of *N*-alkylsulfonamides with elemental fluorine diluted in nitrogen.[147] These compounds are more stable than *N*-fluoro-2-pyridone and provide better yields of fluorinated products as shown in Table XIII (entries 1 and 11, 3 and 12, 5 and 13).

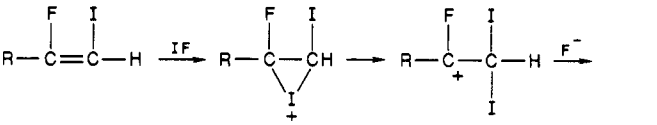
C. Halogen Monofluorides

An excellent, comprehensive review was recently published by Boguslavskaya[12] on the utility of halogen fluorides in organic synthesis. Rozen et al.[149–152] have used elemental fluorine to generate IF and BrF in situ. Table XIV is a compilation of the iodofluorination and bromofluorination products from various alkenes and alkynes. IF reacted with olefins regioselectively in Markovnikov fashion as shown by entries 12 and 13.

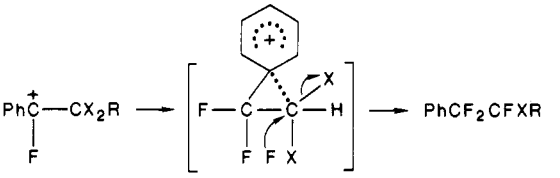
SCHEME IX



SCHEME X



SCHEME XI



The reaction proceeded by way of an iodonium ion and resulted in stereospecific anti addition (entries 18–21). The addition of BrF is less regioselective but the Markovnikov isomer predominated (entry 14). Because of the greater reactivity of BrF, a proton source such as ethanol or isopropyl alcohol was needed as a moderator. A drawback to the reagent is an accumulation of up to 10% of the solvent incorporated bromoether.

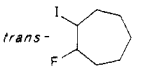
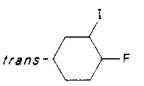
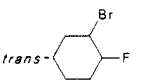
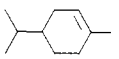
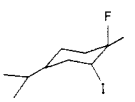
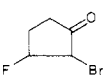
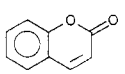
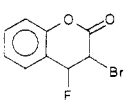
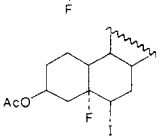
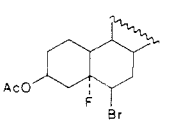
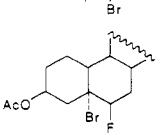
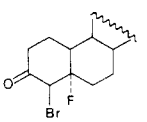
Both IF and BrF reacted with aliphatic alkynes, both terminal and nonterminal, to generate CF_2 groups (entries 1–11).[150] The anticipated mechanism for the reaction is similar to that for olefins with a second molecule of IF adding across the halogenated π bond so as to generate the more stable carbocation at the fluorinated carbon (Scheme X).

Phenylacetylene (entry 4) gave in addition to the expected difluoro product, a trifluoro derivative. A phenonium ion was the postulated intermediate in this reaction as illustrated in Scheme XI. The formation of 1,1,2,2-tetrafluorodiphenylethane, obtained from diphenyl acetylene (entry 8), was attributed to the facile ionization of the intermediate benzylic iodide.[150]

VIII. Conclusion

The synthetic applications for elemental fluorine have grown considerably in the past 25 years. No longer are perfluorinated hydrocarbons the major area of study in fluorine chemistry. The importance of selective fluo-

TABLE XIV. Iodofluorination and Bromofluorination Products

entry	substrate	XF	product(s)	% yield	ref
1	$CH_3(CH_2)_3C{\equiv}CH$	Br	$CH_3(CH_2)_3CF_2CHBr_2$	60	150
2	$CH_3(CH_2)_3C{\equiv}CH$	I	$CH_3(CH_2)_3CF_2CHI_2$	80	150
3	$CH_3C{\equiv}CCH_3$	I	$CH_3CF_2CI_2CH_3$	85	150
4	$PhC{\equiv}CH$	I	$PhCF_2CI_2H$	40	150
			$PhCF_2CFIH$	45	
5	$PhC{\equiv}CH$	Br	$PhCF{=}CBr_2$	40	150
			$PhCF_2CBr_2H$	45	
6	$PhC{\equiv}C(CH_2)_4CH_3$	I	$PhCF_2CI{=}CH(CH_2)_3CH_3$	45	150
			$PhCF_2CFI(CH_2)_4CH_3$	20	
7	$PhC{\equiv}C(CH_2)_4CH_3$	Br	$PhCF_2CFBr(CH_2)_4CH_3$	45	150
8	$PhC{\equiv}CPh$	I	$PhCF_2CF_2Ph$	60	150
			$PhCF_2COPh$	20	
			PhCOCOPh	10	
9	$PhC{\equiv}CPh$	Br	$PhCF_2CBr_2Ph$	65	150
			PhCOCOPh	15	
10	$PhC{\equiv}CCO_2Et$	Br	$PhCF_2CBr_2CO_2Et$	70	150
11	$MeOCOC{\equiv}CCO_2Me$	Br	$MeOCOCF_2CBr_2CO_2Me$	70	150
12	$CH_3(CH_2)_5CH{=}CH_2$	I	$CH_3(CH_2)_5CHFCH_2I$	70	150, 151
13	$CH_3(CH_2)_9CH{=}CH_2$	I	$CH_3(CH_2)_9CHFCH_2I$	70	149
14	$CH_3(CH_2)_9CH{=}CH_2$	Br	$CH_3(CH_2)_9CHFCH_2Br$	66	149, 152
			$CH_3(CH_2)_9CHBrCH_2F$	18	
15	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2CHO$	I	$(CH_3)_2CFCH(I)(CH_2)_2CHCH_2CH(CH_3)CH_2CHO$	50	149
16	$CH_3(CH_2)_9CF{=}CH_2$	I	$CH_3(CH_2)_9CF_2CH_2I$	75	149
17	$CH_3(CH_2)_9CHFCH_2I$	Br	$CH_3(CH_2)_9CF_2CH_2Br$	40	149
18		I		45	149, 151
19		I		64	149, 151
20		Br		61	149, 152
21		I		45	149, 151
22	*trans*-PhCH=CHPh	I	*meso*-PhCHFCHFPh	42	149
			dl-PhCHFCHFPh	42	
23	*cis*-PhCH=CHPh	I	*meso*-PhCHFCHFPh	15	149
			dl-PhCHFCHFPh	65	
24	*trans*-PhCH=CHPh	Br	*erythro*-PhCHFCHBrPh	84	149, 152
25	*cis*-PhCH=CHPh	Br	*threo*-PhCHFCHBrPh	65	149, 152
26	(*Z*)-PhC(CH_3)=CHPh	I	*threo*-PhC(CH_3)FCHFPh	75	149
			erythro-PhC(CH_3)FCHFPh	15	
27	*trans*-*p*-$CH_3COC_6H_4CH{=}CHPh$	I	*p*-$CH_3COC_6H_5CHFCHFPh$	75	149
			erythro:*threo*= 9:1		
28	$MeOCOCH_2CH{=}CH_2$	Br	$MeOCOCH_2CHFCH_2Br$	50	149, 152
			$MeOCOCH_2CHBrCH_2F$	30	
29		Br		90	149, 152
30		Br		50	149, 152
31	cholesterol acetate	I		65	149
32	cholesterol acetate	Br		15	149
				55	149
33	progesterone	Br	 #p	60	149

rination methods and biologically active fluorinated compounds are gaining increasing recognition in the scientific community, with special emphasis on radiolabeled fluorinated compounds (as medicinal tracers), fluorinated enzyme inhibitors, pharmaceutically useful compounds, and pesticides. Selectivity and product yields are no longer the exception to the rule, and are becoming more commonplace. The exploration of moderating reagents such as acetyl hypofluorite, cesium fluoroxysulfate, and halogen monofluorides are further extending the applications of fluorine to the production of new compounds that in the past years have been elusive.

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