Electrophilic NF Fluorinating Agents

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Contents

I. Introduction

It is well recognized that the presence of fluorine in medicinals[1,2] and plant-protection compounds[2−4] can profoundly influence their biological properties. The need for a regioselective formation of carbon−fluorine bonds in these and other,[5] often complex, organic molecules, has stimulated the development of new synthetic methods that employ a variety of fluorinating agents. These may be classified[6] as sources of fluoride ion (F^-) or fluorine radicals ($F^•$) and as compounds that can deliver electrophilic fluorine (F^+).

Most fluorine-containing commodity chemicals and polymers are made starting from hydrogen fluoride or other sources of the fluoride ion.[7,8] Examples of such nucleophilic fluorinating agents that are useful for laboratory use or fine chemical synthesis processes are pyridine·HF, $Bu_4N^+\ HF_2^-$, activated alkali metal fluorides, etc., and also SF_4 and (diethylamino)-sulfur trifluoride (DAST), which can convert carbon-oxygen to carbon−fluorine bonds.[9,10]

The fluorination of electron-rich centers, in particular, a direct conversion of C−H to C−F linkages, is usually not feasible with HF-based chemistry; for this radical or electrophilic sources of fluorine are needed. Elemental fluorine can be used for this purpose, but there are significant remaining challenges. At near-ambient temperatures, when acting as a source of $F^•$ radicals, it is quite indiscriminate in its chemistry toward organic substrates. However, under carefully regulated conditions fluorine can be a useful synthetic reagent.[11,12] An efficient perfluorination of hydrocarbons and some ethers can, for instance, be accomplished by the LaMar and aerosol-controlled fluorination techniques.[13] A regioselective limited introduction of fluorine by direct reaction with the element has in principle been demonstrated for many organic substrates, including carbanions, enolates, olefins, and certain aromatics. Reactions are done with N_2-diluted F_2, at low temperatures sometimes in the presence of F−F bond-polarizing solvents or reaction modifiers.[11−15] Here, the key to selectivity appears to be in using reaction systems where fluorine is delivered in a positive mode, i.e., as an electrophile (F^+ source) rather than radical fluorine. Even so, it is in general difficult to achieve high reaction yields in a direct fluorination of organics. An indication of this is that there are few industrial-scale fluorination processes that are based on F_2, a notable example being the synthesis of 5-fluorouracil.[16]

The difficulties associated with direct fluorination have stimulated the development of alternate sources of positive fluorine: electrophilic reagents that can be easily and safely employed in organic syntheses. Perchloryl fluoride, $FClO_3$, xenon difluoride, XeF_2, trifluoromethyl hypofluorite, CF_3OF, and various acyl and perfluoroacyl hypofluorites, RC(O)OF and R_fC-(O)OF, were among the first reagent sources of positive fluorine. These compounds display the classical F^+ source reactivity as in the addition of fluorine to carbanions and enolates and in the electrophilic fluorination of aromatics.[9,17]

While $FClO_3$, XeF_2, and the hypofluorites are generally more selective electrophilic fluorination reagents than F_2, there are limitations that have precluded their widespread use. While perchloryl fluoride has been employed in the industrial scale fluorination of steroid enolates, it has the drawback that with organic compounds it can be a dangerous

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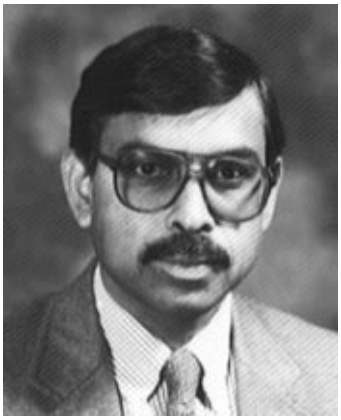


G. Sankar Lal, a native of Guyana, received the Ph.D. degree in natural products synthesis from the University of New Brunswick, Canada, in 1984. After postdoctoral assignments at Smith Kline Beecham Laboratories and Drexel University, he joined Air Products where he is now a Senior Principal Research Chemist. His work has focused on developing synthetic methodologies for the preparation of fluorine-containing biologically active compounds.

Guido P. Pez was born in Italy and educated in Australia. He received the Ph.D. degree in inorganic chemistry from Monash University in 1967. After postdoctoral studies at McMaster University, Canada, he joined Allied Signal Corp. and has since 1981 been at Air Products' Corporate Science Center. He currently holds the position of Chief Scientist with research interests in inorganic and fluorine chemistry, gas separation technologies, and catalysis.

oxidant. Xenon difluoride is a valuable laboratory fluorination reagent but may not be economical for use on a large scale. The hypofluorites are also very powerful oxidizing as well as fluorinating agents. While CF_3OF can be stored at room temperature, acetyl and perfluoroacetyl hypofluorites are less stable and are usually generated *in situ* from their acetate salts and fluorine.[18]

In recent years, a number of NF fluorinating agents have emerged as generally safer, and easier to handle, selective sources of electrophilic fluorine. These are either neutral, R_2NF compounds or quaternary ammonium $R_3N^+F\ A^-$ salts where A^- is a non-nucleophilic anion. Here the R_2N- and R_3N^+- organonitrogen fragments are chosen to be good leaving groups, thus promoting a reactivity of the bound fluorine with nucleophiles, as illustrated below for the quaternary salt reagents:

$$R_3N^+\text{-}F + Nu^- \longrightarrow \left[R_3N^{\delta+}\text{---}F\text{---}Nu^{\delta-}\right] \longrightarrow R_3N + F\text{-}Nu \qquad (1)$$

Robert G. Syvret was born in Canada and in 1987 received the Ph.D degree in main-group fluorine chemistry from McMaster University. In 1987, he joined the Corporate Science Center at Air Products. He is now a Senior Principal Research Chemist in the Company's Specialty Gas Department where he is continuing with his work in the area of selective fluorination.

Single electron transfer (SET) pathways are also possible (see section V). The NF reagents are generally synthesized by the direct reaction of R_2NH and R_3N precursors with fluorine. As sources of F^+, all behave as oxidizing agents, as most commonly indicated by a usually quantitative conversion of aqueous iodide solutions to iodine.

$$R_3N^+F + I^- \xrightarrow{H_2O,\ H^+} R_3NH^+ + 1/2\ I_2 + F^- \qquad (2)$$

The currently known NF reagents display a wide range of oxidizing and fluorinating power toward nucleophiles. Systems that can be fluorinated include benzene and activated aromatics, stabilized carbanions, activated olefins (aryl-substituted alkenes, alkyl and silyl enol ethers, enol acetates, and enamines), certain organometallics, and aliphatic sulfides. While their reactivity toward these substrates may not be as great as exhibited by XeF_2 and some of the *in situ* prepared hypofluorites, the NF reagents' ease of use and growing commercial availability has provided the synthetic chemist with a valuable new tool for an efficient selective introduction of fluorine into organic compounds.

The preparation, fundamental properties, and reactivity of the *N*-fluoro electrophilic fluorinating agents are the subject of this review, which is organized as follows. General preparative methods for the neutral R_2NF and $R_3N^+F\ A^-$ salt reagent classes are presented in section II. Then there is a detailed, similarly structured, account of the synthesis and physical and spectroscopic properties of specific NF compounds. Applications of the most common of these reagents in organic synthesis are described in section IV. Finally, unifying concepts on relative fluorination reactivity and reaction mechanisms are discussed. A partial coverage of the chemistry of electrophilic NF compounds may be found in refs 6, 9, 12, 19 and 20.

II. General Preparative Methods

The electrophilic NF reagents, for the majority of examples, must be prepared from neat or diluted fluorine, with the only exceptions being a few sub-

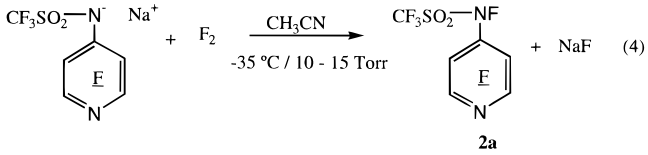
strates that have been prepared by electrochemical fluorination (ECF),[21−23] cobalt trifluoride fluorination,[24,25] or transfer fluorination.[26,27]

For the ternary class of NF reagents (R_2NF) there are four distinct preparative methodologies (**M-1** to **M-4**), which are described below. Each method is illustrated here by an example and is referred for the specific reagents that are listed in Table 1.

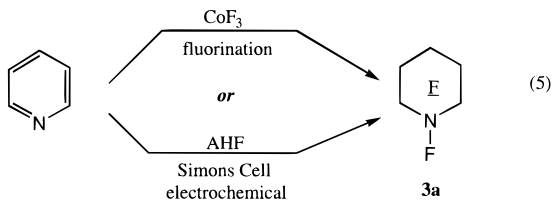
The first of these (**M-1**) involves fluorination of the parent acid of the desired reagent using elemental fluorine with concomitant formation of HF. This is illustrated by the preparation of DesMarteau's compound (**1a**)[28−30] (eq 3).

$$(CF_3SO_2)_2NH + F_2 \xrightarrow[1570\ \text{Torr}]{22\ ^\circ\text{C}} \underset{\mathbf{1a}}{(CF_3SO_2)_2NF} + HF \qquad (3)$$

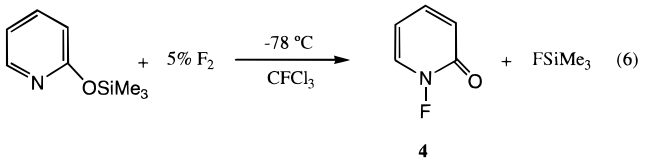
The second method (**M-2**) involves fluorination of an alkali metal salt of the parent acid with concomitant formation of the NF reagent and an alkali metal fluoride, as in eq 4 for the synthesis of **2a**.[31]



In the next example (**M-3**) elemental fluorine is not used for the preparation of the NF compound. Instead, electrochemical fluorination (ECF) in anhydrous HF (AHF)[21−23] or cobalt trifluoride fluorination[24,25] methods lead to the desired reagent. This is illustrated in two parts by eq 5 for the synthesis of perfluoropiperidine **3a**.

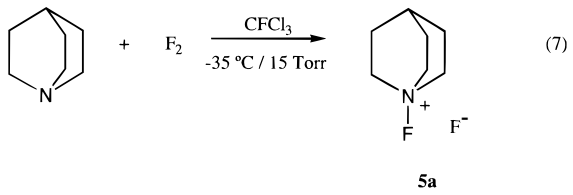


The fourth method (**M-4**) involves fluorination of a substrate which contains a fluorination facilitating group, i.e., $-SiMe_3$, and is illustrated by eq 6 in the preparation of Purrington's compound (**4**).[32,33]

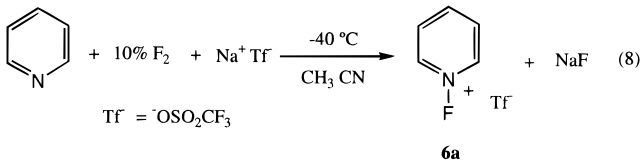


The quaternary class of electrophilic NF reagents ($R_3N^+F\ A^-$) are prepared through the action of either neat or dilute fluorine on an appropriate substrate or by transfer fluorination. The five distinct methods (**M-5** to **M-9**) for the synthesis of this class of compounds are given in the following:

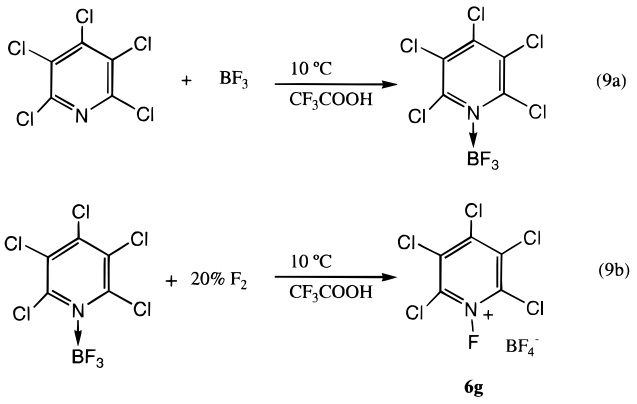
M-5 involves fluorination of the parent tertiary amine of the desired reagent using elemental fluorine. This method is illustrated by eq 7 for Banks' *N*-fluoroquinuclidinium fluoride (**5a**).[34,35]



In the next example (**M-6**), fluorination of an amine precursor, in the presence of an equimolar amount of an alkali metal salt of a weakly nucleophilic anion, leads to the NF reagent and an alkali metal fluoride byproduct. This is illustrated in eq 8 by this synthesis of Umemoto's *N*-fluoropyridinium triflate (**6a**).[36−40]



In **M-7**, a Lewis acid, i.e., BF_3, adduct of the parent amine of the desired reagent undergoes reaction with elemental fluorine to give the NF cation portion and the corresponding fluoride−Lewis acid anion. This method is illustrated in eq 9 below wherein the preformed boron trifluoride adduct (eq 9a) of pentachloropyridine is fluorinated (eq 9b), resulting in formation of the tetrafluoroborate salt of the desired NF reagent.[39]



In **M-8**, a preformed Bronsted acid salt of the parent amine undergoes reaction with elemental fluorine to give the NF compound with concomitant formation of HF as a byproduct. This important preparative sequence for *N*-fluoropyridinium compounds is illustrated in eq 10a,b by the preparation of *N*-fluoropentachloropyridinium triflate (**6h**).[39]

In **M-9**, a preformed trimethylsilyl (Me_3Si) or dimethylphenylsilyl ($PhMe_2Si$) salt of the parent amine undergoes reaction with elemental fluorine to give the NF compound with liberation of the corresponding fluorosilane as a byproduct. This preparative method is illustrated below in eq 11a,b by the

Table 1. Preparation and Physical and Spectroscopic Properties of Selected NF Reagents

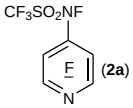
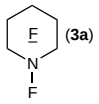
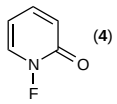
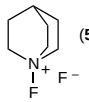
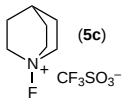
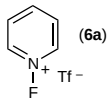
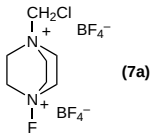
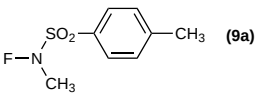
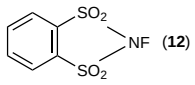
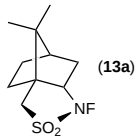
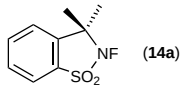
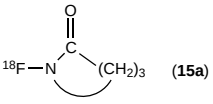
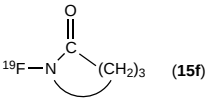
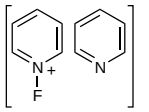
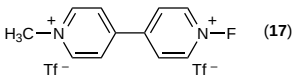
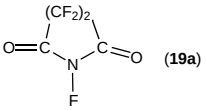
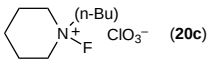
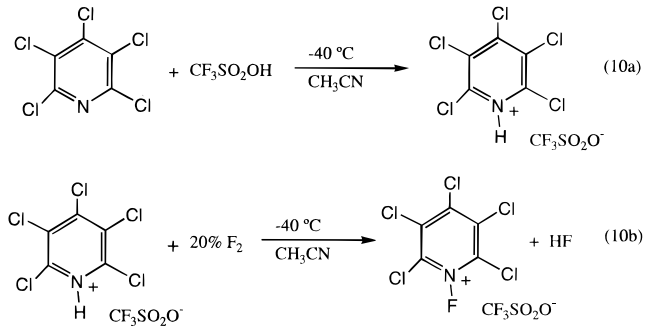
compd	prep method[a] **M**, solvent, *T* (°C) (yield, %)[b]	ref	phys properties	anal. data avail.[c]	$\delta(^{19}F)$[d] of the NF fluorine, ppm (solvent)	commercial avail.[e]
(CF_3SO_2NF (**1a**)	**M-1**, no solvent, 22 (95%)	28−30	colorless liquid, mp −69.8 °C, bp 90−91 °C vp: 30 Torr (22 °C), 40 Torr (25 °C)	i−v	−33.7 ($CDCl_3$)	not currently avail. N/A
 (**2a**)	**M-2**, CH_3CN, −35 (89%)	31	pale yellow semisolid when contaminated with 10 mol % NH compd	ii, v	−24.5 ($CDCl_3$)	N/A
 (**3a**)	**M-3**, AHF, rt (8−13%)	21−23, 92	liquid, bp 49 °C	i−vi	−112.2 ($CFCl_3$)	avail. from FLCHEM
 (**4**)	**M-4**, $CFCl_3$, −78 (63%)	32	waxy white solid, mp 50−53 °C	i−iii, vii	−33 (solvent not specified)	N/A
 (**5a**)	**M-5**, $CFCl_3$, −35 (86%)	34, 35	hygroscopic white solid, mp 126−128 °C	i−iv	58.6 (D_2O)	N/A
 (**5c**)	**M-6**, CH_3CN, −30 to −35 (88%)	79, 80	cryst white solid, mp 266−268 °C dec	i, ii, iv, v	58.0 (D_2O)	avail. from FLCHEM
 (**6a**)	**M-6**, CH_3CN, −40 (80%)	36−40	cryst white solid, mp 185−187 °C	i, ii, iv, v	48.8 (CD_3CN)	avail. from ALD, FLCHEM, PCR
 (**7a**)	**M-6**, CH_3CN, −40 (89%)	42, 43, 81	cryst white solid, mp 234 °C dec	i, ii, v	49.0 (D_2O)	avail. from ALD, APCI, FLCHEM, JANCHIM
$NF_4^+ SbF_6^-$ (**8a**)	**M-11**, no solvent, 250 (not given)	44, 93	white solid	ii, iii	214.7 (AHF)	N/A
 (**9a**)	**M-1**, $CFCl_3/CHCl_3$ (1:1), −78 (59%)	46, 48	solid, mp 42−44 °C, bp 90 °C (0.01 Torr)	i−iv	−37.6 ($CDCl_3$)	avail. from ALD, PCR
$FN(SO_2Ph)_2$ (**10**)	**M-1**, CH_3CN, −40 (70%)	51, 54	white solid, mp 114−116 °C	i	−37.8 (solvent not specified)	avail. from ALD, ALD-SGL, FLCHEM, PCR
$FN(SO_2CH_3)_2$ (**11a**)	**M-1**, CH_3CN, −40 (90%)	52	white solid, mp 45−48 °C	i	not reported	N/A
 (**12**)	**M-1**, $CFCl_3/CHCl_3$ (1:1), −40 (>90%)	53, 54	white cryst solid, mp 139−141 °C with dec	i−v	−12 (C_6D_6)	N/A
 (**13a**)	**M-1**, $CFCl_3/CHCl_3$ (1:1), −40 (75%)	55, 56	colorless cryst solid, mp 112−114 °C	i, ii	−64.9 (solvent not specified)	N/A
 (**14a**)	**M-1**, $CFCl_3/CHCl_3$ (1:1), −40 (75%)	57, 94	white cryst material, mp 114−116 °C	i, ii, v	9.8 ($CDCl_3$)	N/A
 (**15a**)	**M-1**, $CFCl_3$, 0 (76%)	66	not isolated	i	−69.98	N/A
 (**15f**)	**M-1**, H_2O, 0−5 (16.5%) or **M-1**, no solvent, 0−5 (24%)	69 69	liquid, bp 37−38 °C (0.15 Torr) liquid, bp 38−39 °C (0.2 Torr)	i−iii	−71.2 (solvent not specified)	N/A

Table 1. (Continued)

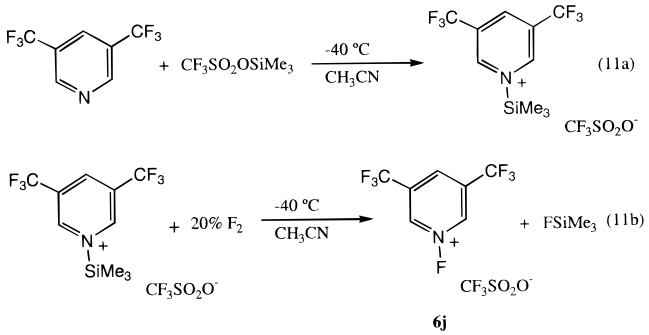
compd	prep method[a] **M**, solvent, *T* (°C) (yield, %)[b]	ref	phys properties	anal. data avail.[c]	$\delta(^{19}F)$[d] of the NF fluorine, ppm (solvent)	commercial avail.[e]
 $B_2F_7^-$ (**16**)	**M-7**, CH_3CN, 0 (33%)	78	tan crystals, mp 196−197 °C	i, ii, v	48.2 (CH_3CN)	avail. from ALD, ALD-SGL, FLCHEM, PCR
 (**17**)		47	the properties of this compd have not yet appeared in the literature			N/A
$(FSO_2)_2NF$ (**18**)	**M-1**, no solvent, 25 °C	88	liquid, mp −79.9 °C, bp 60.8 °C	i−v	−28.5 ppm (neat) (25 °C)	N/A
 (**19a**)	modified **M-10**−XeF_2 transfer reagent, CF_2Cl_2, 0−20 (55−65%)	89	liquid, bp 62−63 °C (25 Torr)	i, ii, v	−71.0 (CH_2Cl_2)	N/A
 (**20c**)	modified **M-10**−$FClO_3$ transfer reagent, CCl_4, <−20 (87%)	90	solid, dec above 70 °C	i, v	155.1 (D_2O)	N/A

[a] Preparative method **M-1** to **M-11** as described in section II. [b] Yield is for the NF compound for the fluorination step only. [c] Some analytical data are reported for the NF compound: (i) mp/bp; (ii) NMR; (iii) IR; (iv) mass spec; (v) elemental analysis; (vi) refractive index; (vii) UV. [d] The fluorine chemical shifts ($\delta^{19}F$) are referenced with respect to $CFCl_3$. A positive chemical shift indicates a resonance occurring to low field of the reference. [e] Reagents are currently (1996) commercially available from the following companies: ALD, Aldrich Chemical Company, Milwaukee, WI 53201; ALD-SGL, Allied-Signal, Inc., Buffalo, NY 14210; APCI, Air Products and Chemicals, Inc., Allentown, PA 18195-1501; FLCHEM, Fluorochem Ltd., Wesley St., Old Glossop, Derbyshire, SK13 9RY U.K.; JANCHIM, Janssen Pharmaceuticalaan, 3,2440 Geel, Belgium; and PCR, PCR Inc., Gainesville, FL 32602.



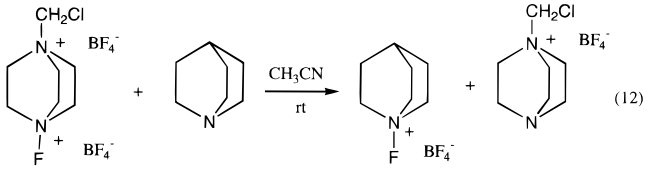
6h

preparation of *N*-fluoro-3,5-bis(trifluoromethyl)pyridinium triflate (**6j**).[39]



6j

In the method **M-10**, described as transfer fluorination, a fluorine atom from an electrophilic fluorinating reagent is transposed to the nitrogen atom of a tertiary amine, thus forming an electrophilic fluorination reagent of lesser strength[41] than that of its predecessor. Transfer fluorination with **7a**,[42,43] which is referred to in this review as the Selectfluor reagent and also in the literature as F-TEDA-BF_4, has recently been used[26] as a convenient means of obtaining the popular electrophilic *N*-fluoroquinuclidinium moiety (**5b**) (eq 12).



7a **5b**

The final example (**M-11**) involves the high-temperature and high-pressure use of neat elemental fluorine for the preparation of the highly electrophilic NF_4^+ salts.[44,45] This is illustrated by eq 13 for the synthesis of NF_4^+ SbF_6^- (**8a**).

$$2NF_3 + 2F_2 + SbF_5 \xrightarrow[72\ h,\ 70\ atm]{250\ °C} \underset{\mathbf{8a}}{NF_4^+SbF_6^-} \quad (13)$$

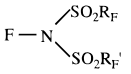
III. Survey of NF Reagents

It is convenient here to again divide the discussion into ternary R_2NF and quaternary $R_3N^+F\ A^-$ classes. Within each class, the compounds are grouped according to structural similarities in their R substituents. Representative structures for each group of NF compounds are collected in Chart 1.

A. Neutral Compounds R_2NF

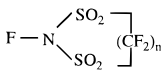
The electrophilic NF reagents of this class cover a very wide range of physical and chemical properties. For instance, reagent **1a** is a volatile liquid that is powerful enough as an electrophile to fluorinate benzene even at room temperature.[28] On the other hand, the Barnette reagents (see section III.A.1.c below), typified by *N*-fluoro-*N*-methyl-*p*-toluene-

Chart 1. Structural Examples of Electrophilic NF Reagents



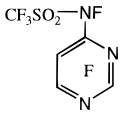
1

R_F	R'_F	example	
CF_3	CF_3	$(CF_3SO_2)_2NF$	**1a**
CF_3	C_nF_{2n+1}	$CF_3SO_2N(F)SO_2C_4F_9$	**1b**
C_nF_{2n+1}	C_nF_{2n+1}	$C_4F_9SO_2N(F)SO_2C_4F_9$	**1c**

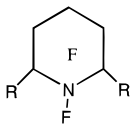


n = 2 (**1d**),3(**1e**),4(**1f**)

2a

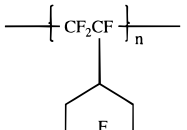


2b

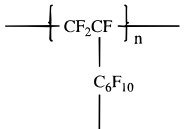


3a R = F

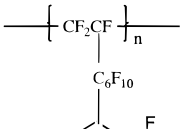
3b R = CF_3



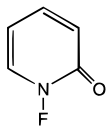
3c



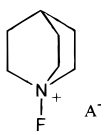
3d



3e



4



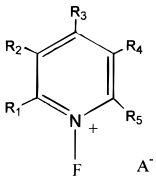
5a A = F

5b A = BF_4

5c A = CF_3SO_3

5d A = CF_3CO_2

5e A = n-$C_3F_7CO_2$



6a: R_1 -R_5 = H; A = OSO_2CF_3

6b: R_1 -R_5 = H; A = BF_4

6c: R_1 -R_5 = H; A = F

6d: R_1 = R_2 = R_3 = Me; A = BF_4

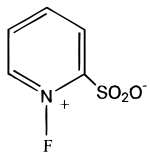
6e: R_2 = R_4 = Cl; A =OSO_2CF_3

6f: R_1 = R_5 = Cl; A = BF_4

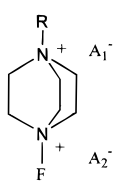
6g: R_1 -R_5 = Cl; A = BF_4

6h: R_1 -R_5 = Cl; A = OSO_2CF_3

6j: R_2 = R_4 = CF_3; A =OSO_2CF_3



6i



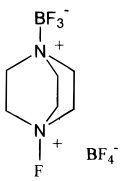
7a: R = CH_2Cl; A_1 = A_2 = BF_4

7b: R = Me; A_1 = A_2 = OSO_2CF_3

7c: R = CF_3CH_2; A_1 = A_2 = OSO_2CF_3

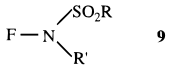
7d: R = OH; A_1 = A_2 = BF_4

7e: R = F; A_1 = A_2 = BF_4



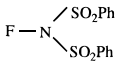
7f

$NF_4^+ A^-$ { A = SbF_6 (**8a**); A = AsF_5 (**8b**); A = BF_4 (**8c**) } N_2F_2 (**8d**); $N_2F^+ AsF_6^-$ (**8e**)

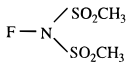


9

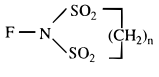
R	R'
p-tolyl	Me (**9a**), *t*-butyl (**9b**), 2-norbornyl (**9c**), cyclohexyl (**9d**) neopentyl (**9e**), n-butyl (**9f**), n-propyl (**9g**)
Ph	*t*-butyl (**9h**)
n-butyl	neopentyl (**9i**)
t-butyl	Me (**9j**), neo-pentyl (**9k**), n-butyl (**9l**)
CF_3	Me (**9m**), n-butyl (**9n**)
C_6F_5	n-propyl (**9o**), neo-pentyl (**9p**)



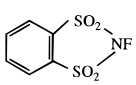
10



11a



n = 1(**11b**), 2(**11c**), 3(**11d**)



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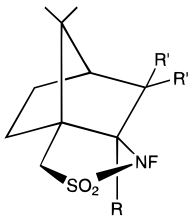
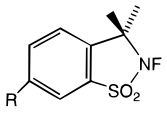


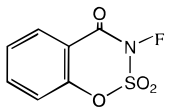
13a R = R' = H

13b R = Me; R' = H

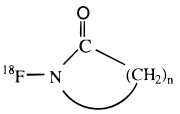
13c R = H; R' = Cl



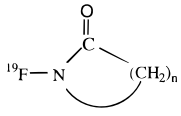
14a R = H; **14b** R = NO_2



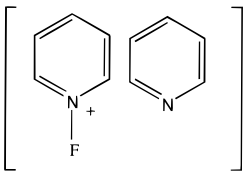
14c



n = 3(**15a**), 4(**15b**), 5(**15c**), 6(**15d**), 7(**15e**)



n = 3(**15f**), 4(**15g**)



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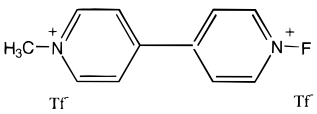

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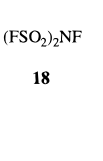
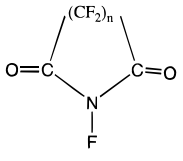
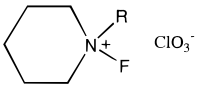


18



19a, n = 2

19b, n = 3



R = Me (**20a**), Et (**20b**), n-Bu (**20c**)

sulfonamide (**9a**), are typically low-melting solids that degrade on standing at room temperature and, as fluorination electrophiles, are active only in the presence of highly activated nucleophilic centers, i.e., carbanions.[46]

1. Sulfonyl Derivatives $RSO_2N(F)R'$

1a. *N*-Fluoroperfluoroalkylsulfonimides, $R_fSO_2N(F)SO_2R_f'$, 1a−f. Some of the most powerful electrophilic NF reagents known are the perfluoroalkylsulfonimides **1**, which were first reported by DesMarteau and co-workers[28] and are shown in Chart 1. The physical properties and characterization data of the most common member of this class, **1a**, are summarized in Table 1.

1b. *N*-Fluoroperfluoro[*N*-(4-pyridyl)-*N*-methanesulfonyl]amide, 2a, and *N*-Fluoroperfluoro-[*N*-(4-pyrimidyl)-*N*-methanesulfonyl]amide, 2b. The title examples, **2a** and **2b,** represent the only members of this type of NF reagent (see **2a** in Table 1) and are somewhat analogous to the perfluorosulfonimides, but contain a perfluoroaryl moiety.[31,47]

1c. *N*-Fluoro-*N*-alkylsulfonamides, $RSO_2N(F)R'$, 9a−p. Because of the presence of an *N*-alkyl group and only a single sulfonyl group, these NF reagents are the weaker electrophilic counterparts to the perfluoro examples discussed previously. Within this group of reagents[46,48−50] can be found a wide variety of *N*-alkyl substituents and alkyl and aryl sulfonyl groups as illustrated in Chart 1. Typical is one of the Barnette reagents, *N*-fluoro-*N*-methyl-*p*-toluenesulfonamide (**9a**),[46,48,49] whose physical properties and characterization data are provided in Table 1.

1d. *N*-Fluorobenzenesulfonimide, $(PhSO_2)_2NF$, 10. The single member[51] of this class (see **10** in Table 1) became popular in the early 1990s owing to its reactivity, which is situated somewhere between the powerful perfluorosulfonimides **1a−f** and the less reactive alkylsulfonamides **9a−p**.

1e. *N*-Fluoroalkylsulfonimides 11a−d. These hydrocarbon analogs[52] of the DesMarteau-type reagents **1a−f** are shown as **11a−d** in Chart 1. The properties of a representative example, **11a**, are given in Table 1.

1f. *N*-Fluoro-*o*-benzenesulfonimide, 12. The final variant of the popular sulfonimide NF reagents is **12** (see Table 1), which was developed in the early 1990s by Davis and co-workers.[53,54] Although very similar to **10**, it is said to have the advantage of an easier purification because its sulfonimide precursor is water soluble.[52]

1g. *N*-Fluorosultams 13a−c and 14a,b and *N*-Fluorooxathiazinone Dioxide, 14c. The first enantioselective fluorination reagents, **13a** and **13b**, were disclosed in the late 1980s by Differding and Lang[55] and are shown in Chart 1. These reagents, as well as the chlorine-containing analog **13c**, reported some years later by Davis and co-workers,[56] are based on camphor and contain the *N*-fluorosultam moiety. Shortly following their initial report of **13a** and **13b**, the authors prepared and described a similar structural type that is based on the saccharin moiety[57,58] and is illustrated by **14a** and **14b** in Chart 1.

As one might expect, the fluorinating power of these *N*-fluorosultam species is on the order of that observed for the Barnette-type reagents **9a−p** discussed previously in section III.A.1.c. The physical properties and characterization data for **13a** and **14a** are given in Table 1. Recently, a new electrophilic NF reagent containing both an acyl and sulfonyl functionality has been reported[59] and is shown as **14c** in Chart 1.

2. N-Fluoroamines and N-Fluoroamides

2a. *N*-Fluoroperfluoroheterocycles 3a−e. The perfluoropiperidine derivatives **3a−c** have been known for some time.[21−23] Compound **3a** (see Table 1) is interesting from a historical perspective insofar as it was used by Banks to first demonstrate that an NF species could deliver an electrophilic fluorine atom.[60] Subsequently, **3a**[61−63] and **3b**[64] have been employed in the fluorination of other substrates but have not gained much popularity or been used extensively because of the low-yield methods available for their preparation.[21−25]

Polymeric versions **3c**, **3d**, and **3e** exist but are also difficult to prepare in high yield[65] (Chart 1).

2b. *N*-Fluorolactams 15a−g. The [^{18}F]-*N*-fluorolactams[66] **15a−g** are only a small subset of the larger and broader class of *N*-fluoroamides that are known. However, it is only the [^{18}F]lactams depicted in Chart 1 that have been reported in the literature as fluorinating reagents. Many of the other examples, which include *N*-fluorocarbamates,[67] *N*-fluoroureas,[68] and even the ^{19}F counterparts[69] of **15a** and **15b**, have been known for some time but have not been exploited as electrophilic fluorination reagents (see Table 1 for **15a** and **15f**).

2c. *N*-Fluoro-2-pyridone, 4. Configurationally similar to the *N*-fluorolactam **15b**, compound **4** (Table 1) was first reported by Purrington and Jones[32,33] in the early 1980s and has been shown to deliver electrophilic fluorine to activated substrates.

B. Quaternary ($R_3N^+F\ A^-$) Compounds

The number of *N*-fluoro quaternary $R_3N^+F\ A^-$ compounds is at least as large as for the ternaries. Moreover, these compounds have gained increasing popularity among synthetic organic chemists because of the commercial availability of several stable and easy to use specific reagents.[70] Generally speaking, the $R_3N^+F\ A^-$ compositions are more powerful electrophilic fluorinating reagents than those of the R_2-NF class, with a notable exception being $(CF_3SO_2)_2NF$ (**1a**), which clearly ranks above any of the commercially available quaternary compounds[41] in terms of electrophilic strength.

The $R_3N^+F\ A^-$ reagents are categorized according to similarities in structure and discussed in turn below.

1. N-Fluoropyridinium Salts

1a. *N*-Fluoropyridinium A^-, 6a−j. The first reports of a molecular complex formed between pyridine and fluorine at low temperatures came from the early work of Simons[71] and later from Meinert.[72,73] It was in Meinert's work that *N*-fluoropyri-

dinium fluoride **6c**, although not stable when isolated, was first proposed and reportedly used for the electrophilic fluorination of uracil. Later, it was Umemoto's realization that *substitution of the fluoride anion with a less nucleophilic counteranion would lead to stabilization of the N-fluoropyridinium moiety*, which led to the first isolated *N*-fluoropyridinium compounds[36] (see **6a** in Table 1). A reinvestigation[39] of the fluorine−pyridine system by ^{19}F NMR spectroscopy confirmed the *N*-fluoropyridinium structure as was first proposed. However, it was not possible to reproduce the reported fluorination of uracil with this system.[74]

There has been a prolific synthesis of *N*-fluoropyridinium salts[37−40,75,76] (Chart 1) as well as process improvements[77] for their manufacture, and even a review dedicated solely to this class of compounds.[19]

1b. *N*-Fluoropyridinium Pyridine Heptafluorodiborate, 16. The name of the title composition implies a uniqueness about its structure (see **16** in Table 1), which unfortunately, is not supported by the data provided in its disclosure.[78] In particular, there is no evidence for the interesting, cited $B_2F_7^-$ anion.

1c. Bipyridyl Derivative 17. Reagent **17** (Table 1) is a bipyridyl species that has been reported by Banks et al.;[47] no description of its reactivity is available.

2. Saturated Derivatives

2a. *N*-Fluoroquinuclidinium X^- 5a−e. This contribution by Banks and co-workers[34,35,79,80] of the first bicyclo NF reagents **5a**−**e** is shown in Chart 1. Some of the physical properties and characterization data of compounds **5a** and **5c** are given in Table 1.

2b. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-Octane $2X^-$ 7a−f. This series of doubly-quarternized *N*-fluoro-1,4-bicyclo[2.2.2]octane derivatives[42,43,81] shown in Chart 1 are exemplified by compound **7a** (Table 1). These compounds are relatively powerful electrophilic fluorine sources with a reactivity that is somewhat dependent on the inductive strength of the R quaternizing group. Recently, the preparation of a similar composition, **7d**, was announced.[82] The 1,4-difluoro-1,4-diazabicyclo[2.2.2]-octane bis(tetrafluoroborate)salt (**7e**) has also recently been synthesized[83,84] and shown to function as a powerful, but less than stoichiometric, source of electrophilic fluorine. In ref 83 the preparation of 1-fluoro-4-aza-1-azoniabicyclo[2.2.2]octane tetrafluoroborate trifluoroborane (**7f**) is described.

C. Nitrogen Fluorides

While some of the title compounds **8a**−**e** (Chart 1) have been used in a few electrophilic fluorination reactions,[45,85,86]safety considerations and the experimentally rigorous conditions required for their preparation[44,85−87] may have limited their widespread application.

D. Potential Electrophilic NF Compounds

There are a large number of NF compounds that have not been reported to function as NF electrophilic fluorination reagents but are potentially active in this regard. Some examples given in Chart 1 include *N*-fluoroimidodisulfuryl fluoride[88] (**18**), *N*-fluoroperfluorosuccinimide[89] (**19a**), *N*-fluoroperfluoroglutarimide[89] (**19b**), and the three *N*-alkyl-*N*-fluoropiperidinium[90] salts **20a**−**c**.

Other examples that may be included in this group are the numerous *N*-fluorocarbamate derivatives prepared by Grakauskas and Baum,[67] the *N*-fluoroureas that are described by Banks and co-workers[68] and the various *N*-fluoroamides prepared by Barton et al.[91]

IV. Applications in Organic Synthesis

A. Synthesis of Fluoroaromatics

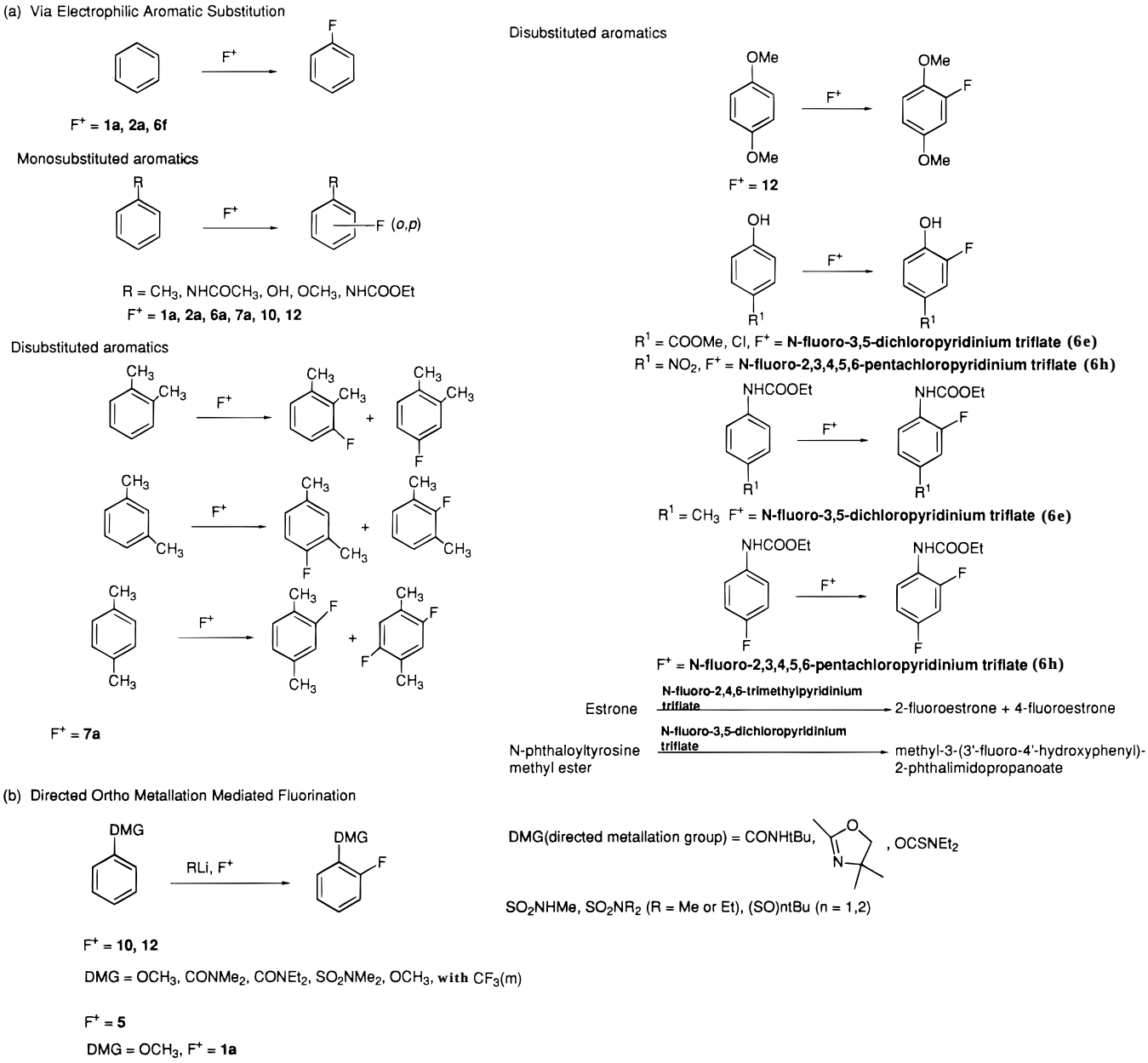
The classical method for introducing fluorine into an aromatic compound is via the Balz−Schiemann reaction.[95] This constitutes the replacement of an aryl-NH_2 by the fluorine atom through a diazo derivative. Alternatively, the exchange of other halogen atoms or the nitro group for fluorine with metal fluorides has been employed.[95] In the quest for new ways to selectively introduce fluorine into biologically active aromatic compounds electrophilic fluorination has been found to provide a useful complement to other available methods.[96]

Reagents such as *N*-fluoroperfluoro[*N*-(4-pyridyl)-*N*-methanesulfonyl]amide (Chart 1 and Table 1, **2a**),[31] *N*-fluoropyridinium salts (**6**),[38] *N*-fluorobenzenesulfonimide (**10**),[51] NF_4BF_4 (**8c**),[97] and $(CF_3SO_2)_2$-NF (**1a**)[28] have been employed in electrophilic aromatic substitution reactions (Scheme 1). Compounds with varying degrees of activation toward electrophilic aromatic substitution have been efficiently fluorinated. These include phenols, anisole, acetanilide, xylene, toluene, benzene, and naphthalene. Among the known NF reagents a wide range of reactivity was observed. The reactions can be carried out in a variety of solvents (halocarbons, CH_3CN, or in HF) or in the substrate itself, and the products are usually mixtures of *o*/*p*-isomers. While in most cases, monofluorinated products are obtained, multiple fluorination has been observed in some reactions with the more reactive reagents NF_4BF_4(**8c**),[97] (CF_3-$SO_2)_2NF$ (**1a**),[28] Selectfluor (or F-TEDA-BF_4) (**7a**),[98] and *N*-fluoropyridinium salts (**6**).[38]

The known strategy of directed ortho-lithiation,[96] followed by electrophilic fluorination, has been successfully applied to the synthesis of regioisomerically pure ortho-fluorinated aromatic compounds. A range of carbon, oxygen, and sulfur orthometalation directing groups on aromatic compounds have been used to prepare *o*-lithiated substrates. These react readily with *N*-fluorobenzenesulfonimide (**10**),[96] *N*-fluoro-*o*-benzenesulfonimide (**12**), $(CF_3SO_2)_2NF$ (**1a**),[99] and *N*-fluoroquinuclidinium triflate (**5c**)[99] to yield the selectively fluorinated aromatics as shown in Scheme 1b.

While XeF_2[100] readily fluorinates pyrroles and bromofluorofurans are generated from the reaction of **7a** with bromofuroic acids,[101] there are, otherwise, not many reported examples of electrophilic fluorination of aromatic heterocycles.[38] However, lithiopyrroles react readily with *N*-fluorobenzene sulfonimide (**10**)[102] to generate the corresponding fluorinated

Scheme 1. Synthesis of Fluoroaromatic Compounds



products in good yields, and fluorothiophene has been obtained by the reaction of *N*-fluoroquinuclidinium fluoride (**5a**)[34,35] or N_2F_2 (**8d**)[86] with 2-lithiothiophene.

Polyaromatic compounds such as naphthalene and phenanthrene react with **7a** to give, respectively, 1- and 2-fluoronaphthalene, and 9-fluorophenanthrene.[103] A corresponding reaction with anthracene in CF_3COOH afforded 9-(trifluoroacetoxy)anthracene. The product of fluorination of 9-methoxyphenanthrene was highly dependent on the solvent, and 9-fluoro-10-methoxyphenanthrene was obtained on fluorination in CF_3COOH. Brunavs and co-workers[104] observed a slow fluorination of the anthraquinone nucleus on reaction of dimethyl rhein methyl ester with **7a**. The reaction of 1-naphthol with *N*-fluoropyridinium triflate **6a** afforded a mixture of 2-fluoro-1-naphthol, 4-fluoro-1-naphthol, and 2,2-difluoro-1-(2*H*)-naphthalenone, while 2-naphthol reacted with 3,5-dichloro-1-fluoropyridinium triflate to produce 1-fluoro-2-naphthol and 1,1-difluoro-2(1*H*)-naphthalenone.[38]

B. Fluorination of Carbanions

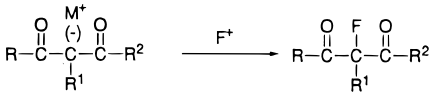
As expected, reactions of carbanions with the NF reagents are generally more facile than those with neutral nucleophilic substrates. Aryl and alkyl Grignard reagents react readily to produce the corresponding fluorides.[33,38,53,98] While some fluorinating reagents only react with stabilized carbanions, others have proven useful for the fluorination of both highly reactive carbanions as well as those that are stabilized with a variety of functionalities including CN,[38] $ArSO_2$,[33,98] $PO(OR)_2$,[98] CO,[35,38,46,51−53,57,98,105,111] COOR,[33,34,35,38,46,53,57,98,105−111] and NO_2.[34,111] The following section details the reactions of carbonyl-stabilized carbanions.

1. Synthesis of α-Fluoro Carbonyl Compounds

The introduction of a fluorine atom adjacent to the carbonyl functionality increases the electrophilicity of the carbonyl carbon atom and consequently facilitates the addition of nucleophiles. Nucleophilic ad-

Scheme 2. Fluorination of β-Dicarbonyl Compounds

(a) Via metal enolates



R = O-alkyl, alkyl, aryl

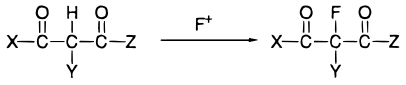
R^1 = alkyl, aryl, Cl, H

R^2 = alkyl, aryl, O-alkyl

M = Na, K

F^+ = **1a, 4, 5a, 6, 7a, 9, 10**

(b) Via the neutral compound



X = alkyl, N-dialkyl, aryl, O-alkyl

Y = alkyl, aryl, H

Z = alkyl, aryl, N-dialkyl

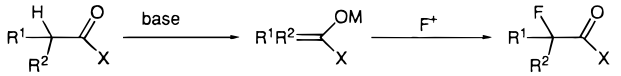
F^+ = **6, 7a, 1a**

dition of enzyme active sites to the carbonyl group of α-fluoro ketones has been suggested as being responsible for the inhibition of a variety of enzymes.[1] α-Fluoro carbonyl compounds have been prepared by fluoride ion displacement of a halide from a α-halo carbonyl or by the reaction of a diazo derivative with HF.[1] Electrophilic fluorination of metal enolates[33,36,38,46,51,53,57,105−111] silyl enol ethers,[38,51,98,112] and enol acetate[38,98,112] is now a well-established route to the title compositions.

1a. Via β-Dicarbonyl Compounds. The metal enolates of malonates and monosubstituted malonates react with *N*-fluoroquinuclidinium salts **5**,[34,35] 1-fluoro-2-pyridone (**4**),[33] *N*-fluorobenzene sulfonimides **10**,[51] $(CF_3SO_2)NF$ (**1a**),[109] *N*-fluoro-*N*-alkylsulfonamides **9**,[46] and *N*-fluoro-2,4,6-trimethylpyridinium triflate[38] to produce the corresponding fluorinated derivatives. The *N*-fluoropyridinium salts **6** also react with β-keto esters and β-diketones in the presence of Lewis acids to generate the mono- and difluorinated β-dicarbonyl compounds[38] (Scheme 2).

Reaction of **7a** with monosubstituted malonates, β-keto esters and β-keto amides gives the corresponding monofluorinated products in high yields under neutral conditions[111] or via the metal enolates.[98] While β-diesters are inert toward fluorination by **7a,** their sodium salts provide excellent yields of fluorinated products. The corresponding 2,2-difluoro derivatives can also be obtained in high yields on fluorinating the sodium salts of the monofluoro compounds. *N*-Fluoroperfluoroalkylsulfonimides (**1**) also afford the singly fluorinated products on reaction with monosubstituted malonates, β-diketones, and β-keto esters under neutral conditions or via their metal enolates.[107−109] With **7a**, β-diesters cannot be fluorinated under neutral conditions. Unsubstituted

Scheme 3. Synthesis of α-Fluorocarbonyl Compounds via Metal Enolates



R1 = H, alkyl, aryl,

R2 = H, alkyl, aryl

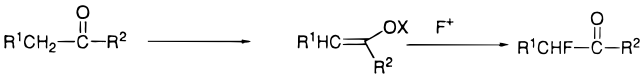
X = O-alkyl, N-dialkyl, alkyl, aryl

M = Li, Na, K

F^+ = **1a, 9, 10, 14**

Scheme 4. Synthesis of α-Fluorocarbonyl Compounds

(a) via silyl enol ethers and alkyl enol ethers

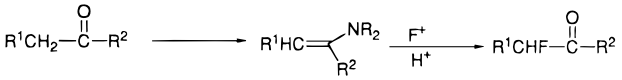


R^1, R^2 = alkyl, aryl

X = $SiMe_3$, alkyl, $COCH_3$

F^+ = **6a, 7a, 10, 16**

(b) Via enamines



R^1, R^2 = alkyl or aryl, R = alkyl

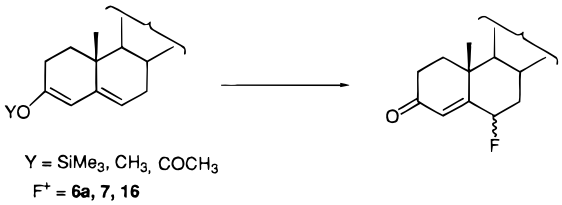
F^+ = **4, 5, 6, 16, 19**

β-diketones and β-keto esters afford α,α-difluorinated products when 2 equiv of $(CF_3SO_2)_2NF$ (**1a**) is used. However, the reaction can be stopped at the monofluorinated stage if the acidic byproduct $(CF_3SO_2)_2NH$ is removed by conducting the reaction in an aqueous/organic solvent system.[110]

1b. Via Monocarbonyl Enolates and Derivatives. A simple method for obtaining α-fluoro carbonyl compounds involves the reaction of carbonyl-derived metal enolates with electrophilic fluorinating agents containing the reactive NF bond (Scheme 3). The *N*-fluorosulfonamides **9** and *N*-fluorosulfonimides **1** and **10** have been shown to be quite effective for this purpose. For example, $(CF_3SO_2)_2NF$ (**1a**) reacts with the lithium enolates of esters, amides, and ketones to afford exclusively[107] the α-fluoro carbonyl compounds. Differding and co-workers utilized *N*-fluorobenzenesulfonimide (**10**)[51] and the *N*-fluorosultam derivative of saccharin (**14**)[57] to produce α-fluoro ketones and α-fluoro esters from the corresponding lithium salts, while Davis and co-workers obtained good yields of fluorinated products by reacting *N*-fluoro-*o*-benzenesulfonimide (**12**) with the sodium enolates of ketones, imines, and esters.[53] The *N*-fluoro-*N*-alkylsulfonamides (**9**) produce α-fluoro ketones from the lithium enolates of ketones.[46]

An alternative method of generating α-fluoro carbonyl compounds is by treating a preformed carbonyl derivative with the fluorinating agent. Enol ac-

Scheme 5. Synthesis of γ-Fluorocarbonyl Compounds



etates,[38,98,112] silyl enol ethers,[38,51,98,112] enamines,[34,38,80,86,112] and enol ethers[38] of carbonyl compounds have been employed in this regard with a variety of NF-type reagents to synthesize many structurally diverse α-fluoro carbonyl compounds. The reactions are generally quite facile and proceed in good yields (Scheme 4).

2. Synthesis of γ-Fluoro Carbonyl Compounds

The introduction of a fluorine atom at the γ-position from a carbonyl functionality using electropositive fluorine sources has been especially popular for the synthesis of 6-fluorosteroids. The conjugated vinyl acetates derived from Δ^1-3-keto- or $\Delta^{1,4}$-3-ketosteroids react readily with some NF-type reagents to afford exclusively 6-fluorosteroids as a mixture of α,β-isomers[38,98,112] (Scheme 5). The Selectfluor reagent **7a** is particularly effective in this regard: it reacts rapidly at room temperature giving only the 6-position fluorosteroids in high yield.[98] While **7a**[98] and the *N*-fluoropyridinum salts **6**[38] produce mixtures of 4-fluoro- and 6-fluorosteroids from the alkyl and silyl enol ether derivatives of α,β-unsaturated 3-ketosteroids, Poss and co-workers reported exclusive 6-position fluorination of these compounds using *N*-fluoropyridinium pyridine heptafluorodiborate (**16**).[112] These workers also reported a C-6 fluorination of steroids by the reaction of enoxyboronates of Δ^4-3-ketosteroids with *N*-fluorobenzenesulfonimide (**10**).[113]

C. Fluorination of Olefins

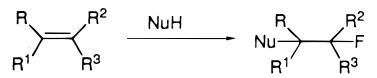
The electrophilic fluorination of olefins in the presence of weak nucleophiles has been studied with several electrophilic fluorinating agents, e.g., XeF_2,[114] $CsSO_4F$,[115] and CF_3COOF.[116] This type of reaction has been described only for the more reactive reagents of the NF class such as **7a**,[98] $(CF_3SO_2)_2NF$ (**1a**),[117] and 1-fluoro-2,3,4,5,6-pentachloropyridinium triflate.[38]

In the presence of weak nucleophiles, H_2O, AcOH, HF·pyridine, or MeOH in CH_3CN, **7a** reacts with styrene derivatives, introducing a fluorine atom and the nucleophilic component on the adjacent carbon (Scheme 6).[98]

The reaction proceeds according to Markovnikov-type regioselectivity in high yields. Stavber and coworkers[118] found that the rate of fluorination of styrene derivatives with **7a** in MeOH is highly dependent on the substitution pattern of the carbon−carbon double bond with the parent styrene molecule being the least reactive. These investigators also observed the stereochemical outcome on fluorination of phenyl-substituted benzocyclenes to be highly

Scheme 6. Fluorination of Olefins

(a) Aryl-substituted olefins

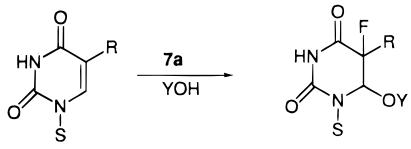


R = aryl, R^1 = H, aryl or alkyl, R^2 = H , aryl or alkyl, R^3 = H, aryl or alkyl

NuH = AcOH, H_2O, ROH (R= alkyl), or HF. pyridine

F^+ = **1a,7a, N-fluoro-2,3,4,5,6-pentachloropyridinium triflate (6h)**

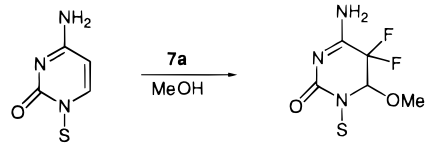
(b) Pyrimidine bases



S = sugar component of nucleoside or H

YOH = H_2O, AcOH, MeOH

R = CH_3 or H



S = sugar component of nucleoside

dependent on the size of the olefin-containing ring with 3-phenyl-1*H*-indene, giving a mainly *syn* product, while 9-phenyl-6,7-dihydro-5*H*-benzocycloheptene gives exclusively an *anti* product. The fluorination of aryl, alkyl-substituted tertiary alcohols with **7a** in refluxing CH_3CN affords fluorohydrin products, presumably by fluorohydroxylation of an intermediate olefin obtained by dehydration of the tertiary alcohol.[119]

Pentachloropyridinium triflate (**6h**) in the presence of AcOH or alkoxysilanes reacts with styrene and derivatives with Markovnikov regioselectivity to provide the corresponding fluorinated products.[38] Alkyl-substituted olefins were also easily fluorinated in acetic acid to give the fluoroacetoxy adducts.

DesMarteau et al. investigated the reaction of olefins with $(CF_3SO_2)_2NF$ (**1a**).[117] Electron-rich olefins react to produce a complex mixture of products in solvents of low nucleophilicity, e.g., CH_2Cl_2, Freon 113, or THF. However, in solvents of higher nucleophilicity, e.g., H_2O and AcOH, styrene and its derivatives produce the expected Markovnikov addition products. Olefin fluorination with **1a** appears to proceed via an α-fluorocarbocation intermediate, and the outcome of the reaction is highly solvent dependent with polar solvents such as AcOH increasing the reaction rate. It is interesting to note that only olefins capable of producing highly stabilized carbonium ions incorporate the fluorine atom on reaction. Alkenes such as cyclohexene, 1-octene, and 2,3-dihydro-2*H*-pyran afford no fluorinated products. In addition, less efficient fluorinations were observed when reactions were carried out in the presence of

free radical scavengers, e.g. *p*-dinitrobenzene and 1,4-benzoquinone.

The nucleoside bases uracil and thymine react with aqueous **7a** on heating at 90 °C to produce the corresponding fluorohydrin.[120] A similar fluorination of the base component of the nucleosides 2′,3′,5′-triacetyluridine, 2′,3′,5′-triacetylcytidine, and 3′,5′-diacetylthymidine in H_2O, MeOH, or CH_3COOH takes place to produce, respectively, the corresponding fluorohydrin, fluoromethoxy, and fluoroacetoxy derivatives.[120]

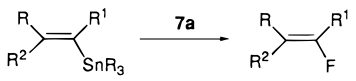
D. Fluorination of Organometallic Compounds

The electrophilic fluorination of alkenyl and heteroarylstannanes with F_2,[121] $CsSO_4F$,[122] and XeF_2/$AgPF_6$[123] have been well documented. In recent reports,[124,125] **7a** has been shown to be as effective for the fluorination of these organometallics. The reaction of terminal vinyl stannanes and fluorovinyl stannanes with **7a** in refluxing CH_3CN generate respectively monofluoroolefins or difluoroolefins in very good yields[124] (Scheme 7a). Moderate yields of 2-fluoroindoles and 3-fluoroindoles were obtained on reaction of the corresponding stannylated indole at room temperature in CH_3CN[125] (Scheme 7b). The ortho-stannylated anisole, bis(2-methoxyphenyl)dimethyltin, prepared from *o*-lithioanisole and dimethyltin dichloride reacts with **7a** to afford exclusively *o*-fluoroanisole.[126]

McClinton and Sik[127] prepared 5-fluorocyclopentadiene by reacting cyclopentadienylthallium with **7a** (Scheme 7c). The product was shown to be a useful Diels−Alder diene in reaction with various dienophiles forming adducts having exclusively *syn* orientation.

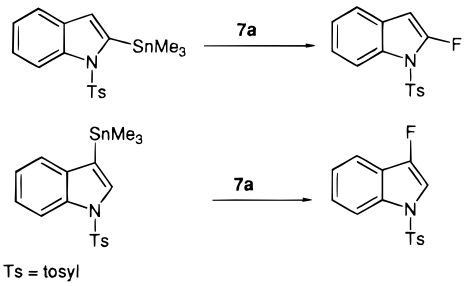
Scheme 7. Fluorination of Organometallic Compounds

(a) Vinyl stannanes



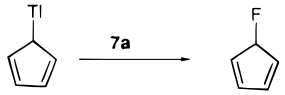
R, R_2 = alkyl or aryl, R_1 = H or F, R_3 = alkyl

(b) Stannylindoles



Ts = tosyl

(c) Cyclopentadienylthallium



E. Synthesis of (Fluoromethyl)phosphonates—Precursors to Mono- and Difluoroolefins

The Horner−Emmons variation of the fluoro-Wittig reagent has been successfully used to prepare fluoroolefins.[128] The reagents can be obtained by reaction of halofluorocarbons with phosphites.[129] Other methods include the reaction of diethyl chlorophosphate with substituted fluoromethyl anions[130] and the reaction of phosphonate ylides with electrophilic fluorinating reagents.[131]

The sodium salt of diethyl [(phenylsulfonyl)methane]phosphonate reacts with **7a** at room temperature in THF/DMF to afford a mixture of diethyl [(phenylsulfonyl)fluoromethane] phosphonate (60%), diethyl [(phenylsulfonyl)difluoromethane] phosphonate (15%), and starting material (25%). However, when the sodium salt of diethyl [(phenylsulfonyl)iodomethane]-phosphonate is contacted with **7a** in THF/DMF, fluorination occurs instantaneously with liberation of I_2 to afford diethyl [(phenylsulfonyl)fluoromethane]-phosphonate in 84% overall yield from diethyl [(phenylsulfonyl)methane]phosphonate.[132]

A sequential replacement of both hydrogen atoms of the methylene group of diethyl [(phenylsulfonyl)-methane]phosphonate with fluorine atoms can be realized by reaction of the sodium salt of this compound with **7a**. Hydrolysis of the diethyl phosphonate component of diethyl [(phenylsulfonyl)difluoromethane]phosphonate with aqueous NaOH at room temperature produces difluoromethyl phenyl sulfone in >80% yield.[132] This compound has been found to be very useful for introducing the difluoroolefin entity at C2′ of cytidine.[133]

The $(CF_3SO_2)_2NF$ reagent (**1a**) also proved quite effective for fluorinating the phosphonate derived ylide. The lithium salt of diethyl (cyanomethyl)-phosphonate reacts rapidly to afford the monofluorinated phosphonate in good yields.[131] This resulting Horner−Emmons fluorinating reagent is a useful precursor to cyano-substituted vinyl fluoride.

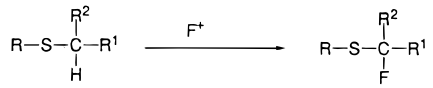
Another practical method for the synthesis of vinyl fluorides involves the electrophilic fluorination of vinyl anions.[51] Akenyl iodides on lithiation with t-BuLi react with *N*-*tert*-butyl-*N*-fluorobenzenesulfonamide (**9h**) to prepare alkenyl fluorides.[49]

F. α-Fluorination of Sulfides

The α-fluoro sulfides constitute an important class of fluorinated compounds that has proven to be valuable in modifying the biological activity of β-lactam antibiotics[134] and amino acids.[135] They also serve as useful synthetic intermediates to medicinally active compounds.[136] Various electrochemical processes have been used for α-fluorination of sulfides.[137] Electrophilic fluorination of sulfides to produce α-fluoro sulfides has been demonstrated with XeF_2[138] and with *N*-fluoropyridinium salts.[139] Sulfides bearing α-hydrogens react with *N*-fluoropyridinium salts (**6**) in CH_2Cl_2 at room temperature (<15 min) to produce α-fluoro sulfides via the Pummerer-like rearrangement.[139] A similar conversion of sulfides to α-fluoro sulfides was demonstrated with **7a** (Scheme 8).

This strategy for α-fluorination of sulfides has been especially important for introducing the fluorine atom

Scheme 8. α-Fluorination of Sulfides



R, R^1 = alkyl or aryl

R^2 = H or sugar component of nucleoside

F^+ = **6, 7a**

into the sugar component of nucleosides. Fluorination of C2′, C3′, and C5′ thioaryl-substituted nucleosides with **7a** affords the corresponding fluorinated products in 40−50% yield[140] (Scheme 8).

G. Asymmetric Fluorination with NF Reagents

Optically active fluorine-containing compounds where one of the chiral centers bears a fluorine atom have been utilized in studies of enzyme mechanisms and as synthetic intermediates in asymmetric transformations.[141,142] Electrophilic fluorination provides a viable route to nonracemic α-fluoro carbonyl compounds. Ihara et al.[143a,b] developed a general procedure for the synthesis of optically active monofluorinated malonic acid derivatives by reaction of the lithium salt of methyl (1*R*,3*R*,4*S*)-8-phenylmenthyl alkyl malonates with 1-fluoro-2,4,6-trimethylpyridinium triflate. A high yield and diastereoselectivity (*R*:*S* = 3.8:1) was obtained from the 2-methyl-substituted malonate. A lower yield, but higher stereoselectivity (*R*:*S* = 5.7:1) was obtained on fluorination with *N*-fluoro-*N*-propylsulfonamide. Using *N*-fluoro-*o*-benzenesulfonimide (**12**) as the electrophilic fluorine source, Davis and co-workers obtained high diastereoselectivities (up to 97% de) on reaction of chiral oxazolidinone enolates.[143c] The fluorination of ketone and ester enolates with the enantiomerically pure *N*-fluorodichlorocamphorsultam (**13c**)[56] and *N*-fluorocamphorsultam (**13a**)[55] provided optically active α-fluoro carbonyl compounds with enantioselectivities that are dependent on the enolate structure and reaction conditions.

V. Reaction Mechanisms and Relative Reactivity

In electrophilic fluorinating compounds the traditional role of fluorine as a nucleophile is reversed.[17] This apparent anomaly has led to much discussion in the literature on the concept of an electrophilic fluorine and on the mechanism(s) by which this fluorine is transferred from reagent sources to carbanionic-type organic substrates.

A. Concept of Electrophilic Fluorine

Elemental fluorine is potentially a source of F• radicals, F^- ions, and cationic fluorine, F^+. The energetics for their formation is as follows:[144]

$$F_2 \rightarrow 2\ F^\bullet \qquad \Delta H^\circ = 158.8\ \text{kJ mol}^{-1}$$

$$F_2 \rightarrow F^+ + F^-$$

$$\Delta H^\circ = 1760.1 - 248.6 = 1511.5\ \text{kJ mol}^{-1}$$

The homolytic dissociation of fluorine is a much more facile process than heterolysis, principally because of the great instability of F^+. While F• radicals and solvated and even "bare" F^- ions[145] have well-established chemistry, F^+ (and also the $F_2^{\bullet+}$ radical cation[146]) have only been observed spectroscopically in the gas phase:[147,148] there are no known fluoronium, F^+A^- salts. The highly oxidizing cations, XeF^+, N_2F^+, and NF_4^+ have been viewed[144] as stabilized forms of F^+. This notion of stable compounds comprising and being able to deliver a positive fluorine has been the subject of some controversy. As early as 1968, Barton et al.[149] commented on the significance of being able to realize direct aromatic substitution with "electrophilic" fluorine, as derived from fluoroxytrifluoromethane CF_3OF. The unusual $X^{\delta-}F^{\delta+}$ polarity later proposed[150] to account for the electrophilic fluorinating properties of fluoroxy compounds ($X = CF_3O$) and of perchloryl fluoride, $FClO_3$, was challenged on the grounds that fluorine as the most electronegative element cannot be polarized in this direction, i.e., carrying a more positive charge than the group to which it is attached.[151,152] It was noted in reply that electronegativity arguments should be used with restraint in molecules where there are only small electronegativity differences or where fluorine is joined to delocalized electron systems where back-bonding from fluorine can occur.[144,150]

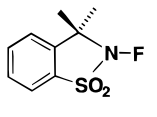
The meaningful assignment of partial atomic charges in molecules is a continuing conceptual problem that is the subject of current discussions in quantum chemistry.[153] While an adequate quantitative description of charge distribution for R_fOF (R_f = perfluoroalkyl), R_2NF, and $R_3N^+A^-$ reagents would be desirable, there is currently little doubt, from the observed organic chemistry (section IV), that such molecules react with nucleophiles, in effect, delivering a positive fluorine. However, the mechanism by which this occurs is not well understood and has also been a subject of considerable debate in the recent literature.

B. Reaction Mechanisms

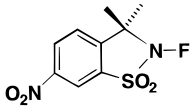
1. Electron Transfer Chemistry

The conceptually simplest possible chemistry of the *N*-fluoro reagents is in electron transfer processes where there is cleavage of the nitrogen−halogen bond and ultimate reduction to fluoride. This is seen, for instance, in their reaction with aqueous iodide (eq 2), which has emerged as a useful test for sources of positive (or radical) fluorine.

The elegant studies by Andrieux, Saveant et al.[154] of the electrochemical reduction of aromatic *N*-halosultams have provided valuable insights into the potential mechanisms by which NF compounds react with electron donors and organic nucleophiles. A reduction of *N*-fluorosaccharin sultam **14a** at an inert electrode was shown to take place by a concerted mechanism where electron transfer is accompanied by NF bond cleavage, elimination of fluoride, and subsequent reduction to the amide ion (eqs 14 and 15).



14a



14b

$$>NF + e^- \rightarrow >N^\bullet + F^- \quad (14)$$

$$>N^\bullet + e^- \rightarrow >N^- \quad (15)$$

Interestingly, reduction of the 4-nitro-substituted *N*-fluorosaccharinsultam **14b** takes place by a stepwise process with formation of an intermediate $[NF]^{\bullet-}$ radical anion species:

$$>NF + e^- \rightarrow [>NF]^{\bullet-} \rightarrow >N^\bullet + F^- \quad (16)$$

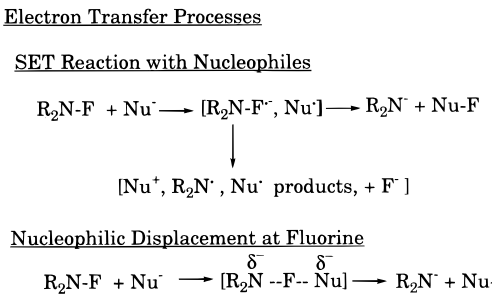
The encountered reaction path is a function of both the *N*-halogen bond dissociation energy and the substrate's electron affinity. It is proposed that, in general, a concerted simultaneous reduction and cleavage may be expected where the *N*-halogen bond is relatively weak. On the other hand, when the substrate has a relatively high electron affinity (where there is a low-lying π^* orbital for the incoming electron), the stepwise process will be favored. Sultams **14a** and **14b** have nearly the same NF bond dissociation energy (65 kcal/mol), but the 1.6 eV lower π^* level of the nitro compound apparently dictates its reduction by the sequential mechanism (eq 16) where the anion radical appears as an intermediate on the reaction pathway. These electrochemical studies have also furnished some of the first standard potentials for NF compounds: −0.12 V vs SCE for **14a** and −0.89 V vs (aqueous) SCE for **14b**. Values of redox potentials and intrinsic barriers for electron transfer were used to provide insight on ET transfer vis-à-vis S_N2 fluorination mechanisms as discussed below (section 2b)

2. Reactivity with Organic Nucleophiles

In reactions of R_2NF and $R_3N^+F\ A^-$ fluorinating agents with nucleophiles there is characteristically a transfer of charge from these substrates to fluorine, with organofluorine compounds or simply ionic fluoride as potential products. How this transfer takes place, whether by discrete electron transfer (SET) steps, as in the just-described electrochemical processes, or by a direct attack of the nucleophile at fluorine, is an interesting topic for review and discussion. Mechanistic possibilities are represented schematically for the neutral R_2NF reagents in Scheme 9.

2a. SET Reactions with Nucleophiles. Umemoto et al.[38] explain the observed reactivity of their *N*-fluoropyridinium (**6a**−**j**) salts with anionic and neutral substrates by one-electron transfer (SET) processes involving the $F^\bullet$ radical species (Scheme 9). For the anionic substrates they cite as supporting evidence for this mechanism the greater reactivity of the reagents toward Grignards (which are known to undergo SET chemistry) than the organolithiums. Also, there are arguments based on observed product distributions. For olefin and aromatic substrates it is proposed that the electron transfer takes place

Scheme 9



through the initial formation of a (charge-transfer) π complex. DesMarteau et al.[117] propose a similar SET mechanism for fluorinations by *N*-fluoro-perfluoroalkylsulfonimides **1a**−**f**. They also cite the formation of sometimes highly colored charge-transfer complexes, which could be intermediates to products that contain some, or even no, fluorine. A localized SET transfer process has been invoked to explain the ortho-directed fluorination of *N*,*N*-dimethylaniline by perfluoropiperidine (**3a**).[155]

Kochi et al.[156−158] have established an interesting and particularly revealing link between the mechanisms of electrophilic aromatic nitration and fluorination with, respectively, *N*-nitropyridium (O_2NPy^+) and *N*-fluoropyridium cations. Nitration of aromatics[156] with the former was shown to take place via a multistep pathway involving the rapid initial formation of charge-transfer (CT) or electron donor−acceptor (EDA) complexes (eq 17).

$$ArH + O_2NPy^+ \overset{K_{EDA}}{\rightleftharpoons} [ArH, O_2NPy^+] \quad (17)$$

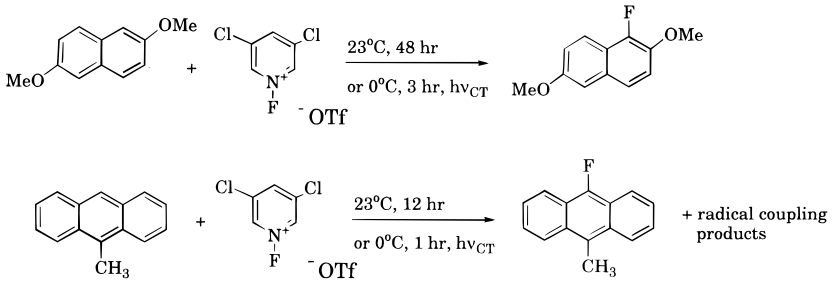
EDA complexes display characteristic charge-transfer (CT) absorption bands in the UV/vis region, which in this case correspond to the following transition, eq 18.

$$[ArH + O_2NPy^+] \xrightarrow{h\nu_{CT}} [ArH^{\bullet+}, PyNO_2^\bullet] \quad (18)$$

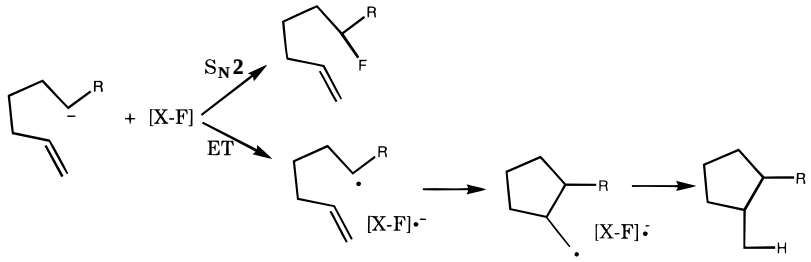
There is a strong correlation between the activation energy for nitration and this electronic excitation energy $h\nu_{CT}$, which, in turn, is a function of the HOMO−LUMO gap between the aromatic donor and acceptor electrophilic cation. The activation process of eq 18 occurs thermally, as in conventional nitration, or where it is stimulated in photolytic reactions by irradiation at the CT band energy ($h\nu_{CT}$). In both instances, the $[ArH^{\bullet+}, PyNO_2^\bullet]$-activated complex is transformed in several steps into the $[HAr^+NO_2]$ classical Wheland intermediate that leads to the final nitration product.

Related, though much less extensive, studies by Kochi et al.[157, 158] point to the occurrence of similar mechanisms in the electrophilic fluorination of aromatics by *N*-fluoropyridinium salts. *N*-Fluoro-3,5-dichloropyridinium triflate was shown to interact with a series of aromatic donor substrates forming EDA complexes with characteristic CT absorption bands. A correlation was established between this CT energy ($h\nu_{CT}$) and the ionization potential (I_p) of the aromatic donors, as was done for nitration. With a progressive decrease in I_p, $h\nu_{CT}$ correspondingly

Scheme 10



Scheme 11



diminishes, making the excited charge-transfer state [$ArH^{\bullet+}$, $FPy^{\bullet}$] more accessible and the substrate thus potentially more reactive to electrophilic fluorination. The aromatics of listed I_p values (eV), durene (8.05), 1-methoxynaphthalene (7.72), anthracene (7.55), 2,6-dimethoxynaphthalene (7.58), and 9-methylanthracene (7.31), all form colored CT complexes with the fluorinating reagent, but only for the last two, more electron-rich substrates, was the color slowly bleached on standing (in the dark). However, all were fluorinated under photolysis by irradiating at the CT energy. Remarkably, the thermal and photolytic charge-transfer fluorination of the noted two substrates gave essentially the same product distribution. In both cases, for 2,6-dimethoxynaphthalene only the 1-fluoro derivative was obtained, while 9-methylanthracene gave 9-fluoro-10-methylanthracene and coupling products of the intermediate benzyl radical (see Scheme 10).

These results (which are similar to findings with nitration) point to a close relationship between the activated complex in the thermal fluorination process and the ion−radical pair, i.e., [$ArH^{\bullet+}$, $FPy^{\bullet}$] in the charge-transfer photochemical synthesis.[158]

2b. Nucleophilic Displacement at Fluorine. As illustrated in Scheme 9, this is the classical S_N2 reaction mechanism. Attack on fluorine by the nucleophile results in the displacement of the R_2N^- group, which must necessarily be a better leaving group than fluoride.[17] In recent terminology, this may be viewed as a "fluorophilic" reaction.[159] It is the mechanism first invoked in the present context by Banks and Williamson[60] to explain the fluorination of some carbanions by perfluoropiperidine (**3a**). It was subsequently invoked by Barton[160] to explain the fluorination of activated olefins by CF_3OF and has remained an alternative to the discussed SET formalism.

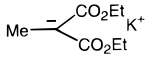
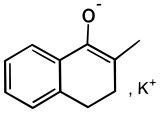
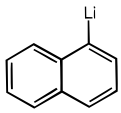
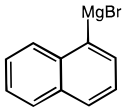
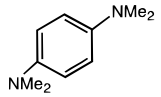
Differding et al.[161,162] in conjunction with Saveant, Andrieux, and co-workers,[154] have provided the most incisive analysis of this question of nucleophilic substitution versus electron transfer in electrophilic fluorination. Experiments with a radical clock fluorination substrate and kinetic studies in the context of ET theory predictions appear to rule out radical pathways, thus pointing to the operation of an S_N2 mechanism, at least for the investigated reagent/substrate combinations.

The general concept of using a radical clock as a mechanistic probe is illustrated with reference to Scheme 11.

The fluorination substrate is a carbanion containing a 5-hexenyl carbon chain, which if oxidized to a radical in the fluorination process should cyclize to a cyclopentylmethyl radical intermediate. Reaction of a specific citronellic ester enolate probe of this kind with the three NF reagents **14a, 10**, and **5c** resulted only in fluorination at the carbanionic carbon of the enolate; no cyclic products were detected. While the use of xenon difluoride leads to the same fluorinated compounds, a cyclic non-fluorinated product is also formed. This indicates that free radicals are not intermediates in the fluorination path, but may be involved, as with XeF_2, in side reactions to give nonfluorinated compounds. The fluorination of this model enolate is thus most simply accounted for by an S_N2 mechanism, with ET as a potential competitive but "unproductive" process as seen in the reaction with XeF_2. It is noted, however, that these results do not exclude the possibility of electron transfer, i.e., (>NF, Nu^-) to (>$NF^{\bullet-}$, $Nu^{\bullet}$) followed by a very fast recombination within a solvent cage to fluorinated products, but merely fix a lower limit to the rate constant for this process.

Further insight into the problem of nucleophilic substitution versus electron transfer was obtained from a comparison between observed rate constants for electrophilic fluorination and calculated rates from ET theory.[154,162] Rate constants were measured for reactions of *N*-fluorosultam **14a** with a series of nucleophiles of known redox properties. The rate calculation for dissociative electron transfer requires a knowledge of the standard redox potentials ($E°$) and the Marcus reorganization energies of the two reactive partners. The standard potential, $E°$ for **14a**

Table 2. Reaction of *N*-Fluorosultam 14a with Nucleophiles: Comparison between Predicted[154] Dissociative Electron Transfer Rate Constants k_{DET} and Experimental[169] k_{EXP} Rate Constants

Nu	E°(Nu)	Solvent (°C)	k_{EXP}	k_{DET}	NuF yield (%)
	0.34	Et_2O(0)	$>8x10^{-2}$	$5x10^{-15}$	94
	-0.4	THF(-78)	$>3.2x10^{-2}$	$3x10^{-15}$	80
	-0.39	THF(-75)	$1.9x10^{-2}$	$9x10^{-13}$	72
	-0.29	THF/Et_2O(0)	$6.8x10^{-2}$	$(14x10^{-7})$*	17
	-0.00	CH_3CN(22)	$1.3x10^{-3}$	$2x10^{-5}$	0

* From ref 162, calculated using an estimated $E°$ for **14a** of −0.67 V vs SCE; other k_{DET} values in this table were apparently arrived at[154] using the electrochemically derived $E°$ for **14a** −0.12 V vs SCE.

(−0.12 V vs SCE), was derived from the electrochemical R_2NF reduction studies described[154] earlier in this review (section V.B.1). Results are summarized in Table 2 where for the listed nucleophiles computed dissociative electron-transfer rate constants[154] are compared with experimental rate data and fluorination yields.[162] For the first three substrate nucleophiles, the observed rates are from 11 to 13 orders of magnitude faster than would be expected from a dissociative ET pathway. Electron transfer is too slow to account for the observed fluorination rates, and a nucleophilic attack on fluorine is therefore invoked. The apparent decrease in fluorination yield for the last two substrates is ascribed to the occurrence of competing ET reactions that do not lead to fluorinated products. The extreme case of this is the dissociative electron transfer reaction of **14a** with *N*,*N*,*N*′,*N*′-tetramethyl-1,4-phenylenediamine, which yields only the aromatic radical cation and fluoride.

It is clear in reviewing this section that there is currently no single widely-accepted mechanism for electrophilic fluorination. There is the view of an initial charge-transfer complex that undergoes electron and fluorine radical transfer steps as postulated by Umemoto and DesMarteau and substantiated by Kochi's studies in the broader context of electrophilic aromatic substitution. On the other hand, evidence presented by Differding, Saveant et al. seems to rule out (with certain caveats) an ET pathway for fluorination of their substrates, and an S_N2 displacement on fluorine is, therefore, invoked as the most likely mechanism. However, there is common ground. There seems to be agreement that there can be ET processes that do not lead to fluorination, but yield instead radical coupling products (Schemes 10 and 11) or total charge-transfer as in the formation of the *N*,*N*,*N*′,*N*′-tetramethyl-1,4-phenylenediamine radical cation (Table 2). Also, it should be noted that the mechanistic studies were done on quite different NF reagent/substrate systems: cationic *N*-fluoropyridinium and neutral *N*-fluorosultam reagents, employing, respectively, aromatic and carbanionic-type substrates. Perhaps as mechanistic studies are extended to a greater reactivity range of reagents and nucleophiles a more unified mechanistic view of electrophilic fluorination will emerge.

C. Relative Reactivity

The NF compounds described in section III display a very wide range of chemical reactivity as sources of electrophilic fluorine or simply as oxidants. Demonstrably, the most powerful are the NF_4^+ salts, which even fluorinate nitrobenzene[97] and methane[163] by apparently electrophilic mechanisms. Further down on a purely qualitative reactivity scale is $(CF_3SO_2)_2NF$ (**1a**), which at room temperature readily fluorinates benzene, but not chlorobenzene.[28] Then there are a number of NF reagents, cationic and neutral of greatly varying fluorinating power. Of these it is the $R_3N^+F\ A^-$ salts that are usually the more reactive. Thus, *N*-fluoropentachloropyridinium triflate (**6h**) in CH_2Cl_2 fluorinates benzene at reflux[38] and may be comparable in reactivity to **1a**. The Selectfluor reagent **7a** in CH_3CN reacts with toluene at 80 °C to give 2- and 4-fluorotoluenes.[41] Neutral reagents such as the *N*-fluorosulfonimides **10** and **12** react only with more activated aromatics.[54] At the other extreme are the *N*-alkyl-*N*-fluoro-*p*-toluenesulfonamides **9a**−**p**, which apparently, will only react with appropriate aromatic carbanion substrates.[46]

There have been only limited attempts to quantitatively rank electrophilic fluorination agents in terms of relative reactivity and overall usefulness. Christe and Dixon,[164] on the basis of quantum-mechanical calculations, developed a scale of F^+ detachment energies for a series of XFn^+, so-called oxidative fluorinators. Values of these energies (in kcal mol), with respect to F^+ set at zero, for KrF^+ (for reference) and the cited NF compounds are KrF^+ (115.9), N_2F^+ (139.3), NF_2O^+ (175.3), and NF_4^+ (180.1), which correspond in this series to an increasing thermodynamic stability of the *N*-fluorocation. It would clearly be of interest to extend these calculations to the other R_3N^+F cationic reagents that have been described in this review.

A fundamental quantity that should provide an indication of the relative reactivity of NF reagents is their electrochemical standard potential, $E°$. Unfortunately, reduction of these species at electrodes is in most cases irreversible, and only data on peak potentials (E_p) usually observed at a considerably negative overvoltage[58] are available.[165] Such data (at specified experimental conditions) have nevertheless proved useful in providing some measure of the relative reactivity of NF reagents.

Peak reduction potentials for 10 NF fluorinating agents measured in CH_3CN at a Pt electrode were used as a basis for a relative reactivity scale.[41] A listing of compounds of decreasing E_p values corre-

sponding to an expected diminishing electrophilic fluorination reactivity was provided. The ordering from $(CF_3SO_2)_2NF$ (**1a**) (E_p = 0.18V vs SCE) to the least reactive *N*-fluorosulfonamide, $H_3C(C_6H_4)SO_2N(C_3H_7)F$ (E_p = −2.20V vs SCE) was shown to be consistent with available qualitative reactivity data on the fluorination of model aromatic substrates.

Electrochemical reduction data for *N*-fluorosultam, *N*-fluorosulfonamide reagents, the ring-substituted *N*-fluoropyridium, and *N*-fluoroquinuclidinium salts was provided by Differding et al.[58] Because different experimental conditions were employed, a detailed comparison of this data with peak potentials from ref 41 is not possible. There are, however, similar trends as in the very significant changes in E_p (and reactivity) with different substituents of the nitrogen atom.

Sudlow and Woolf[166] have criticized the ordering of chemical reactivity from electrochemical measurements, citing specifically ref 41. Principal reasons given relate to claimed uncertainties in the measurement and interpretation of E_p values, issues which were addressed in this work and are noted above. As an alternative, they have described an approach that is based solely on data from semiempirical molecular orbital calculations and is illustrated as follows. For a series of R_3N^+F reagents and R_3N precursors the calculated enthalpy of the "reduction couple" represented here by $[\Delta H_f°(R_3N) - \Delta H_f°(R_3N^+F)]$[167] was correlated with the LUMO energy of the R_3N^+F cation. A (surprisingly) linear relationship between these two quantities was noted for the *N*-fluoropyridium cation and several ring-substituted analogs. The result is said to be consistent with these reagents' relative reactivity, with low LUMO energies and more negative "reduction couples" corresponding to greater fluorinating power. However, the correlation did not extend to R_3N= piperidine, quinuclidine, N_2, and FCN systems. It is concluded that by this computational approach an adequate ordering in fluorination reactivity can only be obtained for a closely related set of reagents. Reports of similar molecular orbital calculations on *N*-fluoropyridinium reagents have appeared.[168]

More recently, Solkan et al.,[169] also using semiempirical molecular orbital methods, calculated the formation enthalpies of a number of ring-substituted *N*-fluoropyridinium reagents both under gas phase conditions and in the presence of a (hypothetical) polar solvent. As expected, the largest enthalpy changes in passing from the gas phase to solution are seen for *N*-fluoropyridinium salts containing charged ring substituents. In fact, solution and ion-pairing effects can greatly influence fluorination reactivity.[38] Thus, *N*-fluoropyridinium triflate reacts readily with a model silyl enol ether in methylene chloride; the reaction is slower in CH_3CN but does not proceed at all in THF. In this system triflate is generally a more effective counteranion than BF_4^-, SbF_6^-, etc. This is ascribed to a greater solubility of its salts in low polarity solvents and a lesser tendency to ion pair, thus maintaining the effective positive charge on the *N*-fluoro nitrogen atom.[38]

There have been attempts to correlate NF, ^{19}F chemical shifts with fluorinating power as was done for fluoroxy compounds.[170] For *N*-fluoropyridinium salts[171] the ^{19}F resonance shifts downfield with substitution by increasingly electron-withdrawing groups at the β and γ positions on the ring. This correlates with the pK_a values of the corresponding pyridines and is consistent with the notion that electrophilic fluorination reactivity is a function of the electron density on nitrogen. For substituents at the α positions, however, there are no clear trends between the ^{19}F shift and reactivity, but there is still a correlation with the pK_a's of the corresponding substituted pyridines.

VI. Conclusion

The clearly exhibited—even if not well understood—electrophilic fluorinating behavior of the described NF compounds, the hypofluorites, xenon difluoride, etc., is a manifestation of the extreme electronegative character of fluorine. Reagents of the NF class, several of which are now commercially available, provide the organic chemist with a relatively safe and practical means of selectively positioning fluorine at chosen carbanionic-type sites in molecules. However, the reagents' stability in storage and ease of use are achieved at the cost of employing an R_2N- or R_3N^+- organic carrier. For many large-scale uses elemental fluorine, somehow "tamed" to act as a predictably-selective electrophile, would ultimately be the most economical and environmentally "greener" alternative.

Acknowledgments

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