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Recent Advances in Electrophilic Fluorination

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Contents

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1. Introduction

It has been known for many years that the substitution of a hydrogen atom(s) for a fluorine atom(s) in an organic compound can sometimes dramatically alter its physical, chemical and biological properties.[1-5] Consequently, the synthesis of organofluorine compounds has become an important area of chemistry in both academia and industry. A wide variety of methods have been developed for introducing fluorine into organic compounds.[6] One approach that is rapidly becoming one of the most important methods is electrophilic fluorination. In this approach, fluorine acts as an electrophile rather than as a nucleophile (F^-) or a radical ($F^{\cdot}$). A variety of electrophilic fluorinating reagents have been developed over the last 40-50 years such as perchloryl fluoride ($FClO_3$),[7] xenon difluoride (XeF_2),[8] fluoroxy compounds (such as acyl hypofluorites, CF_3OF, $CsSO_4F$)[9] and fluoronitrogen compounds (R_2N-F or R_3N^+-F).[10] In the presence of highly polar protic solvents and modifiers such as Lewis acids, dilute solutions of elemental fluorine (F_2) have been used as a source of electrophilic fluorine at low temperatures.[9c,11,12-16] All of these reagents have been used extensively for the preparation of organofluorine compounds and exhibit traditional electrophilic reactivity patterns.

This review is devoted almost exclusively to the topic of the synthesis of compounds bearing the C-F bond by electrophilic fluorination.[17] A number of review articles have recently appeared in the literature that have covered various aspects of the synthesis of organofluorines via electrophilic fluorination as well as other topics related to the synthesis of organofluorine compounds.[7-11,18] The most extensive of these recent reviews appeared in 1995[8a,18] and 1996.[9a,10,11a] Consequently, this review covers mainly, though not exclusively, the literature from approximately the middle of 1995 to the middle of 1999. It begins with a brief description of new electrophilic fluorinating agents that have appeared in this time period. The rest of the review deals with reports on the synthesis of various classes of organofluorine compounds with these new and other more established electrophilic fluorinating agents that have appeared in the general scientific literature[19] during this time period. However, for certain topics that have increased in importance in recent years, such as stereoselective fluorination of α-carbons of carbonyl compounds (section 3) and the synthesis of α-fluorophosphonates (section 5), we felt a more extensive review of the literature was in order. Consequently, some of the literature on certain topics prior to mid-1995 has also been covered in this review. Some reviews covering specific electrophilic fluorinating agents[20,21] or on the synthesis of specific classes of organofluorine compounds via electrophilic fluorination[21,22] have appeared very recently. Some overlap with these recent reviews was unavoidable.

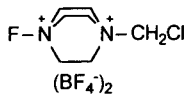
2. New electrophilic fluorinating agents

Since 1995, a number of reports describing new electrophilic fluorinating agents or modifications of existing electrophilic fluorinating agents have appeared in the literature. These are discussed below.

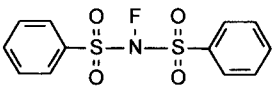
2.1 New N-F Reagents

One of the most important developments in the field of electrophilic fluorination in the last decade has been the invention of a variety of N-F electrophilic fluorinating agents.[10,23] Unlike many other types of

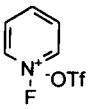
electrophilic fluorinating agents, these reagents are usually stable and easy to handle.[10,23] They are prepared from relatively inexpensive starting materials (usually prepared by reacting the corresponding N-H compound with F_2) and a number of these agents are now commercially available.[10] Indeed, it has been the development and commercialization of some of these reagents, such as 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), also known as F-TEDA-BF_4 or Selectfluor® (compound **1**),[24] N-fluorobenzene sulfonimide, also known as NFSI (compound **2**),[25] N-fluoropyridinium triflate (compound **3**),[26] N-fluoroquinuclidinium triflate (compound **4**)[27] and others[10] that has resulted in a virtual explosion of work in the area of electrophilic fluorination in the last several years. Thus, it is hardly surprising that the majority of new electrophilic fluorinating agents that have appeared since 1995 have been of the N-F type.



1 (F-TEDA-BF_4 or Selectfluor)



2 (NFSI)



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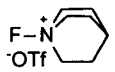

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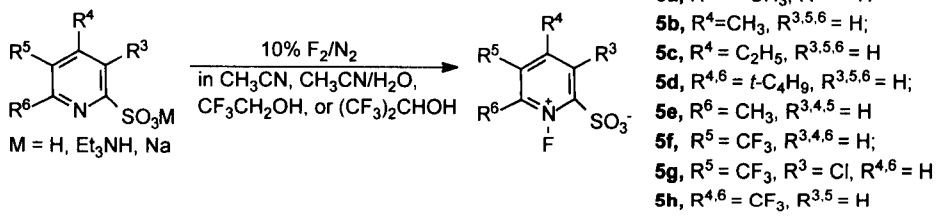
2.1.1 N-fluoropyridinium salts

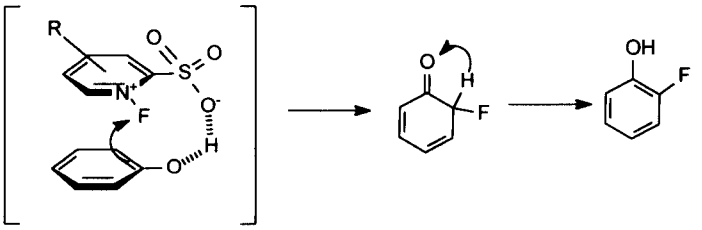
In an attempt to modify the fluorinating power of N-fluoropyridinium reagents, Umemoto and coworkers have prepared a series of fluorinating agents based on the N-fluoropyridinium-2-sulfonate scaffold (**5a-h**, Scheme 1).[28] The fluorinating power of this series was found to parallel the pK_a of the pyridines and so



Scheme 1

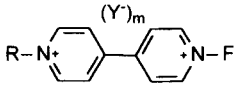
increased with the number of electron withdrawing groups attached to the pyridinium ring. These compounds also exhibited increased solubility in organic solvents in comparison to the parent compound N-fluoropyridinium-2-sulfonate which had been used previously by Umemoto.[29] Reagents **5f-h** were found to exclusively or highly selectively fluorinate phenol, naphthol, phenylurethane and the TMS ether of phenol at the *ortho* position. This selectivity was attributed to an interaction between the 2-sulfonate anion and the hydroxy , NH group or silicon atoms (Scheme 2) of the substrates. Conjugated trialkylsilyl dienol ethers of a steroid were regioselectively fluorinated at the 6-position over the 4-position with **5b-e** (see section 6). β-Dicarbonyl compounds were directly α-monofluorinated with **5h** in 66-98% yields. Compound **5h** reacted

with styrene and β-methylstyrene in AcOH to give the fluoroacetoxy products in 24% and 51% yield respectively. α-Fluorination of thioanisole was achieved with **5a** in 80% yield.

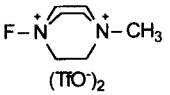


Scheme 2

Banks and coworkers have reported the synthesis of the N-fluoropyridinium salts **6** and **7** and compared their reactivity to that of the F-TEDA reagent **8** using activated aromatics as substrates.[30,31] In general, it was found that **6** and **7** were less efficient at fluorinating aromatic substrates than **8**.

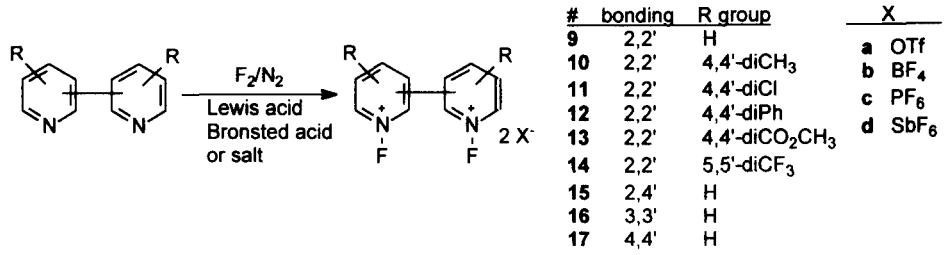


6, R = BF_3^-, Y = BF_4^-, m = 1
7, R = CH_3, Y = TfO^-, m = 2



8

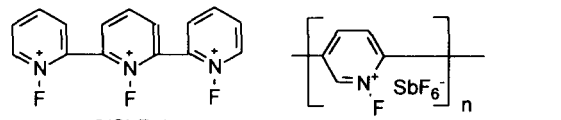
In an attempt to increase the effective fluorine content of N-F fluorinating agents, Umemoto and coworkers synthesized and studied the reactivity of a series of N,N'-difluoropyridinium salts **9-17** (Scheme 3) as well as the higher homologues **18** and **19**.[32] The relative reactivity was determined to be 2,2'-(**9a**)>>2,4'-(**15a**)>3,3'-(**16a**)~4,4'-(**17a**)>>N-fluoropyridinium triflate using 2-acetylcyclohexanone as the model substrate (α-fluorination of the β-dicarbonyl moiety). Thus the reactivity increases with the decrease in pK_a of the bipyridyls. The two N-F moieties were both found to be effective since the yield of fluoro product exceeded 50% using a half molar amount of the difluorobipyridinium salts. Fluorination by the two N-F moieties was found to occur in a step-by-step manner and the reactivity differences between the first and second fluorinations was very small indicating that the N-hydropyridinium moiety resulting from the first fluorination still exerted a strong electron withdrawing effect. Since compound **9b** was the easiest and least expensive to prepare, it was chosen for further studies. Compound **9b** was found to fluorinate a wide variety of compounds such as β-dicarbonyl compounds (α-mono- and α-difluorination), conjugated enol ethers or acetates of a steroid derivative (see section 6), and activated aromatics in modest to good yields. The fluorination of the α/β double bond in β-methylstyrene using AcOH as solvent yielded fluoroacetoxy adducts in 51% yield while the same reaction with styrene was difficult. Reactivity studies for compounds **18** and **19** were not reported.



#	bonding	R group
9	2,2'	H
10	2,2'	4,4'-diCH$_3$
11	2,2'	4,4'-diCl
12	2,2'	4,4'-diPh
13	2,2'	4,4'-diCO$_2$CH$_3$
14	2,2'	5,5'-diCF$_3$
15	2,4'	H
16	3,3'	H
17	4,4'	H

X	
a	OTf
b	BF$_4$
c	PF$_6$
d	SbF$_6$

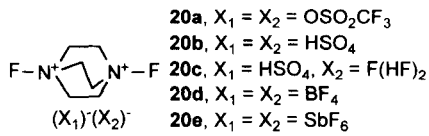
Scheme 3



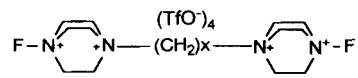
18 **19**

2.1.2 N-Fluorotriethylenediamine (F-TEDA) and quinuclidinium salts

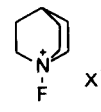
Umemoto has produced N,N'-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts, **20a-f**, containing two N-F moieties.[33] Compounds **20a**, **20b**, **20d**, and **20e** were assessed for fluorinating activity using fluoroanisole as a model substrate. In formic acid at room temperature, all were more effective fluorinating agents than F-TEDA-BF$_4$, producing fluorinated products in 45-62% yields as opposed to 5% for F-TEDA-BF$_4$. **20d** was examined in more detail and was found to readily fluorinate electron rich aromatics, β-dicarbonyl compounds and their sodium enolates to give α-fluoro dicarbonyl compounds, substituted styrenes to give vicinal fluoromethoxy and fluoroacetoxy compounds, and the conjugated enol acetate of a steroid derivative to give a 6-fluoro steroid (see section 6) in modest to good yields. One N-F moiety of the salt was effective for fluorination while the other N-F aided in activation via electron withdrawing effects.



20a, $X_1 = X_2 = OSO_2CF_3$
20b, $X_1 = X_2 = HSO_4$
20c, $X_1 = HSO_4$, $X_2 = F(HF)_2$
20d, $X_1 = X_2 = BF_4$
20e, $X_1 = X_2 = SbF_6$
20f, $X_1 = X_2 = PF_6$



21, X = 2
22, X = 3



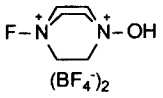
23a, $X^- = BF_4^-$; **23b**, $X^- = PF_6^-$
23c, $X^- = FSO_3^-$; **23d**, $X^- = F^-$

Banks and coworkers have prepared the bisfluoro-1,4-diazoniabicyclo[2.2.2]octane salts **21** and **22**.[30] Very limited reactivity studies were performed with **22** using the enamine 1-morpholinocyclohexene, phenol and anisole as model substrates. Reaction of **22** with the enamine followed by acidic workup gave α-fluorocyclohexanone in 57% yield which was comparable to that obtained with **8**. While both **22** and **8** showed comparable reactivity with phenol, with anisole, **22** was found to be less effective than **8**.

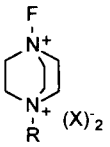
Banks and Babeesh have prepared two new N-fluoroquinuclidinium salts **23b** and **23c**, and compared the behavior of these fluorinating agents to the known fluorinating agents **23a**, **23d** and **4**.[34,35] Studies with a

variety of substrates indicated that **23b** and **4** were the most easily handled and effective fluorinating agents. Comparisons to other fluorinating agents were not reported.

Shia and Poss as well as Stavber and Zupan have reported the utility of 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **24** (known as NFTh or Accufluor®) as a highly versatile electrophilic fluorinating agent.[36-44] This reagent has been used to prepare, in good to excellent yields, vicinal fluorohydroxy, fluoromethoxy, fluoroacetoxy and fluoroacetamides from alkenes (see section 7),[36,37] α-monofluoroketones via the direct fluorination of ketones (see section 4.2),[38] cyclic α,α-difluoroketones from aromatics and hydroxyaromatics (see section 4.6),[39] α,α–difluorophenones from phenyl-substituted alkynes (see section 4.5),[39] fluorinated polyaromatic hydrocarbons,[40,41] fluorinated aromatics from electron-rich aromatics,[42] fluorosteroids from dienol steroid derivatives (see section 6),[42] α-monofluoroketones from enol acetates, enol ethers and trimethylsilylenol ethers (see section 3)[42] and α-mono- and α,α-difluoro β-ketoesters and β-diketones from β-dicarbonyl compounds.[42] This reagent is now commercially available.[43] The reactivity of **24** appears to be similar to F-TEDA-BF_4, **1**. Recent mechanistic studies by Zupan and coworkers suggest the involvement of ionic intermediates in the fluorination of alkenes with this reagent.[44]



24

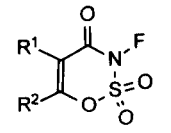


25a, R = Me, X_2 = BF_4
25b, R = Me, X_2 = PF_6
25c, R = Me, X_2 = TfO, BF_4
25d, R = Me, X_2 = TfO, PF_6
25e, R = Me, X_2 = TfO, FSO_3
25f, R = CH_2Cl, X_2 = TfO
25g, R = CH_2Cl, X_2 = PF_6
25h, R = Et, X_2 = TfO
25i, R = CF_3CH_2, X_2 = TfO
25j, R = C_8H_{17}, X_2 = TfO

Banks and coworkers have prepared and examined the reactivity of 1-alkyl-4-fluoro TEDA salts **25a-j**.[45] The order of reactivity follows the relative electron-withdrawing power of the alkyl group. All of these reagents were found to fluorinate enamines, β-dicarbonyl compounds and electron-rich aromatics in good to excellent yields. Only **25i** was capable of fluorinating benzene, albeit in very modest yield (using 1:1 molar ratio of **25i** to benzene and using 10% TFA in CH_3CN:H_2O (4:1), as solvent).

2.1.3 Other N-F fluorinating agents

Cabrera *et al* have synthesized the N-F sulfam agent **26-28**.[46] Compounds **26** and **27** were found to be difficult to purify and not stable at room temperature. However, **28** was found to be an effective electrophilic fluorinating agent successfully fluorinating a phenylmagnesium bromide (52%), sodium salts of β-dicarbonyl compounds (77-86%), direct α-monofluorination of a β-keto ester (66%), anisole (neat 150 °C, 77%, *o:p* 56:44) and a conjugated enol acetate derivative of a steroid at the 6-position (58%, α:β 1:2.5) (see section 6). The reactions could be carried out in most common organic solvents including very apolar solvents such as hexane.

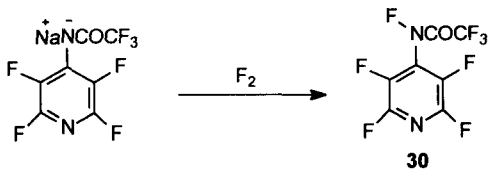


26; $R^1 = H$, $R^2 = CH_3$
27; $R^1 = R^2 = CH_3$
28; $R^1 = R^2 = -(CH{=}CH)_2$

29

Very recently, Laali *et al* reported the synthesis of N-fluoro-2,4-dinitroimidazole (**29**) and its application to the synthesis of fluorinated polycyclic aromatic hydrocarbons.[47] A wide variety of polycyclic aromatic hydrocarbons were examined as substrates. In general, the yields were low and the regioselectivity ranged from good to poor. However, the authors reported that attempts to fluorinate certain polycyclic aromatic hydrocarbons with **1** led to intractable mixtures and that this was less of a problem with **29**.

Banks and coworkers have reported the synthesis of perfluoro-[N-fluoro-N-(4-pyridyl)acetamide] (**30**, Scheme 4) in 80% purity (contaminated with its N-H analogue) from the corresponding sodium salt.[48] Limited reactivity studies with the impure material with diethyl sodio(phenyl)malonate, 1-morpholinocyclohexene, phenol and anisole were encouraging in that electrophilic fluorination of these substrates occurred in good to excellent yields. Further studies are necessary to ascertain the general utility of this class of N-F fluorinating agents.



30

Scheme 4

2.2 New electrophilic fluorinating agents not containing the N-F bond

To our knowledge, since 1995, there has only been one report of new electrophilic fluorinating agents not bearing an N-F bond. Lementov and coworkers have recently reported the synthesis of $PhSeF_3$, $PhSeF_3$ and $PhTeF_5$ and examined their utility as electrophilic fluorinating agents.[49] $PhSeF_3$ was generated *in situ* by reacting PH_2Se_2 with 3 equivalents of XeF_2. $PhSeF_3$ reacts readily with olefins at room temperature to produce 1,2-selenofluorine compounds or 1,2-difluorides. 1,2-Difluorides are only formed in cases where the intermediate $PhSeF_2$ group occupies a benzylic position. Otherwise, the reaction stops at the selenofluorine products. $PhTeF_5$ and $PhSeF_5$ were generated *in situ* by reacting $PhSe_2$ or $PHTe_2$ with 5 equivalents of XeF_2. Both $PhTeF_5$ and $PhSeF_5$ are highly potent electrophilic fluorinating agents of olefins and produce only the corresponding 1,2-difluorides.

3. Stereoselective electrophilic fluorination of α-carbons of carbonyl compounds

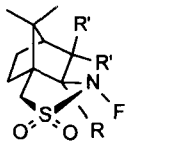
Optically active compounds having one or more stereocenters bearing fluorine have been used as enzyme inhibitors, for studying enzyme mechanisms and as intermediates in asymmetric synthesis.[50a-d] Consequently, there has been considerable interest in the development of methods for the asymmetric

introduction of fluorine into organic compounds. Much of the literature on the preparation of chiral organofluorine compounds by electrophilic fluorination and other methods has been covered in a number of review articles.[50a-d] Two of these reviews[50a,b] appeared quite recently and the reader is referred to these reviews for a more in-depth discussion on the topic of asymmetric fluorination. For discussions on recent reports pertaining to the asymmetric fluorination of steroids and carbohydrates see sections 6, 7 and 10.1.

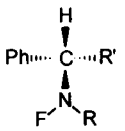
Electrophilic fluorination has proven to be a particularly effective method for the synthesis of optically active α-fluoro carbonyl compounds.[18,22,50a,b] Three different approaches have been used for the stereoselective electrophilic fluorination of α-carbons of carbonyl compounds: (1) asymmetric fluorination of enolates using chiral electrophilic fluorinating agents, (2) diastereoselective electrophilic fluorination of chiral enolates or enol ethers and, (3) preparation of silyl enol ethers using a chiral base followed by fluorination.

3.1 Chiral electrophilic fluorinating agents

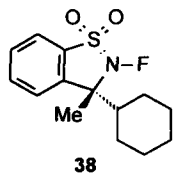
In 1988, Differding and Lang reported the enantioselective fluorination of metal enolates using the chiral (-)-N-fluoro camphorsultams **31** and **32**.[51] However, the yields and ee's were generally low (for examples see Table 1) with the exception of cyclopentanone-2-carboxylate (Table 1, entry 1) which underwent the fluorination reaction using NaH/**31** at 0 °C to room temperature to give the monofluoro product in 63% yield and an ee of 70% (absolute stereochemistry not determined). More recently, Davis and coworkers examined **31**, as well as the closely related (-)-N-fluoro camphor sultams **33** and **34**, as asymmetric fluorinating agents of tertiary enolates.[52-54] In general, the α-fluorocarbonyl compounds were obtained in low to modest yield and ee (for examples see Table 1). The yields and ee's were dependent upon the structure of the product, the geometry of the enolates and the counterion. Camphorsultam **33** generally gave better yields and ee's than **31**. This was attributed to the greater reactivity of **33**, with which the reaction could be performed at –78 °C, as opposed to room temperature for **31**. Fluorination with **34** proceeded in reasonable yields, however, the asymmetric induction was almost negligible (<5%). The highest ee was reported for the fluorination of the sodium enolate of 2-methyl tetralone by **33** to give the α-fluoroderivative in 53% yield and an ee of 76% (Table 1, entry 7).



31, R = R' = H;
32, R = CH_3, R' = H
33, R = H, R' = Cl
34, R = H, R' = OMe



35, R = Ts, R' = CH_2OAc
36, R = Ts, R' = CH_3
37, R = Ms, R' = CH_3

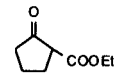
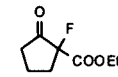
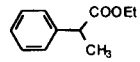
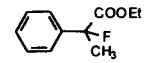
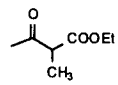
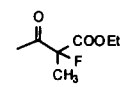
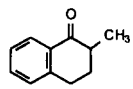
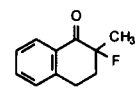
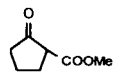
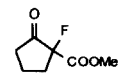
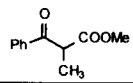
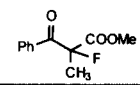


38

Takeuchi and coworkers have examined chiral N-fluorotosyl and mesyl derivatives **35-37** as enantioselective electrophilic fluorinating agents of metal enolates.[55] In general, both the yields (0-55%) and ee's (2-48%) were poor. The best result was obtained with 2-benzyl-1-tetralone/KHMDS and **36** to give the

fluorinated tetralone in 53% yield and 48% ee. More recently, Takeuchi *et al* have reported the asymmetric fluorination of lithium enolates of tetralone, indanone and benzosuberone derivatives using the chiral N-fluoro sultam **38**.[56a,b] Yields (39-73%) and ee's (18-74%) ranged from poor to modest with the exception of the fluorination of 2-benzyl-1-tetralone which gave (S)-2-fluoro-2-benzyl-1-tetralone in 79% yield with a highly respectable ee of 88%.

Table 1. Asymmetric Fluorination of Enolates

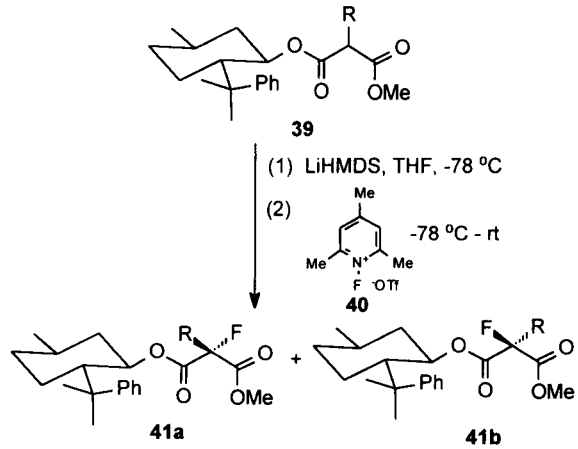
Entry	Ketone	Base	NF reagent	Product	% ee (%yield)	Ref.
1		NaH	(-)-**31**		70 (63)	51
2	"	KH	(+)-**32**	"	<10 (<5)	51
3		LDA	(-)-**31**		35 (27)	51
4	"	LDA	(+)-**32**	"	<10 (34)	51
5		LiH	(-)-**31**		10 (31)	51
6		LDA	(-)-**31**		35 (<5)	51
7	"	NaHMDS	(+)-**33**	"	76 (S) (53)	53
8	"	LDA	(+)-**33**	"	10 (10)	53
9	"	NaHMDS	(+)-**34**	"	5 (41)	53
10		NaH	(+)-**31**		70 (63)	52
11		NaHMDS	(+)-**33**		0 (41)	53
12		NaHMDS	(+)-**33**		33 (54)	53

3.2 Diastereoselective electrophilic fluorination of chiral enolates, chiral imide enolates and enol ethers

To date, diastereoselective electrophilic fluorination of chiral enolates, imide enolates or enol ethers has proven to be a more effective method for preparing enantiomerically enriched α-fluorocarbonyl compounds than asymmetric fluorination using chiral electrophilic fluorinating agents. Much of the early

work in this area was performed on enolates or enol ethers of steroid derivatives.[50a-d] Some of the more recent work on diastereoselective electrophilic fluorination of chiral enolates, imide enolates or enol ethers is discussed below.

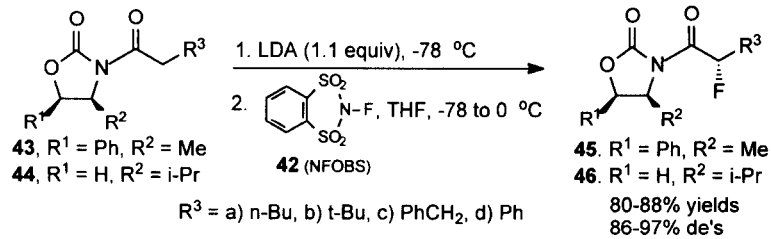
In 1990, Ihara *et al* reported the electrophilic fluorination of chiral lithium enolates of methyl phenylmenthyl malonate derivatives of type **39** with N-fluoropyridinium derivative **40**. Monofluoro products **41a** and **41b** were produced in high yields (88-96%) but with low stereoselectivities (Scheme 5).[57,58]



R	41a:41b
Me (**39a**)	3.8:1
Et (**39b**)	1:2
Pr (**39c**)	1:2
CH_2Ph (**39d**)	1:1.6

Scheme 5

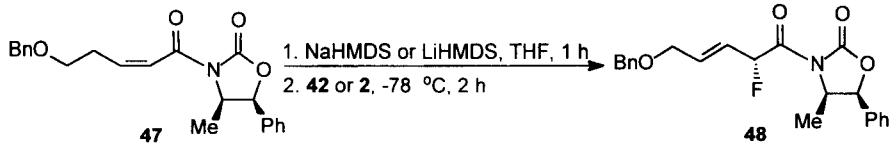
Perhaps the most significant work in this area has been performed by Davis and coworkers.[59-62] In 1992, Davis and Han reported that highly diastereoselective electrophilic fluorinations of imide enolates could be achieved using Evan's oxazolidinone as a chiral auxiliary[63] and N-fluoro-*o*-benzenedisulfonimide (**42**) (NFOBS)[64,65] as the electrophilic fluorinating agent (Scheme 6).[59] In this instance, chiral imides **43** and **44**



Scheme 6

were metallated with LDA at - 78 °C followed by reaction with **42** at –78 - 0 °C. Good to excellent yields (80-88%) and de's (86-97%) of the α-fluoro compounds **45** and **46** were obtained. Compound **42** was found to approach from the less sterically hindered *si*-face of the chiral imide enolate. More recently, Davis and Qi have performed this reaction on the α,β-unsaturated chiral imide enolate of **47** to give **48** using both NFOBS and NFSI as fluorinating agents (Scheme 7).[60] In general, the de's were better with NFSI (**2**) than with **42**. The higher de's obtained with NFSI were attributed to the greater steric bulk of NFSI compared to **42**.

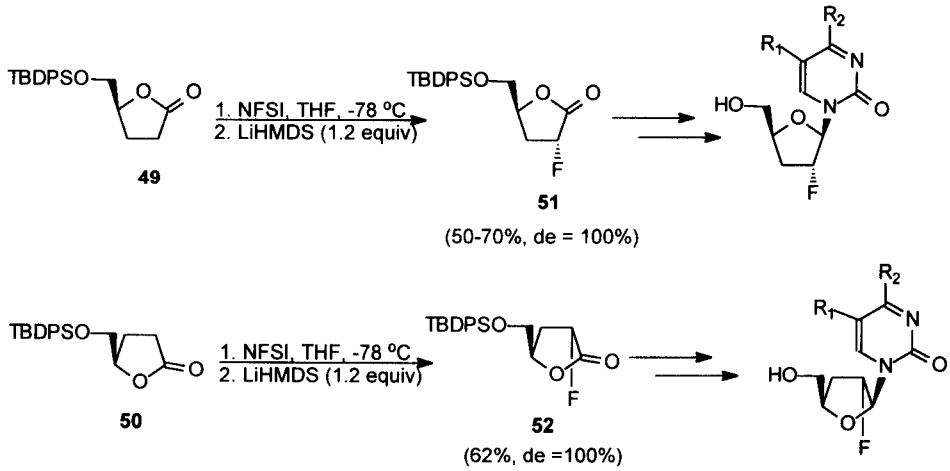
Commercially available NFSI now appears to be the electrophilic fluorinating agent of choice for the preparation of non-racemic fluorinated oxazolidinones.[61,62,66] Compound **48** was used as a key intermediate in the stereoselective synthesis of 2-deoxy-2-fluoropentoses.[60] The non-racemic α-fluorinated oxazolidinones have also been used by Davis and others as key intermediates in the highly successful asymmetric syntheses of α-fluoroacids,[59] β-fluorohydrins,[59] α-fluoro esters,[66] α-fluoroaldehydes,[61] and α-fluoro ketones.[62]



base	F^+ reagent	% yield	% de
NaHMDS	NFOBS	78	82
LiHMDS	NFOBS	78	88
LiHMDS	NFSI	76	100

Scheme 7

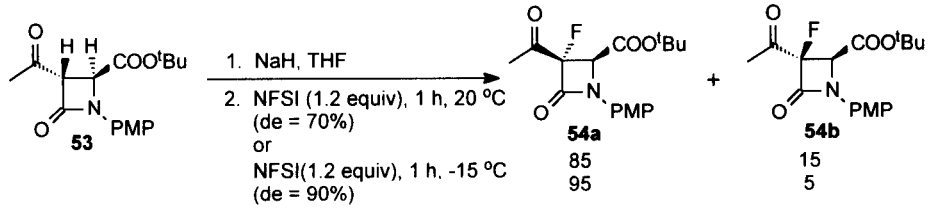
Liotta and coworkers have reported the completely stereoselective reaction of the enolates of enantiomeric lactones **49** and **50** (Scheme 8) using NFSI.[67] In this case, addition of NFSI to the enolate generated using LiHMDS gave poor yields of the desired monofluorinated lactones **51** and **52**. Many byproducts were formed including the difluorinated compound. However, it was found that by slow addition of the LiHMDS to a solution of the lactones and NFSI at – 78 °C, **51** and **52** could be obtained in 50-70 % yield and 100% de. The production of a single diastereomer was attributed to the steric bulk of both the TBDPS group and NFSI. Fluorolactones **51** and **52** were used as intermediates in the synthesis of novel 2'-fluoronucleosides (Scheme 8).



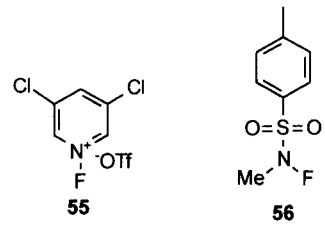
Scheme 8

Genet *et al* have reported the stereoselective fluorination of β-lactam **53** to give 3-fluoroazetidinone derivatives **54a** and **54b** using NaH/NFSI (Scheme 9).[68] The de of the reaction was found to improve when performing the reaction at –15 °C (de = 90%, 70% yield) as opposed to room temperature (de = 70%, 70%

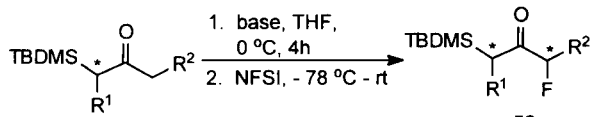
yield). The stereoselectivity was explained by an approach of the NFSI to the less sterically hindered face of the enolate. These workers also examined N-fluoropyridinium triflates **3**, **55**[69,70] and Barnette's N-fluorosulfonimide **56**[71] as electrophilic fluorinating reagents for the reaction, however, starting material or complex mixtures of products were obtained using these reagents.[68]



Scheme 9



Enders *et al* have reported the regio- and enantioselective synthesis of α-fluoroketones by electrophilic fluorination of enantiopure α-silyl enolates (Scheme 10).[72] Metallation of chiral α-silyl ketones **57** with LDA or LiHMDS at 0 °C followed by electrophilic fluorination of the resulting enolates using NFSI at –78 °C led to the formation of α-fluoro-α'-silylketones **58** in good to excellent de's (67-98%) and good yields (59-85%) (Table 2). For the acyclic ketones, alternative employment of LDA and LiHMDS allowed for the formation of both α-fluoro epimers in good yields and de's (Table 2). This result was rationalized by the differing enolate geometries [LDA (E), LiHMDS (Z)] and was confirmed by NMR analysis of the appropriate silylenol ethers. Desilylation of the α-fluoro-α'-silylketones with HF/(n-Bu)$_4$NF/NH$_4$F/KH$_2$PO$_4$ in THF at -78 °C yielded α-fluoroketones without racemization.



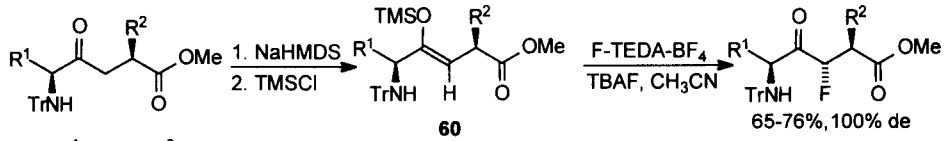
Scheme 10

Recently, Hoffman and Tao have reported a stereoselective synthesis of monofluoro ketomethylene dipeptide isosteres using electrophilic fluorination (Scheme 11).[73] Their approach was to first prepare the silyl enol ethers of type **60** from ketones **59a-d** using NaHMDS/TMSCl. The bulky trityl group promotes enolate formation regiospecifically distal from the α-amino group. NMR studies allowed the Z-geometry to be assigned to the enol ethers. The enol ethers were treated with F-TEDA-BF$_4$ in the presence of TBAF to give

Table 2. Yields and diastereomeric excesses for the synthesis of α-fluoro-α'-silylketones **58**.

58	R^1	R^2	Base	Yield [%]	de [%]
(S,R)-**58a**	Et	Et	LiHMDS	80	89
(S,R)-**58b**	Pr	Pr	LiHMDS	75	82
(R,S)-**58c**	Et	$PhCH_2$	LiHMDS	70	78
(S,S)-**58c**	Et	$PhCH_2$	LDA	59	67
(R,R)-**58d**	$(CH_2)_3$		LDA	81	98
(R,R)-**58e**	$(CH_2)_4$		LDA	85	98

the desired monofluoroketomethylene dipeptide isosteres **61** in yields of 65-76% and with 100% de. Calculations (AM1) using R^1, $R^2 = CH_3$, suggest that the preferred conformation of **60** is one in which the N-trityl group and the methyl group at C-2 are above one face of the enol double bond (Scheme 12). The remarkable stereoselectivity of these reactions was attributed to the fluorinating agent having to approach from the face opposite the trityl and methyl groups for steric reasons.

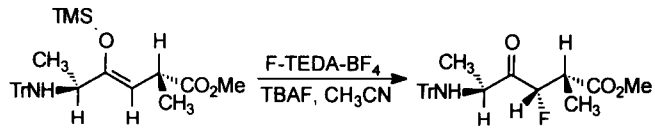


59a, R^1 = i-Bu, $R^2 = CH_3$
59b, R^1 = i-Bu, $R^2 = CH_2C_6H_{11}$
59c, $R^1 = CH_3$, R^2 = i-Bu
59d, R^1 = Bn, R^2 = n-Pr

60

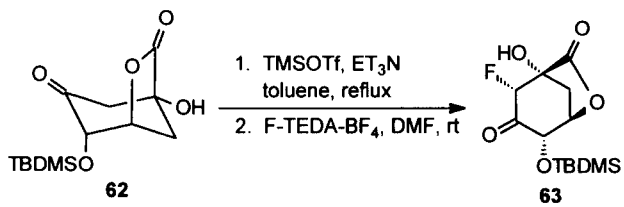
61a, R^1 = i-Bu, $R^2 = CH_3$
61b, R^1 = i-Bu, $R^2 = CH_2C_6H_{11}$
61c, $R^1 = CH_3$, R^2 = i-Bu
61d, R^1 = Bn, R^2 = n-Pr

Scheme 11



Scheme 12

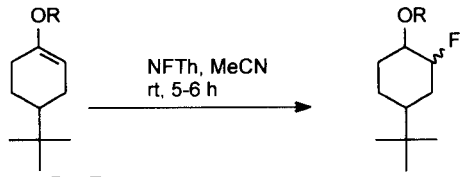
Recently, Manthey *et al* have used F-TEDA-BF_4 (**1**) to prepare (2R)-2-fluoro-dehydroquinic acid **63** (Scheme 13) in 89% yield by a regio and stereoselective fluorination the trimethylsilyl enol ether of **62**.[74]



62 **63**

Scheme 13

Poss and Shia have reported the stereoselective fluorination of enol ethers **64** and **65** using **24** (NFTh, Accufluor®, Scheme 14).[42] Little stereoselectivity was found with the enol acetate **66**.



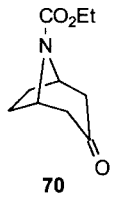
64, R = Et
65, R = TMS
66, R = Ac

67, R = Et (43%, cis/trans = 12.8:1)
68, R = TMS (44%, cis/trans = 9.8:1)
69, R = Ac (74%, cis/trans = 1:1.2)

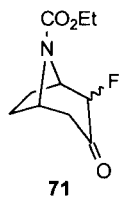
Scheme 14

3.3 Stereoselective introduction of fluorine using chiral bases

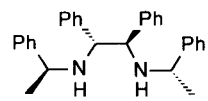
Armstrong and Hayter have described the first attempt to enantioselectively introduce fluorine using a chiral base.[75] Fluorination of the silyl enol ether of the tropinone derivative **70** with F-TEDA-BF_4 yielded **71** as a racemic mixture. However, treatment of **70** with the chiral lithium amide base of amine **72** (1 equiv), in the presence of TMSCl (5 equiv) and LiCl (1 equiv) gave the crude silyl enol ether which was reacted with F-TEDA-BF_4 to give **73** in 36% yield and 60% ee. Several recrystallizations yielded the tropinone **73** in >98% ee.



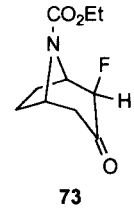
70



71



72



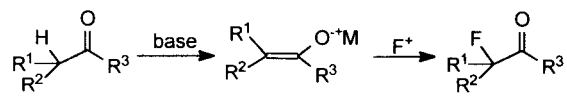
73

4. Synthesis of racemic α-fluorocarbonyl compounds

There are numerous reports in the literature describing the synthesis of α-fluorocarbonyl compounds by electrophilic fluorination. This area of chemistry has been extensively reviewed.[8-10,18,20,22,76] One of these reviews, which is devoted solely to the synthesis of α-fluoroaldehydes and α-fluoroketones, has appeared very recently.[22] Some recent examples using electrophilic fluorination are discussed below (see also sections 2 and 3).

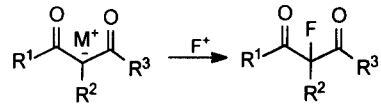
4.1 Via fluorination of metal enolates

There are numerous examples in the literature describing the preparation of α–mono- and α-difluorocarbonyl compounds via electrophilic fluorination of metal enolates derived from mono-carbonyl (Scheme 15) and β-dicarbonyl (Scheme 16) compounds.[8-10,18,20,22,76] The reaction has been accomplished with



R^1 = H, alkyl, aryl
R^2 = H, alkyl, aryl
R^3 = alkyl, aryl, O-alkyl, N-dialkyl,
M^+ = Li, Na, K

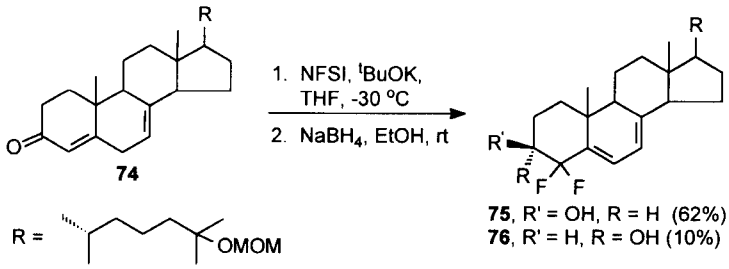
Scheme 15



R^1 = alkyl, aryl, O-alkyl
R^2 = H, alkyl, aryl, Cl
R^3 = alkyl, aryl, O-alkyl
M^+ = Na, K

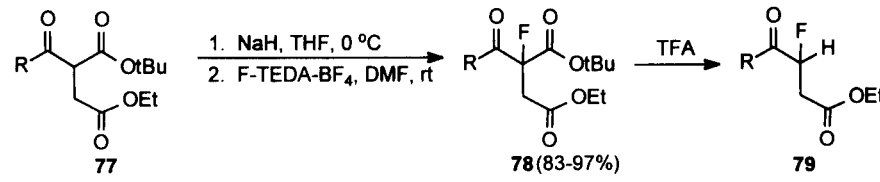
Scheme 16

a variety of electrophilic fluorinating agents (N-F, O-F, XeF_2).[8-10,18,20,22,76] The yields depend upon a variety of factors such as the F^+ reagent, substrate, counterion and reaction conditions (temperature, reaction time, order of addition of reagents).[8-10,18,20,2,76] For the fluorination of metal enolates derived from mono-carbonyl compounds, certain N-F reagents such as NFSI, NFOBS (**42**) and $(CF_3SO_2)_2NF$ (Desmarteau's reagent) have proven to be particularly effective.[10,18,22] Of these reagents, only NFSI is commercially available.[25] Consequently, NFSI appears to have become the most common reagent for affecting this transformation. F-TEDA type fluorinating agents are less effective for the fluorination of metal enolates derived from mono-carbonyl compounds due to a competing Hoffman-type elimination reaction that can occur between the strongly basic carbanion and the F-TEDA reagent.[77] F-TEDA type reagents and a variety of other N-F reagents have been found to be very effective for fluorinating metal enolates derived from β-dicarbonyl compounds.[10,18,20,22] The majority of the more recent work in this area has focussed on using this reaction to prepare biologically active fluorine-containing compounds. For example, Yamada and coworkers have prepared the α,α-difluoro alcohols **75** and **76** by reacting steroid **74** with NFSI/KOtBu under thermodynamic conditions to give the α,α-difluoro ketone followed by reduction of the ketone moiety (Scheme 17).[78] Compounds **75** and **76** were used as a key intermediate in the preparation of a novel fluorinated vitamin D analogue.[78]



Scheme 17

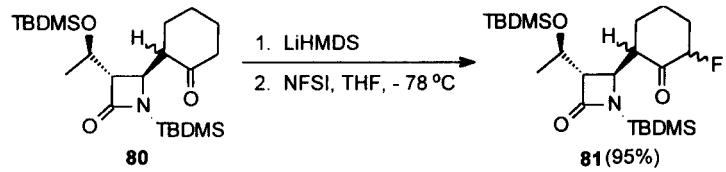
Hoffman and Saenz have prepared monofluoro ketomethylene peptide isosteres **79** using electrophilic fluorination of tricarbonyl compounds **77** as the key step (Scheme 18).[79] Compound **3**, N-fluoropyridinium heptafluorodiborate complex and F-TEDA-BF_4 were examined as fluorinating agents with either the enol (Lewis acid catalysis), the silyl enol ether or the enolate as the reactive species. NaH/F-TEDA-BF_4 was found to be the best method yielding the desired α-fluorinated derivatives **78** in good to excellent yields.



R = Me, neopentyl, cyclohexyl, Ph, Bn, phenethyl

Scheme 18

Padova *et al* have described the preparation of fluorolactam **81** via a regioselective electrophilic fluorination of an intermediate lithium enolate, derived from **80**, with NFSI (Scheme 19).[80] Compound **81** was used as a key intermediate in the synthesis of a novel fluorinated tribactam.[80]

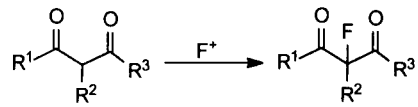


Scheme 19

Takeuchi and coworkers have reported the α-fluorination of ethyl α-cyano-*p*-tolylacetate in 90% yield using $NaH/FClO_3$.[81] The resulting α-fluoroester was used as an intermediate in the synthesis of a novel chiral derivatizing agent.

4.2 Via direct fluorination of carbonyl compounds

There are numerous examples in the literature describing the direct α-fluorination of neutral β-dicarbonyl compounds with a variety of electrophilic fluorinating agents (Scheme 20).[8,9,10,18,20,22,76] A number of the N-F type fluorinating agents have proven to be particularly effective and safe reagents for affecting this transformation.[10,18,20,22] Researchers have also begun to examine molecular fluorine as a reagent for affecting this transformation in acidic solvents.[15,82] However, the site selectivity is not very high and the reaction is difficult to control at the monofluorination stage.



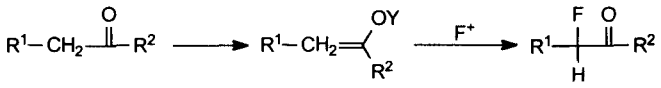
R^1 = alkyl, aryl, O-alkyl, N-dialkyl
R^2 = H, alkyl, aryl, F
R^3 = alkyl, aryl, N-dialkyl

Scheme 20

There are few reports describing the direct fluorination of mono-carbonyl compounds. Stavber and Zupan have reported the direct α-monofluorination of both cyclic and acyclic ketones using **24** (NFTh) in refluxing CH_3CN.[38] The isolated yields were generally greater than 70%. These workers also reported that reaction of 2-tetralone with F-TEDA-BF_4 gave the α-monofluoro ketone in a yield (83%) comparable to that obtained using **24**.

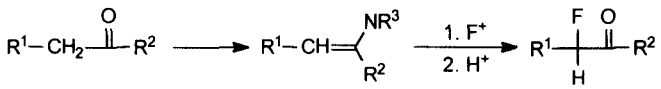
4.3 Via fluorination of enol ethers, enamines and imines

The preparation of α-fluoro carbonyl compounds via fluorination of enol ethers, enol acetates, and silyl enol ethers followed by hydrolysis (Schemes 21) has been well documented and can be accomplished with a variety of N-F and O-F fluorinating agents, as well as F_2/N_2 and XeF_2 (see also section 2).[8-11,18,20,22,76] Yields are generally good to excellent. Commercially available N-F fluorinating agents such as F-TEDA-BF_4 and NFSI are now perhaps the most common electrophilic fluorinating agents used to affect this transformation.[10,18,20,22] Most of the recent work in this area has focussed on the stereoselective introduction of fluorine using prochiral enol ethers (see section 3).



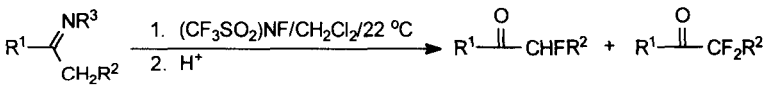
Scheme 21

The electrophilic fluorination of enamines (Scheme 22) with N-F type reagents, as well as with XeF_2, followed by hydrolysis is also an effective method for preparing α-fluoro ketones.[8,10,18,20,22] Recently,



Scheme 22

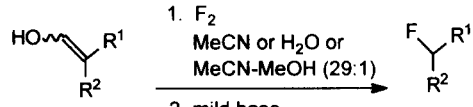
DesMarteau and coworkers reported the direct fluorination of imines using N-fluoro-bis[(trifluoromethyl)sulfonyl]imide (Scheme 23).[83] Monofluoroketones were obtained in 20-30% yields along with lesser amounts of difluoro products when 0.67 equiv of fluorinating agent was used. Difluoro ketones were the sole products (58-83%) when using 2 or more equivalents. It is believed that the reactions proceed via the enamine tautomers.



Scheme 23

4.4 Via fluorination of hydroxymethylene compounds

Recently, Sato and coworkers have described the use of the α-hydroxymethylene substituent as a directing and activating group for the direct preparation of α-monofluorocarbonyl compounds, **82c-e**, and α-monofluoro-β-dicarbonyl compounds **82a** and **82b**, with molecular fluorine (Scheme 24).[84] Studies to determine the mechanism of this reaction (radical versus electrophilic) were not performed.

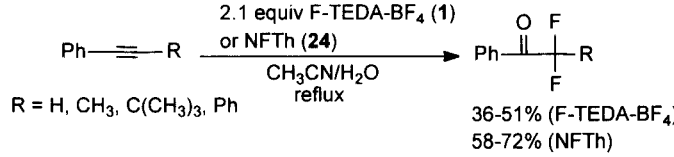


82a, $R^1 = R^2 = CO_2Me$
82b, $R^1 = CO_2Et$, $R^2 = COMe$
82c, $R^1 = CO_2Me$, $R^2 = CN$
82d, $R^1 = CO_2Et$, $R^2 = Ph$
82e, $R^1 = COPh$, $R^2 = Me$

Scheme 24

4.5 Via fluorination of alkynes

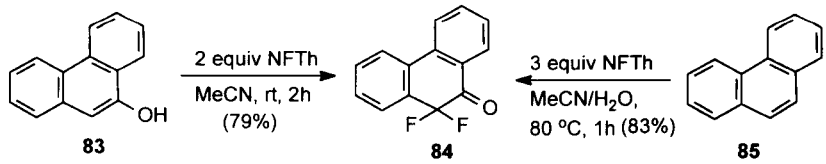
Zupan and coworkers have reported that reaction of F-TEDA-BF_4[85] or NFTh[39] with substituted phenylacetylenes in refluxing MeCN/H_2O yields α,α-difluoroketones (Scheme 25). Higher yields were obtained with NFTh.



Scheme 25

4.6 Via fluorination of hydroxy aromatics

Stavber and Zupan have reported the synthesis of α,α-difluoroketones from hydroxy aromatics in good to excellent yields using NFTh (**24**).[39] For example, treatment of 9-phenanthrol (**83**) with 2 equivalents of NFTh in MeCN at room temperature for 2h gave the difluoro ketone **84** in 79% yield (Scheme 26). Interestingly, these workers also reported that **84** can be prepared in 82% yield by treating phenanthrene **85** with a three-fold excess of NFTh in a 9:1 MeCN/H_2O at 80 °C for 1h.[39]



83 **84** **85**

Scheme 26

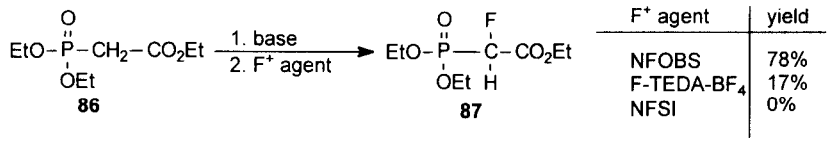
5. Fluorination of organophosphorus compounds

5.1 Synthesis of α-fluorophosphonates

A considerable amount of attention has been paid to the synthesis of α-fluorinated phosphonates in recent years. There are two major reasons for this. One is that α-fluorophosphonates are considered to be excellent non-hydrolyzable phosphate mimetics[86] and are therefore often found to be potent inhibitors of

enzymes that bind or hydrolyze phosphate esters.[87] Another is that these compounds can be used as Wadsworth-Horner-Emmons reagents for the preparation of fluoroolefins.[88] Electrophilic fluorination of phosphorus stabilized carbanions is rapidly becoming an important method for preparing α-fluorinated phosphonates.

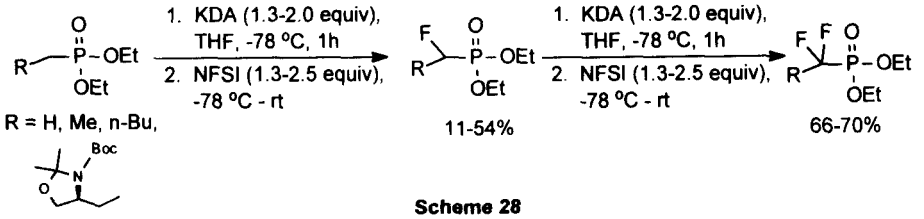
Early work on the preparation of α-fluorophosphonates via electrophilic fluorination of phosphonate carbanions employed $FClO_3$ as fluorinating agent. This reagent was used to fluorinate in reasonable to good yields mainly highly stabilized phosphonate carbanions derived from phosphonoacetates,[89] methylene bisphosphonates,[90,91] phenylsulfonylmethanephosphonate[92] and α-ketophosphonates.[93] More recently, this class of compounds has been prepared using the N-F electrophilic fluorinating agents. Blackburn and coworkers have reported that N-fluoroperfluoropiperidine and N-fluoro-2,6-dimethyldifluoropiperidine partially α-fluorinate tetraethylmethylene bisphosphonate although the details were not given.[90] α-Monofluorination of diethyl cyanomethanephosphonate has been accomplished in 51% yield using 1.1 equiv n-BuLi and 1.3 equiv *N*-fluorobis(trimethanesulfonyl)imide (Desmarteau's reagent) at -78 °C.[94] Reaction of diethyl[(phenylsulfonyl)methane]phosphonate with NaH/F-TEDA-BF_4 afforded a mixture of diethyl[(phenylsulfonyl)fluoromethane]phosphonate (60%), diethyl[(phenylsulfonyl)difluoromethane]-phosphonate (15%) and unreacted starting material (25%).[10,20,77] Diethyl[(phenylsulfonyl)difluoromethane]phosphonate can be prepared in 80% yield by sequential fluorination of the sodium salt of diethyl[(phenylsulfonyl)methane]phosphonate using F-TEDA-BF_4.[10] Davis has reported the synthesis of triethyl α-fluorophosphonoacetate (**87** in Scheme 27) in 78% yield by reacting triethylphosphonoacetate **86** with 1.1 equiv NaHMDS at - 78 °C followed by the addition of 1.2 equiv of **42** (NFOBS) and then warming to room temperature.[65] Surprisingly, a recent study reported that this reaction does not proceed well or at all with F-TEDA-BF_4 and NFSI (Scheme 27).[95]



Scheme 27

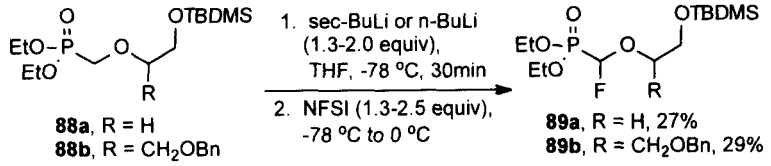
The fluorination of less stabilized phosphonate carbanions has proven to be more challenging. Koizumi *at al* reported that less stabilized phosphonate carbanions do not yield the expected fluorinated products using $FClO_3$.[92] However, Blackburn and coworkers have reported that diethyl lithiomethanephosphonate can be monofluorinated with $FClO_3$ in 46% yield if the reaction is conducted at -80 to -100 °C.[96] Attempts by Differding to fluorinate the α-carbanion generated from diethyl ethylphosphonate using N-fluorocollidinium triflate, XeF_2 and an N-fluorosultam failed to give the desired fluorinated product in greater than 10% yield.[97] However, shortly thereafter, Differding reported the less stabilized carbanions derived from simple alkylphosphonates can be fluorinated using KDA as base, NFSI as fluorinating agent and

performing the reaction at -78 to -90 °C (Scheme 28).[98] The monofluorinated products were obtained in 45-54% yields with the exception of diethyl methanephosphonate where the yield was only 11%. To obtain the



Scheme 28

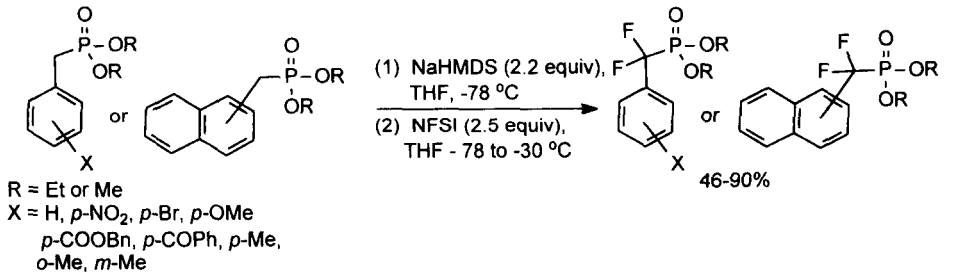
difluorinated compounds a two step process was found to work best in which the monofluorinated compounds were first isolated and then subjected to deprotonation at -90 °C followed by fluorination (Scheme 28).[98] This



Scheme 29

methodology has recently been employed by Chen and coworkers for the preparation of α-monofluoro derivatives **89a** and **89b** which were used to construct acyclic nucleotide analogues some of which exhibited anti-viral activity (Scheme 29).[99,100]

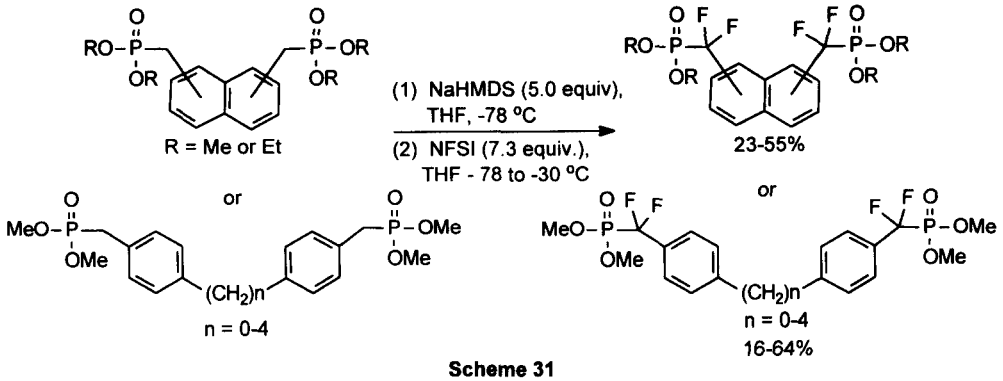
NFSI has proven to be a particularly effective reagent for the preparation of α,α-difluoro- and α-monofluorobenzylphosphonates. This is an important class of compounds due to their ability to act as potent inhibitors of medicinally important protein tyrosine phosphatases and kinases.[87a-f,101,102] A wide variety of



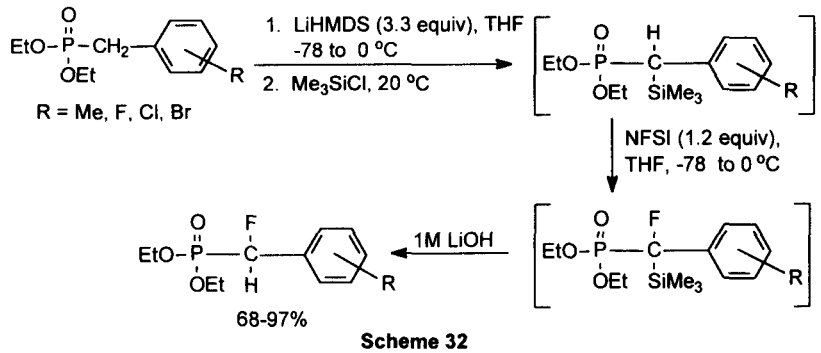
Scheme 30

benzylphosphonates can be difluorinated in good yield in a single step at - 78 °C when using 2.2 equiv NaHMDS and 2.5 equiv NFSI (Scheme 30).[103,104] Compounds bearing more than one benzylphosphonate moiety can also be α-fluorinated (Scheme 31).[103,104] Although the α-monofluorobenzylphosphonates can be prepared in reasonable yields using 1.1 equiv NaHMDS and 1.1 equiv NFSI, the reaction inevitably produces a mixture of mono and difluorinated products that must be separated.[103] However, Savignac and coworkers have developed a procedure in which the α-monofluorinated compounds can be prepared in good to excellent

yield in a one-pot procedure by electrophilic fluorination with NFSI of α-carbanions of α-trimethylsilyl benzylphosphonates followed by deprotection using 1M LiOH (Scheme 32).[105]



Scheme 31



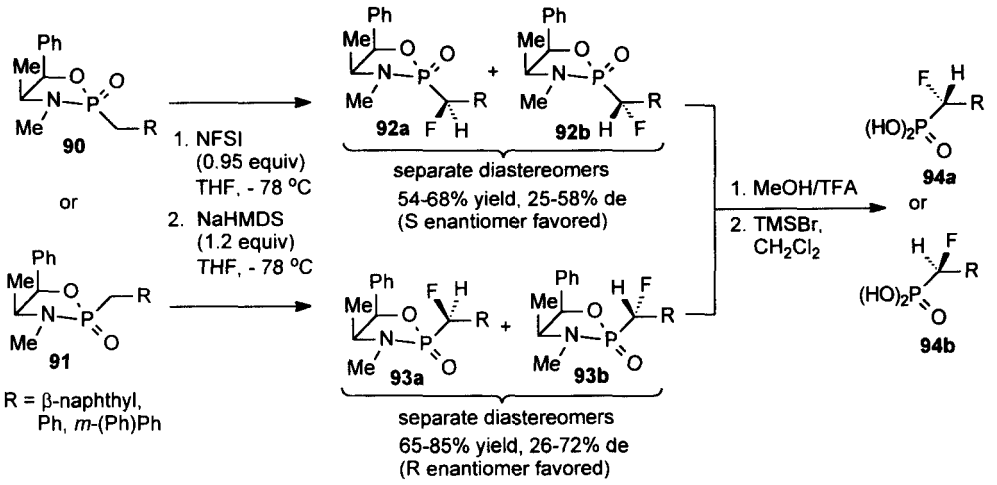
Scheme 32

5.2 Synthesis of α-fluorophosphonamidates

Recently, Taylor *et al* have used electrophilic fluorination for the preparation of chiral benzylic α-monofluorophosphonic acids.[106] The key step in the synthesis was the diastereoselective electrophilic fluorination, using NFSI, of α-carbanions of asymmetric phosphonamidates of type **90** and **91** bearing (-)-ephedrine as a chiral auxiliary (Scheme 33). In general, the fluorinated phosphonamidates were obtained in good yield. Although the de's of the reactions were modest, the diastereomeric fluorinated phosphonamidates (**92a-b** and **93a-b**) exhibited large differences in mobility on silica gel and were readily separated by silica gel flash chromatography. Compounds **92a-b** and **93a-b** are crystalline compounds and their absolute stereochemistry was determined by X-ray crystallography. Removal of the ephedrine auxiliary using MeOH/TFA followed by treatment with TMSBr afforded enantiomerically pure α-monofluorophosphonic acids of type **94a-b**.

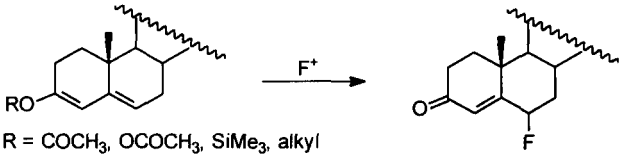
6. Synthesis of γ-fluorocarbonyl compounds and the preparation of 6-fluorosteroids

Interest in the synthesis of γ-fluorocarbonyl compounds stems mainly from the importance of certain 6-fluorosteroids as anti-inflammatory agents. Electrophilic fluorination has been used extensively for the



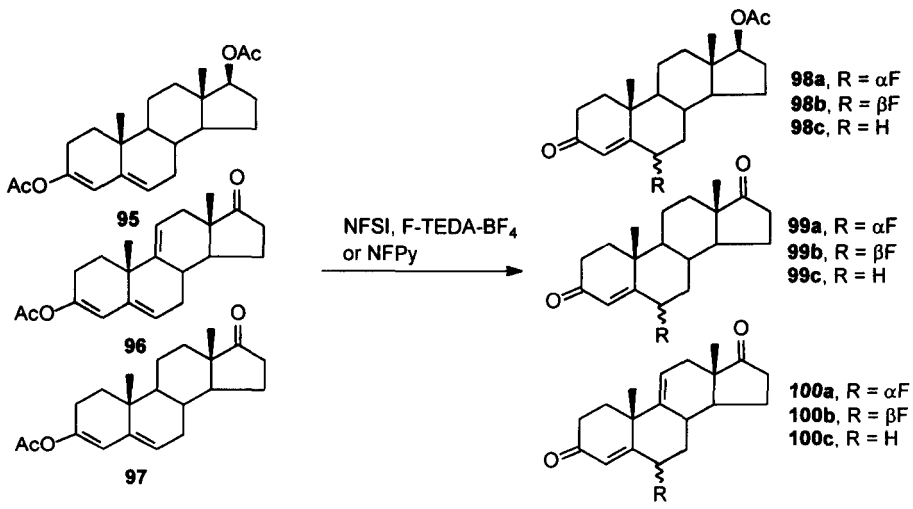
Scheme 33

preparation of 6-fluorosteroids from conjugated enol ethers or acetates (Scheme 34) with the first report appearing as early as 1964.[107] A variety of electrophilic fluorinating agents (O-F, N-F, XeF_2, F_2/N_2) have been used for this reaction and the literature on this subject up to mid 1995 has been sufficiently reviewed elsewhere.[8-10,18,20,50a-c] Recent work in this area has focussed on examining the utility of N-F fluorinating agents since these reagents would be a safer alternative to F_2 and O-F fluorinating agents that are currently in use in industry.



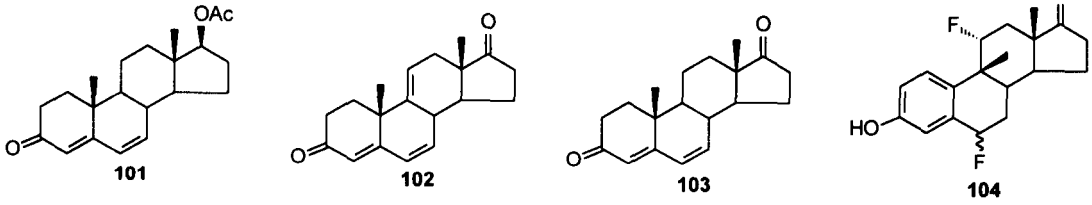
Scheme 34

Recently, Herrinton and coworkers from Pharmacia/Upjohn have performed a detailed analysis of the reaction of three N-F reagents, NFSI, F-TEDA-BF_4 and N-fluoropyridinium pyridine heptafluorodiborate (NFPy) with 3,5-dienolacetates **95**, **96** and **97** to selectively prepare the 6α-fluoro steroid products **98a**, **99a** and **100a** (Scheme 35).[108] Reaction of **95** with 1.5 equiv NFSI at 40 °C in THF for 24 h gave a 5:95 mixture of **98a**:**98b** in 55-60% yield. No explanation as to the origin of this unusual selectivity for the β-isomer was given. Prior to Herrinton's work, Poss and coworkers had reported that the fluorination of **95** with NFPy at 40 °C produced a 1:1 mixture of **98a**:**98b** in 90% yield.[109] However, performing the same reaction at 80 °C gave a 57% yield and a 4:1 ratio of **98a**:**98b**. Reaction of **95** with F-TEDA-BF_4 had also been previously studied and found to give a 95% yield of a 1:1.4 mixture of **98a**:**98b**.[110] Similar results have been reported for the fluorination of **96** with F-TEDA-BF_4[110] and NFPy.[109] Since the reaction of **95** with NFPy at elevated temperatures favors formation of the α-isomer, Herrinton and coworkers examined the effect of temperature



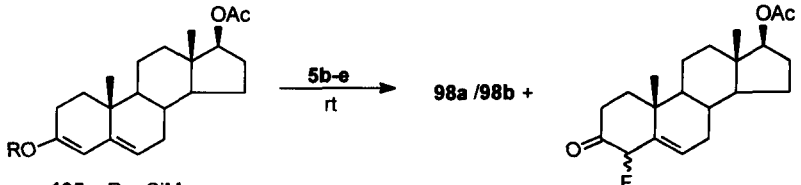
Scheme 35

on the reaction of **95**, **96** and **97** with NFPy (40 and 80 °C, CH_3CN, 3h) and F-TEDA-BF_4 (0 and 80 °C, CH_3CN, 3h). At lower temperatures, both reagents gave approximately a 1:1 mixture of α- and β-isomers. However, F-TEDA-BF_4 gave essentially complete conversion while NFPy gave only 15-20% conversion. At higher temperature, less of the β-fluoro isomers were detected in the products however, a significant quantity of the 3-keto-4,6-dienone steroids **101-103**, were produced as byproducts. Increasing the reaction time with NFPy (40 °C, 120 h) until starting material was consumed also lead to a decrease in the amount of β-fluoro isomers and an increase in the formation of byproducts **101-103**. Close examination of the fluorination



reactions revealed that the α- and β- isomers were initially formed in a 1:1 mixture but as the reaction proceeded the β-fluoro isomer disappeared without an increase in the α-isomer while the amount of byproducts **101-103** increased. This suggests elimination of HF, which is more likely for the β-isomers because of the axial orientation of the fluorine. NFPy gave more of the byproducts due to the presence of pyridine. With **97**, use of excess F-TEDA-BF_4 (6h at 80 °C) resulted in the reaction of the 9,11 double bond to produce phenol **104** (24% after 6h) as an additional byproduct.[111] This reaction did not take place with the less electrophilic fluorinating agent NFPy. By lowering the reaction temperatures, using shorter reaction times and reducing the number of equivalents of F-TEDA-BF_4, the yield of **100a/100b** was increased to 80-85% in a 1.3:1 ratio. It was also found that the mixture of α and β-isomers could be converted to the desired α-isomer by selective recrystallization from an equilibrating acidic solution of the isomeric mixture.

Umemoto has reported that fluorination of steroid derivatives **105a-105d** with **5b-5e** at room temperature resulted in the formation of mixtures of the 6-fluoro isomers, **98a** and **98b**, and the 4-fluoroisomers **106** (Scheme 36) in modest to excellent yields.[28] The amount of 6-fluoro isomers increased with increasing steric bulk of the silyl moiety. Exclusive 6-fluorination was obtained using **5b** and the triisopropyl silyl ether. The β-isomer was formed preferentially in all cases. In contrast, N-fluoropyridinium triflate (**3**) yielded a 4.1:1 ratio of the 6-F and 4-F isomers in 33% yield.[28]

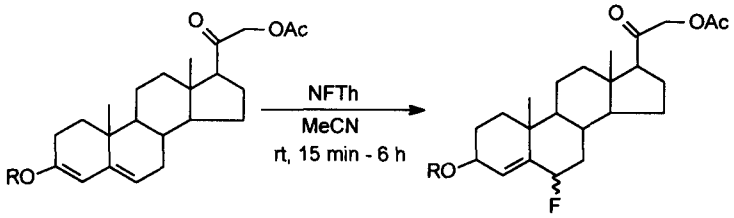


105a, R = $SiMe_3$,
105b, R = TBDMS
105c, R = $SiEt_3$
105d, R = $Si\textit{i}Pr_3$

106

Scheme 36

Umemoto has also recently reported that the fluorination of **95** with **9b** in MeCN/$NaHCO_3$ at 70 °C gives a mixture of **98a** and **98b** (1:1.7) in 82% yield.[32] Fluorination of **95** with **20b** in MeCN at -20 °C gives a mixture of **98a** and **98b** (1:1.5) in 81% yield.[33] Reaction of **105c** with **9b** in MeCN/$NaHCO_3$ at room temperature gives a mixture of **98a** and **98b** (1:1.4) and **106** in an overall 65% yield.[32] Poss and Shia have recently reported the fluorination of **107a** and **107b** to give 6-fluoro steroids **108a** and **108b** in good yield using NFTh (Scheme 37).[42]

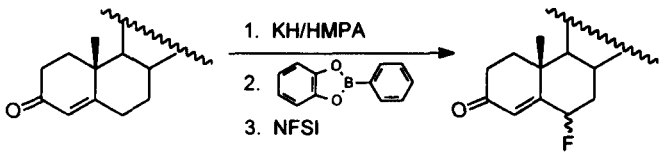


107a, R = Ac
107b, R = CH_3

108a, R = Ac (89%, α/β = 1:2.2)
108b, R = CH_3 (72%, α/β = 1:2.4)

Scheme 37

Preparation of 6-fluoro steroids has also been achieved by reacting potassium dienoxy boronates of Δ^4-3-ketosteroids with NFSI (Scheme 38).[112] This reaction has been carried out on a number of cholesterol derivatives producing the 6-fluoro products in 58-82% yield. It was also found that the potassium dienoxy boronate derived from the β,γ-ethylenic ketone, 5-cholesten-3-one, also gave the 6-fluoro unsaturated ketone. In addition, this procedure was also used to prepare 4-fluoro-5-cholesten-7-one in 72% yield from 5-cholesten-7-one.[112] In all of the above cases, the β-isomer was favored over the α-isomer by 4-10 fold.

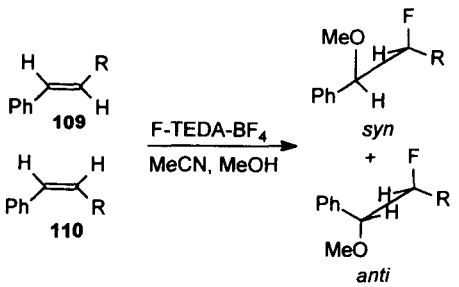


Scheme 38

7. Fluorination of alkenes and glycals

The reaction of electrophilic fluorinating agents with alkenes has been covered in several earlier reviews.[8-11,18,20] The reaction has been carried out with a wide variety of electrophilic fluorinating agents of both the N-F[10] and O-F[9] type as well as with XeF_2[8] and F_2.[11] These reactions are addition or addition-elimination processes in which β-fluorocarbocations are postulated intermediates. The reaction generally proceeds in good yield with Markovnikov type regioselectivity. A phenyl group, or some group capable of stabilizing the carbocation, bonded along a C-C double bond, significantly enhances the reactivity of the alkene. When using F_2, XeF_2 and some O-F reagents, the presence of an external nucleophile is not necessary since the nucleophilic component of the fluorinating agent reacts with the carbocation intermediate.[8,10,11] With N-F reagents, external nucleophiles are usually necessary to prevent the formation of complicated product mixtures.[10] Some examples on electrophilic fluorination of alkenes that have appeared in the literature since 1995 are discussed below.

Stavber and coworkers have reported a detailed analysis of the reaction of phenyl substituted alkenes **109** and **110** with F-TEDA-BF_4 (Scheme 39).[113] In the presence of various alcohols, vicinal fluoroalkoxy products were formed in good yields with Markovnikov type regioselectivity. The nature of the substituents moderately affected the stereochemical outcome (*syn* vs. *anti*) as did the configuration of the alkene (Scheme 39).



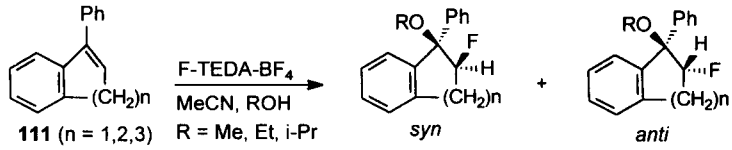
alkene	R	*syn*	*anti*	yield (%)
109a	Ph	28	72	75
110a	Ph	55	45	78
110b	Me	50	50	75

Scheme 39

In the case of **109a**, the stereochemical results using F-TEDA-BF_4 were found to be similar to those obtained after fluorine addition using $XeF_2/CH_2Cl_2/HF$.[114] Methoxy-fluorination with $CsSO_4F$/MeOH or CF_3OF/MeOH gave an opposite stereochemical preference.[114] Stereochemical results with **110a** and F-TEDA-BF_4 were similar to those obtained with $XeF_2/CH_2Cl_2/HF$ and $CsSO_4F$/MeOH.[114] An approximately 1:1 ratio of *syn*:*anti* products were formed when the study was carried out on phenyl-substituted cycloalkenes indene, acenaphthalene and dibenosuberenone.[113] Hammett analysis of the reaction of a series of substituted

α,α-diphenyl-substituted alkenes with F-TEDA-BF_4 in MeCN/MeOH yielded a ρ^+ of -1.42.[113] These results and other kinetic studies[113] indicate that there is a moderate electron deficiency on the reactive center in the rate-determining step.

The reaction of 1-phenyl-substituted benzocyclenes of type **111** with F-TEDA-BF_4 and various alcohols was also examined by Stavber and coworkers (Scheme 40).[113] The yields of vicinal *syn* and *anti* fluoroalkoxy products ranged from 74-82%. Treatment of the products with aqueous HBr yielded 2-fluoro-1-phenyl-substituted benzocyclene derivatives. With the five-membered ring system, the *syn* diastereomer was favored with MeOH and EtOH whereas equal mixtures were obtained using iPrOH. The *anti* isomer was always favored (by approximately 2:1) in the six-membered ring system. In the seven-membered ring system, the nucleophile greatly affected the *syn:anti* ratio. When MeOH was employed, the *syn:anti* ratio was 1:99. With isopropanol, this ratio changed to 86:14. The stereochemical results obtained with the 5-membered ring system and F-TEDA-BF4 is similar to that obtained with $CsSO_4F$.[114] With the six-membered ring system, the stereochemical results with F-TEDA-BF_4 were almost the same as those obtained with XeF_2 in CH_2Cl_2, and $CsSO_4F$/MeOH.[114]



111 (n = 1,2,3) R = Me, Et, i-Pr *syn* *anti*

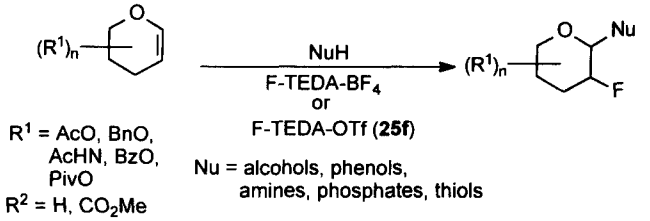
Scheme 40

Stavber and coworkers have also examined the reaction of NFTh with alkenes.[36] Near quantitative and Markovnikov-type formation of vicinal fluorohydroxy, fluoromethoxy or fluoroacetoxy products were obtained when the reaction was performed with acyclic alkenes using MeCN as solvent in the presence of water, methanol or acetic acid. Stereochemical studies in MeCN/MeOH using indene and acenaphthalene as model substrates indicated a slight preference of the *syn* isomer. Stereochemical studies using 1-phenyl-substituted benzocyclenes of type **111** as substrates were also performed in MeCN/MeOH. In most instances mixtures of *syn* and *anti* fluoro-methoxy products were produced with the exception of the seven-membered ring system which yielded almost exclusively *anti* product.

Stavber and coworkers have recently shown that a variety of alkenes can be converted into vicinal fluoroacetamides in high yield by reaction with NFTh in MeCN.[37] Limited stereochemical studies indicated that the reaction proceeds with little or no stereoselectivity. The reaction is believed to proceed via the formation of β-fluoro carbocation intermediates which are attacked by MeCN followed by a Ritter-type reaction.

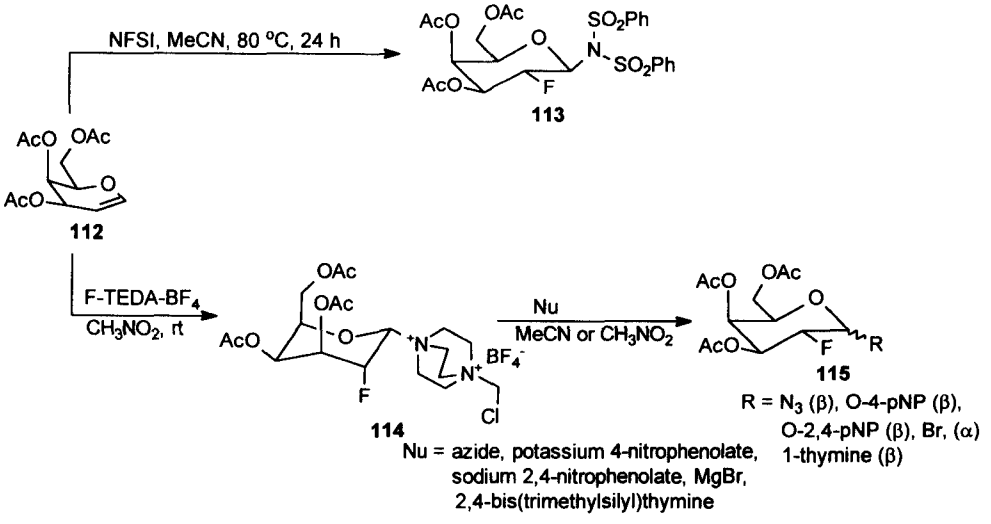
The synthesis of carbohydrates bearing fluorine at the 2-position has been a subject of interest for many years due to their importance in biochemical studies and medicinal chemistry research. One of the most common methods for preparing 2-deoxy-2-fluoro aldoses has been via electrophilic fluorination of glycals. Until fairly recently, this reaction had been performed using reagents such as CF_3OF, AcOF, XeF_2 or F_2 to

give 1,2-difluorosugars which were then hydrolyzed in acid to give the desired 2-deoxy-2-fluoro sugars.[115] In general, these reactions were low yielding. More recently, Wong and coworkers have reported that 2-deoxy-2-fluoro carbohydrates can be obtained in good to excellent yields using F-TEDA-BF_4 or F-TEDA-OTf (**25f**) (Scheme 41).[116a,b] When using F-TEDA-BF_4, 1,2-difluorosaccharides are formed as side products presumably by attack of fluoride from the BF_4^- counterion. This side reaction can be avoided and yields can be significantly improved by using a triflate counterion (F-TEDA-OTf, **25f**). When MeCN is used as solvent the nucleophile must be in excess. When the reaction is performed in MeCN with one equivalent of nucleophile, MeCN participates in the reaction with attack at the anomeric position and addition of the nucleophile to the nitrile carbon. This side reaction can be avoided by using nitromethane as solvent. The α/β stereochemistry of the fluorine addition is determined by steric and solvent effects. Mechanistic studies using a radical probe indicated that the reaction between the glycals and **25f** does not occur via a single electron transfer mechanism.



Scheme 41

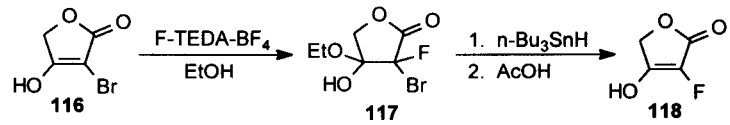
Shortly after Wong's initial report,[116a] Albert *et al* reported a detailed study of the reaction of glycals with several N-F reagents.[117] Treatment of glycal **112** with N-fluoropyridinium tetrafluoroborate or N-fluoro-2,4,6-trimethylpyridinium triflate at room temperature or with heating did not result in any reaction. Reaction of **112** with NFSI for 24 h at 80 °C in CH_3CN gave **113** as the sole product (Scheme 42). Reaction of **112**



Scheme 42

with F-TEDA-BF_4 at room temperature in nitromethane yielded the N-glycosyl compound **114** in 82% yield with the fluorine oriented exclusively axial and the imide substituent exclusively equatorial. This stereochemistry suggests a concerted *syn*-addition not yet observed with any N-halo compounds. A similar *syn*-addition mechanism was later reported by Wong and coworkers.[116b] Compound **114** was found to react readily with a number of nucleophiles to give an array of 2-fluoro, C-1 substituted carbohydrate derivatives of type **115** (Scheme 42) in reasonable yields.

Kirk and Ge have reported the preparation of 2-fluorotetronic acid **118** (Scheme 43).[118] Direct reaction of tetronic acid with F-TEDA-BF_4 gave only trace amounts of product. However, reaction of the bromo derivative **116** with F-TEDA-BF_4 in EtOH gave the fluoro derivative **117** in 87% yield which was then converted into **118**. Interest in **118** stems from a number of natural products and synthetic compounds that contain the tetronic acid moiety.

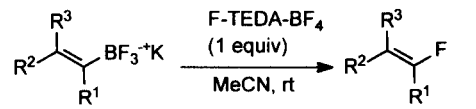


116 **117** **118**

Scheme 43

It has been known for many years now that the introduction of fluorine into certain positions of purines and pyrimidines can significantly alter the biological activity of these molecules.[1] Electrophilic fluorination using a variety of F^+ reagents such as F_2, XeF_2, CF_3OF has been used as a key step in the preparation of fluoropyrimidines.[119] Relatively recently, 5-fluoro-6-hydroxy, 5-fluoro-6-methoxy and 5-fluoro-6-acetoxy adducts of various uridine and cytidine derivatives have been prepared in good to excellent yields by reacting uridine and cytidine derivatives with F-TEDA-BF_4 in the presence of H_2O, MeOH and AcOH.[120,10,20] More recently, Barrio and coworkers have reported the first preparation of protected 8-fluoropurines in approximately 30% yields by direct fluorination of protected purines using F_2 in EtOH in the presence of triethylammonium hydroxide.[121] Fluorination yields with unprotected purines were less than 10%.

Olah and coworkers has shown that alkenyl trifluoroborates of type **119** react with one equivalent F-TEDA-BF_4 in MeCN to produce Z/E mixtures of the corresponding fluoroalkenes **120** in good yield (Scheme



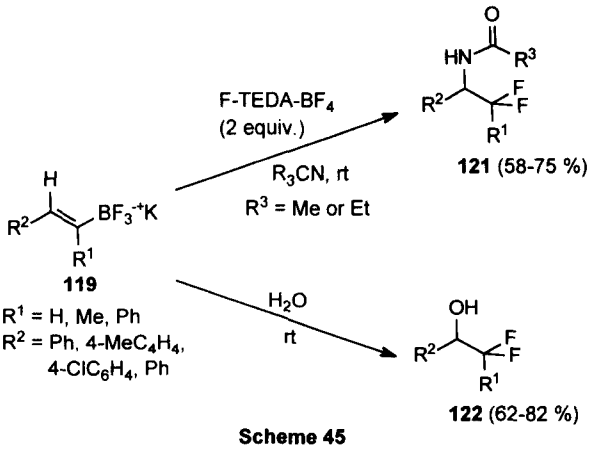
119 **120** (58-89%)

R^1 = H or Ph
R^2 = Ph, Bu, 4-MeC_4H_4, 4-ClC_6H_4, Ph
R^3 = H or Br

Scheme 44

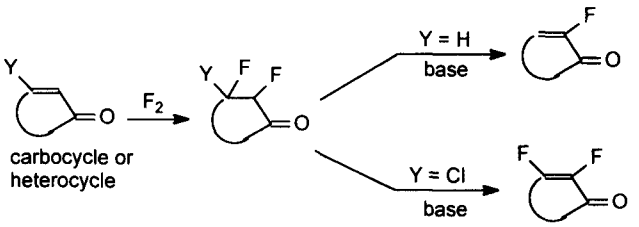
44).[122] When the reaction was performed with two equivalents of F-TEDA-BF_4 using acetonitrile or propionitrile as solvent, difluoromethyl amide products **121** are produced (Scheme 45). This reaction can be

considered to be the fluoro analogue of the Ritter reaction.[123] When the reaction is performed in water with two equivalents of F-TEDA-BF_4, difluoromethylene alcohols **122** are formed (Scheme 45).



Scheme 45

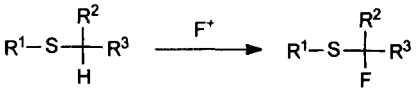
Sato *et al* have reported the fluorination of carbocyclic systems or heterocyclic β-chloro enone systems, including uracil derivatives, with F_2/N_2 in Rozen's solvent (fluorotrichloromethane:chloroform:ethanol, 10:10:1) to give the β-chloro-α,β-difluoro derivatives (Scheme 46).[124] Treatment of the adducts with mild base results in the selective elimination of HCl to give α,β-difluoro-α,β-unsaturated carbonyl compounds. This is in contrast to the fluorination of enones with F_2/N_2 which had previously reported to give α-fluoro enones.[125]



Scheme 46

8. Synthesis of α-fluorosulfides, -sulfoxides, -sulfones and -sulfonates

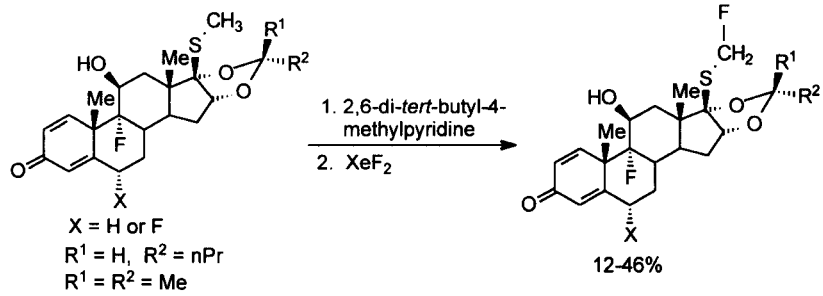
A number of electrophilic fluorination reagents of the N-F type, as well as XeF_2, have been used to affect the transformation of sulfide into α-fluorosulfides (Scheme 47) and the literature on this subject up to mid-1995 has been covered in a number of review articles.[8,10,20] α-Fluorination of sulfides has proven to be an



R1, R2 = aryl, alkyl
R3 = H or alkyl

Scheme 47

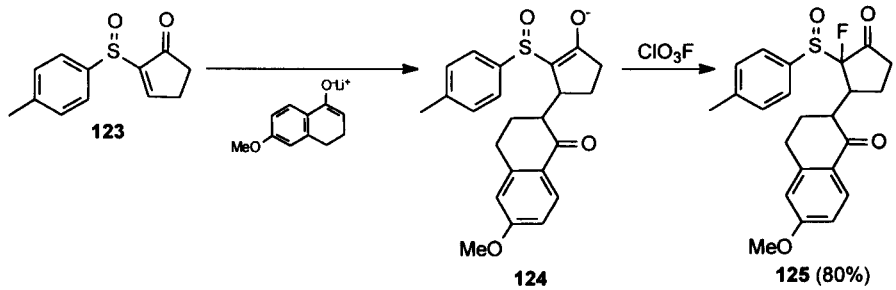
effective means of altering the biological activity of certain sulfide-bearing compounds.[126,127] Consequently, a considerable amount of the work in this area has focussed on the preparation of α-fluorosulfides with potential biological applications such as the preparation of nucleosides bearing an α-fluorosulfide moiety.[128-132] A more recent example of the preparation of an α-fluorosulfide with biological applications was recently reported by Ashton and coworkers.[133] These workers used XeF_2 to prepare a number of novel glucocorticoid steroids bearing an α-fluorosulfide moiety in low to modest yield (Scheme 48). Some of these compounds were found to exhibit enhanced anti-inflammatory activity compared to their non-fluorinated analogues.[133]



Scheme 48

Concerning reactions of this type not related to biological studies, Lu *et al* have reported that the reaction of XeF_2 with a series of O,S-acetals ($ArOCH_2SCH_3$) yields, in most instances, α-fluoro ethers ($ArOCH_2F$).[134] The fluorinated O,S-acetals ($ArOCH_2SCH_2F$) were formed either as minor products or not at all.

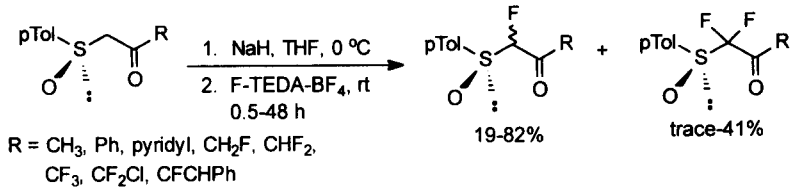
There have been only a few reports describing electrophilic fluorination of sulfoxides.[135-137] Posner and Frye reported the synthesis of α-fluoro-β-keto sulfoxide **125** by treating cyclopentenone sulfoxide **123** with the enolate ion of 6-methoxytetralone and then reacting the resulting enolate ion **124** with perchloryl fluoride (Scheme 49).[136] A similar reaction was also performed using vinylmagnesium bromide.[136]



Scheme 49

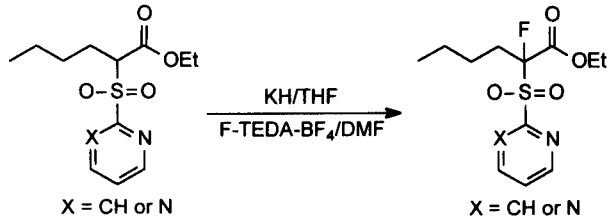
Arnone *et al* reported that treatment of enantiomerically pure β-ketosulfoxides with 1 equivalent of NaH at 0 °C followed by the addition of F-TEDA-BF_4 at room temperature for 0.5-48h yielded diastereomeric

mixtures of α-monofluorinated β-ketosulfoxides without altering the sulfinyl stereocenter (Scheme 50).[137] In most instances, small amounts of α,α-difluorinated products formed. The amount of difluoro product was greater for those substrates bearing electron withdrawing groups (EWG's) (R = EWG in Scheme 50). It was also found that the difluoro products could be obtained in quantitative yield by subjecting the isolated monofluorinated products to the fluorination conditions.

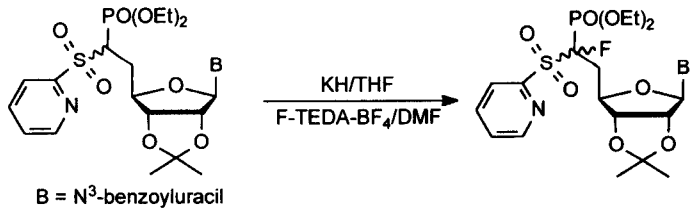


Scheme 50

There have been several reports in the literature describing the α-fluorination of sulfones by electrophilic fluorination.[138-141] Wnuk and Robbins[138] have shown that the α-fluorination of α-sulfonyl carboxylic acid esters (Scheme 51) and α-sulfonyl phosphonate esters[139] (Scheme 52) can be affected using KH/F-TEDA-BF_4 in DMF. However, specific yields were not given. Desulfonylation with tributylstanne yielded the corresponding α-fluoro carboxylic or phosphonate esters.[138]

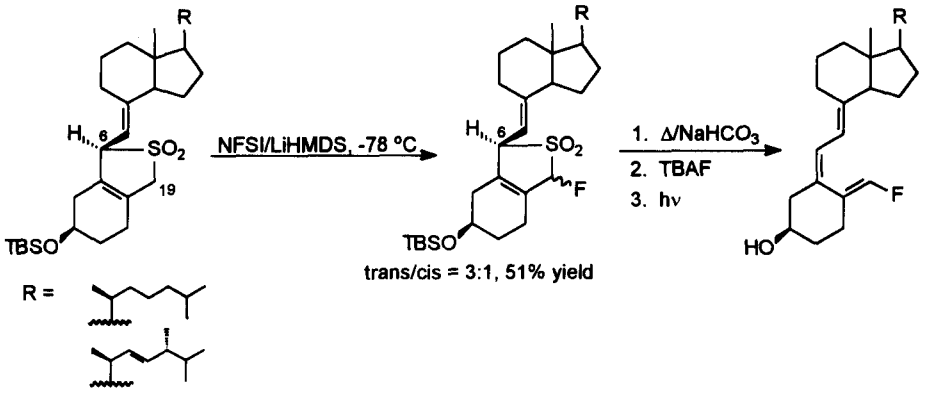


Scheme 51



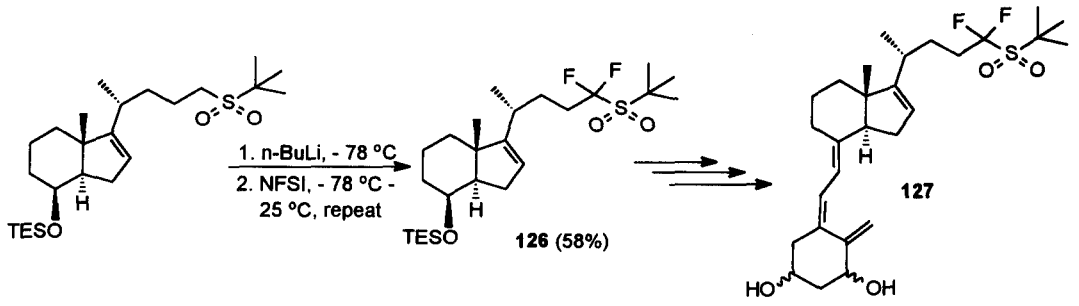
Scheme 52

An interesting example of the electrophilic α-fluorination of a sulfone and its use in organic synthesis was recently reported by Iwasaki *et al.*[140] Here, 6S-SO_2 adducts of vitamin D3 were treated with LiHMDS in THF/HMPA at - 78 °C followed by the addition of NFSI. This yielded the 19-fluorinated adducts as a 3:1 mixture of the 6,19-*trans*-isomer and the 6,19-*cis* isomer in 51% yield (Scheme 53). No epimerization at C-6 occurred. A similar result was obtained with the 6R-SO_2 adduct. Desulfonylation followed by desilylation and photoisomerization yielded 19-fluorovitamin D derivatives.



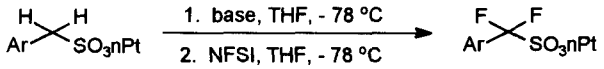
Scheme 53

Posner *et al* have used NFSI to prepare the fluorinated sulfone **126** (Scheme 54).[141] Compound **126** was used as an intermediate in the preparation of a new sulfone analog of the hormone 1α,25-dihydroxyvitamin D3 (**127**).



Scheme 54

Only a single report has appeared describing the electrophilic fluorination of sulfonate esters.[142] Very recently, Taylor and coworkers reported that neopentyl (nPt) esters of benzylic α,α-difluorosulfonates can be obtained in good to excellent yields via electrophilic fluorination (Scheme 55).[142] This involved treating the corresponding non-fluorinated esters with strong base, such as t-BuLi, NaHMDS or LDA, at -78 °C followed by the addition of NFSI. The reaction was also attempted using the methyl, ethyl and isopropyl esters,

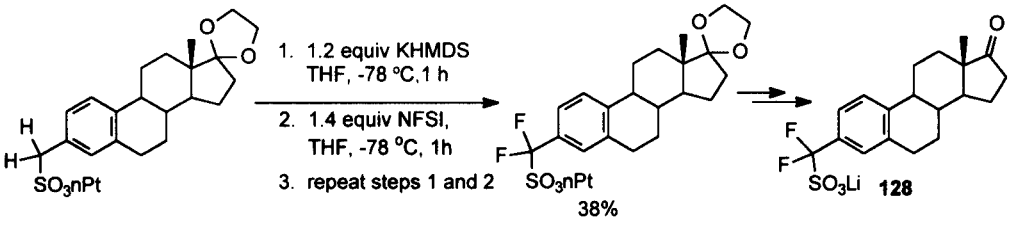


Ar = Ph, 4-NO_2Ph, 4-BrPh, 4-MePh, 3-(Ph)Ph, β-naphthyl

Scheme 55

however, only unidentified decomposition products were obtained and this was the case irrespective of the base employed. This may be due to competing reactions involving nucleophilic attack of the base at the methylene carbon of the alkoxy group of the ester and loss of the benzyl sulfonate moiety (with the methyl or ethyl esters) or removal of the β-proton of the alkoxy group followed by elimination of the benzyl sulfonate

moiety (ethyl or isopropyl esters). These side reactions must occur less readily with the neopentyl ester due to lack of a β-proton or steric hindrance. Fluorination of neopentyl phenylmethanesulfonate using 1.1 equiv of t-BuLi and 1.1 equiv NFSI yielded the α-monofluoro product in excellent yield indicating that this procedure can be used for preparing α-monofluorosulfonate esters. Removal of the neopentyl group to give the sulfonic acids as their lithium salts can be accomplished in high yield by treatment of the esters with LiBr in refluxing butanone. This procedure has recently been used by Taylor and Chen to prepare a novel estrone-3-sulfate analogue (**128**) in which the sulfate group is replaced with an α,α-difluorosulfonate (CF_2-SO_3^-), a non-hydrolyzable sulfate mimetic (Scheme 56).[143]



Scheme 56

9. Fluorination of aromatics and aromatic heterocycles

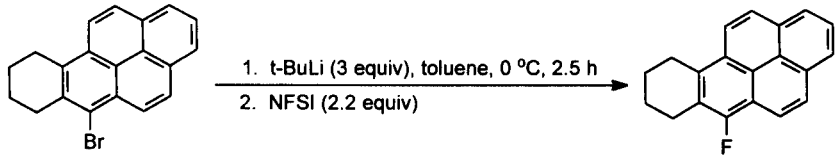
Electrophilic fluorination has been used extensively for the introduction of fluorine into aromatics using a wide variety of fluorinating agents (N-F, O-F, XeF_2) and this reaction has been covered in earlier reviews.[8-11,18,20] The majority of reactions of this type have involved the direct reaction of the F^+ reagent, sometimes in the presence of an acid catalyst (for XeF_2), using mono-substituted phenyl derivatives as substrates. Electron-rich substituents are often necessary to promote the reaction. The yield varies with the reactivity of fluorinating agent and the reaction conditions and multiple fluorination of the ring often occurs. The products are often a mixture of *ortho*- and *para*-isomers, however, by judicious choice of fluorinating agent and reaction conditions, highly selective *ortho*-fluorination can be achieved (for example see section 2). Disubstituted phenyl derivatives and, to a lesser extent, tri- and tetrasubstituted aromatic rings, have also been employed as substrates.[144]

The fluorination of aromatics has also been achieved using elemental fluorine.[145] One of the major problems using elemental fluorine is the tendency for fluorine to cleave homolytically thus producing highly reactive fluorine radicals which results in low selectivity. However, heterolytic cleavage of fluorine, and consequently, formation of fluoroaromatics via an electrophilic mechanism, can be encouraged by using Lewis acids[12] and polar solvents such as TFA,[13] formic acid,[14,15] sulfuric acid[14,15] and trifluoromethanesulfonic acid.[16] Using these highly polar solvents, even phenyl derivatives not bearing electron rich substituents such as benzene, benzoic acid and 4-fluorobenzoic acid can be readily fluorinated in modest to good yield even at low temperature. Substitution patterns are consistent with the mechanism for electrophilic substitution. In order to obtain decent yields of monofluorinated products, the molar ratio of fluorine to substrate has to be less than one.[13] Low *ortho/para* selectivity is usually found. It should also be pointed out that the mechanism of

the process is not entirely clear since the interaction of the acidic solvents with fluorine could lead to formation of O-F species which could then act as the source of electrophilic fluorine.

The preparation of fluorinated polyaromatic hydrocarbons by electrophilic fluorination has been reported using a number of electrophilic fluorinating agents (see also section 2.1.3).[8-10] However, achieving good regioselectivity, the formation of polyaromatic hydrocarbon dimers in certain cases and low yields are often serious problems. Zupan and coworkers have shown that the type of functionalization of certain polyaromatic hydrocarbons with F-TEDA-BF_4 is highly solvent dependent.[146] Ueno and coworkers have reported the electrophilic fluorination of azulenes with a variety of N-F reagents.[147] Electrophilic fluorination of azulene and 2-substituted azulenes gave a mixture of 1-fluoro and 1,3-difluoro azulene in overall low to modest yields.

Fluorination of aromatics has also been achieved via electrophilic fluorination of metallated aromatics.[8-11,18,20] Zajc has recently reported the preparation of fluorinated pyrene derivative **130** in 75% yield by reaction of bromo derivative **129** with t-BuLi followed by reaction with NFSI (Scheme 57).[148] Sniekus and coworkers have demonstrated that fluoroaromatics can be prepared in a regiospecific manner and

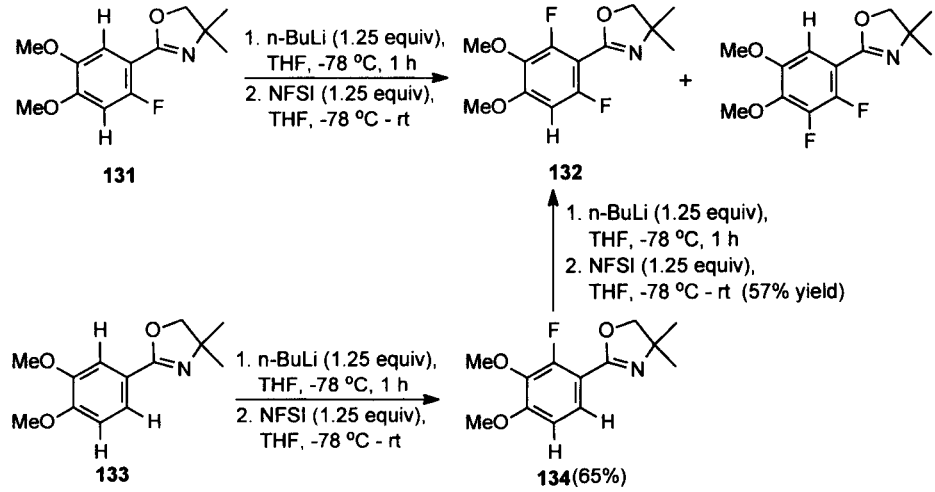


129 **130** (75%)

Scheme 57

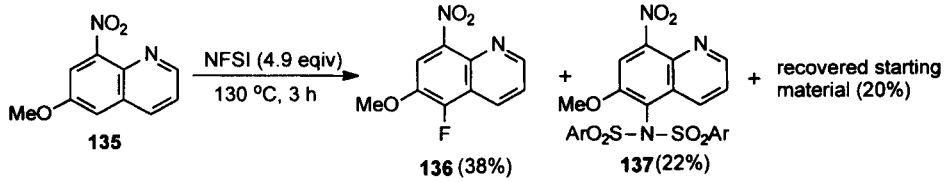
in modest to good yields by directed *ortho*-lithiation followed by electrophilic fluorination with both NFSI and NFOBS.[149,150] With the exception of $CONEt_2$ and $OCONEt_2$, a range of oxygen-, carbon- and sulfur-based directed metallation systems were found to undergo reaction with NFSI.[149] This approach to the preparation of fluorinated aromatics was used by Nie and Kirk to prepare fluoro and polyfluoroveratraldehydes.[151] Following the *ortho*-directing order oxazoline>methoxy>fluorine, established by Sniekus, Nie and Kirk proposed that fluorination of **131** would result in high selectivity at the double activated position 2 to give **132**. However, a mixture of difluorooxazolines was obtained (Scheme 58). Nevertheless, it was found that **132** could be prepared by subjecting **133** to lithiation/fluorination to give **134** which was purified and then the procedure was repeated on **134** to give **132** (Scheme 58).

In contrast to the fluorination of aromatics, there are only a handful of examples of the direct electrophilic fluorination of aromatic heterocycles. Fluoropyrolles have been prepared by direct fluorination using XeF_2[152] and by fluorodecarboxylation using F-TEDA-BF_4.[153] Fluorodecarboxylation has also been used to prepare fluorofurans.[154] Recently, O'Neil *et al* reported the synthesis of the fluoroquinoline derivative **136** via direct regiospecific electrophilic fluorination of the quinoline derivative **135** (Scheme 59) with NFSI.[155a,b] In addition to the desired fluoroquinoline **136**, the sulfonimide **137** was also obtained as a



Scheme 58

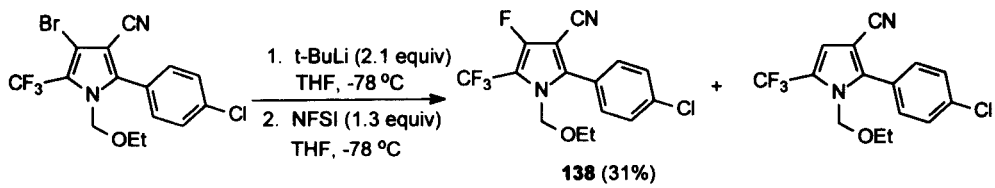
byproduct most likely by nucleophilic aromatic substitution of **136** by dibenzene sulfonimide. Attempts to prepare **136** using N-fluoropyridinium triflate yielded only polymeric tars.



Scheme 59

Zupan and coworkers have reported a detailed investigation into the fluorination of dibenzofuran with a variety of N-F fluorinating agents and XeF_2.[156,157] Fluorination of dibenzofuran with F-TEDA-BF_4, NFTh, N-fluoro-2,6-dichloropyridinium tetrafluoroborate and XeF_2 under a variety of different conditions yielded a mixture of 1-fluorodibenzofuran, 2-fluorodibenzofuran and 3-fluorodibenzofuran in yields of 30-40% with a modest preference for the 2-fluoro product. No reaction was found to occur using NFSI.

Synthesis of fluorinated heterocycles has also been achieved by electrophilic fluorination of metallated heterocycles.[8-10,20] Fluorothiophene has been prepared by reacting N-fluoroquinuclidinium fluoride[158,159] or N_2/F_2[160] with 2-lithiothiophene. Barnes and coworkers have used this approach to prepare the highly substituted fluoropyrrole **138** using NFSI as the fluorinating agent (Scheme 60).[161]

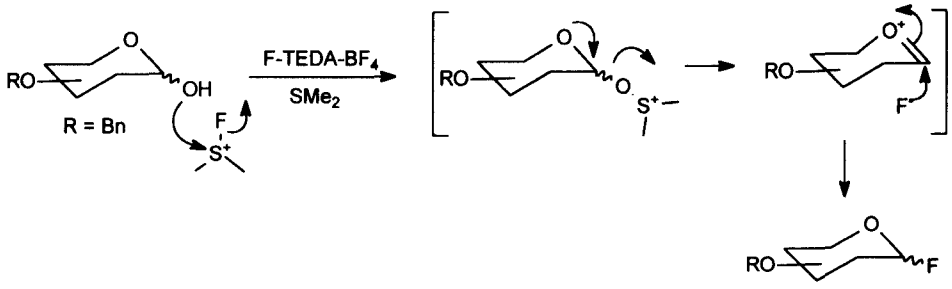


Scheme 60

10. Miscellaneous electrophilic fluorination reactions

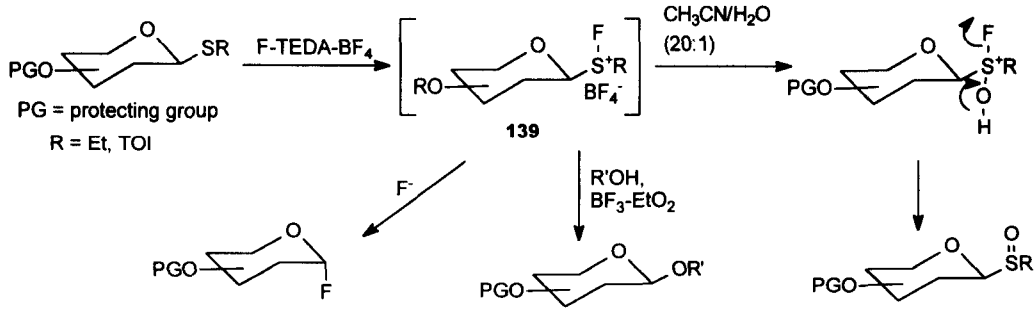
10.1 Conversion of 1-hydroxy sugars to fluoroglycosides and conversion of thioglycosides to fluoro-, oxy- and sulfonylglycosides.

Wong and coworkers have recently reported that F-TEDA-BF_4 in conjunction with methylsulfide transforms 1-hydroxy monosaccharides to 1-fluoro glycosides in good to excellent yields (Scheme 61).[116a,b] It is believed that the reaction proceeds via a fluorosulfonium ion which then reacts with the anomeric hydroxy group followed by displacement of the sulfoxide by fluoride (Scheme 61). Wong also reported that



Scheme 61

F-TEDA-BF_4 is an effective reagent for converting thioglycosides into glycosyl fluorides in good yield. (Scheme 62).[116a,b] Both of the above transformations have been previously accomplished with DAST. However, since F-TEDA-BF_4 is cheaper, easier and safer to handle than DAST, it is likely that this procedure will supplant DAST for carrying out these transformations. Wong and coworkers have also shown that F-TEDA-BF_4 can be used as an activator of thioglycosides to produce oxyglycosides in near quantitative yields (Scheme 62).[116a,b] In addition, F-TEDA-BF_4 in MeCN-H_2O (20:1) can quantitatively oxidize thioglycosides to sulfonyl glycosides.[116b] All of these reactions are believed to proceed via a fluoro-sulfonium cation (**139**).

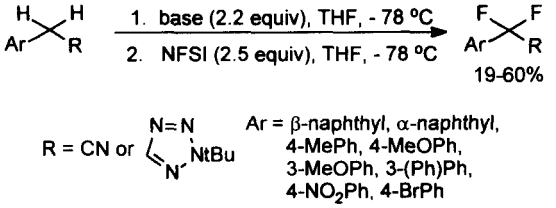


Scheme 62

10.2 α-Fluorination of benzylic nitriles and tetrazoles

Taylor and coworkers have recently reported that benzylic nitriles and benzylic *t*-butyl-protected tetrazoles can be α,α-difluorinated in moderate yields in a single step using 2.2 equiv of a strong base, such as t-BuLi, followed by electrophilic fluorination of the resulting carbanions with 2.5 equiv NFSI (Scheme 63).[141] The α,α-difluoro cyano compounds could be readily converted into α,α-difluorotetrazoles by reaction with

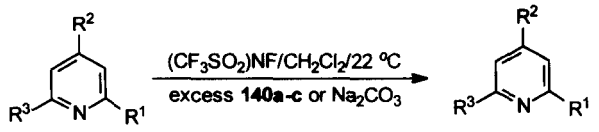
NaN_3 in DMF. The α-monofluoro products were also synthesized in ~60% yield using 1.1 equiv base and 1.3 equiv NFSI.



Scheme 63

10.3 Fluorination of methyl-substituted pyridines

DesMarteau and coworkers have reported the direct fluorination of methylsubstituted pyridines **140a-c** using N-fluorobis[(trifluoromethyl)sulfonyl]imide to give fluoromethyl products **141a-c** (Scheme 64) in low



140a, $R^1 = R^2 = R^3 = CH_3$
140b, $R^1 = CH_3$, $R^2 = R^3 = H$
140c, $R^1 = R^3 = H$, $R^2 = CH_3$

141a, $R^1 = CH_2F$, $R^2 = R^3 = CH_3$ (52%)
141b, $R^1 = CH_2F$, $R^2 = R^3 = H$ (20%)
141c, $R^1 = R^3 = H$, $R^2 = CH_2F$ (72%)

Scheme 64

to good yield.[83] In some instances small amounts of fluoropyridines were formed. The pyridinium salts did not undergo the reaction nor did 3,5-lutidine suggesting that the reaction proceeds via the enamine tautomers.

10.4 Reactions of N-F class reagents with solvents

Zupan and coworkers have studied the reaction of F-TEDA-BF_4, NFTh and to a lesser extent, NFSI with solvents such as water, MeCN, alcohols and aqueous NaOH solutions.[162] After 24 h at room temperature in water, MeCN and alcohols, the largest decrease in activity with F-TEDA occurred in MeOH (7%). NFTh was more stable than F-TEDA-BF_4. NFSI was studied in CH_3CN only and found to be very stable even at 54 °C. The addition of MeCN to an aqueous solution of F-TEDA-BF_4 enhanced activity loss. The decomposition of F-TEDA-BF_4 in aq. hydroxide solutions was found to increase as the mole ratio of base to F-TEDA-BF_4 increased. When the base was in excess (mole ratio 2:1) the decomposition was usually complete after just 30 minutes.

11. Conclusions

This review has highlighted some of the recent advances in electrophilic fluorination from the middle of 1995 to the middle of 1999. It appears that the traditional electrophilic fluorinating agents such as perchlorylfluoride, xenon difluoride, elemental fluorine and fluoroxy compounds are being supplanted by N-F reagents, such as F-TEDA-BF_4 and NFSI, that are either safer and easier to handle or less expensive to produce. Since several N-F reagents are now commercially available from a number of sources, we predict rapid progress will be made in the synthesis of organofluorine compounds over the next few years.

Nevertheless, we expect that the search for yet more effective electrophilic fluorinating agents, not only of the N-F type but other classes of fluorinating reagents as well, will remain an important area in fluorine chemistry.

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