Site-Selective Fluorination of Organic Compounds Using 1-Alkyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane Salts (Selectfluor Reagents)

G. Sankar Lal

Corporate Science and Technology Center, Air Products and Chemicals, Inc., Allentown, Pennsylvania 18195-1501

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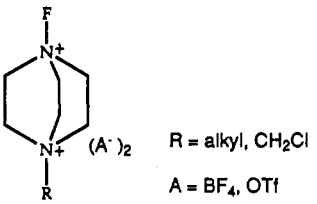
The new "N-F"-type electrophilic reagent family of 1-alkyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane salts[8d] (derived from elemental fluorine (F_2) and 1-alkyl-1,4-diazabicyclo[2.2.2]octane salts) has been found to be very effective for the fluorination of a wide variety of organic substrates. These include steroidal enol acetates and silyl enol ethers, phenyl-substituted olefins, sulfides bearing α-H atoms, certain carbanions, and mildly activated aromatic compounds. The products were obtained with good yields and regioselectivity under very mild reaction conditions.

Introduction

Since the discovery by Fried[1] of the increased therapeutic effect conferred by fluorine in 9α-fluorohydrocortisone acetate, a growing interest has emerged in the medicinal chemistry of organofluorine compounds. During the past 40 years, several useful advances in organofluorine chemistry have been translated into products of medicinal importance.[2] The reason for this enhanced therapeutic activity has been rationalized mainly on the basis of the physicochemical properties of the fluorine atom in these compounds.[3]

Electrophilic fluorination represents one of the most direct methods available for a selective introduction of fluorine into organic compounds.[4] One of the earliest reagents employed for this purpose is perchloryl fluoride.[5] Its application has declined dramatically in recent years owing to difficulties in handling and danger associated with its use. There are also fluorinating reagents incorporating the O-F bond including CF_3OF, CF_3COOF, and $CsSO_4F$.[6] Although these are potent sources of electrophilic fluorine, the high reactivity of the compounds has contributed to low selectivity and the requirement for low-temperature conditions in many instances. Xenon difluoride[7] has also proven very effective for the fluorination of nucleophilic substrates, but its commercial use has been limited owing to its high cost of production. During the last 6 years, a new generation of electrophilic fluorinating reagents has emerged: molecules which incorporate a reactive N-F bond.[8a-d] These reagents, which are generally less reactive than those previously described, have proven to be relatively stable and selective for the fluorination of carbanionic organic substrates.

The latest addition to this "N-F" class of electrophilic fluorinating reagents are the *N*-fluoro derivatives of 1,4-diazabicyclo[2.2.2]octane, also known as triethylenediamine, TEDA (a DABCO catalyst).



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These compounds (Selectfluor reagents), which were synthesized by Banks et al.[8d] and developed at Air Products and Chemicals, Inc., are white, free-flowing, virtually nonhygroscopic, high-melting solids (R = CH_2Cl, A = BF_4, mp = 170 °C). A comparison of reactivity as quantified by electrochemical studies indicates that these are relatively more reactive than most of the available "N-F" reagents.[9] The compounds have proven to be highly effective for the fluorination of a wide variety of organic substrates.[10] This paper gives details of methods which have been developed for the application of these Selectfluor reagents in the synthesis of organofluorine compounds.

Results and Discussions

The 1-alkyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane salts constitute a family of electrophilic fluorinating reagents. The alkyl substituent (R) can be modified to change the chemical reactivity. It has been found that there is a slightly greater ease of "F^+" transfer as the electronegativity of the quaternary group increases.[10] However, no significant reactivity differences have been observed by variation of the counteranion (A^-). The compounds are soluble in fairly polar solvents, e.g., CH_3CN or DMF, because of their ionic character. In this paper, the fluorination chemistry of 1-(chloromethyl)-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF_4), a representative member of this reagent family, with various substrates will be discussed.

Fluorination of Steroidal Enol Acetates and Silyl Enol Ethers. The silyl enol ether, alkyl enol ether, and

(1) Fried, J.; Subo, E. F. *J. Am. Chem. Soc.* **1954**, 1455.
(2) Filler, R. *Chem. Tech.* **1974**, *4*, 752.
(3) (a) Filler, R., Kobayashi, Y., Eds.; *Biomedical Aspects of Fluorine Chemistry*; Elsevier Biomedicinal Press: New York, **1982**. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 14, 3123.
(4) German, L., Zemskov, S., Eds.; *New Fluorinating Agents in Organic Synthesis*; Springer-Verlag: Berlin, Heidelberg, 1989.
(5) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 225.
(6) Mukametshin, F. M. Reference 4, pp 69-116.
(7) Bardin, V. V.; Yagupolskii, Y. L. Reference 4, pp 1-34.
(8) (a) Murtagh, V. *Perform. Chem.* **1991**, *6*, 4, 36. For an extensive, up-to-date list of primary references, see also: (b) Banks, R. E.; Murtagh, V.; Tsiliopoulous, E. *J. Fluorine Chem.* **1991**, *52*, 389. (c) Resnati, G.; DesMarteau, D. D. *J. Org. Chem.* **1991**, *56*, 4925. (d) Banks, R. E. U.S. Patent, 5,086,178, 1992.
(9) Gilicinski, A. G.; Pez, G. P.; Syvret, R. G.; Lal, G. S. *J. Fluorine Chem.* **1992**, *59*, 157.
(10) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595.

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Table I. 6-Position Fluorination of Steroids

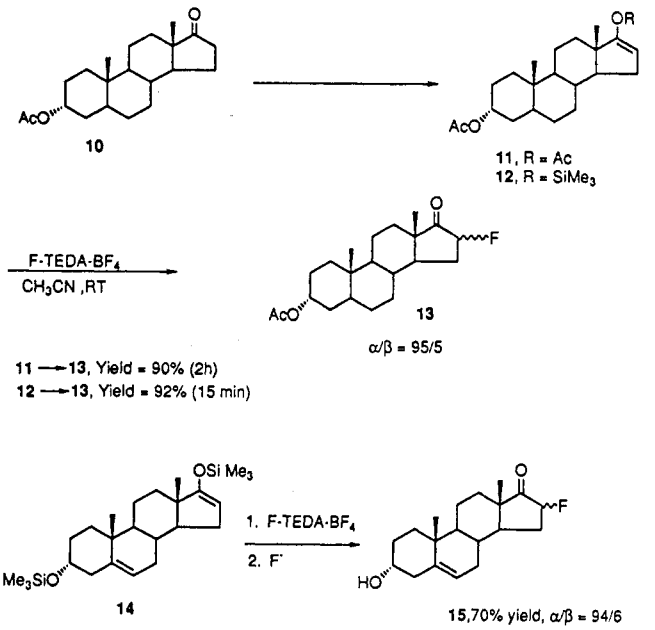
starting material	reaction condns	product (% yield), α/β
3,11β,17α,21-tetraacetoxy-1,3,5-pregnatriene-3,20-dione (prednisolone dienol acetate) (2)	F-TEDA-BF_4, CH_3CN rt, 15 min	6-fluoro-11β,17α,21-triacetoxy-1,4-pregnadiene-3,20-dione (6-fluoroprednisolone triacetate) (3) (88) 57/43
3,17β-diacetoxy-3,5-androstadiene-3-one (testosterone dienol acetate) (4)	F-TEDA-BF_4, CH_3CN rt, 15 min	17β-acetoxy-6-fluoroandrost-4-en-3-one (6-fluorotestosterone acetate) (5) (95) 42/58
3,11β,17α,21-tetraacetoxy-3,5-pregnadiene-3,20-dione (hydrocortisone dienol acetate) (6)	F-TEDA-BF_4, CH_3CN rt, 15 min	6-fluoro-11β,17α,21-triacetoxy-1,4-pregnene-3,20-dione (6-fluorohydrocortisone triacetate) (7) (88) 47/53
3,17α-diacetoxy-3,5-pregnadiene-3,20-dione (progesterone dienol acetate) (8)	F-TEDA-BF_4, CH_3CN rt, 15 min	17α-acetoxy-6-fluoro-4-pregnene-3,20-dione (6-fluoroprogesterone acetate) (9) (90) 30/70

enamine of Δ^4- or $\Delta^{1,4}$-3-keto steroids produce a mixture of 4-fluoro and 6-fluoro products as observed for similar reactions with other electrophilic fluorinating reagents.[11] However, the dienol acetate intermediate proved to be very useful for effecting the 6-position fluorination. As shown in Table I, the reaction is highly regioselective and tolerates a wide variety of functionalities. It is also extremely facile requiring short reaction times and ambient temperature conditions. While the yield for the fluorination step was virtually quantitative, there was some loss in yield on fluorination of dienol acetate derived from $\Delta^{1,4}$-3-ketosteroids (prednisolone) due to the acid-catalyzed dienone–phenol[12] rearrangement during acetylation with isopropenyl acetate/*p*-TsOH. Higher overall yields were obtained on fluorination of Δ^4-3-ketosteroid-derived dienol acetates (compounds 4, 6, 8) where the acetylated product from the Ac_2O/*p*-TsOH reaction was obtained in virtually quantitative yield. In this application, the F-TEDA–BF_4 reagent appears to offer significant advantages in terms of both yields and reaction rates as compared to other known N–F compounds.[8a-d] For example, the fluorination of testosterone dienol acetate with *N*-fluoropyridinium salts produced the 6-fluoro compound in yields ranging from 55% to 72% in refluxing CH_2Cl_2 over 16–46 h.[11] This fluorination was accomplished in 2 days at 40 °C with N-fluoropyridinium pyridine heptafluorodiborate.[13] Similar syntheses of 6-fluorotestosterone have been reported using $FClO_3$[5] and CH_3COOF[6] but the explosive nature of the former and the difficulty in handling of the latter have made these reagents less suitable for commercial-scale synthesis of 6-fluoro steroids.

The 16-position fluorination of steroids was also very efficiently carried out (see Scheme I). High yields of products with excellent stereoselectivity (α/β = 95/5) were obtained on fluorination of either an enol acetate or a silyl enol ether intermediate. The reaction was slower than for 6-position fluorination but could be carried out at room temperature in acetonitrile.

Nakanishi and Jensen reported the reaction of 3β-acetoxy-17-acetamino-5,16-androstadiene with $FClO_3$ to produce 3β-acetoxy-16α-fluoro-5-androsten-17-one.[14] A similar conversion was effected with *N*-fluoropyridinium pyridine heptafluorodiborate.[13] In the synthesis of 3β-acetoxy-16α-fluoro-5-androsten-17-one using F-TEDA-BF_4, it was found that the 17-keto-derived silyl enol ether can substitute the enamide with very good results. In addition, the fluorination of a 17-keto-derived enol acetate with F-TEDA-BF_4 gave an excellent yield of the corresponding 16-fluoro product for steroids lacking unsaturation in other parts of the molecule.

Scheme I. 16-Position Fluorination of Steroids

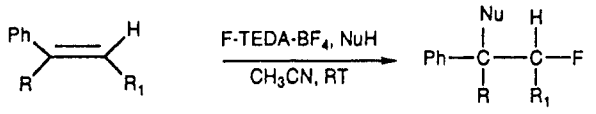


Fluorination of Olefins. The electrophilic fluorination of olefins in the presence of weak nucleophiles has been studied with some of the more reactive fluorinating reagents, e.g., XeF_2,[15] $CsSO_4F$,[16] CF_3COOF,[4] 1-fluoro-2,3,4,5,6-pentachloropyridinium triflate,[11] and *N*-fluorobis[(perfluoromethyl)sulfonyl]imide.[17] However, most of these fluorinations cannot be carried out in the presence of water owing to the ease of hydrolysis of these compounds. Des Marteau et al.[17] reported that the fluorination of phenyl-substituted olefins in CH_2Cl_2/H_2O gave only low yields of the corresponding fluorohydrin together with unidentified fluorinated products.

In the presence of weak nucleophiles, H_2O, AcOH, HF·pyridine, or MeOH in CH_3CN, F-TEDA-BF_4 reacts with styrene derivatives to introduce a fluorine atom and the nucleophile component on adjacent carbon atoms (Table II). The reaction proceeds at room temperature in high yields. While the reaction with α-methylstyrene in H_2O or MeOH gave only addition products, reactions carried out in more acidic media, HF·pyridine or AcOH produced the elimination product[11] $CH_2 = C(Ph)CH_2F$ as well as the addition product. The fluorination of *trans*-stilbene proceeded more slowly than for α-methylstyrene giving only the addition product. The fluorination of the parent styrene molecule, however, was found to be relatively difficult. No addition product was obtained when MeOH, AcOH, or HF·pyridine were the counter-nucleophiles, but the fluorination in the presence of water proceeded slowly to produce the required fluorohydrin.

(11) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
(12) Bailey, E. J.; Elks, J.; Oughton, J. F.; Stephenson, L. *J. Am. Chem. Soc.* **1961**, *83*, 4535.
(13) Poss, A. J.; Van der Puy, M.; Nalewajek, D.; Shia, G. A.; Wagner, W. J.; Frenette, R. L. *J. Org. Chem.* **1991**, *56*, 5962.
(14) Nakanishi, S.; Jensen, E. V. *J. Org. Chem.* **1962**, *27*, 702.
(15) Zupan, M.; Pollak, A. *J. Org. Chem.* **1977**, *42*, 9, 1559.
(16) Staver, S.; Zupan, M. *Tetrahedron* **1986**, *42*, 18, 5035.
(17) DesMarteau, D. D.; Zu, Z. Q.; Witz, M. *J. Org. Chem.* **1992**, *57*, 629.

Table II. Fluorination of Styrene and Substituted Styrene in the Presence of Weak Nucleophiles



starting material	product no.	R	R_1	Nu	% yield (erythro/threo)
styrene (16a)	17a	H	H	OH	48
α-methylstyrene (16b)	17b	CH_3	H	OMe	98
	17c	CH_3	H	OH	89
	17d	CH_3	H	OAc	65
	17e	CH_3	H	F	66
trans-stilbene (16c)	17f	H	Ph	OMe	75 (72/28)
	17g	H	Ph	OH	86 (69/31)
	17h	H	Ph	OAc	77 (60/40)
	17i	H	Ph	F	65 (66/34)

The mechanism proposed for the fluorination of olefins by electrophilic fluorinating reagents involves the formation of a carbocationic intermediate.[17] The results obtained from our studies also provide evidence for the involvement of such an intermediate. The lack of diastereoselectivity observed in the fluorination of *trans*-stilbene is one piece of evidence is support of this mechanism. In addition, it has been observed that olefins which cannot produce a highly stabilized carbonium ion on addition of F^+, e.g., 1-octene or cyclohexene, did not react.

The stereochemistry of the products from the reactions of *trans*-stilbene was determined from NMR spectra[18] (^1H and ^{19}F). The $J_{H,H}$ coupling constants were used to assign the erythro and threo isomers. When a pair of very electronegative atoms, e.g., F,F or F,O, are vicinal to each other, the gauche conformation is preferred and $J_{H,H}$(threo) > $J_{H,H}$(erythro).

Fluorination of Carbanions. The fluorination of the Grignard reagents, dodecylmagnesium bromide, and phenylmagnesium bromide was carried out by addition of an ether solution of the reagent to a suspension of the F-TEDA-BF_4 in dry diethyl ether at room temperature. The reaction proceeded slowly owing to the poor solubility of the fluorination reagent in diethyl ether. However, good yields of products were obtained after 16 h at room temperature (Table III). In contrast, the fluorination of highly stabilized carbanions, e.g., sodium salts of substituted malonates,[11] β-diketone,[11] and phosphonate,[19] occurred rapidly and in high yields. In these reactions the monofluorinated compound was the exclusive or predominant product obtained. The results obtained from these studies are similar to those reported for other electrophilic fluorinating reagents.[4]

The fluorination of the highly reactive ketone enolates in THF or Et_2O was less successful. Only low yields (<20%) of the α-fluoro ketone were obtained together with a large amount of starting material using compound 1 (R = CH_2Cl or CH_3). This apparent disadvantage of the reagent can, however, be overcome using silyl enol ether or enol acetate derivatives of ketones by which the same products can be obtained in high yields (Table I, Scheme I). The low-yielding reaction with reactive ketone enolates is possibly due to a Hofmann degradation of the reagent

Table III. Fluorination of Carbanions

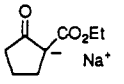
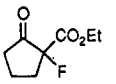
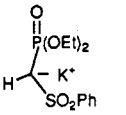
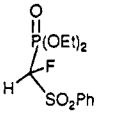
substrate	reaction condns	product (% yield)
PhMgBr **18**	Et_2O,RT 16 h,	PhF **19**, (61)
$CH_3(CH_2)_{11}MgBr$ **20**	Et_2O,RT 16 h,	$C_{12}H_{25}F$ **21**, (58)
Ph(CO2Et)2 Na+ **22**	THF/DMF 30 min, RT	Ph(F)(CO2Et)2 **23**, (94)
CH3(CO2Et)2 Na+ **24**	THF/DMF 30 min, RT	CH3(F)(CO2Et)2 **25**, (92)
 **26**	THF/DMF 30 min, RT	 **27**, (95)
 **28**	t-BuOH/DMF 10 min, RT	 **29**, (61)

Table IV. Fluorination of Aromatic Compounds

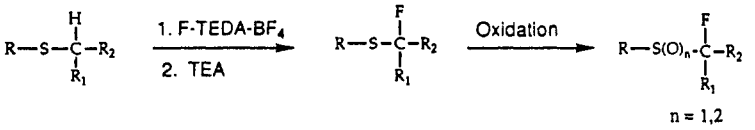
substrate	reaction condns	product (yield %)
toluene (30)	F-TEDA-BF_4, CH_3CN, reflux, 16 h	**31a**, *o*-fluorotoluene (60) **31b**, *p*-fluorotoluene (20)
o-xylene (32)	F-TEDA-BF_4, CH_3CN, reflux, 16 h	**33a**, 1,2-dimethyl-3-fluorobenzene (49) **33b**, 1,2-dimethyl-4-fluorobenzene (29) **33c**, 3,6-difluoro-1,2-dimethylbenzene (17)
m-xylene (34)	F-TEDA-BF_4, CH_3CN, reflux, 16 h	**35a**, 1,3-dimethyl-4-fluorobenzene (42) **35b**, 1,3-dimethyl-2-fluorobenzene (23) **35**, 1,3-difluoro-4,6-dimethylbenzene (23)
p-xylene (36)	F-TEDA-BF_4, CH_3CN, reflux, 16 h	**37a**, 1,4-dimethyl-2-fluorobenzene (65) **37b**, 2,5-difluoro-1,4-dimethylbenzene (32)

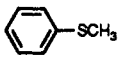
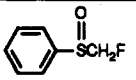
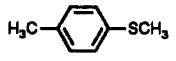
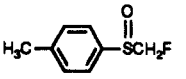
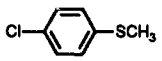
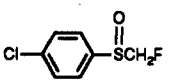
(a quaternary ammonium compound) induced by the highly acidic protons on the carbon atoms adjacent to the N–F bond.

Fluorination of Aromatic Compounds. In a preliminary communication,[10] we reported the fluorination of some highly activated aromatic compounds by F-TEDA-BF_4. The fluorination of anisole and acetanilide was found to proceed quite readily in refluxing CH_3CN to produce an ortho,para mixture of products in high yields. Table IV illustrates the results on fluorination of the less activated alkyl-substituted aromatic compounds. The fluorination of toluene was effected quite efficiently in refluxing CH_3CN to obtain a mixture of ortho,para-isomers in high yield. Under similar conditions, the fluorination of *o*-, *m*-, or *p*-xylene proceeded quite readily. However, complete conversion of starting material was only observed when 2.0 equiv of reagent were used. Regardless of the amount of fluorination reagent used, the xylenes gave substantial quantities of difluorinated products in addition to the monofluorinated isomers. The results obtained from these studies are similar to those observed for the reaction of toluene and xylene with XeF_2[20] and *N*-fluorobis-

(18) Rozen, S.; Lerman, O. *J. Org. Chem.* **1980**, *45*, 672.
(19) Koizumi, T.; Hagi, T.; Horie, Y.; Takeuchi, Y. *Chem. Pharm. Bull.* **1987**, *35*, 3959.
(20) Shaw, M. J.; Hyman, H. H.; Filler, R. *J. Am. Chem. Soc.* **1970**, *92*, 6498.

Table V. Synthesis of 2-Fluoro Sulfide, Sulfoxide, or Sulfone



sulfide	fluorination condns	oxidation condns	product (yield, %)
 **38**	1. F-TEDA-BF_4, rt, CH_3CN 2. TEA	NBS, MeOH, H_2O, CH_2Cl_2, rt, 30 min	 **39** (48)
 **40**	1. F-TEDA-BF_4, rt, CH_3CN 2. TEA	NBS, MeOH, H_2O, CH_2Cl_2, rt, 30 min	 **41** (61)
 **42**	1. F-TEDA-BF_4, rt, CH_3CN 2. TEA	NBS, MeOH, H_2O, CH_2Cl_2, rt, 30 min	 **43** (51)
$CH_3SC_9H_{19}$ **44**	1. F-TEDA-BF_4,rt, CH_3CN 2. TEA	*m*-CPBA, CH_2Cl_2, rt, 6 h	$CH_2FSO_2C_9H_{19}$ **45** (35)
$CH_3SCH_2CO_2Et$ **47**	1. F-TEDA-BF_4, rt, CH_3CN 2. TEA	*m*-CPBA, CH_2Cl_2, rt, 6 h	$CH_3SO_2CHFCO_2Et$ **48** (58)

[(perfluoromethyl)sulfonyl]imide[21] where ring-fluorinated products were obtained and in contrast to the reaction with $CsSO_4F$ where side-chain fluorination was significant.[22]

α-Fluorination of Sulfides. In recent years, the α-fluoro sulfides have emerged as an important class of fluorinated compounds. They have proven to be very valuable in modifying the biological activity of β-lactam antibiotics[23a] and amino acids.[23b] In addition, they serve as useful synthetic intermediates for other medicinally active compounds.[23c]

Zupan reported the synthesis of fluoromethyl phenyl sulfide by the reaction of XeF_2 with thioanisole.[24] A similar conversion to α-fluoro sulfides from sulfides bearing α-hydrogen atoms was demonstrated by Umemoto and Tomizawa using *N*-fluoropyridinium salts.[25]

It has been found that sulfides possessing α-hydrogens react rapidly with F-TEDA-BF_4 in CH_3CN at room temperature forming the fluorosulfonium salt which conceivably undergoes a Pummerer-like rearrangement on treatment with base (triethylamine or DBU) to produce the α-fluoro sulfide[25] (Table V).

$$RSCH_2R^1 \xrightarrow[CH_3CN]{\text{F-TEDA-BF}_4} RS^+(F)CH_2R^1 \xrightarrow{\text{base}} RSCHFR^1$$

This process was applied to a variety of aryl and alkyl sulfides to obtain the fluorinated products in moderate yields. The fluorination of the aromatic sulfides proceeded readily, forming monofluorinated products with the ease of reaction being highly dependent on the nucleophilicity of the sulfur atoms. Ethyl (methylthio)acetate gave the product resulting from deprotonation of the more acidic methylene proton while the unsymmetrical sulfide, methyl *n*-nonyl sulfide afforded the fluorination product expected from a kinetic deprotonation of the methyl hydrogen. Since most of the α-fluoro sulfides are unstable to standard chromatographic purification techniques, they were isolated only after conversion to the corresponding sulfoxide (with NBS, H_2O) or sulfone (with *m*-chloroperbenzoic acid).

Experimental Section

The steroids were obtained from Sigma Chemical and used as received. The malonates, β-diketone, aromatic, olefinic, and sulfide substrates were purchased from Aldrich Chemical Co. The phenylsulfonyl-substituted phosphonate was prepared by a standard literature procedure.[26] The reagents isopropenyl acetate, acetic anhydride, *p*-toluenesulfonic acid, acetic acid, methanol, HF·pyridine, and triethylamine were obtained from Aldrich Chemical Co. and used without further purification. The solvents CH_3CN and DMF were dried with calcium hydride prior to use. Diethyl ether and THF were dried with sodium/benzophenone ketyl prior to use. Other solvents, hexane and ethyl acetate, were used without further purification.

NMR spectra were obtained on a Brucker ACP-300FT spectrometer operating at 282.4 MHz (^{19}F), 300.13 MHz (^1H). Chemical shifts were referenced to neat $CFCl_3$(^{19}F) or neat TMS (^1H). Mass spectra were obtained on a VG 2AB-EQ instrument with FAB ionization (perfluorokerosene as reference). GC/MS were recorded on a HP 5890 GC (30-m × 0.25-mm SPB-5 column) and a VG Quattro MS with EI ionization.

Fluorination of $\Delta^{1,4}$- and Δ^4-3-Ketosteroids. A solution of the steroid (1.39 mmol) in isopropenyl acetate (2.5 mL) under N_2, contained in a 25-mL three-neck flask, was treated with *p*-TsOH (50 mg, 0.26 mmol) and heated at 80 °C. The progress of the reaction was monitored by the disappearance of the starting

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material and/or formation of product by TLC (1:1 ethyl acetate/hexane). After 3–16 h, the reaction was complete. The solution was cooled to room temperature and quenched with 100 μL of triethylamine. The solvent was removed under vacuum (0.1 mmHg). The residue was dissolved into CH_3CN (15 mL), and F-TEDA-BF_4 (1.39 mmol, 492 mg) was added and stirred at room temperture. After 15 min, the solution was poured into ethyl acetate (50 mL), washed three times with 25-mL portions of H_2O, dried ($MgSO_4$) filtered, and evaporated in vacuo. The product was purified by flash chromatography on silica gel to obtain the pure product.

Alternatively, Δ^4-3-ketosteroids (1.39 mmol) were acetylated with acetic anhydride (6.0 mL) containing 50 mg (0.26 mmol) of *p*-TsOH. The reaction was monitored by TLC for completion (3–16 h). The mixture was quenched with 100 μL of triethylamine, and the solvent was removed by distillation in vacuo (0.1 mmHg). The residue was treated as above to obtain the following pure products. **6-Fluoro-11β,17α,21-triacetoxy-1,4-pregnadiene-3,20-dione**[27] **(3)**: 88%, α/β = 57/43. **17β-Acetoxy-6-fluoroandrost-4-en-3-one**[11] **(5)**: 95%, α/β = 42/58. **6-Fluoro-11β,17α,21-triacetoxy-4-pregnene-3,20-dione**[28] **(7)**: 88%, α/β = 47/53. **17α-Acetoxy-6-fluoro-4-pregnene-3,20-dione**[29] **(9)**: 90%, α/β = 30/70.

Fluorination of 17-Ketosteroids. (a) Via Enol Acetate. A solution of 3β-acetoxyandrosterone (0.5 g, 1.52 mmol) in isopropenyl (5.0 mL) was heated at 80 °C for 24 h under N_2. The reaction was cooled and quenched by addition of 200 μL of triethylamine. The solvent was removed by distillation in vacuo (0.1 mmHg), and the residue was dissolved into CH_3CN (25.0 mL). The F-TEDA-BF_4 (537 mg, 1.52 mmol) was added, and the reaction was monitored by TLC (1:4 ethyl acetate/hexane). After 2 h, the solution was poured into EtOAc (25 mL), washed with water (3 × 25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Flash chromatography of the residue on silica gel (1:4 ethyl acetate/hexane) afforded 474 mg (90%) of **3β-acetoxy-16-fluoroandrosterone**[10] **(13)** ($\alpha/\beta \approx 94/6$), which had spectroscopic properties consistent with those reported in the literature.

(b) Via Silyl Enol Ether. A solution of 3β-hydroxy-5-androsten-17-one (1.0 g, 3.47 mmol) in toluene (6.0 mL) under N_2 was treated with triethylamine (8.39 mmol, 11.69 mL) and TMS triflate (1.60 g, 1.39 mL) and refluxed for 1.5 h. The solution was cooled to room temperature, diluted with 100 mL of hexane, washed with saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was suspended into DMF (50 mL) and treated with F-TEDA-BF_4 (1.23 g, 3.47 mmol) at room temperature under N_2. After 15 min, the solution was reacted with 3.47 mL (3.47 mmol) of 1.0 M $(Bu)_4N^+F^-$ in THF for 5 min and then poured slowly into 100 mL of H_2O with stirring. The resulting precipitate was stirred for 2 h, filtered, and washed with water (25 mL) to obtain the product. Flash chromatography on silica gel (1:9 ethyl acetate/hexane) afforded 765 mg (72%) of **16-fluoro-3β-hydroxy-5-androsten-17-one**[11] **(15)** ($\alpha/\beta \approx 95/5$), with spectroscopic characteristics identical to that reported.

Fluorination of Olefins. A solution of the olefin (1 mmol) in 10 mL of CH_3CN containing 1.0 mL of the nucleophilic compound (H_2O, MeOH, AcOH, HF·pyridine) under N_2 was treated with the F-TEDA-BF_4 reagent (354 mg). The solution was stirred at room temperature and monitored by gas chromatography for completion. The solution was then poured into Et_2O (50 mL), washed with H_2O (2 × 25 mL) and saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash chromatography on silica gel afforded the following pure products. **2-Fluoro-1-Hydroxy-1-phenylethane**[17] **(17a)**: 48%. **1-Fluoro-2-methoxy-2-phenylpropane (17b)**: 98%; ^1H NMR ($CDCl_3$) δ 7.35–7.15 (m, 5 H), 4.25 (dt, 2 H), 3.10 (s, 3 H), 1.58 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ −222 (t); ^{13}C NMR ($CDCl_3$) δ 140.30 (d, J = 3.5 Hz), 128.33 (2 C) 127.72, 126.53 (2 C), 88.94 (d, J = 181.7 Hz, C-1), 78.28 (d, J = 17.7 Hz, C-2), 50.67, 19.00 (d, J = 4.0 Hz); high-resolution mass spectrum molecular ion calcd for $C_{10}H_{13}FO$, M^+ = 168.0950, found M^+ = 168.0950. **1-Fluoro-2-hydroxy-2-phenylpropane (17c)**: 89%; ^1H NMR ($CDCl_3$) δ 7.40–7.15 (m, 5 H), 4.35 (dq, 2 H), 2.70–2.50 (s, br, 1 H), 1.50 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ −222 (t); ^{13}C NMR ($CDCl_3$) δ 142.98, 128.31 (2 C), 127.47, 125.10 (2 C), 89.43 (d, J = 177.3 Hz, C-1), 73.71 (d, J = 18.3 Hz, C-2), 25.12; high-resolution mass spectrum molecular ion calcd for $C_9H_{11}FO$, M^+ = 154.1848, found M^+ = 154.0794. **2-Acetoxy-1-fluoro-2-phenylpropane (17d)**: 65%; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 5 H), 4.45 (dq, 2 H), 2.05 (s, 3 H), 1.85 (s, 3 H); ^{19}F NMR ($CDCl_3$) δ −222 (t); ^{13}C NMR ($CDCl_3$) δ 169.30, 140.01 (d, J = 2.7 Hz), 128.40 (2 C), 127.79, 124.85 (2 C), 87.70 (d, J = 183.2 Hz, C-1), 81.71 (d, J = 17.8 Hz, C-1), 21.86, 20.61 (d, J = 3.6 Hz); high-resolution mass spectrum calcd for $C_{11}H_{13}FO_2$ M^+ = 196.0900, found, M^+ = 196.0904. **1,2-Difluoro-2-phenylpropane**[30] **(17e)**: 66%. **1,2-Diphenyl-2-fluoro-1-methoxyethane**[31] **(17f)**: 75%; erythro/threo = 72/28. **1,2-Diphenyl-2-fluoro-1-hydroxyethane**[18] **(17g)**: 86%; erythro/threo = 69/31. **1-Acetoxy-1,2-diphenyl-2-fluoroethane**[32] **(17h)**: 77% erythro/threo = 60/40. **1,2-Difluoro-1,2-diphenylethane**[15] **(17i)**: 65%; erythro/threo = 66/34.

Fluorination of Carbanions. (a) Grignard Reagents. A solution of the Grignard reagent in diethyl ether was added under N_2 to a suspension of F-TEDA-BF_4 in diethyl ether (5.0 mL). The mixture was stirred at room temperature and monitored by GC for completion. After 24 h, the product was poured into Et_2O (10 mL), washed with water (3 × 25 mL), dried ($MgSO_4$), and filtered. ^{19}F NMR of the product containing α,α,α-trifluorotoluene was done to determine the yield. **Fluorobenzene**[11] **(19)**: 61%. **Dodecyl fluoride**[11] **(21)**: 58%.

(b) Stabilized Carbanions. A THF solution (50 mL) of the compound (1 mmol) was added to an oil-free suspension of NaH (40 mg of 60%, 24 mg, 1 mmol) in THF (5.0 mL) under N_2 at 0 °C. The solution was stirred at 0 °C for 30 min and then at room temperature for 1 h. The sodium salt was diluted with DMF (2.0 mL), and the F-TEDA-BF_4 (354 mg) was added.

After being stirred for 30 min at room temperature, the mixture was poured into Et_2O, washed with 5% H_2SO_4 (10 mL) and saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by flash chromatography on silica gel afforded the pure products. **Diethyl 2-Fluoro-2-phenylmalonate**[11] **(23)**: 94%. **Diethyl 2-Fluoro-2-methylmalonate**[11] **(25)**: 92%. **2-Carbethoxy-2-fluorocyclopentane**[11] **(27)**: 95%. **[Fluoro(phenylsulfonyl)methyl]phosphonic Acid Diethyl Ester**[26] **(29)**: 61%.

Fluorination of Aromatic Compounds. A solution of F-TEDA-BF_4 (708 mg, 2.0 mmol) in acetonitrile (20 mL) was treated under N_2 with 2.0 mmol of the aromatic compound. The resulting solution was refluxed and monitored by GC for formation for product. On completion, the solution was poured into Et_2O (50 mL), washed with water (2 × 25 mL) and saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and evaporated. Yield was determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. ***o*-Fluorotoluene**[21] **(31a)**: 60%. ***p*-Fluorotoluene**[21] **(31b)**: 20%. **1,2-Dimethyl-3-fluorobenzene**[22] **(33a)**: 49%. **1,2-Dimethyl-4-fluorobenzene**[22] **(33b)**: 29%. **3,6-Difluoro-1,2-dimethylbenzene**[33] **(33c)**: 17%. **1,3-Dimethyl-4-fluorobenzene**[22] **(35a)**: 42%. **1,3-Dimethyl-2-fluorobenzene**[22] **(35b)**: 23%. **1,3-Difluoro-4,6-dimethylbenzene**[34] **(35c)**: 23%. **1,4-Dimethyl-2-fluorobenzene**[22] **(37a)**: 65%. **2,5-Difluoro-1,4-dimethylbenzene**[33] **(37b)**: 32%.

α-Fluorination of Sulfides. A solution of F-TEDA-BF_4 (885 mg, 2.50 mmol) in CH_3CN (10 mL) under N_2 was treated dropwise with a solution of the sulfide (2.0 mmol) in CH_3CN (1.0 mL) and stirred at room temperature for 10 min. Triethylamine (347 μL, 2.50 mmol) was added and the mixture stirred for a further 10 min. The solution was poured into H_2O, extracted with CH_2Cl_2 (15 mL), dried (Na_2CO_3), and filtered. The resulting α-fluoro sulfide solution was subjected to oxidation. For sulfoxide formation, the solution was cooled to 0 °C, and MeOH (3.0 mL),

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and H_2O (300 μL) were added followed by NBS (712 mg, 4 mmol). After 30 min at 0 °C, the solution was washed with 10% aqueous sodium thiosulfate (25 mL), 5% H_2SO_4 (25 mL), and saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was purified by flash chromatography on silica gel (2:1 hexane/ethyl acetate). For sulfone formation, the CH_2Cl_2 solution of α-fluoro sulfide was cooled to 0 °C and treated with *m*-CPBA (1.70 g of 50%, 5 mmol) and stirred for 30 min. The solution was then stirred with 50 mL of saturated aqueous sodium sulfite solution for 2 h at room temperature. The CH_2Cl_2 layer was washed with saturted $NaHCO_3$ (50 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. Flash chromatography on silica gel afforded the pure products. **Fluoromethyl Phenyl Sulfoxide**[25] **(39)**: 48%. **Fluoromethyl *p*-Tolyl Sulfoxide**[25] **(41)**: 61%. ***p*-Chlorophenyl Fluoromethyl Sulfoxide**[25] **(43)**: 51%. **Fluoromethyl *n*-Nonyl Sulfone (45)**: 35%; ^1H NMR ($CDCl_3$) δ 5.15 (d, 2 H, J = 48 Hz), 3.05 (t, 2 H, J = 9 Hz), 1.75–1.95 (m, 2 H, 1.40–1.20 (m, 12 H), 0.95–0.85 (t, 3 H, J = 7 Hz); ^{19}F NMR ($CDCl_3$) δ −213 (t); ^{13}C NMR ($CDCl_3$) δ 89.94 (d, J = 218 Hz), 50.63, 31.72, 29.11, 29.08, 28.91, 28.36, 22.58, 21.37, 14.03; high-resolution mass spectrum calcd for $C_{10}H_{21}FO_2S$, $(M + H)^+$ = 225.1324, found $(M + H)^+$ = 225.1331. **Ethyl 2-Fluoro-2(methanesulfonyl)acetate**[25] **(47)**: 58%.

Conclusion

The F-TEDA-BF_4 electrophilic fluorinating reagent has proven to be very useful in the fluorination of diverse organic substrates. These include steroidal enol acetates and silyl enol ethers, phenyl-substituted olefins, sulfides bearing α-H atoms, carbanions, and certain aromatic compounds. The reactions were generally carried out under mild conditions, and the products were obtained in good to excellent yields. The chemistry of F-TEDA-BF_4 is at present being further explored in areas of medicinal and agrochemical interest.

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