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Recent Highlights in Electrophilic Fluorination with 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane Bis(tetrafluoroborate)

RAJENDRA P. SINGH AND
JEAN'NE M. SHREEVE*
Department of Chemistry, University of Idaho, Moscow, Idaho 83844-2343

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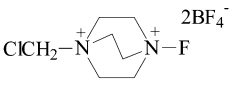
ABSTRACT

Synthetic and structural aspects of organofluorine compounds continue to be the focal points of vigorous research activities, as evidenced by the appearance of a large number of publications. Among the various useful methodologies for the introduction of fluorine into organic molecules, electrophilic fluorination is a promising and exciting area of research. While a variety of electrophilic fluorinating reagents are available, currently 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) provides a remarkably straightforward and effective route. The breadth of applications realizable from this reagent in its role as a key electrophilic fluorinating reagent is highlighted here. This Account covers the literature for electrophilic fluorination reactions that employ Selectfluor during the period January 1999−January 2003.

I. Introduction

An amazingly diverse and constantly expanding range of commercial products emanating from the fluorochemicals industry is driven by the dramatic changes in the physical and biological properties and chemical reactivities of organic materials that arise from the introduction of fluorine.[1] In particular, these changes, including enhanced stability and lipophilicity, have been exploited in the fields of pharmaceutical, agrochemical, and polymer chemistry.[2−4] The efficacy of many pharmaceuticals and agrochemicals is often enhanced by or is dependent on the presence of a single fluorine atom in the molecular structure.[5] Frequently, such compounds can be synthesized from smaller molecules in which fluorine is located at a specific site, or often it is desirable to introduce the element directly in order to obtain the desired chemical composition.[6,7] Electrophilic fluorination is one of the most direct methods for selective introduction of fluorine into organic compounds. Elemental fluorine itself is one of the most powerful reagents.[8] However, fluoroxy compounds, such as CF_3OF, $CF_3C(O)OF$, $CsSO_4F$, and $CH_3C(O)OF$, some of which are generated in situ, are exciting reagents for the introduction of fluorine electrophilically into a wide variety of organic compounds.[9] The rather hazardous perchloryl fluoride has lost favor to other electrophiles, including xenon difluoride, which has been employed as a particularly interesting and easily handled source of electrophilic fluorine.[10] More recently, much attention has been given to the fluoronitrogen compounds, including *N*-substituted fluoropyridinium and *N*,*N*′-difluorobipyridinium salts, such as *N*,*N*′-difluorobipyridinium tetrafluoroborate (MEC-31, Daikin)[11] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, Air Products).[12] While the latter two reagents are readily available commercially, unfortunately some of the most powerful electrophilic NF reagents, e.g., the perfluoroalkylsulfonimides ($R_fSO_2N(F)SO_2R_f'$), have not been commercialized.[13] These N−F compounds are generally somewhat less reactive than the fluoroxy reagents described above, but nevertheless they have proved to be particularly useful with a wide range of organic nucleophiles.

While these fluorinating reagents and methodologies have been developed to fulfill the increasing demand for site-selective fluorination of organic and biological molecules, the applications of Selectfluor (**1**) are remarkedly broad. Because it is a stable, nonvolatile, user-friendly reagent,[12] it has been used widely in one-step reactions to introduce fluorine into organic compounds electophilically. Our interest in applying electrophilic synthetic methods for introducing fluorine or a fluorinated group into a large variety of organic/inorganic compounds encouraged us to describe the recent highlights in fluorination reactions specifically using **1** as the key electrophilic fluorinating reagent. The literature from January 1999−January 2003 is reviewed.



1-chloromethyl-4-fluoro-1,4-diazoniabicyclo(2.2.2)octane bis(tetrafluoroborate) (Selectfluor™)

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Rajendra P. Singh was born in India and received his Ph.D. degree from Banaras Hindu University with Professor V. D. Gupta in 1985. In 1987, he was awarded a UNESCO fellowship at Tokyo Institute of Technology and received a diploma in homogeneous catalysis. He subsequently served as a lecturer at H. D. College Zamania (India). In 1992, he was awarded a Science & Technology Agency fellowship at the National Institute of Materials and Chemical Research (NIMCR), Tsukuba, Japan, with Prof. Masato Tanaka in organosilicon chemistry. Subsequently, he joined the Molecular Catalysis Project in 1993 as an Exploratory Research for Advance Technology (ERATO) researcher in Japan with Prof. Ryoji Noyori. In 1995, he became a postdoctoral fellow in Prof. D. S. Matteson's research group at Washington State University in the area of asymmetric synthesis via boronic esters. In 1998, he joined the University of Idaho's fluorine research group, where he was a research scientist until March 2003, when he became Associate Director of Research at Advance Research Chemicals, Inc., Catoosa, OK. His research interests center around new synthetic methodologies via electrophilic and nucleophilic fluorinating reagents.

Jean'ne M. Shreeve is a Montana native. She received a B.A. in chemistry from the University of Montana, M.S. in analytical chemistry from the University of Minnesota, and Ph.D. in inorganic chemistry from the University of Washington, Seattle. She joined the University of Idaho faculty in 1961, became department head in 1973, and in 1987, assumed the role of Vice-President for Research and Graduate Studies. In January 2000, she returned to full-time research. She was privileged to have worked with three of the finest gentlemen of fluorine chemistry—Professors George H. Cady, Harry J. Emeléus, and Oskar Glemser. Her research interests include the syntheses, characterization, and reactions of new fluorine-containing compounds, as exemplified by more than 350 refereed publications.

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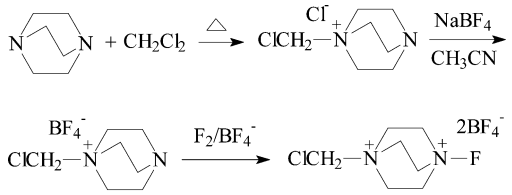
Scheme 1



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II. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane Bis(tetrafluoroborate) (Selectfluor)

A. Synthesis. Selectfluor (**1**) is produced commercially by Air Products[14] via the process in Scheme 1. The details of the chemistry are fully described.[15]

B. Properties. Selectfluor is a white solid (mp 190 °C), stable in air and to moisture. The X-ray crystal structure has been reported.[16] It is a dicationic salt that is very soluble in cold water or dilute hydrochloric acid. However, it decomposes in dilute sodium hydroxide and reacts with cold DMSO (rapidly and exothermally) and with DMF (slowly on heating). It is moderately soluble in acetonitrile, but only slightly soluble in lower alcohols and acetone, which makes the former the solvent of choice. Occasionally, reactions in these solvents were accelerated by adding a small amount of water or trifluoroacetic acid. Bulk quantities of **1** should be stored in a cool, dry place and should not be heated above 80 °C. Fainzil'berg et al. have measured the reduction potentials of Selectfluor and other N−F compounds. With a positive reduction potential, $E_{1/2}$ = 0.33 V, Selectfluor is predicted to be a more reactive fluorinating reagent than, e.g., *N*-fluorobenzenesulfonimide, with $E_{1/2} = -1.24$ V.[17]

III. Fluorination Reactions Using Selectfluor

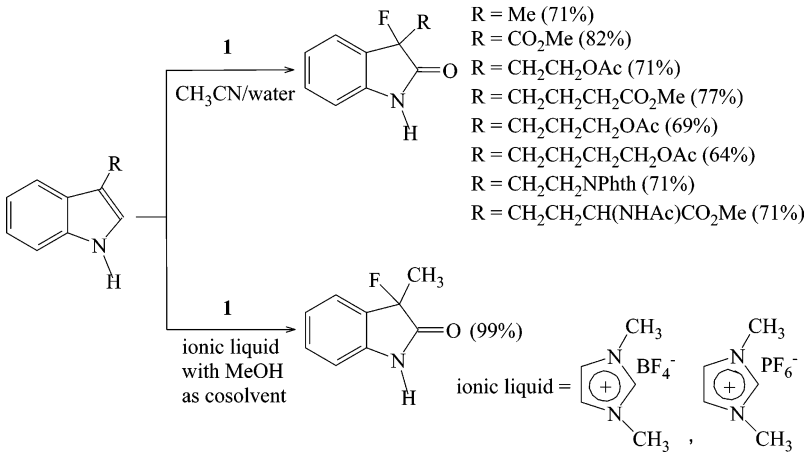
Selectfluor is a reactive source of an electrophilic [F^+] species that interacts with organic, inorganic, and biological molecules. It can be reacted with aromatic, aliphatic, alkene, amine, glycol, and silicon compounds. Most of the reactions have been performed in acetonitrile, but DMF and DMA have also been used. Reaction conditions depend on the substrate used and the nature of the products formed. In the case of less reactive substrates, a higher temperature is required. In asymmetric synthesis, lower temperatures are preferred in order to achieve high enantiomeric excess. Possible mechanisms of the reactions of "electrophilic" fluorinating reagents with organic compounds are not well understood. The question is whether the reactions occur via direct fluorine transfer or through discrete electron transfer (SET). As a classical S_N2 process, fluorine transfer results when nucleophilic attack of an electron-rich reaction center on fluorine displaces the ligand portion of the reagent. The SET mechanism demands the initial formation of a charge-transfer complex between an electron-rich organic molecule and the electron-deficient fluorinating reagent that transforms to an organic molecule cation radical active intermediate as the precursor of non-fluorinated or fluorinated products. While there is confirmation of cation radicals that tend to support the SET reaction pathway, it is generally accepted that the course of these fluorination reactions is strongly related to the structure of the N−F reagent, the organic molecule, and the reaction conditions used. It is very difficult to define unequivocally the reaction pathway through which the products are formed.[12b]

The chemistry of Selectfluor with various classes of compounds is described in the following sections.

A. Electrophilic Fluorination of Aromatic Compounds and Their Derivatives. Arenes react with **1** with difficulty, but aromatic compounds with an electron-donating group in the ring were found to be reactive under appropriate conditions. Reaction of 3-substituted indoles with **1**, either in acetonitrile/water[18] or in an ionic liquid,[19] led to the formation of the 3-fluorooxindole in good to high yields (Scheme 2). Formation of the non-fluorinated oxindole as a side product has also been reported. High yield and better chemoselectivity were claimed when ionic liquids were employed as the reaction media.[19]

A proposed reaction mechanism for the formation of fluorinated oxindoles is shown in Scheme 3. Reaction of indole (**X**) with **1** gave 3-fluoroindolenine (**A**) as an unstable intermediate that underwent loss of HF due to

Scheme 2



Scheme 3

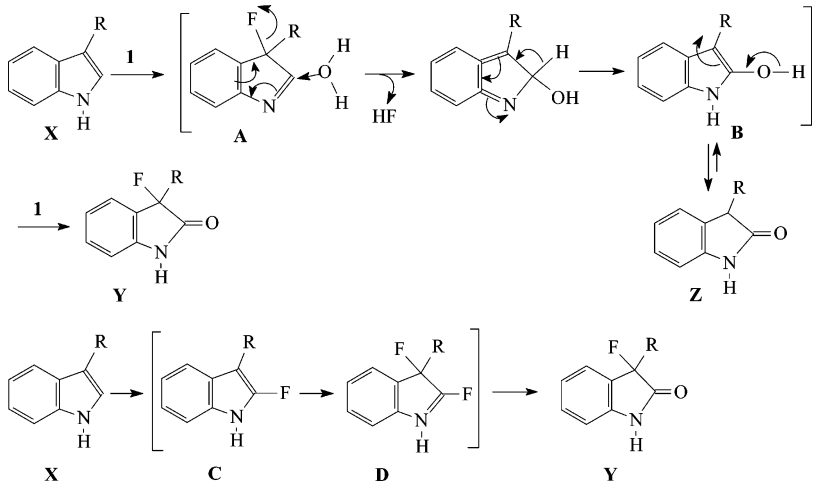
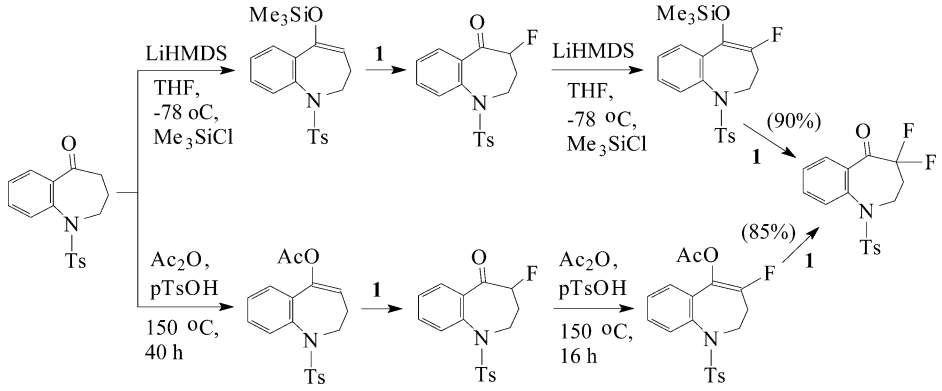


Table 1. Electrophilic Fluorination of Arenes with 1[a]

arenes (ArH)	ArH:**1**	yield, % (NMR)	composition of products mixture (%)
p-xylene[a]	10:1	24	2-fluoro-1,4-dimethylbenzene (100)
p-xylene[a]	10:1	51	2-fluoro-1,4-dimethylbenzene (100)
p-methylanisole	4:1	56	2-fluoro-4-methylanisole (93) 3-fluoro-4-methylanisole (6) 2,6-difluoro-4-methylanisole (1)
p-chloroanisole	10:1	50	2-fluoro-4-chloroanisole (95) 2,6-difluoro-4-chloroanisole (5)
p-fluoroanisole	4:1	24	2,4-difluoroanisole (100)
naphthalene	4:1	88	1-fluoronaphthalene (91) 2-fluoronaphthalene (7) 1,8-difluoronaphthalene (2)
dibenzofuran	4:1	49	1-fluorodibenzofuran (20) 2-fluorodibenzofuran (41) 3-fluorodibenzofuran (39)
1-methylnaphthalene	2:1	23	1-fluoro-4-methylnaphthalene (53) 1-fluoro-8-methylnaphthalene (15) 5-fluoro-1-methylnaphthalene (11) 2-fluoro-1-methylnaphthalene (21)
mesitylene[a]	4:1	52	2-fluoromesitylene (100)

[a] The solvent was ethylmethylimidazolium triflate except for the first reaction with *p*-xylene where the anion was BF_4^- and with mesitylene where the solvent was butylmethylimidazolium hexafluorophosphate.

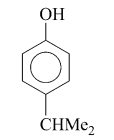
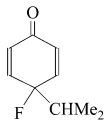
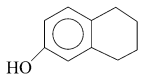
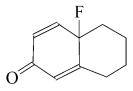
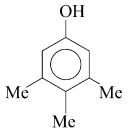
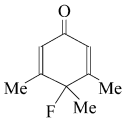
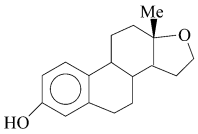
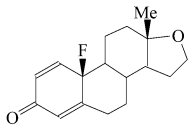
Scheme 4



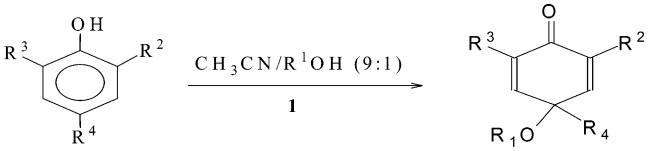
addition of water. A subsequent 1,5-prototropic shift gave the enol **B**. Fluorination of **B** with additional **1** resulted in oxindole (**Y**) as the final product. Formation of non-fluorinated oxindole (**Z**) as a minor side product was explained by the tautomerism of enol (**B**), catalyzed by water (solvent). An alternative pathway for the formation of **Y** from **X** can be considered via the formation of 2-fluoroendole (**C**) and 2,3-difluoroindolenine (**D**) intermediates, especially in nonaqueous media.

The fluorination of arenes using an ionic liquid as the reaction medium (assisted by sonication) was examined with **1**. With reactive aromatics, the optimal fluorinated yields obtained with 1 equiv of **1** in ionic liquids are ~50% (Table 1).[20] Usually the yields are found to be comparable

Table 2. Fluorination of 4-Substituted Phenols with 1

Phenol	Time	temp (°C)	products	yield (%)
	20	22		60
	4.5	22		86
	4.5	22		93
	3.5	45		90

Scheme 5

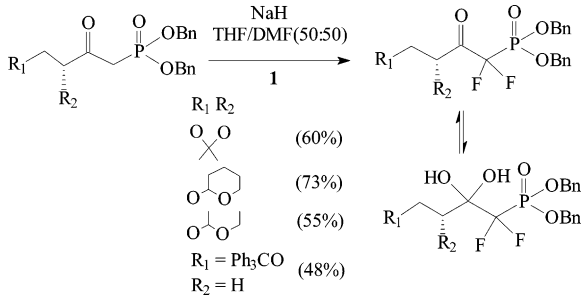


R^1	R^2	R^3	R^4	Yield (%)
Me	*t*-Bu	*t*-Bu	*t*-Bu	86
Et	*t*-Bu	*t*-Bu	*t*-Bu	84
Pr	*t*-Bu	*t*-Bu	*t*-Bu	86
H	*t*-Bu	*t*-Bu	Me	88
Me	*t*-Bu	*t*-Bu	Me	91
Et	*t*-Bu	*t*-Bu	Me	85
$HOCH_2CH_2$	t-Bu	*t*-Bu	Me	92
Me	Me	Me	Me	93
Et	Me	Me	Me	92
CF_3CH_2	Me	Me	Me	86

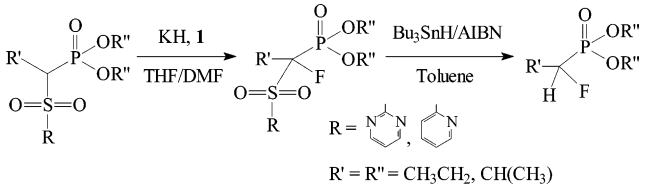
with, and in some cases exceed, those obtained in acetonitrile and trifluoroacetic acid but are not as high as in those obtained in trifluoromethanesulfonic acid. A comparative study has shown that **1** is more reactive than 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate (Accufluor) and *N*-fluoropyridinium salts.[20]

Aminofluorothiophenes are possible precursors that can be used in the synthesis of fluoroquinolone antibiotics.[21] Although **1** has shown reasonable reactivity for the fluorination of acetanilide, it was incompatible with acetamidothiophene, and the fluorinated derivatives were obtained in very low yields.[22] Two possible routes to 2,2-difluoro-1-keto-5-tosylbenzazepine using **1** are available.[23] In the first procedure, the 1-keto-5-tosylbenzazepine was

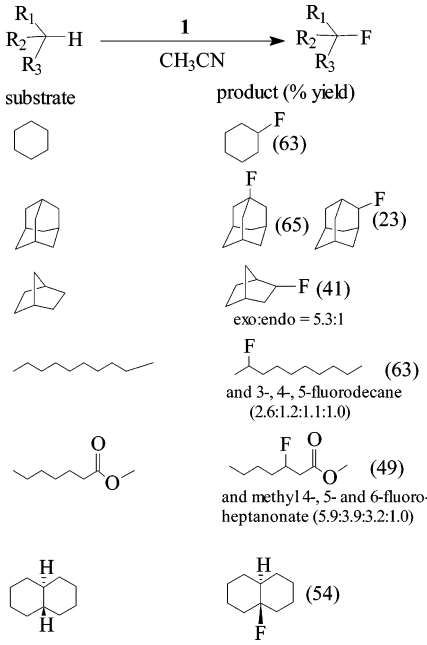
Scheme 6



Scheme 7



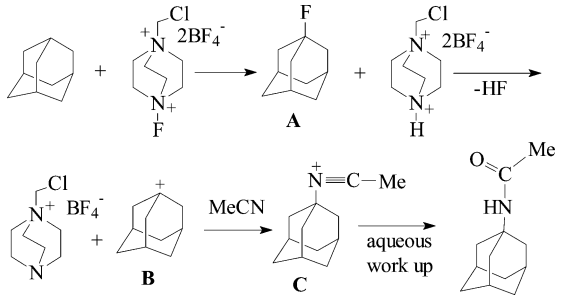
Scheme 8



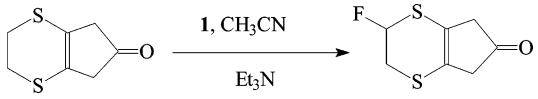
reacted with lithium hexamethyldisilazane (LHMDS) in THF to generate lithium enolate and then with trimethylsilyl chloride to furnish the corresponding silylenol ether. The latter reaction, with **1** in acetonitrile, gave monofluorobenzazepine. The sequence of enolization, silyl ether formation, and fluorination with **1** was applied to the monofluoro derivative in order to obtain 2,2-difluoro-1-keto-5-tosylbenzazepine in 90% yield (Scheme 4). The second route involved the generation of an enol acetate derivative from 1-keto-5-tosylbenzazepine, followed by the reaction with **1** in acetonitrile to give the monofluorobenzazepine derivative, which was subsequently fluorinated with **1** to form the difluoro product in 85% yield. In both the processes, ~2−4% of the monofluoro derivative remained.

Stavber has utilized **1** in the high-yield, direct synthesis of 4-fluorocyclohexa-2,5-dienone derivatives. Estrogen

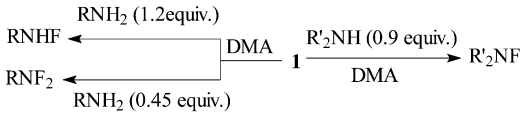
Scheme 9



Scheme 10

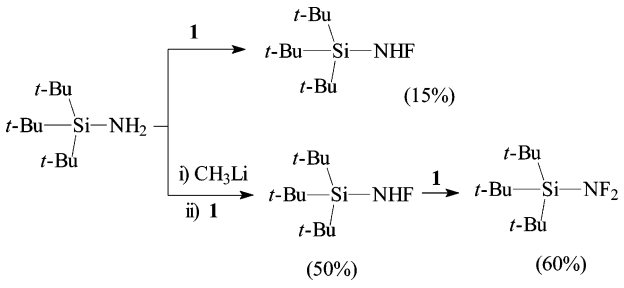


Scheme 11



substrate	product	yield (%)
t-BuNH$_2$	*t*-BuNF$_2$	80
BuNH$_2$	BuNF$_2$	72
i-PrNH$_2$	*i*-PrNF$_2$	78
PrNH$_2$	PrNF$_2$	75
i-BuNH$_2$	*i*-BuNF$_2$	74
t-BuNH$_2$	*t*-BuNHF	85
BuNH$_2$	BuNHF	80
i-PrNH$_2$	*i*-PrNHF	82
PrNH$_2$	PrNHF	63
i-BuNH$_2$	*i*-BuNHF	66
Et$_2$NH	Et$_2$NF	65
i-Bu$_2$NH	*i*-Bu$_2$NF	73
Pr$_2$NH	Pr$_2$NF	66

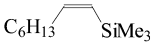
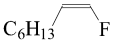
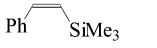
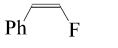
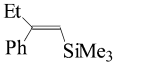
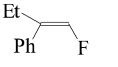
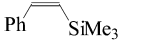
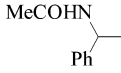
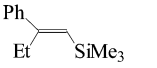
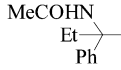
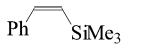
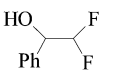
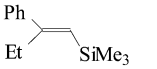
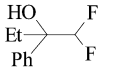
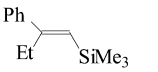
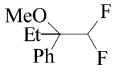
Scheme 12



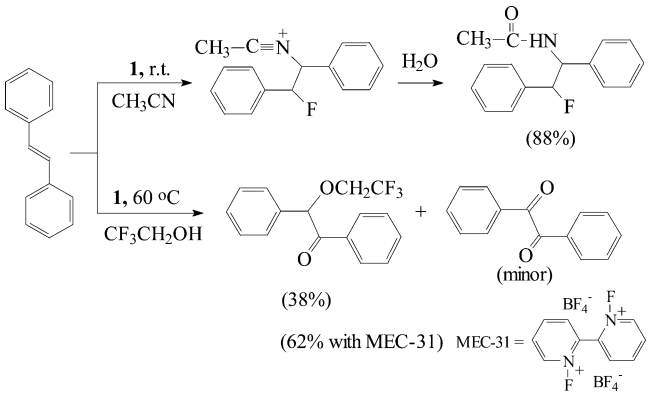
steroids were also readily converted to 10β-fluoro-1,4-estradiene-3-one derivatives in good yields (Table 2).[22b]

Hindered 2,4,6-trialkyl-substituted phenols were also selectively converted to *p*-quinols in high yield by reaction with **1**. The effects of temperature and the presence of different external nucleophiles have been studied (Scheme 5).[22c] Reactions of hindered phenols with **1** require well-defined conditions in order to ensure the selectivity of the course of reaction. At least for phenols with **1**, it appears

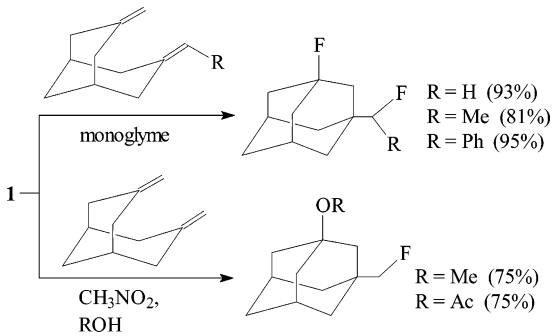
Table 3. Reaction of Vinylsilane Derivatives with 1

substrate	nucleophile	product	yield (%)
			44 (Z/E 80:20)
			32 (Z/E 65:35)
			57 (Z/E 58:42)
	CH_3CN		70
	CH_3CN		86
	HOH		45
	HOH		83
	MeOH		79

Scheme 13



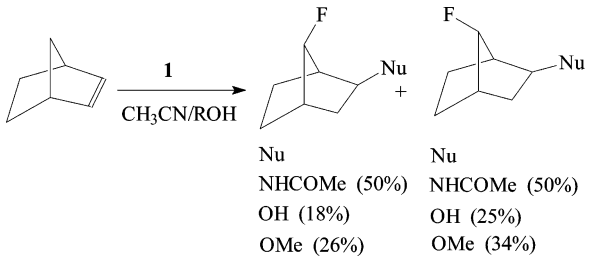
Scheme 14



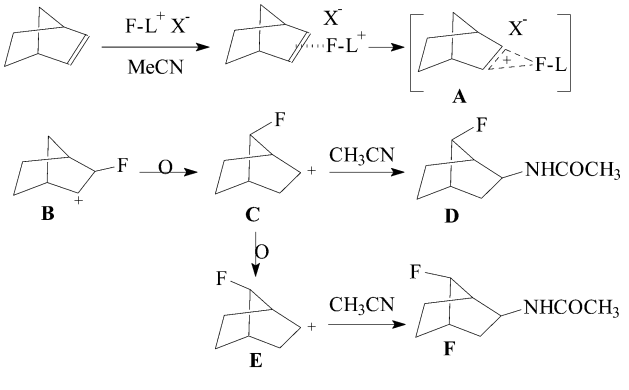
that the ET process is the main and most probable reaction pathway via the formation of a cation radical as the key step.

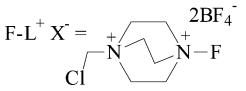
B. Electrophilic Fluorination of Aliphatics and Hydrocarbons. Several diphosphonates and phosphonophosphates were shown to be valuable inhibitors of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) enzyme. It was demonstrated that α,α-difluoromethyl-β-ketophosphonates have higher affinities than their corresponding non-fluorinated analogues for GAPDH. Thus,

Scheme 15

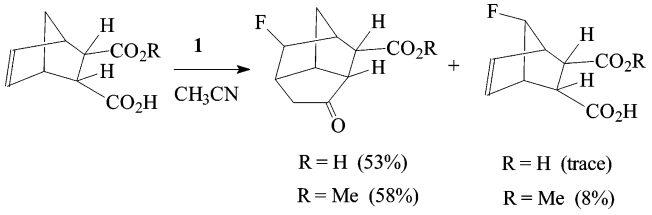


Scheme 16



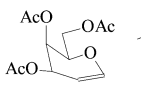
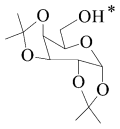
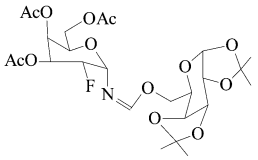
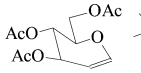
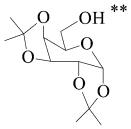
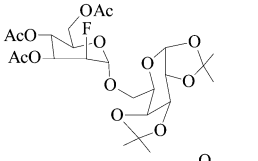
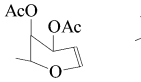
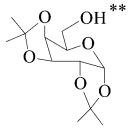
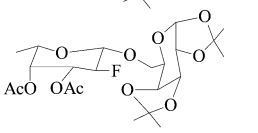
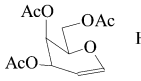
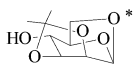
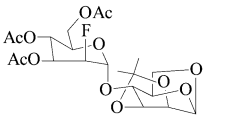


Scheme 17



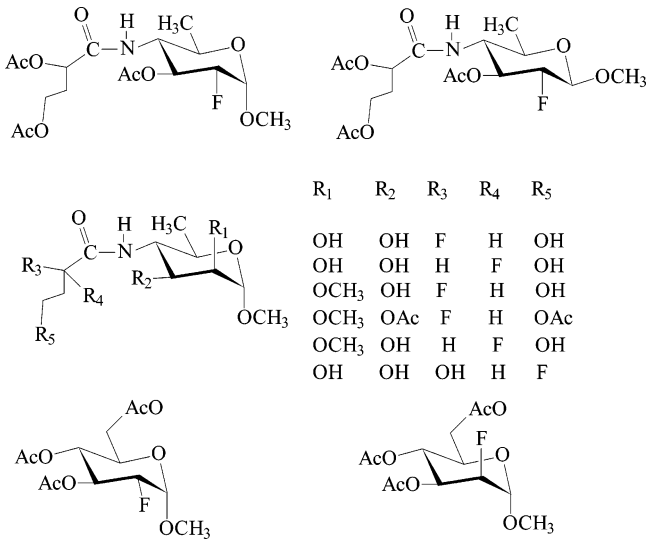
various α,α-difluoro-*β*-ketophosphonates have been synthesized and characterized by addition of the [F^+] electrophile from **1** to the enolate form of the corresponding dibenzyl-*β*-ketophosphonates (Scheme 6) that exist in equilibria with their hydrated forms.[24] Various α-fluorophosphonates were synthesized by treatment of the α-carbanions generated from several α-(pyrimidine- or pyridine-2-ylsulfonylalkylphosphonates) with **1**, followed by deprotection with tributyltin hydride/AIBN (Scheme 7).[25] This method has also been used to make nonphosphofluoro esters.[26] Chambers et al. have shown the transformation of carbon−hydrogen bonds to carbon−fluorine bonds at saturated secondary and tertiary carbon sites with **1**. One major and several minor products are formed selectively, with concomitant formation of other isomers (Scheme 8).[27] When the reaction time was increased, an acidic medium was produced due to formation of HF, and the final products obtained were the hydrocarbon amides. The mechanism of the amide formation from admantane and other hydrocarbons during electrophilic fluorination reaction with Selectfluor in acetonitrile is shown in Scheme 9. Upon standing, HF was eliminated from the fluorinated admantane **A** to give the

Table 4. Reaction of Glycals with 1 in the Presence of Nucleophiles[a]

glycal	nucleophile	products	yield(%) BF_4^- (OTf^-)
			54
			29 (75)
			40 (80)
			33 (67)

[a] *, in acetonitrile; **, in nitromethane.

Scheme 18



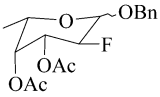
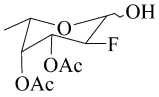
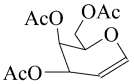
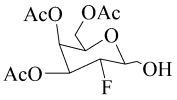
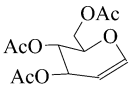
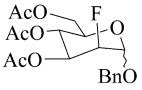
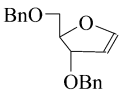
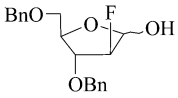
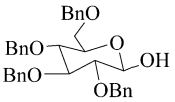
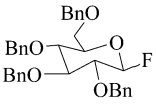
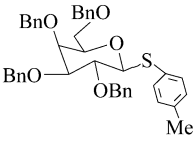
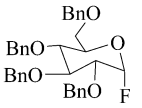
corresponding tertiary carbanion **B**. The latter reacted with acetonitrile in a Ritter-type process to give **C**, which was subsequently hydrolyzed to the amide.[27]

A dithio heterocycle was found to be reactive with **1** to give the corresponding monofluoro derivative (Scheme 10).[28]

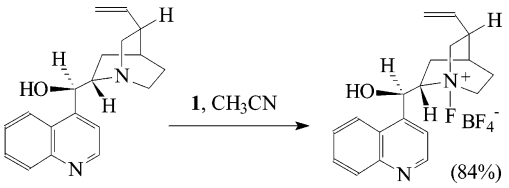
C. Electrophilic Fluorination of Aliphatic Amines. Reactions of primary and secondary amines with **1** yield a straightforward route to RNHF, RNF_2, and R'_2NF at ambient temperature. While the reactions proceed smoothly in acetonitrile, DMA or DMF was found to be a more suitable solvent due to a greater difference in solvent/product boiling points (Scheme 11).[29]

We have also developed a new nucleophilic difluoroaminating reagent, $(t\text{-Bu})_3SiNF_2$, whose synthesis takes advantage of the fluorination of a sterically hindered

Table 5. Synthesis of 2-Deoxy-2-fluoro Sugars, Glycosyl Fluoride, and Glycosides with 1

substrate	condition	products	selectivity (C-F bond)	yield (%)	α/β ratio
	**1** (1.5 equiv) MeCN/BnOH (3/1) r.t.		100	91	0:1
	**1** (1.5 equiv) DMF/H_2O (3/1) r.t.		100	97	1:1
	**1** (1.5 equiv) DMF/H_2O (3/1) r.t.		75	79	1:1
	**1** (1.5 equiv) 2,6-di-*t*-Bu-4-methyl pyridine (1.5 equiv) MeCN/BnOH (3/1)		67	60	1:2.5
	**1** (1.5 equiv) DMF/H_2O (3/1) r.t.		88	73	-
	**1** (3 equiv) DMF/SMe_2 (1/1) r.t.		-	70	1:1
	**1** (3 equiv) MeCN/4A M.S. 0 °C		-	82	1:0

Scheme 19



silylamine. Direct reaction of $(t\text{-Bu})_3SiNH_2$ with **1** in acetonitrile resulted in marked cleavage of the silicon−nitrogen bond to form $(t\text{-Bu})_3SiF$ and $(t\text{-Bu})_3SiNHF$ in about 15% yield. Alternatively, $(t\text{-Bu})_3SiNHF$ was isolated in about 50% yield when the monolithium salt was reacted with **1**. However, the desired product, $(t\text{-Bu})_3SiNF_2$, was isolated in about 60% yield when the reaction of $(t\text{-Bu})_3SiNHF$ was carried out with approximately 1 equiv of **1** in acetonitrile (Scheme 12).[30]

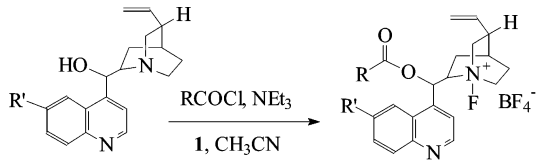
D. Electrophilic Fluorination of Alkenes and Their Derivatives. Fluorodesilylation of alkenyltrimethylsilanes, an easy route to fluoroalkenes as well as difluoromethyl-substituted amides, alcohols, and ethers, is realized by using **1**. Reactions of various alkyltrimethylsilanes with 1 equiv of **1** led to the formation of monofluoroalkenes. When the reactions were carried out with 2.5 equiv of **1** in acetonitrile, the resulting products were difluoromethylated amides. The presence of an external nucleophile, such as water or alcohol, with acetonitrile gave difluoromethylated alcohols or ethers (Table 3).[31]

The reaction of *trans*-stilbene with **1** in the presence of weak nucleophiles (NuH, Nu = OMe, OH, OAc) in acetonitrile gave erythro/threo mixtures of monofluorinated compounds.[32] The use of fluorinated alcohols as nucleophiles in acetonitrile did not give the desired product. At the end of the reaction, a Ritter-type monofluorinated amide was isolated in good yield.[33] However, the above reaction with trifluoroethanol, in the absence of acetonitrile, gave the α-keto ether in moderate yield (Scheme 13).[34] The formation of benzil was also detected. The yields of the α-keto polyfluorinated ethers were found to be higher when *N*,*N*-difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31, Daikin) was used as the electrophilic fluorinating reagent.

Interaction of **1** with 3,7-bis-methylenebicyclo[3.3.1]nonane derivatives in monoglyme results in the transannular cyclization of the dienes to form 1-fluoro-3-fluoroalkyladmantanes. In the presence of nucleophiles, using nitromethane as a solvent, monofluoro derivatives were produced (Scheme 14).[35]

Fluorination of norbornene with **1** in acetonitrile resulted in the formation of two rearranged Ritter-type products, 2-*exo*-acetamido-7-*syn*-fluoronorbornane and

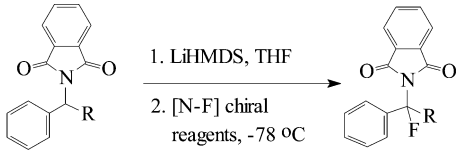
Scheme 20[a]



[N-F] reagent[a]	% yield esterification	% yield transfer fluorination	δ 19F[b] N-F
F-AcCD-BF_4	90	95	43.8
F-AcQD-BF_4	96	98	35.7
F-AcQN-BF_4	99	96	44.7
F-AcDHQD-BF_4	83	83	40.1
F-*p*ClBzCD-BF_4	92	90	44.0
F-*p*ClBzCN-BF_4	99	87	38.4
F-*p*ClBzQD-BF_4	93	89	39.1
F-*p*ClBzQN-BF_4	99	95	43.8
F-*p*ClBzDHQD-BF_4	80	82	39.5
F-*p*MeOBzQN-BF_4	95	98	44.4
F-*p*NO_2QN-BF_4	81	91	44.5

[a] CD, cinchonidine; CN, cinchonine; QD, quinidine; QN, quinine; DHQD, dihydroquinidine; DHQN, dihydroquinin. [b]Measured in acetone-d_6, standard $CFCl_3$.

Scheme 21[a]



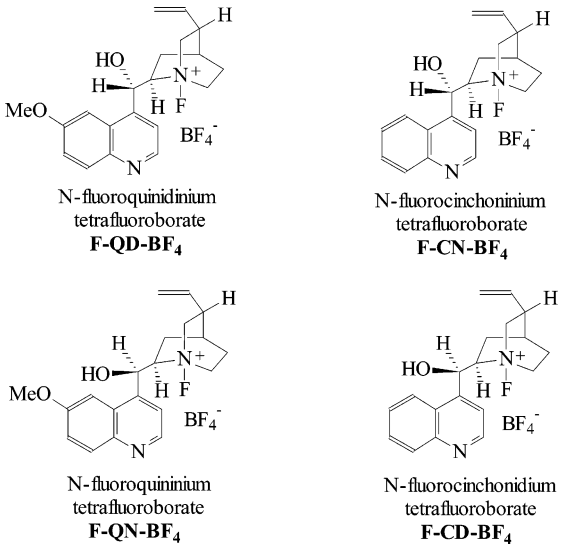
[N-F] reagents[a]	R = CO_2Et ee (%)	R = CO_2Et yield (%)	R = CN ee (%)	R = CN yield (%)
F-AcCD-BF_4	42	87	52	91
F-CN-BF_4	26	62	48	68
F-AcQN-BF_4	76	79	80	88
F-AcDHQD-BF_4	50	60	75	72
F-*p*ClBzCN-BF_4	28	67	66	70
F-pClBzQN-BF_4	68	73	91	70
F-pClBzDHQD-BF_4	38	65	82	64
F-pClBzDHQN-BF_4	76	86	92	65
F-pMeOBzQN-BF_4	66	64	94	56
F-pNO_2BzQN-BF_4	60	60	90	58

[a] CD, cinchonidine; CN, cinchonine; QD, quinidine; DHQD, dihydroquinidine; DHQN, dihydroquinin.

2-*exo*-acetamido-7-*anti*-fluoronorbornane, in a 1:1 ratio. The presence of an external nucleophile, e.g., water or methanol, resulted in formation of two additional rearranged products, 2-*exo*-hydroxy or methoxy-7-*syn*-fluoronorbornane and 2-*exo*-hydroxy or methoxy-7-*anti*-fluoronorbornane (Scheme 15).[36]

A plausible reaction mechanism for the formation of these monofluoronorbornane derivatives is shown in Scheme 16. The first step could be the π-complex formation and its transformation through a three-centered transition state (**A**) to the β-fluorocarbonium ion **B**. Formation of **C** can be expected by Meerwein−Wagner rearrangement. The reaction of **C** with acetonitrile as a nucleophile led to the formation of 2-*exo*-acetamido-7-

Scheme 22



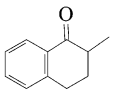
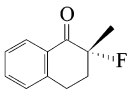
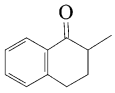
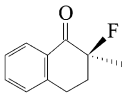
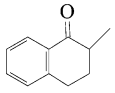
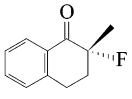
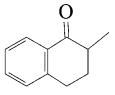
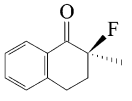
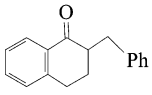
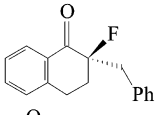
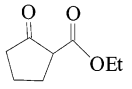
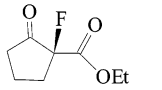
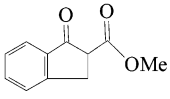
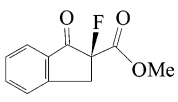
N-fluoroquinidinium tetrafluoroborate **F-QD-BF_4**

N-fluorocinchoninium tetrafluoroborate **F-CN-BF_4**

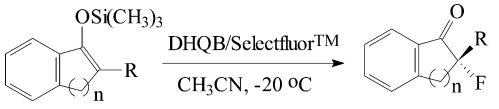
N-fluoroquininium tetrafluoroborate **F-QN-BF_4**

N-fluorocinchonidium tetrafluoroborate **F-CD-BF_4**

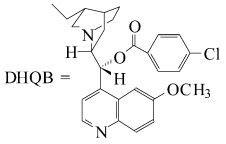
Table 6. Enantioselective Fluorination of Sodium Enolates

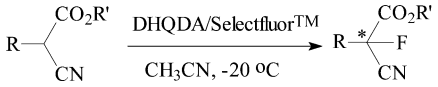
substrate	reagent	product	ee (%)	yield (%)
	**F-QD-BF_4**		27	87
	**F-QN-BF_4**		20	98
	**F-CN-BF_4**		40	70
	**F-CD-BF_4**		50	98
	**F-QD-BF_4**		42	96
	**F-QD-BF_4**		40	96
	**F-QD-BF_4**		36	95

Scheme 23

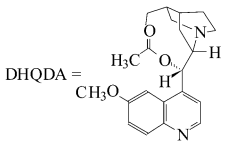


R	n	yield (%)	ee (%)
Me	1	93	53
Bn	1	99	89
Et	1	100	73
Me	2	94	40
Bn	2	95	71

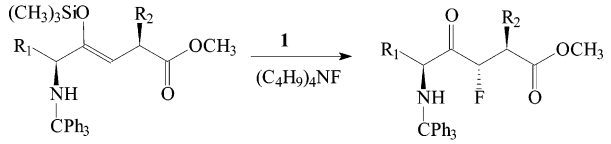




R	R'	yield (%)	ee (%)
Tol	Et	60	87
Np	Me	87	76
Ph	Et	81	83
Cl-Ph	Me	56	68
*i*Pr-Ph	Me	82	84

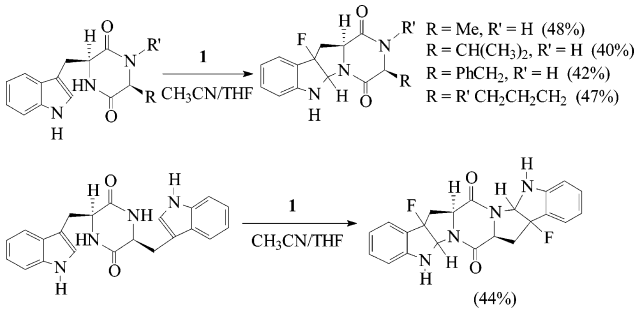


Scheme 24



$R_1 = Me_2CHCH_2$, $R_2 = CH_3$ (76%)
$R_1 = Me_2CHCH_2$, $R_2 = CH_2C_6H_{11}$ (73%)
$R_1 = CH_2C_6H_{11}$, $R_2 = CH_3(CH_2)_3$ (65%)
$R_1 = Me$, $R_2 = Me_2CHCH_2$ (75%)
$R_1 = Me(CH_2)_3$, $R_2 = MeCH_2CH_2$ (68%)

Scheme 25

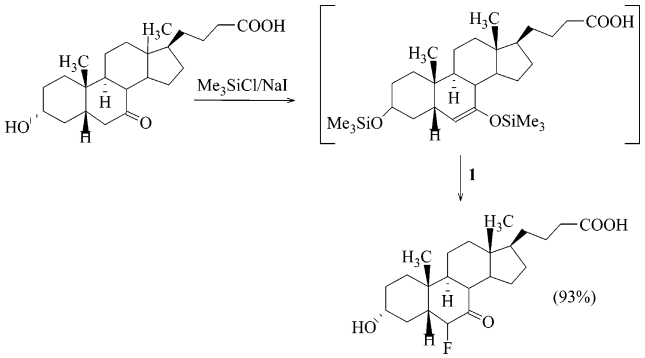


syn-fluoronorbornane **D** after water workup. The hydride-shift rearrangement of fluorocarbonium ion **C** can give fluorocarbonium ion **E**, which reacts with acetonitrile, giving 2-*exo*-acetamido-7-*anti*-fluoronorbornane **F**. In the presence of an external nucleophile, hydroxy and methoxy derivatives can be obtained.[36]

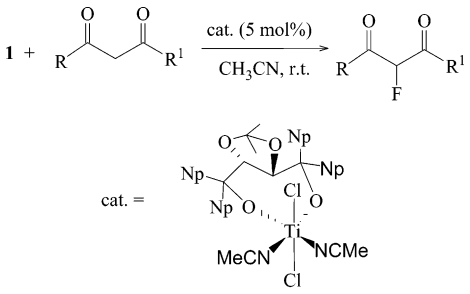
Reaction of **1** with *cis*-5-norbornene-*endo*-2,3-dicarboxylic acid, its monomethyl ester, and 5-norbornene-*endo*-2-carboxylic acid in acetonitrile led to the formation of the corresponding fluorinated γ-lactones (Scheme 17).[37]

E. Electrophilic Fluorination of Glycals. Various glycals were found to react with **1** in acetonitrile in the presence of alcohol-type nucleophiles to give the monofluorinated

Scheme 26

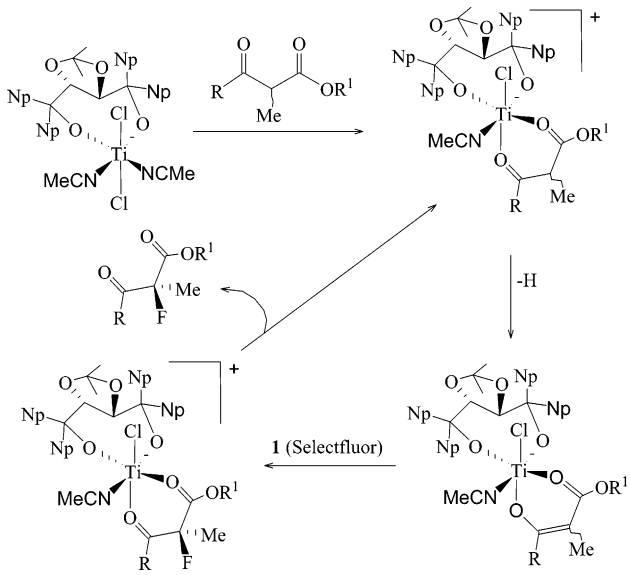


Scheme 27



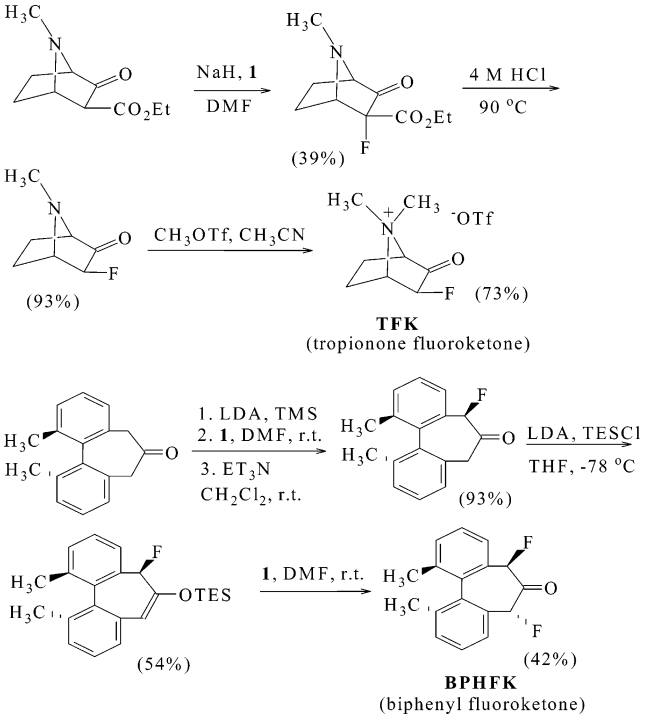
R	R_1	time	%ee
PhCO	CO_2CPh_2	40 min	82
CH_3CH_2CO	CO_2CPh_2	1day	81
CH_3CH_2CO	CO_2CH_2Ph	20 min	71
CH_3CO	CO_2CH_2Np	7 min	68

Scheme 28

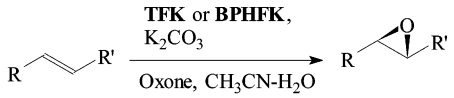


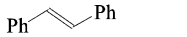
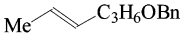
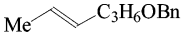
disaccharides. Acetonitrile also participated in these reactions. Thus, to avoid solvent participation, nitromethane was found to be suitable. Reactivity of **1** as its triflate derivative was also compared and found to give higher yields (Table 4).[38a] The authors attribute the higher yields with the triflate derivative vis-à-vis the tetrafluoroborate salt to a side reaction between the latter anion and one

Scheme 29



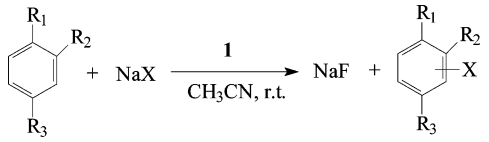
Scheme 30



substrate	fluoroketone	time (h)	products yield (%)	ee (%)
	**TFK**	72	79	58
	**BPHFK**	72	46	94
	**TFK**	5	85	35
	**BPHFK**	10	80	88
	**TFK**	9	97	8
	**BPHFK**	11	72	68
	**TFK**	5	93	7
	**BPHFK**	4	78	59
	**TFK**	4	78	14
	**BPHFK**	11	67	12
	**TFK**	30	90	29
	**BPHFK**	30	55	12

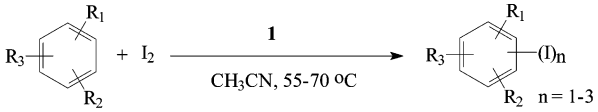
of the reaction products which does not occur with triflate. Earlier studies show no convincing evidence for the operation of a counterion effect and suggest that there is not much to choose from, from the viewpoints of handling and product yield, between triflate, tetrafluoroborate, and hexafluorophosphate. The tetrafluoroborate is most cost-effective.[38b] Other researchers have also fluorinated glycals

Scheme 31



aromatic (mmol)	NaX (mmol)	**1** (mmol)	time (h)	product distribution (mol%)
phenol 10.0	$NaNO_2$ 14.5	9.9	68	nitrophenol (81) fluoronitrophenol (16) unknown (3)
phenol 10.0	NaBr 15.1	9.9	3	bromophenol (87) 2,4-dibromophenol (12) fluorophenol (1)
anisole 20.3	NaSCN 19.7	20.0	21	SCN-anisole (94) unknown (6)
anisole 19.9	NaBr 20.1	20.9	21	4-bromoanisole (100)
acetanilide 10.0	NaBr 17.0	9.9	3	bromoacetanilide (99) fluoroacetanilide (1)
dimethylaniline 18.4	NaSCN 21.3	19.8	18	4-SCN-dimethylaniline (100)
aniline 21.5	NaSCN 22.4	20.0	17	SCN-aniline (96) fluoroaniline (4)
benzene 10.0	NaCl 10.1	10.0	72	4-chlorobenzene (97) dichlorobenzene (3)
benzene 10.0	NaBr 10.5	10.0	72	bromobenzene (100)
4-nitrophenol 10.1	$NaNO_2$ 10.1	10.0	45	2,4-dinitrophenol (100)

Scheme 32

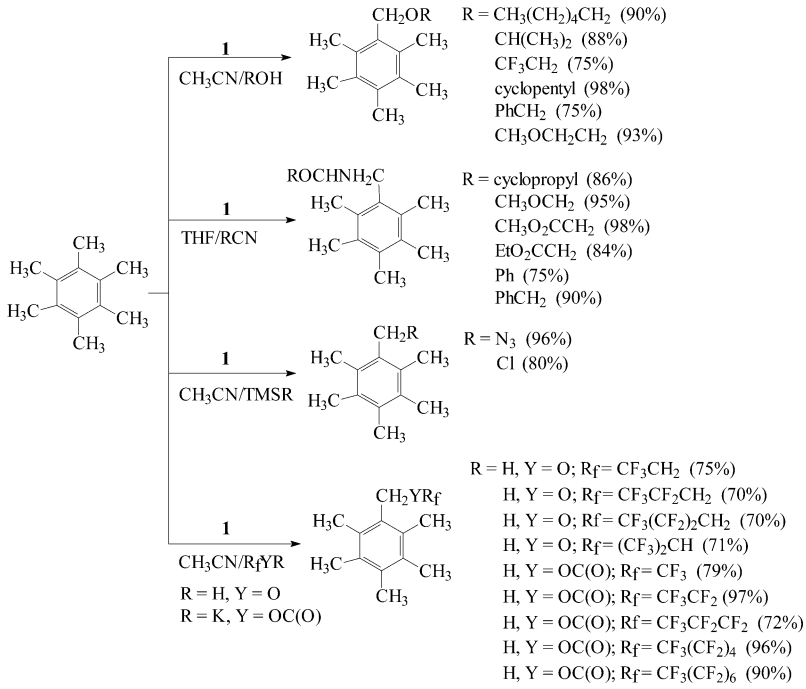


substrate	reactant ratio substrate:I_2:**1**	time (h)	product	yield (%)
isopropylbenzene	1:0.75:0.75	4	1-iodo-isopropylbenzene	88
1,4-dimethylbenzene	1:1.5:1.5	5	1,4-diiodo-2,5-dimethyl-benzene	81
	1:5:5	24	1,3,4-diiodo-2,5-dimethyl-benzene	65
1,2,4,5-tetramethyl benzene	1:0.75:0.75	1.5	3-iodo-1,2,4,5-tetramethyl-benzene	88
	1:2:2	24	1,4-diodo-2,3,5,6-tetramethyl-benzene	69
t-butylbenzene	1:0.75:0.75	3	1-(t-butyl)-4-iodobenzene	90
	1:1.5:1.5	6.5	4-(t-butyl)-4-iodobenzene	87
4-methyl-1-t-butyl benzene	1.0:0.6:0.6	3	4-(t-butyl)-2-iodo-1-methyl-benzene	88
	1:2.5:2.5	5	5-(t-butyl)-1,3-diiodo-2-methyl-benzene	80
1,3,5-tri-isopropyl benzene	1.0.75:0.75	2	2-iodo-1,3,5-triisopropylbenzene	90
1,3-t-butylbenzene	1:0.6:0.6	4.5	1,3-di(t-butyl)-5-iodobenzene	83

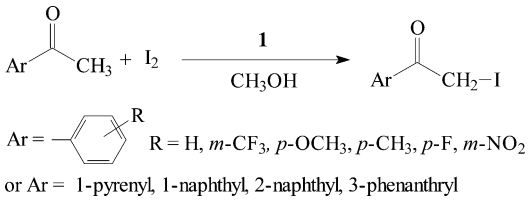
with **1** at position 2 to achieve additional fluorinated glycal products, as shown in Scheme 18.[39,40]

Wong and co-workers have reported one-pot syntheses of 2-deoxy-2-fluoro sugars and their glycosides from glycals using Selectfluor (**1**) in the presence of nucleo-

Scheme 33



Scheme 34



philes. This methodology has been further extended to the synthesis of glycosyl fluorides and glycosides from anomeric hydroxy or thioglycoside derivatives (Table 5).[40b] Interestingly, **1**, in conjunction with methyl sulfide, transforms 1-OH monosaccharides to 1-F derivatives, presumably as does diethylamino sulfur trifluoride (DAST), proceeding via a fluorosulfonium ion. Similarly, DAST maybe replaced by **1** as a fluorinating reagent in the conversion of thioglycosides to glycosyl fluorides (Table 5, entries 6 and 7).

IV. Stereoselective Electrophilic Fluorination Reactions

A. Syntheses of Chiral N−F Reagents and Their Uses in Asymmetric Syntheses. Selectfluor (**1**) has been used to transfer fluorine onto various cinchona alkaloids to generate chiral electrophilic fluorination reagents.[41] The first enantioselective fluorinating reagent, the N-fluoro quaternary ammonium salt of cinchonidine, was prepared in a one-step transfer-fluorination of the quinuclidine moiety with **1** (Scheme 19).[42] The X-ray crystal structure showed the N−F distance is 1.409(7) Å, which approaches that found in other N−F electrophilic fluorinating reagents. Later, various other chiral N−F electrophilic fluorinating reagents were synthesized and characterized (Scheme 20).[43] Using these reagents, enantioselective electrophilic fluorination of *N*-phthaloylphenylglycine derivatives resulted (Scheme 21). Under usual fluorination conditions, the enantiomeric excess of *N*-phthaloylphenylglycinonitrile was consistently higher than that of *N*-phthaloyphenylglycine ethyl ester, as determined by HPLC.

The fluorination of the enolate of 2-methyl-1-tetralone with **F-QD-BF$_4$**, **F-CN-BF$_4$**, **F-QN-BF$_4$**, and **F-CD-BF$_4$** (Scheme 22) demonstrated that **F-CD-BF$_4$** has better enantioselectivity. Thus, using **F-CD-BF$_4$**, various other enolates have been reacted to give chiral monofluoro derivatives (Table 6).[44]

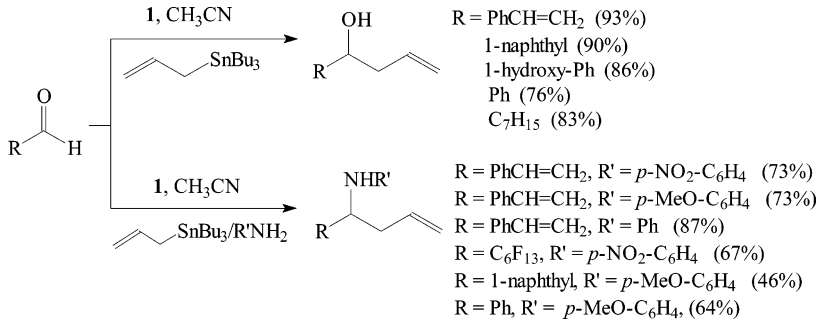
B. In Situ Generation of Chiral N−F Reagents and Their Uses in Asymmetric Synthesis. Cinchona alkaloid/Selectfluor combinations efficiently fluorinate a variety of carbonyl compounds in a highly enantioselective manner to furnish chiral α-fluorocarbonyl compounds. The DHQB/Selectfluor and DHQDA/Selectfluor combinations were effective for the enantioselective fluorination of indanones, tertalone, and acyclic and cyclic ester derivatives (Scheme 23).[45]

C. Direct Application of Selectfluor in Stereochemical Syntheses. Stereochemical syntheses of monofluoro ketomethylene dipeptide isosteres were also developed. N-Tritylated ketomethylene dipeptide isosteres (prepared from N-tritylated amino acids) were converted to the *Z*-trimethylsilyl enol ethers, which were fluorinated with **1** to yield monofluoro derivatives (Scheme 24).[46]

Shibata et al. have recently shown the syntheses of fluorogypsetin and fluorobrevianamide with **1** (Scheme 25).[47]

Bile acids are aliphatic compounds synthesized in the liver from cholesterol. Fluorination of these bile acids at the 6α-position prevents bacterial dehydroxylation, and this concept led to the identification of 6α-fluoroursodeoxycholic acid as a potential agent for the prevention and treatment of colorectal cancer.[48] The treatment of the silyl

Scheme 35



enol ether derivative of cholesterol with **1** gave the corresponding monofluorinated product in 93% yield (Scheme 26)[49a]

Catalytic enantioselective fluorination of β-ketoesters occurred with **1**. However, the monosubstituted β-ketoester does not react with Selectfluor in acetonitrile, which may be due to minimal enolization. However, addition of a range of Lewis acids efficiently catalyzed the reaction. Among various Lewis acids tested, it was evident that the titanium-based Lewis acids constitute the most potent catalysts and gave good % ee (Scheme 27).[49b]

A reaction mechanism for the formation of chiral β-keoesters using the chiral titanium catalyst was suggested.[49c] It was assumed that, at first, the β-ketoester coordinates to the catalyst as an enolate and substitutes one of the two chloride atoms and one of the acetonitrile molecules (Scheme 28). Thus, the octahedral monochloro Ti(enolate) complex is the reactive species and is fluorinated by Selectfluor in the C−F bond-forming step. Computational and experimental studies have been also explored.

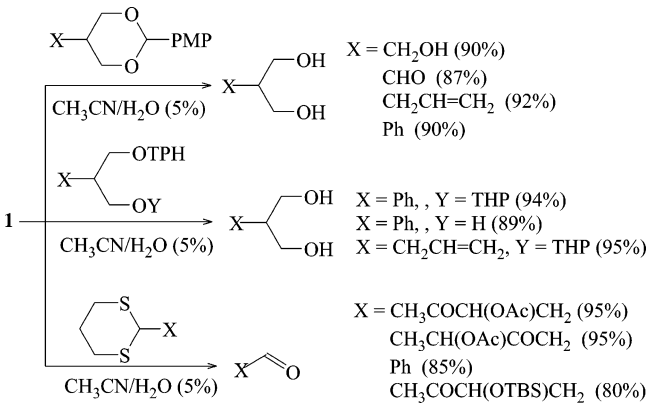
Some chiral fluorinated ketones, **TFK** and **BPHFK**, have been synthesized using **1** (Scheme 29), and their potential as enantioselective catalysts for asymmetric epoxidation with Oxone (potassium peroxy monosulfate) has been evaluated.[50] The troponine-based fluoroketone (**TFK**) has shown excellent reactivity but only modest enantioselectivity. The biphenyl-based fluoroketone (**BPHFK**) exhibited only modest reactivity, but complete conversion occurred in a reasonable time. The enantioselectivity of this catalyst was much higher but also depended on the substrate (Scheme 30).

V. Selectfluor-Mediated Organic Reactions

Selectfluor (**1**) is an electrophilic fluorinating reagent, but under its mediation, additional organic syntheses were also performed. Electrophiles such as Cl^+, Br^+, SCN^+, and NO_2^+ can be generated from their respective sodium salts using **1** in acetonitrile solution at room temperature. These electrophiles subsequently react in situ with a variety of aromatic substrates containing one or more substituent groups, including H, F, Cl, CH_3, COOH, C(O)-CH_3, and NO_2 (Scheme 31).[51]

Direct iodination reactions of various benzene derivatives under the mediation of **1** occur. The iodine atom

Scheme 36



was introduced at the most electron-rich and the least sterically hindered position on the benzene ring (Scheme 32).[52,53]

The direct introduction of alkoxy, amido, azido, or halogeno functional groups at the benzylic position in hexamethylbenzene, mediated by **1** in the presence of alcohols, carboxylic acids, nitriles, or trimethylsilyl derivatives as sources of external nucleophiles, proceeds quite well. Functionalization of hexamethylbenzene with a perfluoroalkyl moiety containing a functional group also occurs smoothly in the presence of polyfluorinated alcohols or potassium salts of polyfluoroalkane carboxylic acids (Scheme 33).[54,55]

Reactions of aryl alkyl ketones in methanol solution of iodine in the presence of **1** resulted in the formation of the corresponding α-iodoketones in good yield (Scheme 34).[56]

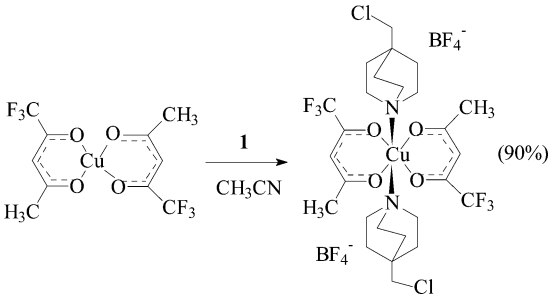
Reactions of aldehydes and imines with allyltributyltin, catalyzed by **1** in acetonitrile, gave homooallylic alcohols and amines (Scheme 35).[57]

It was shown that **1** can cleave *p*-methoxybenzylidine (PMP), tetrahydropyranyl (THP), and 1,3-dithiane groups efficiently (Scheme 36).[58]

An attempt to fluorinate metal β-diketonates with **1** resulted in the formation of a six-coordinate complex. In this case, **1** did not act as a fluorinating reagent, but fluorine was lost, and the remainder of the ligand formed a donor complex whose structure was confirmed by single-crystal X-ray (Scheme 37).[59]

Reaction of the cobalt bis(dicarbollide) anion [*commo*-3,3′-Co(3,1,2-$CoC_2B_9H11)_2^-$] with **1** in anhydrous acetone led to the formation of the corresponding 8,8′-difluoro

Scheme 37



derivative of the anion [*commo*-3,3′-Co-8F-3,1,2-$CoC_2B_9H10)_2^-$]. The structure of the NBu_4^+ salt of the 8,8′-difluoro derivative has been determined by single-crystal X-ray crystallography.[60]

VI. Conclusion

This Account has highlighted the chemistry of Selectfluor as an effective electrophilic fluorinating reagent with organic substrates. Fluorination of a wide variety of organic compounds, such as hydrocarbons, aromatics, alkenes, carbohydrates, etc., is described. Selectfluor has been utilized in the syntheses of various chiral cinchona alkaloid N−F reagents that show very good applications in asymmetric synthesis of chiral fluorine-containing compounds. In some reactions, novel organic syntheses of non-fluorinated compounds have been performed in the presence of Selectfluor.

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