Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and DAST

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Abstract: Selective fluorination of organic compounds continues to be a stimulating and exciting area of research. While a variety of fluorinating reagents and methodologies have been developed to fulfill the increasing demand for site selective fluorination of organic compounds, applications of Deoxofluor and DAST continue to be used widely. Our interest in applying synthetic methods for introducing fluorine or a fluorinated group into a large variety of organic compounds encouraged this review which highlights recent progress in fluorination reactions using Deoxofluor [bis(2-methoxyethyl)aminosulfur trifluoride] and DAST (diethylaminosulfur trifluoride) as key nucleophilic fluorinating reagents. This review covers the literature for fluorination reactions of organic compounds using Deoxofluor and DAST from January 1999 through July 2002.

1 Introduction
2 Synthesis of Deoxofluor [Bis(2-methoxyethyl)aminosulfur Trifluoride] and DAST (Diethylaminosulfur Trifluoride)
3 Fluorination Reactions with Deoxofluor and DAST
3.1 Alcohols, Amino Alcohols, and Diols
3.2 Carbohydrates
3.3 Aldehydes and Ketones
3.4 Dicarbonyls
3.5 Sulfides, Sulfoxides, Thioesters and Thiocarbonyls
3.6 Carboxylic Acids and Acid Chlorides
3.7 Glyoxal Hydrates and Anhydrous Glyoxals
3.8 Epoxides (Oxiranes)
3.9 Peptides
3.10Ketoximes
4 Miscellaneous Reactions
4.1 Synthesis of Functionalized Oxazolines and Oxazoles
4.2 Synthesis of Amides from Carboxylic Acids
4.3 Synthesis of Cholest-5-ene-3β,4β-diyl Diacetate (Steroid)
4.4 Cycloetherization
5 Reaction Mechanisms Using Deoxofluor and DAST
5.1 Alcohols
5.2 Aldehydes and Ketones
5.3 Carboxylic Acids
5.4 Sulfoxides
5.5 Glyoxal Hydrates
5.6 Ketoximes
6 Conclusions

Key words: Deoxofluor, DAST, nucleophilic reactions, fluorination, halogenation

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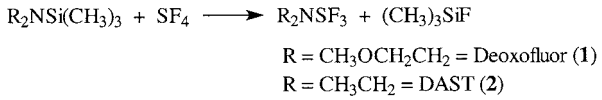
1 Introduction

Nucleophilic fluorination reactions of organic compounds using fluorinating reagents are one of the most widely used methodologies in the field of fluorine chemistry. Deoxofluor [$(CH_3OCH_2CH_2)_2NSF_3$] and DAST [$(CH_3CH_2)_2NSF_3$] are widely utilized in one-step reactions for the introduction of fluorine into organic compounds. The fluorine atom or fluorinated group is an important structural moiety in diverse classes of bioactive organic molecules. The presence of the C–F bond results in greater stability and lipophilicity of the molecule and the introduction of a fluorine atom or fluorinated group into organic molecules often changes their physical, chemical, and physiological properties.[1] These changes have been exploited in pharmaceutical and agrochemical fields.[2,3] The *N*,*N*-dialkylaminosulfur trifluorides,[4] and, in particular the mild, easily handled fluorinating reagent DAST (diethylaminosulfur trifluoride), were developed.[5] DAST tends to be somewhat thermally unstable, often undergoing detonation when heated to >90 °C. The more thermally stable Deoxofluor [bis(2-methoxyethyl)aminosulfur trifluoride] has been synthesized recently,[6] and has similar and, in some cases, better reactivity than DAST. The purpose of this review is to summarize the most recent advances in the introduction of fluoro- and fluorinated groups into organic compounds using Deoxofluor and DAST as nucleophilic fluorinating reagents.

2 Synthesis of Deoxofluor [Bis(2-methoxyethyl)aminosulfur Trifluoride] and DAST (Diethylaminosulfur Trifluoride)

Deoxofluor was synthesized[6] by a reaction procedure similar to that reported for DAST.[5] Bis(2-methoxyethyl)aminotrimethylsilane or diethylaminotrimethylsilane were reacted with sulfur tetrafluoride to produce Deoxofluor (**1**) or DAST (**2**) which were easily separated from the volatile trimethylfluorosilane (Scheme 1). While a comparison of the thermal stabilities of **1** and **2** as determined by differential scanning calorimetry (DSC),[6] showed that the decomposition temperature of both compounds is essentially the same (~140 °C), **2** does degrade much more rapidly and with somewhat larger heat evolution than **1**. Deoxofluor (**1**) showed a more gradual exotherm over a wider temperature range. These results indicated that



Scheme 1

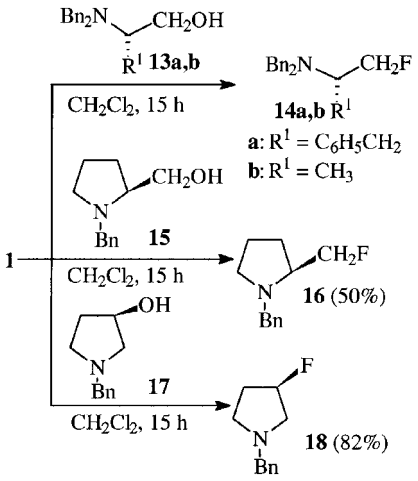
Deoxofluor (**1**) should be safer to use than DAST (**2**) on a larger, practical scale.[6]

3 Fluorination Reactions with Deoxofluor and DAST

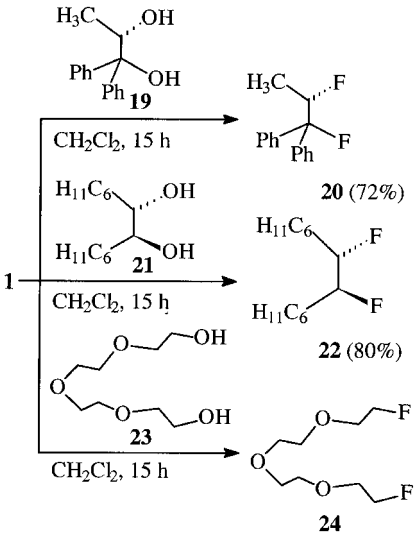
3.1 Alcohols, Amino Alcohols, and Diols

Simple alcohols are readily converted to the corresponding monofluorides using **1** or **2**. Moderate to excellent yields were obtained with a variety of structurally diverse substrates, such as primary, secondary, tertiary, allylic and benzylic alcohols. For most of the compounds, fluorination proceeds below room temperature, sometimes as low as –78 °C. However, in some cases it was necessary to warm the reaction mixture to room temperature for complete conversion. The rate of reaction was dependent on the structure of the alcohols used and not surprisingly steric hindrance plays a major role. Some examples using **1** as a fluorinating reagent are given in Table 1. Alcohols **5** and **11** gave monofluorides **6** and **12** in excellent yields whereas **9** gave **10** in only 73% yield.[6]

We have found that when **1** was reacted with various chiral amino alcohols **13a**,**b**, **15**, **17** at room temperature in dichloromethane, the corresponding chiral fluorinated compounds **14a**,**b**, **16**, **18** were produced in good yields (Scheme 2).[7] Under similar reaction conditions, diols **19**, **21**, **23** reacted with **1** to give good yields of the corresponding difluorinated products **20**, **22**, **24** (Scheme 3).[7]

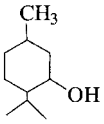
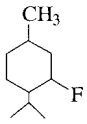


Scheme 2



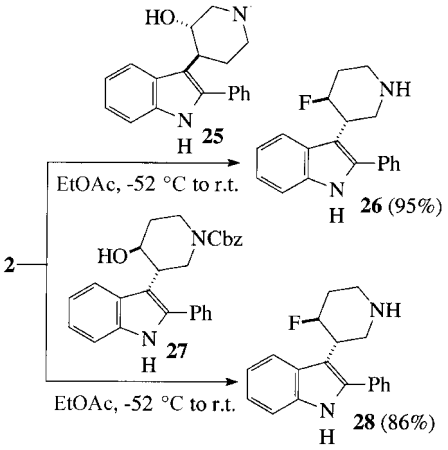
Scheme 3

Table 1 Fluorination of Alcohols with Deoxofluor (**1**)[6]

Substrate	Conditions[a]	Product	Yield (%)
 **3**	–78 °C, 2 h, r.t.,2 h	 **4**	44
$PhCH_2OH$ **5**	–78 °C, 3 h	$PhCH_2F$ **6**	96
$PhCH_2CH_2OH$ **7**	r.t., 16 h	$PhCH_2CH_2F$ **8**	85
$CH_3CH(OH)CO_2Et$ **9**	–78 °C, 2 h, r.t.,3 h	CH_3CHFCO_2Et **10**	73
$CH_3C(CH_3)(OH)\ CO_2Et$ **11**	–78 °C, 2 h, r.t.,8 h	$CH_3C(CH_3)FCO_2Et$ **12**	89

[a] Solvent: CH_2Cl_2.

The hydroxyl group, located on the carbon of a piperidine ring, also reacted easily with DAST. Thus, the reaction of **25** and **27** with **2** in ethyl acetate at –52 °C led to the formation of the corresponding monofluorides **26**, **28** after debenzylation (Scheme 4).[8]



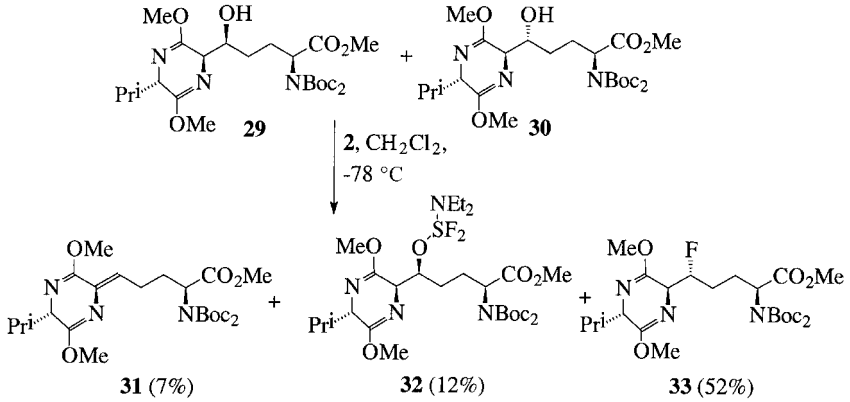
Scheme 4

Treatment of **29** and **30** with freshly distilled DAST (**2**) led to isolation of only the dehydrated compound **31**, which is formed by base elimination of the activated intermediate **32**. It has been observed that the dehydration could be suppressed by using **2** in the presence of a trace amount of water that causes the formation of HF. This results in the stabilization of the intermediate **32**, thereby allowing the preparation of the fluoro derivative **33** as a single diastereomer in 52% yield. The dehydrated product **31** was formed only in trace amounts (7%) (Scheme 5).[9]

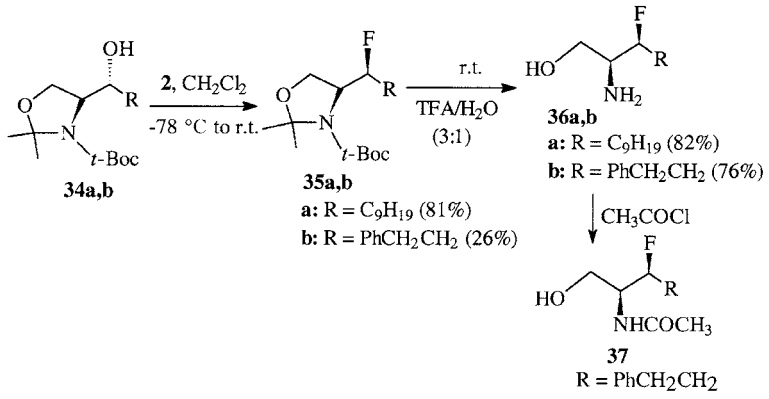
Fluorination of alcohols **34a**,**b** with **2** produced the monofluoro oxazolidines **35a**,**b** with inverted configuration. Simultaneous cleavage of the oxazolidine ring and deprotection of *t*-Boc group by treatment with trifluoroacetic acid gave the L-*threo*-3-fluorosphinganine analogues, **36a**,**b**, which could be preferentially acylated at the amino group to give **37**.(Scheme 6).[10]

Phosphonates **38**, **40**, **42**, **44** have many carbonyl groups and only one hydroxyl group in their backbone (except **42**). It has been found that they react with **2** resulting in the formation of **39**, **41**, **43**, **45** (Scheme 7).[11–13] These compounds have been designed and synthesized for reactive immunization towards the hydrolysis of organophosphorus nerve agents.[14]

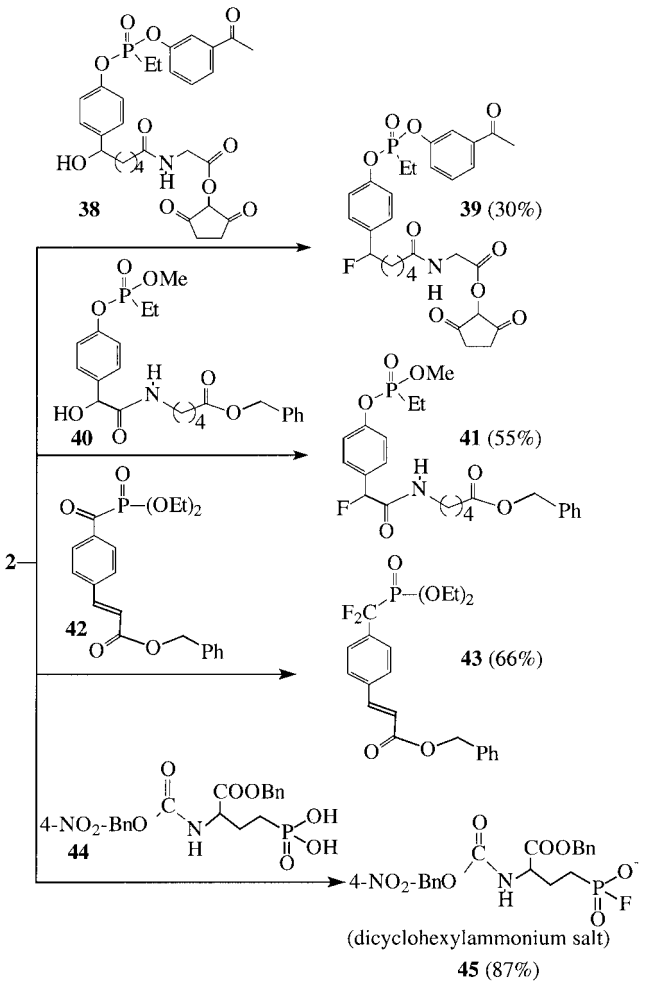
The chemistry of β-diketones with **1** and **2** has been explored, and the final products obtained were *E* and *Z* mixtures of vicinal difluoroenones. This arises from the apparent existence of keto and enol tautomerism. Leaving group flourine and secondary deuterium multiple kinetic isotope effects have been determined for the base promoted HF elimination form 4-flouro-4-(4′-nitrophenyl)-(1,1,1,3,3-D_5)butene-2-one (**47**). The latter was obtained from a β-keto alcohol (**46**) (Scheme 8).[15]



Scheme 5

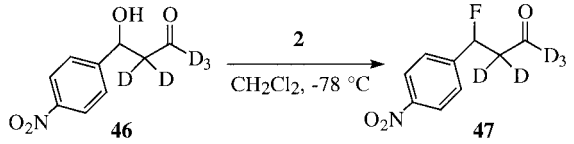


Scheme 6

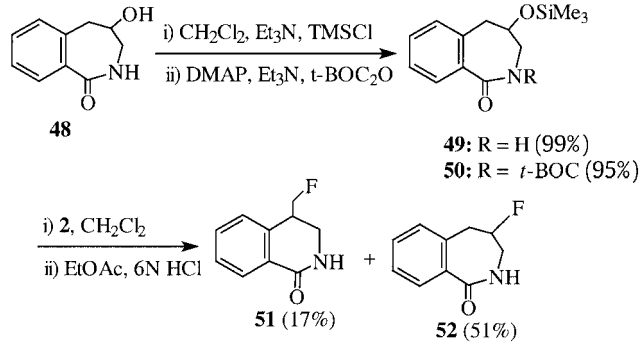


Scheme 7

Treatment of *N*, and *O*-protected **50** with **2** followed by deprotection of the amide in a biphasic mixture of aqueous 6 N HCl and EtOAc yielded **51** and **52** as a 1:3 mixture. As shown in Scheme 9, it was found that the protection of the OH group with $OSiMe_3$ and NH with Boc was necessary, because the treatment of the unprotected secondary alcohol **48** with DAST gave **51** and **52** in <5% yields.[16]



Scheme 8



Scheme 9

3.2 Carbohydrates

There are only a very small number of naturally occurring fluorinated carbohydrate compounds, an example of which is nucleocidin (**53**),[17] an antibiotic isolated from *streptomyces clavus*. Because of their low natural abundance, but widespread utility and acidity, the syntheses of fluorinated carbohydrates are of great importance. However, because numerous protection and deprotection steps are required to set up the desired hydroxyl group for substitution with fluorine, introduction of fluorine into a carbohydrate moiety is difficult. Deoxofluor (**1**) and DAST (**2**) have been utilized for such molecules (Table 2).[6,18–29]

Table 2 Fluorination of Hydroxyl Group Located on a Pyranoside Ring

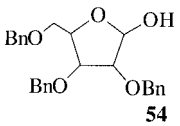
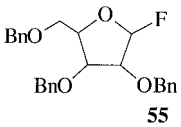
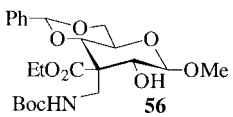
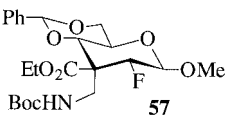
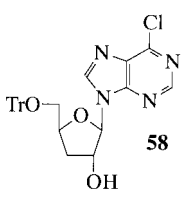
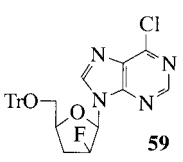
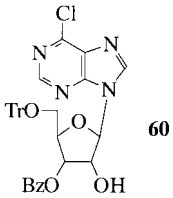
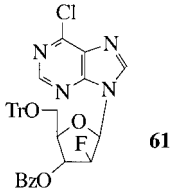
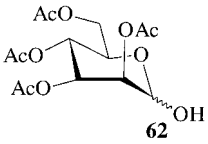
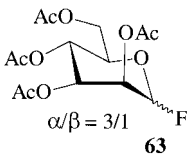
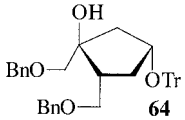
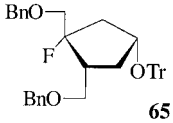
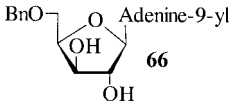
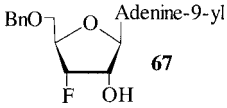
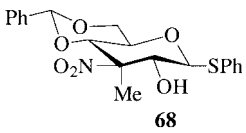
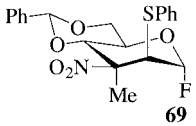
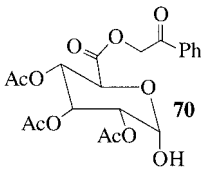
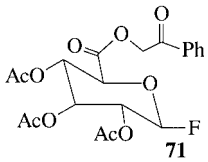
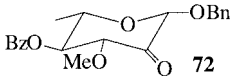
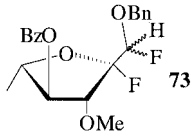
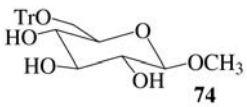
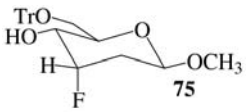
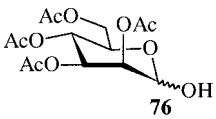
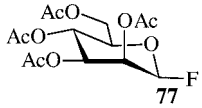
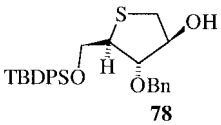
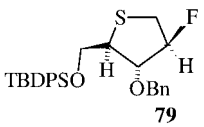
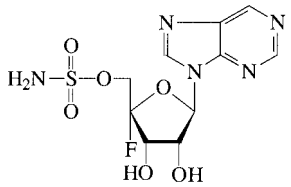
Reactant	Reagent	Conditions[a]	Product	Yield (%)	Ref.
 **54**	1	r.t., 0.5 h	 **55**	98 α/β = 9:91	6
 **56**	2	reflux, 5 h	 **57**	51	18
 **58**	2	pyridine, reflux, 4 h	 **59**	42.6	19

Table 2 Fluorination of Hydroxyl Group Located on a Pyranoside Ring (continued)

Reactant	Reagent	Conditions[a]	Product	Yield (%)	Ref.
 **60**	2	pyridine, reflux, 5 h	 **61**	78	20
 **62**	2	r.t., 0.5 h	 **63**	21	21
 **64**	1	pyridine, reflux, 18 h	 **65**	43	22
 **66**	2	pyridine, reflux, 5 h	 **67**	24	23
 **68**	2	0 °C to r.t., 1 h	 **69**	97	24
 **70**	2	reflux, 2 h	 **71**	56	25
 **72**	2	r.t., 8–24 h	 **73**	52	26
 **74**	2	–40 °C to r.t., overnight	 **75**	50	27
 **76**	2	r.t., 0.5 h	 **77**	21	28
 **78**	2	r.t., 2 h	 **79**	77	29

[a] In CH_2Cl_2, unless otherwise noted.



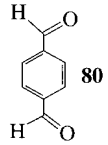
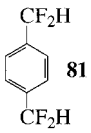
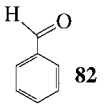
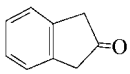
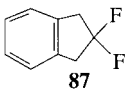
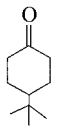
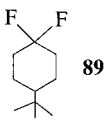
53

Figure 1 The structure of nucleocidin (**53**)

3.3 Aldehydes and Ketones

Reactions of **1** and **2** with a variety of aldehydes and ketones have been utilized in order to prepare geminal difluoro compounds. The fluorination of aldehydes and ketones was conducted in dichloromethane in the presence of catalytic amounts of HF, generated in situ, by adding trace amounts of EtOH to the reaction mixture. Reactions of structurally different aldehydes and ketones with **1** are shown in Table 3.[6]

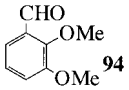
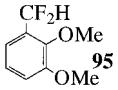
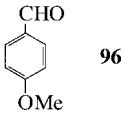
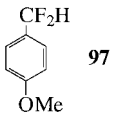
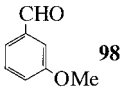
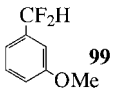
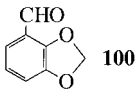
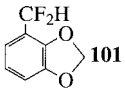
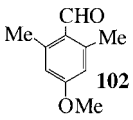
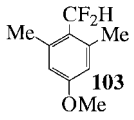
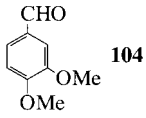
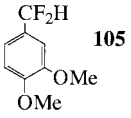
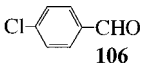
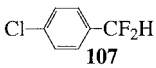
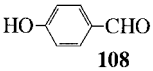
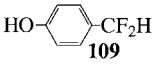
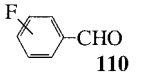
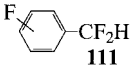
Table 3 Fluorination of Aldehydes and Ketones with **1**[6]

Starting Material	Reaction Conditions[a]	Product	Yield (%)
 **80**	**1** (3.0 equiv), reflux, 16 h	 **81**	94
 **82**	**1** (1.7 equiv), r.t., 16 h	 **83**	95
$PhOCOCH_3$ **84**	**1** (1.7 equiv), r.t., 16 h, HF (0.2 equiv)	$PhOCF_2CH_3$ **85**	98
 **86**	**1** (1.7 equiv), r.t., 16 h, HF (0.2 equiv)	 **87**	42
 **88**	**1** (1.7 equiv), r.t., 16 h, HF (0.2 equiv)	 **89**	85
$PhCOCO_2Et$ **90**	**1** (1.7 equiv), r.t., 16 h, HF (0.2 equiv)	$PhCF_2CO_2Et$ **91**	81
$PhCOCH_3$ **92**	**1** (1.5 equiv), neat, 85 °C, 16 h	$PhCOCH_3$ **93**	92

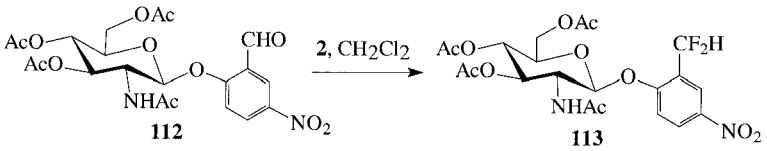
[a] Except for the reaction with $PhCOCH_3$, which is neat, all reactions were carried out in CH_2Cl_2.

We have also studied the reaction of various substituted aromatic aldehydes with **1**.[30] Reactions of solid substrates were carried out in dichloromethane, whereas neat conditions were used for liquids (Table 4). A critical analysis of the reaction conditions reveals that an electron-donating substituent, such as OMe at the *meta*-position of the aromatic ring, has no influence on the reactivity and, consequently, 100% conversion of the aldehyde moiety to difluoromethyl is achieved. However, the same substituent at the *ortho*- or *para*-position reduces the electrophilic character of the CHO functionality (Table 4). As a result, the presence of HF and higher temperatures are necessary to drive such reactions to completion. Treatment of the *meta*-nitro substituted aldehyde **112** with **2** gave the corresponding difluoro aryl derivative **113** in 60% yield (Scheme10).[31]

Table 4 Fluorination of Substituted Aromatic Aldehydes with **1**[30]

Substrate	Conditions	Product	Conversion (%)	Yield (%)
 **94**	CH_2Cl_2, 45 °C, 16 h	 **95**	83	70
 **96**	neat, 75 °C, 16 h	 **97**	57	44
 **98**	neat, r.t., 16 h	 **99**	100	94
 **100**	CH_2Cl_2, 45 °C, 16 h	 **101**	80	65
 **102**	CH_2Cl_2, 45 °C, 12 h	 **103**	90	62
 **104**	CH_2Cl_2, 45 °C, 16 h	 **105**	80	68
 **106**	CH_2Cl_2, r.t., 3 h	 **107**	100	90
 **108**	CH_2Cl_2, r.t., 8 h	 **109**	100	85
 **110**	neat, r.t., 8 h	 **111**	100	80

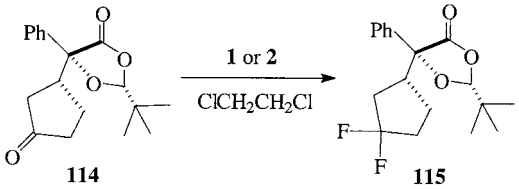
It has been observed that the difluorination of **114** with SF_4/HF was not very successful, but the use of **1** at 40 °C gave the product **115** in 80% yield.[32] Using **2** as a fluori-



112 **113**

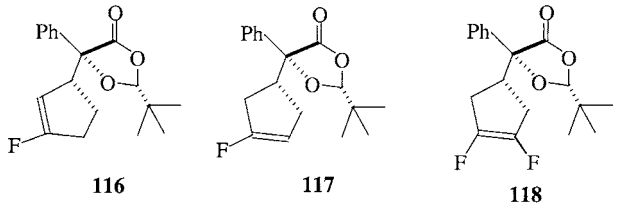
Scheme 10

nating reagent, the formation of **115** can be achieved in comparable yield, but the reaction required drastic conditions (high temperature) (Scheme 11). Despite the good yield of **115**, impurities **116**, **117** and **118** were also formed and were difficult to separate (Figure 2). The use of an acid, such as CF_3CO_2H or $BF_3{\cdot}OEt_2$, as an additive reduced the formation of the byproducts.



114 **115**

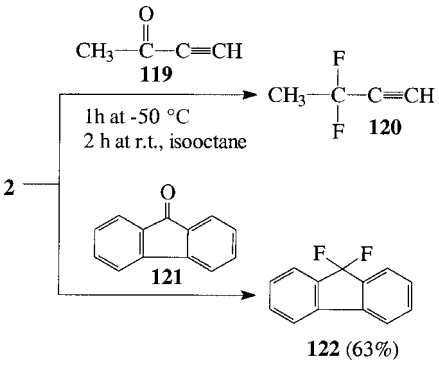
Scheme 11



116 **117** **118**

Figure 2 The structures of the side products **116**, **117**, **118** obtained in the reaction of **1** with **114**

Reaction of but-1-yn-3-one (**119**) with **2** in anhydrous isooctane at –50 °C for 1 hour followed by 2 hours at room temperature led to the formation of 3,3-difluorobut-1-yne (**120**) (Scheme 12). Raman and infrared spectra, vibrational assignment, internal rotation barrier and *ab initio* calculations of **120** have been described.[33] 9,9-Difluorofluorene (**122**) has been also synthesized from **121** using **2** (Scheme 12).[34]

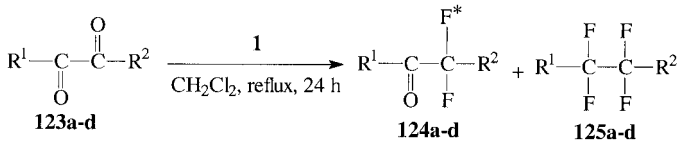


Scheme 12

3.4 Dicarbonyls

Recently we have studied the reactions of various dicarbonyl compounds with **1**.[35] The reactivities of α-diketones with **1** are very much dependent on the nature of the substituents vicinal to the keto functionalities (Scheme 13). For example, the reaction of benzil (**123a**) with 3 equivalents of **1** in the presence of a catalytic amount of HF, gave the corresponding tetrafluoro derivative **125a** in 75% yield with concomitant formation of the difluoro product **124a**. However, the reaction of 1-phenylpropane-1,2-dione (**123c**) with an excess of **1** under similar reaction conditions gave the difluoro compound **124c** in 88% yield with the tetrafluoro derivative **125c** being observed only in trace amounts (Scheme 13).[35] The phenyl groups adjacent to the diketo system apparently activate the nucleophilicity of the ketonic carbons due to the electron-withdrawing nature of the groups and the conjugation of the compounds. The alkyl group, as an electron-releasing group, deactivates one of the carbonyl carbons.

Both symmetrical and unsymmetrical β-diketones **126e**–**g** were found to be more reactive with **1** than α-diketones, with the products obtained being the vicinal di-



123a-d **124a-d** **125a-d**

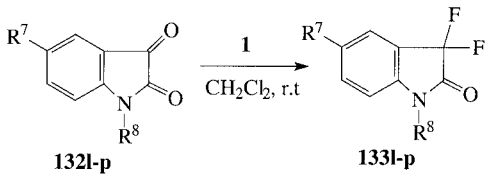
a: $R^1 = R^2 = Ph$;
b: $R^1 = R^2 = 4\text{-Me-}C_6H_4$
c: $R^1 = Me$, $R^2 = Ph$
d: $R^1 = Me$, $R^2 = Et$ (* addition occurred at either carbonyl)

Scheme 13

fluoroenones that were isolated in good yields as a mixture of (*E*)-**127e–g** and (*Z*)-**128e–g** isomers (Scheme 14).[35] In general, the reaction of β-diketones with **1** and **2** were found to be similar. However, with **2,** the yield of the vicinal difluoroenone was found to be low (40–60%) and longer reaction time was required (48–64 h) to reach completion.[36]

Reaction with **1** was found to be sluggish at 25 °C when the carbonyl groups in **129h–k** are separated by two methylene spacers or an aromatic moiety. However, when the temperature was raised to 60 °C for 24 hours in the presence of a catalytic amount of HF, the difluoro products **130h–k** were obtained in moderate yields (Scheme 15). These were slowly converted into the corresponding tetrafluoro products **131h–k**.[35]

Deoxofluor (**1**) reacted poorly with acyclic α-keto amides, such as $PhCOCONEt_2$ whereas with 3 equivalents of **1** in refluxing dichloromethane for 24 hours $PhCF_2CONEt_2$ was isolated in 20% yield. The yield of the product did not change even after refluxing for 72 hours. On the other hand, cyclic α-keto amides **132l–p** react with **1** in the presence of a catalytic amount of HF at room temperature for 8 hours to give difluoro products **133l–p** in excellent isolated yields (Scheme 16).[35]



l: $R^7 = H$, $R^8 = Ph$
m: $R^7 = H$, $R^8 = Me$
n: $R^7 = H$, $R^8 = CH_2Ph$
o: $R^7 = F$, $R^8 = CH_2Ph$
p: $R^7 = OCF_3$, $R^8 = CH_2Ph$

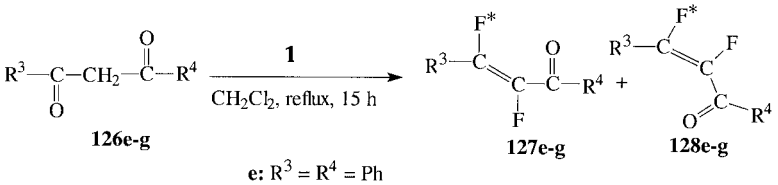
Scheme 16

3.5 Sulfides, Sulfoxides, Thioesters and Thiocarbonyls

The α-fluorosulfides have proven to be important fluorinating intermediates leading to β-lactams, amino acids, and other medicinally active compounds.[37] Sulfides **134**, **136** react with **1** in a manner analogous to **2** to produce α-fluorosulfoxides **135**, **137** in excellent yields after oxidation (Table 5).[6] An α-fluorosulfide **139** was also isolated from **138** in 83% yield. Phenyl methyl sulfoxide (**140**) as well as the more complicated 2′-aryl sulfoxide substituted nucleoside, 3′,5′-di-*O*-acetyl-2′-*S*-(4-methoxyphenyl)-2′-sulfinyluridine (**142**) were also fluorinated with **1** to give the corresponding fluorinated products **141**, **143** in very good yields after reduction with NBS. Fluorination of the thioester, PhCSOMe (**144**), proceeded well with **1** in the presence of a catalytic amount of HF to furnish **145** (Table 5).[6]

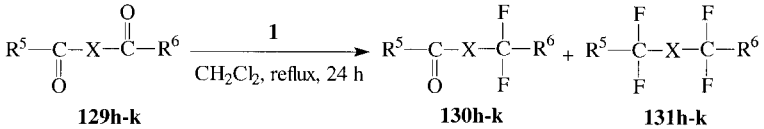
Various α-fluorinated ethers **147a–d**, **149** were also prepared by treatment of sulfoxides **146a–d**, **148** with 1.5 equivalents of **2** in dichloromethane at ambient temperature (Scheme 17).[38]

Interestingly, it has been found that neither **1** nor HF/pyridine alone can fluorinate diaryl sulfoxides. However, S-fluorination can be affected by activating the sulfoxides via protonation with HF/pyridine (70:30) to form sulfoxonium ions **150** in equilibrium with **1** which are then S-fluorinated in situ with **1** to give Ar_2SF_2 compounds **151a–f** (Scheme 18).[39] Here, the conversion strongly depends on steric factors and the



e: $R^3 = R^4 = Ph$
f: $R^3 = R^4 = Me$
g: $R^3 = Me$, $R^4 = Ph$ (* addition occurred at either carbonyl)

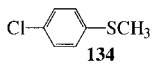
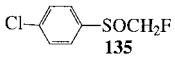
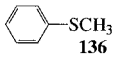
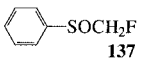
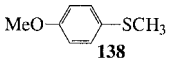
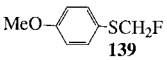
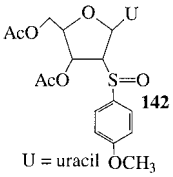
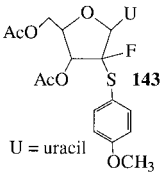
Scheme 14



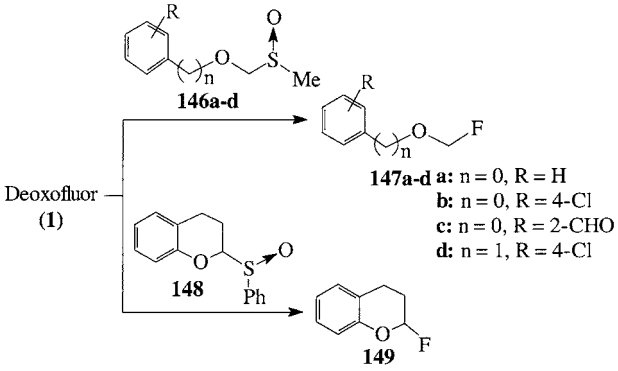
h: $R^5 = R^6 = Ph$, X = -CH=CH-
i: $R^5 = R^6 = Me$, X = $-C_6H_4C_6H_4-$
j: $R^5 = R^6 = Ph$, X = $-CH_2CH_2CH_2-$
k: $R^5 = R^6 = Me$, X = $-CH_2CH_2-$

Scheme 15

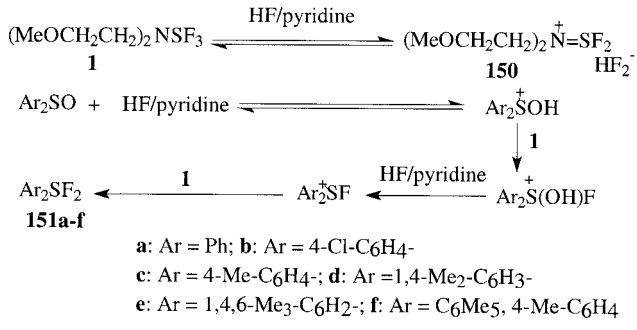
Table 5 Fluorination of Sulfur Compounds with **1**[6]

Starting Material	Conditions[a]	Product	Yield (%)
 **134**	i) 48 h; ii) NBS, MeOH–H_2O, 0 °C, 0.5 h	 **135**	95
 **136**	i) 18 h; ii) NBS, MeOH–H_2O, 0 °C, 0.5 h	 **137**	94
 **138**	3 h	 **139**	83
$PhSOCH_3$ **140**	18 h	$PhSCH_2F$ **141**	82
 **142**	16 h	 **143**	80
$PhCSOCH_3$ **144**	3 h	$PhCF_2OCH_3$ **145**	96

[a] All reactions were run in CH_2Cl_2 with **1** and $SbCl_3$.



Scheme 17

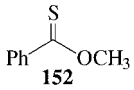
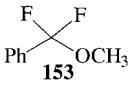
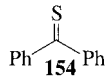
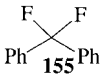
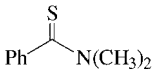
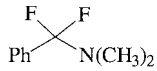
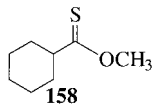
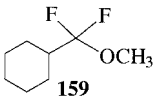
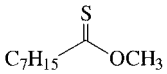
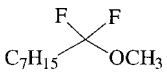
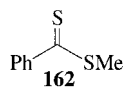
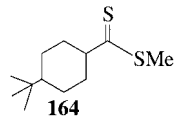
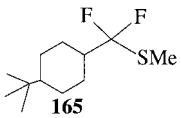
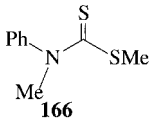
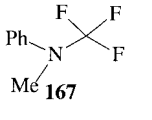


Scheme 18

reactions require the use of excess Deoxofluor (**1**) and HF/pyridine.

A variety of thiocarbonyl derivatives, **152**, **154**, **156**, **158**, **160**, **162**, **164**, **166** (thioketones, thioesters, thioamides, dithioesters, and dithiocarbamates) were converted to the corresponding *gem*-difluorides **153**, **155**, **157**, **159**, **161**, **163**, **165**, **167** in good yields on reaction with Deoxofluor (**1**) (Table 6).[40]

Table 6 Fluorination of Thiocarbonyls with **1**[6]

Starting Material	Conditions[a]	Product	Yield (%)
 **152**	4 h	 **153**	96
 **154**	48 h	 **155**	89
 **156**	48 h	 **157**	78
 **158**	0.5 h	 **159**	95
 **160**	2 h	 **161**	95
 **162**	1 h	 **163**	71
 **164**	1 h	 **165**	74
 **166**	4 h	 **167**	95

[a] All reactions with **1** were in CH_2Cl_2 with $SbCl_3$ at r.t.

3.6 Carboxylic Acids and Acid Chlorides

It has been shown that **1** can be used for the synthesis of trifluoromethyl substituted aromatic and aliphatic compounds from the corresponding carboxylic acid or acid chlorides. A facile initial conversion to the carbonyl fluoride is achieved by the reaction of **1** with carboxylic acid or acid chloride at 0 °C. The monofluoro product is then heated at 85 °C with **1** under neat conditions to obtain the trifluoromethyl derivatives (Table 7).[6] It was reported that **1** converted various *tert*-butoxycarbonyl and benzyloxycarbonyl protected amino acids into the corresponding

Table 7 Fluorination of Carboxylic Acids and Acid Chlorides with **1**[6]

Starting Material	Conditions	Product	Yield (%)
$C_{11}H_{23}CO_2H$	0 °C, 0.5 h[a]	$C_{11}H_{23}COF$	97
$PhCO_2H$	0 °C, 0.5 h[a]	PhCOF	96
PhCOCl	0 °C, 0.5 h[a]	PhCOF	95
PhCOF	48 h[b]	$PhCF_3$	58
$C_{11}H_{23}COF$	85 °C, 48 h[b]	$C_{11}H_{23}CF_3$	63

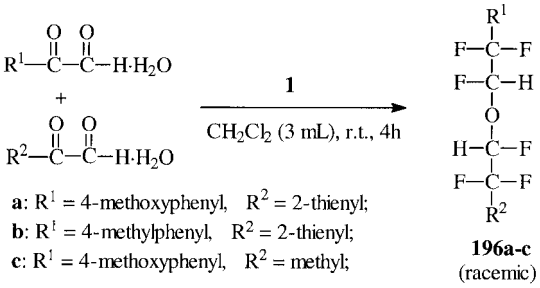
[a] Deoxofluor (**1**) in CH_2Cl_2.
[b] No solvent was used.

amino acid fluorides. All of the compounds have been isolated as crystalline solids in good yields and high purity.[41]

3.7 Glyoxal Hydrates and Anhydrous Glyoxals

Reactions of **1** with glyoxal hydrates and glyoxals have been studied. In concentrated solutions of dichloromethane, a variety of glyoxal hydrates are effectively fluorinated to form polyfluoroethers as meso and racemic mixtures (~1:1) in good yields (Table 8).[42] The meso and racemic compounds were separated by flash chromatography.

Under similar reaction conditions, when the reactant was a mixture of two different glyoxal hydrates, mixed polyfluoro ethers **196a–c** were formed as the major products . The yields of the mixed polyfluoro ethers depend on the ratio of the different glyoxal hydrates used (Scheme 19).[42]



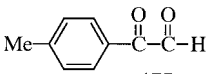
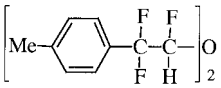
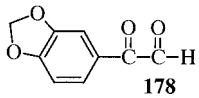
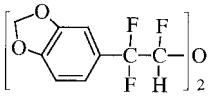
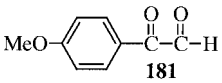
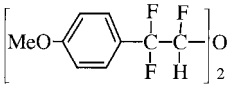
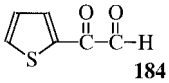
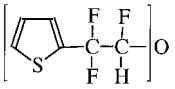
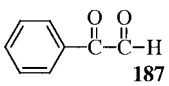
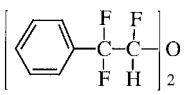
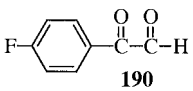
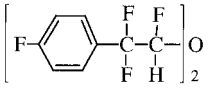
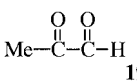
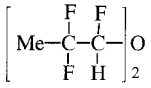
a: R^1 = 4-methoxyphenyl, R^2 = 2-thienyl;
b: R^1 = 4-methylphenyl, R^2 = 2-thienyl;
c: R^1 = 4-methoxyphenyl, R^2 = methyl;

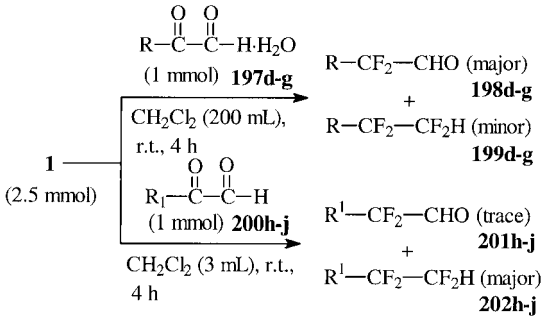
196a-c (racemic)

Scheme 19

Interestingly, when glyoxal hydrates **197d–g** were reacted with **1** under very dilute conditions, difluoroaldehydes **198d–g** or tetrafluoroalkanes **199d–g** were formed rather than polyfluoro ethers (Scheme 20). Also, the reactions of concentrated solutions of nonhydrated glyoxals **200h–j** in dichloromethane with Deoxofluor (**1**) produced the tetrafluoroalkanes **202h–j** in good yields with only a trace amount of difluoroaldehydes **201h–j** being formed (Scheme 20).[42]

Table 8 Reaction of Glyoxal Hydrates with **1** at Room Temperature[42]

Substrate (as hydrate)	Product	Yield (%) meso	Yield (%) racemic
 **175**		**176** (47)	**177** (46)
 **178**		**179** (47)	**180** (44)
 **181**		**182** (48)	**183** (45)
 **184**		**185** (44)	**186** (46)
 **187**		**188** (45)	**189** (46)
 **190**		**191** (45)	**192** (45)
 **193**		**194** (21)	**195** (24)

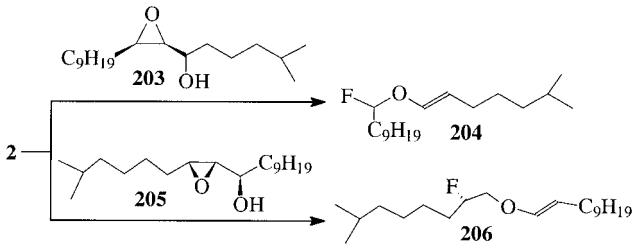


d: R = 4-methoxyphenyl; **e**: R = 3,4-methylenedioxyphenyl;
f: R = 4-methylphenyl; **g**: R = 4-fluorophenyl;
h: R^1 = 4-cyclohexylphenyl; **i**: R^1 = 4-biphenyl;
j: R^1 = 4-nitrophenyl

Scheme 20

3.8 Epoxides (Oxiranes)

An unusually easy C–C bond cleavage was observed when epoxy alcohols **203**, **205** are reacted with **2**, leading exclusively to monofluoro vinyl ethers **204**, **206** (Scheme 21).[43,44]



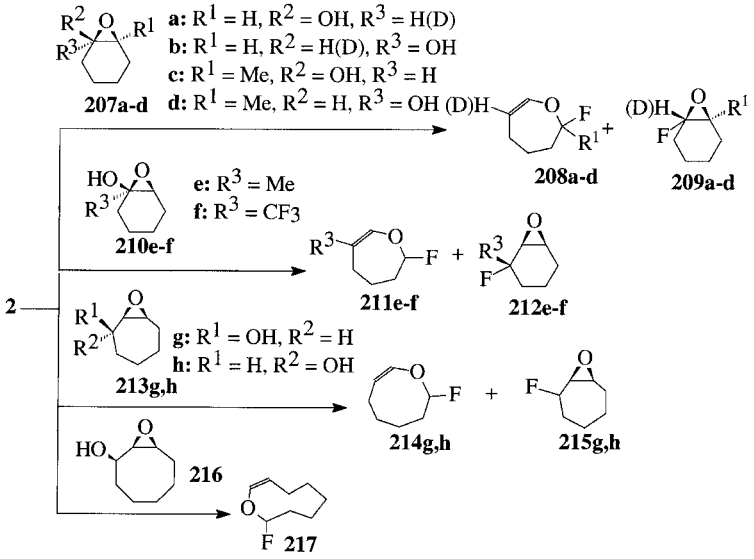
Scheme 21

Based on the above results, the chemistry of bicyclic epoxy alcohols with **2** led to the formation of new ring expansion products. Various bicyclic epoxides were reacted with **2** to synthesize oxygenated heterocycles by ring expansion (Scheme 22).[43]

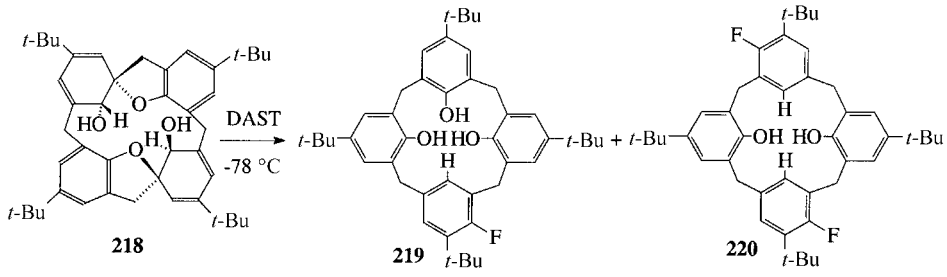
Extraannular fluorinated calixarenes **219**, **220** were prepared by the reaction of **2** with bis(spirodienol) derivatives (epoxy compounds, **218**) (Scheme 23).[45]

3.9 Peptides

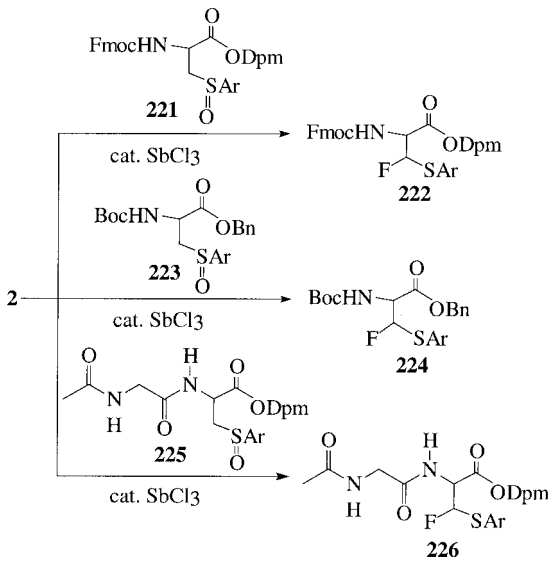
Peptides containing (*E*)- and (*Z*)-3-fluorodihydroalanine have been reported from serine via a fluoro-Pummerer rearrangement using **2** (Scheme 24).[46]



Scheme 22



Scheme 23



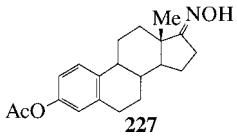
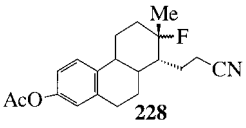
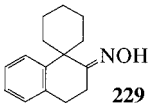
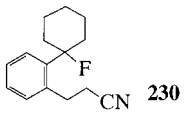
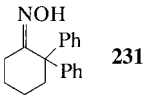
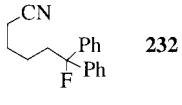
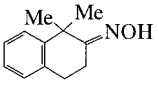
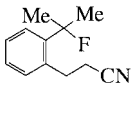
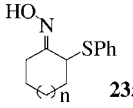
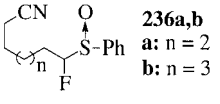
Scheme 24

3.10 Ketoximes

DAST (**2**) reacted with cyclic ketoximes that have carbocation-stabilizing substituents to cause fluorinative fragmentation thus affording fluorinated carbonitriles (Table 9) in good yields. Ketoximes that lacked such substituents afforded complex mixtures.

However, the introduction of a sulfur-containing functionality into the ketoxime which can stabilize a carbocation and can be easily removed from the reaction products was effective for producing fluorinative fragmentation.[47]

Table 9 Reaction of **2** with Ketoximes[47]

Substrate	Product	Yield (%)
 **227**	 **228**	63
 **229**	 **230**	91
 **231**	 **232**	75
 **233**	 **234**	77
 **235a,b**	 **236a,b** **a:** n = 2 **b:** n = 3	51 75

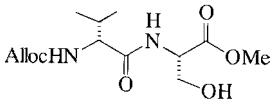
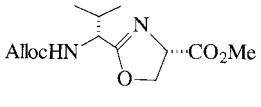
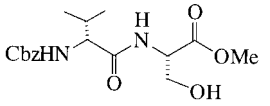
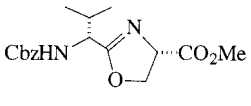
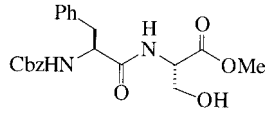
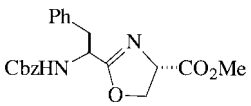
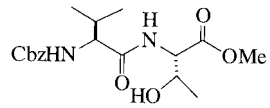
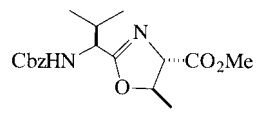
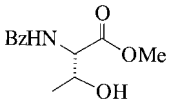
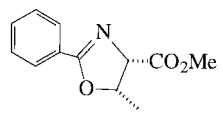
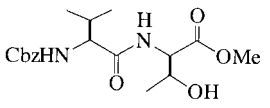
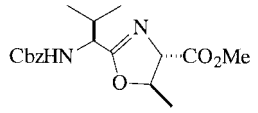
4 Miscellaneous Reactions

Deoxofluor (**1**) and DAST (**2**) are nucleophilic fluorinating reagents but under certain conditions, some novel organic syntheses have resulted.

4.1 Synthesis of Functionalized Oxazolines and Oxazoles

A mild and highly efficient cyclization of β-hydroxy amides to oxazolines is reported using **1** as well as **2** (Table 10).[48] In these reactions, dehydration takes place easily in their presence. Various peptidyl β-hydroxy amides have been cyclized with **1** (1.1 equiv) at –20 °C in the presence of a base. In general, the yields obtained with **1** are comparable to those obtained with **2** (Table 10).

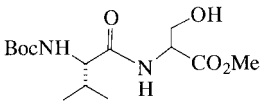
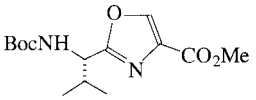
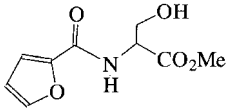
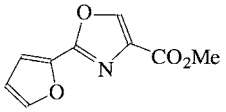
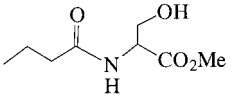
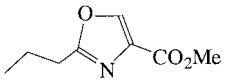
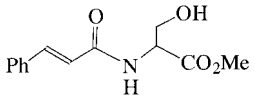
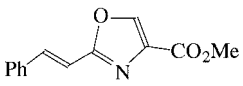
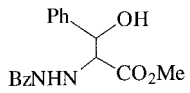
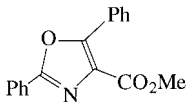
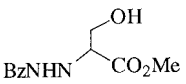
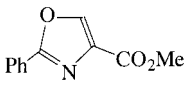
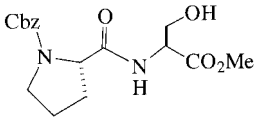
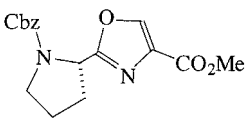
Table 10 Comparative Data for the Cyclization of Peptidyl-β-hydroxy Amides to Oxazolines with **1** and **2**[48]

Substrate	Product	Yield (%) **1/2**
 **237**	 **238**	80/90
 **239**	 **240**	83/92
 **241**	 **242**	72/86
 **243**	 **244**	72/72
 **245**	 **246**	91/86
 **247**	 **248**	72/27

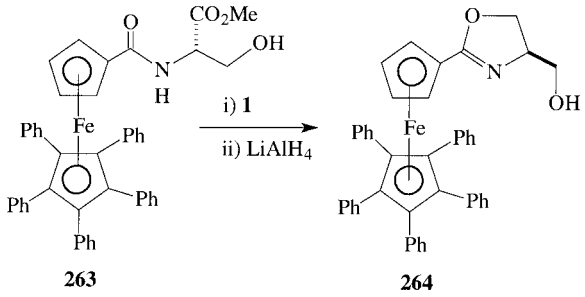
Reagent **1** has been also used to prepare various oxazoles in one pot reactions. Treatment of β-hydroxy amides with a slight excess of **1** (1.1 equiv at –20 °C for 0.5 h), followed by bromotrichloromethane and 1,8-diazabicy-

clo[5.4.0]undec-7-ene (DBU) led to the formation of oxazoles (Table 11).

Table 11 One-Pot Cyclizations of β-Hydroxy Amides to Oxazole with **1**[48]

Substrate	Product	Yield (%)
 **249**	 **250**	62
 **251**	 **252**	67
 **253**	 **254**	49
 **255**	 **256**	88
 **257**	 **258**	70
 **259**	 **260**	82
 **261**	 **262**	65

In the presence of **1**, the (*S*)-serine methyl ester **263** is readily transformed into 4-(hydroxymethyl)oxazoline ligand **264** containing 2-(1,2,3,4,5-pentaphenyl)ferrocene in excellent yield (Scheme 25).[49]



263 **264**

Scheme 25

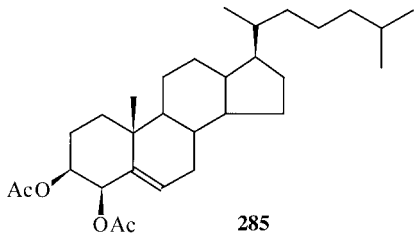
4.2 Synthesis of Amides from Carboxylic Acids50

N-Methoxy-*N*-methyl amides are useful building blocks in organic synthesis. Several methods are known to convert carboxylic acids to the corresponding amides by using coupling reagents which are expensive and also it is difficult to remove the excess of reagents.

Since it converts carboxylic acids to the corresponding acid fluorides, Deoxofluor (**1**) was found to be a suitable reagent for the synthesis of such amides. These can be then reacted with *N*,*O*-dimethylhydroxylamine to give the corresponding amides in high yields The reaction proceeds without racemization when optically active acids are used as the starting materials to provide the products in high purity (Table 12).

4.3 Synthesis of Cholest-5-ene-3b,4b-diyl Diacetate (Steroid)

The steroid **285** was prepared in 62% yield by the reaction of **2** (7.5 mmol) with 5α-hydroxycholestan-3β,4β-diacetate in glyme. Its structure has been confirmed by single crystal X-ray analysis.[51]



285

Figure 3 The structure of cholest-5-ene-3β,4β-diyl diacetate (**285**)

4.4 Cycloetherization

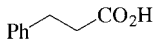
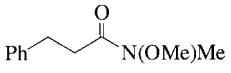
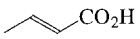
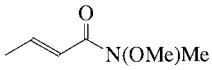
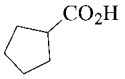
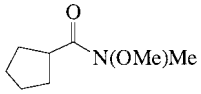
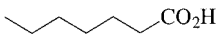
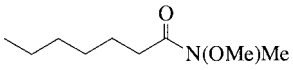
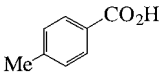
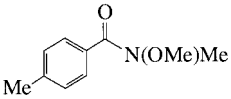
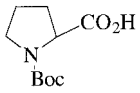
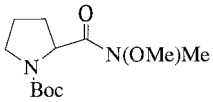
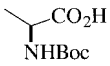
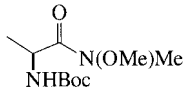
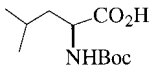
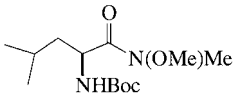
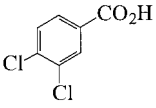
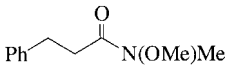
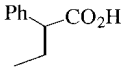
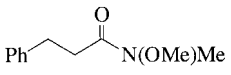
Using **2**, compound **286** was converted into a cyclic ether derivative **287** (Scheme 26).[52] An unexpected epimerization resulting from the reaction of α-D-glucopyranosyl derivative with **2** has been also reported.

5 Reaction Mechanisms Using Deoxofluor (1) and DAST

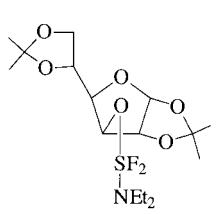
5.1 Alcohols

The reaction mechanism of nucleophilic fluorination of simple alcohols using **1** and **2** are similar. The first step is the nucleophilic displacement of fluorine on sulfur by oxygen of the hydroxy compound followed by the elimination of hydrogen fluoride (Scheme 27). Intermediate **288** has not been isolated but the existence of compound **289** is supported by ^{19}F NMR spectral data.[53] An intermediate

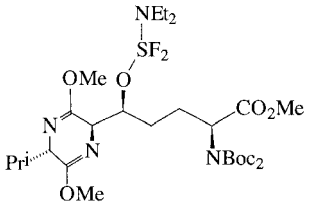
Table 12 Synthesis of Amides from Carboxylic Acids and HN(OMe)Me with **1**[50,]

Acid	Product	Yield (%)
 **265**	 **266**	86
 **267**	 **268**	73
 **269**	 **270**	85
 **271**	 **272**	82
 **273**	 **274**	91
 **275**	 **276**	86
 **277**	 **278**	90
 **279**	 **280**	91
 **281**	 **282**	92
 **283**	 **284**	83

of type **290** (Figure 4) has also been isolated as a single diastereomer and found to be stable to column chromatography. Compound **290** has been characterized by using IR, NMR (^{1}H, ^{19}F, ^{13}C) and HRMS.[9]

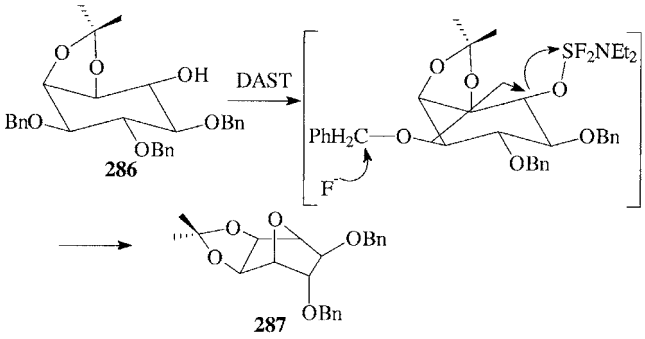


289



290

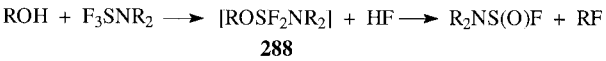
Figure 4 The structure of intermediates **289**, **290** in the conversion of alcohols to fluorides



286

287

Scheme 26



288

Scheme 27

β-Diketones exist in keto **291** and enol **292** forms. The enol form **292** reacts with one molecule of **1** or **2**. The hydroxyl group is replaced by fluorine, and an α-fluoro derivative **294** is formed which also exists in equilibrium with the enol form **295**. This then reacts with another molecule of the fluorinating reagent to yield α,β-difluoro products **297** as a mixture of equal parts of *E*- and *Z*-isomers. (Scheme 28).[35]

5.2 Aldehydes and Ketones

In contrast to the reaction of **1** and **2** with hydroxy compounds, no sulfur- and nitrogen-containing intermediates have been claimed in the reaction of aldehydes and ketones. It has been suggested that the initial step is the addition of HF, formed from the reagent and traces of water, across the carbonyl group. The resulting α-fluoro alcohol then reacts with the aminosulfur reagent as described above as for alcohols (Section 5.1) and affords intermediate **298** (Scheme 29).

5.3 Carboxylic Acids

The formation of acyl fluorides from carboxylic acids proceeds by a mechanism analogous to that of the reaction of alcohols with **1** and **2**. The conversion of the carboxyl

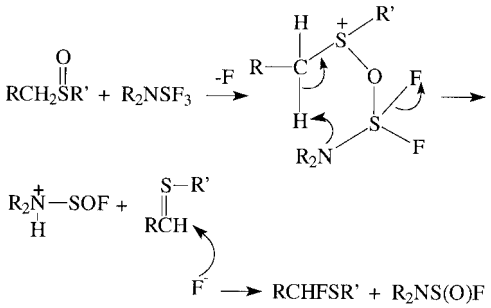
group into a trifluoromethyl group occurs by a mechanism analogous to that for aldehydes and ketones (Section 5.2).

5.4 Sulfoxides

The reaction of **1** and **2** with dialkyl or aryl alkyl sulfoxides having at least one α-hydrogen atom gives α-fluorosulfides. The proposed mechanism is very similar to that of a Pummerer rearrangement (Scheme 30).[54]

5.5 Glyoxal Hydrates

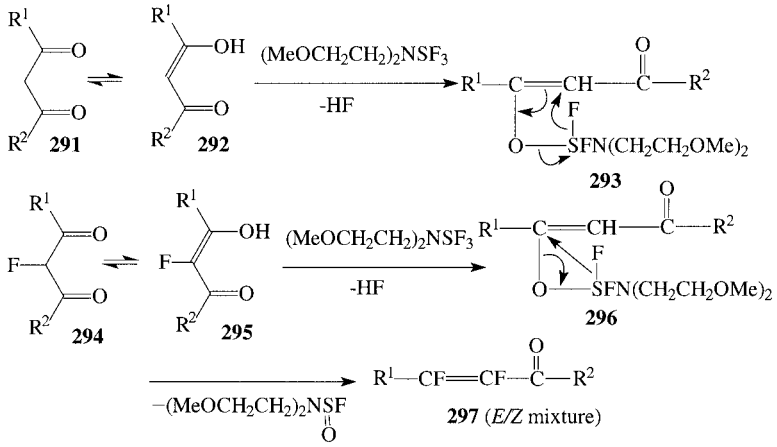
The mechanism for the formation of difluoroaldehydes or tetrafluoroalkanes by the reaction of **1** with glyoxal hydrates in dilute solution and with anhydrous glyoxal is similar to that of the reaction with simple aldehydes or ketones. The mechanism for the formation of fluorinated symmetrical or mixed polyfluoroethers with glyoxal hydrate in concentrated solution is proposed in Scheme 31.[42] It is known that **1** fluorinates alcohols ROH, to produce the corresponding fluorinated derivative, RF. When **299** reacts, a fluorinated alcohol **300** is formed which is unstable with respect to loss of HF or **300** can react under highly concentrated conditions with HF to give an unstable intermediate **301**. Compound **300** attacks at the highly electrophilic carbon of **301**, resulting in the formation of intermediate **302**. Under acidic conditions (HF), the formation of ether **303** is quite possible. It seems as if acidic conditions would discourage the formation of HF and **303**. Under very dilute conditions, if appropriate nucleophiles are not available, the intermediates, **300**, **301** and **302** readily decompose and fail to give polyfluoroethers **303**.



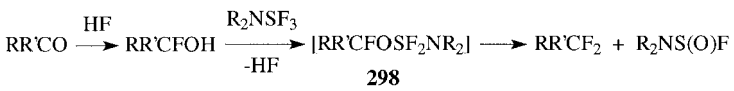
Scheme 30

5.6 Ketoximes[49]

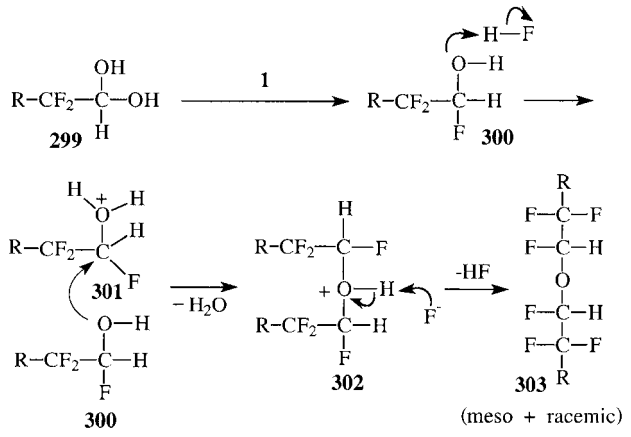
The reaction mechanism of ketoximes with **2** is depicted in Scheme 32. The first step is a nucleophilic displacement of a fluorine atom in **2** by the oxygen of the oximino substrate **304** with the subsequent elimination of HF. Next, the elimination of diethylaminosulfinyl fluoride from intermediate **305** causes bond cleavage and produces the carbocation intermediate **306**. Finally, fluoride ion attacks **306** to afford the fluorinated carbonitrile **307** (path a). In the case of compounds lacking substituents to stabilize the α-carbocation, the reaction proceeds through a mechanism similar to that of the 'normal' Beckmann rearrangement. The carbon–carbon bond *anti* to the imino leaving group in intermediate **305** migrates to the nitrogen atom to afford the carbocation **308**. The fluoride ion attacks **308** to give the unstable compound **309**, which leads to a complex mixture (path b) (Scheme 32).



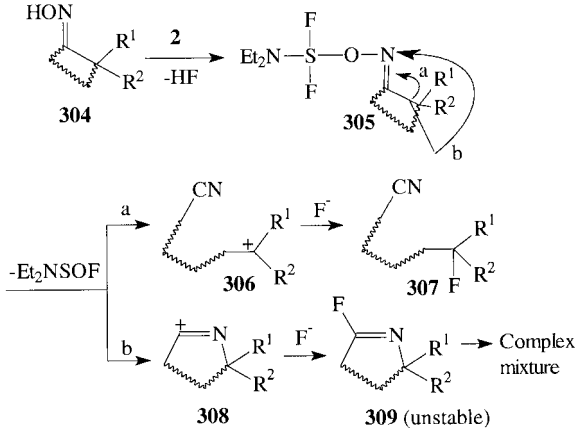
Scheme 28



Scheme 29



Scheme 31



Scheme 32

6 Conclusions

This review has highlighted the applications of Deoxofluor (**1**) and DAST (**2**) for introduction of fluorine into various organic substrates that have appeared in the literature from from January 1999 through July 2002. Various substrates, such as alcohols, aldehydes, ketones, carboxylic acids, acid chlorides, glyoxals, epoxides, peptides, and a majority of carbohydrates were converted to fluorine-containing products in a one-step process. In some of the reactions, the novel syntheses of some nonfluorinated compounds have been described in the presence of **1** or **2**.

While reactions with **1** and **2** may be carried out in glass equipment which may be superficially etched by the reaction byproducts, polyethylene or polytetrafluoroethylene reaction vessels are preferable. Fluorinations with **1** and **2** were most frequently conducted in anhydrous solvents such as CH_2Cl_2, $CHCl_3$, CCl_3F, hexane, isooctane, toluene, H_2O and glyme. In some cases, reactions were carried out effectively without solvent. Since both **1** and **2** are sensitive to hydrolysis, protection from atmospheric moisture by using an nitrogen or argon atmosphere was essential. Moisture and air sensitive products were isolated by distillation of the crude reaction mixture. In the majority of cases, the reaction mixture was worked up by pouring into an ice cold solution of $NaHCO_3$. Products were isolated by extraction with suitable solvents. Both **1** and **2** are commercially available from Aldrich and are used without purification. All the reactions carried out with **1** and **2** given below are general procedures.

Deoxofluor (1)[6]

Deoxofluor (**1**) was prepared by reacting $(CH_3OCH_2CH_2)_2NSiMe_3$ with SF_4.[6] A 300 mL stainless steel Parr reactor, equipped with a magnetic stirrer, was charged with bis(2-methoxyethyl)trimethylsilylamine (5.05 g) dissolved in Et_2O (100 mL). The reaction vessel was held at –30 °C and connected via an entry port to vacuum/pressure metal manifold through which SF_4 (37 mmol) was added slowly. After the vessel was sealed, it was warmed to 0 °C, and the contents were for stirred 3 h. Volatile compounds were then removed by passing through a soda lime trap. The remaining liquid was transferred to a 250 mL glass flask. Evaporation under vacuum resulted in 2.6 g (51%) of **1** as a light yellow liquid. It was purified by distillation in glass at 71 °C/0.4 mmHg to give a colorless liquid.

^{1}H NMR ($CDCl_3$): δ = 3.5 (t, 4 H), 3.15 (t, 4 H), 3.05 (s, 6 H).

^{19}F NMR ($CDCl_3$): δ = 55 (br s, 2 F), 28 (br s, 1 F).

DAST (2)

DAST (**2**) was obtained according to the procedure described for **1** using Et_2NSiMe_3 and SF_4.[5]

Fluorination of Alcohols with Deoxofluor (1)[6]

A solution of an alcohol (10 mmol) in anhyd CH_2Cl_2 (3.0 mL) was added at an appropriate temperature, under N_2, to a solution of **1** (2.43 g, 11 mmol) in CH_2Cl_2 (2.0 mL) in a 50 mL three-necked flask equipped with a N_2 inlet tube, septum, and a magnetic stirring bar. The progress of the reaction was monitored by GC/MS in order to determine the disappearance of the starting material. On completion, the mixture was poured into aq sat. $NaHCO_3$ (25 mL). After CO_2 evolution ceased, the solution was extracted with CH_2Cl_2 (3×15 mL), the combined CH_2Cl_2 layers were dried (Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in hexane–EtOAc afforded the pure products.

Fluorination of Aldehydes and Ketones with Deoxofluor (1)[6]

To a solution of an aldehyde or ketone (10 mmol) in CH_2Cl_2 (3.0 mL) in a 25 mL Teflon vessel equipped with N_2 inlet tube and stirring bar, was added a solution of **1** (3.76 g, 17 mmol) in CH_2Cl_2 (2.0 mL) at 25 °C (Table 3). EtOH (92 mg, 2 mmol) was added, and the mixture was stirred at r.t. GC/MS was used to monitor the progress of the reaction. On completion, the solution was poured into aq sat. $NaHCO_3$, and after the CO_2 evolution had ceased, it was extracted with CH_2Cl_2 (3×15 mL); the combined CH_2Cl_2 layers were dried(Na_2SO_4), filtered, and evaporated in vacuo. Flash chromatography on silica gel in hexane–Et_2O afforded the pure products.

Fluorination of Carboxylic Acids with Deoxofluor (1)[6]

Conversion of Carboxylic acid to Acyl Fluoride: The carboxylic acid (10 mmol) in CH_2Cl_2 (5.0 mmol) was added to **1** (2.43 g, 11 mmol) under N_2 and stirred for 16 h at 25 °C. The workup procedure was similar to that reported for fluorination of aldehydes and ketones.

Conversion of Acyl Fluoride to Trifluoromethyl Derivative: To the acyl fluoride (10 mmol) in a Teflon bottle equipped with N_2 inlet tube, was added Deoxofluor (**1**; 4.42 g, 20 mmol) and the mixture was heated to 85 °C. The progress of the reaction was monitored by GC/MS. Workup procedure was similar to that reported for aldehydes and ketones).

Fluorination of Thiocarbonyls with Deoxofluor (1)[40]

To a solution of the thiocarbonyl compound (10 mmol) in CH_2Cl_2 (3.0 mL) in a three-necked round-bottomed flask fitted with a rubber septum, stopper and N_2 inlet tube, were added $SbCl_3$ (0.01–0.1

equiv) and **1** (3.09 g, 2.57 mL, 14 mmol). The resulting solution was stirred under N_2, and the reaction was monitored by GC/MS for disappearance of the starting material. Workup procedure was as reported for aldehydes and ketones.

Fluorination of Dicarbonyls with Deoxofluor (1)[35]

In a typical experiment, the diketone (2 mmol) was dissolved in CH_2Cl_2 (5 mL). Deoxofluor (**1**; 1.32 g, 6 mmol) was added at r.t., followed by the addition of 2 drops of EtOH (to generate a catalytic amount of HF). The reaction mixture was heated at 60 °C for 24 h. The mixture was quenched by the slow addition to aq $NaHCO_3$ solution until effervescence was complete. The CH_2Cl_2 layer was separated and dried ($MgSO_4$). It was filtered and removal of the solvent gave the product.

Fluorination of Glyoxal Hydrates at High Concentration with Deoxofluor (1);[42]

In a typical experiment, an arylglyoxal hydrate (2 mmol) was dissolved in CH_2Cl_2 (3 mL), and **1** (0.993 g, 4.5 mmol) was added dropwise at r.t. The reaction mixture was stirred at 25 °C for 4 h. The reaction was quenched by the slow addition of aq $NaHCO_3$ solution until effervescence was complete. The CH_2Cl_2 layer was separated and dried ($MgSO_4$). The resulting solution was filtered and the solvent was removed at reduced pressure. The product was purified by flash chromatography. The same procedure was used to prepare the mixed polyfluoroethers.

Fluorination of Glyoxal Hydrates with Deoxofluor (1) in Dilute Solutions[42]

An arylglyoxal hydrate (1 mmol) was dissolved in CH_2Cl_2 (200 mL), and neat **1** (553 mg, 2.5 mmol) was added dropwise with vigorous stirring. The reaction mixture was stirred at 25 °C for 4 h. The workup procedure was similar as described for the reaction at higher concentration.

Fluorination of Epoxides (Oxiranes) with DAST (2)[43]

To a stirred solution of bis(spirodienol) (2.4 mmol) in anhyd CH_2Cl_2 (180 mL) at –78 °C was added **2** (6 mL, 43.5 mmol) over 10 min under an inert atmosphere. The temperature was raised slowly to 25 °C, and the mixture was stirred for 12 h. The excess of DAST was quenched with H_2O (100 mL). After phase separation, the organic phase was washed several times with H_2O and evaporated. The residue was treated with Et_2O (30 mL) and the undissolved material (a mixture of monofluorinated product and a nonfluorine-containing open ring product based on NMR) was filtered. The residue obtained after evaporation of the solvent was purified by chromatography.

Miscellaneous Reactions Mediated by Deoxofluor (1) or DAST (2)

Synthesis of Oxazolines:[48] In a general procedure, **1** (24.0 mL, 0.130 mmol) was added dropwise to a suspension of peptidyl-β-hydroxy amide (40.6 mg, 0.115 mmol) in CH_2Cl_2 (1 mL) cooled to –20 °C (Table 10). After 30 min, the reaction mixture was quenched with sat. aq $NaHCO_3$ at –20 °C. After warming to 25 °C, additonal sat. aq $NaHCO_3$ was added and the mixtures was extracted with $CHCl_3$. The combined organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (SiO_2, 1:1 hexane–EtOAc) gave the desired oxazoline as a colorless solid.

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