Electrophilic Perfluoroalkylating Agents

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Contents

I. Introduction

Compounds containing the perfluoroalkyl (R_f) group are of importance in fluorine chemistry and in industry because the R_f group has unique properties such as high electronegativity, stability, lipophilicity, and water and oil repellency.[1] Thus, many reagents have been developed to introduce the R_f group into organic molecules.[1,2] This review deals with perfluoroalkylating agents which react via electrophilic perfluoroalkylation and also with related electrophilic α,α-dihydroperfluoroalkylating agents.

Electrophilic perfluoroalkylation is one of three fundamental methods of perfluoroalkylation: nucleophilic, free radical, and electrophilic. Electrophilic perfluoroalkylation is more difficult than electrophilic alkylation in hydrocarbon chemistry. Electrophilic alkylation has been accomplished by treating alkyl halides (iodides, bromides, or chlorides) with nucleophiles, and alkyl esters such as dialkyl sulfates, alkyl tosylates, and alkyl triflates are even more reactive than the halides. These alkylating agents are each regarded as a combination of an alkyl group and a leaving group.

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As a result of the extreme difficulty in generating perfluoroalkyl cations caused by the high electronegativities of fluorine (4.0) or R_f groups (CF_3; 3.45),[3] electrophilic *perfluoro*alkylation has not been obtained in similar accord. Electrophilic perfluoroalkylation via an S_N2 mechanism may also be inhibited by steric effects in addition to these electronic effects;[4] however, perfluoroalkyl cations, especially CF_3^+, are readily observed in the gas phase during mass spectroscopic analysis of perfluorocarbons or perfluoroalkyl-containing compounds.[5] This has been attributed to the facile generation of CF_3^+, in which the lone pair electrons on the three fluorine atoms stabilize the centeral carbon cation by resonance effects.[1a] Unfortunately, perfluoroalkyl cations ob-

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tained with such high-energy gas-phase techniques cannot be applied to synthetic approaches for mild and selective reactions in solution.

Perfluoroalkyl iodides (R_f—I, **1**) are generally attacked by nucleophiles at the iodine atom instead of the carbon atom because of reverse polarization due to the low electronegativity (2.1) of the iodine atom (eq 1). These halophilic reactions have been studied

$$\underset{\mathbf{1}}{R_f\overset{\delta-}{-}I\overset{\delta+}{}} \xrightarrow{:Nu^-} R_f^- + I\text{—}Nu \qquad (1)$$

well and have provided some useful methods for preparing fluoroorganic compounds.[6] In their most recent paper, Howell et al. reported that the halophilic reaction shown in eq 2 is accompanied by a free radical chain reaction and that perfluoroalkyl bromides (R_f—Br) undergo this same halophilic reaction.[6i]

$$\underset{\mathbf{1}}{R_f\text{-}I} \xrightarrow[\text{exothermic}]{\text{NaOMe}} R_fH \quad 85\text{-}93\% \qquad (2)$$

R_f; n-C_4F_9, n-C_6F_{13}, n-C_8F_{17}, n-$C_{10}F_{21}$

In contrast to R_f—I and R_f—Br, perfluoroalkyl fluorides (R_f—F), namely perfluoroalkanes, are inert gases or fluids, and show no chemical reactivity under normal conditions.[7] And even perfluoroalkyl triflates (R_f—OTf) which combine an R_f group with OTf, one of the strongest leaving groups, still do not undergo electrophilic perfluoroalkylation;[8] the nucleophile instead attacks the sulfur.[9] (Perfluoroalkyl)aryliodonium salts and (perfluoroalkyl)chalcogen salts have therefore been turned to as electrophilic perfluoroalkylation reagents, and will be discussed in this review.

The substitution reactions of R_f—I and R_f—Br with selected nucleophiles have been extensively studied, but they will not be discussed in this review. These substitution reactions occur through a single electron transfer followed by a free radical chain reaction. Although the overall synthetic transformation is the perfluoroalkylation of a nucleophile, these substitutions are mechanistically different from the one-to-one molecular interactions characteristic of a general electrophilic reaction. R_f—I and R_f—Br have also been used for many years as reagents for nucleophilic and radical perfluoroalkylations. Several books and reviews on the reactions on R_f—I and R_f—Br have been published.[2a,10]

II. (Perfluoroalkyl)aryliodonium Salts

A. (Perfluoroalkyl)aryliodonium Chlorides and Tetrafluoroborates

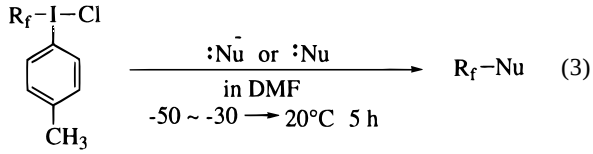
Yagupolskii et al. reported a new method for perfluoroalkylating nucleophiles such as arenethiolate, areneselenolate, nitrate, thiocyanate, and selenocyanate anions, and *N*-methyl- and *N*,*N*-dimethylaniline using (perfluoroalkyl)-*p*-tolyliodonium chlorides (**2**) in a polar solvent under mild conditions (eq 3 and Table 1).[11] Previous methods of perfluoroalkylation using R_f—I or R_f—Br required drastic conditions, such as high temperatures or UV irradiation. Each reaction of **2** produced *p*-iodotoluene quantitatively.

Table 1. Perfluoroalkylation of Nucleophiles with 2

Run	Nucleophile	2	Product R_f-Nu	Yield (%)
1	PhSNa	R_f=C_3F_7	$PhSR_f$	81
2	*p*-Tolyl-SNa	C_3F_7	*p*-Tolyl-SR_f	96
3	*p*-O_2N-C_6H_4SNa	C_3F_7	*p*-O_2N-C_6H_4-SR_f	56
4	PhSeNa	C_3F_7	$PhSe(O)R_f$*	87
5	*N*-methylaniline	C_3F_7	*p*-R_f-*N*-methylaniline	36
6	*N*,*N*-dimethylaniline	C_3F_7	*p*-R_f-*N*,*N*-dimethylaniline	35
7	$NaNO_2$	C_6F_{13}	R_fNO_2	60
8	KSCN	C_3F_7	R_fSCN	59
9	KSeCN	C_3F_7	R_fSeCN	45

* The reaction mixture was treated with Cl_2.

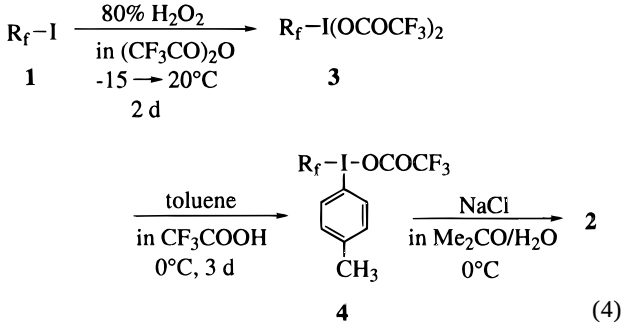
Also, although *p*-perfluoroalkylated anilines were obtained from the aniline reactions, the yields of these products were low (runs 5 and 6 in Table 1).



(3)

2 (R_f=n-C_3F_7, n-C_6F_{13})

The chlorides **2** were prepared in 70% overall yield by oxidation of **1** with trifluoroperacetic acid to form **3**, followed by condensation with toluene and subsequent treatment with sodium chloride.[11] Condensation with benzene instead of toluene was very slow under these conditions.[11]



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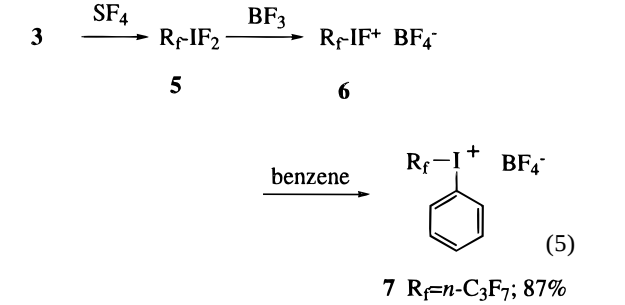
Yagupolskii et al. later reported the synthesis of the (perfluoroalkyl)phenyliodonium tetrafluoroborates **7** and **8** as shown in eq 5.[12] These tetrafluo-



(5)

7 R_f=n-C_3F_7; 87%
8 R_f=n-C_6F_{13}; 83%

roborates were more effective perfluoroalkylating agents than were the chlorides. The perfluoroalkylation of dibenzocrown-ethers using **8** was reported a decade after the synthesis of **8**.[13]

B. (Perfluoroalkyl)phenyliodonium Triflates (FITS Reagents) and Their Analogs

In the course of our work, we became independently aware of the low reactivities and stabilities of the chlorides **2**. These compounds were unable to react with alkenes, alkadienes, nonactivated aromatics, and other relatively non-nucleophilic compounds. We therefore developed the (per*f*luoroalkyl)phenyl-*i*odonium *t*rifluoromethanesulfonates (FITS reagents) **9** and **10**, their *p*-fluorophenyl analogs [FITS(F)] **11** and **12**, and the (per*f*luoroalkyl)phenyl*i*odonium hydrogensulfates **15** (FIS) and **16** [FIS(F)] as highly reactive electrophilic perfluoroalkylating agents.[14] The OTf group increased the reactivity of the iodonium salts the most, while the phenyl and *p*-fluorophenyl groups increased the salts' stabilities relative to the tolyl salt. (Perfluoropropyl)-*p*-tolyliodonium triflate formed unstable crystals which decomposed largely within a day at room temperature. In contrast, the mesylate and benzenesulfonate salts, as well as bis-[(perfluoropropyl)-*p*-tolyliodonium] sulfate, formed crystals which were stable at room temperature.[14c]

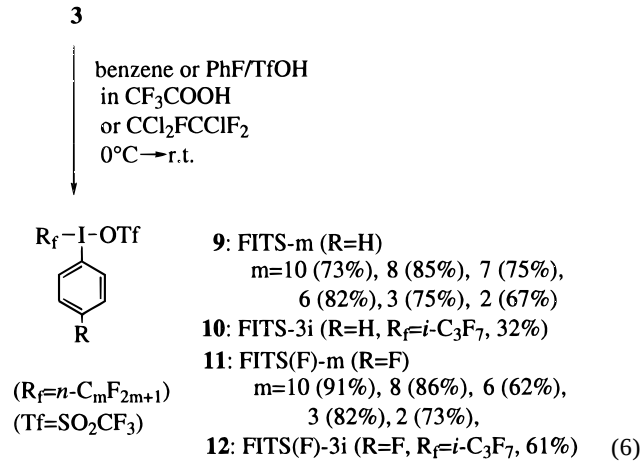
1. Syntheses of FITS Reagents and Their Analogs[14]

A series of FITS-m reagents **9** (R_f = *n*-C_mF_{2m+1}) were synthesized in good yields by treating **3** with benzene[15] in the presence of an equimolar amount of triflic acid (eq 6). The mechanism of this reaction is shown in eq 7. Because of its superacidity, triflic acid activates the iodonium salts for condensation with benzene and replaces the trifluoroacetoxy counteranion in the iodonium salts. FITS-3i (R_f = *i*-C_3F_7, **10**) was synthesized in a similar manner, although its yield was low (32%). The precursors **3** were safely prepared by oxidation of **1** using 30% H_2O_2 and a large excess of trifluoroacetic anhydride, in which the anhydride consumed all of the H_2O which was present, in addition to the H_2O_2.[14e]

FITS-3i was also prepared in 29% overall yield by the direct fluorination of perfluoroisopropyl iodide with 20% F_2/N_2. This formed 2-(difluoroiodo)perfluoropropane, which was then reacted with benzene in the presence of triflic acid (1 equiv) to produce FITS-3i.[14c]

When reaction 6 was run with fluorobenzene instead of benzene, the (perfluoroalkyl)(*p*-fluorophenyl)iodonium triflates **11** [FITS(F)-m] and **12** [FITS-(F)-3i] were produced in good yields. The *p*-fluorophenyl group increased the stability or crystalline nature of the iodonium salts relative to the phenyl group. Thus, by crystallization, the isolated yield of FITS(F)-3i (61%) was higher than that of FITS-3i (32%).

The (per*f*luoroalkyl)phenyl- and -(*p*-fluorophenyl)-*i*odonium hydrogensulfates **15** and **16** [FIS and FIS-(F)] were obtained in good yields when sulfuric acid was substituted for triflic acid in reaction 6 (eq 8).



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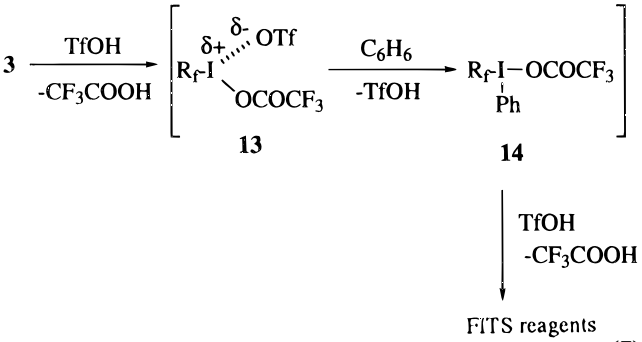

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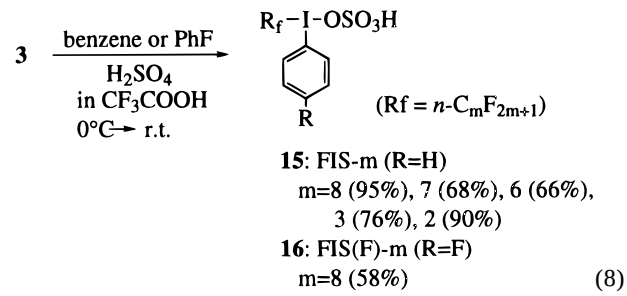
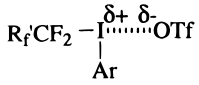


(8)

Similarly, fluorosulfonic acid reacted with **3** (R_f = *n*-C_8F_{17}) to give (perfluorooctyl)phenyliodonium fluorosulfonate in 70% yield. This crystalline fluorosulfonate is miosture-sensitive and readily hydrolyses to the corresponding hydrogen sulfate, FIS-8 . The analogous reaction with methanesulfonic acid produced (perfluorooctyl)phenyliodonium mesylate, however, this reaction was very slow (room temperature, 2 weeks) and gave a low yield of the mesylate (26%).

(Trifluoromethyl)aryliodonium salts have not been successfully prepared.[12b,14c] Their synthetic intermediates, $CF_3I(OCOCF_3)_2$, CF_3IF_2, or CF_3IO, have low stability compared to intermediates having R_f groups with two or more carbons.[16] The weak CF_3-I bond is probably cleaved during condensation of the trifluoromethyl intermediates with benzene or toluene. This is in agreement with Naumann's report that the reaction of CF_3IF_2 with $B(C_6F_5)_3$ formed perfluorotoluene, C_6F_5I, and $B(C_6F_5)_{3-x}F_x$ with cleavage of the CF_3-I bond.[17] Naumann also detected the $(CF_3)_2I^+$ cation in the reaction mixtures of CF_3IX_2 and $Cd(CF_3)_2 \cdot 2CH_3CN$ in the presence of Lewis acid at temperatures up to −20 °C.[18] Schack et al. reported that solids having the empirical composition $R_fI(ClO_4)_2$ possess the ionic structure $(R_f)_2I^+ I(ClO_4)_4^-$. These compounds were obtained as a nonvolatile



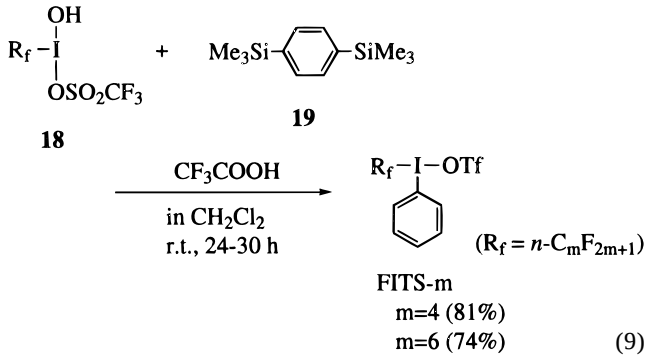
17

Figure 1.

residue from the reaction of R_fI [$R_f = (CF_3)_2CF$ and n-C_7F_{15}] with $ClOClO_3$.[19]

The ^{19}F NMR chemical shifts for the α-CF_2 in a series of (perfluoroalkyl)phenyliodonium salts were dependent on the electronegativity or leaving ability of the counteranion. The chemical shifts moved downfield in the order, Cl (85.5 ppm) > OSO_2CH_3 (78.4) > OSO_3H (73.7) > OTf (67.8). This indicates that the bonding between the iodine atom and the counteranion is not completely ionic in these salts and that the triflates are the most polarized (Figure 1).[14c] This incomplete ionization is the reason why the structural formulas of (perfluoroalkyl)aryliodonium salts are written in neutral form. Triflates are the most reactive species in this series, because they are the most polarized.

Recently, Zhdankin et al. reported an alternative method for the preparation of (perfluoroalkyl)aryliodonium triflates (FITS reagents), mesylates, and tosylates using [hydroxy(sulfonyloxy)iodo]perfluoroalkanes **18** and trimethylsilylarenes or bis(trimethylsilyl)arenes.[20] Reactions of **18** with 1,4-bis(trimethylsilyl)benzene resulted in desilylation of the arene and formation of the FITS reagents in high yields (eq 9).



18 **19**

FITS-m
m=4 (81%)
m=6 (74%) (9)

2. Electrophilic Perfluoroalkylation with FITS Reagents and Their Analogs

FITS reagents are highly reactive electrophilic perfluoroalkylating agents which react according to the general scheme shown in eq 10. Iodobenzene and triflic acid are quantitatively produced along with the perfluoroalkylated compounds (except that FITS(F) gave *p*-fluoroiodobenzene instead of iodobenzene and FIS produced sulfuric acid instead of triflic acid).

$$\text{FITS} + \text{NuH} \longrightarrow R_f\text{-Nu} + \text{PhI} + \text{TfOH} \quad (10)$$

2.1. Perfluoroalkylation of Carbanions.[21] FITS perfluoroalkylated various carbanions as shown in Table 2. The product yields from these reactions depended on the nature of both the carbanions and their counterions. Thus, the alkyl and alkynyl magnesium halides formed R_f products in good yields (runs 1, 4−6, and 8), while the alkenyl magnesium halide formed its R_f-product in low yield (run 7). The R_f products from the alkyllithium reagents were obtained in low yields, but the alkynyllithiums gave

Table 2. Perfluoroalkylation of Carbanions with FITS-m

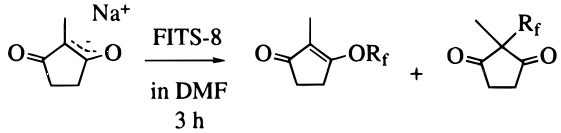
Run	Carbanion	m	Conditions**	Product	Y. (%)
1	n-$C_8H_{17}MgCl$	8	-78°C, 2 h	n-C_8H_{17}-R_f	58
2	n-$C_8H_{17}Cu$	8	-78°C, 2 h	n-C_8H_{17}-R_f	26
3	n-$C_8H_{17}Li$	8	-78°C, 2 h	n-C_8H_{17}-R_f	9
4	$PhCH_2MgCl$	3	-78°C, 1.5 h	$PhCH_2$-R_f	63
5	$PhCH_2MgCl$	3	-110°C, 2 h	$PhCH_2$-R_f	82
6	CH_2=$CHCH_2MgBr$	8	-30°C, 2 h	CH_2=$CHCH_2$-R_f	40
7	CH_2=$CHMgBr$	8	-78°C, 2 h	CH_2=CH-R_f C_6H_5-R_f	8 2
8	PhC≡CMgCl	8	-78°C, 1 h	PhC≡C-R_f	58
9	PhC≡CLi	8	-78→-30°C 0.5 h	PhC≡C-R_f	66
10*	PhC≡CLi	8	-78→-30°C 0.5 h	PhC≡C-R_f PhCH=CH-R_f***	37 11

* Reverse addition; acetylide was added into a mixture of FITS in THF. **in THF. ***$trans/cis$=1/1.

R_f products in good yields (runs 3 and 9). Lowering the temperature of run 4 from −78 °C to −110 °C increased the yield (run 5). Interestingly, adding the reagents from run 9 in reverse order (run 10) lowered the yield of the substitution product to 37% and also gave 11% of β-R_f-styrene. The reaction of FITS produced iodobenzene which reacted with vinylmagnesium halide to give phenylmagnesium halide, which underwent further perfluoroalkylation to yield C_6H_5-R_f as a byproduct (run 7).

Unlike FITS, R_f−I does not perfluoroalkylate alkyl- or aryllithium or -magnesium halides. Instead, a metal exchange reaction occurs to form perfluoroalkyl metals and alkyl or aryl iodides. This is a useful method for preparing perfluoroalkyl metals.[22] Farnham et al. reported that pentafluorophenyllithium reacted with C_6F_5I to give $[C_6F_5{-}I{-}C_6F_5]^-Li^+$, which was converted to isolable $[C_6F_5{-}I{-}C_6F_5]^-\ Li^+\cdot 2TMEDA$, and that $R_f^-TAS^+$ reacted with R_f−I to give isolable $[R_f{-}I{-}R_f]^-TAS^+$ [$R_f = (CF_3)_3C$; $TAS^+ = (Me_2N)_3S^+$].[23] These are clear evidence that a nucleophile attacks an iodine atom of R_f−I, and support the proposed mechanism for the metal exchange reaction.

FITS reacted with the sodium salt of a β-diketone **20** to give *O*-R_f and *C*-R_f products **21** and **22** (eq 11).



20 **21** **22**

Temp	21	22
r.t.	27%	0%
0°C	26%	7%
-30°C	19%	16%
-55°C	7%	31%

(11)

Scheme 1

$$R_f\text{-}I \;(\mathbf{1}) + Nu:^- \longrightarrow [R_f\text{-}I]^{\cdot -} + Nu^{\cdot}$$

$$[R_f\text{-}I]^{\cdot -} \longrightarrow R_f^{\cdot} + I^-$$

$$R_f^{\cdot} + Nu:^- \longrightarrow [R_f\text{-}Nu]^{\cdot -}$$

$$[R_f\text{-}Nu]^{\cdot -} + R_f\text{-}I\;(\mathbf{1}) \longrightarrow R_f\text{-}Nu + [R_f\text{-}I]^{\cdot -}$$

$(Nu:^-;\ ^-:C(CH_3)_2NO_2)$

The *O*/*C* ratios increased with the reaction temperature. The sodium salt of ethyl 2-methylacetoacetate, a β-keto ester, gave similar results.[21b] A similar temperature dependence of the *O*/*C* ratios was observed in an all-hydrocarbon system during butylation of an enolate anion of ethyl acetoacetate with butyl halides.[24] The FITS reaction differed from the photoreaction of β-diketones with R_f—I in liquid ammonia, which gave only *C*-R_f products.[25]

The perfluoroalkylations of sodium salts of the diethyl 2-methylmalonate and 2-nitropropane with FITS each produced only a *C*-R_f product. The *C*-R_f product was also obtained from the photoreaction of the sodium salt of 2-nitropropane with R_f—I in DMF.[26] These perfluoroalkylations with R_f—I are believed to proceed via a single electron transfer followed by a free radical chain reaction as shown in Scheme 1.[26]

2.2. Perfluoroalkylation of Alkenes and Alkadienes.[27] R_f—I react with alkenes when heated, irradiated or supplied with a radical initiator, to produce addition products.[28a–h] However, FITS reacted with these alkenes or alkadienes to form a cationic intermediate which then gave substitution products, nucleophile addition products, cyclization products, or hydride shift deprotonation or cyclization products, depending on the reaction. From a synthetic viewpoint, the perfluoroalkylations with FITS have an additional advantage in that they are achieved under almost neutral reaction conditions by using an equimolar amount of pyridine as an acid trap.

As shown in Table 3, FITS reacted with styrene to give *trans*-β-R_f-styrene in good yield (run 1). FITS is the only reagent which has been reported to substitute an R_f group for an olefin proton of the easily polymerizable styrene in good yield. According to a report of Kamigata et al., a free radical reaction of perfluorohexanesulfonyl chloride with styrene catalyzed by ruthenium(II) complex gave the substitution product, but as a minor component, together with the chloroperfluoroalkylated styrene.[28i] Perfluoroalkylation of 1-heptene, cyclopentene, and 1,3-cyclopentadiene with FITS produced double-bond rearrangement products, while propene, α-methylstyrene, and 1,3-pentadiene each gave a mixture of the rearrangement and nonrearrangement products. The rearrangement appears to be driven by the thermodynamic instability of an olefin with an R_f group directly bonded to a vinyl position, as opposed to an allyl position.

Under similar conditions, FITS reacted smoothly with ethylene and butadiene to give pyridine addition R_f products **24** and **26**, respectively, in high yields (eq 12). Likewise, various perfluoroalkylation addition reactions of ethylene, propene, and butadiene were carried out using water, methanol, ethylene glycol, formic acid, sodium acetate, and methacrylic acid as the nucleophiles. These reactions are shown in Table 4.

Table 3. Perfluoroalkylation of Alkenes and Alkadienes with FITS

Run*	Alkene or Alkadiene	FFITS-m	Product	Y.(%)
1	styrene	m=8	*trans*-β-R_f-styrene	73
2	CH_2=CHC_5H_{11}	7	R_fCH_2CH=CHC_4H_9 (t/c=3/1)**	71
3	CH_2=$CHCH_3$	8	$R_fCH_2CH(OTf)CH_3$ R_fCH=$CHCH_3$ R_fCH_2CH=CH_2	54 20 7
4	CH_2=$C(CH_3)Ph$	8	R_fCH=$C(CH_3)Ph$ $R_fCH_2CH(=CH_2)Ph$	8 42
5	cyclopentane	8	3-R_f-cyclopentene	46
6	CH_2=$CHCH$=$CHCH_3$	8	R_fCH=$CHCH$=$CHCH_3$ R_fCH_2CH=$CHCH$=CH_2	7 45
7	1,3-cyclopentadiene	2	5-R_f-1,3-cyclopentadiene	37

*Reaction conditions; pyridine (1 equiv.) in CH_2Cl_2, reflux, 0.5 h.
**t/c=*trans*/*cis*.

Table 4. Reactions of FITS or FIS with Alkenes or Alkadienes in the Presence of Nucleophiles

Run*	Alkene or Alkadiene	FITS or FIS	Nu.	Base**	Product	Y. (%)
1	ethylene	FITS-8	CH_3OH	A	$R_fCH_2CH_2OCH_3$	50
2	ethylene	FITS-8	H_2O	A	$R_fCH_2CH_2OH$	42
3	propene	FITS-8	H_2O	B	R_fCH_2-$CH(OH)CH_3$	43
4	butadiene	FIS-8	H_2O	B	R_fCH_2-CH=$CHCH_2OH$	59
5	butadiene	FITS-8	AcONa	-	R_fCH_2-CH=$CHCH_2OAc$	30
6	butadiene	FIS-8	HCOOH	B	R_fCH_2CH=$CHCH_2OCHO$	79
7	butadiene	FITS-8	ethylene glycol	A	R_fCH_2CH=CH-$CH_2OCH_2CH_2OH$	67
8	butadiene	FIS-3	methacylic acid	B	R_fCH_2CH=$CHCH_2$-$OCOC(CH_3)$=CH_2	25

* Reaction conditions; in CH_2Cl_2, r.t., 1 h.
** A=Na_2CO_3, B=$NaHCO_3$.

$$CH_2{=}\left(CHCH{=}\right)_n CH_2 \xrightarrow[\text{in } CH_2Cl_2,\ \text{r.t., 1 h}]{\text{FITS-8 / Py}} R_fCH_2\left(CH{=}CH\right)_n CH_2\text{-}\overset{+}{N}\!\left(\text{pyridinium}\right)\ {}^-OTf$$

23 (n=0)
25 (n=1)

24 (n=0) 91%
26 (n=1) 81% (12)

Table 5. Reactions of FITS or FIS with Alkenes or Alkadienes in Amide Solvents

Run*	Alkene or Alkadiene	FITS or FIS	Amide**	Product	Y.(%)
1	ethylene	FIS-8	DMF	$R_fCH_2CH_2OCHO$	73
2	ethylene	FITS-8	DMAc	$R_fCH_2CH_2OAc$	64
3	ethylene	FITS-8	FA	$R_fCH_2CH_2OCHO$	38
4	styrene	FIS-3	DMF	$R_fCH_2CH(Ph)OCHO$	56
5	butadiene	FITS-8	DMF	$R_fCH_2CH{=}CH{-}CH_2OCHO$	92
6	butadiene	FITS(F)-8	DMF	$R_fCH_2CH{=}CH{-}CH_2OCHO$	86
7	1,3-pentadiene	FITS-8	DMF	$R_fCH_2CH{=}CH{-}CH(CH_3)OCHO$	47

*Reaction conditions; r.t., 1 h.
**FA=formamide, DMAc=*N,N*-dimethylformacetamide.

Carrying out the perfluoroalkylation reaction in *N,N*-dimethylformamide (DMF) resulted in the production of R_f-alkyl or R_f-alkenyl formates in good yields (Table 5). Using *N,N*-dimethylacetamide (DMAc) or formamide (FA) as the solvent gave the corresponding acetates and formates, respectively (runs 2 and 3).

FITS reacted with alkenes bearing a nucleophilic functional group to give perfluoroalkylated cyclic products. Thus, the reaction with **27** and **29** produced β- and γ-lactones **28** and **30**, respectively (eq 13).

$$CH_2{=}CH(CH_2)_nCOOH \xrightarrow[\text{in } CH_2Cl_2,\ \text{r.t., 1 h}]{\text{FITS-8 / Py}} R_fCH_2\text{-}\langle O,\ O{=},\ (CH_2)_n \rangle$$

27 (n=1), **29** (n=2)

28 (n = 1) 36%, **30** (n = 2) 69% (13)

Similarly, allyl hydroxyethyl ether **31** produced a mixture of two isomers, the cyclization product **32** and the rearrangement−cyclization product **33**.

$$CH_2{=}CHCH_2OCH_2CH_2OH \xrightarrow[\text{in } CH_2Cl_2,\ \text{r.t., 1 h}]{\text{FITS-8 / Py}} R_fCH_2\text{-}\langle O,O \rangle + R_fCH_2CH_2\text{-}\langle O,O \rangle$$

31

32 16% **33** 47% (14)

As shown in eq 15, the reaction of FITS with allyl alcohol (**34**) or its derivative **37** also gave two products, epoxide **35** or **38**, respectively, and aldehyde or ketone **36** or **39**, respectively. The ratio of these products depended on the solvent used, with the polar solvent DMSO yielding only the aldehyde or ketone.

$$CH_2{=}CHCR^1R^2OH \xrightarrow[\text{r.t., 1 h}]{\text{FITS-8 / Py}} R_fCH_2CH(O)CR^1R^2 + R_fCH_2CH_2COR^1$$

34 ($R^{1,2}$=H)
37 (R^1=CH_3, R^2=H)
40 ($R^{1,2}$=CH_3)

	35 ($R^{1,2}$=H)	**36** (R^1=H)
in CH_2Cl_2	25%	59%
in CH_3CN	14%	70%
in DMF	2%	75%
in DMSO	0%	67%

	38 (R^1=CH_3, R^2=H)	**39** (R^1=CH_3)
in CH_2Cl_2	41%	41%
in DMSO	0%	67%

	41 ($R^{1,2}$=CH_3)
in CH_2Cl_2	77%

(15)

Scheme 2

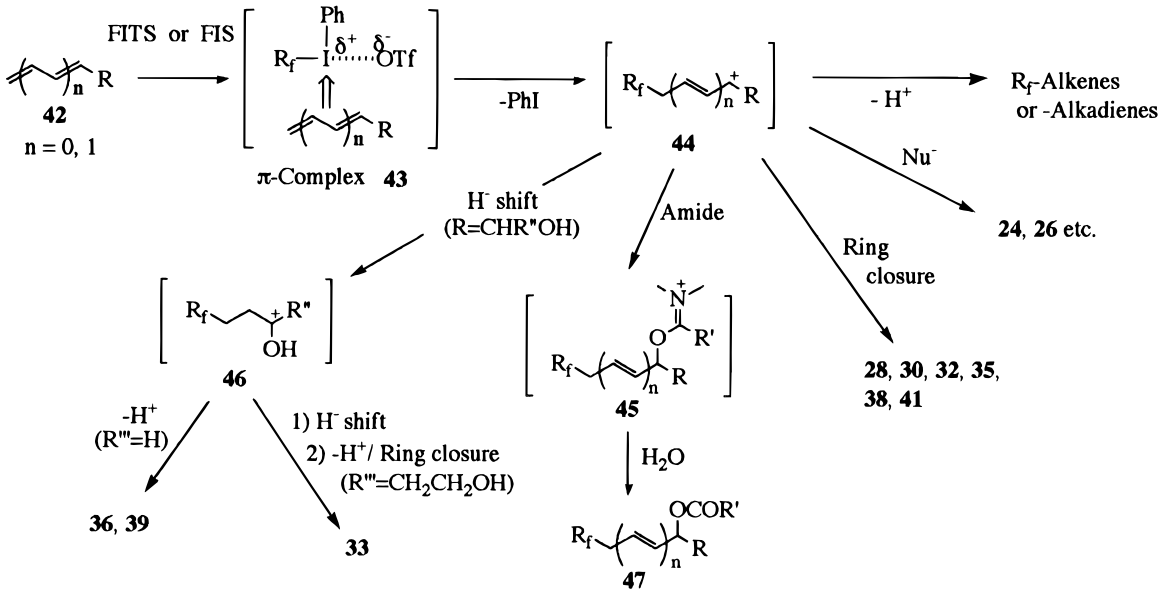


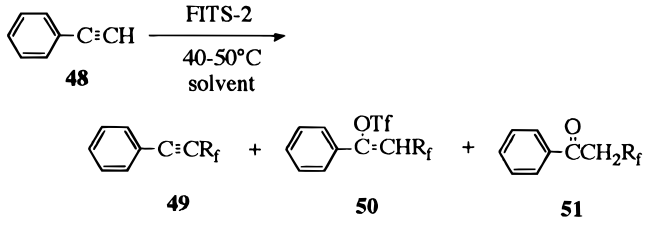
Table 6. Reactions of FITS-2 with Phenylacetylene

Run	Solvent	Additive	Yeild (%) 49	50	51
1	CH_2Cl_2	pyridine (1 equiv.)	47	36	4
2	CH_2Cl_2	-	15	31	0
3	DMF	-	45	0	0
4	CH_3OH	-	100	0	0
5	HCOOH	-	4	0	86

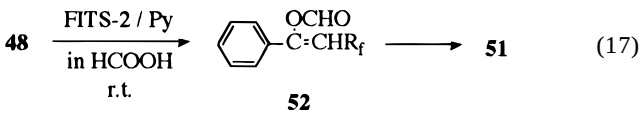
The dimethyl derivative **40** produced exclusively epoxide **41** in high yield.

The perfluoroalkylation of styrene with FITS was not inhibited by quinone, indicating that the perfluoroalkylation does not proceed by a free radical mechanism. In fact, all the products were clearly explained by the intermediate formation of cation **44**, as shown in Scheme 2. Cation **44** may form via π-complex **43**; however, this mechanism has not been completely elucidated. The final products are obtained by reaction of **44** by either attack of another nucleophile, deprotonation, cyclization, or a hydride shift followed by deprotonation or cyclization. The reaction of **44** in the presence of amides, followed by hydrolysis during work up produced R_f-alkyl or R_f-alkenyl formates or acetates **47**.

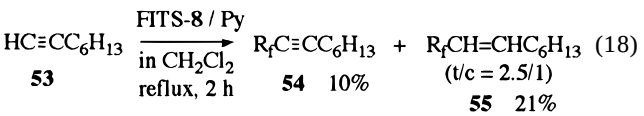
2.3. Perfluoroalkylation of Alkynes.[29b] As shown in eq 16 and Table 6, FITS reacted with phenylacetylene to give a mixture of three products **49**, **50**, and **51** (run 1). The ratio of these products greatly depended on the reaction conditions. Thus, methanol solvent gave a quantitative yield of R_f-alkyne **49** (run 4), while formic acid as the solvent gave an 86% yield of the R_f ketone **51** (run 5). As shown in eq 17, combining formic acid solvent with pyridine (1 equiv), led to isolation of the R_f-vinyl formate **52**. Compound **52** slowly converted to **51** under the reaction conditions; therefore, **52** is believed to be an intermediate in the reaction identified as run 5.



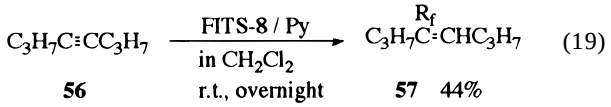
(16)



(17)



(18)



(19)

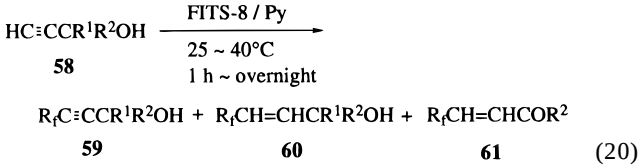
Table 7. Reactions of 58 with FITS-8

Run	58 R^1,R^2	Solvent	Yield (%) 59	60	61[c]
1	R^1=R^2=H	CH_2Cl_2	42	13[a]	7
2	R^1=R^2=H	DMF	trace	36[a]	11
3	R^1=R^2=H	DMSO	trace	11[a]	25
4	R^1=CH_3, R^2=H	CH_2Cl_2	38	13[b]	0
5	R^1=CH_3, R^2=H	DMF	0	45[b]	11
6	R^1=CH_3, R^2=H	DMSO	0	8[b]	32
7	R^1=R^2=CH_3	CH_2Cl_2	34	11[c]	0
8	R^1=R^2=CH_3	DMF	1	73[c]	0

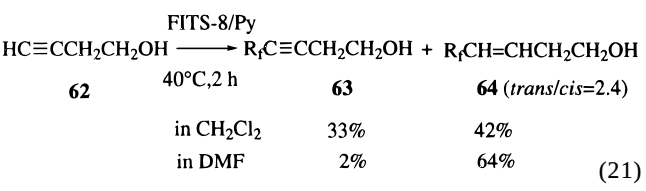
a) *trans*/*cis*=2.5 b) *trans*/*cis*=5.7 c) *trans* isomer

1-Octyne reacted with FITS in methylene chloride to give the 1-R_f-octene **55** in addition to the 1-R_f-octyne **54** (eq 18), while 4-octene produced only 4-R_f-octene **57** under the similar conditions (eq 19). The 1-R_f-octene **55** was formed exclusively in 41% yield when the 1-octyne reaction was run in DMF.

As shown in eq 20 and Table 7, propargyl alcohol (**58**, R^1 = R^2 = H) and its methyl derivative (**58**, R^1 = H, R^2 = CH_3) each gave either two or three of the products: R_f-alkynol **59**, R_f-alkenol **60**, or R_f-alkenal or R_f-alkenone **61**, depending on the solvent. Methylene chloride favored **59** as the major product, while the polar DMF or DMSO yielded **60** and **61**, respectively, as major products. The dimethyl derivative of propargylalcohol (**58**, R^1 = R^2 = CH_3) produced **59** and **60** but not R_f-alkenone **61**. Utilizing polar solvents increased the yield of R_f-alkenol **60** (R^1 = R^2 = CH_3). Likewise, alkynol **62** produced **63** and **64**, however, it did not form a cyclic product (eq 21).



(20)



(21)

The reaction mechanism shown in Scheme 3 has been proposed to account for the different products obtained from the alkyne reactions. Products **49**–**52** are thought to be formed via the vinyl cation **67** (R^4 = Ph), which is stabilized by the neighboring phenyl group. Products **54**, **59**, and **63** are formed by deprotonation of **67**, while the R_f-alkenal or R_f-alkenone **61** was produced from **67** by a H^- shift followed by deprotonation. R_f-alkenes **55**, **57**, **60**, and **64** are believed to arise from an R_f-vinyl radical **69**, rather than the cation **67**, wherein **69** abstracts a

Scheme 3

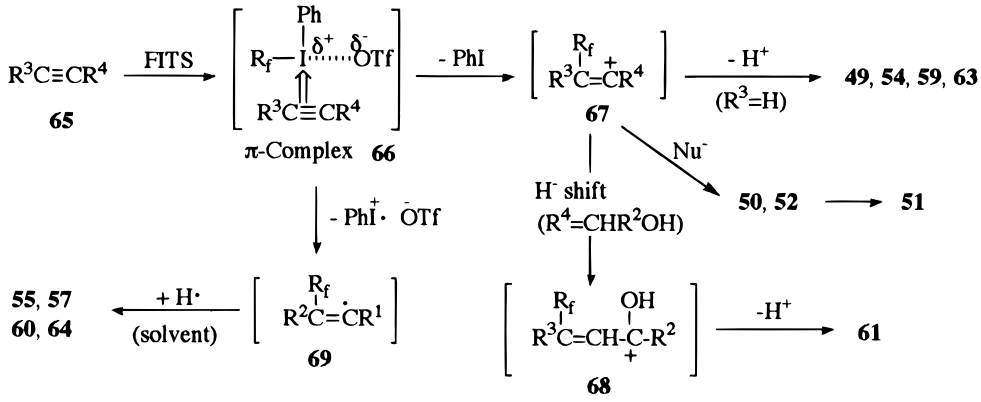
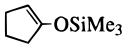
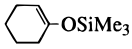
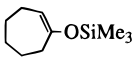
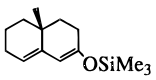
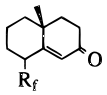


Table 8. Perfluoroalkylation of Enol Trimethylsilyl Ethers

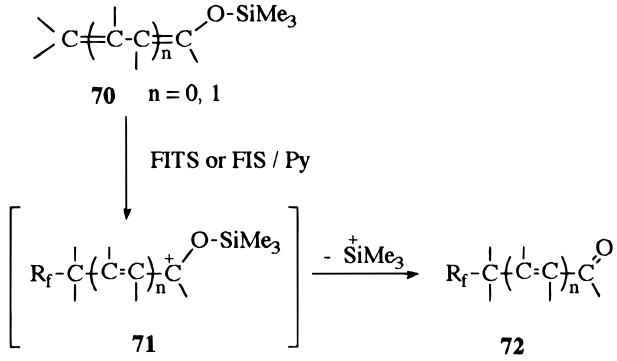
Run*	Ether **70**	FITS or FFIS	Solv.	Product **72**	Y. (%)
1	$CH_3C(OSiMe_3)=CH_2$	FITS-8	CH_2Cl_2	$CH_3COCH_2R_f$	88
2	$PhC(OSiMe_3)=CH_2$	FITS-3i	CH_2Cl_2	$PhCOCH_2R_f$	79
3	t-Bu-$C(OSiMe_3)=CH_2$	FITS-8	CH_3CN	t-Bu-$COCH_2R_f$	82
4		FIS-8	CH_3CN		76
5		FITS-6	CH_3CN		71
6		FIS-6	CH_3CN		83
7		FITS-3	CH_2Cl_2		85

*Reaction conditions;pyridine (1 equiv.), r.t. ~ 45°C, 0.5 h ~ overnight.

hydrogen from the solvent molecules. Formation of the R_f-alkenes predominated in polar solvents such as DMF and with relatively hindered alkynes such as **56**. The free radical **69** is probably formed by an electron exchange with iodobenzene while in the π-complex **66**, since forming the corresponding nonstabilized vinyl cation is very difficult. It has also previously been reported that R_f−Cu generate perfluoroalkyl free radicals which react with alkynes to produce R_f-alkenes via R_f-vinyl radicals.[30]

2.4. Perfluoroalkylation of Enol Trimethylsilyl Ethers.[31] FITS readily reacted with the enol trimethylsilyl ethers of ketones or α,β-unsaturated ketones **70** in the presence of pyridine (1 equiv). These reactions produced α-R_f ketones or γ-R_f-α,β-unsaturated ketones **72** in high yields as shown in eq 22 and Table 8. The use of FITS-3i in this reaction allowed a bulky perfluoroisopropyl group to be added to a ketone in high yield (run 2). Formation of these products is believed to proceed via desilylation of the cation intermediate **71**. The trimethylsilyl cations that are generated are trapped by pyridine in the reaction mixture.

An alternative method for preparing α-R_f and γ-R_f-α,β-unsaturated ketones is to react R_f−I with enol alkyl ethers or enamines, followed by acid hydrolysis.[32] However, this method has a disadvantage in that dehydrofluorination of α-R_f ketones occurs during the acid hydrolysis. Reaction of R_f−I with enol trimethylsilyl ethers initiated by Et_3B, a radical initiator, in the presence of 2,6-lutidine provided mixtures of perfluoroalkylated enol trimethylsilyl ethers and α-R_f ketones.[33]



(22)

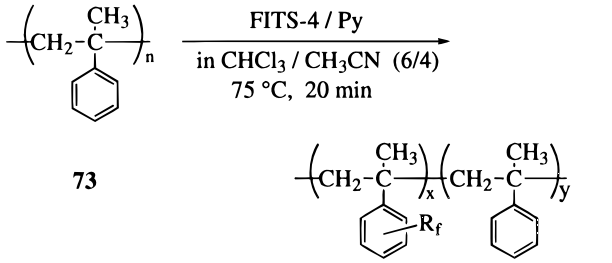
2.5. Perfluoroalkylation of Aromatic Compounds.[34] As shown in Table 9, heating FITS-6 in benzene gave (perfluorohexyl)benzene in a 97% yield (run 1). The reagent, FIS-6 also gave a 70% yield of this product. An approximately stoichiometric amount (1.5 equiv) of durene was likewise perfluoroalkylated by FITS in acetonitrile (run 2), although the yield from this reaction was low. FITS easily perfluoroalkylated activated aromatics such as phenol, anisole, and *N*,*N*-dimethylaniline, however. These reactions were run in either methylene chloride or acetonitrile, and produced *o*- and *p*-perfluoroalkylated aromatics as the major products (runs 3−5). Similarly, FITS reacted with naphthalene, anthracene, and the electron-rich heteroaromatics furan, thiophene, and pyrrole. Anthracene and the heteroaromatics each formed only a single product, which was obtained in high yield (runs 9−12). Deactivated aromatics such as methyl benzoate[34] and nitrobenzene[35] were also successfully perfluoroalkylated by FITS in refluxing acetonitrile (runs 6 and 7). Pyridine appeared to assist these perfluoroalkylations, and 1 equiv was included in the reaction mixture. A 1:1:1.3 mixture of *o*-, *m*-, and *p*-R_f isomers was obtained from the methyl benzoate reaction (run 6), while the nitrobenzene did not produce any of *m*-R_f isomer (run 7). This technique was extended to the perfluoroalkylation of

Table 9. Perfluoroalkylation of Aromatics

Run	Aromatic (equiv.)	FITS	Additive* (1 equiv.)	Conditions	Product (o:m:p)	Y. (%)
1	benzene (excess)	m=6	Py	in benzene reflux, 1 h	R_f-Ph	97
2	durene (1.5)	8	Py	in CH_3CN, 60°C, 7 min	R_f-durene	32
3	phenol (1.1)	8	Py	in CH_2Cl_2 r.t., 10 min	R_f-phenol (4.1:1:4.6)	55
4	anisole (0.92)	2	BMP	in CH_2Cl_2 reflux, 0.5 h	R_f-anisole (4:1:2)	61
5	*N,N*-diMe-aniline (2.1)	8	-	in CH_3CN, r.t., 1 h	R_f-*N,N*-diMe-aniline (1:0:2.7)	37
6	methyl benzoate (1.1)	8	Py	in CH_3CN, reflux, 1 h	R_f-C_6H_4COOMe (1:1:1.3)	54
7	nitro-benzene (1.1)	8	Py	in CH_3CN reflux, 1 h	R_f-$C_6H_4NO_2$ (1.3:0:1)	16
8	naphtha-lene (2.1)	8	Py	in CH_3CN, 60°C, 5 min	R_f-naphthalene (α/β=4/1)	82
9	anthra-cene (1)	3	Py	in CH_2Cl_2, 0°C, 1 h	9-R_f-anthracene	63
10	furan (2)	8	Py	in CH_2Cl_2, r.t., 0.5 h	α-R_f-furan	87
11	thio-phene (1.1)	8	Py	in CH_2Cl_2, r.t., 15 min	α-R_f-thiophene	73
12	pyrrole (1.1)	8	Py	in CH_2Cl_2, r.t., 0.5 h	α-R_f-pyrrole	92

*Py=pyridine, BMP=2,6-di-*t*-butyl-4-methylpyridine.

polymers such as poly(α-methylstyrene) **73** and poly-(phenyl methacrylate) (eq 23).[36]

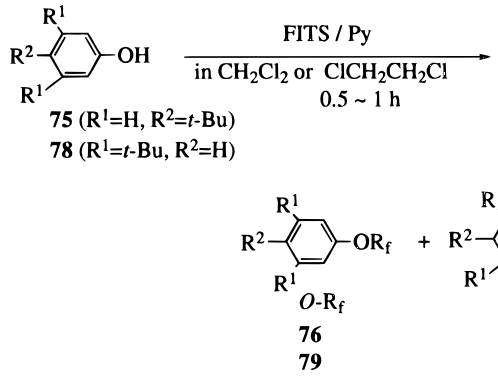


73 **74** 33%

(23)

An equimolar mixture of FITS and pyridine in a halocarbon or acetonitrile solvent did not undergo any reaction at room temperature. However, when FITS-8 was dissolved in pyridine at room temperature, a reaction occurred which gave a 1.5:1 mixture of α- and β-R_f-pyridine in 48% yield.[35]

FITS perfluoroalkylation of the sterically hindered phenols **75** and **78** led to *O*-perfluoroalkylation along with *C*-perfluoroalkylation.[37] As seen in eq 24, the extent of *O*-perfluoroalkylation increased with an increase in the reaction temperature, an increase in the bulkiness of the R_f, or an increase in the number of *tert*-butyl substituents on the phenol.



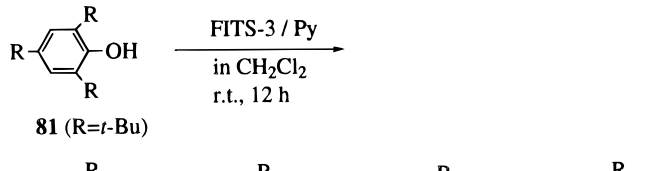
75 (R^1=H, R^2=*t*-Bu)
78 (R^1=*t*-Bu, R^2=H)

O-R_f **76** **79** *C*-R_f **77** **80**

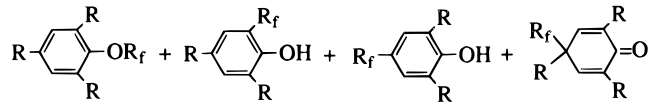
	FITS	Temp.	*O*-R_f	*C*-R_f	*O*/*C* ratio
75	FITS-3	r.t.	9%	14%	0.22
75	FITS-3	83°C	14	29	0.48
75	FITS-3i	-78°C → r.t.	11	48	0.23
75	FITS-3i	r.t.	27	21	1.3
75	FITS-3i	83°C	31	15	2.1
78	FITS-3i	r.t.	50	15	3.3
78	FITS-3i	83°C	56	16	3.5

(24)

The highly hindered tri-*tert*-butylphenol (**81**) was also treated with FITS (eq 25).[37] This reaction was



81 (R=*t*-Bu)



82 5% **83** 34% **84** 9% **85** 40%

(25)

unique in that the solution turned blue; the blue color then disappeared. *C*-Perfluoroalkylation proceeded predominantly at the *ortho*- and *para*-positions to form **83**, **84**, and **85**. Cyclohexadienone **85**, which is an intermediate to the *p*-R_f substitution product **84**, was isolated from the reaction. The blue color suggests the presence of a radical cation of **81**, which could result from a single electron transfer to FITS. This change in mechanism probably occurs because the three bulky *tert*-butyl substituents hinder the approach of FITS to the π-electron-rich aromatic ring.

The perfluoroalkylation of aromatics is thought to proceed through the π-complex **86** followed by the Meisenheimer complex **87**, as shown in Scheme 4. In the pyridine-assisted perfluoroalkylation of deactivated aromatics, it appeared that the ionic reaction was accompanied by a free radical reaction. For strongly deactivated aromatic compounds such as nitrobenzene, this free radical reaction proceeded exclusively, leading to the *o*- and *p*-R_f isomers, but not the *m*-R_f isomer. The *O*-perfluoroalkylation of the hindered phenols is attributed to the greater

Scheme 4

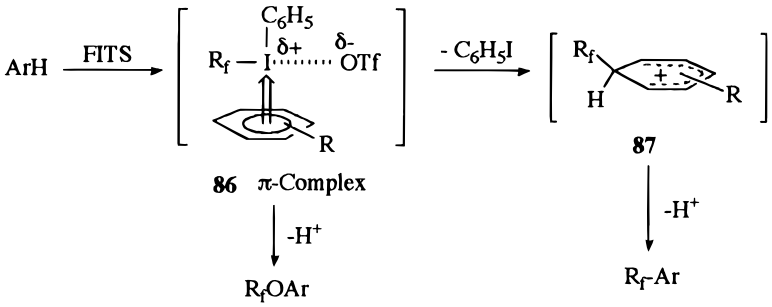


Table 10. Perfluoroalkylation of Thiols

RSH (**88**) —FITS-m / Py in CH_2Cl_2, r.t.→ RSR_f (**89**)

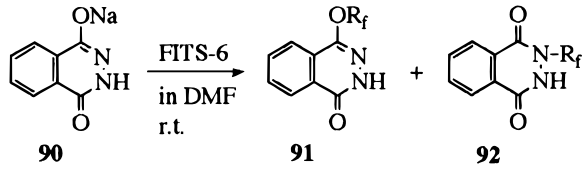
Run	89	FITS-m	Time (min)	Y.(%)
1	R_fSCH_2COOBu	m=3	10	88
2	R_fSCH_2COOH	8	60	93
3	$R_fSCH(COOH)CH_2COOH$	8	40	63
4	$R_fSCH_2CH_2OH$	8	20	83
5	$R_fSCH_2CH(OH)CH_2OH$	8	60	83
6	$R_fSCH_2CH_2SH + (R_fSCH_2-)_2$	8	30	46 (1.3:1)
7	R_fSPh	2	60	59
8	$R_fSCH_2CH_2N(CH_3)_2$	8	120	52

thermodynamic stability of the *O*-R_f products, as compared to the *C*-R_f products.

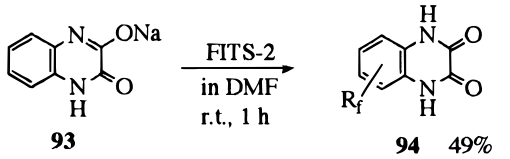
The perfluoroalkylation of electron-rich aromatics such as aniline, phenol, and pyrrole with R_f—I or R_f—Br in the presence of sulfur dioxide as a radical mediator was reported later. This reaction was induced by a single electron transfer from the sulfur dioxide radical anion to the perfluoroalkyl halide.[10e,38]

2.6. Perfluoroalkylation of Thiols.[39] FITS readily reacted with various thiols under mild conditions in the presence of 1 equiv of a base such as pyridine to give R_f sulfides **89** in good to high yields (Table 10). *S*-Perfluoroalkylation occurred selectively in the presence of functionality such as carboxy, hydroxy, oxycarbonyl, or dimethylamino groups. Ethanedithiol gave a mixture of mono-R_f and di-R_f products (run 6). The *S*-perfluoroalkylation of thiols has also been obtained by the photoreaction of thiolate anions and R_f—I or R_f—Br in a polar solvent (DMF or NH_3). This reaction is believed to proceed via a single electron-transfer mechanism.[10e,40−42] This photochemical method does not work well with deactivated thiolate anions such as arenethiolates with electron-withdrawing substituents.

2.7. Others.[14d] The sodium salt of phthalohydrazide **90** reacted with FITS to give the *O*-R_f product **91** and the *N*-R_f product **92** in 47% yield (*O*/*N* = 1.7/1) (eq 26).[43] Meanwhile, the sodium salt of 2,3-dihydroxyquinoxaline (**93**) formed the *C*-R_f products **94**, as a 1:2 mixture of the 5- and 6-isomers, in 49% yield (eq 27).[34] This difference is due to delocalization of the anion electrons onto the benzene ring. The *N*-perfluoroalkylation observed with **90** is the first example of an *N*-perfluoroalkylation. Benzaldehyde



47% (1.7 : 1) (26)

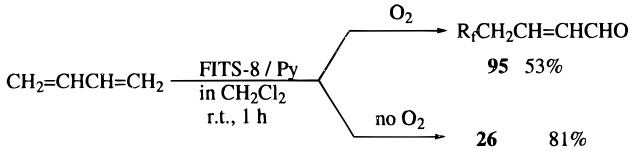


(5-/6-isomer=1/2) (27)

oxime formed the *O*-R_f product in a 13% isolated yield;[43] however, the *O*-perfluoroalkylation of alkoxide anions did not occur.

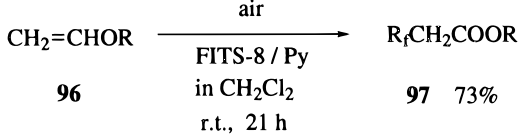
3. Oxyperfluoroalkylation with FITS Reagents[44]

FITS reacted with butadiene under an oxygen atmosphere and in the presence of pyridine to give 4-R_f-2-butenal (**95**) in 53% yield (eq 28). In the absence of oxygen, *N*-(R_f-butenyl)pyridinium triflate (**26**) was obtained in high yield (see section 2.2). Thus both oxygen and base are essential components in this new oxyperfluoroalkylation.



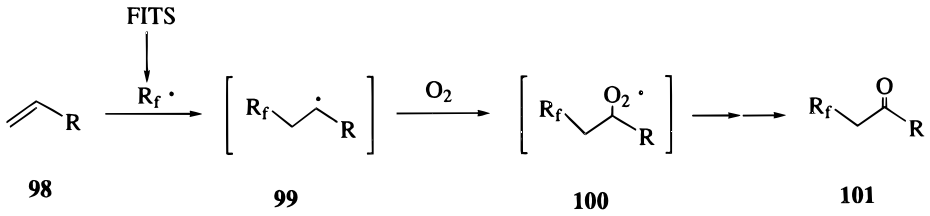
(28)

Successful oxyperfluoroalkylation required an electron-rich double bond. Therefore, the reaction did not occur with ethylene, but did occur with propene. Alkyl vinyl ethers preferentially underwent the oxyperfluoroalkylation, even under an air atmosphere, to give alkyl 2-R_f-acetate (**97**, eq 29). The participation of molecular oxygen in the oxyperfluoroalkylation was demonstrated by the reaction of butadiene



(29)

Scheme 5

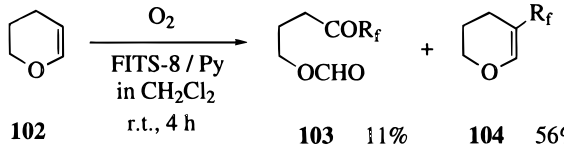


in the presence of $^{18}O_2$. This reaction produced ^{18}O-labeled **95**.

Oxyperfluoroalkylation probably proceeds via the formation of radical intermediate **99**, which can react with molecular oxygen to form peroxide **100**, as shown in Scheme 5. However, the mechanism by which a R_f free radical is generated from FITS is not clear.

Uneyama et al. reported a similar oxyperfluoroalkylation of the electron-poor alkene, butyl acrylate, by an electrochemical reaction. Trifluoroacetic acid was electrooxidized in the presence of butyl acrylate and oxygen to provide a mixture of butyl 4,4,4-trifluoro-2-oxo- and -hydroxybutanoate.[45]

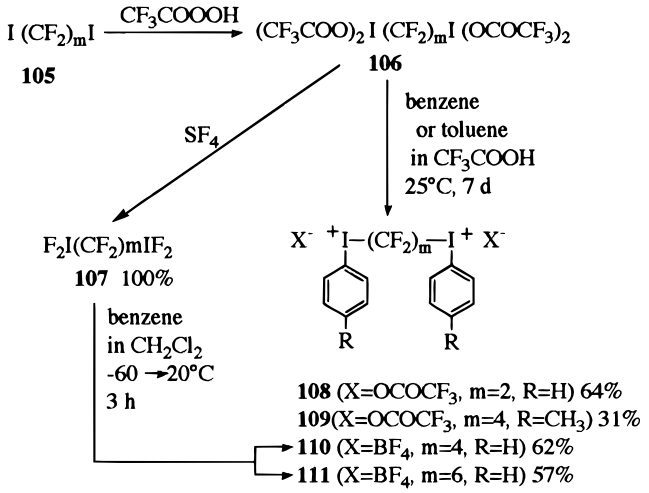
Dihydropyran (**102**) gave a slightly different type of oxyperfluoroalkylated product **103**, in addition to the nonoxygenated, normal substitution product **104**, when reacted with FITS in the presence of oxygen (eq 30).



(30)

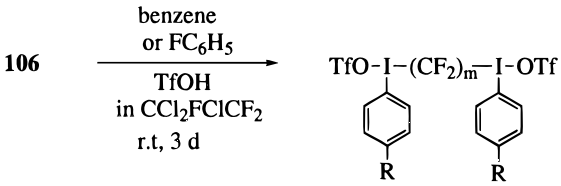
C. Perfluoroalkylene Bisphenyliodonium Salts

Yagupolskii et al. synthesized a series of perfluoroalkylene bis(phenyl- and bis(*p*-tolyliodonium trifluoroacetates) and tetrafluoroborates) **108**−**111** from **106** or α,ω-bis(difluoroiodo)perfluoroalkanes **107** (eq 31).[12b,46] The reactions of sodium *p*-chlorothiophenolate with **110** and **111** produced α,ω-bis[(*p*-chlorophenyl)thio]perfluorobutane and -hexane in 81% and 68% yields, respectively.



(31)

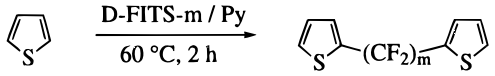
We independently developed perfluoroalkylene bis(phenyliodonium triflates), or double-FITS (D-FITS) reagents (eq 32).[47] Two highly reactive D-FITS reagents **112** were prepared by treatment of **106** with benzene and triflic acid. D-FITS(F) **113** was similarly obtained by the treatment of **106** with fluorobenezene.[47]



112 D-FITS-3 (R=H, m=3) 49%
D-FITS-3 (R=H, m= 8) 62%
113 D-FITS(F)-8 (R=H, m=8) 55%

(32)

Heating D-FITS-3 and -8 in benzene produced α,ω-diphenylperfluoropropane and -perfluorooctane in 76% and 87% yields, respectively. Similarly, α,ω-dithien-2-ylperfluoropropane (**114**) and -perfluorooctane (**115**) were obtained by heating D-FITS-3 and -8 in thiophene (eq 33).



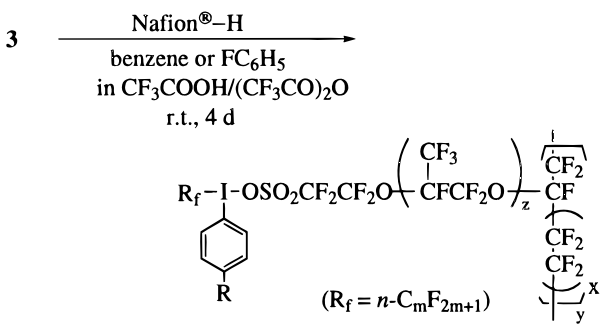
(33)

114 m = 3, 75%
115 m = 8, 62%

D. Polymer-Supported FITS Reagents[48]

FITS reagents exhibit two major problems: (1) isolating FITS from the reaction mixture requires repeated recrystallizations; and (2) recovery of the expensive triflic acid produced from the FITS is troublesome. FITS was therefore immobilized on a resin in an attempt to solve these problems.

The reagents in series **3** were treated with perfluorosulfonic acid resin (Nafion-H, 0.86 mmol/g)[49] and benzene to obtain a series of polymer-supported FITS reagents (FITS-m-Nafion) **116** in good yields (eq 34



116 FITS-m-Nafion; R=H
117 FITS(F)-m-Nafion; R=F

(34)

Table 11. Synthesis of Polymer-Supported FITS Reagents

Run	FITS-Nafion	Effective concentration mmol/g	Yield (%)
1	FITS-8-Nafion **116a**	0.39	65
2	FITS-6-Nafion **116b**	0.44	70
3	FITS-4-Nafion **116c**	0.39	54
4	FITS-3-Nafion **116d**	0.46	68
5	FITS-2-Nafion **116e**	0.36	51
6	FITS(F)-3-Nafion **117**	0.43	72

and Table 11). FITS(F)-m-Nafion **117** was also synthesized in the same manner. The polymer-supported reagents FITS- and FITS(F)-m-Nafion were readily isolated by filtration from the reaction mixture. The effective concentration of each of the resins was determined by GC analysis of liberated iodobenzene or *p*-fluoroiodobenzene. The iodo- and *p*-fluoroiodobenzenes were liberated by reaction of the resin with an excess of propanethiol. The yields of the polymer-supported FITS reagents were calculated on the basis of these effective concentrations.

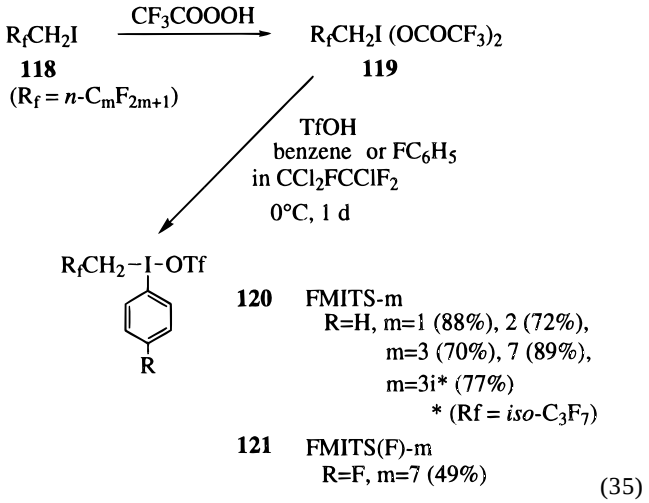
The FITS-8-Nafion resin (0.39 mmol/g) was heated in benzene and thiophene in the presence of pyridine at 80 °C for 2 h to give α,ω-diphenylperfluorooctane and **115** in 89% and 95% yield, respectively. The spent sulfonic resin was easily recovered from the reaction mixture by filtration.

III. (Polyfluoroalkyl)aryliodonium Salts and (Dihydroperfluoroalkyl)phenyliodonium Triflates (FMITS Reagents)

Electrophilic α,α-dihydroperfluoroalkylation, like perfluoroalkylation, is difficult to achieve, because the R_fCH_2 group remains highly electronegative. The halides (R_fCH_2X) have very low reactivity toward nucleophiles, as do the analogous[50] tosylates,[51] mesylates,[52] nitrobenzenesulfonates,[53] triclates,[54] and triflate.[55] Therefore, more reactive α,α-dihydroperfluoroalkylating agents were needed to enable the electrophilic reaction.

We synthesized (α,α-dihydroperfluoroalkyl)phenyliodonium triflates (**120**) (FMITS reagents)[56] and the *p*-fluoro derivative **121** [FMITS(F)] to serve as highly reactive electrophilic α,α-dihydroperfluoroalkylating agents. These reagents were formed from the corresponding iodides **118** as shown in eq 35.[57] The corresponding hydrogen sulfate and fluoro sulfonate were also synthesized.[57]

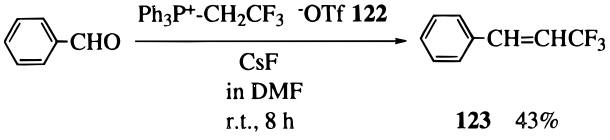
These dihydroperfluoroalkylating agents readily reacted with a variety of nucleophiles under mild conditions.[58−60] Amines, lithium salts of alcohols and phenols, carboxylic acids, thiols, carbanions, enol silyl ethers, activated aromatics, sulfides, sulfoxides, pyridines, pyridine *N*-oxide, benzothiazole, dibenzothiophene, and phosphines were dihydroperfluoroalkylated as shown in Table 12. Dialkylation was also



(35)

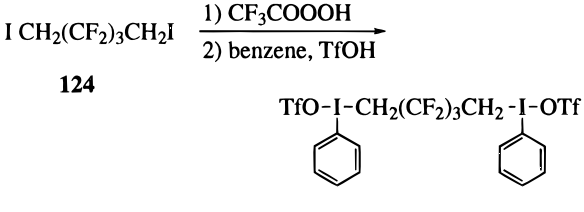
readily achieved under mild conditions using these dihydroperfluoroalkylating agents (run 2).[60]

The (2,2,2-trifluoroethyl)triphenylphosphonium triflate (**122**), obtained by the reaction of FMITS with triphenylphosphine (run 15), proved useful as a Wittig reagent. For example, **122** reacted with benzaldehyde in the presence of cesium fluoride to give β-(trifluoromethyl)styrene (eq 36).[60]



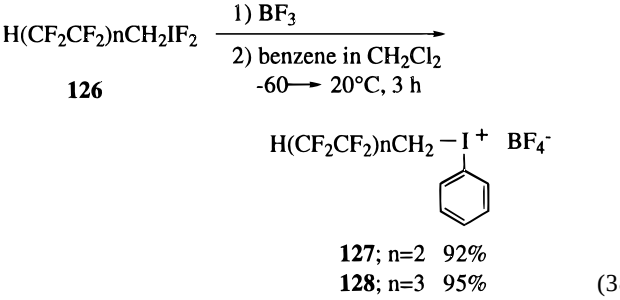
(36)

(α,α,ω-Trihydroperfluoroalkyl)phenyliodonium salts were synthesized in a manner similar to the synthesis of the FMITS reagents.[57] The α,α,ω,ω-tetrahydroperfluoropentamethylenebis(phenyliodonium triflate) **125** D-FMITS-3 was also synthesized by this procedure (eq 37).[57]



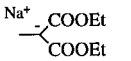
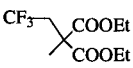
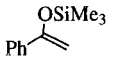
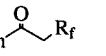
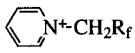
(37)

Yagupolskii et al. synthesized the (α,α,ω-trihydroperfluoroalkyl)phenyliodonium tetrafluoroborates **127** and **128** (eq 38) and used them to α,α,ω-trihydro-

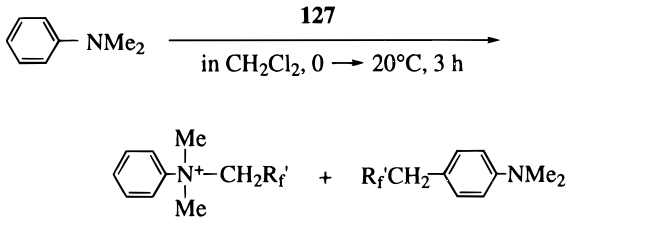


(38)

Table 12. α,α-Dihydroperfluoroalkylation of Various Compounds with FMITS Reagents

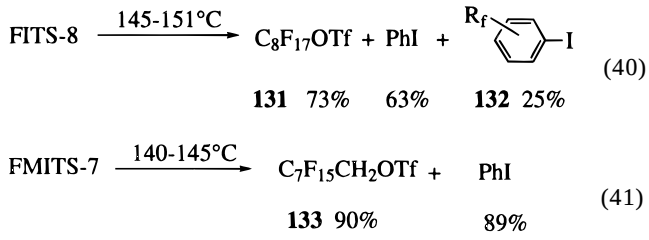
Run	Substrate	FMITS-m	Additive	Solv.	Temp. (°C)	Time	Product	Yield (%)
1	$PhNH_2$	m=1	2,4,6-collidine	CH_2Cl_2	r.t.	1.5 h	$PhNHCH_2R_f$	98
2	$PhNH_2$	m=1 (2 equiv.)	2,6-di-*t*-butyl-4-methylpyridine (2 equiv.)	CH_2Cl_2	r.t.	2 h	$PhN(CH_2R_f)_2$	70
3	$PhN(CH_3)_2$	m=1	-	CH_2Cl_2	r.t.	0.5 h	$PhN^+(CH_3)_2CH_2R_f$ ^-OTf	89
4	PhOLi	m=1	-	CH_2Cl_2	0	0.5 h	$PhOCH_2R_f$	79
6	$PhCH_2CH_2OLi$	m=1	-	CH_2Cl_2	0	0.5 h	$PhCH_2CH_2OCH_2R_f$	61
7	PhCOOH	m=1	2,4,6-collidine	CH_2Cl_2	r.t.	0.5 h	$PhCOOCH_2R_f$	99
8	$n\text{-}C_{12}H_{25}SH$	m=1	-	CH_2Cl_2	r.t.	0.5 h	$n\text{-}C_{12}H_{25}SCH_2R_f$	80
9		m=1	-	DMSO	r.t.	1 h		25
10	$PhCH_2CH_2MgBr$	m=7	-	Et_2O	r.t.	0.5 h	$PhCH_2CH_2CH_2R_f$	36
11		m=1	KF	CH_2Cl_2	r.t.	1.5 h		87
12		m=7	2,4,6-collidine	furan	50	24 h		52
13		m=1	-	CH_2Cl_2	r.t.	10 min		83
14	Ph_2S	m=1	-	CH_2Cl_2	r.t.	2 h	$Ph_2S^+\text{-}CH_2R_f$ ^-OTf	90
15	Ph_3P	m=1	-	CH_2Cl_2	r.t.	1 h	$Ph_3P^+\text{-}CH_2R_f$ ^-OTf **122**	95

perfluoroalkylate *p*-chlorothiophenol, aniline, *N*,*N*-dimethylaniline, and pyridine.[61] In contrast to FMITS (Table 12, run 3) which produced only the *N*-polyfluoroalkylated product **129** ($R_f' = CF_3$), the tetrafluoroborate reagent **127** produced both *N*- and *C*-polyfluoroalkylated products **129** and **130** ($R_f' = (CF_2CF_2)_2H$) (eq 39).[61] The dependence of the products' identities on the counteranins ^-OTf and BF_4^- is noteworthy. However, FITS did produce a small amount of the *C*-dihydroperfluoroalkylated product in addition to the *O*-dihydroperfluoroalkylated product when reacted with lithiun salts of more active phenol derivatives. For example, the lithium salt of *p*-methoxyphenol (1.5 equiv) was reacted with FMITS-1 at 0 °C for 30 min to give 6% of 1-methoxy-4-(trifluoroethoxy)(trifluoroethyl)benzene in addition to 36% of 1-methoxy-4-(trifluoroethoxy)benzene.[62] The substitution position of the *C*-trifluoroethylation could not be determined. In contrast to (2,2,2-trifluoroethyl)phenyliodonium triflate (FMITS-1) which was synthesized in high yield,[57] (2,2,2-trifluoroethyl)phenyliodonium tetrafluoroborate could not be synthesized by the same method as **127** and **128**.[61] (1,1,3-Trihydrotetrafluoropropyl)phenyliodonium tetrafluoroborate could not be synthesized.[61]



(39)

The FITS and FMITS reagents were compared by thermolysis.[57b] Thermolysis of the FITS reagent gave three products, the R_f-triflate **131**, iodobenzene, and the R_f-iodobenzene **132**. In contrast, thermolysis of the FMITS reagent gave two products, the $R_f'CH_2$-triflate **133** and iodobenzene (eqs 40 and 41). Triflates **131** and **133** most likely result from an ionic reaction while **132** probably arises from the homolytic cleavage of the R_f—I bond. This data suggests that FITS could act as the source of a perfluoroalkyl free



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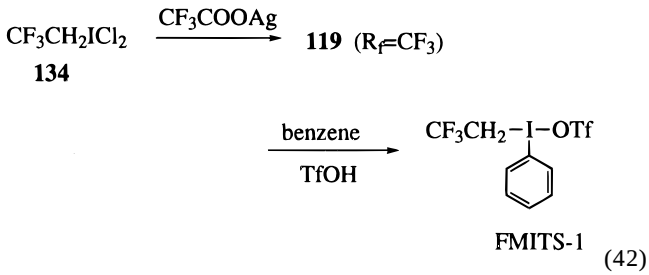
(41)

radical in addition to being a source of the perfluoroalkyl cation, depending on the reaction conditions. However, FMITS can only provide the α,α-dihydroperfluoroalkyl cation. This is what was observed in the reactions of these reagents, as described above. In general, FITS reacted at the aromatic *C*-sites on phenol and *N*,*N*-dimethylaniline, while FMITS reacted at the *O*- and *N*-sites on phenol and *N*,*N*-dimethylaniline, respectively.

The FMITS-2, -3, and -7 reagents were converted to (*trans*-1*H*-perfluoro-1-alkenyl)phenyliodonium triflates by treatment with sodium hydride.[57b]

Montanari et al. recently prepared the FMITS-1 reagent from **134** in two steps.[63] Compound **134** was readily obtained from the reaction of CF_3CH_2I with Cl_2 (eq 42).[64] FMITS-1 preferentially *N*-trifluoroethylated several amino alcohols.[63]

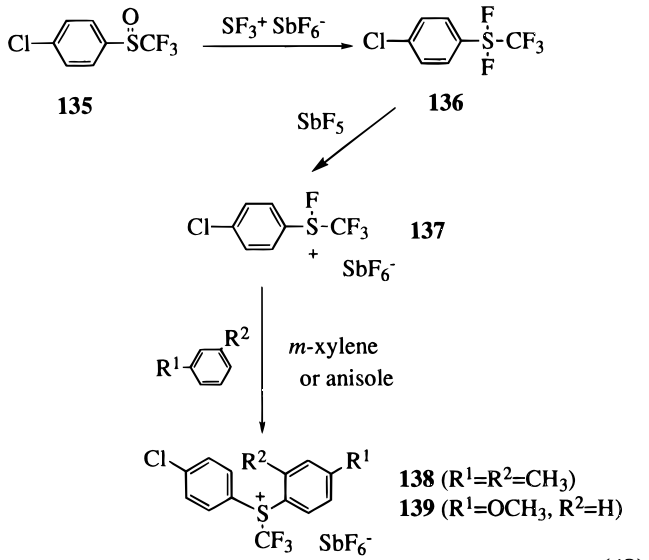


(42)

IV. (Perfluoroalkyl)chalcogen Salts

A. *S*-(Trifluoromethyl)diarylsulfonium Hexafluoroantimonates[65]

Yagupolskii et al. developed the trifluoromethyl sulfonium salts **138** and **139** as trifluoromethylating agents. These salts were synthesized from the extremely hygroscopic intermediate **137** by treating it with the electron-rich arenes, *m*-xylene, and anisole. These arenes yielded **138** and **139**, respectively, as shown in eq 43.



(43)

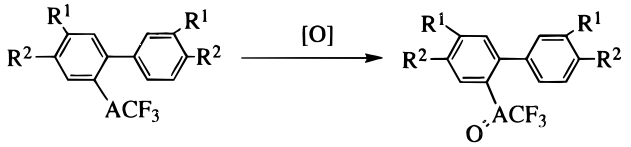
Compounds **138** and **139** reacted with sodium *p*-nitrothiophenolate in DMFA to give *p*-nitrophenyl trifluoromethyl sulfide. However, they did not react with the highly activated aromatic compound *N*,*N*-dimethylaniline, even at elevated temperatures. Thus, the reactivity of these trifluoromethyl diarylsulfonium salts was very low.

B. Power-Variable Trifluoromethylating Agents, *S*-, *Se*-, and *Te*-(Trifluoromethyl)dibenzothio-, -seleno-, and -tellurophenium Salt Systems[66]

We developed a new series of reactive trifluoromethyl dibenzoheterocyclic salts which are electrophilic trifluoromethylating agents. The reactivities of these reagents vary depending on the heteroatoms and ring substituents which are present. The dibenzoheterocyclic system is particularly useful since its ring system is readily formed by intramolecular cyclization and functionalized by nitration and sulfonation. The rings' ease of functionalization is attributed to their high degree of π-electron resonance.

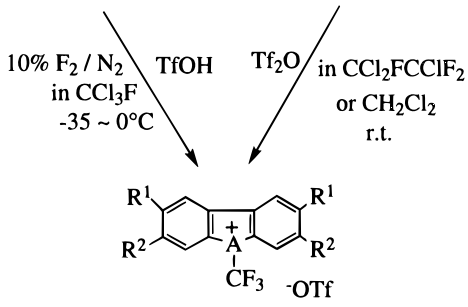
1. Syntheses of S-, Se-, and Te-(Trifluoromethyl)-dibenzothio-, -seleno-, and -tellurophenium Salts and Their Analogs

Thio- and selenophenium salts and their alkyl derivatives, **147**, **148**, and **150**, were synthesized in



140 (A=S, R^1=R^2=H)
141 (A=S, R^1=CH_3, R^2=H)
142 (A=S, R^1=H, R^2=*t*-Bu)
143 (A = Se, R^1=R^2=H)

144 (A=S, R^1=R^2=H) 98%
145 (A=S, R^1=H, R^2=*t*-Bu) 85%
146 (A=Se, R^1=R^2=H) 96%



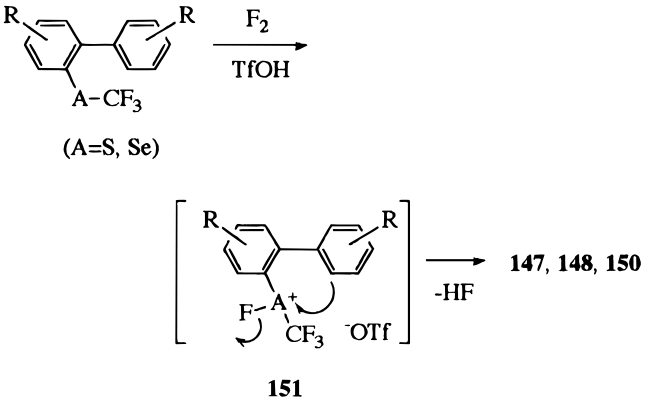
147 (A=S, R^1=R^2=H) 83% (75%*)
148 (A=S, R^1=CH_3, R^2=H) 76%
149 (A=S, R^1=H, R^2=*t*-Bu) (83%*)
150 (A = Se, R^1=R^2=H) 76% (94%*)

(* from **144**, **145** or **146**)

(44)

good yields by fluorination of the sulfides **140** and **141** and selenide **143** with 10% F_2/N_2 in the presence of triflic acid (1 equiv). Two of these salts **147** and

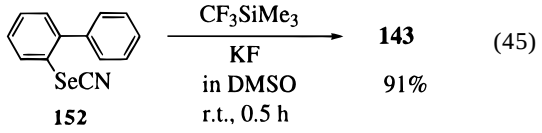
Scheme 6



150 were also synthesized by treatment of the corresponding sulfoxide **144** and the selenoxide **146** with triflic anhydride (Tf_2O). Di-*tert*-butylthiophenium salt **149** was synthesized by similar treatment of sulfoxide **145**. Trifluoroacetyl triflate was also used in place of Tf_2O and resulted in a smoother reaction.[67]

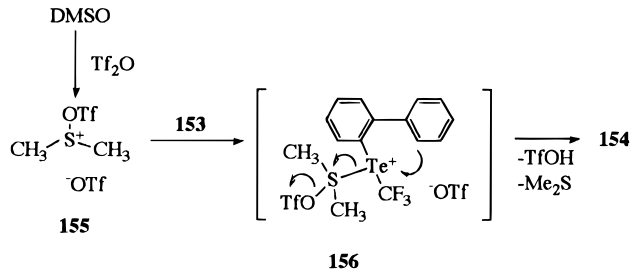
The synthesis of **147**, **148**, and **150** by direct fluorination in the presence of triflic acid involves a cyclization which is initiated by the fluorination of the sulfur. This fluorination is followed by an intramolecular cyclization as shown in Scheme 6. The direct fluorination method can also be accomplished with the use of HBF_4 or BF_3 in place of the triflic acid, in which case the corresponding tetrafluoroborate salts are produced.[66b]

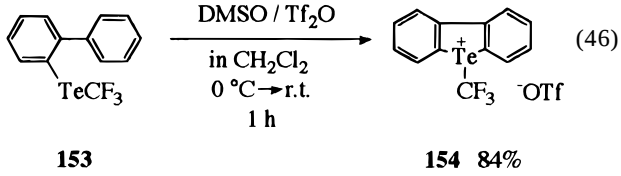
The sulfide starting materials **140**−**142** were prepared by photoreaction of the sodium salts of the corresponding arenethiols with CF_3Br. The selenide starting material **143** was readily prepared in high yield by F^--catalyzed nucleophilic trifluoromethylation of 2-(selenocyanato)biphenyl (**152**) with CF_3-$SiMe_3$ (eq 45).[68]



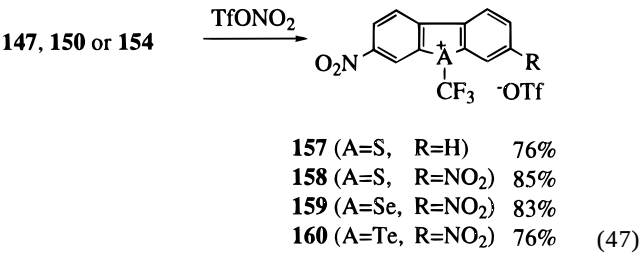
The tellurophenium salt **154** was readily synthesized in high yield by treatment of the telluride starting material **153** with an equimolar mixture of triflic anhydride and DMSO (eq 46) or diphenyl sulfoxide.[66b] This represents a new method of tellurium activation, and its proposed mechanism is shown in Scheme 7. The telluride starting material **153** was prepared by treating bis(2-biphenylyl) ditelluride with sodium borohydride/methanol in the presence of CF_3I or CF_3Br in THF.[66b]

Scheme 7

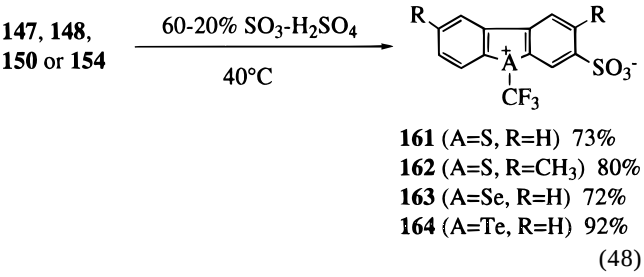




Nitro derivatives **157**−**160** were synthesized by the mono- or dinitration of compounds **147**, **150**, and **154** with nitronium triflate. Using nitromethane as the solvent in the nitration resulted in the exclusive formation of the mononitro derivative. Alternatively, using an excess of the nitronium triflate in the absence of nitromethane gave the dinitro derivative **158** in high yield.



Sulfonate derivatives **161**−**164** were synthesized in good yields by treating the dibenzoheterocyclic salts **147**, **148**, **150**, and **154** with fuming sulfuric acid (eq 48).[69]



The mixed nitro-sulfonate derivative **165** (Figure 2) was also synthesized in good yield by nitration of the monosulfonate derivative **161**.[69]

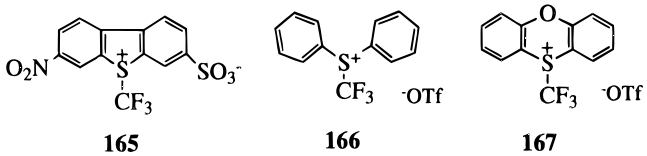
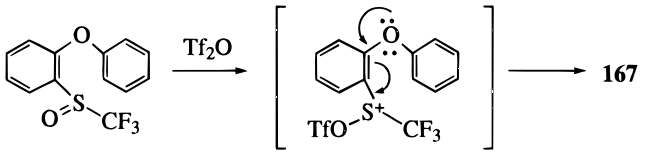


Figure 2.

Compound **166**, the noncyclized analog of thiophenium salt **147**, was synthesized in 59% yield by the triflic anhydride-induced condensation of phenyl trifluoromethyl sulfoxide with benzene. However, this intermolecular condensation was very slow (room temperature, 4 d). The intramolecular condensation of 2-phenoxyphenyl trifluoromethyl sulfoxide (**168**) with triflic anhydride to give the phenoxathiinium salt **167** was also very slow (room temperature, 6 d) (eq 49). The yield of **167** from this reaction was low (26%), and a considerable amount of **168** was recovered. Stabilization of the cationic sulfur atom in intermediate **169** by resonance with the ether oxygen

at the *o*-position may account for the slowness of this reaction.[66b]



(49)

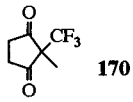
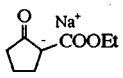
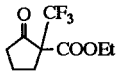
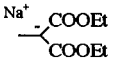
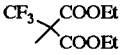
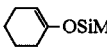
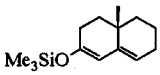
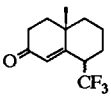
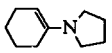
2. Electrophilic Trifluoromethylation by the Power-Variable Trifluoromethylating Agents[66,69]

The trifluoromethylating power of the *S*-, *Se*- and *Te*-salts, **147**−**150**, **154**, **157**−**160**, and **166** were determined by comparing their relative rates of trifluoromethylating aniline. From this comparison, the power order for the series was determined to be **154** < **166** < **148** < **149** < **150** ≤ **160** < **147** < **157** < **159** < **158**. A similar order, **161** < **165**, was observed for the *S*-(trifluoromethyl)dibenzothiophenium-3-sulfonates. Thus, the heterocyclic salts were more reactive than the nonheterocyclic salt and the trifluoromethylating power increased in the order Te < Se < S and 2,8-dialkyl < 3,7-dialkyl < H < 3-nitro < 3,7-dinitro. This order reflects the electron deficiency of the CF_3 group as influenced by the electronegativity of the chalcogens and ring substituents, rather than the inherent nature of the chalcogens. These results explain why **138** and **139** showed low reactivities, since these agents are nonheterocyclic salts with totally electron-donating substituents.[66b]

The ^{19}F NMR chemical shifts of the trifluoromethyl groups support the relationship of CF_3 electron deficiency to trifluoromethylating power. A good linear correlation was obtained when the ^{19}F chemical shifts were plotted vs the Hammett constants σ_p or σ_m for each reagent in the sulfur and selenium series.[66b]

The broad range of trifluoromethylating powers exhibited by the various agents makes it possible to trifluoromethylate a wide range of nucleophilic substrates which differ in reactivity. These substrates

Table 13. Trifluoromethylations of Various Compounds by Power-Variable Trifluoromethylating Agents

Run	Nucleophile	CF_3^+	Molar ratio	Additive*	Solv	Temp (°C)	Time	Product	Yield (%)
1	**20**	**147**	1.3		DMF	-45 → r.t.	6 h	 **170**	84
2		**147**	1.0		DMF	-65 → r.t.	2.5 h		67
3		**147**	1.0		DMF	-65 → r.t.	5 h		38
4	PhC≡CLi	**150**	1.1		THF	-78 → r.t.	1.25 h	PhC≡C-CF_3	89
5		**147**	1.0	Py	DMF	80	overnight	2-$CF_3C_6H_9O$**	65
6		**147**	1.0	Py	DMF	100	overnight	 **171α,β** (α/β=3.6/1)	69
7		**147**	1.0	DMPy	DMF	0	2 h	2-$CF_3C_6H_9O$** 2,6-di(CF_3)$_2C_6H_8O$***	57 26
8	aniline	**158**	2.0		DMF	r.t.	0.5 h	*o*-CF_3-aniline *p*-CF_3-aniline	54 20
9	2-naphthol	**158**	1.0	DMPy	DMF	-20 → r.t.	1.25 h	1-CF_3-2-naphthol 8-CF_3-2-naphthol	52 6
10	*p*-hydroquinone	**158**	1.0	Py	DMF	r.t.	2 h	2-CF_3-*p*-hydroquinone di(CF_3)$_2$-*p*-hydroquinone	61 11
11	pyrrole	**147**	2.5		DMF	80	1.5 h	2-CF_3-pyrrole	90
12	*n*-$C_{12}H_{25}SNa$	**150**	1.0		THF	r.t.	0.5 h	*n*-$C_{12}H_{25}SCF_3$	87
13	2-Ph-C_6H_4SNa	**147**	1.0		DMF	-30 → r.t.	1 h	2-Ph-$C_6H_4SCF_3$	78
14	NaI	**147**	1.0		DMF	r.t.	3 days	CF_3I	70
15	Ph_3P	**158**	1.2		CH_3CN	r.t.	5 h	$Ph_3P^+CF_3$ ^-OTf	78

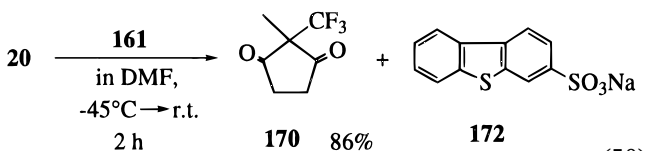
*DMPy=4-(dimethylamino)pyridine. **2-(Trifluoromethyl)cyclohexanone. ***2,6-Bis(trifluoromethyl)cyclohexanone.

include carbanions, activated aromatics, heteroaromatics, enol silyl ethers, enamines, phosphines, thiolate anions, and iodide anions. The less reactive substrates were trifluoromethylated smoothly by the more powerful trifluoromethylating agents, while the more reactive substrates required less powerful trifluoromethylating reagents. Substrates of intermediate reactivity were satisfactorily trifluoromethylated by moderately reactive reagents. This suggests that a quantifiable correlation exists between the electrophilicity of an electrophile and the nucleophilicity of a nucleophile which in combination give the best electrophilic trifluoromethylation. In practice, trifluoromethylations were carried out using three reagents: the most powerful **158**, the intermediately powerful **147**, and the less powerful **150**. These reagents successfully trifluoromethylated the nucleophilic substrates in their corresponding ranges.

As shown in Table 13, **158** smoothly trifluoromethylated activated aromatic compounds such as aniline and phenols, and triphenylphosphine. Compounds **147** and **150** did not trifluoromethylate triphenylphosphine even at elevated temperatures, where they instead decomposed. The very reactive phenylacetylide anion and the easily oxidizable alkanethiolate anions were trifluoromethylated in the highest yields by **150**. The reaction of sodium dodecanethiolate with **147** produced a considerable amount of the corresponding didodecyl disulfide as a byproduct. Sodium salts of active methylene compounds (runs 1−3), enol trimethylsilyl ethers (runs 5 and 6), an enamine (run 7), a reactive heteroaromatic (run 11), and sodium iodide (run 14) were satisfactorily trifluoromethylated by **147**. The trifluoromethylations of *n*-butyl- and phenyllithium, *n*-octyl- and phenylmagnesium chloride, and vinylmagnesium bromide using **147**, **149**, **150**, or **154** were not successful, and trifluoromethane was detected in most cases.

These (trifluoromethyl)dibenzoheterocyclic salts could not trifluoromethylate aromatic compounds whose π-electron densities are less than that of phenol. Moderately reactive aromatics such as benzene, toluene, xylene, mesitylene, biphenyl, naphthalene, and other monohalo derivatives were trifluoromethylated by reacting with carbon tetrachloride and anhydrous hydrogen fluoride at elevated temperature (in an stainless steel autoclave).[70] This useful Friedel−Craft type of reaction very likely proceeded via trichloromethyl aromatics as intermidates, which were converted to the trifluoromethyl aromatics under the reaction conditions. However, this method required the special technique because of dangerous hydrogen fluoride. A variation using $CFCl_3$−$AlCl_3$ has been also reported.[70b]

Trifluoromethylations utilizing the (trifluoromethyl)dibenzoheterocyclic salts produced water-insoluble dibenzothio-, -seleno-, or -tellurophene together with the desired products. However, the reagents **161**−**165** which possess an $-SO_3^-$ substituent on the



(50)

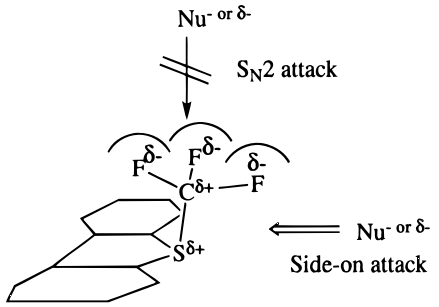


Figure 3.

heterocyclic ring led to water-soluble products, making them very practical as trifluoromethylating agents. The trifluoromethylated products are easily separated from dibenzothiophene-3-sulfonic acid or the analogous salt, **172**, by washing with water (eq 50).[69]

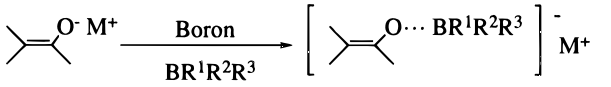
The nitrated reagent **158** decomposed at a lower temperature (140 °C) than its parent compound **147** (200 °C). These salts have potential as good sources of the CF_3^+ cation because their decomposition produced trifluoromethyl triflate (**173**) in high yields.[66b]

Alkaline hydrolysis of **147**, **150**, **157**, and **159** yielded only the corresponding dibenzothiophene *S*-oxide or dibenzoselenophene *Se*-oxide. However, alkaline hydrolysis of the most powerful reagent, **158**, gave a 1:4 mixture of 3,7-dinitrodibenzothiophene and its *S*-oxide. This formation of the dinitrodibenzothiophene indicates that some hydroxide anions attack the CF_3 group, which in turn suggests that variations in the reagents' powers may lead to a change in the reaction mechanism.

The trifluoromethylation of aniline with **147**, **158**, or the nonheterocyclic salt **166** produced *o*- and *p*-(trifluoromethyl)aniline. The kinetic parameters for this reaction were determined as follows: $\Delta H^{\ddagger}$ (kcal/mol), $\Delta S^{\ddagger}$ (eu), and $\Delta G^{\ddagger}$ (kcal/mol) were 21.2, −11.2, and 24.5 for **147**; 17.0, −9.1, and 19.7 for **158**; and 12.1, −47.1, and 26.1 for **166**.[4] The reactivity order of these three reagents is **166** < **147** ≪ **158**, as quantitatively determined from the activation energy, $\Delta G^{\ddagger}$. The kinetic parameters indicated that the increased reactivity of the heterocyclic salt **147** compared to the nonheterocyclic salt **166** is due to a steric factor (entropy term) in the transition state, as opposed to the restoration of lost aromaticity.[71] The higher reactivity of **158**, on the other hand, is due to the electron deficiency induced by the nitro groups. A conventional S_N2 attack mechanism can be ruled out on the basis of the reagents' X-ray crystallographic structures, molecular orbital calculations, and a comparison of the reagents' kinetic data with that of their *S*-methyl analogs (which are known to react by a standard S_N2 mechanism). Instead, the reaction appears to proceed by the side-on attack of a nucleophile to the S−CF_3 bond (Figure 3).[4,72] The difficulty in obtaining a conventional S_N2 attack on the CF_3 by a nucleophile can be explained by the electron distribution calculated for CF_3 [$C^{\delta+}(F^{\delta-})_3$] as compared to the electron distribution calculated for CH_3 [$C^{\delta-}(H^{\delta+})_3$]. Thus, the CF_3 carbon atom is covered by three negatively charged fluorine atoms which are somewhat larger in size than the positively charged hydrogen atoms (Figure 3).[4]

3. Trifluoromethylation of Enolate Anions by Combination with Boron Lewis Acids[73]

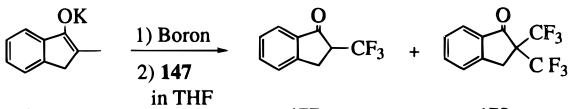
None of the power-variable trifluoromethylating agents were able to satisfactorily trifluoromethylate enolate anions (**174**), as the reactivity of these anions



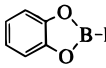
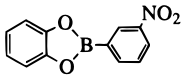
174 **175** (51)

was too great. A more suitable match between the nucleophilicity of the enolate anions and the electrophilicity of the trifluoromethylating agents was obtained by complexing the enolate anions to various boron Lewis acids (**175**), as shown in eq 51. In this manner, we were able to develop a new methodology for trifluoromethylation which consists of combining trifluoromethylating agents with boron Lewis acids. This methodology was successfully applied to the regio-, diastereo-, and enantioselective trifluoromethylation of enolate anions. These reactions provide additional evidence that the electrophilicity−nucleophilicity balance is crucial to electrophilic trifluoromethylation.

Table 14. Effect of Boron Lewis Acids on Trifluoromethylation by 147

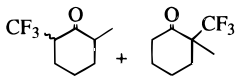
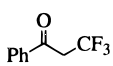
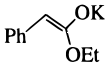
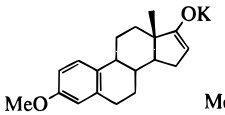
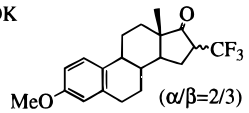


176 **177** **178**

Run	Boron Lewis acid	177	178	CF_3H
1	None	0.8%	8%	17%
2	Et_3B	47	10	13
3	Ph_3B	61	4	3
4		44	1	15
5	$(MeO)_3B$	36	trace	11
6	 **179**	85	0	trace
7		56	0	trace

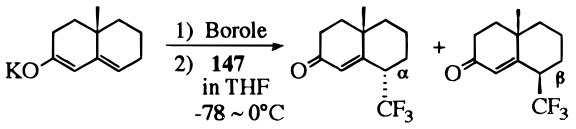
As shown in Table 14, combining trifluoromethylating agent **147** with the boron Lewis acid 2-phenyl-1,3,2-benzodioxaborole (**179**) gave the desired product in the greatest yield. With weaker boron acids, the decomposition reaction leading to the production of CF_3H increased, while with stronger boron acids, a large amount of the trifluoromethylating agent remained unreacted. Various enolates were therefore treated with **147** in the presence of boron **179** to produce trifluoromethylated ketones in high yields as shown in Table 15. The less sterically crowded enolate anion from run 2 yielded the regioselectivly trifluoromethylated ketone **180**, while the sterically hindered enolate anion from run 3 underwent considerable scrambling of the enolate to give a 3:4 mixture of the isomers **180** and **181**.

Table 15. Trifluoromethylation of Enolate Anions by a Combination of 147 and Boron Lewis Acid 179

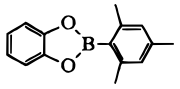
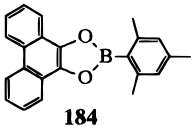
Run	Enolate	Product	Y.(%)
1			71
2		 **180** (c/t=7/5) **181**	60 (59:1)
3		**180** + **181** (c/t=8/7)	70 (3:4)
4			92
5			40
6		 (α/β=2/3)	58

As shown in Figure 4, combining trifluoromethylating agent **147** with the boron Lewis acid 2-phenyl-1,3,2-benzodioxaborole (**179**) gave the desired product in the greatest yield. With weaker boron acids, the decomposition reaction leading to the production of CF_3H increased, while with stronger boron acids, a large amount of the trifluoromethylating agent remained unreacted. Various enolates were therefore treated with **147** in the presence of boron **179** to produce trifluoromethylated ketones in high yields as shown in Table 15. The less sterically crowded enolate anion from run 2 yielded the regioselectivly trifluoromethylated ketone **180**, while the sterically hindered enolate anion from run 3 underwent considerable scrambling of the enolate to give a 3:4 mixture of the isomers **180** and **181**.

The trifluoromethylation of the enol trimethylsilyl ether from run 6 in Table 13 predominantly formed the thermodynamically stable α-CF_3 isomer **171**α. However, the trifluoromethylation of the enolate anion **182** shown in eq 52 with boron **179** formed the thermodynamically less stable β-CF_3 isomer **171**β as the major product. The ratio of the β-isomer which



182 **171α** **171β**

Boroles	Yield (%)	Ratio of isomers 171α : 171β
179	81%	1 : 2.5
 **183**	50%	1 : 3
 **184**	51%	1 : 4

(52)

was produced increased with increasing bulkiness of the boron compounds such that the bulkiest boron, **184**, afforded a ratio of $\alpha/\beta = 1/4$. This can be explained on the basis of the conformation of the intermediate complex which is shown in Figure 4. This conformation forces the reagent to attack the complex from the less hindered β-face, which then leads to formation of the β-isomer.

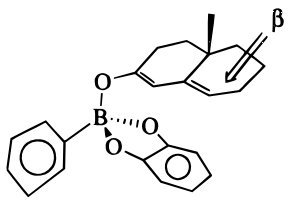
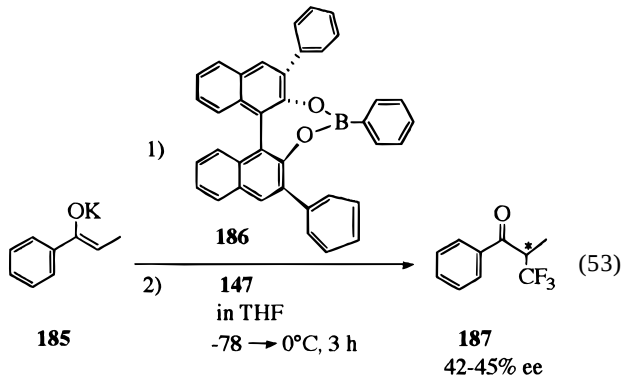


Figure 4.

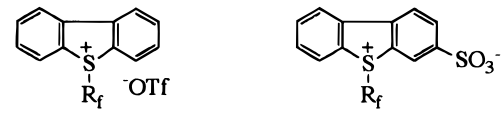
Enantioselective trifluoromethylation was achieved by using the bulky, optically acitive boron **186** as shown in eq 53. Nucleophilic, enantioselective trifluoromethylations have also been reported.[74]



(53)

C. Power-Variable Perfluoroalkylating Agents[66,69,73]

S-(Perfluoroalkyl)dibenzothiophenium triflates **188**-**191** and the corresponding 3-sulfonates **192** - **194** (R_f = C_2F_5; C_3F_7; C_4F_9; and C_8F_{17}) (Figure 5) were



188 $R_f = C_2F_5$
189 $R_f = n\text{-}C_3F_7$
190 $R_f = n\text{-}C_4F_9$
191 $R_f = n\text{-}C_8F_{17}$

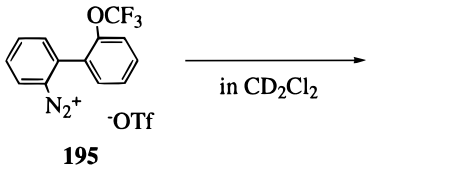
192 $R_f = C_2F_5$
193 $R_f = n\text{-}C_4F_9$
194 $R_f = n\text{-}C_8F_{17}$

Figure 5.

synthesized in a manner similar to the *S*-(trifluoromethyl) salts. These perfluoroalkyl reagents reacted similarly to the trifluoromethyl reagents; however, their reactivities differed from those of the related FITS reagents. For example, treatment of sodium salt **20** with **193** produced 2-methyl-2-(perfluorobutyl)cyclopentane-1,3-dione in 86% yield.[69] Thus, these perfluoroalkyl chalcogen salts gave *C*-perfluoroalkylation, while the FITS reagents gave both *C*- and *O*-perfluoroalkylations. These perfluoroalkyl chalcogen salts were also considerably less reactive than the FITS reagents. FITS readily reacted with anthracene at 0 °C (in CH_2Cl_2), while the most powerful dinitrothiophenium salt, **158**, did not do so even at 80 °C (in DMF).

D. *O*-(Trifluoromethyl)dibenzofuranium Salts[75]

O-(Trifluoromethyl)dibenzofuranium salts are expected to act as very strong electrophilic trifluoromethylating agents, since oxygen is the most electronegative member of the chalcogen series. Although trifluoromethyl oxonium salts have not been reported yet, we have succeeded in generating them as reactive species.[76] For example, heating 2-(trifluoromethoxy)biphenylyl-2′-diazonium triflate (**195**) in methylene chloride-d_2 at 41 °C for 3 h produced trifluoromethyl triflate (**173**) and dibenzofuran **196** (eq 54).

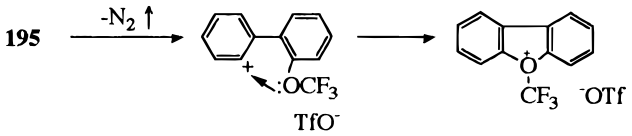


195

173 65% **196** 75% (54)

These products are believed to result from *O*-(trifluoromethyl)dibenzofuranium triflate (**198**), the formation of which is shown in Scheme 8, by immediate

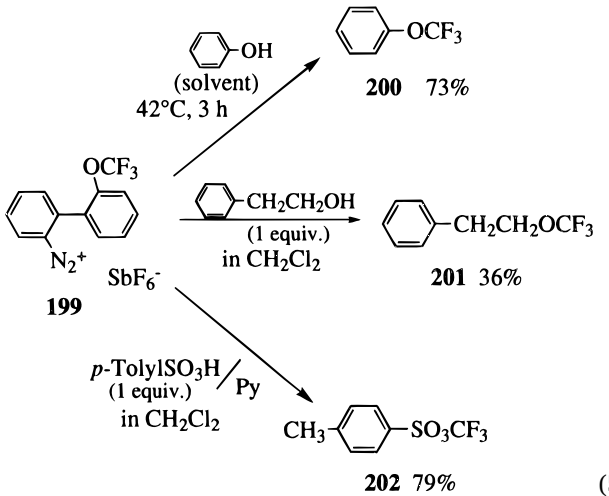
Scheme 8



197 **198**

decomposition to **196** and a CF_3^+ cation. The CF_3^+ cation combines with the $^-$OTf counteranion to give **173**. Thus, this reaction proceeded via an S_N1 mechanism, which is further supported by the fact that an analogous diazonium salt, 2,6-bis[2′-(trifluoromethoxy)phenyl]phenyldiazonium hexafluoroantimonate, decomposed to produce CF_4. This CF_4 is formed by generation of a CF_3^+ cation which then abstracts an F^- from the nonnucleophilic SbF_6^- anion. The reactions demonstrate that a mild and useful method for generating actual CF_3^+ cations in solution has finally been developed.

We found the diazonium hexafluoroantimonate **199** to be very useful for *O*-trifluoromethylating phenols, alcohols, and sulfonic acids or salts as shown in eq 55.[75]



199 **200** 73% **201** 36% **202** 79% (55)

There have been only a few other reports of *O*-trifluoromethylation. Makarov et al. reported the formation of methyl trifluoromethyl ether by treating trifluoronitrosomethane with hydroxylamine in methanol.[77] Olah et al. reported the formation of **173** by heating a mixture of triflic acid and fluorosulfonic acid,[78] while we reported its synthesis by thermolysis of **147** and **158**.[66b] The preparation of α,α,α-trifluoroanisole from phenol and $CF_3S(O)n(OCF_3)_2$ ($n = 0,1$) was reported by Shreeve et al., however they proposed that the mechanism proceeded via an intramolecular nucleophilic attack by the trifluoromethoxy group.[79] Naumann et al. reported that the photoreaction of $Te(CF_3)_2$ with *p*-benzoquinone formed 1,4-bis(trifluoromethoxy)benzene (**203**) as a minor component. In this case, the formation of **203** was believed to result from the attack of CF_3 free radicals on the oxygen atoms of *p*-benzoquinone.[80] Various aryl trifluoromethyl ethers were prepared by reacting phenols with carbon tetrachloride and hydrogen fluoride at elevated temperature.[81] These reactions proceeded via aryl trichloromethyl or polychlorofluoromethyl ethers as intermediates.

V. Concluding Remarks

A considerable number of electrophilic perfluoroalkylating agents have been developed, some of which are now commercially available.[14f,66c] Thus, perfluoroalkyl-containing compounds, which were difficult to prepare by conventional free radical or nucleophilic methods, can now be easily prepared by electrophilic methods. This should lead to the development of new medicines and agricultural chemicals, new materials for electronics, and other new and useful fluorinated compounds. Despite all the new electrophilic perfluoroalkylating agents which have been developed, however, R_f−I and R_f−Br may still be useful for perfluoroalkylations of selected nucleophiles. These simple reagents are more readily available and they give equivalent or better product yields in selected reactions.

Much work still remains to be done in developing additional electrophilic perfluoroalkylation reagents and in elucidating the electrophilic perfluoroalkylation mechanisms. Because fluoroalkylation mechanisms are often completely different from hydrocarbon alkylation mechanisms, these mechanistic studies have the potential to uncover new, unique reaction concepts which are not endemic to hydrocarbon chemistry.

Acknowledgments

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(15) *Note*: Spectrophotometric grade of benzene was recommended, because clear white crystals of FITS reagents were obtained when such pure benzene was used.

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