Perfluoroalkylation with Organosilicon Reagents

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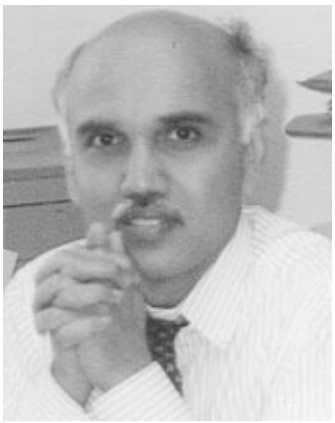
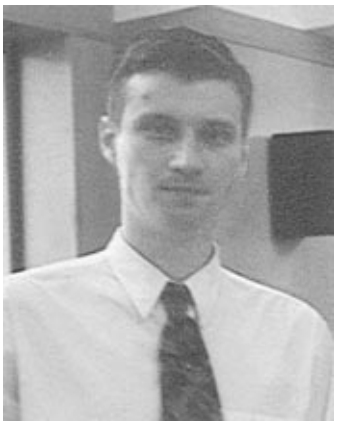


Surya Prakash was born in Bangalore, India, in 1953. He received a B.Sc. (Honors) degree in 1972 from the Bangalore University and a M.Sc. degree from Indian Institute of Technology, Madras, in 1974. He obtained a Ph.D. degree in 1978 from the University of Southern California (USC) in 1978 under the tutelage of George A. Olah. After postdoctoral work at USC, he was appointed to Research Assistant Professor position at the Loker Hydrocarbon Research Institute at USC in 1981 and soon promoted to Research Associate Professorship. In 1990, he accepted an Associate Professor position in the Chemistry Department at USC in the tenure track. He was promoted to full professorship in 1994. Currently, he holds the Olah Nobel Laureate Chair in Hydrocarbon Chemistry with research contributions and interests in new fluorination methods, new synthetic methods, mechanistic studies of organic reactions, electrochemistry, and superacid and hydrocarbon chemistry. He has published more than 300 papers, book chapters, and review articles; co-authored 4 books; and holds 3 patents. He has received many honors and recognition. He is currently an Advisory Editor of the *International Journal of Porphyrins and Pthalocyanins*.



Andrei Yudin was born in Moscow, Russia, in 1970. He received his B.S. degree in 1992 at the Moscow State University where he carried out research work in the labortory of Professor Nicolai S. Zefirov. In 1992 he joined the research group of Professor G. K. Surya Prakash at the University of Southern California where he obtained his Ph.D. degree in 1996. Currently, he is a postdoctoral associate in Professor K. Barry Sharpless' group at the Scripps Research Institute. His main research interests are in organofluorine chemistry and asymmetric catalysis.

1. Introduction

Partially fluorinated organic compounds often possess properties that make them suitable for diverse applications in materials science, agrochemistry, and pharmaceutical industry.[1,2] Generally, the unique behavior of fluorinated systems is attributed to the high electronegativity of fluorine (4.0 on Pauling's electronegativity scale) combined with the relatively close size of the fluorine atom to hydrogen (the van der Waal's radii of F and H atoms are 1.47 and 1.2 Å, respectively) leading to the increase in oxidative, hydrolytic, and thermal stability (the C−F bond energy averages about 116 kcal/mol).

Straightforward and reliable procedures for the introduction of the perfluoroalkyl groups are highly desirable. In recent years, R_fSiR_3 reagents have become very useful in applications where perfluoroalkylation is involved. Authors' interest in this field

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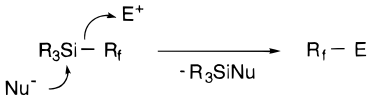
Scheme 1



began with the studies on the development of (trifluoromethyl)trimethylsilane and other (perfluoroalkyl)trialkylsilanes as reagents for perfluoroalkylation. Generally, nucleophilic activation of the silicon center in these species allows transfer of the perfluoroalkyl functionality to varied electrophiles taking advantage of silicon's high fluoro- and oxophilicity (Scheme 1). Under these conditions, the perfluoroalkylated silane behaves as a synthetic equivalent of "R_f^-" and thus is capable of reacting with electrophiles.

Relative nontoxicity, stability, ease of handling, and availability of the silylated species make them convenient reagents for different transformations. No comprehensive review on this fast developing field has appeared since 1992.[3] The present effort is aimed at summarizing the recent results in silicon-assisted perfluoroalkylation. The chemistry of the following groups attached to the silicon center is covered: CF_3, CF_2X (X = H, Cl, Br), $CF{=}CF_2$, C_nF_{2n+1}, C_6F_5, $(CF_2)_n$, CF_2R (R = alkyl, alkenyl). Special attention is centered on the preparation and applications of the CF_3-containing organosilanes. A comprehensive review on general methods for the introduction of the trifluoromethyl group was published in 1992.[4]

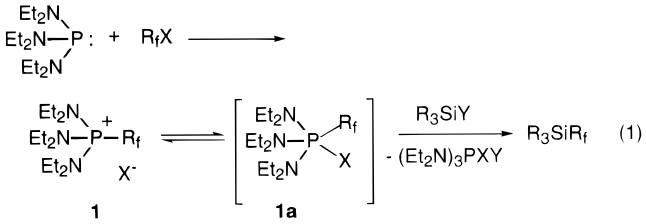
2. General Methods for the Preparation of Perfluoroalkylated Organosilicon Compounds

One of the most general methods for the preparation of organosilicon compounds is based on the reactions between silyl halides and organometallic reagents (such as derivatives of magnesium and lithium).[5] Following Gilman's studies, various perfluoroalkylated organosilanes are accessible using this methodology.[6,7] Notable exceptions are CF_3-containing organosilanes whose inaccessibility is attributed to the kinetic lability of the CF_3-organometallic precursors that readily decompose to give the corresponding carbene species along with the formation of strong metal−fluorine bonds.[8] Alternative methods have been developed in order to avoid this problem. General procedures that are currently employed for the preparation of compounds containing Si−R_f bond(s) are discussed in this section.

2.1. Ruppert's Procedure and Its Modifications

Ruppert's original method for the preparation of (trifluoromethyl)trimethylsilane involves condensation between CF_3Br and Me_3SiCl, mediated by $(Et_2N)_3P$.[9] The reaction is accompanied with a net loss of $(Et_2N)_3PClBr$ (eq 1, $R_f = CF_3$, X = Br, Y = Cl).

Mechanistically, the process is considered to include the formation of the phosphonium salt **1** through a "bromophilic" attack of the phosphorus center of $(Et_2N)_3P$ by CF_3Br. The salt **1** is in equilibrium with pentavalent intermediate **1a** which reacts with Me_3SiCl by *in situ* CF_3^- transfer to afford

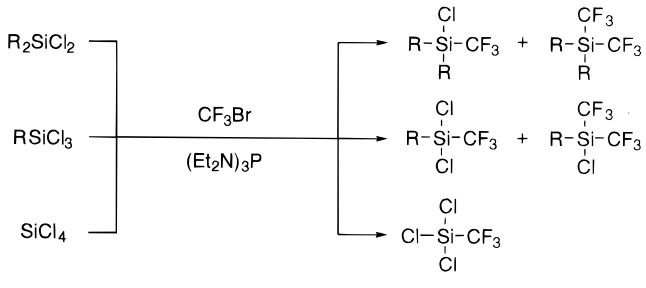


Me_3SiCF_3 (**2**) as a colorless, volatile liquid (bp 54−55 °C). A modified procedure, developed by Prakash *et al.*, significantly simplified the original method.[10] A variety of other perfluoroalkylated silanes can be obtained using this general protocol. Table 1 features representative examples from the literature. Chlorinated organosilanes also react with CF_2X_2 (X = Cl, Br) under these conditions to give the monosilylated products (Table 1, entries 5−7).[13] The trimethylsilylated halofluoromethanes thus obtained are amenable to reduction which selectively substitutes chlorine and bromine atoms for hydrogen(s) to yield compounds with the formula $Me_3SiCF_xH_y$. Polyfluorinated alkenyl halides are silylated with the retention of geometry at the double bond (Table 1, entry 11). Selective monosubstitution of a chlorine atom in 1,2-dichlorooctafluorocyclohexene (Table 1, entry 14, $n = 2$) was achieved by Bardin *et al.*[14a] Long-chain perfluorooxaalkyl iodides were used by Chen *et al.* to obtain the corresponding trimethylsilylated adducts (Table 1, entries 15−17).[16] In the case of secondary long-chain perfluorooxa derivatives, Grignard route is also applicable but gives inferior yields compared to the modified Ruppert's method.

In a related case, Ruppert *et al.* showed that polychlorinated organosilanes give the corresponding poly(trifluoromethyl) derivatives (Scheme 2).[9,17] Additionally, it was demonstrated that trichloro(trifluoromethyl)silane CF_3SiCl_3 is readily transformed into **2** using MeMgBr as the methylating agent (see section 3.4). Some of the polyhalogenated CF_3-containing chlorosilanes were also investigated with respect to the preparation of the corresponding polysiloxanes (see section 3.4). Using Ruppert's procedure, Bürger *et al.* obtained and characterized the compounds $(CF_3)_2SiH(NR_2)$ (R = Me, Et, *i*-Pr).[18] These authors also succeeded in the preparation of the first tris(trifluoromethyl)silane derivative, $(CF_3)_3SiNEt_2$. Bardin *et al.* converted $Me_2SiClOEt$ into bis(pentafluorophenyl) derivative using Ruppert's protocol.[14b]

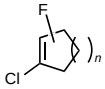
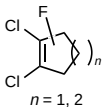
An X-ray structure of the phosphonium salt **1a** (R_f = CF_3, X = Br) was recently determined by

Scheme 2



(R = Me, Ph)

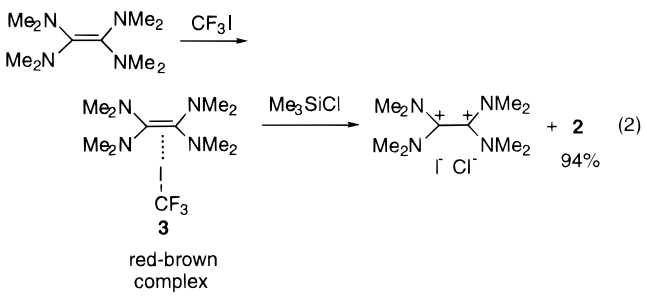
Table 1. Preparation of (Perfluoroalkyl)trialkylsilanes by Ruppert's Procedure and Its Modifications

entry	R_fX	R_3SiY	yield (%)[a]	ref
1	CF_3Br	Me_3SiCl	95	9[b]
			75	10
2	CF_3Br	Et_3SiCl		11
3	CF_3Br	$PhMe_2SiCl$		12
4	CF_3Br	$Ph_2MeSiCl$		12
5	CF_2ClBr	Me_3SiCl	10	13
6	CF_2Br_2	Me_3SiCl	80	13
7	$CFClBr_2$	Me_3SiCl	75	13
8	C_2F_5Br	Me_3SiCl	50	10
9	n-C_3F_7Br	Me_3SiCl	68	10
10	$CF_2{=}CFBr$	Me_3SiCl	85	14
11	$(CF_3)_2CFCF{=}CFI$	Me_3SiCl	77	14
12	C_6F_5Br	Me_3SiCl	70	15
13		Me_3SiCl	41 ($n = 1$)	14
14	 $n = 1, 2$	Me_3SiCl	78 ($n = 2$)	14
			59 ($n = 2$)	14
			54 ($n = 1$)	14
15	$(CF_3)_2CFO(CF_2)_4I$	Me_3SiCl	75	16
16	$C_3F_7OCF(CF_3)CF_2OCF(CF_3)I$	Me_3SiCl	69	16
17	$C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)I$	Me_3SiCl	89	16
18	CF_3Br	$H[N(CH_3)_2]_2SiCl$	86	13

[a] Blank space in the yield column indicates that no yield was reported. [b] High yield was reported, but the reaction conditions were not fully given.

Röschenthaler *et al.* confirming the mechanistic rationale for the overall trifluoromethylation process proposed earlier.[19] **1a** can be isolated as a colorless, hygroscopic solid, soluble in THF. Furthermore, its reactions with aldehydes lead to trifluoromethylated carbinols upon fluoride ion initiation supporting the *in situ* generation of "CF_3^-" during the preparation of **2**. Phosphorus-based electrophiles such as 1,2-bis-(dichlorophosphino)ethane, were also found to be good acceptors for the "CF_3^-" generated from the reagent combination $CF_3Br/P(NMe_2)_3$.[20] Trifluoromethyl iodide is unsuitable for the preparation of a similar iodinated derivative due to the different electron affinity of CF_3I which leads to the preferential formation of a covalent adduct $CF_3P(NMe_2)_3$ and a salt $[P(NMe_2)_4]^+I^-$.[19]

Pawelke reported that a charge-transfer complex **3**, formed between CF_3I and tetrakis(dimethylamino)-ethylene also acts as a trifluoromethylating agent in reactions with Me_3SiCl producing **2** in good yield (eq 2).[21] CF_3Br was found to be ineffective in this case.



(2)

Bürger *et al.* extended Pawelke's method to the dibromofluoromethylation of a variety of organosilyl halides (Table 2). Compounds with the general formula $R_{4-n}SiCl_{n-1}(CFBr_2)$ are available using this method.[22] When CH_2FSiBr_2Me was stored in a benzene solution for several weeks, complete transformation to the rearranged product $CH_2BrSiFBrMe$ was noted. High fluorophilicity of silicon is revealed here. In addition, it was further found that the reduction of the C−Br bond(s) in $R_{4-n}SiCl_{n-1}(CFBr_2)$ gives the corresponding CFH_2^- derivatives in good yields.

Table 2. Preparation of the $CFBr_2^-$ Containing Organosilanes

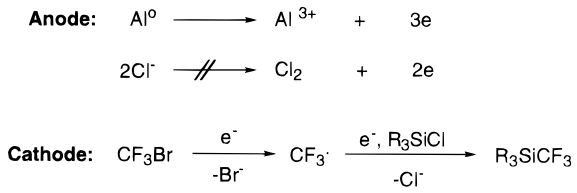
entry	$R_{4-n}SiCl_n$	product	yield (%)
1	$SiCl_4$	$CFBr_2SiCl_3$	30
2	$MeSiCl_3$	$CFBr_2SiMeCl_2$	44
3	Me_2SiCl_2	$CFBr_2SiMe_2Cl$	35
4	Me_3SiCl	$CFBr_2SiMe_3$	54
5	$EtSiCl_3$	$CFBr_2SiEtCl_2$	49
6	Et_2SiCl_2	$CFBr_2SiEt_2Cl$	51
7	n-$PrSiCl_3$	$CFBr_2Si(n\text{-}Pr)Cl_2$	42
8	i-$PrSiCl_3$	$CFBr_2Si(i\text{-}Pr)Cl_2$	36
9	i-$BuSiCl_3$	$CFBr_2Si(i\text{-}Bu)Cl$	39
10	s-$BuSiCl_3$	$CFBr_2Si(s\text{-}Bu)Cl_2$	27

The common byproducts in the preparation of perfluoroalkylated organosilanes are siloxanes produced due to the reactions between the corresponding chlorosilane and residual water. Tedious purification of the products from the siloxane impurities by a fractional distillation can be avoided. Siloxanes are conveniently removed by treatment with 98% sulfuric acid that does not affect perfluoroalkylated derivatives.[23] As a general rule, the perfluoroalkylated silanes are relatively stable to acid and water—a considerable advantage over related widely utilized organometallic reagents.

2.2. Aluminum-Induced Reductive Methods

The main disadvantage of the methods discussed so far is their relative practical inconvenience and high cost of the reagents involved, $[(Et_2N)_3P$ in Rup-

Scheme 3



Overall Reaction:

$$CF_3Br + R_3SiCl + 2/3\ Al \xrightarrow{2e^-} \mathbf{2} + Br^- + Cl^- + 2/3\ Al^{3+}$$

entry	R_3SiCl	reaction medium	yield (%)[a]	reference
1	Me_3SiCl	PhOMe/HMPA (10:1)	73	24
2	Me_3SiCl	DMF		25
3	t-$BuMe_2SiCl$	THF/HMPA (10:1)	40	26

a, blank space indicates that no yield was reported;

pert's procedure and CF_3I in Pawelke's]. In order to circumvent these limitations, several aluminum-mediated reductive methods have been developed.

Although the two-electron reduction of bromotrifluoromethane yields a highly unstable trifluoromethyl anion, the conditions under which it could be efficiently generated and trapped, were found. The sacrificial aluminum anode technique was applied to convert bromotrifluoromethane into **2** in good isolated yield.[24−26] In this method, the readily oxidizable aluminum anode prevents the formation of elemental chlorine (through the oxidation of chloride ions, Scheme 3). The outlined process, an example of electroassisted Barbier reaction, is possible because chlorotrimethylsilane is not reduced at cathodic potentials more positive than −3.0 V *vs* SCE, whereas CF_3Br is more easily reduced (−1.7 V *vs* SCE).[27] This ensures that halogenation and other side reactions of the reduced species are largely suppressed permitting the synthesis in an undivided cell. The reduction of CF_3Br occurs at the surface of a nickel cathode where the electrogenerated anions are coupled with Me_3SiCl to afford **2**. It follows from the work of Deffieux, Bordeaux, Biran, and Dunoguès that aluminum cations in the reaction medium make the generated "CF_3^-" a softer base which is critical for the silylation reaction.[28] DMF was used as a reaction medium in a similar preparation, described by Nédélec *et al.*[25] It should be noted that the electrochemical technique was also found to be suitable for the mono- and bis(trimethylsilylation) of CF_2Br_2.[26]

Using these results, Grobe *et al.* have found that the aluminum/***N***-methylpyrrolidinone (NMP) combination induces the two-electron reduction of bromotrifluoromethane to produce **2** without the electrochemical activation.[29]

Various perfluoroalkylated silanes (eq 3 and Table 3) are similarly obtained by this method at room temperature. Prakash *et al.* have found that the

$$-\overset{|}{\underset{|}{Si}}-X\ (1.5\ eq) \xrightarrow[NMP,\ Al\ (0.7\ eq),\ rt]{YCF_2Br} -\overset{|}{\underset{|}{Si}}-CF_2Y \qquad (3)$$

(X = halogen)

carbon−bromine bond of CF_2BrCl is selectively reduced by aluminum powder in NMP in the presence of Me_3SiCl at room temperature and Me_3SiCF_2Cl (**4**)

Table 3. Preparation of Perfluoroalkylated Silanes Using Aluminum/NMP Combination

entry	R_3SiX	Y	yield (%)	ref
1	Me_3SiCl	F	62	29
2	Me_3SiCl	CO_2Et	80	26
3	Me_3SiCl	Cl	75	30
4	Me_3SiBr	Br	55	30
5	Me_2SiCl_2	Cl	45	26
6	$MeSiCl_3$	Cl	38	26

is obtained in good isolated yield on a preparative scale (Table 3, entry 3).[30] Singlet difluoromethylene involvement can also explain the observed chemistry. However, it is ruled out when Me_3SiBr is used as an electrophile giving **4** with no traces of alternative Me_3SiCF_2Br. The formation of a gaseous CF_2ClH as a byproduct also supports the anionic mechanism. The cationic aluminum species formed during the oxidation of aluminum in the system must efficiently stabilize the intermediate "CF_2X^-" anions in this procedure.

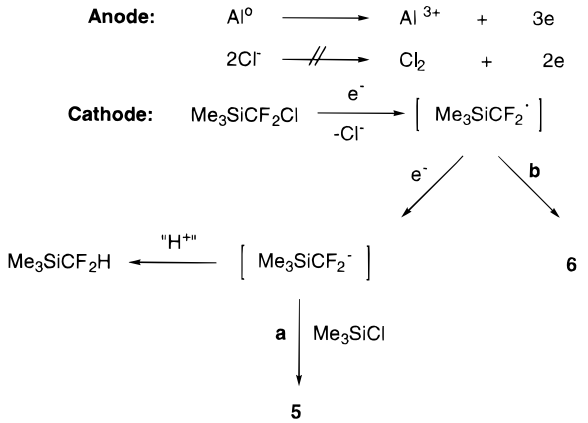
The presence of carbon−chlorine bond in **4** suggests the possibility of further reductive coupling with electrophiles. The aluminum/NMP combination, however, is not reactive enough to reach the reduction potential of the C−Cl bond of **4** and promote its subsequent coupling with Me_3SiCl or other electrophilic agents. Ruppert's procedure starting from the corresponding dihalide is also unsuitable. Again, the desired transformation becomes possible with electrochemical methods (eq 4).[30]

$$Me_3SiCF_2Cl \xrightarrow[NBu_4Br,\ 100\mu A]{+2e^-,\ Me_3SiCl} Me_3SiCF_2SiMe_3 + Me_3SiCF_2CF_2SiMe_3 \qquad (4)$$

	5	**6**
THF/HMPA (10 : 1)	90	10
THF/TDA-1 (3 : 1)	15	85

A strong solvent effect on the electroreduction allows the preparation of difluorobis(trimethylsilyl)-methane (**5**), or tetrafluoro-1,2-bis(trimethylsilyl)-ethane (**6**) depending on the nature of the medium. Using HMPA as a cosolvent with THF predominantly leads to the formation of the anionic product **5** (Scheme 4, path a), whereas when tris(3,6-dioxaheptyl)amine (TDA-1) is used, the homocoupled product

Scheme 4



6 dominates (Scheme 4, path b). This finding allows the reaction to be funneled through a radical or anionic pathway depending on the medium. The solvent TDA-1 increases the lifetime of the radical cage formed during the first electron-transfer step of the reduction, permitting the dominance of the radical-derived product **6**, whereas HMPA, a well-known solvent for its stabilizing effect on the anionic species, favors the formation of anion-derived product **5**. Alternatively, TDA-1 can assist in the desorption of Me_3SiCF_2 radicals from the electrode surface into the medium preventing further reduction. Analogous organometallic routes to **5** and **6** from CF_2Br_2 and CF_2BrCF_2Br, respectively, suffer from the competition of α- and β-elimination of the halide ions.[31] The electrochemical methodology thus seems to be a method of choice for the straightforward preparation of the reagents **5** and **6** from readily available starting materials.

2.3. Grignard and Related Organometallic Routes

The long-chain perfluorinated organosilanes are readily accessible via Grignard or Barbier-type reactions between the corresponding perfluorinated halides and trimethylsilyl chloride following Gilman's studies.[4a,6,7] Markedly, this method is not applicable to CF_3 halides due to the competition from α-elimination of the fluoride ion from the precursor organometallic species. On the other hand, the long-chain perfluoroalkylated organometallics are relatively stable which allows them to be efficiently trapped with halogenated silanes. The isolated yields are generally nearly quantitative. Metal−halogen exchange between the corresponding R_fBr and methyl or ethyl magnesium bromide in the presence of chlorotrimethylsilane (Barbier-type procedure) is preferred for the preparation of primary R_fSiMe_3 (eq 5). Farnham showed that bis(silylated) derivatives can also be readily prepared with this method. Production of R_fH by competitive protonation is not significant.[16,32]

$$R_fBr + Me_3SiCl \xrightarrow[2.\ HCl]{1.\ Mg,\ THF} R_fSiMe_3 \qquad (5)$$

yield 80 - 85%

$R_f = CF_3(CF_2)_n$ n = 5, 7
$R_f = -(CF_2)_m$ m = 6, 8, 10
$R_f = (CF_3)_2CFO(CF_2)_4$

Tarrant *et al.* obtained (perfluorovinyl)triethylsilane via proton−lithium exchange reaction of trifluoroethylene with *n*-butyllithium followed by trapping of the resulting organometallic derivative with chlorotriethylsilane (Table 4).[33] An improved procedure by Hiyama *et al.* employs coupling between the readily available chlorotrifluoroethylene and the corresponding chlorosilane mediated by *n*-butyllithium.[34] Li−Cl exchange and spontaneous silylation take place selectively giving the target compounds in good yields. The use of methyllithium was reported to further simplify purification of the products.[35] Additionally, olefinic fluorine atom, *trans* to the silyl group of the fluorovinylated silane obtained with this method, is amenable to the substitution by various organometallic reagents (mainly the derivatives of lithium), providing an additional approach

Table 4. Preparation of (Perfluorovinyl)silanes

entry	alkene	chlorosilane	metalating agent	yield (%)	ref
1	CF_2=CFH	Et_3SiCl	*n*-BuLi	79	33
2	CF_2=CClH	Et_3SiCl	*n*-BuLi	10	34
3	CF_2=CFCl	Et_3SiCl	*n*-BuLi	85	34
4	CF_2=CFCl	(*n*-Pr_3SiCl	*n*-BuLi	93	34
5	CF_2=CFCl	$Me_2PhSiCl$	*n*-BuLi	88	34
6	CF_2=CFCl	$PhCH_2Me_2SiCl$	*n*-BuLi	93	34
7	CF_2=CFCl	$Ph_2MeSiCl$	*n*-BuLi	79	34
8	CF_2=CFCl	Et_2SiCl_2	*n*-BuLi	88	34
9	CF_2=CFCl	Ph_2SiCl_2	*n*-BuLi	88	34
10	CF_2=CFCl	$PhSiCl_3$	*n*-BuLi	52	34
11	CF_2=CFBr	Et_3SiCl	MeLi	88	35

to functionalized (difluorovinyl)silanes (R_3SiCF=CFX, X = *n*-Bu, *t*-Bu, SEt).[36]

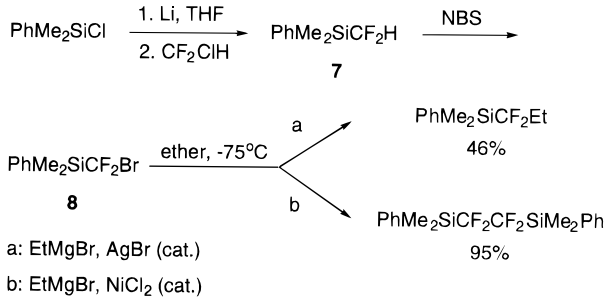
Quenching *gem*-difluoroallyllithium with dimethyl(*n*-butyl)chlorosilane can be used for the preparation of Me_2(*n*-Bu)$SiCF_2CH$=CH_2, a formal equivalent of the *gem*-difluoroallyl anion.[37] Under similar conditions the isolation of the corresponding bis(difluoroallylated) derivative in 73% yield was also reported.

Fluoroalkanes containing electron-withdrawing groups connected to the α-carbon are easily converted into the corresponding silylated derivatives upon proton−lithium exchange and subsequent silylation. In these CF_2XY derivatives the derived anions are stabilized by the electron-withdrawing substituents that reduce the possibility of unwanted α-elimination of the fluoride ion from the intermediate "CF_2X^-" species (eq 6).[38]

$$HCF_2P(O)(OEt)_2 \xrightarrow[2.\ Me_3SiCl]{1.\ LDA,\ THF,\ -78^oC} Me_3SiCF_2P(O)(OEt)_2 \qquad (6)$$

(Difluoromethyl)phenyldimethylsilane (**7**) was prepared by Ojima *et al.* via substitution of chlorine in chlorodifluoromethane by (phenyldimethylsilyl)lithium obtained from the phenyldimethylchlorosilane by metalation (Scheme 5).[39] It was found, that *N*-bromosuccinimide (NBS) readily brominates the C−H bond in **7** giving the bromodifluoromethylated derivative **8**. Its properties with respect to coupling with Grignard reagents were also investigated. In the reactions with ethylmagnesium bromide, nickel dichloride as a catalyst leads to preferential homocoupling, whereas silver bromide induces the bromide substitution.

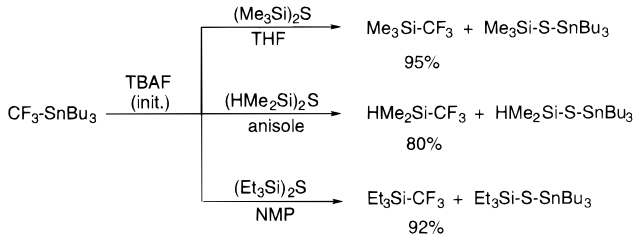
Scheme 5



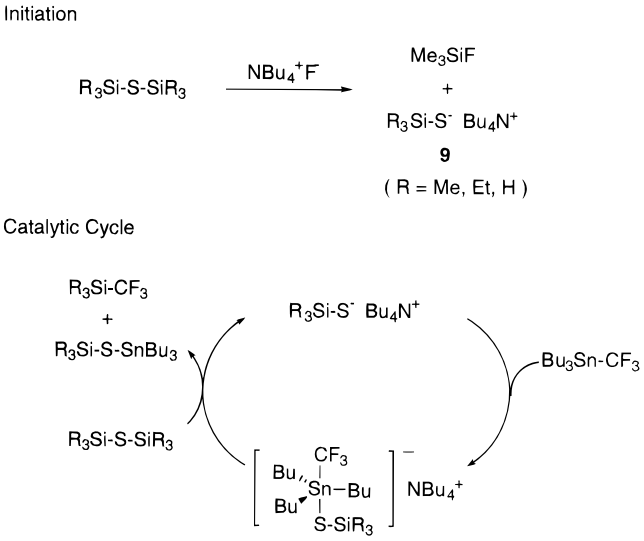
2.4. Other Routes

For the first time elusive **2** was observed by Eaborn *et al.* in the course of the palladium-catalyzed cross-

Scheme 6



Scheme 7

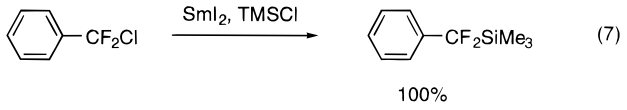


coupling between iodotrifluoromethane and hexamethyldisilane.[40] This, however, is not a preparative method since only traces of the product were detected.

Now even commercially available from several suppliers **2** can be used as a starting material for the preparation of other trifluoromethylated silanes via "transtrifluoromethylation".[41] In this method, **2** is first converted into Bu_3SnCF_3 (see section 3.1.8). Bu_3SnCF_3 is in turn allowed to react with various disilyl sulfides according to Scheme 6 whereby the formation of a Sn−S bond is accompanied with a transfer of the trifluoromethyl group from tin to silicon. The reaction can be explained on the grounds of the HSAB principle: tin is a softer acid than silicon, therefore the affinity of tin to sulfur is higher than that of silicon which provides a driving force for the process. Facile formation of (trifluoromethyl)dimethylsilane is particularly noteworthy since the presence of the Si−H bond in the precursor chlorosilane (Me_2HSiCl) makes it incompatible with the reductive methods discussed earlier that are widely employed for the synthesis of (trifluoromethyl)trialkylsilanes (Scheme 6). Among possible applications, trifluoromethyl group in Me_2HSiCF_3 is expected to facilitate hydrosilylation of double bonds providing a novel approach to other Si−CF_3 species.

Mechanistically, the reaction involves an initial attack by the fluoride ion on the silicon atom of the corresponding disilyl sulfide generating the intermediate tetrabutylammonium (trimethylsilyl)thiolate **9** (Scheme 7). Further attack of **9** on the tin atom of the Bu_3SnCF_3 results in nucleophilic activation of tin. The pentavalent tin species subsequently reacts producing R_3SiCF_3 and [(trimethylsilyl)thio]tributylstannane. The application of this "transtrifluoromethylation" of the Si−S bond-containing compounds for the synthesis of (trifluoromethyl)trialkylsilanes is quite general.

Yoshida *et al.* have recently demonstrated that a two-electron reduction of $ArCF_2Cl$ with samarium(II) diiodide in the presence of Me_3SiCl and HMPA as a solvent gives $ArCF_2SiMe_3$ in high yield (eq 7).[42a]



(7)

Alternatively, electroreduction of $ArCF_3$ on a sacrificial aluminum electrode was reported to yield $ArCF_2SiMe_3$.[42b] The latter can be viewed as a synthetic equivalent of "$ArCF_2^-$" anion. Introduction of this functionality is of considerable interest in agrochemistry and related disciplines.

Preparation of bis(trimethylsilyl)difluoromethane (**5**) was briefly described by Fritz *et al.*[43] This bis(silylated) compound was obtained via insertion of the singlet CF_2 (difluorocarbene), produced from trifluoromethyl(trimethyl)tin at elevated temperatures, into the silicon−silicon bond of $FMe_2SiSiMe_2F$. (The absence of the silicon-bound fluorine atoms renders the Si−Si bond in a related $Me_3SiSiMe_3$ unreactive toward difluorocarbene.) The resulting $FMe_2SiCF_2SiMe_2F$, isolated by gas chromatography, was reacted with methyllithium to afford **5** as a product of selective Si-alkylation. The apparent experimental difficulties, however, do not permit preparative use of this procedure. Aluminum-induced reductive methods are more convenient in this case (*vide supra*).

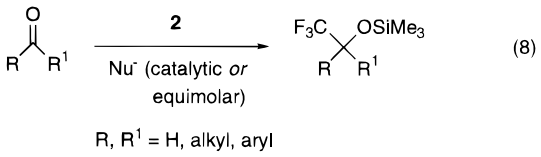
3. Synthetic Applications of (Perfluoroalkyl)trimethylsilanes

3.1. Trifluoromethylation Reactions

Trifluoromethylation with **2** is based on the susceptibility of its silicon center toward nucleophilic attack followed by the transfer of the CF_3 group to a suitable electrophile. To evaluate the strength of the Si−CF_3 bond in **2**, electron diffraction studies were performed on related CF_3SiH_3.[44] This showed a quite long Si−CF_3 bond (1.923 Å) which represents a significant elongation compared to the corresponding value of 1.864 Å in the parent hydrido species, CH_3SiH_3. Physical characteristics of the Si−CF_3 bond were further analyzed by Eujen using gas-phase IR and Raman spectroscopy. The force constant of 2.63 N cm $^{-1}$ has been determined for the Si−CF_3 bond in **2**.[45] Overall, these results indicate the relative weakness of the Si−CF_3 bond, which can be viewed as a result of the repulsion between the highly positively charged carbon atom of the CF_3 group and the silicon center. Remarkably, the thermal stability of **2** with regard to decomposition into Me_3SiF and the difluorocarbene species is surprisingly high, but should be regarded as kinetic in origin due to the anticipated highly electrophilic character of the silicon atom adjacent to the highly electron-withdrawing CF_3 group.

3.1.1. Aldehydes and Ketones

General trifluoromethylation reaction between **2** and a carbonyl compound proceeds according to eq 8, whereby the trifluoromethylated alcohol in its trimethylsilylated form is obtained upon the addition of an appropriate nucleophilic initiator to the reaction mixture.

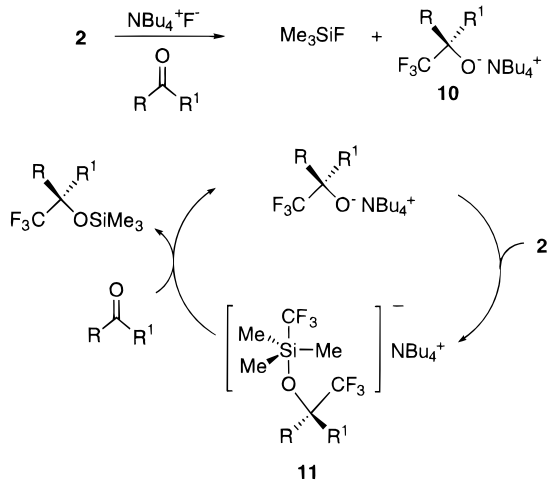


(8)

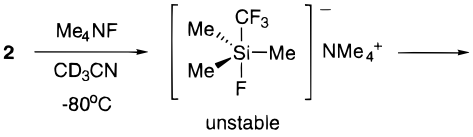
The initial addition step is usually followed by desilylation that furnishes the desired alcohol. Depending on a particular carbonyl compound, the reaction conditions may vary in initiator, solvent, and desilylating agent. Most commonly, THF is used as a solvent; tetrabutylammonium fluoride (TBAF), as an initiator; and aqueous HCl, as a desilylating agent. Other nucleophilic initiators such as tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF), potassium fluoride, $Ph_3SnF_2^-NBu_4^+$, and RO^-M^+ are also suitable for this purpose. The solvent effect on the reaction has also been investigated.

3.1.1.1. General Mechanistic Considerations. Upon addition of a catalytic amount of TBAF to the reaction mixture consisting of the carbonyl compound and **2** in a suitable solvent (*vide infra*), the process (Scheme 8) commences with the initial formation of gaseous Me_3SiF and an alkoxide adduct **10**, stabilized by tetrabutylammonium cation. Only a small amount of TBAF (5−10 mol %) is needed for the overall reaction because the catalytic cycle is further maintained by the affinity of the silicon atom of **2** to the anionic oxygen center of **10**. The reaction between **2** and **10** subsequently leads to the formation of the pentavalent complex **11**. This step is followed by the transfer of the CF_3 group to the electrophilic carbon of the carbonyl function (likely precoordinated via oxygen to the silicon center of **11**) until all of the starting material has reacted. Other oxyanionic species, such as potassium *tert*-butoxide and sodium trimethylsilanolate are also quite effective as initiators. Use of the term "autocatalytic" in this case refers to the continuous regeneration of the anionic species that carries the process. An essential advantage of using silylated derivatives to transfer perfluoroalkyl groups to electrophiles is evident here. Silicon is capable of coordinating electron-rich substrates (preferably "hard" nucleophiles, such as fluorine and oxygen), expanding its coordination number to 5 and 6. Therefore, the trifluoromethyl group attached to the silicon center has the advantage of reacting in an essentially intramolecular fashion. This allows reactions to be carried out at or near room temperature. Absence of the byproducts derived from singlet difluorocarbene supports such a masked nature of the "CF_3^-" in this case. Relatively low efficiency of labile (trialkylsilyl)(trifluoromethyl)diazenes as trifluoromethylating agents reported by de Meijere *et al.* can be explained in this context: CF_3 group in these species is further separated from the silicon center by two nitrogen atoms.[46a] Therefore, in this case, the silicon center does not play its essential role of serving as a template for the reaction of highly unstable "CF_3^-".

Scheme 8



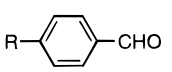
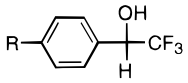
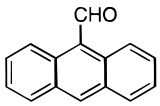
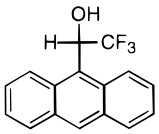
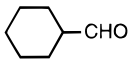
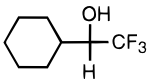
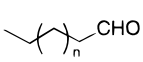
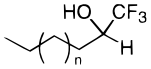
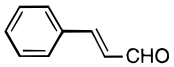
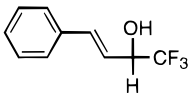
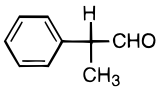
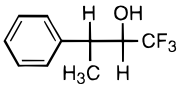
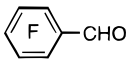
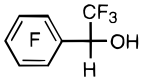
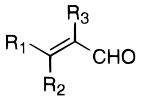
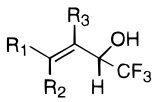
It is noteworthy that despite the fact that a plethora of hypercoordinate silicon species have been observed and fully characterized,[46b] all attempts to detect a putative pentavalent intermediate formed upon nucleophilic activation of **2** were unsuccessful. This is best explained by the kinetic instability of "CF_3^-" anion and its preference for α-elimination and proton abstraction from the medium generating gaseous CF_3H. Proton abstraction was observed even from acetonitrile or propionitrile when these solvents were employed in NMR experiments (eq 9). Anhydrous tetramethylammonium fluoride was used to prevent reactions with residual water.[47] The highly basic nature of the "CF_3^-" anion reveals itself here: in the absence of a suitable electrophile, proton abstraction prevails. This fact, together with high propensity to eliminate α-fluoride renders pentavalent CF_3 intermediate elusive. However, the pentavalent trifluoromethylated silicon species can be stabilized by the attachment of fluorine atoms to the silicon center. Bürger *et al.* characterized stable $F_4SiCF_3^-$ anion as a product of decomposition of $(CF_3)_2SiHNEt_3$. Fluorine atoms must efficiently stabilize the negative charge in this case preventing decomposition and allowing the preparation of $(F_4SiCF_3)^-$ at room temperature in benzonitrile solution.[18]



(9)

3.1.1.2. Trifluoromethylation of Aldehydes and Ketones. Since the initial report in 1989 by Prakash *et al.* on the trifluoromethylating properties of **2**, a variety of aldehydes were reacted with **2** using our protocol making the corresponding trifluoromethylated adducts easily accessible (Table 5).[4a,10,12,15,26,48−51] Among other useful products, synthetically valuable trifluoromethyl ketones are available from these

Table 5. Trifluoromethylation of Aldehydes

entry	aldehyde	product	yield[a]	reference
1			R = H 85% Cl OCH_3 $(EtO)_2CH$	48, 49 12 4
2				50
3			80%	48, 49
4			n = 1 2	50 12
5				12
6				12
7				15
8			$R_1 = R_2 = H, R_3 = H$ $R_1 = R_2 = CH_3, R_3 = H$ $R_1 = H, R_2 = CH_3, R_3 = H$ $R_1 = Ph, R_2 = Cl, R_3 = H$ $R_1 = Ph, R_2 = Cl, R_3 = CH_3$ $R_1 = Ph, R_2 = Cl, R_3 = Ph$	50 50 50 51 51 51

[a] Blank space in the yield column indicates that no yield was reported.

Table 6. Nonionic Initiators for the Reactions of Me_3SiCF_3 with Aldehydes and Ketones

entry	initiator	yield (%)	ref
1	$NH(n\text{-}C_4H_9)_2$	68	12
2	pyridine	37	12
3	$[(CH_3)_2NCH_2]_2$	82	12
4	$P(C_6H_5)_3$	70	12
5	$P(n\text{-}C_4H_9)_3$	79	12
6	$As(C_6H_5)_3$	54	12
7	$Sb(C_6H_5)_3$	22	12

secondary carbinols by oxidation with the Dess–Martin periodinane.[52]

A number of initiators and solvents have been employed for the trifluoromethylation reaction. Coordinating solvents like THF are most suitable. Solvents that contain acidic protons (for example, chloroform) should be avoided. Rapid quenching of the transient "CF_3^-" forming CF_3H is observed in these cases.

A series of novel initiators for the trifluormethylation of common aldehydes and ketones were recently investigated by Fuchikami.[12] Table 6 shows some of the results obtained. With dimethylformamide as a solvent, the reactions of **2** are promoted with catalytic amounts (5–10 mol %) of amines, phosphines, and even derivatives of arsenic and antimony. To the best of our knowledge, Lewis acids do not induce any reactions between **2** and electrophiles—a notable difference from other widely used silicon-based reagents.

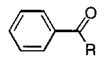
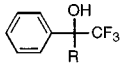
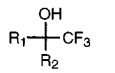
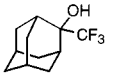
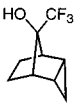
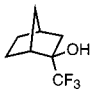
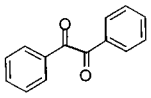
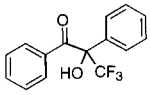
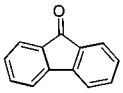
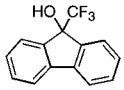
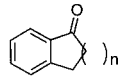
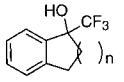
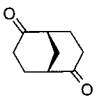
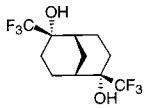
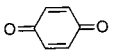
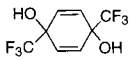
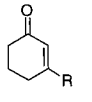
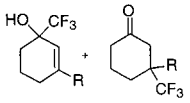
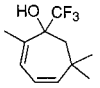
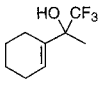
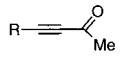
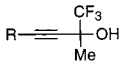
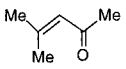
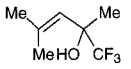
Compound **2** was employed to prepare trifluoromethylated amino alcohols from the corresponding protected amino acid derivatives such as *t*-BOC-L-phenylalanal (eq 10). The protected trifluoromethyl

(10)

alcohols can be directly prepared by this method. Appropriate deprotection gives good yields of amino alcohols that are used to prepare trifluoromethyl-substituted tripeptides as potential inhibitors of human leukocyte elastase (HLE).[53]

The reactions of **2** with ketones in the presence of a catalytic amount of TBAF proceed in good yields giving trifluoromethylated tertiary alcohols as shown in Table 7. Nelson *et al.* showed that initiation of the reactions with certain hindered ketones is troublesome when TBAF, K_2CO_3, KF, and CsF are employed as initiators (Table 7, entries 5 and 6). The addition of TBAF in these cases leads to the preferential

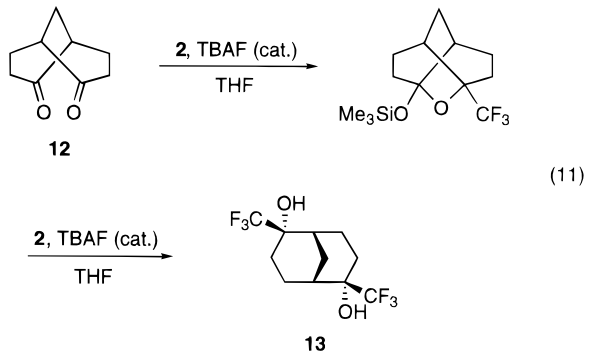
Table 7. Trifluoromethylation of Ketones

entry	ketone	product	yield[a]	reference
1			R = CH_3 (65%) cyclopropyl C_6H_5 (85%) *i*-Pr	50 50 50 50
2			$R_1 = R_2 = CF_3$ $R_1 = CF_3$, $R_2 = CF_2Cl$ $R_1 = CF_3$, $R_2 = CF_2H$ $R_1 = n\text{-}C_4H_9$, $R_2 = n\text{-}C_4H_9$ $R_1 = R_2$ = cyclopropyl (70%) R_1 = Me, R_2 = cyclopropyl (60%)	54 54 54 50 50 50
3			n = 0 (68%) 3 (78%) 4 5	50 50 50 50
4				4a
5				55
6				55
7				4a
8			85%	50
9			90%	50
10			n = 1 (67%) n = 2 (88%)	56 50
11			93%	57
12		 (*cis* and *trans*)		26
13			R 1,2 : 1,4 H (60%) 90 : 10 Me (57%) 97 : 3	50 50
14			89%	50
15			56%	50
16			84%	50
17			R = Ph (76%) R = Et (70%)	50 50
18			78%	50

a, blank space in the yield column indicates that no yield was reported.

deprotection of the intermediate silyl ether with significant formation of the byproducts. On the other hand, the KF/KO*t*-Bu mixed system was found to initiate vigorous reactions that each goes to completion within several minutes. Subsequent *in situ* deprotection furnishes the desired tertiary carbinols.[55] These facts can be rationalized by the relatively hindered nature of the substrates which necessitates the use of the initiators with smaller counterions. Gassman *et al.* prepared 1-trifluoromethylindene starting from 1-indanone.[56] 1,2-Diketones give only the monoadduct. Highly enolizable 1,3-diones do not react under these conditions. A series of α,β-conjugated enones and ynones readily react with **2** to give predominant 1,2-addition products. Certain aromatic ketones, such as 1,2-diphenylcyclopropenone fail to react due to the π-participation of the aromatic rings.[50]

Interesting transannular reactivity of Meerwein's diketone **12** with **2** under fluoride initiation was noted by Quast *et al.* (Table 7, entry 11).[57] When subjected to nucleophilic trifluoromethylation with 2 equiv of **2**, diketone **12** can be readily converted into the expected bisadduct **13**. Its isolation follows the initial formation of the corresponding monoaddition product. Interestingly, oxatwistane hemiketal species can be isolated *en route* to **13** (eq 11). The formation of this species is rationalized by proximity of the two carbonyl groups in **12**. After the first act of trifluoromethylation, the reversible formation of the hemiketal occurs through nucleophilic oxygenation of the second carbonyl group. Another equivalent of **2** subsequently leads to the final product.



(11)

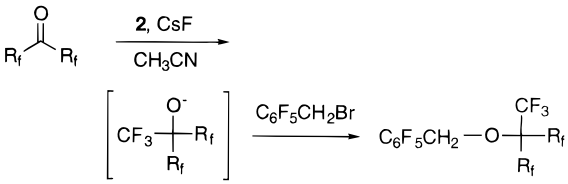
An extensive study of the trifluoromethylation of perfluorinated carbonyl compounds with **2** was performed by DesMarteau *et al.* (Table 7, entry 2).[54] Among other useful products, perfluoro-*tert*-butyl alcohol can be easily obtained from hexafluoroacetone, **2**, and anhydrous KF as an initiator in acetonitrile. Several interesting observations were made in this report. First, the reactions with perfluorinated ketones are not catalytic in fluoride. This is consistent with the proposed mechanism of the reaction since the propagating species in this par-

Table 8. Preparation of Trifluoromethylated Dienones

entry	quinone	silane	yield (%)
1	1,4-benzoquinone	Et_3SiCF_3	72
2	2,6-di-*tert*-butyl-1,4-benzoquinone	$(n\text{-}Bu)_3SiCF_3$	70
3	3,5-di-*tert*-butyl-1,2-benzoquinone	Et_3SiCF_3	90
4	1,4-naphthoquinone	Et_3SiCF_3	44
5	9,10-anthraquinoe	Et_3SiCF_3	86
6	9,10-phenanthrenequinone	Et_3SiCF_3	86

ticular case should be only weakly nucleophilic perfluoro-*tert*-butyl alkoxide, unable to further activate silicon center of **2**. Evaluation of various fluoride sources revealed an overall increase in reactivity in the series KF−CsF−TBAF. In the case of TBAF, its solubility in organic phase is an obvious advantage. However, since the process is not catalytic in fluoride, the use of TBAF should be avoided due to its highly hygroscopic nature which leads to rapid quenching of the incipient trifluoromethyl anion with water to produce CF_3H. More polar acetonitrile is the preferred solvent in this case.

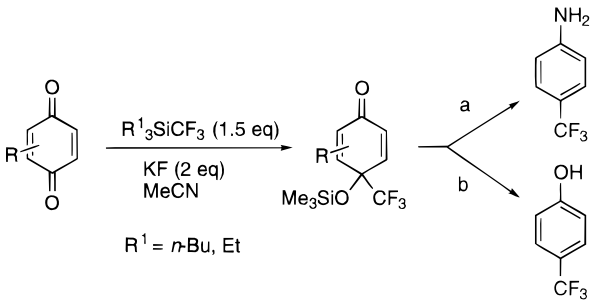
Per- and polyfluoroalkoxides are generated in reactions between perfluoro carbonyl compounds with **2** (eq 12). These compounds readily react with highly electrophilic perfluorophenyl benzyl bromide giving the corresponding perfluorinated aromatic ethers in good yields. The importance of these polyfluorinated ethers as high temperature lubricants and solvent elastomers is well documented.[58]



(12)

R_f	yield
CF_3	75%
C_6F_5	53%

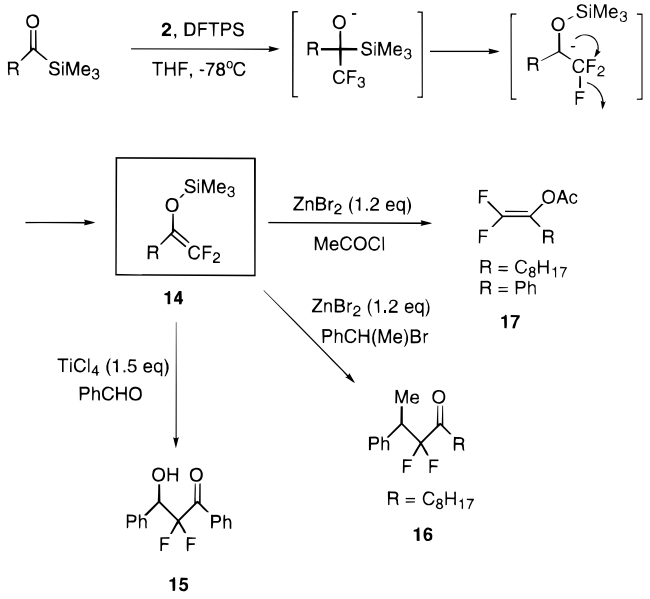
1,4-Quinones can also undergo double addition in TBAF-initiated reactions with **2**. When 2 equiv of **2** are employed, the *trans* product readily crystallizes out of the reaction mixture during the workup (Table 7, entry 12).[26] The corresponding monoadducts to both 1,4- and 1,2-quinones were thoroughly studied by Stahly *et al.* (eq 13 and Table 8).[59] Triethylsilyl-



(13)

and tri-*n*-butyl(trifluoromethyl)silane have been used

Scheme 9



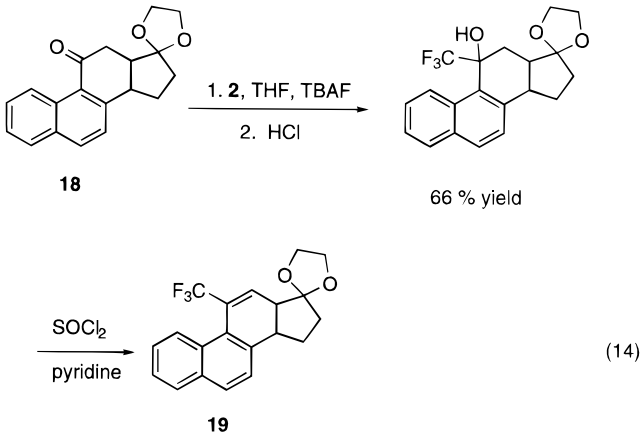
to transfer the CF_3 groups and their higher boiling points allow one to conduct reactions at elevated temperatures. Reduction and reductive amination of the trifluoromethylated alcohols can be used to obtain trifluoromethylated phenols and anilines, respectively. This procedure is a mild method for aromatic trifluoromethylation that avoids harsh conditions used in some of the traditional aromatic trifluoromethylation methods (e.g. SF_4-mediated conversion of benzoic acid derivatives into CF_3 compounds).[4]

Difluoroeneoxysilanes can be readily obtained from **2** and acylsilanes using Portella's method (Scheme 9).[60a] Initial fluoride-catalyzed formation of the alkoxide adduct is followed by the Brook rearrangement. β-Fluoride elimination subsequently gives the difluoroeneoxysilane **14**. However, when TBAF is employed as an initiator, **14** cannot be isolated. Rather, it is directly consumed in fluoride-catalyzed self-condensation. In order to avoid this route, the less nucleophilic tetrabutylammonium difluorotriphenylstannate (DFTPS) is employed. Under these conditions, eneoxysilane can be isolated and further used. For example, its treatment with hydrochloric acid yields CF_2H ketones. Other intriguing applications can be carried out in one pot, where the *in situ*-generated eneoxysilane **14** undergoes the Mukayiama aldol condensation with benzaldehyde mediated by titanium tetrachloride. The possibility to use dichloromethane as solvent for trifluoromethylation allows such one-pot reaction. Alkylation with 1-bromo-1-phenylethane gives the corresponding benzylated difluoro derivative **16**. Additionally, the O-acylated product **17** is obtained exclusively upon the addition of $ZnBr_2$ and acetyl chloride to the crude solution of **14**.

Using similar procedures difluoro-*C*-glycosides and *C*-disaccharides have been prepared.[60b] Michael and subsequent annelation reactions led to 3-substituted 4,4-diflurocyclohexenone and/or 3-substituted-4-fluorophenols.[60c]

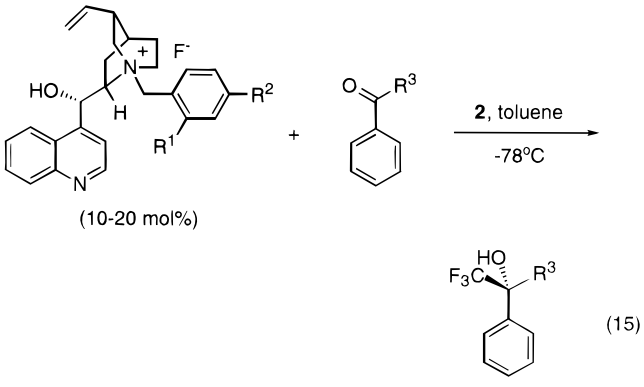
Coombs *et al.* showed that trifluoromethylation of aromatic ketone **18** proceeds in 66% isolated yield (eq 14).[61] Interestingly, dehydration of the resulting

alcohol with thionyl chloride in pyridine at 0 °C furnishes the corresponding trifluoromethyl group-bearing olefin considered as a bay region CF_3 analog of a potent polycyclic aromatic carcinogen of the cyclopenta[*a*]phenanthrene class. Olefin **19** was used for the study of the electron-withdrawing substituent effects on carcinogenicity.



(14)

3.1.1.3. Stereoselectivity in Trifluoromethylation. The importance of optically pure trifluoromethylated compounds in medicinal chemistry and in optoelectronic applications is well established and has been repeatedly emphasized.[2,4] Several reports dealing with attempts of enantioselective trifluoromethylation of aldehydes and ketones with **2** appeared recently. Prakash *et al.* have found that the use of *N*-benzylquinidinium fluoride in dichloromethane as a solvent at −78 °C allows trifluoromethylation of 9-anthraldehyde in 95% ee.[62] According to the mechanism of trifluoromethylation discussed earlier, the tetrabutylammonium cation is closely associated with the alkoxy adduct during the reaction. It is therefore reasonable to expect that the process could show enantioselectivity if chiral ammonium cation is used. Kobayashi *et al.* reported the use of *N*-[4-(trifluoromethyl)benzyl]cinchonium fluoride as a potential catalyst for asymmetric introduction of a trifluoromethyl group (eq 15). Typically, **2** is allowed to react with

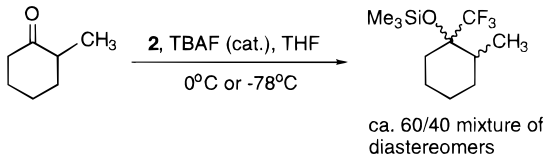


(15)

R^1	R^2	R^3	ee (% R)
CF_3	CF_3	H	46
H	CF_3	Me	48
H	CF_3	*i*Pr	51

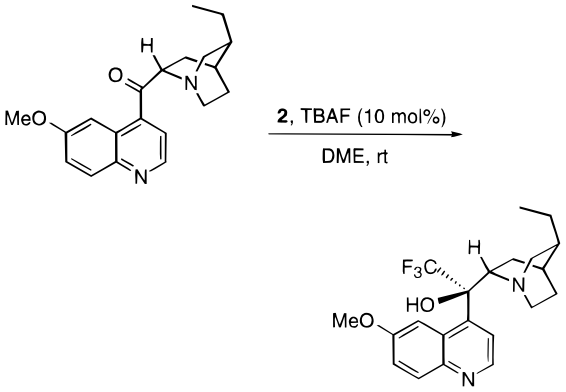
carbonyl compounds and chiral fluoride (10−20 mol %) at −78 °C in toluene. Usual workup permits isolation of the corresponding alcohols in high yields and moderate enantiomeric excesses.[63a] Interestingly, quinine itself is capable of enantioselective trifluoromethylation of aldehydes using related Et_3SiCF_3, albeit, with low enantioselectivities and yields.[63b] In this case hydroxyl oxygen of the quinine moiety must activate the silicon center of Et_3SiCF_3.

Diastereoselectivity of addition was also explored. Thus, 2-methylcyclohexanone was treated with **2** in the presence of a catalytic amount of TBAF in THF. The relative ratio of the two diastereomers remained the same at 0 °C and at −78 °C (eq 16). Changing one methyl group of **2** into *tert*-butyl results in improved diastereoselectivity of addition.



(16)

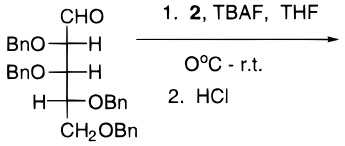
In another example, dihydroquinine, converted using Swern oxidation into the corresponding dihydroquininone (obtained as a mixture of two epimers), was efficiently trifluoromethylated, giving high a level of diastereomeric excess. These easily obtained chiral trifluoromethylated adducts are expected to find applications in asymmetric catalysis.[26]



(17)

3.1.1.4. Trifluoromethylation of the Carbohydrate Derivatives. Introduction of the hydrophobic trifluoromethyl moiety in place of the methyl group of carbohydrates is of interest in investigating carbohydrate−carbohydrate interactions. Trifluoromethyl analogs are artificial inhibitors for the Le^x−Le^x interaction. The hydrophobic region of the polysaccharides having an L-fucose residue plays an important part in recognition processes.[64] In this context, acyclic perbenzylated derivative **20** of D-lyxose was efficiently trifluoromethylated by Toyokuni *et al.* using **2**.[65] With a catalytic amount of TBAF, **20** is converted into **21** (approximately 1:1 mixture of diastereomers) in THF at room temperature. Subsequent treatment that includes acidic hydrolysis followed by catalytic hydrogenation with palladium hydroxide, selective oxidation with Collins reagent, and desilylation furnishes the trifluoromethyl analog of L-fucose and of 6-deoxy-D-altrose as an equilibrium

mixture of two pyranoses (P α, β) and two furanoses (F α, β) in 38 and 36% overall yields, respectively. It is worth noting that the replacement of the methyl with the trifluoromethyl group increases the furanose content especially in the case of trifluoromethylated 6-deoxy-D-altrose (which exists predominantly in the furanose form).



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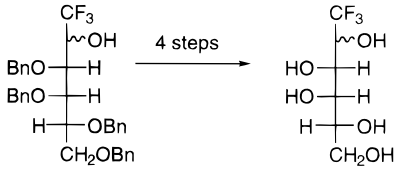
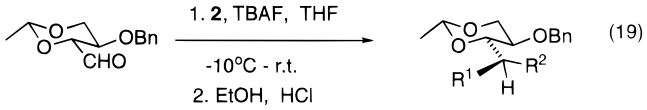


(18)

21

Trifluoromethylation of the cyclic D-erythrose derivative **22** was performed by Anker *et al.* in order to circumvent the stereoselectivity problems in carbohydrate trifluoromethylation previously encountered in the noncyclized cases (eq 19).[66a] However,



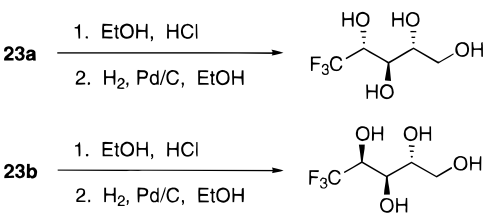
(19)

22

23a $R^1 = CF_3$, $R^2 = OH$ (60%)
23b $R^1 = OH$, $R^2 = CF_3$ (40%)

in spite of the more strained cyclic structure, poor diastereoselection was observed. The respective tetrols **23a** and **23b** can be isolated in 95% overall yield after acidic hydrolysis at elevated temperatures followed by hydrogenation on Pd/C (Scheme 10). Trifluoromethylation of the corresponding lactone derivatives of the starting compounds enables better stereocontrol (*vide infra*).

Scheme 10

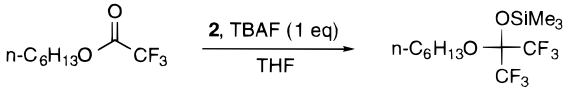


Trifluoromethylation of 3-*O*-allyl(or benzyl)-1,2-*O*-isopropylidine-α-D-*xylo*-pentodialdo-1,4-furanose in methylene chloride with **2** activated by $Ph_3SnF_2^-$, gave quantitatively the corresponding L-*ido* and D-*gluco* derivatives in a ratio of 80/20, whereas a similar reaction on 3-oxoglucose or -xylose derivatives was highly stereoselective (*vide infra*).[66b]

3.1.1.5. Steroidal Ketones. Modification of the steroidal skeleton by attachment of the CF_3 group is expected to influence the biological activity. The use of **2** under nucleophilic catalysis allows quantitative conversion of the corresponding ketones into the respective trifluoromethylated carbinols (Table 9). Due to the hindered nature of the carbonyl group in the starting materials, the size of ammonium cation (which is closely associated with the alkoxide species in the catalytic cycle) plays a significant role in the overall process (see section 3.1.1.1). As such, tetramethylammonium fluoride was found by Wang *et al.* to be superior to TBAF in promoting the "CF_3^-" transfer.[67] The obtained silyl ethers can be readily desilylated using 40% aqueous HF in acetonitrile giving trifluoromethylated alcohols which exhibit high contraceptive activity.

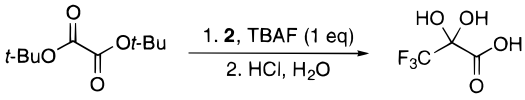
3.1.2. Esters, Lactones, α-Keto Esters, Cyclic Anhydrides, and Oxazolidinones

Simple esters are not sufficiently electrophilic to react with **2** even when stoichiometric amounts of fluoride are used to promote the process. The reaction takes place, however, when an activated ester function is present. For example, *n*-hexyl trifluoroacetate does react with **2** in the presence of an equimolar amount of TBAF to give the silylated hemiketal (eq 20). The conversion is, nevertheless, rather low (35%). Protic impurities in the medium lead to rapid quenching of the incipient trifluoromethide species giving trifluoromethane as a significant byproduct.[4a]



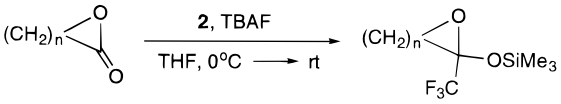
(20)

In another example of addition to an activated ester, Geffken *et al.* reacted di-*tert*-butyl oxalate with **2** which resulted in a two-step synthesis of trifluoropyruvic acid monohydrate upon further acidification (eq 21).[68,69]



(21)

In the case of lactones, efficient reactions with **2** proceed only in the case of five- and six-membered rings (eq 22). Prakash *et al.* have found that despite smooth addition to four-, five-, six-, and seven-membered ring lactones, the expected silylated ketals can be cleanly isolated only in the case of five- and six-membered rings.[4a]

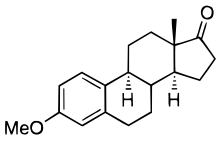
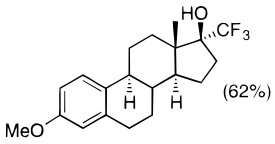
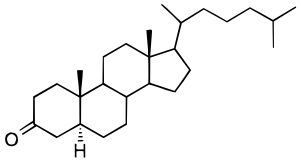
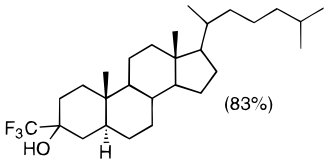
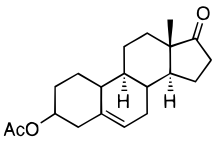
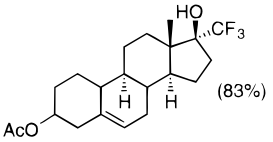
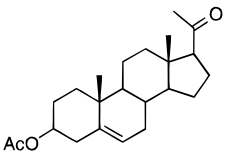
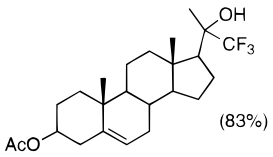
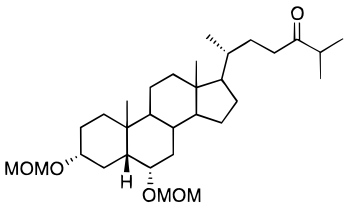
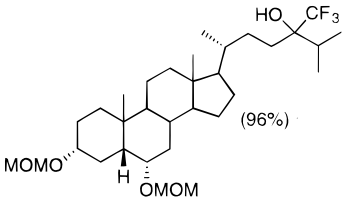


(22)

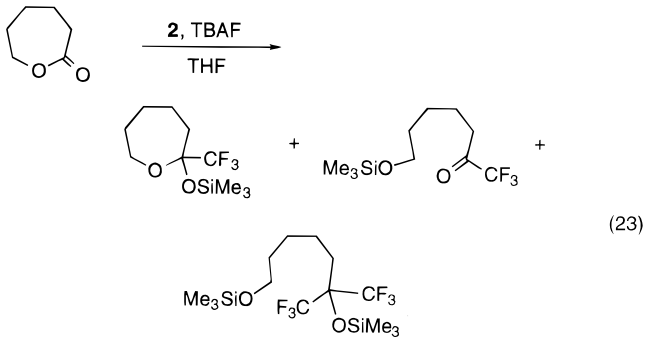
n = 2 - 5

n = 3 70%
n = 4 75%

Table 9. Trifluoromethylation of Steroidal Ketones

entry	ketone	product (yield)	reference
1		 (62%)	4a
2		 (83%)	4a
3		 (83%)	67
4		 (83%)	67
5		 (96%)	67

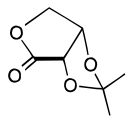
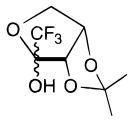
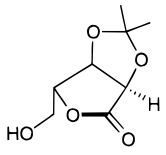
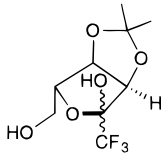
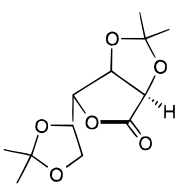
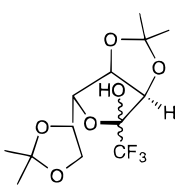
The four-membered hemiketal is obtained cleanly in solution, but is thermally unstable and decomposes significantly during distillation. In the case of a seven-membered ring lactone, fluoride-mediated ring opening and subsequent trifluoromethylation of the resulting highly electrophilic ketone furnishing bis-(trifluoromethyl) product are significant side reactions (eq 23).



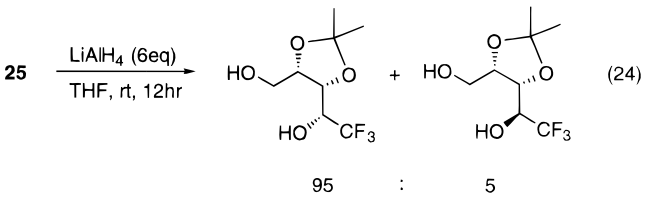
(23)

Carbohydrate 1,4-lactones are readily converted into 5-deoxy-5,5,5-trifluoro-D- and L-ribose and lyxose derivatives (Table 10).[66] Addition of the CF_3 group to lactone **24** gives hemiketal **25** as a mixture of α- and β-isomers in equilibrium. Subsequent reduction shows different selectivity depending on the reducing

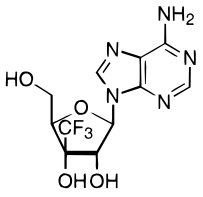
Table 10. Trifluoromethylation of Carbohydrate Lactones

entry	lactone	product	yield (%)	ref
1	 **24**	 **25**	91	66
2			92	66
3			98	66

agent which allows the preparation of CF_3-substituted diols in good yields (eq 24).



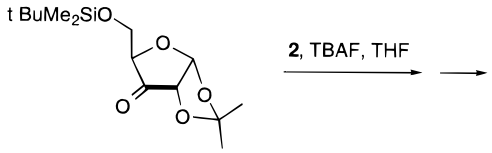
Similarly, Johnson *et al.* added **2** to 5-*O*-benzoyl-1,2-*C*-isopropylidene-α-D-*erythro*-pento-3-ulose to obtain 5-*O*-benzoyl-1,2,3-*tri*-*O*-acetyl-3-*C*-trifluoromethyl-*β*-D-ribofuraniside.[70] The latter is a starting material for the preparation of 3-*C*-trifluoromethyl-*β*-D-ribofuranosyl nucleosides of thymine, uracil, and adenine (e.g. adenine-based compound **26**).



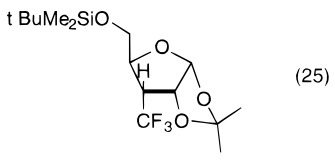
26

More than 1 equiv of TBAF was used to avoid the isolation of the trimethylsilyl derivative in the case of **26**. Using Vorbruggen's method, 9-(3-*C*-trifluoromethyl-*β*-D-ribofuranosyl) is obtained and found to be active against herpes simplex virus-1 (KOS). Remarkably, its cytotoxicity is considerably lower than the 3′-methyl nucleoside. Similar trifluoromethyl-containing furanosides were also used by Morisawa *et al.* as starting materials for the preparation of 2′,3′-dideoxy-3′-(trifluoromethyl)pentafuranosyl nucleosides, useful as antitumor agents and agrochemicals.[71]

Portella *et al.* employed an interesting sequence of nucleophilic trifluoromethylation with **2** followed by radical deoxygenation. This treatment allows 3-deoxy-3-*C*-(trifluoromethyl)-D-ribose derivatives to be obtained from D-xylose and D-glucose, respectively (eq 25).[72] For example, reaction of the silyl ether **27** with



27

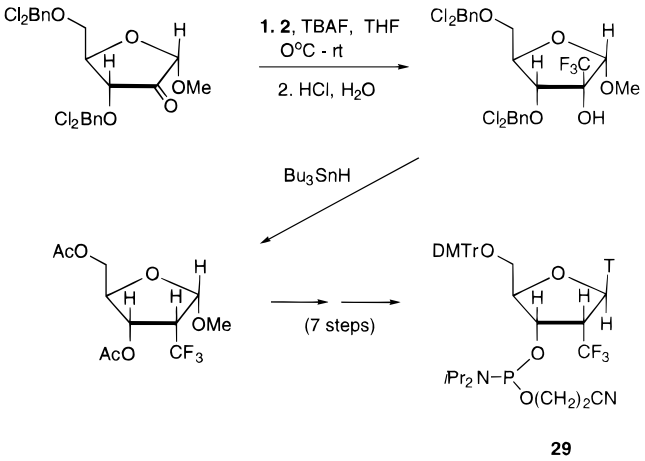


(25)

28

2 under catalytic fluoride activation leads to the bis(silylated) 3-*C*-(trifluoromethyl)-D-ribose derivative which can be specifically desilylated in methanol solution by adding a catalytic amount of sodium. Subsequent conversion into methyl oxalate and treatment with tributyltin hydride gives **28** in a predominantly α-epimer form.

Scheme 11



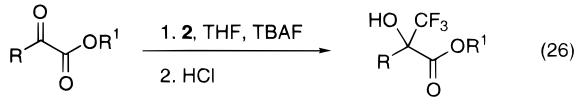
29

Table 11. Trifluoromethylation of α-Keto Esters

entry	R	R^1	yield (%)	ref
1	Me	Et	83	74
2	Me	Me	72	74
3	Me_2CH	Et	76	74
4	Ph	Et	70	74
5	CH(Et)Me	Et	82	74

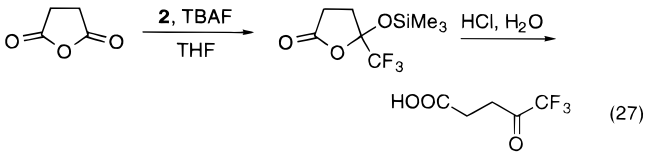
A single stereoisomer resulting from the attack of the CF_3 group to the *β*-face of the carbohydrate, 2-ketofuranoside moiety was obtained by Schmit in a reaction between **2** and 2′-keto lactone derivative (Scheme 11).[73] Further treatment included radical deoxygenation with tributyltin hydride and coupling with bis(silylated) thymine in acetonitrile furnishing the respective *β*-nucleoside and finally, phosphoramidite **29**. This compound was incorporated into oligonucleotides in the DNA synthesizer to study their hybridization properties.

α-Keto esters can be easily converted into *β*,*β*,*β*-trifluorolactic acid derivatives using **2** and a catalytic amount of TBAF in THF according to eq 26[74] (Table 11). No competitive addition to ester carbonyl group takes place. This method provides a means to direct conversion of the phenyl keto ester into α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) and other valuable derivatives.



(26)

Cyclic anhydrides readily react with **2** (eq 27).[4a] However, a stoichiometric amount of TBAF is required for this transformation. For example, succinic anhydride adds **2** efficiently to form the initial adduct which affords the trifluoroacetyl-substituted carboxylic acid upon hydrolysis. Acyclic anhydrides react less cleanly under similar conditions.

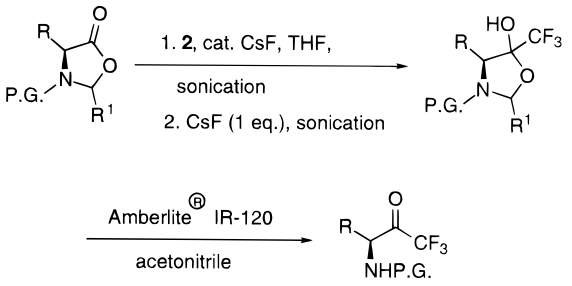


(27)

Table 12. Trifluoromethylation of Oxazolidinones

entry	R	PG	R^1	yield (%)	ref
1	CH_2Ph	Z	H	95	75
2	Me	Z	H	85	75
3	CH_2CO_2Me	Z	H	50	75
4	$(CH_2)_2CO_2Me$	Z	H	70	75
5	CH_2Ph	BOC	H	80	75
6	Me	BOC	H	85	75
7	H	BOC	H	60	75
8	$CH(CH_3)_2$	BOC	H	85	75
9	$CH_2CH(CH_3)_2$	BOC	H	95	75
10	CH_2SCH_2Ph	BOC	H	65	75
11	Ch_2Ph	Z	Ph	60	75
12	Ch_2Ph	Z	*p*-$MeOC_6H_4$	95	75
13	Me	Z	*p*-$MeOC_6H_4$	95	75

Oxazolidin-5-ones, easily obtained from N-protected amino acids, were found to react with **2** providing an efficient route to trifluoromethylated derivatives of amino acids (eq 28).[75] Representative examples



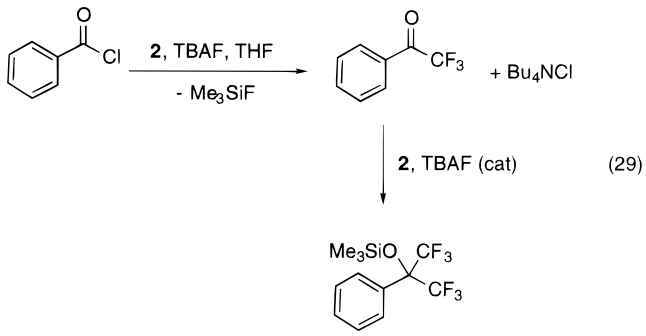
(28)

are collected in Table 12. TBAF as an initiator is less effective in this case giving the desired products in moderate yield and stereoselectivity (40%). However, the use of CsF under sonication in THF gives excellent yield of the adduct as a single diastereomer. Various substrates can be trifluoromethylated according to this protocol. The five membered rings are readily cleaved in acetonitrile in the presence of strongly acidic ion exchange resin (Amberlite IR-120) to afford synthetically valuable N-substituted α-amino(trifluoromethyl) ketones.

3.1.3. Carboxylic Acid Halides

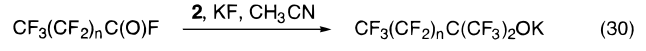
The first example of the trifluoromethylation of carboxylic acid chlorides was reported by Prakash *et al.*[4a,49] The reaction between **2** and benzoyl chloride proceeds with the formation of the expected ketone as well as bis(trifluoromethylated) tertiary alcohol in its trimethylsilylated form (eq 29). More than 1 molar equiv of TBAF is required since the first addition of "CF_3^-" is not catalytic in fluoride. Second addition occurs due to the higher reactivity of the initially formed trifluoromethylated ketone compared to the starting benzoyl chloride.

In contrast to acid chlorides, similar reactions with acid fluorides are expected to be catalytic in initiator since the fluoride anion, stabilized by tetrabutylammonium cation is regenerated after the first step via elimination from the intermediate alkoxide. DesMarteau *et al.* has demonstrated that perfluorinated acid fluorides are readily converted into the corresponding tertiary alkoxides using **2** and KF in



(29)

acetonitrile (eq 30).[54] Subsequent acidification with

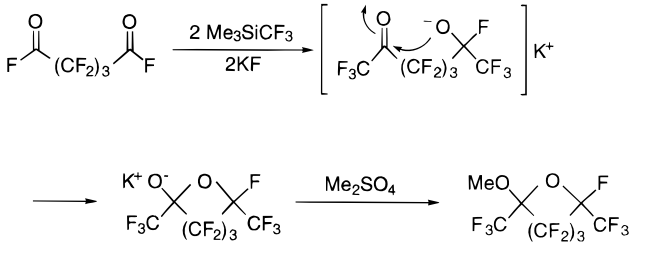


(30)

n	yield (%)
1	66.7
2	73.5
6	10.4

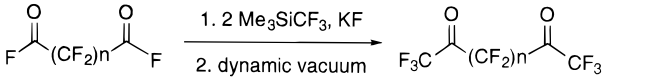
sulfuric acid leads to perfluorinated alcohols. Intermediate ketones were isolated in some cases. Using this protocol, difluorophosgene can be directly converted into perfluorinated *tert*-butyl alcohol. However, phosgene itself leads only to difluorophosgene without the expected further bis(trifluoromethylation) of the latter. This puzzling behavior is explained by poisoning of the KF surface with KCl generated during the initial KF-mediated difluorination of phosgene. Additionally, it was found that catalytic amounts of KF promote the formation of ketone, whereas equimolar amounts favor tertiary alkoxide adducts. When higher homologs of $R_fC(O)F$ are used, the yields generally drop due to the decreased solubility of the products.

Diacid fluorides readily react with **2** in the presence of excess KF in benzonitrile to afford initially the cyclic alkoxides (eq 31). These species are trapped



(31)

in their methylated form using dimethyl sulfate. Additionally, they undergo 1,4-loss of KF when exposed to dynamic vacuum giving trifluoromethylated diketones in good isolated yields (eq 32).[76,77]



(32)

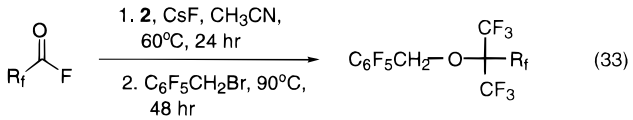
n	yield (%)
2	71.4
3	89.8

Figure 1. Cyclic diols obtained from Me_3SiCF_3 and diacid fluorides.

When treated with water, the highly electron-deficient diketones obtained from diacids are converted into the cyclic diols (Figure 1). These intriguing compounds were fully characterized by NMR and X-ray diffraction.[76]

An attempt to prepare $CF_3C(O)C(O)CF_3$ from the parent oxalyl fluoride and **2** in the presence of KF results in the quantitative conversion into $CF_3C(O)F$.[15] When large excesses of both **2** and KF are reacted with oxalyl fluoride, an oligomer with a composition $(CF_3)_3CO(C(CF_3)_2O)_nC(O)CF_3$ ($n = 2, 4$) is obtained. The preparation of these branched fluorinated polyethers is difficult by other means.

Polyfluoroaromatic ethers are obtained from acid fluorides, **2**, and bromo(perfluorophenyl)methane similar to the corresponding reactions of fluoroalkylated ketones (*vide supra*).[58] In this method, the intermediate perfluorinated alkoxide ion is trapped by bromo(perfluorophenyl)methane—a strong electrophile present in the reaction mixture (eq 33).

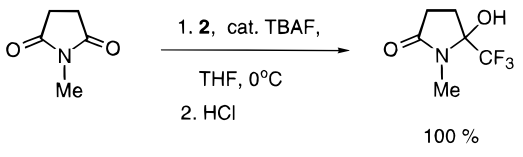


(33)

R_f	yield (%)
CF_3	75
C_6F_5	40

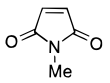
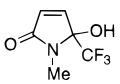
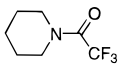
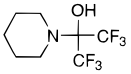
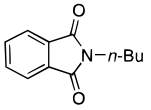
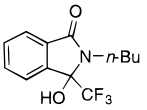
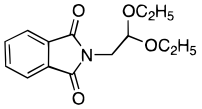
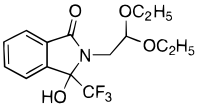
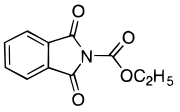
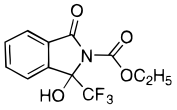
3.1.4. Amides, Imides, and Azirines

Simple amides, such as benzamide and acetamide, do not react with **2** even when an equimolar amount of initiator is used.[4a] Similarly, lactams, such as caprolactam do not react with **2** under these conditions. The carbonyl group in these systems is deactivated toward nucleophilic addition by the electron donation from the nitrogen atom. However, *N*-methylsuccinimide, an imide with an activated carbonyl function, reacts smoothly to afford the expected hemiaminal upon acid hydrolysis (eq 34). Heterocyclic derivatives bearing the trifluoromethyl group can be prepared from this important starting material. Other examples of trifluoromethylated derivatives of amides and imides are presented in Table 13. Trifluoromethylation of *N*-trifluoroacetoxypiperidine (Table 13, entry 2) followed by hydrolysis allows facile preparation of hexafluoroacetone hydrate.[50] The trifluoromethylation of succinimide itself is hampered by the presence of a highly acidic proton which leads to the predominant formation of CF_3H.

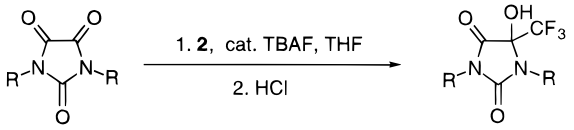


(34)

Table 13. Trifluoromethylation of Amides and Imides

entry	amide or imide	product	yield (%)	ref
1			40	50
2			88	50
3			68	50
4			78	50
5			87	50

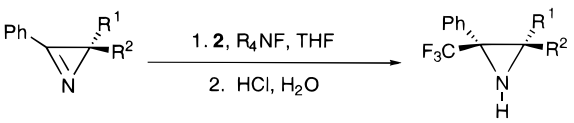
Similarly, imidazolidinetrione-based systems containing an activated amide carbonyl undergo facile reactions with **2** in THF catalyzed by TBAF according to eq 35.[78] 5-(Trifluoromethyl)-5-hydroxyimidazolidine-2,4-diones can be obtained in moderate yields. They can be further used for the construction of heterocycles.



(35)

R	yield (%)
CH_3	50
cyclohexyl	58
C_6H_5	25

No reaction occurs between (trifluoromethyl)trimethylsilane and imines. The relative weakness of the silicon−nitrogen bond compared to the silicon−oxygen bond does not provide sufficient driving force to push the reaction in the forward direction. This follows from the mechanism of the overall trifluoromethylation process which is based on an autocatalytic reaction propagated by a high affinity of silicon to oxygen. In comparison to imines, azirines contain carbon−nitrogen double bond which is more reactive toward nucleophilic attack due to the strain associated with its ring system. Laurent and coworkers succeeded in adding **2** to azirines under nucleophilic catalysis according to eq 36.[79] Biologically important (*E*)-aziridines containing trifluoromethyl group can be selectively obtained using this



(36)

Table 14. Trifluoromethylation of Azines

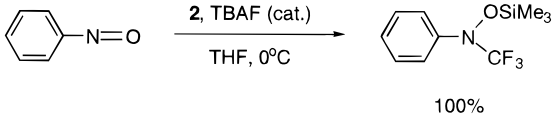
entry	R_4NF	R^1	R^2	yield (%)	ref
1	Et_4NF^a	Me	H	51	79
2	Bu_4NF^b	Me	Me	41	79
3	Et_4NF^a	Ph	H	86	79
4	Bu_4NF^a	CO_2Me	H	67	79

[a] Catalytic reaction (20 mol %). [b] Stoichiometric reaction.

method. Two sources of fluoride (TBAF, TEAF) were tried. Interestingly, the reaction works using catalytic amounts of fluoride ion which suggests that thermodynamically unfavorable addition resulting in the formation of the silicon−nitrogen bond can be circumvented by incorporation of strain into the system which is capable of promoting the reaction (Table 14).

3.1.5. Nitroso Group

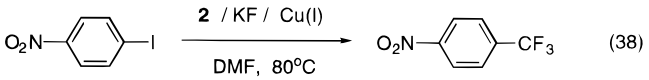
Nitroso compounds, such as nitrosobenzene, afford the *O*-silylated trifluoromethylated hydroxylamine in quantitative yield.[4a] The product, nonetheless, slowly decomposes to unidentified materials.



(37)

3.1.6. Alkyl, Allyl, Aromatic, and Vinyl Halides

(Trifluoromethyl)trimethylsilane **2** can be used for the *in situ* preparation of CF_3Cu in the presence of KF and copper(I) iodide at 80 °C in a DMF solution. Fuchikami *et al.* have demonstrated that the trifluomethylated copper(I) species thus obtained undergoes cross-coupling reactions with various alkenyl and aryl iodides and bromides.[80] Some amounts (up to 4%) of pentafluoroethyl derivatives are isolated in the case of aromatic substrates. This side reaction is rationalized by considering an insertion of a singlet difluoromethylene carbene formed from the labile "CF_3^-" into the Cu−CF_3 bond. It was also found that copper iodide does not work catalytically in this case. Other copper(I) species (cyanide, bromide, and chloride) are equally effective, whereas Zn(II), Ni, and Pd derivatives are inert toward oxidative addition. The best results are obtained when the DMF/NMP (1:1) mixed system is used as a medium.

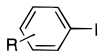
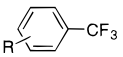
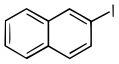
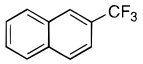
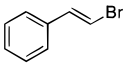
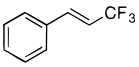
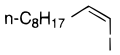
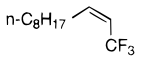
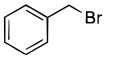
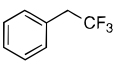
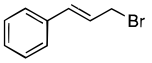
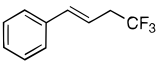


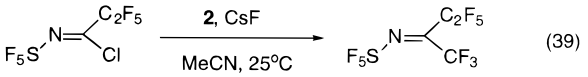
(38)

Vinyl, benzyl, and allyl halides can also be trifluoromethylated under similar conditions (Table 15). Notably, complete retention of olefin stereochemistry is observed when vinyl halides are used as starting materials.

Shreeve *et al.* showed that electron-deficient fluoroazenes that contain vinylic chlorine atom react with **2** to afford the products of a formal substitution of the chlorine atom (eq 39).[81] The reaction most probably operates by addition−elimination mechanism.

Table 15. Trifluoromethylation of Aryl, Vinyl, Benzylic, and Allyl Halides

entry	halide	product	yield (%)	ref
1			R = 4- NO_2 (85) 2-Me (86) 3-Me (78) 4-Me (82) 4-OCH_3 (48) 4-Cl (33) 4-CO_2Et (94) 4-C(O)CH_3 (45)	80 80 80 80 80 80 80 80
2			94	80
3			51	80
4			90	80
5			73	80
6			23	80

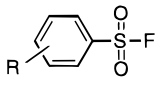
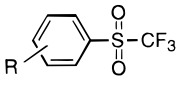
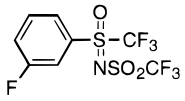
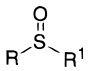
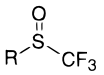
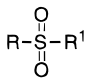
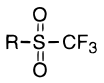
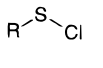
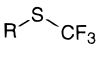


(39)

3.1.7. Sulfur-Based Electrophiles

Trifluoromethanesulfonylated aromatic compounds are of interest for the preparation of agrochemicals, dyes, and pharmaceuticals. Conventional organic methods, available for the preparation of these chemicals, generally involve tedious isolation and use of expensive reagents. The reactions between **2** and sulfur-based electrophiles provide a viable alternative to these methods. Trifluoromethylation of sulfonyl fluorides with **2** was explored by Yagupolskii *et al.* (Table 16).[82] It was found that aryl trifluoromethyl sulfones are conveniently produced in high isolated yields in one-pot reactions between arenesulfonyl fluorides and **2** in the presence of catalytic amounts of TASF (10 mol %). The reactions are generally completed within 0.5−1.5 h. A 2-fold molar excess of **2** should be used for clean conversions. Arenesulfonyl chlorides can also be employed in this case.[83a] TASF is a fluoride ion source of choice in this slightly exothermic reaction, giving results superior to TBAF or tris(diethylamido)phosphonium difluoride. The electronic nature of substituents does not affect the yields. Interestingly, the process is not sensitive to the polarity of the solvent: dimethylformamide and petroleum ether are equally effective. In a related example, *N*-(trifluoromethylsulfonyl)-substituted aza analogs of arenesulfonyl chlorides were reacted with **2** in the presence of catalytic amounts of TASF in THF to give the corresponding sulfoximines in 70% yield.[83b]

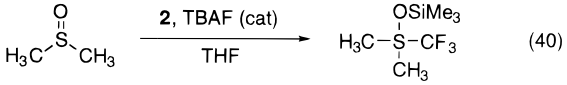
Table 16. Trifluoromethylation of Sulfur-Based Electrophiles

entry	electrophile	product	yield (%)	ref
1			R = H (99) 3-NO_2 (73) 4-Cl (96) 4-Me (96)	82, 83 82, 83 82, 83 82, 83
2			70	84
3			R = R^1 = Cl R = R^1 = F R = CF_3, R^1 = F R = Ph, R^1 = Cl R = 4-NO_2 C_6H_4, R^1 = Cl (56) R = 4-ClC_6H_4 , R^1 = Cl (58) R = 4-MeC_6H_4 , R^1 = Cl (61)	15 15 15 15 83 83 83
4			R = R^1 = Cl R = R^1 = F R = CF_3, R^1 = Cl	83 83 83
5			R = Ph (59) 4-ClC_6H_4 (72) 4-$NO_2C_6H_4$ (69)	83 83 83

Langlois *et al.* have shown that disulfides and diselenides react with **2** in the presence of TBAF (2 equiv) furnishing trifluoromethyl sulfides or selenides in 25−80% isolated yields.[84a] Similarly, thiocyanates and selenocyanates are converted into the corresponding trifluoromethyl sulfides and selenides, respectively, on treatment with **2** in the presence of TBAF.[84b]

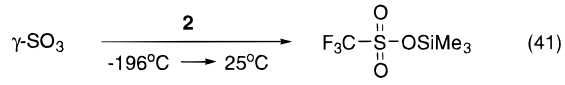
The use of **2** also provides a one-step route to trifluoromethyl sulfides and sulfoxides which are difficult to prepare using other methods. With the use of **2** and TBAF, aryl trifluoromethyl sulfides and sulfoxides are formed in THF or pentane at 3−5 °C in good isolated yields starting from the readily available arenesulfenyl and -sulfinyl chlorides, respectively. Pentane was found to be a solvent of choice in this reaction. Kirchmeier and co-workers also obtained trifluoromethyl sulfoxides and sulfur oxydifluorides reacting **2** with various sulfur-containing electrophiles using similar protocol.[15]

The reaction between **2** and dimethyl sulfoxide in THF in the presence of a catalytic amount of TBAF resulted in the isolation of the first [(fluoroalkyl)oxy]-sulfurane containing more than two sulfur−carbon bonds.[15] The process (eq 40) is highly dependent on the solvent as well as on the fluoride ion source. No reaction takes place in acetonitrile or benzonitrile. When potassium fluoride is employed, no product is formed regardless of the solvent system used.



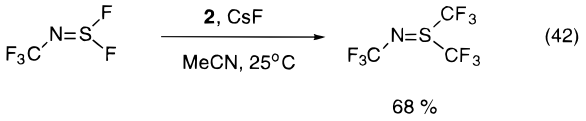
(40)

Compound **2** mildly reacts with γ-SO_3 giving the product of a formal insertion of the SO_3 unit into the Si−CF_3 bond of **2**.[85] This transformation permits the preparation of trimethylsilylated derivative of synthetically useful triflic acid in one step (eq 41).



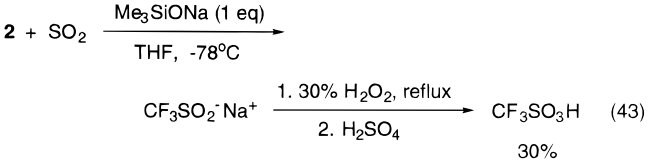
(41)

Sulfimides readily react with **2** to give the perfluorinated products in high yields.[81,86] Addition−elimination mechanism must operate in this case.



(42)

Sulfur dioxide reacts with **2** in the presence of Me_3-SiONa to give sodium trifluoromethanesulfinate. This adduct has been further oxidized to trifluoromethanesulfonic acid in 30% overall yield.[4a]

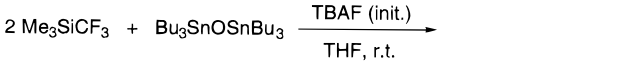


(43)

3.1.8. Organometallic Reagents

Bis(tributyltin)oxide can be readily converted in quantitative yield at room temperature into (tri-

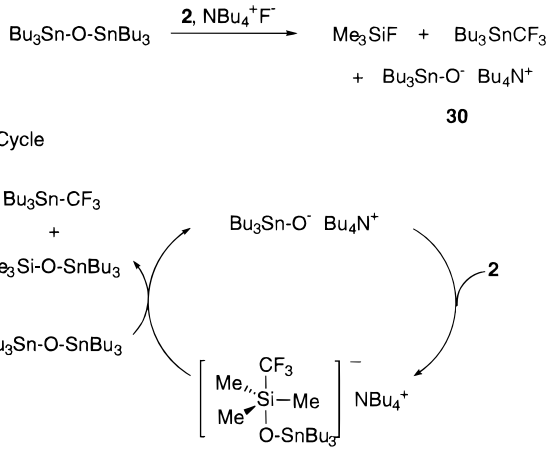
fluoromethyl)tributyltin when reacted with **2** (eq 44).[41] The mechanism of this process is shown in



(44)

Scheme 12. The initiation by the fluoride ion leads to the formation of the alkoxide **30**. The catalytic cycle is then perpetuated by the oxophilicity of the silicon atom in **2**.

Scheme 12

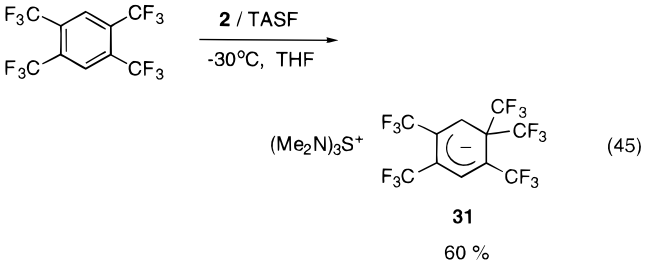


Hexamethyldisiloxane along with THF is removed under vacuum. Further purification by a short-path vacuum distillation yields Bu_3SnCF_3 as an analytically pure colorless liquid.

3.1.9. Aromatic Compounds

Under certain conditions **2** can be used to transfer *in situ* generated "CF_3^-" to activated aromatic compounds, giving products of formal addition or addition−elimination. In some cases, intermediate Meisenheimer complexes can be isolated.

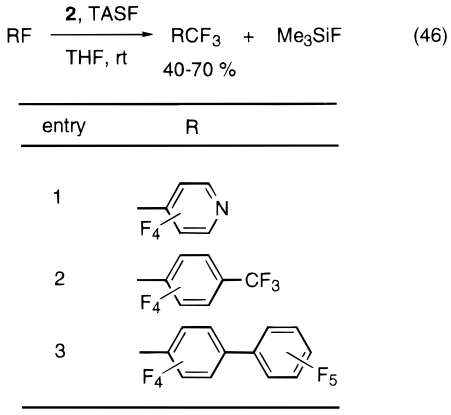
For example, the **2**/TASF (1:1) combination was used to add the nucleophilic "CF_3^-" anion to 1,2,4,5-tetrakis(trifluoromethyl)benzene via *ipso* attack on one of the CF_3-bearing carbon atoms whereby stable carbanion salt **31** can be isolated as a dark yellow oil (eq 45).[87]



(45)

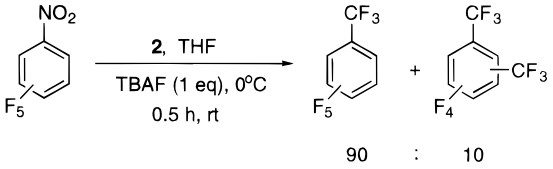
The presence of electron-withdrawing CF_3 groups activates the ring toward attack by nucleophiles, in this case a masked form of highly nucleophilic "CF_3^-" anion. TAS^+ cation stabilizes the resulting complex against elimination of the fluoride anion.

Perfluorinated aromatic compounds are also susceptible to the substitution of fluorine by nucleophilic trifluoromethyl anion obtained *in situ* from **2**.[88] Bardin *et al.* showed that treating **2** with RF and TASF in THF at room temperature for 2−3 h results in a clean substitution of fluorine atom for trifluoromethyl group (40−70% yield). Formation of the strong Si−F bond accompanies the reaction (eq 46).



(46)

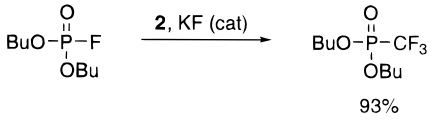
Pentafluoronitrobenzene reacts readily according to eq 47 to afford octafluorotoluene as well as bis(trifluoromethyl)tetrafluorobenzene in a 90:10 ratio via *ipso* substitution of the nitro group and fluoride, respectively (eq 47). Anhydrous TBAF should be used to minimize the formation of CF_3H. Dinitrobenzene, however, gives a mixture of trifluoromethylated products.[4a]



(47)

3.1.10. Organophosphorus Compounds

Treatment of $(BuO)_2P(O)F$ with **2** under nucleophilic initiation using KF gives $(BuO)_2P(O)CF_3$ in 93% isolated yield.[4a]



(48)

3.2. Halodifloromethylation, Difluoromethylation, and Related Reactions

The effects of *gem*-difluorination on biological activity has been a subject of continuous investigations in recent years. Relatively little steric perturbation takes place as hydrogen is replaced for fluorine. Consequently, the CH_2-CF_2 transposition in many instances preserves or even augments the biological activity.[89] The CF_2 group is also known for its isosteric and isopolar relation to oxygen, a property which has been widely explored in the area of difluorinated analogs of carbohydrates and other oxygenated biomolecules. Additionally, the difluoromethylene group increases the electrophilic character of the neighboring carbonyl function which facilitates the formation of stable hydrates and hemiketals. These compounds are used as tetrahedral transition-state mimics.[90] The blockage of certain metabolic oxidation pathways is also credited to difluoromethylene functionality.

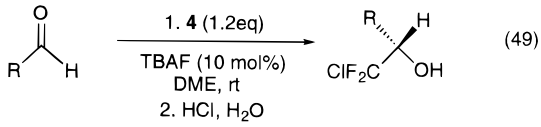
Table 17. Chlorodifluoromethylation of Carbonyl Compounds with Me_3SiCF_2Cl

entry	aldehyde	product	solvent	initiator	yield (%)
1	PhC(O)H	$PhCH(OH)CF_2Cl$	DME	TBAF	75
2	$PhCH_2CH_2C(O)H$	$PhCH_2CH_2CH(OH)CF_2Cl$	DME	TBAF	45
3	$PhCH_2C(O)H$	$PhCH_2CH(OH)CF_2Cl$	DME	TBAF	80
4	n-$C_6H_{13}C(O)H$	n-$C_6H_{13}CH(OH)CF_2Cl$	DME	TBAF	64
5	PhC(O)Ph	$Ph_2C(OH)CF_2Cl$	THF/NMP (1:1)	TBAF	32

Compared with the studies on the development of trifluoromethylation methods in recent years, silicon-assisted introduction of the difluoromethyl and difluoromethylene groups have received less attention.

Recently, Prakash *et al.* demonstrated that readily available Me_3SiCF_2Cl (**4**) serves as a source for "CF_2Cl^-" in reactions with aldehydes and ketones.[30] Under TBAF initiation in THF **4** was found to be less reactive than Me_3SiCF_3 (**2**) toward nucleophilic group transfer. This fact reflects the difference in polarity between the Si−CF_3 and Si−CF_2Cl bonds which renders **4** less susceptible to nucleophilic attack. More coordinating solvents are, nonetheless, capable of promoting the reactions through the activation of the silicon center toward nucleophilic attack and stabilization of the anionic intermediates involved in the catalytic cycle. Mechanistically chlorodifluoromethylation closely resembles trifluoromethylation (*vide supra*). THF/NMP (1:1) and 1,2-dimethoxyethane (DME) are both suitable as the reaction media. The lower boiling point of the latter simplifies the work-up procedure. For efficient conversions, higher amounts of initiator (10 mol % vs 2−3 mol % of TBAF) are required.

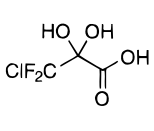
A series of aromatic and aliphatic aldehydes can be chlorodifluoromethylated at room temperature using the outlined protocol providing an efficient way to the valuable class of difluoromethyl-containing secondary alcohols under mild conditions (eq 49 and Table 17). Tetrabutylammonium fluoride (TBAF) is



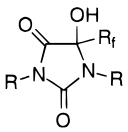
(49)

superior to both KF and CsF as an initiating species. However, due to its hygroscopic properties, TBAF should be predried in order to minimize the formation of CF_2ClH. In some cases the initial silylated CF_2Cl^- adducts are quite resistant toward treatment with HCl which is normally used to remove the trimethylsilyl group. In these cases, 40% HF solution in acetonitrile is adequate. Ketones also react with **4** at room temperature under TBAF initiation furnishing the corresponding chlorodifluoromethylated adducts. Not unexpectedly, lower reactivity is observed compared to aldehydes. The carbon−chlorine bond in the resulting carbinols can be reduced with hydride-transfer reagents giving secondary difluoromethylated alcohols which are of interest as potential enzyme inhibitors.[90,91]

Geffken *et al.* reported that **4** and related Me_3SiCF_2Br induces halodifluoromethylation of the activated carbonyl compounds in THF similar to **2**. With di-*tert*-butyl oxalate an expedient synthesis of the corresponding halodifluoropyruvic acids monohydrates (**32**) was reported. 5-(Halodifluoromethyl)-5-hydroxyimidazolidine-2,4-diones (**33**) can also be obtained and further used for the construction of heterocycles.[13,69,78]



32



33

R = CH_3, cyclohexyl, C_6H_5
R_f = CF_2Cl, CF_2Br

Bis(trimethylsilyl)difluoromethane (**5**) is a synthetic equivalent of "CF_2H^-" anion. Compound **5** can be used for the direct difluoromethylation of aldehydes, giving the corresponding CF_2H^- alcohols.[30] These reactions are carried out in THF/NMP or DME media using TBAF as an initiator followed by the usual acidic workup (Scheme 13). Ketones also react with **5** at room temperature, albeit at much slower rate. The only detectable byproducts are CF_2H_2 and $TMSCF_2H$ formed during the protonation of CF_2H^- and $TMSCF_2^-$, respectively. From a mechanistic point of view, the overall process is considered to involve the initial formation of the silylated adduct **34** which starts the catalytic cycle (Scheme 13, path a). The aldehyde moiety is then siladifluoromethylated as indicated. Acidic work-up of the adduct furnishes the desired difluoromethylated carbinols **35** (Table 18). An alternative pathway might be considered: Me_3SiCF_2H formed *in situ* from **5**, TBAF, and subsequent protonation could be regarded as a species that is involved in this transformation considering the highly basic nature of perfluoroalkylated anionic species (Scheme 13, path b).

For efficient conversions difluoromethylation requires higher amounts of TBAF in comparison with

Scheme 13

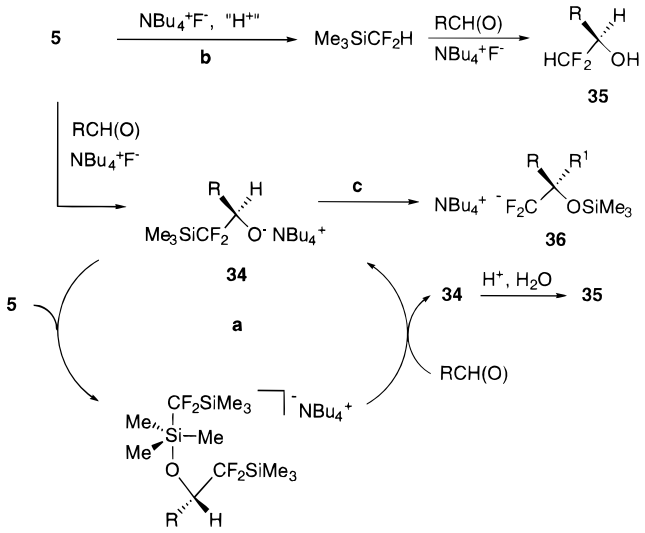
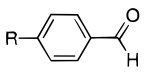
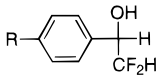
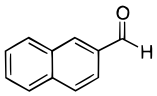
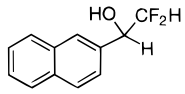
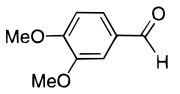
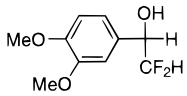
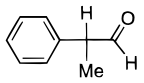
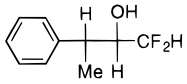
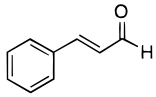
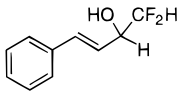
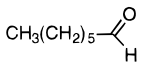
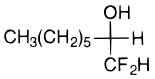
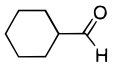
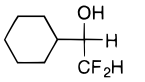


Table 18. Difluoromethylation of Carbonyl Compounds with $Me_3SiCF_2SiMe_3$

entry	aldehyde	product	solvent	yield (%)
1	PhC(O)H	$PhCH(OH)CF_2H$	DME	75
2	$PhCH_2CH_2C(O)H$	$PhCH_2CH_2CH(OH)CF_2H$	DME	66
3	$PhCH_2C(O)H$	$PhCH_2CH(OH)CF_2H$	DME	78
4	n-$C_6H_{13}C(O)H$	n-$C_6H_{13}CH(OH)CF_2H$	DME	55
5	PhC(O)Ph	$Ph_2C(OH)CF_2H$	NMP	40

Table 19. Difluoromethylation of Carbonyl Compounds with $PhMe_2SiCF_2H$

entry	carbonyl compound	product	yield	reference
1			R = H (82%) MeO (74%) Cl (80%)	92 92 92
2			77%	92
3			70%	92
4			52%	92
5			55%	92
6			56%	92
7			43%	92
8			R R' Et Et 25% Ph Me 20% Ph CF_3 35%	92 92 92

trifluoromethylation. This fact is attributed to the inhibition through the competitive migration of the oxophilic trimethylsilyl group in **34** generating **36** (Scheme 13, path c) which is not capable of further maintaining the reaction due to the lack of the nucleophilic oxygen center.

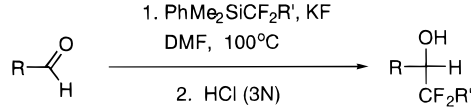
Structurally related Me_3SiCF_2H (bp 50 °C), could also be viewed as a means of generating "CF_2H^-" *in situ*. However, it is hydrolytically unstable and much more volatile than **5** (bp 130 °C). Additionally, the silylated adducts **34** could be envisioned to react with other electrophiles besides "H^+" (acidic workup) which permits **5** to display general "CF_2^{2-}" properties.

Fuchikami *et al.* recently reported on the difluoromethylating properties of a related silane, $PhMe_2SiCF_2H$ which reacts with aldehydes at elevated temperatures in polar solvents (100 °C, DMF) with KF as an initiator (Table 19).[92,93] The observed relative inertness might be a result of the presence of the phenyl substituent. It was also reported that the reactions with enolizable carbonyl compounds in THF at room temperature result in the formation of silyl enol ethers.[49]

Table 20. Introduction of CF_2R' (R' = Alkyl) Function

entry	R′	R	yield (%)
1	Et	Ph	70
2	*i*-Pr	Ph	71
3	cyclohexyl	Ph	trace
4	Et	$CH_3(CH_2)_5$	38
5	*i*-Pr	$CH_3(CH_2)_5$	37
6	cyclohexyl	$CH_3(CH_2)_5$	trace

Similarly, $PhMe_2SiCF_2R$ (R = alkyl) compounds undergo addition to aldehydes under similar conditions according to eq 50. Table 20 features representative examples.



(50)

Hiyama *et al.* employed $PhMe_2SiCF_2CH{=}CH_2$ as a source for the metal-free difluoroallyl anion (eq 51). By using a catalytic amount of TASF, carbonyl compounds are converted into the corresponding

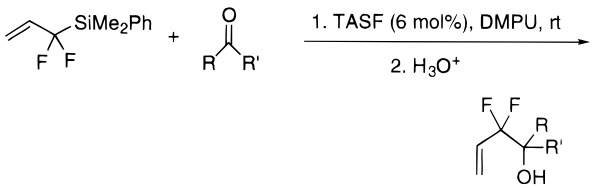
Table 21. Introduction of 1,1-Difluoroallyl Functionality

entry	R	R′	yield (%)
1	Ph	H	93
2	4-Cl-C_6H_4	H	100
3	PhCH=CH	H	52
4	*n*-$C_{10}H_{21}$	H	44
5	*t*-Bu	H	53
6	Ph	Ph	34

Table 22. Introduction of (Diethylphosphinyl)difluoromethyl Functionality

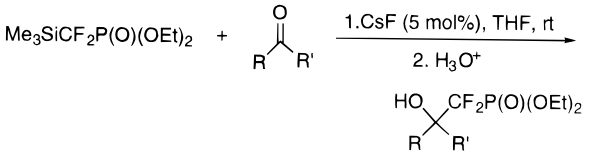
entry	R	R′	yield (%)
1	Ph	H	58
2	4-BuO-C_6H_4	H	66
3	4-MeO-C_6H_4	H	67
4	4-NO_2-C_6H_4	H	87
5	4-NO_2-C_6H_4	CH_3	38
6	4-pyridyl	H	57
7	2-thiophene	H	84

homoallylic alcohols. Interestingly, isomeric $PhMe_2SiCH_2CH{=}CF_2$ gives the same product under these conditions[94,95] (Table 21).



(51)

Diethyl(trimethylsilyl)(difluoromethyl)phosphorane, readily obtained from the corresponding lithiated derivative, is used for the generation of (diethylphosphinyl)difluoromethyl carbanion species under neutral conditions (eq 52 and Table 22). The reaction occurs with the aid of a catalytic amount of cesium fluoride. This method allows facile addition of the difluoromethyl unit stabilized by the phosphinyl group to carbonyl compounds.[96]



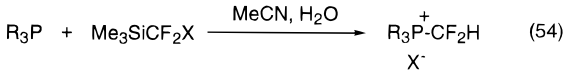
(52)

Yudin showed that $Me_3SiCF_2CO_2Et$, readily available from $BrCF_2CO_2Et$ (section 2.2), can be used to generate *in situ* "$^-CF_2CO_2Et$" under TBAF initiation which allows to obtain Reformatsky-type products in reactions with aldehydes in moderate yields.[26] Notably, this method is applicable to easily reduced systems that can undergo homocoupling and other side reactions under traditional Reformatsky conditions that involve reduction with zinc metal.

Me_3SiCF_3 (**2**) can also be employed as a difluoromethyl equivalent. A variety of difluoromethylated products can be obtained according to Portella's procedure (see section 3.1.1.2). Additionally, treatment of **2** with an anhydrous fluoride source such as TASF in THF results in the generation of singlet difluorocarbene. In the presence of a suitable acceptor such as tetramethylethylene, the corresponding adduct can be isolated (eq 53).[4a]

(53)

Yudin has showed that CF_2H-containing phosphonium salts can be readily obtained in high yields from $Me_3SiCF_2Cl(Br)$ and the corresponding phosphine in acetonitrile (eq 54).[26] The reaction commences with a chlorophilic attack of the phosphorus center on the CF_2Cl group in Me_3SiCF_2Cl followed by protodesilylation. The obtained salts can be viewed as donors of the nucleophilic difluoromethyl function. Ylide generation with a suitable base has also been explored.



(54)

R	X	yield (%)
Ph	Br	35
NMe_2	Cl	80
Ph	Cl	43

3.3. Other Perfluoroalkylation Reactions

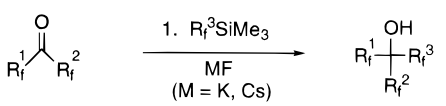
3.3.1. Perfluoroalkylation

The application of perfluoroalkyl(trialkyl)silanes as R_f^- transfer reagents is based on the same principles that operate in the chemistry of Me_3SiCF_3 (**2**). For example, (pentafluoroethyl)- and (heptafluoropropyl)-trimethylsilane readily convert carbonyl compounds into the corresponding alcohols (Table 23). The competitive formation of silyl enol ethers with enolizable ketones and aldehydes is not observed. The facial selectivity of addition parallels that of **2** which predominantly gives less hindered regioisomers (Table 23, entries 4 and 5).

TBAF, the most commonly used initiator, sometimes results in the deprotection of the initially formed silylated adducts resulting in unwanted side reactions. The mixture of potassium *tert*-butoxide with anhydrous potassium fluoride was reported by Nelson *et al.* to give better results in these cases. The obtained silyl ethers are further treated with aqueous HCl, furnishing the desired carbinols.[55]

Pentafluoroethylation of imidazolidenetriones was explored by Geffken *et al.* These authors also succeeded in similar transformation of di-*tert*-butyl oxalate. The reactions proceed similarly to the corresponding trifluoromethylations with **2**.[69,78]

High molecular weight perfluorinated tertiary alcohols were prepared by Chen *et al.* (eq 55, Table 24).[16] It was found, that (perfluoroalkyl)- and (per-



(55)

Table 23. Perfluoroalkylation of Carbonyl Compounds

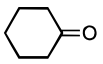
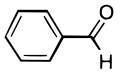
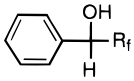
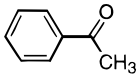
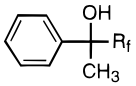
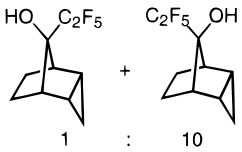
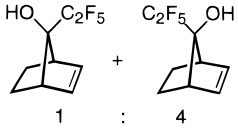
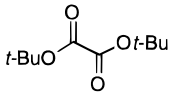
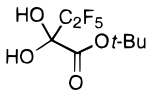
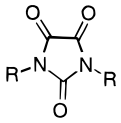
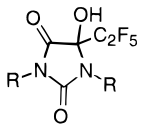
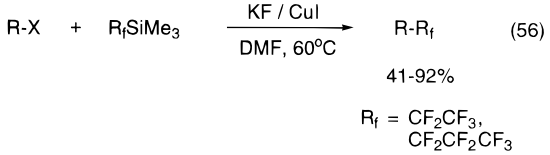
entry	carbonyl compound	product	yield	reference
1			$R_f = C_2F_5$ (82%) C_3F_7 (81%)	49 49
2			$R_f = C_2F_5$ (81%) C_3F_7 (78%)	49 49
3			$R_f = C_2F_5$ (86%) C_3F_7 (66%)	49 49
4			95%	55
5			96%	55
6			89%	69
7			R = CH_3 (48%) C_6H_5 (25%) C_6H_{11} (31%)	78 78 78

Table 24. Preparation of the Long-Chain Perfluorinated Group Containing Alcohols

entry	R_f^1	R_f^2	R_f^3
1	n-C_8F_{17}	CF_3	n-C_6F_{13}
2	$(CF_3)_2CFO(CF_2)_4$	CF_3	n-C_6F_{13}
3	$C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)$	CF_3	n-C_6F_{13}
4	n-C_8F_{17}	$CF_3O[CF_2CF(CF_3)O]_2(CF_2)_2$	$(CF_3)_2CFO(CF_2)_2$
5	$(CF_3)_2CFO(CF_2)_4$	$(CF_3)_2CFO(CF_2)_4$	$C_3F_7OCF(CF_3)CF_2OCF(CF_3)$

fluorooxaalkyl)trimethylsilanes readily react with fluoroalkyl ketones. Stoichiometric amounts of metal fluorides should be employed for the efficient generation of the nucleophilic "R_f^-" species. The experimental conditions are critical and significantly affect the yield. Thus, in the optimal case, CsF in a ≥1:1 ratio to ketone is used in diethyl ether medium at 0 °C. Secondary R_fSiMe_3 generally require much longer reaction times than primary systems due to steric reasons as well as solubility considerations. Increase in the size of the ketone's perfluorinated groups has similar effect. Interestingly, the addition of perfluoro-2-butyltetrahydrofuran (~25% by volume) significantly improves the yield in some cases. This observation might be rationalized by an overall increase in solubility of the reaction products as well as starting materials in "fluorous" media, a novel term recently introduced by Horváth and Rábai.[97]

The *in situ* preparation of CuR_f from R_fSiMe_3 (R_f = C_2F_5, C_3F_7) was reported in the presence of KF and copper(I) iodide at 60 °C in a DMF solution. The copper(I) species undergoes cross-coupling reactions, giving perfluoroalkylated aromatics in 41−90% yield (eq 56).[80]

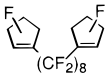
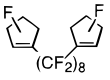
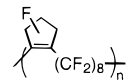


Further, activation of the silicon center in R_fSiMe_3 was reported using various anionic catalysts (CsF, TASF, $RCOO^-$, R_fO^-). Under these conditions R_f-$SiMe_3$ readily reacts with acid fluorides, releasing fluorotrimethylsilane and forming the corresponding ketone. This is particularly valuable since there is no general method to obtain such ketones. Further reactions leading to the perfluorinated tertiary alcohols generally do not take place. It was found that perfluorinated acyl fluorides react considerably better

Table 25. Preparation of Ketones Containing Long-Chain Perfluorinated Groups

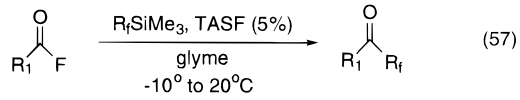
entry	R_1	R_f	yield (%)	ref
1	$CF_3(CF_2)_2$	C_8F_{17}	88	32
2	Ph	C_8F_{17}	60	32
3	$C_3F_7OCF(CF_3)$	C_8F_{17}	85	32
4	$C_3F_7OC(CF_3)FCF_2OCF(CF_3)$	$(CF_3)_2CF(CF_2)_4$	83	16

Table 26. Perfluoroalkylation of Perfluoroalkenes

R_fSiMe_3	alkene	product	yield (%)
$C_8F_{17}SiMe_3$	$CF_3CF=CF_2$	$CF_3CF=CFC_8F_{17}$	58
$C_8F_{17}SiMe_3$			90
$Me_3Si(CF_2)_8SiMe_3$			95
$Me_3Si(CF_2)_8SiMe_3$		 $M_n \sim 3200$, $M_w \sim 4300$	a

a, yield not reported

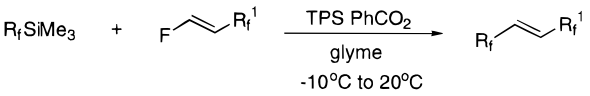
than nonfluorinated ones (eq 57, Table 25). A com-



(57)

mon side reaction in these processes is the formation of isomeric perfluoroalkenes by catalytic elimination of the fluoride ion. Slow addition of silane solves this problem to some extent. Farnham *et al.* also developed protocols for the similar preparation of perfluoroalkylated diketones using $Me_3Si(CF_2)_nSiMe_3$ reagents, readily obtained via Barbier-type reactions.[32]

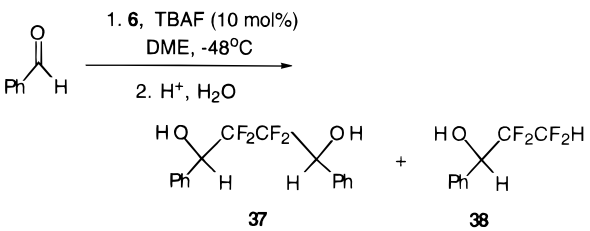
Fluorinated alkenes react with R_fSiMe_3 to give the corresponding adducts according to eq 58 by addition−elimination mechanism. Bis(perfluoroalkylat-



(58)

ed) products as well as low molecular weight polymeric materials are also readily available[32] (Table 26).

Although β-fluoride ion elimination in Me_3SiCF_2-CF_2SiMe_3 **6** is highly favored at room temperature (*vide infra*), at −48 °C in DME the preferential formation of the diol **37** containing the perfluoroethylene unit takes place (eq 59).[30] Thus, **6** acts as a



(59)

37 **38**

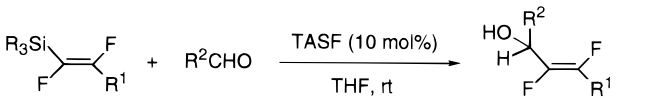
synthetic equivalent of "$^{-}CF_2CF_2^{-}$" dianion equivalent. Competitive protonation results in the formation of tetrafluoroethylated carbinol **38**. A quite long value of 1.935 Å for the Si−CF_2 bond in **6** was obtained by Prakash *et al.* using X-ray structure analysis. Weakness of this linkage accounts for the high reactivity of **6**. In comparison, a value of 1.923 Å was obtained by Bürger and Eujen for the Si−CF_3 bond in CF_3SiH_3 using the electron diffraction study combined with the normal coordinate analysis.[44,45] Fuchikami has shown that $PhMe_2SiCF_2CF_2SiMe_2Ph$ undergoes similar reactions with carbonyl compounds in highly polar solvents.[98] However, elevated temperatures are required in order to activate the silicon center of this phenylated derivative. Little selectivity with respect to perfluorovinylation *vs* perfluoroalkylation was observed at higher temperatures.

3.3.2. Perfluoroolefination

The presence of the perfluorovinyl group in a molecule can be further used for various purposes taking advantage of several useful properties of this unit. For example, the "CF_2=CF" functionality can be considered as a building block for the preparation of polymeric materials. Additionally, the presence of the fluorine atoms is expected to facilitate reactions with nucleophiles. In this context, various additon−elimination products can be envisioned in view of the great leaving group ability of the fluoride ion in elimination reactions.

Among the available sources of this important group, silylated reagents are once again preferred due to the mild reaction conditions that are required for the generation of the anionic species. In comparison, (trifluoroethenyl)lithium is very labile and should be handled below −78 °C.[8]

Hiyama *et al.* showed that metal-free "CF_2=CF^{-}" is readily generated from Et_3SiCF=CF_2 using catalytic amount of TASF in THF solution. Further reactions with aldehydes afford perfluorovinylated carbinols (eq 60, Table 27).[95]



R^1 = H, Cl, F, Alkyl alkyl ; R^2, R^3= alkyl, aryl (60)

Polymerization of trifluorovinylsilanes was explored. When triethyl(trifluorovinyl)silane is heated at 180 °C in the presence of cesium fluoride for 10 days, the formation of the polymeric material is observed (Scheme 14).[34] Overall, the process can be rationalized by the intermediate formation of difluoroacetylene through the elimination of Et_3SiF and subsequent copolymerization with the starting material. Alternatively, elimination of Et_3SiF can take place from the poly(trifluoroethylene) intermediate formed from Et_3SiCF=CF_2.

Bis(trimethylsilyl)tetrafluoroethane **(6)**, the second homolog of the series $Me_3Si(CF_2)_nSiMe_3$ readily reacts

Table 27. Perfluorovinylation of Aldehydes with $R_3SiCF{=}CFR^1$ Reagents

entry	aldehyde	silane	yield (%)	ref
1	PhCOH	$Et_3SiCF{=}CF_2$	66	95
2	PhCH=CHCHO	$Et_3SiCF{=}CF_2$	43	95
3	*n*-$C_{10}H_{21}CHO$	$Et_3SiCF{=}CF_2$	59	95
4	PhCHO	$Et_3SiCF{=}CF$*n*-Bu (trans)	38	95
5	PhCHO	$Me_3SiCF{=}CF$*t*-Bu (trans)	86	95
6	*n*-$C_{10}H_{21}CHO$	$Et_3SiCF{=}CFCl$ (cis)	39	95
7	*n*-$C_{10}H_{21}CHO$	$Et_3SiCF{=}CFH$ (trans)	47	95

Scheme 14

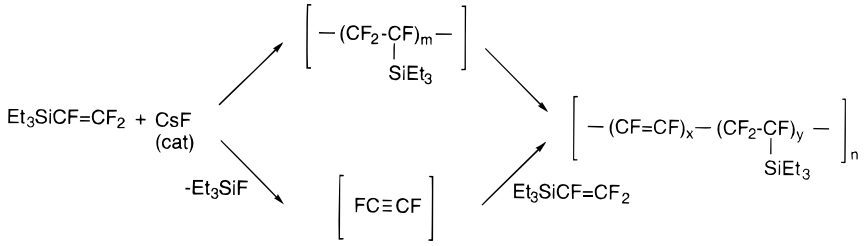
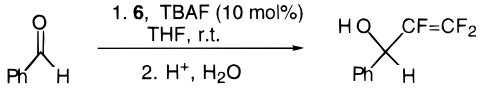


Table 28. Perfluorovinylation of Carbonyl Compounds with $Me_3SiCF_2CF_2SiMe_3$ (6)

entry	carbonyl compound	product	solvent	yield (%)
1	PhC(OH)	$PhCH(OH)CF{=}CF_2$	THF	75
2	$PhC(O)CH_3$	$PhCCH_3(OH)CF{=}CF_2$	THF	80
3	$C_6H_{13}C(O)H$	$C_6H_{13}CH(OH)CF{=}CF_2$	THF	64

with aldehydes and ketones in THF under TBAF initiation at room temperature.[30] The net transfer of the perfluorovinyl group to the carbonyl carbon accompanied by Me_3SiF elimination takes place under these conditions resulting in the formation of perfluorovinylated carbinols **39** (eq 61 and Table 28).



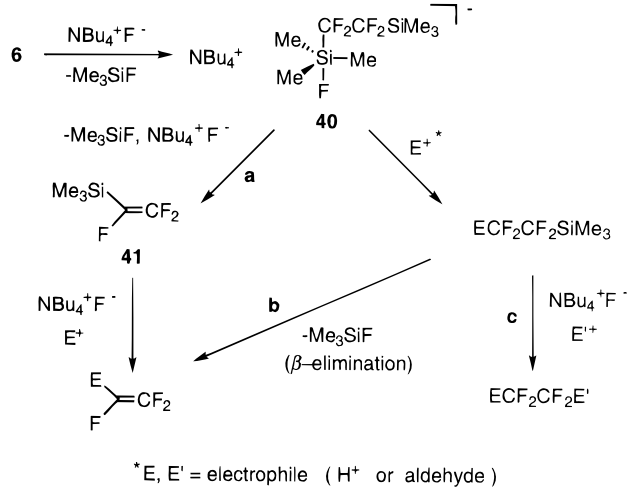
(61)

39

Consequently, **6** acts as a convenient, *in situ* source of "$CF_2{=}CF^-$". The corresponding secondary and tertiary perfluorovinylated compounds can be obtained in high yields.

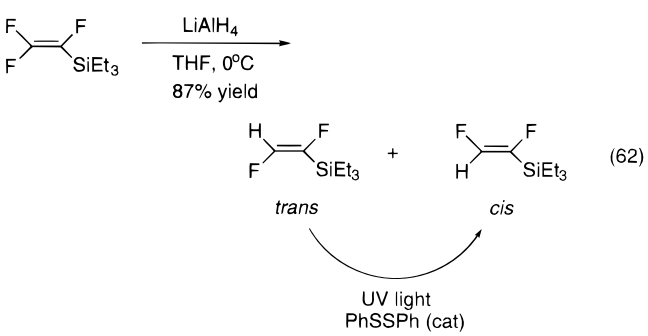
Scheme 15 depicts some reactivity considerations. After the initial attack of fluoride on the silicon atom of **6**, the transient species **40** can undergo β-fluoride ion elimination, forming (perfluorovinyl)trimethylsilane **41** which further reacts with electrophiles present in the reaction mixture (Scheme 15, path a). The regeneration of TBAF makes the formation of **41** catalytic in initiator. Upon addition of an aldehyde or a ketone to the reaction mixture, transfer of the perfluorovinyl unit occurs in an autocatalytic fashion discussed above (section 3.1.1.1). At the same time, **40** itself can undergo addition to an aldehyde followed by the β−fluoride ion elimination giving the trifluorovinyl products (Scheme 15, path b).

Scheme 15



Generally, (perfluorovinyl)silanes are less reactive toward electrophiles compared to other silicon-based "R_f^-" transfer reagents. A theoretical study of $Me_3SiCF{=}CF_2$ species carried out by Kirchmeier *et al.* suggests rather small effect of the vinyl group on the length and, therefore, the strength of the C(sp^2)−Si. Fluorination causes only a small lengthening from 1.867 Å in $Me_3SiCH{=}CH_2$ to 1.877 Å in $Me_3SiCF{=}CF_2$.[99] This contrasts with a significant bond elongation in the case of the CF_3-containing silanes (*vide supra*).

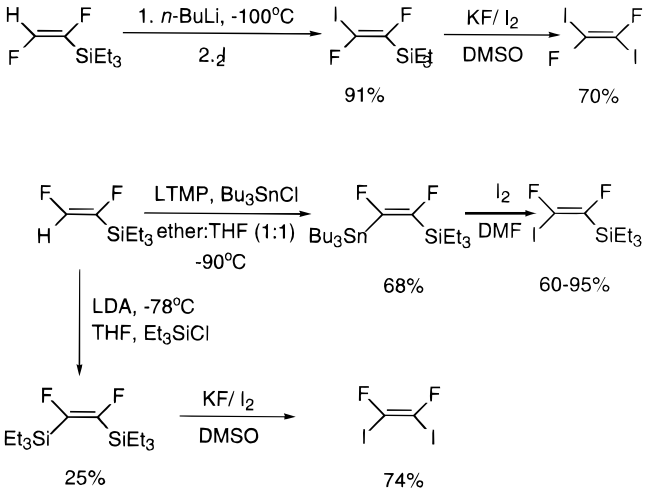
Burton *et al.* have recently described the use of silylated fluoroolefins as starting materials for a variety of other fluorinated products. It was found that neat *trans*-1,2-difluoro(triethylsilyl)ethylene undergoes ultraviolet light-promoted isomerization catalyzed by phenyl disulfide to afford the corresponding *cis* derivative[35] (eq 62). Further, metalation of the



(62)

olefinic C−H bond in the corresponding *cis*- or *trans*-silane followed by trapping of the resulting carbanion species by tributyltin chloride or triethylsilyl chloride leads to the geometrically pure stannyl and silyl

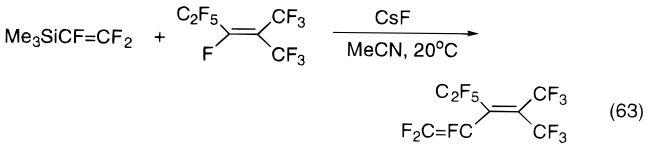
Scheme 16



derivatives, respectively, (Scheme 16). Iodinated *cis*- and *trans*-1,2-difluoroethylenes are subsequently available via fluoride-induced reactions with molecular iodine.

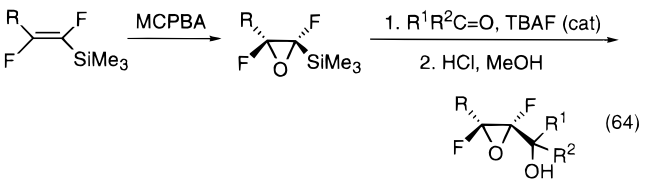
Similar to **2**, $(n\text{-}C_3H_7)_3SiCF{=}CF_2$ undergoes formal insertion into the sulfur−oxygen bond of $\gamma\text{-}SO_3$.[100] The product silyl ester is readily hydrolyzed to give polyfluorovinylated sulfonic acid and other valuable products.

The reactivity of $Me_3SiCF{=}CF_2$ toward addition to perfluoroalkenes was investigated by Petrov *et al.*[101] It was found that substitution of olefinic fluorine atom readily occurs at room temperature through addition−elimination mechanism (eq 63).



(63)

Sauvêtre and co-workers demonstrated that difluorinated epoxides can be obtained from the corresponding silylated fluoroolefins using MCPBA as an oxidant. These epoxides undergo facile fluoride-induced desilylation followed by nucleophilic addition to carbonyl compounds. Catalytic amount of TBAF is sufficient in this case. The resulting epoxides are valuable fluorinated building blocks.[36,102]



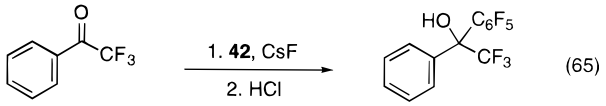
(64)

entry	R^1	R^2	yield(%)
1	Me	H	85
2	Pr	H	65
3	Ph	H	70
4	CH_3-CH=CH	H	61
5	Ph-CH=CH	H	63
6	CH_3	CH_3	48
7	Ph	CH_3	48

3.3.3. Perfluoroarylation

The perfluorinated phenyl group is known for its electron-withdrawing properties and great stacking ability with electron-rich arenes which makes it attractive for applications ranging from molecular recognition to the design of novel catalysts. (Pentafluorophenyl)trimethylsilylane (**42**) can be used to introduce this important fluorinated group into various electrophilic substrates under mild conditions. The generation of "$C_6F_5^-$" from **42** upon nucleophilic activation is generally followed by the addition to electrophiles similar to the corresponding reactions of **2**.

For example, Gostevskii *et al.* used (perfluorophenyl)trimethylsilane to carry out the perfluorophenylation of aldehydes in the presence of cyanide ion under neutral conditions (eq 65).[103−106] Cesium fluoride can also be used as an initiator for this process. In the absence of an anionic initiator the addition proceeds only at 170 °C.[107] Enolizable ketones lead to silyl enol ethers rather than to addition products under these conditions. This is attributed to the stabilizing effect of perfluorophenyl group on the evolving negative charge in the course of enolization.[103−106] When **42** is added to the perfluorinated ketones in the presence of highly electrophilic $C_6F_5CH_2Br$, the corresponding benzylated adducts are isolated (see section 3.1.1.2 for similar reactions of **2**). Gostevskii *et al.* also established that **42** reacts with other electrophiles under similar conditions (Table 29).

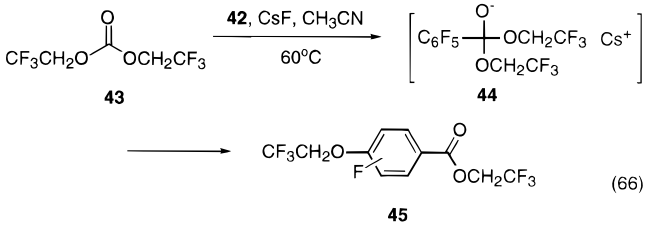


(65)

Table 29. Reactions of $C_6F_5SiMe_3$ with Electrophiles

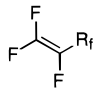
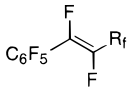
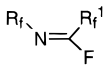
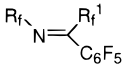
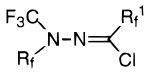
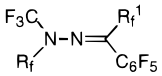
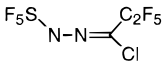
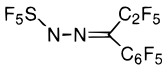
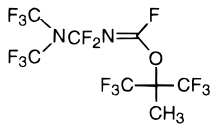
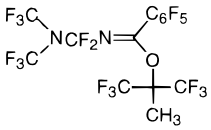
entry	T °C	electrophile	product	yield (%)
1	20	I_2	C_6F_5I	53
2	20	Br_2	C_6F_5Br	93
3	20	D_2O	C_6F_5D	59
4	20	CH_3I	$C_6F_5CH_3$	59
5	20	$C_6F_5CF_3$	4-[$(CF_3)C_6F_4$]C_6F_5	50
6	20	$C_6F_5HgOCOCF_3$	$Hg(C_6F_5)_2$	62

The reaction between **42** and bis(trifluoroethyl)-carbonate **43** proceeds with the initial formation of the pentafluorophenylated adduct **44** (eq 66).[58] This species subsequently liberates highly stabilized $CF_3CH_2O^-$ anion which ultimately leads to the formation of ester **45** in 27% overall yield.



(66)

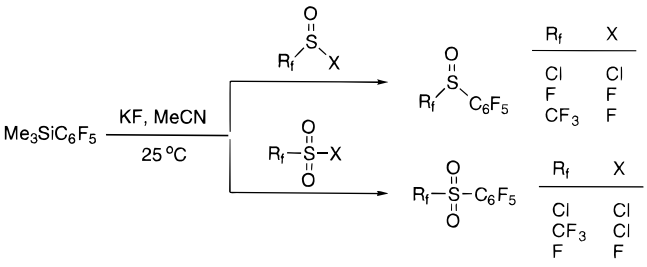
Table 30. Pentafluorophenylation of Halogenated Olefins

entry	olefin	product	yield (%)	reference
1			R_f $(CF_2)_4CFClCF_2Cl$ (51) C_6F_5 (80)	111 111
2			R_f R_f^1 C_2F_5 CF_3 63 *n*-C_4F_9 *n*-C_3F_7 56	111 111
3			R_f R_f^1 C_2F_5 C_2F_5 65 CF_3 CF_3 68 CF_3 CF_3 60	81 81 81
4			55	81
5			a	81

a, yield not reported

Sulfur-based electrophiles that contain highly reactive S−X (X = F, Cl) bond are readily pentafluorophenylated giving valuable substitution products (Scheme 17).[85] Similar to trifluoromethylation of sulfimides, pentafluorophenylation can be carried out under mild conditions. γ-SO_3 was also shown to react with **42** to give the products of the formal insertion of the perfluorophenyl unit into the sulfur−oxygen bond.

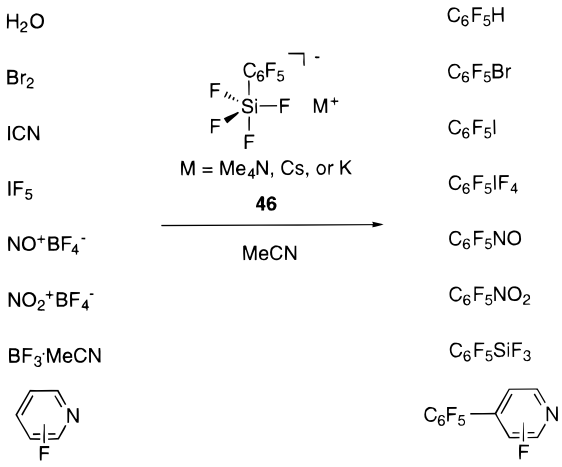
Scheme 17



Certain reactive halogenated olefins give the addition-elimination products with **42** using stoichiometric amounts of the initiator (Table 30).[81,108−111]

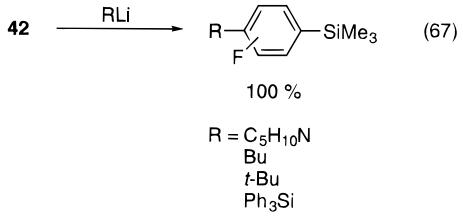
The involvement of (pentafluorophenyl)trimethylfluorosilicates has been postulated in the described processes. However, the proof of their existence was obtained only recently by Frohn *et al.*[112] It was found that in order to isolate and characterize such a pentavalent species, $F_3SiC_6F_5$ must be employed. By using Me_4NF, CsF, or KF, the pentavalent complexes **46** can be isolated as a white, moisture-sensitive solid which shows slight solubility in polar aprotic solvents. Fluorine atoms must efficiently stabilize the negative charge in these compounds. The obtained complexes are capable of reacting with electrophiles to afford products that are normally formed during the corresponding fluoride-induced reactions of **42**. This supports the involvement of highly reactive hypercoordinate intermediates in the reaction (Scheme 18).

Scheme 18



In addition to the reactivity of the Si−C bond in **42**, aromatic fluorine atoms are susceptible to nucleophilic displacement. For instance, Bardin *et al.* used carbon- and nitrogen-based nucleophiles to

obtain products of the formal fluorine substitution in the *para* position of the aromatic ring (eq 67).[108,112]



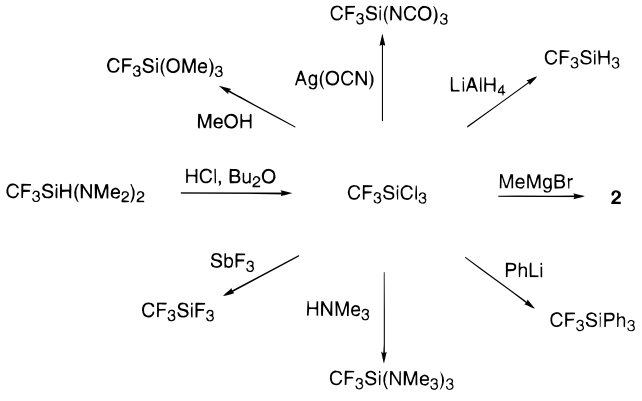
(67)

3.4. Reactions of Halogenated (Perfluoroalkyl)-silanes

As mentioned earlier, certain transformations of the perfluoroalkylated organosilanes do not proceed with the cleavage of the Si−R_f. These reactions have a considerable potential application for the preparation of the novel Si−R_f-containing species including polymeric materials.

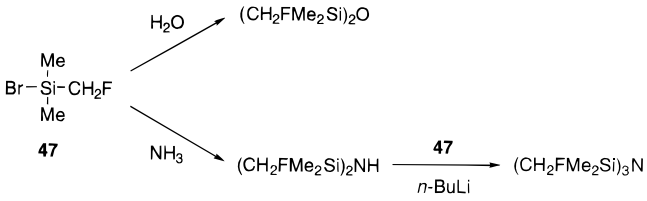
For example, interesting transformations of the halogenated (perfluoroalkyl)silanes were described by Ruppert *et al.* (Scheme 19).[17,22] It was shown that (trifluoromethyl)trichlorosilane, produced from the amino derivative $CF_3SiH(NMe_2)_2$ (as well as from tetrachlorosilane, section 2.1), can undergo selective fluorination of the Si−Cl bonds with antimony(III) fluoride. In addition, the substitution of the chlorine atoms for various oxygen, nitrogen, and carbon nucleophiles can be readily carried out. The CF_3 moiety remains intact, showing unusual stability under these conditions. The compounds obtained have been characterized by IR, NMR, and mass spectra.

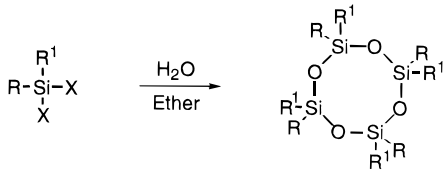
Scheme 19



Similarly, CF_3, CF_2Cl, and CH_2F groups are resistant to solvolysis of the CF_3-, CF_2Cl-, and CH_2F-containing mono- and dichlorinated silanes, respectively (Scheme 20 and eq 68). In the case of the

Scheme 20





(68)

R	R^1	X	reference
Me	CH_2F	Br	113
Me	CF_2Cl	Cl	26

monochlorinated derivatives, the corresponding disiloxanes can be isolated. Bürger *et al.* obtained the corresponding tetrameric siloxane from the CH_2F-containing dichlorosilanes as a crystalline material that gives crystals, suitable for the X-ray structure analysis.[113] An essentially planar Si_4O_4 ring system with the SiOSi angles averaging 157.9(5)° was detected. Notably, NMR of the reaction mixture shows the random distribution of all possible stereoisomers. Yudin *et al.* showed that under hydrolytic conditions chloro(chlorodifluoromethyl)dimethylsilane is transformed into the CF_2Cl- containing disiloxane, whereas dichloro(chlorodifluoromethyl)methylsilane furnishes the cyclic siloxane. Trichlorinated silanes that contain CF_2Cl group afford cross-linked polysiloxanes upon hydrolysis.[26]

4. Conclusions

Silicon-assisted perfluoroalkylation has become a useful method for achieving "R_f^-" group transfer to electrophiles under mild reaction conditions. The significance of the R_3SiR_f reagents is particularly revealing when $R_f = CF_3$ or CF_2X. The lability of the corresponding organometallic counterparts makes silylated reagents indispensable in these cases.

Generally, the essential role of silicon in perfluoroalkylation processes is to stabilize the transient "R_f^-" preventing its thermodynamically favored decomposition pathways. Even in the case of the long-chain perfluoroalkyl groups for which metalated species are known, the silylated reagents provide an advantage of mildness and convenience of handling. For instance, organometallic compounds must be used in equimolar amounts which may lead to the formation of the unwanted products derived from highly basic nature of "R_f^-". In the case of R_3SiR_f the reaction benefits from silicon's ability to coordinate nucleophiles that makes silicon center a "template" for the nucleophilic transfer and minimizes the unwanted exposure of "R_f^-". In other words, the strong thermodynamic preference to form the decomposition products containing the Si−F bond is compensated by favorable kinetic factors.

On the basis of the number of protocols encountered in the current literature that were successfully applied to perfluoroalkylation the following generalizations can be made. First of all, the reaction can be either equimolar or catalytic in nucleophilic activator depending on the nature of the silane and the substrate. Clearly, the possibility to conduct the process under catalytic conditions is one of its most attractive features. However, this holds only in those

cases where the addition to an electrophile produces a new silaphilic anionic center that subsequently activates another molecule of R_3SiR_f. In the catalytic cycle thus established, the cation which originates from the initiator is associated with the propagating anionic species. Coordinating solvents are therefore preferred due to their ability to stabilize the charged species formed along this pathway. On the other hand, if the electron-rich substrates are involved or the propagating species are of low nucleophilicity, catalytic conditions may not result in practical conversions. In these cases, the use of equimolar amounts of initiator has been found to adequately push the reaction in the forward direction. In these instances, residual moisture should be excluded due to the highly basic properties of the incipient "R_f^-" that leads to R_fH as a common byproduct. However, in substrates that contain acidic protons, protection is not needed: use of the excess reagent can be employed to carry out the process. An additional degree of freedom in the reaction comes from the nature of the cation which plays a very significant role. For example, hindered substrates are known to undergo slow additions. In order to accelerate the process, smaller cations may be involved which reduces the steric requirements of the ion pairs formed. In fact, the size of initiator cations may vary dramatically from cinchona alkaloid-derived systems to metal fluorides. Solvent is also an important parameter in influencing the cation−anion interaction. Thus, enantioselectivity in trifluoromethylation can be achieved when nonpolar solvents are employed to maximize the contacts of the propagating species with the chiral cation which controls the enantiofacial discrimination. On the other hand, the use of metal fluorides, the smallest initiators employed, may require solvents of increased polarity due to the solubility considerations. Additionally, substituents attached to the $Si-R_f$ unit may also vary which could result in better facial selectivity.

Prospects of the silicon-assisted perfluoroalkylation are seen mainly in developing novel R_3SiR_f species for the transfer of fluorinated functional groups. Additionally, exploring new possibilities of the existing transformations particularly with relation to selectivity and preparation of new fluorinated materials can be envisaged. With the documented herein advances in the preparation methods as well as applications based on the mechanistic picture of the involved processes, new, more efficient applications will likely emerge in the near future.

5. Acknowledgments

Support of our work in part by Loker Hydrocarbon Research Institute is gratefully acknowledged. This review is dedicated to Professor George A. Olah on the occasion of his 70th birthday.

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